HANDBOOK OF ORGANOPALLADIUM CHEMISTRY FOR ORGANIC SYNTHESIS

Volume 2

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PREFACE

Organic compounds mostly consist of just ten to a dozen non-metallic elements including C, H, N, P, O, S, and halogens. This may be one of the main reasons why chemists, until relatively recently, tended to rely heavily on those reactions involving only non-metallic elements. Many of them including the Diels-Alder reaction, the Claisen and Cope rearrangements continue to be important. Even so, their combined synthetic scope has been rather limited.

Regardless of how one defines metallic elements, more than three quarters of the elements may be considered to be metals. It is therefore not surprising that some of them, mostly main group metals such as Li, Na, K, and Mg, have been used as reagents or components of reagents for many decades primarily for generating carbanionic and other anionic species. Some other main group metals, such as Al and B, have also been used for many years primarily as components of Lewis acid catalysts in the Friedel-Crafts and other acid-catalyzed reactions. The significance of metal's ability to readily provide low-lying empty orbitals has become gradually but widely recognized and led to the development of a modern synthetic methodology involving B, Al, and other predominantly Lewis-acidic main group metals.

Some d-block transition metals (transition metals hereafter) including Ni, Pd, Pt, Rh, Ru, and so on have long been used as catalysts or catalyst components for hydrogenation and other reductions, while some others, such as Cr and Mn, have been used in stoichiometric oxidation reactions. Even some transition metal-catalyzed C—C bond-forming reactions, such as Roelen's oxo process was discovered as early as 1938. However, it was not until the 1950s that the full synthetic potential of transition metals began to be recognized. The discovery and development of the Ziegler-Natta polymerization indicated the ability of some early transition metals, such as Ti and Zr, to serve as superior catalysts for C—C bond formation. Development of the Dewar-Chatt-Duncanson synergistic bonding scheme provided a theoretical foundation for the "carbenoidal" characteristic of transition metals, as discussed in **Sect. II.3.1**. The discovery of ferrocene in 1951 and the subsequent clarification of its structure triggered systematic investigations that have made available a wide range of metallocene and related transition metal complexes for reagents and catalysts. In the area of organopalladium chemistry, it is widely agreed that invention of the Wacker oxidation in 1959 may have marked the beginning of the modern Pd-catalyzed organic synthesis (**Sect. I.1**).

Over the last thirty to forty years, compounds containing roughly ten to a dozen transition metals have been shown to serve as versatile and useful catalysts in organic synthesis. Today, they collectively represent the third major class of catalysts, enzymes and non-transition metal acids and bases being the other two. Of various factors, the following two appear to be critically responsible for rendering them superior catalysts and catalyst components. One is their ability to provide readily and simultaneously both filled nonbonding and low-lying empty orbitals. Together, they provide effective frontier orbitals, namely HOMO and LUMO, for concerted and synergistic interactions leading to

low energy-barrier transformations. The other is their ability to undergo simultaneously and reversibly both oxidation and reduction under one set of reaction conditions.

Then, why Pd? This is a very interesting but rather difficult question. Nonetheless, an attempt to answer this question is made in **Sect. I.2**, and the generalization summarized in **Table 2** of **Sect. I.2** is further supported by the experimental results presented throughout this Handbook. In short, Pd simultaneously displays wide-ranging reactivity and high stereo-, regio-, and chemo-selectivities. Its complexes are, in many respects, highly reactive. And yet, they are stable enough to be used as recyclable reagents and intermediates in catalytic processes. These mysteriously favorable characteristics appear to be reserved for just a few late second-row transition metals including Pd, Rh, and Ru that offer a combination of (i) moderately large atomic size and (ii) relatively high electronegativity, both of which render these elements very "soft", in addition to (iii) ready and simultaneous availability of both filled nonbonding and empty valence-shell orbitals and (iv) ready and reversible availability of two oxidation states separated by two elections mentioned above. The general lack of serious toxicity problems and ease of handling, which may not require rigorous exclusion of air and moisture in many cases are two additional factors associated with them.

The versatility of Pd is very well indicated by the contents of this Handbook listing nearly 150 authored sections spread over ten parts. This Handbook cannot and does not list all examples of the organopalladium reactions. However, efforts have been made to consider all conceivable Pd-catalyzed organic transformations and discuss all known ones, even though it was necessary to omit about ten topics for various unfortunate reasons.

Part I discusses the historical background of organopalladium chemistry (**Sect. I.1**) as well as the fundamental properties and patterns of the reactions of Pd and its complexes (**Sect. I.2**). In **Part II**, generation and preparation of Pd complexes are discussed. These discussions are rather brief, as the main focus of this Handbook is placed on Pd-catalyzed organic transformations.

In some of the previously published books on organopalladium chemistry, topics are classified according to the organic starting compounds. This may be a useful and readily manageable classification from the organometallic viewpoint. However, it is envisioned that the prospective readers and users of this Handbook are mostly synthetic organic chemists who are primarily interested in knowing how the organic compounds of their interest might be best prepared by using Pd complexes as catalysts. This perspective, however, does not readily lend itself to an attractive and satisfactory means of classifying the organopalladium chemistry. For both synthetic organic chemists and those who wish to learn more about the organopalladium chemistry from a more organometallic perspective, it appears best to classify the organopalladium chemistry according to some basic patterns of organometallic transformations representing the starting compound—product relationships. As discussed in **Sect. I.2**, formation of carbon—carbon and/or carbon—heteroatom bonds through the use of organotransition metals can be mostly achieved via the following four processes: (i) reductive elimination, (ii) carbometallation, (iii) nucleophilic or electrophilic attack on ligands, and (iv) migratory insertion. As a versatile transition metal, Pd has been shown to participate in them all.

Thus, in **Part III**, the Pd-catalyzed cross-coupling including the carbon-carbon cross-coupling represented by the Negishi, Stille, and Suzuki protocols as well as the Sonogashira alkynylation (**Sect. III.2**) and the more recently developed carbon-heteroatom coupling reactions (**Sect. III.3**) are presented. In most of these reactions, reductive

elimination is believed to be a critical step. This is followed by **Part IV** in which a systematic discussion of carbopalladation represented by the Heck reaction (**Sect. IV.2**) is presented. The scope of carbopalladation, however, extends far beyond that of the Heck reaction, and these other topics are discussed in **Sects. IV.3–IV.11**. There are two major topics that pertain to nucleophilic attack on ligands of organopalladium complexes discussed in **Part V**. One is the Tsuji-Trost reaction. This and related reactions of allylpalladium derivatives are discussed in **Sect. V.2**. The other is the Wacker oxidation. This and related reactions involving Pd π-complexes are discussed in **Sect. V.3**. In **Part VI**, carbonylation and other migratory insertion reactions of organopalladium compounds are discussed. In **Parts III–VI**, the significance of applications of the above-mentioned reactions to the synthesis of natural products (**Sects. III.2.17.1**, **III.2.18**, **IV.8**, **V.2.6**, **V.3.6**, and **VI.6**) and polymers of material chemical interest (**Sects. III.2.17.2**, **VI.4.2**, and **VI.8**) are recognized and discussed in the sections shown in parentheses.

Aside from the systematic classification mentioned above, the synthetic significance of Pd-catalyzed reduction and oxidation is abundantly clear. Some of those reduction and oxidation reactions that are not discussed in **Parts III–VI** are therefore discussed in **Parts VII** and **VIII**, respectively. It should be noted, however, that many of the reactions discussed in **Parts III–VI** also leads to oxidation or reduction of organic compounds. Despite the high propensity to undergo concerted reactions, organopalladium derivatives can also serve as sources of carbocationic species as indicated in **Part V**. In some cases, this can lead to skeletal rearrangements similar to the pinacol-pinacolone rearrangement. Other more concerted rearrangements are also observable, as discussed in **Part IX**. These reactions add extra dimensions to the diverse chemistry of organaopalladium compounds. Lastly, some significant technological developments including aqueous palladium catalysis (**Sect. X.1**), immobilized Pd catalysts (**Sect. X.2**) and combinatorial organopalladium chemistry (**Sect. X.3**) are making organopalladium chemistry even more important and useful in organic synthesis.

Looking back, it all started when one of my senior colleagues, Professor H. Feuer, repeatedly visited my office several years ago to persuade me to write a book for VCH and later Wiley. Despite my initial firm determination not to write any book, a notion of preparing this Handbook on a topic that has occupied a significant part of my own research career grew in my mind, and I was finally persuaded by him and Dr. Barbara Goldman of Wiley. My life-long mentor and a 1979 Nobel Prize winner, Professor H. C. Brown, has directly and indirectly influenced and encouraged me throughout my career, including this Handbook writing. I wish to dedicate my own contributions to these two senior colleagues at Purdue. I should also like to acknowledge that, through the generosity of Professor and Mrs. Brown, the Herbert C. Brown Distinguished Professorship was established in 1999, of which I have been the very fortunate inaugural appointee. This has had many favorable influences on my involvement in this Handbook preparation. In this and other connections, I am very thankful to my colleagues in the Chemistry Department, especially Dean H. A. Morrison and former Head R. A. Walton.

The actual overall and detailed layout of the Handbook was finalized during my two-month stay in Göttingen, Germany, as an Alexandar von Humboldt Senior Researcher Awardee during the summer of 1998. My German host and Associate Editor of the Handbook, Professor A. de Meijere has not only enthusiastically supported my plan but also heavily contributed to the Handbook both as an author and as a member of the editorial board. I am also deeply indebted to the other eight editorial board members,

namely Professors J. E. Bäckvall, S. Cacchi, T. Hayashi, Y. Ito, M. Kosugi, S. I. Murahashi, K. Oshima, and Y. Yamamoto. They all have contributed one or more sections and sacrificed their extremely precious time in the editorial phase. In fact, the ten editorial board members have authored and coauthored nearly one half of all sections.

It is nonetheless unmistakably clear that this Handbook is a joint production by a community or group of 141 chemists and that the great majority of writing and drawing works have actually been performed by the 131 contributors whom I sincerely thank on behalf of the editorial board including myself. Without their massive contributions and cooperation, it would have been absolutely impossible to publish a book of this magnitude. It is my particular pleasure to note that no less than 21 current and former associates of my own research group have made their massive contributions and enthusiastically supported my activities. They are, in the order of appearance, D. Choueiry, L. Anastasia, S. Huo, C. Xu, F. Liu, B. Liao, S. Gagneur, F. Zeng, T. Sugihara, K. Takagi, F. T. Luo, A. Alimardanov, Y. Dumond, Z. Tan, M. Kotora, T(amotsu) Takahashi, A. O. King, C. Coperet, S. Ma, S. Y. Liou, and H. Makabe.

While I must refrain from mentioning the names of the other 110 contributors, most of them are indeed my long-time colleagues and friends, to whom I deeply thank for their collaborations and contributions. I have also greatly appreciated and enjoyed collaborations with my new colleagues, some of whom I have not yet met. Many of my other esteemed colleagues were too busy to participate in the project. Some of them nevertheless made valuable suggestions that have been very useful in the planning stage.

Typing and a significant part of drawing of our own manuscripts and, more importantly, a seemingly infinite number of correspondences as well as a myriad of other Handbook-related jobs have been handled by Ms. M. Coree (through 2000) and Ms. Lynda Faiola (since 2001). The preparation of this extensive Handbook would not have been possible without their dedicated work for which I am deeply thankful. Many direct and indirect assistances made by my wife, Sumire, and other members of my family are also thankfully acknowledged.

Last but not least, I thank editorial staff members of Wiley, including compositors and freelancers, especially Dr. Barbara Goldman in the initial phase, Dr. Darla Henderson, Amy Romano, and Christine Punzo for their interest, encouragement, and collaboration in this project.

One of the undesirable and yet inevitable consequences of this kind of publication requiring a few years of preparation time is that the book is outdated by at least a few years at the time of publication. There are at least two approaches to cope with this problem. One is to keep publishing as frequently as possible quick and hopefully up-to-date collections of reviews. This approach, however, is not conducive to a systematic, thorough, and penetrating discussion of the chosen topic. Each publication is outdated in due course and forgotten. The other is to publish once a systematic, comprehensive, and well-organized collection of authoritative and penetrating reviews and use it as the foundation for future periodical updating activities. I intend to use this Handbook in this manner. The part and section numbers have therefore been assigned with future updating in mind. They will indeed be retained and used in our future updating. Thus, it is my plan to continue surveying and classifying the Pd-related publications by abstracting them with the use of a computerized abstract form and assigning one to a few pertinent section numbers to each. The classified abstracts may then be published periodically in the conventional book form and/or electronically. Hopefully, these updates will, in turn, continuously revive and reinforce the value of the original Handbook. With the classified updated information, some

seriously outdated sections may be revised and published as supplementary volumes at appropriate times. In this regard, I have already received oral consents from more than a dozen colleagues, and I am currently seeking a dozen or so additional collaborators.

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ABBREVIATIONS

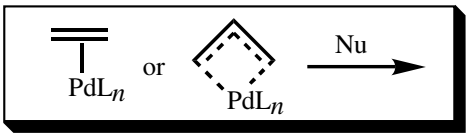
Ac, Acetyl
acac, Acetylacetonate
AIBN, Azobis(isobutyronitrile)
AMPHOS, 2,2′–Bis(diphenylarsino)–1,1′ binaphthyl
Ar, aryl
9-BBN, 9–Borabicylo[3.3.1.]nonane
BHT, 2,6-Di-*tert*-butyl-4-methylphenol
BINAP, (2*R*, 3*S)*, 2,2′-Bis-(diphenylphosphino)-1,1′-binapthyl
BINAPO, 2′-Diphenylphosphino-1,1′-binaphthalenyl-2-ol
BINAS, 2,2′–Bis(diphenylarsino)–1,1′ binaphthyl
BIPHEMP, 2,2′-Bis(diphenylphosphino)-6,6′-dimethylbiphenyl
Bipy(BPY), Bipyridine
Bn, Benzyl
Bz, Benzoyl
BNPPA, Binaphthyl–2′,2–dyl hydrogenphosphate
BPPFA, *N*–Dimethyl–1–[1′,2–bis(diphenylphosphino)ferrocenyl] ethylamine
BPPFOH, *(R)*–α–[*(S)*–1′,2–Bis(dipnenylphosphino)ferrocenyl] ethyl alcohol
BPPM, 1–*t*–Butoxycarbonyl–4–diphenylphosphino–2–(diphenylphosphinomethyl) azolidine
BSA, Bistrimethylsilyl acetamide, *N, O*–Bis(trimethylsilyl)acetamide
BTMC, Benzyltrimethylammonium carbonate
Bu, Butyl
c-, Cyclo-
CAN, Ceric ammonium nitrate
Cbz, Carbobenzyloxy
CHIRAPHOS, (*R*,*R*)- or (*S*,*S*)- 2,3-Bis(diphenylphosphino)butane
COD, Cyclooctadiene
Cp, Cyclopentadienyl
CSA, Camphosulfonic acid
Cy, Cyclohexyl
DABCO, 1,4-Diazobicyclo[2.2.2]octane
DBA(often shown as dba), Dibenzalacetone
DBN, 1,5-Diazabicyclo[4.3.0] non-5-ene
DBPF, 1–Bis–di–*t*–butylphosphinoferrocene
DBU, 1,8-Diazabicyclo[5.4.0] undec-7-ene
DCC, 1,3-Dicyclohexylcarbodiimide
DCD model, Dewar–Chatt–Duncanson model
DCE, Dichloroethane
DDQ, 2,3-Dichloro-5,6-dicyano-1, 4-benzoquinone
DEA, Diethylamine
DEAD, Diethylazodicarboxylate
Dec, Decyl
DFT, Density functional theory
DIBAH, Diisobutylaluminum hydride
DIBAL-H = DIBAH (sometimes shown as DIBAL)
DIEA, Diisopropylethylamine
DIOP, (4*R*,5*R*)–*trans*–4,5–Bis[(diphenylphosphino)methyl]–2;2–dimethyl–1,3–dioxolane,
Diphos, See DPE.
DMA, *N,N*–Dimethylacetamide
DMAD, Dimethyl acetylenedicarboxylate
DMAP, 4-Dimethylaminopyridine
DME, Dimethoxyethane
DMF, Dimethylformamide
DMI, 1,3–Dimethyl–2–imidazolidinone, N,N′–Dimethyl–2–imidazolidinone

DMSO, Dimethylsulfoxide
DP, Degrees of polymerization
DPEphos, Bis(*o*-diphenylphosphinophenyl) ether
DPEPY, 2–(2–Diphenylphosphinoethyl)pyridine
DPMEPY, 2–(Diphenylphosphonomethyl)pyridine
DPPB (dppb), 1,4–bis(Diphenylphosphino)butane
DPPE (dppe), 1,2-Bis(diphenylphosphino)ethane
DPPF (dppf), Bis-(diphenylphosphino)ferrocene
DPPP (dppp), 1,3–Bis-(diphenylphosphino)propane
EDA, Ethylenediamine
EL, Electroluminescence
Et, Ethyl
EWG, Electron–withdrawing group
FBS, Fluorous biphasic system
FOS, Formal oxidation state
GPC, Gel permeation chromatography
Hex, Hexyl
HIV, Human immunodeficiency virus
HMDS, Hexamethyldisilazane
HMPA, Hexamethylphosphoramide
HOMO, Highest occupied molecular orbital
ICPs, Integrated chemical processes
i-, Iso- *i*-Pr or ^{i}Pr, Isopropyl
L, Ligand
LAH, Lithium aluminum hydride, $LiAlH_4$
LDA, Lithium diisopropylamide
LED, Light–emitting diodes
LUMO, Lowest unoccupied molecular orbital
MCPBA, *m*-Chloroperoxybenzoic acid
MCR, Multicomponent reactions
Me, Methyl
MEM, β-Methoxyethoxymethyl
Mes, Mesityl
Ms, Mesyl, Methanesulfonyl
MOM, Methoxymethyl
MOP ligands, 2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
n-, Normal
Naph, Naphthyl
NBS, *N*-Bromosuccinimide
NCS, *N*-Chlorosuccinimide
NDMBA, *N,N′*–Dimethylbarbituric acid
NIS, *N*-Iodosuccinimide
NIT, Nitronyl nitroxide
NMM, *N*–methylmorpholine
NMP, *N*–Methylpyrrolidone
NMR, Nuclear magnetic resonance
NOE, Nuclear Overhauser effect.
NORPHOS, 2,3-Bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene
Oct, Octyl
PAA, Polyacrylamide
PCC, Pyridinium chlorochromate
PDC, Pyridinium dichromate
PEG, Polyethylene glycol
Pent, Pentyl
PFS, Pentafluorostyrene
PG, Prostaglandin
Ph, Phenyl
PHANEPHOS, 4,12-Bis(diphenylphosphino)[2.2]paracyclophane
Phen, 1, 10-Phenanthroline
PHOPHOS, 2,2′–Bis(diphenylarsino)–1,1′binaphthyl
PL, Photoluminescence
PMHS, Polymethylhydrosiloxane
PMP, 1, 2, 6–Pentamethylpiperidine
PPA, Polyphosphoric acid
PPE, Poly(phenylene ethinylene)
PPP, Poly(*para*-phenylene)
Pr, *n*-Propyl
Py, Pyridine
PROPHOS, 1,2-Bis(diphenylphosphino)propane
PTA, 1,3,5–Triaza–7–phosphaadamantane
PTC, Phase–transfer catalyst
PTSA, *p*-Toluenesulfonic acid
R, An organic group
RAMP, R-(+)-Amino-2-(methoxymethyl)pyrrolidine
R_f, Perfluoroalkyl
Red-Al, $Na[AlH_2(MeOCH_2CH_2O)_2]$
SAMP, S-(−)-Amino-2-(methoxymethyl)pyrrolidine
Sec; *s*, Secondary
s-Bu, ^{s}Bu, *sec*-Bu, Secondary butyl.

SEM, 2-(Trimethylsilyl)ethoxymethyl
(S)-(R)-BPPFA, Ferrocenylbisphosphine
(S)-(R)-PPFA, Ferrocenylmonophosphine
tert, *t,* Tertiary
TADDOL $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-4,5-dimethoxy-1,3-dioxolane
TASF, Tris-(Diethylamino)sulfonium difluorotrimethyl silicate
TBAF, Tetrabutylammonium fluoride
TBDMS, *tert*–Butyldimethylsilyl
TBS = TBDMS
t-Bu, ^{t}Bu, *tert*-Bu, Tertiary butyl
TCPP, Tris(*p*–chlorophenyl)phosphine
TDMPP, Tris(2,6–dimethoxyphenyl) phosphine
TEBA, Triethylbenzylammonium chloride
Terpy, Terpyridine
Tf, Trifluoromethanesulfonyl, triflyl
TFA, Trifluoroacetic acid
TFP, Tris(2–furyl)phosphine
THF, Tetrahydrofuran
THP, Tetrahydropyran(yl)
TIBAH, Triisobutylaluminum
TMDHS, Tetramethyldihydrosiloxane
TMEDA, Tetramethylethylenediamine
TMM, Trimethylenemethane
TMM-Pd, Trimethylenemethane palladium
TMOF, Trimethyl orthoformate
TMS, Trimethylsilyl
TMU, *N*,*N*,*N*′,*N*′–Tetramethylurea
TOF, Turnover frequency
Tol, Tolyl
Tol-BINAP, 2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TON, Turnover number
TPPTS, Triphenylphosphane *m*–trisulfonate sodium salt
Tr, Trityl
Ts, Tosyl, *p*-Toluenesulfonyl
WGS, Water gas shift reaction

PART V
Palladium-Catalyzed Reactions Involving Nucleophilic Attack on Ligands

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
ISBN 0-471-31506-0



V.1 Background for Part V

EI-ICHI NEGISHI

As discussed in **Part I**, complexation with transition metals renders π-compounds more reactive toward nucleophilic reagents. Thus, β,γ-unsaturated organopalladiums, such as allyl- and propargylpalladium derivatives, readily react with a wide variety of nucleophilic reagents to undergo nucleophilic substitution reactions in which Pd serves as the key atom in a leaving group (**Sect. V.2**). The attacking reagents may be carbon nucleophiles (**Sect. V.2.1**), group 16 and 15 atom nucleophiles (**Sect. V.2.2**), as well as hydrogen and metal nucleophiles (**Sect. V.2.3**).

The reaction of butadiene with $PdCl_2$ reported in 1957[1] most probably represents the first synthesis of allylpalladium complexes. This was followed by the development of their preparation via oxidative addition of allylic electrophiles[2] and transmetallation[3] as discussed in **Sect. II.3**. Early investigations of allylpalladiums, however, mainly dealt with structural and other organometallic aspects.

From the organic synthetic viewpoint, the report in 1965 by Tsuji et al. [4] on the reaction of π-allylpalladium chloride with diethyl sodiomalonate to give the allylated malonate (**Scheme 1**) was a significant milestone, marking the birth of the Tsuji–Trost reaction. Interestingly, however, this reaction remained stoichiometric in Pd for several years, and its catalytic versions were developed only in the 1970s.[5]–[9] Over the last quarter of the century, the chemistry of allylpalladium and related derivatives, especially their substitution reactions, has become one of the most important branches of organopalladium chemistry from the viewpoint of organic synthesis.

Oxidative addition of Pd to β,γ-unsaturated alkyl electrophiles has been shown to proceed with inversion.[10] This process is generally thought to involve prior π-complexation followed by intramolecular nucleophilic displacement of a leaving group by Pd with inversion (**Sect. II.3**). Depending on ligands, solvents, and other structural parameters, either σ- or π-complexes may be formed, even though distinction between them is often very loosely made. In fact, their representation using π-allyl structures has been widely practiced. Although this practice is probably correct and reasonable in most cases, casual selection of the π-allylpalladium structures may have to be questioned in some cases.

Depending primarily on the nature of nucleophiles, either attack on the π-allyl ligand or attack at Pd has been observed. Thus, for example, the reaction of π-allylpalladium complexes with *soft* carbon nucleophiles generally involves attack on the π-allyl ligands proceeding via inversion at the site of substitution leading to

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Scheme 1

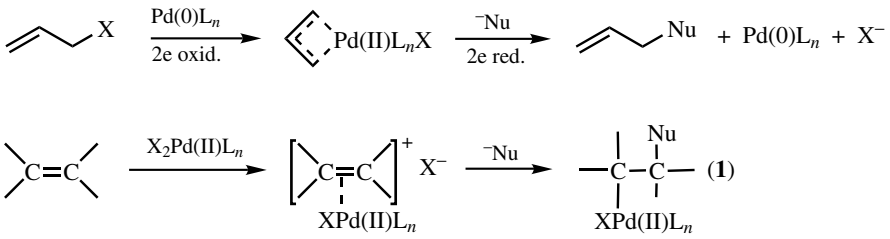
substitution, of allylic electrophiles with overall retention,[11] whereas their reaction with *hard* carbon nucleophiles, such as organometals containing Mg, Zn, Al, and so on, must involve attack at Pd, which is followed by reductive elimination to effect an allylic substitution with overall inversion at the allylic carbon atom.[12] For this and other reasons, the Pd-catalyzed cross-coupling reactions of allylic derivatives with *hard* organometals are discussed in **Part III** (**Sects. III.2.9** and **III.2.10**). Hydrogenolysis of β,γ-unsaturated alkyl derivatives via Pd-catalyzed nucleophilic substitution also proceeds with an overall inversion, suggesting that H nucleophiles attack Pd rather than π-ligands. For practical reasons, however, it is discussed in this Part (**Sect. V.2.3.1**) rather than in **Sect. III.3.1**. Hydrogenolysis not only provides a means of reducing β,γ-unsaturated organic electrophiles but also serves as a method of removal of such unsaturated groups from their derivatives containing alcohols, carboxylic acids, amines, and other active hydrogen-containing compounds, thereby providing a method for their deprotection (**Sect. V.2.3.2**).

The Pd-catalyzed reactions of allylic electrophiles with metal nucleophiles can produce the corresponding allylmetal derivatives (**Sect. V.2.3.3**), which can, in turn, serve as allylic nucleophiles. This protocol provides a means of utilizing allylpalladium and related derivatives as nucleophiles rather than electrophiles (**Sect. V.2.3.4**). Many of the substitution reactions mentioned above can be asymmetric. Because of their special significance in organic synthesis, Pd-catalyzed asymmetric allylation and related reactions are discussed in **Sect. V.2.4**.

Although the chemistry of allylpalladium and related derivatives has been dominated by substitution reactions, they also undergo other types of reactions, such as addition, elimination, and rearrangement. Elimination of allylpalladium derivatives gives conjugated dienes, as discussed in **Sect. V.2.5.1**. While this may constitute an undesirable side reaction in the substitution reactions, it can also provide an attractive route to conjugated dienes. β-Trialkylsilymethyl-substituted allypalladium derivatives have been shown to serve as dipolar trimethylenemethane derivatives and participate in [3 + 2], [3 + 4], and other cycloaddition reactions. These reactions are discussed in **Sect. V.2.5.2**. The ambident nature of allyl, propargyl, and allenyl derivatives leads to [1,3] rearrangements, which can be catalyzed by Pd. In cases where the anionic moiety is also ambident, as is often the case, Pd-catalyzed [3,3] rearrangements may be observed. These rearrangements are discussed in **Sect. V.2.5.3**. Another topic of growing significance in this area is the synthesis of natural products via allylpalladium and related derivatives discussed in **Sect. V.2.6**.

Mainly for practical reasons, other topics are discussed in other parts. In addition to Pd-catalyzed cross-coupling involving allyl, propargyl, and allenyl derivatives discussed in **Sects. III.2.9** and **III.2.10**, allylpalladation and related reactions with alkenes, alkynes, and other π-compounds, which can best be viewed as carabopalladation processes, are discussed in **Sect. IV.4**, while carbonylation and related reactions of allylpalladium and related derivatives are discussed in **Sect. VI.3**.

π-Complexation of Pd with alkenes, alkynes, and related π-compounds also leads to their activation toward nucleophiles. In contrast with the formation of allyl-, propargyl-, and allenylpalladium derivatives, however, no oxidative addition is involved in the cases of alkenes and alkynes. This difference is responsible for the contrasting behavior exhibited by these two classes of compounds toward nucleophiles, as summarized in **Scheme 2**.

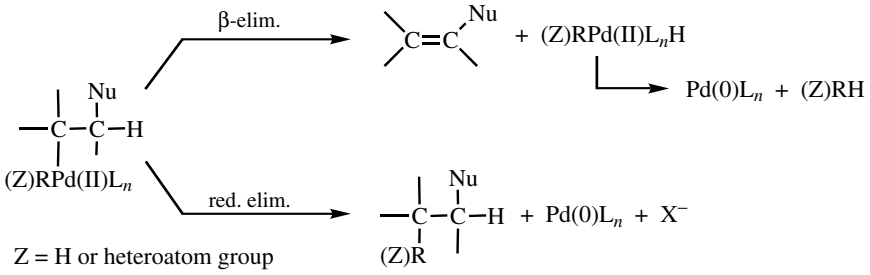


Scheme 2

The allylic substitution reaction normally involves oxidative addition of allylic electrophiles to give allyl-substituted Pd(II) species, which are then reduced to regenerate Pd(0) complexes in the nucleophilic substitution step. So, the allylic starting compounds themselves serve as both oxidizing and reducing agents in these two steps, which makes it possible to devise catalytic processes without any external reagents, as amply demonstrated in **Sect. V.2**. On the other hand, the same nucleophiles undergo formal addition with Pd–alkene π-complexes to produce **1**. Neither oxidation nor reduction occurs in this reaction. As such, this reaction is only stoichiometric in Pd, and it must therefore be followed by one or more additional processes in which Pd is dissociated from organic products for both completion of organic synthesis and recycling Pd complexes as catalysts. One such process is β-dehydropalladation, which is thought to be a key step in the Wacker oxidation[13],[14] (**Sect. V.3.1.1**) and related reactions (**Sect. V.3.1.2**). This process does complete an organic synthesis, but Pd complexes are reduced to Pd(0) species. As a result, reoxidation of Pd(0) species to Pd(II) species is necessary to complete a cycle that is catalytic in Pd. A wide variety of external oxidants including O_2 used in conjunction with $CuCl_2$ have been employed to effect oxidation of Pd(0) species back to Pd(II) species.

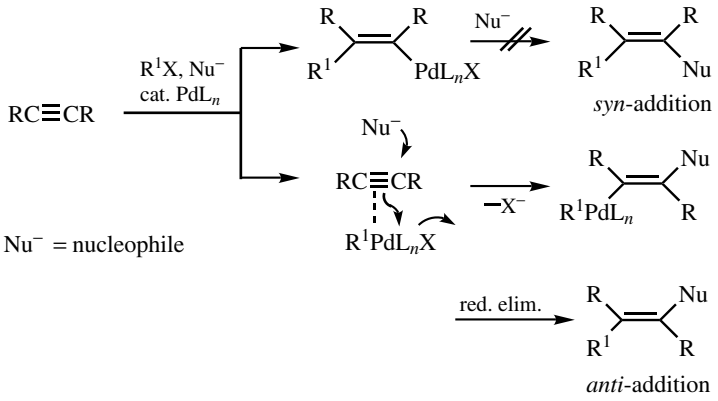
One very significant finding that appears to have gradually evolved in this area is that β-dehydropalladation can be substituted with reductive elimination reactions as shown in **Scheme 3**. In cases where the reductive elimination step is followed by oxidative addition of organic halides, active hydrogen compounds, and others used as the starting compounds, the overall process can be catalytic in Pd. Indeed, a number of synthetically attractive Pd-catalyzed tandem and cascade processes of this class have been developed, as discussed in **Sects. V.3.1.3**, **V.3.2.2**, **V.3.3.2**, and **V.3.4**.

As in the allylic substitution reactions, a wide variety of nucleophiles including oxygen and other group 16 atom nucleophiles (**Sects. V.3.1** and **V.3.2**), nitrogen and other group 15 atom nucleophiles (**Sect. V.3.3**), and carbon nucleophiles (**Sect. V.3.4**) have been employed for nucleophilic attack on the π-ligands of Pd–alkene and Pd–alkyne π-complexes. In cases where an organic halide is used as one of the starting compounds, the



Scheme 3

overall process may appear to proceed via carbopalladation as shown in the top half of **Scheme 4**. However, intermolecular nucleophilic substitution of σ-alkyl- and σ-alkenylpalladium species is generally not a facile process. Furthermore, the observed stereochemical outcome is not consistent with the carbopalladation–substitution tandem. On the other hand, a tandem process consisting of nucleophilic attack on the π-ligand of a Pd–alkyne π-complex and reductive elimination is in agreement with the observed results (**Sect. V.3.4**). A similar dichotomy of *syn- versus anti*-addition has also been observed in halopalladation (**Sect. V.3.5**).



Scheme 4

In cases where either addition or substitution proceeding via double bond migration is involved, one or more asymmetric carbon centers may be generated. Thus, face selective π-complexation with chiral Pd complexes can, in principle, lead to asymmetric processes [15],[16] (**Sect. V.3.1.1**), although this possibility has not yet been extensively investigated.

A number of natural products have been synthesized using various reactions discussed in **Sect. V.3**, as indicated by the examples shown in **Sect. V.3.6**. Despite a fair number of examples discussed in **Sect. V.3.6**, this area of research still remains relatively unexplored. Thus, for example, natural products synthesis via Pd-catalyzed lactonization of ω-alkynoic acids had not been reported until a few years ago.[17]–[19] Undoubtedly, many more examples will be published in the future.

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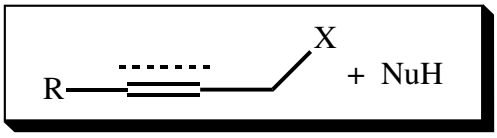

V.2 Palladium-Catalyzed Nucleophilic Substitution Involving Allylpalladium, Propargylpalladium, and Related Derivatives

V.2.1 The Tsuji–Trost Reaction and Related Carbon–Carbon Bond Formation Reactions

V.2.1.1 Overview of the Palladium–Catalyzed Carbon–Corbon Bond Formation via π-Allylpalladium and Propargylpalladium Intermediates

JIRO TSUJI

A brief overview of the well-established chemistry of Pd-catalyzed carbon–carbon bond-forming reactions involving allylic and propargylic compounds is presented.

A. ALLYLIC AND RELATED ELECTROPHILES

A.i. Introduction

The reaction of π-allylpalladium chloride with malonate and acetoacetate as soft carbon nucleophiles to give allylmalonate and allylacetoacetate, discovered by this author in 1965, is the first example of the carbon–carbon bond formation mediated by a Pd complex (**Scheme 1**).[1] In addition to the allylation of malonate, the reaction of cyclohexanone enamine with π-allylpalladium chloride gave 2-allylcyclohexanone after hydrolysis.[1] The discovery of the allylation of nucleohphiles with π-allylpalladium chloride means the birth of π-allylpalladium chemistry, which has developed as a remarkably useful synthetic method.

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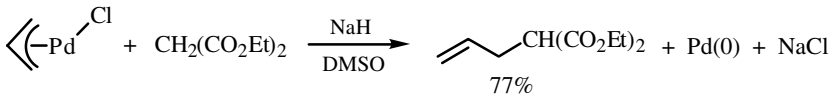
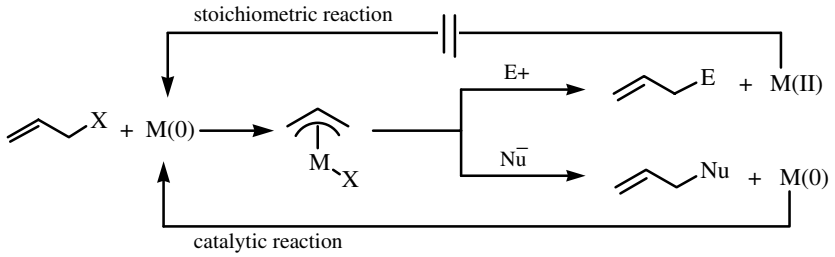


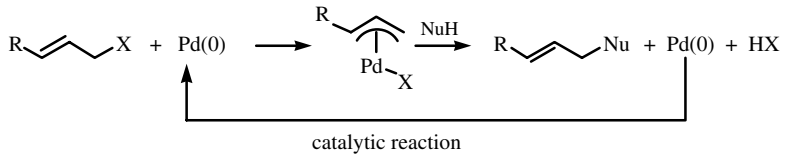
Scheme 1

Significantly, this discovery showed that π-allylpalladium is an electrophilic allyl complex, and Pd(0) is generated after the reaction with nucleophiles, indicating the possibility of a catalytic reaction. In contrast, allylic compounds of some other transition metals and main group metals, such as allyl Grignard reagent, are nucleophilic, and their reactions with electrophiles involve oxidation of the metals, and hence the reaction is stoichiometric, because *in situ* reduction of the oxidized metals is practically impossible (**Scheme 2**).



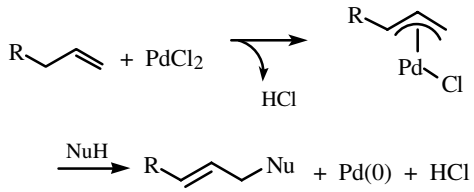
Scheme 2

The catalytic version of allylation of nucleophiles via π-allylpalladium intermediates was discovered in 1970 using allylic esters and allyl phenyl ethers as substrates (**Scheme 3**).[2],[3] Formation of π-allylpalladium complexes by oxidative addition of various allylic compounds to Pd(0) and subsequent reaction of electrophilic π-allylpalladium complexes with soft carbon nucleophiles are the basis of the catalytic allylation. After the reaction, Pd(0) is regenerated, which undergoes oxidative addition to the allylic compounds again, making the whole reaction catalytic. The efficient catalytic cycle is ascribed to the characteristic feature that Pd(0) is more stable than Pd(II). Allylation of carbon nucleophiles with allylic compounds via π-allylpalladium complexes is called the Tsuji–Trost reaction. The reaction has wide synthetic applications, particularly for cyclization.[4]



Scheme 3

Also, reactions involving π-allylpalladium complexes prepared from monoenes and Pd(II) are known. The reaction is stoichiometric because *in situ* reoxidation of reduced Pd to Pd(II) is difficult (**Scheme 4**).



Scheme 4

In addition to allylation of soft carbon nucleophiles, cross-coupling of π-allylpalladium intermediates with hard carbon nucleophiles of organometallic compounds of main group metals is possible. Cross-coupling of allylic compounds occurs by transmetallation between π-allylpalladium intermediates and organometallic compounds of Mg, Zn, B, Al, Si, Sn, and Hg, and subsequent reductive elimination. These carbon–carbon bond-forming reactions are discussed in **Sect. III.2**.

Characteristic features of Pd-catalyzed reactions of allylic and propargylic electrophiles with soft carbon nucleophiles are summarized with typical examples in the following.

A.ii. Source of Allylpalladium Intermediates

A number of allylic leaving groups shown in **Figure 1** are used for Pd-catalyzed reactions.

Their reactivities are different. Although allylation with allylic chlorides proceeds without a Pd catalyst, their reaction is accelerated in the presence of a Pd catalyst. Allylic alcohols are rather poor substrates. Instead, their esters, typically allylic acetates, are used for smooth allylation. Allylic phosphates are more reactive than allylic acetates, and the chemoselective reaction of the allylic phosphate moiety of the bis-allylic compound with 1 equiv of malonate without attacking the allylic acetate moiety occurs (**Scheme 5**). Then the aminated product is obtained by the addition of amine.[5]In addition to allylic esters, even allylic nitro compounds[6],[7]and sulfones[8]–[10] are used for allylation. Reactions of the allylic esters are carried out usually in the presence of a stoichiometric amount of bases. Recently, however, it was reported that allylic acetates react with soft carbon nucleophiles, except malonate, under neutral conditions.[11]

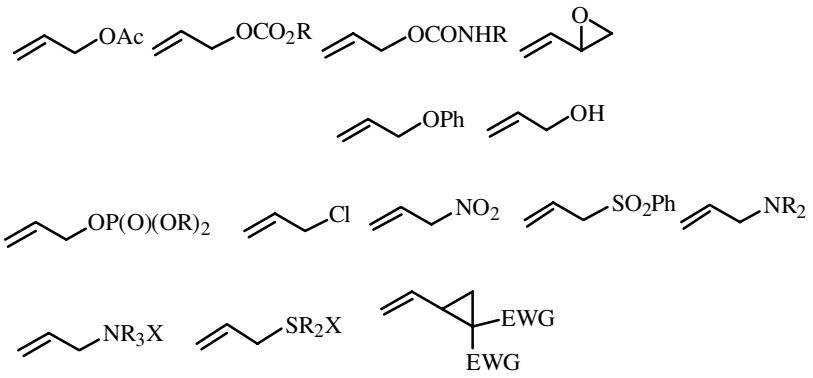
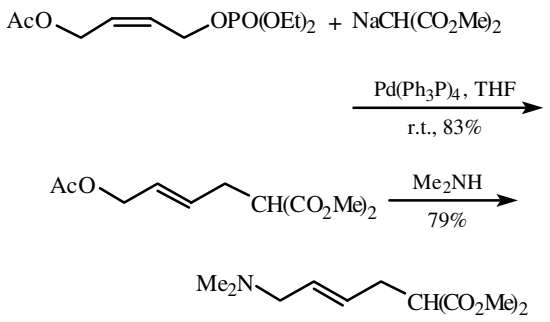


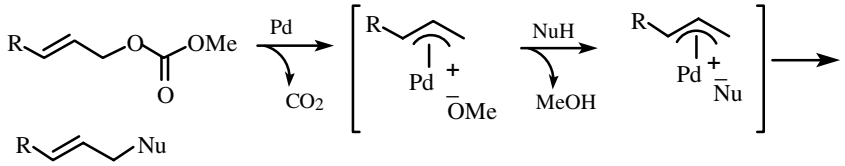
Figure 1



Scheme 5

A.iii. Allylation Under Neutral Conditions

Reactions that proceed under neutral conditions are highly desirable. An important event in π-allylpalladium chemistry is the introduction of highly reactive allylic carbonates (**Sect. V.2.1.3**). Their reactions can be carried out under mild neutral conditions.[12]–[14] Also, reactions of allylic carbamates,[14] allyl aryl ethers,[2],[15] and vinyl epoxides[16],[17] proceed without addition of bases. As shown by the mechanism in **Scheme 6**, the oxidative addition of allyl methyl carbonates is followed by decarboxylation as an irreversible process to afford π-allylpalladium methoxide, and the generated methoxide picks up a proton from pronucleophiles (NuH), such as active methylene compounds. This *in situ* formation of the alkoxide is the reason why the reaction of allyl carbonates can be carried out without addition of bases from outside. Alkoxides are rather poor nucleophiles, and alkyl allyl ethers are not formed from them. In addition, formation of π-allylpalladium complexes from allylic carbonates involving decarboxylation is irreversible. In contrast, the formation of π-allylpalladium acetate from allyl acetate is reversible.

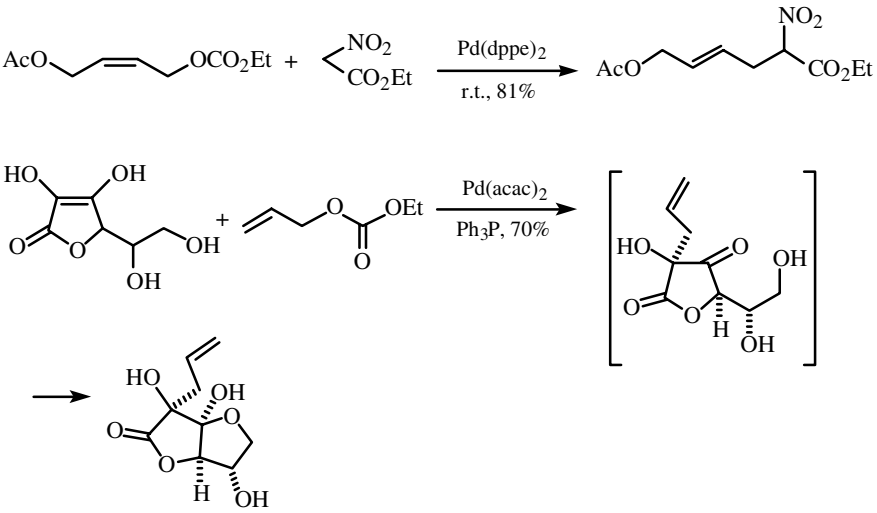


Scheme 6

The chemoselective C-allylation of nitroacetate with the bis-allylic compound proceeds under neutral conditions only at the carbonate moiety, while the acetate group remains untouched. The chemoselective reaction clearly shows the higher reactivity of allylic carbonates than allylic acetates.[18] No O-alkylation of nitroacetate, usually observed under basic conditions, occurs.

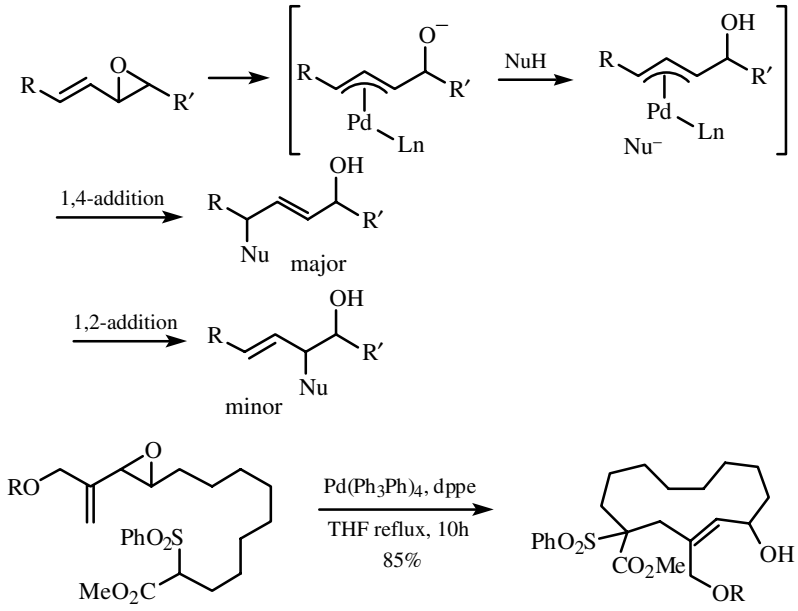
The neutral allylation with allylic carbonates has wide applications to alkylation of rather labile compounds, which are sensitive to acids or bases. As an example, the smooth C-allylation of the sensitive molecule of ascorbic acid is possible under neutral conditions only with allyl carbonates (**Scheme 7**).[19]

Vinyl epoxides (vinyloxiranes) are reactive allylating agents. The oxidative addition of Pd(0) to the vinyl epoxides with cleavage of the epoxide ring occurs to generate



Scheme 7

π-allylpalladium alkoxide complex. Since the alkoxide abstracts a proton from pronucleophiles (NuH), the allylation proceeds without addition of a base. In addition, mainly the 1,4-adduct is formed regioselectively rather than the 1,2-adduct (**Scheme 8**).[16],[17] As an application to natural product synthesis, the 13-membered ring intermediate for roseophilin synthesis was prepared efficiently by the cyclization of the vinyl epoxide.[20] Similarly the 26-membered ring model for a synthesis of the ring system of tetrin was obtained in 92% yield.[21]



Scheme 8

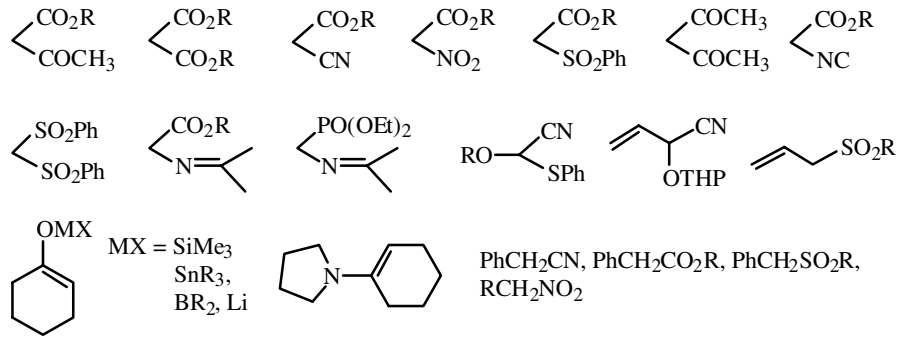
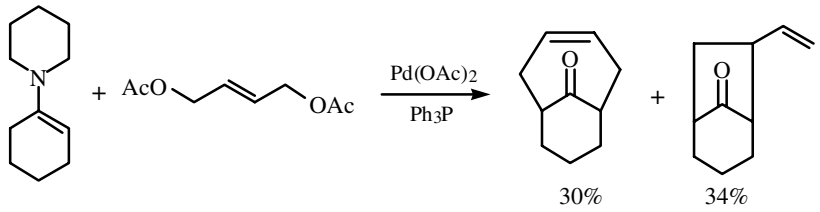


Figure 2

A.iv. Range of Soft Carbon Nucleophiles

In general, soft carbon nucleophiles with two EWGs (electron-withdrawing groups) are allylated smoothly. The EWGs are ester, ketone, aldehyde, nitro, sulfone, and nitrile. As exceptions, some carbon nucleophiles such as nitro alkanes and phenylacetonitrile are allylated without being activated by other EWGs (**Figure 2**).

No allylation of simple ketones, aldehydes, and esters without additional EWGs occurs. Allylation of ketones is carried out indirectly. For example, enamines, prepared from ketones, are allylated easily and allyl ketones are obtained after hydrolysis (**Scheme 9**).[22]

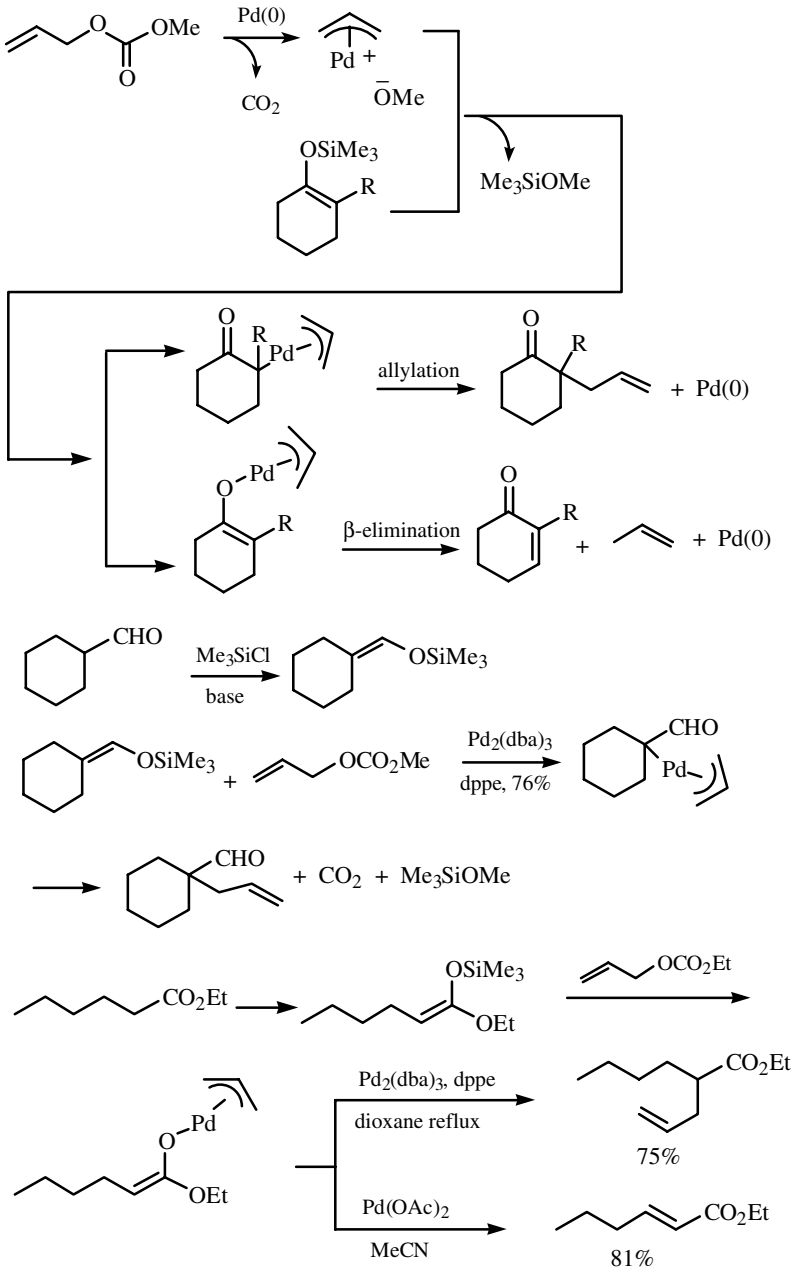


Scheme 9

A.v. Indirect Allylation of Carbonyl Compounds Via Their Enolates

Although it is mechanistically different from the Tsuji–Trost allylation, indirect allylations of ketones, aldehydes, and esters via their enolates are briefly summarized here. Related reactions are treated in **Sect. V.2.1.4**. Pd-catalyzed allylation of aldehydes, ketones, and esters with allylic carbonates is possible via the π-allylpalladium enolates of these carbonyl compounds. π-Allylpalladium enolates can be generated by the treatment of silyl and stannyl enol ethers of carbonyl compounds with allyl carbonates, and the allylated products are obtained by the reductive elimination of the π-allylpalladium enolates.

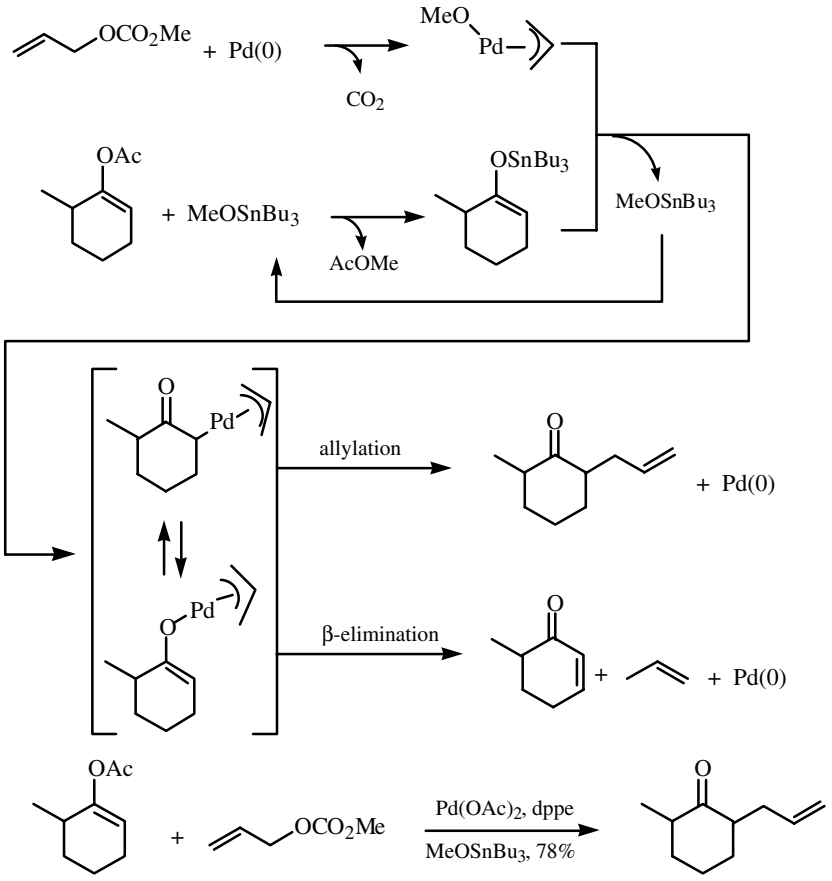
In the allylation of the silyl enol ethers with allyl carbonates, the transmetallation of the silyl enol ethers with the π-allylpalladium methoxides, generated from allyl methyl carbonates, gives the π-allylpalladium enolates. Depending on the reaction conditions, allyl ketones are formed by reductive elimination (**Scheme 10**).[12],[13],[23] When a ratio of Ph_3P to Pd is small, the α,β-unsaturated ketones are obtained by β-elimination.[24] For example, the silyl enol ether of aldehyde is allylated with allyl carbonate to give the



Scheme 10

α-allyl aldehyde via the π-allylpalladium enolate. Also, the α-allyl esters are obtained by the allylation of the esters with allyl carbonate after conversion of the esters to the ketene silyl acetals. The α,β-unsaturated esters are obtained by the elimination of β-hydrogen.[25] Since the silyl group is trapped with the methoxy group in these reactions, no other trapping agent is necessary.

It is known that stannyl enolates can be generated by the reaction of enol acetates of ketones and aldehydes with $MeOSnBu_3$.[26] Based on this reaction, π-allylpalladium enolates can be generated by the treatment of the enol acetates with allyl carbonate in the presence of Pd(0) and $MeOSnBu_3$ as the bimetallic catalyst. In this case, transmetallation of the π-allylpalladium methoxides with the generated stannyl enolate gives the π-allylpalladium enolates. At the same time, $MeOSnBu_3$, one of the catalysts, is regenerated. Allyl ketones are formed by reductive elimination of the π-allylpalladium enolates,[27] and the enones are formed by β-elimination.[28],[29] As an example, the enol ester of 2-methylcyclohexanone is allylated regioselectively with allyl carbonate to give 2-allyl-6-methylcyclohexanone using Pd(0) and $MeOSnBu_3$ as the catalysts (**Scheme 11**).

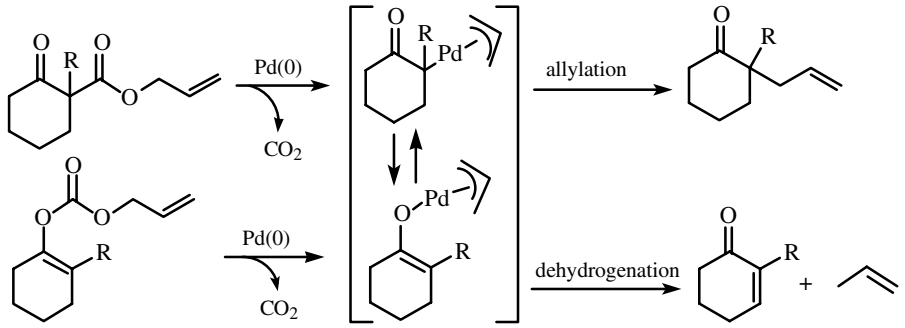


Scheme 11

A.vi. Palladium-Catalyzed Reactions of Allyl β-Keto Carboxylates, Malonates, and Enol Carbonates

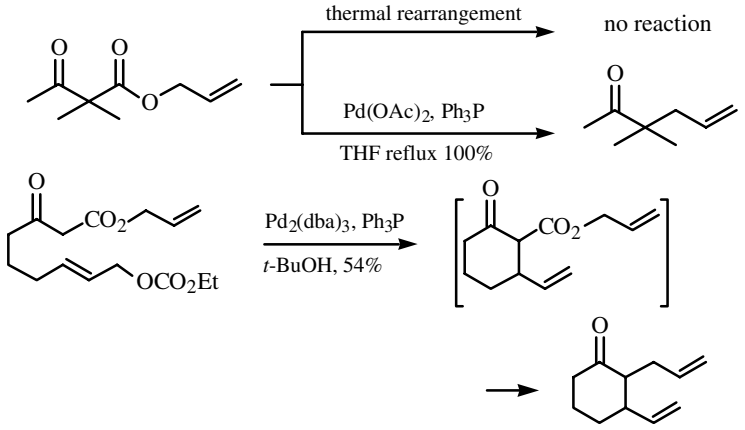
Needless to say, β-keto esters are important compounds in organic synthesis. The usefulness of β-keto esters has been remarkably expanded based on Pd-catalyzed reactions of allyl β-keto carboxylates. Cleavage of the allylic carbon–oxygen bond and facile decarboxylation occur by the treatment of allyl β-keto carboxylates with Pd(0) catalysts,

forming π-allylpalladium enolates. They undergo various transformations depending on reaction conditions, expanding synthetic uses of β-keto esters (**Scheme 12**). These reactions proceed without addition of bases.[12],[13] In addition to allyl β-keto carboxylates, allyl enol carbonates as structural isomers of allyl β-keto esters, undergo similar reactions via the formation of π-allylpalladium enolates. In addition, derivatives of allyl acetate, which have other EWGs such as malonates, nitroacetates, cyanoacetates, and sulfonylacetates, undergo Pd-catalyzed decarboxylation, followed by further transformations.



Scheme 12

The reductive coupling of π-allylpalladium enolates gives allylated ketones. This reaction is also possible thermally and is called the Carroll rearrangement. While the Carroll rearrangement proceeds by heating the substrates up to 200 °C, Pd-catalyzed Carroll-type rearrangement can be carried out under mild conditions even at room temperature by reductive elimination of the π-allylpalladium enolates.[30],[31] The Pd-catalyzed reaction is different mechanistically from the thermal reaction, and more versatile than the latter, which is explained as a [3.3] sigmatropic rearrangement of the enolate forms. For example, the thermal Carroll rearrangement of allyl α,α-dimethylacetoacetate is not possible, because there is no possibility of enolization. On the other hand, it rearranges to α,α,α-allyldimethylacetone smoothly with the Pd catalyst via the π-allylpalladium enolate (**Scheme 13**). 2-Allyl-3-vinylcyclohexanone is prepared by intramolecular allylation of allyl β-keto carboxylate with the



Scheme 13

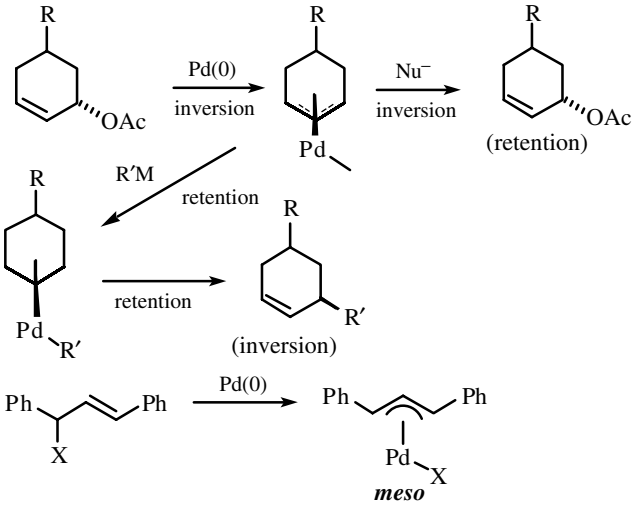
allyl carbonate moiety, followed by the decarboxylation– allylation of the β-keto carboxylate formed as an intermediate. The diallylation reaction is based on the fact that the intramolecular allylation of the β-keto ester with the allylic carbonate moiety is faster than the decarboxylation of the allyl β-keto carboxylate.[32]

A.vii. Stereochemistry of Palladium-Catalyzed Allylation

Stereochemistry of the allylation of nucleophiles has been studied extensively using substituted 2-cyclohexenyl acetate (**Scheme 14**).[33]–[35] As the first step, formation of π-allylpalladium complex by the attack of Pd(0) on an allylic acetate moiety proceeds by inversion (*anti* attack). Subsequent reactions of soft carbon nucleophiles, N- and O-nucleophiles, proceed by inversion. Thus, overall retention is observed. On the other hand, the transmetallation of π-allylpalladium with hard carbon nucleophiles of organometallic compounds is the retention, and the final product is obtained by reductive elimination, which is the retention. Thus, overall inversion is observed in this case.[36],[37]

Successful asymmetric allylations have been carried out with high ee values using many kinds of chiral ligands.[38],[39] 1,3-Diphenylallyl acetate is used as a standard substrate to compare different chiral ligands based on desymmetrization of its *meso*-π-allylpalladium intermediate. Asymmetric allylation is treated in **Sect. V.2.4**.

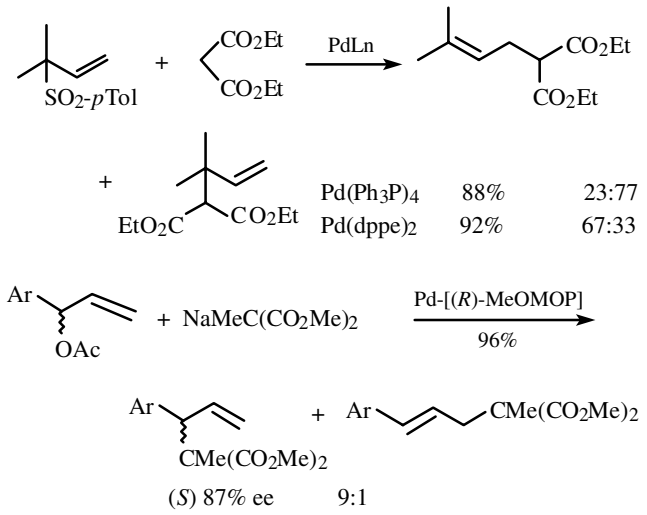
Concerning the geometrical isomerization, (E)-type products are obtained generally even when the (Z) form of allylic compounds is used as shown by **Scheme 5**.



Scheme 14

A.viii. Regioselectivity

Pd-catalyzed reaction of nucleophiles with substituted π-allyl systems usually occurs at the less substituted side with high regioselectivity with few exceptions (**Scheme 15**).[10],[39] But in some cases the regioselectivity depends on ligands and leaving groups. For example, regioselectivity in the allylation of malonate with allyl sulfones is changed by ligands.[10] Also, the reaction of dimethyl methylmalonate at the more substituted side of

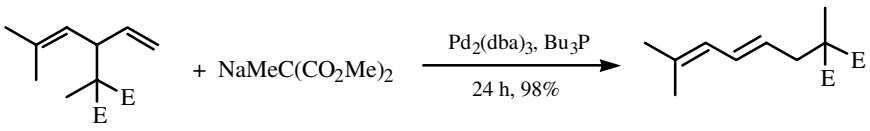


Scheme 15

1-aryl-2-propenyl acetate took place with high regioselectivity (9:1) as well as high enantioselectivity (87% ee) when the bulky (*R*)-MeO-MOP was used as a ligand.[40]

A.ix. Reversibility

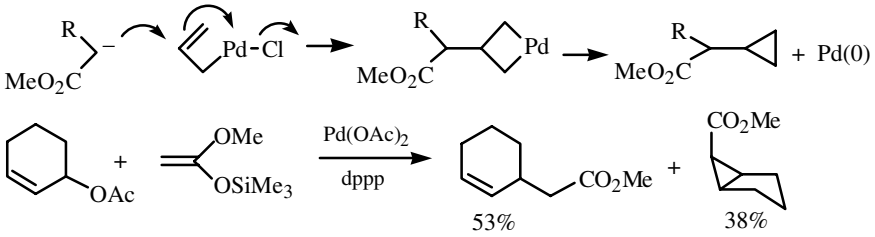
Interestingly, allylation of stabilized carbon nucleophiles has been found to be reversible. Complete transfer or rearrangement of dimethyl methylmalonate moiety from the secondary carbon to the primary carbon, involving C—C bond cleavage, was observed by treatment of the allylated malonate with a Pd catalyst in 24 h, showing that the C—C bond cleavage of the monoallylic system proceeds slowly (**Scheme 16**).[41]



Scheme 16

A.x. Cyclopropanation

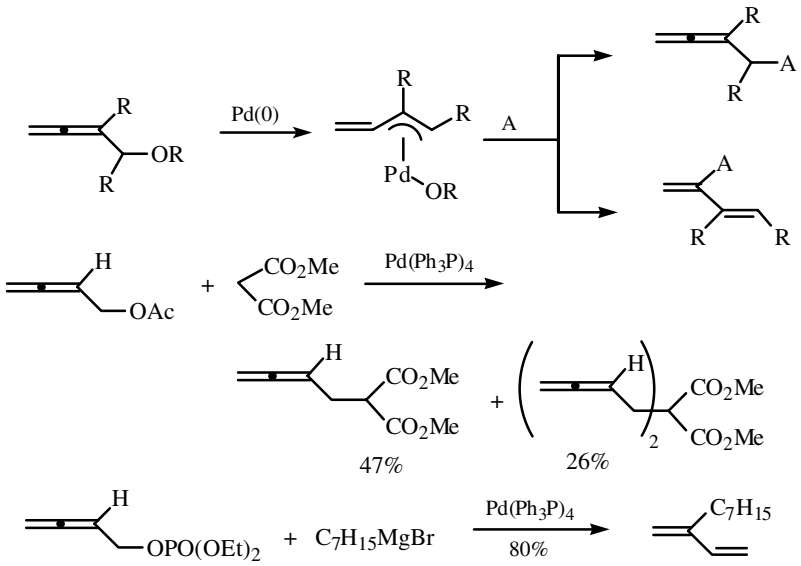
In addition to allylation by the usual nucleophilic attack at the terminal carbon of allylic systems, substituted cyclopropanes are formed by the attack of a nucleophile at the central sp^2 carbon of the allylic systems via palladacyclobutane under certain conditions.[42] Cyclopropanation can be understood by the attack of the enolate ion at the central carbon of π-allylpalladium to form palladacyclobutane, followed by reductive elimination (**Scheme 17**). 2-Cyclohexenyl acetate reacts with the ketene silyl acetal of methyl acetate using the Pd catalyst coordinated by dppp, to afford cyclopropane and the expected methyl 2-cyclohexenylacetate.[43] Cyclopropanation becomes the main path when TMEDA as a ligand and thallium acetate are added.[44]



Scheme 17

A.xi. α-Methylene-π-allylpalladiums

α-Methylene-π-allylpalladiums are generated from esters of 2,3-alkadienyl alcohols. The complexes are reactive and give either 1,2- or 1,3-dienes depending on reactants (**Scheme 18**). The reaction of the 2,3-alkadienyl acetate with malonate affords dimethyl 2,3-butadienylmalonate.[45] On the other hand, hard carbon nucleophiles such as Mg or Zn reagents react with the 2,3-alkadienyl phosphate to give the 2-alkyl-1,3-butadiene.[46]



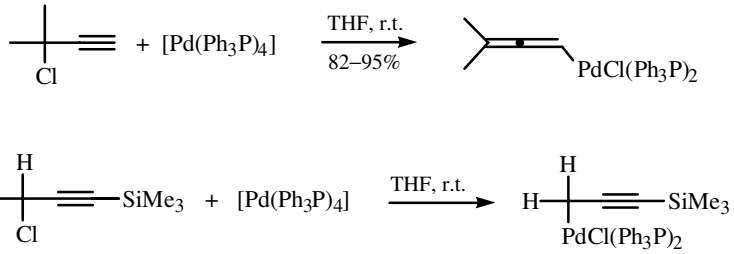
Scheme 18

B. PROPARGYLIC ELECTROPHILES

B.i. Introduction

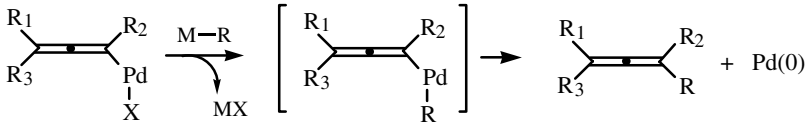
Propargylic compounds (2-alkynyl compounds) are derivatives of alkynes and undergo several types of transformations in the presence of Pd catalysts. However, the Pd-catalyzed reactions of propargylic compounds, particularly their esters and halides, are clearly different mechanistically from those of simple alkynes, except for a few cases.

The Pd(0)-catalyzed reactions of propargylic compounds can be understood by the following mechanistic consideration.[47] Complex formation by a stoichiometric reaction of propargylic chlorides with $Pd(Ph_3P)_4$ has been studied, and σ-allenylpalladium and propargylpalladium (or σ-prop-2-ynylpalladium) were isolated as yellow powder (**Scheme 19**).[48] π-Allenylpalladium chloride is formed by S_N2' type displacement of the chlorine with Pd(0). Propargylpalladium is formed when a bulky group such as TMS is present at the alkyne terminal. The Pd(0)-catalyzed carbon–carbon bond-forming reactions of various propargylic compounds using carbon nucleophiles are explained by the formation of the σ-allenylpalladium complexes as intermediates.



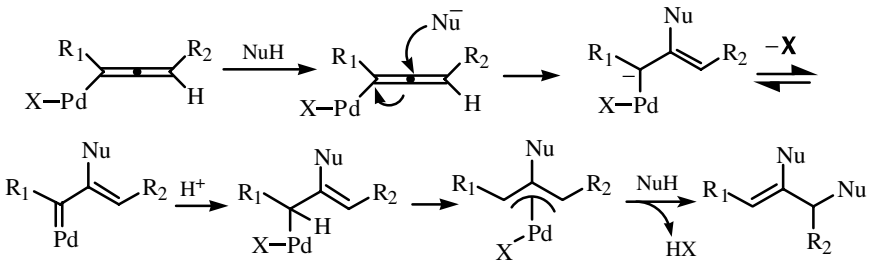
Scheme 19

Carbon–carbon bond formation occurs by the reaction of soft carbon nucleophiles. Also, cross-coupling with hard carbon nucleophiles is possible, which proceeds via the transmetallation of the σ-allenylpalldium complex. Thus, the reactions of soft and hard carbon nucleophiles give different kinds of products. The transmetallation with hard carbon nucleophiles M′R (M′ = main group metals, Mg, Zn, B) such as Grignard reagents and metal hydrides MH and subsequent reductive elimination give rise to allene derivatives as final products (**Scheme 20**). The reactions of propargylic halides, acetates, and phosphates with hard carbon nucleophiles M′R give the allenyl derivatives. This chemistry is treated in **Sect. III.2**.



Scheme 20

Reactions of soft carbon nucleophiles derived from active methylene compounds such as β-keto esters or malonates proceed by attack of the nucleophiles at the central sp carbon of the allenyl complexes. The attack of the nucleophiles generates σ-allyl anion intermediates, which are regarded as palladium–carbene complexes. These intermediates pick up a proton from the active methylene compound to form π-allylpalladium complexes, which undergo further reaction with the nucleophile as expected, and hence the alkenes are formed by introduction of two molecules of the carbon nucleophiles (**Scheme 21**).

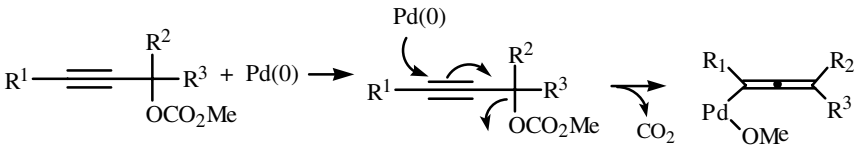


Scheme 21

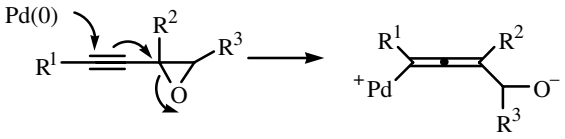
B.ii. Range of Propargylic Compounds

Several propargylic derivatives can be used for Pd-catalyzed reactions. But they have different reactivities. Although propargyl halides react without catalysts, the reaction sometimes is not clean. Propargyl esters such as acetates are less reactive. Propargylic carbonates and alkynyl oxiranes are highly reactive and undergo various Pd-catalyzed reactions smoothly, especially under neutral conditions. σ-Allenylpalladium methoxides are generated by facile irreversible oxidative addition of methyl propargyl carbonates with evolution of CO_2 (**Scheme 22**). Extensive studies on Pd-catalyzed propargylic compounds have been carried out mainly using propargylic carbonates as convenient substrates.[47]

Also, 2-(1-alkynyl)oxiranes undergo facile reactions using Pd(0) catalysts under neutral conditions by forming 4-alkoxyallenylpalladium complexes as intermediates (**Scheme 23**).



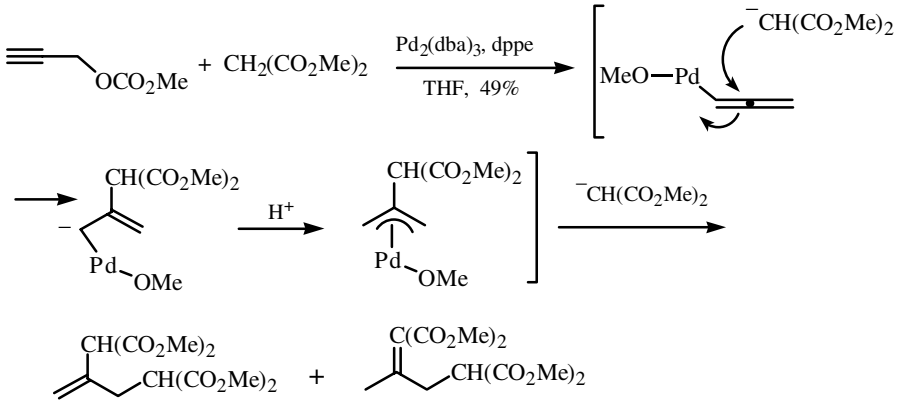
Scheme 22



Scheme 23

B.iii. Reactions of Soft Carbon Nucleophiles

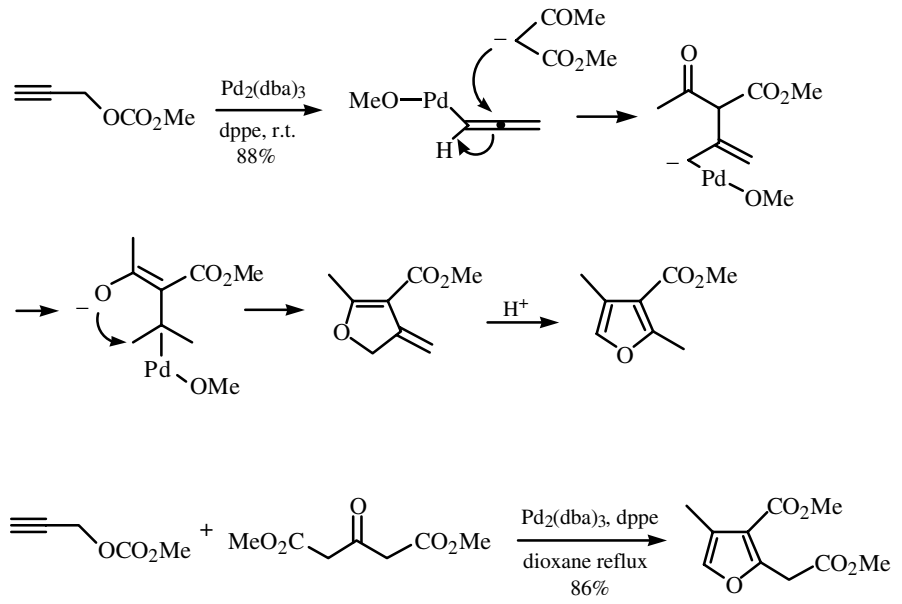
The reaction of some nucleophiles occurs at the central sp carbon of the allenylpalladium. Soft carbon nucleophiles such as β-keto esters and malonates react with propargylic carbonates under neutral conditions using dppe as a ligand (**Scheme 24**).[49] 2,3-Disubstituted propenes are obtained by the reaction of methyl 2-propynyl carbonate with 2 moles of dimethyl malonate in boiling THF. Attack of the carbanion at the central sp carbon of the allenylpalladium generates the anionic σ-allylpalladium, which picks up a proton from the



Scheme 24

malonate to form the π-allylpalladium intermediate. As expected, the attack of another malonate anion on the π-allylpalladium intermediate affords a mixture of the olefins bearing two malonate moieties.[49],[50] Thus, propargylic carbonates have two reaction sites for soft carbon nucleophiles. The best ligand for the reaction is dppe. The reaction is slow when Ph_3P is used. Two molecules of methyl α-monosubstituted acetoacetate, bearing one active hydrogen, react with propargyl carbonate to give similar products.

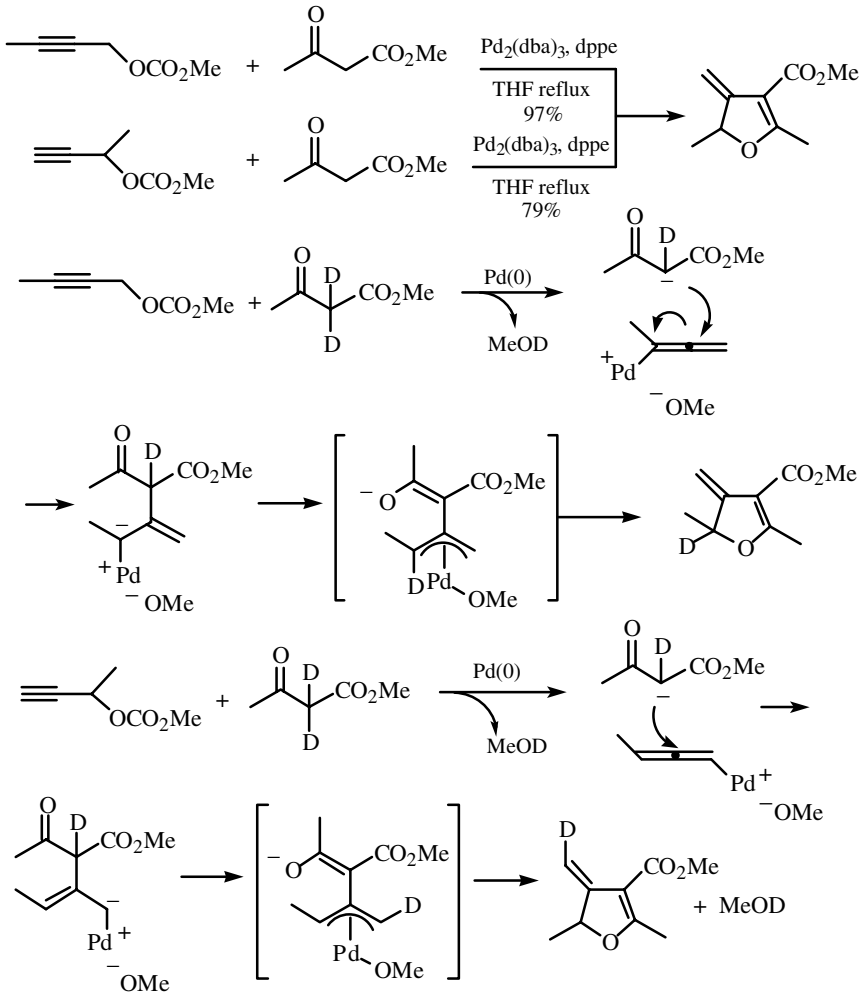
Unsubstituted methyl acetoacetate, bearing two active hydrogens, behaves differently. It reacts with methyl propargylic carbonate in a 1:1 ratio in THF at room temperature, giving an entirely different product (**Scheme 25**). In this case, at first C-alkylation of the central sp carbon of the allenylpalladium generates the π-allylpalladium intermediate bearing the



Scheme 25

enolate moiety. The intramolecular attack of the oxygen nucleophile of the enolate at the π-allylpalladium moiety affords 4-(methoxycarbonyl)-5-methyl-3-methylene-2,3-dihydrofuran in 88% yield. The methylenefuran is unstable and isomerizes to the stable furan quantitatively under slightly acidic conditions.[49],[50] Thus, the C- and O-alkylations of acetoacetate or β-keto esters with propargylic carbonates offer a new synthetic method for furans. Formation of the furan by the reaction of acetonedicarboxylate with methyl propargyl carbonate is another example.

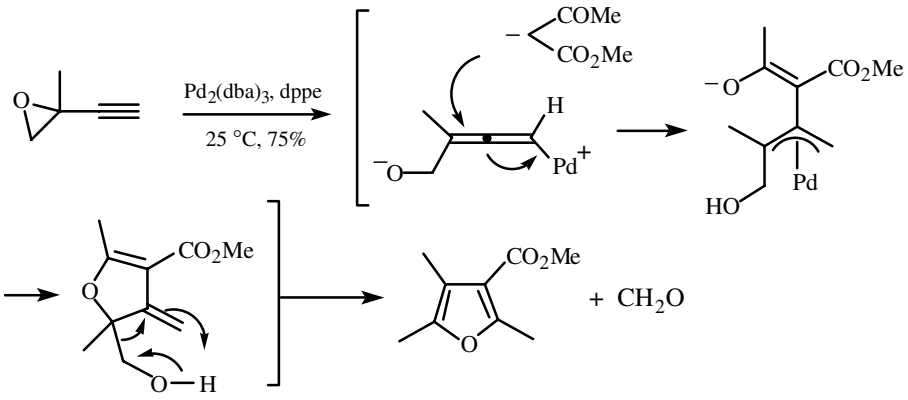
The mechanism of the furan formation can be explained by the following reactions. The reactions of isomeric 2-butynyl methyl carbonate and 1-methylpropynyl methyl carbonate with methyl acetoacetate give the same product, showing that furan formation from both carbonates proceeds via a common intermediate (**Scheme 26**). However, the reactions of the two isomeric propargyl carbonates with methyl 2,2-bisdeuterioacetoacetate give the products deuterated at different carbons; namely, the 2-deuterio-3-hydrofuran is obtained from 2-butynyl carbonate. On the other hand, the reaction of 1-methylpropynyl carbonate with the



Scheme 26

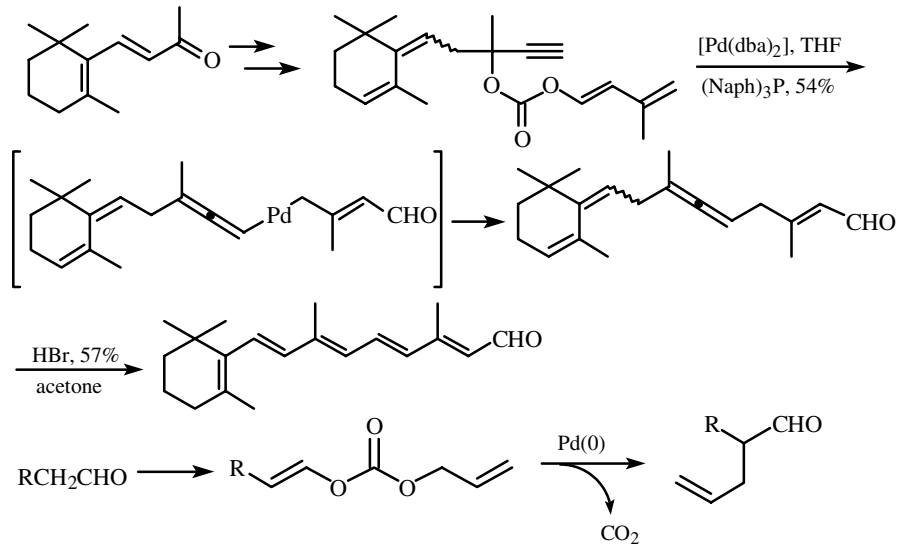
dideuterated acetoacetate affords the furan, deuterated at the exomethylene carbon. These results are explained by assuming that the attack of the oxygen nucleophile (O-allylation) occurs at the more substituted side of the intermediary π-allylpalladium systems.

2-Ethynyloxiranes undergo Pd-catalyzed furan annelation with soft nucleophiles (**Scheme 27**).[50],[51] The allenylpalladium is generated from 2-methyl-2-ethynyloxirane, and the attack of acetoacetate anion at the central carbon of the allenylpalladium forms π-allylpalladium intermediate. The oxygen anion attacks the more substituted side of the π-allylpalladium system to afford tetrasubstituted furan after elimination of formaldehyde from the primary product.



Scheme 27

Allenyl α,β-unsaturated isoprenoid aldehydes can be prepared in high yields by the rearrangement of propargyl enol carbonates (**Scheme 28**). The dienyl propargyl carbonate was prepared from β-ionone and subjected to Pd-catalyzed rearrangement. The allenyl alde-



Scheme 28

hyde as an *E/Z* mixture was obtained as the main product using trinaphthylphosphine as a ligand. Allenylpalladium is an intermediate of the rearrangement and its reductive elimination affords allenyl aldehyde, which is converted to the conjugated polyenal by treatment with hydrogen bromide, and the all-*trans* isomer of retinal was obtained by a simple equilibration.[52] It should be added that the corresponding allyl enol carbonates, prepared from aldehydes, undergo a similar rearrangement to give α-allyl aldehydes in high yields.[53]

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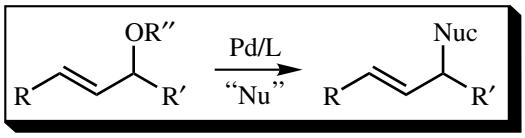

V.2.1.2 Synthetic Scope of the Tsuji–Trost Reaction with Allylic Halides, Carboxylates, Ethers, and Related Oxygen Nucleophiles as Starting Compounds

LARA ACEMOGLU and JONATHAN M. J. WILLIAMS

A. INTRODUCTION

Pd-catalyzed allylic substitution reactions can cover a wide range of nucleophiles, leaving groups, and substrates.[1],[2] The prototype reaction is provided by the conversion of allyl acetate **1** into the substitution product **2**.[3] In this case, the nucleophile **3** is an enolate derived from malonate and provides a typical example of a stabilized nucelophile (**Scheme 1**).

The palladium catalysts most frequently employed can be preformed palladium(0) complexes, such as $Pd(PPh_3)_4$,[4] or complexes made *in situ*, for example, a combination of $Pd(dba)_2$ or $Pd_2(dba)_3$ (dba = dibenzylidene acetone) with PPh_3.[5] Another common source of palladium is from $[Pd(allyl)Cl]_2$ with a suitable phosphine, typically triphenylphosphine. $[Pd(allyl)Cl]_2$ is in oxidation state +2 but is reduced to Pd(0) by nucleophilic attack on the allyl group.[6] The standard phosphine is triphenylphosphine but bidentate[7] and aliphatic phosphines[8] can also be used.

The generally accepted mechanism for Pd-catalyzed allylic substitution involves association of the palladium(0) catalyst to the substrate, and oxidative addition to provide a π-allyl complex. The equilibrium between the neutral π-allyl complex and the more reactive cationic π-allyl complex depends on the nature/concentration of phosphine ligand.[9] Nucleophilic addition to the ligand involves direct attack on the ligand when stabilized enolates are employed. After dissociation of the product, the palladium is able to continue in the next catalytic cycle (**Scheme 2**). In general, the reaction proceeds via a Pd(0)/Pd(II) shuttle, although a Pd(II)/Pd(IV) pathway is also possible.

B. RANGE OF LEAVING GROUPS

As well as the standard acetate leaving groups, there are many alternatives. Halides have been used as the leaving group on a few occasions.[10] For example, the chloride **4** has been reacted with a range of stabilized enolates including the anion of dimethylmalonate. The regioisomeric products **5** and **6** were formed in good yield (**Scheme 3**).[11]

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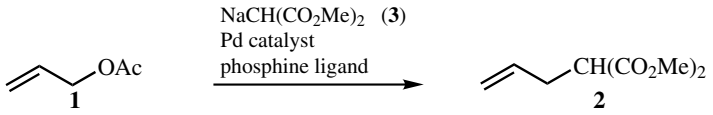
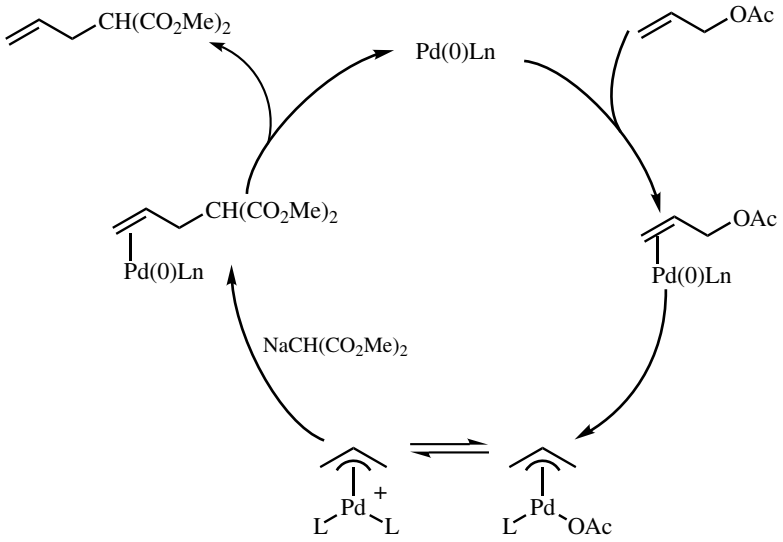
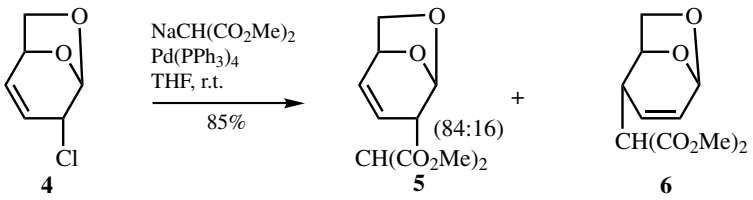


Scheme 1



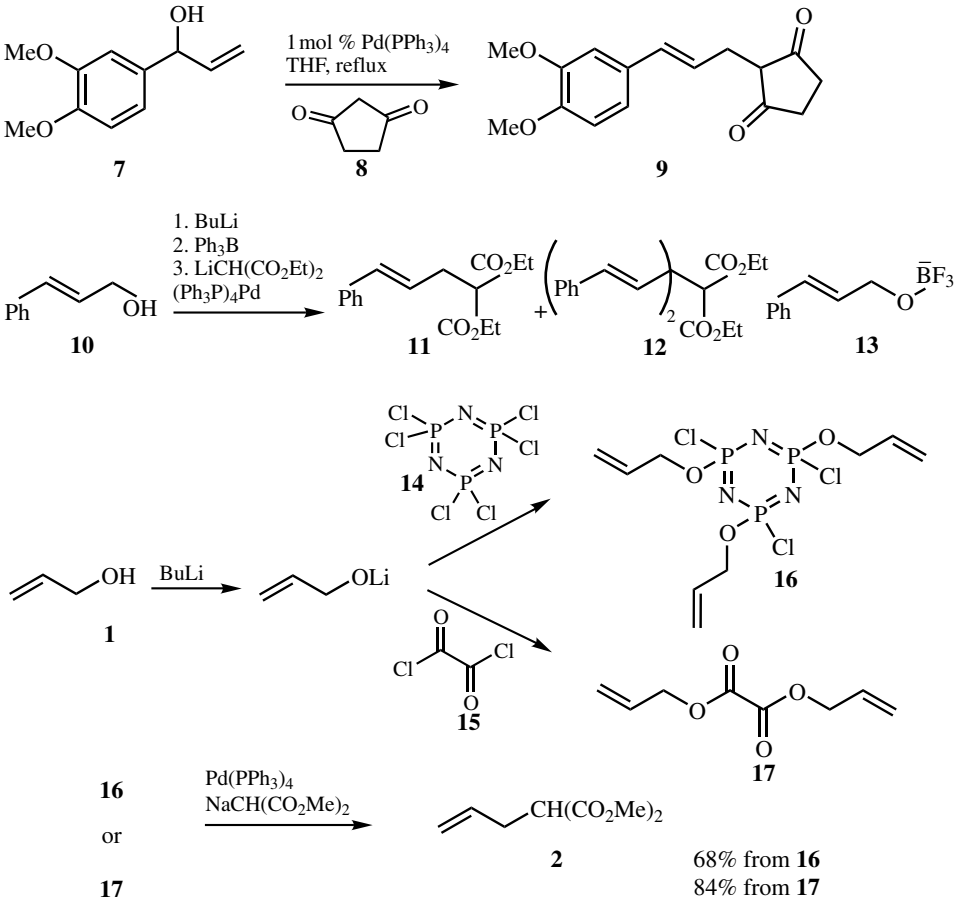
Scheme 2



Scheme 3

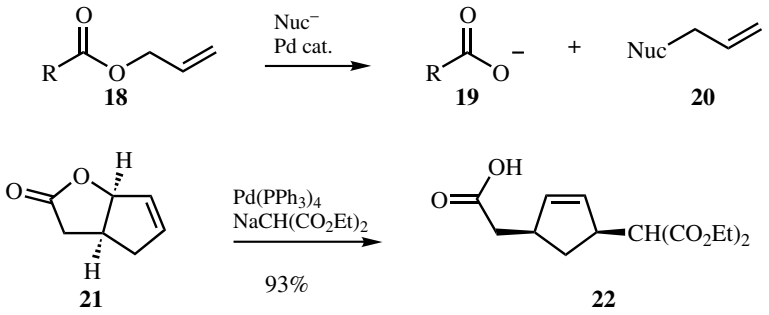
Allylic alcohols are not generally used as substrates, as the alcohol is not a good enough leaving group.[12] However, when the substrate is especially prone to ionization, such as with the allyl alcohol **7**,[13] which is activated by a methoxyphenyl group, high yields have been recorded in Pd-catalyzed allylic substitution reactions of allyl alcohols (**Scheme 4**). It is also possible to activate the allyl alcohol *in situ*.[14] For example, Kocovsky and co-workers have treated allylic alcohols with butyllithium and then triphenylboron, which affords an activated species **13** that undergoes allylic substitution.[15],[16] Thus, cinnamyl alcohol **10** was converted into the substitution products **11** and **12**, where the diethylmalonate is either mono- or dialkylated.

Activation of allylic alcohols has also been achieved with either hexachlorophosphazene **14** or oxalyl chloride **15**.[17] In these cases, the alcohol was deprotonated with butyllithium, and then treated with the activating agent to give intermediates **16** or **17**. Pd-catalyzed allylic substitution with the sodium enolate of dimethylmalonate afforded the product **2** with some dialkylation.



Scheme 4

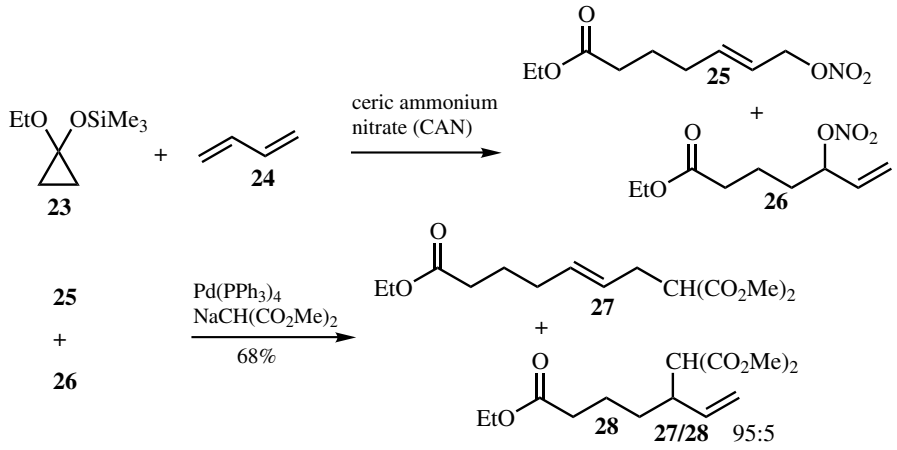
Carboxylates other than acetate can be used as the leaving group, including pivalate and benzoate (**Scheme 5**).[18] Allyl groups can be used as protecting groups for carboxylates, since Pd-catalyzed allylic substitution can remove these groups.[19],[20] Usually, stabilized enolates are not employed, since other reagents can be removed more easily at the end of the reaction.



Scheme 5

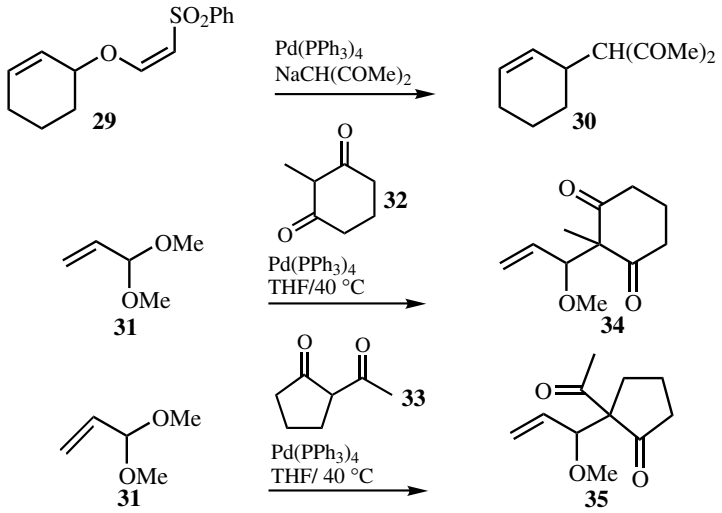
Unsaturated lactones are interesting substrates for Pd-catalyzed allylic substitution reactions.[21] Aggarwal and co-workers have examined the ring opening reactions of a range of lactones, including the parent substrate **21**.[22],[23]

Allylic nitrates **25** and **26** have been generated by the oxidative addition of trimethylsilyloxy-cyclopropanes **23** to butadiene **24** (**Scheme 6**).[24] The regioisomeric mixture of allylic nitrates undergoes allylic substitution with various nucleophiles including $NaCH(CO_2Me)_2$ to give a reasonably good yield of the regioisomeric products **27** and **28**.



Scheme 6

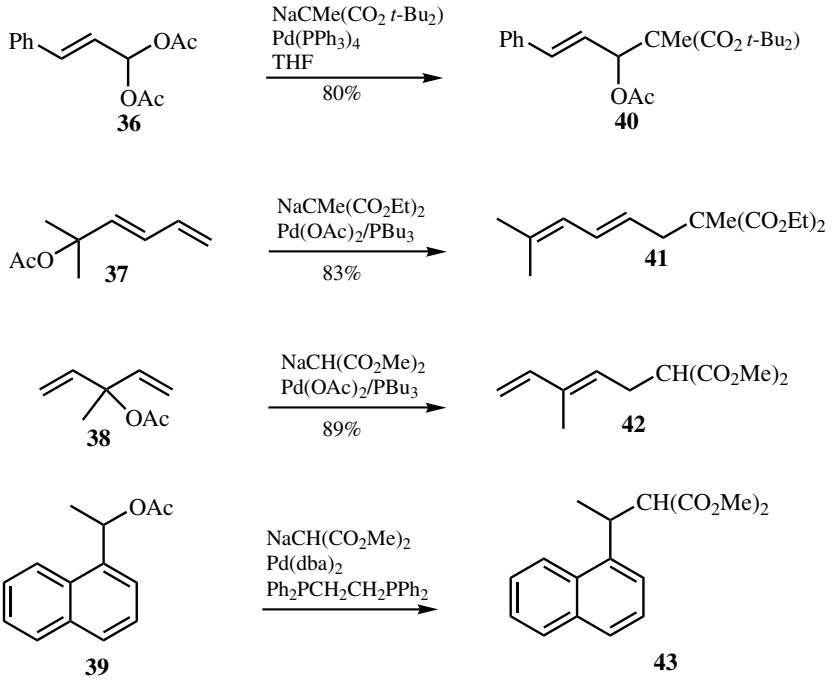
Other activated oxygen leaving groups include the vinylogous sulfonate leaving group, used on the substrate **29** (**Scheme 7**).[25] Reaction with the enolate of pentane 2,4-dione affords the substituted product **30**. The vinylogous sulfonate group provides a more rapid reaction in comparison with acetates.



Scheme 7

Phosphates[26] and sulfonates[27] have been used as leaving groups. Ethers have also been used as leaving groups[28] and work best when either phenyl esters[29] or epoxides (see **Sect. V.2.1.5**) are employed. Even acrolein acetal **31** has been used as a substrate for Pd-catalyzed allylic substitution.[30] With this substrate, the nucleophile is deprotonated during the course of the reaction by the alkoxy leaving group. The reaction was found to be more effective using diketones than with diesters. This difference was attributed to the lower pK_a of diketones. Thus, diketones **32** and **33** were alkylated to give the substitution products **34** and **35**(**Scheme 7**).

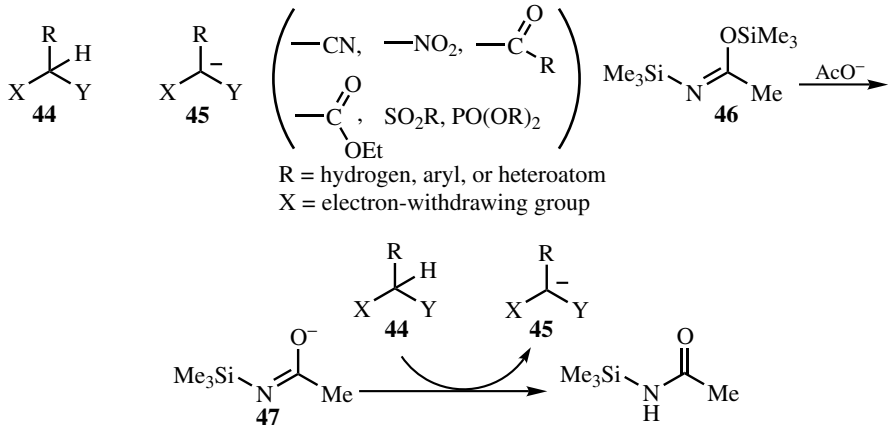
The use of allyl acetates has been extended to incorporate related structures including the general allylic diacetates **36**,[31] dienyl acetates **37** and **38**,[32],[33] and even the naphthyl substrate **39** (**Scheme 8**).[34],[35]



Scheme 8

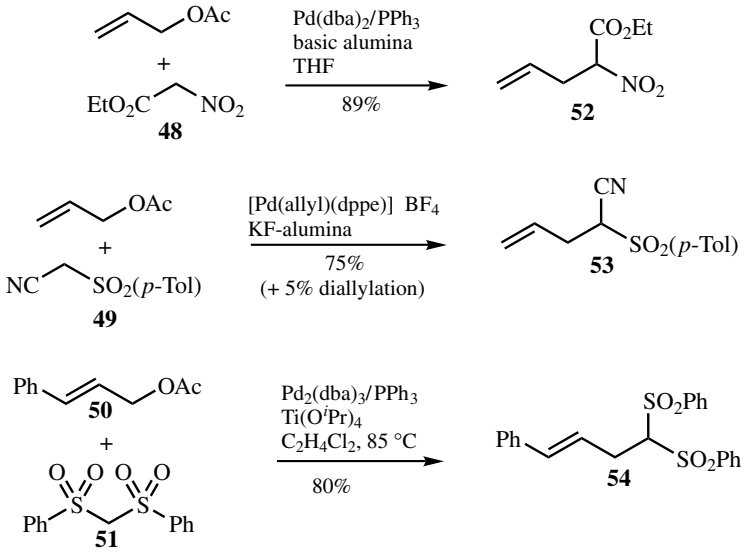
C. RANGE OF STABILIZED CARBON NUCLEOPHILES

The nucleophiles that can be considered as behaving in a similar way to stabilized enolates have the general structure **45**. In general, the anion (enolate) is preformed by addition of base, often sodium hydride, to the pronucleophile **44**. If the pK_a of the pronucleophile is sufficiently low, then the acetate leaving group can act as an *in situ* base.[36] Another common procedure is the use of bistrimethylsilyl acetamide (BSA) as a convenient method for deprotonation of the pronucleophile when allylic acetates are being used.[37] The liberated acetate generates the base **47**, which deprotonates the pronucleophile (**Scheme 9**). It is normal to add a small amount of acetate at the outset in order to start the process off.



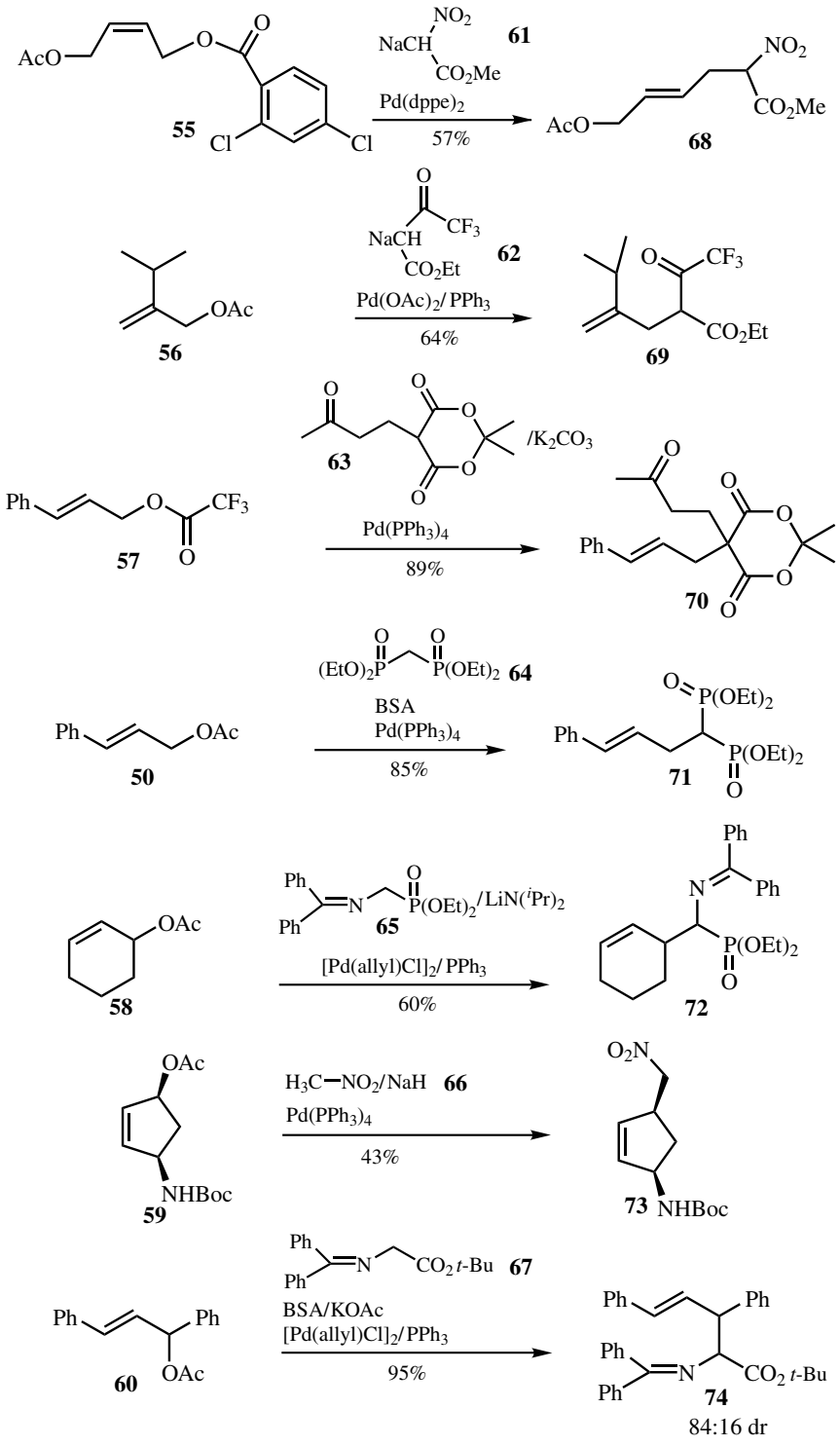
Scheme 9

Nucleophiles have also been activated by other mild procedures (**Scheme 10**). Basic alumina and KF-alumina have been used to activate a range of pronucleophiles including the nitro ester **48** and sulfone **49**.[38] Titanium tetraisopropoxide has also been used to promote Pd-catalyzed allylic alkylations, as exemplified by the reaction of cinnamyl acetate **50** with the bis-sulfone **51**.[39]



Scheme 10

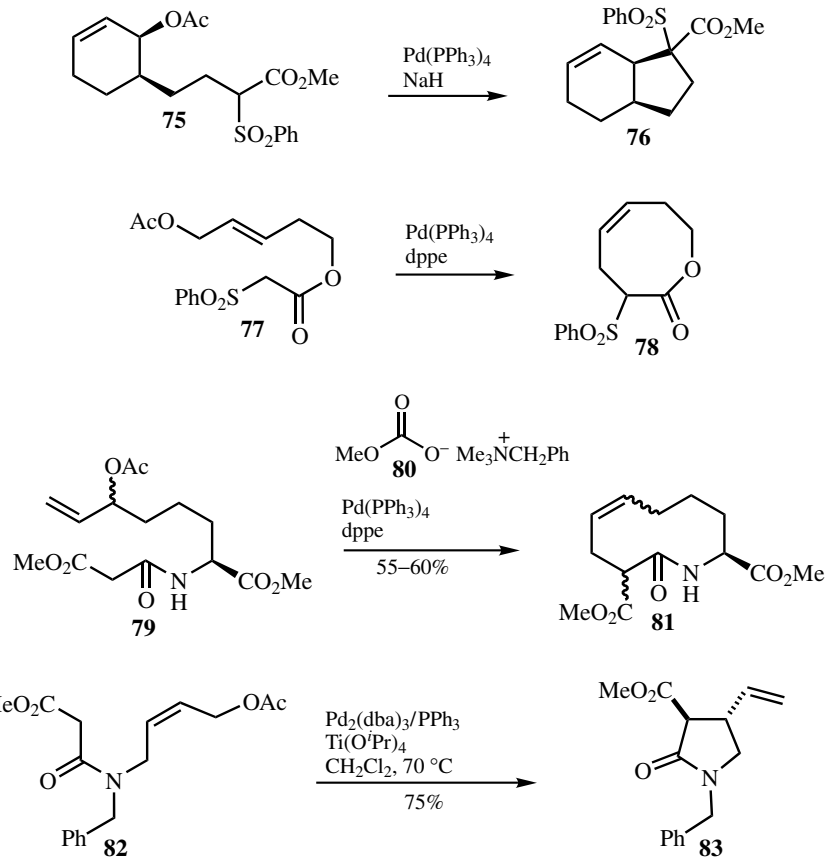
Further examples of stabilized carbon-centered nucleophiles used in Pd-catalyzed allylic substitution are given in **Scheme 11**.[40]–[47] It is noteworthy that the dichlorobenzoate group of substrate **55** leaves selectively over the acetate, and that the (*Z*)-stereochemistry of the substrate becomes (*E*)-stereochemistry in the product **68**. Nitromethane **66** is sufficiently acidic that there are no problems in the substitution reaction with acetate **59**. Relative stereochemistry is preserved in the product **73**.


AcO
55
Cl
Cl
NaCH(NO2)CO2Me
61
Pd(dppe)2
57%
AcO
NO2
CO2Me
68
56
OAc
NaCH(COCF3)CO2Et
62
Pd(OAc)2/PPh3
64%
O
CF3
CO2Et
69
Ph
O
CF3
O
57
63
/K2CO3
Pd(PPh3)4
89%
70
(EtO)2P(O)CH2P(O)(OEt)2
64
BSA
Pd(PPh3)4
85%
50
OAc
Ph
71
P(OEt)2
O
58
OAc
Ph2C=N-CH2-P(O)(OEt)2/LiN(iPr)2
65
[Pd(allyl)Cl]2/PPh3
60%
72
59
OAc
NHBoc
H3C-NO2/NaH
66
Pd(PPh3)4
43%
O2N
73
NHBoc
60
Ph
OAc
Ph2C=N-CH2-CO2t-Bu
67
BSA/KOAc
[Pd(allyl)Cl]2/PPh3
95%
74
84:16 dr

Scheme 11

D. CYCLIZATION REACTIONS

Cyclization reactions (**Scheme 12**) have played an important role in Pd-catalyzed allylic substitution chemistry, and the area was reviewed in 1989.[48] In many cases, the same principles apply as in intermolecular variant of the reaction. The first example of a Pd-catalyzed cyclization involving allylic substitution was reported by Trost and Verhoeven in 1977.[49] It involved the cyclization of allyl acetate **75** to give the *cis*-fused product **76**.



Scheme 12

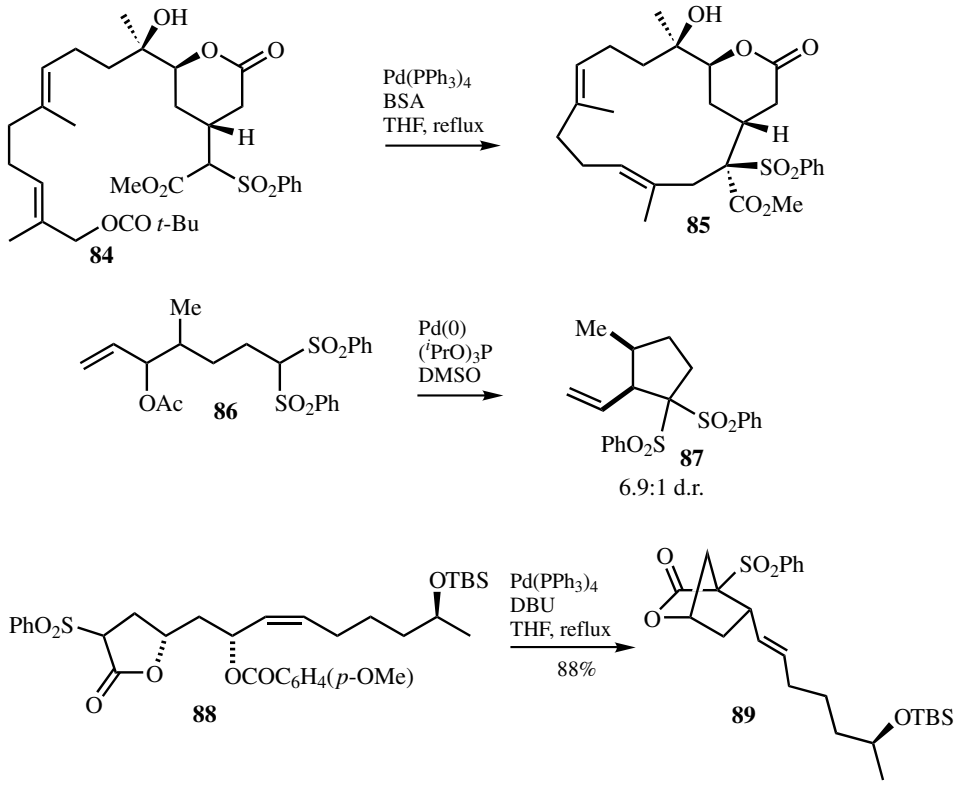
Interestingly, the substrate **77**, which has the option of closing to give either a six-membered ring or an eight-membered ring, actually affords the larger ring **78**.[50] The reaction is controlled by the nucleophile approaching from the less hindered end of the intermediate allylpalladium species. This is also observed in the cyclization of the amido ester **79**, which gives the ten-membered ring product **81**.[51] The carbonate salt provides a supply of base during the course of the reaction, allowing deprotonation of the active methylene group.

Cyclization of the amidoester **82** has been achieved using titanium tetraisopropoxide as a promoter. The pyrrolidinone **83** was formed as the *trans* diastereomer.[36]

Further examples of cyclization reactions involving Pd-catalyzed allylic substitution processes are given in **Scheme 13**. Macrocyclization of substrate **84** proceeds to give the product **85** as a single diastereomer.[52]

Diastereoselectivity was also observed in the cyclization of substrate **86**, where the methyl and vinyl groups are formed selectively in the *cis*-configuration when DMSO was used as solvent.[53] However, the selectivity was very dependent on the solvent employed.

Cyclization of the lactone **88** afforded the bicyclic lactone **89** using DBU as an *in situ* base.[54]



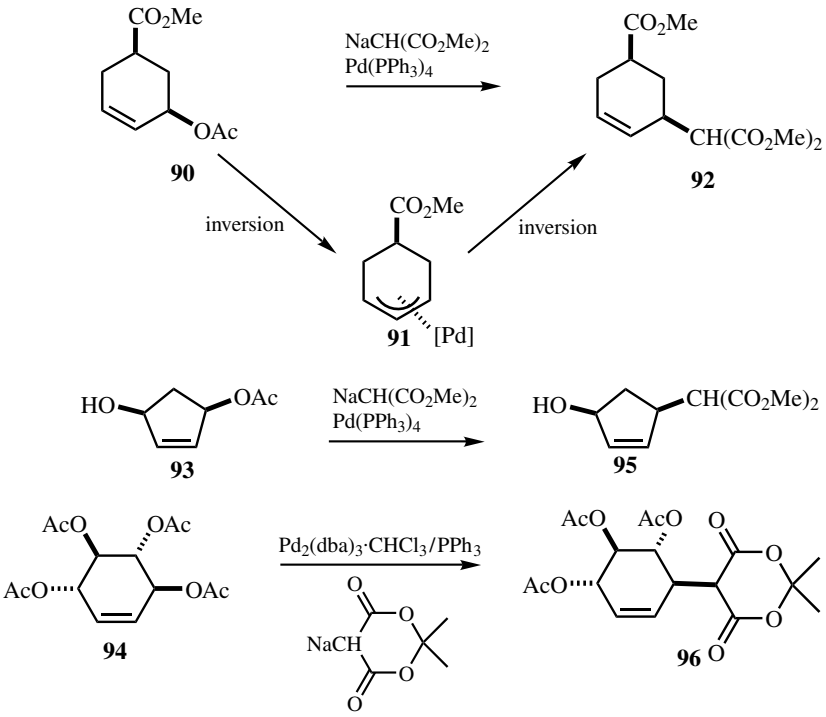
Scheme 13

E. STEREOCHEMISTRY OF ALLYLIC SUBSTITUTION REACTIONS

Soft nucleophiles react with overall retention of stereochemistry with suitable substrates (**Scheme 14**). For example, the relative stereochemistry of cyclohexenyl acetate **90** is retained upon reaction with stabilized enolates.[55]

The mechanism proceeds via a double inversion. The palladium displaces the acetate with inversion to give complex **91** and the incoming nucleophile approaches from the opposite face to the palladium, again with inversion. Therefore, overall retention of stereochemistry is observed in the product **92**.

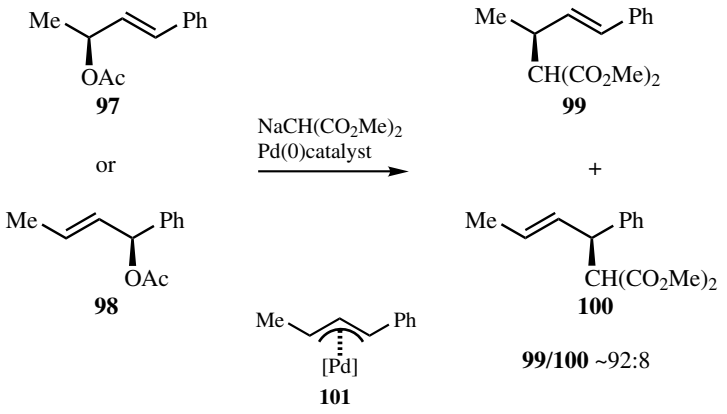
Further examples indicating the retention mechanism in cyclic substrates are provided by the reactions of substrates **93**[56] and **94**[57] that lead to the respective products **95** and **96**.



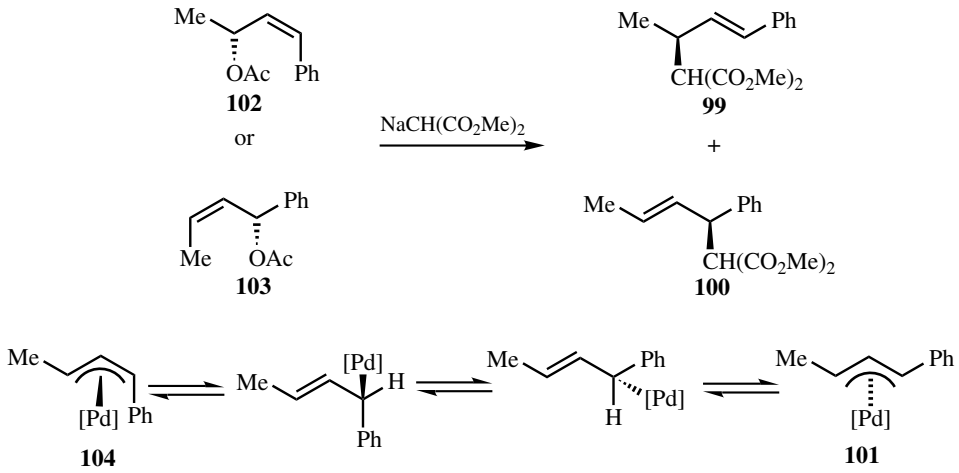
Scheme 14

There have also been examples of retention of stereochemistry in acyclic substrates (**Scheme 15**). The enantiomerically pure acetates **97** and **98** undergo Pd-catalyzed allylic substitution with retention of stereochemistry.[58] The regioisomeric ratio of products **99** and **100** is almost identical, indicating that the reaction proceeds via the common intermediate **101**.

Interestingly, the same enantiomers of products **99** and **100** are formed starting from the other enantiomer of the (*Z*)-allyl acetates **102** and **103** (**Scheme 16**).



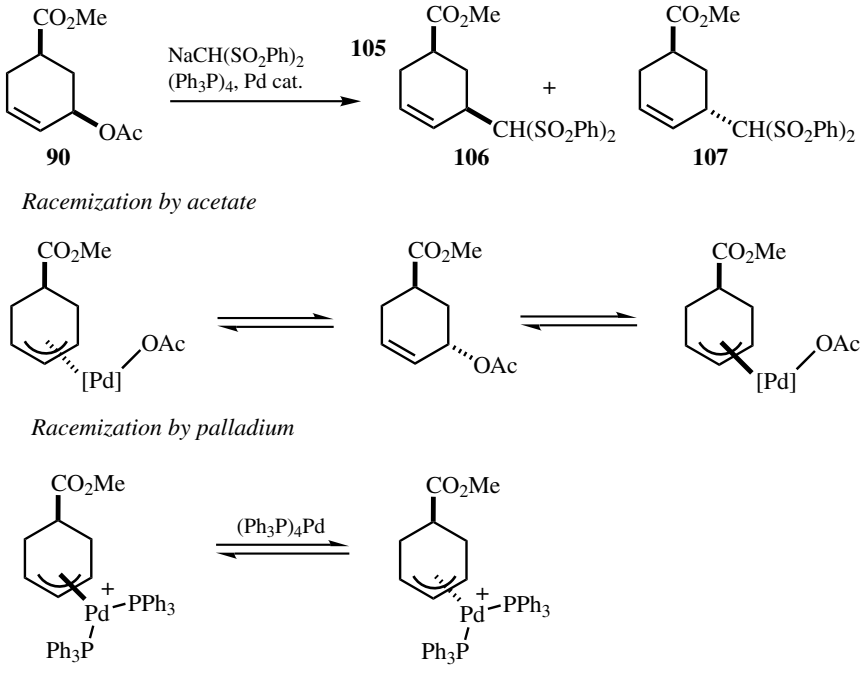
Scheme 15



Scheme 16

It is reasoned that the initially formed π-complex **104** undergoes π–σ–π rearrangement to give the common intermediate **101** prior to attack of the nucleophile.

In fact, the stereochemical integrity of allyl acetates is not always faithfully preserved in the reaction to give the substitution products. It is known that acetate can scramble the stereochemistry of allylpalladium complexes. The mechanism probably involves delivery of acetate from the palladium to the allyl moiety (**Scheme 17**). In cases where the nucleophile attacks slowly, an erosion of stereochemical integrity will be seen.

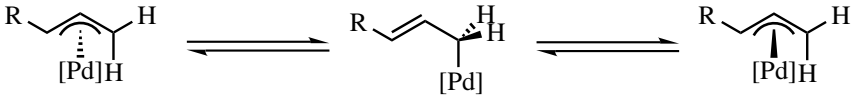


Scheme 17

For example, the bulky nucleophile **105** reacts slowly with the intermediate allylpalladium complex, which allows time for inversion to take place as indicated in **Scheme 17**.[59]

The racemization or epimerization of allylpalladium complexes can also be caused by additional palladium(0).[60] The palladium exchange is particularly problematic when high concentrations of catalyst are employed.[58]

Allylpalladium complexes are also able to undergo racemization via a $\pi-\sigma-\pi$ mechanism. This occurs rapidly when one terminus of the allyl group contains identical substituents, often hydrogen. Temporary formation of a σ-complex affords an achiral species, which can revert to either enantiomer of π-complex (**Scheme 18**).Thus, while the well-known double-inversion mechanism can provide a route for the conversion of enantiomerically pure substrate into enantiomerically pure product, this may not always be observed.

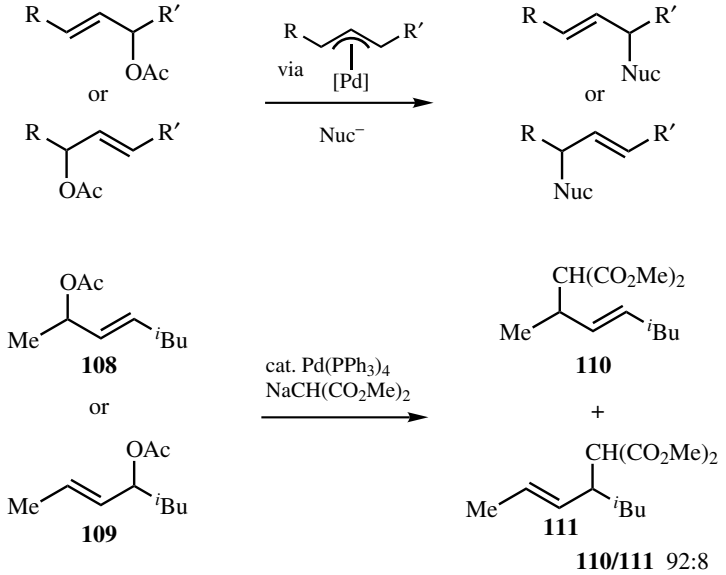


Scheme 18

F. REGIOCHEMISTRY OF ALLYLIC SUBSTITUTION

There have already been several examples described earlier of Pd-catalyzed allylic substitution reactions where more than one regioisomer could be formed selectively.

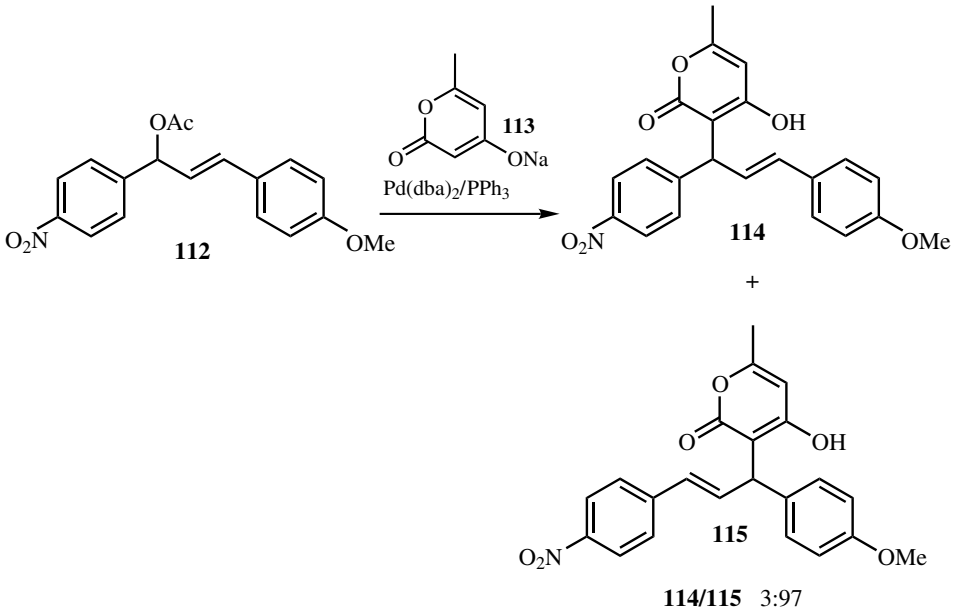
As shown in **Scheme 19**, nucleophilic attack could occur at either terminus of the intermediate allylpalladium complex, affording a mixture of regioisomeric products. The control of regiochemistry is affected by steric and electronic factors.



Scheme 19

In general, stabilized nucleophiles will attack the less sterically hindered end of the allyl moiety, although ligand effects can overturn this selectivity.[61] This general selectivity for attack at the less hindered end is illustrated by the reaction of sodiodimethylmalonate with either regioisomer of the starting acetate **108** or **109**.[62] The nucleophile selectively adds at the less sterically demanding position, affording the product **110** with good selectivity over the regioisomer **111**. It is reasonable to assume that the effect is primarily sterically controlled.

An example that appears to be electronically controlled involves the allylic substitution reactions of substrate **112** and related structures (**Scheme 20**).[63] The para-substituents exert a strong electronic influence but are expected to be similar on steric grounds. The nucleophiles attack selectively away from the electron-deficient nitro group.

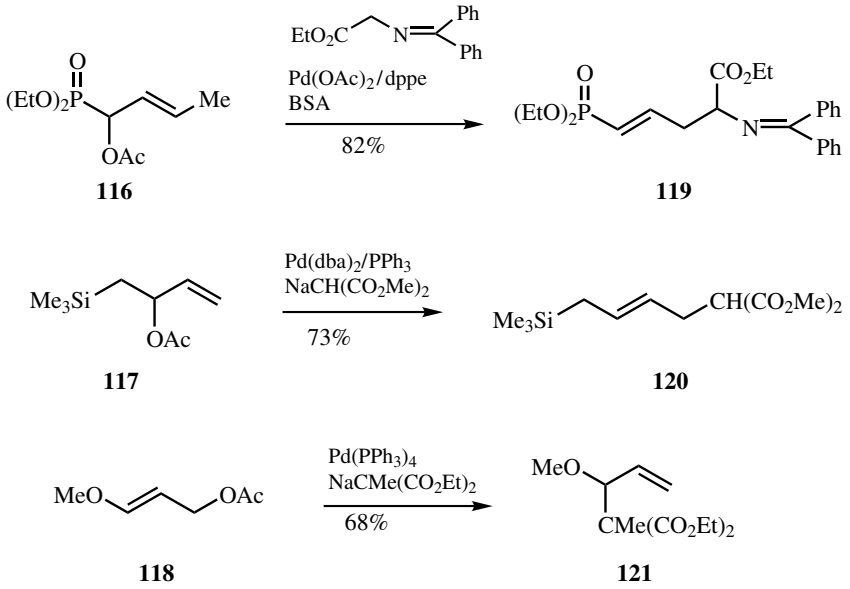


114/115 3:97

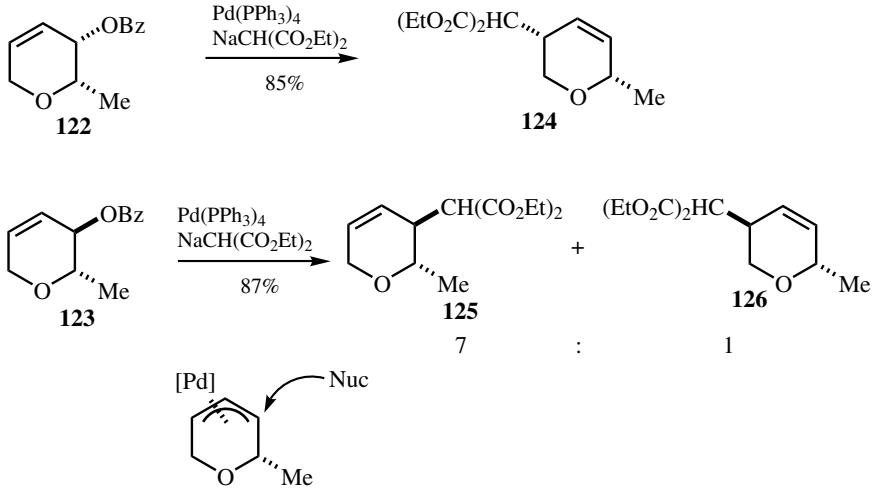
Scheme 20

Many functional groups direct nucleophilic attack to the remote terminus.[64],[65] Examples shown in **Scheme 21** include phosphonate **116**[66] and the silylated substrate **117**.[67] However, the alkoxy group in substrate **118** directs nucleophilic attack next to itself.[68],[69]

Unusual regioselectivity effects have been observed with the diastereomeric benzoates **122** and **123** (**Scheme 22**).[70] The reaction proceeds with diastereomer **122** to provide the expected substitution product **124**, where nucleophilic attack has occurred from the less substituted end. However, the other substrate diastereomer **123** selectively affords the other regioisomer of product **125**, with only a minor amount of "expected" regioisomer **126**. The anomolous behaviour of substrate **123** was ascribed to a distortion of the intermediate allylpalladium complex, such that the palladium is pushed away from the methyl group. This perturbation encourages nucleophilic attack at the position closer to the methyl group.



Scheme 21



Scheme 22

G. SOLID PHASE CATALYSIS

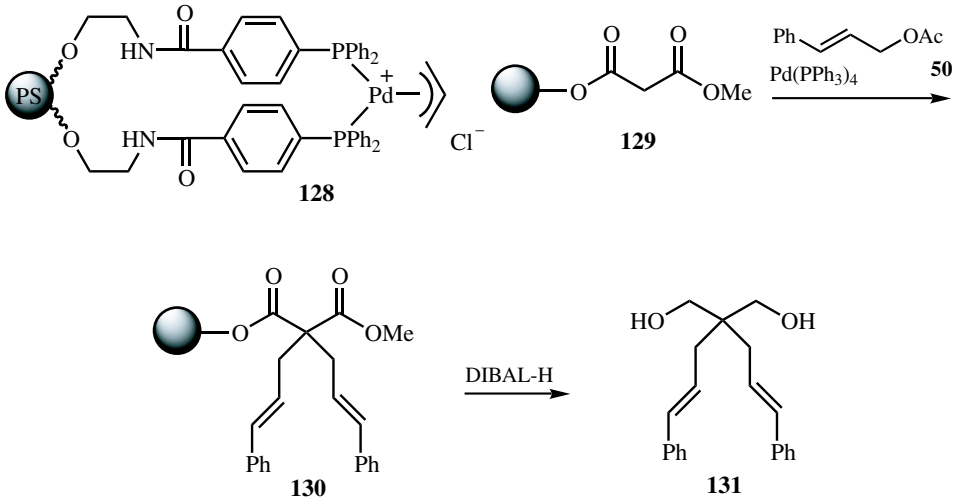
The use of catalysts that are supported on a solid phase is becoming increasingly popular. Such procedures allow for catalyst recycling and also reduce the levels of palladium/phosphine contamination in the final product. The use of palladium on graphite or alumina has been reported to be effective for catalyzing the reaction between allyl acetate and the enolate derived from diethylmalonate.[71]

The polyethylene-bound palladium complex **127**[12] and the polyethylene glycol–polystyrene copolymer **128**[72] have both been used successfully in allylic substitution reactions (**Scheme 23**). The malonate nucleophile has also been attached to polymer **129** and reacted with various allylic acetates, including cinnamyl acetate **50**.[73] The resin-bound product **130** can be washed to remove palladium and phosphine impurities prior to cleavage from the resin, in this case with DIBAL-H to give the free product **131**.

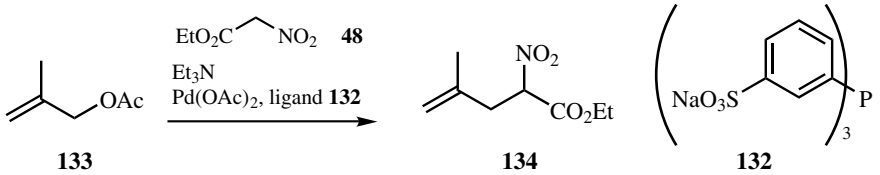
Pd-catalyzed allylic substitution reactions can also be performed using water-soluble phosphine ligands, including TPPTS **132**, as shown by the reaction of nitroester **48** with allyl acetate **133** to give the substitution product **134** (**Scheme 24**).[74],[75] The use of water-soluble palladium catalysts has been the subject of a review.[76] Water-soluble catalysts have also been applied to supported liquid phase reactions. A silica bead supports a thin film of polar solvent in which the palladium complex resides.[77],[78] The substrates and product reside in the bulk organic phase and can be decanted from the glass bead catalyst at the end of the reaction.

$[Bu\text{-}(CH_2\text{-}CH_2)_n\text{-}CH_2CH_2PPh_2]_{4\text{-}n}Pd(PPh_3)_n$

127



Scheme 23



Scheme 24

In summary, the Pd-catalyzed allylic substitution reaction between allyl acetates (and related electrophiles) with "soft" enolates has a wide scope and continues to attract considerable interest as a synthetic tool.

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[76] J. P. Genet and M. Savignac, *J. Organomet. Chem.*, **1999**, *576*, 305–317. Recent Developments of Palladium(0) Catalyzed Reactions in Aqueous Media.
[77] L. Tonks, M. S. Anson, K. Hellgardt, A. R. Mirza, D. F. Thompson, and J. M. J. Williams, *Tetrahedron Lett.*, **1997**, *38*, 4319.
[78] S. dos Santos, Y. Tong, F. Quignard, A. Choplin, D. Sinou, and J. P. Dutasta, *Organometallics*, **1998**, *17*, 78.

Allyl-O-CO-OR + Nu-H

V.2.1.3 Palladium-Catalyzed Allylation with Allyl Carbonates

MARCIAL MORENO-MAÑAS and ROSER PLEIXATS

A. INTRODUCTION AND HISTORICAL BACKGROUND

There are many recent useful reviews and books on Pd-catalyzed organic reactions,[1]–[3] some of them specifically covering allylations,[4]–[8] as well as a database available in book[9] and in CD-Rom forms.[10] However, this section deals only with allylic carbonates in Pd-catalyzed allylations. This is possible because allylic carbonates offer important advantages when compared with other typical esters such as acetates, and therefore, they are extensively used since 1982 as substrates in Pd(0)-catalyzed chemistry. We have tried to cover not only those reactions firmly established as useful synthetic methods, but also reactions that have found much more limited use in synthetic organic chemistry despite being potentially useful. Therefore, the extension given to the different reactions holds no relation with their popularity among the chemical community. For several reasons carbonates are more useful than acetates, the other more usual substrates as precursors of electrophilic η^3-allylpalladium complexes. This has been emphasized by many authors and will not be systematically underlined here apart from a few selected cases. However, the advantages of carbonates will be evident in the pages to follow.

Since this section is part of a general multiauthored handbook, duplications and overlapping with other sections are unavoidable. We have written this section keeping in mind that some duplications are better than omissions. Certain reactions of allylic carbonates are not usually categorized as allylations, and they are covered in other sections. However, at least one mechanistic step is a real allylation. In such cases a brief discussion has been incorporated.

Some articles could have been discussed in more than one paragraph. Therefore, at the end of many paragraphs the reader will find references to other discussions.

In 1982 Jiro Tsuji and co-workers published a communication launching allyl carbonates as substrates in the Pd(0)-catalyzed allylation of nucleophiles.[11] It was followed three years later by a full paper.[12] The overall reaction and catalytic cycle are shown in **Scheme 1**. One of the advantages over acetates is that addition of external base is not required. Indeed, the pronucleophile Nu-H reacts with the *in situ* generated alkoxide to form the actual nucleophile. The maximal concentration of base at any moment in the reaction medium depends on the relative rates of the individual steps of the cycle, but cannot be higher than the maximal quantity of the catalytic species PdL_2. Therefore, the reaction takes place formally in

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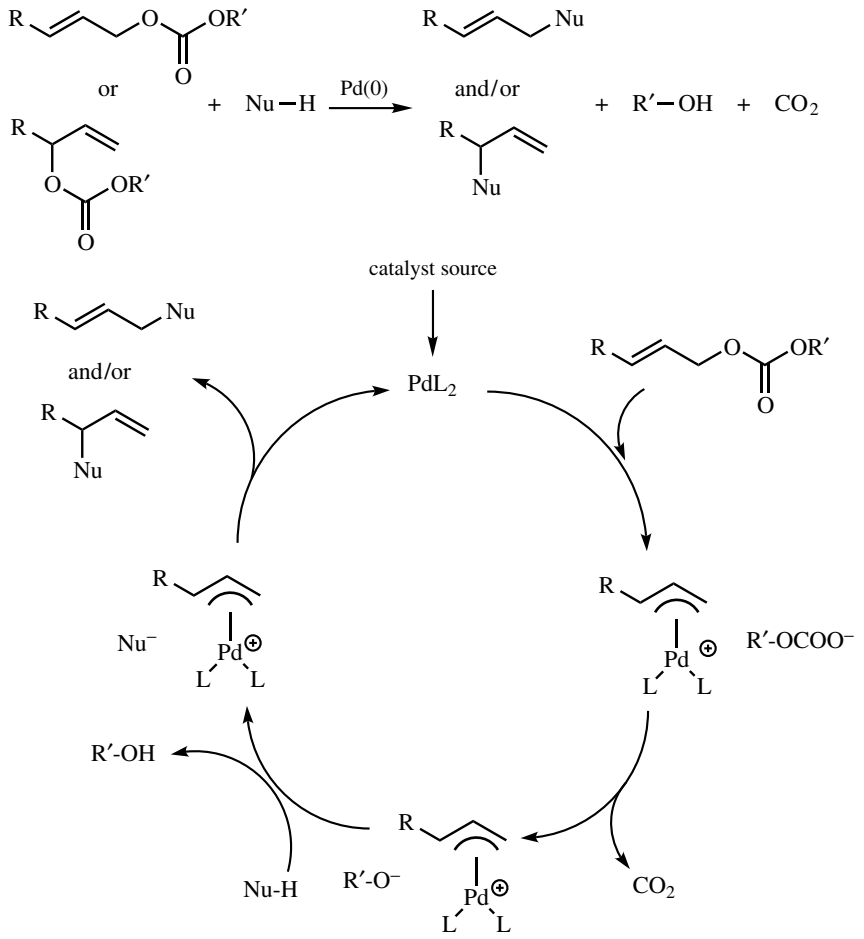
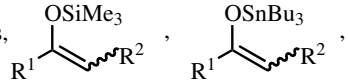
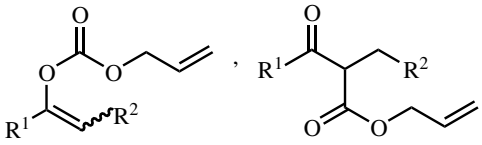


Nu-H: $CH_2(EWG)_2$, $RCH(EWG)_2$, R-CH_2–NO_2, Ar-CH_2–EWG, vinyl-CH_2–EWG,

"H" to 1-alkenes,  , ,

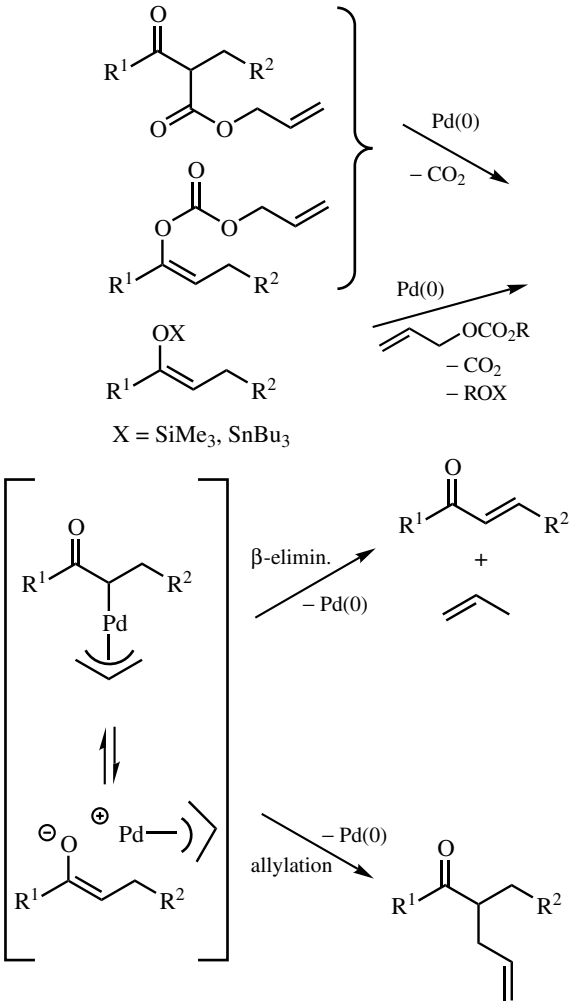
 ,

Scheme 1

neutral medium, and this has important consequences on the scope. Moreover, since carbonate is a better leaving group than acetate, milder reaction conditions are required. Tsuji and co-workers extended the allyl carbonate method to convert allyl β-ketoesters into α,α,α-triallylketones[13] and described intramolecular versions[14]–[16] that revealed overall retention of configuration at the electrophile for stabilized carbon nucleophiles. It is remarkable that in 1984 Tsuji and co-workers proposed S_N2 displacement of PdL_2 by PdL_2 on

η^3-allylpalladium complex as a possible reason for stereochemical scrambling,[16] a hypothesis firmly reinforced by Bäckvall and co-workers much later.[17],[18]

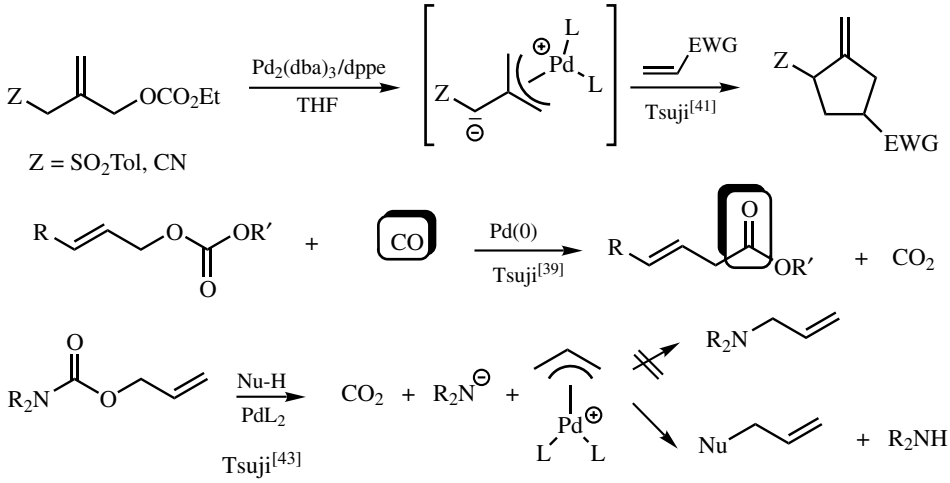
Nucleophiles used in the seminal papers by Tsuji and co-workers were mostly stabilized carbon nucleophiles, and the method found an early synthetic application in a preparation of steroids.[19] It soon became evident that many other types of nucleophiles could be used. In particular, hydride ion equivalents led to 1-olefins[20],[21] (see **Sect. V.2.3.1**). Silyl and stannyl enolates of simple ketones and aldehydes[22],[23] and esters[24] can be allylated, as well as allyl enol carbonates[25],[26] (see **Sect. V.2.1.4**). This is an indirect α-allylation of ketones, aldehydes, and esters. Enol derivatives can take another reaction course under Pd(0) catalysis (**Scheme 2**). Thus, oxidation to α,β-unsaturated carbonyl compounds ensues if reactions are performed in acetonitrile under precise sources of catalyst precursor.[24],[27]–[32] A full discussion on the dichotomy of allylation–oxidation has been published,[33] as well as a comparison of the usefulness of several transition metals as catalysts in allylation of nucleophiles.[34]



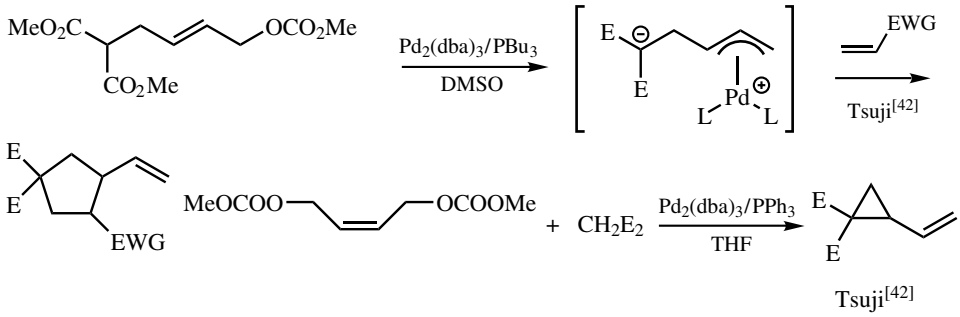
Scheme 2

An extension of the Pd-catalyzed oxidation to alkyl allyl carbonates met with less success since ruthenium catalysis was shown to be superior.[34]–[36] A late example from another group has been published.[37]

Other results obtained by Tsuji's group up to 1987 using allyl carbonates are carbonylations to afford β,γ-unsaturated esters[38]–[40] (**Scheme 3**) (see **Sect. VI.3**), cycloadditions of trimethylenemethane palladium complex to afford methylenecyclopentanes[41] (**Scheme 3**), and cycloadditions of zwitterions to afford substituted vinylcyclopentanes[42] (**Scheme 4**) (see **Sect. V.2.5.2**). 2-Butene-1,4-diol dicarbonates afford a variety of cyclic structures by reaction with dinucleophiles under Pd(0) catalysis (see **Sect. I**). The first case reported seems to be the formation of the vinylcyclopropane of **Scheme 4**.[42]



Scheme 3



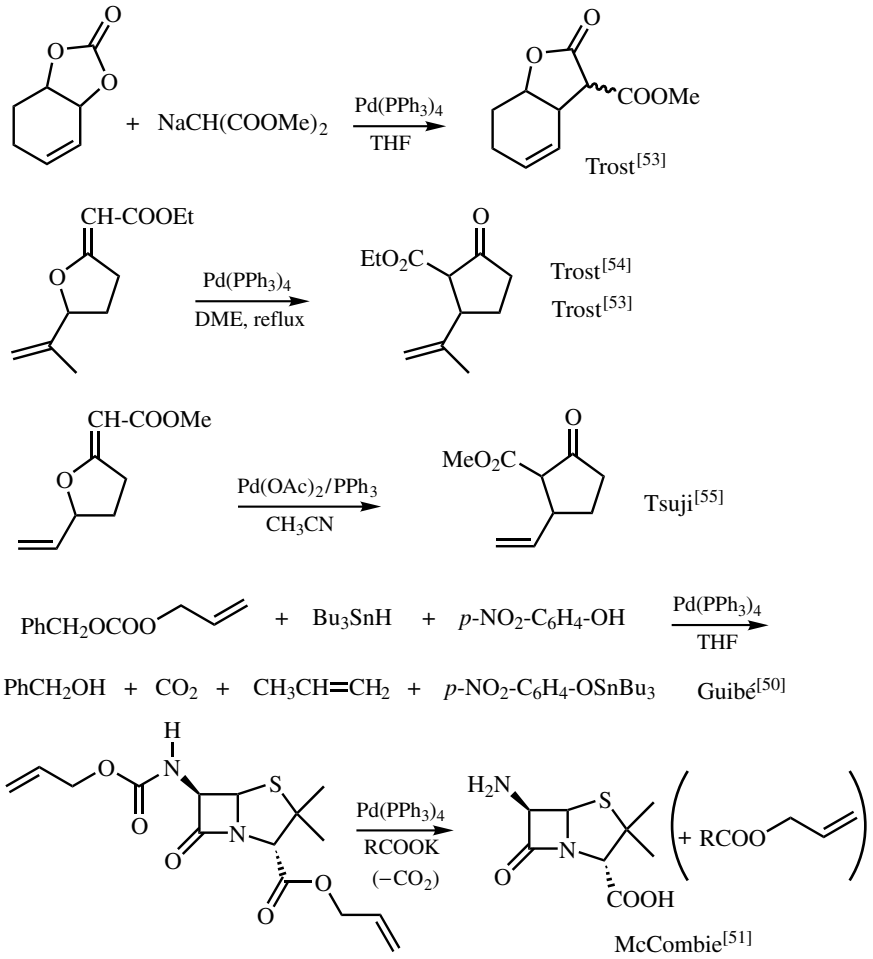
Scheme 4

Extension of the allylation method to the related allyl carbamates (**Scheme 3**) was also reported by Tsuji and co-workers.[43]

The initial contributions by Tsuji were summarized in several reviews.[44]–[49]

However, we should mention that use of allyl carbonates to protect alcohols, including deprotection under Pd(0) catalysis, was reported in 1981 by Guibé and Saint M'Leux[50] (**Scheme 5**). The same strategy to protect and deprotect amines was reported by Jeffrey and McCombie in 1982[51] and patented by McCombie in 1980 with an application to the

United States in 1979![52] Since nucleophiles are required to scavenge the allyl part of the protecting allyloxycarbonyl group, Bu_3Sn-H hydride donor and potassium alkanoates were used by Guibé and McCombie, respectively (**Scheme 5**).



Scheme 5

Trost and Runge announced in 1981 the use of simple allyl carbonates[53] and described even earlier the Pd(0)-catalyzed rearrangement of allyl ethers of enolic β-ketoesters into the isomeric α-allyl-β-ketoesters[53],[54] (**Scheme 5**). Allyl ethers of enolic β-ketoesters are vinylogous of allyl carbonates! In 1980 Tsuji and co-workers described a similar rearrangement,[55] declaring that "the palladium-catalyzed rearrangement of a similar cyclic ether has been presented in a lecture by B.M. Trost at the Ist Intern. Kyoto Conf. Org. Chem., Dec., 6, 1979."

Moreover, in 1982 a patent was filed in which the use of allylic carbonates for the allylation of stabilized nucleophiles is mentioned.[56] Other colleagues were aware very soon of the advantages of using carbonates instead of acetates. Therefore, several papers appeared in this early historical period that we, arbitrarily, have

limited to 1987, the year when the last of the already mentioned reviews by Tsuji was published.[49]

B. MECHANISMS

Before detailed descriptions of the reactions are given, the following should be kept in mind.

1. Carbonates are more active than acetates. This is a general observation realized by many authors. The enhanced reactivity of the substrates with the better leaving groups has been interpreted as that the rate-determining step of the allylation of nucleophiles is the oxidative addition of the allyl substrate to palladium(0).[57] A related topic is the effect of the leaving group on the enantioselectivity, which has been studied by Fiaud and Legros.[58]

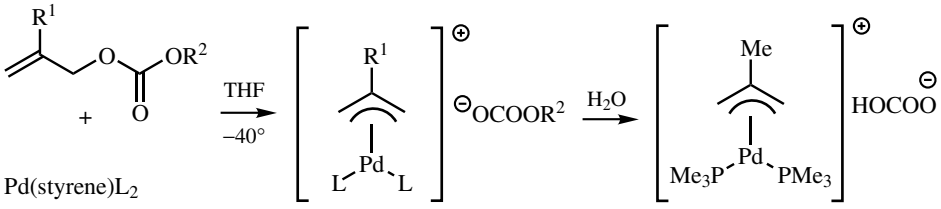
2. The success of carbonates depends on the full deprotonation of pronucleophile Nu-H by liberated alkoxide anion. Otherwise, attack of alkoxide on the cationic η^3-allylpalladium(II) complex would afford allyl ethers, and this is sometimes a side reaction. Allylation of nucleophiles by allylic carbonates is customarily carried out in more or less polar aprotic solvents (THF, DMSO, DMF), and less frequently in dichloromethane, toluene, and even in water. The orders of acidity in dipolar aprotic solvents and in water are quite different, and this should be taken into account to know the position of the acid–base equilibrium. Lists of pK_a values in DMSO are available.[59],[60] Orders of acidities in THF and in DMSO are probably not different. Examples of pK_a (DMSO) are: $MeCOCH_2COOEt$ (14.4), $CH_2(COOEt)_2$ (16.4), PhOH (18.0), methanol (29.0), aniline (30.6), water (31.2), and ammonia (estimated 40).

3. η^3-Allylpalladium(II) alkylcarbonates of **Scheme 6** have been isolated and shown to be ionic.[61] The hydrogenocarbonate is also ionic as determined by X-ray diffraction. Formate ion is the frequent source of hydride in reduction of allyl carbonates (and other esters).[20],[21] The corresponding η^3-allylpalladium(II) formates are postulated intermediates in the catalytic cycle of reduction. They have been independently prepared, featuring ionic character if enough auxiliary ligand is present and covalent character if a limited amount of ancillary ligand is incorporated into the coordination sphere of the metal.[62]

4. The steps of the catalytic cycle are reversible and allyl carbonates and carbamates are obtained under carbon dioxide atmosphere (**Scheme 7**).[63]

5. One consequence of the practical reversibility of the decarboxylation step is that loss of CO_2 is not instantaneous. Stereochemically homogeneous cyclic carbonates sometimes equilibrate under palladium(0) catalysis when $Pd(PPh_3)_4$ is used as the catalyst source, or in other words, when monodentate phosphines are used to stabilize Pd(0), but not in the presence of bidentate phosphines[64],[65] (**Scheme 8**).

The general situation is exemplified in **Scheme 9** for a particular type of nucleophile.[65] The pronucleophiles 4-nitroaniline and 2,4-dinitroaniline (pK_a (DMSO) 20.9 and 15.9) are more acidic than methanol (29.0) in DMSO and therefore also in THF. Under $Pd(PPh_3)_4$, equilibration of *cis* and *trans* carbonates is faster than attack by nucleophile. This means that the system is under Curtin–Hammett preequilibrium conditions. Equilibration of *cis* and *trans* isomeric carbonates occurs by two different mechanisms: (i) coordination of alkyl carbonate to palladium and reductive elimination (internal delivery) with retention of configuration, and (ii) by S_N2 displacement of



Pd(styrene)L_2

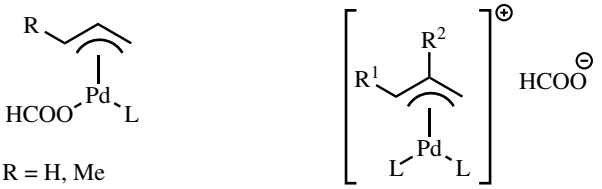
R^1 = H, Me

R^2 = Me, Et

L = PMe_3, PMe_2Ph, $PMePh_2$

X-Ray

Ozawa, Yamamoto[61]



R = H, Me

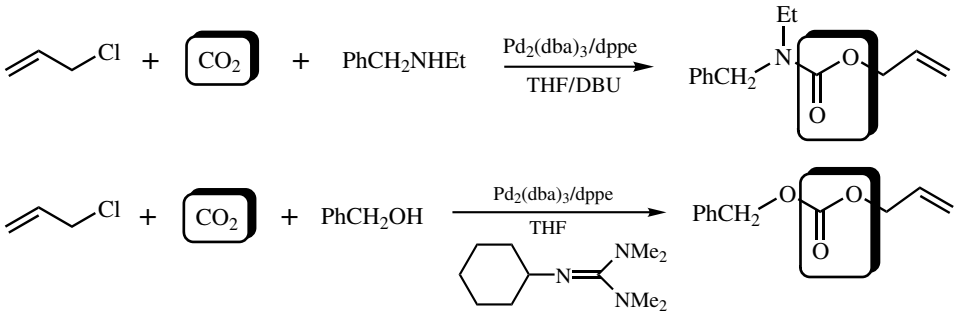
L = $PMePh_2$, PMe_2Ph, P(*o*-tol)$_3$

R^1 = H, Me; R^2 = H, Me

L = PMe_3, $PMePh_2$

Shimizu, Yamamoto [62]

Scheme 6

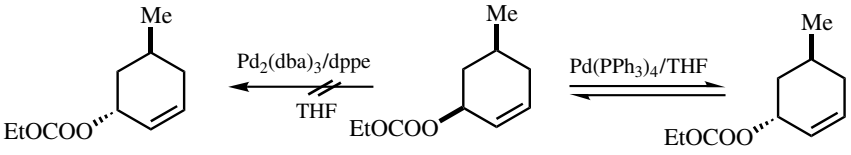


R_2NH + CO_2 $\overset{\text{base}}{\rightleftharpoons}$ $R_2N\text{-}COO^{\ominus}$

ROH + CO_2 $\overset{\text{base}}{\rightleftharpoons}$ $RO\text{-}COO^{\ominus}$

McGhee[63]

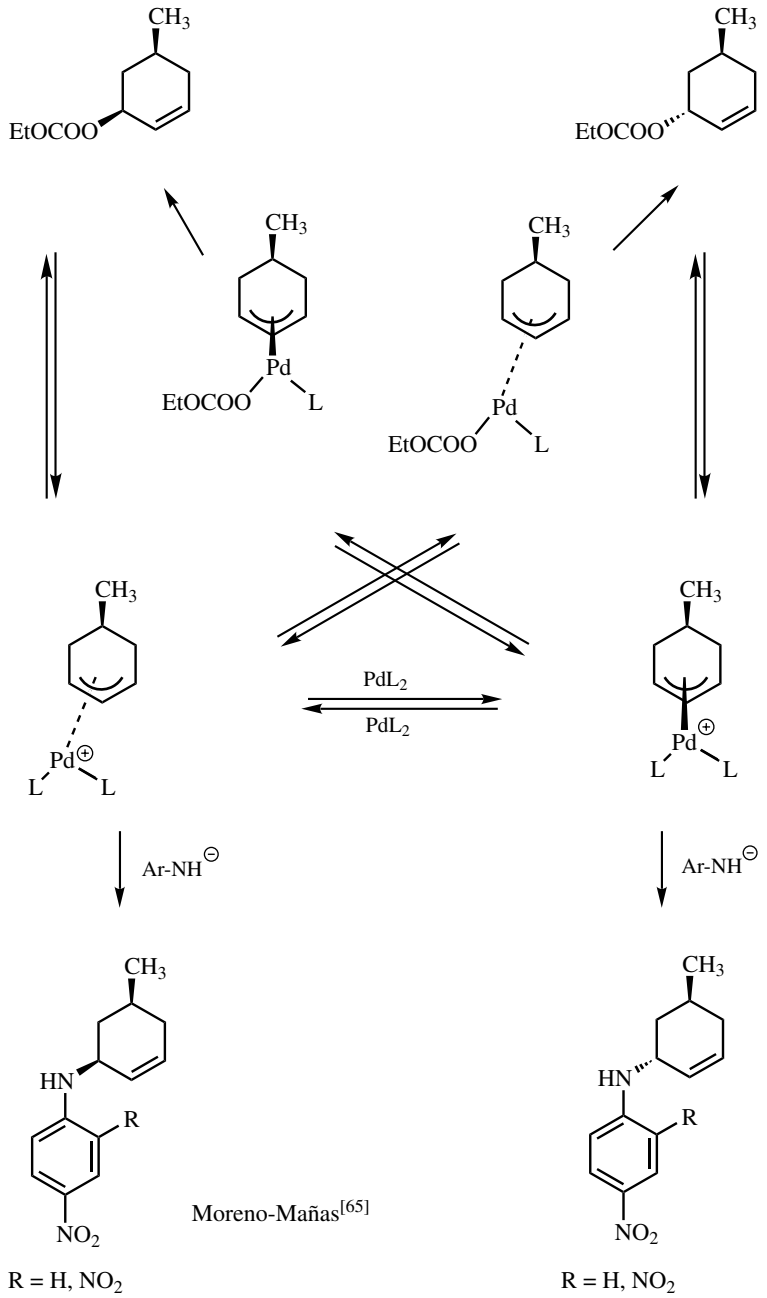
Scheme 7



Moreno-Mañas[65]

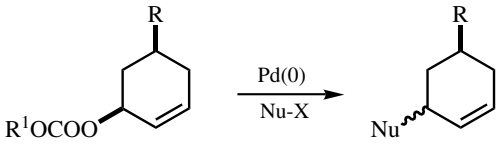
Scheme 8

PdL_2 by PdL_2 as postulated by Tsuji and co-workers in 1984.[16] Convincing evidence for the operation of the last mechanism has been presented by Kurosawa[489]–[491] and Bäckvall and co-workers.[17],[18] For a detailed discussion on this isomerization mechanism, which is independent of the leaving group, see the original papers by Bäckvall and co-workers.



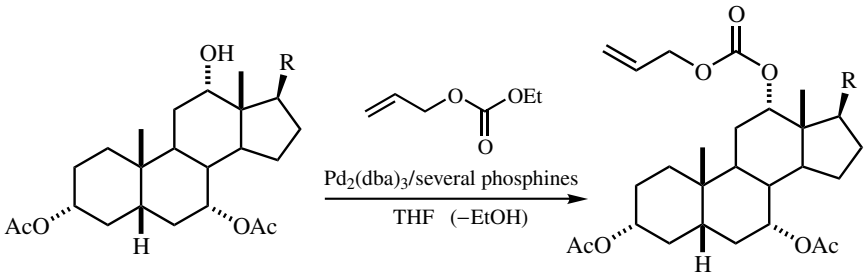
Scheme 9

Cyclic allyl carbonates have decreased propensity to equilibrate when compared with acetates. Their reactions are stereochemically cleaner and better defined. Thus, they have been used as stereochemical probes to check the overall stereochemical outcome of the reactions. The formation of the η^3-allylpalladium(II) intermediate occurs with inversion of configuration at the allyl framework. The nucleophilic attack can occur directly on the allylic termini involving a second inversion of configuration (overall retention) or indirectly by previous attachment of the nucleophile to the Pd atom followed by reductive elimination with retention (overall inversion). The reported examples involving cyclic allylic carbonates are in **Scheme 10** and **Table 1**.



Scheme 10

6. One case of transesterification or delivery of allyloxycarbonyl group instead of allylation has been reported[77] (**Scheme 11**). Two cases of transamidation have also been reported although catalysis by Pd was not recognized.[78],[79]



Davis[77]

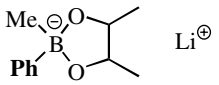
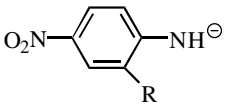
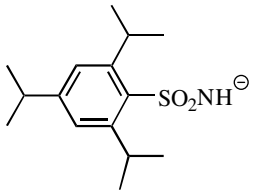
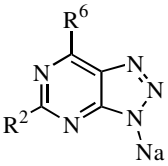
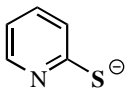
Scheme 11

C. ALLYLATION OF C-NUCLEOPHILES

C.i. Allylation of Stabilized C-Nucleophiles

Stabilized carbanions (acetoacetates, malonates, Meldrum acid, nitroderivatives, and the like) are efficiently allylated by allylic carbonates under Pd catalysis without added base (**Scheme 1**). Apart from the cases reported up to 1987 (*vide supra*), many references witness the possibilities of this type of reaction.[66],[80]–[109] Attention has been paid to asymmetric versions (see **Sect. V.2.4**),[110]–[121] to several stereochemical and mechanistic aspects,[66] and to remote asymmetric induction[122] (**Scheme 33**). New O- to C-rearrangements similar to those of **Scheme 5** have been published.[123] Cyanide should be considered also as stabilized C-nucleophile despite its overall inversion stereochemical behavior[68],[124] (**Scheme 10** and **Table 1**).

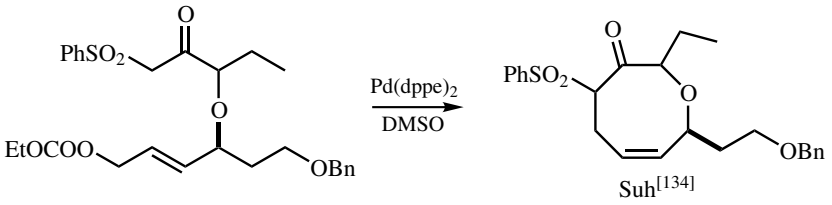
TABLE 1. Stereochemical Behavior

Nucleophile	R	Stereochemistry	Researcher
$LiCH(COOEt)_2$	COOMe	Retention	Kocovsky[66]
[**2-Furyl**$B(OMe)_3]^-Li^+$	COOMe	Inversion[a]	Kobayashi[67]
	COOMe	Inversion[a]	Kobayashi[67]
NC-$SiMe_3$	COOMe	Inversion	Y. Tsuji[68]
 R = H, NO_2	CH_3	Retention[b]	Moreno-Mañas[65]
	CH_3	Retention[b]	Moreno-Mañas[69]
 $R^6 = NH_2$, $R^2 = H$ $R^6 = Cl$, $R^2 = H$ and NH_2	$CH_2OTBDMS$	Retention[c]	Vince[70] Vince[71]
RCOONa	COOMe	Retention	Trost[72]
PhO^-	COOMe	Retention[b]	Sinou[73]
PhS-$SiMe_3$	COOMe	Retention	Trost[74]
	COOMe	Retention[b]	Sinou[75]
$PhSO_2Na$	COOMe	Retention	Trost[76]

[a] Ni(0) Catalysis.
[b] Countercation is the η^3-allylPd(II) cation.
[c] From *trans*-carbonate.

Intramolecular versions are particularly efficient, permitting preparation of differently sized carbo and heterocyclic rings: five-membered,[125]–[127] including the carbapenem skeleton[128]; six-membered[129]–[132]; eight-membered[133],[134] (**Scheme 12**); nine-membered oxonenes[135]; 11-membered[136]; 14- and 15-membered macrolides,[137] as well as bicyclic systems[138],[139] have been prepared by intramolecular allylation of

stabilized carbon nucleophiles under neutral conditions. The formation of an eight-membered ring instead of the also possible six-membered ring is remarkable (**Scheme 12**). The polycyclic skeleton of gelsemium-type alkaloid family has been prepared by an intramolecular allylation using allyl carbonate as electrophilic reagent.[140]

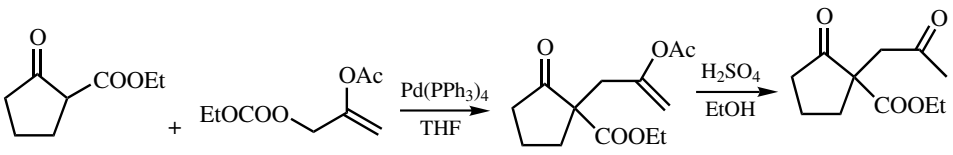


Suh[134]

Scheme 12

Syntheses of significant products include steps categorized under allylation of stabilized C-nucleophiles: strychnine,[141] the antidepressant Rolipram®,[142],[143] $\Delta^{9(12)}$-capnellene,[144] aspochalasin B,[136] pheromones,[145],[146] dendrobine,[130] hydrindene skeleton,[147] steroid side chains,[148] methyl jasmonate,[149] polyene side chains of tocopherol, terpenes, and related products[150]–[154] are accesible by the Pd–allyl carbonate method. Cyclopentanic systems are prepared by cyclization of precursors available by carbonate chemistry.[113],[155]–[157]

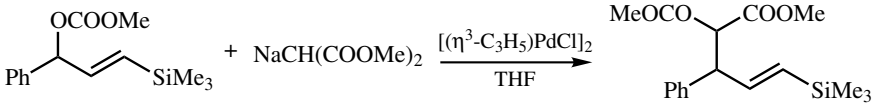
Allyl carbonates substituted at C-2 in the allyl moiety by a hydrolyzable OR group are synthetic equivalents of ketones[136],[158]–[160] (**Scheme 13**).



Mitsudo, Watanabe[158]

Scheme 13

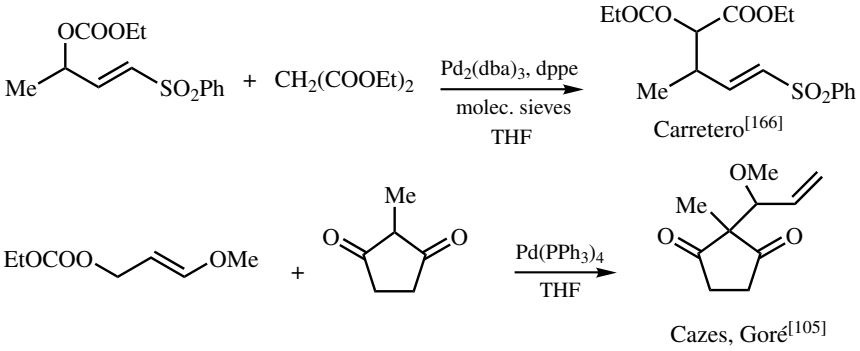
Silicon has a remarkable effect on the regioselectivity (**Scheme 14**). Regioselectivity is frequently dominated by steric effects (**Scheme 1**) if monodentate or symmetrical bidentate phosphines are the ancillary ligands, which is usual in preparative work. But systems such as that of **Scheme 14** react at the terminus of the allyl system remote from silicon, giving rise to the product that has lost the conjugation.[118],[161]–[163] The silicon function is eliminated by protonation, and the peculiar regioselectivity followed by protonation has been utilized in the preparation of HIV protease inhibitors.[164] The silicon effect is independent of the leaving group. However, all the examples mentioned here have been worked out with allyl carbonates.



Romero[118]

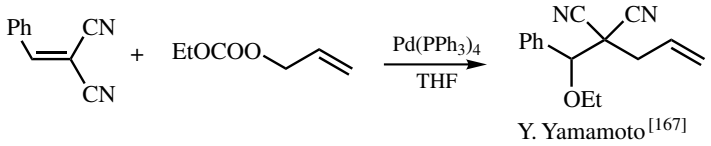
Scheme 14

The effect of strong polar groups in the regioselectivity is dramatically exemplified by the reactions of **Scheme 15**. Electron-withdrawing groups such as sulfone direct the attack at the point remote from the functional group,[165],[166] whereas electron-donating groups such as methoxy[102],[105] have the opposite effect. The vinylsulfone of **Scheme 15** is a powerful acceptor in conjugate additions, and if the related acetate ester is used only conjugate addition of malonate is observed.[165],[166]



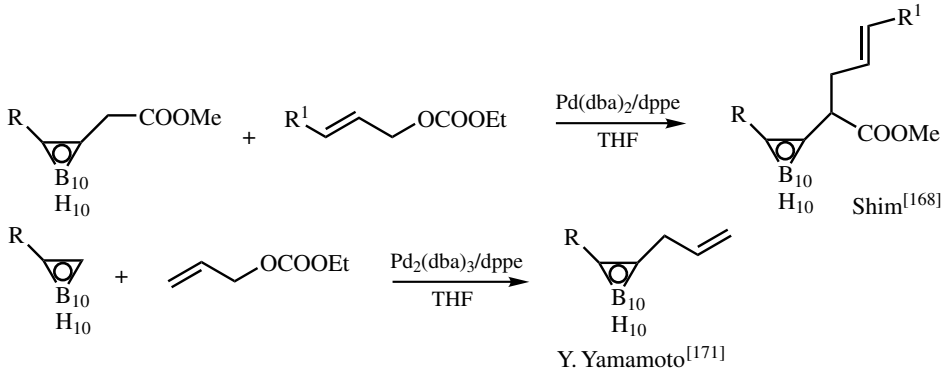
Scheme 15

An alkoxyallylation of activated olefins is shown in **Scheme 16**. Conjugate addition of the generated alkoxide gives rise to the stabilized carbanion, which attacks the η^3-allylpalladium complex.[167]



Scheme 16

Allyl carbonates are particularly useful in alkylation of nucleophilic carboranes, both at the side chain[168]–[170] or directly at the carborane skeleton[171],[172] (**Scheme 17**). The reverse situation is encountered in a carborane bearing an allyl carbonate in the side chain, which reacts with a highly functionalized C-nucleophile under Pd catalysis.[173] Functionalized carboranes hold promise in the field of neutron capture.



Scheme 17

Overall retention of configuration (double inversion) is the rule with stabilized carbon nucleophiles.

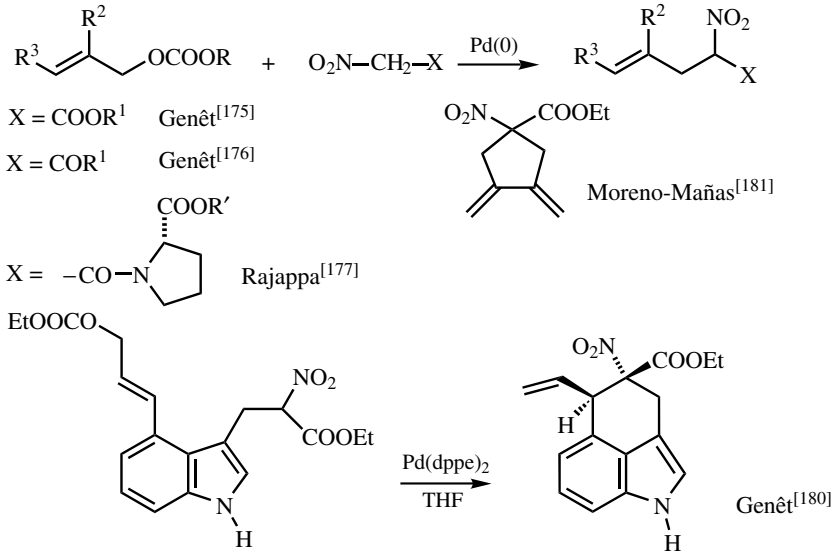
Although this review is not intended to cover catalysis by other metals, it is worth mentioning that nickel(0) has met with some success in the allylation of stabilized nucleophiles and phenols with allylic carbonates.[174]

See also **Sects. F.ii**, **I**, **J**, **L**, **N**, **O**, **Q.i**, and **Q.ii**.

C.ii. Allylation of Amino Acid Precursors

Carbonates have met with great success in the preparation of amino acid derivatives, which, eventually, are transformed into target amino acids.

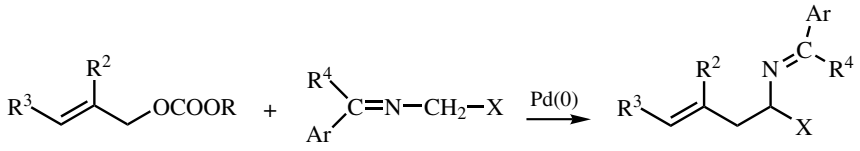
Nitroacetic acid esters[175],[176] and amides[177] are potential precursors of amino acids. They are good substrates in Pd(0)-catalyzed allylation with carbonates (**Scheme 18**) the same as the structurally related open-chain[178] and cyclic α-nitroketones.[179] An intramolecular version is aimed at the preparation of precursors of alkaloid ergoline.[180] 3,4-Dimethylenecyclopentane nitroacetate is prepared in one synthetic step from allyl carbonate (R^2 = Br, R^3 = H) including a C—C bond formation by Pd-catalyzed reductive coupling.[181],[182] There are more examples of Pd(0)-catalyzed allylation of nitroderivatives including nitromethane.[84],[91],[104],[107]



Scheme 18

Benzophenone or 4-chlorobenzaldehyde imine protection of the amino group of glycine[176],[183]–[185] and alanine esters[176],[183],[184] produces enhancement of CH acidity, thus permitting allylation by allyl carbonates (**Scheme 19**). The same applies to cyano[183],[184],[186] and phosphonate analogs.[176],[187] Camphorsultam (X_c) derivative produces de higher than 90%.[185]

Related results are obtained in alkylation by a phosphonate-containing allylation reagent[188] (**Scheme 20**). Note again the clear-cut regioselectivity imposed by the electron-withdrawing group.



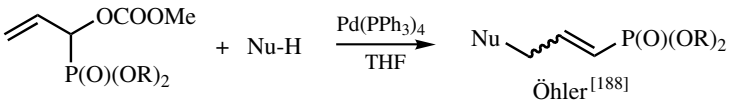
X = $COOR^1$ Genêt[176, [183], [184]
Salaün[185]

X = CN Genêt[183], [184]
Salaün[186]

X = $P(O)(OEt)_2$ Genêt[176], [187]

X = COX_c Salaün[185] (de > 90%)

Scheme 19



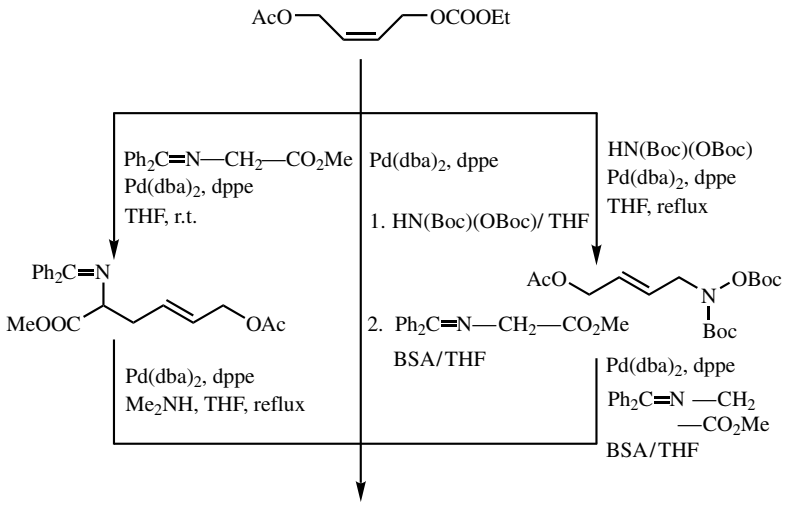
Nu-H = AcNH–**CH**$(COOEt)_2$

Ph_2C = N–CH_2–Z; Z = COOEt, CN

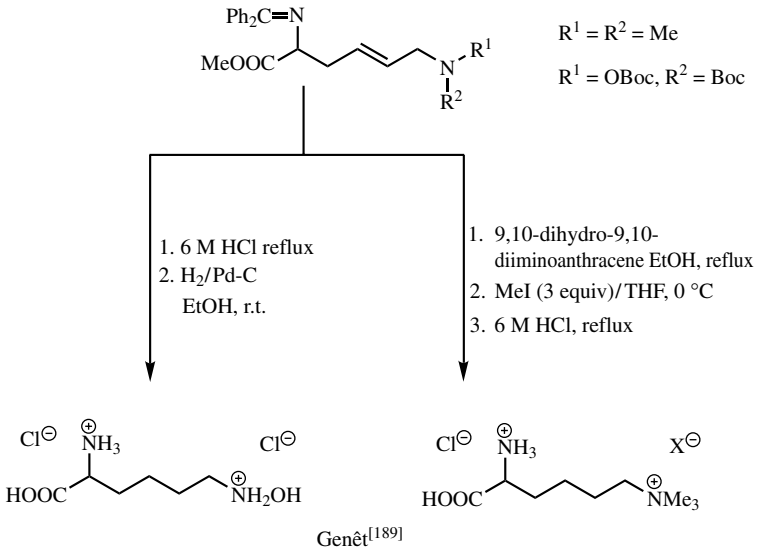
Scheme 20

The usefulness of glycine nucleophiles and nitrogen-based nucleophiles is shown in the preparation of racemic *N*-hydroxylysine and laminine by Genêt and co-workers[189] (**Scheme 21**).

2-Cyclopropylideneethanol carbonate (**Scheme 22**) reacts with many nitrogen and stabilized carbon nucleophiles, including benzophenone imine of ethyl glycinate.[190]

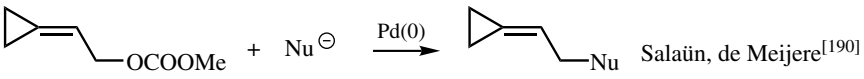


Scheme 21 (*Continued*)



Genêt[189]

Scheme 21



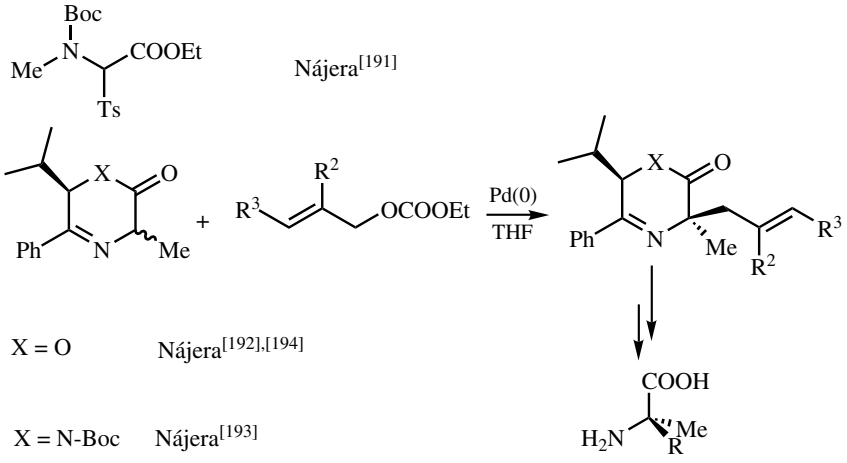
Salaün, de Meijere[190]

Nu⊖ = carbon and nitrogen based nucleophiles, $Ph_2C{=}N{-}CHLi{-}COOEt$

Scheme 22

Temporal activation of CH in N-protected glycine can be achieved by a tosyl group[191] (**Scheme 23**).

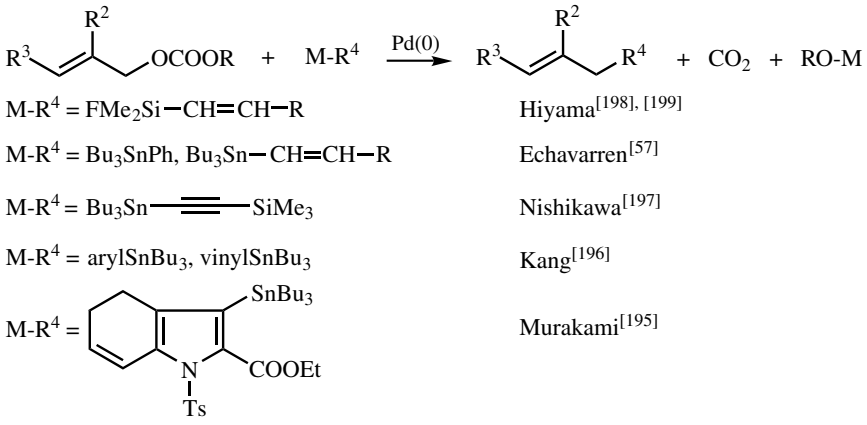
Excellent chemical yields and de values have been obtained in the allylation of heterocyclic amino acid precursors by Nájera[192]–[194] (**Scheme 23**). These reactions afford precursors of α,α-disubstituted glycines, which can be converted into the corresponding amino acids.



Scheme 23

C.iii. Allylation of Nonstabilized C-Nucleophiles

Reactions of allylic carbonates with nonstabilized C-nucleophiles are rather scarce. **Table 1** contains some examples of stereochemical studies performed with boron-based C-nucleophiles. Overall inversion (inversion + retention) is the result. However, these cases are under Ni catalysis.[67] Examples under Pd catalysis are in **Scheme 24**. Tin-based C-nucleophiles have been used more frequently,[57],[195]–[197] although examples of Si-based nucleophiles have also been reported.[198],[199] Phosphines are detrimental for the tin-based allylation.[57],[200]–[202]

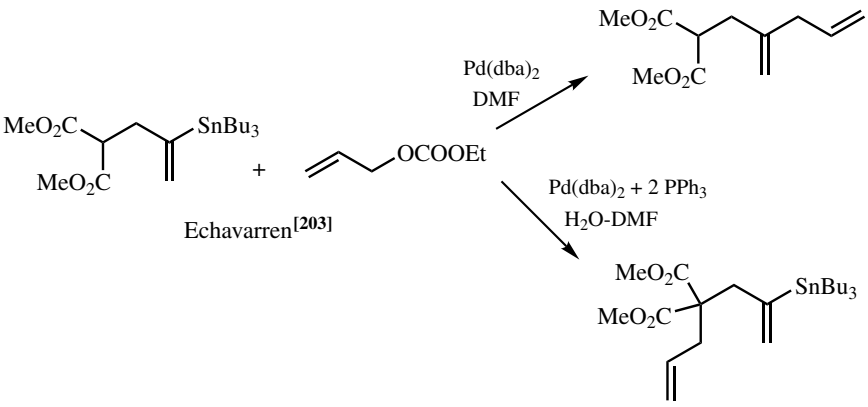


Scheme 24

This is consistent with the finding by Echavarren and co-workers on the regiodivergent pathways followed by vinyltin malonate of **Scheme 25** when treated with allyl carbonate in the absence and in the presence of triphenylphosphine.[203]

Couplings of 2,3-alkadienyl carbonates with organoboron compounds have been reported.[204]

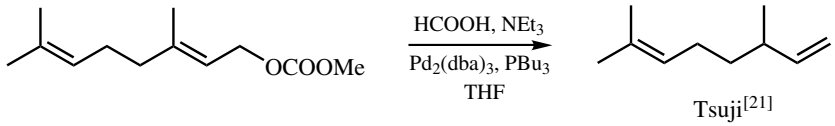
See also **Sect. J**.



Scheme 25

D. SYNTHETIC EQUIVALENTS OF HYDRIDE ION AS NUCLEOPHILES

This topic is covered in **Sect. V.2.3.1**. Therefore, only the role of carbonates will be emphasized here. The introduction of hydride as nucleophile produces the reduction of allylic carbonates, and therefore of allylic alcohols into alkenes. Tsuji and co-workers studied the synthetic possibilities very early,[20],[21] concluded that carbonates were better substrates than acetates, and observed that hydride attacks to the more substituted end of the allylic moiety. This is very useful to prepare the thermodynamically less stable 1-alkenes (**Scheme 26**). A good hydride source is formate anion, generated from formic acid and a tertiary amine, that is, triethylamine in many examples reported by Tsuji, who also suggested tributylphosphine as auxiliary ligand. The intermediate η^3-allylpalladium complex featuring formate as counteranion is postulated as intermediate in the reaction. Some stable formates have been isolated and shown to be ionic in the presence of enough ligand[62] (**Scheme 6**).



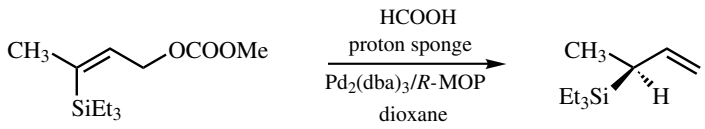
Tsuji[21]

Scheme 26

Tsuji's group developed synthetic applications as the elaboration of steroid side chains[205]–[208] and vitamin D_3 skeleton.[19],[209] The reduction occurs with overall inversion of configuration.[207],[209] Some reviews summarize these results.[210]–[212]

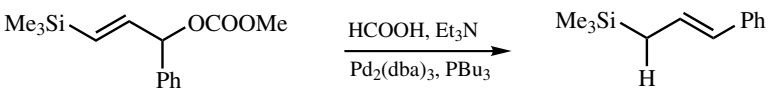
The group of Hayashi studied the asymmetric version of the Pd(0)-catalyzed hydride reduction of carbonates.[213]–[216]

Silicon effect is also evident in these reductions, and hydride incorporates with a regioselectivity different from other nucleophiles, at the allylic terminus bearing the silicon,[161],[162],[215] even if conjugation is lost (**Scheme 27**).



60% ee

Hayashi[215]



Tsuji[162]

Scheme 27

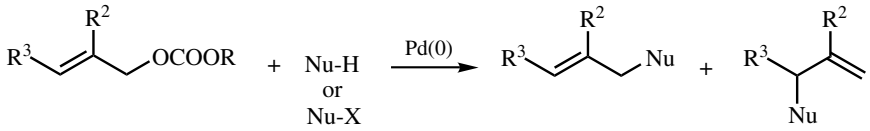
Other authors have used the combination of allylic carbonates with hydride sources,[217],[218] with particular success in syntheses of the natural pigment *dl*-shikonin[219] and of (+)-α-allokainic acid.[220] Reduction of allylic cyclic carbonates has been reported[221] (see **Sect. J**).

E. ALLYLATION OF N-NUCLEOPHILES

E.i. Allylation of N-Nucleophiles: General

The Pd-catalyzed allylation of heteroatom nucleophiles is covered in **Sect. V.2.2.1** for any leaving group.

Carbonates are clearly more versatile than acetates when nucleophiles are acidic. The general reaction is in **Scheme 28** and the N-nucleophiles are listed in **Table 2**. When reactions are performed in more or less polar aprotic solvents, the comments on relative acidities of **Sect. B** should be taken into account. Nucleophiles are divided in **Table 2** according to their pK_a, known or estimated, in DMSO. Basic nucleophiles such as aliphatic amines are less acidic than methanol or ethanol. Therefore, they are not deprotonated by alkoxide and they are nucleophilic as neutral species. Anilines are possibly on the borderline since aniline (pK_a (DMSO) = 30.6) is only slightly less acidic than methanol (pK_a (DMSO) = 29.0).[59] On the contrary, acidic nucleophiles require prior deprotonation by alkoxide.



Scheme 28

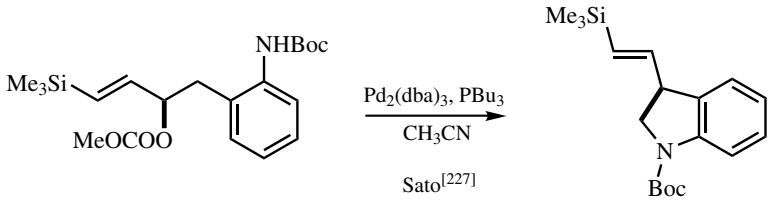
Benzylamine reacts with overall retention with the carbonate of cyclic terpene carveol.[222] Many more examples of the use of allylic carbonates in Pd(0)-catalyzed allylation of primary and secondary aliphatic amines have been reported (**Table 2**), many for them in the search for good asymmetric induction.[121],[223]–[233] A process for the preparation of *N*-allylpiperidines including the use of allylic carbonates under Pd(0)-catalysis has been patented.[234]

Anilines have received less attention.[65] At the other side of the acidity spectrum, nitroanilines,[65] arenesulfonamides,[69] and azapurines[70],[71] react also with overall retention of configuration.

Other acidic N-nucleophiles successfully allylated by carbonates include synthetic equivalents of ammonia,[115],[116],[235],[236] hydroxylamine,[189],[237]–[239] and hydrazine,[228] cyanamide,[69] diarylamines,[65] sulfamide,[69] arenesulfonamides[225],[227],[228],[240]–[242] (see also **Scheme 33**[122]), a glutarimide derivative,[226] trimethylsilyl azide,[243]–[245] and amino esters activated at the nitrogen atom with an electron-withdrawing group.[246]

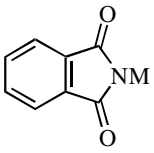
Silicon effect has been observed.[227] We have selected the example of **Scheme 29**, for which it could be argued that other reasons, apart from the silicon effect, could militate in favor of a five-membered ring in front of a seven-membered ring. However, in intermolecular reactions the silicon effect is evident.[227]

See also Sects. **C.ii**, **F.ii**, **I**, **J**, **L**, **N**, **Q.i**, and **Q.ii**.



Scheme 29

TABLE 2. Nitrogen-Based Nucleophiles Reported to React with Allylic Carbonates

Basic Nucleophile	Researcher	Observations
$PhCH_2NH_2$	Trost[222]	Overall retention
	Hayashi, Ito[225]	Asymmetric substitution; also other benzylamines
	Sato[227]	Silicon effect
	Pfaltz, Helmchen[228]	Asymmetric substituion
	Togni[229]–[231]	Asymmetric substitution
	Buono[232]	Asymmetric substitution; also veratrylamine
	Evans[121]	Asymmetric substitution
$BuNH_2$	Takinaga[224]	
Piperidine	Nwokogu[223]	
Piperazines	Kuo[226]	Preparation of buspirone and gepirone
H_2NCHR^1COOMe	Trost[233]	
Anilines	Moreno-Mañas[65]	4-Methyl and 2,6-dimethylaniline
Acidic Nucleophile	**Researcher**	**Observations**
$(Boc)_2NH$	Ito[235]	Asymmetric substitution
	Cacchi[236]	
	Trost[115],[116]	Asymmetric substitution
M = Na, K		
BocO—NHBoc		Genêt[189],[237]
	Öhler[238,239]	
AcO-NHAc	Öhler[238]	Preparation of phosphonic acids
PhCON**H$_2$**	Pfaltz, Helmchen[228]	Asymmetric substitution; sodium salt
Nitroanilines	Moreno-Mañas[65]	Overall retention
NC—NH_2	Moreno-Mañas[69]	Overall retention
Diarylamines	Moreno-Mañas[65]	
Arylsulfonamides	Hayashi, Ito[225]	Asymmetric substitution
	Sato[227]	Silicon effect
	Pfaltz, Helmchen[228]	Asymmetric substitution; sodium salt
	Mori[240]	Synthesis of mesembrane and mesembrine
	Mori[241]	Synthesis of amaryllidaceae alkaloids
	Nakai[122]	Remote asymmetric induction

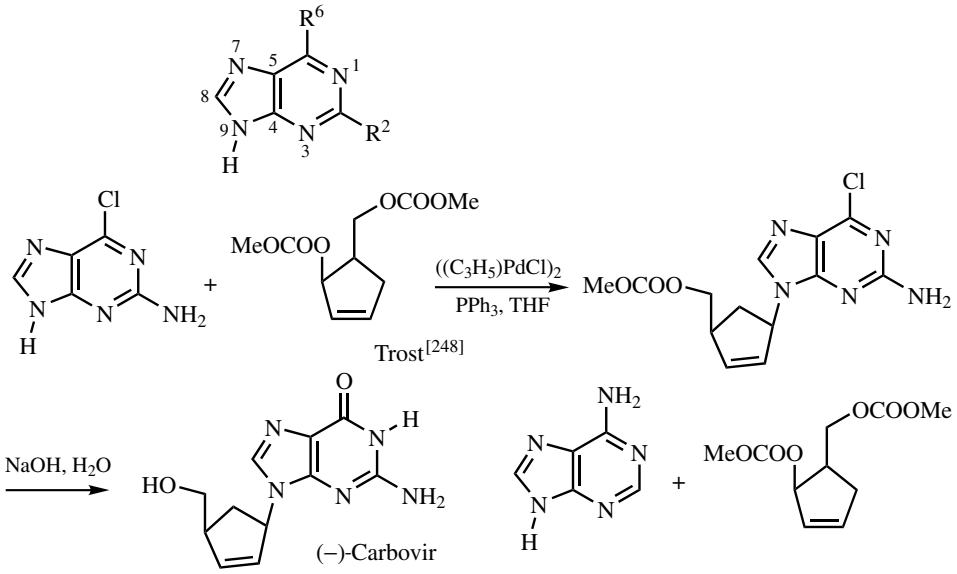
(*Continued*)

TABLE 2. (*Continued*)

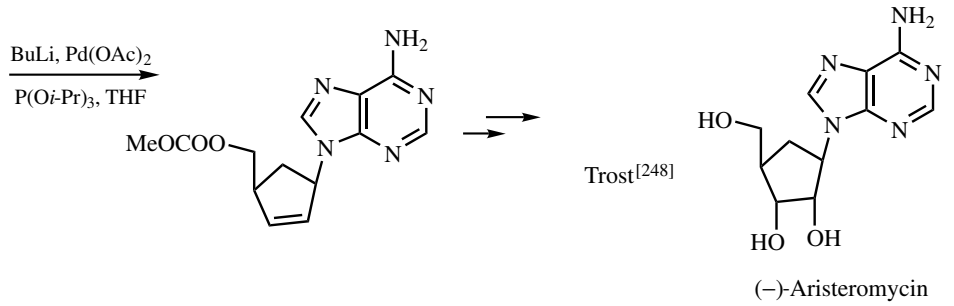
Basic Nucleophile	Researcher	Observations
	Moreno-Mañas[69]	Overall retention
	Trost[242]	Intramolecular; synthesis of alkaloid anatoxin-a
$H_2N\text{-}SO_2\text{-}NH_2$	Moreno-Mañas[69]	
Azapurines	Vince[70]	Overall retention; sodium salt
	Vince[71]	Preparation of carbanucleosides
Glutarimides	Kuo[226]	Preparation of buspirone and gepirone
$ZNH\text{-}CHR^1\text{-}COOR$	Kazmaier[246]	Z = CF_3CO—, 4-$MeC_6H_4SO_2$—
$N_3\text{-}SiMe_3$	Sinou[243]	
	Trost[245]	Asymmetric substitution
	Trost[244]	Asymmetric substitution; synthesis of (+)-pancratistatin

E.ii. Preparation of Carbanucleosides

Pd(0)-catalyzed allylation of purine derivatives with cyclopentenol esters and other alicyclic allylic esters is a key step in the preparation of natural and unnatural carbanucleosides with antiviral activity.[247] Carbanucleosides cannot be hydrolyzed as conventional nucleosides are since the anomeric carbon atom is absent; therefore, their activity and stability render carbanucleosides valuable compounds. Although much work has been performed with allylic acetates, a few examples of the application of allylic carbonates in carbanucleoside synthesis have been reported and their number will increase in the future. Two earlier examples by Trost and co-workers[248] are in **Scheme 30**, including the numbering system of the purine skeleton. Other examples refer to more couplings of purines with five-membered rings[249]–[252] or with six-membered rings.[70],[71],[253]



Scheme 30 (*Continued*)



Scheme 30

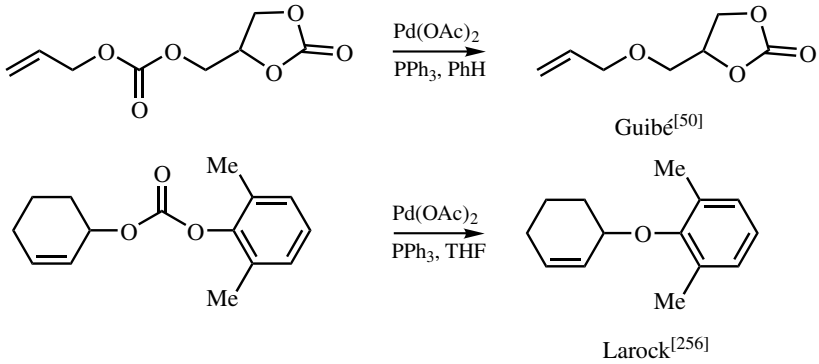
Purines are in general regioselectively allylated at N-9, although sometimes minor amounts of products of reaction at N-7 have been isolated. Other examples of ambident nucleophiles will be dealt with in **Sect. H**.

For more carbanucleosides see also **Sects. J** and **Q.i**.

F. ALLYLATION OF O-NUCLEOPHILES

F.i. Allylation of O-Nucleophiles: General

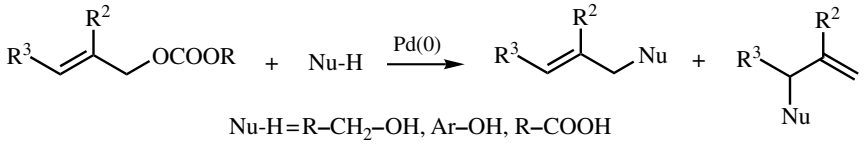
The pioneering work by Guibé and Saint M'Leux described the Pd-catalyzed extrusion of CO_2 from an alkyl allyl carbonate to afford the corresponding ether[50] (**Scheme 31**). The alkoxide formed in the mechanistic cycle (**Scheme 1**), in the absence of any pronucleophile, acts itself as the nucleophile, attacking the cationic η^3-allylpalladium complex. Applications to the preparation of allyl aryl ethers were reported later.[254]–[256] The formation of allyl aryl ethers occurs with overall retention of configuration.[256]



Scheme 31

Three types of simple O-nucleophiles have been reported to react with allyl carbonates under Pd catalysis (**Scheme 32**, **Table 3**): carboxylates[72] and carbamic acid conjugate base,[257] phenols,[73],[258]–[267] and alcohols.[122],[261],[268],[269] As previously stated allylation of nucleophiles with allylic carbonates can be performed in the absence of base, and the total amount of real nucleophile present at any moment in the reaction medium cannot be higher than the amount of palladium added. However, in asymmetric reactions it is sometimes

advisable to work with an equivalent of the actual nucleophile, that is, the conjugate base of carboxylic acid,[72] of phenol,[265] or of others (**Table 3**). The reason is that there are mechanisms for isomerization of the η^3-allylpalladium complex, which compromise the stereochemical outcome of the reaction. **Scheme 9** contains only some of the mechanistic pathways of isomerization, but in open-chain compounds there is still another one: *syn–anti* isomerization of complexes, which does not operate in six-membered cyclic systems. A higher initial concentration of actual nucleophile increases its rate of reaction with the *initially* formed η^3-allylpalladium complex, minimizing the isomerization of the last.



Scheme 32

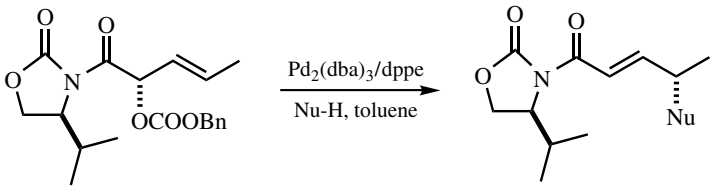
Phenols are more acidic than alcohols and therefore successful Pd-catalyzed allylation of phenols with allylic carbonates is common (**Table 3**). The situation with alcohols is different since the acidity of the pronucleophile alcohol is similar to the acidity of methanol or ethanol. However, good intramolecular versions have been reported in syntheses of vinyltetrahydrofurans[269] and of linalyl oxides.[268] The use of carbonates of alkyl allyl alcohols in which the alkyl part is coherent with the pronucleophile is particularly successful, as shown in the remote asymmetric induction[122] of **Scheme 33**.

See also **Sects. F.ii.**, **I**, **J**, **L**, and **Q.i**.

Nickel(0) has met with some success in the allylation of stabilized nucleophiles and phenols with allylic carbonates.[174]

TABLE 3. Oxygen-Based Nucleophiles Reported to React with Allylic Carbonates

O-Nucleophile	Researcher	Observations
R-COOH	Trost[72]	Asymmetric reaction; sodium salt
RNHCOOTBDMS	Ohfune[257]	Intramolecular; under fluoride action
Ar-OH	Sinou[258]	Scope and limitations
	Shaikh[259]	Bisphenols
	Sinou[73]	Phenols, β-naphthol; overall retention
	Achiwa[260]	Intramolecular version; asymmetric reaction
	Sinou[261]	Asymmetric reaction
	Trost[262]	Asymmetric reaction; reversed regioselectivity
	Cacchi[263]	Reversible allylation
	Nishiyama[264]	Asymmetric reaction; overall retention
	Trost[265]	Asymmetric reaction: cesium salt
	Trost[266]	Asymmetric reaction; effect of Bu_4NCl
	Sinou[267]	Intramolecular version
RCH_2OH	Sinou[261]	R = Ph, asymmetric reaction
	Sinou[268]	Intramolecular version; linalyl oxides
	Sinou[269]	Intramolecular version
	Nakai[122]	Overall retention; alcohol coherent with carbonate

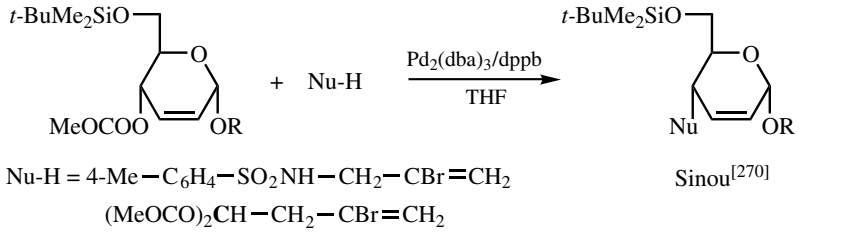


Nu-H = $CH_2(COOMe)_2$, $PhCH_2OH$, Ts-NH_2 Nakai[122]

Scheme 33

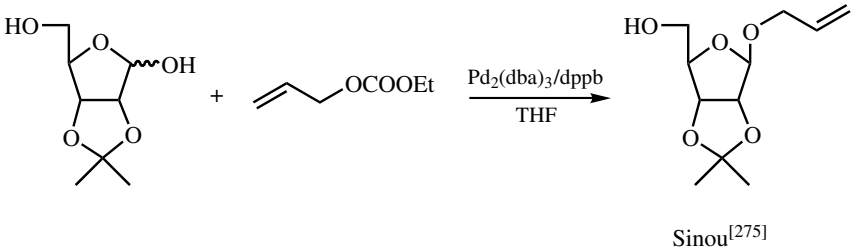
F.ii. O-Allylations in Carbohydrate Chemistry

Pd(0)-catalyzed O-allylation based on carbonates has been particularly successful in carbohydrate chemistry, mainly due to the contribution by Sinou's group. The allyl moiety can be situated in the carbohydrate, which is therefore the electrophilic partner, as in the first example[270] of **Scheme 34**. Note the clear-cut retention of configuration for stabilized carbon and acidic nitrogen nucleophiles. Other examples have been reported.[271]–[274]

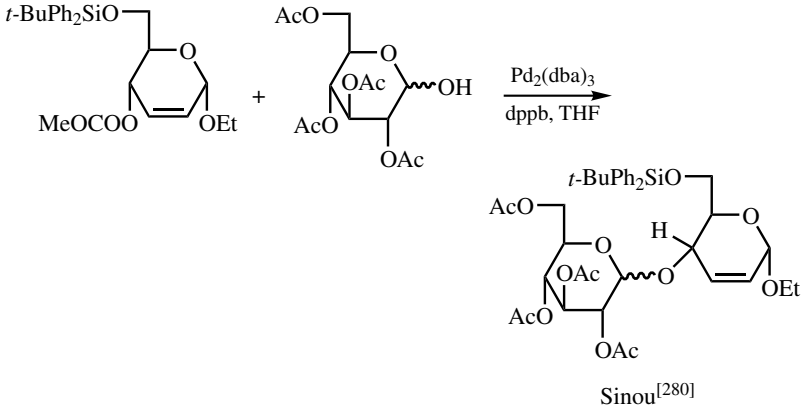


Nu-H = 4-Me$-C_6H_4-SO_2NH-CH_2-CBr=CH_2$

$(MeOCO)_2CH-CH_2-CBr=CH_2$ Sinou[270]



Sinou[275]



Sinou[280]

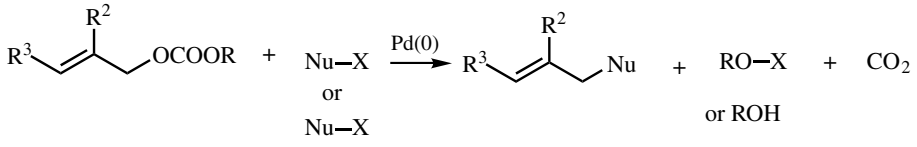
Scheme 34

A free OH group of the carbohydrate can be the nucleophilic partner. Although in theory similar acidities for several OH groups could give rise to nonspecific processes, in practice the reactions such as the second example[275] of **Scheme 34** work properly, with the following order of reactivity: anomeric OH > primary OH > secondary OH. Addition of excess allyl carbonate is sometimes advisable.[275]–[279]

Particularly interesting is the combination of electrophile and nucleophile both in carbohydrate skeletons as in the third example[280] of **Scheme 34**. Disaccharides and even trisaccharides have been prepared by this method.[280]–[283]

G. ALLYLATION OF S-NUCLEOPHILES

It is remarkable that sulfur nucleophiles are compatible with Pd(0) catalysts, and several examples of allylation of S-nucleophiles with allylic carbonates have been reported (**Scheme 35**, **Table 4**). The nucleophiles are of three types: alkyl and arylthiols,[74],[75],[284]–[287] sodium and lithium sulfinates,[76],[115],[286],[288] and thioacetate.[289],[290] In one case overall retention has been confirmed.[74]
See also **Sects. J** and **Q.ii**.

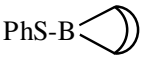


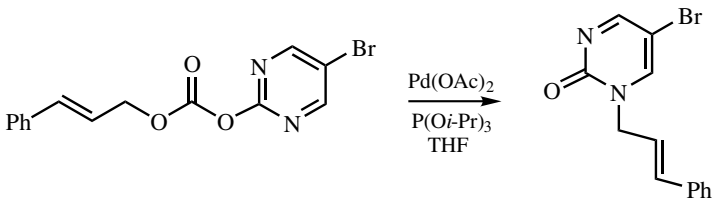
Scheme 35

H. ALLYLATION OF AMBIDENT NUCLEOPHILES

In 1993 Undheim and co-workers reported the Pd(0)-catalyzed extrusion of CO_2 from the arbonate of **Scheme 36**.[291] This reaction is similar to the formation of allyl aryl ethers by extrusion of CO_2 from allyl aryl carbonates (**Scheme 31**). However, allylation at nitrogen instead of at oxygen occurs here. The nucleophilic conjugate base of 2-hydroxypyrimidine or 2-pyrimidin-2-one is an ambident nucleophile (N versus O).

TABLE 4. Sulfur-Based Nucleophiles Reported to React with Allylic Carbonates

S-Nucleophile	Researcher	Observations
$RS\text{-}SiMe_3$	Trost[74]	R = Ph, Et; overall retention
t-BuS-$SiMe_3$	Gais[286]	Asymmetric reaction
	Miyaura[285]	
PhS-B 		
Ar-SH	Sinou[75],[284]	
R-SH	Gais[287]	Asymmetric reaction
$ArSO_2Na$	Trost[76],[115]	Ar = Ph; asymmetric reaction
	Trost[288]	Asymmetric reaction
t-$BuSO_2Li$	Gais[286]	Asymmetric reaction
CH_3COSK	Sinou[289]	
	Sinou[290]	Asymmetric reaction

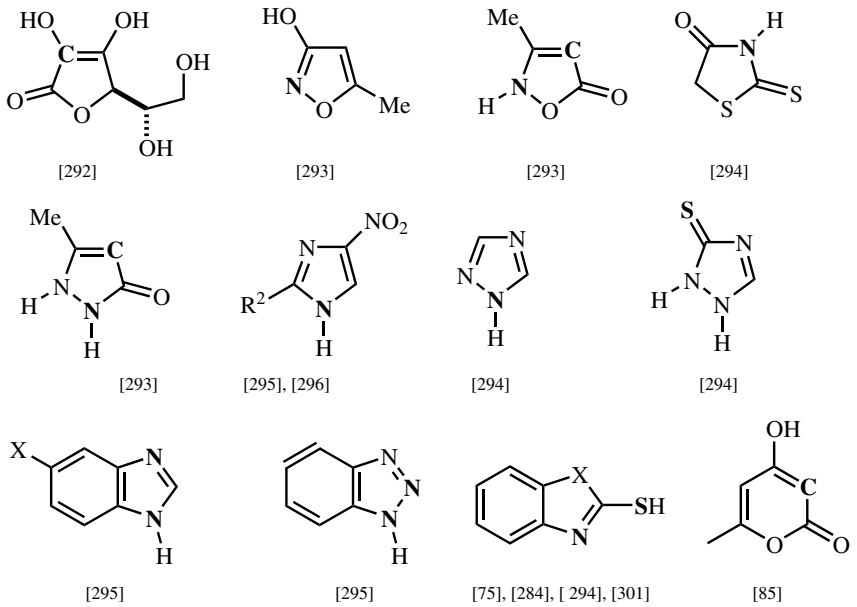


Undheim[291]

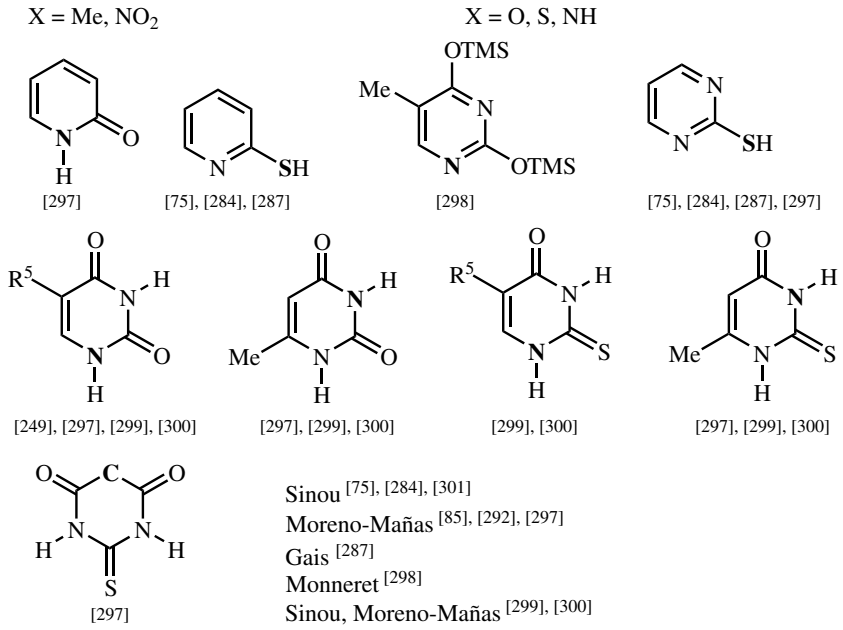
Scheme 36

Many Pd(0)-catalyzed allylations of ambident nucleophiles derived by deprotonation of heterocyclic aromatic rings have been described, and a review covering all possible leaving groups has been published.[247] We use the term aromatic so as to include all heterocycles for which a tautomeric or a resonant form can be written, fulfilling the classical Hückel rule of $4n + 2$ cyclically conjugated π electrons. Many of these heterocycles are more acidic than usual alcohols, and therefore they are ideal substrates to react with allylic carbonates under Pd(0) catalysis. The regioselectivity is defined either by kinetic control or by thermodynamic control. In many instances both types of control favor the same regioisomer; the regioisomer formed faster is also the more stable. However, in a few cases this is not so (N versus S).

Heterocycles alkylated by allylic carbonates are shown in **Scheme 37**. The reactive atom is in bold type. The following general preferences are observed when both atoms are connected: C > N, C > O, N > O. For pyrimidine bases N-1 > N-3 unless N-1 is sterically hindered, as in 6-methyluracil (N-3 preferred).

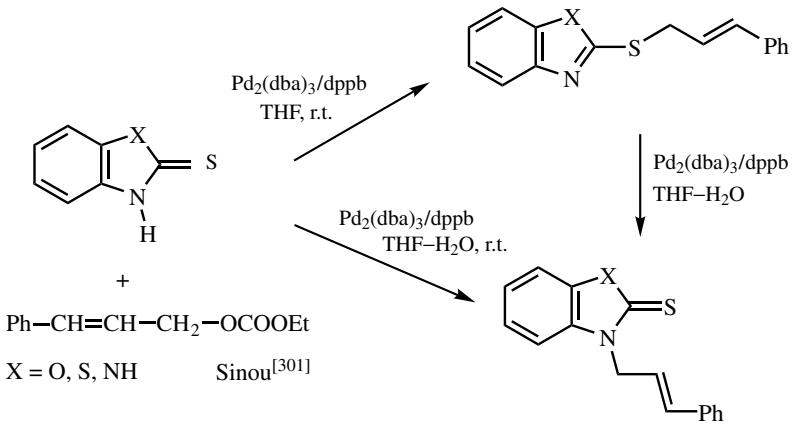


Scheme 37 (*Continued*)

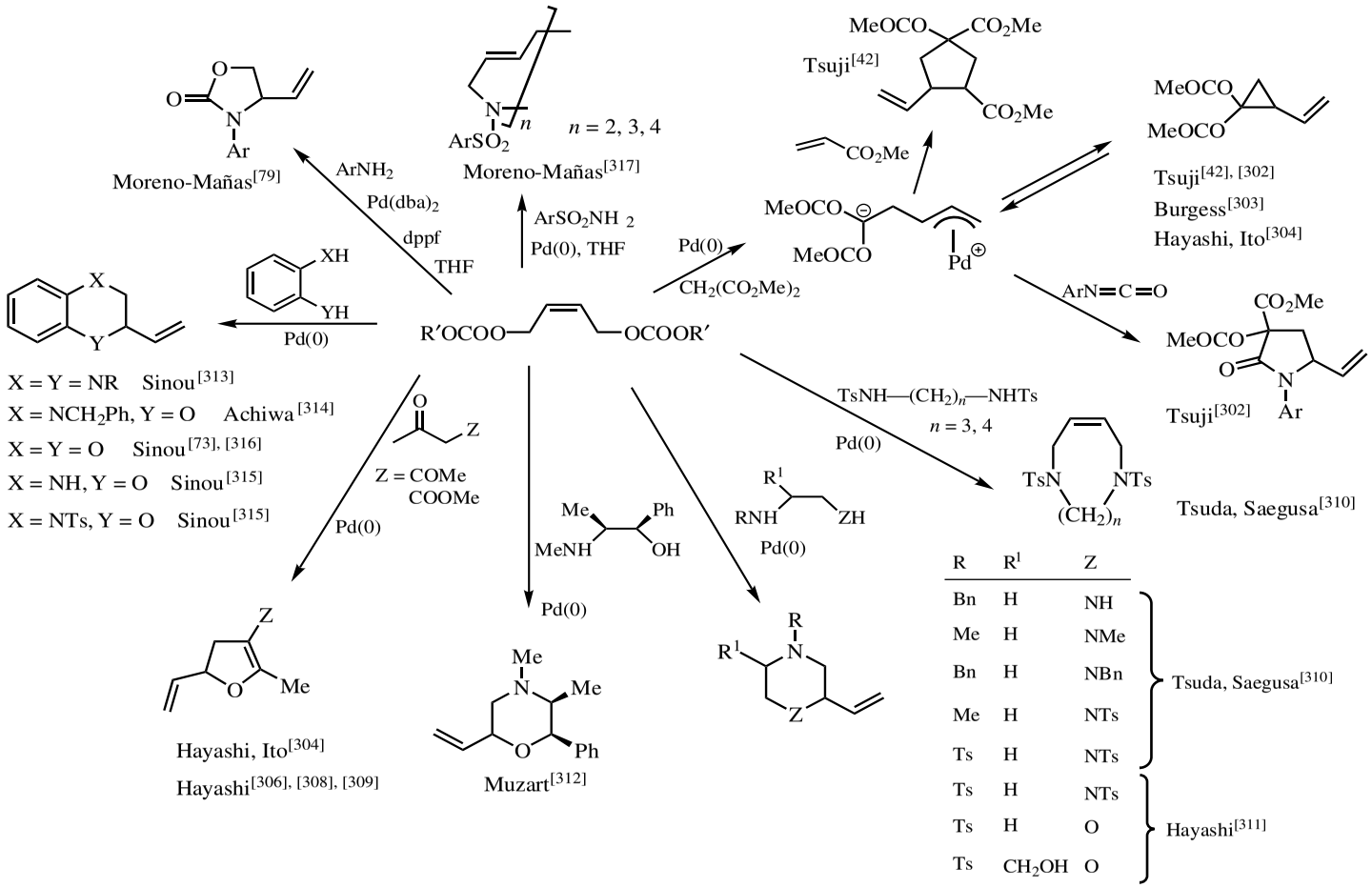


Scheme 37

When both N and S centers are present in the ambident nucleophile the situation is less clear-cut. Frequently, the kinetically controlled S-allylated compound is isolated. However, in some cases the thermodynamically controlled N-allylated product is regioselectively formed. Since the heterocycles are acidic, their conjugate bases are leaving groups, and some allylations are reversible. A case in point is the regioselectivity control for 2-mercaptobenzoxazole, benzothiazole, and benzimidazole reported by Sinou and co-workers either by forcing experimental conditions or by changing the solvent system.[301] It is remarkable the effect of water as reaction medium. Moreover, the S-allyl compounds are isomerized to the N-allyl regioisomers under Pd(0) catalysis in THF–water solvent (**Scheme 38**). Similar solvent effects on the regioselectivity have been found for uracils and thiouracils.[299],[300]



Scheme 38


Moreno-Mañas[79]
ArNH2
Pd(dba)2
dppf
THF
Moreno-Mañas[317]
n = 2, 3, 4
ArSO2NH 2
Pd(0), THF
Tsuji[42]
Pd(0)
CH2(CO2Me)2
Tsuji[42], [302]
Burgess[303]
Hayashi, Ito[304]
ArN=C=O
Tsuji[302]
X = Y = NR Sinou[313]
X = NCH2Ph, Y = O Achiwa[314]
X = Y = O Sinou[73], [316]
X = NH, Y = O Sinou[315]
X = NTs, Y = O Sinou[315]
Pd(0)
R′OCOO OCOOR′
TsNH—(CH2)n—NHTs
n = 3, 4
Pd(0)
Tsuda, Saegusa[310]
Z = COMe
COOMe
Pd(0)
Pd(0)
Pd(0)
Hayashi, Ito[304]
Hayashi[306], [308], [309]
Muzart[312]
R Z
Bn H NH
Me H NMe
Bn H NBn
Me H NTs
Ts H NTs
Tsuda, Saegusa[310]
Ts H NTs
Ts H O
Ts CH2OH O
Hayashi[311]

Scheme 39

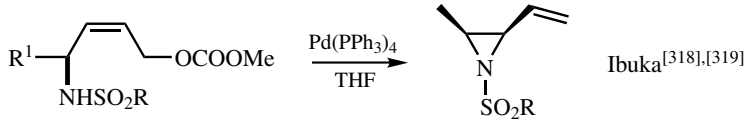
I. PALLADIUM(0)-CATALYZED REACTIONS OF ALLYLIC DIOL DICARBONATES

cis-1,4-Butenediol is commercially available and Pd(0)-catalyzed nucleophilic substitutions on its esters have been studied extensively. Attack by nucleophiles at the terminal carbon atom is followed by formation of the second η^3-allylpalladium complex. If nucleophiles are bifunctional, cycles of different sizes are formed (**Scheme 39**). **Scheme 39** contains only examples based on the more simple unsubstituted 2-butene-1,4-diol, by far the most extensively studied. Other examples will be mentioned separately.

Thus, reaction of the dicarbonate with malonate produces vinylcyclopropanes as reported by Tsuji and co-workers[42] in the early times of Pd/carbonates chemistry. Formation of cyclopropanes is reversible under Pd(0) catalysis and further cycloadditions with electronically poor olefins[42] or aryl isocyanates[302] were reported. This will be discussed in **Sect. L**. Other authors have also prepared vinylcyclopropanes,[303],[304] including a report by Trost and co-workers on a more complicated acyclic dicarbonate.[305] If the β-dicarbonylic nucleophile is enolizable, 5-vinyldihydrofurans are formed.[304],[306]–[309] 1,4-Dinucleophiles such as 1,2-diamines or 1,2-aminodiols produce vinylpiperazines[310],[311] or vinylmorpholines.[311],[312] Hayashi and co-workers have reported the same results in the formation of vinylmorpholines using either the *Z* or the *E* dicarbonates.[311] Equilibration at the cationic complex level is responsible for these results. *ortho*-Diaminobenzenes and *ortho*-aminophenols produce the vinylbenzopiperazines[313] and vinylbenzomorpholines,[314],[315] whereas *ortho*-diphenols give rise to vinylbenzo-1,4-dioxane.[73],[316] Note that the vinyl group appears always in the position adjacent to the less nucleophilic atom of the initial dinucleophile, that is, the atom that attacks second. Curiously, seven- and eight-membered rings maintaining *cis* stereochemistry are formed when 1,3-propanediamine and 1,4-butanediamine ditosylates react with the dicarbonate.[310]

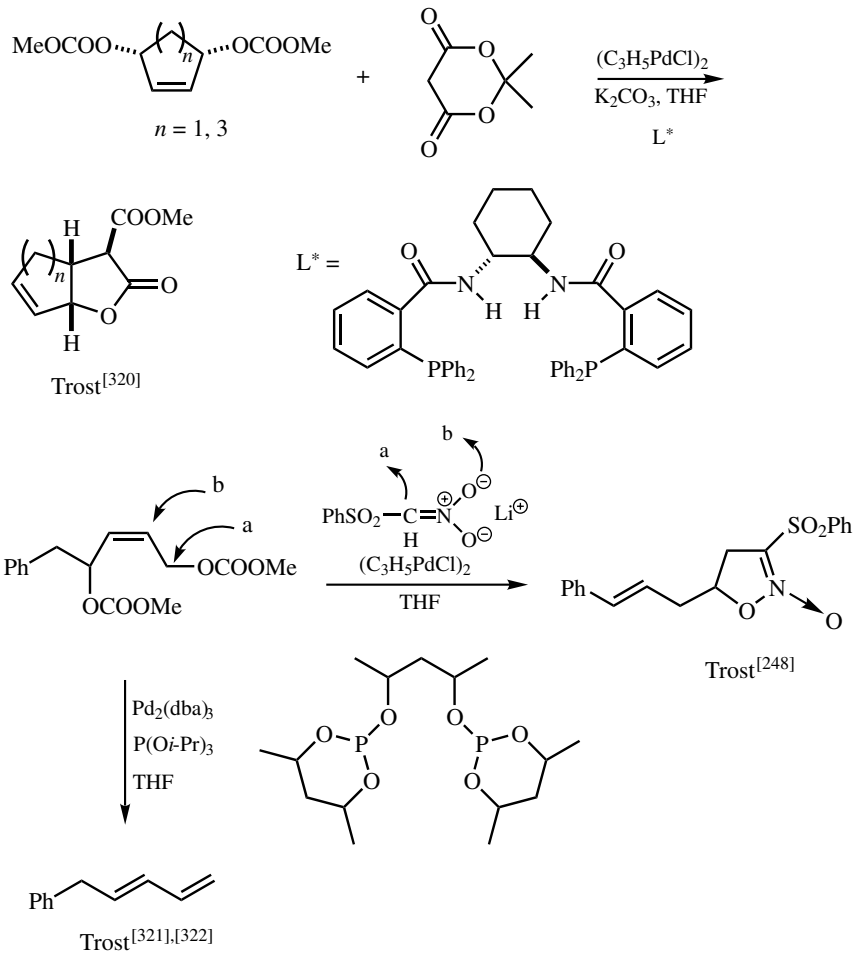
The reaction of the dicarbonate with acidic anilines produces 3-aryl-4-vinyloxazolidine-2-ones.[79] Finally 10-, 15-, and 20-membered rings have been isolated in the reaction of arenesulfonamides with the butene-1,4-diol dicarbonate, and higher rings have been detected by mass spectrometry techniques.[317] In these reactions a stable Pd(0) complex of the 15-membered ring is isolated, and cyclic monomeric compounds are always accompanied by polymeric material.

A related case (**Scheme 40**) is the intramolecular reaction of butene-1,4-aminoalcohol derivative bearing an electron-withdrawing group at nitrogen, to afford vinylaziridines.[318],[319] Note that *cis*-2,3-disubstituted aziridines are more stable than the *trans* isomers and that vinylaziridine formation is reversible under Pd(0) catalysis.



Scheme 40

Scheme 41 summarizes three different reactivities of 1,4-diol dicarbonates reported by Trost and co-workers. Thus, bicyclic butanolides are formed with high ee from *meso*

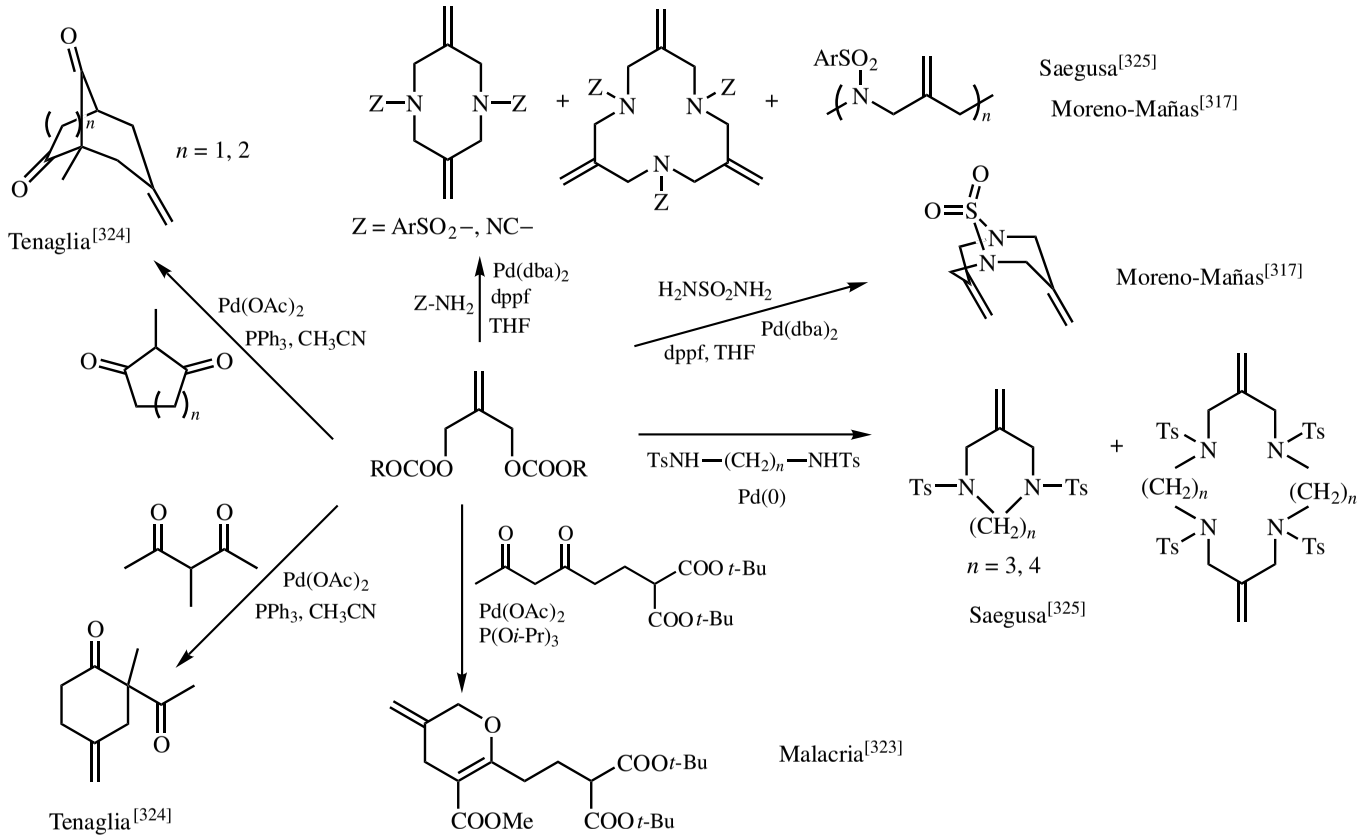


Scheme 41

cyclic 1,4-diols.[320] Related work has been published by Suh and co-workers[139] Another cyclization affording isoxazoline *N*-oxides requires the lithium salt of phenylsulfonylnitromethane.[248] A less exploited reactivity of dicarbonates of 1,4-diols is the reductive elimination to afford dienes.[321],[322]

2-Methylene-1,3-diol esters have been less studied, but they produce interesting results summarized in **Scheme 42**. β-Ketoesters afford six-membered cyclic enol ether as shown by Malacria and co-workers[323] However, Buono and Tenaglia have studied stabilized nucleophiles possessing only one intercarbonilic proton. In these cases the carbon atom in *alpha* position to only one carbonyl group acts as second nucleophile.[324]

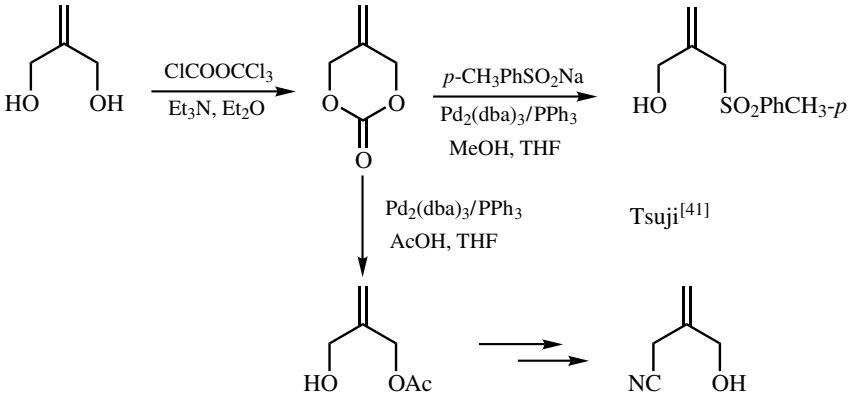
Sulfamide produces a dimethylene bicyclic sulfamide featuring the [3.3.0] skeleton,[317] whereas arenesulfonamides produce 8- and 12-membered rings with methylene substituents.[317] Polymers are formed in the reactions of sulfonamides, and conditions have been reported that favor the polymers.[325] Bisarenesulfonamides also produce polymers.[325] Note that all compounds of **Scheme 42** possess methylene groups as substituents.


n = 1, 2
Tenaglia[324]
Z = ArSO2−, NC−
Saegusa[325]
Moreno-Mañas[317]
Moreno-Mañas[317]
Pd(OAc)2
PPh3, CH3CN
Z-NH2
Pd(dba)2
dppf
THF
H2NSO2NH2
Pd(dba)2
dppf, THF
ROCOO
OCOOR
TsNH—(CH2)n—NHTs
Pd(0)
n = 3, 4
Saegusa[325]
Pd(OAc)2
PPh3, CH3CN
Pd(OAc)2
P(Oi-Pr)3
COO t-Bu
COO t-Bu
Malacria[323]
COOt-Bu
COOMe
COO t-Bu
Tenaglia[324]

Scheme 42

J. PALLADIUM(0)-CATALYZED REACTIONS OF ALLYLIC CYCLIC CARBONATES

Several types of cyclic carbonates have been used in Pd(0) chemistry. They will be treated separately. Perhaps the most simple case is the cyclic carbonate of 2-methylene-1,3-diol (**Scheme 43**). Tsuji and co-workers[41] and Breuilles and Uguen[326] used this compound to activate one alcohol function toward substitution while protecting the other. Note that dicarbonate of the same diol activates both alcohols (**Scheme 42**).



Scheme 43

The reaction of cyclic carbonate of 3-cyclohexen-1,2-diol with sodium malonate was announced in 1981 by Trost and Runge[53] as already commented in **Sect. A** (**Scheme 44**).

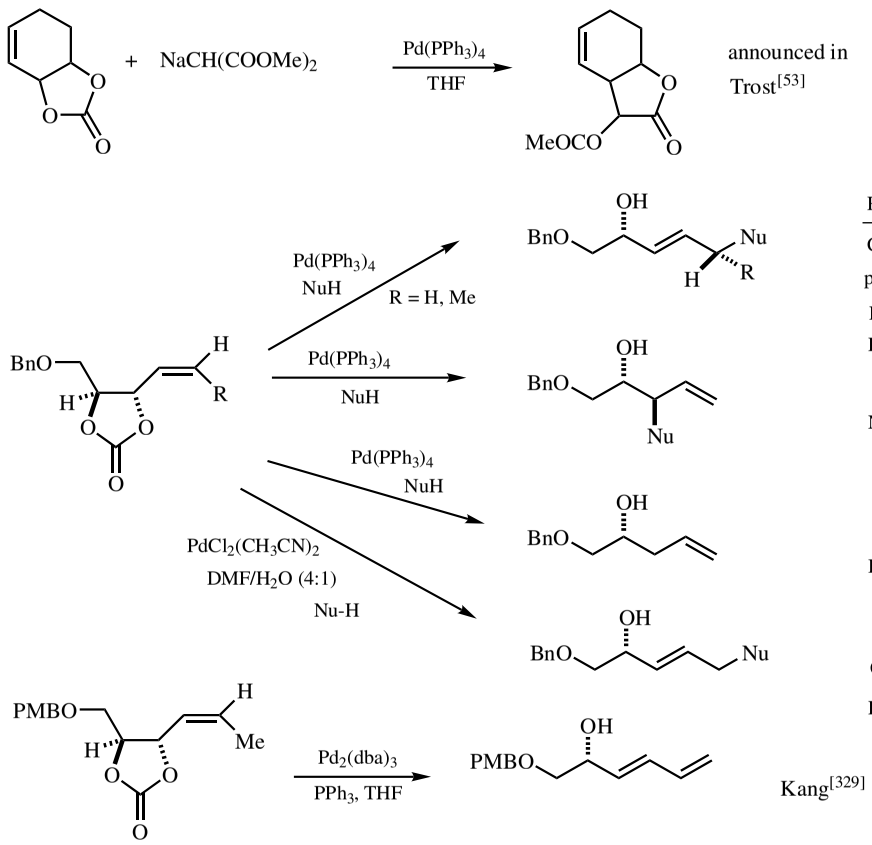
Kang and co-workers have reported reactions of open-chain vinyl-substituted cyclic carbonates with many stabilized and nonstabilized carbon nucleophiles,[327] heteroatom nucleophiles,[327],[328] hydride equivalent,[221] and vinyl and aryltin reagents.[196] Retention of configuration has been observed for malonate, for thiophenolate, and for the conjugate base of phthalimide. In the absence of nucleophile a proton elimination ensues[329] (**Scheme 44**). The reaction with iodobenzene produces a reductive ring opening by a variant of the Heck reaction.[330]

One method to prepare cyclic carbonates of the structural type shown in **Scheme 44** is by direct reaction of 1,2-diols with a phosgene synthetic equivalent, but they can also be prepared by Pd(0)-catalyzed reaction of vinylepoxides with carbon dioxide.[331] Trost and Granja have found that the behavior of vinylepoxides and their related carbonates in Pd(0)-catalyzed allylations is different from the stereochemical viewpoint.[332]

Conversion of cyclic carbonates into unsaturated aldehydes (**Scheme 45**) requires acetic acid as solvent to protonate the intermediate alkoxide. The more acidic protons for elimination from the intermediate are now those in the —CH_2OH group.[333]

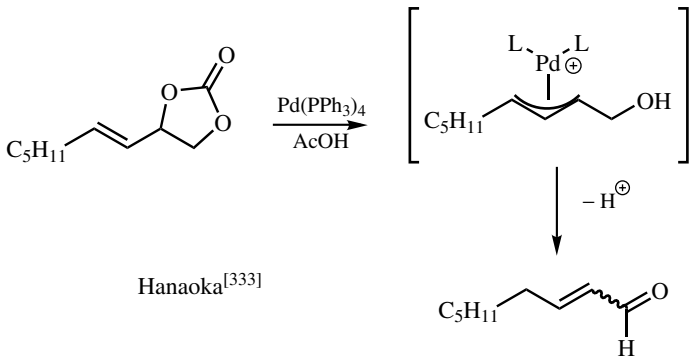
Six-membered cyclic carbonates of the 1,3-dioxane type have found applications in the preparation of carbanucleosides[251],[334] (**Scheme 46**).

Tamaru and co-workers have studied the opening of 4-vinyl-1,3-dioxan-2-ones in the presence of isocyanates. Cyclic carbamates of *trans* stereochemistry are formed under thermodynamic control if a substituent is in C-5.[335],[336] Similar results have been reported by Trost and Van Vranken[337]



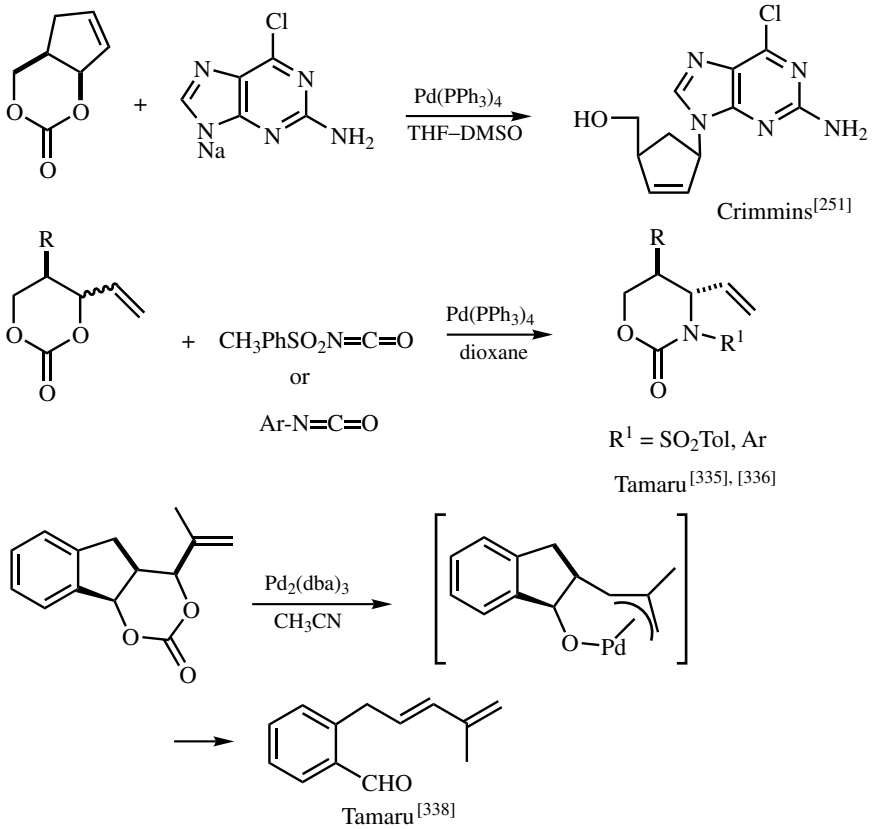
Representative NuH	
$CH_2(COOEt)_2$	Kang[327]
phthalimide	Kang[327]
$PhOH/NEt_3$	Kang[328]
$PhSO_2Na$	Kang[328]
NaSPh	Kang[328]
$HCOONH_4$	Kang[221]
CH_2=CH—$SnBu_3$	Kang[196]
$PhSnBu_3$	Kang[196]

Scheme 44



Hanaoka[333]

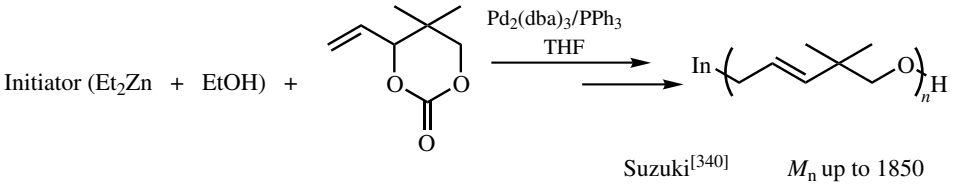
Scheme 45



Scheme 46

A variant produces aldehydes by cleavage of a C—C bond of the six-membered carbonate.[338] The complexities of the reactivity of these substrates have been discussed.[339]

Polymerization of cyclic six-membered vinylcarbonates occurs under Pd(0) catalysis. The initiator is a mixture of Et_2Zn and ethanol. Liberation of CO_2 produces the alkoxide that attacks the cationic complex of the next molecule[340] (**Scheme 47**).

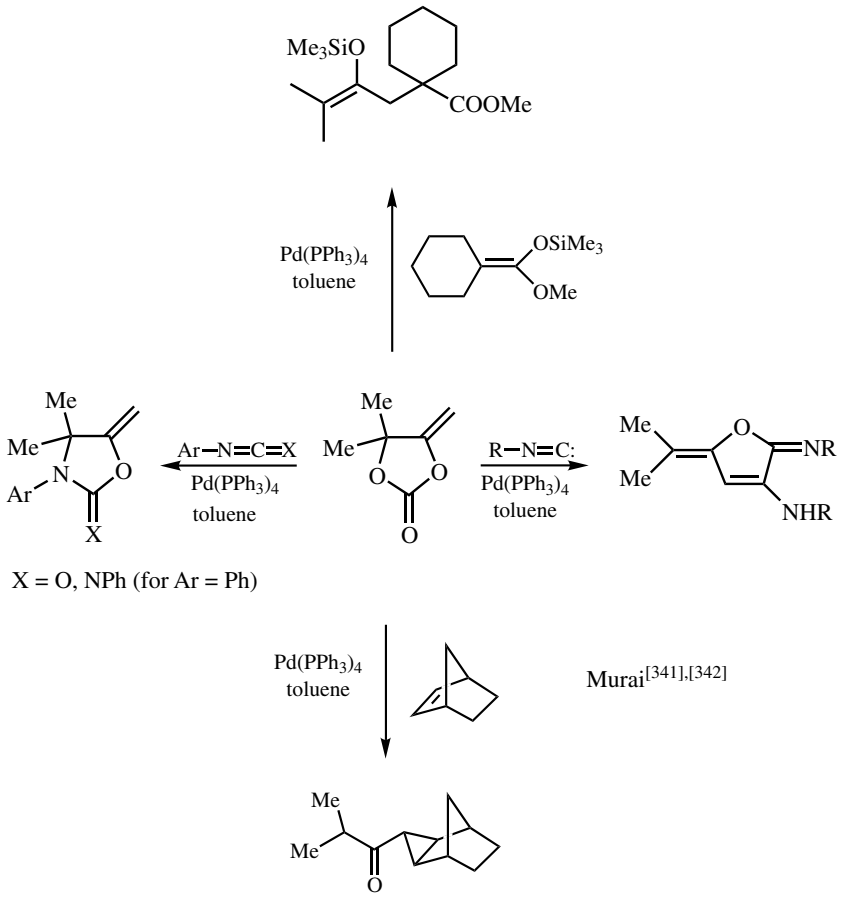


Scheme 47

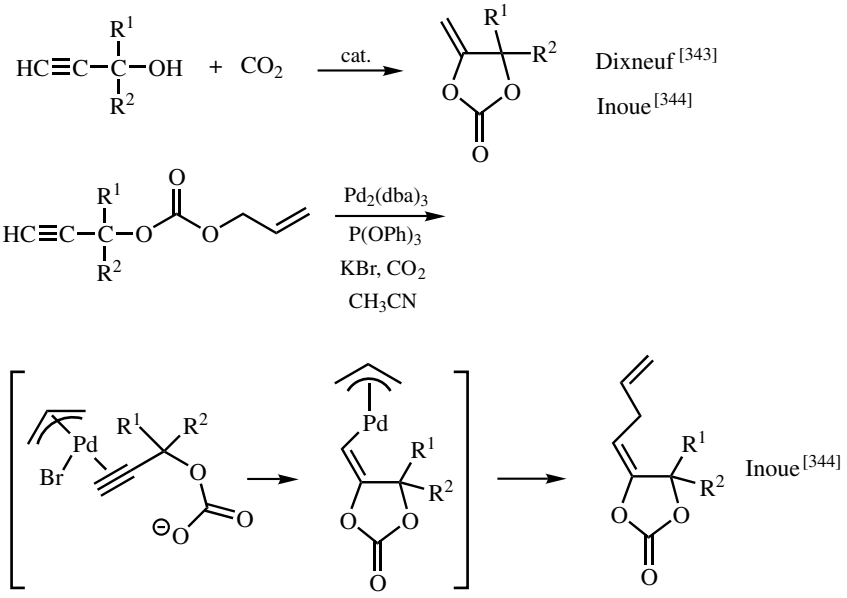
4-Methylene-1,3-dioxolane-2-one reactivity under Pd(0) catalysis has been studied by Murai and co-workers.[341],[342] The array of different structures issued from reactions with olefins, isocyanides, heterocumulenes, and ketene derivatives is shown in **Scheme 48**.

Carbonates of the structural type represented in **Scheme 48** can be obtained by reaction of propargyl alcohols with CO_2 [343],[344] (**Scheme 49**). A curious coupling of allyl propargyl carbonates under Pd(0) catalysis has been described by Inoue and co-workers.[344]

See also **Sect. P**.



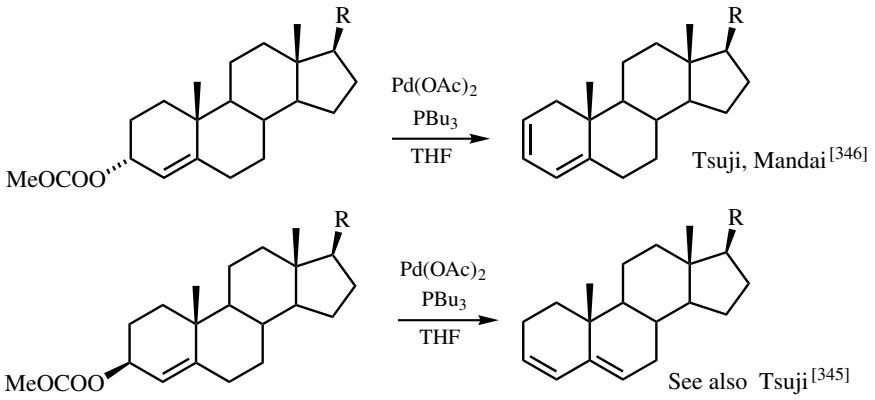
Scheme 48



Scheme 49

K. ELIMINATIONS

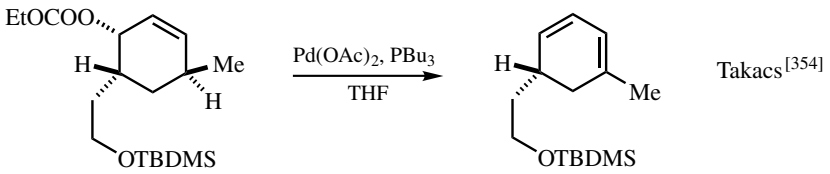
When the cationic η^3-allylpalladium(II) complex is formed in the absence of nucleophiles, elimination of proton and conjugate diene formation ensues (see **Sect. V.2.5.1** for a specific coverage of eliminations). Formally this is a dehydration of allylic alcohols in neutral medium by prior conversion into allylic carbonate; however, in some cases a tertiary base is added to accelerate proton elimination. Tsuji's group has reported the elimination in steroidal and related compounds.[211],[345],[346] Different configurations at C-3 (A ring) afford different diene systems (**Scheme 50**). The combination of $Pd(OAc)_2$ and tributylphosphine is the precatalytic combination preferred by this group, which uses NMR to control the quality of the catalytic mixture.[347]



Scheme 50

Synthetic applications of the elimination of allylic carbonates have been reported by other groups,[348],[349] including steps in the synthesis of diterpenoid forskolin[350] and triterpenoid azadirachtin.[351] Asymmetric eliminations have been explored.[352],[353]

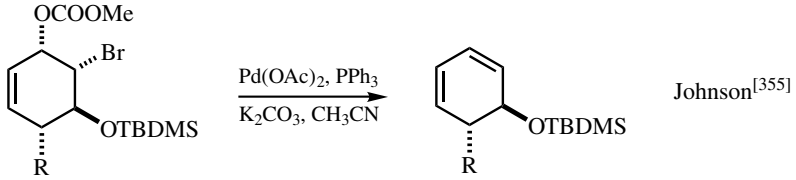
Overall *syn* elimination of H and ROCOO fragments has been determined by Takacs and co-workers[354] (**Scheme 51**). Thus, *anti* elimination of H and Pd fragments in the intermediate complex is favored on stereoelectronic grounds.



Scheme 51

A curious variant eliminates Br (instead of H) and carbonate fragments, that is, the components of BrOMe, probably as HBr and formaldehyde[355] (**Scheme 52**).

See also **Sects. J**, **L**, and **Q.i**.



Scheme 52

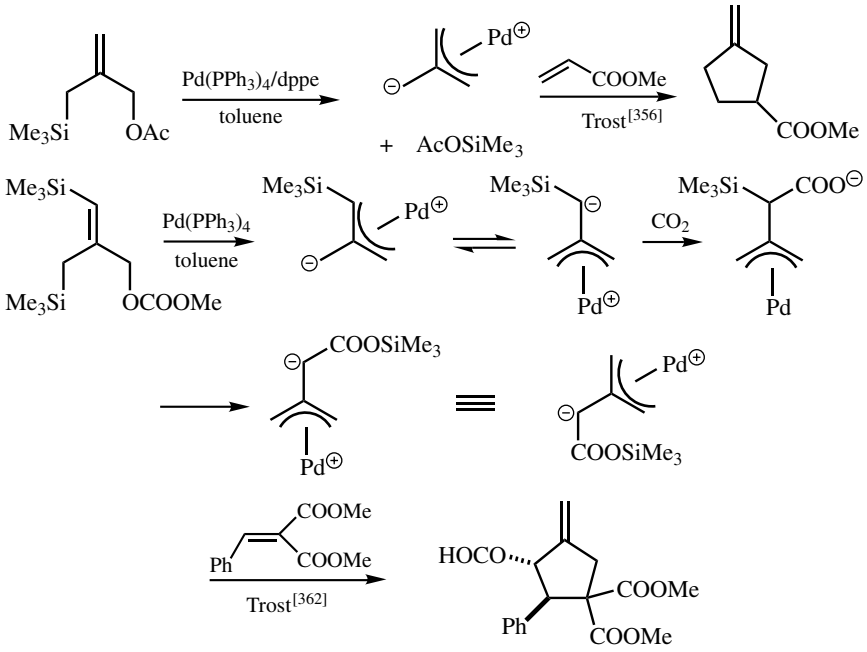
L. CYCLIZATIONS BASED ON η^3-ALLYLPALLADIUM COMPLEXES

Scheme 39 summarizes cyclizations requiring allylic dicarbonates as starting material. Other cyclizations are based on allylic monocarbonates and will be dealt with here. However, see **Sect. V.2.5.2** for specific coverage of cycloadditions.

Perhaps the more extensively used cyclizations are those of **Scheme 53**, affording methylenecyclopentanes. Since 1979, Trost's group has studied in depth cyclizations based on allylic acetates.[356] The most simple reaction is at the top of **Scheme 53**. The liberated acetate anion attacks silicon to form a zwitterion with dipole reactivity toward polarized olefins and other multiple bonds. Note that even using acetates a the base is not required. Work with the more active carbonates by Trost and co-workers[357]–[359] includes preparation of loganin aglucon.[360] Some allylic carbonates can behave in a peculiar manner. Thus, CO_2 liberated from the bistrimethylsilyl carbonate (**Scheme 53**) incorporates in the final product after several equilibria.[361],[362] Intramolecular versions[363]–[365] as well as studies on regioselectivity[366] are due also to Trost's group.

The reaction has been extended to dipolarophile carbonyl[367] and *N*-tosylimine[368] groups. The carbonyl group of cinnamaldehyde[369] and its C═N—Ts derivative[368] are more reactive than the olefin (**Scheme 54**).

Silicon function is not the only solution to generate a dipole from the cationic η^3-allylpalladium complex. This can also be achieved by placing Z—CH_2— groups

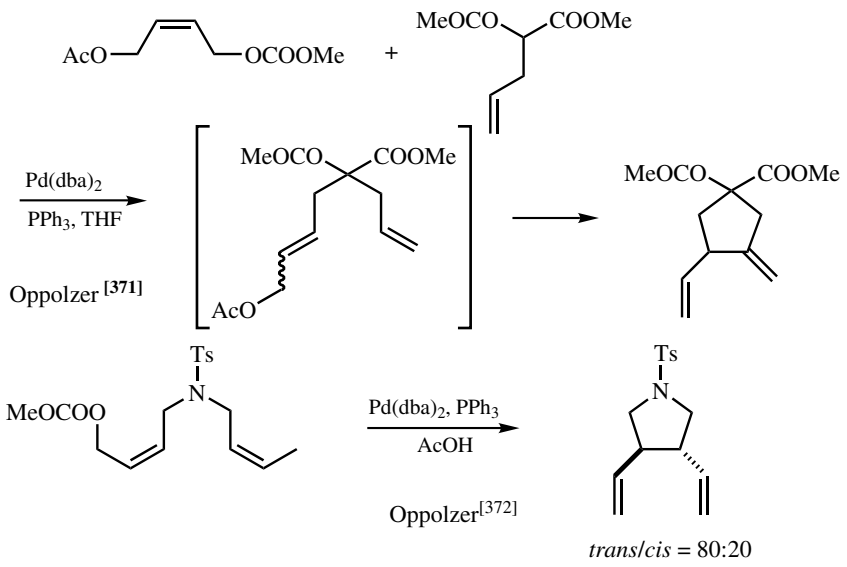


Scheme 53

(Z strong electron-withdrawing function) at C-2. This was done by Tsuji and co-workers[41] (**Scheme 3**) and by Breuilles and Uguen.[326] An asymmetric version has been published.[370]

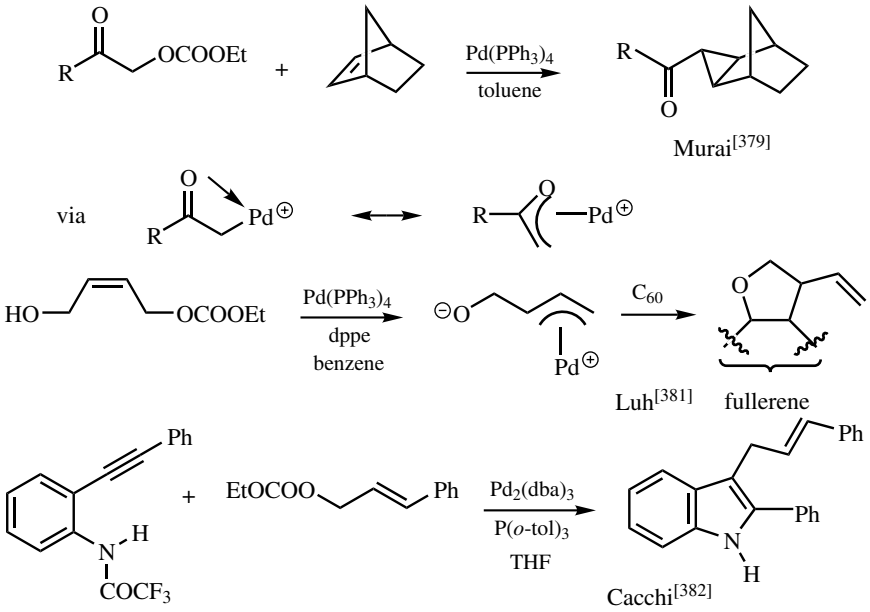
Another type of ring formation is the so-called palladium-ene cyclizations[371],[372] developed by Oppolzer[373] (**Scheme 55**). The presence of an olefin near the cationic η^3-allylpalladium complex facilitates its insertion into the C—Pd bond. Reductive elimination and proton elimination result in the formation of cyclic dienes. Similar reactions have been reported by others.[374]–[378]

Scheme 54



Scheme 55

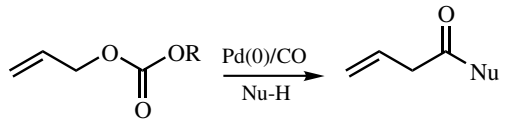
More specific cyclizations are shown in **Scheme 56**. Carbonate of hydroxyacetone is not an allyl carbonate, but it can give rise to an η^3-1-oxaallylpalladium complex, which reacts with rigid olefins to afford cyclopropylketones.[379],[380] Monocarbonate of *cis*-butene-1,4-diol forms a zwitterionic η^3-allylpalladium complex, which reacts as a dipole with fullerene C_{60} to afford a vinyltetrahydrofuran derivative of fullerene.[381] A preparation of indoles is based on the Pd(0)-catalyzed reaction of allyl carbonates with *ortho*-(trifluoroacetylamino)phenylacetylenes.[382]



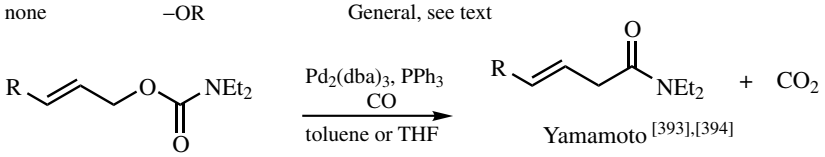
Scheme 56

M. DECARBOXYLATION–CARBONYLATION

The cationic η^3-allylpalladium complex inserts carbon monoxide forming the σ complex allyl-CO-Pd(L_2)-X, which reacts with nucleophiles to afford allyl-CO-Nu (+HX + PdL_2).[383],[384] Use of allylic carbonates introduces the nucleophile in the form of the *in situ* generated alkoxide. Therefore, by a process of decarboxylation–carbonylation allylic carbonates are converted into allyl carboxylates (see **Sect. VI** for coverage of carbonylation reactions). Tsuji and co-workers presented early examples[38]–[40] (**Scheme 3**). Related results have been published mainly by Tsuji's and Yamamoto's groups.[385]–[389] Addition of external phenol or thiol generates their conjugate bases by proton transfer to the basic alkoxide. In such cases the corresponding aryl esters[390] or thioesters[391] are formed. Amides are produced if amines are present[392] and by an analogous reaction from carbamates[393],[394] (**Scheme 57**).



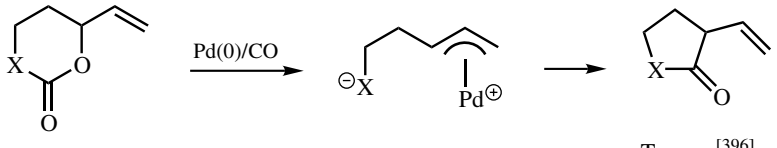
Nu-H	Nu	
PhOH	–OPh	Sinou[390]
R^1NH_2	$-NHR^1$	Loh[392]
PhSH	–SPh	Alper[391]
none	–OR	General, see text



Yamamoto [393],[394]

Scheme 57

These strategies provide an entry to butanolides and butirolactames when the cyclic carbonates and carbamates of **Scheme 58** are opened under Pd(0) catalysis in the presence of CO.[395],[396]

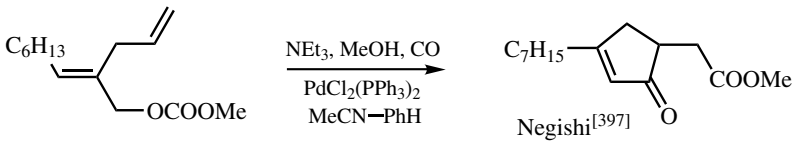


X = O, NR

Tamaru [396]

Scheme 58

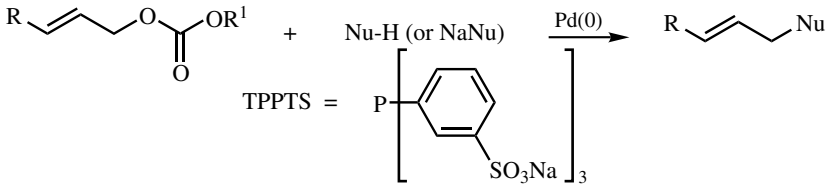
Still another application of carbon monoxide consists of a palladium-ene process followed by carbonylation[397],[398] (**Scheme 59**). Applications to synthesis have been described by Oppolzer and co-workers in the preparation of alkaloid (+)-3-isorauniticine.[399] Cases of triple bonds reacting intramolecularly are also reported by Oppolzer and co-workers in the syntheses of terpenoid pentalenolactone E methyl ester[400] and of tricyclic terpenoid hirsutene.[401]



Scheme 59

N. RECOVERY OF THE CATALYSTS: CATALYSTS ANCHORED TO POLYMERS AND BIPHASIC CATALYSIS

The main concerns in catalysis are high efficiencies measured in terms of turnover numbers and turnover frequencies (TONs and TOFs) and recovery of catalysts. The problem of catalyst recovery has been addressed by anchoring the catalytic species to inorganic or organic robust polymers, which can be filtered and reused many times. Other alternatives consist of the use of two liquid phases, one in which the final product is soluble, and the other in which the catalyst is soluble. The catalyst solution is introduced in a new reaction. The most explored combination consists of water and an organic solvent.[402] Of course, some problems have to be addressed such as leaching from the solid phase in the solid phase catalysis and efficient mixing and good separation of phases in two-phase catalysis. In any case a great deal of attention is presently dedicated to the reuse the catalysts, mainly if expensive transition metals and ligands are used. Application of the above strategies to palladium catalysis has several examples, and in particular those requiring allylic carbonates as starting materials will be considered here (**Scheme 60**, **Table 5**). Since the main focus here is on the recovery of catalysts, the allylation reactions have been performed with very simple carbonates and also very simple stabilized carbon and nitrogen nucleophiles.



Scheme 60

TABLE 5. Catalysts Anchored to Polymers and Biphasic Catalysis

Strategy	Palladium	Researcher
Solid Pd	Pd-graphite, THF	Boldrini[403]
Solid Pd	Pd-silica, DME	Baba[404],[405]
Solid Pd	PolypyrroleN$(CH_2)_5PPh_2$-Pd, THF	Jugé[406]
H_2O-RCN (ABS)	$Pd(dba)_2$/TPPTS	Sinou[409]
H_2O-RCN (ABS)	$Pd(OAc)_2$/TPPTS	Sinou, Genêt[410]
[Silica-H_2O]Pd–PhCN (SAPC)	$Pd(OAc)_2$/TPPTS	Sinou[418],[419]
THF-C_7F_{14} (FBS)	$Pd_2(dba)_3$/P[C_6H_4—$CH_2CH_2C_6F_{13}$-*p*]$_3$	Sinou, Leitner, Pozzi[417]
Water-soluble Polymer-bound Pd	Poly(*N*-isopropyl)acrylamide—$(CH_2)_3$—PPh_2/ Pd/THF–H_2O	Bergbreiter[420]

As early as 1984 Pd on graphite was reported as a catalyst in the alkylation of malonate diester[403] and few other examples of Pd in solid phases have followed.[404]–[406] Anchoring the nucleophile to the solid support under conventional catalysis has been reported in connection with combinatorial chemistry.[407]

The combination of water and an organic nitrile as the solvent system (aqueous biphasic system, ABS) permits one to separate the catalyst in the water solution, coordinated to a water-soluble phosphine, TPPTS, the trisodium salt of trisulfonated triphenylphosphine.[408] The groups of Sinou and Genêt have studied this strategyy.[409],[410] Allylic carbonates are quite stable to the potentially hydrolytic conditions since the reactions occur in neutral medium and only traces of base are generated in the catalytic cycle. Organic–aqueous phase palladium catalysis has been reviewed extensively.[411]–[416]

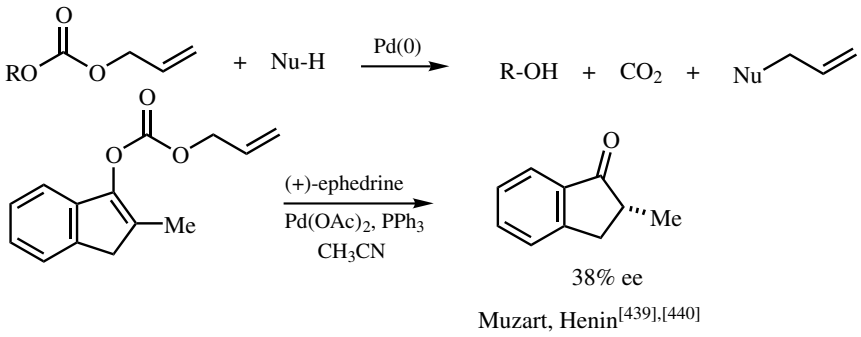
Another useful solvent system is made of THF and a perfluorinated solvent (fluorous biphasic system, FBS). Ligands bearing long polyfluorinated chains are required in order to solubilize the metal complexes in fluorous phases.[417]

Another possibility is to dissolve the catalyst in water, which is supported on a solid phase such as silica. The catalyst is not directly anchored to the solid phase but is dissolved in a film of water, which in turn is linked to the surface of the solid. This approach is termed supported aqueous phase catalysis (SAPC) and has successfully been applied to allylic carbonates.[418],[419]

Bergbreiter and Liu have described the use of a polyacrylamide containing phosphine groups for anchoring of palladium. This Pd-containing polymer is soluble in a mixture of water–THF, where the reaction occurs. Recovery of the active polymer is carried out either by temperature change or by precipitation upon addition of a third solvent[420] (**Scheme 60** and **Table 5**).

O. ALLYLIC CARBONATES AS PROTECTING GROUPS FOR ALCOHOLS

Protection of alcohols and amines as allylic carbonates and carbamates is at the origin of the topic of this section (see **Sect. A** and **Scheme 5**).[50]–[52] The mixed allylic carbonate is treated with a nucleophile in the presence of Pd(0) to afford the allylated nucleophile, which in this case is less important than the liberated alcohol. Cases of protection–deprotection in organic media[421]–[430] and in organic–aqueous media[431]–[436] have been reported. Recent reviews are available[437],[438] (**Scheme 61**). Since **Sect. V.2.3.2** of this handbook is specifically devoted to this topic, we will not discuss further details here.



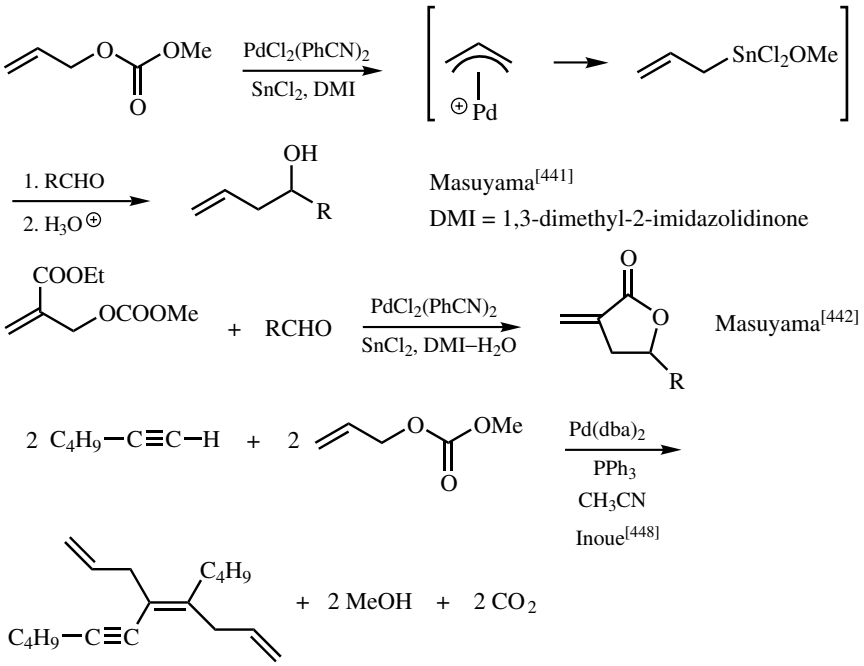
Muzart, Henin[439],[440]

Scheme 61

A very different application is the enantioselective protonation of the cyclic allyl enol carbonate of **Scheme 61**. Liberation of the enolate is followed by protonation in the presence of an enantiomerically pure base.[439],[440]

P. OTHER REACTIONS

A few Pd(0)-catalyzed reactions of allylic carbonates cannot be classified under **Sects. A–O**. Cationic η^3-allylpalladium complexes can be reduced by tin(II) chloride to afford a tin–allyl intermediate provided with nucleophilic reactivity (*umpolung*), which reacts with carbonyl groups (**Scheme 62**). Tin(II) chloride has been used by Masuyama and co-workers in Pd(0)-catalyzed reduction of allylic carbonates,[441],[442] allylic cyclic carbonates,[443] and even allylic alcohols,[444] followed by reaction with carbonyl compounds. Related results with cyclic carbonates have been reported by Kang and co-workers[445] Diethylzinc[446] and samarium(II) iodide have been used as the reducing reagent. Protonation of the allylsamarium intermediate gives overall reduction of the C—O into C—H bond.[447]



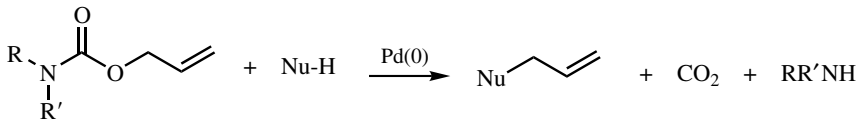
Scheme 62

Formation of tetrasubstituted olefins by reaction of monosubstituted acetylenes with allyl methyl carbonate has been described[448] (**Scheme 62**). Related results have been reported by Deng and co-workers.[449],[450]

Miyaura and co-workers reported the reaction of bis(pinacolato)diboron (B—B bond) with one allylic carbonate under $Pd(dba)_2$ in DMSO to afford the diallyl dimer $CH_2{=}CPh{-}CH_2{-}CH_2{-}CPh{=}CH_2$. However, only one single case was reported, whereas acetates afford the normal coupling products.[451]

Q. PALLADIUM(0)-CATALYZED ALLYLATION WITH OTHER FUNCTIONAL GROUPS BASED ON CARBON IN FOURTH DEGREE OF OXIDATION

Allylic carbonates are in general the substrates of choice for Pd(0)-catalyzed allylation of nucleophiles. However, in certain cases other functional groups based on a carbon atom in the fourth degree of oxidation can be quite useful and deserve comment. Allylic carbamates are at the origin of the chemistry described in this section, since in 1980 a patent was filed covering the use of allylic carbonates and carbamates as protecting groups for alcohols and amines[52] (**Scheme 63**); of course, deprotection was performed under Pd(0) catalysis. These results were later published in the form of a regular paper by Jeffrey and McCombie.[51] Tsuji and co-workers reported also an early contribution to the field.[452] Since then, this type of protection has become very popular (see **Sect. O**, **Sect. V.2.3.2**, and recent reviews by Guibé[437],[438]).

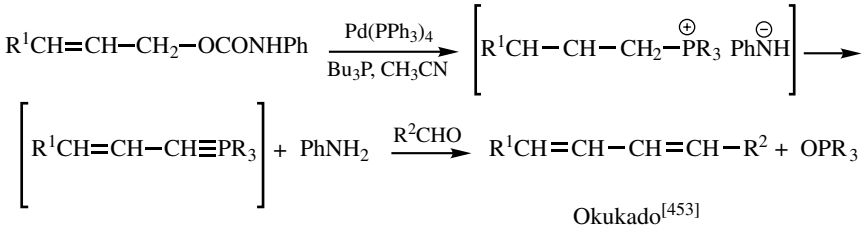


Scheme 63

Q.i. Carbamates

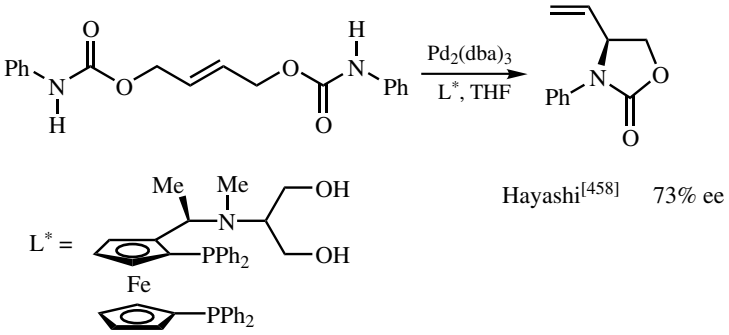
Clearly the reaction of **Scheme 63** can be used not only to deprotect amines but also for Pd(0)-catalyzed allylation of nucleophiles using carbamates as substrates, as proposed by J. Tsuji and co-workers[12],[43] However, carbonates are preferred since amines liberated when working with carbamates are strongly nucleophilic and can react further. To avoid this side reaction Tsuji proposed the use of *N,N′*-diisopropyl carbamates, which liberate the moderate nucleophile diisopropylamine. However, the side reaction is much less important with alcohols.

Okukado and co-workers have described a Wittig-type olefinization based on carbamates[453] (**Scheme 64**). The basicity of the conjugate base of the amine is enough to deprotonate the allylphosphonium cation and to generate the Wittig reagent. However, this type of reaction can be performed even with allylic alcohols.[454]–[456] Phosphines are usually stabilizing ligands for Pd(0); therefore, it is surprising how it is generally forgotten that phosphines are strongly nucleophilic towards η^3-allylpalladium complexes. Probably this is a reversible reaction with phosphines themselves being efficient leaving groups.



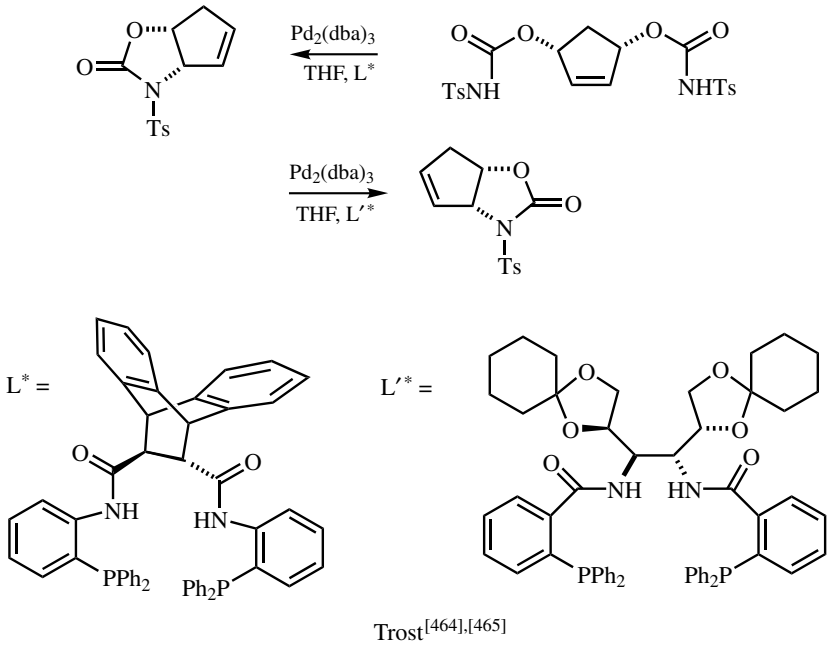
Scheme 64

Dicarbamates of both *cis*- and *trans*-2-butene-1,4-diol afford 4-vinyloxazolidinones under Pd(0) catalysis[457],[458] (**Scheme 65**). One carbamate reacts as the leaving group whereas the second acts as the nucleophile at the nitrogen atom. Reasonable enantiomeric excesses were reported by Hayashi and co-workers[458] Related results have been published by Trost and Bunt.[112]



Scheme 65

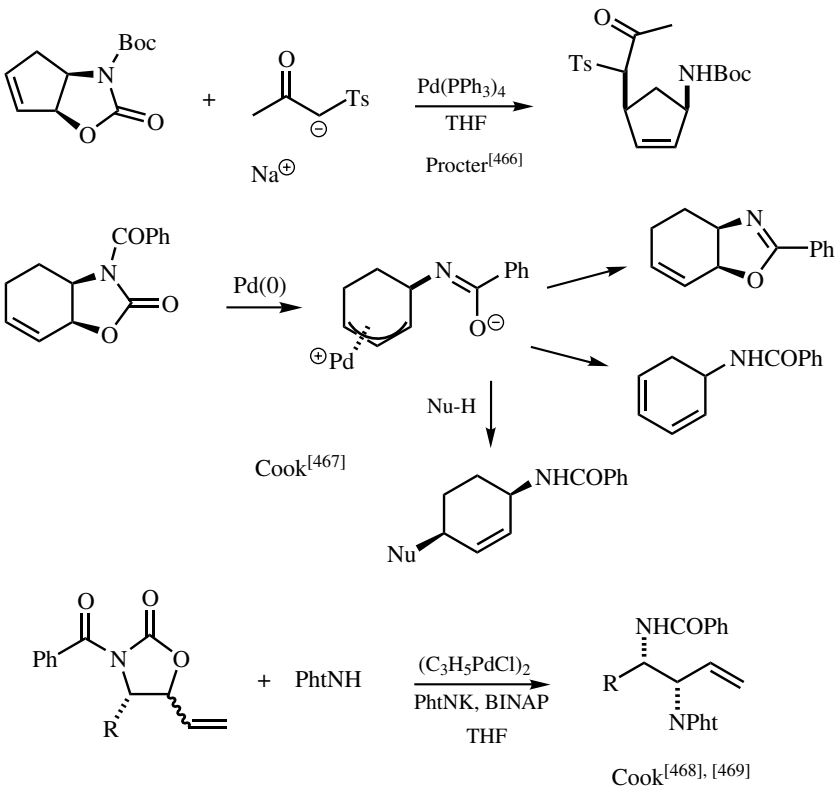
Trost has described desymmetrizations of cyclic *meso* diols as exemplified in **Scheme 66**. This is part of a synthetic effort targeting natural products, mainly glycosidase inhibitors featuring aminocyclopentitol structure.[112],[337],[459]–[463] These results have been reviewed, including a rationale of the relation between the sense of the enantiomeric excesses and the structures of the ligands.[464],[465]



Scheme 66

Other applications of cyclic carbamates are shown in **Scheme 67**. N-Boc protection permits clean opening of the bicyclic carbamate to obtain a *cis*-1,4-difunctionalized cyclopentene, a type of structure important in the preparation of carbanucleosides.[466]

However, the analogous *N*-benzoyl derivative reacts in three different ways depending on the experimental conditions and on the presence or absence of external nucleophiles.[467]



Scheme 67

N-Benzoyl-5-vinyloxazolidinones are converted into enantiomerically defined open-chain 1,2-diamine derivatives.[468],[469]

M. Suzuki and co-workers reported the preparation of hyperbranched dendritic polyamines by multibranching polymerizations of cyclic carbamates[470],[471] (**Scheme 68**).

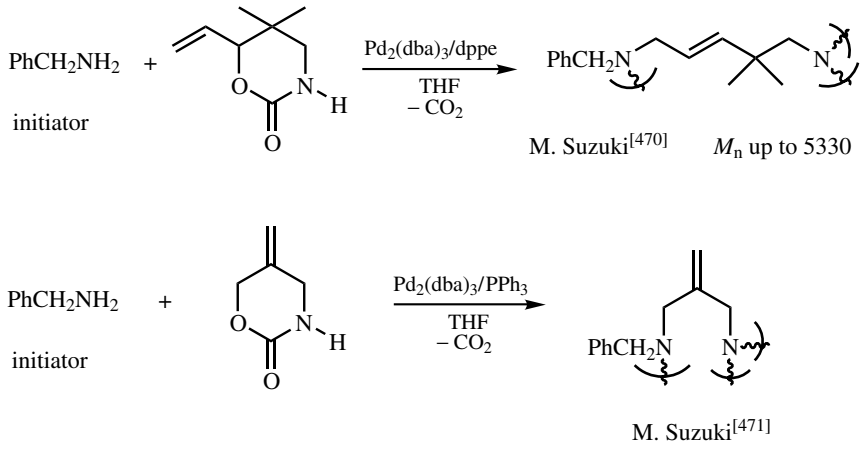
Yamamoto and co-workers have reported the decarboxylation–carbonylation reaction of allyl carbamates to afford β,γ-unsaturated amides[393],[394] (**Scheme 57**).

Murai and co-workers have described chemistry analogous to that in **Scheme 48** featuring an N-Ts instead of oxygen at the ring position next to the vinyl group.[472]

See also **Sect. M**.

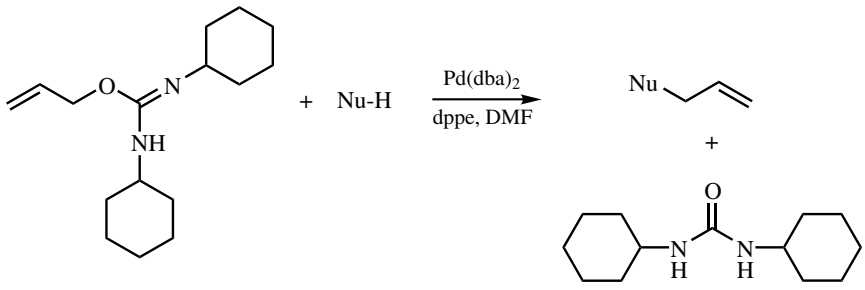
Q.ii. Other Functional Groups

Inoue and co-workers have reported the use of O-allylisoureas as substrates for Pd(0)-catalyzed allylation of amides, sulfamides, and thioamides,[473] ketones and



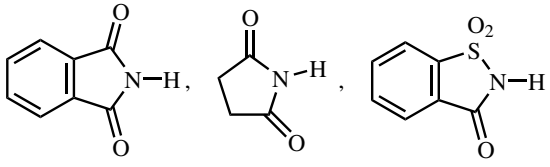
Scheme 68

aldehydes,[474],[475] and N-H acidic compounds such as phthalimide, succinimide, and saccharin[476] (**Scheme 69**). The required isourea ethers are easily available by reaction of allylic alcohols with dicyclohexylcarbodiimide. The other product of the allylation, *N,N′*-dicyclohexylurea, is easily eliminated because it is quite insoluble in organic solvents. Note that this is possibly the only method for direct Pd(0)-catalyzed allylation of nonactivated aldehydes and ketones.



Nu-H = $RCONH_2$, $ArSO_2NH_2$, CH_3CSNH_2 Inoue[473]

R-CH_2-CO-R′ R′ = H, alkyl, aryl Inoue[474], [475]



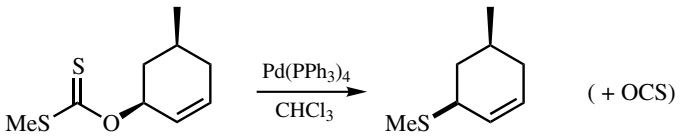
Inoue[476]

Scheme 69

Inoue and co-workers have also reported a variant of the Wittig-type reaction described in **Scheme 64** based on isourea ethers.[477]

Oxime carbonates of type $R_2C{=}N{-}O{-}CO{-}O{-}$allyl have been mentioned in the context of this paragraph.[478]

O-Allyl-*S*-alkyl dithiocarbonates[479],[480] and *S*-allyl-*S*-alkyl ditiocarbonates[480] have been proposed for preparation of alkyl allyl sulfides. The reaction occurs with overall retention of configuration[479] (**Scheme 70**).



Auburn[479]

Scheme 70

R. LATE ADDITIONS

Very recent applications of allylic carbonates are incorporated here in the form of the following additions:

1. Further examples of allylation of stabilized carbon nucleophiles.[481]

2. Allylation at carbon of zinc-chelated enolates of amino acid esters of type EWG-NH-CHR-COOR′ to afford disubstituted glycine derivatives.[482]

3. Use of tolylsulfonamides in Pd(0)-catalyzed allylations in a synthesis of mesembrine.[483]

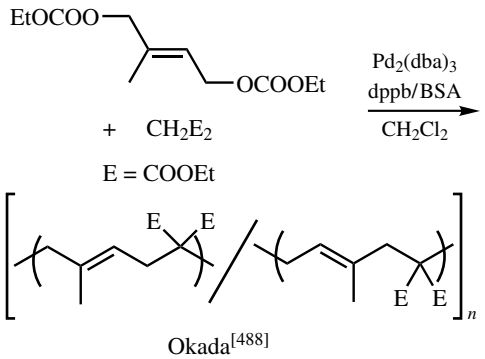
4. Kinetic resolution in cyclohexene derivatives with a tolylsulfonamide and with malonate as nucleophiles.[484]

5. A further example of a hydroxylamine derivative as nucleophile.[485]

6. More examples of intramolecular aziridine formation from 4-(*N*-aryl(or alkyl)sulfonylamino)-2-alken-1-ol carbonate (see **Scheme 40**).[486]

7. Additional examples of desymmetrization of *meso* cyclopentenediol tosylcarbamates.[487]

8. In general, reaction of malonate with butene-1,4-diol dicarbonate affords vinylcyclopropane (see **Scheme 39**).[42],[302]–[305] However, Okada and co-workers have found experimental conditions that afford polymer instead of cyclopropane (**Scheme 71**).[488]



Okada[488]

Scheme 71

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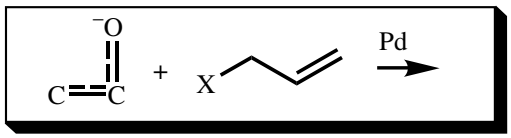

V.2.1.4 Palladium-Catalyzed Allylation and Related Substitution Reactions of Enolates and Related Derivatives of "Ordinary" Ketones, Aldehydes, and Other Carbonyl Compounds

EI-ICHI NEGISHI and SHOW-YEE LIOU

A. BACKGROUND AND EARLY RESULTS

α-Allylation, α-propargylation, and α-benzylation of ketones, aldehydes, esters, and related carbonyl compounds have traditionally been achieved by reactions of the corresponding enolates containing alkali metals and other related countercations, such as ammonium cations.[1],[2] Although these reactions may be considered to be generally facile, they are nonetheless capricious due to complications involving (i) unwanted multiple alkylation, (ii) α-to-α' regiochemical scrambling, (iii) regiochemical scrambling of allylic groups, (iv) their stereochemical scrambling, and (v) the stereochemistry of allylic groups relative to the existing stereochemistry of the carbonyl compounds.

The advent of the catalytic Tsuji–Trost reaction in the early 1970s[3],[4] (**Sects. V.2.1.1** and **V.2.1.2**) has significantly expanded the scope of enolate allylation and related reactions. Noteworthy among others is that the range of allylic electrophiles was vastly expanded from allylic halides, such as chlorides and bromides, to a much wider range of derivatives including not only halides but also O, S, N, and other heteroatom-containing derivatives. Curiously, however, the scope of the Tsuji–Trost reaction had essentially been limited to the Pd-catalyzed allylation of "extra-stabilized" enolates, such as those derived from malonate and acetoacetate esters, until around 1980.

The Pd-catalyzed reaction of the acetone-derived enolate presumably containing an alkali metal countercation with allyl acetate was reported in 1980 to give a 2:1 mixture of the diallylated and monoallylated products[5] (**Scheme 1**). A year later, the reaction of lithium enolates of a few "ordinary" ketones with allylic acetates under the influence of 1 mol % each of $Pd(dba)_2$ and dppe was reported to give the desired monoalkylated products mostly in moderate yields with no specification of the extents of diallylation[6] (**Scheme 2**).

In the meantime, attempts to improve the Pd-catalyzed allylation of "ordinary" enolates and widen its scope through countercation screening were initiated. Whereas the applicability of silylated enolates, commonly known as silyl enol ethers, was reported to be limited to the parent allyl acetate,[5] the use of a few other metal countercations

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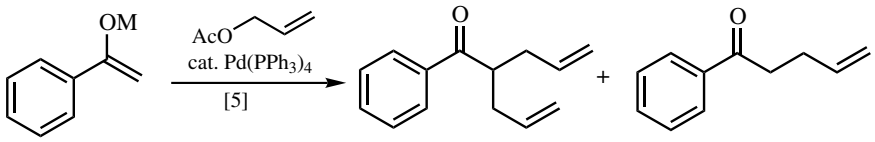
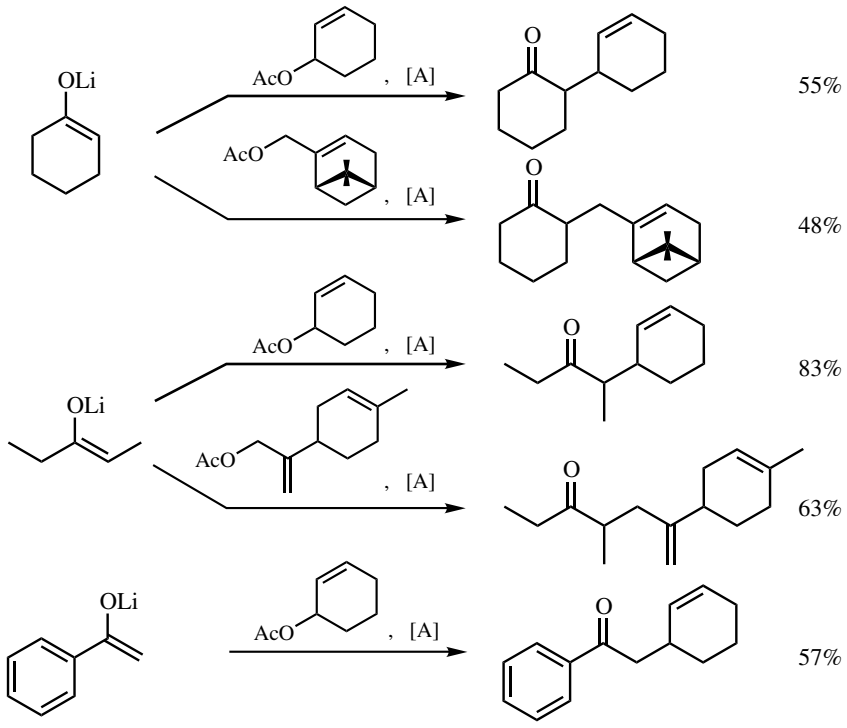
(i.e., Zn,[7] B,[7],[8] and Sn[5]) led to some highly satisfactory results. It is particularly noteworthy that both "kinetic" and "thermodynamic" enolates of 2-methylcyclohexanone were selectively generated using $KBEt_3$ as the countercation and that their Pd-catalyzed allylation with geranyl and/or neryl acetates was achieved in good yields with (i) excellent regio- and stereospecificities (≥98%) of the allylic electrophiles and (ii) excellent regiospecificity with respect to the position of allylation (≥98%).[7],[8] There was no indication of diallylation. So, the only uncontrolled feature in this reaction was the relative stereochemistry of the 2-Me and the allylic group (*cis*/*trans* = 2.9:1) (**Scheme 3**).

These results once again indicate that it is indeed important and useful to optimize the Pd-catalyzed cross-coupling with respect to the metal countercation and that Zn, B, and Sn appear to be three metals of choice.



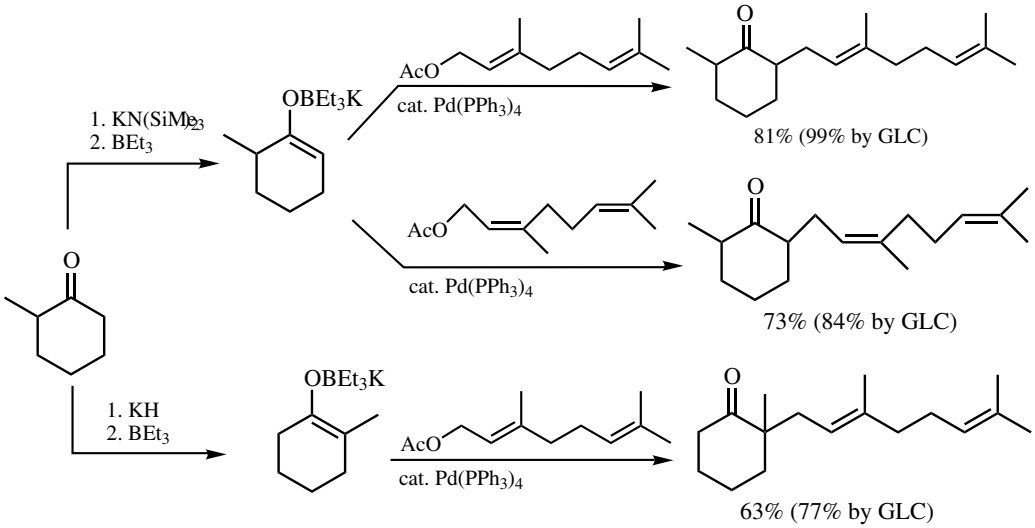
a 2:1 mixture

Scheme 1



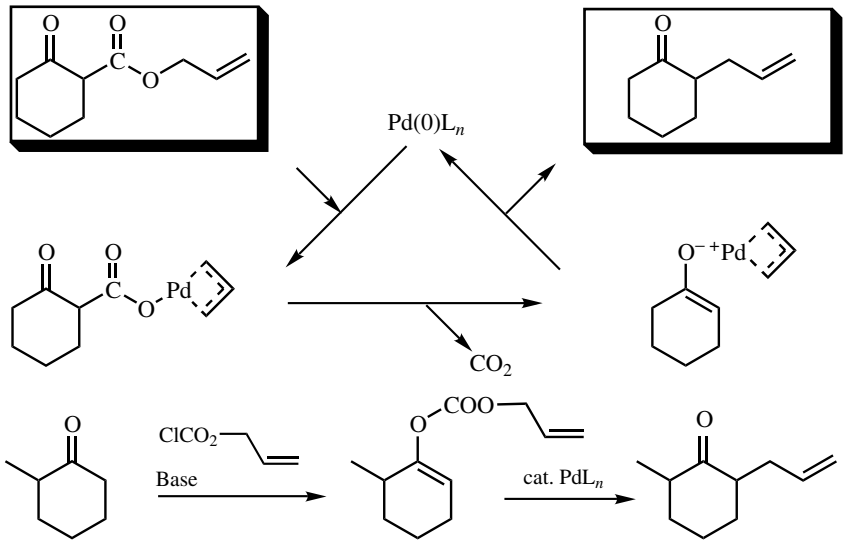
[A] = 1 mol % $Pd(dba)_2$, 1% dppe.

Scheme 2



Scheme 3

Although outside the scope of this section, the concurrent development of the Pd-catalyzed allylation of β-ketocarboxylic acids via the formation and decomposition of allyl β-ketocarboxylates is noteworthy[9]–[18] (**Sects. V.2.1.1** and **V.2.1.2**). The mechanism shown in **Scheme 4**, which involves (i) oxidative addition of allyl β-ketocarboxylates, (ii) decarboxylation, and (iii) intermolecular enolate allylation was proposed and experimentally supported.[9] Unfortunately, α-allylation with γ,γ-disubstituted allyl derivatives, such as geranyl carboxylates, proceeds in low yields, and there are some indications that the reaction may lack some specificity features, for example, stereospecificity of the allylic moiety.



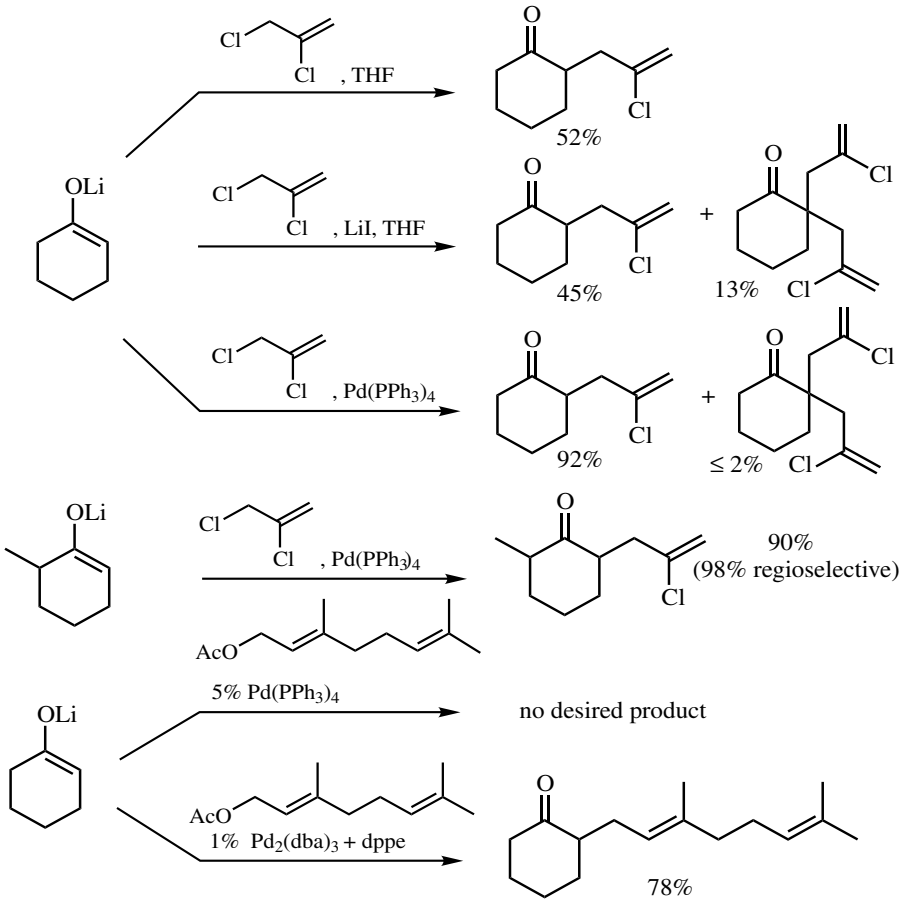
Scheme 4

Yet another alternative that is complementary with that mentioned above involves the base-promoted reaction of ketones with allyl chloroformates to form the corresponding allyl enol carbonates followed by their Pd-catalyzed decomposition to give α-allylated ketones[12] (**Scheme 4**).

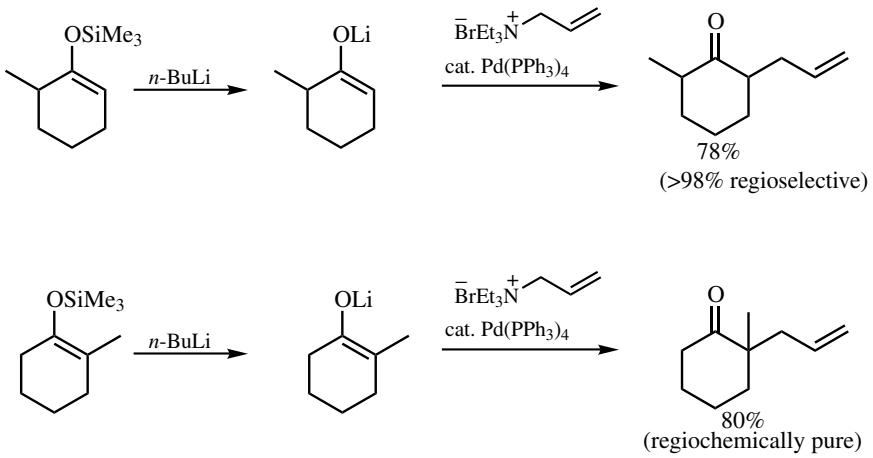
B. SCOPE, LIMITATIONS, MECHANISM, AND APPLICATIONS OF THE PALLADIUM-CATALYZED α-ALLYLATION OF METAL ENOLATES AND RELATED DERIVATIVES

B.i. Optimization of Enolate Countercations

As mentioned in **Sect. A**, the Pd-catalyzed α-allylation of enolates has been carried out with enolates containing various metal countercations, such as Li,[5]–[7],[19],[20] Mg,[7] Zn,[7],[9] B,[7],[9],[19],[21],[22] Al,[7] Si,[5],[7],[23],[24] and Sn.[5],[7],[25],[26] Since these metal enolates are mostly prepared via those containing alkali metals, especially Li, lithium enolates should be the reagents to be considered first, and some satisfactory results have indeed been reported (**Scheme 2**,[6] **Scheme 5**,[7] and **Scheme 6**[20]).



Scheme 5



Scheme 6

Despite some favorable results discussed above, various limitations associated with the use of lithium enolates, such as diallylation (**Scheme 1**)[5] and frequently encountered low yields, have also been observed. It is reasonable to state that the Pd-catalyzed allylation of lithium enolates is at best of rather limited scope, unpredictable, and often disappointing.

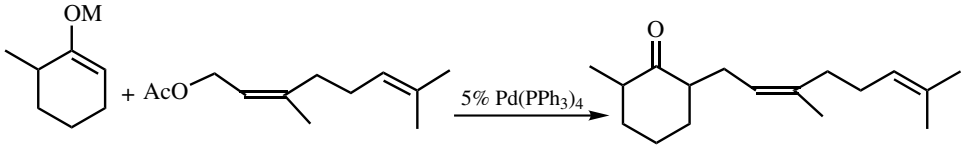
A systematic countercation survey using the reaction of 6-methyl-1-cyclohexenolates with neryl acetate in the presence of $Pd(PPh_3)_4$ as a catalyst[7] has revealed that, under the conditions used, those enolates containing $KBEt_3$ and ZnCl as the countercation along with lithium 6-methylcyclohexenolate in the presence of 2 equiv of BEt_3 are satisfactory, while the Bu_3Sn derivative gives the desired product in a fair yield. The use of Li, MgCl, $AlMe_2$, $AlMe_3Li$, $AlMe_3K$, $SiMe_3$, and $TiCp_2Cl$ does not give significant yields of the desired product. These results are summarized in **Table 1**.[7]

Retention of the stereo- and regiochemical identity of γ-monosubstituted allylic electrophiles is generally more difficult than that of γ,γ-disubstituted analogs. Nonetheless, the Pd-catalyzed reaction of lithium cyclopentenolate in the presence of 2 equiv of BEt_3 with (*E*)- or (*Z*)-2-octenyl acetate (but not chloride or bromide) proceeds satisfactorily, producing only minor amounts of undesirable by-products[19] (**Table 2**). High stereospecificity figures are, in fact, observable in the uncatalyzed reaction of lithium cyclopentenolate with (*Z*)-2-octenyl iodide and bromide, but the product yields were substantially lower. So, those results that are satisfactory in an overall sense are obtainable only in cases where the reaction is run with 2-octenyl acetate in the presence of BEt_3 and a Pd catalyst.

Although silyl enol ethers are rather unreactive in the Pd-catalyzed allylation, the use of allylic carbonates in conjunction with 5 mol % of $Pd_2(dba)_3CHCl_3$ and 10 mol % of dppe in refluxing THF has been shown to give satisfactory results, as summarized in **Scheme 7**.[24] Silyl enol ethers derived from aldehydes also serve as satisfactory enolates.

Similarly, the Pd-catalyzed allylation of stannyl enol ethers can be optimized to produce the desired products in good yields, as indicated by the results shown in **Scheme 8**. It should be noted, however, that the Pd-catalyzed allylation of stannyl enol ethers often fail to display high regio- and stereospecificity levels, which can be attributable, to a considerable extent, to the lower intrinsic reactivity of stannyl enol ethers. Specifically,

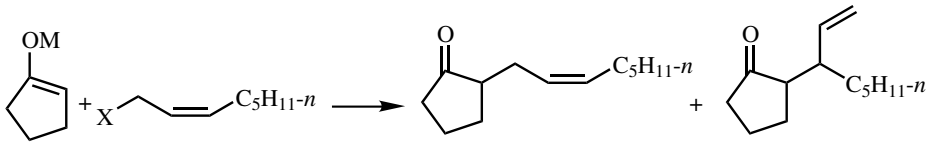
TABLE 1. Comparison of the Countercations in the Reaction of Metal 6-Methyl-1-cyclohexenolates with Neryl Acetate in the Presence of $Pd(PPh_3)_4$ at Room Temperature in THF



M	Time (h)	Product Yield (%)[a]	6-Me/2-Me	Retention (%) of the Neryl Identify
Li	24	0	—	—
Li + 2 BEt_3	12	78 (62)	91/9	≥98
MgCl	24	17	—	—
ZnCl	12	84 (73)	95/5	≥98
BEt_3K	12	— (64)	96/4	≥98
$AlMe_2$, $AlMe_3Li$, or $AlMe_3K$	24	0	—	—
$SiMe_3$	24	0	—	—
$SnBu_3$	72	35	—	—
$TiCp_2Cl$	24	0	—	—

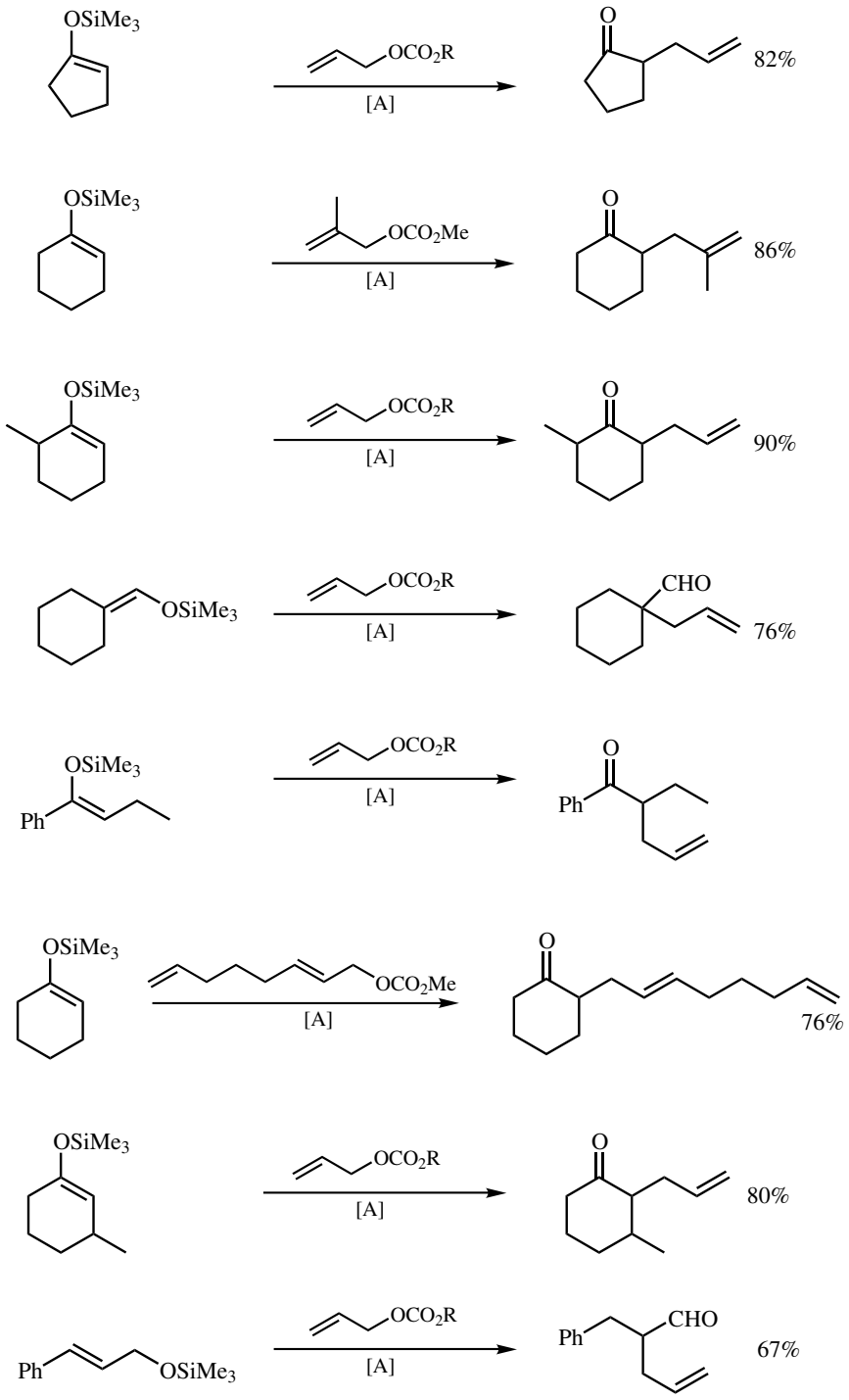
[a] The numbers in parentheses are isolated yields.

TABLE 2. Reaction of Cyclopentenolates with 2-Octenyl Electrophiles



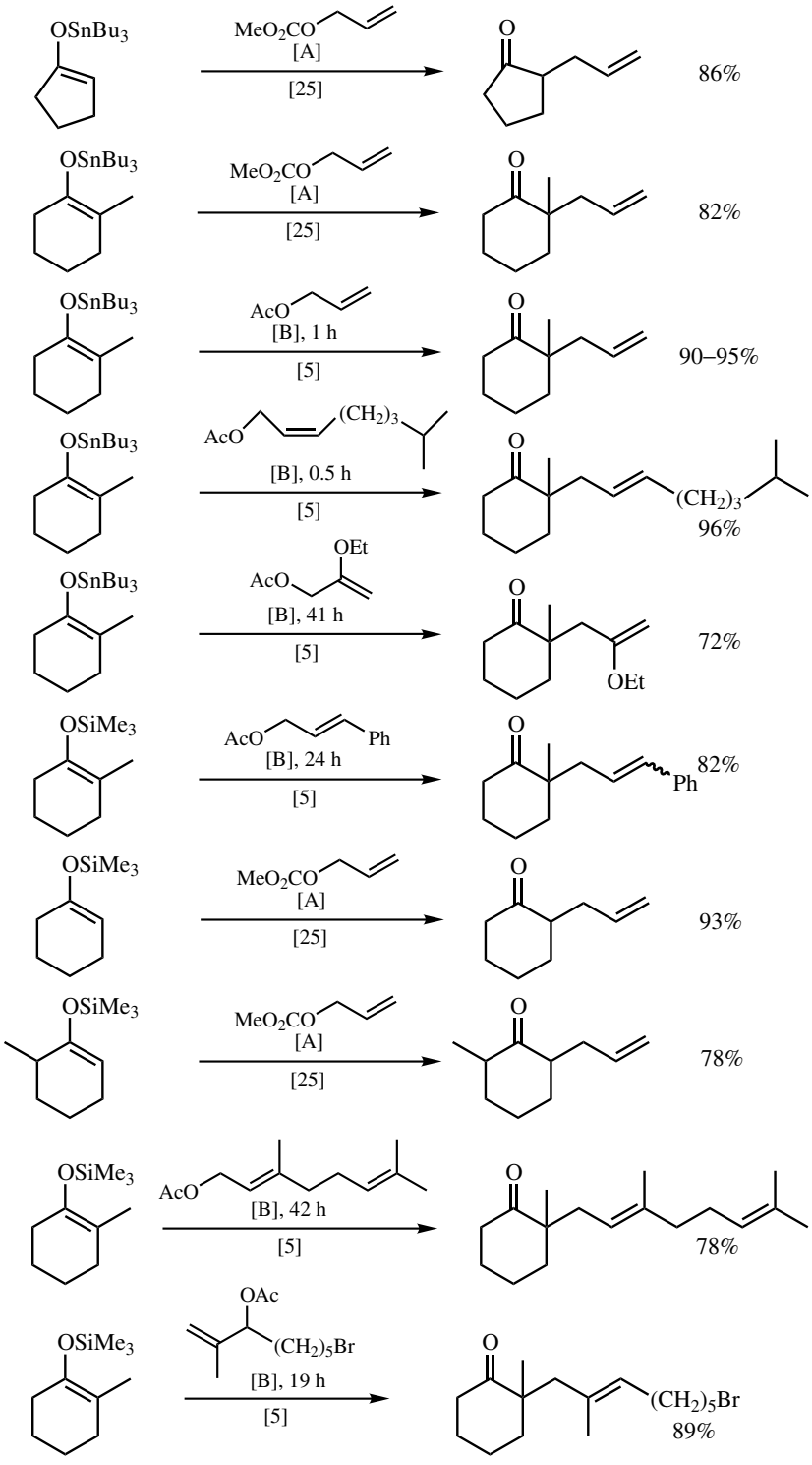
M	X	Time (h)	$Pd(PPh_3)_4$ (%)	Yield (%)[a]	*Z*/*E*	Regioisomer Yield (%)
Li + 2 BEt_3	OAc	3	2	91 (74)	≥97:3	5–10
Li + 2 BEt_3	OAc[b]	3	2	— (77)	≥2:98	<1
Li + 2 BEt_3	Cl	3	2	81 (75)	60:40	5–10
Li + 2 BEt_3	Br	3	2	84 (75)	54:46	5
Li + 2 BEt_3	OAc	24	0	Trace	—	—
Li	OAc	24	2	2	—	—
Li	I	12	0	48 (43)	96:4	<1
Li	Br	12	0	55 (50)	87:13	6

[a] GLC yield. The numbers in parentheses are isolated yields.
[b] (*E*)-2-Octenyl acetate was used.

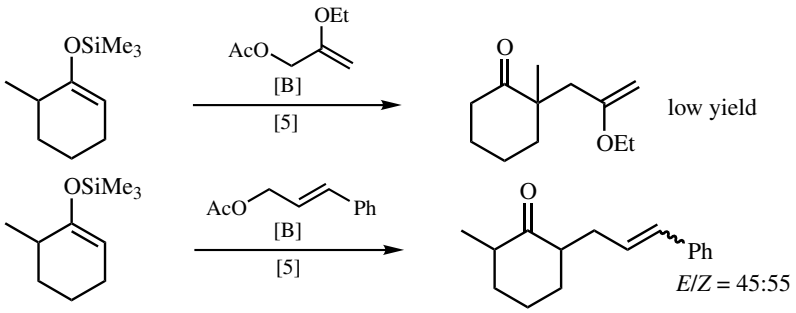


R = allyl. [A] = 5% $Pd_2(dba)_3 \cdot CHCl_3$, 10% dppe, THF.

Scheme 7


OSnBu3
MeO2CO
[A]
[25]
O
86%
OSnBu3
MeO2CO
[A]
[25]
O
82%
OSnBu3
AcO
[B], 1 h
[5]
O
90–95%
OSnBu3
AcO
(CH2)3
[B], 0.5 h
[5]
O
(CH2)3
96%
OSnBu3
OEt
AcO
[B], 41 h
[5]
O
OEt
72%
OSiMe3
AcO
Ph
[B], 24 h
[5]
O
Ph
82%
OSiMe3
MeO2CO
[A]
[25]
O
93%
OSiMe3
MeO2CO
[A]
[25]
O
78%
OSiMe3
AcO
[B], 42 h
[5]
O
78%
OSiMe3
OAc
(CH2)5Br
[B], 19 h
[5]
O
(CH2)5Br
89%

Scheme 8



[A] = $Pd_2(dba)_3 \cdot CHCl_3$, dppe. [B] = $Pd(PPh_3)_4$.

Scheme 8 (*Continued*)

(*Z*)-2-alkenyl derivatives tend to undergo *Z*-to-*E* isomerization,[5] and the regiospecificity of allylation tends to be unpredictable and dependent on structural and other parameters.

In summary, the Pd-catalyzed α-allylation of ketones can be achieved with the corresponding enolates containing Li, Li + $2BEt_3$, ZnX, BEt_3K, $SiMe_3$, and SnR_3 as the metal countercations. In some demanding cases, however, the most satisfactory results may be obtained through the use of Li + 2 BEt_3, ZnX, or BEt_3K as the countercation.

Some other representative results not included in the schemes and tables are summarized in **Table 3**.

B.ii. Palladium-Catalyzed α-Allylation of Ester Enolates and Related Nucleophiles

The Pd-catalyzed α-allylation of esters was first achieved by the reactions of allylic carbonates with ketene silyl acetals that can be generated by treating esters with Me_3SiCl in the presence of a base.[27] The yields of the desired products based on ketene silyl acetals were generally good except in the allylation of lactones (**Scheme 9**).[28] Selection of solvents is critical since the use of nitriles, such as MeCN and PhCN, leads only to the formation of α,β-unsaturated esters rather than the α-allylated products. Both Reformatsky reagents[29] and lithium enolates[30] of esters have also been successfully α-allylated in the presence of Pd catalysts (**Scheme 10**). A highly regio- and stereospecific allylation of γ-butyrolactone with (*E*)-2-hexenyl acetate is noteworthy. Since the lithium enolate of esters would react with allylic chlorides even in the absence of a Pd catalyst, however, it is not clear to what extent the reaction is catalyzed by a Pd complex.

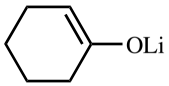
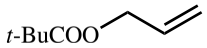
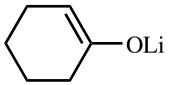
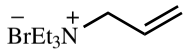
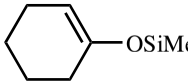
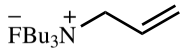
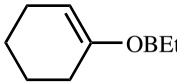
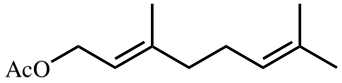
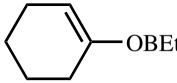
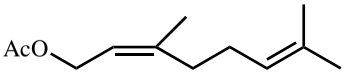
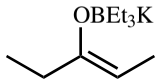
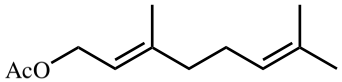
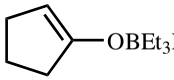
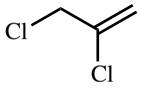
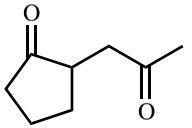
The Pd-catalyzed reaction of allylic carbonates with the lithio derivatives of dioxolanone prepared by the treatment of mandelic acid with acetone dimethyl acetal gives the desired α-allylation products in good yields. Upon treatment with HCl in ethanol the corresponding α-hydroxy ethyl esters can be obtained[31] (**Scheme 11**).

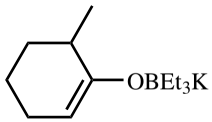
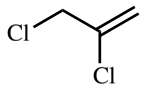
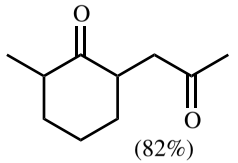
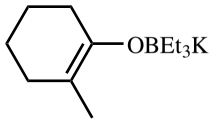
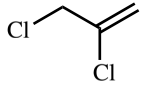
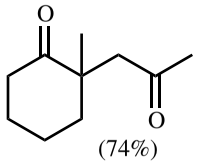
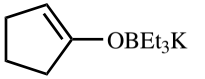
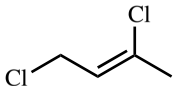
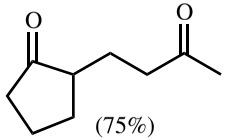
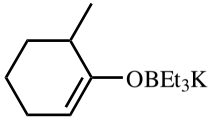
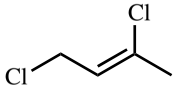
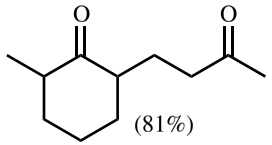
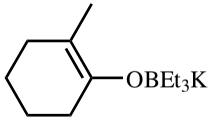
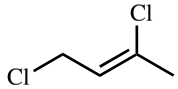
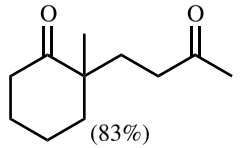
The Pd-catalyzed reaction of the lithio derivatives of nitroalkanes with allylic acetates gives the α-allylated products in fair-to-good yields in variable regioselectivity (**Table 4**).[32]

B.iii. Mechanism

Since allylic halides are known to react with enolates containing electropositive metals, such as Li and other alkali metals, the catalytic effect of Pd complexes must clearly be

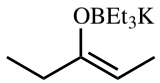
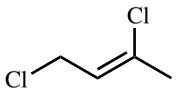
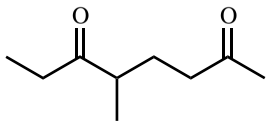
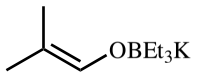
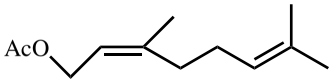
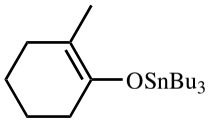
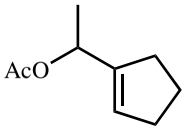
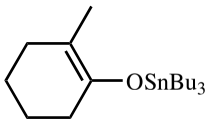
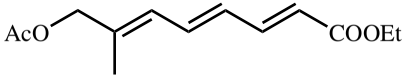
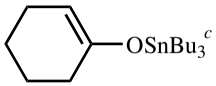
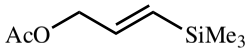
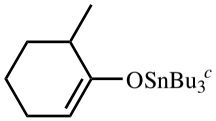
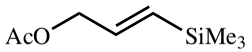
TABLE 3. Other Representative Examples of the Pd-Catalyzed α-Allylation of "Ordinary" Ketone and Aldehyde Enolates

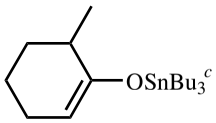
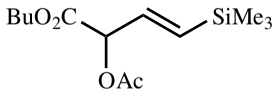
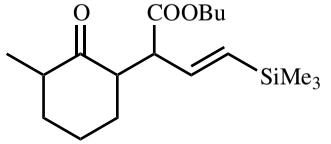
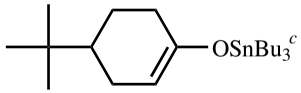
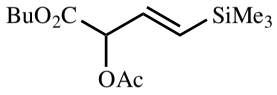
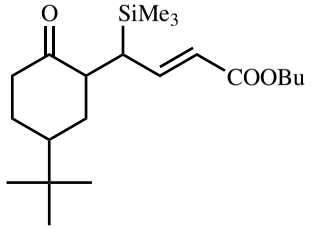
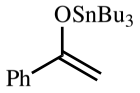
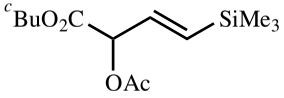
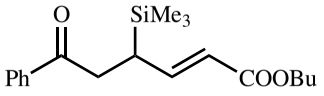
Metal Enolate	Allylic Electrophile	Pd Catalyst at Other Conditions[a]	Product Yield (%)[b]	Comments	Reference
		[A] , THF, r.t.	64		[6]
		$Pd(PPh_3)_4$, THF , <0 °C	39		[20]
		$Pd(PPh_3)_4$	10		[20]
		$Pd(PPh_3)_4$, THF	81	≥98% *E*	[8]
		$Pd(PPh_3)_4$, THF	70	≥98% *Z*	[8]
		$Pd(PPh_3)_4$, THF	68	≥98% *E*	[8]
		$Pd(PPh_3)_4$, THF	72 (85)	 (76%)	[21]

		$Pd(PPh_3)_4$, THF	81 (92)	 (82%)	[21]
		$Pd(PPh_3)_4$, THF	77 (82)	 (74%)	[21]
		$Pd(PPh_3)_4$, THF	72 (81)	 (75%)	[21]
		$Pd(PPh_3)_4$, THF	72 (79)	 (81%)	[2]
		$Pd(PPh_3)_4$, THF	74 (90)	 (83%)	[2]

(*Continued*)

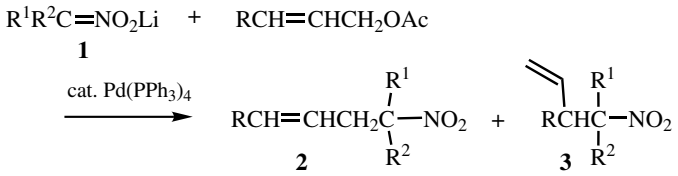
TABLE 3. (*Continued*)

Metal Enolate	Allylic Electrophile	Pd Catalyst at Other Conditions[a]	Product Yield (%)[b]	Comments	Reference
		$Pd(PPh_3)_4$, THF	86 (91)	 (73%)	[2]
		$Pd(PPh_3)_4$, THF	60	≥98% *Z*	[2]
		$Pd(PPh_3)_4$, THF	24		[1]
		$Pd(PPh_3)_4$, THF	77		[1]
 [c]		$Pd(PPh_3)_4$, dppe	61		[26]
 [c]		$Pd(PPh_3)_4$, dppe	60	*cis*/*trans* = 1.4	[26]

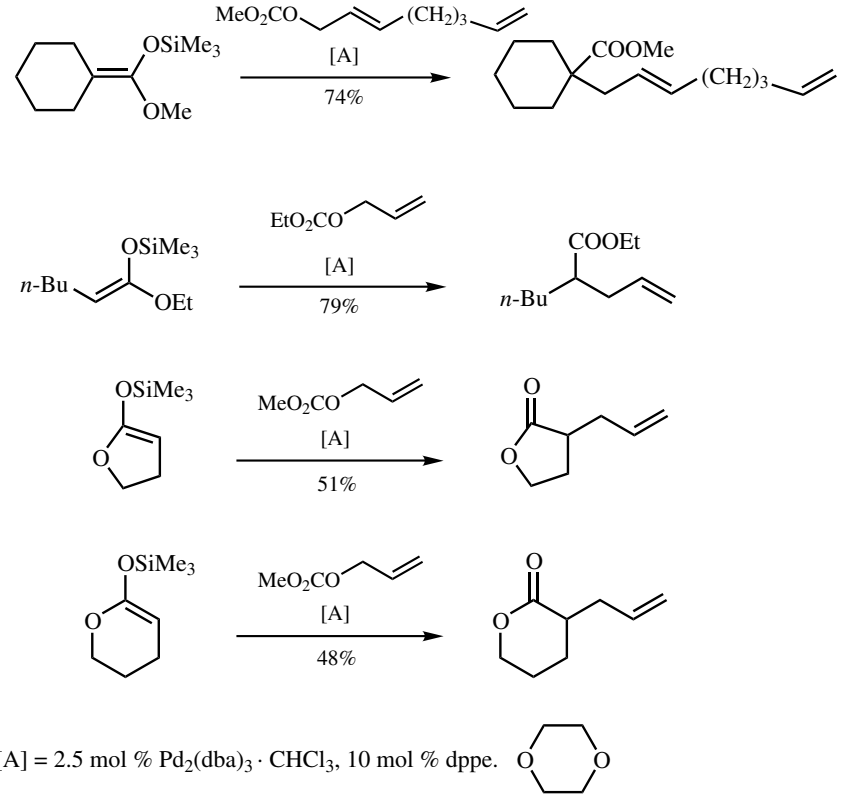
		$Pd(PPh_3)_4$, dppe	49		[26]
		$Pd(PPh_3)_4$, dppe	61		[26]
		$Pd(PPh_3)_4$, dppe	52		[21]

[a] [A] = 1% $Pd(dba)_2$ + dppe.
[b] The numbers in parentheses are GLC yields.
[c] Generated by the treatment of the lithium enolate with $Bu_3Sn{\cdot}OCOCF_3$.

TABLE 4. Pd-Catalyzed α-Allylation of Nitroalkanes

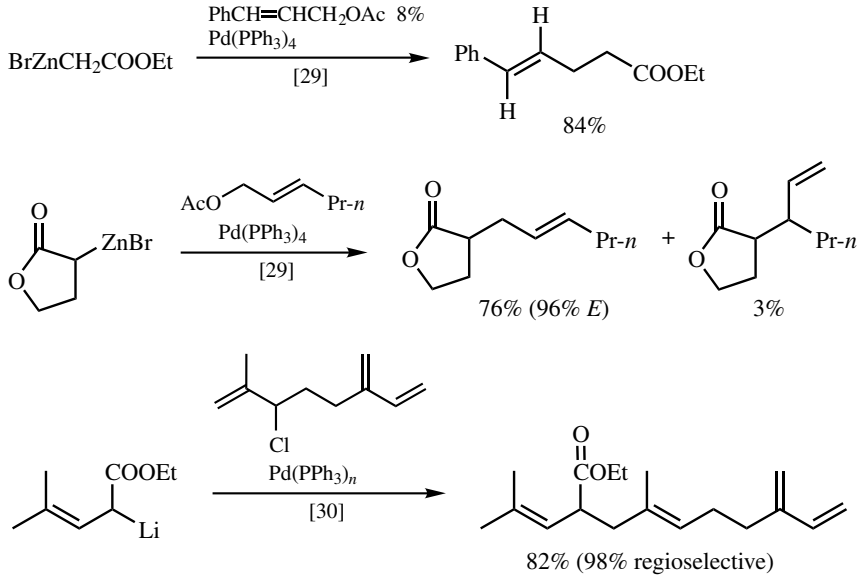


$R^1R^2C{=}NO_2Li$ **1**	R of $RCH{=}CHCH_2OAc$	**2** + **3** (%)	**2/3**
$CH_3CH{=}NO_2Li$	Ph	54	87:13
n-$BuCH{=}NO_2Li$	Ph	57	86:14
$PhCH{=}NO_2Li$	Ph	84	79:21
$PhCH{=}NO_2Li$	Me	81	49:51
$EtO_2CCH{=}NO_2Li$	Ph	73	>96:4
$EtO_2CC(Et){=}NO_2Li$	Ph	89	>97:3
$Me_2C{=}NO_2Li$	Ph	29	>93:7

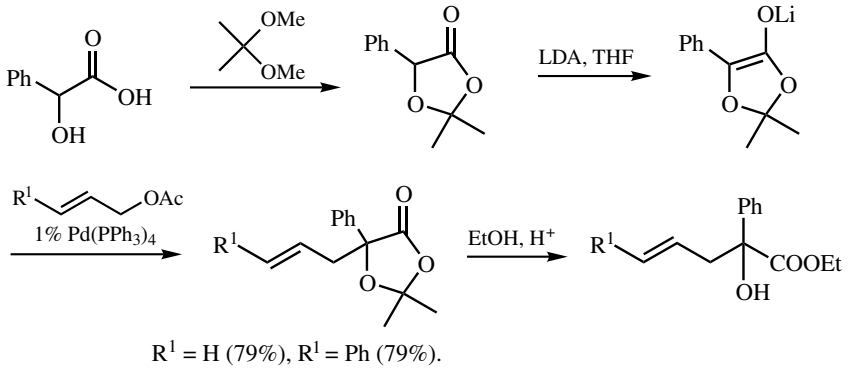


[A] = 2.5 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 10 mol % dppe.

Scheme 9



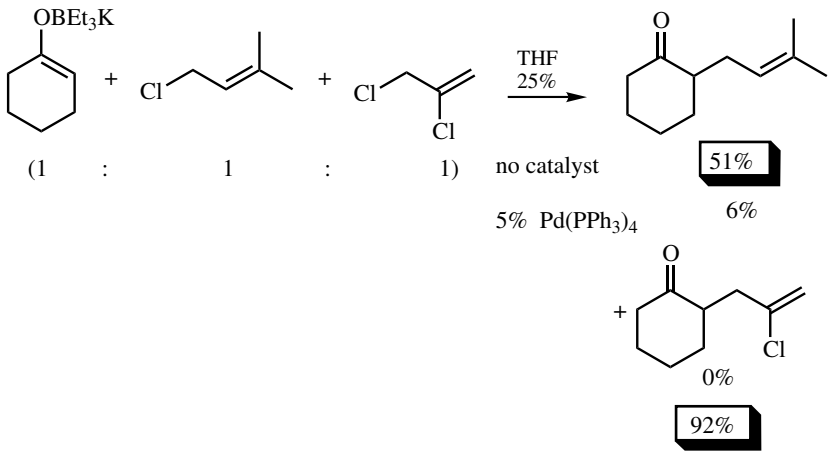
Scheme 10



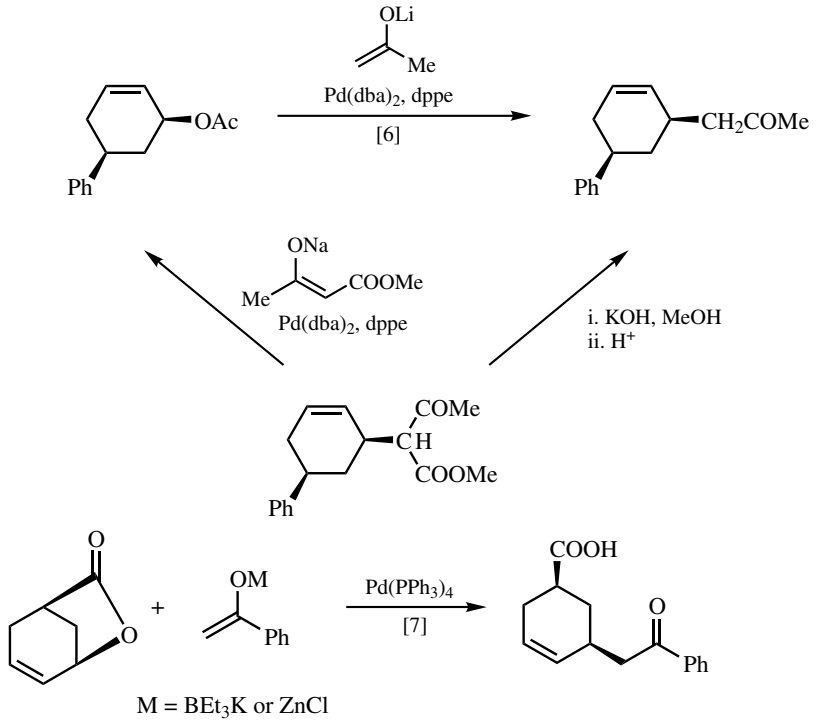
Scheme 11

established in such cases. For example, the sharply contrasting results presented in **Scheme 12** point to the unquestionable catalytic effect of $Pd(PPh_3)_4$.[8] Evidently, the higher reactivity of the more electron-deficient 2,3-dichloropropene in the oxidative addition steps is reflected in the results of the catalytic reaction.

The Pd-catalyzed allylation of "ordinary" enolates has been shown to proceed with net retention of the stereochemistry at the allylic carbon center[6],[12] just as in the reaction of "extra stabilized" enolates. The results shown in **Scheme 13** seem to rule out mechanisms involving attack of Pd by the enolates, favoring those involving the attack at the allylic carbon centers on the side opposite to Pd. As discussed below, however, the reaction in some cases may proceed by yet other mechanisms. In cases where more electronegative metals, such as Si and Sn, are involved, some addition–elimination mechanisms observed in the Heck reaction are likely candidates.



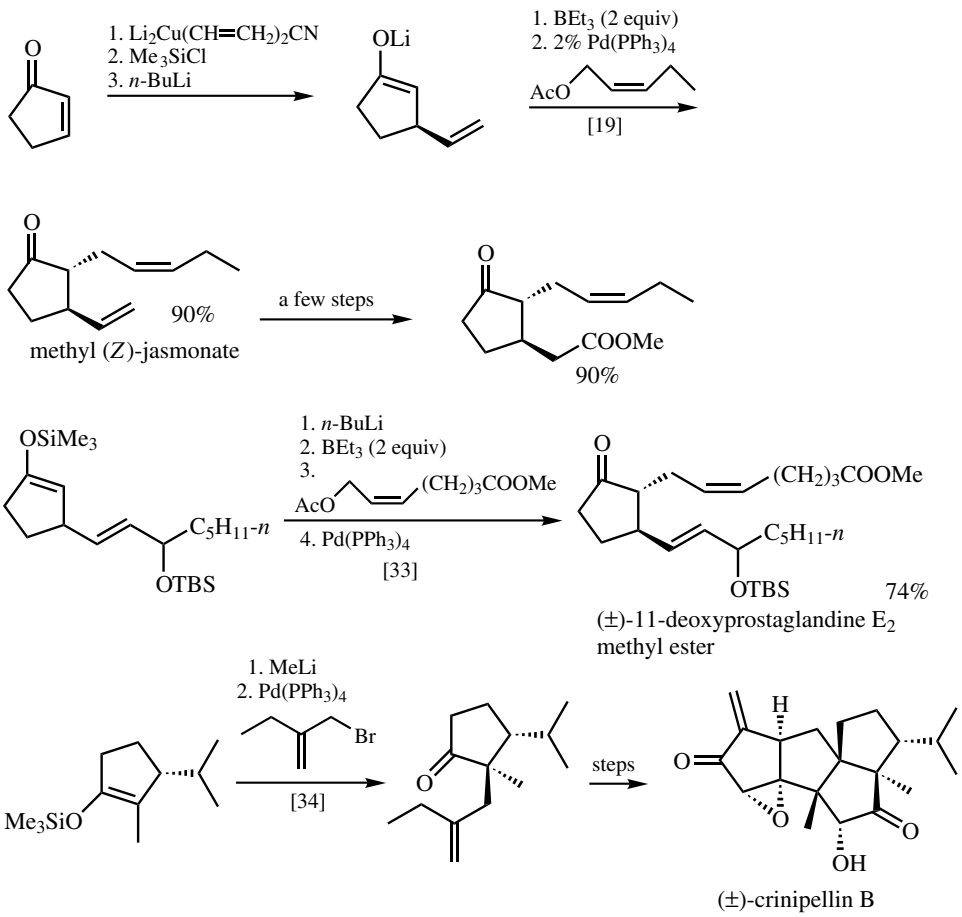
Scheme 12



Scheme 13

B.iv. Application to the Natural Products Synthesis

Although the Pd-catalyzed α-allylation of "ordinary" ketone enolates has not yet been extensively applied to the natural products synthesis, the number of such examples may be expected to increase in the future. A few representative examples are shown in **Scheme 14**.[19],[33],[34]



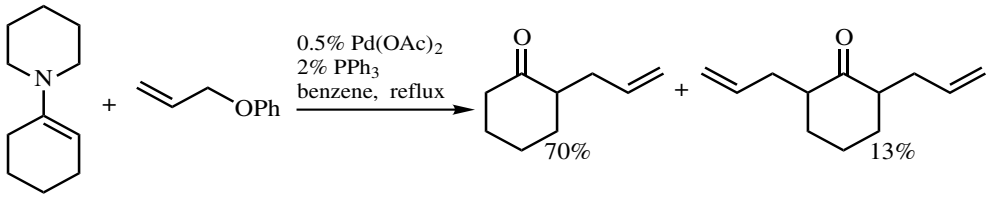
Scheme 14

C. PALLADIUM-CATALYZED ALLYLATION OF ENAMINES, IMINES, AND ENOL ETHERS

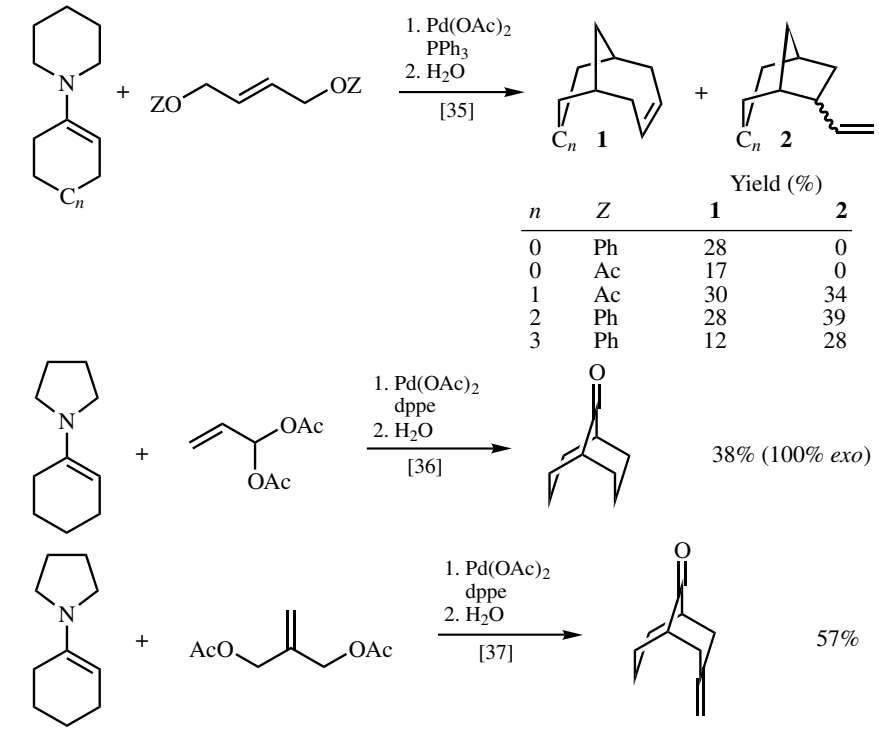
C.i. Palladium-Catalyzed Allylation of Enamines and Imines

Log before the Pd-catalyzed allylation of "ordinary" enolates was developed, the reaction of enamines with allyl phenyl ether was shown to be catalyzed by $Pd(OAc)_2$ and PPh_3[35] (**Scheme 15**).

Further details of the monoallylation do not appear to have been systematically investigated. So, its merits relative to those described in **Sect. B** are not clear. However, the reaction may be prone to diallylation as indicated by the results shown in **Scheme 15**. It should be noted that, unlike the reaction of metal enolates, the enamine reaction must produce iminium salts, which can readily be converted to the corresponding enamine for the second allylation under the reaction conditions. Indeed, this tendency to undergo diallylation has been exploited in the synthesis of bridged bicyclic ketones[35] and further expanded in subsequent investigations[36],[37] (**Scheme 16**).



Scheme 15



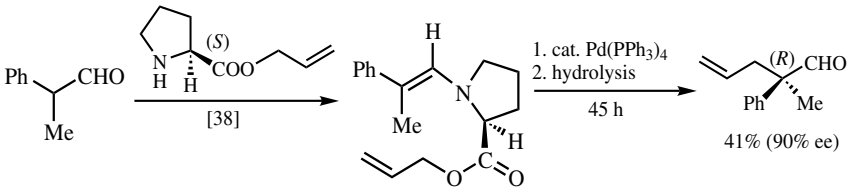
		Yield (%)	
n	*Z*	**1**	**2**
0	Ph	28	0
0	Ac	17	0
1	Ac	30	34
2	Ph	28	39
3	Ph	12	28

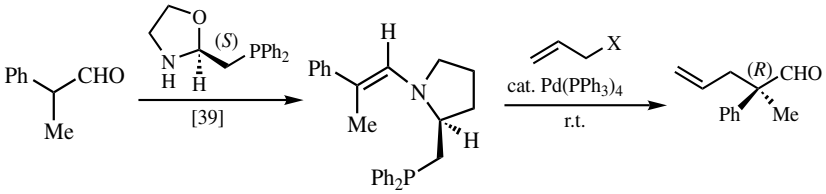
Scheme 16

More recently, the Pd-catalyzed allylation of enamines and imines has been applied to the enantioselective α-allylation of aldehydes and ketones in ee values up to 90%.[38]–[42] Until several years ago, the results obtained in this investigation represented some of the most favorable cases of the Pd-catalyzed enantioselective allylation. Several representative results are summarized in **Scheme 17**.[38]–[40] For the Pd-catalyzed allylation of 2-phenylpropionaldehyde with (*S*)-proline allyl ester, a mechanism involving an organopalladium complex shown in **Scheme 18**[38] has been proposed, and it does appear very plausible.

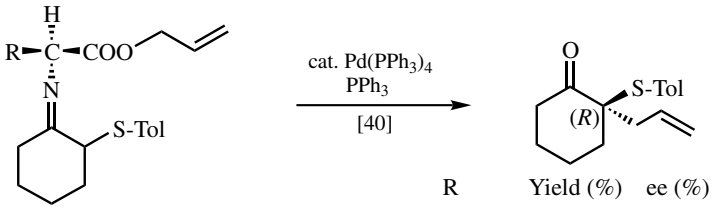
C.ii. Palladium-Catalyzed Allylation of Enol Ethers

The Pd-catalyzed Claisen rearrangement of allyl vinyl ethers to give α-allylated carbonyl compounds is a synthetic equivalent to those allylation reactions of enolates, enamines, and imines discussed in **Sects. B** and **C.i** as well as to the Tsuj–Trost reaction discussed in other sections. Although it is mostly discussed in **Part IX** as a rearrangement reaction,

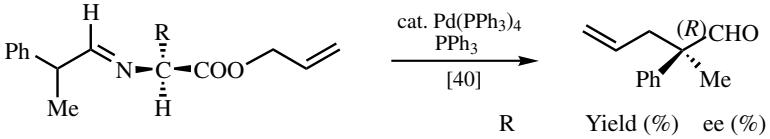




X	Time (h)	Yield (%)	ee (%)
p-$NO_2C_6H_4CO_2$	45	83	71
p-$MeC_6H_4SO_3$	45	77	79
o-$MeC_6H_4SO_3$	45	80	84
Br	45	77	88

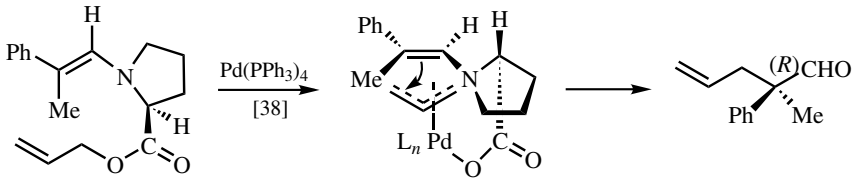


R	Yield (%)	ee (%)
i-Pr	58	87
s-Bu	80	77

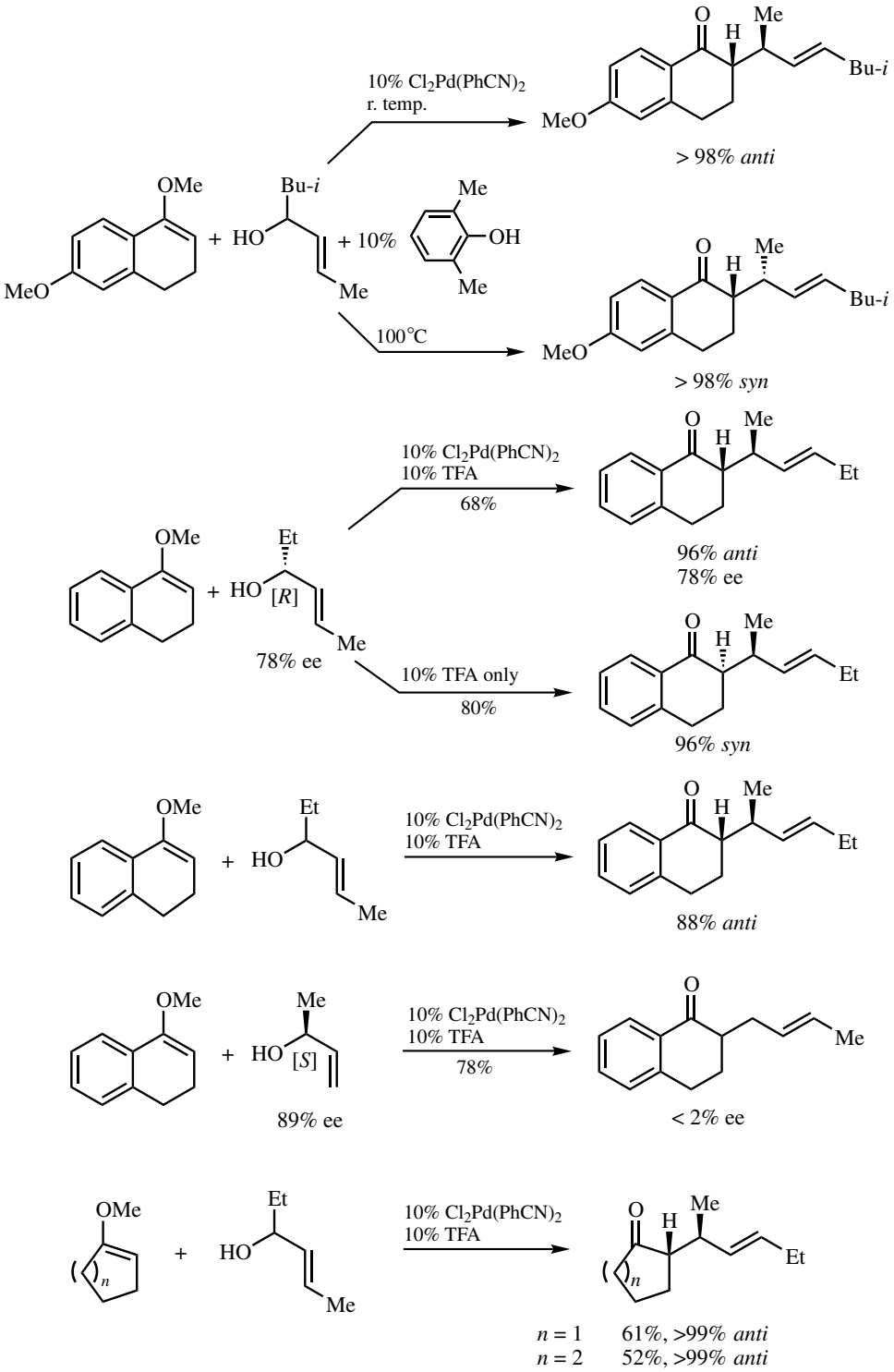


R	Yield (%)	ee (%)
i-Pr	67	99
s-Bu	89	81

Scheme 17



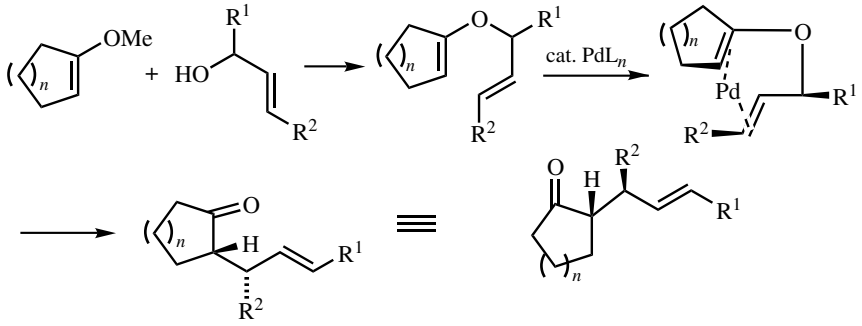
Scheme 18


10% Cl2Pd(PhCN)2
r. temp.
> 98% anti
100°C
> 98% syn
10% Cl2Pd(PhCN)2
10% TFA
68%
96% anti
78% ee
78% ee
10% TFA only
80%
96% syn
10% Cl2Pd(PhCN)2
10% TFA
88% anti
89% ee
78%
< 2% ee
n = 1 61%, >99% anti
n = 2 52%, >99% anti

Scheme 19

its variant involving the Pd-catalyzed reaction of alkenyl ethers with allylic alcohols[43] (**Scheme 19**) can be viewed as a variant of α-allylation reactions of carbonyl compounds. The results summarized in **Scheme 19** display several noteworthy features. First, in sharp contrast with the reaction catalyzed by 10 mol % of 2,6-dimethylphenol at 100 °C producing the *syn* product (>98% *syn*), the Pd-catalyzed reaction at room temperature (r.t.) gives the *anti*-product in >98% diastereoselectivity. Second, the reaction is highly regiospecific and proceeds with allylic rearrangement. The results indicate that the formation of full-fledged π-allylpalladium species may not be involved. The formation of such π-allylpalladium derivatives from 4-hexen-3-ol, for example, would be expected to lead to a mixture of two regioisomers. Third, the reaction is stereoconvergent but not stereospecific with respect to the alkene geometry in the allylic reagent. Fourth, a strict 1,3-chirality transfer within (3*R*,4*E*)-4-hexen-3-ol accompanied by inversion of the sense of chirality has been observed in its Pd-catalyzed reaction with 1-methoxy-3,4-dihydronaphthalene. However, the use of (*S*)-3-buten-2-ol (89% ee) in otherwise the same reaction has led to complete racemization.

The strict regiospecificity involving allylic rearrangement does not appear to be compatible with any of the mechanisms discussed earlier in this section or with any Heck-type addition–elimination reactions involving allylpalladium species directly derived from allylic alcohol via oxidative addition. On the other hand, it is consistent with the *in situ* formation of alkenyl allyl ethers, which can subsequently undergo a Pd-catalyzed Claisen-type rearrangement, as suggested by Nakai and co-workers[43] (**Scheme 20**). Even so, further mechanistic clarification of the reaction is highly desirable.



Scheme 20

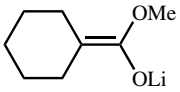
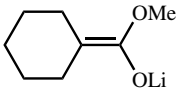
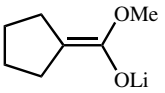
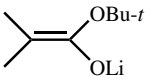
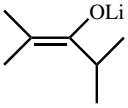
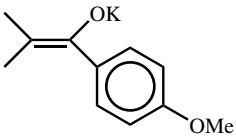
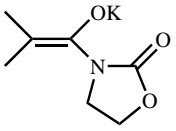
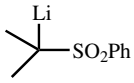
D. CYCLOPROPANATION OF ENOLATES BY π-ALLYLPALLADIUM DERIVATIVES

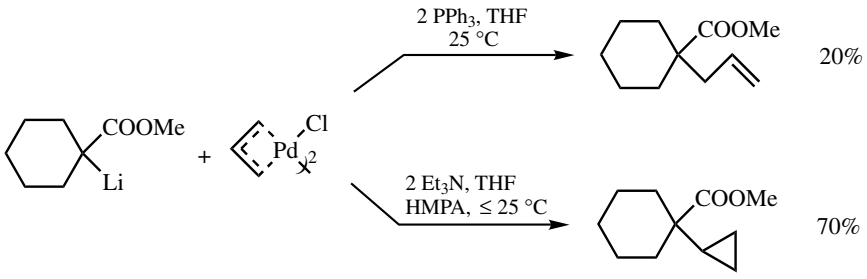
It was reported as early as 1980[44] that the reaction of the Li enolate of methyl cyclohexanecarboxylate with π-allylpalladium chloride can give either the expected α-allylated product or α-cyclopropyl derivative depending on the base and solvents used (**Scheme 21**).

The scope of this reaction has recently been expanded by the use of TMEDA and CO as added ligands, as indicated by the results shown in **Table 5**.[45],[46]

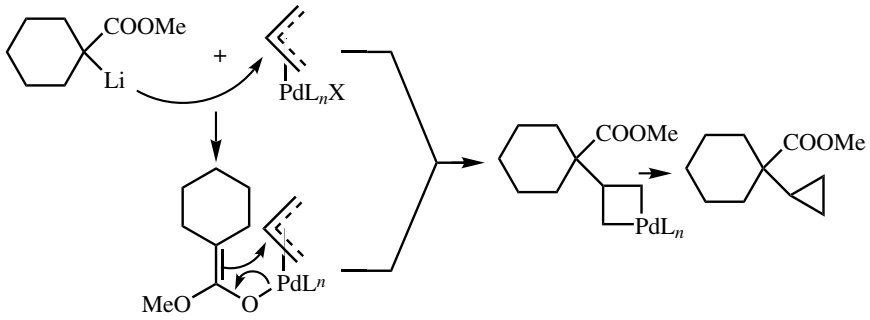
Nucleophilic attack at the central carbon atom of π-allylpalladium derivatives by enolates shown in **Scheme 22** has been suggested as a likely course of the reaction.[44]

TABLE 5. Scope of the Cyclopropanation of Enolates with π-Allylpalladium Chloride

Enolate	Added Ligands	Product Yield (%)	Reference
	HMPA, NEt_3	41	[45]
	TMEDA, CO	84	[45]
	TMEDA, CO	72	[45]
	TMEDA, CO	60	[45]
	TMEDA, CO	65	[46]
	TMEDA, CO	70	[46]
	TMEDA, CO	74	[46]
	TMEDA, CO	63	[46]



Scheme 21



Scheme 22

Although the reaction shown in **Scheme 21** and **Table 5** has been performed stoichiometrically, a related reaction of silyl ketene acetals has been carried out with catalytic amounts of Pd complexes,[47]–[49] and it promises to be synthetically useful.

E. SUMMARY

1. Contrary to earlier notions that the Pd-catalyzed α-allylation of carbonyl compounds would be limited to those carbonyl compounds that are "extrastabilized" (the Tsuji–Trost reaction), the use of Zn, B in the forms of BR_3K or Li + 2 BR_3, where R = Et, and so on, Si, and Sn has been shown to permit the use of those enolates of "ordinary" ketones, aldehyde esters, and so on, where the pK_a of the carbonyl compounds may be $\geq$20. In some cases, however, even lithium enolates can provide satisfactory results. Since most of the enolates mentioned above are derived via alkali metal enolates containing Li, Na, or K, these parent enolates should be tested before converting or modifying them with reagents containing other metals.

In more difficult and demanding cases where regio-, stereo-, and chemoselectivities associated with the carbonyl compounds and the allylic reagents are to be maintained at very high levels, Zn, B, and Sn, especially Zn and B, have often been effective. Through the use of BEt_3K as the countercation, for example, both regio- and stereospecificities associated with the allylic reagents and the regiospecificity with respect to the enolates can be higher than 90–95%.

2. As in the other Pd-catalyzed allylation, a wide range of allylic derivatives containing halogens (e.g., Cl), carboxylates (e.g., OAc), carbonates (e.g., phenyl ethers), and so on can satisfactorily be employed. That the reaction of allyl halides can indeed be catalyzed by Pd complexes is clearly seen in those cases where the order of reactivity of allylic reagents is reversed through the use of Pd complexes in addition to the rate acceleration.

3. As in the Tsuji–Trost reaction, the stereochemistry at the leaving group-bearing allylic carbon center is retained. The results support the double-inversion mechanism involving a nucleophilic attack of the π-allyl ligands by the enolate on the side opposite to Pd. The results seem to rule out the reductive elimination mechanism widely accepted for various Pd-catalyzed cross-coupling (**Part III**), which involves a nucleophilic attack of Pd by the nucleophilic reagent. However, some other mechanisms involving allylpalladation

and β-elimination, as in the Heck reaction, must seriously be considered, although not yet strongly supported by mechanistic studies. The addition–elimination mechanism is particularly likely in cases where highly electronegative metals, such as Si, are used.

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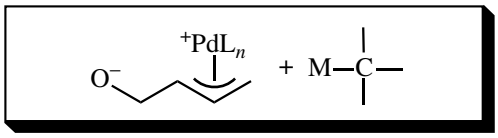

V.2.1.5 Palladium-Catalyzed Substitution Reactions of Alkenyl Epoxides

CHRISTINE COURILLON, SERGE THORIMBERT, and MAX MALACRÌA

A. INTRODUCTION

The reaction of alkenyl epoxides with organometallic species (lithium, magnesium, copper, and boron) affords allylic alcohols, following an S_N and/or $S_{N'}$ mechanism. These processes can accommodate only little organic functionality and exhibit low regio- and/or stereoselectivity. Under smooth conditions, C—C bond formation proceeds by nucleophilic alkylation of vinyl epoxides in the presence of catalytic amounts of zerovalent palladium. Regio- and stereoselectivity can be achieved via the formation of a π-allylpalladium complex. Trost and Molander[1] and Tsuji and co-workers[2] simultaneously reported the first studies in 1981. Since then, numerous papers have dealt with this subject. Essentially, after chelation and oxidative addition of the palladium onto the vinyl epoxide, the zwitterionic π-allylpalladium complex deprotonates the nucleophile, which can in principle attack either carbon 2 (proximal attack) or 4 (distal attack) (**Scheme 1**).

The use of substituted vinyloxiranes shows that electronic and steric effects can strongly influence the reaction. Inter- or intramolecular reactions, acyclic or cyclic precursors, and applications to the synthesis of natural molecules will be presented in this section. We will analyze some general aspects of the reactivity of these electrophiles and focus on the regio- and stereochemical course of this reaction. The influence of the nucleophiles will be discussed, and finally, the overall potential of this Pd-catalyzed alkylation will be shown through some applications to the synthesis of cyclic molecules.

B. INTERMOLECULAR REACTIONS

B.i. Acyclic Vinyl Epoxides

B.i.a. ***Reactivity and Regioselectivity.*** As a model for studies on the Pd-catalyzed addition of carbon nucleophiles on acyclic vinyl epoxides, butadiene monoxide[1],[3]–[5] has been studied extensively. Nucleophiles attack predominantly at the less hindered position of the cationic π-allylpalladium complex. Due to steric effects and in some part for electronic reasons, it appeared that with vinyl epoxides, highly regioselective reactions took place and 1,4-addition of the nucleophile is generally the major process.

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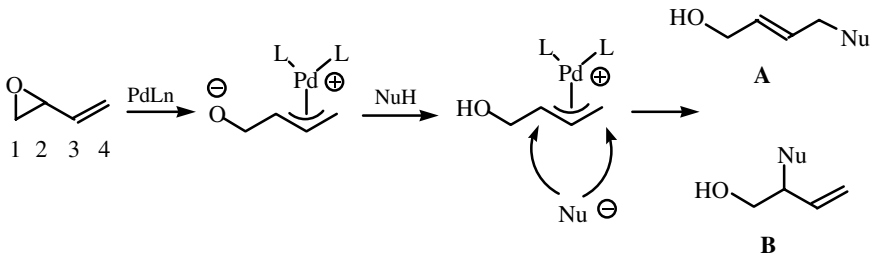
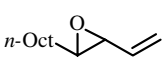
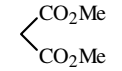
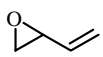
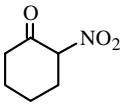
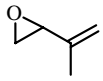
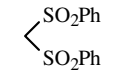
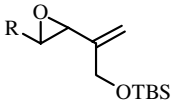
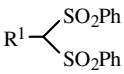
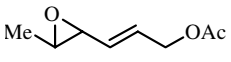
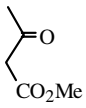
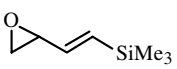
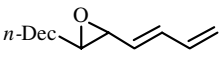
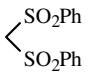


Scheme 1

Alkyl, alkenyl, aryl, and silyl substituents have been introduced with success on the four available carbon atoms.[1],[2],[6],[7] Some examples are reported in **Table 1**.[2],[8]–[11]

Some positions are more strategic than others: substitutions at position 1 or 2 have little effect and regio- and stereoselectivities are partially influenced.[12] In contrast, C3 and C4 substituents tend to dramatically change the addition products. C3 groups are more likely to influence the stereochemistry of the double bond. Indeed, the *E*/*Z* ratio decreases when the bulkiness of the C3 substituents increases. In the recent synthesis of

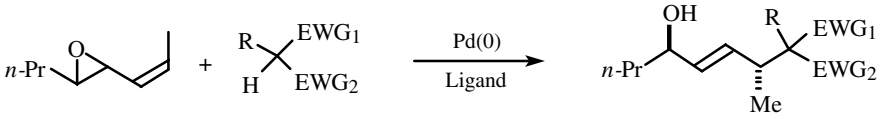
TABLE 1. Pd-Catalyzed Alkylation of Stabilized Nucleophiles with Vinyl Expoxides

Vinyl Epoxide	Nucleophile	Catalyst	Yield (%)	1,4/1,2	E/Z	Reference
		I	84	100:0	96:4	[2]
		I	90	100:0	100:0	[8]
		II	66	100:0	80:20	[9]
		I	84	100:0	42:58	[10]
		III	72	89:11	n.d.	[2]
	"	IV	76	0:100	100:0	[11]
		I	92	1,6 addition	100:0	[8]

I = $Pd(PPh_3)_4$. II = $Pd_2(dba)_3$, dppe. III = $Pd_3(TBAA)_3{\cdot}CHCl_3$, ETPB. IV = $Pd_2(dba)_3$, PPh_3.

furanoterpenes and of Roseophilin,[10],[13] Fürstner and co-workers reported that in some cases the *Z* addition product was favored. Vinyl epoxides are usually very reactive species in the presence of zerovalent palladium. In the initial study, Tsuji and co-workers demonstrated that such epoxides reacted efficiently, even in the presence of allylic acetates or ethers in the same molecule.[2]

Substituents at C4 may have a very pronounced effect on the reactivity or the regioselectivity. For example, due to strong stereoelectronic effects, trimethylsilyl groups[11] were found to completely reverse the usual regioselectivity to give the 1,2-adduct as the unique product. Vinyl groups may also change the regioselectivity by the possible migration of the double bond to give the product resulting from the 1,6-attack of the nucleophile at the less hindered, distal position.[8] With C4 alkyl substituents, the bulkiness of the nucleophile is now critical and the presence of too hindered substituents either inhibits the reaction or leads to the rearranged α,β-unsaturated ketones or to the 1,2-addition products.[8],[14] The following scheme presents the effect of the substitution pattern at C4 with different nucleophiles (**Scheme 2**).

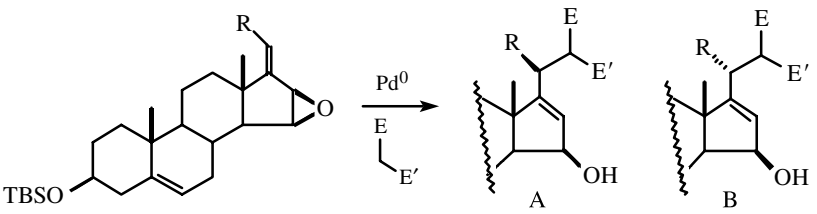


R	EWG_1	EWG_2	Pd Complex	Yield (%)
H	$PhSO_2$	$PhSO_2$	$Pd(PPh_3)_4$	62
Et	$PhSO_2$	$PhSO_2$	$Pd(PPh_3)_4$	0
H	$PhSO_2$	MeCO	$Pd(dba)_2$, ETPB	55
Me	$PhSO_2$	CN	$Pd(OAc)_2$, P(O*i*-Pr)$_3$	55
Et	Meldrum's acid		$Pd(OAc)_2$, P(O*i*-Pr)$_3$	75

Scheme 2

The effect of the catalyst and the ligands has not been discussed yet; however, it plays an important role. For example, by replacing the classical phosphine ligands by a hydrosoluble sulfonated triphenylphosphine (TPPTS), Safi and Sinou carried out a reaction with butadiene monoxide and ethyl acetoacetate in a two-phase aqueous–organic medium.[15] The recycled water layer containing the catalyst could be reused with very high efficiency for a second reaction. As a matter of fact, the corresponding ethyl ester of the 2-acetyl-6-hydroxy-4-hexenoic acid was isolated in 80% and 87% yield (*Z*/*E* = 15:85) after the first and the second reaction, respectively.

B.i.b. ***Stereoselectivity–Chirality Transfer.*** Very few examples are reported in the literature of intermolecular reactions with acyclic precursors concerning the possible chiral transfer from the 2 to the 4 position. The first publication appeared in 1985 with the stereoselective synthesis of steroids.[16] It has been shown that sometimes a slight loss of the stereochemistry (less than 5%) occurred during the addition (**Scheme 3**). Other examples[14],[17] have reported total chirality transfer and good yields. In the synthesis of allopumiliotoxin 339B, Trost and Scanlan reported[18] total regio- and stereocontrol during the addition of a sulfone on an indolizidine bearing a vinyl epoxide moiety.

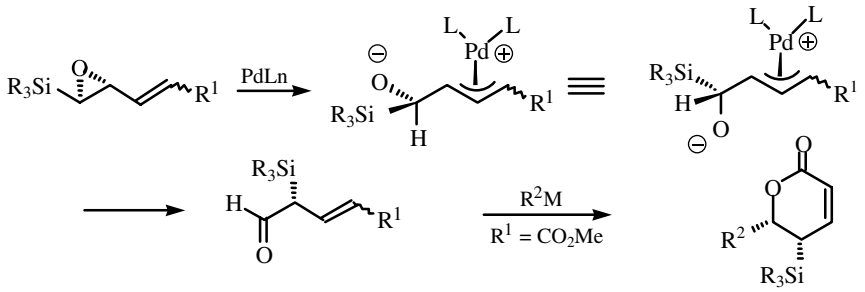


R	E	E′	Pd^0 (mol %)	Yield	A/B
C_6H_{13}	CO_2Me	CO_2Me	5	83	95:5
C_6H_{13}	$TolSO_2$	CO_2Me	10	73	95:5
C_6H_{13}	$PhSO_2$	$PhSO_2$	10	—	—
CH_3	*i*-BuCO	CO_2Me	5	91	100:0

Pd^0: $Pd(TBAA)_3$, $CHCl_3$ + ETPB, THF, r.t.

Scheme 3

For some years, we have been investigating the Pd-catalyzed rearrangement of chiral silylated vinyl epoxides.[19] Depending on the substituents attached to the silyl group and the ligands borne by the palladium, a very fast, totally stereoselective 1,2-carbon to carbon transfer of the silyl group was observed. Application to the enantioselective preparation of α,β-unsaturated lactones has been developed (**Scheme 4**).



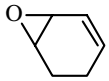
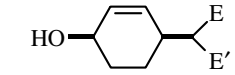
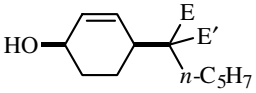
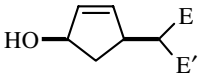
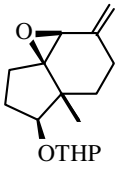
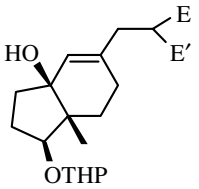
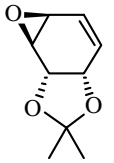
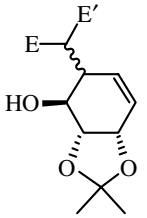
Scheme 4

B.ii. Cyclic Vinyl Epoxides

Alkylations of cyclic vinyl epoxides are highly regio- and stereoselective. Some representative examples are given in **Table 2**.

1,4-Addition is usually the main process and products are isolated in good yields. In one particular case reported in 1997, the nonstereoselective 1,2-alkylation of dimethyl malonate on the monoepoxide derived from *cis*-1,2-dihydroxy catechol has been explained by electronic and steric effects of the bulky side chain dioxolane ring.[21] One can say that almost every vinyl epoxide is a good electrophile for Pd-catalyzed alkylations. The possible variation around the metal center and the tolerance toward aqueous or organic solvents extend the long list of nucleophiles available for C—C bond formation.

TABLE 2. Pd-Catalyzed Alkylation of Cyclic Vinyl Oxiranes

Electrophile	E	E′	Product	Yield(%)[a]	Reference
	CO_2Me	CO_2Me		74	[1]
	SO_2Ph	SO_2Ph		49[b]	[5]
	CO_2Me	CO_2Me		57	[1]
	CO_2Me	CO_2Me		83	[20]
	CO_2Me	CO_2Me		87	[1]
	CO_2Me	CO_2Me		65	[21]

[a] Reactions performed with $Pd(PPh_3)_4$ as catalyst.
[b] Yield for two consecutive Pd-catalyzed alkylations.

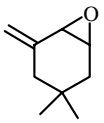
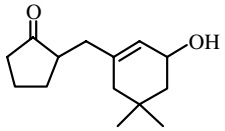
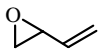
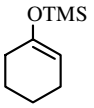
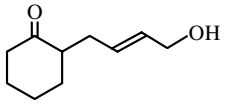
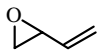
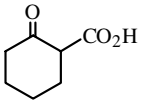
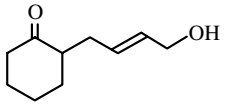
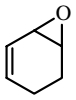
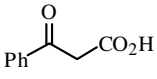
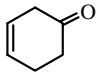
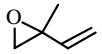
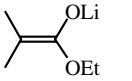
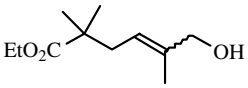
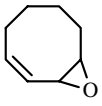
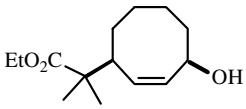
The next section presents some other nucleophilic systems used in Pd-catalyzed C—C bond formation.

C. NONSTABILIZED NUCLEOPHILES

C.i. Preformed or Masked Enolates

We mentioned that by mixing vinyl epoxides and zerovalent palladium, the alcoholate formed was usually sufficiently basic to deprotonate the pronucleophile entity. In some cases, especially with ketones, low reactivity and yields were reported (**Table 3**).[1] To overcome the problem of the weak basicity of the alcoholate, silyl enol ethers, keto acids, or preformed lithium enolates have successfully been employed.[3],[4],[22],[23] β-Keto acids are masked enolates via the decarboxylation of the intermediary π-allylpalladium β-ketocarboxylate complexes. The main limitation of the use of keto acids as pronucleophiles seems to be their low reactivity toward the hindered cyclic vinyl epoxides. In these cases, the cationic π-allylpalladium complex undergoes β-elimination. Indeed, the reaction between benzoyl acetic acid and cyclobutadiene monoxide in the presence of $Pd(PPh_3)_4$ gives only the corresponding cyclopentanone and acetophenone as the

TABLE 3. Nonstabilized Nucleophiles

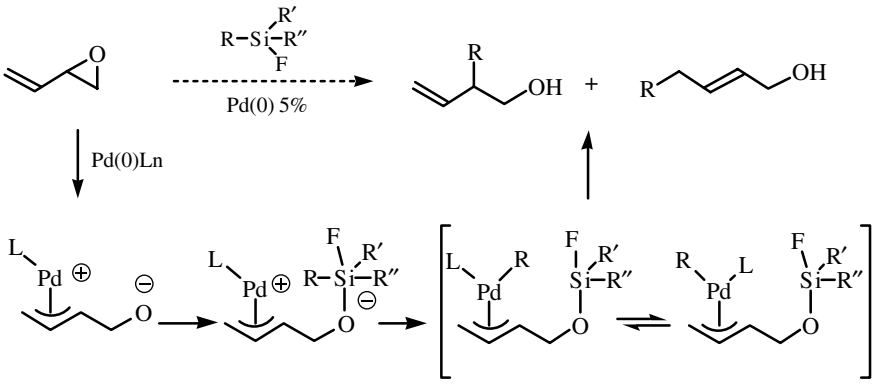
Vinyl Epoxide	Pronucleophile	Catalyst[a]	Product	Yield % (*E*/*Z*)	Reference
		I		29	[1]
		II		n.d.[b]	[3]
		I		86 (92:18)	[4]
		I		73	[4]
		II		90 (80:20)	[22]
	"	II		57	[23]

[a] Catalyst: I = 5 mol % $Pd(dppe)_2$. II = 5 mol % $Pd(PPh_3)_4$.
[b] Yield was 63% after two other reactions.

products. Lithium enolates of α,α-disubstituted esters react with butadiene monoxides in moderate to good yields to give mainly the expected *E*-adduct with total transfer of the chirality. This efficient access to the *E*-ethyl-2,2-dimethyl-6-hydroxyhex-4-enoate framework has been applied to the total synthesis of the *epi*-illudol.

C.ii. Vinyl and Aryl Nucleophiles

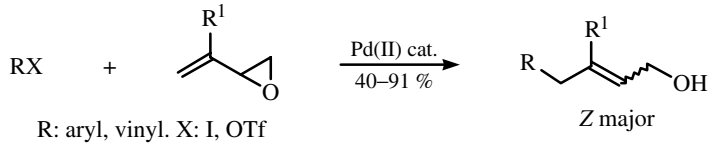
C.ii.a. ***Silyl Derivatives.*** A Japanese group recently reported an original Pd-catalyzed reaction with vinyl- or aryl-fluoro silyl derivatives and vinyl epoxides.[24] A mechanism involving a zwitterionic η^3-allylpalladium silicate intermediate has been proposed (**Scheme 5**). Intramolecular transmetallation can give two η^3-allylorganopalladium complexes in equilibrium. The steric bulkiness of the phosphine ligand as well as its electronic affinity are responsible for the 1,2/1,4-product distribution.



Scheme 5

C.ii.b. ***Organometallic Derivatives.*** The Pd-catalyzed reaction of organoboron, stannanes, and mercurial derivatives with vinyl epoxides has been developed over the last two decades.

Alkenyl boranes react with epoxybutene derivatives to form the corresponding coupling products in moderate to good yields. The branched versus linear selectivity depends on the nature of the palladium catalyst.[25] Another approach reported by Larock and co-workers[26],[27] with vinyl epoxides or oxetanes consists in using organomercuric derivatives as nucleophiles. The addition of a stoichiometric or catalytic amount of Pd(II), in connection with aqueous NH_4Cl, clearly influences the *Z*/*E* ratio. Under catalytic conditions, $CuCl_2$ (1 equiv) and an oxygen atmosphere were required to regenerate the catalyst. Neat 1,4-addition is observed for acyclic vinyl epoxides. In contrast, cyclopentadiene monoxide underwent phenyl palladation to afford a mixture of two regioisomers, both *trans*-substituted allylic alcohols. Mechanistic insight is thus available. After transmetallation, the addition of the aryl- or vinyl-palladate to the olefin is followed by an *anti* elimination of the palladium and the oxygen. Another approach related to this work was published in 1990 and 1993.[28],[29] The authors replaced the organometallic reagents by more readily available organic halides or triflates. Good yields of the desired allylic alcohols can be achieved using $Pd(OAc)_2$ as catalyst in the presence of a mixture of an ammonium salt, an amine, and a formate (**Scheme 6**). The stereochemistry of the vinylic halide is retained during this cross-coupling process but low stereoinduction is observed for the newly formed carbon–carbon double bond.



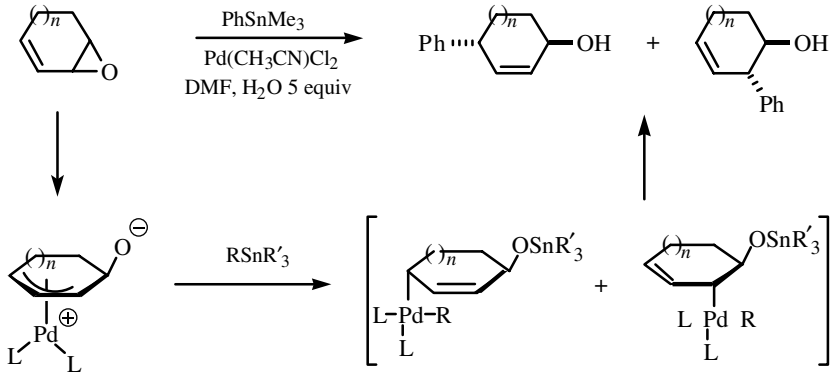
Conditions: 10 mol % $Pd(OAc)_2$; 5 equiv HCOONa; 2 equiv *n*-Bu_4NCl; 3 equiv *i*-Pr_2NEt; 5 equiv of vinylic epoxide and 1 equiv of RX in DMF, 80 °C, 1 day.

Scheme 6

The requirement of an excess of vinyl epoxide constitutes the limiting aspect of this reaction, which offers a very efficient palladium methodology of high synthetic power.

Starting from organotin derivatives, Stille, Echavarren, and co-workers[7],[30] reported the isolation of the coupled products in good yields and regioselectivities. Optimization of the reaction conditions showed that addition of 5 equiv of water to the DMF solution containing the reagents and the catalyst increases the efficiency of the reaction in terms of regio- and stereoselectivity. The olefin geometry is maintained in the vinyltin reagent but usually lost in the vinyloxirane moiety. As for organomercurial nucleophiles, global inversion of the configuration was observed. After formation of the zwitterionic π-allylpalladium complex, the weakly coordinated palladium(II) species presumably acts as an electrophile in breaking the tin carbon sp^2 bond. *Syn* reductive elimination could then explain the yielding of the two regioisomers (**Scheme 7**). In a competitive study, it has been shown that weakly ligated palladium catalysts favor the Stille cross-coupling products whereas classical ligands favor the Tsuji–Trost alkylation.[31]

Applications of all these Pd-catalyzed processes in cyclizations will be discussed in the following subsections.



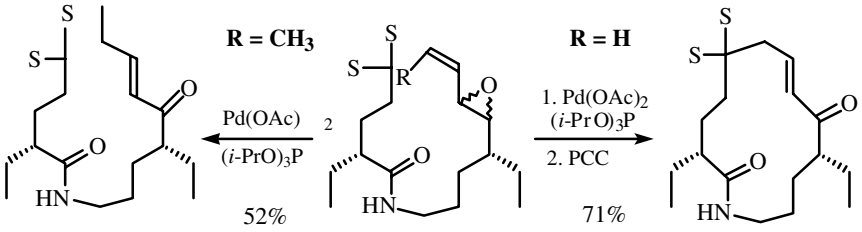
Scheme 7

D. PALLADIUM-DIRECTED CYCLIZATIONS

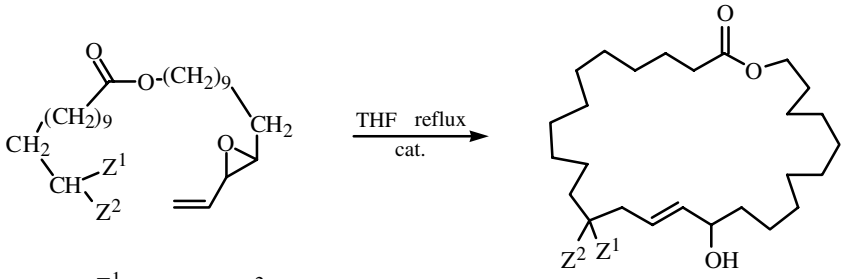
D.i. Macrocyclizations

Among the intramolecular processes, macrocyclizations are the closest to intermolecular reactions. Substituents attached to the double bond of the starting vinyloxirane may have a dramatic effect on the course of the macrocyclization (**Scheme 8**).[14],[32]

Scheme 8 illustates how the terminal epoxyolefin cyclizes into a 14-membered ring product whereas the methyl-substituted vinyloxirane isomerizes into the conjugated enone. Macrolide formation (**Scheme 9**)[33] may be achieved with polymer-supported palladium, which avoids high dilution of the medium. A 27-membered ring is obtained in a stereoselective manner as an [*E*]-allylic alcohol derivative. The success of this reaction is strongly dependent on the nature of the nucleophile included in the starting alkenyl epoxide. Replacement of one of the sulfone groups by a methyl ester function failed to produce the macrolide. Indeed, drastic regiochemical directing effects have been reported in Pd-catalyzed alkylations with polyene electrophilic partners. Disulfones



Scheme 8



Z^1	Z^2	Yield (%)	Catalyst
SO_2Ph	SO_2Ph	70%	P—Pd
SO_2Me	SO_2Me	87%	P—Pd
SO_2Me	$COOCH_3$	97%	$Pd(PPh_3)_4$

Scheme 9

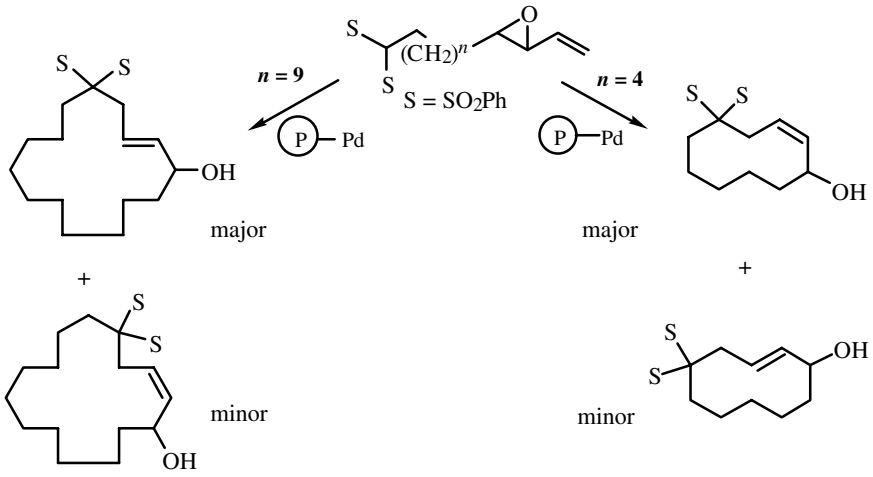
are responsible for attack on the most remote pole of the π-allyl unit leading to large rings.[8] Trost has compared different pronucleophiles in this macrocyclization process. The bis-methanesulfonyl derivative ($Z = SO_2CH_3$) (**Scheme 9**) cyclizes in 15 minutes versus 3 hours for the bis-benzenesulfonyl compound ($Z = SO_2Ph$), although the latter is more acidic than the former.

Therefore, this behavior could not be monitored by thermodynamics. The role of the "active site" of the catalyst was demonstrated by submitting the sulfone/ester derivative to a homogeneous catalyst (5 mol % $Pd(Ph_3P)_4$, 10 mol % dppe) at 0.001 M in THF, which led to cyclization (**Scheme 9**).

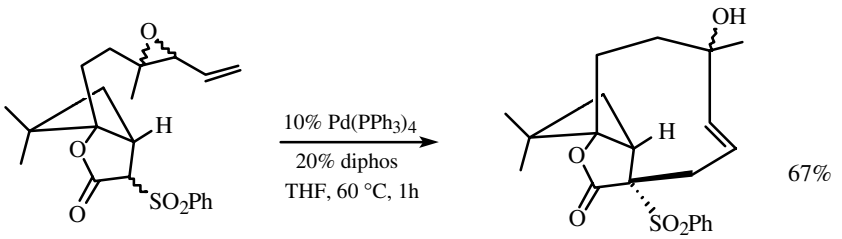
The technique of "pseudodilution" using palladium on a polymer support avoids a high level of dilution and leads to a more efficient macrocyclization but stereoselectivity is poor.[34] **Scheme 10** depicts the formation of a 2:1 ratio of diastereomeric alkenes included in medium sized ($n = 4$) rings as well as a 4:1 ratio in the case of larger rings ($n = 9$).

Reaction of the smaller vinyloxirane ($n = 4$) with 5 mol % $Pd(PPh_3)_4$ in the presence of dppe yielded only oligomeric product, proving therefore the necessity of polymer-supported palladium for monomeric cyclizations.

The dramatic regioselectivity makes Pd-catalyzed macrocyclizations of vinyl epoxides valuable key steps in total synthesis. A wide variety of skeletons are thus attainable. Kende and co-workers synthesized the sesquiterpenic Punctaporonine B via a highly regioselective transformation of a diastereomeric mixture of a bicyclic vinyloxirane into an epimeric mixture of (*E*)-cyclononene alcohols (**Scheme 11**).[35]

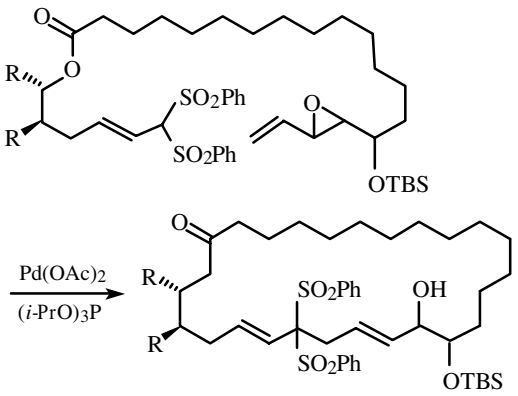


Scheme 10



Scheme 11

In the field of natural dienic macrocycles, formation of the Tetrin A skeleton was targeted through Pd-based macrolactonization of an alkenyl epoxide (**Scheme 12**) to afford the dienic 26-membered ring,[36] with a yield of 92% in the case of a good π-acceptor ligand such as tri-*iso*-propyl-phosphite, which reduces palladium diacetate to zerovalent palladium.

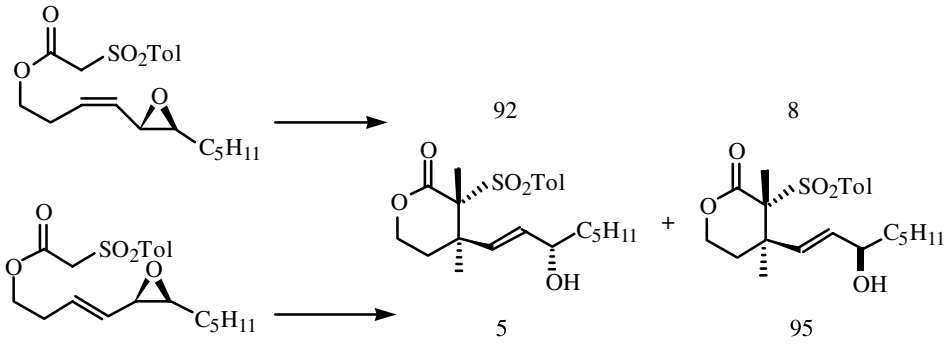


Scheme 12

Occurrence of these poorly favorable macrocyclizations can be explained by close proximity of the charged poles in the π-allylic intermediate.

D.ii. Medium Sized Cyclizations

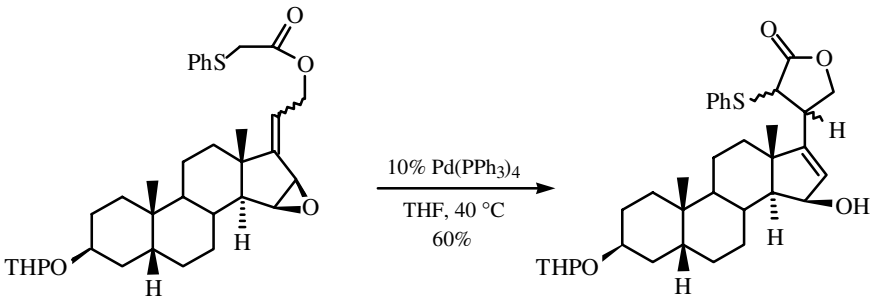
Pd-catalyzed cyclizations of 1,3-diene monoepoxides have thoroughly been studied due to their powerful applications in the total synthesis of natural products such as steroid precursors, vitamin intermediates, or δ-lactone moieties. For example, diastereo- and regioselective cycloisomerization of a diestervinyloxirane leads to the δ-lactonic precursor of Cholestane (**Scheme 13**).



Scheme 13

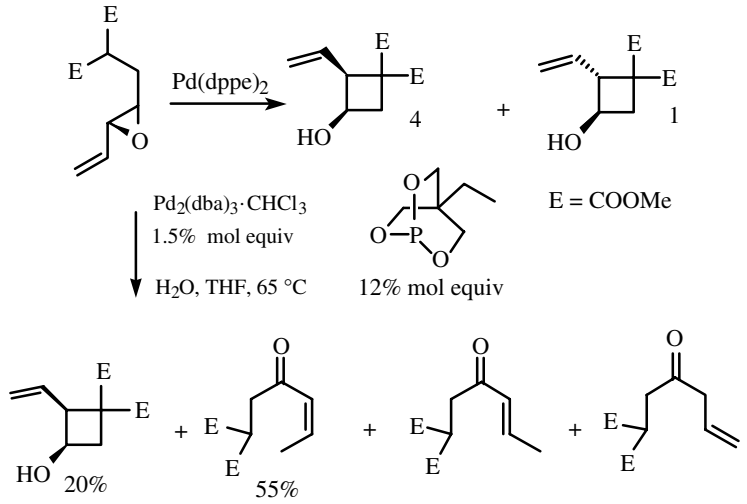
The presence of a base or high concentrations of palladium lead to racemization.[37] Neither the *Z* olefinic isomer nor the eight-membered lactone was isolated, indicating a preference for a 6-*exo-trig* rather than an 8-*endo-trig* path. The *trans* stereochemistry of the newly created C—C bond was established by NMR. The two diastereomeric δ-lactones are epimeric at the hydroxylated carbon.[38]

A 5-*exo-trig* process was reported for the formation of γ-lactones by isomerization of a vinyloxirane borne by a steroid skeleton. Yields of these lactones are strongly linked to the preparation of the catalyst.[39],[40] **Scheme 14** depicts the key step in the synthesis of Digitoxigenin.



Scheme 14

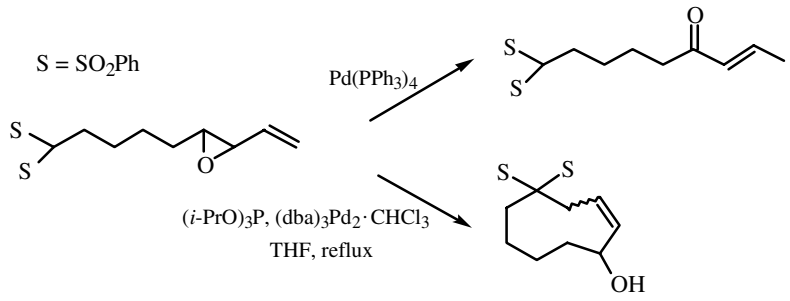
In an attempt to obtain some 6-*endo-trig* cyclization product, a β-disubstituted vinyloxirane was submitted to various zerovalent palladium sources (**Scheme 15**). Only a 4-*exo-trig* cyclization resulting from a proximal attack was observed and the formation of two diastereomeric cyclobutanol derivatives demonstrates a high regioselectivity in these Pd-catalyzed reactions.[41] Depending on the nature of the ligand some rearrangement acyclic products could be isolated. The vinyl cyclobutane diesters did not undergo any further 6-*endo-trig* cyclization as has been shown in the case of a substituted double bond linked to the cyclobutane moiety.[42]



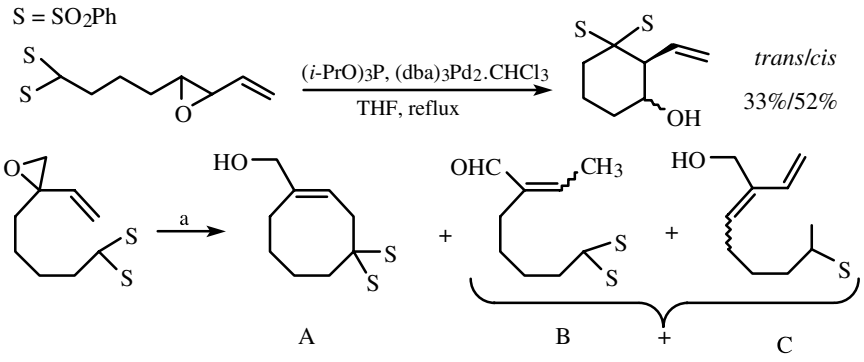
Scheme 15

The influence of palladium ligands may be drastic in terms of stabilization of the π-allyl complex, directing the reaction toward a 9-*endo-trig* process or a rearrangement (**Scheme 16**).

An analogous vinyloxirane, which can cyclize as an eight-membered ring, is transformed into a cyclohexanol (6-*exo-trig*) despite the great steric demand of the bissulfone moiety. Enhancing this steric effect favors the less thermodynamically preferred 8-*endo-trig* mechanism (**Scheme 17**).[43]



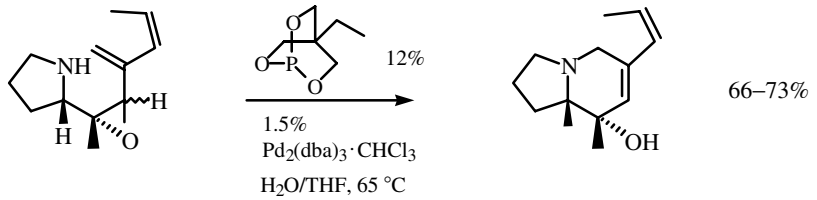
Scheme 16



a: $(i\text{-PrO})_3P$	$(dba)_3Pd_2\cdot CHCl_3$	A	B + C
8	1	1.2	1
23	1	2.6	1

Scheme 17

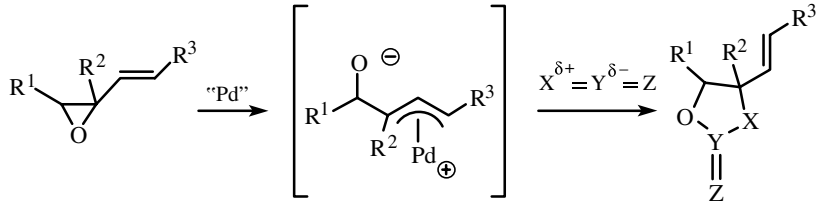
Heterocycles can be formed through C–heteroatom bonding occuring via Pd-catalyzed cyclization (**Scheme 18**). This latter example, a 6-*endo-trig* cyclization, is the key step in the allopumiliotoxin 339B synthesis.[18]



Scheme 18

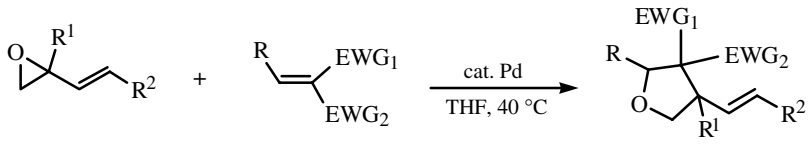
D.iii. Cycloadditions

Less common than the previously described macrocyclizations, Pd-catalyzed reactions of unsaturated substrates ($X^{\delta+}{=}Y^{\delta-}{=}Z$) with vinyloxiranes yield cycloadducts. Hetero-cumulenes have been used (**Scheme 19**) : isocyanates (RN═C═O) and carbodiimides (RN═C═NR′) give oxazolidinone derivatives, whereas carbon dioxide (O═C═O) yields cyclic carbonates.[44]–[47]



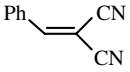
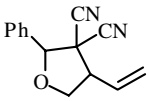
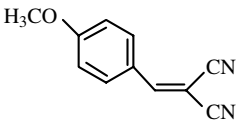
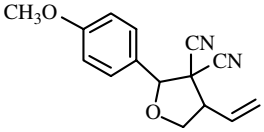
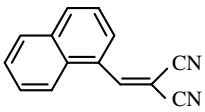
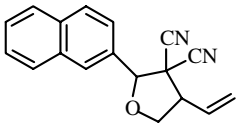
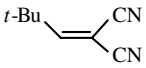
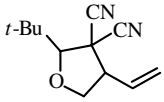
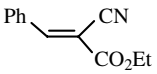
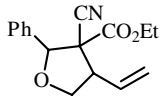
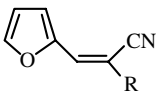
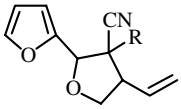
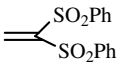
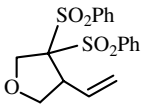
Scheme 19

Further synthetic applications are offered by the reaction of vinyloxiranes with some Michael acceptors, which lead to tetrahydrofuran derivatives through a [3 + 2] cycloaddition in good to excellent yields (**Scheme 20**).[48] The effect of solvents and catalysts on the chemical yield of the reaction was investigated: best results occur with $Pd(PPh)_3$ in THF, whereas $Pd(dba)_2$ in hexane gave poor results. The effect of substituents at the β-position of the activated olefins shows the importance of the steric demand from the electron-withdrawing groups (**Table 4**).



Scheme 20

TABLE 4. Pd-Catalyzed [3 + 2] Cycloadditions of Butadiene Monoxide[a]

Michael Acceptor	Product	Yields (%) (*cis/trans*)[b]
		90 (56:44)
		77 (61:39)
		71 (51:49)
		74 (54:46)
		81 (64:36)
		R = CO_2Et 89 (66:34) R = SO_2Ph 88 (72:28) R = CN 94 (55:45)
		47

[a] All reactions were conducted in THF, at 40 °C, for 1 h.
[b] Isolated yields were based on Michael acceptor.

Mechanistically, the key step of these cycloadditions, which need palladium to proceed, is a Michael addition of the π-allylpalladium species to the activated olefin. No reaction occurs with β-cyanostyrene, being only monosubstituted by an electron-withdrawing group.

E. CONCLUSION

This section has stressed the reactivity of vinyloxiranes in the presence of zerovalent palladium. Different types of starting vinyloxiranes have been reviewed. Acyclic epoxides react predominantly in a regioselective 1,4-addition pathway. Cyclic vinyloxiranes react with a high degree of stereoselectivity. In all the cases reported, the reactions work at moderate temperatures and in neutral media. Under equally smooth experimental conditions, cycloisomerizations occur regio- and stereoselectively. Sometimes these intramolecular Pd-catalyzed processes yield macrocycles, which are usually disfavored and hence difficult to reach through other methods. This efficiency has largely been exploited to serve the purpose of organic synthesis. The large panel of results reported on the transformation of vinyloxiranes via zerovalent palladium catalysis opens the way to the preparation of more complex polycyclic molecules from acyclic vinyloxiranes as precursors. Pd-catalyzed cascade reactions are already well-known and could be applied to the transformation of epoxyolefins.

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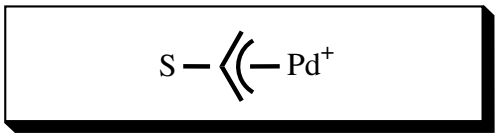

V.2.1.6 Palladium-Catalyzed Substitution Reactions of Sulfur and Other Heavier Group 16 Atom-Containing Allylic Derivatives

KUNIO HIROI

A. INTRODUCTION

As described in **Sect. II.2.4**, organosulfur functionality such as sulfenyl and sulfinyl groups can directly participate in Pd-catalyzed reactions, normally by coordination of the sulfinyl sulfur atom to palladium in the case of sulfinyl groups. Few reports have been published so far concerning nucleophilic substitution reactions of π-allylpalladium complexes bearing chiral sulfinyl groups.

In general, chiral sulfinyl groups in allylic systems can participate in the Pd-catalyzed reactions, if sterically possible, by the coordination of the sulfinyl sulfur atoms to π-allylpalladium complexes generated. When the steric requirement for the coordination is rather severe, the effect of chiral sulfinyl groups is simply understandable, without the direct participation, by the steric bulk of the sufinyl substituents.

B. ALLYLIC DERIVATIVES BEARING CHIRAL SULFINYL GROUPS

There have appeared a few reports of Pd-catalyzed substitution reactions of organosulfur group-containing allylic derivatives.

The first example of Pd-catalyzed asymmetric nucleophilic substitutions of chiral β-sulfinyl allylic systems was reported in 1995.[1] The reaction of a chiral olefinic sulfoxide (*S*s)-**1** with dimethyl sodiomalonate was carried out in THF at room temperature (r.t.) in the presence of $Pd(OAc)_2$ (0.1 equiv) and a phosphine ligand (0.2 equiv), giving (*S*,*S*s)-(*Z*)-**2** with 29–79% de (**Scheme 1**). The degree of the asymmetric induction was largely dependent on the phosphine ligand used. With dpph as a ligand, the highest enantioselectivity was obtained.

The plausible mechanism of asymmetric induction is proposed (**Scheme 2**). The palladium catalyst reacts from the sterically less crowded downward direction of the lone pair side of the chiral sulfinyl group in the conformationally most stable form of (*S*s)-**1** with s*yn*-coplanality between the sulfinyl–oxygen bond and the carbon–carbon double bond of the chiral vinyl sulfoxide, forming **3**. Based on the stereochemistry of the product, the

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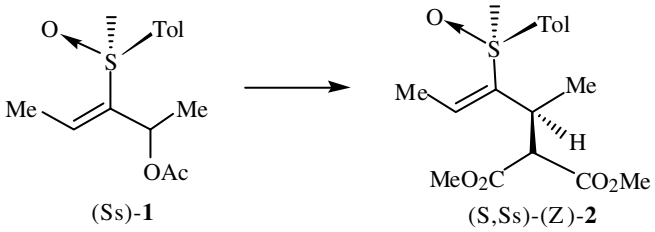
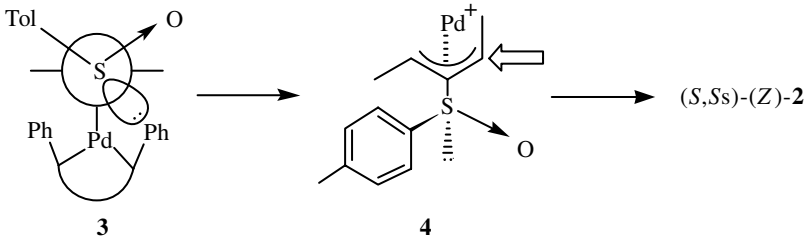


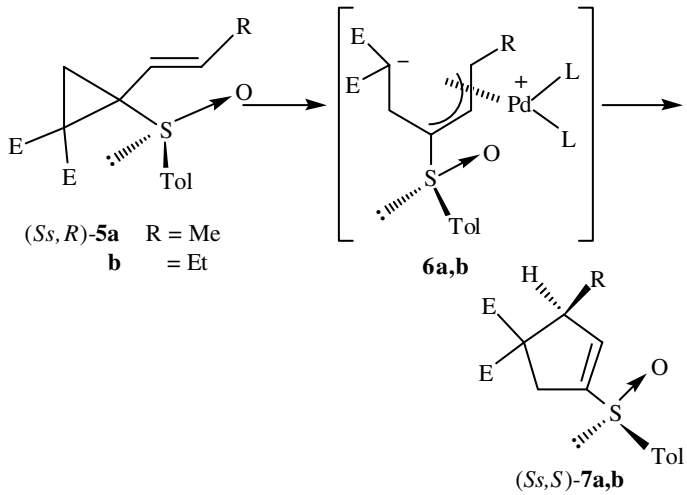
Scheme 1



Scheme 2

nucleophile attacks the allyl terminus from the back side of the palladium in **4**, affording (*S*,*S*s)-(*Z*)-**2**.

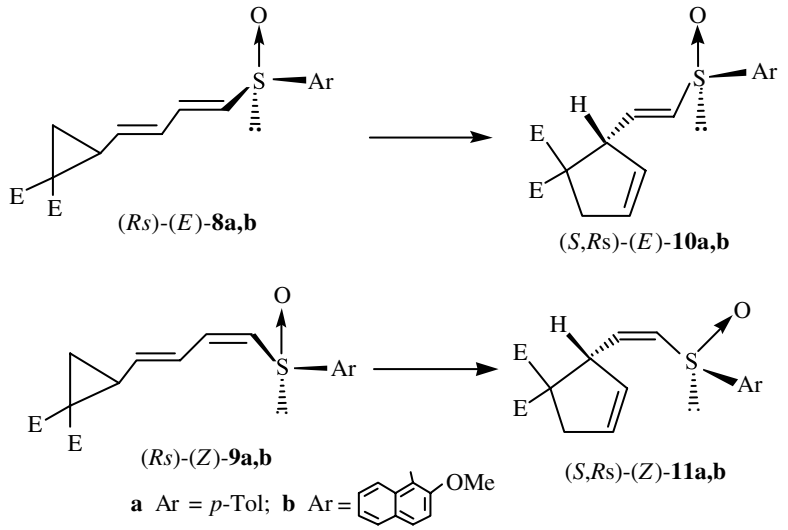
π-Allylpalladium complexes bearing chiral sulfinyl groups are derived from sulfinylated olefinic cyclopropane derivatives. Chiral olefinic cyclopropyl sulfoxides (*S*s,*R*)-**5** undergo asymmetric vinylcyclopropane-cyclopentene rearrangements via the corresponding π-allylpalladium complexes **6** under Pd-catalyzed reaction conditions to provide optically active cyclopentene derivatives **7** with high stereospecificity (**Scheme 3**).[2] The Pd-catalyzed reaction of (*S*s,*R*)-**5a** was carried out in MeCN at reflux for 18 h in the presence of $Pd(PPh_3)_4$ (0.15 equiv) and PPh_3 (0.66 equiv) to give (*S*s,*S*)-**7a** with highest stereospecificity (89%).



Scheme 3

Pd-catalyzed reactions of geometrical isomers of chiral (4-arylsulfinyl-1,3 (*E*) or (*Z*)-butadienyl)cyclopropanes were studied.[3] The Pd-catalyzed reaction of (*R*s)-(*E*)-**8** was carried out in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and phosphine ligands to give (*S*,*R*s)-(*E*)-**10** with high de. However, the reaction of (*R*s)-(*Z*)-**9** under the same reaction conditions gave (*S*,*R*s)-(*Z*)-**11** with high de, retaining the (*Z*)-configuration of the starting olefin. The Pd-catalyzed reactions of (*R*s,)-(*E*)-**8b** or (*R*s)-(*Z*)-**9b** in toluene at room temperature using dppf or dppb as a ligand provide (*S*,*R*s)-(*E*)-**10b** or (*S*,*R*s)-(*Z*)-**11b** with 94% or 90% de, respectively.

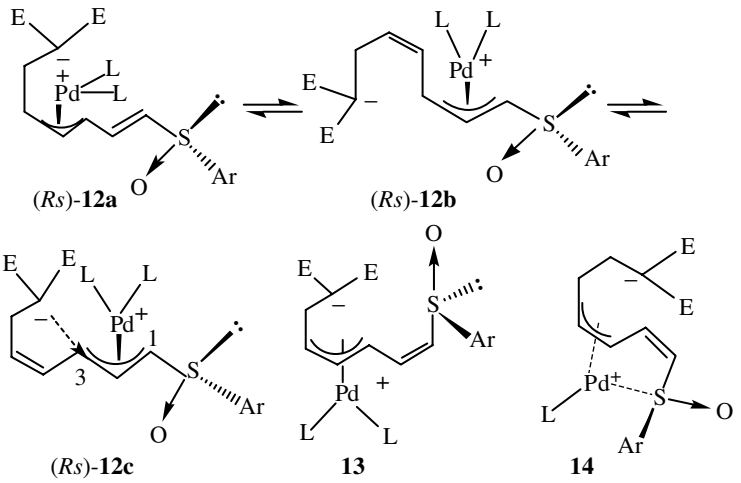
The retention of the (*Z*)-geometry of the starting olefin in this reaction is rationalized by formation of the conformationally stable π-allylpalladium complex with coordination of the sulfinyl sulfur atom to palladium (**Scheme 4**).



Scheme 4

An initially formed π-allylpalladium complex (*R*s)-**12a** derived from (*R*s)-(*E*)-**8** would be equilibrated into the more stable π-allyl systems (*R*s)-**12b,c**; in the most preferred π-allyl system, (*R*s)-**12c**, with the *syn*-arylsulfinyl group at C_1 and the *syn*-substituent at C_3, the palladium–phosphine moiety is orientated at the sterically less crowded upper side (the lone pair side of the sulfinyl group) in the electronically most advantageous conformation with the sulfinyl sulfur–oxygen bond coplanar to the π-allyl system. The intramolecular substitution of the carbanion in (*R*s)-**12c** occurs at C_3 of the allyl site from the opposite side of the palladium in a highly stereoselective fashion to afford (*S,R*s)-(*E*)-**10** with high de.

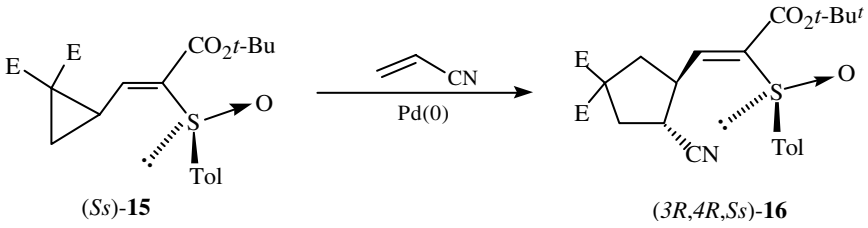
In the case of (*R*s)-(*Z*)-**9**, the direct participation of the chiral sulfinyl group to the palladium should be crucial; the initially formed π-allylpalladium complex (*R*s)-(*Z*)-**13** is stabilized by the coordination of the sulfinyl sulfur atom to the palladium, forming **14** with the retained (*Z*)-configuration of the olefin. The subsequent intramolecular nucleophilic substitution from the opposite side of the palladium provides (*S,R*s)-(*Z*)-**11** in a highly stereoselective fashion (**Scheme 5**).



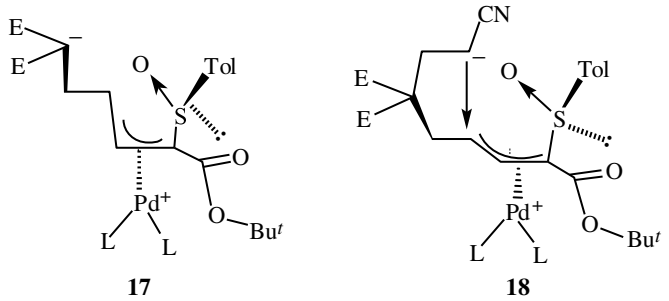
Scheme 5

A Pd-catalyzed asymmetric cycloaddition reaction of a chiral (β-sulfinyl)vinylcyclopropane derivative with acrylonitrile provides an optically active cyclopentane derivative.[4] The asymmetric cycloaddition reaction of (*S*s)-**15** with acrylonitrile was carried out under heating in THF for 3 h in the presence of $Pd(PPh_3)_4$ (0.1 equiv) and PPh_3 (0.2 equiv) to give stereoselectively (3*R*,4*R*,*S*s)-**16** with 66% de (**Scheme 6**).

The mechanism of this asymmetric cycloaddition reaction is rationalized by Michael addition of a carbanion in the π-allylpalladium complex **17** (generated from (*S*s)-**15**) to acrylonitrile followed by the nucleophilic substitution from the back side of the palladium catalyst in **18** (**Scheme 7**).



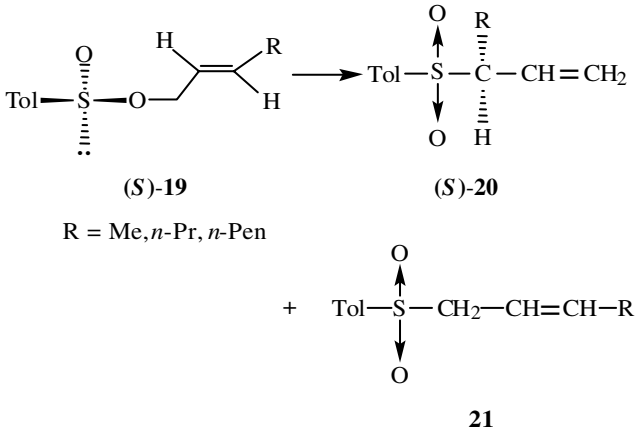
Scheme 6



Scheme 7

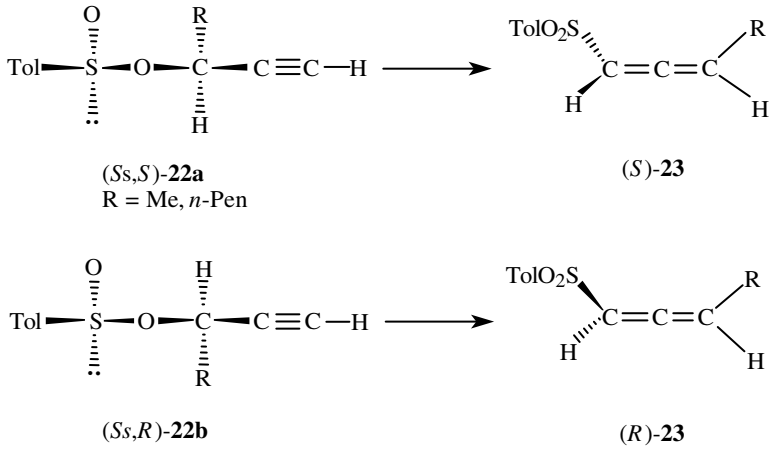
C. ALLYLIC DERIVATIVES BEARING CHIRAL SULFINATE GROUPS

Transformation of allylic sulfinates (*S*)-**19** with chirality on the sulfur atoms into chiral allylic sulfones (*S*)-**20** were facilitated with palladium catalysts via the sulfonylation of intermediary π-allylpalladium complexes.[5] The Pd-catalyzed reactions of (*S*)-**19** were carried out in THF at 0 °C or room temperature in the presence of $Pd(PPh_3)_4$ (0.15 equiv) and PPh_3 (0.66 equiv) to give (*S*)-**20** with high enantioselectivity along with **21** as a minor product (**Scheme 8**).



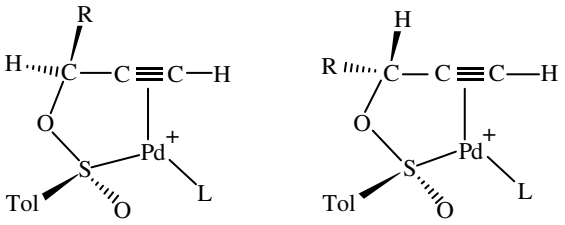
Scheme 8

A similar transformation was observed in the Pd-catalyzed reactions of chiral 2-alkynyl sulfinates.[6],[7] The Pd-catalyzed reactions of (*Ss*,*S*)-**22a** and (*Ss*,*R*)-**22b** were carried out in THF at room temperature in the presence of $Pd(OAc)_2$ (0.05 equiv) and 1,6-bis(diphenylphosphino)hexane (dpph) (0.075 equiv) to give optically active allenes (*S*)- or (*R*)-**23**, respectively, with high enantiospecificity (**Scheme 9**).



Scheme 9

On the basis of the difference in the conversion rate of the diastereomeric sulfinates (the conversion rate of (*S*s,*R*)-**22b** was much faster than that of (*S*s,*S*)-**22a**), the mechanism was rationalized by a route via five-membered-like intermediates. The reaction via **24b** could proceed more easily than that via **24a**, since **24a** has steric hindrance between the substituent *R* and the tolyl group due to the *cis*-configuration (**Scheme 10**).



24a **24b**

Scheme 10

D. SUMMARY

A few papers have been reported on Pd-catalyzed substitution reactions of organosulfur group-containing allylic derivatives, in which the effects of chirality of sulfinyl groups in asymmetric synthesis were studied, associated with participation of the chiral sulfinyl functionality in the coordination to palladium.

Chiral sulfinyl sulfur atoms can coordinate to palladium in Pd-catalyzed reactions of allylic systems bearing chiral sulfinyl groups at the appropriate site, if the steric environment allows the sulfinyl sulfur atoms to access the π-allylpalladium complexes generated for participation by the coordination.

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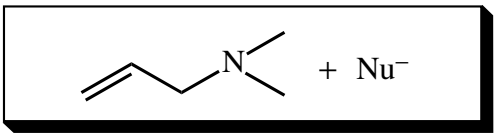

V.2.1.7 Palladium-Catalyzed Substitution Reactions of Nitrogen and Other Group 15 Atom-Containing Allylic Derivatives

SHUN-ICHI MURAHASHI and YASUSHI IMADA

A. INTRODUCTION

Pd-catalyzed reactions of allylic esters such as allyl acetates, carbonates, and phosphates with soft carbon nucleophiles such as malonate esters are useful for carbon–carbon bond formation (**Sects. V.2.1.1–V.2.1.5**). In this section, Pd-catalyzed substitution reactions of nitrogen-containing allylic derivatives such as allylic amines, ammonium salts, tosylimides, and nitro compounds are described (**Scheme 1**). The allylic derivatives of other group 15 atoms have never been used as allyl unit source in Pd-catalyzed alkylation reactions so far.

B. ALLYLIC AMINES, AMMONIUM SALTS, AND TOSYLIMIDES AS SUBSTRATES

The Pd-catalyzed reaction of allylamines with active methylene compounds was first reported in 1970. *N*,*N*-Diethylallylamine undergoes reaction with 2,4-pentanedione in the presence of $Pd(acac)_2$ (0.5 mol %) and PPh_3 (1.5 mol %) at 85 °C to give 3-monoallylated and 3,3-bisallylated products in 70% and 20% yields, respectively (**Scheme 2**).[1] Nickel(0) complexes are found to be a more active catalyst for allylation. Thus, more than 600 h^{-1} of turnover frequency was achieved for the allylation of methyl 3-oxobutanoate with *N*,*N*-diethylallylamine in DMF at 80 °C using $Ni(dppb)_2$ catalyst.[2]

Quaternary allylic ammonium is a better leaving group toward Pd(0) species as compared with allylic amine. Typically, the reaction of allyltriethylammonium bromide with $Pd(PCy_3)_2$ at room temperature affords the oxidative addition product, whereas the addition of *N*,*N*-diethylallylamine to $Pd(PCy_3)_2$ does not occur.[3] Treatment of allyltriethylammonium bromide with diethyl sodiomalonate in the presence of $Pd(PPh_3)_4$ (5 mol %) in THF at room temperature (r.t.) gives diethyl 2-allylmalonate (62%) and diethyl 2,2-diallylmalonate (13%) (**Scheme 3**).[4]

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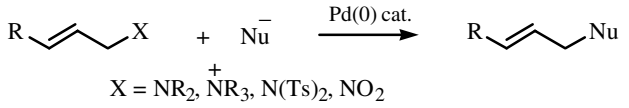
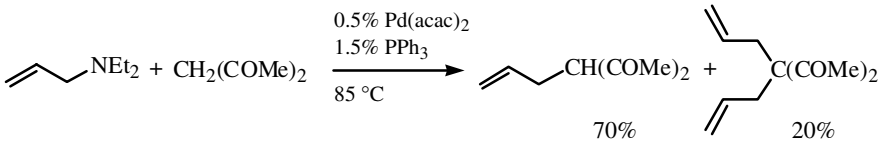
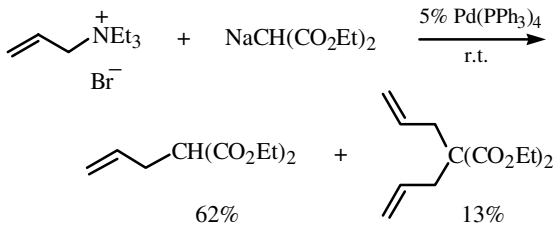


Scheme 1



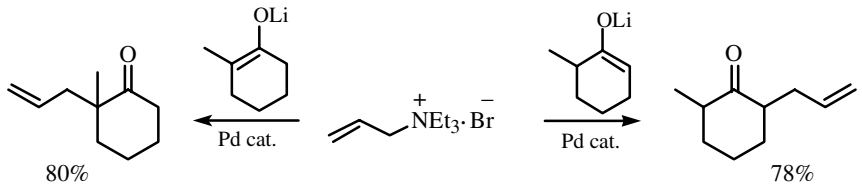
Scheme 2



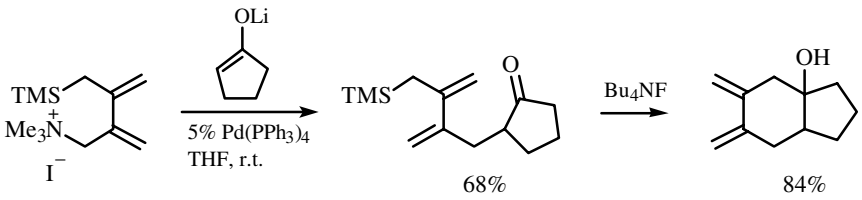
Scheme 3

The enolate anions, derived from 2-methyl-1-trimethylsilyloxy-1-cyclohexene and 6-methyl-1-trimethylsilyloxy-1-cyclohexene with BuLi, undergo Pd-catalyzed allylation reactions to give allylated methylcyclohexanones (**Scheme 4**).[4]

The trimethylammonium iodide of 2-(dimethylaminomethyl)-3-(trimethylsilylmethyl)-1,3-butadiene is a useful reagent for the introduction of both electrophile and nucleophile. Treatment with lithium enolate in the presence of $Pd(PPh_3)_4$ catalyst gives the allylated cyclopentanone, and subsequent intramolecular allylation of carbonyl group in the presence of Bu_4NF gives vicinal exocyclic alcohol (**Scheme 5**).[5]

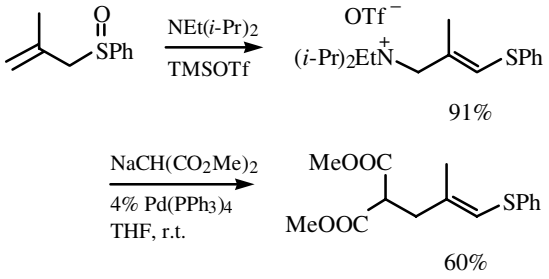


Scheme 4



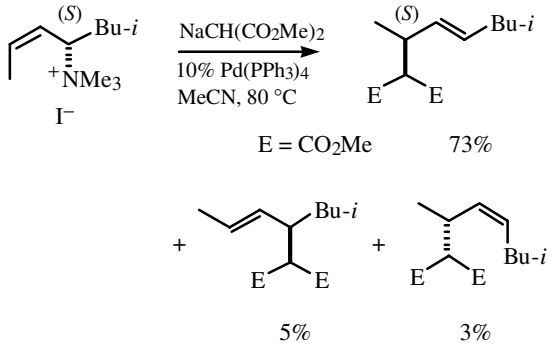
Scheme 5

The quaternary allylammonium salt, formed by the nucleophilic addition of Hünig's base to the Pummerer vinylthionium ion intermediate, undergoes Pd-catalyzed reaction with dimethyl sodiomalonate highly regioselectively (**Scheme 6**).[6]



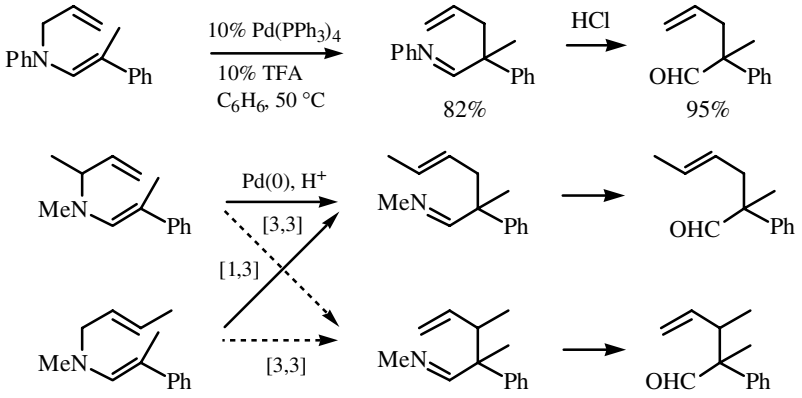
Scheme 6

Pd-catalyzed alkylation of an optically active allylammonium salt (>98% ee) with dimethyl sodiomalonate in acetonitrile at 80 °C proceeded smoothly to give optically active allylated product (82% ee) in 73% yield in addition to its regio- and stereoisomers in 5% and 3% yields, respectively (**Scheme 7**).[7]



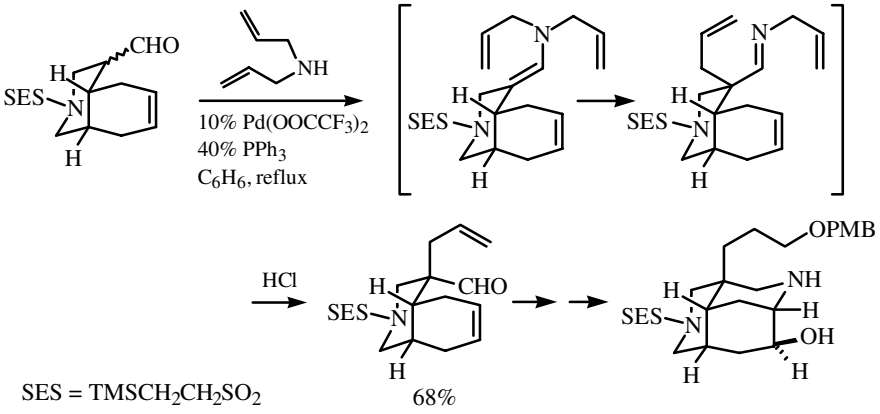
Scheme 7

The Pd-catalyzed 3-aza-Cope rearrangement of *N*-allylenamines proceeds efficiently in the presence of a catalytic amount of TFA to give δ,ε-unsaturated imines, which are hydrolyzed to give γ,δ-unsaturated carbonyl compounds (**Scheme 8**).[8],[9] The reaction can be rationalized by assuming the mechanism involving π-allylpalladium intermediates, which is supported by the regiochemistry of the reactions of substituted *N*-allylenamines. Thus, *N*-(1-buten-3-yl)enamine was converted into the [3,3] rearranged product, while *N*-(2-butenyl)enamine was converted into the [1,3] rearranged product. The role of the catalytic amount of acid is the formation of reactive *N*-allylenammonium ions, which undergo oxidative addition to Pd(0) species to form π-allylpalladium intermediates. Since enamines are excellent nucleophiles toward π-allylpalladium complexes to form carbon–carbon bonds,[10] allylation took place smoothly at the less hindered allyl terminus to give the corresponding imines.



Scheme 8

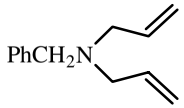
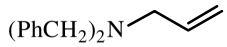
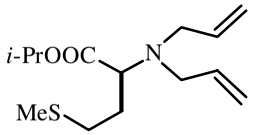
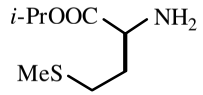
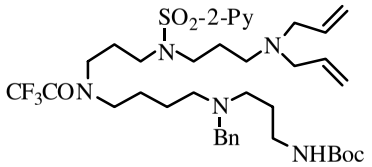
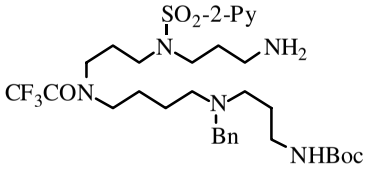
The 3-aza-Cope rearrangement is successfully applied to the key step in a concise approach to the tricyclic core of a marine alkaloid. A requisite quaternary center and attendant stereochemistry are established by condensation of the corresponding aldehyde with diallylamine followed by 3-aza-Cope rearrangement via a π-allylpalladium intermediate (**Scheme 9**).[11]



Scheme 9

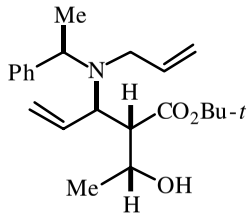
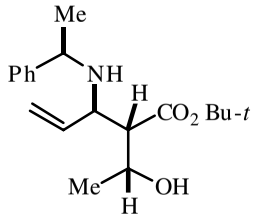
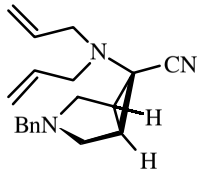
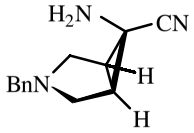
In addition to being a powerful tool for carbon–carbon bond formation, Pd-catalyzed allylic alkylation has increased the use of allylic groups in protective group chemistry by offering a new general method for deprotection.[12] Pd-catalyzed deallylation of mono and diallylamines can be performed highly efficiently using *N*,*N*′-dimethylbarbituric acid (NDMBA) as an allyl group scavenger. Typically, *N*,*N*-diallylbenzylamine and *N*-allyldibenzylamine were deallylated smoothly upon treatment with NDMBA (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (2 mol%) in CH_2Cl_2 at 30 °C to give benzylamine and dibenzylamine in quantitative yields, respectively (**Table 1**, entries 1 and 2).[13] NDMBA is a β-dicarbonyl compound of high acidity ($pK_a = 4.7$) and acts as an acid to protonate allylamines. The resulting allylammonium salts react with Pd(0) species and

TABLE 1. Deallylation of Allylamines Using Pd/NDMBA System [a]

Entry	Allylamine	Deallylated Amine	Yield (%)	Reference
1		$PhCH_2NH_2$	100	[13]
2		$(PhCH_2)NH$	96	[13]
3			95	[13]
4			98	[14]

(*Continued*)

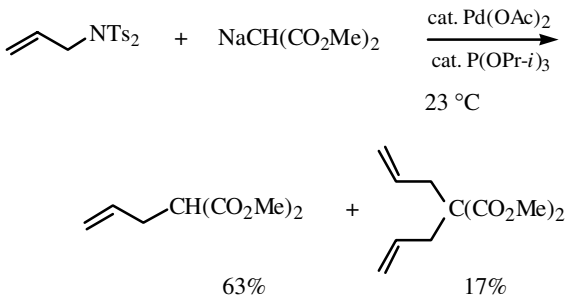
TABLE 1. (*Continued*)

Entry	Allylamine	Deallylated Amine	Yield (%)	Reference
5			98	[15]
6			69	[16]

[a] The deallylation reactions were carried out using *N,N′*-dimethylbarbituric acid (NDMBA) (1.5 molar equiv) in the presence of $Pd(PPh_3)_4$ catalyst in CH_2Cl_2.

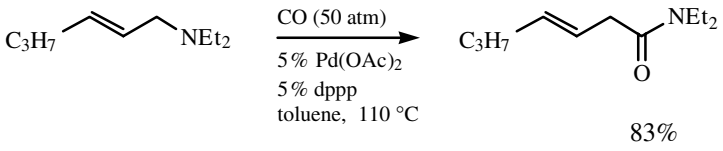
generate π-allylpalladium intermediates, of which allyl groups are then transferred to NDMBA. The deprotection of optically active amino acid derivatives occurred without racemization (entry 3). The Pd-catalyzed deallylation reaction has been used for construction of complex molecules such as protected polyamine thermopentamine (entry 4)[14] and precursors of thienamycin (entry 5)[15] and Gyrase inhibitor trovafloxacin (entry 6).[16]

Allyl *N*,*N*-ditosylimides and allyl *N*-acyl-*N*-tosylimides can be used as substrates for the Pd-catalyzed reaction with nucleophiles. The Pd-catalyzed allylation of dimethyl sodiomalonate gives mono- and diallylated dimethyl malonate (**Scheme 10**).[17]



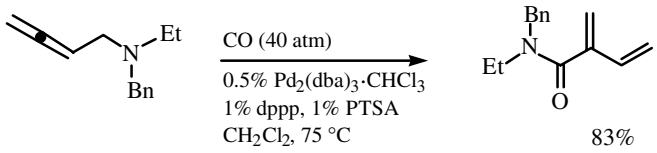
Scheme 10

In view of the homologation of allylic skeletons, allylic carbonylation is an attractive alternative to the allylic alkylation. In analogy to Pd-catalyzed allylic alkylations, allylic esters such as acetates, carbonates,[18] phosphates,[19],[20] and formates[21] have been used as substrates for allylic carbonylation. Allylamines can be used as substrates for Pd-catalyzed allylic carbonylations. Carbon monoxide inserts at the less hindered allylic terminus selectively to give β,γ-unsaturated amides in the presence of Pd(0) catalyst prepared from $Pd(OAc)_2$ (5 mol%) and dppp (5 mol%) (**Scheme 11**).[22],[23] Noteworthy is that the leaving group of a secondary amine reacts with the original allyl skeleton after insertion of carbon monoxide. This is the first example of the Pd-catalyzed insertion of carbon monoxide into a carbon–nitrogen bond. Selective reduction of the carbonyl group can be performed upon treatment with $LiAlH_4$ to give homoallylamines. In the presence of excess amounts of alcohols, alkoxycarbonylation takes place to give β,γ-unsaturated esters.



Scheme 11

Carbonylation of 2,3-alkadienylamines occurs regioselectively at the central carbon of the allenyl unit to give α-vinylacrylamides (**Scheme 12**).[24] The insertion of carbon monoxide occurs selectively via 1,3-alkadien-2-ylpalladium intermediates rather than 2,3-alkadienylpalladium species.



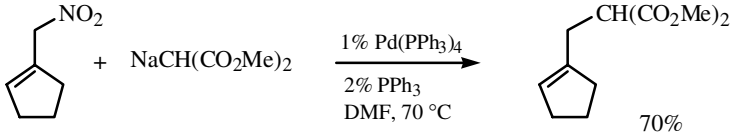
Scheme 12

C. ALLYLIC NITRO COMPOUNDS AS SUBSTRATES

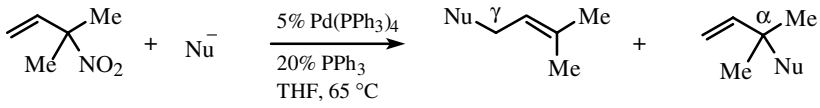
Allylic nitro compounds[25] react with Pd(0) species to form π-allylpalladium complexes, which undergo reaction with nucleophiles to give substitution products. 1-(Nitroalkyl)-cycloalkenes react with dimethyl sodiomalonate in DMF in the presence of $Pd(PPh_3)_4$ catalyst to give alkylated product regioselectively (**Scheme 13**).[26],[27]

Acyclic allylic nitro compounds undergo allylic alkylation with stabilized carbanions in the presence of $Pd(PPh_3)_4$ catalyst to give a mixture of two regioisomers.[27]–[30] The regiochemistry is governed primarily by the steric effect of the nucleophiles (**Scheme 14**).[30]

The Pd-catalyzed reaction of "ate" complexes, prepared from lithium enolates and BEt_3, with tertiary acyclic allylic nitro compounds affords monoallylated products regioselectively as shown in **Scheme 15**.[31]

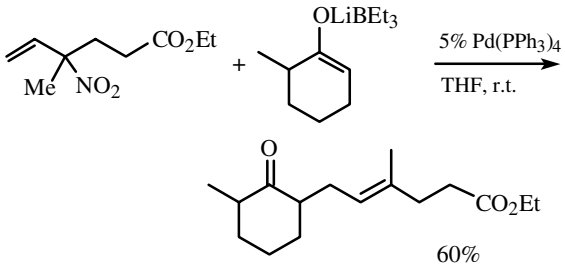


Scheme 13



Na^+Nu^-	Yield (%)	Ratio (γ/α)
NaCH(CN)(CO_2Me)	75	1:99
NaC(Me)(Ts)(CO_2Et)	90	100:0

Scheme 14



Scheme 15

D. SUMMARY

The allylic nitrogen derivatives, such as allylic ammonium salts, tosylimides, and nitro compounds, react with Pd(0) species under mild reaction conditions to form π-allylpalladium intermediates, which undergo coupling reaction with various nucleophiles to give allylated nucleophiles. Carbon monoxide reacts with the π-allylpalladium species derived from allylamines to give β,γ-unsaturated amides.

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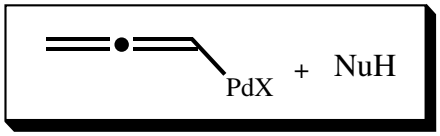

V.2.1.8 Palladium-Catalyzed Substitution Reactions with Propargyl and Related Electrophiles

TADAKATSU MANDAI

A. INTRODUCTION

It has been well established that propargylic compounds add oxidatively to Pd(0) species to produce propargyl and/or allenylpalladium complexes, which are in equilibrium depending on the substituents. Most of the Pd-catalyzed reactions of propargylic compounds proceed via allenylpalladium complexes, while the reactions via propargylpalladium complexes are very rare. Complex formation by the reaction of stoichiometric $Pd(PPh_3)_4$ with propargylic chlorides and acetates has been studied, and σ-allenyl- and/or propargylpalladium complexes were isolated as yellow powders depending on the steric congestion of the substrates.[1],[2] Propargyl acetate is less reactive, but the same complex formation from propargylic acetate takes place in the presence of zinc or lithium chloride (**Scheme 1**).[2]

Several propargylic compounds such as halides, acetates, phosphates, oxiranes, and carbonates can be used for the Pd-catalyzed reactions, but they have different reactivities. Among them, propargylic carbonates are highly reactive and undergo various Pd-catalyzed reactions smoothly, especially under neutral conditions.[3]

B. CLASSIFICATION OF CATALYTIC REACTIONS BASED ON MECHANISTIC CONSIDERATIONS

B.i. Insertion of Olefins into Allenylpalladium Complexes

The Pd–carbon bond in the allenylpalladium complex **A** has reactivity similar to that of σ-bond formed by the oxidative addition of alkenyl halides to Pd(0) in the Heck reaction.[4],[5] Smooth insertion of alkenes into the allenylpalladium complexes **A** and subsequent elimination of β-hydrogen affords 1,2,4-trienes (**Scheme 2**).

The reaction proceeds smoothly in DMF at 70 °C using $Pd(OAc)_2$ and PPh_3 as a catalyst (**Scheme 3**).[6] An aldehyde is provided when allyl alcohol is used as the alkene.

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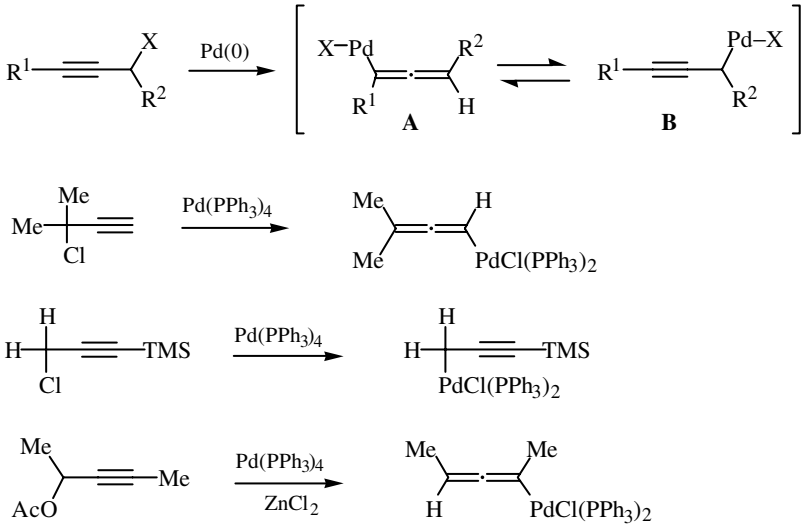
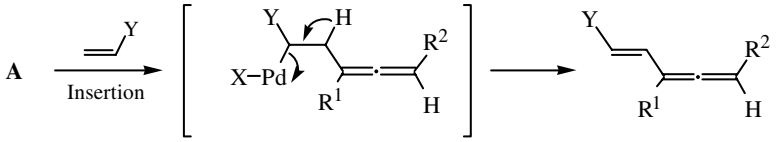
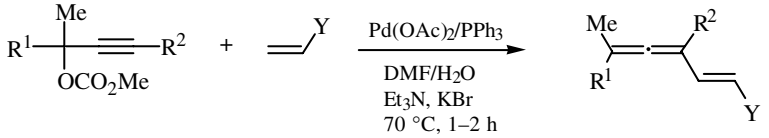
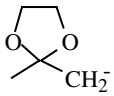
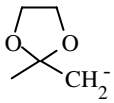


Scheme 1

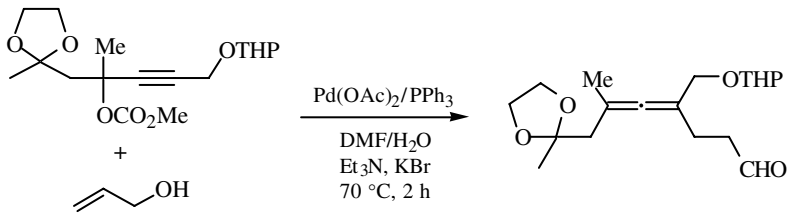


Scheme 2



R^1	R^2	Y	Yield (%)
	CH_2OTHP	CO_2Me	76
	*n*-Bu	CO_2Me	73
n-C_6H_{13}	CH_2OTHP	CO_2Me	71
n-C_6H_{13}	CH_2OTHP	CO_2Me	58

Scheme 3 (*Continued*)

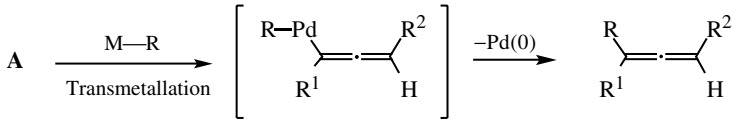


Scheme 3

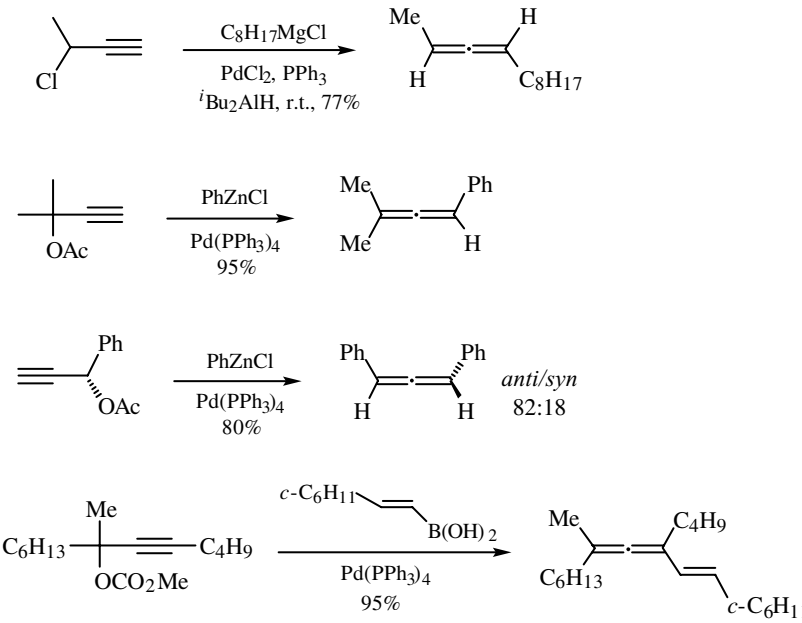
B.ii. Transmetallation of Allenylpalladium Complexes

Hard carbon nucleophiles M—R (M = Mg, Zn, B, Cu, etc.) undergo facile transmetallation with the allenylpalladium intermediate **A** followed by reductive elimination to give allene derivatives (**Schemes 4** and **5**).[7]–[10]

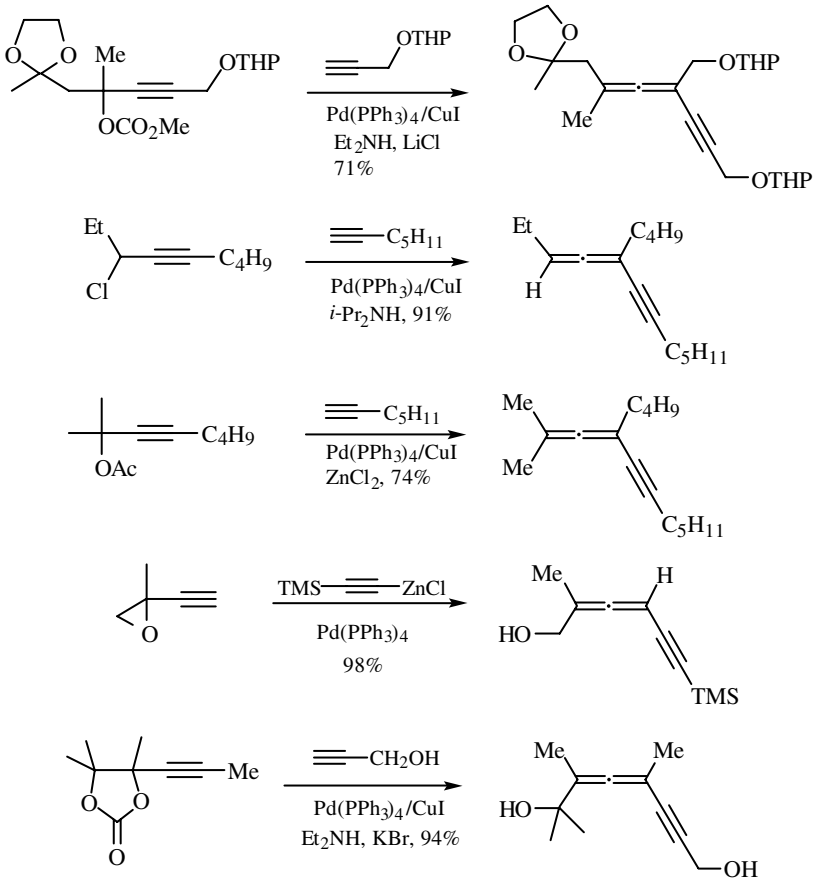
1,2-Dien-4-ynes can also be prepared in good yields by the Pd-catalyzed coupling of terminal alkynes with propargylic compounds such as carbonates, halides, and acetates in the presence of a catalytic amount of cuprous iodide as a cocatalyst (**Scheme 6**).[11]–[15]



Scheme 4



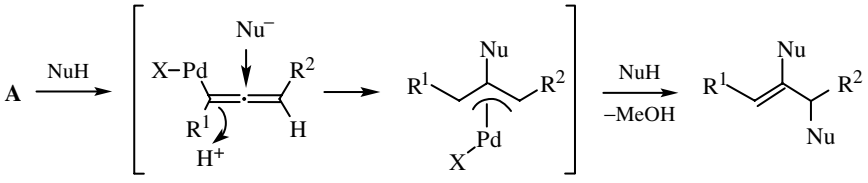
Scheme 5



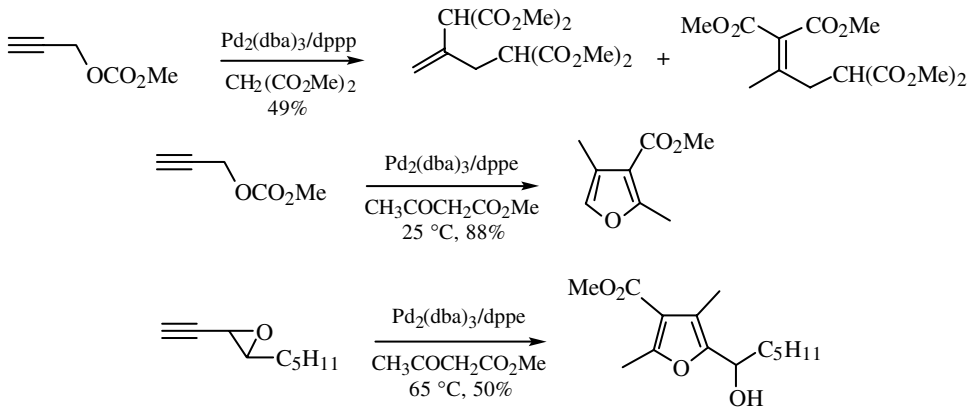
Scheme 6

B.iii. Attack of Soft Carbon Nucleophiles on sp Carbon of Allenylpalladium Complexes

A soft carbon nucleophile attacks the sp carbon of the allenylpalladium complex **A** to give a π-allylpalladium complex. Another soft carbon nucleophile attacks the π-allylpalladium complex thus formed to afford an alkene, into which the same nucleophiles are doubly introduced (**Schemes 7** and **8**).[16]–[18] The reaction with β-keto esters provides furan derivatives, the formation of which is explained by the reaction of the enol oxygen generated from the initially attacked β-keto ester with the π-allylpalladium intermediates followed by olefin isomerization.



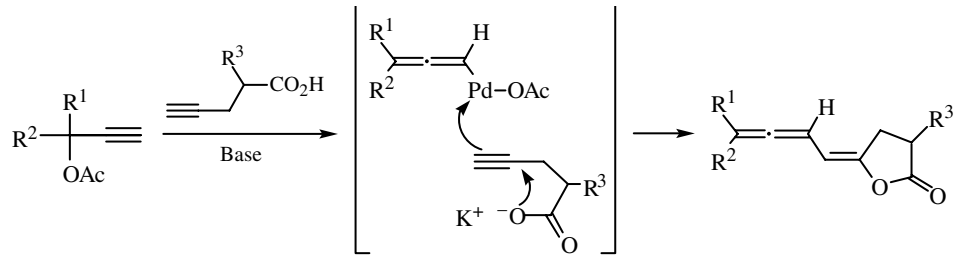
Scheme 7



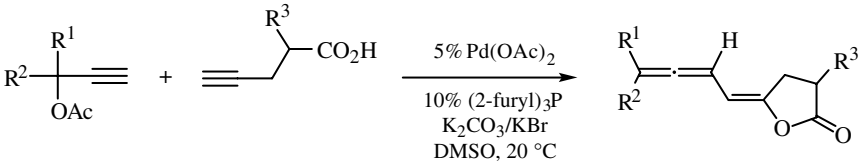
Scheme 8

B.iv. Oxypalladation of Acetylenes with Allenylpalladium Complexes

The Pd(II) species on an allenylpalladium complex **A** has ample Lewis acidity to activate a triple bond, on which a suitably arranged carboxylate anion attacks intramolecularly. Reductive elimination of Pd(0) species completes the formation of exo-enol lactones (**Scheme 9**).[19] The Pd-catalyzed coupling of the propargylic acetates with 4-pentynoic acids proceeds very smoothly in the presence of potassium bromide using tris(2-furyl)phosphine (TFP) as the ligand (**Scheme 10**).



Scheme 9



R^1	R^2	R^3	Time (h)	Yield (%)
Me	Me	H	14	61
H	Ph	H	22	50
—$(CH_2)_5$—		H	2	54

Scheme 10

C. SUMMARY

In general, Pd-catalyzed reaction of propargyl compounds provides synthetically valuable allenyl compounds through addition, transmetallation, or oxypalladation of allenylpalladium intermediates. Exceptionally, soft carbon nucleophiles such as malonate and methyl acetoacetate attack the sp carbon of allenylpalladium intermediates to afford allylic compounds and furan derivatives.

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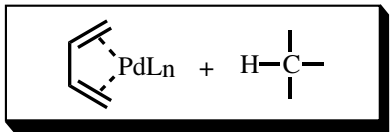

V.2.1.9 Palladium-Catalyzed Reactions of Soft Carbon Nucleophiles with Dienes, Vinylcyclopropanes, and Related Compounds

HIROYUKI NAKAMURA and YOSHINORI YAMAMOTO

A. INTRODUCTION

Since Pd-catalyzed dimerization of butadine was found by Hagihara and co-workers in 1967,[1] much attention has been focused on the Pd-catalyzed reaction of conjugated dienes with various nucleophiles such as oxygen, nitrogen, and carbon nucleophiles.[2]–[4] The reaction of butadienes with activated methylene compounds proceeds in the presence of Pd(0) or Pd(II) catalysts to afford octa-2,7-dienyl derivatives.[5]–[7] It is believed that an active species in the Pd-catalyzed dimerization of conjugated dienes is a zerovalent palladium complex, which forms, for example, the bis-π-allylpalladium complex **1** of dimerized octyl derivative upon treatment with butadiene (**Scheme 1**, route a). Palladium(II) catalysts are reduced by bases such as NaOPh, Et_3N, and KOAc, which exist in the reaction mixture, to generate Pd(0) *in situ*. The bis-π-allylpalladium complex **1** undergoes β-hydrogen elimination to afford 1,3,7-octatriene **3** or react with nucleophiles (HNu), such as activated methylene compounds, amines, and alcohols, to produce the corresponding nucleophile adducts **6**. Tsuji proposed that the reaction would proceed via the palladium hydride complexes **4**.[8] The nucleophilic carbon (Nu) attacks one of two π-allyl groups of palladium complexes **1** to generate the palladium hydride complexes **4**, and the corresponding adducts **6** are produced by the reductive elimination from **4**. Jolly and co-workers examined the reaction of η^1, η^3-octadienyl palladium complex **9** with methyl malononitrile and confirmed the π-allylpalladium complex **10** by $^{13}C\{^1H\}NMR$ (**Scheme 2**).[9]–[11] Thus, they proposed the alternative mechanism as follows. The hydrogen of nucleophiles (HNu) reacts, at first, with complex **1** to generate the π-allylpalladium complexes **5**. The reductive coupling of the π-allyl group with the nucleophilic carbon skeletons (Nu) on the palladium gives the adducts **6**. In these reactions, tertiary monodenate phosphine complexes of palladium are effective as catalysts or catalytic components. If bidentate phosphines are used as a ligand of palladium, the coordination of only one molecule of 1,3-butadiene to palladium becomes possible (**7**), giving the 1:1 adducts **8** (**Scheme 1**, route b).

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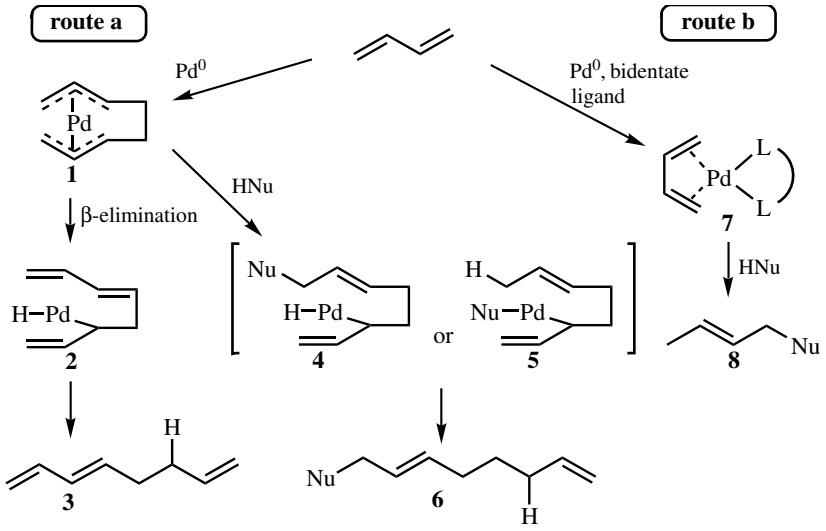
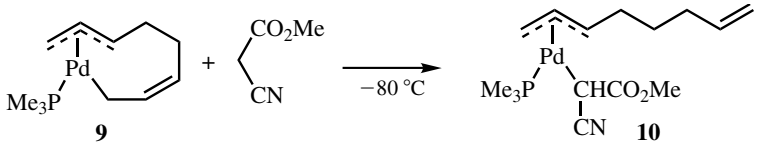


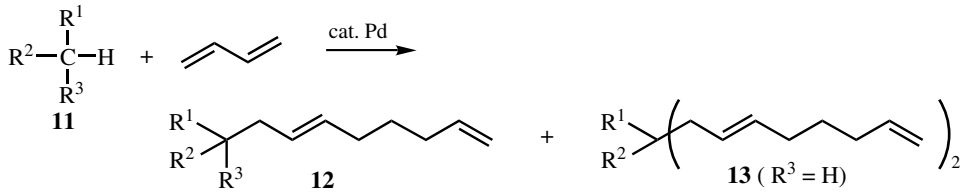
Scheme 1



Scheme 2

B. DIMERIZATION–ADDITION OF SOFT CARBON NUCLEOPHILES TO CONJUGATED DIENES

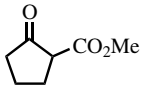
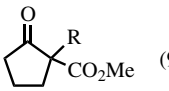
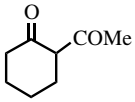
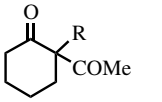
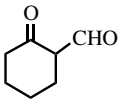
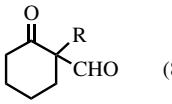
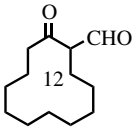
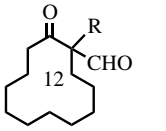
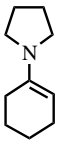
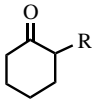
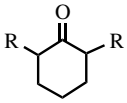
Soft carbon nucleophiles, such as activated methylene or methyne compounds **11**, react with butadiene to give a mixture of the mono- (**12**) and di-(2,7-octadienyl) adducts (**13**) in the case of $R^3 = H$ (activated methylenes), and to give the monoadduct **12** in the case of activated methynes, as expected (**Scheme 3**). The addition reactions with various carbon nucleophiles, such as β-keto esters, β-diketones, malonate and malononitrile, α-formyl ketones and esters, α-cyano ketones and esters, cyanoacetoacetamide, phenylsulfonyl acetate,[5],[6] nitroalkanes,[7],[12] and an enamine,[13] are summarized in **Table 1**. $PdCl_2(PPh_3)_2$–NaOPh is often used as a catalyst for the dimerization reaction. Complexes



R^1, R^2 = electron-withdrawing groups; R^3 = H or organofunctional groups.

Scheme 3

TABLE 1. Pd-Catalyzed Reaction of Carbon Nucleophiles with 1,3-Butadiene

Carbon Nucleophiles	Catalyst[a]	Products[b] (%)	
β-Keto Esters			
$CH_3COCH_2CO_2CH_3$	I	$CH_3COCHRCO_2CH_3$ (63)	$CH_3COCR_2CO_2CH_3$ (7)
	I	 (93)	
β-Diketones			
$CH_3COCH_2COCH_3$	I	$CH_3COCHRCOCH_3$ (62)	$CH_3COCR_2COCH_3$ (18)
	I	 (87)	
Malonate and Malononitrile			
$CH_2(CO_2CH_3)_2$	I	$RCH(CO_2CH_3)_2$ (49)	$R_2C(CO_2CH_3)_2$ (3)
$NCCH_2CN$	I	NCCHRCN (10)	$NCCR_2CN$ (34)
α-Formyl Ketones and α-Formyl Esters			
	I	 (85)	
	II	 (87)	
$PhCH(CHO)CO_2C_2H_5$	II	$PhCR(CHO)CO_2C_2H_5$ (90)	
α-Cyano Ketones and α-Cyano Esters			
$CH_3COCH(CH_3)CN$	I	$CH_3COCR(CH_3)CN$ (66)	
$PhCOCH_2CN$	I	PhCOCHRCN (47)	$PhCOCR_2CN$ (35)
$NCCH_2CO_2C_2H_5$	I	$NCCHRCO_2C_2H_5$ (23)	$NCCR_2CO_2C_2H_5$ (46)
Miscellaneous			
$NCCH_2CONH_2$	III	$NCCHRCONH_2$ (trace)	$NCCR_2CONH_2$ (67)
$PhSO_2CH_2CO_2C_2H_5$	I	$PhSO_2CHRCO_2C_2H_5$ (91)	
$CH_3CH_2CH_2NO_2$	III	$CH_3CH_2CHRNO_2$ (54)	$CH_3CH_2CR_2NO_2$ (42)
 **14**	IV	 (66)[c]	 (21)[c]

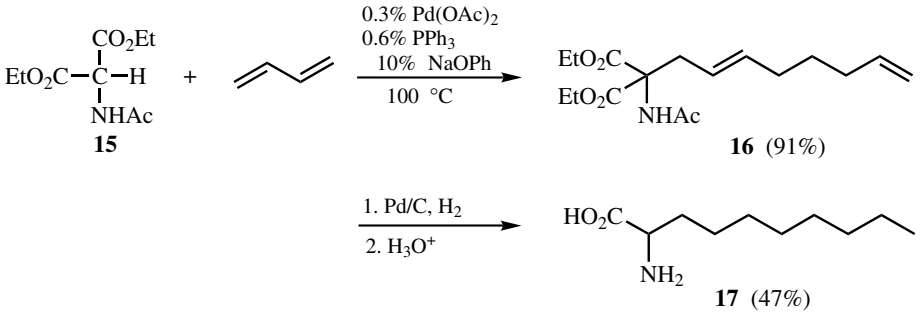
[a] [I] $PdCl_2(PPh_3)_2$–NaOPh; [II] $PdCl_2(PPh_3)_2$–NaOMe; [III] $Pd(PPh_3)_4$; [IV] $Pd(OAc)_2$–2 PPh_3–NaOPh.

[b] R = —$CH_2CH{=}CH(CH_2)_3CH{=}CH_2$.

[c] Products isolated after hydrolysis.

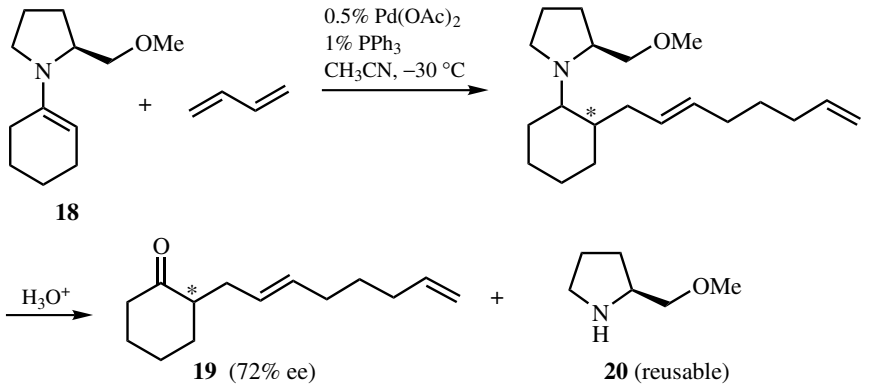
of Pd(0) such as $Pd(PPh_3)_4$ and $Pd(PPh_3)_2$–maleic anhydride also are effective catalysts. The $PdCl_2$–NaOPh catalyst system is less effective than the above effective catalysts and the dimerization proceeds in the absence of the basic sodium components. Reaction of the enamine **14**, derived from pyrrolidine and cyclohexanone, with butadiene also proceeds smoothly in the presence of $Pd(OAc)_2$–PPh_3 as a catalyst in acetonitrile, and a mixture of 2-(2,7-octadienyl)cyclohexanone and 2,6-di(2,7-octadienyl)cyclohexanone was isolated after hydrolysis.

The use of (acylamino)malonate as a nucleophilic reagent toward 1,3-dienes is an efficient route for the synthesis of α-amino acid derivatives.[14] The reaction of diethyl acetamidomalonate **15** with butadiene in the presence of $Pd(OAc)_2$–PPh_3–NaOPh as a catalyst produces diethyl 1-octa-2,7-dienylacetamidomalonate **16** in 91% yield as a major product. Subsequent hydrogenation followed by hydrolysis gave octyl glycine **17** in 47% yield (**Scheme 4**).



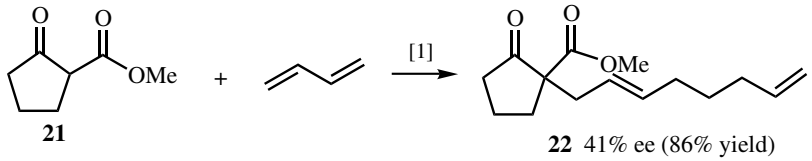
Scheme 4

Furthermore, asymmetric dimerization is also examined by introducing either a chiral auxiliary to the nucleophile or a chiral ligand to the palladium catalyst. Diastereoselective dimerization of butadiene with the chiral enamine **18** followed by hydrolysis gave optically active 2-(2,7-octadienyl)cyclohexanone **19** with 72% ee, although the chemical yield was not mentioned in the literature.[15] In this case, (*S*)-(−)-2-(methoxymethyl)pyrrolidine **20** used as a chiral auxiliary can be recovered (**Scheme 5**).



Scheme 5

Catalytic asymmetric dimerization of butadiene with 2-methoxycarbonylcyclopentane **21** is carried out by using 0.15 mmol % $Pd(OAc)_2$–BPPM [(2*S*,4*S*)-*N*-*t*-butoxycatbonyl-2,4-bis(diphenylphosphino)methylpyrrolidine], which affords the dimerization product **22** in 86% yield with 41% ee (**Scheme 6**).



21

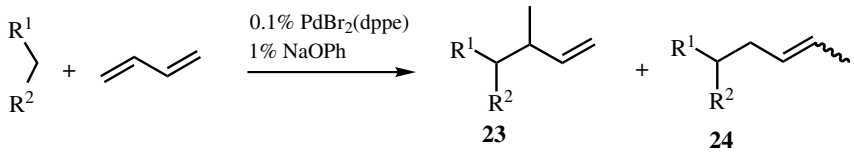
22 41% ee (86% yield)

[1] 0.15% $Pd(OAc)_2$–BPPM–NaOH, isopropanol, −10 °C

Scheme 6

The dimerization of butadiene is a useful method for the synthesis of various natural products. Pellitorine, which is an insecticidal compound isolated from *Anacyckus pyrethrum* roots,[16] queen substances, which are well-known honey bee pheromones,[17],[18] *cis*-civetone, which is a naturally occurring unique symmetric 17-membered cyclic ketone,[19] and recifeiolide, which consists of a 12-membered lactone framwork,[20] can readily be synthesized from butadiene dimers.

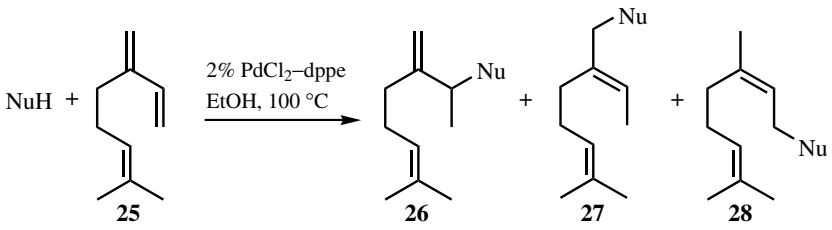
In contrast to the reaction catalyzed by the monodentate phosphine–palladium complexes described above, the reaction of butadiene with carbon nucleophiles catalyzed by the palladium complexes combined with bidentate phosphines, such as $PdBr_2$dppe–NaOPh and $Pd(dppe)_2$, affords a mixture of 1:1 adducts **23** and **24** (**Scheme 7**).[21],[22] Not only butadiene but also isoprene, 1,3-pentadiene, 2,3-dimethyl-1.3-butadiene, and hexatriene also underwent the monoaddition reaction with various carbon (and oxygen) nucleophiles.[23] The coordination of the bidentate phosphine is essential to give the 1:1 addition products: it decreases the number of coordination sites for 1,3-diene from two to one, inhibiting the dimerization of 1,3-diene to yield the monoadduct quite selectively. Myrcene **25** also undergoes the selective monoaddition reaction with activated methylenes in the presence of $PdCl_2$–dppe catalyst to give a mixture of **26**, **27**, and **28** in 40–73% yields (**Scheme 8**).[24] Variation of 1,3-dienes is explored using bis(phenylsulfonyl)methane as a carbon nucleophile under [(π-C_3H_5)PdCl]$_2$–dppp–NaOMe catalyzed condition in THF at 100 °C and excellent yields of 1:1 adducts are obtained in all cases (**Scheme 9**).[25]



23 **24**

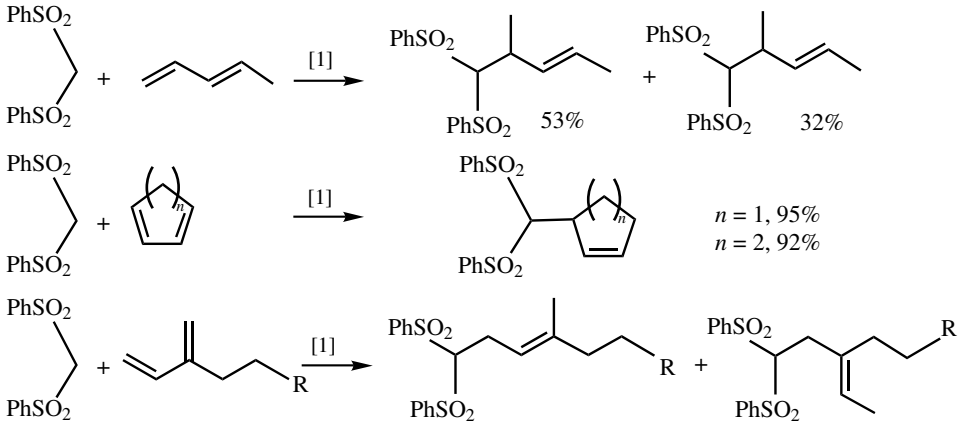
R^1	R^2	**23** (%)	**24** (%)
COMe	CO_2Et	35	36
COMe	COMe	17	43
CO_2Et	CO_2Et	18	18

Scheme 7



NuH = $CH(CO_2Et)_2$ (73%) (**26**/**27**/**28** = 30:52:18)
$CH(COCH_3)CO_2Et$ (57%) (**26**/**27**/**28** = 5:50:45)
$CH(COCH_3)_2$ (40%) (**26**/**27**/**28** = 6:42:52)

Scheme 8



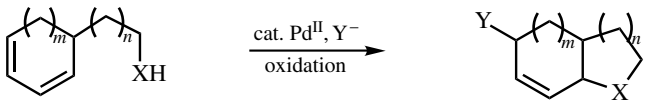
R =			
$CH{=}C(CH_3)_2$	58%	27%
Ch_2OH	12	84
CO_2Me	57	39
COPh	57	36

[1] 1% [(π-C_3H_5)PdCl]$_2$, 3% dppp, 3% NaOMe, THF, 100 °C.

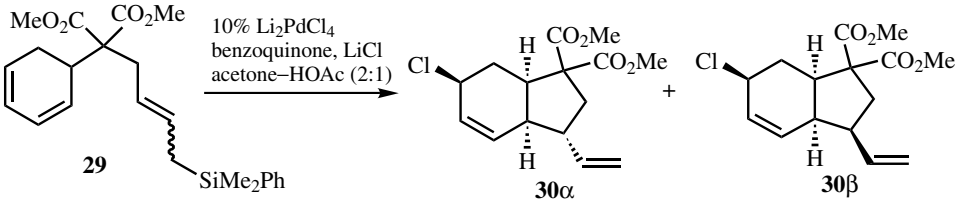
Scheme 9

C. INTRAMOLECULAR ADDITION OF SOFT CARBON NUCLEOPHILES TO CONJUGATED DIENES

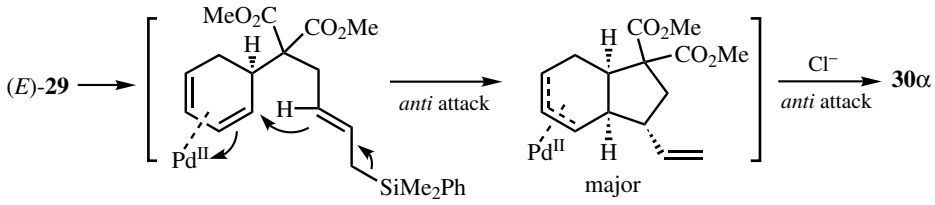
Intramolecular addition of a 1,3-diene having a carbon nucleophile in the side chain is catalyzed by Pd(II), leading to an overall 1,4-oxidation of the diene (**Scheme 10**). Allylsilane can be used as a carbon nucleophile in the Pd(II)-catalyzed carboannulation. The reaction of the 1,3-diene (*E*)-**29** with a catalytic amount of Li_2PdCl_4 in the presence of *p*-benzoquinone (1.5 equiv), which acts as an oxidant of Pd(0) generated in the reaction, and LiCl (2 equiv) in acetone–acetic acid (2:1) gives a mixture of two isomeric allylic chlorides **30** (α/β = 3:1) in 68% yield (**Scheme 11**).[26] The addition of the carbon and chloride across the diene proceeds completely in a stereoselective manner and only the 1,4-*syn*-addition products are obtained.



Scheme 10

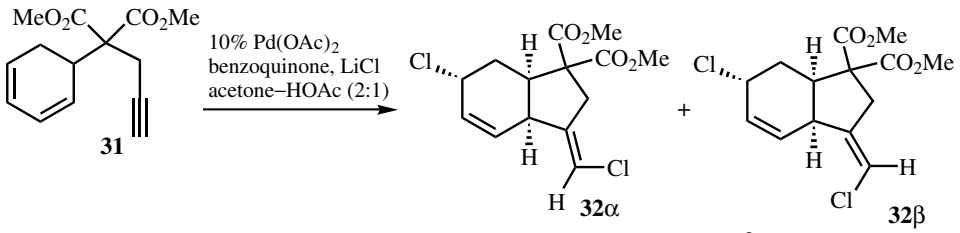


(*E*)-**29** 68% (**30**α/**30**β = 3:1)
(*Z*)-**29** 72% (**30**α/**30**β = 1:3)



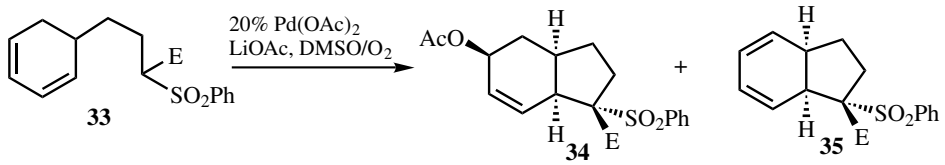
Scheme 11

Under the same condition, (*Z*)-**29** gives a 1:3 mixture of **30**α and **30**β in 72% yield; interestingly, the isomer ratio is opposite to that obtained from (*E*)-**29**. The *anti* stereochemistry between Cl and the vinyl group in **30**α obtained from (*E*)-**29** is explained by an external *anti* attack by the allylsilane on the coordinated diene to give a π-allylpalladium intermediate followed by an external *anti* attack by Cl^-. The reaction of the dienyne **31** with LiCl and benzoquinone in the presence of $Pd(OAc)_2$ (10 mol %) affords a mixture of the cyclization products **32**α and **32**β in a ratio of 1:1.5 (**Scheme 12**).[27] It is thought that the addition of vinylpalladium species, which can be obtained *in situ* from an acetylene via chloropalladation, to the diene generates a π-allylpalladium complex, which is trapped by Cl^-, giving the cyclic adducts.[28] The activated methyne compounds **33** undergo the intramolecular 1,4-addition reaction by using the O_2/DMSO oxidation system to afford the cyclization products **34** and **35** (**Scheme 13**).[29]



65% (**32**α/**32**β = 1:1.5)

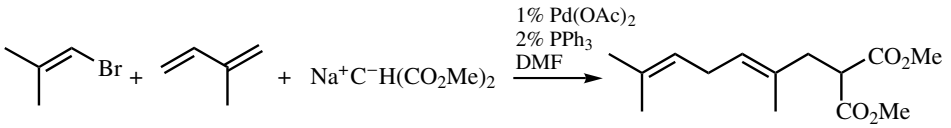
Scheme 12



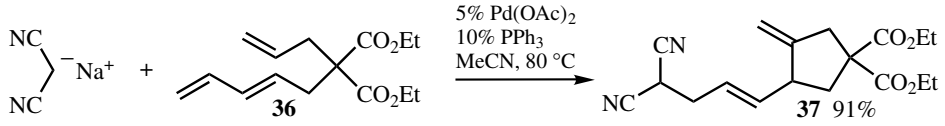
Scheme 13

D. THREE-COMPONENT COUPLING REACTIONS

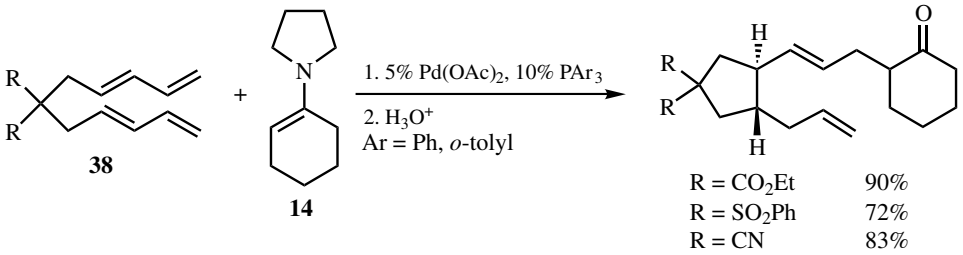
The three-component coupling reaction of 1-bromo-2-methylpropene, isoprene, and dimethyl sodiomalonate proceeds in the presence of $Pd(OAc)_2$–PPh_3 to give dimethyl(2,6-dimethylhepta-2,5-dien-1-yl)malonate in 22% yield (**Scheme 14**).[30] The similar type of three-component coupling reactions, including a partial intramolecular process, also takes place smoothly. Intramolecular tamdem carbon–carbon bond formation of sodiomalononitrile with 6,6-diethoxycarbonyl-1,3,8-nonatriene **36** is catalyzed by $Pd(OAc)_2$–$2PPh_3$ to afford the five-membered carbocycle **37** in 91% yield (**Scheme 15**).[31] Furthermore, the treatment of the 1,3,8,10-undecatetraene derivatives **38** with 2 equiv of the pyrrolidine enamine of cyclohexanone (**14**) in refluxing CH_2Cl_2 gives the corresponding carbocyclization products, which are hydrolyzed to afford the α-alkylated cyclohexanones in 72–90% yields (**Scheme 16**).[32]



Scheme 14

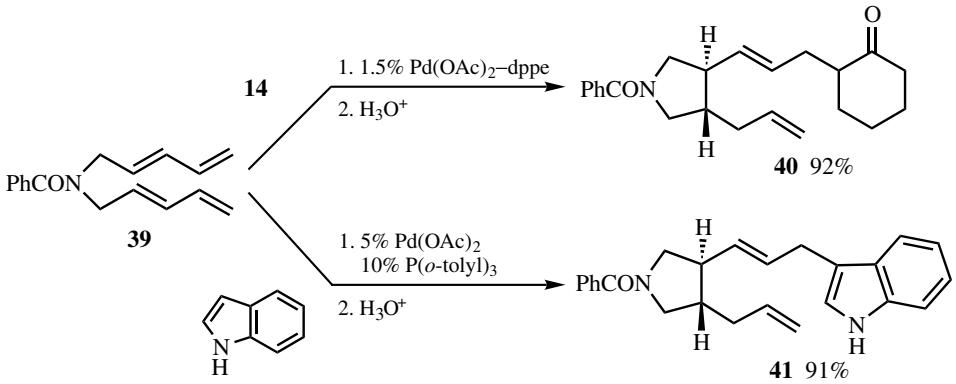


Scheme 15

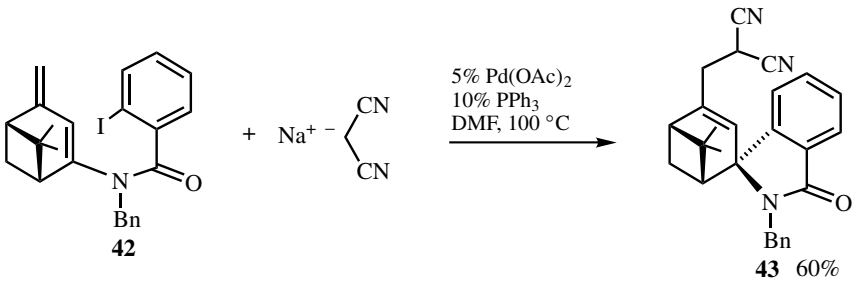


Scheme 16

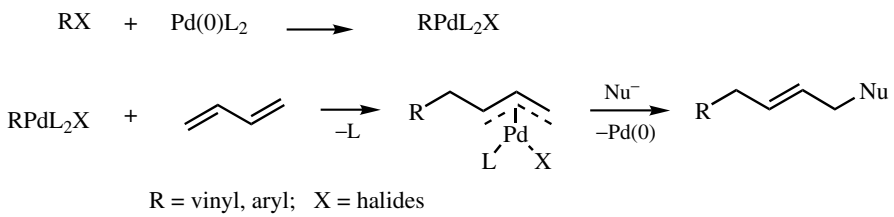
The cyclization of the benzamide tetraene **39** with the enamine **14** gives *N*-acylpyrrolidine **40** in 92% yield. Indole also proves to be an effective carbon nucleophile in the reaction of **39**. The adduct **41** is obtained in 91% yield from the cyclization in the presence of $Pd(OAc)_2$–(o-Tol_3P) catalyst (**Scheme 17**).[32] Intramolecular coupling reaction of the dienamide **42** with sodiomalononitrile under the Pd-catalyzed conditions affords the cyclic product **43** in 60% yield (**Scheme 18**).[31] This reaction proceeds through a Heck-type mechanism as mentioned in **Sect. IV.2**. The σ complex formed by the oxidative addition of vinyl or aryl halides to a Pd(0) species reacts with a 1,3-diene to generate the π-allylpalladium intermediates, which undergo nucleophilic attack by nucleophiles (dimethyl malonate anion in the case of **Scheme 18**) to produce the three-component coupling products (**Scheme 19**).[30],[33]



Scheme 17



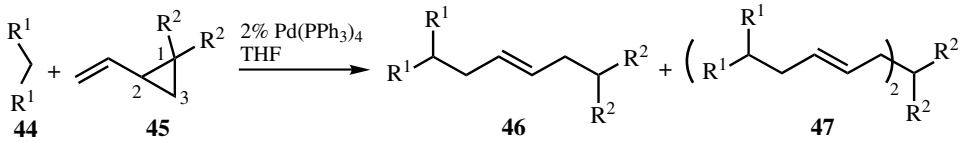
Scheme 18



Scheme 19

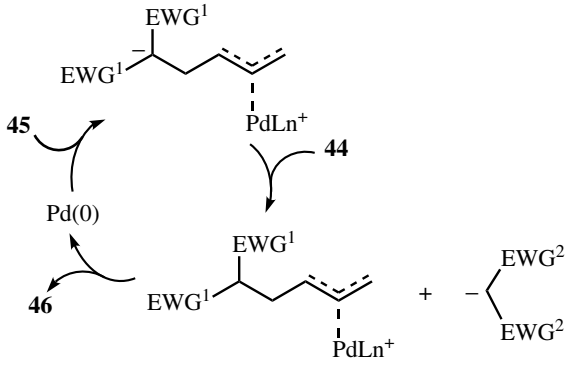
E. ADDITION OF SOFT CARBON NUCLEOPHILES TO VINYLCYCLOPROPANES

The regiospecific conjugate addition of the activated methylenes **44** to the activated vinylcyclopropanes **45** proceeds in the presence of $Pd(PPh_3)_4$ catalyst to afford the monoadducts **46** along with the diadducts **47** (**Scheme 20**).[34],[35] Pd(0) complex might cleave the 1,2-bond of the cyclopropanes **45** to form zwitterionic π-allylpalladium intermediates, which could deprotonate the activated methylenes **44** to produce the stabilized enolates, which would be free to add the π-allyl terminus (**Scheme 21**).



R^1	R^2	**46** (%)	**47** (%)
COMe	CO_2Me	30	59
SO_2Ph	CO_2Me	94	—
COMe	SO_2Ph	62	32

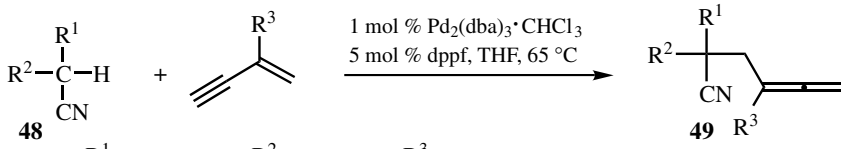
Scheme 20



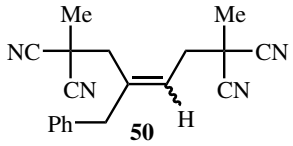
Scheme 21

F. ADDITION OF SOFT CARBON NUCLEOPHILES TO CONJUGATED ENYNES

The Pd-catalyzed reaction of conjugated enynes with the activated methynes including at least one CN group in the molecules **48** gives allenes **49** in good to high yields (**Scheme 22**).[36] The combination of $Pd_2(dba)_3 \cdot CHCl_3$–dppf (dba = dibenzylidene acetone, dppf = bis-diphenylphosphinoferricene) is an effective catalyst for this reaction and the use of an excess of nucleophiles causes further addition reaction to the generated allenes **49** (as mentioned in **Sect. V.2.2.3**), affording the 1,3-dinucleophile adducts (e.g., **50**).



R^1	R^2	R^3	Yield (%)
Ph	CO_2Et	Me	100
Me	CO_2Et	Me	60
Me	CN	Me	75
Ph	CO_2Et	CH_2Ph	95
Me	CO_2Et	CH_2Ph	65
Me	CN	CH_2Ph	28
Ph	CO_2Et	$SiMe_3$	100
Me	CO_2Et	$SiMe_3$	90
Me	CN	$SiMe_3$	100



Scheme 22

G. SUMMARY

1. 1,3-Dienes undergo dimerization–addition with various nucleophiles, such as alcohols, amines, enamines, and activated methylenes and methynes, in the presence of Pd(0) or Pd(II) catalysts to afford the corresponding octa-2,7-dienyl derivatives.

2. Phosphine ligand controls the reaction course of butadiene dimerization. The use of monodentate phosphines gives the dimerization products (2:1 adducts), octa-2,7-dienyl derivatives, while the use of bidentate phosphines, such as dppe and dppp, prevents the coordination of two molecules of 1,3-dienes to palladium to afford the 1:1 adducts, 2-butenyl derivatives.

3. Bis-π-allylpalladium intermediates are involved in the dimerization–addition reaction of 1,3-dienes with nucleophiles.

4. The C—C σ-bond of cyclopropanes undergoes the oxidative cleavage by Pd(0) to give the π-allylpalladium intermediates (**Schemes 20** and **21**). The transition metal catalyzed C—C bond activation is a relatively unexplored field, compared to C—H and C—X activation. Perhaps, the C—C activation of **45** takes place relatively easily owing to the following formation of rather stable π-allylpalladium intermediate. This seems to suggest how to induce the C—C bond activation.

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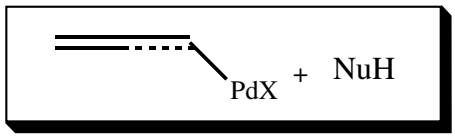

V.2.2 Palladium-Catalyzed Allylic, Propargylic, and Allenic Substitution with Nitrogen, Oxygen, and Other Groups 15–17 Heteroatom Nucleophiles

V.2.2.1 Palladium-Catalyzed Substitution Reactions of Allylic, Propargylic, and Related Electrophiles with Heteroatom Nucleophiles

TADAKATSU MANDAI

A. INTRODUCTION

Substitution reactions of π-allylpalladium complexes with heteroatom nucleophiles have been well documented. In sharp contrast, the reactions of allenyl and/or propargylpalladium complexes with heteroatom nucleophiles are very rare, and only one reaction has been recorded so far that provides propargylic amines through S_N2' type substitution reactions of allenylpalladium complexes with aromatic amines.

B. ALLYLIC COMPOUNDS

B.i. Nitrogen Nucleophiles

Nitrogen compounds serve as reactive nucleophiles toward π-allylpalladium complexes (**Scheme 1**). Diethylamine is allylated with allyl alcohol.[1] Allylic chlorides react with amines without a Pd catalyst, but the reaction is accelerated with such a catalyst. For example, in the Pd-catalyzed reaction of 1-acetoxy-4-chloro-2-butene with diethyl amine at 25 °C, only the allylic chloride is displaced without attacking the allylic acetatoxy moiety. The uncatalyzed reaction proceeds at 80 °C.[2],[3] The secondary amine is obtained without significant formation of a tertiary amine when the reaction is carried out in a homogeneous aqueous medium using water-soluble TPPTS as a ligand.[4] The primary allylic amine is prepared by the highly selective monoallylation of 4,4′-dimethoxybenzhydrylamine, which is easily removed by treatment with 80% formic acid.[5] A hydroxylamine is smoothly

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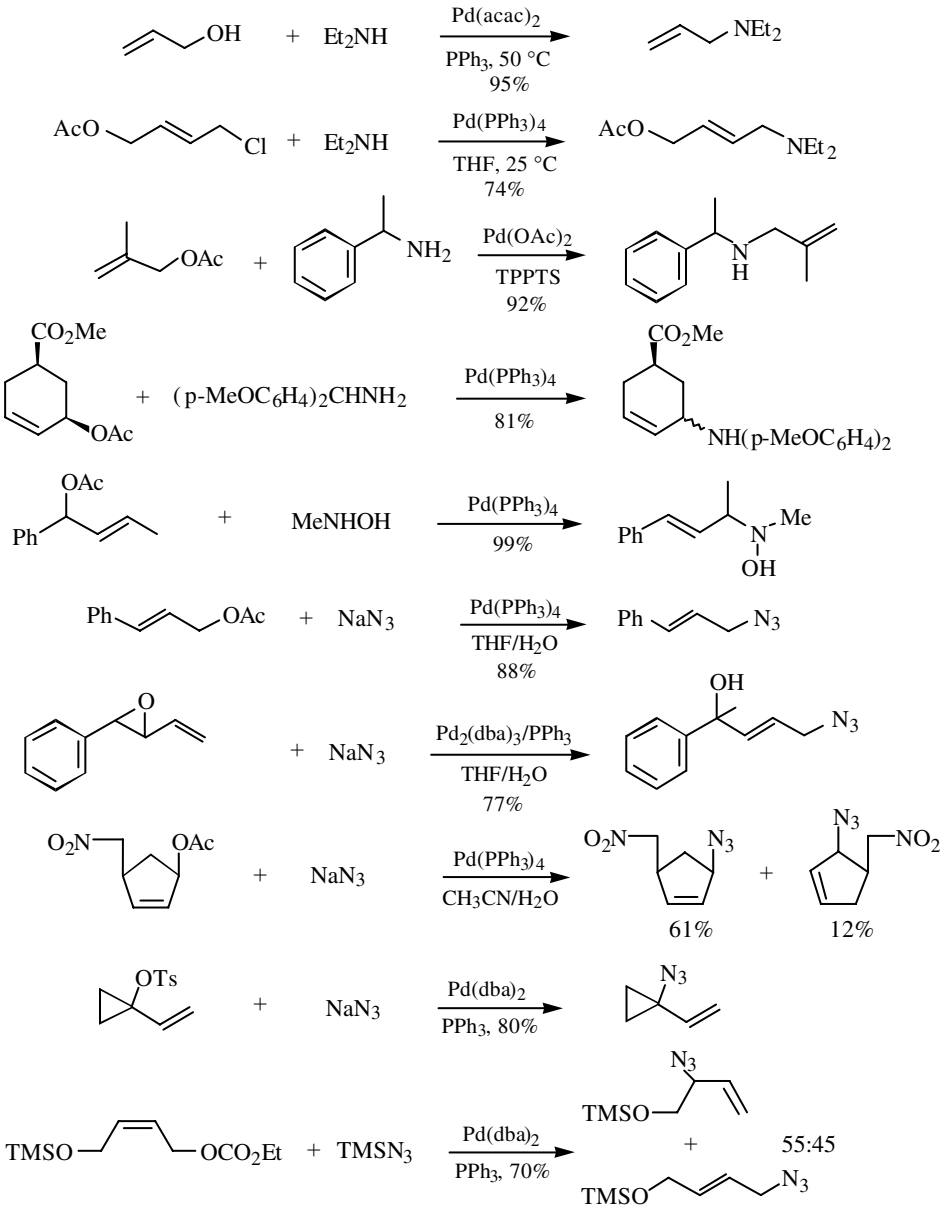
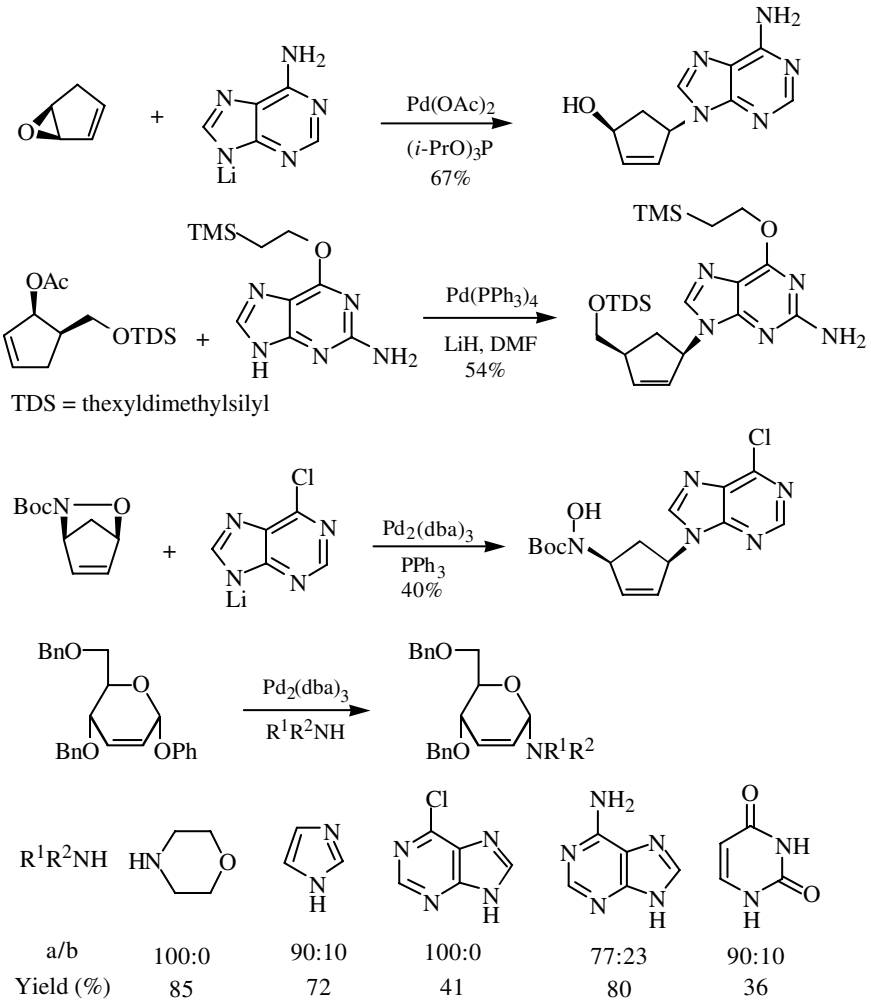
allylated to give an *N*-allylhydroxylamine, which, on reduction with Zn in a dilute HCl solution, provides an allylic amine.[6] The reaction of sodium azide or trimethylsilylazide followed by the treatment with triphenylphosphine is another preparative method for primary allylic amines.[7]–[13]

Purine analogs and imidazoles can be *N*-allylated (**Scheme 2**). Carbocyclic analogs of nucleosides can be synthesized by the regio- and stereoselective N-alkylation of allylic substrates such as cyclopentenyl acetate or cyclopentadiene monoepoxide with purine



Scheme 1

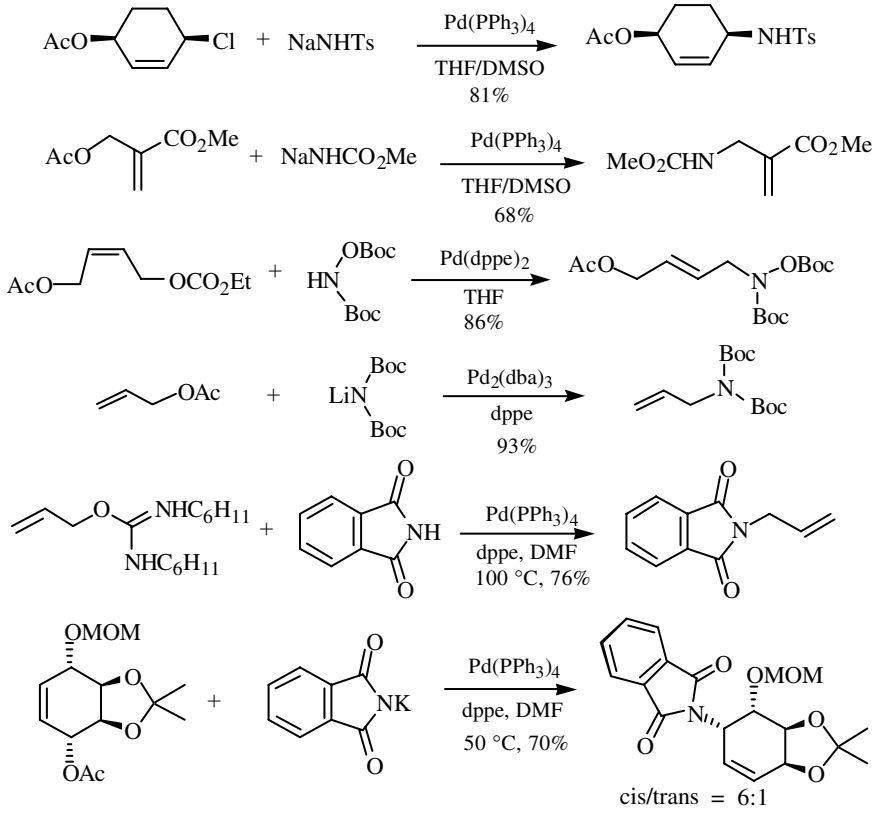
bases.[14]–[16] A bicyclic isoxazolidine also generates a π-allylpalladium intermediate, which leads to a convenient synthesis of 4′-amino substituted carbocyclic adenosine analogs.[17] *N*-Glycopyranosides are prepared by a regioselective amination at an anomeric carbon of a glucal derivative with retention of configuration.[18]



Scheme 2

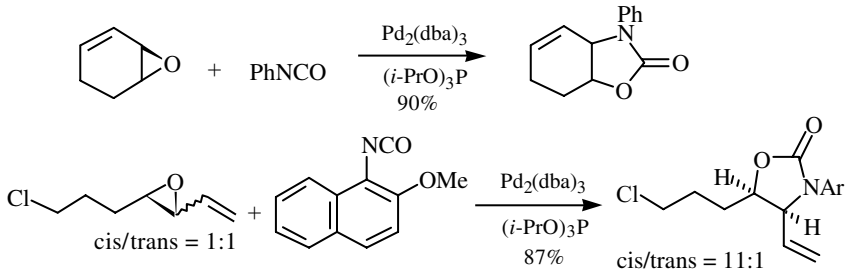
Amides, carbamates, imides, and their metal salts also serve as reactive nucleophiles (**Scheme 3**). Sodium *p*-toluenesulfonamide attacks 1-acetoxy-4-chloro-cyclohex-2-ene to give an allylic amide in a highly chemoselective manner with retention of configuration.[19] Sodium salt of methylcarbamate is also alkylated in DMSO or HMPA.[20] (*N*, *O*)-Bis-*ter*-Boc hydroxylamine reacts with an allylic carbonate chemo- and regioselectively to provide a protected *N*-allylhydroxylamine, in which an ethoxy anion, a counterion of Pd in a π-allylpalladium complex, serves to generate an anion of (*N*, *O*)-bis-*ter*-Boc hydroxylamine.[21] Preparation of primary allylamines by a selective monoallylation of ammonia is not possible and they are prepared by indirect methods. The monoallylation

of Li or Na amides of di-*t*-butoxycarbonyl (Boc) followed by hydrolysis affords a primary allylamine.[22] Phthalimide is allylated with an allylisourea at room temperature in the absence of a base.[23] A potassium salt of phthalimide is allylated with an allylic acetate at 100 °C.[24]



Scheme 3

A Pd-mediated reaction of a vinyl epoxide with an isocyanate offers synthetically useful transformation (**Scheme 4**). A diastereoselective vicinal hydroxyamination is established, which involves trapping an initial zwitterion with an isocyanate and subsequent nucleophilic attack of a nitrogen anion on a π-allylpalladium intermediate (**Scheme 4**).[25],[26]



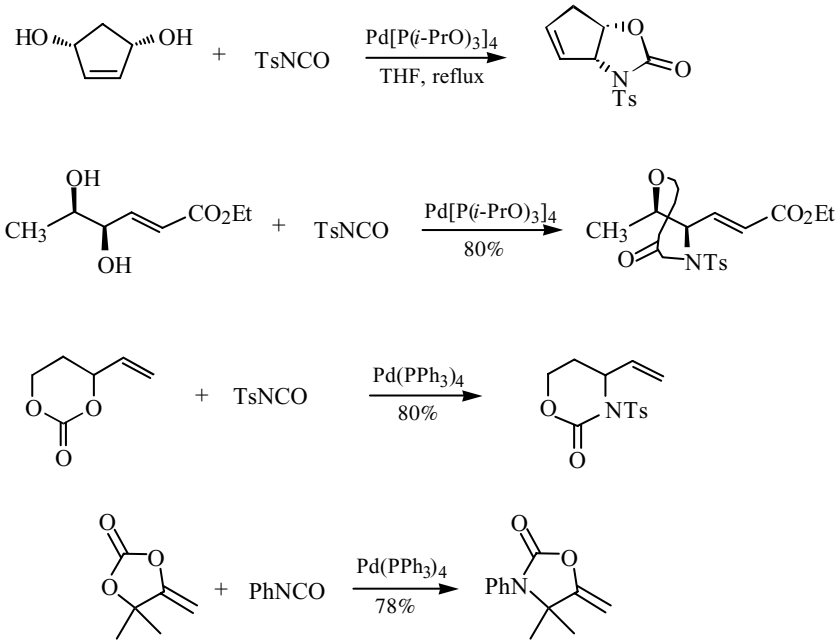
Scheme 4

Oxazolidin-2-ones are afforded by the reaction of ene diols with 2 equiv of *p*-toluenesulfonyl isocyanates (**Scheme 5**).[27],[28] Cyclic carbamates are synthesized by the reaction of cyclic carbonates with aryl isocyanates.[29],[30]

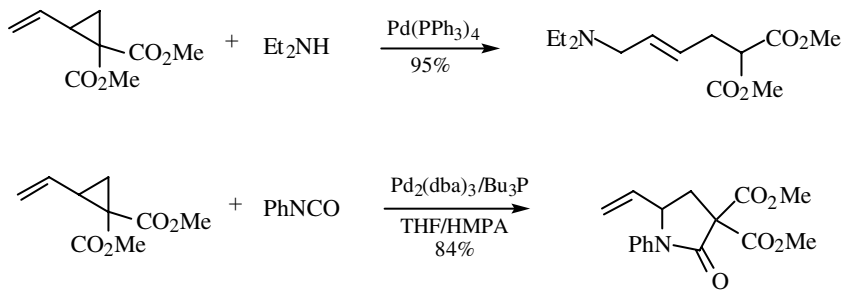
A vinylcyclopropanedicarboxylate forms a zwitterionic π-allylpalladium intermediate, which undergoes attack by diethylamine to afford an allylic amine (**Scheme 6**).[31],[32] Similarly, the reaction with phenyl isocyanate provides a γ-lactam derivative.[33]

Intramolecular amination with allylic acetates is used for the synthesis of cyclic alkaloids (**Scheme 7**).[34] This protocol can be applied to a synthesis of 21-membered cyclic amine skeleton of the spermidine alkaloid [35] and 1-azaspirocycles.[36]–[39] 3-Methylenepyrolidines are provided by the nucleophilic addition of allylzinc reagents to imines and subsequent Pd-catalyzed intramolecular allylation.[40]

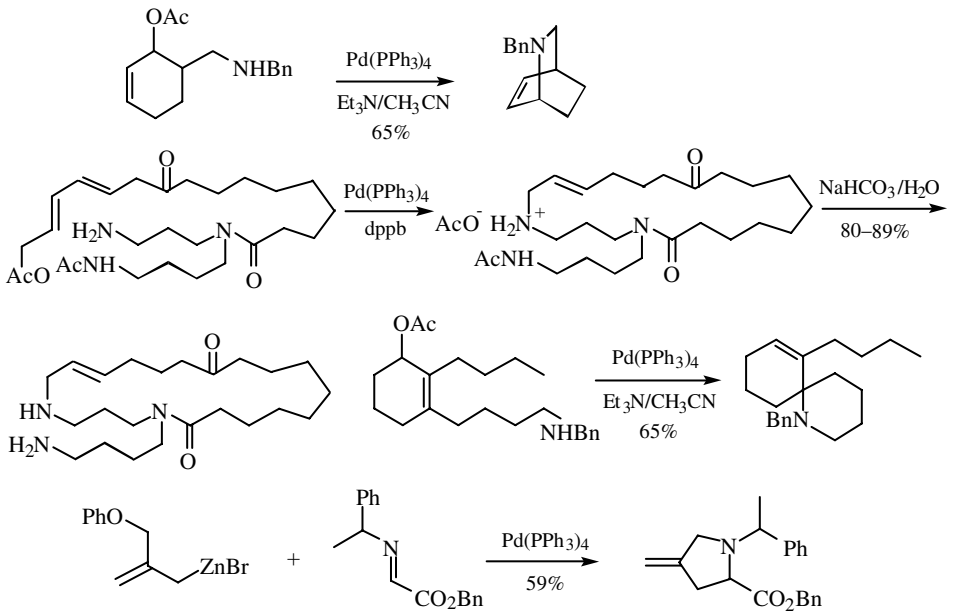
Dienyl aziridines and dienyl azetidines can be rearranged to 3-pyrroline and piperidine derivatives, respectively (**Scheme 8**).[41]



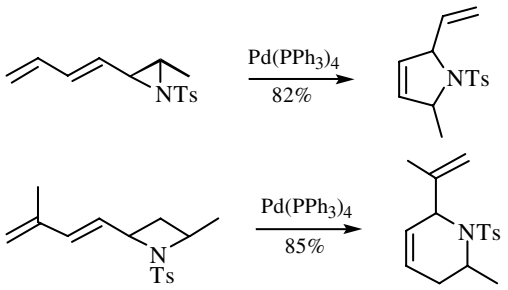
Scheme 5



Scheme 6



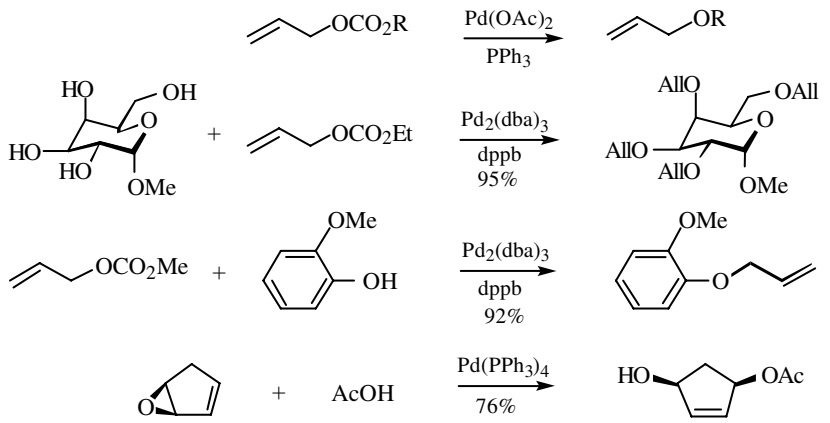
Scheme 7



Scheme 8

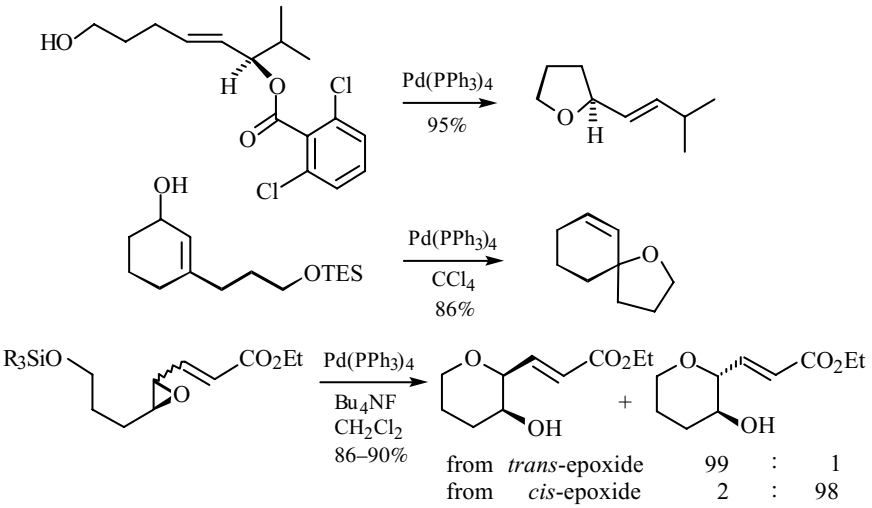
B.ii. Oxygen Nucleophiles

Pd-mediated allylation of alcohols to form allyl alkyl ethers is somewhat sluggish because of poor nucleophilicity of alcohols (**Scheme 9**). As one method, allyl alkyl carbonates are decarboxylated to give allyl alkyl ethers in the absence of other nucleophiles.[42] Methyl α-D-galactoside is conveniently allylated by the reaction of an excess of allyl ethyl carbonate.[43] An allyl ethyl carbonate, on exposure to palladium catalyst, gives a π-allylpalladium complex ($CH_2{=}CHCH_2PdOEt$) with CO_2 evolution. The ethoxy group is exchanged by the hydroxy groups in a carbohydrate, and then the Pd(0) species is reductively eliminated to give an allylic ether. Phenols are highly reactive O-nucleophiles and allylated easily with allylic carbonates under neutral conditions. The reaction is facilitated by the electron-donating groups on phenols.[44] Cyclopentadiene monoepoxide is attacked by acetic acid regio- and stereoselectively via a π-allylpalladium complex to give *cis*-1-acetoxy-4-hydroxycyclopent-2-ene. [45],[46]



Scheme 9

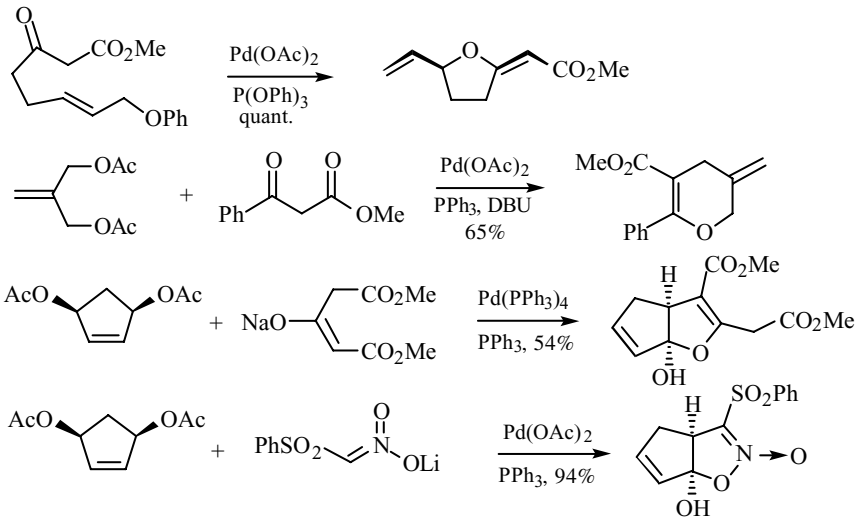
Complete chirality transfer is observed in the intramolecular allylation of an alcohol with an activated allylic ester of 2,6-dichlorobenzoic acid to give a 2-substituted tetrahydrofuran (**Scheme 10**).[47] Allylic alcohols can serve as a leaving group.[48] If CCl_4 is used as the solvent in the $Pd(PPh_3)_4$-catalyzed reaction, PPh_3 liberated from the complex reacts with CCl_4 to form $(PPh_3—CCl_3)^+Cl^-$ salt. Reaction of this intermediate with an allylic alcohol provides $HCCl_3$ and an oxophosphonium ion $R—O—P^+Ph_3$, a precursor to a π-allylpalladium complex. Then Cl^- generated *in situ* unmasks the OTES group to leave the alkoxide nucleophile, which cyclizes to an oxaspirocycle. This protocol however, is, largely susceptible to a ring size owing to its competitive chlorination. In the stereocontrolled synthesis of *cis*- and *trans*-2-alkenyl-3-hydroxytetrahydropyrans, it has been disclosed that an ammonium alkoxide is much superior to an alcohol itself with respect to the stereoselectivity and the chemical yield.[49],[50] Interestingly, the reaction undergoes a dramatic solvent effect, being greatly facilitated in either chloroform or dichloromethane to give excellent yields as well as complete stereoselectivities.



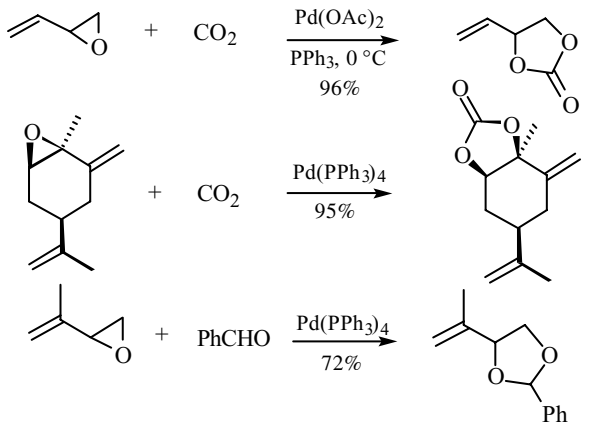
Scheme 10

Allylation of β-keto esters brings a classic problem of O-versus C-alkylation (**Scheme 11**). Intramolecular allylation of a β-keto ester possesing an allylic phenyl ether results in the exclusive formation of cyclic ethers when $P(OPh)_3$ is used as a ligand.[51],[52] A pyran derivative is provided by the allylation of methyl benzoylacetate with 2-methylene-1,3-propandiol diacetate. Initially, the allylation takes place on the carbon of the ambident nucleophile, and then O-alkylation ensues intramolecularly.[53] Analogously, the allylation of a sodium enolate of dimethyl 3-oxoglutarate with *cis*-1,4-diacetoxycyclopent-2-ene gives a cyclopentene derivative, an asymmetric synthesis of which is extensively studied at the same time.[54] Furthermore, a 3-(phenylsulfonyl)isoxazoline 2-oxide is successfully furnished by the reaction of lithium[(phenylsulfonyl)methylene]nitronate with *cis*-1,4-diacetoxycyclopent-2-ene.[55]

Carbon dioxide readily reacts with 1,3-butadiene monoepoxide to afford vinylethylene carbonate in a quantitative yield (**Scheme 12**).[56] The Pd-mediated vicinal cleavage of an allylic epoxide with carbon dioxide proceeds with retention of stereochemistry to



Scheme 11

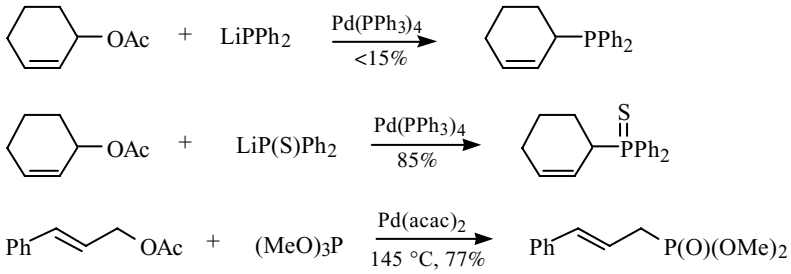


Scheme 12

give an allylic cyclic carbonate.[57],[58] Dioxolane is conveniently prepared by the reaction of an allylic epoxide with benzaldehyde.[59]

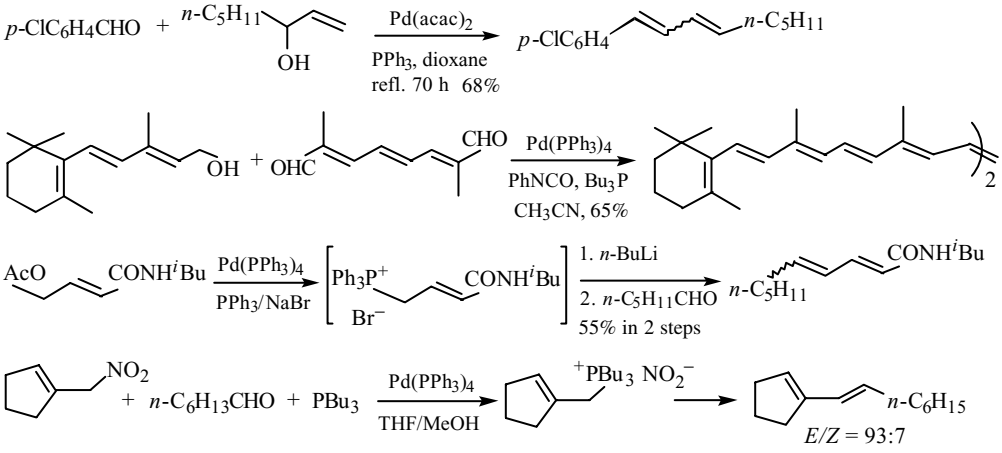
B.iii. Phosphorus Nucleophiles

Carbon–phosphorus bonds are formed by the Pd-catlyzed allylation of various phosphorus compounds (**Scheme 13**). The reaction of 1-acetoxy-2-cyclohexene with $LiPPh_2$ in refluxing THF provides an allylic phosphine in low yield (<15%). The phosphine produced deactivates the catalyst by coordination, which lowers the yield. In contrast, the reaction of $LiP(S)Ph_2$ with 1-acetoxy-2-cyclohexene takes place at room temperature to give allylic diphenylphosphine sulfides in 85% yield.[60] Pd-catalyzed Michaelis–Arbuzov reaction of cinnamyl acetate with trimethyl phosphite affords a dimethyl allylic phosphonate. With the reaction conditions being rather severe, this method may not be applicable to an allylic acetate that can produce a conjugated diene via β-hydride elimination from the intermediate π-allylpalladium complex.[61]



Scheme 13

Pd-mediated reaction of allylic alcohols with phosphines affords phosphonium salts, which react with aldehydes to form conjugated dienes by a Wittig-type reaction (**Scheme 14**).[62]–[64] The reaction of an allylic alcohol, phenyl isocyanate, and PBu_3 produces a phosphonium salt under mild conditions, in which an allylic phenylcarbamate

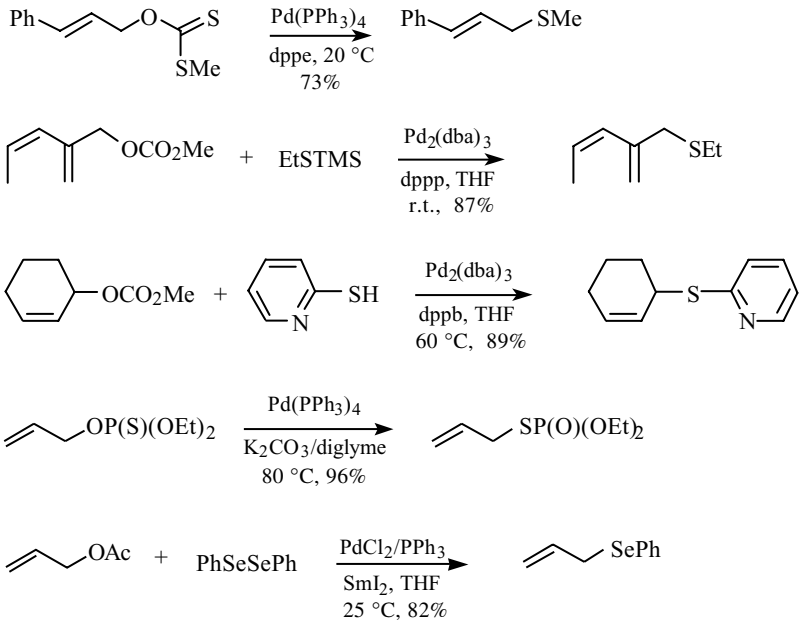


Scheme 14

initially formed reacts with Pd(0) to afford a π-allylpalladium complex with the release of carbon dioxide. Then, PBu_3 attacks the π-allylpalladium complex to form an allylic phosphonium salt, which is converted to a phosphorane by the deprotonation with an anilide anion.[65] The Pd-catalyzed reaction of an allylic acetate and PPh_3 in the presence of NaBr provides a phosphonium salt at room temperature (r.t.), which, on treatment with *n*-BuLi followed by addition of an aldehyde, gives a conjugated diene amide.[66] The Pd-catalyzed reaction of an allylic nitro compound with PBu_3 provides a phosphonium salt, which, on treatment with *n*-BuLi followed by addition of an aldehyde, produces a conjugated diene in a highly stereoselective manner.[67]

B.iv. Sulfur and Selenium Nucleophiles

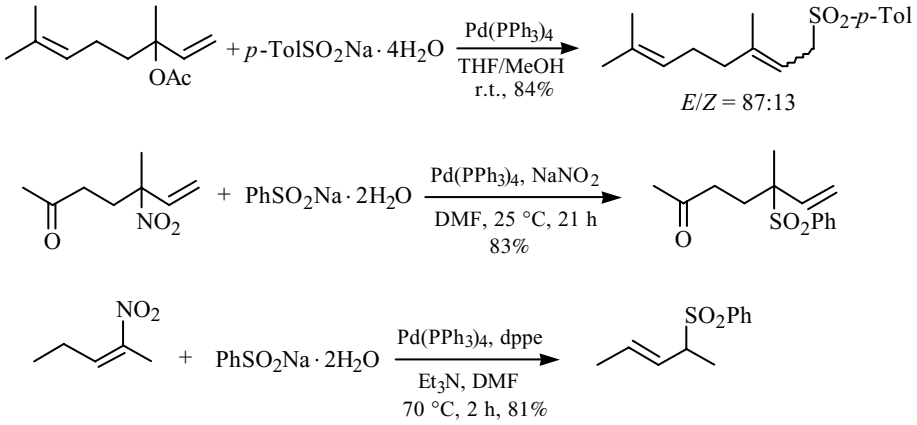
Various sulfur and selenium nucleophiles are allylated. The Pd-catalyzed reaction of an *O*-allyl *S*-methyl dithiocarbonate takes place under mild conditions in one step to afford an allylic sulfide.[68],[69] An *O*-allyl *S*-methyl dithiocarbonate oxidatively adds to the Pd(0) to form a π-allylpalladium complex together with *S*-methyl dithiocarbonate ion, from which carbon oxide sulfide (COS) and MeS^- nucleophile are spontaneously released. The latter attacks an allylic terminus to afford an allylic sulfide. Monodentate ligand such as PPh_3 is not effective for this reaction because the catalyst is deactivated by the coordination of the carbon oxide sulfide (COS) released. Thus, dppe instead of PPh_3 is necessary for this reaction since it coordinates stronger to Pd than PPh_3 and thus prevents the coordination of carbon oxide sulfide. An allylic carbonate reacts with alkyl- or arylthiotrimethylsilane to give an allylic sulfide.[70],[71] An *O*-allyl phosphorothionate undergoes the thiono–thiolo allylic rearrangement to afford an *S*-allylphosphorothiolate.[72],[73] An allyl phenyl selenide is obtained by the reaction of allylacetate with $(PhSe)_2$ in the presence of SmI_2 (**Scheme 15**).[74]



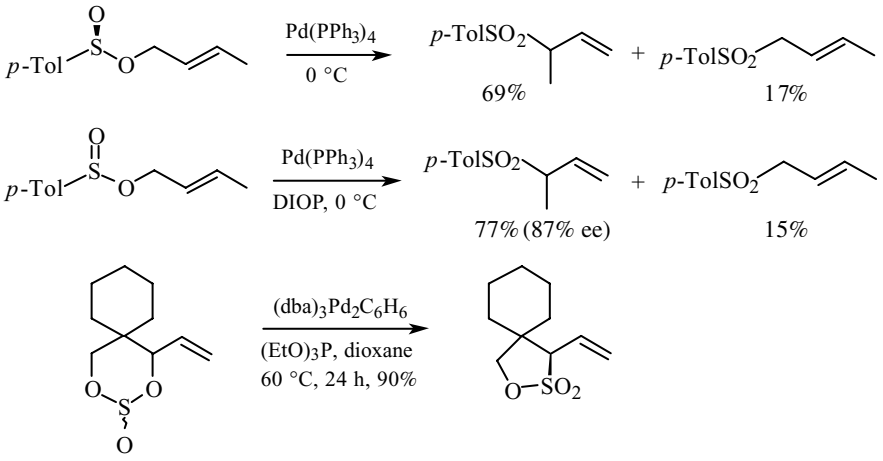
Scheme 15

Pd-catalyzed reaction of linalyl acetate with sodium *p*-toluene sulfinate tetrahydrate at 0 °C exclusively affords linalyl *p*-tolylsulfone, which is completely converted to geranyl *p*-tolylsulfone in a thermodynamically controlled reaction at room temperature (**Scheme 16**).[75] An allylic nitro compound undergoes denitrosulfonylation with sodium phenylsulfinate to give a more substituted allylic sulfone under kinetic control product.[76],[77] In this catalytic system under kinetic control, the addition of $NaNO_2$ plays a crucial role to deactivate the Pd catalyst, which would facilitate the allylic rearrangement of the initially formed allylic sulfone. An allylic sulfone is also obtained from the reaction of an α-nitro olefin with sodium benzene sulfinate in the presence of triethylamine.[78],[79]

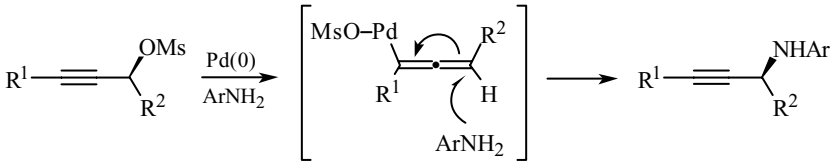
Pd-catalyzed allylic sulfinate–sulfone rearrangement of a chiral sulfinate proceeds to give a sulfone with a chirality transfer of 91.8%.[80],[81] Asymmetric induction of 87% is observed in the Pd-catalyzed rearrangement of a sulfinate using DIOP as a chiral ligand.[82] A cyclic allylic sulfite readily undergoes a formal [2,3] sigmatropic rearrangement to give a 1-vinyl sultone (**Scheme 17**).[83]



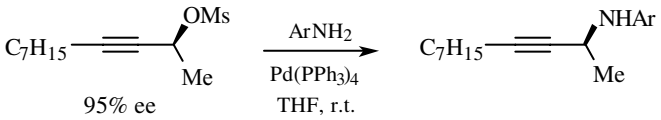
Scheme 16



Scheme 17



Scheme 18



Ar	Time (h)	Yield (%)	ee (%)
Ph	1	78	90
p-MeC_6H_4	0.5	71	90
p-$MeO_2CC_6H_4$	3	75	84
p-$H_2NSO_2C_6H_4$	25	75	-
p-$MeOC_6H_4$	0.75	75	90

Scheme 19

C. PROPARGYLIC COMPOUNDS

Propargylic substitution products are obtained by the Pd-catalyzed reaction of mesylates with aromatic amines, which proceeds with retention of configuration. This transformation would involve an anti-S_N2' type oxidative addition of the mesylates to Pd(0) and subsequent anti-S_N2' attack by the aromatic amines on the allenylpalladium intermediate (**Scheme 18**). In fact, a highly efficient chirality transfer is observed as shown in **Scheme 19**.[84] Treatment of the mesylate with aniline in the absence of a Pd(0) catalyst affords a propargylamine of opposite rotation to that of the amine obtained in the Pd-catalyzed reaction.

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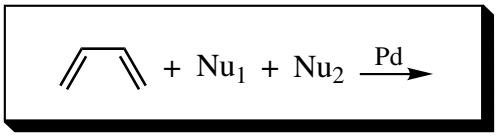

V.2.2.2 C—O and C—N Bond Formation Involving Conjugated Dienes and Allylpalladium Intermediates

PHER G. ANDERSSON and JAN-E. BÄCKVALL

A. INTRODUCTION

Conjugated dienes coordinated to a transition metal can readily be transformed into a π-allylmetal complex by functionalization at the 4-position.[1],[2] This makes dienes useful substrates for catalytic transformations since the π-allyl complex formed can undergo further reaction.[3],[4] A number of Pd-catalyzed reactions of conjugated dienes are known that proceed via π-allylpalladium intermediates and lead to useful 1,4- or 1,2-funtionalization of the diene. There are two types of reactions of this kind: (i) Pd(0)-catalyzed reactions that involve initial oxidative addition and (ii) Pd(II)-catalyzed reactions that involve electrophilic activation of the diene by the metal followed by nucleophilic attack. This section deals with C—N and C—O bond formation via these two types of reactions. This topic has previously been reviewed in connection with Pd-catalyzed additions to conjugated dienes.[3c], [5]–[11] The present review will focus mainly on the work published since 1997 but will also briefly discuss previous work.

B. REACTIONS VIA Pd(0) CATALYSIS

In the Pd(0)-catalyzed transformation of conjugated dienes the reaction is initiated by an oxidative addition to the Pd(0) catalyst. Typically, an organohalide RX or a pronucleophile HX reacts with Pd(0) to give RPdX or HPdX, respectively. These species will react with the conjugated diene through an insertion of one of the double bonds of the diene into the R—Pd or H—Pd bond, respectively, which results in the formation of a π-allylpalladium complex (**Scheme 1**).

B.i. 1,4-Hydroamination and 1,4-Addition of Alcohols

Pd-catalyzed reactions of 1,3-dienes with amines or oxygen pronucleophiles have extensively been studied and are known to give octadiene derivatives via 2:1 telomerization.[12],[13] The selectivity for 1:1 adduct between 1,3-diene and amine increases if an amine hydrochloride is employed as cocatalyst and in this way 1,4-hydroamination products were obtained (Eq. 1).[13]

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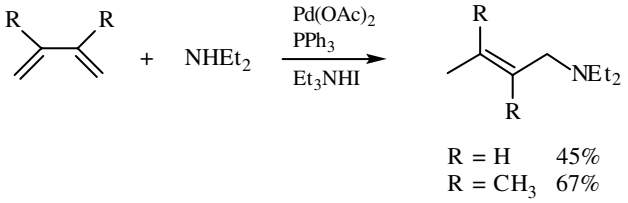
It was found that the use of sterically hindered bis(dialkylphosphino)ethane as ligands increased the selectivity for 1:1 adducts.[14] Thus, the Pd-catalyzed reaction of 1,3-dienes with alcohols employing these ligands afforded dienyl ethers in good selectivity (Eq. 2).[14]



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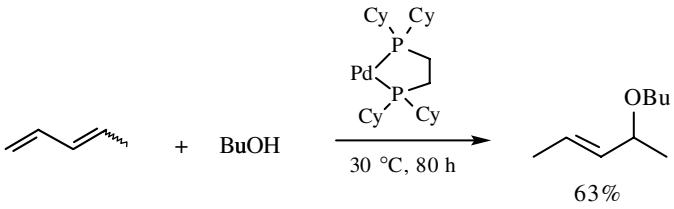

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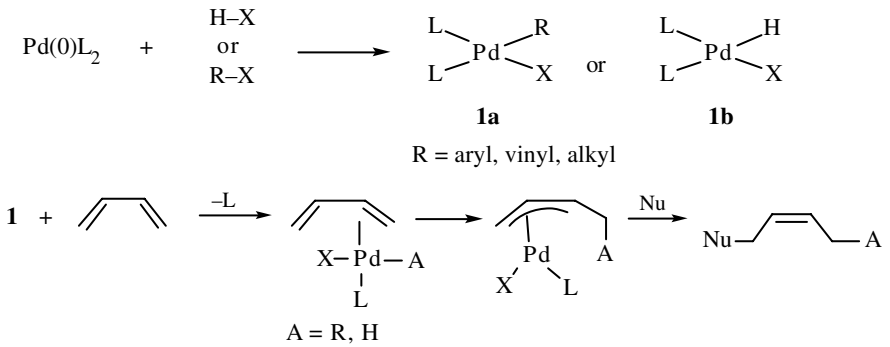


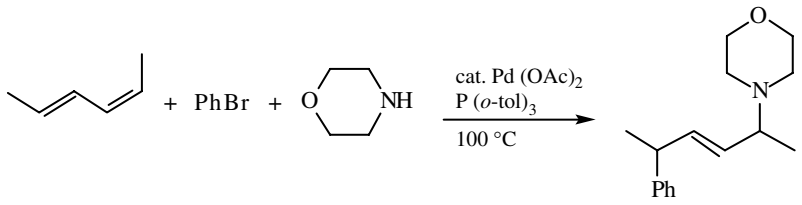
Scheme 1

B.ii. 1,4-Carboamination

Pd-catalyzed Heck-type reaction of a conjugated diene in the presence of an amine leads to a 1,4-carboamination. In the original version the reaction was performed in the presence of a phosphine. Various aryl and vinyl bromides react with a 1,3-diene and an amine in the presence of the palladium(0) catalyst (usually generated from $Pd(OAc)_2$ and phosphine) to produce 1,4-carboamination products.[15],[16] One example is given in Eq. 3.

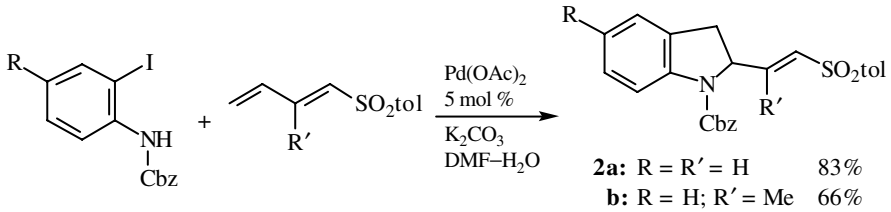
Elimination reactions to give dienes are competing side reactions in these systems, and replacement of the phosphine by a tertiary amine produced mainly 1-aryl-1,3-dienes.[17]

Intramolecular aryl- or vinylpalladation in the first step leading to a carbocylization followed by amine attack has been employed in synthetic transformations.[18]–[20] In these reactions the diene and the vinyl or aryl halide are part of the same molecule.[11]



(3)

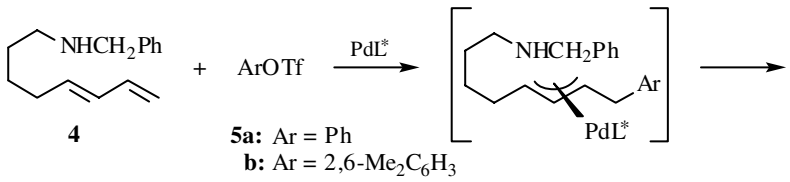
In another approach for intramolecular 1,4-carboamination of 1,3-dienes an *o*-iodoaniline was employed as substrate. The use of an *o*-iodoaniline in the Pd(0)-catalyzed reaction with 1,3-dienes results in a cyclization in the second step (amine attack on the π-allyl complex) with the formation of indolines.[21]–[23] This reaction was already described in 1986 by Dieck[21] and was further developed by Larock.[22] Recently, the reaction was applied to 1-sulfonyl-1,3-dienes, which afforded synthetically useful 2-(sulfonylvinyl)indolines **2** (Eq. 4).[23]



2a: R = R′ = H 83%
b: R = H; R′ = Me 66%
c: R = OMe; R = H 78%

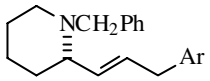
(4)

The reaction has also been applied to another intramolecular version where a cyclization occurs in the second step (**Scheme 2**).[24] With the use of chiral ligands enantioselectivities of up to 80% ee were obtained. Thus, with ligand **3**, dieneamine **4** and aryltriflates **5a** and **5b** gave the corresponding products, **6a** and **6b** in 70% and 77% ee, respectively. Attempts to use BINAP as the ligand in these reactions were unsuccessful and gave low levels of enantioselectivity (12% ee).

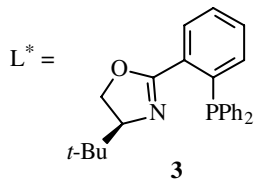


4

5a: Ar = Ph
b: Ar = 2,6-$Me_2C_6H_3$



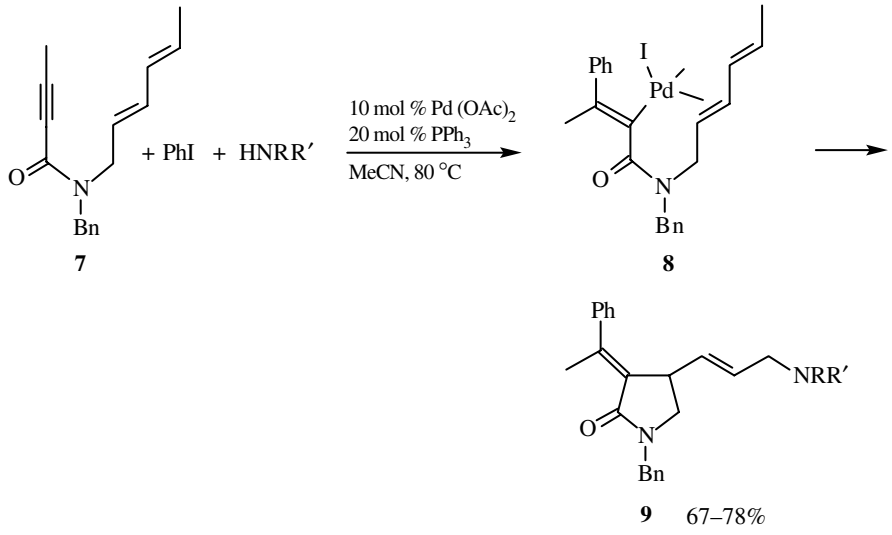
6a: 61% (70% ee)
b: 54% (77% ee)



3

Scheme 2

An interesting Pd(0)-catalyzed tandem cyclization of alkyn-*N*-(2,4-dienyl)amides **7** was recently reported by Xie and Lu (**Scheme 3**).[25] An arylpalladium species, formed via oxidative addition of PhI to Pd(0), adds to the acetylene to give a vinylpalladium intermediate **8**. Insertion of the coordinated double bond of the diene into the palladium–vinyl bond to give a π-allyl complex followed by amine attack would account for the product **9**.



7 **8** **9** 67–78%

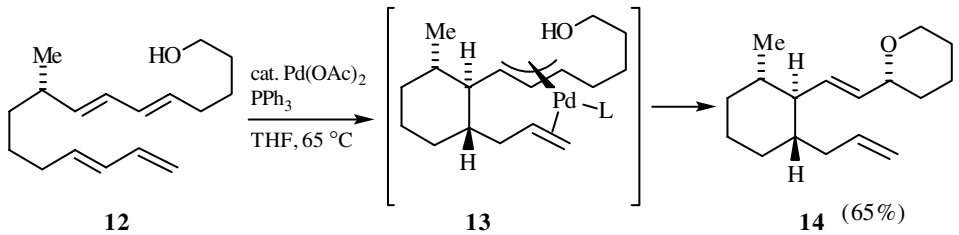
RR′NH: piperidine, morpholine, pyrrolidine
benzylamine, isobutylamine,
butylamine, aniline

Scheme 3

B.iii. 1,4-Addition of Carbon and Oxygen

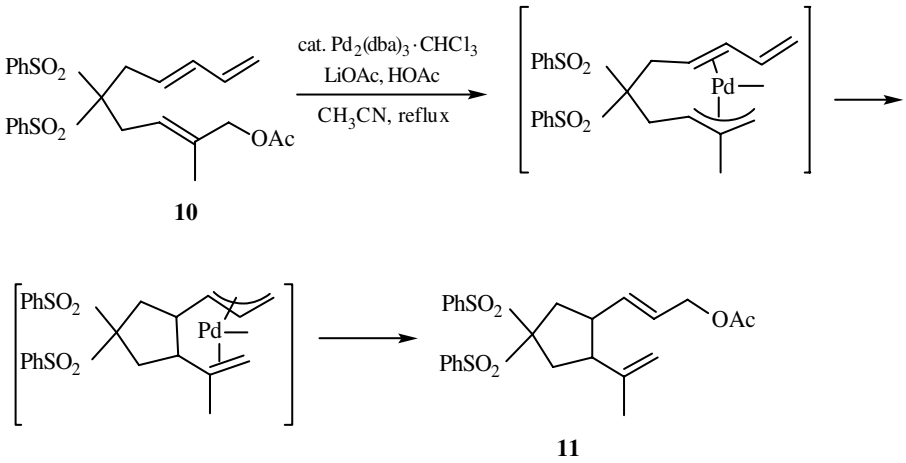
Pd-catalyzed isomerization of 1-acetoxy-2,7,9-decatrienes **10** to **11** formally involves a 1,4-addition of a carbon and an oxygen nucleophile to a conjugated diene moiety (**Scheme 4**).[11],[26]

Intramolecular Pd(0)-catalyzed reaction of 1,3,9,11-tetraenes in the presence of oxygen nucleophiles resulted in a carbon–carbon bond formation and attack by the oxygen nucleophile in the 1-position of the unsaturated system (Eq. 5).[27]–[29] By the use of substrate **12** it was shown that the 1,4-addition of the carbon and oxygen function to



12 **13** **14** (65%)

(5)

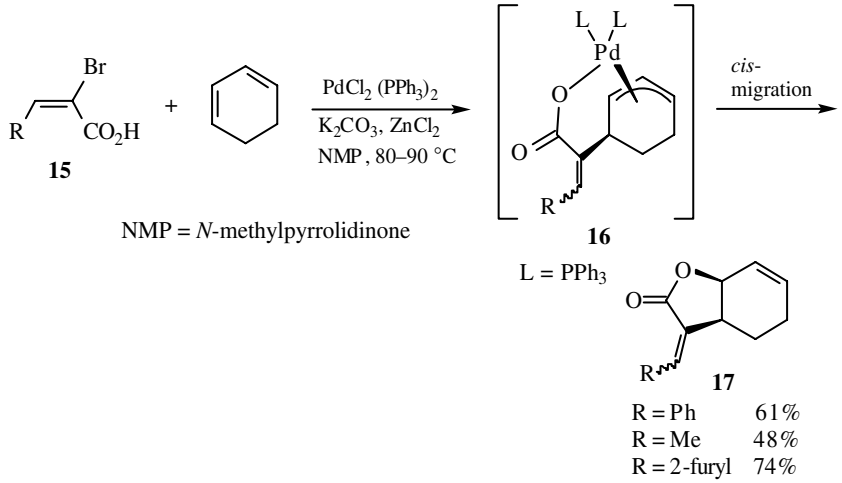


Scheme 4

the diene occurs *anti* to give **13**.[28],[29] This implies a *syn* carbopalladation followed by *trans* nucleophilic attack by the oxygen nucleophile in π-allyl complex **13**.

Pd(0)-catalyzed reaction of bromoacrylic acid **15** with various conjugated dienes afforded lactones in moderate to good yields.[30] Annulation to 1,3-cycohexadiene afforded lactones **17** (**Scheme 5**). After oxidative addition of **15** to Pd(0), a vinylpalladation should produce the intermediate π-allylpalladium complex **16**, which via *cis*-migration of coordinated carboxylate[31] would produce the *cis*-lactone **17**.

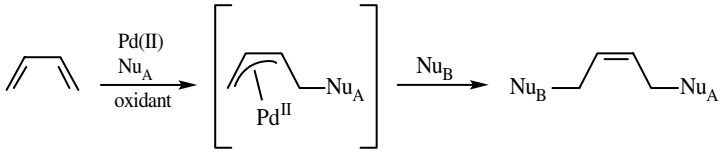
Larock[22] has studied the Pd-catalyzed arylation of 1,3-dienes followed by intramolecular attack by an oxygen nucleophile. *o*-Iodophenols and *o*-iodobenzyl alcohol were used as substrates. These annulation reactions lead to a 1,2-addition to the conjugated dienes with formation of interesting heterocyclic systems.



Scheme 5

C. REACTIONS VIA Pd(II) CATALYSIS

Reactions via Pd(II) catalysis involve a nucleophilic addition to the terminal position of the 1,3-diene to give a π-allylpalladium intermediate (**Scheme 6**). Subsequent nucleophilic attack on the π-allyl complex gives a 1,4-addition product. The reaction is carried out in the presence of an oxidant and in this way Pd(II) is regenerated in the second reaction step.

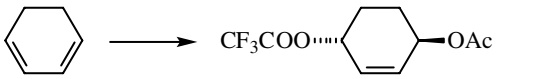


Scheme 6

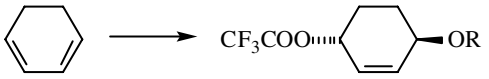
C.i. Intermolecular Additions

C.i.a. ***1,4-Addition of Two Oxygen Nucleophiles.*** Efficient procedures for 1,4-diacetoxylation, 1,4-chloroacetoxylation, and 1,4-dialkoxylation were reported in the 1980s. In the latter reactions nucleophiles were introduced in the 1- and 4-positions.[11],[32],[33] An important issue is to introduce two different nucleophiles in the 1- and 4-positions, respectively. Synthetically useful procedures for the 1,4-acetoxy-trifluoroacetoxylation and 1,4-alkoxy-trifluoroace-toxylation were recently reported (Eqs. 6 and 7).[34]

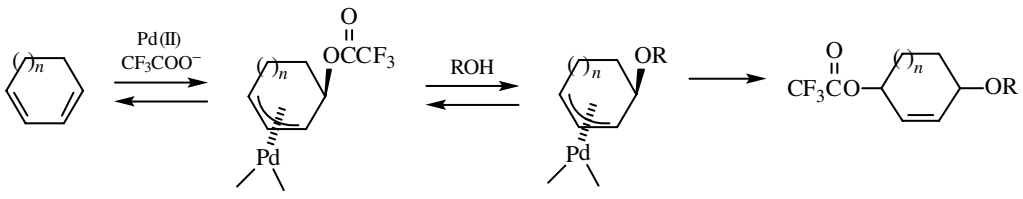
The success of these reactions is based on the fact that the trifluoroacetate is the strongest nucleophile present under the acidic conditions employed. The initially formed π-allyl complex is therefore a 4-trifluoroacetoxy π-allyl complex **18** (**Scheme 7**). However, complex **18** is kinetically unstable under the reaction conditions and therefore the trifluoroacetate



74% (>93% *trans*) (6)



R = Me; 61% (>92% *trans*)
R = Et; 67% (>93% *trans*)
R = Bn; 68% (>93% *trans*) (7)



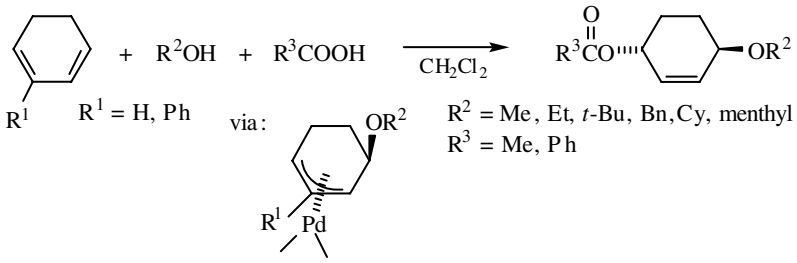
18 **19** R = Ac
R = alkyl

Scheme 7

group is exchanged by acetate or alkoxy to give π-allyl complex **19**. Subsequent nucleophilic attack by trifluoroacetate anion produces the unsymmetrical 1,4 adduct.

DFT calculations on palladium complexes **18** and **19** confirmed that the 4-trifluoroacetoxy group (**18**) is more reactive toward exchange than the 4-acetoxy and 4-alkoxy groups (**19**).[34]

By tuning the reaction system and using 2.5 mol % of H_2SO_4 together with 5 mol % of $Pd(OAc)_2$, 2.6 equiv of acid, and 4 eqiuv of alcohol, an unsymmetrical alkoxy–acyloxylation was obtained (**Scheme 8**).[35]

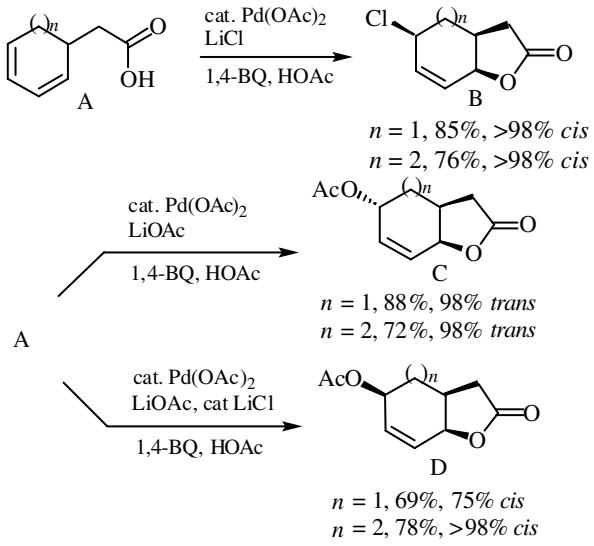


Scheme 8

C.ii. Intramolecular Additions

The 1,4-oxidation of conjugated dienes can easily be extended to the synthesis of heterocycles by the use of an intramolecular nucleophile. So far, both nitrogen and oxygen nucleophiles have successfully been employed.

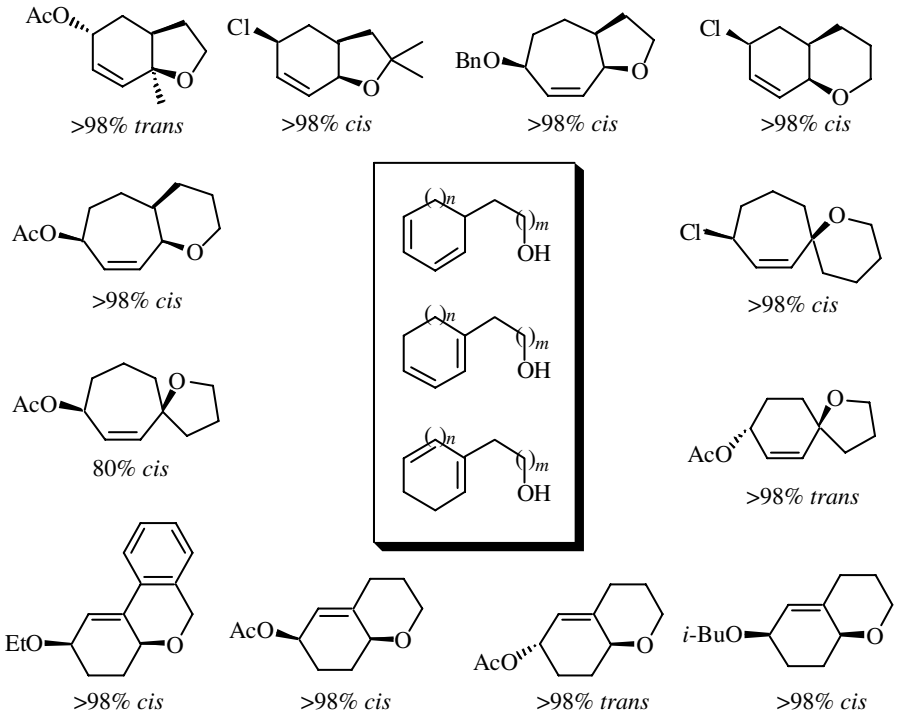
C.ii.a. ***Intramolecular Attack by Oxygen Nucleophiles.*** The first intramolecular reaction was done with a 1,3-cyclohexadiene having a carboxylate attached to the 5-position.[36] Just as with the intermolecular additions, it turned out that the amount of LiCl plays a crucial role, in terms of both the stereo- and chemoselectivities (**Scheme 9**). Without any



Scheme 9

added LiCl, a *trans*-acetoxylactonization took place, furnishing B in good yield. When a catalytic amount of LiCl was employed, the stereoselectivity was reversed and the *cis*-acetate C was formed instead. Finally, in the presence of a stoichiometric amount of LiCl a halolactonization takes place giving D.

The intramolecular reaction was readily extended to the use of alcohols in the side chain of the diene. By variations of the diene[37] as well as the length and position[38] of the tether, a great number of various tetrahydrofurans and tetrahydropyrans can be prepared in a highly stereoselective manner (**Scheme 10**).

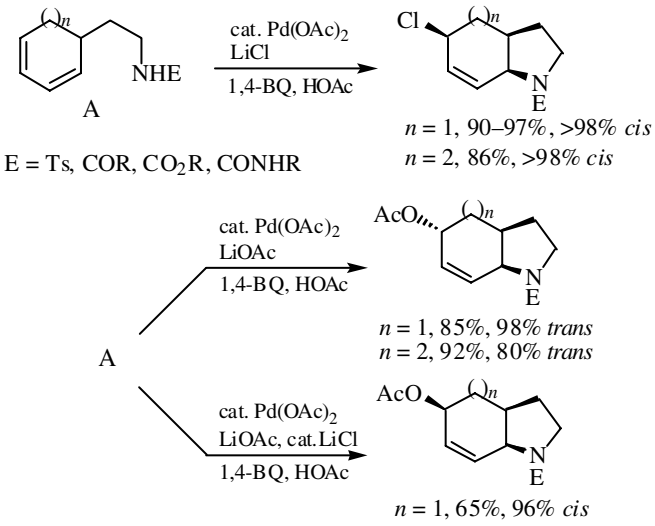


Scheme 10

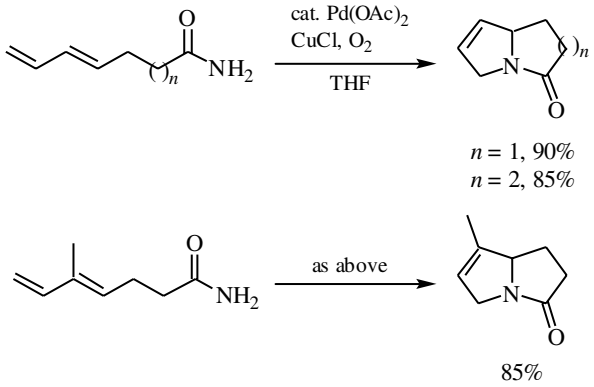
C.ii.b. ***Intramolecular Attack by Nitrogen Nucleophiles.*** The nitrogen nucleophiles, which are compatible with the reaction conditions (HOAc and 1,4-benzoquinone), consist of electron-deficient ones such as amides, carbamates, ureas, and sulfonamides. Because of the low nucleophilicity of these, no intermolecular 1,4-additions involving C—N bond formation is known. However, if the nitrogen is tethered to the diene, a cyclization takes place in good yields.

Depending on the reaction conditions, it is possible to obtain either *trans*- or *cis*-1,4-acetoxyamination by choice (**Scheme 11**). As with the other 1,4-additions, LiCl is used to obtain full stereocontrol. When the LiCl is added in a stoichiometric amount, a *cis*-1,4-chloroamination takes place.[39]

The intramolecular oxidation using nitrogen nucleophiles was developed further by using an amide with the ability to undergo a twofold attack on the diene (**Scheme 12**). This leads to a bicyclic system and constitutes a useful [4 + 1] intramolecular cycloaddition, which gives access to pyrrolizidine and indolizidine alkaloids.[40]



Scheme 11

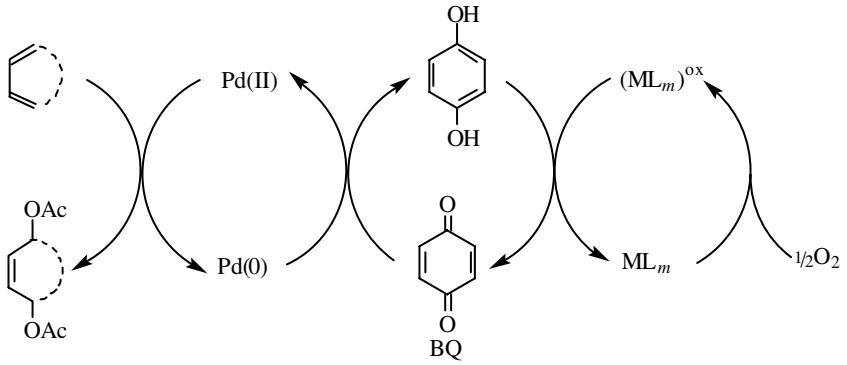


Scheme 12

C.iii. 1,4-Additions Using O_2 as Oxidant

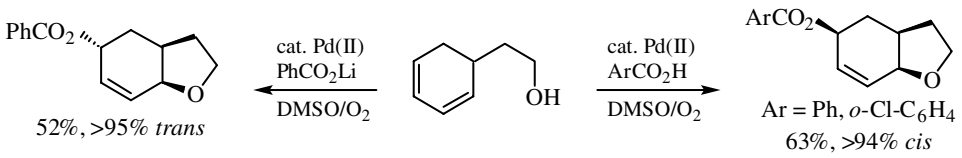
All 1,4-oxidations discussed so far have relied on the use of 1,4-benzoquinone or MnO_2 (in combination with 1,4-benzoquinone) as the stoichiometric oxidant. For obvious reasons molecular oxygen would constitute a much more attractive oxidant. Recent developments have made it possible to use molecular oxygen as the terminal reoxidant, either via activation by metal macrocycles[41] or heteropolyacids.[42] In both cases the oxidation of palladium is done by benzoquinone, which in turn is reoxidized by the metal macrocycle or heteropolyacid (**Scheme 13**).

An alternative approach consists of the use of a O_2–DMSO system for the direct reoxidation of palladium without any need of benzoquinone. These systems have been proposed to involve colloidal palladium(0)[43] and the role of DMSO would then be to dissolve such cluster-like particles. The coordination properties of DMSO are expected to keep the clusters in solution by coordination to individual palladium atoms.



Scheme 13

Since these systems do not tolerate any added LiCl (even small amounts of halide ions inhibit the reaction between palladium and O_2–DMSO), other ways to control the stereoselectivity of the reaction were examined. It was found that the stereochemical outcome of these reactions was strongly dependent on the nature of the nucleophile (**Scheme 14**). Thus, the use of a lithium salt of benzoic acid gave a 1,4-*trans* addition (>95% *trans*), whereas the use of benzoic acid itself resulted in the formation of the 1,4-*cis*-addition product (90% *cis*). The *cis*-selectivity could be further enhanced by the use of *o*-chlorobenzoic acid (94% *cis* addition).[44]



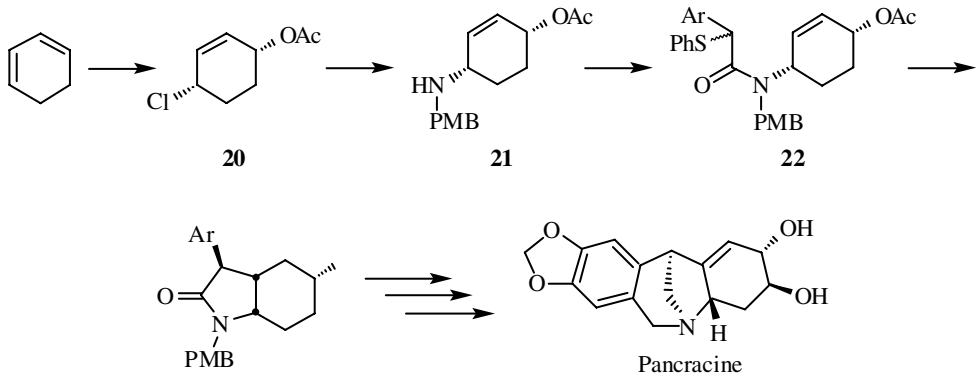
Scheme 14

C.iv. Applications of 1,4-Oxidations in Total Synthesis

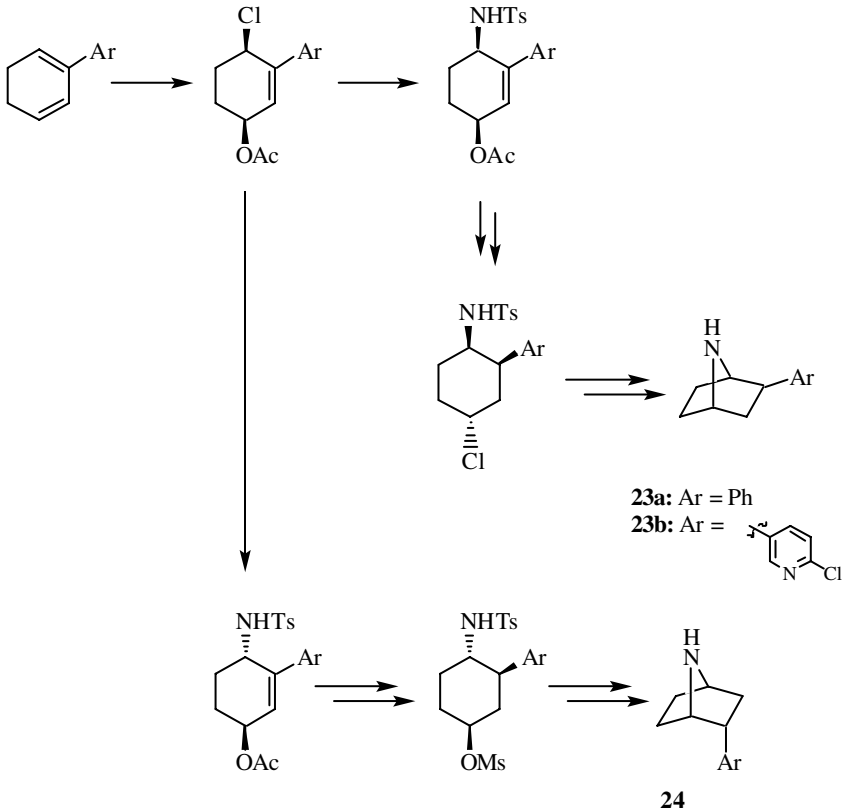
The high regio- and stereocontrol of the chloroacetoxylation reaction makes it useful in organic synthesis. This was shown in a recent formal total synthesis of (±)-Pancracine, where the first step consisted of a chloroacetoxylation of 1,3-cyclohexadiene (**Scheme 15**).[45] Pd(0)-catalyzed reaction of the chloroacetate **20** with *p*-methoxybenzylamine (PMB–NH_2) afforded **21**, which was subsequently transformed to (±)-Pancracine via a stereoselective radical cyclization of **22**.

The synthesis of (±)-Epibatidine **23b** and analogs thereof was realized by regioselective chloroacetoxylation of 2-aryl-1,3-cyclohexadiene.[46] Subsequent stereoselective substitution of the chloro group by tosylamide with either retention or inversion provided both stereoisomers of the aminoalcohol derivative. Highly stereoselective hydrogenation of the allylic amides gave the requisite stereoisomers for synthesis of the *exo*- and *endo*-isomers (**Scheme 16**).

An intramolecular lactonization was used as a key step in the enantiospecific synthesis of Paeonilactones A and B from *S*-(+)-Carvone (**Scheme 17**).[47] The product from the lactonization was hydrolyzed and the corresponding alcohol treated with



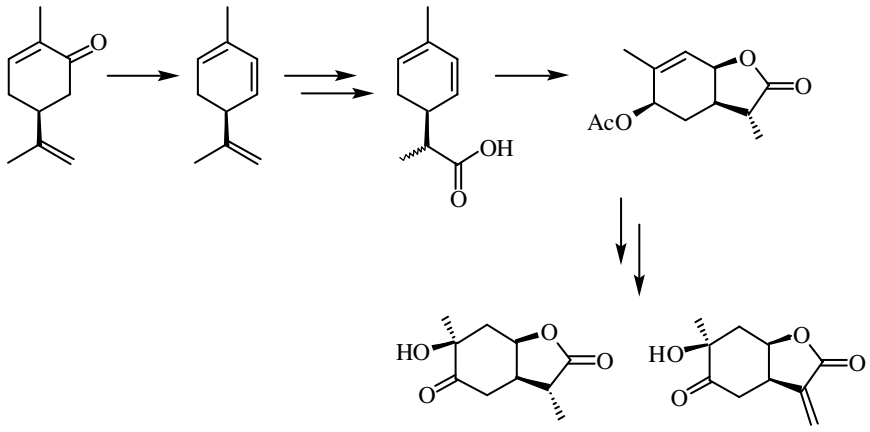
Scheme 15



Scheme 16

iodide and Cl_3CCHO to give a iodotrichloroacetal. Subsequent reduction of the iodide, opening of the acetal, and oxidation of the alcohol furnished Paeonilactone in good overall yield.

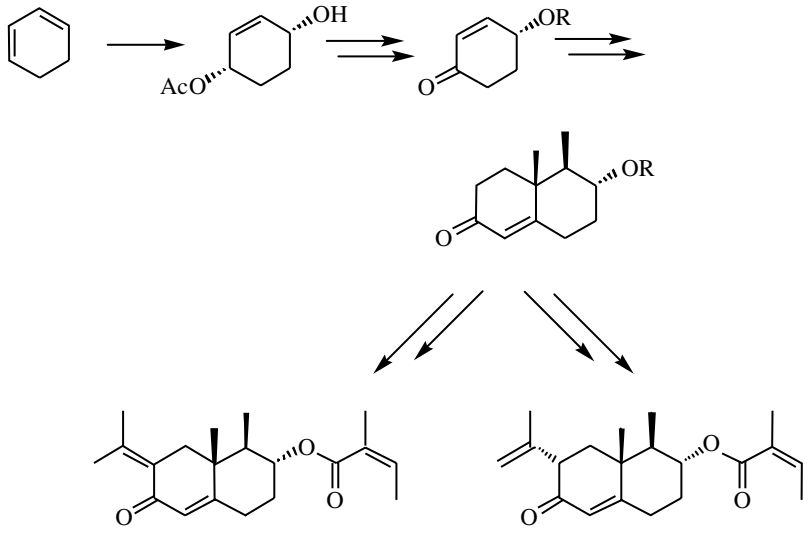
The *cis*-diacetoxylation reaction together with subsequent enzymatic resolution of the corresponding *meso*-diacetate constitutes a rapid and efficient route to enantiomerically



Paeonilactone A Paeonilactone B

Scheme 17

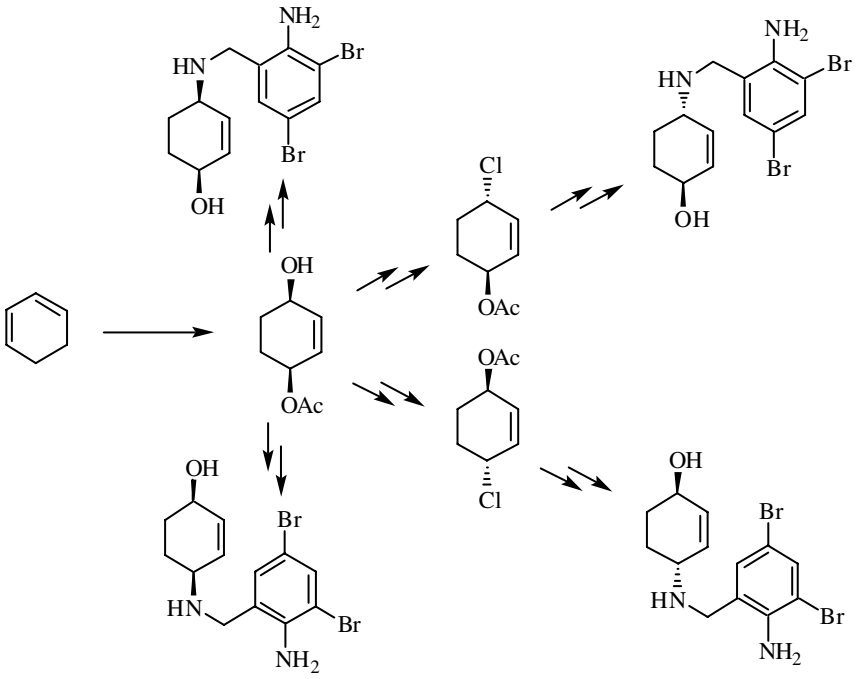
pure monoacetylated diols. These compounds have proved to be very useful intermediates in a number of syntheses. Starting from 1,3-cyclohexadiene the optically pure alcohol was obtained in 49% overall yield. This compound was then transformed into (+)-Petasin and (+)-Isopetasin in a multistep synthesis (**Scheme 18**).[48]



(+)-Isopetasin (+)-Petasin

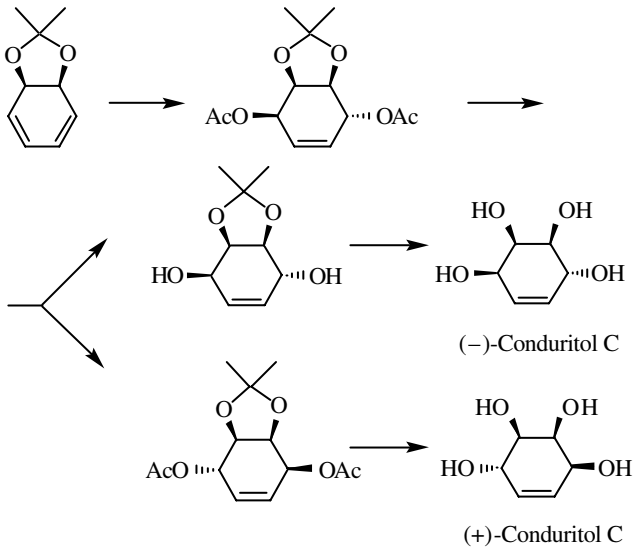
Scheme 18

The same intermediate was used in the preparation of Ambroxole and chiral analogs thereof (**Scheme 19**).[49] Manipulation of the relative reactivity of the two allylic oxygen moieties toward Pd(0)-catalyzed allylic amination allowed for the stereo- and regioselective synthesis of all four possible stereoisomers of 4-aminocyclo-2-hexenol.



Scheme 19

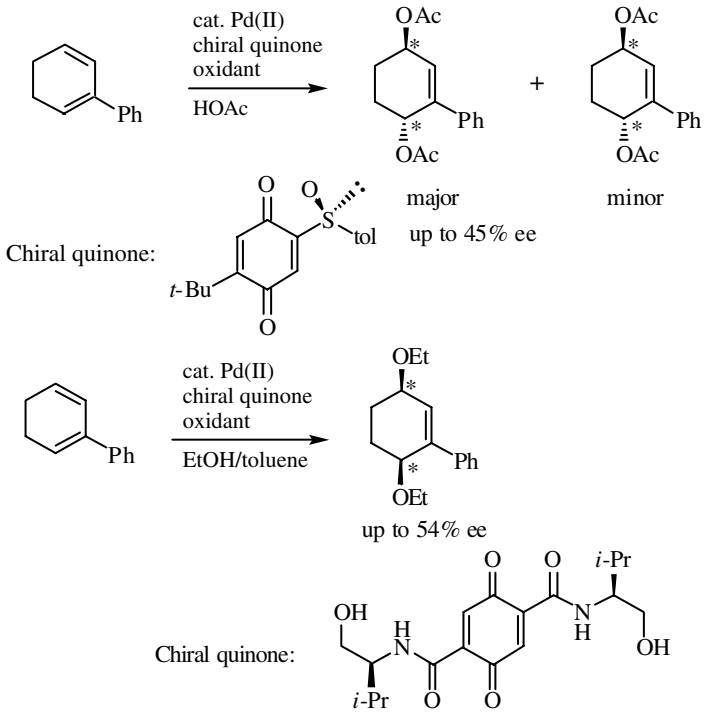
Finally, using a similar strategy, the protected functionalized cyclohexadienediol was used as starting material in the synthesis of (±)-, (+)-, and (−)-Conduritol C (**Scheme 20**).[50] Enzymatic hydrolysis of the diacetate produced enantiomerically pure (−)-diol and (+)-diacetate. Subsequent hydrolysis of the diol and diacetate afforded (+)- and (−)-Conduritol C, respectively.



Scheme 20

C.v. Enantioselective 1,4-Oxidations

The Pd(II)-catalyzed 1,4-oxidation of conjugated dienes is a useful reaction for the preparation of highly functionalized compounds. A wide range of nucleophiles are tolerated, the reaction is highly regio- and stereoselective, both inter- and intramolecular versions are possible, and it has been utilized in natural product synthesis. For these reasons, an enantioselective version of this reaction would be highly desirable. Contrary to the numerous reports on successful asymmetric Pd(0)-catalyzed reactions, there are only a few examples on asymmetric Pd(II)-catalyzed reactions. A likely explanation for this is that the electrophilicity of the Pd(II) is substantially decreased on coordination of a chiral ligand. So far, the two most successful examples of a catalytic asymmetric 1,4-oxidation has relied on the use of a chiral benzoquinone (**Scheme 21**). In these cases enantioselectivities up to 45% and 54% have been obtained for the diacetoxylation[51] and dialkoxylation,[52] respectively.



Scheme 21

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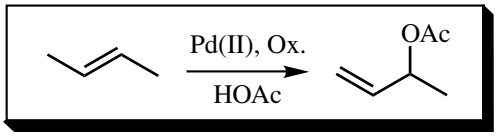

V.2.2.3 Use of Alkenes as Precursors to π-Allylpalladium Derivatives in Allylic Substitution with O, N, and Other Heteroatom Nucleophiles

BJÖRN ÅKERMARK and KRISTER ZETTERBERG

A. INTRODUCTION

The direct, Pd(II)-catalyzed addition of heteroatom and stabilized carbon nucleophiles to alkenes is generally not a successful reaction. An exception is the addition of water, which gives carbonyl compounds and has been developed into an important industrial process, the Wacker process.[1] This has been reviewed extensively.[2]–[5] By contrast, the stoichiometric addition of nucleophiles such as amines is facile.[6],[7] However, if alkenes could be converted catalytically into π-allylpalladium complexes, the problems with nucleophilic addition to alkenes could be circumvented and amines and other heteroatom nucleophiles could be employed. A range of alkenes have been converted into π-allyl complexes in a stoichiometric fashion,[8]–[13] but catalytic reactions have proved more difficult. However, allyl acetates and similar compounds readily exchange the acetate group for heteroatom nucleophiles in a Pd(0)-catalyzed reaction, which proceeds via π-allylpalladium(II) intermediates (**Scheme 1**). Since this reaction has been developed into a very important synthetic reaction,[14],[15] an efficient procedure for catalytic conversion of alkenes into allyl acetates would have great synthetic potential.

B. EARLY STUDIES

The stoichiometric addition of palladium acetate to alkenes has been studied extensively. (For a review, see Ref. [4].) For instance, 1-butene was found to give the vinyl acetate as the major product, accompanied by small amounts of the allyl acetates[16],[17] (**Scheme 2**).

However, under similar conditions, 2-butene gave 1-acetoxy-2-butene as the nearly exclusive product.[16],[17] Cyclohexene gave two major products, one allylic and one homoallylic[18] (**Scheme 3**). As a whole, the selectivity is thus fairly poor. (For an extensive discussion of early results, see Ref. [19].)

Also, catalytic systems were studied by early workers. With palladium chloride or palladium acetate as catalyst, and copper(II) chloride as oxidant, complicated reaction

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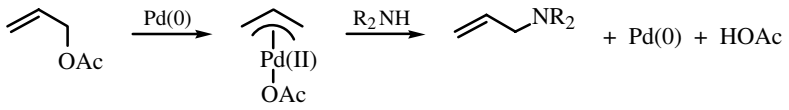
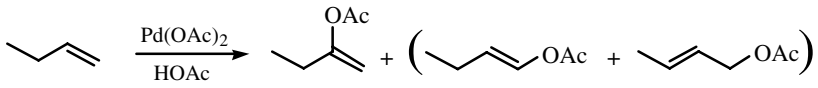
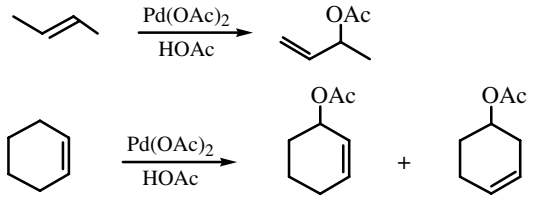


Scheme 1



Scheme 2



Scheme 3

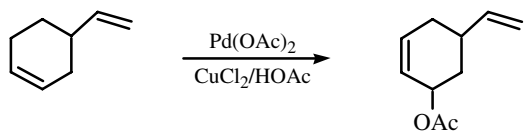
mixtures were obtained with linear alkenes as well as with cyclohexene.[20]–[23] With a mixed solvent (acetic acid–dimethylformamide) somewhat improved selectivity for the desired allyl acetate was observed.[24]

Other oxidants besides copper(II) chloride have also been studied, including nitric acid, benzoquinone, and molecular oxygen,[18],[22]–[26] but the selectivity was quite low.

C. CATALYTIC REACTIONS

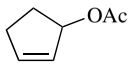
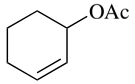
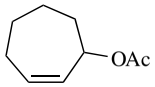
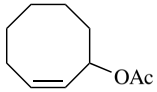
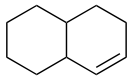
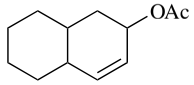
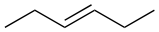
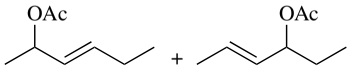
Although the early studies suggested that copper(II) chloride is unselective, the acetoxylation of 4-vinylcyclohexene (and related compounds) was later shown to give a high yield of 3-acetoxy-5-vinylcyclohexene as the exclusive product[27],[28] (**Scheme 4**). Also, the oxidation of limonene, using a variety of oxidants, including copper(II) chloride, copper(II) acetate, and benzoquinone, was capable of giving one allyl acetate in good selectivity in a reaction that was fairly strongly dependent on the reaction conditions. If a strong acid, *p*-toluene sufonic acid, was present also, methanol could be added in place of acetate.[28]

Some years ago, we found that the combination of manganese dioxide and a catalytic amount of benzoquinone (or hydroquinone) led to efficient conversion of cyclohexene into cyclohexenyl acetate if palladium acetate was used as catalyst.[29] With the exception of cyclooctene, other cycloalkenes also gave cycloalkenyl acetates in fair to good yields[30],[31] (**Table 1**).

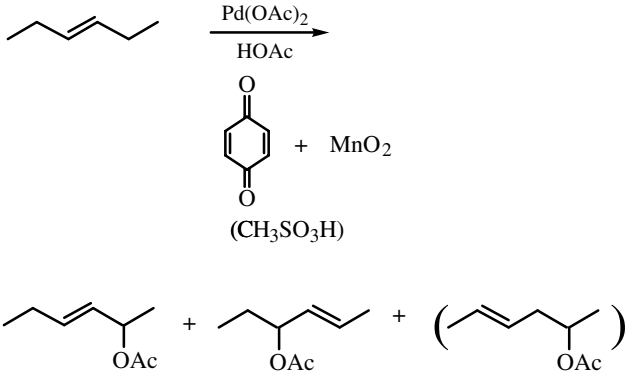


Scheme 4

TABLE 1. Acetoxylation of Cyclic and Internal Alkenes using Palladium Acetate as Catalyst

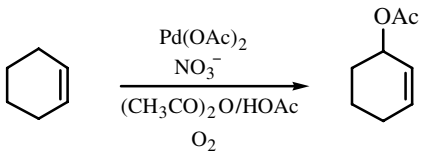
Substrate	Temperature, °C	Time (h)	Conversion (%)	Products	Isolated Yield (%)
	50	16	95		66
	60	50	95		77
	60	28	98		73
	60	90	60		35
	60	300	93		78
	60	72	—		>80

Also, open chain internal alkenes gave alkenyl acetates in good yields, but, for example, 3-hexene gave equal amounts of two isomeric allylic acetates (**Scheme 5**). An interesting observation was that addition of a strong acid, methane sulfonic acid, resulted in the formation of the homoallylic acetate as the exclusive product, although in moderate yield.[31]



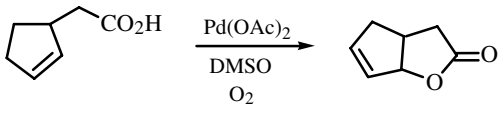
Scheme 5

A number of studies of other oxidants have also been performed. A reinvestigation of nitrate systems[32] showed that in the presence of acetic anhydride, a catalytic amount of nitrate and palladium acetate gave quite good yields of cyclohexenyl acetate, using oxygen as oxidant[33] (**Scheme 6**). Also, cyclohexenyl nitrite functioned as an intermediate catalyst for oxygen uptake.



Scheme 6

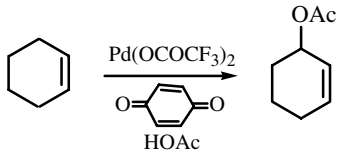
Using dimethyl sulfoxide as solvent, Larock and co-workers found that, with palladium acetate as catalyst, oxygen can be used without a cooxidant in internal carboxylation reactions[34] (**Scheme 7**).



Scheme 7

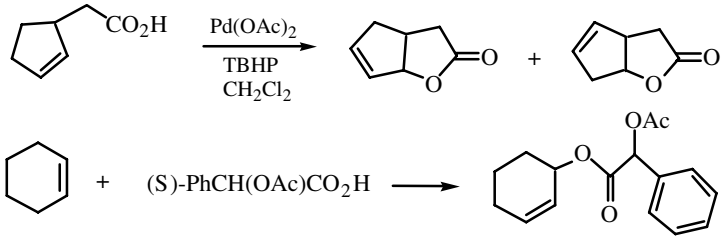
Quinones have been used as oxidants but the early studies indicated rather unselective reactions in allylic oxidation.[22],[23] This is in clear contrast to our results, which use

manganese dioxide as a cooxidant.[29]–[31] It is also in contrast to the results of McMurry and Kocovsky, who used the more electrophilic palladium trifluoroacetate as catalyst and benzoquinone as oxidant[35] (**Scheme 8**).



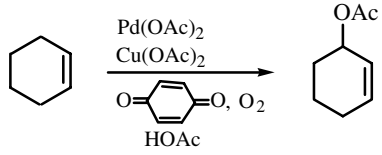
Scheme 8

With hydrogen peroxide or, better, *t*-butylhydroperoxide as the oxidant, the combination of palladium acetate and hydroquinone forms an efficient catalyst system, which does not require other cocatalysts. Using *t*-butylhydroperoxide as the oxidant, it is possible to react a series of different carboxylates with alkenes in methylene chloride solution. For instance, (*S*)-*O*-acetylmandelic acid was reacted with cyclohexene to give the addition product with a modest chiral induction (de ca. 20%). Also, intramolecular cyclization could be achieved; for example, 2-cyclopenten-1-acetic acid gave mainly the allylic lactone in good yield, accompanied by a small amount of the double bond isomer[36] (**Scheme 9**).



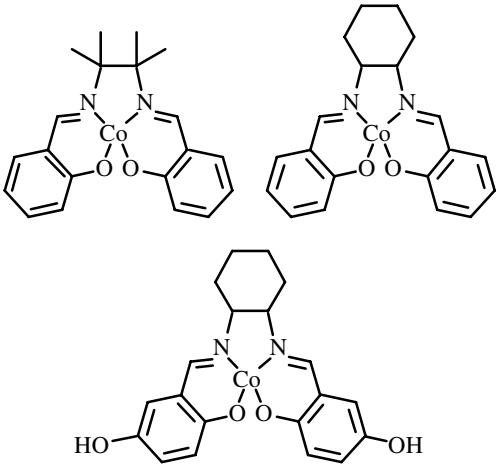
Scheme 9

Earlier studies have also shown that a catalyst system consisting of palladium(II) and copper salts plus oxygen for the reoxidation did not work well,[4],[24] in contrast to the result with the Wacker oxidation. However, if quinone or hydroquinone was added to a mixture of palladium acetate and copper acetate, oxygen could be used as an efficient oxidant for conversion of alkenes into allylic acetates. Thus, cyclohexene gave better than 85% cyclohexenyl acetate (**Scheme 10**). The combination of oxygen and cobalt or manganese acetate also works, but less well.[37]



Scheme 10

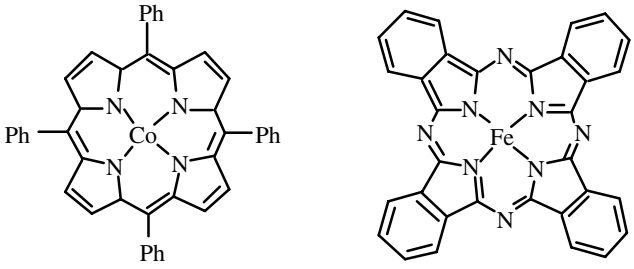
A more efficient system was obtained if copper acetate was replaced by salen-type cobalt complexes as catalysts, operating together with hydroquinone or quinone. Finally, incorporation of a hydroquinone as part of the salen ligand gave an even more efficient catalyst that did not require cocatalysis by quinone[37] (**Scheme 11**).



Scheme 11

In related work, Bäckvall and co-workers have used salophen, phthalocyanine, and porphyrin complexes in combination with hydroquinone and oxygen to effect allylic acetoxylation of cyclohexene and related compounds[38] (**Scheme 12**). Phthalocyanine, in particular, proved to be a very active catalyst.

Very efficient systems for Pd-catalyzed allylic acetoxylation have thus been developed. They work well with cycloalkenes and internal alkenes but are less efficient with terminal alkenes. The result probably reflects the operation of different mechanisms for terminal alkenes and the other classes of alkenes.

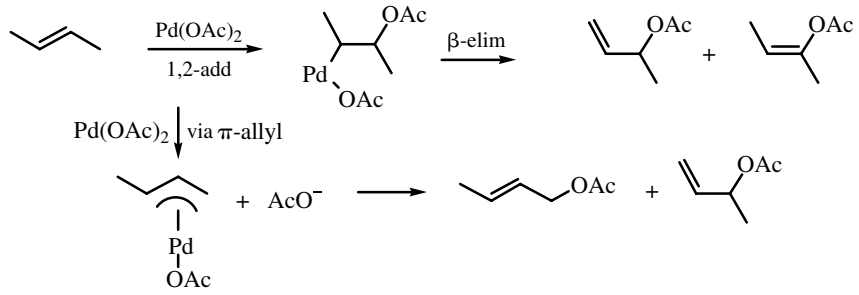


Scheme 12

D. MECHANISM

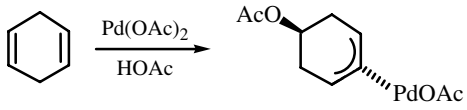
The fact that 1-butene gave the vinylic acetate as the major product is a strong indication of a 1,2-addition process. In contrast, the formation of 3-acetoxy-1-butene from 2-butene

is compatible with both a 1,2-addition process and a reaction via a π-allyl species[16] (**Schemes 2**, **3**, and **13**). However, the 1,2-addition should give some vinylic acetate, which is not observed. On the other hand, the π-allyl route should give some 1-acetoxy-3-butene, which is also not observed, in addition to 3-acetoxy-1-butene (**Scheme 13**).



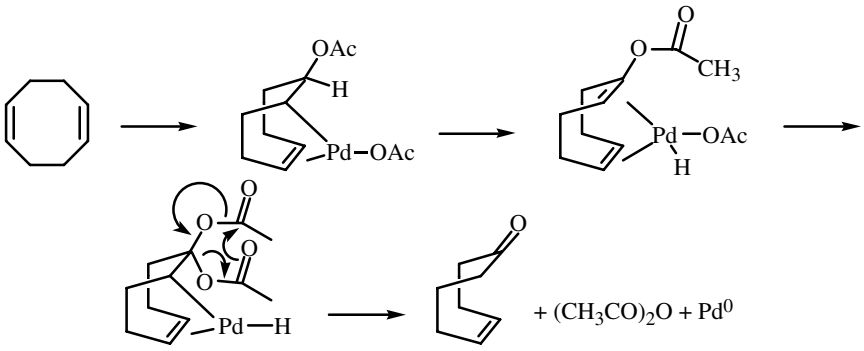
Scheme 13

The interpretation of the early results is not obvious and in his review of 1980 (Ref. [4], pp. 84–103), Henry favored the 1,2-addition mechanism for all substrates. With the formation of the *trans*-acetoxy π-allyl complex from acetoxylation of 1,4-cyclohexadiene, clear evidence for the 1,2-addition process was later obtained[39] (**Scheme 14**).



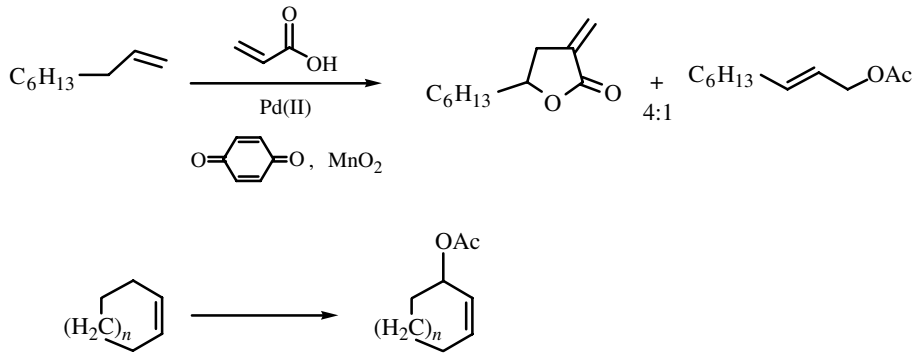
Scheme 14

Also, the conversion of 1,5-cyclooctadiene to cyclooct-4-en-1-one and acetic anhydride[40] is best explained by a 1, 2-addition process, which is followed by a second addition, reductive elimination, and conversion of the 1,1-diacetoxy group into acetic anhydride and ketone (**Scheme 15**).

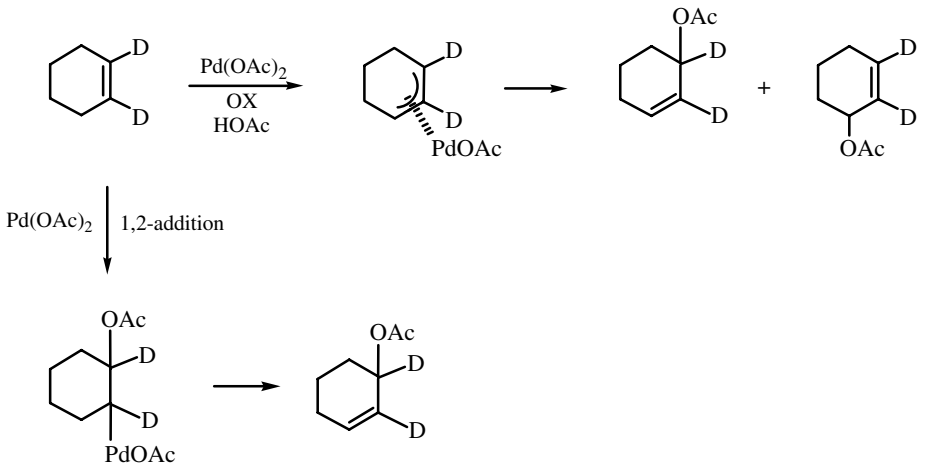


Scheme 15

Even better evidence for a 1,2-addition was provided by Waegell and co-workers, who studied acryloxylation of alkenes. It was found that the reaction of 1-octene with acrylate in acrylic acid as solvent gave a 4:1 mixture of the γ-lactone and the internal allylic acrylate (**Scheme 16**). None of the terminal allyl acrylates was formed. This shows conclusively that terminal alkenes react mainly via a 1,2-addition process.[41],[42]



Scheme 16



Scheme 17

The fact that cyclic and internal alkenes relatively readily give π-allyl complexes is an indication that these might react preferentially via π-allyl intermediates. Although there is some early conflicting evidence,[43] this is indicated by product patterns obtained in acetoxylation using the benzoquinone–manganese dioxide system.[30] Also, the products from acryloxylation of cyclic alkenes support a route via π-allyl complexes[42] (**Scheme 16**). The early results of Wolfe and co-workers using labeled cyclohexene, a palladium(II) catalyst, and nitric acid as oxidant[25],[26] are best explained in terms of π-allyl intermediates.

The latter reaction conditions may not be representative but a recent study, using several different oxidation systems, including benzoquinone–manganese dioxide and benzoquinone–iron phthalocyanine–oxygen as catalytic systems, suggests that cyclohexene reacts exclusively via the π-allyl route. This was shown by using 1,2-dideuteriocyclohexene as substrate and analyzing the position of deuterium in the product allyl acetate,[44] compatible with a π-allyl route.[45] A 1:1 mixture of the two shown isomeric acetates in **Scheme 17** was obtained. In parallel, it was shown that the cyclohexenylacetates did not isomerize under the reaction conditions. This result is only compatible with the π-allyl route, since 1,2-addition, followed by β-elimination, would give only one allylic compound.[44]

E. CONCLUSION

While it is evident that allylic acetoxylation and related reactions proceed via two different mechanisms, mainly depending on the structure of the alkenes, it is less clear how to choose reaction conditions in order to favor one route or the other. There is some evidence from early studies that the use of polar solvents such as DMF will promote allyl acetate formation.[24] It also appears that excess acetate promotes the formation of products compatible with the π-allyl route. This is also suggested by recent factorial experiments with variation of carboxylate concentration.[46] Since trimeric palladium acetate will induce π-allyl formation from a series of monoolefins, it might be assumed that high concentration of palladium acetate could be used for creating conditions that favor a π-allyl route.[47],[48] Another possibility is adding strong acids, which can increase the electrophilicity of the catalyst, but this can drive the reaction toward homoallylic acetates and other isomerized products.[31]

At present, the allylic acetoxylation reaction, especially in combination with catalytic allylic substitution, is useful for functionalizing cyclic and internal alkenes. There is ample room for improvement of the selectivity of the reaction of terminal alkenes but with an increased knowledge of the structure of the intermediate complexes and with an improved understanding of the influence of reaction conditions, this reaction should also have considerable synthetic potential.

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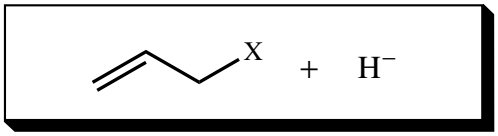

V.2.3 Palladium-Catalyzed Allylic, Propargylic, and Allenic Substitution with Hydrogen and Metal Nucleophiles

V.2.3.1 Palladium-Catalyzed Hydrogenolysis of Allyl and Related Derivatives

KATSUHIKO INOMATA and HIDEKI KINOSHITA

A. INTRODUCTION

Pd-catalyzed hydrogenolysis of allylic compounds with various hydride sources is important not only for the preparation of alkenes, but also for a deprotection of allyl-derived protecting group. The latter will be discussed in **Sect. V.2.3.2**.

It is well known that allylic compounds undergo facile Pd-catalyzed transformation via formation of π-allylpalladium complex as an intermediate, followed by attack of various nucleophiles (**Scheme 1**). Hydride attack on the π-allylpalladium intermediate affords the corresponding alkenes as hydrogenolysis products.[1],[2]

In 1973, Hey and Arpe first reported Pd-catalyzed hydrogenolysis of allylic esters, phenyl ether, and amine using formic acid as a hydride source. In their attempt to prepare allylic formates from various allylic acetates by Pd-catalyzed transesterification, they obtained a mixture of alkenes instead of the expected allylic formates[3] (**Scheme 2**).

Tsuji and co-workers found that Pd-catalyzed hydrogenolysis of allylic compounds with formates such as ammonium or triethylammonium formate affords terminal olefins with high regioselectivity.[4]–[6] It is proposed that decarboxylation and hydride transfer is a concerted process in which the hydride attacks regioselectively the more substituted (or the more electropositive) side of the allylic system in a cyclic mechanism (S_Ni transfer of hydride) shown in **Scheme 3** to give the terminal olefins. Formation of a palladium hydride from the intermediary allylpalladium formate does not take place.[7],[8] The proposed π-allylpalladium formate intermediate was confirmed by NMR spectroscopy.[9] Based on this mechanism, it is expected that Pd-catalyzed hydrogenolysis proceeds with overall inversion of configuration, because π-allylpalladium complex formation involves inversion of configuration.[10]

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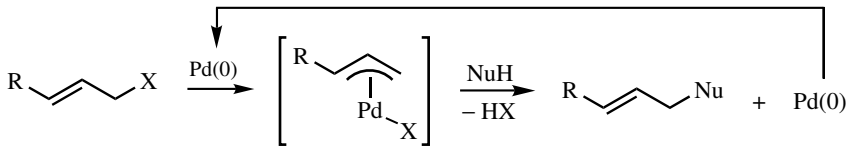
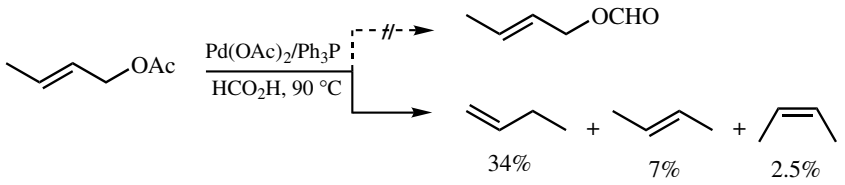
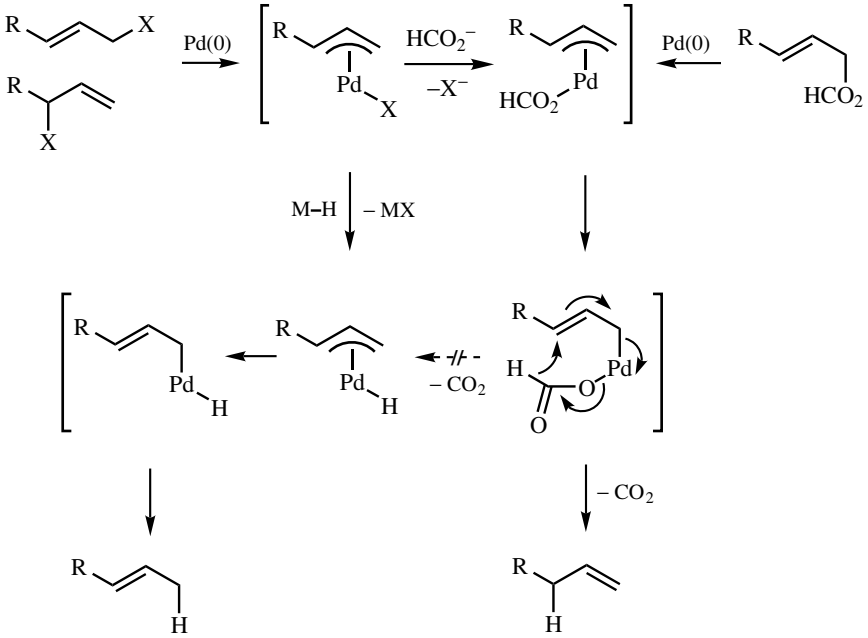


Scheme 1

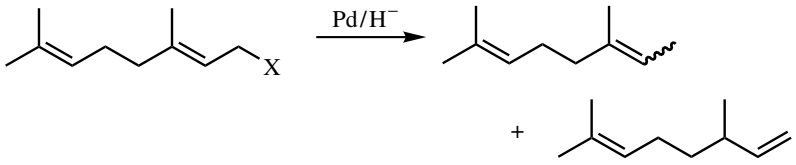


Scheme 2



Scheme 3

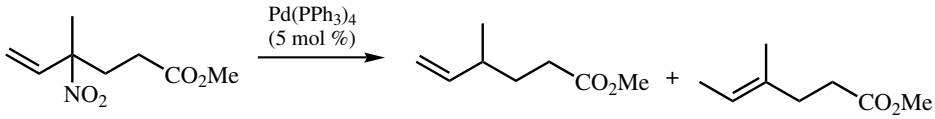
In contrast to formates, other hydride sources such as $LiAlH_4$,[7],[11] borohydride,[7],[12]–[16] hydrosilanes (PMHS: polymethylhydrosiloxane),[7],[17],[18] Bu_3SnH,[19] *n*-butylzinc chloride,[20] *N*-propyl-1,4-dihydronicotinamide,[21] SmI_2/*i*-propanol,[22] and electrolysis[23] generate the palladium hydride. Formation of a π-allylpalladium hydride (**Scheme 3**) results in attack at less substituted allylic carbon by reductive elimination to produce the more substituted olefins as major products in most cases[1],[2] (**Scheme 4**). In addition to allylic acetates, other allylic compounds such as allylic carbonates, ethers, sulfides, sulfones, selenides, halides, and nitro compounds can be used as substrates for



X	Catalysts	Hydrides	Product Ratio	Reference
OAc	$Cl_2Pd(PPh_3)_2$	HCO_2NH_4	6:94	[4]
OCO_2Me	$Pd_2(dba)_3/Bu_3P$	HCO_2H/Et_3N	0:100	[5]
OPh	$Pd(PPh_3)_4$	$LiHBEt_3$	98:2	[7]
OAc	$Pd(PPh_3)_4$	PMHS	52:48	[17]
OAc	$Pd(PPh_3)_4$	BuZnCl	97:3	[20]
OAc	$Pd(PPh_3)_4$	SmI_2/i-PrOH	93:7	[22]

Scheme 4

Pd-catalyzed hydrogenolysis. An additional example to show the difference of the regioselectivity depending on the hydride sources is depicted for allylic nitro compound[24] (**Scheme 5**).



HCO_2NH_4/PPh_3 (10 mol %), THF, 60 °C, 20 h; 56%	90:10
$NaBH_4$ (1.2 equiv)/dppe (10 mol %), THF/*i*-PrOH, 20 °C, 2 h; 70%	4:96

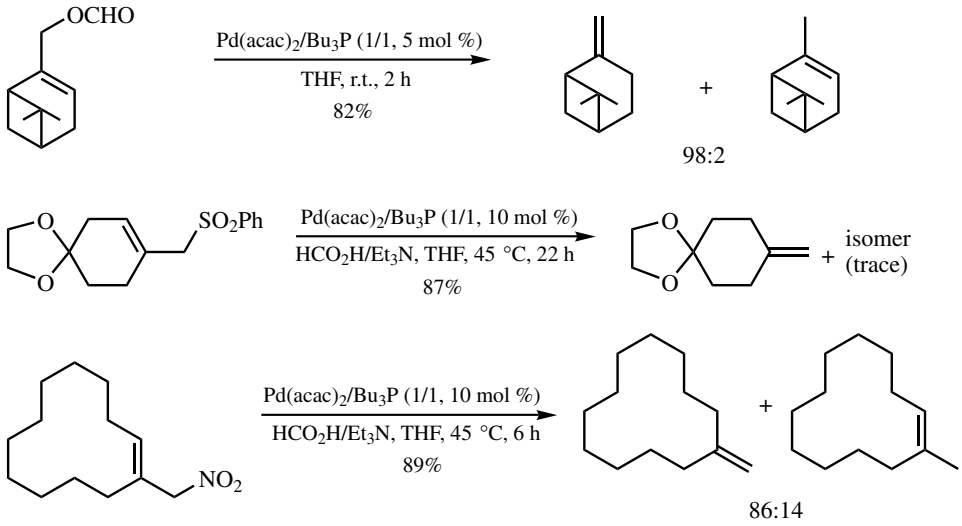
Scheme 5

B. PALLADIUM-CATALYZED HYDROGENOLYSIS WITH FORMATES

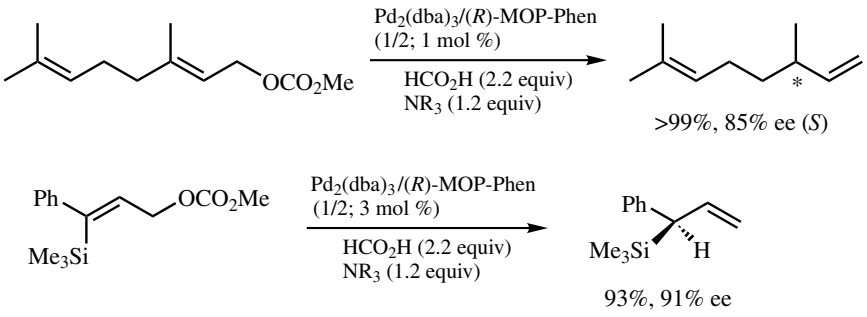
Pd-catalyzed hydrogenolysis of allylic compounds with formates is an efficient and mild method. The most important feature of the hydrogenolysis is that the hydride generated from the palladium formate attacks the more substituted side of the allylic system to give less substituted olefins. Various terminal allylic compounds are converted to 1-alkenes.[5],[6]

Regioselective hydrogenolysis with formates is used for the preparation of exomethylene compounds from cyclic allylic compounds by the formal *anti* thermodynamic isomerization of internal double bonds to the exocyclic position[25] (**Scheme 6**).

Asymmetric hydrogenolysis of allylic carbonates was realized by the use of chiral ligand, (*R*)-MOP-Phen, with 1,8-bis(dimethylamino)naphthalene (NR_3) as a base to afford the optically active terminal olefins[26]–[29] (**Scheme 7**).



Scheme 6



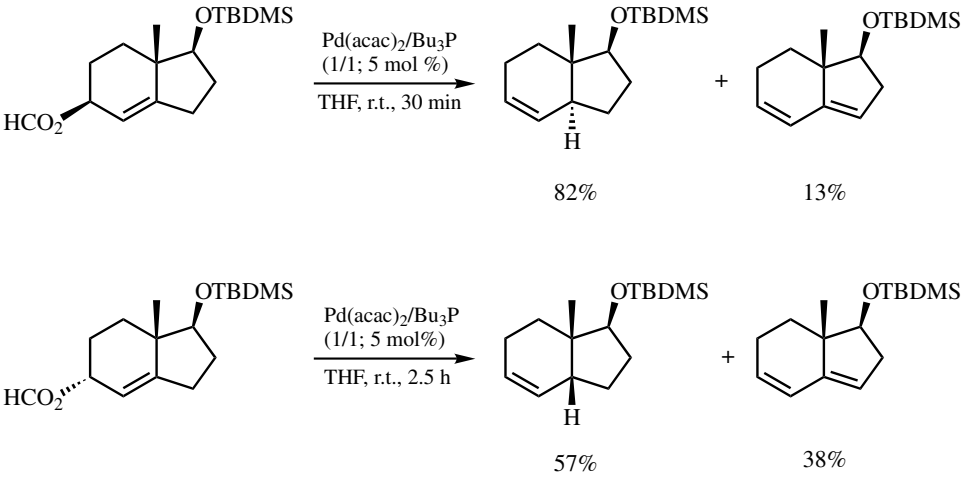
Scheme 7

In addition to regioselectivity, high stereospecificity was observed in the hydrogenolysis of cyclic allylic systems and has been applied successfully to the regioselective and stereospecific generation of *cis* and *trans* ring junctions in decalin and hydrindan systems from the corresponding allylic formates (**Scheme 8**). Formation of the regioisomer was not observed. The reaction is applicable to the preparation of *cis* and *trans* junctions in AB rings of steroids.[30]–[32]

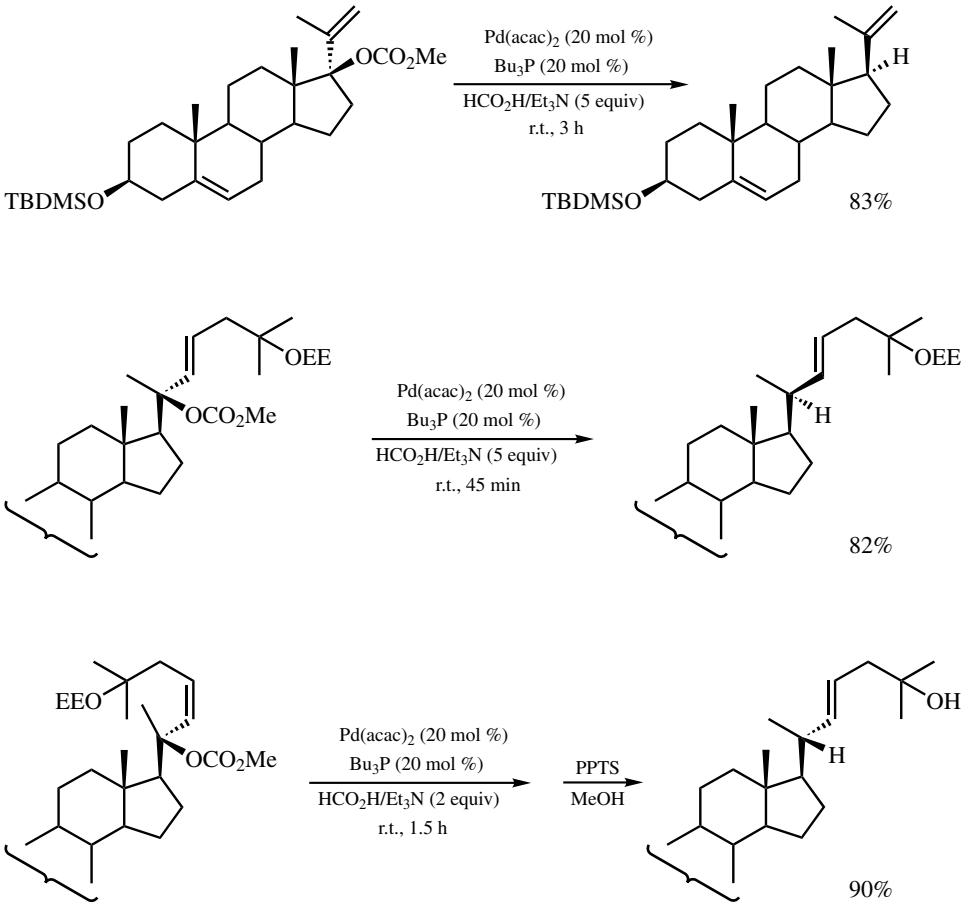
Stereospecific generation of natural C-17 stereochemistry and the natural and unnatural C-20 epimers of steroids was achieved by Pd-catalyzed hydrogenolysis of C-17 and (*E*)- and (*Z*)-C-20 β-allylic carbonates, which are readily available from the keto steroids.[8],[33] (**Scheme 9**).

Formation of the C-20 epimer from the *Z* isomer is considered to proceed through the transformation of the initially formed unstable *anti* form of π-allylpalladium formate to the stable *syn* form by rotation of σ-allylpalladium prior to the hydride transfer as shown in **Scheme 10**.[8]

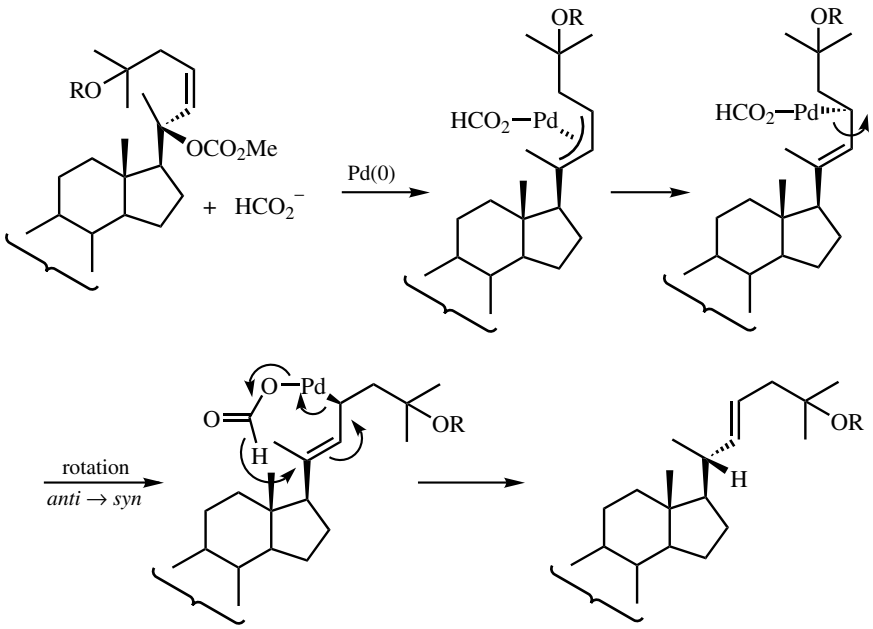
A synthesis of novel allyl 1,1-hetero- and homobimetallic compounds (M = Sn or Si) was explored by Pd-catalyzed hydrogenolysis employing ammonium formate.



Scheme 8



Scheme 9



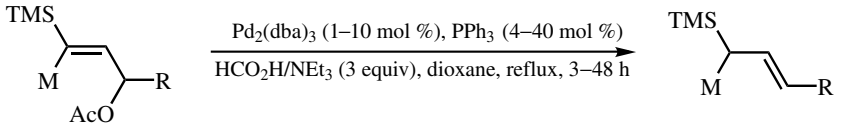
Scheme 10

The regioselectivity in the reductions is routinely >99:1 in favor of the allyl 1,1-bimetallic rather than the vinyl 1,1-bimetallic regioisomer[34] (**Scheme 11**).

Pd-catalyzed hydrogenolysis of vinyloxiranes affords the homoallylic alcohols regioselectively, rather than allylic alcohols, and has been applied to the synthesis of several natural products[35]–[41] (**Scheme 12**).

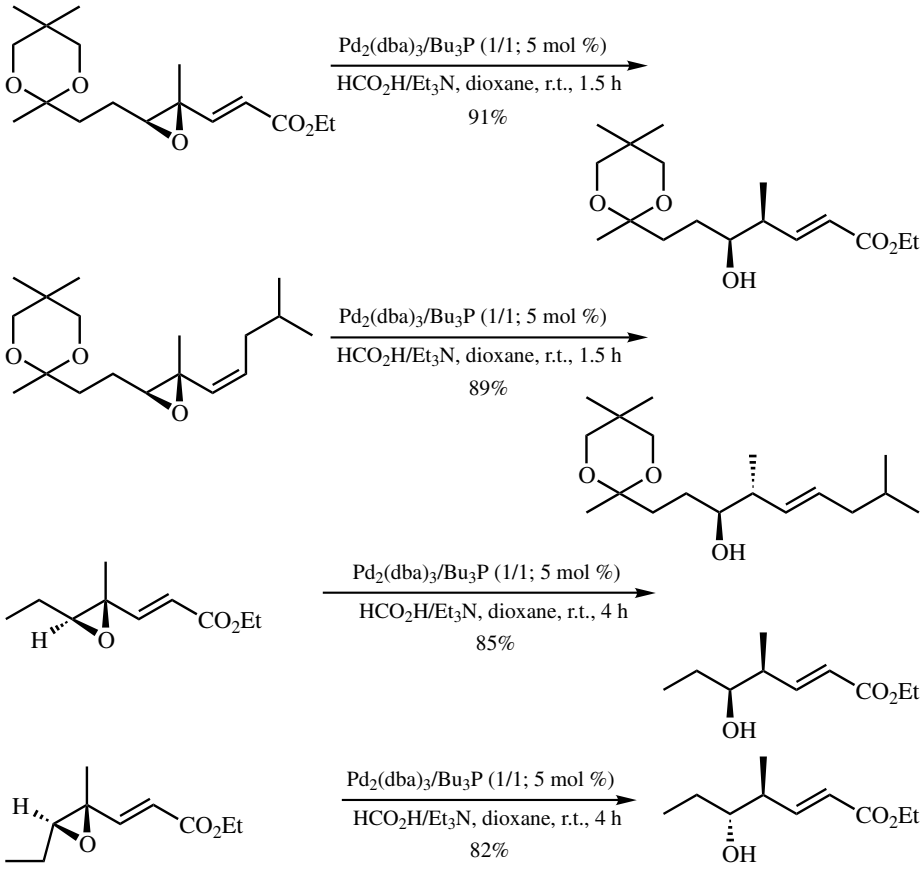
Hydrogenolysis of various N-substituted aziridines bearing α,β-unsaturated ester groups with formate and the stereochemistry of the reaction products have been investigated in detail.[42],[43] In all cases of *N*-arenesulfonylaziridines examined, (*Z*)-α,β-enoates, (*E*)-α,β-enoates, and (*E*)-β,γ-enoates bearing amino functionality at the δ-position were obtained. The formation of these three reduction products was taken as an indication that Pd-catalyzed isomerization occurs prior to the reduction step (**Scheme 13**).

Regio- and stereoselective Pd-catalyzed reductive cleavage of alkenylcyclopropane is possible with formate in the case where a stabilized carbanion is formed by ring cleavage and has been applied to the syntheses of clavukerin A and isoclavukerin A[44],[45] (**Scheme 14**).

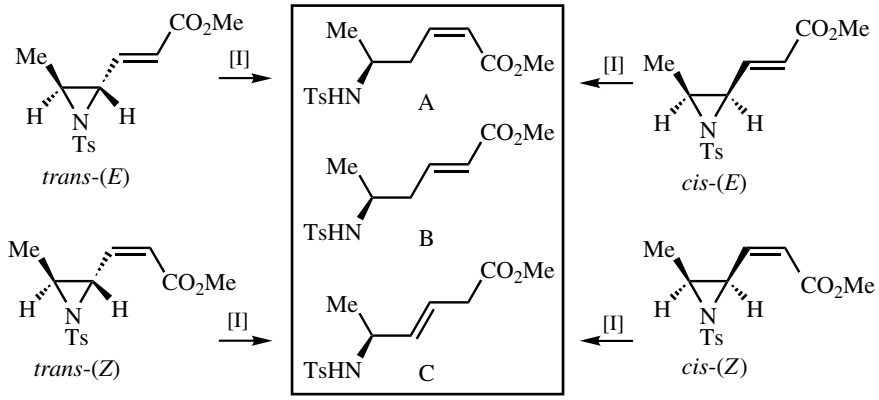


M	R	Yield (%)	M	R	Yield (%)
Bu_3Sn	H	99	TBDMS	H	90
Bu_3Sn	*n*-Pr	99	TBDMS	*n*-Pr	89
Bu_3Sn	*cyclo*-Hex	98	TBDMS	*cyclo*-Hex	40

Scheme 11



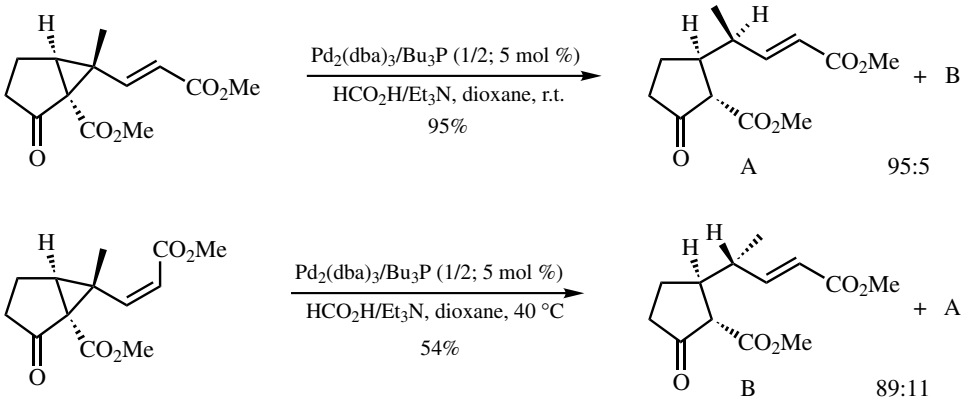
Scheme 12



A/B/C = 4–6:78–81:10–13

[I] = $[ClPd(\eta^3\text{-allyl})]_2$ (5 mol %), maleic anhydride (20 mol %), HCO_2H (5 equiv), Et_3N (2 equiv), DMSO

Scheme 13

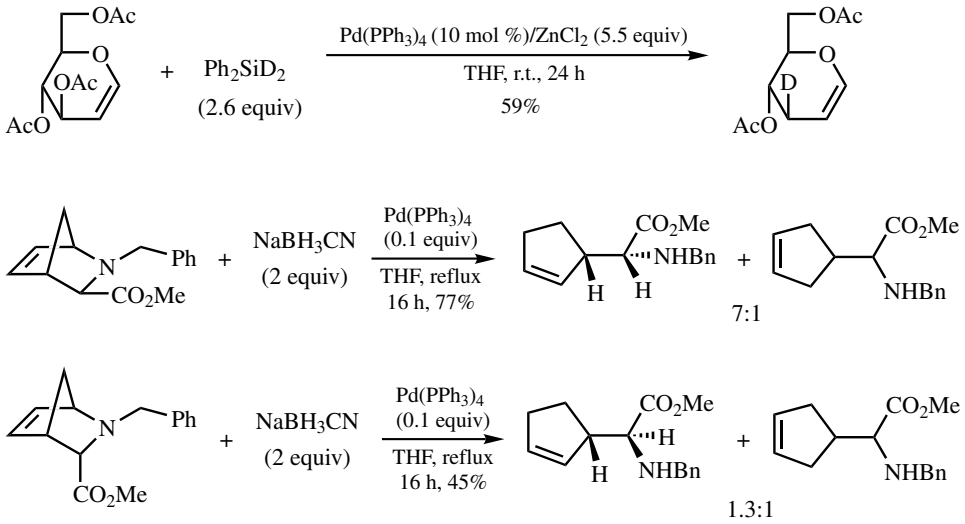


Scheme 14

C. PALLADIUM-CATALYZED HYDROGENOLYSIS WITH OTHER HYDRIDE SOURCES

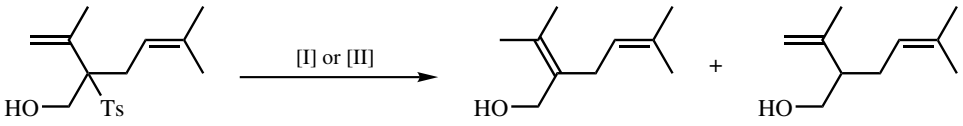
Allylic heteroatom functional groups are cleaved by Pd-catalyzed hydrogenolysis using other hydride sources such as $LiAlH_4$,[7],[11] borohydride,[7],[12]–[16] hydrosilanes,[7],[17],[18] Bu_3SnH,[19] *n*-butylzinc chloride,[20] *N*-propyl-1,4-dihydronicotinamide,[21] SmI_2/*i*-propanol,[22] and electrolysis.[23] Some examples are shown in **Scheme 15**.[18],[46]

Desulfonylation of allylic sulfones may be one of the synthetically most useful reactions among the Pd-catalyzed hydrogenolysis of allylic compounds using metal hydrides, because regioselective carbon–carbon bond formation and 1,3-rearrangement[47] of sulfonyl group are known for allylic sulfones, which are readily available starting from the corresponding allylic esters by Pd-catalyzed reaction.[48]



Scheme 15

Reductive desulfonylation of allylic sulfones is not so straightforward. For example, desulfonylation of the 2-tosyl homoallyl alcohols obtained by coupling of allylic sulfone with aldehyde using reducing agents such as Al(Hg), Na(Hg), Li-$EtNH_2$, or SmI_2-HMPA, which are most frequently employed for alkyl sulfones, occasionally induce overreduction to transform the olefinic bond to a single bond, migration of double bond, and/or retroaldol reaction. Alternatively, Pd-catalyzed reductive desulfonylation is a most promising reductive desulfonylation method due to the high reactivity of allylic sulfones toward Pd(0).[12] Regioselective desulfonylation of 2-tosyl homoallyl alcohols was achieved by using LiH-BEt_3 in the presence of Ph_3SiH (0.2 equiv) or $LiBH_4$ using different Pd-catalyst to afford either allylic or homoallylic alcohols. Lavandulol and isolavandulol were prepared regioselectively from a common allylic alcohol by this method[15] (**Scheme 16**).



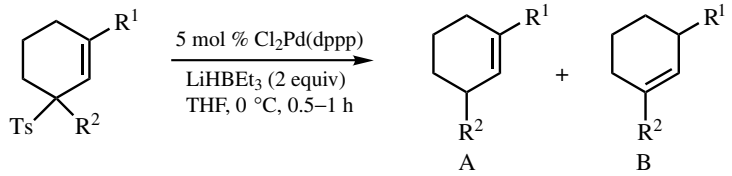
	Isolavandulol	Lavandulol
[I]	98%	2%
[II]	6%	94%

[I] = $Cl_2Pd(dppb)$ (5 mol %), Ph_3SiH (0.2 equiv), $LiHBEt_3$ (3 equiv), THF, 20 °C, 3 min.

[II] = $Cl_2Pd(PPh_3)_2$ (5 mol %), $LiBH_4$ (5 equiv), THF, –45 °C, 8 h.

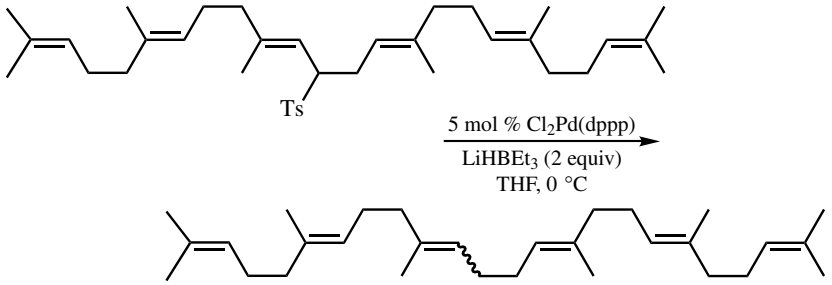
Scheme 16

Desulfonylation of allylic sulfones with $LiHBEt_3$ catalyzed by $Cl_2Pd(dppp)$ proceeds through attack at the less substituted side to give the more substituted olefins[13] (**Scheme 17**). This method was applied successfully to the total syntheses of various natural products such as squalene [13] (**Scheme 18**), coenzyme Q_{10}[14],[49] (**Scheme 19**), ambrein[50] (**Scheme 20**), dolicol derivative[51] (**Scheme 21**), and the aglycone part of the sex pheromone lurlene,[52] without formation of regioisomeric by-products.



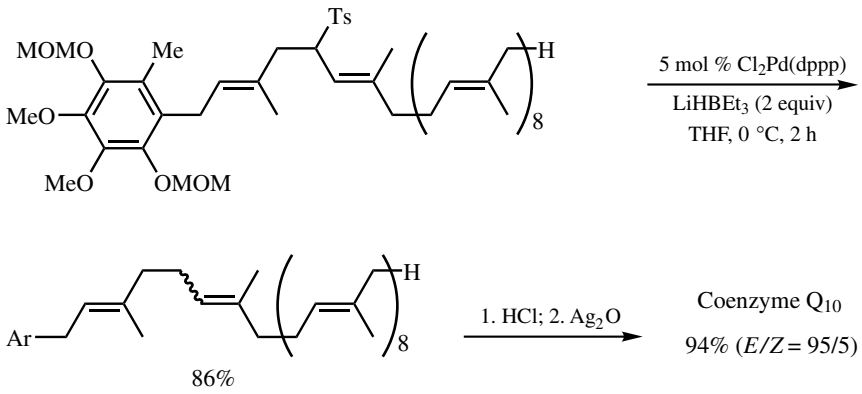
R^1	R^2	Total Yield (%)	Ratio A/B
H	$C_6H_5CH_2$	89	—:>99
$C_6H_5CH_2$	H	84	>99:—
H	$C_6H_5(CH_2)_2$	99	—:>99
$C_6H_5(CH_2)_2$	H	89	>99:—
H	$CH_3(CH_2)_{10}$	91	31:69
$CH_3(CH_2)_{10}$	H	97	>99:—

Scheme 17

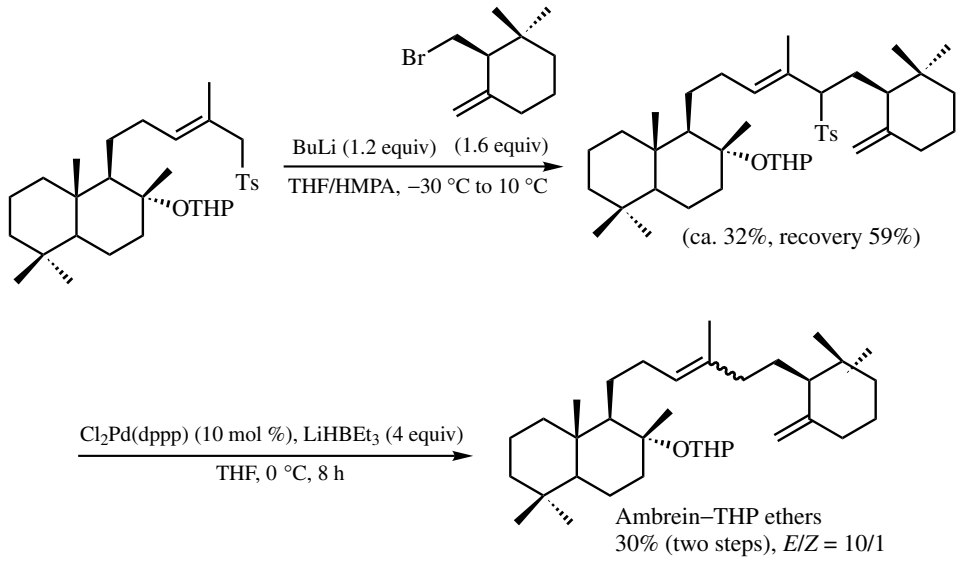


Squalene, 94% (E/Z = 97/3)

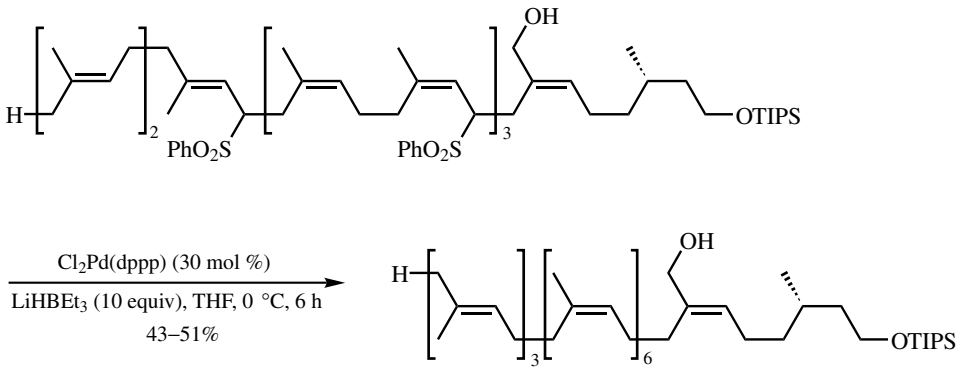
Scheme 18



Scheme 19



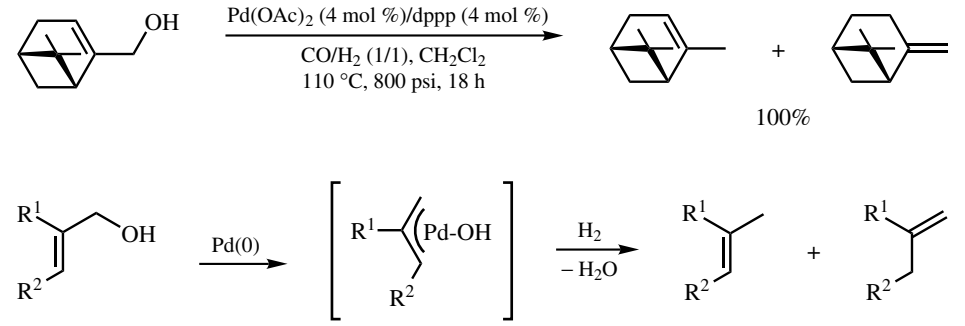
Scheme 20



Scheme 21

This Pd-catalyzed $LiHBEt_3$ reduction is applicable to "integrated chemical processes" (ICPs), which allows integration of alkylation of allylic sulfones and reductive desulfonylation under mild basic conditions in one pot to prepare various olefins.[53],[54]

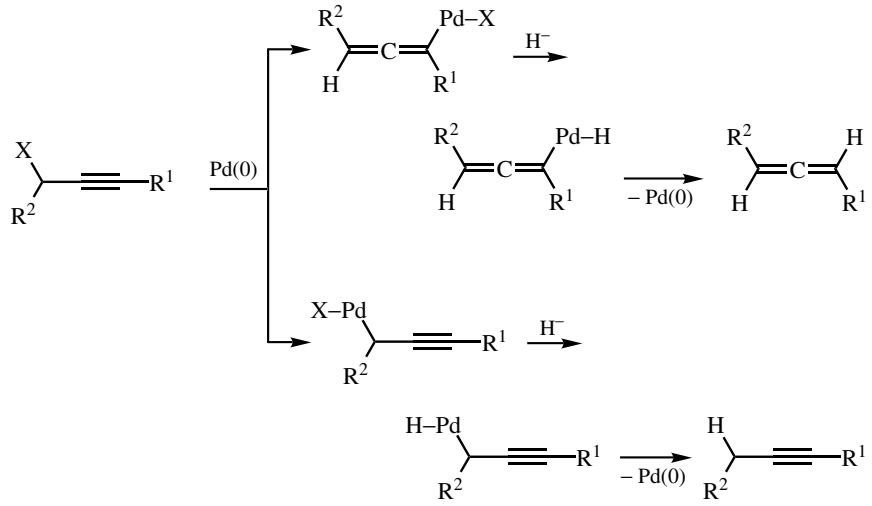
Brunner and Alper observed the formation of the alkenes as the side products in the Pd-catalyzed cyclocarbonylation of β,γ-substituted allylic alcohols. Especially in the case of (1*R*)-myrtenol, (1*R*)-α- and β-pinene are obtained but no carbonylation products. They assumed that a hydroxyallylpalladium complex was involved, which reacts with the hydrogen present to form H_2O and thereby releasing the alkenes[55] (**Scheme 22**).



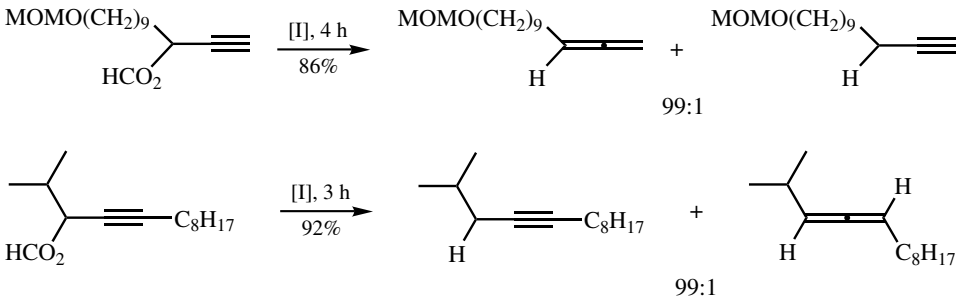
Scheme 22

D. PALLADIUM-CATALYZED HYDROGENOLYSIS OF PROPARGYLIC COMPOUNDS

Pd-catalyzed hydrogenolysis of propargylic compounds affords either allenes or alkynes depending on the structure of the propargylic compounds[56] (**Schemes 23** and **24**). Thus, when R^1 is a bulky group, the propargylpalladium complex is predominantly formed and the alkyne is obtained. The hydrogenolysis products of cyclic alkynyl carbonate with triethylammonium formate were dependent on the phosphine ligand employed[57] (**Scheme 25**).

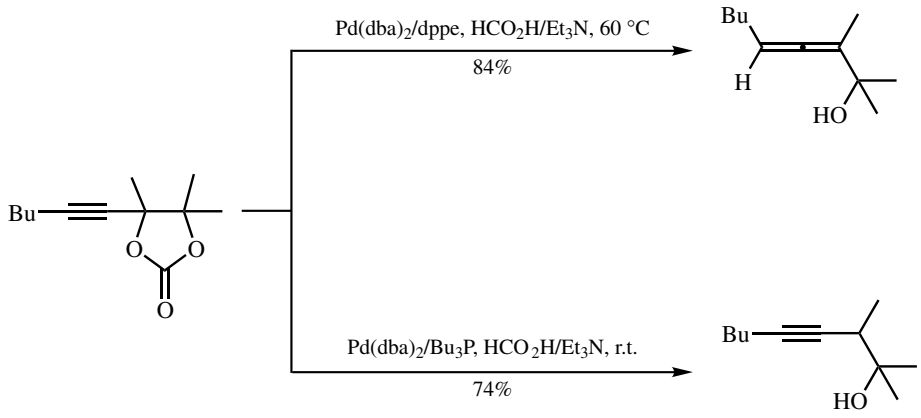


Scheme 23



[I] = $Pd(acac)_2/Bu_3P$ (1/1; 10 mol %), C_6H_6, r.t.

Scheme 24



Scheme 25

E. SUMMARY

Pd-catalyzed hydrogenolysis of allylic compounds with formates is an efficient and mild method. The hydride generated from the palladium formate attacks the more substituted side of the allylic system to give less substituted olefins in contrast to the case with other hydride sources. Pd-catalyzed hydrogenolysis of propargylic compounds affords either allenes or alkynes depending on the structure of the propargylic compounds.

Enantioselective Pd-catalyzed hydrogenolysis is still very rare. Many additional examples may be expected to be developed in the future.

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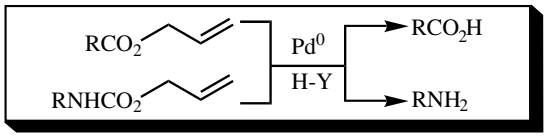

V.2.3.2 Palladium-Catalyzed Deprotection of Allyl-Based Protecting Groups

MARK LIPTON

A. INTRODUCTION

Although in the initial explorations of the Tsuji–Trost reaction (**Sect. V.2.1**), attention was focused on the fate of the π-allylpalladium intermediate (**Scheme 1**), eventually the synthetic utility of the leaving group was also considered. Pd-catalyzed cleavage of the allyl acetate bond in **Scheme 1** can also be viewed as a deprotection of acetic acid; as a consequence, efforts to utilize palladium catalysts in the deprotection of allyl-based protecting groups began[1] in the 1970s and has subsequently emerged as an important tool in organic synthesis.[2]

One attractive feature of deprotection using catalytic palladium(0) is the comparative mildness of the reaction conditions. As the Tsuji–Trost reaction was known to proceed at ambient temperature and with the addition of either mildly acidic or mildly basic nucleophiles, it compared favorably to the majority of deprotection reactions that employed either strong acid or base to effect complete deprotection. Such considerations are especially important in the synthesis of biopolymers such as peptides, carbohydrates, and oligonucleotides—where numerous protecting groups are necessarily employed and the chemoselectivity of deprotection ("protecting group orthogonality") is of paramount importance to the successful pursuit of a synthesis.

B. GENERAL CONSIDERATIONS

As with other examples of the Tsuji–Trost reaction, attention must be paid to the choice of catalyst, ligands, and nucleophile. Although such a choice is necessarily substrate-dependent, and will be discussed further for individual functional groups, a summation of the reagents that have proved useful is provided herein.

B.i. Palladium Catalysts and Ligands

It has been suggested that the active catalytic species in the formation of the crucial π-allylpalladium intermediate is most likely a coordinatively unsaturated Pd^0 complex of either the form PdL_2 or PdL_2X^-, where L is typically a phosphine or phosphite and X a

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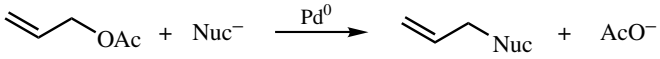
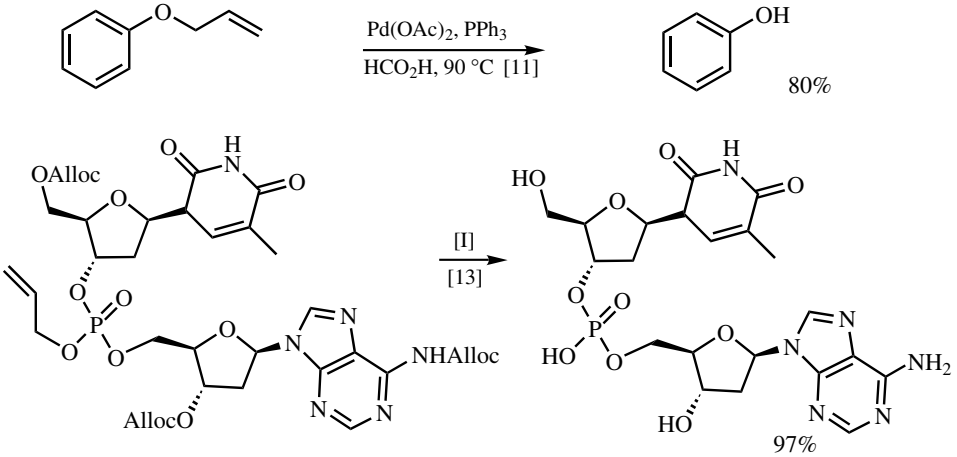


Scheme 1

halide or carboxylate ion.[2]–[5] In light of this, the majority of allyl group deprotections have employed the readily available catalyst $Pd(PPh_3)_4$ in substoichiometric quantity. Although $Pd(PPh_3)_4$ has been found to behave adequately in many examples, it is known that the loss of two phosphine ligands from $Pd(Ph_3P)_4$ to form the putative, catalytically active intermediate $Pd(Ph_3P)_2$ is quite unfavorable.[3]–[5] This problem can be circumvented by the chemical reduction of $Pd(Ph_3P)_2Cl_2$, by either organometallic reductants[6],[7] or electrochemical means,[4],[7] to directly generate a coordinatively unsaturated Pd^0 complex. Other variants have employed the air-stable Pd^0 sources $Pd(dba)_2$ and $Pd_2(dba)_3$–$CHCl_3$ in conjunction with an external phosphine ligand, or the *in situ* reaction of $Pd(OAc)_2$ and excess phosphine or phosphite.[8],[9] More recently, use of Pd^0 complexes of the water-soluble tris(*m*-sulfonato)triphenylphosphine (TPPTS) has facilitated the development of allyl group deprotections in aqueous environments.[10]

B.ii. Nucleophiles

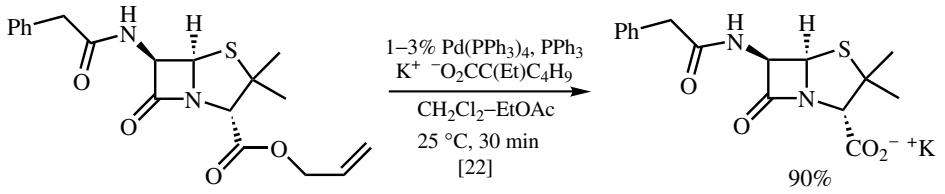
Initially, Pd-catalyzed deprotections were carried out under reductive conditions. The earliest examples of Pd-mediated allyl group deprotection employed formic acid, usually in conjunction with an amine base, at elevated temperature as a hydride source (**Scheme 2**).[1],[11]–[13] Later development of tri-*n*-butyltin hydride as a hydride source has greatly facilitated the reductive deprotection of a wide variety of allyl-based protecting groups, reacting almost instantaneously at ambient temperature.[14]–[16] Additional hydride sources for allyl group deprotection include phenyltrihydrosilane[17] and several different borohydrides (**Scheme 5**).[18],[19] Most recently, Guibé and Albericio have used amine–borane complexes as reducing agents to effect allyl carbamate deprotection.[20]



[I] (Alloc = allyloxycarbonyl) = 20% $Pd(PPh_3)_4$, 80% PPh_3, 40 equiv HCO_2H, 40 equiv $BuNH_2$, 25 °C, 30 min

Scheme 2

When Pd-catalyzed deprotection of an allyl ester is conducted in the presence of external carboxylic acid nucleophile, an equilibrium between two different allyl esters is established. Several strategies have been developed to perturb this equilibrium far enough to ensure complete deprotection. Use of a large excess of acetic acid has been shown to effect the deprotection of allyl carbonates and allyl phosphates.[21] Another approach employs the soluble carboxylate salt potassium 2-ethylhexanoate (**Scheme 3**) for the deprotection of allyl carboxylic esters.[22] Precipitation of the desired potassium carboxylate is used to perturb the equilibrium in the direction of products. Because these deprotection conditions are essentially neutral, they have been employed in the deprotection of particularly sensitive allyl esters.[23]

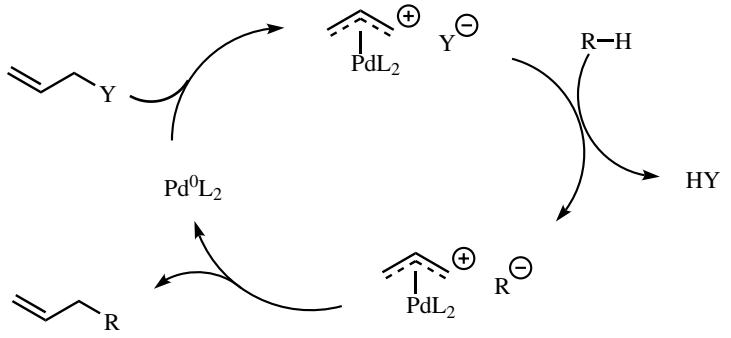


Scheme 3

Kunz introduced the use of nitrogen nucleophiles to scavenge the π-allylpalladium intermediate in deprotections of allyl esters, again through an equilibrium process.[24] Although Kunz's initial report employed excess morpholine as the nucleophile, subsequent work has demonstrated that many different amines can be used, mostly in the deprotection of allyl esters and phosphates.[25]–[27] *N*-Methylaniline has found particular favor as a nucleophile in allyl group deprotection.[28] *O*-Alkylhydroxylamines have also been employed, owing to their increased nucleophilicity.[29] Compatibility of allyl group deprotection with the base-labile Fmoc (9-fluorenylmethoxycarbonyl) protecting group in peptide synthesis has been achieved using *N*-methylmorpholine (NMM) buffered with either dilute HCl or acetic acid.[30],[31] Azide salts have also been used as nucleophiles in aqueous allyl group deprotection reactions.[32]

Since the initial studies of Tsuji and Trost, it has been known that π-allylpalladium complexes react irreversibly with active methylene compounds to form new carbon–carbon bonds. Applying this information, Kunz introduced dimedone[33] and *N,N*-dimethylbarbituric acid (NDMBA)[34] as nucleophiles in the Pd-catalyzed deprotection of allyl carbamates and carbonates. The presumed catalytic cycle for this process is shown in **Scheme 4**. Dimedone and NDMBA have also been employed as nucleophiles in the deprotection of allyl esters. Dimethyl malonate has also been used occasionally in allyl carbamate deprotection, although it appears to be less reactive than the other carbon nucleophiles.[35]

The last class of nucleophiles used to scavenge the π-allylpalladium intermediate is that of sulfur nucleophiles. 2-Thiobenzoic acid has been used as a water-soluble scavenger of π-allylpalladium complexes in allyl carbamate deprotections.[36] More recently, aryl sulfinic acids have been demonstrated to very effectively serve as nucleophiles in the Pd-mediated deprotection of allyl esters, carbamates, amines, and ethers.[37] This reagent appears to afford substantially better reactivity than most other classes of nucleophiles.



Scheme 4

C. PROTECTION–DEPROTECTION OF CARBOXYLIC ACIDS

C.i. Allyl Esters

Allyl-based protecting groups have become a popular choice for the protection of carboxylic acids, especially in peptide and glycopeptide synthesis. Formation of allyl esters from carboxylic acids has typically been carried out using allyl alcohol/DCC/DMAP,[38] allyl bromide/Cs_2CO_3,[39] and Fischer esterification conditions.[40] Additionally, methyl and ethyl esters have been transesterified to allyl esters using NaH, DBU/LiBr, and Ti(O*i*-Pr)$_4$ as catalysts.[41]–[43]

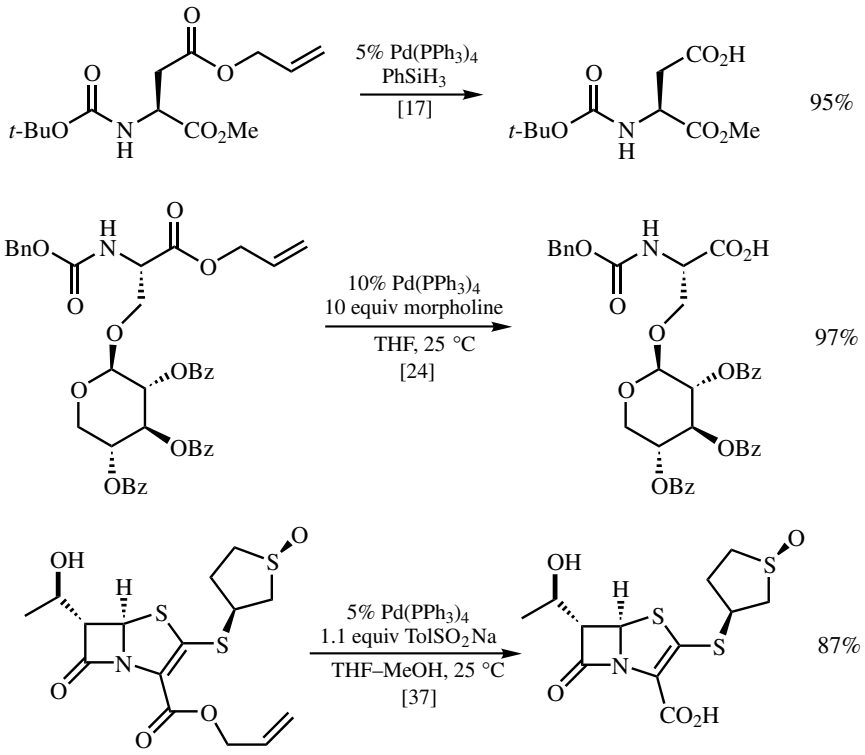
Deprotection of allyl esters has been accomplished using $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ in conjunction with dimedone, NMM,[24] 2-ethylhexanoic acid,[22] Bu_3SnH,[14],[15] $PhSiH_3$,[17] or barbituric acid (**Scheme 5**). The recently introduced sulfinic acid scavengers also look particularly promising for the deprotection of allyl esters.[37] It is noteworthy that allyl esters are compatible with both acid-labile and base-labile protecting groups, making them very attractive choices as a means of introducing an extra degree of orthogonality in peptide synthesis.

C.ii. Prenyl Esters

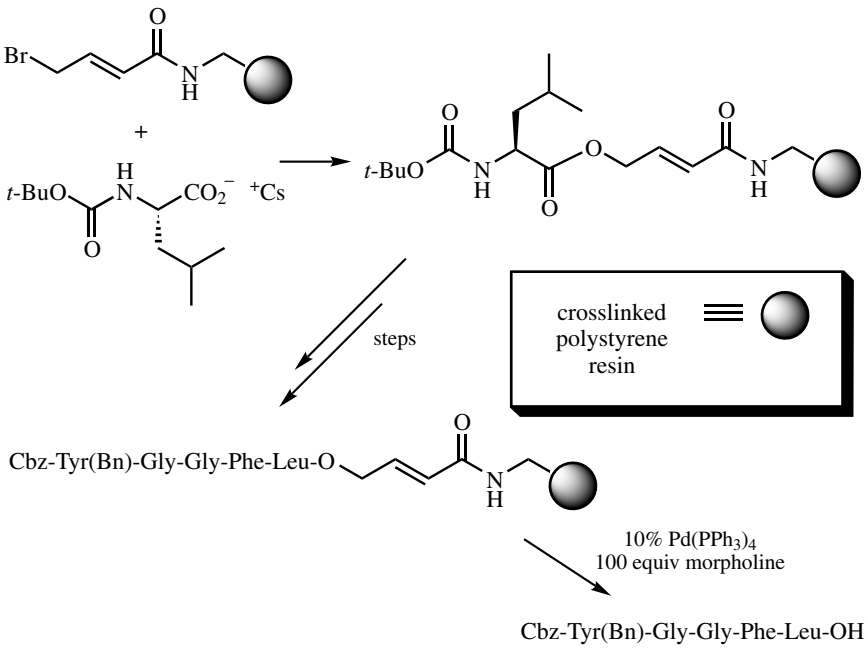
The prenyl (γ,γ-dimethylallyl) ester was introduced as a more robust variant of the allyl ester.[44] Experiments have shown that allyl esters and allyl carbamates can be selectively deprotected in the presence of a prenyl ester,[44],[45] thereby permitting greater precision in the selectivity of deprotection of allyl-based functionality.

C.iii. Allyl-Based Linkers for Solid Phase Peptide Synthesis

The success of allyl-based protection for carboxylic acids led to the development of allyl-based linkers for the attachment of peptides and glycopeptides to a solid support during their synthesis. Kunz developed the first allyl-based linker, hydroxycrotonamide (HYCRAM), in 1988.[46] Displacement of the allylic bromide in the precursor by a carboxylate nucleophile permits the attachment of the C-terminal residue to the solid support (**Scheme 6**). Peptide synthesis using this linker was performed with Boc as the N-terminal blocking group, and the final peptide or glycopeptide was cleaved from the allylic linker



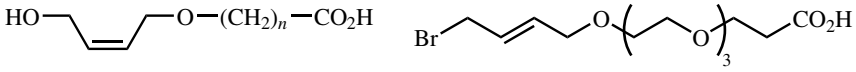
Scheme 5



Scheme 6

with $Pd(PPh_3)_4$ and morpholine. A number of peptides and glycopeptides were successfully synthesized using this methodology.[46]–[48]

The HYCRAM linker is not well suited to an Fmoc synthesis strategy, however, perhaps owing to its potential to undergo Michael addition. This led to the development of a number of alternative allylic linkers, such as the (*Z*)-allylic ethers[49] and the polyether-based Hycron linker[50] developed by Kunz (**Scheme 7**). Typically, these linkers are attached to the C-terminal residue in solution, followed by attachment of the linker to a solid support. These linkers permit the use of Fmoc-based peptide synthesis techniques and have been employed in the solid phase synthesis of glycopeptides.[50],[51] Deprotection from the resin is accomplished using Pd-catalyzed allyl transfer to *N*-methylaniline, conditions that do not result in loss of Fmoc protection. The major problem associated with solid phase peptide synthesis on allyl-based linkers is the increased likelihood of unwanted diketopiperazine formation during acylation of a resin-bound dipeptide. This problem has been attributed to the previously observed increased acidity of allylic alcohols.[52]



(n = 1, 5) "Hycron"

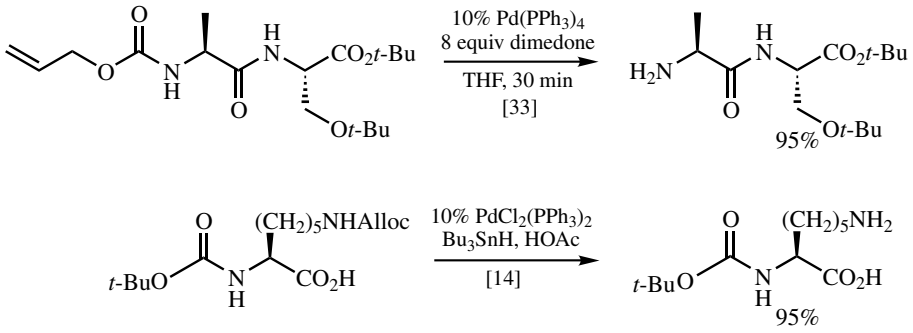
Scheme 7

D. PROTECTION–DEPROTECTION OF AMINES

Although one can *N*-allylate amines, Pd-mediated deprotection of *N*-allylamines has not proved to be reliable or efficient. Instead, the Alloc (allyloxycarbonyl) group was employed by Kunz as a robust, allyl-based protecting group for amines that can be efficiently cleaved under conditions similar to those used to deprotect other allyl esters.[33] Since its introduction, the Alloc group has found application in solid phase peptide synthesis, especially for the synthesis of glycopeptides or cyclic peptides. The Alloc group is typically introduced through acylation of an amine with allyl chloroformate or diallyldicarbonate.[53],[54]

Deprotection of the Alloc group is complicated by the potential for formation of unreactive *N*-allyl side products, formed by interception of the intermediate π-allylpalladium complex by a newly liberated amine. To avoid this complication, two distinct strategies have been employed. The first is to perform the deprotection under acidic conditions using a scavenger that irreversibly undergoes allyl transfer, thereby rendering the product amine as its nonnucleophilic conjugate acid. Using this criterion, Kunz initially employed dimedone as his nucleophile of choice (**Scheme 8**).[33] Concern regarding the potential condensation of the product amine with dimedone to form a stable ketoenamine led him to employ *N*,*N*-dimethylbarbituric acid (NDBMA) as a substitute scavenger.[34]

A second deprotection strategy employs the rapid and irreversible reaction of the π-allylpalladium complex with tri-*n*-butyltin hydride in the presence of an acid (**Scheme 8**).[14] Alternatively, sodium borohydride has been used to reduce the π-allylpalladium complex.[55] Both of these methods have been used in the *in situ* deprotection/acylation of



Scheme 8

Alloc-protected amines to directly convert them to new amine derivatives.[56] Albericio and Barany have also used a mixture of DMSO, THF, 0.1 N HCl, and *N*-methylmorpholine (2:2:1:0.1) to deprotect Alloc from resin-bound peptides that also contain base-sensitive Fmoc groups.[30],[31]

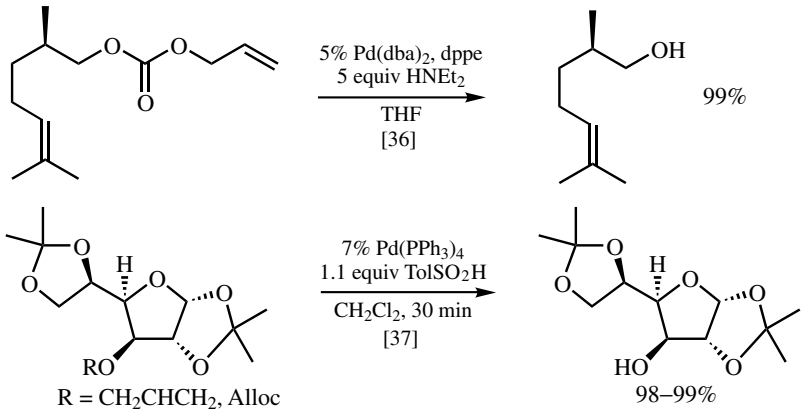
The deprotection of Alloc-protected amines can also be accomplished in aqueous media employing the water-soluble phosphine TPPTS and excess diethylamine as the nucleophilic scavenger.[36],[57] Secondary amines have also been successfully deprotected with no competing *N*-allylation using biphasic conditions in conjunction with $Pd(OAc)_2$, TPPTS and excess diethylamine.[58]

E. PROTECTION–DEPROTECTION OF ALCOHOLS AND PHENOLS

Although allyl ethers have long been employed as protecting groups for alcohols, only in a few isolated cases have they proved amenable to Pd-mediated deprotection, owing largely to the poor leaving group ability of alkoxides. Instead, the allyloxycarbonyl (Alloc) group has been employed as an allyl-based protecting group for alcohols that can be removed by Pd-mediated allyl transfer.[59] The mildness of these reaction conditions has facilitated the use of Alloc groups in carbohydrate chemistry. An alcohol is typically converted to the corresponding allyl carbonate by treatment with allyl chloroformate and pyridine or DMAP.[53] Other conditions have been developed for Alloc protection of unreactive alcohols.[60]

Deprotection of allyl carbonates has been accomplished using a wide variety of nucleophiles (**Scheme 9**), including formate, sodium borohydride, tri-*n*-butyl hydride, dimedone, diethylamine, and sodium azide. A recent, noteworthy development is the use of sulfinic acids as nucleophiles in the deprotection of allyl carbonates.[37] Not only were allyl carbonates quantitatively deprotected in 30 min, but the authors also reported the successful deprotection of an allyl ether using catalytic palladium(0). Should this result prove to be general, it would represent in a major development in allyl-based protection of alcohols.

The allyl ethers of phenols have also been deprotected using catalytic palladium(0) methodology. In this case, the improved leaving group ability of the phenoxide is sufficient to permit reliable deprotection using tri-*n*-butyltin hydride, sodium and lithium borohydrides, and phenyltrihydrosilane as the allyl scavengers.[17],[61],[62]



Scheme 9

F. PROTECTION–DEPROTECTION OF PHOSPHATES

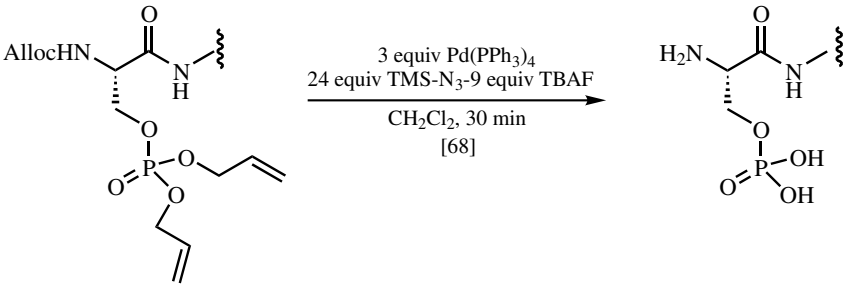
Hayakawa and Noyori first recognized that monoallylphosphotriesters undergo facile reaction with palladium(0) catalysts to afford liberation of the phosphate and have subsequently applied this methodology, in conjunction with Alloc protection of exocyclic amines, to the area of oligonucleotide synthesis.[12],[26],[63],[64] Introduction of the monoallylphosphotriester is typically accomplished using the phosphoramidite method, whereby the alcohol is treated with (allyloxy)bis(diisopropylamino)phosphine to form the allyl phosphoramidite, which, after incorporation into an oligonucleotide, is subsequently oxidized to a monoallylphosphotriester.

Simultaneous deprotection of the monoallylphosphotriesters and Alloc-protected exocyclic amines is accomplished using catalytic $Pd(PPh_3)_4$ or $Pd2(dba)_3$–$CHCl_3$, triphenylphosphine, and a large excess of butylamine/formic acid at 50–60 °C (**Scheme 4**).[12],[64] This methodology has also been used to synthesize base-labile oligonucleotides not amenable to traditional solid phase nucleic acid synthesis methodology.[65] An extension of this methodology has been the development of allyl-based linkers for oligonucleotide synthesis, thereby permitting cleavage of synthesized oligonucleotides from solid supports using Noyori's deprotection conditions.[66],[67]

Allyl-based protection for the phosphate group in phosphoserine-containing peptides has also been employed.[68] In this case, the *N*-alloc-bis(allyl)phosphate of serine was incorporated into a resin-bound peptide using standard solid phase peptide synthesis methodology and deprotected using trimethylsilyl azide and tetrabutylammonium fluoride as the nucleophile (**Scheme 10**).

G. PROTECTION–DEPROTECTION OF THIOLS

In addition to the functional groups already mentioned, allyl-based protecting group schemes have been developed for the protection of thiols, especially the side chain thiol of the cysteine residue in peptide synthesis. Because allyl sulfides are not susceptible to Pd-mediated allyl group deprotection and allyl thiocarbonates are unstable toward nucleophilic attack, the alloxycarbonylmethyl (Allocam) group was introduced for allyl-based



Scheme 10

protection of thiols.[69] The Allocam group is installed by reacting the thiol with allyl *N*-hydroxymethylcarbamate in the presence of acid. Removal of the Allocam group is accomplished using $PdCl_2(PPh_3)_2$, tri-*n*-butyltin hydride and acetic acid. These conditions were essential to prevent poisoning of the palladium(0) catalyst by the product thiol. The limited acid stability of the Allocam group has prompted the search for more acid-stable variants.[70]

H. SUMMARY

The mildness and efficiency of Pd^0-catalyzed allyl transfer has prompted the development of allyl-based protecting groups for a variety of functional groups. This development has, in turn, made available to the organic synthesis community a versatile and important alternative to acid-, base-, and photo-labile protecting groups. This has proved especially important in the area of biopolymer synthesis, where protecting group manipulations are central to the success of the synthesis.

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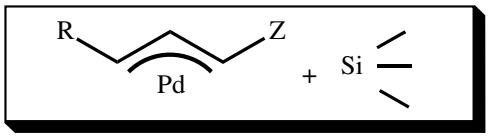

V.2.3.3 Palladium-Catalyzed Allylic and Related Silylation and Other Metallations

YASUSHI TSUJI

A. INTRODUCTION

The allylic silanes and other metals are highly versatile synthetic intermediates and have a large number of applications in C—C bond-formation reactions. Allylic esters such as acetates, carbonates, and phosphates as well as allylic chlorides are easily available starting materials. Therefore, Pd-catalyzed allylic silylation and other metallation of these substrates have been explored to afford the allylic silanes and other metals.

B. ALLYLIC SILYLATION

Tris(trimethylsilyl)aluminum[1] prepared from Me_3SiCl and activated aluminum was used as a silylating reagent for allylic acetates in the presence of a catalytic amount of $Pd(PPh_3)_4$ to afford allylic silanes. $PhMe_2SiAlEt_2$[2] was employed in the silylation reaction of allylic phosphates catalyzed by $Pd(OAc)_2$–$P(o\text{-}CH_3C_6H_4)_3$. As for silylation of allylic chlorides, $PhCl_2SiSiMe_3$[3] and $Cl_2MeSiSiMeCl_2$[4] were utilized with Pd catalyst. In the presence of a chiral ligand, the silylation with $PhCl_2SiSiMe_3$ afforded optically active allylic silanes of up to 61% ee.[3] On the other hand, $Me_3SiSiMe_3$ is more accessible and was employed in Pd-catalyzed silylations of allylic chlorides[4] and acetates[5] at 160–170 °C. Unfortunately, in these potentially useful reactions, substituted allylic chlorides and acetates as the substrates did not afford the corresponding allylic silanes due to elimination to form conjugated dienes. In contrast, by utilizing $Pd(dba)_2$–LiCl as a catalyst, the silylation of various allylic acetates proceeds at 100 °C in high yields without the elimination.[6] Furthermore, when allylic trifluoroacetates were used as the substrates in place of the allylic acetates, the silylation proceeds even at room temperature and the added chloride salt was not necessary as the catalyst component (**Scheme 1**).[7] The reaction would proceed via transmetallation of a π-allylpalladium trifluoroacetate with $Me_3SiSiMe_3$. However, there was no precedent for the transmetallation. Thus, a stoichiometric reaction using a model complex was carried out (**Scheme 2**),[7] in which the π-allylpalladium trifluoroacetate complex reacted with $Me_3SiSiMe_3$ to afford allylic silane and palladium black, suggesting reductive elimination of the resulting (π-allyl) (silyl) palladium complex is very fast.

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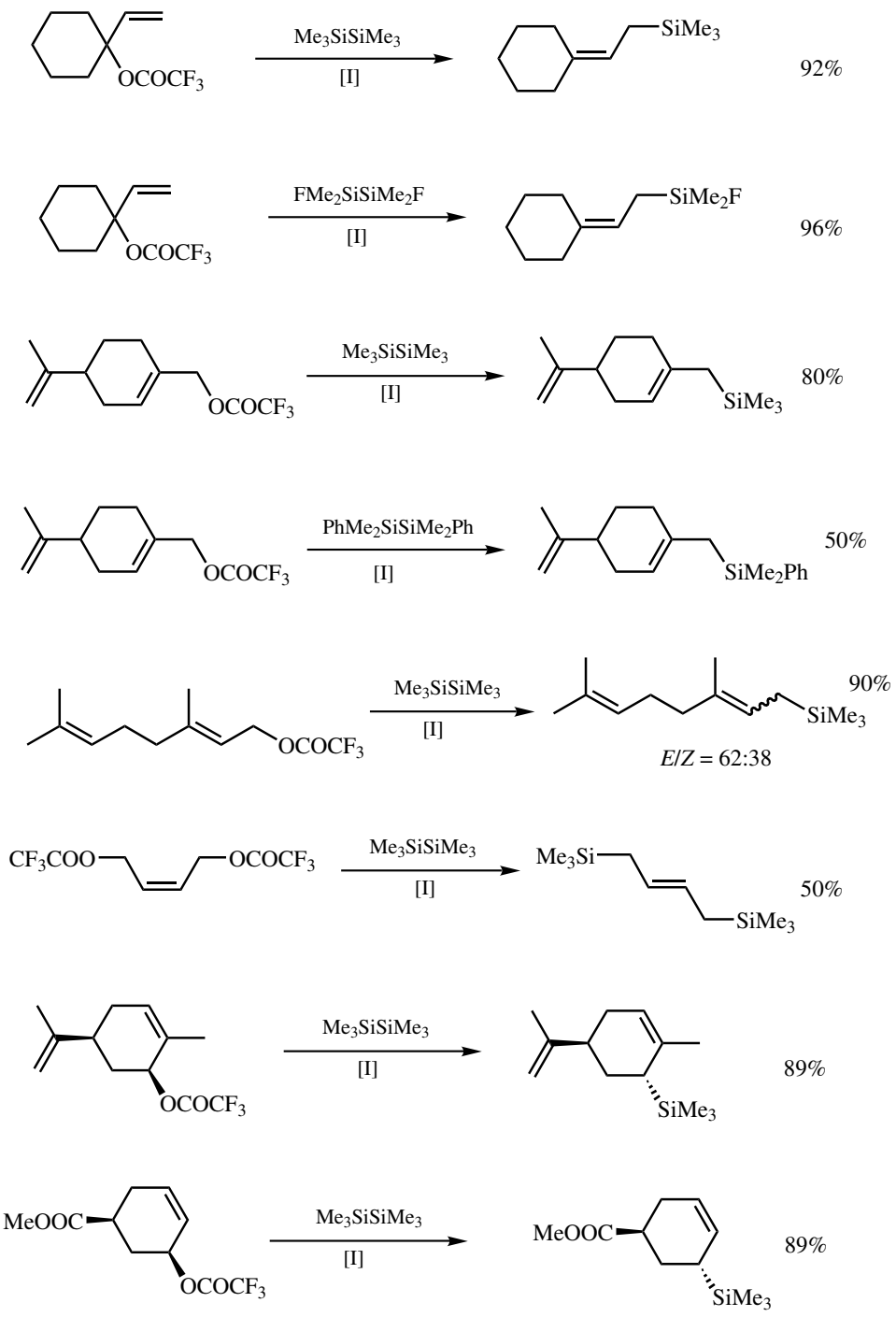
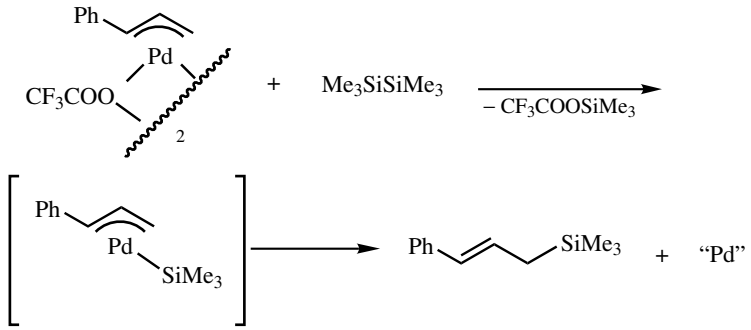


[I] 3mol % $Pd(dba)_2$, room temperature, 12 h

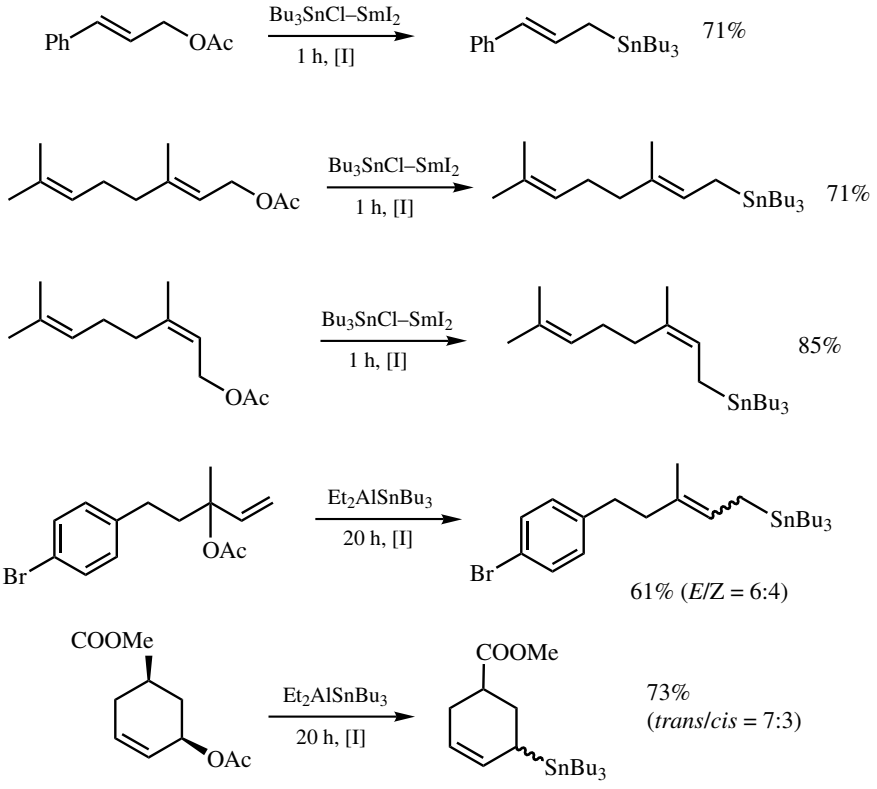
Scheme 1



Scheme 2

C. OTHER METALLATION

In the presence of Pd catalyst, $Bu_3SnCl–SmI_2$[8] and $Bu_3SnAlEt_2$[9] were effective stannation reagents for allylic acetates (**Scheme 3**). Organodistannane (R_3SnSnR_3) reacted with allylic acetates to afford allylic stannanes,[10],[11] which were further utilized in one-pot carbon–carbon bond-formation reactions.



[I] 5mol % $Pd(PPh_3)_4$, room temperature

Scheme 3

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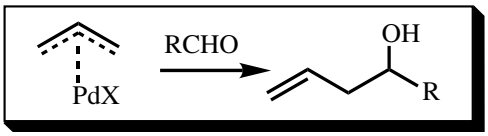

V.2.3.4 Palladium-Catalyzed Reactions of Allyl and Related Derivatives with Organoelectrophiles

Y. TAMARU

A. INTRODUCTION

π-Allylpalladium complexes have long been recognized as an allyl cation equivalent and widely utilized for the allylation of a variety of hard and stabilized carbon nucleophiles. Both allenylpalladium and vinylpalladium complexes are chemically neutral, or very feebly nucleophilic, if any. Under conditions described below, however, these π-allyl-, vinyl-, and allenylpalladium complexes alter their reactivity in mode and behave as nucleophilic species.[1]

The reversal of reactivity or *umpolung* of π-allylpalladium can be accomplished by (i) reduction by electrochemical means (**Sect. B.i**), (ii) reduction with metals (**Sect. B.ii**) or low valent metal salts (**Sects. B.iii** and **B.iv**), (iii) transmetallation of the allyl moiety to more electropositive metals (**Sect. C.i**) or metalloids (**Sects. C.ii** and **E**), and (iv) a structural change from π-allyl- to σ-allylpalladium (**Sects. C.iii** and **D**). Allenylpalladium undergoes nucleophilic addition toward electrophiles by reduction with SmI_2 (**Sect. F.i**) and transmetallation with Et_2Zn (**Sect. F.ii**). Recently, it has been revealed that some vinylpalladium intermediates intramolecularly undergo nucleophilic addition to carbonyl groups (**Sect. H**). Vinylation of carbonyl compounds with vinylpalladium is accomplished by transmetallation of the vinyl group to Cr(III) (**Sect. G**).

B. UMPOLUNG OF π-ALLYLPALLADIUM BY REDUCTION

B.i. Electrochemical Reduction

Under electrochemical reduction conditions allyl acetates undergo Pd-catalyzed reduction to give alkenes in good yield (**Scheme 1**).[2] The reaction may proceed via two-electron (2 e) reduction of the π-allylpalladium intermediate. The allyl anion thus formed is protonated selectively at the terminal position to provide an internal alkene predominantly. In the presence of an excess of chlorotrimethylsilane (ca. 13 equiv), trimethylsilylation takes place at the less substituted allylic termini to provide allylsilanes in moderate to good yield (**Scheme 1**).[2] The same products are obtained in similar yield by the protonation and silylation of α-phenylallyl acetate. The reaction may be

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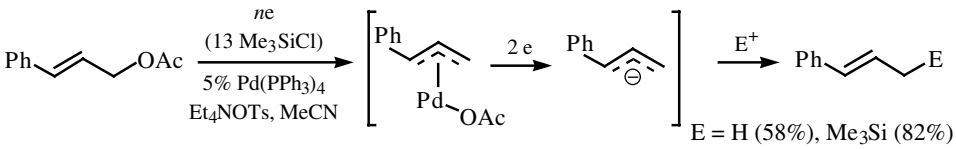
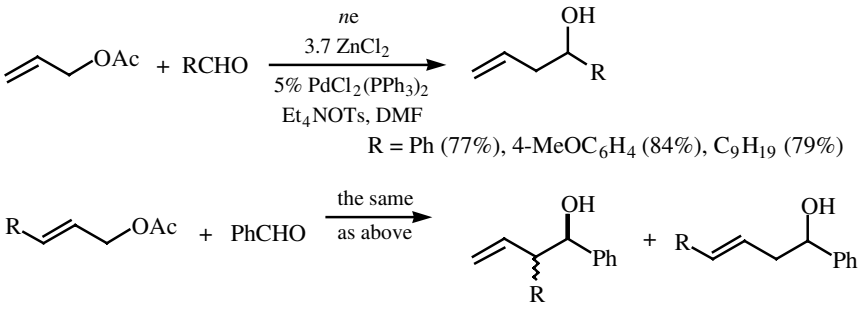
utilized as the deprotection method of allyl carboxylate. For example, under similar conditions, allyl ethyl phthalate is converted into phthalic acid monoethyl ester in 87% yield.



Scheme 1

Under similar electrochemical reduction conditions in the presence of zinc chloride and an aldehyde, an allylation of the aldehyde takes place to provide a homoallyl alcohol in good yield (**Scheme 2**).[3] Crotyl acetate reacts with benzaldehyde to furnish a mixture of branched and straight chain product in 51% and 5% yield, respectively. The diastereoselectivity of the branched product is modest. Cinnamyl acetate shows similar regio- and stereoselectivity. Under the reaction conditions, $ZnCl_2$ is reduced easier than π-allylpalladium, and hence zinc metal may be the real reducing agent for π-allylpalladium.[4]



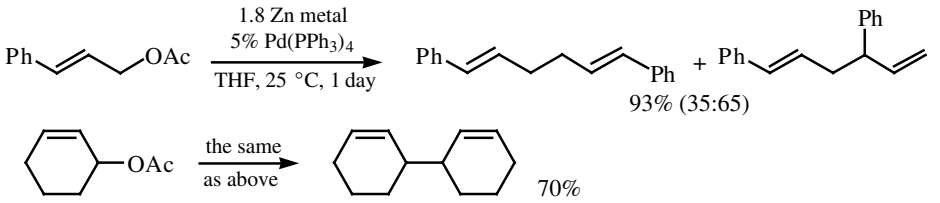
R = Me	51% (*anti*/*syn* = 6:4)	5%
R = Ph	59% (*anti*/*syn* = 7:3)	12%

Scheme 2

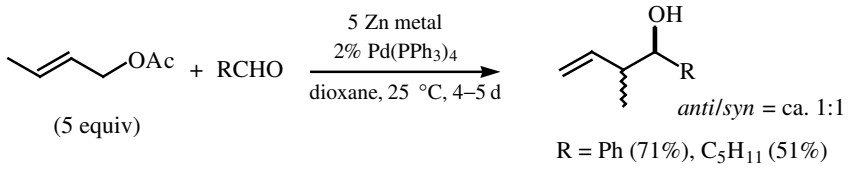
B.ii. Reduction with Zinc Metal

Allyl acetates undergo homocoupling to provide 1,5-hexadiene derivatives in good yield in the presence of 1.8 equiv of zinc powder and 5 mol % of $Pd(PPh_3)_4$ in THF (**Scheme 3**).[5]

Under similar conditions, in the presence of aldehyde, the allylation of aldehyde takes place and homoallyl alcohols are obtained in modest yield (**Scheme 4**).[6] In order to obtain the homoallyl alcohols in acceptable yield, it is necessary to use both allyl acetate zinc metal in large excess (ca. 5 equiv each). With 2 equiv of zinc, for example, the homoallyl alcohol (R = Ph) is obtained in 33% yield. The majority of allyl acetate and zinc metal may be wasted for the production of 1,5-hexadienes.



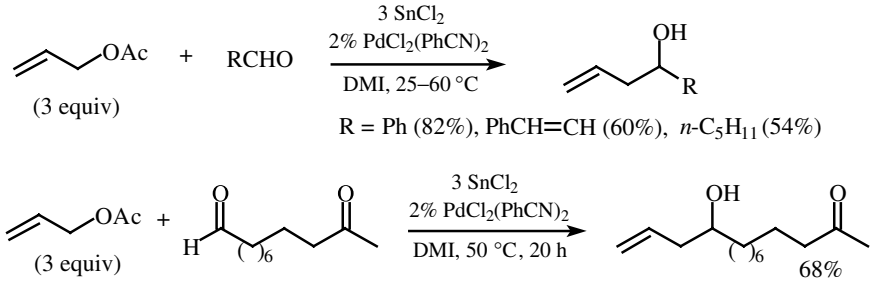
Scheme 3



Scheme 4

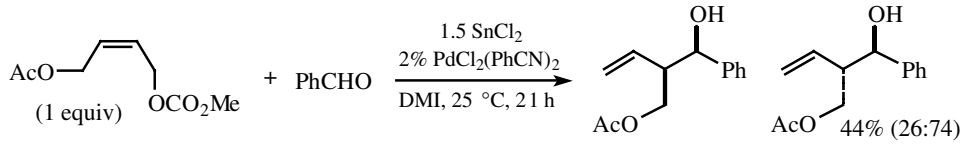
B.iii. Reduction with Tin(II) Chloride

The allyl moiety of allylic acetate undergoes nucleophilic addition to aldehydes and provides homoallyl alcohols in good to moderate yield in the presence of 2 mol % of $PdCl_2(PhCN)_2$ and 3 equiv of tin(II) dichloride in DMI (1,3-dimethyl-2-imidazolidinone) at 25–60 °C (**Scheme 5**).[7],[8] The reaction displays high chemoselectivity and the aldehyde moiety of 10-oxoundecanal is selectively allylated under the conditions shown in **Scheme 5**.



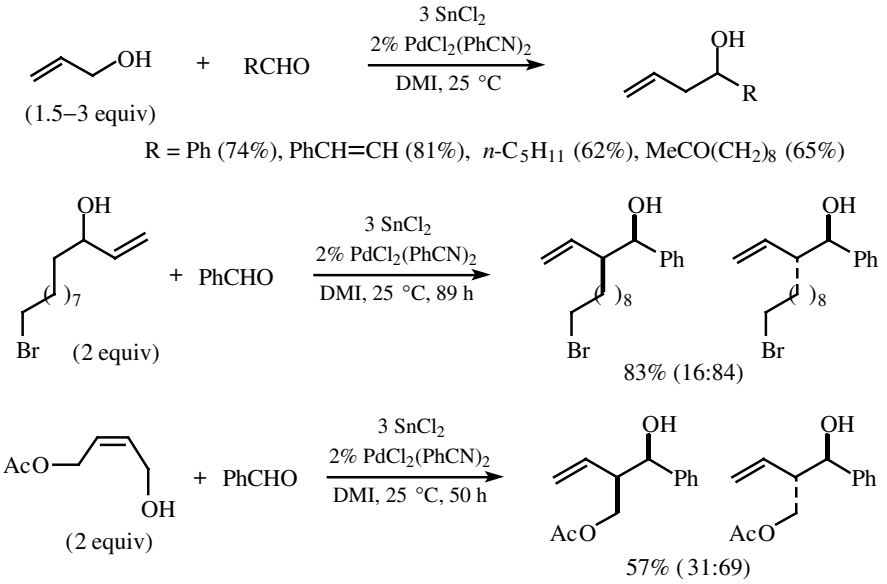
Scheme 5

Judging from the reaction times and temperatures and also from the amounts of allylic substrate and $SnCl_2$ required to obtain the allylation products in reasonable yield, allyl carbonate, in general, is more reactive and practical than the corresponding acetate.[9] In fact, methyl (*Z*)-4-acetoxy-2-butenyl carbonate selectively undergoes allylation at the carbonate moiety, whereby the acetate moiety remains unchanged (**Scheme 6**).[9]



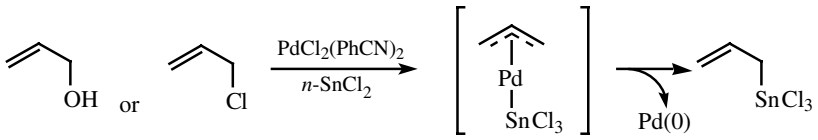
Scheme 6

Surprisingly, even allyl alcohol undergoes the allylation of aldehydes in the presence of 2 mol % of $PdCl_2(PhCN)_2$ and 3 equiv of tin(II) dichloride in DMI (**Scheme 7**).[10],[11] The reaction is compatible with alkyl bromide, aryl bromide, and allyl acetate functionality. The reactivity order of allylic system is allylic carbonate > allylic alcohol > allylic acetate. Unsymmetrical allylic alcohols regioselectively undergo nucleophilic addition at the allylic termini with the highest number of substituent. Generally, *anti*-isomers are produced preferentially over *syn*-isomers.



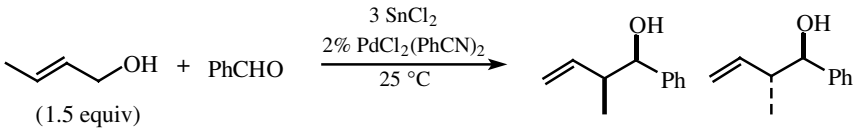
Scheme 7

NMR spectroscopic investigations suggest that the actual allylating agent is allyl(trichloro)tin(IV): ^1H, ^{13}C, and ^{119}Sn NMR spectra of the reaction of allyl alcohol with $PdCl_2(PhCN)_2$–$SnCl_2$ correspond to those of the reaction of allyl chloride with $PdCl_2(PhCN)_2$–$SnCl_2$ (**Scheme 8**).[11] Accordingly, although the detail is not clear, π-allyl(trichlorostannyl)palladium intermediate may be generated via steps from allyl alcohol, $PdCl_2(PhCN)_2$, and $SnCl_2$.



Scheme 8

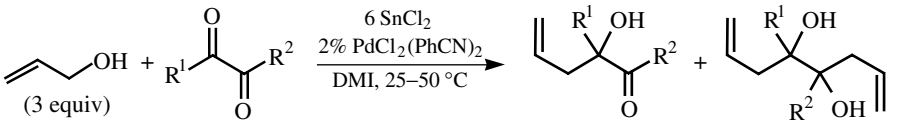
Addition of water as a cosolvent not only accelerates the allylation reaction but also causes a dramatic change in the diastereoselectivity (**Scheme 9**).[12] The diastereoselectivity may be rationalized by invoking either a six-membered chair like transition state or an acyclic (antiperiplanar or synclinical) transition state depending on the reaction medium and the structure of reaction partners.[12]

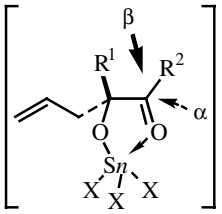


Solvent	Yield %	*syn*/*anti*
DMI	63	29:71
THF (with 10 equiv H_2O)	74	16:84
DMSO (with 3 equiv H_2O)	84	86:14
DMSO (with 170 equiv H_2O)	70	16:84

Scheme 9

Double allylation of α-diketone and α-ketoaldehyde has been accomplished with high diastereoselectivity in the presence of 3 equiv of allyl alcohol, 6 equiv of $SnCl_2$, and 2 mol % of $PdCl_2(PhCN)_2$ (**Scheme 10**).[13] The second allylation proceeds faster than the first allylation probably owing to an activation of the second carbonyl by an intramolecular five-membered chelate structure, which may also contribute to the steric control of the second allylation (α- versus β-face attack). Indeed, α-hydroxyketones, when used as the starting materials, are allylated with high to moderate diastereoselectivity in a sense expected from the five-membered chelate structure.[14] The formation of the monoallylation product as the minor component in the cases of R_2 = Ph may be ascribed to the steric suppression of the second allylation by the phenyl group.[13]



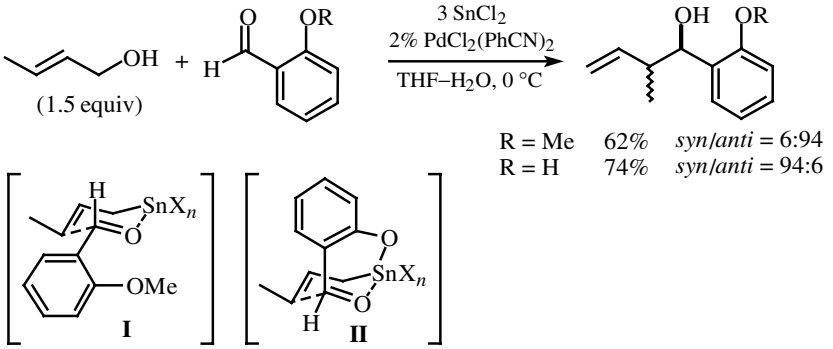


R^1		R^2	Yield %	
Me		Me		59 (*syn*/*anti* = 7:3)
	—$(CH_2)_4$—			46 (only *syn*)
Ph		Ph	22	61 (only *anti*)
H		Ph	7	19 (only *anti*)

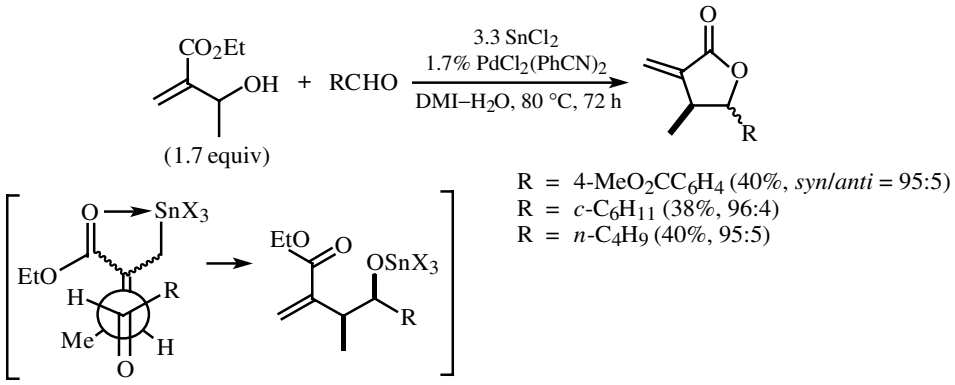
Scheme 10

Contrasting stereoselectivity is observed for the reaction of salicylaldehyde and its methyl ether (**Scheme 11**).[14] The *anti* selective allylation for salicylaldehyde methyl ether may be attributed to a transition state **I** and the *syn* selective allylation of salicylaldehyde may be attributed to a transition state **II** (**Scheme 11**).[14]

The allylation of aldehydes with ethyl α-(α-hydroxymethyl)acrylate and ethyl α-(α-hydroxyalkyl)acrylates is successfully preformed under the conditions shown in **Scheme 12**.[15] The primary product, α-methylene-γ-stannyloxycarboxylate, spontaneously undergoes an intramolecular transesterification to provide α-methylene-γ-butyrolactone in moderate yield. The high *syn*-selectivity may be rationalized on the basis of an antiperiplanar transition state.



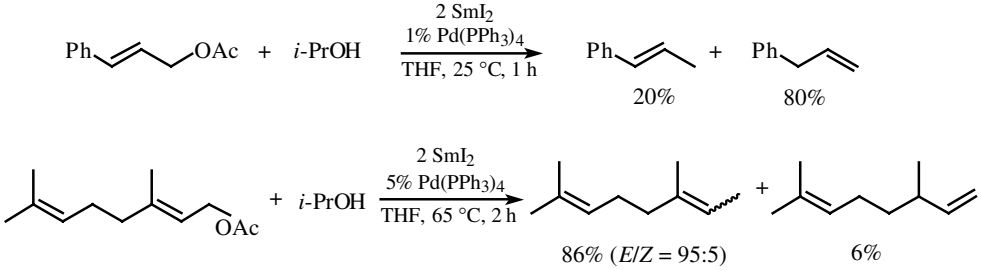
Scheme 11



Scheme 12

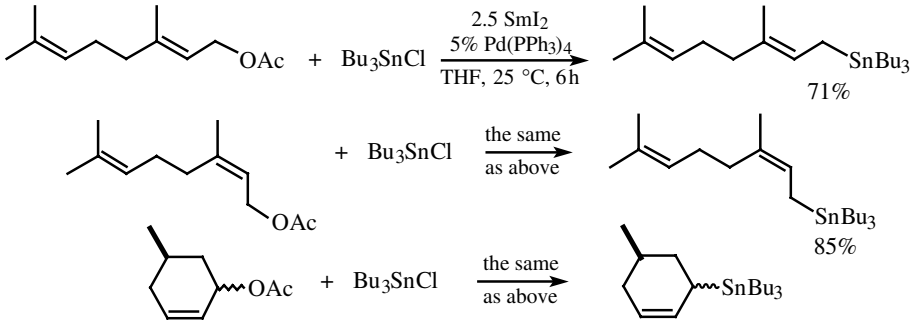
B.iv. Reduction with Samarium(II) Iodide

Allyl acetates are reduced to alkenes by the reaction with 2 equiv of SmI_2 and 1 equiv of isopropanol in the presence of 1–5 mol % of $Pd(PPh_3)_4$ (**Scheme 13**).[16] Samarium(II) iodide may serve as a reducing agent of π-allylpalladium intermediate to generate allyl anion species, which is protonated by isopropanol. Generally, mixtures of isomeric alkenes are formed. Geranyl and neryl acetates produce trisubstituted (*E*)- and (*Z*)-dienes, respectively, with more than 90% selectivity.



Scheme 13

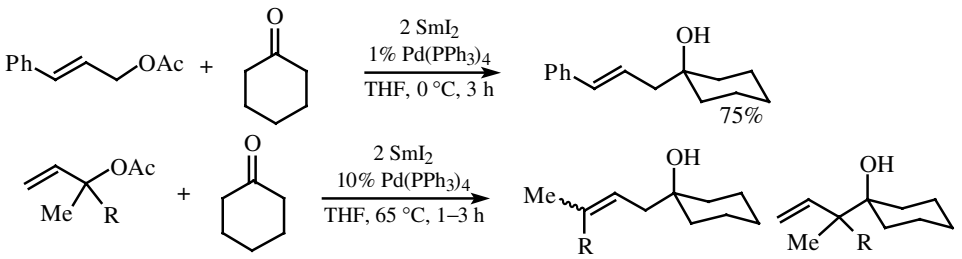
Under similar conditions, by using tributylstannyl chloride as an electrophile in place of isopropanol, allyl acetates are converted to allylstannanes in good yield (**Scheme 14**).[17] As compared with protonation, tributylstannylation is much more regio- and stereoselective. The stannylation of geranyl and neryl acetates proceeds without loss of the stereochemical integrity and selectively provides (*E*)- and (*Z*)-isomers, respectively, in good yield. On the other hand, the stannylation of cyclohexenyl derivatives accompanies the stereochemical isomerization; mixtures of *cis*- and *trans*-cyclohexenylstannanes in the same ratio (*cis*/*trans* = ca. 1:2) are obtained from the mixtures of *cis*-rich and *trans*-rich cyclohexenyl acetates (**Scheme 14**).[17]



Acetate (*cis*/*trans*)	Stannane (*cis*/*trans*)	Yield (%)
32:68	33:67	63
92:8	32:68	72

Scheme 14

The allylic nucleophiles, generated by reduction of π-allylpalladium intermediate with SmI_2, display characteristic regioselectivity for the reaction with ketones, reacting selectively at the allylic termini bearing the least number of substituents (**Scheme 15**).[18] This is in contrast to the regioselectivity observed for the $SnCl_2$-promoted reduction (**Schemes 7**, **9**, and **11**). Room temperature or even 0 °C is sufficient to promote the allylation with primary acetates, while a higher temperature is necessary to promote the allylation with secondary and tertiary acetates. The present method might not be applicable to the allylation of aldehydes, since SmI_2-promoted pinacol coupling of aldehydes might become a serious side reaction.



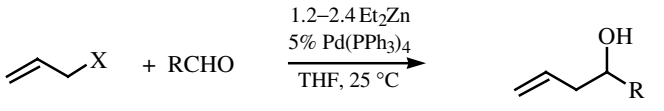
R = H	59%	0%
R = $PhCH_2CH_2$	52%	24%

Scheme 15

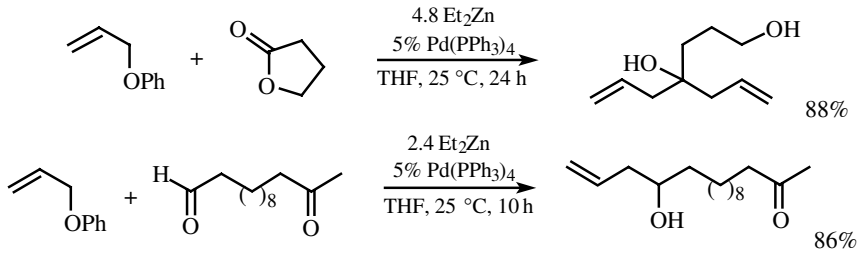
C. UMPOLUNG OF π-ALLYLPALLADIUM BY TRANSMETALLATION WITH ORGANOMETALS

C.i. Transmetallation with Diethylzinc

Allylic benzoate, acetate, carbonate, halide, and phenyl ether undergo allylation of aldehydes, ketones, and even esters at room temperature in the presence of 1.2–2.4 equiv of diethylzinc and 5 mol % of $Pd(PPh_3)_4$ (**Scheme 16**).[19]–[21] All the reactions are undertaken under Barbier conditions. Even in the presence of an excess amount of Et_2Zn, no ethylation of carbonyl compounds is observed. The allylation is highly chemoselective; 12-oxotridecanal selectively reacts at the aldehyde moiety. The relative reactivity of benzaldehyde, acetophenone, and methyl benzoate is roughly estimated to be 7000:100:<1 by competition experiments. This means that the allylation of ketone (1 M solution) may be performed in an ester solvent.



X = OCOPh	R = Ph (88%), *n*-C_8H_{17} (89%), PhCH=CH (97%)
X = OCOMe	R = Ph (69%)
X = OCO_2Me	R = Ph (58%)
X = Br	R = Ph (78%)
X = OPh	R = Ph (87%)

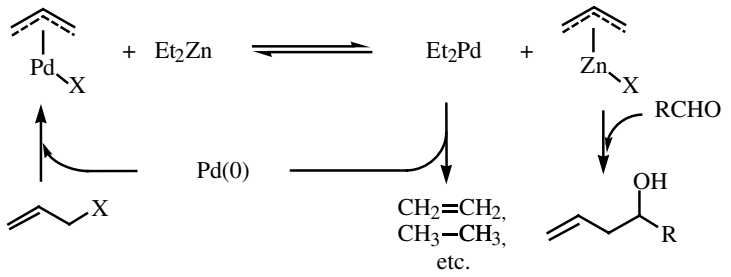


Scheme 16

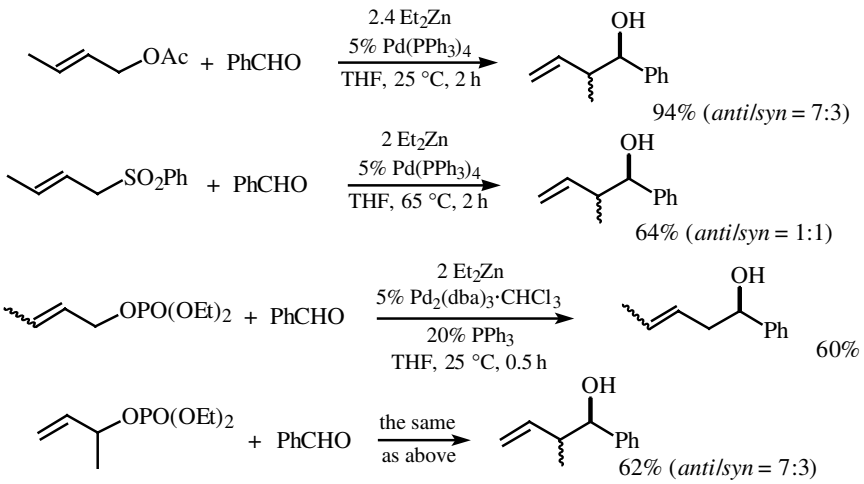
The most plausible mechanism for the diethylzinc-promoted umpolung reaction is shown in **Scheme 17**. Alkyl–allyl exchange between π-allylpalladium intermediate and diethylzinc may generate diethylpalladium and allylzinc. The allylzinc thus formed undergoes the allylation of carbonyl compound, and the diethylpalladium may undergo decomposition (reductive elimination and/or β-hydrogen elimination) to regenerate Pd(0) species and volatile organic compounds. Judging from the thermodynamic stability of the components, the equilibrium may lie far to the left. The equilibrium may be shifted to the right by decomposition of diethylpalladium and the reaction of allylzinc with electrophiles.

Allyl sulfones and phosphates also undergo the allylation of carbonyl compounds via umpolung of π-allylpalladium with diethylzinc (**Scheme 18**). Allyl sulfone is less reactive and the reaction is performed at higher temperature. α,α-Dimethylallyl sulfone reacts with benzaldehyde at the tertiary carbon, while γ,γ-dimethylallyl sulfone is unreactive and recovered under similar conditions.[22] Allyl phosphate shows an interesting regioselectivity

(**Scheme 18**).[23] Crotyl phosphate provides only the straight chain allylation product, and α-methylallyl phosphate yields selectively the branched allylation product. This is in contrast to the regioselectivity observed for other allylic substrates (halides, benzoates, carbonates, phenyl ethers), where both crotyl and α-methylallyl systems give rise to the same branched allylation products.



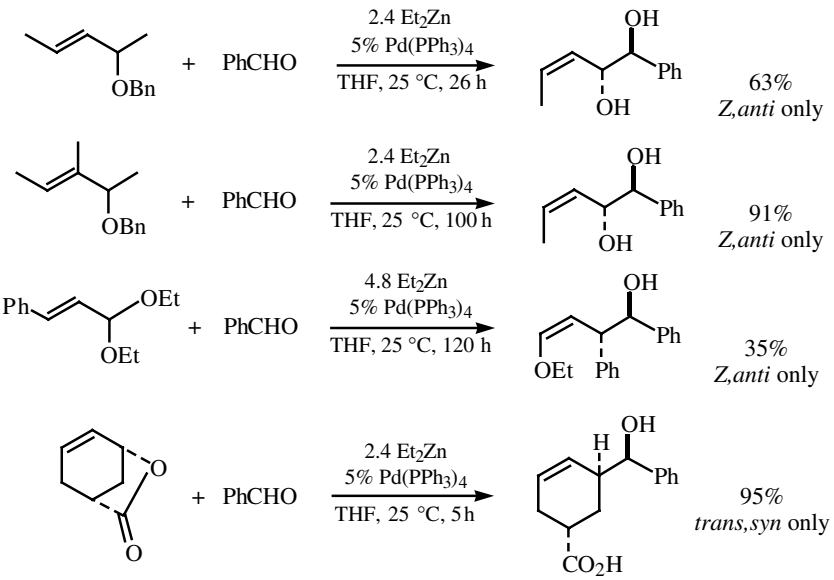
Scheme 17



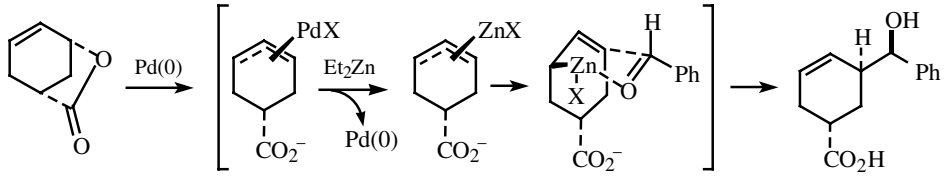
Scheme 18

Although 1- and 3-monosubstituted allylic benzoates (e.g., crotyl and α-methylallyl benzoates) generally show a low diastereoselectivity (**Scheme 18**), 1,3-disubstituted and 1,2,3-trisubstituted allyl benzoates display a remarkably high diastereoselectivity, providing (*Z*)-*anti*-isomers exclusively (**Scheme 19**).[24],[25] Cinnamaldehyde diethyl acetal undergoes umpolung and reacts with benzaldehyde regio- and stereoselectively to furnish (*Z*)-*anti*-isomer exclusively. The bicyclic lactone in **Scheme 19** provides *trans,syn*-adduct as a single diastereomer in quantitative yield.

A rationale for this stereochemical outcome is outlined in **Scheme 20**, which involves oxidative addition of the lactone to Pd(0) with inversion of configuration, transmetallation with diethylzinc with retention of configuration, and allylation of benzaldehyde through a six-membered chair-like transition state, placing the phenyl group in an equatorial position.[24] The generality of this reaction pattern is demonstrated with other cyclohexenyl and cyclopentenyl benzoate derivatives.



Scheme 19

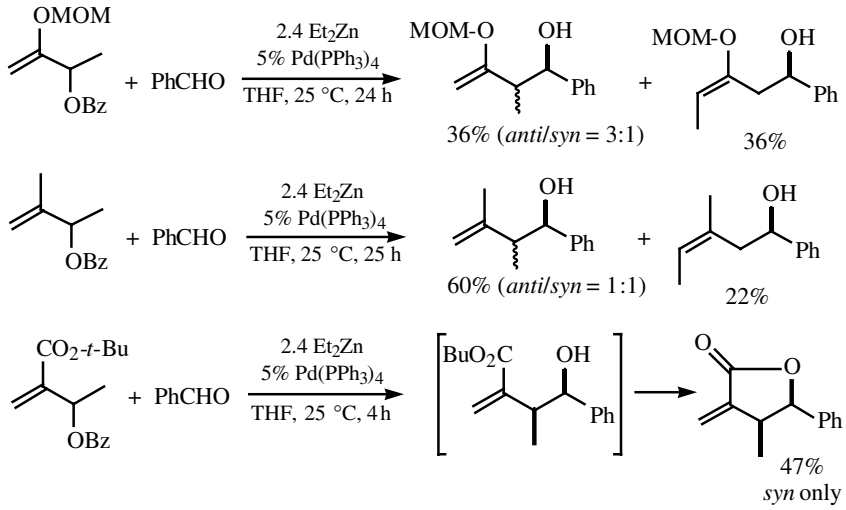


Scheme 20

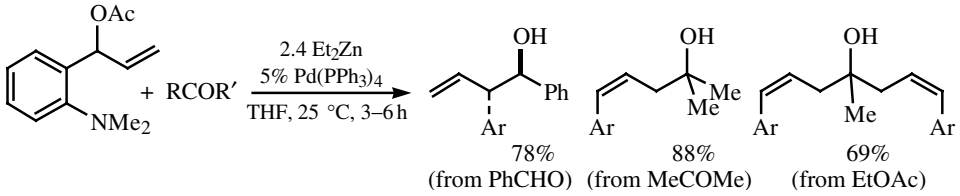
The regioselectivity of the allylation with 1,2- and 2,3-disubstituted allyl benzoates markedly depends on the electronic nature of the 2-substituents (**Scheme 21**).[25] When the substituent is electron attracting (CO_2-*t*-Bu), the regioselectivity is usual and a branched isomer is obtained exclusively, while when it is electron donating (e.g., OMOM=OCH_2OCH_3), in addition to the usual branched isomer, the straight chain isomer with *Z*-configuration is formed in a substantial amount.

In the presence of triphenylphosphine, the π-allylpalladium species generated from aniline derivatives are known to undergo cyclization to give *N*,*N*-dimethyl-1,2-dihydroquinolinium salt.[26] In the presence of diethylzinc and a carbonyl compound, on the other hand, this π-allylpalladium undergoes the allylation of carbonyl compound (**Scheme 22**).[27] The regioselectivity in this allylation exhibits an interesting dependence on the kind of carbonyl compounds. With benzaldehyde, allylation takes place at the most substituted allylic terminus, while with acetone and ethyl acetate, allylation proceeds at the least substituted allylic terminus to provide straight chain products with *Z*-geometry. The formation of the double allylation product from ethyl acetate in the same sense of regiochemistry and stereochemistry attests to the high regio- and stereoselectivity of the present allylation.

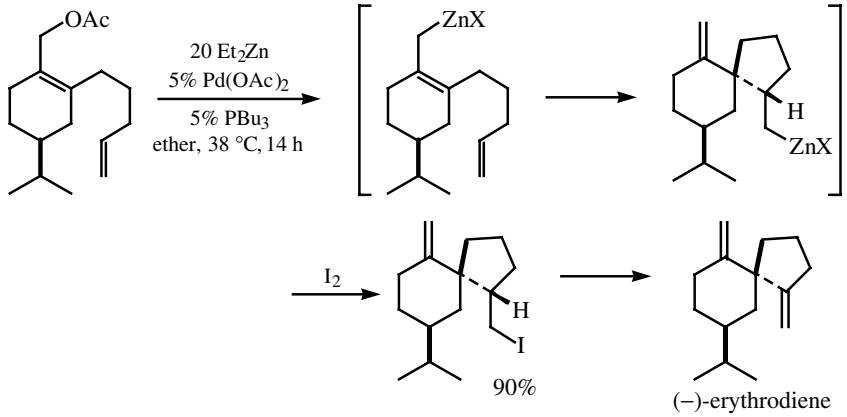
The Et_2Zn-promoted umpolung methodology has been applied to the total synthesis of (−)-erythrodiene, a marine sesquiterpenoid (**Scheme 23**).[28] Thus, the



Scheme 21



Scheme 22

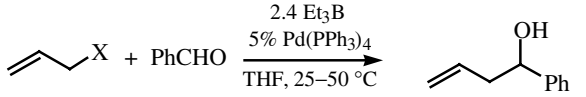


Scheme 23

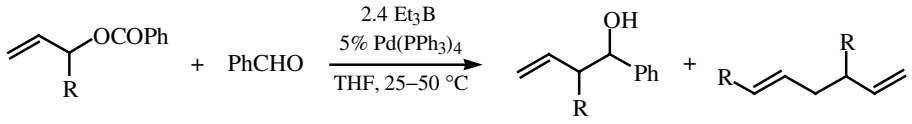
allylzinc species generated from the optically active allylic acetate undergoes zinc-ene reaction to furnish cyclopentylmethylzinc, which is derived to iodide with excellent diastereoselectivity (95:5) upon exposure to iodine. A large excess of diethylzinc is applied, in order to shift the equilibrium (**Scheme 17**) to the right. With 5 mol % of $Pd(PPh_3)_4$, the reaction is slow and the isolated yield of the iodide falls to 52% (80% conversion).

C.ii. Transmetallation with Triethylborane

Triethylborane promotes umpolung of π-allylpalladium generated *in situ* from allyl benzoate and a catalytic amount of $Pd(PPh_3)_4$ in THF and provides the allylation product of aldehydes in moderate to good yield (**Scheme 24**).[29] Triethylborane and tributylborane work similarly well, but triphenylborane and tetrabutylstannane fail to promote the allylation. As the allylic substrates, allyl benzoate, allyl phenyl ether, and even allyl benzyl ether can be utilized with similar efficiency. In the light of the fact that allyl benzyl ether is a poor substrate for the generation of π-allylpalladium, in this reaction Et_3B might serve as a Lewis acid to acitvate the ether functionality as a leaving group. Interestingly, however, allyl chloride and allyl bromide are unreactive and recovered under the conditions. Lithium chloride (1 equiv) inhibits the reaction of allyl benzoate, and the expected homoallyl alcohol is produced in a negligibly small amount. The regio- and stereoselectivities are quite similar to that observed for the diethylzinc-promoted allylation (**Scheme 18**). The reaction may proceed by the mechanism similar to that proposed for the reaction with diethylzinc (**Scheme 17**).



X = $PhCO_2$ (68%), PhO (59%), $PhCH_2O$ (47%), Br (0%)



R		Isolated Yield (%)
Ph	77 (*anti*/*syn* = 2.3:1)	6
Me	60 (*anti*/*syn* = 2.2:1)	—
$PhCH_2CH_2$	76 (*anti*/*syn* = 1.6:1)	21

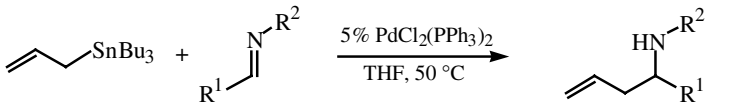
Scheme 24

C.iii. Transmetallation with Allylstannane

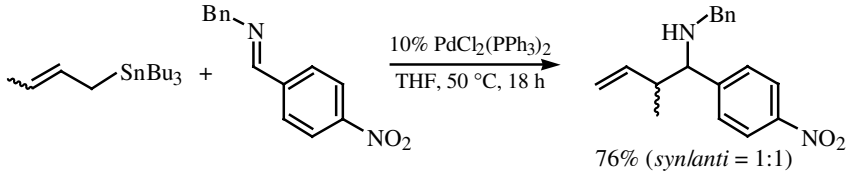
In the presence of 5 mol % of bis(triphenylphosphine)palladium(II) chloride, allyl(tributyl)stannane reacts with a variety of aldimines to provide homoallylamines in good yield (**Scheme 25**).[30] Crotyl(tributyl)stannane reacts regioselectively to furnish the branched homoallylamine in good yield. The stereoselectivity, however, is low and a 1:1 mixture of *syn*- and *anti*-isomer is obtained irrespective of the stereochemical purity of the starting crotylstannane.

Similar allylation of benzaldehyde with allylstannane takes place in the presence of 10 mol % of $PdCl_2(PPh_3)_2$; however, the yield is only moderate. For the allylation of benzaldehyde and other aromatic and aliphatic aldehydes, $PtCl_2(PPh_3)_2$ is a much superior catalyst to $PdCl_2(PPh_3)_2$ (**Scheme 26**).[31]

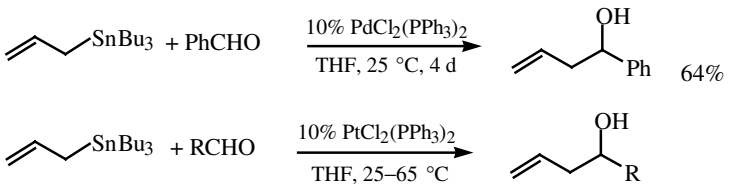
The palladium-catalyzed allylation with allylstannane displays an interesting chemoselectivity (**Scheme 27**).[30] When a 1:1:1 mixture of allylstannane, an aldehyde, and an aldimime is exposed to 10 mol % of π-allylpalladium chloride dimer, the allylation of the aldimime takes place exclusively, the aldehyde being left intact. On the other hand, when the same mixture is exposed to 4 equiv of $BF_3{\cdot}OEt_2$, the allylation of the aldehyde is the



R^1	R^2	Yield (%)
4-$O_2NC_6H_4$	4-$MeO_2CC_6H_4$	77
4-$O_2NC_6H_4$	Bn	98
PhCH=CH	4-$MeO_2CC_6H_4$	90
c-C_6H_{11}	4-$MeOC_6H_4$	72

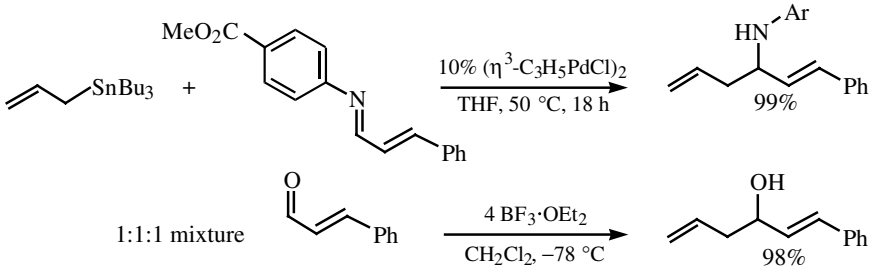


Scheme 25



R = Ph (90%), 4-BrC_6H_4 (83%), 4-$O_2NC_6H_4$ (70%), *c*-C_6H_{11} (99%), $PhCH_2CH_2$ (58%)

Scheme 26

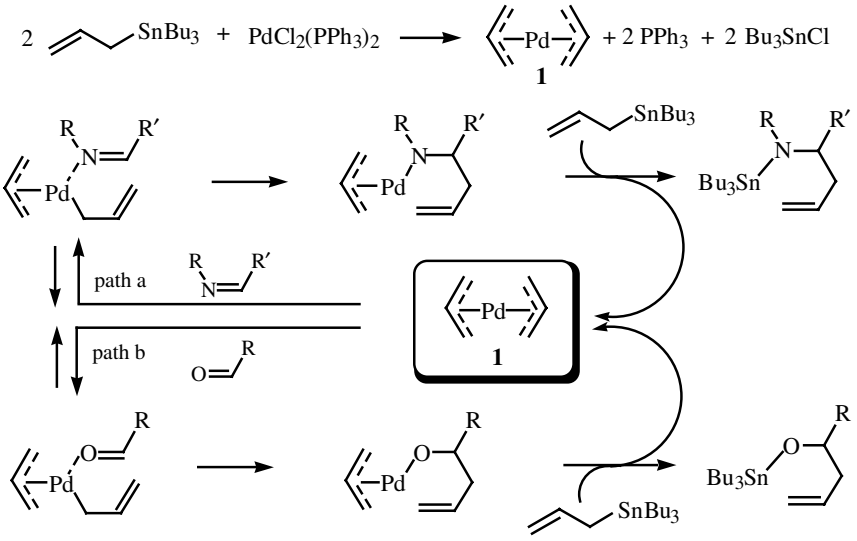


Scheme 27

exclusive reaction observed. The chemoselectivity is general and very high, ranging from 90:10 to >99:1 both for the Pd-catalyzed allylation of aldimines and for the Lewis acid ($BF_3{\cdot}OEt_2$, $TiCl_4$) promoted allylation of aldehydes.

A proposed catalytic cycle of the present allylation with allyl(tributyl)stannanes (**Schemes 25**–**27**) is outlined in **Scheme 28**.[32] The formation of bis-π-allylpalladium(II) (**1**) from $PdCl_2(PPh_3)_2$ and allyl(tributyl)stannane, which involves formation of π-allylpalladium chloride dimer as an intermediate, is confirmed by an NMR spectroscopic method. Coordination of aldimine to **1** (path a) may cause the change of bis-π-allyl structure of **1** to π-allyl-σ-allyl structure and the σ-allyl moiety of the complex attacks the aldimine ligand to form π-allyl(homoallylamino)palladium(II), which undergoes transmetallation with

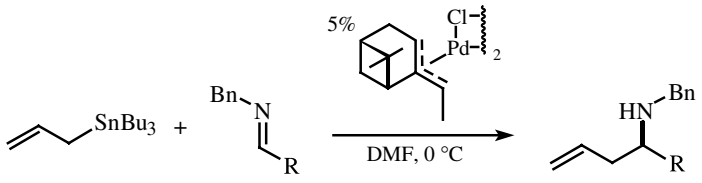
allyl(tributyl)stannane to give **1** and homoallylaminostannane. The allylation of aldehyde may proceed in a similar way (path b).



Scheme 28

Compared with aldehyde, the corresponding aldimine is less reactive toward nucleophilic addition; however, aldimine is able to coordinate to transition metals more strongly. This latter property of aldimine may be more important than the former in the present reaction, and the allylation of aldimine proceeds much easier than the allylation of aldehyde. In order to achieve the Lewis acid promoted allylation of aldehydes and aldimines with allylstannane, an excess amount of Lewis acid (>2 equiv) is required. Under such conditions, both aldehyde and aldimine may be equally activated toward allylation, and the allylation of aldehyde takes place selectively.

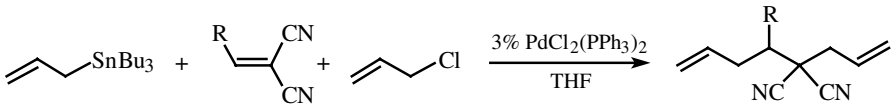
Asymmetric allylation of aldimine providing chiral homoallylamines is accomplished by using 5 mol % of π-allylpalladium chloride dimer derived from (*1S*)-β-(−)pinene (**Scheme 29**).[33] The pinene moiety serves not only as a chiral auxiliary but also as a dummy π-allyl group of unsymmetrical bis-π-allylpalladium intermediate. The asym-metric induction is successful for aldimines derived from alkylamines (benzylamine, *p*-methoxybenzylamine, and isopropylamine); however, no asymmetric induction is observed for aldimines of aniline.



R = Ph (62% isolated yield, 81% ee), 4-$MeOC_6H_4$(48%, 78%), PhCH=CH (68%, 61%), *c*-C_6H_{11} (44%, 40%)

Scheme 29

The amphiphilic nature of bis-π-allylpalladium, the first allyl group of it acting as a–nucleophilic allylating agent and the second one as an electrophilic allylating agent, is demonstrated by the double allylation reaction of alkylidenemalononitrile (**Scheme 30**).[34] Thus, a mixture of alkylidenemalononitrile (1 equiv), allylstannane [1.2 equiv, which generates **1** both from $PdCl_2(PPh_3)_2$ (**Scheme 28**) and from π-allylpalladium chloride dimer], allyl chloride [1.2 equiv, which supplies π-allylpalladium chloride dimer by oxidative addition to Pd(0)], and $PdCl_2(PPh_3)_2$ [or $Pd(PPh_3)_4$, 3 mol %] in THF provides the double allylation product in excellent yield. β-Arylacrylonitriles possessing electron-withdrawing substituent (CO_2Et, SO_2Ph, *p*-nitrophenyl) at the α-position undergo similar double allylation, although the yields in these cases are around 50–60%.



R = Ph (91%), 2-furyl (91%), 4-$MeOC_6H_4$ (81%), *i*-Pr (82%)

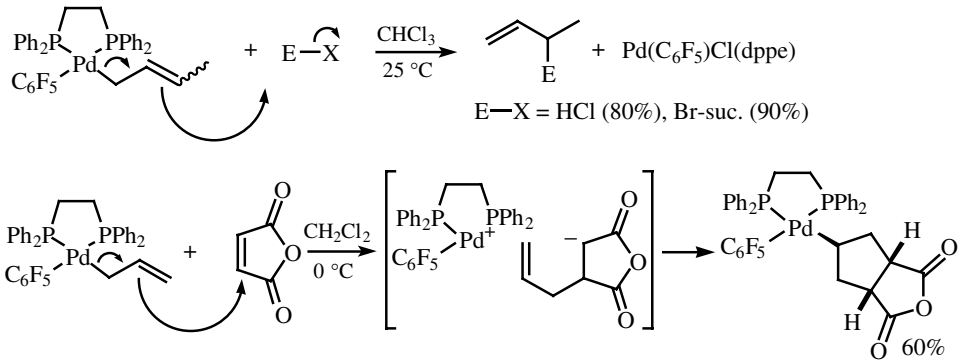
Scheme 30

D. NUCLEOPHILIC REACTION OF η^1-ALLYLPALLADIUM

η^1-Allyl(aryl)palladium(II) complexes display a nucleophilic character and readily react with a variety of electrophiles (**Scheme 31**).[35],[36] The selective formation of 1-butene and 3-bromo-1-butene from η^1-crotylpalladium(II) upon exposure to HCl and *N*-bromosuccinimide, respectively, suggests that these electrophiles directly attack at the γ-position of the η^1-crotyl group. The reaction with CCl_4 in CH_2Cl_2, which may proceed via a radical chain S_H2' pathway, also shows similar regioselectivity and provides 3-(trichloromethyl)-1-butene in 70% yield (E = CCl_3).

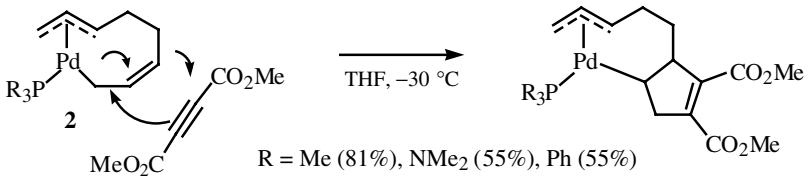
η^1-Allyl(perfluorophenyl)palladium(II) complex readily reacts with maleic anhydride at 0 °C and gives bicyclic anhydride complex in 60% yield (**Scheme 31**).[36] The reaction may proceed via nucleophilic conjugate addition of the allylic moiety of the η^1 species.

A similar annulation reaction is observed for bis(allyl)palladium(II) complex **2**, which is derived from the dimerization of butadiene and contains both an η^1- and η^3-allyl unit



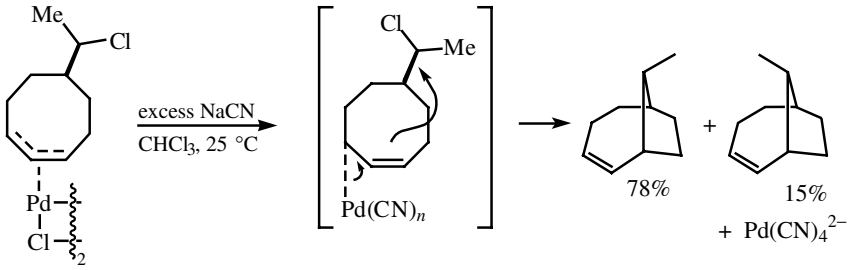
Scheme 31

(**Scheme 32**).[37] They readily react with dimethyl acetylenedicarboxylate at −30 °C to give π-allyl(3-cyclopentenyl)palladium(II) complexes in good yield. The observation that **2** does not react with alkylacetylenes and that it produces intractable mixtures in the reaction with phenylacetylene is consistent with the mechanism shown in **Scheme 32**.



Scheme 32

Upon exposure to an excess amount of NaCN at room temperature, bis(μ-chloro)bis[6-(α-chloroethyl)-η^3-cyclooctenyl]dipalladium(II) readily liberates a mixture of *syn*- and *anti*-9-methyl-bicyclo[4.2.1]-2-nones in good combined yield (**Scheme 33**).[38] Coordination of cyanide ion to Pd(II) may cause a structural change of the complex from η^3 to η^1, of which the η^1-allylic form may undergo an intramolecular nucleophilic substitution reaction.

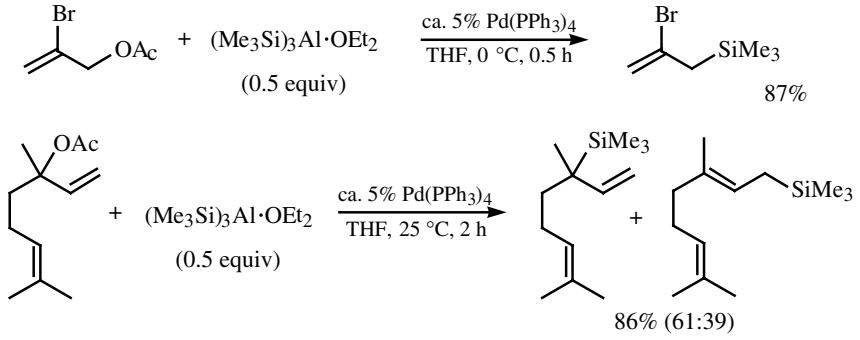


Scheme 33

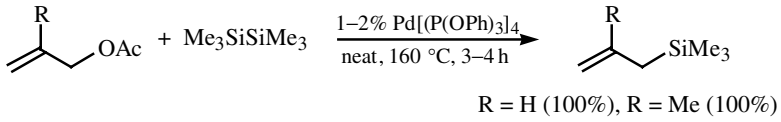
E. UMPOLUNG BY TRANSFORMATION OF ALLYL ESTERS TO ALLYLSILANES, ALLYLBORANES, AND ALLYLSTANNANES

Allyl acetates are readily converted to allylsilanes in good yields, when they are reacted with 0.5 equiv of tris(trimethylsilyl)aluminum etherate and 4–6 mol % of $Pd(PPh_3)_4$ in THF at 0–25 °C (**Scheme 34**).[39] For the reaction with unsymmetrical allyl acetates, the trimethylsilyl group tends to attack the more substituted carbon of the allylic system under Pd-catalyzed conditions. With 10 mol % of $Mo(CO)_6$ (toluene reflux for 2.5 h), on the other hand, the trimethylsilyl group selectively attacks the less substituted carbon as exemplified by the exclusive formation of geranyl(trimethyl)silane in 65% yield. Under the Pd-catalyzed conditions, many functional groups of synthetic importance (e.g., vinyl bromide, acetals, esters, and enones) remain intact.

Allylic acetates react with hexamethyldisilane in the presence of 1–2 mol % of $Pd[P(OPh)_3]_4$ and provide allylsilanes in quantitative yield (**Scheme 35**).[40] Owing to the rather harsh reaction conditions (160–180 °C), the reaction may be limited to the preparation of simple allylsilanes. Double bond isomerization of allylsilanes to vinylsilanes is observed under some conditions.

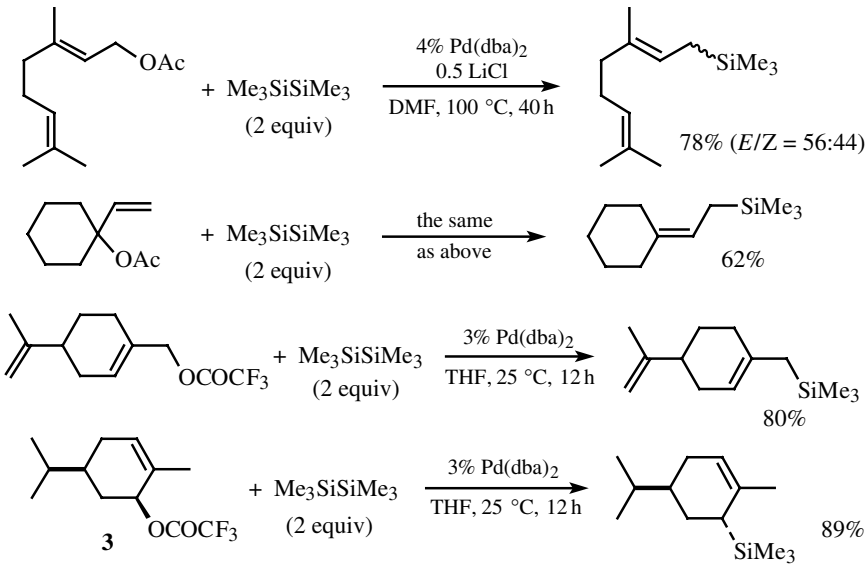


Scheme 34



Scheme 35

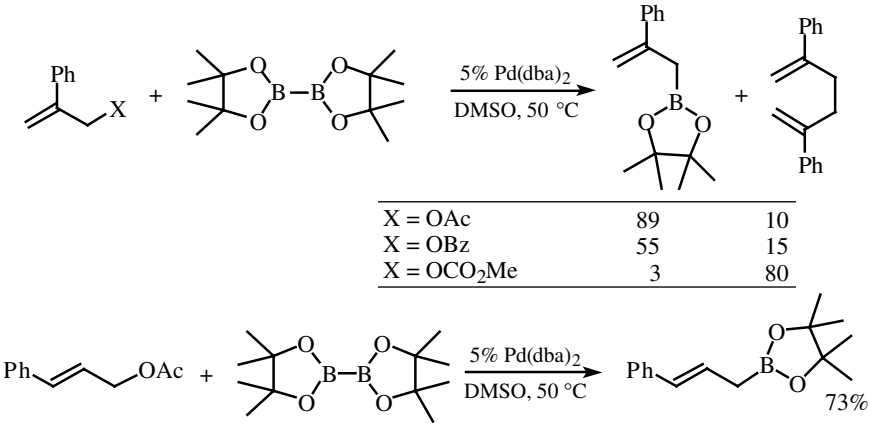
Similar trimethylsilylation of allyl acetates with hexamethyldisilane (and other disilanes such as 1,2-diphenyltetramethydisilane) proceed under much milder reaction conditions, when $Pd(dba)_2$ is used as the catalyst (**Scheme 36**).[41] In this reaction, 0.5 equiv of LiCl is indispensable. The reaction shows high regioselectivity; trimethylsilyl group is delivered to the least substituted allylic termini. Allyl triflates are more reactive and even undergo the silylation at room temperature. The corresponding acetates of the two bottom examples in **Scheme 36** are unreactive and provide the silylation products in less than 10% yield under optimized conditions. For the silylation of allyl triflates, LiCl is not necessary. *cis*-Cyclohexenyl triflate (**3**) provides *trans*-cyclohexenylsilane exclusively in good yield. This



Scheme 36

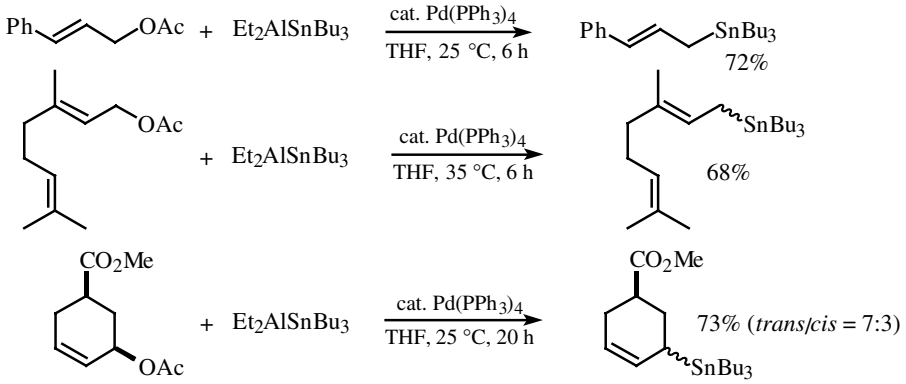
suggests that the reaction proceeds via (i) oxidative addition of **3** to Pd(0) with inversion of configuration at the allylic stereocenter, (ii) trimethylsilyl group transfer to the palladium metal of the π-allylpalladium(II) thus formed, and (iii) reductive elimination of allylsilane with retention of configuration of the allylic moiety.

The cross-coupling reaction of bis(pinacolato)diboron with allyl acetates provides the pinacol esters of allylboronic acids in high yield (**Scheme 37**).[42] The reaction is effectively catalyzed by $Pd(dba)_2$ in DMSO at 50 °C. The reaction more or less accompanies the formation of biallyl, the amount of which markedly depends on the kind of leaving group of the allylic substrates. (*E*)- and (*Z*)-Cinnamyl acetate and α-phenylallyl acetate all provide *trans*-cinnamylboronic acid ester selectively and in almost the same yield, which suggests that the reaction proceeds via π-allylpalladium as a common intermediate.



Scheme 37

Nucleophilic substitution of allylic acetates with tributylstannyl anion is catalyzed by $Pd(PPh_3)_4$ and the corresponding allylstannanes are obtained in good yield (**Scheme 38**).[43],[44] (Tributylstannyl)diethylaluminum reacts with a very high degree of regioselectivity for the less substituted carbon of the allylic system. The crude reaction mixture, after filtration through silica gel, may successfully be used for the allylation of aldehydes in the presence of a stoichiometric amount of Lewis acid (e.g., $BF_3{\cdot}OEt_2$).

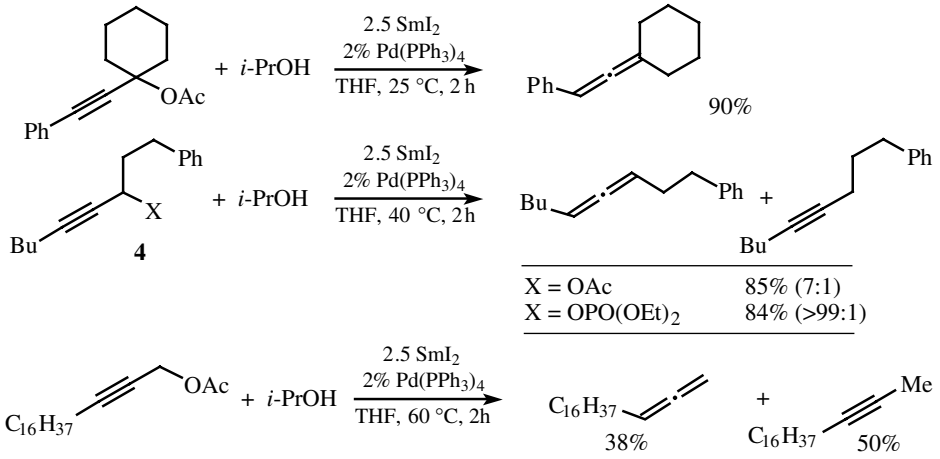


Scheme 38

F. UMPOLUNG OF ALLENYLPALLADIUM (OR PROPARGYLPALLADIUM)

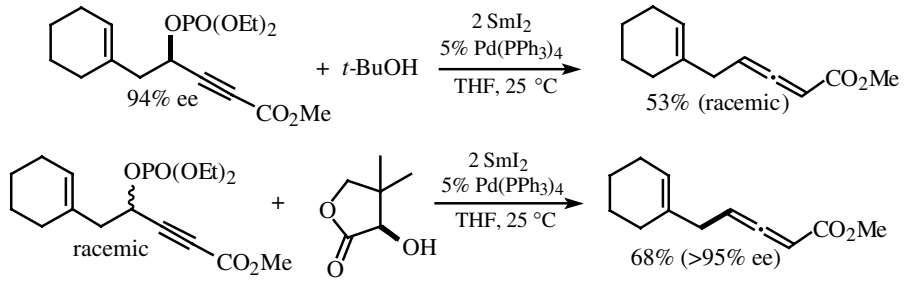
F.i. Reduction with SmI_2

Propargyl acetates are reduced to allenes and alkynes when exposed to 2.5 equiv of SmI_2, 1 equiv of isopropanol, and 2–5 mol % of $Pd(PPh_3)_4$ (**Scheme 39**).[45] The allene/alkyne ratio depends on the structure of the propargyl system, the leaving group, and also on the kind of proton source. Generally, secondary and tertiary propargyl acetates provide allenes selectively, while primary propargyl acetates provide alkynes as the major products. Propargyl phosphates tend to give allenes in a higher proportion than the corresponding acetates. For example, 1-phenyl-4-nonyn-3-yl acetate (**4**) provides a mixture of the corresponding allene and alkyne in a ratio of 7:1, while the corresponding phosphate gives alkyne exclusively.[45],[46] Depending on the kind of the proton source, **4** provides the allene/alkyne mixture in different ratios: 1:1.5 (H_2O), 2:1 (MeOH), 7:1 (*i*-PrOH), 9:1 (PhOH), 15:1 (*t*-BuOH), 20:1 (2,4-dimethyl-3-pentanol).



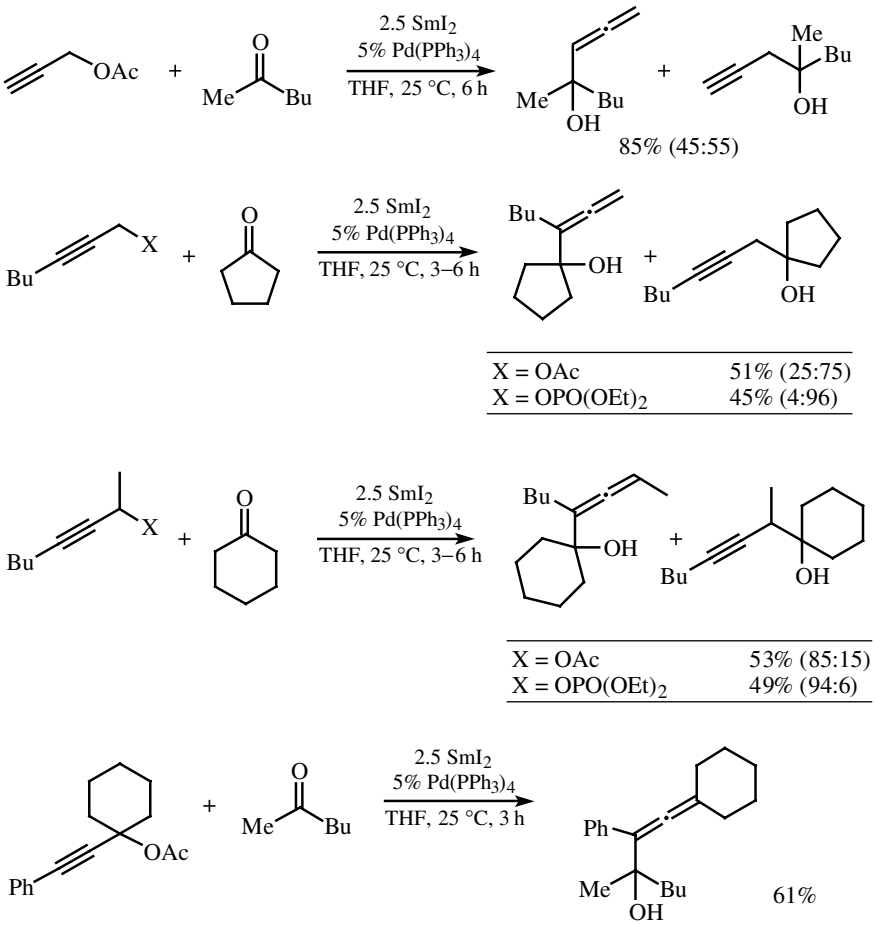
Scheme 39

The chirality of the propargyl phosphate is completely lost during the propargyl phosphate–allene transformation (**Scheme 40**).[47] Racemic propargyl phosphate is converted to an optically active allene with high ee via dynamic kinetic protonation with chiral alcohols.



Scheme 40

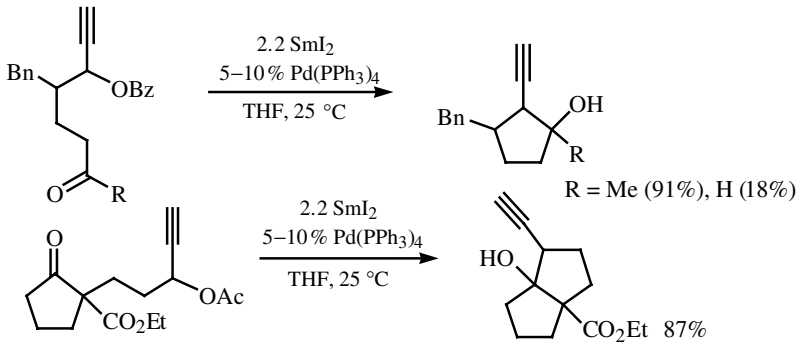
Propargyl acetate undergoes the allenylation and/or propargylation of ketones in moderate to good yield, when it is exposed to 2.5 equiv of SmI_2, 1 equiv of ketone, and 5 mol % of $Pd(PPh_3)_4$ in THF (**Scheme 41**).[48] The reaction may proceed via reduction of *in situ* generated allenyl and/or propargylpalladium with SmI_2. Primary acetates provide mixtures of allenylation and propargylation products in almost equal amount. Secondary and tertiary propargyl acetates tend to provide the allenylation products with high selectivity. This tendency is more apparent for the reaction with propargyl phosphates.[46]



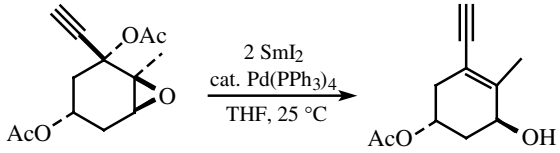
Scheme 41

The present umpolung methodology has proved to be applicable to an intramolecular reaction (**Scheme 42**).[49] The reaction with keto carbonyl groups gives the expected 2-alkynylcyclopentanols and 2-alkynylcyclohexanols in good yield. However, the intramolecular cyclization with aldehyde groups is only marginally successful, owing to side reactions (pinacol coupling).

Epoxide ring opening by nucleophilic displacement with propargyl anion is utilized for the preparation of the A ring synthon of 1-α-hydroxyvitamin D (**Scheme 43**).[50]



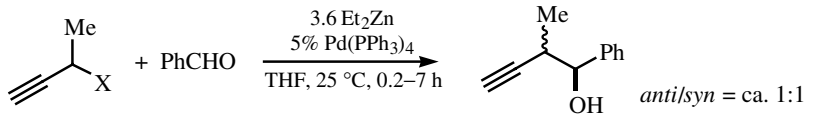
Scheme 42

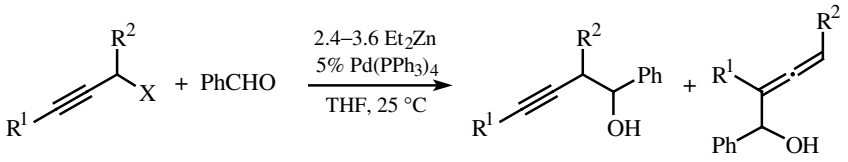


Scheme 43

F.ii. Transmetallation with Diethylzinc

The propargyl system undergoes umpolung under conditions similar to those applied to the umpolung of allylic system (**Scheme 44**).[51] The parent propargyl and 1-substituted propargyl substrates, bearing OBz, OTs, OCO_2Me, or Br as a leaving group, provide homopropargyl alcohols in acceptable yield. The diastereoselectivity is very poor and a mixture of *anti*- and *syn*-isomers is produced in almost equal amount. 1,3-Disubstituted



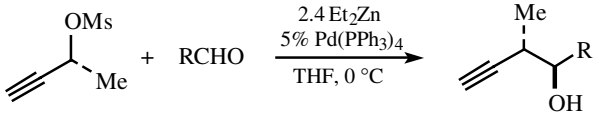


R^1	R^2	Isolated Yield (%)	
H	H	57	0
Me	H	22	56
Ph	H	57	12
Me_3Si	H	80	0
Me	Me	60	0

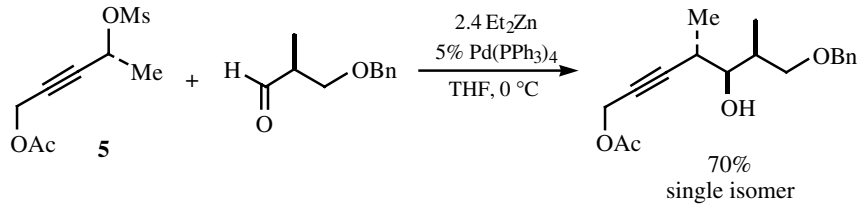
Scheme 44

propargyl benzoates ($R^1 \neq H$, $R^2 \neq H$) also provide the corresponding homopropargyl alcohols selectively; however, 3-monosubstituted propargyl benzoates ($R^1 \neq H$, $R^2 = H$) tend to provide mixtures of propargylation and allenylation products. The homopropargyl alcohol/allenyl alcohol ratio markedly depends on the kind of substituent, ranging from 1:2.5 (R^1 = Me) to 100:0 ($R^1 = Me_3Si$).

The propargylation with 3-butyn-2-yl mesylate under similar conditions to those established in **Scheme 44** proceeds with inversion of configuration at the proparyl stereocenter and the enantiomeric purity of the starting methylate is tranferred into the product almost perfectly (**Scheme 45**).[52] The reaction with sterically demanding aldehydes shows high *anti*-selectivity. The combination of (*R*)-mesylate (**5**) and (*S*)-aldehyde furnishes *anti*-adduct exclusively with complete chirality transfer and with excellent diastereoface selectivity.

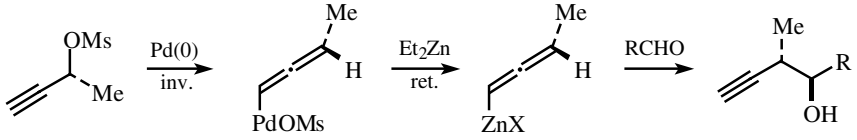


R	Yield (%)	*anti*/*syn*	% ee of *anti*-Isomer
c-C_6H_{11}	85	95:5	95
n-C_6H_{13}	70	88:12	90
(*E*)-BuCH=CH	71	77:23	88
1-Octynyl	60	68:32	90



Scheme 45

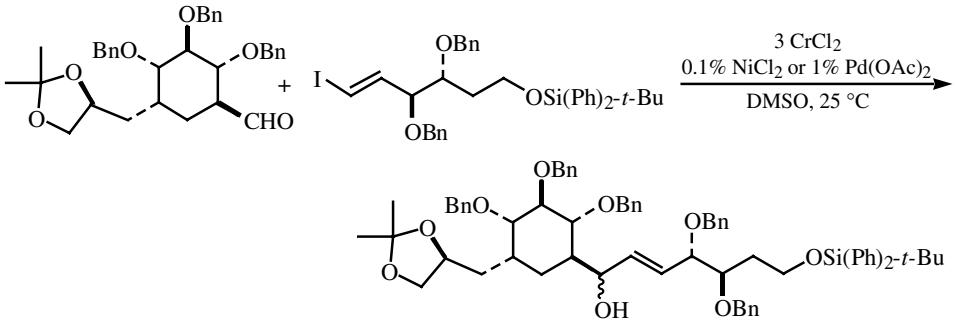
The stereochemical outcome may be rationalized as the result of oxidative addition of mesylate to Pd(0) with inversion of configuration, allenyl–ethyl exchange with retention of configuration, and addition of aldehyde to the allenylzinc thus formed via *syn* addition (a cyclic transition state) (**Scheme 46**). The result of excellent chirality transfer suggests that both allenylpalladium and allenylzinc are configurationally stable and do not isomerize (racemize) under the reaction conditions.[52] The reaction is utilized as the key step for the total synthesis of (+)-discodermolide.[53]



Scheme 46

G. UMPOLUNG OF VINYLPALLADIUM BY TRANSMETALLATION TO CHROMIUM(III)

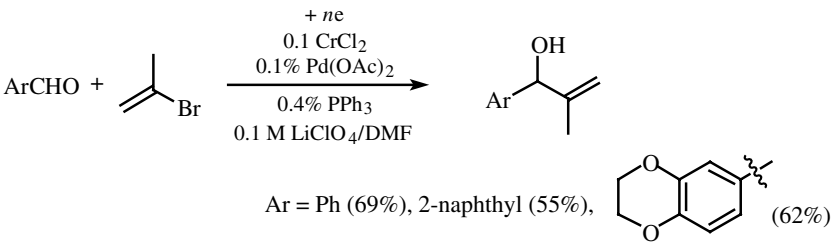
Aldehyde-selective Grignard-type addition of olefinic iodides and bromides with $CrCl_2$ under Barbier conditions has been reported by Nozaki et al.[54] Later, it was proved that this reaction does not proceed with pure $CrCl_2$, and a trace amount of nickel or palladium, these metals having been present as a contaminant of $CrCl_2$ in the original work, is necessary to promote the reaction (**Scheme 47**).[55] The active nucleophilic species is proposed as vinylchromium(III), which is generated *in situ* by oxidative addition of vinyl halide to Pd(0) or Ni(0) and transmetallation of the vinyl group of the vinylpalladium(II) or vinylnickel(II) thus formed to Cr(III). Two moles of Cr(II) is required to reduce Pd(II) or Ni(II) to Pd(0) or Ni(0), respectively. The reaction is remarkable for its chemoselectivity and compatibile with esters (methyl, ethyl), amides, nitriles, ketones, acyls (acetate, benzoate), acetals, ketals, ethers (benzyl, *p*-methoxybenzyl), and silyl ethers [*t*-Bu(Me)$_2$Si, *t*-Bu(Ph)$_2$Si] (**Scheme 47**).[55]



Scheme 47

The alkenylation of aldehydes with alkenyl triflates, however, is only successful with $NiCl_2$ as the catalyst (2 mol % of $NiCl_2$, 4 equiv of $CrCl_2$ in DMF); $PdCl_2$ and other transition metals ($MnCl_2$, $FeCl_3$, $CoCl_2$, CuCl) are all ineffective.[56]

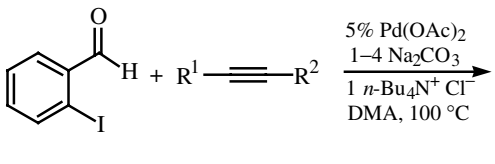
Under electrochemical reduction conditions, 2-propenyl bromide reacts with benzaldehyde in the presence of a catalytic amount of $CrCl_2$ and $Pd(OAc)_2$ and provides α-isopropenylbenzyl alcohols in moderate yield (**Scheme 48**).[57] Phenyl bromide and iodide show similar reactivity and provide benzhydrol derivatives in comparable yield.



Scheme 48

H. INTRAMOLECULAR NUCLEOPHILIC REACTION OF VINYLPALLADIUM

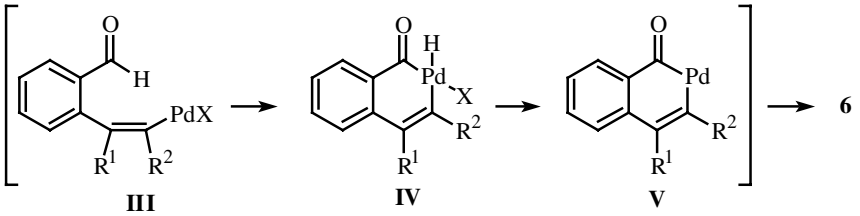
The following examples suggest that, at least for the intramolecular reactions, vinylpalladium(II) is able to undergo nucleophilic addition to carbonyl derivatives (**Scheme 49**).[58],[59] *o*-Bromobenzaldehyde and *o*-iodobenzaldehyde react with disubstituted alkynes in the presence of 5 mol % of $Pd(OAc)_2$, 1–4 equiv of Na_2CO_3, and 1 equiv of tetra-*n*-butylammonium chloride in dimethylacetamide (DMA) to provide 2,3-disubstituted indenones in moderate yields.[58] This annulation is highly regioselective for alkynes containing a sterically bulky group as one of the substituents and provides indenones with the bulky groups at the 2-position. Less hindered alkynes, such as 1-phenyl-1-propyne, produce a 1:1 mixture of regioisomers. 3-Alkyl derivatives tend to isomerize to the β,γ-unsaturated isomers (e.g., **8**) probably owing to the anti-aromatic nature of indenone.[58]



6 + **7**

R^1	R^2	**6**	**7**
Me	Ph	31	31
Me	*t*-Bu	26[a]	
Ph	*t*-Bu	81	
Ph	$SiMe_3$	42	
Ph	$C(Me)_2OH$	58	
t-BuCC	*t*-Bu	58	

[a] 2-*t*-Butyl-3-methyleneindanone **8** in 26%

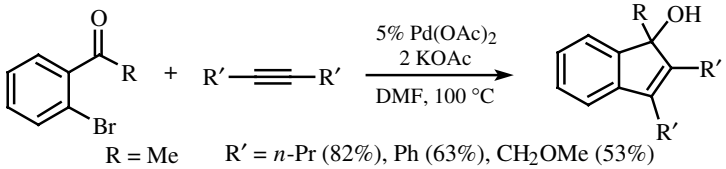


Scheme 49

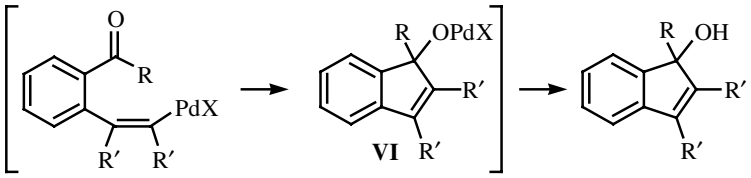
Two mechanisms are proposed. One involves oxidative addition of the aldehdye C—H bond to vinylpalladium(II) (**III**) to form acylpalladium(IV) intermediate (**IV**), which loses HX and undergoes reductive elimination to furnish **6** and Pd(0). The other involves nucleophilic addition of vinylpalladium(II) to carbonyl to give alkoxypalladium(II) [like **VI** (R = H), **Scheme 50**], followed by β-hydrogen elimination to give **6** and Pd(0).[58]

A similar annulation reaction proceeds for the combination of *o*-bromoacetophenone (or *o*-bromobenzophenone) and internal acetylenes in the presence of 5 mol % of $Pd(OAc)_2$ and 2 equiv of KOAc in DMF (**Scheme 50**).[60] In this reaction, no β-hydrogen is available in the intermediate **VI** and indenols are produced. In some cases, slight

modification of conditions (with 10 mol % of PPh_3 or with 10 mol % of PPh_3 and 10 equiv of EtOH) is effective to give better yields. The reaction is proposed to proceed via an intramolecular nucleophilic addition of vinylpalladium(II) to the keto carbonyl. The reactivity order of *o*-bromobenzophenone derivatives, R = 4-$CF_3C_6H_4$ > Ph > 4-$MeOC_6H_4$, is consistent with the proposed mechanism.

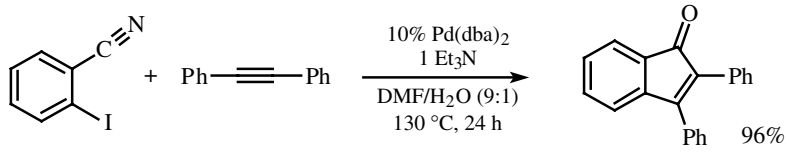


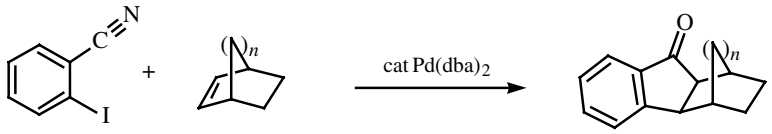
R = Me R′ = *n*-Pr (82%), Ph (63%), CH_2OMe (53%)
R = Ph R′ = *n*-Pr (86%), Ph (75%), CH_2OMe (64%)



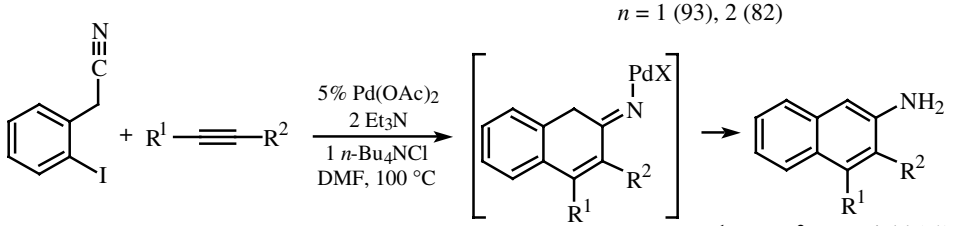
Scheme 50

Similar Pd-catalyzed cyclizations have been reported for the reaction of *o*-–iodobenzonitrile with diphenylacetylene (**Scheme 51**).[61] In this reaction also a vinylpalladium(II) intermediate may undergo nucleophilic addition to the nitrile to provide indenoneiminopalladium, which undergoes hydrolysis under the reaction conditions and provides indenone as the final product.





n = 1 (93), 2 (82)



R^1	R^2	yield (%)
Ph	Ph	83
Me	Ph	65
Me	*t*-Bu	75

Scheme 51

The annulation reaction with bicyclo[2.2.1]hept-2-ene and bicyclo[2.2.2]oct-2-ene suggests that even alkylpalladium(II) intramolecularly behaves like a nucleophile toward the nitrile group.

(*o*-Iodophenyl)acetonitrile, under somewhat different reaction conditions, reacts with internal acetylenes to furnish β-naphthylamines in good yield (**Scheme 51**).[61] The reaction displays high regioselectivity; unsymmetrical acetylenes give exclusively products with the bulkier substituents at the 3-position of β-naphthylamine.

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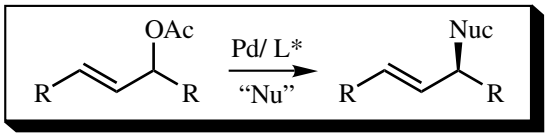

V.2.4 Palladium-Catalyzed Asymmetric Allylation and Related Reactions

LARA ACEMOGLU and JONATHAN M. J. WILLIAMS

A. INTRODUCTION

Asymmetric variants of the Pd-catalyzed allylic substitution reaction have enjoyed considerable attention since the first stoichiometric example reported in 1973.[1] The reaction has been the subject of several reviews,[2]–[5] and in some cases, the levels of enantioselectivity have reached in excess of 99% ee.

B. REACTIONS OF 1,3-DIPHENYLPROPENYL ACETATE

Allyl acetates **1/ent-l** that possess identical R groups undergo allylic substitution via an achiral intermediate **2**. Both enantiomers of starting material proceed via the same intermediate. In the absence of any controlling influence, approach of the nucleophile via pathways "a" and "b" is equally likely, and a racemic product **3/ent-3** will be formed (**Scheme 1**). However, the opportunity for an asymmetric catalytic reaction exists if the reaction can be channeled through one pathway selectively. Overall, the process represents a dynamic resolution, since a racemic starting material is converted into an enantiomerically enriched product.

Well over one hundred papers have been published describing the reaction of the particular substrate **4** reacting with dimethylmalonate **5** to afford the substitution product **6**. This reaction serves as a test-bed for newly designed ligands (**Scheme 2**).

One of the first design principles to address the asymmetric variant of this reaction considered ligands that were able to reach around the allyl moiety and direct the incoming nucleophile to one of the allyl termini selectively. Hayashi and co-workers developed ligands **7** and **8**, which are able to influence the approach of the incoming nucleophile (**Scheme 3**).[6]–[8] Thus, with the standard allyl acetate substrate **4**, ligands **7** and **8** provide high levels of enantioselectivity in the substitution reaction with various stabilized enolates, including the enolate of pentane-2,4-dione **9**, affording the substitution product **10** (**Scheme 3**).

Similar ligands involving a diphosphine ligand on a ferrocene framework with various functionalized pendant groups have been designed. Additionally, other ligands have been

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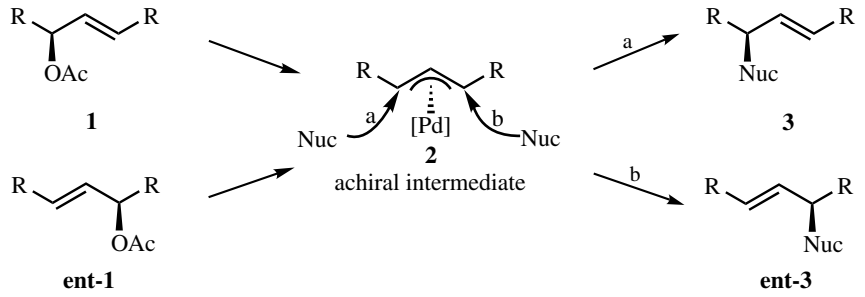
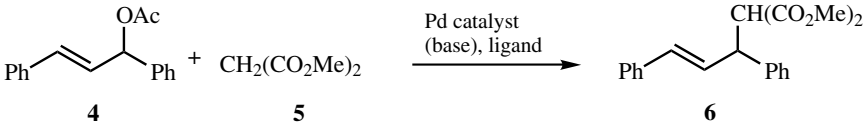
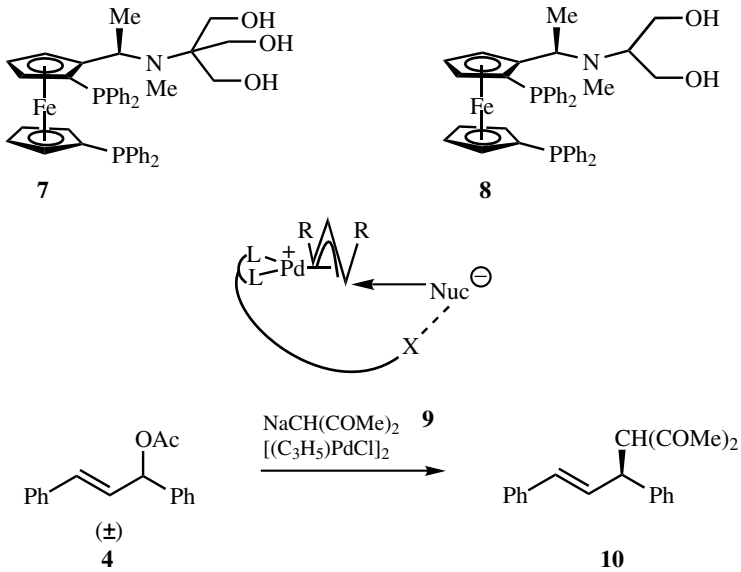


Scheme 1



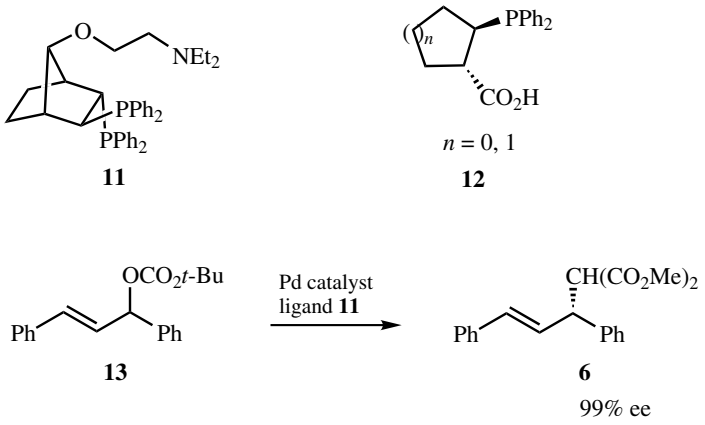
Scheme 2



Scheme 3

prepared with a similar strategy in mind, including ligands **11**[9],[10] and **12.**[11],[12] In the case of ligand **11**, up to 99% ee was obtained in the conversion of pivalate ester **13** into the malonate-substituted product **6** (**Scheme 4**).

The initial concept of an additional functional group providing guidance to the incoming nucleophile gave the first highly enantioselective examples of allylic substitution. However, the majority of ligands have not adopted this approach. The steric effect of a ligand on the allyl group can distort the symmetry of the allyl such that one end is further away from the palladium. It seems that the more remote allylic terminus is generally the



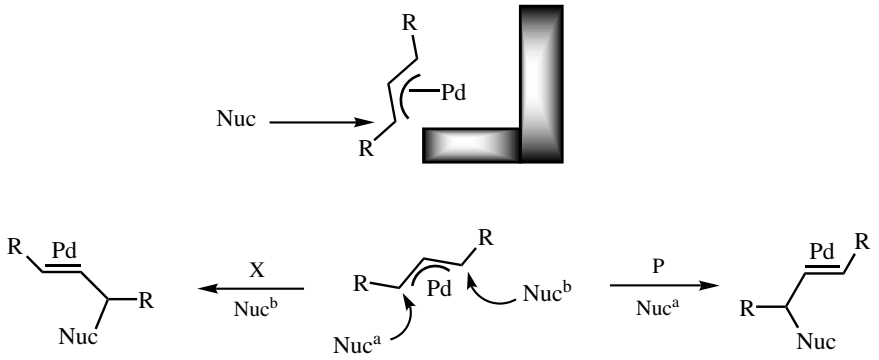
Scheme 4

one that is attacked preferentially. It has also been proposed that a ligand can impart a "twist" to the allyl group, which encourages attack at the allyl terminus, which results in further rotation in the same direction (**Scheme 5**).

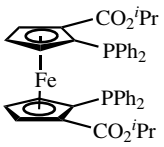
Many bidentate ligands that contain identical donor atoms appear to induce asymmetry according to those ideas, especially when the ligands are C_2 symmetric. Examples of successful diphosphine ligands include the C_2-symmetric ligands **14–20** shown in **Scheme 6**. The quoted enantioselectivities refer to the preparation of the standard product **6**.

The Pd-catalyzed allylic substitution reaction has been one research area where nonphosphorus-based ligands have been actively investigated. There are many successful ligands containing two donor nitrogen atoms including those identified in **Scheme 7**. These ligands are either C_2-symmetric or nearly so (ligands **24** and **28**).

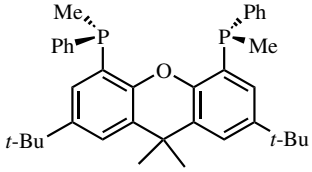
A further model for asymmetric induction in Pd-catalyzed allylic substitution reactions has been to employ ligands that contain two electronically different donor atoms. This approach is typified by the use of P,N ligands, where generally the phosphorus is considered to be a better π-acceptor than the nitrogen. The idea that P,N ligands could perturb the symmetry of allylpalladium complexes had been established before the application to enantioselective catalytic systems.[33] The π-acceptor group has the effect of weakening and lengthening



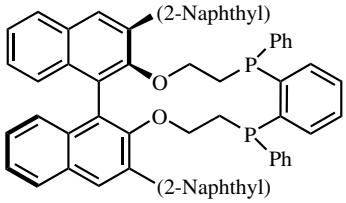
Scheme 5



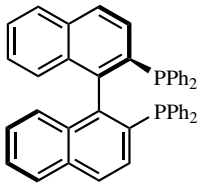
14[13],[14]
94% ee



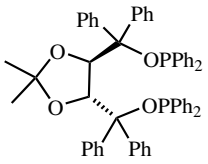
15[15]
85% ee



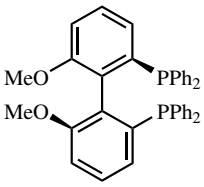
16[16]
98% ee



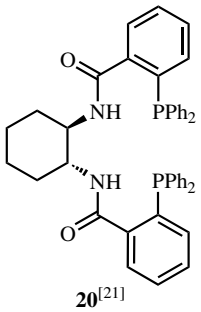
17[17],[18]
95% ee using acetamidomalonate
90% ee using microwaves



18[19]
70% ee

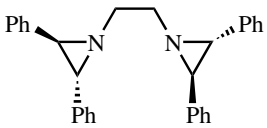


19[20]
95% ee

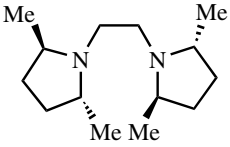


20[21]
(high ee's for suitable substrates)

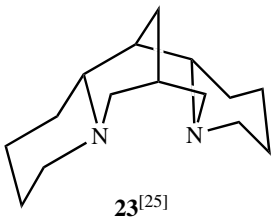
Scheme 6



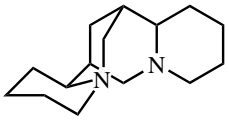
21[22],[23]
>99% ee



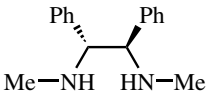
22[24]
91% ee



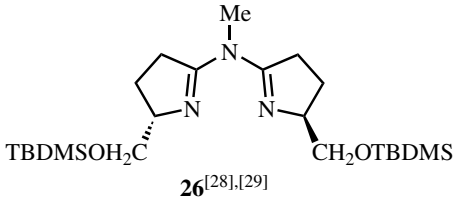
23[25]
95% ee



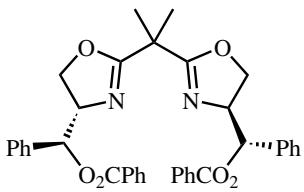
24[26]
85% ee



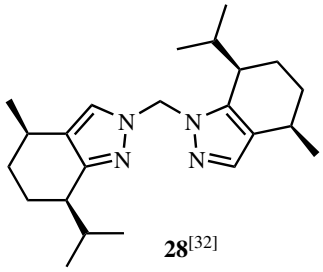
25[27]
95% ee



26[28],[29]
95% ee



27[30],[31]
90% ee

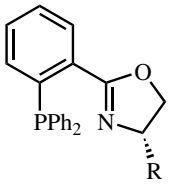


28[32]
84% ee

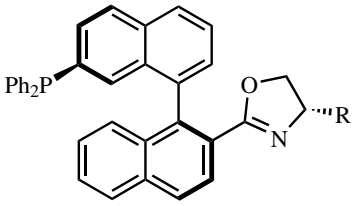
Scheme 7

the Pd—C bond trans to itself (the trans influence). The incoming nucleophile is then better able to attack the compromised terminus of the allyl group. The asymmetric environment generated by the P,N ligand will lead to a preferred orientation (up or down) of the allyl ligand, and hence to an enantioselective process (**Scheme 8**).

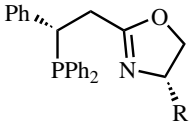
There have been many examples of successful P,N ligands, including the use of phosphines tethered to enantiomerically pure oxazoline groups. The originally reported ligands **29**[34]–[39] have been elaborated into a host of related structures. Ligand **31**[40]–[49] was identified as an effective ligand after screening a range of similar structures in a ligand library.[43]



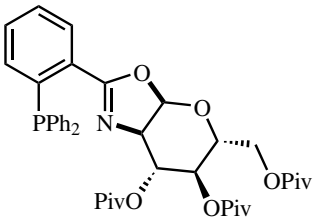
29[34]–[39]
(up to 99% ee)



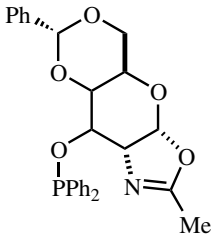
30[40],[41]
96% ee



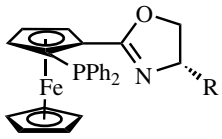
31[42]
98% ee



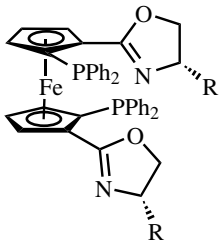
32[43]
98% ee



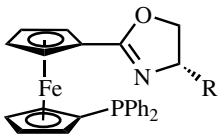
33[44],[45]
96% ee



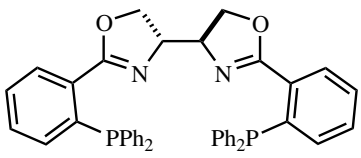
34[46]
99% ee



35[47]
99% ee



36[48]
91% ee



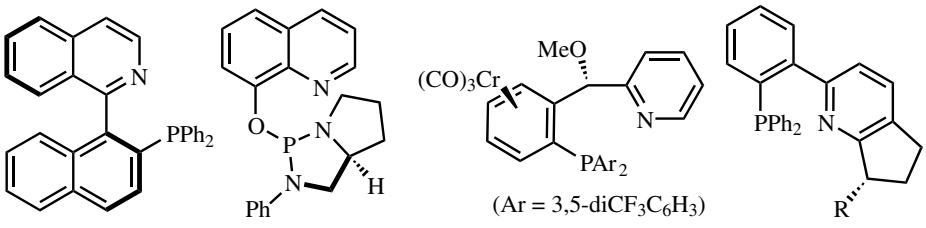
37[49]
97% ee

Scheme 8

Although the combination of a diphenylphosphino group with an oxazoline has been very effective, especially for reactions of 1,3-diphenylpropenyl acetate **4**, other P,N combinations have also been popular.[50]–[59] The nitrogen donor can belong to a C═N unit, as shown in **Scheme 9**. Alternatively, various successful P,N ligands have been reported that do not contain the nitrogen atom within a C═N bond. Some of those structures are identified in **Scheme 10**.[60]–[67]

While most good examples of heterobidentate ligands have been P,N ligands, there have been many other combinations of donor atoms, especially S,N ligands, some of which are clearly related to their P,N counterparts. **Scheme 11** shows some successful S,N ligands.[68]–[77]

There have also been several reports of P,S ligands that have been employed to give high enantioselectivity in the Pd-catalyzed allylic substitution reaction of 1,3-diphenylpropenyl acetate **4** with malonate. Some of these ligands are identified in **Scheme 12**.[78]–[81]

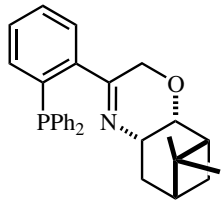


38[50] 98% ee

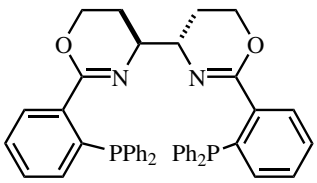
39[51] 85% ee

40[52] 93% ee

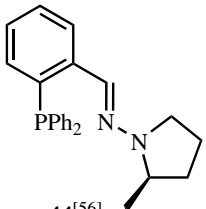
41[53] 98% ee



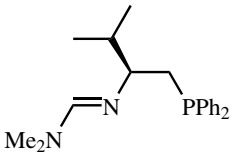
42[54] 95% ee



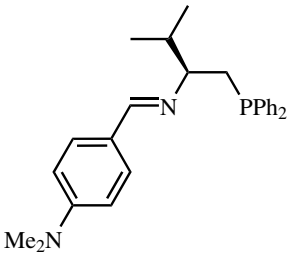
43[55] 84% ee



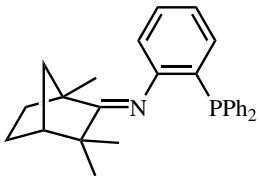
44[56] 92% ee



45[57] 95% ee (with pivalate leaving group)

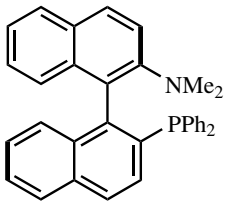


46[58] 92% ee (with pivalate leaving group)

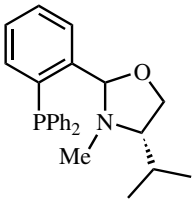


47[59] 90% ee

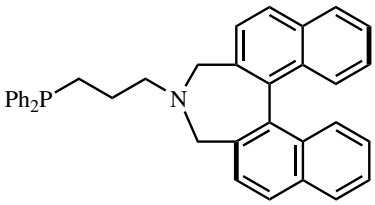
Scheme 9



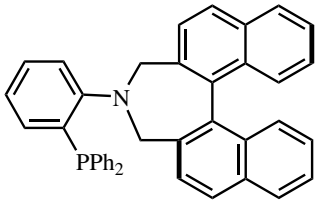
48[60]
71% ee



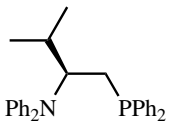
49[61]
98% ee



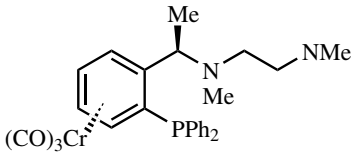
50[62]
96% ee



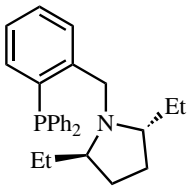
51[63],[64]
96% ee



52[65]
92% ee



53[66]
94% ee



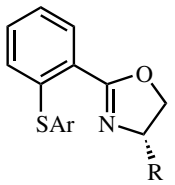
54[67]
90% ee

Scheme 10

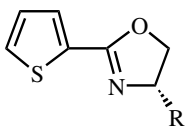
There have been a few reports of heterobidentate ligands containing oxygen donor ligands in combination with nitrogen, sulfur, or phosphorus donor groups.[82],[83] For example, cyclic acetals have been used, as represented by ligands **68**, **69**, and **70** in **Scheme 13**.

Even bidentate ligands that rely on donor atoms of the same element can still impart an electronic asymmetry onto the allylpalladium moiety. This can be achieved by changing the environment of the donor atoms relative to one another. A clear-cut example of this approach is seen in the case of ligand **71**, where the two phosphorus donor atoms are electronically quite distinct from each other.[84] There have also been many examples of non-C_2-symmetric dinitrogen ligands reported.[85]–[91] Their success may be attributed either to steric effects or, in some cases, an electronic difference between the two nitrogen donor atoms (**Scheme 14**).

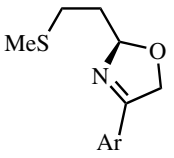
Monodentate ligands form the last significant class of effective ligands for Pd-catalyzed allylic substitution reactions (**Scheme 15**). In principle, either one or two monodentate ligands could be associated to the allylpalladium complex. However, most successful monodentate ligands are bulky, suggesting that only one ligand is present.[92]–[97]



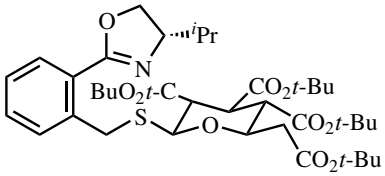
55[68]
99% ee



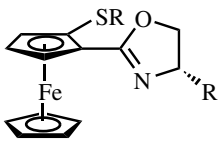
56[69]
81% ee



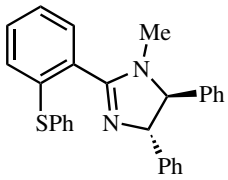
57[70],[71]
88% ee
Ar = Phenyl
Ar = Ferrocenyl



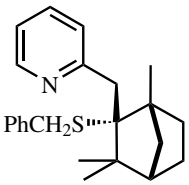
58[72]
97% ee



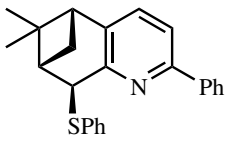
59[73]
98% ee



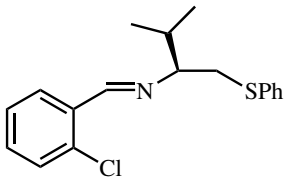
60[74]
96% ee



61[75]
98% ee



62[76]
83% ee



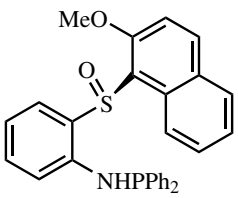
63[77]
94% ee

Scheme 11

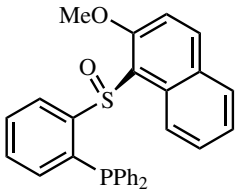
The use of polymer-supported ligands for transition-metal-catalyzed reactions has widely been exploited, including asymmetric examples. However, there are relatively few examples of polymer-supported enantiomerically pure ligands being used in allylic substitution reactions (**Scheme 16**). Hayashi's MOP ligands have been attached to a resin support, to provide palladium catalysts such as complex **82**.[98] Up to 84% was obtained in allylic substitution reactions.

A pyridinooxazoline has been attached to polymeric supports, including TentaGel resin.[99] The supported ligand **83** has been employed to provide up to 80% ee in the standard reaction of allyl acetate **4** with dimethylmalonate **5**.

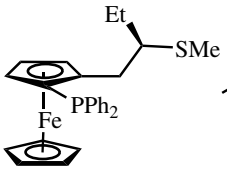
The ligands surveyed in the previous sections have been examined in the test-bed reaction, although this particular reaction conveys little about the success of the various ligands when other substrates are encountered, and it is helpful to consider the reactions of other substrates.



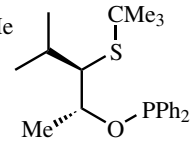
64[78]
97% ee



65[79]
82% ee

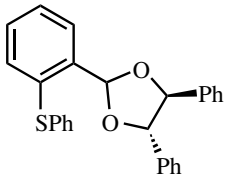


66[80]
97% ee

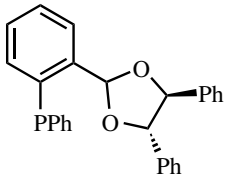


67[81]
98% ee

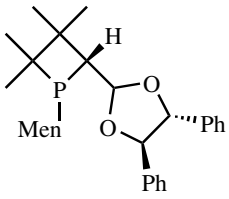
Scheme 12



68[82]
82% ee

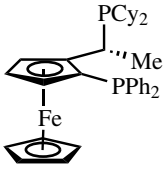


69[82]
88% ee

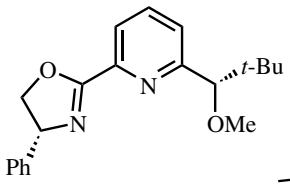


70[83]
91% ee
Men = mentyl

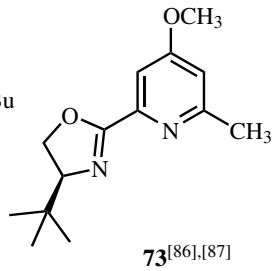
Scheme 13



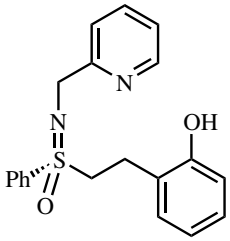
71[84]
93% ee



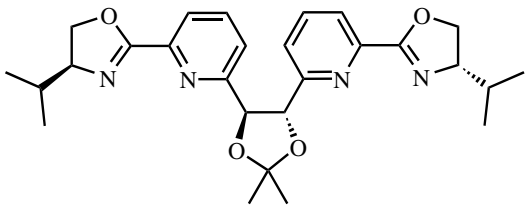
72[85]
99% ee



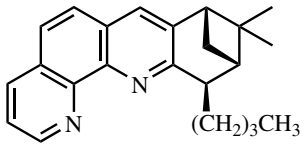
73[86],[87]
93% ee



74[88]
73% ee

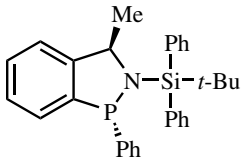


75[89],[90]
98% ee

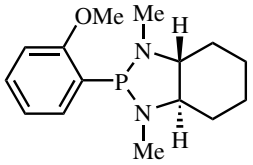


76[91]
84% ee

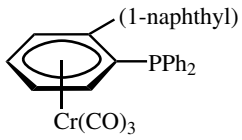
Scheme 14



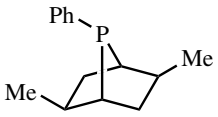
77[92]
91.5% ee



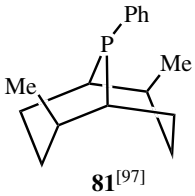
78[93],[94]
89% ee



79[95]
92% ee

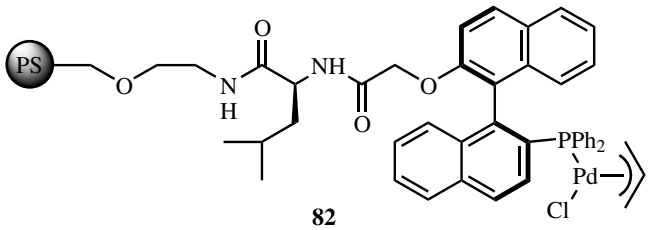


80[96]
97% ee

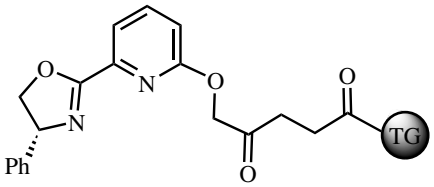


81[97]
96% ee
(using pivalate leaving group)

Scheme 15



82

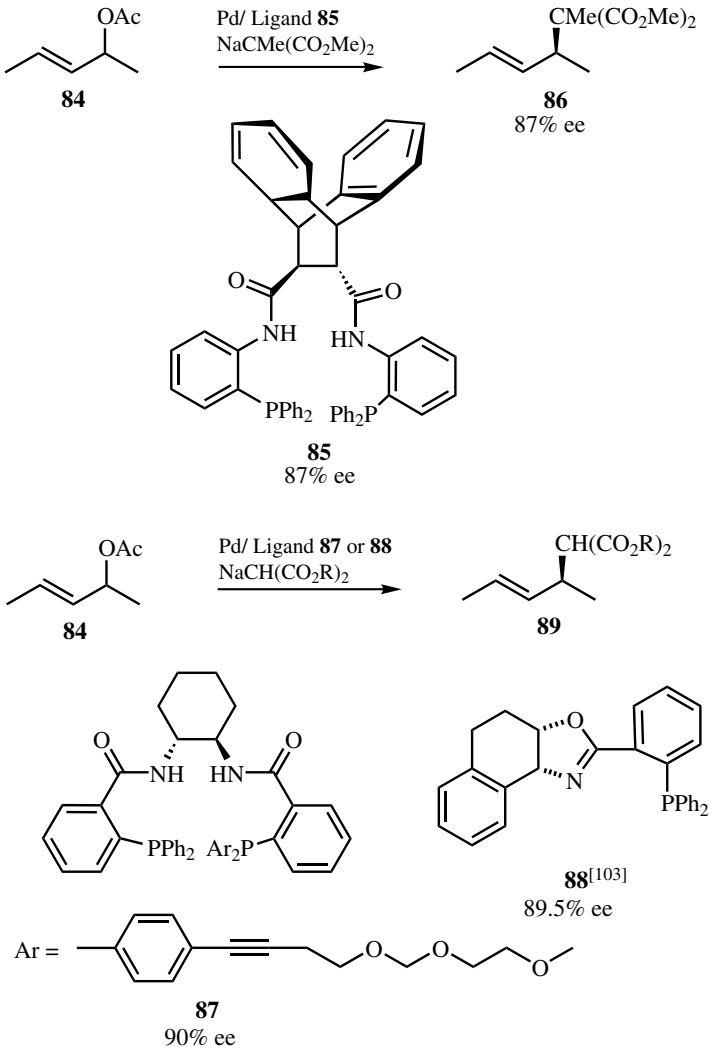


83

Scheme 16

C. OTHER SUBSTRATES

The allyl acetate **84**, which reacts via a dimethyl-substituted allylpalladium complex, usually undergoes substitution reactions with lower enantioselectivity than the diphenyl counterpart **4** (**Scheme 17**). However, Trost's ligand **85** is able to induce up to 87% ee in the substitution product **86**.[100],[101] The enantioselectivity achieved on the dimethyl substrate **84** was also improved upon using a ligand modification, where the phosphine units contain pendant arms able to associate with the nucleophile counterion as shown for ligand **87**.[102]

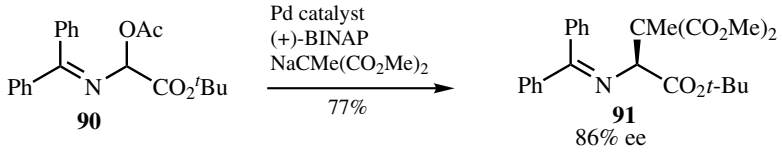


Scheme 17

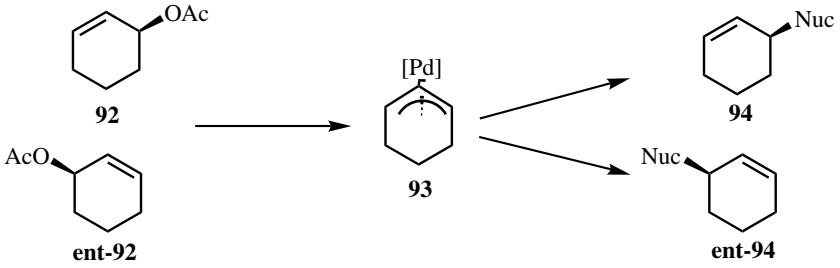
As well as the conventional all-carbon substrates, O'Donnell and co-workers have used the aza-analog **90**.[104] Pd-catalyzed allylic substitution seems to operate in a similar fashion to the carbon analog, with malonate and related nucleophiles being employed in the normal way, affording products including imino ester **91** with good enantioselectivity (**Scheme 18**). This substrate proceeds via an intermediate π-allyl complex, although it is not a meso-system (see also substrate **115**).

Cyclic substrates such as cyclohexenyl acetate **92/ent-92** are also able to proceed via a meso-intermediate. The enantioselectivity of the reaction is determined by the selective approach of a nucleophile to one of the allylic termini of intermediate **93** (**Scheme 19**).

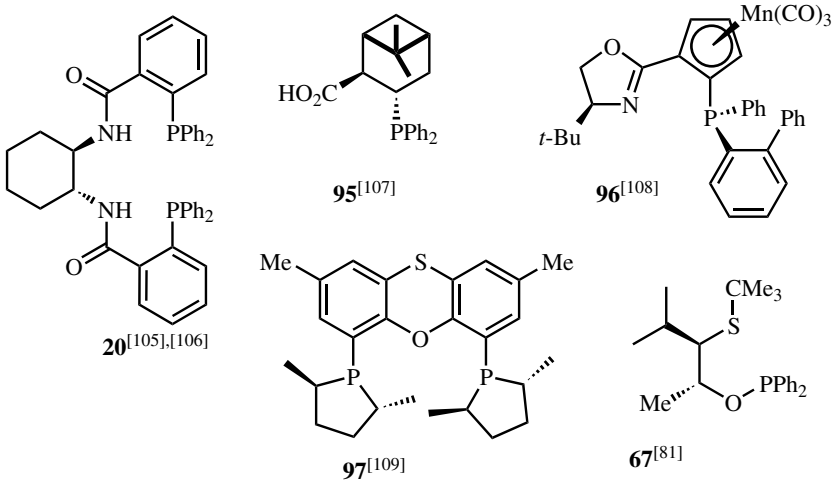
Unfortunately, many of the ligands that give excellent selectivity in the substitution reactions of diphenylpropenyl acetate **4** give poor selectivity when cyclic acetates are used as the substrate. There are also many more cases where this information has not been

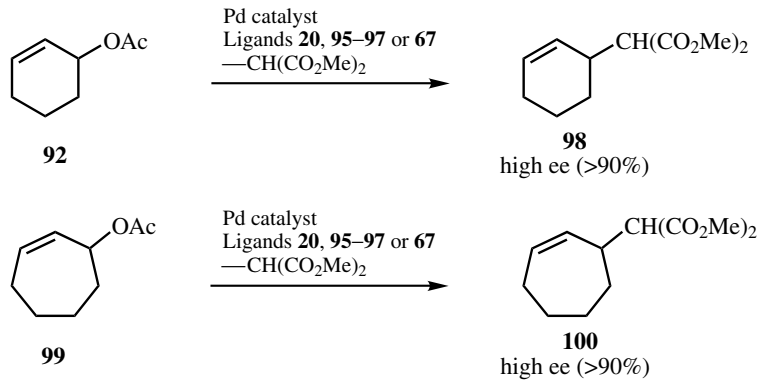


Scheme 18

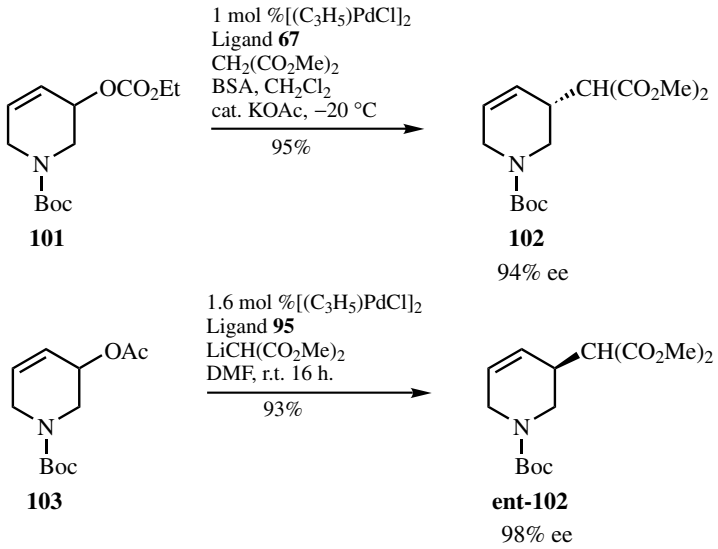


Scheme 19





Scheme 20 (*Continued*)



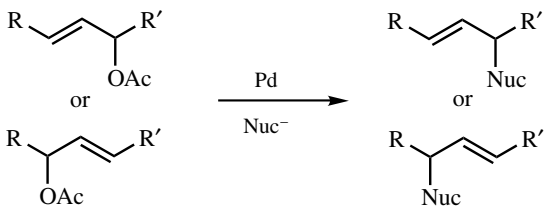
Scheme 20

reported. However, there are ligands that are capable of achieving excellent enantiocontrol for cyclic substrates (**Scheme 20**). Of particular note in this respect are the Trost ligands **20**.[105],[106] The diphosphine ligands have a large "bite angle," which projects the chiral environment of the ligand more deeply into the area where the allyl group resides. Other ligands have also been shown to give high enantioselectivities for such cyclic allyl acetates.[81],[107]–[109] Evans has also performed the allylic substitution reaction on the heterocyclic allyl carbonate **101**,[81] While Helmchen has used the related allyl acetate **103**.[110]

D. REGIOCONTROL IN ENANTIOSELECTIVE ALLYLIC SUBSTITUTION

In instances where the two termini of the allyl moiety possess nonidentical groups, the issues of both regiocontrol and enantiocontrol can become important (**Scheme 21**). Typically, the nucleophile approaches from the less sterically hindered terminus, and the mechanism proceeds via a double inversion (overall retention) of stereochemistry process. Consequently, the use of a racemic substrate is unlikely to lead to a single regioisomeric product with high enantioselectivity.

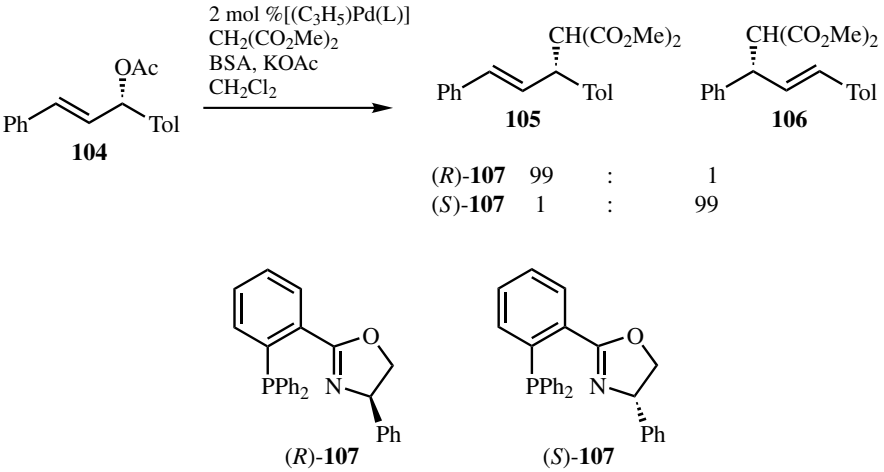
Pfaltz and co-workers have reported an interesting experiment using enantiomerically pure substrate **104**.[111] As expected, by the overall retention of stereochemistry



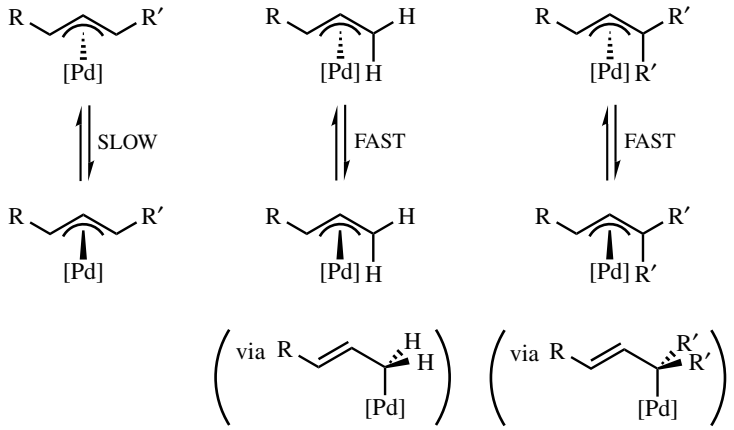
Scheme 21

mechanism, the nucleophile becomes attached to the substrate from the same face that the acetate had left from. However, by using the two enantiomers of ligand **107**, excellent control of regiochemistry could be established, affording either product **105** or **106** selectively (**Scheme 22**).

While racemization of unsymmetrical allylpalladium complexes is slow, in cases where one end of the intermediate allyl complex is attached to two equivalent groups, it is possible for the complex to racemize via a $\pi-\sigma-\pi$ pathway (**Scheme 23**).

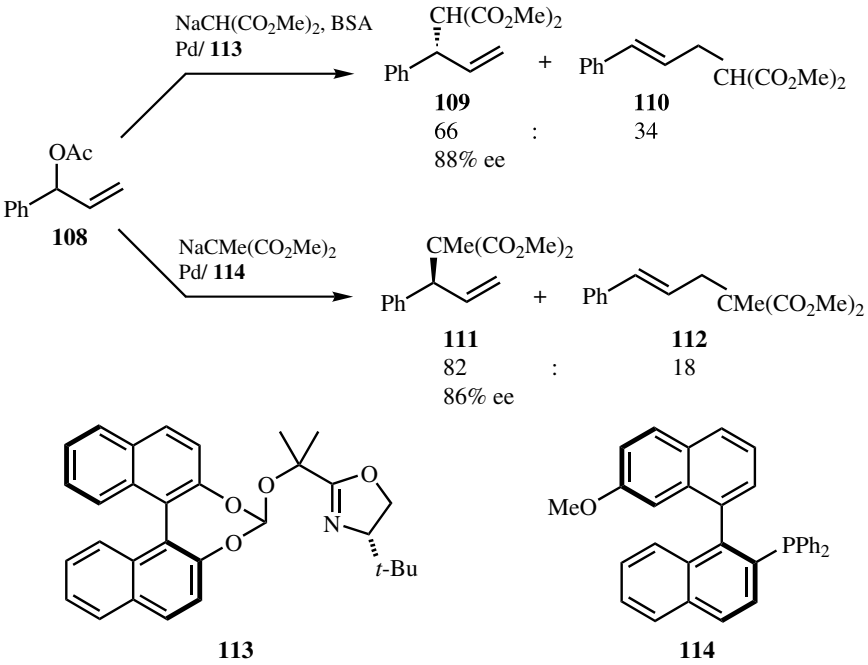


Scheme 22



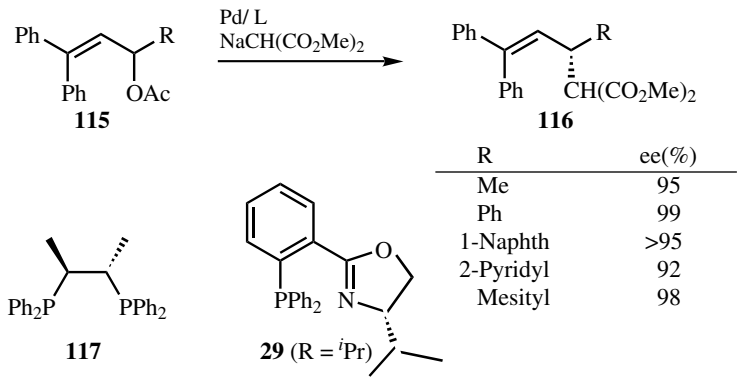
Scheme 23

It is therefore possible to design asymmetric catalytic reactions that proceed through such rapidly racemizing complexes. However, for most palladium/ligand combinations, reaction of the acetate **108** affords mainly the linear products **110** and **112**. But, some ligands can afford a catalytic system that is selective for the branched isomers **109** and **111**, as shown in **Scheme 24**.[112],[113]



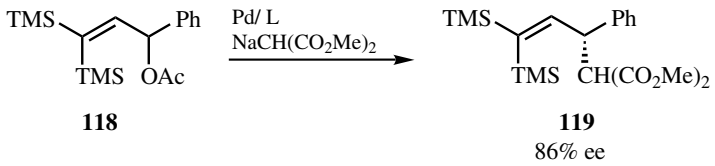
Scheme 24

Substrates with two phenyl groups at one end of the allyl group have been employed in enantioselective allylic substitution reactions. The regiochemical outcome is consistent with the majority of Pd-catalyzed allylic substitution reactions and the reaction has been extended to a range of R groups. Originally, substrates **115** were developed by Bosnich who employed chiraphos **117** as the ligand, affording up to 86% in the substitution product.[114] Sparteine **24**[26] and QUINAP **38**[50] have also been employed in the same reaction. However, phosphino-oxazoline ligands **29** have afforded particularly high enantioselectivities in these reactions (**Scheme 25**).[115] A similar strategy has been reported by Romero and Fritzen, who used the disilylated substrate **118**. The silyl groups could be removed from the product **119** on treatment with acid.[116]



R	ee(%)
Me	95
Ph	99
1-Naphth	>95
2-Pyridyl	92
Mesityl	98

Scheme 25 (*Continued*)



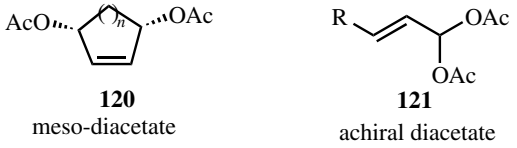
118 **119**
86% ee

Scheme 25

E. REPLACEMENT OF AN ENANTIOTOPIC LEAVING GROUP

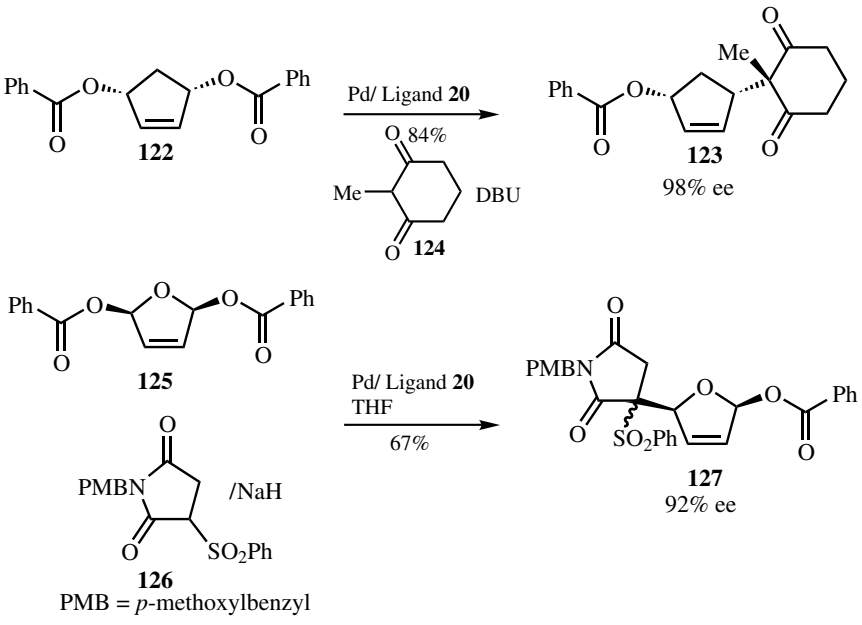
Suitable diacetates are good substrates for enantioselective allylic substitution, when the selective replacement of one group will afford an enantiomerically enriched product. Typical substrates include *meso*-diacetates **120** and achiral diacetates **121** (**Scheme 26**).

These substrates with enantiotopic leaving groups have received considerable attention from Trost's group, and much of the published work has come from this group.[117],[118] Thus, ligand **20** has been used in the conversion of the *meso*-dibenzoate **122** into the monosubstituted product **123** with excellent enantioselectivity using the diketone **124** as nucleophile in the presence of base (**Scheme 27**).

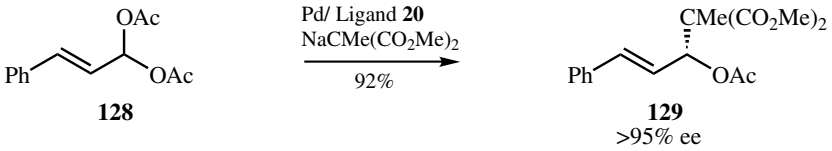


120 **121**
meso-diacetate achiral diacetate

Scheme 26



Scheme 27

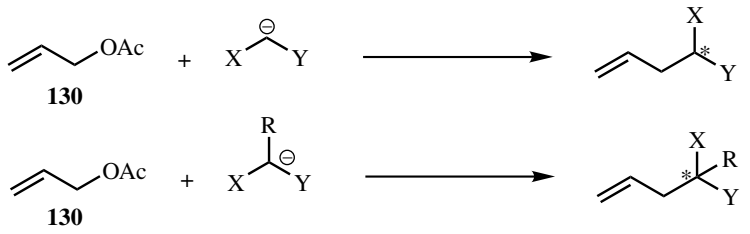


Scheme 27 (*Continued*)

The alkylation of dibenzoate **125** with the unusual nucleophile **126** afforded the monosubstitution product **127** with good enantioselectivity using the standard Trost ligand **20**.[119] Many of the reactions involving *meso*-diacetates have involved nitrogen nucleophiles and are highlighted in a later section. Using the same ligand, the simple diacetate **128** has been shown to undergo enantioselective substitution of one of the acetate groups to give the product **129**.[120]

F. PROCHIRAL NUCLEOPHILES

The use of a prochiral nucleophile in allylic substitution reactions provides an additional opportunity for asymmetric induction. Allyl acetate itself can be used as the electrophilic partner and the new stereogenic center is positioned further away from the allyl group (**Scheme 28**).

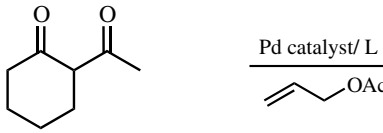


Scheme 28

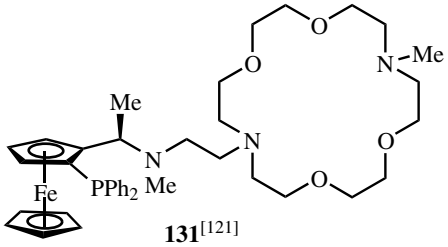
Ligands **131** to **133** that are capable of binding to the palladium and also of steering the incoming nucleophile have been used in the allylation of the diketone **124** (**Scheme 29**).[121]–[123]

Allylation of the β-ketoester **136** was achieved with good enantioselectivity using the Trost ligand **20**.[124] Allylation of the ketone **138** could also be achieved, and although trimethyltin chloride was usually added, it was not an essential feature for obtaining reaction, once the ketone had been deprotonated with lithium diisopropylamide.[125] Alkylation of cinnamyl acetate **140** using the β-ketophosphonate **141** has been carried out using a palladium/BINAP **17** catalyst (**Scheme 30**).[126]

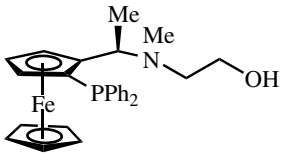
An interesting two-catalyst system has been developed for the highly enantioselective allylation of α-cyanoesters. The allyl carbonate **143** reacts with the nucleophile **144** to give the substitution product **145** with up to a remarkable 99% ee (**Scheme 31**). The nucleophile **144** is activated to deprotonation by the rhodium catalyst, which also seems to be responsible for the control of enantioselectivity. However, in the absence of a palladium catalyst, the allyl carbonate **143** is inert.[127]



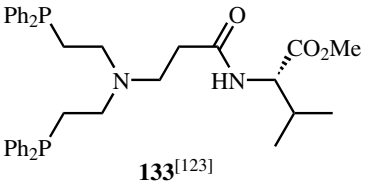
134 **130** **135**



131[121]



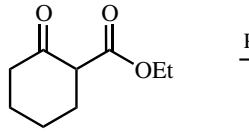
132[122]



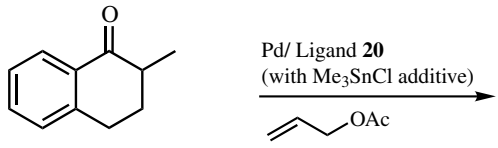
133[123]

Ligand	ee(%)
131	75
132	81
133	52

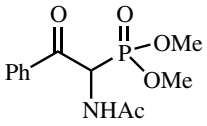
Scheme 29



136 **130** **137**
86% ee

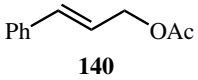


138 **130** **139**
88% ee

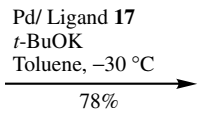


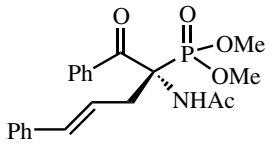
141

+



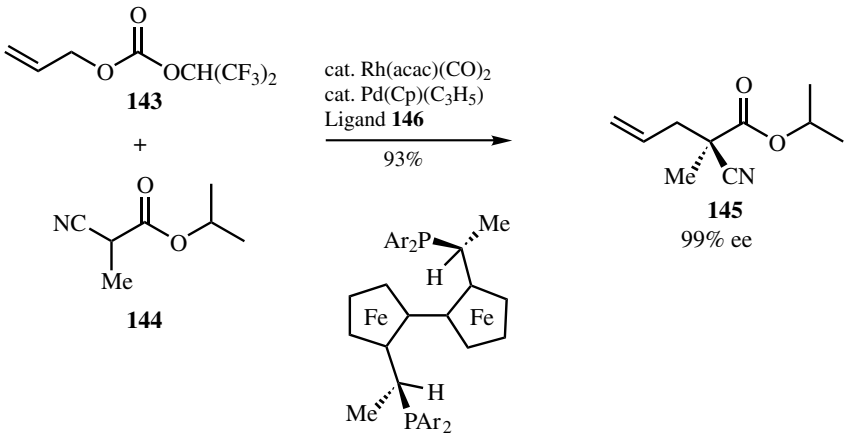
140





142
88% ee

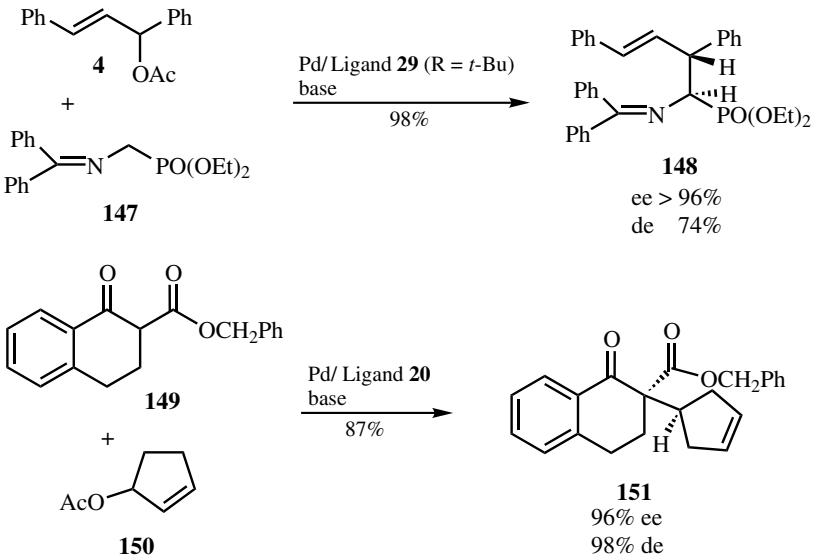
Scheme 30



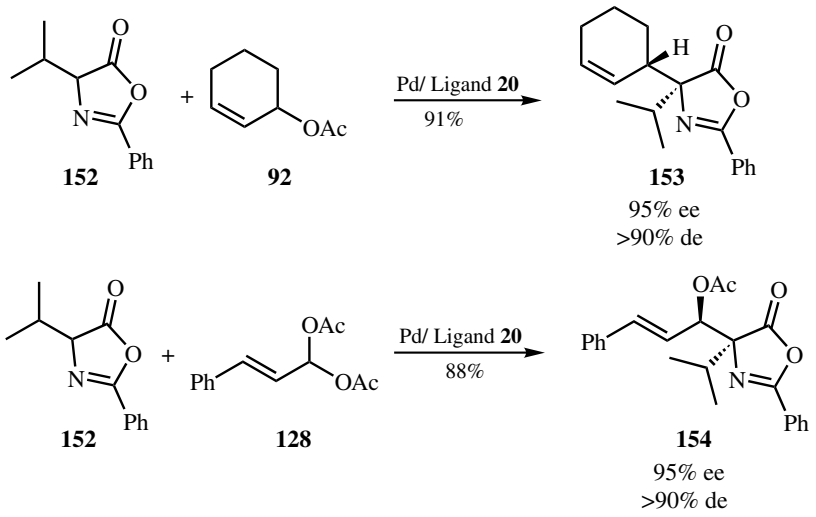
Scheme 31

When prochiral nucleophiles are employed with more complex allyl electrophiles, there is the possibility of forming two sterocenters in the product (**Scheme 32**). For example, imino phosphonate **147** has been used as the nucleophile in the reaction with allyl acetate **4**. The control of enantioselectivity at the benzylic position is very high, but there is lower relative stereocontrol at the newly formed stereocenter α to the phosphonate group.[128]

The reaction of the β-ketoester **149** with cyclopentenyl acetate **150** affords the substitution product **151** with excellent control of both enantioselectivity and diastereoselectivity.[124]



Scheme 32



Scheme 33

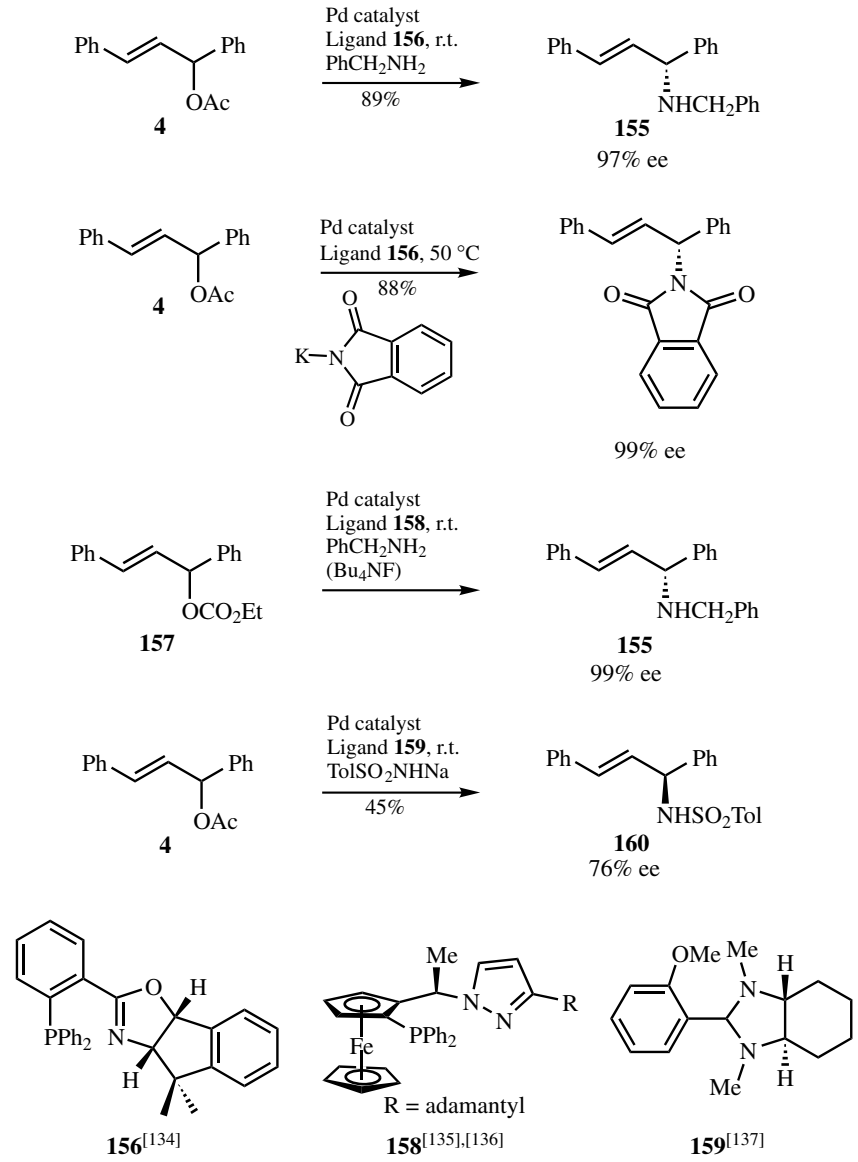
The azalactone **152** has been used as a prochiral nucleophile in a similar process providing the substitution product **153** and **154** upon reaction with either cyclohexenyl acetate **92** or the *gem*-diacetate **128**.[129],[130]

G. AMINATION REACTIONS

Apart from stabilized enolates, such as malonate anions, nitrogen nucleophiles represent the next largest class of nucleophiles to be used in enantioselective allylic substitution reactions.[131] Many of the best ligands for enantioselective allylic substitution with stabilized enolates are also, not surprisingly, good ligands for enantioselective allylic amination. Thus, there is little point in identifying all of the successful allylic amination reactions, but a selection is offered in **Schemes 34** and **35**. For example, the test-bed substrate **4** has been shown by several groups to be amenable to enantioselective amination using phosphine-oxazoline ligands with sulfonamides, hydrazides, and benzylamine.[132],[133] Sudo and Saigo have recommended phosphino-oxazoline **156** as a particularly competent ligand for allylic amination, and high enantioselectivities have been achieved using this ligand.[134] Other groups have used different ligands with carbonate substrates and other nitrogen nucleophiles, again achieving high enantioselectivity.[135]–[137]

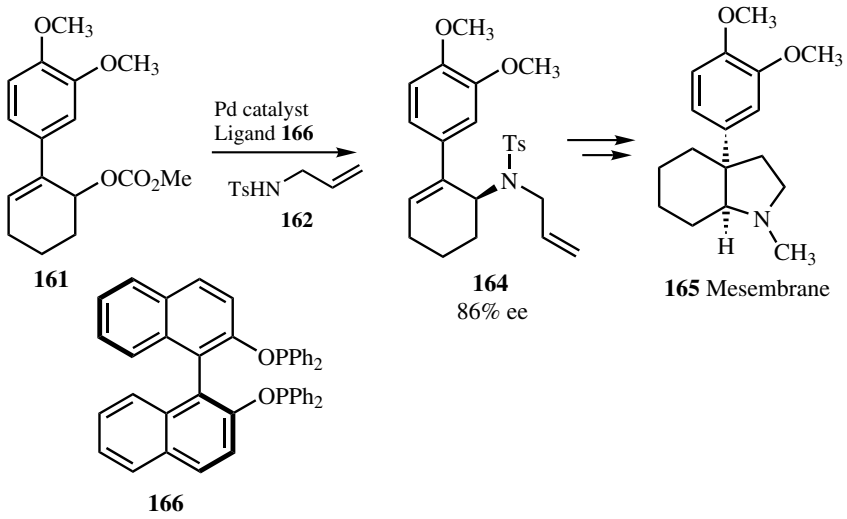
Further examples of allyl substrates that proceed via a symmetrical intermediate include the allyl carbonate **161**, which reacts with allyl sulfonamide **163** to give the product **164**. Elaboration of compound **164** afforded the natural product mesembrane **165**.[138] Related strategies have been used in the synthesis of a range of other natural products.[139]

Butadiene monoepoxide **166** has been used as a substrate for enantioselective allylic substitution reactions. The reaction with phthalimide has been performed with excellent regiocontrol and excellent enantiocontrol. The best results were obtained with a variant **168** of the standard ligand (**Scheme 36**).[140],[141]

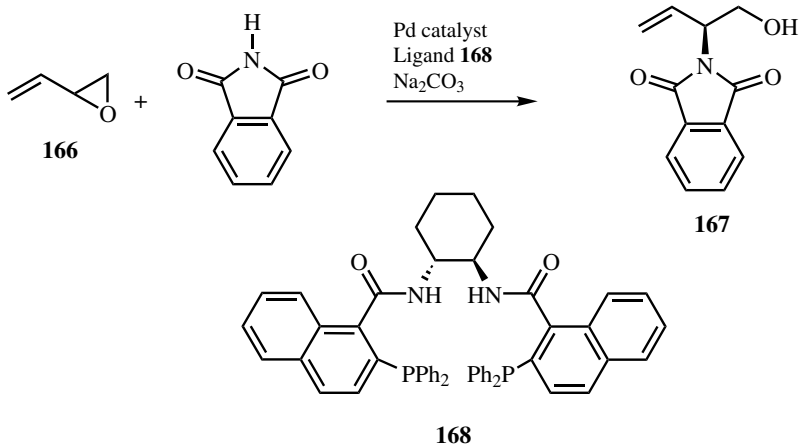


Scheme 34

Amination of substrates with enantiotopic leaving groups has been achieved (**Scheme 37**). Examples include the Pd-catalyzed azidation of the *meso*-dibenzoate **169**.[142] The product **170** was converted into epibatidine **171** by a series of transformations.[143] The *meso*-dibenzoate **172** has been reacted with the aminopurine base **173** to give products **174** and **175**, with good enantioselectivity and reasonable yields.[144] The *meso*-diacetate **176** has been subject to desymmetrization by allylic amination. In the presence of ligand **39**, monoamination occurs with morpholine **177** to give the product **178** with good enantiomeric excess.[145]



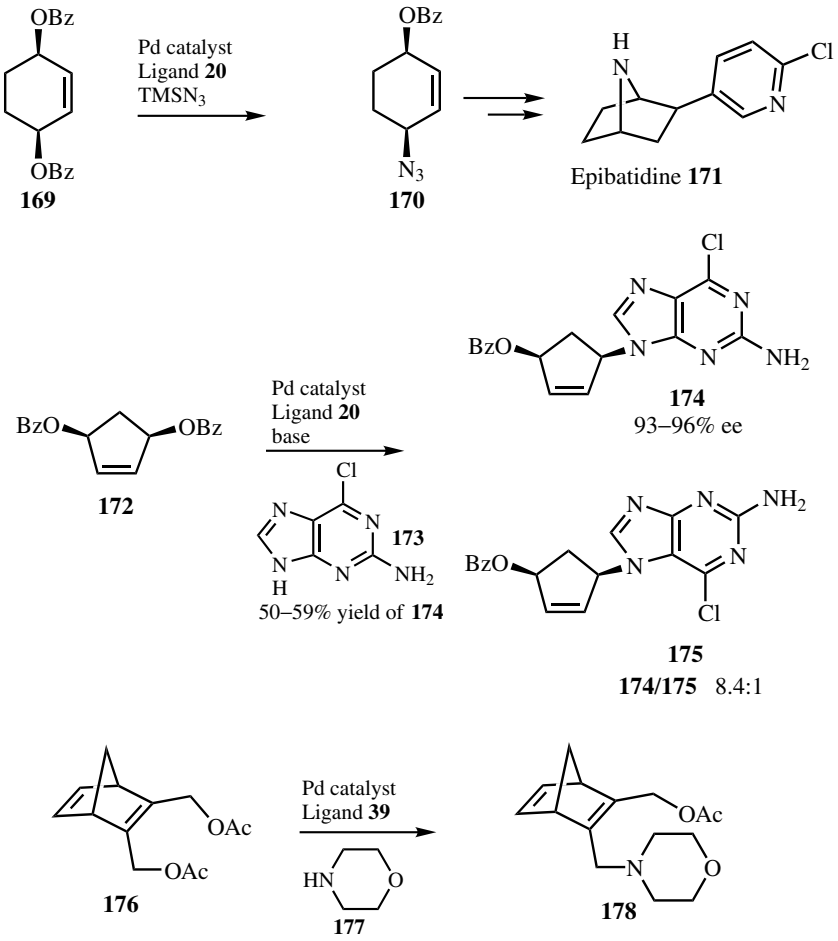
Scheme 35



Scheme 36

H. OTHER HETEROATOM NUCLEOPHILES

While the majority of reports involve the use of carbon- or nitrogen-based nucleophiles, sulfur, oxygen, and even silicon[146] nucleophiles have also been recorded. In principle, oxygen nucleophiles have the potential to add reversibly to allylic systems. Complete reversibility of the reaction will afford racemic products, and hence efforts have been made to minimize reversibility (**Scheme 38**). For example, Trost and Organ have reported the reaction of racemic cyclopentenyl carbonate **179** with sodium pivalate to give enantiomerically enriched cyclopentenyl pivalate **180**.[147] Careful control of temperature was required in order for the product to remain inert under the reaction conditions, but for the more reactive carbonate to still participate.

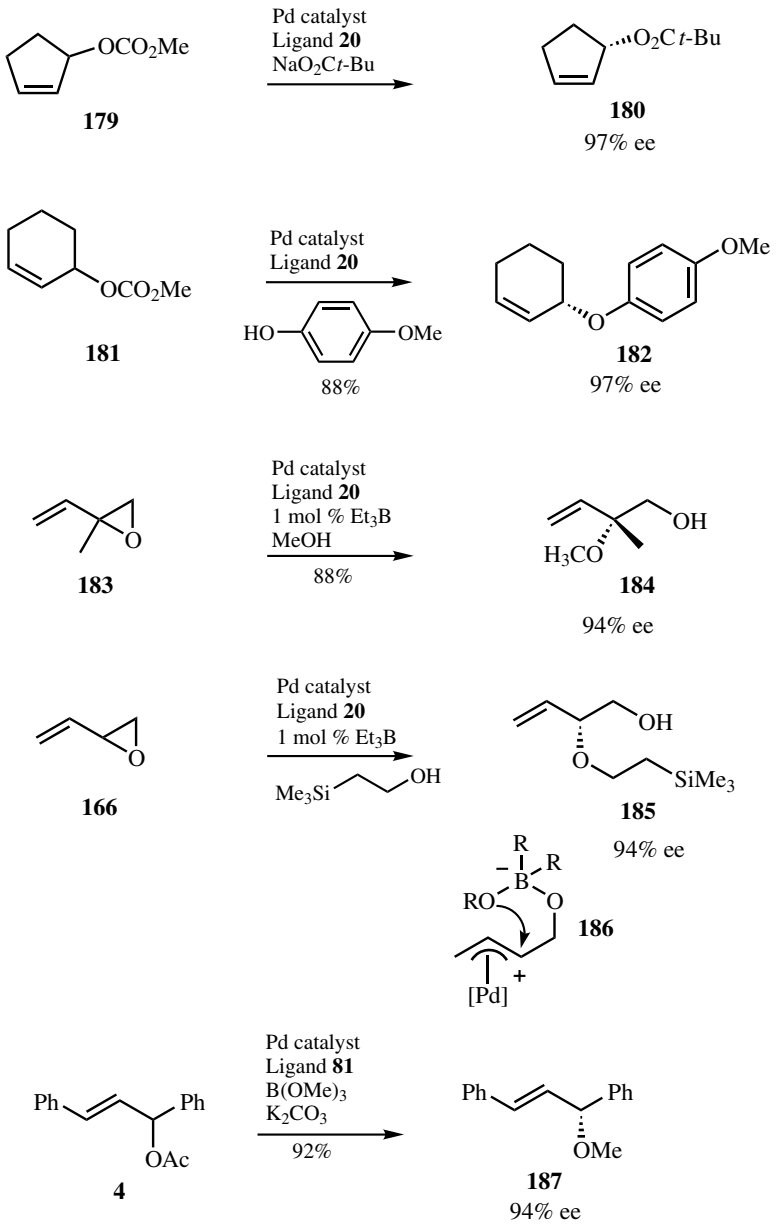


Scheme 37

Phenols have also been used as oxygen nucleophiles in enantioselective Pd-catalyzed allylic substitution reactions. The phenyl ether products **184** and **185** were formed with good enantioselectivity and could be subjected to a subsequent Claisen rearrangement.[148]

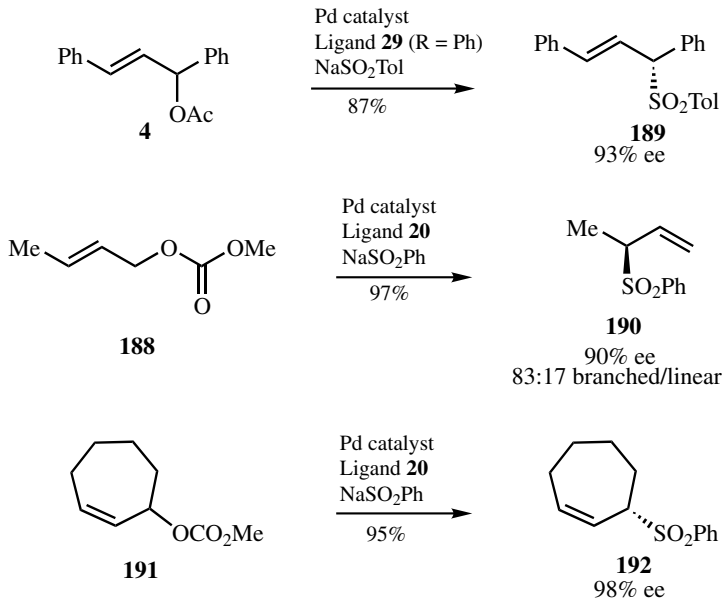
The asymmetric addition of other alcohols is facilitated by the addition of a borane, when epoxides **183** and **166** are used as substates.[149] The reactions are thought to proceed via an intermediate **186**. Trialkylborates have been used as the source of oxygen nucleophiles with the acyclic acetate **4**. While high enantioselectivity (94% ee) is observed in the product **187** using trimethylborate/potassium carbonate, low enantioselectivity was seen when methanol itself was used as the nucleophile (10% ee).[150]

The use of sulfonates as nucleophiles as a method to form enantiomerically enriched allyl sulfones was first reported by Hiroi and Makino in 1986.[151] Acyclic allyl sulfones have been prepared from substrates **4** and **188** under the control of phosphino-oxazoline ligands **29** (R = Ph)[152] or Trost ligand **20**.[153] The reaction has also been applied to cyclic substrates including carbonate **191** (**Scheme 39**).[154]

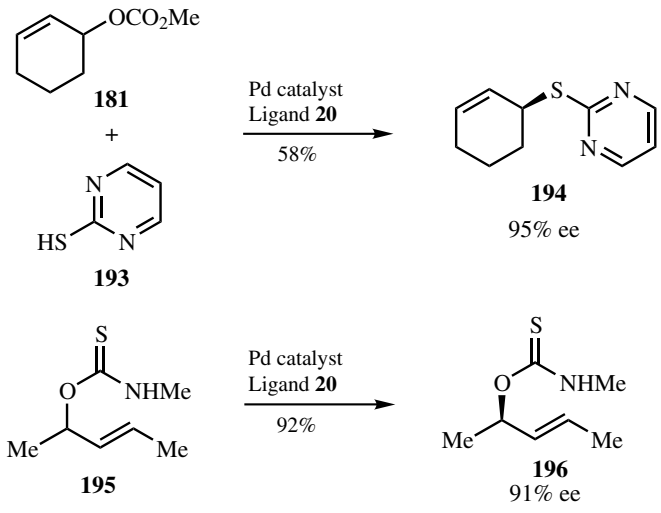


Scheme 38

Allylic sulfides can be prepared in a similar fashion, either using silylsulfides (*t*-$BuSSiMe_3$) or free thiols.[155] For example, the cyclohexenyl carbonate **181** reacts with thiol **193** to give the allyl pyrimidyl sulfide **194** with excellent enantiomeric excess using the Trost ligand **20**. Methodology for the preparation of enantiomerically enriched allylic thiols has been developed using the rearrangement of *O*-allylic thiocarbonate **195** (**Scheme 40**).[156]



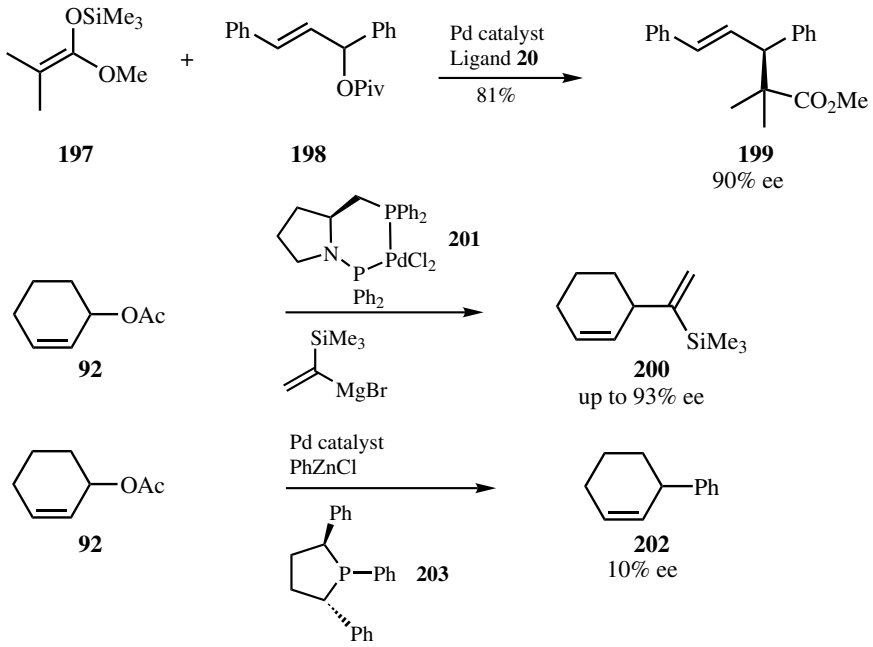
Scheme 39



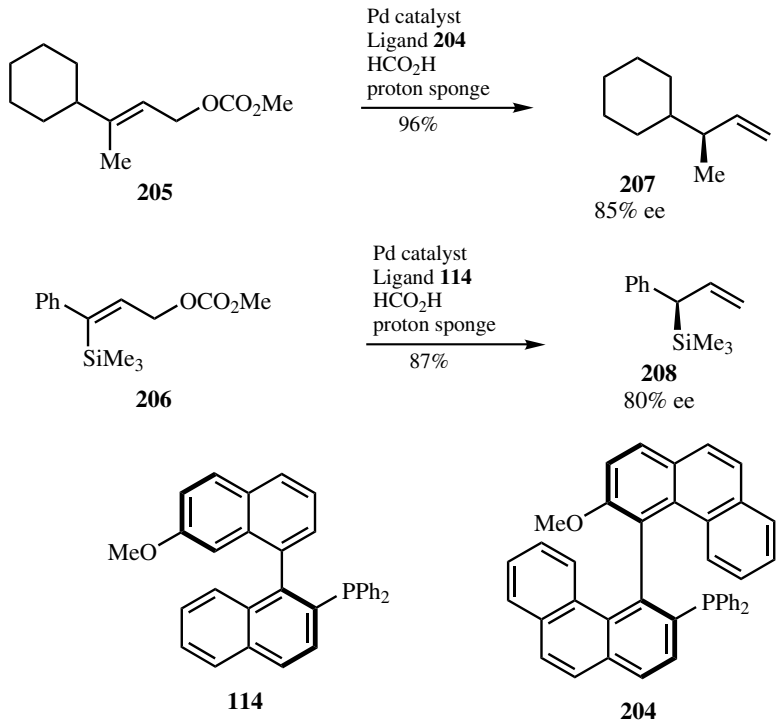
Scheme 40

I. OTHER NUCLEOPHILES

In general, stabilized enolates have been used for enantioselective allylic substitution reactions. However, the use of ketene silyl acetal **197** has been reported to react with good enantioselectivity, affording the monoester **199** as the product (**Scheme 41**).[157] The anion of nitromethane has also been used successfully as a nucleophile in enantioselective allylic substitution.[158]



Scheme 41



Scheme 42

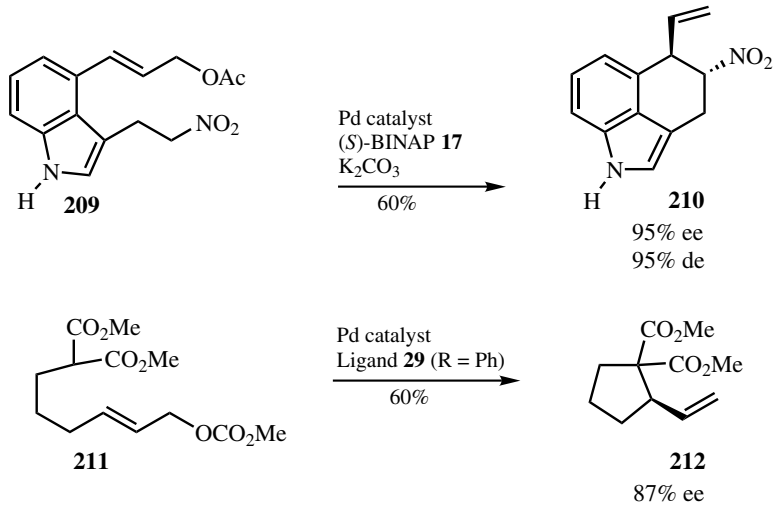
Organometallic reagents including Grignard reagents and organozinc compounds have also been used as nucleophiles, although the enantioselectivities reported to date have been unsatisfactory. For example, cyclohexenyl acetate **92** has been converted into the silylated diene **200** using catalyst **201**,[159] and also into the phenyl-substituted product **202** using ligand **203** as the controlling influence.[160],[161] It seems that there is plenty of scope for improvement, although nickel complexes have been more widely used than their palladium counterparts, and with reasonable success.[162],[163]

The Pd-catalyzed asymmetric reduction of various allylic carbonates has been achieved using formic acid as the hydride source (**Scheme 42**). The monodentate ligands **114** and **204** have been shown to provide good enantioselectivity for these reactions. Examples of this process include reduction of the allylic carbonates **205** and **206** to give the alkene **207**[165] and the allylsilane **208**.[166]

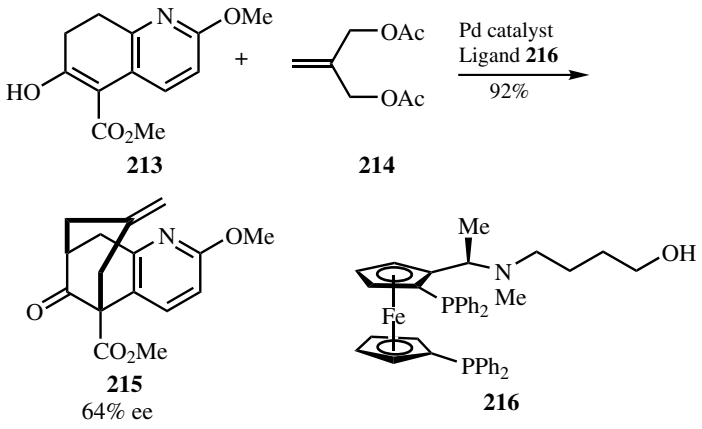
J. CYCLIZATION REACTIONS

In comparison with the large number of publications involving asymmetric Pd-catalyzed allylic substitution reactions, relatively few reports of cyclization reactions are available. However, Kardos and Genet have achieved an impressive cyclization of the substrate **209**, affording the product **210** with excellent enantiocontrol and diastereocontrol.[167] Cyclization reactions involving carbon–carbon bond formation have also been performed on substrate **211**, using a phosphino-oxazoline ligand **29** (R = Ph) to direct the stereochemical outcome.[168] A bicycloannulation reaction has been used in the synthesis of a natural product. Coupling of the β-ketoester **213** (in its enol form) with the diacetate **214** affords the product **215** with good yield and reasonable enantioselectivity (**Scheme 43**).[169]

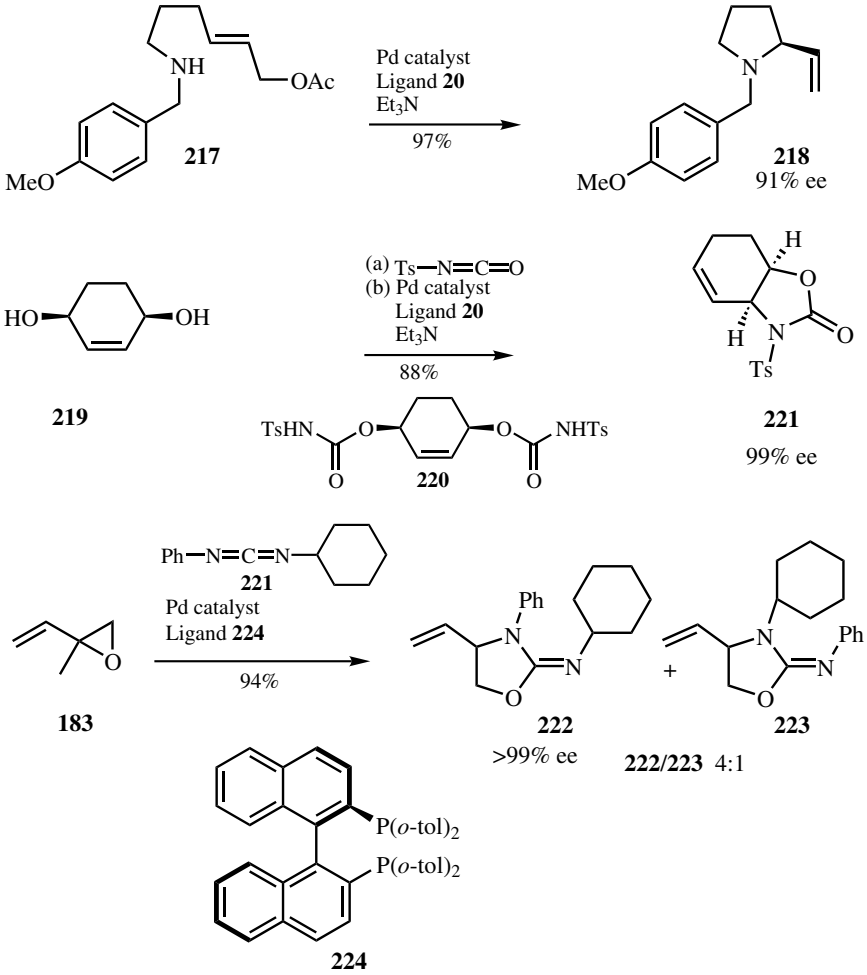
Cyclization of allyl acetates with pendant amino groups has been reported to work with high enantioselectivities in some cases (**Scheme 44**). Cyclization of substrate **217**



Scheme 43 (*Continued*)



Scheme 43

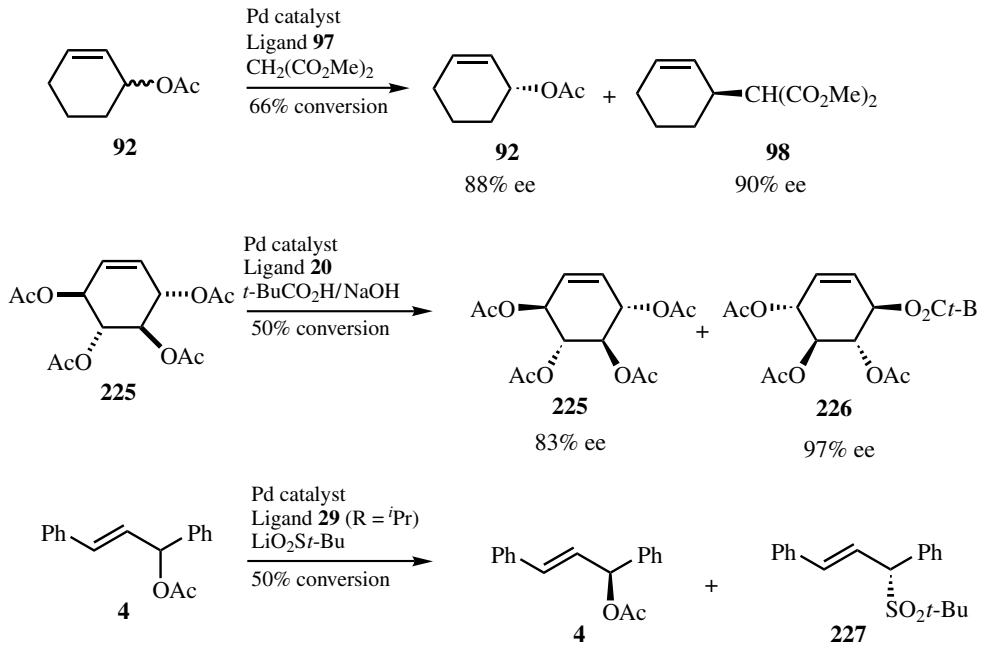


Scheme 44

affords the pyrrolidine **218** with high enantiomeric excess and yield.[153] An enantioselective oxazolidinone synthesis has been performed using cyclohexenediol **219** as the starting material.[170] The reaction proceeds via activation of the diol with tosyl isocyanate to give the intermediate **220**, followed by Pd-promoted cleavage of one C—O bond and subsequent cyclization to give oxazolidinone **221**. The use of triethylamine proved to be critical to the high enantioselectivity. Pd-catalyzed allylic substitution provides a mechanistic pathway for insertion of carbodiimides **221** and related structures into vinyl epoxides **183**. The reaction proceeds via a ring-opening/ring-closing sequence.[171] The enantioselectivity of the process is excellent and even the regiochemistry of the products **222** and **223** is acceptable.[172]

K. KINETIC RESOLUTION

When a racemic allylic substrate is employed in an enantioselective substitution reaction, one of the two substrate enantiomers may react more quickly than the other. This effect is a kinetic resolution and has been noted reasonably often in enantioselective allylic substitution reactions.[173] Several studies on kinetic resolution have been reported,[174],[175] and a few highlight reactions are noted in **Scheme 45**. These include recovery of unreacted cyclohexenyl acetate **92**,[176] as well as the tetraacetate **225**.[177] Kinetic resolution has also been observed in allylic substitution using a sulfinate nucleophile (LiO_2S^tBu) with allyl acetate **4**.[178]

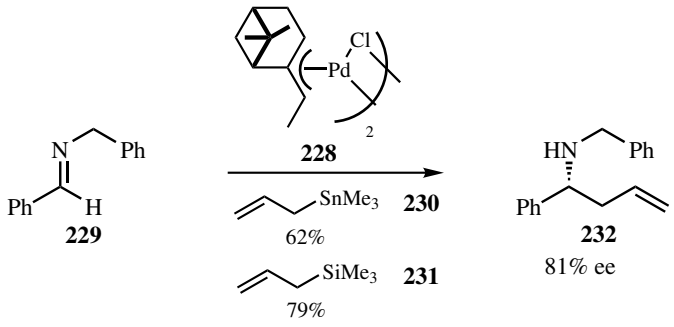


Scheme 45

L. ALLYLATION OF IMINES

Pd-catalyzed allylic substitution reactions generally involve an electrophilic allyl source and a nucleophile. However, Y. Yamamoto and co-workers have developed a useful methodology where a nucleophilic allyl source (tributylallylstannane **230**[179] or trimethylallylsilane **231**)[180] is employed, and the palladium catalyzes the reaction with a suitable electrophile (aldehyde or imine). The reaction does proceed via an intermediate allylpalladium complex and so is discussed in this section.

Rather than conventional P,P or P,N ligands the asymmetric environment is provided by another allyl ligand. Thus, allylpalladium complex **228** has been shown to catalyze the reaction between imine **229** and either tributylallylstannane **230** or trimethylallylsilane **231** (**Scheme 46**).



Scheme 46

M. OTHER METALS

Although the majority of research interest in enantioselective allylic substitution reactions has involved Pd-catalyzed processes, there have been several successful examples using other metals. These include the use of tungsten,[181],[182] molybdenum,[183] nickel,[163] iridium,[184] and platinum-catalyzed reactions.[185]

N. SUMMARY

Pd-catalyzed allylation reactions have been achieved with very high enantioselectivities for a wide range of nucleophiles. Many of the best results have been obtained with a handful of "ideal" substrates. The focus of more recent work has been on synthetically diverse substrates.

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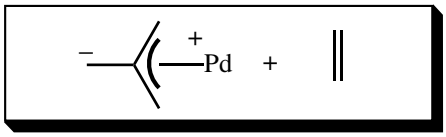

V.2.5.1 Elimination of Allylpalladium and Related Derivatives

ISAO SHIMIZU

A. INTRODUCTION

Similar to β-elimination of Y-Pd-X from alkylpalladium complexes to give olefins, elimination of Y-Pd-X species from π-allylpalladium complexes proceeds to afford 1,3-dienes (**Scheme 1**). A variety of atoms and functional groups represented as "Y" are known in this elimination process; among them elimination of palladium hydride species (H-Pd-X) is the most common.

Since π-allylpalladium complexes are formed by oxidative addition of allylic compounds to zerovalent palladium species, and the eliminated HPdX from π-allylpalladium complexes readily decomposes to regenerate a Pd(0) species with liberation of HX, the elimination processes to 1,3-dienes is catalyzed by palladium complexes. It is considered that the elimination step from HPdX to Pd(0) and HX is reversible; therefore, normally the elimination is carried out in the presence of suitable base (B) to capture HX. The catalytic elimination of HX from allylic compounds for the synthesis of 1,3-dienes under mild conditions provides a useful method (**Scheme 2**).

B. PALLADIUM-CATALYZED ELIMINATION OF ALLYLIC COMPOUNDS

In 1967 elimination of phenol from allyl phenyl ethers to form 1,3-diene in the presence of a palladium catalyst was reported briefly by Smutny.[1] Later, Tsuji applied the Pd-catalyzed elimination reaction of terminal allylic compounds for the synthesis of terminal 1,3-dienes.[2] Thus, elimination of acetic acid and phenol from allylic acetates and allyl phenyl ethers was carried out by refluxing the allylic compounds in dioxane or toluene in the presence of catalytic amounts of palladium acetate and PPh_3 as a ligand for the palladium catalyst (**Table 1**). The allylic isomers were converted to the same products. No reaction takes place with allylic methyl ether, an allylic alcohol, or an allylic amine, which cannot easily form π-allylpalladium complexes by oxidative addition.

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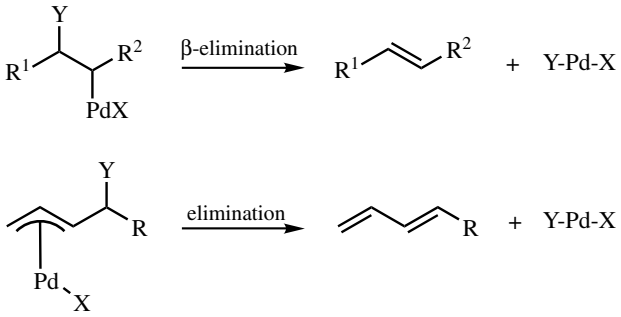
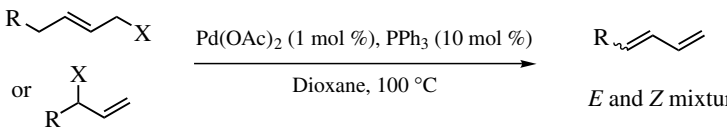
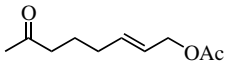
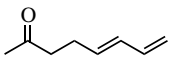
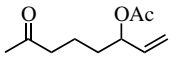
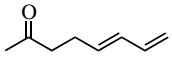
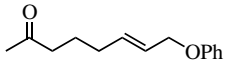
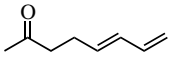
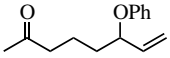
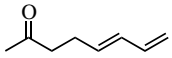
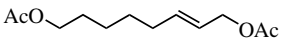
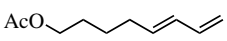
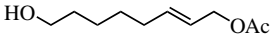
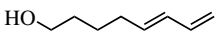
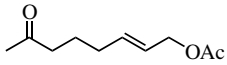
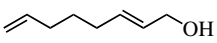
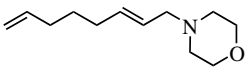


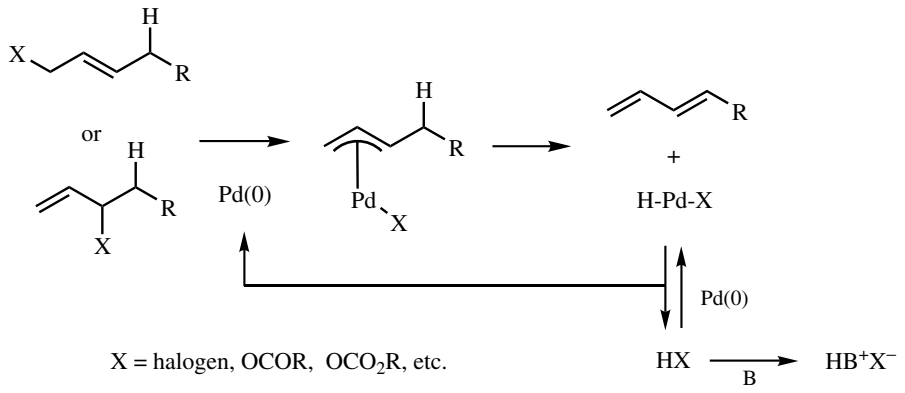
X, Y = H, hologen, OCOR, etc.

Scheme 1

TABLE 1. Pd-Catalyzed Reaction of Allylic Compounds to 1,3-Dienes

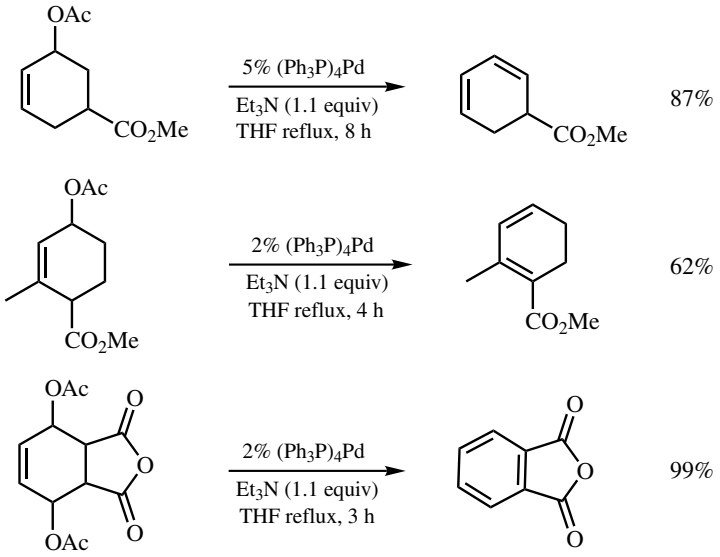


Allylic Compound	1,3-Diene	Conversion (%)	Isolated Yield (%)
		100	78
		100	71
		98	63
		98	62
		100	77
		100	84
		0	0
		0	0
		0	0



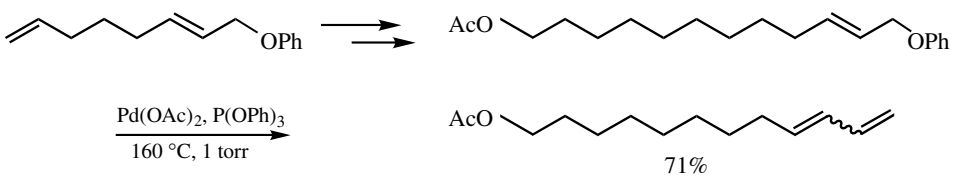
Scheme 2

Elimination of acetic acid from cyclic allylic acetate proceeded in refluxing THF along with the Pd-catalyzed positional and stereochemical isomerization.[3] Various cyclohexenyl acetates were converted to cyclohexadienes in good yields without aromatization in refluxing THF in the presence of $(PPh_3)_4Pd$ and 1.1 equiv of Et_3N (**Scheme 3**). Facile aromatization occurs by bis-elimination of the 1,4-acetoxy-2-cyclohexene.



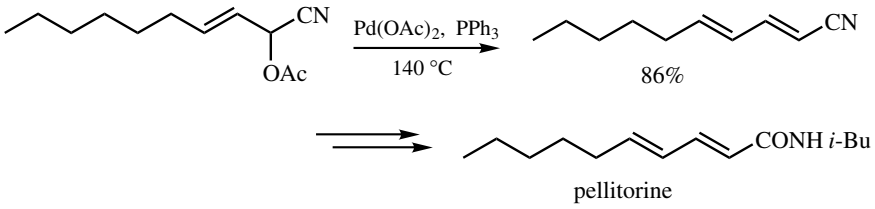
Scheme 3

The Pd-catalyzed elimination reaction was applied to the synthesis of 12-acetoxy-1,3-dodecadiene, an insect sex pheromone from the red bollworm moth, by elimination of phenol with $Pd(OAc)_2$ and $P(OPh)_3$ at 160 °C under reduced pressure (1 torr) from the allyl phenyl ether prepared from a butadiene telomer (**Scheme 4**).[4]



Scheme 4

Facile elimination of acetic acid from the cyanohydrin acetate derived from 2-nornenol was carried out with $Pd(OAc)_2$ and PPh_3 in diglyme or xylene at 140 °C to give 2,4-decadienonitrile, which was a key intermediate for synthesis of an insecticidal compound, pellitorine (**Scheme 5**).[5]



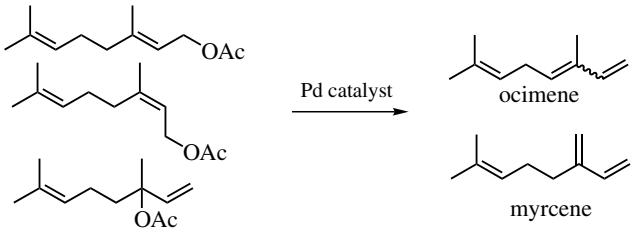
Scheme 5

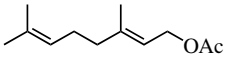
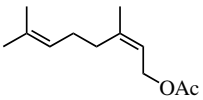
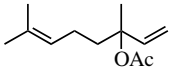
Elimination reaction of geranyl acetate, neryl acetate, and linallyl acetate proceeds in refluxing dioxane under the Tsuji conditions to give a mixture of myrcene, *trans*- and *cis*-ocimene in a nonregioselective manner. Regioselective 1,4-elimination of allylic acetates was achieved in essentially 100% yield using propargylzinc bromide and $Pd(PPh_3)_4$ catalyst.[6] Thus, geranyl acetate was converted into ocimene in essentially quantitative yield to the exclusion of myrcene (<1%), while neryl acetate gave only myrcene in a quantitative yield (**Table 2**). It is worth mentioning that the reaction proceeds rapidly even at room temperature (r.t.), whereas other basic reagents, such as NEt_3, DABCO, and $NaNH_2$, do not show such a remarkable reactivity and selectivity.

The effects of β,γ-unsaturated organometallics as well as propargylzinc bromide for regioselectivity and acceleration of elimination reaction were observed.[7] When the reaction was carried out using an excess of allylstannane, only 1 equiv of organostannane is consumed with concomitant formation of 1 equiv of propene. When the reaction was carried out using pentadeuteriated linalyl acetate, 3-deuteriopropene along with acetoxybutylstannane and a mixture of tetradeuteriated 1,3-dienes was formed. The kinetic isotope effect indicates that cleavage of an allylic C—H bond occurs in the rate-limiting step of the reaction. From these observations, involvement of a six-electron 6-centered cyclic mechanism via the cyclic transition state is postulated, which can also account for the unique regiospecificity as shown in **Scheme 6**.

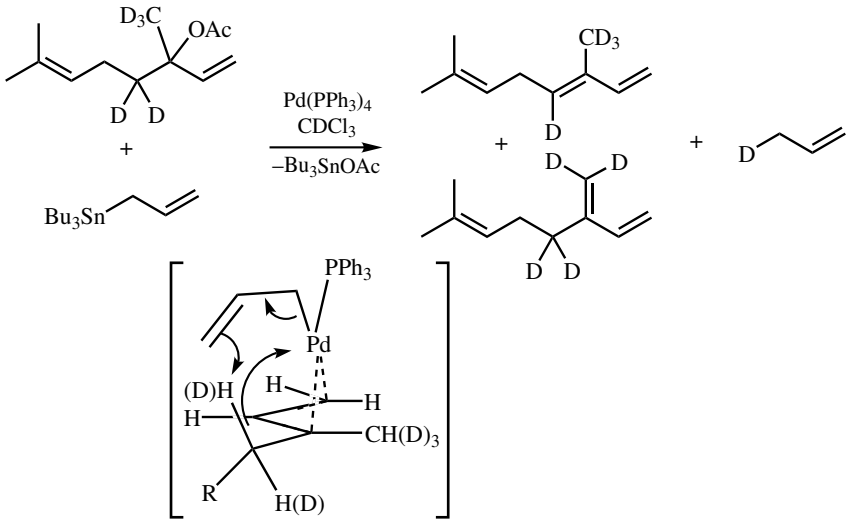
The Pd-catalyzed elimination is extended to the synthesis of conjugated trienes and tetraenes.[8] Reaction of (*E*,*E*)-hexadienyl acetate gave (*E*)-hexatriene exclusively (>*E*/*Z* = 97:3) in 87% yield. On the contrary an 80:20 mixture of isomeric *E*- and *Z*-hexatrienes was formed in 67% yield in the reaction of 3-acetoxy-1,5-hexadiene. (*E*,*E*)-1,3,5,7-Octatriene was also prepared from (*E*,*E*,*E*)-2,4,6-octatrienyl acetate (**Scheme 7**).

TABLE 2. Elimination Reactions of Geranyl Acetate, Neryl Acetate, and Linalyl Acetate

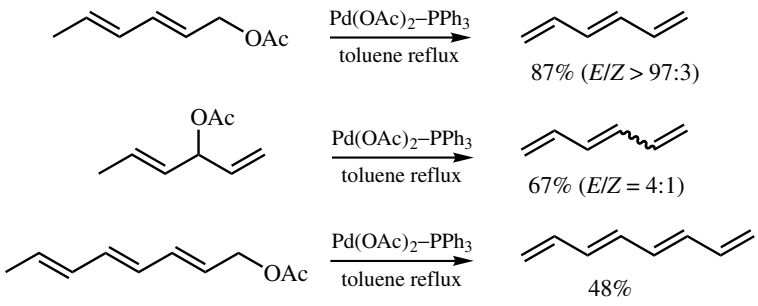


Allylic Acetate	Conditions[a]	Basic Reagent Added	Product Yield (%) Ocimene (*E*/*Z*)	Myrcene
	A	None	74	26
	B	None	40 (1:1)	60
	A	$HC{\equiv}CCH_2ZnBr$	100 (3:1)	0
	A′	NEt_3	33	41
	A′	DABCO	44	56
	A′	$NaNH_2$	28	63
	B	None	26 (4:9)	74
	A	$HC{\equiv}CCH_2ZnBr$	0	100
	B	None	26 (6:7)	74

[a]Conditions: Catalyst A, 5% $Pd(PPh_3)_4$ in THF at r.t. for 3 h.
Catalyst A′, 5% $Pd(PPh_3)_4$ in THF at r.t. for 48 h.
Catalyst B, 1% $Pd(OAc)_2$ and 10% PPh_3 in refluxing toluene for 1 h.



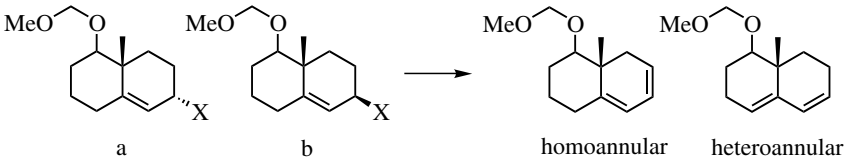
Scheme 6



Scheme 7

Regioselective synthesis of homo- and heteroannular conjugated dienes in polycyclic systems is important in organic synthesis. Dehydration of bicyclic allylic alcohols with methanesulfonyl chloride in pyridine provides the heteroannular conjugated diene as a 1,4-elimination product. Elimination reaction of the corresponding acetate did not proceed with palladium catalyst even in the presence of base. However, elimination of allylic carbonate proceeded in refluxing dioxane in the presence of the palladium catalyst and Bu_3P.[9] Interestingly, when $Pd_2(dba)_3CHCl_3$ and PBu_3 was used as catalyst precursors, homoannular conjugate dienes were obtained from both α- and β-allylic carbonates. It is noteworthy that the selectivity of elimination of the bicylic carbonates is dependent on the method used for preparing the palladium catalysts.[10] When the catalyst was prepared by mixing $Pd(OAc)_2$ and Bu_3P in a 1:1 ratio, elimination of allylic carbonates proceeded rapidly even at room temperature (**Table 3**, condition B). More importantly, either the hetero- or homoannular dienes were obtained regioselectively depending on the

TABLE 3. Elimination of Bicyclic Allylic Comounds



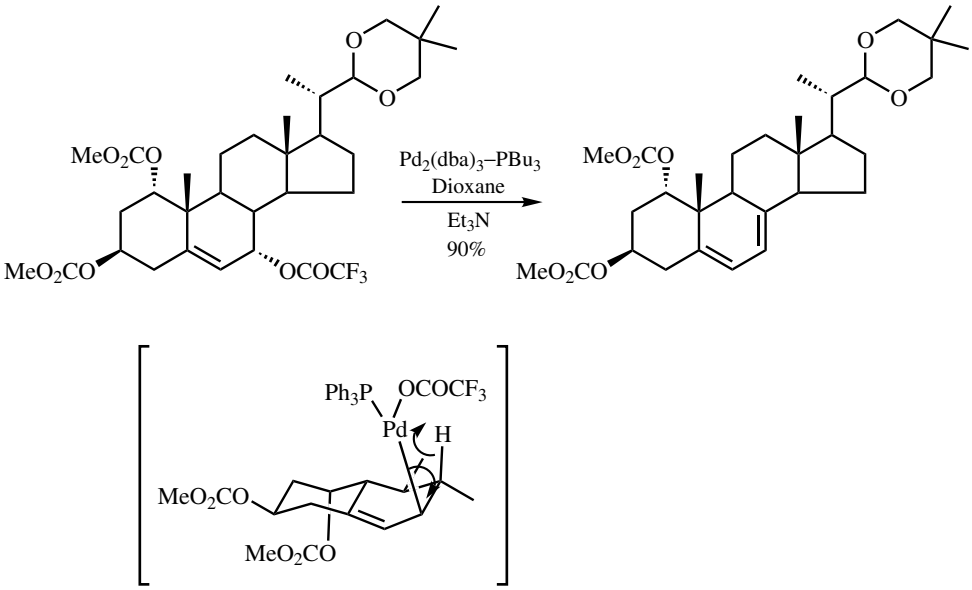
a : X = OCO_2Me; b : X = OH

Allylic Compound	Conditions[a]	Yield (%)	Ratio (Homo/Hetero)
α–a	A	93	93 : 7
	B	95	92 : 8
β–a	A	95	90 : 10
	B	93	<1 : >99
α–b	C	70	1: 99

[a] Conditions: A. 10% $Pd_2(dba)_3{\cdot}CHCl_3$, 80% PBu_3 in refluxing dioxane.
B. 10% $Pd(OAc)_2$, PBu_3 (1 : 1) in benzene at r.t.
C. 2 equiv MsCl, 10 equiv pyridine, 0 °C.

stereochemistry of the allylic carbonates. Thus, the homoannular dienes were obtained as main products and the heteroannular conjugated dienes as minor products when the α-carbonates were treated with the palladium catalyst in THF or benzene at room temperature. On the other hand when the β-carbonates were subjected to the same reaction, the heteroannular dienes were obtained exclusively. The active catalytic species from $Pd(OAc)_2/PBu_3$ (1:1) is not clear, but active phosphine-free palladium(0) species is likely to be generated.[11]

The elimination of bicyclic allylic esters was applied to the synthesis of a steroidal intermediate for vitamin D.[9] The elimination can be carried out from the allylic α-trifluoroacetate to the homoannular diene, and the regioselective reaction is rationalized by easy eliminaion of the C(8)-axial proton syn to palladium, which is probably caused by agostic interactions (**Scheme 8**).



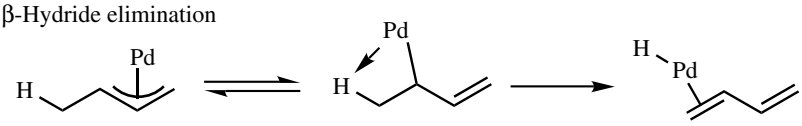
Scheme 8

C. MECHANISM OF ELIMINATION OF π-ALLYLPALLADIUM COMPLEXES

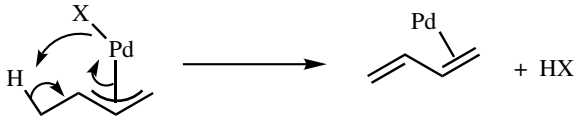
So far three different mechanisms for the elimination from π-allylpalladium complexes are discussed for the diene formation from π-allylpalladium intermediates (**Scheme 9**) First, the elimination from the π-allylpalladium complexes is thought to proceed via a β-elimination process from the intermediate σ-allylpalladium complex (A).[1,9] Intramolecular attack of specific base is postulated for regioselective elimination (B).[7] Recently, the anti-elimination pathway was postulated in the elimination of acetic acid from the cyclic acetates (C).[12]

The regioselectivity and the reaction rate in the elimination of *cis*-cyclohexyl acetate is influenced by the base used (**Scheme 10**). Under the standard conditions using

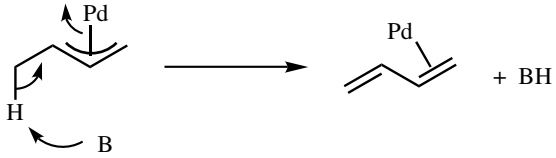
A: β-Hydride elimination



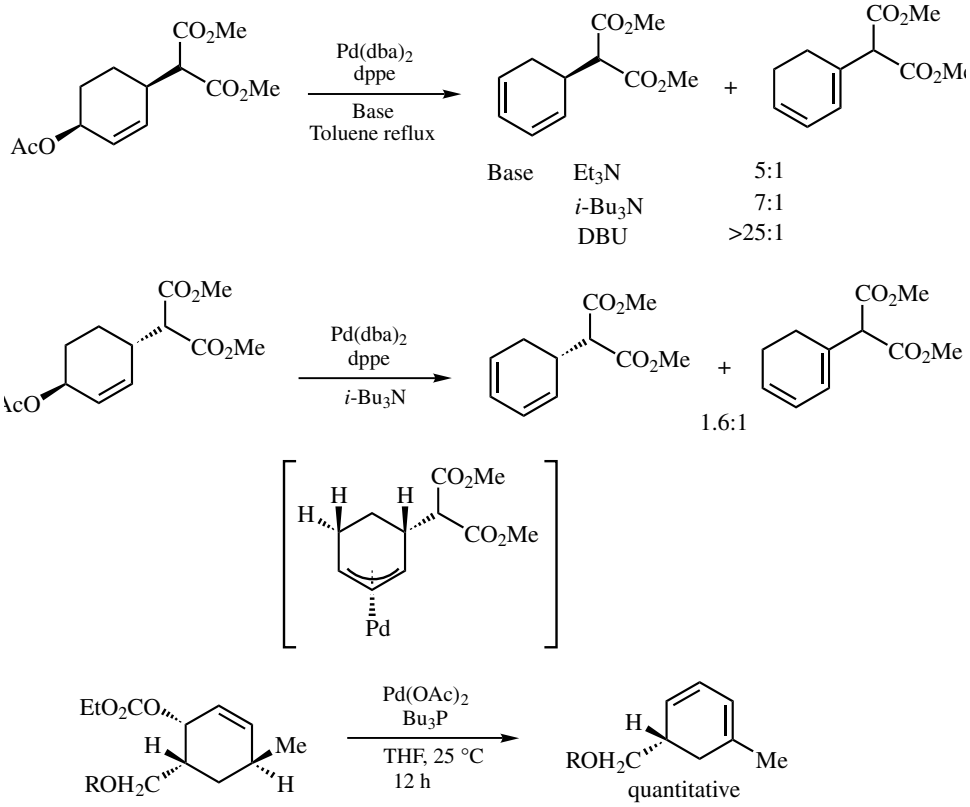
B: Specific base-promoted elimination



C: General base-promoted elimination



Scheme 9

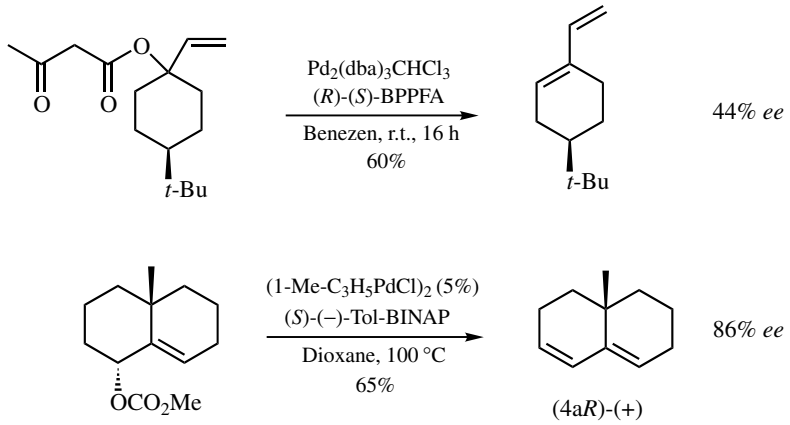


Scheme 10

triethylamine as a base the ratio of regioisomers was 5:1. When the sterically hindered amine, triisobutylamine, was used, the ratio was raised to 7:1. Furthermore, the use of DBU resulted in a very much faster reaction rate and the ratio in the isolated product was more than 25:1 (**Scheme 10**). The influence of choice of base contrasts with the β-elimination mechanism, but rather suggests the involvement of an *anti*-elimination pathway. Even in the reaction of the *trans*-acetate, which has only one cis hydrogen to palladium in the intermediate π-allyl complex, a substantially greater amount of 1-substituted diene isomer (1.6:1) was formed. The *anti*-stereochemistry of the hydride elimination was clarified using a cyclic allylic compound, which has one *syn* and one *anti*-hydrogen atom eliminated (**Scheme 10**, bottom). Actually, the Pd-catalyzed reaction gave overall *syn*-elimination product, which suggests that *anti*-elimination proceeded in the hydride elimination step from the π-allyl intermediate.[13]

D. ENANTIOSELECTIVE ELIMINATION OF ALLYLIC COMPOUNDS

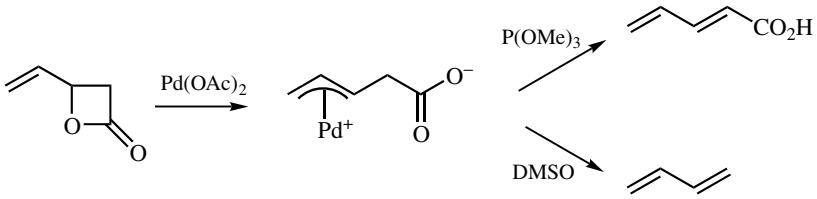
Enantioselective elimination is carried out using chiral phosphines as a ligand for the palladium catalyst. Reaction of the allylic acetoacetate ester of 4-*t*-butyl-1-vinylcyclohexanol with $Pd_2(dba)_3CHCl_3$ and (*R*)-(*S*)-BPPFA as a chiral ligand at room temparature (r.t.) gave (*R*)-1-vinyl-4-*t*-butylcyclohexene in 60% with 44% enantioselectivity (**Scheme 11**).[14] A higher enantioselectivity was observed in the reaction of a bicyclic acetate. Reaction of the allylic carbonate in the presence of $Pd(OAc)_2$ and (*S*)-(−)-BINAP gave the optically active bicyclic diene. Interestingly, the enantioselectivity was dependent on the ratio of (*S*)-(−)-BINAP/$Pd(OAc)_2$. With a ligand/Pd of 1.5:1 the (4a*R*)-(+)-isomer was formed predominantly, whereas with the ratio of 1.8:1 or higher its enantiomer (4a*S*)-(−)-isomer was obtained as the major isomer. When $Pd_2(dba)_3CHCl_3$ and (*S*)-BINAP was used, the same selection [(4a*S*)-(−)-isomer] was observed. In the case of $Pd(OAc)_2$, involvement of phosphine oxide as well as the phosphine is suggested. Actually, when the phosphine oxide, (*S*)-BINAP(O), was used, the opposite enantioselectivity to that of (*S*)-BINAP was observed. Reaction using $(1\text{-Me-}C_3H_5PdCl)_2$ and (−)-*p*-Tol-BINAP gave the bicyclic diene in 65% yield with 86% ee.[15]



Scheme 11

E. REGIOSELECTIVE FORMATION OF DIENES AND RELATED COMPOUNDS BY DECARBOXYLATIVE ELIMINATION

The substituted vinyl-β-lactone undergoes ring-opening isomerization to form 2,4-dienecarboxylic acid in aprotic solvents in the presence of catalytic amount of $Pd(OAc)_2$. Addition of trimethyl phosphite led to almost quantitative isomerization into the unsaturated acid. However, decarboxylation–elimination to form a conjugate diene proceeded in DMF or DMSO.[16] The quantitative evolution of CO_2 in good coordinating aprotic solvents is explained by a poor solvation of the carboxylate anion through the carboxylate (**Scheme 12**).

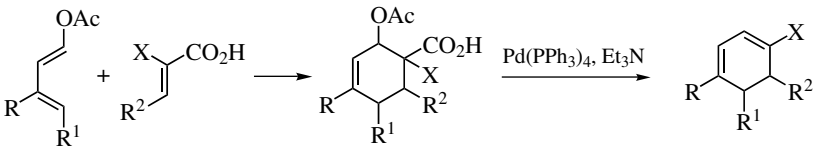


Scheme 12

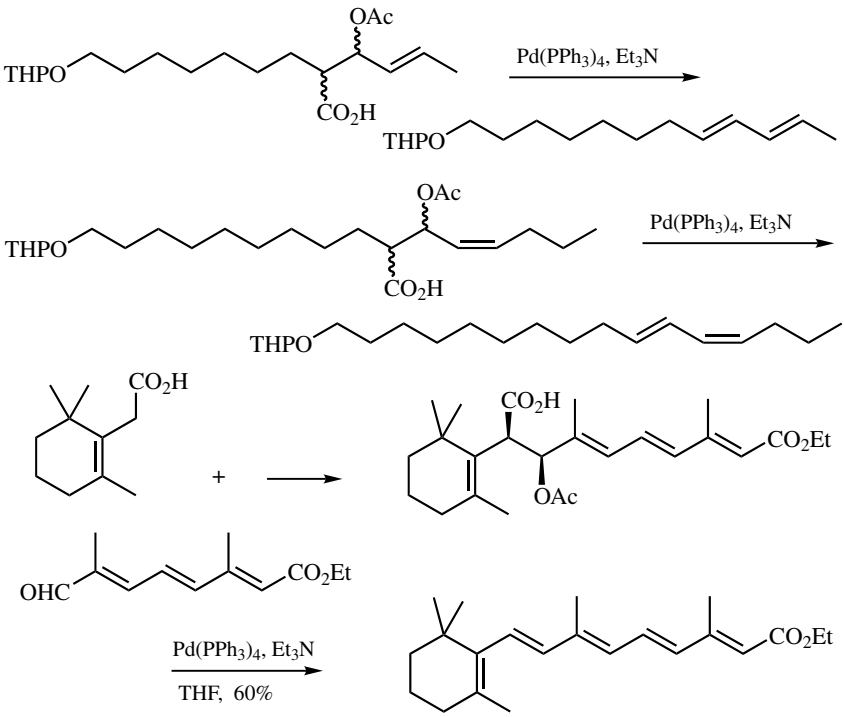
Regio- and stereocontrolled synthesis of 1,3-dienes was accomplished by decarboxylative elimination from 3-acetoxy-4-alkenoic acids, which are obtained from enals and carboxylate enolates (**Scheme 13**, **Table 4**).[17] The reaction was applied to the synthesis of bombykol. The reaction was also used for the construction of a polyene system in vitamin A.[18]

Diels–Alder reaction of 1-acetoxy-1,3-butadienes with α,β-unsaturated acid followed by Pd-catalyzed elimination gave various substituted 1,3-cyclohexadienes. [17]

TABLE 4. Synthesis of Cyclohexadienes



R	R^1	R^2	X	Percentage (%)
H	H	H	H	87
H	H	CO_2Me	H	71
H	C_2H_5	H	H	69
H	H	H	OAc	81
CH_3	H	Ph	H	77
H	H	C_2H_5	H	69

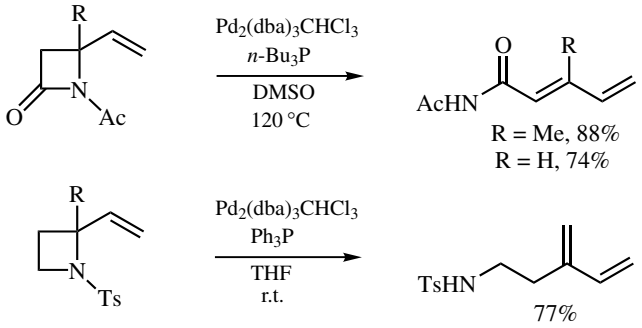


Scheme 13

F. ISOMERIZATION OF ALKENYLOXIRANES AND AZETIDINES

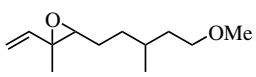
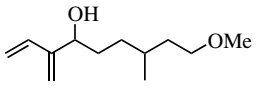
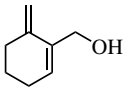
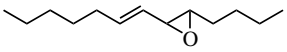
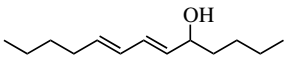
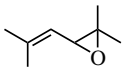
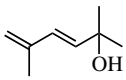
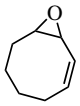
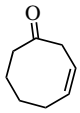
Reaction of palladium complexes with alkenyloxiranes gives π-allylpalladium intermediates, which decompose by elimination to give dienyl alcohols or unsaturated carbonyl compounds (**Table 5**). The selectivity of the elimination depends on the structure of the substrates.[19]

Pd-catalyzed reaction of vinyl azetidinones gave 2,4-pentadieneamide, whereas 2-substituted 1,3-dienes were produced by the reaction of 1-sulfonyl-2-vinylazetidines (**Scheme 14**).[20]



Scheme 14

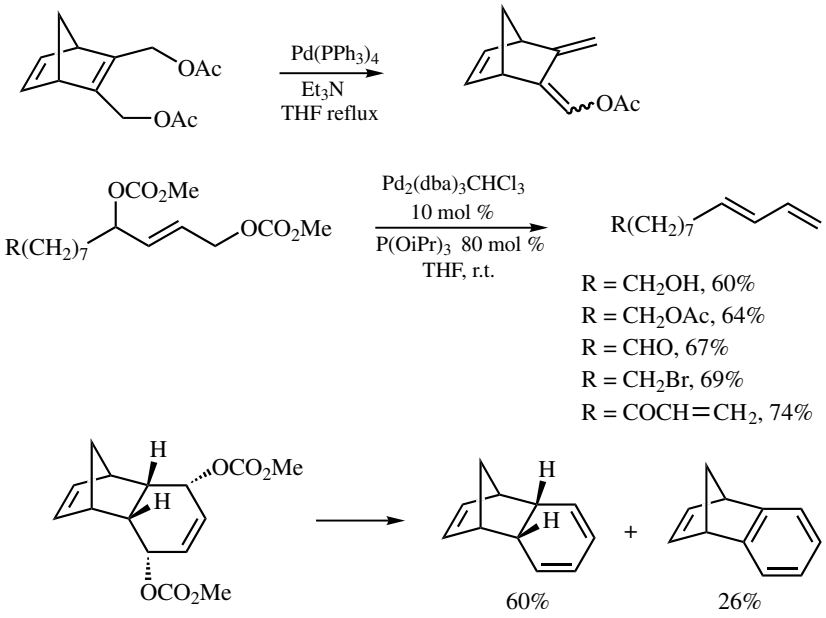
TABLE 5. Pd-Catalyzed Isomerization of Alkenyloxiranes

Alkenyl Oxiranes	Catalyst mol %	Solvent and Temperature (°C)	Products	Isolate Yield (%)
	1.4	THF 60		81
	0.5	THF 50		90
	0.8	THF 60		95
	1.1	PhH 130		79
	0.6	PhH 110		62
	0.5	PhH 25		63
	0.00013	CH_2Cl_2 77		77

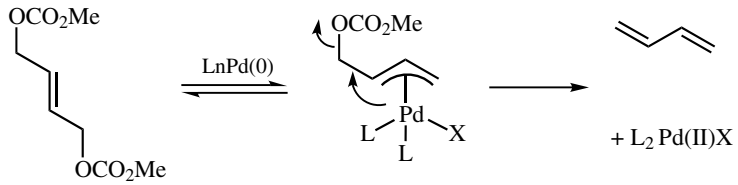
G. SELECTIVE DIENE FORMATION BY REDUCTIVE ELIMINATION

Pd-catalyzed elimination reaction of norbornadiene derivatives gave the dienyl acetate by elimination of HOAc (**Scheme 15**).[21] However, Pd-catalyzed elimination of dicarbonates of 1,4-butenediols gave 1,3-dienes by reductive elimination of dicarbonate. Reaction of *cis*-1,4-dimethoxycarbonyloxy-2-cyclohexene gave the reductive elimination product in 60% with the aromatic product by double elimination of acetic acid using triisopropy-lphosphate. *trans*-1,4-Dimethoxycarbonyloxy-2-cyclohexene did not give the reductive elimination product.[22]

The Pd-catalyzed reductive elimination is explained in **Scheme 16**. Dienes are formed in E_2 elimination manner and the carbonate works as a good leaving group. The generated Pd(II) species is reduced to a Pd(0) species by triisopropyl phosphite.



Scheme 15



Scheme 16

H. SUMMARY

1. Pd-catalyzed elimination of HX from allylic compounds proceeds to give 1,3-dienes in good yields under mild conditions, which provides a useful synthetic method.

2. The elimination of hydrogen and palladium species from π-allylpalladium complexes is explained in three ways: (i) *syn*-β-hydride elimination, (ii) intramolecular specific base-catalyzed elimination, and (iii) normal base-catalyzed anti-elimination.

3. Terminal 1,3-dienes can be prepared from terminal allylic compounds. Decarboxylative elimination and reductive elimination give internal conjugate dienes with high regioselectivity.

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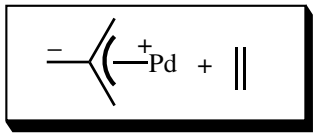

V.2.5.2 Cycloaddition Reactions of Allylpalladium and Related Derivatives

SENSUKE OGOSHI

A. INTRODUCTION

Palladium-catalyzed cycloaddition is one of the most popular and useful reactions for the construction of a variety of cyclic compounds. The first one was the [3 + 2] cycloaddition of 2-[(trimethylsilyl)methyl]allyl ester with olefins bearing electron-withdrawing groups reported in 1979 (**Scheme 1**),[1] and later a large number of cycloaddition reactions were studied, where [3 + 2], [3 + 4], [3 + 6], and [1 + 2] cycloaddition reactions were developed (**Scheme 2**) and applied to natural product synthesis. Most of these catalytic cycloadditions proceed via a trimethylenemethane palladium (TMM–Pd) intermediate or its analogs, oxatrimethylenemethane palladium (OTMM–Pd) and azatrimethylenemethane palladium (ATMM–Pd) (**Scheme 3**).

The other example of cycloaddition reaction of allylpalladium is the stoichiometric reaction of η^1-allylpalladium complexes with electron-deficient olefins to form a five-membered ring (**Scheme 4**).[2],[3]

In this section, we are going to review the scope and mechanisms of the Pd-catalyzed cycloaddition reactions.

B. CYCLOADDITION VIA TMM–PALLADIUM

B.i. [3 + 2] Cycloaddition with Alkenes

The construction of five-membered rings is a very important process for synthesis of the organic compound including natural products, especially the prostaglandins, and hence diverse strategies for efficient synthesis have been reported. The Pd-catalyzed [3 + 2] cycloaddition via TMM–Pd would be a common choice to construct the five-membered rings, since the reaction proceeds under neutral conditions tolerant to functional groups. 2-[(Trimethylsilyl)methyl]allyl ester is a very useful starting material as a TMM precursor for these cycloaddition reactions with electron-deficient olefins where *E*-olefins give *trans*-isomer exclusively but *Z*-olefins give a mixture of *cis*- and *trans*-isomers (**Scheme 5**).[1]

Although the phenyl-substituted TMM precursor gives only one regioisomer (**Scheme 6**),[4] the two isomeric methyl–TMM precursors give a mixture of two isomers

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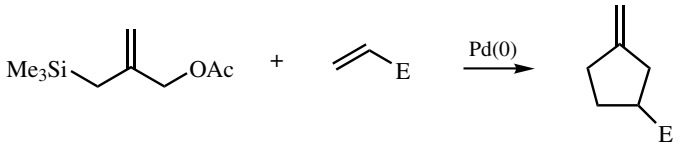
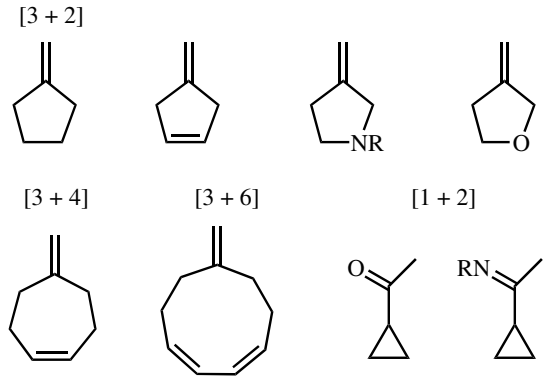
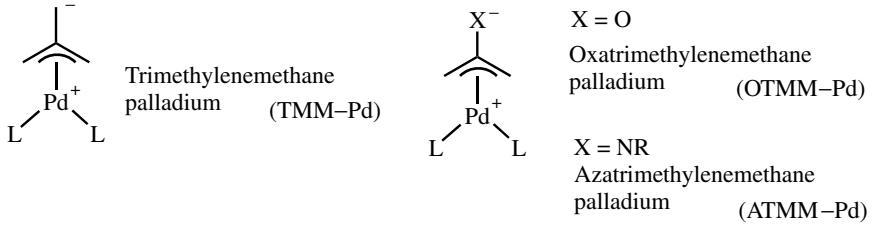


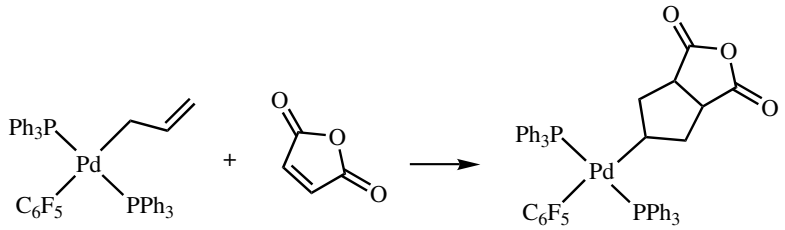
Scheme 1



Scheme 2. Cycloaddition products.

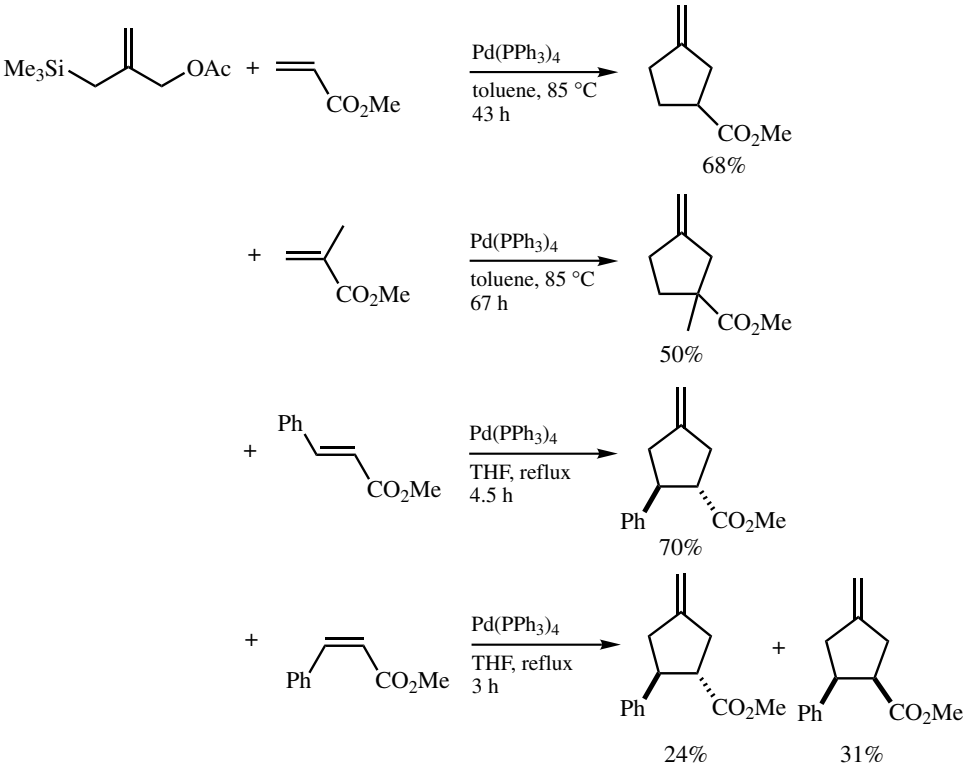


Scheme 3

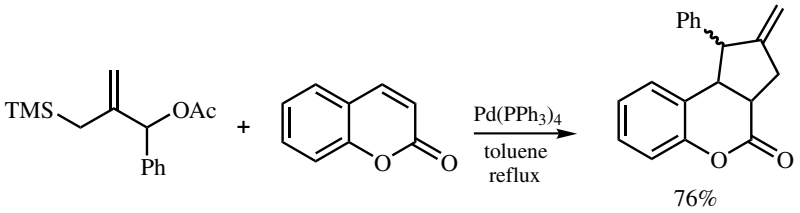


Scheme 4

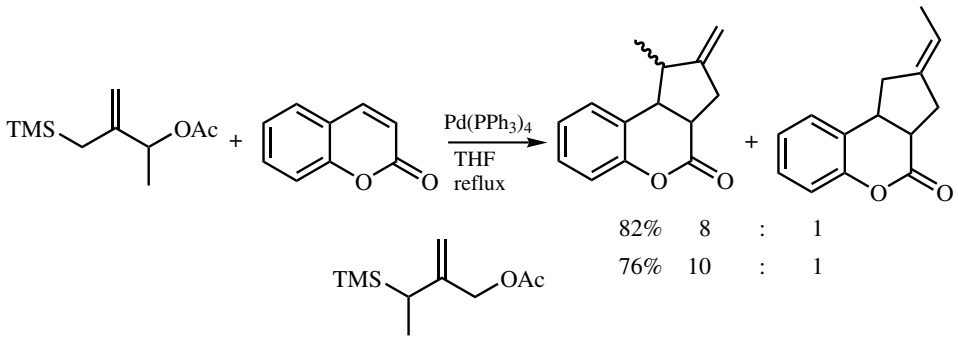
in similar ratio (**Scheme 7**).[5] The regiochemistry in the reaction via TMM–Pd is independent of the precursors but dependent on the stability of the TMM intermediates, since the rotation of the TMM moiety is much faster than the nucleophilic attack on the olefins. Actually, the very rapid rotation of the TMM moiety in TMM–Pd was confirmed by the reaction of the deuterium-labeled TMM precursor with coumarin to give completely scrambled products (**Scheme 8**).[6]



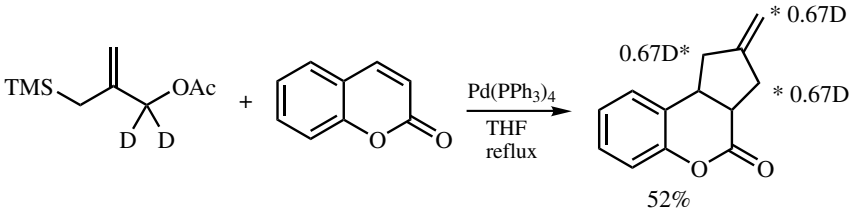
Scheme 5



Scheme 6

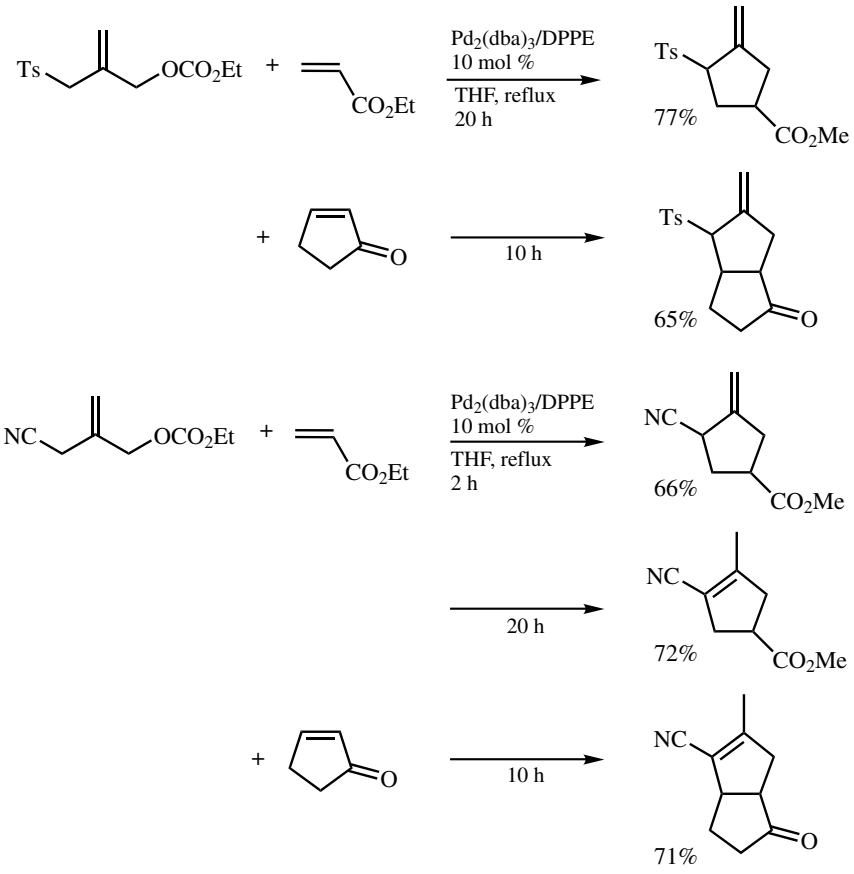


Scheme 7

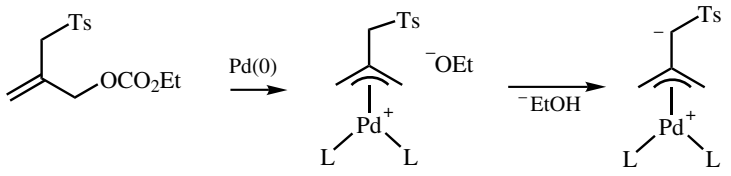


Scheme 8

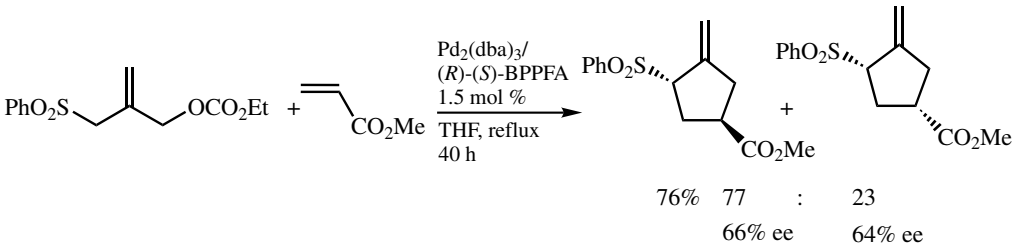
Electron-withdrawing group-substituted TMM precursors undergo the cycloaddition in high regioselectivity. Thus, 2-(sulfonylmethyl)- and 2-(cyanomethyl)allyl carbonate also undergo regioselective [3 + 2] cycloaddition via the most stable TMM–Pd generated by the abstraction of the methylene proton by ethoxide (**Schemes 9** and **10**).[7] In some cases, the cyano-substituted *exo*-olefin products are isomerized to more stable internal olefins after a longer period of reactions. In the presence of chiral diphosphine, (*R*)-(*S*)-BPPFA, an asymmetric cycloaddition reaction proceeded to give a diastereomeric mixture in moderate yields and in moderate enantiomeric excess (**Scheme 11**).[8]



Scheme 9

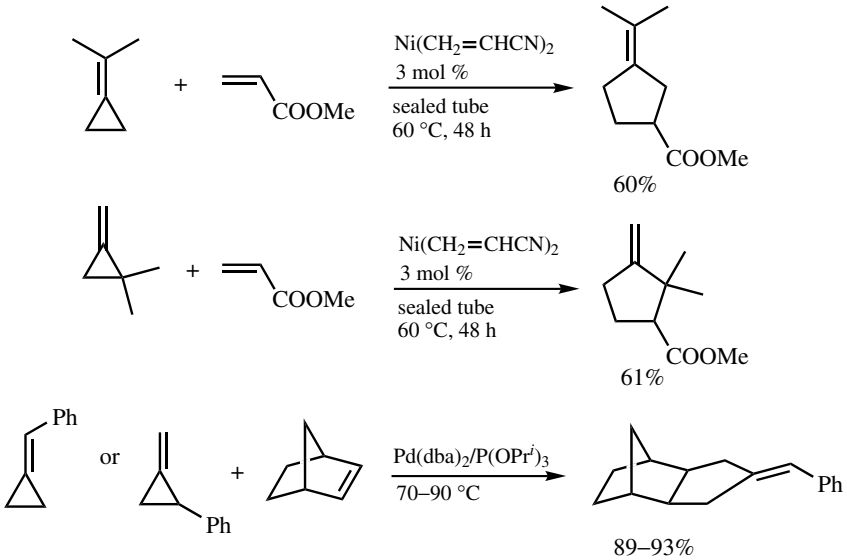


Scheme 10



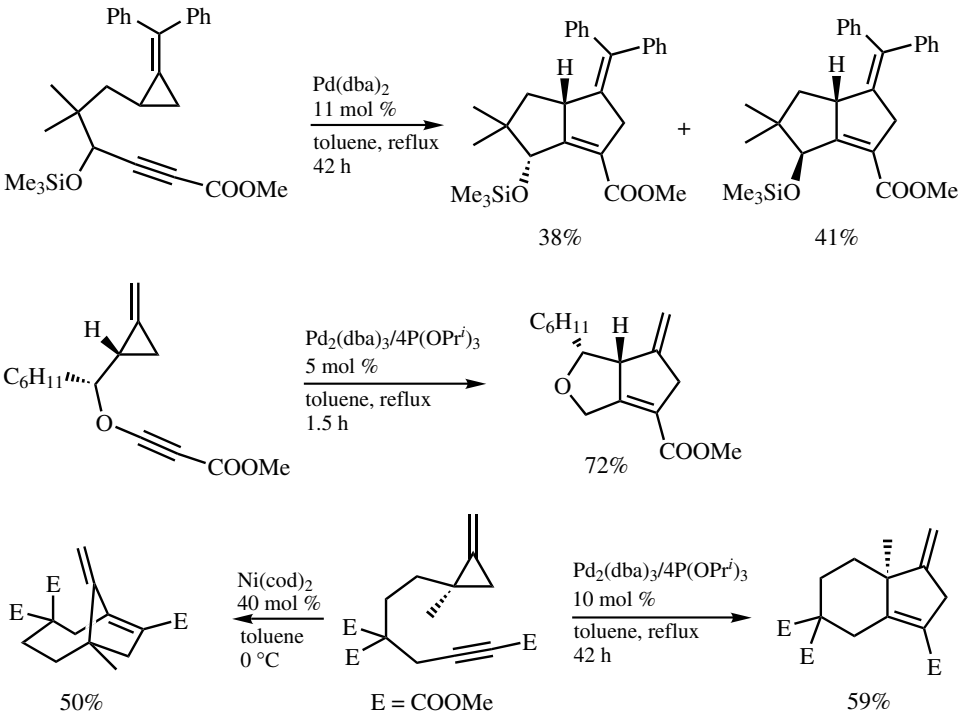
Scheme 11

Methylenecyclopropane is also a convenient TMM precursor for the cycloaddition reaction. Both nickel(0) and palladium(0) complexes can catalyze the [3 + 2] cycloaddition of alkylidenecyclopropanes with alkenes and alkynes (**Scheme 12**).[9],[10] Unlike the Ni-catalyzed reaction, the regioselectivity in the Pd-catalyzed reaction with alkene is independent of the structure of the starting alkylidenecyclopropanes, which indicates that this reaction also proceeds via TMM–Pd as mentioned above. The TMM–Pd generated from alkylidenecyclopropanes can undergo a stereoselective intramolecular cycloaddition with alkynes,[10],[11],[12] and the regiochemistry is different from the Ni-catalyzed reaction

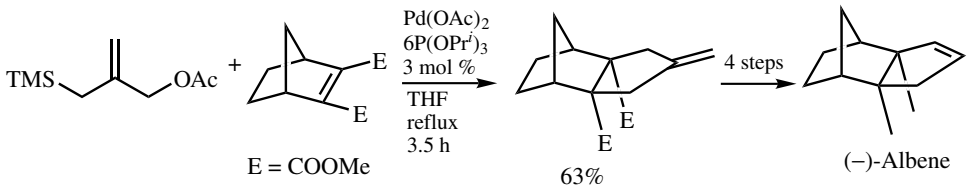


Scheme 12

(**Scheme 13**).[13] These [3 + 2] cycloaddition reactions have been applied to the synthesis of natural products, (±)-hirsutene,[14] (±)-albene,[15] (±)-brefeldin,[16] loganin aglucon,[17] and pentalenene.[18] In earlier applications, reactions with cycloalkenes were employed to construct bicyclic compounds (**Scheme 14**).[15] Then, *trans*-alkenes having a stereogenic center derived from mannitol were employed to control the stereochemistry of the cycloaddition (**Scheme 15**).[16]



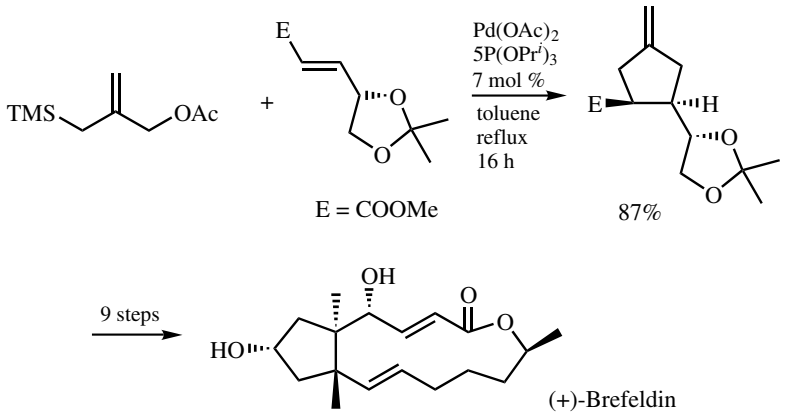
Scheme 13



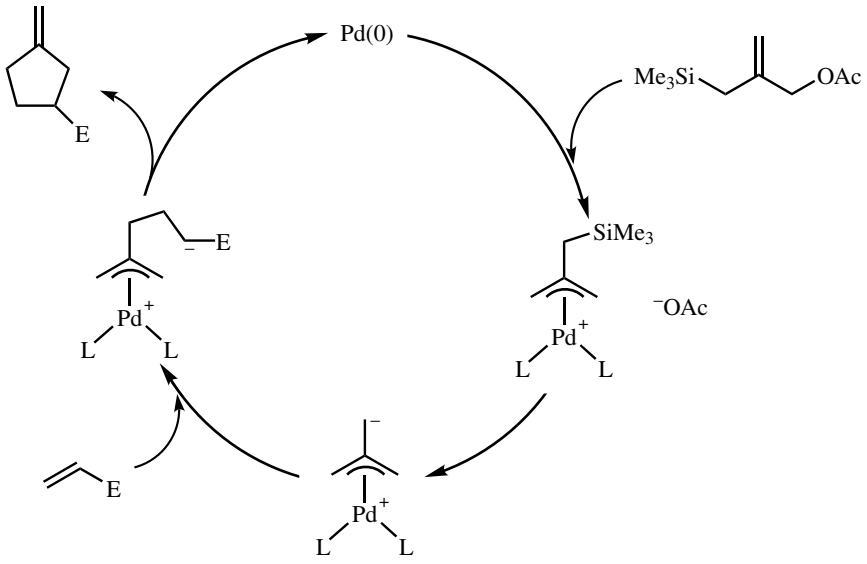
Scheme 14

B.ii. Mechanism

The proposed reaction mechanism for the [3 + 2] cycloaddition via TMM–Pd is shown in **Scheme 16**. Oxidative addition of allyl acetate moiety to the palladium(0) leads to the formation of a η^3-2-silylmethylallypalladium complex followed by nucleophilic attack on the silyl group to generate the TMM–Pd intermediate. Then, the addition of TMM–Pd to



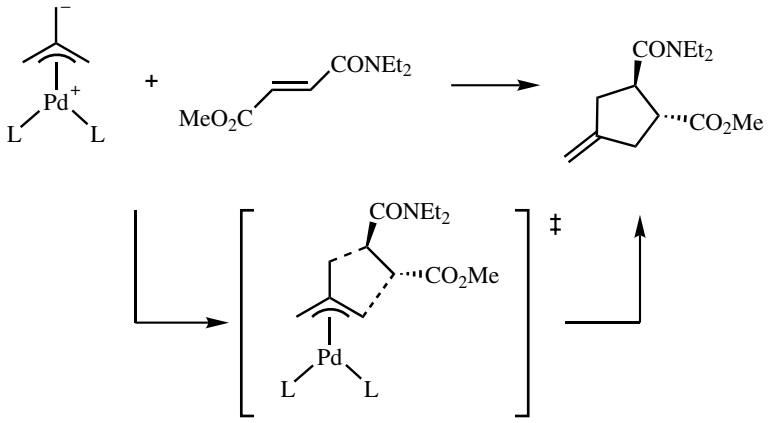
Scheme 15



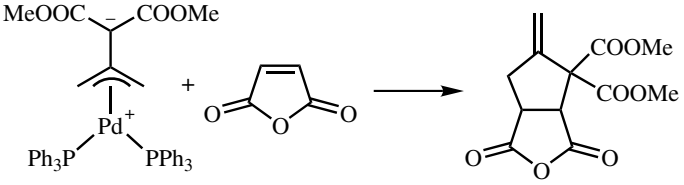
Scheme 16

the Michael acceptors gives rise to the zwitterionic intermediate followed by intramolecular nucleophilic attack on the terminal carbon to afford the five-membered ring. Recently, a concerted cycloaddition mechanism was also proposed. The carbon kinetic isotope effects in the reaction with fumarate ester amide were determined and these results cannot be reconciled with a stepwise cycloaddition mechanism but are interpreted in terms of a concerted cycloaddition (**Scheme 17**).[19]

Although it has been assumed that all of these reactions proceed via a TMM–Pd intermediate, only recently the TMM–Pd complex was isolated for the first time, of which the X-ray structure shows the zwitterionic η^3-coordination mode of the TMM moiety. Furthermore, the isolated complex reacts with electron-deficient olefins to give [3 + 2] cycloaddition products, which is consistent with the proposed mechanism (**Scheme 18**).[20]



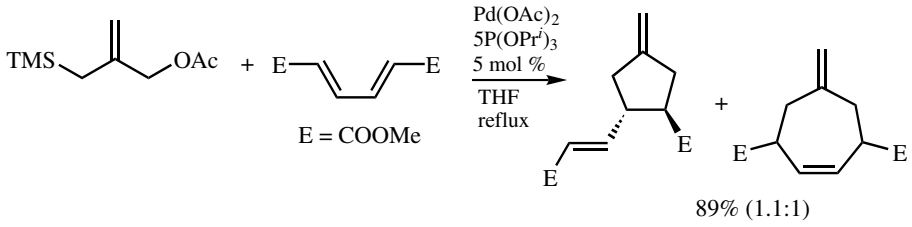
Scheme 17



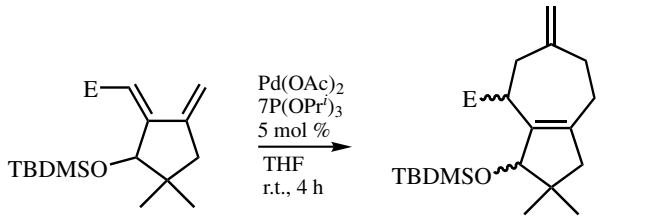
Scheme 18

B.iii. [3 + 4] Cycloaddition, [3 + 6] Cycloaddition

Potentially, any polyene would react with TMM–Pd to give the corresponding large rings and such reactions are very fascinating for organic chemists. However, so far, only a limited number of [3 + 4] and [3 + 6] cycloaddition reactions have been reported. Pd-catalyzed reaction of 2-[(trimethylsilyl)methyl]allyl acetate with an electron-poor diene leads to the formation of a mixture of five-membered and seven-membered rings, where conformationally rigid dienes undergo [3 + 4] cycloaddition in higher selectivity (**Scheme 19**).[21],[22] Selective synthesis of seven-membered rings was accomplished by the use of pyrone derivatives as dienes, where the reaction proceeds via the thermodynamically stable dienolate (**Scheme 20**).[23] On the other hand, the reaction with methyl coumalate analogous to pyrone gives a mixture of five- and seven-membered rings. The tropone reacts with TMM–Pd as a triene to give the corresponding [3 + 6] cycloaddition product (**Scheme 21**).[24]

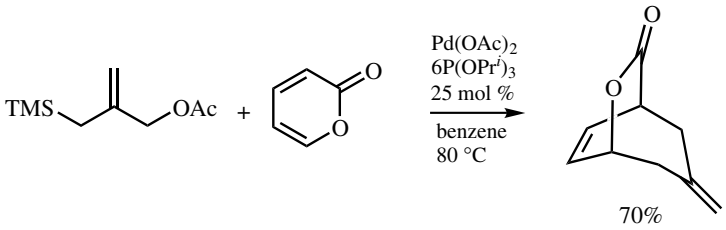


Scheme 19 (*Continued*)



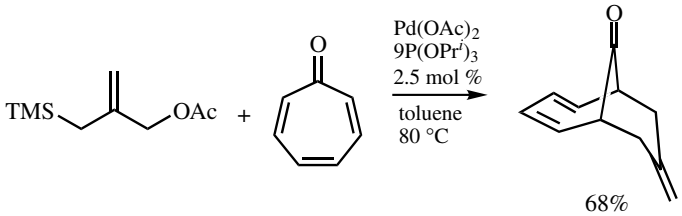
87%
(diastereomeric ratio 2.4:1)

Scheme 19



70%

Scheme 20



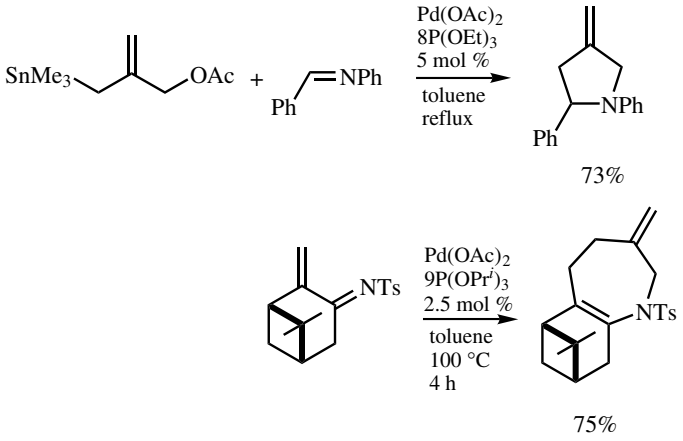
68%

Scheme 21

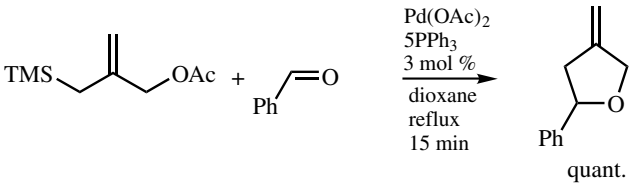
B.iv. [3 + 2] and [3 + 4] Cycloaddition with Aldehyde, Ketone, and Imine

Although 2-[(trimethylsilyl)methyl]allyl esters and halides react with imines to give pyrrolidines (**Scheme 22**),[25],[26] the cycloaddition reaction with carbonyl compounds requires much more drastic conditions. On the other hand, 2-[(trialkylstannyl)methyl]allyl acetate can react with aldehydes to give furanyl compound, where the presence of trialkyltin acetate, as a by-product, is crucial to compel the reaction successfully (**Scheme 23**).[27] In fact, in the presence of the trialkyltin acetate, even the 2-[(trimethyl silyl)methyl]allyl ester undergoes [3 + 2] cycloaddition reactions with aldehydes (**Scheme 24**) and ketones successfully.[28] Similarly, $InCl_3$ is also an efficient additive for the cycloaddition reaction and both aldehydes and ketones are suitable as substrates.[29],[30]

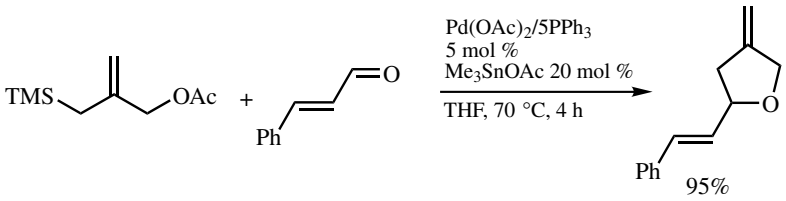
A proposed mechanism for the cycloaddition with carbonyl compounds is depicted in **Scheme 25**.[31] The TMM–Pd intermediate reacts with carbonyl group to give rise to the zwitterionic η^3-allylpalladium complex. Addition of the tin acetate leads to the formation



Scheme 22



Scheme 23

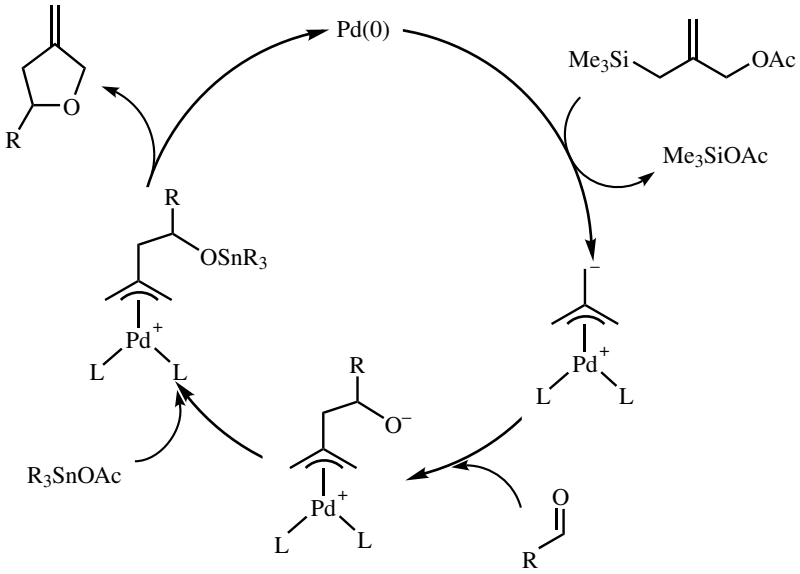


Scheme 24

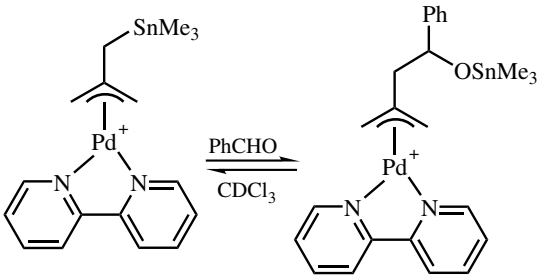
of a stannyl alkoxide, of which the nucleophilicity is now tuned[32] to give the cycloaddition products. Actually, in a different ligand system, the reversible insertion of carbonyl group was observed to lead to the formation of the palladium complex corresponding to the stannyl alkoxide intermediate (**Scheme 26**).[33]

C. CYCLOADDITION VIA OTMM, ATMM–PALLADIUM [1 + 2] CYCLOADDITION

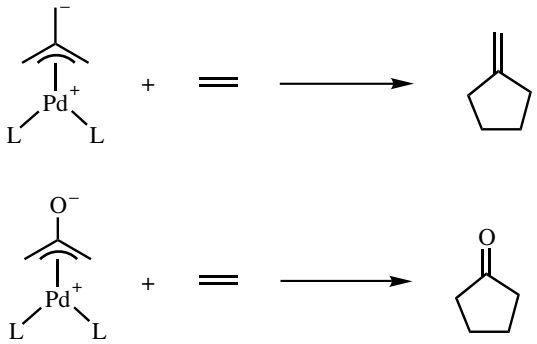
The transfer of the TMM fragment from the TMM–Pd to an olefin leads to the formation of a methylenecyclopentane. Thus, generation of the OTMM–Pd complex followed by the transfer of the OTMM moiety to an olefin would be expected to give a cyclopentanone (**Scheme 27**). However, the 2-(trimethylsiloxy)allyl methyl carbonate, an OTMM



Scheme 25

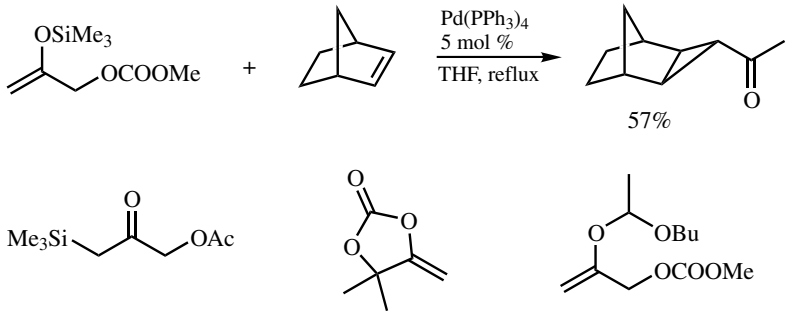


Scheme 26

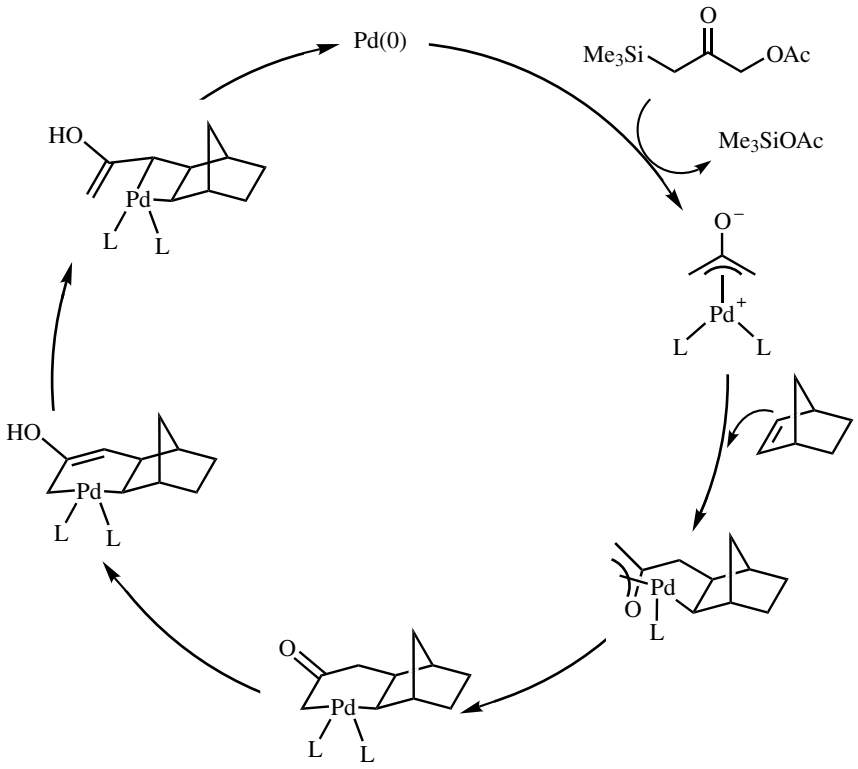


Scheme 27

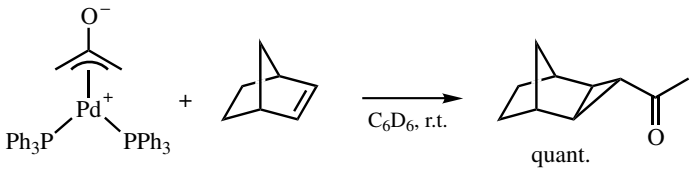
precursor corresponding to the 2-[(trimethylsilyl)methyl]allyl ester, did not undergo [3 + 2] cycloaddition at all. Only [1 + 2] cycloaddition with norbornene derivatives occurred to give three-membered rings. Another OTMM precursor also underwent the same reaction (**Scheme 28**).[34]–[37] In the proposed reaction mechanism for the [1 + 2] cycloaddition, the OTMM–Pd complex adds to norborene followed by isomerization and reductive elimination to give the cyclopropane (**Scheme 29**). In fact, isolated OTMM–Pd reacts with norbornene to give a cyclopropane (**Scheme 30**).[38]



Scheme 28

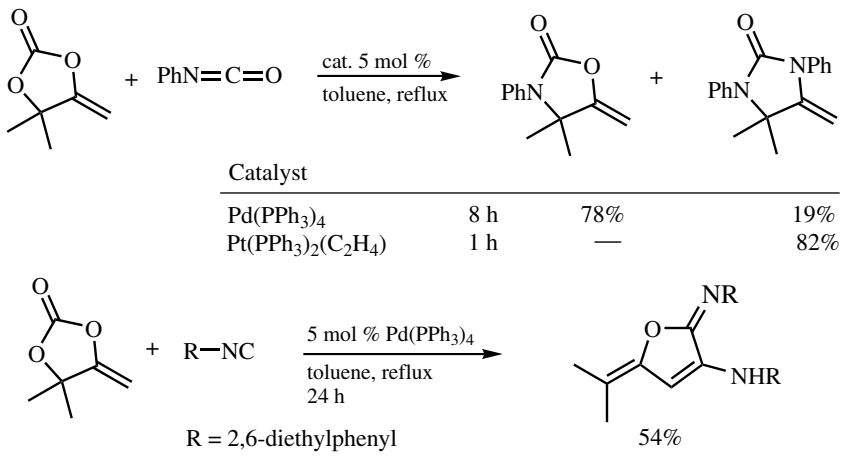


Scheme 29

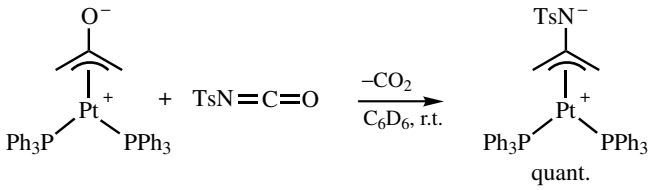


Scheme 30

The OTMM–Pd reacts with several isocyanates or isonitriles in catalytic reactions to afford cycloaddition products (**Scheme 31**).[36] The $Pt(PPh_3)_2(C_2H_4)$ can also catalyze the reaction of an OTMM precursor with isocyanate to give a cyclic carbamate as the sole product, which is the minor product in a Pd-catalyzed reaction. The rationalization for the formation of the cyclic carbamate requires the transformation of OTMM–Pt to ATMM–Pt (or OTMM–Pd to ATMM–Pd) as a key step in the reaction process. Actually, the reaction of the OTMM–Pt with tosylisocyanate gives the corresponding ATMM–Pt complex quantitatively (**Scheme 32**).[39]

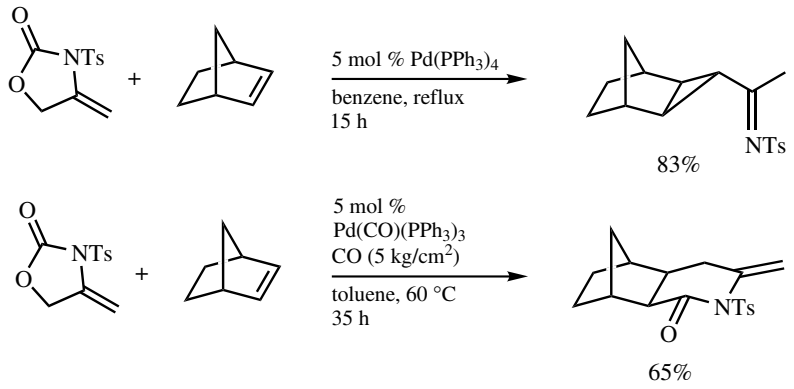


Scheme 31



Scheme 32

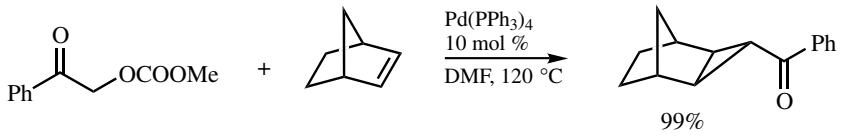
Similarly, the [1 + 2] cycloaddition via ATMM–Pd was also reported. In the presence of carbon monoxide, [3 + 2 + 1] cycloaddition reaction occurred to give the γ-lactam (**Scheme 33**).[40] Although no ATMM–Pd complex has been reported, the corresponding platinum complex was isolated.[41]



Scheme 33

D. OTHERS

The similar [1 + 2] cycloaddition via a η^3-oxaallylpalladium intermediate is also reported, where the benzoyl group-substituted cyclopropane is obtained (**Scheme 34**).[42]



Scheme 34

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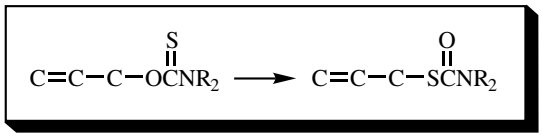

V.2.5.3 Rearrangements of Allylpalladium and Related Derivatives

PAVEL KOČOVSKÝ and IVO STARÝ

A. INTRODUCTION

This section deals with those rearrangements of allylic substrates that involve (η^3-allyl)palladium complexes as intermediates. These reactions give products of formal [1,3] or [3,3] shifts, depending on the substrate structure and other factors: genuine [3,3] sigmatropic shifts occur via a different mechanism and, therefore, are covered in a different section (**Sect. IX.2.1.1**).

Thermal [3,3] sigmatropic shifts can be summarized as shown in **Scheme 1**, Eq. 1. These rearrangements are often catalyzed by an electrophilic metal in a higher oxidation state, that is, by Pd^{2+} or Hg^{2+} (Eq. 2).[1–5] By contrast, [1,3] rearrangements typically occur with Pd(0) and are initiated by the formation of an intermediate (η^3-allyl)Pd complex (Eq. 3). Recombination of the latter complex with the leaving group can then occur in three topologically different fashions (3a, 3b, and 3c), of which the latter (3c) affords the same product as the [3,3] shift.[6,7] Hence, as a rule, Pd(II) catalyzes [3,3] sigmatropic shifts, while Pd(0) complexes typically promote reaction via (η^3-allyl)Pd intermediates. However, in a number of cases, Pd(II) is used as the catalyst precursor that is first reduced by an added phosphine ligand to Pd(0) so that the mechanistic nature of a given reaction may not be obvious at first glance. It is the purpose of this section to make this issue clear.

B. REARRANGEMENTS INVOLVING THE C—O → C—O CONVERSION

Allylic acetates are known to rearrange[8] in the presence of a catalytic amount of both Pd(II)[1,2,9] and Pd(0).[9–11] While Pd(II) promotes the [3,3] sigmatropic shift (Eq. 2 in **Scheme 1**), the reaction with Pd(0) catalyst apparently proceeds via the (η^3-allyl)Pd complex (Eq. 3). Stereochemical studies have revealed the inversion of configuration, which is consistent with the coordination of AcO^- to the metal along the reaction course (**Scheme 2**).[12] Evidence for the migration of AcO^- from Pd to the coordinated allyl group was subsequently provided.[13,14] Partial loss of stereochemical homogeneity, both at the chiral center and at the double bond (for noncyclic substrates), and competing elimination have also been reported.[11,12,15]

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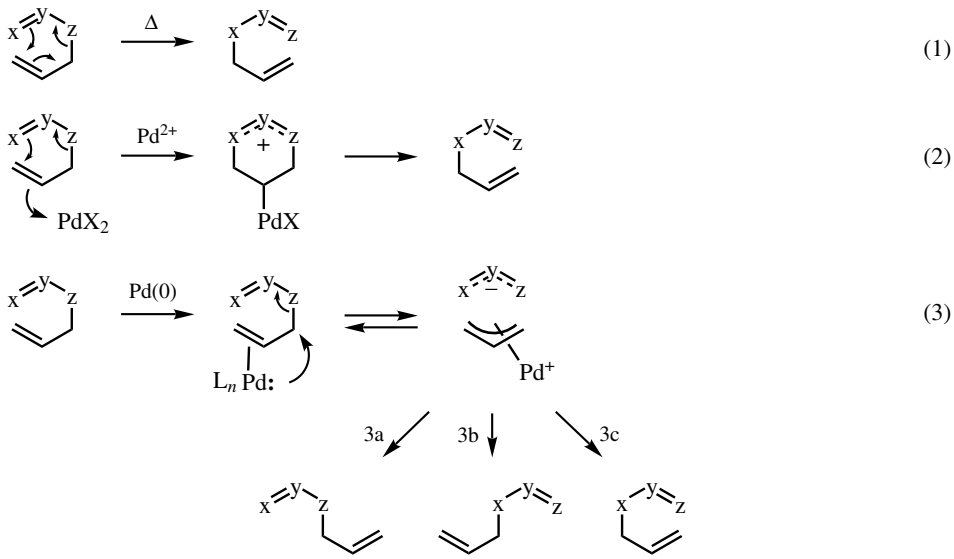
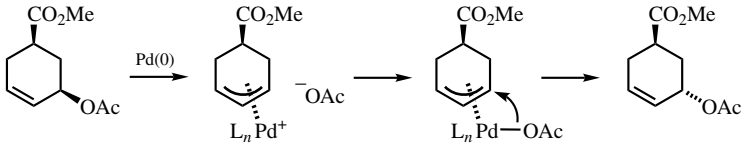
ISBN 0-471-31506-0

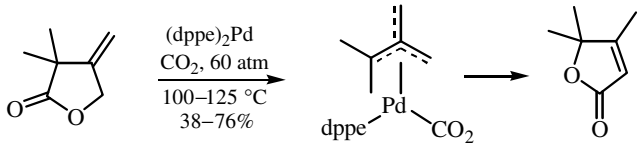


Scheme 1



Scheme 2

An interesting, complex rearrangement involving Pd coordination of the leaving group and cleavage of the tertiary allylic carbon–carboxyl bond is illustrated in **Scheme 3**; although the reaction is catalytic, its stoichiometric version gives better yields.[16]



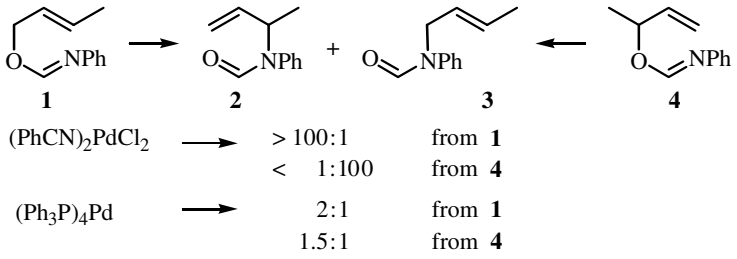
Scheme 3

C. REARRANGEMENTS INVOLVING THE C—O → C—N CONVERSION

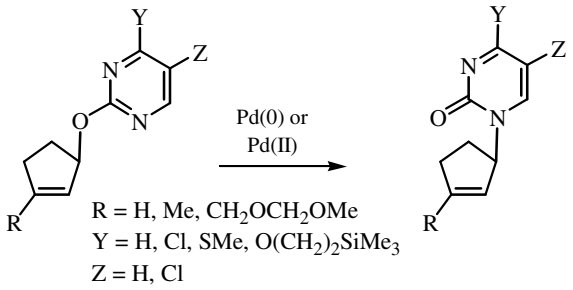
The formal aza-Claisen rearrangement has been reported to be catalyzed by either Pd(II) or Pd(0). While Pd(II) apparently promotes the [3,3] sigmatropic rearrangement (Eq. 2 in **Scheme 1**), Pd(0) favors the formation of the intermediate (η^3-allyl)Pd complex, as evidenced by the regioselectivity of the reaction (**Scheme 4**). Thus, while both **1** and **4** always give the product of [3,3] transposition with excellent regioselectivity in the presence of Pd(II), Pd(0) affords a practically identical mixture of the products **2** and **3** (2:1 and 1.5:1, respectively).[17]

Another C—O → C—N rearrangement has been utilized in the synthesis of pyrimidine carbonucleosides (**Scheme 5**).[18]

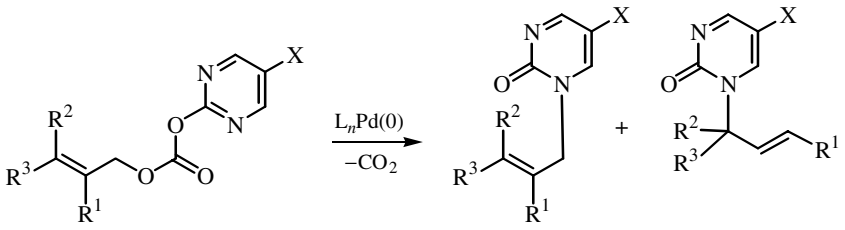
Even more synthetically useful is the analogous rearrangement of readily available 2-pyrimidinyl carbonates that occurs with the extrusion of CO_2.[19] In this case, the regioselectivity is consistent with an intermediate (η^3-allyl)Pd complex (i.e., preferential attack at the less substituted carbon of the allylic moiety) but a dependency on the ligand coordinated to Pd has been noted (**Scheme 6**).[19]



Scheme 4



Scheme 5



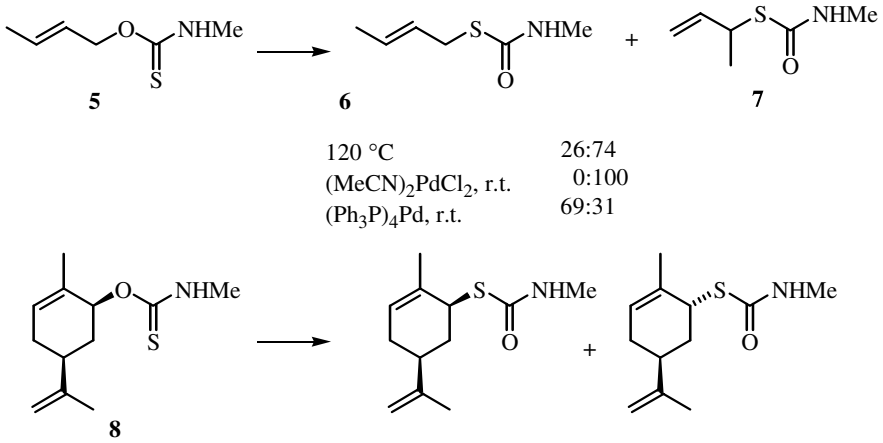
R^1	R^2	R^3	X	L	Product Ratio
Pent	H	H	Cl	$(i\text{-PrO})_3P$	0 : 100[a]
Pent	H	H	Cl	Ph_3P	37 : 63[b]
H	H	Me	Cl	$(i\text{-PrO})_3P$	84 : 16[c]
H	H	Me	Cl	Ph_3P	18 : 82[d]
H	Me	Me	Br	$(i\text{-PrO})_3P$	99 : 1
H	Me	Me	Br	Ph_3P	99 : 1

[a] 2% *cis*. [b] 7% *cis*. [c] 17% *cis*. [d] 2% *cis*.

Scheme 6

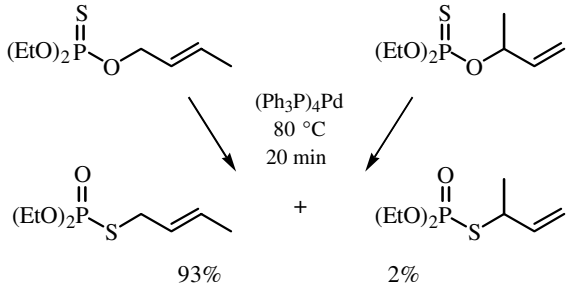
D. REARRANGEMENTS INVOLVING THE C—O → C—S CONVERSION

Allylic thiocarbamates are known to undergo an O⟶S migration under a variety of conditions.[20] A comparison of the individual methods reveals that thermally induced and Pd(II)-catalyzed rearrangements proceed mainly as [3,3] sigmatropic shifts, whereas Pd(0) catalysis exhibits features typical of the involvement of (η^3-allyl)Pd intermediates (**Scheme 7**). Thus, while **5** gives mainly the transposition product **7** on heating or in the presence of Pd(II), the Pd(0)-catalyzed reaction shows a preference for the characteristic attack by the nucleophile on the less substituted carbon (**6**). Furthermore, partial loss of diastereopurity has been observed for the thermal and Pd(II)-catalyzed reaction of the carveyl derivative **8**, whereas the Pd(0)-catalyzed reaction was stereospecific.[20]



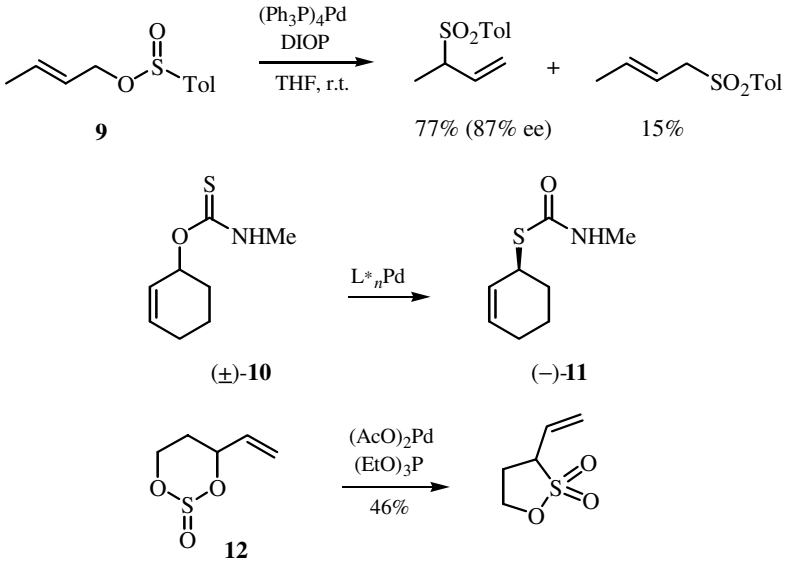
Scheme 7

Similarly, *O*-allylic esters of thionophosphoric acids undergo a Pd(0)-catalyzed rearrangement to their *S*-allylic isomers (**Scheme 8**). The reaction is believed to proceed via a (η^3-allyl)Pd intermediate, a conclusion supported by the formation of the same mixtures of *S*-products starting from either positional *O*-ester.[21],[22] By contrast, Pd(0) is ineffective in the rearrangements of, for example, *S*-allylthioimidates, suggesting a different mechanism,[23],[24] presumably a [3,3] shift.



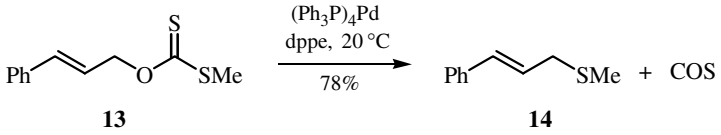
Scheme 8

Allylic *p*-toluenesulfinate–sulfone rearrangement (**Scheme 9**) of the enantiopure sulfinate **9** (chiral at sulfur) has been reported to occur with a high level of enantioselectivity in the chirality transfer (91.8%).[25]–[32] Asymmetric induction (87% ee) was attained for racemic **9** in the presence of DIOP as the chiral ligand.[28],[29] Similarly, rearrangement of racemic *O*-allylic thiocarbamates, such as (±)-**10**, carried out in the presence of Trost's modular ligand, afforded the *S*-allylic thiocarbamate (−)-**11** (97% ee).[32] The rearrangement of sulfonate **12** can also serve as an example of O → S migration.[33]



Scheme 9

Pd(0)-catalyzed rearrangements of dithiocarbonates, such as **13**, readily available from the corresponding alcohol, CS_2, and MeI, proceed under mild conditions with concomitant elimination of COS,[34] offering an interesting route to allyl sulfides **14** (**Scheme 10**).

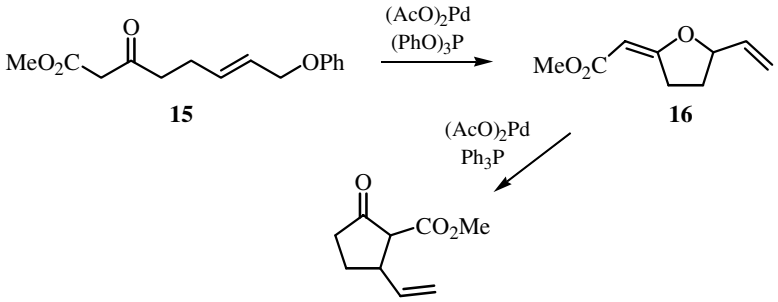


Scheme 10

E. REARRANGEMENTS INVOLVING THE C—O → C—C CONVERSION

Whereas Pd(0)-catalyzed allylic substitution with β-dicarbonyl nucleophiles normally leads to the C-allylated products, there are exceptions to this rule: an intramolecular reaction, under specific conditions, may prefer O-alkylation and the resulting product can often be isomerized to the thermodynamically stable C-alkylated derivative (**Scheme 11**). Thus, O-alkylation has been reported to be favored in the presence of a phosphite ligand

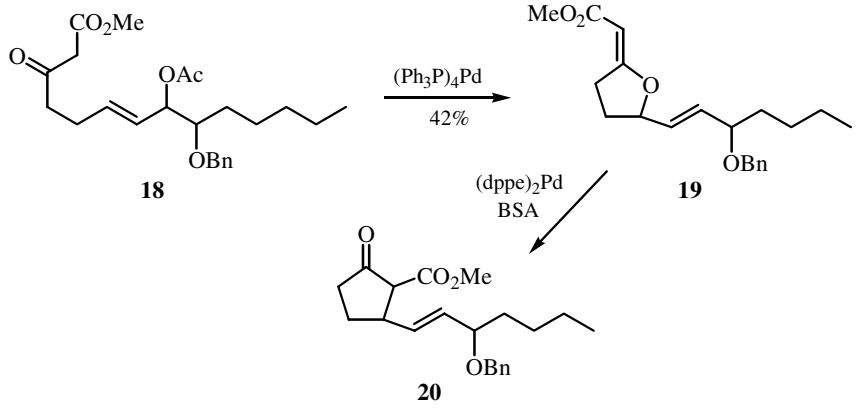
(**15**→ **16**). Subsequent treatment of the resulting tetrahydrofuran derivative with Pd in the presence of dppe or Ph_3P led to isomerization (**16**→ **17**)[35]; the final cyclopentanone product was contaminated by a minor amount of the isomeric cycloheptenone derivative.[35]–[39] Note that the thermal rearrangement of **16** proceeds as a [3,3] shift, affording the cycloheptenone isomer.[40],[41]



15 **16** **17**

Scheme 11

The C/O-alkylation ratio seems to be also dependent on the substrate, rather than just on the ligand (**Scheme 12**). Thus, for instance, treatment of the prostaglandin precursor **18** with Pd(0) even in the presence of Ph_3P has been reported to afford exclusively the O-allylation product **19**. This latter derivative can be rearranged to the C-allylation product **20** in the presence of dppe.[36]



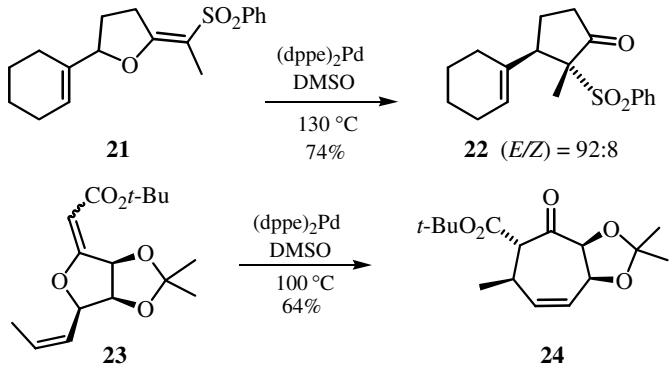
18 **19** **20**

Scheme 12

While in most cases a five-membered C-allylation product is formed (**21**→ **22**; **Scheme 13**), a seven-membered ring was produced exclusively in another instance (**23**→ **24**),[38] presumably owing to the inductive effect of the oxygen atom adjacent to the allylic system in the intermediate (η^3-allyl)Pd complex.[38],[39]

An allylic rearrangement was apparently responsible for earlier discrepancies in the regioselectivity of certain allylic substitutions. It is now generally accepted that reactions carried out at low temperatures for short periods of time are typically under kinetic control, and the resulting product can be isomerized when the reaction is run at high temperatures for longer times to afford thermodynamic products.[42] The regioselectivity is

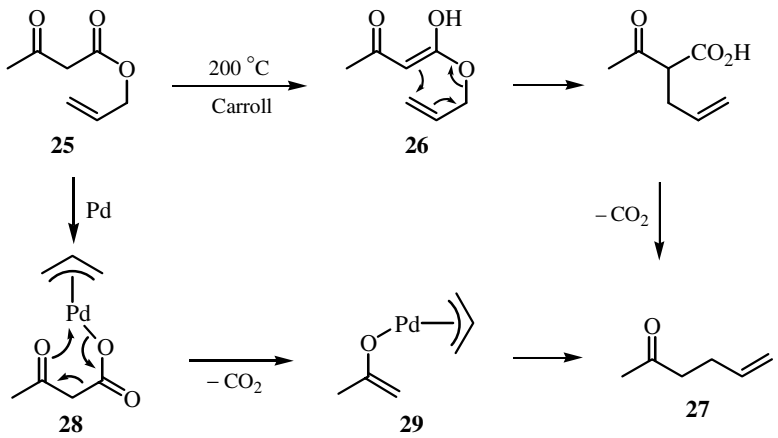
further complicated by the nature of the leaving group, the nucleophile, and the ligand. All these effects can influence the preference for kinetic or thermodynamic control.[43]



Scheme 13

F. PALLADIUM(0)-CATALYZED CARROLL REARRANGEMENT

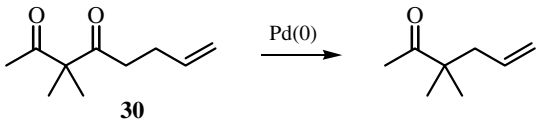
The Carroll rearrangement (**Scheme 14**) that occurs thermally as a typical [3,3] sigmatropic shift (**25**→ **26**→ **27**)[44] can be catalyzed by Pd(0). In the latter case, the reaction proceeds with a different mechanism, involving (η^3-allyl)Pd coordination (**28** and **29**).[45],[46]



Scheme 14

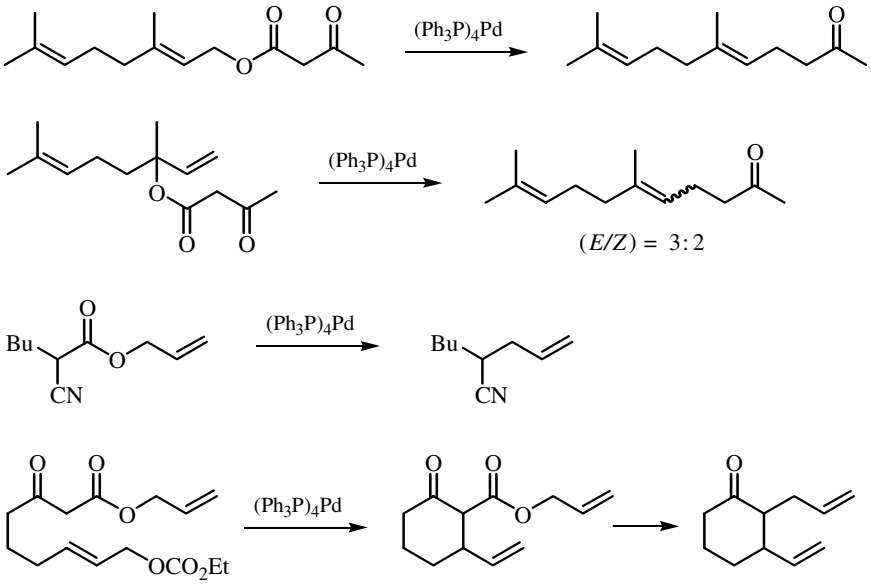
Furthermore, unlike its thermal variant, the Pd-catalyzed Carroll rearrangement does not involve the enolate of the β-dicarbonyl, as evidenced by the ready rearrangement of the β,β-dialkyl substrate **30** (**Scheme 15**) in the presence of Pd (note that this reaction does not occur under thermal conditions).[45],[46]

This rearrangement is fairly versatile and a number of suitable β-dicarbonyl analogs have been reported to follow the general pattern.[45],[47]–[52] Some of the synthetic applications are highlighted in **Scheme 16**.



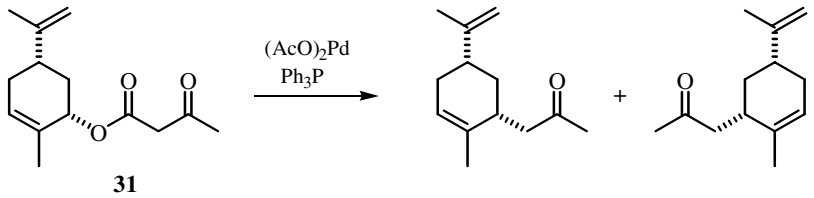
30

Scheme 15



Scheme 16

Racemization, observed for the rearrangement of (−)-*cis*-carvyl acetoacetate (**31**), is consistent with the intermediacy of the (η^3-allyl)Pd complex (**Scheme 17**); $(AcO)_2Pd$ employed in this reaction is apparently reduced to Pd(0) *in situ* by Ph_3P.[53]

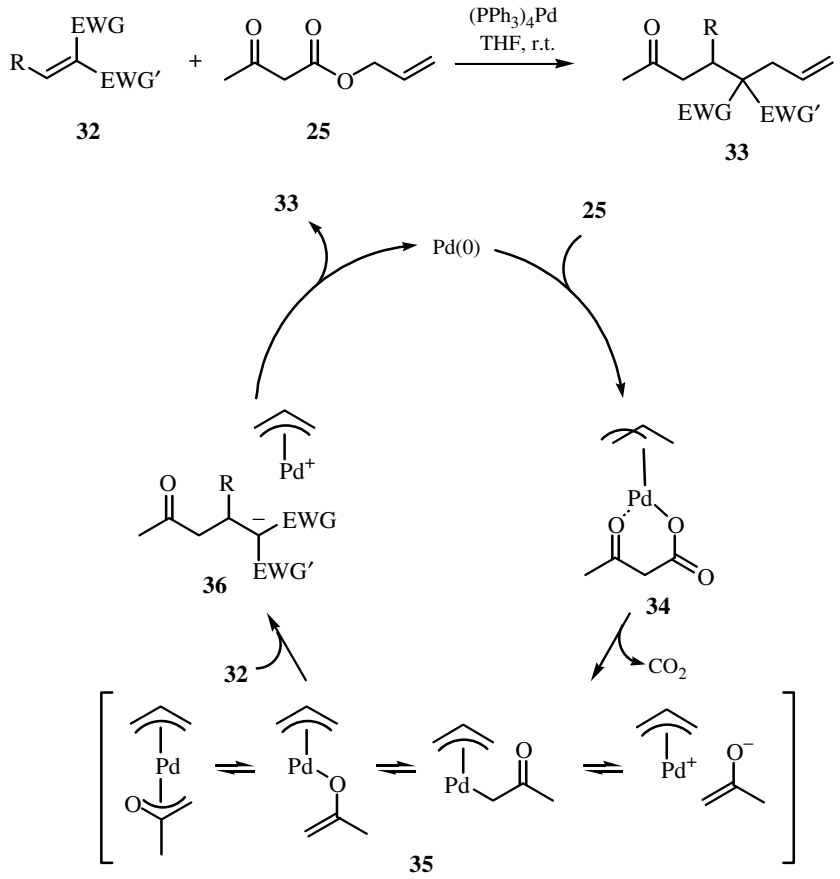


31

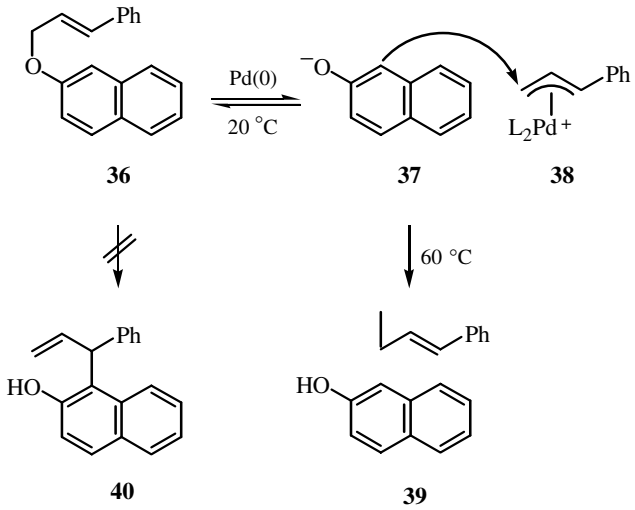
Scheme 17

This chemistry has recently been employed in a regioselective tandem β-acetonation–α-allylation of strongly activated Michael substrates (**Scheme 18**), in which the starting allyl acetylacetonate **25** first generates the chelated (η^3-allyl)Pd complex **34** whose decarboxylation produces the corresponding enolate **35** that is added to the Michael substrate **32** to generate anion **36**; the reaction is completed by the reaction of the latter species with the (η^3-allyl)Pd complex, thereby releasing Pd(0) for the next catalytic cycle.[54]

The Pd(0)-catalyzed reaction of ethyl cinnamyl carbonate with β-naphthol has been shown[55] to give first the O-allylated kinetic product **36** (**Scheme 19**), which is rearranged



Scheme 18

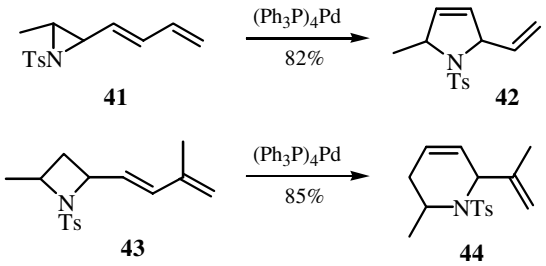


Scheme 19

at higher temperature to the thermodynamic C-alkylated product **39**. Although the latter transformation could be conjectured as occurring via Claisen rearrangement, it has been demonstrated not to be the case, since the Claisen rearrangement should give **40** rather than **39**. Apparently, ArO serves as a leaving group in the presence of Pd(0), which allows for generation of the corresponding η^3 complex **38** together with naphthoxide **37**; recombination then leads to **39** (note, again, the typical attack at the less substituted carbon). Interestingly, this reactivity appears to be confined to naphthoxy derivatives; the corresponding phenoxy systems were inert under the same conditions.[55],[56]

G. REARRANGEMENTS INVOLVING THE C—N → C—N CONVERSION

In some respects, the behavior of vinylic aziridines resembles that of vinyl epoxides: in the presence of a catalytic amount of Pd(0), aziridines undergo a cleavage of the more reactive allylic C—N bond (**Scheme 20**). The intermediate (η^3-allyl)Pd complex thus generated can be recyclized to the isomeric pyrrolidine (**41** → **42**). Similarly, azetidines produce piperidines (**43** → **44**).[57]

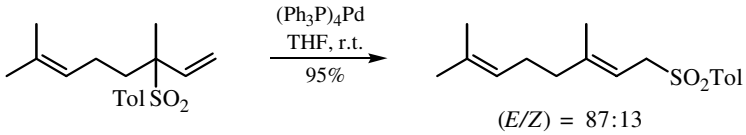


41 **42** **43** **44**

Scheme 20

H. REARRANGEMENTS INVOLVING THE C—S → C—S CONVERSION

Sulfone transposition has been reported as an example of an S—S allylic rearrangement to furnish a thermodynamically more stable product (**Scheme 21**).[58]



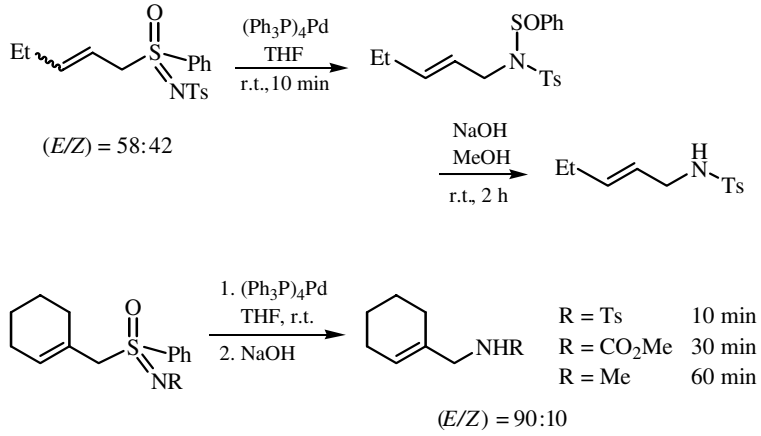
(*E*/*Z*) = 87:13

Scheme 21

I. REARRANGEMENTS INVOLVING THE C—S → C—N CONVERSION

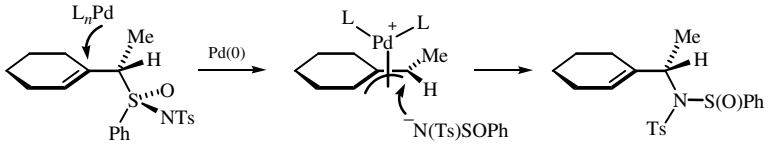
Pd(0)-catalyzed rearrangement of allylic sulfoximines to sulfinamides has been developed recently and appears to be an efficient route to chiral allylic amines (**Scheme 22**). This reaction is also known to occur thermally[59] but only for γ-phenyl-substituted

sulfoximines. In the presence of $(Ph_3P)_4Pd$, the rearrangement occurs at room temperature within 10–60 min and is more general.[60]–[63] The regiochemistry can be understood in terms of the formation of (η^3-allyl)Pd complex that is attacked by the nucleophile at the less substituted terminus.[60]–[63] This mechanism is also compatible with the observed (*Z*) → (*E*) isomerization (occurring at the stage of the η^3 complex). Typically, a tosyl group is attached to the nitrogen atom of the starting material but the corresponding carbamates or *N*-methyl derivatives can also be readily rearranged though the reaction is slightly slower. The product contains a labile SOPh group that is readily removed by hydrolysis with aqueous NaOH.



Scheme 22

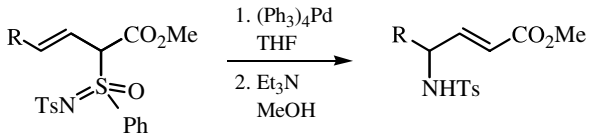
Mechanistically illustrative is the Pd(0)-catalyzed rearrangement of chiral α-substituted sulfoximines (**Scheme 23**), which is believed to proceed via a double inversion mechanism (although no attempt at ruling out double retention[64]–[68] has been made).[62] In contrast to the thermal rearrangement, occurring partly via a [3,2] shift and partly via an ion pair, the Pd(0)-catalyzed reaction proved to occur with 92% retention of configuration and to be completely regioselective (**Scheme 23**).[62] An efficient 1,4-diastereocontrol has been reported to operate in the production of 1,4-aminoalcohols from the corresponding 4-hydroxy derivatives but, in this instance, the mechanistic understanding is rather weak.[69]



Scheme 23

The rearrangement of α-sulfonimidoyl-β,γ-unsaturated esters paved the way for a promising synthesis of γ-amino acids in fair yields (**Scheme 24**).[70] In the presence of a chiral ligand, such as BINAP, moderate asymmetric induction has been reported (20–60% ee).[71]

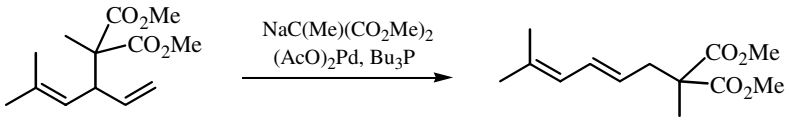
The demonstrated leaving capability of the sufoximino group has been utilized in allylic substitution with typical nucleophiles, such as sodium diethyl malonate, dibenzylamine, and *t*-butyl *N*-(diphenylmethylene)glycinate.[72]



Scheme 24

J. REARRANGEMENTS INVOLVING THE C—C → C—C CONVERSION

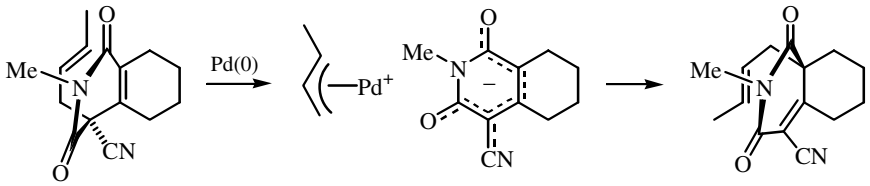
The Pd(0)-catalyzed allylation of stabilized carbon nucleophiles proved to be reversible in those cases where the final product is thermodynamically substantially more stable, for example, due to conjugation (**Scheme 25**). Thus, **45** can be quantitatively isomerized to **46**.[42],[73]



45 **46**

Scheme 25

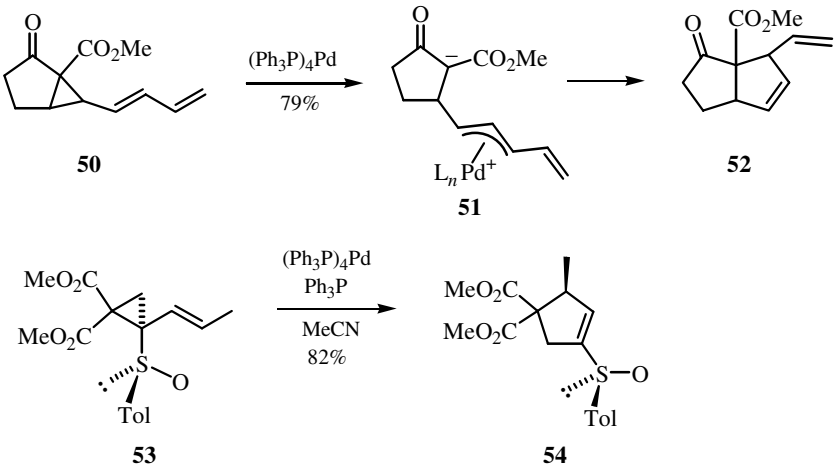
In the Pd(0)-catalyzed rearrangement of **47** (**Scheme 26**), the substitution pattern of the product is not compatible with that expected for a Cope rearrangement; the reaction has been rationalized by the involvement of the (η^3-allyl)Pd intermediate **48** that is attacked by the nucleophilic anion **49** at the less substituted carbon.[74]



47 **48** **49**

Scheme 26

While the above examples are currently rather limited in number, rearrangements of vinyl cyclopropanes with an EWG group attached,[75]–[85] such as **50**, are more common (**Scheme 27**).[83],[84] In this case, **50** undergoes the Pd(0)-catalyzed ring opening and the intermediate **51** is cyclized in a different manner (note the analogy with vinyl aziridines!) to afford the thermodynamically favored product **52**.[83],[84] Similarly, formation of **54** from **53** has also been reported. In the latter case, the enantiopure sulfoxide **53** gave the product with 89% stereoselectivity. In all these reactions, the formation of a stabilized carbanion has been recognized as the driving force for the generation of the (η^3-allyl)Pd intermediate.[85] The intermediate carbanion has also been trapped by typical Michael acceptors (e.g., methyl acrylate)[86] or isocyanates.[87]



Scheme 27

K. SUMMARY

While allylic alcohols and their esters, carbonates, carbamates, thiocarbamates, and so on, are often readily available, other allylic derivatives, such as amines and sulfides, are more difficult to come by. Therefore, the methodology described in this section, namely, the conversion of allylic C—O bonds into C—N, C—S, and C—C bonds via allylic rearrangement, represents a valuable tool in synthetic chemistry. The involvement of (η^3-allyl)Pd intermediates in this approach dictates the overall regio- and stereochemistry. By contrast, the rearrangements catalyzed by Pd(II) invariably occur as [3,3] sigmatropic shifts so that they have different structural requirements and often give different products. Hence, mechanistic understanding is a prerequisite for successful application of this chemistry in organic synthesis.

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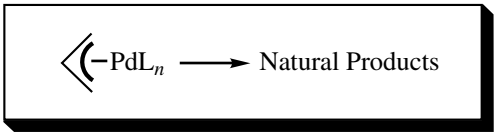

V.2.6 Synthesis of Natural Products and Biologically Active Compounds via Allylpalladium and Related Derivatives

VÉRONIQUE MICHELET, JEAN-PIERRE GENÊT, and MONIQUE SAVIGNAC

A. INTRODUCTION

The development of new strategies in organic synthesis with a minimum of chemical steps has become more and more necessary for the efficient creation of complex molecular structures. The ability of palladium(0) catalysts to exercise control in bond forming has made it an excellent candidate for the synthesis of biologically active molecules. Allylic alkylations catalyzed by palladium have widely been studied and have proved unusually productive because of the extraordinary chemo-, regio-, and diastereoselectivity and the continuing possibility for the development of enantioselectivity.

This section is intended to highlight the use of Pd-catalyzed allylation in the synthesis of natural products or biologically active molecules. We will concentrate on molecules containing small, medium, or large ring systems. Thus, the syntheses of three-membered, five-membered, six-membered, and large-ring natural products or biologically active compounds will be described. Each subsection will present the functionalization of cyclic intermediates using Pd-catalyzed alkylation. Other syntheses of natural products or biologically active molecules using palladium allylation will then be discussed. Pd-catalyzed cyclization as the key step for the synthesis of the main ring will finally be discussed.

B. THREE-MEMBERED RING NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE COMPOUNDS

The cyclopropyl moiety is found as a basic structural element in a wide range of naturally occurring compounds, in plants and in microorganisms, both fungal and bacterial. For example, many fatty acids, terpenes, and steroids are alkyl cyclopropanes. Due to their noteworthy biological activities, natural and nonnatural 1-aminocyclopropanecarboxylic acids also constitute interesting targets. Among all the methods for the synthesis of cyclopropanes, Pd-catalyzed cyclization has constituted an efficient route leading to vinylcyclopropanes, such as chrysanthemic acid[1] based on chirality transfer observed by Stork and Schoofs[2] without palladium. The syntheses of *cis*-chrysanthemonitrile

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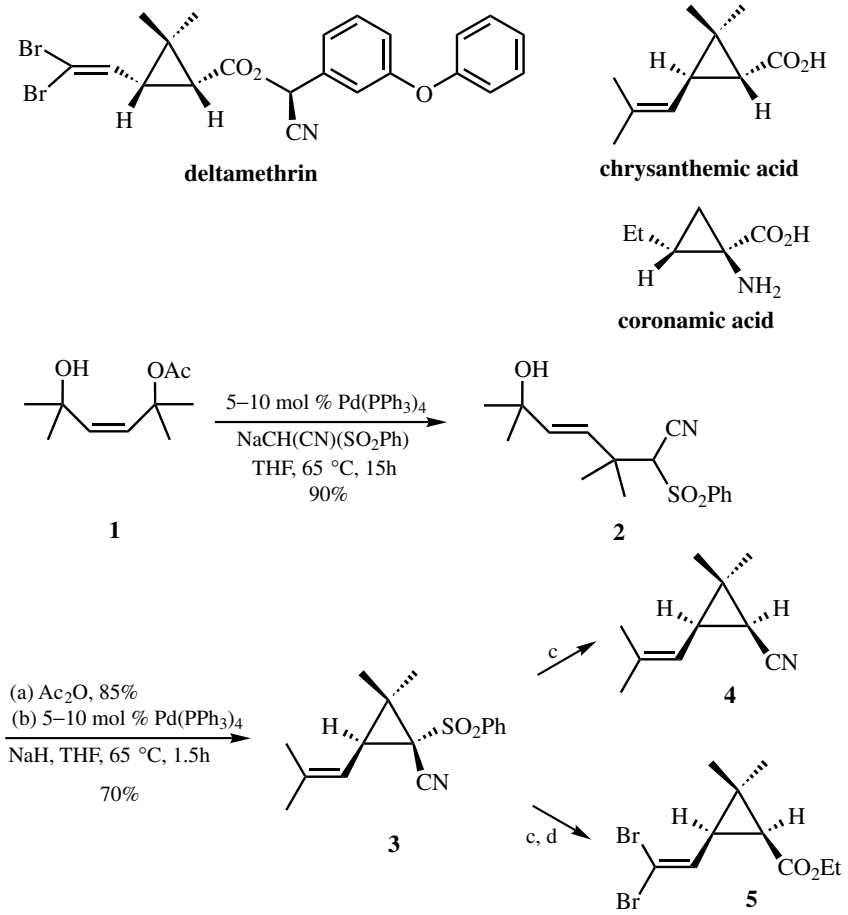
cyclopropane[3] and *cis*-dihalogeno chrysanthemate[4], part of the pyrethroids[5] family of insecticide, have been reported (**Scheme 1**). The acyclic precursor **2** was prepared via a Pd-catalyzed allylic alkylation, which occurred with complete regio- and stereoselectivity. The alcohol was then activated as an acetate before the cyclization. The $S_{N'}$ cyclopropanation was accelerated with a catalytic amount of palladium(0) and led to **3** with a remarkably high stereoselectivity. Desulfonylation with retention of the configuration



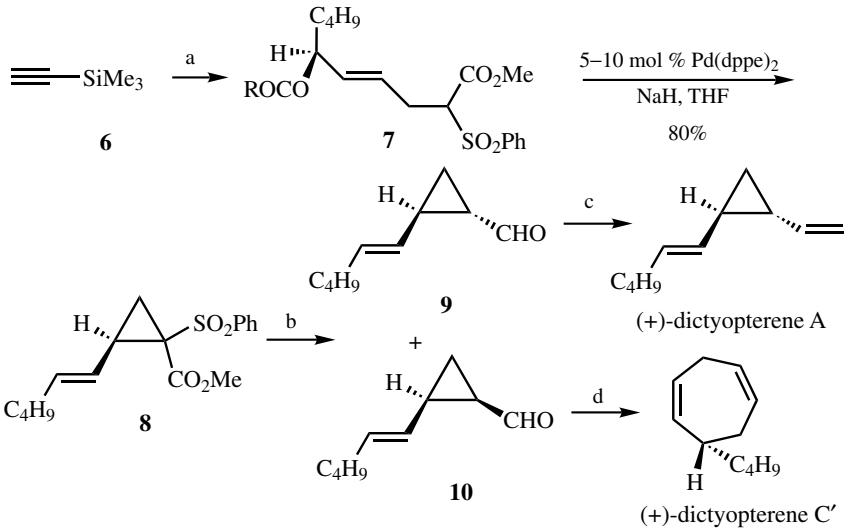
(c) Na/Hg, 100%; (d) O_3; CBr_4, PPh_3; HCl, EtOH, 50% (3 steps).

Scheme 1

gave the *cis*-chrysanthemonitrile compound **4**, which could be transformed into precursor **5** of deltamethrin.

This methodology was also applied in the first enantioselective syntheses[6] of (+)-dictyopterene A and C′, isolated from Hawaian seaweed belonging to genus *Dictyopteris* and presenting physiological activities (**Scheme 2**). The key intermediate, allylic benzoate **7**, was prepared in a few steps starting from trimethylsilylacetylene **6**, with 85% enantiomeric excess. The Pd-catalyzed reaction of **7** in the presence of a catalytic amount of $Pd(dppe)_2$ and sodium hydride as base led cleanly to cyclopropane **8**, which was desulfonylated, reduced, and oxidized to give a mixture of *cis*- and *trans*- (60 : 40) aldehydes.

Treatment of these two chiral aldehydes **9** and **10** afforded the natural dictyopterene A with 85% ee and the unnatural dictyopterene C′ with 85% ee, respectively.

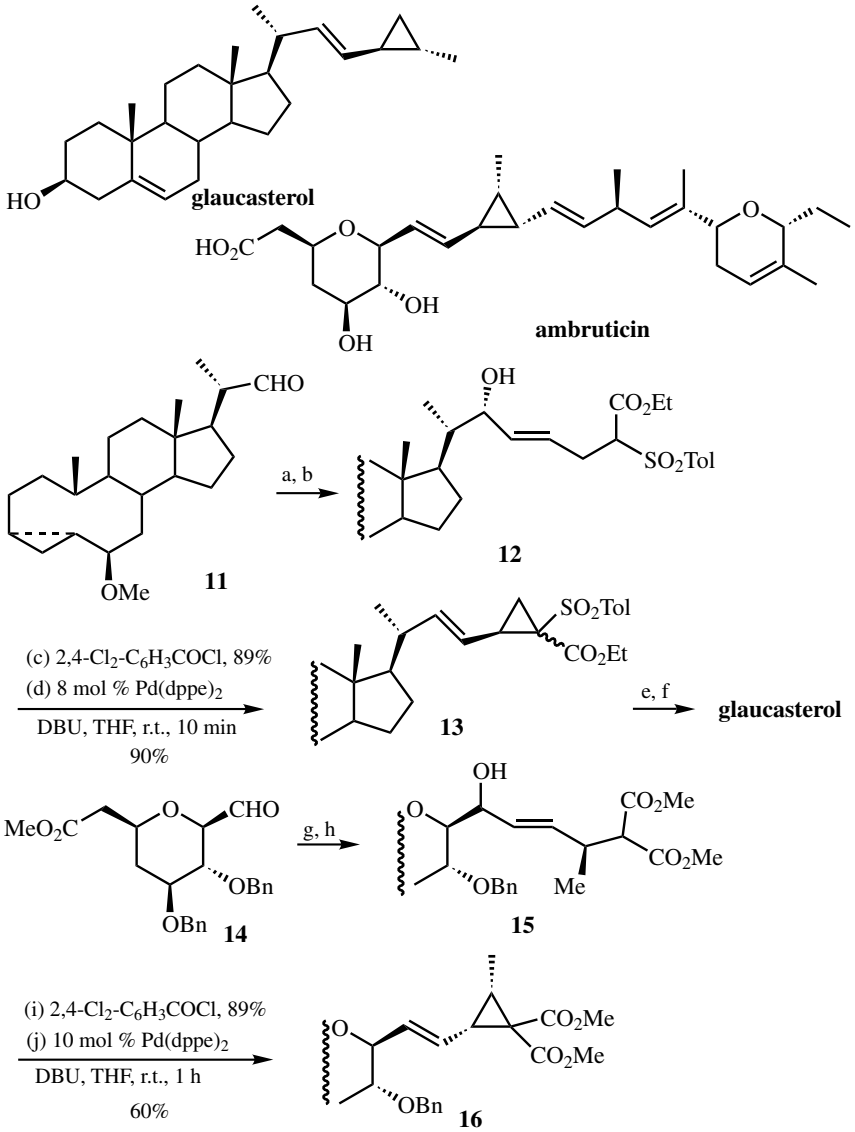


(a) BuLi, MnI_2, C_4H_9COCl; (*S*)-alpine borane. Bu_4NF, ee = 85%; *t*-$BuMe_2SiCl$; EtMgBr, H_2CO; Ac_2O; Bu_4NF; Pd/Lindlar, H_2; $PhSO_2CH_2CO_2Me$, DBU, 5 mol % $Pd(dppe)_2$, THF, 25 °C,1h 15; 2,4-Cl_2-C_6H_3COCl, 18% (9 steps);
(b) Na/Hg; DIBAH; PCC **9**/**10** 40:60; (c) $CH_2{=}PPh_3$; (d) heat.

Scheme 2

Other natural products having vinylcyclopropane as a structural element were targeted such as glaucasterol[7] and ambruticin.[8] Glaucasterol is a marine sterol isolated from the soft coral *Sarcophyton glaucum* and from deep sea gorgonians (**Scheme 3**). The known aldehyde **11** was treated with the lithio acetylide derived from butynoxycarbonate to give a mixture of epimeric alcohols. The major isomer was semihydrogenated and then alkylated via a Pd-catalyzed reaction using $Pd(dppe)_2$ and ethyl *p*-toluenesulfonylacetate to give **12** in good yield. The functionalized ethyl phenylsulfonylacetate alcohol **12** was converted to its benzoate with 2,4-dichlorobenzoylchloride. The intramolecular $S_{N'}$ catalyzed by 8 mol % of $Pd(dppe)_2$ was achieved under very mild conditions giving **13** in 90% yield and with exclusive *E* stereochemistry of the double bond of the vinylic side chain. The transfer of chirality was highly stereoselective via the palladium η^3-allyl species. The final transformation to glaucasterol was accomplished via a classic sequence.

A more complicated case was studied for the approach of ambruticin, isolated from fermentation extracts of the Myxobacteria species *Polyangium cellulosum* var. *fulvum* and possessing antifungal antibiotic properties (**Scheme 3**). The known aldehyde **14** was alkylated with the Grignard reagent of protected chiral alcohol (*R*)-*O*-*tert*-butyldimethylsilylbut-1-yn-3-ol leading to stereoisomeric alcohols. The major diastereomer was efficiently converted to functionalized alkene **15** via a semihydrogenation, protection–deprotection sequence and a Pd-catalyzed alkylation. Compound **15** was obtained as a single isomer based on the regio-, stereo-, and enantioselective Pd-catalyzed allylation. Alcohol **15** was then activated in the same way as previously described for the glaucasterol synthesis. The resulting benzoate was

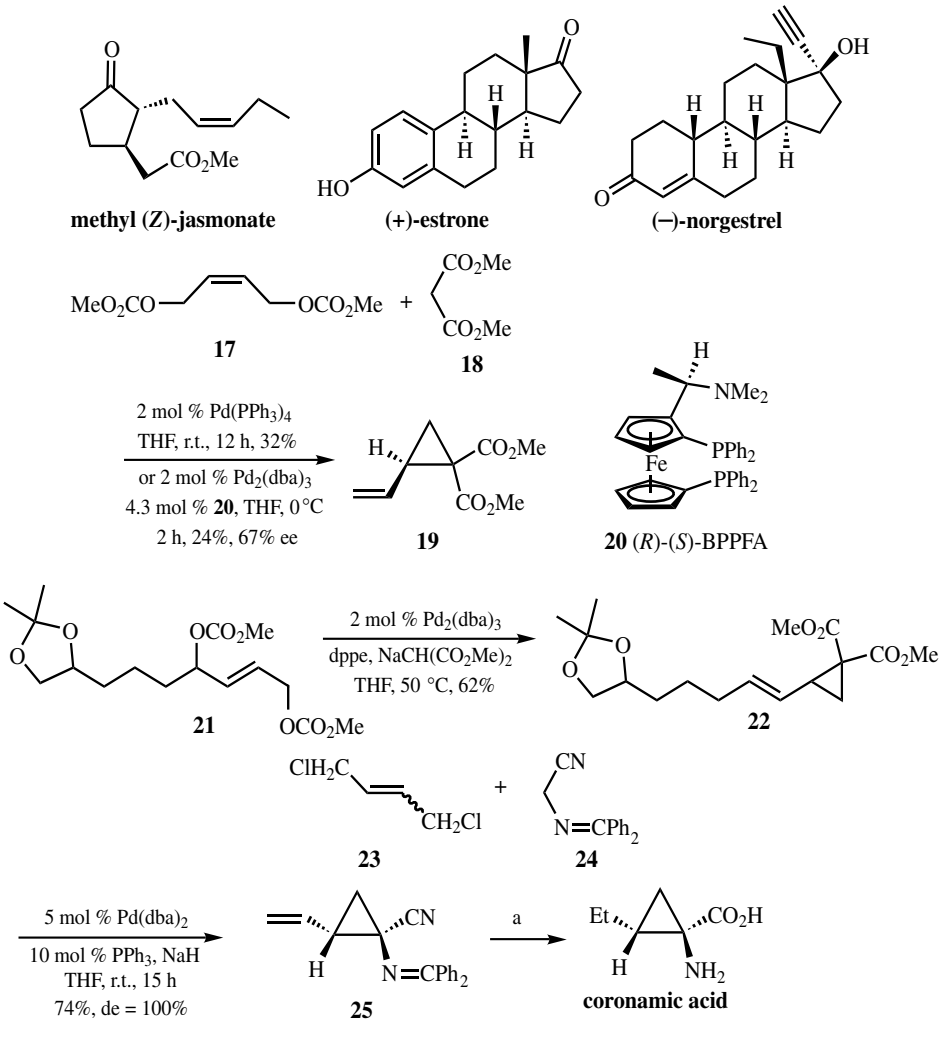


(a) LiC≡CCH$_2$CO$_2$Et; Pd/Lindlar, H$_2$, 58% (2 steps); (b) TolSO$_2$CH$_2$Et, 7 mol % Pd(dppe)$_2$, THF, r.t., 1 h, 76%; (e) Na/Hg; *t*-BuOK; LiAlH$_4$, 56% (3 steps); (f) MeSO$_2$Cl; LiAlH$_4$; *p*-TsOH, 72% (3 steps); (g) (*R*)-BrMgC≡CH(Me)(OTBDMS); ClCO$_2$CH$_2$CH=CH$_2$; Bu$_4$NF; ClCO$_2$Et; Pd(OAc)$_2$, TPPTS, 39% (5 steps); (h) Pd/C, H$_2$, pyridine; 10 mol % Pd(dppe)$_2$, NaCH(CO$_2$Me)$_2$, 34% (2 steps).

Scheme 3

readily cyclized in the presence of 10 mol % of Pd(dppe)$_2$, DBU as base in THF at room temperature (r.t.) leading to cyclopropane **16**, an epimer of the west part of ambruticin. The stereochemistry of the cyclopropane is dictated by the stereochemistry of the alcohol resulting from the hydroxyalkylation of **14**. Moreover, as both isomers of protected butynol are available,[9] this method constitutes an approach to ambruticin analogs.

Other groups have worked on the synthesis of vinylcyclopropanes, precursors of steroids and prostaglandins.[10],[11] Burgess[12] has reported a one-pot synthesis using (*Z*)-2-butenylene dicarbonate **17** and dimethyl malonate **18** in the presence of $Pd(PPh_3)_4$ to produce dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **19** (**Scheme 4**) in modest yield. Hayashi et al.[13] have extended this reaction using chiral ligand (*R*)-(*S*)-BPPFA **20** to form enriched cyclopropane (ee up to 67%). Trost et al.[14] have also worked on this process where the bifunctional alkylating agent **21** demonstrated chemoselectivity for the initial replacement of a primary leaving group in the presence of a secondary one. Subsequent Pd(0)-catalyzed ring closure occurred spontaneously and produced the terminal vinylcyclopropane **22**. Dimethyl-2-vinyl-1,1′-dicarboxylate such as **19** and **22** are key intermediates in the syntheses of (−)-jasmonate methyl ester, (+)-estrone, or (−)-norgestrel.



(a) NH═NH; 6 M HCl. Dowex, 72% (2 steps).

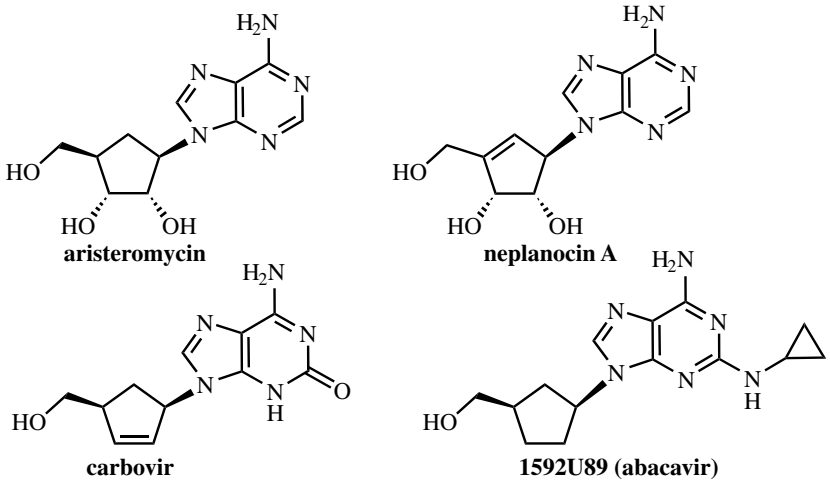
Scheme 4

Aminocyclopropanecarboxylic acids have also been prepared due to their biological properties such as the enzymatic process control and inhibition, the plant growth regulation, and the peptide activation and stabilization.[15] A one-pot Pd(0)-catalyzed tandem alkylation and $S_{N'}$ cyclization of 1,4-dichlorobut-2-ene **23** by the anions of different α-substituted acetonitriles led diastereoselectively[16],[17] to the precursor of aminocyclopropyl acids (**Scheme 4**). For example, **23** was reacted with the aminoacetonitrile **24** in the presence of 5 mol % of Pd(0) catalyst and sodium hydride as the base, to give diastereomerically pure cyclopropane **25** in 74% yield. The reaction performed with asymmetric substrates and/or in the presence of chiral ligands led to modest enantioselectivity ($< 32\%$ ee).[17] Compound **25** was then reduced with diimide. Acidic hydrolysis furnished, after treatment with ion exchange liquid chromatography, the racemic coronamic acid in 72% overall yield from **25**. This method constitutes a short synthesis of racemic methanoaminocyclopropyl acids. Asymmetric synthesis was performed under the Mistunobu reaction conditions for the cyclization step, in the absence of Pd(0).[17]

C. FIVE-MEMBERED RING NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE COMPOUNDS

C.i. Palladium-Catalyzed Allylation in the Synthesis of Five-Membered Ring Natural Product

C.i.a. ***Synthesis of Carbonucleosides by Functionalization of the Cyclopentenyl Moiety.*** Nucleosides are fundamental building blocks of biological systems.[18]–[20] Carbocyclic nucleosides in which the ribofuranose ring oxygen is replaced by a methylene moiety have emerged as antibiotic and antitumor agents since the discovery of natural carbocycle nucleosides aristeromycin[21] and neplanocin A[22] (**Scheme 5**). The biological activity of those carbanucleosides has sparked the search for other nucleoside analogs:[23],[24] carbovir and compound 1592U89 (abacavir) have been discovered and display high antitumor activity against the human immunodeficiency virus. One highly useful strategy for the convergent synthesis of carbocyclic nucleosides is the Pd(0)-catalyzed allylic substitution.



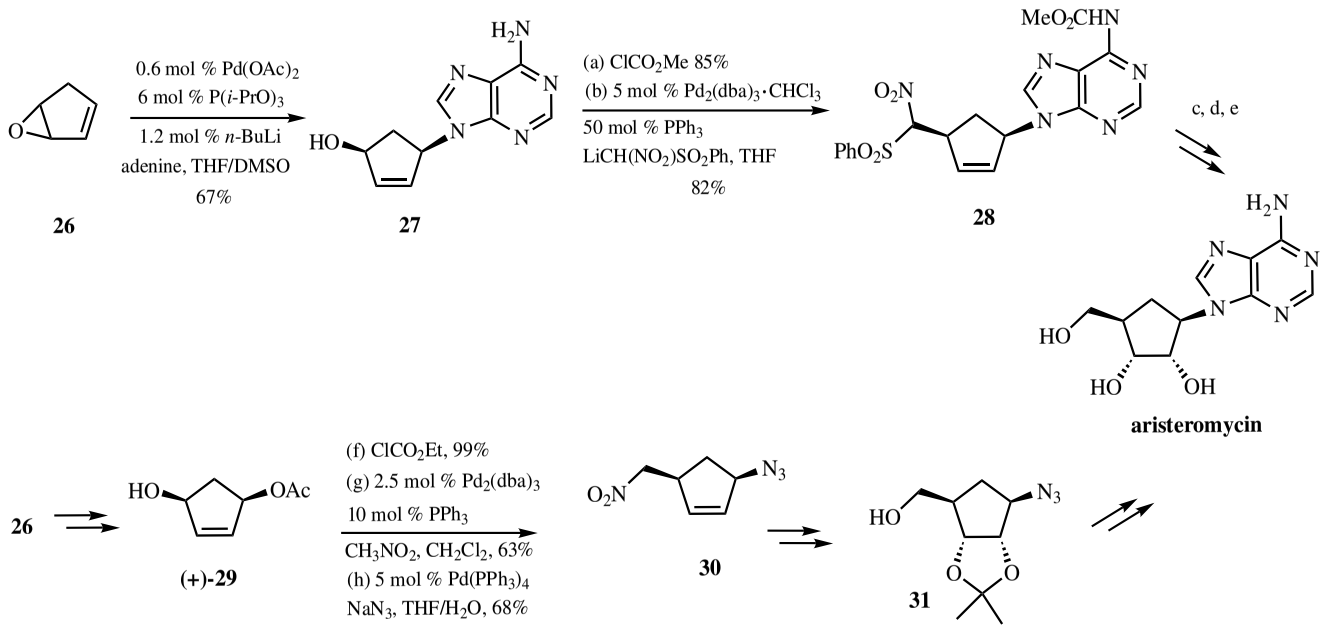
Scheme 5

The first example of direct substitution with a heterocyclic base on a carbocycle employing palladium catalysis was reported by Trost et al.[25] in a racemic synthesis of aristomycin (**Scheme 6**). Reaction of cyclopentadiene monoepoxide **26** and adenine, in the presence of a mixture of palladium acetate, triisopropyl phosphite, and *n*-butyllithium, gave the *cis*-1,4-alkylated product **27** in 67% yield. Further functionalization using a second Pd-catalyzed substitution leading to **28** followed by a dihydroxylation of the olefin, and subsequent conversion of the nitrosulfone to alcohol gave (±)-aristeromycin. Starting also from **26**, Deardoff et al.[26] recently reported a formal synthesis of (−)-aristeromycin using the azide **31** as the key intermediate.[27] The monoacetate[28],[29] (+)-**29** was subjected to two successive Pd(0)-catalyzed substitutions affording the azide **30**. The intermediate **31** was then obtained after the dihydroxylation of the alkene, protection of the resulting diol, followed by Nef and reduction reactions.

Lactone **33**, obtained by a Prins reaction between cyclopentadiene **32** and glyoxilic acid, has also been utilized in enantioselective approaches to aristeromycin. Chirality has been introduced by chemical resolution[30] of lactone **33**, which was converted to diacetate **34**. Pd-catalyzed alkylation of diacetate **34** led to the nucleoside[31] **35**, precursor of aristeromycin (**Scheme 7**). Unfortunately, this synthetic scheme suffers from the limitation that dihydroxylation of **35** led to a mixture of the α- and β-diols. A new route was developed leading to a bicyclic system, which could show high facial stereoselectivity.[32] Treatment of **36** with hydrazine hydrate followed by acetylation afforded the tetraacetylated compound **37**. Pd(0)-catalyzed cyclization was carried out with $Pd(PPh_3)_4$ to give the bicyclic compound **38**. The osmium tetroxide-mediated stereospecific dihydroxylation reaction gave a single diol, which was subsequently functionalized to give compound **39** in excellent overall yield. This aminocyclopentyl derivative might be useful for providing rapid access to a variety of homocarbocyclic nucleoside analogs. Indeed, the presence of the amino function in this intermediate should serve to further elaborate various modified heterocyclic bases.

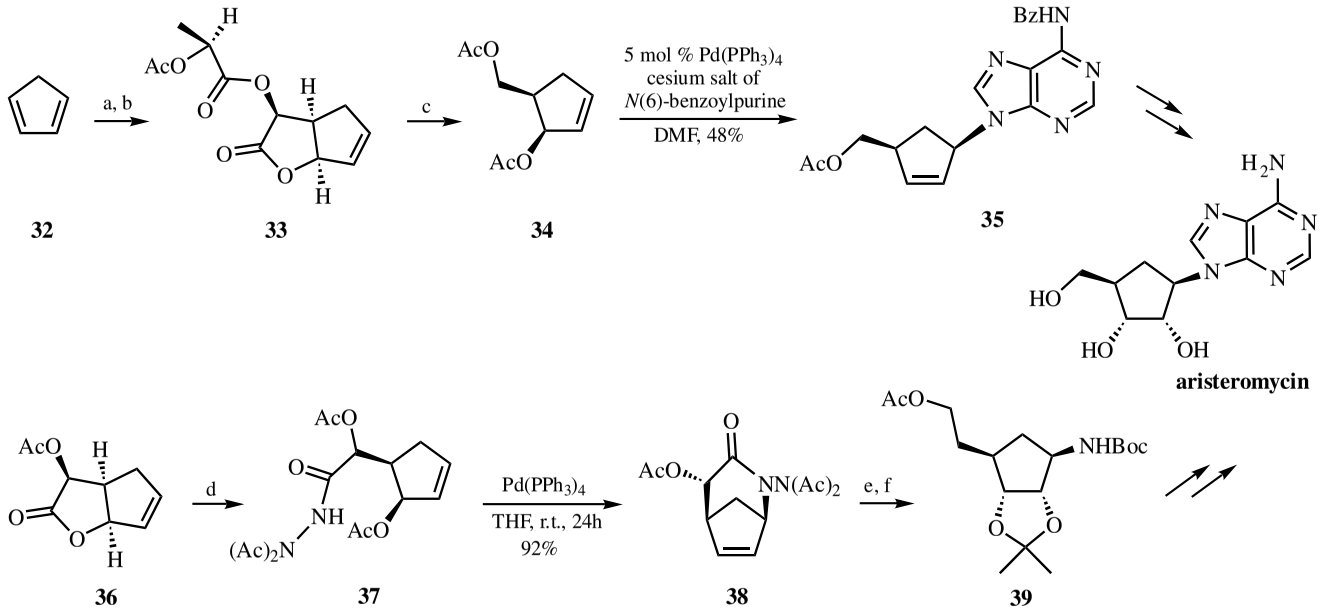
The main drawback of this methodology, using lactone as an intermediate, was that half of the material is lost as the "undesired" enantiomer. Resolution of *meso* intermediates or asymmetric synthesis has constituted the main progress in the synthesis of natural products. Trost and co-workers have introduced the elegant concept of asymmetric desymmetrization of *meso* diester using chiral ligand (+)-1,2-bis-*N*-[2′-(diphenylphosphino)benzoyl]-1(*R*),2(*R*)-diaminocyclohexane (*R*,*R*)-**44** and have applied it for the synthesis of (−)-aristeromycin[33] (**Scheme 8**). The dibenzoate **40** underwent smooth alkylation using (phenylsulfonyl)nitromethane as pronucleophile to give the isoxazoline 2-oxide **41** in 94% yield and 96% ee. The heterocycle functions as a synthon for a *cis*-vicinal hydroxycarboxylic ester whose reduction and esterification produced dicarbonate **42**. Pd(0)-catalyzed coupling of **42** with adenine gave the carbonate **43**, which was converted to (−)-aristeromycin by hydrolysis of the carbonate and subsequent dihydroxylation.

This imaginative methodology is general and has been applied to the efficient synthesis of (−)-neplanocin[34] and (−)-carbovir[35] (**Scheme 9**). Indeed, the natural carbanucleosides were obtained using two Pd(0)-catalyzed key steps. The Pd(0)-catalyzed desymmetrization of dibenzoate **40** with 6-chloropurine gave excellent results with the stilbenediamine-based ligand (+)-1(*S*),2(*S*)-bis-[2′-(diphenylphosphino)benzamido]-1,2-diphenylethane (*S*,*S*)-**45** in the presence of triethylamine at room temperature. Monobenzoate **47** was isolated in 76% yield and with 94% ee. The one carbon unit was then introduced regio- and diastereoselectively by the second Pd(0)-catalyzed alkylation. Compound **48** was subsequently transformed to (−)-neplanocin A via a nine-step synthesis. (−)-Carbovir was obtained by a very short asymmetric synthesis, with some



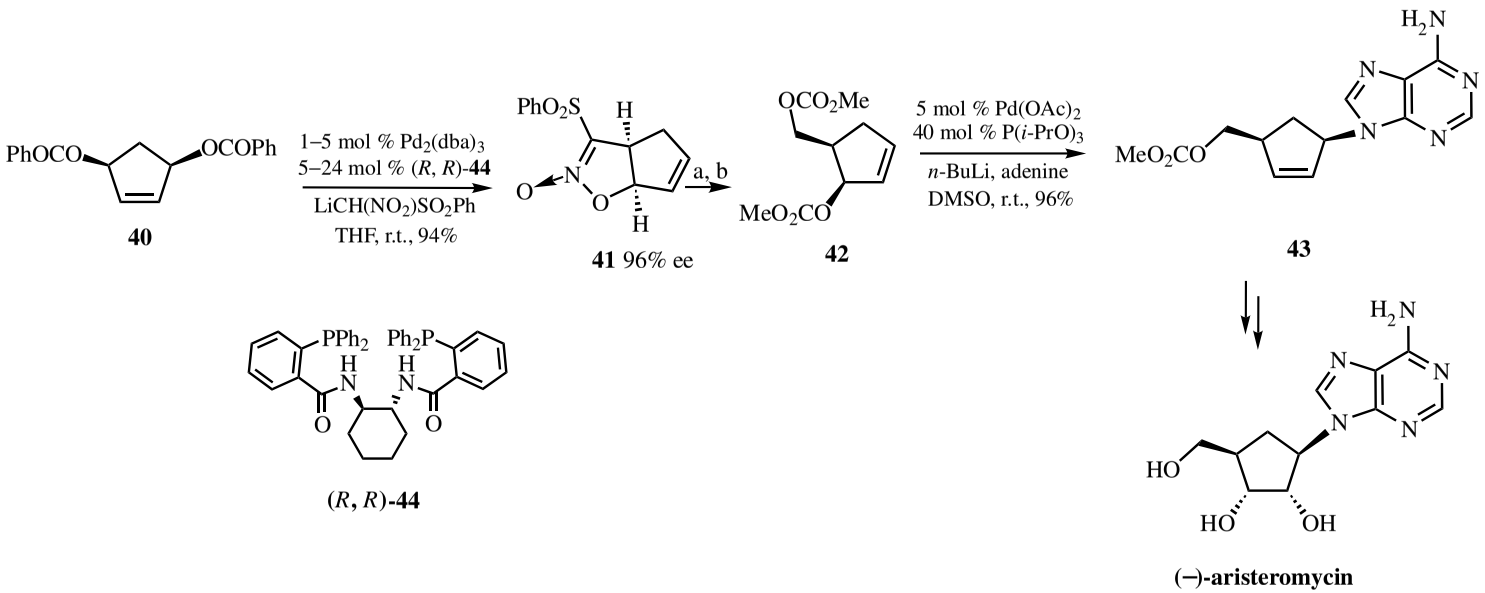
(c) $KMnO_4$; $Me_2C(OMe)_2$, 45% (2 steps); (d) NH_4OH; NaOMe, O_3, 70% (2 steps); (e) DIBAL-H; HCl then Dowex.

Scheme 6



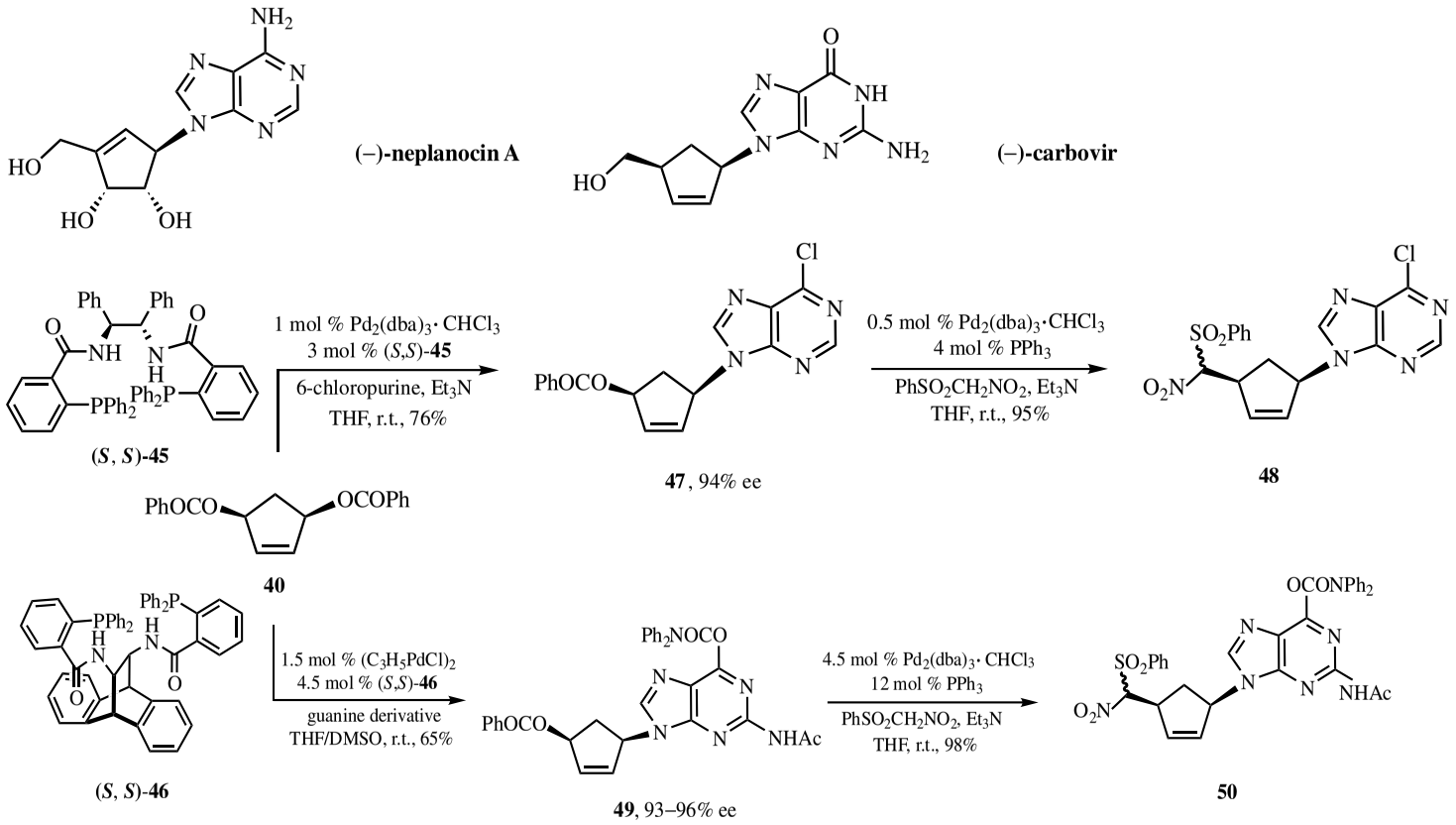
(a) glyoxalic acid, de 1:4, 65%; (b) (*S*)-*O*-acetyllactylchloride, 91%; (c) $LiAlH_4$; $NaIO_4$; $NaBH_4$; Ac_2O 30% (4 steps); (d) NH_2NH_2; Ac_2O, 70% (2 steps); (e) OsO_4; CH_3COCH_3/H^+; Li/NH_3, 59% (3 steps); (f) Boc_2O; $NaBH_4$, then Ac_2O, 56% (2 steps).

Scheme 7



(a) $SnCl_2$–H_2O, 94%; MeOH, K_2CO_3; $Mo(CO)_6$, H_2O, CH_3CN, $B(OH)_3$, 84%; (b) $LiAlH_4$ 95%; *n*-BuLi, $ClCO_2Me$, 98%.

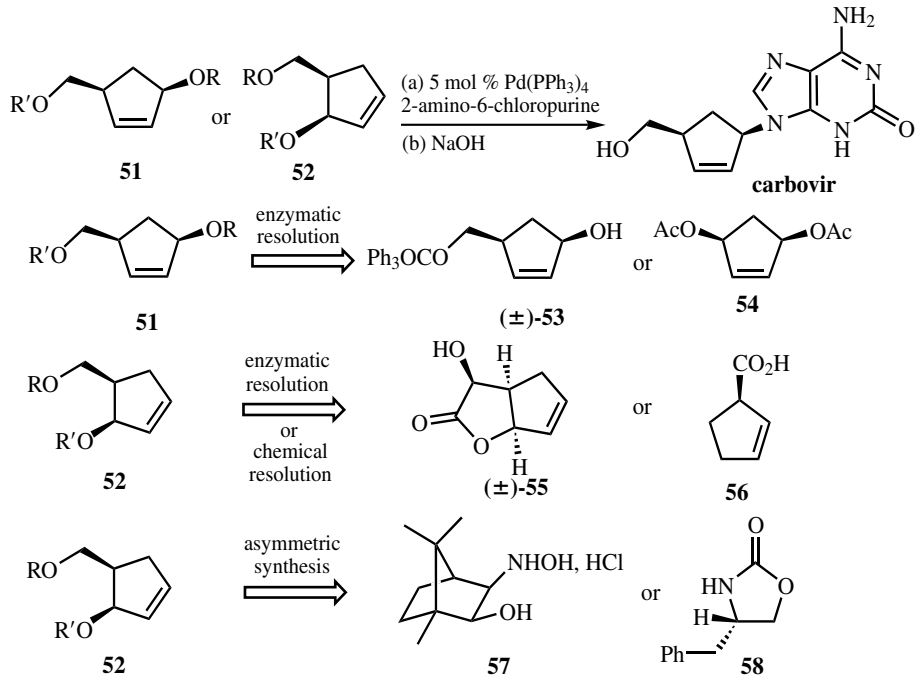
Scheme 8


(–)-neplanocin A
(–)-carbovir
(S, S)-45
1 mol % Pd2(dba)3· CHCl3
3 mol % (S,S)-45
6-chloropurine, Et3N
THF, r.t., 76%
47, 94% ee
0.5 mol % Pd2(dba)3·CHCl3
4 mol % PPh3
PhSO2CH2NO2, Et3N
THF, r.t., 95%
48
40
(S, S)-46
1.5 mol % (C3H5PdCl)2
4.5 mol % (S,S)-46
guanine derivative
THF/DMSO, r.t., 65%
49, 93–96% ee
4.5 mol % Pd2(dba)3· CHCl3
12 mol % PPh3
PhSO2CH2NO2, Et3N
THF, r.t., 98%
50

Scheme 9

improvements in the desymmetrization step using chiral ligand (+)-11(*S*),12(*S*)-bis-[2′-(diphenylphosphino)benzamido]-9,10-dihydro-9,10-ethanoanthracene cyclohexane (*S*,*S*)-**46**. Purines were additioned to dibenzoate **40** with high conversion and a high level of regioselectivity. Oxidation of the tetramethylguanidine salt of **50** followed by reduction and hydrolysis of the guanidine protecting groups completed the synthesis of (−)-carbovir.

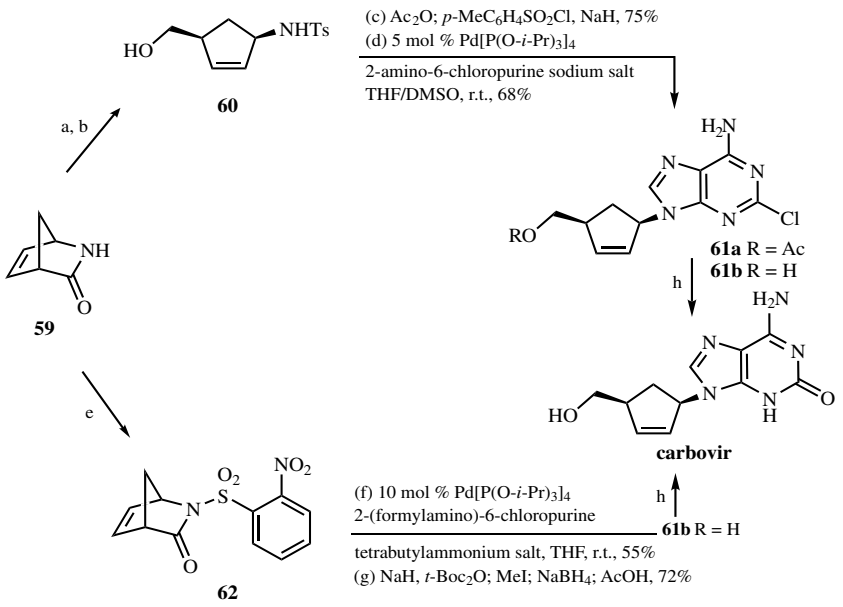
Many other groups have worked toward the synthesis of carbovir. We will focus mainly on the enantioselective approaches (**Scheme 10**). The Pd(0)-catalyzed syntheses differed in the preparation of 1,3- or 1,4-functionalized cyclopentenyl precursors such as **51** or **52**. Both chemical resolution by preparation of diastereomeric salts or chromatographically separable diastereomers as well as enzymatic resolution of *meso* intermediates and enzymatic resolution of chiral, racemic mixtures have been utilized in the enantioselective synthesis of carbovir. Starting from cyclopentadiene and exploiting a Prins reaction, racemic alcohol[36] (±)-**53** and lactone[37] (±)-**55** were respectively resolved with *Pseudomonas fluorescens* lipase. Both syntheses are finalized using Trost's Pd-catalyzed coupling of allylic acetate **51** or carbonate **52** with 2-amino-6-chloropurine. It has to be noted that another resolution of lactone (±)-**55** was previously presented for the formal[31] synthesis of aristeromycin. Starting also from cyclopentadiene, resolutions of monoacetate[38],[39] have also been described and Nokami et al.[40] have accomplished synthesis of both enantiomers of carbovir. The diacetate **54** was selectively hydrolyzed with porcine pancreatic lipase (PPL) to give the alcohol, which was converted to the dicarbonate **51**, a precursor for Pd-catalyzed alkylation. Cyclic carbonate **52** was also synthesized according to a different approach from Hildbrand et al.[41] starting from 1-chloro-2-cyclopentene. Crystallization of the α-phenethylamine salt of acid **56** followed by several classic steps led to the carbonate **52**, which was treated according to the same methodology to give (−)-carbovir.



Scheme 10

Asymmetric synthetic methods have also been employed for the enantioselective synthesis of (−)- or (+)-carbovir. Apart from Trost's approach described previously, two other total syntheses have been described (**Scheme 10**). Berrenger and Langlois[42] have described the synthesis of (+)-carbovir, which relies on an asymmetric cycloaddition of cyclopentadiene to the 3-hydroxylaminoborneol **57**. The second original synthesis reported by Crimmins and King[43] is based on an asymmetric aldol condensation of (*S*)-4-benzyl-2-oxazoline **58** followed by a ring-closing metathesis reaction leading finally to (−)-carbovir.

Two additional syntheses have to be emphasized even though they are racemic ones[44] (**Scheme 11**). Bicyclic lactam **59**, which is now available as a single enantiomer, has been efficiently transformed to hydroxyamide **60**. After protection of the primary alcohol and activation of the nitrogen, Pd-catalyzed displacement of the bis-tosyl amide gave **61a**. Hydrolysis under basic conditions led to (±)-carbovir. More recently,[45] activation of the nitrogen of the bicyclic lactam **59** as the *p*-nitrobenzenesulfonamide **62** facilitated the Pd-catalyzed alkylation. The key intermediate **61b** was then obtained by functionalization under classic conditions. This methodology could be applied to the synthesis of optically active carbovir.



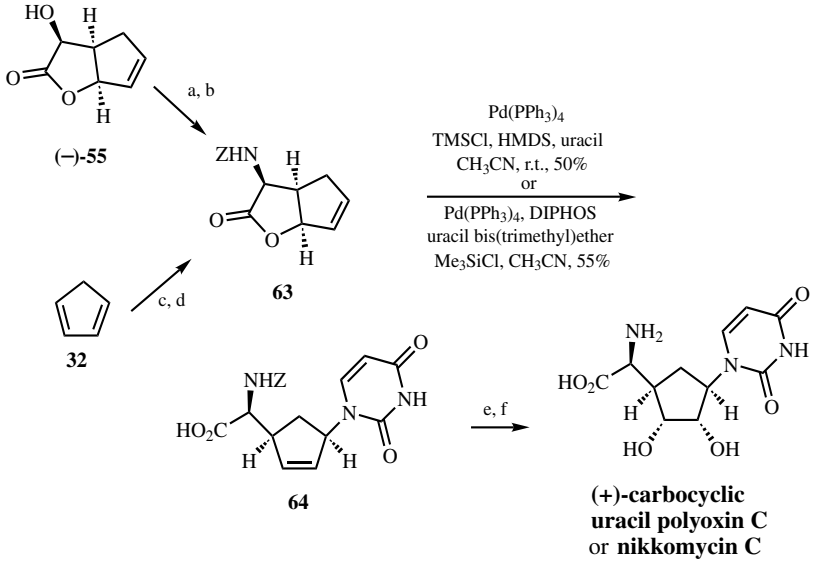
(a) *p*-$MeC_6H_4SO_2Cl$, NaH, 58%; (b) $NaBH_4$, 92%; (e) *o*-$NO_2C_6H_4SO_2Cl$, *n*-BuLi, 83%; (h) 0.5N NaOH, 75%.

Scheme 11

The structurally carbovir-related 1592U89 (**Scheme 5**) constitutes an important target among carbocyclic nucleosides as it is a highly potent and clinically effective anti-HIV agent. It was synthesized by Crimmins and King[43] using 2-amino-6-cyclopropylaminopurine and most of the syntheses of carbovir could be applied for its congener 1592U89.

As the search for nontoxic, nucleoside analogs resistant to phosphorylase is the subject of intense research, carbocyclic derivatives have been described in the literature. For

example, nikkomycins and polyoxins are a family of nucleoside-type antibiotics, which exhibit a broad spectrum of biological activity (**Scheme 12**). Aggarwal and Monteiro[46] described an asymmetric total synthesis of (+)-carbocyclic uracil polyoxin C (carbocyclic nikkomycin C) from lactone (−)-**55**. Transformation of the hydroxyl group to amino-protected **63** followed by Pd(0)-catalyzed alkylation with silylated uracil in the presence of trimethylsilyl chloride and hexamethyldisilazane (HMDS) afforded cyclopentene acid derivative **64**. After benzylation of the acid, the dihydroxylation of the cyclopentene led to the desired diol in a modest yield. Finally, hydrogenolysis of both protecting groups gave carboxylic uracil polyoxin C. Ward et al.[47] reported the racemic synthesis of carbocyclic nikkomycin C starting also from an amino-protected lactone, which was obtained by a cycloaddition of the imminium ion derived from methyl glyoxylate to cyclopentadiene **32**. Pd-catalyzed alkylation using uracil bis(trimethylsilyl)ether afforded the acid **64**, which was benzylated. Dihydroxylation of the alkene followed by hydrogenolysis of the protecting groups gave the required target.

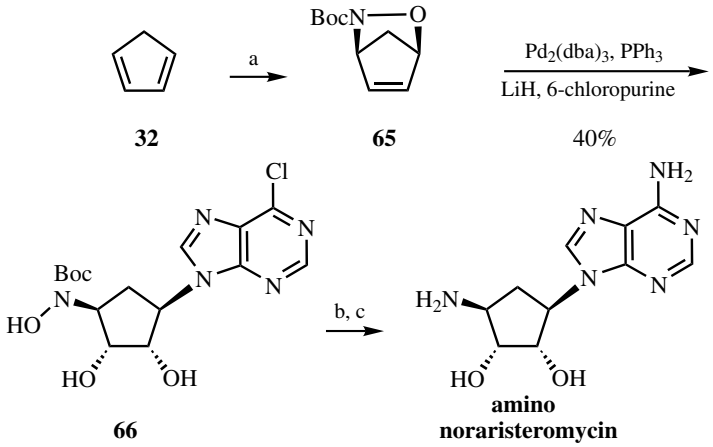


(a) $ZnBr_2$, PPh_3, DEAD; NaN_3, 52% (2 steps); (b) PPh_3; ZCl, 90% (2 steps); (c) NH_4Cl, methyl glyoxylate; ZCl, Z = $PhCH_2OCO$; (d) LiOH; TFA; (e) BnBr, 50% (2 steps); (f) $NaIO_4$, RuO_4, 59% or OsO_4, NMO-H_2O, *t*-BuOH, 52%; Pd/C, H_2, 100%.

Scheme 12

Recently, novel carbocyclic adenosine analogs bearing an amino group at carbon 5′, such as amino noraristeromycin, have been synthesized and tested for the inhibition of adenosine kinase.[48] Several synthetic routes have been used, including one based on palladium alkylation for the construction of the cyclopentane-base bond (**Scheme 13**). Heterobicycle **65** was obtained by a hetero Diels–Alder reaction of cyclopentadiene **32** and the nitrosocarbamate in quantitative yield. Once again, optically enriched analogs have been described and their use would allow the targets to be prepared in enantiomerically pure form. The heterocycle **65** was then treated with the lithium salt of 6-chloropurine in the presence of Pd(0) as a catalyst. Conversion of the cyclopentenyl derivative to

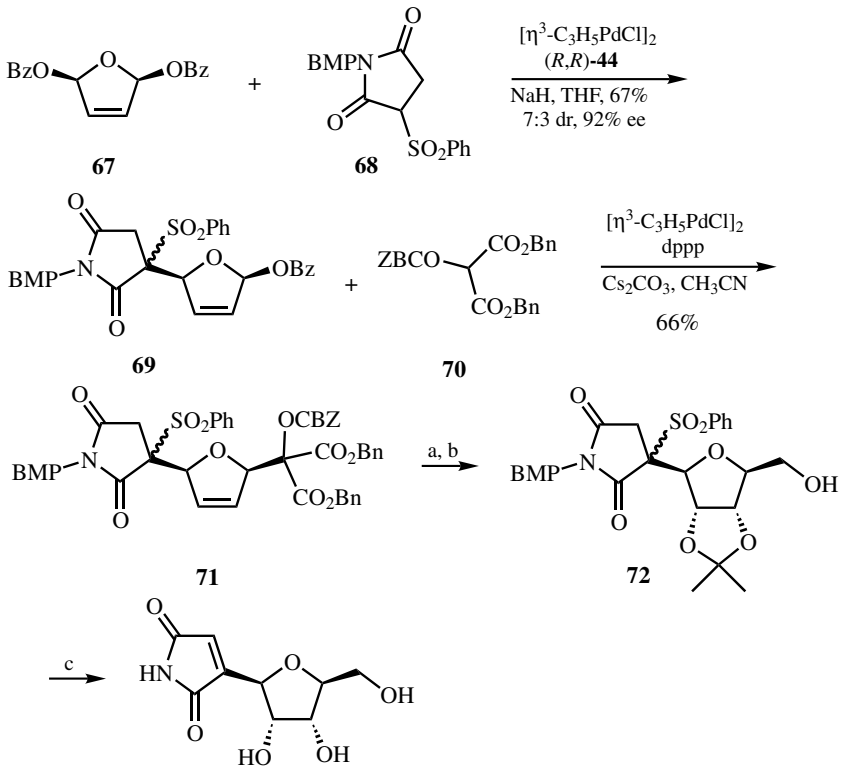
its TBS ether followed by *cis*-hydroxylation of the olefin with catalytic OsO_4 and trimethylamine *N*-oxide led to the diol **66** in 83% yield. When **66** was heated with saturated ammonia in methanol at 95 °C, the chlorine atom was replaced by an amino group, and the TBS group was removed. The Boc protective group was cleaved off under acidic conditions. Hydrogenolysis under 1 atm of hydrogen in 1 M HCl gave amino noraristeromycin.



(a) *t*-BocNHOH, $(Bu_4N)IO_4$, 100%; (b) TBSCl; OsO_4, NMO, 78% (2 steps); (c) NH_3; H_3O^+; H_2, Pd/C, 1M HCl, 41% (3 steps).

Scheme 13

Strategies for the synthesis of carbocyclic nucleosides have therefore provided a large variety of natural and unnatural derivatives. Pd-catalyzed allylic alkylation has been used for the introduction of an amino nucleophile. In the course of the synthesis of new analogs, Trost and Kallander[49] recently focused on the ability to generate either L or D enantiomer. Indeed, the lower toxicity and reduced susceptibility toward metabolism of the L isomers make them particularly interesting. A strategy toward C-nucleoside analogs has been explored via the first example of a carbon nucleophile in the desymmetrization of a heterocyclic substrate. The synthesis of L-showdomycin, the opposite enantiomer of a biologically active antibiotic and antitumor agent, has been accomplished (**Scheme 14**). The heterocyclic substrate **67** was reacted with nucleophile **68** using a catalyst derived from palladium complex and the chiral ligand (*R*,*R*)-**44** (**Scheme 8**) in THF leading to **69** in a diasteromeric mixture of 7:3. For both diastereomers the enantiomeric excess was determined to be 92%. The diastereoselectivity was not optimized because the stereocenter bearing the sulfonyl group was lost in the synthesis of showdomycin. A second regio- and diastereoselective allylic alkylation of **69** with the protected tartronic acid **70** was done with an achiral ligand to give **71** in 66% yield. *cis*-Dihydroxylation of **71** followed by further functionalization gave the alcohol **72**. The completion of the synthesis of showdomycin required removal of the protecting groups and the elimination of the sulfone, which unmasked a maleimide. This was realized in three steps to give L-showdomycin. This synthesis constitutes a novel approach to C-nucleosides. Indeed, this is the first example of a carbon nucleophile in the desymmetrization of a heterocyclic substrate. With alternative carbon nucleophiles, other natural and unnatural C-nucleosides could be synthesized by the same method.



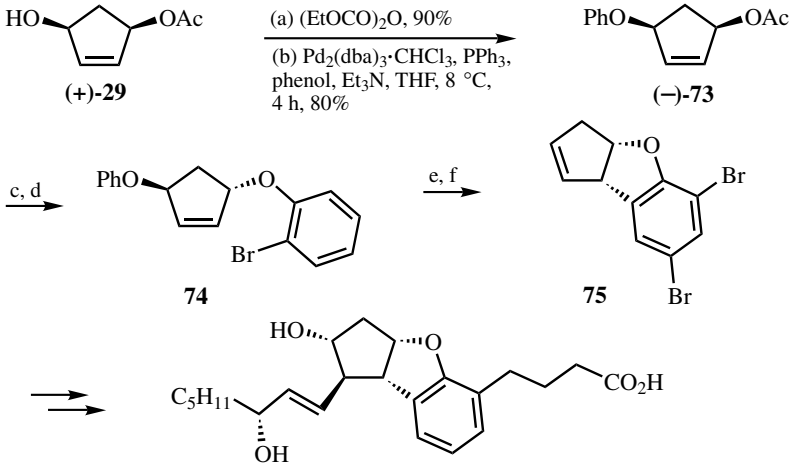
(a) OsO_4; $Me_2C(OMe)_2$; Pd/C, H_2, 79% (3 steps); (b) $Pb(OAc)_4$, H_2O, Me_2CO; HOBT, DCC, then $LiBH_4$, 63%; (c) CAN; TFA; DBU, 20% (3 steps).

Scheme 14

C.i.b. ***Synthesis of Natural Products by Allylation of the Cyclopentenyl Moiety.*** Other natural products or precursors of biologically active molecules have been synthesized by functionalization of cyclopentenyl moiety using Pd-catalyzed alkylation. For example, a precursor **75** of *m*-phyleneprostacyclin (PGI_2-mph), a potent therapeutic agent of thrombosis, has been prepared[50] (**Scheme 15**). Commercially available (+)-**29** was converted to the corresponding ethylcarbonate, which could be successively converted by treatment with phenol and a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$/triphenylphosphine catalyst in THF to the corresponding 4-acetoxycyclopentenyl phenyl ether followed by alkaline hydrolysis to give (−)-**73** in 87% yield. Alkaline hydrolysis of **73** followed by etherification led to **74**. Cyclopentene **74** was then treated with *n*-butyllithium leading to the cyclopenta[*b*]benzofuran, which was brominated to give the optically pure **75** in 53% yield. Transformation of the dibromide derivative to PGI_2-mph was already established by the authors.

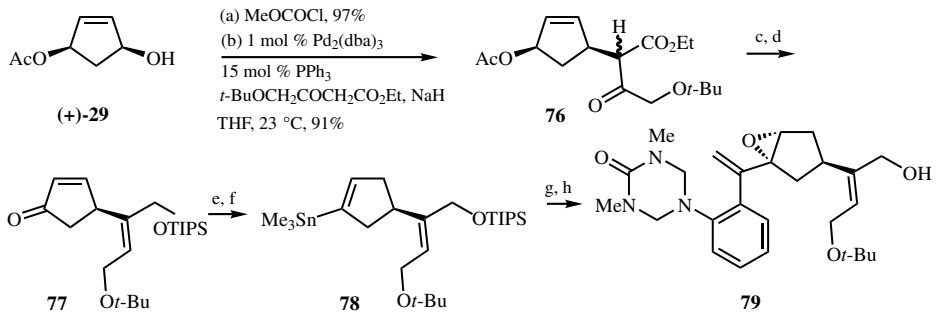
Acetate (+)-**29** was also the key precursor in the synthesis of (−)-strychnine.[51] First isolated in 1818 from *Strychnos ignatii*, strychnine was among the first plant alkaloids obtained in pure form. The structural elucidation was reported in 1946, and by now four total syntheses including two racemic ones have been described. The sequence described

by Overman (**Scheme 16**) constituted the first asymmetric total synthesis of (−)-strychnine. Reaction of (+)-**29** with methyl chloroformate, followed by selective Pd-catalyzed displacement of the allylic carbonate derivative with sodium *α-tert*-butoxyacetoacetate, provided the *cis*-adduct **76** in 88% yield. Compound **76** was then transformed into cyclopentenone **77**. Regioselective conversion of cyclopentenone **77** to the enol triflate derivative followed by Pd-catalyzed coupling of this intermediate with hexamethylditin provided vinylstannane **78**. Pd-catalyzed carbonylative coupling of **78** with the triazone-protected *ortho*-iodoaniline followed by selective epoxidation, Wittig methylenation, and desilylation provided **79** in good yield and enantiomeric purity >95% ee. Cyclization of **79** followed by the key aza-Cope–Mannich reorganization provided the crystalline pentacyclic diamine **80** in 98% yield. Functionalization of **80** within six steps led to (−)-strychnine in 3% overall yield in 20 steps. This synthesis constitutes the most efficient one and considering the latent symmetry of (+)-**29**, this total synthesis could be extended to the preparation of *ent*-strychnine.

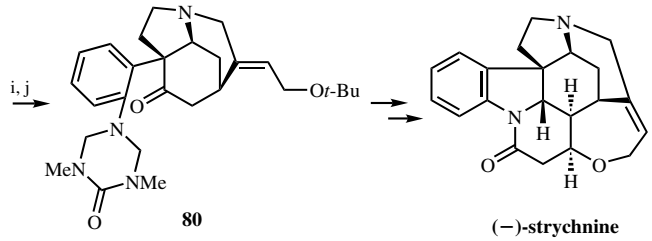


(c) NaOH, 99%; (d) *o*-bromophenol, DEAD, PPh_3, 82%; (e) *n*-BuLi, 55%; (f) Br_2 then Zn, AcOH, 53%.

Scheme 15



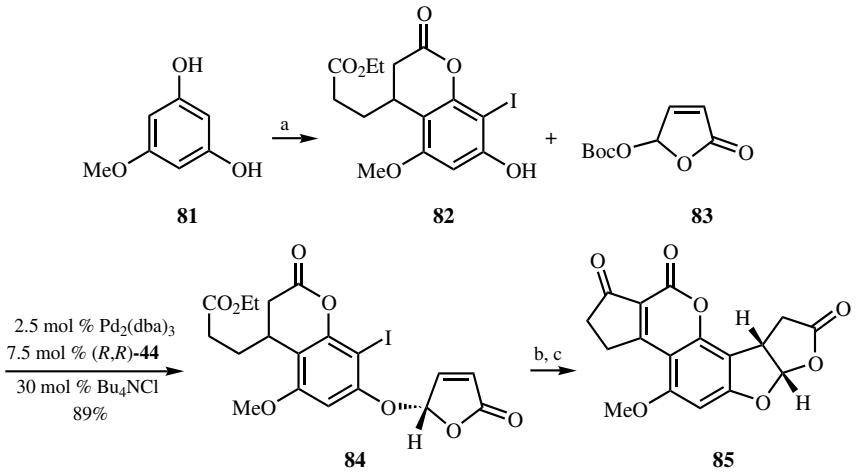
Scheme 16 (*Continued*)



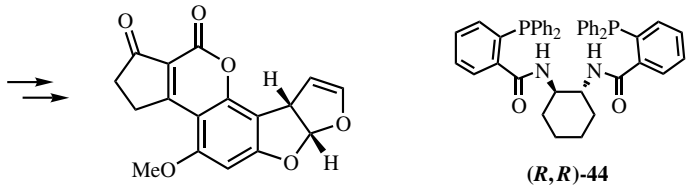
(c) $NaCNBH_3$, $TiCl_4$; DCCC, CuCl; DIBAL, 96% (3 steps); (d) TIPSCl; Jones oxidation; (e) L-Selectride, $PhNTf_2$ 88%; (f) Me_6Sn_2 ,$Pd(PPh_3)_4$, 81%; (g) CO (50 psi), $Pd_2(dba)_3$, Ph_3As, 80%; (h) Triton-B; $Ph_3P{=}CH_2$, then TBAF, 91% (2 steps); (i) MsCl; LiCl, then $NaNHCOCF_3$ (j) $(CH_2O)_n$, 98%.

Scheme 16

Functionalization of oxygenated cyclopentenyl moiety has also been studied and especially the asymmetric synthesis of γ-acyloxybutenolides, which are useful synthons for the synthesis of natural products. Trost and Toste[52] have recently described a Pd-catalyzed kinetic and dynamic kinetic asymmetric transformation of 5-acyloxy-2-(5*H*)-furanone and have applied the methodology to the formal enantioselective synthesis of (−)-aflatoxin B lactone (**Scheme 17**). The highly toxic and exceedingly carcinogenic aflatoxins are mold metabolites produced by a number of *Aspergillus* and *Penicillium* species. The coumarin **82** was prepared by a Pechman condensation of monomethyl phloroglucinol **81** followed by regioselective iodination in 43% overall yield. The sterically demanding coumarin **82** readily participated as the nucleophile in the Pd-catalyzed kinetic asymmetric allylation of butenolide **83**, using $Pd_2(dba)_3$ as catalyst, chiral ligand (*R*,*R*)-**44**, and chloride ion. Adduct **84** was efficiently obtained in 89% yield and an excellent enantiomeric excess of >95% (measured after the Heck reaction). Subjecting **84** to the standard Heck cyclization conditions afforded the tetracyclic coumarin, which was efficiently transformed to the Büchi's intermediate **85** for the synthesis of aflatoxin B.



Scheme 17



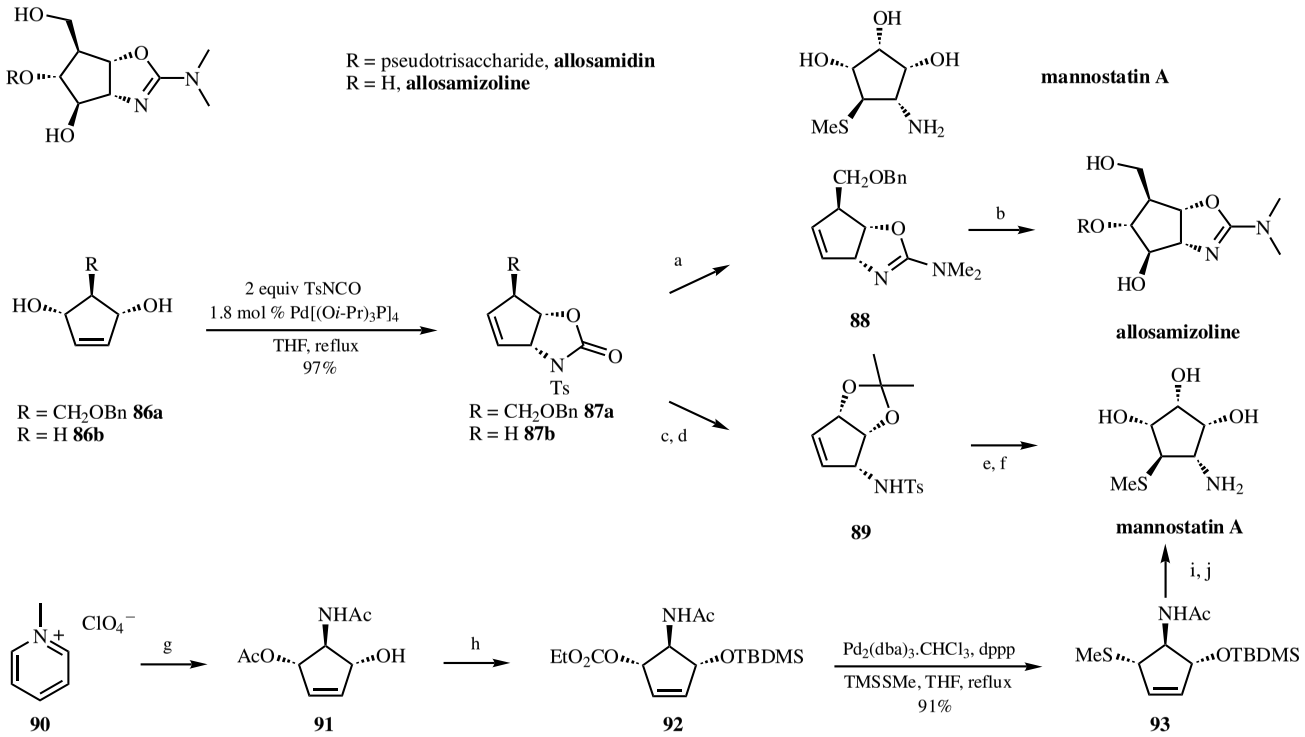
aflatoxin B **(*R*,*R*)-44**

(a) $EtO_2CCH_2CO(CH_2)_2CO_2Et$, HCl; ICl, 43% (2 steps); (b) $PdCl_2(CH_3CN)_2$, 93%, ee > 95%; (c) HOAc; $Sc(OTf)_2$, $LiClO_4$, 32% (2 steps).

Scheme 17 (*Continued*)

Another class of compounds, aminocyclopentitol glycosidase inhibitors, have also been approached via allylic alkylation of the cyclopentyl moiety (**Scheme 18**). Allosamidin and its congeners were isolated from the mycelial extract of *Streptomyces* sp. and were shown to possess specific inhibitory activity against chitinases from various sources. Mannostatin A, isolated from *Streptoverticillium verticillus*, is a highly specific nontoxic nanomolar inhibitor of α-D-mannosidase. An original synthetic strategy was described by Trost and Van Vranken[53] using cyclic diols **86a** and **86b**. Both syntheses began with the Pd-catalyzed ionization/cyclization reaction by the respective treatment of 1,4-diols **86a** and **86b** with 2 equiv of *p*-toluenesulfonyl isocyanate followed by 1.8 mol% tetrakis(triisopropyl phosphite)palladium to afford oxazolidinones **87a** and **87b** in 97% yield. The synthesis of allosamizoline was then accomplished via a reductive desulfonylation, the formation of the heterocyclic oxazoline **88**, and dihydroxylation. The synthesis of mannostatin was realized after an eight-step sequence. Allylic oxidation and $NaBH_4$ reduction followed by protection led to the cyclic carbonate **89** in a good overall yield. The final stage of the synthesis included an epoxidation and the attack of lithium thiomethoxide anion to give mannostatin A. Subsequent to completion of these syntheses, Trost has shown that substitution of triisopropyl phosphite in the palladium reaction with an appropriate chiral ligand provided the carbamates **87a** and **87b** with enantiomeric excesses of 70% and 88%, respectively. Thus, the synthetic routes developed required no changes to complete asymmetric syntheses of natural products. A recent synthesis of (+)-mannostatin A was described by Ling and Mariano[54] using the Trost Pd-catalyzed methylthiolation procedure for the introduction of the thioether (**Scheme 18**). Pyridinium perchlorate **90** was converted to an amido-acetate, which was hydrolyzed to monoalcohol **91** by electric eel acetylcholinesterase (ee = 80%). The alcohol **91** was transformed to carbonate **92**, which gave a single methylthioether **93** under the Trost conditions. Further functionalization including a Wipf inversion of the alcohol finally led to (+)-mannostatin.

C.i.c. ***Synthesis of Prostaglandin Family Derivatives.*** Prostaglandins exhibit diverse pharmacological properties and are now recognized as local hormones that control a multitude of important physiological processes. Tremendous efforts have been made for the realization of an efficient chemical synthesis.[55] Among the different approaches, Pd-catalyzed reactions have been reported and can be classified in three categories. **Section C.ii.a** deals with the approach using Pd-assisted cyclization to form the cyclopentane. We can distinguish two other approaches, one described by Luo and Negishi[56] using allylation of cyclopentenone enolate and one initiated by Tsuji's group[57] and Kurozumi's group[58] using decarboxylation–dehydrogenation and decarboxylation–2-alkenylation,



(a) Na, 91%; CH_3OTf, Me_2NH, 100%; (b) CF_3CO_3H; TFA; H_2, Pd/C, 67% (3 steps); (c) SeO_2, Dess–Martin periodinane; $NaBH_4$, 54% (2 steps); (d) K_2CO_3, $Me_2C(OMe)_2$, 88% (2 steps); (e) CF_3CO_3H; CH_3SLi, 70% (2 steps); (f) Na; CF_3CO_2H, 83% (2 steps); (g) ν; Ac_2O; EEACE, 29% (3 steps); (h) TBDMSCl; NaOMe; EtOCOCl, 87% (3 steps); (i) HF; Burgess reagent, 65% (2 steps); (j) OsO_4; HCl, 74% (2 steps).

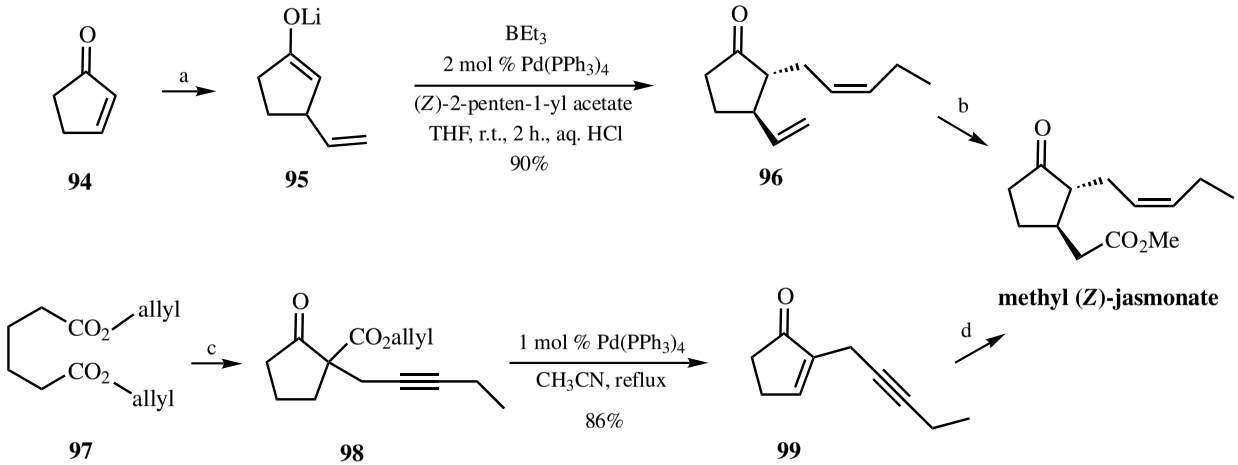
Scheme 18

respectively. A striking example is the preparation of methyl jasmonate, an important constituent for characteristic odor of jasmine oil and very useful in the perfume industry, by Luo and Negishi[59] and Tsuji's group,[57] respectively (**Scheme 19**). The synthesis described by Luo and Negishi started with the lithium 3-vinyl-1-cyclopentenolate **95**, prepared from cyclopentenone **94**. Successive treatment of **95** with triethylborane in tetrahydrofuran, a solution of (*Z*)-2-penten-1-yl acetate and palladium tetrakis-triphenylphosphine (2 mol %), and aqueous hydrochloric acid gave **96** in 90% yield and 97% diastereoselectivity. Its oxidative hydroboration, oxidation, and esterification led to methyl (*Z*)-jasmonate in 90% yield from **96**. This methodology was also applied to the synthesis of (±)-11-deoxyplostaglandin E_2 methyl ester.[56] The second Pd-catalyzed synthesis is based on the decarboxylation–dehydrogenation of the β-keto-ester **98**, prepared from diallyl adipate **97** by a Dieckmann condensation–alkylation sequence in 85% yield. Transformation of **98** to **99** was optimized and the best results were obtained in the presence of palladium diacetate and triphenylphosphine in refluxing acetonitrile. The cyclopentenone **99** was then hydrogenated and transformed into methyl (*Z*)-jasmonate by a two-step sequence (Michael addition and saponification–decarboxylation).

Kurozami and co-workers used an intramolecular Pd-catalyzed decarboxylation–allylic alkylation for the synthesis of (5*E*)-prostaglandin E_2 and new 6-functionalized prostaglandin derivatives.[58],[60] The enolate generated by conjugate addition of organocopper reagent of (*S*,*E*)-3-*t*-butylmethylsilyloxy-1-lithio-1-octene **101** to the chiral enone **100** was trapped by imidazole derivative **102** to afford the 2-alkenyloxycarbonylated three-component coupling product **103** in 41% yield (**Scheme 20**). Treatment of **103** with palladium tetrakistriphenylphosphine (5 mol %) according to Tsuji's conditions in dimethylformamide provided the protected (5*E*)-PGE_2 derivative, which afforded (5*E*)-PGE_2 methyl ester after desilylation. New 6-functionalized derivatives such as 6-methylene-PGE_1 methyl ester and 6-methyl-PGI_1 methyl ester have also been prepared according to the same Pd-catalyzed decarboxylative allylic alkylation methodology.

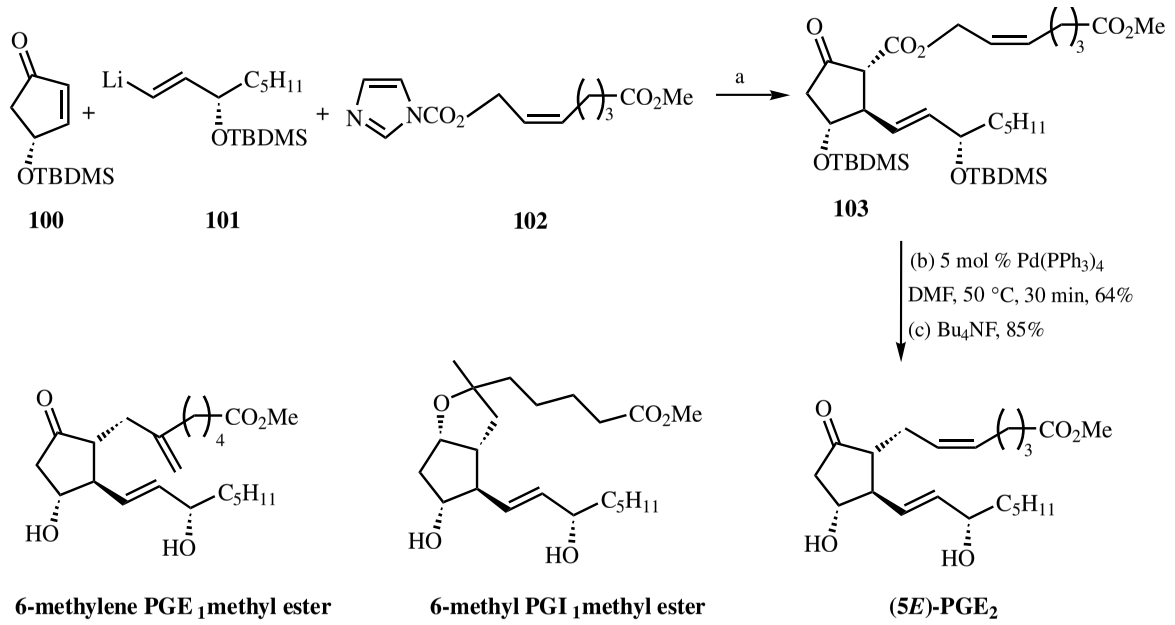
C.i.d. ***Miscellaneous.*** Pd(0)-catalyzed reactions have been employed in many other syntheses, and only a few examples will be described here. The strategy involving the palladium opening of epoxide has led, for example, to the preparation of (−)-pentenomycin I and ircinin-4. (−)-Pentenomycin has been isolated from aerobically cultured broths of a mutant strain of *Streptomyces eurythermus* and is part of a family of antibiotics, which demonstrate a moderate to strong *in vitro* activity against gram-positive and gram-negative bacteria. Achab and Das[61] have described a formal synthesis of (−)-pentenomycin, starting from 1,2-isopropylidene-α-D-glucofuranose **104**, which was easily transformed to vinyl epoxide **105** (**Scheme 21**). The epoxide **105** was subsequently treated with a catalytic amount of palladium tetrakistriphenylphosphine in dichloromethane at ambient temperature to provide a mixture of two isomeric α,β-unsaturated aldehydes **106** in 85% isolated yield. After reduction, protection, and hydrolysis, the mixture of 2-hydroxy-4-oxoaldehyde and its hydrated form was cyclized under Crombie's conditions to furnish the hydroxycyclopentenone **107** in a modest yield.

Ircinin-4 is part of a family of furanoterpenes, produced by the Mediterranean sponges *Ircinia oros* and *I. fasciculata*, that exhibit high activity in the brine shrimp assay and turn out to be selective inhibitors of phospholipase A_2. The first total synthesis was recently described by Fürstner et al.[62] and was based on the Pd-catalyzed opening of vinyloxirane (**Scheme 21**) employing the Tsuji–Trost conditions. Treatment of the epoxide **108**, obtained from the reaction of 3-furyl-acetaldehyde with a sulfur ylide, with catalytic amounts of



(a) $Li_2Cu(CH{=}CH_2)_2CN$; Me_3SiCl; *n*-BuLi, 86%; (b) 9-BBN; H_2O_2; $Na_2Cr_2O_7$; H_2SO_4; MeI, K_2CO_3, 90%; (c) NaH, 2-pentynylchloride, 85%; (d) Pd Lindlar, H_2, 95%; methylmalonate, 98%; NaOH, 90%.

Scheme 19

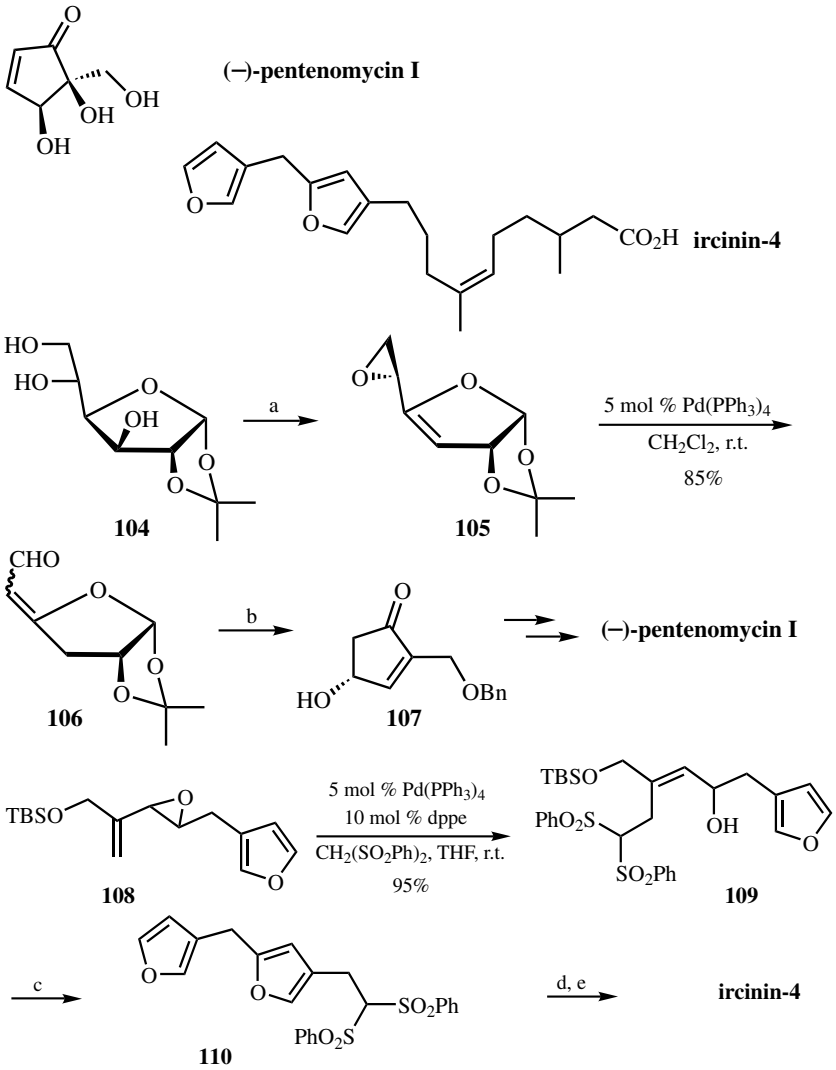


100 **101** **102** **103**

6-methylene PGE $_1$methyl ester **6-methyl PGI $_1$methyl ester** **(5*E*)-PGE$_2$**

(a) CuC≡C*n*-Pr, $P(NMe_2)_3$, 41%.

Scheme 20



(a) PPh_3, DEAD; Tf_2O; DBU, 82% (3 steps); (b) DIBAH; NaH, BnBr; HCO_2H; NaOH, 21% (4 steps); (c) THP; TBAF; MnO_2; HCl, 60% (4 steps); (d) Li, then $BrCH_2R$; TBAF; Na(Hg), 41% (3 steps); (e) PDC; $AgNO_3$, 78% (steps).

Scheme 21

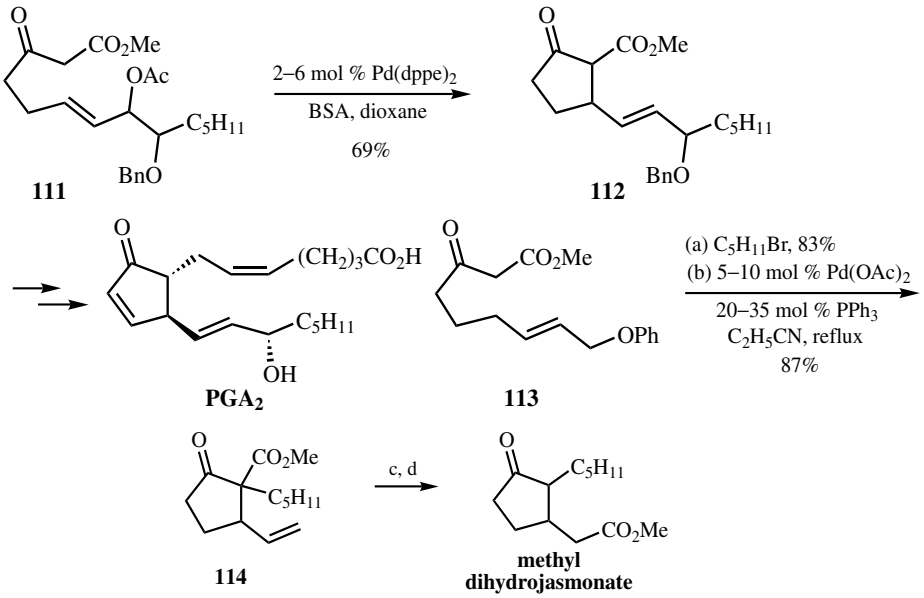
palladium tetrakistriphenylphosphine and DPPE selectively activated its vinyloxirane without affecting the adjacent allyl ether site. Nucleophilic attack of the bis(phenylsulfonyl)methane on the functionalized π-allylpalladium complex afforded regioselectively the allylic alcohol **109** in an excellent yield. Protection–deprotection–oxidation led to the furanylmethylfuran **110**. Reductive metallation of bis-sulfone **110** followed by addition of allylic bromide prepared from β-citronellol and further functionalization led to ircinin-4.

The ability of Pd catalysts to exercise control in bond-forming reactions under very mild conditions made them excellent candidates to facilitate ring formation. Indeed, Pd-catalyzed allylation has widely been used in the formation of natural five-membered ring

products. Cyclization of linear allylic compounds via a π-allyl intermediate had led to carbocycles and heterocycles, according to the nature of the nucleophile (carbon, oxygen, or nitrogen). Another way to form cyclopentanic rings was illustrated by the Pd-catalyzed [3 + 2] cycloadditions, involving the transfer of a trimethylenemethane unit.

C.ii. Cyclization Via Palladium-Catalyzed Allylation

C.ii.a. ***Cyclizations Involving Carbon Nucleophiles.*** Pd-catalyzed cyclization to form cyclopentane was an early area of intense interest in natural products studies. It has been applied for the synthesis of prostaglandin and steroid derivatives. Trost and Jungheim[63] and Tsuji et al.,[64] respectively, reported the synthesis of the Roussel–Uclaf intermediate to PGA_2 and the synthesis of methyl dihydrojasmonate (**Scheme 22**). Treatment of β-ketoester **111** with $Pd(dppe)_2$, a sterically less demanding catalyst than $Pd(PPh_3)_4$, in the presence of *O*,*N*-bis(trimethylsilyl)acetamide produced exclusively cyclopentanone **112**, precursor of PG's family. While studying the cyclization conditions of (*E*)-3-oxo-8-phenoxy-6-octanoate **113** catalyzed by palladium(0) under neutral conditions, Tsuji and co-workers described efficient syntheses of natural products, such as an 18-functionalized steroid intermediate,[65] 18-hydroxyestrone,[66] and sarkomycin.[67] We will only focus here on the preparation of methyl dihydrojasmate, obtained from the cyclopentanone **114**. Decarboxylation of **114** followed by hydroboration, oxidation, and methylation afforded methyl dihydrojasmonate.

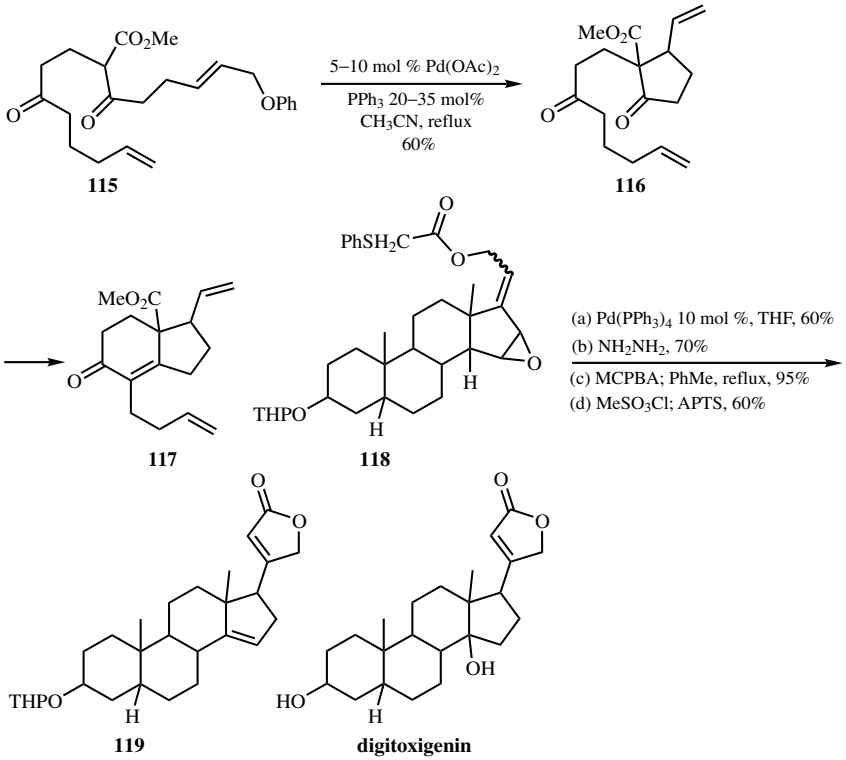


(c) NaI, HMPA, 88%; (d) 9-BBN; CrO_3; CH_2N_2, 65% (3 steps).

Scheme 22

This methodology has also been applied to the synthesis of CD rings of steroids **117**, first by Tsuji et al.[68] and then by others (**Scheme 23**). The trisannulation reagent **115** prepared from 1,7-octadien-3-one and (*E*)-3-oxo-8-phenoxy-6-octanoate was subjected to cyclization under neutral conditions to give cyclopentanone **116**. Construction of the CD

ring of steroid **117** was then accomplished by an aldol condensation. Wicha and Kabat[69] described a formal synthesis of digitoxigenin, which is an important heart-stimulating steroid-type drug. The diethyl ether **118** was cyclized employing the conditions developed by Trost and Molander for alkylation of allylic epoxides to afford cardanolide, which was transformed in four steps to unsaturated compound **119**, which is a known precursor to digitoxigenin. It can be noted that Pd-catalyzed opening of allylic epoxides has been also widely used by Tsuji and co-workers for the synthesis of steroid side chains.[70]

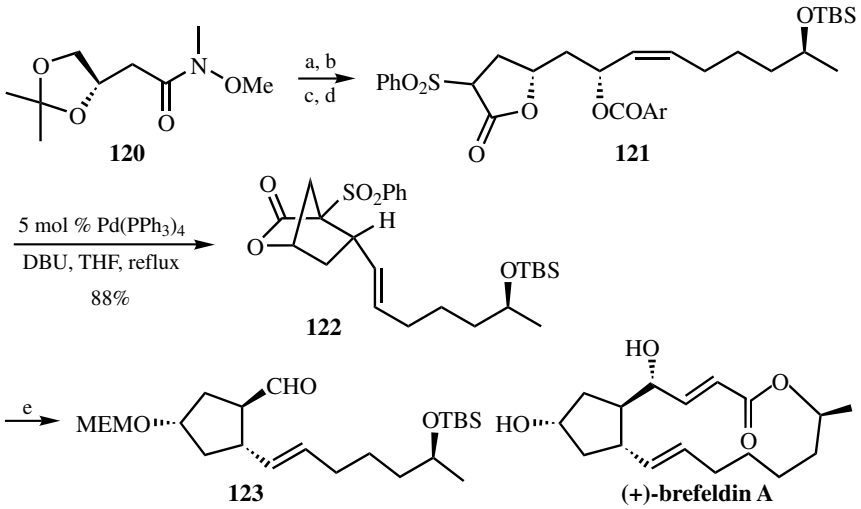


Scheme 23

More recently, a biologically active compound, brefeldin A, has been synthesized. Brefeldin A, a significant target because of its antifungal, antimitotic, antiviral, and antitumor activities, has recently been approached via a Pd-catalyzed cyclization. This constitutes the second synthesis using π-allyl complexes; the other using [3 + 2] cycloaddition will be developed in **Sect. C.ii.d**. The formal synthesis[71] was commenced by preparation of the cyclized precursor **121** from the known Weinreb amide **120** (**Scheme 24**) within eight steps. The crucial cyclization of allylic benzoate **121** was carried out by DBU treatment in the presence of 5 mol % $Pd(PPh_3)_4$. The bicyclic lactone **122** possessed the three requisite stereogenic centers and one *E*-olefin of (+)-brefeldin. The final conversion to the known advanced intermediate **123** was accomplished by an efficient three-step sequence.

Another class of antibiotics that has been approached through Pd-catalyzed cyclization is the carbapenem family. Carbapenems such as (+)-thienamycin, a natural fungal metabolite discovered by the Merck group, or 1 β-methylcarbapenems are very efficient

β-lactam antibiotics closely related to penicillins and cephalosporins. Genêt and coworkers have described a Pd-catalyzed route to the formation of a five-membered ring in β-lactam skeleton (**Scheme 25**).[72] The known functionalized azetidinone **124** was efficiently transformed into vinylester **125** via a stereocontrolled hydrogenation and a classic sequence. The ester was then reduced and the azetidinone nitrogen alkylated to give intermediates **126**, which were cyclized under optimized mild conditions to give bicyclic compounds **127**. This methodology using π-allylpalladium ring-closure strategy constitutes a new route to 1β-methylcarbapenems, and functionalities are present for further modification of the scaffolds.

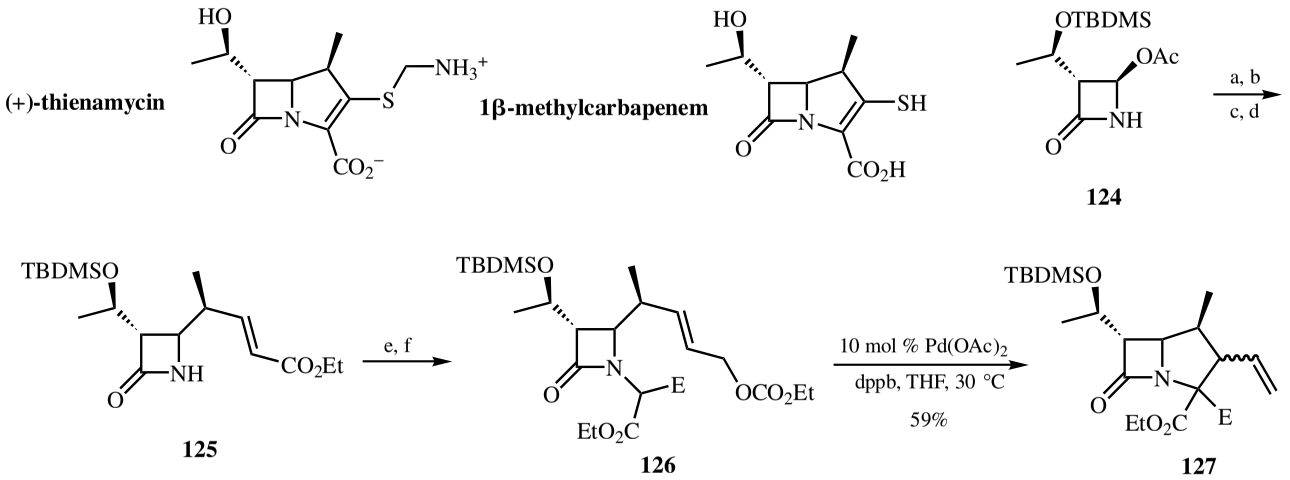


(a) *n*-BuLi, RC≡CH; Lindlar cat., H_2, 77% (2 steps); (b) LAH; $(MeO)_2CHC_6H_4$(*p*-OMe), 80% (2 steps); (c) TsCl; NaH, $PhO_2SCH_2CO_2Me$, 71%; (d) DDQ; DBU, 71%; (e) Na/Hg; DIBAL; MEMCl, then DBU 71% (3 steps).

Scheme 24

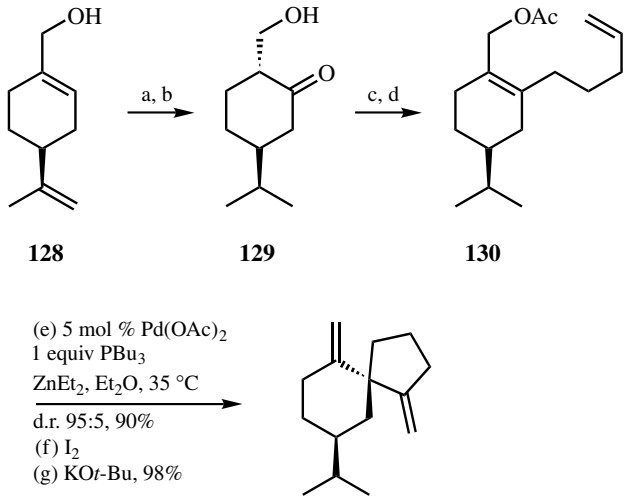
Other molecules have been synthesized according to an ene reaction protocol, developed by Oppolzer.[73],[74] The intramolecular insertion of allylpalladium into alkene and alkyne bonds (metallo-ene type cyclization) has indeed evolved into a synthetically powerful process. A marine sesquiterpenoid isolated from the Caribbean octocoral *Erythropodium caribaeorum,* (−)-erythrodiene, bearing a rare spirobicyclo[4.5]decane skeleton, was recently synthesized by Oppolzer and Flachsmann.[75] Its synthesis from commercially available (−)-(*S*)-perillyl alcohol **128** is outlined in **Scheme 26**. After selective hydrogenation of the exocyclic double bond and hydroboration/oxidation of the endocyclic double bond, the resulting ketone **129** was subjected to base-induced equilibration and functionalized to give acetoxydiene **130**. Exposure of **130** to an excess of diethylzinc in the presence of a catalytic amount of palladium diacetate and tributylphosphine, followed by the addition of iodine, led to the formation of cyclized iodoproduct, which was transformed to (−)-erythodiene by dehydroiodination.

The Pd-catalyzed ene reaction has widely been used combined with subsequent CO insertions. Indeed, the potential of Pd "ene-type cyclization/carbonylation" protocols for the synthesis of fused five-membered ring systems has amply been demonstrated by



(a) $CH_3CH(CO_2Me)(SOPh)$; LDA, then toluene, reflux, 75% (2 steps); (b) DIBAL, 85%; (c) (*R*)(+)BINAPRuBr_2, H_2, de 99%, 90%; (d) Swern; $Ph_3P{=}CHCO_2Et$, 83% (2 steps); (e) DIBAL; $ClCO_2Et$, 84% (2 steps); (f) LiHMSD, $BrCH_2CO_2Et$; LiHMDS, $ClCO_2Et$ or PhSSPh, 86% (2 steps).

Scheme 25

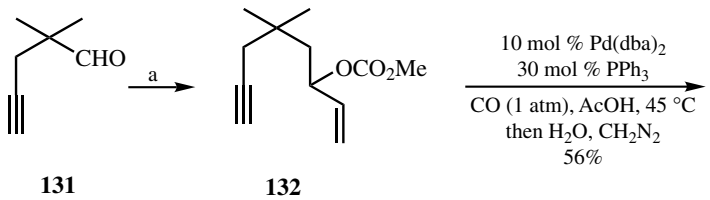


(+)-erythrodiene

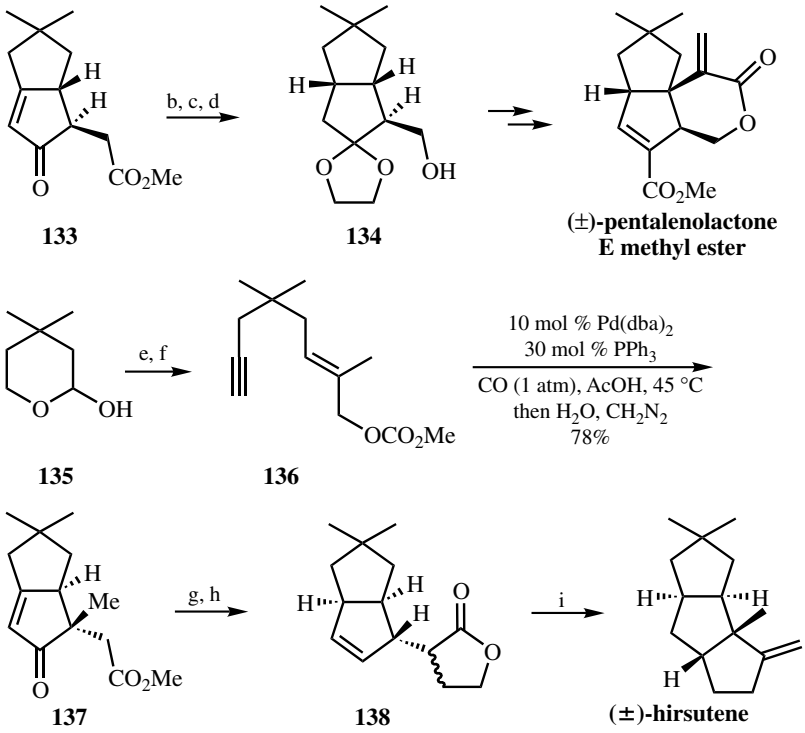
(a) PtO_2, H_2; TIPSCl, 85% (2 steps); (b) $BH_3.Me_2S$, H_2O_2; TPAP; K_2CO_3; 65% (3 steps); (c) $BrMg(CH_2)_3$-CH═CH_2; Bu_4NF, 80% (2 steps); (d) $Py.SO_3$; DIBAH; Ac_2O, 80% (3 steps).

Scheme 26

its employment in the synthesis of pentalenolactone E methyl ester, hirsutene, and (+)-3-isorauniticine. A formal synthesis[76] of pentalenolactone E methyl ester, isolated after esterification of extracts of *Streptomyces* UC 5319, was first described starting from the known aldehyde **131** (**Scheme 27**). Homologation followed by functionalization of **131** led to carbonate **132**. The crucial allylation/carbonylation step was realized with Pd(0) and triphenylphosphine in acetic acid at 45 °C under CO (1 atm) for 72 hours. Bicyclooctenone **133** was isolated after esterification in 56% yield. Transformation to *nor*-alcohol **134** was realized by hydrogenation followed by Barton's radical chain degradation. The key intermediate **134** was therefore obtained via a sequence of nine steps in 13% overall yield. (±)-Hirsutene,[77] a metabolite of the Basidiomycete *Coriolus consors*, was obtained according to the same methodology. Lactol **135** was efficiently transformed to carbonate **136**, which was subjected to the same conditions as for **132** to give bicyclooctenone **137** in 78% yield as a 83 : 17 mixture of epimers. Attachment of the remaining carbon atoms led to **138**, which was cyclized by a radical chain reaction and gave after the *exo*-methylene transformation tricyclic (±)-hirstune (**Scheme 27**).



Scheme 27 (*Continued*)

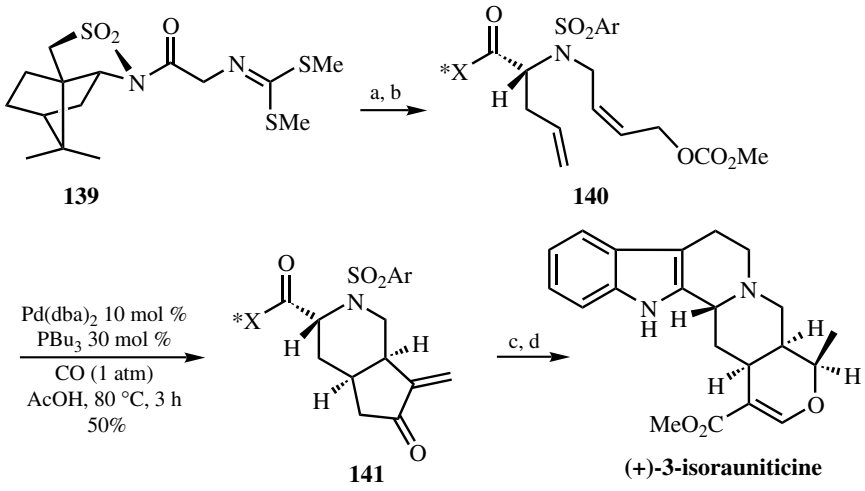


(a) $Ph_3P{=}CHOMe$; vinylMgBr; $ClCO_2Me$, 64%; (b) H_2, $[RhCl(PPh_3)_3]$; $HO(CH_2)_2OH$, 90% (2 steps); (c)LiOH; $(COCl)_2$; 1-hydroxypyridine-2(1*H*)-thione, O_2; $P(OMe)_3$, 41% (4 steps); (d) $Ph_3P{=}C(Me)CO_2Et$; PCC; CBr_4, 86% (3 steps); (e) DIBAH; BuLi; $ClCO_2Me$, 74% (3 steps); (f) H_2, Pd/C; $NaBH_4$, $POCl_3$, 79% (3 steps); (g) LDA, cyclic ethylene sulfate, 48%; (h) PhSeNa; CH_2N_2; Bu_3SnH, AIBN; $LiAlH_4$; PBu_3, $2\text{-}NO_2\text{-}C_6H_4SeCN$; H_2O_2, 50 °C, 83% (6 steps).

Scheme 27

The heteroyohimbine alkaloid (+)-3-isorauniticine, isolated from *Corynanthe mayumbensis,* was synthesized using the intramolecular Pd-catalyzed allylation/carbonylation process[78] (**Scheme 28**). C-Alkylation of commercially available chiral glycinate equivalent **139**, followed by removal of the N-protecting group and N-acetylation, provided sulfonamide. The latter was then alkylated to furnish the dienylcarbonate **140**. Proceeding to the key reaction, carbonate **140** was subjected to Pd(0)-catalyzed cyclization/carbonylation in acetic acid at 80 °C for 3 hours, giving a major isomer **141** in 50% yield. The bicyclic compound **141** was functionalized in nine steps to give (+)-3-isorauniticine. This total synthesis has been accomplished via a sequence of 14 steps, which highlighted the preparative utility of sultam-directed asymmetric alkylation and of transition-metal-catalyzed carbometallation/carbonylation reactions.

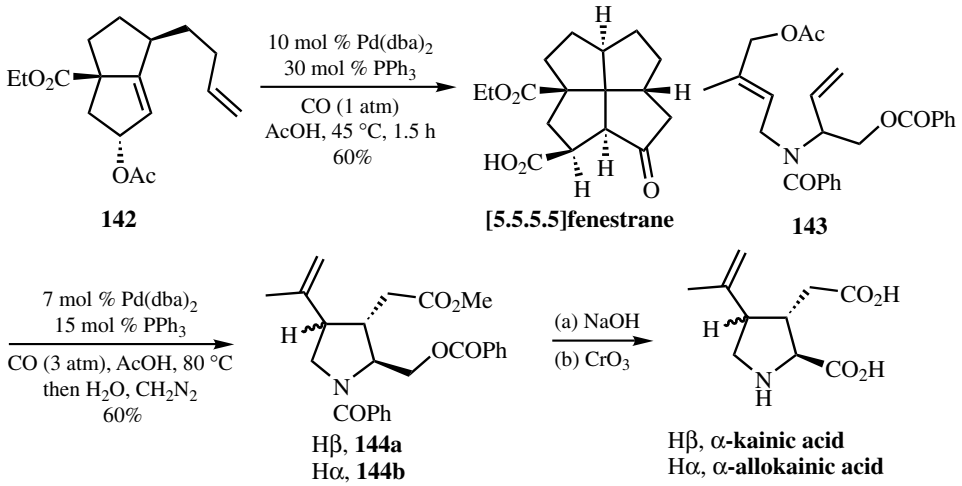
This methodology has been used by other groups to synthesize natural products. A striking example is the efficient synthesis of [5.5.5.5]fenestrane by Pd-catalyzed cyclization/carbonylation of bicyclic acetoxydiene **142** (**Scheme 29**).[79] Thus, four carbon–carbon bonds and four stereocenters were formed selectively in a single



(a) allylI; HCl; mesitylsulfonyl chloride, 69% (3 steps); (b) (*Z*)-1-bromo-4-[(methoxycarbonyl)oxy]-2-butene, 96%; (c) H_2, Pd/C; MCPBA; *p*-nitrobenzylalcohol; HF, pyridine; tryptophyl bromide; Pd/C, H_2, 29% (6 steps); (d) $PhPOCl_2$; NaHMDS, methyl formate; HCl, 24% (3 steps).

Scheme 28

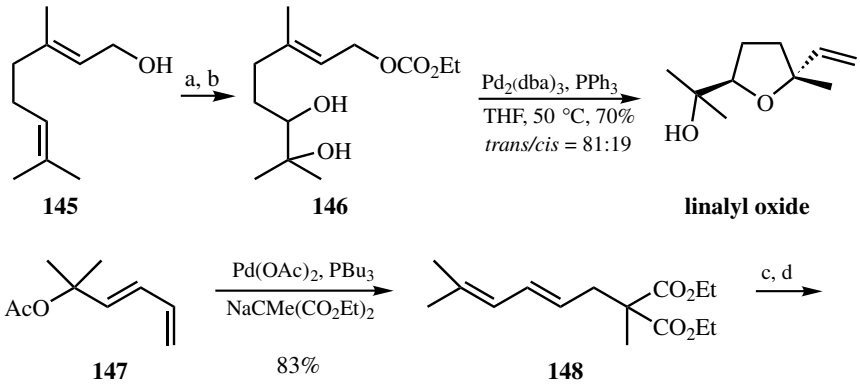
operation. Biologically active molecules have been prepared too. For example, α-kainic acid and α-allokainic acid, isolated from the algae *Digenea simplex* and *Centrocerus clavalatum*, have widely been targeted due to their potent neurotransmitting activity in the central nervous system. The pyrrolidine ring has been constructed using the Pd(0) ene reaction/carbonylation (**Scheme 29**).[80] Cyclization conditions of the benzoyl compound **143** were studied and optimized, affording two major isomers **144a** and **144b** in 25% and 35% yield, respectively. Transformation of **144a** and **144b** into α-kainic acid and α-allokainic acid was done by basic hydrolysis followed by oxidation.



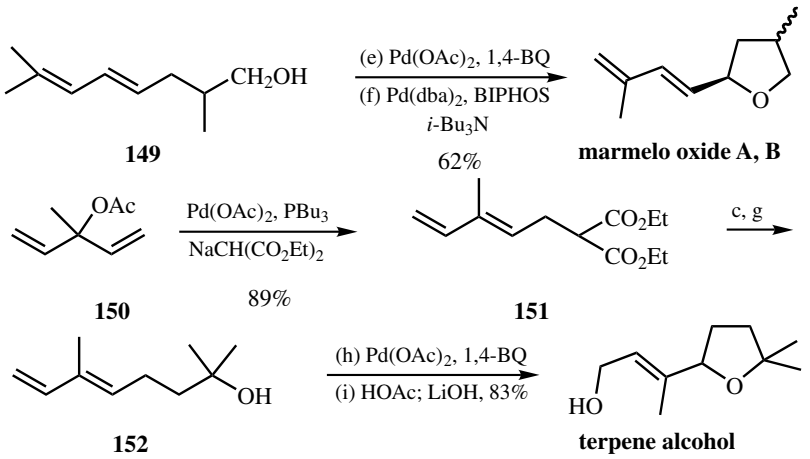
Scheme 29

C.ii.b. ***Cyclizations Involving Oxygen Nucleophiles.*** Substituted tetrahydrofurans are part of many natural products, such as linalyl oxides, marmelo oxides, or terpene alcohol (**Scheme 30**). Linalyl oxides are found in nature, extracted from flowers and fruits, and are mainly used in perfumery and as aromas. Sinou and co-workers have developed a straightforward synthesis starting from geraniol **145**.[81] Geraniol was converted to the corresponding allylic carbonate, which was in a "one-pot" reaction transformed into dihydroxycompound **146**. Cyclization of **146** with Pd(0) catalyst was optimized and probably proceeds in a classical way: oxidative addition of the carbonate to give a cationic π-allyl complex, deprotonation of the hydroxyl group by the methoxide anion, and attack of the less hindered alkoxide to give the major *trans*-tetrahydrofuran. In this case, the most substituted position of the π-allyl system is attacked, but this unusual phenomenon is in agreement with Baldwin's rules, which predict a 5-*exo-trig* cyclization.

Another approach of tetrahydrofurans has been developed by Andersson and Bäckvall[82] for the synthesis of marmelo oxides and a terpene alcohol (**Scheme 30**). Naturally occurring marmelo oxide exists as a 1:1 mixture of epimers and has been shown to be the characteristic flavor component of the quincefruit (*Cydonia oblonga*). The terpene alcohol occurs in peppermint oil extract from most species of the *Mentha* family such as *M. piperita*, *M. cardiaca*, and *M. spicata*. Allylic acetate **147** was regioselectively substituted with sodium diethyl methylmalonate at 40 °C in the presence of a catalytic amount of palladium diacetate and tributylphosphine to give **148** in 83% yield. Compound **148** was then decarboxylated with sodium cyanide to give the monoester, which was reduced with DIBAL. The 1,3-diene alcohol **149** was subsequently subjected to a Pd-catalyzed oxidation, which afforded the cyclized product via a π-allyl intermediate. Finally, a highly regioselective Pd-catalyzed 1,2-elimination of the allylic acetate furnished the marmelo oxides A and B as a 1:1 mixture in 84% yield. The same basic strategy was employed for the synthesis of the terpene alcohol. The Pd-catalyzed alkylation of the allylic acetate **150** with the malonate ester nucleophile gave **151** with a good regioselectivity. Subsequent decarboxylation followed by addition of methyl lithium gave the allylic alcohol **152** in good overall yield. The latter was cyclized and completely rearranged to the desired and thermodynamically more stable acetate by treatment with acetic acid at 100 °C. The hydrolysis was then performed with lithium hydroxide to afford the desired alcohol in high yield. These two syntheses are based on the Pd-catalyzed intramolecular 1,4-addition of nucleophiles to conjugated dienes.



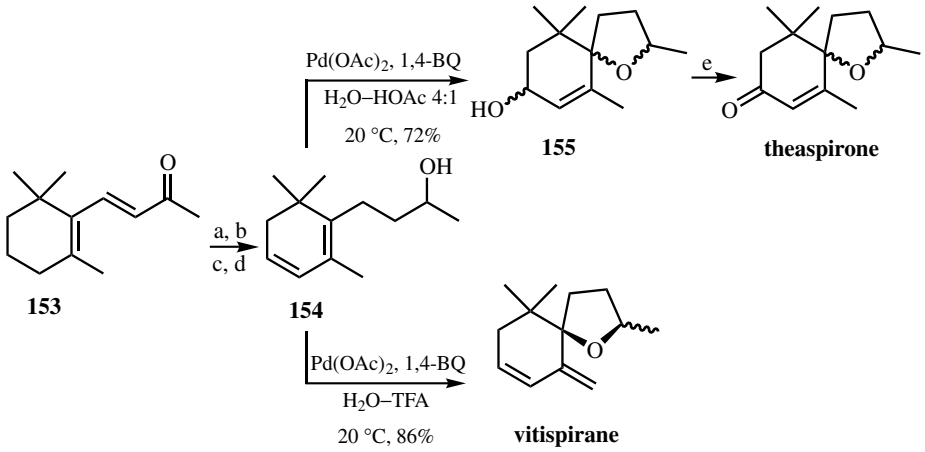
Scheme 30 (*Continued*)



(a) $ClCO_2Et$, 82%; (b) NBS; NaOH; H_2SO_4, 25 °C, 68%; (c) NaCN, 82%; (d) DIBAL, 94%; (g) MeLi, 91%.

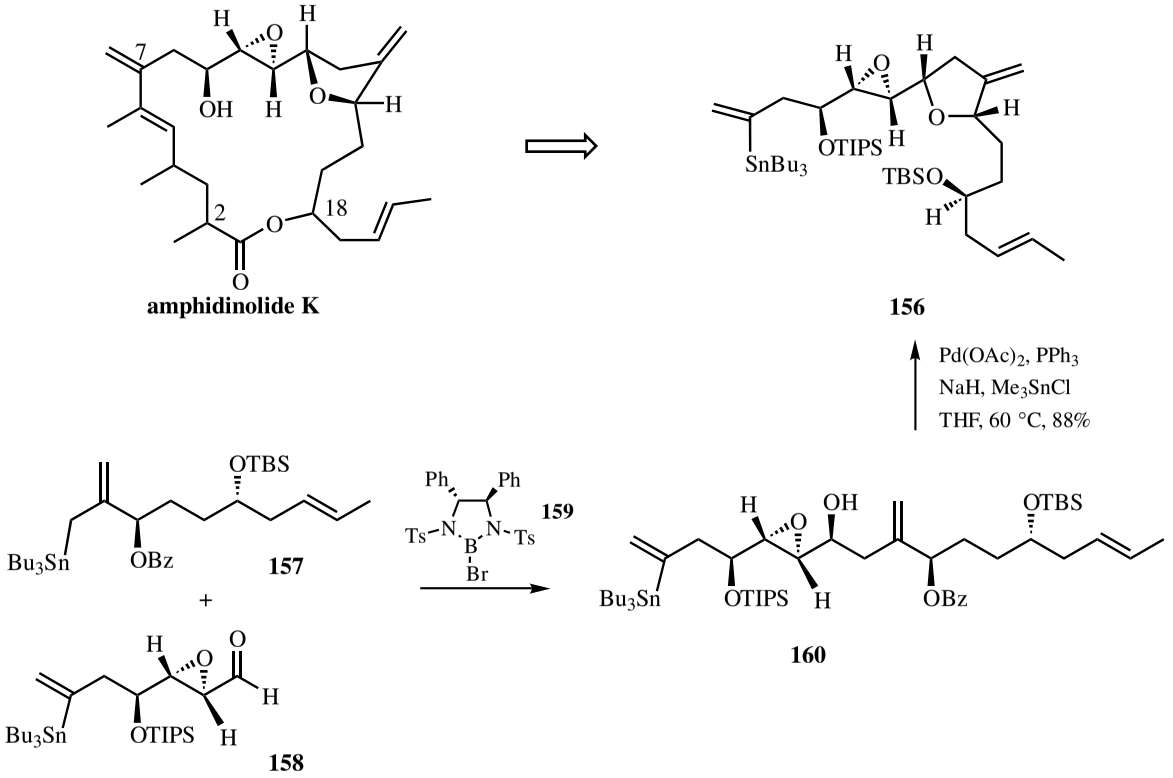
Scheme 30

This useful method was also applied to construct oxygenated heterocyclic natural molecules such as theaspirone and vitispirane[83] (**Scheme 31**). Theaspirone was the first spiro ether isolated from black tea. The starting material **154** for the oxaspirocyclization was prepared from β-ionone **153**, after transformation to diene, and double reduction of the α,β-unsaturated ketone. The conditions of cyclization were optimized to form **155** in the presence of a catalytic amount of palladium diacetate, 1,4-benzoquinone, and a mixture of water and acetic acid. The alcohol **155** was obtained as a 1:1 mixture of diastereomers (*syn* and *anti*) in 72% yield. The alcohols were further oxidized to theaspirone (1:1) in 88% combined yield. Vitispirane was obtained in 86% yield under the same conditions of cyclization replacing acetic acid by trifluoroacetic acid. This methodology was also applied for aminoheterocycles and will be developed in **Sect. C.ii.c**.



(a) NBS, hν; (b) Na_2CO_3, 77% (2 steps); (c) $Pd(PPh_3)_4$, Bu_3SnH, 90%; (d) $NaBH_4$, 90%; (e) MnO_2, 82%.

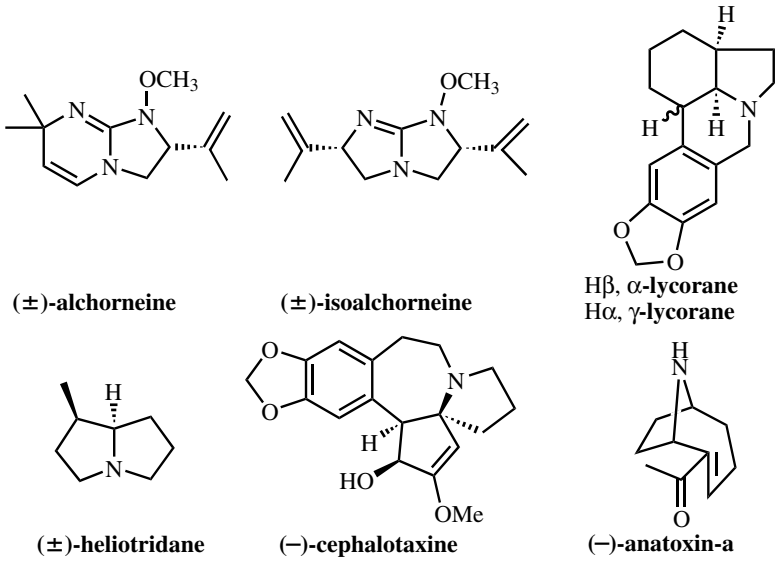
Scheme 31


amphidinolide K
156
Pd(OAc)2, PPh3
NaH, Me3SnCl
THF, 60 °C, 88%
157
159
158
160

Scheme 32

Pd-catalyzed cyclization was also applied to the stereocontrolled preparation of chiral substituted tetrahydrofurans. The synthesis of optically active tetrahydrofurans was pioneered by Stork and Poirier,[84] who described effective chirality transfer in the Pd-assisted $S_{N'}$ cyclization of γ-hydroxy allylic esters. Williams and Meyer[85] deployed a variant of the *O*-capture of π-allylpalladium complexes in the reactions of substituted trimethylenemethane palladium complexes developed by Trost, using allylstannane (**Scheme 32**). A key intermediate **156** in the synthesis of amphidinolide K, a marine natural product, was therefore synthesized starting from enantiopure diastereomer **160**. Compound **160** was prepared by *in situ* transmetallation using the Corey chiral sulfonamide **159** with optically active allylstannane **157** and then condensation with functionalized aldehyde **158**. Formation of the *cis*-2,5-disubstituted tetrahydrofuran **156** occurred with an excellent diastereoselectivity (*cis*/*trans* 13:1) and a good yield (88%) from the *syn*-1,4-precursor **160**.

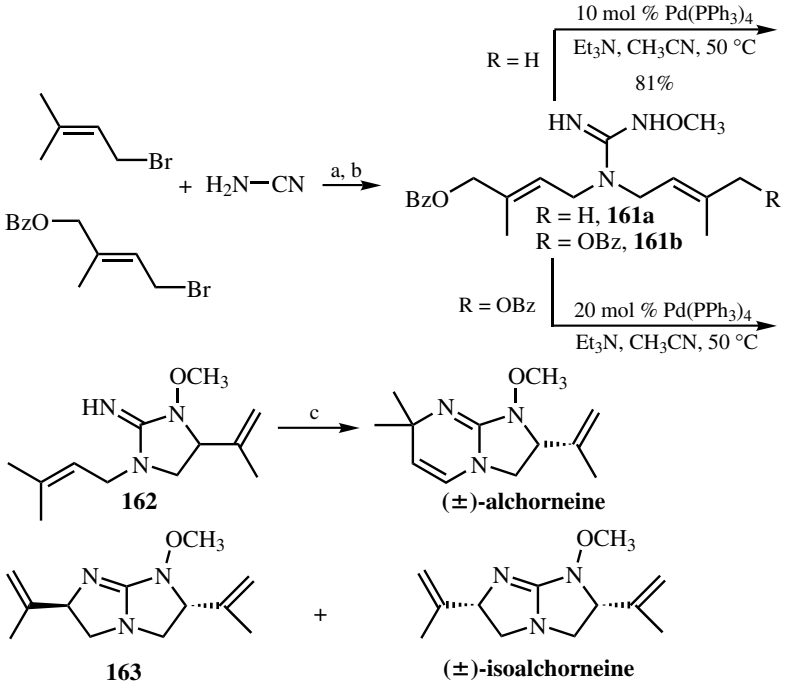
C.ii.c. ***Cyclizations Involving Nitrogen Nucleophiles.*** Heterocyclization catalyzed by palladium complexes has also been applied in nitrogen series for the synthesis of several alkaloids such as (±)-alchorneine, (±)-isoalchorneine, α- or γ-lycorane, (±)-heliotridane, (−)-cephalotaxine, and (−)-anatoxin-a (**Scheme 33**).



Scheme 33

The tetrahydroimidazo[1,2-*a*]pyrimidine alkaloid alchorneine was isolated from *Alchornea floribunda* Muell. (Euphorbiaceae), while its isomer isoalchorneine containing a tetrahydroimidazo[1,2-*a*]imidazole ring is elaborated by *A. hirtella* Benth. The two alkaloids have been prepared[86] from cyanamide in four and three synthetic operations, respectively, using Pd-assisted cyclizations in the critical steps (**Scheme 34**). Disodium cyanamide (generated *in situ* from cyanamide and dimsyl sodium) was alkylated with an equimolar mixture of 1-bromo-3-methyl-but-2-ene and (*E*)-1-(benzyloxy)-4-bromo-2-methyl-but-2-ene to give **161a** and **161b** in a 7:3 ratio. After separation of the alkylcyanamides, they were respectively cyclized in the presence of a catalytic amount of $Pd(PPh_3)_4$ in acetonitrile at 50 °C to give the

(±)-imidazolidine **162** and a 1:1 mixture of isoalchorneine and its *trans* epimer **163**. Oxidative cyclization of **162** afforded (±)-alchorneine in a good overall yield.

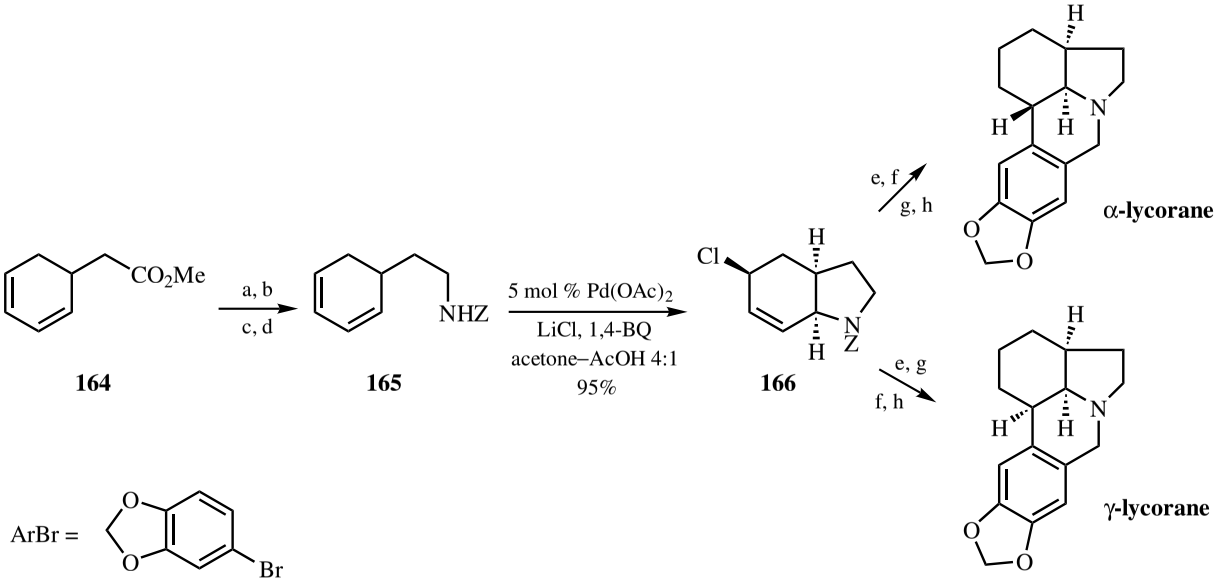


(a) $NaCH_2SOMe$, **161a/161b** 7:3, 72%; (b) $NH_2OMe{\cdot}HCl$; (c) 2 equiv $PdCl_2(CH_3CN)_2$, 46%.

Scheme 34

Bäckvall and co-workers described a stereocontrolled synthesis of racemic lycorane-type Amaryllidaceae alkaloids, namely, α- and γ-lycorane.[87] The strategy is based on Pd-catalyzed intramolecular 1,4-additions to cyclic dienes already seen for the syntheses of theaspirone and vitispirane (**Scheme 31**), involving amides as nucleophiles. The syntheses of alkaloids started with diene ester **164**, which was submitted to reduction, Mitsunobu reaction, and transformation to carbamate **165** in high yields (**Scheme 35**). Pd-catalyzed 1,4-chloroamidation proceeded smoothly with high regio- and stereoselectivities (>98% selectivity) to give **166** in 95% yield. The 3,4-(methylenedioxy)-phenyl group was introduced by a Cu-catalyzed Grignard reaction favoring the γ-attack of the allylic compound. Racemic α-lycorane was finally obtained after reduction of the double bond, Bishler–Napieralski-type cyclization, and reduction of the resulting amide. Racemic γ-lycorane was isolated in high yield and selectivity simply by changing the order of hydrogenation and Bishler–Napieralski cyclization.

A further extension of the Pd-catalyzed intramolecular 1,4-oxidation was the use of amide, whose amino functionality had the ability of making a twofold nucleophilic attack. The use of nitrogen as nucleophile led to pyrrolizidine and indolizidine derivatives. This strategy was applied for the synthesis of another alkaloid, (±)-heliotridane[88] (**Scheme 36**). Pd-catalyzed reaction of dieneamide, obtained from the known ester **167**, in THF employing $CuCl_2/O_2$ as the oxidant afforded the azabicyclic product **168** in 85% yield. The mechanism of this tandem cyclization involved a π-allylpalladium

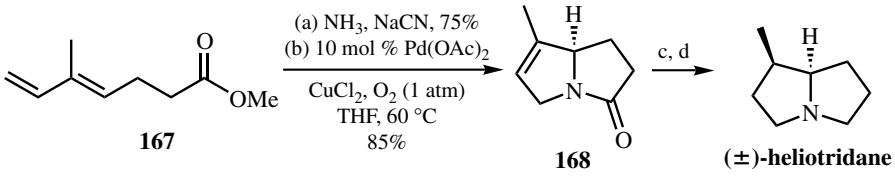


164 **165** **166**

(a) DIBAL, 95%; (b) phthalimide, DEAD, PPh_3, 98%; (c) NH_2NH_2, 98%; (d) ZCl, 96%; (e) ArMgBr, Li_2CuCl_4, 77%; (f) H_2, PtO_2, 95%; (g) $POCl_3$, 72%; (h) $LiAlH_4$, 84–92%.

Scheme 35

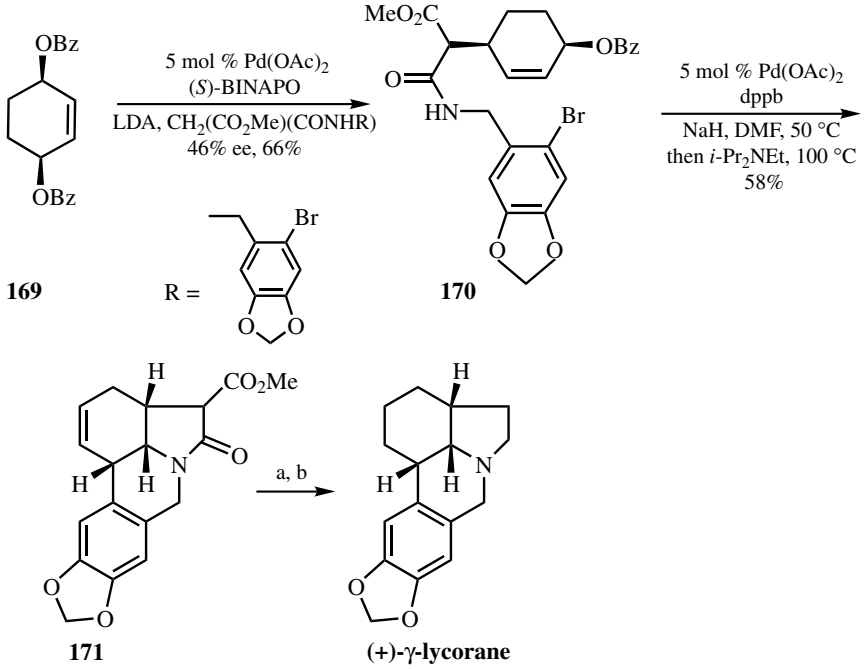
intermediate formed by amide attack on coordinated diene. The pyrrolizidine alkaloid (±)-heliotridane was obtained after hydrogenation and reduction of the amide.



(c) PtO_2, H_2, 95%; (d) $LiAlH_4$, 89%.

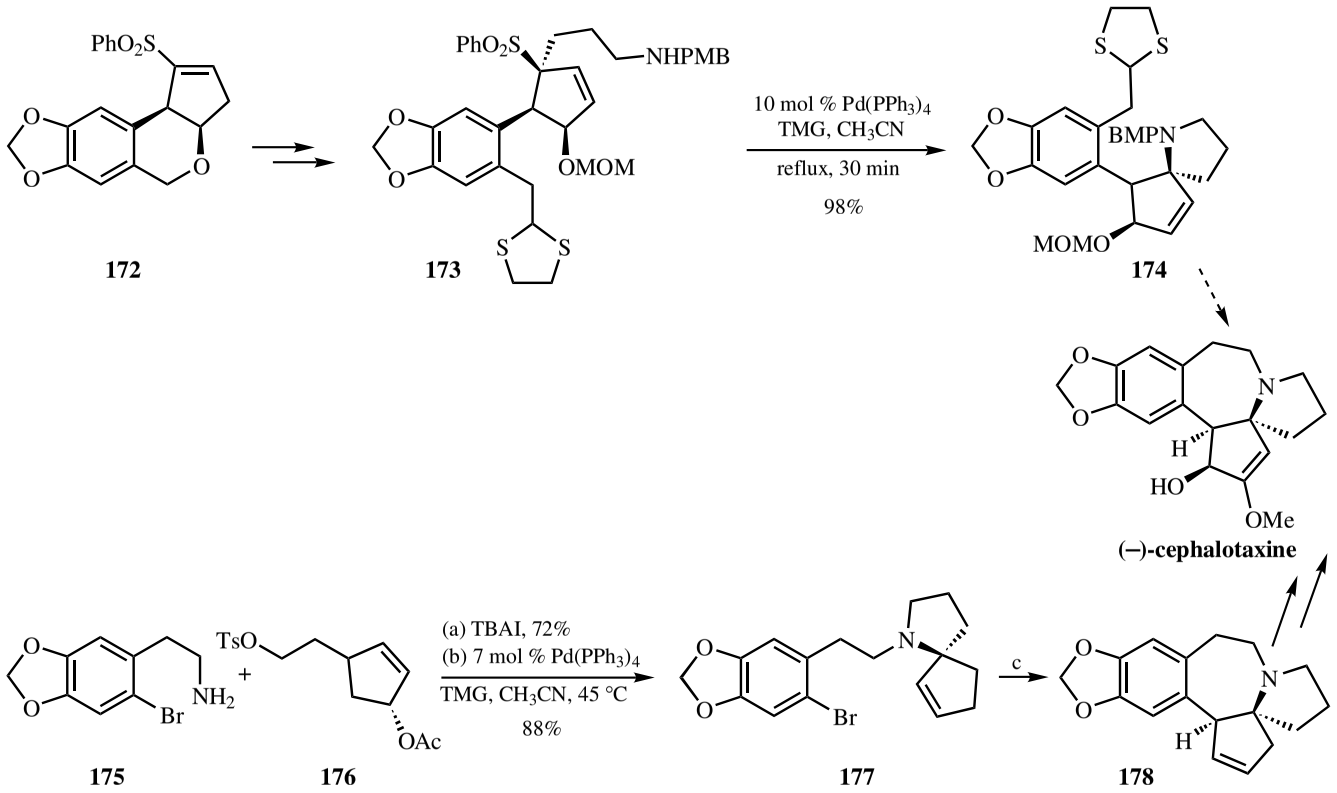
Scheme 36

Another organometallic route to γ-lycorane was described by Mori's group[89] a few years later in an asymmetric way using palladium allylic alkylation (**Scheme 37**). Cyclohexene **169** was monoalkylated in the presence of a catalytic amount of palladium diacetate and a chiral ligand derived from (*S*)-binaphtol with functionalized amidoester nucleophile to form the desired product **170** in 66% yield and 46% ee. The cyclization step was particularly original: intramolecular alkylation was accompanied by Heck reaction to give tetracycle **171** with all *cis* junction protons. Total synthesis was then accomplished via a decarboxylation, hydrogenation, and reduction to give (+)-γ-lycorane. Consequently, the synthesis was realized in five steps in 23% overall yield and a modest ee of 46%. The new generations of ligands, such as those developed by Trost, enhance the importance of Pd-catalyzed reaction in total synthesis and would make this approach more effective.



(a) DMSO, 160 °C, 64%; (b) Pd/C, H_2; $LiAlH_4$, 85% (2 steps).

Scheme 37

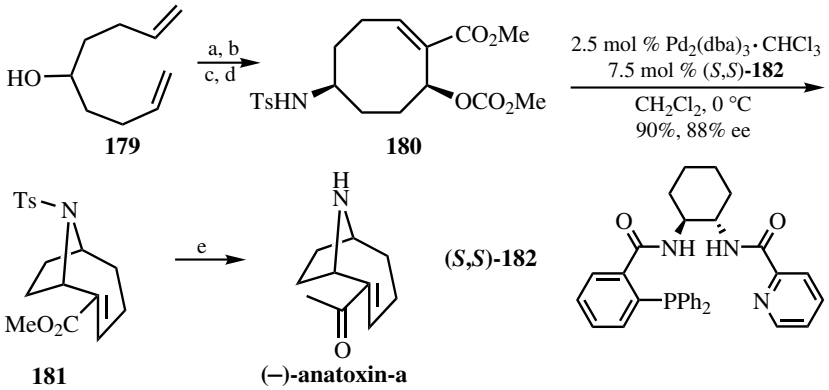


(c) 4 mol % Beller catalyst, *n*-Bu_4NOAc, $CH_3CN/DMF/H_2O$ 5:5:1, 110–120 °C, 81%.

Scheme 38

Cephalotaxine, the major alkaloid isolated from *Cephalotaxus* species, has attracted considerable attention due to the promising antitumor activity of several of its derivatives and its unique structural features. One approach described by Jin and Fuchs[90] relied on Pd-mediated aminospirocyclization of tertiary allylic sulfones and led to an advanced intermediate in the total synthesis. The concept led recently to the formal total synthesis of (−)-cephalotaxine, described by Tietze and Schirok[91] (**Scheme 38**). The racemic synthesis envisaged by Fuchs started with the vinyl sulfone **172**, that was functionalized to introduce the protected amine. Reaction of tertiary allyl sulfone **173** in the presence of palladium tetrakistriphenylphosphine and tetramethylguanidine led smoothly to cyclized intermediate **174**, precursor of (±)-cephalotaxine. The asymmetric synthesis described by Tietze was based on the preparation of enantiomerically enriched (ee = 87%) allylic acetate **176** using Corey's oxazaborolidine method. Alkylation of primary amine **175** derived from piperonal with **176** gave an intermediate, which was cyclized using catalytic amount of palladium(0) and tetramethylguanidine as the base. Complete regio- and stereoselectivities were observed at controlled temperature to avoid competing reaction of haloaryl moiety. Compound **177** was then reacted with Hermann and Beller palladacycle under Heck reaction conditions to give cleanly tetracycle **178** as a single diastereomer in 81% yield. The transformation of **178** to (−)-cephalotaxine by bishydroxylation of the cyclopentene moiety, oxidation of the diol to the diketone, formation of methyl enol ether, and diastereoselective reduction of the remaining keto group had been described by Isono and Mori.[92]

Naturally occurring alkaloid anatoxin-a, known to induce respiratory paralysis and possessing an unusual 9-azabicyclo[4.2.1]nonane skeleton, was recently synthesized by Trost and Oslob[93] via an asymmetric intramolecular allylic alkylation (**Scheme 39**). The alcohol **179**, prepared from 4-bromo-1-butene and ethylformate, was efficiently converted to functionalized cyclooctadiene **180** within six steps. Asymmetric cyclization was performed with a catalytic amount of Pd(0) and several ligands to enhance the enantioselectivity. A new chiral ligand, the (*S*,*S*)-1-(2-diphenylphosphinobenzamido)-2-(2-pico-linamido)cyclohexane, (*S*,*S*)-**182**, was synthesized to alleviate the unfavorable steric interaction and induced under smooth conditions the formation of cyclic **181** in 90% yield and 88% ee. The ester **181** was then converted to the methylketone, which was desulfonated to give (−)-anatoxin-a.

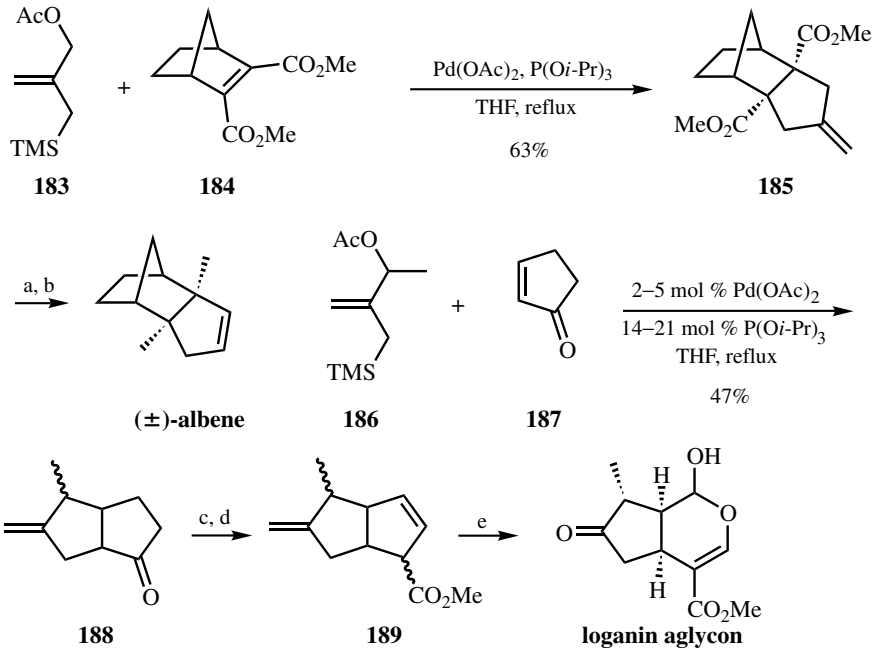


(a) TsNHBoc; PhCH═Ru(Cl)$_2$[(C$_6$H$_{11}$)$_3$P]$_2$, 76% (2 steps); (b) $CHBr_3$; AgOAc; Bp_2O, 72% (3 steps); (c) 5 mol % Pd(PPh$_3$)$_4$, Et$_3$N, CO, 70%; (d) K_2CO_3; *n*-BuLi, $ClCO_2Me$; TFA, 70% (3 steps); (e) LiOH; $(COCl)_2$; $AlMe_3$, $AlCl_3$; Na(Hg), 60% (4 steps).

Scheme 39

Through this synthesis, Trost has demonstrated a new concept of deracemization, which was only performed in an intermolecular way before. Moreover, the study of the "chiral space" brought him to introduce a new class of ligands, suitable for the asymmetric targeted cyclization.

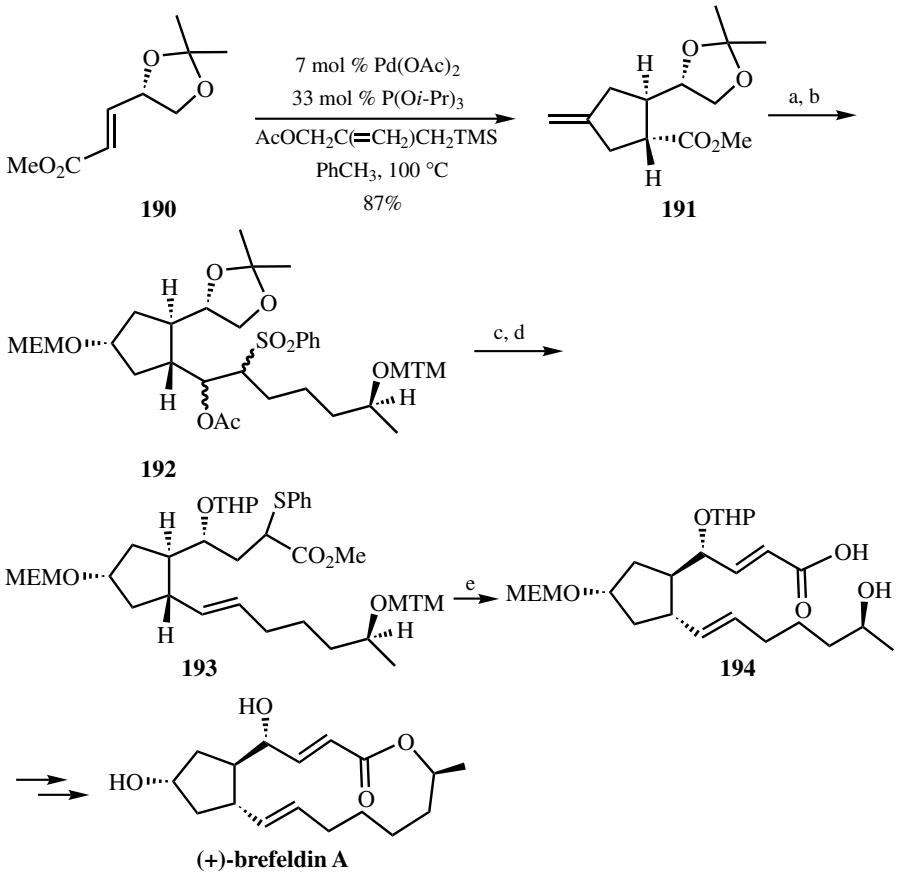
C.ii.d. ***[3 + 2] Cyclizations.*** The [3 + 2] cycloaddition approach to five-membered rings via trimethylenemethane and its equivalents developed by Trost has provided new strategies for the synthesis of natural products. Cyclopentanoid natural products such as the sesquiterpene (±)-albene and the iridoids aglycon of loganin have been synthesized by Trost (**Scheme 40**). The cycloaddition between the bifunctional reagent [2-(acetoxymethyl)-3-allyl]trimethylsilane **183** and the known diester **184** led stereoselectively to adduct **185**, delivering the TMM group on the *endo* side. Conversion of **185** to albene required two separate structural modifications, the conversion of the exocyclic methylene group to a disubstituted endocyclic olefin with loss of the exocyclic carbon and of the ester groups to methyl groups. Ozonolysis followed by reduction of the esters, conversion to tris(phosphoramidate), and reduction led efficiently to (±)-albene.[94] The synthesis of loganin is based on the same principle.[95] Cycloaddition of **186** with cyclopentenone **187** gave cycloadduct **188** in a modest yield. Conversion to the unsaturated ester **189** was realized by the use of Shapiro's conditions of the Bamford–Stevens reaction followed by the deconjugation of the double bond. Ozonolysis followed by reduction with zinc dust led to the hydroxyacetal. Since this ketone has been converted to loganin by reduction and hydroxyl inversion, this five-step synthesis constitutes a new synthesis of loganin.



(a) LAH; O_3; 76% (2 steps); (b) $ClPO(NMe_2)_2$; Li, 55% (2 steps); (c) NH_2NHSO_2Ar; *n*-BuLi, CO_2 53%; (d) LDA; (e) O_3, then Zn dust, AcOH, 50%.

Scheme 40

The antifungal, antiviral agent (+)-brefeldin A, whose recent synthesis using π-allylpalladium complexes has previously been described (**Scheme 24**), was prepared by Trost et al.[96] using the [3 + 2] cycloaddition to form the cyclopentyl ring (**Scheme 41**). Chiral acrylate **190**, prepared from mannitol, was subjected to cyclization conditions to give cycloadduct **191** in 87% yield and an excellent selectivity. Diastereoselectivity in the cycloaddition extended the stereochemistry of **190** into the absolute stereochemistry of **191**, generating three of the five stereocenters of brefeldin A. After ozonolysis, reduction, and protection, the lower side chain was attached to prepare the sulfone **192**. The upper side chain was then introduced, and further functionalization led to the key intermediate **194**, which had already been transformed to (+)-brefeldin A.



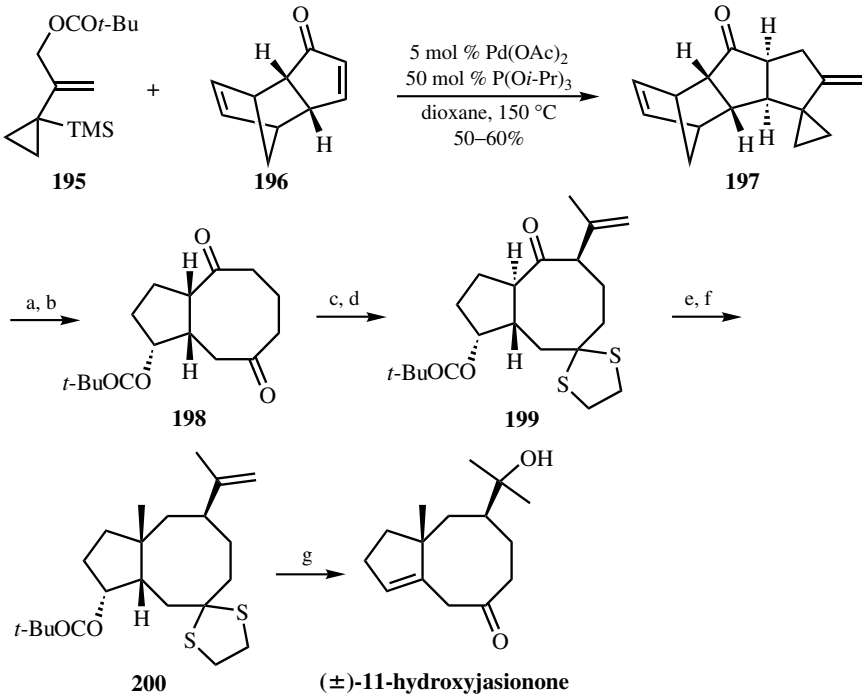
190 **191** **192** **193** **194** **(+)-brefeldin A**

(a) O_3, DMS; DIBAL-H; MEMCl, 55% (3 steps); (b) (*S*)-$PhSO_2(CH_2)_4CH(Me)OMTM$, LDA; $NaBH_4$; Ac_2O, 46% (3 steps); (c) Na(Hg); HCl; TsCl; NaOMe, 45% (4 steps); (d) $PhSCH_2CO_2H$, LDA then CH_2N_2; DHP, 83% (2 steps); (e) NCS, $AgNO_3$; BSA; K_2CO_3, MeOH, 64% (3 steps).

Scheme 41

While the unsubstituted TMM system has proved to be efficient in the synthesis of loganin and the approach of the spiro ring system of the Ginkgolides,[97] the substituted system gave good results in the synthesis of brefeldin. The use of a cyclopropyl derivative culminated in the synthesis of (±)-11-hydroxyjasionone.[98] 11-Hydroxyjasionone is

a constituent of the essential oil derived from the aerial parts of *Jasiona* Montana, which showed antibacterial activity against *Bacillus subtilis* and antifungal activity against *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, and *Candida albicans*. The Pd-catalyzed trimethylenemethane cycloaddition (**Scheme 42**) was performed by heating a mixture of the two reactants **195** and **196** with palladium acetate (5 mol %) and triisopropyl phosphite (50 mol %) in 1,4-dioxane at 150 °C for 1 hour to give the desired adduct **197** in 50–60% yield. Taking advantage of the vinylcyclopropane moiety, the 5,8-fused ring was efficiently created via a tandem retro-Diels–Alder and vinylcyclopropane–cyclopentene rearrangement, followed by oxidative cleavage to give the diketone **198**. Chemoselective protection of the less hindered carbonyl group followed by conjugate addition of isoprenyl afforded ketone **199** with complete stereocontrol of the centers. Regioselective methylation of the thermodynamic enolate followed by radical deoxygenation gave thioacetal **200** in an excellent overall yield. The final assault was efficiently realized to afford (±)-11-hydroxyjasionone. Since resolution of the alcohol precursor of **196** has been reported, it has to be noted that this synthesis also provided an entry into either enantiomer of the natural product.

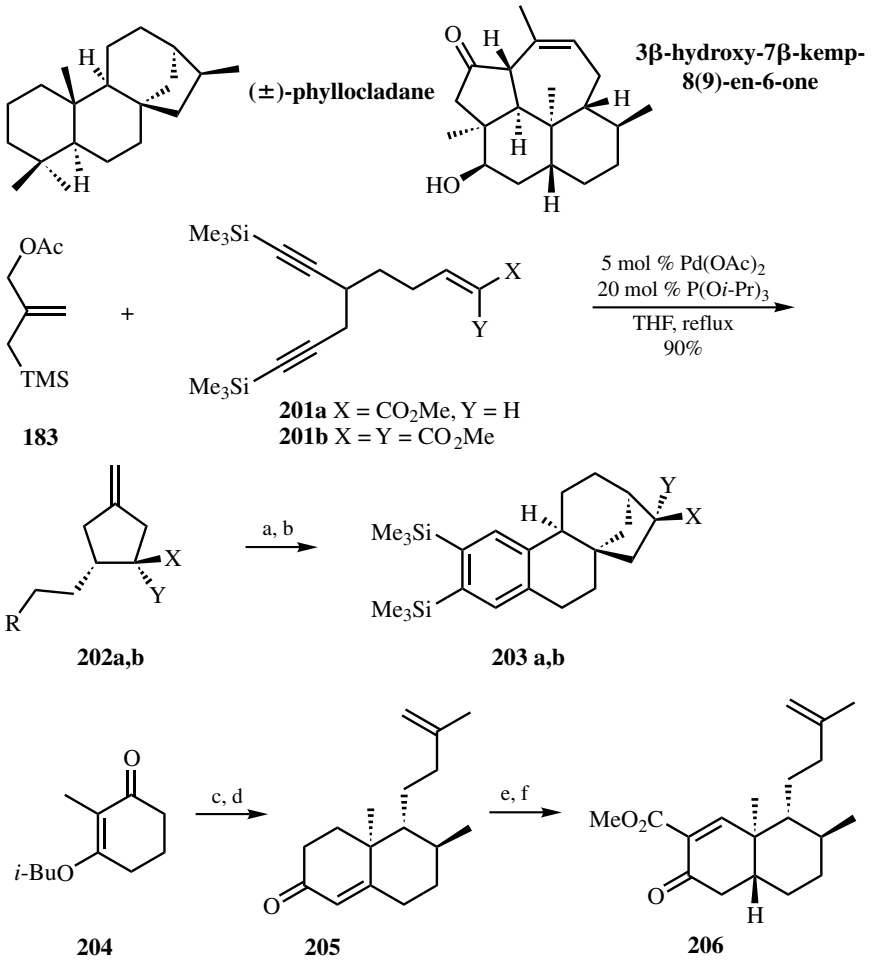


(a) FVT, 600 °C; $NaBH_4$; *t*-BuCOCl, 86% (3 steps); (b) O_3, $NaHCO_3$, 100%; (c) $HS(CH_2)_2SH$; methyl 2-pyridine sulfinate then $CuSO_4$; DBU, 58% (3 steps); (d) $[CH_3C(=CH_2)]$, $CuCNLi_2$, 84%; (e) KH, MeI; $NaBH_4$ 43% (2 steps); (f) $C_6F_5OC(=S)Cl$; Bu_3SnH, 73% (2 steps); (g) $AgNO_3$; KOH then Tf_2O; $Hg(OAc)_2$, then $Na(AcO)_3BH$, 21% (3 steps).

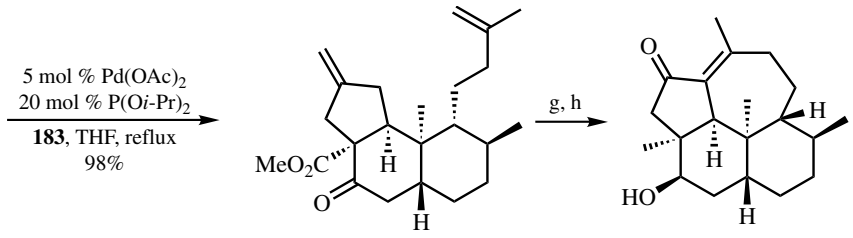
Scheme 42

Apart from Trost, other groups have integrated the powerful [3 + 2] cycloaddition in the course of the synthesis of various targets, such as diterpenoid derivatives. There is a wide distribution of natural compounds belonging to these groups and displaying

important biological activities. Malacria and co-workers envisaged the total stereoselective construction of a variously functionalized phyllocladane basic framework, based on a combination of transition-metal-catalyzed annelation reactions:[99] Trost's Pd-assisted [3 + 2] cycloaddition, Vollhardt's [2 + 2 + 2] Co-catalyzed cyclotrimerization, and an intramolecular Kametani's [4 + 2] cycloaddition (**Scheme 43**). Compounds **201a** and **201b** were prepared via a straightforward sequence and were cyclized through the action of [2-(acetoxymethyl)-3-allyl]trimethylsilane, palladium acetate (5 mol %), and triisopropyl phosphite (20 mol %) in refluxing tetrahydrofuran to afford substituted methylenecyclopentane adducts **202a** and **202b**, respectively, in excellent yields and in complete diastereoselectivity for **202a**. Exposure of desilylated compounds to a catalytic amount of (η^5-cyclopentadienyl)cobalt dicarbonyl and irradiation followed by thermolysis of the resulting benzocyclobutenes led efficiently to the preparation of major tetracyclic compounds **203a** and **203b** in a diastereoselective manner. This sequence of three consecutive cycloaddition reactions therefore allowed the formation of seven C—C bonds in a totally controlled regio-, chemo-, and stereoselective manner and provided a rapid construction of tetracyclic phyllocladane framework.



Scheme 43



207 **208**

(a) KF; $CpCo(CO)_2$ 5 mol %, btmse, 136 °C, $h\nu$, 81% (2 steps); (b) decane, 175 °C, 75–82%; (c) LDA, MeI; RMgBr, HCl, 77% (2 steps); (d) Li, NH_3, α-(trimethylsilyl) vinyl ketone; KOH, 42% (2 steps); (e) Li, NH_3; NaH, $(MeO)_2CO$, 65% (2 steps); (f) DDQ, 77%; (g) $LiAlH_4$; $(NH_4)_6MO_7O_{24}$; $NaBH(OAc)_3$; $(CH_3O)_2C(CH_3)_2$; O_3, then DMS, 51% (5 steps); (h) K_2CO_3; PPTS; CS_2; $[(CH_3)_3Si]_3SiH$, AIBN, 26% (4 steps).

Scheme 43 (*Continued*)

Total syntheses of diterpenoid hydrokempenones have been accomplished by Paquette et al.,[100] using the Pd-catalyzed [3 + 2] cycloaddition methodology. One example is outlined on **Scheme 43** and describes the synthesis of an isomeric compound **208** of 3β-hydroxy-7β-kemp-8(9)-en-6-one, a defense secretion agent of the neotropical species *Nasutitermes octopilis*. 3-Alkoxy-2-cyclohexenone **204** was efficiently functionalized and transformed to bicylic adduct **205** via a Robinson annulation reaction. Reduction of the double bond followed by condensation of dimethyl carbonate and oxidation gave the keto ester **206**, which was treated with [2-(acetoxymethyl)-3-allyl]trimethylsilane, palladium acetate, and triisopropyl phosphite in refluxing tetrahydrofuran to afford a 98% yield of **207**. Substituted methylenecyclopentane **207** was then functionalized by stereoselective reduction and protections, and final closure was done under basic conditions after an ozonolysis step. A modified Barton–McCombie reaction produced the desired tetracyclic adduct **208**.

D. SIX-MEMBERED RING NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE COMPOUNDS

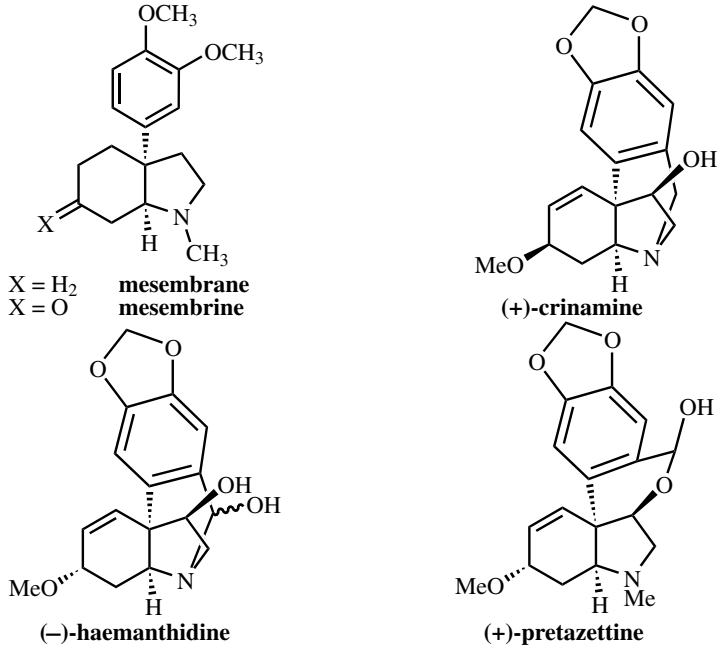
While five-membered ring formation occurs smoothly with a large array of substrates, six-membered ring formation appears less general, presumably because the higher entropy of cyclization to the six-membered ring allowed competing noncyclization reactions to predominate. Functionalization of cyclic intermediates and cyclization via Pd-catalyzed allylation will be presented as in the previous sections.

D.i. Palladium-Catalyzed Allylation in the Synthesis of Six-Membered Ring Natural Products

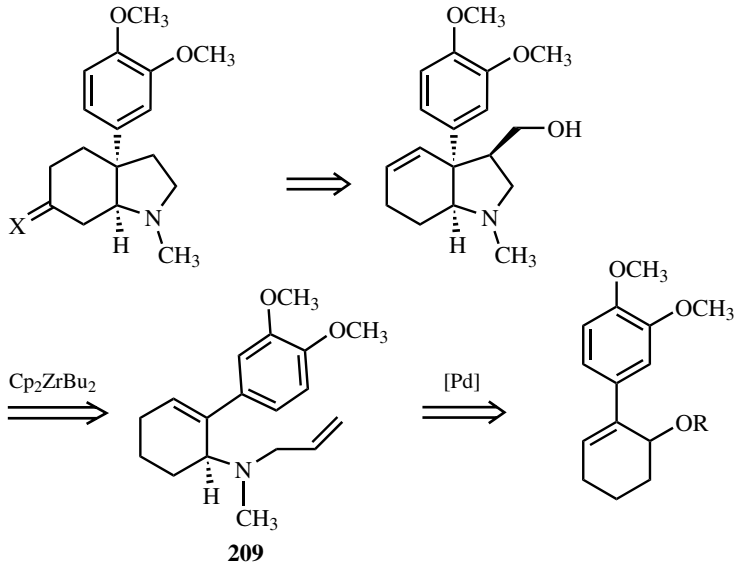
D.i.a. ***Synthesis of Natural Products by Allylation of the Cyclohexenyl Moiety.*** Many alkaloids have a *cis*-3a-aryloctahydroindole skeleton like mesembrane, mesembrine, or crinane-type alkaloids (**Scheme 44**). They have been of interest as synthetic targets due to the wide range of biological activities they exhibit.

Total syntheses of (−)-mesembrane and (−)-mesembrine[101] were based on zirconium-promoted diene, diyne, and enyne cyclizations. This procedure was very useful

because a regio- and stereocontrolled carbon–carbon bond could be formed between these multiple bonds. An important problem in these syntheses was to prepare the chiral starting diene **209**. It was resolved by a Pd-catalyzed alkylation in the presence of a chiral ligand, BINAPO (**Scheme 45**).

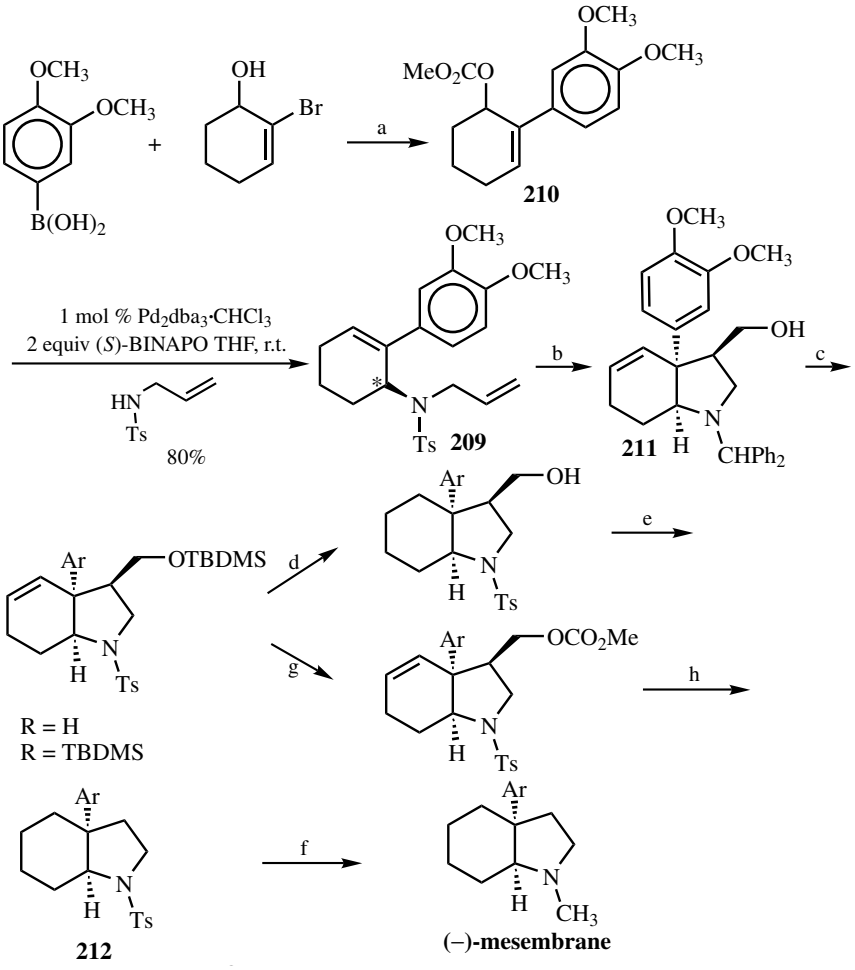


Scheme 44

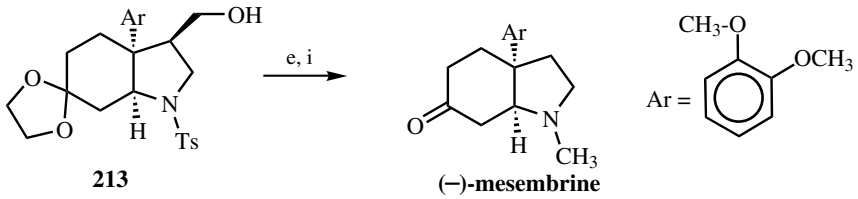


Scheme 45

Suzuki–Miyaura coupling of 3,4-dimethoxyphenylboronic acid and 2-bromo-2-cyclohexen-1-ol proceeded smoothly in the presence of $Pd(PPh_3)_4$ and Na_2CO_3. Reaction of allyl carbonate **210** with *N*-tosylallylamine at room temperature for 19 h in THF, in the presence of $Pd_2dba_3 \cdot CHCl_3$ and (*S*)-BINAPO, afforded **209**. The desired product was obtained in 80% yield with 86% ee and was recrystallized from methanol to give **209** with 99% ee. The reaction of the diene with Cp_2ZrBu_2 followed by treatment with MeMgBr and then molecular oxygen afforded the cyclized product **211** in 63% yield. The methodology described for (±)-mesembrane was then applied to the synthesis of (−)-mesembrane. Dess–Martin oxidation of the protected alcohol to aldehyde and subsequent deformylation with $RhCl(PPh_3)_3$ gave perhydrindole **212**. The tosyl group was converted into a methyl group to afford (−)-mesembrane. On the other hand, the TBDMS protecting group of **209** was converted into the methoxycarbonyl group and the allylic oxidation with CrO_3 gave enone, which was subjected to hydrogenation and ketalization to give **213**. Using a treatment similar to that for the synthesis of (−)-mesembrane, Mori succeeded in the total synthesis of (−)-mesembrine (**Scheme 46**).



Scheme 46 (*Continued*)

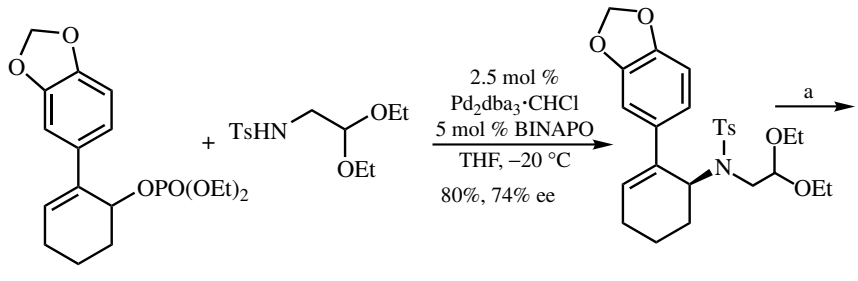


213 **(−)-mesembrine**

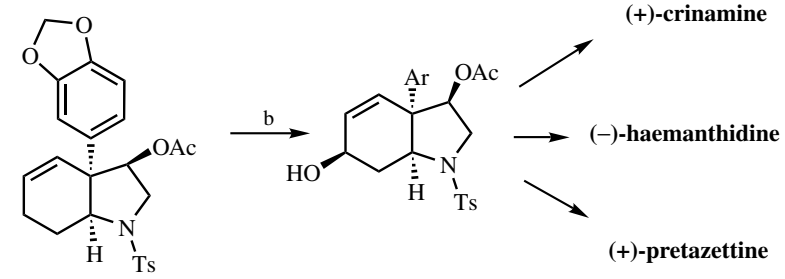
(a) $Pd(PPh_3)_4$, Na_2CO_3 68%; $ClCO_2Me$; (b) Na-naphthalenide 71%; Ph_2CHCl 45%; Cp_2ZrBu_2 then MeMgBr; O_2; H_3O^+; (c)TBDMSCl; Pd/C, H_2; TsCl, py; (d) Pd/C, H_2; (e) Dess–Martin; $RhCl(PPh_3)_3$; (f)Na-naphthalenide; $ClCO_2Me$; $LiAlH_4$; (g) Bu_4NF; $ClCO_2Me$; (h) CrO_3; Pd/C-H_2; $(TMSOCH_2)_2$ TMSOTf; K_2CO_3; (i) Na-naphthalenide; BuLi, MeI; 10% HCl.

Scheme 46

The same methodology[102] was applied to the synthesis of the key intermediate **216** of the crinane-type alkaloids, (+)-crinamine, (−)-haemanthidine, and (+)-pretazettine (**Scheme 44**). Treatment of the substrate **214**, synthesized according to the same procedure as for **210** by acetal **215** in the presence of $Pd_2dba_3{\cdot}CHCl_3$ and (*S)*-BINAPO, afforded cyclohexylamine **216** in 80% yield with 74% ee up to 99% ee by recrystallization in MeOH. The intramolecular carbonyl-ene reaction was then carried out as outlined in **Scheme 47** to give **217** in 72% yield and 99% ee. The asymmetric total synthesis of (+)-crinamine was achieved in nine steps from **214** in 20% overall yield.



214 **215** **216**

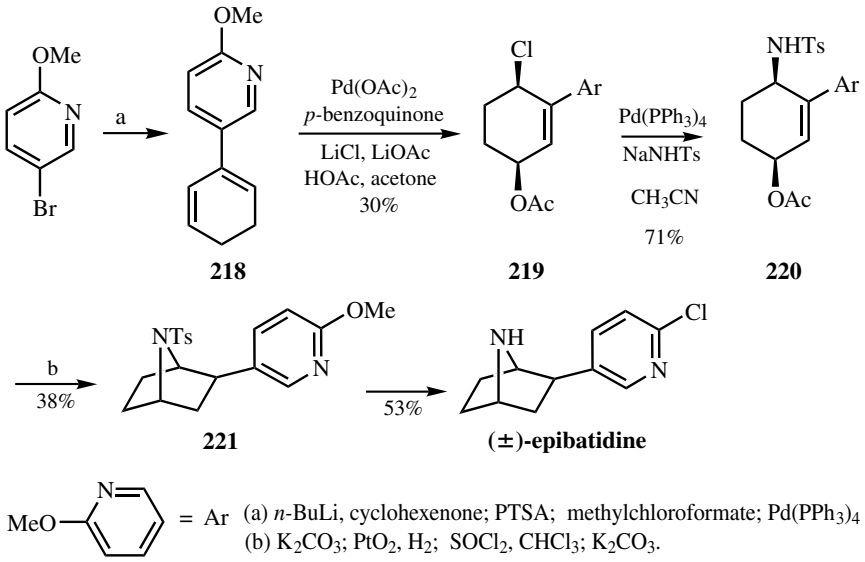


217 99% ee

(a) $FeCl_3{\cdot}SiO_2$; 230 °C; Ac_2O, py; (b) SeO_2.

Scheme 47

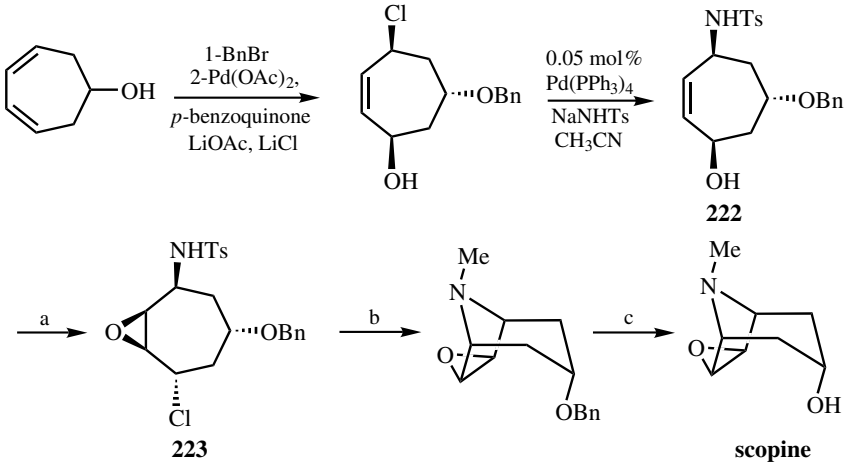
Bäckvall and co-workers have developed a regio- and stereoselective 1,4-functionalization of 2-aryl-1,3-cyclohexadienes via Pd(II)-catalyzed 1,4-chloroacetoxylation and the application to the synthesis of bicyclic compounds like epibatidine.[103] The alkaloid epibatidine, a 7-azabicyclo[2.2.1]heptane ring system, was isolated and characterized in 1992 and has been shown to possess remarkable analgesic properties, superior to morphine. The synthesis of starting material **218** began with addition of 5-bromo-3-methoxypyridine to 2-cyclohexen-1-one. Treatment with *p*-toluenesulfonic acid of allylic alcohol resulted in the rearranged allylic alcohol, which was transformed into the corresponding allylic carbonate. A regioselective elimination was observed with $Pd(PPh_3)_4$ to give diene **218**. Pd(II)-catalyzed chloroacetoxylation of **218** afforded chloroacetate **219** in only 30% yield. The amido acetate **220** was obtained in 71% yield using the Pd-catalyzed allylic substitution. Hydrolysis gave the amido alcohol, which was hydrogenated in highly stereoselective reaction. Subsequent inversion of the alcohol by the use of thionyl chloride followed by cyclization gave the bicyclic compound **221**, transformed to (±)-epibatidine in 53% yield as previously described in the literature (**Scheme 48**).



Scheme 48

The same sequence applied to 1,3-cycloheptadienes would afford 8-azabicyclo[3.2.1]octane systems. An important member of these alkaloids is scopine with a unique epoxy bridge between C-6 and C-7. In 1987, Bäckvall et al.[104] reported the preparation of simple tropane alkaloids via the Pd-catalyzed 1,4-acetoxychlorination of cycloheptadienes. The nitrogen was introduced stereoselectively using *p*-toluenesulfonamide as nucleophile. Morever, it is known that an allylic *p*-toluenesulfonamide group has a *syn*-directive effect on the epoxidation of cyclic olefins by 3-chloroperbenzoic acid. Therefore, this methodology could be applied to the synthesis of scopine. However, a poor reproducibility and diamidation were observed with chloroacetate. As presented in **Scheme 49**, Bäckvall and co-workers switched to chloroalcohol, which on subsequent reaction with NaNHTS in the presence of a catalytic amount of $Pd(PPh_3)_4$ in acetonitrile led to amido alcohol **222** in 63% overall yield.[105] The *trans*-1,4-relationship was created by

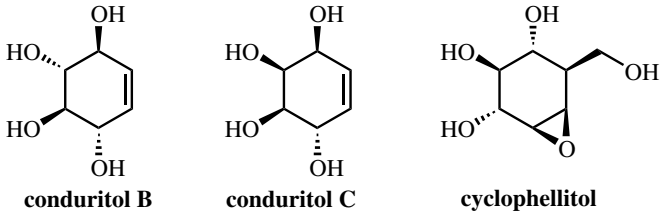
inverting the stereochemistry at C-4 employing a mixture of LiCl–MsCl. Epoxidation using MCPBA in dichloromethane occurred with the desired stereochemistry (>98% *syn*) to give **223**. The subsequent cyclization of **219** using potassium carbonate as base was very efficient. Removal of the *p*-toluenesulfonyl group followed by addition of methyl iodide afforded scopine benzyl ether. Hydrogenolysis in ethanol containing aqueous hydrochloride acid in the presence of Pd/C proceeded smoothly to give pure scopine.



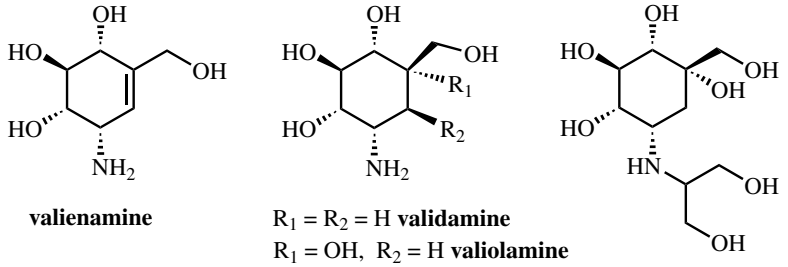
(a) LiCl, MsCl; MCPBA, 67% (2 steps); (b) K_2CO_3, MeOH; sodium naphthalide; MeI, 83% (2 steps); (c) Pd/C, H_2, H^+.

Scheme 49

Functionalization of the cyclohexenyl moiety has also been used in the synthesis of pseudosaccharides. The importance of saccharides in a myriad of cellular functions, including energy transfer and storage, intercellular communication and recognition, and intramolecular protein and lipid function, makes their processing an interesting target for the design and development of therapeutic agents. Pseudosaccharides are potent glycosidase inhibitors and have therapeutic applications in immunology, diabetes, virology, and cancer. Their potent activity stimulated much synthetic activity. Among them, conduritols constitute a class of 5-cyclohexene-1,2,3,4-tetrols with interesting biological activity such as inhibitors of glycosidases. An epoxy derivative, (+)-cyclophellitol, isolated from the mushroom *Phellinus* sp. acts as an inactivator of β-glucosidases and an inhibitor of HIV (**Scheme 50**).

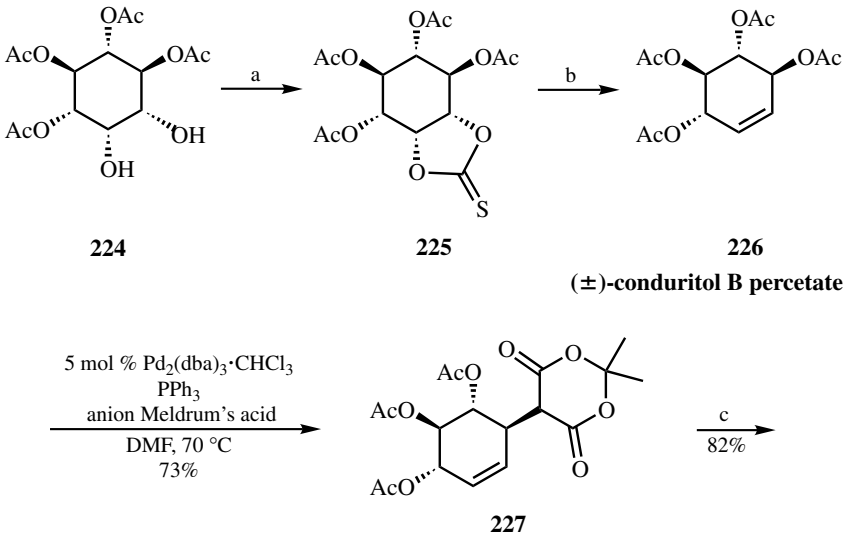


Scheme 50 (*Continued*)

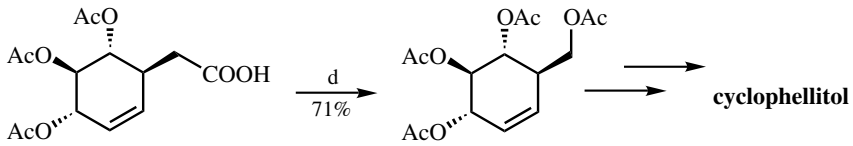


Scheme 50

During their ongoing program on branched-chain cyclitols and their congeners, Barton and collaborators[106] reported a short synthesis of the key intermediate **229**, precursor of cyclophellitol utilizing a Pd(0)-catalyzed allylic substitution of conduritol B peracetate **226**. The starting material **224** was quickly prepared from the readily available myoinositol by a selective protection of the *cis*-hydroxy function, followed by acetylation and hydrolysis of the isopropylidene protecting group. The transformation of the vicinal-diol to conduritol **226** was carried out in a two-step sequence. The diol **224** was converted to thionocarbonate **225** using thiophosgene in the presence of DMAP as base; then **225** underwent a fragmentation reaction at 110 °C in the presence of triphenylphosphite to give the crystalline olefin–tetraacetate **226**. The authors developed a methology for selective monoalkylation; reaction of allylic acetate **226** with the carbanion derived from Meldrum's acid in the presence of palladium(0)–triphenylphosphine complex in DMF at 70 °C afforded the crystalline solid **227** with overall retention of configuration. No trace of dialkylated products was detected. Decarboxylative hydrolysis of **227** provided the acid **228**, which was transformed to the corresponding *nor*-hydroxy derivative by a free-radical decarboxylation reaction. *In situ* acetylation afforded the key precursor of cyclophellitol **229** in good yield (**Scheme 51**).



Scheme 51 (*Continued*)



228 **(±)-229**

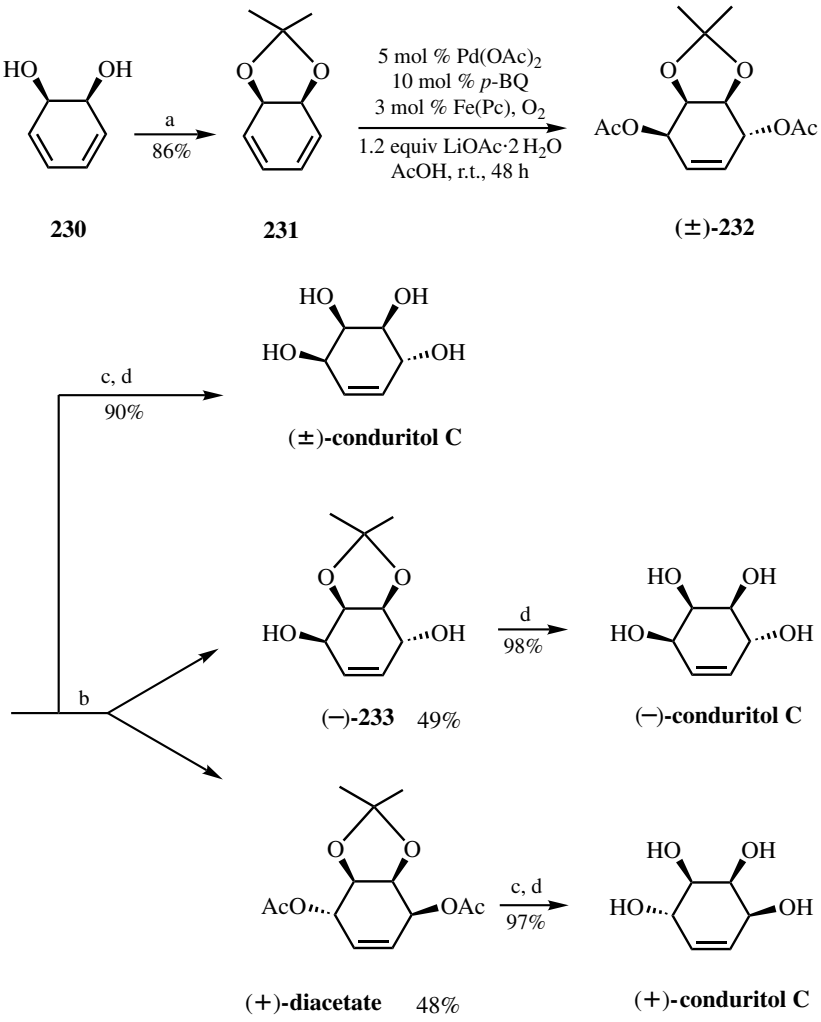
(a) Ac_2O; thiophosgene, DMAP; (b) $(CH_3O)_3P$; (c) $AcOH–H_2O$; (d) $(ClCO)_2$, *N*-hydroxypyridine-2-thione; 2 equiv$(PhS)_3Sb$, $h\nu$; H_2O; Ac_2O.

Scheme 51

The synthetic strategies for introduction of the *trans*-dihydroxy groups were based on stereospecific reduction of ketones or Mitsunobu displacement reactions. Yoshizaki and Bäckvall[107] reported a different strategy involving a Pd-catalyzed *trans*-diacetoxylation of a protected 3,5-cyclohexadiene-1,2-diol. Conduritol C, one of the six possible diastereoisomers of 5-cyclohexene-1,2,3,4-tetrols, has been synthesized by several groups. The commercially available 1,2-dihydrocatechol **230**, on treatment with 2,2-dimethoxypropane, provided the diene **231**. *trans*-1,4-Diacetoxylation carried out by employing 5 mol % of palladium diacetate, 10 mol % of *p*-benzoquinone, 1.2 equiv of lithium acetate dihydrate, and 3 mol % of iron(II) phtalocyanine [Fe(Pc)] as a dioxygen activating agent afforded **232** in 71% yield and >94% *trans* selectivity. The diacetate was hydrolyzed, and the purified *trans*-diol obtained was subsequently deprotected to afford the (±)-conduritol C, in 54% overall yield. To prepare enantiomerically pure (+)- and (−)-conduritol C, the diacetate **232** was hydrolyzed by lipase from *Candida rugosa*, in a phosphate buffer. The acetonide function could effectively be distinguished by the enzyme, and the optical resolution proceeded smoothly and quantitatively. The *trans*-diol (−)-**233** and *trans*-diacetate were, obtained, respectively in 49% and 48% yields. After derivatization, the enantiomeric excesses were determined as >99.5% Deprotection afforded (+)- and (−)-conduritol C in excellent enantiomeric excess and yield (**Scheme 52**).

Recently, Trost and Hembre[108] reported a concise asymmetric synthesis of (+)-cyclophellitol based on the Pd-catalyzed kinetic resolution of racemic conduritol B tetraacetate using the chiral ligand (*R*,*R*)-**44**. Most syntheses have started with enantiomerically pure natural products, notably carbohydrates. Such a strategy normally entails rather a long route. A pivalate was chosen as the carboxylate nucleophile for the resolution because the resultant allyl pivalate was anticipated to ionize much more slowly than the starting material. The tetraacetate (±)-conduritol was synthesized from benzoquinone; the kinetic resolution was carried out using 0.65 equiv of sodium pivalate with 1 mol % of $(\eta^3\text{-}C_3H_5PdCl)_2$ and 3 mol % of (*R*,*R*)-**44** in a two-phase system with tetrahexylammonium bromide as the phase transfer catalyst.

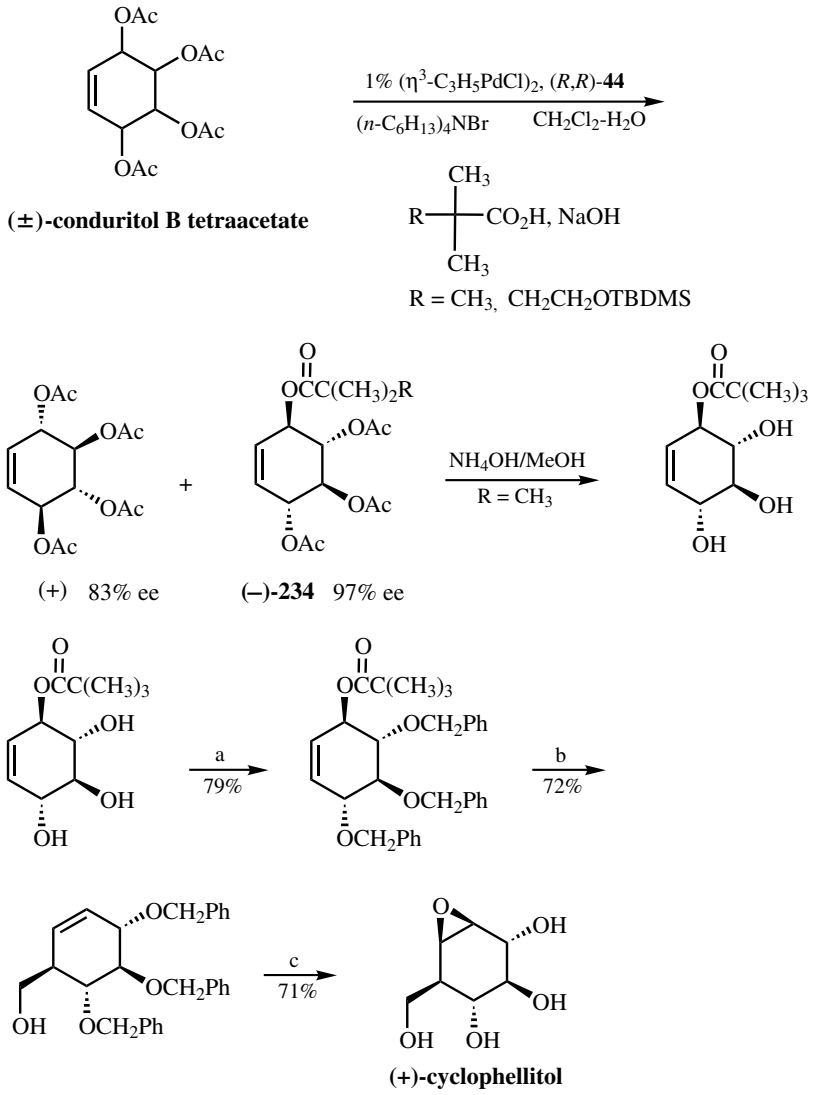
The reaction stopped cleanly at 50% conversion providing a quantitative yield of recovered (+)-tetraacetate and an 88% yield of monopivalate (−)-**234** with only a few percent of dipivalate isolated. The enantiomeric excesses were excellent for both compounds. Cleavage of the acetates in the presence of the pivalate was straightforward with ammonium hydroxide in methanol whereby triol was obtained. From enantiomerically pure triol, (+)-cyclophellitol was synthesized as shown in **Scheme 53**. The 2,3-sigmatropic rearrangement required protection of the free hydroxyl groups. Epoxidation with MCPBA, directed by the homoallylic alcohol, gave 78% yield of the desired epoxide together with a 7% yield of the diastereomeric epoxide. The synthesis was completed using the published hydrogenation procedure.



(a) 2,2-dimethoxypropane; (b) lipase, phosphate buffer (pH 7.0), r.t.;
(c) K_2CO_3; (d) conc. HCl, MeOH, 0 °C.

Scheme 52

The same methodology using allylation of cyclohexyl diacetate was also employed for the synthesis of valienamine. The aminocyclitol unit valienamine is common to pseudooligosaccharides represented by acarbose, adiposin, and trestasin. Derivatives related to valienamine including validamine, valiolamine, and hydroxy-validamine, as shown in **Scheme 50**, are also found as components of pseudooligosaccharides. It has been shown that these aminocyclitols are potent glycosidase inhibitors. For example, the N-alkylated valiolamine AO-128 is undergoing clinical trials for use as an oral antidiabetic. Trost et al.[109] described the first asymmetric synthesis of valienamine from achiral starting material. Their strategy evolved from two newly developed Pd-catalyzed reactions, desymmetrization of *meso*-enedicarboxylates and regioselective *cis*-hydroxyamination derived from the opening of vinyl epoxides with isocyanates. The dibenzoate **235** is available in one step from cyclohexa-1,3-diene. Asymmetric alkylation of dibenzoate **235** with

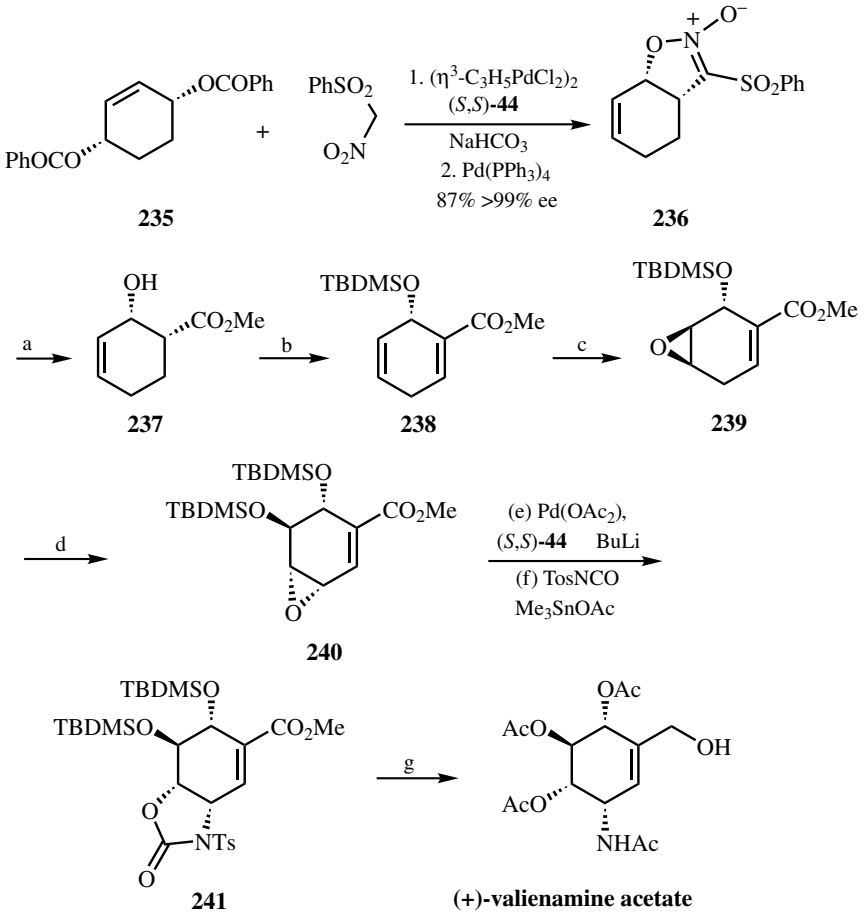


(a) $PhCH_2Br$; (b) DIBALH; $(C_4H_9)_3SnCH_2I$; n-C_4H_9Li;
(c) MCPBA, CH_2Cl_2, 0 °C; H_2 (1 atm), $Pd(OH)_2$/C.

Scheme 53

(phenylsulfonyl)nitromethane was performed in THF–H_2O with less than 0.25 mol % of the palladium catalyst formed by π-allylpalladium chloride dimer and (*S*,*S*)-**44**. The second stage of alkylation leading to cyclized product **236** was considerably slower and an achiral catalyst $Pd(PPh_3)_4$ was added, to achieve the cyclization. Thus, **237** was obtained in enantiomeric pure form according to a previously described methodology.[33] Selenylation gave a mixture of diastereomers (5:1). Silylation and oxidation with MCPBA formed the selenoxide, which produced the desired diene **238**. After chromatography, diene **238** was immediately epoxidized with MCPBA to afford **239**. Base-promoted elimination in the presence of a silyl chloride simultaneously ring-opened the epoxide and silylated the

alcohol to give a cyclohexadiene. Epoxidation to **240** proceeded in 88% yield. The next key step was the ring-opening of the epoxide **240** with isocyanate at the allylic position with retention of configuration, as seen previously. The utilization of a cocatalyst, trimethyltin acetate, was required in this reaction. The optimum conditions employed 5 mol % of $Pd(OAc)_2$, 15 mol % of bidentate ligand (*S*,*S*)-**44**, and 10 mol % of trimethyltin acetate to produce **241** in 70% yield. Transformation of the oxazolidinone to (+)-valienamine, isolated as its pentaacetate, was performed without isolation of the intermediates in 31% overall yield for four steps. The asymmetric synthesis requires 14 steps from dibenzoate **235** to give (+)-valienamine in 1–2% yield (**Scheme 54**).



(a) $SnCl_2$; K_2CO_3; $Mo(CO)_6$, 40% (3 steps); (b) LDA, $(PhSe)_2$; TBDMSCl; MCPBA; (c) $NaHCO_3$, MCPBA; (d) DBU; TBDMSCl; $NaHCO_3$, MCPBA; (g)HF; Na, NH_3; NH_4Cl; $(CH_3CO)_2O$.

Scheme 54

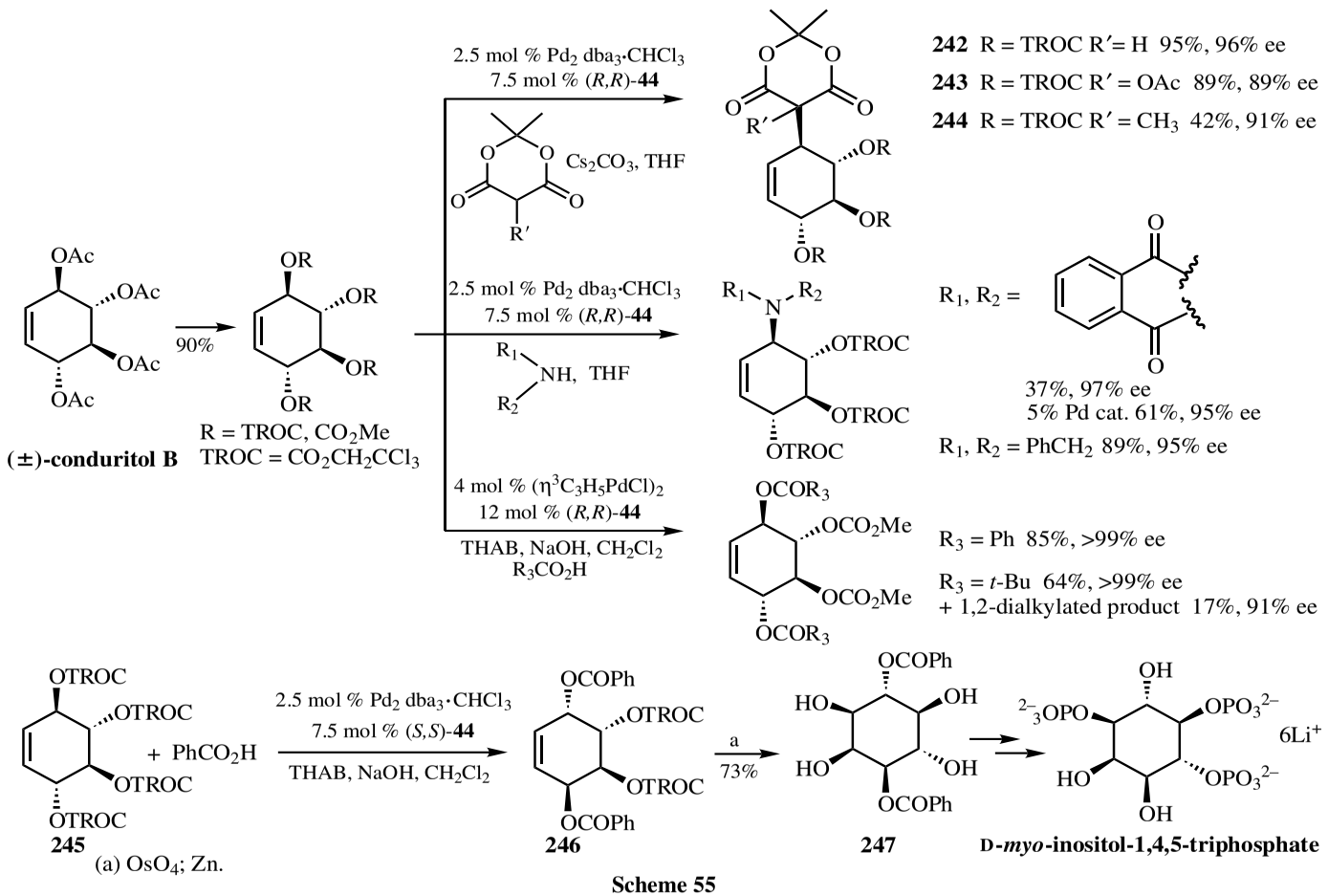
The importance of conduritol B and its derivatives as synthetic building blocks is amply demonstrated by its extensive use in natural product synthesis as presented previously. Trost et al.[110] reported dynamic kinetic asymmetric transformations of

conduritol B tetracarboxylates to provide access to a variety of enantiomerically pure conduritol B derivatives. To achieve this goal, the chiral palladium–ligand complex had to ionize both of the enantiomers of (±)-conduritol B and then convert the resulting *meso*-π-allyl into a single enantiopure product. As shown in **Scheme 55**, the reaction of tetratrichloroethylcarbonate with Meldrum's acid led to 95% yield of monosubstituted product **242** with an enantiomeric excess of 96%. Acetoxy Meldrum's acid behaves similarly. Therefore, both enantiomers of the starting material were converted to the same product, indicating that a dynamic kinetic asymmetric transformation was achieved. When the steric bulk of the carbon nucleophile was increased by using methyl Meldrum's acid, kinetic resolution giving the product **244** in 42% yield was observed. When phthalimide was used in the allylic substitution, the result paralleled those with Meldrum's acid (**Scheme 55**). Moreover, when dibenzylamine was used, a DYKAT was observed. When carboxylate nucleophiles were employed under the conditions for DYKAT reactions, disubstitution was the major process. The enantiomeric series could easily be accessed simply by switching the chirality of the ligand.

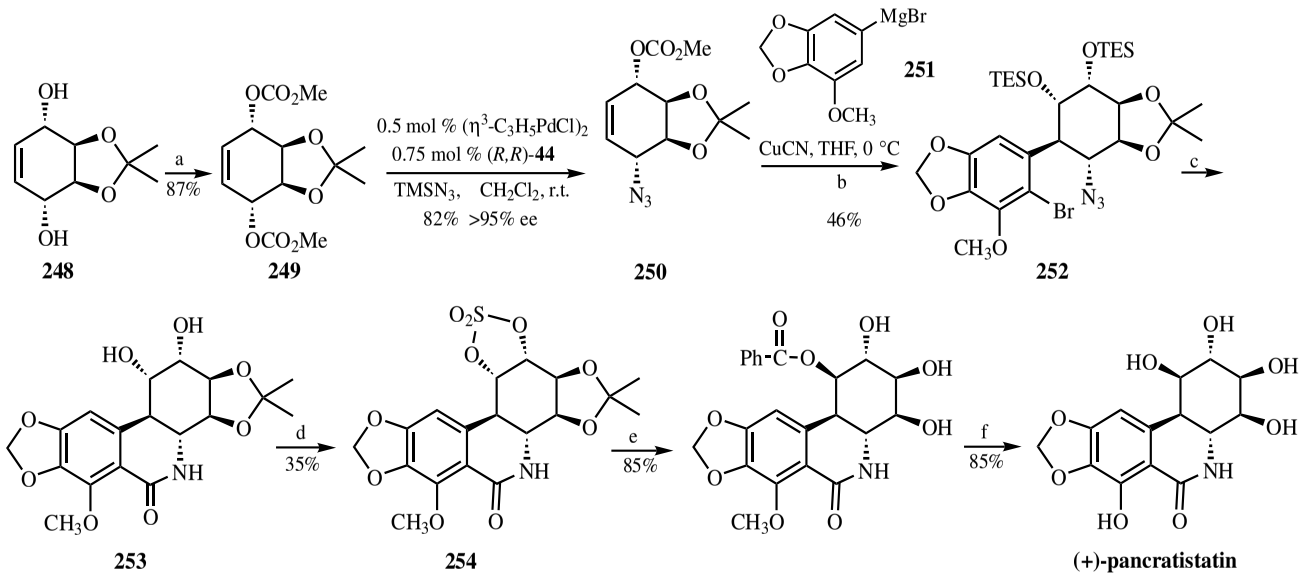
The efficiency of this methodology was also applied to the synthesis of D-*myo*-inositol-1,4,5-triphosphate (1,4,5-IP_3) from **245**. 1,4,5-IP_3 has been recognized as a second messenger to mobilize intracellular calcium ions. Reaction of **245** with benzoic acid in the presence of Pd_2dba_3 and (*S*,*S*)-**44** afforded the dibenzoate, **246** in 80% yield and >99% enantiomeric excess. Dihydroxylation followed by chemoselective removal of the Troc groups with zinc dust gave 73% yield of the tetraol **247** (two steps). Completion of the synthesis as described in the literature[111] afforded pure 1,4,5-IP_3.

Trost and Pulley[112] applied the powerful methodology of desymmetrization of diesters to the synthesis of (+)-pancratistatin, a promising antitumor agent. **Scheme 56** outlines the realization of two key steps: desymmetrization and arylation. Treatment of dicarbonate **249** derived from the well-known available diol **248** with trimethylsilyl azide in the presence of a complex formed from the chiral ligand (*R*,*R*)-**44** and π-allylpalladium chloride gave enantiopure azide **250**. Addition of the Grignard reagent **251** to a mixture of **250** and cuprous cyanide afforded regio- and diastereoselectively the aryl adduct. Using straightforward chemistry, it was transformed in diol as TES ether and the ring was brominated to give **252**. A novel lactamization protocol involved conversion of the azide to its isocyanate derivative followed by *in situ* metal–halogen exchange to generate **253**. Completion of the synthesis required inversion at C-1 involving a *trans* diequatorial ring opening of the cyclic sulfate **254**. Removal of the benzoyl and methyl ether completed the synthesis of (+)-pancratistatin in 11% yield from diol.

D.i.b. ***Miscellaneous.*** Pd-catalyzed allylation reactions have served in many other syntheses of natural products with six-membered ring. For example, (+)-cassiol, a potent antiulcerogenic agent extracted from the bark of Cinnamomum cortex, was described by Trost and Li.[113] Their approach was based on the employment of two catalytic reactions, allylic alkylation and cycloisomerization. The synthesis started with conjugate addition of dimethylmalonate to *N*,*N*-dimethylacrylamide in the presence of a catalytic amount of sodium hydride. A lipase (PLE) served for the desymmetrization of dimethylmalonate. Chemoselective reduction followed by oxidation and addition of vinylmagnesium bromide *in situ* capping by acetic anhydride provided the substrate **255** for the allylic alkylation. Reaction of dimethylmalonate with **255** in the presence of a


2.5 mol % Pd2 dba3·CHCl3
7.5 mol % (R,R)-44
Cs2CO3, THF
2.5 mol % Pd2 dba3·CHCl3
7.5 mol % (R,R)-44
R1 NH, THF R2
4 mol % (η3C3H5PdCl)2
12 mol % (R,R)-44
THAB, NaOH, CH2Cl2
R3CO2H
90%
(±)-conduritol B
R = TROC, CO2Me
TROC = CO2CH2CCl3
242 R = TROC R′= H 95%, 96% ee
243 R = TROC R′ = OAc 89%, 89% ee
244 R = TROC R′ = CH3 42%, 91% ee
R1, R2 =
37%, 97% ee
5% Pd cat. 61%, 95% ee
R1, R2 = PhCH2 89%, 95% ee
R3 = Ph 85%, >99% ee
R3 = t-Bu 64%, >99% ee
+ 1,2-dialkylated product 17%, 91% ee
+ PhCO2H
2.5 mol % Pd2 dba3·CHCl3
7.5 mol % (S,S)-44
THAB, NaOH, CH2Cl2
a
73%
6Li+
245
246
247
D-myo-inositol-1,4,5-triphosphate
(a) OsO4; Zn.

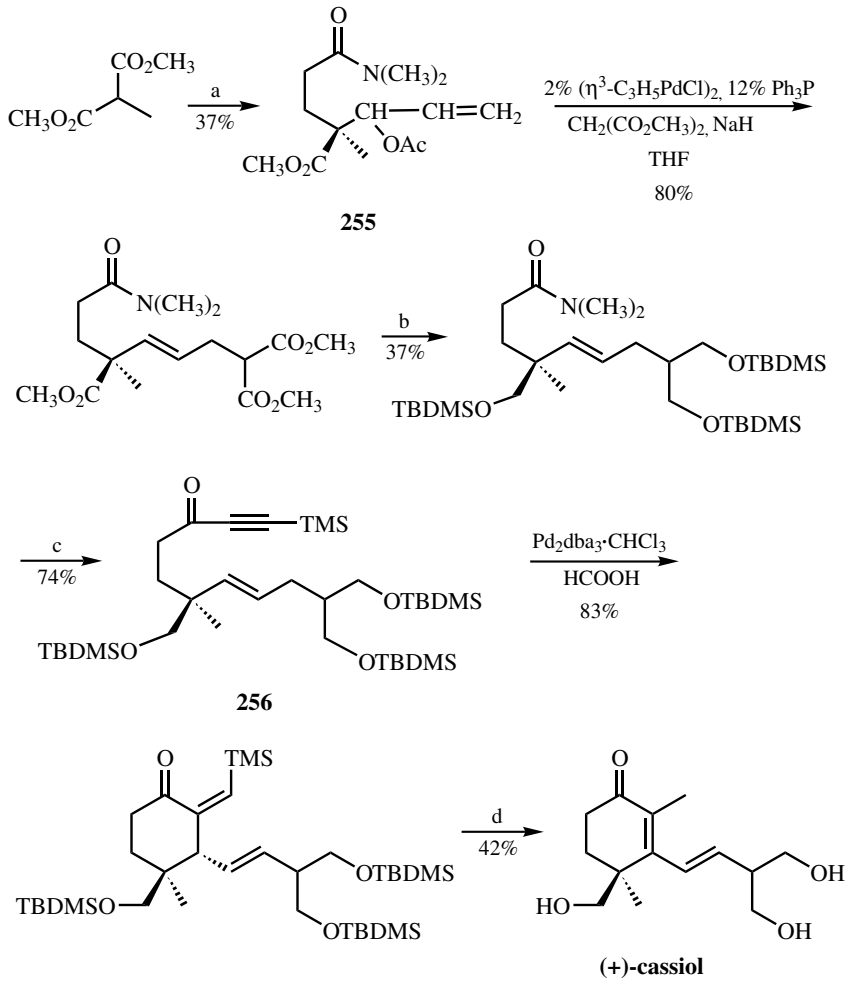
Scheme 55



(a) *n*-BuLi; ClCOOMe; (b)OsO_4; $TESOSO_2CF_3$; NBS; (c) $(MeO)_3P$; $(COCl)_2$; *t*-C_4H_9Li; TBFA; (d) $SOCl_2$; $RuCl_3$, $NaIO_4$; (e) $PhCO_2Cs$; H_2O, H^+; (f) LiI.

Scheme 56

Pd(0) catalyst, obtained from $(\eta^3\text{-}C_3H_5PdCl)_2$ and Ph_3P, introduced the side chain. Excellent regioselec-tivity and geometrical control were observed. After some functional modifications, the precursor **256** was cyclized using a new catalytic system, a so-called "ligandless" palladium catalyst in the presence of formic acid, to give the six-membered ring system. Double bond migration and desilylation completed the synthesis of (+)-cassiol (**Scheme 57**).

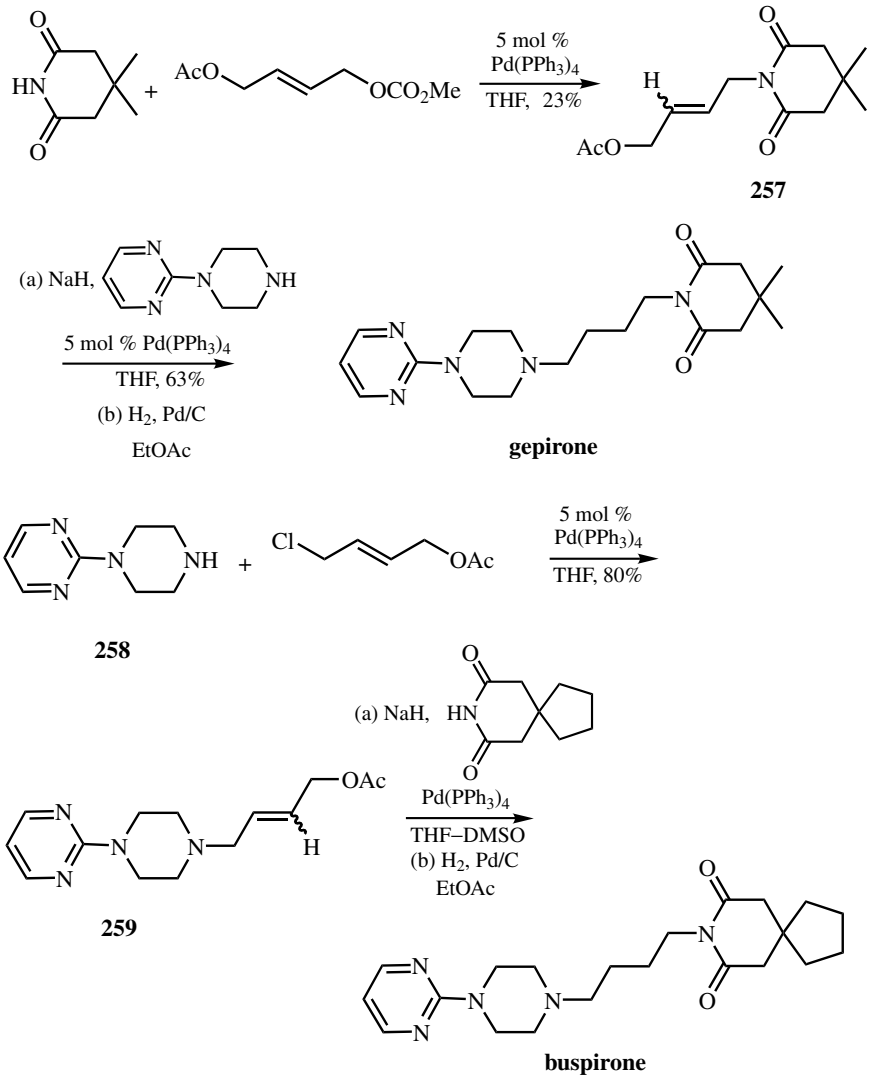


(a) NaH, *N*,*N*-dimethylacrylamide; PLE, phosphate buffer, r.t.; HOBT then $NaBH_4$; DMSO, $(COCl)_2$ then Et_3N; $CH_2{=}CHMgBr$ then Ac_2O; (b) $NaBH_4$; TBDMSCl; (c) TMS—≡—Li; (d) Et_3SiH, $\{[CH_2{=}CHSi(CH_3)_2]_2O\}_2Pt$; DDQ; TBFA.

Scheme 57

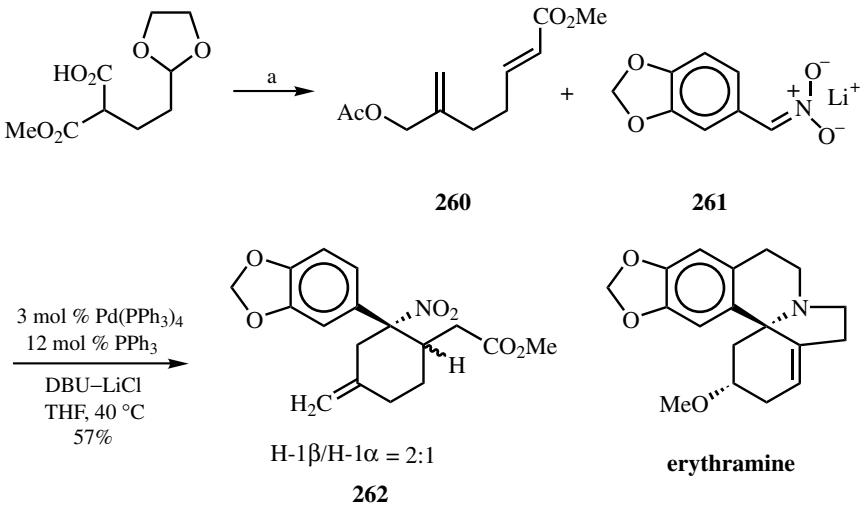
The search for effective anxiolytic drugs has received considerable attention in recent years as a result of the prevalence of various forms of anxiety disorder. This continuing effort has led to the discovery of a number of novel compounds including buspirone and gepirone, which have been shown to alleviate symptoms of anxiety in

humans. Kuo[114] proposed an efficient synthesis of buspirone or gepirone via a Pd(0)-catalyzed sequential amination–imidation sequence as described in **Scheme 58**. Treatment of 4,4-dimethylpiperidine-2,6-dione with (*E*)-4-methoxycarbonyloxybut-2-enyl acetate in the presence of $Pd(PPh_3)_4$ in THF gave the acetate **257** in 23% yield. Furthermore, π-allylic amination followed by catalytic hydrogenation afforded gepirone in poor yield. An alternative and more efficient sequence involved treatment of 2-(1-piperazinyl)pyrimidine **258** with 4-chlorobut-2-enyl acetate in the presence of $Pd(PPh_3)_4$ in THF, which gave the desired acetate **259** as a mixture of geometric isomers (*E*/*Z* = 9:1) in 80% yield. Subsequent treatment with 8-azaspiro[4.5]decane-7,9-dione in the presence of $Pd(PPh_3)_4$ (5 mol%) in THF–DMSO provided, after hydrogenation, buspirone in 40% overall yield.



Scheme 58

Desmaële and co-workers reported an interesting annulation process based on a tandem η^3-allylpalladium complex alkylation–Michael addition for the approach of erythramine.[115] It was well known that arylnitronate anions react with π-allylpalladium derivatives to give C-alkylated products. The unsaturated ester **260** was prepared as described in **Scheme 59**. Treatment of a mixture of diester **260** and arylnitronate **261** with DBU and LiCl in the presence of a catalytic amount of $Pd(PPh_3)_4$ and PPh_3 gave, in a one-pot reaction, nitro esters **262** in 57% yield. Such nitro esters could be suitable intermediates for the synthesis of *Erythria* alkaloids, exemplified by erythramine.



(a) NaOH; H_2CO, Et_3N; DIBALH; 2 N HCl, THF; $Ph_3P{=}CHCO_2Me$; Ac_2O, DMAP.

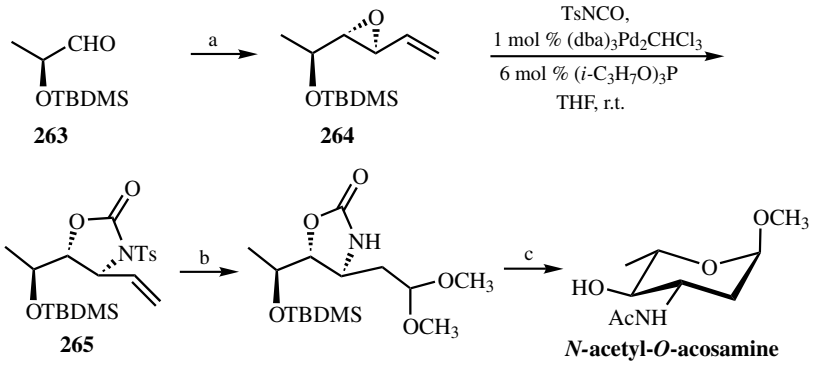
Scheme 59

The synthesis of (−)-*N*-acetyl-*O*-methylacosamine,[116] an amino sugar, is an interesting application of the process of *cis*-hydroxyamination catalyzed by palladium complexes of olefins developed by Trost and Sudhakar. Enantiomerically pure aldehyde **263** was first transformed to vinyl epoxide **264**. The latter reacted smoothly with *p*-toluene sulfonylisocyanate in the presence of 1–3 mol% of palladium and 6–18 mol% of triisopropyl phosphite in THF at room temperature. As thermal reaction favored *O*-alkylation, these conditions led exclusively to *N*-*p*-toluenesulfonyl-2-oxazolidone **265** as shown in **Scheme 60**.

(−)-Acosamine was prepared from 2-hydroxypropanal **263** in 12 steps in 12% yield. The key conversion of the enantiomerically pure vinyl epoxide to the 2-oxazolidone proceeded with complete retention of configuration. It was conveniently isolated as its *N*-acetyl-*O*-methyl glucoside in excellent agreement with the literature.

D.ii. Cyclization Via Palladium-Catalyzed Allylation

D.ii.a. ***Cyclization Involving Carbon Nucleophiles.*** Discoveries of important biological properties of vitamin D_3 metabolites and analogs have stimulated numerous syntheses. The approach using cholesterol or related sterols as starting materials included several low-yield steps. Therefore, the total synthesis appears to provide an efficient strategy for small

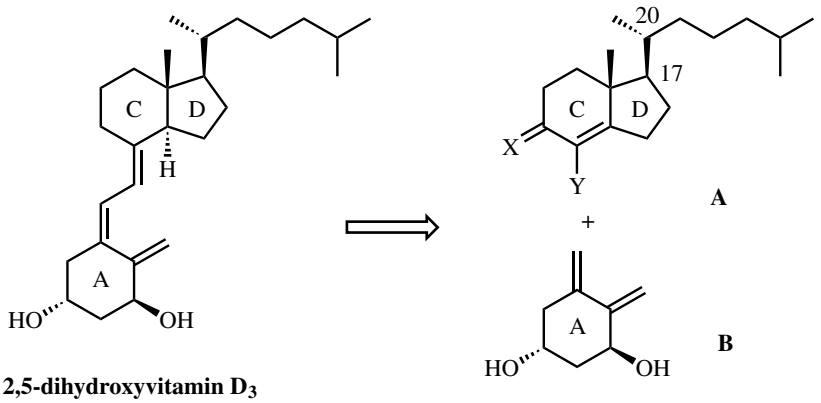


(a) $(CH_3O)_2P(O)CH_2CO_2CH_3$, $(i\text{-}C_3H_7)_2NC_2H_5$, LiCl; DIBALH; $t\text{-}C_4H_9OH$, $Ti(Oi\text{-}C_3H_7)_4$, (+)-DET; Ph_3PCH_3Br, $t\text{-}C_4H_9OK$, THF; (b) $Na^+C_{10}H_8^-$; $(CH_3)_3CHCH(CH_3)]_2BH$ then $NaHCO_3$, H_2O_2; PCC, celite; $(CH_3O)_3CH$, CH_3OH, PPTS; (c) NaOH; Ac_2O; CH_3OH.

Scheme 60

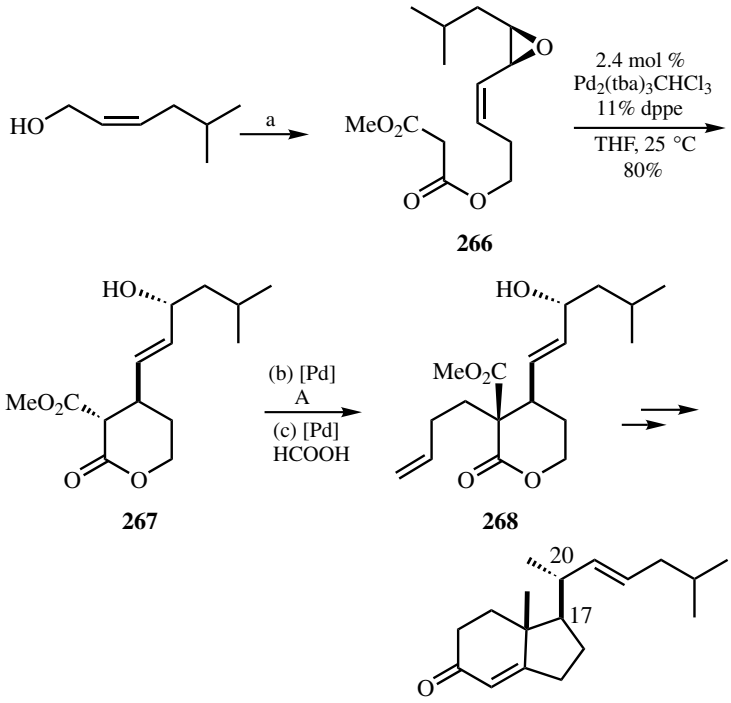
quantities. The classical approach consisted of the separate preparation of the CD ring fragment with side chain and the appropriate ring A fragment (**Scheme 61**).

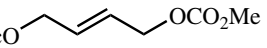
Tsuji and co-workers described the synthesis of the optically active (*2R*,*3R*)-3-[(*3R*)-(*E*)-benzyloxymethoxy-5-methyl-1-hexenyl]-2-(3-butenyl)-2-methyl-1-cyclopentanone as precursor of vitamin D_3 by Pd-catalyzed *syn*-S_N2' cyclization.[117] The key step was the stereocontrolled cyclization of the ene oxide to introduce the relative stereochemistry at C17 and C23 as well as the geometry of the double bond in the lactone (**Scheme 62**).



Scheme 61

The ene oxide **266** was prepared from 5-methyl-(*2Z*)-hexene-1-ol first by Sharpless epoxidation followed by Swern oxidation; the aldehyde was submitted to Wittig reaction and the resulting alcohol was esterified to lead to ene oxide **266**. Pd-catalyzed cyclization in the presence of $Pd_2(tba)_3{\cdot}CHCl_3$ and DPPE in THF at 25 °C gave the lactone **267** with high regio- and stereoselectivities. Introduction of the butenyl chain of the lactone was successful by Pd-catalyzed alkylation with the appropriate allylic carbonate. The allylic substitution proceeded stereoselectively in 51% yield. The Pd-catalyzed hydrogenolysis of allylic acetate with formic acid and triethylamine afforded the lactone **268** (**Scheme 62**).



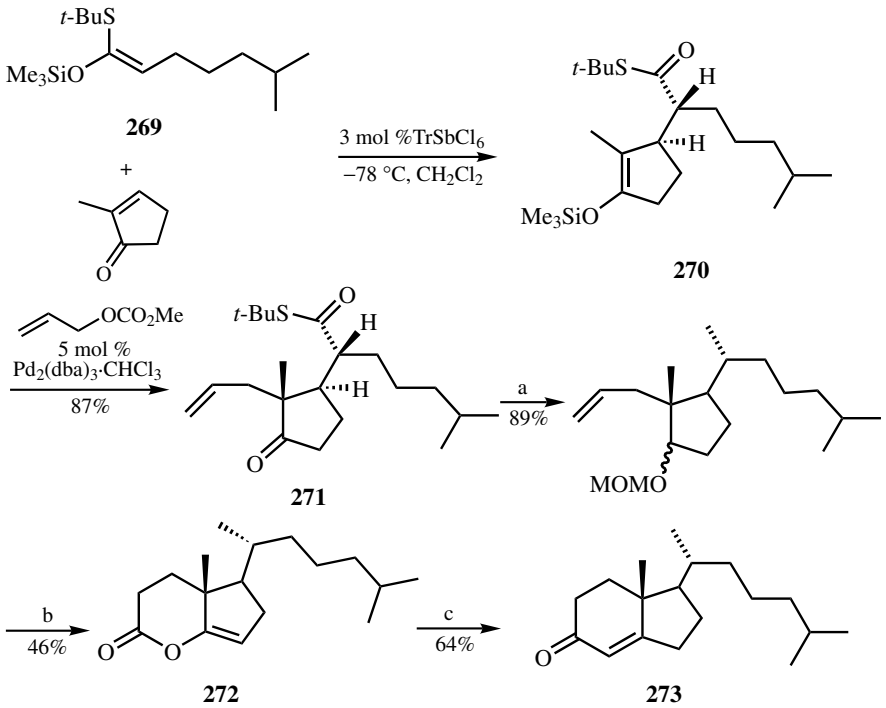
(a) (+)-DET, Ti(O*i*-Pr)$_4$, TBHP; Me_2SO, $(COCl)_2$, Et_3N; $Ph_3PCH_2CH_2CH_2OH$, BuLi; Me_3SiCl; methylmalonate; A = 

Scheme 62

A reported diastereoselective synthesis of precursor A of vitamin D_3 involved the use of 2-methylcyclopent-2-enone as starting material. The Mukaiyama–Michael conjugate addition of ketene acetal **269** in the presence of trityl hexachloroantimonate afforded the adduct **270**. The lateral chain was introduced, according the procedure of Tsuji, by the treatment of crude **270** with allyl carbonate and palladium dibenzylideneacetone[118] (**Scheme 63**). The expected product **271** was obtained in 63% yield from **269**. Reduction of **271** with LAH afforded a mixture of diols that was selectively tosylated at the primary hydroxy group. The secondary hydroxy group was protected with the methoxymethyl group and further functional modifications afforded the lactone **272**. The reaction of lithium dimethyl methylphosphonate with the lactone **272** completed the synthesis of the AB-des-cholestane derivative **273**.

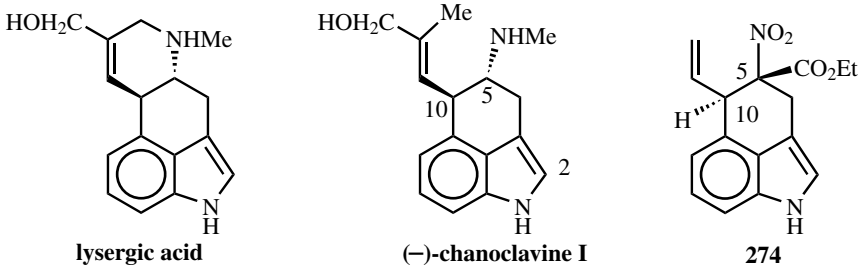
Another class of natural products such as the ergot alkaloids were approached via Pd-catalyzed cyclization. The structural diversity and broad spectrum of biological properties make the ergot alkaloids, metabolites of the parasitic fungus *Claviceps*, unique among the plant bases. In addition to the well-known hallucinogen lysergic acid diethylamide (LSD), a number of tricyclic analogs in which the D ring is not closed are found in nature, as chanoclavine I (**Scheme 64**).

An easy synthesis of the ergoline synthon **274** has been described by Genêt and Grisoni.[119] The key step involved C-5/C-6 intramolecular alkylation of allylic nitro compounds. The starting aldehyde **275** was submitted to a Horner–Emmons reaction with



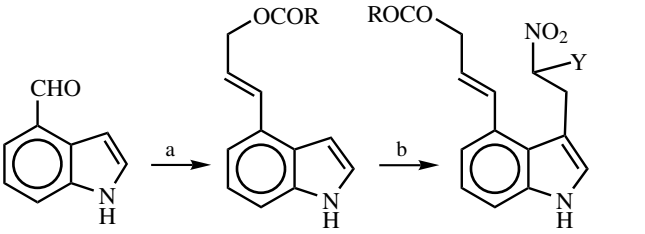
(a) $LiAlH_4$; TsCl, Et_3N; MOMCl; (b) LAH; $BH_3 \cdot Me_2S$ and H_2O_2–NaOH; CrO_3–H_2SO_4; Ac_2O–AcONa; (c) 2 equiv $(MeO)_2P(O)CH_2Li$, THF; AcOH.

Scheme 63

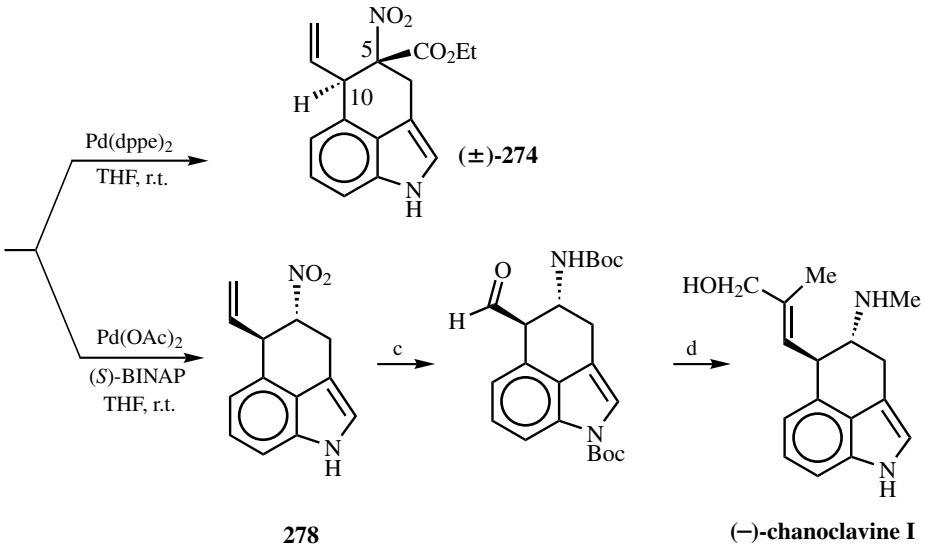


Scheme 64

ethyl diethylphosphinoacetate and potassium acetate as base. Reduction of the unsaturated ester by LAH afforded the allylic alcohol, which was transformed into carbonate **276** by treatment with ethylchloroformate. Reaction of **276** with the mixture of dimethylamine and formaldehyde gave the gramine derivative, which was converted to the precursor **277**. The cyclization was performed under neutral conditions in the presence of $Pd(dppe)_2$ to afford the ergoline synthon **274** in 40% overall yield (**Scheme 65**). Later, the same group[120],[121] described an asymmetric synthesis of an analog of **274** by using $Pd(dba)_2$ and (*S*)-(−)-BINAP in THF at room temperature. The desired enantiomer (5*R*)-**278** was obtained in 60% yield and 95% enantiomeric excess. The first total asymmetric synthesis of (−)-chanoclavine I from **278** was reported as shown in **Scheme 65**.



275 **276** R = Me, OEt **277** Y = H, CO_2Et



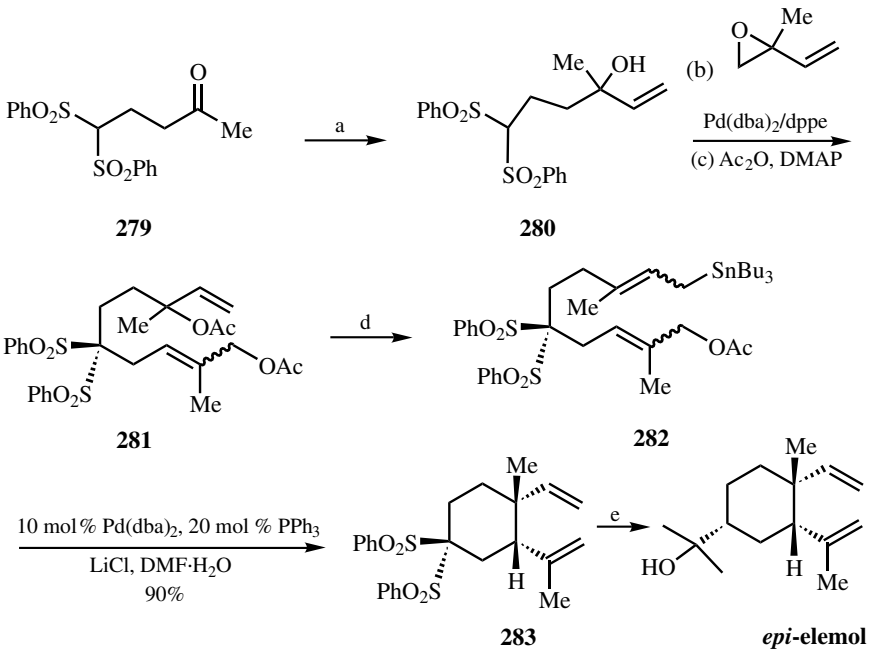
278 **(−)-chanoclavine I**

(a) $(EtO)_2OPCH_2CO_2Et$; LAH; Ac_2O or $ClCO_2Et$; (b) HCHO, $HNMe_2$; $O_2NCH_2CO_2Et$; (c) Zn(Hg): Boc_2O; OsO_4; $NaIO_4$; (d) $Ph_3P{=}C(Me)CO_2Me$; LAH.

Scheme 65

The construction of sesquiterpenes by Ni-promoted allyl/allyl coupling was demonstrated early by Corey in the syntheses of (±)-elemol. However, the reaction requires a stoichiometric amount of catalyst and the regio- and stereoselectivities of the coupling are low. The alternative intramolecular insertion of η^3-allylpalladium complexes into alkenes allowed the efficient synthesis of five- or six-membered ring carbocycles, but increasing the steric hinderance of the allyl and alkyl termini leads to recovering of the unchanged starting materials. Therefore, Echavarren and co-workers examined the cyclization of substrate **282** by an intramolecular Pd-catalyzed cross-coupling of an allylstannane with an allyl acetate and demonstrated that the intramolecular coupling could be efficiently carried out in the presence of water in the solvent.[122] This process was highly stereoselective, allowing the efficient synthesis of *epi*-elemol, isolated from *galbanum resin* a rare member of the elemane family of sesquiterpenes bearing *cis* and isopropenyl groups. The synthesis of the required precursor for the cyclization was completed by using organometallic transformation in all but one step as shown in **Scheme 66**. Reaction of keto disulfone **279** with magnesium bromide gave alcohol **280**, which was allowed to

react with isoprene epoxide in the presence of a palladium catalyst to give **281** as a mixture of *Z*/*E* isomers. A highly regioselective stannylation of **281** afforded **282** in 79% yield. The carbocyclization key step was effected in the presence of 10 mol % $Pd(dba)_2$ catalyst, 20 mol % PPh_3, and an excess LiCl in 0.5% aqueous DMF at 80 °C for 20 h to give **283** as a single isomer in 90% yield. Classical treatments, including reductive desulfonation and acetylation, afforded racemic *epi*-elemol.

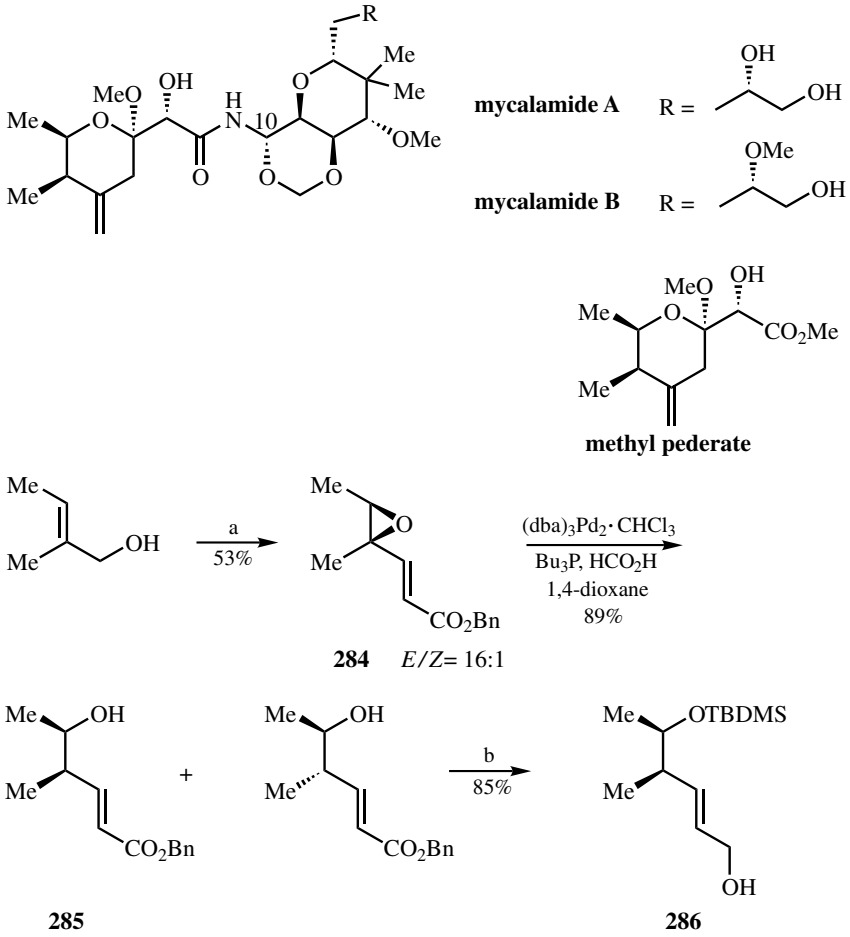


(a) vinylmagnesium bromide; (d) $(Bu_3Sn)(Bu)CuLi$, LiCN;
(e) Na(Hg); BuLi, Ac_2O; Na(Hg), Na_2HPO_4; MeMgBr.

Scheme 66

Mycalamides A and B are strong antiviral and antitumor compounds, isolated from a New Zealand marine sponge. Furthermore, mycalamides were recently reported to exhibit immunosuppressive activity via inhibition of T cell activation. Toyota and co-workers proposed an enantioselective preparation of a possible key intermediate, (+)-methyl pederate, based on a Pd-catalyzed intramolecular allylic alkylation reaction.[123] A Pd-catalyzed regio- and stereoselective hydrogenolysis route was adopted to synthesize the requisite carbonate **287** (**Scheme 68**). Tiglic alcohol was subjected to the Sharpless asymmetric epoxidation (**Scheme 67**). After oxidation, the efficient construction of the (*E*)-olefin **284** (*E*/*Z* = 16:1) was achieved by utilization of the Masamune–Roush procedure. Pd-catalyzed hydrogenolysis of the resulting (*E*)-alkenyloxirane was conducted with $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of Bu_3P-HCOOH-Et_3N to provide the alcohol **285** as the major isomer. The mixture of homoallylic alcohols was subjected to protection followed by DIBAH reduction to give **286** after separation.

Conversion of alcohol **286** to the carbonate **287** was achieved via the reaction sequence summarized in **Scheme 68**. The outcome of the lactonization reaction depended dramatically on the reaction conditions. In the presence of $Pd(OAc)_2$ (10 mol %) and

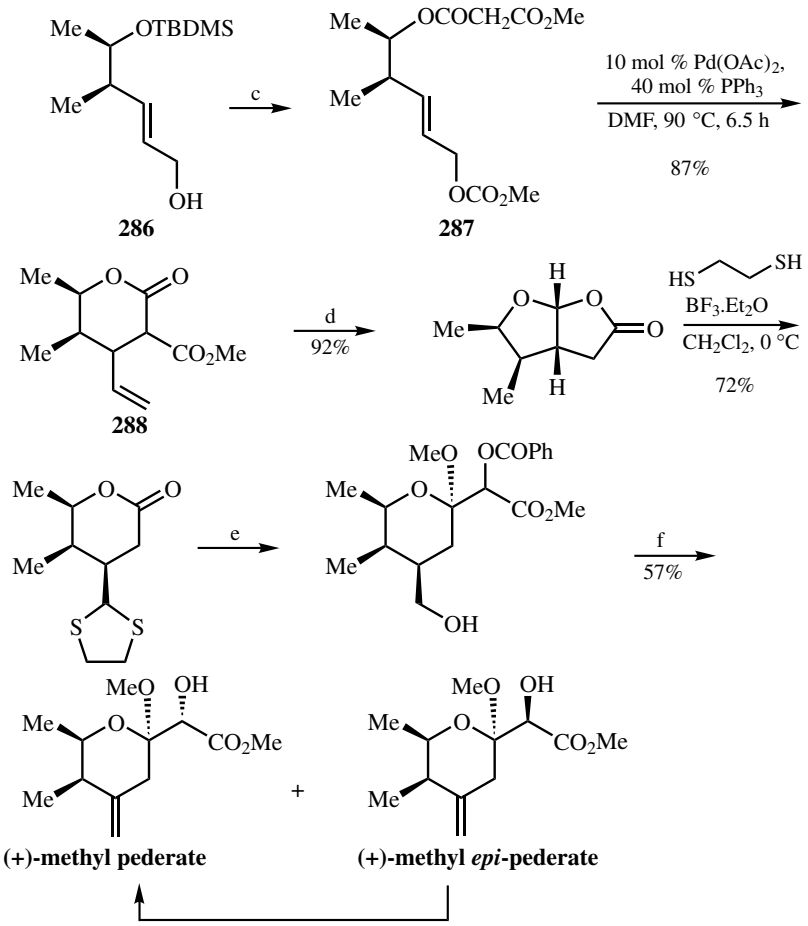


(a) $PhMe_2CO_2H$, (–)-D-DIPT, $Ti(Oi\text{-}Pr)_4$; $n\text{-}Pr_4NRuO_4$, 4-methylmorpholine *N*-oxide; $(EtO)_2P(O)CH_2CO_2Bn$, LiCl; (b) TBDMSOTf, 2,6-lutidine; DIBALH.

Scheme 67

PPh_3 (40 mol %) the δ-lactone **288** was prepared in DMF at 90 °C in 87% yield. Demethoxycarbonylation of **288** and further functional group transformations led to an easily separable 13:12 mixture of (+)-methyl pederate and methyl (+)-*epi*-pederate. The latter could be recycled by Collins oxidation and reduction with $NaBH_4$.

The same approach for effecting the key step of cyclization by Pd-catalyzed methodology has been applied to an efficient synthesis of alloyohimbone, an alkaloid of the yohimbe family. [124] The sequence was initiated by reaction of the Diels–Alder adduct **289** with tryptamine followed by $NaBH_4$ reduction to give the amino allylic acetate **290** in 85% yield. Acylation of the amine provided the π-allyl precursor. Anion formation with NaH and reaction with $Pd(dppe)_2$ catalyst gave **291** possessing exclusively the *cis*-fused ring juncture in excellent yield. The subsequent Bischler–Napieralski reaction completed the synthesis of the pentacyclic ring system. Hydrolysis of the vinyl sulfide gave alloyohimbone in 64% yield (**Scheme 69**).

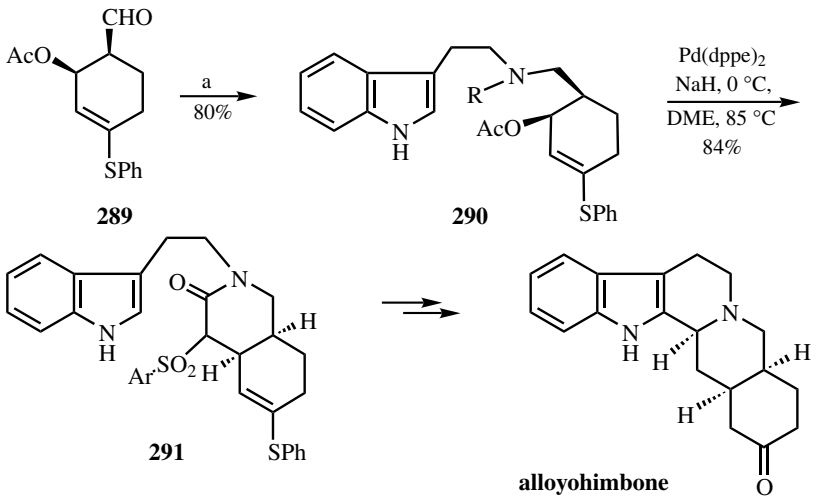


(c) $ClCO_2Me$; Bu_4NF; $MeO_2CCH_2CO_2H$; (d) LiI; O_3; conc. HCl; (e) *O*-(2-methoxy-2-propyl)glycolate; $HC(OMe)_3$; PhCOCl; HgO, $HgCl_2$; $NaBH_4$, 76% (5 steps); (f) *O*-$NO_2PhSeCN$, Bu_3P, H_2O_2; NaOMe, MeOH.

Scheme 68

D.ii.b. ***Cyclization Involving Oxygen Nucleophiles.*** The importance of lipophilic antioxidants in biology has stimulated continued interest in vitamin E and analogs. In addition to vitamin E, trolox and especially MDL-73404 (**Scheme 70**) exhibit biological activity, the latter exhibiting cardioprotective effects during a myocardial infarction. Among the three stereocenters present in vitamin E, the C-2 appears to be the most important for biological potency.

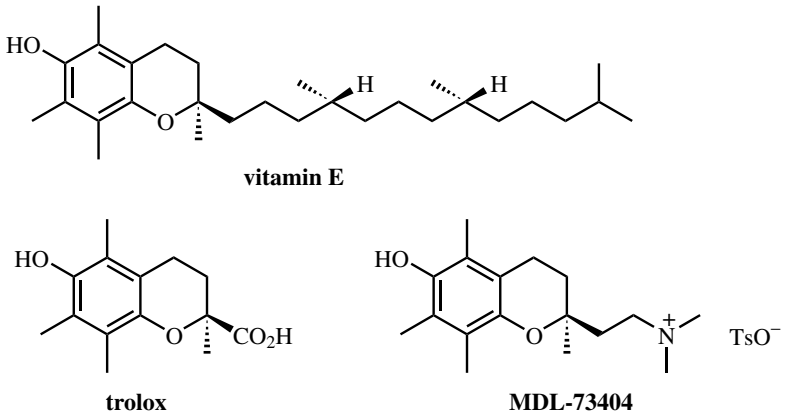
Trost and Asakawa[125] have evolved an efficient asymmetric synthesis of the vinylchroman **293**, an important building block for the synthesis of vitamin E. The requisite substrate **292** was prepared as previously described from hydroquinone[126] in a 45% overall yield. Using the ligand (*R*,*R*)-**44**, the reaction proceeded satisfactorily with either η^3-allylpalladium chloride dimer or $(dba)_3Pd_2{\cdot}CHCl_3$ as palladium source. The yields were generally nearly quantitative but the enantiomeric excess was modest. A variety of



(a) tryptamine, $MgSO_4$; $NaBH_4$, MeOH; $ClCOCH_2(SO_2Ph\text{-}Me)$

R = $-C(=O)-CH_2SO_2Ph\text{-}p\text{-}Me$

Scheme 69



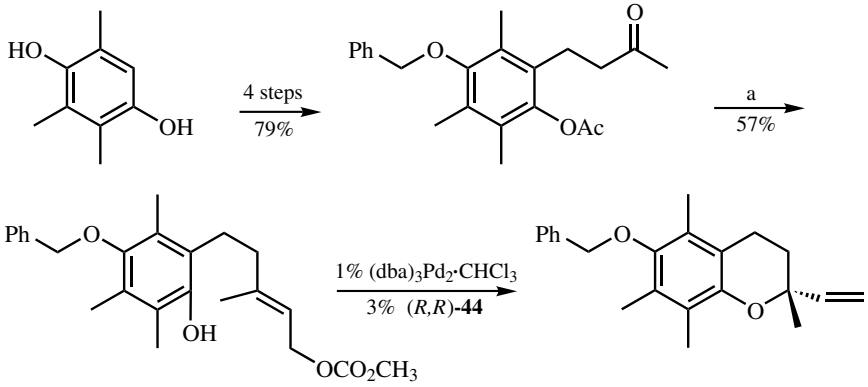
Scheme 70

reaction conditions were explored in the course of optimizing the enantiomeric excess, including testing different solvents, temperatures, additives, and ligands and varying the concentrations of both the substrate and the catalyst. (**Scheme 71**).

Optimum conditions were found to require 0.01 M substrate concentration, 1% of $(dba)_3Pd_2{\cdot}CHCl_3$, and 3% of (*R*,*R*)-**44** in CH_2Cl_2 at room temperature in the presence of triethylamine giving 87% ee. The reaction involved a relatively rare mechanism for asymmetric induction in allylic alkylation-discrimination of enantiotopic faces of a prochiral alkene.

The 1,4-benzodioxane ring is present in a large number of structures of therapeutic agents possessing important biological activities; for example, some of them are antagonists of α-adrenergic receptors such as RX 781094; others exhibit antihyperglycemic properties. It has been shown that these biological properties are considerably influenced

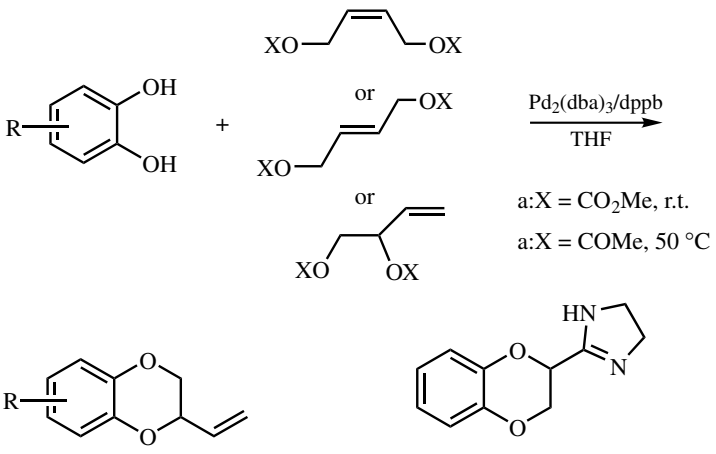
by the chirality of the 1,4-benzodioxane ring. Various substituted dihydrobenzo[1,4]dioxins **294** were obtained by Sinou and co-workers in good yield through a tandem allylic substitution reaction catalyzed by a palladium catalyst prepared *in situ* by mixing $Pd_2(dba)_3$ and ligand DPPB in 1:4 ratio.[127] The reaction was performed in THF during 12 h; regioisomers were formed, the proportion being depending on the substitution pattern. The chiral version of this cyclization was explored under the same conditions using (*R*)-BIPHEMP or (*R*)-BINAP as chiral ligand with moderate ee values up to 45% (**Scheme 72**).



292 (*R*)-**293**

(a) $(CH_3O)P(O)CH_2CO_2CH_3$; DIBALH; $ClCO_2CH_3$, C_5H_5N.

Scheme 71

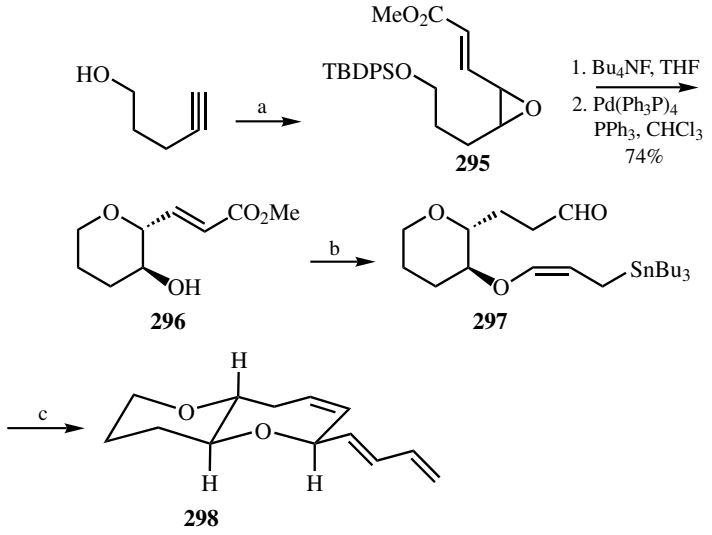


294 **RX 781094**

Scheme 72

Based on the strategy of ene oxide ring opening catalyzed by palladium, an enantioselective synthesis of the AB ring fragment of gambiertoxin 4B has been reported by Yasumoto's group[128] Gambiertoxin 4B, isolated from epiphytic dinoflagellate, *Gambierdiscus toxicus*, caused important diseases in people in subtropical and tropical regions. The precursor **295**

was prepared from 4-pentyn-1-ol by classical reactions. After deprotection of the hydroxy group, the epoxy ester **295** was regio- and stereoselectively cyclized in the presence of catalytic amounts of $Pd(Ph_3P)_4$ and PPh_3 in chloroform to 2,3-*trans*-disubstituted tetrahydropyran **296** in 74% yield. Further transformations afforded the aldehyde **297**. BF_3 etherate-promoted cyclization of **297** provided the AB ring stereo-selectively, and regio- and stereoselective construction of 1,3(*E*),6-triene was achieved as summarized in **Scheme 73**.

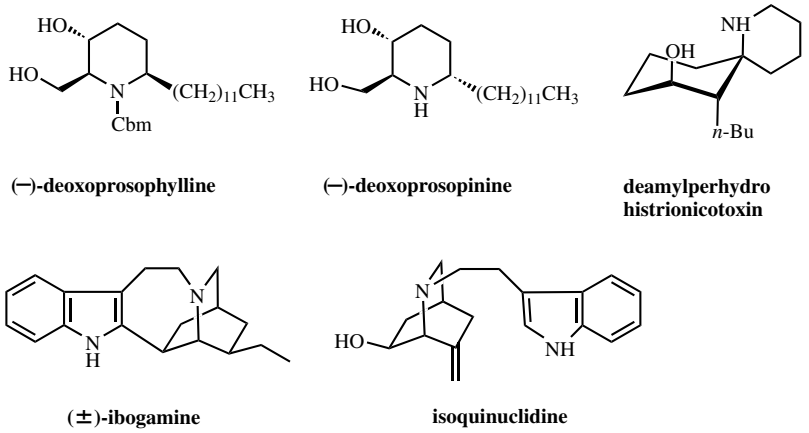


(a) TBDPSCl; BuLi, $(HCHO)_n$; H_2, Pd Lindlar; Ti(O*i*-Pr)$_4$, D-(−)-DET, TBHP; SO_3-py, DMSO, NEt_3; $Ph_3P{=}CHCO_2Me$, 73% (6 steps); (b) H_2, Pd/C; LAH; TBSCl; KH, allyl bromide; Bu_4NF; *s*-BuLi, Bu_3SnCl; MeMgBr, then 1,1′-(diazocarbonyl)dipiperidine, 81% (6 steps); (c) BF_3-Et_2O; ethyl vinyl ether, PPTS; O_3, then PPh_3; 1-bromo-1-propene, Mg; TBDSCl; PPTS; MsCl; DBU; Bu_4NF; 2,4-dinitrobenzenesulfenyl chloride, 30% (10 steps).

Scheme 73

D.ii.c. ***Cyclization Involving Nitrogen Nucleophiles.*** Nitrogen-containing bases found in plants, called alkaloids, have been known for a long time as toxic compounds. Their physiological activities have attracted the attention of chemists from early times. Numerous synthetic approaches are described in the literature. However, intramolecular Pd-catalyzed alkylation could be an efficient methodology in forming a C—N bond and several syntheses of natural products were described, such as (−)-deoxoprosopinine, (−)-deoxoprosophylline, deamylperhydrohistrionicotoxin, and ibogamine (**Scheme 74**).

Alkaloids containing a 2,6-dialkylated piperidine ring are found abundantly in nature and the Prosopis alkaloids, one of the subgroups of these alkaloids, could possess local anesthetic activity. (−)-Deoxoprosopinine and (−)-deoxoprosophylline were enantiospecifically and stereoselectively synthesized from methyl 3,4-dideoxy-α-D-*erythro*-hexopyranoside. The key intermediate **299** was prepared by standard procedures and the dialkylated piperidine ring was formed in the key step by Pd(0)-catalyzed intramolecular N-alkylation of **299**. The cyclization proceeded at room temperature when **299** was treated with NaH in THF in the presence of 1 equiv of *n*-Bu_4NI and a catalytic amount of $Pd(PPh_3)_4$ (**Scheme 75**).



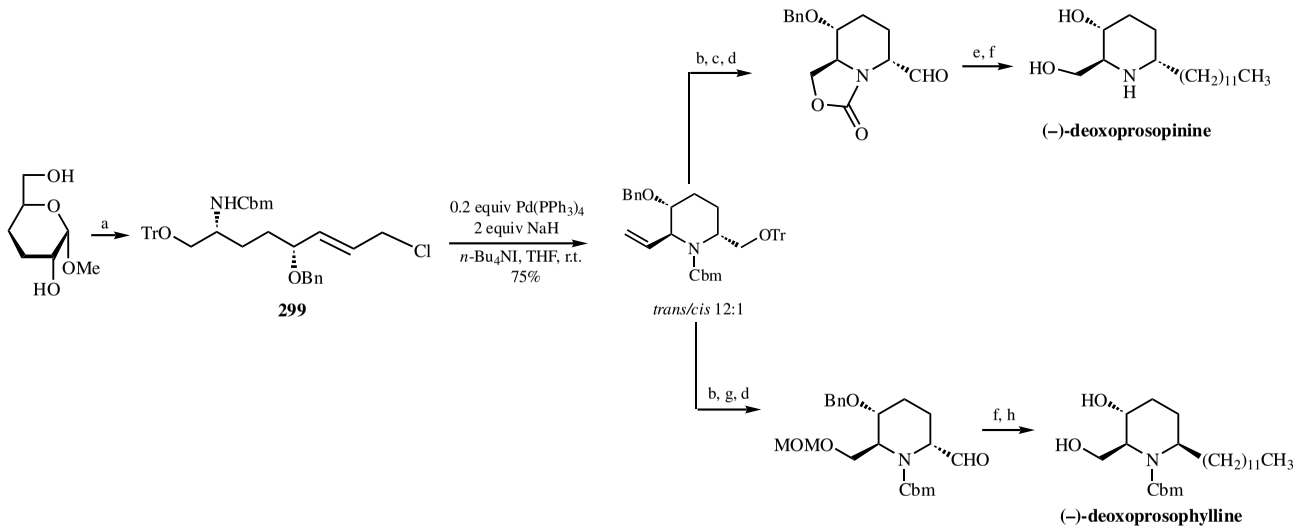
(−)-deoxoprosophylline **(−)-deoxoprosopinine** **deamylperhydro histrionicotoxin**

(±)-ibogamine **isoquinuclidine**

Scheme 74

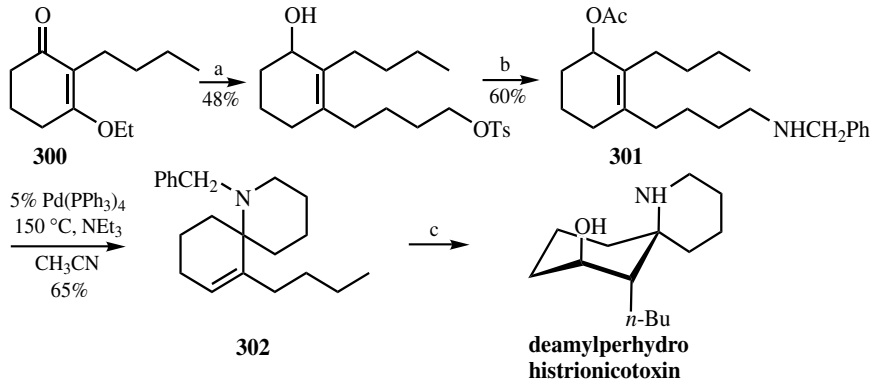
Members of the histrionicotoxin family of alkaloids have attracted considerable interest because of their unique structural features and their important properties as cholnolytics and modifiers of specific ion channels in nerves. Syntheses of perhydrohistrionicotoxin, a nonnatural alkaloid with comparable activity, were described in the literature. Recent reports showed that a variety of simpler analogs of perhydrohistrionicotoxin also possess significant neurological activity. Godleski et al.[129] selected deamylperhydrohistrionicotoxin as a target because it has recently been found to have equal bioactivity. The key step, a spirocyclization, could readily be achieved by a Pd-catalyzed reaction of the amino allylic acetate **301**. This π-allyl precursor was obtained in three steps from **300** (**Scheme 76**). Reaction of **301** with 5–7% $Pd(PPh_3)_4$ in the presence of 1 equiv of NEt_3, in CH_3CN at 150 °C in a sealed tube, afforded the spirocyclic olefin **302** in 65% isolated yield. Hydroboration followed by oxidation with basic hydrogen peroxide provided the isomeric alcohols. The desired alcohol could be chromatographically separated and debenzylated to provided deamylperhydrohistrionicotoxin.

The azabicyclo[2.2.2]octane skeleton is found in many biologically active natural products, including iboga alkaloids as well as nonindole-containing alkaloids such as the cannivonines. These types of compounds are of interest for their biological activity and also as precursors to more complex alkaloids such as vinblastine. The isoquinuclidine ring appears ideally suited to take advantage of π-allylpalladium(0)-catalyzed chemistry, as shown in **Scheme 77**. Thus, a short synthesis of racemic and optically active ibogamine[130] was reported, using this methodology. The racemic synthesis started with 1-acetoxy-4-ethylcyclohexene **303**, prepared by a Diels–Alder reaction between 1-acetoxy-1,3-hexadiene and acrolein. Formation of Schiff base with tryptamine followed by workup with $NaBH_4$ gave the amino acetate **304**, which cyclized in the presence of 3–6 mol % of $Pd(PPh_3)_4$ in acetonitrile at 70 °C to produce the isoquinuclidine **305** (45%). The next cyclization effected by bis(acetonitrile)palladium chloride in the presence of silver tetrafluoroborate afforded, after treatment and purification, ibogamine in 17% overall yield. When the alkyl group was the *O*-methymandeloyl group, optically active ibogamine was obtained.



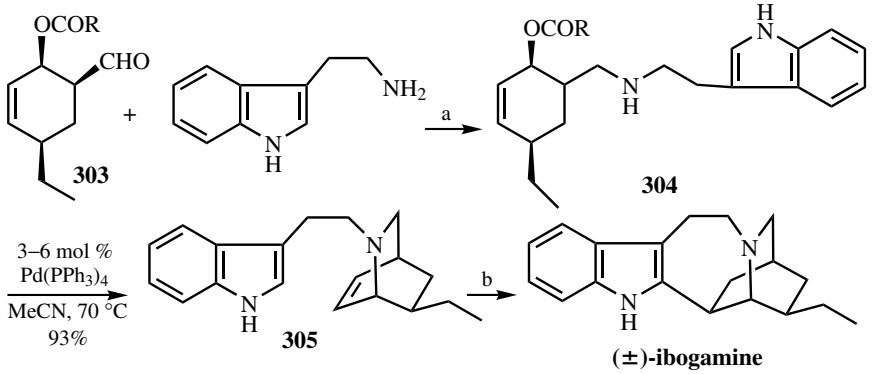
(a) EtSH; $Me_2C(OMe)_2$; BnBr; 50% aq. AcOH; TrCl; MsCl; NaN_3; H_2S; MeOC(O)Cl, K_2CO_3; $HgCl_2$; $(EtO)_2P(O)CH_2CO_2Et$ (65% 9 steps) ; DIBAH; TsCl (83%); (b) O_3, PPh_3; $NaBH_4$; (c) NaH; (d) PTSA; $(COCl)_2$, DMSO then Et_3N; (e) $Ph_3P{=}CH(CH_2)_9CH_3$; H_2, Pd/C; (f) HCl; KOH; (g) $MeOCH_2Cl$; (h) KOH, NH_2NH_2; HCl.

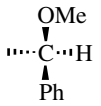
Scheme 75



(a) $ClMg(CH_2)_4OMgCl$; TsCl, py; DIBAH; (b) Ac_2O, NEt_3; $PhCH_2NH_2$, NaI; (c) $BH_3 \cdot Me_2S$ then HO^-, H_2O_2; H_2, Pd/C.

Scheme 76



R = Me, 

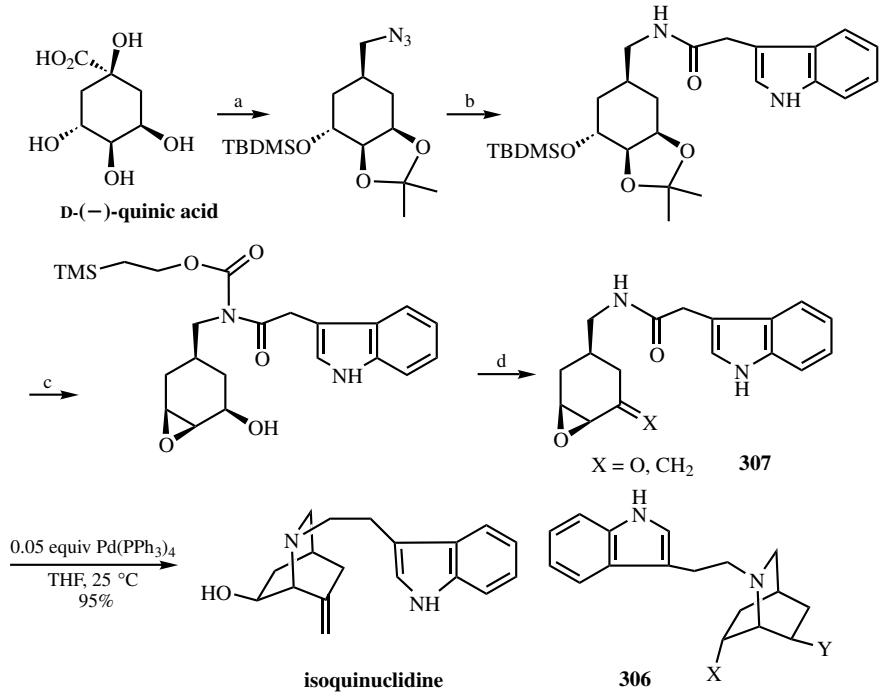
(a) $PhCH_3$, $MgSO_4$ then $NaBH_4$; (b) $(CH_3CN)_2PdCl_2$, $AgBF_4$; then $NaBH_4$, MeOH.

Scheme 77

A new approach toward the isoquinuclidine ring was envisioned by Trost and Romero,[131] based on Pd(0)-catalyzed epoxy ring opening. The isoquinuclidine ring system common to alkaloids ibogamine and catharanthine appears suited to be constructed from the same intermediate **306**, which would allow cyclization at either enantiotopic carbons of the isoquinuclidine nucleus. The effectiveness of the cyclization required that it was faster than Pd-catalyzed proton transfer (**Scheme 78**).

Enantiomerically pure epoxide **307** was synthesized in 16 steps from D-(−)-quinic acid, an inexpensive plant metabolite. Intramolecular cyclization was observed with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) at 25 °C to afford the optically active isoquinuclidine in 95% yield. The introduction of alkyl groups, such as the ethyl group of ibogamine and catharanthine, can easily be accomplished at the epoxy ketone stage.

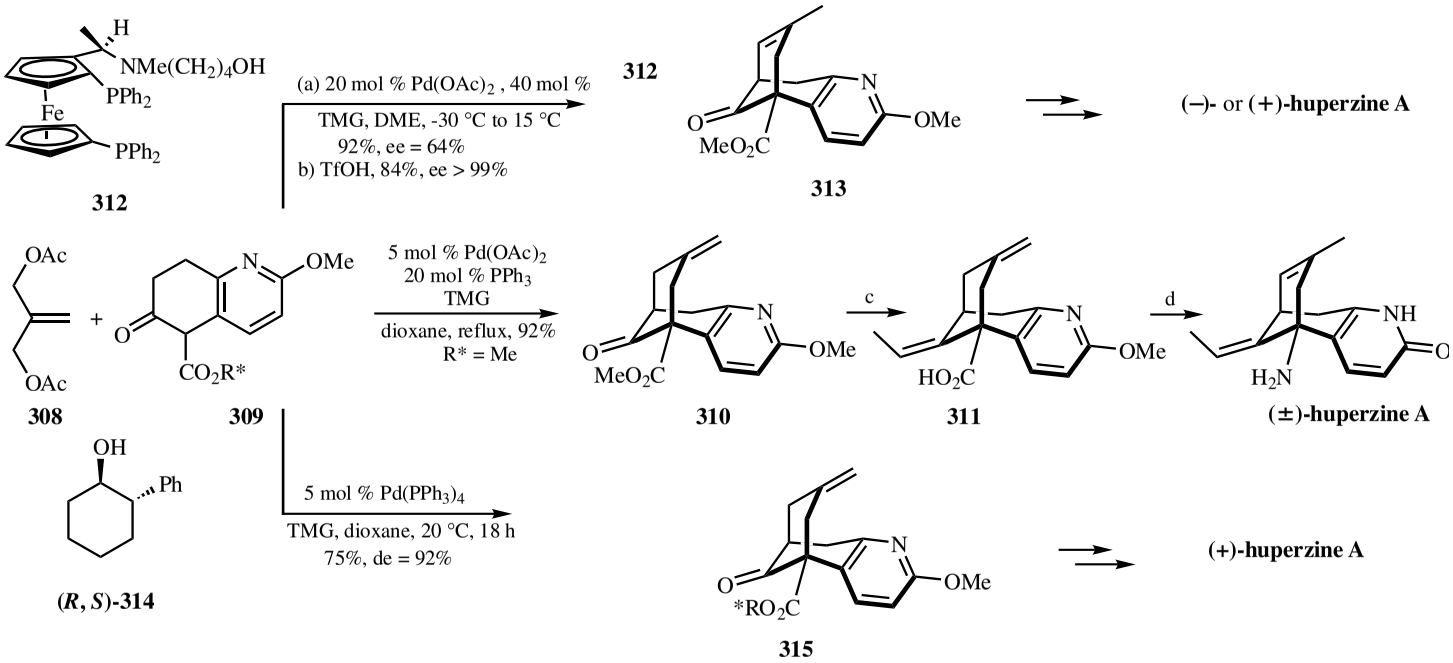
D.ii.d. ***[3 + 2] Cyclizations.*** The capability of [3 + 2] cycloaddition based on trimethylenemethane has served as a useful scaffolding technique in natural products and



(a) dry HCl, Me_2CO; LAH; $(EtO)_3CH$, cat. $PhCO_2H$; H_3O^+; Ac_2O, Et_3N; Me_3Al, BH_3-SMe_2; H_2O_2, NaOH; TsCl, py; NaN_3; TBDMDCl; (b) 1 atm H_2, 10% Pd/C; $(PhO)_2P(O)N_3$, indole-3-acetic acid; (c) DIBALH; $TMSC_2H_4OCOCl$; $(n\text{-}C_4H_9)_4NF$; CH_3SO_2Cl; H_3O^+; NaOH, CH_3OH; (d) Collins oxid.; Ph_3PCH_2; $(n\text{-}C_4H_9)_4$ NF.

Scheme 78

biologically active five-membered ring compound syntheses. One last example is the efficient preparation of huperzine A and analogs based on this Pd-catalyzed reaction to form the six-membered ring. (−)-Huperzine A isolated from *Huperzia serrata*, known to Chinese folk medicine, has been shown to be a potent reversible acetylcholinesterase inhibitor. Since the use of (−)-huperzine can increase the level of the neurotransmitter acetylcholine in the central nervous system, this natural product is anticipated to hold promise in the treatments of Alzheimer's disease and is currently under clinical trials. The model system described by Gravel et al.[132] has inspired Kozikowski and co-workers,[133] who have shown that the Pd-catalyzed bicycloannulation approach of (±)-huperzine A gave the best results (**Scheme 79**). The Pd-assisted cycloaddition reaction of β-keto ester **309** using 1,1,3,3-tetramethylguanidine as a base (to generate the 5,7-dicarbanion equivalent) and 2-methylene-1,3-propanediol diacetate **308** as the bis-electrophile in the presence of Pd(0) in refluxing dioxane afforded methylene-bridged structure **310** in 92% yield. Wittig reaction of **310**, followed by isomerization reaction and acid formation, led to the major (*E*)-acid **311** in a good overall yield. The final stage was based on a Curtius rearrangement, deprotection, and isomerization to furnish (±)-huperzine in 40% overall yield from **309**. The palladium methodology effectively replaced the low-yielding first total synthesis and permitted the synthesis of several analogs. More recently, another group[134] has accomplished an asymmetric synthesis of both enantiomers of huperzine A,



(c) $Ph_3P^+C_2H_5Br^-$, *n*-BuLi, 83%, *E*/*Z* = 1:9; PhSH, AIBN, NaOH, 76% (2 steps), *E*/*Z* = 19:1; (d) $(PhO)_2P(O)N_3$ then MeOH, 82%; TMSI; MeOH; TfOH; 84% (3 steps).

Scheme 79

using chiral palladium catalysts. Studying the influence of chiral ligands, base, solvent, and temperature, the best result of bicycloaddition was obtained using Hayashi's chiral ferrocenylphosphine ligand **312** (both enantiomers *R*,*S* and *S*,*R* were tested), in 1,2-dimethoxyethane, at −30 °C followed by gradual warming to 15 °C. The cycloadduct was obtained in 91% yield and 63% ee. Acid-catalyzed isomerization of the *exo*-methylene moiety afforded tricycle **313**, which could be recrystallized to give optically pure samples (ee > 99%). According to the protocol reported by Kozikowski and co-workers, natural (−)- and unnatural (+)-huperzine A were synthesized from optically pure (+)-**313** and (−)-**313**. A rather similar result was obtained by He et al.,[135] who prepared compound **310** in 52% ee with another modified Hayashi catalyst. Recently, Langlois and co-workers described a formal synthesis of (+)-huperzine A, using Pd-catalyzed bicycloannulation on a chiral ester derived from (1*R*,2*S*)-2-phenylcyclohexanol (*R*,*S*)-**314**.[136] After transesterification of the β-keto ester **309**, the resulting chiral compound was subjected to the Pd-catalyzed annulation conditions using $Pd(PPh_3)_4$ and 1,1,3,3-tetramethylguanidine as base in dioxane at room temperature to give tricyclic compound **315** in 75% yield. A diastereomeric excess of 92% was measured after the Wittig reaction, reduction of the ester, and transformation to the Mosher ester. This method constitutes a complementary competitive route to huperzine A, which can be industrially synthesized using either chiral ligands or chiral precursor.

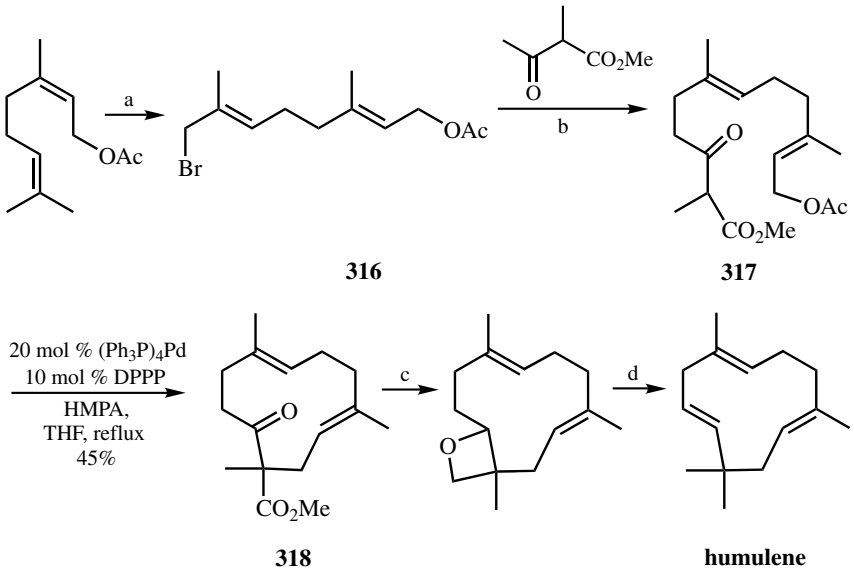
E. LARGE RING NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE COMPOUNDS

Naturally, macrocycles may conveniently be classified in macrolides, which incorporate a lactone moiety and carbocycles. Macrolides, a term initially reserved for the large ring lactone antibiotics isolated from *Streptomyces* organisms, present various structural types, with the polyoxo (erythromycin), polyene (tetrin), ionophoric, and the lactam-containing *ansa* (maytansine) macrolides. Other lactone-containing macrocycles are examplified by vermiculine and brefeldin A. Therapeutic use of some of these compounds attests to their importance. In the same way, large and especially medium ring carbocycles have been identified; among them, sesquiterpenes (caryophyllanes, humulanes), sesterterpenes (ophiobolins), and diterpenes (jatrophone) enjoy a large spectrum of activity. They have been employed as fragrances and have been implicated as potentially antitumor agents.

A general problem associated with the synthesis of macrocyclic natural products has been the efficient construction of medium or large rings, with the methodological approaches categorized into two types: ring expansion or contraction procedures and cyclization of bifunctional acyclic molecules. For a long time, few methods for the construction of medium and large ring compounds by carbon–carbon bond formation existed, which were sufficiently mild and efficient to allow general expansion to complex macrocyclic natural products. Therefore, the potential for application of Pd-catalyzed allylic alkylations to an intramolecular process appeared particularly interesting.

We present here some significant examples in cyclization using Pd-catalyzed allylation, in carbocycle and macrolide chemistry. Humulene, a fundamental monocyclic sesquiterpene, is derived biologically from farnesol by anti-Markownikov cyclization; no synthesis of this terpene by such cyclization had been realized before the highly stereoselective synthesis presented by Yamamoto and co-workers.[137] The acyclic sesquiterpene skeleton was constructed starting with geranyl acetate via the (*E*,*E*)-bromide **316**, which

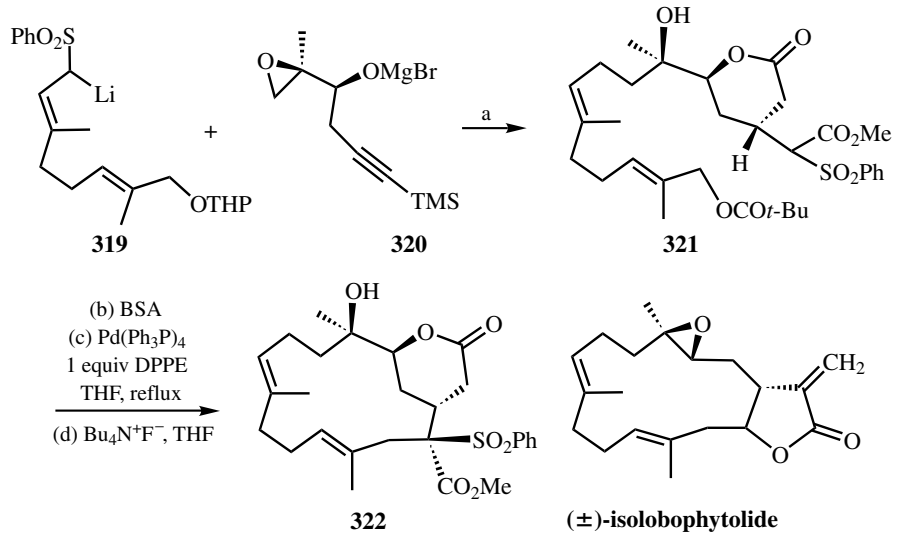
was obtained stereoselectively by a method previously reported. Reaction of **316** with the dianion derived from methyl α-methylacetoacetate gave the keto ester, which was then transformed into acetoxy ketone **317**, the key intermediate of the cyclization. The sodio derivative, generated by treatment with sodium hydride, was subjected to cyclization by addition to a mixture of $Pd(PPh_3)_4$, DPPP, and HMPA in THF. The crucial intermediate, **318**, obtained in 45% yield possessed both trisubstituted ethylenes needed to prepare humulene. The successful accomplishment of the remaining structural modifications, generation of the third double bond selectivity, is presented in **Scheme 80**. During this synthesis, a novel oxetane ring opening was described. The comparison of structural features of the synthetic product (12%) with natural humulene confirmed the structure.



(a) SeO_2; PBr_3; (b) Ac_2O; (c) LAH; TsCl; KO*t*-Bu; (d) $Et_2AlNMePh$; Me_2S-NCS-Et_3N then NH_2NHTs; LAH.

Scheme 80

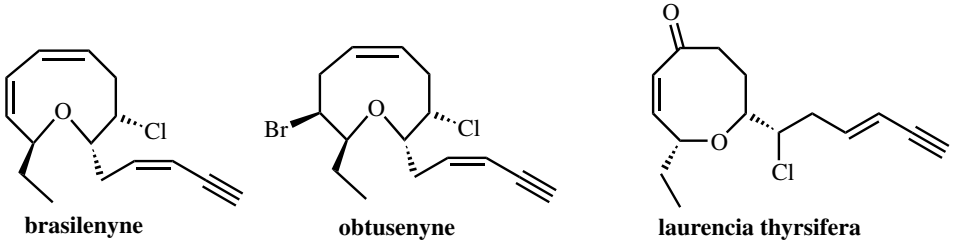
The cembrane diterpenes have emerged as a major class of natural products with widespread origin in both the plant and animal kingdoms. Cembranolides, components of Pacific soft corals, with their fused and bridged lactone structure have received only scant attention. The first total synthesis of racemic isolobophytolide,[138] a complex cembranolide natural product, was described from sulfone diol **321**, prepared via addition of the lithio sulfone **319** to the magnesio alkoxide **320**. Desulfonation, hydrolysis of the THP ether, followed by selective esterification with pivaloyl chloride yielded diol, which was protected as acetonide and carboxylated. Deprotection, partial hydrogenation, and treatment with PTSA led to pentanolide, which upon treatment with potassium methyl α-(phenylsulfonyl)acetate afforded the *trans* adduct **321** in high yield and excellent stereo-selectivity. Intramolecular allylation of the allylic pivalate was observed in the presence of $Pd(PPh_3)_4$ and DPPE in refluxing THF to give the cembranoid sulfonyl ester **322** as a single isomer in 50% yield. Desulfonation afforded lactone ester, which was transformed in several steps as shown in **Scheme 81** to racemic isolobophytolide, identical to the natural product.



(a) Na(Hg); MeOH, PTSA; Me_3CCOCl; $CH_3{=}C(OMe)Me$, $C_5H_5N^+OTs^-$; LDA, $ClCO_2Me$; MeOH, H_3O^+; H_2/Pd-$BaSO_4$; CSA; $PhSO_2CH_2CO_2Me$.

Scheme 81

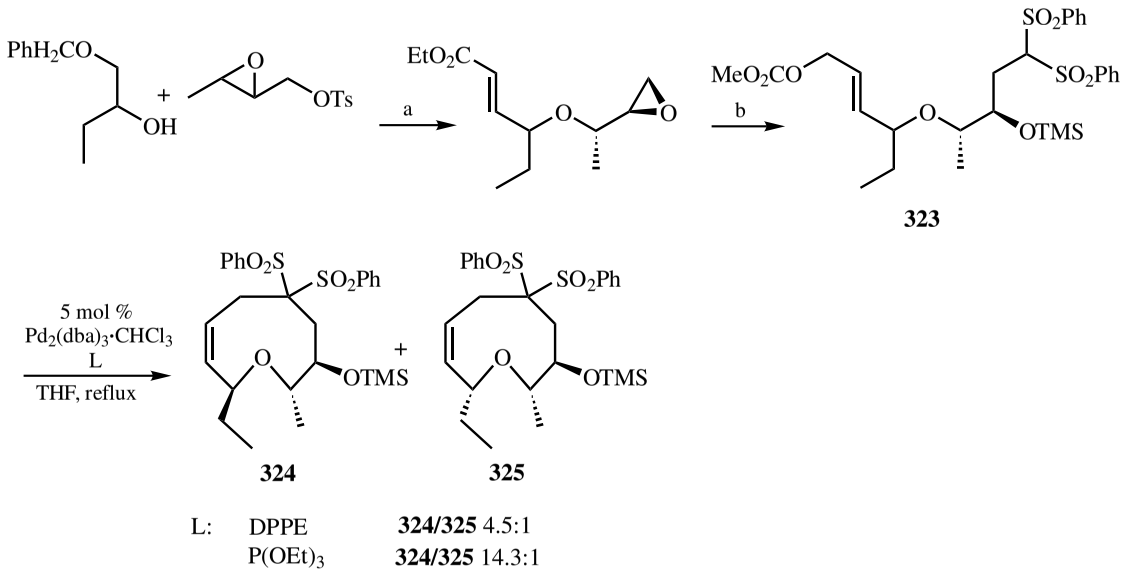
A similar approach was applied to the synthesis of a precursor[139] of brasilenyne or obtusenyne, nine-membered cyclic ethers of the genus *Laurencia*, isolated from marine sources (**Scheme 82**).



Scheme 82

A flexible route was developed. Commencing with racemic epoxy tosylate and mono-protected butane-1,2-diol, the synthesis of the precursor proceeded smoothly through several intermediates (**Scheme 83**) and finally yielded the desired acyclic precursor **323**. When compound **323** was added to a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ and DPPE or $P(OEt)_3$ ligand, the nine-membered rings **324** and **325** were formed in 71–88% overall yield. Stereocontrol of all three chiral centers has therefore been accomplished in the key steps.

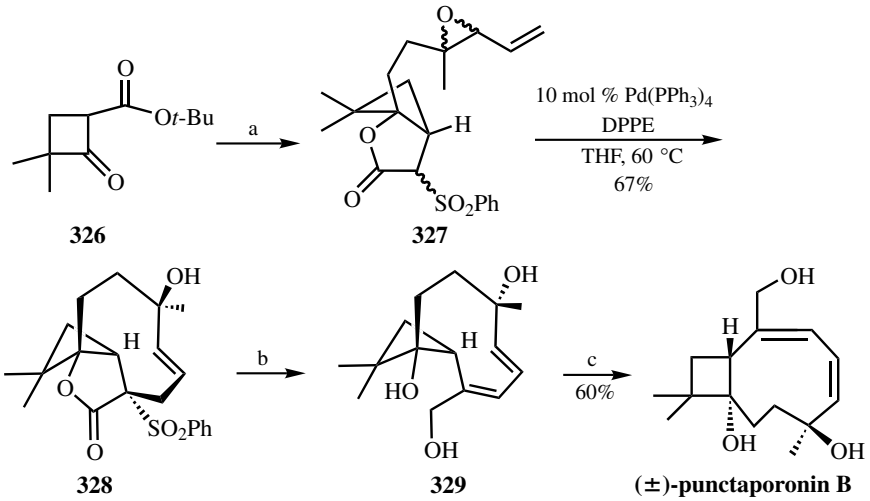
Among the family of terpenes, the 9,4-bicyclic terpenes, such as caryophyllene or punctaporonin B, have also received scant attention, except caryophyllene, synthesized by Corey. Punctaporonin B was isolated from extracts of the drug fungus *Poronia punctata*. Kende et al.[140] described the first total synthesis of racemic punctaporonin B by an efficient and potentially general strategy for the construction of such fused 9,4 systems. The construction of the key intermediate **327** from readily accessible cyclobutanone **326**



(a) $BF_3{\cdot}Et_2O$; Pd/C; K_2CO_3; $SO_3{\cdot}$py, DMSO then Et_3N; $(EtO)_2POCH_2CO_2Et$; (b) $(PhSO_2)_2CH_2$, *n*-BuLi; $BF_3{\cdot}Et_2O$; DIBAH; MeO_2CCl; BSA.

Scheme 83

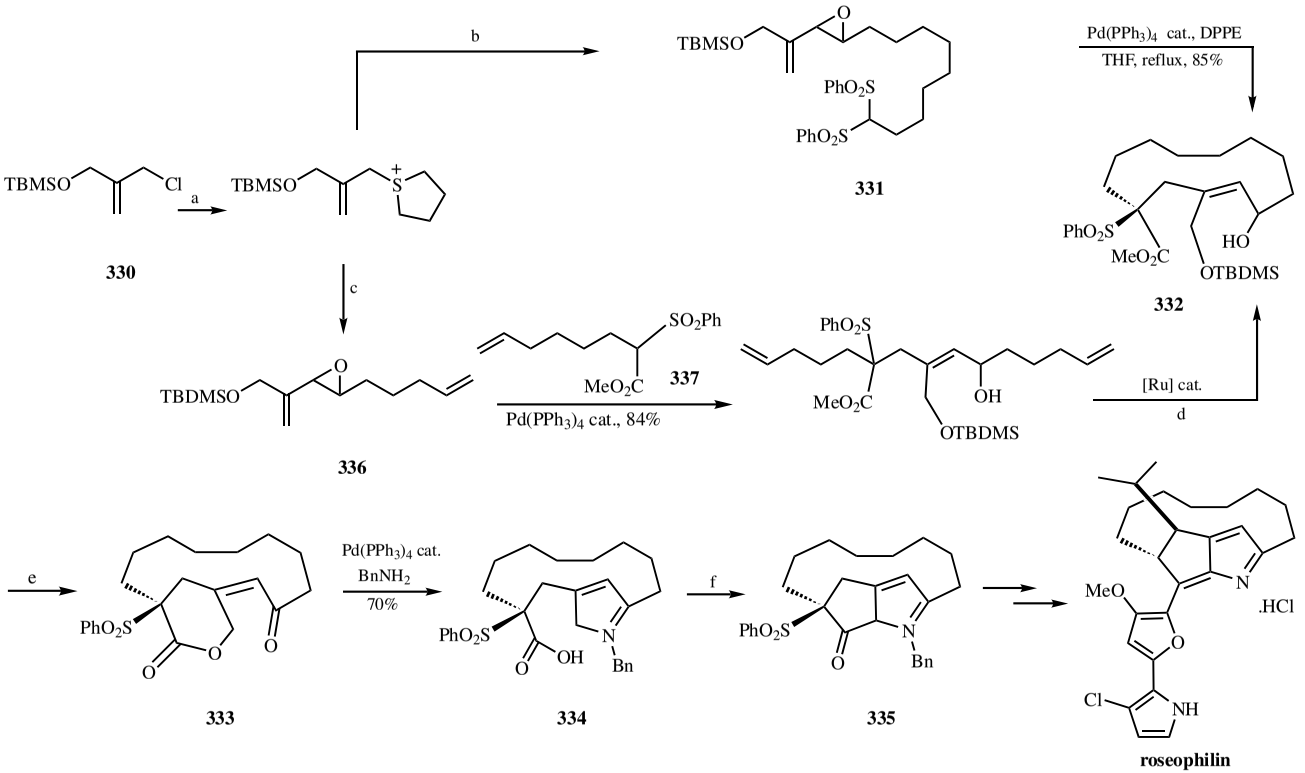
is summarized in **Scheme 84**. C-alkylation and subsequent decarbo-*tert*-butoxylation gave γ-keto ester. Addition of Grignard reagent followed by phenylselenation produced thioethers, which were directly oxidized to yield the diastereomeric mixture of the epoxy sulfones **327**. Intramolecular alkylation of vinyl epoxide was carried out with 10 mol % of $Pd(PPh_3)_4$ and 20 mol % DPPE in THF at 60 °C to afford a mixture of (*E*)-cyclononene alcohol epimers **328** in 67% yield. The reaction was regioselective and no trace of cycloheptene regioisomers could be observed. Generation of the second double bond gave the (*E*,*E*)-diene triol **329**, which was irradiated to yield 60% of racemic punctaporonin B.



(a) NaH, $BrCH_2CO_2Et$; PTSA; 3-methylhexa-3,5-dienylmagnesium bromide; LDA, PhSSPh; MCPBA, 24% (3 steps); (b) Na(Hg); LDA, $PhSO_2Ph$; LAH; Ac_2O, py; $NaIO_4$; KOMe, 16% (4 steps); (c) *hv*.

Scheme 84

Roseophilin, a novel antibiotic isolated from *Streptomyces griseoviridis*, possesses a topologically unique skeleton combining a rather strained macrocyclic entity with an extended heterocyclic chromophore and exhibits promising cytotoxic properties. Fürstner and Weintritt[141] reported the synthesis of the macrocyclic core based on a manifold of Pd-catalyzed reaction for the formation of *ansa*-bridged pyrroles, which proceeds via vinyl oxirane **331** and allyl lactone **333** as key intermediates. **Scheme 85** outlines the synthesis starting from the known protected alcohol **330**. The sequence provided gram amounts of the desired vinyl oxirane **331**, which cyclized smoothly to the 13-membered carbocyclic ring **332** in 85% yield when slowly added to a refluxing solution of $Pd(PPh_3)_4$ and DPPE in THF. Desilylation and subsequent oxidation provided ketone **333**. A second Pd-catalyzed reaction with benzylamine as nucleophile resulted in the formation of the desired pyrrole carboxylic acid **334**, which was converted into pyrrolophane **335**. The isopropyl substituent was installed in a stereoselective manner and the synthesis of the macrocyclic core has been achieved in 11 steps. Synthesis of the pyrrolylfuran side chain and addition to **335** thus complete the total synthesis of roseophilin.

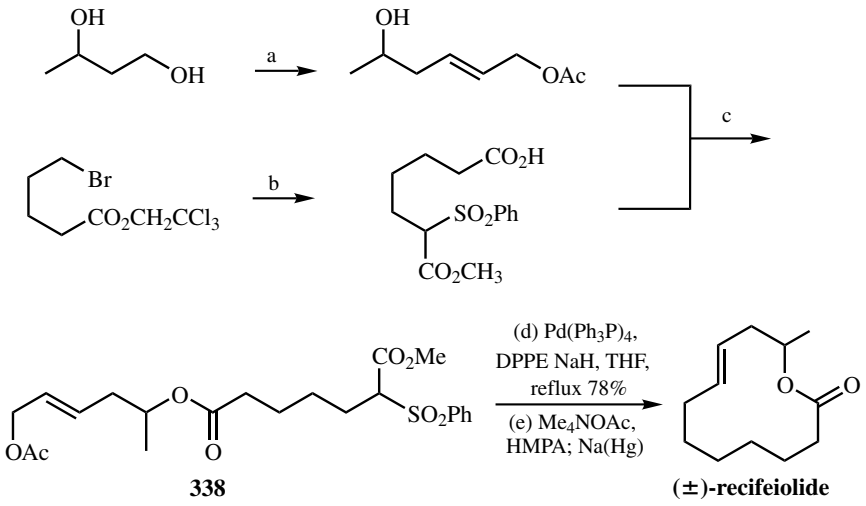


(a) NaI; tetrathiophene; $AgBF_4$; (b) *t*-BuLi, 2-bromononal; methyl(phenylsulfonyl)acetate, KH, 42% (3 steps); (c) 5-hexenal, *t*-BuLi; (d) $RhCl(PPh_3)_3$ cat.; (e) TBAF, NH_4F; Dess–Martin, 53% (2 steps); (f) α-chloroenamine, $SnCl_4$.

Scheme 85

The next year, Fürstner et al.[142] modified their strategy of the synthesis of the macrocycle **332** as is outlined in **Scheme 85**. The key steps of this approach consisted in a Pd(0)-catalyzed reaction of vinyl oxirane **336** with sulfone **337** and in a subsequent ring-closing metathesis reaction for the 13-membered compound **332**.

Trost and Verhoeven[143] have extensively studied the intramolecular reaction of stabilized anions with allylic acetates catalyzed by Pd(0) complexes. This reaction proceeded with high regioselectivity and was applied to the total syntheses of natural macrolides (±)-recifeiolide and (±)-phoracantholide. The synthesis of the 12-membered ring lactone recifeiolide, isolated from the fungus *Cephalosporium recifei*, is outlined in **Scheme 86**. 1,3-Butanediol and 2,2,2-trichloroethyl ester of 5-bromopentanoic acid were the starting materials. Conversion of the key intermediate **338** to the anion with sodium hydride and addition to a solution of 9 mol % palladium(0) catalyst produced only the 12-membered ring lactone. Decarbomethoxylation and reductive desulfonylation gave (±)-recifeiolide. Noteworthy was the complete retention of olefin geometry and exclusive cyclization at the less substituted position of the allyl moiety.



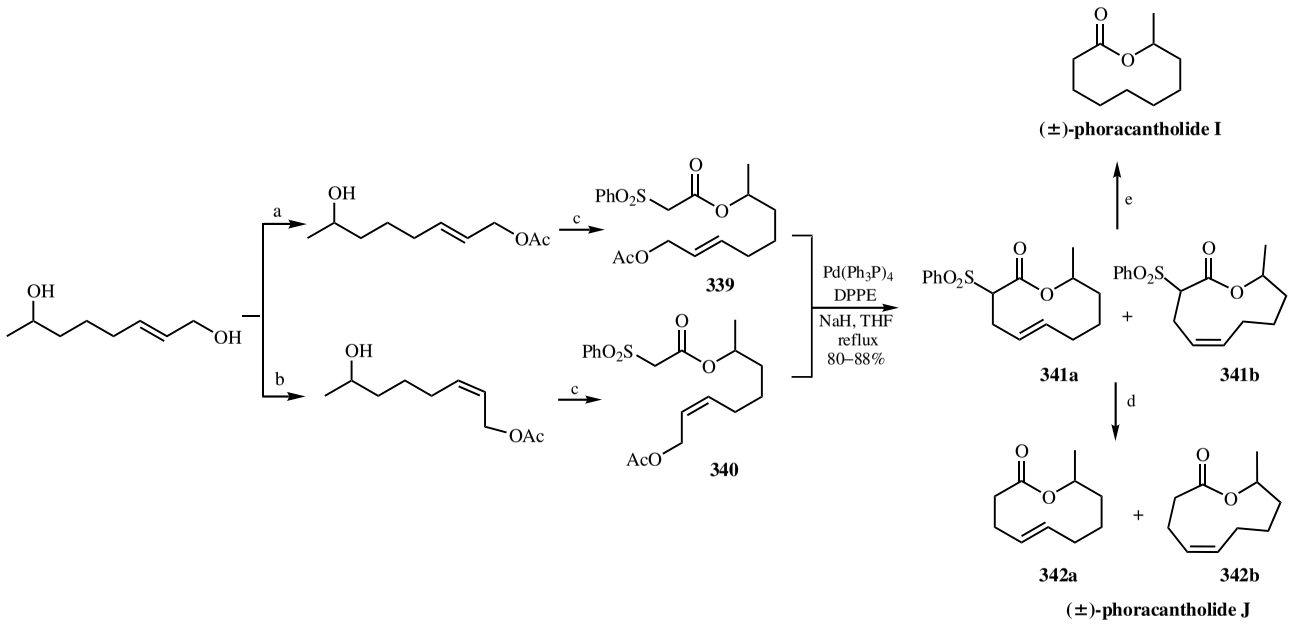
338 **(±)-recifeiolide**

(a) PhCOCl; TBDMSCl; NaOH; PCC; $(EtO)_2POCH_2CO_2Et$, NaH; DIBAH; CH_3COCl; $HClO_4$, 45% (8 steps); (b) $PhSO_2CH_2CO_2Et$, NaH; Zn, DMF; $SOCl_2$; (c) py.

Scheme 86

The same regioselectivity was observed in the synthesis of phoracantholide I and J, two 10-membered ring lactones isolated from the secretion of the eucalypt longicorn, *Phoracantha synonyma*. However, in contrast to the 12-membered ring case, substantial loss of olefin geometry accompanied these cyclizations as shown in **Scheme 87**. Noteworthy is the higher percentage of *Z* isomer (**342a/342b** = 65:35) obtained in cyclization of **340** in comparison to the reaction with **339** (**342a/342b** = 88:12). Compound **342** was identified as phoracantholide J. Catalytic hydrogenation of the mixture **341a/341b** followed by desulfonylation gave phoracantholide I as the sole product.

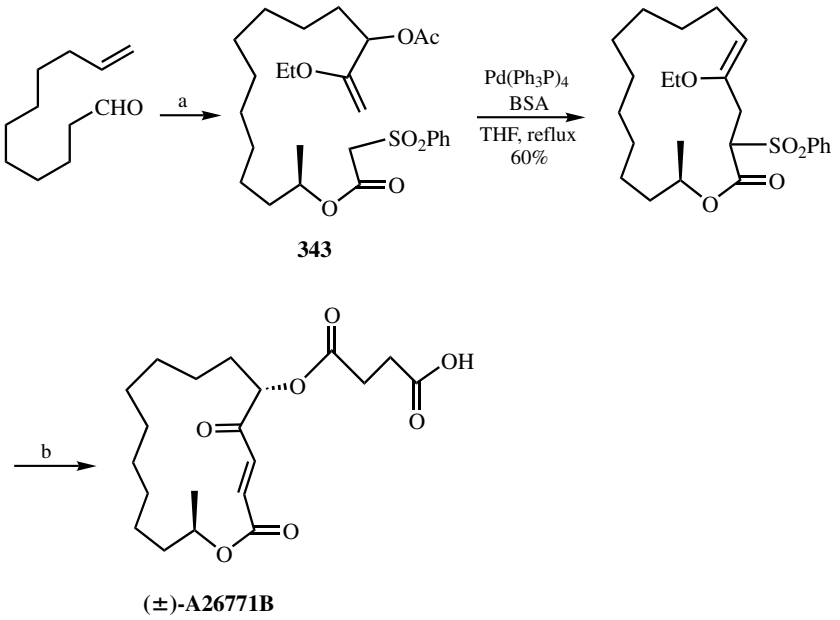
Antibiotic A26771B includes in its structure a 2-ene-1,4-dione functionality, present in the cytochalasins, a group of fungal metabolites. Trost and Brickner[144] reported a synthetic strategy for the construction of the macrocycle and simultaneously a creation of the



(a) Ac_2O, py; (b) TBDMSCl; MCPBA; $LiPPh_2$, MeLi; $HClO_4$; Ac_2O, py; (c) $PhSO_2CH_2CO_2H$, DEAD; (d) Na(Hg), 87–90%; (e) Pd-$CaCO_3/H_2$, then (d) 83%.

Scheme 87

functionalities. The macrocyclization employed a β-keto sulfone as an electrofugal group and a 2-ethoxyallyl acetate as a nucleophile group mediated by $Pd(PPh_3)_4$ and a bidentate ligand as DPPE or DPPP. **Scheme 88** outlines the straightforward synthesis of the key intermediate **343** in 40% overall yield from 10-undecenal. In the final stages, the benzenesulfonyl group served as a stereochemical control element, which directed the hydroxylation. The total synthesis of antibiotic A26771B was completed in 12 steps from 10-undecenal.

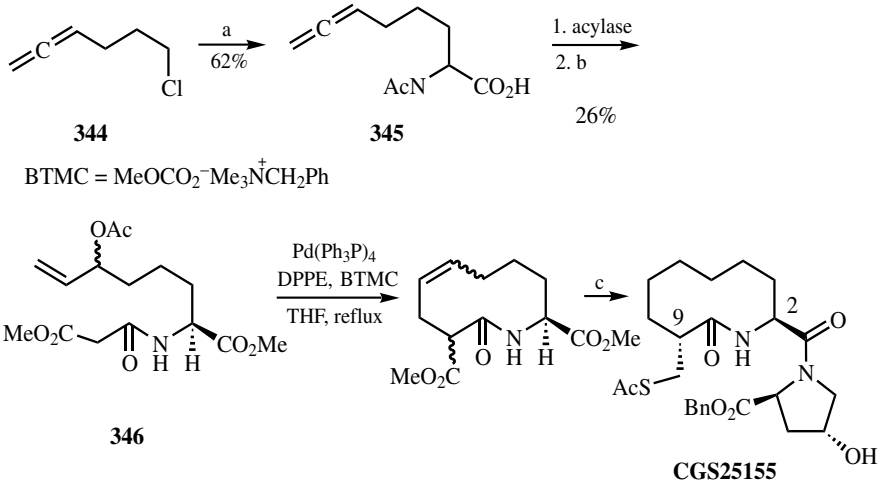


(a) MeMgI; TBDMSCl; disoamylborane then H_2O_2, NaOH; PCC; (1-ethoxyvinyl)lithium; Ac_2O, py; *n*-Bu_4F; $PhSO_2CO_2H$; (b) OsO_4, $NaHCO_3$; anhydride succinique, DMAP; -Bu_4NF.

Scheme 88

Macrolactamization via palladium π-allyl alkylation was developed in the synthesis of multigram quantities of CGS25155, a powerful inhibitor of neutral endopeptidase.[145] Allene **344** was transformed in functionalized allene **345**, which was resolved with Acylase I (*Aspergillus*). Esterification, amidification, and transformation of allene to allylic acetate afforded the key intermediate **346**. During the cyclization, much polymeric material was formed using previous conditions: $Pd(PPh_3)_4$ and DPPE or DPPP. However, using benzyltrimethylammonium carbonate (BTMC) as source of methoxide increased the crude yield. Synthesis of CGS25155 was completed by reduction, introduction of the methylene group at C-9 position, and the thioacetate and 4-hydroxy-*L*-proline benzyl ester units. CGS25155 was obtained in 4% overall yield and 97.3% diastereomeric purity (**Scheme 89**).

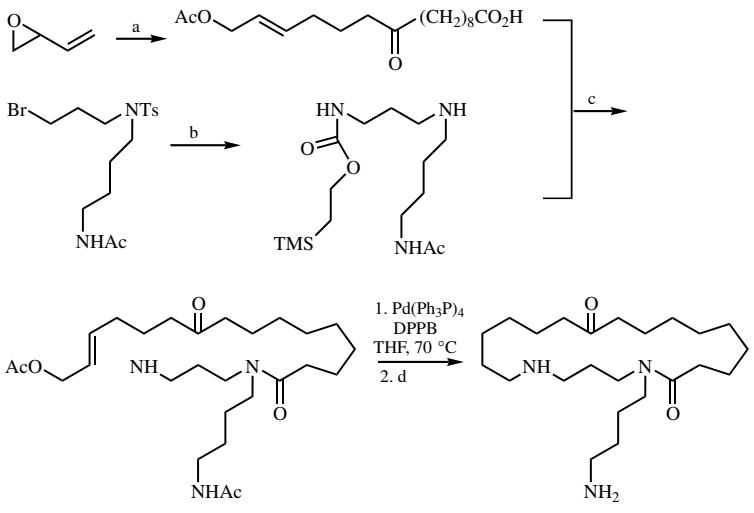
The Pd-mediated cyclization also provided a useful entry to macroheterocycles. Among these, macrocyclic amines derived from spermine and spermidine are particularly interesting because of their ionophoric properties. Thus, the synthesis of inandenin-12-one[146] was



(a) NaI; di-Et acetamidomalonate, KO-*tert*-amylate; KOH then citric acid; (b) $SOCl_2$, MeOH; MeO_2CCH_2COCl; NaOAc, AgOTf; (c) NaOH; Pd/C, H_2; HCl; $(CH_2O)_n$, piperidine; HCl; *trans*-4-hydroxy-*L*-proline benzyl ester HCl, HOBt; AcSH.

Scheme 89

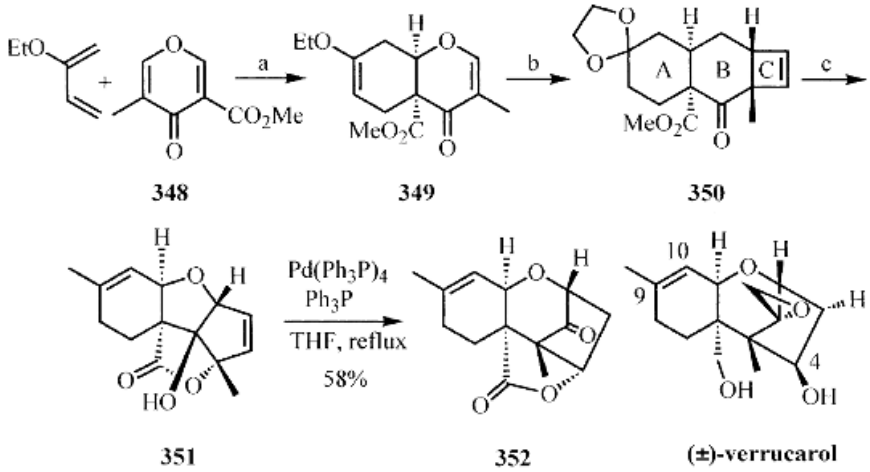
accomplished in 23% overall yield from butadiene monoepoxide and spermidine as outlined in **Scheme 90**. Subjecting **347** to a solution of 10 mol % $Pd(PPh_3)_4$ and 8 mol % DPPB, in THF at 70 °C, led to lactame in 80–89% yield. Hydrogenation and acidic methanolysis liberated pure inandenin-12-one.



(a) $CH_2(CO_2CH_3)_2$, $Pd(Ph_3P)_4$; DHP, PTSA; KOAc, Me_2SO, 140 °C; LAH; MsCl; NaI; *t*-BuLi, $CH_3(CH_2)_8CHO$; Me_2SO, $(COCl)_2$, Et_3N; Dowex 50-W-8NaOH, MeOH; Ac_2O, $NaHCO_3$; (b) NaN_3, EtOH; $HS(CH_2)_3SH$; $TMSCH_2CH_2OCOCl$, DMAP; Na, NH_3; (c) DCC, DMAP; (d) Pd/C, H_2; HCl, MeOH.

Scheme 90

Verrucarol belongs to the family of trichothecenes, a large family of sesquiterpenoid fungal metabolites. Some of them have pronounced physiological properties. Lactone **352**, an intermediate in the synthesis of (±)-verrucarol,[147] was prepared via a route that began from 3-carbomethoxy-5-methyl-4-oxo-2*H*-pyran **348**. Diels–Alder reaction of this pyrone with 2-ethoxybuta-1,3-diene gave the bicyclic adduct **349**, and a second annulation employing photoaddition of acetylene led to the cyclobutene **350**. The latter underwent an acid-catalyzed Cargill rearrangement to lactone **351**. Exposed to a catalytic quantity of $Pd(PPh_3)_4$ in the presence of excess PPh_3, the lactone **351** gave in good yield (58%) the isomeric lactone **352** via a π-allylpalladium complex. The lactone **352** was identical to that previously prepared by Trost in the course of his synthesis of (±)-verrucarol (**Scheme 91**).



(a) toluene, 200 °C, 50%; (b) $(HOCH_2)_2$; acetylene, *hv*, 42% (2 steps); (c) PTSA; MeMgBr; $POCl_3$, py, 34% (3 steps).

Scheme 91

F. CONCLUSION

This survey has shown the usefulness of Pd-catalyzed allylic alkylation in numerous syntheses. In many cases, the chemo-, regio-, and stereoselectivities of the Pd-mediated reactions have succeeded in building complex structures. Formation of carbon–carbon and carbon–heteroatom bonds has been realized under mild conditions and in the presence of a large variety of functional groups. Many strides have been made in the course of total synthesis. Enantioselectivity in the reactions, which was a challenge in the 1980s, has been widely exemplified and has led to outstanding results for the syntheses of natural products or biologically active compounds.

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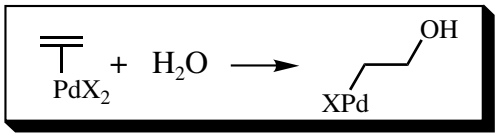

V. 3 Palladium-Catalyzed Reactions Involving Nucleophilic Attack on π-Ligands of Palladium–Alkene, Palladium–Alkyne, and Related Derivatives

V. 3. 1 The Wacker Oxidation and Related Intermolecular Reactions Involving Oxygen and Other Group 16 Atom Nucleophiles

V.3.1.1 The Wacker Oxidation and Related Asymmetric Syntheses

PATRICK M. HENRY

A. INTRODUCTION

The Wacker oxidation was discovered by Smidt and co-workers at Consortium für Electrochemie (a subsidiary of Wacker Chemie and Farbwerken Bayer).[1] It is actually a combination of known reactions and thus not a catalytic reaction in the strictest sense (**Scheme 1**). The first and most basic reaction, the oxidation of ethene in aqueous solution was first discovered by Phillips in 1894.[2] The precipitation of palladium metal from a palladium(II) chloride solution was used as a test for olefins. However, it was the discovery by Smidt and co-workers that the Pd(0) formed could be regenerated by cupric chloride that made the reaction a commercial success. The final step, the oxidation of CuCl to $CuCl_2$ is one of the fastest reactions in inorganic chemistry.[3] The three reactions add up to the simple air oxidation of ethene to ethanal. At one point over two billion pounds a year of ethanal was produced by the Wacker process. Presently, the Monsanto acetic acid process has largely replaced the Wacker procedure.[4]

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$$PdCl_4^{2-} + C_2H_4 + H_2O \rightarrow Pd(0) + CH_3CHO + 2\,HCl + 2\,Cl^-$$
$$Pd(0) + 2\,CuCl_2 + 2\,Cl^- \rightarrow 2\,CuCl + PdCl_4^{2-}$$
$$2\,CuCl + \frac{1}{2}O_2 + 2\,HCl \rightarrow 2\,CuCl_2 + H_2O$$
$$C_2H_4 + \frac{1}{2}O_2 \rightarrow CH_3CHO$$

Scheme 1

The Wacker process is important not only in its own right, but because it opened up the field of palladium catalytic chemistry, which proved to be very rich in potential industrial processes as well as new synthetic organic chemistry. The richness of this new chemistry is witnessed by this book.

A complete coverage of the older literature on the Wacker chemistry is not possible in the allotted space. This section will cite only earlier references necessary for an understanding of the Wacker mechanism. The reader is referred to a book by the author, which covers the literature up to about 1980.[5]

B. MECHANISM OF THE WACKER REACTION

B.i. Initial Studies and Proposed Mechanism

The Wacker reaction has been called a textbook example of a homogeneous transition-metal-catalyzed reaction since its mechanism has been studied in such detail. The kinetics are complicated. The rate expression exhibits a second order chloride inhibition and a first order proton inhibition (Eq. 1).[6]–[8]

$$-d[C_2H_4]/dt = k[PdCl_4^{2-}][C_2H_4]/[H^+][Cl^-]^2 \quad (1)$$

All workers agree the chloride squared inhibition results from the two rapid equilibria in **Scheme 2**, where the value of K_1 has been measured by fast reaction techniques.[6]

It is the proton inhibition that has sparked the controversy over the mechanism of the Wacker reaction. Fortunately, one obvious mechanism, anti attack of hydroxide on the olefin π-complex, $PdCl_2(C_2H_4)(H_2O)$, can be eliminated by kinetic considerations. Using measured values of K_1 and estimated minimum values of K_2, the rate of hydroxide attack can be shown to be faster than a diffusion-controlled process and thus clearly impossible.[6] The remaining possibilities, shown in **Scheme 3**, are anti attack of water in an equilibrium step or an acid–base equilibrium followed by syn attack of coordinated hydroxide in the rate-determining step.

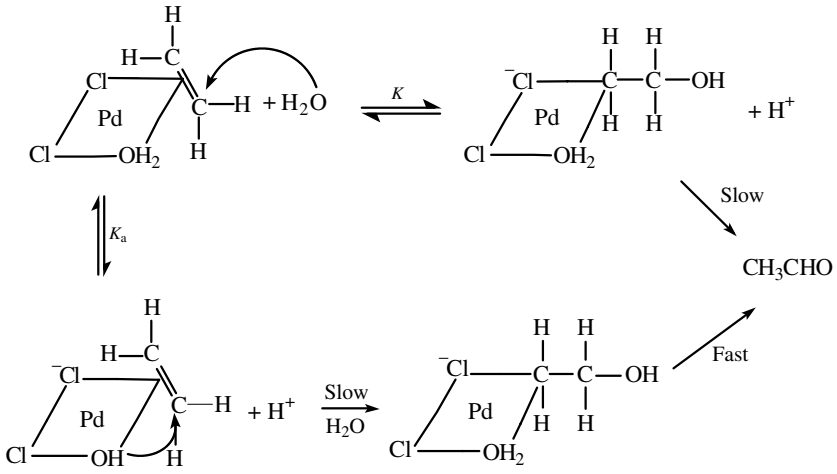
Original selection of syn hydroxide attack was based largely on comparison of kinetic and competitive deuterium isotope effects. If C_2D_4 is oxidized in H_2O, only CD_3CDO is formed. Likewise, if C_2H_4 is oxidized in D_2O, only CH_3CHO is formed. Thus, in the decomposition step, a C—H(D) bond is broken and reformed on the adjacent carbon. As shown in **Scheme 4**, the kinetic isotope effects were indeed small.[6]

Before any definite conclusions could be drawn concerning the rate-limiting step of the Wacker process, it was necessary to determine the actual isotope effects for the decomposition reaction. This was accomplished by competitive isotope effects using 1,2-dideuteroethene.[9]–[11] As shown in **Scheme 5**, the competitive isotope effect was approximately two.

$$PdCl_4^{2-} + C_2H_4 \overset{K_1}{\rightleftharpoons} PdCl_3(C_2H_4)^- + Cl^- \qquad 1/[Cl^-]\ \text{term}$$

$$PdCl_3(C_2H_4)^- + H_2O \overset{K_2}{\rightleftharpoons} PdCl_3(C_2H_4)(H_2O) + Cl^- \qquad 1/[Cl^-]\ \text{term}$$

Scheme 2



Scheme 3

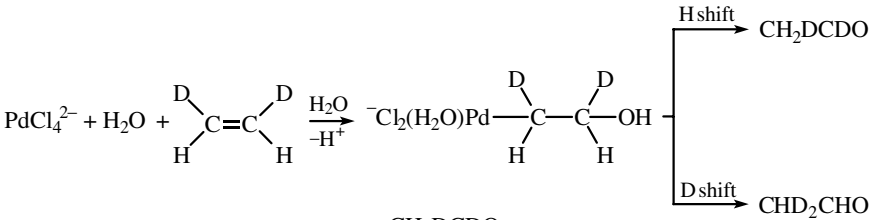
Kinetic isotope effect

$$C_2D_4 + PdCl_4^{2-} + H_2O \rightarrow CD_3CDO + Pd(0) + 2\,HCl + 2\,Cl^- \qquad k_D$$

$$C_2H_4 + PdCl_4^{2-} + H_2O \rightarrow CH_3CHO + Pd(0) + 2\,HCl + 2\,Cl^- \qquad k_H$$

k_H/k_D = kinetic isotope effect = 1.07

Scheme 4



$$\text{Competitive isotope effect} = k_H/k_D = \frac{CH_2DCDO}{CHD_2CHO} = \sim 1.9$$

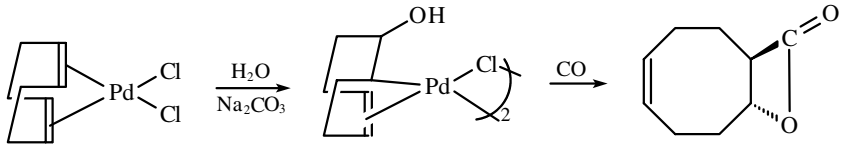
Scheme 5

The fact that the kinetic isotope effect is negligible while the competitive isotope effect is appreciable indicates the rate-determining step occurs *before* the decomposition step. This would seem to rule out the equilibrium anti hydroxypalladation mechanism, leaving the syn hydroxide insertion from the coordination sphere of Pd(II) as the only likely mechanism. Admittedly, the conclusion rested entirely on kinetic evidence. As aldehydes and ketones

were the products of the reaction, the author assumed that stereochemical studies could not be used to determine the mode of addition. This was a rather naive assumption since, as discussed next, such studies suggested that the addition was actually an anti process.

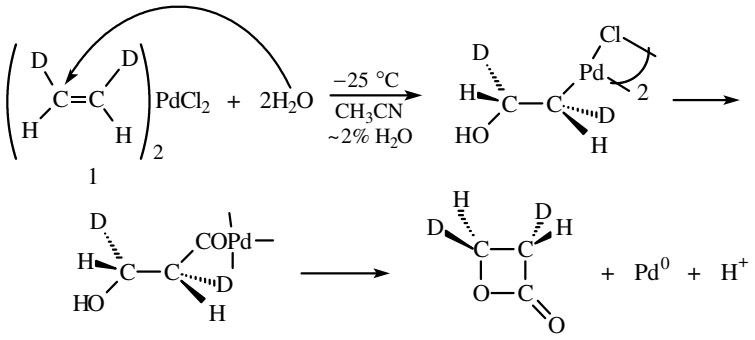
B.ii. Initial Stereochemistry Studies

The earlier stereochemical studies involved chelating diolefins such as 1,5-cyclooctadiene, which give stable oxypalladation adducts. These stable adducts were reacted with CO to give β-lactones whose stereochemistry can be determined.[12] As shown in **Scheme 6** the addition was always anti. However, it was realized that these chelating diolefins were quite different from acyclic olefins and not good model compounds since they occupied two coordination positions on Pd(II).



Scheme 6

Since the products with acyclic olefins are aldehydes and ketones, the reaction conditions must be altered to form saturated products whose stereochemistry can be determined. The basic assumption is that the *change in reaction conditions does not change the mode of addition.* The first study with a monoolefin, which is outlined in **Scheme 7**, used 1,2-dideuteroethene as substrate and CO to trap the intermediate to form a lactone whose stereochemistry could be determined.[13] This lactone could only have arisen from anti addition to the initial π-complex, **1**. Several facts concerning this study need to be emphasized. First, the solvent is CH_3CN rather than water, which could have a profound effect on mechanism. Second, in this system the Pd(II) almost certainly exists as dimers and it had been shown previously that dimeric species in wet acetic acid underwent anti hydroxypalladation.[14] Third, the system is chloride starved so $PdCl_4^{2-}$, which is reactive in water, cannot be formed. Finally, the reactive species is almost certainly not **1** but rather Pd(II)–carbonyls since CO bonds very strongly to Pd(II). The CO coordination

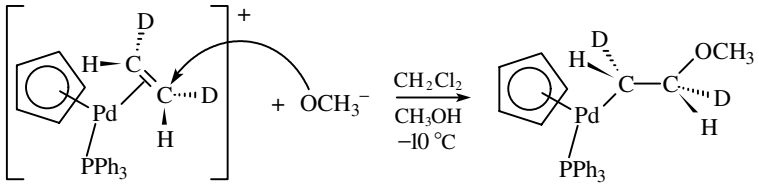


Scheme 7

would prevent coordination of water, which is required for syn addition. Whenever Pd(II) has strongly coordinating ligands it tends to add anti because the second coordination site necessary for syn addition is not available.

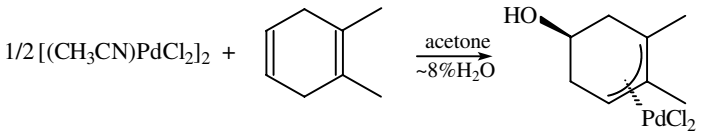
Similar studies were conducted in methanol solvent using *E*- and *Z*-2-butene. The configurations of the methyl-3-methoxy-2-methylbutanoates were consistent with anti addition. The comments above also apply to this system.[15]

It should also be emphasized that these same strongly complexing ligands also stabilize the oxypalladation adduct against decomposition to oxidation products because they prevent the open coordination site necessary for hydride shift from forming. Thus, the same factors that favor anti addition also favor stable oxypalladation adducts. An example is the addition of methoxide to a strongly coordinated Pd(II)–dideuteroethene π-complex shown in **Scheme 8**.[16]



Scheme 8

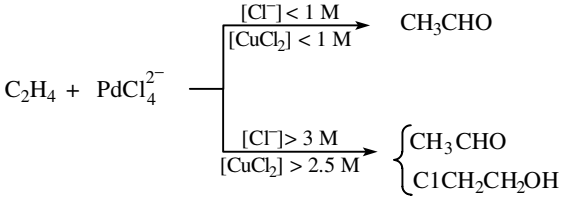
Another study used a novel approach involving a nonchelating diolefin, which forms a stable π-allyl complex upon hydroxypalladation.[17] As shown in **Scheme 9** the stereochemistry of the consistent complex was only with anti addition. Some of the objections applied to previous studies apply here. The solvent is not pure water and the system is chloride starved. However, an even more important objection applies in this example. Thus, as will be discussed in **Sect. C**, cyclohexene-type structures undergo anti hydroxypalladation even under the usual Wacker conditions. Thus, the cyclohexadiene is not a valid model for the acyclic olefins of interest.



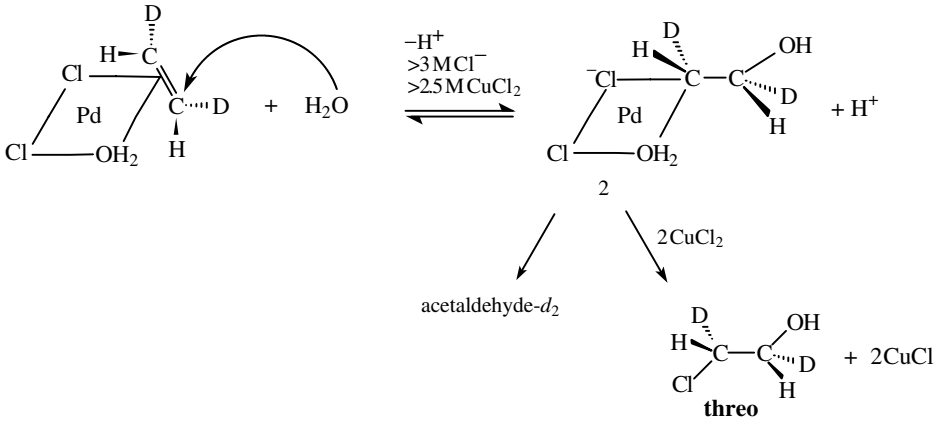
Scheme 9

However, a very convincing stereochemical study carried out in aqueous solution, the actual medium for the Wacker reaction, convinced many, including a number of textbook authors, that the stereochemistry of the Wacker process was anti.[18] These elegant studies proved to be essential to solving the complicated puzzle of the Wacker mechanism. Although the author does not agree with the original interpretation of the results, the study did establish that hydroxypalladation at high [Cl^-] was anti. This result is important in relation to studies discussed in **Sects. B.iii** and **B.iv**. As shown in **Scheme 10**, at low [Cl^-] ethene is oxidized only to ethanal, while at high [Cl^-] and [$CuCl_2$] a new product, 2-chloroethanol, appears. Bäckvall, Åkermark, and Ljunggren used this reaction to

define the stereochemistry of the hydroxypalladation for the reaction pathway leading to 2-chloroethanol and assumed the stereochemistry was the same for the reaction pathway leading to ethanal. They used specifically deuterium-labeled ethene and determined the stereochemistry of their product by microwave spectroscopy. **Scheme 11** outlines the postulated reaction sequence.



Scheme 10



Scheme 11

These results clearly indicate anti hydroxypalladation for the 2-chloroethanol pathway. Now the assumption must be made that the same intermediate that decomposes to acetaldehyde is the one intercepted by $CuCl_2$. This certainly seems like a reasonable assumption but it should be remembered that 2-chloroethanol requires not only high concentrations of $CuCl_2$, *but also high chloride concentrations (>3 M)*. If **Scheme 11** is correct it is not obvious why high [Cl^-] is required.

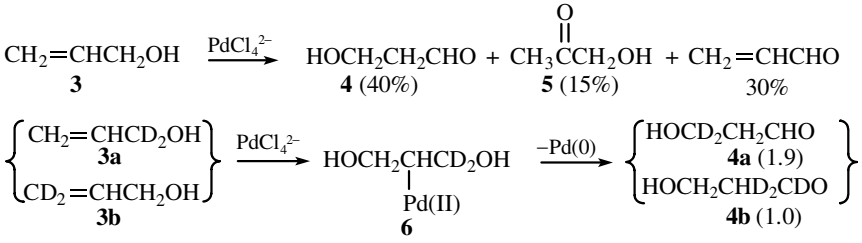
Bäckvall and co-workers explained the isotope effects discussed earlier by assuming that the rate-determining step for ethanal formation is loss of a chloride from **2**. The loss of chloride frees a coordination position required for hydride transfer, which initiates decomposition to ethanal. Thus, the decomposition step occurs after the rate-limiting step and a primary isotope effect would not be predicted.

B.iii. Recent Kinetic and Product Distribution Studies

Although the stereochemistry studies discussed above were not completely definitive, the doubt cast on the author's original suggestion of syn hydroxypalladation required further

mechanistic studies. From a kinetic standpoint the main difference between the two mechanisms shown in **Scheme 3** was the identity of the rate-determining step. What is needed for this determination is an olefinic substrate, which will undergo a measurable change if hydroxypalladation is an equilibrium reaction. The oxidation of deuteriated allyl alcohol was used for that purpose.

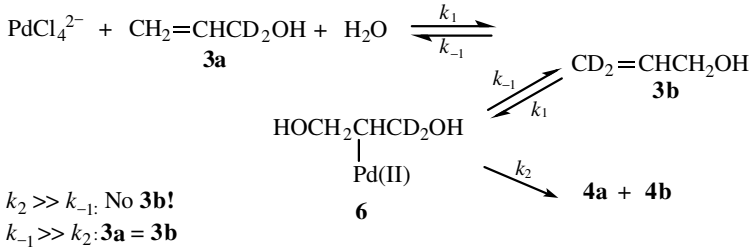
The oxidation of nondeuteriated allyl alcohol (**3**) under Wacker conditions gave a complicated reaction mixture because of side reactions.[19] The main products are shown in **Scheme 12**. The 2-hydroxypropanal (**4**) and hydroxyacetone (**5**) products arise from Wacker-type oxidation, while acrolein arises from direct hydride extraction from the alcohol carbon. As would be expected from the mechanism of the Wacker reaction, allyl-1,1-d_2 (**3a**) and allyl-3,3-d_2 (**3b**) alcohols gave the same hydroxypalladation adduct and thus the same distribution of deuteriated 2-hydroxypropanals, **4a** and **4b** (**Scheme 12**). The deuterium isotope effect, k_H/k_D = **4a**/**4b** = 1.9, has the same value found previously for oxidation of 1,2-ethene-d_2.[9]–[11]



Scheme 12

The oxidation obeyed the same rate expression (Eq. 1) as ethene and other acyclic olefins under Wacker conditions. This indicates allyl alcohol is oxidized by the same mechanism as other acyclic olefins.[20]

Now we are in a position to determine if hydroxypalladation is an equilibrium process as is required by the anti mechanism shown at the top of **Scheme 3**. The hydroxypalladation intermediate, **6**, can eliminate hydroxyl from either end of the molecule and, if hydroxypalladation is an equilibrium process, oxidation of either **3a** or **3b** should give a 1:1 mixture of the two after the reaction has proceeded to a small extent. The deuterated allyl alcohol, **3a**, was oxidized under Wacker conditions and the reaction stopped after one half-life and the unreacted allyl alcohol was analyzed for isomerization.[20] The reaction scheme is shown in **Scheme 13**. After one half-life the isomerization product **3b** was



Scheme 13

less than 3% of the total deuteriated allyl alcohol. Thus, the hydroxypalladation could not be an equilibrium process! This result corroborates the isotope results discussed previously, which indicated hydroxypalladation was the slow step of the reaction scheme.

The mystery becomes the reason for the anti stereochemistry observed at high chloride and cupric chloride concentrations, conditions for ethylene chlorohydrin formation. An examination of the early data of Stangl and Jira provide a clue.[21] Thus in **Table 1** the data indicate that the chlorohydrin is formed only when *both* $[CuCl_2]$ *and* $[Cl^-]$ concentrations are high.

The need for high $[Cl^-]$ suggests that chloride is stabilizing an intermediate so it does not decompose to ethanal but has a long enough lifetime to be intercepted by $CuCl_2$. To study this possibility, the reaction of deuteriated allyl alcohol was studied at high $[Cl^-]$.[22] Surprisingly, it was found that allyl alcohol did *not* undergo oxidation under these conditions but only underwent a Pd(II) catalyzed *isomerization* by a rate expression different from that for the oxidation under Wacker conditions. That rate expression given in Eq. 2 has only a single chloride inhibition and no proton inhibition.

$$-d[C_3H_6O]/dt = k[PdCl_4^{2-}][C_3H_6O]/[Cl^-] \tag{2}$$

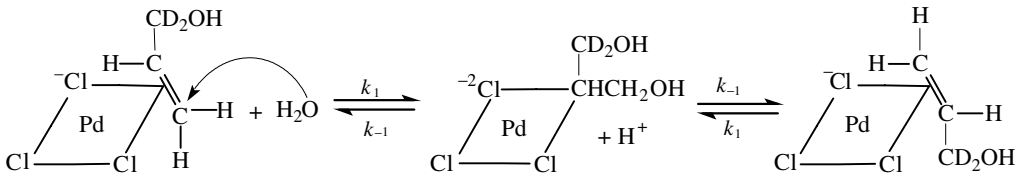
This rate expression is consistent with replacement of one chloride by allyl alcohol to give a π-complex followed by *anti* attack of water to give a hydroxypalladation adduct that can now reverse the steps to give isomerization. The reaction scheme is given in **Scheme 14**.

Thus, the anti attack and equilibrium hydroxypalladation postulated to occur at lower $[Cl^-]$ actually does occur at high chloride concentrations. In **Scheme 13**, for the oxidation of deuterated allyl alcohol at low chloride, the value of k_{-1} is not much greater than k_2. In fact, k_2 is so slow that it is not detected. At high $[Cl^-]$, k_{-1} is much greater than k_2. In regard to the overall mechanism, this means the reactions at high and low chlorides are quite different and proceed by two completely different routes. What is happening at high chloride is simply that the hydroxypalladation adduct, which is formed by an anti attack because there is not a second freely available coordination site on Pd(II) to coordinate water, is also stabilized against decomposition by hydride transfer because of this same lack of a vacant coordination site. Thus, once again, the factors that favor anti addition favor stability of the adduct.

The reason for the different stereochemistries at high and low $[Cl^-]$ now becomes crystal clear. *The intermediate hydroxypalladation adduct intercepted by cupric chloride was not* **2** *in* ***Scheme 11*** *but rather* **7** *in* ***Scheme 14***. The reason **7** is intercepted is the fact that it is stabilized against oxidative decomposition and thus has a long enough lifetime to react with cupric chloride to give 2-chloroethanol. Thus, the stereochemical studies of Bäckvall, Åkermark, and Ljunggren are very useful in defining the complete picture. Since **7** is formed by anti attack, the stereochemistry of hydroxypalladation to form 2-chloroethanol would be expected to be anti. It is only the assumption that the same intermediate gives both ethanal and 2-chloroethanol that is invalid.

TABLE 1. Ethylene Chlorohydrin Production

			Yields (in grams)	
$[PdCl_4^{2-}]$(M)	$[CuCl_2]$(M)	$[Cl^-]$(M)	CH_3CHO	$ClCH_2CH_2OH$
0.0164	4	0	1.26	0.06
0.0164	4	10	0.36	1.6

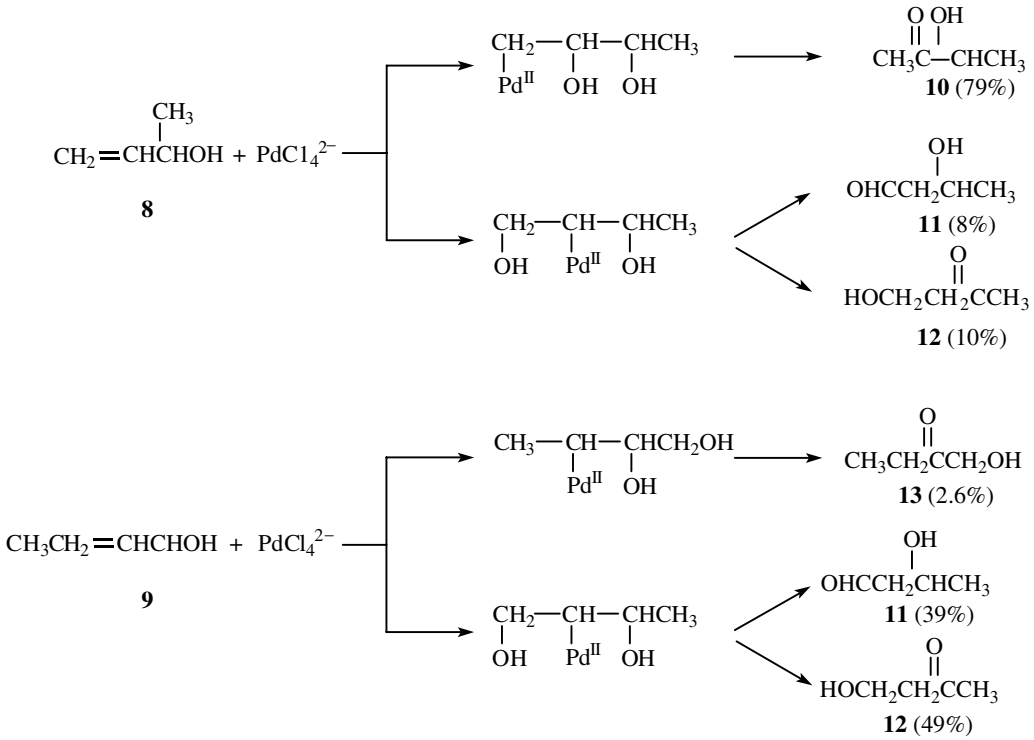


7

Scheme 14

At this point it became apparent that the use of the directing influence of the hydroxy group in allylic alcohols would allow further kinetic and stereochemical studies to finally settle the Wacker controversy. First a measure of the directing influence was needed. For this purpose the author initiated studies of the oxidation of several allylic alcohols (**Scheme 15**).

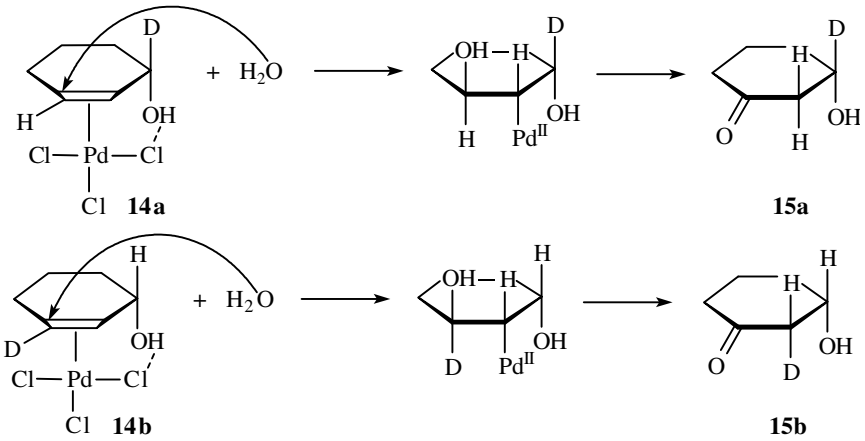
The first allylic alcohols studies were 3-buten-2-ol (**8**) and 2-buten-1-ol (**9**).[23] As shown in **Scheme 15**, **8** gave mainly **10**, which resulted from the Markovnikov type of hydroxypalladation. The ratio of **10** to the products, **11** and **12**, resulting from the non-Markovnikov addition was about 4:1. On the other hand, the products from the internal olefin, crotyl alcohol (**9**), were predominantly those (**11** and **12**) resulting from the hydroxypalladation, which put the palladium next to the alcohol function. The ratio of **11** + **12** to **13**, the non-Markovnikov product, was about 35:1.



Scheme 15

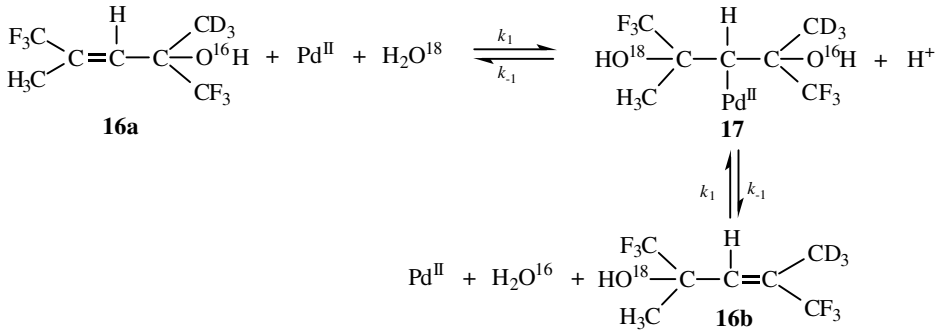
These results are consistent with the results of allyl alcohol oxidation (**Scheme 12**). Propene gives acetone as the major product (90%) and propanal as a minor product (~10%). With allyl alcohol the corresponding products are hydroxy acetone (**5**) and 2-hydroxypropanal (**4**) in a ratio of 1:2.7. Thus, the hydroxyl must be directing the palladium to mainly add to the central carbon to give the intermediate corresponding to **6**.

Studies of the oxidation of deuteriated 2-cyclohexenol provided some surprises.[24] First, the rate expression for oxidation was not the rate expression for Wacker oxidation of acyclic olefins. Rather, it was the same form (Eq. 2) as that observed for isomerization of deuteriated allyl alcohol at high [Cl^-]. Second, as shown in **Scheme 16**, the deuterium distributions from the two deuteriated isomers, **14a** and **14b**, are consistent only with anti addition if the hydroxyl group is directing the Pd(II) to the same side of the ring as the hydroxyl group.



Scheme 16

At this point the author tried a new approach to provide further evidence in the Wacker controversy. This approach involved the study of a very simple reaction whose rate-limiting step is hydroxypalladation. Such a "kinetic probe" is the exchange reactions of tetrasubstituted allylic alcohols, which cannot undergo oxidation. This would give us a very simple reaction where the rate-determining step must be hydroxypalladation. Thus, consider **Scheme 17**, where the CF_3 groups are incorporated for hydrolytic stability in aqueous acid solution.



Scheme 17

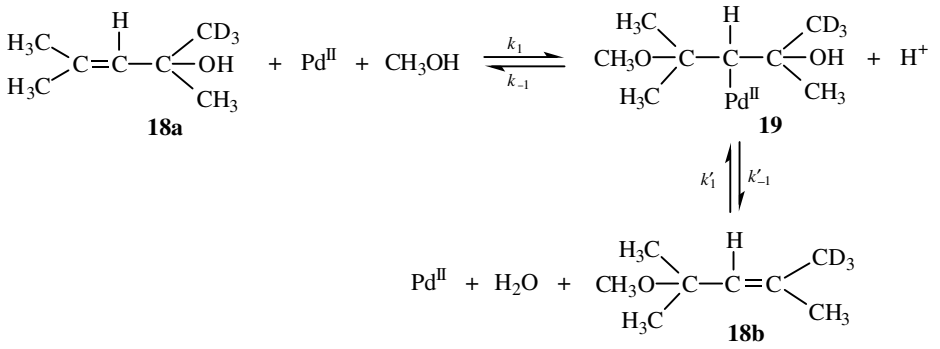
The rate-determining step for ^{18}O exchange or isomerization must be hydroxypalladation, since once **16a** undergoes hydroxypalladation, it cannot be oxidized. All it can do is dehydroxypalladate, which results in exchange or isomerization half the time **17** is formed since **17** is chemically symmetrical and the rates of reversal to **16a** and **16b** are the same. Thus the rate = $\frac{1}{2}k_1$. Now consider the anti equilibrium hydroxypalladation mechanism suggested for the Wacker reaction. If the proton inhibition results from this equilibrium it would not show up in the exchange rate expression and the rate expression for exchange would be (AA = allylic alcohol in Eq. 3)

$$\text{rate} = k[PdCl_4^{2-}][AA]/[Cl^-]^2 \tag{3}$$

When the kinetics of isomerization and exchange of **16a** were measured, it was found that the rate expression had a proton inhibition term and was identical to the Wacker rate expression.[25] This result means the proton inhibition term has to result from an equilibrium that occurs before the hydroxypalladation step, which is consistent with the syn addition mechanism shown in **Scheme 3**.

As expected from the earlier results with allyl alcohol (**Scheme 14**), the rate expression for ^{18}O exchange or isomerization at high [Cl^-] was given by Eq. 2.[26]

For purposes of the stereochemical studies described in the next section, it is important to show that the oxidation in methanol proceeds by the same mechanism as in aqueous solution. Earlier experiments indicate the two solvents have similar mechanisms for Wacker-type oxidation. The oxidation of ethene to the corresponding acetal obeys Eq. 1, the Wacker rate expression.[27] Experiments analogous to those pictured in **Scheme 17** were conducted using the dimethylpentenol, **18**, shown in **Scheme 18**. In methanol solvent the trifluoromethyl groups were not required for hydrolytic stability. At low [Cl^-] the rate expression was analogous to the Wacker expression, Eq. 1, while at high [Cl^-] the rate expression was analogous to Eq. 2, the rate expression for nonoxidative isomerization of allyl alcohol.[28]



Scheme 18

Olefins, which are capable of undergoing Wacker-type oxidation, were also studied under the conditions of high and low chloride. As expected, oxidation, whose kinetics obeyed Eq. 1, occurred at low [Cl^-] while exchange, whose kinetics obeyed Eq. 2, occurred at high [Cl^-]. The reaction schemes for allyl alcohol, **3**, and the trisubstituted

allyl alcohol, **21**, is shown in **Scheme 19**. It is noteworthy that the only oxidation product observed is **20**. The Markovnikov mode of addition, which would produce hydroxyacetone ketal, does not occur. Thus, the directing influence of the hydroxyl group is stronger in methanol than in water. This is not surprising since methanol has a lower dielectric constant than water and is a poorer solvating solvent, so the directing influence of the O—H···Cl—Pd hydrogen bonding interaction might be expected to be stronger in methanol than in water.

Low [Cl⁻] (<1.0 M): rate = $k[PdCl_4^{2-}][olefin]/[H^+][Cl^-]^2$

$$\underset{\mathbf{3}}{CH_2{=}CHCH_2OH} \xrightarrow[CH_3OH]{PdCl_4^{2-}} \underset{\mathbf{20}}{CH_3OCH_2CH_2CH{=}O}$$

$$\underset{\mathbf{21}}{(CH_3)_2C{=}CHCH(CH_3)OH} \xrightarrow[CH_3OH]{PdCl_4^{2-}} CH_3O(CH_3)_2CCH_2C(CH_3){=}O$$

High [Cl⁻] (>2.0 M): rate = $k[PdCl_4^{2-}][olefin]/[Cl^-]$

$$\underset{\mathbf{3}}{CH_2{=}CHCH_2OH} \xrightarrow[CH_3OH]{PdCl_4^{2-}} CH_3OCH_2CH{=}CH_2$$

$$\underset{\mathbf{21}}{(CH_3)_2C{=}CHCH(CH_3)OH} \xrightarrow[CH_3OH]{PdCl_4^{2-}} CH_3O(CH_3)_2C{=}CHCH_3$$

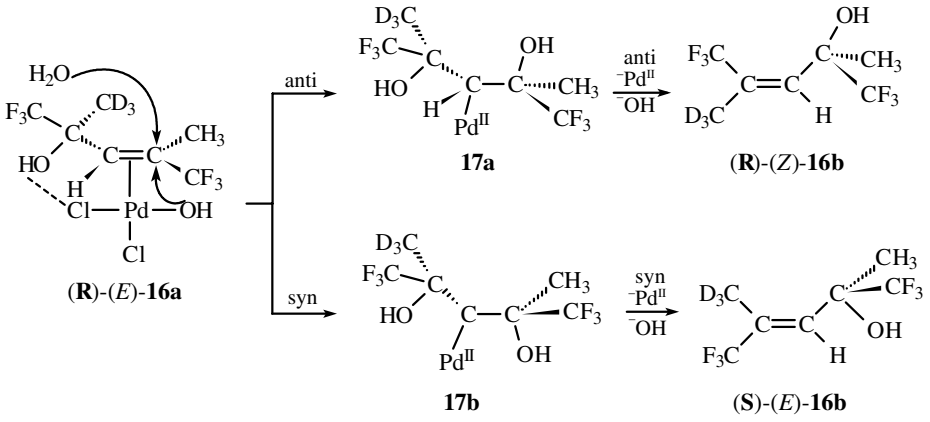
Scheme 19

B.iv. Recent Stereochemical Studies

At this point it became evident that the kinetic approach had been exhausted. The final answer to the Wacker controversy required a means of determining stereochemistry of hydroxypalladation under Wacker conditions and under high chloride conditions. Chirality transfer, which relies on the directing influence of the hydroxyl group, provides just such a technique. The directing influence of the hydroxyl group has been demonstrated by the studies described in the previous section and has been observed in a number of reactions including Pd(II)-catalyzed reactions.[29] Initial studies used one chiral isomer of the substrate **16a** in **Scheme 17**. As shown in **Scheme 20** the most stable rotamer of (***R***)-(*E*)-**16a** is the one in which the CF_3 and OH groups are as far away from the CH_3 group as possible. The face to which the Pd(II) is directed will depend on the absolute configuration of the starting alcohol. The absolute configuration of the product will depend on the geometry of the olefin as well as the factors mentioned above.

As discussed previously, the kinetics of the isomerization obeyed Eq. 1 under Wacker oxidation conditions. The reaction was stopped at various times and the reaction mixture analyzed for the degree of isomerization and the distribution of optical isomers. It was found that the isomerized product consisted entirely of the (***S***)-(*Z*)-**16b** isomer when (***R***)-(*E*)-**16a** was the starting material.[25] When (***S***)-(*E*)-**16a** was the starting material (***R***)-(*E*)-**16b** was the product. *Thus, under Wacker conditions, hydroxypalladation is clearly a syn process.*

On the other hand, the same experiment carried out at $[Cl^-] > 2.5$ M gave a somewhat different result. The rate expression obeyed Eq. 2 and the (***R***)-(*Z*)-**16b** isomer was formed when (***R***)-(*E*)-**16a** was the starting material.[26] Thus, the stereochemistry of addition at high chloride is anti. *The only possible conclusion is that the stereochemistries of hydroxypalladation at high and low [Cl⁻] are different and the extrapolation from high to*



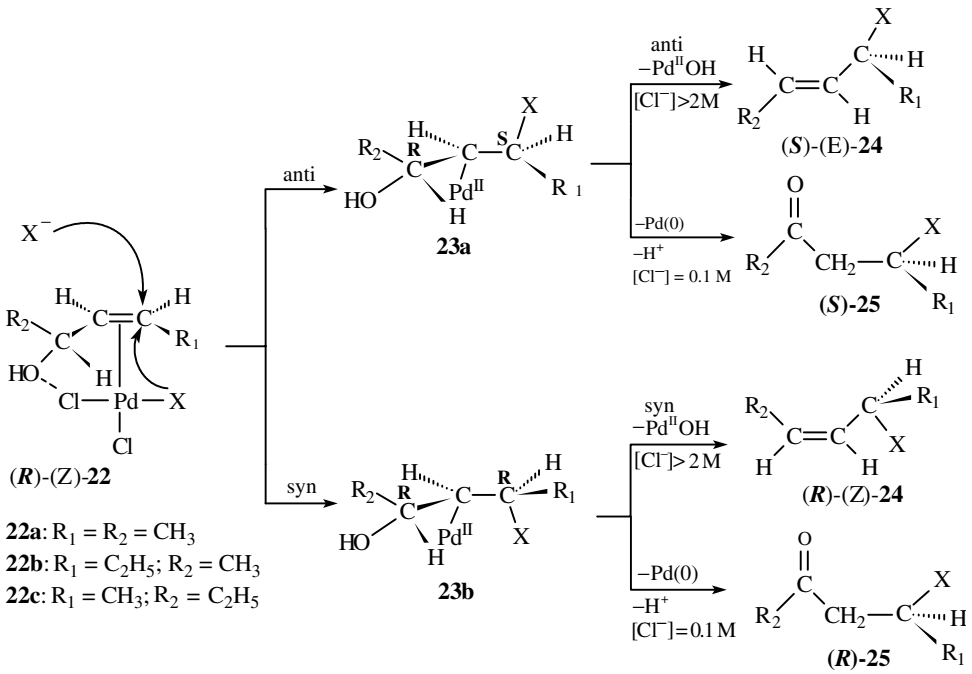
Scheme 20

low chloride is invalid. Note that the determination of absolute configurations is not required for these studies. All that is important is the fact a given optical isomer gives different enantiomers at low and high chloride concentrations, indicating the modes of addition are different under these two sets of conditions. The stereochemical results of Bäckvall and co-workers show that addition is anti at high [Cl^-],[18] so addition must be syn at low [Cl^-].

Although the results of the studies are compelling, they are not completely satisfactory because these tetrasubstituted allylic alcohols are not typical substrates for Wacker oxidations. A study using substrates that can be oxidized at low chloride and still undergo nonoxidative isomerization at high chloride would be much more convincing. Also, a demonstration that a nucleophile that can only add syn gives the same enantiomer at high and low chloride concentrations would enforce the mechanistic arguments. Fortunately, a set of substrates, whose absolute configurations as well as those of the products are known, or can readily be determined, are available.

The complete reaction sequence is shown in **Scheme 21**. The important point is that one type of addition will give **23a** or **23b**, which will decompose to oxidation and isomerization products with the same absolute configuration. To test this assumption, a nucleophile whose mode of addition is known and is the same at both high and low chloride concentrations is required. Phenyl is such a nucleophile (Heck reaction). This nucleophile was chosen because, being a carbanoid species, it can only exist in hydroxylic solvents bonded to Pd(II). For that reason it must add syn under all experimental conditions and syn addition has been demonstrated for this nucleophile.[30],[31] For reasons of solubility, methanol was employed as solvent. As discussed previously, methanol behaves in the same fashion as water in Wacker chemistry. In fact, at low [Cl^-], (***R***)-(*Z*)-**22a** reacted to form (***R***)-**25** (X = Ph), while at high [Cl^-], (***S***)-(*Z*)-**22a** produced (***S***)-(*Z*)-**24a** (X = Ph).[32] This result is consistent with syn addition to the most stable π-complex at both high and low chloride concentrations.

Next, attention was turned to the stereochemistry of addition of hydroxide.[32] At [Cl^-] = 0.1 M, (***R***)-(*Z*)-**22b** was oxidized to (***R***)-**25** (X = OH). At [Cl^-] = 2 M, (***R***)-(*Z*)-**22c** was isomerized to (***R***)-(*Z*)-**24b** (X = OH: identical to **22b**). *These results are only consistent with syn addition to the most stable π-complex at low [Cl^-] and anti addition of water to the most stable π-complex at high [Cl^-].*



Scheme 21

Finally, the stereochemistries of addition were studied in methanol solvent to confirm the similar behavior of water and this solvent. At $[Cl^-] = 0.1$ M, (***R***)-(*Z*)-**22a** was oxidized to (***R***)-**25** (X = OCH_3). At $[Cl^-] = 2.5$ M, (***S***)-(*Z*)-**22a** produced (***R***)-(*Z*)-**24a** (X = OCH_3). Thus, the stereochemical results were analogous to those in water: syn addition at low $[Cl^-]$ and anti addition at high $[Cl^-]$.

The reaction sequence shown in **Scheme 21** provides a tool for determining the stereochemistry of addition of a number of nucleophiles. One initial study provided some surprises. In the chloride-free as well as the chloride-containing system in acetic acid, previous kinetic studies had suggested anti addition. However, stereochemical studies using chiral **22a** as reactant indicated syn addition in both systems.[33] Furthermore, the addition of LiCl to the chloride-containing system completely reversed the addition to anti. These two reactions require further study.

C. EFFECT OF NEUTRAL LIGANDS ON REACTIVITY

Mechanistic studies are most valuable when they predict conditions that will result in a useful change in the reaction pathway. The studies described in the previous section permit just such a prediction. The intermediate **7** in **Scheme 14** is stabilized against oxidative decomposition because the high chloride concentration prevents the release of a chloride to open a labile coordination site for hydride transfer, which initiates decomposition to Wacker-type products. Consider the effect of adding a neutral ligand to the coordination sphere of Pd(II). The charge on **7** is −2. Addition of a neutral ligand would change this charge to −1. A chloride would dissociate much more readily from the −2 intermediate than from an

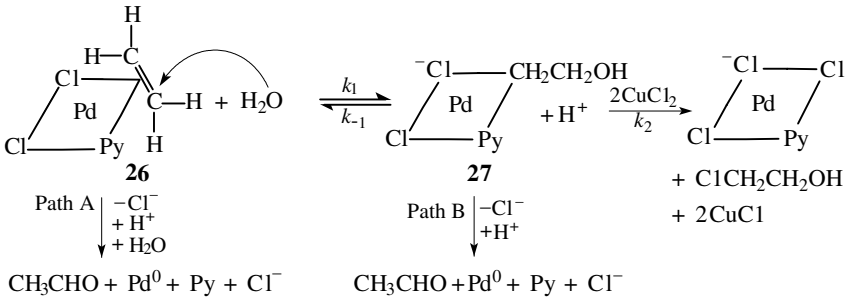
TABLE 2. Product Distributions for the Oxidation of Ethene with $PdCl_3(Py)^-$ in the Presence of $CuCl_2$[a]

$[CuCl_2]$	% Acetaldehyde[b]	% 2-Chloroethanol[b]
1.0	100.0	0.0
4.0	52.8	47.2
6.0	17.0	83.0
8.0	2.0	98.0

[a]Conditions: $[Cl^-] = 0.2$ M, $[H^+] = 0.4$ M, $[Pd(II)] = 0.082$ M, $T = 25$ °C. All runs were carried out under 1 atm of ethylene pressure.
[b]Determined by ^1H NMR.

intermediate with a -1 charge. Thus, addition of a neutral ligand might extend the range under which nonoxidative isomerization occurs to lower $[Cl^-]$. By stabilizing the hydroxypalladation adduct it might also extend the range for chlorohydrin formation.

The studies were conducted using a catalyst with pyridine as the neutral ligand.[34] The results with $PdCl_3(pyridine)^-$ were dramatic. The rate expression for oxidation of ethene to ethanal was of the form of Eq. 1. *However, the value of the rate constant was decreased by a factor of 750.* Even more exciting was the effect on the chlorohydrin reaction. As shown in **Table 2**, at chloride concentrations as low as 0.2 M, the chlorohydrin became the major product from ethene oxidation at cupric chloride concentrations above 4 M. This new procedure for preparing chlorohydrins from olefins under conditions of low chloride concentrations led to the new asymmetric chlorohydrin syntheses discussed in the next section. As discussed above, the kinetics of isomerization of **16a** (**Scheme 17**) with $PdCl_4^{2-}$ obeyed the Wacker kinetics (Eq. 1). On the other hand, **16a** obeyed the exchange kinetics at high $[Cl^-]$ (Eq. 2). Thus, for $PdCl_3(Py)^-$ the hydroxypalladation step is an equilibrium at low $[Cl^-]$. Stereochemical studies were conducted using the enantiomers of the trisubstituted allyl alcohol, (*E*)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol.[35] As with the allyl alcohols in **Scheme 21**, this olefin can undergo both oxidation and exchange. At $[Cl^-] > 0.2$ M, only exchange was observed with the $PdCl_3(Py)^-$ catalyst. The stereochemical results were consistent only with anti attack of water as would be expected from the kinetics. At $[Cl^-] = 0.05$ M appreciable oxidation occurred along with isomerization. The configuration of the oxidation product was not one enantiomer as was observed for the oxidation with $PdCl_4^{2-}$. Rather, the ketone product contained both isomers, indicating both anti and syn additions were occurring. The reaction sequence, which explains these observations, is shown in **Scheme 22** using ethene as substrate for simplicity.

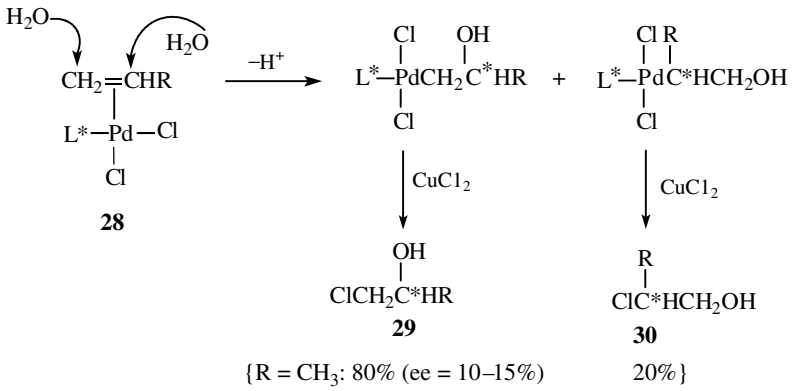


Scheme 22

The original π-complex, **26**, can undergo the oxidation reaction by the Wacker mechanism given in the bottom portion of **Scheme 3** (**Path A**) but most of the time it undergoes anti attack by water to produce **27**. The intermediate, **27**, in the absence of $CuCl_2$, reverts to **27** most of the time at chloride concentrations greater than 0.05 M. However, at chloride concentrations ≤ 0.05 M, decomposition to ethanal occurs some of the time by **Path B**. *Thus, the anti addition mechanism, depicted in the upper part of* ***Scheme 3****, invoked to explain the stereochemical results at high* [Cl^-], *is actually operative to some extent with* $PdCl_3(Py)^-$.

D. ASYMMETRIC CHLOROHYDRIN SYNTHESIS

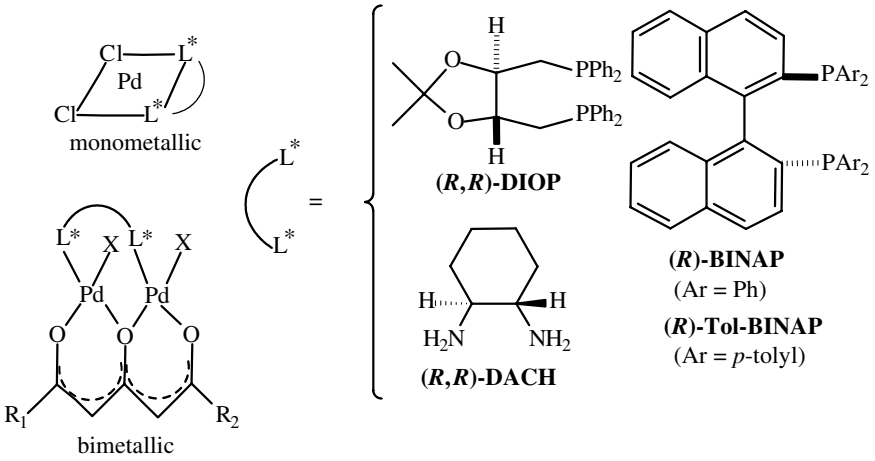
The studies described in the last section provided the background for the development of a new asymmetric chlorohydrin synthesis. If the neutral ligand that encourages chlorohydrin formation is made chiral, there is the possibility of forming chiral chlorohydrins. First, pyridine was replaced with chiral monodentate ligands such as (*S*)-(−)-*N*, *N*-dimethyl-1-phenethylamine.[36],[37] **Scheme 23** shows the general reaction sequence. As might be expected the enantioselectivities were low; 10–15% for propene. The Wacker oxidation product, acetone, was a side product in the reaction.



Scheme 23

Scheme 23 also outlines a potential problem with the syjnthesis. The initial attack can occur at either end of the double bond of the π-complex, **28**, to give the two isomers **29** and **30** in a ratio of 4:1. These two isomers are expected from Wacker chemistry since propene produces both acetone and propanal in about the same ratio from the two modes of addition. However, as shall be discussed below, this is not a serious problem with most α-olefins. The same catalyst oxidizes methyl vinylketone only to 4-chloro-3-hydroxy-2-butanone (**29**; R = C(═O)CH_3). The optical purity was still only about 12%.

Chiral bidentate ligands should both increase the enantioselectivity and increase the selectivity toward chlorohydrin as opposed to Wacker carbonyl products. This was found to be the case and the remainder of the studies used this type of catalyst. The catalysts consisted of two general types: monometallic and bimetallic. The structures of these two catalysts along with examples of some of the chiral ligands are shown below. With the



mixed solvent system initially employed (H_2O/THF = 4:1), the monometallic catalysts, being neutral species, were insoluble. Sulfonating the aromatic groups of the diphosphine ligands achieved the required solubility. In particular, tetrasulfonated Tol-BINAP was most often used in these studies. Later, it was found that mixed aqueous solvents containing greater proportions of THF (H_2O/THF = 1:2) dissolved the unsulfonated Tol-BINAP.

Representative data for the oxidation of olefins by the monometallic catalyst with sulfonated and unsulfonated Tol-BINAP are given in **Table 3**. At low H_2O/THF ratios the unsulfonated catalyst is soluble in the reaction media. The enantioselectivities are fair to good and are consistently higher with the unsulfonated catalyst.

Previous studies indicate the lower the degree of sulfonation, the higher the enantioselectivity. Thus, monosulfonated Tol-BINAP might give higher % ee values. For runs 1–3 the last column gives the catalyst turnovers. The reaction is, like the Wacker reaction, a

TABLE 3. Results for the Oxidation of Several Olefins by Sulfonated and Unsulfonated Tol-BINAP Catalysts in the Presence of 6 M $CuCl_2$ at 25 °C[a]

Run	Ligand	H_2O/THF	Substrate	**24/25** Ratio[b]	% ee of **24**
			Sulfonated Catalysts		
1	(*R*)-Tol-BINAP	4:1	Propene	12	44
2	(*R*)-Tol-BINAP	4:1	CH_2═$CHC(O)CH_3$	>95	76
3	(*R*)-Tol-BINAP	3:2	CH_2═$CHCH_2OPh$	>95	68
			Unsulfonated Catalyst		
4	(*R*)-Tol-BINAP	1:2	Propene	5.5	56[c]
5	(*R*)-Tol-BINAP	1:2	CH_2═$CHC(O)CH_3$	>95	82
6	(*R*)-Tol-BINAP	1:2	CH_2═$CHCH_2OPh$	>95	80

[a]All runs contain 0.1–0.3 mmol of chiral catalyst in 25–50 mL of solvent and are 0.2 M in LiCl.
[b]The reaction mixture also contained varying amounts of the Wacker ketone product (5–30%).
[c]Absolute configuration determined to be (*R*) by conversion to the epoxide and comparing with an authentic sample.

net air oxidation. In the propene runs, for safety reasons, propene uptake was measured but with the liquid olefins the turnovers were measured by oxygen uptake. Regioselectivity was a factor only with propene. With the other two olefins only the **29** isomer was formed.

Table 4 lists representative data for the oxidation of several substrates by the bimetallic catalyst. Runs 1–3 demonstrate the relative effectiveness of the three chiral ligands studied. In all cases studied the BINAP or Tol-BINAP ligands gave the highest enantiomeric selectivity with DIOP next and DACH last. The similarity of the enantioselectivities for runs 5–7 indicates electronic factors do not play an important role.

The high asymmetric induction obtained with the bimetallic catalysts is probably the most unexpected and interesting result in **Table 4**. The highest ee obtained with the monometallic catalysts (**Table 3**) was 82%. Formally, the bimetallic catalyst, with one phosphine per Pd(II), is analogous to the monometallic catalysts **28**. Two factors almost certainly explain the high enantioselectivity observed. The first is the rigid structure of the bridging diphosphine ligand. Without the free rotation of the monodentate ligand in **28** the asymmetric induction is increased. The second factor is the coordination sphere of the Pd(II). With a bidentate β-diketone and a phosphine ligand, there is only one open coordination site available to the olefin. The site is adjacent to the chiral phosphine ligand where the asymmetric induction will be the highest. Note that in catalyst **28** the site trans to the chiral ligand would experience little chiral induction.

The closest comparison to the present reaction is the Pd(II)-catalyzed synthesis of chiral chlorohydrins using an olefin containing a chiral allylic amine ligand.[38] This very interesting conversion gives a chiral chlorohydrin containing the chiral amine in poor to modest optical purities (ee = 1–77%). As the chiral agent is monodentate, the system is analogous to catalyst **28** in **Scheme 2**. The fact that the optical yields were generally

TABLE 4. Results for the Oxidation of Several Olefins by Chiral Bimetallic Pd(II) Catalysts in the Presence of $CuCl_2$[a]

Run	Chiral Ligand	Substrate	**24**/**25**[b] Ratio	% ee of **24**	Turn overs
1	(*S*)-BINAP	Propene	3.5	94[c]	195[d]
2	(+)-DIOP	Propene	2.8	68	113[d]
3	(−)-DACH	Propene	2.7	50	61[d]
4	(+)-DIOP	$CH_2{=}CHC(O)CH_3$	>90	84	274[e]
5	(*S*)-BINAP	$CH_2{=}CHCH_2OPh$	>95	93	170[e]
6	(*S*)-Tol-BINAP	$CH_2{=}CHCH_2O\{(p\text{-}Cl)Ph\}$	>95	92	210[e]
7	(*S*)-Tol-BINAP	$CH_2{=}CHCH_2O\{(p\text{-}CN)Ph\}$	>95	93	140[e]
8	(*S*)-BINAP	$CH_2{=}CHCH_2O(1\text{-}Naph)$	>95	80	175[e]
9	(*S*)-Tol-BINAP	Styrene	>95	80[f]	100[e]

[a]All runs contain 0.1–0.3 mmol of chiral catalyst in 25–50 mL of solvent and are 3–5 M in $CuCl_2$. Temperature = 25 °C. The solvent was a H_2O/THF mixture containing 30–92% THF by volume.

[b]Also contained 5–20% of the carbonyl product.

[c]Absolute configuration determined to be (*S*) by conversion to the epoxide and comparing with an authentic sample.

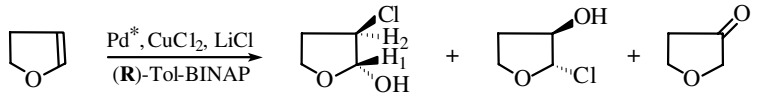
[d]Measured by propene uptake using gas burets.

[e]Dioxygen is oxidant; turnovers measured by O_2 uptake using gas burets. In calculating turnovers dioxygen is assumed to be a four-electron oxidant.

[f]Styrene chlorohydrin was converted to styrene oxide by treatment with NaOH. The configuration of the styrene oxide was found to be (*S*) by comparison with an authentic sample.

higher than those obtained with **28** can be rationalized by the fact that the system is rigid in the same fashion as the bimetallic catalyst in the present studies.

The overall stereochemistry of the reaction for both the mono- and bimetallic catalysts was determined using 2,3-dihydrofuran. Oxidation of 2,3-dihydrofuran gave the three products shown in **Scheme 24**. The three products were identified as 3-chloro-2-hydroxytetrahydrofuran (**31**), 2-chloro-3-hydroxytetrahydrofuran (**32**), and 3-oxo-tetrahydrofuran. The relative percentages of each depended on the catalyst but **31** was by far the major product (75–80%). The stereochemistry of **31** was determined to be (*E*) from the coupling constant ($J_{1,2} = 2.96$ Hz).[39]

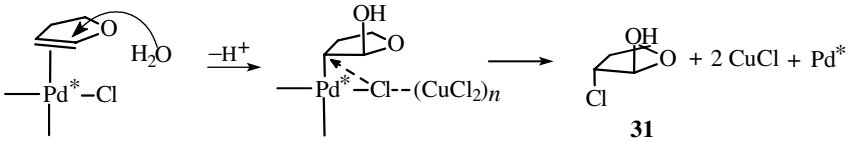


Pd* = mono- or bimetallic catalyst

Scheme 24

The stereochemical results for runs 1 and 4 in **Table 3** and run 9 in **Table 4** in conjunction with the results with 2,3-dihydrofuran provide some mechanistic insight into the reaction. Molecular models indicate that the stereochemical results in all three runs are consistent with anti addition to the most stable π-complex. Anti addition is expected for Pd(II) catalysts containing a neutral ligand.[37] The formation of (*R*)-**4** is consistent with decomposition occurring from the coordination sphere of the Pd(II) or a $CuCl_2$ attached to the Pd(II). The reaction sequence is shown in **Scheme 4**. With cyclic olefins this scheme predicts chlorohydrin products with the (*E*) configuration. Indeed, 3-dihydrofuran did give chlorohydrins with the (*E*) configuration. If the hydroxypalladation is anti, the decomposition must occur from the coordination sphere of the Pd(II) in order to give the overall (*E*) configuration. A plausible reaction sequence is shown in **Scheme 25**.

Although the Cl^- is shown arising from the coordination sphere of Pd(II), it is also possible that it comes from the coordination sphere of the copper(II).



Scheme 25

E. SUMMARY

1. The mechanism of the Wacker reaction is much more complicated than originally believed. The hydroxypalladation is syn at low chloride concentrations ($[Cl^-] < 1$ M) and anti at high chloride concentrations ($[Cl^-] > 2$ M).

2. At high chloride concentrations isomerization, rather than oxidation, occurs. The controlling factor is the availability of vacant coordination sites. It is the intermediate present at high chloride concentrations that is intercepted by cupric chloride to give 2-chloroethanol.

3. The addition of neutral ligands completely changes the course of the reaction. Isomerization occurs at $[Cl^-] = 0.2$ M. Also at $[Cl^-] = 0.2$ M, 2-chloroethanol is formed in the presence of cupric chloride.

4. These observations resulted in the development of a new asymmetric chlorohydrin synthesis. Mono- and bimetallic Pd(II) catalysts containing bidentate chiral ligands gave good to excellent enantioselectivities.

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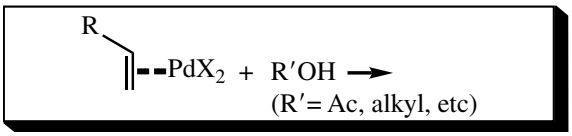

V.3.1.2 Other Intermolecular Oxypalladation–Dehydropalladation Reactions

TAKAHIRO HOSOKAWA and SHUN-ICHI MURAHASHI

A. INTRODUCTION

The Wacker reaction of ethylene or terminal alkenes proceeds via nucleophilic attack of water to coordinated alkenes to give oxypalladation intermediates from which β-Pd–H elimination takes place. This process produces vinyl alcohols, which, under the influence of palladium, lead to acetaldehyde or methyl ketones as the final product (**Scheme 1**).

The use of other oxygen nucleophiles such as acetic acid or alcohols also results in oxypalladation. Subsequent β-Pd–H elimination produces vinyl acetates or vinyl ethers. However, these are not necessarily the final products. When acetic acid is used as the nucleophile, allylic acetates often become the major product. In the case of alcohols, another alcohol reacts with the resulting vinyl ether to give an acetal (**Scheme 2**). Focusing on such product compositions, the oxypalladation of alkenes with carboxylic acids and alcohols followed by dehydropalladation is described here.

B. OXYPALLADATION OF ALKENES WITH CARBOXYLIC ACIDS

After the invention of the Wacker process, much attention was devoted to the commercial production of vinyl acetate via the acetoxylation of ethylene. The study originated from the result reported by Moiseev and co-workers that no acetoxylation of ethylene in acetic acid takes place in the absence of NaOAc (**Scheme 3**).[1],[2] The reaction of $Pd(OAc)_2$ and ethylene gives vinyl acetate. Since the palladium(II) salt employed in these reactions is reduced to Pd(0), co-oxidants are required for the catalysis, similar to the Wacker process. However, a simple combination of $PdCl_2$, $CuCl_2$, and O_2 in AcOH results in various products as shown in **Scheme 4**.

After a number of efforts, the commercial production of vinyl acetate from ethylene and AcOH was initially established as a liquid phase process represented by the equation shown in **Scheme 5**. This process was later replaced by a gas phase process using a supported Pd catalyst. The commercial production of allyl acetate from propene and AcOH (**Scheme 6**) was also established by the gas phase. Allyl alcohol is produced by using this process. The outline of such developments was reviewed by Tsuji.[3]

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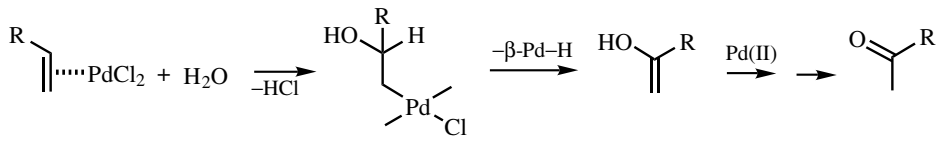
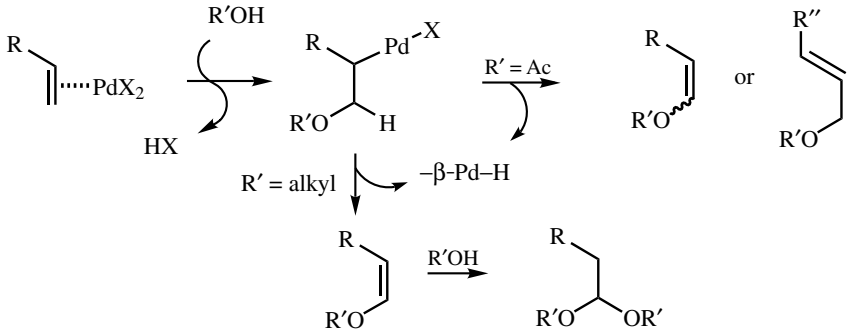
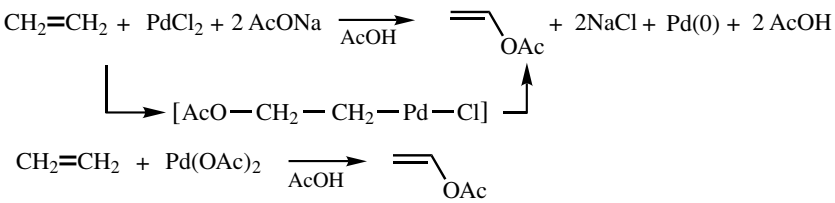


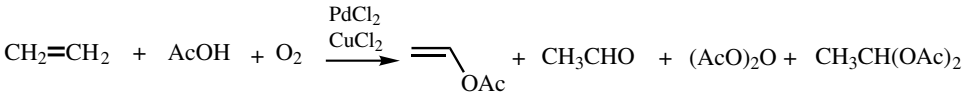
Scheme 1



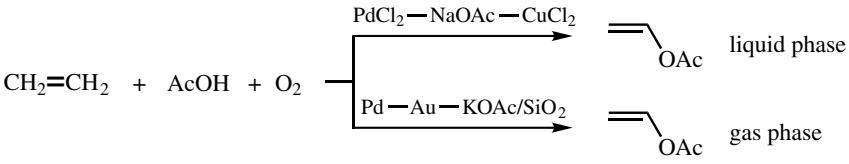
Scheme 2



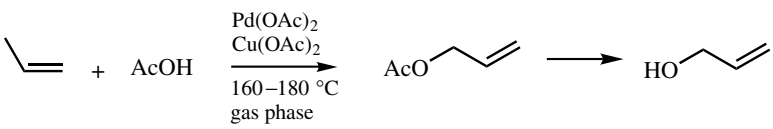
Scheme 3



Scheme 4

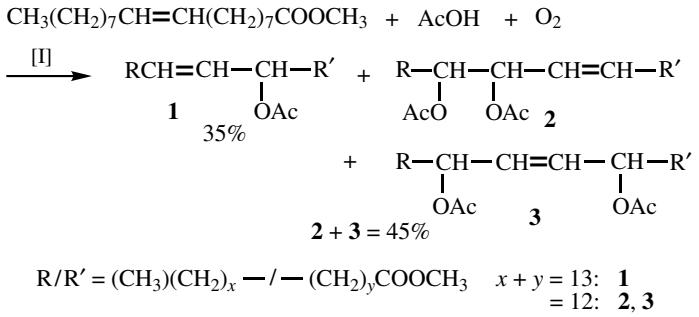


Scheme 5



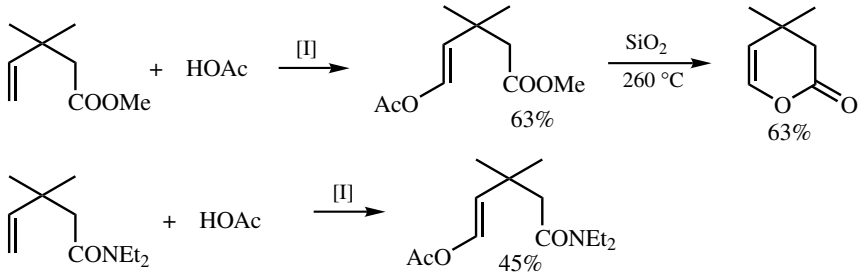
Scheme 6

The acetoxylation of higher alkenes with $Pd(OAc)_2$ is synthetically less useful, since it is always accompanied by allylic acetoxylation and/or diacetoxylation.[4],[5] For instance, the acetoxylation of methyl oleate gives various products as shown in **Scheme 7**.[6] 3,3-Dimethyl-4-pentenoates, in which the allylic position is blocked by two Me groups, react with AcOH in the presence of $Pd(OAc)_2$ catalyst to give the corresponding vinyl acetate, selectively (**Scheme 8**).[7] The catalysis is exerted by the use of O_2 alone as the co-oxidant.



[I] = 5 mol % $PdCl_2$, 1 equiv CuCl, 1 equiv NaOAc, 100 °C, 24 h.

Scheme 7

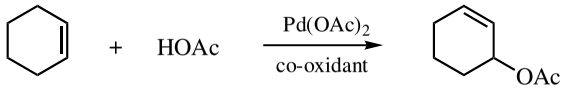


[I] = 2 mol % $Pd(OAc)_2$, O_2 (50 atm), 80 °C, 22 h.

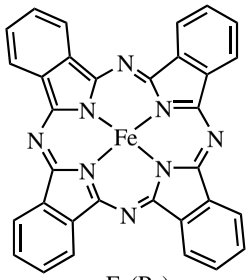
Scheme 8

In contrast to linear alkenes, the acetoxylation of cyclohexene has been so far extensively investigated by using $Pd(OAc)_2$ catalyst, and a variety of co-oxidants[8]–[18] have been developed as shown in **Table 1**. With these methods, 3-acetoxycyclohexene is selectively obtained generally in good yields. A stoichiometric amount of MnO_2 can be used as the co-oxidant together with a catalytic amount of benzoquinone (entry 1). When O_2 is employed as the oxidant, a combination of a metal complex [e.g., Fe(Pc) and Co(TPP)] and hydroquinone (entries 2–4) or $Cu(OAc)_2$ and Co(salen) is effective (entry 6). A combination of O_2 and $Fe(NO_3)_3$ also acts as the co-oxidant (entry 8). The use of mixed addenda heteropolyoxometallates such as NPMoV as an additive (entry 9) is remarkable under such an aerobic condition. Hydroperoxides such as *t*-BuOOH and H_2O_2 serve as stoichiometric oxidants when combined with a catalytic amount of benzoquinone or TeO_2 (entries 10–13). A remarkable high turnover (10,000) per Pd has been attained in the system of H_2O_2 (70%, 1.1 equiv) and benzoquinone (20 equiv) (entry 12).

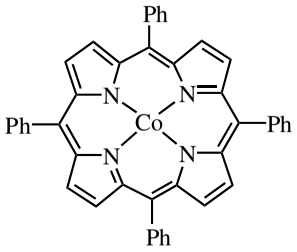
TABLE 1. Pd(II)-Catalyzed Allylic Oxidation of Cyclohexane in Acetic Acid



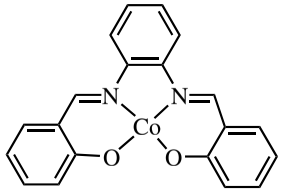
Entry	$Pd(OAc)_2$ (mol %)	Co-oxidants (mol %)	Additive (mol %)	Temperature (°C)	Time (h)	Yield (%)	Reference
1	0.5	MnO_2 (110)–benzoquinone (20)	—	60	2	95	[8–10]
2	5	O_2–Fe(Pc) (5)–hydroquinone (20)	LiOAc	60	2	90	[11]
3	5	O_2–Co(TPP) (0.5)–hydroquinone (20)	LiOAc	60	4	93	[11]
4	5	O_2–Co(salophen) (5)–hydroquinone (20)	LiOAc	60	4	100	[11]
5	5	O_2–$Cu(OAc)_2$ (5)–hydroquinone (10)	—	50	22	>85	[12]
6	5	O_2–$Cu(OAc)_2$ (5)–Co(salen) (5)	—	50	40	90	[12]
7	5	O_2–$Cu(OAc)_2$ (5)–Co(cyclosalen) (5)	—	50	40	68	[12]
8	5	O_2–$Fe(NO_3)_3$ (5)	Ac_2O	40	5	92	[13]
9	5	O_2–hydroquinone (20)-NPMoV[a] (25 mg)	Na_2CO_3	60	4	>99	[14]
10	5	*t*-BuOOH (150)–benzoquinone (20)	—	50	2	77	[15]
11	5[b]	*t*-BuOOH (50)-TeO_2(5)	—	25	72	34	[16]
12	0.2	H_2O_2 (70%, 1.1 equiv)–benzoquinone (20)	—	50	~15	80[c]	[17]
13	5	H_2O_2 (35%, 150)–benzoquinone (20)	—	50	2	71	[15]
14	5[d]	Benzoquinone (100)–*o*-methoxyacetophenone (20)		r.t.	48	80	[18]



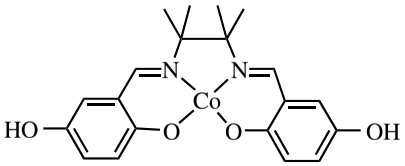
Fe(Pc)



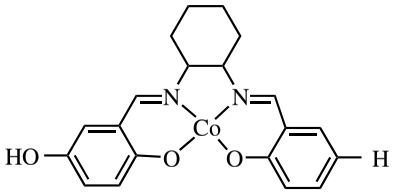
Co(TPP)



Co(salophen)



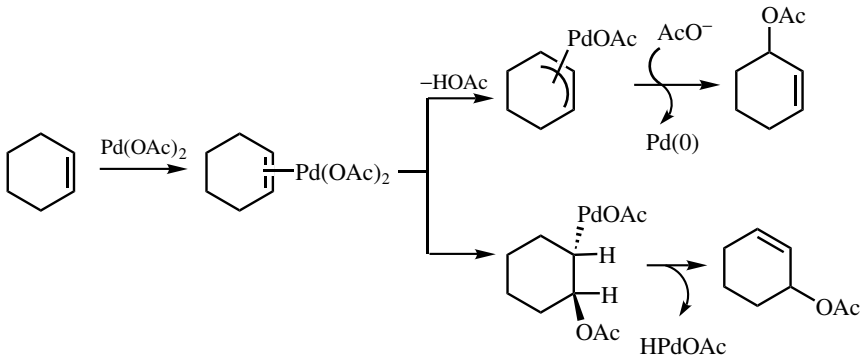
Co(salen)



Co(cyclosalen)

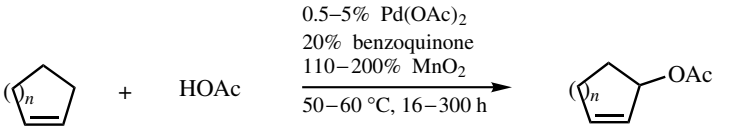
[a]NPMoV, molybdovanadophosphate.
[b]A combination of $PdCl_2$ and AgOAc was used.
[c]Conversion of alkene (selectivity was 93%).
[d]$Pd(OCOCF_3)_2$ was used.

The cyclohexenyl acetate arises either via acetoxypalladation or π-allylpalladium intermediate, or via both, depending on the conditions used. Using 1,2-dideuteriocyclohexene, the allylic acetoxylation of cyclohexene by a catalyst system of $Pd(OAc)_2$–MnO_2–benzoquinone has been demonstrated to proceed via π-allylpalladium intermediate (**Scheme 9**).[19]

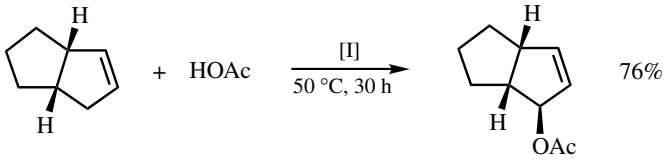


Scheme 9

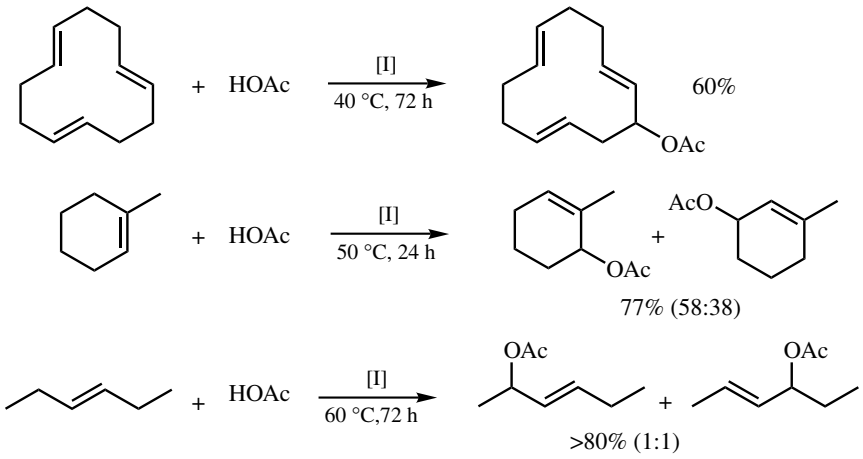
Acetoxylation of vious alkenes has been surveyed by using a catalyst system of $Pd(OAc)_2$–MnO_2–benzoquinone, and reported in *Organic Syntheses*.[10] Some representative results of these are given in **Scheme 10**. The products formed are not vinyl acetate, but allylic acetates, which arise again either via acetoxypalladation or π-allylpalladium intermediate, or via both, depending on the structure of substrates. Similar to the results shown in **Scheme 10**, the allylic acetoxylation of various alkenes by use of H_2O_2 (35%) as the co-oxidant (entry 13 in **Table 1**) or by use of O_2–hydroquinone–NPMoV (entry 9) has been reported.[14],[15]



n	Yield (%)
1	66
2	77
3	73
4	35
6	78
8	72



Scheme 10

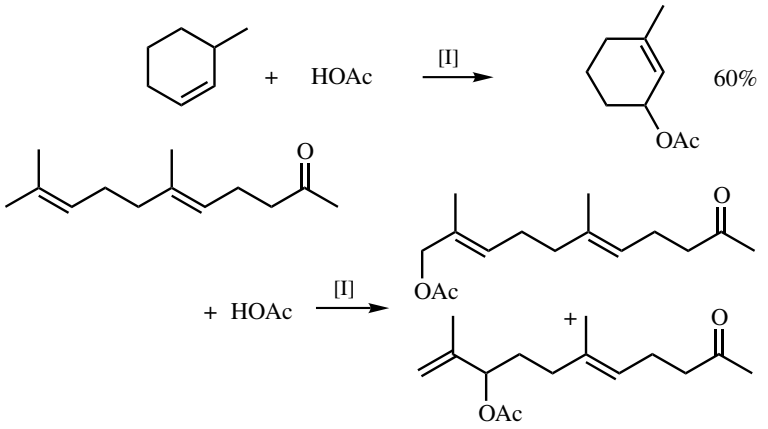


[I] = 5 mol % $Pd(OAc)_2$, 20 mol % benzoquinone, 110–200 mol % MnO_2.

Scheme 10 (*Continued*)

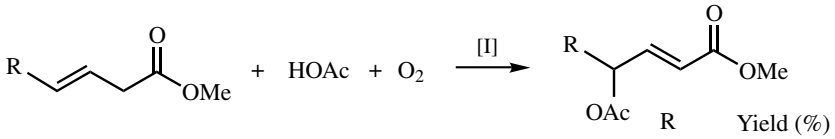
The use of $Pd(OCOCF_3)_2$ as the catalyst together with benzoquinone and *o*-methoxyacetophenone induces the allylic acetoxylation of alkenes.[18] With this system, a terminal methyl group of geranylacetone is acetoxylated as shown in **Scheme 11**. A combination of $PdCl_2$ catalyst with pentyl nitrite ($C_5H_{11}ONO$) and KOAc has been reported to induce the allylic acetoxylation of β,γ-unsaturated esters, regioselectively (**Scheme 12**).[20]

Shown in **Scheme 13** is the result of allylic carboxylations of cyclohexene with various carboxylic acids by the use of *t*-BuOOH as the co-oxidant.[15] Furthermore, treatment of acrylic or methacrylic acid with alkenes by using a catalyst system of $Pd(OAc)_2$–MnO_2–benzoquinone gives the corresponding acrylation products (**Scheme 14**).[21] The reaction of acrylic acid with norbornene results in α-methylene-γ-lactone via acryloxypalladation followed by cyclization.

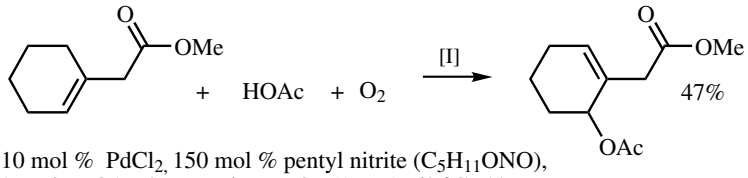


[I] = 5 mol % $Pd(OCOCF_3)_2$, 20 mol % *o*-methoxyacetophenone 85% (~2:1)
1 equiv benzoquinone, r.t., 48 h, Ar.

Scheme 11

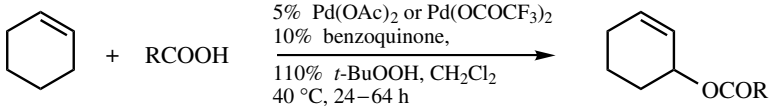


R	Yield (%)
H	45
Me	54
Et	52
Hex	52



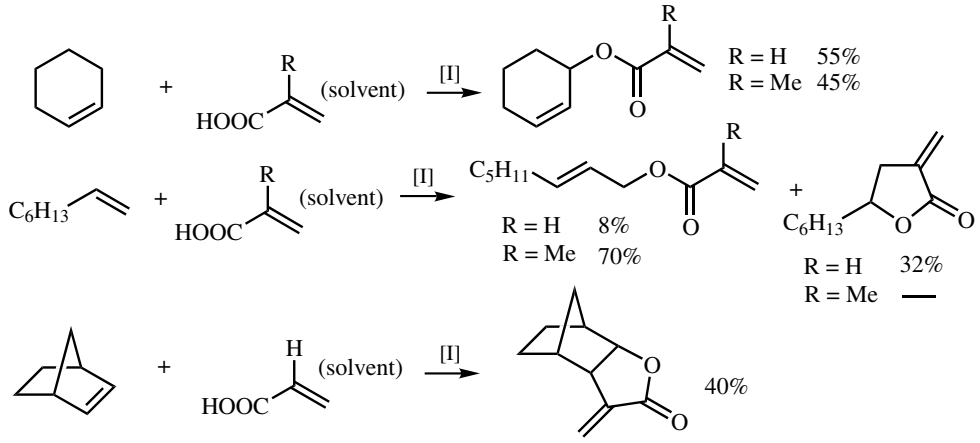
[I] = 10 mol % $PdCl_2$, 150 mol % pentyl nitrite ($C_5H_{11}ONO$), 1 equiv KOAc, benzoquinone, O_2 (1 atm), 60 °C, 5 h.

Scheme 12



R	Yield (%)
Ph	77
t-Bu	65
p-NO_2-Ph	82
p-MeO-Ph	85
PhCH=CH	89
(*S*)-PhCH(OAc)	82

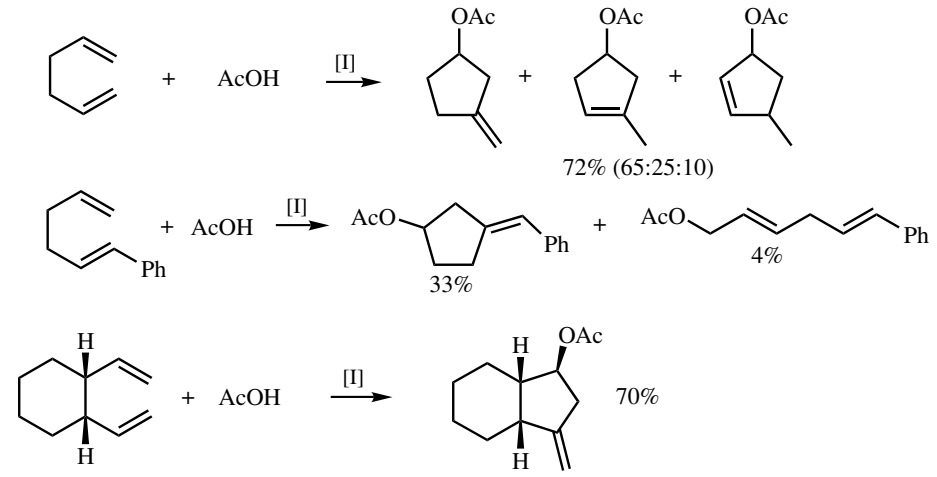
Scheme 13



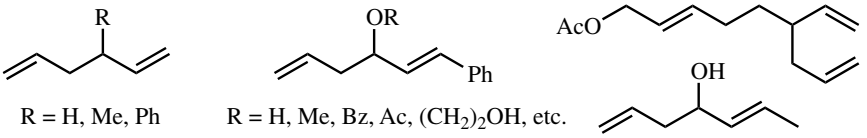
[I] = 5 mol % $Pd(OAc)_2$, 20 mol % benzoquinone, 1.2 equiv MnO_2

Scheme 14

The reaction of *cis*-1,2-divinylcyclohexane and AcOH with a catalyst system of $Pd(OAc)_2$–MnO_2–benzoquinone results in acetoxylation and cyclization to give 7-acetoxy-9-methylenebicyclo[4.3.0]nonane as the sole product (**Scheme 15**).[22],[23] This type of cyclization, originally reported by Adachi, Matsuda, and co-workers,[24] has been extensively studied by Moberg and Heumann. 1,5-Hexadiene itself affords a mixture of isomeric cyclopentenes with respect to the olefin position.[23] *trans*-1-Phenyl-1,5-hexadiene yields the corresponding acetoxymethylenecyclopentane. Remarkably high diastereoselectivity was observed on the cyclization of *cis*-1,2-divinylcyclohexane. With other 1,5-dienes listed in **Scheme 15**, the product selectivity and stereoselectivity are not much higher.[23] The acetoxylation and cyclization of 6-(2-ethenyl)-2,8-nonadienol, derived from Pd-catalyzed telomerization of 1,3-butadiene, gives *exo*-methylene cyclopentyl acetate (**Scheme 16**), which serves as the precursor of sativene[25] or diquinanes.[26]



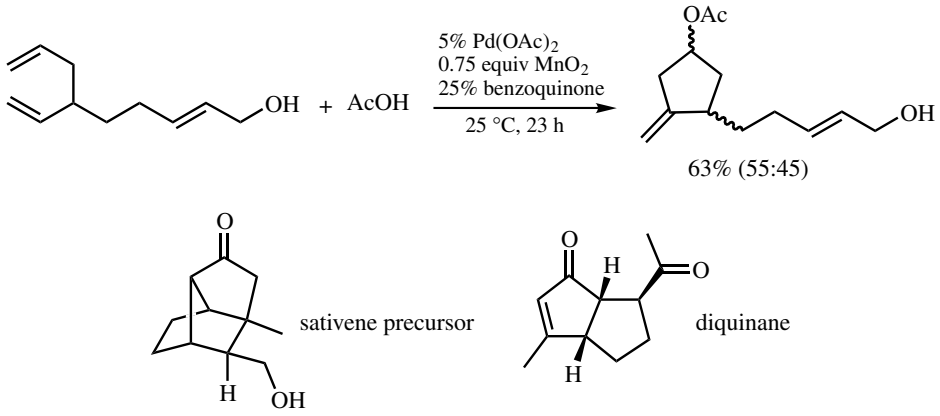
[I] = 5 mol % $Pd(OAc)_2$, 20 mol % benzoquinone, 100% MnO_2, r.t., 42 h.



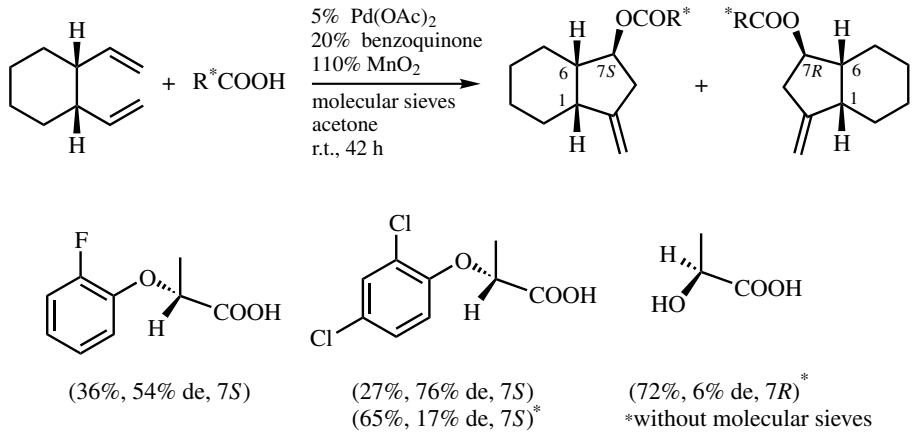
R = H, Me, Ph R = H, Me, Bz, Ac, $(CH_2)_2OH$, etc.

Scheme 15

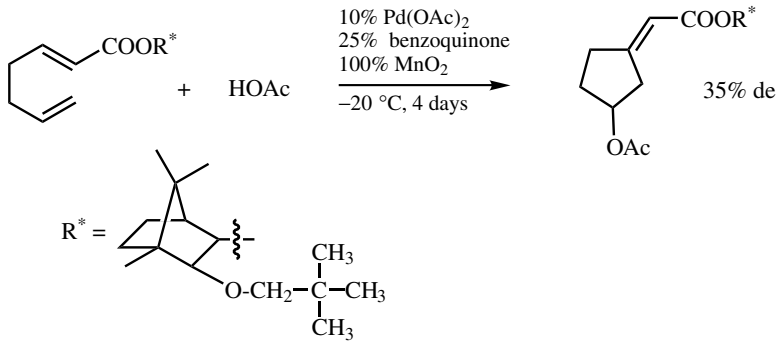
Asymmetric, oxidative cyclization of 1,2-*cis*-divinylcyclohexane has been attained by using chiral carboxylic acids as the nucleophile.[27]–[29] Typical results are given in **Scheme 17**, where the product yield (%), diastereoselectivity (% de), and predominant configuration of C-7 carbon of the product are shown in parentheses. Among various chiral carboxylic acids, a high diastereoselectivity (76% de) was obtained by the use of (*R*)-2-(2,4-dichlorophenoxy)propionic acid as the chiral nucleophile. Addition of molecular sieves to the reaction system has been shown to improve the diastereoselectivity.[29] Incorporation of a chiral unit into diene molecules also induces the asymmetric cyclization (**Scheme 18**). Thus, (1*R*,2*S*,3*R*)-2-neopentoxy-3-bornanyl-2,6-heptadienoate gives the corresponding cyclization product in 35% de.[30]



Scheme 16



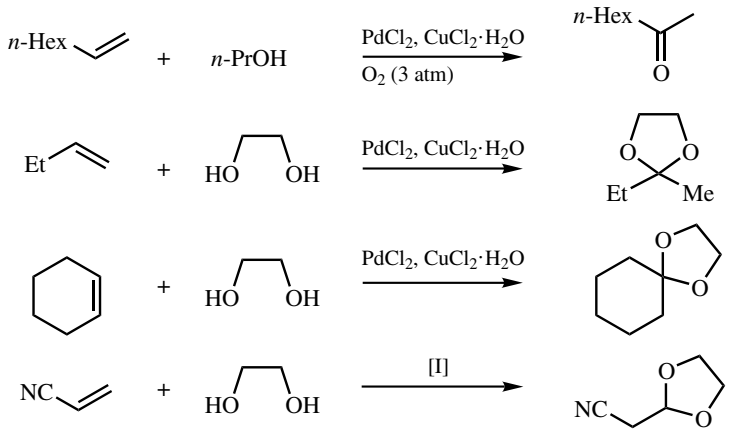
Scheme 17



Scheme 18

C. OXYPALLADATION OF ALKENES WITH ALCOHOLS

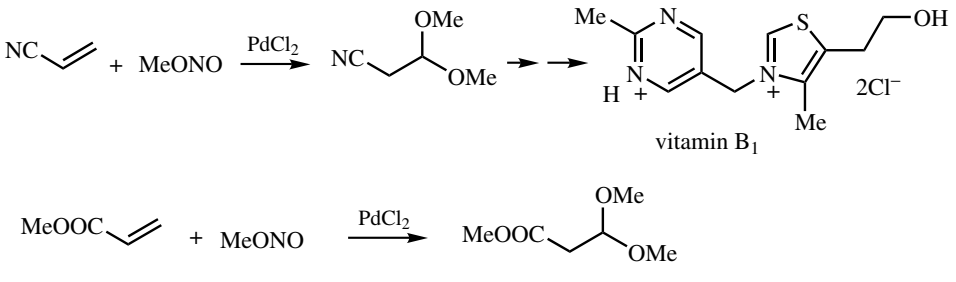
In the early 1960s, the reaction of ethylene with alcohols was first reported by Moiseev et al.[1] and Stern and Spector[2] in a brief note. In 1968, Ketley and Fisher[31] studied the reaction of π-complexes of alkene–$PdCl_2$ with alcohols leading to acetals. In 1969, Lloyd and Luberoff[32] investigated the acetalization of various alkenes with alcohols using a catalyst system of $PdCl_2$–$CuCl_2$–O_2 from a synthetic viewpoint (**Scheme 19**). This study, albeit not systematic, provides fundamental features of $PdCl_2$-catalyzed acetalization of alkenes with alcohols. Namely, the reaction of 1-alkenes with simple alcohols such as MeOH and *n*-PrOH gives ketones predominantly. The use of diols such as ethanediol produces acetals. From alkenes bearing electron-withdrawing substituents, such as CN, acetals become the major product.



[I] = 0.02 M $PdCl_2$, 0.1 M $CuCl_2 \cdot H_2O$, O_2 (3 atm), 80 °C, 3 h.

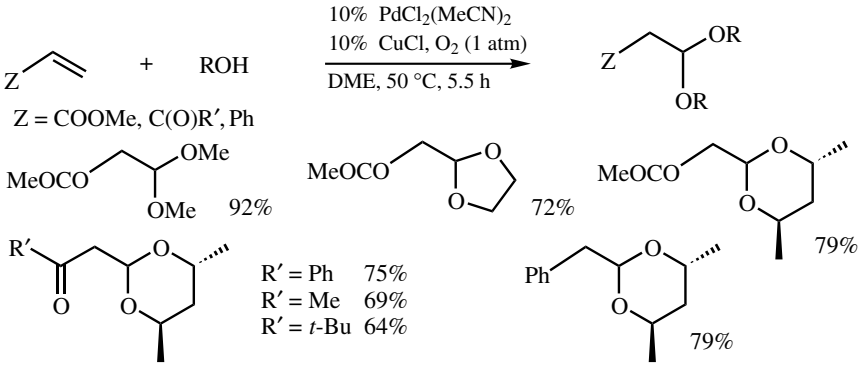
Scheme 19

In 1985, the industrial production of 3,3-dimethoxypropionitrile was established by using methyl nitrite and acrylonitrile (**Scheme 20**). The acetal becomes a starting material for the synthesis of vitamin B_1. Methyl acrylate reacts similarly to give 3,3-dimethoxypropionate, which is also commercially produced. Such a development was reviewed by Tsuji.[3]



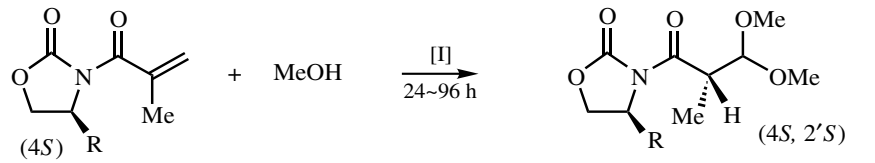
Scheme 20

Our studies on the acetalization of alkenes, first reported in 1983,[33] revealed that terminal alkenes bearing electron-withdrawing substituents such as those shown in **Scheme 21** are regioselectively acetalized at the terminal olefinic carbon with ROH or diols by $PdCl_2$–CuCl catalyst under O_2.[34],[35] Homochiral acetals, which serve as the chiral reagents,[36] are readily synthesized by the use of optically active (*R*,*R*)-2,4-pentanediol.



Scheme 21

Geminal disubstituted alkenes are less reactive due to ineffective coordination of Pd(II) to the alkenes. For instance, methacrylic esters undergo only ~30% conversion under the same conditions in which acrylic esters are acetalized for more than 90% yield. However, the reactivity of methacryloyl moiety is enhanced by incorporation of oxazolidinones. Thus, as shown in **Scheme 22**, prochiral geminal disubstituted alkenes bearing optically active oxazolidinone are effectively acetalized with MeOH to give the corresponding acetals in good yields.[37],[38] The alkenes bearing (4*S*)-*t*-butyloxazolidinone give the (4*S*,2′*S*)-acetals in 95% de, and pure (*S*)-azetidinone is derived from such acetals. The stereochemical outcome in the asymmetric acetalization shown in **Scheme 22** provides detailed information on the reaction pathways (**Scheme 23**) involving oxypalladation, Pd—H elimination, and its readdition to the coordinated alkene.[34],[38]

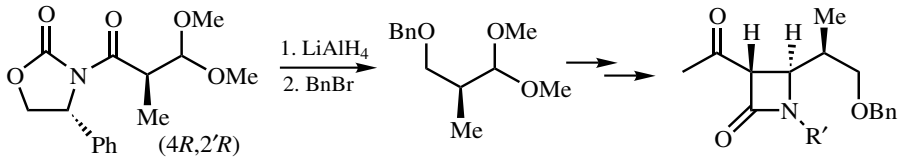


[I] = 10 mol % $PdCl_2$, 1 equiv CuCl, 25 equiv MeOH, O_2 (1 atm), 25 °C.

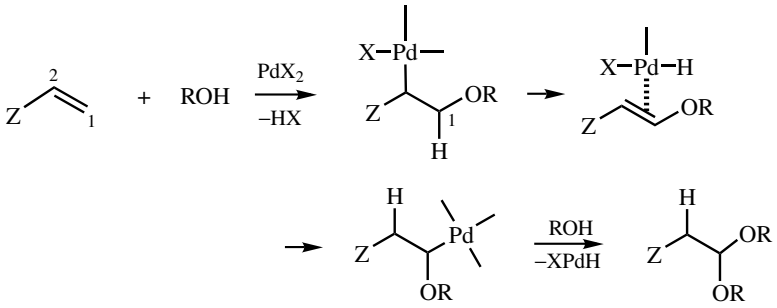
R	Yield (%)	de (%)
i-Pr	66	61
Me	61	23
Bn	30	32
Ph[a]	92	71
Ph[b]	88	80
t-Bu	89	95

[a] At 50 °C.
[b] CH_2Cl_2 was used as solvent.

Scheme 22



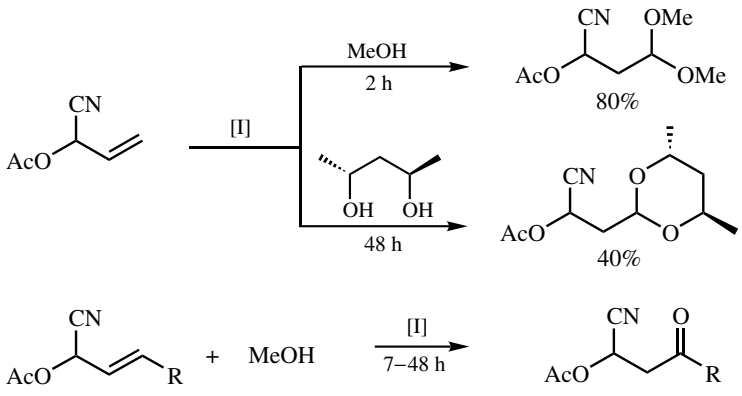
Scheme 22 (*Continued*)



Scheme 23

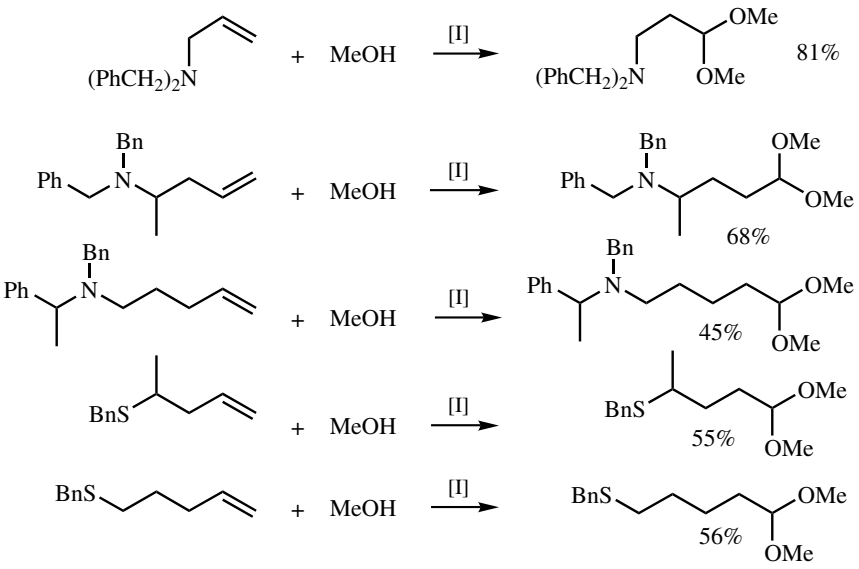
α-Cyanoallyl acetate is regioselectively acetalized at the terminal olefinic carbon with MeOH or (*R*,*R*)-2,4-pentanediol[39] (**Scheme 24**). However, no acetals are formed from allylic acetates bearing substituents at the terminal olefinic carbon; instead, ketones are obtained.

Allylic amine and its higher homologues are acetalized also at the terminal olefinic carbon, because of the directing influence of the N atom shown in **Scheme 25**.[40] Similarly, 3-butenyl and 4-pentenyl sulfide are acetalized at the terminal olefinic carbon. Such a directing influence is also observed with tosyl group[41] (**Scheme 26**).

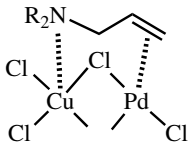


[I] = 10 mol % $PdCl_2(MeCN)_2$, 10 mol % CuCl, 10 mol % HMPA
O_2 (1 atm), DME, 50 °C.

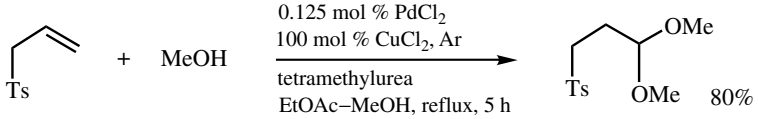
Scheme 24



[I] = 10 mol % $LiPdCl_4$, 300 mol % $CuCl_2$, Ar, MeOH, 50 °C, 10–72 h.

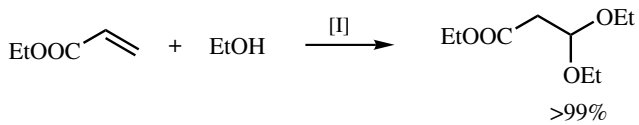


Scheme 25



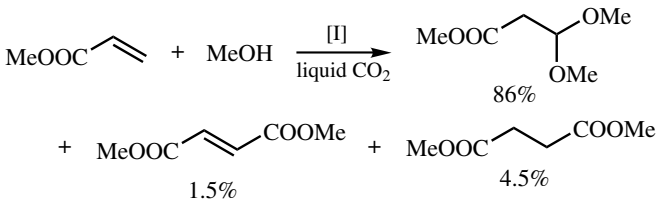
Scheme 26

The acetalization of ethyl acrylate with ethanol is effected by the use of mixed addenda heteropolyoxometallates such as molybdovanadophosphate (NPMoV) with a catalyst system consisting of $Pd(OAc)_2$–hydroquinone and O_2[14] (**Scheme 27**). Recently, the use of supercritical carbon dioxide (*se*CO_2) as a solvent in Pd(II)-catalyzed acetalization of methyl acrylate with MeOH (**Scheme 28**) has been reported.[42]



[I] = 5 mol % $Pd(OAc)_2$ (2 mmol), NPMoV (35 mg), 20 mol % hydroquinone, CH_3SO_3H (20 mg).

Scheme 27

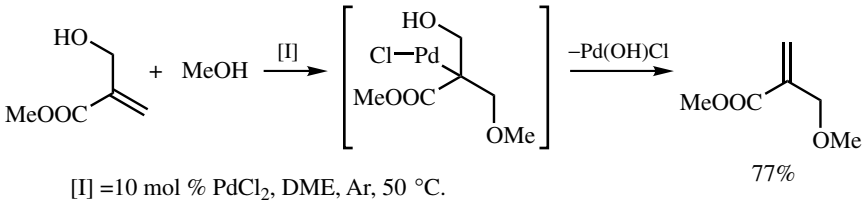


[I] = 3 mol % $PdCl_2$, 0.4 equiv CuCl, O_2.

Scheme 28

The reaction of methyl (α-hydroxymethyl)acrylate with MeOH does not give the corresponding acetal; however, interestingly exclusive elimination of β-Pd—OH takes place from the oxypalladation intermediate shown in **Scheme 29** to give methyl (α-methoxymethyl)acrylate.[43]

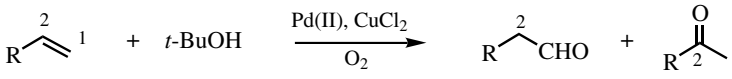
The reaction of 1-alkenes bearing alkyl substituents with ROH or diols in the presence of PdX_2 catalyst usually gives methyl ketones (**Scheme 30**), where palladium attacks at the sterically less hindered site (C-1) of alkenes. When bulky alcohols such as *t*-BuOH are used as the nucleophile, the regioselectivity of ketonization is altered to a certain extent.[44]–[47] The representative results are given in **Table 2**.



[I] =10 mol % $PdCl_2$, DME, Ar, 50 °C.

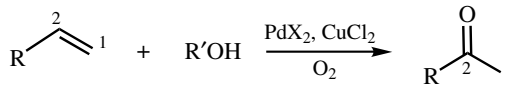
Scheme 29

TABLE 2. Aldehyde Formation from 1-Alkenes Using Pd(II) Catalysts and O_2



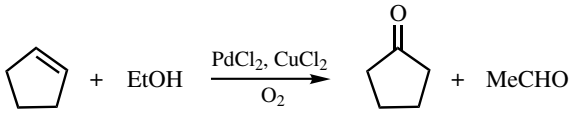
Entry	R	Catalyst System	Yield (%)	Aldehyde/Ketone	Reference
1	C_6H_{13}	3.6 mol % $PdCl_2(MeCN)_2$ $CuCl_2$, CuCl, LiCl	38	31:69	44
2	C_8H_{17}	10 mol % $PdCl(NO_2)(MeCN)_2$ 40 mol % $CuCl_2$	28	60:40	45
3	Ph	10 mol % $PdCl(NO_2)(MeCN)_2$ 40 mol % $CuCl_2$ (40 mol %)	9	100:0	45
4	C_6H_{13}	2 mol % $PdCl(NO_2)(MeCN)_2$ 8 mol % $CuCl_2$, amide[a]	54	60:40	46,47

[a] *N*, *N*,-Diethylpivaloylamide or *N*,*N*′-tetraethyloxalic acid amide.



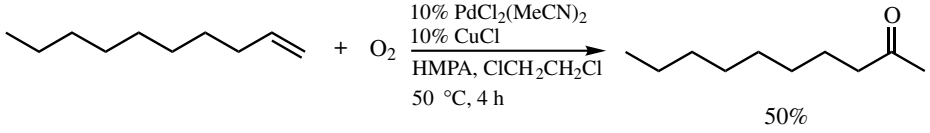
Scheme 30

The reaction of cyclopentene with EtOH by the use of a catalyst system of $PdCl_2$–$CuCl_2$–O_2 gives cyclopentanone, where co-oxidation of EtOH to MeCHO takes place[48],[49] (**Scheme 31**). The catalysis is assumed to be operative by oxygenation of the resulting Pd—H species with O_2. A similar oxidation of 1-alkenes by $[Pd(NH_4)_4]Cl_2$ or $[Pd(NH_3)_2(NO_2)_2]$ catalyst combined with $CuCl_2$ and LiCl has recently been reported.[50] In these reactions, one O atom of O_2 is incorporated into the alkene. The use of Pd–NO_2 complexes as the catalyst also effects the oxidation of 1-alkenes. These subjects are reviewed by Heumann et al.[51]



Scheme 31

Finally, note the oxygenation of 1-alkenes with O_2 under anhydrous conditions. Thus, when a catalyst system consisting of $PdCl_2(MeCN)_2$–CuCl and hexamethylphosphoramide (HMPA) is used in anhydrous 1,2-dichloromethane, the oxidation of 1-decene by O_2 proceeds catalytically to give 2-decanone[52] (**Scheme 32**).

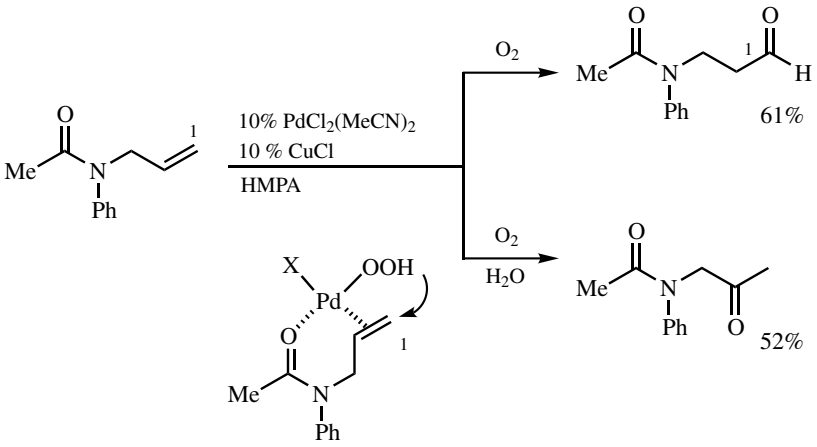


Scheme 32

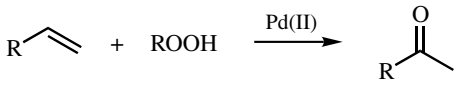
In this reaction, two O atoms of O_2 are incorporated into the product. Also remarkable in the catalyst system is the regioselective transformation of *N*-allylamides into aldehydes, while methyl ketones become the major product in the presence of water. A typical example is given in **Scheme 33**.[53] The regioselective O atom transfer to the terminal olefinic carbon of *N*-allylamides must be attained via the chelating Pd—OOH species formed *in situ* (**Scheme 33**). The oxidation of alkenes with peroxides such as *t*-BuOOH and H_2O_2 (**Scheme 34**) has been reviewed by Mimoun.[54]

D. OXYPALLADATION OF ALKYNES WITH CARBOXYLIC ACIDS AND ALCOHOLS

Compared to intramolecular oxypalladation of alkyne with RCOOH or ROH (**Sect. V.3.2.1**), examples of its intramolecular version are rare. Recently, heterometallic Pd



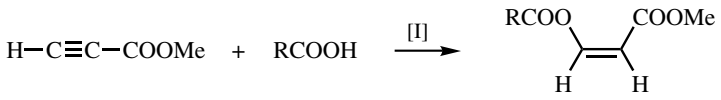
Scheme 33



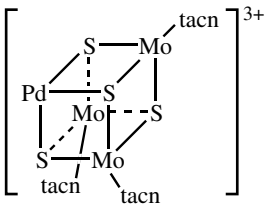
Scheme 34

clusters shown in **Schemes 35** and **36** have been reported to effect the intramolecular oxypalladation of alkynes with carboxylic acids[55] and alcohols,[56] which results in the stereoselective addition of ROH to the acetylene or the acetalization of alkyne.

In summary, oxypalladation of unsaturated carbon–carbon bonds followed by Pd—H elimination has been studied extensively with alkenes using carboxylic acids and alcohols, but not much with alkynes. The chirality generated by this type of



R	Yield (%)	*Z*/*E*
Me	62	98:2
Ph	76	98:2
m-ClPh	72	97:3
$CH_2C{=}C(Me)$	73	98:2
$PhCH{=}CH$	73	96:4
t-$BuOCONHCH_2$	48	94:6

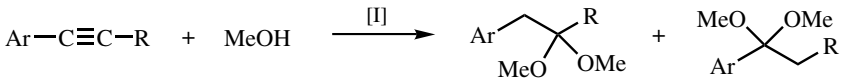


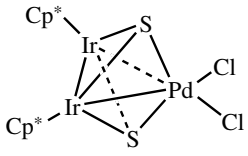
$PdMo_3S_4$ cat.

(tacn = 1,4,7-triazacyclononane)

[I] = $PdMo_3S_4$ (9 μmol), alkyne (9 mmol), RCOOH (3 mmol), NEt_3 (0–0.15 mmol), MeCN, 40 °C, 8–30 h.

Scheme 35





$[(Cp^*Ir)_2(\mu_3\text{-}S)_2PdCl_2$

Ar	R	Yield (%)	Ratio
Ph	Me	88	88:2
Ph	*i*-Bu	65	98:2
p-ClPh	Me	95	97:3
p-Tol	Me	82	91:9
p-MeOPh	Me	59	66:34
Ph	H	50	13:87
n-Hex	H	55	0:100

[I] =$[(Cp^*Ir)_2(\mu_3\text{-}S)_2PdCl_2$ (56 μmol), alkyne (1.67 mmol), MeOH (2 mL), 50 °C, 480 h.

Scheme 36

reaction has been found to be controlled in a diastereoselective manner. How to attain high enantioface selection of C═C bond using chiral ligands will be a future research subject for chemistry.

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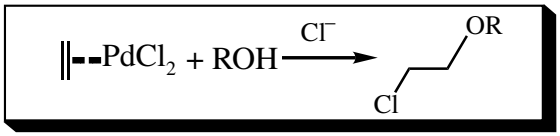

V.3.1.3 Intermolecular Oxypalladation not Accompanied by Dehydropalladation

TAKAHIRO HOSOKAWA and SHUN-ICHI MURAHASHI

A. INTRODUCTION

Oxygen nucleophiles such as water, alcohols, and acetic acid react with alkenes coordinated to PdX_2 (X = Cl, OAc, etc.) to give oxypalladation adducts. In general, a subsequent pathway is β-Pd—H elimination from the intermediate as shown in **Scheme 1**.

If the β-Pd—H elimination is either retarded or inhibited, the σ-Pd—C bond in the oxypalladation intermediate reacts with various reagents (Y) such as carbon monoxide, alkenes, alkynes, alcohols, amines, and metal salts. The reactivity of this σ-Pd—C bond certainly enlarges the field of organic chemistry of palladium. One method to suppress the β-Pd—H elimination is to use excess amounts of $CuCl_2$ and Cl^- ion (e.g., LiCl), which act as the co-oxidant and ligand of palladium, respectively. When water is used as the nucleophile under such conditions, the resulting σ-Pd—C bond in hydroxypalladation adduct is cleaved by the Cl ion of copper, resulting in the hydroxychlorination of alkenes (**Scheme 1**). Thus, ethylene is converted into chlorohydrin itself[1] (**Scheme 2**). Although this reaction has been used as a mechanistic probe of the Wacker reaction,[2] the hydroxychlorination of higher alkenes has not attracted much attention from a synthetic viewpoint for a long time. Since the cleavage of σ-Pd—C bond with $CuCl_2$ affords $PdCl_2$ and CuCl, the reaction is catalytic in palladium (**Scheme 2**). Keeping this catalysis in mind, the synthetic utility of the hydroxychlorination and related reactions will be highlighted in this section.

B. HYDROXYCHLORINATION AND ALKOXYCHLORINATION OF ALKENES

Until the early 1990s, there was no practical use of the hydroxychlorination of alkenes. Recently, Dai and co-workers have enhanced the synthetic utility of this reaction by employing allylic amines and sulfides as the substrate.[3] When a combination of DMF or THF with H_2O is used as the solvent, the hydroxychlorination of these substrates proceeds smoothly and regioselectively to give chlorohydrins in high yields (**Scheme 3**). The product chlorohydrins serve as the precursors of epoxides. Unfortunately, with allyl amines bearing chiral moieties such as (*R*)-phenethylamine, the diastereoselectivities of

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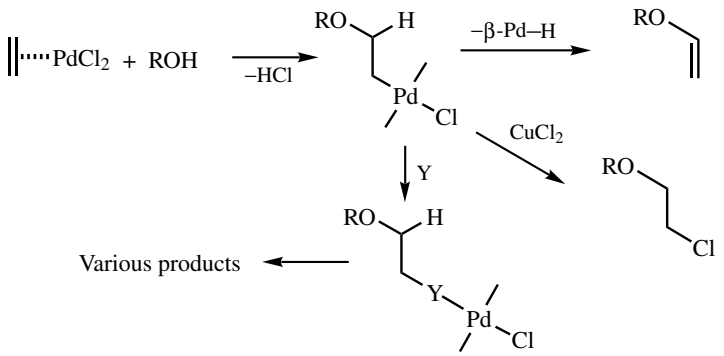
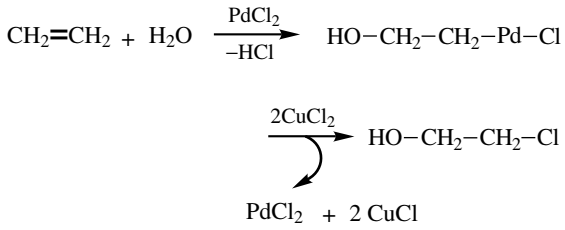
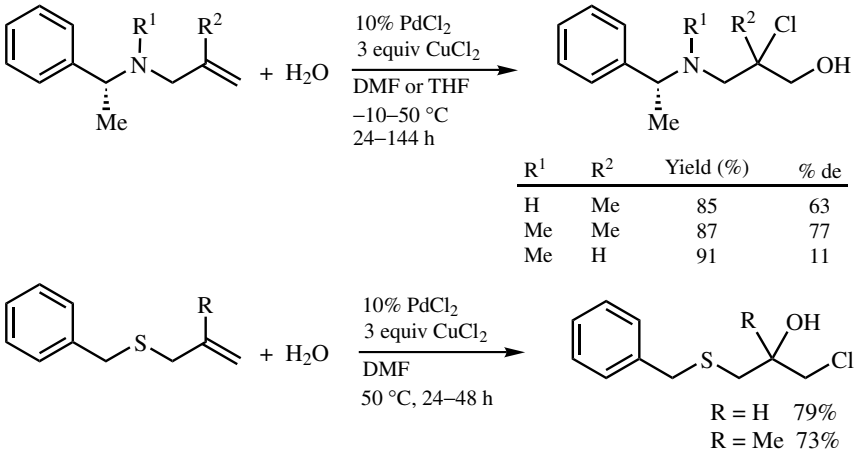


Scheme 1



Scheme 2

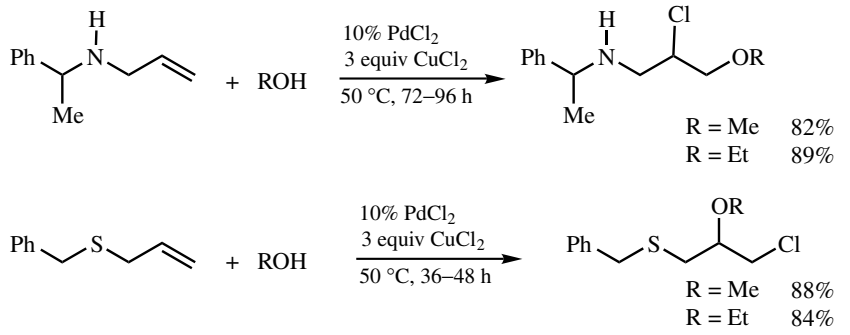


R^1	R^2	Yield (%)	% de
H	Me	85	63
Me	Me	87	77
Me	H	91	11

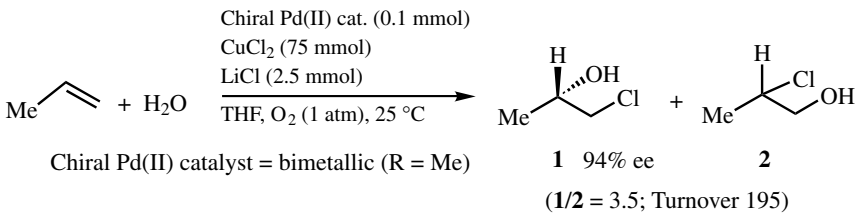
Scheme 3

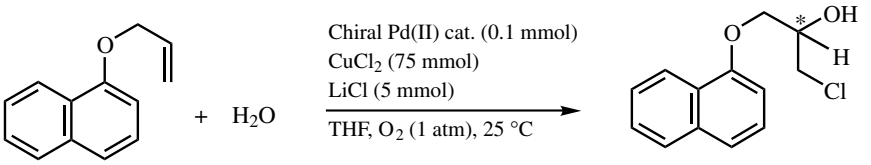
the products are moderate to low. When alcohols are used as the solvent, alkoxychlorination of alkenes similarly takes place to afford the corresponding products in good yields[4] (**Scheme 4**).

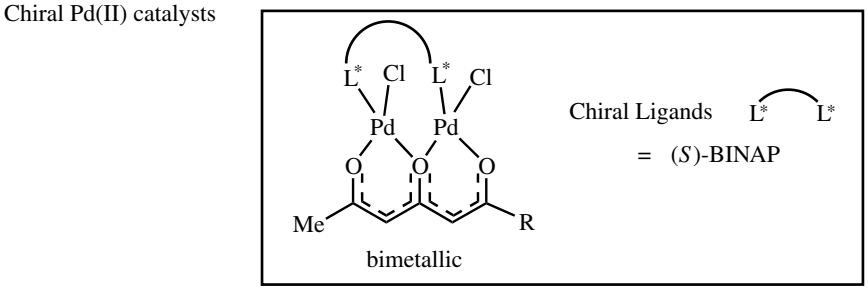
More recently, the asymmetric hydroxychlorination of alkenes has been achieved by Henry and co-workers [5],[6] Given in **Scheme 5** are representative examples in which the chiral catalyst used was either a bimetallic or a monomeric palladium(II) complex bearing

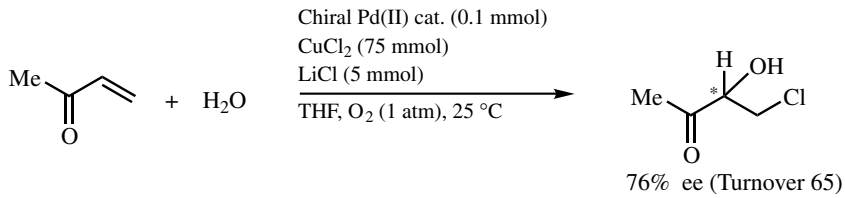


Scheme 4



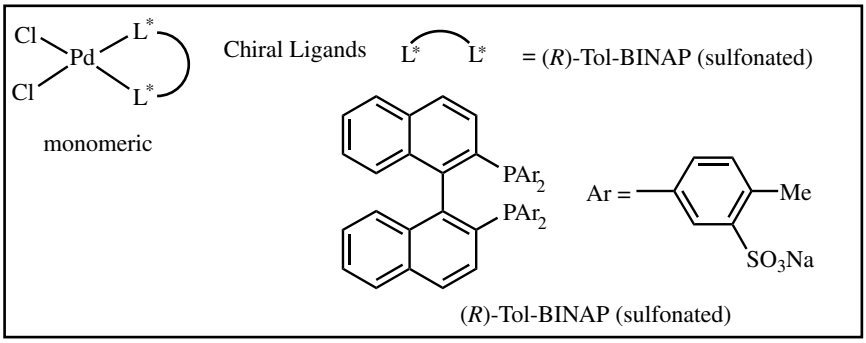






Scheme 5 (*Continued*)

Chiral Pd(II) catalyst



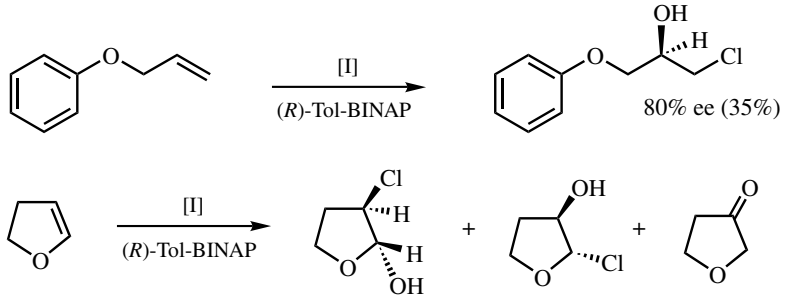
Scheme 5

chelating diphosphines such as BINAPs. Using the chiral systems shown in **Scheme 5**, high enantioselectivities (ranging from 94% to 76% ee) are attained with propene, allyl naphthyl ether, and methyl vinyl ketone. Noteworthy is that even in the presence of oxidizable phosphine ligands, the asymmetric reactions can be carried out under an atmosphere of O_2. As mentioned earlier (**Scheme 2**), this type of reaction produces CuCl, which is readily reoxidized to $CuCl_2$ by O_2 as shown in Eq. 1.

$$2\,CuCl + 2\,HCl + \tfrac{1}{2}\,O_2 \longrightarrow 2\,CuCl_2 + H_2O \qquad (1)$$

Thus, the phosphine ligands tolerate the oxidation by O_2. In addition, the progress of the reaction can be monitored by O_2 uptake measurement.

A simple combination of chiral ligands such as (*R*)-Tol-BINAP and $PdCl_2$ also catalyzes the asymmetric hydrochlorination.[6] Typical examples are shown in **Scheme 6**.



56% ee (relative yield 75:5:20)

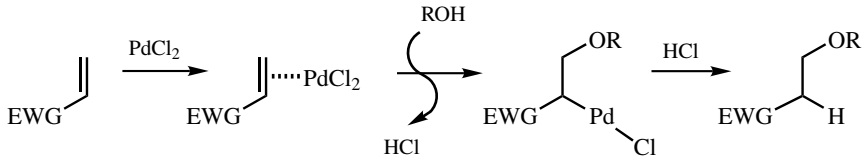
[I] = $PdCl_2$ (0.1 mmol), $CuCl_2$ (75 mmol), LiCl (5 mmol), H_2O–THF (5:1) (25 mL), O_2(1 atm), 25 °C.

Scheme 6

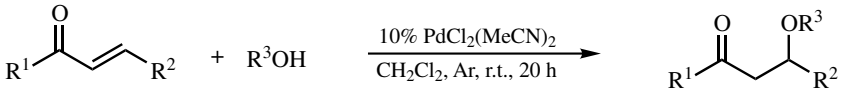
C. ADDITION OF ALCOHOLS TO ALKENES

Under the conditions using excess CuCl and Cl^-, alcohols react with alkenes to give the alkoxychlorination products. In the absence or presence of lesser amounts of CuCl and Cl^-, the acetalization or ketonization of alkenes usually takes place as mentioned in **Sect. V.3.1.2**. However, when alkenes bearing electron-withdrawing groups are allowed to react with alcohols in the absence of $CuCl_2$ and Cl^-, the resulting σ-Pd—C bond in the alkoxypalladation adduct is readily cleaved by HCl formed *in situ*, as schematically shown in **Scheme 7**. Thus, vinyl ketones are readily converted into alkoxyketones in good yields (**Scheme 8**).[7] The chiral acetal derived from acrolein reacts similarly.

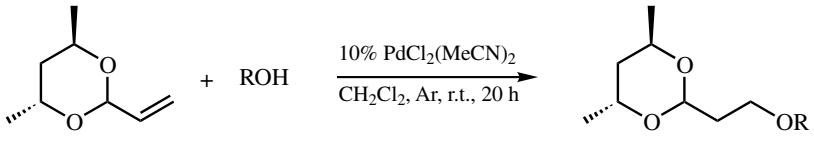
When water is used as the nucleophile, addition of water takes place similarly (**Scheme 9**); however, at present this reaction does not appear to be synthetically useful in terms of catalytic turnover and product selectivity.[8]



Scheme 7

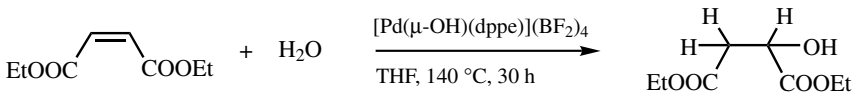


R^1	R^2	R^3	Yield (%)
Ph	H	Me	97
Ph	H	*i*-Pr	98
Ph	H	*t*-Bu	53
Ph	H	$ClCH_2CH_2$	92
Me	H	$PhCH_2$	96
Ph	Me	$PhCH_2$	82
Ph	H	CH_3CO	71



R = $PhCH_2$	89%
R = CH_3CO	52%

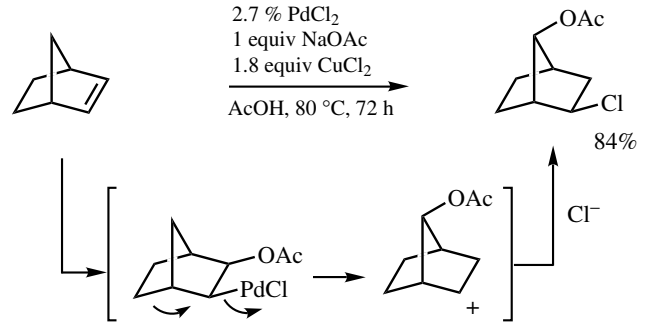
Scheme 8



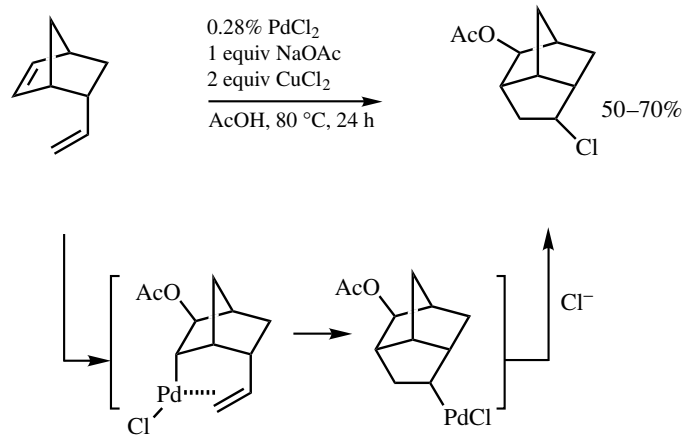
Scheme 9

D. ACETOXYCHLORINATION OF ALKENES

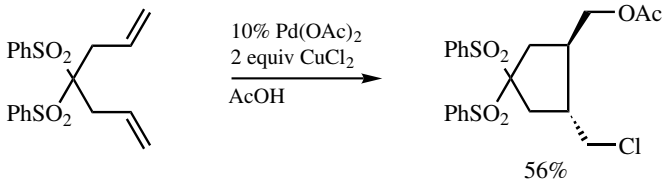
When acetic acid is used as the nucleophile in the presence of excess $CuCl_2$, alkenes are acetoxychlorinated. In this case, as in the acetoxylation of alkenes (**Sect.V.3.1.2**), NaOAc is required to promote the reaction. This type of reaction has so far been applied mainly to bicyclic alkenes. A typical and useful example is the reaction of norbornene with HOAc, where skeletal rearrangement is accompanied as shown in **Scheme 10**.[9] In the case of nonconjugated dienes[10]–[12] (**Scheme 11**), the σ-Pd—C bond in the acetoxypalladation adduct adds to the remaining alkene, resulting in cyclization. Acetoxychlorination products arise from subsequent chlorination of the Pd—C bond with $CuCl_2$. A brendane derivative is thus formed from vinylnorbornene (**Scheme 11**).[11],[12]



Scheme 10



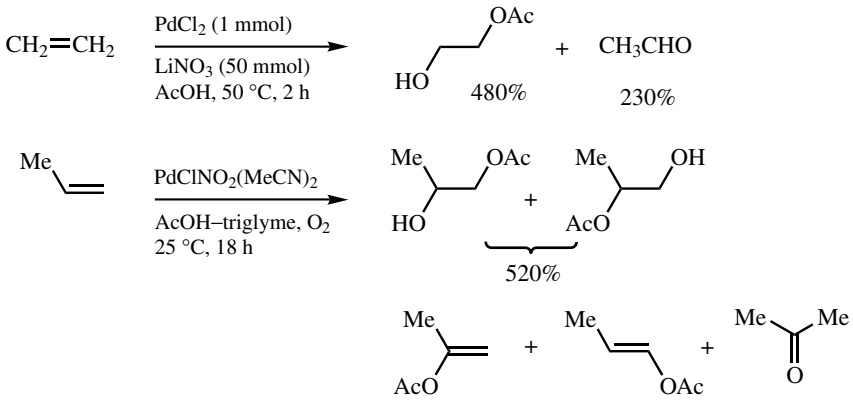
Scheme 11



Scheme 11 (*Continued*)

E. ACETOXYHYDROXYLATION OF ALKENES

The reaction of alkenes with acetic acid in the presence of nitrate anion (e.g., $LiNO_3$) results in the addition of OAc and OH across the double bond. Thus, ethylene is converted into glycolmonoacetate under the conditions given in **Scheme 12**.[13] The use of a palladium nitro complex with O_2 induces this type of reaction.[14] Obviously, these reactions have potential utility in terms of the industrial production of ethylene glycol and propylene glycol. Although the mechanism of this type of reaction has attracted attention,[15],[16] its application to organic synthesis has not yet been explored.



Scheme 12

In summary, interception of σ-Pd—C formed by oxypalladation of alkenes with various reagents such as $Cl^-$and NO_3^- opens a new synthetic method for functionalization of alkenes. This will not be limited to alkenes. Other substrates bearing unsaturated carbon–carbon bonds must follow similar pathways. Some examples with alkynes are given in **Sect.V.3.2.1.E**.

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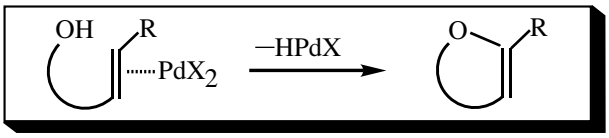

V.3.2 Intramolecular Oxypalladation and Related Reactions Involving Other Group 16 Atom Nucleophiles

V.3.2.1 Oxypalladation–Dehydropalladation Tandem and Related Reactions

TAKAHIRO HOSOKAWA and SHUN-ICHI MURAHASHI

A. INTRODUCTION

One versatile method for synthesizing O-atom containing heterocycles is electrophilic cyclization of alkenes, which involves intramolecular attack upon the C═C double bond by OH functionalities such as OH, COOH, and NOH.[1],[2] Such cyclizations may be carried out by using palladium(II) catalysts, for example, $PdCl_2$ and $Pd(OAc)_2$. The palladium coordinates to the alkene and activates it toward nucleophilic attack; subsequent β-Pd—H elimination leads to cyclized product in its thermodynamically stable form (**Scheme 1**). Such a mechanism is quite similar to that involved in the Wacker process for the preparation of acetaldehyde from ethylene in water. Thus, cyclizations of this type are often called intramolecular Wacker-type reactions or oxidations. Whereas the Wacker process uses water both as the solvent and the nucleophile, its intramolecular version employs organic solvents such as CH_3CN, benzene, DMF, DMSO, and MeOH to solubilize the organic substrates, and $PdCl_2(CH_3CN)_2$ is frequently used to solubilize $PdCl_2$ in such organic solvents.

The first report on this cyclization appeared in 1973,[3],[4] in which the sodium salts of 2-allylphenols were used as the substrates. This cyclization gave 2-substituted benzofurans, upon treatment with a stoichiometric amount of $PdCl_2(PhCN)_2$ in benzene (**Scheme 2**). Thereafter, various cyclizations of this type have been developed to provide methodologies for the synthesis of O-atom containing heterocycles. In addition, techniques for constructing the catalysis of palladium(II), besides using a combination of $CuCl_2$ and O_2, have been advanced. In this section, the intramolecular oxypalladation of ydroxy alkenes and alkynes is described in view of its synthetic utility. Let's first survey Pd(II)-catalyzed cyclization of alkenes containing phenolic group.

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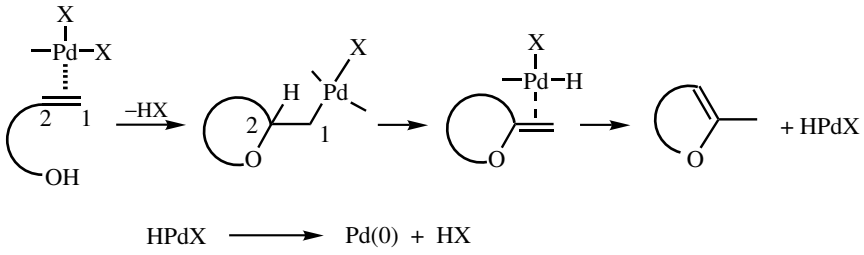
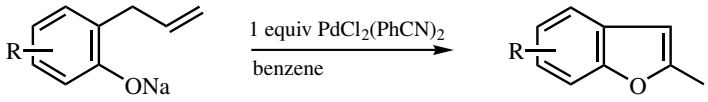
ISBN 0-471-31506-0



Scheme 1

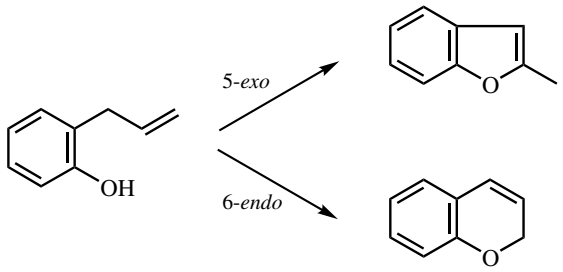


Scheme 2

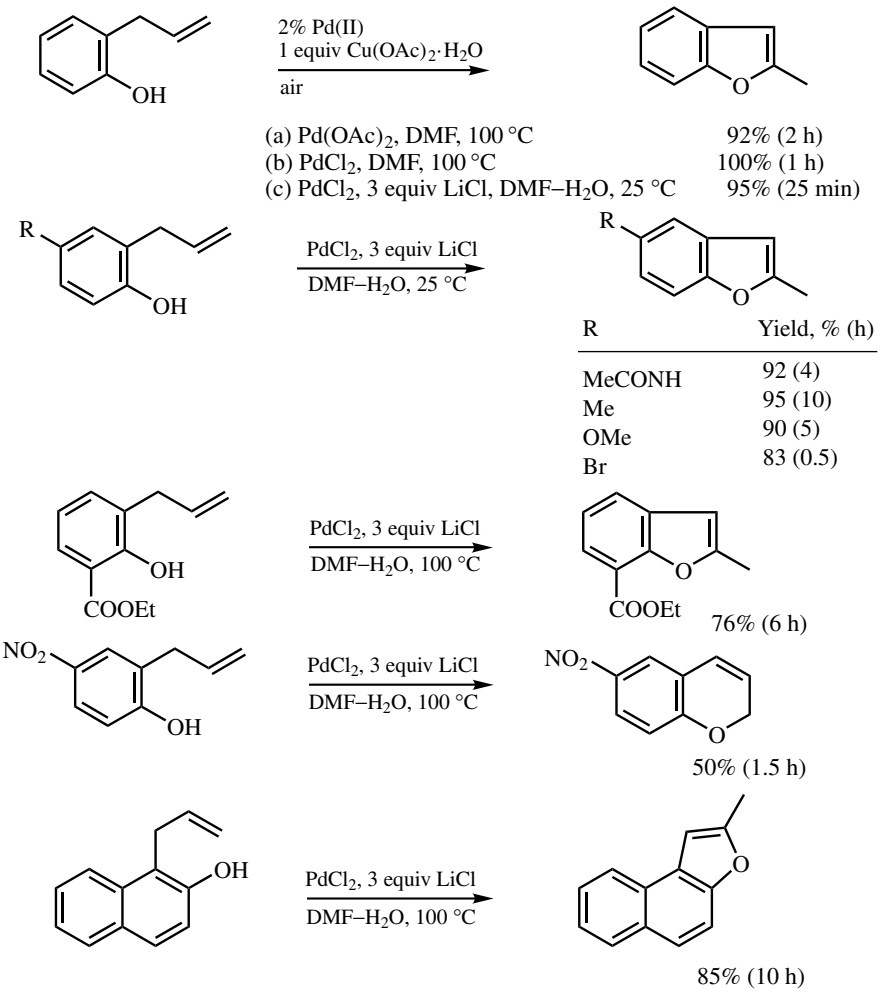
B. INTRAMOLECULAR OXYPALLADATION OF ALKENES CONTAINING PHENOLIC GROUP

2-Allylphenol undergoes either 5-*exo-trig* or 6-*endo-trig* cyclization, depending on the catalyst system used (**Scheme 3**). A catalyst system consisting of $PdCl_2$, $Cu(OAc)_2$, and LiCl in aqueous DMF has recently been reported to result in the 5-*exo* cyclization leading to 2-methylbenzofuran[5] (**Scheme 4**). The use of $Pd(OAc)_2$ in place of $PdCl_2$ in anhydrous DMF effects the catalytic cyclization, but it requires a higher temperature (100 °C). Addition of water in DMF solvent accelerates the reaction; however, no cyclization takes place when water alone is used as the solvent. In this cyclization, the electronic property of the substituents on the phenyl ring gives subtle effect on the rate of cyclization. In the case of a nitro substituent, even the mode of cyclization is altered to give the 6-*endo* form, although the reason is not yet clear.

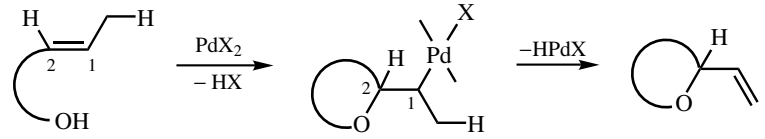
When an alkyl substituent such as Me group is in the terminal position of allylic side chain, the oxypalladation intermediate has two possibilities of β-Pd—H elimination. This intermediate generally produces the energetically favorable vinyl substituent rather than the *exo*-methylene substitution (**Scheme 5**).



Scheme 3

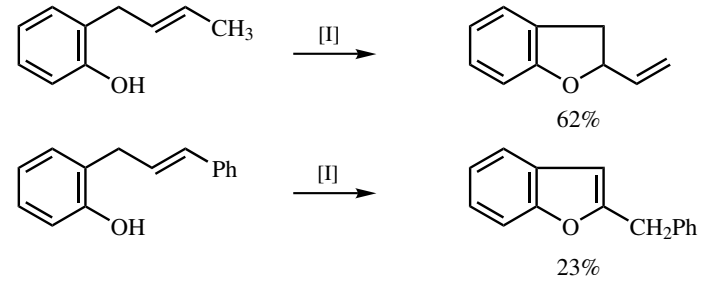


Scheme 4

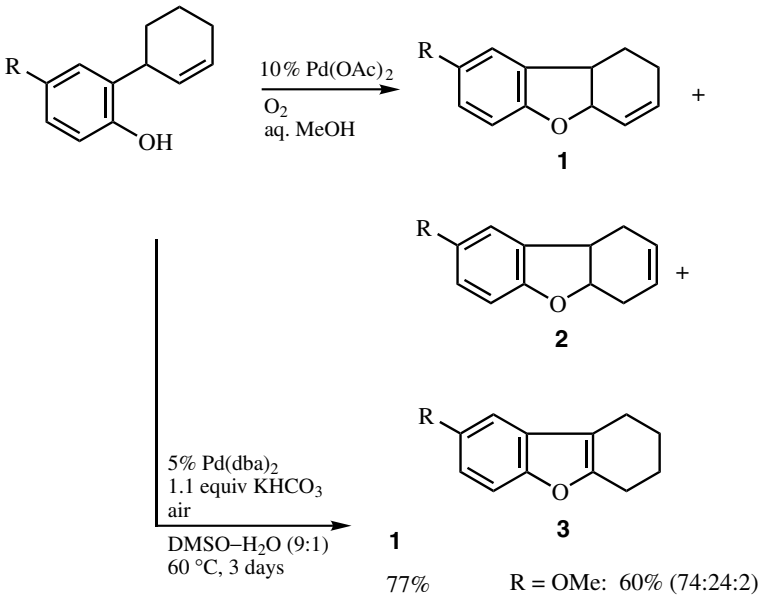


Scheme 5

Thus, as shown in **Scheme 6**, 2-(2-butenyl)phenol can be converted catalytically into 2-vinyl-2,3-dihydrobenzofuran by using $Cu(OAc)_2$ under O_2.[6],[7] 2-(2-Cyclohexenyl) phenol also gives mainly the corresponding cyclized product **1**, accompanied by its positional isomers **2** and **3** of olefin.[8] Noteworthy is that this cyclization proceeds catalytically by the use of O_2 alone and $Pd(OAc)_2$. When a phenyl substituent is in the terminal position of allylic side chain, 2-benzylbenzofuran becomes the product.



[I] = 10% $Pd(OAc)_2$, 10% $Cu(OAc)_2$, O_2, MeOH, 36 °C, 24 h.

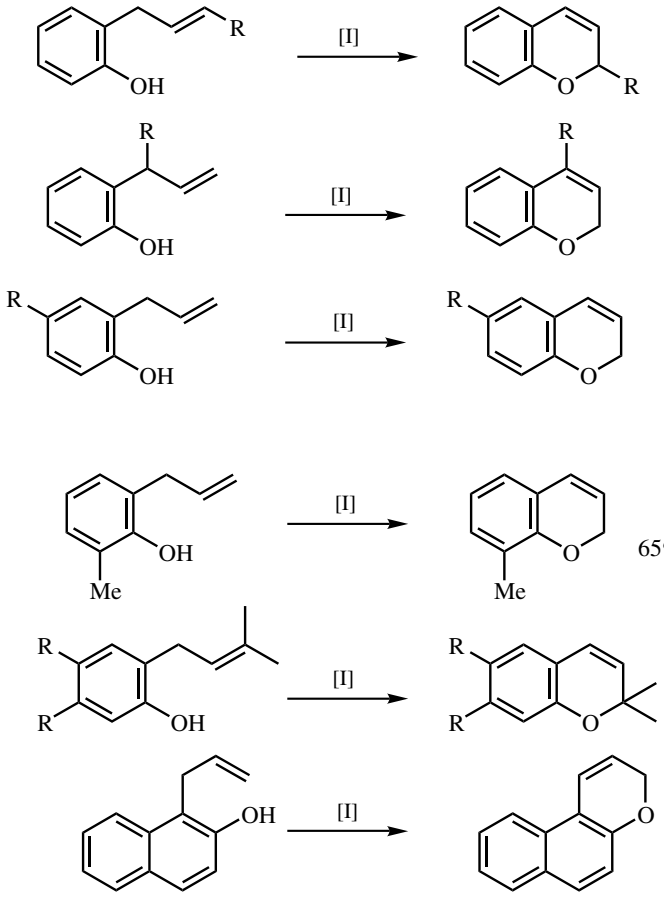


Scheme 6

A combination of $Pd(dba)_2$ catalyst and $KHCO_3$ in aqueous DMSO under air results in the 6-*endo* cyclization to give chromenes (2H-1-benzopyrans). Using this system, a wide variety of chromenes have been cleanly synthesized from 2-allylphenols (**Scheme 7**),[9] although the reaction time is rather long (3 days). The reaction could be accounted for by oxypalladation followed by Pd—H elimination. Alternatively, the allylic moiety may directly be converted into a π-allylpalladium intermediate formed *in situ*, and subsequently the oxygen nucleophile attacks at the remote end of the allylic system to give the chromene.

2-Alkenylphenols bearing 3-pentenyl moieties undergo 6-*exo* cyclization to give 2-vinylchromans.[7] Application of this cyclization to 2-methyl-2-vinylchroman corresponding to a vitamin E moiety has been made by using the alkenylphenol prepared from 2,5-dimethoxy-3,4,6-trimethylbenzyl chloride and 2-methyl-*trans*-2-butenyl phosphate with magnesium (**Scheme 8**).[10]

Note here that, as shown in **Scheme 9**, the methyl carbon of 2-butenyl or 2-pentenyl moiety of the starting 2-alkenylphenols can be functionalized via the resulting 2-vinyl-2,3-dihydrobenzofuran or 2-vinylchroman with nucleophiles in the presence of palladium(0) catalyst.[7]

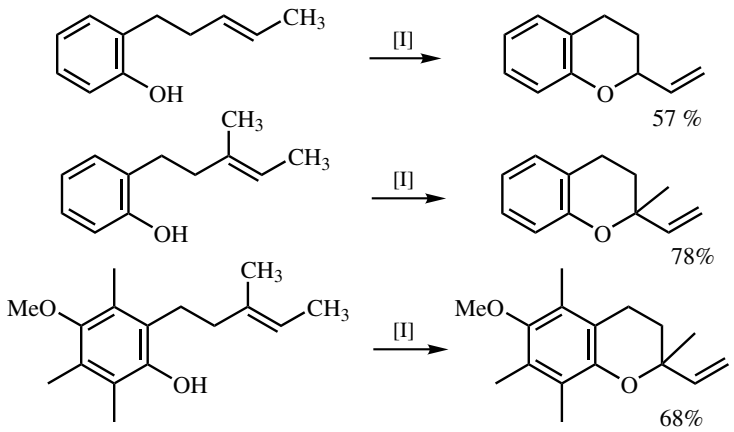


R	Yield (%)
OCH_3	71
CH_3CO	23[a]
CN	41[a]

[a] 5 mol% $Pd(OAc)_2$ was used.

[I] = 5 mol % $Pd(dba)_2$, 1.1 equiv $KHCO_3$, air, DMSO–H_2O (9:1) 60 °C, 3 days.

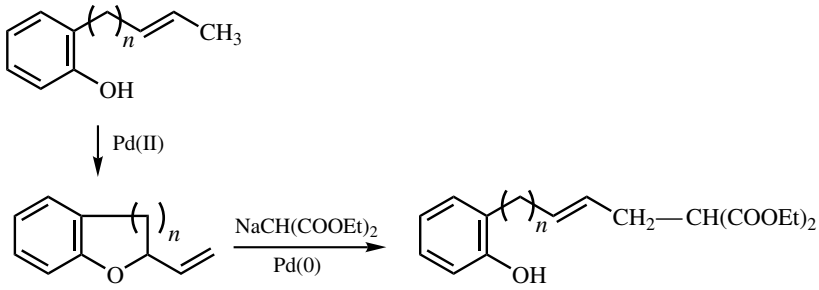
Scheme 7



[I] = 10 mol % $Pd(OAc)_2$, 10 mol % $Cu(OAc)_2$, O_2, MeOH, 36 °C.

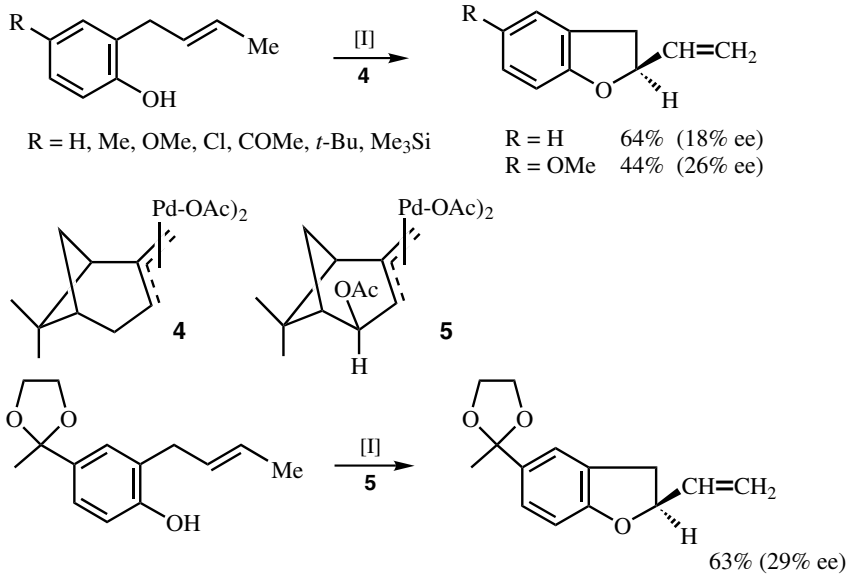
Scheme 8

The utility of this cyclization is enhanced by the use of palladium(II) catalysts bearing chiral ligands, which enables chiral products to be prepared. In the first example reported in 1978[11],[12] (**Scheme 10**), $[(3,2,10\text{-}\eta\text{-pinene})PdOAc]_2$ (**4**), readily prepared from (−)-pinene and $Pd(OAc)_2$, was used as the catalyst in the presence of $Cu(OAc)_2$ and O_2. 4-Substituted 2-(2-butenyl)phenols are asymmetrically cyclized by this catalyst system to give (*S*)-2-vinyl-2,3-dihydrobenzofurans (**Scheme 10**).[13] The use of $[(3,2,10\text{-}\eta\text{-}cis\text{-}4\text{-acetoxy-pinene})PdOAc]_2$ (**5**) as the catalyst leads to the opposite enantiomer.[14] Although the enantioselectivity of the cyclized products is not high (e.g., R = OCH_3, 26% ee), the $[\alpha]_D$ value of the product was found to be constant, irrespective of the reaction times. This observation indicates that the valency of Pd(II) does not change during the reaction.[12]



n = 1: 3 mol % $Pd(PPh_3)_3$ 76%
n = 2: 3 mol % $PdCl_2(PEt_3)_2$ 63%

Scheme 9



R = H, Me, OMe, Cl, COMe, *t*-Bu, Me_3Si

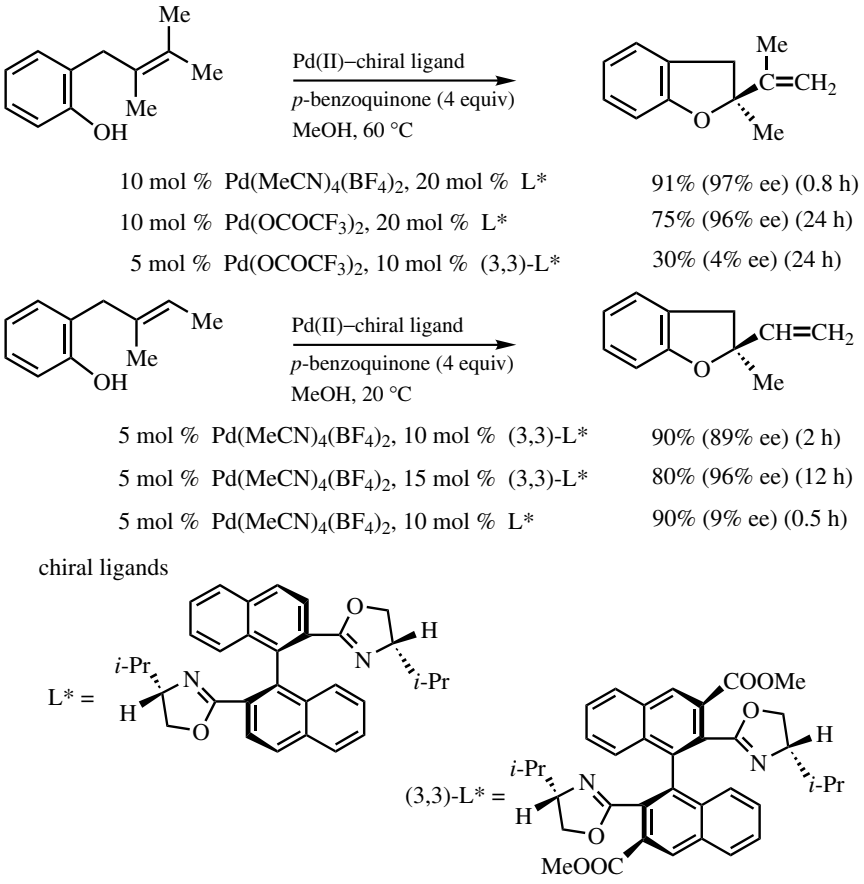
R = H 64% (18% ee)
R = OMe 44% (26% ee)

63% (29% ee)

[I] = 10 mol % Pd catalyst, 10 mol % $Cu(OAc)_2$, O_2, aq. MeOH, 36 °C.

Scheme 10

On the basis of this observation, more effective chiral ligands have been developed by Uozumi, Hayashi, and co-workers[15],[16] in the cyclization of 2-(2,2-dimethyl-2-butenyl)phenols where (*S*,*S*)-2,2′-bis[4-isopropyloxazolyl]-1,1′-binaphthyl was utilized as the chiral ligand (L*) of palladium(II) catalysts such as $Pd(OCOCF_3)_2$, and *p*-benzoquinone as the co-oxidant (**Scheme 11**). The chiral ligand was intact also during the reaction and recovered quantitatively after the reaction. The chiral bis(oxazoline) ligand based on 1,1′-binaphthyl backbone is essential for high enantioselectivity, and for higher reactivity, $OCOCF_3$ as the ligand of palladium and MeOH as the solvent are required, respectively.

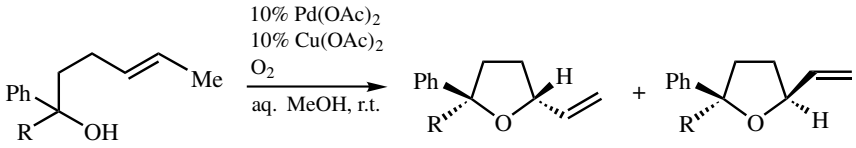


Scheme 11

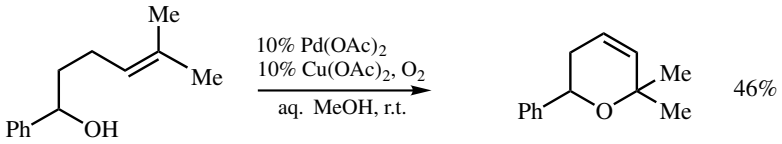
C. INTRAMOLECULAR OXYPALLADATION OF HYDROXYALKENES

Unsaturated alcohols similarly undergo cyclization as shown in **Scheme 12**.[17] For instance, 2-vinyltetrahydrofurans are formed catalytically from γ,δ-unsaturated alcohols via 5-*exo* cyclization. This protocol has recently been applied for the synthesis of C-vinyl furanosides[18] as shown in **Scheme 13**, where the catalyst system is constructed by using $Pd(OAc)_2$ and O_2 in the presence of NaOAc in DMSO solvent, and no copper salt is

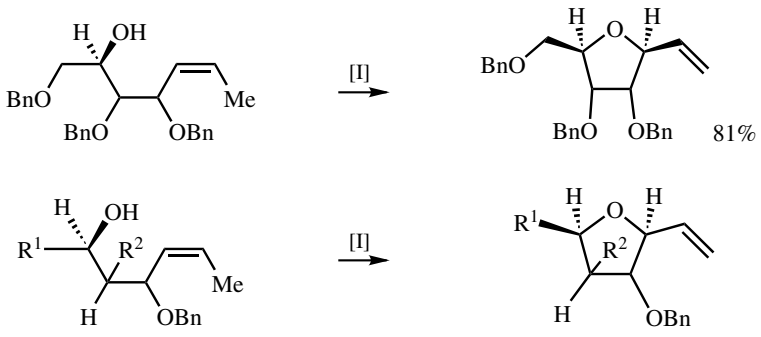
utilized. This catalyst system was firstly disclosed by Larock and Hightower[19] in 1993, and subsequently by van Benthem and co-workers[20] in 1994 (*vide infra*). The crucial point is that if DMSO is used as the solvent, no copper salt is required for the catalysis. The uniqueness of this solvent was originally found by Semmelhack and Epa[21] in the stoichiometric cyclization of a hydroxyalkene shown in **Scheme 14**, where the mode of the β-Pd—H elimination process was controlled by the coordination ability of DMSO to palladium.



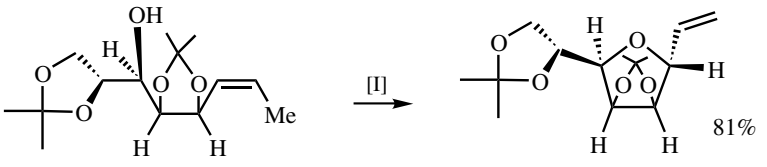
R	Yield (%)	Yield (%)
H	40	—
Me	21	31
Et	15	21
Ph	15	—



Scheme 12

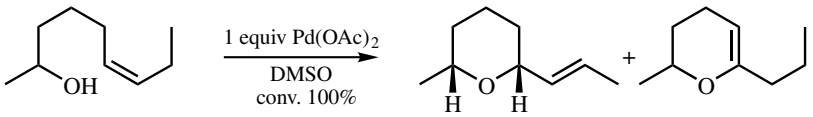


$R^1 = CH_2OBn$, $R^2 = OBn$ 83% (α:β = 3:2)
$R^1 = Me$, $R^2 = OMe$ 79% (α:β = 3:2)



[I] = 10 mol % $Pd(OAC)_2$, 2 equiv NaOAc, O_2, DMSO, 50 °C, 12–18 h.

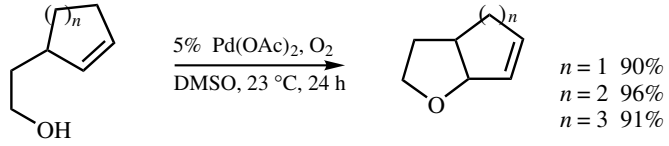
Scheme 13



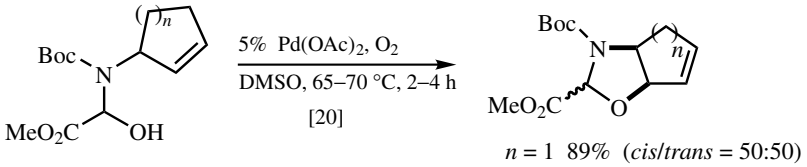
Scheme 14

Rönn, Bäckvall, and Andersson[22] have applied the catalyst system to the cyclization of cycloalkenyl alcohols leading to bicyclic ethers (**Scheme 15**). In this cyclization, the use of $Cu(OAc)_2$ and NaOAc as cocatalysts retards the rate of reaction.

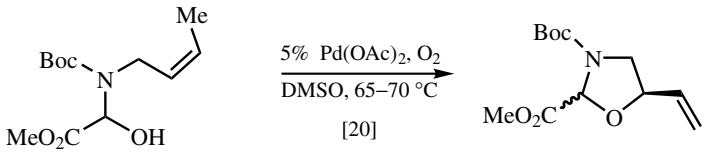
Study of the $Pd(OAc)_2/DMSO/O_2$ system by van Benthem and co-workers[20],[23],[24] has opened a route to oxazolidine derivatives from alkenes bearing *N*-Boc-protected amino alcohols (**Scheme 16**). The oxazolidines obtained can readily be converted into *N*-Boc-protected β-amino alcohols through anodic oxidation and hydrolysis.



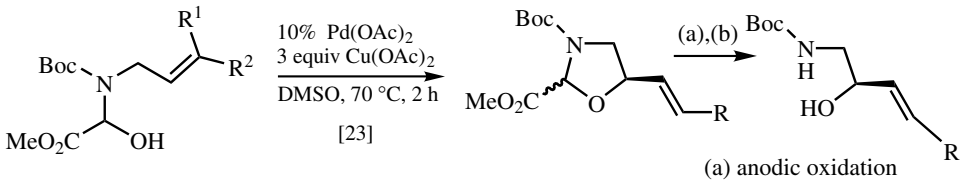
Scheme 15



n = 1 89% (*cis*/*trans* = 50:50)
n = 2 90% (*cis*/*trans* = 50:50)
n = 4 58% (*cis*/*trans* = 33:67)



80% (*cis*/*trans* = 24:76)

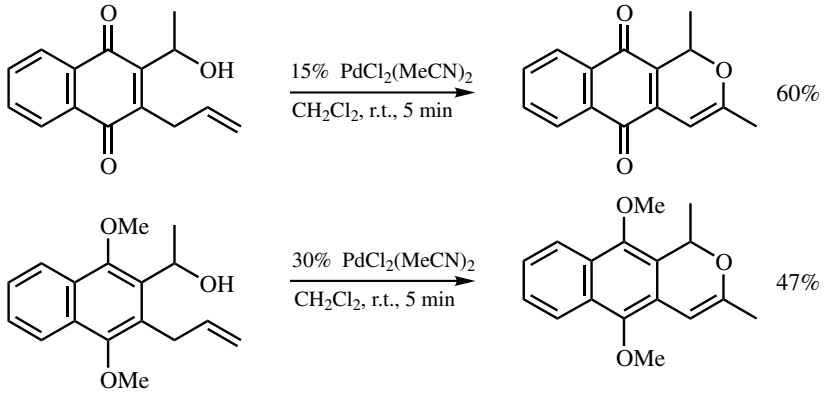


(a) anodic oxidation
(b) hydrolysis

R^1	R^2	R	Yield (%)
Me	H	H	76 (3:1)
H	Me	H	64 (1:1)
Pr	H	Et	80 (3:1)
H	Pr	Et	56 (1:1)

Scheme 16

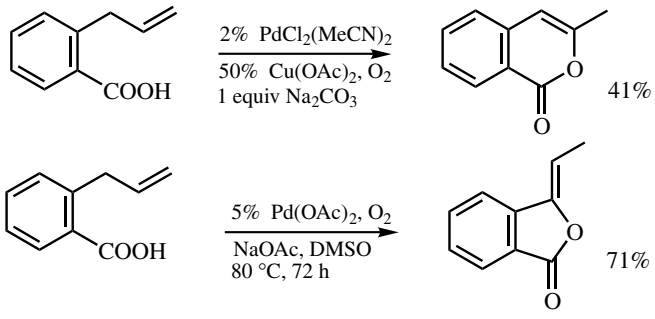
The cyclization of 2-allyl-3-(1′-hydroxyethyl)naphthoquinone or naphthalene by using $PdCl_2(MeCN)_2$ catalyst in CH_2Cl_2 proceeds rapidly to give the corresponding 6-*endo* cyclized product via isomerization of C═C bond to the conjugated position (**Scheme 17**).[25]



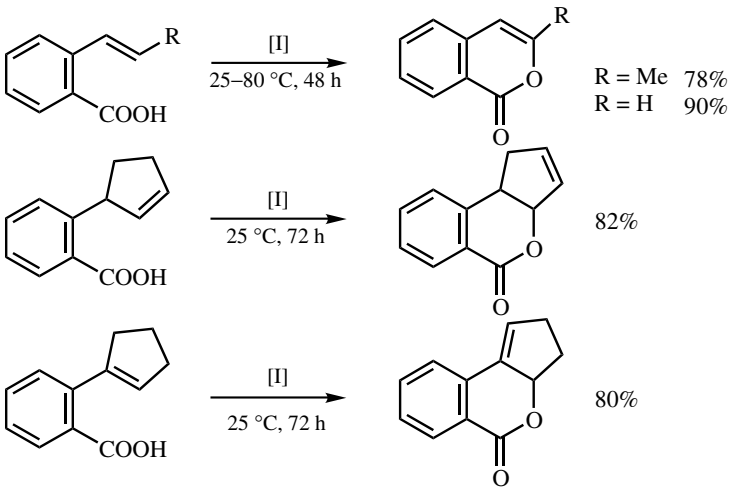
Scheme 17

Unsaturated carboxylic acids also undergo cyclization of this type.[26] In 1977, Korte, Hegedus, and Wirth[27] reported that the use of $PdCl_2$ catalyst with $Cu(OAc)_2$ and O_2 produces 3-methyl-3,4-dihydroisocoumarin from 2-allylbenzoic acids. This 6-*endo-trig* pathway via C═C isomerization has recently been shown to be altered to 5-*exo-trig* mode leading to *Z*-phthalide, when the $Pd(OAc)_2/O_2$/DMSO system is employed (**Scheme 18**).[19] The cyclization also involves isomerization of C═C bond to the conjugated position. Furthermore, as shown in **Scheme 19**, the use of $Pd(OAc)_2/O_2$/DMSO results in the 6-*endo* cyclization of 2-vinylbenzoic acids into isocoumarines. With this system, *o*-cyclopentenylbenzoic acids similarly undergo the same type of cyclization, regardless of 1- or 2-position of the alkene.

Alkenoic acids given in **Scheme 20** are also cyclized to give good yields of lactones.[19],[28] The relative reactivity of alkenes generally follows the order: disubstituted > trisubstituted > monosubstituted, probably due to a fine balance between the electron density and steric bulkiness. *exo*-Methylene-γ-butyrolactones can similarly be synthesized from the corresponding alkenyl carboxylic acids.[29]

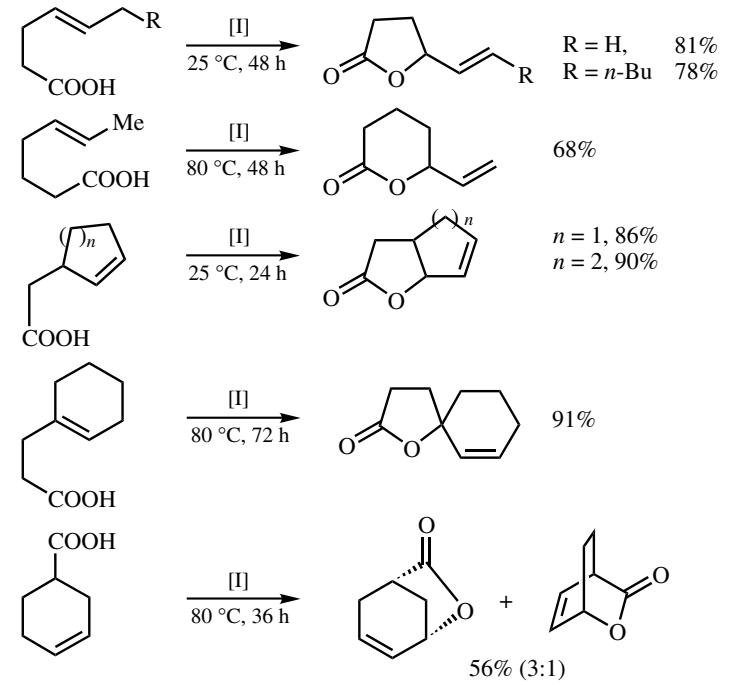


Scheme 18

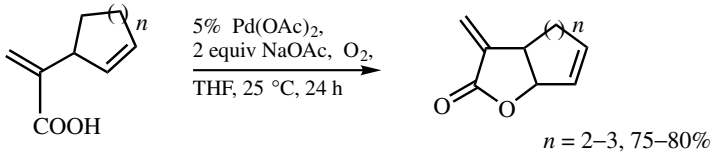


[I] = 5 mol % $Pd(OAc)_2$, O_2, NaOAc (2 equiv), DMSO.

Scheme 19



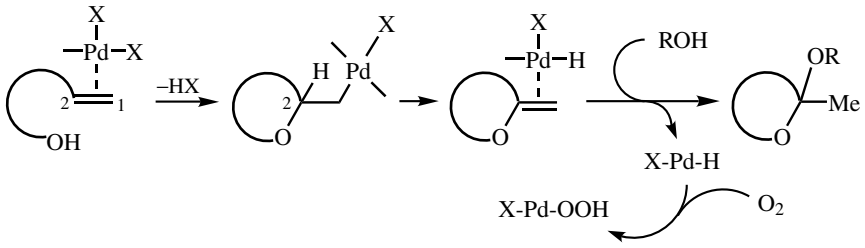
[I] = 5 mol % $Pd(OAc)_2$, O_2, NaOAc (2 equiv), DMSO, 25 °C.



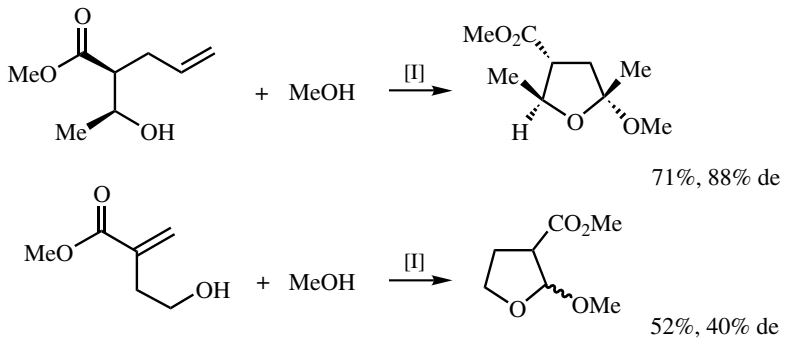
Scheme 20

D. INTRAMOLECULAR ACETALIZATION OF HYDROXYALKENES

Intramolecular oxypalladation of hydroxyalkenes in the presence of alcohols or water produces acetals or hemiacetals. When an oxypalladation intermediate leads to *exo*-methylene substituent, nucleophilic attack of ROH to the alkene gives acetals via a process formally represented in **Scheme 21**. The catalysis is thought to be operative by the oxygenation of the Pd—H by O_2 or by the regeneration of PdX_2 with excess CuX_n ($n = 1$ or 2). Under the conditions using CuCl and O_2, (2*S*,3*S*)-2-allyl-3-hydroxybutyrate is catalytically converted to acetal by using $PdCl_2(MeCN)_2$ catalyst and MeOH (**Scheme 22**).[30] Intramolecular acetalizations of disubstituted hydroxyalkenes are shown in **Scheme 23**.[31] In this case, an excess amount of CuCl is used for the catalysis.

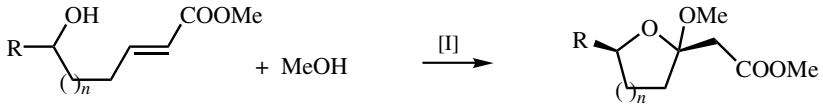


Scheme 21



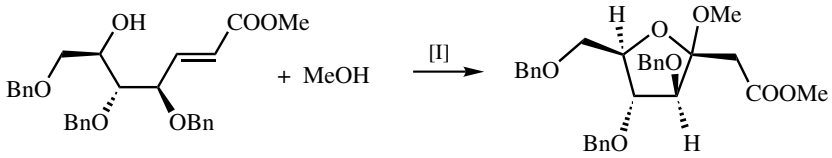
[I] = 10 mol % $PdCl_2(MeCN)_2$, 20% CuCl, O_2, 15 mol % Na_2HPO_4, DME, 50 °C, 1 h.

Scheme 22



R	*n*	Yield (%)
H	1	87
H	2	62
Bn	2	61
Hept	2	61
Pent	1	87

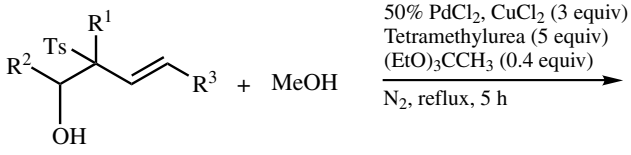
Scheme 23



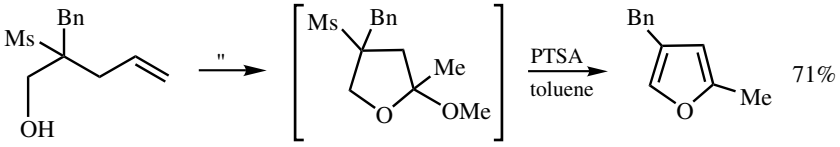
[I] = 10% $PdCl_2$, 3 equiv CuCl in the presence or absence of 6 equiv LiCl.

Scheme 23 (*Continued*)

Homoallylic alcohols bearing a tosyl group on the allylic position afford cyclic acetals via 6-*endo-trig* cyclization (**Scheme 24**), where a catalyst system is constituted of $PdCl_2$ and $CuCl_2$ together with tetramethylurea, and ethyl orthoacetate is used for a HCl quencher.[32] 2-Benzyl-2-methanesulfonyl-4-pentenol shown in **Scheme 24** gives a furan derivative after treatment of the resulting cyclic acetal with an acid catalyst. Simple homoallyl alcohols such as 1-penten-4-ol undergo cyclization of this type,[33] when a Pd–nitro complex is used as the catalyst together with $CuCl_2$ and O_2 in *t*-BuOH or *i*-PrOH (**Scheme 25**).

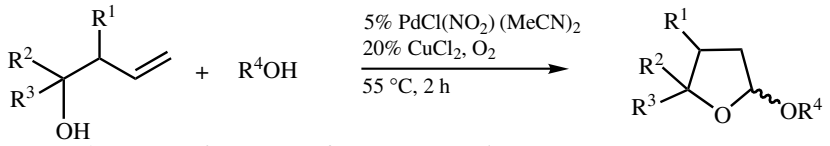


R^1	R^2	R^3	Yield (%)
H	$PhCH_2CH_2$	H	95
H	$CH(CH_2)_8$	H	79
H	$(CH_3)_2CHCH_2$	H	81
H	Me	H	69
$PhCH_2$	H	H	23
H	$PhCH_2CH_2$	H	52



Scheme 24

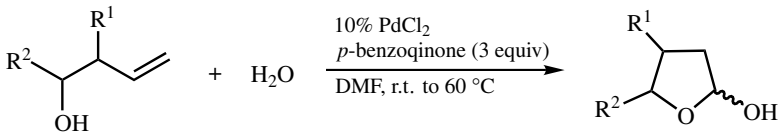
When water is used as the nucleophile, hemiacetals are formed as shown in **Scheme 26**, where a combination of $PdCl_2$ and 3 equiv of *p*-benzoquinone is used for the catalyst system.[34] With this method, optically active deoxyribose in a protected form can be obtained from 3-benzyloxy-4-hydroxy-5-benzoyloxy-1-pentene (**Scheme 26**). A precursor of the "Eastern half" of Rosaramicin[35] and various C-glycosides[36] can similarly be synthesized from highly functionalized homoallyl alcohols. These results are given in **Schemes 27** and **28**.



R^1	R^2	R^3	R^4	GC Yield (%)	
H	H	H	*i*-Pr	26	
H	H	H	*t*-Bu	94	(30)[a]
H	Me	Me	*t*-Bu	100	(80)[a]
H	Ph	Ph	*i*-Pr	80	
Me	Me	Me	*t*-Bu	96	(70)[a]
H	Me	COOEt	*t*-Bu	63	
H	Ph	COOEt	*t*-Bu	>90	

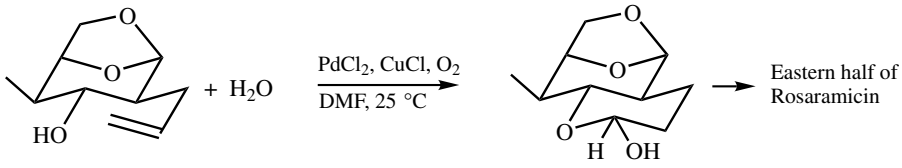
[a] Isolated yield in parentheses.

Scheme 25

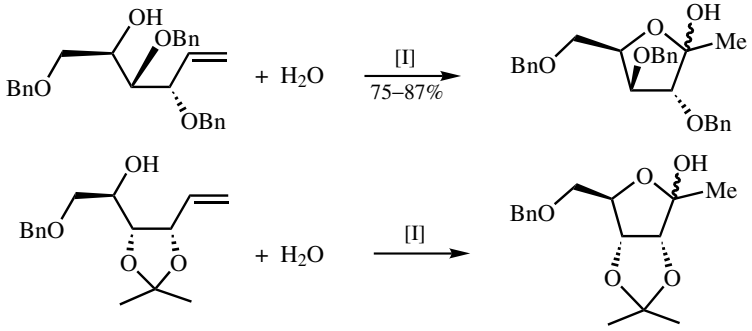


R^1	R^2	Yield (%)	
$(CH_2)_7COOMe$	Pent	74	
$(CH_2)_7COOMe$	H	58	
COOMe	Hex	62	
Ts	Hex	82	
Me	Hex	64	($CuCl–O_2$)

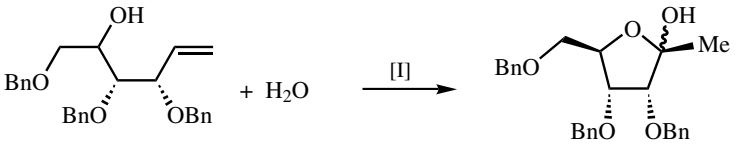
Scheme 26



Scheme 27



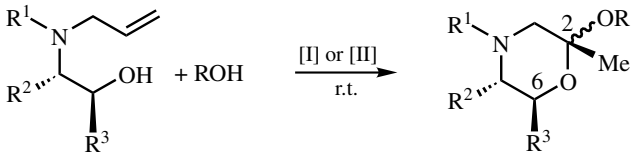
Scheme 28



[I] = 10 mol % $PdCl_2$, CuCl (1 equiv), O_2, H_2O–MeCN (1:7).

Scheme 28 (*Continued*)

From hydroxyalkenes derived from (*R*)-(−)- or (*S*)-(+)-phenethylamine and/or (*S*)-(+)-lactic acid or (1*R*, 2*S*)-(−)-ephedrine, optically active tetrahydro-1,4-oxazines have been synthesized by using either MeOH or H_2O as the nucleophile (**Scheme 29**).[37] The diastereoselectivities observed are high. In this case, the use of excess amounts of copper salts makes the reaction catalytic even in the absence of O_2. Interception of the Pd—C bond in oxypalladation adduct by chloride ion yields 2-chloromethyl-1,4-oxazines as shown in **Scheme 30**.[37]

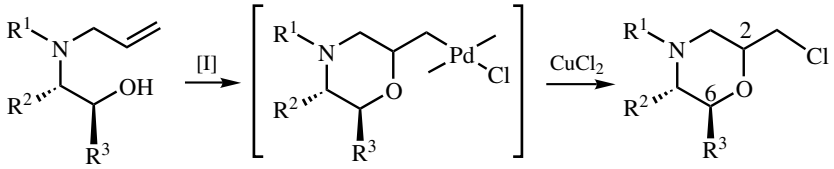


R^1	R^2	R^3		R	Yield (%)	% de	Configuration
(*S*)-PhCHMe	H	H	[I]	Me	76	<1	
(*S*)-PhCHMe	H	Me	[I]	Me	83	76	2*R*,6*S*,*S*
(*R*)-PhCHMe	H	Me	[I]	Me	92	71	2*R*,6*S*,*R*
Bn	H	Me	[I]	Me	96	91	2*R*,6S
Me (2*S*,5*R*)	Me	Ph	[I]	Me	73	>99	2*S*,5*S*,6*R*
(*S*)-PhCHMe	H	H	[II]	H	84	87	2*R*,6*S*, *S*
Bn	H	Me	[II]	H	78	91	2*R*,6*S*
Me (5*S*,6*R*)	Me	Ph	[II]	H	74	>99	2*S*,5*S*,6*R*

[I] = 10 mol % Li_2PdCl_4, 3 equiv $CuCl_2$, MeOH, 36–48 h.

[II] = 10 mol % Li_2PdCl_4, 3 equiv $CuCl_2$, H_2O–THF, 24–48 h.

Scheme 29

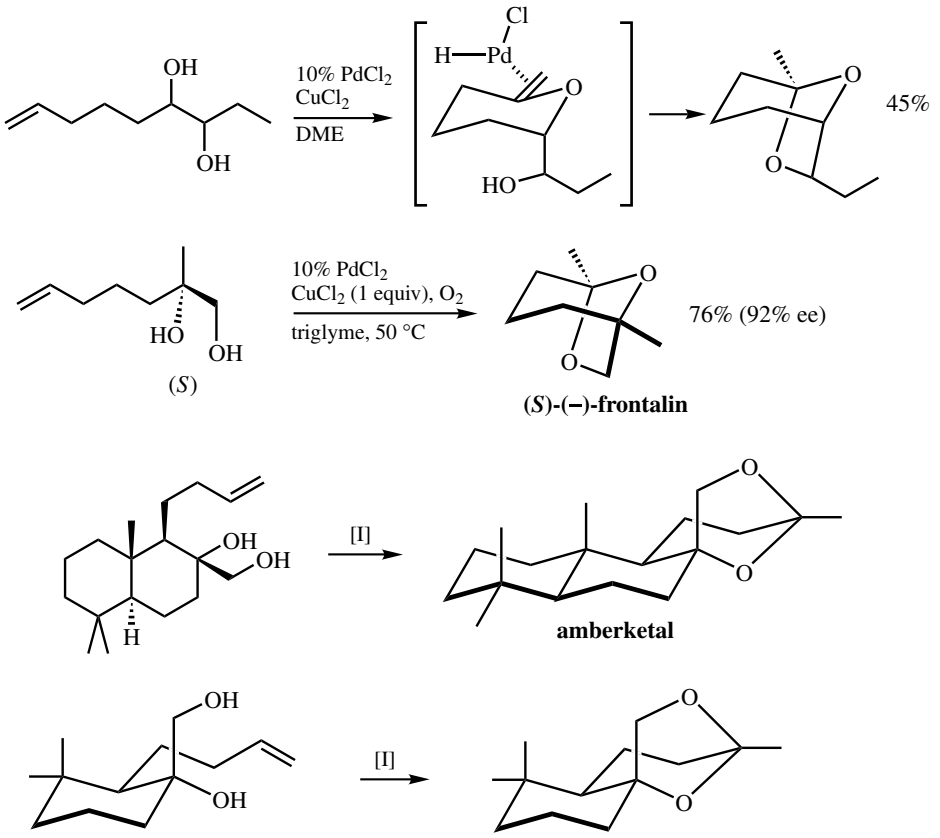


R^1	R^2	R^3		Yield (%)	% de	Configuration
(*R*)-PhCHMe	H	Me	[I]	80	83	2*S*,6*S*,*R*
Me (5*S*,6*R*)	Me	Ph	[I]	75	>98	2*R*,5*S*,6*R*

[I] = 10 mol % Li_2PdCl_4, 3 equiv $CuCl_2$, THF–CF_3COOH, 48–72 h.

Scheme 30

Bicyclic acetals are obtained in the cyclization of alkenyl diols as shown in **Scheme 31**, where the attack of OH group toward an internal alkene formed after the oxypalladation process takes place.[38]–[40] Thus, optically active natural (*S*)-(−)-frontalin[41]–[43] can be prepared from (*S*)-6,7-dihydroxy-6-methyl-1-heptene. Amberketal and its homologue are able to be similarly synthesized.[44]

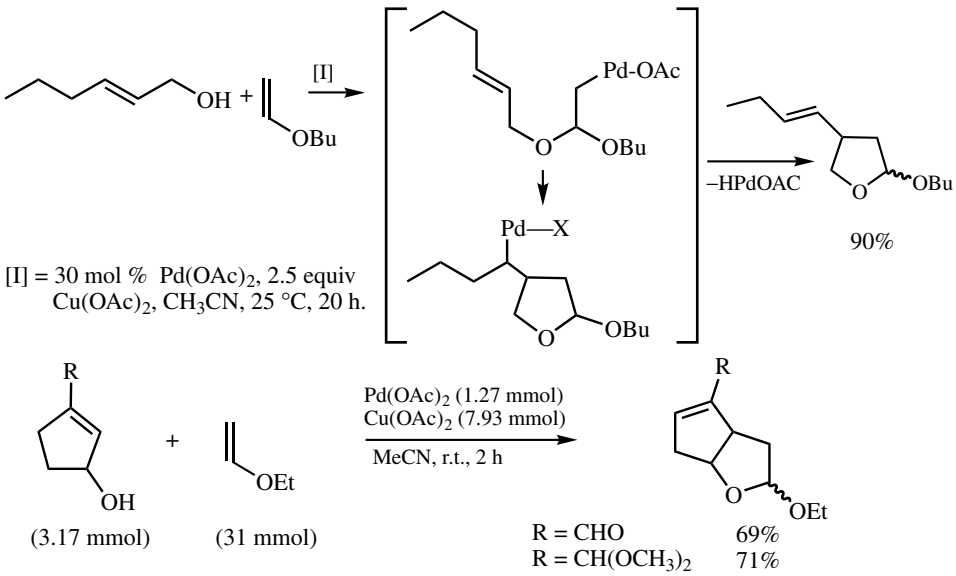


[I] = $PdCl_2$, $CuCl_2$, O_2, DME, 65 °C.

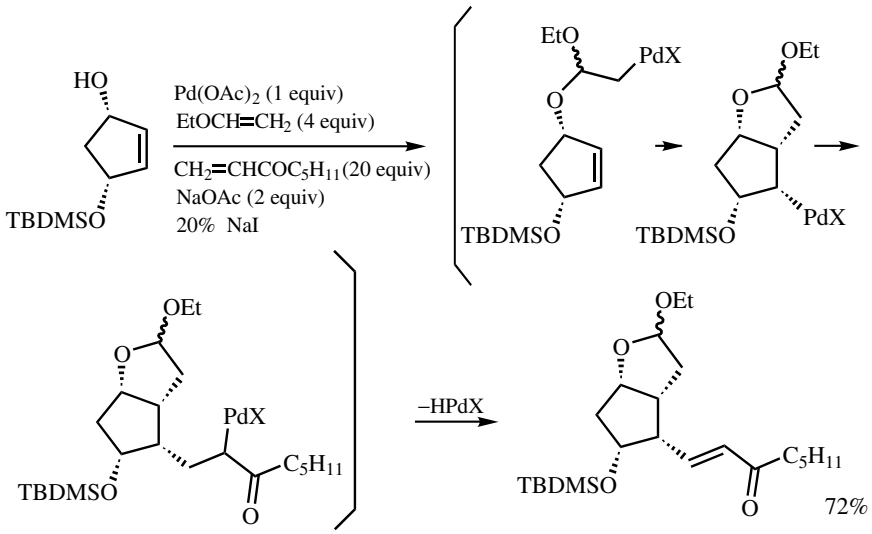
Scheme 31

As shown in **Scheme 32**, when allylilc alcohols are allowed to react with vinyl ethers, the resulting σ-bond in oxypalladation intermediate adds intramolecularly to the C═C bond of allylic moiety.[45],[46] Subsequent β-Pd—H elimination leads to cyclic acetals. With this method, albeit stoichiometric in palladium(II), a unique approach to the synthesis of prostaglandins was attained by Larock and Lee as shown in **Scheme 33**.[47]

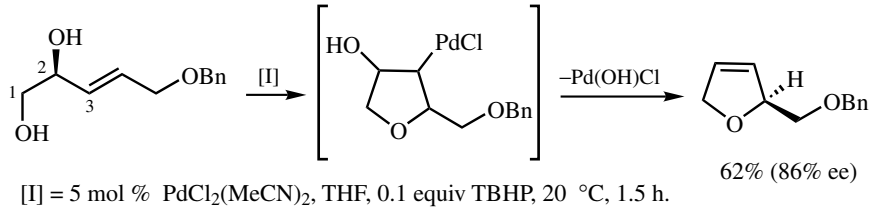
Cyclization of homoallylic alcohols bearing an OH group at the allylic position gives an oxypalladation intermediate in which the OH group is in the adjacent position of Pd—C bond. In such cases, elimination of Pd—OH predominates to give dihydrofurans as shown in **Scheme 34**.[48] The same type of cyclization and elimination occurs with β-diketones bearing allylic alcohol moiety. The cyclization proceeds via keto-enol tautomerism (**Scheme 35**).[49]



Scheme 32

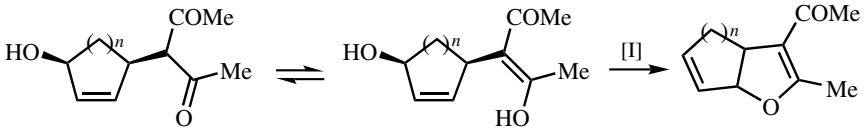


Scheme 33



[I] = 5 mol % $PdCl_2(MeCN)_2$, THF, 0.1 equiv TBHP, 20 °C, 1.5 h.

Scheme 34

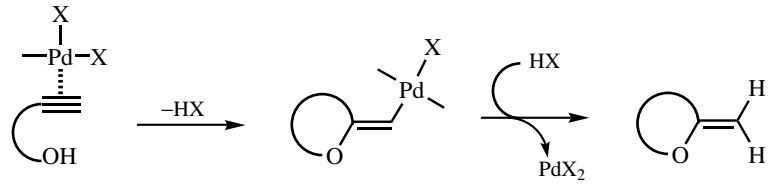


[I] = 5 mol % $PdCl_2(MeCN)_2$, acetone, 25 °C, 1 h.

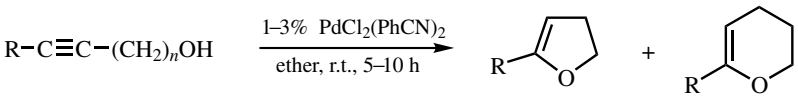
Scheme 35

E. INTRAMOLECULAR OXYPALLADATION OF HYDROXYALKYNES

Intramolecular oxypalladation of carbon–carbon triple bond by PdX_2 leads to a vinyl palladium species. The resulting σ-C—Pd bond is readily cleaved by HX formed *in situ* to give oxygen heterocycles, and PdX_2 is regenerated (**Scheme 36**). Thus, the catalysis is exerted only by the use of PdX_2. This type of cyclization was first reported by Utimoto in 1983[50] and thereafter became a useful synthetic tool for O-heterocycles. In general, alkynyl alcohols undergo either 5-*exo-dig* or 6-*endo-dig* cyclization, depending on the length of side chain or the configuration of cyclic compounds (**Schemes 37** and **38**).[50]

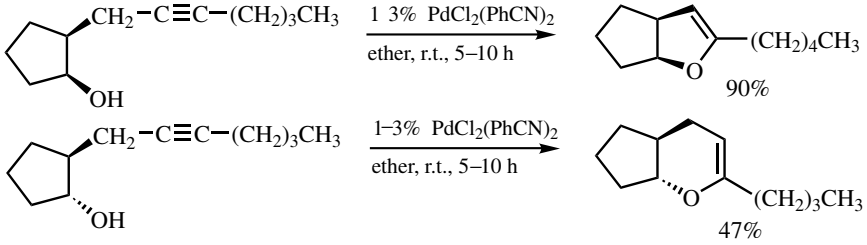


Scheme 36



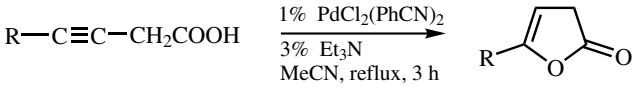
R	*n*	Yield (%)	
$CH_3(CH_2)_5$	2	60	—
$CH_3(CH_2)_5$	4	—	50
$CH_3(CH_2)_6$	3	50	45

Scheme 37



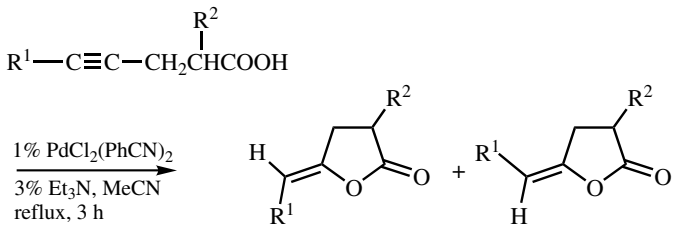
Scheme 38

Alkynyl carboxylic acids[50],[51] are similarly cyclized to give lactones via 5-*endo*, 5-*exo*, or 6-*exo* cyclization (**Schemes 39** and **40**). Insertion of allyl chloride into the resulting σ-C—Pd bond of the vinyl palladium species followed by elimination of $PdCl_2$ leads to incorporation of an allylic moiety into oxygen heterocycles as shown in **Scheme 41**.[52],[53]



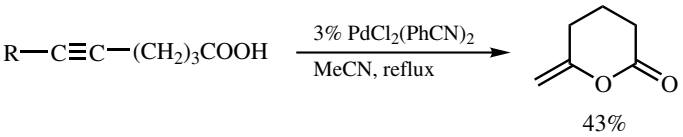
R	Yield (%)
Me	95
n-Hex	84
n-Oct	88
Ph	38

Scheme 39



R^1	R^2	Yield (%)	Yield (%)
H	H	100[a]	—
H	Bu	81	—
H	Hex	84	—
H	Ph	96	—
H	Ben	85	—
H	Me_3Si	63	—
Me	H	87	14
Ph	H	85	—
Hex	H	66	9

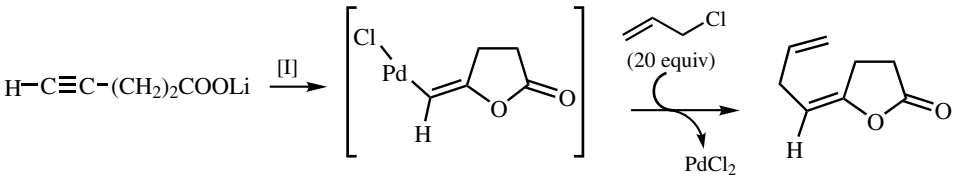
[a] $PdCl_2(MeCN)_2$ was used as the catalyst.



43%

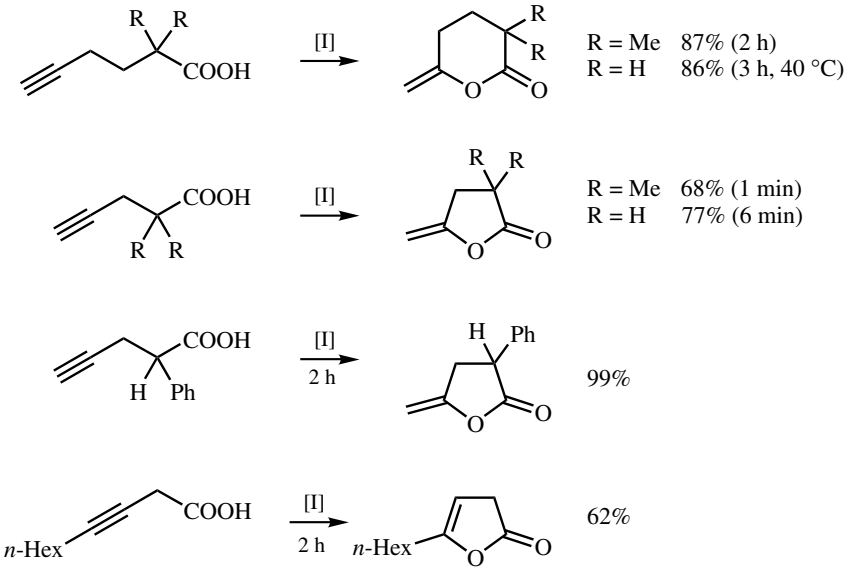
Scheme 40

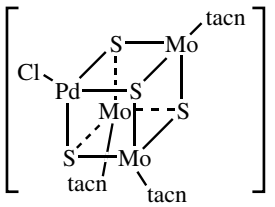
Recently, a cuboidal $PdMo_3S_4$ cluster has been reported to act as a highly effective catalyst for the cyclization of 3-, 4-, and 5-alkeynoic acid to the corresponding enol lactones (**Scheme 42**).[54] The catalytic activity of the cluster has been evaluated to be 17 times higher than that of $PdCl_2(PhCN)_2$. Furthermore, a 100,000 turnover number per Pd (19 h, 40 °C) has been attained in the cyclization of 4-pentynoic acid.



[I] = 5 mol % $PdCl_2(PhCN)_2$, THF, r.t., 5 h.

Scheme 41





[I] = 0.3 mol % $PdMo_3S_4$ cat, 3 mol % NEt_3, MeCN, r.t.

$PdMo_3S_4$ cat. (tacn = 1,4,7-triazacyclononane)

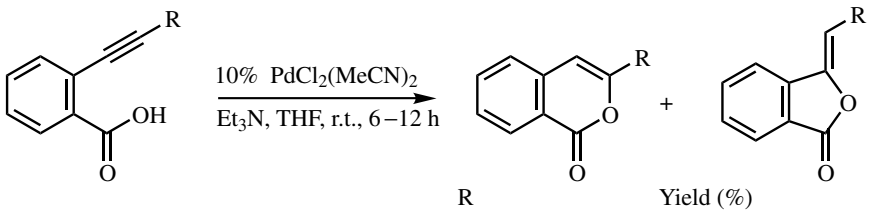
Scheme 42

As shown in **Scheme 43**, treatment of *o*-ethynylbenzoic acids with $PdCl_2(MeCN)_2$ catalyst in THF results in the 6-*endo-dig* cyclization to give 3-substituted isocoumarins as the major product.[55]

Trimethylsilyl homopropargylic alcohols, when treated with $PdClNO_2(MeCN)_2$ catalyst and 1 *N* HCl in MeCN solvent or with wet DMF, give various γ-butyrolactones (**Scheme 44**).[56] The γ-butyrolactone is thought to be formed by the Wacker reaction of 4-silylated 2,3-dihydrofurans formed *in situ*. Silyl-substituted bis(homo)propargylic

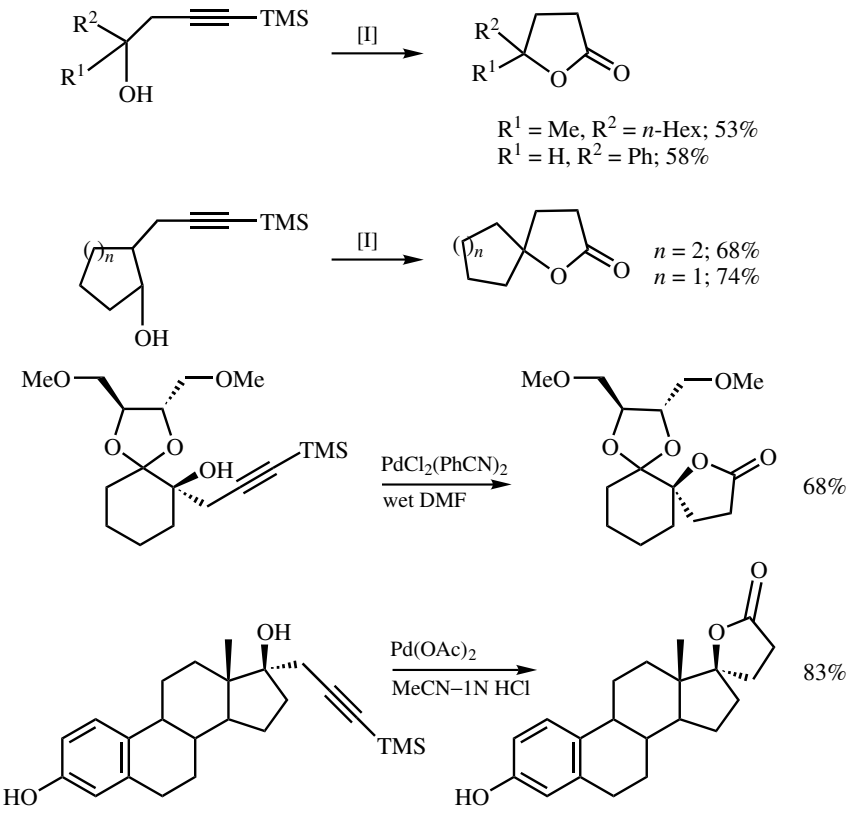
alcohols, when treated with $Pd(OAc)_2$ catalyst and HCl, undergo 5-*exo-dig* ring closure to give 2,3-dihydrofurans with elimination of the terminal silyl group (**Scheme 45**).[57]

β,γ-Acetylenic ketones produce furans by intramolecular oxypalladation followed by protodemetallation as shown in **Scheme 46**.[58]



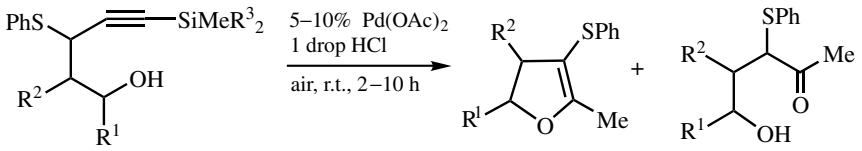
R		Yield (%)
Me	81	—
Bu	73	—
t-Bu	48	38
Ph	56	23
TMS	31	41

Scheme 43



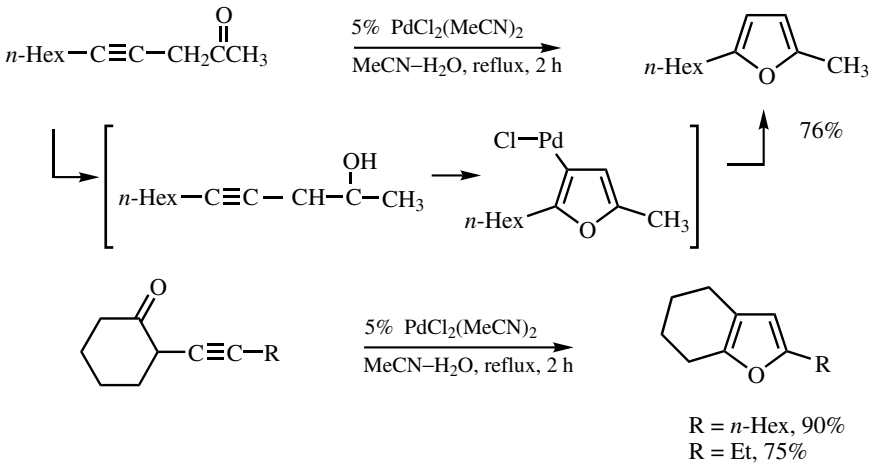
[I] = 5 mol % $PdClNO_2(MeCN)_2$, 25 mol % $CuCl_2$, 1N HCl, air.

Scheme 44



R^1	R^2	R^3	Yield (%)	Yield (%)
Me	H	Me	56	18
$BnOCH_2$	H	Ph	51	21
sec-C_5H_{11}	Me	Ph	54	15

Scheme 45



Scheme 46

In summary, the intramolecular oxypalladation followed by Pd—H elimination is undoubtedly useful for synthesizing O-heterocycles. In addition, some reactions of this type serve as useful probes for developing novel catalyst systems of palladium(II). A highly enantioselective oxypalladation has been developed by incorporation of chiral ligands in the catalyst system. However, it does not appear that the catalyst system applies to a broad range of substrates. Efforts focusing on the control of chirality are expected to continue in this field.

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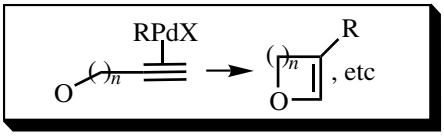

V.3.2.2 Oxypalladation–Reductive Elimination Domino Reactions with Organopalladium and Hydridopalladium Derivatives

SANDRO CACCHI and ANTONIO ARCADI

A. INTRODUCTION

The reaction of organopalladium and hydridopalladium complexes with alkynes can give rise to the formation of η^2-alkyne-organo- and η^2-alkyne-hydridopalladium intermediates **1** (**Scheme 1**). When the starting alkynes contain proximate oxygen nucleophiles, these intermediates can undergo an intramolecular nucleophilic attack across the activated carbon–carbon triple bond. *Endo-dig* (**Scheme 1a**) or *exo-dig* (**Scheme 1b**) σ-vinylpalladium adducts are generated depending on the number of atoms in between the acetylenic fragment and the oxygen. Subsequent reductive elimination of palladium(0) species affords oxygen-containing heterocycles and regenerates the catalyst. When η^2-alkyne-palladium intermediates are generated from organopalladiums, the reductive elimination step leads to the formation of a new carbon–carbon bond whereas in the presence of hydridopalladiums a hydrogen–carbon bond is formed.

B. REACTIONS WITH ORGANOPALLADIUM DERIVATIVES

Most of the chemistry involving the oxypalladation–reductive elimination domino sequence has been performed with organopalladium derivatives. Aryl and alkenyl halides or triflates, 1-halo-1-alkynes, allyl esters, propargyl esters, and propargyl ethers have usually been employed as starters. Oxygen atoms of alcoholic, phenolic, and carboxylic groups have been used as nucleophiles. Terminal alkynes and internal alkynes containing alkyl, alkenyl, and aryl groups can successfully be employed. A number of reaction variables such as the nucleophilicity of the oxygen, the substitution pattern of the alkyne, the absence or the presence—as well as the nature—of phosphine ligands, the solvents, and the added salts exert an influence on the reaction course.

As to the nucleophilic strength of the oxygen, apparently the presence of a strong anionic oxygen is required to allow the oxypalladation to occur. Proton removal from the hydroxy group in the transition state leading to the oxypalladation adduct might also be involved. Whatever the real mechanism of the nucleophilic attack may be, it remains that

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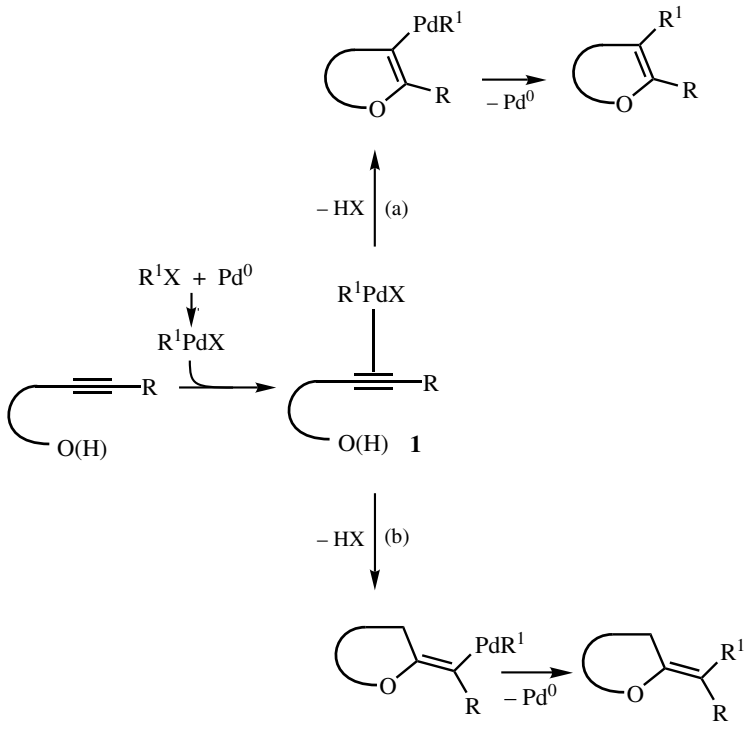


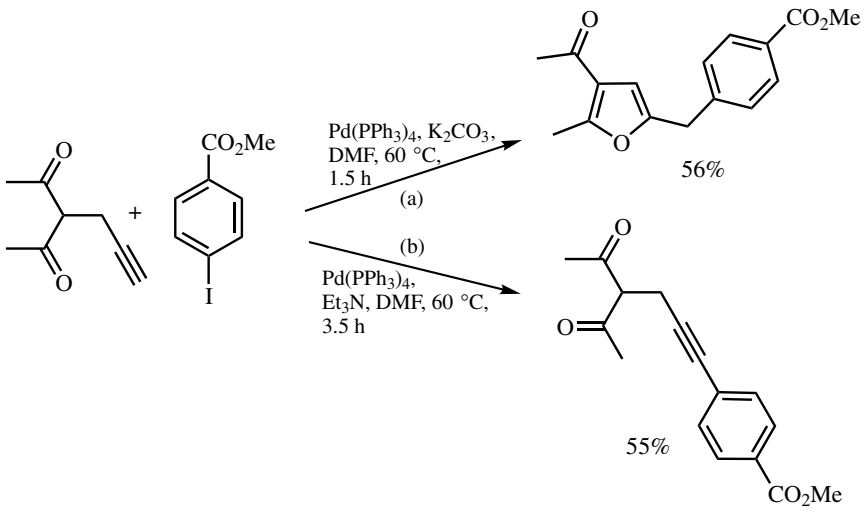
R^1 = aryl, vinyl, alkyl, alkynyl, allyl, propargyl, H

Scheme 1

organopalladiums seem to be less effective than palladium dichloride or palladium diacetate in promoting such a reaction. A variety of cyclizations of alkynes containing proximate hydroxy groups promoted by palladium dichloride or palladium diacetate under neutral or acidic conditions[1]–[4] appear to support this view.

The nature of the acetylenic partner is also important. With terminal hydroxy-containing alkynes, competition between the cyclization and coupling process may be observed. The nature of the added base plays a pivotal role in controlling such a competition. As an example, the reaction of 3-acetyl-5-hexyn-2-one with methyl 4-iodobenzoate[5] gives different products depending on whether potassium carbonate or triethylamine is used. With potassium carbonate the intramolecular nucleophilic attack of the oxygen across the carbon–carbon triple bond coordinated to palladium is favored and the furan derivative is formed (**Scheme 2a**). In the presence of triethylamine coordination to palladium results in the activation of the terminal hydrogen atom toward basic attack and the coupling product is obtained (**Scheme 2b**). In the latter case, a σ-alkyne-σ-organopalladium intermediate is most probably involved, from which the coupling derivative is generated via reductive elimination. This is a clear indication that the reaction outcome in processes of this kind is often the result of an intriguing combination of various effects.

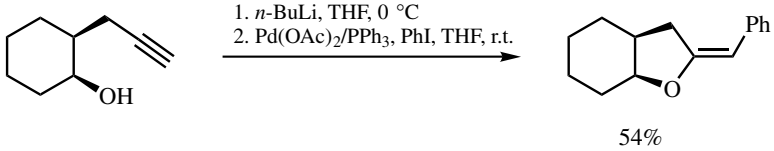
Specific examples of the influence of other factors critical to the success of the process (solvents, added salts, phosphine ligands) will be illustrated later.



Scheme 2

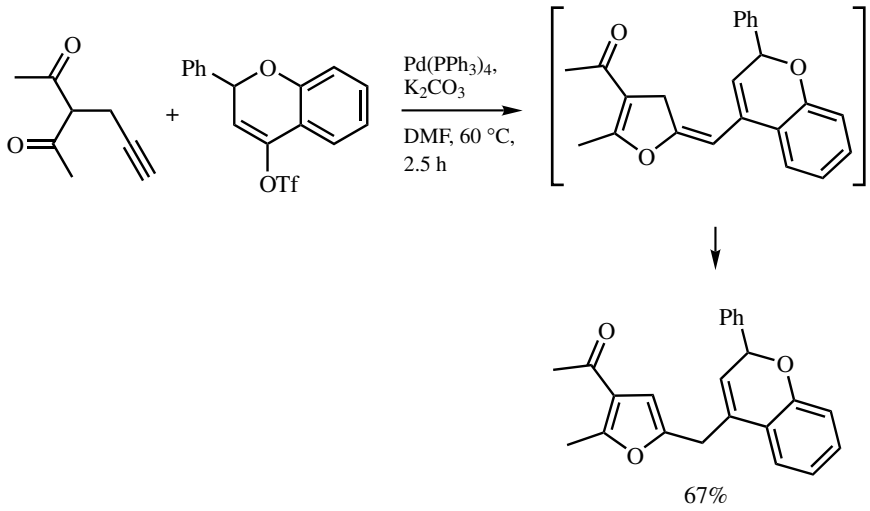
B.i. Organopalladium Derivatives Generated from Aryl, Heteroaryl, and Alkenyl Halides or Triflates

B.i.a. ***Alkynes Containing Proximate Alcoholic Groups.*** The reaction of acetylenic alkyl alcoholates with organic halides produces 2-alkylidenetetrahydrofurans[6] (**Scheme 3**). The reaction is quite stereoselective and only products arising from *trans* oxypalladation adducts have been isolated. The best results have been obtained by treatment of alkyl acetylenic alcohols with *n*-BuLi in THF at 0 °C, followed by addition of $PdCl_2$ or $Pd(OAc)_2$ and PPh_3 in THF and the organic halide. The use of $NaHCO_3$ or MeONa as the base, $Pd(dba)_2$ or $PdCl_2(PPh_3)_2$/DIBAL-H as the catalyst system, or dimethylformamide, chloroform, benzene, or toluene as the solvent has given only low yields or undetectable amounts of the desired products. The employment of zinc alkoxide also has proved unsuccessful.



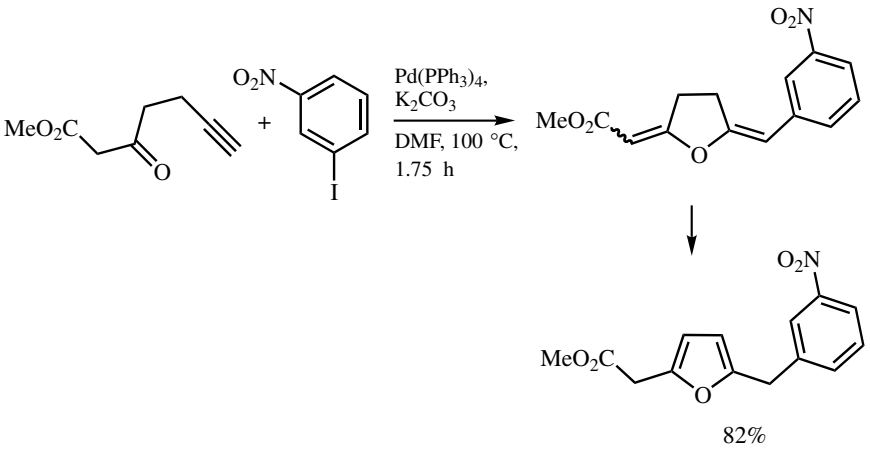
Scheme 3

B.i.b. ***Alkynes Containing Proximate 1,3-Dicarbonyl Groups.*** 2-Propargyl-1,3-dicarbonyl compounds react with alkenyl triflates or alkenyl/aryl/heteroaryl halides to give 2,3,5-trisubstituted-furans[5] (**Scheme 4**). The process probably proceeds through an oxypalladation step that involves a nucleophilic attack of a stabilized enolate across the activated carbon–carbon triple bond, reductive elimination of a palladium(0) species from the resultant oxypalladation adduct, and isomerization of the initially formed alkylidene derivative.



Scheme 4

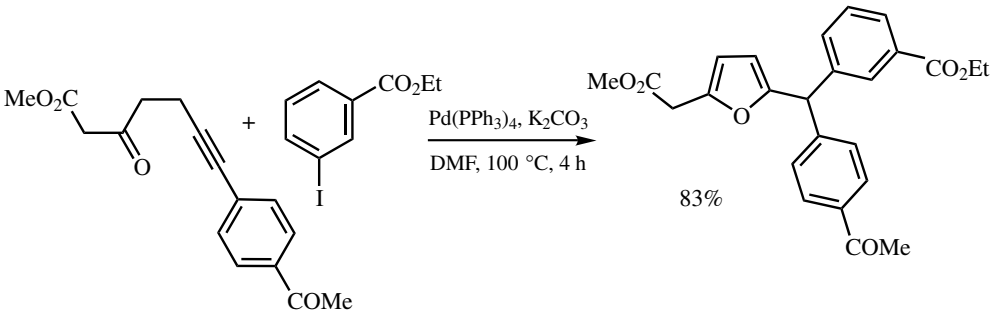
Extension of this chemistry to alkyl 3-oxo-6-heptynoates affords 2,5-disubstituted-furans[7] (**Scheme 5**). The reaction is highly chemoselective. No evidence has been attained of cyclization products arising from the nucleophilic attack of the carbon terminus of the putative enolate intermediate. Higher temperatures than those typically employed in the reaction of 2-propargyl-1,3-dicarbonyl compounds are needed to obtain the best results. This is most probably due to the energy requirements for the base-catalyzed double bond migration in the stereoisomeric 2,5-dialkylidenetetrahydrofuran derivatives initially formed through the stereoselective oxypalladation–reductive elimination sequence. The relative stability of 2,5-dialkylidenetetrahydrofuran derivatives is highlighted by the fact that they have been isolated in significant yields at 60 °C. With 2-propargyl-1,3-dicarbonyls none of the corresponding alkylidene products have been observed under these conditions.



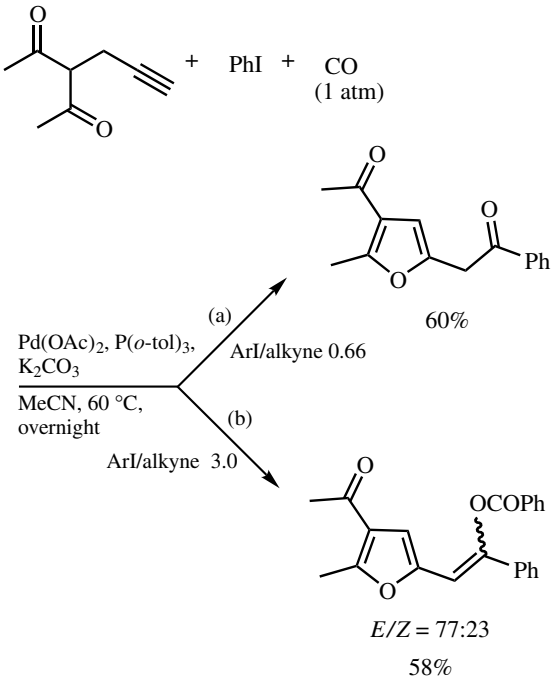
Scheme 5

Use of alkyl 3-oxo-7-substituted-6-heptynoates provides an entry into 2,5-disubstituted-furans containing a branched side chain (**Scheme 6**).

When 2-propargyl-1,3-dicarbonyl compounds are treated with aryl iodides under a balloon of carbon monoxide 2,3,5-trisubstituted-furans containing a 5-acylmethyl group (**Scheme 7a**) or its enol ester (**Scheme 7b**) can be obtained.[8] Formation of the acylmethyl derivative or its enol ester depends on the aryl iodide to alkyne ratio. Excess alkyne affords the acylmethyl derivative as the main product whereas employment of an excess of the aryl iodide favors the formation of the enol ester. The enol ester product is very likely formed from the acylmethyl product via trapping of the corresponding enolate with an acylpalladium complex.

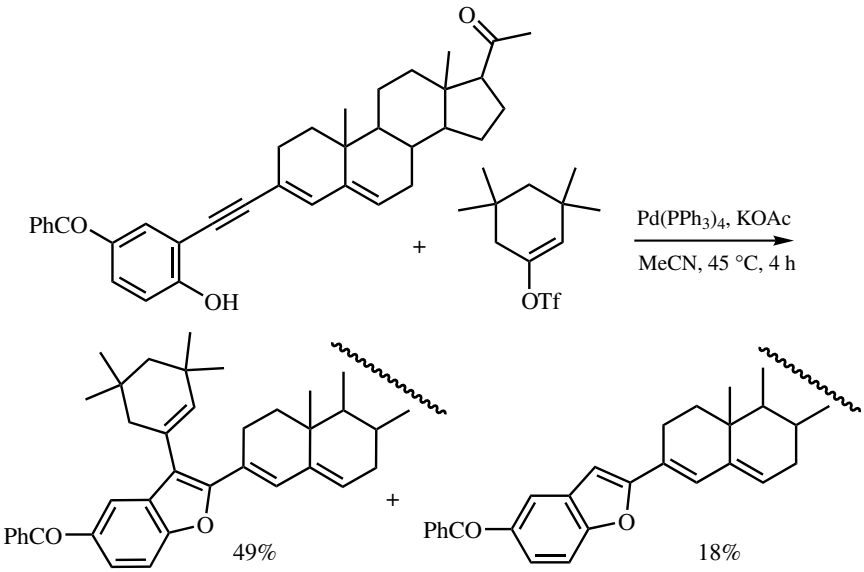


Scheme 6



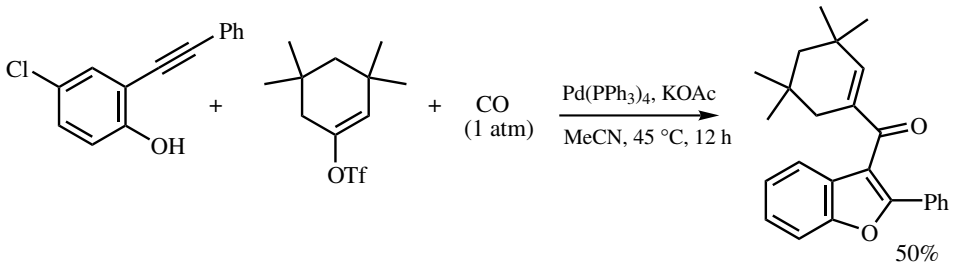
Scheme 7

B.i.c. ***Alkynes Containing Proximate Phenolic Groups.*** *o*-Alkynylphenols exhibit a strong tendency to cyclize to 2-substituted-benzo[*b*]furans under basic conditions. However, their reaction with alkenyl triflates in the presence of potassium acetate and $Pd(PPh_3)_4$ can form 2-substituted-3-alkenylbenzo[*b*]furans,[9] though in moderate yield, via the oxypalladation–reductive elimination domino reaction (**Scheme 8**). Apparently, under these conditions, coordination of the acetylenic fragment to the σ-alkenylpalladium complex—followed by the intramolecular nucleophilic attack of the oxygen across the carbon–carbon triple bond and the reductive elimination of palladium(0) species from the resultant σ-benzofurylpalladium intermediate—can compete effectively with the base-catalyzed cyclization.



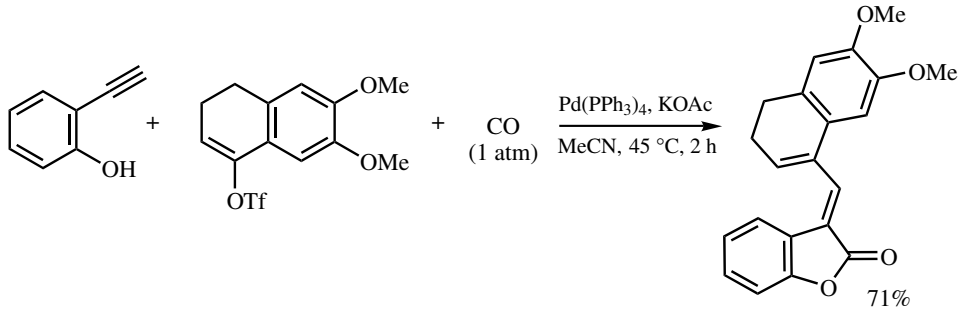
Scheme 8

Treatment of *o*-alkynylphenols with alkenyl triflates under the same conditions—potassium acetate and $Pd(PPh_3)_4$—under an atmosphere of carbon monoxide produces 2-substituted-3-acylbenzo[*b*]furans[9] (**Scheme 9**). Depending on the substitution pattern of the reagents, variable amounts of 2-substituted-3-alkenylbenzo[*b*]furans, 2-substituted-benzo[*b*]furans, and O-acyl derivatives of the starting alkyne have also been isolated.

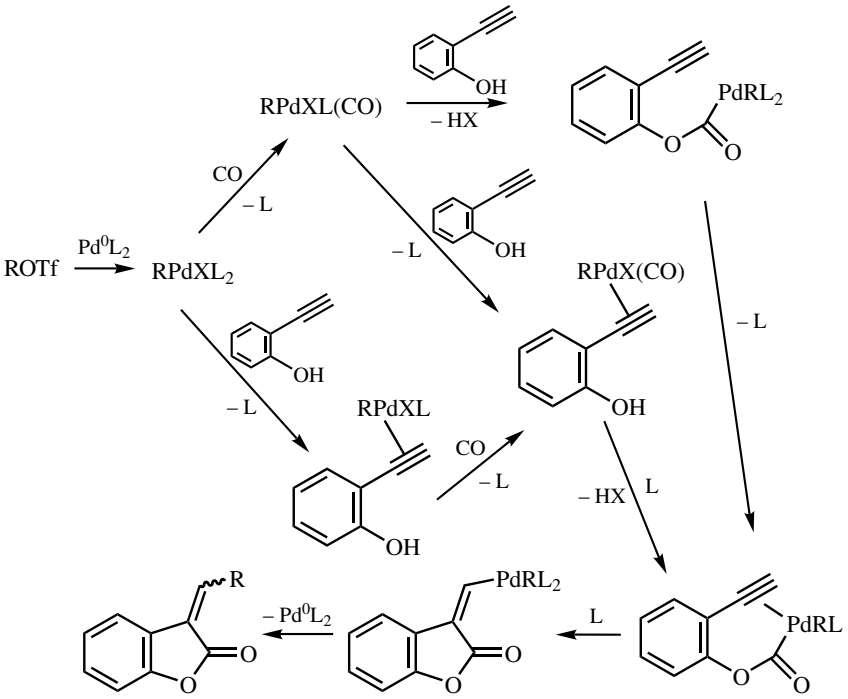


Scheme 9

Interestingly, extension of this procedure to *o*-ethynylphenols results in the formation of 3-alkylidene-2-coumaranones[10] (**Scheme 10**). KOAc and K_2CO_3 can be used as the bases. The different behavior of *o*-ethynylphenols as opposed to *o*-alkynylphenols has been suggested to depend on steric and electronic effects. The reaction is envisioned to involve the intermediacy of an η^2-alkyne-σ-oxycarbonylpalladium complex, which undergoes an intramolecular *syn* addition of the carbonylpalladium fragment to the carbon–carbon triple bond (**Scheme 11**). Reductive elimination of a palladium(0) species from the resultant σ-alkenylpalladium adduct affords the coumaranone derivative and regenerates the catalyst.



Scheme 10

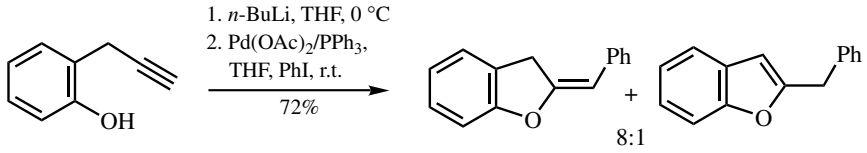


R = vinyl
X = OTf or OAc (in the presence of KOAc)

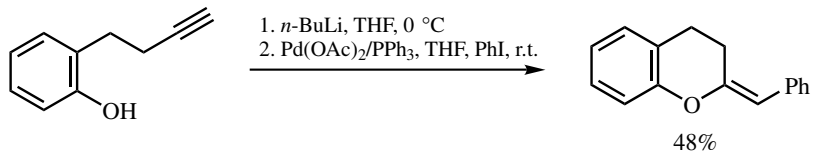
Scheme 11

According to this mechanistic proposal, the reaction would be expected to form (*Z*)-3-alkylidene-2-coumaranones. On the contrary, (*E*)-isomers are preferentially obtained with the majority of the substrates that have been investigated. Experimental evidence appears to support the view that the observed stereochemistry depends on the relative thermodynamic stability of the geometrical isomers and that the (*E*)-isomers are produced through a thermal isomerization of the reductive elimination product formed initially from the *syn*-σ-alkenylpalladium adduct. A *cis–trans* isomerization of the latter[11]–[14] might also contribute to the product distribution.

Lithium salts of *o*-(alk-2-ynyl)phenols and *o*-(alk-3-ynyl)phenols (preformed through the reaction of phenols with *n*-butyllithium at 0 °C) react with iodobenzene, 2-iodothiophene, benzyl bromide, and methyl iodide in the presence of a palladium catalyst to give 2-(alkylidene)-3-hydrobenzo[*b*]furans (**Scheme 12**) and 2-(alkylidene)chromanes (**Scheme 13**), respectively.[6] Both palladium diacetate and palladium dichloride have proved effective catalysts, whereas $Pd(dba)_2$ and $PdCl_2(PPh_3)_2$/DIBAL-H have given very low yields of the desired products. Minor amounts of isomerized products have been obtained by using palladium diacetate or palladium dichloride and triphenylphosphine whereas the employment of $Pd(PPh_3)_4$ has been found to afford only the isomerized benzofuran derivative in low yield.

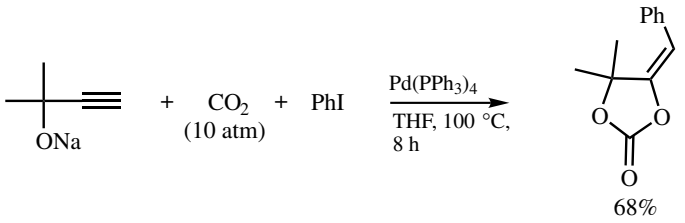


Scheme 12



Scheme 13

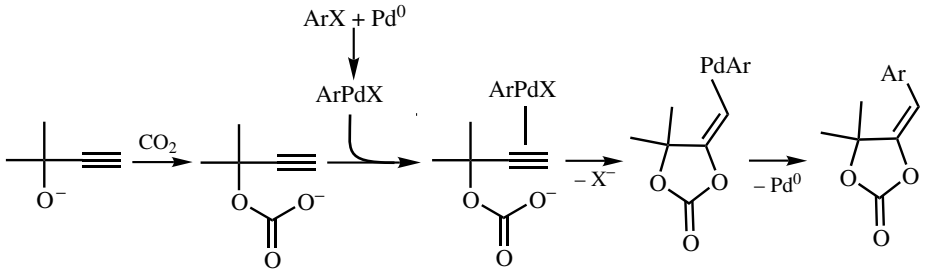
B.i.d. ***Alkynes Containing Proximate Carboxylic Groups.*** Stereodefined cyclic alkenylidene carbonates have been synthesized from the sodium salt of α-ethynyl tertiary alcohols and aryl halides under 10 atm of carbon dioxide, in the presence of a palladium catalyst[15] (**Scheme 14**). Sodium salts have been prepared from the alcohol and a slight excess of sodium hydride. $Pd(PPh_3)_4$ provides the best results. Several palladium catalyst systems, based on the $Pd(dba)_2$–bidentate phosphine combination, give lower yields and $PdCl_2(PhCN)_2$ and $PdCl_2(PBu_3)_2$ fail to give the desired products. In addition to iodobenzene, other aryl and alkenyl halides such as bromobenzene, *p*-bromochlorobenzene, *p*-bromobenzaldehyde, and β-bromostyrene afford the corresponding alkenylidene products, though in moderate to low yield. None of the cyclization products are obtained with *o*-bromotoluene and *p*-bromoanisole. With allyl acetate and chloride cyclization products are obtained in low yield by using lithium alcoholate instead of sodium



Scheme 14

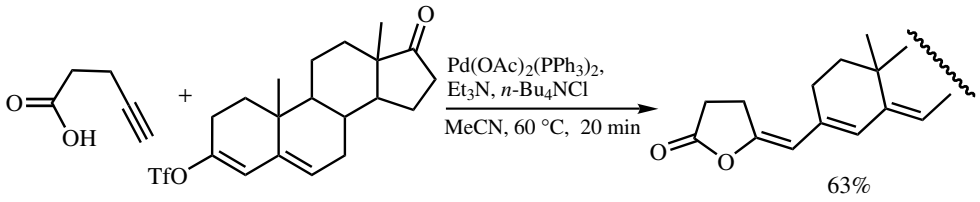
alcoholate. Internal acetylenic alcoholates such as those derived from 2-methyl-3-octyn-2-ol and 2-methy-4-phenyl-3-butyn-2-ol fail to give the expected cyclization derivatives with iodobenzene.

The nucleophilic carboxylate anion needed for the cyclization step is generated via trapping of the carbon dioxide with the alcoholate. The proposed reaction mechanism is outlined in **Scheme 15**.

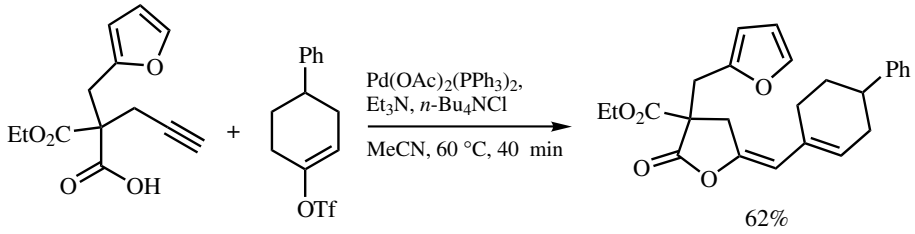


Scheme 15

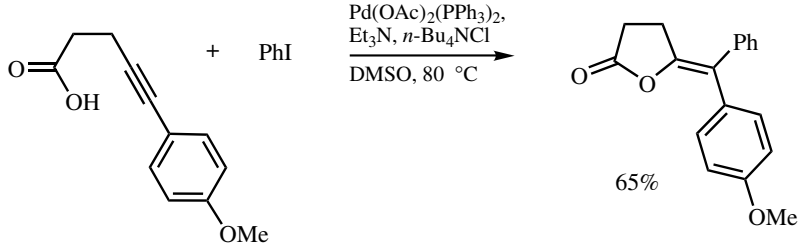
The reaction of alkenyl triflates and alkenyl/aryl halides with 4-pentynoic acid (**Scheme 16**) and 2,2-disubstituted 4-pentynoic acids (**Scheme 17**) provides a valuable methodology for the regio- and stereoselective synthesis of (*E*)-γ-alkylidene-γ-butyrolactones.[16] 5-Substituted-4-pentynoic acids can also be used as the starting alkynes[16] (**Scheme 18**). The best results have been obtained in the presence of $Pd(OAc)_2(PPh_3)_2$ or $Pd(PPh_3)_4$, Et_3N, and *n*-Bu_4NCl. The addition of *n*-Bu_4NCl to the reaction mixture has a profound effect on the process. When it is omitted, more complex reaction mixtures and lower yields of the enol lactone product have been observed, especially with alkenyl triflates.



Scheme 16

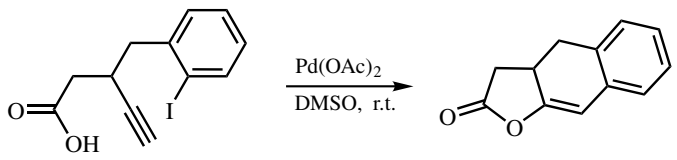


Scheme 17



Scheme 18

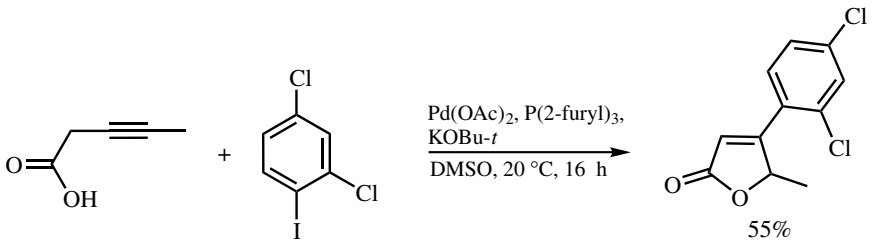
The intramolecular version of this methodology has provided a useful synthetic method for the preparation of tricyclic γ-alkylidenebutyrolactones[17] (**Scheme 19**). The best results have been obtained by using palladium diacetate, tri(2-furyl)phosphine in DMSO at room temperature in the presence of KOBu-*t* as the base. Replacement of tri(2-furyl)phosphine with triphenylphosphine produces trace amounts of the lactone product. However, the addition of a tetraalkylammonium chloride salt has a beneficial effect. In the presence of palladium diacetate, triphenylphosphine, triethylbenzylammonium chloride (TEBA), and triethylamine, the expected product is obtained in 60% yield.



tri(2-fury1)phosphine, KOBu-*t*, 30 min	78%
PPh_3, KOBu-*t*	traces
PPh_3, TEBA, Et_3N, 45 min	60%

Scheme 19

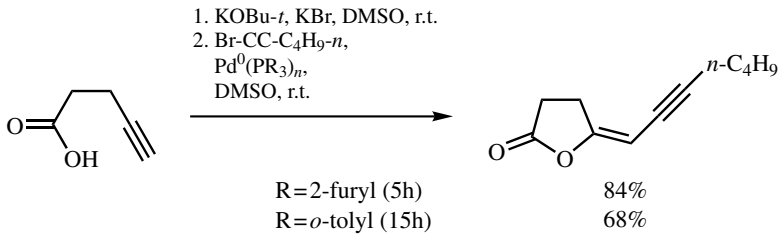
The procedure has been extended to include 4-aryl-3-butynoic acids and 3-alkynoic acids, which have been reacted with aryl, heteroaryl, and alkenyl halides to give 4,5-disubstituted-5*H*-furan-2-ones[18] (**Scheme 20**). Utilization of 3-butynoic acid as the starting alkyne in the reaction with phenyl iodide met with failure.



Scheme 20

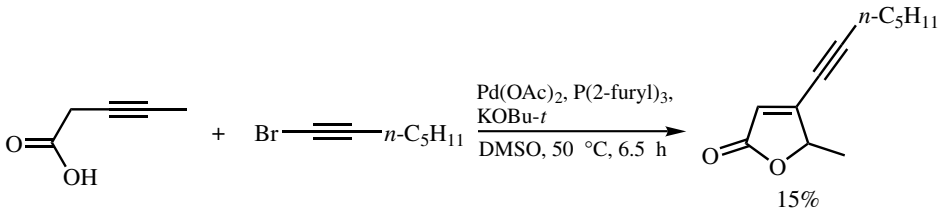
B.ii. Organopalladium Derivatives Generated from 1-Halo-1-alkynes

The reaction of potassium salts of 4-pentynoic acids—prepared from the acid and KOBu-*t* or KH—with 1-bromo-1-alkynes affords δ-(*E*)-alkylidene-γ-butyrolactones[19] (**Scheme 21**). Lithium and sodium carboxylates have proved unsuccessful. Addition of potassium bromide, use of DMSO, and excess 4-pentynoic acid have been found to increase the yield, whereas 1-iodo-1-alkynes lead to the formation of the expected lactone along with major amounts of δ-iodo-γ-methylene-γ-butyrolactone. Tri(*o*-tolyl)phosphine and tri(2-furyl)phosphine can promote an efficient transformation. The latter, however, has been found to give the best results.



Scheme 21

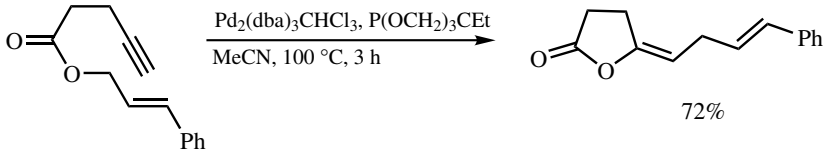
The oxypalladation–reductive elimination of 3-pentynoic acid with 1-bromo-1-heptyne has also been described[18] (**Scheme 22**). However, 4-methyl-4-(1-heptynyl)-5*H*-furan-2-one was isolated in low yield. Substitution of 1-iodo-1-heptyne for 1-bromo-1-heptyne resulted in the formation of the diyne derivative as the only reaction product. Most probably, the diyne derivative is formed via Pd-catalyzed coupling of the 1-halo-1-alkyne.



Scheme 22

B.iii. Organopalladium Derivatives Generated from Allyl Esters and Ethers

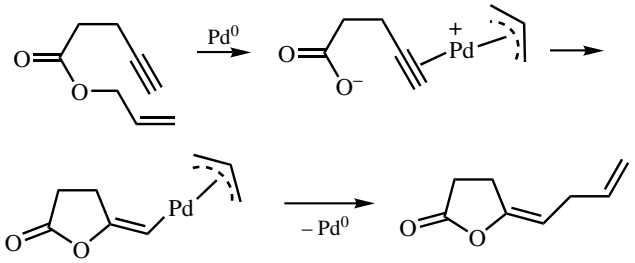
Subjection of allyl alkynoates to a palladium catalyst, generated from $Pd_2(dba)_3{\cdot}CHCl_3$ and trimethylolpropane phosphite, in acetonitrile at 100 °C produces γ-(*E*)-alkylidene-γ-butyrolactones[20] (**Scheme 23**). Ligands and solvents exert a strong influence on the formation of the lactone. Trimethylolpropane phosphite has been found to be the best ligand. Triisopropyl phosphite has been similarly effective, while triphenylphosphine has shown a medium effect and the use of trimethyl or triphenylphosphite has proved unsuccessful. As to the solvent, acetonitrile or mixed solvents containing acetonitrile have given good results. None of the lactone product has been observed in benzene or THF. The oxypalladation–reductive elimination process is regio- and stereoselective. The regioselectivity of the carbon–carbon bond formation toward the allylic moiety, as well as its stereochemistry, depends on the nature of the allyl donor.



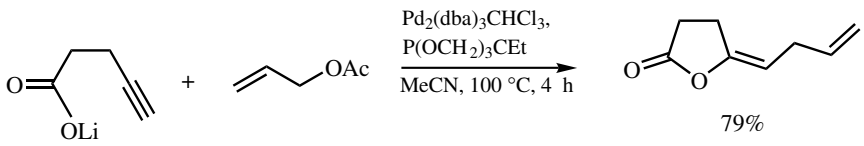
Scheme 23

The reaction has been suggested to proceed through the formation of an η^3-allylpalladium cation, which activates the carbon–carbon triple bond toward the intramolecular nucleophilic attack of the carboxylate anion to give a σ-alkenyl-η^3-allylpalladium adduct (**Scheme 24**). Subsequent migration of the alkenyl group onto one of the termini of the allylic fragment affords the alkylidene derivative and regenerates the palladium catalyst.

Similar results can be obtained upon reaction of lithium alkynoates with allylic acetates (**Scheme 25**).

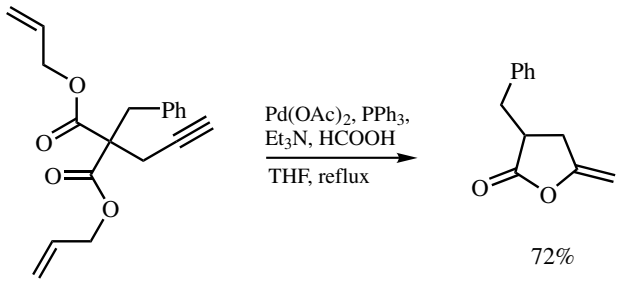


Scheme 24



Scheme 25

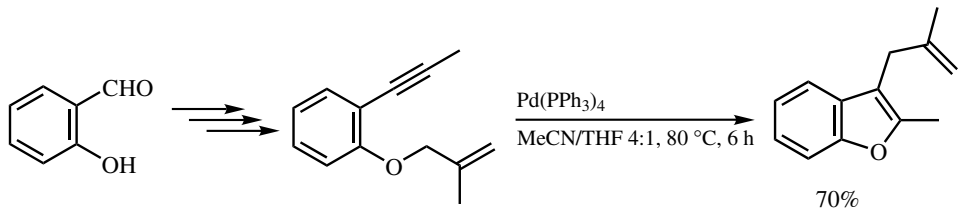
γ-Methylene-γ-butyrolactones have been prepared from diallyl 2-propynylmalonates[21] (**Scheme 26**). The reaction is carried out in the presence of palladium diacetate, triphenylphosphine, triethylamine, and formic acid. Under these conditions, no allyl fragment is transferred to the carbon–carbon triple bond, the formate trapping of the σ-alkenyl-η^3-allylpalladium intermediate being faster than the reductive elimination leading to the allyl derivative of the methylene lactone. The result is that the oxypalladation step is followed by the formation of a carbon–hydrogen bond.



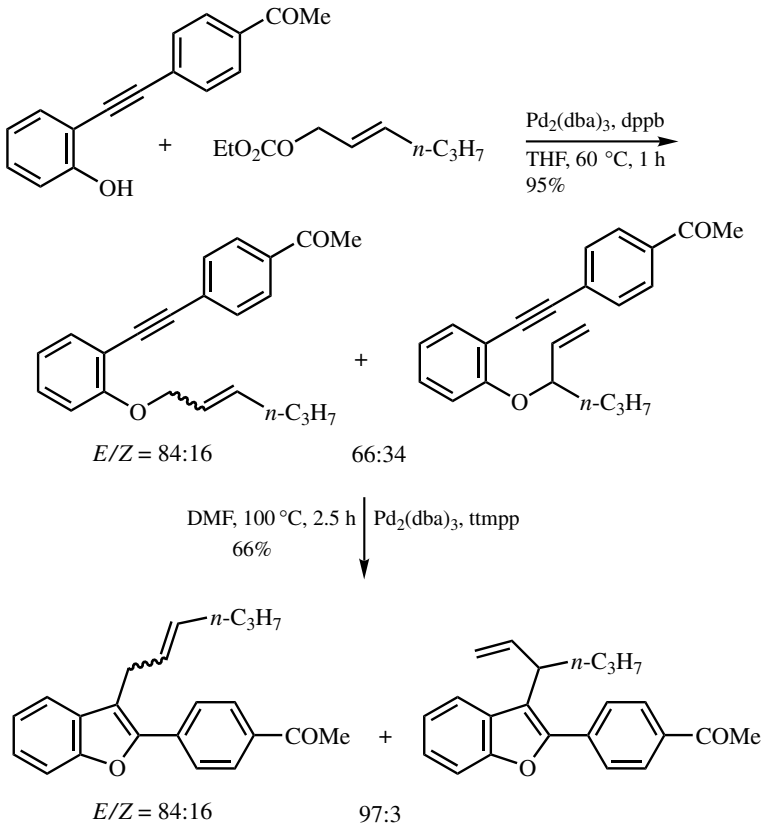
Scheme 26

Allyl ethers are usually less effective than allyl esters as precursors of η^3-allylpalladium complexes. However, allyl ethers derived from phenols can be used in allylation reactions. *o*-(Alkynylphenyl)allyl ethers, prepared from *o*-hydroxybenzaldehyde[22] (**Scheme 27**) or by the Pd-catalyzed reaction of *o*-alkynylphenols with allylcarbonates[23] (**Scheme 28**), have been employed in the synthesis of 2-substituted-3-allylbenzo[*b*]furans. The reaction of *o*-alkynylphenols with allylcarbonates (**Scheme 28**) produces regioisomeric mixtures of *o*-(alkynylphenyl)allyl ethers. This fact, however, does not pose any problem from a synthetic standpoint. The regiochemistry of the new carbon–carbon bond in the benzofuran product has been shown to be almost independent of the regiochemistry of the *o*-(alkynylphenyl)allyl ethers. High regioselectivity in the *cis* migration step has been observed with the catalyst containing the electron-rich sterically encumbered ligand tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp). Employment of ttmpp has resulted in the formation of 3-allylbenzofurans in which the benzofuran unit is bound to the less substituted allyl terminus almost exclusively. Some loss of the stereochemistry of the carbon–carbon double bond of the allyl fragment is observed.

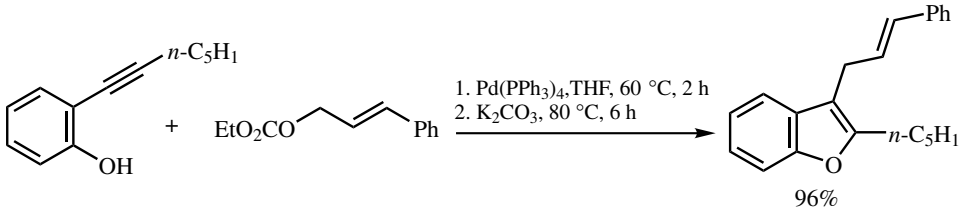
Preparation of 2-substituted-3-allylbenzo[*b*]furans from *o*-alkynylphenols and allylcarbonates through a one-pot protocol that omits the isolation of the corresponding ethers has also been described[23] (**Scheme 29**).



Scheme 27



Scheme 28

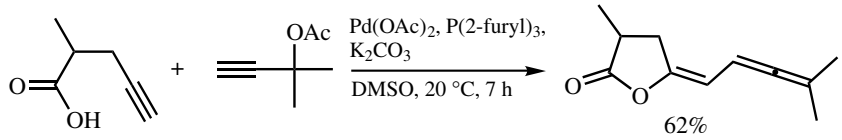


Scheme 29

B.iv. Organopalladium Derivatives Generated from Propargyl Esters and Ethers

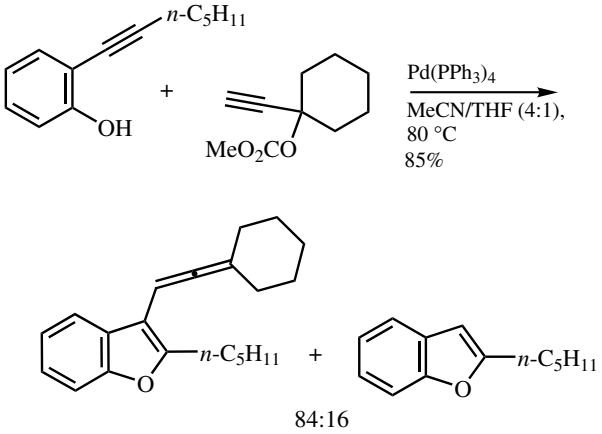
Propargyl esters have been used as allenyl donors in the oxypalladation–reductive elimination methodology. Reactions have been performed with 4-pentynoic acids and *o*-alkynylphenols.

Treatment of 4-pentynoic acids with propargyl acetates in the presence of palladium diacetate, tri(2-furyl)phosphine and potassium carbonate in DMSO affords 5-(*E*)-(2-allenylidene)-tetrahydro-2-furanones[24] (**Scheme 30**). Employment of potassium carboxylates generated by the reaction of 4-pentynoic acids with KOBu-*t* produces lower yields.



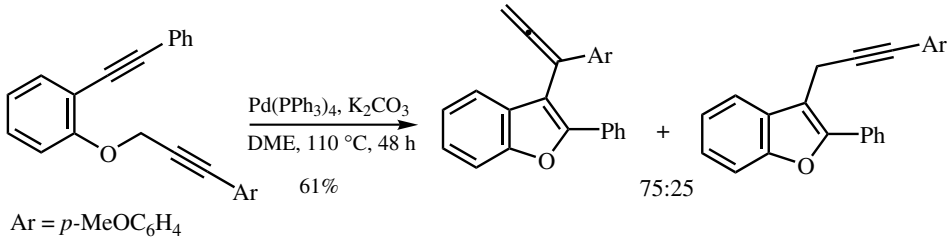
Scheme 30

The reaction of propargyl carbonates with *o*-alkynylphenols produces 2-substituted-3-allenylbenzo[*b*]furans under neutral conditions, most probably through the intermediacy of η^2-alkyne-σ-allenylpalladium complexes[25] (**Scheme 31**). The best results have been obtained with tertiary propargyl carbonates in the presence of tetrakis(triphenylphosphine)palladium(0) in refluxing acetonitrile-tetrahydrofuran. No stable products can be obtained with primary propargyl carbonates whereas secondary propargyl carbonates give rise to complex reaction mixtures from which the allenyl product is isolated in very low yield. Formation of variable amounts of 2-substituted-benzo[*b*]furans derived from the direct cyclization of the starting alkyne has been observed.

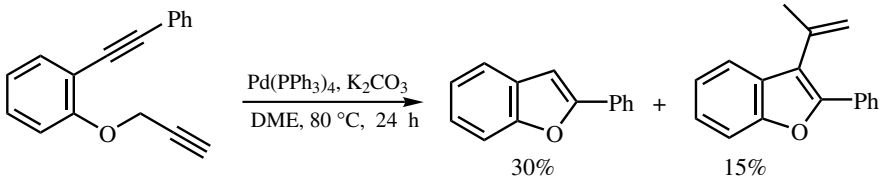


Scheme 31

Another class of 2-substituted-3-allenylbenzo[*b*]furans has been prepared via the Pd-catalyzed cyclization of propargylic *o*-(alkynyl)phenyl ethers[26] (**Scheme 32**). In this case the σ-allenylpalladium complex needed to activate the carbon–carbon triple bond toward the intramolecular nucleophilic attack of the phenolic oxygen is generated from the ether itself through the Pd-promoted ionization of the C_{sp^3}–oxygen bond. Depending on the substitution pattern of the starting alkyne, variable amounts of isomeric 2-substituted-3-propargylbenzo[*b*]furans have been isolated. The presence of a propargyl fragment containing a substituent on the terminal acetylenic carbon is crucial for the success of the reaction. When propargyl *o*-phenylethynyl ether was subjected to cyclization conditions a mixture of 2-phenyl- and 2-phenyl-3-(2-propenyl)benzo[*b*]furan was obtained along with other unidentified products (**Scheme 33**). Apparently, none of the allenyl and/or propargyl product was formed.



Scheme 32

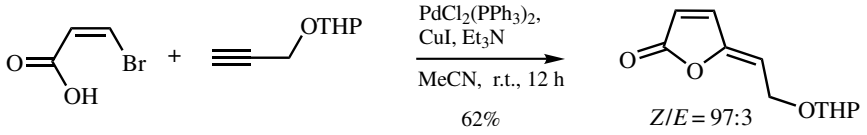


Scheme 33

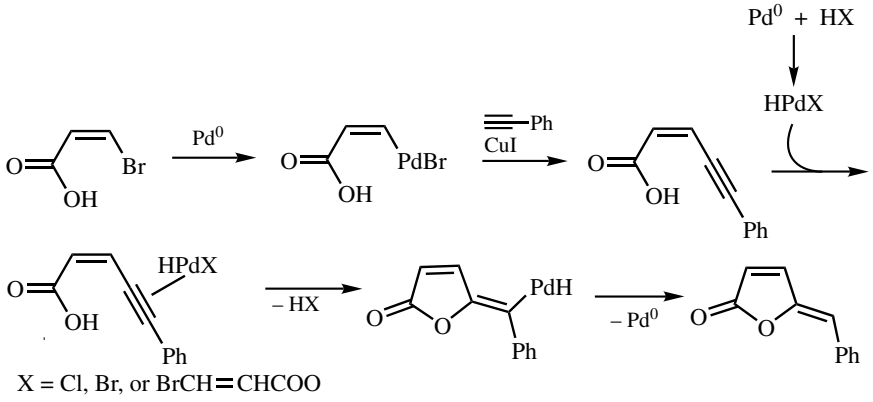
C. REACTIONS WITH HYDRIDOPALLADIUM DERIVATIVES

Oxypalladation promoted by hydridopalladium derivatives has been suggested to be involved in the regio- and stereoselective synthesis of γ-(*Z*)-alkylidene-γ-butyrolactones from 1-alkynes and (*Z*)-3-bromopropenoic acid[27] (**Scheme 34**).

The proposed reaction mechanism is outlined for the Pd-catalyzed reaction of (*Z*)-3-bromopropenoic acid with phenylacetylene in **Scheme 35**.



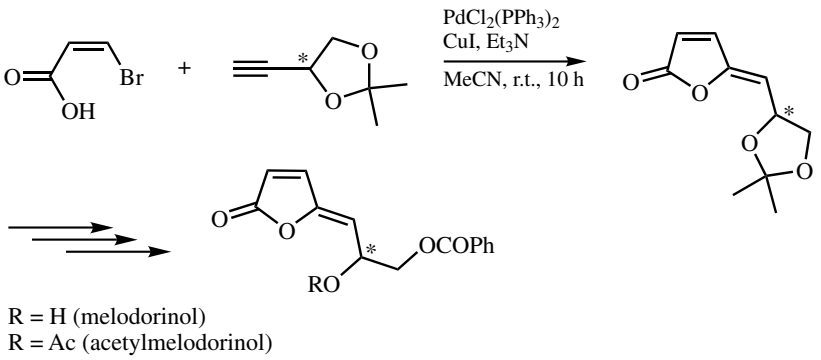
Scheme 34



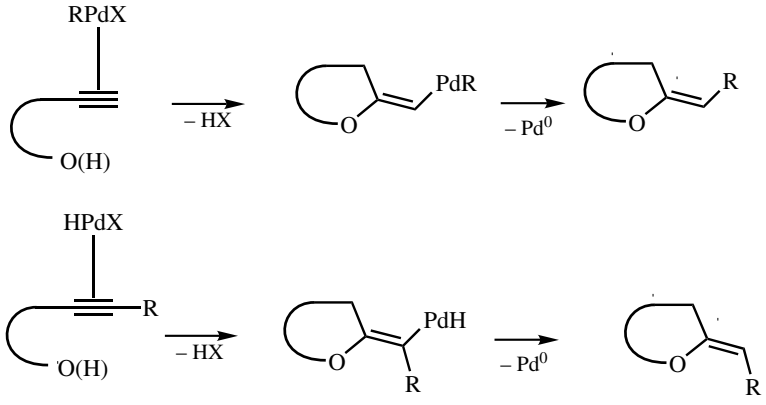
Scheme 35

This chemistry has been developed as a useful total synthesis of both enantiomers of melodorinol, a member of a group of natural antitumor compounds isolated from *Melodorum fruticosum*, which exhibits the γ-(*Z*)-alkylidenebutenolide structural unit[28] (**Scheme 36**).

Generally, the utilization of organopalladiums and hydridopalladiums in the oxypalladation–reductive elimination domino reactions may provide, through a proper choice of the reactants, a flexible tool for the design of either (*E*)- or (*Z*)-alkylidene functionalities (**Scheme 37**).



Scheme 36



Scheme 37

D. SUMMARY

The oxypalladation–reductive elimination domino reaction with organopalladium and hydridopalladium derivatives provides a powerful and flexible tool for the construction of oxygen-containing rings.

The high regio- and stereoselectivities of the process as well as its tolerance of functional groups underline the potential of the methodology. Its wide synthetic applicability is demonstrated by the preparation of a variety of functionalized heterocycles from readily available alkynes. Aryl and alkenyl halides or triflates, alkynyl halides, allyl and

propargyl esters, and propargyl ethers have been employed as precursors of organopalladiums. In the presence of carbon monoxide, aryl and alkenyl halides or triflates can react with alkynes containing proximate oxygen nucleophiles to afford cyclic products that incorporate a molecule of carbon monoxide.

Future developments are expected to provide a better understanding of the influence of reaction variables, such as ligands and added salts, on the reaction outcome and this will enhance the efficiency and widen the scope of the methodology. Its application to the preparation of complex molecules can reasonably be anticipated.

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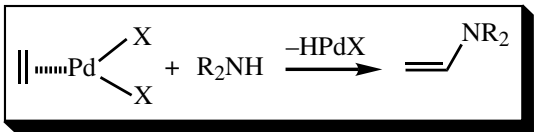


V.3.3 Aminopalladation and Related Reactions Involving Other Group 15 Atom Nucleophiles

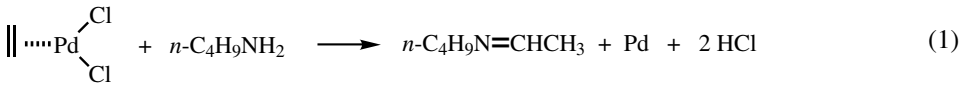
V.3.3.1 Aminopalladation–Dehydropalladation and Related Reactions

TAKAHIRO HOSOKAWA

A. INTRODUCTION

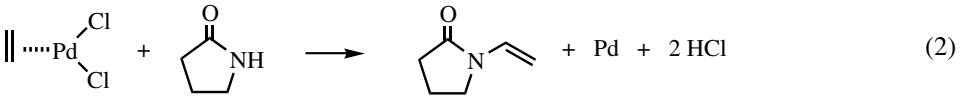
Amination of alkenes coordinated to Pd(II) followed by Pd—H elimination is expected to give enamines (**Scheme 1**). However, the use of amines as nucleophiles leads to somewhat complicated results, compared to that of oxygen nucleophiles.

In 1961, Stern and Spector[1] first reported the reaction of alkenes and amines with palladium(II) salts in a brief note. Subsequently, Hirai et al.[2] showed that the reaction of bis(ethylene)palladium(II) chloride complex with *n*-butylamine gives a 16% yield of the Schiff base (Eq. 1):



(1)

They also reported that the ethylene–$PdCl_2$ complex reacts with amides such as pyrrolidone to afford *N*-vinylpyrrolidone[3] (Eq. 2):



(2)

These results provide the fundamental characteristics of the Pd(II)-catalyzed reactions of alkenes with amines or its analogs. Thus, aliphatic amines coordinate strongly to electrophilic Pd(II). Therefore, alkenes coordinated to the metal are readily replaced by these amines, resulting in $(amine)_2PdCl_2$ complexes from which the Schiff base is formed

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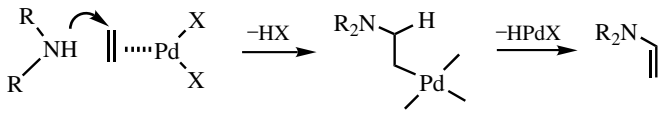
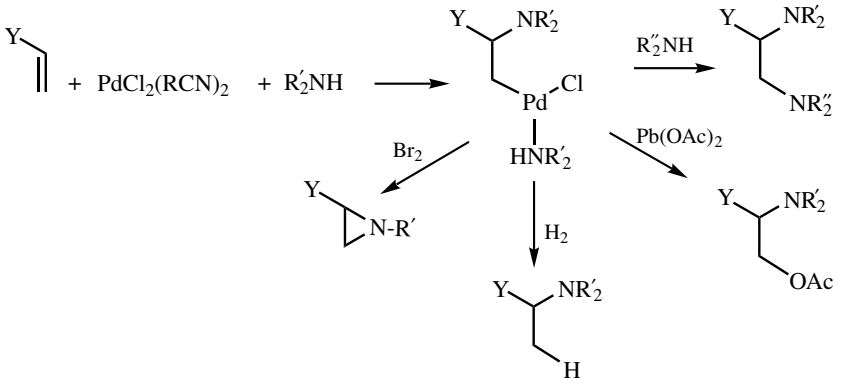


Scheme 1

as exemplified in Eq. 1. On the other hand, no such displacement takes place with less basic amides, resulting in the amidation of alkenes (Eq. 2). Considering the basicity and nucleophilicity of the N atoms of amines and its analogs, we survey the Pd(II)-catalyzed amination of alkenes and related reactions in this section.

B. INTERMOLECULAR AMINATION OF ALKENES AND RELATED REACTIONS

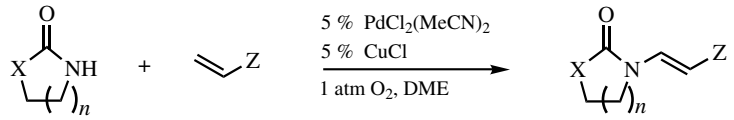
The Pd(II)-catalyzed amination of alkenes with aliphatic amines does not proceed well. However, under controlled conditions such as −50 °C, a stoichiometric reaction of simple alkenes with the amines gives the aminopalladation intermediates in which coordination of the amines to Pd(II) is involved. The aminopalladation adducts undergo various unique reactions as shown in **Scheme 2**.[4],[5] However, these reactions appear to be synthetically less useful because of the use of a stoichiometric amount of palladium.

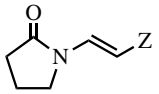
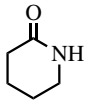
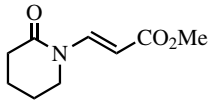
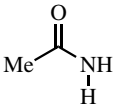
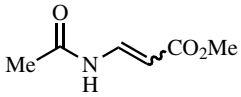
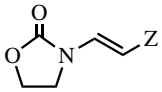
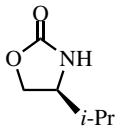
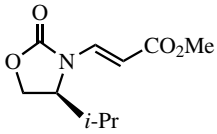


Scheme 2

Since an amide nitrogen is far less basic than that of an aliphatic amine, amides do not displace alkene from palladium. The N atom of an amide is thus able to attack alkenes coordinated to Pd(II) to give vinyl amides, according to **Scheme 1**. Given in **Table 1** is an example of the amidation of alkenes.[6] The amidation can be made catalytic by using a combination of CuCl and O_2 in the presence or absence of hexamethylphosphoramide (HMPA). The use of O_2 alone also makes the reaction catalytic. The amidation does not proceed well with simple alkenes; however, electron-deficient alkenes such as methyl acrylate and vinyl ketones undergo an effective catalytic amidation. Note that cyclic carbamates, because of the higher nucleophilicity of the N atom, are more reactive than cyclic amides.

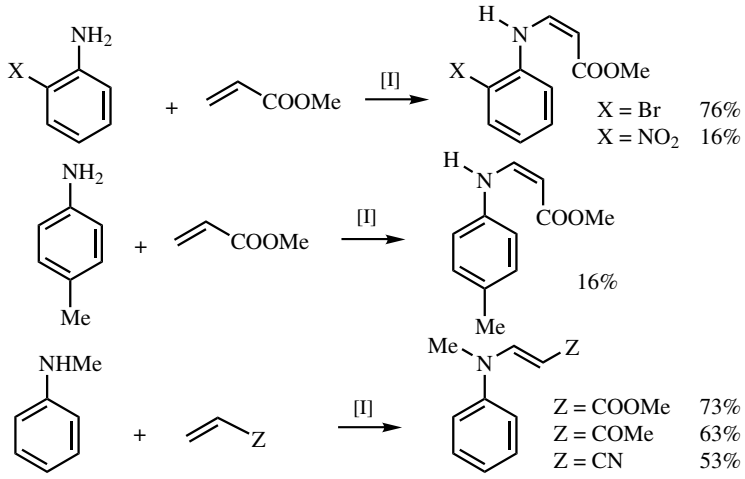
TABLE 1. Pd(II)-Catalyzed Amidation of Alkenes



Amide	Enamide		Yield (%)
		Z = CO_2Me Z = COMe Z = CHO Z = $CONEt_2$	85 (93)[a] 80[a] 67[a] 60[a]
			75
			65 (*E*/*Z* = 61:39)
		Z = CO_2Me Z = Ph	84 40
			85

[a]HMPA (5 mol %) was added.

Arylamines are also less basic than aliphatic amines and thus undergo the amination reaction, again with electron-deficient alkenes[7] (**Scheme 3**). To make such aminations catalytic, a combination of *p*-benzoquinone and LiCl has been used. The reaction is quite dependent on the nature of the amines. Thus, whereas aniline itself fails to amidate

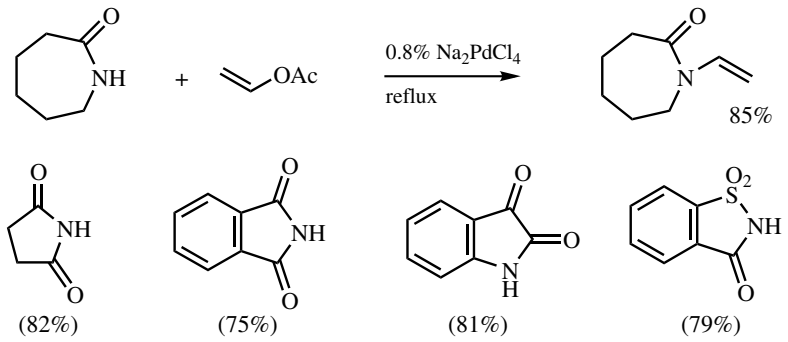


[I] = 10 mol % $PdCl_2(MeCN)_2$, benzoquinone (1 equiv), LiCl (10 equiv), THF.

Scheme 3

alkenes, *o*-bromoaniline reacts cleanly as does *N*-methylaniline. In general, secondary amines react more readily than primary amines, and similar behavior was observed in the stoichiometric amination of simple alkenes.[4]

In the amidation of vinyl acetate, the acetate group is exchanged by amide as shown in **Scheme 4**.[8] The reaction must proceed via amidopalladation followed by Pd—OAc elimination. Other nitrogen nucleophiles such as those shown in **Scheme 4** also react with vinyl acetate to give *N*-vinyl products in good yields as shown in parentheses.



Scheme 4

C. INTRAMOLECULAR AMINOPALLADATION AND RELATED REACTIONS

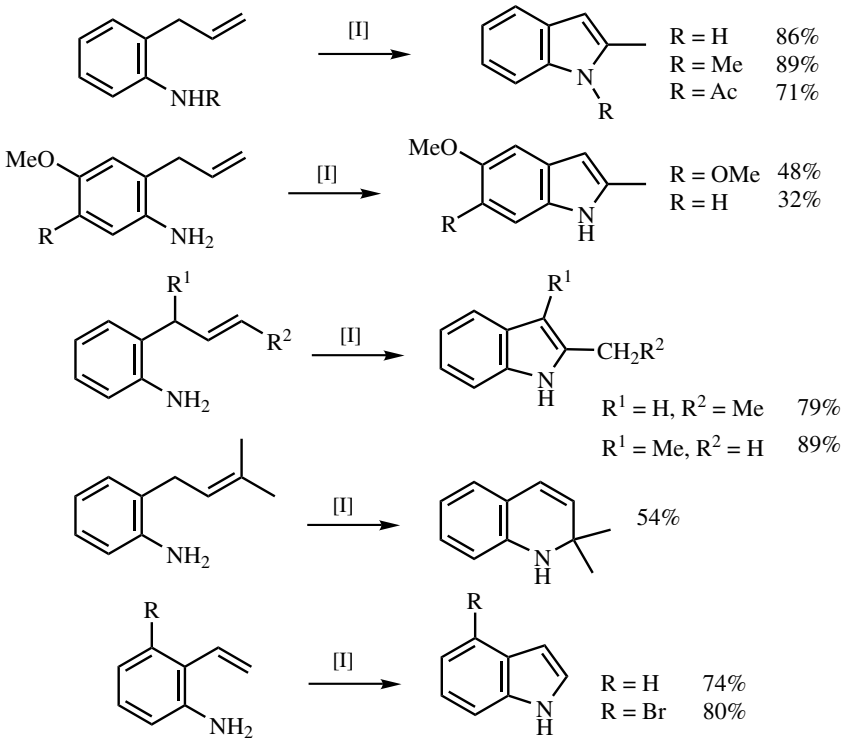
Because intramolecular cyclization, in general, is entropically favorable, intramolecular aminopalladation of alkenes followed by Pd—H elimination appears to proceed well. However, the basicity of the amine again becomes a crucial factor. The first successful reaction of this type was carried out in 1976 by Hegedus et al.,[9],[10] where less basic arylamines were used as the nucleophiles. Thus, *o*-allylanilines undergo the intramolecular amination of alkenes to give indoles as shown in **Scheme 5**.

Even if substituents are on the allylic moiety, cyclization takes place. Disubstitution at γ-position leads to a six-membered heterocycle. 2-Vinylanilines afford indoles. Not only arylamines but also unsaturated aminoquinones undergo cyclization to give indoloquinones[11] (**Scheme 6**).

Functionalization on the indole ring is also possible, when the tert-butyldimethylsiloxy (OTBDMS) substituent is introduced in the allylic side chain[12] (**Scheme 7**).

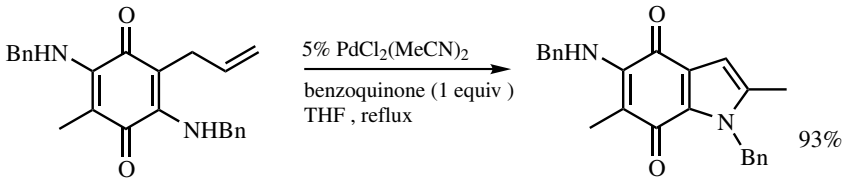
In the case of aliphatic amines, it is necessary to decrease the basicity of the amine moiety by having electron-withdrawing substituents such as R = Ts and SO_2Me on the N atom. When this technique is used, various aliphatic amines undergo intramolecular aminopalladation followed by Pd—H elimination to give *N*-heterocycles[13],[14] (**Scheme 8**).

A combination of benzoquinone, LiCl, and Na_2CO_3 has been used to make the reaction catalytic. A recent study has shown that the reactions proceed catalytically only by the use of molecular oxygen in DMSO[15] (**Scheme 9**). Larock and co-workers have also reported the cyclization of olefinic tosylamides with the $Pd(OAc)_2/O_2$/DMSO/NaOAc system as shown in **Scheme 10**.[16] The catalytic system generally results in five- or six-membered



[I] = 10 mol % $PdCl_2(MeCN)_2$, benzoquinone (1 equiv), LiCl (10 equiv), THF, reflux.

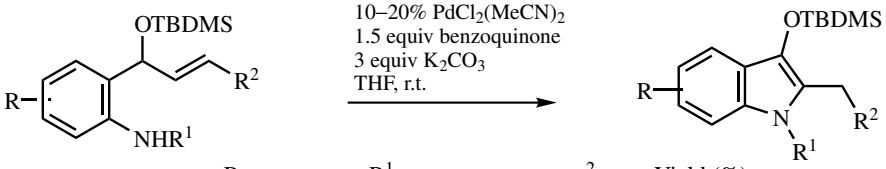
Scheme 5

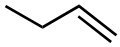


Scheme 6

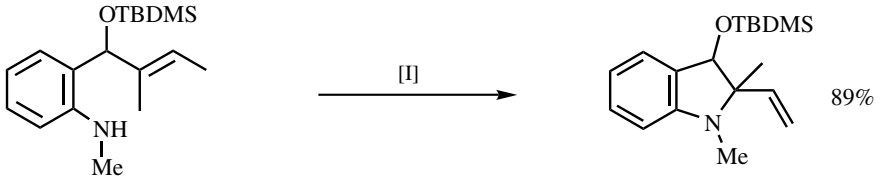
ring products containing an *allylic* nitrogen moiety. This is in contrast to the results shown in **Scheme 8**, where *N-vinylic* tosylamides are formed exclusively. Furthermore, while *N*-allylaniline is cyclized to 2-methylindole of a five-membered ring by $PdCl_2(MeCN)_2$ catalyst (**Scheme 5**), the use of $Pd(OAc)_2/O_2$/DMSO system gives exclusively the six-membered ring 1,2-dihydroquinoline. In the case of 2-prenylaniline, such a reversal of the regioselectivity has also been observed (**Scheme 10**).

The regiochemistry of the intramolecular cyclizations of some alkenic sulfonamides is dependent on the amount of palladium used. *N*-Tosyl-4-pentenylamines, when treated with a catalytic amount of $PdCl_2(MeCN)_2$ in the presence of *p*-benzoquinone, produce five-membered cyclic products in moderate to good yields[13] (**Scheme 11**). The use of a stoichiometric amount of palladium alters the regiochemistry to give a six-membered product.



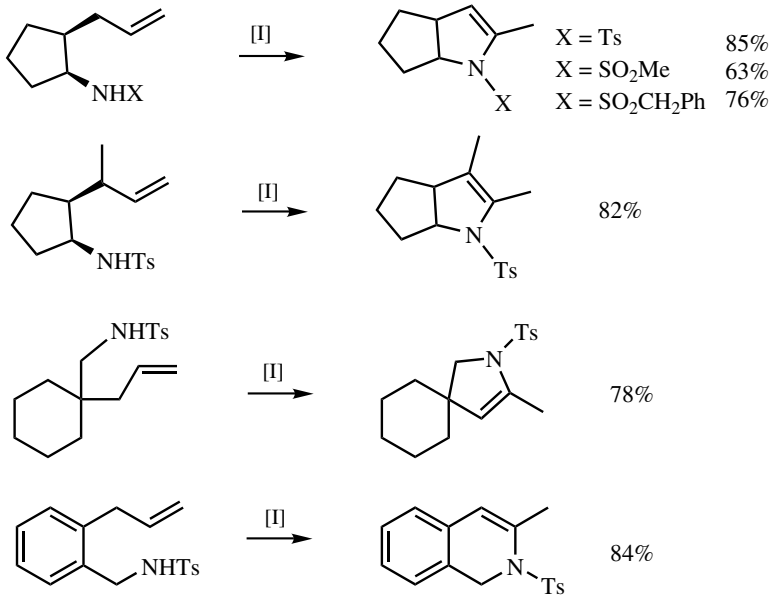
R	R^1	R^2	Yield (%)
H	Me	H	77
H	Me	Me	50[a, b]
H	Me	Ph	47[a]
4-OMe	$CH_2C_6H_4Br$-*p*	H	84
H		H	54[a]

[a] LiCl (10 equiv) was used.
[b] At 85 °C.



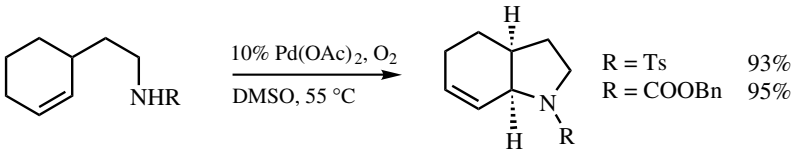
[I] = 10–20 mol % $PdCl_2(MeCN)_2$, 1.5 equiv benzoquinone, 3 equiv K_2CO_3, 10 equiv LiCl, THF, 85 °C.

Scheme 7

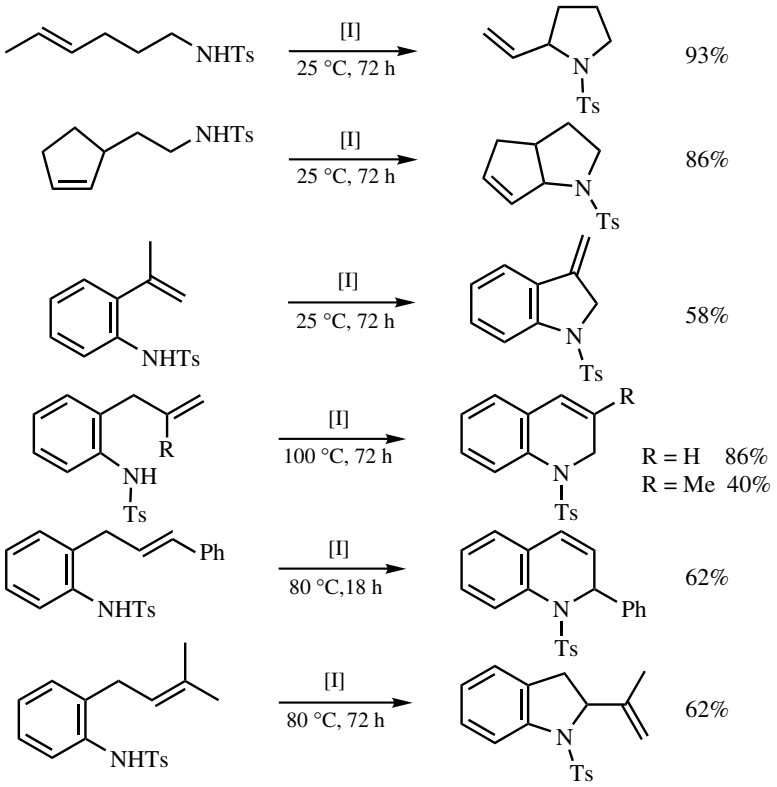


[I] = 10 mol % $PdCl_2(MeCN)_2$, benzoquinone (1 equiv), LiCl (2 equiv), Na_2CO_3 (2 equiv), THF, reflux.

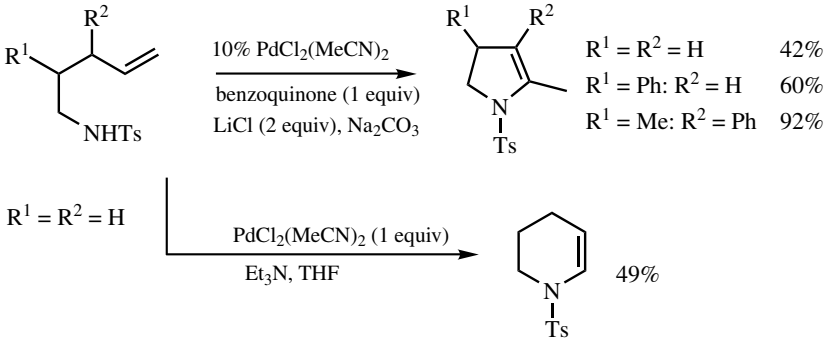
Scheme 8



Scheme 9



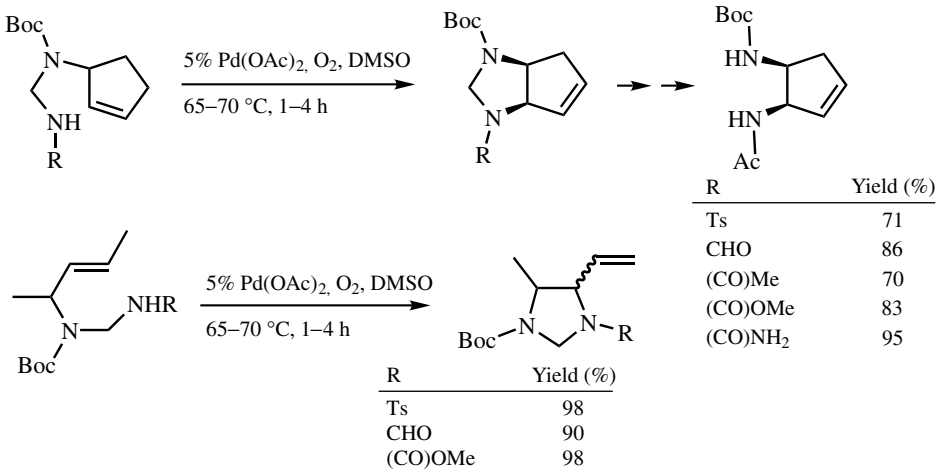
[I] = 5 mol % $Pd(OAc)_2$, 2 equiv NaOAc, O_2 (1 atm), DMSO.



Scheme 11

Formaldehyde aminals derived from *N*-Boc-protected allylic amines are readily cylized into imidazolidines by using the catalyst system of $Pd(OAc)_2/O_2$/DMSO (**Scheme 12**).[17] A imidazolidine (R = CHO) becomes the precursor of diamine shown in **Scheme 12**.

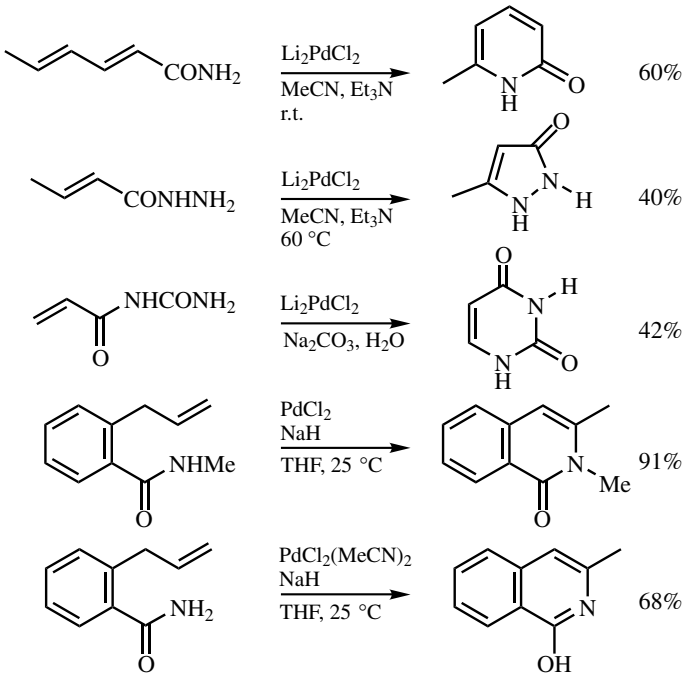
Shown in **Scheme 13** are some of the stoichiometric intramolecular aminations so far reported.[18] The application of recent advances in techniques may enhance the synthetic utility of these reactions by making them catalytic.



R	Yield (%)
Ts	71
CHO	86
(CO)Me	70
(CO)OMe	83
$(CO)NH_2$	95

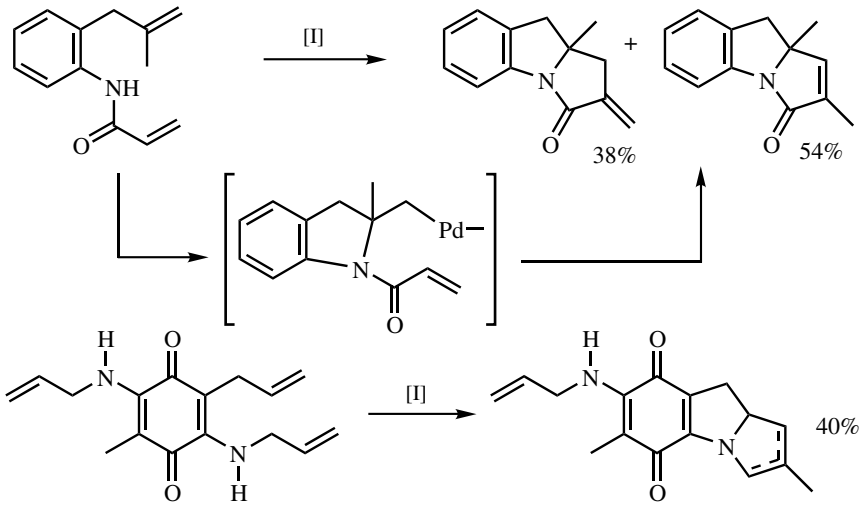
R	Yield (%)
Ts	98
CHO	90
(CO)OMe	98

Scheme 12



Scheme 13

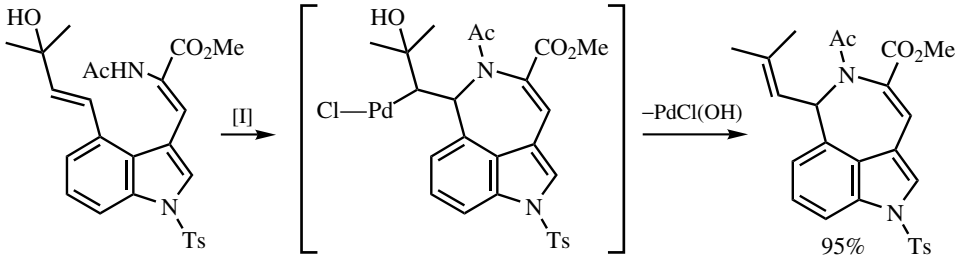
A tandem cyclization of an amide bearing two olefinic moieties is shown in **Scheme 14**.[19],[20] Intramolecular amidopalladation followed by insertion of the resulting C—Pd bond into another olefinic moiety present in the molecule leads to a bicyclic heterocycle after β-Pd—H elimination. An analogous reaction is also given in **Scheme 14**.[11]



[I] = 8 mol % $PdCl_2(MeCN)_2$, benzoquinone (1 equiv), THF/DMF = 2:1, 65 °C.

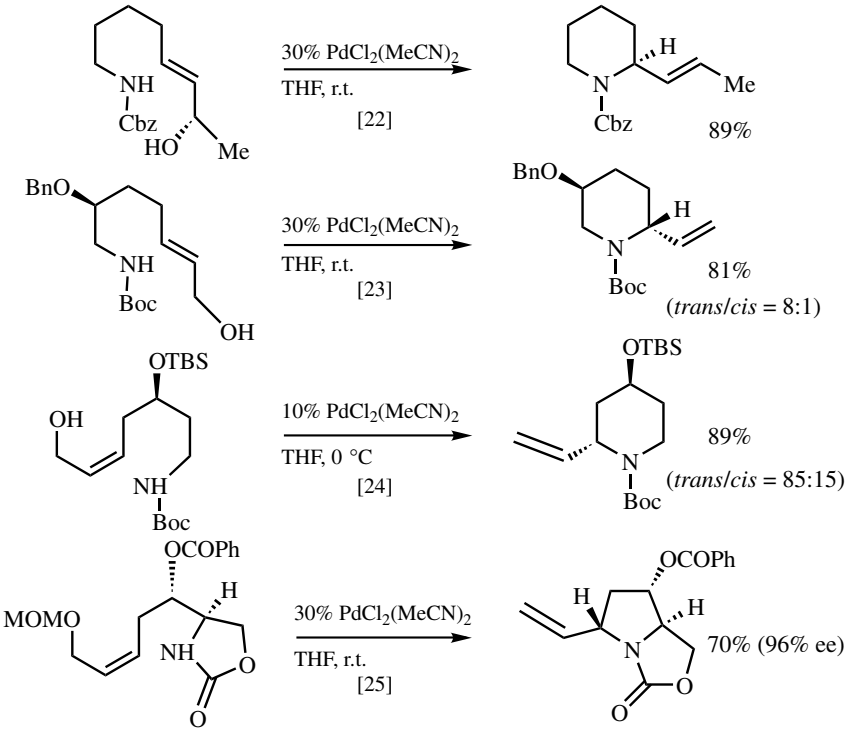
Scheme 14

Another interesting method for constructing *N*-heterocycles uses compounds containing an allylic alcohol moiety as shown in **Scheme 15**.[21] Aminopalladation toward the alkene of the allylic alcohol moiety results in a Pd—C bond bearing an OH group at the adjacent carbon (β-position). Elimination of this β-OH group by palladium affords the *N*-heterocycle and PdCl(OH). Since this palladium species is still in the +2 oxidation state, it can also catalyze the reaction. Similar cyclizations[22]–[27] using Pd(II) catalysts result in either an effective chirality transfer or retention of the chirality present in the molecule (**Scheme 16**). Furthermore, such a β-Pd—OH elimination has been reported in the 5-*endo-trig* cyclization of 2-hydroxybut-3-enylamines, which give pyrrolines and pyrroles (**Scheme 17**).[28] Interestingly, compounds possessing both allylic alcohol and allylic amine moieties undergo preferentially aminopalladation to give *N*-heterocycles (**Scheme 17**). No oxypalladation takes place.

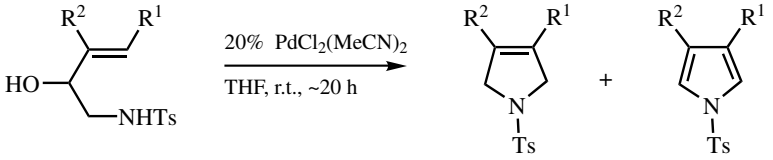


[I] = 15 mol % $PdCl_2(MeCN)_2$, MeCN, reflux.

Scheme 15

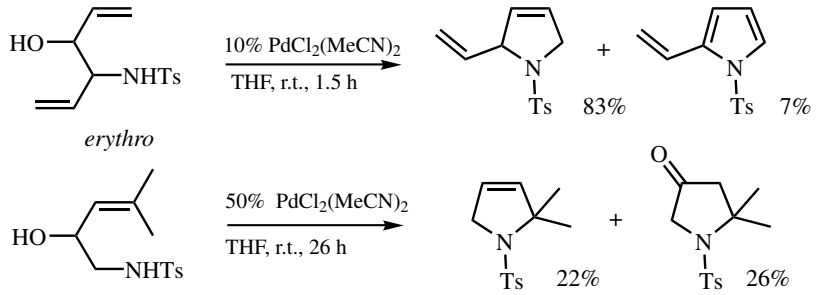


Scheme 16



R^1	R^2	Yield (%)	
H	H	55	22
Me	H	72	24
H	Me	—	41[a]

[a] $CuCl_2$ (2 equiv) was used.

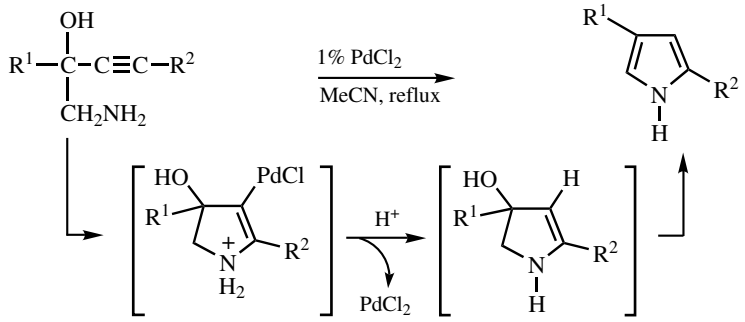


Scheme 17

D. INTRAMOLECULAR AMINATION OF ALKYNES AND RELATED REACTIONS

The first report on Pd(II)-catalyzed intramolecular cyclization of alkenylamines was made by Utimoto et al.[29] in 1981, in which 1-amino-3-alkyn-2-ols were used as the substrates. Heating the substrate in acetonitrile under reflux in the presence of $PdCl_2$ (1 mol %) gives pyrroles as shown in **Scheme 18**. The cyclizations are accounted for by the involvement of nucleophilic attack of the N atom on the palladium-complexed alkynes to form σ-vinylpalladium(II) species. The σ-bond is then cleaved by the HCl formed *in situ* to give the product, and $PdCl_2$ is regenerated. Thus, the catalysis is exerted only by Pd(II) salts such as $Pd(OAc)_2$. Pd(0) complexes such as $Pd(PPh_3)_4$ are not effective, although silver acetate, rhodium chloride, and copper(I) chloride show some activity as the catalyst.[30]

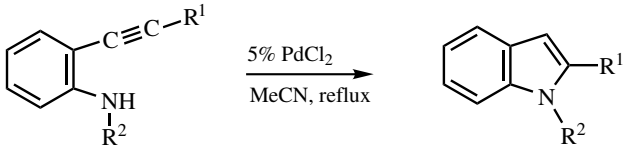
2-Alkynylanilines similarly undergo this cyclization to give indoles bearing alkyl substituents at the 2-position[31] (**Scheme 19**). This method has been extended to the synthesis of various indole bearing substituents on the phenyl ring[32] (**Scheme 20**).



R^1	R^2	Yield (%)
n-Hex	Et	84 (73)[a]
n-Hex	*t*-Bu	85
n-Hex	Et	84
Ph	H	100

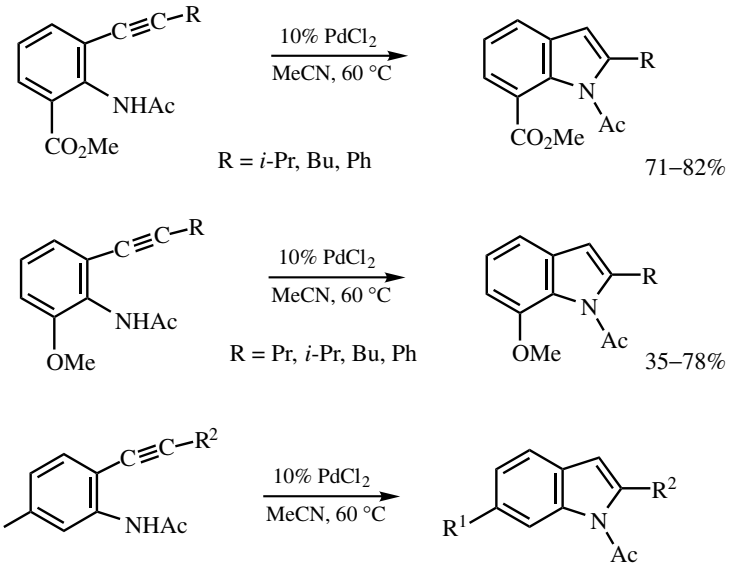
[a] 1 mol % $Pd(OAc)_2$ was used.

Scheme 18



R^1	R^2	Yield (%)
n-Bu	H	81
t-Bu	H	77
Hex(Me)CH	H	83
Ph	H	52
n-Bu	Ac	74
n-Bu	COOMe	78

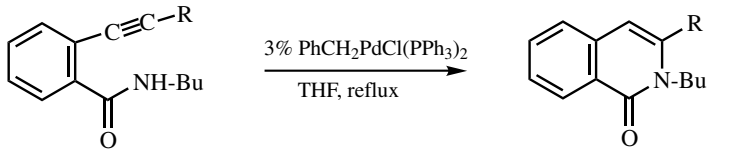
Scheme 19



R^1	R^2	Yield (%)
Me	Pr	82
Me	Ph	80
Me	$(CH_2)_2OTBDMS$	37
Cl	Pr	76
Cl	Ph	48
OTf	Bu	65
OTf	Ph	53

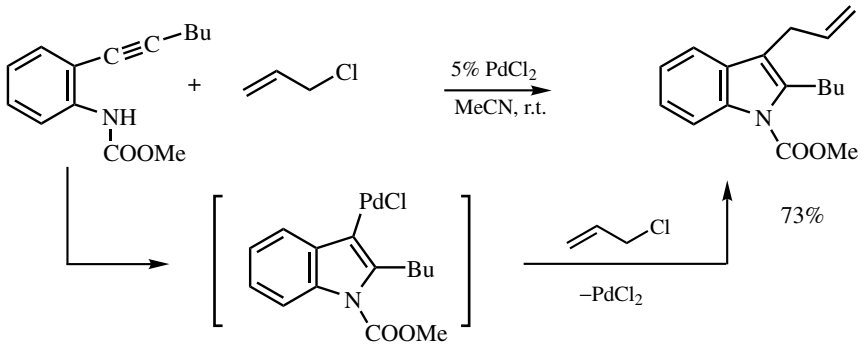
Scheme 20

Treatment of *o*-ethynylbenzamides with a catalytic amount of $PhCH_2PdCl(PPh_3)_2$ in THF at reflux results in 6-*endo-dig* cyclization to give isoquinolin-1-ones (**Scheme 21**).[33] Intercepting the σ-vinylpalladium(II) intermediate derived from *N*-carbomethoxy-2-alkynylaniline shown in **Scheme 22** by allyl chloride produces 2-alkyl-3-allylindoles.[31] This result proves involvement of the σ-bonded palladium(II) species.



R	Yield (%)
Me	75
Bu	77
Ph	64

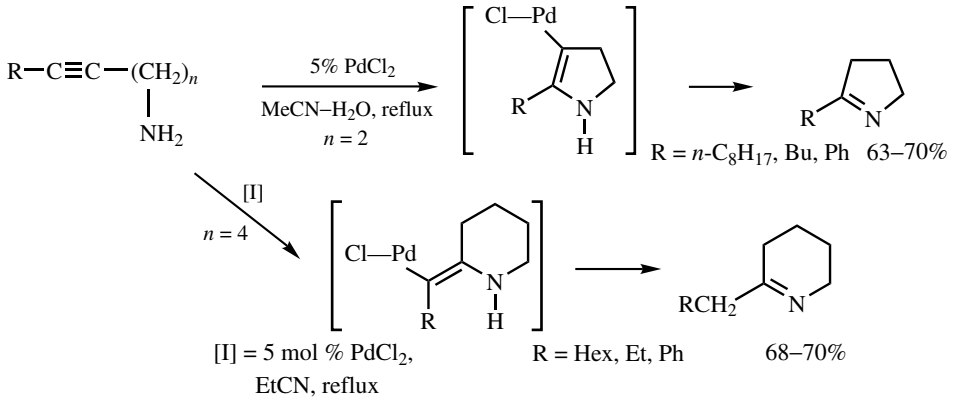
Scheme 21



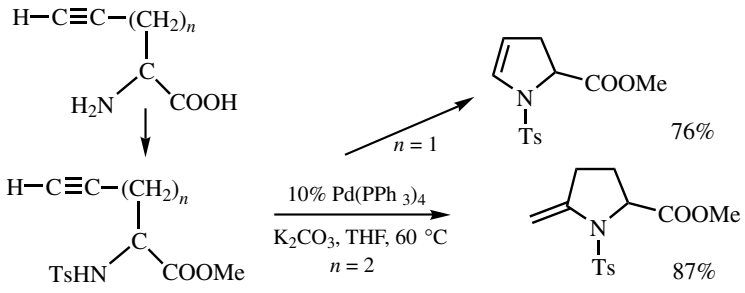
Scheme 22

Aliphatic alkynylamines also undergo cyclization even without a protecting amino group[34] (**Scheme 23**). Thus, 3-alkynylamines give 1-pyrrolines in good yield via 5-*endo-dig* cyclization, whereas 5-alkynylamines undergo a 5-*exo-dig* cyclization to afford 2,3,4,5-tetrahydropyridines. In the case of 4-alkenylamines, both five- and six-membered cyclic imines are produced.

Alkenyl tosylamides obtained from amino acids in the enantiopure form, when treated with $Pd(PPh_3)_4$ and K_2CO_3, give pyrroline derivatives. In this case, either 5-*endo* ($n = 1$) or 5-*exo* ($n = 2$) cyclization takes place, depending on the length of the side chain [35] (**Scheme 24**).

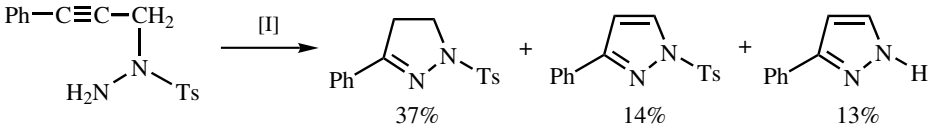


Scheme 23



Scheme 24

Treatment of *N*-tosyl-*N*-(1-phenyl-1-propyn-3-yl)hydrazine with $PdCl_2$ catalyst gives pyrazols (**Scheme 25**)[36]; however, the product selectivity is not high.



[I] = 5 mol % $PdCl_2$, MeCN, reflux.

Scheme 25

In summary, intramolecular aminopalladation, which has been studied extensively, compared to its intermolecular version, is undoubtedly useful for synthesizing *N*-heterocycles. Control of basicity and nucleophilicity of the N atom is crucial in this type of reaction. Considering such a fundamental feature, efforts will be directed toward the development of an asymmetric version of aminopalladation, which has not been studied much so far.

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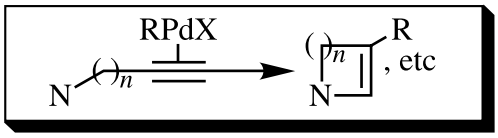

V.3.3.2 Aminopalladation–Reductive Elimination Domino Reactions with Organopalladium Derivatives

SANDRO CACCHI and FABIO MARINELLI

A. INTRODUCTION

The reaction of aryl, heteroaryl, alkenyl halides or triflates, and allyl esters with terminal or internal alkynes is generally considered to involve the initial formation of η^2-alkyne-organopalladium intermediates, which, depending on a variety of reaction variables, appear to be able to react according to a number of reaction pathways. For example, they can afford carbopalladation adducts[1]–[4] (**Scheme 1a**) or, when terminal alkynes are used as the acetylene components, coupling derivatives[5] (**Scheme 1b**). With starting alkynes containing nitrogen nucleophiles close to the carbon–carbon triple bond, the putative η^2-alkyne-organopalladium intermediates may undergo an intramolecular nucleophilic attack across the activated carbon–carbon triple bond. *Endo-dig* (**Scheme 2a**) or *exo-dig* (**Scheme 2b**) aminopalladation adducts are generated depending on the number of atoms in between the acetylenic fragment and the nitrogen atom. Subsequent reductive elimination of palladium(0) species regenerates the catalyst and produces a new carbon–carbon bond. A variety of five- and six-membered nitrogen-containing heterocycles have readily been prepared through synthetic processes based on this methodology.

B. FACTORS INFLUENCING THE REACTION

The nucleophilic strength of the nitrogen, the substitution pattern of the alkyne, the absence or the presence—as well as the nature—of phosphine ligands, the solvents, the added salts, and even the ratios between them are among the main factors influencing the course of the aminopalladation–reductive elimination domino reaction.

The strength of the nitrogen nucleophile is of primary importance for the success of such a reaction. Apparently, organopalladium complexes are less effective than palladium dichloride or diacetate in activating the carbon–carbon triple bond toward nucleophilic attack. This general idea is supported by a number of reactions where alkynes containing amino groups close to the acetylenic fragment undergo cyclization reactions via activation of the carbon–carbon triple bond by palladium dichloride or diacetate[6]–[8] and fail to

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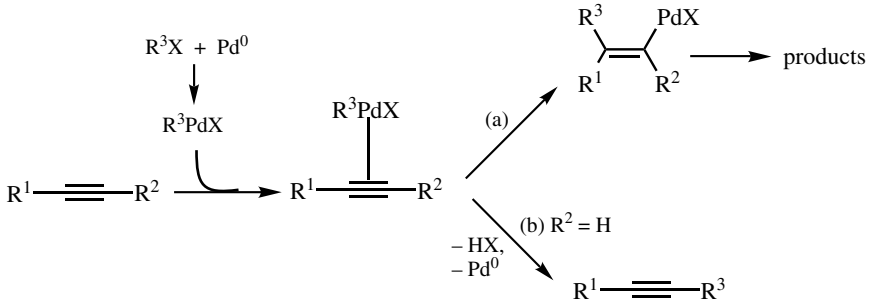
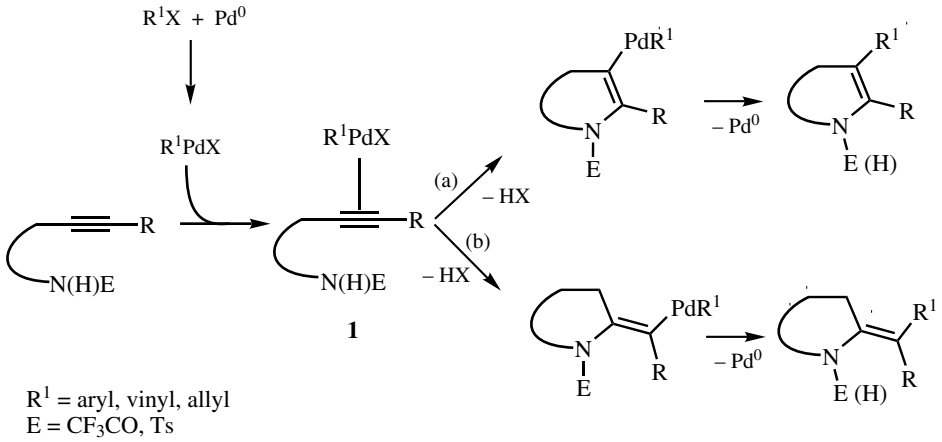


Scheme 1

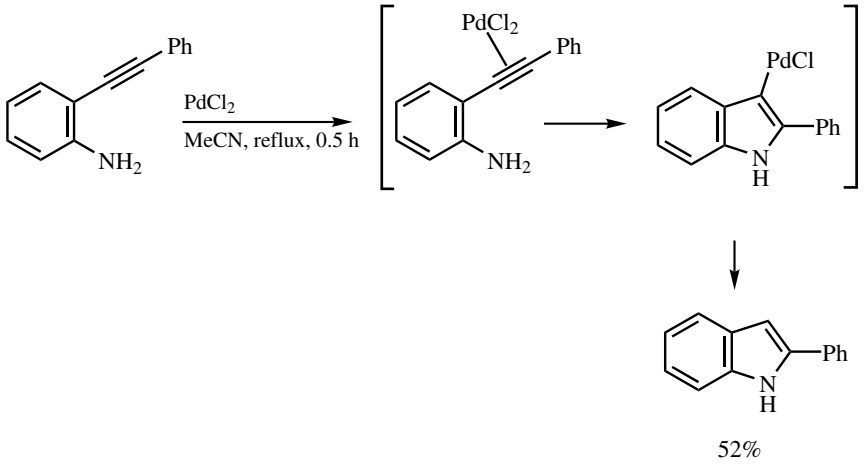


Scheme 2

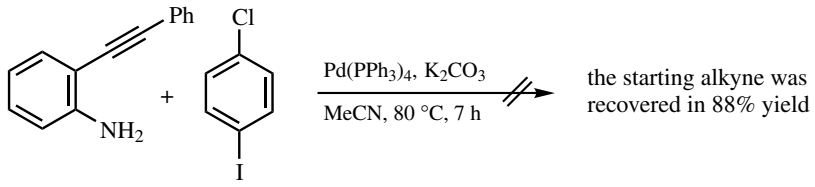
give the corresponding cyclization derivative under conditions that are expected to activate the carbon–carbon triple bond by coordination to σ-aryl- or σ-alkenylpalladium complexes.[9] A convincing example of this is given in **Schemes 3** and **4**. Subjection of *o*-(phenylethynyl)aniline to palladium dichloride in refluxing acetonitrile affords 2-phenylindole in satisfactory yield[6] (**Scheme 3**), whereas no indole product is obtained in the reaction of *o*-(phenylethynyl)aniline with *p*-chlorophenyl iodide in the presence of tetrakis(triphenylphosphine)palladium(0)[9] (**Scheme 4**).

When the reaction is carried out employing the trifluoroacetamido derivative of the alkyne partner (**Scheme 5**), the corresponding 2,3-disubstituted indole is obtained in high yield.[9] These data appear to support the notion that the acidity of the nitrogen–hydrogen bond plays a crucial role in this type of reaction. Presumably, when carbon–carbon triple bonds are activated via coordination to organopalladiums, anionic nitrogen nucleophiles, or nitrogen atoms whose nucleophilic attack can possibly be assisted by proton removal in the transition state leading to the aminopalladation adduct, are required to produce the desired cyclization products (**Scheme 5**).

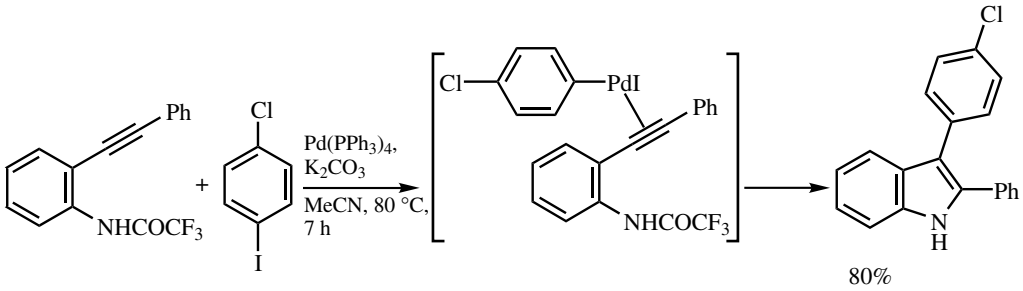
The substitution pattern of the acetylenic fragment is another factor that may exert a strong influence on the course of the reaction. The most evident effect is observed when comparing the behavior of terminal and internal alkynes. With terminal alkynes, the



Scheme 3



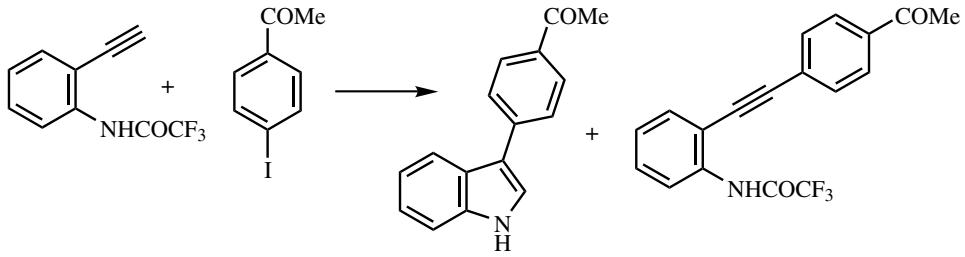
Scheme 4



Scheme 5

intermediacy of η^2-alkyne-organopalladiums may result in the formation of coupling products (**Scheme 1b**). In fact, coordination of palladium to the acetylenic fragment, in addition to activating the carbon–carbon triple bond toward intramolecular nucleophilic attack, can also favor the dissociation of the C_{sp}—H bond. In some cases—depending on the relative strength of the base as opposed to the strength of the proximate nitrogen nucleophile—the latter may be the preferred reaction pathway. Subsequent formation of a bond between the incipient acetylide anion and the coordinated palladium is likely to give a σ-alkynyl-σ-organopalladium intermediate that is converted into the corresponding coupling product through reductive elimination of palladium(0) species. The nature of phosphine ligands

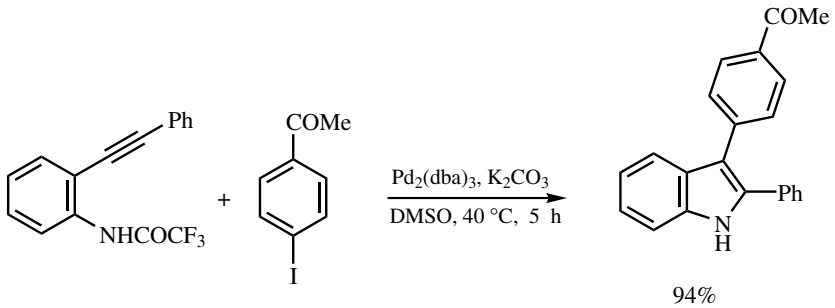
has been found to play a significant role in controlling the cyclization to coupling ratio. The reaction of *o*-ethynyltrifluoroacetanilide with *p*-iodoacetophenone provides an interesting example[5] (**Scheme 6**). Use of tetrakis(triphenylphosphine)palladium(0) gives a mixture of cyclization and coupling products whereas with tris(*p*-chlorophenyl)phosphine (tcpp) no indole product was obtained and the coupling derivative was isolated in high yield.



$Pd(PPh_3)_4$, K_2CO_3 . MeCN, 80 °C, 1 h	23%	37%
$Pd_2(dba)_3$, PPh_3, K_2CO_3, THF, 60 °C, 24 h	—	44%
$Pd_2(dba)_3$, tcpp, K_2CO_3, THF, 60 °C, 7 h	—	83%

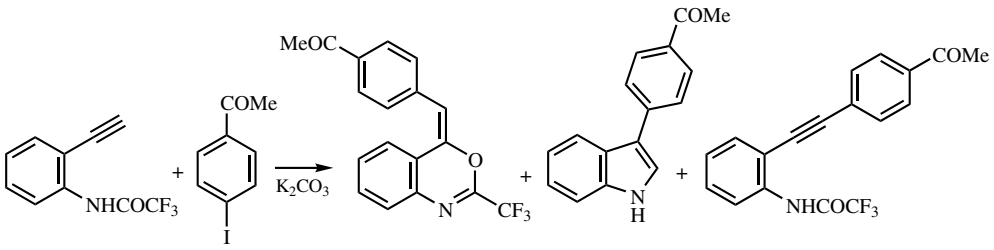
Scheme 6

The substituents joined to the acetylenic carbons may control the reactivity of η^2-alkyne-organopalladium intermediates even by affecting the electron density of the carbon–carbon triple bond. An example of how this effect might control the reaction outcome appears to be provided by the Pd-catalyzed reaction of *o*-(phenylethynyl)trifluoroacetanilide and *o*-ethynyltrifluoroacetanilide with aryl halides.[5] *o*-(Phenylethynyl)trifluoroacetanilide affords the corresponding 2,3-disubstituted indole product in high yield (**Scheme 7**), whereas *o*-ethynyltrifluoroacetanilide, under the same reaction conditions, gives a mixture of the expected 3-arylindole, the coupling derivative, and a cyclization product derived from an oxypalladation–reductive elimination domino reaction (**Scheme 8a**). The formation of the latter compound may involve the intramolecular nucleophilic attack of the oxygen terminus of the bidentate trifluoroacetamido nucleophile across the activated carbon–carbon triple bond. This O-cyclization derivative becomes the main reaction product in the presence of the sterically encumbered strongly basic tris(trimethoxyphenyl)phosphine (ttmpp) (**Scheme 8b**).



94%

Scheme 7



(a)	17%	64%	8%
(b)	61%	18%	5%

(a) $Pd_2(dba)_3$, DMSO, 40 °C, 1.25 h; (b) $Pd_2(dba)_3$, ttmpp, THF, 60 °C, 7 h

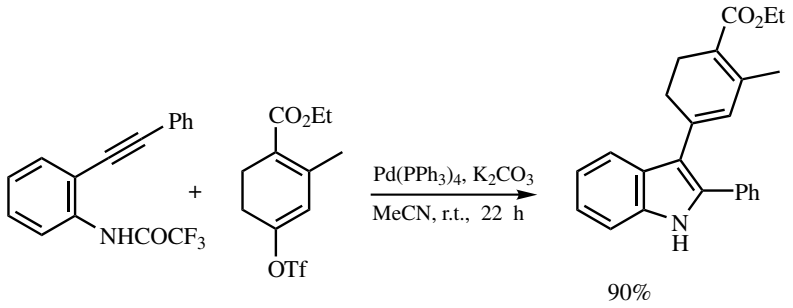
Scheme 8

The electron density of the carbon–carbon triple bond might influence the reaction outcome of this reaction as follows. Semiempirical calculations have shown that the highest negative charge is on the carbon joined to the aromatic ring bearing the *o*-trifluoroacetamido group in the *o*-(phenylethynyl)trifluoroacetanilide and on the terminal carbon in the *o*-(ethynyl)trifluoroacetanilide. Moreover, the charge difference between the two carbons in *o*-(phenylethynyl)trifluoroacetanilide is much higher than in *o*-(ethynyl)trifluoroacetanilide. Consequently, assuming that the charge distribution in the starting alkyne is a measure of the charge distribution in the more polarized η^2-alkyne-organopalladium complex that undergoes the intramolecular nucleophilic attack, electronic effects should favor the nucleophilic attack leading to the aminopalladation adduct with *o*-(phenylethynyl)trifluoroacetanilide. The nucleophilic attack of the oxygen, leading to a seven-membered ring oxypalladation adduct, would be disfavored by the size of the ring being formed. The alternative nucleophilic attack leading to a six-membered ring oxypalladation adduct would be disfavored by the low electrophilicity of the carbon linked to the aromatic ring bearing the *o*-trifluoroacetamido substituent. With *o*-(ethynyl)trifluoroacetanilide, where the charge difference between the two acetylenic carbons decreases, the oxypalladation leading to a six-membered ring adduct may compete more effectively and, in the presence of a proper phosphine ligand, it turns out to be the main reaction path.

The influence of phosphine ligands, solvents, and added salts on the reaction—the most difficult factors to generalize—largely remains to be clarified. Specific examples will be shown later.

C. REACTIONS WITH ORGANOPALLADIUM DERIVATIVES GENERATED FROM ARYL/HETEROARYL, ALKENYL HALIDES OR TRIFLATES

The Pd-catalyzed reaction of aryl iodides or alkenyl triflates with readily available 1-aryl-1-alkynes bearing an *o*-trifluoroacetamido substituent provides a valuable methodology for the synthesis of 2,3-disubstituted indoles[9] (**Scheme 9**). The reaction is very broad in scope. Generally, alkynes containing alkyl, alkenyl, and aryl fragments work well. As to the C_{sp^2} donor, both electron-withdrawing and electron-donating substituents appear to be tolerated.



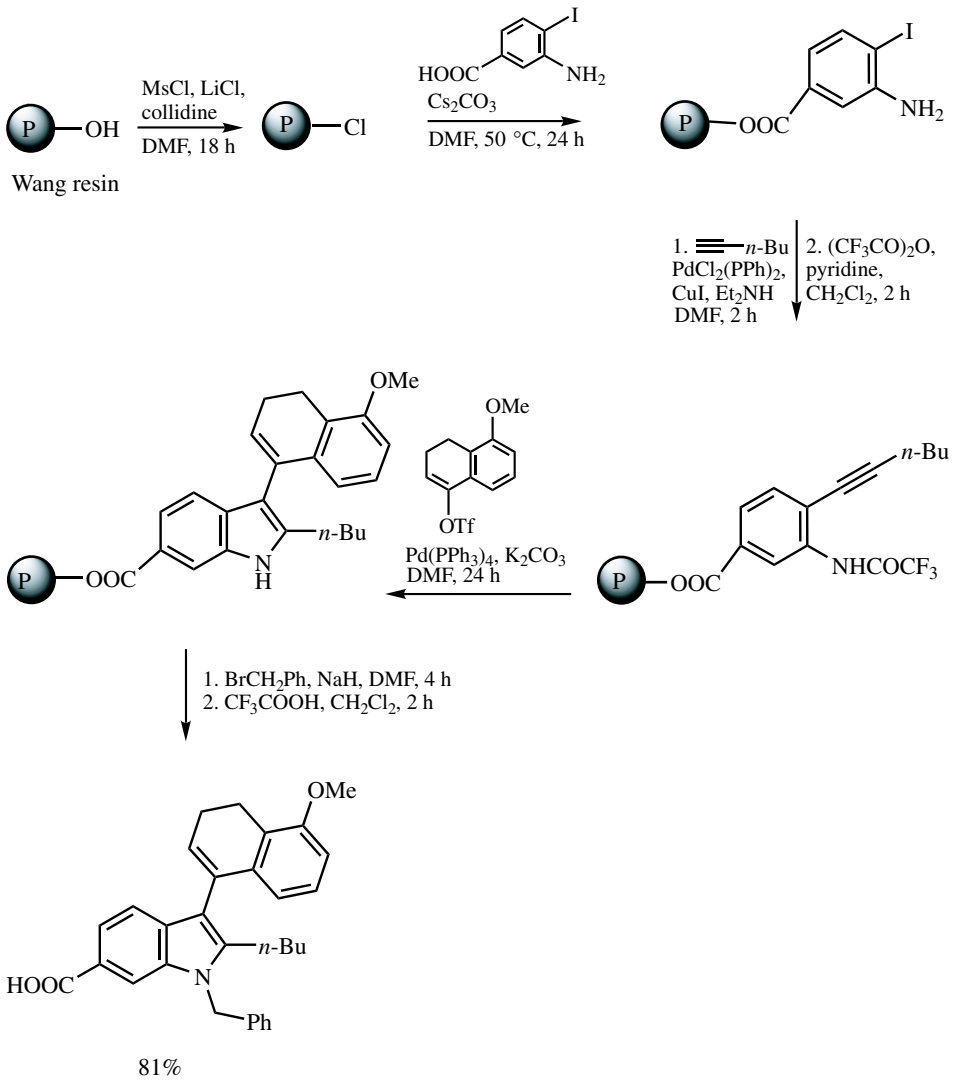
Scheme 9

Heteroaryl iodides have also been used. Preparations have been carried out using tetrakis(triphenylphosphine)palladium(0) at room temperature with alkenyl triflates and at 80 °C with aryl halides. The best results have been obtained by employing K_2CO_3 as the base. With triethylamine little product has been obtained. The presence of the trifluoroacetamido group appears crucial for the success of the reaction. No indole products have been obtained using *o*-(phenylethynyl)aniline or *o*-(phenylethynyl)acetanilide as the acetylenic partners. Employment of benzyl bromide as the organic halide under the same reaction conditions used with aryl iodides affords the 3-benzylindole product in moderate yield.[10] 2-*n*-Butyl-3-benzylindole was isolated in 47% yield upon reaction of benzyl bromide with *o*-(hexynyl)trifluoroacetanilide. The *N*-benzyl derivative of the starting alkyne was isolated in 50% yield.

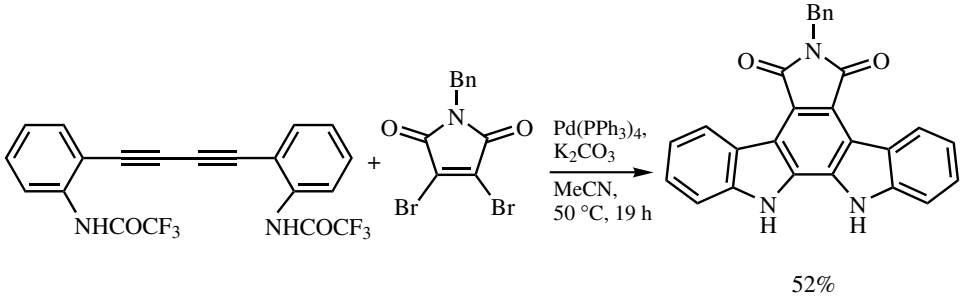
Adapted to a solid-supported synthesis, the reaction provides a convenient route to indoles with three independently variable components[11] (**Scheme 10**). Such a process may allow the preparation of combinatorial libraries with a high degree of potential diversity. K_2CO_3 is the optimal base for cyclization even in the solid phase reaction.

This chemistry has provided one of the most direct routes to the indolo[2,3-*a*]carbazole alkaloid ring system[12] (**Scheme 11**), a common functionality of several biologically active molecules such as the potent antitumor agent rebeccamycin and arcyriaflavin A. The indolo[2,3-*a*]carbazole derivative has been obtained in satisfactory yield through the reaction of 1,4-di(*o*-trifluoroacetamidophenyl)-1,3-butadiyne with 3,4-dibromomaleimide in the presence of tetrakis(triphenylphosphine)palladium(0) and potassium carbonate. The proposed mechanism of this polyannulation process, which generates four new bonds in a single step, is outlined in **Scheme 12**.

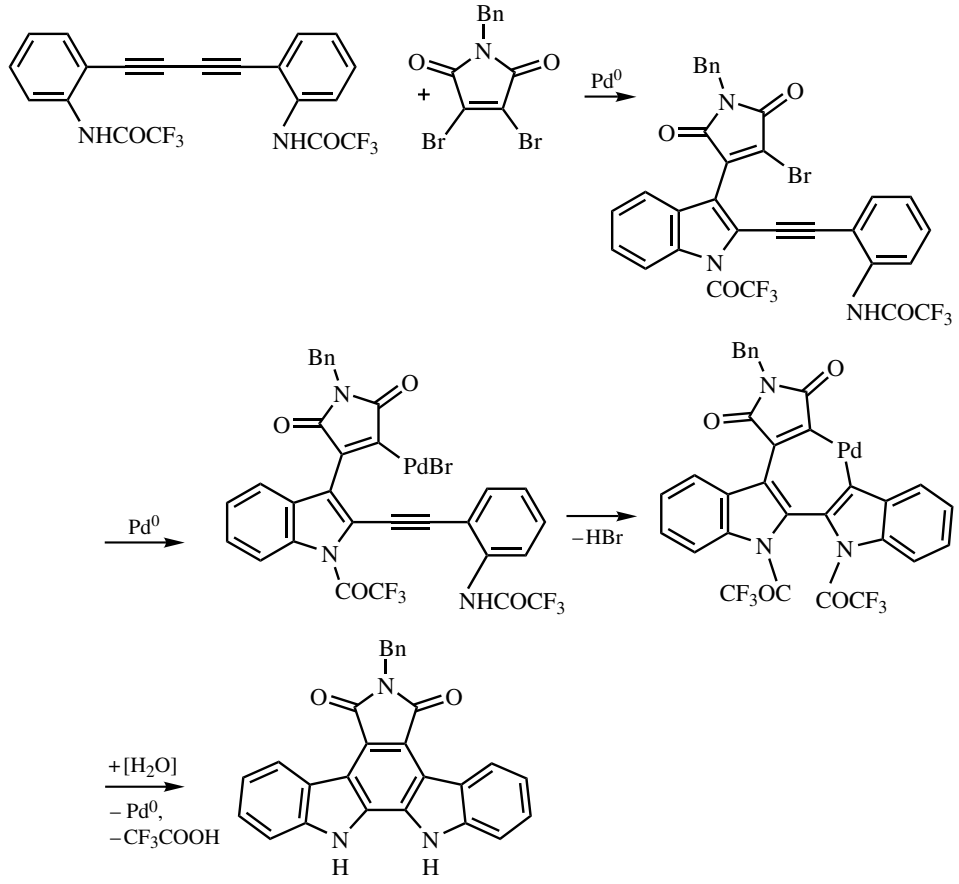
This alkyne cyclization chemistry for the construction of the important indole ring system has been extended to the synthesis of 2-unsubstituted 3-arylindoles[5] (**Scheme 13**) by employing *o*-ethynyltrifluoroacetanilide as the starting alkyne. Solvents, the nature of the base, ligands, and the palladium to ligand ratio were found to play a crucial role in controlling the reaction outcome. The best results have been obtained with $Pd_2(dba)_3$, omitting phosphine ligands, in the presence of DMSO and potassium carbonate. Use of cesium carbonate as the base also gives good results. The addition of phosphine ligands leads to more complex reaction mixtures. Coupling products and cyclic derivatives formed through the oxypalladation–reductive elimination domino reaction involving the amido oxygen are among the main by-products. Aryl iodides bearing both electron-donating and electron-withdrawing substituents give the corresponding indole derivatives in good yield, whereas none of the desired 2-substituted indole products were observed with aryl bromides. Notably, when aryl bromides are employed, they are recovered in



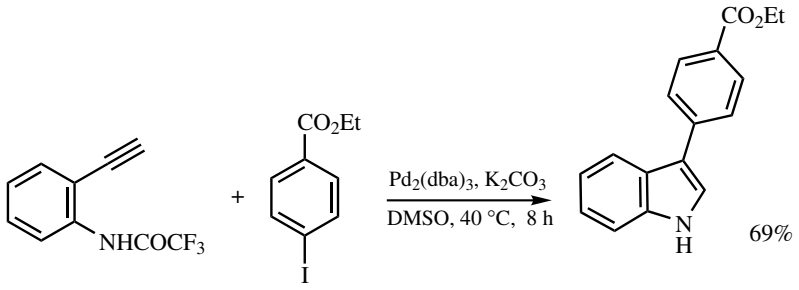
Scheme 10



Scheme 11



Scheme 12

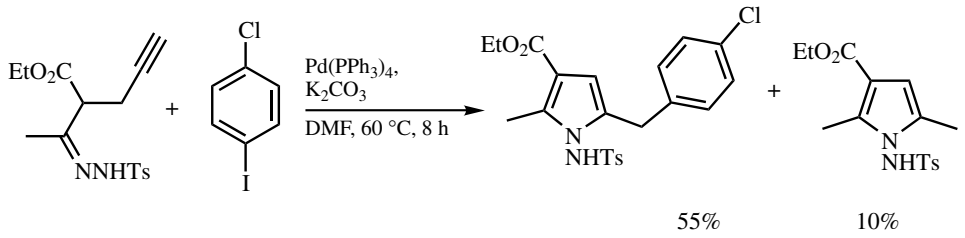


Scheme 13

high to almost quantitative yield, whereas the starting *o*-ethynyltrifluoroacetanilide is converted into indole in good yield, most probably through a Pd-catalyzed reaction.

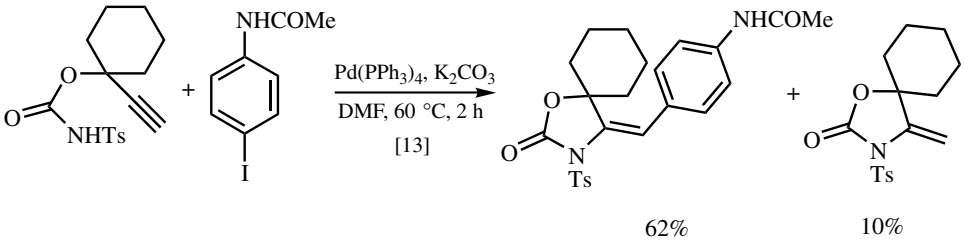
Alkynes containing nonaromatic amino groups close to the acetylenic fragment have also been used in this chemistry and a variety of new procedures for five- and six-membered ring heterocycles have been developed. The Pd-catalyzed reaction of ethyl 2-acetyl-4-pentynoate

tosylhydrazone with aryl iodides affords 1,2,3,5-tetrasubstituted pyrroles[13] (**Scheme 14**). Formation of the 2,5-dimethyl pyrrole product, apparently derived from a Pd-catalyzed cyclization of the starting alkyne, which does not involve the aryl donor, has been observed.



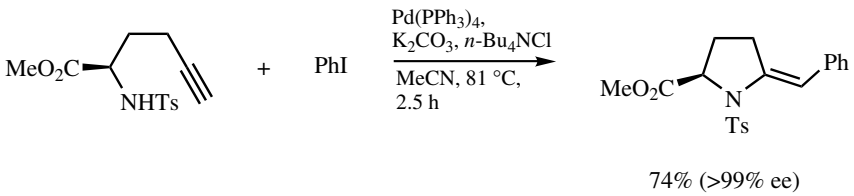
Scheme 14

Propargyl tosylcarbamates have been treated with aryl halides or alkenyl triflates in the presence of a palladium catalyst to give regio- and stereoselectively (*E*)-4-alkylidene-3-tosyloxazolidin-2-ones[14].[15] (**Scheme 15**). Various reaction conditions can be used to obtain the desired products: $Pd(PPh_3)_4$, K_2CO_3, *n*-Bu_4NCl, DMF, 60 °C (alkenyl triflates); $Pd(PPh_3)_4$, K_2CO_3, DMF, 60 °C (aryl iodides); or $Pd(OAc)_2$, tri(2-furyl)phosphine, *n*-Et_4NCl, MeCN, 25 °C (aryl iodides and alkenyl triflates). Depending on the substitution at the propargylic position, the reaction produces variable amounts of 4-methylene-3-tosyloxazolidin-2-ones, the formation of which may be limited by increasing the temperature or the C_{sp^2} donor to propargyl tosylcarbamate ratio.

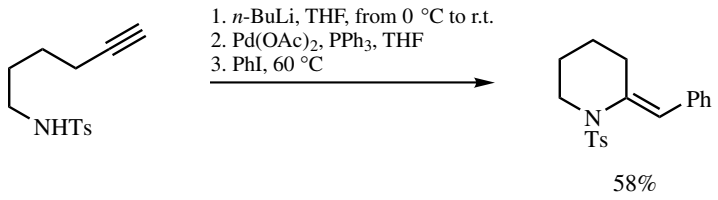


Scheme 15

Acetylenic tosylamides have been used as building blocks for the preparation of α-alkylidenepyrrolidine[16] (**Scheme 16**) and α-alkylidenepiperidine[17] (**Scheme 17**) products.



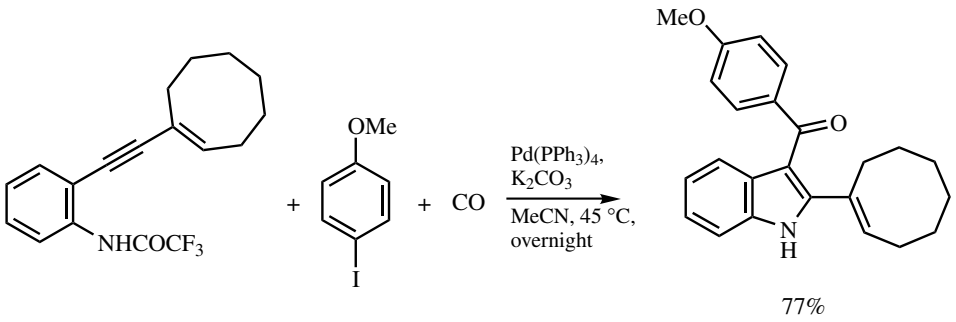
Scheme 16



Scheme 17

C.i. Reactions with Aryl- and Alkenylpalladium Derivatives in the Presence of Carbon Monoxide

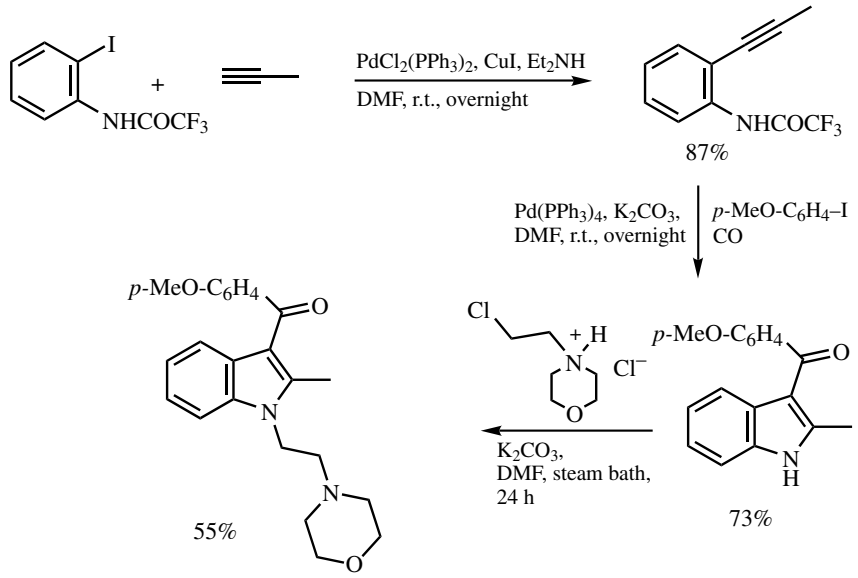
When alkynes containing proximate nitrogen nucleophiles are subjected to aryl and alkenyl halides or triflates under an atmosphere of carbon monoxide, the reaction can form highly substituted nitrogen-containing heterocycles incorporating a molecule of carbon monoxide. This synthetic approach to the construction of heterocyclic rings has been used for the preparation of 2-substituted 3-acylindoles from a variety of *o*-alkynyltrifluoroacetanilides and aryl iodides or alkenyl triflates[10] (**Scheme 18**). Employment of tetrakis(triphenylphosphine)palladium(0) or bis(triphenylphosphine)palladium diacetate and potassium carbonate in acetonitrile under a balloon of carbon monoxide gives good results with aryl iodides bearing electron-donating or moderately electron-withdrawing groups. Minor amounts of noncarbonylative cyclization products have occasionally been observed. In some cases, the reaction affords higher yields of the desired 3-acylindole product by increasing the pressure of carbon monoxide. With alkenyl triflates, the best results have been obtained by using anhydrous acetonitrile. With aryl iodides bearing strongly electron-withdrawing substituents, both anhydrous acetonitrile and a higher pressure of carbon monoxide appear necessary. In the latter case, the utilization of $Pd(dba)_2$ and tri(*o*-tolyl)phosphine in acetonitrile, under a balloon of carbon monoxide, may provide an alternative procedure but its effectiveness is to be evaluated each time. As found in other aminopalladation–reductive elimination domino reactions, *o*-alkynylanilines fail to produce the indole products. As an example, the reaction of *o*-phenylethynylaniline with *p*-iodoanisole under standard conditions gave the corresponding *N*-acylation derivative in 19% yield. The starting alkyne was recovered in 75% yield and no indole product was observed. When benzyl bromide was used as the organic halide under the same conditions employed with alkenyl triflates and aryl iodides, minor amounts of the desired 3-acylindole were isolated, the main reaction product being the *N*-benzyl derivative.



Scheme 18

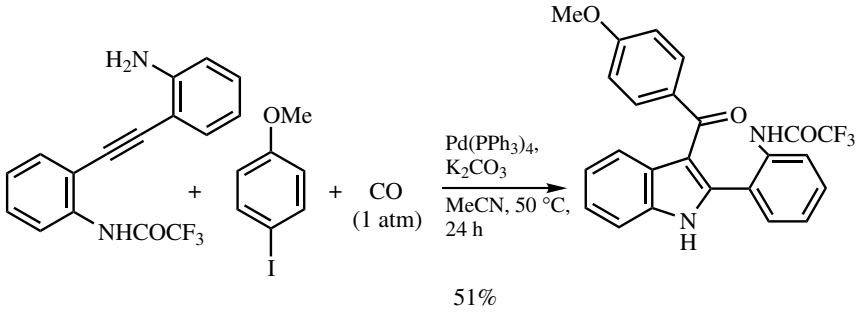
The ring closure step in this carbonylative aminopalladation–reductive elimination process presumably involves the intramolecular nucleophilic attack of the nitrogen across the carbon–carbon triple bond activated by an η^2-akyne-σ-acylpalladium complex, although the role of other possible reaction pathways is still to be cleared up.

This chemistry has been developed as a convenient new approach to pravadoline, an acylindole designed as nonacidic analog of nonsteroidal anti-inflammatory drugs (NSAIDs) (**Scheme 19**).

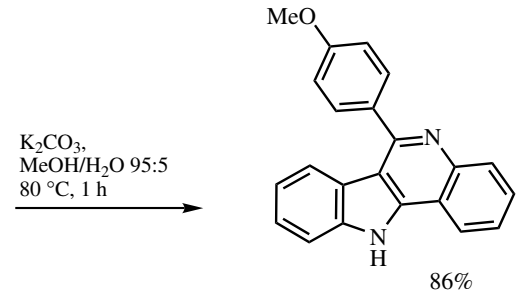


Scheme 19

The methodology has also been applied to the synthesis of functionalized indolo[3,2-*c*] quinolines by employing *o*-(*o′*-aminophenylethynyl)trifluoroacetanilide and aryl iodides as substrates[18] (**Scheme 20**). The desired indolo[3,2-*c*]quinolines can be prepared by a step-wise procedure involving the isolation of an acylindole intermediate or by a one-pot process, which usually gives higher yields.

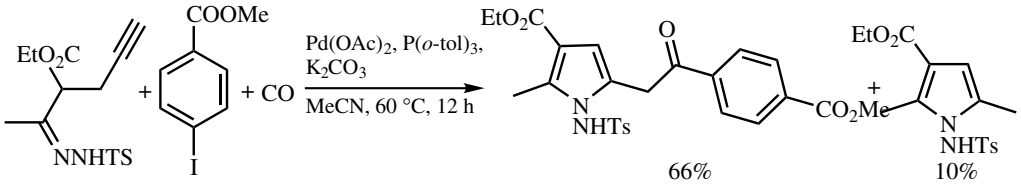


Scheme 20 (*Continued*)



Scheme 20

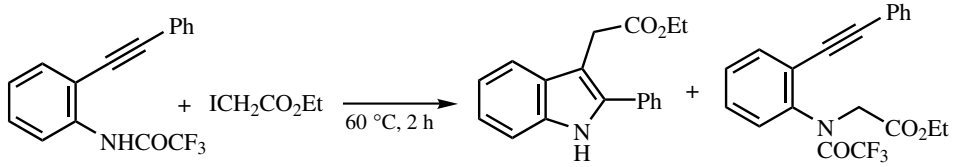
The reaction of ethyl 2-acetyl-4-pentynoate tosylhydrazone with aryl iodides under an atmosphere of carbon monoxide affords 1,2,3,5-tetrasubstituted pyrroles that incorporate a molecule of carbon monoxide[13] (**Scheme 21**). Formation of minor amounts of the corresponding 2,3-dimethyl pyrrole product has been observed.



Scheme 21

D. REACTIONS WITH ORGANOPALLADIUM DERIVATIVES GENERATED FROM ALKYL HALIDES

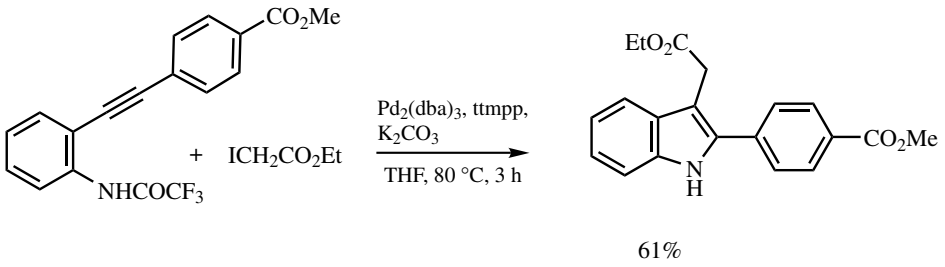
Extension of the aminopalladation–reductive elimination domino methodology to the commercially available ethyl iodoacetate provides a new approach to the construction of indole rings containing the 3-(ethoxycarbonyl)methyl group.[19] Employment of the same conditions reported for the preparation of 2,3-disubstituted indoles[9] and 2-unsubstituted 3-arylindoles[5] fail to give the desired indole derivatives, at least with the model system, the *N*-alkyl derivative being the main or sole reaction product (**Scheme 22**).



([9]) $Pd(PPh_3)_4$, K_2CO_3, MeCN 7% 75%
([5]) $Pd_2(dba)_3$, K_2CO_3, DMSO — 56%

Scheme 22

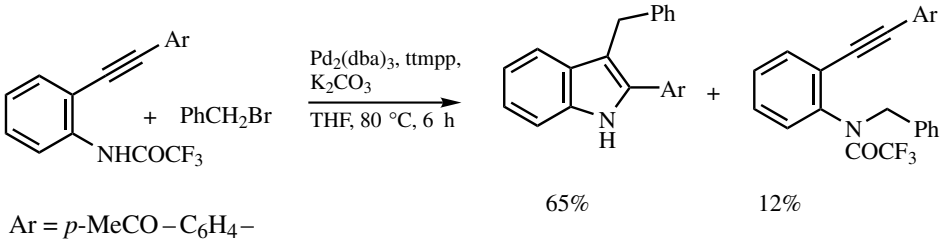
The best results with regard to reaction rate and cyclization to *N*-alkylation ratio have been obtained by employing $Pd_2(dba)_3$ in conjunction with ttmpp in THF (**Scheme 23**). The utilization, in THF, of $Pd_2(dba)_3$ and P(*o*-tol)$_3$ or P(Bu-*t*)$_3$ can also give satisfactory results whereas the *N*-alkyl derivative was isolated as the main reaction product by using $Pd_2(dba)_3$ and PPh_3 or P(*p*-MeO-C_6H_5)$_3$. Depending on the nature of the alkyne, unalkylated indoles have been isolated, sometimes in significant yield.



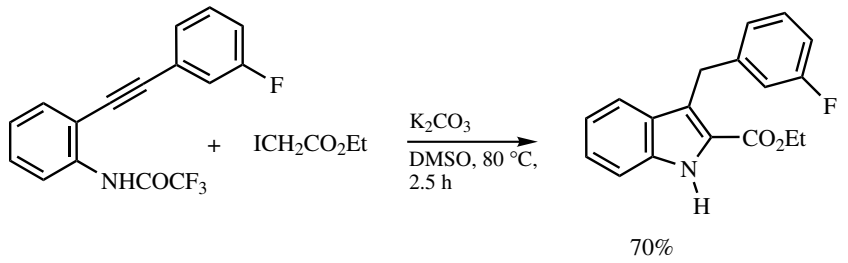
Scheme 23

Likewise, subjection of *o*-alkynyltrifluoroacetanilides to benzyl bromide in the presence of $Pd_2(dba)_3$ and ttmpp in THF furnishes 3-benzyl indoles (**Scheme 24**).

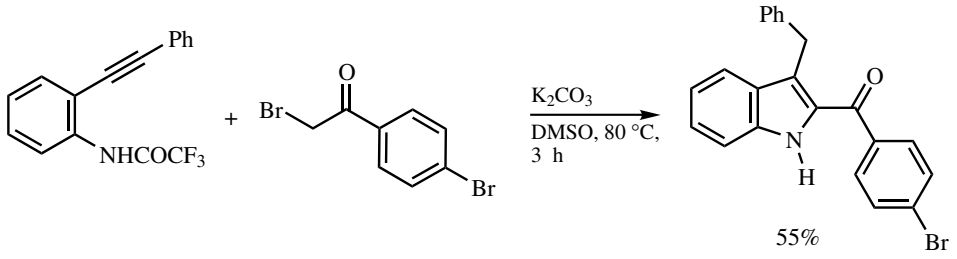
The solvent has a remarkable effect on the reaction outcome. For example, keeping all the other parameters the same but otherwise substituting DMSO for THF leads to the formation of 2-ethoxycarbonyl-3-alkylindoles as the main reaction products. This reaction is independent of the palladium catalyst and may provide a facile and useful entry into indole-2-carboxylates (**Scheme 25**) and 2-acylindoles (**Scheme 26**).[20]



Scheme 24



Scheme 25



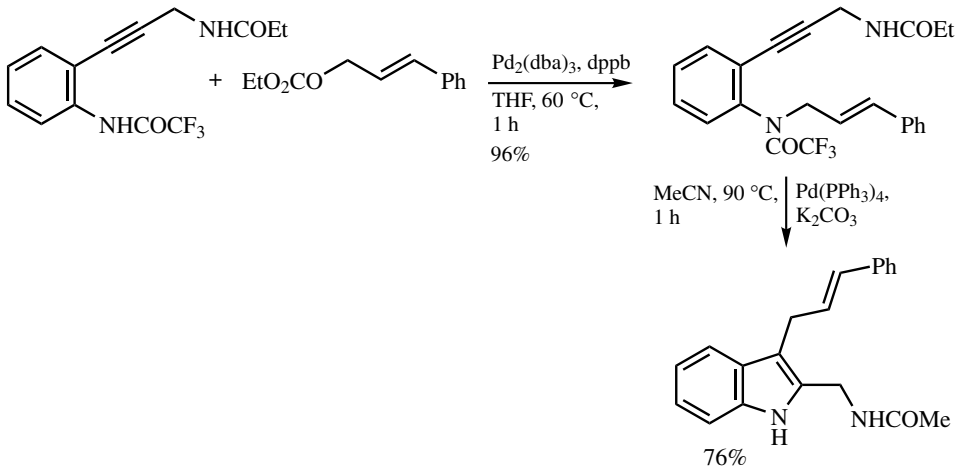
Scheme 26

As to the formation of these compounds, very likely the reaction proceeds through an *N*-alkylation step, which is followed by a cyclization step whose mechanism should be similar to that proposed for related base-catalyzed cyclizations of alkynes containing close (pro) nucleophiles.[21],[22]

E. REACTIONS WITH ORGANOPALLADIUM DERIVATIVES GENERATED FROM ALLYL AMIDES AND ESTERS

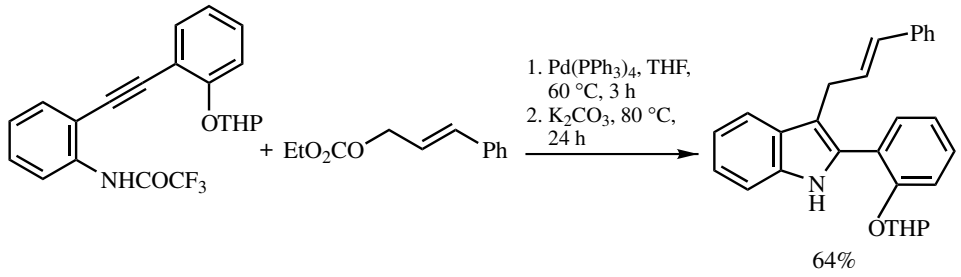
Allyl esters are known to react with palladium catalysts to afford η^3-allylpalladium complexes that can undergo a nucleophilic attack to give allylation products.[23]–[25] Accordingly, treatment of allyl carbonates with *o*-alkynyltrifluoroacetanilides or *o*-ethynyltrifluoroacetanilide in the presence of $Pd_2(dba)_3$, dppb [1,4-bis(diphenylphosphino)butane] in THF at 60 °C affords the corresponding *N*-allyl derivatives in high yield, with the nitrogen–carbon bond formed regioselectively at the less substituted terminus of the allylic system.

Subjection of these *N*-allyl derivatives to $Pd(PPh_3)_4$ and K_2CO_3 in MeCN at 90 °C or $Pd_2(dba)_3$ and ttmpp in DME at 100 °C produces 2-substituted 3-allylindoles in good to high yield[26] (**Scheme 27**). 2-Unsubstituted 3-allylindoles have also been prepared, albeit



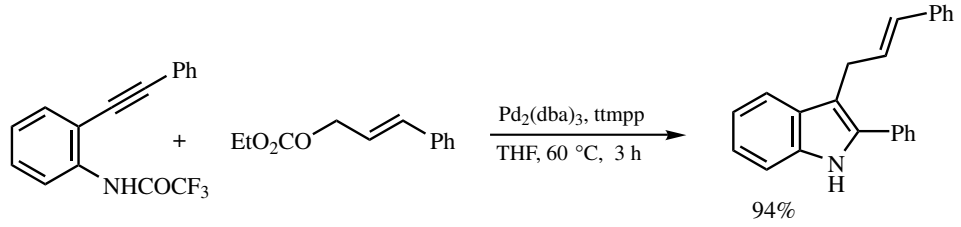
Scheme 27

in moderate yield. The reaction can be performed even as a one-pot process that omits the isolation of the *N*-allyl derivatives: the allyl ester and starting alkyne are in this case treated with $Pd(PPh_3)_4$ in THF at 60 °C until the disappearance of the latter, K_2CO_3 is added, and the temperature is raised to 80 °C[26] (**Scheme 28**).



Scheme 28

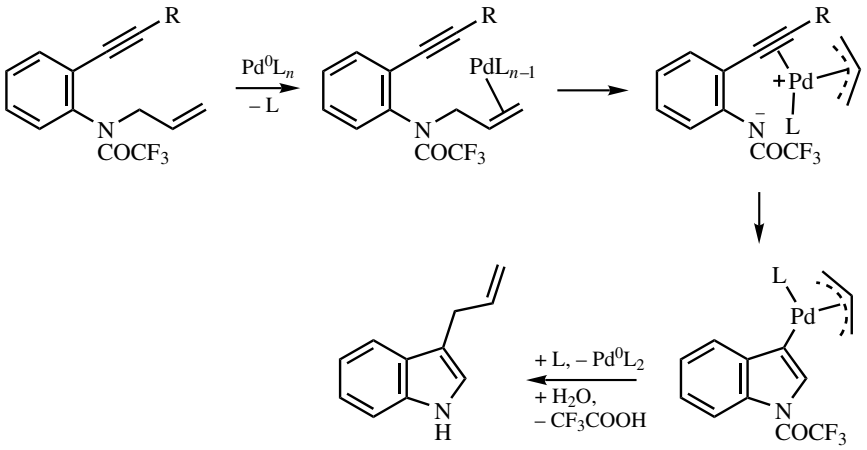
2-Substituted 3-allylindoles can also be prepared through a third procedure that is based on the reaction of *o*-alkynyltrifluoroacetanilides with allyl carbonates in the presence of the $Pd_2(dba)_3$–ttmpp catalyst system in THF at 60 °C and that apparently does not involve *N*-allyl intermediates[26] (**Scheme 29**).



Scheme 29

The regiochemistry of the carbon–carbon bond formed between indolyl and allyl fragments is influenced by several factors: steric and electronic effects relative to phosphine ligands, steric and electronic effects exerted by the substituents joined to the C_{sp} far from the *o*-(trifluoroacetamido)phenyl group, and the nature of the allylating agent. Employment of tetrakis(triphenylphosphine)palladium(0) can give good results with allyl esters producing symmetrical η^3-allylpalladium intermediates or containing markedly different allylic termini. When steric differences between the two allylic termini are small, remarkable regioselectivity is observed by using ttmpp. In this case, almost exclusive formation of 3-allylindoles with the indolyl moiety bound to the less substituted allyl terminus is usually observed. The process is accompanied by some loss of olefin geometry.

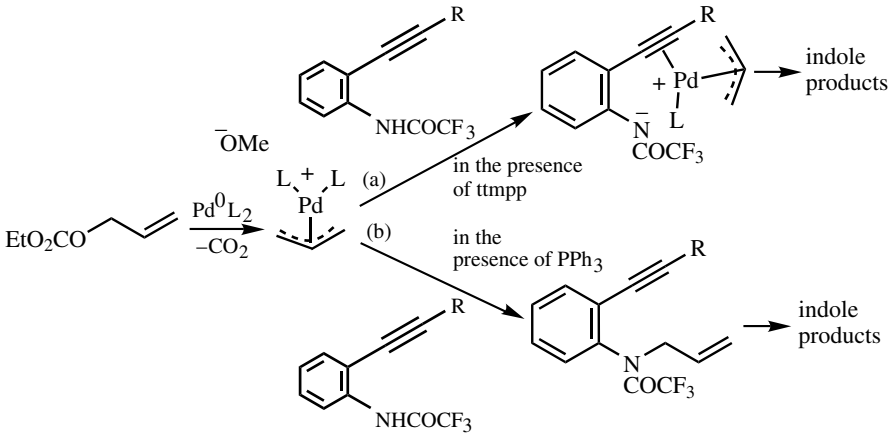
The formation of the indole ring from *N*-allyl derivatives has been proposed to proceed as outlined in **Scheme 30** using the parent *N*-allyl derivative: (i) coordination of the olefin moiety of the *N*-allyl intermediate to palladium affords an η^2-olefinpalladium complex; (ii) ionization of the η^2-olefinpalladium complex and displacement of one ligand to the palladium by the carbon–carbon triple bond to give an η^2-alkyne-η^3-allylpalladium



Scheme 30

complex; (iii) intramolecular nucleophilic attack of the nitrogen across the activated carbon–carbon triple bond to form a σ-indolyl-η^3-allylpalladium; and (iv) migration of the indolyl fragment onto one of the allylic termini and regeneration of the Pd(0) catalyst. Notably, according to this scheme, stepwise and one-pot protocols are based on the ambivalent behavior of the amido group, which intervenes as a nucleophile in the *N*-allylation step and as a leaving group in the conversion of the η^2-olefinpalladium complex into the η^2-alkyne-η^3-allylpalladium complex.

As to the process that affords 3-allylindoles without the intermediacy of an *N*-allyl derivative, a possible explanation considers the reaction of the *o*-alkynyltrifluoroacetanilide with the η^3-allylpalladium intermediate derived from the allyl carbonate. The strongly basic sterically encumbered ligand ttmpp might control the reactivity of the latter so as to favor the formation of the η^2-alkyne-η^3-allylpalladium complex via coordination of the alkyne moiety to the palladium (**Scheme 31a**) at the expense of the nucleophilic attack of the nitrogen on the allylic fragment, which would lead to the formation of the *N*-allyl product (**Scheme 31b**).



Scheme 31

F. SUMMARY

The aminopalladation–reductive elimination domino reaction of alkynes containing nitrogen nucleophiles close to the carbon–carbon triple bond has been shown to be a valuable methodology for the synthesis of the pharmaceutically important indole ring system and a variety of nitrogen-containing heterocycles.

The reaction takes advantage of the ease with which the functionalized alkynes used as starting material can be prepared and of the fact that a number of aryl and alkenyl halides or triflates, alkyl halides, and allyl esters can successfully be used as carbon donors. In the presence of carbon monoxide, a three-component process can take place, widening the scope of the reaction and providing a useful, straightforward entry into cyclization products incorporating a molecule of carbon monoxide.

The high regio- and stereoselectivities are another important facet of this cyclization chemistry. One can anticipate that future studies will not only lead to a better understanding of the process but will provide new applications for the preparation of complex molecules, particularly in the area of biologically active compounds.

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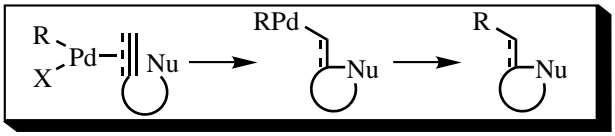

V.3.4 Palladium-Catalyzed Reactions Involving Attack on Palladium–Alkene, Palladium–Alkyne, and Related π-Complexes by Carbon Nucleophiles

GENEVIÈVE BALME, DIDIER BOUYSSI, and NUNO MONTEIRO

A. INTRODUCTION

Coordination of palladium(II) compounds to alkenes, to form π-alkene palladium(II) complexes, activates the alkene to nucleophilic attack. In general, nucleophilic attack by carbon nucleophiles occurs on the face opposite the metal atom, resulting in the formation of a σ-bond palladium(II) alkyl complex. A wide variety of mechanisms are possible for the liberation of the carbon ligand, the nature of the product obtained being dependent on the conditions employed and the nature of the complex.

These carbopalladation reactions may be divided into two distinct types of reaction: those involving palladium(II) salts and those involving organopalladium(II) complexes. These two reaction types will be treated separately herein.

B. CARBOPALLADATION INVOLVING PALLADIUM(II) SALTS

When palladium(II) salts are employed, stoichiometric quantities of the salts are required. In certain cases palladium has been used catalytically by addition of a suitable reoxidant, most usually copper(II) salts.

The first example of a reaction[1] of a carbon nucleophile with an olefin dates back to 1965 when Tsuji and Takahashi discovered that cyclooctadiene (COD) treated with $PdCl_2$ afforded a stable complex **1** (**Scheme 1**). When this complex was treated with active methylene compounds under basic conditions a new complex **2** with both π- and σ-Pd—C bonds were formed. Cyclization to the diethyl bicyclo[6.1.0]non-4-ene-9,9-dicarboxylate **3** then occurred readily under the basic conditions. When 1 equiv of the active methylene compound was added to complex **2**, the tetraethyl bicyclo[3.3.0]octane-2,6-dimalonate **4** was formed by a transannulation reaction (**Scheme 1**).[2]

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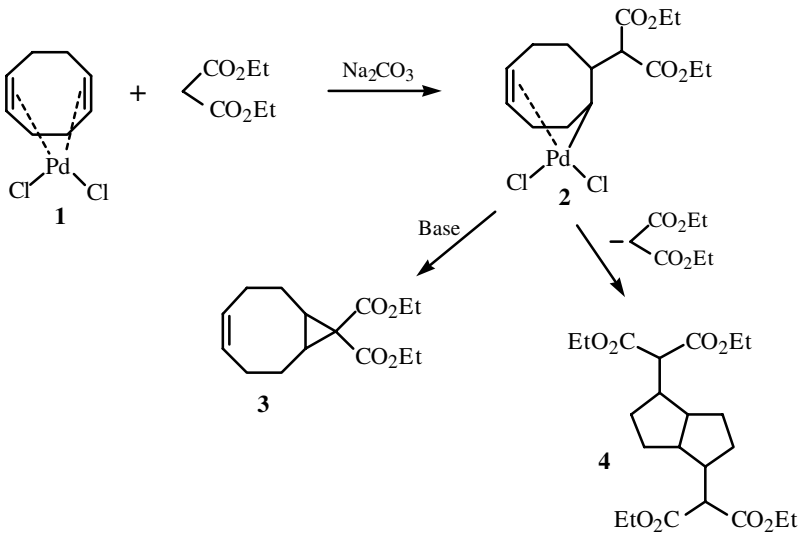


Scheme 1

B.i. Carbopalladation of Simple Alkenes

Unlike the facile reaction of COD with carbon nucleophiles, alkylation of monoalkenes with palladium(II) salts is most difficult. However, when $PdCl_2$ and 2 equiv of Et_3N are employed, stabilized carbanions ($pK_a = 10–17$) may successfully alkylate monoalkenes (**Scheme 2**).[3] The ligating effect of Et_3N is essential to the success of this reaction. The nature of the product obtained is determined by the reaction conditions. Allowing the reaction to warm to room temperature affords the corresponding alkene, whereas bubbling hydrogen into the reaction mixture at -50 °C results in the formation of a saturated product.[4],[5]

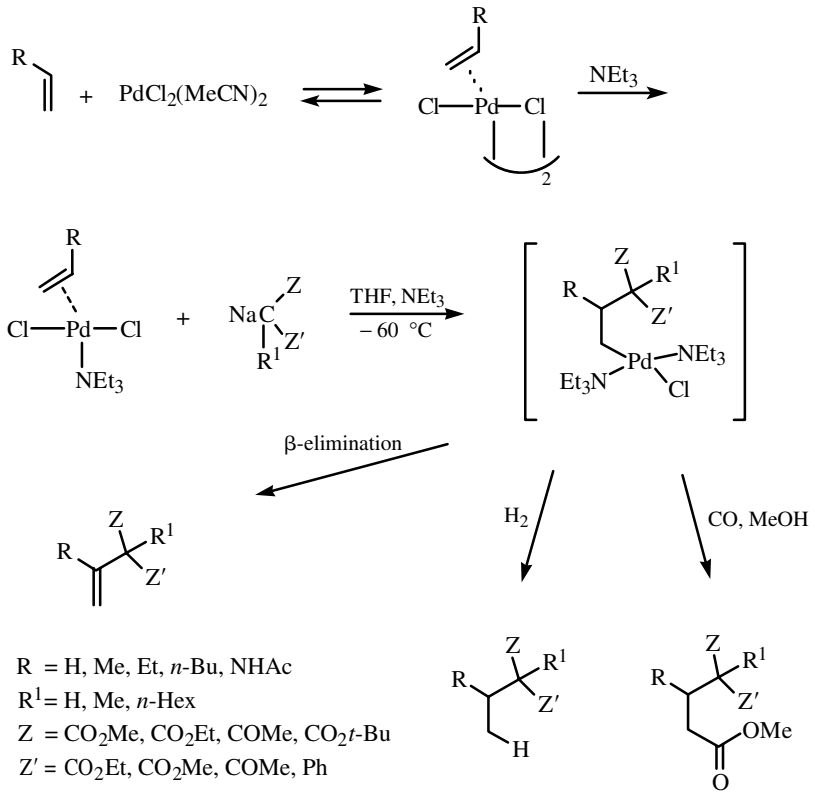
Interestingly, attack of the nucleophile is regiospecific to the most hindered carbon of the alkene, which is consistent with an external, *trans* nucleophilic attack. Olefins complexed to palladium(II) may also react with the anions of malonates and then be acylated by treatment with CO and methanol.[6] The overall process is a difunctionalization of the olefinic substrate.

This reaction may also be performed intramolecularly.[5] Methyl 2-carbomethoxyhex-5-enoate **5** when treated with NaH, $PdCl_2$, and Et_3N affords dimethylcyclopentane-1,1-dicarboxylate **6** in modest yield (42%) (**Scheme 3**).

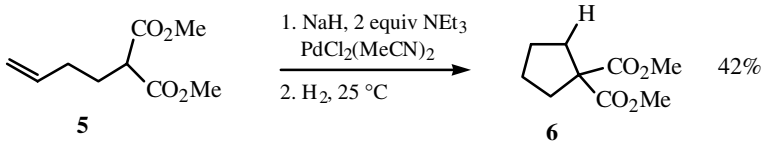
The nature of the alkene is important in determining reactivity. Indeed, electron-rich alkenes such as enamides, enoenamides, and alkenyl ethers are notably more reactive to carbopalladation.

B.ii. Carbopalladation of Alkenyl Ethers

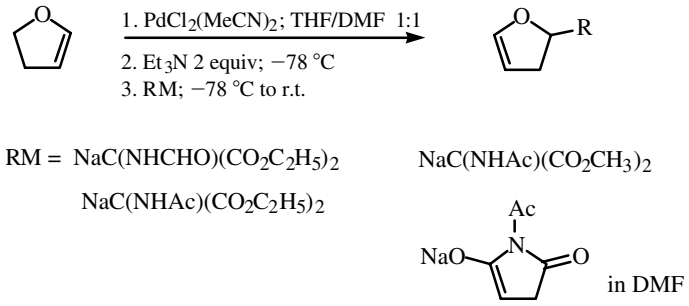
In the carbopalladation of alkenyl ethers it was found that stabilized carbanions added regioselectively to 2,3-dihydrofuran.[7] When treated with $PdCl_2(MeCN)_2$ and 2 equiv of Et_3N in 1:1 THF/DMF at room temperature (r.t.), addition at the oxygen-bearing carbon is observed along with migration of the double bond. This latter phenomenon appears to be the result of a series of elimination and readdition cycles by "Pd—H" (**Scheme 4**).



Scheme 2



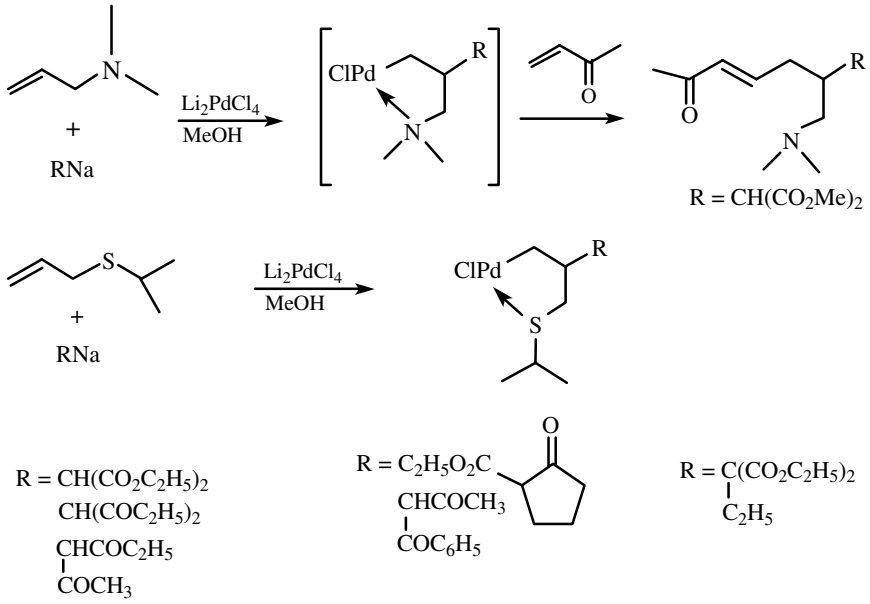
Scheme 3



Scheme 4

B.iii. Carbopalladation of Allylic and Homoallylic Amines and Sulfides

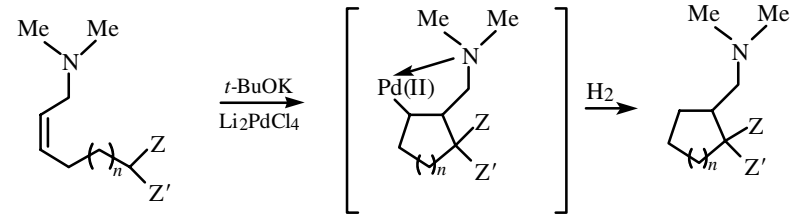
Allylic amines when treated with lithium tetrachloropalladate and a stabilized carbanion undergo carbopalladation to form stable five-membered palladacycles. The Pd atom may then be substituted by hydrogen,[8] a functionalized alkene,[9] or carboxylate,[10] depending on the conditions employed (**Scheme 5**). The carbopalladation of allylic sulfides also results in the formation of five-membered chelates.[8]



Scheme 5

When adapted to an intramolecular version, allylic amines and sulfides afford fused bicyclic palladacycles in the presence of lithium tetrachloropalladate and base.[11] Hydrogenation of these complexes liberates the cycloalkanes (**Scheme 6**).

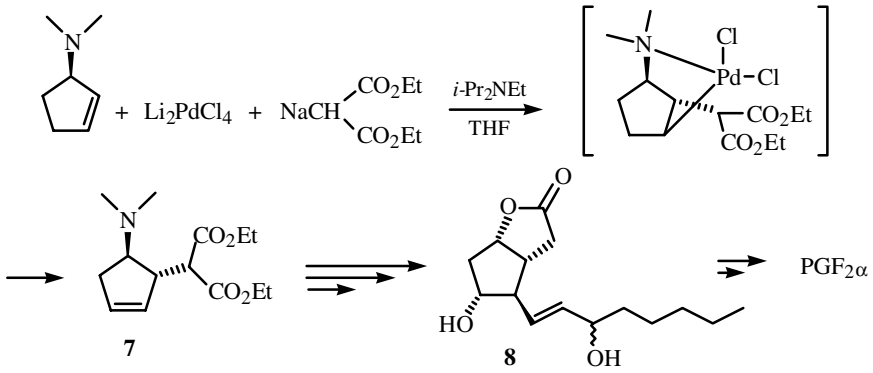
A similar reaction using allylic amines has been employed in an elegant synthesis of a prostaglandin.[12] The dimethylamino substituent directs alkylation to the 2-position while controlling the resulting stereochemistry. Addition of the carbon nucleophile is always



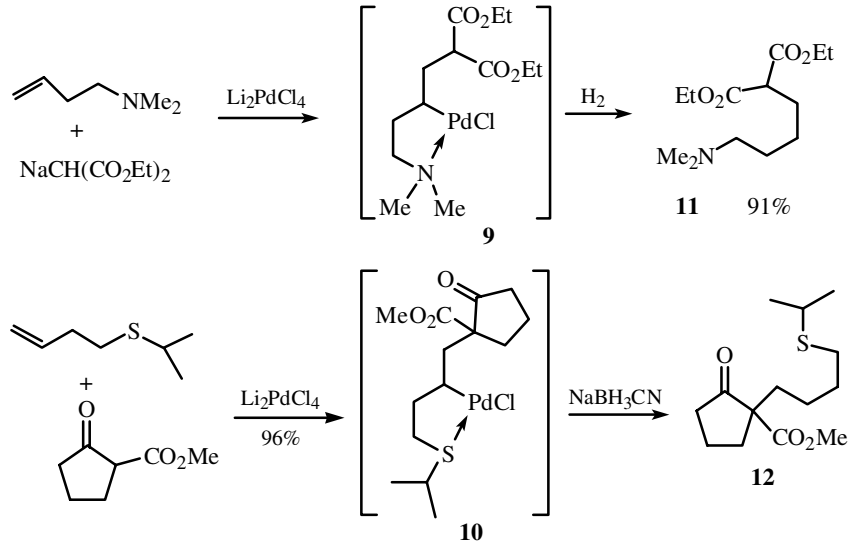
Scheme 6

trans to the amino substituent under these conditions (**Scheme 7**). The amino diester **7** was further transformed into Corey's lactone **8**, which had previously been converted to $PGF_{2\alpha}$ in two chemical steps and 80% overall yield.

A closely related reaction has been developed on homoallylic amines and sulfides.[13] These substrates undergo regiospecific carbopalladation in the presence of stabilized enolates and lithium tetrachloropalladate to provide stable five-membered palladacycles. Reduction of the complexes **9** and **10**, respectively, affords the alkylated diester **11** and keto ester **12** (**Scheme 8**).



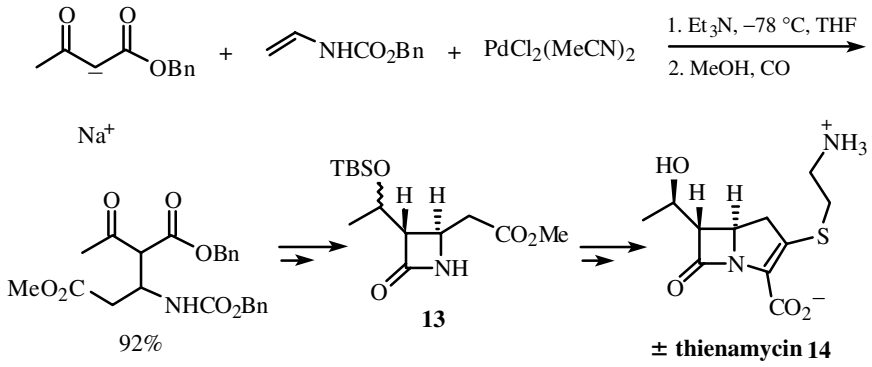
Scheme 7



Scheme 8

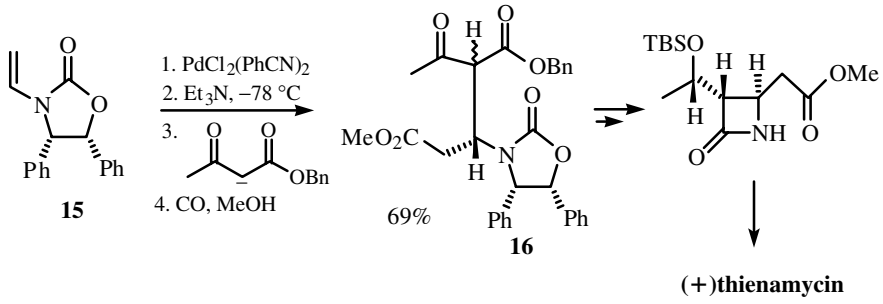
B.iv. Carbopalladation of Enamides

As with alkenyl ethers, carbopalladation of enamides[14] takes place exclusively at the α-position. The β-lactam **13**, an intermediate in the synthesis of (±)-thienamycin **14**, has been synthesized by this method with subsequent carbonylation by CO and MeOH (**Scheme 9**).



Scheme 9

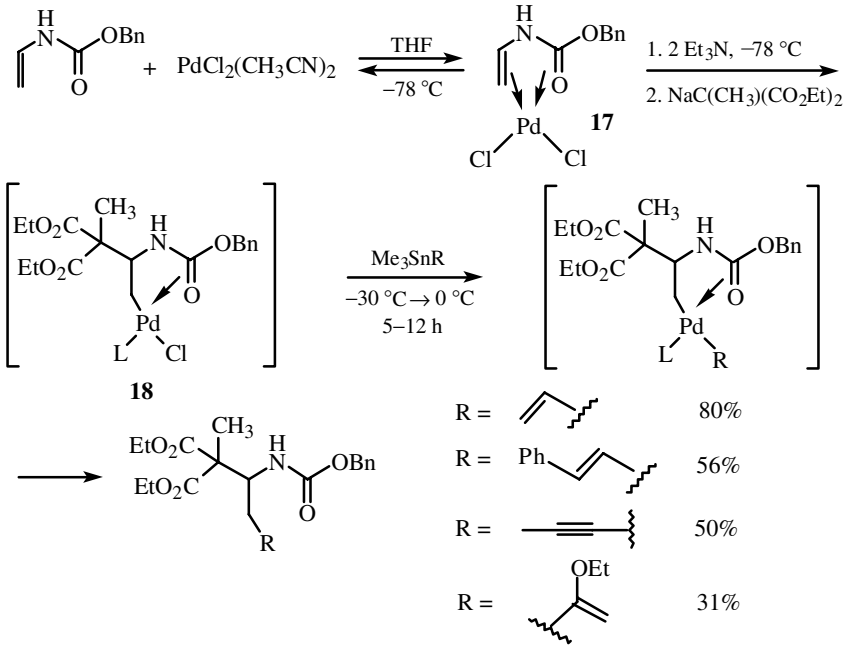
This Pd(II)-assisted tandem alkylation/carbonylative coupling procedure was then performed on the optically active ene carbamate **15**.[15] This reaction occurred with complete stereocontrol of the single chiral center generated, leading to **16**. This compound was then converted to a known precursor of (+)-thienamycin in very high optical yield (**Scheme 10**).



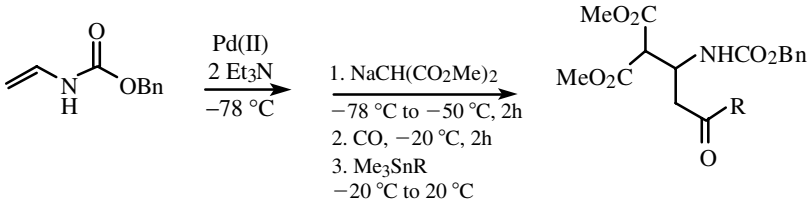
Scheme 10

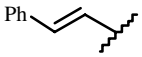
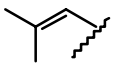
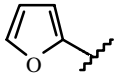
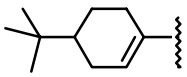
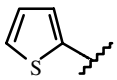
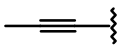
The treatment of trialkylorganostannanes with σ-alkylpalladium(II) complex **18**, generated by attack of sodium diethyl methylmalonate on π-olefinpalladium(II) complex **17**, resulted in coupling via transmetallation/reductive elimination.[16] Vinyl trimethyltin coupled in good yield whereas lower yields were obtained with other trimethyltin reagents (**Scheme 11**). Treatment of σ-complex **18** with 1 atm of carbon monoxide for 2 hours at -20 °C followed by addition of the tin reagent produced carbonylative coupled products in good yield. When the reaction was performed at a temperature below -20 °C, mixtures of coupled and carbonatively coupled products were formed,[16] indicating that the process must proceed in a stepwise fashion. Therefore, stoichiometric quantities of palladium are required (**Scheme 12**).

A similar approach was taken to the synthesis of (+)-Negamycin **20**.[17] Palladium(II) assisted alkylation of the optically active enamide **15** followed by carbonylation with CO, and a vinyl trimethyltin afforded the intermediate **19** (**Scheme 13**).

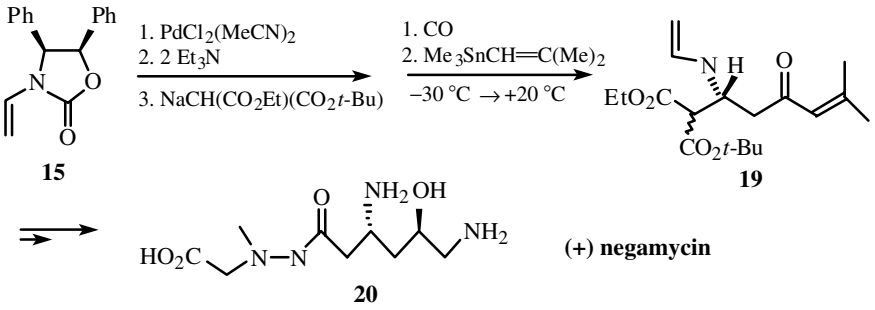


Scheme 11



R	Yield %	R	Yield %
	79	*p*-MeOPh	93
	72	*p*-ClPh	59
	74		59
	70		62
Ph	77		69
p-MePh	95		

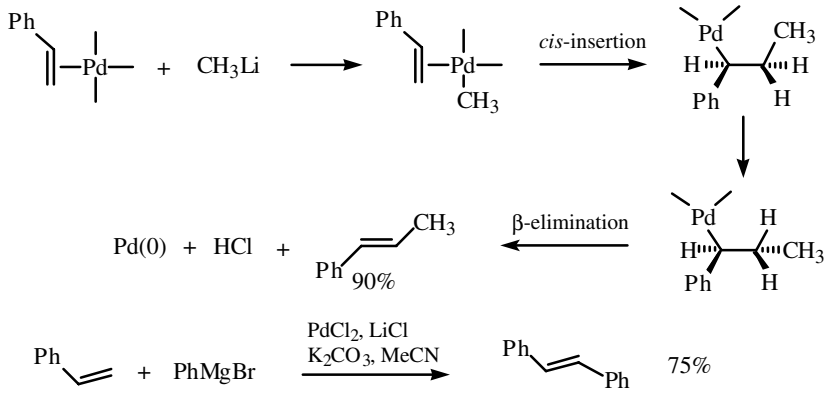
Scheme 12



Scheme 13

B.v. Carbopalladation Involving Hard Carbon Nucleophiles

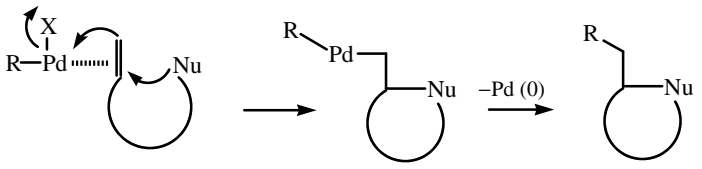
The reactions discussed so far involved attack of soft nucleophiles on π-alkene palladium(II) complexes. Hard carbon nucleophiles such as methyl lithium also react with these complexes.[18] The alkylation proceeds here by initial attack at the palladium atom. Subsequent *cis*-insertion of the olefin into the Pd—C bond and *cis*-β-hydride elimination result in liberation of the alkylated alkene. The arylation of styrene by Grignard reagents can also be performed,[19] the reaction being realized in the presence of stoichiometric or catalytic quantities of palladium chloride (**Scheme 14**).



Scheme 14

C. CARBOPALLADATION INVOLVING ORGANOPALLADIUM(II) COMPLEXES

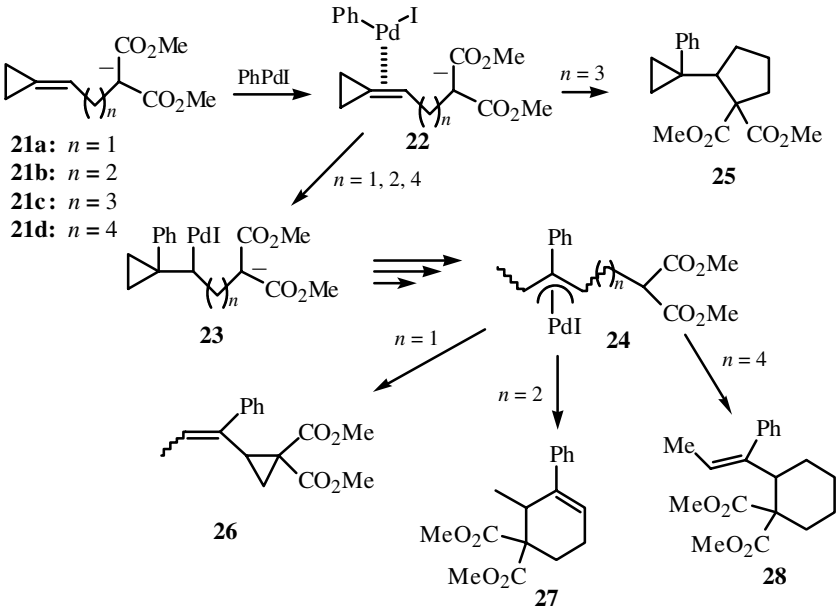
The first reported example of an intramolecular nucleophilic attack on an unsaturation electrophilically activated by an organopalladium complex dates back to 1987. In this new reaction the activating species is generated *in situ* by oxidative addition of an unsaturated halide to the metal. The cyclization process generates a σ-bonded palladium complex, which undergoes reductive elimination. This liberates the cyclization product and completes the catalytic cycle (**Scheme 15**).[20]



Scheme 15

It was during an investigation into the Pd(0)-mediated intramolecular cyclization of alkylidenecyclopropanes **21** that a curious result was observed (**Scheme 16**).

The alkylidenecyclopropanes where $n = 1, 2, 4$, reacted as expected. The π-allylpalladium complex **24** was obtained by a ring opening rearrangement of the σ-cyclopropylpalladium intermediate **23**. This was then followed by nucleophilic attack of the anionic malonate moiety affording the new cyclic compounds **26–28**. In marked contrast, the reaction of **21c** ($n = 3$) led to the formation of a bicyclic compound **25**. In this latter case the reaction must proceed via attack of the nucleophile on the Pd–alkene complex, a hitherto unknown phenomenon. This serendipitous discovery has opened up a new area of research into palladium(0) catalysis.

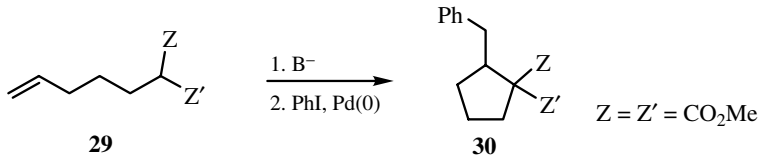


Scheme 16

C.i. Intermolecular Reactions

This new Pd(0)-catalyzed cyclization was observed when the same reaction was performed on linear δ-ethylenic-stabilized carbon nucleophiles of type **29**. This study revealed the important effect of the nature of the counterion.[21] Whereas reaction of sodium malonates required elevated temperatures, the softer potassium malonates were found to react efficiently at room temperature in THF (**Table 1**).

TABLE 1. Catalytic Cyclization of Dimethyl 4-Pentenylmalonate with Phenyl Iodide.



29 **30**

Solvent[a]	Base	Catalyst	Additive[b]	Conditions	Yield (%)[c]
DMSO	NaH	$Pd(dba)_2$ + dppe	—	85 °C, 1 h 30 min	75
NMP	*t*-BuOK	Pd(dppe)	—	20 °C, 3 h	82
THF	*t*-BuOK	Pd (dppe)	—	20 °C, 2 h	80
NMP	*t*-BuOK	$Pd(OAc)_2$	—	25 °C, 24 h	60
NMP	*t*-BuOK	$Pd(OAc)_2$	Aliquat 336 (0.1 equiv)	—	80
NMP	*t*-BuOK	$Pd(OAc)_2$	TDA 1 (0.1 equiv)	25 °C, 1 h 30 min	78
Toluene	*t*-BuOK	$Pd(OAc)_2$	—	25 °C, 100 h	*d*
	t-BuOK	$Pd(OAc)_2$	18-crown-6 (0.1 equiv)	25 °C, 1 h	79

[a] All the reactions were performed on a millimole scale with 1.1 equiv of base, 1.1 equiv of phenyl iodide, and 0.04 equiv of catalyst.
[b] TDA 1 = tris(3.6 dioxaheptyl)amine.
[c] Based on quantities of **30** purified by flash chromatography.
[d] Only 30% of **29** is engaged. The transformed product consists essentially of **30**.

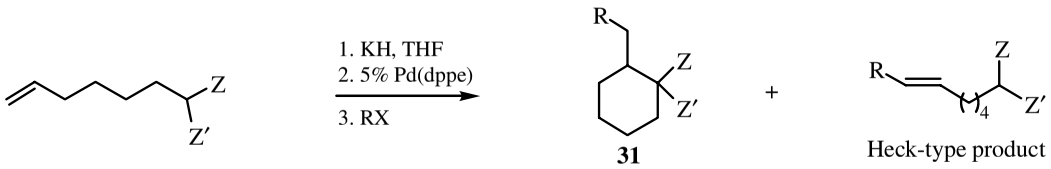
Initial attempts to extend this methodology to the formation of cyclohexane derivatives were unsuccessful.[21] The carbopalladation reaction of dimethyl 5-hexenylmalonate in the presence of phenyl iodide only gave rise to products issued from the classical Heck reaction (**Table 2**). No traces of the desired 6-*exo* cyclization product were detected. Further investigation, however, showed that the course of the reaction is strongly affected by the nature of the nucleophile.[22] When one or both of the malonate esters were replaced by a nitrile, then no Heck reaction was observed under identical conditions. Instead, the cyclization products **31** were obtained.

This new Pd-mediated cyclization reaction was also applied to the acetylenic homologs **32** (**Table 3**). One important feature of these reactions is that the configuration of the exocyclic double bond in the reaction product is always such that the substituent introduced from the aryl halide lies *trans* with respect to the bond bearing the stabilized nucleophile.[23],[24]

This same stereoselectivity was observed when the cyclopentene **34** was cyclized under similar conditions (**Scheme 17**). The reaction product **35** was obtained as a single stereoisomer.[25]

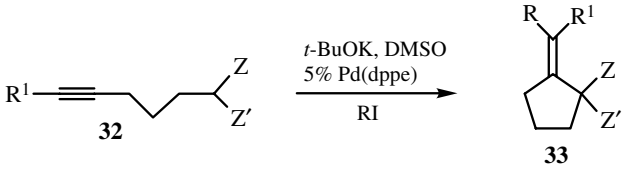
The stereochemical control exhibited during the formation of the stereocenters in these latter two examples supports the idea that these reactions proceed via a Wacker-type mechanism in which an organopalladium halide is the electrophile partner in the reaction, rather than a palladium dicarboxylate or dihalide as in other Wacker-type reactions (Scheme 18).

TABLE 2. Formation of Cyclohexanes *versus* Heck Reaction Depending on the Nature of the Active Methine Compound.

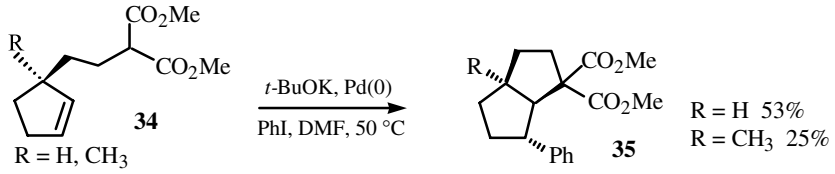


Starting Material	RX	Conditions	Product **31**	Yield (%)
$Z = Z' = CO_2Me$	Iodobenzene	THF, 60 °C, 24 h	Only Heck-type product R = Ph	60
$Z = CO_2Me$ $Z' = CN$	Iodobenzene	THF, 30 °C, 24 h	$Z = CO_2Me$, $Z' = CN$ Two diastereomers 70:30 R = Ph	55
$Z = SO_2Ph$ $Z' = CN$	Iodobenzene	THF, 60 °C, 10 h	$Z = SO_2Ph$, $Z' = CN$ Two diastereomers 80:20 R = *p*-MeO_2CPh	64
$Z = SO_2Ph$ $Z' = CN$	Methyl-4-iodobenzoate	THF, 40 °C, 24 h	$Z = SO_2Ph$, $Z' = CN$ Two diastereomers 70:30	71
$Z = Z' = CN$	Iodobenzene	NMP, 60 °C, 44 h	R = Ph $Z = Z' = CN$	84
$Z = SO_2Ph$ $Z' = CO_2Me$	Iodobenzene	NMP, 60 °C, 19 h	Only Heck-type product	65

TABLE 3. Carbocyclization of Pentynylated Active Methine Compounds with Aryl (or vinyl) Halides.



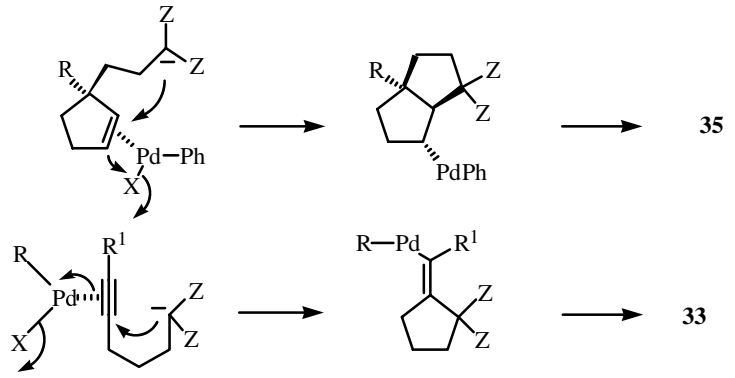
Substrate **32**	Halide	Experimental Conditions		Product	Yield (%)
		T (°C)	Time		
Z = Z′ = CO_2Me R^1 = H	Iodobenzene	30 °C	14 h	Z = Z′ = CO_2Me R^1 = H, R = Ph	80
Z = Z′ = CO_2Me R^1 = H	2-Iodoanisole	30 °C	14 h	Z = Z′ = CO_2Me R^1 = H, R = 2-MeO-Ph	70
Z = Z′ = CO_2Me R^1 = H	2-Bromopropene	30 °C	14 h	Z = Z′ = CO_2Me R^1 = H, R = 2-Me-vinyl	75
Z = CO_2Me, Z′ = COMe R^1 = H	Iodobenzene	30 °C	14 h	Z = CO_2Me, Z′ = COMe R^1 = H, R = Ph	88
Z = CO_2Me, Z′ = SO_2Ph R^1 = H	Iodobenzene	30 °C	14 h	Z = CO_2Me, Z′ = SO_2Ph R^1 = H, R = Ph	57
Z = Z′ = CO_2Me R^1 = TMS	Iodobenzene	30 °C	14 h	Z = Z′ = CO_2Me R^1 = H, R = Ph	52
Z = Z′ = CO_2Me R^1 = Me	Iodobenzene	70 °C	3 h	Z = Z′ = CO_2Me R^1 = Me, R = Ph	71
Z = Z′ = CO_2Me R^1 = CH_2OTHP	Iodobenzene	70 °C	18 h	Z = Z′ = CO_2Me R^1 = CH_2OTHP R = Ph	73
Z = Z′ = CO_2Me R^1 = $(CH_2)_2OTHP$	Iodobenzene	70 °C	22 h	Z = Z′= CO_2Me R^1= $(CH_2)_2OTHP$ R = Ph	70



Scheme 17

C.ii. Intramolecular Reactions

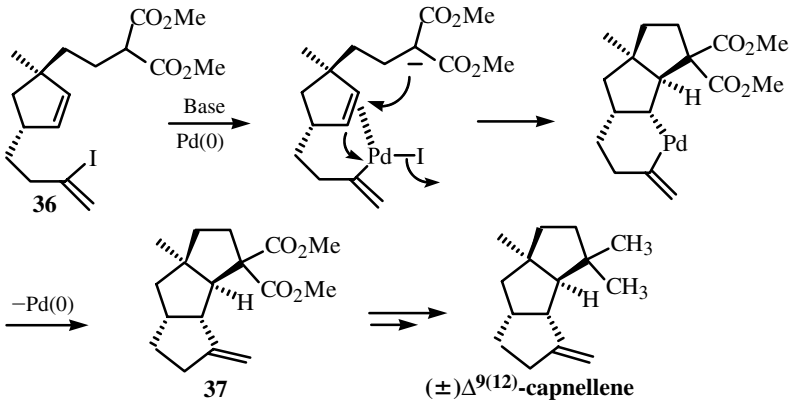
From **Scheme 17**, it is clear that functionalized diquinanes may be synthesized stereoselectively and in good yield using this reaction. The reaction of intramolecular vinyl halides may then allow the synthesis of triquinanes, a structural motif present in many



Scheme 18

biologically active molecules. When applied to compound **36** the optimal conditions for this cyclization were found to be $Pd(OAc)_2$ (0.05 equiv), dppe (0.05 equiv), and potassium hydride (1.1 equiv) in THF (**Scheme 19**).

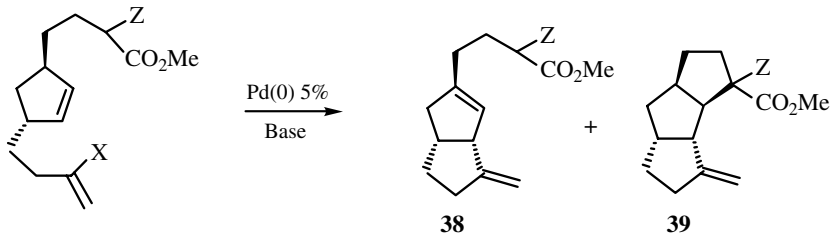
The reaction, at room temperature (16 h), afforded the triquinane **37**, a key intermediate in the synthesis of ($\pm$)$\Delta^{9(12)}$-capnellene, in 70% yield along with traces of the isomer having an internal double bond.[26] Indeed, **37** could be converted to capnellene as a single isomer in three steps using conventional synthetic methods (50% overall yield).



Scheme 19

In the absence of the angular methyl group, only traces of the triquinane were obtained. Instead, a Heck reaction was observed leading to the formation of diquinane **38**. Further investigations revealed two important factors in governing which of the two products **38** and **39** should be obtained from the reaction: the nature of the nucleophile and that of the vinyl halide (**Table 4**). First, by changing the nature of the vinyl halide from iodide to bromide, as much as 40% of the triquinane could be obtained. Second, by using a less sterically hindered nucleophile, Z = CN and Z′ = CO_2Me, in the presence of the vinyl iodide, the yield of the triquinane **39** could be further improved. Finally, the triquinane could be selectively obtained by switching to methyl cyanoacetate as nucleophile and

TABLE 4. Synthesis of Triquinanes through Intramolecular Carbopalladation and Cross-Coupling of Cyclopentenyl Derivatives *versus* Heck Reaction.



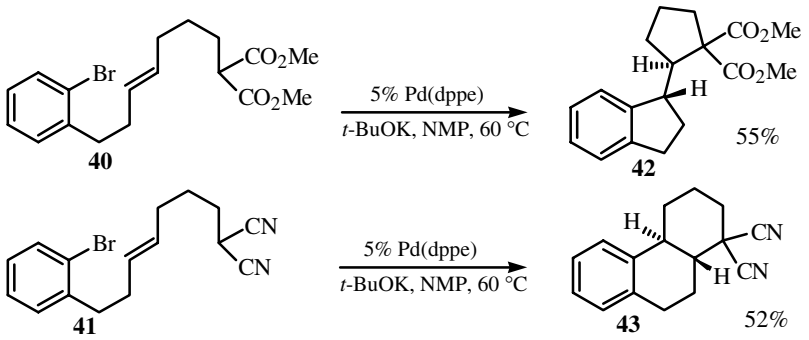
38 **39**

Substrate[a]	Heck-Type Product	Wacker-Type Product	Yield%
X = I, Z = CO_2Me	Major	Traces	
X = Br, Z = CO_2Me	60%	40%	75
X = I, Z = CN	45%	55%	75
X = Br, Z = CN	**0%**	**100%** (**two diastereomers**)	**85**

[a] Reaction conditions: 1.1 equiv KH, 0.5 equiv 18-C-6, 5% $Pd(OAc)_2$, THF, 25 °C.

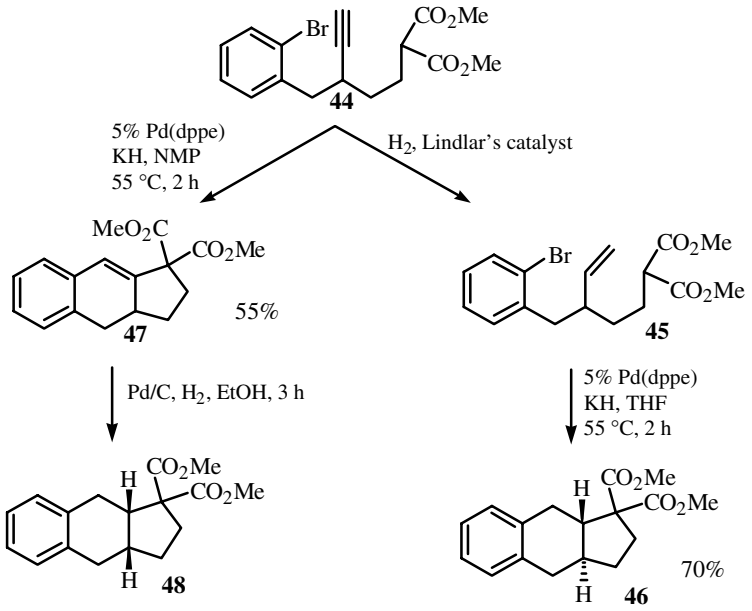
bromine as halogen. Under these conditions, no traces of compounds resulting from a Heck reaction were detected.[27]

This Pd-catalyzed cascade bis-cyclization reaction can also be applied to *trans* linear substrates **40** and **41**. It was possible to effect either 5-*exo* or 6-*endo* cyclization *selectively* by an appropriate choice of the electron-withdrawing substituents of the nucleophile, as illustrated in **Scheme 20**. *Exo*-cyclizations were observed when sterically encumbered nucleophiles were employed. Cyclopentanes were obtained as a result of steric interactions between the nucleophile and one of the allylic hydrogens of the linear substrate. *Endo*-cyclizations leading to *trans*-octahydrophenanthrene were the only reactions observed when less sterically demanding nucleophiles were employed. Notably, these cyclizations proceed in a completely stereoselective *trans* manner. Attack of the carbon nucleophile onto a double bond electrophilically activated by the palladium species results in a *trans* configuration of the fused ring junction.[28] This stereochemistry is defined by that of the double bond in the initial substrate; the relative configuration of compound **42** or **43** is hereby controlled.



Scheme 20

This "one-step" synthesis of tricyclic systems has also been extended to provide a synthetic strategy for both *cis*- and *trans*-hexahydro-1*H*-benz[*f*]indene starting from a common acetylenic precursor (**44**) (**Scheme 21**). Hydrogenation of **44** over Lindlar's catalyst gave **45**. This compound would then be involved in a Pd-catalyzed cascade process, resulting in a bis-cyclization reaction. This reaction, performed in THF, at 55 °C, with potassium *t*-butoxide and 5% Pd(dppe) led to the exclusive formation of *trans*-hexahydro-1*H*-benz[*f*]indene. The stereochemical control of this reaction may be explained if it were to pass through a transition state in which the benzylic substituent lies in a pseudoequatorial orientation.

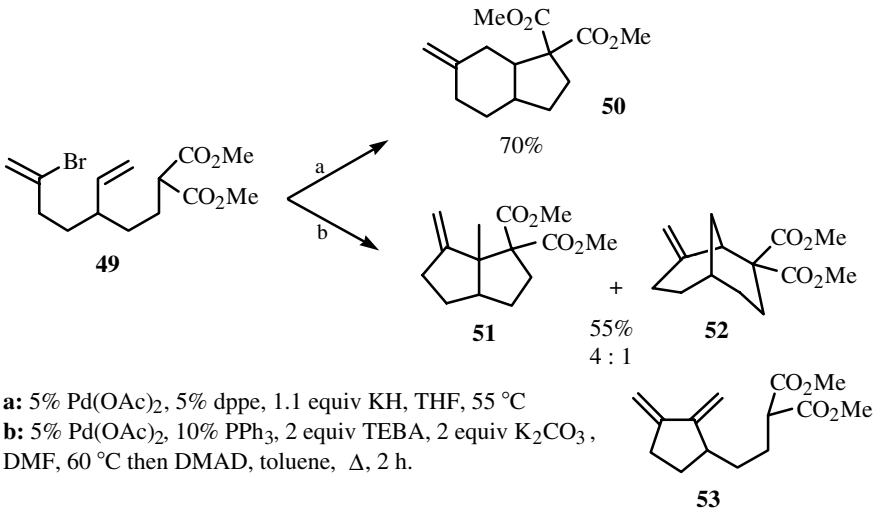


Scheme 21

By reversing the reaction sequence, it was possible to invert the configuration of the hexahydro-1*H*-benz[*f*]indene product. Carbopalladation of the acetylenic substrate under the same conditions used above but in 1-methyl-2-pyrrolidinone as the solvent gave rise to **46**. Hydrogenation of **47** over Lindlar's catalyst afforded the *cis* isomer **48** of hexahydro-1*H*-benz[*f*]indene in quantitative yield.[29]

Consistent with the observations detailed above, annelation of the vinyl bromide **49** under identical conditions (1.1 equiv of KH, 5 mol % Pd(dppe), THF, 55 °C) also proceeded with diastereoselectivity. Bicycle **50** was obtained as a single isomer with a *trans*-hydrindane system in 70% yield (**Scheme 22**).[30]

It has also been possible to change the course of the reaction in order to favor a Heck process by simple alterations to the reaction conditions. The most effective change to be made was the nature of the base. By using 5% $Pd(OAc)_2$ with PPh_3 as ligand (10%) in the presence of 2 equiv of a quaternary ammonium salt (benzyltriethylammonium chloride) and 2 equiv of carbonate bases (K_2CO_3 or $KHCO_3$) in DMF at 60 °C, the reaction may be made to favor a Heck reaction.[31]–[33] Indeed, the same starting material gave rise to compounds



a: 5% $Pd(OAc)_2$, 5% dppe, 1.1 equiv KH, THF, 55 °C
b: 5% $Pd(OAc)_2$, 10% PPh_3, 2 equiv TEBA, 2 equiv K_2CO_3, DMF, 60 °C then DMAD, toluene, Δ, 2 h.

Scheme 22

51, **52**, and **53**. An intermolecular Diels–Alder reaction effected on the bis-*exo*-cyclic 1,3 diene **53** allowed it to be separated from the two bicyclic products.[30]

C.iii. Synthesis of Substituted Tetrahydrofurans

An analogous carbopalladation–cyclizaton process has been applied to the synthesis of various substituted tetrahydrofurans using three components. This "one-pot" procedure involves an intermolecular addition of allylic alkoxides to Michael acceptors. The resulting enolate undergoes cyclization via nucleophilic attack on the alkene–Pd complex. So as to avoid undesired side reactions such as the premature trapping of the alkoxide by the organopalladium species, the alkoxide should be added via a syringe pump.[34]

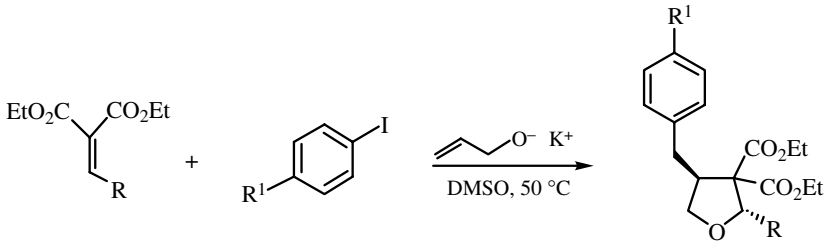
The scope and limitations of this Pd-mediated three-component "Michael addition–carbopalladation cyclization process" were investigated. The reaction of various iodobenzenes, bearing electron-withdrawing or electron-donating substituents, with allyl alcohol and several Michael acceptors were studied and the main results are shown in **Table 5**.

C.iv. Wacker Reaction Initiated by a Palladium(II) Hydride Species

In all reactions discussed in the two preceding paragraphs, an unsaturated organic palladium species was acting as the electrophilic mediator of the cyclization process. A Pd-mediated cyclization initiated by a palladium(II) hydride species was also developed on ω-unsaturated β-dicarbonyl compounds. In this way, δ-acetylenic potassium enolates, generated from the reaction of compounds of type **32** with potassium *t*-butoxide, smoothly underwent cyclization when treated with a palladium(0) complex in THF. This led to the formation of methylenecyclopentanes **54** or unsaturated esters **55**, depending on the reaction conditions, and particularly on the amount (stoichiometric or catalytic) of potassium *t*-butoxide (**Table 6**).[35]

Although the precise mechanism has not yet been clarified, it was speculated that it involves an attack of the carbon nucleophile on the triple bond through a "Wacker-type"

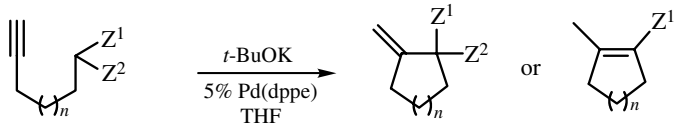
TABLE 5. Sequential Hetero-Michael Addition/Carbopalladation of Allylic Alcohol: A Three-Component Synthesis of Tetrahydrofurans.



Michael Acceptor	Iodoarene	Yield (%)
R = Phenyl	R^1 = H	60
R = Phenyl	R^1 = F	70
R = Phenyl	R^1 = OMe	66
R = *p*-Fluorobenzene	R^1 = H	60
R = *p*-Methoxybenzene	R^1 = H	66
R = Isopropyl	R^1 = H	60

process in which the unsaturation is activated by a σ-alkynylpalladium hydride. Such a species would be generated *in situ* from insertion of the metal into the C—H bond of the terminal acetylene.[36] The initially formed compound **54**, isolated when using a catalytic amount of base, is supposed to result from a reductive elimination of the vinylpalladium species **56**. In the presence of a stoichiometric amount of base, it was transformed *in situ* to monofunctionalized substrates **55** via a retro-Claisen reaction.[37]

TABLE 6. Catalytic Cyclization of Alkynylated Active Methine Compounds.



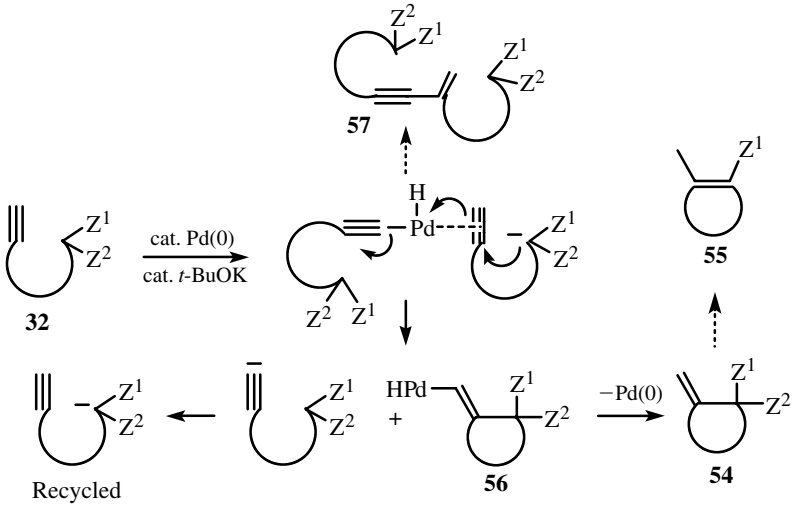
32 **54** **55**

Entry	Starting Material **32**			Reaction Conditions[a]	Product	Yield (%)
	n	Z^1	Z^2			
1	1	CO_2Me	CO_2Me	(I), 67 °C, 18 h	**54**	76
2	1	CO_2Me	CO_2Me	(II), 67 °C, 3 h	**55**	75
3	2	CO_2Me	CO_2Me	(III), 67 °C, 48 h	**54**	40
4	1	CO_2Me	COMe	(I), 20 °C, 16 h	**54**	80
5	1	CO_2Me	COMe	(II), 20 °C, 6 h	**55**	91
6	2	CO_2Me	COMe	(III), 67 °C, 30 h	**54**	42
7	1	COMe	COMe	(I), 20 °C, 14 h	**54**	87
8	1	COMe	COMe	(II), 20 °C, 3 h	**55**	77
9	1	CN	CO_2Me	(I), 50 °C, 14 h	**54**	84
10	1	CN	CO_2Me	(II), 50 °C, 2 h	**55**	86

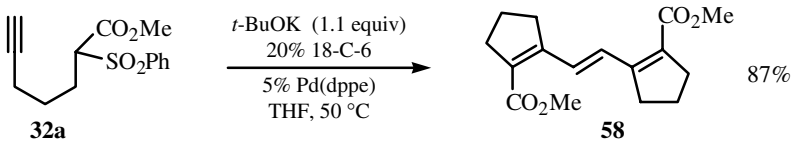
[a] Reaction conditions: (I) = 20 mol % *t*-BuOK, 20 mol % 18-C-6. (II) = 1.1 equiv *t*-BuOK. (III) = 1.1 equiv *t*-BuOK, 20 mol % 18-C-6.

It is worth noting that self-coupling of the terminal alkynes occurred when no base at all was used, leading to the formation of enynes **57**. Such compounds were also isolated as side products of the cyclohexane derivatives (**Scheme 23**).

During the development of this reaction, the unexpected behavior of α-sulfonyl ε-acetylenic ester **32a** was observed.[38] When **32a** was treated under the same reaction conditions (1 equiv of *t*-BuOK, 0.05 equiv of Pd(dppe), refluxing THF, 1 h), it led exclusively to triene diester **58** in 87% yield (**Scheme 24**).



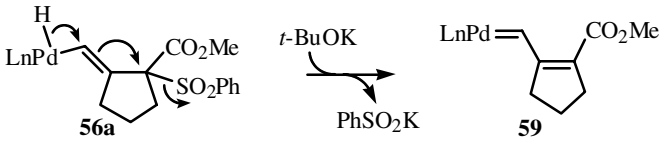
Scheme 23



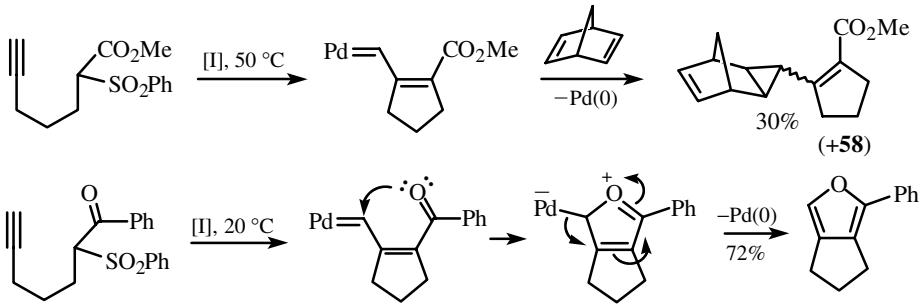
Scheme 24

The mechanism was supposed to involve a vinylalkylidene palladium intermediate **59**, which could result from the attack of potassium *t*-butoxide on the vinylic palladium hydride intermediate **56a** (**Scheme 25**).

The existence of this intermediate carbene species was demonstrated through its involvement in a set of reactions typical of carbenes, including cyclopropanation and intramolecular capture by a keto group (**Scheme 26**).[39]



Scheme 25



[I] = *t*-BuOK (1.1 equiv), 20% 18-C-6, 5% Pd(dppe), THF.

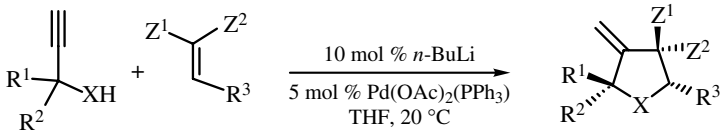
Scheme 26

C.v. Synthesis of Highly Functionalized Tetrahydrofurans and Pyrrolidines

The strategy used for the formation of methylenecyclopentanes was applied to the one-pot synthesis of various 3-methylenetetrahydrofurans. The methodology was based on an oxygen nucleophile initiated Michael addition of propargyl alcohols to alkylidene or arylidenemalonates followed *in situ* by a Pd-mediated cyclization.[40]

Best results were obtained when *n*-BuLi as base (10%) and $Pd(OAc)_2(PPh_3)$ as catalyst were used. This reaction has provided an efficient route to highly functionalized 3-methylene tetrahydrofurans since electron-rich and electron-poor arylidene acceptors as well as enolizable alkylidene malonates reacted. This methodology was later applied to the synthesis of methylene pyrrolidines (**Table 7**).[41]

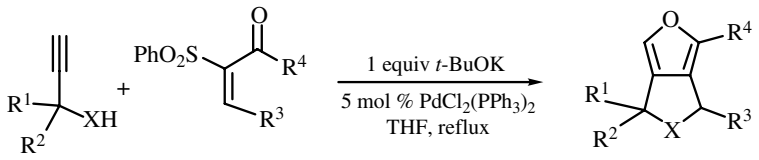
TABLE 7. Two-Component Synthesis of 3-(4)-Methylene Tetrahydrofurans and Pyrrolidines.



	Propargylic Nucleophile			Michael Acceptor			Yield
Entry	X	R^1	R^2	Z^1	Z^2	R^3	%
1	O	H	H	CO_2Et	CO_2Et	Ph	94
2	O	H	H	CO_2Et	CN	Ph	47
3	O	H	H	CO_2Et	COMe	Ph	86
4	O	H	H	CN	CN	Ph	51
5	O	H	H	CO_2Et	CO_2Et	Me	66
6	O	Ph	H	CO_2Et	CO_2Et	Ph	92[a]
7	O	Me	Me	CO_2Et	CO_2Et	Ph	82[b]
8	NMe	H	H	CO_2Et	CO_2Et	Ph	79
9	NMe	H	H	CO_2Et	CN	Ph	75[c]
10	NMe	H	H	CO_2Et	CO_2Et	C_6H_{11}	48

[a] Mixture of diastereomers (*cis*/*trans* = 34:66).
[b] 20 mol % of base was used.
[c] Mixture of diastereomers (*cis*/*trans* = 15:85).

TABLE 8. Formation of Furo[3,4,c] Heterocycles from α-Sulfonyl-α,β-Unsaturated Ketones.



X	R^1	R^2	R^3	R^4	Yield (%)
O	H	H	Ph	Ph	57
	H	H	Ph	3,4-(OCH_2O)-Ph	52
	H	H	Ph	*p*-F-Ph	58
	H	H	Ph	C_6H_{11}	42
	H	H	*i*-Pr	Ph	60
	H	H	*p*-OMe-Ph	Ph	45
	H	H	*p*-NO_2-Ph	Ph	47
	Me	Me	Ph	Ph	50
NMe	H	H	Ph	Ph	54
NBn	H	H	Ph	Ph	52

By applying the same tandem Michael addition carbocyclization to arylidene β-ketosulfones in the presence of 1 equiv of potassium *t*-butoxide, once again a metal-stabilized carbene was formed. Then internal trapping of this carbene by the carbonyl oxygen led to a variety of furo[3,4-*c*]furans and furo[3,4-*c*]pyrroles (**Table 8**). [42]

D. SUMMARY

Unactivated olefins are inert toward attack of nucleophiles. When complexed to palladium(II) salts, stabilized carbanions ($pK_a = 10–17$) react intermolecularly with these olefinpalladium(II) complexes to generate σ-alkylpalladium complexes. Alkylation occurs predominantly at the 2-position after a reductive or β-elimination procedure or an insertion reaction with carbon monoxide. Nonstabilized carbanions attack the palladium directly, forming alkylpalladium complexes that lead to alkene alkylation products at the 1-position. All these reactions required stoichiometric amounts of palladium salts.

In contrast, unactivated olefins and alkynes complexed to organopalladium species generated *in situ* by oxidative addition of an unsaturated halide to a palladium(0) complex react intramolecularly with stabilized nucleophiles. These reactions that require catalytic quantities of the metal result in overall difunctionalization of the olefinic or acetylenic substrates.

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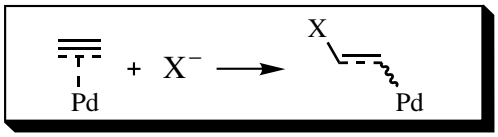

V.3.5 Palladium-Catalyzed Reaction via Halopalladation of π-Compounds

XIYAN LU

A. INTRODUCTION

Halopalladation is a reaction in which a halide ion, as a nucleophile, adds to the palladium complexed unsaturated compounds. Chloropalladation of unsaturated organic substrates is an important reaction in organopalladium chemistry. Additions of Pd—Cl to allenes,[1]–[4] olefins,[5]–[8] acetylenes,[9]–[12] and conjugated dienes[13]–[15] have been reported. While a lot of works concerning the halopalladation reactions of unsaturated substrates were studied, only a few papers related to the catalytic reactions initiated by halopalladation of organic substrates were reported until recently.

B. ALKYNES

Most of the useful reactions initiated by halopalladation are concentrated on the alkynes. Halopalladation of alkynes will give the vinylpalladium complexes, which are versatile reactive intermediates in a number of catalytic reactions.[16]–[21] Another way of generating a vinylpalladium complex is by the oxidative addition of a vinyl halide or triflate to palladium(0).[16],[17] While the latter approach has had many applications in catalytic reactions,[16],[17] the application of the former one is still limited.

B.i. Stereochemistry of Halopalladation of Alkynes

In the literature, many works reported that alkynes seem to undergo both *cis*- and *trans*-chloropalladation.[22]–[26] The stereochemistry of halopalladation of alkynes was recently studied in detail by Bäckvall et al.[27] The chloropalladation of a few substituted alkynes has been studied under different conditions.

B.i.a. ***Trapping the Palladium Complex with Allyl Chloride.*** Reaction of alkynes with $PdCl_2$–LiCl at a low chloride concentration afforded mainly (*Z*)-isomer, a result consistent with a *cis*-chloropalladation pathway (**Scheme 1a**). Increasing chloride concentration increased the yield of the (*E*)-isomer, that is, increased the *trans*-chloropalladation[27] (**Scheme 1b**).

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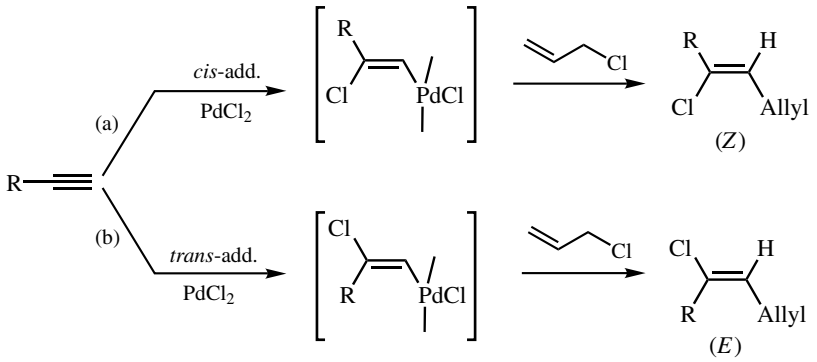
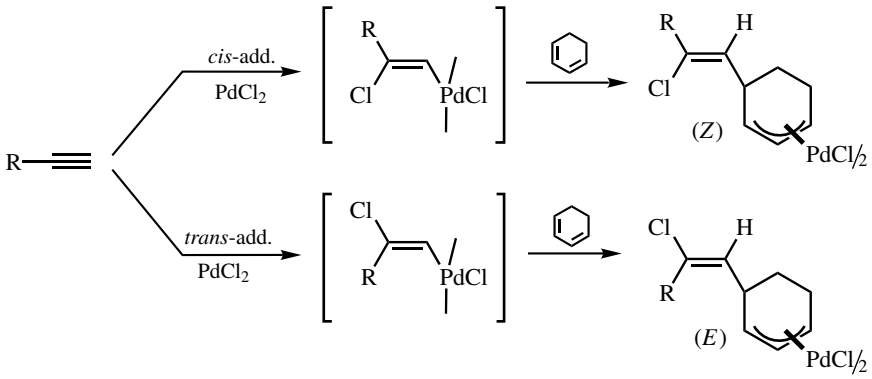


Scheme 1

B.i.b. ***Trapping the Palladium Complex with 1,3-Cyclohexadiene.*** This method (**Scheme 2**) was employed because of the uncertainty that the first method may involve an alternative path via a π-allylpalladium intermediate from the allyl chloride.



Scheme 2

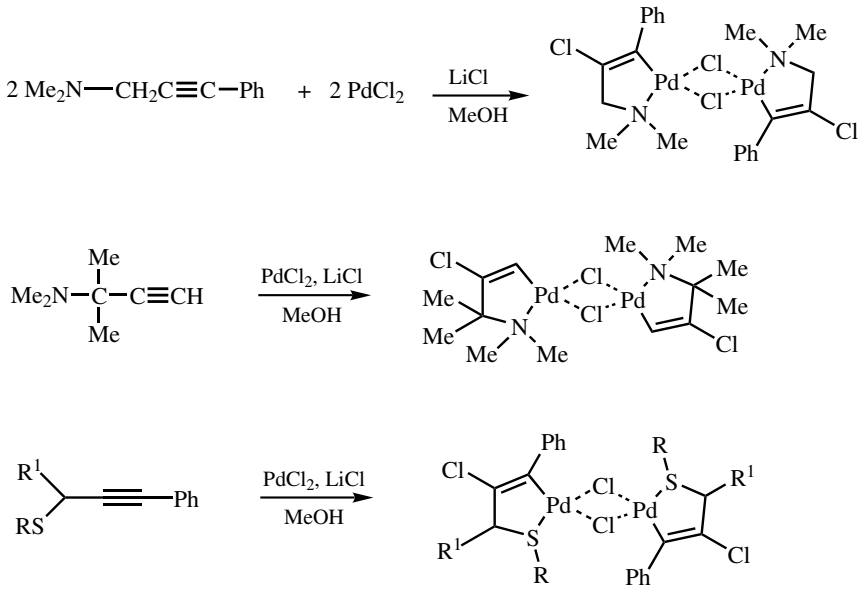
The results are in accordance with those obtained from the trapping with allyl chloride.[27] Halopalladation of alkynes having a heteroatom at suitable position will change the stereochemistry of halopalladation due to the coordination of the heteroatom to the palladium[25],[28],[29] (**Scheme 3**).

B.ii. Halopalladation-Initiated Carbonylative Cyclization of Yndiols to β-Chloro-γ-butenolides

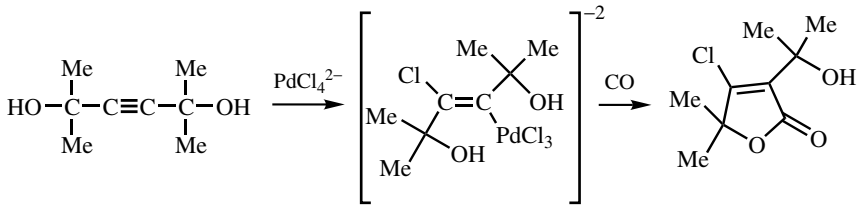
Larock and Riefling reported the synthesis of β-chloro-γ-butenolides from 2,5-dimethyl hex-3-yn-2,5-diol, palladium chloride, and lithium chloride [30] (**Scheme 4**). Unfortunately, the reaction is stoichiometric to palladium chloride.[30]

B.iii. Halopalladation-Initiated Catalytic Oligomerization of Alkynes

As early as 1894, F. C. Phillips observed the formation of metal-containing dark-red precipitates when acetylene was bubbled into aqueous solution of palladium chloride.[31]



Scheme 3

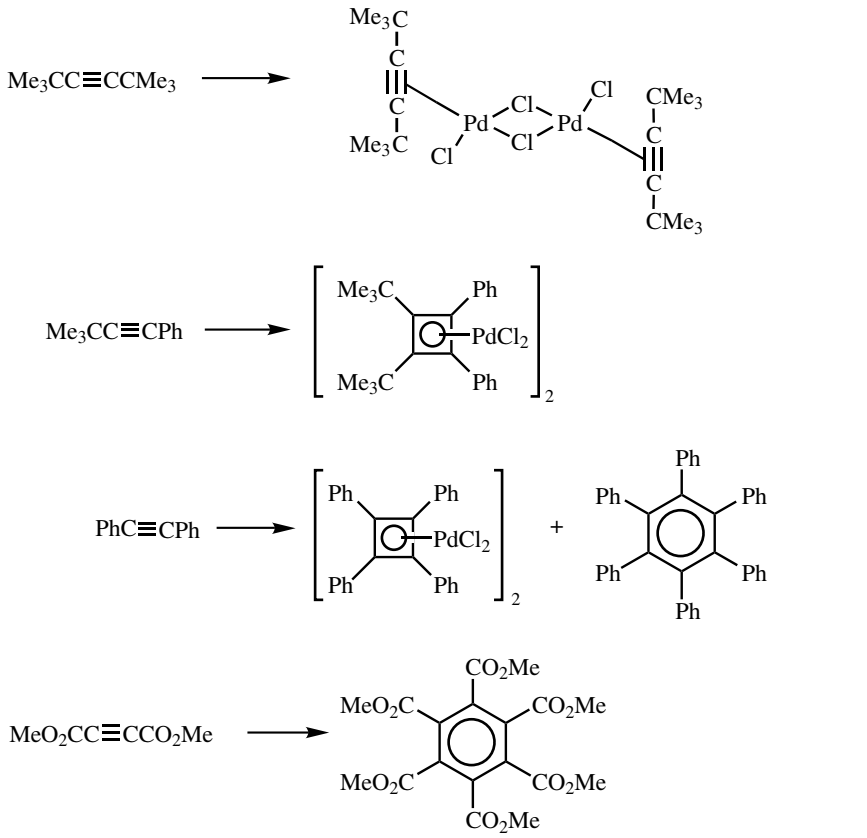


Scheme 4

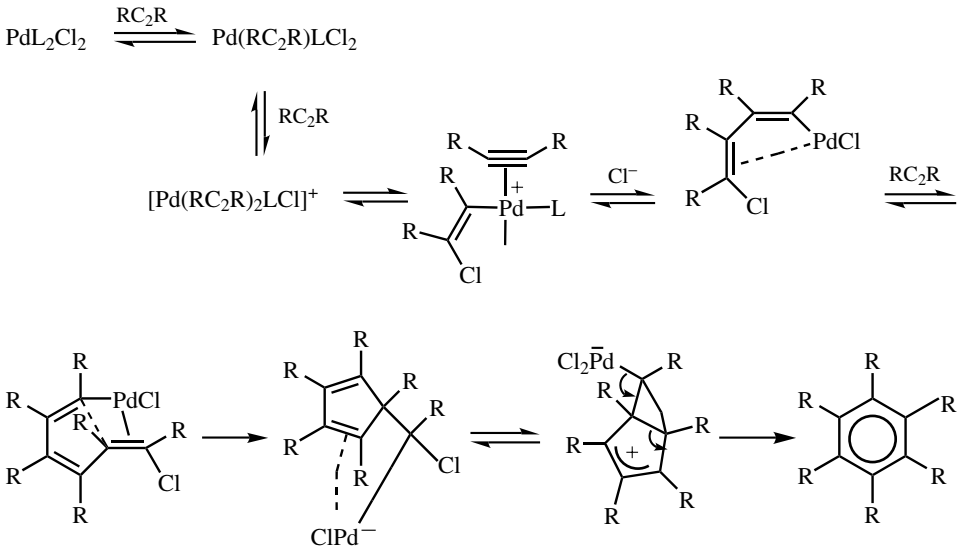
Virtually all alkynes react readily with palladium chloride under ambient conditions to give red-brown complexes: single substances are usually obtained from disubstituted alkynes, but the reaction of most monosubstituted alkynes and acetylene itself leads to the formation of complex mixtures.[26],[32],[33]

The extent of the reaction is very much governed by the size of the alkynic substituents (**Scheme 5**); for example, if both substituents are bulky *tert*-butyl groups, no oligomerization occurs and only the 1:1 alkyne complex is formed.[12] When one *tert*-butyl is replaced by the smaller phenyl substituent, dimerization takes place and the cyclobutadiene complex is the only product.[34] However, diphenyl acetylene gives a mixture of the cyclobutadiene complex and the benzenoid trimer.[35] The somewhat smaller carboxymethyl groups ensure that dimethyl acetylene dicarboxylate gives only the trimer.[36]

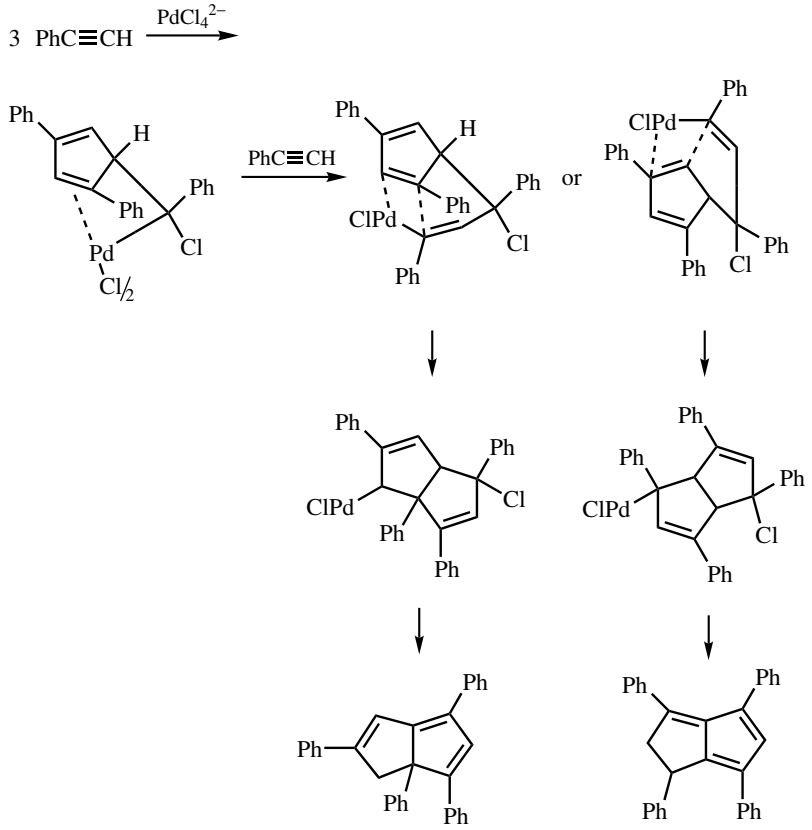
The mechanism of alkyne oligomerization induced by $PdCl_2$ is therefore seen to involve a series of stepwise *cis*-insertion of coordinated alkynes as shown in **Scheme 6**.[32],[33],[37],[38] Similarly, phenylacetylene can react with $PdCl_4^{2-}$ to give the tetramer product as shown in **Scheme 7**.[33]



Scheme 5



Scheme 6



Scheme 7

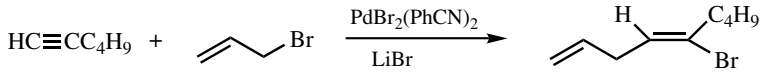
B.iv. Halopalladation-Initiated Codimerization of Alkynes and Allyl Halides

Homooligomerization of alkynes using palladium chloride as catalyst has been studied extensively.[39] However, few examples are known of cooligomerization of alkynes and monoolefins probably because of the difficulty due to the large difference in coordination ability between alkynes and alkenes to the metal center; alkynes are more reactive to metals than alkenes are, which results in exclusive polymerization of the alkynes. Therefore, in order to accomplish the cooligomerization of alkynes and alkenes, it is very important to select suitable alkynic or alkenic compounds with similar orders of coordination ability to a metal, or to devise reactive conditions in which extensive alkyne polymerization is prevented.

B.iv.a. ***Synthesis of 1,4-Dienes from the Codimerization of Alkynes and Allyl Halides.*** Kaneda et al.[40]–[43] found that the selective oligomerization of various alkynes and allyl halides proceeds smoothly with divalent palladium catalysts under mild conditions providing a facile and useful 1,4-diene synthesis.

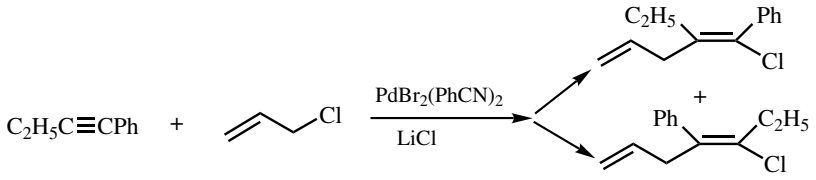
Various palladium compounds, for example, PdX_2, $PdX_2(PhCN)_2$, $Pd(OAc)_2$–LiX, and (π-allylPdX)$_2$ (X = halogen), had catalytic activity for the codimerization; $PdX_2(PhCN)_2$ showed the highest activity.

Terminal Alkynes. The reaction of 1-hexyne and allyl chloride gave 5-chloro-1,4-nonadiene in almost quantitative yield in the presence of the $PdCl_2(PhCN)_2$ catalyst. The bromide analog reacted similarly. The configuration about the double bond bearing the halogen was found to be (*Z*)[43] (**Scheme 8**).



Scheme 8

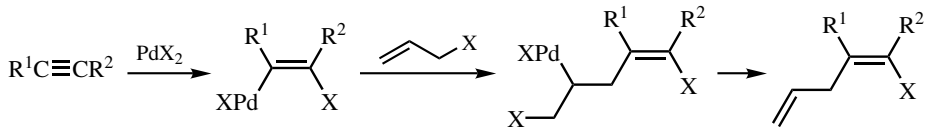
Disubstituted Alkynes. The reactions of unsymmetrical alkynes give mixtures of double bond regioisomers[43] (**Scheme 9**).



Scheme 9

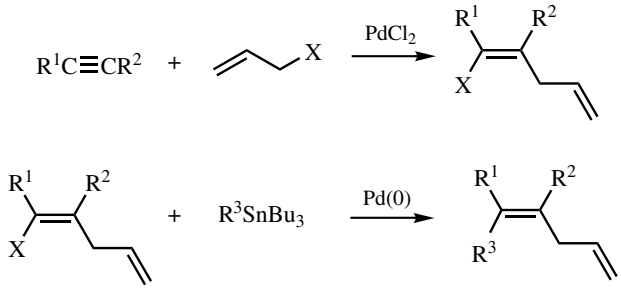
Acetylene. The reaction of acetylene and allyl chloride gave a cotrimer (two molecules of acetylene and one molecule of allyl chloride) as well as the codimer.[43]

Mechanism. The insertion of acetylene into a palladium–halogen bond occurs as the first step and subsequently allyl halide inserts into a palladium–vinyl bond. The β-elimination of PdX_2 gives a codimer and regenerates the active palladium catalyst. In the case of unsubstituted acetylene, the cotrimer is formed by the successive insertion of acetylene and allyl halide into the palladium–vinyl bond [43] (**Scheme 10**).

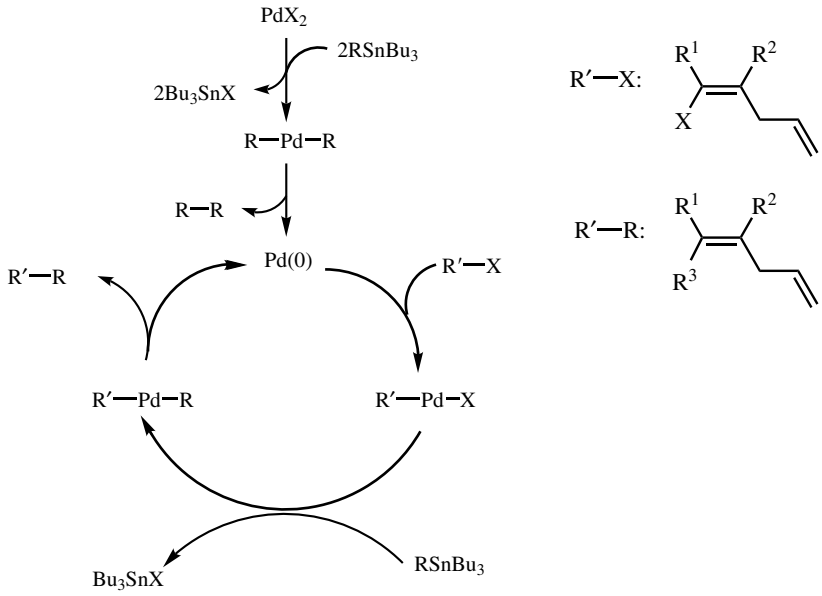


Scheme 10

B.iv.b. ***Synthesis of 1-Substituted 1,4-Pentadienes.*** The combination of the above reaction with an organotin reagent constitutes a new reaction to synthesize 1-substituted 1,4-pentadienes in one pot [44] (**Scheme 11**). The first reaction generates $PdCl_2$ as the catalytic species, which can react with the tin compound R^3SnBu^3 to yield Bu^3SnCl and Pd(0) species that can be the active catalytic species in the second reaction. After the first reaction was carried out, excess allyl halide was removed under reduced pressure; then the second reaction may be carried out. Thus, two Pd-catalyzed reactions involving different catalytic species of Pd(II) and Pd(0) could be composed into the consecutive one-pot process [44] (**Scheme 12**).



Scheme 11

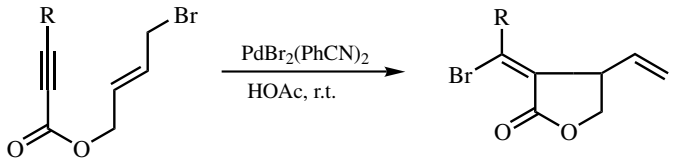


Scheme 12

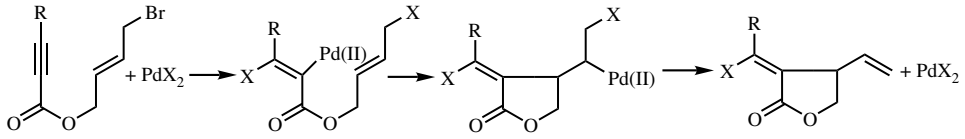
B.v. Halopalladation-Initiated Cyclization of Allylic Alkynoates

Allylic alkynoates are a group of special enynes with an electron-deficient triple bond and an ester linkage between the double bond and triple bond. Based on the reaction described in **Sect. B.iv.a**, an intramolecular version could be developed, for example, an α-alkylidene-γ-butyrolactone structure could easily be assembled through halopalladation, carbon–carbon double bond insertion, and dehalopalladation[22],[45]–[48] (**Scheme 13**). The mechanism may be summarized as shown in **Scheme 14**.[22]

The key point in divalent Pd-catalyzed cyclization of allylic alkynoates is the method of quenching of the carbon–palladium bond formed after cyclization. In order to develop a divalent Pd-catalyzed reaction, a divalent palladium species must be regenerated in the quenching of the carbon–palladium bond. Lu and co-workers developed different quenching methods for the carbon–palladium bonds, for example, β-heteroatom elimination, copper halide mediated oxidative cleavage, and carbonylation and protonolysis of



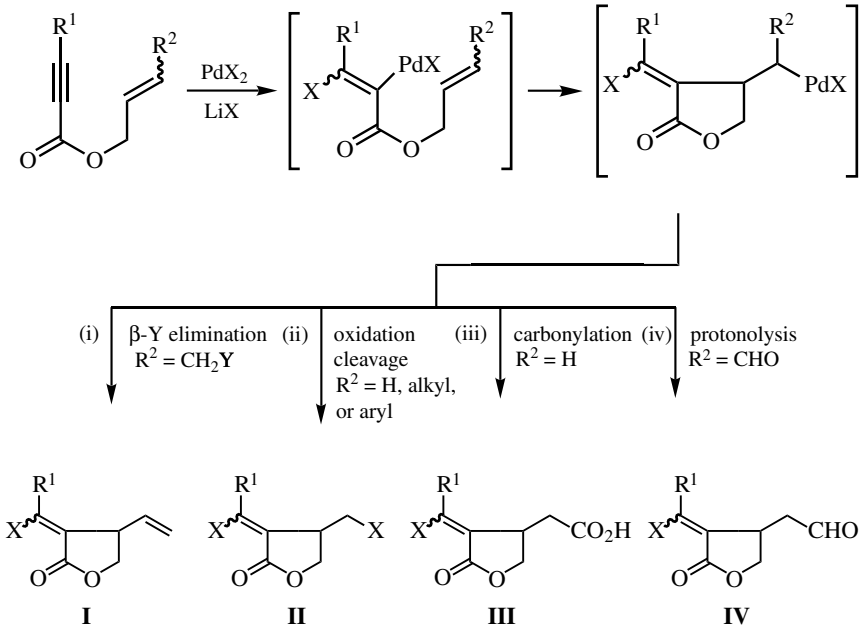
Scheme 13



Scheme 14

carbon–palladium bonds to yield β-vinyl,[22],[45],[46] β-halomethyl,[48]–[51] β-oxycarbonylmethyl,[52] and β-formylmethyl[53] substituted γ-butyrolactones, respectively, as shown in **Scheme 15**.

The results of the four types of Pd(II)-catalyzed reactions are summarized in **Table 1**. In addition, the stereochemistry of the β-heteroatom elimination and the oxidative cleavage reaction were also studied. The results show that the β-heteroatom elimination proceeds in an *anti* manner, most probably through an E_2-like mechanism with a reactivity order Cl > OMe > OAc > OH ~H.[54] While the oxidation cleavage in this reaction occurs with retention of configuration.[55]



Scheme 15

TABLE 1. Pd(II)-Catalyzed Synthesis of γ-Lactones from Allylic Alkynoates

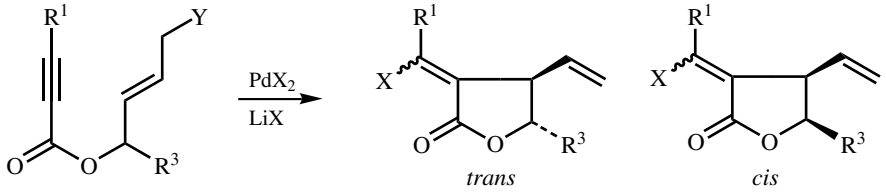
Method	Starting Material	Method of Quenching the C—Pd Bond	Reaction Conditions	Product	Reference
(i)	$R^2 = CH_2Y$ (Y = halogen, OAc, OH, OR)	β-Heteroatom elimination	$Pd(OAc)_2$, LiX, HOAc, r.t.	**I**	[22],[46]
(ii)	R^2 = H, alkyl, or aryl	Oxidative Cleavage	PdX_2, CuX_2, LiX, CH_3CN, r.t.	**II**	[49],[50]
(iii)	R^2 = H	Carbonylation	$Pd_2(dba)_3 \cdot CHCl_3$, CO, $CuCl_2$, LiCl, HOAc, r.t.	**III**	[52]
(iv)	R^2 = CHO	Protonolysis	$Pd(OAc)_2$, LiX, HOAc, r.t.	**IV**	[53]

B.v.a. ***Stereoselectivity of the Exocyclic Double Bond.*** The polarity of the triple bond in the substrate determines the regiospecificity of the reaction to give five-membered ring product. The *E*- or *Z*-selectivity of the exocyclic double bond in the cyclization product was mainly controlled by the stereochemical course of halopalladation.[22],[46],[49],[50] The stereochemistry was mainly affected by the polarity of the solvent and the concentration of the halide ion. In nonpolar solvents only low to moderate yield with poor selectivity was observed. While low halide concentration was not applicable in these reactions, the increase of halide amount from low to high provided the facile control of the *E,Z*-selectivity mainly to give the *Z*-isomers.

B.v.b. ***Diastereoselectivity.*** When a substituent is introduced into the 1′-position of the 2′-alkenyl group of the starting 2-alkynoates, significant and interesting results were found in the stereochemistry of the cyclization of different alkynoates.[56],[57]

Table 2 is a brief summary of the stereochemical control in this cyclization reaction, in which *the substitution pattern of the triple bond determines the β,γ-relative stereochemistry of the lactone product*. Cyclization of *unsubstituted propynoates* mainly afforded *trans*-β,γ-disubstituted lactones, while cyclization of *3-substituted 2-alkynoates* yielded

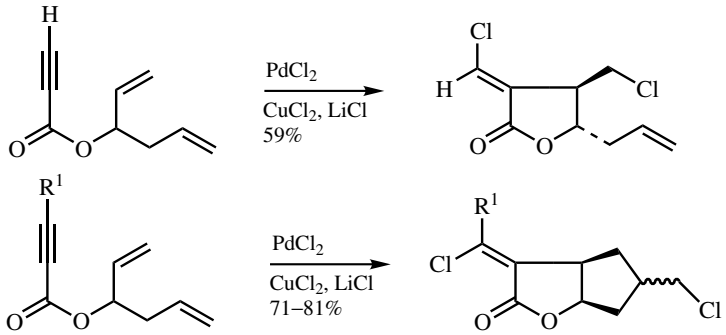
TABLE 2. Influence of the Substituent R^1 on the Diastereoselectivity of the Cyclization Reaction I (Scheme 15)[56]



R^1	β,γ-Stereochemistry
H	*trans*
alkyl	*cis*

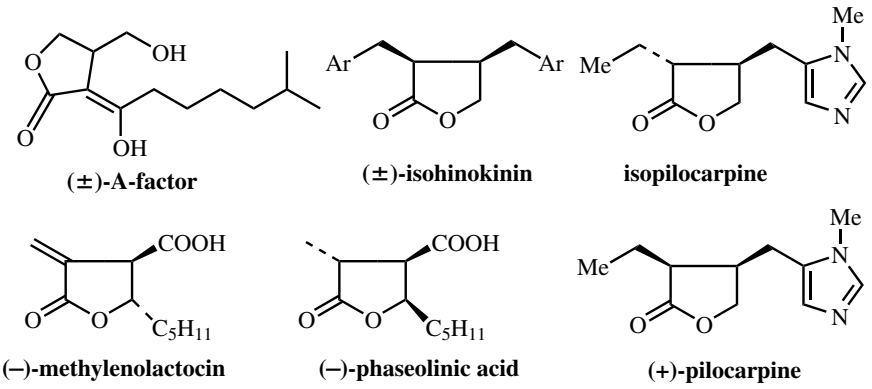
cis-β,γ-disubstituted lactones. The bulkiness of the R^3 group also increases the diastereoselectivity. Thus, this reaction constitutes a highly efficient route for constructing the γ-butyrolactone structure units with different stereochemistry in a single operation.[56]

The diastereoselectivity in the Pd(II)–LiX–CuX_2-catalyzed cyclization of 2′-alkenyl 2-alkynoates [50] is similar to that in the Pd(II)–LiX-catalyzed cyclization of 4′-heteroatom-2′-alkenyl 2-alkynoates. The similar diastereoselectivity was observed in the synthesis of α-alkylidene-γ-butyrolactams.[58] The diastereoselectivity is further supported by the cascade cyclization reaction.[59] A monocyclic product was obtained in the reaction of 1′,5′-hexadien-3′-yl propynoate. The failure of the second cyclization might be due to the *trans-configuration* of the β,γ-disubstituents in the product. The reaction of 1′,5′-hexadien-3′-yl 3-substituted 2-alkynoates under the same conditions yielded the *cis*-fused bicyclic α-(*Z*)-chloroalkylidene-γ-butyrolactone derivatives implying the *cis*-diastereochemistry of the β,γ-disubstituents in the first cyclization [59] (**Scheme 16**).



Scheme 16

B.v.c. ***Natural Product Synthesis.*** With these methodologies, natural products with the α-alkylidene-γ-butyrolactone structure unit are readily synthesized: for example, (±)-A-factor,[50] (±)-isohinokinin,[60] (+)- or (−)-methylenolactocin (β,γ-*trans*),[61],[62] (−)-phaseolinic acid (β,γ-*cis*),[63] isopilocarpine (formal synthesis),[64] and (+)-pilocarpine (formal synthesis) [53] (**Scheme 17**).



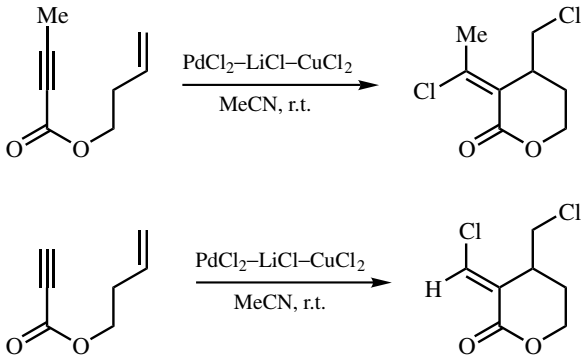
(±)-A-factor **(±)-isohinokinin** **isopilocarpine**

(−)-methylenolactocin **(−)-phaseolinic acid** **(+)-pilocarpine**

Scheme 17

B.vi. Halopalladation-Initiated Cyclization of Homoallylic Alkynoates

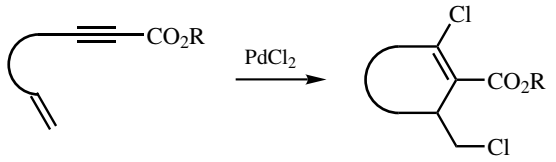
Similarly, in the presence of $PdCl_2$, LiCl, and $CuCl_2$ in MeCN, the reaction of homoallylic 2-butynoates afforded only *Z*-form product, while in the case of homoallylic 2-propynoates, *E*-form was the sole product. This result is consistent with that of allylic alkynoates [65] (**Scheme 18**).



Scheme 18

B.vii. Halopalladation-Initiated Cyclization of ω-Alken-2-alkynoates

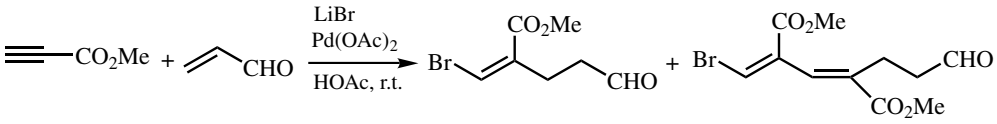
For the $PdCl_2$-catalyzed reactions, the direction of chloropalladation of the triple bond conforms to their electron properties. Thus, nucleophilic chloride ion attacks the β-carbon of the 2-alkynoates, forcing the carbon–palladium bond to form at the α-carbon [65] (**Scheme 19**).



Scheme 19

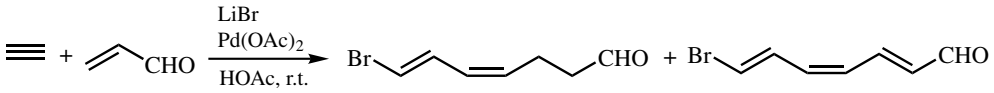
B.viii. Divalent Palladium-Catalyzed Halide–Alkyne-α,β-Unsaturated Carbonyl Coupling

As an intermolecular version of the reaction of type **IV** of **Scheme 15**, in the presence of halide, the Pd(II)-catalyzed coupling of alkynes and α,β-unsaturated carbonyls yields the conjugate addition products, γ,δ-unsaturated carbonyls [66] (**Scheme 20**).



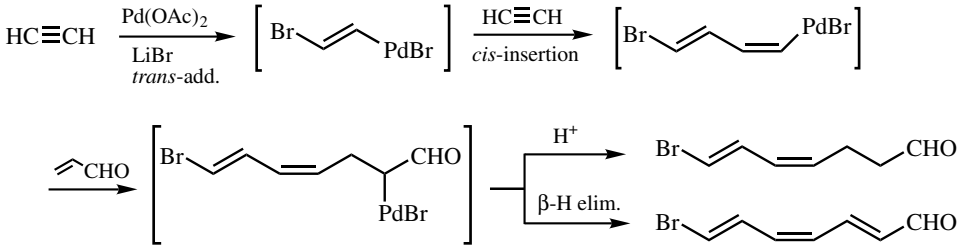
Scheme 20

This method was further developed to use acetylene as the substrate to yield *E,Z*-dienes[67] (**Scheme 21**).



Scheme 21

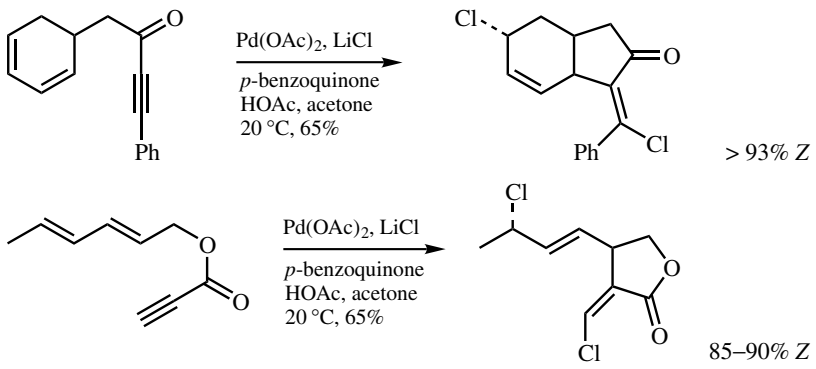
The formation of the two products could be explained with the following mechanism, which also rationalizes the stereoselectivity [67] (**Scheme 22**):



Scheme 22

B.ix. Halopalladation-Initiated Carbocyclization of Dienynes

A number of intramolecular Pd-catalyzed 1,4-oxidations of conjugated dienes were developed.[68]–[70] In these reactions, two nucleophiles are added across the diene,[69] one of which adds intramolecularly. So far, only heteroatom nucleophiles have been employed. In order to extend these intramolecular 1,4-oxidations to carbon nucleophiles, it was found that a vinylpalladium species can be obtained *in situ* from an alkyne via a chloropalladation.[22],[23] The approach is particularly attractive since it involves a Pd(II) chloride salt and could be compatible with the rest of the catalytic cycle. Reaction of dienyne with LiCl, and benzoquinone in the presence of palladium acetate as the catalyst, afforded the carbocyclization products. The reaction resulted in an overall stereoselective *anti*-addition of carbon and chlorine across the diene[23],[70],[71] (**Scheme 23**).

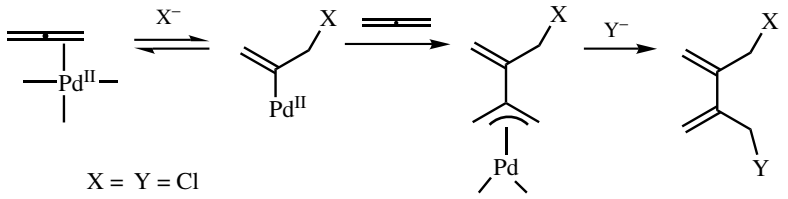


Scheme 23

C. ALLENES

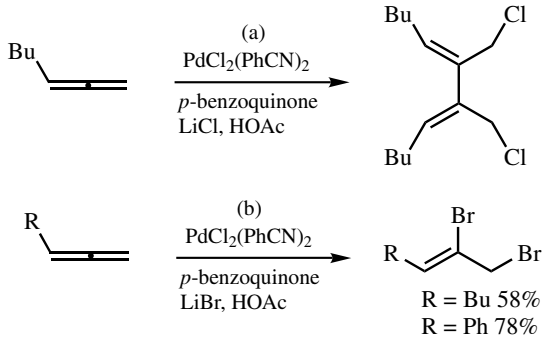
C.i. Pd-catalyzed 1,2-Oxidation of Allenes

In analogy with the Pd(II)-catalyzed oxidation of dienes,[17],[68],[70] the Pd-catalyzed oxidation of allenes with $CuCl_2$ as the oxidant was found to give the dimerization product [2],[4],[72] (**Scheme 24**).



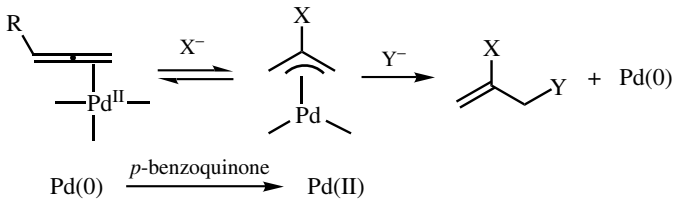
Scheme 24

A catalytic reaction using benzoquinone as the oxidant also yields the dimeric product when LiCl was used [73] (**Scheme 25a**). However, when the same reaction was run in the presence of LiBr in place of LiCl, the monomeric dibromide was obtained in 58% yield [73] (**Scheme 25b**).



Scheme 25

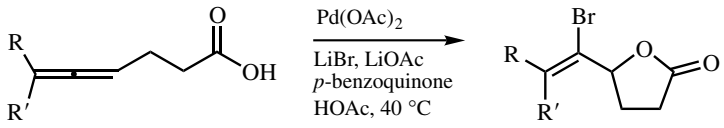
The mechanism is suggested as follows [73] (**Scheme 26**):



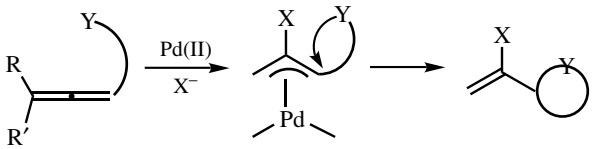
Scheme 26

This reaction can be extended to an intramolecular version in which an allenic acid is transfomed to a bromolactone under mild reaction conditions[74] (**Scheme 27**).

The reaction pathway is shown is **Scheme 28**.



Scheme 27

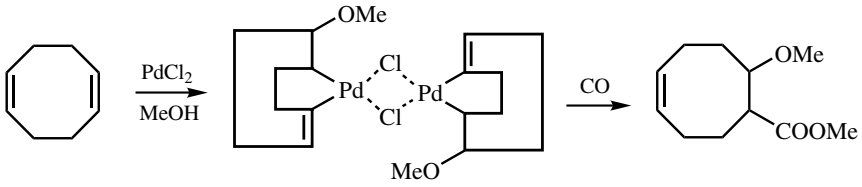


Scheme 28

D. ALKENES

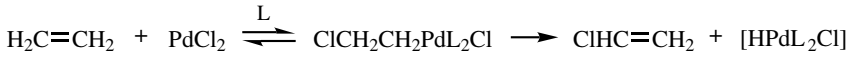
In the case of chloropalladation of alkenes, chloride is not a strong nucleophile as compared to the reaction with alkynes. Thus, in the presence of other nucleophiles such as methoxy ions, the product of the reaction of $PdCl_2$, LiCl, and alkene in the presence of methanol is the methoxy derivative.

The 1:2 addition of $PdCl_2$ to olefinic compounds gives the metal–carbon bonded complexes that can react further with carbon monoxide to form the acyl derivatives. Only in the cases where chelating groups are present, can the intermediate of adducts be isolated. A good example is the reaction of $PdCl_2$ in methanol with 1,5-cyclooctadiene. The isolable methoxypalladation adduct indicates that the chloro group has been replaced by the methoxy group [75],[76] (**Scheme 29**).



Scheme 29

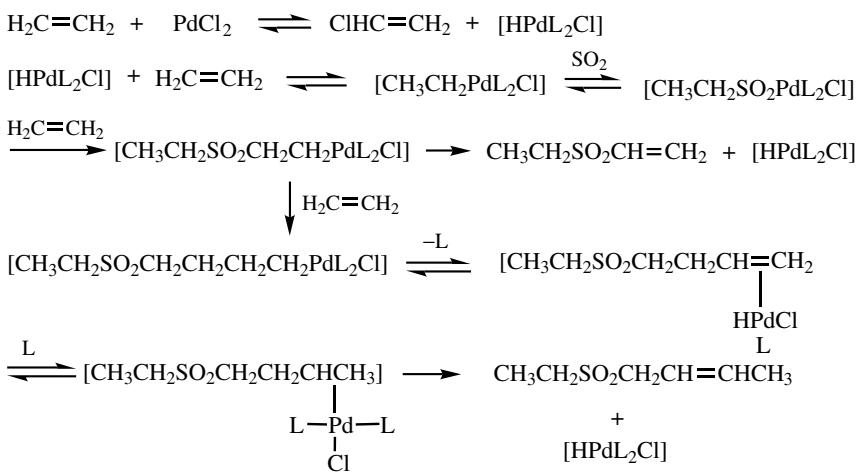
Palladium chloride at 100 °C in anhydrous dimethyl formamide reacts in a stoichiometric reaction with ethylene producing vinyl chloride in 80% yield.[77] Even though palladium chloride elimination is favored over hydride elimination, the addition recurs until the palladium is eliminated irreversibly as the hydride (**Scheme 30**).



Scheme 30

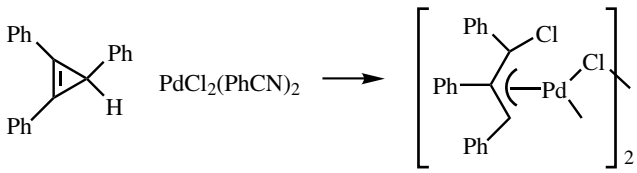
The palladium chloride reacts with olefins in a different course if water is present. Carbonyl compounds rather than chlorides are formed. The reaction with ethylene produces acetaldehyde and it can be done catalytically in the presence of oxygen and cupric chloride, which is known as the Wacker process. The process is one of the most important commercially useful reactions employing transition metal catalysts.[77],[78]

An interesting reaction between ethylene and SO_2 occurs with palladium chloride as catalyst forming mainly crotyl ethyl sulfone and, to a minor extent, ethyl vinyl sulfone. The mechanism probably involves a hydridochloropalladation complex as the true catalyst [79] (**Scheme 31**).



Scheme 31

A special example is the chloropalladation of cyclopropenes [80] (**Scheme 32**).



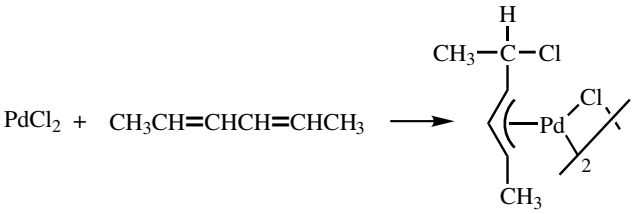
Scheme 32

E. DIENES

E.i. Conjugated Dienes

Palladium chloride reacts with conjugated dienes to form 1-chloromethyl π-allyl-palladium derivatives[13],[81],[82] (**Scheme 33**):

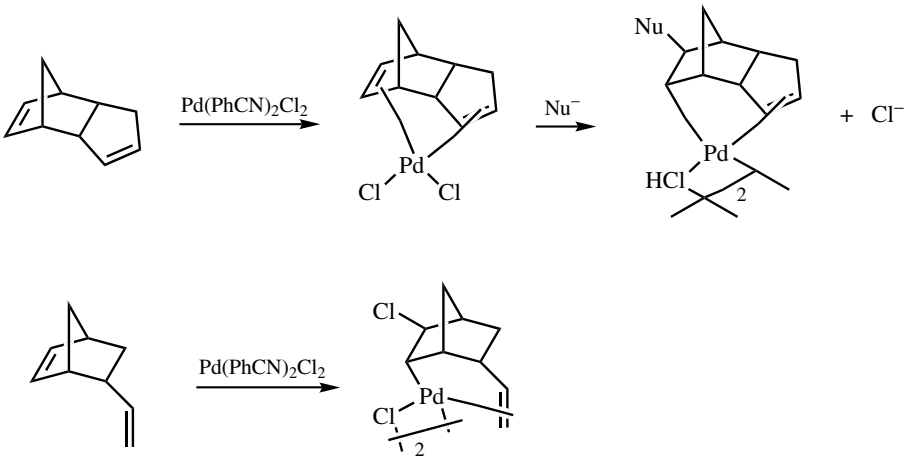
In alcoholic solution, the conjugated diene–palladium chloride reaction yields π-(1-alkoxyethyl)allyl derivatives, indicating that the chloro group may easily be replaced by other ligands.[14],[83],[84]



Scheme 33

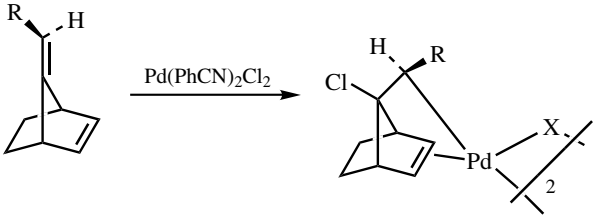
E.ii. Nonconjugated Dienes

As a nonconjugated diene, dicyclopentadiene forms first a monomeric π,π-complex, which is attacked by nucleophiles at the norbornene double bond giving the δ-bonded dimeric complex. [82],[83] If the diene has an acyclic double bond this is also preferentially attacked [20],[85] (**Scheme 34**).



Scheme 34

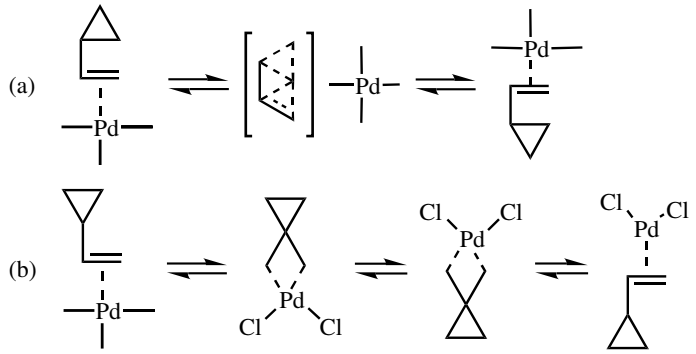
For the halopalladation reaction of 7-methylenebicyclic[2.2.1]hept-2-enes with the complexes $PdX_2(PhCN)_2$ (X = Cl, Br) using both solvents of low polarity (CH_2Cl_2 and $CHCl_3$) and methanol, the products result from *trans*-addition of Pd—X to the exocyclic double bond [86] (**Scheme 35**).



Scheme 35

F. CHLOROPALLADATION OF VINYLCYCLOPROPANE

Vinylcyclopropane forms a π-complex with $PdCl_2$ through the olefinic bond but some hydrogen transfer process occurs rapidly enough in the complex so that only a time averaged spectrum is observed in the NMR. Two possibilities are: a rapid interchange of the vinyl and cyclopropyl systems (**Scheme 36a**); and a similar interchange proceeding by a hydrogen migration and the formation of σ-bonded cyclopropane complexes [87] (**Scheme 36b**).

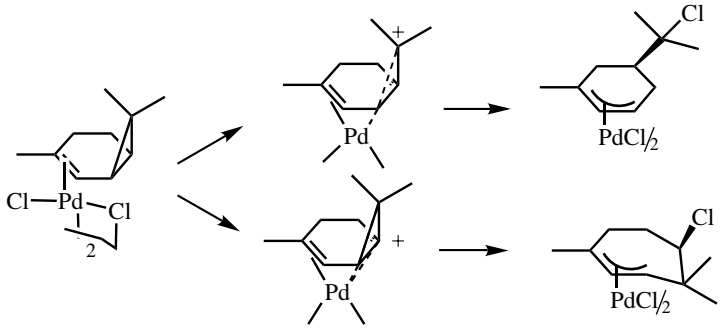


Scheme 36

Heating $PdCl_2$ with vinylcyclopropanes at 40 °C is known to give a mixture of chloropalladated adducts [87]–[90] (**Scheme 37**).

Scheme 37

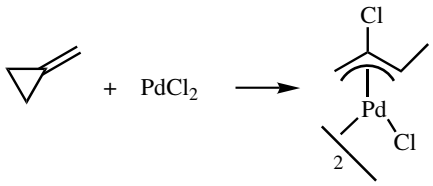
Bäckvall and co-workers reported the chloropalladation of (+)-2-carene. The *trans*-relationship between the palladium atom and the chloro group on the ring shows that the chloropalladation of the cyclopropane ring has occurred with overall *trans*-stereochemistry.[91],[92] The cyclopropane ring in bicyclo[5.1.0]oct-3-ene gave a similar chloropalladation reaction [93] (**Scheme 38**).



Scheme 38

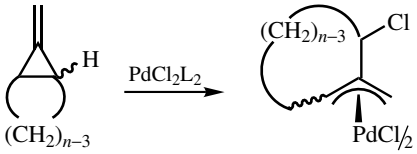
G. CHLOROPALLADATION OF METHYLENECYCLOALKANES

Methylenecyclopropane reacts with $PdCl_2$ to give di-μ-chloro-bis(2-chloro-1-methyl-π-allyl)dipalladium(II) in nearly quantitative yield.[94] Chloropalladation also occurs in bicyclic methylenecyclopropanes [95] (**Scheme 39**).



Scheme 39

Methylenecycloalkanes react similarly [95]–[97] (**Scheme 40**).



Scheme 40

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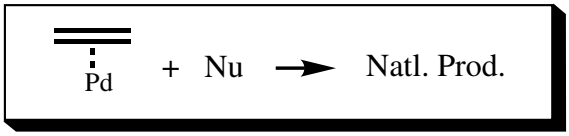

V.3.6 Synthesis of Natural Products via Nucleophilic Attack on π-Ligands of Palladium–Alkene, Palladium–Alkyne, and Related π-Complexes

CAIDING XU and EI-ICHI NEGISHI

A. INTRODUCTION

Nucleophilic attack on Pd-bound ligands, be they σ, π, or σ-π, provides an assortment of excellent methods for the formation of carbon–carbon and carbon–heteroatom bonds, as represented by general transformations shown in **Scheme 1**. In particular, these processes have provided three major methods for the formation of the carbon–heteroatom bonds, and they have extensively been applied to the synthesis of natural products. More recently, the Pd-catalyzed cross-coupling has also been developed so as to be applicable to the formation of C—N, C—O, and other carbon–heteroatom bonds, as discussed in **Sect. III.3**, even though the current scope of their application to natural product synthesis is still rather limited.

In this section, various examples of the application of the Wacker-type oxy-, amino-, and other heteropalladation reactions as well as related C—C bond formation reactions represented by Eq. 2 in **Scheme 1** to the synthesis of natural products are presented primarily in the form of a series of tables arranged in the order listed below. For those natural products syntheses involving the transformations represented by Eqs. 1 and 3, the readers are referred to **Sects. VI.6** and **V.2.6**, respectively.

Subsection	Topic	Pertinent Section Number
B	Oxypalladation	**V.3.1** and **V.3.2**
C	Aminopalladation	**V.3.3**
D	Reaction of Pd π-Complexes with Carbon Nucleophiles	**V.3.4**
E	Halopalladation	**V.3.5**

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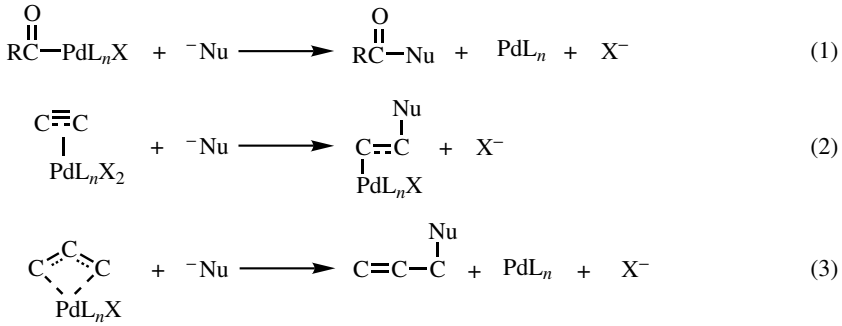
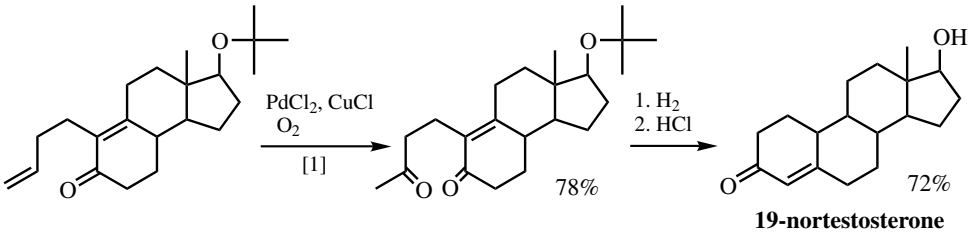


Scheme 1

B. SYNTHESIS OF NATURAL PRODUCTS VIA THE WACKER OXIDATION AND RELATED OXYPALLADATIONS

The Wacker-type oxypalladation can take place both intermolecularly (**Sect. V.3.1**) and intramolecularly (**Sect. V.3.2**). The intermolecular Wacker oxidation of terminal alkenes provides the corresponding 2-ketones rather than aldehydes. This reaction has widely been used as a step in the syntheses of natural products and related compounds, as exemplified by **Scheme 2**,[1] and no attempts are made to thoroughly catalogue such examples here.

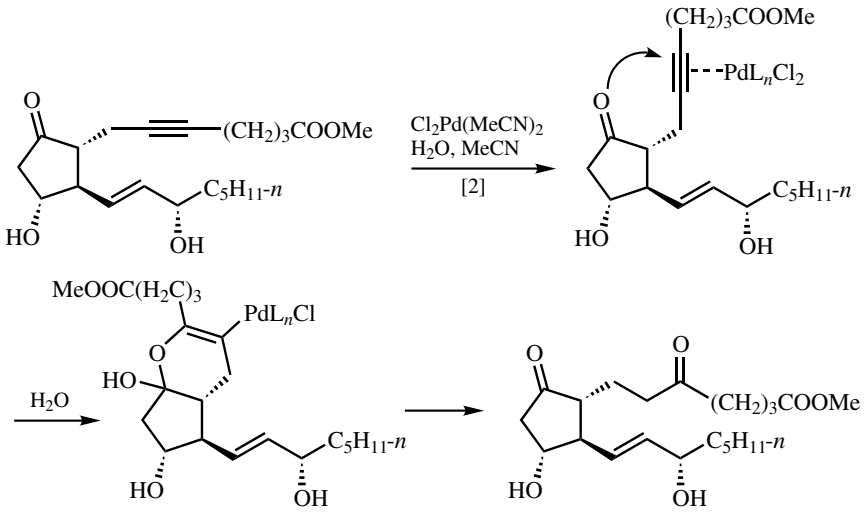


Scheme 2

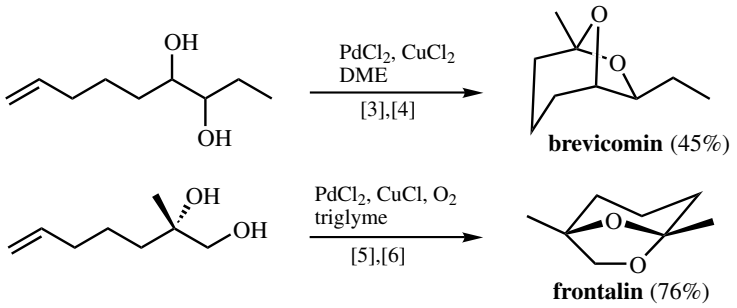
Another prototypical example of the application of intermolecular oxypalladation to the synthesis of natural products and related compounds is shown in **Scheme 3**.[2] Unlike the Wacker oxidation of alkenes to give ketones, the conversion of alkynes to ketones is a net nonredox process involving hydration of the triple bond. It should also be clearly noted that the observed high regioselectivity can most readily be explained in terms of intramolecular oxypalladation involving anchimeric participation by the cyclopentanone moiety followed by hydrolysis.

More genuine examples of intramolecular oxypalladation applied to the natural product synthesis involve conversion of alkenediols into cyclic acetals, as exemplified by the synthesis of brevicomin[3],[4] and frontalin[5],[6] shown in **Scheme 4**. The brevicomin synthesis reported in 1976 may well be the first reported example of the application of intramolecular oxypalladation to the synthesis of natural products.

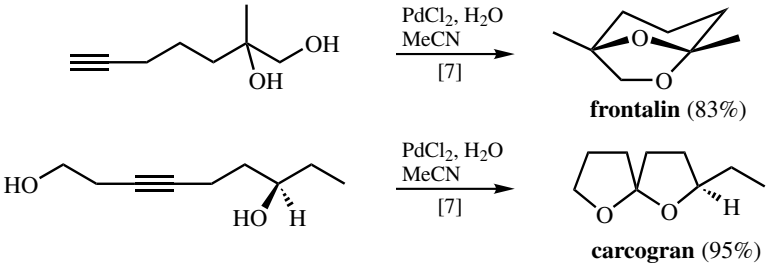
Closely related are the bicyclization reactions of alkynediols shown in **Scheme 5**.[7] Here again, these reactions are net nonredox processes. This reaction has been applied to a stereoselective synthesis of prostacyclin[8] (**Scheme 6**). It is striking and puzzling that



Scheme 3

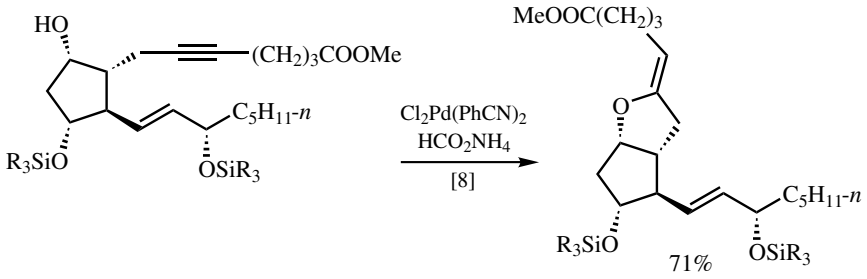


Scheme 4



Scheme 5

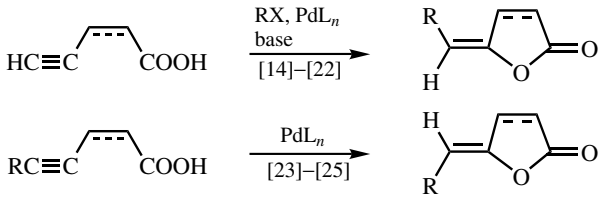
the cyclization process shown in **Scheme 6** involves an *exo*-mode cyclic oxypalladation, whereas that shown in **Scheme 3** must involve an *endo*-mode oxypalladation. As the reaction conditions used in these cases appear to be very similar, the contrasting results may be attributable to the fact that one involves an OH group, whereas the other must involve a carbonyl group.



Scheme 6

Some other representative examples of the application of hydroxypalladation to the syntheses of natural products are summarized in **Table 1**.

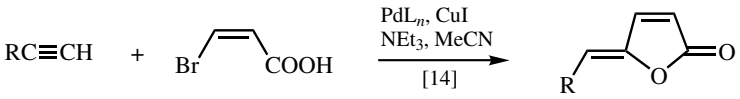
Another important class of oxypalladation reactions involves carboxypalladation of alkynoic acids to produce lactones. Depending on the structure of the alkynoic acids and the type of group that displaces Pd from the putative alkenylpalladium intermediate, this carboxypalladation–reductive elimination tandem process can give stereoselectively either (*E*)- or (*Z*)-γ-alkylidenebutenolides and possibly higher homologues as well (**Scheme 7**).



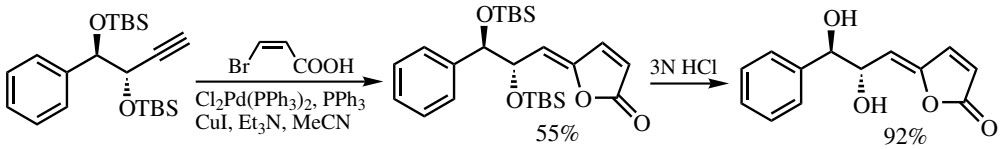
Scheme 7

An even more efficient lactone synthesis was developed recently, which involves a cross-coupling–carboxypalladation–reductive elimination cascade[26] (**Scheme 8**).

Despite all these methodological developments, their applications to the synthesis of natural products had not been reported until goniobutenolide A was synthesized in 1996 (**Scheme 9**).[27]



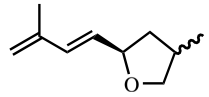
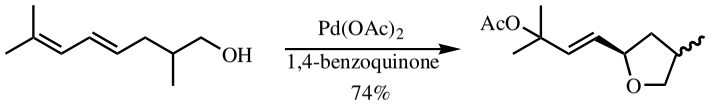
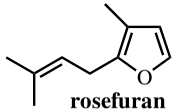
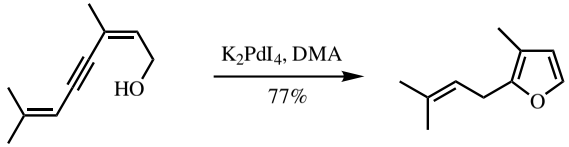
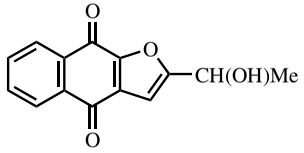
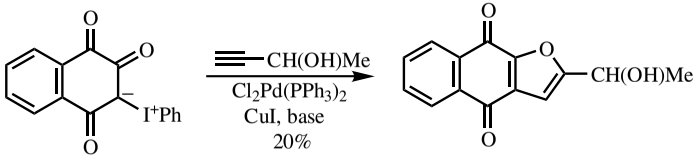
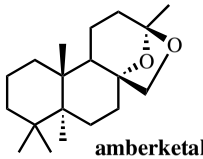
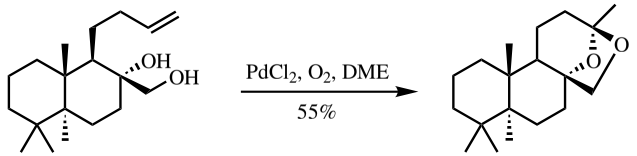
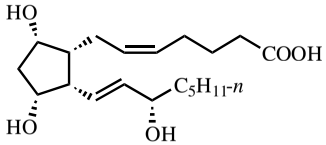
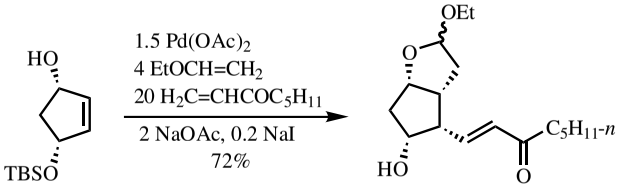
Scheme 8



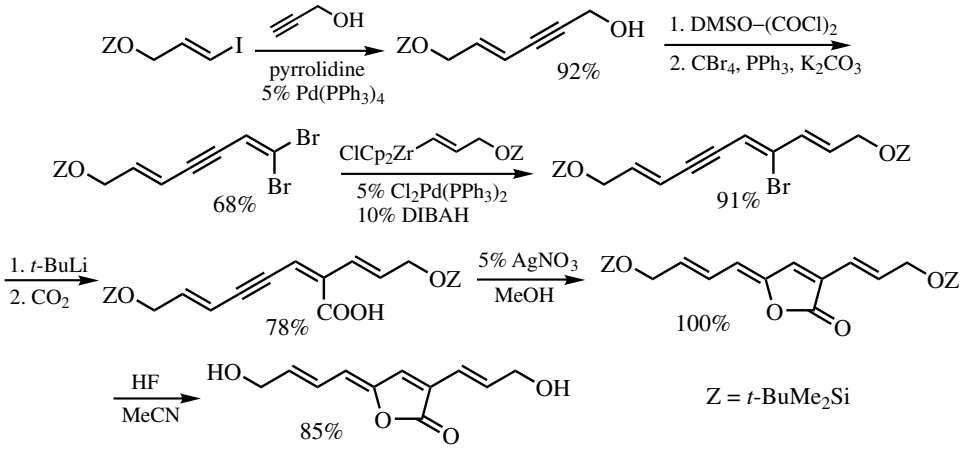
(+)-goniobutenolide A

Scheme 9

TABLE 1. Synthesis of Natural Products Via the Wacker Oxidation and Related Oxypalladations

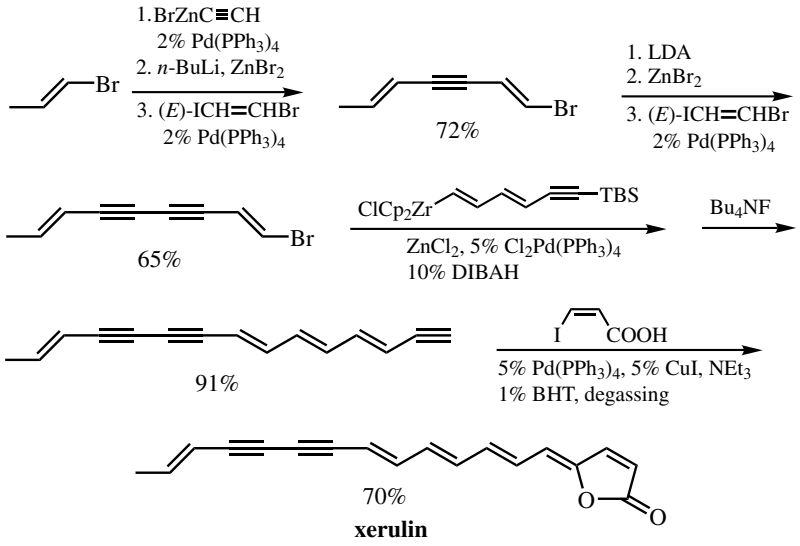
Number of C Atoms	Natural Product	Key Step	Reference
C_{10}	 **marmelo oxides A and B**		[9]
C_{10}	 **rosefuran**		[10]
C_{14}	 **2-(1-hydroxyethyl)naphtho-[2,3-*b*]furan-4,9-dione**		[11]
C_{20}	 **amberketal**		[12]
C_{20}	 **12-epi-PGF$_{2\alpha}$**		[13]

Since then, extensive studies to further improve both tandem and cascade versions shown in **Schemes 7** and **8** have been conducted to alleviate several undesirable side reactions for optimizing the product yields,[23],[28]–[30] and a number of naturally occurring (*Z*)-γ-alkylidenebutenolides have been synthesized, as summarized in **Table 2** and **Schemes 10**[24] and **11**.[33] A similar but less efficient synthesis of lissoclinolide has also been reported.[34] The currently available data suggest that the Pd- or Ag-catalyzed lactonization of appropriate alkynoic acids and their precursors provides by far the most efficient and satisfactory method for the synthesis of γ-alkylidenebutenolides, which represent a large number of biologically and medicinally important compounds.



lissoclinolide

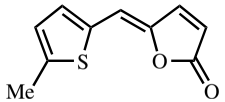
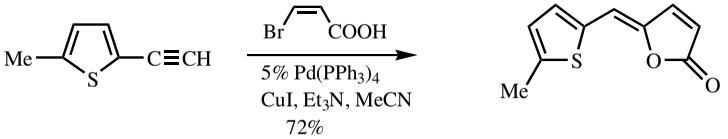
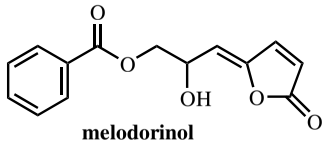
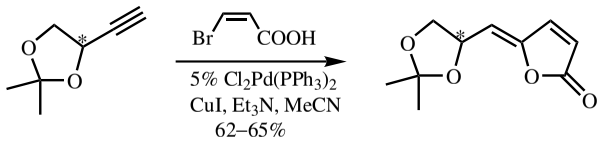
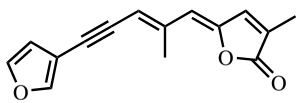
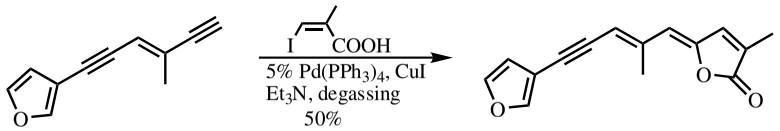
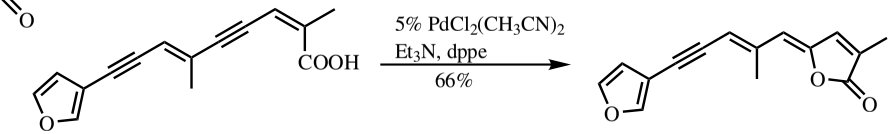
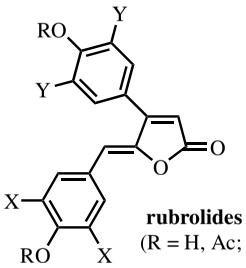
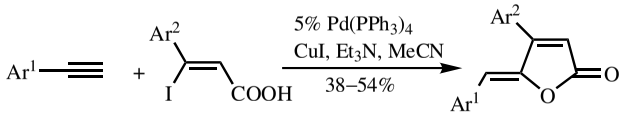
Scheme 10



xerulin

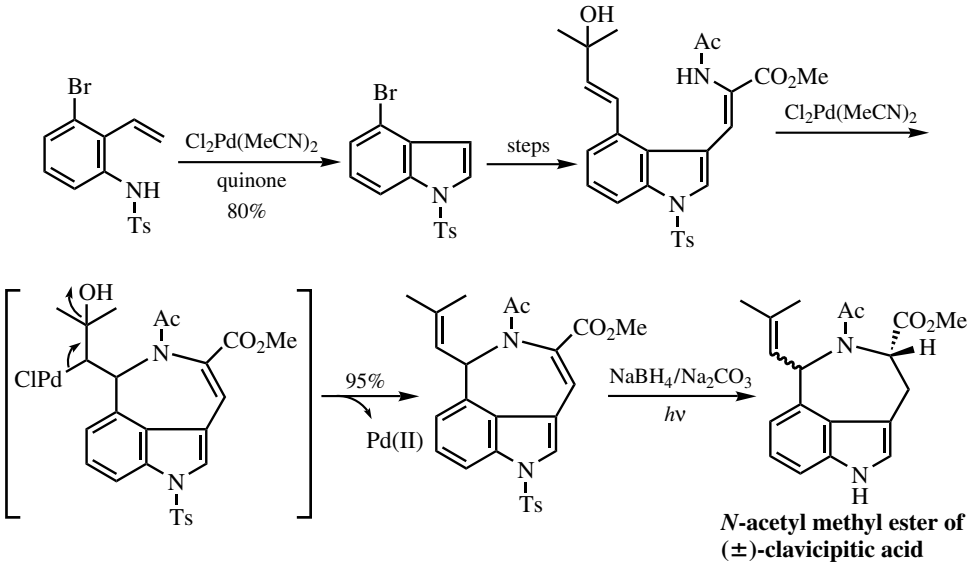
Scheme 11

TABLE 2. Synthesis of Naturally Occurring (Z)-γ-Alkylidenebutenolides Via Oxypalladation

Number of C Atoms	Natural Product	Key Step	Reference
C_{10}	 **thiophenelactone**	 5% $Pd(PPh_3)_4$, CuI, Et_3N, MeCN, 72%	[31]
C_{14}	 **melodorinol**	 5% $Cl_2Pd(PPh_3)_2$, CuI, Et_3N, MeCN, 62–65%	[32]
C_{15}	 **freelingyne**	 5% $Pd(PPh_3)_4$, CuI, Et_3N, degassing, 50%	[29]
		 5% $PdCl_2(CH_3CN)_2$, Et_3N, dppe, 66%	[25]
C_{17}	 **rubrolides A, C, D, E** (R = H, Ac; X, Y = H, Br)	 5% $Pd(PPh_3)_4$, CuI, Et_3N, MeCN, 38–54%	[23]

C. SYNTHESIS OF NATURAL PRODUCTS VIA AMINOPALLADATION

Aminopalladation–reductive elimination tandem reactions have provided a valuable methodology for the construction of nitrogen-containing heterocycles in the syntheses of natural products and related compounds. An early example is the synthesis of clavicipitic acid shown in **Scheme 12**.[35] In this synthesis, intramolecular aminopalladation was used in two key steps. The first is the intramolecular aminopalladation of *N*-tosyl-3-bromo-2-vinylaniline in the presence of $PdCl_2(MeCN)_2$ to give the corresponding indole derivative. The other is also an intramolecular aminopalladation to produce a nitrogen-containing seven-member ring. It should be noted that, unlike the first aminopalladation reaction requiring quinone as an external oxidant for Pd catalysis, the last step does not require an external oxidant, since the allylic alcohol substrate serves an internal oxidant.

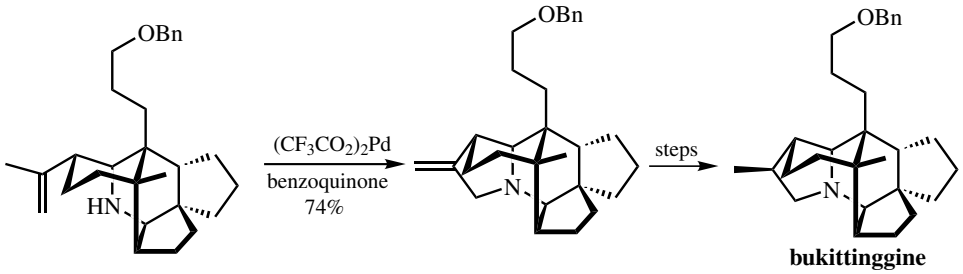


Scheme 12

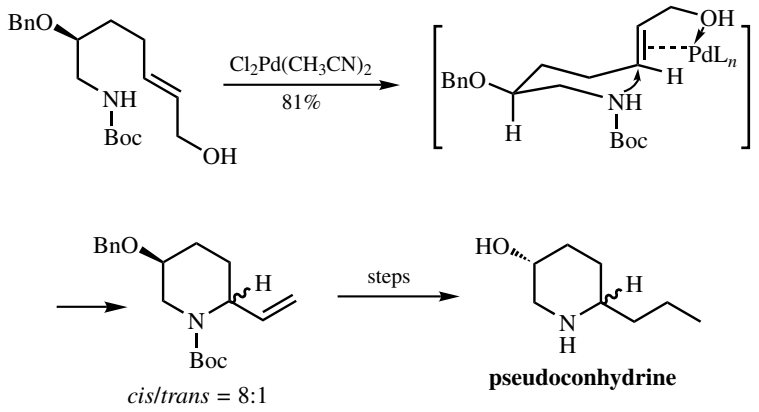
Aliphatic amines have failed to undergo this Pd-catalyzed amination.[35] Presumably, their high basicity leads to the formation of Pd–amine complexes that are too stable to be effective catalysts. However, some aliphatic amines, such as a sterically hindered secondary amine containing two secondary alkyl groups shown in **Scheme 13**, readily participate in the Pd-catalyzed amination of alkenes, and the reaction has been employed as a critical step in the syntheses of alkaloids, such as bukittinggine (**Scheme 13**).[36]

Conversion of amines into less basic derivatives, such as methanes and amides, appears to be also effective, as indicated by the synthesis of pseudoconhydrine (**Scheme 14**).[37]

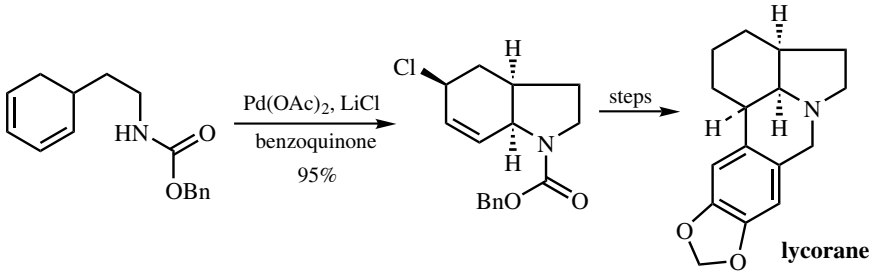
Stereocontrolled Pd-catalyzed intramolecular 1,4-chloroamidation is applied as a key step in the total syntheses of (±)-α- and (±)-γ-lycorane[38] (**Scheme 15**).The diene carbamate is smoothly cyclized in the presence of $Pd(OAc)_2$ and LiCl, with high regio- and stereoselectivities ($>98\%$ selectivity), to give the desired bicyclic carbamate in which Cl and N are *cis* to each other.



Scheme 13



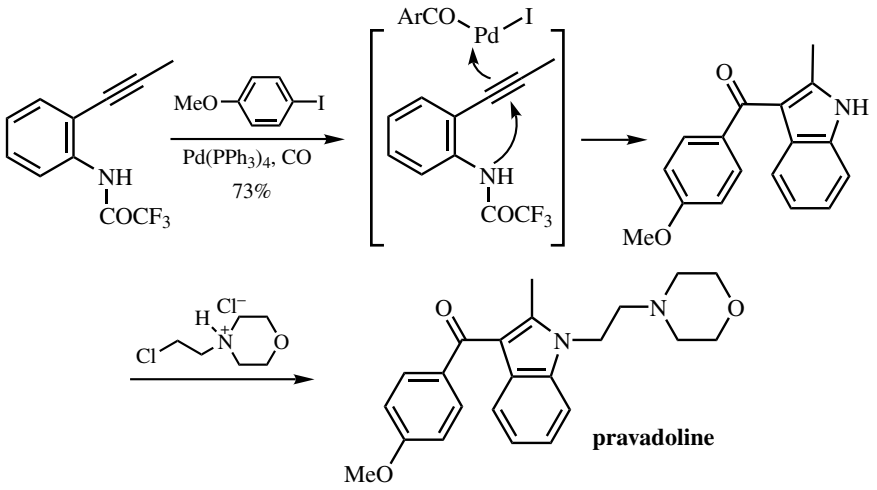
Scheme 14



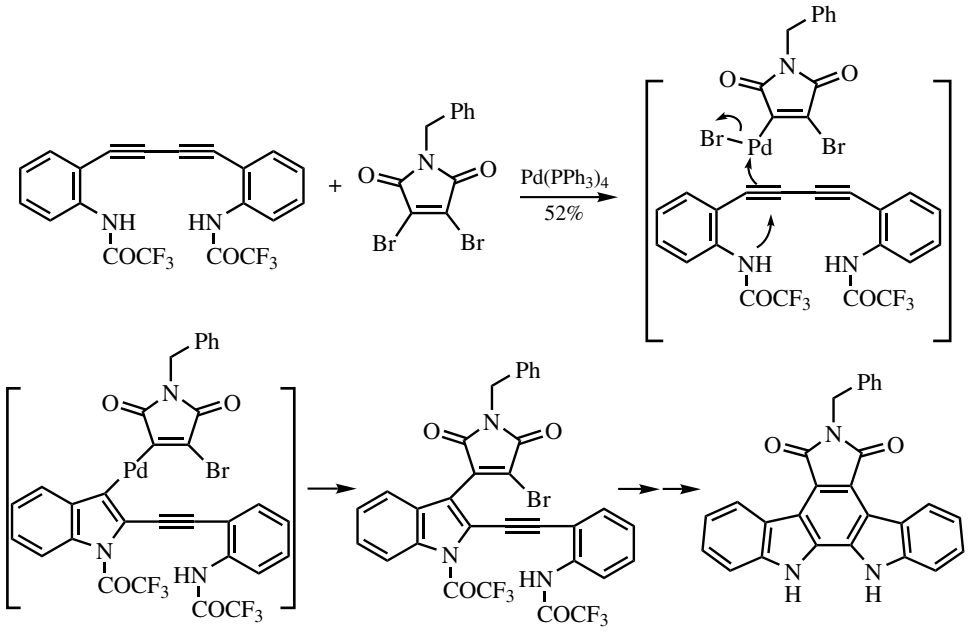
Scheme 15

2-Alkynylanilines similarly undergo aminopalladation to give indoles bearing alkyl substitutes at the 2-position. This reaction has been applied to the syntheses of pravadoline[39] (**Scheme 16**) and a rebeccamycin-related indole[2,3-a]carbazole ring system[40] (**Scheme 17**).

The mechanism of this cyclization can be rationalized in terms of the formation of π-alkynylpalladium complexes and intramolecular nucleophilic attack by amides. The trifluoromethyl group must effectively attenuate the nucleophilicity of the nitrogen base.



Scheme 16



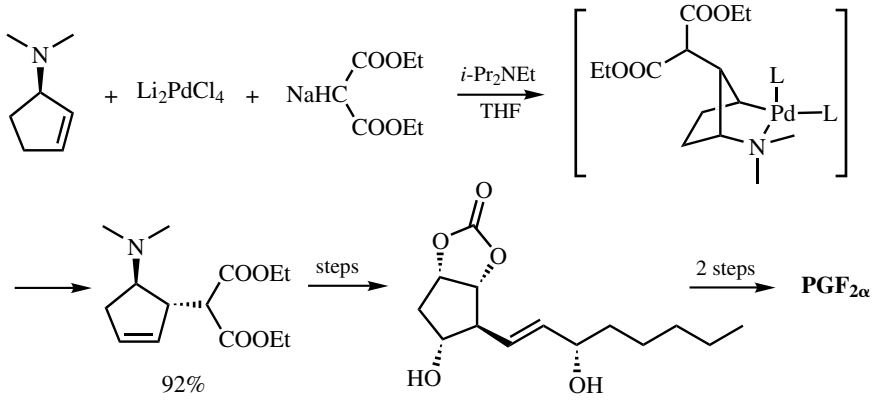
Scheme 17

D. SYNTHESIS OF NATURAL PRODUCTS BY THE REACTION OF PALLADIUM π-COMPLEXES WITH CARBON NUCLEOPHILES

Pd-catalyzed reactions involving attack on palladium–alkene, palladium–alkyne, and related π-complexes by carbon nucleophiles are discussed in **Sect. V.2.3**. Complexation of alkenes and alkynes to palladium(II) compounds activates alkenes and alkynes to nucleophilic attack. In general, when Pd(II) salts are employed, stoichiometric quantities of Pd

reagent are required. Otherwise some oxidants, such as copper(II) salts, must be added for catalysis by Pd complexes. If the reaction involves complexation of an olefin or alkyne to organopalladium (II) species generated *in situ* by oxidative addition of an unsaturated halide to a Pd(0) complex, only a catalytic amount of Pd complex is required.

Nucleophilic attack by carbanions on Pd π-complexes provides an excellent method for carbon–carbon bond formation. The first example of natural product synthesis by the reaction of Pd π-complex with carbon nucleophiles appears to be Holton's synthesis of prostanoids via treatment of an allylic amine with the stoichiometric amount of lithium tetrachloropalladate and sodium diethyl malonate, followed by addition of diisopropylethylamine, which led to the formation of an isomerically pure bicyclic Pd–amine complex in 92% yield[41] (**Scheme 18**). The carbon nucleophile ends up α and *trans* to the dimethylamino group. Both regio- and stereochemistries must be controlled by the Me_2N group. The amino diester intermediate was further transformed into Corey lactone diol, which had previously been converted to $PGF_{2\alpha}$ in two steps and 80% overall yield.

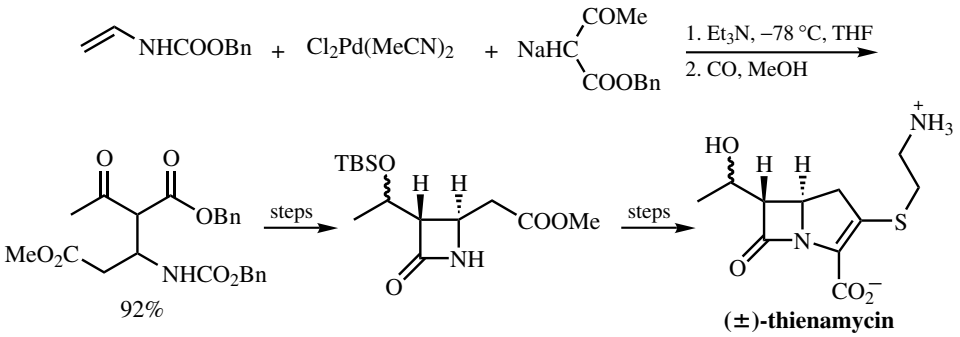


Scheme 18

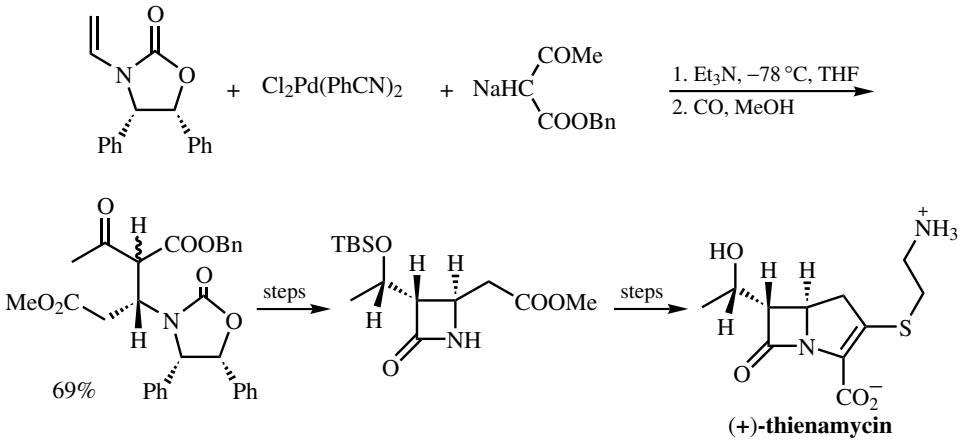
Alkylpalladium derivatives formed by the attack of Pd–alkene complexes with stabilized carbanions can undergo carbon monoxide insertion, leading to the formation of 1,5-dicarbonyl derivatives. With enamides as the alkene substrates, nucleophilic attack occurs exclusively α to N, and the carbonylation produces highly functionalized β-amino acid derivatives, which can be cyclized to β-lactams, as indicated by the synthesis of (±)-thienamycin shown in **Scheme 19**.[42]

When optically active enamine derivatives are used as substrates, full control of absolute stereochemistry is feasible, and the process is applicable to the synthesis of a known precursor of (+)-thienamycin in very high optical yield[43] (**Scheme 20**).

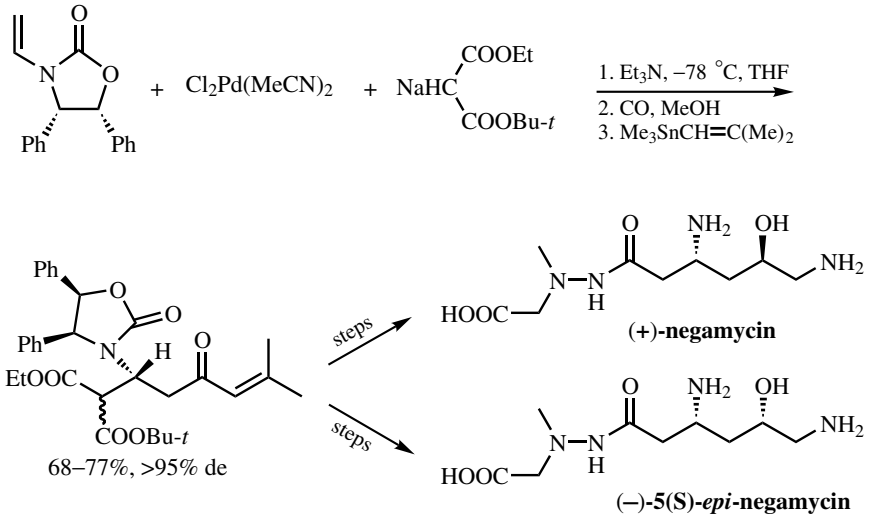
This approach has also been applied to the synthesis of (+)-negamycin and (−)-5(*S*)-*epi*-negamycin[44] (**Scheme 21**). Treatment of optically active enamine derivatives with $Cl_2Pd(MeCN)_2$, Et_3N, and the sodium anion of *tert*-butyl ethyl malonate at −78 °C, followed by exposure to 1 atm of CO and addition of isobutenyltrimethylstannane, afforded 68–77% yields of the expected product as a 1:1 mixture of diastereoisomers about the malonate carbon but isomerically pure at the N-bearing carbon atom. From this highly functionalized, optically active product, (+)-negamycin and (−)-5(*S*)-*epi*-negamycin were synthesized in 13% and 20% overall yield, respectively.



Scheme 19

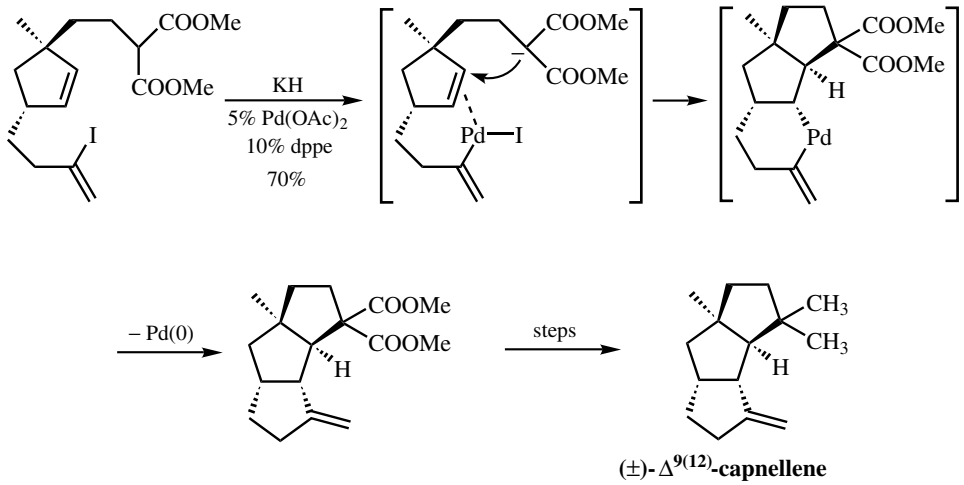


Scheme 20



Scheme 21

More recently, a cascade process that presumably consists of (i) oxidative addition of Pd to an alkenyl iodide, (ii) Pd–alkene π-complex formation, (iii) *anti*-attack by a carbon nucleophile, and (iv) reductive elimination has been devised. This cascade process has been used for the synthesis of (±)-$\Delta^{9(12)}$-capnellene[45] (**Scheme 22**).



Scheme 22

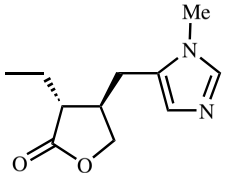
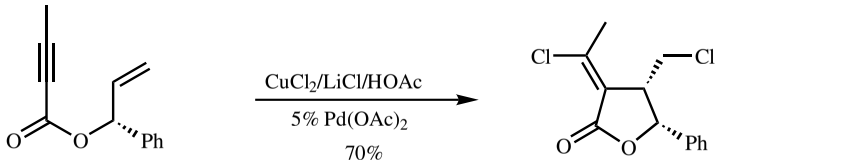
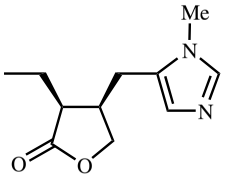
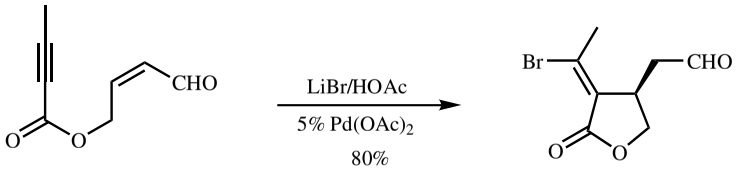
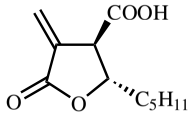
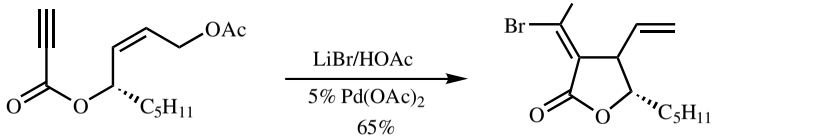
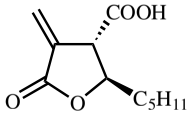
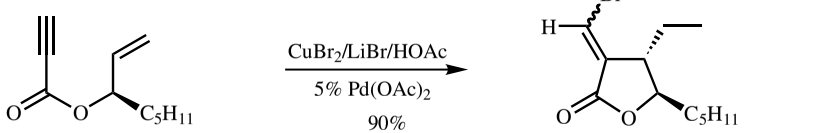
It is noteworthy that, although Pd-catalyzed zipper mode cyclization under the Heck reaction conditions has widely been used for the construction of polycyclic systems, it would not be suitable for the construction of the capnellene skeleton with the *cis-anti-cis* stereochemistry, since the Heck reaction involves *syn* addition of an organopalladium species to the carbon–carbon double bond followed by the *syn* elimination of a palladium hydride. Indeed, only the *cis-syn-cis* triquinane skeleton would be formed, and this has indeed been the case.[46]

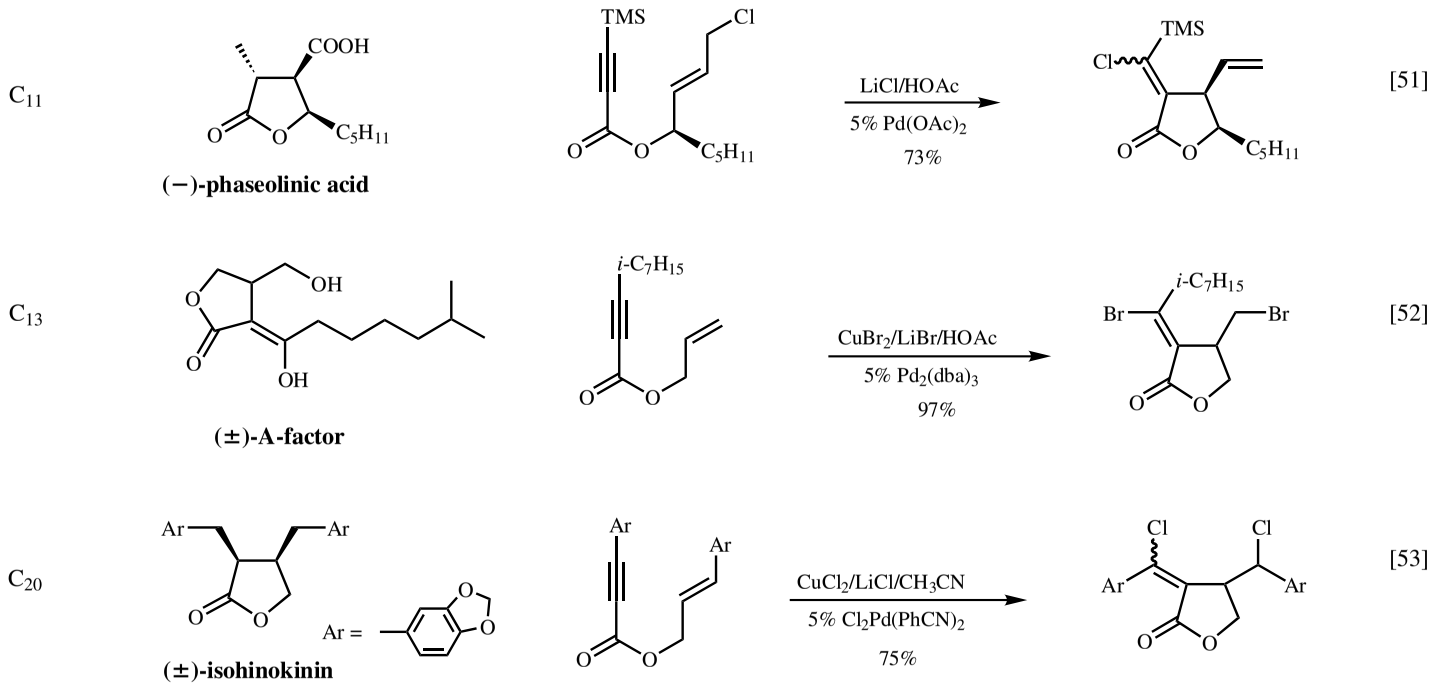
E. SYNTHESIS OF NATURAL PRODUCTS VIA HALOPALLADATION OF PALLADIUM π-COMPLEXES

As discussed in **Sect. V.3.5**, halide ions can also add to the palladium π-complexes, and the process may be termed halopalladation. Addition of Pd and a halogen, such as Cl and Br, to olefins, acetylenes, allenes, and conjugated dienes has been reported. However, most of the currently useful reactions initiated by halopalladation involve the use of alkynes as the substrates. Halopalladation of alkynes gives vinylpalladium intermediates, which can undergo intramolecular carbopalladation to form cyclized products. Pd-catalyzed cyclization of allylic alkynoates can produce π-alkylidene-γ-butyrolactones, which represent a basic structural unit in a wide variety of biologically active natural products.

Some representative examples of the application of the halopalladation–cyclic carbopalladation cascade to the synthesis of natural products are shown in **Table 3**.

TABLE 3. Synthesis of Natural Products Via Halopalladation of Pd π-Complexes

Number of C Atoms	Natural Product	Key Step	Reference
C_{11}	 **isopilocarpine**		[47]
C_{11}	 **(+)-isopilocarpine**		[48]
C_{11}	 **(–)-methylenolactocin**		[49]
C_{11}	 **(+)-methylenolactocin**		[50]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73%
TMS
Cl
O
O
C5H11
[51]
C13
OH
O
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97%
i-C7H15
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C20
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PART VI
Palladium-Catalyzed Carbonylation and Other Related Reactions Involving Migratory Insertion

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VI.1 Background for Part VI

EI-ICHI NEGISHI

Migratory insertion and its microscopic reversal, that is, migratory deinsertion, are two of the 20 or so fundamental processes discussed in **Sect. I.2** in which Pd participates. In principle, they should be observed with a wide variety of substrates. In reality, however, the current scope of these processes observable with organopalladiums is almost totally limited to those that involve CO and related compounds, such as isonitriles. Consequently, the migratory insertion–deinsertion chemistry of organopalladium compounds at present is essentially synonymous with their carbonylation–decarbonylation reactions.

Despite its well-known toxicity, CO is, of course, a very valuable and convenient reagent for a variety of reasons. First, it is thermally quite stable and yet chemically reactive. Its relatively high reactivity, especially toward Pd and other transition metal complexes, largely stems from the fact that it can readily provide both a carbon-centered nonbonding pair of electrons and a carbon-centered valence shell empty orbital. Thus, CO is very much like singlet carbene (**Scheme 1**). With a pair of a high-lying HOMO and a low-lying LUMO, it can readily react with coordinatively unsaturated Pd complexes.

Second, it is an inexpensive carbon source, which can be incorporated into a variety of organic compounds in its entirety without producing any undesirable by-products. Since its toxicity problem can satisfactorily be dealt with in most instances, CO is, in fact, an environmentally friendly and convenient C source in an overall sense, even though extensively engineered apparati, which must often be operated at high pressures and temperatures, are required in many instances.

Ready incorporation of the carbon–oxygen bond into organic products also renders CO a highly versatile reagent applicable to the synthesis of a wide variety of oxygenated compounds, such as ketones, aldehydes, carboxylic acids and their derivatives, and alcohols, as well as nitrogenated and other heteroatom-containing compounds.

Synthesis of organic compounds with CO and Pd complexes used as catalysts begins with the formation of Pd—CO complexes, which can readily be generated as discussed above. Critical processes of carbon–carbon and carbon–heteroatom bond formation can occur via either migratory insertion (Pattern **18** in **Table 3** of **Sect. I.2**) or nucleophilic attack at the C atom of the coordinated CO (Pattern **20**), as shown in **Scheme 2**. The intramolecular migratory insertion process must involve a concerted [1,2]-shift proceeding with retention of configuration of the migrating group. It should be recognized that distinction between these two processes in carbonylation can be very subtle and often difficult to

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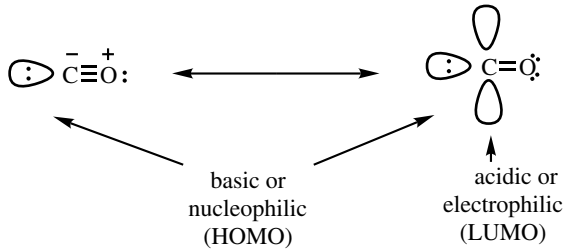
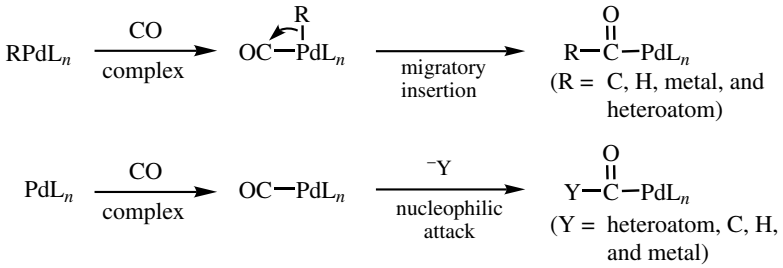


Scheme 1



Scheme 2

make, since the overall transformation can be the same. Despite such mechanistic ambiguities, the formation of acylpalladium derivatives and their heteroatom analogues via complexation of CO and formation of a C—C or C—X bond, where X is H, metal, or other heteroatom, must take place in all of the carbonylation reactions discussed in this **Part**. As might be expected from the concerted nature of CO complexation and migratory insertion, both of these processes can readily be reversed to effect decarbonylation (**Sect. VI.5.1**).

To complete organic synthesis via Pd-catalyzed carbonylation, the acylpalladium and related derivatives, represented by RCOPdL$_n$ and YCOPdL$_n$ in **Scheme 2**, must undergo further transformations including C—Pd bond cleavage as a mandatory step. In addition, some organopalladium interconversion processes, such as acylpalladation, may take place prior to C—Pd bond cleavage.

The most widely observed process for the conversion of acylpalladium derivatives into organic compounds is their reaction with a variety of nucleophiles, which may take place either intermolecularly or intramolecularly (**Sects. VI.2.1.1** and **VI.2.1.2**). Acylpalladium derivatives may be derived via some organopalladium interconversion reactions, such as carbopalladation and oxy- and aminopalladation. In the carbopalladation–carbonylative termination cascade process, the carbopalladation process may have been the more critical step of the two. For this reason, it is discussed in **Sect. IV.3.3**, while the heteropalladation–carbonylative termination cascade is discussed in **Sect. VI.2.1.3**. In some of these Pd-catalyzed carbonylative reactions with nucleophiles, double carbonylation has been observed. As is well known, double or multiple CO insertion is a thermodynamically unfavorable process,[1] even though isonitriles and other reagents are known to undergo double and even multiple migratory insertion. It has been found that Pd complexes containing two acyl and/or related carbonyl groups can be generated and that they undergo reductive elimination to give double carbonylation products, as detailed in **Sect. VI.2.1.4**.

Trapping of acylpalladium derivatives via hydrogenolysis must be a critical step in the classical Rosenmund reduction[2] of acyl halides to give aldehydes. Aldehydes can now be

synthesized by a variety of processes involving generation and hydrogenolysis of acylpalladium derivatives, as discussed in **Sect. VI.2.4**. Over the past two decades, trapping of acylpalladium derivatives with organometals and other carbon nucleophiles has been developed as a route to ketones (**Sect. VI.2.2**). In the meantime, it has also been found that enolates can serve as either *O*- or *C*-nucleophiles for trapping acylpalladium derivatives (**Sect. VI.2.3**). Although the reactions of acylpalladium derivatives derivable from allyl-, propargyl-, and allenylpalladiums are similar to those derivable from alkyl-, aryl-, alkenyl-, and alkynylpalladiums, there are a number of unique features associated with them, as discussed in **Sect. VI.3**.

Currently, the most significant organopalladium interconversion process that acylpalladium species undergo is acylpalladation, which can be observed with alkenes, alkynes, allenes, dienes, and polyenes, and even with arenes, as discussed in **Sect. VI.4**. Independent and concurrent investigations over the last two decades have demonstrated that acylpalladation can take place both intramolecularly (**Sect. VI.4.1**) and intermolecularly (**Sects. VI.4.2** and **VI.4.3**). It is noteworthy that CO insertion, which cannot be repeated due to unfavorable thermodynamics, can perfectly alternate with alkene insertion to give polyketones. Heteroatom-containing Pd–carbonyl derivatives, that is $XCOPdL_n$ and $XCOOPdL_n$, where X is O, N, and so on, can also undergo addition reactions similar to acylpalladation, as discussed in **Sect. VI.4.4**.

Acylpalladium derivatives can be converted to organic products by some other reactions. Decarbonylation (**Sect. VI.5.1**) mentioned earlier is one such reaction. In cases where acylpalladium derivatives contain H atoms in the α or γ position, they may readily be converted to ketenes, which may then undergo further transformations characteristic of ketenes, such as [2 + 2] addition and reactions with various nucleophiles (**Sect. VI.5.2**).

A large number of natural products have been synthesized by using Pd-catalyzed carbonylation, as discussed in **Sect. VI.6**.

In most of the reactions discussed in the above-mentioned sections, redox processes take place, and the formal oxidation state of the C atom of CO changes from $+2$ to various levels ranging from -4 to $+4$. In the reactions discussed in **Sects. VI.2–VI.6**, some reactant, a part or the whole of which is incorporated in the organic products, serves as an oxidant or a reductant. The scope of the Pd-catalyzed carbonylation chemistry can significantly be expanded, if many additional carbonylation reactions of organopalladium species, which are otherwise stoichiometric, can be made catalytic through the use of external or strategically incorporated internal oxidants and reductants. Some such reactions are discussed in **Sect. VI.7**.

Finally, as stated at the outset, the migratory insertion chemistry of organopalladium derivatives should be, in principle, of broad scope. Although the current limited scope does not permit an extensive and systematic discussion of other migratory insertion reactions, synthesis of oligomers and polymers via migratory insertion of isonitriles represents a prototypical example (**Sect. VI.8**). Many additional Pd-catalyzed novel migratory insertion reactions will be discovered and developed in the near future.

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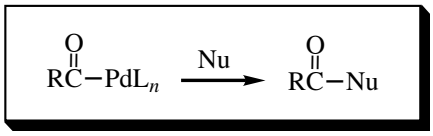

VI.2 Migratory Insertion Reactions of Alkyl-, Aryl-, Alkenyl-, and Alkynylpalladium Derivatives Involving Carbon Monoxide and Related Derivatives

VI.2.1 Reactions of Acylpalladium Derivatives with Oxygen, Nitrogen, and Other Group 15, 16, and 17 Atom Nucleophiles

VI.2.1.1 Intermolecular Processes

VI.2.1.1.1 Palladium-Catalyzed Carbonylation of Aryl and Vinylic Halides

MIWAKO MORI

A. INTRODUCTION

A method for synthesizing esters from aryl, vinyl, and benzyl halides and alcohols under carbon monoxide in the presence of a palladium catalyst was developed in 1974.[1]–[3] In a similar manner, syntheses of amides or carboxylic acids were also subsequently achieved using primary or secondary amines or water instead of alcohols (**Scheme 1**).

Enol triflate, which is easily obtained from the keto-carbonyl group regioselectively, can be converted into ester or amide using Pd-catalyzed carbonylation. This means that we can introduce the ester or amide group on the keto-carbonyl carbon to form α,β-unsaturated ester or amide.

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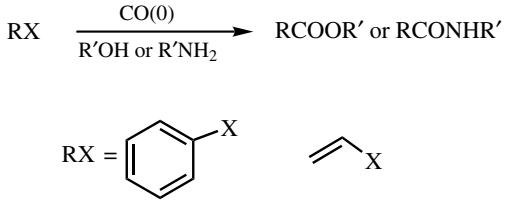
Pd(0)-catalyzed carbonylation.

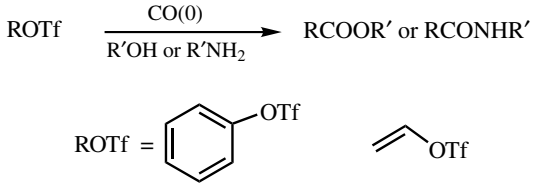
A. Carbonylation of aryl or vinyl halide



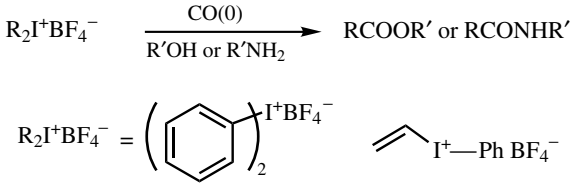
B. Carbonylation of alkyl halide

RX = Benzyl or others

C. Carbonylation of aryl or enol triflate



D. Carbonylation of pseudo aryl or vinyl halide



Scheme 1. Pd(0)-catalyzed carbonylation.

Now Pd-catalyzed carbonylation was used as one carbon elongation method and it has been used for the synthesis of biologically active substances and natural products. In this section, Pd-catalyzed carbonylation of aryl, vinyl, and benzyl halides and pseudo aryl or vinyl halides is described.

B. CARBONYLATION OF ARYL AND VINYL HALIDES

In 1974, Heck reported the synthesis of ester using Pd-catalyzed carbonylation by a very simple procedure.[1] In this procedure, a solution of aryl iodides and an alcohol was heated under carbon monoxide (1 atm) at 100 °C in the presence of a tertiary amine and a catalytic amount of palladium–triphenyl phosphine complex to form ester. $Pd(OAc)_2$,

$PhPdI(PPh_3)_2$, $PdBr_2(PPh_3)_2$, or $PdCl_2(PPh_3)_2$ can be used as the palladium catalyst. Generally, the reaction proceeded by 1–2 mol % of palladium catalyst. Electron-withdrawing groups on the aromatic ring increased the reaction rate, and electron supplying-groups decreased it (**Table 1**).

$$\text{Ar halide or vinyl halide} \xrightarrow[\text{BuOH, } Bu_3N,\ 100\ ^\circ C]{\text{CO (1 atm)}\ Pd(OAc)_2\text{–}PPh_3} \text{Ar halide or vinyl halide} \qquad (1)$$

Bromobenzene and benzyl chloride also afforded ester, but chlorobenzene did not give the desired product. The reaction is applicable for the synthesis of α,β-unsaturated ester from vinyl halide, and it is tolerant of a variety of functional groups. *cis*- and *trans*-Vinyl halides were carbobutoxylated for retaining the initial stereochemistry in the product (**Table 2**).

$$RX + CO + R'NH_2\ \ R_3''N \xrightarrow{PdX_2(PPh_3)_2} RCONHR' + R_3''NHX \qquad (2)$$

Later, Heck also reported the synthesis of amide from various aryl, heterocyclic, and vinylic halides and primary or secondary amines in the presence of a palladium catalyst.[4] The reaction was carried out under an atmosphere of carbon monoxide, and a tertiary amine was generally added to neutralize the hydrogen halide formed in the reaction. The reaction is also highly stereospecific with *cis*- and *trans*-vinyl halides (**Table 3**).

The most important point in these reactions is that they used stable divalent palladium complex such as $Pd(OAc)_2$ or $PdBr_2(PPh_3)_2$, not zerovalent palladium complex. Because of the easy handling of divalent palladium complex, this reaction has widely been used by many people. Although the reaction mechanism for the generation of Pd(0) from Pd(II) was later reported by Hayashi and Ozawa,[5] at this stage, it is considered that Pd(0) would be generated from Pd(II) by olefin or carbon monoxide in the presence of a base *in situ*. Two reaction pathways were proposed for this reaction (**Scheme 2**). In path a, oxidative addition of aryl halide to Pd(0) affords arylpalladium complex **i**, and then the aryl-carboalkoxypalladium species **ii** was formed by a nucleophilic attack of alcohol on the carbon monoxide on palladium. The reductive elimination of **ii** gives ester, and Pd(0) is regenerated. In the latter pathway (path b), the acylpalladium species **iii** is formed from arylpalladium complex **i** coordinated by carbon monoxide, and then a nucleophilic attack of alcohol on the acyl group on palladium gives ester. The generated HX is neutralized by a tertiary amine, and Pd(0) is regenerated.

TABLE 1 Carbobutoxylation of Aryl and Benzyl Halides

Run	Halides	Catalyst	Time (h)	Product (% Yield)
1	C_6H_5I	$Pd(OAc)_2$	20	C_6H_5COOBu (70)
2	4-$MeOCOC_6H_4I$	$Pd(OAc)_2$	16	4-$MeOCOC_6H_4Bu$ (83)
3	4-$MeOC_6H_4I$	$Pd(OAc)_2$	16	4-$MeOC_6H_4COOBu$ (69)
4	2,6-$(CH_3)_2C_6H_3I$	$Pd(OAc)_2$	40	2,6,-$(CH_3)_2C_6H_3COOBu$ (63)
5	C_6H_5I	$PhPdI(PPh_3)_2$	30	C_6H_5COOBu (96)
6	C_6H_5Br	$PhPdBr(PPh_3)_2$	24	C_6H_5COOBu (78)
7	4-NCC_6H_4Br	$PdBr_2(PPh_3)_2$	14	4-NCC_6H_4COOBu (89)
8	$C_6H_5CH_2Cl$	$PdCl_2(PPh_3)_2$	40	$C_6H_5CH_2COOBu$ (45)

TABLE 2. Carbobutoxylation of Vinylic Halides

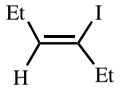
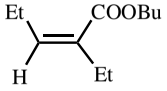
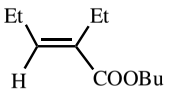
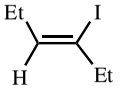
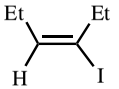
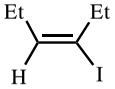
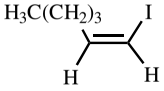
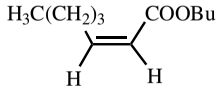
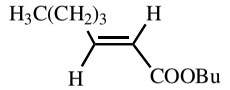
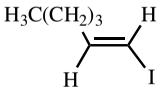
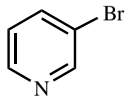
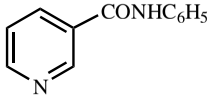
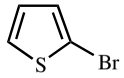
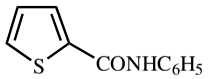
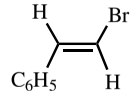
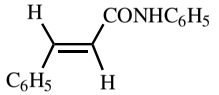
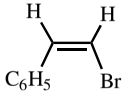
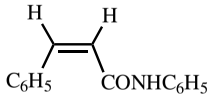
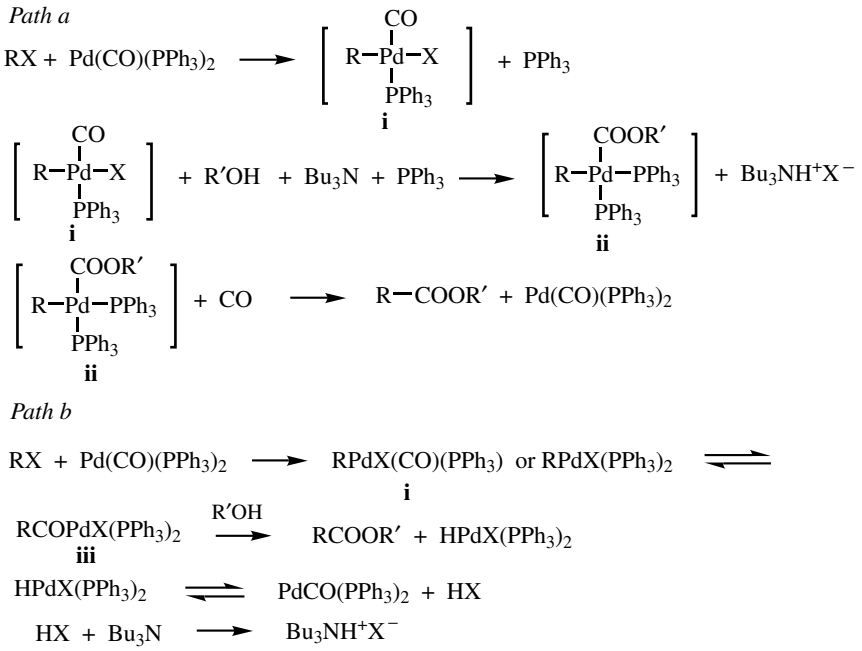
Halides	Catalyst	Temperature (°C)	Time (h)	Products		
	$Pd(OAc)_2$	100	17			
				(23)	(29)	(21)
	$PdI_2(PPh_3)_2$	100	4.5	(45)	(13)	(24)
	$PdI_2(PPh_3)_2$	100	4.5	(11)	(69)	(19)
	$PdI_2(PPh_3)_2$	60	40	(74)	(6)	
	$PdI_2(PPh_3)_2$	80	1.5			
				(79)	(6)	
	$PdI_2(PPh_3)_2$	100	2	(0)	(83)	

TABLE 3. Amidation of Aryl and Vinylic Halides

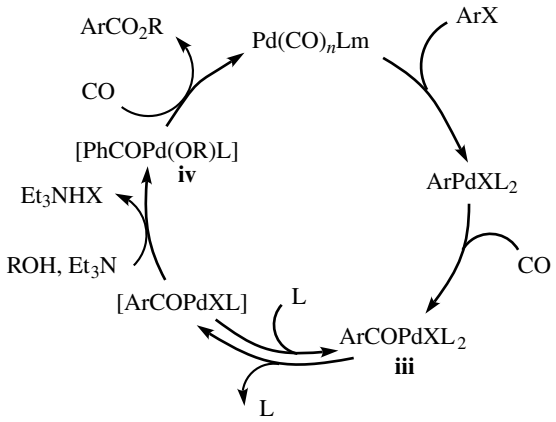
Run	Halides	Amine	Catalyst	Temperature (°C)	Time (h)	Product (%)	
1	C_6H_5Br	$C_6H_5NH_2$	$C_6H_5PdBr(PPh_3)_2$	100	3.5	$C_6H_5CONHC_6H_5$	(94)
2	C_6H_5Br	$C_6H_5CH_2NH_2$	$PdBr_2(PPh_3)_2$	100	3	$C_6H_5CONHCH_2C_6H_5$	(79)
3	$4\text{-}MeOCOC_6H_4Br$	$C_6H_5NH_2$	$PdBr_2(PPh_3)_2$	100	3.5	$4\text{-}MeOCOC_6H_4CONHC_6H_5$	(86)
4	$4\text{-}MeOC_6H_4Br$	$C_6H_5NH_2$	$PdBr_2(PPh_3)_2$	100	10	$4\text{-}MeOC_6H_4CONHC_6H_5$	(76)
5	$4\text{-}NO_2C_6H_4Br$	$C_6H_5NH_2$	$PdBr_2(PPh_3)_2$	100	7.5	$4\text{-}NO_2C_6H_4CONHC_6H_5$	(57)
6		$C_6H_5NH_2$	$PdBr_2(PPh_3)_2$	100	5.5		(65)
7		$C_6H_5NH_2$	$PdBr_2(PPh_3)_2$	100	2		(63)
8		$C_6H_5NH_2$	$PdBr_2(PPh_3)_2$	60	3		(81)
9		$C_6H_5NH_2$	$PdBr_2(PPh_3)_2$	60	4		(80)



Scheme 2. Possible reaction pathway.

During the course of the mechanistic study of keto-ester formation in the double carbonylation of aryl or benzyl halide,[6]–[11] Ozawa and Yamamoto proposed that ester formation would proceed via path b.[10]

The aroylpalladium species **iii** (**Scheme 3**) serves as an intermediate to give ester. A phosphine ligand is dissociated, and then the intermediate aroyl–alkoxide complex **iv** is formed upon reaction with the alcohol and base, and reductive elimination of aroyl and alkoxide ligands affords ester.

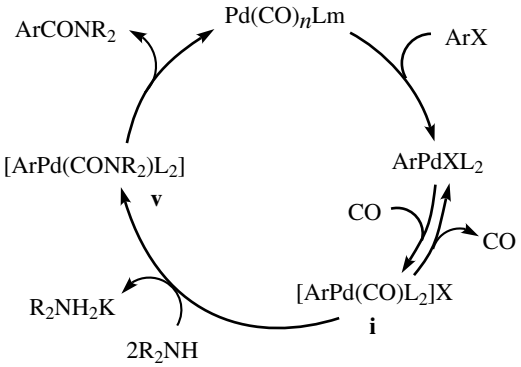


Scheme 3. Reaction mechanism of the formation of ester.

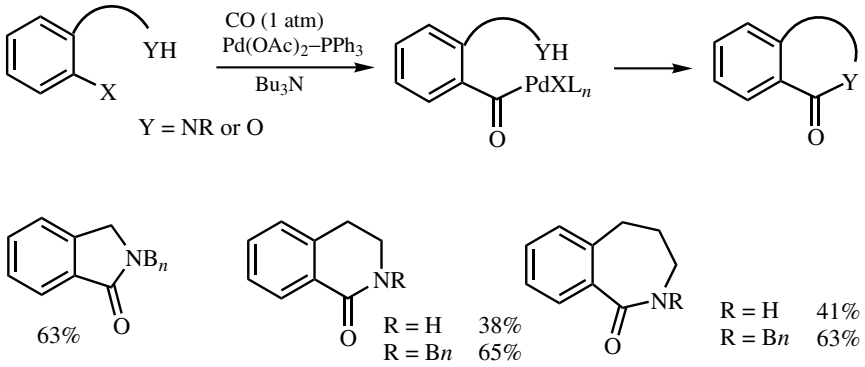
The mechanism of the formation of amide is different from that of ester (**Scheme 4**).[11] It is generally believed that amide is formed by a nucleophilic attack of amine on an aroylpalladium complex. However, using the trimethylphosphine ligands, a reaction was

proposed to give an aryl-carbamoylpalladium complex **v** that gives amide by reductive elimination.[9]

By application of this method to intramolecular cyclization, a novel method of synthesizing benzolactams and benzolactones has been developed,[12]–[16] and many heterocyclic compounds have been synthesized using this method (**Scheme 5**).



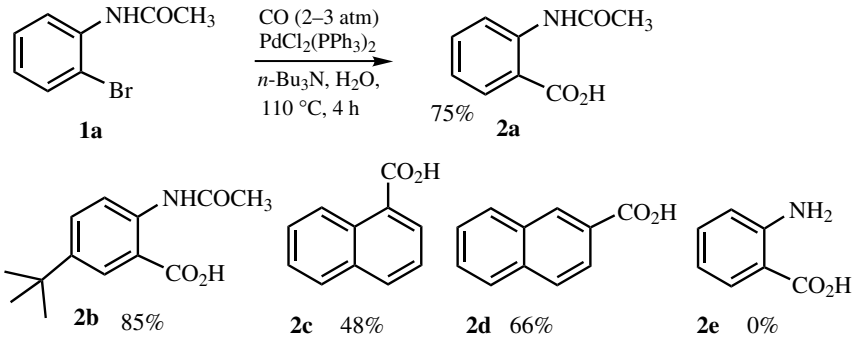
Scheme 4. Reaction mechanism of the formation of amide.



Scheme 5. Synthesis of lactams.

In the presence of water, we can obtain carboxylic acid. Using the phase-transfer technique, Pd-catalyzed carbonylation of organic halide was reported by Cassar (Eq. 3).[17] The carbonylation reaction was carried out by mixing an aqueous solution of NaOH with a xylene solution of the $Pd(PPh_3)_4$ in the presence of salt, $PhCH_2NEt_3Cl$. Tilley reported the synthesis of anthranilic acid using this method.[18] Pd-catalyzed carbonylation of 2-bromoaniline did not afford anthranilic acid **2e** (**Scheme 6**), but N-acetylated 2-bromoaniline **1a** afforded the desired *N*-acetylanthranilic acid **2a** in high yield. Carbonylation of aqueous media under 1 atm pressure in the presence of palladium complexes without phosphine ligand and some bases leads to the formation of aromatic acid.[19]

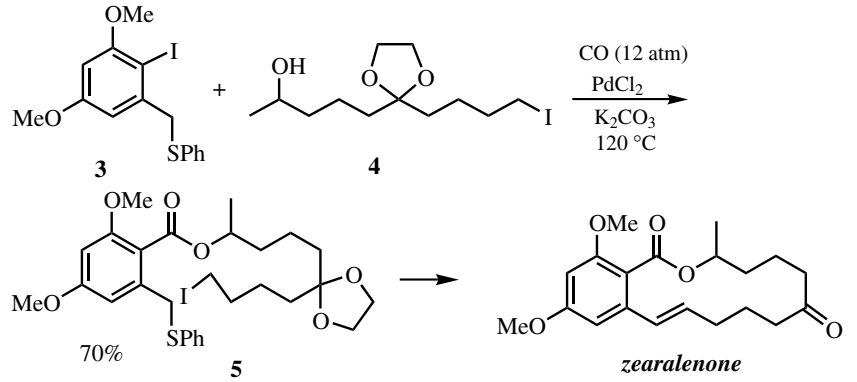
$$RX + CO\ (5\ atm) + 2\ NaOH \xrightarrow[\substack{NaOH\ aqueous/xylene \\ PhCH_2NEt_3Cl}]{Pd(PPh_3)_4,\ 95\ ^\circ C} RCOONa + NAX \qquad (3)$$



Scheme 6. Synthesis of aroylacids using Pd-catalyzed carbonylation.

Since the reaction proceeds under an atmospheric pressure of carbon monoxide, a balloon filled with carbon monoxide can be used. Moreover, a stable divalent palladium complex can be used. Therefore, many syntheses of ester, amide, or carboxylic acid from aryl or benzyl halides have been reported.

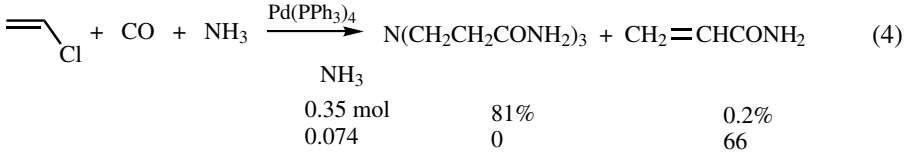
Tsuji reported a total synthesis of zearalenone using Pd-catalyzed carbonylation.[20] In this total synthesis, they synthesized the key compound by Pd-catalyzed carbonylation. The reacion of 1-iodo-2-phenylthiomethyl-4,6-dimethoxybenzene **3** (**Scheme 7**) with 10-iodo-6,2′-[1,3]dioxolane-2-decanol **4** was carried out under carbon monoxide (12 atm) to afford the corresponding ω-iodoalkyl ester of 2-phenylthiomethyl-4,6-dimethoxybenzene **5**.



Scheme 7. Total synthesis of zearalenone.

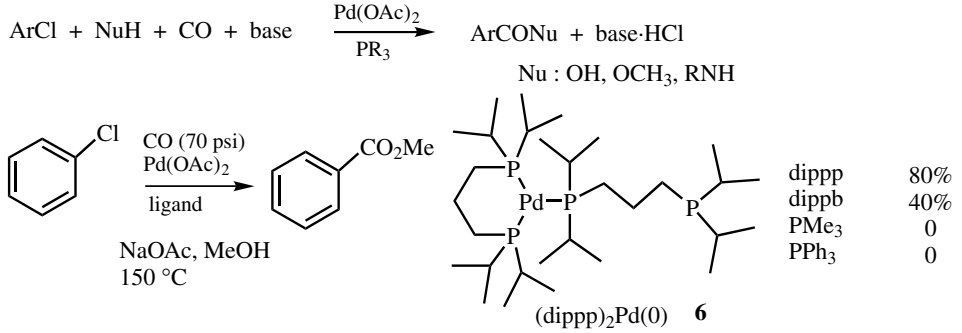
In the presence of molecular sieves under base-free conditions, organic halides were successfully converted into carboxylic acids or esters with water or alcohol, respectively, under carbon monoxide pressure by a palladium catalyst in good yields.[21]

In these reactions, aryl bromides or iodides can be used, but aryl chlorides are generally unreactive. This is one serious limitation, because the utilization of aryl chlorides is obviously more attractive as starting materials than that of aryl bromides or iodides, and this would hinder industrial utilization. Thus, various attempts have been made to use aryl chlorides. It is interesting that nonsubstituted vinyl chloride provided carbonylated products (Eq. 4).[22]



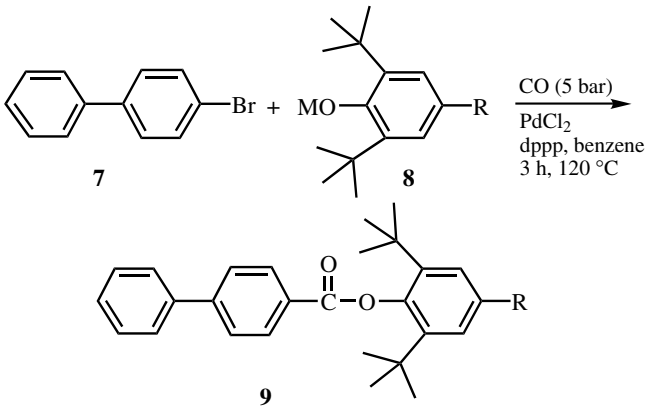
(4)

The chelate-stabilized, electron-rich Pd(0) complex, $(dippp)_2Pd(0)$ **6** (**Scheme 8**) was an efficient catalyst for carbonylation of aryl chlorides.[23] Alper reported that bis(tricyclohexylphosphine)palladium dichloride is an active catalyst for the carbonylation of aryl chlorides to carboxylic acid.[24] Neat aryl chlorides reacted with carbon monoxide and aqueous KOH in the presence of catalytic amounts of this catalyst to give the corresponding carboxylic acids upon subsequent acidification. The Pd-catalyzed amidation of electron-deficient aryl chloride readily afforded a carbonylation product in the presence of low CO pressure and a slight excess of an iodide salt.[25] Alkoxycarbonylation of aryl chlorides using palladium catalyst $Pd(PCy_3)_2(dba)$ has been reported.[26]



Scheme 8. Pd-catalyzed carbonylation of aryl chloride.

Recently, an efficient carbonylation of aryl bromide with a hindered phenoxy moiety has been reported. In this reaction, potassium ion as a countercation gave a good yield (**Scheme 9**).[27],[28] The reaction of **7** with potassium salt of **8** gave hindered phenyl ester **9** in high yield (**Table 4**).



Scheme 9. Aryloxycarbonylation of 2,6-di-*tert*-butylphenyl ester.

TABLE 4. Synthesis of Hindered Phenyl Ester

M	R	Temp (°C)	Yield (%)
K	Me	100	84
K	Me	120	80
K	OMe	120	77
Na	OMe	120	60
Li	OMe	120	0

Although acid fluorides are a versatile class of compounds, their preparation requires limited kinds of starting compounds and fluorinating agents, which are hard to handle. A new method for the synthesis of acid fluoride by the carbonylation of aryl iodides in the presence of CsF has been reported (**Table 5**).[29],[30]

$$\mathrm{ArI} + \mathrm{CO} + (\mathrm{CH_3})_2\mathrm{CHOH} \xrightarrow{\mathrm{CsF},\ \mathrm{PdCl_2(PPh_3)_2}} \mathrm{ArCOF} \qquad (5)$$

C. CARBONYLATION OF ALKYL HALIDE

Application of aliphatic halides to Pd-catalyzed carbonylation has been hindered because of the lower reactivity for oxidative addition of alkyl halides to a low-valent palladium complex and because of the occurrence of β-hydrogen elimination from σ-alkylpalladium complex generated by the oxidative addition of alkyl halide. However, some allylic or benzylic compounds, such as allylic or benzylic halides, esters, ethers, carbonates, and alcohols, have successfully been carbonylated to give carboxylic acid derivatives. Pd-catalyzed carbonylations of benzyl halides in homogeneous systems and biphasic systems using phase- transfer catalysts have widely been investigated.[31] When benzyl chloride was treated with carbon monoxide (200 psi) and MeOH in the presence of a base and a catalytic amount of $PdCl_2(PPh_3)_2$, carboalkoxylation of benzyl chloride was achieved.[32] The best yield was obtained using 1,8-bis(dimethylamino)naphthalene (proton sponge) as a base. The carbonylation of α-bromoacetophenone in methanol gave α-carbomethoxyacetophenone in 64% yield (Eqs. 6 and 7).

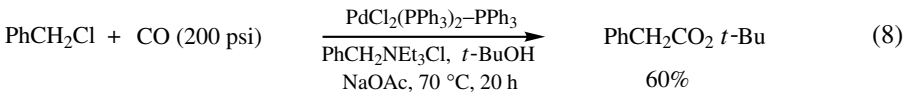
$$\mathrm{PhCH_2Cl} \xrightarrow[\mathrm{MeOH,\ proton\ sponge}]{\mathrm{CO\ (200\ psi)},\ \mathrm{PdCl_2(PPh_3)_2{-}PhCH_2Cl}} \mathrm{PhCH_2COOMe} \quad 91\% \qquad (6)$$

$$\mathrm{PhCOCH_2Br} \xrightarrow[\mathrm{PdCl_2(PPh_3)_2}\ \mathrm{proton\ sponge}]{\mathrm{MeOH,\ CO}} \mathrm{PhCOCH_2COOMe} \quad 64\% \qquad (7)$$

TABLE 5. Synthesis of Acid Fluoride

Substrate	Solvent	*P*co	Temperature (°C)	Conversion (%)	Yield (%)
4-ClC_6H4I	CH_3CH_2CN	1	80	91	80
4-$MeOC_6H_4I$	CH_3CH_2CN	1	80	87	82
2-Iodothiophene	CH_3CH_2CN	1	80	53	100
C_6H_5Br	CH_3CN	1	80	15	0
C_6H_5Br	CH_3CN	150	150	64	19
1-Bromonaphthalene	CH_3CN	150	150	99	98

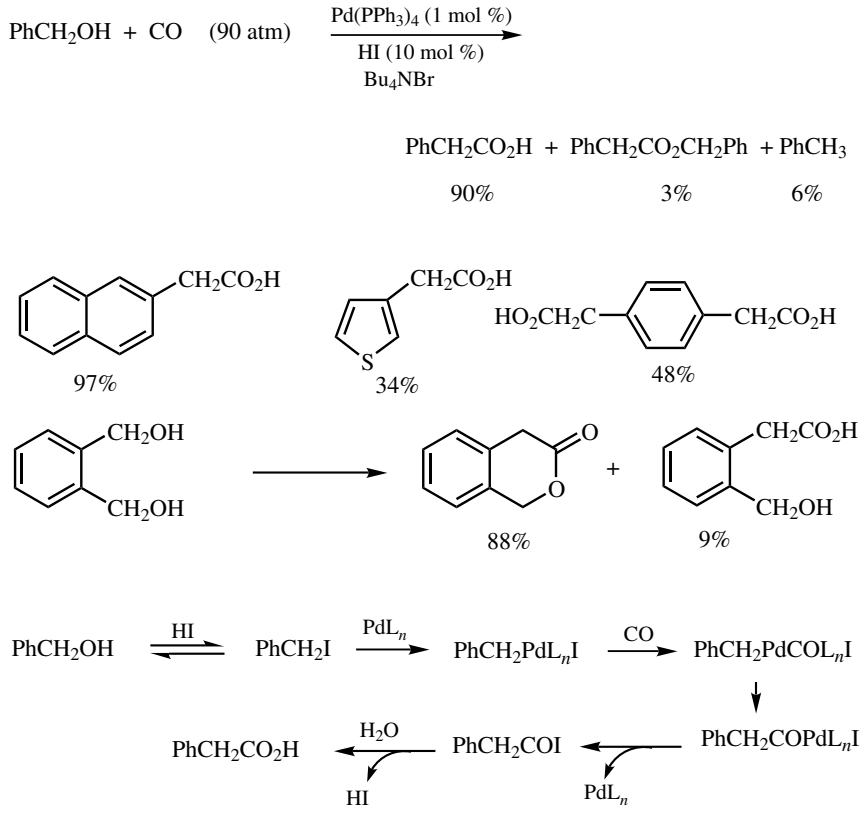
It has been shown that in the Pd-catalyzed carbonylation of benzyl halides, the ligand attached to the metal has a great effect on the course of the reaction.[33],[34] Although Pd-catalyzed carbonylation of benzyl halide is well documented, the preparation of *tert*-butyl ester has been described.[35]



(8)

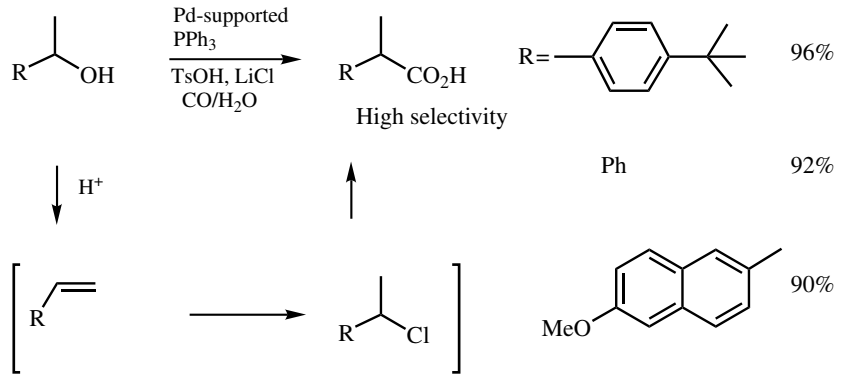
Catalytic carbonylation of aryl methanols has been less explored (**Scheme 10**). Direct carbonylation of benzyl alcohol to phenyl acetic acid has been reported.[36]

The process is promoted by HI in an aqueous solution but not by HCl.[37] By the interaction of benzyl alcohol with HI, benzyl iodide is formed and then it is oxidatively added to Pd(0) to form a benzylpalladium complex. It reacts with CO to give a benzyl(carbonyl)palladium complex, followed by CO insertion to produce a phenylacetylpalladium complex. Reductive elimination of $PhCH_2COI$ and its hydrolysis gives the corresponding acid.



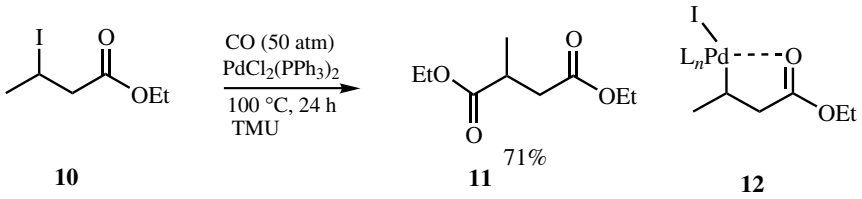
Scheme 10. Carbonylation of aromatic methanols.

Utilization of a polymer-supported palladium catalyst in the presence of phosphine ligands, TsOH, and LiCl significantly improved the regioselectivity on the carbonylation of 1-arylethanol to 2-arylpropionic acids (**Scheme 11**).[38]



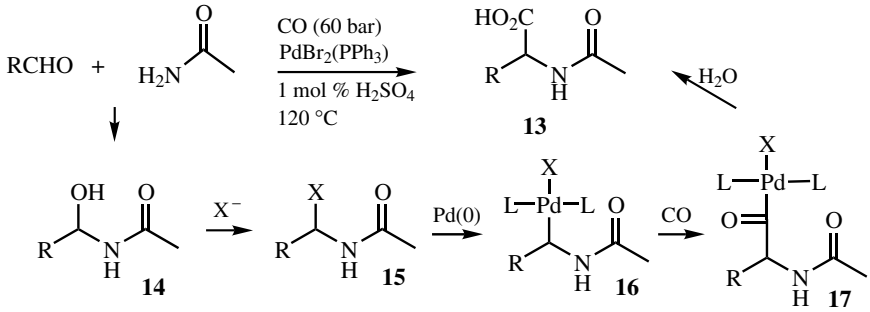
Scheme 11. Polymer-supported palladium complex.

The carbonylation of ethyl 3-iodobutanoate **10** (**Scheme 12**) was attempted because the intermediary σ-alkylpalladium complex **12** would be stabilized by the carbonyl group of ester and β-hydrogen elimination would not occur. The reaction was performed in *N*,*N*,*N*′,*N*′-tetramethylurea (TMU) in the absence of a base. The desired diester **11** was obtained in 71% yield.[39]

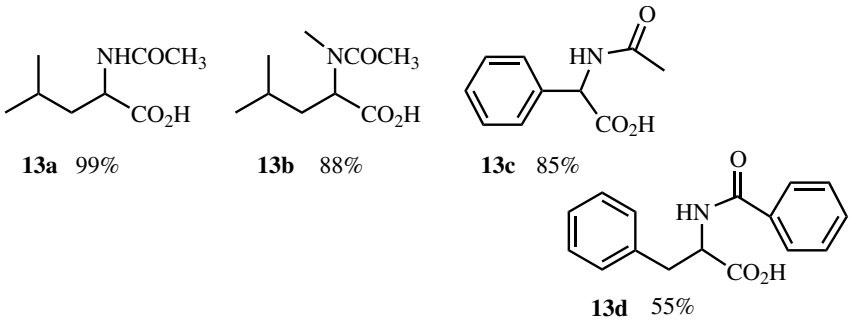


Scheme 12. Carbonylation of ethyl 3-iodobutanoate.

An efficient three-component coupling reaction for the synthesis of *N*-acyl-α-amino acids from aldehydes, amides, and carbon monoxide, namely, amidocarbonylation, was first described by Wakamatsu in 1971.[40] Recently, amidocarbonylation has successfully been catalyzed by palladium (**Scheme 13**).[41],[42] The reaction would proceed as follows. Condensation of aldehyde with amide affords **14**, whose hydroxyl group is converted into halide **15**. Oxidative addition of alkyl halide **15** to Pd(0) gives σ-alkylpalladium complex **16**. Then insertion of carbon monoxide into the carbon–Pd bond of **16** gives **17**, and then nucleophilic attack by H_2O occurs to give amino acid derivative **13**.

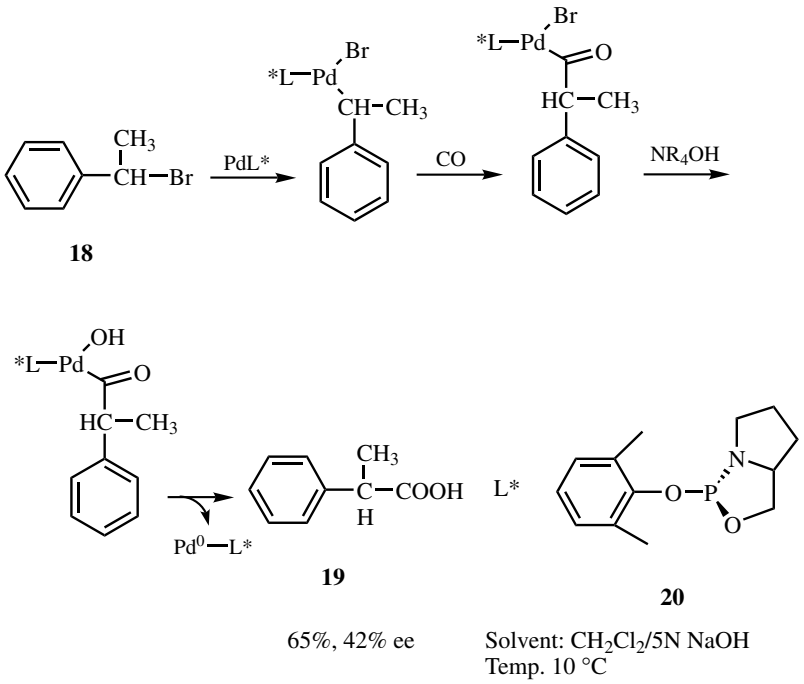


Scheme 13. Pd-catalyzed amidocarbonylation. (*Continued*)



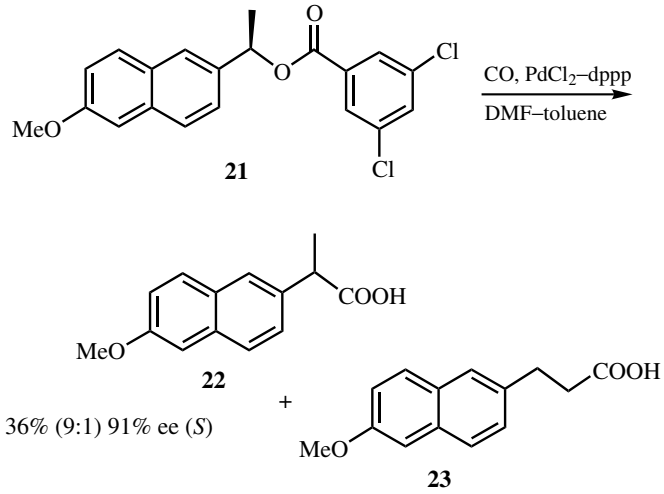
Scheme 13. Pd-catalyzed amidocarbonylation.

Arzoumanian reported the first example of the use of a metal catalyst bearing chiral ligands under phase-transfer conditions leading to optically active substances.[43] The Pd-catalyzed carbonylation of α-methylbenzyl bromide **18** (**Scheme 14**) was carried out using 5 N NaOH and CH_2Cl_2 at room temperature (r.t.) and 1 atm of pressure of carbon monoxide in the presence of $Pd(dba)_2$, and a series of 2-substituted 3,1,2-oxazaphospholane **20** resulted in the formation of 2-phenylpropionic acid **19** with significant enantiomeric excess.



Scheme 14. Asymmetric carbonylation of α-methylbenzyl bromide.

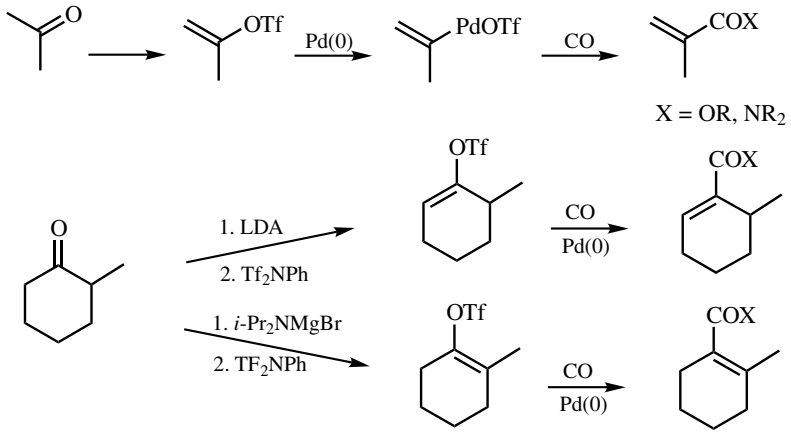
Lee reported that selected chiral ester **21** (**Scheme 15**) could be carbonylated directly to optically active 2-arylpropanoic acid **22** with net inversion of its configuration at carbon.[44]



Scheme 15. Synthesis of naproxene.

D. CARBONYLATION OF ARYL OR ENOL TRIFLATE

Stille[45]–[47] and Ortar[48] independently reported that enol triflate, which was easily prepared from ketones and triflic anhydride in the presence of 2,3-di-*tert*-butyl-4-methyl pyridine, could oxidatively be added to a low-valent palladium complex to give an aryl- or vinylpalladium complex. Stille succeeded in transmetalation of this complex with vinylstannane to give 1,3-diene.[45] Ortar reported that enol triflate could react with olefin to produce 1,3-diene (**Scheme 16**).[48]

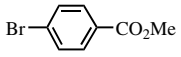


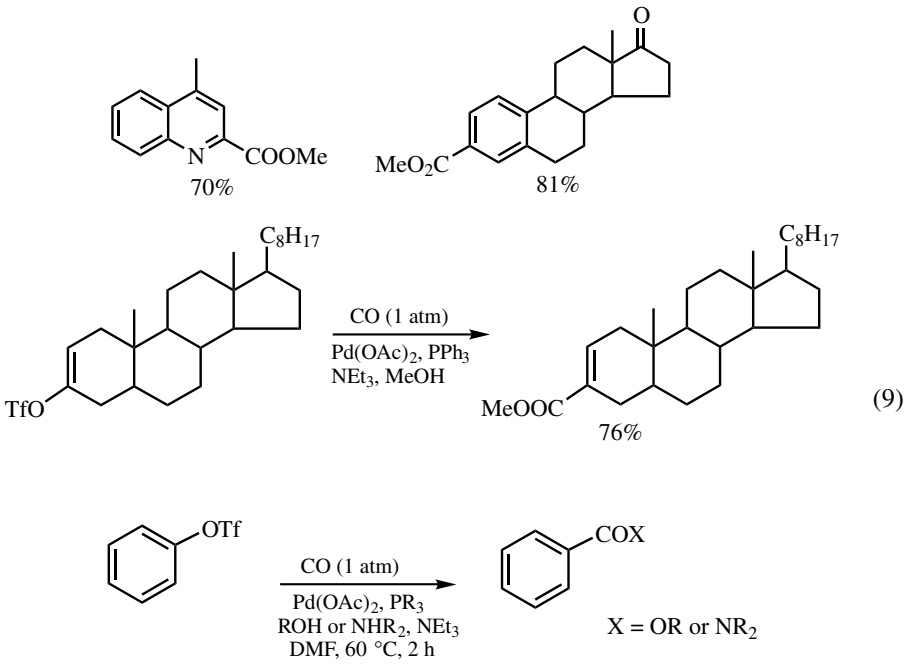
Scheme 16. Carbonylation of enol triflate.

These results indicate that we can introduce various substituents onto the carbonyl carbon using a palladium catalyst.[49]–[58] Thus, aryl triflates were converted into aryl esters or amides (**Scheme 17**, **Table 6**), and enol triflates could be converted into α,β-unsaturated esters or amides by a Pd-catalyzed reaction with carbon monoxide and alcohols or amines (Eq. 9).[49],[50]

TABLE 6. Pd-Catalyzed Carbonylation of Aryl Triflates

Trflate	Phosphine	ROH or NHR_2	Temperature (°C)	Time (°C)	Yield (%)
1-Naphthyl triflate	PPh_3	^{i}PrOH	60	2	80
1-Naphthyl triflate	PPh_3	piperidine	60	1.5	70
4-$MeOC_6H_4OTf$	DPPF	piperidine	80	1	59
3-$MeOC_6H_4OTf$	DPPF	piperidine	80	1	68
4-$MeO_2CC_6H_4OTf$	DPPF	MeOH	60	1	77
4-BrC_6H_4OTf	DPPF	MeOH	40	20	50[a]

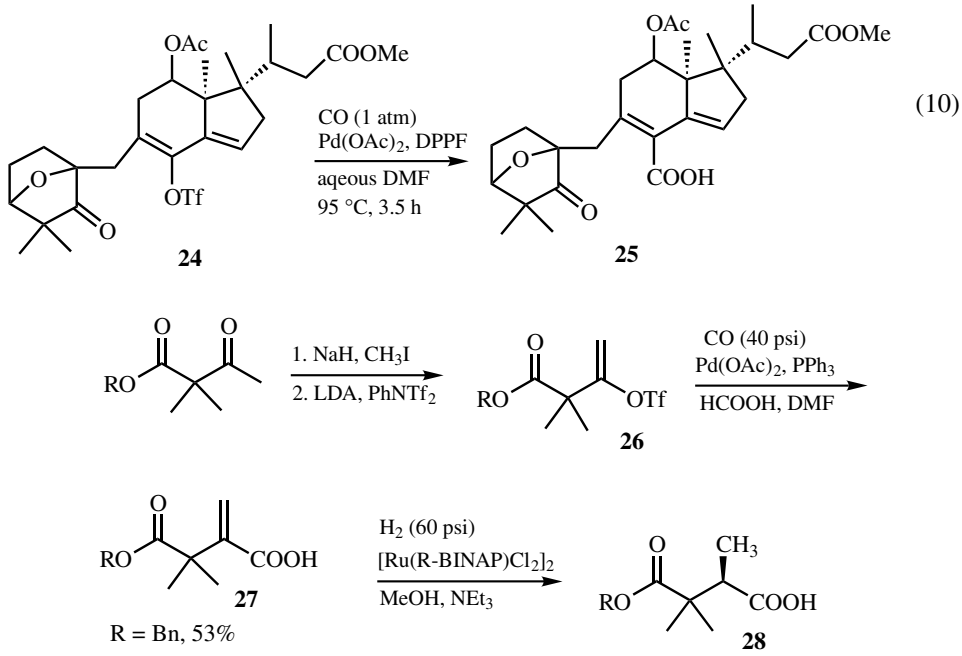
[a]  was obtained.



Scheme 17. Carbonylation of aryl triflate.

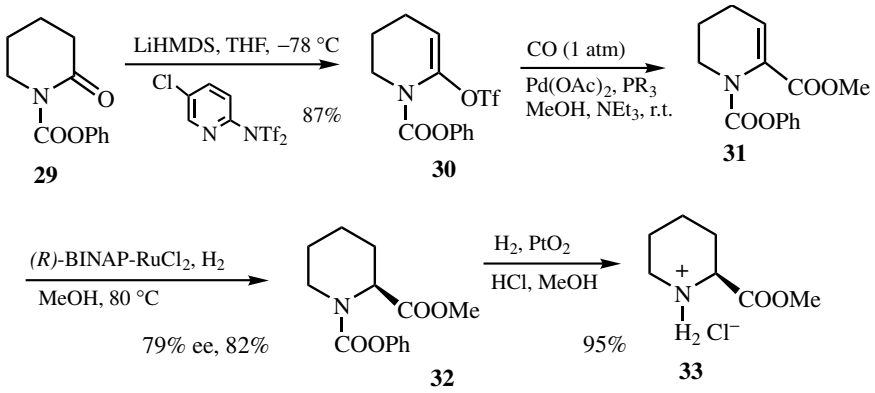
Murai and Masamune succeeded in the total synthesis of glycinoeclepin. In this total synthesis, they used Pd-catalyzed carbonylation of enol triflate **24** to synthesize intermediate ester **25**.[59]

Freskos reported the synthesis of chiral succinate using Pd-catalyzed carbonylation of enol triflate **26** (**Scheme 18**) followed by asymmetric hydrogenation of resulting α,β-unsaturated ester **27** using a ruthenium complex.[60],[61] In the absence of HCOOH, the yield was low (15–20%). Similarly, when water was substituted for formic acid, low product yields (15–20%) were observed. As one possible pathway to produce **27**, reductive elimination from the palladium complex to yield a mixed anhydride derived from the product and triflic acid would be considered.



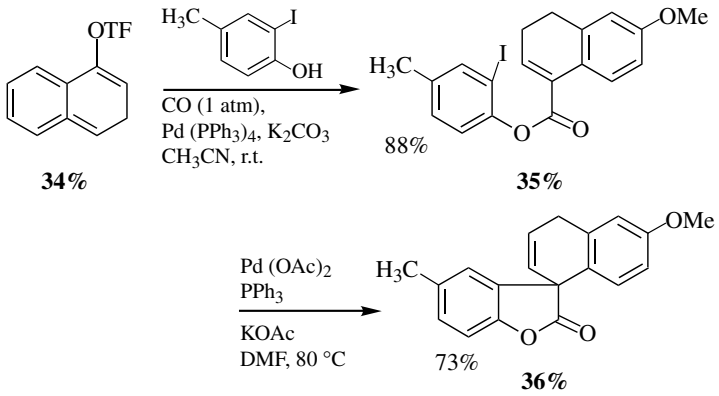
Scheme 18. Synthesis of chiral succinate.

Synthesis of enol triflate from N-acylated lactam has been reported.[62],[63] Comins synthesized (*S*)-pipecolic acid **33** (**Scheme 19**) from enol triflate **30** of piperidone derivative **29** by Pd-catalyzed carbonylation followed by aymmetric hydrogenation using a ruthenium catalyst with (*R*)-BINAP.[62] Preparation of the first enantiopure lactam-derived enol triflate from (*S*)-pyroglutamic acid was achieved, and the synthesis of a proline analog was obtained in good yield (86% de).[63]



Scheme 19. Synthesis of methyl ester of (*S*)-pipecolic acid.

A convenient synthesis of 3-spiro-fused benzofuran-2(3*H*)-ones was reported *via* Pd-catalyzed chemoselective carbonylation of vinyl triflates in the presence of *o*-iodophenols, followed by a regioselective intramolecular Heck reaction (**Scheme 20**).[64]



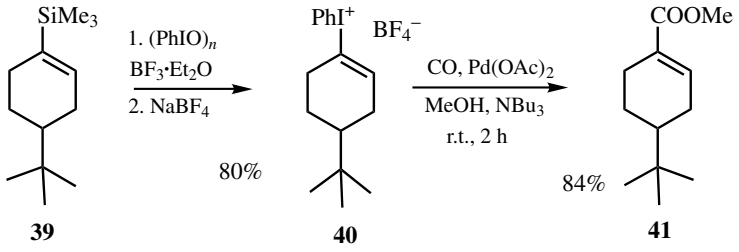
Scheme 20. Synthesis of 3-spiro-fused benzofuran-2-(3*H*)-one.

E. CARBONYLATION OF PSEUDO ARYL OR VINYL HALIDE

The Pd catalyzed carbonylation reaction of arenediazonium tetrafluoroborates **37** was carried out in the presence of sodium carboxylate in acetonitrile at room temperature to give mixed anhydrides **38** in good yields (**Table 7**).[65],[66] These results indicate that aniline derivatives can be used as pseudo aryl halide via diazonium salt and converted into arenecarboxylic acid derivatives.

$$\underset{\mathbf{37}}{ArN_2BF_4} + CO\ (9\ kg/cm^2) \xrightarrow[RCO_2Na,\ CH_3CN\ r.t.,\ 5\ h]{Pd(OAc)_2} \underset{\mathbf{38}}{ArCO_2COR} \qquad (11)$$

Vinyl iodonium salt **40**, which is highly effective as an activated species of vinyl iodide, could be synthesized from vinyl silanes **39** by the reaction with iodosyl benzene and triethyloxonium tetrafluoroborate.[67],[68] Thus, from vinyl silane, α,β-unsaturated ester **41** could be synthesized by Pd-catalyzed carbonylation (Eq. 12). Alkynylphenyliodonium tosylates **42** were easily prepared from 1-alkynes with PhI(OH)OTs or by reaction

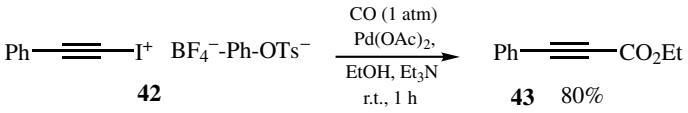


(12)

TABLE 7. Preparation of Mixed Acid Anhydride

$C_6H_5CO_2COH$	86%	4-$BrC_6H_4CO_2COMe$	83%
$C_6H_5CO_2COMe$	73%	4-$BrC_6H_4CO_2COPh$	59%
4-$MeC_6H_4CO_2COH$	74%	4-$IC_6H_4CO_2COMe$	68%
2-$MeOC_6H_4CO_2COMe$	56%	4-$NO_2C_6H_4CO_2COMe$	65%

of 1-trimethylsilyl-1-alkynes with iodosylbenzene activated with $BF_3{\cdot}Et_2O$ followed by treatment with sodium tosylate. Alkynylphenyliodonium tosylate **42** was carbonxylated in EtOH or MeOH in the presence of a base and a catalytic amount of a palladium catalyst. The carbonylation was carried out at room temperature under an atmosphere of carbon monoxide for 1 h to give ester **43** in high yield (Eq. 13).[69]



42 **43** 80% (13)

Since the discovery of Pd-catalyzed carbonylation of aryl, vinyl, and benzyl halides by Heck in 1974, this reaction has been used for the synthesis of ester, amide, acid, and acid anhydride. We can use enol triflate, aryl triflate, aniline derivatives, and vinyl silane as the pseudo aryl or vinyl halide. This reaction has now been further extended for the synthesis of aldehyde and ketone by combination with transmetalation. These reactions have widely been used in organic syntheses, especially the syntheses of biologically active substances in the field of fine chemistry and the syntheses of natural products.

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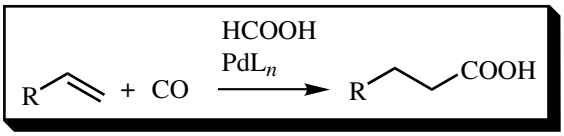

VI.2.1.1.2 Palladium-Catalyzed Hydrocarboxylation and Related Carbonylation Reactions of π-Bonded Compounds

BASSAM EL ALI and HOWARD ALPER

A. INTRODUCTION

The catalytic hydrocarbonylation and hydrocarboxylation of olefins, alkynes, and other π-bonded compounds are reactions of important industrial potential.[1]–[7] Various transition metal complexes, such as palladium, rhodium, ruthenium, or nickel complexes, have widely been used in combination with phosphines and other types of ligands as catalysts in most carbonylation reactions.[11]–[14] The reactions of alkenes, alkynes, and other related substrates with carbon monoxide in the presence of group VIII metals and a source of proton affords various carboxylic acids or carboxylic acid derivatives.[1],[3],[5],[6],[11] While many metals have successfully been employed as catalysts in these reactions, they often lead to mixtures of products under drastic experimental conditions.[1],[6],[11]–[13] In the last twenty years, palladium complexes are the most frequently and successfully used catalysts for regio-, stereo-, and enantioselective hydrocarbonylation and hydrocarboxylation reactions.[1],[5]–[11]

It is well known that homogeneous catalysis, in comparison to its heterogeneous counterpart, has the advantage of high activity and high selectivity achieved under mild conditions. However, the major problem of homogeneous catalytic systems regarding the difficulty of separating the catalyst from the reaction products has, in most cases, not yet been solved. The use of liquid–liquid two-phase systems is the alternative method to solve this particular problem. Over the last decade many publications, accounts, and reviews have appeared in the literature reporting palladium complex-catalyzed carbonylation reactions in homogeneous, heterogeneous, and two-phase systems.[1],[14] However, the existing methodologies are still limited by the low selectivity and by the need for high pressures of carbon monoxide.

This section focuses on recent developments in Pd-catalyzed hydrocarbonylation, hydrocarboxylation, and other related reactions of π-bonded compounds. Recent achievements in thiocarbonylation of unsaturated compounds catalyzed by palladium and phosphine ligands will also be discussed.

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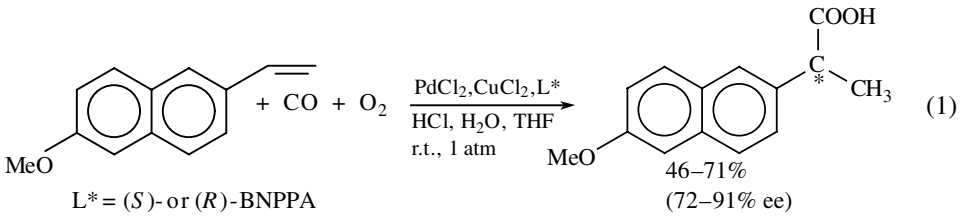
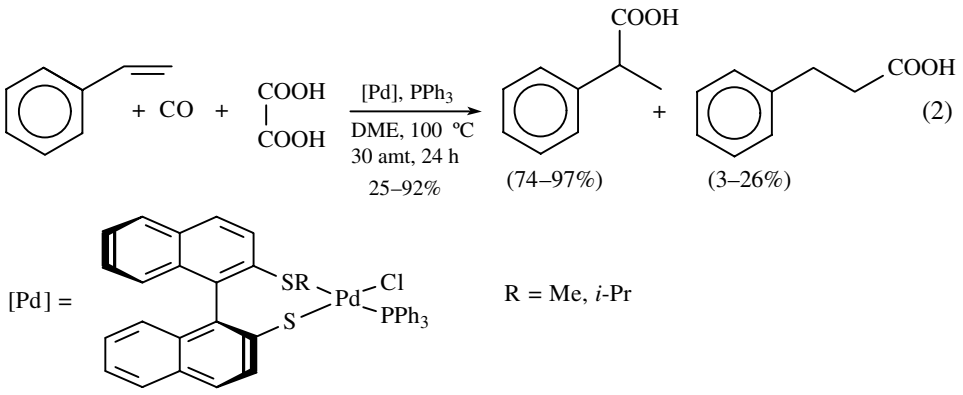
B. HYDROCARBOXYLATION OF π-BONDED COMPOUNDS

The one-step catalytic synthesis of carboxylic acids via the carbonylation of olefins in the presence of water catalyzed by transition metal complexes is known as the hydrocarboxylation reaction. Existing patents and literature publications reveal that palladium complexes are among the most active; however, some reactions need drastic conditions (high pressures and high temperatures) to effect this transformation. These reactions generally afford mixtures of straight- and branched-chain carboxylic acids.[1],[5]–[13] In the beginning of the 1980s a convenient method was discovered for the regioselective hydrocarboxylation of olefins to branched-chain acids. The process was successfully achieved under mild conditions to form acids in high yields by the use of carbon monoxide and oxygen in acidic media (HCl), and catalytic amounts of palladium chloride and copper(II) chloride at room temperature.[15] The concentration of HCl and the presence of dioxygen have a significant influence on the rate and yield of the reaction. The application of this simple catalytic process enables one to synthesize some important nonsteroidal anti-inflammatory agents such as ibuprofen and naproxen. In fact, the hydrocarboxylation reaction of 2-vinyl-6-methoxynaphthalene under the same experimental conditions but in the presence of (*R*)-(−) or (*S*)-(+)-binaphthyl-2,2-dyl hydrogenphosphate (BNPPA) gave optically active naproxen (72–91% ee) in good chemical yields (46–71%) (Eq. 1).[16]



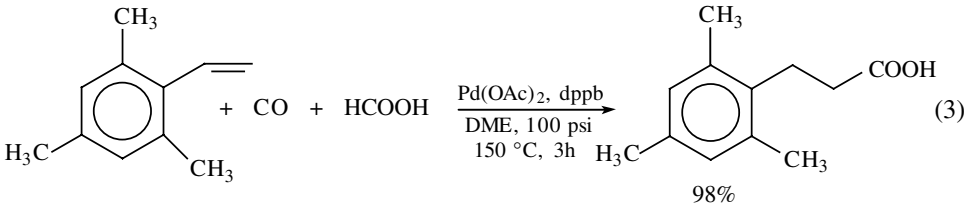
(1)

Recently, new mononuclear and dinuclear palladium complexes containing one neutral and one anionic sulfur donor center derived from the atropisomeric thiol-thioether derivative (RHbinas) were used as catalysts for the hydrocarboxylation of styrene in the presence of triphenylphosphine and oxalic acid. The new complexes are active catalysts for the hydrocarboxylation of styrene, showing a high regioselectivity toward the branched product (97%) under relatively mild conditions (Eq. 2).[17]



(2)

The selective synthesis of linear carboxylic acids is a challenging task for many chemists working in this area. Linear carboxylic acids were obtained in excellent yields and selectivities (80–100%) by the reaction of olefins such as 2,4,6,-trimethylstyrene with formic acid catalyzed by palladium acetate in the presence of 1,4-bis(diphenylphosphino)butane (dppb) at 100 psi of carbon monoxide and 150 °C in 1,2-dimethoxyethane as the solvent (Eq. 3).[18] Formic acid acts as a hydride source in this process and no reaction was observed in the absence of CO. Useful bifunctional products were obtained from the hydrocarboxylation reaction, including ketoacids, diacids, and cyanoacids. The application of the active catalytic system $Pd(OAc)_2$–dppb–HCO_2H–CO to methylenecycloalkanes led to high yields and excellent selectivities for cycloalkylacetic acids (Eq. 4).[19] Some of these acids have anti-inflammatory properties or are important intermediates in medicinal chemistry.[20]



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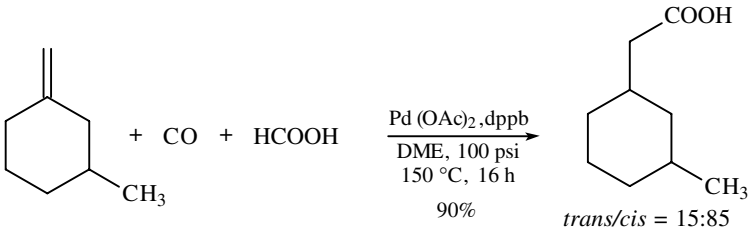
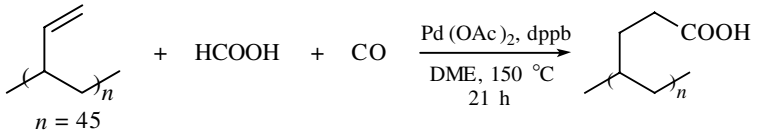


(4)

The regioselective hydrocarboxylation of alkenes and methylenecycloalkanes to linear carboxylic acids was also achieved in good yields and selectivity by the use of oxalic acid (in place of formic acid) as the source of hydrogen and carbon monoxide, with the catalytic system $Pd(OAc)_2$–dppb–PPh_3 at 150 °C and 20 atm.[20]

The production of polymers with carboxylated backbones is of particular interest due to potential application of such polymers in films and surface coating.[21],[22] The polycarboxylic acids can now be easily prepared via catalytic hydrocarboxylation of 1,2-polybutadiene with full conversion of the pendant double bonds and complete selectivity for the straight-chain acid units in the presence of the catalytic system $Pd(OAc)_2$–dppb–HCO_2H–CO (Eq. 5).[23] Furthermore, the oxidative carbonylation of 1,2-polybutadiene using $PdCl_2$–$CuCl_2$–HCl–O_2–CO did occur with 44% conversion and 56% selectivity for hydrocarboxylation.



(5)

The hydrocarboxylation of 1,4- and 1,2-polybutadienes was previously studied with different Pd-based catalytic systems.[24] For example, the use of $PdCl_2(PPh_3)_2-SnCl_2$ led to the placement of carboxylic acid units at the 1,2-positions. Both 1,4- and 1, 2-carboxylate polymers are formed when the reaction was effected with $PdCl_2(PPh_3)_2$–PPh_3 at 170 °C in benzene, or with $PdCl_2$–$CuCl_2$ in THF.[24]

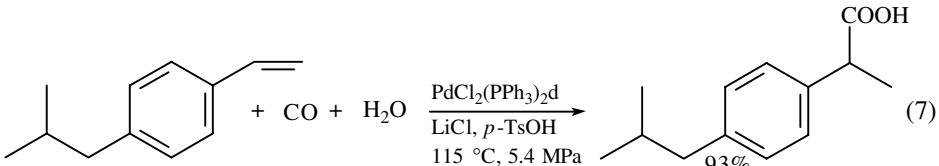
Interestingly, the hydrocarboxylation of fluorinated olefins [3,3,3-trifluoropropene (TFP) and pentafluorostyrene (PFS)] was realized to form useful fluorinated acids. The palladium complex $PdCl_2$(dppf) [dppf = 1,1-bis(diphenylphosphino)ferrocene] in the presence of $SnCl_2$ at 125 °C and at 10 atm CO showed the highest catalytic activity with TFP (yield = 93%, selectivity = 99% in linear acid), and the catalyst $PdCl_2$(dppb) afforded PFS hydrocarboxylation products in excellent yield and selectivity (Eq. 6).[25]

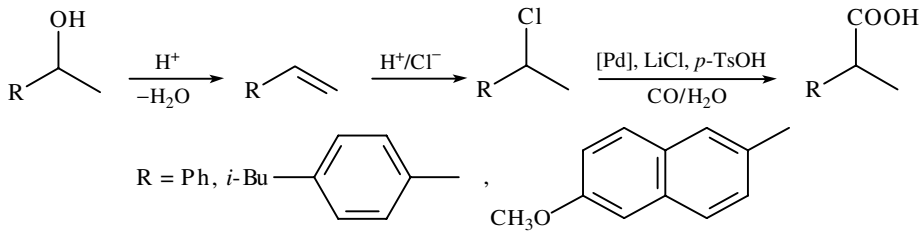
$$R_fCH{=}CH_2 + CO/H_2 \xrightarrow[AcOH-H_2O]{PdCl_2\,(dppf)} R_fCH_2CH_2COOH \qquad (6)$$

$R_f = CF_3, C_6F_5$

dppf = 1,1-bis (diphenylphosphino) ferrocene

Recently, Chaudhari and co-workers have published several papers on the direct catalytic hydrocarboxylation of vinyl aromatics, and indirectly via the carbonylation of 1-arylethanols into 2-arylpropanoic acids.[26]–[28] In fact, various substituted and nonsubstituted 2-arylpropanoic acids have been synthesized in high yields and excellent selectivity (up to 99.8%) by the catalytic carbonylation of vinyl aromatics. The catalytic system consists of $PdCl_2(PPh_3)_2$, H_2O, and CO in the presence of *p*-TsOH and LiCl as promoters (Eq. 7).[26] It is important to note that the reaction seems to proceed via the intermediate formation of 1-chloroethylaryl derivatives. Interestingly, the reaction is applicable to terminal as well as internal olefins forming the corresponding 2-arylpropanoic acids in good yields. On the other hand, styrene derivatives, formed *in situ* from 1-arylethanols, were selectively carbonylated into 2-arylpropanoic acids by using a homogeneous catalytic system consisting of $PdCl_2(PPh_3)_2$, *p*-TsOH, and LiCl (**Scheme 1**),[27] or palladium on carbon, γ-alumina, or H-ZSM-5, in the presence of a monophosphine ligand, *p*-TsOH, and LiCl.[28] High conversions and excellent selectivity for 2-arylpropanoic acids usually resulted from these reactions.





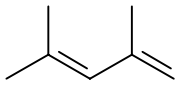
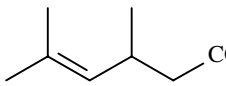
Scheme 1

In the last five years interesting publications have appeared on the hydrocarboxylation of olefins in aqueous-organic two-phase systems.[29],[30] The catalytic systems consist of water-soluble phosphine ligands and a palladium complex in an acidic medium, resulting in high yields and selectivities for the hydrocarboxylation of styrene derivatives and terminal olefins (Eq. 8).[31]

$$RCH{=}CH_2 + CO + H_2O \xrightarrow[HX\ (X = Cl^-, Br^-, I^-, PF6,^-...)]{Pd/P\ (C_6H_4SO_3Na)_3} RCH_2CH_2COOH + \underset{R = H,\ alkyl,\ aromatic}{\overset{\overset{COOH}{|}}{RCHCH_3}} \quad (8)$$

The hydrocarboxylation of higher olefins has not been completely solved because it requires mass transfer promoters due to their low water solubility.[31] For instance, the selectivity obtained during the hydrocarboxylation of 1-decene reached 90% with per(2,6-di-*o*-methyl)-*p*-cyclodextrin, versus 53% for 1-methyl-2-pyrrolidinone (one of the most suitable cosolvents) and 20% without a mass transfer promoter.

Di- and trisubstituted 1,3-dienes were converted to γ-δ-unsaturated acids by using the previously described catalytic system involving formic acid, carbon monoxide, and Pd-C/PPh_3/dppb in 1,2-dimethoxyethane (DME). The hydrocarboxylation of isoprene, for example, occurs under 6.2 atm of CO and at 110 °C to form the corresponding β-γ-unsaturated acid in 52% yield (Eq. 9).[32],[33]


+ HCO_2H + CO $\xrightarrow[DME,\ 100\ psi\ 110\ °C]{Pd\text{-}C,\ dppb,\ PPh_3}$

(9)

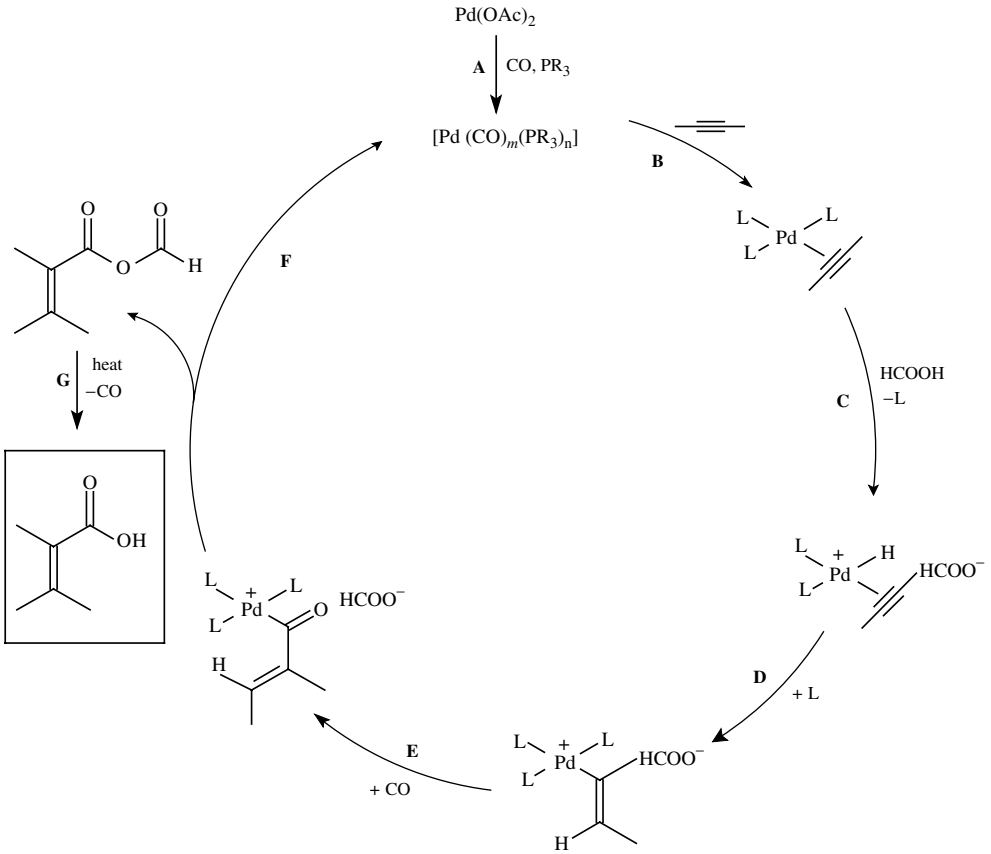
The metal-complex-catalyzed hydrocarboxylation of alkynes is of value for the synthesis of α,β-unsaturated acids and their derivatives.[1],[5]–[11] The direct regioselective hydrocarboxylation of alkynes to α,β-unsaturated carboxylic acids can be achieved using the catalytic system $Pd(OAc)_2$, dppb, and PPh_3 in the presence of formic acid at 120 psi of CO and 100–110 °C. The use of a mixture of the two ligands, dppb and PPh_3, significantly improves the yields (Eq. 10).[34]

$$R{-}C{\equiv}C{-}R' + HCOOH + CO \xrightarrow[DME,\ 100{-}110\ °C\ 120\ psi]{Pd(OAc)_2,\ dppb,\ PPh_3} \underset{1}{\overset{R}{\underset{HOOC}{\overset{R'}{\underset{H}{=}}}}} + \underset{2}{\overset{R}{\underset{H}{\overset{R'}{\underset{COOH}{=}}}}} \quad (10)$$

The distribution of the products (**1** and **2**) is approximately 9:1 in favor of **1** when R is phenyl or a straight-chain alkyl group; **2** is favored when R is *t*-Bu and is the exclusive product when R is $SiMe_3$. Internal alkynes (R, R′ ≠ H) also undergo catalytic hydrocarboxylation with formic acid, but the regioselectivity is not as high as for terminal alkynes.[34]

A tentative mechanism has been proposed for the $Pd(OAc)_2$-catalyzed hydrocarboxylation of alkynes with formic acid (**Scheme 2**). Beginning with step **A**, the solid-state structure of $Pd(OA)_2$ breaks down and the Pd(II) complex is reduced to Pd(0) under CO. The catalytic species $[Pd(CO)_m(PR_3)]_x$ is then formed in the presence of phosphine

ligands and CO. The complex $[Pd(CO)_m(PR_3)]$ can then undergo ligand substitution (step **B**) and coordinate to the alkyne. Formic acid may react by forming a metal hydride (step **C**). Pd(0) electron-rich species are known to form Pd—H bonds in the presence of strong acids. The formate anion is a counteranion to the cationic species. The hydridoalkyne intermediate would then undergo intramolecular 1,2-addition (insertion) of Pd—H to the alkyne triple bond (step **D**). Carbonyl insertion via a ligand migration pathway (step **E**), followed by cleavage of the palladium acyl intermediate, leads to the formation of the products and the regeneration of the active catalytic species (step **F**). The most probable candidate for such a cleavage is the formate counteranion, which would give a mixed anhydride. The latter is very unstable under the experimental conditions and decomposes readily to give the carboxylic acid (step **G**).

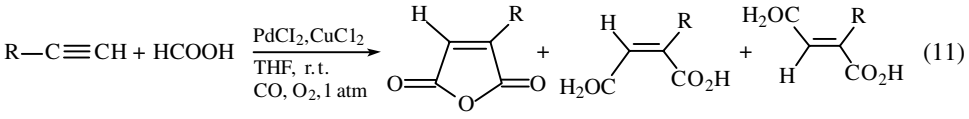


Scheme 2

The hydrocarboxylation of alkynes with formic acid or oxalic acid was also achieved using the heterogeneous catalyst Pd/C, in the presence of dppb and PPh_3 at 40 atm of CO and 110 °C. The catalytic activities of the heterogeneous and homogeneous systems were similar. The yield of α-β-unsaturated acids are good (61–78%) and the reaction is regioselective.[35]

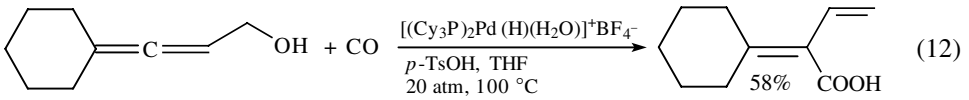
Formic acid reacts with terminal alkynes, $PdCl_2$, $CuCl_2$, CO, and O_2 at room temperature affording monosubstituted maleic anhydrides and the corresponding maleic and

fumaric acids in 30–75% total yield. The regioselectivity of the reaction depends on the type of alkyne used (Eq. 11).[36]



(11)

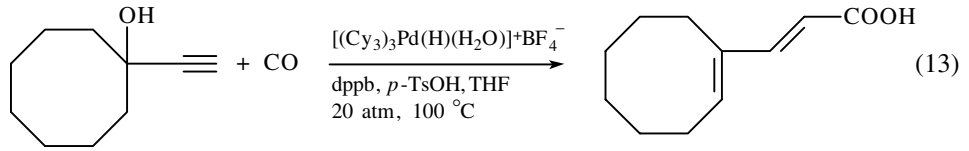
Interestingly, α-vinylacrylic acids were obtained by the carbonylation of α-allenic alcohols using *trans*-$[(Cy_3P)_2Pd(H)(H_2O)]^+ BF_4^-$ and *p*-TsOH as catalysts at 20 atm of CO and 100 °C in THF (Eq. 12).[37]



(12)

A series of trisubstituted and 1,3-disubstituted α-allenic alcohols were carbonylated under the reaction conditions. The reaction of 1,3-disubstituted α-allenic alcohols was stereoselective, exclusively affording the *E*-isomer.[37]

The same cationic hydridopalladium complex catalyzes the regioselective hydrocarboxylation of alkynols and alkynediols to carboxylic acids (Eq. 13).[38]

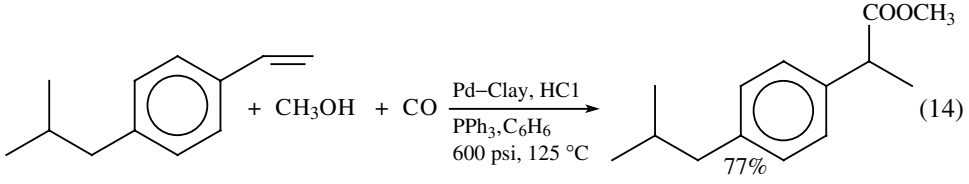


(13)

C. HYDROESTERIFICATION OF π-BONDED COMPOUNDS

The hydroesterification of alkenes is, like hydrocarboxylation, an industrially important reaction and is of interest from a synthetic point of view. Palladium chloride and copper(II) chloride or $[(Cy_3P)_2Pd(H)(H_2O)^+BF_4^-$ and dppb catalyze the hydroesterification of olefins in acidic alcohol in the presence of carbon monoxide and oxygen (1 atm). Branched-chain esters were obtained as the principal and, in some cases, as the only reaction products.[39]–[41]

Palladium acetate immobilized on montmorillonite is another effective catalyst for the hydroesterification of olefins to form branched-chain esters as the major products. The reaction proceeded at 600 psi of carbon monoxide, in the presence of PPh_3, methanol, and an acid promoter (Eq. 14).[42]



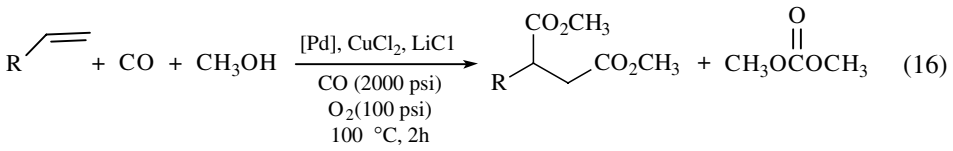
(14)

The regiospecific hydroesterification of vinylsilanes, catalyzed by a palladium complex intercalated into montmorillonite in the presence of PPh_3, *p*-TsOH, and various alcohols, afforded β-silyl esters in high yields and excellent selectivity. The hydroesterification of trimethylvinylsilane in the presence of a diol selectively gives the monoesterification product (Eq. 15).[43]

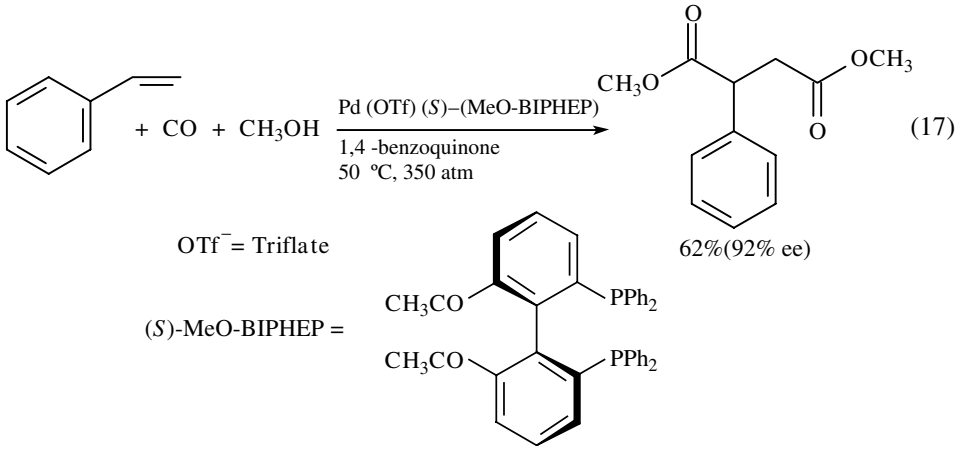
$$(CH_3)_3SiCH{=}CH_2 + HOCH_2CH_2OH \xrightarrow[\substack{PPh_3, CH_2Cl_2, p\text{-TsOH} \\ 500\ psi\ CO,\ 100\ ^\circ C,\ 72h}]{Pd\text{–}montmorillonite} (CH_3)_3SiCH_2CH_2C(=O)OCH_2CH_2OH \quad (15)$$

95%

Palladium/graphite in combination with copper(II) chloride and lithium chloride is a good catalytic system for the oxidative dicarbonylation of alkenes using a 20:1 ratio of CO/O_2 (Eq. 16).[44] The ratio of diester to dimethyl carbonate is sensitive to the nature of the palladium catalyst precursor (Pd/graphite or $PdCl_2$).



The asymmetric hydroesterification of methyl methacrylate to a 1,4-diester was realized with [(*R*,*R*)-DIOP]$PdCl_2$ as the catalyst precursor.[45],[46] Recently, cationic palladium(II) complexes of the type $[Pd(L\text{-}L')(S_2)]X_2$ (where L-L′ is a chelate ligand with C_2 symmetry, S is a solvent molecule, and X is an anion with low coordination properties) were found to be catalytically active for the enantioselective bis-alkoxycarbonylation of 1-olefins to substituted succinates. Using atropisomeric fully aromatic ligands, high enantio- and chemoselectivities have been obtained when styrene is the substrate. For aliphatic olefins, such as propene and 4-methyl-l-pentene, the chemoselectivities were obtained when styrene was the substrate. In these cases the degree of enantioselectivity is usually modest, probably due to two competing regiochemical pathways for the insertion of the olefin into the palladium carbomethoxyintermediate.[47] High enantiomeric excess (92–93%) was obtained; however, the reaction required drastic pressures of carbon monoxide (350 atm) (Eq. 17).

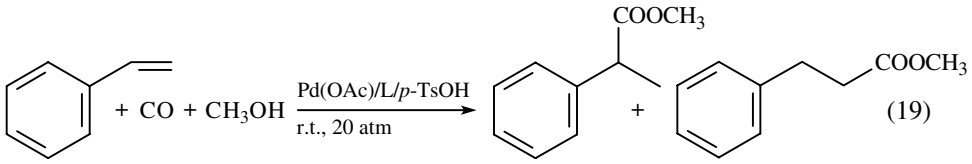


Interestingly, methyl formate was successfully used in the absence of carbon monoxide for the catalytic hydroesterification of ethylene by the complex $[PdH(Cl)(PBu_3)_2]$, generated *in situ* by addition of 1 equiv of $NaBH_4$ to $PdCl_2(PBu_3)_2$ (Eq. 18).[48]

$$CH_2{=}CH_2 + HCO_2CH_3 \xrightarrow[\text{MeOH, 130 °C}]{PdCl_2(PBu_3)_2,\ NaBH_4} CH_3CH_2CO_2CH_3 \qquad (18)$$

The mild palladium(II)–copper(II)–CO–O_2–HCl system was also applied to the oxidative carbonylation of formate esters and olefins. Higher yields as well as branched/linear ester ratio were obtained by using excess rather than an equimolar quantity of formate ester to substrate.[49] In addition, allenes and terminal alkynes undergo regioselective hydroesterification to unsaturated mono- and diesters using the same catalytic system.[50],[51]

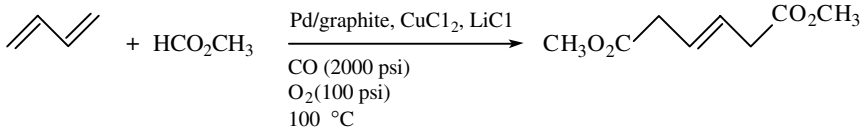
The cationic palladium(II) complex $[Pd(MeCN)_2(PPh_3)_3](BF_4)_2$ is an active catalyst for the hydroesterification of styrene using CO and methanol under very mild conditions. The catalytic system, Pd(Oac)–PPh_3–*p*-toluenesulfonic (*p*-TsOH) could also produce the branched ester regioselectively in excellent yield at ambient temperature. The catalytic asymmetric hydroesterification of styrene by the use of chiral phosphines, such as (*S*)-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyldimethylamine, and (*S*)-(*R*)-BPPFA as ligands (Eq. 19).[52]



(19)

	Yield	Branched	Linear
L = PPh_3	95%	93%	7%
L = (S)-BPPFA	17%	44% (86% ee)	56%

The oxidative dicarbonylation of 1,3-butadiene to generate dimethyl hex-3-ene-1, 6-dioate resulted using Pd/graphite, in combination with $CuCl_2$ and LiCl (Eq. 20).[44]

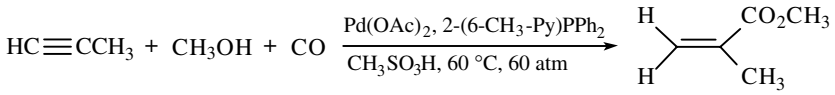


(20)

Conjugated dienes were successfully converted to β-γ-unsaturated esters using $PdCl_2$–$CuCl_2$–CO–O_2–HCl–CH_3OH. However, it was essential to dry the mixture of $PdCl_2$, methanol, and conc. HCl over molecular sieves prior to addition of the diene and cupric chloride. Furthermore, the addition of a quarternary ammonium salt such as Aliquat-336 is important to prevent polymerization.[32],[33]

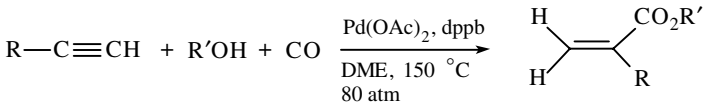
An efficient palladium cationic catalyst was used for the selective production of methyl methacrylate from propyne. The active catalytic system consists of a ligand containing a 2-pyridylphosphine moiety, a palladium(II) species, and a proton source containing weakly

coordinating anions. High selectivity for methyl methacrylate (99.9%) can be obtained under mild conditions (Eq. 21).[53]



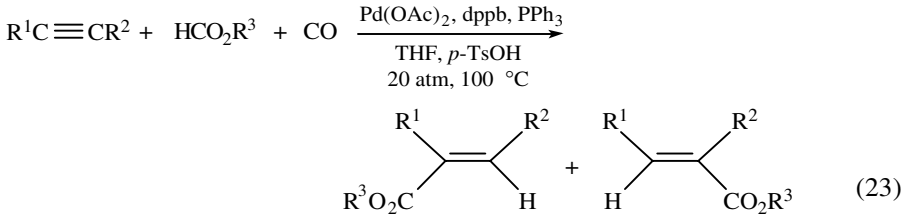
(21)

The conversion of alkyne into *t*-alkyl esters represents a challenging reaction in chemistry. However, the use of $Pd(OAc)_2$ and dppb at 150 °C and 80 atm of CO in the presence of *t*-butyl alcohol successfully catalyzes this process leading to *t*-alkyl esters in acceptable yield and excellent regioselectivity. The use of primary and secondary alcohols gave low yields of esters (Eq. 22).[54]

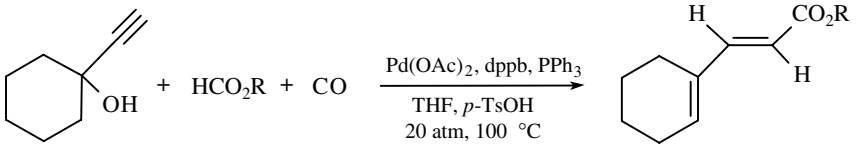


(22)

Interestingly, it was found that the reactivity of formate esters is opposite to that of the alcohols described in the previous system (Eq. 23). Regioselective hydroesterification of alkynes and alkynols using formate esters and the catalytic system $Pd(OAc)_2$–dppb–PPh_3 in the presence of *p*-TsOH at 20 atm of CO gave unsaturated esters in good selectivity (Eqs. 23 and 24).[52]



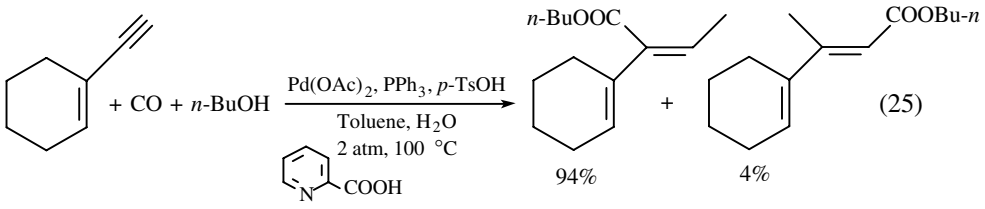
(23)



(24)

For the same type of reactions *t*-butyl formate ester gave the lowest yield (32%) of atropic acid ester, and the highest yield (80%) was obtained with *n*-butyl formate in the hydroesterification of phenylacetylene.[55]

Recently, the carbonylation of alkynes has been carried out using $Pd(OAc)_2$, a monophosphine ligand, *p*-TsOH, and semilabile anionic bidentate ligands such as pyridine or piperidine carboxylic acids. It was observed that the concentration of the acid promoter (*p*-TsOH) has a strong effect on the reaction rates. At higher concentrations (the ratio of *p*-TsOH/Pd > 10) the catalyst decomposed to palladium metal after 25% conversion of the alkyne. Therefore, an excess of phosphine ligand was used to stabilize the catalyst. In addition, the catalytic activity was strongly influenced by the polarity of the solvent. Less polar solvents such as toluene, benzene, and chlorobenzene gave the highest catalytic activity (Eq. 25).[56]



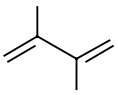
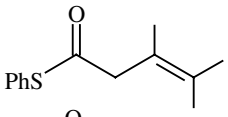
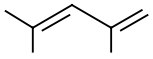
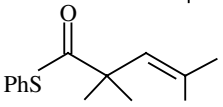
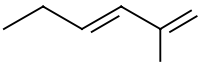
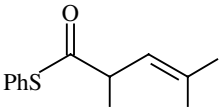
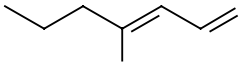
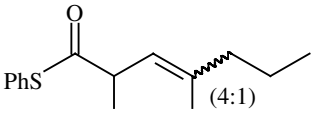
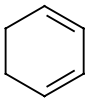
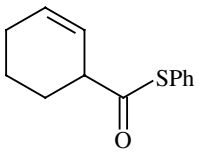
(25)

D. THIOCARBONYLATION OF π-BONDED COMPOUNDS

Transition-metal-catalyzed carbonylation reactions of sulfur-containing compounds and the thiocarbonylation of thiols to various substrates[57]–[60] have been extensively developed during the past decade. Sulfur-containing compounds have long been considered as poisons of many noble metal catalysts due to their strong coordinating and adsorptive properties, which cause them to block the reactive sites of metals.[61] In fact, there have been relatively few investigations of metal-catalyzed synthetic reactions involving organosulfur compounds as reactants.[57]–[60]

Recently, the carbonylation of dienes in the presence of thiophenol was achieved to give β,γ-unsaturated thioesters in fine yields.[62] The regioselectivity of the reaction depends mainly on steric factors of the dienes forming either the 1,2- or 1,4-products of addition with *E*-isomers predominant in all cases (**Table 1**). In addition, the stereochemistry of the

TABLE 1. Pd-Catalyzed Thiocarbonylation of Dienes with Thiophenol [a]

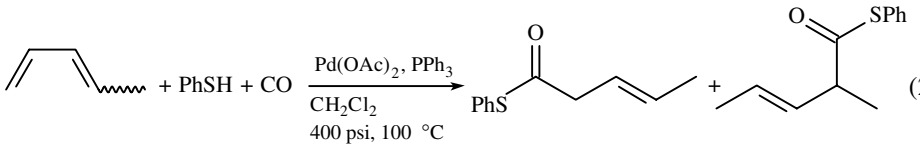
Diene	Product (*E*/*Z*)[b]	Yield (%)[c]
		90
		64
		86
		69
		84

[a] Reaction conditions: diene (5.0 mmol), thiophenol (1.0 mmol), $Pd(OAc)_2$ (0.03 mmol), PPh_3 (0.12 mmol), CH_2Cl_2 (15 mL), CO (400 psi), 100 °C.

[b] The *E*/*Z* ratio was determined by ^1H NMR.

[c] Based on thiophenol employed.

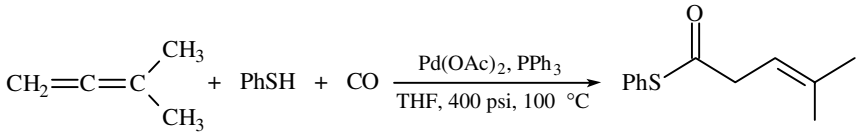
products is independent of the stereochemistry of the dienes (Eq. 26). For example, using dienes as reactants in the ratio of $E/Z = 1$, $E/Z = 9.9$, or $Z/E = 9.9$, the major as well the as the minor β,γ-unsaturated thioesters have the *E*-stereoisomer as the dominant isomer.[62] The reaction probably proceeds via coordination of Pd—SPh to the less or the more substituted part of the double bond forming either $CH_3CH{=}C(PdSPh)CH_3$ or $PdSPhCH_2CH{=}CCH_3$; subsequent CO insertion followed by reductive elimination leads to the formation of the corresponding thioesters.[62]



(26)

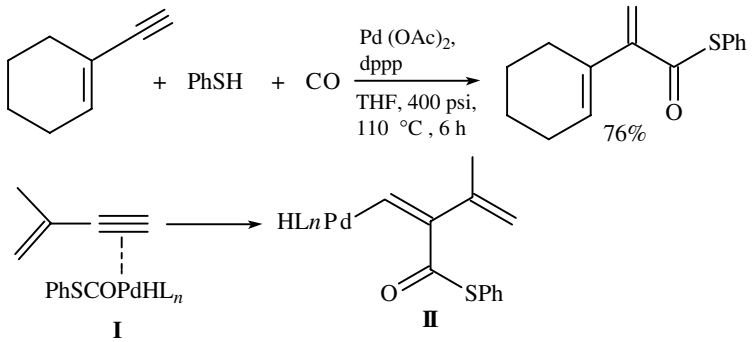
1.	*E*/*Z* = 1:1	23 % (*E*/*Z* = 4:1)	77 % (*E*/*Z* = 9:1)
2.	*E*/*Z* = 99:1	20 % (*E*/*Z* = 4:1)	80 % (*E*/*Z* = 8:1)
3.	*E*/*Z* = 1:99	28 % (*E*/*Z* = 4:1)	72 % (*E*/*Z* = 9:1)

The direct thiocarbonylation of a series of mono- and disubstituted allenes with thiols and carbon monoxide also gave the corresponding β,γ-unsaturated thioesters in 73–94% yields. This reaction requires catalytic quantities of $Pd(OAc)_2$ and triphenylphosphine in THF at 400 psi of CO and 100 °C for 48 h. Other palladium catalyst systems such as $Pd_2(dba)_3{\cdot}CHCl_3$–PPh_3, $Pd(PPh_3)_4$, and $Pd(OAc)_2$–dppp are also effective for this reaction. The thiocarbonylation reaction is believed to proceed via a π-allylpalladium intermediate. The reaction exhibits high regioselectivity, in which the thiophenyl group adds to the less substituted double bond of allenes to give β,γ-unsaturated thioesters (Eq. 27, **Table 2**).[63]



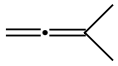
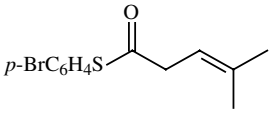
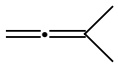
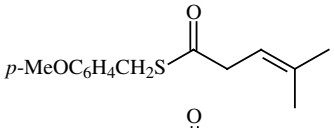
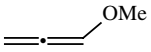
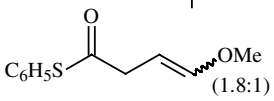
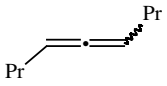
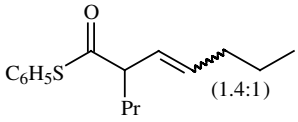
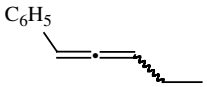
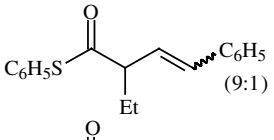
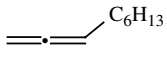
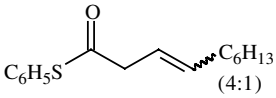
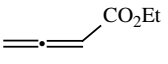
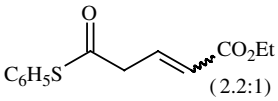
(27)

The reaction of 1,3-enynes bearing a terminal triple bond with thiols and carbon monoxide catalyzed by $Pd(OAc)_2$and 1,3-bis(diphenylphosphino)propane, dppp, in THF at 110 °C gave 2-(phenylthiocarbonyl)-1,3-dienes in moderate to good yields. The thiocarbonylation takes place with high chemo- and regioselectivities, with the attack by the phenylthiocarbonyl group occurring exclusively at carbon-2 of the 1,3-conjugated enyne (Eq. 28, **Table 3**).[64] The



(28)

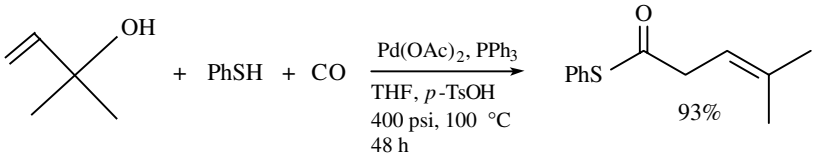
TABLE 2. Pd-Catalyzed Thiocarbonylation of Allenes with Thiols[a]

Allene	Thiol	Product (*E*/*Z*)[b]	Yield (%)[c]
	*p*-BrC_6H_4SH		73
	*p*-$MeOC_6H_4CH_4SH$		83
	C_6H_5SH	 (1.8:1)	83
	C_6H_5SH	 (1.4:1)	86
	C_6H_5SH	 (9:1)	87
	C_6H_5SH	 (4:1)	80
	C_6H_5SH	 (2.2:1)	88

[a] Reaction conditions: allene (2.0 mmol), thiol (2.0 mmol), $Pd(OAc)_2$ (0.06 mmol), PPh_3 (0.24 mmol), THF (7 mL), CO (400 psi), 100 °C.
[b] The *E*/*Z* ratio was determined by ^1H NMR.
[c] Based on thiophenol employed.

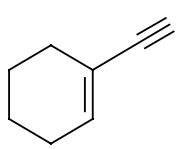
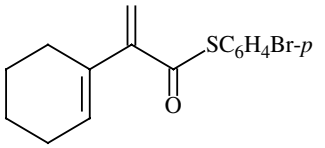
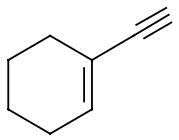
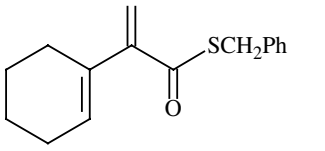
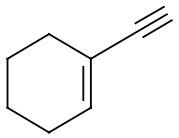
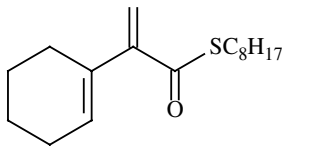
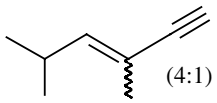
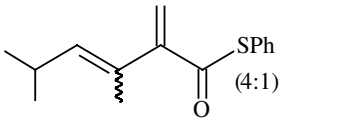
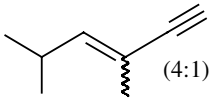
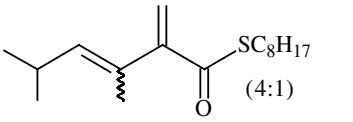
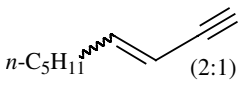
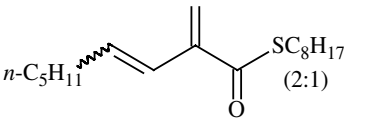
reaction may proceed by the oxidative addition of thiophenol to a palladium intermediate forming the PhSPdH species, which undergoes coordination to the triple bond of the enyne and then insertion of CO to form **I**. Regioselective intramolecular acylpalladation of **I** may afford **II** as an intermediate.

The thiocarbonylation of allylic alcohols catalyzed by $Pd(OAc)_2$, triphenylphosphine, and *p*-TsOH leads to an interesting reaction affording β,γ-unsaturated thioesters in good to excellent yields. Other palladium catalyst systems such as $Pd_2(dba)_3$–$CHCl_3$–PPh_3–*p*-TsOH, $Pd(PPh_3)_4$–*p*-TsOH, and $Pd(OAc)_2$–dppb–*p*-TsOH are also effective for this transformation. The reaction occurs highly regioselectively at the least hindered allylic terminal carbon of the substrate to give the products. This new carbonylation procedure was readily applied to a variety of allylic alcohols and both aromatic and aliphatic thiols (Eq. 29, **Table 4**).[65]



(29)

TABLE 3. Pd-Catalyzed Thiocarbonylation of Enynes with Thiols[a]

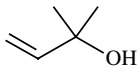
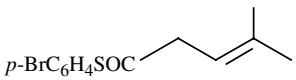
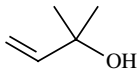
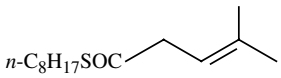
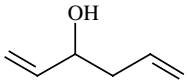
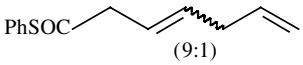
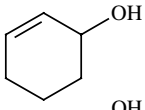
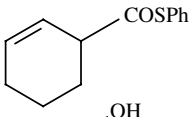
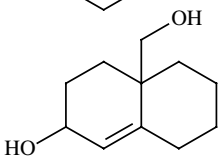
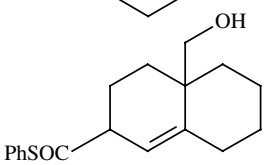
Enyne (*E*/*Z*)	Thiol	Product (*E*/*Z*)[b]	Yield (%)[c]
	*p*-BrC_6H_4SH		70
	$PhCH_2SH$		73
	*n*-$C_8H_{17}SH$		73
	C_6H_5SH		52
	*n*-$C_8H_{17}SH$		72
	C_6H_5SH		74

[a] Reaction conditions: enyne (3.0–5.0 mmol), thiol (1.0 mmol), $Pd(OAc)_2$ (0.03 mmol), dppp (0.06 mmol), THF (15 mL), CO (400 psi), 110 °C.
[b] The *E*/*Z* ratio was determined by ^1H NMR.
[c] Based on thiol employed.

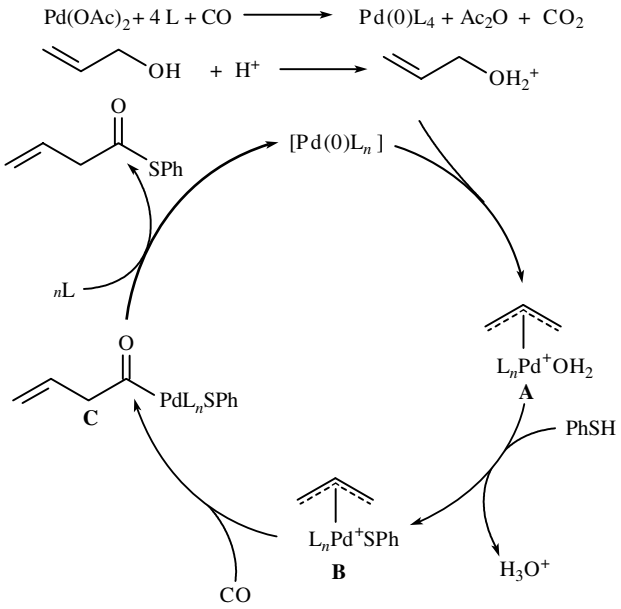
A probable mechanism for the thiocarbonylation of allylic alcohols is outlined in **Scheme 3**. It is well-known that $Pd(OAc)_2$ is easily reduced to Pd(0) *in situ* in the presence of phosphine ligands and carbon monoxide. Oxidative addition of protonated allylic alcohol to Pd(0) gives the π-allylpalladium complex **A**, which may undergo substitution of H_2O by SPh to form the π-allylpalladium sulfide complex **B**. Insertion of CO into **B** affords the acylpalladium complex **C**. Reductive elimination of Pd(0) would form the β,γ-unsaturated thioesters.

A Pd-catalyzed carbonylative coupling reaction of propargyl alcohols and thiols has been developed by using different reaction conditions. Monothioesters, dithioesters, or sulfur-containing furanones can be produced in good to excellent yield and selectivity. This methodology is attractive for the preparation of thioesters and sulfur-substituted

TABLE 4. Pd-Catalyzed Thiocarbonylation of Allyl Alcohols with Thiols[a]

Allyl Alcohol	Thiol	Product (*E*/*Z*)[b]	Yield (%)[c]
	*p*-BrC_6H_4SH		88
	*n*-$C_8H_{17}SH$		87
	PhSH	 (9:1)	78
	PhSH		84
	PhSH		63

[a] Reaction conditions: alcohol (2 mmol), thiol (2 mmol), $Pd(OAc)_2$ (0.06 mmol), PPh_3 (0.06 mmol), *p*-TsOH (0.1 mmol), CH_2Cl_2 (10 mL), CO (400 psi), 120 °C.
[b] The *E*/*Z* ratio was determined by ^1H NMR.
[c] Based on thiophenol employed.



Scheme 3

lactones and also demonstrates the utility of transition metal catalysts in the reactions of sulfur compounds (Eq. 29).[66]

E. CONCLUSIONS

The hydroesterification and hydrocarboxylation reactions catalyzed by transition metals and their complexes demonstrate the versatility of these processes. Palladium complexes are particularly useful catalysts for these reactions. Indeed, the hydrocarbonylation of a large variety of substrates has been selectively achieved by using palladium catalysts in homogeneous, heterogeneous, or biphasic systems. The results obtained for the thiocarbonylation showed excellent regio- and stereoselectivity control for most substrates. It is anticipated that the prochiral nature of most of the reactants and products will open a new venue for the asymmetric synthesis of acids, esters, and thioesters of substantial development in the future.

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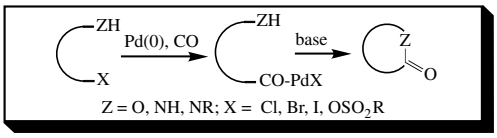

VI.2.1.2 Intramolecular Cyclization Processes via Palladium-Catalyzed Carbonylative Lactonization and Lactamization

VITTORIO FARINA and MAGNUS ERIKSSON

A. OXYGEN NUCLEOPHILES

A.i. By Oxidative Addition Processes

Palladium-catalyzed lactonization with CO insertion is a useful method that has been developed over the years to become an important tool in organic synthesis. The most straightforward approach consists of an oxidative addition of Pd(0) to a vinyl/aryl halide or a pseudohalide (e.g., triflate) followed by insertion of carbon monoxide and subsequent intramolecular attack of the oxygen nucleophile onto the carbonyl, with regeneration of the Pd(0) catalyst. An appropriate base is necessary to trap the acid released during the reaction (**Scheme 1**).

The first examples of this methodology were reported by Ban and co-workers, who demonstrated the synthesis of five-, six- and seven-membered ring benzolactones (**Scheme 2**).[1]

In a related process, formation of benzofuranone from carbonylation of 2-iodobenzyl alcohol in supercritical carbon dioxide was recently reported by Kayaki et al.[2] The rate of reaction in supercritical CO_2, using palladium chloride in combination with trialkyl or triaryl phosphites as ligands, was reported to be higher than that in typical organic solvents.

Cowell and Stille reported on the formation of butenolides from alkenyl iodides (**Scheme 3**).[3],[4] The most useful catalyst was $Pd(PPh_3)_2Cl_2$ and the solvent was THF or DMF. Hydrazine was added to effect the reduction of Pd(II) to the active Pd(0) species.

Carbonylation of alkenyl iodides according to the above protocol was applied by Hoye and co-workers to the total synthesis of naturally occurring butenolides.[5],[6] An example from the synthesis of (+)-asimicin and (+)-bullacitin is shown in **Scheme 4**.

Further work in this area by Martin and Stille has led to a method for the formation of α-methylene γ-lactones.[7] Good yields were obtained using $Pd(PPh_3)_4/K_2CO_3$ in acetonitrile (**Scheme 5**).

The selectivity for formation of γ-lactones over δ-lactones is illustrated by carbonylation of the diol shown in **Scheme 6**. Only the γ-lactone was produced.

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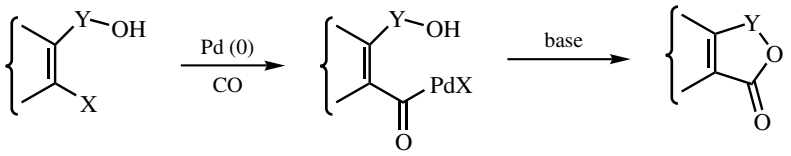
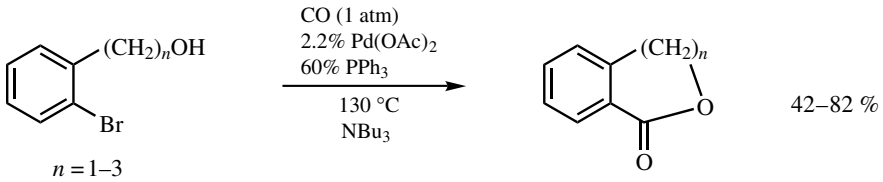
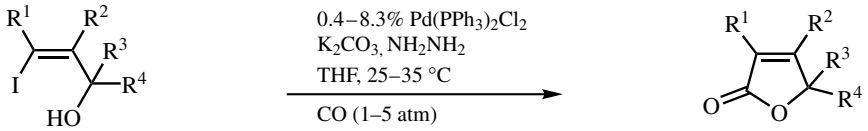


Z = carbon chain; X = Br, I, OTf

Scheme 1

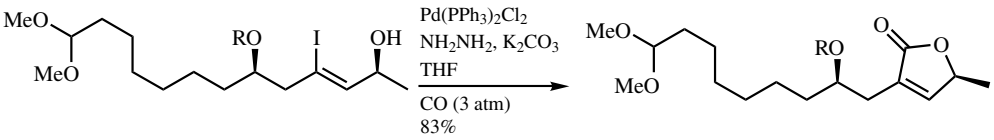


Scheme 2

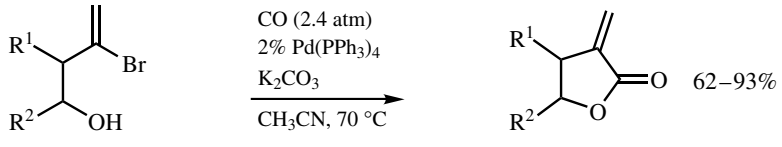


R^1	R^2	R^3	R^4	Yield %
H	H	H	H	76
H	H	H	Me	95
Me	H	H	H	100
Me	Me	H	H	99
Me	H	H	Ph	46
Ph	H	H	Me	69
Me	H	Me	Et	84

Scheme 3

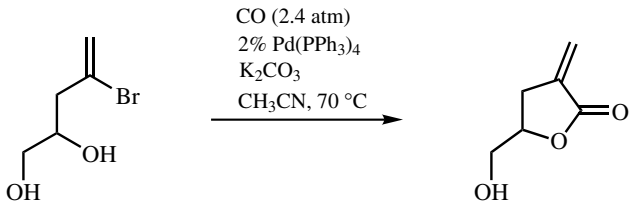


Scheme 4



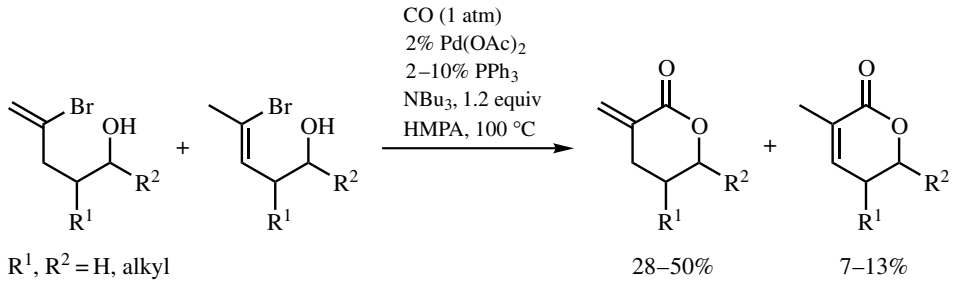
R^1, R^2 = H, alkyl

Scheme 5



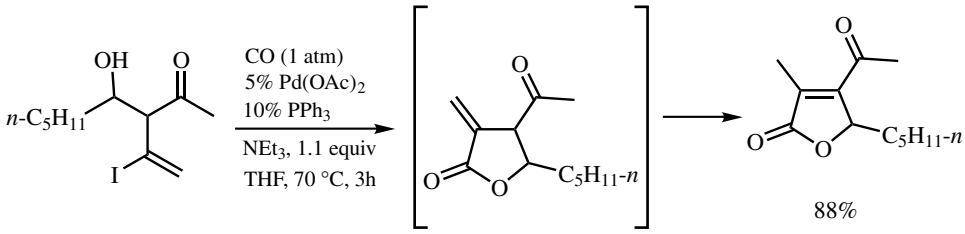
Scheme 6

The synthesis of unsaturated δ-lactones from alkenyl halides was reported by Mori et al.[8] (**Scheme 7**). The ratio of *exo* to *endo* olefinic lactone reflects the corresponding ratio in the starting vinyl bromides and does not change during the reaction. Even seven-membered α-methylene lactones can be synthesized using this protocol.



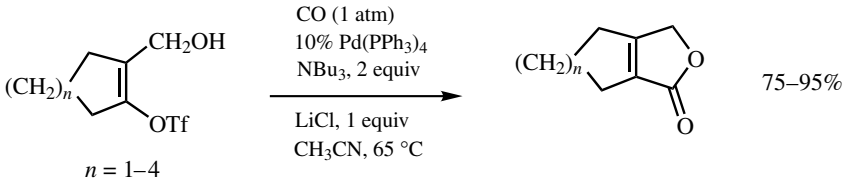
Scheme 7

A similar synthesis of (*Z*)-α-alkylidene-γ-lactones from alkenyl iodides was reported by Luo et al.[9] In a related procedure,[10] the presence of an acetyl group α to the hydroxyl group of the iodide led to the formation of α,β-unsaturated butenolides. The presumed intermediate α-methylene lactone probably undergoes isomerization to the more stable butenolide under the reaction conditions, as shown in **Scheme 8**.



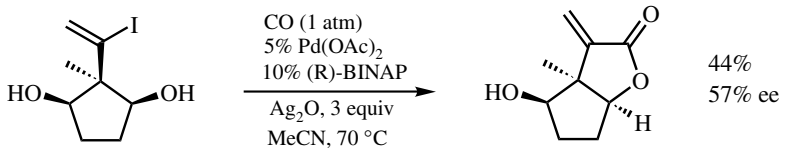
Scheme 8

The use of vinyl triflates in place of halides is attractive due to their easy formation from ketones and the readiness with which they undergo Pd-catalyzed chemistry. A method for the carbonylation of hydroxy alkenyl triflates using $Pd(PPh_3)_4$ as catalyst was developed by Crisp and Meyer.[11] A variety of fused butenolides were synthesized in good to excellent yields using this protocol, as shown in **Scheme 9**.



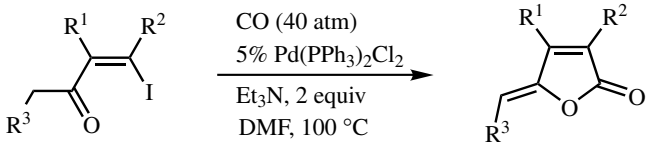
Scheme 9

A catalytic asymmetric synthesis of α-methylene lactones by carbonylation of a *meso* substrate (**Scheme 10**) was developed by Shibasaki and co-workers.[12] The combination of $Pd(OAc)_2$, (*R*)-BINAP, and Ag_2O gave 44% yield of lactone with a modest ee. No asymmetric induction occurred in the absence of Ag_2O. Presumably the role of Ag_2O is to promote formation of an intermediate cationic palladium species, which could retain bidentate coordination of the chiral ligand throughout the catalytic process.



Scheme 10

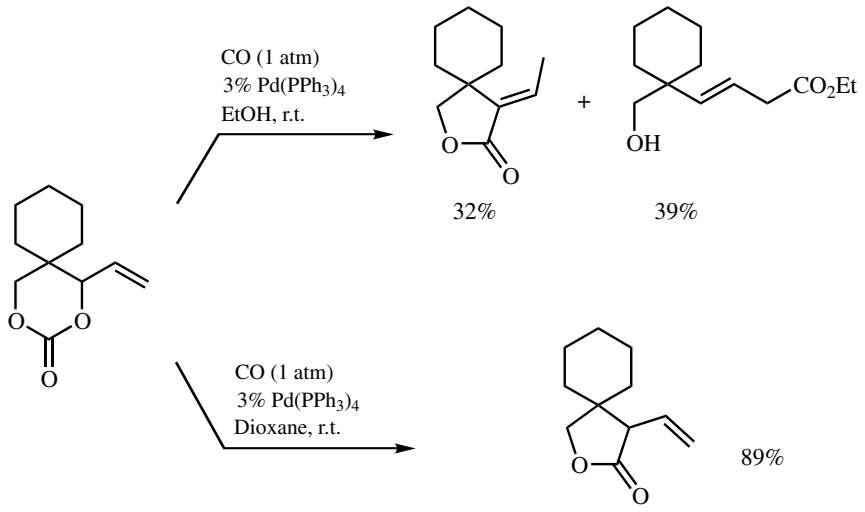
Formation of lactones from alkenyl halides has also been reported as part of natural product syntheses, as in Marshall's approach to (±)-aristolactone,[13] or as a means to support stereochemical assignments.[14],[15] So far, the reactions discussed have all involved attack of a free hydroxyl group on the acylpalladium species. A closely related approach involves attack of an *O*-enolate, which is usually generated from the corresponding ketone. The concept is shown in **Scheme 11**.



Scheme 11

This type of transformation has been reported starting with alkenyl halides,[16],[17] benzyl chlorides,[18] and aryl halides and triflates.[17],[19],[20] **Section VI.2.3** provides a detailed overview of this topic.

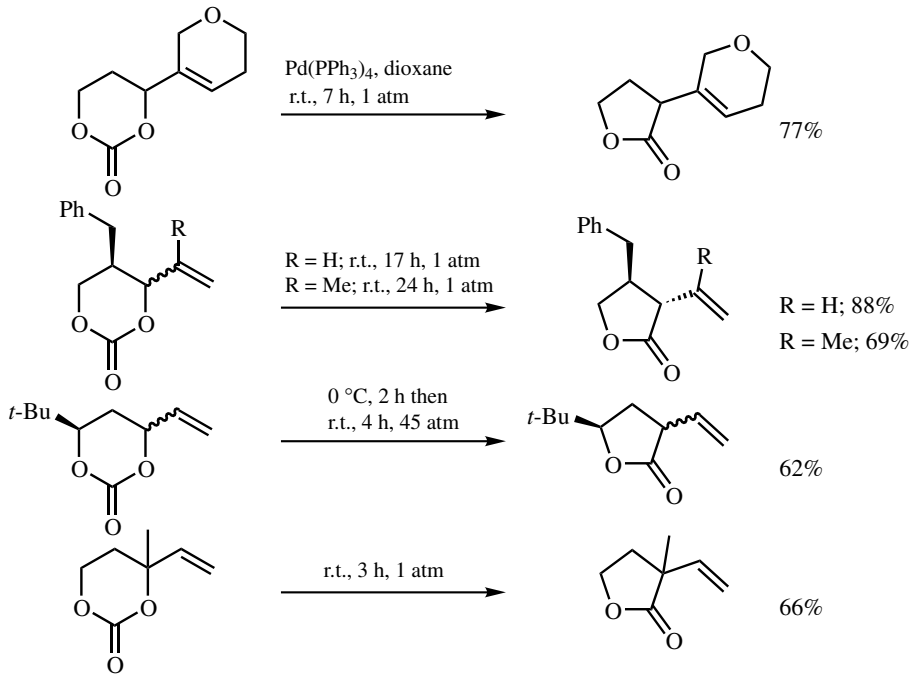
Formation of β-lactones through these procedures is rare: carbonylation of alkenyl oxiranes gives these products in low yields.[21] Allyl carbonates may also serve as precursors to butyrolactones in a method developed by Tamaru et al.[22] A protic solvent such as ethanol gives a ca. 1:1 mixture of the isomerized α,β-unsaturated lactone and the acyclic ester, whereas an aprotic solvent (e.g., dioxane, THF, benzene) leads exclusively to the expected lactone (**Scheme 12**).



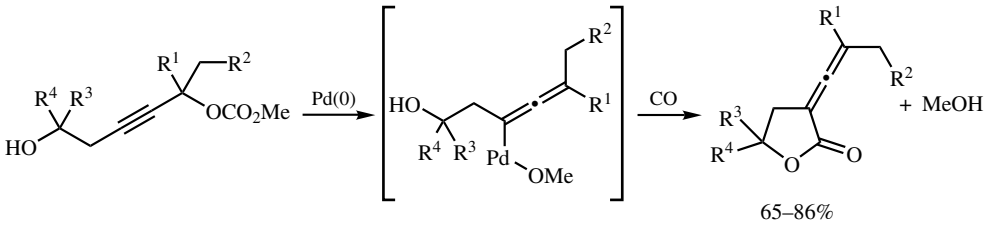
Scheme 12

Further examples of this decarboxylative carbonylation reaction are shown in **Scheme 13**.[23] Note that no base is used in this process, because the reactive nucleophile, the alkoxide, is generated directly *in situ*.

In a related method, the preparation of α-vinylidene-γ-lactones from propargyl carbonates has been reported (**Scheme 14**).[24]



Scheme 13

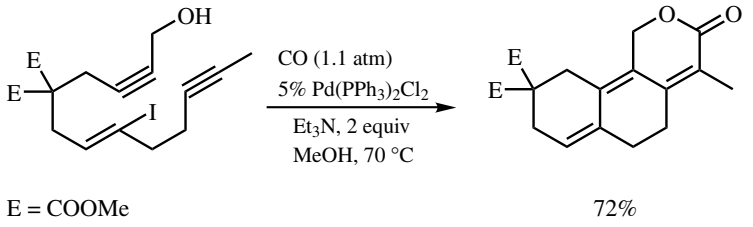


Scheme 14

In this case, bidentate ligands like dppp or dppf work better than triphenylphosphine, which gave slow reactions.

An interesting method recently developed by Negishi combines cascade carbopalladations with termination by carbonylation, to afford fused polycyclic lactones, as exemplified in **Scheme 15**.

Surprisingly, methanol was a suitable solvent for this transformation and the amount of intermolecular methoxycarbonylation products was only 2–3%.[25] Furthermore, acylpalladation of alkenyl iodide was disfavored versus the desired intramolecular 6-*exo*-carbopalladation. Further examples of this type of CO-terminated cascade processes can be found in **Sect. IV.3**.



Scheme 15

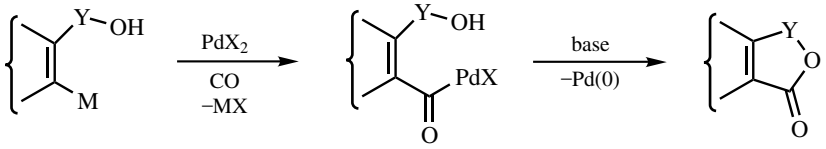
A.ii. By Transmetallation and Related Processes

A variant of the chemistry just discussed involves the formation of the required alkenyl- or aryl-Pd(II) intermediate by transmetallation rather than oxidative addition (**Scheme 16**).

In this strategy, transmetallation is followed by CO insertion and intramolecular acylation, yielding Pd(0), which must be oxidized to reenter the catalytic cycle. An example of this strategy has been reported by Larock and Fellows.[26]

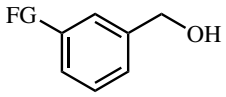
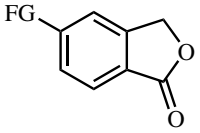
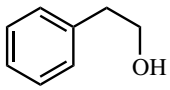
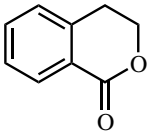
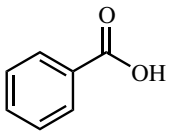
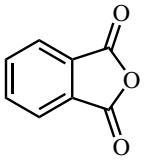
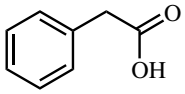
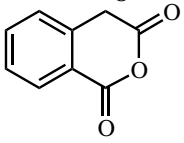
As shown in **Scheme 17**, thallation of an aromatic alcohol gives the *o*-metallated species, which then transmetallates with $PdCl_2$ and undergoes cyclocarbonylation to furnish the lactone products. In this protocol, the thallium salt also serves to reoxidize Pd(0) to the requisite Pd(II) species.

In a related method, shown in **Scheme 18**, the organomercurials obtained from ring-opening of cyclopropanes may undergo Pd(II)-catalyzed carbonylations to afford fused lactones.[27] Here, *p*-benzoquinone proved superior to Cu salts as reoxidant for Pd(0). Furthermore, by clever control of the conditions for the cleavage of the cyclopropyl ring, access to both *cis*- and *trans*-fused products was possible.

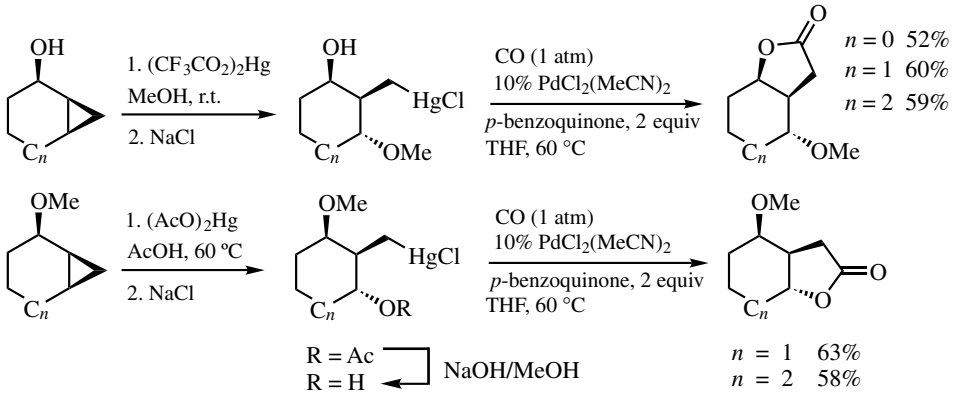


Y = carbon chain; M = metal

Scheme 16

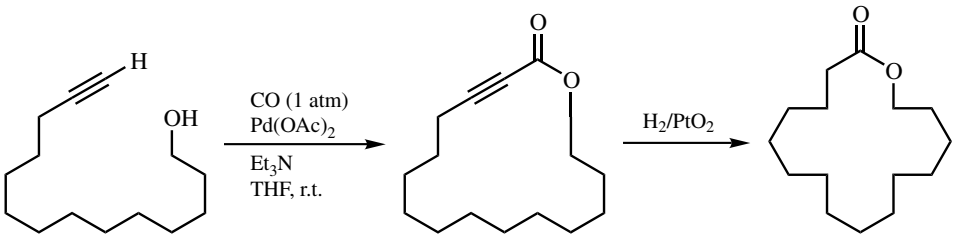
ArH	Product	Yield (%)
 FG = H,OH,OCH_3		33–95
		62
		44
		56

Scheme 17



Scheme 18

Finally, H for Pd metathesis in a terminal alkynol, followed by carbonylation, leads to formation of lactones containing a triple bond (**Scheme 19**).[28]

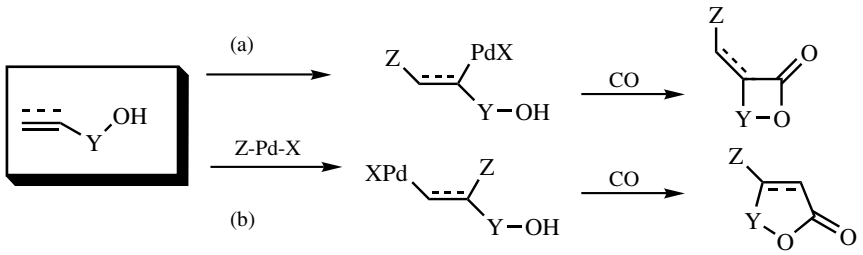


12–29% exaltolide

Scheme 19

A.iii. By Additive Processes of Pd(II) Species Across Double and Triple Bonds

Addition of a Z-Pd-X species across a multiple bond is a very interesting way of generating an alkyl/alkenyl palladium(II) species that can then undergo carbonylation and then capture by an intramolecular hydroxyl group. Because two distinct regiochemistries are possible in an addition across a multiple bond, two pathways, (a) and (b) (**Scheme 20**), are possible, leading to isomeric products characterized by different ring sizes.

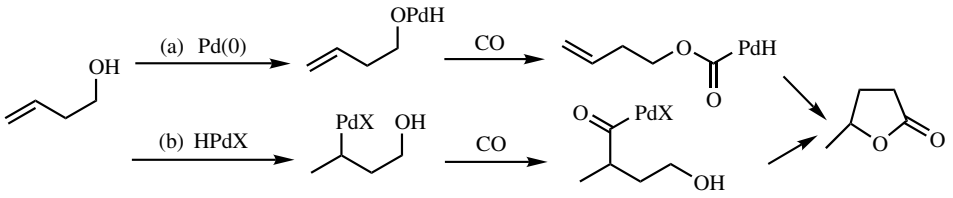


Y = carbon chain; X = halogen, acetate; Z = H, X, C,O, S, Se, or N substituent

Scheme 20

The formal addition of "H-Pd-X" across double bonds, followed by carbonylation, constitutes the simplest embodiment of the above strategy. Mechanistically speaking, hydrocarbonylation processes of unsaturated alcohols appear to be distinguishable according to two separate pathways (**Scheme 21**): the first (path a) involves in the key step an intramolecular carbopalladation of the double bond, and as such will be referred to as the *carbopalladative approach*; the second (path b) involves instead an intermolecular hydropalladation of the double bond, and as such is referred to as the *hydropalladative approach*. The latter is the only one of the two that, according to the classification of this section, ought to be discussed here.

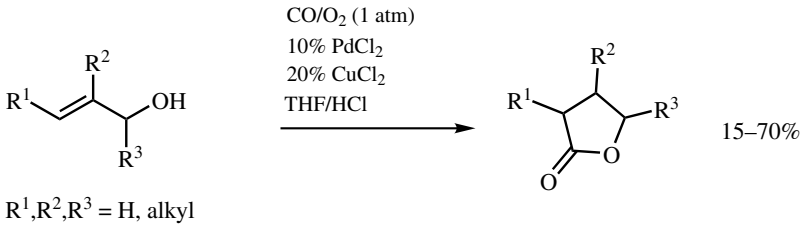
In actuality, however, it is often difficult to separate the two processes, and a brief discussion of both will be given, with an emphasis on processes that have been demonstrated



Scheme 21

to proceed by hydropalladation, that is, those that involve, as a final step, a true cyclization via nucleophilic attack of the alcohol functionality.

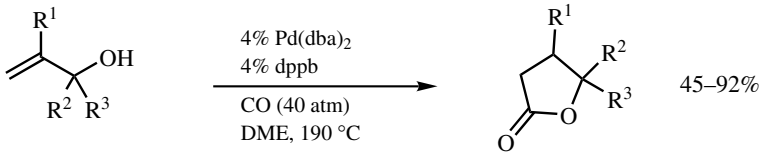
Alper and Leonard reported carbonylations of allylic alcohols under oxidative conditions using $PdCl_2$, HCl, O_2, and $CuCl_2$ in THF.[29] The reaction requires both oxygen and HCl to proceed (**Scheme 22**), but its mechanistic component remains uncertain. An extension of this work employing chiral ligands as additives afforded lactones with low to moderate ee.[30]



R^1,R^2,R^3 = H, alkyl

Scheme 22

Ali and Alper later developed a method for γ-lactone formation under neutral conditions from allylic alcohols according to **Scheme 23**, involving Pd(0) and dppb. The same protocol was also applied to synthesis of α,β-butenolides from propargylic alcohols.[31] Other bidentate or monodentate ligands give inferior results, and this correlates well with bite angle effects on the rate of the CO insertion reaction. Also, the allylic alcohol needs to be α-alkyl substituted to facilitate ring closure, in accordance with other studies.[32]–[34] This process was postulated by the authors to be of the *carbopalladative type*.

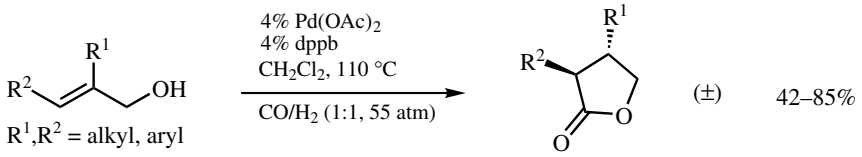


R^1 = H, alkyl; R^2 = alkyl, aryl; R^3 = H, alkyl

Scheme 23

Further developments by Brunner and Alper have led to a method for preparation of butyrolactones under reductive conditions from trisubstituted olefins, most likely a true

hydropalladative process, given the reductive conditions employed (**Scheme 24**).[35] In the absence of hydrogen, only minor amounts of lactone were produced or none at all. As shown below, the addition of "H-Pd-X" is highly stereospecific (*syn*), leading to 2,3-*trans*-dialkylbutyrolactones in high specificity.

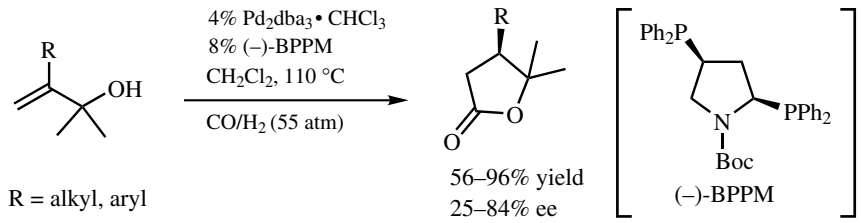


Scheme 24

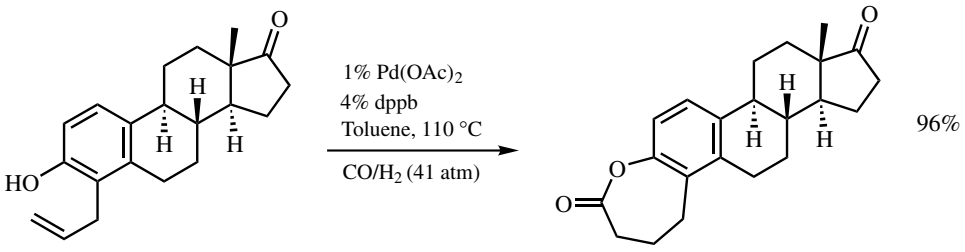
A very similar protocol (**Scheme 25**) was used for the catalytic asymmetric synthesis of butyrolactones, employing the chiral ligand (−)-BPPM.[34]

The protocol has a wide scope in terms of R substituents, alkyl as well as aryl groups being well tolerated, whereas the enantioselectivity appears to be higher for the aryl-substituted derivatives than the sterically more demanding alkyl groups.

Alper and co-workers also reported on the cyclocarbonylation reaction of *o*-allyl phenols.[36] These cyclizations were achieved using a cationic Pd complex or $Pd(OAc)_2$ combined with dppb under elevated pressures of CO/H_2. Reactions in toluene gave the highest selectivities for seven-membered ring lactones, whereas the use of CH_2Cl_2 switched the selectivity toward benzofuranones. The authors propose that *hydropalladative* and *carbopalladative* mechanisms may be in competition here. The isomerization of the double bond observed under some conditions prior to cyclization strongly supports a *hydropalladative* component. This cyclocarbonylation method was recently applied to the synthesis of new estrone derivatives containing a seven-membered ring lactone, starting from 4-allyl estrone (**Scheme 26**).[37]

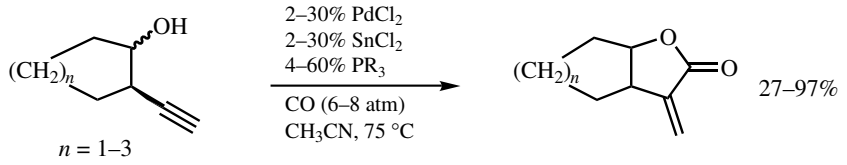


Scheme 25



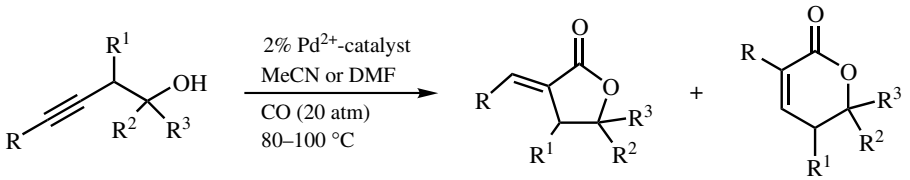
Scheme 26

The synthesis of α-methylene- γ-lactones from 3-butyn-1-ols, reported by Norton and co-workers[38,39] is clearly a *carbopalladative* process, as demonstrated by careful mechanistic and kinetic studies. Nevertheless, from a synthetic standpoint, the process is closely related to the lactonization reactions that form the topic of this section, and for this reason it is briefly mentioned here. The catalyst system that was developed for this reaction comprises $PdCl_2/SnCl_2/PR_3$[40] and was successfully applied to a number of different alkynols to prepare fused ring lactones (**Scheme 27**) in fair to excellent yields.



Scheme 27

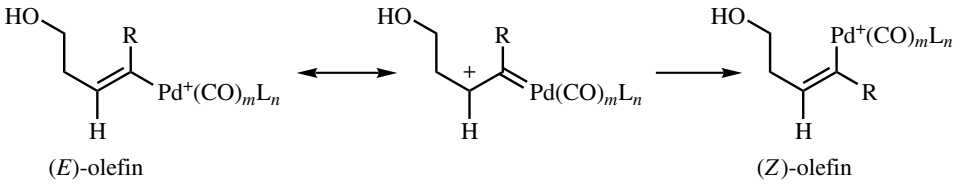
Many applications of this reaction have subsequently appeared, but their discussion is outside the scope of this section. However, an interesting mechanistic dichotomy between carbonylations in acetonitrile and DMF was recently observed in the cyclocarbonylation of 3-butyn-1-ols to give α-methylenebutyrolactones or α,β-unsaturated valerolactones as shown in **Scheme 28**.[41]



				MeCN		DMF	
R	R^1	R^2	R^3	Yield %	Ratio	Yield %	Ratio
H	H	H	H	77	26:74	49	100:0
H	H	H	CH_3	65	34:66	66	96:4
H	H	H	Ph	73	25:75	50	100:0
H	H	CH_3	CH_3	61	36:64	45	99:1
H	—$(CH_2)_3$	—	H *trans*	10	14:86	38	100:0
H	—$(CH_2)_3$	—	H *trans*	63	22:78	53	81:19
CH_3	H	H	H	30	53:47	11	100:0
$(CH_3)_3Si$	H	H	H	62	100:0	61	100:0

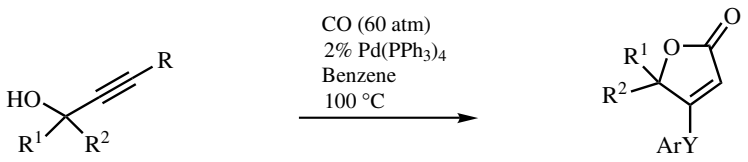
Scheme 28

In this protocol, palladium hydride addition to the triple bond (i.e., hydropalladation) is invoked as the key step to explain the formation of the six-membered ring lactones, which would require isomerization about the olefin in order to occur. Addition of the palladium hydride across the triple bond leads to the (*E*)-olefin shown in **Scheme 29**, which can isomerize to the (*Z*)-olefin via an intermediate cationic vinylpalladium species. The cyclization then can easily proceed via the (*Z*)-olefinic alcohol.



Scheme 29

An innovative procedure for the synthesis of sulfur- or selenium-containing lactones from propargyl or homopropargyl alcohols involves the formal addition of "ArS-Pd-X" or "ArSe-Pd-X" to a multiple bond as the key step.[42] When a propargyl alcohol is treated with CO under Pd(0) catalysis in the presence of diarylsulfides or diarylselenides, butenolides substituted in the β-position with S- or Se-based residue are formed (**Scheme 30**).



R^1	R^2	$(ArY)_2$	Yield %
H	H	$(PhS)_2$	43
H	H	$(PhSe)_2$	53
H	H	$(p\text{-}CF_3C_6H_4Se)_2$	74
H	Me	$(PhS)_2$	52
H	Me	$(PhSe)_2$	54
Me	Me	$(PhS)_2$	16
Me	Me	$(PhSe)_2$	57
	$—(CH_2)_4—$	$(PhS)_2$	14
	$—(CH_2)_4—$	$(PhSe)_2$	70

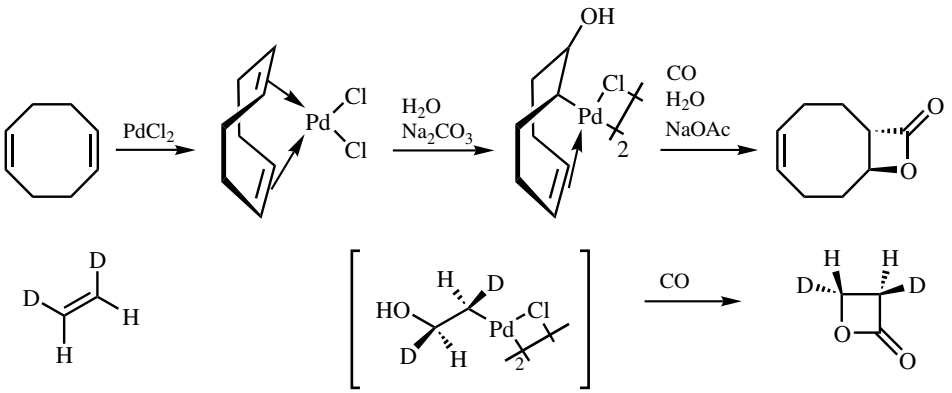
Scheme 30

Even a homopropargyl alcohol, 3-butyn-1-ol, may be used with satisfactory results.

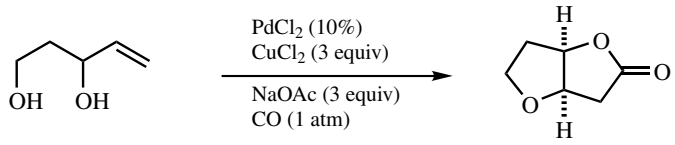
In a variant of the Wacker process, Stille and co-workers coupled the *anti*-addition of "HO-Pd-X" to an olefin with a lactonization process to confirm the stereochemistry of the hydroxypalladation of olefins (**Scheme 31**).[43],[44] The result supports the notion that the nucleophile attacks the olefin–palladium complex in an *anti* fashion. Further evidence for this came from the reaction of the *cis*-dideuterated ethylene with CO and water, which led to a lactone with the two deuterium atoms *trans* to each other.

A interesting variant of the above reaction type was applied to the synthesis of fused lactones. It involves the formal addition of "RO-Pd-X" to a double bond. When both alcohol nucleophiles are intramolecular, lactones fused to cyclic ethers result (**Scheme 32**).[45]

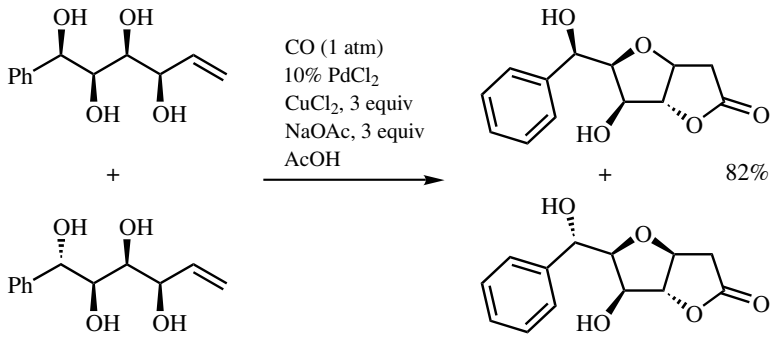
The most worrisome side reaction is reduction at the allylic position. Applications of this reaction to polyols as substrates have been reported. Among others, the synthesis of enantiomerically pure goniofufurone used, as a key step, the lactonization shown in **Scheme 33**.[46],[47] Following the above conditions, a high combined yield of the two epimeric lactones was obtained.



Scheme 31



Scheme 32

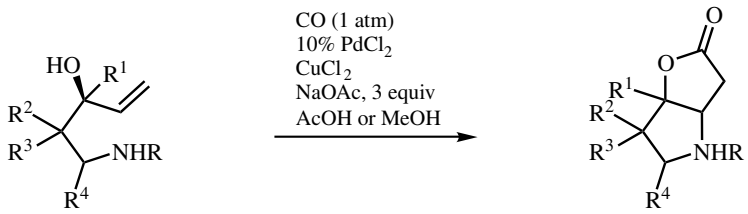


Scheme 33

A similar reaction was applied to the synthesis of naphthoquinone antibiotics.[48]

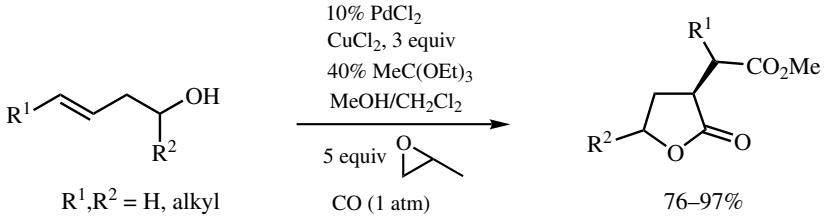
A versatile protocol for the formation of fused pyrrolidine γ-lactones from 3-hydroxypent-4-enylamides has been reported by Tamaru and co-workers[49],[50] This process involves the formal intramolecular addition of RNZ-Pd-X to the double bond as the key step. The key to the success of the reaction is the use of acetic acid as the solvent. Methanol gives high yield in some cases but leads generally to the formation of undesired side products. Substitution on the olefin is not tolerated and a *gem*-dimethyl or a *trans*-methyl group at the terminal position of the double bond leads to low or no yield of lactone, depending on the protective group on the nitrogen (**Scheme 34**).

Another process reported by Tamaru (**Scheme 35**) involves the formal addition of "ROOC-Pd-X" to a double or triple bond, followed by lactonization, although the sequence of events is not certain.



R	R^1	R^2	R^3	R^4	Solvent	Yield %
SO_2Tol	H	H	H	H	AcOH	90
CO_2Me	H	H	H	H	AcOH	95
CO_2Me	H	H	H	H	MeOH	35
CO_2Me	H	H	H	H	THF	<10
CONHPh	H	Me	Me	H	MeOH	97
CONHPh	H	Me	Me	H	AcOH	85
SO_2Tol	H	H	H	Ph	AcOH	74
SO_2Tol	H	Me	H	H	AcOH	70
SO_2Tol	Me	H	H	H	AcOH	66(30)
CO_2Me	Me	H	H	H	AcOH	79

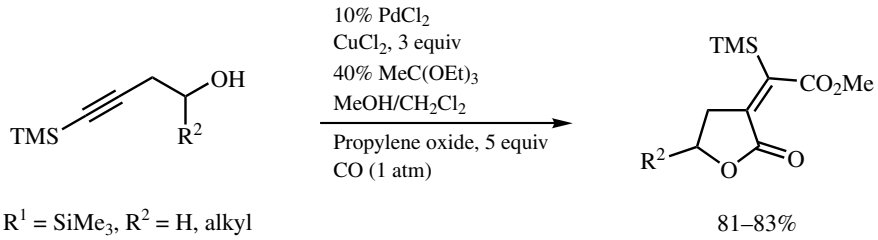
Scheme 34



Scheme 35

This lactone synthesis therefore involves a double carbonylation of the multiple bond and is therefore a very powerful and useful strategy in organic synthesis (**Scheme 36**).[51],[52]

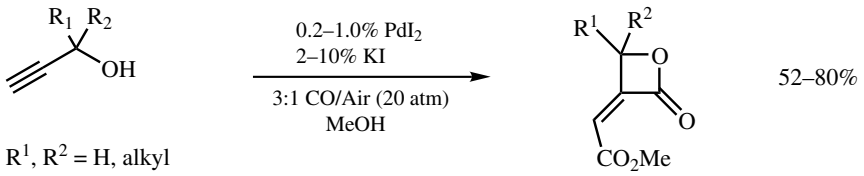
The reaction shown in **Scheme 35** is stereospecific, which was confirmed by using *cis* and *trans* 4-substituted olefinic alcohols, leading to opposite single diastereomeric lactones. The 3,5-*cis*/*trans* ratio obtained, however, was very close to 1:1. The role of propylene oxide is to react with the HCl formed during the reaction, thus keeping reaction conditions close to neutrality.



Scheme 36

This work has since been extended to an enantioselective protocol using chiral bisoxazoline ligands in combination with palladium.[53] Enantiomeric excesses were low to fair.

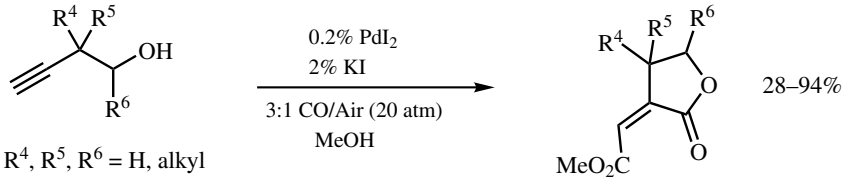
A more recent method for the synthesis of β- and γ-lactones from propargyl alcohols and 3-butyn-1-ols, respectively, was reported by Gabriele *et al.*[32],[33] Heating a methanol solution of the alkynyl alcohol under a mixture of CO and air in the presence of PdI_2 gives good yields of β-lactones (**Scheme 37**).



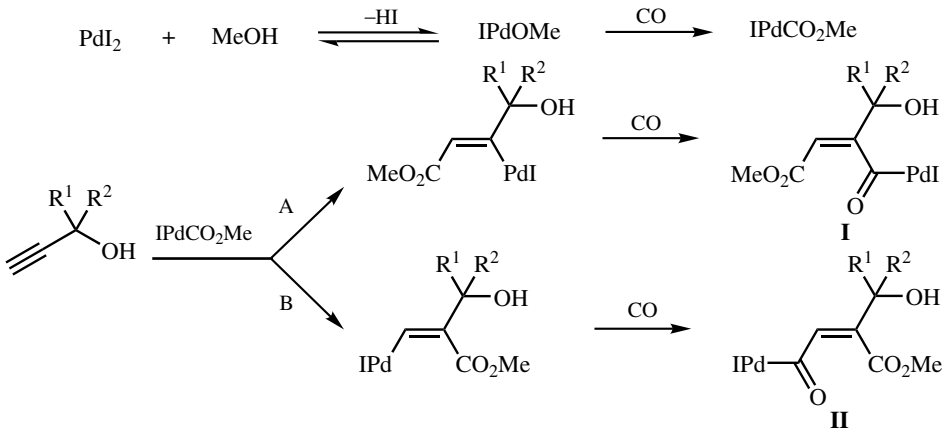
Scheme 37

In accordance with the Thorpe–Ingold effect, cyclization to the lactone is promoted by α,α-dialkyl substitution in the propargyl alcohol. The use of 3-butyn-1-ols leads to γ-lactones, as shown in **Scheme 38**.

The proposed mechanism for this transformation is outlined in **Scheme 39**. An acylpalladium complex adds to the alkynol following either path A or B, to give **I** or **II** after insertion of CO into the palladium–olefin bond. Formation of a β-lactone could then occur by attack of the hydroxyl group in **I** onto the acylpalladium complex.



Scheme 38



Scheme 39

As an alternative, **II** would undergo intermolecular attack of MeOH at the acylpalladium moiety to afford a maleic diester, which would then furnish the product after lactonization. However, path A was shown to be operative since the maleic diester, separately prepared by another method, did not cyclize to a lactone under the reaction conditions.

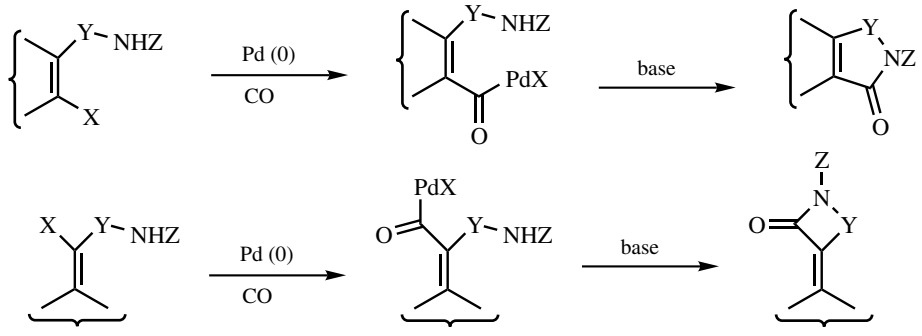
B. NITROGEN NUCLEOPHILES

B.i. By Oxidative Addition Processes

The great majority of lactam syntheses by Pd-catalyzed CO insertion proceed by the well-established oxidative addition of a Pd(0) species to an alkenyl or aryl halide, followed by CO insertion and cyclization. The unsaturation can be *endo* to the newly formed ring or *exo* to it, as shown in **Scheme 40**: examples of both strategies abound.

A more limited number of examples involving allylic and propargylic electrophiles also exist and will be listed at the end of this section.

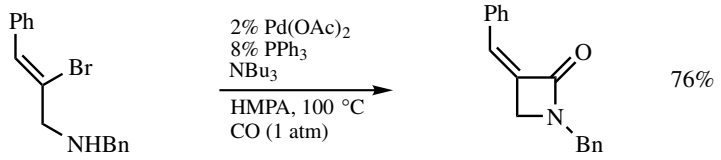
The substrates used for the operations in **Scheme 40** are usually aryl, heteroaryl, or alkenyl bromides and iodides. Triflates have also been used satisfactorily,[54] and one special case involving an N-based leaving group was reported (*vide infra*). The most common ring sizes prepared by this method are four, five, and six; seven-membered N-heterocycles have also been prepared, but the yields are frequently inferior to the ones observed for the smaller ring sizes. When five- and six-membered ring closures are in direct competition, the five-membered ring cyclization mode is slightly faster.[55] The great majority of studies report the use of secondary amines as the internal nucleophile. While tertiary amines cannot normally be used because they lack an abstractable proton, a case where a pyridine nucleophile was used has been reported.[56] With primary amines, a competing process is often amine carbonylation with formation of isocyanates and/or symmetrical ureas.[55],[57] Secondary amides have also been used, often with good results. In some cases, as in the formation of larger rings (e.g., seven-membered), direct intramolecular amination (the Hartwig–Buchwald reaction, see **Sect. III.3.2**) is a competing side process,[58] and the use of secondary amides gives better yields than the corresponding



Scheme 40

benzylic secondary amine. The conditions used in these reactions are rather standard, and a wide range of catalysts have not been explored. A source of either Pd(0), for example, Pd–dba complexes, or Pd(II), for example, $Pd(OAc)_2$, which is reduced *in situ* to the active species, is typically used, coupled with varying proportions of PPh_3 as the ligand. The base is usually a tertiary amine: tributylamine is the most popular, but other bases, such as KOAc,[59] TlOAc,[60] and K_2CO_3 have also been used from time to time. Finally, dipolar aprotic solvents like HMPA, DMF, and acetonitrile are the most common. Water does not harm the reaction (although too much of it could, in principle, give rise to carboxylic acids).[56] In some cases, nonpolar solvents such as toluene and anisole have been used, and many times the reactions have been run neat. The temperatures to be employed are typically in the range 80–100 °C. The pressure of CO employed is often 1 atm, but higher pressures have often been used to improve yields and cut down on side processes.

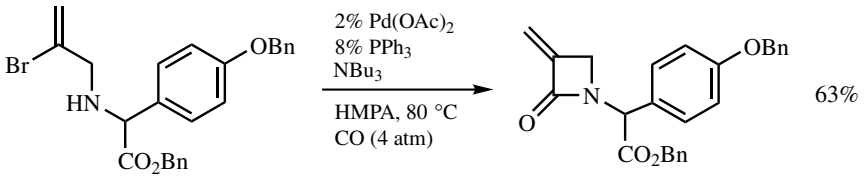
Formation of azetidinones via CO insertion has been generalized by Mori and co-workers and is a stereospecific process, as expected (**Scheme 41**).[61],[62]



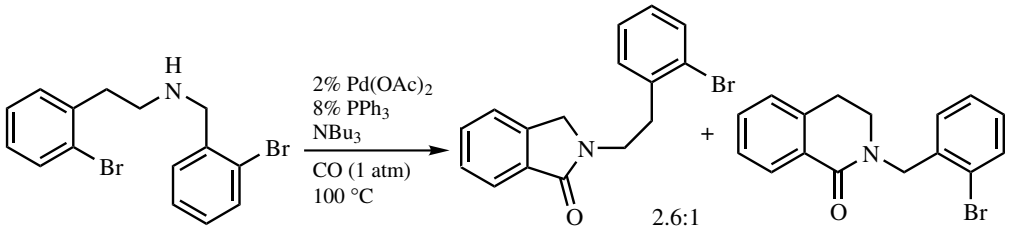
Scheme 41

A bicyclic system can also be obtained via this method.[63] Applications to the synthesis of β-lactam antibiotics, such as amino-nocardicinic acid (**Scheme 42**)[64],[65] and others,[57] have been reported.

Examples of formation of five- and six-membered rings by this type of process abound: Mori and co-workers have generalized both the *endo*-[55] and the *exo*-type process described in **Scheme 40**.[8] As part of the former study, a competition experiment (**Scheme 43**)



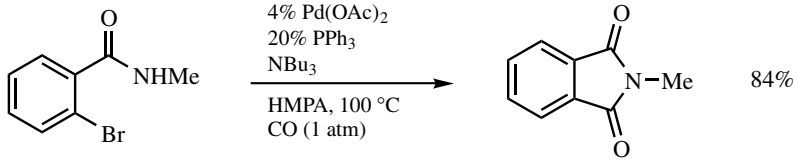
Scheme 42



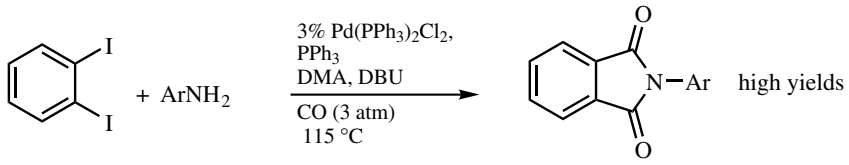
Scheme 43

provides the first estimate of relative cyclization rates of the five- versus six-membered ring, although the ratio may also reflect the relative rate of oxidative addition of the two aryl bromide moieties. Applications to the synthesis of yohimbane alkaloids[66] and sendaverine[67],[68] follow closely the above protocol.

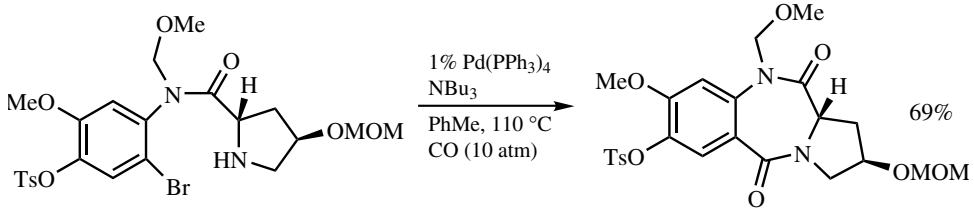
The use of secondary amides as nucleophiles has been also documented by Mori et al.[69] Synthesis of imides by this method is not always satisfactory, but phthalimides are prepared in high yield (**Scheme 44**). An interesting modification of this method consists of the double carbonylation of *o*-aryl diiodides and proceeds via an initial intermolecular amidation, followed by the intramolecular one described by Mori (**Scheme 45**).[70] The formation of seven-membered rings was demonstrated by the synthesis of diazepam[59] and a number of anthramycin alkaloids,[71],[72] including Prothracarcin and Tomaymycin (**Scheme 46**).[58] As mentioned above, for seven-membered rings direct amination is observed as a side reaction. Secondary ureas are also substrates for this reaction, yielding seven-membered cyclic ureas.[73]



Scheme 44



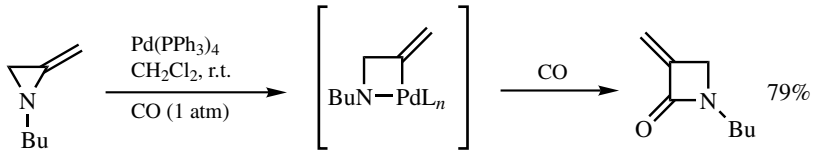
Scheme 45



Scheme 46

Alper and Hamel have reported an interesting case of Pd-catalyzed CO insertion reaction, involving ring expansion of aziridines to azetidinones (**Scheme 47**). It seems reasonable to assume that the reaction is initiated by oxidative addition of Pd(0) across the strained C—N bond, as shown below.[74]

As mentioned above, allylic and propargylic substrates have also been used, although no general study has been reported. This is an area that is ripe for further studies and



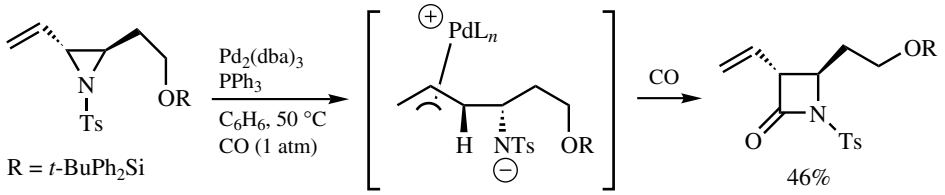
Scheme 47

interesting applications are sure to emerge: the stereo- and regiochemical issues arising with allylic electrophiles are an opportunity to carry out complex, selective organic transformations.

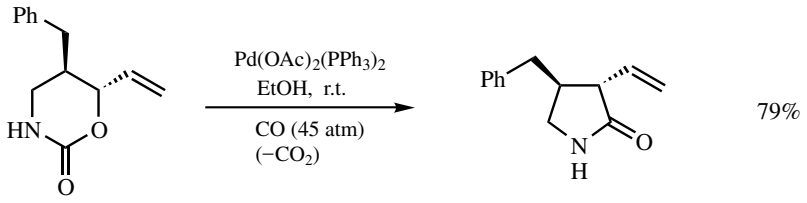
Tanner and Somfai have reported that 2-vinyl-*N*-tosyl aziridines can be ring-expanded by CO insertion, in a stereospecific manner (**Scheme 48**),[75] whereas Bando and coworkers reported a stereospecific decarboxylative carbonylation of cyclic carbamates (**Scheme 49**).[23]

Finally, propargylic carbonates bearing pendant amines give rise to allenyl azetidinones. In many cases, however, isomerization of the allene moiety to an alkyne is a side reaction (**Scheme 50**).[76]

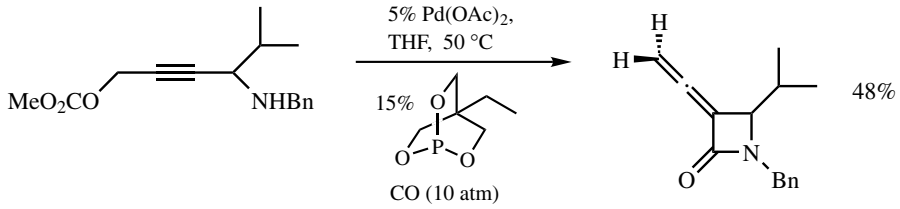
In conclusion, the synthesis of N-heterocycles by Pd(0)-mediated oxidative addition processes/CO insertion is a powerful tool whose scope needs to be further investigated



Scheme 48



Scheme 49

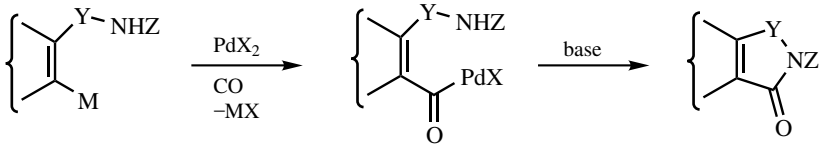


Scheme 50

and generalized. Mechanistic investigations are also lacking: although the mechanism is expected to be similar to the one of the corresponding intermolecular processes, the rate-determining step, due to the intramolecular versus intermolecular nature of the amidation reaction, may in principle be different.

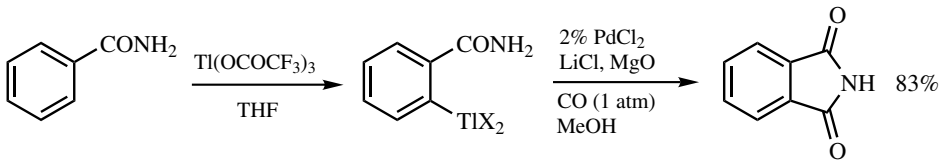
B.ii. By Transmetallation Processes

In a process of this kind, the active R-Pd(II) species is formed by transmetallation of an active organometallic agent with a preformed Pd(II) salt. In this scheme, the Pd(II) is reduced, at the end of each cycle, to Pd(0) and a reoxidant must be employed (**Scheme 51**). Surprisingly, examples of this strategy are extremely rare.



Scheme 51

Larock and Fellows, for example, have reported an *in situ* thallation/cyclocarbonylation to afford phthalimides. In this case, an organothallium compound is formed *in situ* by *ortho*-metallation; transmetalation by Pd(II) is followed by CO insertion and cyclization (**Scheme 52**).[26] The Pd(0) is reoxidized by the Tl(III) salt. Operations of this kind are more involved than the ones described in **Sect. B.i** but have the obvious advantage of not requiring activation of a C—X bond to trigger the cyclization process, and therefore employ simpler and cheaper starting materials. These processes, therefore, ought to be investigated more extensively, perhaps using metals that are less toxic than thallium.

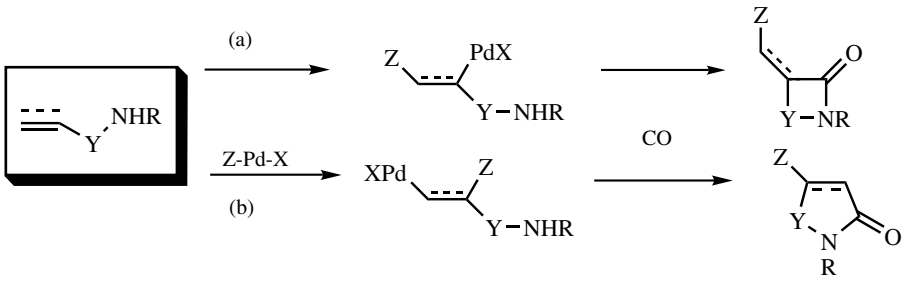


Scheme 52

B.iii. By Additive Processes of Pd(II) Species Across Double and Triple Bonds

In processes of this kind, a Z-Pd-X species is added across a multiple bond. The resulting alkyl (or alkenyl) Pd(II) species must be stable enough to undergo carbonylation, followed by capture by an internal N-based nucleophile (**Scheme 53**). Because addition across a multiple bond can occur with two distinct regiochemistries (paths a and b), this process can in principle generate two types of products, differing in ring size.

Examples of this strategy are rare, but the possibilities are many, and this type of process undoubtedly represents a very fruitful field for further research and applications.



Y = carbon chain; X = halogen, acetate; Z = H, X, C, or N substituent; R = alkyl, aryl

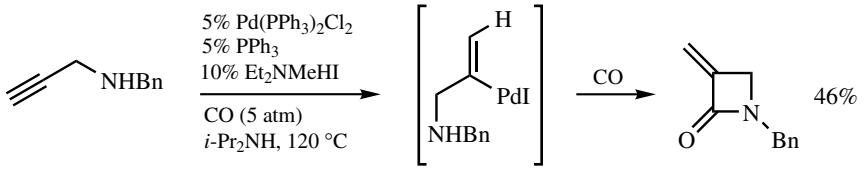
Scheme 53

A subset of this type of reaction, that is, the Heck and/or other multiple insertion reactions terminated by carbonylation, has been reviewed in **Sect. IV.3.3** and will be mentioned only briefly here.

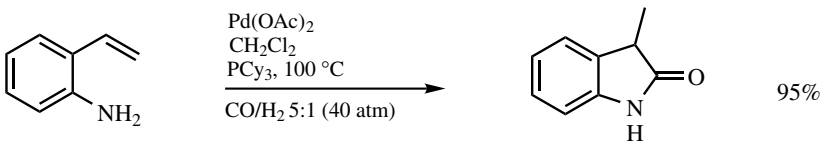
The formal addition of "H-Pd-I" to the triple bond has been invoked to explain the reductive cyclocarbonylation of propargyl amines devised by Torii et al.[77] (**Scheme 54**).

When applied to olefinic anilines, this type of process leads to fused lactams. While *o*-vinyl anilines selectively yield indolones (**Scheme 55**), *o*-allyl anilines afford complex mixtures of five-, six-, and seven-membered rings.[36]

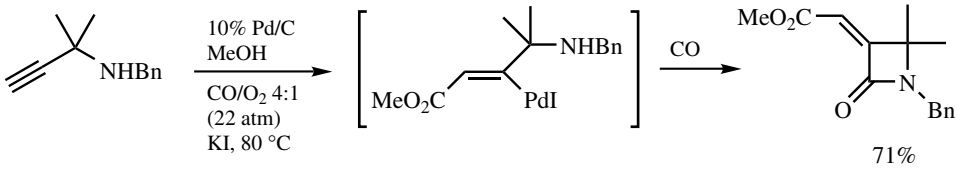
Alkoxycarbonylation/palladation across triple bonds, that is, addition of "ROOC-Pd-X," can also be used as the initiating reaction (**Scheme 56**), and the addition is stereospecific, favoring palladation at the internal alkyne carbon.[78]



Scheme 54



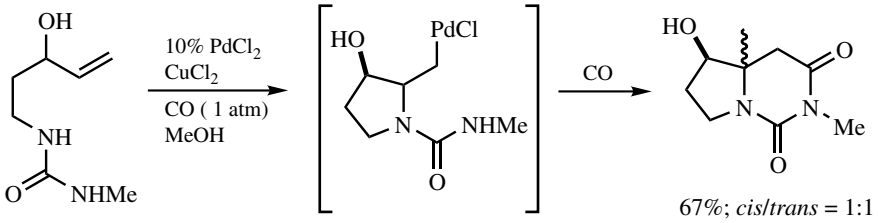
Scheme 55



Scheme 56

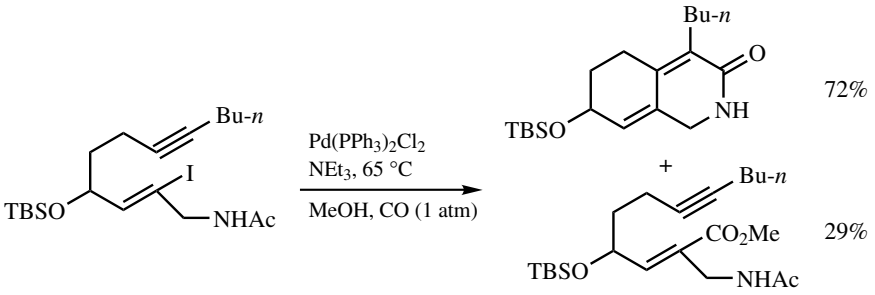
Addition of Pd-N species can be envisioned (proceeding probably in an *anti* mode, with prior coordination of the olefin by Pd), but surprisingly this strategy has not been pursued extensively.

An example is shown in **Scheme 57**.[50] In this case the first ring is formed in a stereo-random manner. A more general study on the scope of this two-stage process would be desirable.



Scheme 57

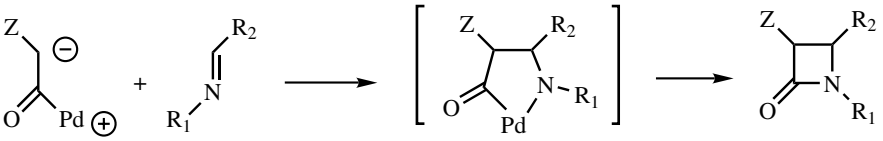
Finally, cascade insertion processes can be terminated by carbonylation to form lactam rings. This is discussed in detail in **Sect. IV.3.3**. An example of this process is shown in **Scheme 58**. In this case, direct carbonylation interferes appreciably with the desired insertion across the triple bond.[16],[79]



Scheme 58

B.iv. By Cycloaddition Processes

This very ingenious type of process was recently reported by Torii and co-workers, who proposed a mechanism proceeding via a dipolar-type cycloaddition followed by CO insertion, as shown in **Scheme 59**.[80],[81] This is an interesting approach to β-lactams, as it

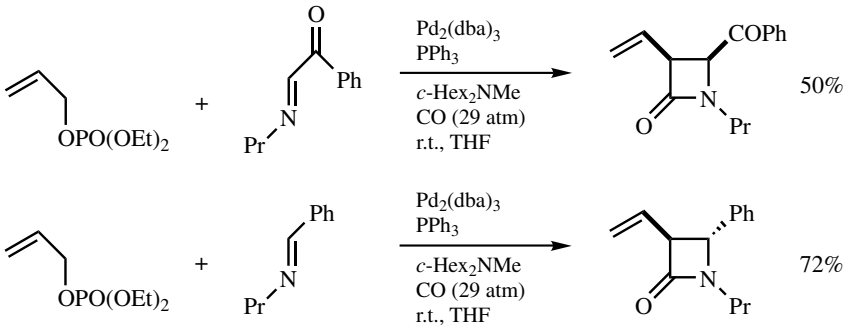


Z = alkenyl, aryl; R_1 = alkyl; R_2 = acyl, aryl

Scheme 59

is often highly stereoselective, but in a manner that is complementary to the classical Staudinger reaction.

Selected applications are shown in **Scheme 60**. The reaction is highly stereoselective, imines from α-ketoaldehydes yielding mostly or exclusively *cis*-azetidinones, whereas imines from benzaldehydes yield only *trans*-isomers. The approach has been extended to benzyl electrophiles in place of allyl phosphates.[82] A synthesis of cephems using this novel [2 + 2] cycloaddition has been reported by Zhou and Alper.[83] This method represents a potential entry into the medicinally important class of β-lactam antibiotics, and further applications are expected.



Scheme 60

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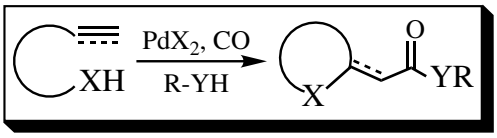

VI.2.1.3 Tandem and Cascade Processes Terminated by Carbonylative Esterification, Amidation, and Related Reactions

HANS-GÜNTHER SCHMALZ and OLIVER GEIS

A. INTRODUCTION

An elegant way to generate acylpalladium derivatives is based on the combination of nucleophilic attack on η^2-alkene- or alkyne-Pd(II) complexes (e.g., alkoxy- or aminocarbonylation; see **Sect. V.3**) and subsequent carbonylation. The resulting acylpalladium intermediates can then further react with group 15 or 16 atom nucleophiles to form carboxylic acid derivatives as discussed in the previous sections (**Sects. VI.2.1.1** and **VI.2.1.2**). This section focuses on transformations of the general type shown in **Scheme 1**, where the initial nucleophilic attack occurs in an intramolecular fashion. Such tandem reactions have a great synthetic potential as they involve the formation of three new bonds to give substituted five- or six-membered heterocycles, often with a high degree of stereoselectivity.[1]–[5]

The general mechanism of this chemistry is shown in **Scheme 2**. At first, the *in situ* generated η^2-alkene- (or alkyne-) Pd(II) complex (**1**) is intramolecularly attacked by a nucleophile, for example, an alcohol or an amine, to form an alkoxy- or aminopalladated species (**2**). In the presence of carbon monoxide this intermediate rapidly undergoes migratory insertion, usually faster than the competing β-hydride elimination. The resulting acylpalladium derivative (**3**) is finally trapped by a second nucleophile (usually the solvent) to give the product (**4**). To close the catalytic cycle, the released Pd(0) must be converted back to Pd(II). This is usually achieved by the addition of stoichiometric amounts of $CuCl_2$. In principle, oxygen can be used as the stoichiometric oxidant as in the Wacker oxidation; however, this seems to be efficient only in certain cases.

B. ALKOXYCARBONYLATION

B.i. Synthesis of Substituted Hydrofurans and Hydropyrans

After James and Stille had shown the general possibility to link (intermolecular) alkoxypalladation and carbonylation processes,[6] Semmelhack and co-workers were the

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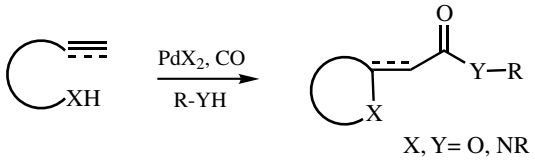
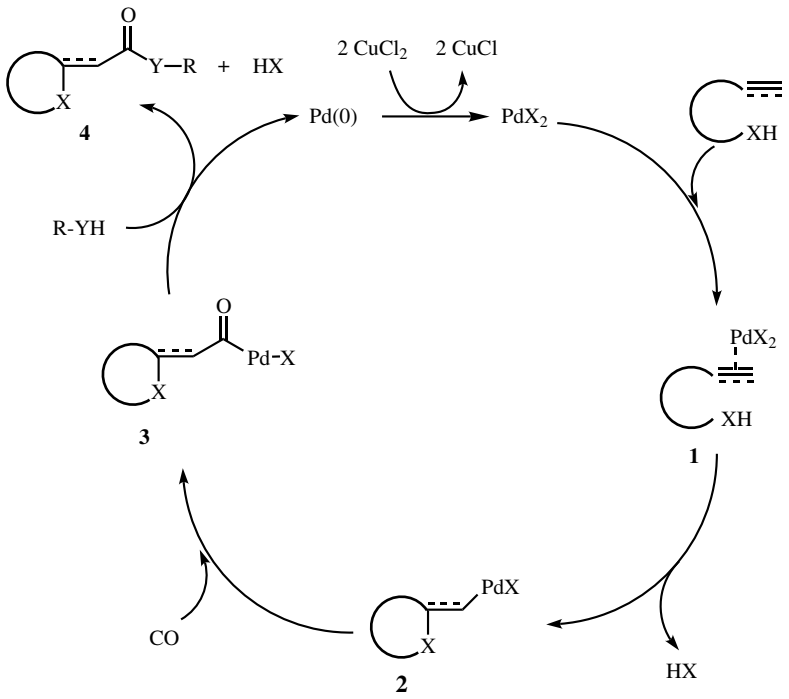
ISBN 0-471-31506-0

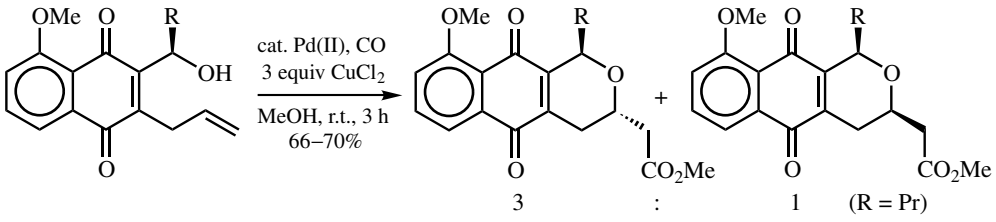


Scheme 1



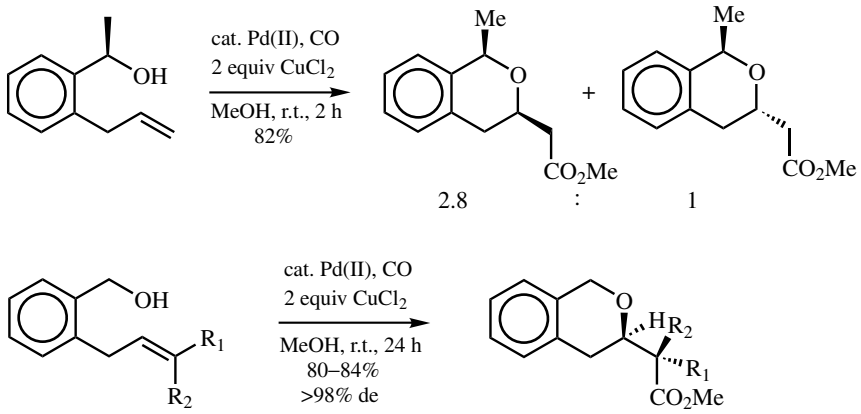
Scheme 2

first to achieve Pd-catalyzed intramolecular alkoxycarbonylation reactions (**Scheme 3**), which they used as key reactions in the total synthesis of naphthoquinone antibiotics such as nanaomycin A and desoxyfrenolicin.[7]–[10] In a typical reaction, the substrate is stirred at room temperature (r.t.) in methanol under an atmosphere of CO (1.1 atm) in the presence of 5–10 mol % of $PdCl_2$ and an excess (3 equiv) of $CuCl_2$. Although the



Scheme 3

cis/*trans*-diastereoselectivities are usually only moderate in these cases, the amount of *trans*-product can be enhanced by subsequent equilibration. In model experiments, the stereospecificity of the alkoxypalladation step (*anti* addition) was demonstrated with substrates having a stereogenic double bond (**Scheme 4**).[11]

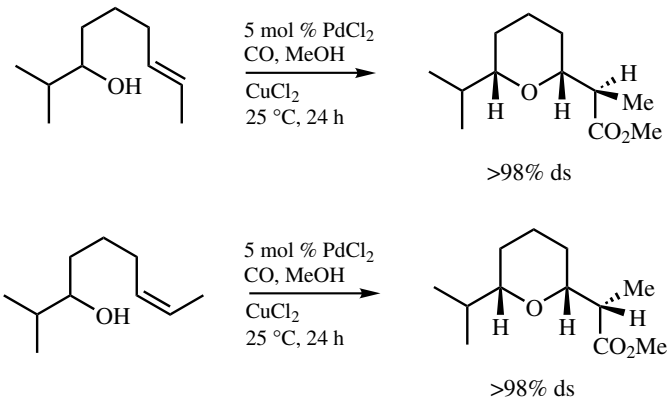


a: R^1 = Me, R^2 = H
b: R^1 = H, R^2 = Me

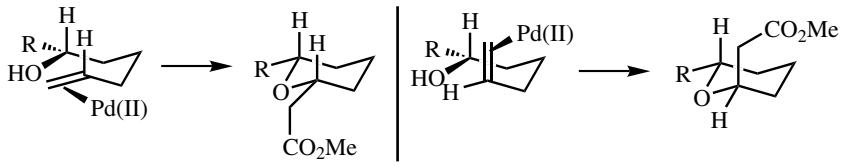
a: R^1 = Me, R^2 = H
b: R^1 = H, R^2 = Me

Scheme 4

After these initial successes, the use of acyclic substrates has systematically been investigated.[12]–[14] In the reaction of (*E*- or *Z*-configured) 1,6-disubstituted 5-hexenols only one diastereomer of the resulting tetrahydropyrans could be isolated (**Scheme 5**). The 2,6-*cis* arrangement of side chains could be explained in terms of a pseudochair conformation in the transition state of the nucleophilic addition.[13] The *trans* stereochemistry is disfavored because it would require the η^2-alkene-Pd(II) moiety to adopt a pseudoaxial position (**Scheme 6**).

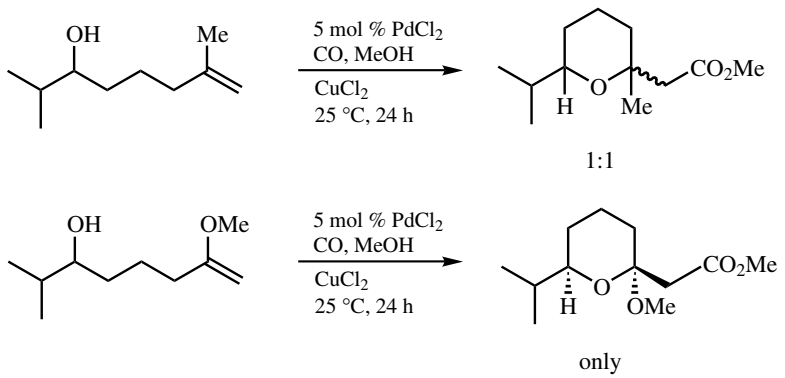


Scheme 5



Scheme 6

With 1,5-disubstitued 5-hexenols *cis*- and *trans*-2,6-disubstituted tetrahydropyrans are formed in a 1:1 ratio when the substituent in 5-position is a methyl group; however, only the *cis*-product is observed if this substituent is a methoxy group (**Scheme 7**). The reason for this is the preference of the methoxy group to take an axial position (anomeric effect).[12]

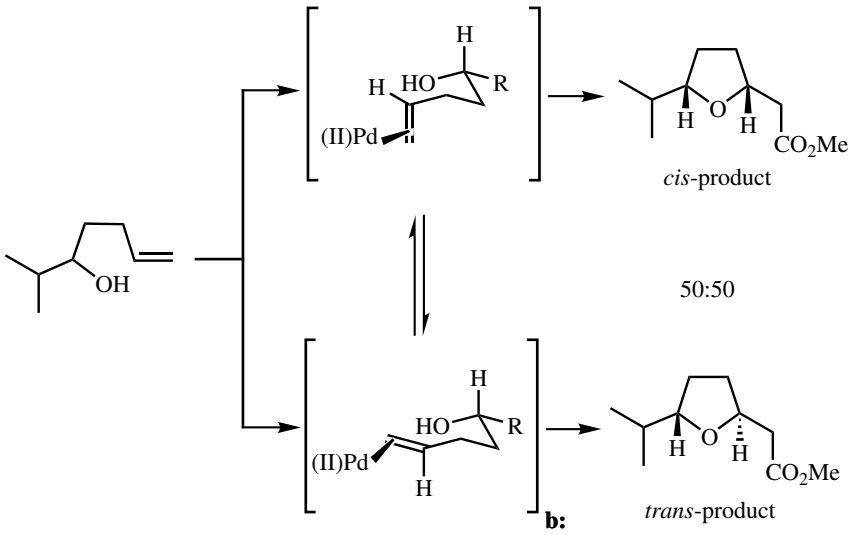


Scheme 7

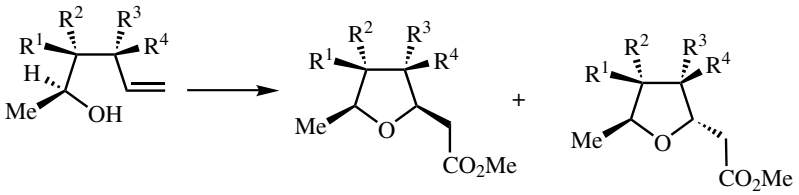
Starting from 1-substituted 4-pentenols, tetrahydrofurans are formed without significant diastereoselectivity.[13] Obviously, the two competing transition states leading to the *cis*- and the *trans*-product, respectively, are of comparable energy in this case (**Scheme 8**).

Semmelhack and Zhang also examined the influence of substituents in 2- and 3-positions on the selectivity of the cyclization of 1-substituted 4-pentenols. Substituents in 2-position were found to have nearly no influence on the diastereoselectivity, while substituents in 3-position induced significant selectivities. Depending on the substrate configuration, either the *cis*- or the *trans*-products are formed predominantly (*cis*/*trans* ratios $\leq$ 9:1) (**Scheme 9**).[14]

Goldsmith and co-workers probed the scope of this reaction by employing 1,3-disubstituted hex-4-en-1-ols, which give rise to 2,3,5-substituted tetrahydrofurans with up to four stereogenic centers (**Scheme 10**).[15] With substrates having trisubstituted double bonds no cyclization was observed under standard conditions. However, the addition of 0.1–0.2 equiv of triethylamine accelerated the cyclization. These authors also examined the competing formation of five-membered versus six-membered rings. It was found that the substitution pattern at the olefin has a strong influence on the regioselectivity (tetra hydropyran versus tetrahydrofuran formation).



Scheme 8

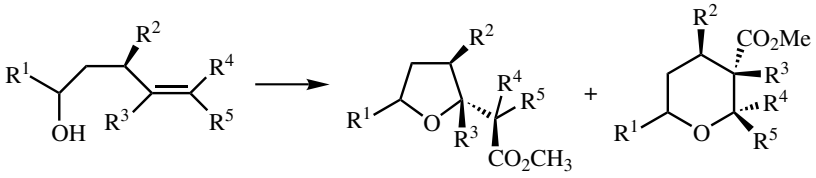


	R^1	R^2	R^3	R^4	Ratio *cis*/*trans*
1	Me	H	H	H	38:62
2	H	Me	H	H	50:50
3	H	H	Me	H	10:90
4	H	H	Ph	H	0:100
5	H	H	H	Me	87:13
6	H	H	H	Ph	93:7

Scheme 9

More recently, White and co-workers investigated the influence of substituents in the synthesis of highly substituted tetrahydropyrans starting from 5-hexenol derivatives.[16] In all cases 2,6-*cis*-configured products were observed. The configuration of the substituents in positions 3 and 4 was found to have a crucial influence on the yields (0–61%), as shown in **Table 1**.

Surprisingly, the product with two axial substituents in its chair conformer (**Table 1**, entry 4) is formed with the highest yield (61%) while the all-equatorial product (**Table 1**, entry 2) was not observed at all under the same conditions. This phenomenon was explained with the assumption of a pseudochair transition state and repulsive steric interactions of

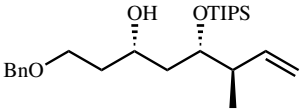
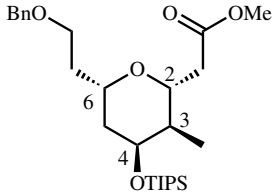
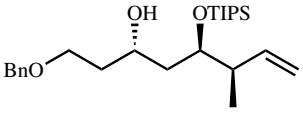
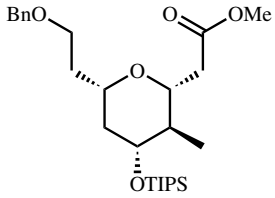
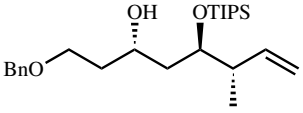
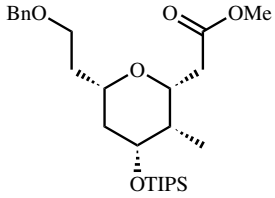
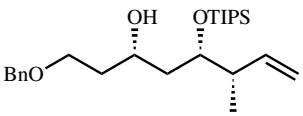
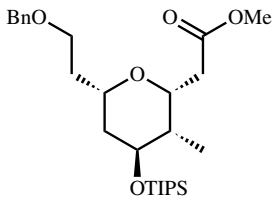


5 **6**

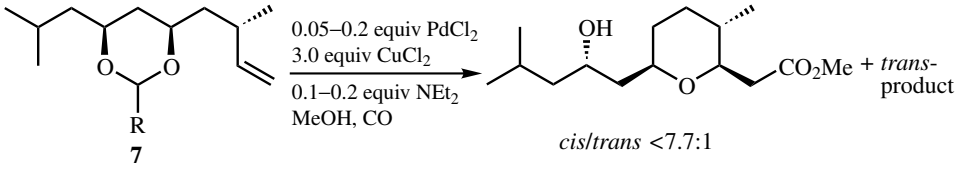
	R^1	R^2	R^3	R^4	R^5	Yield (%)	Ratio **5/6**
1	H	Me	H	H	H	87	**5** only
2	Ph	Me	H	Me	H	85–87	**5** only
3	H	Me	Me	H	Me	65	**5** only
4	H	Me	H	Me	Me	66	**6** only
5	H	Me	H	H	Me	75	1:4
6	Me	^{i}Pr	H	Me	H	80–84	**5** only

Scheme 10

TABLE 1. Pd-Catalyzed Cyclization–Carbonylative Esterification Tandem Process Giving Tetrahydropyrans

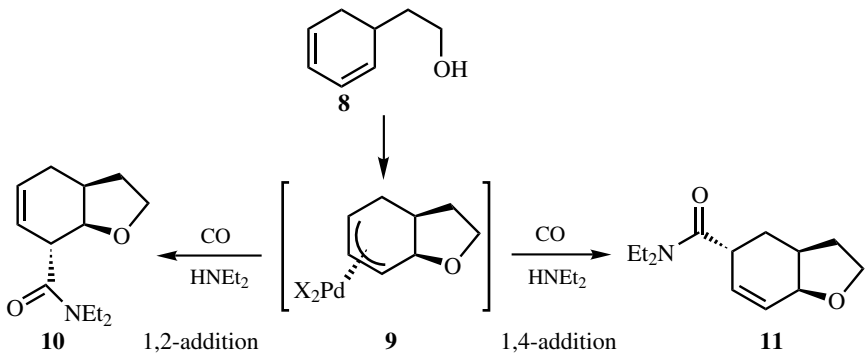
Entry	Substrate	Product	Yield (%)
1			20
2			0
3			40
4			61

the Pd fragment with the other substituents.[16] Acetals of type **7** can also be employed in the synthesis of cyclic ethers (**Scheme 11**). In this case, the yield and the *cis*/*trans* diastereomer ratio were found to depend on the substituent at the acetal carbon.[17]

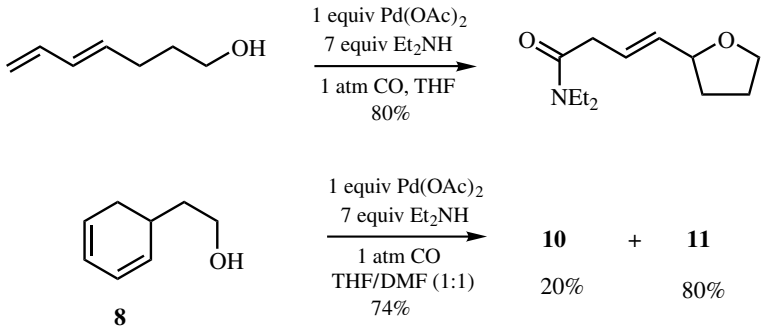


Scheme 11

Anderson and Aranyos documented the alkoxycarbonylation of hydroxy 1,3-dienes **8**; however, they used stoichiometric amounts of $Pd(OAc)_2$ (**Scheme 12**).[18] At first, the substrates react with Pd(II) to form an intermediate π-allylpalladium complex **9**, which is subsequently carbonylated to give either the 1,2- or the 1,4-addition product (**10** and **11**). With acyclic substrates the selectivity is 95:5 in favor of the 1,4-addition product (**Scheme 13**). In the case of cyclic substrates, however, the selectivity depends on the solvent and the CO pressure. The best results with **8** were obtained in a THF/DMF mixture (1:1) and a CO pressure of 1 atm to give a 4:1 mixture in favor of the 1,4-addition product **11**.

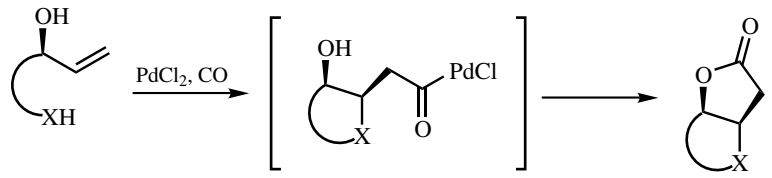


Scheme 12



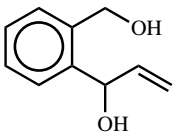
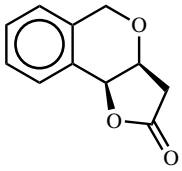
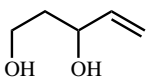
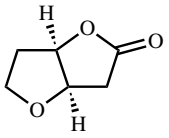
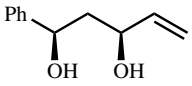
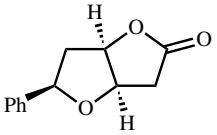
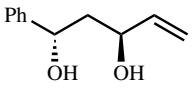
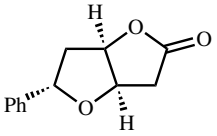
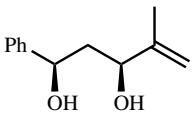
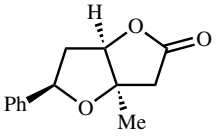
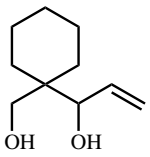
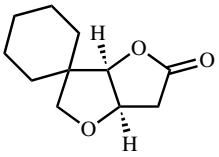
Scheme 13

When additional hydroxy functionalities are appropriately placed in the substrate, the intermediate Pd-acyl species are intramolecularly trapped to form *cis*-fused bisheterocyclic γ-lactones (**Scheme 14**). The first examples of such tandem reactions (**Table 2**) were published by Semmelhack et al.[19] and Tamaru et al.[20]



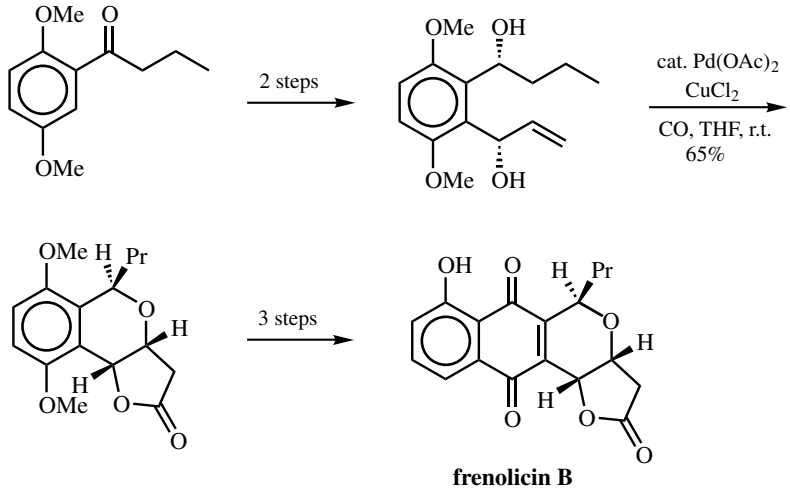
Scheme 14

TABLE 2. Termination of Pd-Catalyzed Formation of Cyclic Ethers by Carbonylative Lactonization

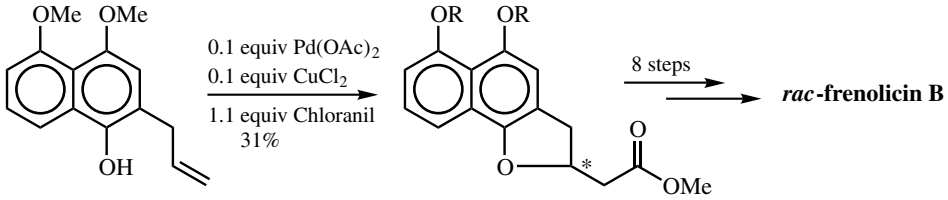
Substrate	Product	Yield (%)	Reference
		68	[10]
		60	[11]
		80	[11]
		70	[11]
		80	[11]
		86	[11]

In a remarkably short and enantioselective total synthesis of frenolicin, Kraus and co-workers demonstrated the practical use of this chemistry (**Scheme 15**).[21],[22]

In a different approach to racemic frenolicin B, which also makes use of an intramolecular alkoxycarbonylation, chloranil was introduced as the stoichiometric oxidant. However, the key reaction proceeded only with rather low yield (**Scheme 16**).[23]

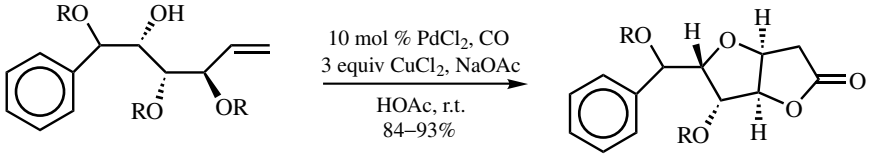


Scheme 15



Scheme 16

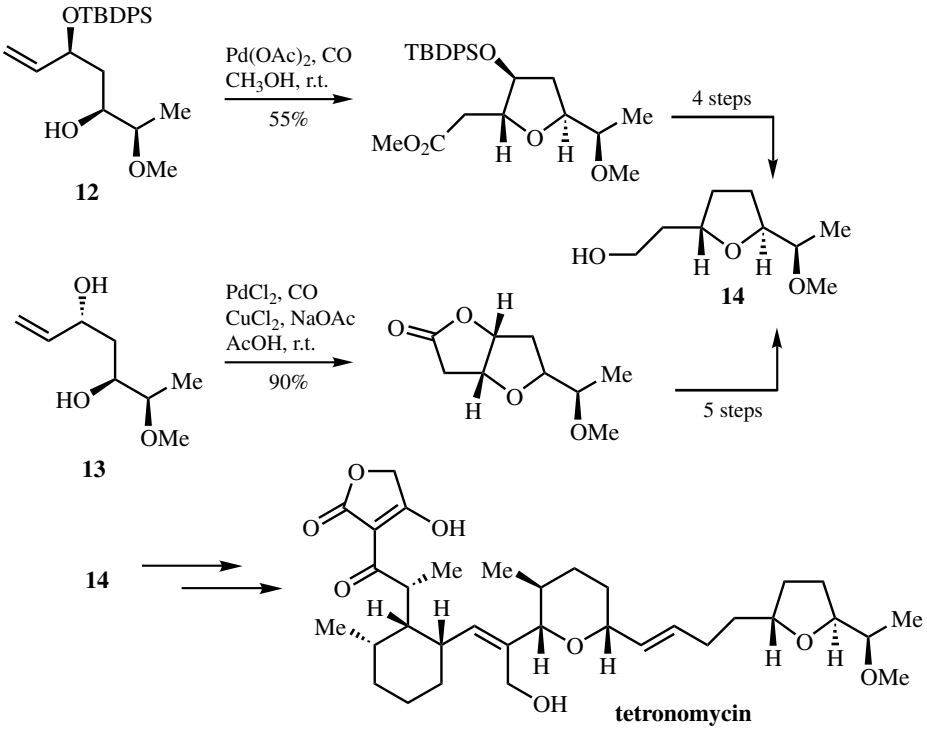
Jäger and co-workers demonstrated that the Pd-catalyzed alkoxycarbonylation of unsaturated polyoles represents a powerful tool for the ω-homologation of aldoses. In general, *cis*-fused bicyclic lactones are obtained with high selectivities.[24]–[26] For instance, D-*gluco*-configurated products are generated in high yield starting from D-lyxose derivates (**Scheme 17**). This methodology was exploited in a concise synthesis of (−)-goniofufurone.[24]–[26]



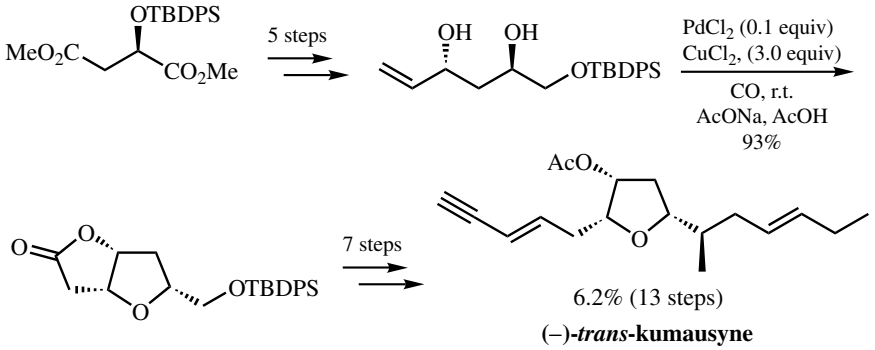
Scheme 17

Another convincing application of the alkoxycarbonylation chemistry represents the total synthesis of tetronomycin by Semmelhack et al.[27],[28] Here, the two pseudoepimeric substrates **12** and **13** could both be converted into the desired intermediate **14**, which served as the eastern part of the target molecule (**Scheme 18**).

Recently, Boukouvalas et al.[29] accomplished a very short synthesis of the red algal metabolite *trans*-kumausyne (**Scheme 19**). The precursor for the alkoxycarbonylation was prepared from dimethyl (*R*)-malate. The key transformation then proceeded in high yield, and only seven more steps were needed to reach the desired product (6.2% overall yield).



Scheme 18

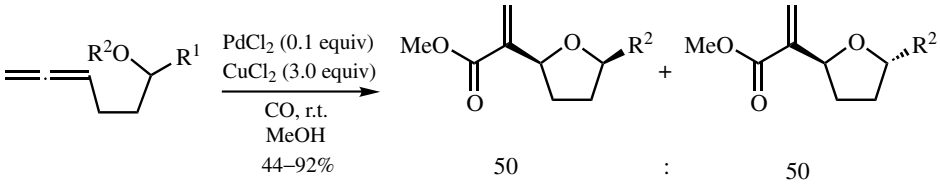


Scheme 19

B.ii. Use of Allenic Substrates

It was first demonstrated by Walkup and Park that γ-oxygenated allenes can be transformed to 2-(2-tetrahydrofuranyl) acrylates by alkoxycarbonylation, however, without any significant *cis*/*trans* diastereoselectivity (**Scheme 20**).[30]

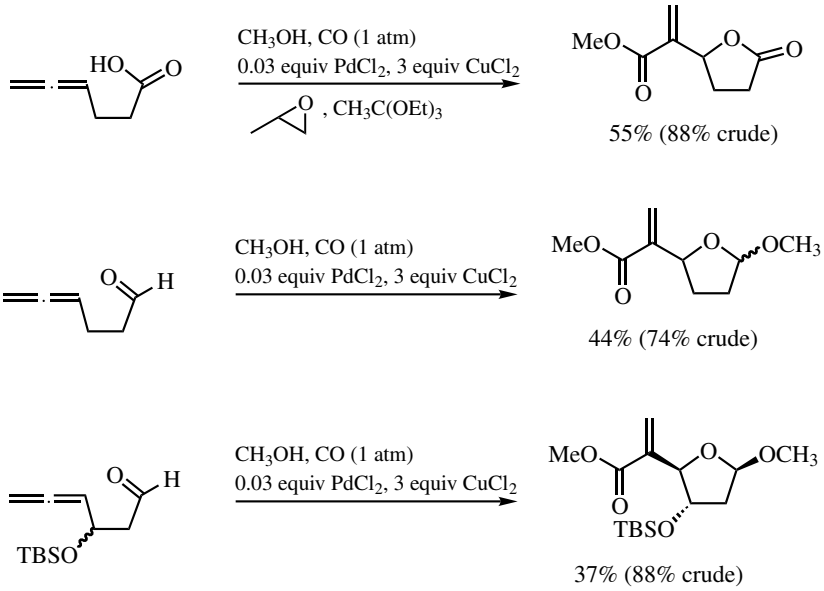
In a related study, high *cis*-selectivities were obtained with trialkylsilyl-protected substrates when the ring formation was initiated by oxymercuration prior to the Pd-catalyzed carbonylation step.[31]–[34]



R^1 = H, CH_3, CH_2COR
R^2 = H, OTBS

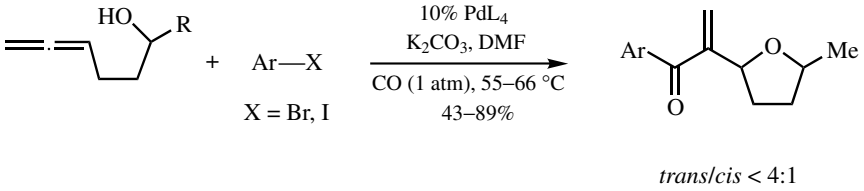
Scheme 20

The conversion of 4,5-hexadienoic acids to furanones and of 4,5-hexadienals to furanosides was achieved in a one-pot acetalization–cyclization–methoxycarbonylation procedure (**Scheme 21**).[35] Trialkylsiloxy substituents in β-position induce high stereo selectivities. This method was applied in a synthesis of nucleoside analogs bearing a branched difunctional side chain.[36]

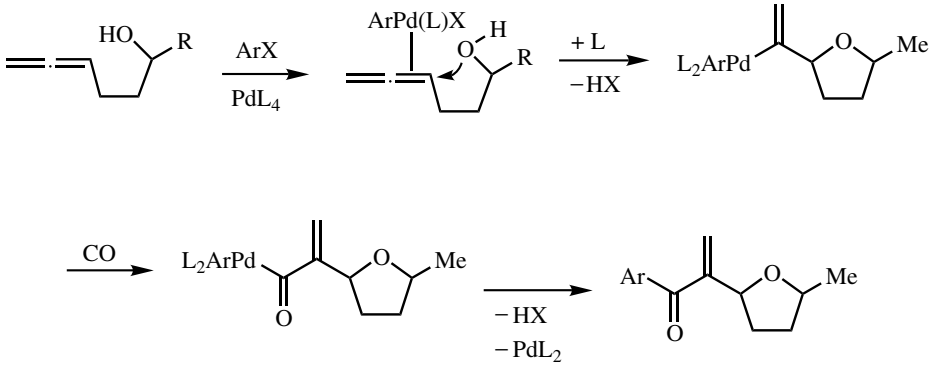


Scheme 21

In the presence of arylhalides γ-hydroxyallenes give rise to aryl(tetrahydrofuran-2-yl)vinyl ketones (**Scheme 22**).[37] In this case, the Pd(0) inserts into the aryl–halide bond (oxidative addition) prior to the oxypalladation and CO insertion step (**Scheme 23**). In general, the *trans*-products are formed predominantly.



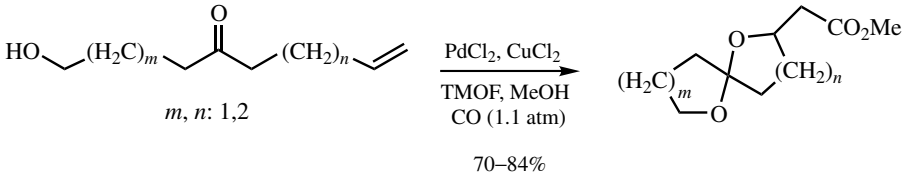
Scheme 22



Scheme 23

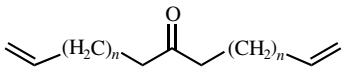
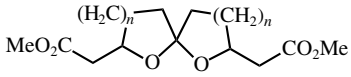
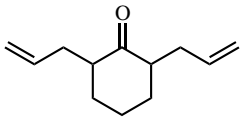
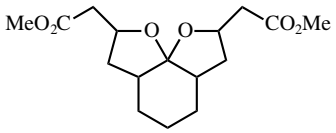
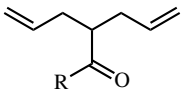
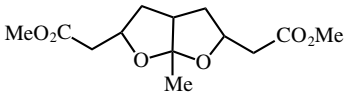
B.iii. Synthesis of Spiroacetals

The alkoxycarbonylation reaction is also useful for the synthesis of spiroacetals (**Scheme 24**).[38] Thus, certain hydroxyenones react under the standard conditions in the presence of trimethyl orthoformate (TMOF) to afford the corresponding spiroacetals via hemiketal intermediates in high yield. It is also possible to prepare spiroacetals starting from dienones (**Table 3**).[39] The stereochemistry of the products was not established; however, this method is of potential value for the synthesis of bioactive compounds with spiro acetal substructure.



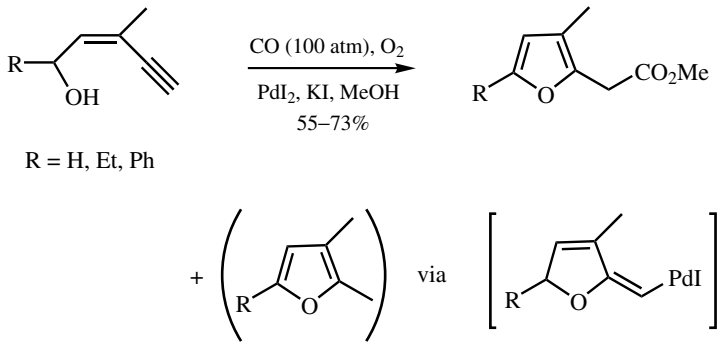
Scheme 24

TABLE 3. Pd-Catalyzed Conversion of α,ω-Dienyl Ketones into Bicyclic Diethers

Substrate	Product		Yield (%)
		$n = 1$ $n = 2$	50 85
			75
		$R = CH_3$ $R = Ph$	54 90

B.iv. Intramolecular Alkoxycarbonylations Involving Alkynes

Chiusoli and co-workers succeeded in preparing furan-2-acetic esters by Pd-catalyzed intramolecular alkoxycarbonylation of (*Z*)-2-en-4-yn-1-ols under oxidative conditions (**Scheme 25**).[40] However, a high carbon monoxide pressure (up to 100 atm) and an excess of KI are crucial for the efficiency of the reaction, which probably proceeds via vinylpalladium intermediates. In a related reaction, acetylenic ureas gave rise to a mixture of three different products.[41]

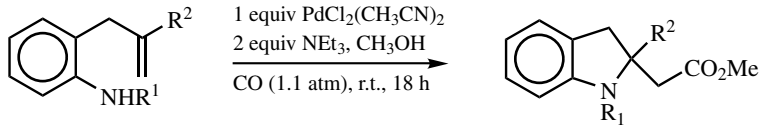


Scheme 25

C. AMINOCARBONYLATION

C.i. Aminocarbonylation with Alkenes

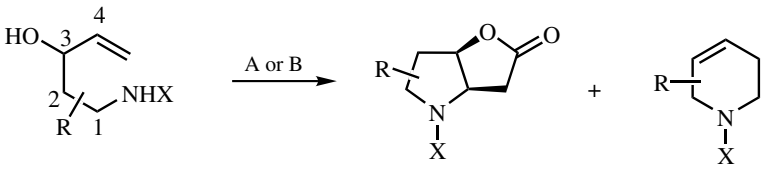
The first Pd-catalyzed intramolecular aminocarbonylations were reported by Hegedus et al.[42]–[44] Starting from *o*-allylaniline, derivates 2,3-dihydro-1*H*-indole-2-acetates were obtained in good yields under mild conditions (**Scheme 26**).



R^1 = Me, R^2 = H: 75%
R^1 = Me, R^2 = Me: 72%
R^1 = Ac, R^2 = H: 21%

Scheme 26

The conditions for related reactions were optimized by Yoshida and co-workers (**Scheme 27**). The formation of lactones **15** proceeds similar to the reaction shown in **Scheme 14**.[45] The choice of solvent was found to be crucial: under standard conditions, as used for alkoxycarbonylations (**Scheme 27**, conditions A), piperazine side products **16** are formed. However, in acetic acid (procedure B) this side reaction is suppressed and the desired products (**15**) are obtained in high yield. This chemistry has found application in syntheses of the Geissman–Waiss lactone[46] and of 1,4-iminoglycitols.[47]



15 **16**

Procedure A:
0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$, CH_3OH, MeOH, CO, r.t.

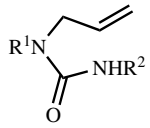
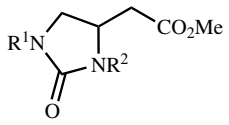
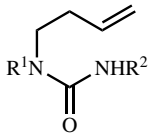
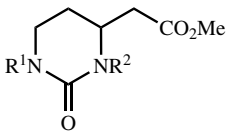
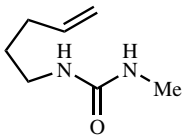
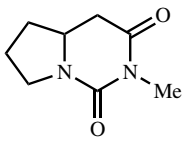
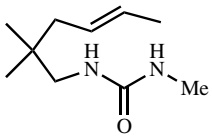
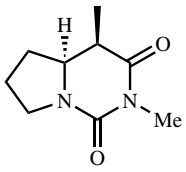
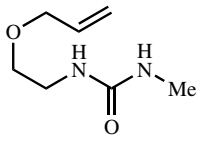
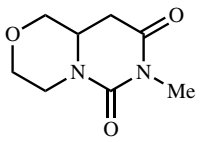
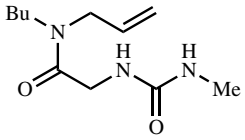
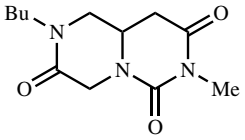
Procedure B:
0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$, 3 equiv NaOAc AcOH, CO, r.t., 1–3 d

R	X	Procedure	Yield (%) **15**	Yield (%) **16**
H	CO_2Me	A	35	24
H	SO_2Tol	A	37	43
H	SO_2Tol	B	90	0
1-Ph	SO_2Tol	B	80	0
2-Me	SO_2Tol	B	70	<5
$2\text{-}Me_2$	CO_2Me	A	70	<5
3-Me	SO_2Tol	B	66	30

Scheme 27

Tamaru, Yoshida, and co-workers expanded the scope of this methodolgy by employing urea derivatives, which are known as ambident nucleophiles (**Table 4**).[48] The attempt to use chirally modified ureas resulted only in moderate diastereoselectivities (de $\leq$ 56%). Interestingly, substrates with two free NH functions gave rise to bicyclic products in high yield, with both nitrogens acting as nucleophiles. By comparing different amino nucleophiles, ureas were found to be more reactive than carbamates and *N*-tosylamides.

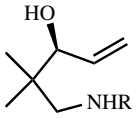
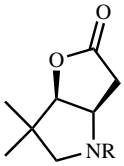
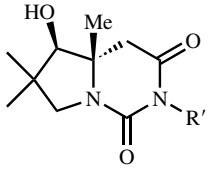
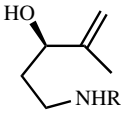
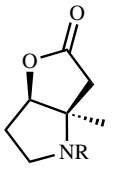
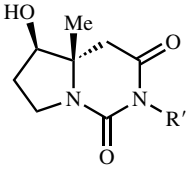
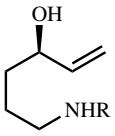
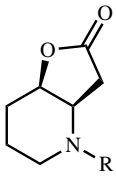
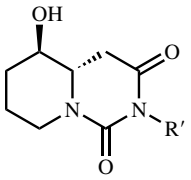
TABLE 4. Pd-Catalyzed Cyclic Amidation–Carbonylative Esterification Tandem Reaction

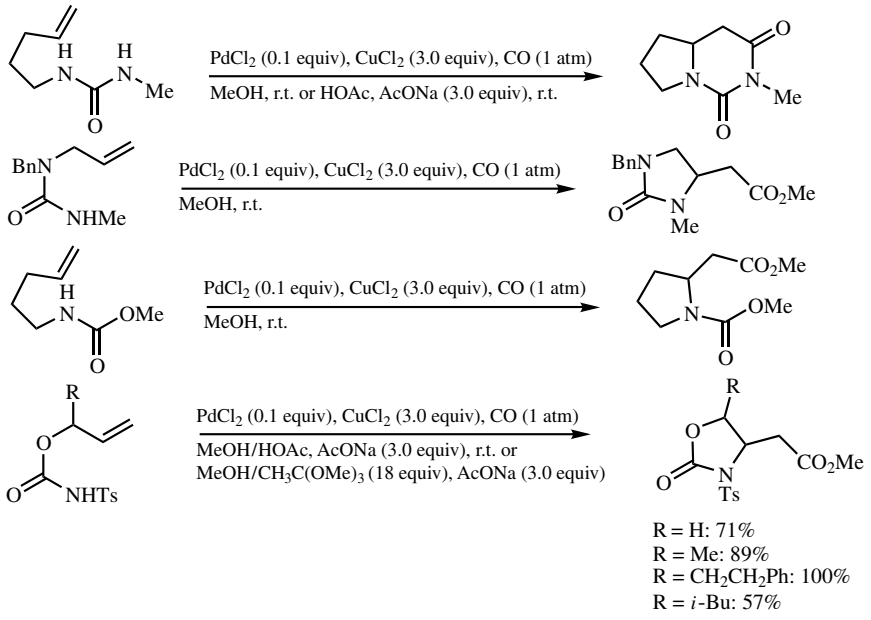
Substrate	Product	Isolated Yield
		$R^1 = CH_2Ph$; R^2 = Me: 92% R^1 = *i*-Pr; R^2 = *i*-Pr: 85%
		$R^1 = CH_2Ph$; R^2 = Me: 82% R^1 = *i*-Pr; R^2 = *i*-Pr: 84% R^1 = *i*-Pr; R^2 = *i*-CH(Me)Ph: 75% (56% de)
		95%
		69%
		95%
		71%

The intramolecular cyclization of ureas derived from 3-hydroxy-4-pentenylamines and 4-hydroxy-5-hexenylamines was also investigated (**Table 5**).[49] From these (chiral) substrates two different products can arise because the intermediate Pd-acyl species can either react with the hydroxy group to form a lactone or with the nitrogen function to form a cyclic urea derivative. The selectivity was found to depend both on the substrate and on the acidity of the solvent (MeOH or AcOH).

Under standard conditions Tamaru and co-workers were able to cyclize various ureas and carbamates. In the case of *N*-tosyl carbamates, the reactions have to be performed under buffered conditions, either in neat methyl orthoacetate or in methanol containing NaOAc and methyl orthoacetate (**Scheme 28**).[50]

TABLE 5. Pd-Catalyzed Cyclic Amination–Carbonylative Lactonization Tandem Reaction

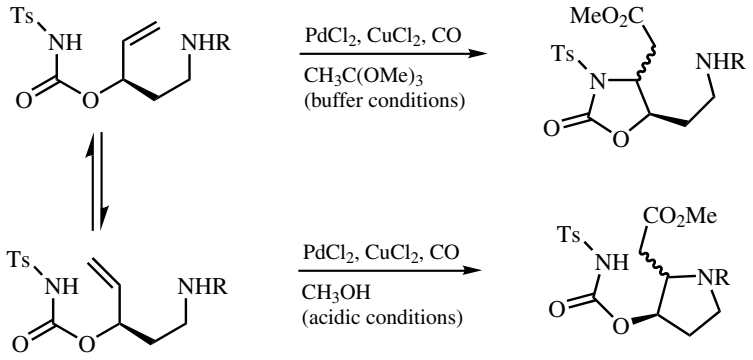
Substrate		Products (Yield %)	
			
	R = CONHMe R = CONHPh	75 85	17 0
			
	R = CONHMe R = CONHPh	46 44	23 0
			
	R = CONHMe R = CONHPh	22 35	26 0



R = H: 71%
R = Me: 89%
R = CH_2CH_2Ph: 100%
R = *i*-Bu: 57%

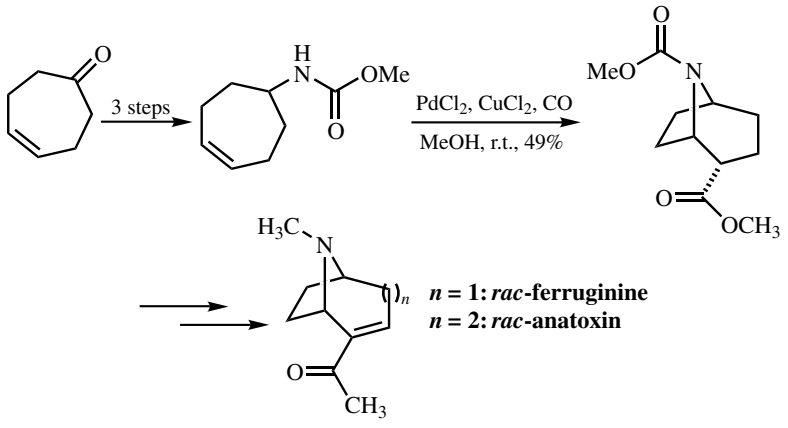
Scheme 28

Substrates containing both an *endo*-carbamate moiety *and* an *exo*-carbamate moiety (or an *exo*-urea or an *exo*-tosylamide) in the same molecule open interesting selectivity aspects. Here the aminocarbonylation proceeds chemoselective in either direction depending on whether acidic or buffered conditions are chosen (**Scheme 29**).[51],[52] Methyl orthoacetate, methyl orthoformiate, 2,2-dimethoxypropane, or propylene oxide can be used as HCl scavengers (buffers). In the presence of orthoacetates the cyclizations also proceed with high stereoselectivity (*trans*/*cis* ≤ 20:1).



Scheme 29

Recently, Ham and co-workers exploited the intramolecular aminocarbonylation in the synthesis of the tropane alkaloids *rac*-ferruginine [53] and *rac*-anatoxin[54] (**Scheme 30**). In the synthesis of *rac*-ferruginine the precursor for the aminocarbonylation is easily prepared in three steps from 4-cycloheptenone.

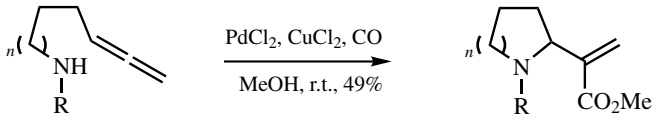


Scheme 30

C.ii. Aminocarbonylation with Allenic Substrates

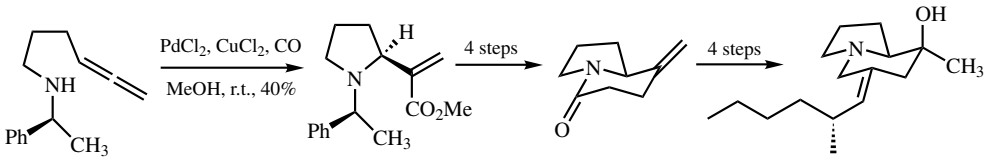
Already in 1986, Gallagher and co-workers reported the cyclization of N-protected aminoallenes to form 2-pyrrolidine acrylates or piperazine acrylates, respectively

(**Scheme 31**).[55],[56] Based on this type of chemistry an enantioselective synthesis of the alkaloid pumiliotoxin 251D was achieved (**Scheme 32**).[57] The initial aminocarbonylation of the chirally modified 4,5-hexadienylamine afforded the 2-substituted 2-pyrrolidine without significant diastereoselectivity. However, the desired diastereomer could be isolated in 40% yield on a multigram scale.



R = CH_2Ph, n = 1: 67%, n = 2: 42%
R = SO_2Tol, n = 1: 57%, n = 2: 20%
R = CO_2Me, n = 1: 56%, n = 2: 0%

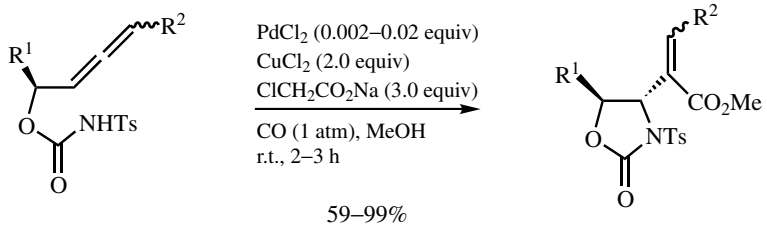
Scheme 31



pumiliotoxin 251D
6.3% overall yield

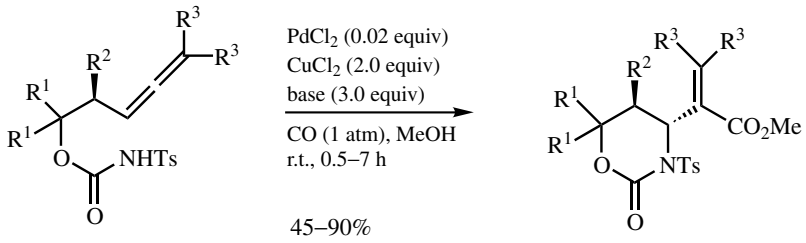
Scheme 32

Tamaru and co-workers demonstrated that *N*-tosyl carbamates derived from allenic alcohols readily cyclize under buffered conditions (**Scheme 33**).[58] That way, 1,3-oxazolidin-2-ones and 1,3-oxazin-2-ones with an α-acrylate side chain are accessible in high yield. It is noteworthy that only small amounts of $PdCl_2$ are necessary in these cases and only the *trans*-isomers are detected.



R^1 = H, Me, Et, *n*-Pr, *t*-Bu, Ph
R^2 = H, Me

Scheme 33



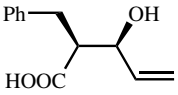
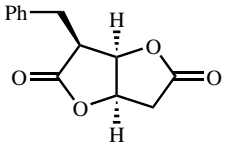
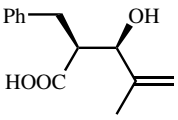
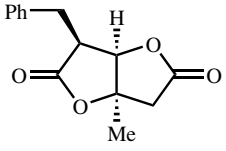
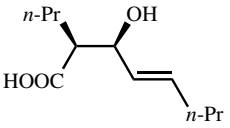
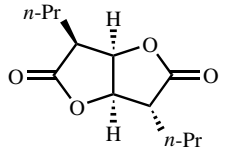
R^1, R^2, R^3 = H
R^1, R^3 = H; R^2 = CH_3
R^1 = CH_3; R^2, R^3 = H
R^1, R^3 = CH_3, R^2 = H

Scheme 33 (*Continued*)

D. CARBOXYCARBONYLATION

It should finally be mentioned that the nucleophilic group in Pd-catalyzed tandem reactions based on oxycarbonylation can also be a carboxyl function.[35],[42] Some convincing examples were reported by Yoshida, Tamaru, and co-workers[59] who used this reaction for the stereoselective synthesis of bislactones (**Table 6**). Following the mechanistic pattern shown in **Scheme 14** the carboxyl group at first attacks the alkene. The intermediate Pd-acyl species then reacts with the hydroxy function to give a *cis*-fused bislactone. A substituent in 2-position increases the reactivity; however, substituents at the double bond have no significant influence on the reaction.

TABLE 6. Pd-Catalyzed Conversion of β-Hydroxy-4-pentenoic Acids into Bicyclic Dilactones

Substrate	Product	Yield (%)
		60
		84
		83

E. SUMMARY

The Pd(II)-induced intramolecular attack of heteroatom nucleophiles to alkenes or alkynes with subsequent carbonylation leads to acylpalladium intermediates, which in turn can further react to carboxylic acid derivatives. This chemistry opens highly efficient tandem transformations, which are of outstanding value for the synthesis of complex heterocyclic molecules. While the chemo- and regioselectivities of such reactions can be efficiently controlled in many cases by proper choice of substrates and reaction conditions, the control of the absolute configuration in the case of chirogenic reactions still remains a challenge for future research and development.

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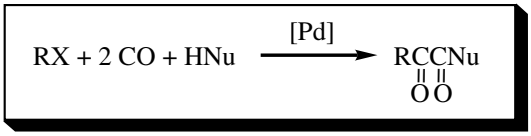

VI.2.1.4 Palladium-Catalyzed Double Carbonylation Reactions

YONG-SHOU LIN and AKIO YAMAMOTO

A. INTRODUCTION

Introduction of two adjacent CO groups into organic compounds provides useful synthetic means in organic synthesis, since the organic compounds having the adjacent two carbonyl groups may serve as convenient starting materials for preparation of various useful organic derivatives.[1] For example, α-keto acid derivatives can readily be converted into α-amino acids or α-hydroxy acids of biological importance and the catalytic double carbonylation processes may offer new synthetic routes to these compounds. In contrast to the well-known Pd-catalyzed processes of introducing one carbonyl group into organic compounds (Heck process, Eq. 1),[2]–[7] the double carbonylation process has been realized only recently.

$$\mathrm{RX} + \mathrm{CO} + \mathrm{HNu} + \mathrm{Base} \xrightarrow[-\mathrm{HX}\cdot\mathrm{Base}]{[\mathrm{Pd}]} \mathrm{RCONu} \qquad (1)$$

R = aryl, alkenyl; HNu = HOR′, HNR_2'', H_2O; X = Halide

The first double carbonylation process of converting benzyl halides was realized using cobalt carbonyl.[8] Later in 1982, Pd-catalyzed double carbonylation of aryl and alkenyl halides has been reported independently by two groups (Eq. 2).[9],[10]

$$\mathrm{RX} + \mathrm{CO} + \mathrm{HNu} + \mathrm{Base} \xrightarrow[-\mathrm{HX}\cdot\mathrm{Base}]{[\mathrm{Pd}]} \mathrm{RCOCONu} + \mathrm{RCONu} \qquad (2)$$

R = aryl, alkenyl; HNu = HOR′, HNR_2'', H_2O; X = Halide

Double carbonylation of this type will mainly be dealt with here. The other type of processes introducing two adjacent carbonyl groups, such as production of oxalic acid derivatives catalyzed by palladium complexes, will also be treated here.[11] The processes to

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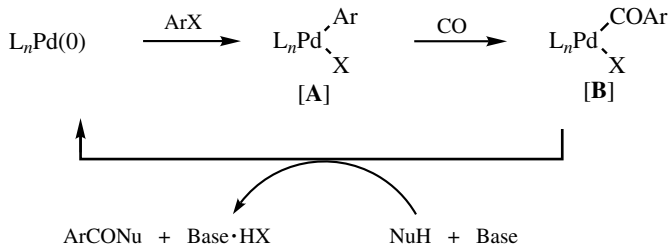
introduce two nonadjacent CO groups will briefly be touched upon and double carbonylation processes using transition metal complexes other than palladium will be mentioned only to illustrate the difference between the carbonylation processes. A number of reviews on the double carbonylation reactions have been published.[12]–[20]

B. DOUBLE CARBONYLATION OF ARYL HALIDES TO GIVE α-KETO ACID DERIVATIVES CATALYZED BY PALLADIUM COMPLEXES

Before discussing the double carbonylation processes it may be helpful to understand the mechanism of the single carbonylation of aryl halides into carboxylic acid derivatives (Heck processes). The first step in the catalytic process is oxidative addition of an aryl halide to Pd(0) species formed from a catalyst precursor to yield an arylpalladium halide intermediate (**A**) in **Scheme 1**. Insertion of carbon monoxide into the aryl–palladium bond in **A** gives an acylpalladium halide complex (**B**). Attack of a nucleophile such as alcohol, amine, and water assisted by a base on the acylpalladium complex yields carboxylic ester, amide, and carboxylic acid, although details of the mechanism have not been unequivocally established. The palladium(0) species regenerated in the process further undergoes oxidative addition to carry out the catalytic cycle (**Scheme 1**).



Scheme 1. Mechanism of single carbonylation of an aryl halide to a carboxylic acid derivative with a nucleophile NuH in combination with a base.

If the acylpalladium species can undergo further CO insertion to give α-ketoacylpalladium species and the complex should be attacked by a nucleophile, the double carbonylation process might be realized. However, the CO insertion into the acyl–transition metal bond seems to be a thermodynamically unfavorable process and the double CO insertion process is considered not operative for Pd-catalyzed double carbonylation of aryl halides.[21]

An alternative route for double carbonylation comprises a process involving combination of two acyl groups. Insertion of one CO into the aryl–palladium bond gives an aroyl group and nucleophilic attack on a Pd-coordinated CO ligand yields another acyl ligand; reductively, elimination of the two acyl ligands liberates the α-keto acid derivative. Amines, alcohols, and water can be used as the nucleophile in combination with a base to produce α-keto amides, α-keto esters, and α-keto acids. For the double carbonylation with secondary and primary amines no base is necessary if amine is used in an excess amount. In fact, double carbonylation to α-keto amide was first achieved using secondary amines.

B.i. Preparation of α-Keto Amides

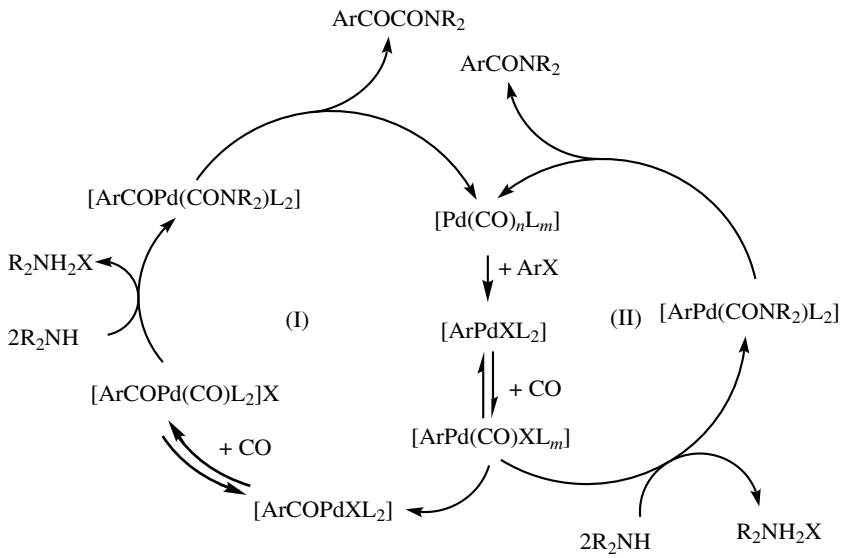
Detailed mechanistic studies on the elementary processes putatively involved in the catalytic double carbonylation process established that the latter mechanism involving the reductive elimination of the bis-acyl ligands most reasonably accounts for the features of the double carbonylation. **Scheme 2** presents the proposed mechanisms for generation of the α-keto amide and amide in the reaction of an aryl halide with CO in the presence of a secondary amine and a catalytic amount of a palladium complex (*vide infra*). **Table 1** summarizes the representative results of the double carbonylation with various aryl halides.

Various aryl halides can be converted into α-keto amides on heating in solution under CO pressure in the presence of a secondary amine and a palladium catalyst. Aryl iodides are most susceptible to the double carbonylation followed by bromides. Aryl chlorides could not be converted into the double carbonylation products even at temperatures as high as 200 °C. An electron-withdrawing substituent at the para position of the phenyl bromide was found more favorable than the electron-donating one for promoting the double carbonylation. Various palladium complexes can serve as catalysts for the double carbonylation. Employment of the tertiary phosphine ligands is essential for successful operation of the catalytic double carbonylation and no double carbonylation was observed when tertiary phosphine-free compounds such as $Pd(OAc)_2$, $PdCl_2$, and $PdCl_2(bpy)_2$ were used. Among other transition metal complexes examined, copper and cobalt complexes having tertiary phosphine ligands such as $CuBr(PPh_3)_3$, $CoCl(PPh_3)_3$, and $CoH(N_2)(PPh_3)_3$ showed mild catalytic activities.[9],[22]

TABLE 1. Double Carbonylation of Aryl Halides in the Presence of Amine[a]

ArX	Temperature (°C)	Time (h)	Product Ratio		Total Yield(%)[b]
			$ArCOCONR_2$	$RCONR_2$	
PhI[c]	60	5	93	7	100
PhI	100	2	61	39	43
PhBr[d]	100	24	91	9	27
PhBr	100	24	82	9	73
PhCl	200	12			0
p-NC-C_6H_4Br	100	24	35	65	98
p-F_3C-C_6H_4Br	100	50	63	37	89
p-Ac-C_6H_4Br	100	50	67	33	100
p-Cl-C_6H_4Br	100	50	69	31	91
p-PhO-C_6H_4Br	100	50	91	9	89
p-Me-C_6H_4Br	100	45	84	16	84
p-MeO-C_6H_4Br	100	50	92	8	22
p-Me_2N-C_6H_4Br	100	50	86	14	26
3-Br-C_5H_4N	100	63	58	42	100
2-Br-C_4H_3S	100	43	15	85	80

[a] Reaction conditions: $PdCl_2(PMePh_2)_2$ as catalyst, in the presence of Et_2NH, $p(CO) = 10$ atm unless noted elsewhere.
[b] Based on ArX by GLC.
[c] $p(CO) = 20$ atm.
[d] $p(CO) = 24$ atm.



Scheme 2. Catalytic cycles for α-keto amide formation (I) and amide formation (II).

The catalytic activity of the palladium complex is greatly affected by the basicity and steric bulkiness of the tertiary phosphine employed. Neither too strongly coordinating ligand nor too weakly bonding one is suitable for obtaining the α-keto amide in the highest yield. Among the catalysts examined $PdCl_2(PMePh_2)_2$ and $PdCl_2$(dppb) were found most effective for production of α-keto amides.[14],[22]

The rate of α-keto amide formation is first order in the concentration of the palladium complex when aryl iodide was used. For aryl bromide, the oxidative addition process seems to be the rate-limiting step.[22]

Higher CO pressure enhances both the rate of the reaction of phenyl iodide and the selectivity for α-keto amide formation. However, different effects of the CO pressure were observed in the reaction of phenyl bromide. The selectivity for the double carbonylation was somewhat enhanced with increase in CO pressure, but the reaction rate was decreased.[22]

The nature of amine gives considerable influence on the course of double carbonylation. Both basicity and bulkiness of the secondary amine employed strongly affect the rate and selectivity for the α-keto amide formation. Selectivity for the formation of α-keto amide was decreased in the following order: $Pr_2NH > Et_2NH >$ hexamethyleneimine $>$ piperidine $> Me_2NH >$ pyrrolidine. On the other hand, the influence on the reactivity shows the reverse order: $Me_2NH \gg$ piperidine $> Et_2NH > Pr_2NH$. Thus, employment of secondary amine with a suitable basicity and a moderate steric bulkiness is required for getting the α-keto amide in both high selectivity and yield.[14]

Primary amines also serve as reagents for the double carbonylation to give α-keto amides or their Shiff bases, which are produced by further attack of the primary amines on the α-keto amides generated in the reaction (Eq. 3).[20],[22] α-Amino amide can be produced by Pd-catalyzed hydrogenation from the corresponding Shiff base (Eq. 4).[20]

$$ArX + 2CO + 2RNH_2 \xrightarrow[-RNH_3X]{[Pd]} ArCOCONHR \xrightarrow[-H_2O]{RNH_2} Ar-\underset{\underset{RN}{\|}}{C}-\underset{\underset{O}{\|}}{C}-NHR \quad (3)$$

$$Ar-\underset{\underset{RN}{\|}}{C}-\underset{\underset{O}{\|}}{C}-NHR \xrightarrow[H_2]{[Pd]} Ar-\underset{\underset{H}{|}}{\overset{\overset{NHR}{|}}{C}}-\underset{\underset{O}{\|}}{C}-NHR \quad (4)$$

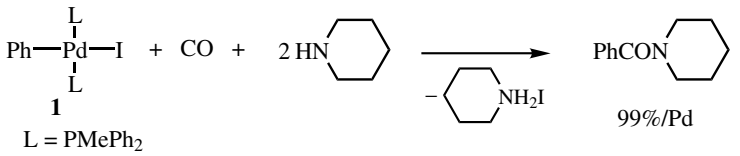
B.ii. Mechanisms of Formation of Amide and α-Keto Amide Catalyzed by Palladium Complexes

Detailed investigation of the catalytic systems converting aryl halides into α-keto amides and amides in association with fundamental studies on the reactions of model organopalladium complexes indicated that the essential features of the catalytic processes can be accommodated by **Scheme 2**.[13],[21]–[29]

On the left hand of **Scheme 2** is shown the catalytic cycle to produce α-keto amide (Cycle I), whereas the right-hand catalytic cycle shows the route to amide (Cycle II). The process common to both processes is oxidative addition of aryl halide to give arylpalladium halide. Further CO coordination to the arylpalladium intermediate gives a CO-coordinated complex. If CO insertion into the aryl–palladium bond takes place, an acylpalladium complex is produced to drive the double carbonylation cycle. Further coordination of CO followed by attack of amine on the carbonyl ligand produces the aroyl(carbamoyl)palladium species as the bis-acyl-type intermediate. Reductive elimination of the α-keto amide by combination of the benzoyl ligand with the carbamoyl ligand regenerates the Pd(0) species that carries the catalytic cycle.

On the other hand, if the CO coordinated on the arylpalladium complex is attacked by secondary amine prior to the CO insertion into the Ar—Pd bond, an aryl(carbamoyl)palladium species may be formed to drive cycle II. Reductive elimination of the aryl group with the carbamoyl group liberates amide, the single carbonylation product, with regeneration of the Pd(0) intermediate (**Scheme 2** is somewhat modified from the original scheme proposed in Ref. 22). The nucleophilic attack of amine on the coordinated CO will take place more readily when less bulky and more basic amines are used in larger concentration to favor the formation of the single carbonylation product. The preferential formation of the amide causes decrease in the selectivity for the catalytic double carbonylation. A later study revealed involvement of another catalytic cycle comprising reaction of the acylpalladium complex with amine to produce amide.[30] However, the process is not included in **Scheme 2** to avoid the complication of the scheme.

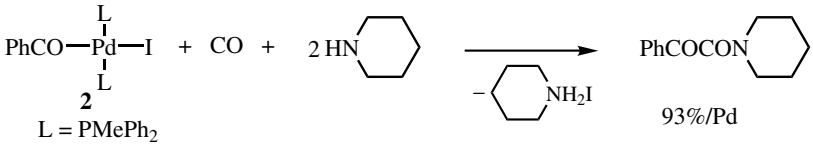
Monophenylpalladium halides (**1**) having two tertiary phosphine ligands in mutually *trans* positions have been isolated and characterized as model complexes for the active species in the catalytic processes. Comparison of the behavior of the phenylpalladium complexes **1** with that of neutral and cationic benzoylpalladium complexes **2** and **3** with CO and secondary amines provided important information on the reaction courses to give α-keto amide and amide.[23]–[27] The reaction of phenylpalladium iodide **1** having two $PMePh_2$ ligands with CO and piperidine yielded amide in 99% yield (Eq. 5), whereas the similar reaction of the benzoylpalladium iodide having the $PMePh_2$ ligands afforded the α-keto amide exclusively (Eq. 6). The results support the proposed mechanisms for the single and double carbonylation processes as depicted in **Scheme 2**.



(5)

1

L = $PMePh_2$

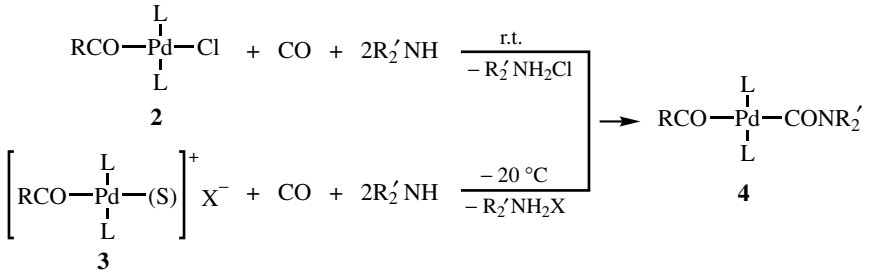


(6)

2

L = $PMePh_2$

Employment of a very compact and basic trimethylphosphine ligand proved to be convenient to stabilize the model complexes. *Trans*-benzoyl(carbamoyl)palladium complexes with two PMe_3 ligands (**4**) have been synthesized as key model complexes in the catalytic double carbonylation shown in **Scheme 2** either from the reaction of benzoylpalladium chloride complex (**2**) with secondary amine under CO or by treatment of a cationic CO-coordinated benzoylpalladium complex (**3**) with secondary amine (Eq. 7).[23],[27]



(7)

2

3

4

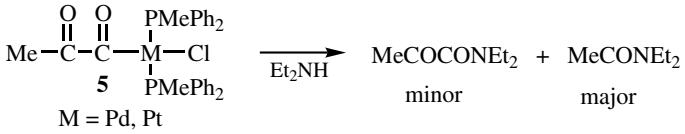
L = PMe_3; $R_2'NH$ = Me_2NH, piperidine, pyrrolidine; S = acetone; X = BF_4^-, PF_6^-

For a concerted reductive elimination of α-keto amide and amide from the intermediate aroyl(carbamoyl)palladium and aryl(carbamoyl)palladium complexes to take place, the organopalladium complexes are required to have the two ligands in adjacent positions. Thus, if *trans* form is produced by attack of a nucleophile on the coordinated CO as in Eq. 7, *cis-trans* isomerization is necessary. Further information on the *cis-trans* isomerization courses was obtained by studying the behavior of the corresponding platinum analogs.[13],[24],[31]

Although high catalytic activities have not been found with other transition metal complexes, the route to generate α-keto amides from acyl(carbamoyl)transition metal complexes seems to be general with other transition metal complexes as revealed from study of the behavior of cobalt, ruthenium, manganese, and rhenium complexes.[32],[33]

The possibilities of consecutive CO insertion to give an α-ketoacyl species that is attacked by a nucleophile to give α-keto acid derivatives were excluded on the basis of studies concerning the reactivities of α-ketoacylpalladium and α-ketoacylplatinum complexes. α-Ketoacylpalladium complexes, *trans*-$Pd(COCOR)Cl(PR_3')_2$ **5** (R = Ph and Me, PR_3' = PPh_3 and $PMePh_2$), have been prepared as model complexes.[21],[34]–[36] These α-ketoacylpalladium complexes showed the tendency to be easily decarbonylated into

acylpalladium complex at room temperature in CH_2Cl_2. On treatment with a secondary amine the ketoacyl complex, *trans*-Pd(COCOMe)Cl($PMePh_2$)$_2$, gives amide as the main product together with only a small amount of α-keto amide (Eq. 8).[21]



(8)

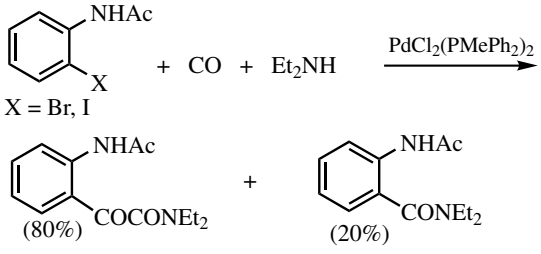
The result is in sharp contrast to the reaction of the corresponding acyl complex, *trans*-Pd(COMe)Cl($PMePh_2$)$_2$, with Et_2NH under CO atmosphere, where $MeCOCONEt_2$ was obtained as the major product. Treatment of benzoylformylpalladium(II) complex with Et_2NH under ^{13}CO gives PhCO $^{13}CONEt_2$ in high yield (>96%).[34] These observations provided further evidence against the mechanism involving consecutive insertion of CO into the Pd—C bond.

Although these experimental results all support the double carbonylation mechanism through the bis-acylpalladium intermediates, a report has been made claiming the consecutive CO insertion mechanism.[37] The work seems to need further validation.

Recently, a promotion effect of copper halides or $Fe(CO)_5$ on the double carbonylation of phenyl iodide in the presence of diethylamine has been reported.[38] The promoters were found effective in both CO insertion and attack of CO by diethylamine. An iodide bridged, copper-containing complex was proposed as the intermediate.

An application of the double carbonylation process was reported (Eq. 9).[14],[15],[39] The Pd-catalyzed double carbonylation of *o*-haloacetanilides in the presence of Et_2NH gives corresponding α-keto amide together with amide.

Treatment of the double carbonylation product under appropriate conditions led to isatin and quinoline derivatives (Eq. 10).



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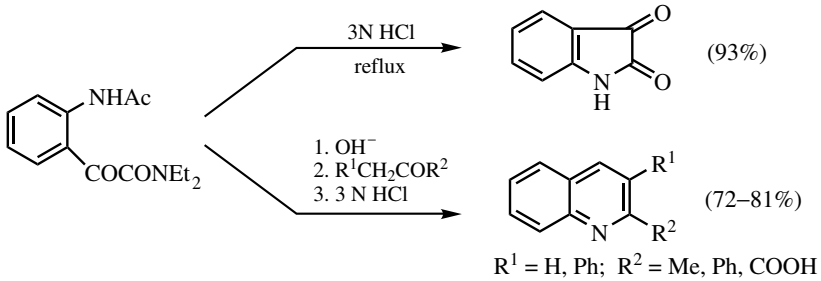


(10)

A silica-supported polytitazane–palladium complex (Ti–N–Pd) has been developed as a catalyst for the double carbonylation of phenyl halide to give α-keto amide.[40] The reactivity of phenyl halide decreases in the following order in the process where palladium–phosphine catalysts are used: PhI > PhBr > PhCl. This kind of inorganic polymer catalyst was claimed to be very stable and to have great activity and selectivity in the catalytic reactions.

Recently, application of the Pd-catalyzed double carbonylation process to synthesis of heteroaromatic compounds has been reported using 2- and 4-iodopyridines as the starting materials.[41]

B.iii. Preparation of α-Keto Esters

The α-keto amides are less susceptible to hydrolysis and preparation of α-keto esters and acids are preferable for synthesizing various derivatives thereof. Various aryl iodides and bromides can be converted into α-keto esters on reactions with alcohols and carbon monoxide in the presence of a base such as tertiary amines or potassium acetate with catalytic amounts of tertiary phosphine-coordinated palladium complexes (Eq. 11).[42]–[46] High yields of α-keto esters can be achieved only when iodide substrates are used. Double carbonylation of aryl bromides to α-keto esters can be accomplished with difficulty at much slower rates. Alkyl and benzyl iodides give no double carbonylation products.

$$\mathrm{ArX + 2CO + ROH + Base} \xrightarrow{\mathrm{[Pd]}} \mathrm{ArCOCOOR + ArCOOR + Base{\cdot}HX} \qquad (11)$$

$\mathrm{X = Br, I;\ Base = Et_3N, KOAc}$

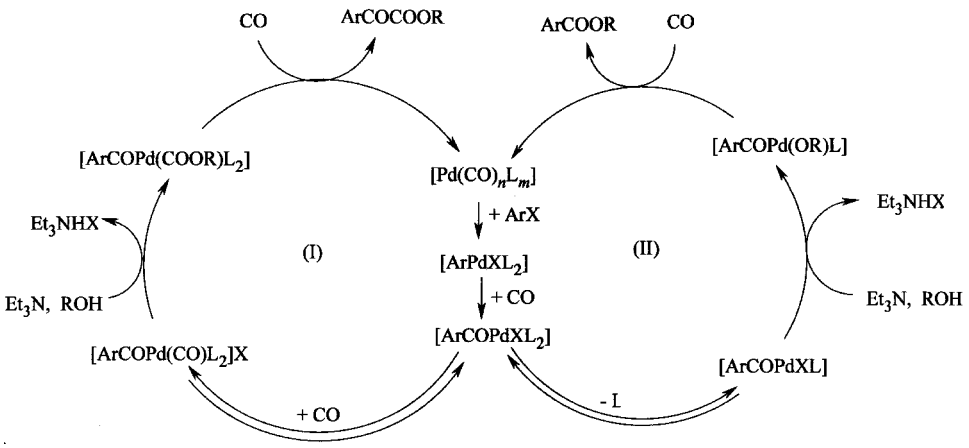
The factors affecting the selectivity of α-keto ester formation have been examined.[43],[45],[46] The steric influence of phosphine ligands in palladium catalyst dominates the selectivity for α-keto ester formation. Bulkier tertiary phosphine ligand is more favorable. On the other hand, coordination of two phosphine ligands to palladium atom is essential in maintaining the double carbonylation activity but the addition of excess ligand retards both the double and single carbonylation processes. Both electronic and steric factors of the alcohol are important in α-keto ester formation. Secondary alcohols of moderate bulkiness give α-keto esters in high selectivity, whereas primary alcohols such as methanol and ethanol give mainly single carbonylation products. In addition, higher CO pressure is necessary to obtain higher yield of α-keto ester.

Heteroaromatic iodides, such as 2-thiophenic iodide and 2-naphthyl iodide, can also be doubly carbonylated to corresponding α-keto esters.[29],[42],[45]

B.iv Mechanistic Studies on the Double Carbonylation of Aryl Halides to Give α-Keto Esters

The proposed mechanism of double carbonylation of aryl iodide with alcohol and triethylamine to give α-keto ester is shown in **Scheme 3**.

The mechanism is supported by fundamental studies of the behavior of model organopalladium complexes.[43],[45] The processes are composed of two catalytic cycles that lead to α-keto ester and ester, respectively. The catalytic cycle for giving α-keto ester (Cycle I) is analogous to the one proposed for the formation of α-keto amide as shown in



Scheme 3. Catalytic cycles for α-keto ester formation (I) and ester formation (II).

Scheme 2. Oxidative addition of phenyl iodide with zerovalent palladium species gives phenylpalladium iodide, which affords benzoylpalladium intermediate on CO insertion. Coordination of a second carbon monoxide to the benzoylpalladium species followed by nucleophilic attack by alcohol assisted by tertiary amine gives benzoyl(alkoxycarbonyl)palladium complex. The latter complex undergoes reductive elimination of the benzoyl and alkoxycarbonyl ligands to α-keto ester with regeneration of the palladium(0) species as carrier of the catalytic cycle. Both *cis* and *trans* isomers of the corresponding platinum analogs, benzoyl(alkoxycarbonyl)platinum complexes, have been synthesized on treatment of *cis*- and *trans*-$[Pt(PPh_3)_2(CO)(COPh)]BF_4^-$ with OMe^-.[35] *cis*-Acyl(methoxycarbonyl)palladium complex, *cis*-[Pd(COMe)(COOMe)(bpy)], was also prepared by insertion of carbon monoxide into both Pd—OMe and Pd—Me bonds.[47],[48]

The mechanism for the ester formation (Cycle II) is somewhat different from the one proposed for the single carbonylation process for the amide formation as shown in **Scheme 2**. Model studies of the reaction of isolated phenyl- and benzoylpalladium complexes toward alcohols and tertiary amine under CO demonstrate that the benzoylpalladium(II) species formed in the insertion of CO into phenyl–palladium bond serves as the common intermediate for both the ester and α-keto ester formation in the catalytic process.[43] A benzoylpalladium alkoxide species is assumed as a key intermediate in affording ester on reductive elimination. More recent detailed mechanistic studies regarding ester formation support the above-mentioned proposition in which an acyl(alkoxyl)palladium species is involved.[30]

B.v. Preparation of α-Keto Acids

Pd-catalyzed double carbonylation of phenyl halides in the presence of water and triethylamine gives α-keto acids together with methyl benzoate and benzaldehyde as by products (Eq. 12).[49]

$$ArI + 2CO + H_2O + Et_3N \xrightarrow[-Et_3NHI]{PdCl_2(PPh_3)_2} ArCOCOOH \qquad (12)$$

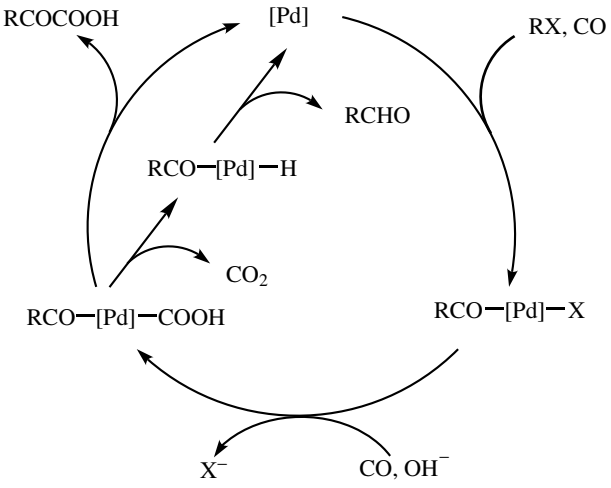
Combination of the processes of double carbonylation to give α-keto acid with Meerwein–Ponndorf-type reduction leads straightforwardly to α-hydroxyl acids (Eq. 13).[50] In the catalytic reactions, an inorganic base such as calcium hydroxide or lithium hydroxide and a primary or secondary alcohol are utilized as reducing agent.

$$\mathrm{ArI + 2CO + H_2O + Base \xrightarrow[\text{Alcohol}]{PdCl_2L_2} Ar{-}\overset{\overset{OH}{|}}{\underset{\underset{H}{|}}{C}}{-}COOH + Base\cdot HI} \qquad (13)$$

Base = $Ca(OH)_2$, LiOH; L = PPh_3, $PMePh_2$, PMe_2Ph

B.vi Mechanistic Studies on the Double Carbonylation of Aryl Halides to Give α-Keto Acids

The mechanism for the α-keto acid formation was proposed as shown in **Scheme 4**, which is reminiscent of those for α-keto amide and ester formation.[49] Benzoyl(hydroxycarbonyl)palladium complex was assumed as a key intermediate, which undergoes reductive elimination to form α-keto acid. Decarboxylation of this intermediate giving a benzoylpalladium hydride species followed by reductive elimination was proposed to give benzaldehyde as by-product.



Scheme 4

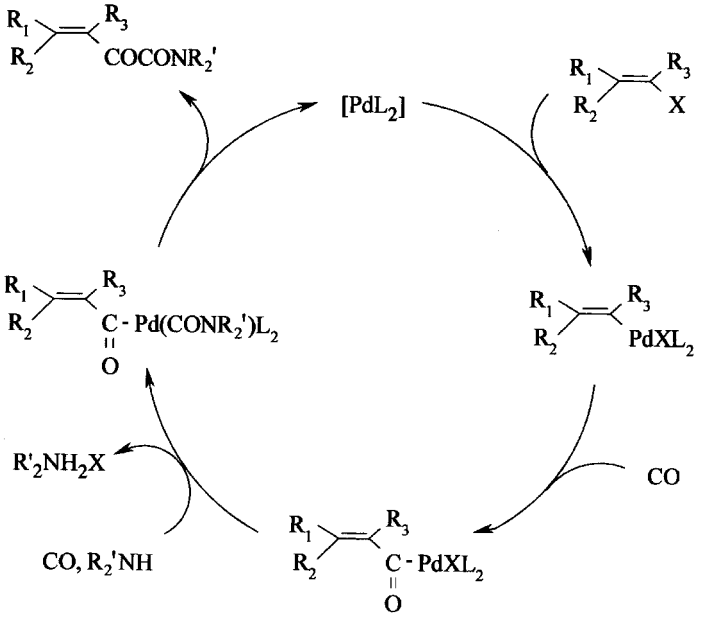
C. CATALYTIC DOUBLE CARBONYLATION OF ALKENYL HALIDES CATALYZED BY PALLADIUM COMPLEXES

Alkenyl bromides or iodides having phenyl substituent(s) on the vinyl group are doubly carbonylated to corresponding α-keto amides together with amides, the single carbonylation by-product (Eq. 14).[9],[10],[14],[51] The alkenyl halides without phenyl substituent afford amides exclusively.

$$R^1R^2C{=}CHX + 2CO + 2R_2NH \xrightarrow[-R_2NH_2X]{[Pd]} R^1R^2C{=}CHCOCONR_2 + R^1R^2C{=}CHCONR_2 \quad (14)$$

R^1, R^2 = H, Ph

Scheme 5 gives the proposed mechanism for the double carbonylation based on the model studies of alkenyl- and alkenoylpalladium(II) complexes.[51]

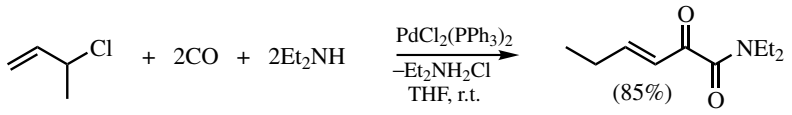


Scheme 5

D. DOUBLE CARBONYLATION OF ALLYLIC HALIDES CATALYZED BY PALLADIUM COMPLEXES

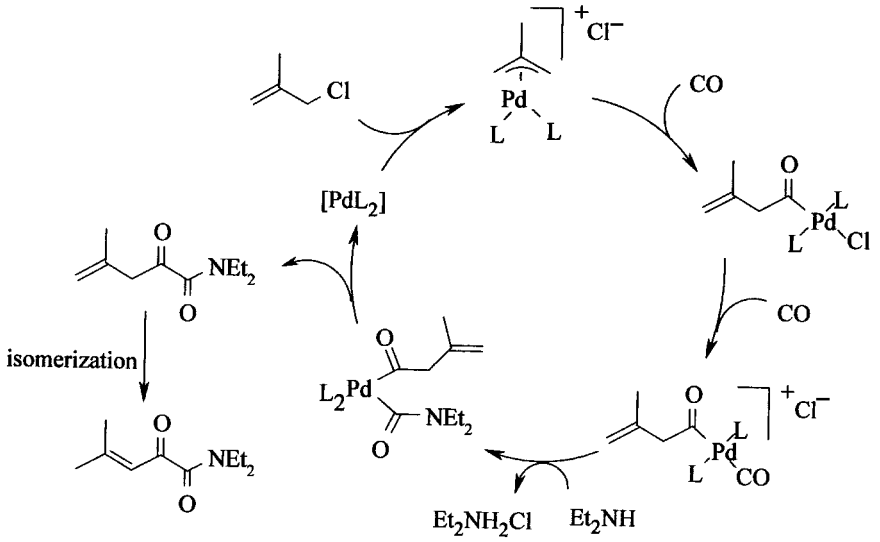
Alkyl halides are usually considered to be less suitable for double carbonylation because of the possibility of the direct reaction of alkyl halides with nucleophiles and of instability of alkyl–transition metal complexes involved in the catalytic process. However, allylic halides were found amenable to double carbonylation promoted by zerovalent palladium complex. It is well known that allylic halides undergo ready oxidative addition with a Pd(0) species to produce η^3-allylpalladium halide complexes. Thus, it was reasoned that the double carbonylation process might be realized if CO insertion into the allyl–palladium bond proceeds before attack of amine on the η^3-allylpalladium halide takes place. On the basis of fundamental studies on the behavior of η^3-allylpalladium halide complexes with CO and secondary amines, double carbonylation processes of substituted allyl halides to give α-keto amides in high yields have recently been achieved (Eqs. 15 and 16).[12],[52]

$$\text{Cl} + 2CO + 2Et_2NH \xrightarrow[-Et_2NH_2Cl,\ \text{THF, r.t.}]{PdCl_2(PPh_3)_2} \underset{(94\%)}{\text{O}=\text{C}(\text{NEt}_2)\text{CH}=\text{CHCH}_3} \quad (15)$$



(16)

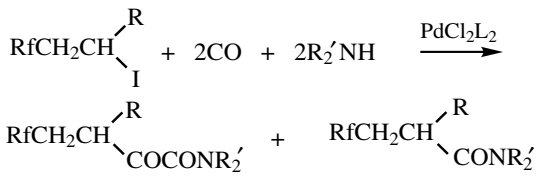
Simple allyl chloride and cinnamyl chloride did not give a double carbonylation product. Higher pressure of CO is crucial in obtaining higher selectivity of α-keto amide. Lower temperature is more favored for the double carbonylation reaction. Also important is the usage of a minimum amount of secondary amine. Otherwise the amine may attack the η^3-allylpalladium complex to release allylic amine prior to the CO insertion into the allyl–palladium bond. Palladium complex with triphenylphosphine ligands was found to be an effective catalyst in comparison with those complexes having bidentate tertiary phosphines or $PMePh_2$ ligands.[12],[53] Involvement of the following processes is assumed to account for the double carbonylation of allylic chlorides catalyzed by a palladium complex: (i) oxidative addition of allylic chloride to the Pd(0) species to afford an η^3-allylpalladium chloride complex; (ii) insertion of CO into allyl–palladium bond to give an acylpalladium complex; (iii) second CO coordination to form a cationic acylpalladium complex; (iv) attack of the secondary amine on the coordinated CO to give an acyl(carbamoyl)palladium intermediate; and (v) reductive elimination of α-keto amide, which undergoes isomerization of the double bond to give an α-keto amide with internal double bond (**Scheme 6**).



Scheme 6

E. PALLADIUM-PROMOTED PREPARATION OF α-KETO AMIDES FROM OTHER ORGANIC SUBSTRATES

With the exception of double carbonylation of allylic halides catalyzed by palladium–phosphine complexes as described above, there are few precedents of the catalytic double carbonylation of other kinds of aliphatic substrates. One example is the double carbonylation of 1-perfluoroalkyl-substituted 2-iodoalkanes promoted by palladium–phosphine complexes to give corresponding α-keto amides in good yields (Eq. 17).[54]



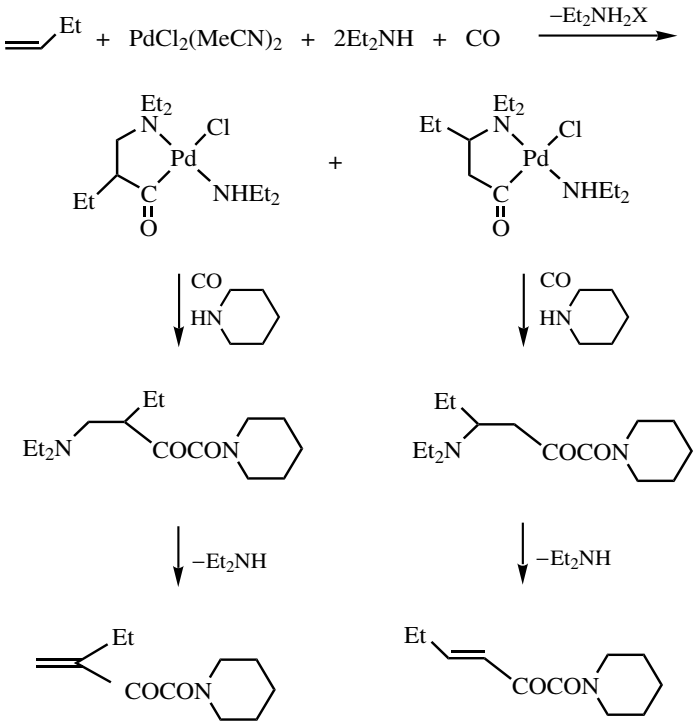
(17)

Rf = perfluoroalkyl group; R = H, Me;
$R_2'NH$ = Et_2NH, *i*-Pr_2NH, *t*-$BuNH_2$, piperidine; L = PPh_3, PCy_3, $PMePh_2$

In this reaction, both secondary and primary amines can be used as a base. Aliphatic hydrocarbons were found to be the best solvents for the double carbonylation. The palladium complexes having relatively bulky phosphine ligands such as $PdCl_2(PPh_3)_2$ and $PdCl_2(PCy_3)_2$ were proved to have higher activities for the double carbonylation reaction. α-Amino acids can easily be obtained from the corresponding α-keto amide formed from the double carbonylation of perfluoroalkyl iodides by hydrolysis under acidic conditions followed by treatment with hydroxylamine and hydrogenolysis catalyzed by PtO_2.[54]

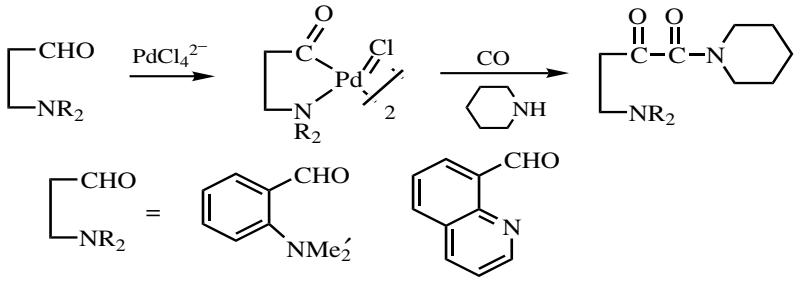
It is also worthy to mention that 1-butene can be converted to corresponding β,γ-unsaturated α-keto amides stoichiometrically by double carbonylation via an aminopalladation process (**Scheme 7**).[55]

In a stoichiometric reaction, aromatic aldehydes containing nitrogen donor were converted into α-keto amides by reaction with tetrachloropalladium(II) salt followed by treat-



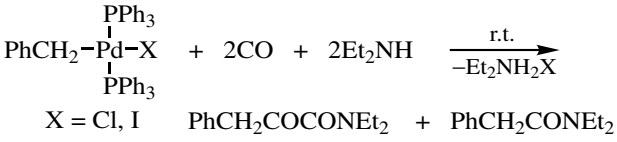
Scheme 7

ment with CO and piperidine (Eq. 18).[56] The conversion was confirmed to proceed via a C—H bond activation and formation of aroylpalladium complexes.



(18)

Double carbonylation of benzylpalladium(II) halides, which can be prepared by addition of benzyl halides to Pd(0) complexes, has been realized in the presence of diethylamine at room temperature (r.t.) to give α-keto amide together with amide (Eq. 19).[30] Occurrence of CO insertion into the η^3-benzyl–palladium bond and coordination of a second CO to give (phenylacetyl)(carbonyl)palladium complex have been confirmed by the observation of the NMR at low temperature under ^{13}CO pressure (**Scheme 8**).[30],[57] Treatment of the CO-coordinated (phenylacetyl)palladium complex with $HNEt_2$ gives α-keto amide and amide as double and single carbonylation products, respectively.[30]



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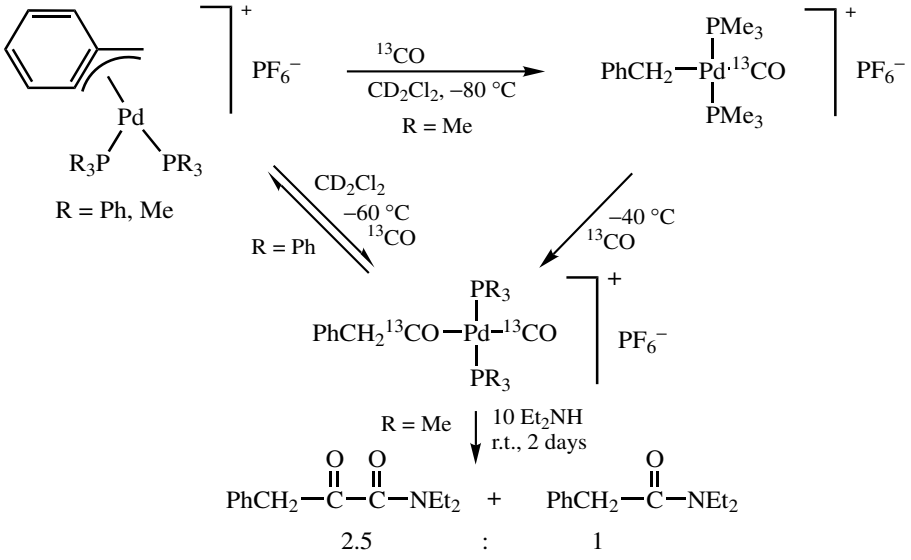
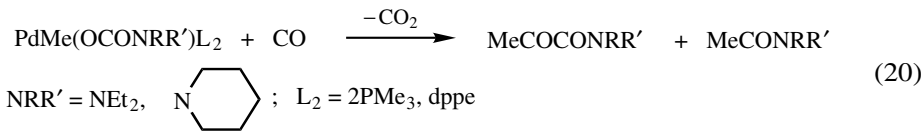


Scheme 8

Further studies revealed that there are two courses leading to amide from the carbonylation of benzylpalladium complexes depending on the amount of secondary amine employed. One involves the formation of benzyl(carbamoyl)palladium intermediate, from which amide is produced on reductive elimination when neat amine is used. The other is composed of the CO insertion into benzyl–palladium bond to give phenylacetylpalladium intermediate, which may further react with amine to liberate the single carbonylation product. The latter process takes place when a limited amount of amine is employed.[30]

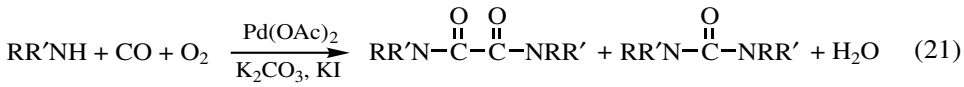
The α-keto amides were found to be produced in the reaction of carbon monoxide with *trans*- and *cis*-methylpalladium carbamate complexes, $PdMe(OCONRR')L_2$, accompanied by formation of amides (Eq. 20).[58] The process was assumed to involve decarboxylation of the carbamate ligand associated with CO insertion and attack of the amide entity on the coordinated CO.



(20)

F. OXAMIDE, OXALATE, AND OXAMATE FORMATION FROM PALLADIUM-CATALYZED DOUBLE CARBONYLATION

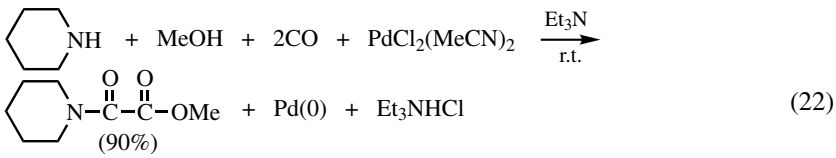
Oxamides, dialkyl oxalate esters, and oxamic acid esters can be prepared by Pd-catalyzed double carbonylation of secondary amines and alcohols via incorporation of two molecules of carbon monoxide into amines and/or alcohols. Pd-catalyzed double carbonylation reactions of amines in the absence or presence of alcohol were reported earlier to give oxamides and oxamic acid ester.[59]–[61] Selective formation of oxamides has been achieved by double carbonylation of secondary amines in the presence of iodide ion and dioxygen catalyzed by $Pd(OAc)_2$ (Eq. 21).[62]



(21)

The mechanism for the formation of oxamides was proposed as shown in **Scheme 9**.[52],[62]

Pd-catalyzed cross double carbonylation of secondary amines and alcohols to give oxamic acid esters together with the formation of carbamate, urea, and oxamide was also developed by employing CuI as a cocatalyst.[11],[63] In a stoichiometric reaction, oxamate can be formed selectively by treatment of $PdCl_2(MeCN)_2$ with a secondary amine and alcohol under CO (Eq. 22).[63]



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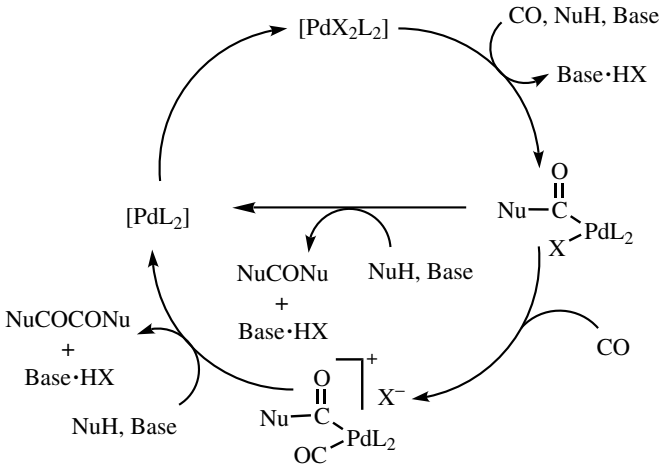
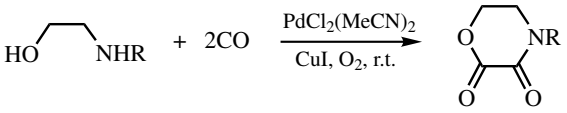


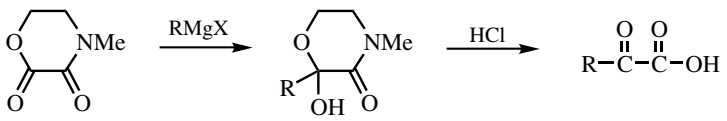
Scheme 9

Morpholine-2,3-diones are formed by intramolecular double carbonylation of β-amino alcohols catalyzed by palladium complex as shown in Eq. 23.[60],[63] The stoichiometric formation of morpholine-2,3-dione by the double carbonylation of amino alcohol has been reported previously.[64] The mechanism of formation of morpholine-2,3-dione has been proposed as shown in **Scheme 10**.



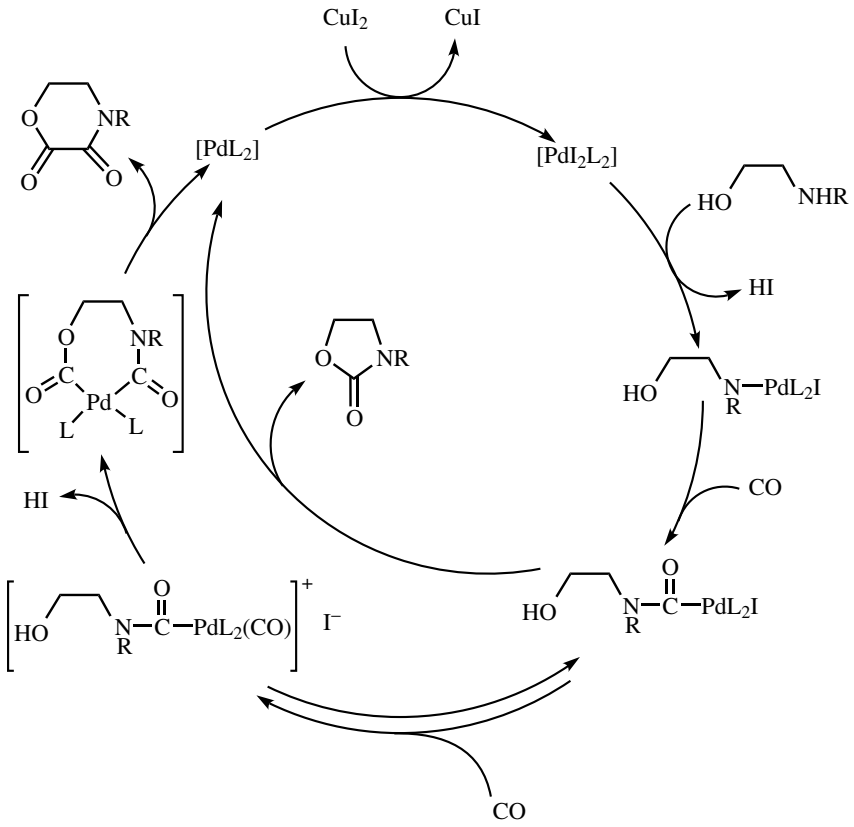
(23)

The catalytic cycles consist of amination, migratory CO insertion to give carbamoylpalladium complex, and the second CO coordination followed by intramolecular nucleophilic attack of the hydroxyl group on the coordinated CO ligand to form a seven-membered ring palladacyclic (carbamoyl)(alkoxycarbonyl)palladium intermediate. The ensuing reductive elimination produces the cyclic oxamate as the double carbonylation product. Reoxidation of Pd(0) species by copper salt drives the catalytic cycle. The morpholine-2,3-diones can be converted into α-keto acids in high yields by treatment with Grignard reagents followed by acidic hydrolysis (Eq. 24).[63]



(24)

Dialkyl oxalate esters can be synthesized by oxidative carbonylation catalyzed by palladium complexes with a cocatalyst in the presence of alcohol.[65]–[67] The process of



Scheme 10

formation of dialkyl oxalate ester can be regarded as a double carbonylation of alcohol. A mechanism, involving a bis(alkoxycarbonyl)palladium intermediate and reductive elimination, has been proposed for the formation of the oxalate ester, although the possibility of involvement of another mechanism cannot be excluded.[68]

Formation of dialkyl oxalate esters[69] and polyoxalates[70] by Pd-catalyzed carbonylation of alkyl nitrites and alkane α,ω-dinitrite esters in a homogeneous or heterogeneous system has been reported (Eq. 25).

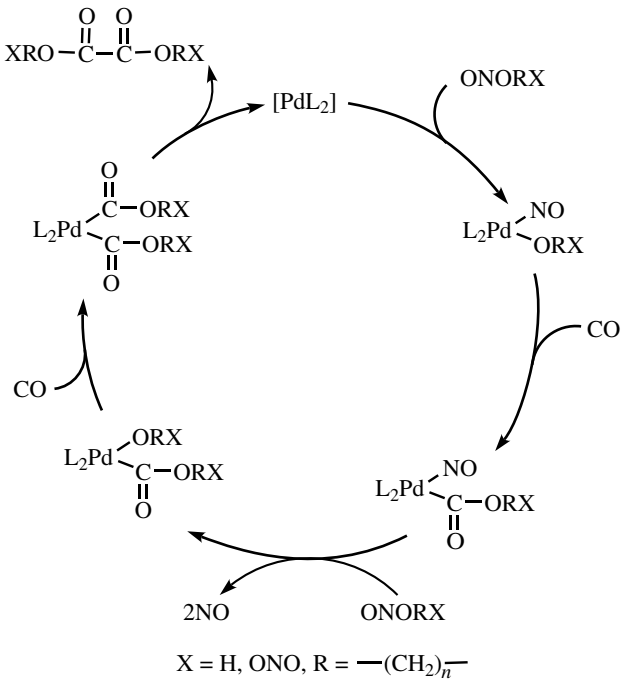
$$\mathrm{X{-}R{-}ONO} + \mathrm{CO} \xrightarrow[-\mathrm{NO}]{[\mathrm{Pd}]}$$

$$\mathrm{X = H,\ NO_2;\ R = {-}(CH_2)_n{-}} \qquad (25)$$

$$\mathrm{XRO{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}ORX} \xrightarrow[-n\mathrm{NO}]{n\mathrm{CO},\ [\mathrm{Pd}]} \left(\mathrm{O{-}R{-}O{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}}\right)_n$$

$$\mathrm{X = NO_2}$$

The CO insertion into nitrite-substituted alkoxy–palladium bonds to give a $Pd(COORONO)_2$ species followed by reductive elimination of dinitrite-substituted oxalate ester was proposed as a mechanism in this Pd-catalyzed carbonylation of alkane dinitrite (**Scheme 11**).[69],[70]



Scheme 11

G. DIKETONE FORMATION FROM PALLADIUM-PROMOTED DOUBLE CARBONYLATION

Diaryl-α-diketones were obtained in the carbonylation of diaryliodonium salts catalyzed by $Pd(OAc)_2$ in the presence of zinc.[71] In addition to diketones, formation of diaryl ketones, biaryls, and aryl iodides was also found. A synthetic method to yield α-diketones has been developed by carbonylative coupling between diorganozincs and acid halides promoted by palladium complexes (Eq. 26).[72] A diacylpalladium intermediate was proposed in the course of formation of α-diketone.

$$\mathrm{PhCOCl} + \mathrm{Et}_n\mathrm{M} \xrightarrow{[\mathrm{Pd}]} \mathrm{PhCOCOEt} + \mathrm{PhCEt(OH)COEt} + \mathrm{PhCOCEt_2(OH)} \quad (26)$$

M = Zn, $n = 2$
M = Al, $n = 3$

[Pd] = $PdCl_2(PR_3)_2$, $Pd(PPh_3)_4$; R = Ph, p-FC_6H_4

The mechanism of Pd-catalyzed coupling and carbonylative coupling of acid halides with organometals has been studied by employment of platinum(II) complexes as models. *cis*-Diacylplatinum complexes have been prepared either by the carbonylation of *trans*-acyl(alkyl)platinum complexes or by a strong nucleophile addition to a *cis*-acyl(carbonyl)platinum(II) cation.[73]–[75] Vicinal diketone can be generated together with ketone from the corresponding *cis*-diacylplatinum complex by thermal decomposition.[73],[74]

In the thermal decomposition of dimethylpalladium complex under CO, dimethyl diketone is produced together with acetone.[12],[76] The process of alkyl migration to coordinated CO in the reactions of *cis*- and *trans*-dialkylpalladium complexes has been established on the basis of the observation of the distribution of the products.[12],[16],[76],[77]

H. DOUBLE CARBONYLATION REACTIONS PROMOTED BY OTHER TRANSITION METAL COMPLEXES

As we mentioned in **Sect. A**, the first catalytic double carbonylation reaction was found to take place by using cobalt carbonyl complex as catalyst. In fact, there are a few other transition metals that can promote the double carbonylation process in addition to palladium complexes. The following is a brief description of the double carbonylation process promoted by transition metals other than palladium.

H.i. Double Carbonylation Reactions Catalyzed by Cobalt Complexes

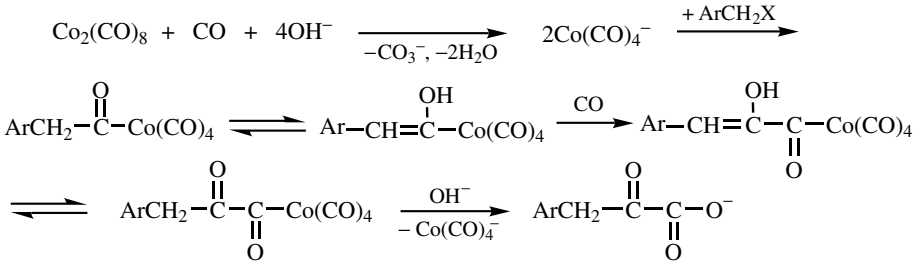
The double carbonylation process was first found in the conversion of substituted benzyl halides to corresponding arylpyruvic acids catalyzed by cobalt carbonyl complexes in a phase transfer system (Eq. 27).[8],[78]

$$\begin{aligned} &ArCH_2X + 2CO + Base \xrightarrow[-Base\cdot HX]{CO_2(CO)_8} \\ &ArCH_2CO_2H + ArCH_2COCO_2H + Ar-\underset{\displaystyle CH_2Ar}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}}-COCO_2H \end{aligned} \tag{27}$$

α-Arylethyl halides have successfully been converted under phase transfer conditions into β-aryl-α-ketobutanoic acids, important biochemical agents (Eq. 28).[79]–[81]

$$\begin{aligned} &Ar-\underset{\displaystyle CH_3}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}}-X + 2CO + Base \xrightarrow[-Base\cdot HX]{CO_2(CO)_8} \\ &X = Cl, Br \\ &Ar-\underset{\displaystyle CH_3}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}}-COCO_2H + Ar-\underset{\displaystyle CH_3}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}}-CO_2H \\ &\qquad + ArCH_2CH_2CO_2H \end{aligned} \tag{28}$$

The mechanism of the Co-catalyzed double carbonylation reaction of benzylic compounds has been proposed as shown in **Scheme 12** to involve the formation of enolic intermediate, which undergoes the subsequent insertion of carbon monoxide followed by nucleophilic attack.[18],[78],[79],[82]–[84] The proposed mechanism can circumvent the difficulty involved in the double CO insertion processes. The CO insertion into acyl–transition metal bond is considered thermodynamically unfavorable, but CO insertion into vinyl–metal bond generated by enolization of the aryl–acetyl bond may make the second insertion a feasible process. Some evidence supporting the intermediacy of the enol form has been presented.[82]



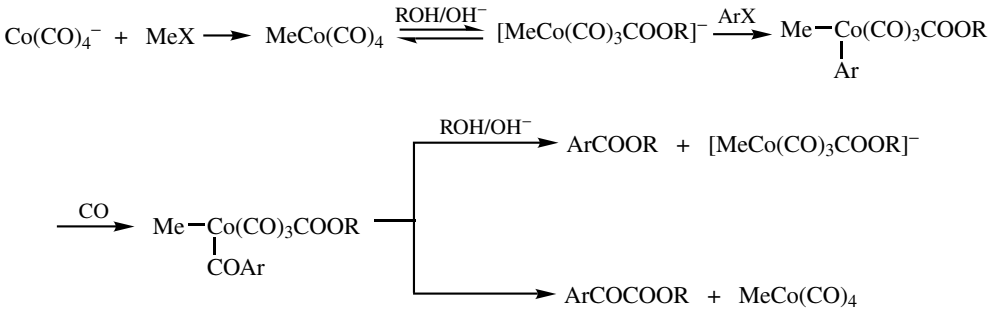
Scheme 12

A very recent result that vinylmanganese complex was isolated by treatment of manganese acyl complex with triethylsilane gives further support for the formation of enolic species in the catalytic reaction.[85] Carbonylation of the siloxyvinyl derivatives followed by protonation gives α-ketoacylmanganese complexes.

Aryl halides have also been doubly cabonylated to corresponding α-keto acids in Co-catalyzed phase transfer system in the presence of MeI.[79],[81],[83],[86],[87] A mechanism, involving the formation of an acyl(alkoxycarbonyl)cobalt intermediate, has been proposed for the formation of α-keto acid (**Scheme 13**).[32],[79],[81],[83],[86]

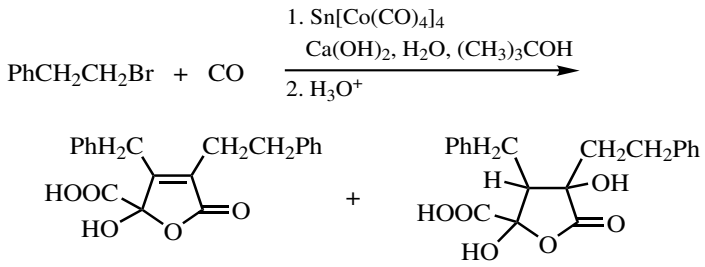
Under photostimulation conditions, *o*-halogenated benzoic acid has been doubly carbonylated to give phthalonic acid catalyzed by cobalt carbonyl complex.[88]

Alkyl halides other than benzylic substrates have also been reported to undergo Co-catalyzed double carbonylation to give corresponding α-keto acids, but in some cases more drastic conditions are necessary and the selectivity for α-keto acid is not high.[89]–[93] Styrene oxides are doubly carbonylated to furandiones catalyzed by $Co_2(CO)_8$ in the presence of MeI and NaOH in a phase transfer system.[94]



Scheme 13

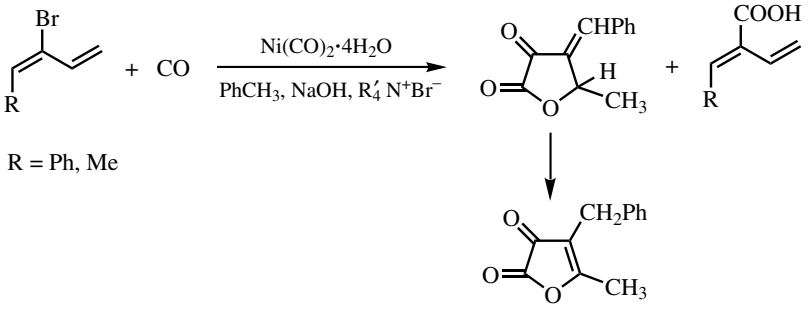
Instead of $Co_2(CO)_8$, use of $Sn[Co(CO)_4]_4$ as catalyst was reported in conversion of β-phenylethyl bromide into lactones (Eq. 29),[95] rather than benzylpyruvic acid $PhCH_2CH_2COCOOH$.[92],[93]



(29)

H.ii. Double Carbonylation Reactions Catalyzed by Nickel Complexes

Under phase transfer conditions, nickel can also catalyze double carbonylation of halide substrates. 2-Halo-1,3-dienes have been converted into α-keto-β-alkylidene acids or lactones catalyzed by nickel cyanide in the presence of a phase transfer agent (Eq. 30).[96]–[98] The CO insertion into a nickel–acyl bond and formation of a nickel metallacyclic intermediate have been proposed to be responsible for the formation of α-keto compounds.[98]



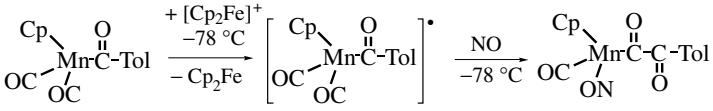
(30)

H.iii. Multiple CO Insertion Processes Promoted by Other Transition Metal Complexes

Scattered examples of incorporation of the two CO groups into organic compounds using iron complexes to afford 1,2-diketones and acyl lactones are known.[99]–[101]

Although the successive CO insertion into an acyl–transition metal complex is considered thermodynamically unfavorable,[102] a rare example of the successive CO insertion into an acyl–Mn complex in the presence of NO has been reported (Eq. 31).[103]–[106]

Triple successive insertion of carbon monoxide between a cyclopentadienyl anion and iron has been achieved in the reaction of $Fe(CO)_5$ with the cyclopentadienyl anion in the presence of acyl chlorides.[107]



(31)

The CO insertion mode regarding early transition metals and f-elements is different from that of late transition metals. Thus, carbene-like dihaptoacyl bonding mode is observed with these acyl complexes formed in the first CO insertion. The subsequent course of the reaction with the second CO may differ considerably from that of late transition metals.[108]–[112]

I. SUMMARY

Past papers on double carbonylation with palladium catalysts have been reviewed. The majority of contributions are on the double carbonylation of organic halides catalyzed by palladium complexes. The other types of oxidative double carbonylation of nucleophiles to give oxalic acid derivatives are also discussed. Detailed studies on the mechanisms of the double carbonylation of aryl and alkenyl halides, based on examination of the behavior of presumed intermediates, revealed that catalytic double carbonylation reactions consist of the following processes: oxidative addition to give arylpalladium halides, CO insertion into aryl–Pd bond, the second CO coordination, a nucleophilic attack on the coordinated CO to give a bisacylpalladium intermediate, and reductive elimination of α-keto acid derivatives. An alternative possibility involving successive double CO insertion has been excluded in such Pd-promoted double carbonylation reactions of aryl halides. The previous limitation that the process was applicable only to aromatic halides or vinyl halides carrying aromatic substituents was removed by development of a catalytic process converting allylic chlorides into α-keto acid derivatives.

Further studies will make the double carbonylation process of wider synthetic use for preparation of α-keto acid derivatives as precursors of various useful compounds.

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VI.2.2 Reactions of Acylpalladium Derivatives with Organometals and Related Carbon Nucleophiles

YOSHINAO TAMARU and MASANARI KIMURA

A. INTRODUCTION

In this section we describe ketone synthesis via Pd-catalyzed carbonylative cross-coupling reaction of organic halides (and triflates, RX) and organometallic reagents (R′M, **Scheme 1**).

In planning ketone synthesis, the obvious and straightforward strategy is to connect two substituents to the carbon atom of carbon monoxide. A variety of such processes have been developed by the use of transition metal catalysis.[1] Among transition metals, palladium has been studied most extensively and has proved to be the most versatile. For the carbonylative cross-coupling reaction, there are two pathways that differ in the active acyl species. One involves acylpalladium (RCOPdX), which serves as the electrophile and reacts with nucleophilic organometals (R′M) to yield unsymmetrical ketones (path a). The other involves acylmetals (R′COM), which serve as the nucleophile and react with electrophilic organopalladium(II) (RPdX) species to yield ketones (path b). This process has been developed recently. The success of these two paths depends on how effectively acylpalladium and acylmetal species can be generated; otherwise noncarbonylative cross-coupling of RPdX and R′M to yield R—R′ may become a serious side reaction. Compared with the synthesis of aldehydes and carboxylic acid derivatives, however, only a limited number of methods for the synthesis of ketones under carbonylation conditions have been reported, probably reflecting the difficulties associated with this process. The carbonylative cross-coupling reaction of organic halides (triflates) and soft nucleophiles (ketone and ester enolates) is described in **Sect. VI.2.3**. Pd-catalyzed coupling reaction of acyl halides and organometals is a useful alternative for the unsymmetrical ketone synthesis; however, this subject is not described here.

B. ARYLMERCURIC SALTS AS R′M

The Pd-catalyzed formation of symmetrical diaryl ketones from arylmercuric salts was first reported by R. F. Heck.[2] The reaction of phenylmercuric chloride with carbon monoxide

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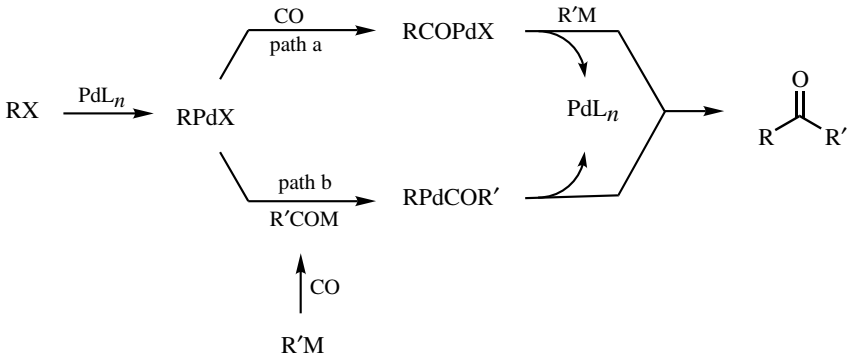
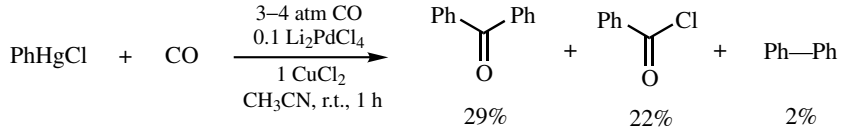


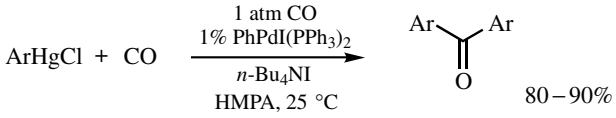
Scheme 1

in acetonitrile at room temperature (r.t.) in the presence of 10% of Li_2PdCl_4 and 1 equiv of $CuCl_2$ produces benzophenone in 29% yield together with benzoyl chloride and biphenyl (**Scheme 2**). Diaryl ketone is formed preferentially over benzoyl chlorides at higher pressures of carbon monoxide.

A similar reaction also proceeds under very mild conditions and with a much higher selectivity by using $PhPdI(PPh_3)_2$ as the catalyst in the presence of tetrabutylammonium iodide, which greatly increases the reaction rate (**Scheme 3**).[3] Pd complexes without phosphine ligands, for example, $PdCl_2(PhCN)_2$ and $[(\eta^3\text{-}C_3H_5)PdCl]_2$, do not promote the reaction.



Scheme 2



Scheme 3

C. ORGANOSTANNANE AS R′M

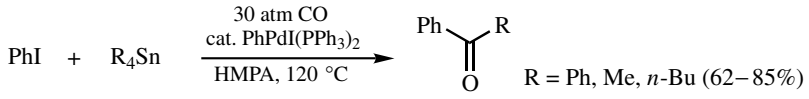
The Pd-catalyzed carbonylative cross-coupling reaction of organic halides (or triflates) with organostannanes is an especially valuable and versatile synthetic method of unsymmetrical ketone.[4] One serious drawback is the high toxicity of organostannanes.

C.i. Aryl Halide and Aryl Triflate as RX

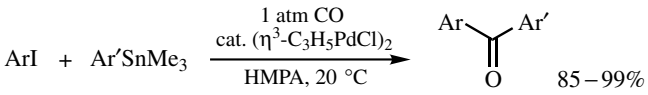
M. Tanaka reported for the first time that $PhPdI(PPh_3)_2$ catalyzed the carbonylative cross-coupling of iodobenzene with tetraalkylstannane to provide unsymmetrical

ketones.[5] This prototype requires harsh conditions; a high temperature of 120 °C and a high pressure of 30 atm of CO (**Scheme 4**). The use of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ as the catalyst and HMPA as the solvent makes it possible to perform the reaction of aryl iodides with aryltrimethylstannanes under extremely mild conditions (20 °C and 1 atm of CO) (**Scheme 5**).[3]

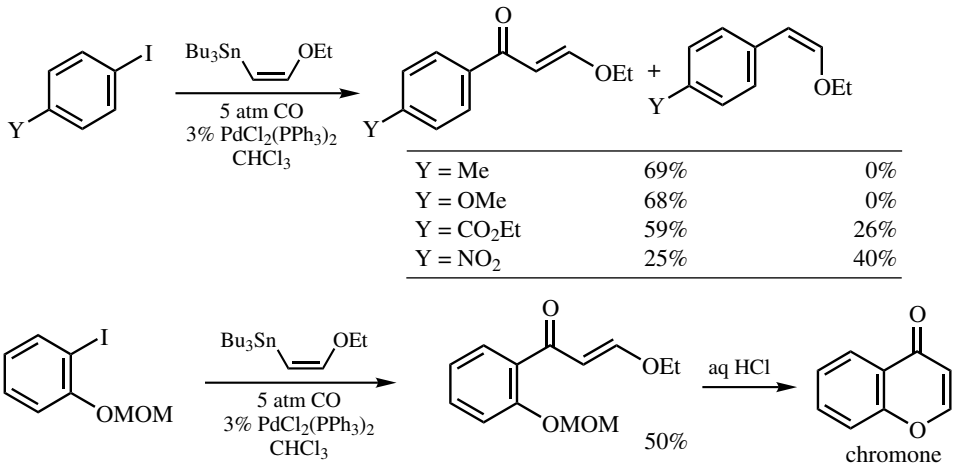
Aryl iodides bearing electron-donating groups react with (*Z*)-1-ethoxy-2-(tributylstannyl)ethene to selectively provide the carbonylative cross-coupling products, while those bearing electron-withdrawing substituents tend to give the direct coupling products (**Scheme 6**).[6] The reaction is applied to the synthesis of chromone (**Scheme 6**).[6]



Scheme 4

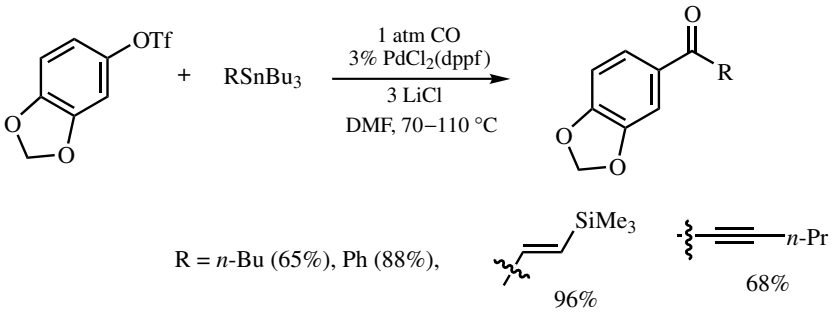


Scheme 5



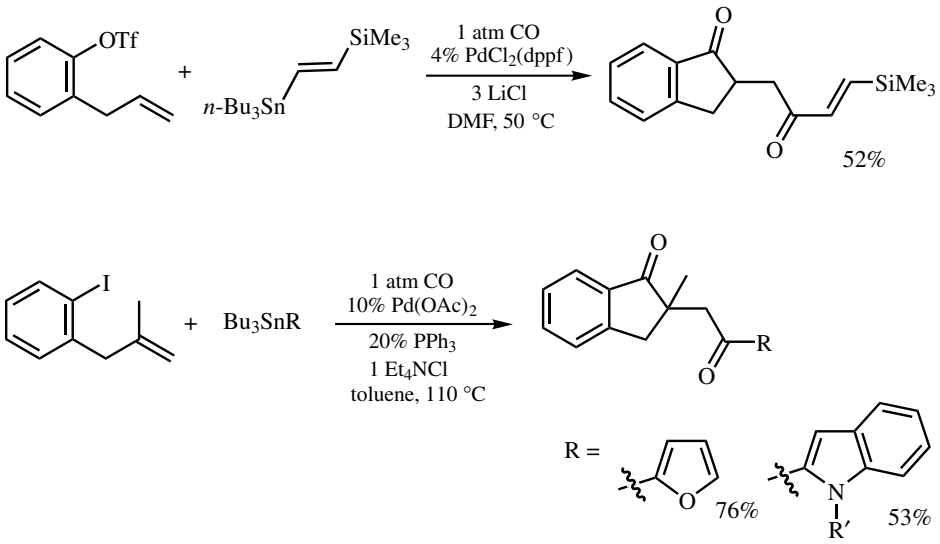
Scheme 6

Aryl triflates react with organostannanes in the presence of 3 equiv of lithium chloride and 3% of $PdCl_2$(dppf) under 1 atm of CO to afford a variety of aryl ketones in high yields (**Scheme 7**).[7] The catalyst is unique in that it is only one of several palladium catalysts that give consistently high yields of product. The reaction tolerates functional groups such as alcohol, aldehyde, ester, and halide on the coupling partners. Vinyl, acetylenic, alkyl, and aryl groups of organostannanes transfer to yield the corresponding ketones. Allylstannanes fail to give ketones in good yields; instead, a direct coupling reaction prevails to give allylarenes.



Scheme 7

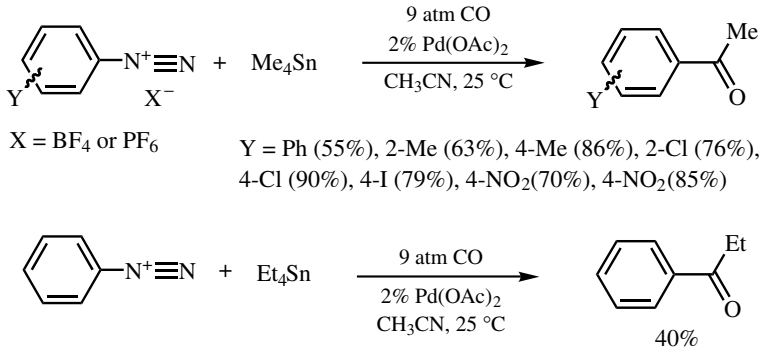
Under similar reaction conditions, *o*-allylphenyltriflate reacts with vinylstannane to furnish the dicarbonylation product (**Scheme 8**).[7] Similar cascade carbonylation termination by organostannanes takes place with aryl iodides and seems to be a general reaction pattern. The reaction may be useful for the preparation of indanones possessing 2-oxoethyl groups at the 2-position (**Scheme 8**).[8]



Scheme 8

Arenediazonium salts, irrespective of the electronic nature and the position of the substituents on the aromatic ring, undergo a smooth carbonylative cross-coupling reaction with tetramethylstannane in the presence of 2% of $Pd(OAc)_2$ under 9 atm of CO at room temperature (**Scheme 9**).[9] Tetraethylstannane is less reactive and aryl ethyl ketones are obtained in less than 50% yields. Tetrabutylstannane does not react under these conditions. The reaction is successful for X = BF_4 and PF_6, but not for X = Cl. In this case, the yields drop to less than 10% and intractable tarry material results (**Scheme 9**).[9]

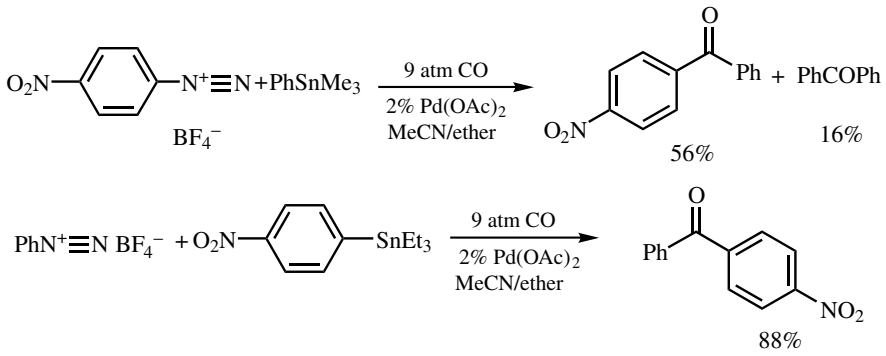
Aryltrialkylstannanes selectively transfer the aryl group rather than the alkyl group. The use of a mixed CH_3CN–Et_2O solvent increases the selectivity and the reaction rate;



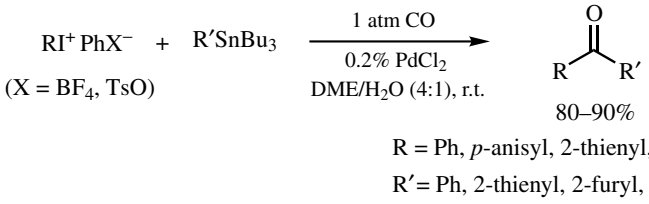
Scheme 9

however, a proper combination of arenediazonium salts and aryltrialkylstannanes is important for the success of the cross-coupling reaction (**Scheme 10**).[10] In general, phenyltrialkylstannanes and aryltrialkylstannanes with electron-donating substituents tend to give symmetrical diaryl ketones. The examples shown in **Scheme 10** are illustrative.

Hypervalent iodonium salts (RI^+PhX^-) selectively transfer the R group (phenyl, *p*-anisyl, 2-thienyl, (*E*)-β-styryl) and couple with R′ of $R'SnBu_3$ to furnish unsymmetrical ketones in excellent yields under very mild reaction conditions within a short period of time (1 atom of CO, 0.2% of $PdCl_2$, 25 °C, 20 min) (**Scheme 11**).[11] The reaction is most successfully performed in an aqueous medium (DME/H_2O, 4:1). In dry DME, the reaction does not give clean products.



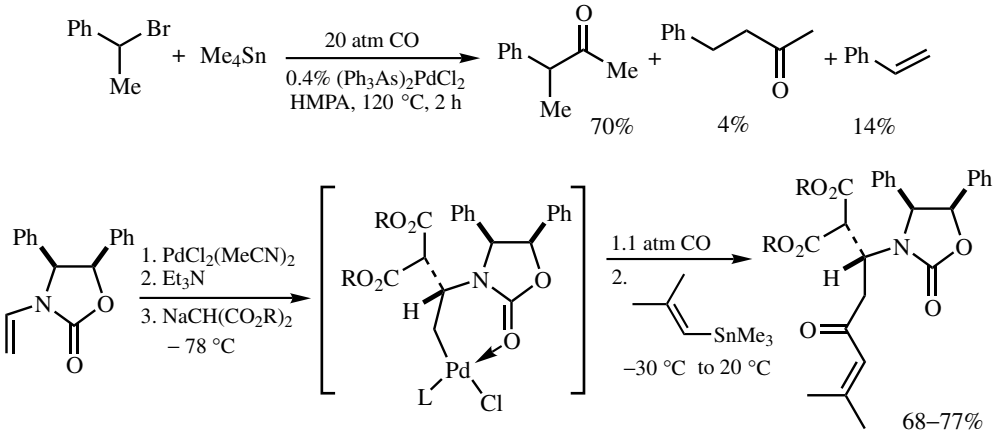
Scheme 10



Scheme 11

C.ii. Alkyl Halide as RX

Generally, alkylpalladium(II) intermediates possessing hydrogen at the 2-position are rather unstable. They tend to undergo β-hydrogen elimination to give alkene and/or sequential β-hydrogen elimination–hydropalladation to cause positional isomerization. In fact, the carbonylative cross-coupling reaction of α-phenethyl bromide with tetramethylstannane, even under optimized conditions, is plagued by the formation of styrene and methyl β-phenethyl ketone as side products (**Scheme 12**).[12] In the reaction of α-bromophenylpropane the elimination product, β-methylstyrene, was produced as the major product.



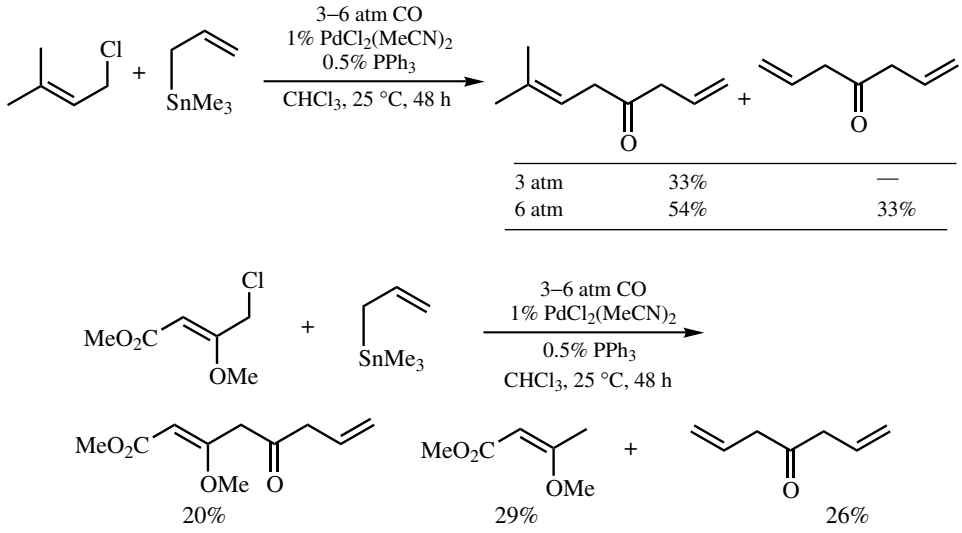
Scheme 12

Some alkylpalladium species may withstand the β-hydrogen elimination and provide the carbonylative cross-coupling product in a reasonable yield (**Scheme 12**).[13] The product was used for the total synthesis of (+)-negamycin.

C.iii. Allyl Halide as RX

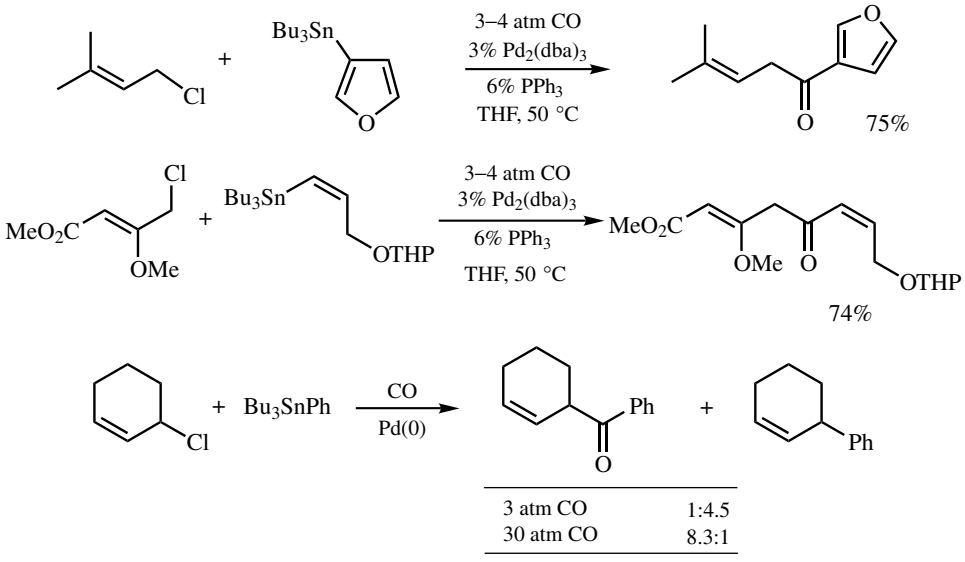
Diallyl ketones are prepared by the reaction of allylic chlorides and allyltrimethylstannanes under 3–6 atm of CO at 25 °C (**Scheme 13**).[14] The optimized Pd/PPh_3 ratio of 2 is somewhat unusual. Higher carbon monoxide pressures improve the yield, although higher temperatures cause the further addition of allylstannane to the ketone to yield triallylmethanol. Allyltrimethylstannane shows higher reactivity and more satisfactory result than allyltributylstannane. For the same reasons, allylic chlorides are preferred to allylic bromides. The carbonylative coupling reaction takes place exclusively at the least hindered site of unsymmetrical allyl halides and tolerates functional groups (ester, nitrile, vinyl ether) on the allyl halide partner. Major side reactions are the carbonylative homocoupling of allylstannanes and the reduction of allyl halides, which severely limit the synthetic utility of the present method.

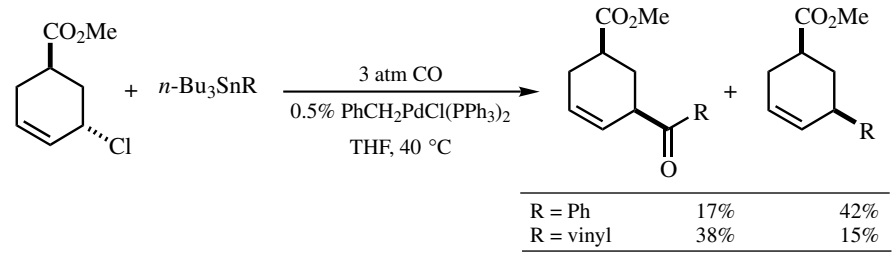
The carbonylative cross-coupling reaction of allyl chlorides with phenyl-, 3-furyl-, and vinylstannanes is more fruitful than the reaction with allylstannanes (**Scheme 14**).[15],[16] Under the conditions, no double bond isomerization into the conjugation with ketone is



3 atm	33%	—
6 atm	54%	33%

Scheme 13



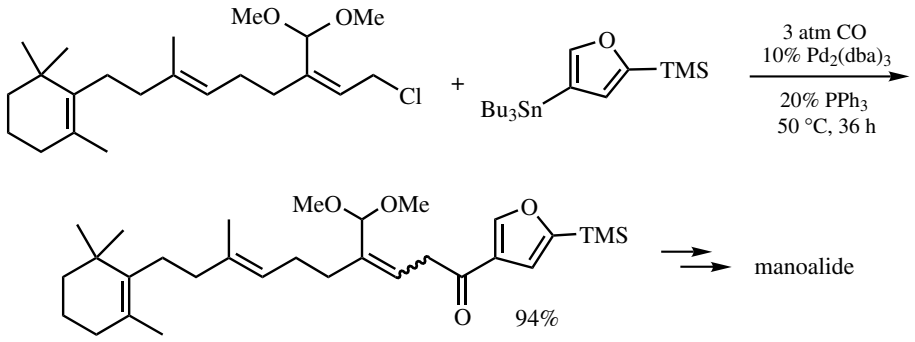


Scheme 14

observed. (*Z*)-Vinylstannanes is transformed into (*Z*)-vinyl ketones without losing the stereochemical integrity. For some allyl chlorides (e.g., 1-chloro-2-cyclohexene), direct coupling becomes the major pathway. In such cases, higher pressures of CO may be beneficial for the alteration of the reaction course in favor of the formation of carbonylation products.

The cross-coupling reaction of *trans*-3-chloro-5-carbomethoxycyclohexene with either phenyltributylstannane or vinyltributylstannane proceeds with net inversion of configuration (100%) at the allylic carbon center to give *cis*-ketone (**Scheme 14**). This is rationalized as a result of the sequence: (i) oxidative addition of Pd(0) into C—Cl bond with inversion, (ii) carbonylation of π-allylpalladium thus formed with retention to give acylpalladium(II), (iii) transmetallation of vinyl or phenyl group from organostannane to palladium metal of the acylpalladium(II), and (iv) reductive elimination of acylvinylpalldium(II) or acylphenylpalladium(II) with retention of configuration.[15],[16]

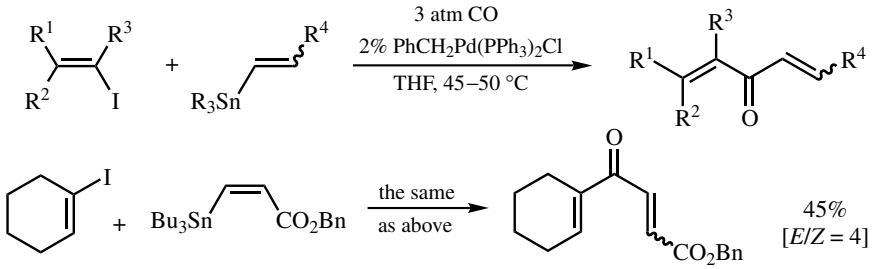
Total synthesis of manoalide, an inhibitor of phospholipase A_2, is achieved by using the present methodology as the key step (**Scheme 15**).[17]



Scheme 15

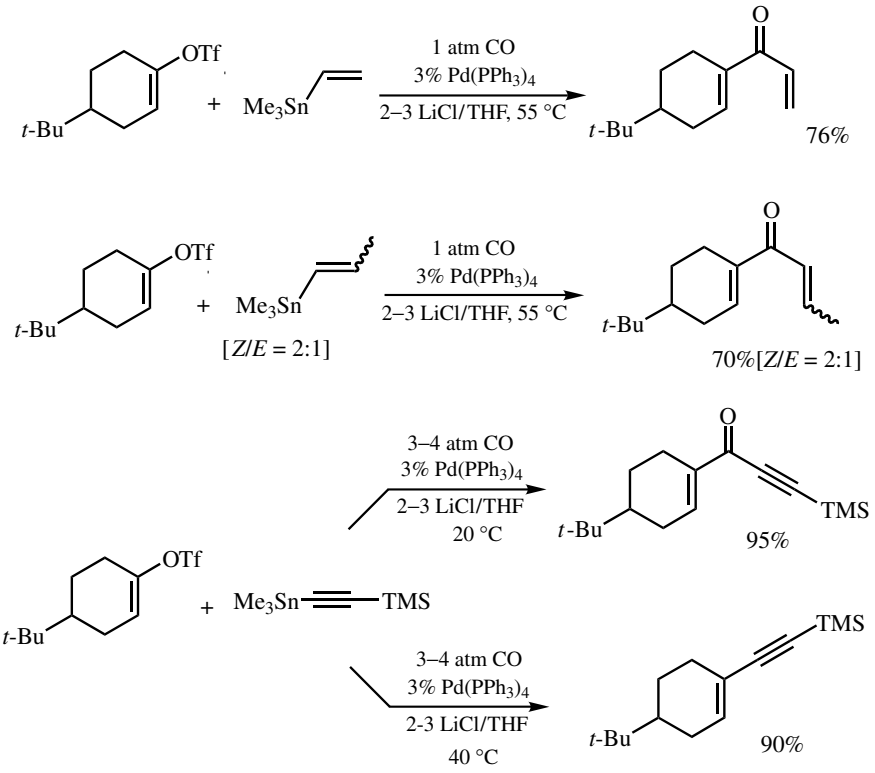
C.iv. Vinyl Halide and Triflate as RX

The Pd-catalyzed three-component connection reaction of vinyl iodides, vinylstannanes, and CO proceeds smoothly under mild, neutral conditions (40–50 °C) under moderate carbon monoxide pressures (3 atm) to provide the corresponding unsymmetrical divinyl ketones in good yields (**Scheme 16**).[18] The reaction is highly catalytic and requires only 2% of $PhCH_2Pd(PPh_3)_2Cl$ or $PdCl_2(PPh_3)_2$.



Scheme 16

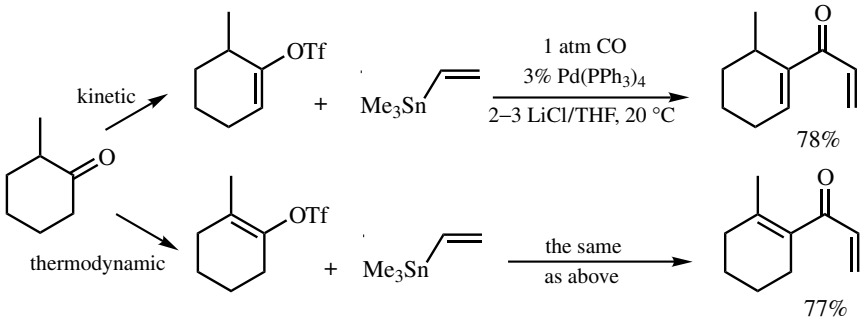
The *E* geometry of the double bond in both partners remains intact in the coupling product. The *Z* configuration of the double bond of vinylstannanes is lost in the products and (*E*)-vinyl ketone predominates. For example, the reaction of cyclohexenyl iodide with benzyl (*Z*)-3-(tributylstannyl)propenoate for 80 h results in a coupled product having an *E*/*Z* ratio of 4. The recovered unreacted tin reagent remains unisomerized (**Scheme 17**).[18]



Scheme 17

Vinyl triflates undergo the Pd-catalyzed carbonylative coupling reaction with various tin reagents in the presence of 2–3 equiv of lithium chloride and give the cross-coupled ketones in good yield (**Scheme 17**).[19] In the absence of LiCl, no carbonylation takes place. Reaction temperature is another important factor; the reaction of 4-*t*-butylcyclohexyl triflate with trimethylvinylstannane is extremely slow at temperatures below 45 °C, while at temperatures above 65 °C a considerable quantity of the noncarbonylated cross-coupling product is observed. Similar and more drastic temperature dependence on the reaction course is observed for the reaction with ethynylstannanes; at 20 °C, the carbonylative cross-coupling product is obtained exclusively in quantitative yield, while at 40 °C, the noncarbonylative cross-coupling product is produced in quantitative yield. In sharp contrast to the reaction with vinyl iodides (**Scheme 16**), the reaction with vinyl triflates may not accompany the *Z* to *E* isomerization of the products (**Scheme 17**).[19] For example, the *Z*,*E*-composition of the starting 1-propenylstannane (*Z*/*E* = 2:1) is retained in the carbonylation product.

Another important aspect of the triflate methodology is the ready availability of both kinetic and thermodynamic triflates with high regioselectivity (more than 93%) and their carbonylative cross-coupling reaction with vinylstannane with more than 95% regioselectivity (**Scheme 18**).[19]

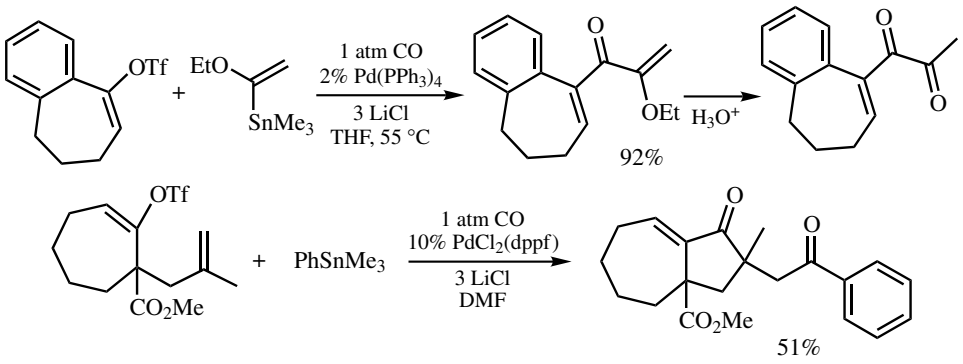


Scheme 18

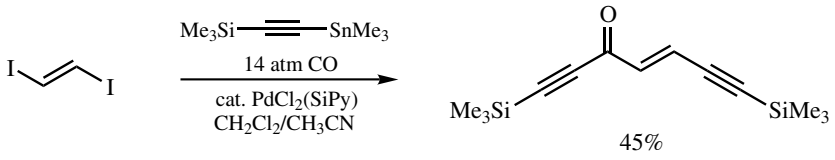
The methyl group of tetramethylstannane and the aryl group of aryltrimethylstannanes also participate in the carbonylative cross-coupling reaction with vinyl triflates. For this reaction to proceed, in addition to 2–3 equiv of LiCl, 1 equiv of $ZnCl_2$ is indispensable (3 atm of CO).[19]

Under the conditions established above, vinyl triflates and (α-ethoxyvinyl)trimethylstannane undergo the carbonylative cross-coupling reaction (**Scheme 19**).[20] The α-methoxyvinyl group of the products is readily hydrolyzed to acetyl group; thus, this reaction may be regarded as a dicarbonylative cross-coupling reaction. Vinyl triflates, possessing an extra double bond at an appropriate position, may undergo carbonylative cascade reaction. In the example shown in **Scheme 19**, a tetramolecular process, involving two molecules of CO, is realized.[21]

The carbonylative coupling reaction of ethynylstannane and 1,2-diiodoethylene produces 1,7-bis(trimethylsilyl)hept-1,6-diyn-4(*E*)-en-3-one (**Scheme 20**) in the presence of a catalytic amount of $[Me_2Si(2\text{-pyridyl})_2]PdCl_2$.[22] It is noteworthy that only a single molecule of carbon monoxide is used per cross-coupling reaction of diiodoalkene.



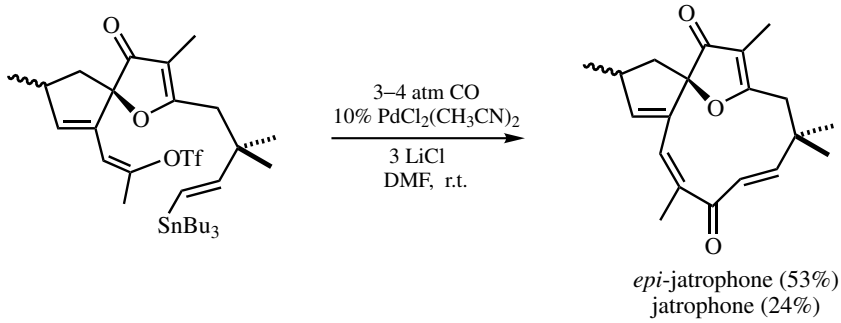
Scheme 19



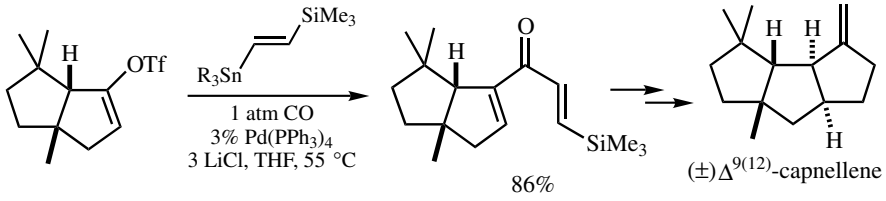
Scheme 20

The total syntheses of racemic *epi*-jatrophone (the β-Me isomer) is completed by the use of the Pd-catalyzed intramolecular carbonylative coupling reaction of vinyl triflate and vinylstannane as the key macrocycle-forming step (**Scheme 21**).[23] The reaction is performed under moderate dilution (0.03 M in DMF). Racemic jatrophone (the α-Me isomer) is also prepared under similar conditions.

The carbonylative coupling reaction followed by a Nazarov cyclization is utilized for a sequential annulation to assemble the fused five-membered ring structure of marine natural product $\Delta^{9(12)}$-capnellene (**Scheme 22**).[19,24]



Scheme 21



Scheme 22

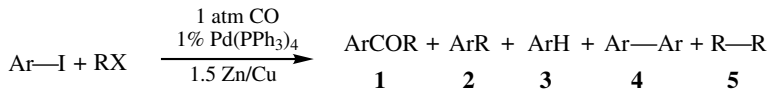
D. ORGANOZINC AS R′M

D.i. Aryl Iodide as RX

Unsymmetrical ketone synthesis is performed by the carbonylative coupling reaction of aryl iodides and alkyl iodides in the presence of a stoichiometric amount of zinc–copper couple and 1% of $Pd(PPh_3)_4$ under 1 atm of CO (**Scheme 23**).[25],[26] The reaction may proceed via coupling of *in situ* generated aroylpalladium(II) and alkylzinc species. Phenyl

TABLE 1. Unsymmetrical Ketone Synthesis from Aryl Iodide and Alkyl Halide

				Isolated Yield (%)				
Run	ArI	RX	Reaction Conditions	**1**	**2**	**3**	**4**	**5**
1	PhI	*n*-PrI	50 °C, 24 h	90	0	0	0	0
2	PhI	*i*-PrI	r.t., 42 h	86	0	0	0	0
3	4-$MeOC_6H_4I$	*n*-PrI	50 °C, 22 h	90	0	0	0	0
4	4-BrC_6H_4I	*n*-PrI	50 °C, 8 h	38	0	0	27	0
5	2-$MeO_2CC_6H_4I$	*n*-PrI	50 °C, 22 h	0	0	23	23	0
6	PhI	BnCl	−78 °C, 2 h; 60 °C, 2 h	57	0	0	0	42
7	4-$MeOC_6H_4I$	4-$ClC_6H_4CH_2Cl$	−78 °C, 2 h; 60 °C, 19 h	81	7	0	0	9

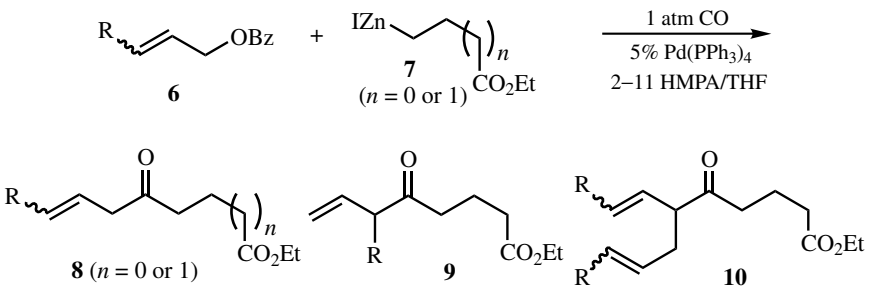


Scheme 23

iodide and aryl iodides with electron-donating substituents react selectively to provide aryl alkyl ketones in good yields (runs 1–3, **Table 1**). Aryl iodides with electron-withdrawing substituents fail to give the expected ketone and provide a mixture of the reduction product and direct homocoupling product (run 5). Under similar conditions, benzyl chloride tends to undergo homocoupling and provides bibenzyl in substantial amount. In order to reduce the amount of bibenzyl and increase the yield of unsymmetrical ketone, it is necessary to initiate the reaction at −78 °C and gradually increase the temperature to 60 °C (runs 6 and 7). No ketones are obtained by the reaction of phenyl bromides and alkyl iodides.

D.ii. Allyl Benzoate and Phosphate as RX

Organozinc halides undergo a Pd-catalyzed carbonylative cross-coupling reaction with allylic benzoates and phosphates to furnish allyl alkyl ketones under 1 atm of CO (**Scheme 24**).[27],[28] In **Table 2** are summarized typical examples for the reaction with β-zincioester (**7**, $n = 0$) and γ-zincioester (**7**, $n = 1$).



Scheme 24

TABLE 2. Three-Component Connection Reaction of 6, CO, and 7[a]

Run	**6**	**7**	Solvent/Additive (equiv)	Temperature, Time	Isolated Yield (%)
1	H	$n = 0$	THF/HMPA (11.3)	r.t., 18 h	**8** (62)[b]
2	H	$n = 1$	Toluene/HMPA (2.3)	40 °C, 30 h	**8** (40), **10** (28)
3	Me	$n = 0$	THF/HMPA (11.3)	r.t., 23 h	**8** (67)
4	Me	$n = 1$	Toluene/HMPA (2.3)	r.t., 24 h	**8** (40)
5	Ph	$n = 1$	THF/HMPA (4.5)	r.t., 22 h	**8** (41), **9** (29) **10** (5)

[a]Organozinc **2** (2.5 mmol) was used in runs 1 and 3; organozinc **3** (1.5 mmol) was used in runs 2, 4, and 5.
[b]In addition to **8**, diethyl 4-oxopimelate was isolated in 12%.

β-Zincioester **7** ($n = 0$) undergoes a smooth carbonylative coupling reaction with a variety of allyl benzoates to give unsymmetrical ketones **8** in good yields (**Table 2**). Unsymmetrically substituted allylic benzoates provide the ketones with the lowest number of substituents at the position α to the keto carbonyl. γ-Zincioester **7** ($n = 1$) displays apparently different reactivity from β-zincioester, and the reaction is somewhat complicated. For the reaction with cinnamyl benzoate, the branched isomer **9** is obtained in a comparable amount to the straight chain isomer **8** (run 5). Furthermore, the reactions with allyl benzoate and cinnamyl benzoate provide considerable amounts of the doubly allylated products **10** (runs 2 and 5, in **Table 2**). The formation of **10** can be completely suppressed by performing the reaction in the presence of trimethylsilyl chloride, and **8** is obtained in better yields.[27]

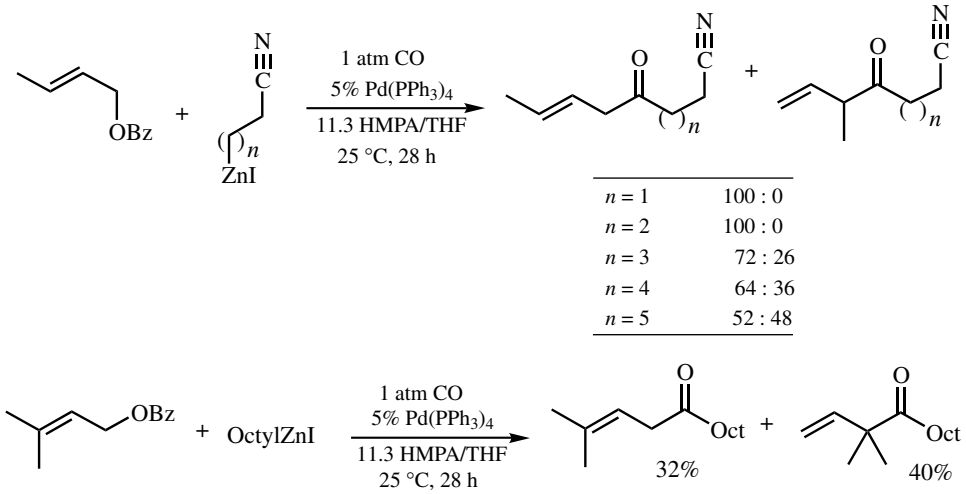
The reaction is highly dependent on the kind and amount of cosolvent. For the carbonylation of organozinc halides to proceed successfully, the use of HMPA is essential. The optimal amounts of HMPA differ for each organozinc halide.

β- and γ-Zincionitriles react with crotyl benzoate to selectively provide the straight chain isomers (**Scheme 25**) as with the cases of β- and γ-zincioesters (**Table 2**). Interestingly, however, the amount of the branched isomer increases gradually with an increase in the number of the methylene unit connecting the zinc metal and nitrile group. The reaction with ζ-zincionitrile ($n = 5$) furnishes a mixture of the straight and branched isomers in almost equal quantities. Similar regiochemical outcome is observed for the reaction with octylzinc iodide (**Scheme 25**).[28]

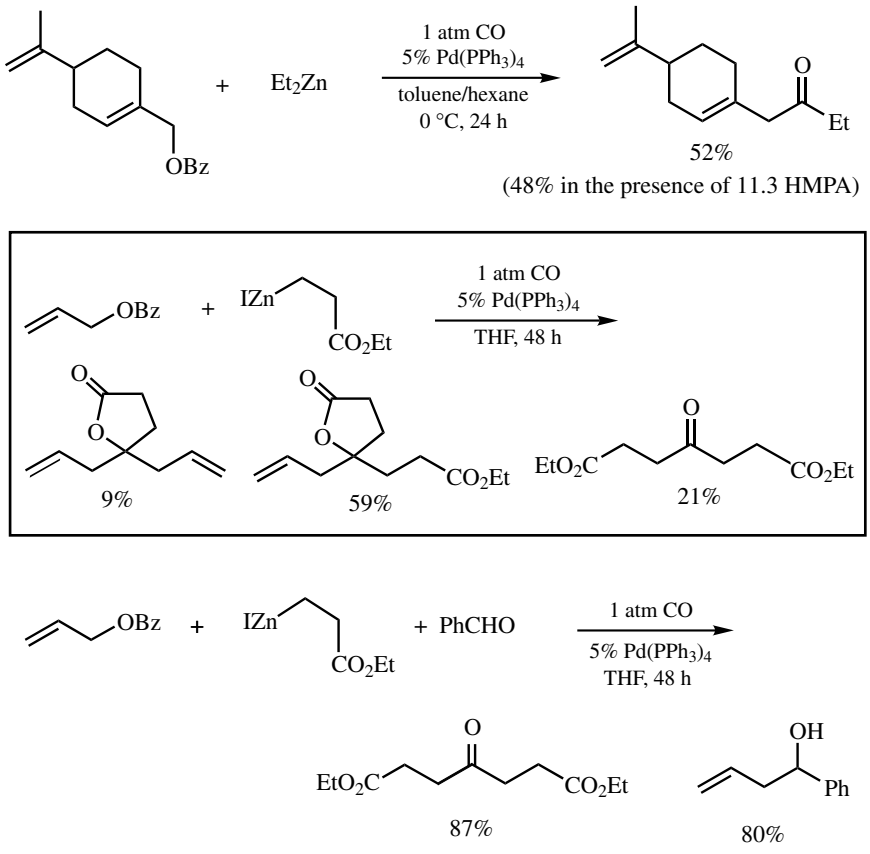
Dialkylzincs display reactivity completely different from alkylzinc halides. For example, diethylzinc even undergoes the three-component connection reaction smoothly at 0 °C irrespective of the absence or presence of HMPA (**Scheme 26**).[28]

On the other hand, alkylzinc halides, in the absence of HMPA, display completely different results. For example, under similar conditions to those of run 1, **Table 2**, β-zincioester does not provide the expected unsymmetrical ketone **8** in any detectable amounts; instead, a mixture of two lactones and diethyl 4-oxopimelate is produced in a good combined isolated yield (**Scheme 26**).[28] The minor lactone may be derived by the allylation of the usual unsymmetrical ketone **8** at the keto function followed by lactonization, and the major lactone may be derived by the allylation of diethyl 4-oxopimelate. Indeed, under similar conditions, in the presence of benzaldehyde, benzaldehyde is selectively allylated to provide the homoallyl alcohol in good yield, and diethyl 4-oxopimelate remains intact and is isolated in quantitative yield (**Scheme 26**).

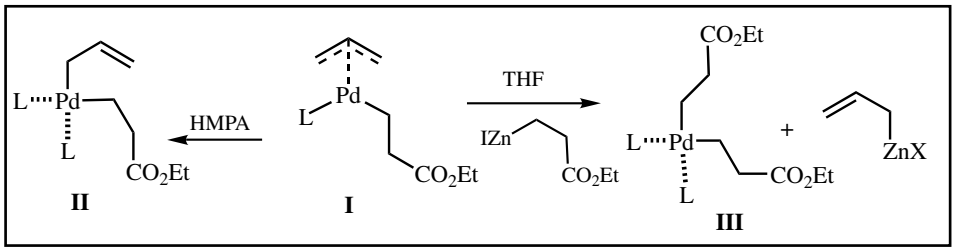
These contrasting results are rationalized by supposing that the π-allylalkylpalladium intermediate **I** is converted to the σ-allylalkylpalladium complex **II** in the presence of



Scheme 25



Scheme 26

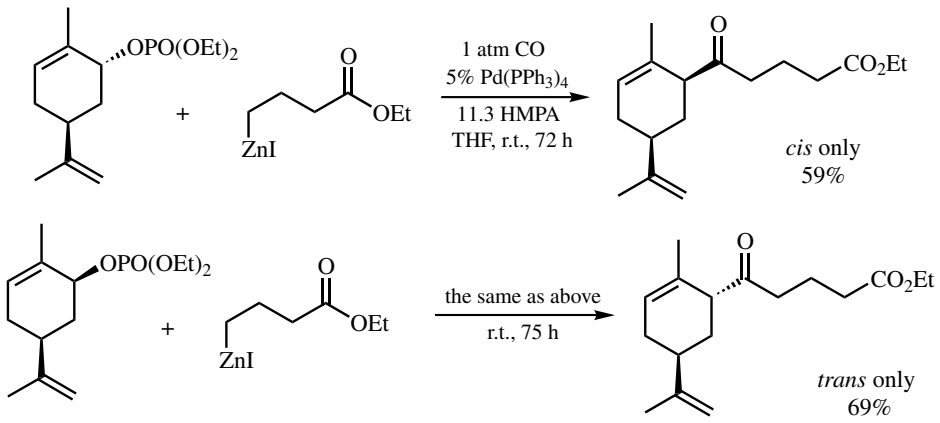


Scheme 26 (*Continued*)

HMPA, through which a carbonylative coupling of allyl and alkyl groups proceeds to provide unsymmetrical ketone and Pd(0) species. On the other hand, in the absence of HMPA, an alkyl–allyl exchange reaction takes place between **I** and organozinc and gives rise to the mixture of symmetrically substituted dialkylpalladium **III** and allylzinc. Carbonylation of the intermediate **III** produces symmetrical ketone and regenerates Pd(0). Allylzinc thus formed is responsible for the formation of the lactones and the homoallyl alcohol in **Scheme 26**.[28]

It may be pertinent to note that the π-allylalkylpalladium intermediate **I** resists both the expected reductive elimination, giving ethyl 5-hexenoate, and β-hydrogen elimination, providing a mixture of ethyl acrylate and propene. The transformation of **I** to **III**, that is, umpolung of electrophilic π-allylpalladium to nucleophilic allylzinc via allyl-alkyl exchange between π-allylpalladium and alkylzinc, has proved to be a quite general phenomenon and this has opened a new field of π-allylpalladium chemistry (**Sect. V.2.3.4**).

The Pd-catalyzed carbonylative cross-coupling reaction of *trans*-carvyl phosphates with γ-zincioester proceeds nicely in the presence of 11.3 equiv of HMPA at room temperature under 1 atm of CO and yields the corresponding *cis*-ketone as a single isomer in 59% yield (**Scheme 27**).[28] Under similar conditions, *cis*-carvyl phosphate exclusively provides the *trans*-isomer. These stereochemical outcomes clearly indicate that the carbonylative coupling reaction proceeds stereospecifically with overall inversion of configuration at the allylic stereocenters.

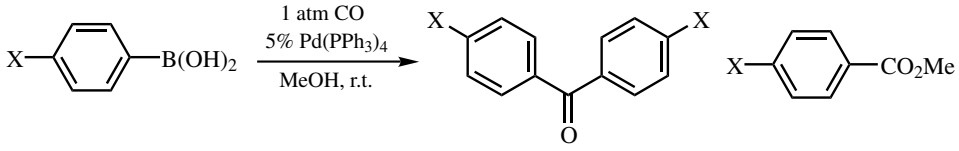


Scheme 27

E. ORGANOBORANE AS R′M

Organoboranes have many advantages as the organometallic component (R′M) for the Pd-catalyzed carbonylative cross-coupling reaction with organic halides (RX). They can be prepared in many ways and are compatible with a variety of functional groups of synthetic importance. Most boronic acids and esters are stable to air and moisture.

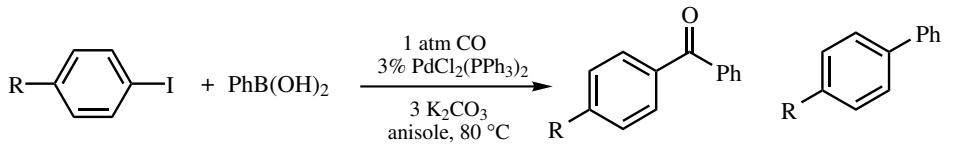
Arylboronic acids react with carbon monoxide in methanol in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give symmetrical diaryl ketones as the major products together with methyl benzoates as the side products (**Scheme 28**).[29]



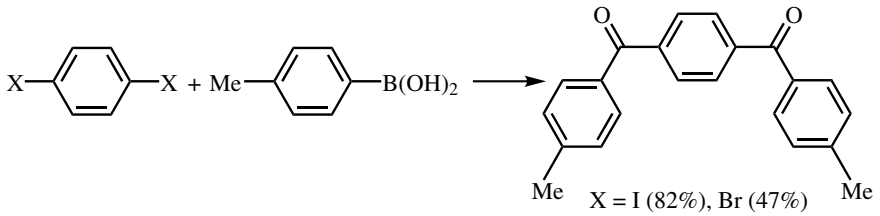
X = H	26%	10%
X = Me	20%	5%
X = OMe	50%	17%

Scheme 28

The Pd-catalyzed carbonylative cross-coupling reaction of arylboronic acids with aryl electrophiles nicely proceeds under 1 atm CO in anisole at 80 °C. The reaction is substantially affected by the kind of bases, solvents, and palladium complexes. The reaction with aryl iodides is most satisfactory when K_2CO_3 (3 equiv), anisole or dioxane, and $PdCl_2(PPh_3)_2$ (3%) are used (**Scheme 29**).[30] For arylbromides and aryltriflates, the combination of K_2CO_3 (3 equiv), KI (3 equiv), anisole, and $PdCl_2$(dppf) (3%) is most satisfactory.[31] The high yield formation of *p*-nitro- and *p*-acetylphenyl ketones is remarkable



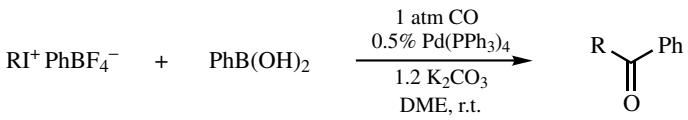
R = COMe	84%	11%
R = NO_2	89%	< 10%
R = NH_2	89%	—



Scheme 29

(**Scheme 29**), since arylpalladium bearing electron-attracting substituents is reluctant to undergo carbonylation and tends to give the direct coupling product, Ar—Ar′. Reflecting this, a double carbonylative cross-coupling reaction is achieved in good yield from 1 mole of *p*-dihalobenzene and 2 moles of *p*-tolylboronic acid (**Scheme 29**). Similar satisfactory results are obtained for a variety of heteroaromatic halides containing N, O, and S. Phenylboronic acid dibutyl esters and 9-phenyl-9-BBN give poor results.[31]

The cross-coupling reactions of organoboronic acids and carbon monoxide with hypervalent iodonium salts affords unsymmetrical ketones (**Scheme 30**).[32] The reaction proceeds smoothly at room temperature and in most cases completes within 0.5 h. Aryl-, alkenyl-, and alkynyliodonium salts react with arylboronic acids in the presence of 0.5% of $Pd(PPh_3)_4$ and 1.2 equiv of K_2CO_3 in DME to provide unsymmetrical aromatic ketones in high yields (**Scheme 30**).[32] Phenylboronic acid dimethyl ester can be utilized as efficiently as phenylboronic acid. In most cases, a small amount of the direct cross-coupling product (R—Ph, less than 7–8%) is produced.



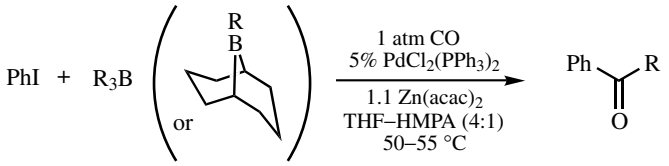
R = Ph (88%), 2-thienyl (82%), β-styryl (87%), 2-phenylethynyl (80%)

Scheme 30

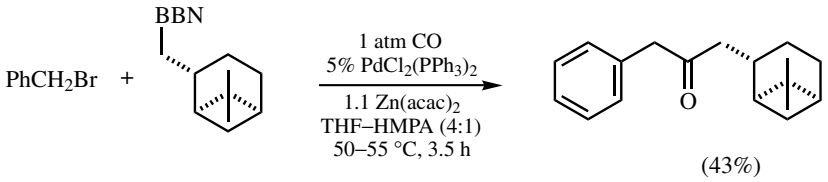
$Zn(acac)_2$ promotes the Pd-catalyzed carbonylative cross-coupling of aryl or benzyl halides with the alkyl group of trialkylboranes or 9-alkyl-9-borabicylo[3.3.1]nonanes (9-alkyl-9-BBN). The reaction proceeds under 1 atm of CO at 50–55 °C in the presence of 5% of $PdCl_2(PPh_3)_2$ and 1.1 equiv of $Zn(acac)_2$ in THF/HMPA (**Scheme 31**).[33] HMPA is indispensable for the complete reaction. $Zn(acac)_2$ accelerates the reaction; however, curiously $Zn(OAc)_2$ and other metal acetylactetonato salts, such as Li(acac), $Mg(acac)_2$, $Al(acac)_3$, $Fe(acac)_3$, and $Co(acac)_3$, are all ineffective. Under similar conditions, *p*-bromo- and *p*-acetylphenyl iodide react with trialkylborane or 9-alkyl-9-BBN to give the corresponding aryl alkyl ketones in good yields. 9-Alkyl-9-BBN with primary alkyl–B bond is reactive, but that with secondary alkyl–B bond is unreactive under the conditions, and no expected unsymmetrical ketone is obtained.

t-Butylisocyanide can be utilized as the synthetic equivalent of CO for the Pd-catalyzed unsymmetrical ketone synthesis from aryl iodides and 9-alkyl-9-BBN (**Scheme 32**).[34] The use of K_3PO_4 as a base and nonpolar solvent is essential. Stronger bases, such as NaOMe, and polar solvents, such as THF and DMF, produce the direct coupling product as the major products. The coupling reaction is restricted to 9-alkyl-9-BBN and aryl iodides; neither trialkylboranes nor aryl bromides provide the expected ketones. The reaction is sensitive to the stoichiometry of 9-alkyl-9-BBN to isocyanide. The yields of octyl phenyl ketone are as follows: 97% for 1.0 (= 9-octyl-9-BBN/*t*-butylisocyanide), 85% for 1.1, 21% for 1.2, 4% for 1.3.

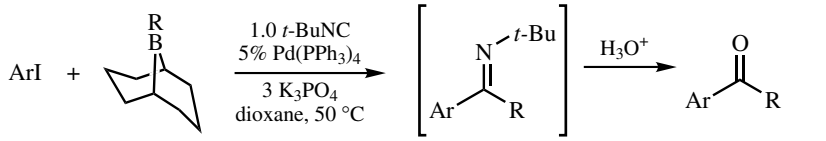
Pd-catalyzed carbonylative cross-coupling reaction of 9-alkyl-9-BBN with 1-halo-1-alkenes is effectively promoted in the presence of K_3PO_4 at room temperature to provide alkyl vinyl ketones in good yields (**Scheme 33**).[35] $Zn(acac)_2$ is not effective for the present carbonylative coupling reaction (cf. **Scheme 31**). The ready availability of 9-alkyl-9-BBN

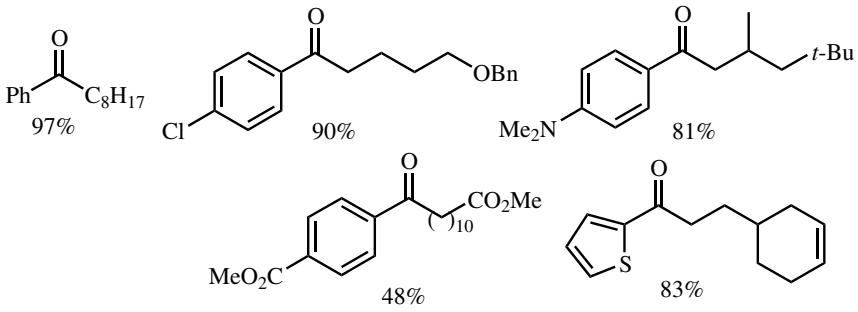


R = Et (from Et_3B)	82%
R = Hex (from Hex_3B)	70%
R = $PhCH_2CH_2$ (from 9-R-9-BBN)	69%
R = $MeO_2C(CH_2)_{10}$ (from 9-R-9-BBN)	74%



Scheme 31



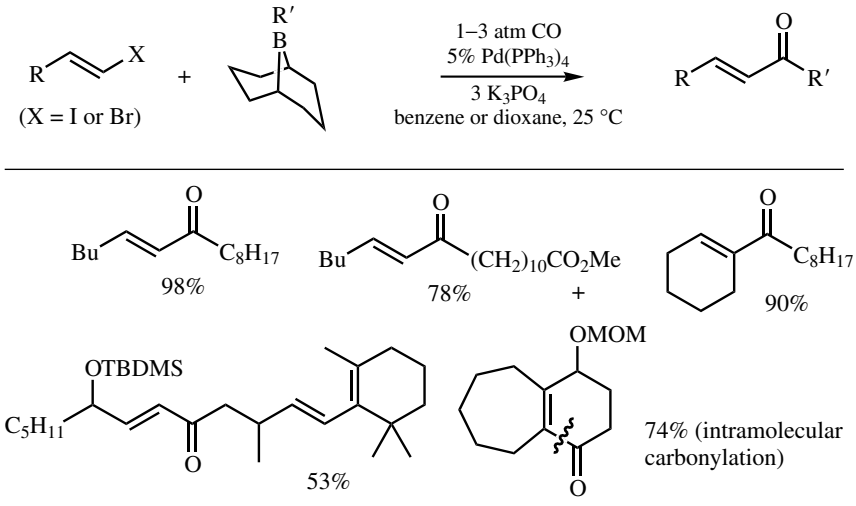


Scheme 32

of a wide structural variety via hydroboration of terminal olefins (the first three examples, **Scheme 33**) and dienes (the fourth example) significantly expands the scope. The final example in **Scheme 33** demonstrates the intramolecular version of the present method, which may be useful for the synthesis of cycloalkenones.

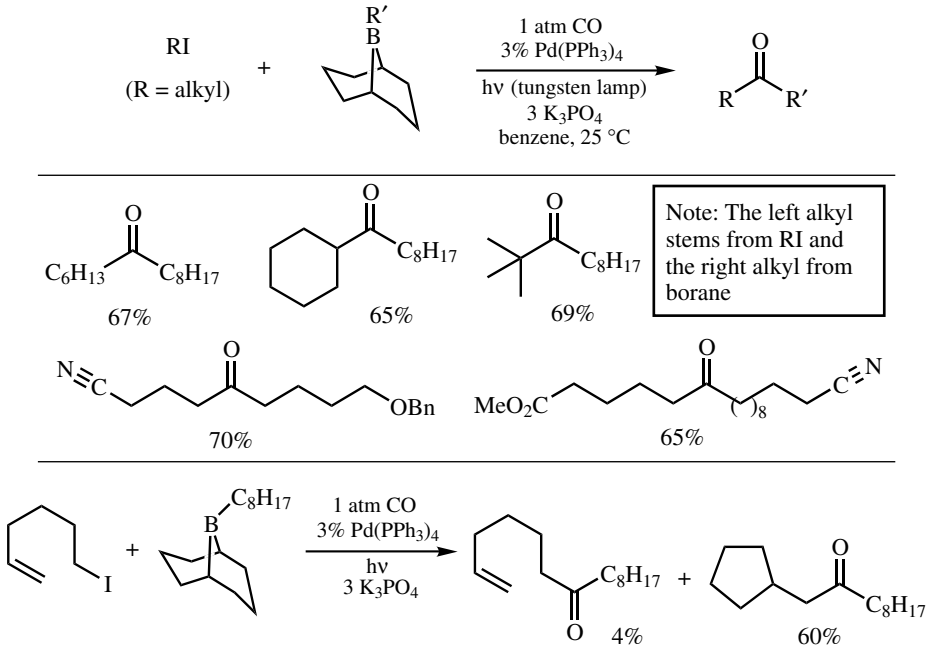
Vinyl iodides bearing electron-attracting groups at the β-position (e.g., 3-iodo-2-cyclohexenone and 1-iodo-1-octen-3-one) fail to give the expected unsymmetrical ketones. With these iodides, the direct coupling products are obtained as the major products.[35]

9-Alkyl-9-BBN reacts smoothly at room temperature with primary, secondary, and tertiary alkyl iodides under 1 atm of CO in the presence of 3 equiv of K_3PO_4 and 3% of



Scheme 33

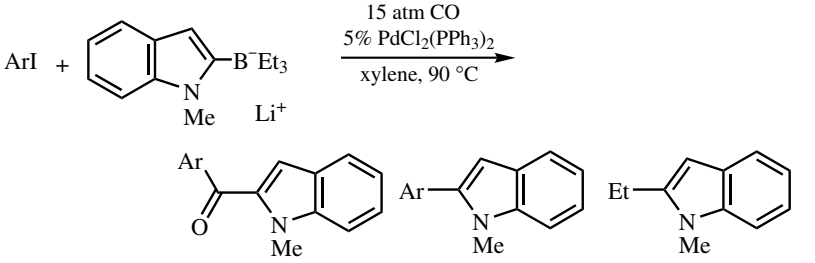
$Pd(PPh_3)_4$ to provide unsymmetrical dialkyl ketones in good yields under the irradiation of a 100-W tungsten light (**Scheme 34**).[36] The reaction proceeds very slowly in the dark. For example, in the dark, the reaction of 1-iodohexane and 9-octyl-9-BBN provides hexyl octyl ketone in 18% yield after 52 h. The same ketone is obtained in 67% yield under irradiation conditions for 24 h. The reaction tolerates a variety of functional groups both in



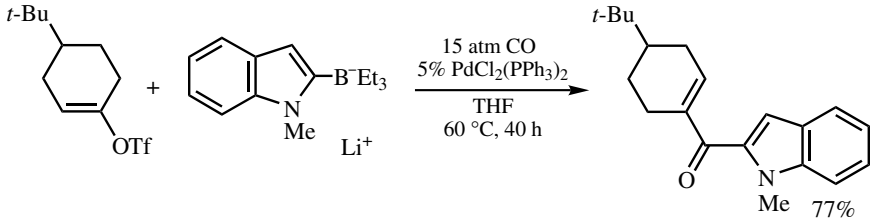
Scheme 34

alkyl halide and 9-alkyl-9-BBN components. The reaction behavior of 6-iodo-1-hexene, which provides cyclopentylmethyl octyl ketone selectively along with 5-hexenyl octyl ketone as the minor product, suggests that the reaction involves a radical process at the stage of oxidative addition of Pd(0) to the C—I bond of alkyl iodide.

Lithium triethyl(2-indoyl)borate, generated *in situ* from 2-lithio-1-methylindole and triethylborane, undergoes carbonylative coupling reaction with aromatic iodides under rather harsh conditions (**Scheme 35**).[37] The 2-indoyl group is selectively transferred rather than the ethyl group. Yields of 2-indoyl aryl ketones are acceptable except for those having an electron-withdrawing group on the benzene ring (4-COOMe, 4-COMe). 2-Ethyl-1-methylindole is produced as the minor product in all cases. Vinyl triflates and iodides may also be utilized as the electrophilic reaction partner.



Ar = C_6H_5	80	0	3
Ar = 4-MeC_6H_4	76	0	5
Ar = 4-BrC_6H_4	72	0	10
Ar = 4-$MeO_2CC_6H_4$	20	20	5
Ar = 4-$MeCOC_6H_4$	0	0	0

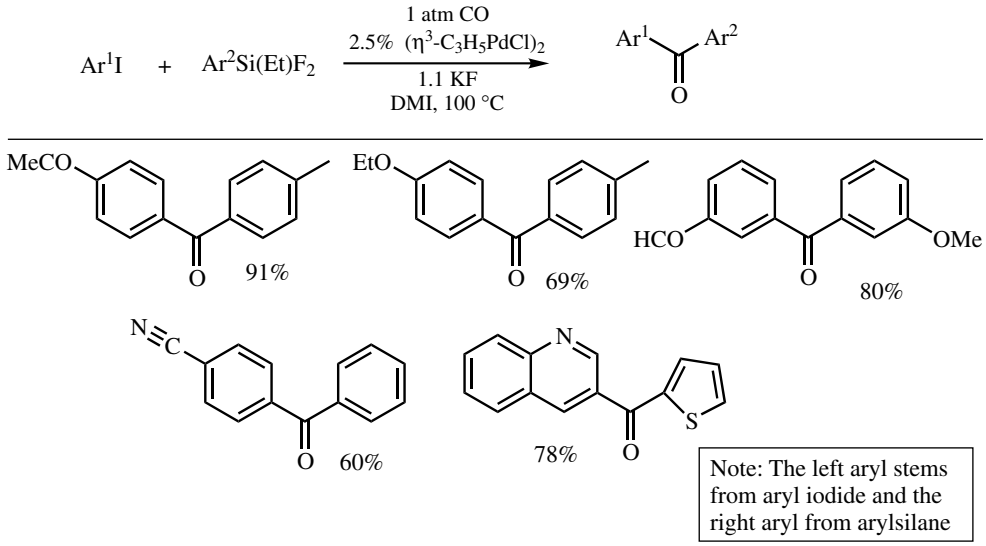


Scheme 35

F. ORGANOSILANE AS R′M

The Pd-catalyzed cross-coupling reaction of organosilicon compounds with organic electrophiles provides efficient methods for the highly selective carbon–carbon bond formation.[38] Aryl(alkyl)difluorosilanes activated by potassium fluoride nicely participate in the Pd-catalyzed carbonylative cross-coupling reaction with aryl iodides, especially bearing electron-attracting groups, to give unsymmetrical diaryl ketones in good yields (**Scheme 36**).[39]

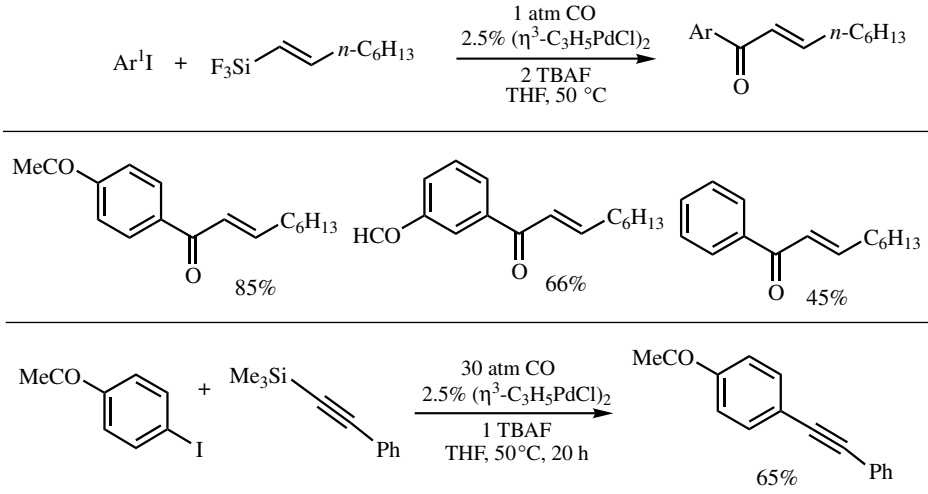
DMI (*N*,*N*-dimethyl-2-imidazolidinone) is the most suitable solvent. No reaction proceeds in THF or dioxane. In DMF the expected diaryl ketones are produced in moderate



Scheme 36

yields. Electron-withdrawing substituents on aryl iodides and electron-donating group on arylsilanes, in general, accelerate the reaction, and the combination of such partners gives diaryl ketones in good yields. $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ are less potent catalysts. The reaction temperature is another important factor; at higher temperatures, for example, at 150 °C and 1 atm of CO, the reaction of 4-acetylphenyl iodide and 4-tolyl(ethyl)difluorosilane selectively provides the direct cross-coupling products, 4-acetyl-4′-methylbiphenyl, in 73% yield.[39]

The above established conditions cannot be successfully applied to the reaction with alkyl(vinyl)difluorosilanes (**Scheme 37**).[40] For the preparation of aryl vinyl ketones



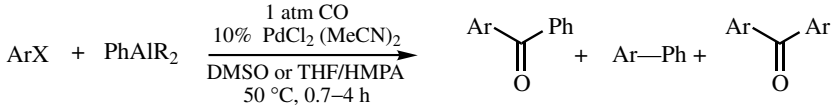
Scheme 37

based on silicate chemistry, vinyl*trifluoro*rsilanes as the vinyl source, 2 equiv of TBAF as the fluoride ion source, and THF as the solvent are recommended. (*E*)-1-Octenyltrifluorosilane provides (*E*)-octenyl ketone selectively, while (*Z*)-1-octenyltrifluorosilane furnishes a mixture of (*E*)- and (*Z*)-vinyl ketones as the result of isomerization of the first formed (*Z*)-isomer to the (*E*)-isomer under the conditions.

The carbonylative cross-coupling reaction with ethynylsilane has not been realized so far (**Scheme 37**). Even under 30 atm of CO, the direct cross-coupling product is obtained as the single product. This may be attributed to an extremely rapid alkynyl transfer from Si to ArPdI as compared with the CO insertion into the Ar—PdI bond.

G. ALKYLALUMINUM AS R′M

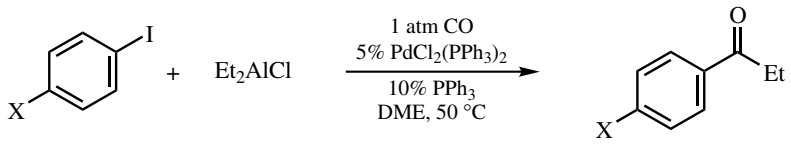
Triphenylaluminum reacts with aryl iodides and 1 atm of CO in the presence of 10% of $PdCl_2(MeCN)_2$ in DMSO to produce aryl phenyl ketone in good yield (**Scheme 38**).[41] When aryl iodides with electron-withdrawing substituents are used, the direct cross-coupling reaction competes with the carbonylative cross-coupling reaction. Diisobutylphenylaluminum selectively transfers the phenyl group to form aryl phenyl ketone in good yield. In this case, the appropriate solvent (DMSO, THF, or THF–HMPA) may differ from reaction to reaction.



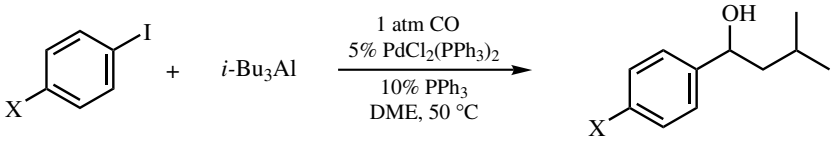
Ar	R	Yield (%)		
C_6H_4-*p*-NO_2	Ph	41	55	—
C_6H_4-*p*-CN	Ph	96	3	—
C_6H_5	Ph	95	—	—
C_6H_4-*p*-OMe	Ph	98	—	—
2-Thienyl	Ph	99	—	5
C_6H_4-*p*-NO_2	*i*-Bu	90	—	—
C_6H_4-*p*-CN	*i*-Bu	94	5	—
C_6H_5	*i*-Bu	80	—	—
C_6H_4-*p*-OMe	*i*-Bu	84	—	34
2-Thienyl	*i*-Bu	82	—	13

Scheme 38

Diethylaluminum chloride undergoes the Pd-catalyzed carbonylative coupling reaction with aryl iodides under 1 atm of CO in DME at 50 °C (**Scheme 39**).[42] The yield of aryl ethyl ketones is moderate. Under similar conditions, triisobutylaluminum provides aryl(isobutyl)methanols in good yield, which may be formed via carbonylative cross-coupling, followed by reduction of the ketone thus formed with isobutylaluminum species. With triethylaluminum, mixtures of ethyl phenyl ketone, ethyl(phenyl)methanol, and diethyl(phenyl)methanol are produced in varying ratios, depending on the relative amount of triethylaluminum and phenyl iodide charged. In all cases, the direct cross-coupling products are not detected.



X = H (79%), CO_2Me (61%), Br (63%)

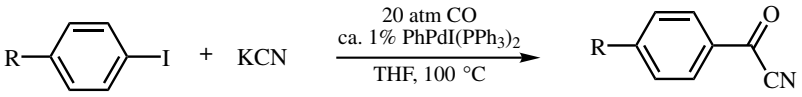


X = H (95%), Me (82%), OMe (73%), Br (83%)

Scheme 39

H. METAL CYANIDE AS R′M

Pd-catalyzed cyanocarbonylation of aryl iodides with potassium cyanide is effected by 1% of $PdPdI(PPh_3)_2$ under 20 atm of CO at 100 °C (**Scheme 40**).[43] The optimum ratio of KCN to ArI differs from aryl iodide to aryl iodide, and the best yield of aroyl cyanides is usually obtained with 0.5–0.3 equiv of KCN. The direct coupling product (arylcyanide) is produced in negligibly small amount (< 2%) except for the reaction of 2-thienyl iodide, which furnishes a mixture of cyano 2-thienyl ketone (45%) and 2-cyanothiophene (22%, under 8 atm CO, 100 °C, 24 h). Aryl bromides do not work well.



R = H (91%), OMe (92%), CO_2Me (<10%)

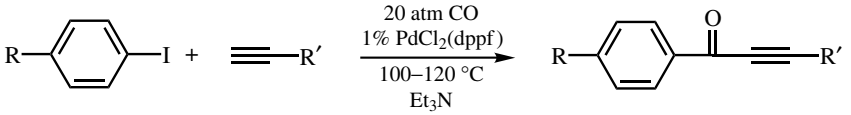
Scheme 40

I. METAL ACETYLIDE AS R′M

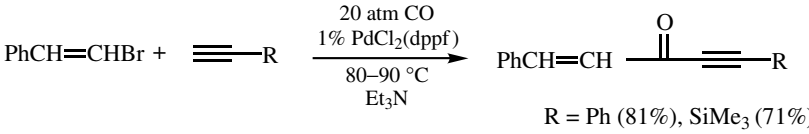
Aryl iodides undergo carbonylative cross-coupling reaction with terminal alkynes under 20 atm of CO in the presence of 1% of $PdCl_2$(dppf) in triethylamine as the solvent (**Scheme 41**).[44] The corresponding aryl bromides show the lower yields of the products. The direct cross-coupling products (ArC≡CR′) and homocoupling products (R′C≡CC≡CR′) are produced in negligible amounts under the conditions.

Vinyl bromides furnish the carbonylative cross-coupling products, ethynyl vinyl ketones, in fair to good yields (**Scheme 41**).

Under similar conditions, *o*-iodophenol reacts with terminal alkynes to furnish 2-substituted chromones in moderate yields (**Scheme 42**).[45] Diethylamine (81% for R = Ph) gives the better yield than triethylamine (61% for R = Ph). The reaction may involve

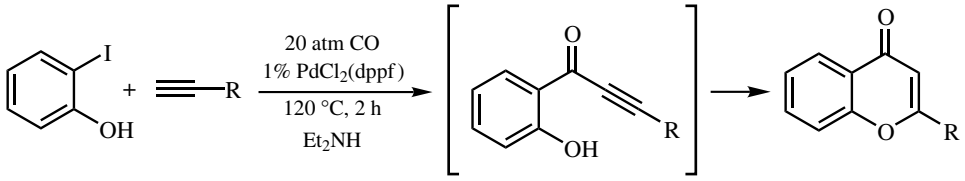


R	% Yield for R′= Ph	% Yield for R′= $SiMe_3$
H	86	88
CO_2Et	79	70
NO_2	58	51



R = Ph (81%), $SiMe_3$ (71%)

Scheme 41

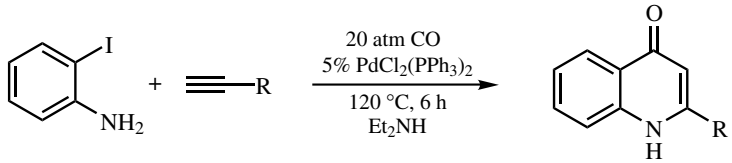


R = Ph (81%), C_6H_4-*p*-OMe (54%), 2-thienyl (50%), *n*-pentyl (58%)

Scheme 42

carbonylative cross-coupling of *o*-iodophenol and terminal acetylene, followed by an intramolecular conjugate addition of phenolate to the acetylenic ketone.

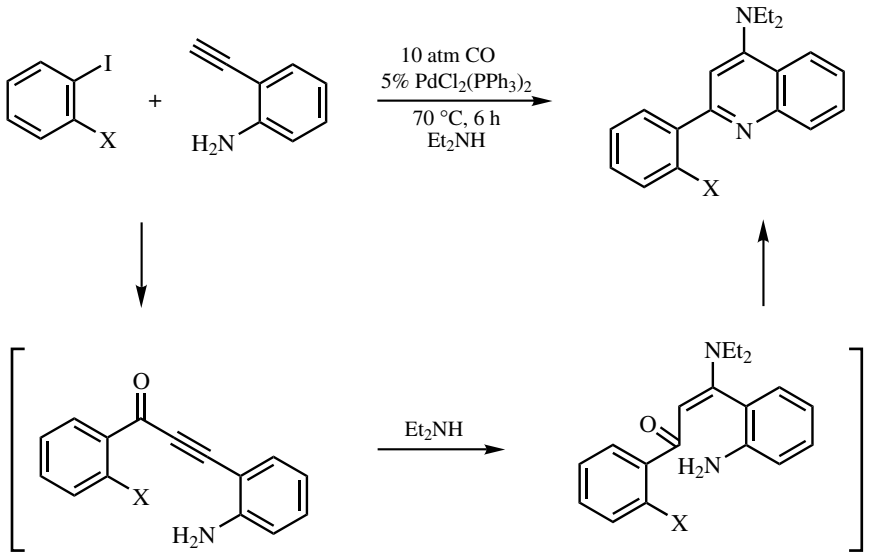
A similar reaction pattern has been observed for the carbonylative cross-coupling reaction of *o*-iodoaniline and terminal acetylenes, where 2-substituted 1,4-dihydro-4-oxoquinolines are obtained in good yields (**Scheme 43**).[46] The reaction of aromatic acetylenes generally gives a better yield than that of aliphatic acetylenes. Functional groups such as acetal, THP, and ester are compatible with the reaction conditions. Other authors have reported that $PdCl_2$(dppf) is similarly effective and the yield depends on the amine used.[47] For example, 2-phenyl-1,4-dihydro-4-oxoquinoline is obtained in 83% (diethylamine), 70% (triethylamine), 60% (piperidine), and 61% (morpholine) yields under 20 atm of CO in the presence of 10% of the catalyst at 120 °C for 1 h.



R = Ph (90%), C_6H_4-*p*-OMe (95%), C_6H_4-*p*-CO_2Me (85%),
n-hexyl (75%), CH_2OTHP (64%), $(CH_2)_3OAc$ (66%)

Scheme 43

Interestingly, for the Pd-catalyzed carbonylative cross-coupling reaction of *o*-iodophenol and *o*-iodoaniline with *o*-aminophenylacetylene, the X groups (NH_2 and OH) of the primary acetylenic ketone products do not undergo an intramolecular conjugate addition; instead, diethylamine does so intermolecularly, and 2-(*o*-aminophenyl)-4-diethylaminoquinoline and 2-(*o*-hydroxylphenyl)-4-diethylaminoquinoline are produced in good yields (**Scheme 44**).[48]



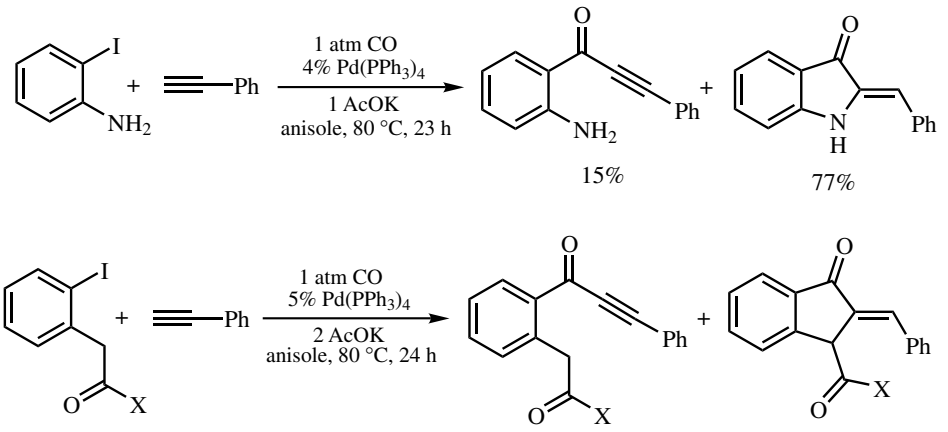
X = H (57%), OH (77%), NH_2 (80%)

Scheme 44

A slight modification of reaction conditions causes a dramatic change in the reaction course. *o*-Iodoaniline reacts with phenylacetylene in the presence of 4% of $Pd(PPh_3)_4$ and 1 equiv of potassium acetate under 1 atm of CO in anisole to provide a mixture of 2-benzylidene derivative of indoxyl and acetylenic ketone in a good combined isolated yield (**Scheme 45**).[49] The former may be formed via an *exo*-mode cyclization of the latter. No *endo*-mode cyclization product as in **Schemes 42** and **43** is detected. A similar type cyclization proceeds with the carbon nucleophile analog (**Scheme 45**).[50] The cyclization of the isolated alkynyl ketone is promoted by $Pd(OAc)_2(PPh_3)_2$ at 40 °C, where Pd(II) species may form C-palladium(II) enolate and at the same time coordinate with the triple bond to facilitate the *exo*-mode cyclization. The first formed 2-(*Z*)-benzylideneindanone may isomerize to the thermodynamically more stable (*E*)-isomer under the reaction conditions.

J. ORGANOCHROMIUM AND ORGANOZIRCONIUM AS R′M

Under 1 atm of CO and in the presence of 1% of $Pd(PPh_3)_4$, aroyl- and alkanoylchromates serves as acyl nucleophiles toward allyl bromides to provide unsymmetrical ketones in good



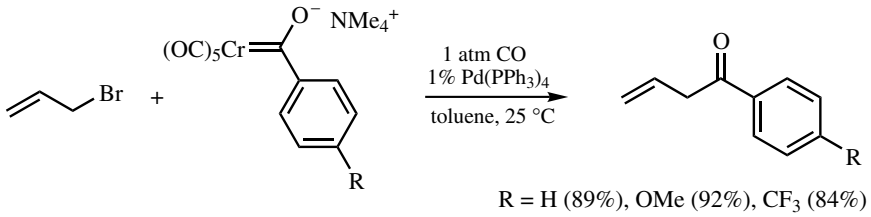
X = OMe	8%	74%
X = NEt_2	77%	15%

Scheme 45

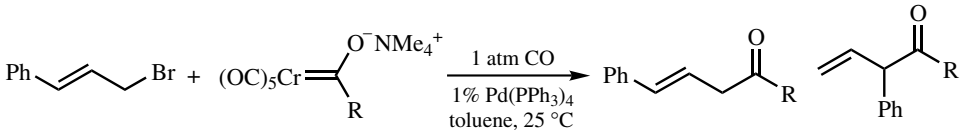
yields (**Scheme 46**).[51] Unsymmetrical allyl bromides provide the regioisomeric mixture of ketones. The palladium catalyst is essential for the reaction; however, CO is not essential: under argon the same products are obtained though in lower yields. Chromium allyloxy(aryl)carbene complexes, in the presence of $Pd(PPh_3)_4$, undergo a smooth rearrangement at room temperature to furnish allyl aryl ketones (**Scheme 46**).[52] Also in this reaction, CO is not essential, but it effects the selective formation of allyl aryl ketones. In the absence of CO, aryl 1-propenyl ketone may be produced in a comparable amount. Although the reaction mechanism is not clarified yet, a sort of π-allylpalladium acylchromate bimetallic intermediate may be involved, which is expected to readily release coordinatively saturated $Cr(CO)_6$, unsymmetrical ketone, and Pd(0) upon exposure to CO.

Nonanoylzirconocene chloride (**1**), readily prepared by the reaction of 1-octene and zirconocene hydrochloride (Schwartz reagent) followed by exposure to 1 atm of CO, serves as an unmasked acyl anion and provides ketones or α-diketones in moderate to good yields by the reaction with electrophiles (aryl iodide, benzyl bromide, acyl chloride, allyl chloride, allyl acetate) in the presence of 5% of $PdCl_2(PPh_3)_2$ (**Scheme 47**).[53]

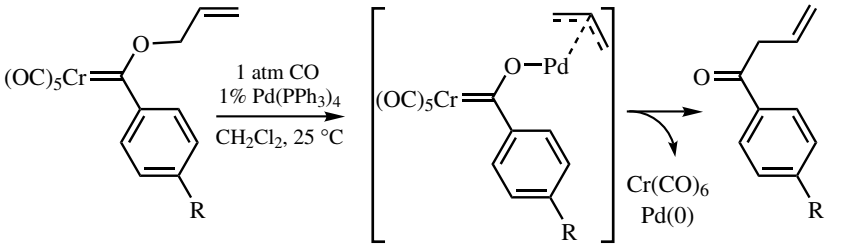
Nonanoyl group of **1** adds to α,β-unsaturated ketones selectively in either 1,2- or 1,4-fashion depending on the catalytic systems (**Scheme 48**).[54] Thus, 5% $PdCl_2(PPh_3)_2$ promotes the selective 1,2-addition to α,β-unsaturated ketones to provide α-hydroxyketones in good yields, while 10% $Pd(OAc)_2$ in combination with 1 equiv of $BF_3{\cdot}OEt_2$ in a $Et_2O{\cdot}THF$ mixed solvent selectively promotes the 1,4-addition to furnish 1,4-diketones in modest yields. The 1,2/1,4 selectivity is generally high ($> 95\%$) except for unsubstituted vinyl ketones, which provide mixtures of 1,2- and 1,4-addition products. The role of triphenylphosphine in the selective formation of α-hydroxyketone may be explained by the preferred formation of the sterically less crowded π-ally(acyl)palladium complex **I** rather than **II** and subsequent reductive elimination of Pd(0) from **I**. Enantioselective 1,2-acylation of cycloalkenones is realized by using 5% $Pd(OAc)_2$ and 10% chiral MOP ligand (**Scheme 48**).[55] The ee for acyclic unsaturated ketones is rather low ($< 20\%$).



R = H (89%), OMe (92%), CF_3 (84%)

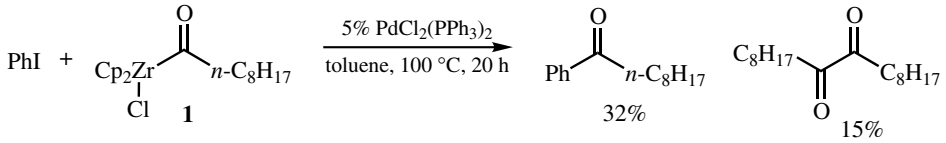


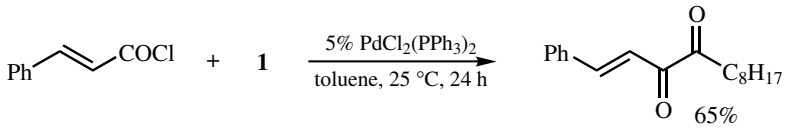
R = Ph	69%	27%
R = *n*-Bu	50%	25%

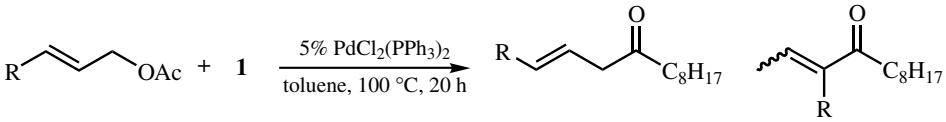


R = Me (71%), OMe (92%)

Scheme 46

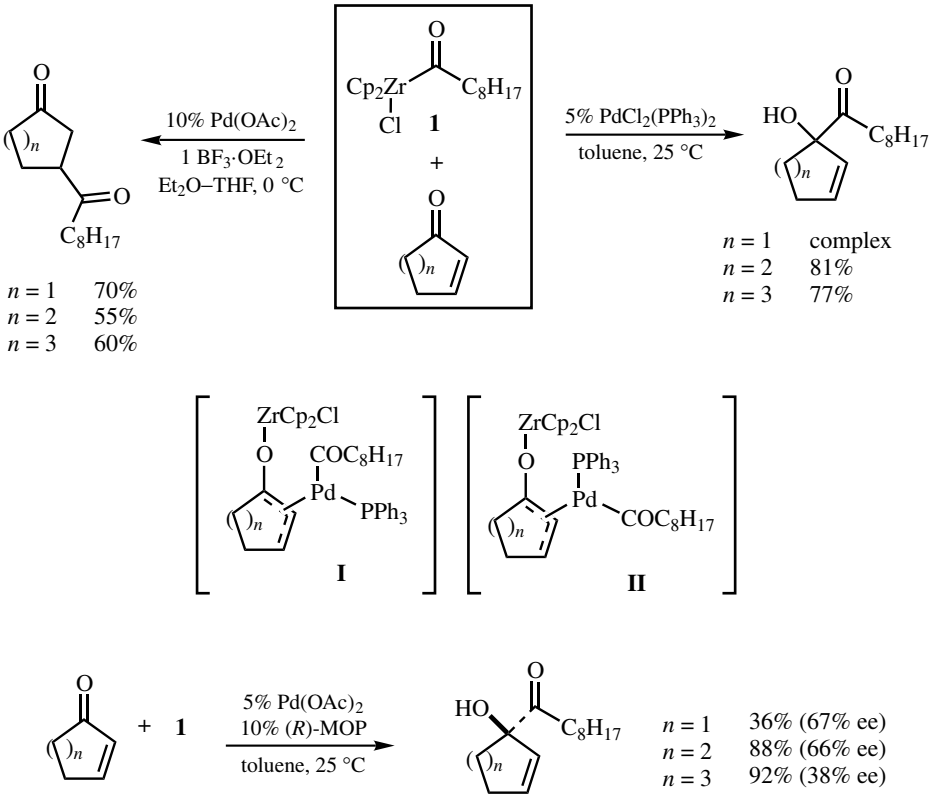






R = Me	91% (1:5)
R = Ph	80% (1.2:1)

Scheme 47



Scheme 48

K. SUMMARY

The success in unsymmetrical ketone synthesis via the carbonylative cross-coupling reaction of organic electrophiles and nucleophiles primarily depends on how selectively and effectively the organic residue of organonucleophile is transferred to organoacylpalladium(II) rather than organopalladium(II). Fortunately, organoacylpalladium(II) is more electrophilic than organopalladium(II); hence, as is described in this section, for most organonucleophiles, the carbonylative cross-coupling is preferred to the direct cross-coupling process. Although the mechanism is not clear yet, the organo-group transfer from organonucleophile to organoacylpalladium(II) is quite fast and weakly nucleophilic organometals (zinc, aluminum, mercury) and even organometalloids (silicon, stannane, boron) participate in the reaction. It is possible to prepare unsymmetrical ketones RCOR′, in which R and R′ are alkyl, benzyl, allyl, vinyl, or aryl. The compatibility of these organonucleophiles with many functional groups of synthetic importance widens the scope of the present methodology. Some of the methods presented here have been utilized for the total synthesis of rather complex natural products. Development in this field is very rapid and many modifications and innovative findings will be made in the future.

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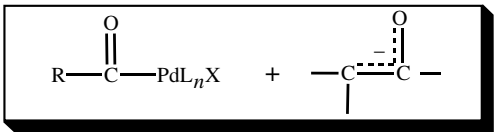

VI.2.3 Reactions of Acylpalladium Derivatives with Enolates and Related Amphiphilic Reagents

EI-ICHI NEGISHI and HIDEFUMI MAKABE

A. INTRODUCTION

In view of the facile reactions of acylpalladium derivative with a wide variety of groups 14–17 atom nucleophiles discussed in **Sects. VI.2.1** and **VI.2.2**, it might readily be expected that acylpalladium derivatives should react with enolates, which can, in principle, serve as amphiphilic *O* and/or *C* nucleophiles (**Scheme 1**). Somewhat surprisingly, these reactions had not been reported until 1986.

During the development of a Pd-catalyzed procedure for benzoquinone synthesis, the formation of γ-alkylidenebutenolides was unexpectedly observed, when $Pd(OAc)_2$–PPh_3 was used as a catalyst in conjunction with an excess of NEt_3 (**Scheme 2**). In sharp contrast, the use of 5 mol % of phosphine-free $Pd(dba)_2$ and 1 equiv of NEt_3 produced the desired benzoquinone in 93% yield.[1] The lactone formation must have taken place via base-induced trapping of the acylpalladium intermediate with an essentially 1:1 mixture of *in situ* generated *E*- and *Z*-enolates (**Scheme 2**).

Also in 1986, intermolecular versions of the reaction of putative acylpalladium derivatives with the enolates derived from malonic esters and a few ketones were independently reported.[2] Two different courses of reaction were observed with malonate esters (**Scheme 3**). However, both involve selective *C*-acylation. In cases where the *C*-acylation products, which are β-keto diesters, still contain an acidic β C—H bond, they will further react with acylpalladium derivatives as *O*-enolates rather than *C*-enolates, as detailed in the following section.

These two seemingly unrelated studies appear to mark the beginning of this section of organopalladium chemistry.

B. INTERMOLECULAR REACTIONS OF ACYLPALLADIUM DERIVATIVES WITH ENOLATES

The original investigation by Kobayashi and Tanaka[2] delineated the courses of reaction of acylpalladium derivatives with malonates (**Scheme 3** and **Table 1**). On the other

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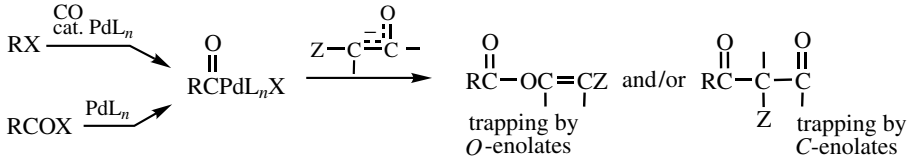
TABLE 1. Pd-Catalyzed Carbonylation of Aryl and Alkenyl Halides in the Presence of Malonates in Triethylamine[a]

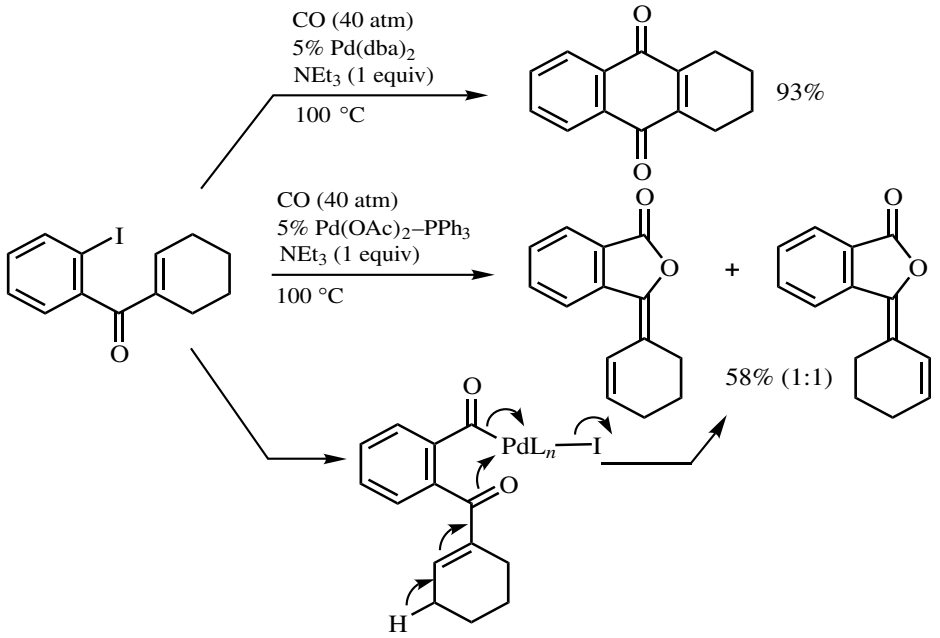
Halide	Malonate	Catalyst[a]	Product	Yield (%)
PhI	$MeCH(COOEt)_2$	I	$PhCOC(Me)(COOEt)_2$	75
PhI	$MeCH(COOEt)_2$	II	$PhCOC(Me)(COOEt)_2$	55
PhBr	$MeCH(COOEt)_2$	I	$PhCOC(Me)(COOEt)_2$	63
p-$EtO_2CC_6H_4I$	$MeCH(COOEt)_2$	I	*p*-$EtO_2CC_6H_4COC(Me)(COOEt)_2$	69
p-ClC_6H_4I	$MeCH(COOEt)_2$	I	*p*-$ClC_6H_4COC(Me)(COOEt)_2$	81
PhCH═CHBr	$MeCH(COOEt)_2$	I	$PhCH{=}CHCOC(Me)(COOEt)_2$	36
PhI	$CH_2(COOEt)_2$	I	$PhCOO(Ph)C{=}C(COOEt)_2$	73
PhI	$CH_2(COOPr\text{-}i)_2$	I	$PhCOO(Ph)C{=}C(COOPr\text{-}i)_2$	72
PhI	$NCCH_2COOEt$	I	$Ph(HO)C{=}C(CN)(COOEt)_2$	30

[a]The reaction was carried out at 20 atm of CO using 1 mol % of either $Cl_2Pd(dppf)$ (I) or $Cl_2Pd(PPh_3)_2$ (II) in NEt_3 at 120 °C.

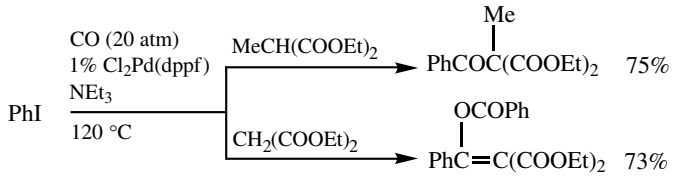


R = carbon group. X = halogen. Z = COR, COOR, SO_2Ph, etc.

Scheme 1



Scheme 2



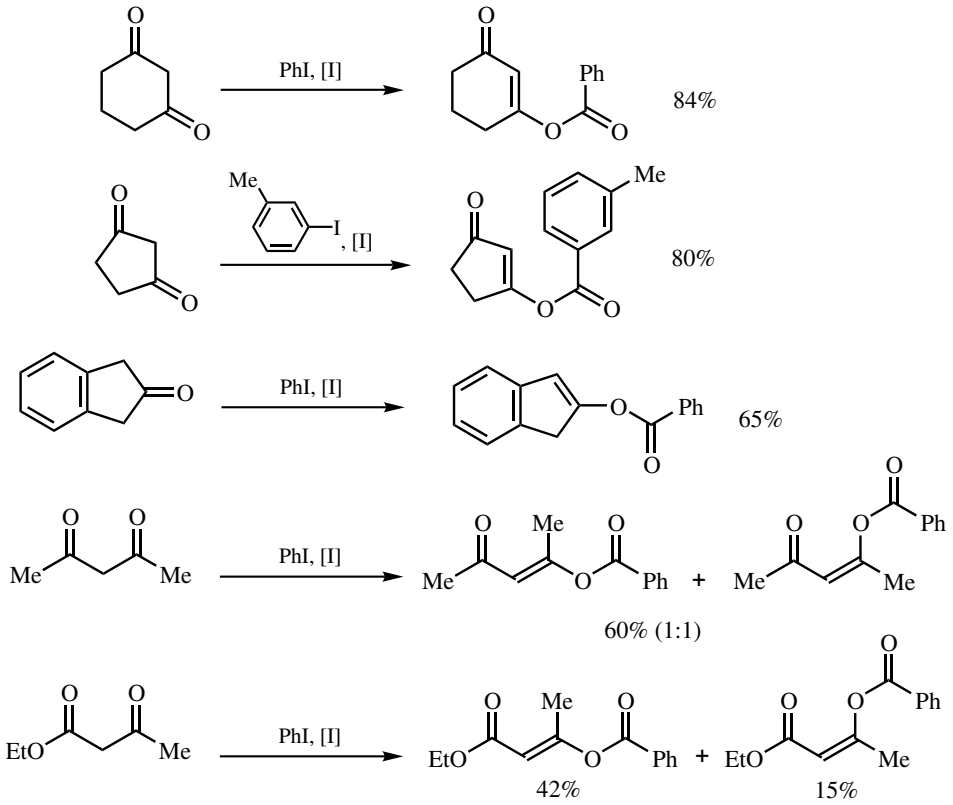
Scheme 3

hand, the scope and course of their reaction with ketone enolates largely remained to be clarified. Later systematic studies with ketone enolates[3],[4] have established the following generalizations (**Schemes 4** and **5**).

1. Enolizable 1,3-diketones and other ketones of relatively high acidity, such as acetoacetic esters and 2-indanone, can readily be acylated with acylpalladium derivatives in high yields.

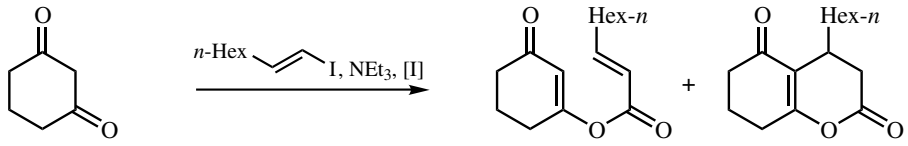
2. In contrast with esters, all ketones examined to date react as *O*-enolates.

3. Acylpalladium derivatives generated from alkenyl halides, that is, acryloyl derivatives, may be converted to the expected enoxy esters and/or the corresponding 3,

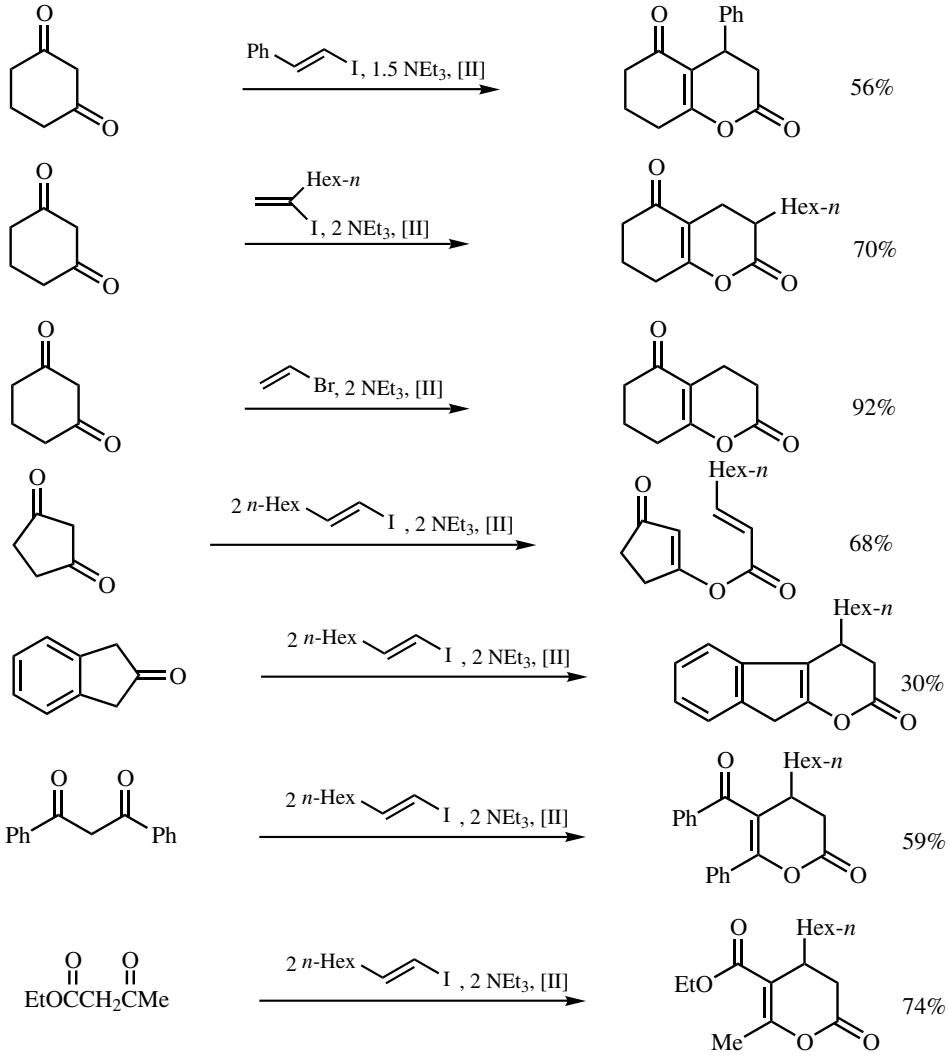


[I] = CO (40–45 atm), 5 mol % $Cl_2Pd(PPh_3)_2$, 2 equiv NEt_3, DMF, 100 °C, overnight.

Scheme 4



Dione/Iodide/NEt_3	Acyclic	Cyclic
1:1:1.2	85%	<5%
1:1:2	<5%	78%



[I] = CO (40−45 atm), 5 mol % $Cl_2Pd(PPh_3)_2$, DMF, 100 °C, overnight.
[II] = CO (40−45 atm), 5 mol % $Cl_2Pd(PPh_3)_2$, MeCN–THF, 100 °C, overnight.

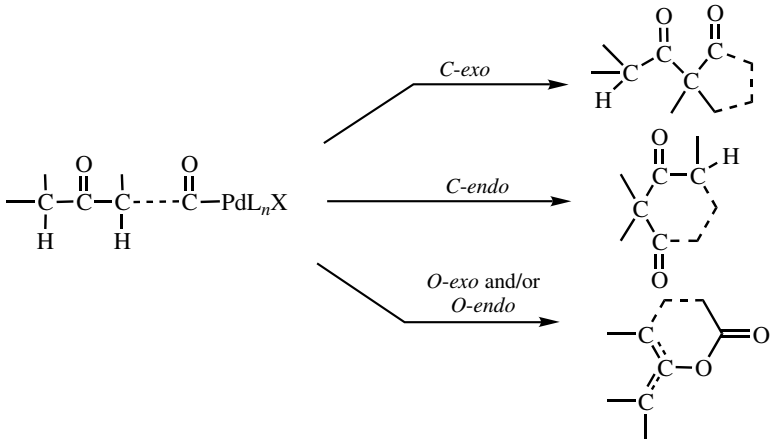
Scheme 5

4-dihydro-2*H*-pyran-2-ones. Formation of the latter is promoted by an excess of base, such as NEt_3. However, the product ratio is also dependent on other factors, such as substrate structure, and it may not be accurately predicted.

C. INTRAMOLECULAR REACTIONS OF ACYLPALLADIUM DERIVATIVES WITH ENOLATES

C.i. Overview

A systematic investigation of the intramolecular reactions of acylpalladium derivatives containing at least one additional carbonyl group, which is in a 1,4-, 1,5-, 1,6-, 1,7-, or 1,8-relationship with the carbonyl group of the acylpalladium group, has shown that they can produce cyclic ketones and/or lactones in high yields.[5],[6] In cases where the carbonyl group is ketonic, the enolates generated *in situ* may function as either *O*- or *C*-enolates. Depending on whether the α H atom abstracted is on the side of the acylpalladium moiety or on the opposite side, trapping by *C*-enolates will place that carbonyl group either exocyclic or endocyclic, respectively. Trapping with *O*-enolates will incorporate the carbonyl-derived C—O bond in the lactone ring. However, the enolic C═C bond may end up either exocyclic or endocyclic. Thus, these processes may be unequivocally defined by (i) the size of cyclic compounds produced, (ii) *C*-enolate trapping producing cyclic ketones versus *O*-enolate trapping producing lactones, and (iii) *exo* or *endo* relationship of the C═O or C═C bond (**Scheme 6**). For example, the lactone formation in **Scheme 2** may be termed as a 5-*O*-*exo* process.



Scheme 6

The currently available data permit the following generalizations:

1. The course of reaction is primarily governed by the size of the ring compounds that is formed by the reaction. Specifically, five- or six-membered rings are preferentially produced regardless of whether such rings are cyclic ketones or lactones.

2. In cases where both cyclic ketones and lactones that can be formed are of the same ring size, lactone formation via trapping with *O*-enolates takes place preferentially.

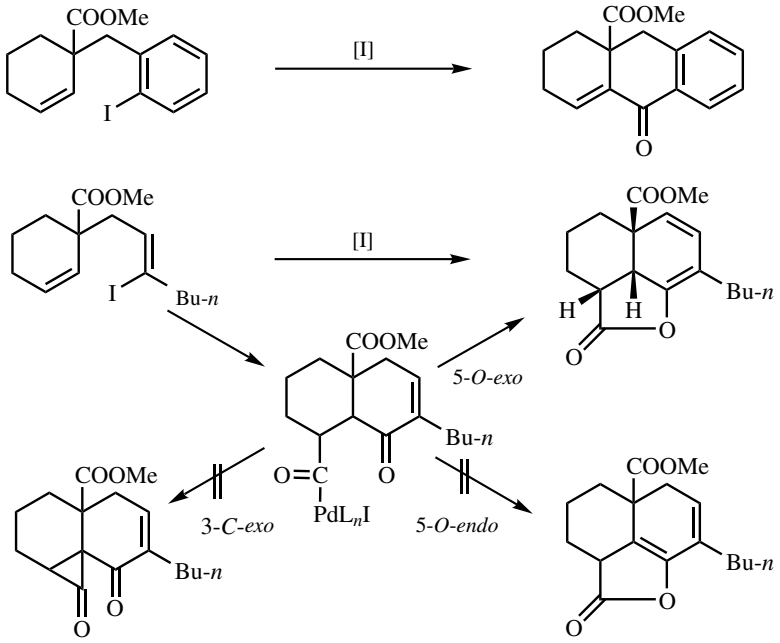
3. Five-membered lactones favor an exocyclic alkenyl group, while six-membered homologues place the enolic C═C bond in the lactone ring.

4. In contrast with the intermolecular processes, the intramolecular reactions can proceed satisfactorily even with ordinary ketones as enolate precursors.

Various results presented below are in full agreement with the above-presented generalizations.

C.ii. 5-*O-exo* Process Versus 5-*C-endo* and 3-*C-exo* Processes: Synthesis of γ-Lactones

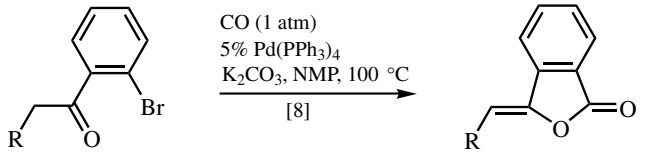
In a pair of closely related Pd-catalyzed carbonylative cyclization reactions shown in **Scheme 7**, a 5-*O-exo* lactonization process was observed.[3] There was little or no indication for either the 5-*O-endo* or 3-*C-exo* process, and the 5-*C-endo* process is judged to be even less probable than any of the above-mentioned processes[6] (**Scheme 7**).



[I] = CO (40–45 atm), 5 mol % $Cl_2Pd(PPh_3)_2$, 2 equiv NEt_3, DMF, 100 °C, overnight.

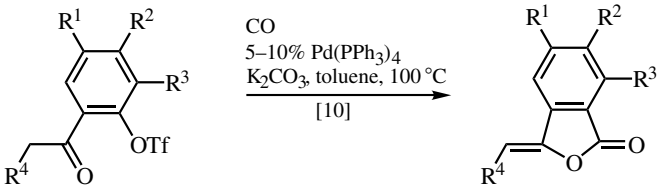
Scheme 7

A wide variety of *o*-haloaryl ketones [7]–[10] (**Schemes 8** and **9**) and (*Z*)-β-halo-α,β-unsaturated ketones[11] (**Schemes 10** and **11**) undergo carbonylative 5-*O-exo* cyclization to give predominantly (*Z*)-γ-alkylidene-γ-lactones. In cases where the α-carbon center is substituted, the *Z*/*E* ratio of the *exo*-alkylidene group is generally high (≥50). If it is unsubstituted, the *Z*/*E* ratio is generally <10.[11]



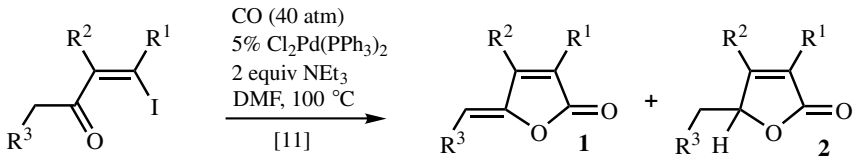
R	Yield (%)
H	83
n-Pr	87
Ph	88

Scheme 8



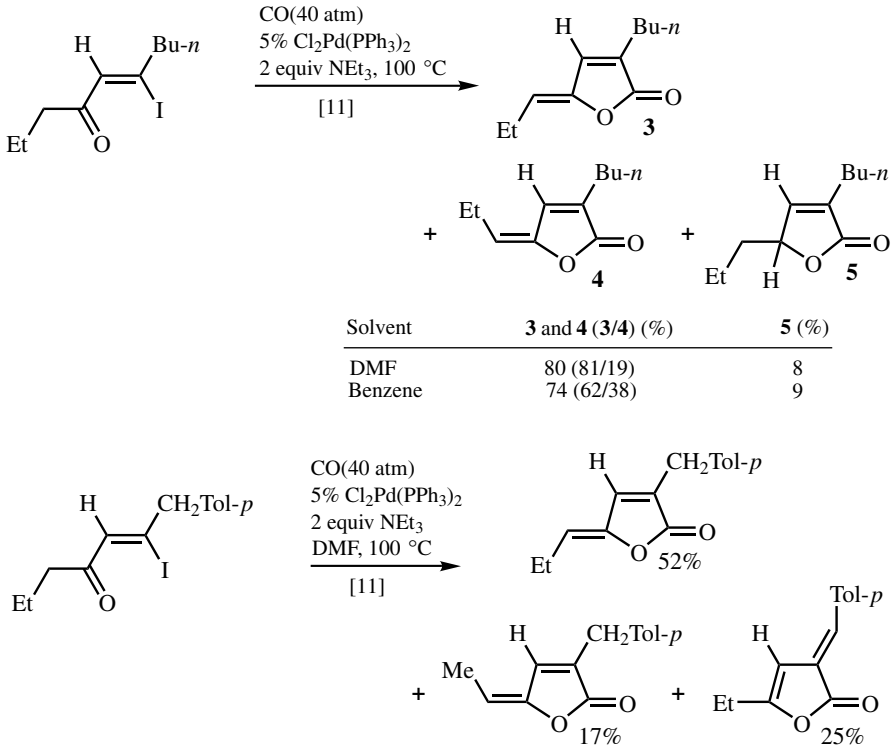
R^1	R^2	R^3	R^4	Yield (%)
H	H	H	H	94
Me	H	H	H	98
Cl	H	H	H	81
H	OMe	H	H	78
Me	H	H	Me	84
OMe	H	H	Me	92
H	OMe	H	Me	95
Me	H	Me	Et	74
H	H	H	Pr-*n*	86
H	H	H	Pr-*i*	83
H	H	H	Ph	82

Scheme 9



R^1	R^2	R^3	**1** (%)	**2** (%)
n-Pr	*n*-Pr	H	66	<2
n-Pr	*n*-Pr	*n*-Pent	75	4
Ph	*n*-Pr	Me	72	8
Ph	*n*-Pr	Ph	68	6
Me	Me	*n*-Hept	84	4
Me	Me	*n*-Bu	82	4

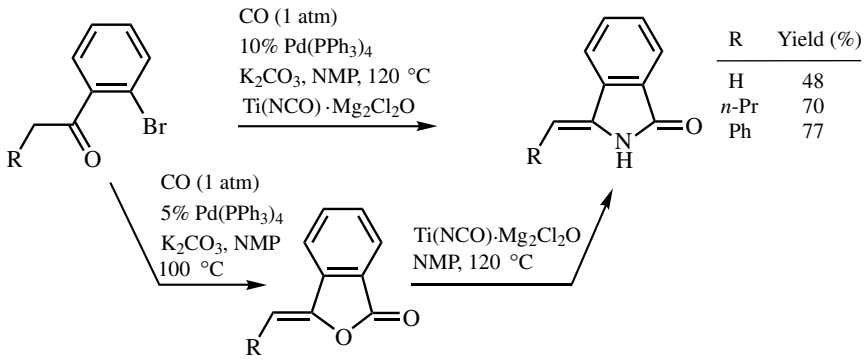
Scheme 10



Solvent	**3** and **4** (**3**/**4**) (%)	**5** (%)
DMF	80 (81/19)	8
Benzene	74 (62/38)	9

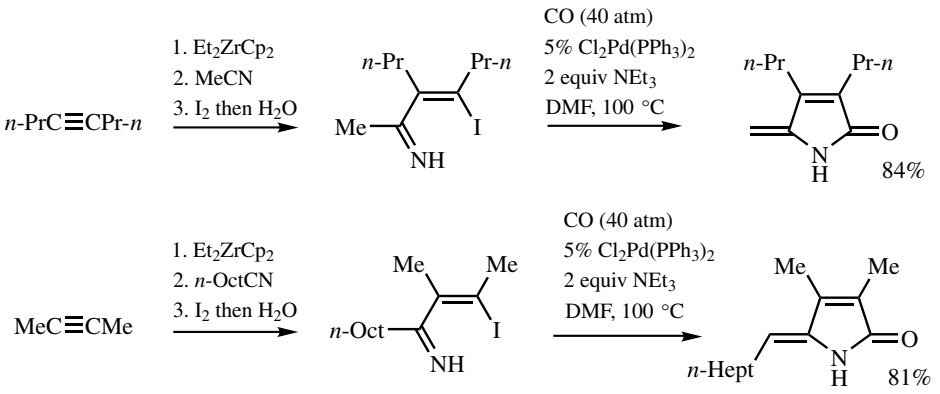
Scheme 11

The corresponding lactams can also be prepared. One protocol is to run the Pd-catalyzed carbonylation reactions presented above in the presence of $Ti(NCO)\cdot Mg_2Cl_2O\cdot 3THF$ (3 equiv).[5],[8],[9] Alternatively, preformed lactones may subsequently be treated with $Ti(NCO)\cdot Mg_2Cl_2O\cdot 3THF$[7]–[9] (**Scheme 12**). Yet another very promising approach is to use β-halo-α,β-unsaturated imines that are readily available via cocyclization of alkynes with nitriles promoted by Et_2ZrCp_2 followed by iodinolysis as the starting compounds in the Pd-catalyzed carbonylation[11] (**Scheme 13**).



R	Yield (%)
H	48
n-Pr	70
Ph	77

Scheme 12



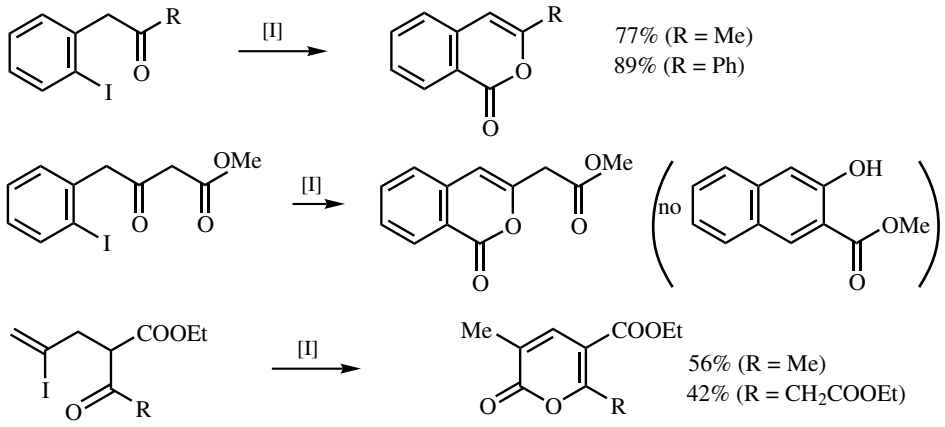
Scheme 13

C.iii. 6-*O*-*endo* Process Versus 6-*C*-*endo* and 4-*C*-*exo* Processes

The Pd-catalyzed reaction of γ-haloketones takes place selectively via a 6-*O*-*endo* process as shown in **Scheme 14**. The other possible processes, such as 6-*C*-*endo* and 4-*C*-*exo*, do not appear to detectably compete with the 6-*O*-*endo* process. This is true even in cases where the 6-*C*-*endo* process can, in principle, give benzenoid aromatic compounds. Also noteworthy is that little or no exocyclic alkene-containing products are detectable. Some representative results supporting the generalizations made above are shown in **Scheme 14**.[6]

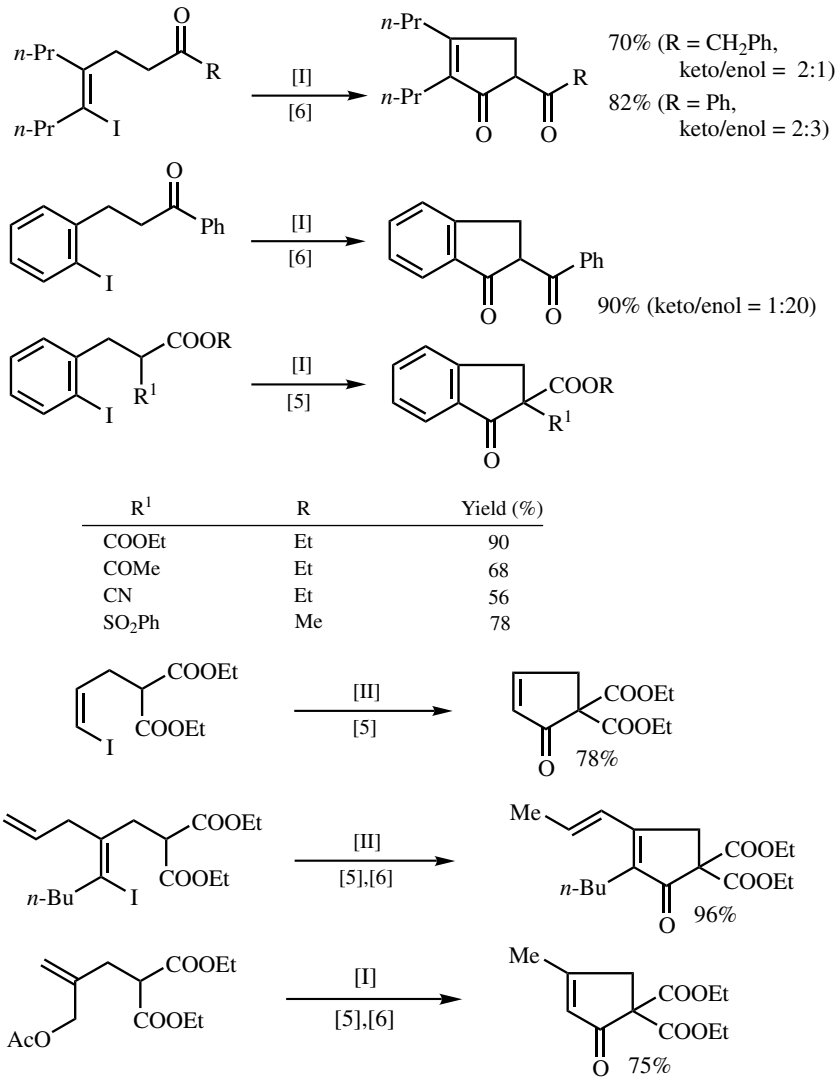
C.iv. 5-*C*-*exo* Process Versus 7-*C*-*endo* and 7-*O* Processes

Although trapping by *O*-enolates is generally favored in the reactions of ketone enolates, the 5-*C*-*exo* process is decidedly preferred to the 7-*C*-*endo* and 7-*O* processes, as convincingly demonstrated in the first equation of **Scheme 15**.[5],[6] As might be expected, mixtures of keto and enol isomers are formed in cases where both isomers are possible.



[I] = CO (40 atm), 5 mol % $Cl_2Pd(PPh_3)_2$, THF–MeCN or DMF, 100 °C, overnight.

Scheme 14



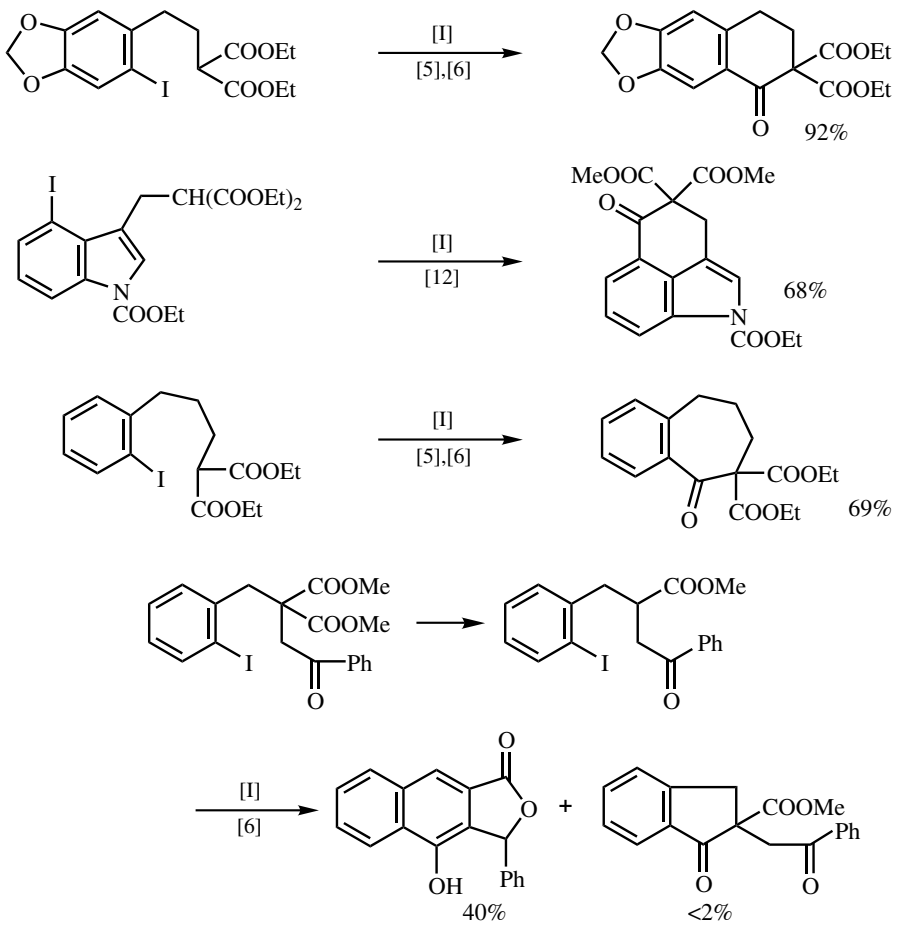
R^1	R	Yield (%)
COOEt	Et	90
COMe	Et	68
CN	Et	56
SO_2Ph	Me	78

[I] = CO (40 atm), 5 mol % $Cl_2Pd(PPh_3)_2$, NEt_3 (1–2 equiv), MeCN–THF, 100 °C.
[II] = Same except that $Pd(PPh_3)_4$ is used in place of $Cl_2Pd(PPh_3)_2$.

Scheme 15

C.v. 6-*C-exo* and 7-*C-exo* Processes

Although rigorous competitive experiments have not been performed, 6-*C-exo* and 7-*C-exo* processes are reasonably facile as indicated by the results shown in **Scheme 16**.[5],[6],[12] No attempts to achieve cyclization for producing eight-membered and larger rings appear to have been made. Likewise, no attempts to promote three- or four-membered ring formation by blocking all other possible paths appear to have been documented.



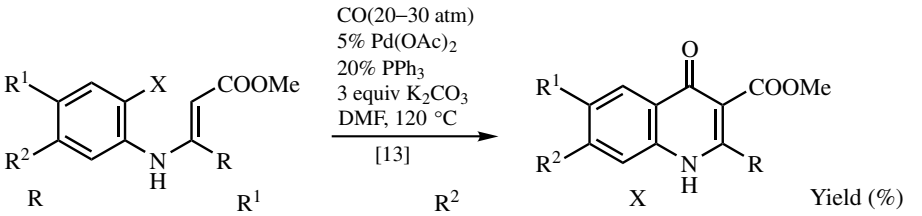
[I] = CO (40 atm), 5 mol % $Cl_2Pd(PPh_3)_2$, NEt_3(2 equiv), MeCN, 100 °C.

Scheme 16

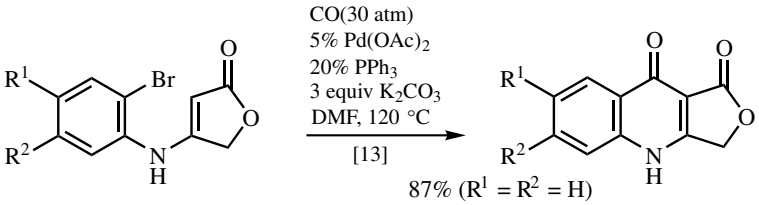
In the competition between the 5-*C-exo* process with an ester and the 6-*C-exo* process with a ketone shown in the last equation in **Scheme 16**, the latter predominates, suggesting that monoesters might not be sufficiently acidic.[6] Clarification of these subtle points seems to require further investigation. In this connection, the 6-*C-exo* reaction shown in **Scheme 17** is instructive as this represents an extension of potentially high synthetic utility.[13]

D. TANDEM AND CASCADE PROCESSES INVOLVING CYCLIC ACYLPALLADATION–TRAPPING WITH ENOLATES

In all but one reaction discussed in this section up to this point, the carbonyl compounds serving as enolate precursors are either externally added or present in the starting substrates. In the lactone formation shown in **Scheme 7**, however, the ketone moiety serving as an enolate precursor is generated *in situ* via cyclic acylpalladation. We may therefore



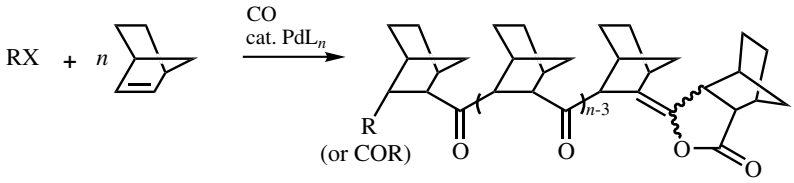
R	R^1	R^2	X	Yield (%)
Me	H	H	I	82
Me	H	H	Br	82
Me	F	Cl	Br	75
Me	F	F	Br	37
MeO_2CCH_2	H	H	I	67
MeO_2CCH_2	Cl	F	Br	55
MeO_2C	H	H	I	24



87% ($R^1 = R^2 = H$)
82% ($R^1 = F$, $R^2 = Cl$)

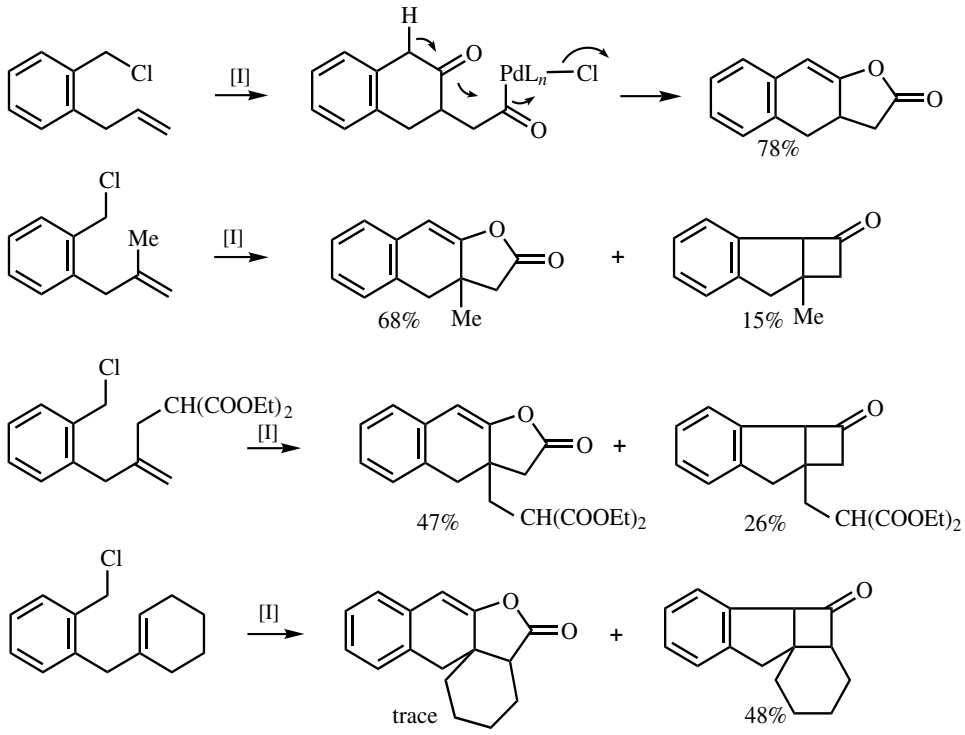
Scheme 17

classify this as a cyclic acylpalladation–lactonization via a 5-*O-exo* trapping tandem process. In the Pd-catalyzed perfectly alternating copolymerization of norbornene and CO by cascade acylpalladation, one chain termination process has been shown to involve a 5-*O-exo* process, as shown in **Scheme 18**.[14],[15] The overall process may then be classified as an acylpalladation–lactonization via a 5-*O-exo* trapping cascade process. In **Sect. VI.4** these processes are termed Type III AcPd processes.



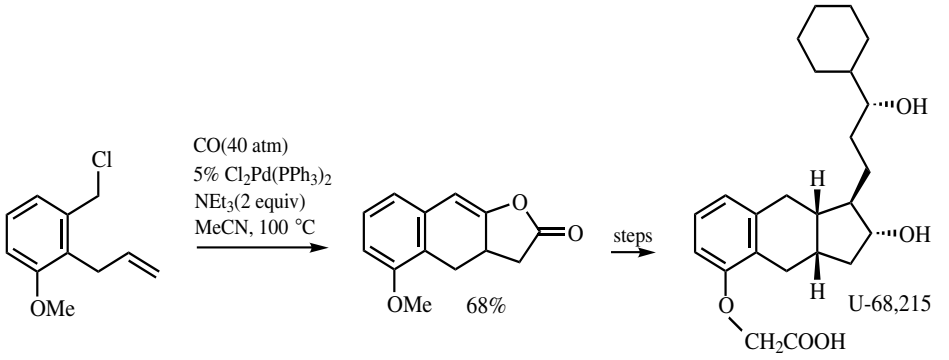
Scheme 18

As might be expected, trapping of acylpalladium derivatives by internal enolates is particularly facile in the acylpalladation reaction of benzyl halides[16] (**Scheme 19**). This reaction has provided an efficient route to a tricyclic enol lactone, which has been used as a key intermediate for the synthesis of a promising anti-ulcer agent, U-68,215[16] (**Scheme 20**). However, the 5-*O-exo* lactonization process can be competed by yet another unexpected cyclization process, which most probably involves ketene formation–[2 + 2] ketene cycloaddition and tends to become increasingly competitive with increasing steric demand of the alkenyl group[16] (**Scheme 19**).



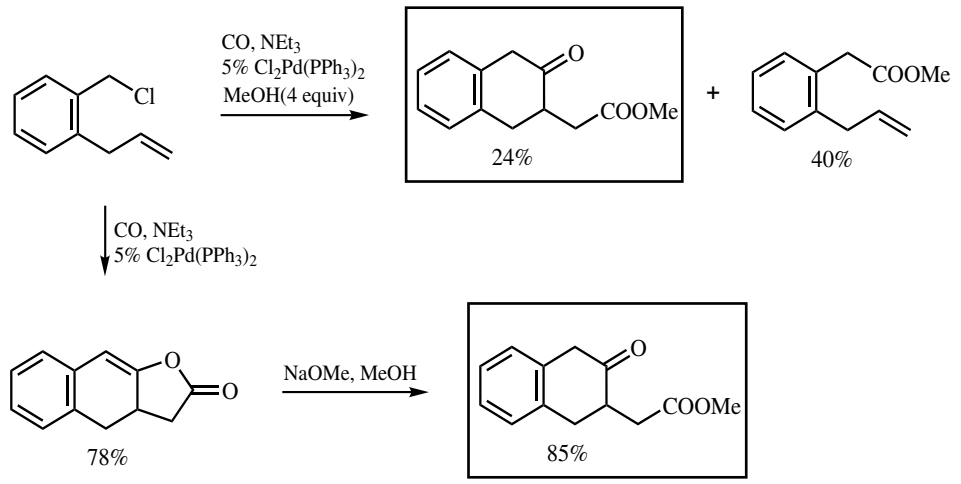
[I] = CO (40 atm), 5 mol % $Cl_2Pd(PPh_3)_2$, NEt_3(2 equiv), MeCN, 100 °C.

Scheme 19

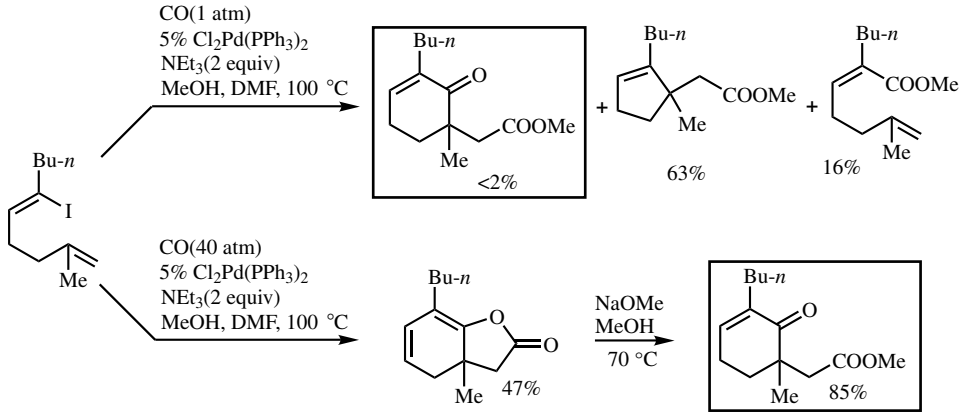


Scheme 20

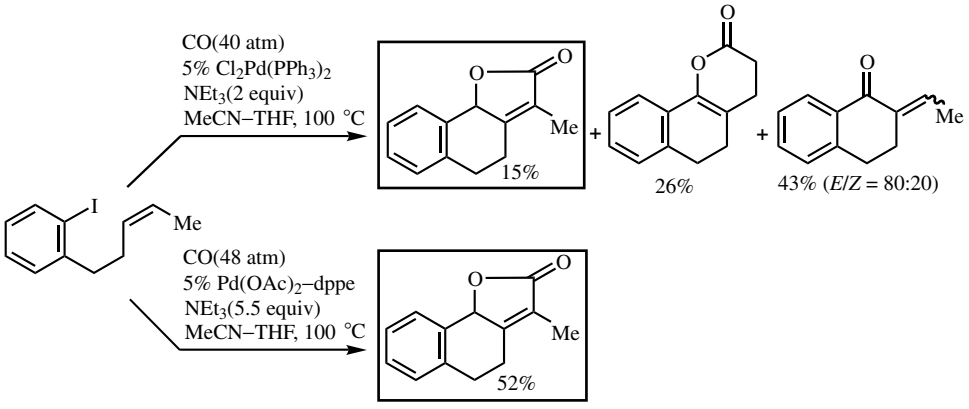
The cyclic acylpalladation process can be terminated by carbonylative esterification, that is, Type II AcPd process, as discussed in **Sect. VI.4.1**. In some cases, however, this process can be overshadowed by premature esterification.[16] This difficulty can be circumvented by a two-step alternative consisting of Type III AcPd process followed by methanolysis[16],[17] (**Schemes 21** and **22**). The results shown in **Scheme 23**[18] suggest that further optimization of the reaction conditions for the Type III AcPd process appears to be promising and highly desirable.



Scheme 21

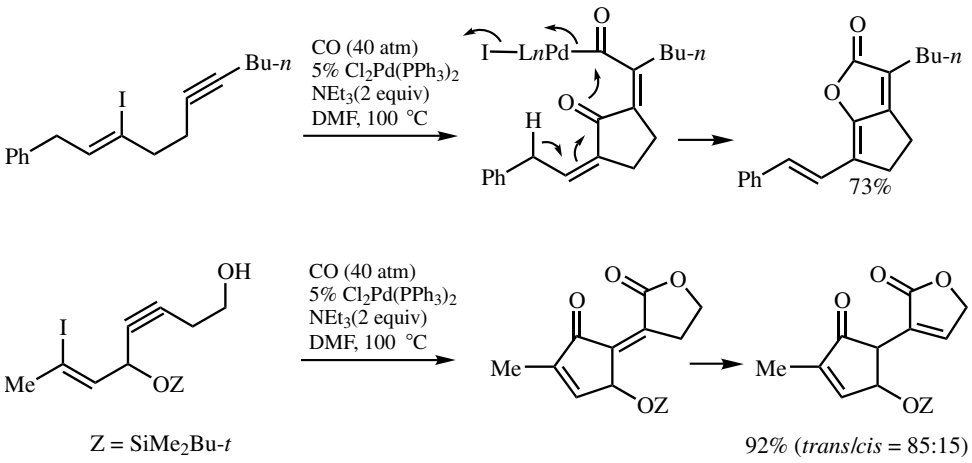


Scheme 22



Scheme 23

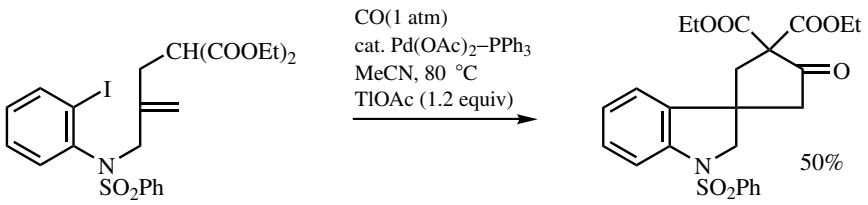
Cyclic acylpalladation of alkynes had until recently been highly elusive, since non-carbonylative cyclic carbopalladation is generally dominant. However, in the competition between noncarbonylative cyclic carbopalladation producing four-membered rings and cyclic acylpalladation producing five-membered ketones, the latter is significantly favored, and otherwise "live" acylpalladium intermediates are trapped by internal enolates to produce γ-lactones[19] (**Scheme 24**). Tetrasubstituted exocyclic alkenes appear to be generally unstable, and they undergo double bond migration.



Scheme 24

E. TANDEM AND CASCADE PROCESSES INVOLVING CYCLIC CARBOPALLADATION–TRAPPING WITH ENOLATES

In principle, a variety of other tandem and cascade processes terminated by trapping of acylpalladium derivatives by enolates are conceivable. In reality, examples of such processes are still very rare. One such process shown in **Scheme 25** involves a cyclic carbopalladation–cyclic ketone formation via a 5-*C*-*exo* trapping tandem process.[19] Many additional examples of such tandem and cascade processes will be devised in efforts to develop efficient routes to bicyclic and polycyclic natural products and related compounds.



Scheme 25

F. SUMMARY

1. Both intermolecular and intramolecular reactions of acylpalladium derivatives with enolates have been shown to be highly general reactions over the last dozen or so years.

2. Enolates may serve as either *C*- or *O*-nucleophiles. In the intermolecular reactions, ketone enolates generally act as *O*-nucleophiles, while ester enolates lacking a keto group generally serve as *C*-nucleophiles.

3. In the intramolecular reactions, ring size is the decisive factor, and five- or six-membered ring formation is favored regardless of whether that involves *C*- or *O*-enolates. However, in cases where both *C*- and *O*-enolates can, in principle, give ketones and lactones of the same ring size, respectively, the lactone formation predominates. In the five-membered lactone formation, the enolic C═C bond usually ends up exocyclic, while it ends up endocyclic in the formation of six-membered lactones. Thus, the 5-*O*-*exo* process provides a promising route to (*Z*)-γ-alkylidene-γ-lactones, and the corresponding lactam synthesis can be achieved similarly with imines. The 6-*O*-*endo* process provides a promising route to pyrones, while the 5-*C*-*exo*, 6-*C*-*exo*, and 7-*C*-*exo* processes permit the synthesis of the corresponding cyclic ketones.

4. Tandem and cascade processes involving acylpalladation–trapping of acylpalladiums with enolates (Type III AcPd process) provides not only a novel route to γ-alkylidene-γ-lactones but also a potentially useful alternative to Types I and II acylpalladation processes (**Sect. VI.4.1**) providing novel routes to cyclic ketones. Many applications to the efficient and selective syntheses of natural products and related compounds may be anticipated. The reaction also serves as a process of terminating Pd-catalyzed alkene–CO copolymerization. Although other types of tandem and cascade processes terminated by trapping of acylpalladiums with enolates are still very rare, many additional examples may be expected to be developed in the future.

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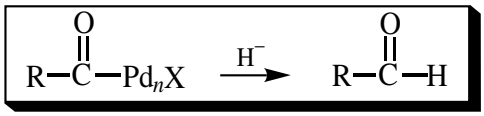

VI.2.4 Synthesis of Aldehydes via Hydrogenolysis of Acylpalladium Derivatives

ROBERT D. LARSEN and ANTHONY O. KING

A. INTRODUCTION

An acylpalladium intermediate **1** can undergo reduction to yield the corresponding aldehyde **2**. Although hydrogen is the most commonly used reducing agent, hydrides have been increasingly applied. The reactions can be categorized according to how the acylpalladium intermediate is prepared. Either oxidative addition of palladium onto an acyl derivative or CO insertion into a palladium–carbon bond can be used (**Scheme 1**). The reduction of an acyl derivative (Eq. 1), such as an acid chloride is the more traditional method. The carbonylation of vinyl and aryl halides (Eq. 2), and to a lesser degree alkyl halides, is an increasingly more effective approach. The hydroformylation of olefins (Eq. 3) continues to have problems in being fully exploited but with improved modifications may achieve a level of practicality.

B. REDUCTION OF ACYL DERIVATIVES

In the reduction of an acyl derivative, Pd undergoes oxidative addition inserting between the acyl group and X. Hydrogen or a substituted hydride adds to the palladium(II) followed by reductive elimination to regenerate Pd(0) and release the aldehyde (Eq. 1 **Scheme 1**).

B.i. Reduction of Acid Chloride

By far the oldest method to prepare an acylpalladium intermediate for reduction to the aldehyde is the Pd-catalyzed hydrogenation of an acid chloride, more commonly referred to as the Rosenmund reduction.[1] The literature of this reaction was last fully reviewed in 1948.[2] The reaction generally uses a supported palladium catalyst, such as $Pd/BaSO_4$ or Pd/C. A detailed study of the metamorphosis and actual state of the palladium catalyst in the reaction was reported by Maier and co-workers.[3],[4] Changes in the structure of the Pd were found to be responsible for the selectivity issues experienced in the Rosenmund reduction.

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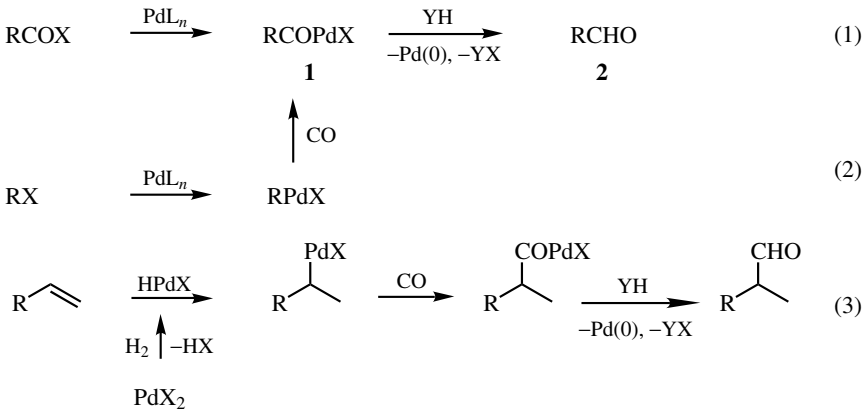
ISBN 0-471-31506-0



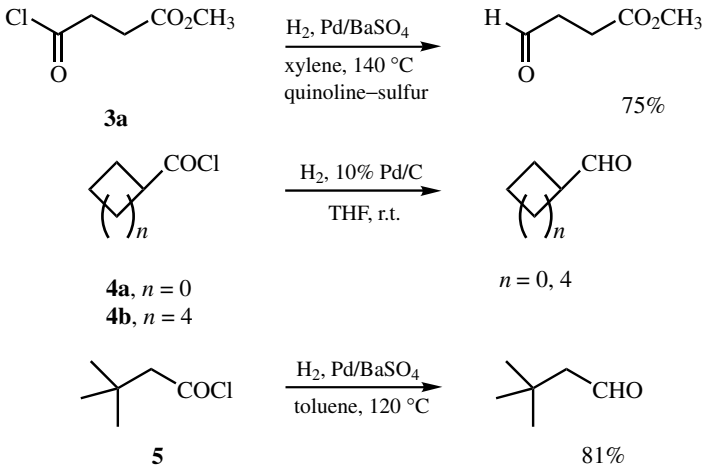
R = carbon group; X = halogen or equivalent; Y = H, SiR_3', SnR_3'.

Scheme 1

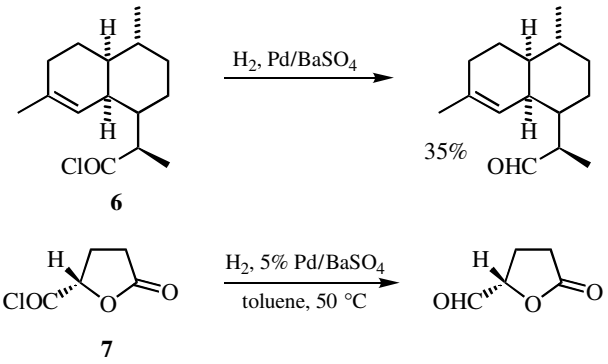
Since the acylpalladium intermediate can undergo decarbonylation or the aldehyde can be reduced further to the alcohol, a "poisoned" catalyst or a "regulator/modifier" is often required.[1],[4] Aromatic substrates have been typically susceptible to these side reactions, whereas hindered acid chlorides often undergo decarbonylation. Due to the selectivity issues with the reaction and the forcing conditions required with many substrates—generally refluxing toluene or xylene—the transformation of an acid derivative to an aldehyde was increasingly run with a hydride reducing agent.[5]

Effective applications have appeared in the literature using the original procedure. Aliphatic acid chlorides **3a**[6] and **4**[7] can be reduced very effectively (**Scheme 2**). Even sterically hindered acid chlorides such as **5** were reduced in good yield.[8]

Of great utility is the lack of epimerization of an adjacent chiral center (**Scheme 3**) that is observed with acid chlorides **6**[9] and **7**.[10]

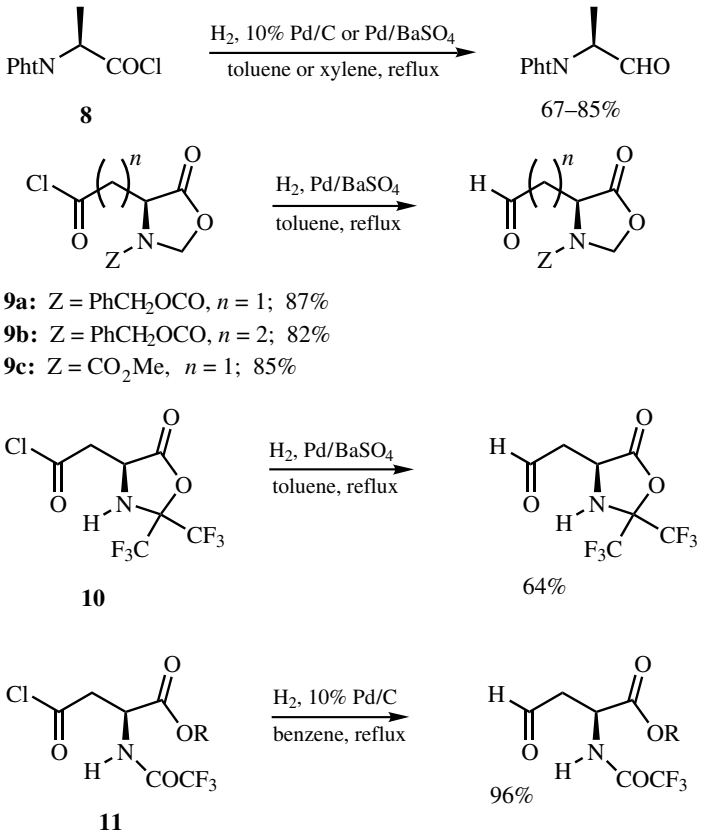


Scheme 2



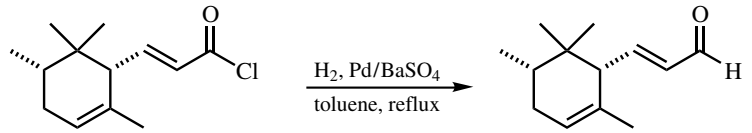
Scheme 3

The reduction of protected amino acid chlorides **8**,[11]–[14], **9**,[15],[16] **10**,[17] and **11**[18] to the aldehydes without epimerization (**Scheme 4**) provides useful intermediates for asymmetric synthesis.

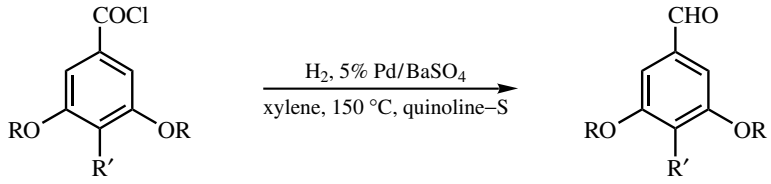


Scheme 4

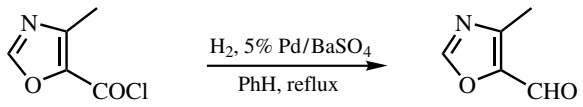
The unsaturated acid chloride **12** undergoes reduction with no isomerization of the double bond (**Scheme 5**).[19] Aromatic and heteroaromatic acid chlorides **13**[20],[21] and **14**,[22] respectively, can also be reduced to the aldehydes.



12 93%



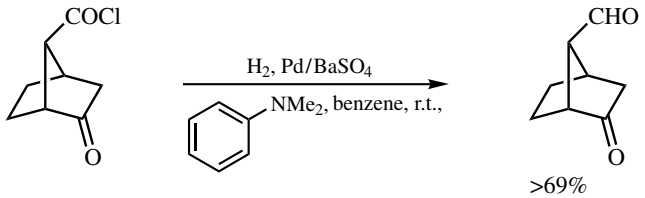
13a: R = $CH_3(CH_2)_{11}$ —, R′ = H R′ = H, 61%
13b: R = $CH_3(CH_2)_{11}$ —, R′ = OR R′ = OR, 99%



14 76%

Scheme 5

Although it appeared that after 1950 the Rosenmund reduction would be made obsolete by the use of hydride reagents,[23],[24] modifications have vastly improved on this method to provide a mild, high-yielding reaction. The addition of a base to the system vastly aided in providing a more selective reaction that could be run under mild conditions and no longer required the use of a poisoned catalyst. Sakaurai and Tanabe reported dimethylaniline as an effective additive that allowed room temperature reactions in acetone at atmospheric pressure to provide aldehydes in 80–90 % yield.[25] This method was used for the preparation of the bicyclo aldehyde **15** as part of the synthesis of *ent*-multifidene (**Scheme 6**).[26]

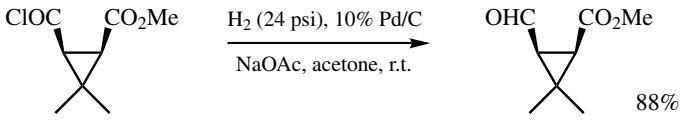


>69%

15

Scheme 6

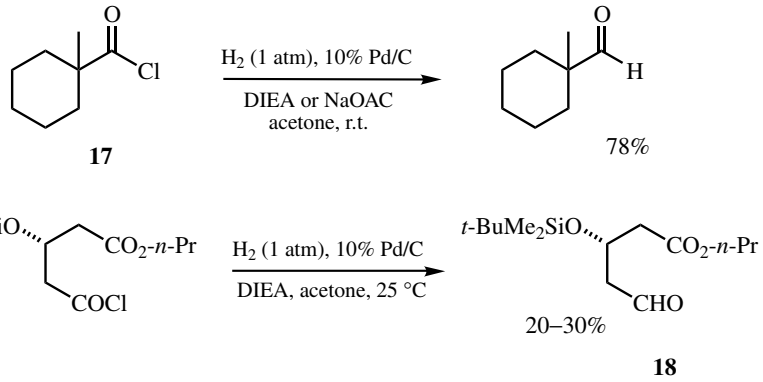
Unfortunately, dimethylaniline can undergo hydrogenation as well in the reaction. Sodium acetate was subsequently reported as an alternative base. Interestingly, with the addition of base the modified-Rosenmund process no longer requires a poisoned catalyst. Pd/C was effective for the reduction of the cyclopropyl acid derivative **16** (**Scheme 7**).[27]



16

Scheme 7

Peters and van Bekkum reported diisopropylethylamine (DIEA) as an alternative for the reduction of aliphatic, **17**, and aromatic acid chlorides under mild conditions (**Scheme 8**).[28],[29] This method was also used in the preparation of the lactone building block **18** for HMG CO-A reductase inhibitors.[30] The improved conditions are from the selective adsorption of the acid chloride on the catalyst surface and the partial poisoning of the catalyst by the DIEA.



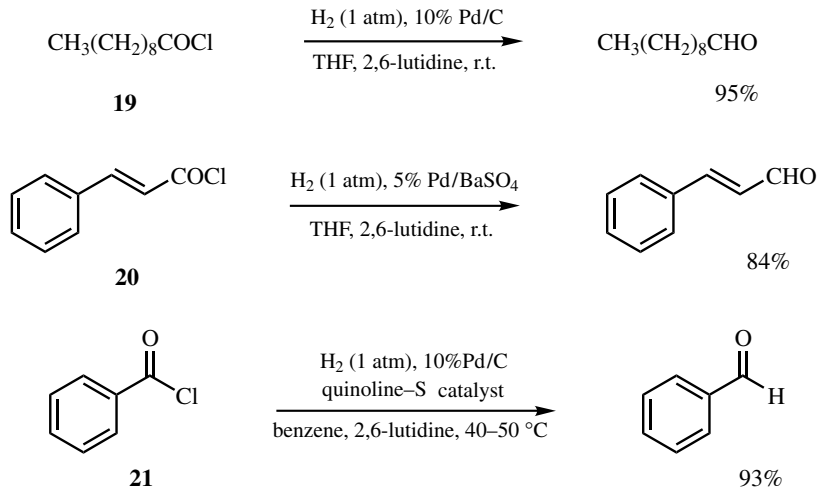
17

18

Scheme 8

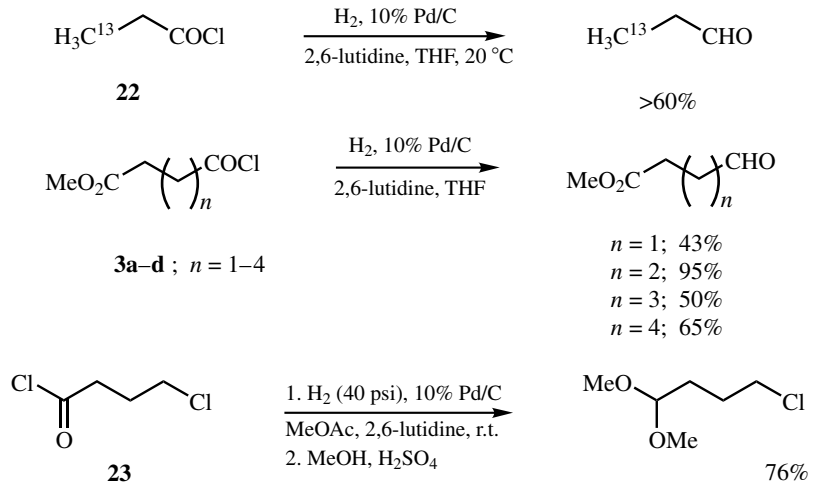
The most significant improvement in the Rosenmund reduction was the use of 2,6-lutidine as an additive first reported by Burgstahler and co-workers.[31] This base is a better alternative to dimethylaniline, due to its reduction, or DIEA, which may be too strong of a base for many acid chlorides. DIEA was reported by Burgstahler to generate color bodies and to be limited to aliphatic and alicyclic acid chlorides, although DIEA was later applied by Peters and Van Bekkum[29] to aromatic acid chlorides quite effectively. The reactions with 2,6-lutidine can be carried out at room temperature over 1–2 h in THF at atmospheric pressure (**Scheme 9**). In these cases the base acts as a poison for the palladium, preventing over-reduction to the alcohol. Therefore, palladium on carbon with added poison is suitable for the reaction of simple acid chlorides, such as **19**. Significantly, a hindered acid chloride such as dehydroabietic acid chloride undergoes high-yielding reduction to the aldehyde without the decarbonylation normally observed.

Olefinic acid chlorides **20** are best reduced with $Pd/BaSO_4$ to prevent over-reduction. However, the base is not as effective as DIEA for the reduction of benzoyl chloride (**21**) derivatives. In order to reduce aromatic acid chlorides effectively, higher temperatures were required with the use of a quinoline–S poisoned catalyst.



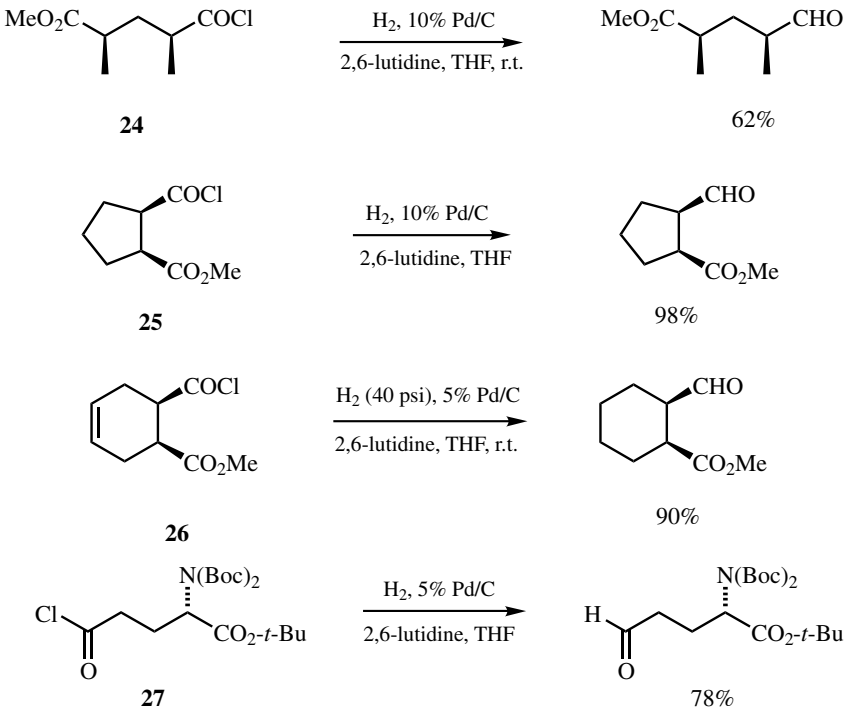
Scheme 9

Numerous examples of the Burgstahler–modified-Rosenmund reduction have since appeared in the literature (**Scheme 10**). The reaction was used to prepare radiolabeled propionaldehyde[32] from the labeled propionyl chloride (**22**). The conditions are mild enough to prepare a variety of α,ω-ester aldehydes from **3a–d**.[33]–[36] The hydrogenation of **23** was used in the preparation of aldehyde precursors for the Fisher indole reaction in the synthesis of tryptamine-based $5HT_{1D}$ agonists for the treatment of migraine.[37]



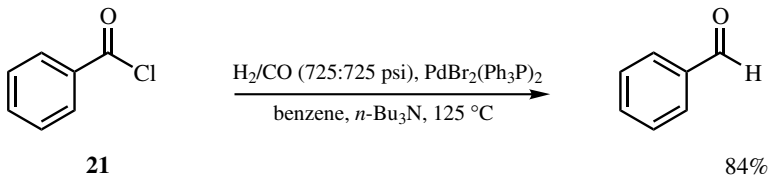
Scheme 10

The reaction is mild enough to prevent epimerization of chiral intermediates (**Scheme 11**). *meso*-Diesters can be converted to chiral acid esters. Conversion of the resultant acid chlorides **24** through **26**, for example, to the aldehydes,[38]–[40] provides useful chiral building blocks. The addition of 2,6-lutidine also helps when acid-sensitive functional groups are present such as the Boc protecting group of **27**.[15]



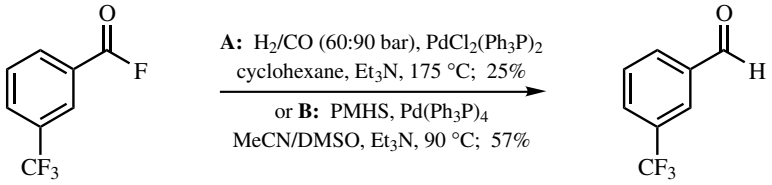
Scheme 11

For the most part the Rosenmund reduction and modifications are carried out with a heterogeneous catalyst. Schoenberg and Heck reported the hydrogenation of acid chlorides with the soluble catalyst $Pd(Ph_3P)_2X_2$ (X = Cl, Br) in the presence of a trialkylamine (Et_3N or Bu_3N).[41] However, the reactions required high temperatures (120–145 °C) and high pressures of hydrogen (725–1380 psi), as well as carbon monoxide (1:1), to work successfully. The carbon monoxide is needed to overcome the propensity of the acylpalladium species to decarbonylate. The phosphine ligands induce this undesired reaction and suppress the hydrogen exchange. Due to this the reaction is not a viable process. In any event, in the reduction of benzoyl chloride to benzaldehyde an 84% yield was obtained (**Scheme 12**).



Scheme 12

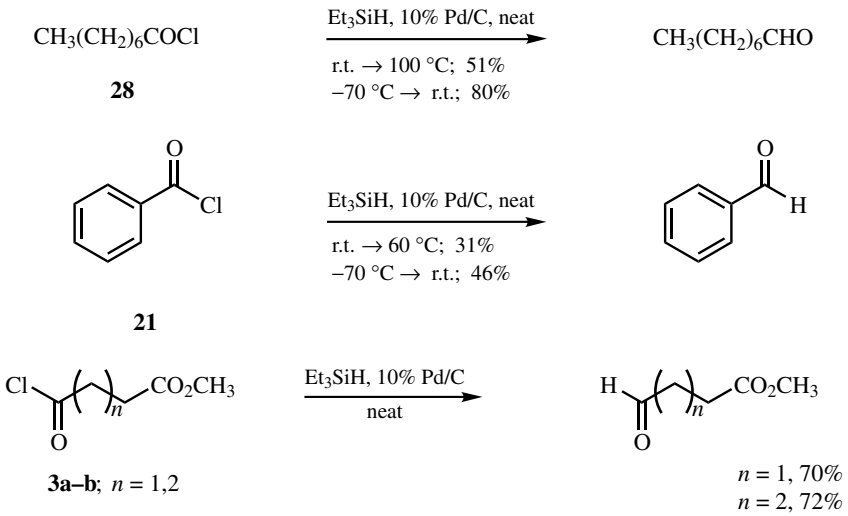
One example of an acylfluoride reduction was reported,[42] although the yield was poor (**Scheme 13**). In order to minimize the decarbonylation side product trifluoromethylbenzene (7%), the reduction was run with $PdX_2(Ph_3P)_2$ (X = Cl, Br) under an atmosphere of H_2/CO (50–120 : 40 bar), much as reported by Schoenberg and Heck above. By using polymethylhydrosiloxane (PMHS) as an alternative hydrogen source the reaction was carried out under milder conditions with higher yield.



Scheme 13

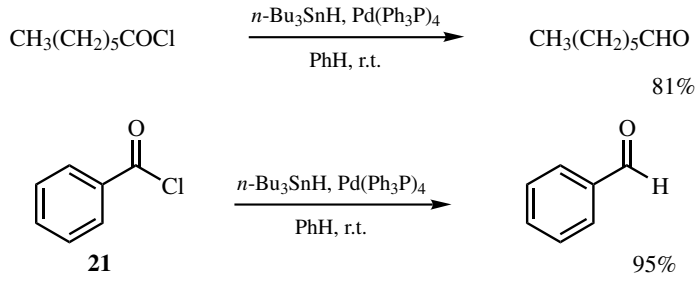
The mechanism as proposed by Tsuji and co-workers proceeds first by oxidative addition to form an acylpalladium(II) chloride species.[43] Exchange of hydrogen on the palladium and release of HCl produces the acylpalladium(II) hydride, which undergoes reductive elimination to the aldehyde. Without hydrogen present the intermediate, under forcing conditions, can undergo decarbonylation to the olefin via β-hydride elimination of the alkylpalladium intermediate or to chlorobenzene via the reductive elimination of the arylpalladium chloride.

Improvements in the Pd-catalyzed reduction of acid chlorides have utilized alternative hydrogen sources. Trialkylsilyl hydrides also effectively reduce acid chlorides to the aldehydes (**Scheme 14**).[44] Triethylsilyl hydride proved to be the best; however, the success of the reaction was not broad. For example, aliphatic substrates (**28**) gave mixed results, but the aromatic substrates (**21**) were more consistent. This method was later applied to the reduction of the acid chlorides **3a,b** as part of the synthesis of α-amino dicarboxylates.[45]

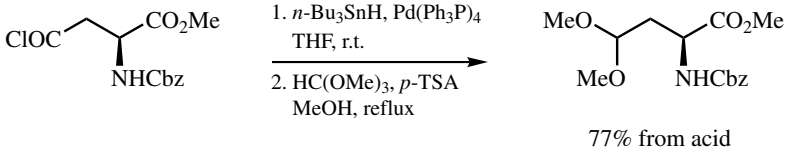


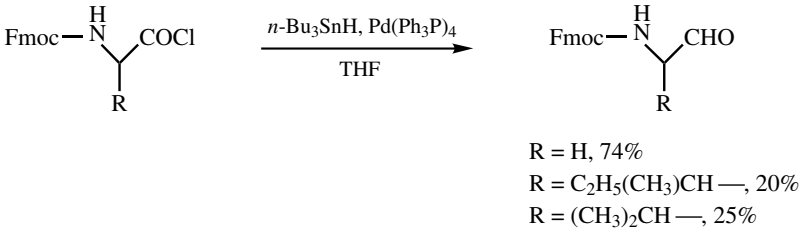
Scheme 14

Tributyltin hydride was subsequently tested in the conversion of acid chlorides to the aldehydes (**Scheme 15**).[46],[47] The homogeneous catalyst $Pd(Ph_3P)_4$ as well as Pd(II) complexes, such as $PdCl_2$, can be used instead of a supported catalyst. The reaction proceeds under very mild conditions, especially compared to the Rosenmund reduction, and affords the aldehydes in very good yield. The reaction tolerates a variety of functional groups and can even convert α,β-unsaturated acid chlorides to the α,β-unsaturated aldehydes. Without the Pd the tin hydrides will reduce the acid chloride by a radical mechanism to a mixture of aldehydes and esters. With the Pd the reaction is much more rapid and selective for the aldehyde. The reaction has been applied to the synthesis of α-amino aldehydes (**Scheme 16**)[48],[49] and a nicotinaldehyde derivative[50] (**Scheme 17**).

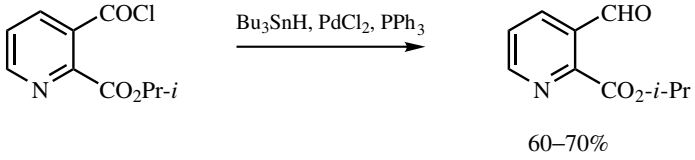


Scheme 15



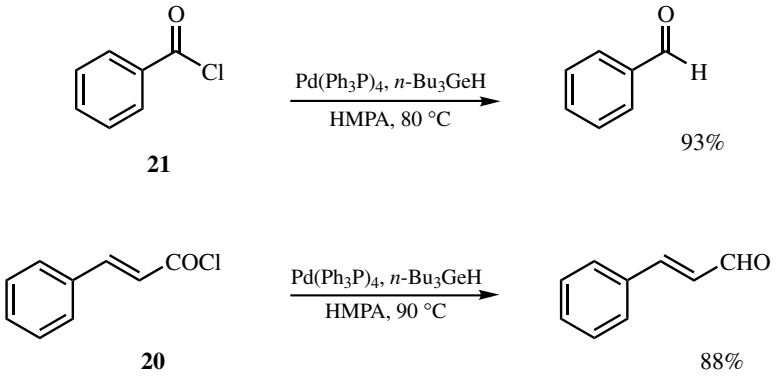


Scheme 16



Scheme 17

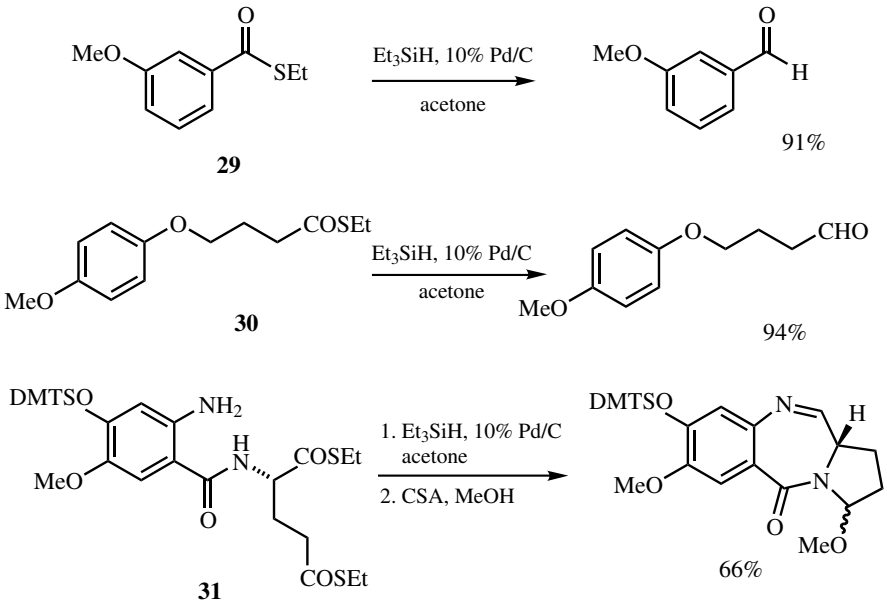
Completing the series, tributylgermanium hydride also reduces acyl chlorides to the aldehydes in the presence of $Pd(Ph_3P)_4$, but under more stringent conditions (**Scheme 18**).[51] The reactions are only effective at 80–100 °C in HMPA. In the case of **20** the product could be fully reduced to phenylpropionaldehyde in 37% yield if 3 equiv of the hydride was used and the reaction temperature was increased to 100 °C.



Scheme 18

B.ii. Reduction of Thioester

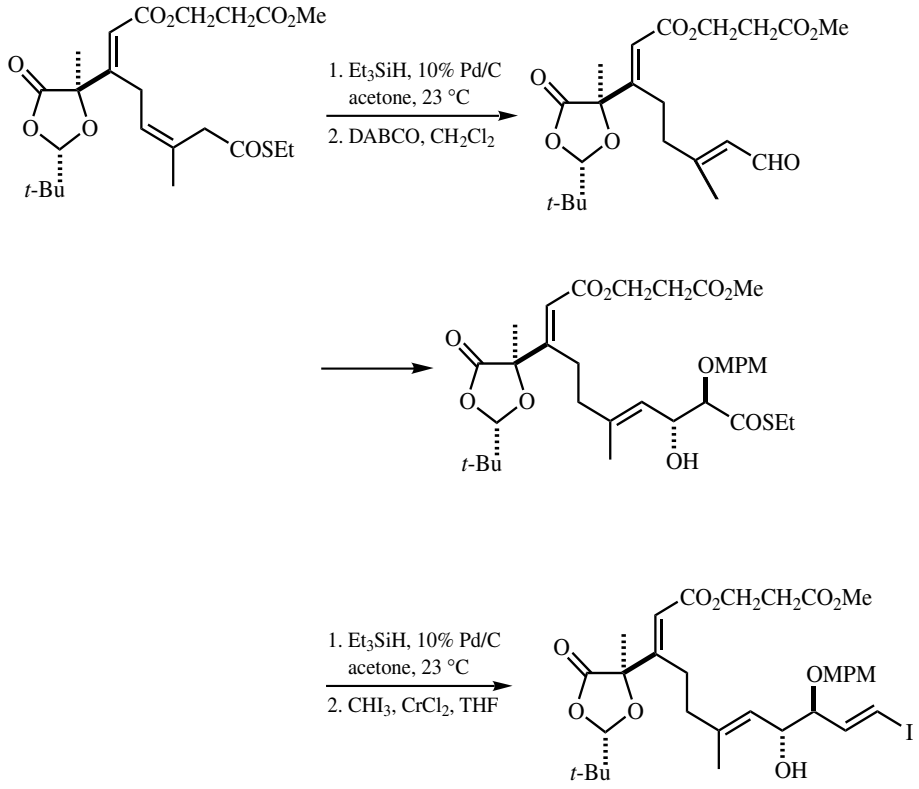
In 1990 Fukuyama and co-workers reported the mild and selective reduction of thioesters to aldehydes with triethylsilane using palladium as a catalyst (**Scheme 19**).[52],[53] The reaction can be used with aromatic (**29**) and aliphatic (**30**) thioesters and tolerates chiral centers very well as applied to the intermediate **31** in the synthesis of (+)-neothramcycin.



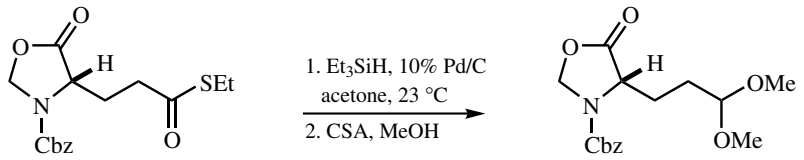
Scheme 19

Fukuyama and co-workers later used this method for the synthesis of (+)-leinamycin (**Scheme 20**)[54] and porothramycin B (**Scheme 21**).[55]

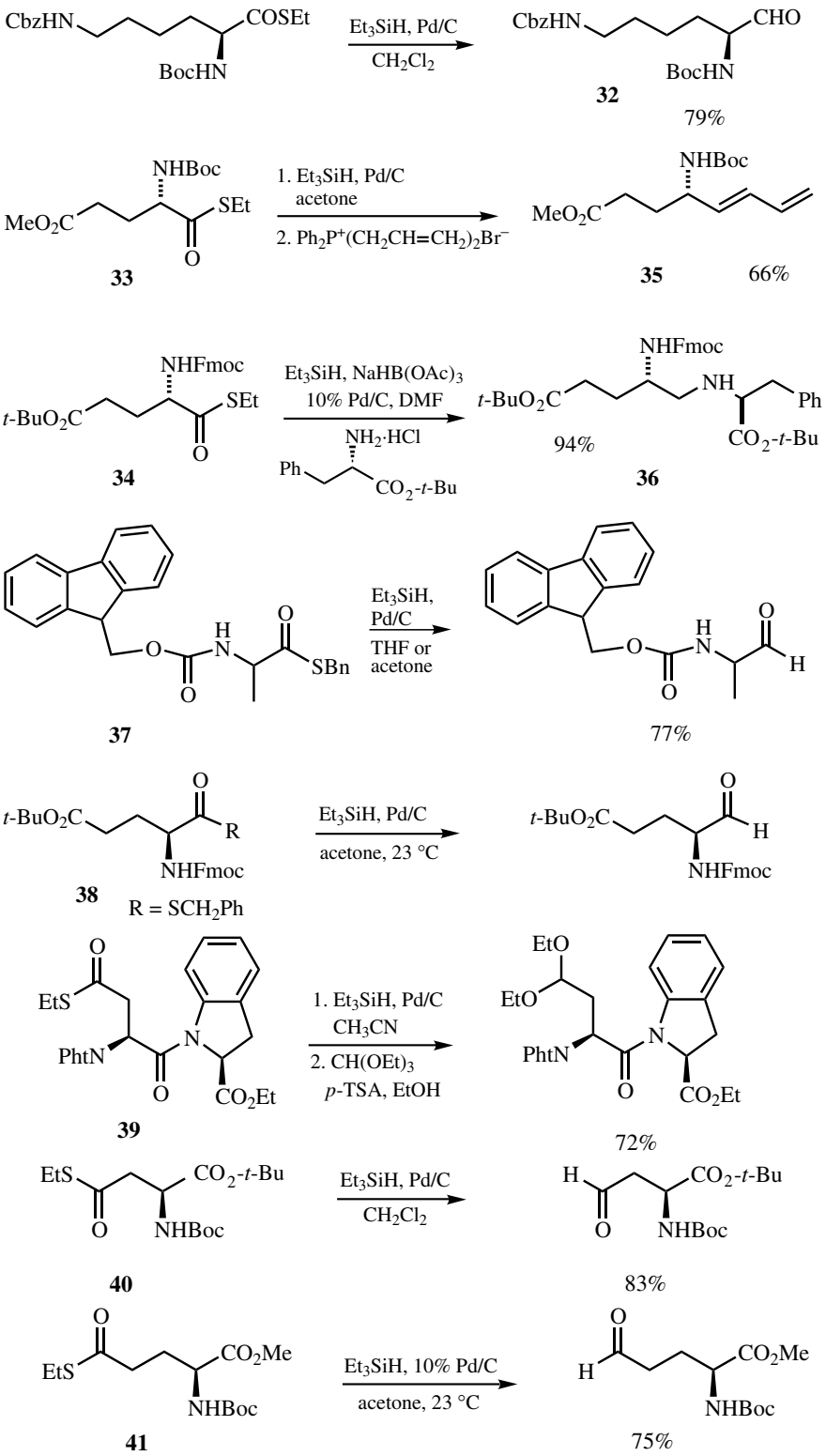
Due to the mild conditions and tolerance for a variety of functional groups, the method has become widely used in the synthesis of N-protected amino aldehydes (**Scheme 22**). α-Amino aldehydes (**32**) are prepared with no epimerization.[56]–[58] In the reduction of **33** and **34** the intermediate aldehydes are converted directly to the diene **35**[59] or amine **36**,[60] respectively, as a through process. In the reduction of **37**[61] and **38**[62] the benzyl thioester was used in place of the ethyl thioester. β-Amino aldehydes can be prepared from the aspartic acid derivatives **39**[63] and **40**.[64] Similarly, the glutamic acid derivative **41** is converted cleanly to γ-aminoaldehyde.[65],[66] In one example the method was used



Scheme 20



Scheme 21


CbzHN
COSEt
BocHN
Et3SiH, Pd/C
CH2Cl2
CbzHN
CHO
BocHN
32
79%
NHBoc
MeO2C
SEt
O
33
1. Et3SiH, Pd/C
acetone
2. Ph2P+(CH2CH=CH2)2Br−
NHBoc
MeO2C
35
66%
NHFmoc
t-BuO2C
SEt
O
34
Et3SiH, NaHB(OAc)3
10% Pd/C, DMF
NH2·HCl
Ph
CO2-t-Bu
NHFmoc
t-BuO2C
NH
Ph
CO2-t-Bu
94%
36
O
H
N
SBn
Et3SiH,
Pd/C
THF or
acetone
H
37
77%
t-BuO2C
R
NHFmoc
38
R = SCH2Ph
Et3SiH, Pd/C
acetone, 23 °C
t-BuO2C
H
NHFmoc
EtS
PhtN
N
CO2Et
39
1. Et3SiH, Pd/C
CH3CN
2. CH(OEt)3
p-TSA, EtOH
EtO
EtO
72%
EtS
CO2-t-Bu
NHBoc
40
Et3SiH, Pd/C
CH2Cl2
H
83%
EtS
CO2Me
NHBoc
41
Et3SiH, 10% Pd/C
acetone, 23 °C
75%

Scheme 22

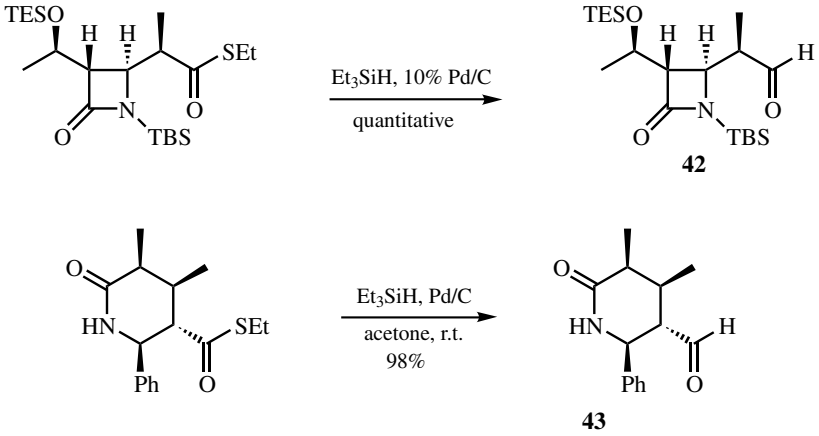
to prepare vinylogous analogs of cyclosporin through conversion of the acid to the aldehyde followed by a Wittig reaction.[67]

The reduction is particularly useful with the highly labile β-lactam system **42**[68]–[70] and in the synthesis of chiral piperidone derivative **43** (**Scheme 23**).[71] The method was used in the synthesis of (+)-methylpederate (**Scheme 24**).[72]

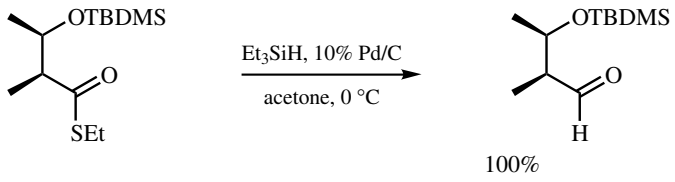
The reduction has successfully been applied in the synthesis of a number of natural products (**Scheme 25**), where the carboxylic acid intermediates are conveniantly converted to the thioesters. The compatibility of the reaction with a variety of functional groups and chiral centers makes it the method of choice for the selective reduction to aldehydes. Evans and co-workers prepared the aldehyde intermediate **44** in the synthesis of rutamycin B.[73]–[75] Smith and co-workers utilized the aldehyde **45** in the total synthesis of (+)-acutiphycin.[76],[77] Morimoto and co-workers applied the method to the synthesis of the aldehyde **46** as part of the syntheses of (−)-stenine.[78]

In two examples Evans, Black, and Johnson reported that the olefin reduction side reactions of **47**[79],[80] and **48**[81] were prevented by using a poisoned catalyst (**Scheme 26**). With **48** the addition of 1-decene was also preventative.

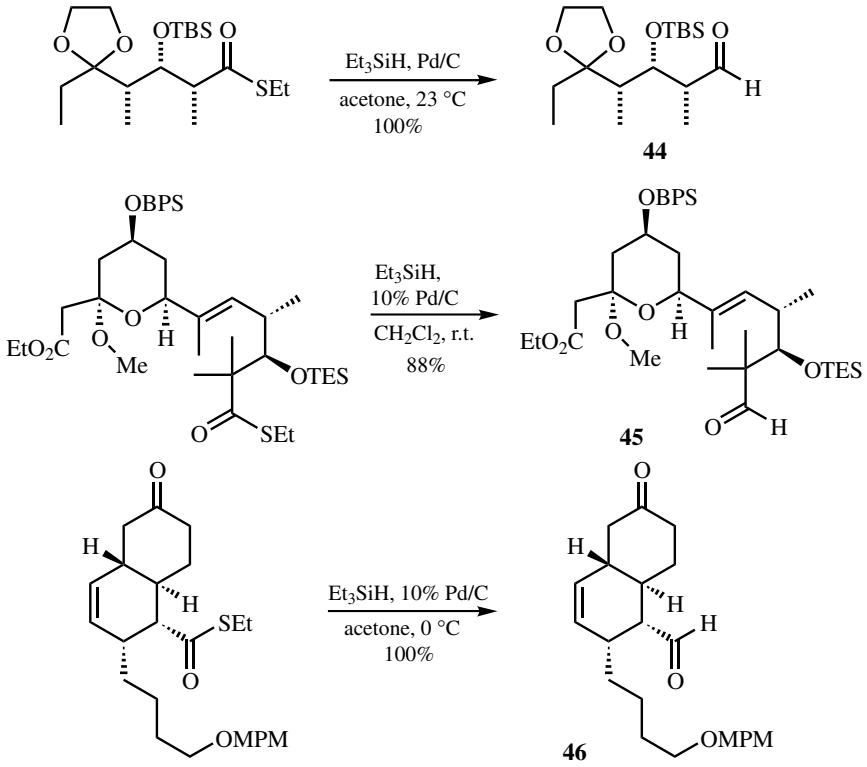
Along the same means, the tributyltin hydride reduction of thioesters[82] and selenoesters[83] to aldehydes with palladium catalysis was reported (**Scheme 27**). A detailed discussion of the mechanism was presented.



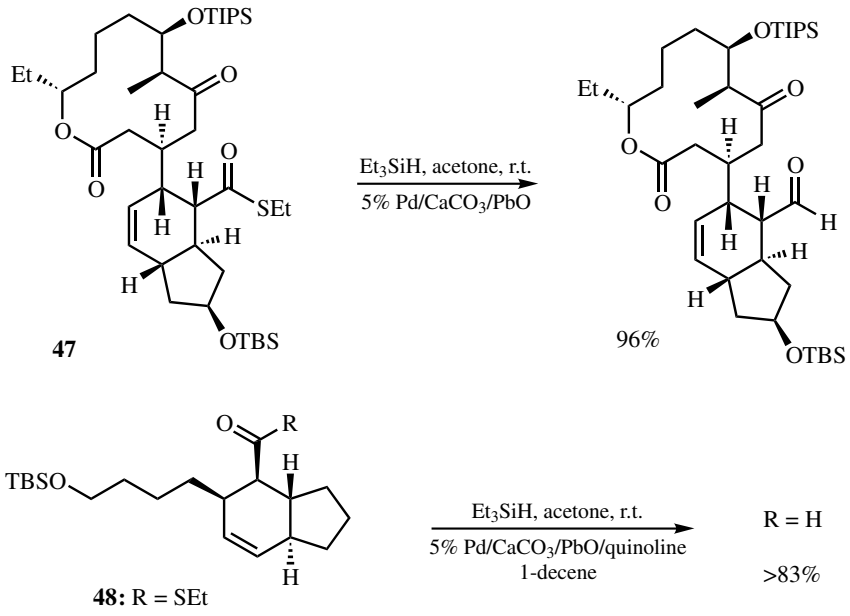
Scheme 23



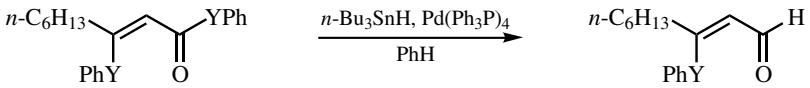
Scheme 24



Scheme 25



Scheme 26

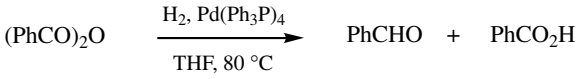


Y = S, 93%
Y = Se, 91%

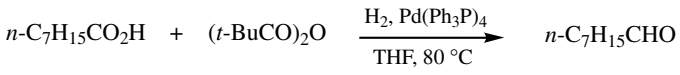
Scheme 27

B.iii. Reduction of Anhydrides

An earlier report of the Pd-catalyzed reduction of anhydrides to aldehydes utilized $Pd/BaSO_4$. The reaction was not general having only reduced acetic and propionic anhydride with 15–20% of the product experiencing over-reduction to the alcohol.[84] The reduction of a mixed anhydride of N-acylated α-amino acids was reported.[14],[85] The α-amino aldehydes were obtained with substantial racemization. Yamamoto and co-workers reacted acyclic acid anhydrides with the styrene adduct $Pd(styrene)(PMe_3)_2$, which underwent oxidative addition at the C—O bond to yield the stoichiometric carboxylato-Pd(II) species.[86] Reaction with hydrogen afforded aldehyde and acetic acid. Octanoic and benzoic acid anhydrides were both converted to the aldehydes with $Pd(Ph_3P)_4$ (**Scheme 28**). The problem of losing 1 equiv of the acid was overcome by adding pivalic anhydride to any acid (**Scheme 29**). The less-hindered, desired acyl group was converted to the aldehyde directly. This serves to maximize the yield of the desired acid and simplifies the process by avoiding an anhydride formation step.[87]



Scheme 28



98%

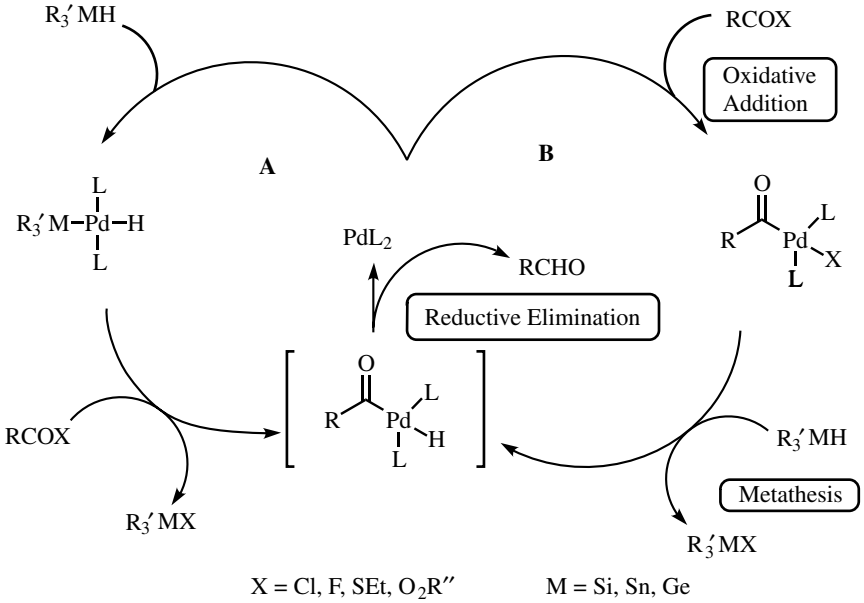
Scheme 29

B.iv. Miscellaneous Acyl Reductions

The conversion of an acylsilane to the aldehyde using hydrogenation conditions with Pd/C as catalyst was reported.[88] It was necessary to use the phenyldimethylsilyl derivative to achieve the reduction. Although this reaction appears to be analogous to the other acyl derivatives, the existence of a silylated acylpalladium intermediate was not expected. Similar to acid chlorides, aryl and heteroaryl imidoyl chlorides undergo reduction with $PdCl_2(Ph_3P)_2$ to the aldimines in good yield in the presence of triethylamine at 120 °C via an imidoylpalladium intermediate.[89] Primary and secondary aliphatic imidoyl chlorides decompose under the reaction conditions. Interestingly, the use of the traditional catalyst $Pd/BaSO_4$ only afforded the reduced amines.

B.v. Proposed Mechanism of Reduction Via Acylpalladium

The mechanism of the hydrogenolysis of the acyl derivatives to aldehydes can be generically written as in **Scheme 30**. The pathways differ in regard to the species undergoing the oxidative addition step. In the hydride reduction of acyl chlorides, pathyway **B** is thought to be most likely with exchange of the hydride onto the acylpalladium intermediate.[51] Although the mechanism of the thioester reduction was not discussed,[52],[53] it most likely proceeds by oxidative addition of palladium with triethylsilylhydride to form the palladium hydride intermediate as in pathway **A**.[47],[82] Ligand exchange with the acyl thioester releases triethylsilyl ethylsulfide. The acylpalladium hydride species then undergoes reductive elimination to the aldehyde, although either pathway could predominate depending on the substrate, reagents, and reaction conditions.



Scheme 30

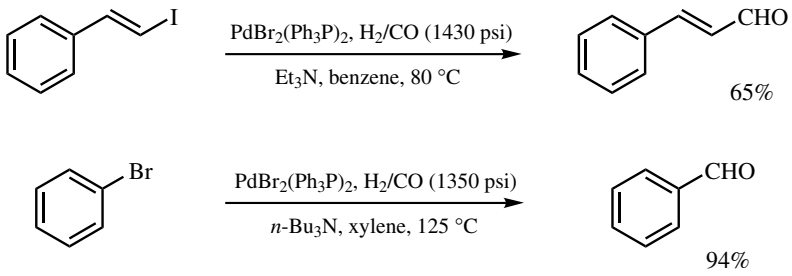
C. FORMYLATION

Pd-catalyzed formylation or carbonylation reactions of organic halides with carbon monoxide[90] are becoming increasingly useful reactions. In the early literature reactions required high temperatures and high pressures of synthesis gas (CO/H_2) to accomplish the formylation. Great progress has occurred in the last twenty years to make it possible to run these reactions under more moderate conditions. The reaction can be carried out on aromatic, vinyl, benzyl, and allylic halides but fails with alkyl halides due to the propensity of alkylpalladium species to undergo the β-hydride elimination.[91]

The effect of aldehyde desorption/adsorption on Pd surfaces as part of the formylation or further reduction of the aldehyde was studied.[92],[93]

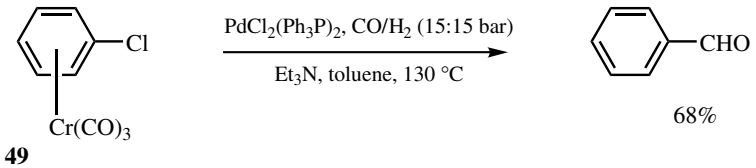
C.i. Formylation of Aryl and Alkenyl Halides

Formylation of aryl or alkenyl halides to the respective benzaldehydes or vinyl aldehydes[94] was first introduced by Schoenberg and Heck[41] using $PdX_2(Ph_3P)_2$ as catalyst (**Scheme 31**). The reaction, however, requires high pressures at ~1200 psi and high temperatures of 80–150 °C. An amine base is a key additive to the reaction. The reaction is limited to organic halides, which do not undergo the β-hydride elimination. Interestingly, *o*-dibromobenzene produces only benzaldehyde under the reaction conditions. A variety of substrates were prepared in good to excellent yields. A detailed study of the mechanism based on the kinetics of the formylation of iodobenzene was reported.[95] Interestingly, the mechanism is different from that for the related methoxycarbonylation to the methyl benzoate. Subsequently, and apparently independently, Ito and co-workers reported the formylation of iodobenzene with Pd black as part of their kinetic study of the methoxycarbonylation reaction.[96] Formylation of aryl halides (~15% yield) was a side reaction in the double carbonylation (3–50% yield) through loss of CO_2 from the acylpalladium formate intermediate producing the acylpalladium hydride species.[97]



Scheme 31

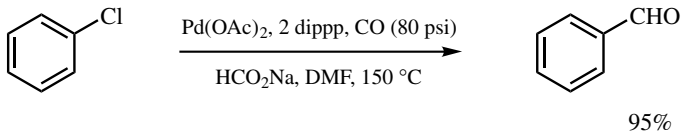
Aryl chlorides do not undergo the oxidative addition as readily, requiring forcing conditions that decompose the catalyst system. However, activation as the Cr complex **49** allows formylation under 15 bar each of CO/H_2 using $Pd(Ph_3P)_2Cl_2$ as catalyst (**Scheme 32**).[98] The Cr group is lost under the reaction conditions providing the benzaldehyde directly. Some uncoordinated starting material is produced due to the competing carbonylation of the chromium center. Besides the formylation, reduced product is obtained as well.[99]



49

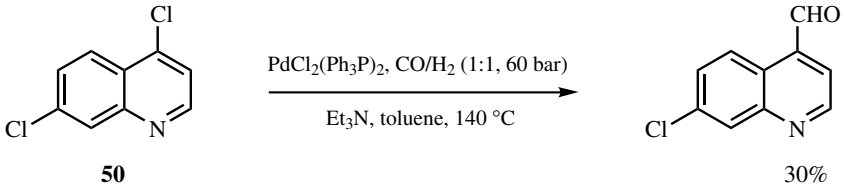
Scheme 32

By using an electron-rich, bidentate ligand, dippp [1,3-bis(diisopropylphosphino)propane] aryl chlorides are converted to benzaldehydes in high yield without the need for activation (**Scheme 33**).[100] Rather than hydrogen, sodium formate is used as the hydride source. Chlorobenzene was converted to benzaldehyde with only 5% reduction to benzene with no substrate left unreacted.



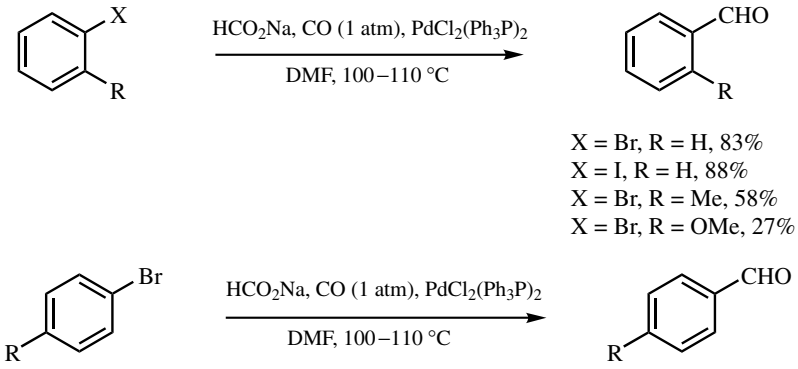
Scheme 33

The formylation of 4,7-dichloroquinoline (**50**) was studied with the 4-position being the more reactive.[101] However, 70% of the converted material (50%) underwent reduction to 7-chloroquinoline (**Scheme 34**).

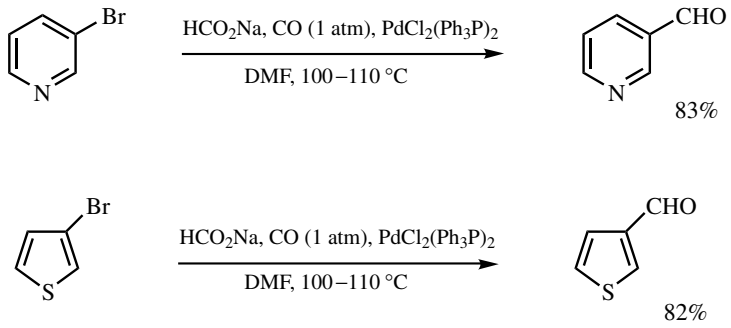


Scheme 34

Because of the high pressures and temperatures required in the Heck formylation, alternative hydride sources to hydrogen have been sought. Apparently, the oxidative addition and carbonylation to the acylpalladium species are relatively facile. The exchange to form the acylpalladium hydride species with hydrogen is slow, however. By using sodium formate as the reducing agent the formylation of aryl bromides can be carried out at 1 atm of CO at 110 °C in DMF (**Scheme 35**).[102] Interestingly, sodium formate was not a good hydride source for the reduction of benzoyl chloride directly, as opposed to silyl and tin hydrides. This was a result of the formate adding directly to the acid chloride releasing benzoic acid and CO. Under stoichiometric conditions with palladium, benzoyl chloride did form the acylpalladium species, which was reduced by formate to benzaldehyde.

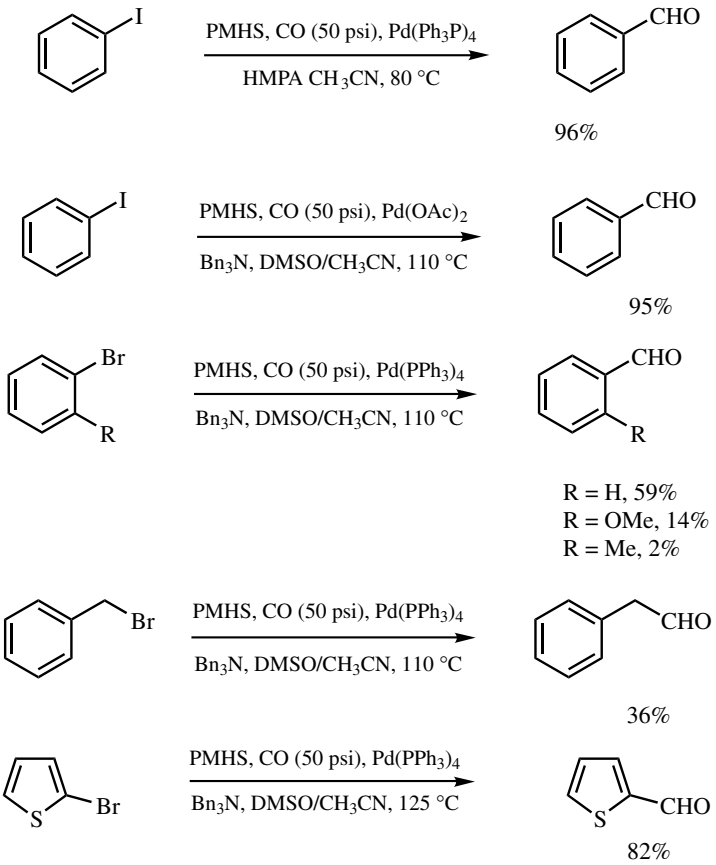


Scheme 35

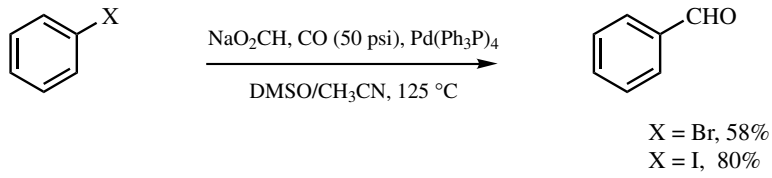


Scheme 35 (*Continued*)

Using poly(methylhydrosiloxane) (PMHS) in the presence of tribenzylamine (**Scheme 36**) or sodium formate (**Scheme 37**) the reaction can be run at 50 psi CO, 80 °C to afford aldehydes in high yields.[103] Either Pd(0) or Pd(II) reagents were successful. The reaction worked well for aryl iodides, but only moderately for aryl bromides. The intermediacy of an acylpalladium species was supported by conversion of benzoyl chloride to benzaldehyde with PMHS, tribenzylamine, and $(Ph_3P)_4Pd$.



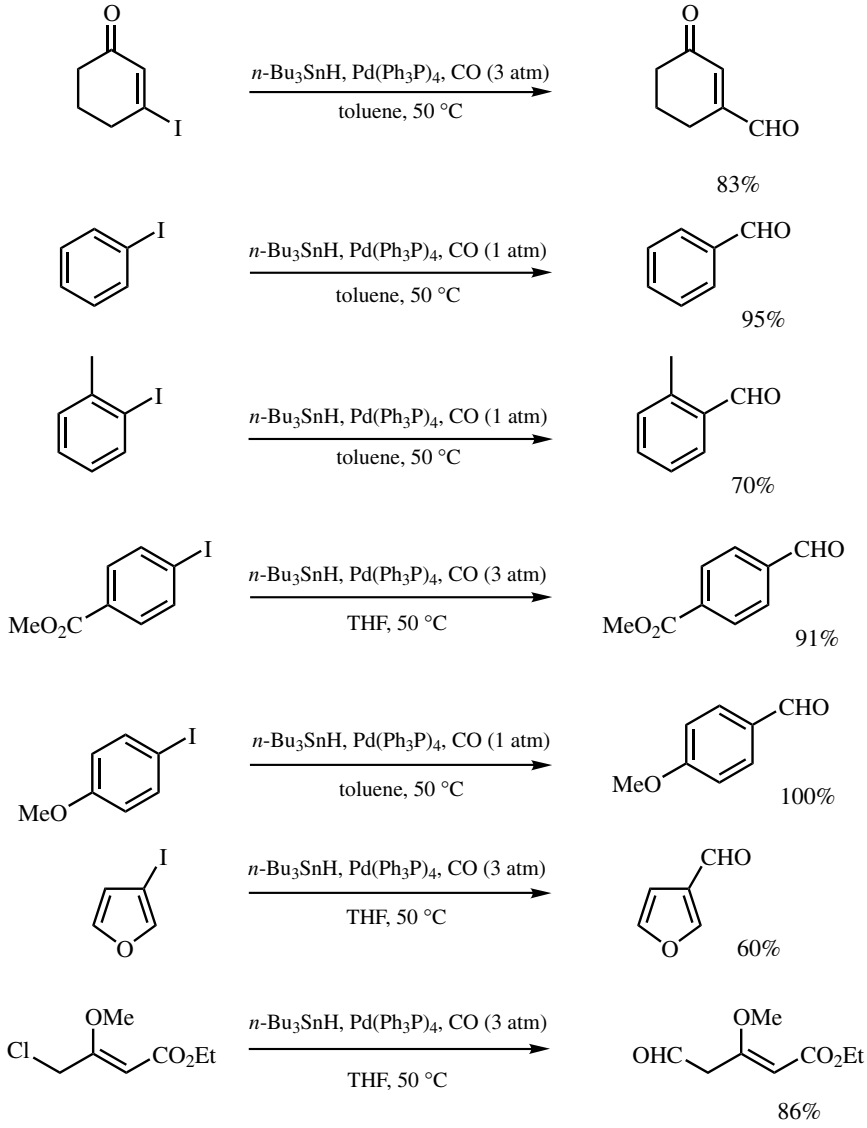
Scheme 36



Scheme 37

Stille applied tributylltin hydride as the hydrogen source in the formylation of aryl, vinyl, benzyl, and allyl halides, which allows the reaction to be run at 50 °C and 1–3 atm of CO with $(Ph_3P)_4Pd$ (**Scheme 38**).[14],[105]

A number of applications of the formylation reaction with tributyltin hydride have been used to prepare compounds of medicinal interest (**Scheme 39**). The 4-iodo position

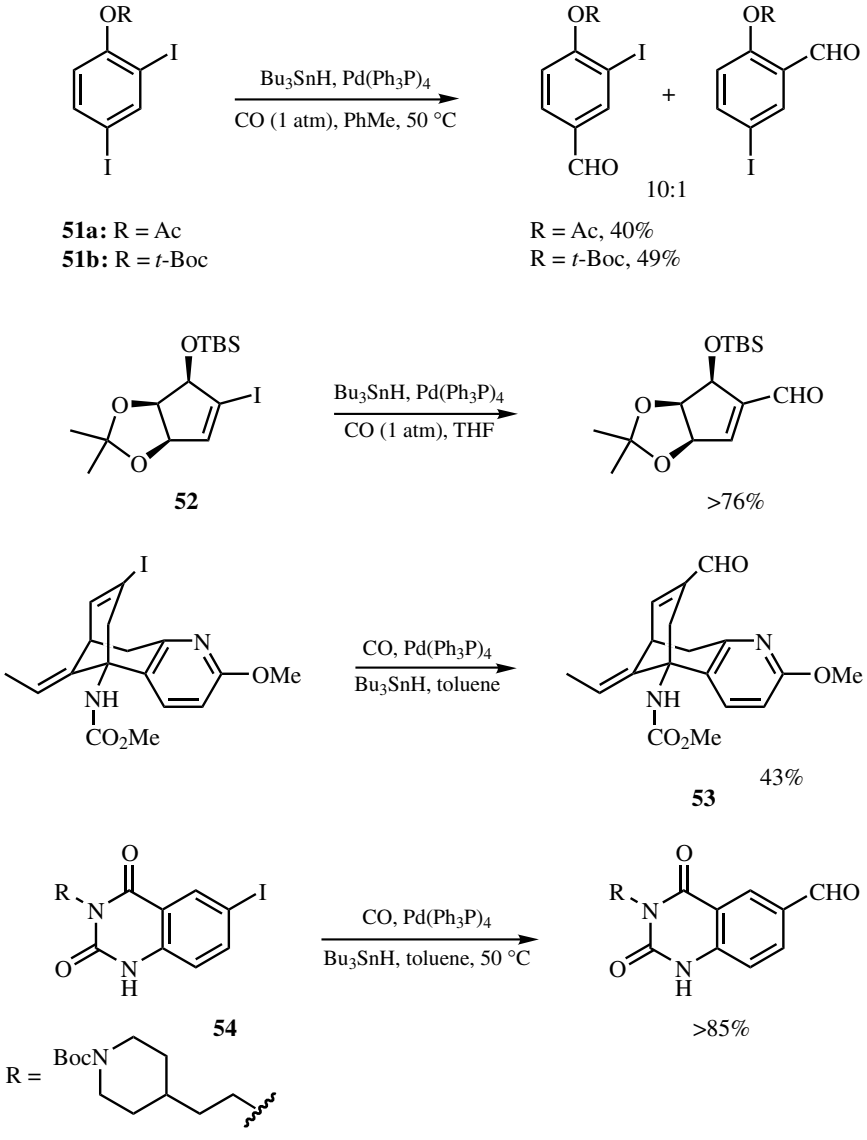


Scheme 38

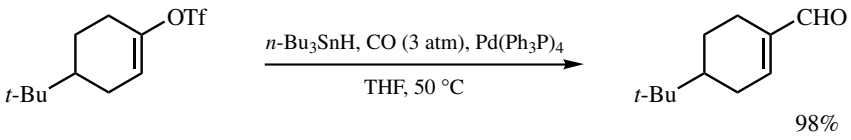
of **51** was selectively formylated to provide a 10:1 mixture of the benzaldehydes.[106],[107] The iodopentenol **52** was formylated as part of the synthesis of nojirimycins.[108] The aldehyde **53** was an intermediate in the synthesis of fluoro derivatives of huperzine A.[109] The quinazolinedione **54** was formylated in the preparation of glycoprotein IIb/IIIa inhibitors.[110] In order to prevent the competing reduction of the aryl (vinyl) palladium intermediate, the Bu_3SnH is often best added slowly to allow the acylpalladium intermediate to form.

The reaction was further extended to vinyl triflates (**Scheme 40**).[105]

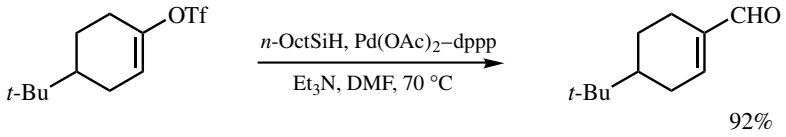
Similarly, aromatic and vinyl triflates undergo formylation with $Pd(OAc)_2$/dppp with trioctylsilane as the reducing agent (**Scheme 41**).[111]



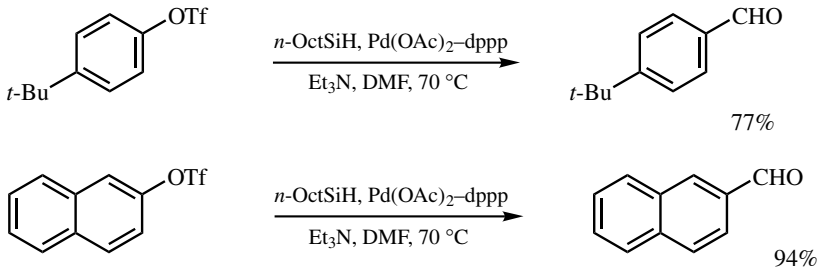
Scheme 39



Scheme 40



dppp = 1,1′-bis(diphenylphosphino)propane



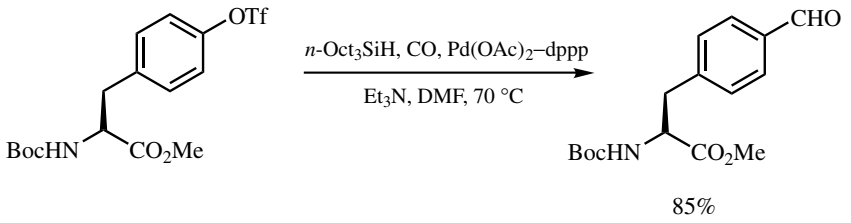
Scheme 41

This methodology was applied to synthesis of tyrosine analogs (**Scheme 42**).[112]

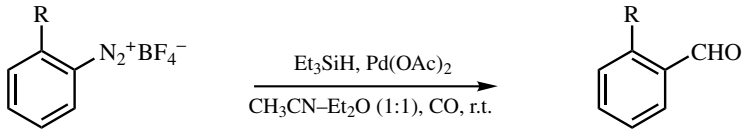
Arene diazonium salts will also undergo formylation using Et_3SiH (**Scheme 43**) or PMHS (**Scheme 44**) as the hydride source.[113]

Under conditions that convert formic acid electrochemically to formate, formic acid was a suitable hydride source for the formylation of aryl iodides using $PdCl_2(Ph_3P)_2$ as catalyst (**Scheme 45**).[114],[115]

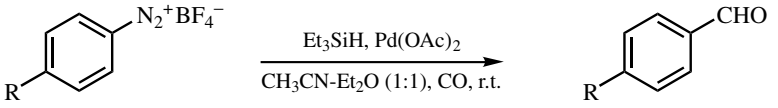
Using bimetallic catalysis aryl and alkenyl iodides were formylated using a mixed catalyst system of $PdCl_2(Ph_3P)_2$ and $Ru_3(CO)_{12}$ in a CO/H_2 atmosphere of 50 atm each (**Scheme 46**).[116] The palladium is thought to undergo oxidative addition and carbonylation to the acyl palladium species. The Ru reagent is converted to $[HRu_3(CO)_{11}]^-$ or $[HRu(CO)_4]^-$ by the hydrogen. The ruthenium hydride transfers the hydride to palladium



Scheme 42

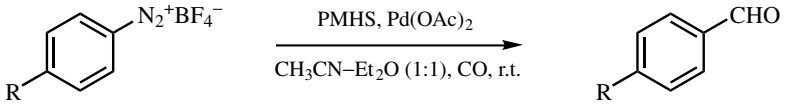


R = Me, 79%
R = Cl, 78%



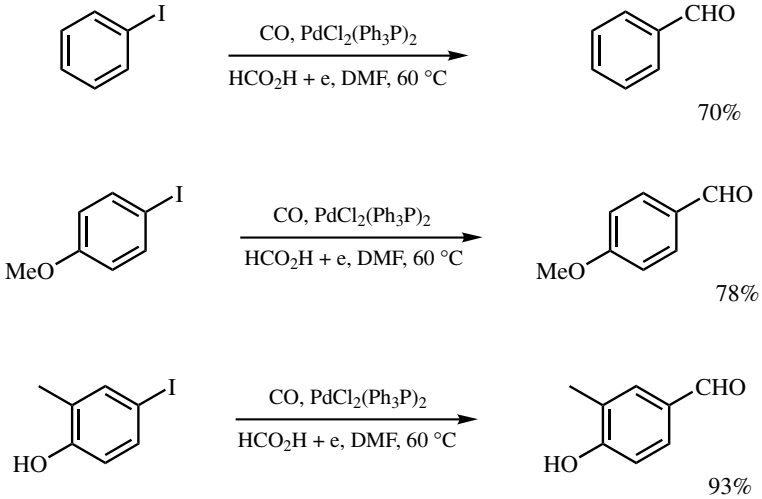
R = EtO_2C, 83%
R = MeCO, 72%

Scheme 43

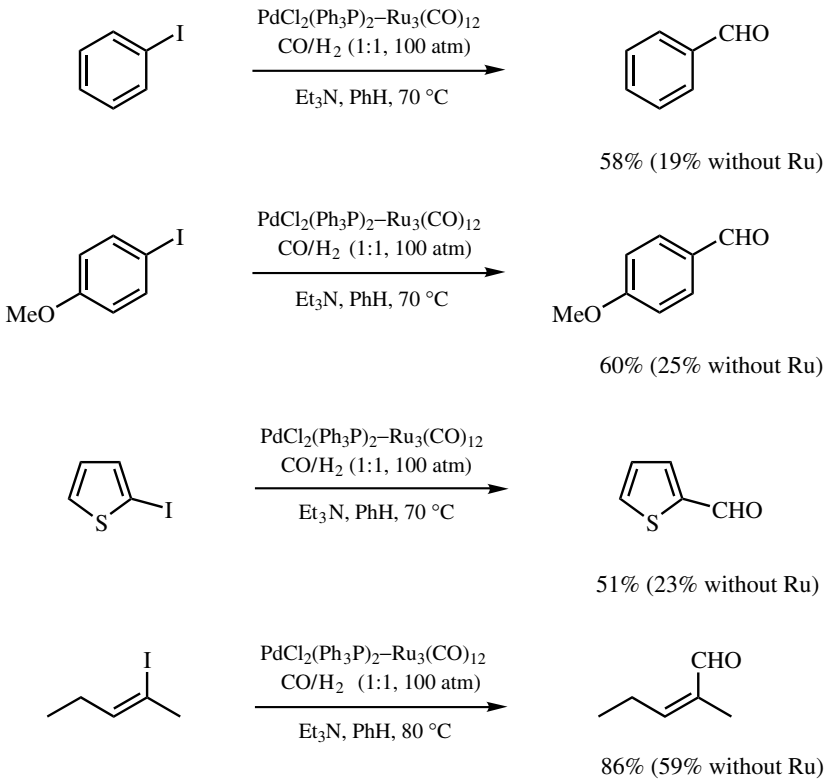


R = EtO_2C, 84%
R = Me, 60%

Scheme 44



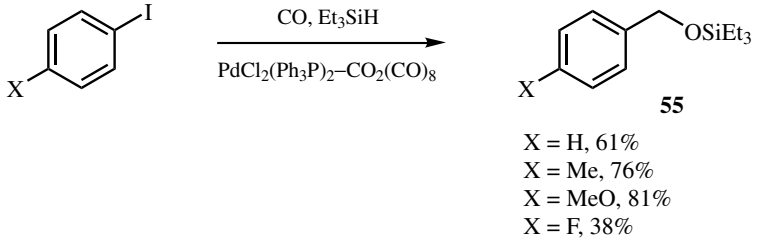
Scheme 45



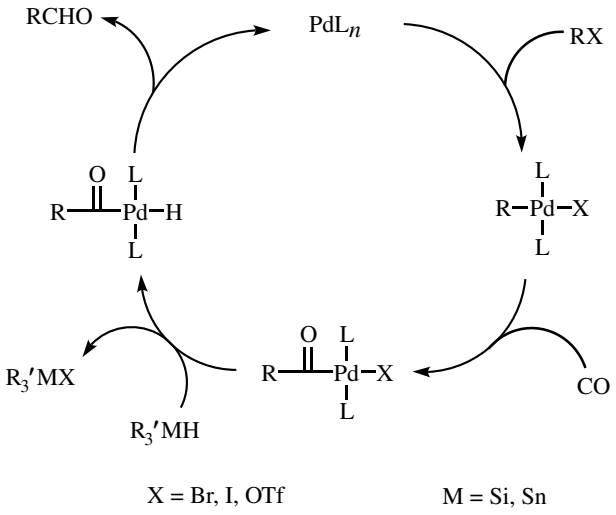
Scheme 46

followed by reductive elimination to the aldehyde. The same workers studied the similar Pd–Ru and Pd–Co system using triethylsilane as the hydride source.[117] In these cases the intermediate aldehyde is reduced further to the triethylsilylbenzyl alcohol **55** (**Scheme 47**).

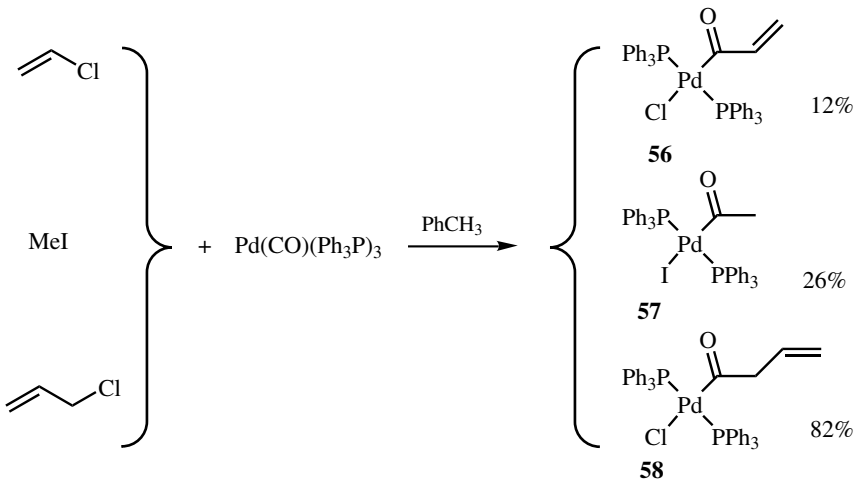
The mechanism (**Scheme 48**)[105] is expected to proceed through the acylpalladium species much as in the Rosenmund reduction. Indeed, the acyl complex **56** from oxidative addition of vinyl chloride with $Pd(CO)(Ph_3P)_3$ was isolated (**Scheme 49**).[118] The reaction of acid chlorides with the same catalyst provides aldehydes. However, aliphatic acid chlorides do not reduce effectively. The phosphine ligands present in the Heck acylpalladium intermediate are thought to be the cause, allowing decarbonylation and elimination to occur. Interestingly, the formylation will not occur with the Rosenmund catalyst.



Scheme 47



Scheme 48



Scheme 49

C.ii. Formylation of Alkyl Halides

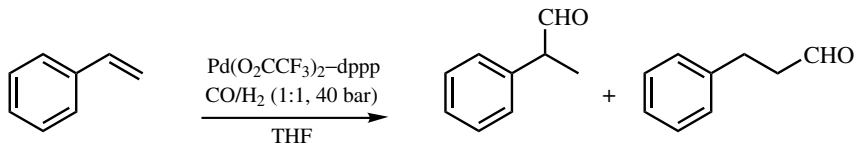
Alkyl halides do not formylate due to the propensity of the palladium species to undergo β-hydride elimination.[90] The conversion of organic halides containing a β-hydride to the methyl ketone was reported using tetramethyltin, but no mention of formylation has followed to the best of our knowledge.[119] Methyl alcohol was converted to acetaldehyde using a mixed catalyst system of CO and Pd.[120] In an earlier report the acylpalladium adducts **57** and **58** from the oxidative addition of methyl iodide and allyl iodide, respectively, with Pd(CO)(Ph$_3$P)$_3$ were prepared and isolated (**Scheme 49**).[118]

D. HYDROFORMYLATION

Pd-catalyzed hydroformylation of olefins or alkynes with carbon monoxide[90] is not nearly as successful as the formylation reactions described above. Limited examples have been reported in the literature. However, some progress has been made through modification of the reaction conditions and the use of cocatalysts.

D.i. Hydroformylation of Olefins

Pd-catalyzed hydroformylation of olefins has not been as successful or widely used as with Rh, Co, and Pt catalysts.[121]–[126] By modifying the reaction conditions and additives, palladium catalysis has become increasingly successful. Styrene was formylated to a mixture of 2- and 3-phenylpropanol (9:86) using $Pd(O_2CCF_3)_2$(dppp) with 97% conversion and 80% yield under 20 bar each of CO and H_2 (**Scheme 50**).[127] The selectivity of the reaction was very dependent on the ligand and anion. With other ligands greater amounts of ketone dimers and oligomers were obtained.



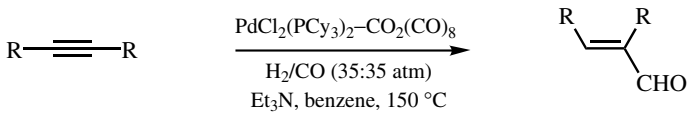
80% as 86:9 mixture

Scheme 50

Sodium cation was observed to lower the activation energy of the hydroformylation of propene over silica-supported Pd.[128],[129] The cation is thought to facilitate the CO insertion and to stabilize the acylpalladium species. Using the bidentate ligand $(Ph)_2P(CH_2)_3$–$P(Ph)_2$ and trifluoroacetic acid, as an anion source for the intermediate XPd–H species, effective hydroformylation of octenes to nonylaldehyde (72%) was achieved under 68 bar of CO/H_2.[130] Internal olefins were observed to isomerize to the terminal olefins, which reacted at a four to five times faster rate. Propene undergoes hydroformylation with palladium trimethylphosphinecarbonyl (TMPC) clusters in zeolite NaY at medium pressure.[126] A detailed study of the reaction and selectivity relative to the formation of heptanone isomers was reported. Pd/SiO_2 is a useful catalyst for the hydroformylation of ethylene to propionaldehyde. The effects of palladium dispersion on the catalytic activity were discussed.[131] The proper preparation of the catalyst afforded almost the same activities in the hydroformylation of ethene observed with Rh catalysts.[132] Lanthanides promote the Pd/SiO_2-catalyzed hydroformylation of propene.[133],[134] Modification of the Pd/SiO_2 with Rh increased the selectivity to propionaldehyde formation as compared to ethane generation and the overall reactivity of the hydroformylation.[135] Pd–Co complexes anchored to phosphinate SiO_2 hydroformylate olefins.[136],[137] The mechanism of action and the reasons for the synergistic effect are discussed. The bimetallic system composed of Pd/Nb_2O_5 converts ethene to the aldol side product 2-methyl-2-pentenal.[138] The promotion of the Pd–Fe bimetallic cluster-derived catalysts on hydroformylation of olefins was reported.[139]

D.ii. Hydroformylation of Alkynes

The hydroformylation of alkynes with palladium, in particular, has had limited success. A bimetallic catalyst system consisting of $PdCl_2(PCy_3)_2$–$CO_2(CO)_8$ was developed for the hydroformylation of internal acetylenes (**Scheme 51**).[140] Although the reaction would proceed with the catalyst $PdCl_2(PCy_3)_2$ alone, the catalytic activity was improved by adding $CO_2(CO)_8$ as a cocatalyst. All the olefins were obtained as 95% of the *E*-isomer except for R = Ph, which was obtained as 90% *E*. The role of the CO is not fully understood, but two scenarios were considered. The CO could aid in CO insertion but, more likely, facilitated the hydride transfer to the acylpalladium intermediate.



R	Yield (%) GLC (Isolated)
n-C_3H_7	95 (81)
C_2H_5	88 (47)
n-C_4H_9	90 (70)
n-C_5H_{11}	95 (89)
Ph	53

Scheme 51

E. SUMMARY

The hydrogenation of acylpalladium species is a very effective means for preparing the aldehyde functionality. The reduction of a carboxylic acid derivative is very reliable and high yielding, whether a modified-Rosenmund procedure or the Fukuyama thioester reduction is used. Most notable is the tolerance of these reactions for other functionalities and chiral centers.

The formylation reaction is a mixed success. While the coupling of aryl, vinyl, or allyl halides (triflates) is effective, quite often the conditions are harsh. The formylation of alkyl halides or hydroformylation olefins and acetylenes with palladium is not the method of choice for preparing the corresponding aldehydes.

However, in reviewing the literature of the last two decades the application of Pd-catalyzed formylations to the more difficult substrates is showing promise. By finding the appropriate ligand or hydride source the difficult step(s) in the reaction pathway can be overcome. Bimetallic catalysis exploits the synergistic effect of metals. For example, where palladium works well in the oxidative addition or complexation to a double bond, the added metal can aid in transfer of the CO or hydride. It is certain that the deficiencies of the Pd-catalyzed hydroformylation will be overcome in time.

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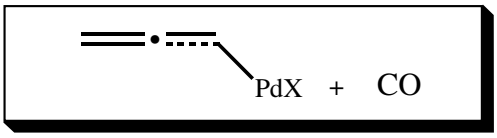

VI.3 Migratory Insertion Reactions of Allyl, Propargyl, and Allenylpalladium Derivatives Involving Carbon Monoxide and Related Derivatives

TADAKATSU MANDAI

A . INTRODUCTION

Palladium-catalyzed carbonylation of allylic and propargylic compounds offers many synthetically useful transformations. The reaction of an allylic compound with Pd(0) gives a π-allylpalladium complex, which is converted to an acylpalladium complex via coordination of carbon monoxide and ensuing migratory insertion. In a similar fashion, a propargylic compound affords an allenylacylpalladium complex. These acylpalladium complexes easily undergo attack of various nucleophiles, insertion of olefins, or transmetallation with organometallic compounds to afford synthetically valuable intermediates.

B. ALLYLIC COMPOUNDS

Allylic chlorides readily undergo Pd-catalyzed carbonylation (**Scheme 1**). Carbonylation of allyl chloride proceeds smoothly in THF to give 4-chlorobutyl ester in good yield.[1]–[3] Smooth carbonylation of allyl chloride proceeds under atmospheric pressure at room temperature in two-phase aqueous sodium hydroxide–benzene medium using a water-soluble ligand, giving 3-butenoic acid in a high yield.[4]–[5] β, γ-Unsaturated esters are efficiently provided by the carbonylation of allylic halides using EtONa and dppe.[6] Allylic chlorides containing an additional alkene moiety in a suitable position can induce cyclic acylmetallation followed by carbonylative esterification to produce α-methoxycarbonylmethyl cyclopentenones.[7] 3,7-Octadienoate is obtained by the carbonylation of allyl chloride and butadiene.[8]

Among the various allylic compounds, allylic carbonates are most reactive toward Pd(0) species. The reaction of an allylic carbonate with Pd(0) initially provides a π-allylpalladium carbonate complex, which immediately loses carbon dioxide to form a π-allylpalladium ethoxide complex irreversibly. Thus, their carbonylation proceeds under mild conditions, namely, at 50 °C under 1–20 atm of carbon monoxide (**Scheme 2**).[9]–[13]

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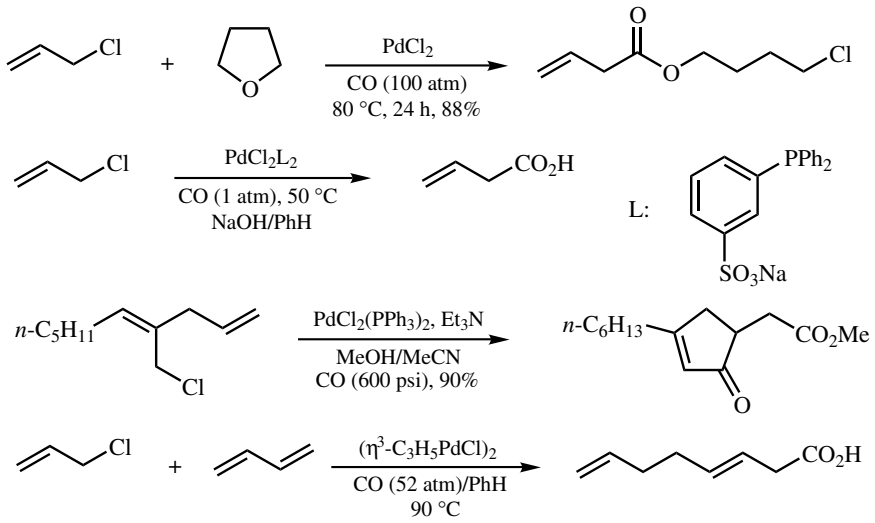
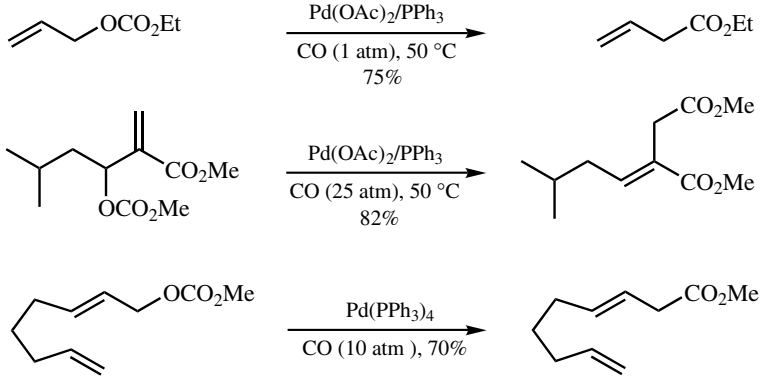


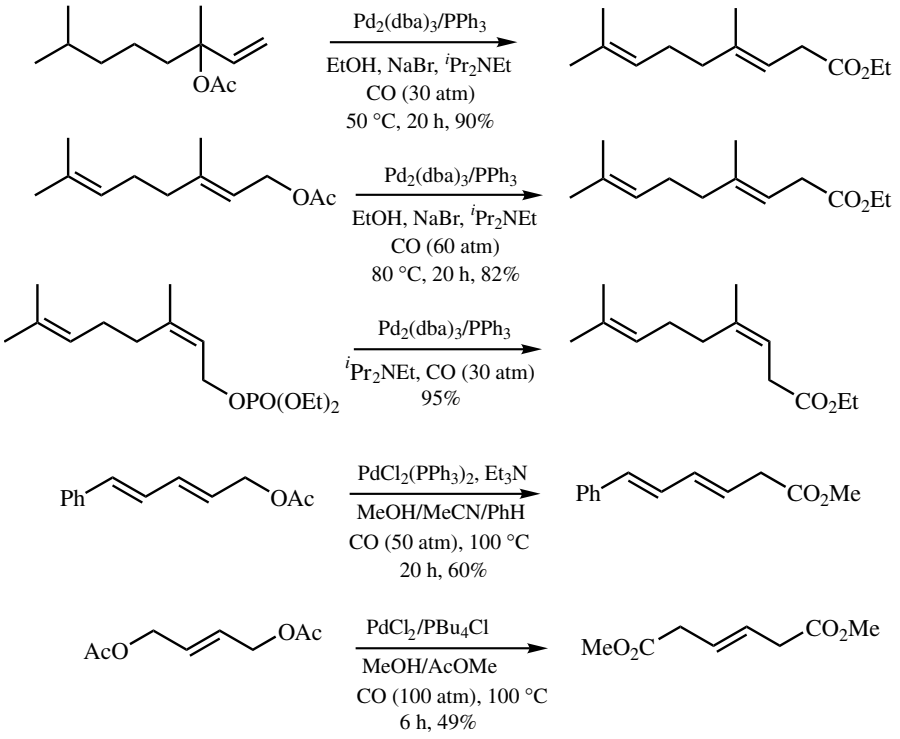
Scheme 1



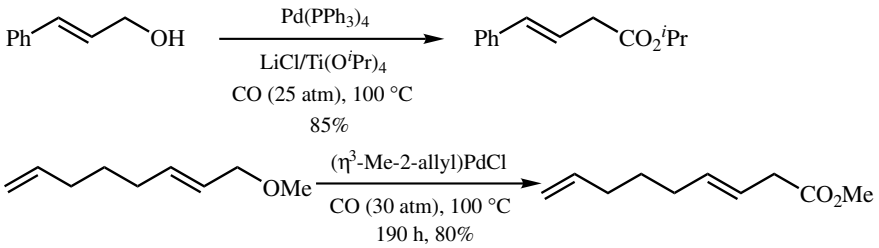
Scheme 2

Carbonylation of allylic acetates themselves are rather difficult in general because π-allylpalladium acetates, readily formed by oxidative addition of allylic acetates to Pd(0), undergo back-reaction to give the starting allyl acetates rather than insertion of carbon monoxide to give β,γ-unsaturated esters.[14],[15] However, facile carbonylation of linalyl acetate takes place in the presence of a catalytic amount of NaBr, in which more reactive π-allylpalladium bromide may be formed *in situ* by the ligand exchange reaction of π-allylpalladium acetate with bromide ion (**Scheme 3**).[16],[17] Also, diethyl nery phosphate is smoothly carbonylated in the presence of *i* -Pr_2NEt as a less nucleophilic amine to give an ester maintaining the geometric integrity of the double bond.[16],[17] However, the carbonylation of 5-phenyl-2,4-pentadienyl acetate proceeds in the presence of triethylamine instead of NaBr at 100 °C to yield an ester.[18],[19] Dicarbonylation of 1,4-diacetoxy-2-butene proceeds by the aid of tetrabutylphosphonium chloride as a ligand to give 3-hexenedioate.[20]

Carbonylation of allylic alcohols requires severe conditions in general.[2] The carbonylation of allylic alcohols proceeds efficiently in the presence of LiCl and Ti(O*i*-Pr)$_4$ (**Scheme 4**).[21] In this reaction an allyl titanate, produced from an allylic alcohol and Ti(O*i*-Pr)$_4$, reacts with Pd(0) species to form a π-allylpalladium complex. The titanium alkoxide is replaced by the ligand exchange with the chloride ion to give a π-allyl palladium complex, which undergoes facile carbonylation. Allylic methyl ethers can be carbonylated under severe conditions to give esters.[22]–[25]



Scheme 3

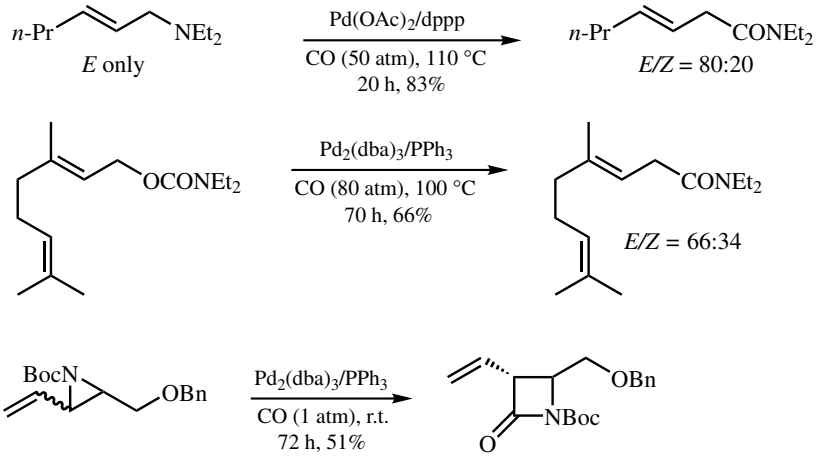


Scheme 4

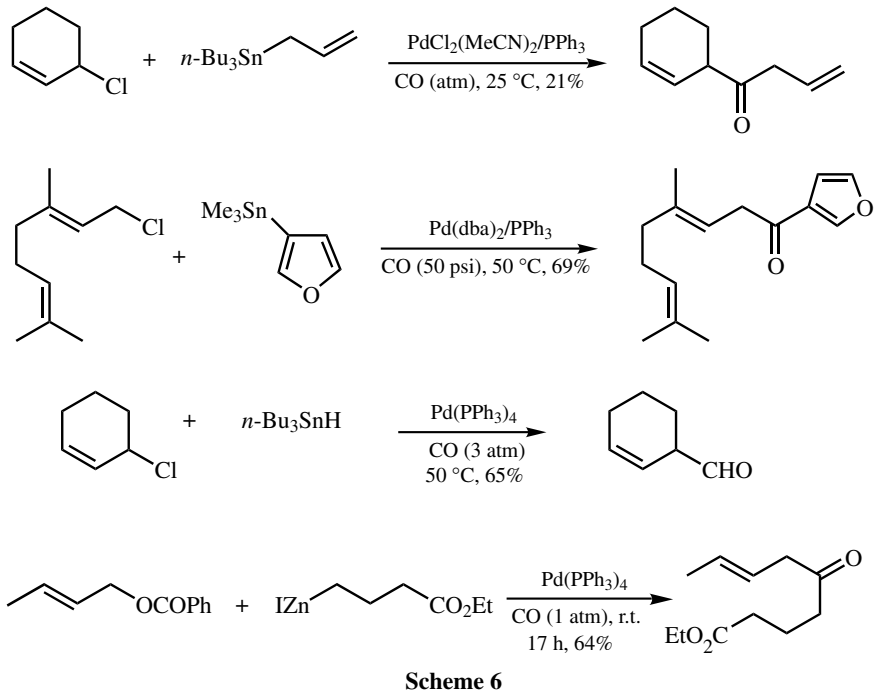
The carbonylation of allylic amines proceeds under severe reaction conditions to give β,γ-unsaturated amides by using dppp as a ligand (**Scheme 5**).[26],[27] Decarboxylation–carbonylation of allyl diethylcarbamates under severe conditions affords β,

γ-unsaturated amides.[28] 3-Vinylaziridines are converted into the α-vinyl-β-lactams under mild conditions.[29]

An acylpalladium intermediate undergoes facile transmetallation with various organometallic reagents (**Scheme 6**). Various ketones are provided by the carbonylation of allylic chlorides in the presence of allyl- or vinyltin compounds.[30]–[33] Aryl, benzyl, vinyl, and allylic halides are converted directly to aldehydes by the carbonylation in the presence of n-Bu_3SnH.[34],[35] Zincioesters are easily transmetallated with acylpalladium complexes to give ketones possessing an ester functionality.[36]



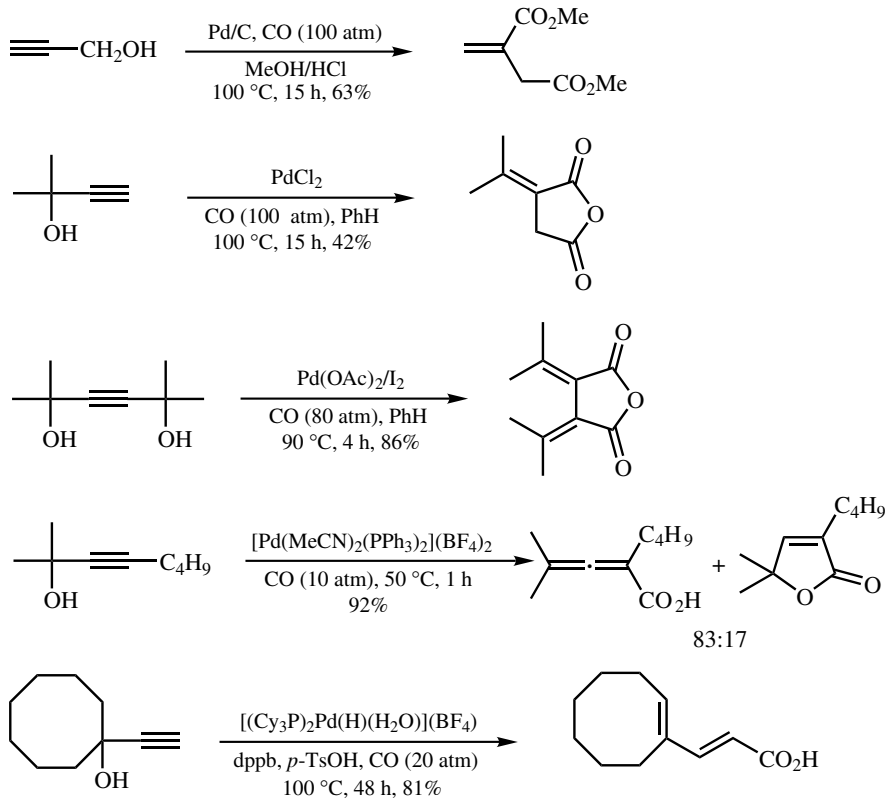
Scheme 5



Scheme 6

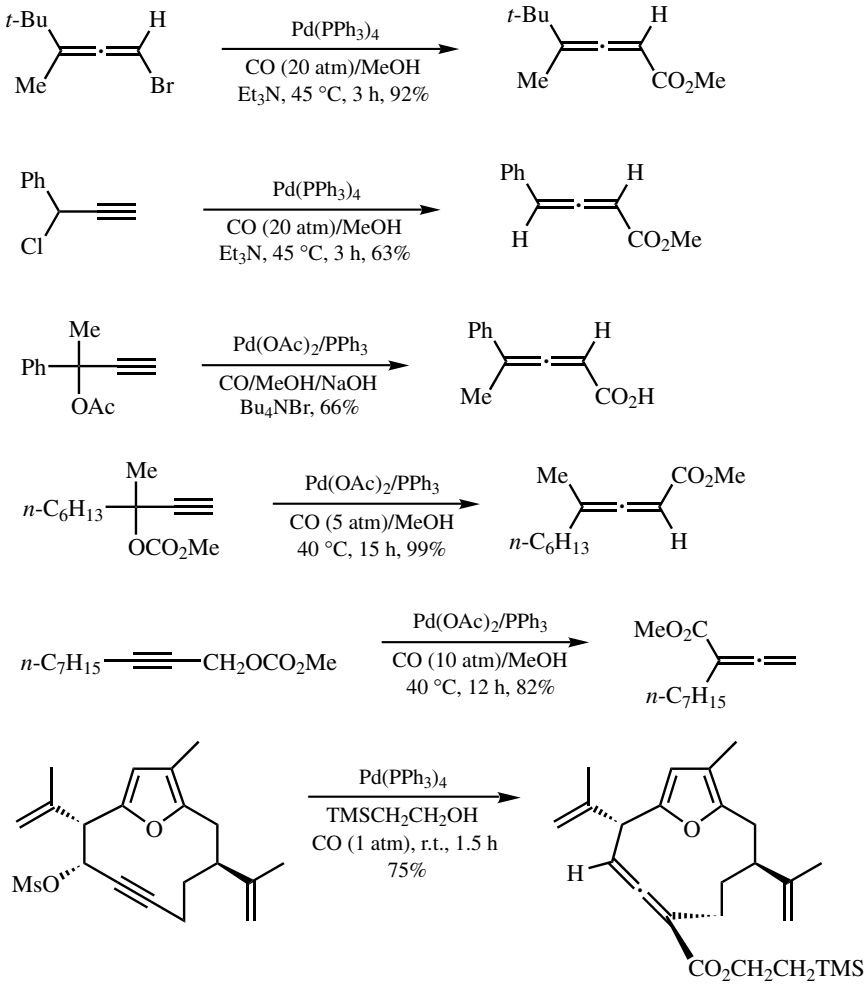
C. PROPARGYLIC COMPOUNDS

Carbonylation of propargylic alcohols proceeds under harsh conditions (**Scheme 7**). The carbonylation of propargyl alcohol in the presence of HCl affords itaconate as the main product.[37],[38] One possible pathway of the reaction can be proposed as follows: oxidative addition of HCl to Pd(0) species, generated by the reduction of $PdCl_2$ with CO, produces HPdCl, which would further be transformed into HPdCOCl or HPdCOOMe species. On the other hand, the reaction of propargyl alcohol and HCl produces propargyl chloride, which undergoes the facile carbonylation via an allenylpalladium complex to give methyl 2,3-butadienoate. Insertion of methyl 2,3-butadienoate into the HPdX (X: Cl, COCl, or COOMe) gives rise to $CH_2{=}C(PdX)CH_2CO_2Me$ leading to itaconate. In sharp contrast, the carbonylation of propargylic alcohols in benzene instead of methanol provides derivatives of succinic anhydride.[37]–[39] The carbonylation initially generates a 2,3-dienoic acid, which inserts into the HPdX (X: Cl, or COCl) to form $Me_2C{=}C(PdX)CH_2CO_2H$. Then, the intramolecular nucleophilic attack of the carboxylate on the acylpalladium complex generates the derivatives of succinic anhydride. Fulgides (derivatives of dimethylenesuccinic anhydride) have been synthesized by the carbonylation of 2-butyne-1,4-diols using a catalytic system of $Pd(OAc)_2/I_2$. 2,3-Dienoic acids or 2,4-dienoic acids are provided by the cationic Pd(II)-catalyzed carbonylation of propargylic alcohols.[40],[41]



Scheme 7

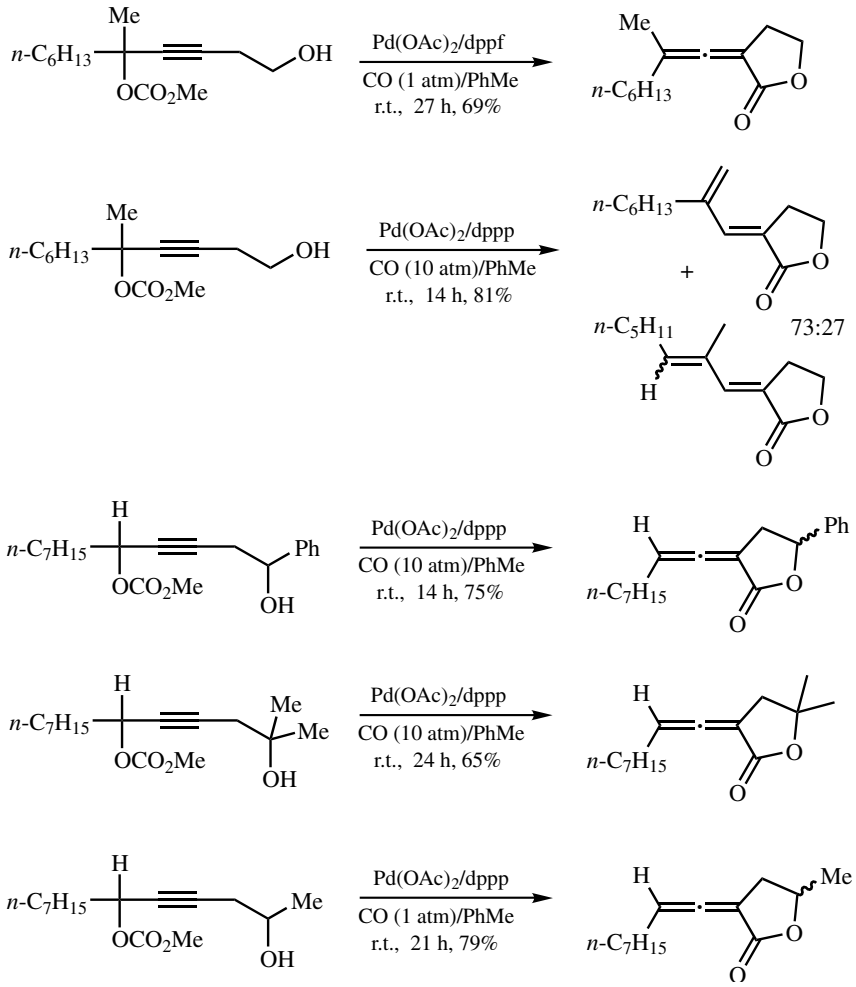
Carbonylation of allenyl and propargylic halides proceeds via allenyl and/or propargylpalladium complexes to produce 2,3-dienoates (**Scheme 8**).[42] 2,3-Dienoic acids are provided by the carbonylation of propargylic acetates in a two-phase system in the presence or absence of Bu_4NBr.[43] Propargylic carbonates are most reactive among the propargylic substrates and the carbonylation proceeds under mild and neutral conditions.[44],[45] Complete chirality transfer is observed in the carbonylation of a propargylic mesylate.[46],[47]



Scheme 8

A facile γ-lactone formation is realized by the carbonylation of 5-hydroxy-2-alkynyl methyl carbonates at room temperature (r.t.) under 1–10 atm of CO (**Scheme 9**).[48] The primary products of the carbonylation are α-vinylidene-γ-lactones, but partial or complete isomerization of the α-vinylidene group to the conjugated 1,3-diene takes place depending on the reaction conditions.

Besides alcohols, an acylpalladium intermediate can be trapped by amines. The α-vinylidene-β-lactams are prepared by the carbonylation of propargylic carbonates



Scheme 9

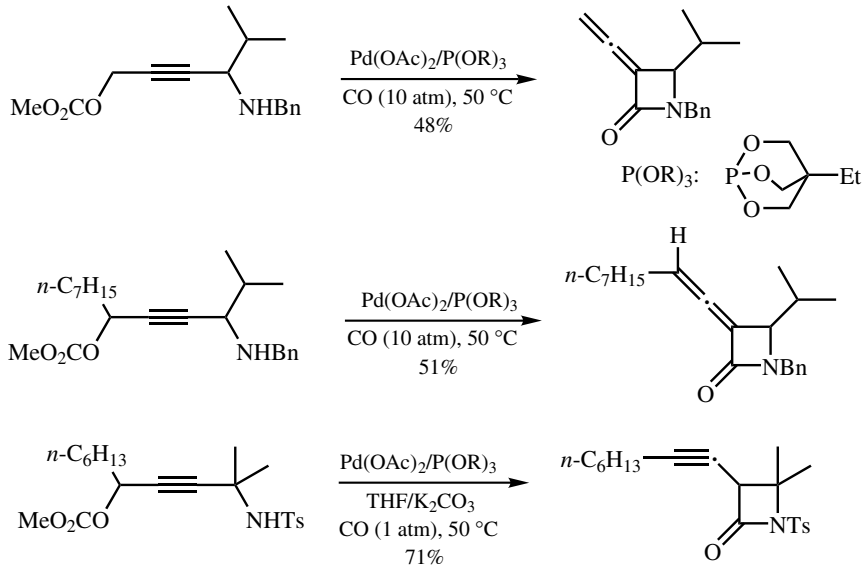
possessing adjacent amino groups (**Scheme 10**).[49] The ligand plays a crucial role, the cyclic phosphite being most effective for the facile carbonylation. In cases where the amino protection is a tosyl group, the reaction proceeds in the presence of K_2CO_3 to yield α-alkynyl-β-lactams via the isomerization of the vinylidene group to the less strained alkyne.

An acylpalladium intermediate can also be trapped by soft carbon nucleophiles (**Scheme 11**).[50] The carbonylation of propargylic carbonates proceeds in the presence of enolates of malonate derivatives to give allenyl ketones.

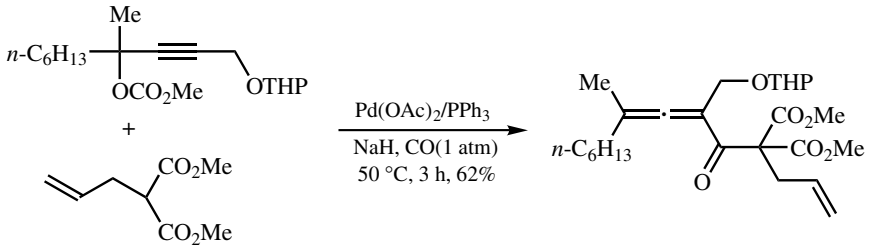
Intermediary α-vinyl allenic esters, produced by the carbonylation of 4-en-2-ynyl methylcarbonates, are reactive enough to undergo an intramolecular Diels–Alder reaction with a suitably arranged double bond (**Scheme 12**).

The intramolecular Diels–Alder reaction proceeds under 1 atm of CO at 50 °C to give cyclic compounds (5-6-*n* systems) in high yields (**Scheme 13**).[51]

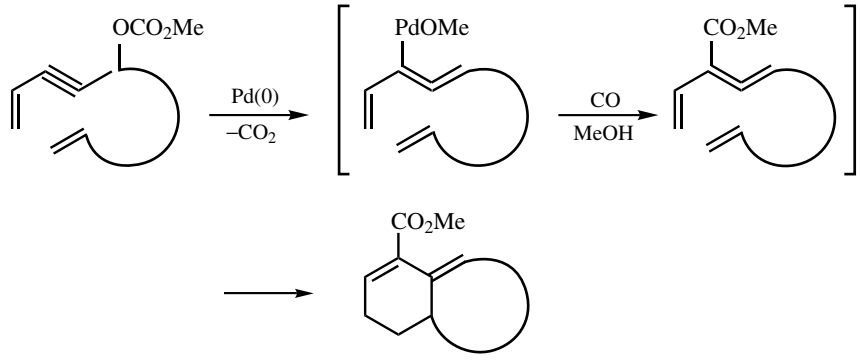
Interestingly, the carbonylation of 4-en-2-ynyl methyl carbonates provides cross-conjugated 4-oxo-5-alkylidene-2-cyclopentene-carboxylates in cases where no relevant



Scheme 10

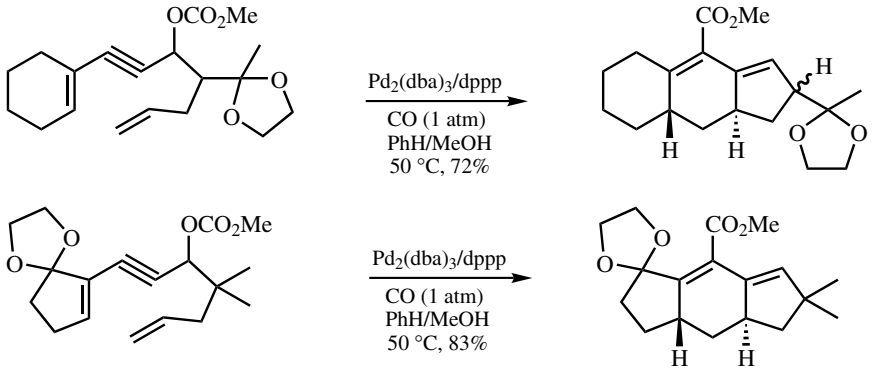


Scheme 11

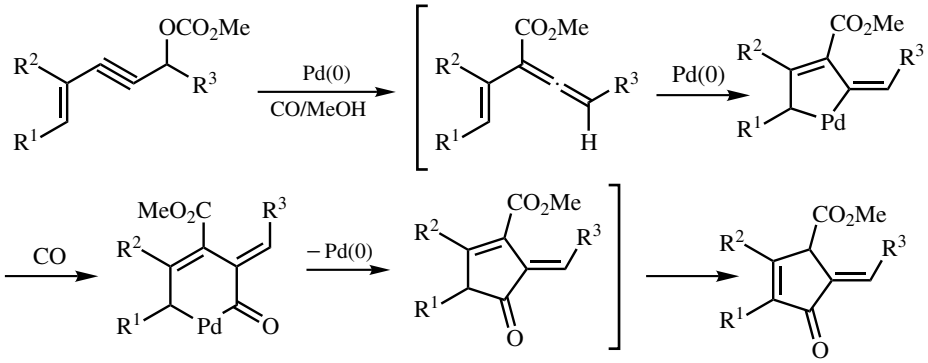


Scheme 12

double bond exists in the molecule (**Scheme 14**). Intermediary α-vinyl allenic esters would undergo nucleophilic attack of Pd(0) species to form five-membered palladacycles, which lead to the cyclopentenone derivatives through migratory insertion of CO, reductive elimination of Pd(0), and the ensuing olefin isomerization. The carbonylation



Scheme 13



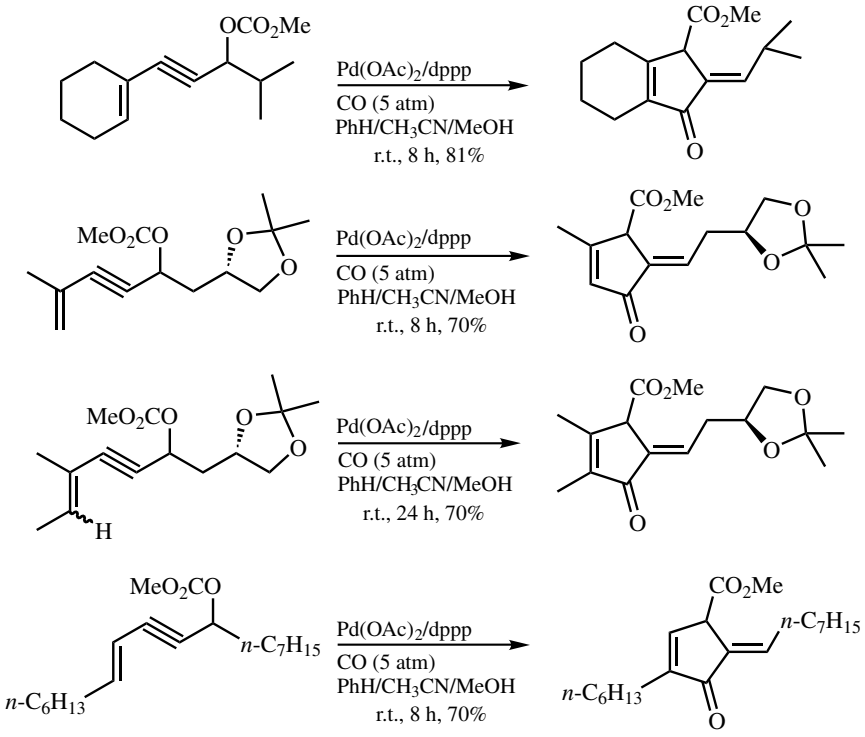
Scheme 14

can be executed in a single pot at room temperature under an atmosphere of CO (≤ 5 atm) (**Scheme 15**).[52]

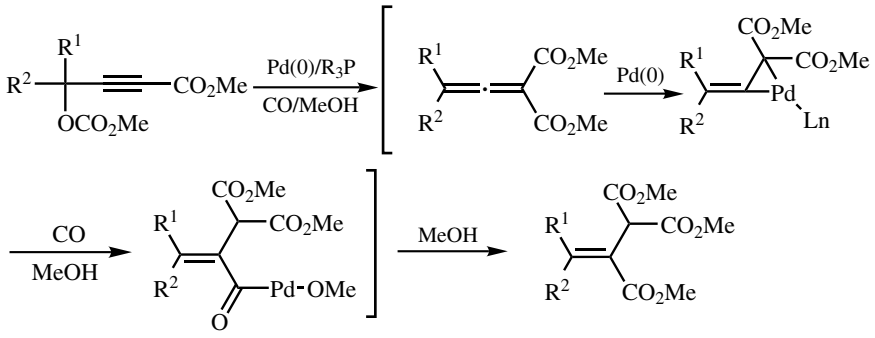
1-Substituted-3-methoxycarbonyl-2-propynyl methyl carbonates are smoothly carbonylated to give triesters. The sequence of reactions is postulated in **Scheme 16**.[53] That is, an allenyl geminal diester generated by the first carbonylation process is reactive enough for the Pd(0) species to nucleophilically attack the sp carbon, leading to a three-membered palladacycle even at room temperature. An alkylidenepalladacycle thus formed should be reactive again enough for the second CO insertion to give rise to an acylpalladium complex, from which a triester is released by methanolysis. The reaction proceeds under 1–5 atm of CO at room temperature, giving triesters in good yields. Secondary carbonates are less reactive than tertiary ones, whereas the reaction is much accelerated by increasing pressure of CO (5 atm) (**Scheme 17**).

The same intermediary allenyl geminal diester would be extremely susceptible to an intramolecular ene process so that the second carbonylation process mentioned above is virtually interrupted (**Scheme 18**).[54]

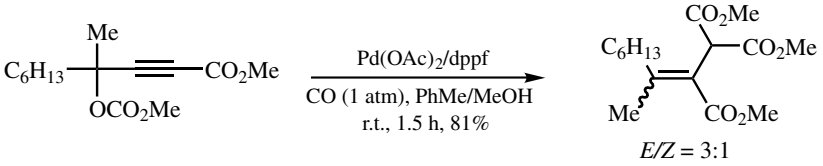
The substrates bearing an isopropenyl terminus undergo an intramolecular ene process and ensuing thermodynamically controlled olefinic isomerization from 1,4- to 1,3-diene to afford 1,3-cyclohexadiene systems. On the other hand, cyclopentene derivatives are provided for the substrates bearing 2-methyl-1-propenyl terminus, whereas no olefinic migration is observed (**Scheme 19**).



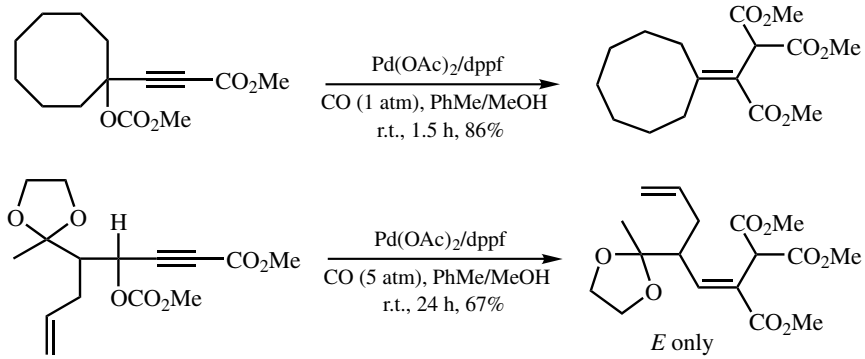
Scheme 15



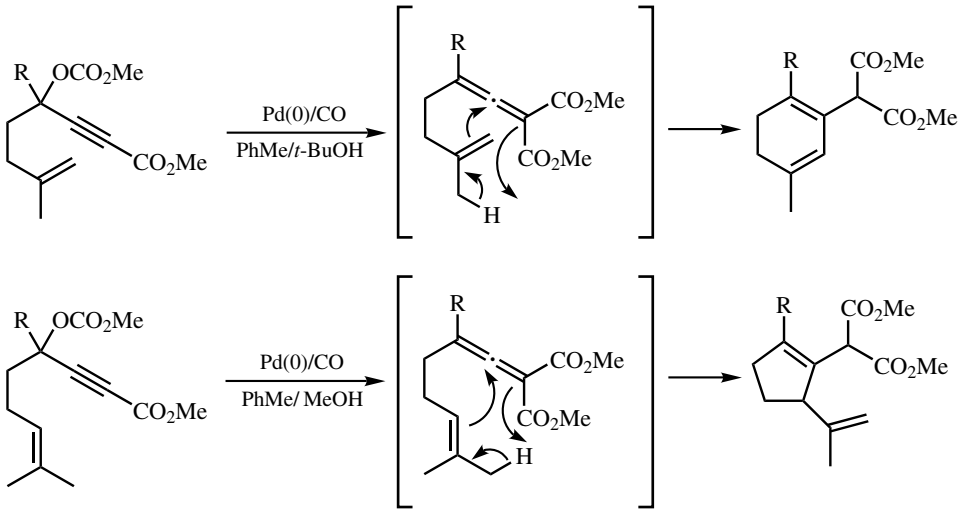
Scheme 16



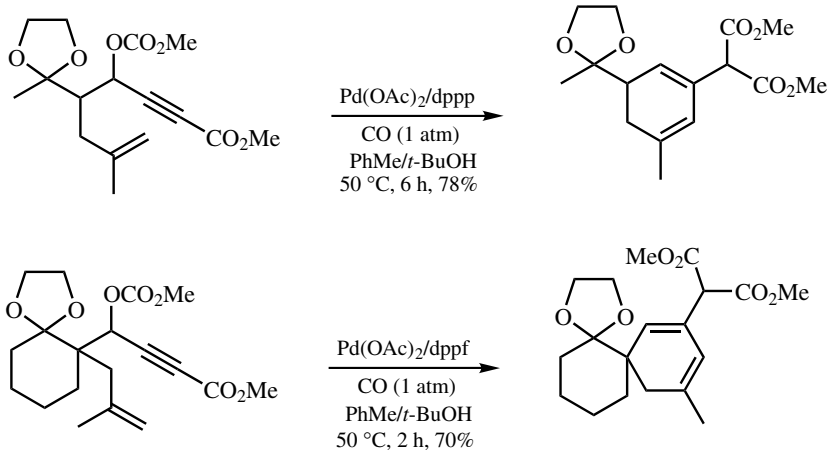
Scheme 17



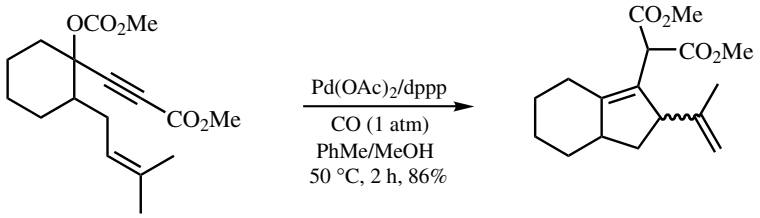
Scheme 17 (*Continued*)



Scheme 18



Scheme 19 (*Continued*)



Scheme 19

D. SUMMARY

Palladium-catalyzed carbonylation of allylic and propargylic compounds offers a potential tool of one-carbon homologation. Particularly, pd-catalyzed carbonylation of propargylic compounds further provides synthetically valuable transformations because of the high reactivity of the intermediary allenyl esters.

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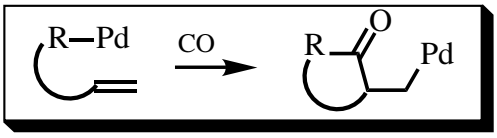

VI.4 Acylpalladation and Related Addition Reactions

VI.4.1 Intramolecular Acylpalladation

VI.4.1.1 Intramolecular Acylpalladation Reactions with Alkenes, Alkynes, and Related Unsaturated Compounds

CHRISTOPHE COPÉRET and EI-ICHI NEGISHI

A. INTRODUCTION

Palladium-catalyzed carbonylative reactions normally begin with *migratory insertion* of CO to produce acylpalladium derivatives. As amply demonstrated in **Sects. VI.2** and **VI.3**, the acylpalladium derivatives thus generated are most commonly converted to organic products via either *reductive elimination* or *nucleophilic attack* at the carbonyl carbon atom (**Scheme 1**). It should be recognized that distinction between reductive elimination and nucleophilic ligand attack is very subtle and that it may well be a mechanistic and/or semantic issue, which has remained vague in most cases. Accordingly, no serious attempt is made to sharply distinguish the two processes in this section. In any event, three of the four general patterns available for the formation of carbon–carbon and carbon–heteroatom bonds via organopalladiums, that is, reductive elimination (**Pattern 14**), migratory insertion (**Pattern 18**), nucleophilic or electrophilic attack on ligands (**Pattern 20**), and carbopalladation (**Pattern 9**) in **Table 3** of **Sect. I.2** appear in **Scheme 1**. On the other hand, carbopalladation or, more specifically acylpalladation in the present discussion, which is conspicuously absent in **Scheme 1**, had remained much less well known until about 1980.

Two concurrent but independent developments mostly since 1980 have made acylpalladation a widely observable carbon–carbon bond-forming process of considerable synthetic significance. One is the Pd-catalyzed alternating copolymerization of alkenes and CO, which is thought to involve migratory CO insertion and acylpalladation of alkenes. This reaction was discovered in 1965 by Tsuji and Hosaka[1] using norbornadiene as an alkene (**Scheme 2**). However, it was not until the 1980s that extensive investigations

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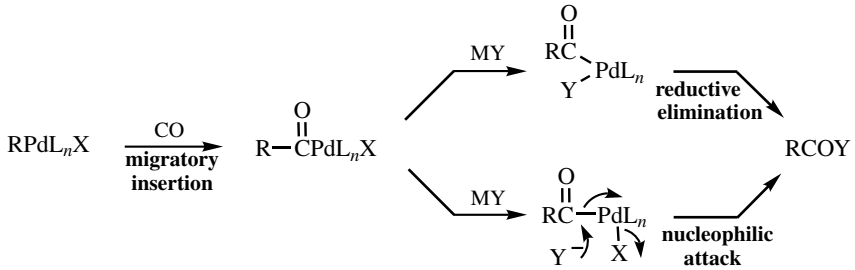
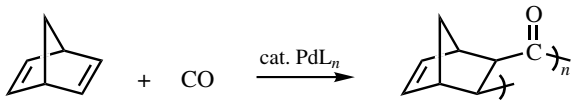


R = C group. X = halogen or a related leaving group.
M = metal or H. Y = nucleophilic group cotaining C, H, N, O, etc.

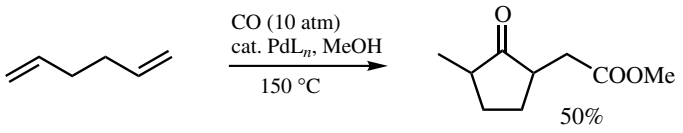
Scheme 1



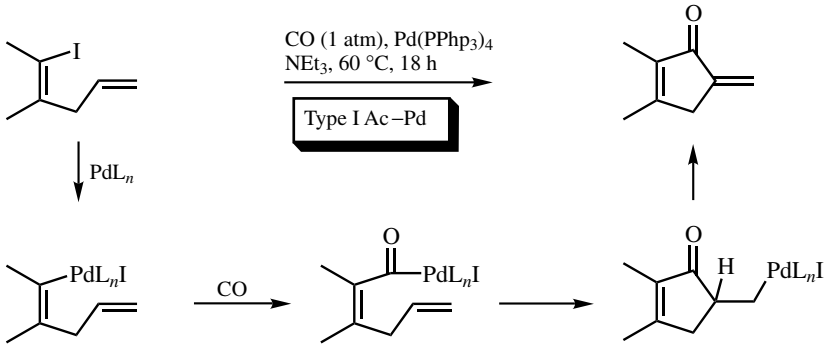
Scheme 2

using ethylene and monosubstituted alkenes made it an organometallic process not only of basic scientific interest but also of considerable industrial significance, as detailed in **Sect. VI.4.2** and references cited therein.[2],[3]

The other is intramolecular cyclic acylpalladation discussed in this section. Cyclic acylpalladation of dienes, such as 1,5-hexadiene, was briefly investigated by Brewis and Hughes[4],[5] in the mid-1960s (**Scheme 3**). However, more extensive and systematic studies with ω-haloalkenes and related compounds were triggered by the discovery of a cyclization process shown in **Scheme 4** reported by Negishi and Miller[6] in 1983. The



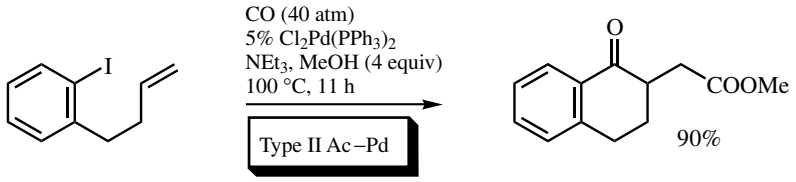
Scheme 3



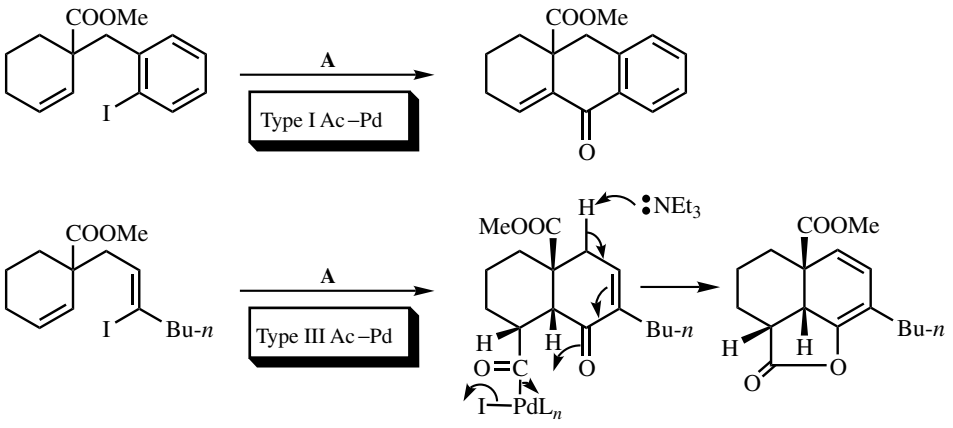
Scheme 4

experimental results are not only consistent with the mechanism involving acylpalladation but also most readily explained by this mechanism (**Scheme 4**). Although this particular reaction shown in **Scheme 4** was only stoichiometric in Pd, later studies have shown that, in most of the other cases, the reaction termed the Type I Ac–Pd process is catalytic, as discussed later. In attempts to devise alternate catalytic acylpalladation processes, a cyclic acylpalladation–carbonylative esterification tandem process termed the Type II Ac–Pd process was discovered[7] (**Scheme 5**). During the development of the Type I Ac–Pd reaction, it was discovered that γ-oxoacylpalladiums generated via an acylpalladation–CO insertion tandem process can undergo trapping of acylpalladium species by internal enolates.[8],[9] As detailed in **Sect. VI.2.3**, both intramolecular and intermolecular trapping of acylpalladium species by *C*- and/or *O*-enolates has turned out to be a generally observable process.[10],[11] Moreover, it has been shown that trapping of acylpalladiums with internal enolates can play a significant role in terminating cyclic acylpalladation processes[12],[13] (**Scheme 6**). The overall tandem sequence termed the Type III Ac–Pd process can be catalytic in Pd. It not only holds considerable promise as a synthetically useful reaction, as detailed later, but has also been shown to serve as a process for terminating the alternating copolymerization reaction of alkenes with CO[14] (**Scheme 7**).

In all of the three cyclic acylpalladation reactions, that is, Types I–III Ac–Pd processes, polymeric acylpalladation discussed in **Sect. VI.4.2** and direct noncarbonylative carbopalladation discussed in **Sect. IV.3.3** can be not only serious side reactions but even dominant processes depending on the reaction conditions. The polymeric acylpalladation process

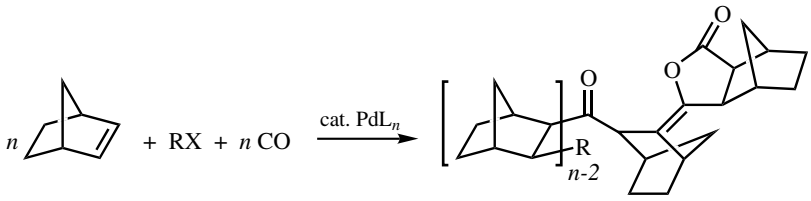


Scheme 5



A = CO (40 atm), 5 mol % $Pd(PPh_3)_4$, NEt_3 (1.5 equiv), 100 °C

Scheme 6



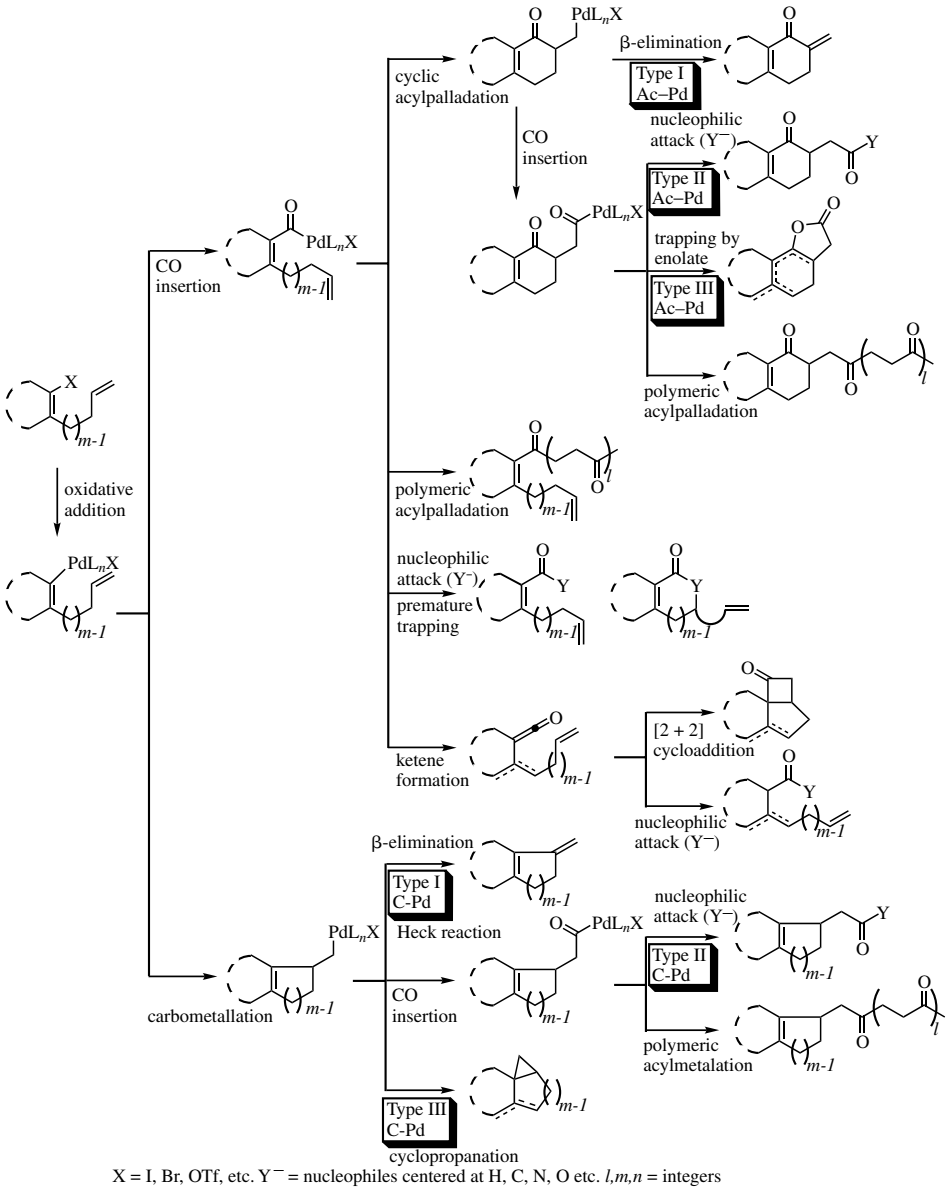
Scheme 7

can be suppressed through the use of external and internal nucleophiles. However, premature trapping of acylpalladium species by nucleophiles can then be a serious side reaction, which must be kept at a minimum. In cases where acylpalladium intermediates contain acidic H atoms in α or γ to the COPd group, ketenes may be generated,[13] and they may undergo some reactions that are characteristic of ketenes, such as [2 + 2] cycloaddition and nucleophilic attack on ketenes, as discussed in **Sect. VI.5.2**. All of these possible reaction paths are summarized in **Scheme 8**. It is important to note that despite all these various possibilities, suitable reaction conditions permitting selective transformations of choice can be found in many cases. In this section, attention is focused on the three cyclic acylpalladation processes (Types I–III Ac–Pd processes).

In **Scheme 8**, the first organopalladium intermediate is generated via oxidative addition of the starting organic halide or a related electrophile. However, organopalladium species may also be generated by roughly ten or so different methods discussed in **Sects. I.2** and **II.3**. Particularly important in connection with the current discussion are hydrometallation, carbometallation, as well as halo- and related heterometallation reactions. Although not fully established, the prototypical example of a Type II cyclic Ac–Pd process shown in **Scheme 3** presumably is initiated by hydropalladation of the starting 1,5-hexadiene.[4] Noncarbonylative carbopalladation can not only provide a general route to the required organopalladium intermediates but substantially expands the scope of the cyclization methodology based on intramolecular cyclic acylpalladation. Both the "living" nature of carbopalladation including acylpalladation and the ready reversibility of CO migratory insertion permit a large number of possibilities for cascading these processes (also called domino processes), as detailed in **Sect. C**.

The "living" nature of carbopalladation or acylpalladation permitting various types of organopalladium interconversions, however, mandates that the products of carbopalladation or acylpalladation must somehow be decomposed or trapped under the same catalytic conditions so as not only to produce Pd-free organic products but also to recycle Pd complexes as catalysts. Here again, ten or so fundamentally different methods for cleaving C—Pd bonds discussed in **Sect. I.2** are available. In reality, however, dehydropalladation as in the Heck reaction (**Sect. IV.2**) leading to the Type I Ac–Pd process and trapping (or decomposition) of acylpalladium intermediates with various nucleophiles including those containing O, S, N, C, and H nucleophilic centers either intermolecularly or intramolecularly (Type II Ac–Pd) have mostly been used. A significant variation of the Type II Ac–Pd process is trapping of acylpalladium intermediates by internally generated enolates leading to Type III Ac–Pd processes.

With the general discussion presented above in mind, various specific examples of Types I–III Ac–Pd processes as well as other related processes will be discussed in the following sections.



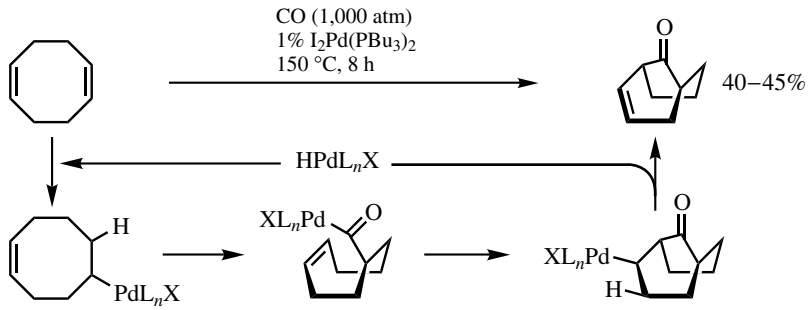
X = I, Br, OTf, etc. Y$^-$ = nucleophiles centered at H, C, N, O etc. *l,m,n* = integers

Scheme 8

B. SINGLE-STAGE CYCLIC ACYLPALLADATION PROCESSES

B.i. Type I Ac–Pd Process

Brewis and Hughes[5] reported in 1966 what appears to be the first example of a Type I Ac–Pd process shown in **Scheme 9**. Although unclear, the initial organopalladium intermediate was thought to have been formed via hydropalladation. This reaction had



Scheme 9

remained as a single isolated example of a Type I Ac–Pd process until the example shown in **Scheme 4**[6] was reported in 1983.

Although the initial experiments in the investigation represented by **Scheme 4** required stoichiometric quantities of Pd complexes,[6] subsequent studies, such as that represented in **Scheme 6**,[9] indicated that, as expected, the process can be catalytic in Pd. A strong chelation effect hindering the desired catalysis may be suspected in cases where α-methyleneketones are the products, as in **Scheme 4**.

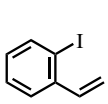
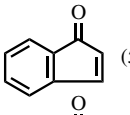
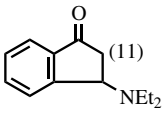
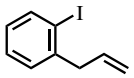
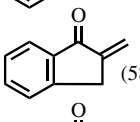
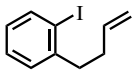
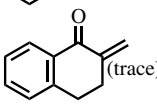
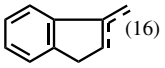
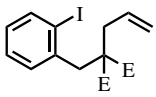
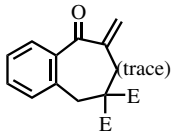
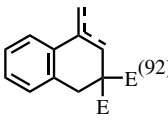
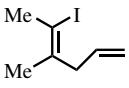
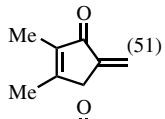
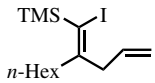
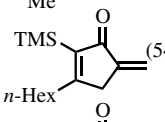
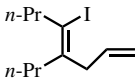
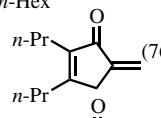
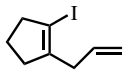
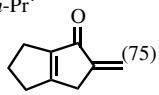
A subsequent systematic study of the Type I Ac–Pd reaction of 1-iodo-2-alkenylbenzenes[15] and 1,4-, 1,5-, and 1,6-dienyl iodides[16] has delineated its scope and limitations, as detailed below.

B.i.a. ***Type I Ac–Pd Cyclization of Terminal Vinyl-Containing Iodobenzenes and Iododienes.*** Those aryl and alkenyl iodides containing a terminal vinyl group can produce reactive and hence unstable α-methyleneketones, which are known to readily undergo conjugate addition and other reactions. A systematic investigation of the Type I Ac–Pd reaction of terminal vinyl-containing substrates[15],[16] has led to the results summarized in **Table 1**, which indicates the following.

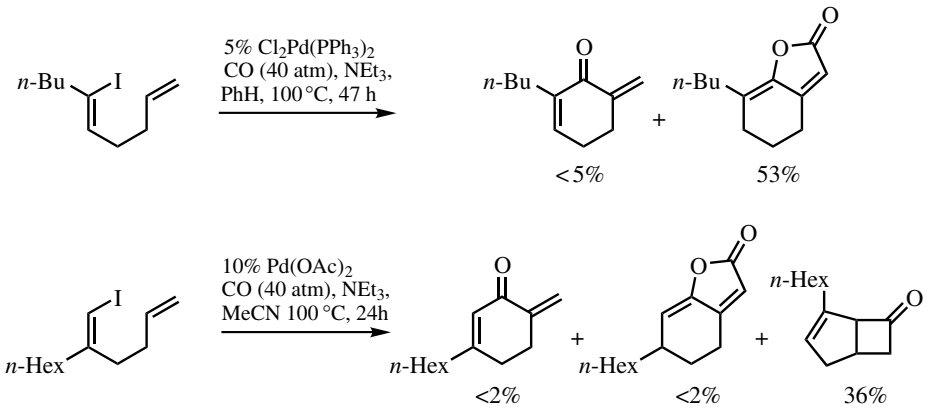
The scope of the Type I Ac–Pd reaction of terminal vinyl-containing iodobenzenes and iododienes is essentially limited to the synthesis of five-membered enones. Neither three- and four-membered small ring ketones nor larger rings, such as six- and seven-membered enones, are obtained in useful yields. Interestingly, the reaction of 2-vinyl-1-iodobenzene gave 1-indenone (50%) and 3-diethylamino-1-indanone (9%) as the only cyclic ketones. The former is a formal *endo*-mode cyclization product rather than the more usual *exo*-mode cyclization product. The exact courses of those reactions in which the yields of the desired ketones are low are mostly unclear, but the reaction of dimethyl *o*-iodobenzyl-(allyl)malonate produced cleanly the cyclic Heck reaction product in 92% yield even under the carbonylative conditions. In the reactions of iododienes, a Type III Ac–Pd process and ketene formation and [2 + 2] cyclization can be significant side reactions[16] (**Scheme 10**).

B.i.b. ***Type I Ac–Pd Cyclization of Iodobenzenes and Iododienes Containing Di- and Trisubstituted Alkenes.*** In cases where the ω-alkenyl group is di- and trisubstituted, a Type I Ac–Pd process is significantly more favorable, as indicated by the results summarized in **Table 2**. Thus, not only five-membered ketones but six-membered ketones can also be formed in high yields, although the scope is still limited to the synthesis of five- and six-membered ketones.

TABLE 1. Type I Cyclic Acylpalladation of ω-Vinyl-Containing Iodobenzenes and Iododienes

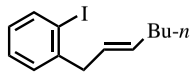
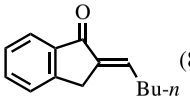
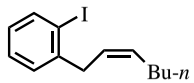
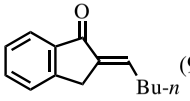
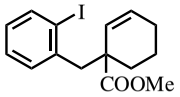
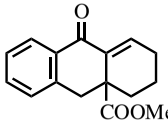
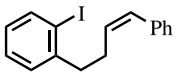
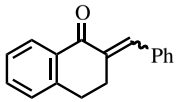
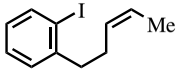
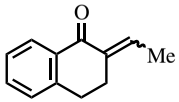
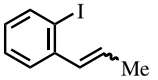
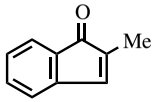
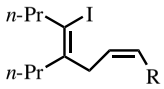
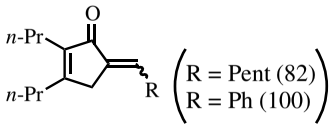
Substrate	Catalyst (%)	Solvent	Other Conditiions[a]	Yield (%) Product	By-products	Reference
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I	 (50)	 (11)	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –THF	II	 (58)	—	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	DMF	III	 (trace)	 (16)	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –THF	III	 (trace)	 (92)	[15]
	$Pd(PPh_3)_4$ (100)	THF	IV	 (51)	—	[4],[16]
	$Pd(PPh_3)_4$ (100)	THF	IV	 (54)	—	[4],[16]
	$Pd(PPh_3)_4$ (100)	THF	IV	 (76)	—	[16]
	$Pd(PPh_3)_4$ (100)	THF	IV	 (75)	—	[16],[17]

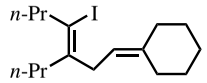
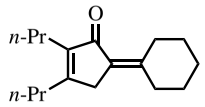
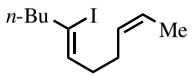
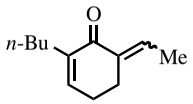
[a] I = CO (1 atm), NEt_3 (1.5–4 equiv), 80 °C, 6 h. II = CO (30–50 atm), NEt_3 (1.5–4 equiv), 80 °C, 18 h
III = CO (1 atm), NEt_3 (1.5–4 equiv), 100 °C, 12–24 h. IV = CO (1 atm), NEt_3 (1.1 equiv), 60 °C, 24 h.



Scheme 10

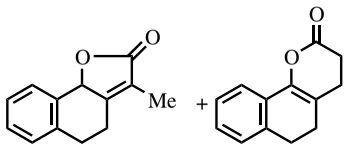
TABLE 2. Type I Cyclic Acylpalladation of Iodobenzenes and Iododienes Containing Di- and Trisubstituted Alkenes

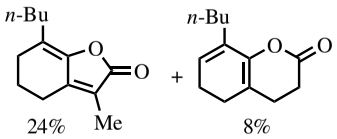
Substrate	Catalyst (%)	Solvent	Other Conditions[a]	Yield (%) Product	Yield (%) By-products	Reference
	$Cl_2Pd(PPh_3)_2$ (5)	DMF	I	 (82)	—	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	DMF	I	 (91)	—	[15]
	$Pd(PPh_3)_4$ (5)	MeCN –THF	I	 (67)	—	[9],[15]
	$Cl_2Pd(PPh_3)_2$ (5)	DMF	I	 (96)[b]	—	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –THF	I	 (43)[c]	*d*	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	II	 (22)	—	[16]
	$Cl_2Pd(PPh_3)_2$ (5)	DMF	III	 (R = Pent (82), R = Ph (100))		[16]

	$Cl_2Pd(PPh_3)_2$ (5)	DMF	IV		(77)	—	[16]
	$Cl_2Pd(PPh_3)_2$ (5)	Benzene	IV		(34)	*e*	[16]

[a] In all reactions, NEt_3 (1.5–4 equiv) was used as a base. I = CO (40 atm), 100 °C, 17–28 h. II = CO (1 atm), 80 °C, 12 h. III = CO (40 atm), 100 °C 10–12 h. IV = CO (100 atm), 100 °C, 24 h.

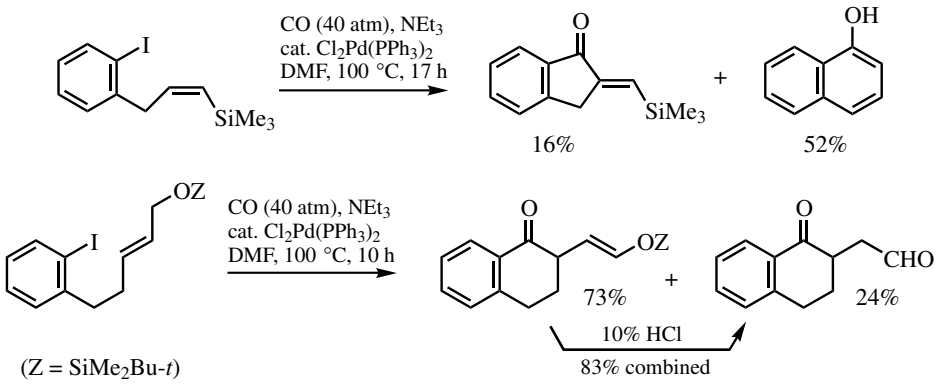
[b] *E*/*Z* = 58/42. [c] *E*/*Z* = 82/18.

d 
15% 26%

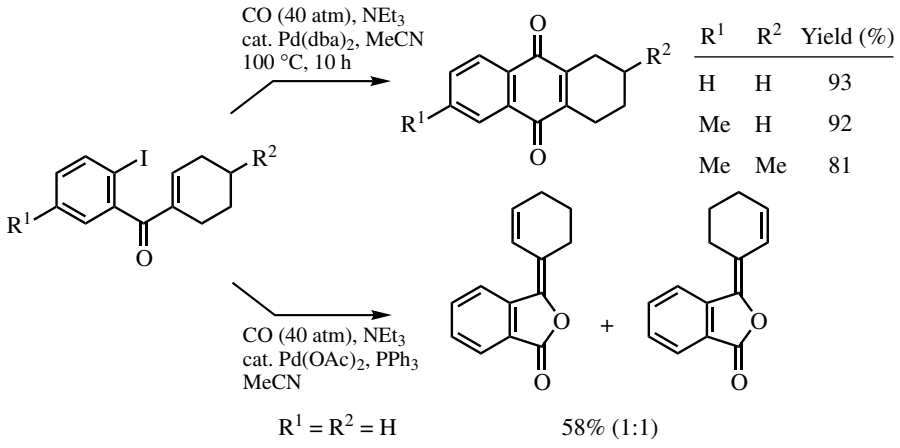
e 
24% 8%

In cases where the alkene moiety is heterosubstituted, there can be significant influences exerted by such heterofunctional groups. Some examples of Type I Ac–Pd reactions producing unexpected products due to the presence of heterofunctional groups are shown in **Scheme 11**.[15] In the formation of α-naphthol, the Me_3Si group must exert a strong influence on the observed reversal of regiochemistry, that is, *exo* $\rightarrow$ *endo*.

More striking examples displaying complete reversal of regiochemistry of acylpalladation was achieved in the quinone synthesis shown in **Scheme 12**.[8] The use of PPh_3 as a ligand led to premature trapping by the internally generated enolates (**Sect. VI.2.3**).



Scheme 11



Scheme 12

B.ii. Type II Ac–Pd Process

The organopalladium species generated via cyclic acylpalladation is a γ-ketoalkylpalladium derivative that can undergo β-dehydropalladation to give α,β-unsaturated enones in the Type I Ac–Pd process. Under the conditions of carbonylation, however, this species can undergo the second CO insertion to give the second acylpalladium species. As indicated in **Scheme 8**, this species has at least four reaction paths that it can follow. To the

extent that CO insertion is reversible, it can undergo decarbonylation, which should be a function of CO pressure. It can also undergo the Type III Ac–Pd process, which has already been shown to occur as a side reaction of the Type I Ac–Pd process (cf. **Table 2**). In some cases, it can totally overshadow Type I Ac–Pd processes, as shown in **Scheme 6**. And then, there is always the possibility for any acylpalladium species to undergo intermolecular acylpalladation leading to oligomers and polymers. Such intermolecular acylpalladation may be expected to be significantly slower than facile cyclic acylpalladation leading to the formation of five- and six-membered ketones. All of these processes can occur in the absence of external reagents.

In the presence of externally added nucleophilic reagents, the second acylpalladium species can be trapped and converted to various organic products. The same external nucleophiles can also react with the first acylpalladium species generated before cyclic acylpalladation. So, one of the key requirements for observing Type II Ac–Pd processes is that intramolecular cyclic acylpalladation must be faster than the reaction with an externally added nucleophile, which, in turn, must be faster than intermolecular acylpalladation. As the results summarized in **Tables 3** and **4** as well as in **Scheme 15** indicate, the above-mentioned requirement must indeed be satisfied in many cases of the formation of five- and six-membered ketones. Here again, however, the current scope of the Type II Ac–Pd process is limited to the synthesis of five- and six-membered ketones.

B.ii.a. ***Trapping of Acylpalladium Species with Alcohols and Related Heteroatom Nucleophiles.*** Trapping of acylpalladium species formed via cyclic acylpalladation with external heteroatom nucleophiles has been achieved almost exclusively by using alcohols, such as MeOH, EtOH, *i*-PrOH, and *t*-BuOH. Their nucleophilicity is such that the above-mentioned requirement for the relative rates among three competing processes, that is, intramolecular Ac–Pd > nucleophilic trapping > intermolecular Ac–Pd, can often be satisfied at least in cases where five- and six-membered ketones are desired.

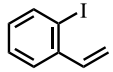
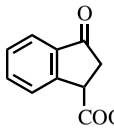
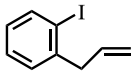
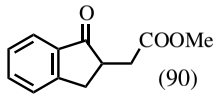
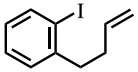
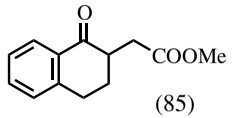
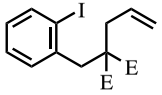
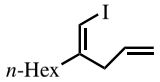
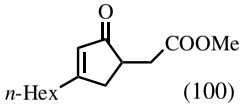
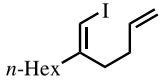
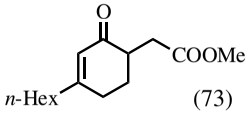
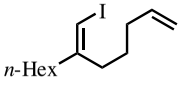
With the exception of a couple of isolated examples reported in 1965,[4] essentially all of the examples of this class have been reported since 1985.[7] Some representative examples of the Type II Ac–Pd process involving the use of alcohols as external nucleophiles are summarized in **Tables 3–5**. **Table 3** shows the results obtained with ω-vinyl-containing iodobenzenes and iododienes.

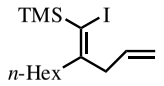
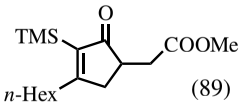
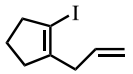
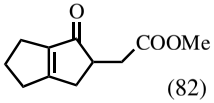
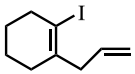
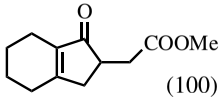
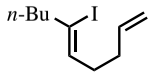
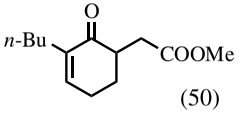
Comparison of the results shown in **Tables 1** and **3** indicates the following. First, the Type II Ac–Pd reaction with ω-vinyl-substituted derivatives is generally cleaner and higher-yielding than the corresponding Type I Ac–Pd reaction. Notably, even six-membered ketones can be obtained from ω-vinyl-containing substrates in high yields, whereas such substrates have failed to provide the Type I Ac–Pd products (cf. **Table 1**). Even so, however, the formation of six-membered ketones is generally more sluggish, and it tends to be lower-yielding than that of five-membered ketones.

The results of the Type II Ac–Pd reactions of di- and trisubstituted alkene-containing aryl and dienyl iodides are summarized in **Table 4**.

With di- and trisubstituted alkene-containing substrates, the Type I Ac–Pd process and premature esterification are two main possible side reactions. The Type II Ac–Pd/Type I Ac–Pd ratio is a function of CO pressure, and the Type II Ac–Pd process incorporating two molecules of CO is favored by high CO pressures ($\sim$100 atm). In cases where premature esterification is a problem, the use of sterically more demanding alcohols, such as *i*-PrOH, can significantly increase the yield of the desired Type II Ac–Pd products. This aspect deserves to be investigated further. In the reaction shown in **Scheme 13**, the yield

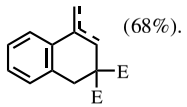
TABLE 3. Type II Cyclic Acylpalladation of ω-Vinyl-Containing Aryl and Dienyl Iodides Using Alcohols and External Nucleophiles

Substrate	Catalyst (%)	Solvent	Other Conditions[a]	Yield (%) Product	Yield (%) By-products	Reference
	$Cl_2Pd(PPh_3)_2$ (5)	PhH	I	 (74)	—[b]	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	DMF	I	 (90)	—[b]	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I	 (85)	—[b]	[7],[15]
 (E = COOMe)	$Cl_2Pd(PPh_3)_2$ (5)	PhH	II	—[c]	—[d]	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I	 (100)	—[c]	[7],[16]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I	 (73)	—[b]	[7],[16]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I	—[c]	—[e]	[16]

	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I	 (89)	—[c]	[7],[16]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I	 (82)	—[b]	[16],[17]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I	 (100)	—[c]	[16],[17]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I	 (50)	—[b]	[16]

[a] I = CO (40 atm), MeOH (4 equiv), NEt_3, 100 °C, 6–24 h. II = CO (40 atm), *t*-BuOH (4 equiv), NEt_3, 100 °C, 24 h.

[b] Not determined. [c] Not detectable.

[d]  (68%).

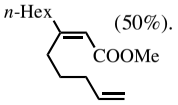
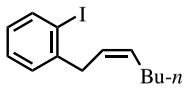
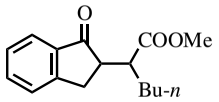
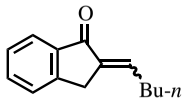
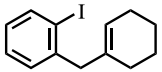
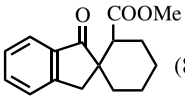
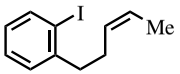
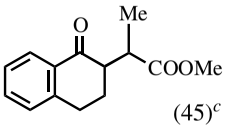
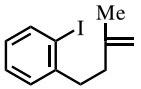
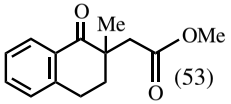
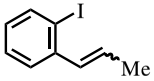
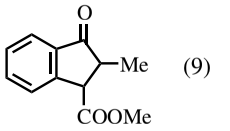
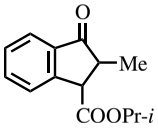
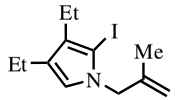
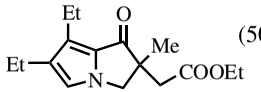
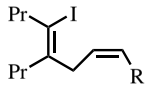
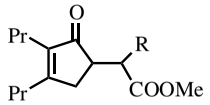
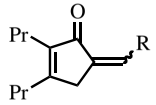
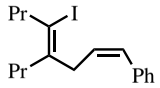
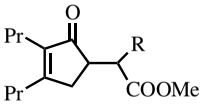
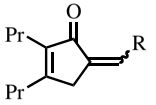
[e]  (50%).

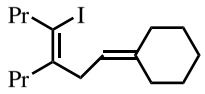
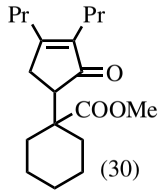
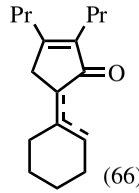
TABLE 4. Type II Cyclic Acylpalladation of Iodoarenes and Iododienes Containing Di- and Trisubstituted Alkenes

Substrate	Catalyst (%)	Solvent	Other Conditions[a]	Product(%)	By-products(%)	Reference
	$Cl_2Pd(PPh_3)_2$ (5)	DMF MeOH	I			
			CO (1 atm)	37	50[b]	[15]
			CO (14 atm)	63	31[b]	[15]
			CO (42 atm)	80	15[b]	[15]
			CO (84 atm)	90	8	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I, CO (40 atm)	 (84)	—	[7],[15]
	$Cl_2Pd(PPh_3)_2$ (5)	DMF	I, CO (40 atm)	 (45)[c]	—[d]	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I, CO (40 atm)	 (53)	—[e]	[15]
	$Cl_2Pd(PPh_3)_2$ (5)	MeCN –PhH	I, CO (40 atm)	 (9)	—[f]	[15]

	$Cl_2Pd(PPh_3)_2$ (5)	PhH	II, CO (40 atm)	 (63)[g]	—[h]	[15]
	$Pd(OAc)_2$ (10) PPh_3 (20)	MeCN EtOH	III, CO (1 atm)	 (50)	—	[18]
	$Cl_2Pd(PPh_3)_2$ (5)					[16]
(R = Pent-*n*)		DMF	IV, CO (40atm)	53 (60:40)	45 (*E*/*Z* = 67:33)	
		MeOH	V, CO (55 atm)	76 (60:40)	14 (*E*/*Z* = 80:20)	
		DMF –MeOH	IV, CO (100 atm)	93 (54:46)	5 (*E* only)	
	$Cl_2Pd(PPh_3)_2$ (5)					[16]
		DMF	I, CO (40 atm)	63 (60:40)	34 (*E*/*Z* = 1:1)	
		DMF –MeOH	I, CO (100 atm)	94 (60:40)	Trace	

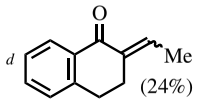
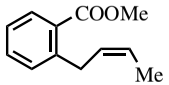
(*Continued*)

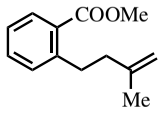
TABLE 4 (*Continued*)

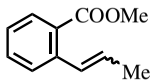
Substrate	Catalyst (%)	Solvent	Other Conditions[a]	Product(%)	By-products(%)	Reference
	$Cl_2Pd(PPh_3)_2$ (5)	DMF –MeOH	IV, CO (100 atm)	 (30)	 (66) *exo/endo* = 50:16	[16]

[a] I = MeOH (≥4 equiv), NEt_3 (1.5–4 equiv), 100 °C, 4–28 h. II = *i*-PrOH (4 equiv), NEt_3 (1.5–4 equiv), 100 °C, 24 h. III = EtOH, TlOAc (1.2 equiv), 80 °C, 24 h. IV = MeOH (≥4 equiv), NEt_3, 100 °C, 37–69 h. V = MeOH (100 equiv), K_2CO_3 (2 equiv), 100 °C, 48 h.

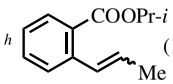
[b] *E*/*Z* = 93/7. [c] Contains a regioisomer (10%).

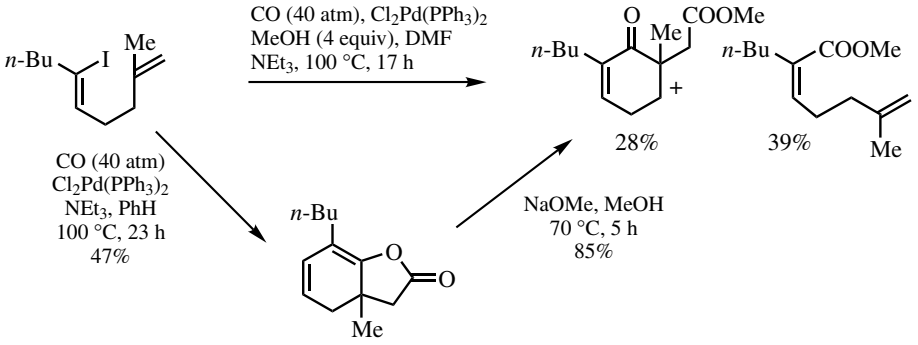
[d]  (24%) and  (31%).

[e]  (17%).

[f]  (77%).

[g] *trans*/*cis* = 90:10.

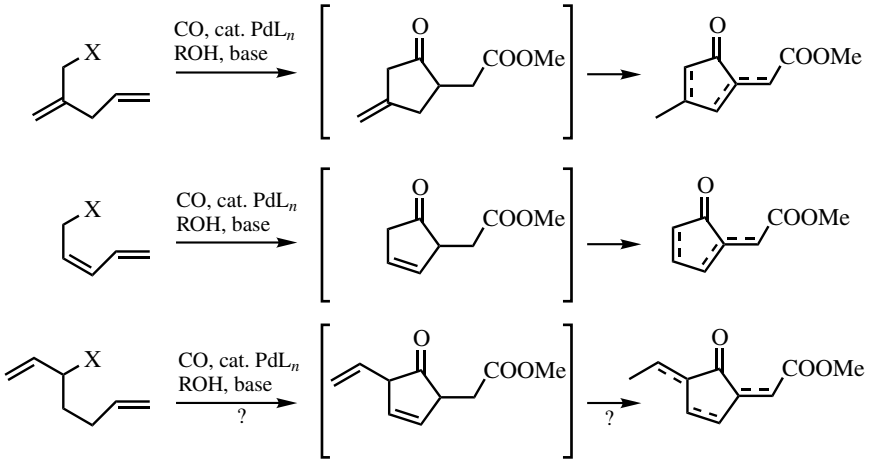
[h]  (15%).



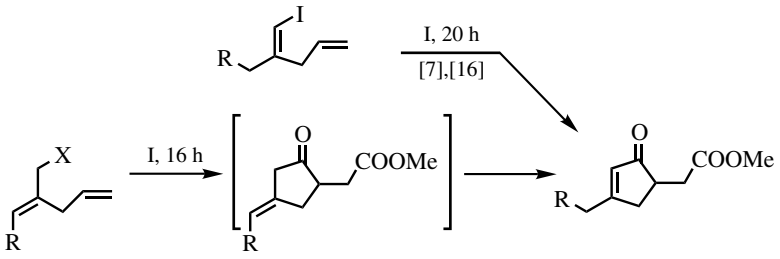
Scheme 13

of the desired Type II Ac–Pd product was limited to 28%.[16] Although not yet very satisfactory, it was possible to obtain the same product in higher overall yield by the preparation of the Type III Ac–Pd product followed by its methanolysis. This aspect also needs to be explored further.

The scope of the Type II Ac–Pd cyclization has been expanded significantly by the finding that not only aryl and alkenyl iodides but also allyl electrophiles can participate in the reaction.[19] Of three conceivable classes of Type II Ac–Pd processes of allylic substrates shown in **Scheme 14**, the first two have been shown to be feasible and potentially useful, as indicated by the results summarized in **Scheme 15**.[19] The third class of Type II Ac–Pd processes might be feasible if dehydropalladation to produce conjugated dienes could be prevented; no such example has as yet been reported. It should be noted that these reactions usually involve C═C bond migration to give conjugated enones. Consequently, they can provide an alternative route to those products obtainable by the Type II Ac–Pd reaction of the corresponding iododienes discussed above. Furthermore, the significantly higher reactivity of allylic electrophiles toward Pd complexes permits the use of a wider range of leaving groups, as shown in **Scheme 15**.[19]



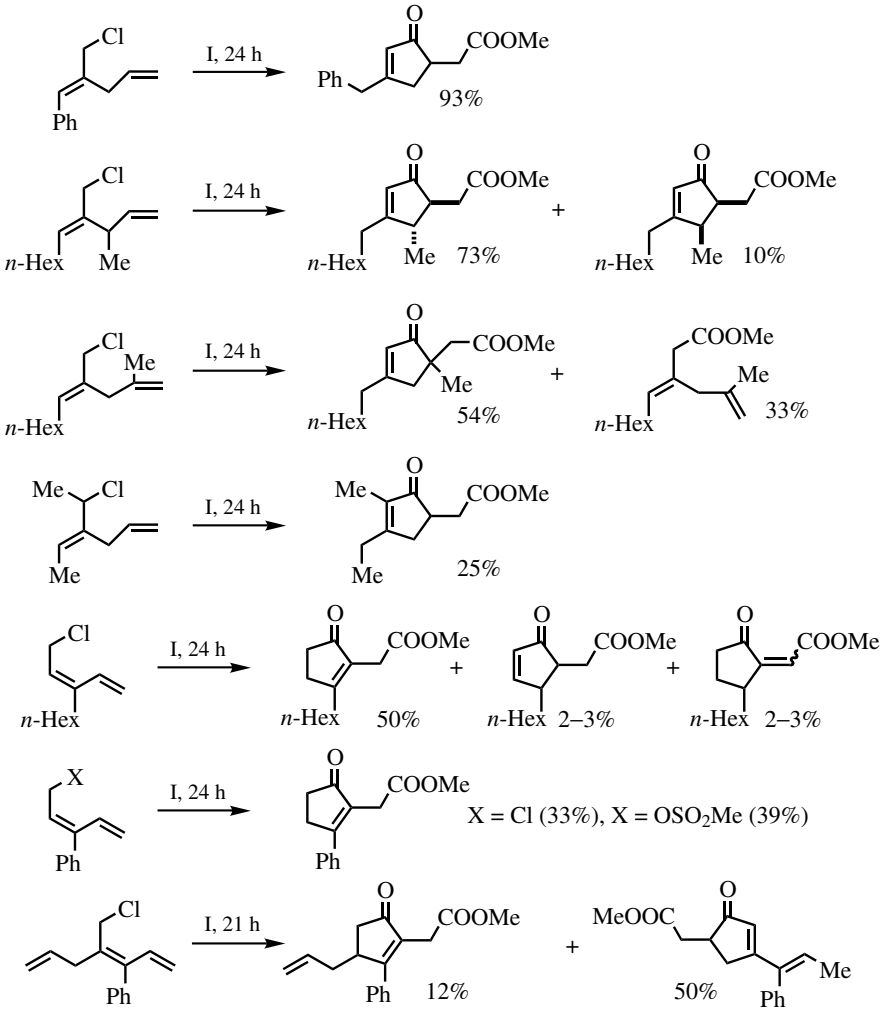
Scheme 14



(R = *n*-Pent or *n*-Hex)

Note: The results shown are for those cases where R is *n*-Hex.

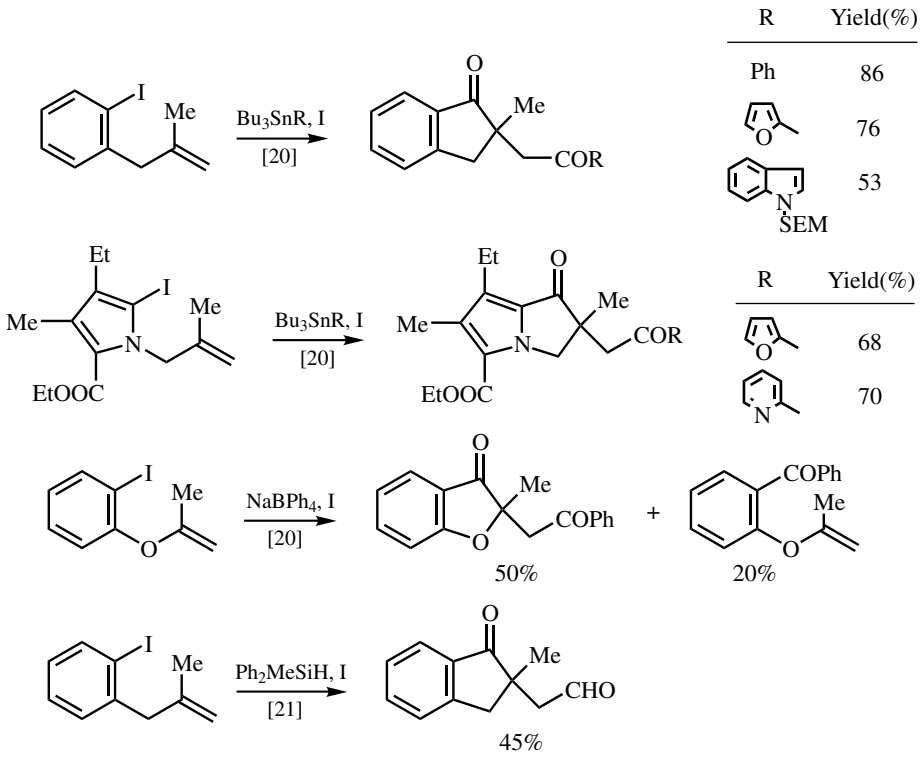
X	Yield(%)	X	Yield(%)
Cl	88	OCOOMe	65
Br	94	$OPO(OEt)_2$	76
OAc	42	OSO_2Me	82



I = CO (40 atm), NEt_3 (1.5 equiv), 5% $Cl_2Pd(PPh_3)_2$, MeCN–PhH, 100 °C.

Scheme 15

B.ii.b. ***Trapping of Acylpalladium Species with Carbon and Hydrogen Nucleophiles.*** The use of organotins, typically Bu_3SnR,[20] and organoborons, such as $NaBPh_4$,[20] as well as metal hydrides, such as Ph_2MeSiH,[21] has recently been shown to permit trapping of acylpalladium species with both C and H nucleophiles to produce ketones[20] and aldehydes.[21] Since the same requirement for the relative rates of the three potentially competing processes discussed above must be satisfied, the trapping agents must be of appropriate reactivity. Relatively slow-reacting organotins and organoborons evidently are better suited for this purpose than more reactive organometals containing Zn. Currently, there are only a small number of examples of these reactions, and some prototypical examples are shown in Scheme 16. Further investigation of the scope and limitations of these reactions is desirable.

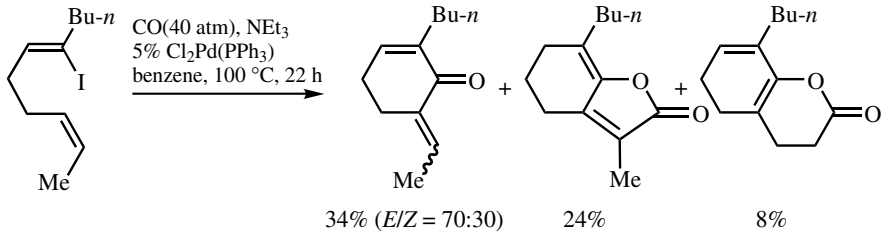


I = CO (1atm), 10% $Pd(OAc)_2$, 20% PPh_3, NEt_4Cl, toluene or anisole, 110–120°C.

Scheme 16

B.iii. Type III Ac–Pd Process

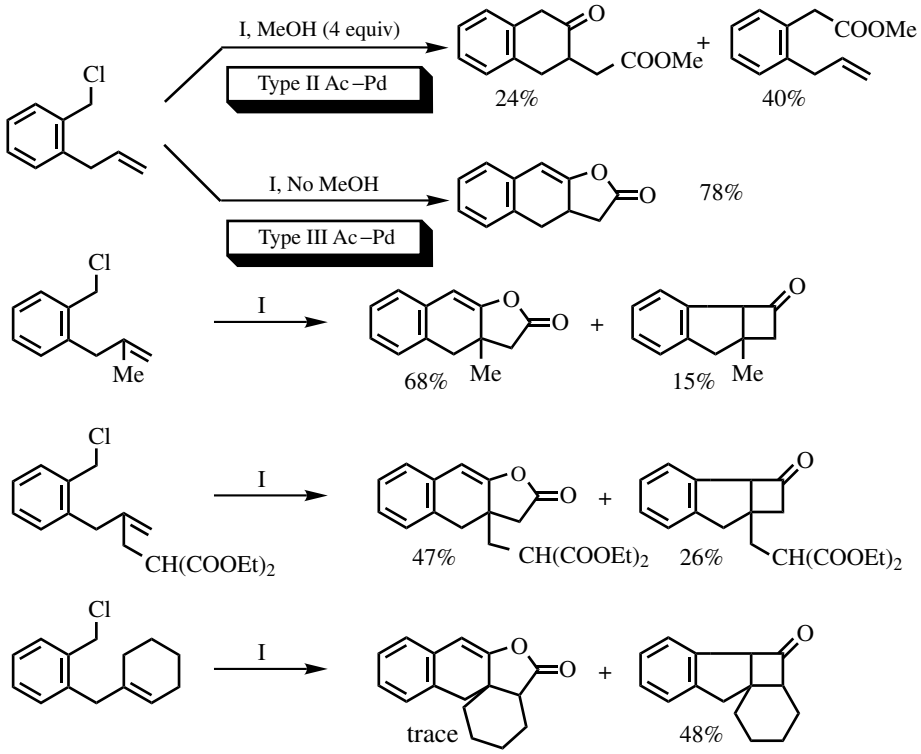
It has been indicated in **Scheme 6** that the Type III Ac–Pd process involving trapping of the second acylpalladium intermediates with enolates generated *in situ* within the same molecules can take place in preference to the Type I Ac–Pd process under those reaction conditions that are otherwise suitable for the Type I Ac–Pd process. Although rare, formation of a mixture of both Types I and III Ac–Pd products has also been observed, as exemplified by the results shown in **Scheme 17**.[16]



Scheme 17

The Type I/Type III ratio is largely a function of substrate structure at the moment, and a systematic investigation as to how to change and control the ratio with a given substrate is highly desirable. As might be expected, arylacetylpalladium species derivable from benzylic halides have been shown to be very prone to undergoing the Type III Ac–Pd process (**Scheme 18**).[13]

The results shown in **Scheme 18** indicate the following. First, the Type III Ac–Pd process can be a useful alternative to the Type II Ac–Pd process in cases where premature esterification is a serious side reaction in the latter. The results shown earlier in **Scheme 13** further support this statement. Second, it is noteworthy that the Type III Ac–Pd process of

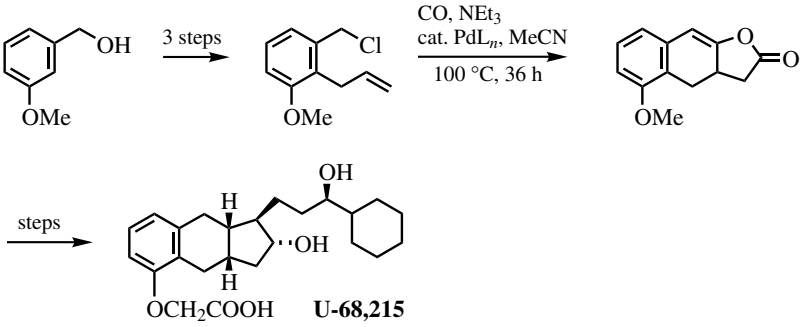


I = CO (40 atm), 5% $PdCl_2(PPh_3)_2$, NEt_3(2 equiv), MeCN, 100 °C.

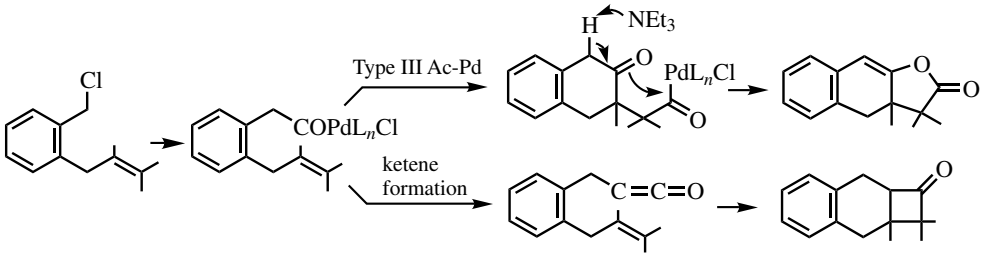
Scheme 18

allylic substrates has not been reported (cf. **Sect. B.ii.a**), whereas similarly structured benzylic substrates readily undergo the Type III Ac–Pd process. Third, the Type III Ac–Pd process, which can compete and often totally overshadow the Type I Ac–Pd process, tends to compete against yet another process—the presumed ketene formation followed by their [2 + 2] cycloaddition to give cyclobutanones. This side reaction evidently becomes more competitive as the Type III Ac–Pd process becomes more sluggish for steric and other reasons. The formation and reaction of ketenes is the subject of **Sect. VI.5.2**. The synthesis of a key intermediate for an antiulcer agent, U-68,215 shown in **Scheme 19**, shows the potential utility of the Type III Ac–Pd process.[13]

Although not fully investigated, the mechanistic scheme shown in **Scheme 20** readily accommodates the results shown in **Schemes 18** and **19**.



Scheme 19



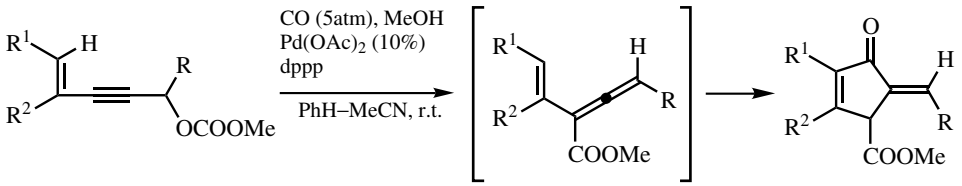
Scheme 20

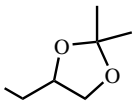
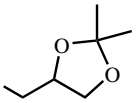
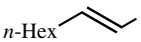
B.iv. Other Related Carbonylative Cyclization Reactions

The formation and cyclization of ketenes discussed above indicates that, in addition to Types I–III Ac–Pd processes, other carbonylative cyclization reactions may take place under the same or similar reaction conditions. In some cases, the mechanisms of such reactions are not very clear.

For example, the Pd-catalyzed carbonylative cyclization of 4-en-2-ynyl carbonates gives 5-alkylidene-2-cyclopentenones, as shown in **Table 5**.[22] The reaction presumably proceeds via methoxycarbonyl-substituted conjugated enallenes, but the course of their transformation into the final products remains unclear.

TABLE 5. Pd-Catalyzed Carbonylative Cyclization of 4-En-2-ynyl Carbonates



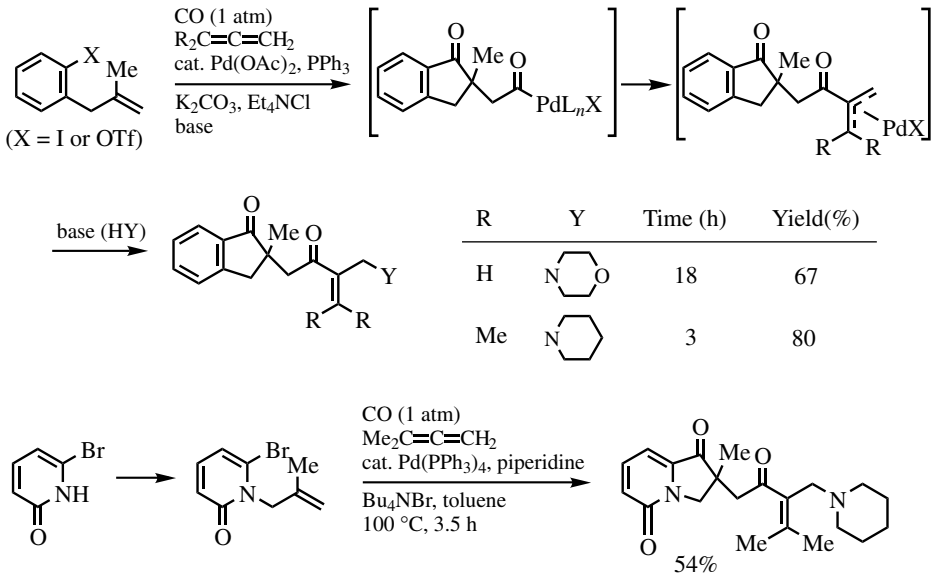
	R	Time (h)	Yield (%)
	*i*-Pr	8	81
		4	82
		24	70
		8	69
	*n*-Hept	8	64

A very special mode of trapping of acylpalladium species is seen in a variant of the Type II Ac–Pd process shown in **Scheme 21**.[23] Very recently, an interesting variant of the Type I Ac–Pd process was carried out in as high as 96% ee (**Scheme 22**).[24] Although their synthetic values are not yet known, they nonetheless expand the scope of the Pd-catalyzed carbonylative cyclization methodology and are potentially useful in synthesis.

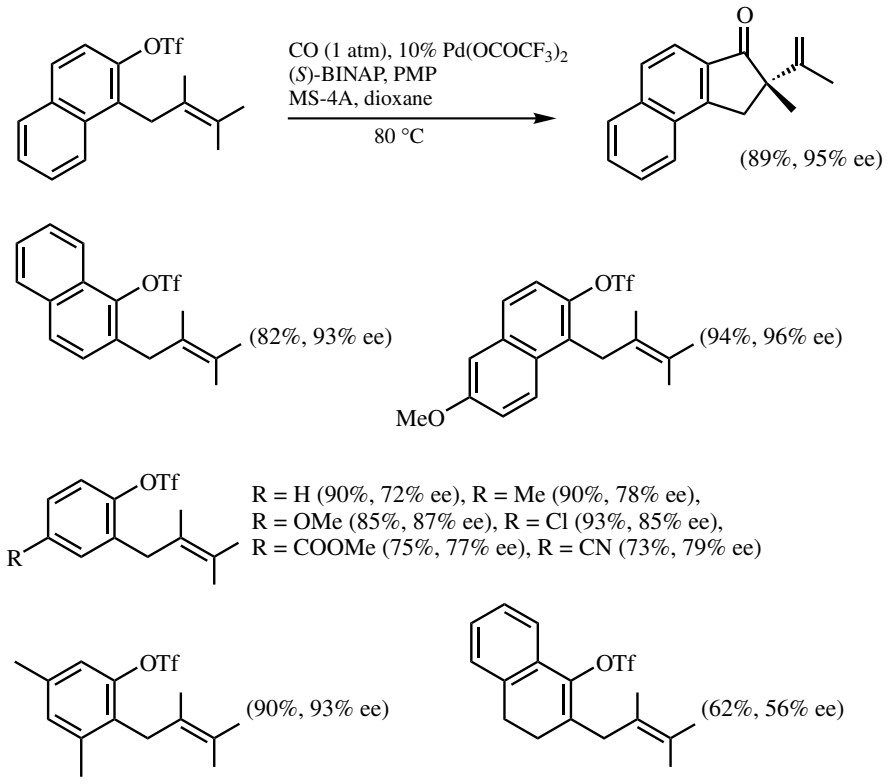
B.v. Acylpalladation of Alkynes

All of the acylpalladation processes discussed above involve interaction of acylpalladium bonds with C═C bonds. The corresponding acylpalladation of C≡C bonds proved to be rather elusive. Thus, for example, attempts to observe cyclic acylpalladation of alkyne-containing iodobenzenes totally failed,[25] even though the corresponding alkene derivatives undergo cyclic acylpalladation[15] (**Scheme 23**). The contrasting behavior of alkene and alkyne substrates is also schematically summarized in **Scheme 23**.

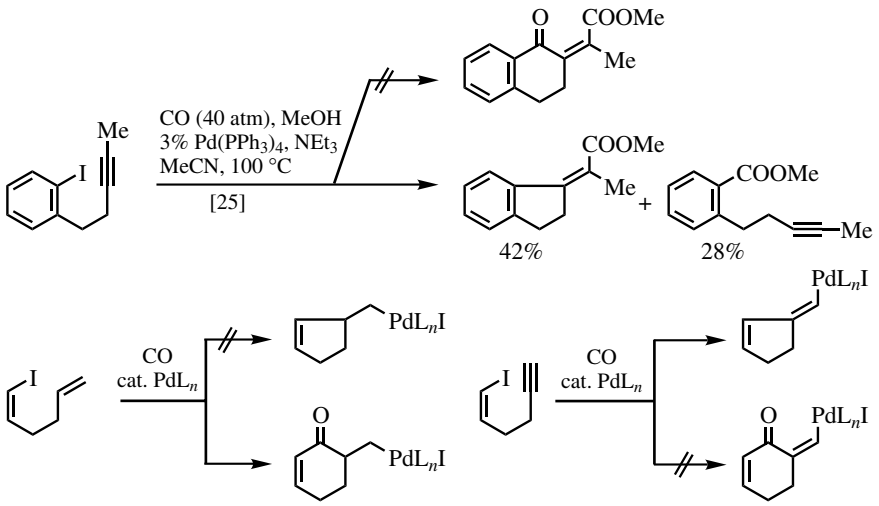
In fact, the preferential cyclic carbopalladation even in the presence of large excesses of CO and MeOH has been exploited in developing cyclic carbopalladation cascades terminated by carbonylative esterification, as discussed in **Sect. IV.3.3**. More recent attempts



Scheme 21



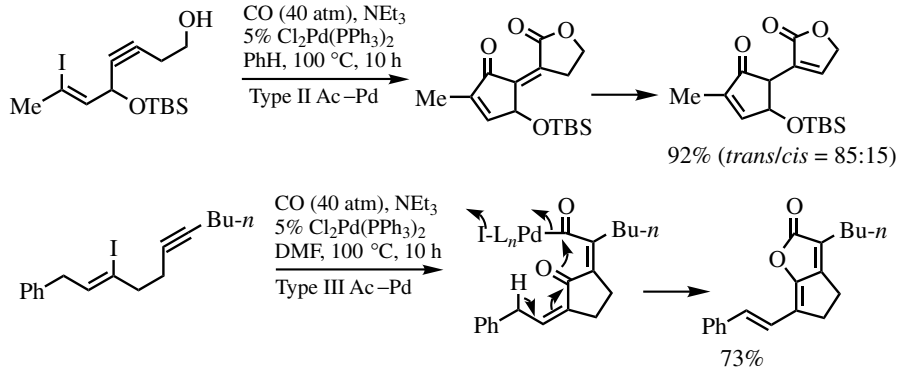
Scheme 22



Scheme 23

to observe intermolecular acylpalladation of alkynes led to the discovery of an interesting lactonization reaction[26] discussed later in **Sect. VI.4.3**.

A few *bona fide* examples of acylpalladation of alkynes were finally observed, as shown in **Scheme 24**.[27] The first equation provides an example of the Type II Ac–Pd process, while the second one represents the Type III Ac–Pd process. The extents to which two potentially competing processes—cyclic acylpalladation and cyclic carbopalladation—occur must largely be a function of ring size, and the generalization shown at the bottom of **Scheme 24** appears to be reasonable.



Competition	Carbopalladation	Acylpalladation
4 vs. 5	Disfavored	Favored
5 vs. 6	Favored	Disfavored
6 vs. 7	Favored	Disfavored

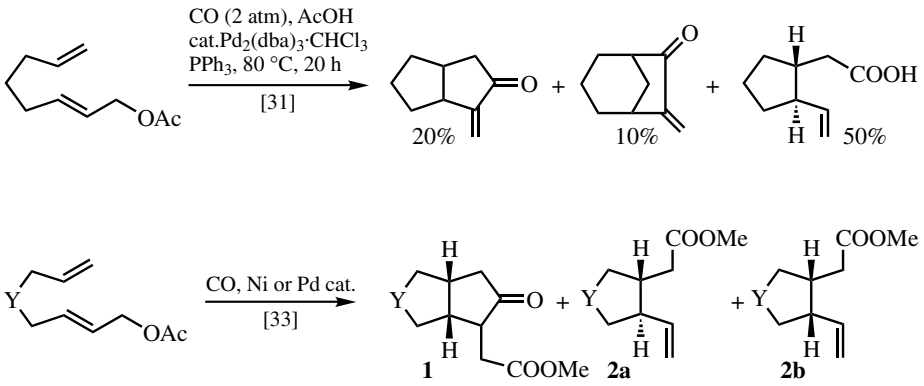
Scheme 24

C. TANDEM, CASCADE, OR DOMINO ACYLPALLADATION AND CARBOPALLADATION PROCESSES

The "living" nature of acylpalladium and other organopalladium species permits a series of their interconversions under one set of conditions, one representative example being the Pd-catalyzed copolymerization of alkenes and CO (**Sect. VI.4.2**). A series of such processes can also occur in cyclic manners, and they are the subject of this subsection. Some chemists call combinations of two same or different successive processes "tandem" processes. These chemists have tended to call successively occurring multiple processes "cascade" processes, which may include "tandem" processes. Other chemists, on the other hand, would call them "domino" processes. Since these are rather loosely defined terms involving fundamentally nonchemical words, selection among them is a subjective matter, and all are used here and throughout this Handbook.

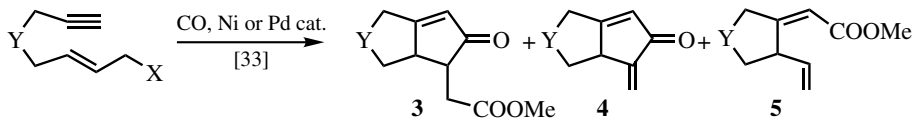
C.i. Cyclic Allylpalladation-Acylpalladation Cascade Processes

A systematic investigation of cascading cyclic allylpalladation and Ac–Pd processes was carried out by Oppolzer who initially adapted the stoichiometric acylnickelation of Camps and Moretó[28],[29] to devise a Ni-catalyzed allylmetallation–acylmetallation tandem cyclization to produce fused bicyclo[3.3.0]octanone derivatives.[30] The scope of the cyclic allylmetallation–acylmetallation cascade was soon expanded by adaptation of the Pd-catalyzed Types I and II Ac–Pd processes developed systematically by Negishi (**Sect. B**). Specifically, the reactions shown in Scheme 25 were reported in 1989 by Yamamoto and co-workers[31],[32] as well as by Oppolzer and co-workers.[33]



Y	X	Catalyst	Other Conditions[a]	Product Yield (%) 1[b]	2a	2b
$C(COOMe)_2$	I	$Ni(CO)_3PPh_3$	A, 36 h	62 (4/1)	3	15
$C(COOMe)_2$	OAc	$Pd(dba)_2$, PPh_3	B, 20 h	10 (3/1)	62	1
NTs	I	$Ni(COD)_2$, dppb	A, 12 h	80 (10/1)	—	—
NTs	OAc	$Pd(dba)_2$, PPh_3	B, 12 h	16 (8/1)	53	1

Scheme 25 (*Continued*)



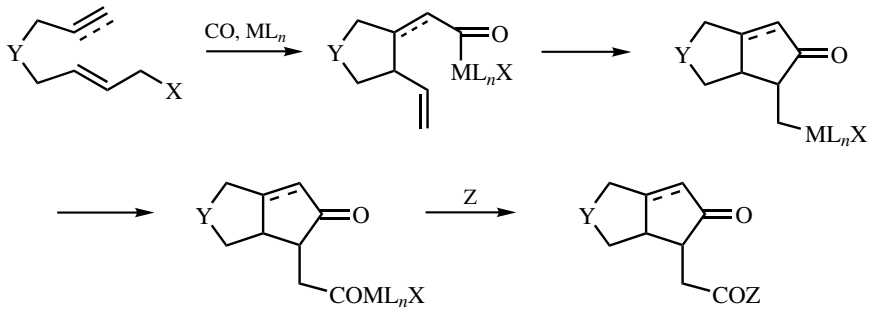
Y	X	Catalyst	Other Conditions[a]	Product Yield (%) 3[b]	4	5
$C(COOMe)_2$	I	$Ni(COD)_2$, dppb	A, 15 h	87 (27/1)	—	—
$C(COOMe)_2$	OAc	$Pd(dba)_2$, PPh_3	B, 7 h	74 (11/1)	3	—
NTs	I	$Ni(COD)_2$, dppb	A, 12 h	57 (20/1)	—	23
NTs	OAc	$Pd(dba)_2$, PPh_3	B, 2 h	50 (7/1)	16	13

[a] A = 25 mol % Ni catalyst, CO (1 atm), THF–MeOH, r.t. B = 10 mol% Pd catalyst, CO (1 atm), HOAc, 45 °C.
[b] The ratios in parentheses indicate the epimeric ratios.

Scheme 25

The results summarized in **Scheme 25** indicate the following. First, both Ni and Pd catalysts can induce and catalyze the desired bicyclization. Second, the product yields observed with Pd catalysts tend to be modest and lower than those observed with Ni catalysts. Both classes of catalysts have, however, been used in subsequent studies. The comparative usefulness of Ni and Pd catalysts in a given case should probably be experimentally determined. One significant factor affecting the yield of cascade bicyclization is the stereochemistry of the initial allylmetallation. If this step leads to *trans*-1,2-disubstituted cyclopentane derivatives, they would not be converted to the desired bicycles, unless the stereochemistry is corrected under the reaction conditions. This stereochemical problem does not exist in cases of the enyne reaction. Presumably for this reason, the bicyclization yields appear to be more favorable in the enyne bicyclization. The cyclic allylmetallation–Type II acylmetallation cascade mechanism shown in **Scheme 26** has been suggested and generally accepted.

The initial investigations by Oppolzer and co-workers[33],[34] and Yamamoto and co-workers [31],[32] dealt with cyclic allylpalladation–Type I Ac–Pd cascades of dienic

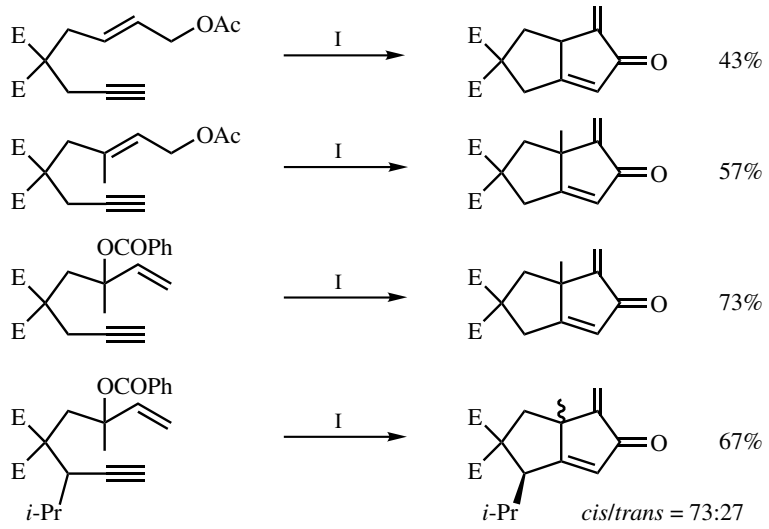


X = I, OAc, etc., Y = $C(COOMe)_2$, NTs, etc., Z = OH, OR, etc., ML_n = Ni or Pd cat.

Scheme 26

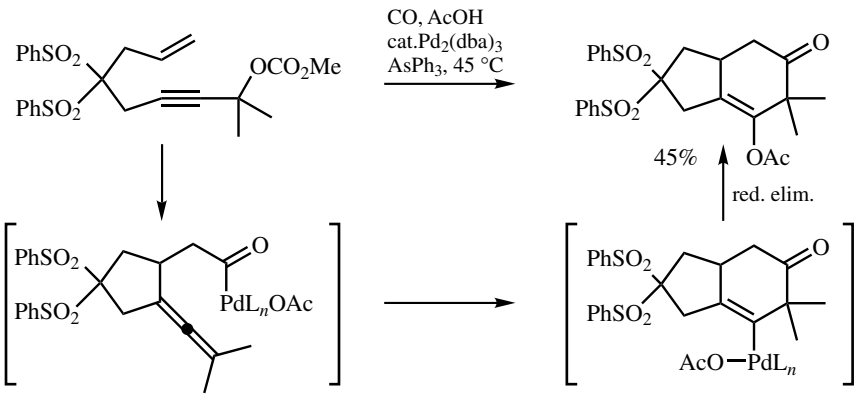
electrophiles and cyclic allylpalladation–Type II Ac–Pd cascades of both dienyl and enynyl electrophiles (**Scheme 25**). A later study[35] supplemented these earlier works by providing examples of the cyclic allylpalladation–Type I Ac–Pd cascades, as shown in **Scheme 27**. An interesting variant of the cyclic allylpalladation–Type I Ac–Pd cascade of enynyl electrophiles shown in **Scheme 28**[36] involves the use of propargylic carbonates and presumed cyclic acylpalladation of allenic intermediates.

Despite generally moderate product yields, these reactions have been applied to a number of noteworthy syntheses of natural and unnatural organic compounds of considerable complexity. The synthesis of tetracyclic[5.5.5.5]fenestranes by Keese and co-workers[37],[38] (**Scheme 29**) is particularly noteworthy, and it persuasively demonstrates the synthetic utility of the cyclic acylpalladation methodology. A series of elegant syntheses of terpenoids by Oppolzer and co-workers[39],[42] are discussed later in this section.

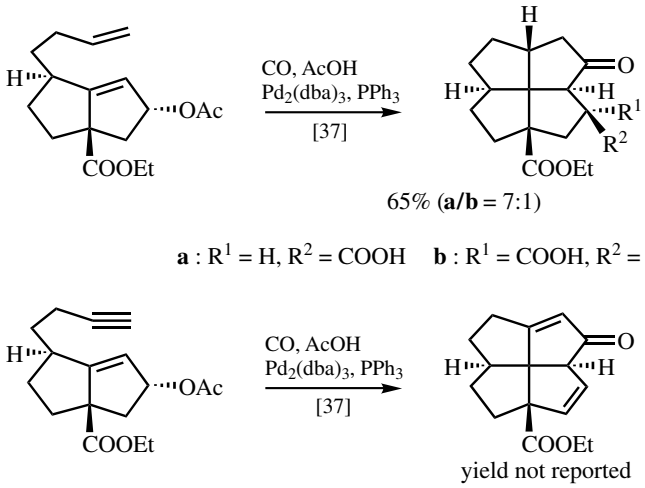


E = COOMe, I = CO, $Pd_2dba_3 \cdot CHCl_3$, PPh_3, LiCl, THF, H_2O, 70 °C.

Scheme 27



Scheme 28



Scheme 29

C.ii. Other Carbopalladation–Acylpalladation Cascades

Many different combinations of carbopalladation and/or acylpalladation processes are conceivable for devising cascading di- and multicyclization processes. Those consisting only of straightforward carbopalladation processes have been systematically investigated by a number of chemists since around 1988, as detailed in **Sect. IV.3**. Aside from these carbopalladation cascades and those allylpalladation–acylpalladation cascades discussed above, only a small number of scattered examples are known, as shown below, and this area needs to be explored further.

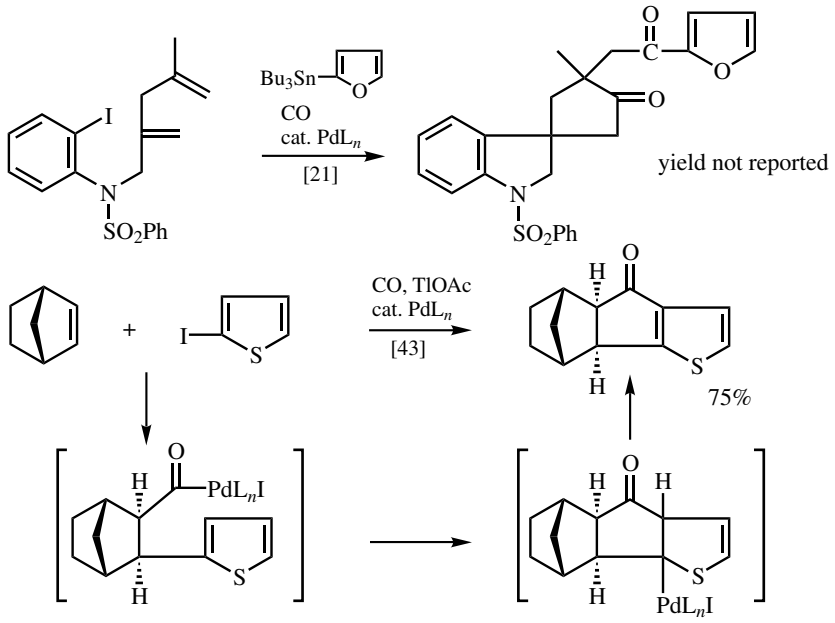
C.ii.a. ***Carbopalladation–Acylpalladation Cascades.*** The reaction shown at the top of **Scheme 30**[21] is a prototypical example of the intra–intra carbopalladation–acylpalladation cascade, while that shown at the bottom of **Scheme 30**[43] is an example of the inter–intra carbopalladation–acylpalladation cascade.

C.ii.b. ***Double and Multiple Acylpalladation Cascades.*** The alternating copolymerization of alkenes and CO[1]–[3] discussed in **Sect. VI.4.2** falls into this category. The scope of cyclic versions of double and multiple acylpalladation is currently very limited, and the following prototypical examples were reported only during the past several years[44],[45] (**Scheme 31**). The tetracyclic products in the second and third equations are the products of triple acylpalladation cascades.

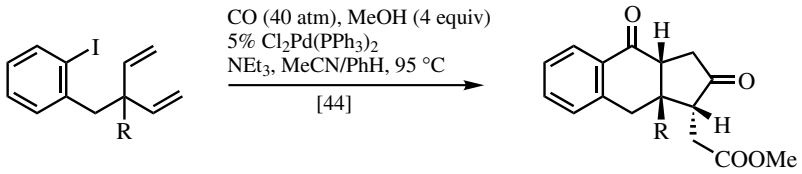
The cascade process shown at the bottom of **Scheme 31** must proceed via double allylpalladation followed by double acylpalladation producing all four rings in one step.[45]

D. SYNTHESIS OF NATURAL PRODUCTS VIA ACYLPALLADATION

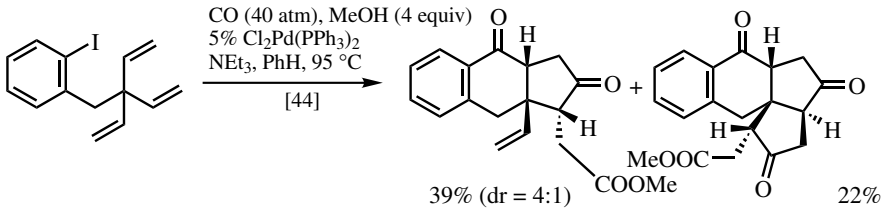
The synthesis of methylenomycin B[6] shown in **Scheme 4** represents the first application of cyclic acylpalladation (Type I Ac–Pd process) to the synthesis of natural products. Applications of Ac–Pd reactions to the syntheses of more complex natural products have been made through the use of the cyclic allylpalladation–acylpalladation cascade processes, as indicated by the results shown in **Scheme 32**.

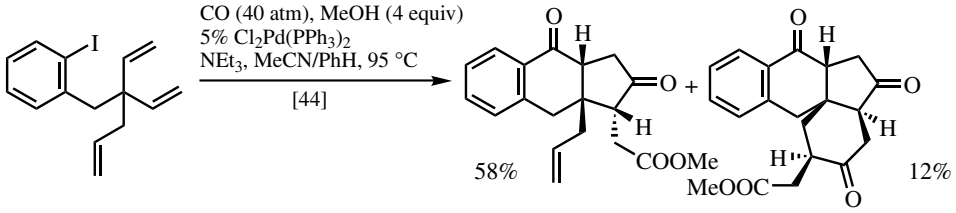


Scheme 30

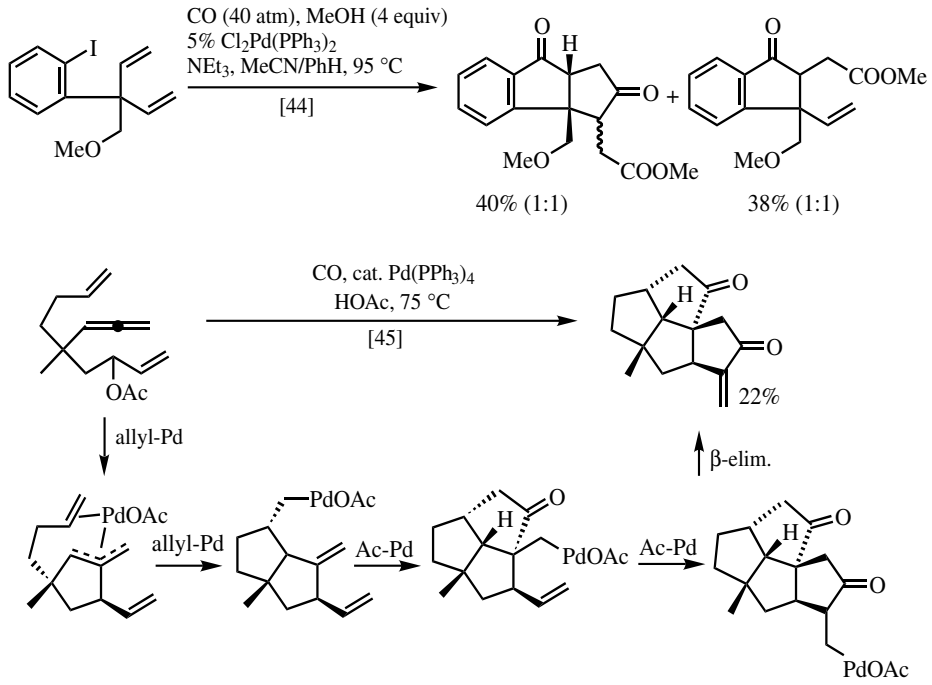


R	Time (h)	Yield (%)	dr
Me	8	70	2:2:1
CH_2OMe	14	72	2:1
$CH_2C{\equiv}CC_4H_9$	6	54	2:1



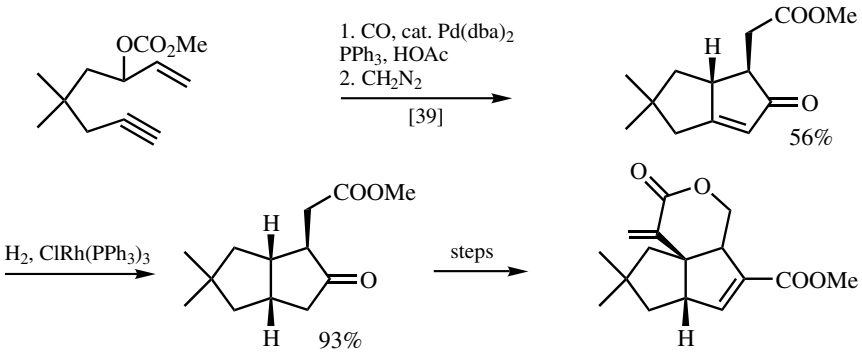


Scheme 31 (*Continued*)



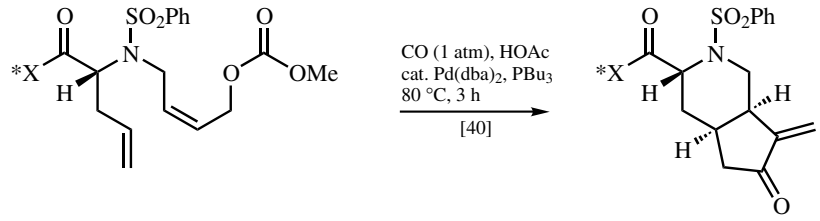
Scheme 31

(±)-pentalenolactone E methyl ester[39]

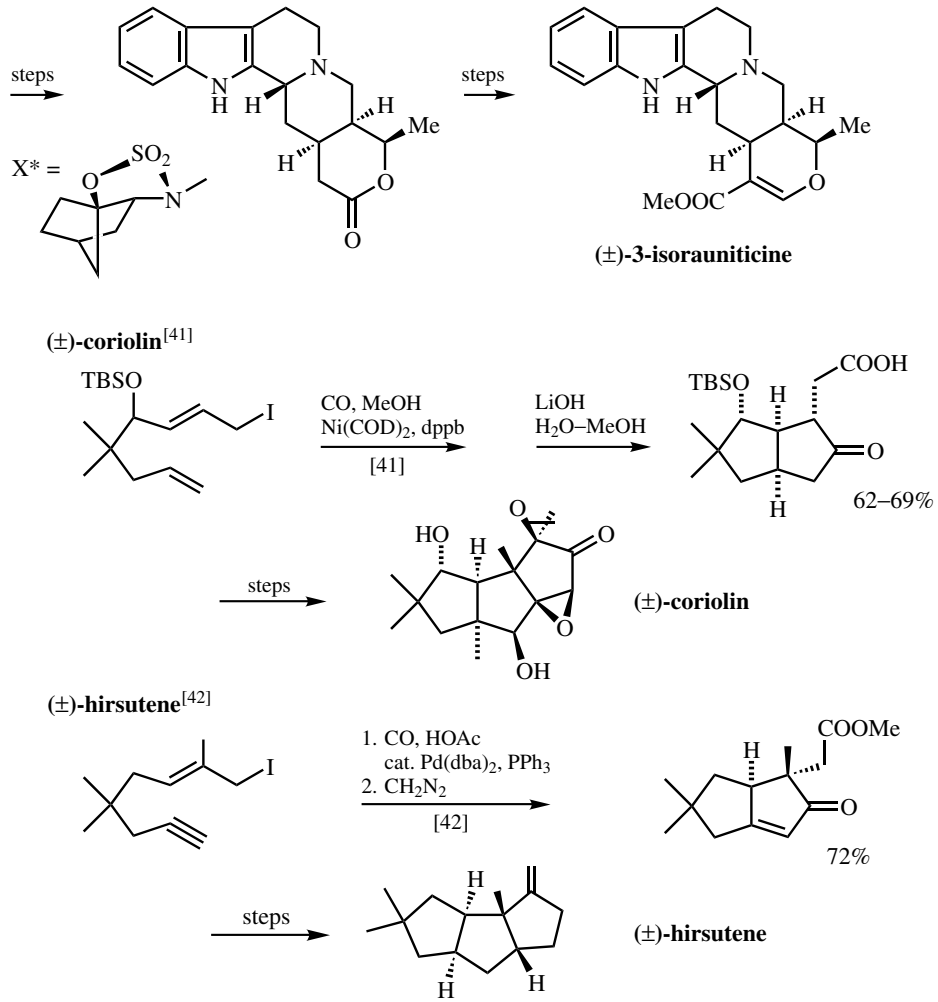


(±)-pentalenolactone E methyl ester

(±)-3-isorauniticine[40]



Scheme 32

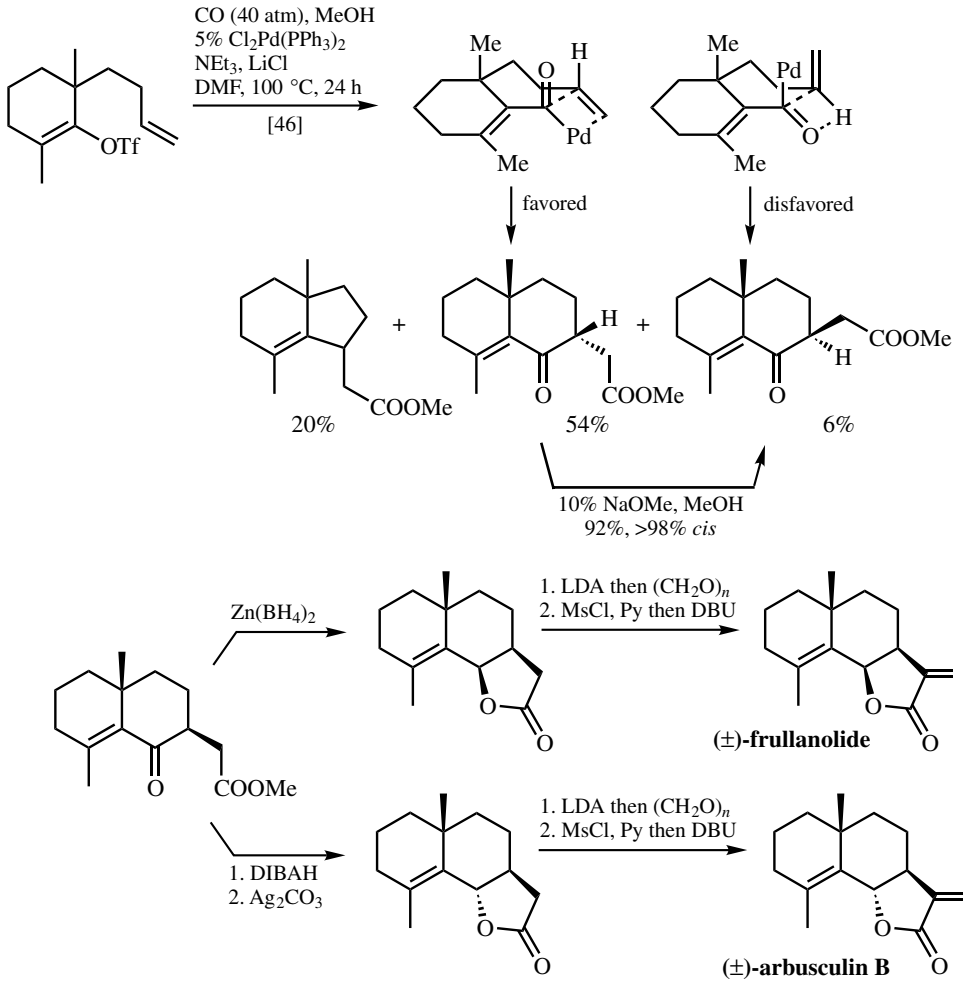


Scheme 32 (*Continued*)

(±)-Frullanolide and its epimer, arbusculin B, were synthesized by using the Type II Ac–Pd reaction, as summarized in **Scheme 33**.[46] Interestingly, the thermodynamically less stable epimer of the desired bicyclic ketone was obtained as the predominant product along with minor amounts of the desired epimer and the cyclic carbometallation–-carbonylative esterification products, but epimerization with 10% NaOMe in MeOH produced the desired *cis*-isomer, which was >98% isomerically pure.

E. SUMMARY

Despite many possible complications and limitations, the Pd-catalyzed cyclic acylpalladation is now a viable and potentially useful synthetic methodology in cases where the desired cyclic ketones are five- or six-membered. After the discoveries by Brewis and



Scheme 33

Hughes[4],[5] in the mid-1960s, however, nothing had been achieved for almost two decades. A systematic investigation by Negishi and co-workers[6]–[13],[15]–[17],[19],[25] mostly during the 1983–1988 period not only developed Types I–III Ac–Pd processes as potentially useful synthetic methods but also identified and clarified essentially all fundamental courses of the reactions that can occur under the Pd-catalyzed carbonylative conditions including ketene formation, cyclic carbopalladation–carbonylative trapping cascade (Type II C–Pd in **Scheme 8**), and cyclopropanation. Furthermore, various factors favoring or disfavoring given paths have been extensively delineated.[47],[48] As a result, suitable conditions for selectively producing five- and six-membered ketones may be experimentally found in many cases, even though accurate prediction of the precise courses among numerous possible paths remains difficult.

Significant expansion of the scope of the Pd-catalyzed cyclic acylpalladation was made by the development of the cyclic allylpalladation–acylpalladation cascades reported mainly during the 1988–1992 period by Oppolzer and co-workers.[30],[33],[34],[36],[39]–[42]

Particularly noteworthy is that their potential utility in the synthesis of complex natural products was repeatedly demonstrated through the synthesis of such targets as pentalenolactone E methyl ester, 3-isorauniticine, and hirsutene.

The development of the Pd-catalyzed cyclic acylpalladation methodology over the past decade has become more diverse and widespread with emphasis on various cascading processes. Notable among others are (i) Grigg's extension of the Type II Ac–Pd process to include organometals and metal hydrides as nucleophilic trapping agents and development of the carbopalladation–acylpalladation cascades developed since 1993,[18],[20],[21],[23],[43] (ii) development of double and triple acylpalladation cascades by Negishi and co-workers[44] and Yamamoto and co-workers[45] since 1996, (iii) application of the Oppolzer protocol to the synthesis of fenestranes by Keese and co-workers,[37] and (iv) development of enantioselective cyclic acylpalladation by Hayashi and co-workers.[24]

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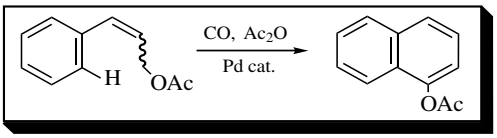

VI.4.1.2 Intramolecular Acylpalladation with Arenes

YOUICHI ISHII and MASANOBU HIDAI

A. INTRODUCTION

Reactions of acylpalladium complexes involving acylpalladation with arenes or formally equivalent processes have been much less exploited compared with those involving acylpalladation with alkenes or alkynes discussed in the previous section, and to the best of our knowledge, their examples are limited to intramolecular reactions. A few reactions that may include the intramolecular acylmetallation with arenes are known in the case of a rhodium catalyst, but the products are limited to a narrow range of compounds such as indenones.[1] In contrast, the Pd-catalyzed carbonylation of 3-arylallyl acetates or halides, most typically cinnamyl acetate, involving intramolecular acylpalladation with arenes results in the construction of 1-naphthol, which is a hiding member of cyclic aromatic ketones. The outline of the conversion is sketched in **Scheme 1**. In fact, this type of carbonylation–cyclization reaction (cyclocarbonylation) can be applied to the synthesis of a variety of fused aromatics, which is summarized in the following subsection.

B. CATALYTIC CYCLOCARBONYLATION OF 3-ARYLALLYL ACETATES

Carbonylation of cinnamyl acetate in the presence of NEt_3, acetic anhydride, and catalytic amounts of a palladium phosphine complex such as $Cl_2Pd(PPh_3)_2$ gives 1-naphthyl acetate in good yield (**Scheme 2**).[2],[3] Esterification of 1-naphthol, the initial product, by acetic anhydride is essential to avoid side reactions leading to a complex mixture. Cinnamyl bromide reacts similarly, but the yield is lower probably because formation of the quaternary ammonium salt from the bromide and NEt_3 competes with the carbonylation. This reaction is applicable to the synthesis of various substituted 1-naphthyl acetates. In the reaction of cinnamyl acetates with a meta-substituent, two possible regioisomeric products are obtained, where the para-cyclization predominates.

3,3-Diarylallyl acetates are converted to biaryls by this carbonylation reaction.[4] When 3-(3,5-dichlorophenyl)-3-(4-methylphenyl)allyl acetate is used as the substrate, only the cyclization at the C_6H_4Me ring is observed, although the stereochemistry of the starting compound is favorable for the cyclization at the $C_6H_3Cl_2$ ring (**Scheme 3**). Since the

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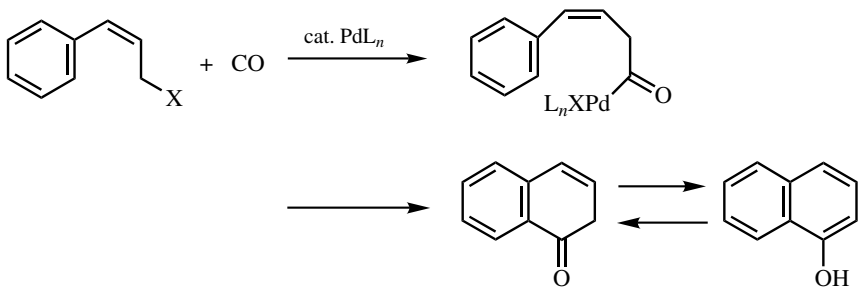
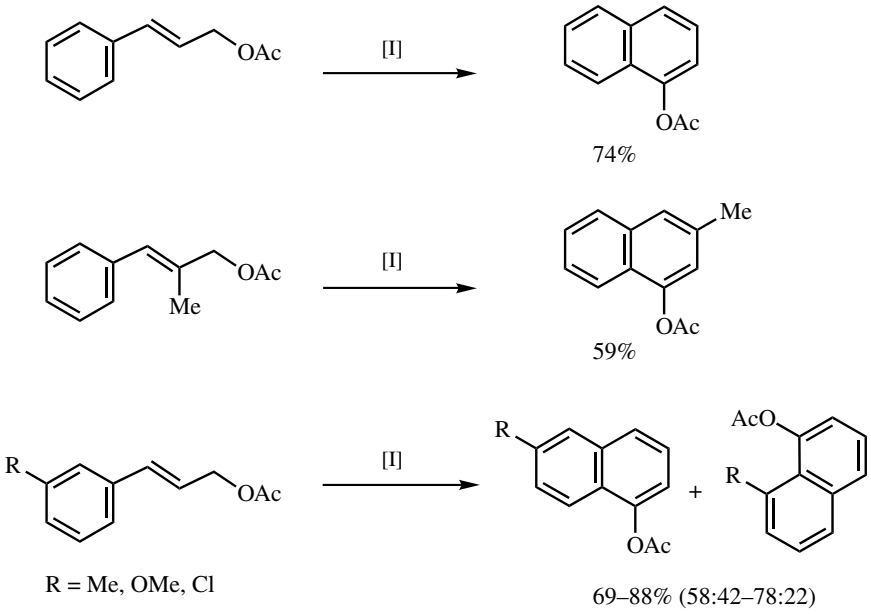


Scheme 1



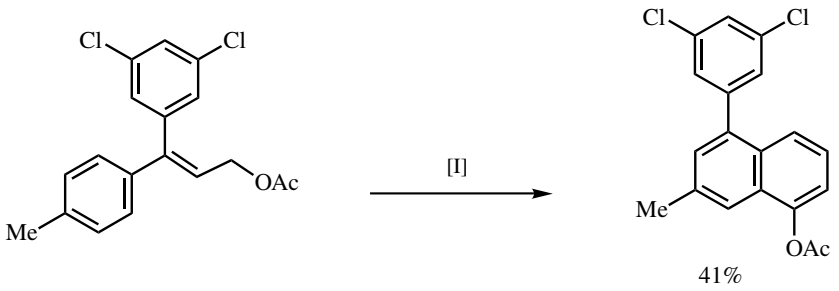
[I] = CO (60 atm), acetic anhydride (2 equiv), NEt_3 (2 equiv), 5 mol % $Cl_2Pd(PPh_3)_2$, benzene, 160 °C, 1 h.

Scheme 2

cyclocarbonylation of 3-(3,5-dimethylphenyl)-3-(4-methylphenyl)allyl acetate gives a 1:1 mixture of the two possible isomeric products, the acylpalladation is considered to occur at the more electron-rich aromatic ring.

Analogous carbonylation of naphthylallyl acetates provides a selective route to synthesize phenanthrenes (**Scheme 4**).[5] 3-(1-Naphthyl)allyl acetates cyclize at the β-position to give 1-phenanthryl acetates. Interestingly, 3-(2-naphthyl)allyl acetates are also transformed into 4-phenanthryl acetates via the selective cyclization at the α-position of the naphthalene ring, and no anthracene derivatives are detected, although the cyclization at the α-position seems to be the sterically less favored process.

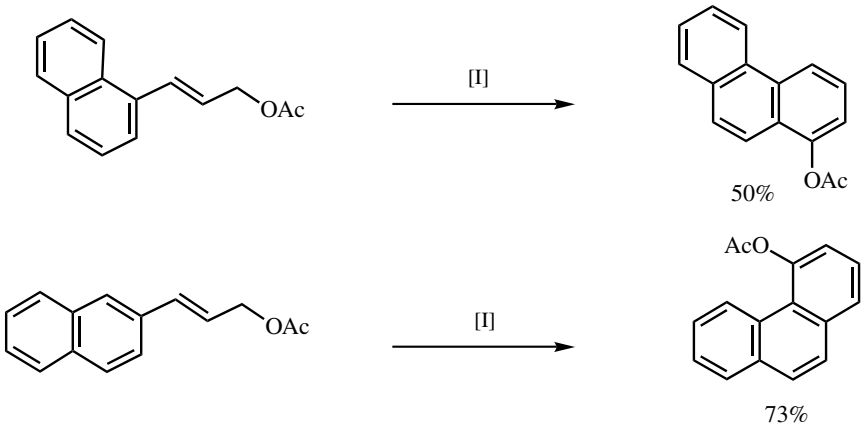
This type of carbonylation can further be applied to the synthesis of a variety of fused heteroaromatic systems.[6],[7] Allylic acetates with a furyl, thienyl, pyrrolyl, or indolyl substituent at the 3-position are transformed into the corresponding benzofuran, benzoth-



41%

[I] = CO (55 atm), acetic anhydride (2 equiv), NEt_3 (2 equiv), 5 mol % $Cl_2Pd(PPh_3)_2$, benzene, 160 °C, 6 h.

Scheme 3



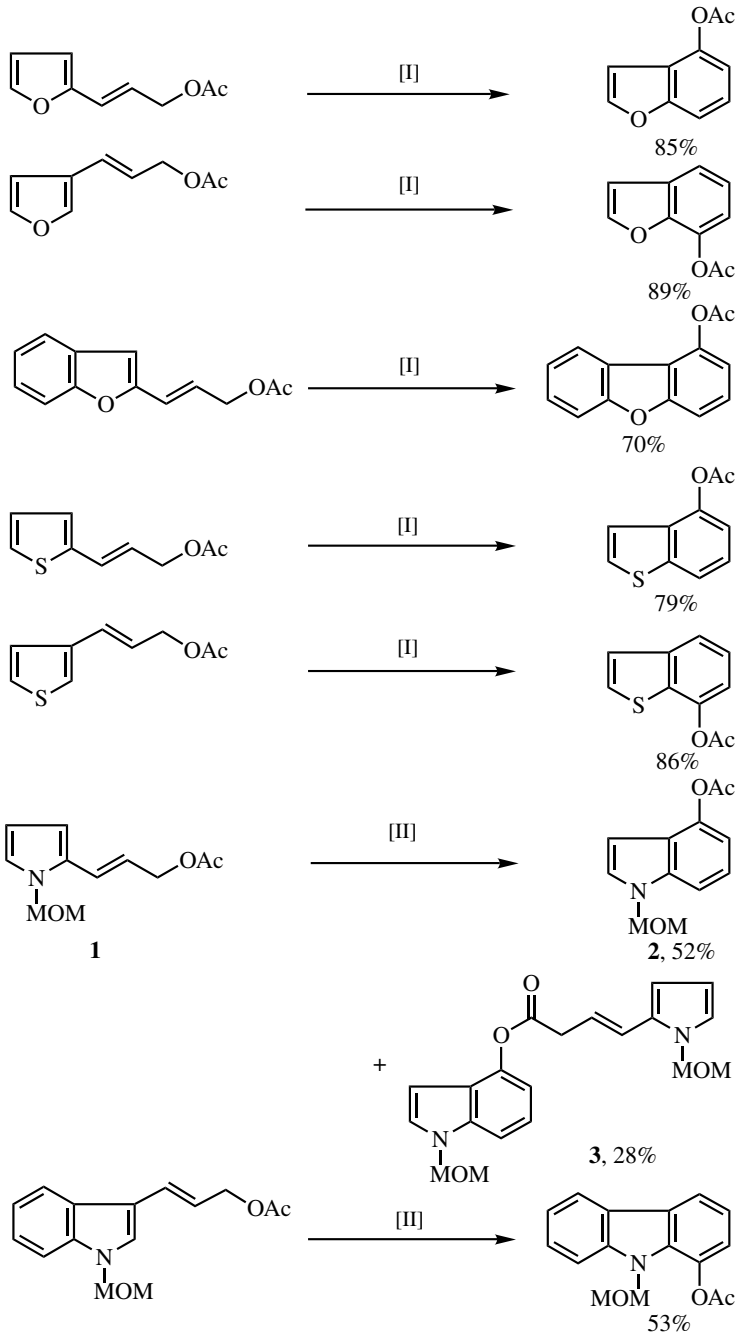
[I] = CO (70 atm), acetic anhydride (2 equiv), NEt_3 (2 equiv), 5 mol % $Cl_2Pd(PPh_3)_2$, benzene, 170 °C, 1.5 h.

Scheme 4

iophen, indole, or carbazole derivatives (**Scheme 5**). 3-(3-Furyl)- and 3-(3-thienyl)allyl acetates underwent selective cyclization at the 2-position of the heteroaromatic nuclei to give 7-benzofuryl and 7-benzothienyl acetates, respectively. This reaction is particularly useful in synthesizing multisubstituted fused-ring aromatics with functional groups at specific positions. One typical example is demonstrated in a facile synthesis of cannabifuran (**5**) (**Scheme 6**). In this case, compound **4** is the only regioisomer formed, and complicated purification procedures can be avoided.

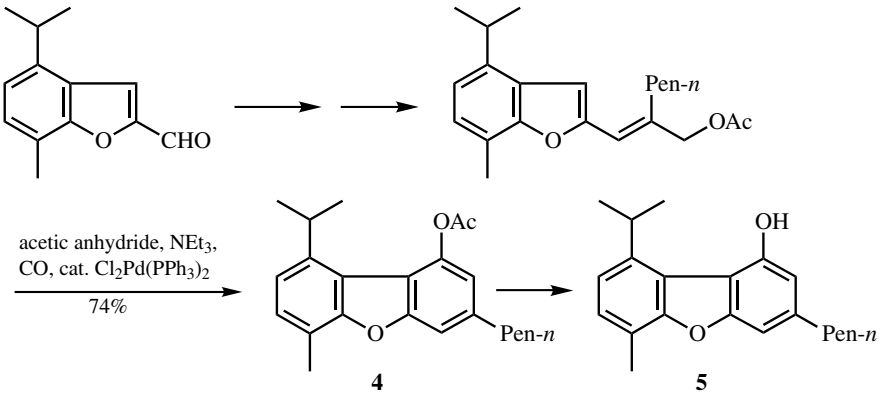
In the carbonylation of cinnamyl acetate, relatively high reaction temperatures (typically 160–170 °C) are necessary, and the yield of 1-naphthyl acetate drops drastically at lower temperatures. On the other hand, 3-(2-furyl)allyl acetate undergoes the cyclocarbonylation even at 100 °C to give 4-acetoxybenzofuran in 48% yield. In contrast, the cyclocarbonylation of 3-(3-pyridyl)allyl acetate is not observed under any conditions examined. The reactivity order of the furan, benzene, and pyridine rings is in agreement with the above-mentioned findings that the more electron-rich aromatic ring shows the higher reactivity for the acylpalladation.

As shown in **Scheme 5**, the carbonylation of 3-(3-pyrrolyl)allyl acetate (**1**) afforded compound **3** in addition to the expected product **2**. The formation of **3** is explained by the



[I] = CO (70 atm), acetic anhydride (2 equiv), NEt_3 (2 equiv), 5 mol % $Cl_2Pd(PPh_3)_2$, benzene, 170 °C, 1.5 h.
[II] = CO (70 atm), acetic anhydride (2 equiv), NEt_3 (2 equiv), 5 mol % $Cl_2Pd(PPh_3)_2$, benzene, 130 °C, 1.5 h.

Scheme 5

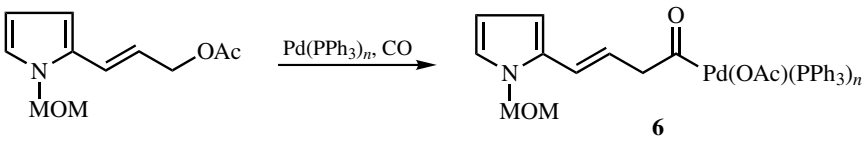


Scheme 6

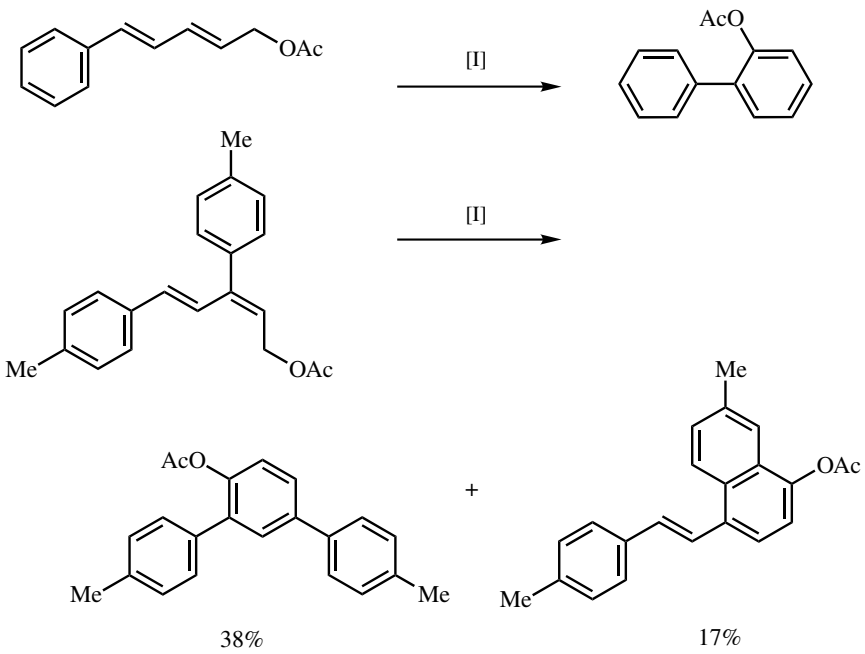
reaction between 4-hydroxy-1-methoxymethylindole and an acylpalladium complex **6**, the latter of which is assumed to be formed by oxidative addition of the allylic acetate to a Pd(0) complex followed by CO insertion (**Scheme 7**). Furthermore, the acylpalladium complex [(PhCH═CHCH$_2$CO)PdBr(PPh$_3$)$_2$] (**7**), which is prepared by the reaction of [Pd(CO)(PPh$_3$)$_3$] and cinnamyl bromide under 20 atm of CO and exists in solution as a 1:1 mixture with [(PhCH$_2$CH═CHCO)PdBr(PPh$_3$)$_2$], gives 1-naphthyl acetate on treatment with acetic anhydride and NEt$_3$ at 160 °C under CO pressure.[3] These facts clearly indicate that unsaturated acylpalladium complexes analogous to **6** and **7** are key intermediates for the cyclocarbonylation of 3-arylallyl acetates.

Although the detailed mechanism of the ring closure of the acylpalladium complexes has not been fully elucidated, the selectivities observed for the above reactions suggest that the ring closure step, which corresponds to the intramolecular acylpalladation, may involve electrophilic attack of the acyl ligand on the aromatic ring. An alternative mechanism includes generation of an alkenylketene intermediate followed by its intramolecular cyclization. In fact, ketene formation from acylpalladium species has been postulated in the carbonylation of several *o*-allylbenzyl chlorides,[8] and chromium-mediated intramolecular cyclization of alkenylketenes with arenes has also been reported to be a key step for the synthesis of naphthol derivatives. However, the Pd-catalyzed reaction of 3-arylallyl acetates is not necessarily congruent with the chromium-mediated reaction in terms of selectivities.[4],[9]

Finally, it would be interesting to compare the above reactions with the related Pd-catalyzed carbonylation of 2,4-pentadienyl acetates to give phenol derivatives (**Scheme 8**).[10],[11] The latter reaction is supposed to proceed via intramolecular acylpalladation with an olefinic C═C bond. The second reaction shown in **Scheme 8**, which affords both cyclization products at the arene ring and the alkene moiety in ca. 1:2 ratio, suggests that the intramolecular acylpalladation with arene rings is as favorable as that with alkenes.



Scheme 7



[I] = CO (50 atm), acetic anhydride (2 equiv), NEt_3 (2 equiv), 3 mol % $Cl_2Pd(PPh_3)_2$, benzene, 140 °C, 3 h.

Scheme 8

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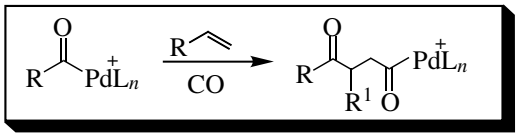

VI.4.2 Polymeric Acylpalladation

GIAMBATTISTA CONSIGLIO

A. INTRODUCTION

The acylpalladation of olefins, when followed by the insertion of carbon monoxide (**Scheme 1**), represents the essential step[1] in the synthesis of the so-called polyketones, namely, of the alternating copolymers of olefins with carbon monoxide. Shell's introduction of Carilon,[2] an alternating carbon monoxide olefin copolymer based on ethene and small amounts of propene, onto the market and the resulting commercial competition[3] have spurred extensive research in this field.

Not only have various copolymers with different structure been synthesized,[4] but the nature of the steps leading to the macromolecular structure has also been extensively investigated both experimentally[5] and theoretically.[6]–[8] It has long been known that it is possible to produce polyketones through the carbonylation of olefins by means of palladium catalysis.[9] However, Sen and Lai were the first to use cationic square planar palladium systems such as $[(PPh_3)_xPd(CH_3CN)_{4-x})](BF_4)_2$.[10] Related cationic complexes, modified by Drent with chelate ligands instead of the monodentate ligands,[11] led to the development of systems with catalytic activity high enough for the industrial production of polyketones.[12] Cationic complexes should ensure the presence of accessible coordination sites, whereas chelate ligands should cause cis-coordination of the groups and, thus, enable easy migratory insertion reactions.

B. GENERAL ASPECTS OF THE SYNTHESIS OF POLY(OLEFIN-*ALT*-CO) COPOLYMERS

An important aspect of the copolymerization reaction is concerned with the structure of the alternating olefin–carbon monoxide copolymers. Depending on the substituent and on the olefin substrate the materials can be isolated with either the expected polyketone structure **1** (**Scheme 2**) or the isomeric polyspiroketal structure **2**.[13]

The relative thermodynamic stability of the two structures is unknown; however, it seems to be subject to enthropic factors. The spiroketal structure is particularly stable for norbornene[14] or bicyclopentadiene.[4] For propene, even if the copolymer is formed with the polyspiroketal structure it transforms easily into the polyketone one when heated[15] or when acidic conditions are applied. The reverse is true for allylbenzene.[16],[17] For

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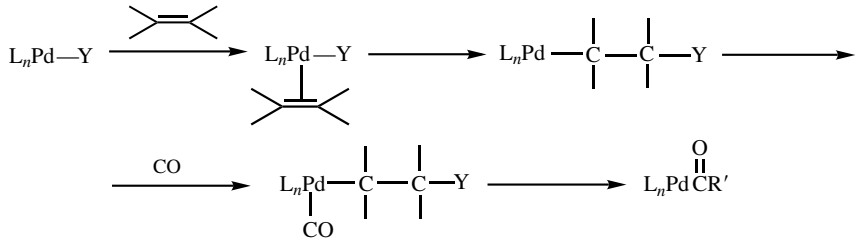
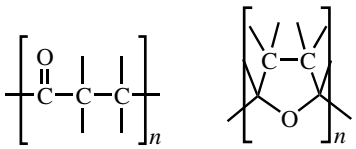


Y = CO—R or —CO—GPC, —H, —COOR (GPC = growing polymer chain)

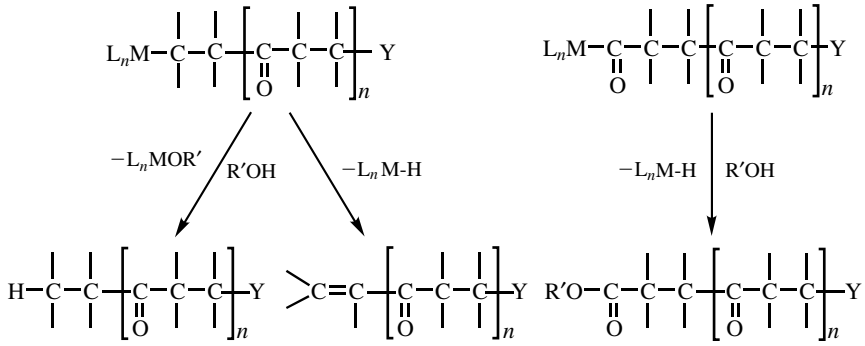
Scheme 1



1 **2**

Scheme 2

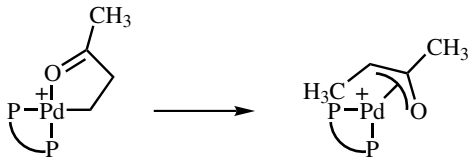
copolymers of 1-hexene[18] and 4-methyl-1-pentene[14] both structures can be observed together. Furthermore, nothing has been reported about the existence of structure **2** for styrene or similar aromatic olefins. The kinetic role of the nonclassical spiroketal structure is, as yet, unknown. It is prevailingly assumed that it is formed after the classical insertion reactions described in **Scheme 1**.[15],[16] This is consistent with the propensity of acylpalladium intermediates for reacting with enolates.[19] End group analysis of the alternating olefin–carbon monoxide copolymers has been reported only in connection with the polyketone structure and reveals the presence of alkyl-, vinyl-, and carbalkoxy terminations.[12],[20],[21] Accordingly, for catalytic systems formed *in situ*, the reaction is initiated by a palladium–hydride or a palladium–carboalkoxy species, depending on the reaction conditions.[22] Sequences of steps (as represented in **Scheme 1**) will lead to the formation of polymeric materials (**Scheme 3**). After carbon monoxide insertion, termination can be caused by alcoholysis; alternatively, after olefin acylpalladation, β-hydrogen elimination or protonolytic cleavage can cause chain growth to cease.



Y = H or COOR′

Scheme 3

The most commonly used catalyst precursors are species of the type $[(L\hat{}L')Pd(S_2)](X_2)$, where L^L′ is a chelate ligand with L = or ≠ L′, S is a weakly coordinating molecule (e.g., a solvent molecule), and X is an anion with low coordination ability. These species can be used as such or can be formed *in situ*. Mixed $[(P\hat{}P')Pd(N\hat{}N')](X_2)$ complexes have also found application.[23],[24] Possible pathways for the formation of the true initiating species (a palladium–hydride[25] or a palladium–carboalkoxy complex[26]) have been identified. Alternatively, preformed complexes close to the propagating species such as $[(L\hat{}L')Pd(CH_3)(S)](X)$[27] or similar compounds containing palladium to carbon σ-bonds[28] have been used as the catalyst precursor. In the latter case, the presence of alcoholic solvents can be avoided, thus suppressing possible termination reactions. As a matter of fact, it has been reported that the copolymerization of 4-*tert*-butylstyrene, with chlorobenzene as the solvent, at ambient temperature and pressure exhibits the characteristics of a living polymerization.[27] However, with the exception of the ethene copolymers,[12] the most important termination appears to be represented by the β-hydrogen elimination.[20],[21] The reaction of $[(P\hat{}P)Pd(COCH_3)\ (CH_3CN)](CF_3SO_3)$ (where P^P is dppp or dppf) with ethene gave the olefin insertion products, which were found to isomerize in the absence of CO to the corresponding enolate complexes (**Scheme 4**), possibly via β-hydrogen elimination and fast reinsertion.[29]



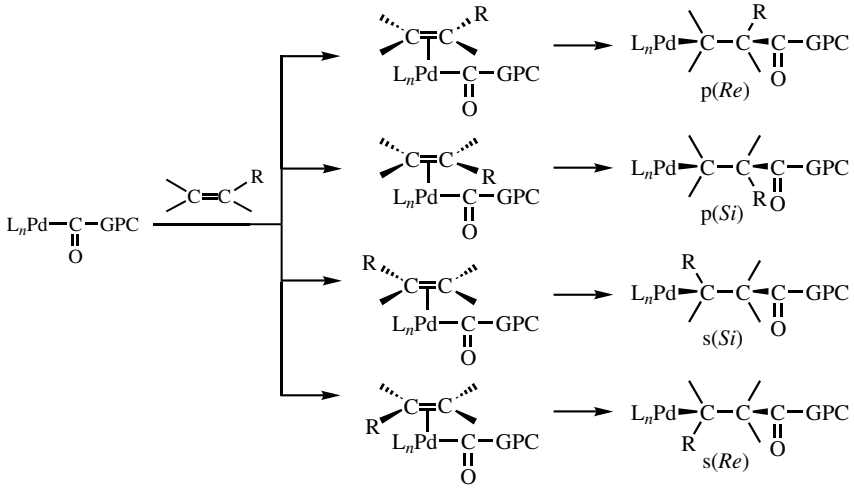
Scheme 4

A copolymerization experiment of ethene using a related *in situ* formed catalytic system, modified with dppp, was carried out in CH_3OD. The produced copolymer showed propionyl end groups, most of which were labeled at the α-position. This result was interpreted by assuming chain transfer through protonation by methanol at the level of the enolate with the intermediate formation of a palladium–methoxy species.

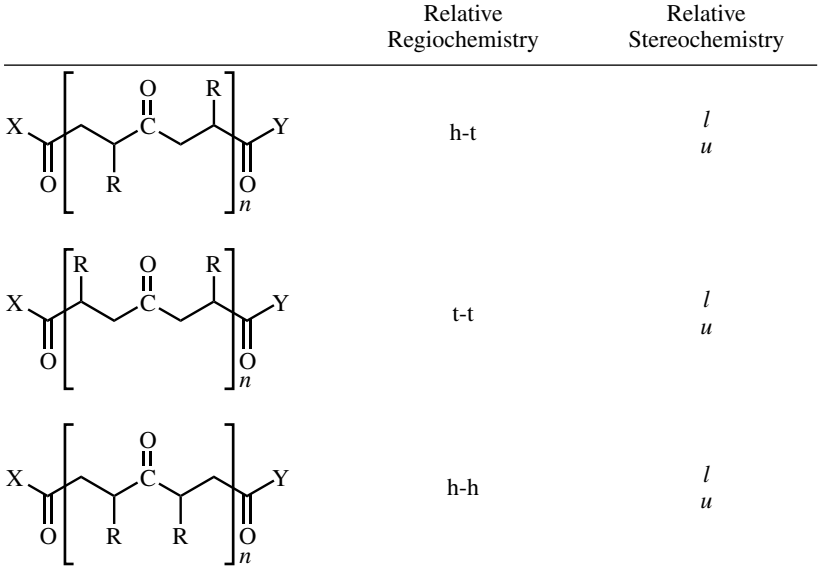
C. OLEFIN ACYLPALLADATION: REGIO- AND STEREOCHEMICAL CONSIDERATIONS

The stereochemistry of the copolymerization reaction corresponds to a *syn*-addition to the double bond, at least with styrene as the substrate.[30] Therefore, to discuss aspects of regio- and stereochemistry, we will consider the olefin coordination possibilities for migratory insertion (**Scheme 5**). This scheme shows the four possibilities that are labeled according to regiochemistry (primary (p) versus secondary (s) insertion) and the inserted enantioface (the stereochemical descriptors are for $R = CH_3$).[31] The structure of the produced materials will be determined by the regio- and stereochemical relationships between two consecutively inserted olefin units (formation of a diad) (**Scheme 6**). When C_s-symmetric olefins are used as the substrate, stereochemical information will always be found in the growing chain. This will, to some extent, modify the stereochemical information arising from the presence of chiral ligands and/or from the geometry of the catalytic species. Even in the absence of chiral

ligands, the catalytic complex could be chiral because of its geometry and, therefore, could cause stereochemical control. To achieve the synthesis of regioregular copolymers of 1-olefins, only the regiospecificity of the insertion is necessary, independent of whether a primary or secondary insertion takes place during acylpalladation.



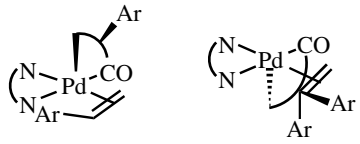
Scheme 5



Scheme 6

The aspect of stereocontrol in achiral systems is particularly evident in the case of the regiospecific copolymerization of styrene[32] (and of homologues thereof[27]) with [(L^L)Pd(S_2)](X_2) or [(L^L)Pd(CH_3)(S)](X) catalyst precursors (L^L is 1,10-phenanthroline or 2,2′-bipyridine) to poly(1-oxo-2-phenyl-1,3-propanediyl) with the prevailing (~90%) formation of *u*-diads, independent of the anionic ligand.[28],[33],[34] According to

Scheme 5, it seems logical that the insertion of the olefin should occur with *l*-topicity with respect to the preceding insertion, when regiochemistry is maintained and the geometry of the species involved in the insertion remains the same. On the other hand, despite the secondary styrene insertion,[34] the efficient enantioface discrimination during acylpalladation remains puzzling, being determined by a rather remote inducing center. Theoretical calculations[6],[7] and model compounds[35] suggest, however, that, in the species responsible for acylpalladation, the metal may be pentacoordinated[4] as a result of chelation of the growing chain caused by the interaction of the first keto-oxygen of the growing chain with the electrophilic metal center. The geometry of the last inserted olefin unit would, therefore, influence the direction of spiralization of the chain to chelate, and this, in turn, will cause stereogenicity at the metal (**Scheme 7**) to efficiently discriminate between the enantiofaces to form a *u*-diad.



Scheme 7

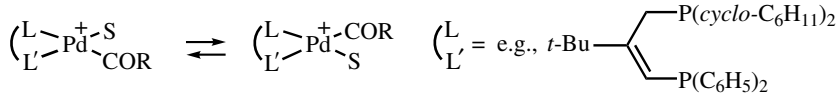
D. OLEFIN ACYLPALLADATION AND CARBON MONOXIDE INSERTION: MODEL STUDIES

Various model studies for the acylpalladation of olefins and for carbon monoxide insertion into palladium–carbyl species have been reported and have recently been summarized.[5] The results obtained with complexes of the type [(L^L)Pd($COCH_3$)(S)](X) (L^L being a diphosphine or a dinitrogen ligand or $2PPh_3$) have proved the greater reactivity of cationic species compared with neutral species.[36],[37] Furthermore, when substrates such as norbornene were used, a diastereospecific *syn*-addition on the *exo*-face was always observed.[26],[38]–[42] Starting with [(Phen)Pd($COCH_3$)(S)][{3,5-$(CF_3)_2C_6H_3$}$_4$B], an active catalyst precursor for styrene, ethene, and norbornene copolymerization, low-temperature NMR spectroscopy revealed formation of the corresponding ethene complex [(Phen)Pd($COCH_3$)(CH_2═CH_2)](X).[43] This led to an accurate definition of the mechanistic aspects of the copolymerization reaction and of the thermodynamic and kinetic parameters responsible for the strict alternation observed. According to this investigation, the insertion of ethene corresponds to the rate-determining step during the copolymerization process, whereas the catalyst resting state is the carbonyl–acyl complex [(Phen)Pd(CO-GPC)(CO)](X). Accordingly, carbon monoxide inhibits the reaction rate.[43] Similar results were obtained with 4-*tert*-butylstyrene as the olefin. In this case exclusive secondary insertion was observed,[27] which has been rationalized on the basis of π-benzylic stabilization of the insertion product. Similarly, a π-benzylic complex seems to form in the insertion of styrene into [(P^P)Pd($COCH_3$)(CH_3CN)](CF_3SO_3) (where P^P is dppp or dppe).[26] However, even when the above intermediate was not evident, as in the case of [(Pr^iDab)Pd($COCH_3$)(S)](X),[44] where Pr^iDab is 1,4-diisopropyl-1,4-diazabuta-1,3-diene, a regiospecific secondary insertion was observed.

The acylpalladation of aliphatic 1-olefins has been studied to a lesser extent. In the reaction of [(dppp)Pd($COCH_3$)(S)](X) and 1-pentene, formation of hept-3-en-2-one (the product of β-hydrogen elimination after secondary olefin insertion) was observed.[26] A

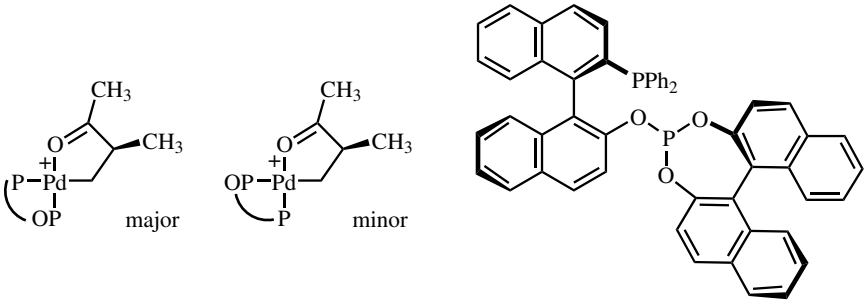
similar [(dppe)Pd($COCH_3$)(S)](X) complex undergoes insertion of cyclopentene to form the corresponding 1,2-addition product, in which the oxygen of the acetyl group coordinates to the metal (compare **Scheme 4**).[45]

The investigation of the olefin insertion using complexes of the type [(L^L′)Pd($COCH_3$)(S)](X) (where L^L′ is a C_s-diphosphine ligand) has proved that the reaction corresponds to a migration of the acyl group on the coordinated olefin.[41],[46] For this type of complex, however, two diastereomeric forms can exist, each with different reactivity (**Scheme 8**). The different stability and reactivity have been associated with the different *trans*-effect of the ligand components L and L′.[42],[47],[48] Greater stability is associated with lower reactivity.



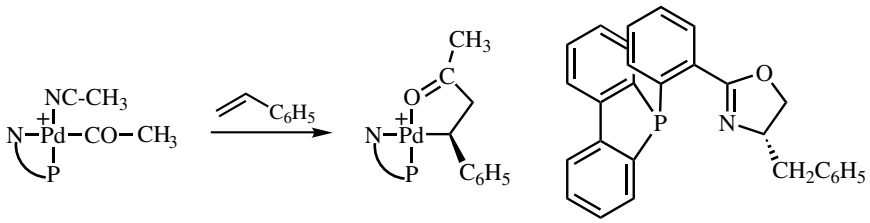
Scheme 8

The enantioselectivity in the acylpalladation of propene (and of labeled 1-dodecene) has been studied in a similar [{(*R*,*S*)-BINAPHOS}Pd($COCH_3$)(S)](X) system, where (*R*,*S*)-BINAPHOS is (*R*)-2-diphenylphosphino-1,1′-binaphtalen-2′-yl-(*S*)-1,1′-binaphthalene-2,2′-diyl-phosphite (**Scheme 9**).[49],[50] In spite of the fact that, in this case, two diastereomeric olefin insertion products are formed in a 80:20 molar ratio (cf. **Scheme 9** for the proposed structure), enantioface discrimination seems to be high. Through the reaction of the insertion products with methanol and carbon monoxide, methyl (*S*)-3-methyl-4-oxopentanoate was recovered with 68% yield and 95% ee. The system produced poly(1-methyl-2-oxo-propanediyl) with complete regioregularity and high isotacticity (*Vide infra*).



Scheme 9

Insertion of aromatic olefins (styrene and/or homologues thereof) was studied not only with the aforementioned N^N-modified catalytic systems[27],[44] (N^N is 2,2′-bipyridine or 1,10-phenanthroline) but also with [{(*S*)-Bz-DBHOSOX}Pd($COCH_3$)(Solvent)](OTf), where (*S*)-Bz-DBPHOSOX is (*S*)-2-[2-(5*H*-benzo[*b*]phosphinindol-5-yl)phenyl]-4-benzyl-4,5-dihydrooxazole (**Scheme 10**).[51],[52] The insertion was regiospecific, both with respect to palladium and to styrene (alkyl and acyl substituents *trans* to N, secondary insertion) and diastereospecific, only one diastereomeric complex being recognizable through multinuclear NMR spectroscopy.



Scheme 10

For related ligands in which the phosphorus substituent is bound to 2-substituted phenyl ring (such as *o*-tolyl or *o*-anysil), some primary insertion was also observed.[53]

D.i. Acylpalladation of Aliphatic 1-Olefins: Olefin–Carbon Monoxide Copolymerization

The discovery that $[(P\hat{}P')Pd(S_2)](X_2)$ catalyst precursors[11] were active enough to cause acylpalladation of 1-olefins in addition to ethene[54]–[56] led to the development of commercial terpolymers and to the synthesis of copolymers of those olefins with carbon monoxide. However, the use of chelate aromatic diphosphine ligands such as dppp or d*o*Anpp gave regioirregular copolymers (**Table 1**). The table gives results obtained in the copolymerization of propene with carbon monoxide using related catalytic systems. Two aspects of the process are particularly important. First, the use of basic ligands (alkyl substituents on the phosphorus) leads to the formation of completely regioregular copolymers. This remarkable improvement in the regioselectivity is essentially independent of steric factors.[21],[57],[58] Second, efficient steric control of the growth process (probably by the chain end) leads to a prevailingly isotactic copolymer, in contrast to the above-mentioned styrene copolymerization with achiral catalysts precursors (*vide infra*). End group analysis of the copolymers[21] as well as the analysis of the composition of the codimers (dimethyl dimethyl-4-oxopimelates, **Scheme 6**, R = CH_3, X = Y = OCH_3) obtained with the same catalytic systems under slightly modified conditions[31] seems to indicate that basic ligands promote migration of the

TABLE 1. Regioselectivity (Expressed as Molar Fraction of the Possible Diads) in the Copolymerization of Propene with Carbon Monoxide Catalyzed by the Complexes $[(CH_2(CHR'PR_2)_2)Pd(H_2O)_2](X_2)$

$CH_2(CHR'PR_2)_2$		Copolymer			
		Regiochemistry			Stereochemistry
R =	R′ =	h-h	h-t	t-t	*l*-diads (%)
C_6H_5	H	0.22	0.56	0.22	—
C_6H_5	CH_3[a]	0.10	0.80	0.10	(65)[a]
o-$CH_3OC_6H_4$	H	0.25	0.50	0.25	—
cyclo-C_6H_{11}	H	~0	~1	~0	80
i-C_3H_7	H	~0	~1	~0	82
C_2H_5	H	>0.5	<0.99	>0.5	83

[a]Chiral ligand; the evaluation is rough due to incomplete regioselectivity.

growing chain on the substituted carbon, leading to a primary insertion. This change in regioselectivity is difficult to rationalize on the basis of the polarization characteristics of the double bond.[59]

Surprisingly, the same primary insertion was observed only in systems containing the phosphine–phosphite ligand (*R*,*S*)-BINAPHOS (**Scheme 9**).[49] This ligand causes a highly enantioselective propene–carbon monoxide copolymerization,[60] as do many other atropisomeric ligands having alkyl substituents on the phosphorus.[21] Furthermore, the catalyst precursor [{(*R*,*R*)-Me-DUPHOS}Pd$(CH_3CN)_2$]$(BF_4)_2$, where (*R*,*R*)-Me-DUPHOS is 1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene, also gives isotactic poly(1-methyl-2-oxo-propane-1,3-diyl).[16] The most active catalyst precursor we found to date is [{(*R*)(S_p)-Josiphos}palladium(II)bisaquo]triflate, where (*R*)(S_p)-Josiphos is 1-[2-(diphenylphosphino)ferrocenyl]ethyl(dicyclohexylphosphine).[61] In spite of the lack of C_2-symmetry, a highly isotactic poly(1-methyl-2-oxo-propane-1,3-diyl) was produced. The microstructure of the copolymer did not change when the same catalyst, modified with the racemic ligand, was used, thus showing that the actual catalyst most probably contains only one ligand molecule and is mononuclear.

It is remarkable that only the polyketone structure was obtained with (*R*,*S*)-BINAPHOS and other related phosphine–phosphite ligands, some of which even contain a basic phosphine moiety (i.e., diethyl or dicyclopentyl),[60] considering that the more basic ligands produce the copolymer in the spiroketal structure. Moreover, the diethyl-substituted phosphine–phosphite system gave a regioirregular copolymer.

The relationship between the sign of the circular dichroism band, associated with the n-π^* transition of the carbonyl chromophore (and of the optical rotation), and the absolute configuration of the asymmetric carbon atoms of poly(1-methyl-2-oxo-propanediyl) (−/*S*) has been established, both on the basis of model studies[18] and on the chiroptical properties of the produced copolymers (octant rule).[21] Furthermore, the enantiomeric purity of the optically active poly(1-methyl-2-oxo-propanediyl) was also evaluated using NMR spectroscopy in the presence of a chiral europium shift reagent.[16] Unfortunately, however, an exact determination of the microstructure of the copolymer at the *n*-ads level has not yet been achieved. Preliminary attempts have been made to interpret the ^{13}C NMR spectral pattern of the carbonyl region of the copolymers produced with the chiral atropisomeric and ferrocenyl diphosphine ligands on the basis of a two-parameter model, associated with enantiomorphic site control and modified by the growing chain.[31] Evaluation of enantioface discrimination shows that, for systems producing isotactic chains, the probability of giving an *l*-diad is greater than the probability of giving a *u*-diad after the enchainment of an olefin unit with the incorrect enantioface; the latter probability is always greater than 0.5.[62]

The role played by the growing chain in the microstructure of the copolymer was studied by investigating the chiroptical properties of terpolymers containing ethene and propene, which were prepared with the above-mentioned [{(*R*)(S_p)-Josiphos}palladium(II)bisaquo]-triflate catalyst precursor.[63] With this catalytic system, the reactivity ratio between ethene and propene is close to 15 and the comonomer distribution seems to be random. Therefore, at low propene concentration, only isolated propene units are present in the chain; for these units, enantioface discrimination is probably controlled only by the enantiomorphic site. The higher intensity of the aforementioned circular dichroism band (and the higher rotatory power) observed for the copolymer rather than for the terpolymer should be associated with a more efficient enantioface discrimination due to the growing chain. This conclusion relies on the reasonable[16] assumption that the contribution to the optical activity normalized to

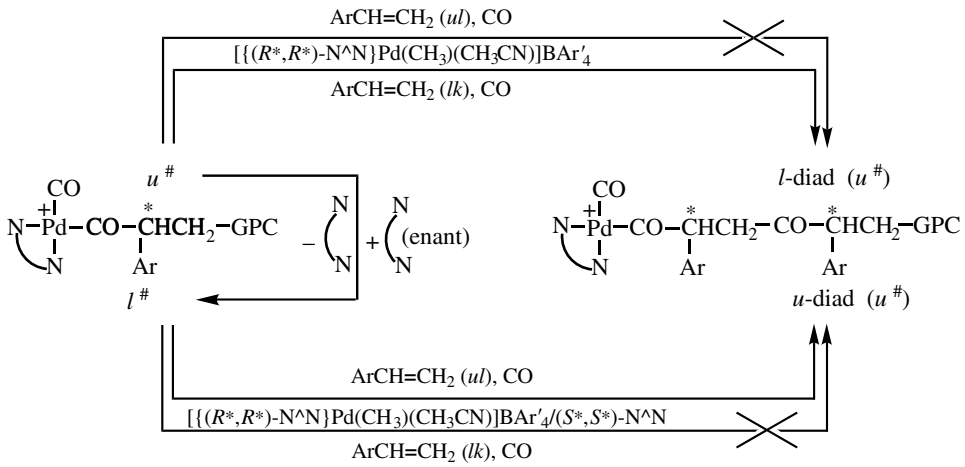
the propene content is not influenced by particular conformational effects caused by the neighboring groups.

D.ii. Aromatic Olefin–Carbon Monoxide Copolymerization

The first successful copolymerization of styrene was achieved by using catalyst precursors modified with dinitrogen ligands (1,10-phenanthroline or 2,2′-bipyridine),[32] usually in the presence of an oxidant such as 1,4-benzoquinone.[64] These catalysts give regioregular syndiotactic copolymers.[33] The diphosphine-modified systems resulted in rapid β-hydrogen elimination after 3-phenypropionyl-palladation of a second styrene unit with secondary insertion, leading to the selective formation of (*E*)-1,5-diphenyl-pent-1-en-3-one.[65] Some modification of the microstructure of the copolymers toward an atactic enchainment was achieved by using dithioethers as the ligands.[66] Those ligands, however, gave systems with marginal catalytic activity. Similarly, atactic copolymers were obtained using $[(P\hat{}N)Pd(H_2O)_2](CF_3SO_3)_2$, where P^N is either 2-(2-diphenylphosphinoethyl)pyridine (DPEPy) or 2-(diphenylphosphinomethyl)pyridine (DPMEPY).[67],[68] The first isotactic arene (i.e., 4-*tert*-butylstyrene) copolymers were obtained with $[(N\hat{}N)Pd(CH_3)(S)](X)$ catalyst precursors, where N^N is the C_2-symmetric ligand 2,2′-propanediylbis(4,5-dihydro-4-(1-methylethyl)-2-oxazole) (Pr^{i}PrOX).[69] Thereafter, a similar 4,4′,5,5′-tetrahydro-4,4′-bis(1-methylethyl)-2,2′-bioxazole (Pr^{i}BOX) was used to produce isotactic styrene or 4-methylstyrene copolymers.[70] Surprisingly, the $[(N\hat{}N')Pd(CH_3)(S)](X)$ system modified by the chiral C_1-ligand (*S*,*S*)-2-(2-pyridyl)-3-phenyl-4-methoxymethyl-4,5-dihydrooxazole (PyEPHOX) gave copolymers with a prevalent syndiotactic structure.[68],[69] Taking advantage of the coordination lability of the above chiral N^N type of ligand and of the seemingly living nature of the copolymerization process, styrene copolymers containing sterically different blocks were synthesized.[71] Starting with $[(N\hat{}N)Pd(CH_3)(S)](X)$, where N^N is (*S*,*S*)-2,2′-propanediylbis({4,5-dihydro-4-methyl}-2-oxazole), isotactic poly(1-oxo-2-(4-*tert*-butylphenyl)-1,3-propanediyl) blocks grew on the catalytic system. Addition of 2,2′-bipyridine caused displacement of the bis-oxazoline ligand on the catalytic system, thus enabling the growth of a syndiotactic block. From the point of view of the factors involved in the stereocontrol, the addition of 1 equiv of the enantiomeric (*R*,*R*)-ligand gave a more interesting result. This again caused the formation of the syndiotactic copolymer with a rate enhancement with respect to the formation of the isotactic copolymer (**Scheme 11**).

It is assumed[71] that ligand exchange is rapid with respect to chain growth (facile ligand exchange was verified by NMR). The intermediate $u^{\#}$-complex, which forms as a consequence of olefin insertion, is less stable than, and transforms rapidly into, the $l^{\#}$-complex. The latter complex is more reactive toward olefin insertion.

Unfortunately, a detailed analysis of the microstructure of the produced copolymers has not yet been made. Even though the mechanism of stereocontrol is clearly of the enantiomorphic site type, the role of the growing chain has not been fully determined. The coordination lability of the above-mentioned bis-dihydrooxazole ligands, as demonstrated by the easy exchange reaction, causes decomposition of the catalytic systems at high carbon monoxide pressures. A greater stability of the catalytic system is obtained using hybrid phosphino-dihydrooxazole ligands (cf. **Scheme 10**); with these systems, high pressures of carbon monoxide can be used.[67] In contrast to the dinitrogen ligands, the rate order with respect to the carbon monoxide of the latter systems is very close to



$u^{\#}$, $l^{\#}$ relative absolute configuration of the ligand and of the center of asymmetry of the growing chain closest to the metal

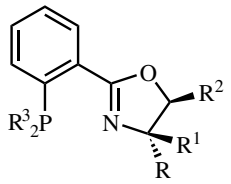
ul, *lk* relative topicity of the center of asymmetry of the growing chain closest to the metal and of the olefin enantioface to be inserted

u, *l* relative absolute configuration of two consecutive centers of asymmetry in the polymeric chain (i.e., name of the diad formed)

N ^ N = 2,2′-propanediyl-bis(4,5-dihydro-4-methyl)-2-oxazole

Scheme 11

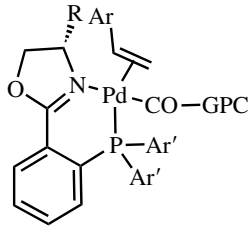
one,[53] so that productivity is increased at higher concentrations of carbon monoxide. Use of various optically active phosphino-dihydrooxazole ligands with different substituents (**Scheme 12**) led us to the following conclusions:[68]



Scheme 12

1. Efficient enantioface selection during insertion is caused by monosubstitution at the C4-carbon atom of the dihydroxazole ring (R or R^1 = H). The enantioface prevailingly inserted (and, therefore, the absolute configuration of the asymmetric carbon atoms in the polymeric chain) depends on the geometry of the C4-carbon atom. The presence of an R^2 substituent is not essential for the discrimination process.
2. In the absence of R^2, when the two substituents at C4 are equal to (R = R^1 = H or CH_3) or when they are both different from hydrogen, essentially atactic copolymers are produced. However, the system containing a chiral ligand (R = CH_3, R^1 = $C_6H_5CH_2$, R^2 = H) also gave the atactic copolymer. Increasing steric hindrance at C4 caused decreased catalytic activity.

The above observations led to a model for olefin insertion as shown in **Scheme 13**. This scheme assumes the ubiquitous secondary insertion for styrene.[72] The enantioface prevailingly reacted is determined by steric interaction between the substituent R on the chiral ligand and that on the olefinic double bond. It is very difficult to precisely evaluate enantioface selectivity, due to the small difference in the chemical shift of diads arising from insertions with different regiochemistry. The growing chain seems to play a secondary role in the polymerization process with this type of ligand. As described in **Sect. C**, the enantioface discrimination for the insertion of styrene into the palladium–acyl bond of [(P^N)Pd($COCH_3$)(S)](OTf) (where P^N is Bz-DBPHOSOX, (**Scheme 10**) seems to be complete. Furthermore, the enantiomeric excess of dimethyl 2-phenylbutanedioate, which forms in trace amounts in the copolymerization experiments and which should derive from styrene insertion into a [{(P^N)Pd($COOCH_3$)(S)](OTf) species, is close to 95%.



Scheme 13

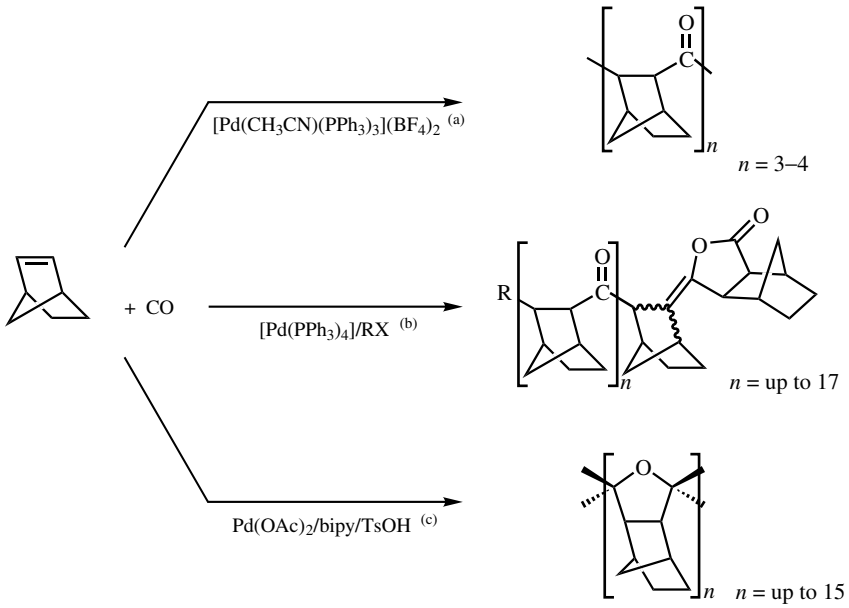
A similar conclusion about the minor role played by the growing chain was reached in the study of the chiroptical properties of the materials obtained in terpolymerization reactions with ethene.[52],[73] The rotatory strength of the circular dichroism band associated with n-π^* transition of the carbonyl chromophore for the terpolymers, extrapolated to 100% styrene content, is only slightly more intense than the band of poly(1-oxo-2-phenylpropanediyl) (maximal deviation ~15%). Terpolymers of styrene and ethene were first synthesized with the 1,10-phenanthroline-modified catalyst precursor.[74] Loss of tacticity (from syndiotactic) was claimed, based on the disappearance of the fine structure (due to coupling) in the proton NMR of the signal corresponding to the styrene units. However, the broadening of the bands might simply be caused by the different chemical environment, due to the presence of ethene units. The terpolymerization with [(N^N′)Pd(H_2O)$_2$](CF_3SO_3)$_2$, where N^N′ is the C_1-ligand 2-(2-pyridyl)-3-phenyl-4-methoxymethyl-4,5-dihydrooxazole, gave terpolymers in which the intensity of the CD band increased with decreasing styrene content (-7.6 L/mol·cm for a terpolymer containg ~7% of styrene).[68] The prevailingly isotactic styrene copolymer, obtained with the same catalyst, showed a $\Delta\varepsilon$ of ca. -1.6. Considering that the maximum intensity of this band obtained with the most enantioselective catalyst precursors was close to -13, these results show the importance of the growing chain in modifying the enantioface discriminating properties of this chiral ligand.

Another aspect of interest related to the terpolymerization with the P^N systems is the relative rate of the copolymerization of styrene and ethene. The aromatic olefin copolymerizes more rapidly than ethene, but, much more ethene is inserted in the terpolymerization experiment. Therefore, the synthesis of terpolymers with high styrene content using

these catalysts is difficult, in contrast to systems containing the N^N-ligands phenanthroline or PyEPHOX. Model experiments have shown that ethene inserts more rapidly than styrene into the palladium–acyl bond of [(Bz-DBPHOSOX)Pd($COCH_3$)(S)](OTf).[52] Thus, the above behavior is ascribed to a nonreversible olefin coordination favoring ethene, followed by a more difficult carbon monoxide insertion into a palladium–primary carbon bond than into a secondary benzylic–carbon bond. Similar effects have been reported for the enantioselective terpolymerization of 4-*tert*-butylstyrene and propene with [((*R*,*S*)-BINAPHOS)Pd($COCH_3$)(S)](X) (see **Scheme 9**) as the catalytic systems.[75] The enantioface discriminating ability of this system toward the two olefinic substrates does not seem to be influenced by the insertion of the alternative olefin comonomer.

D.iii. Copolymerization of Carbon Monoxide with Cyclic and Internal Olefins

The carbonylation of norbornadiene to polyketones with unmodified palladium catalysts was reported long ago.[76] [$(PPh_3)_xPd(S_{4-x})$]$(BF_4)_2$ complexes were also found to be active for this substrate and for norbornene and give low molecular weight materials (**Scheme 14**).[10] Recent investigations using the same catalytic system led to the chromatographic isolation of codimers and cotrimers, the latter with a ketal–lactone structure.[77] Oligomers (up to 2100 molecular weight) with a lactone termination were also obtained using [$(PPh_3)_4Pd$] activated by benzylbromide or β-bromostyrene.[78],[79]



(a) $CHCl_3$ as the solvent, 60 °C.

(b) 1 bar CO, 80 °C in the presence of Na_2CO_3; R = $C_6H_5CH{=}CH$ — or $C_6H_5CH_2$—.

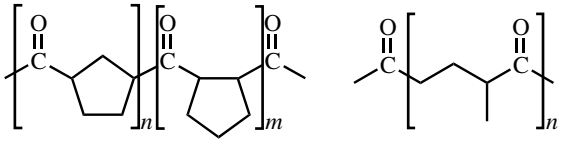
(c) CH_3OH as the solvent, 40 bar CO, 40 °C in the presence of 2,4-$(NO_2)_2C_6H_3CH_3$.

Scheme 14

The copolymers obtained with various cationic systems modified with chelate diphosphine or dinitrogen ligands always showed cis-*exo*-stereochemistry. Cooligomers with the spiroketal structure were obtained in methanol as the solvent using systems formed

in situ.[14] The structure was stable during chromatography on silica using methylene chloride as the solvent. Due to the complexity of the NMR spectra, however, no useful information on the end group was obtained. Analogously, with the same catalytic system the dicyclopentadiene copolymer formed in the spiroketal structure and was stable regardless of heating and acid conditions.[4] Electron-poor bicyclic olefins (diethyl bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate and diethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate) were copolymerized using various neutral palladium(II) initiators, such as iodo(*endo*-6-phenyl-2-norbornene-*endo*-5σ,2π)(triphenylphosphine)palladium(II). The copolymerization is living and gives access to poly(acetylene-*alt*-CO) via a retro Diels–Alder reaction.[80]

The reaction with cyclic unstrained olefins, such as cyclopentene, and with internal olefins is unusual. Despite the clean 1,2-insertion of cyclopentene into the metal–acyl bond of complexes of the type [(P^P)Pd($COCH_3$)(S)](X) (cf. **Scheme 4**), the poly(cyclopentene-*alt*-CO) was produced with a prevailing 1,3-enchainment (**Scheme 15**).[81] The molecular weight of the materials produced with various diphosphine ligands was rather low (highest molecular mass ~8500) in most cases. Similarly, *Z*-2-butene using [(*R,R*)-Me-DUPHOS)-Pd($CH_3CN)_2$]($BF_4)_2$ as the catalyst precursor gave oligomers with 1,3-enchainment (**Scheme 15**). These oligomers showed optical activity and were claimed to be isotactic.



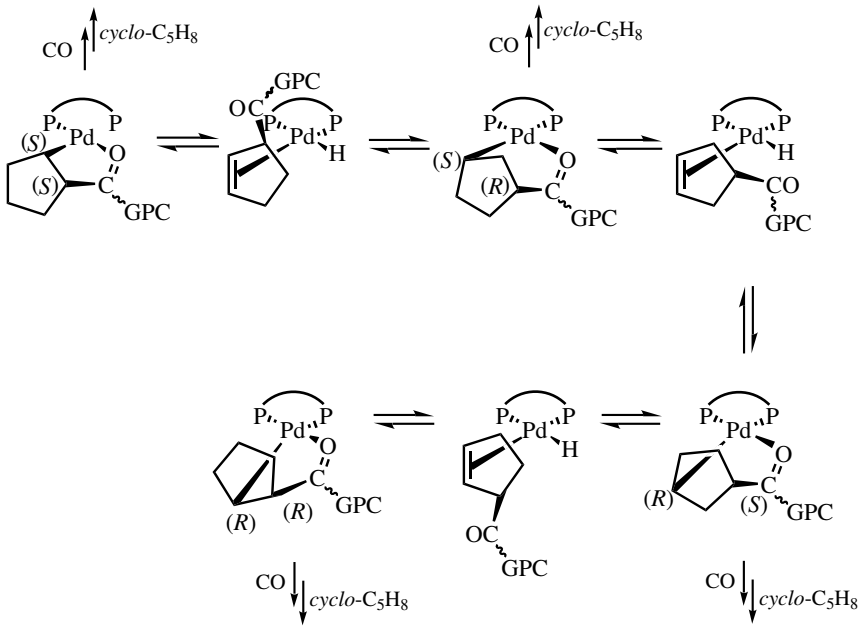
Scheme 15

According to ^{13}C NMR spectroscopy, the cyclopentene copolymers appear to be stereoregular and probably prevailingly diisotactic. Large differences were not observed for materials prepared with the achiral or chiral catalysts modified by either dippp or bdpp. However, the two regiochemical situations have not been clearly identified in the carbonyl region of the spectrum. The prevailing 1,3-enchainment is probably a consequence of the normal 1,2-insertion followed by β-hydrogen elimination and readdition without dissociation of the formed unsaturated moiety to give a less hindered intermediate (**Scheme 16**).[81]

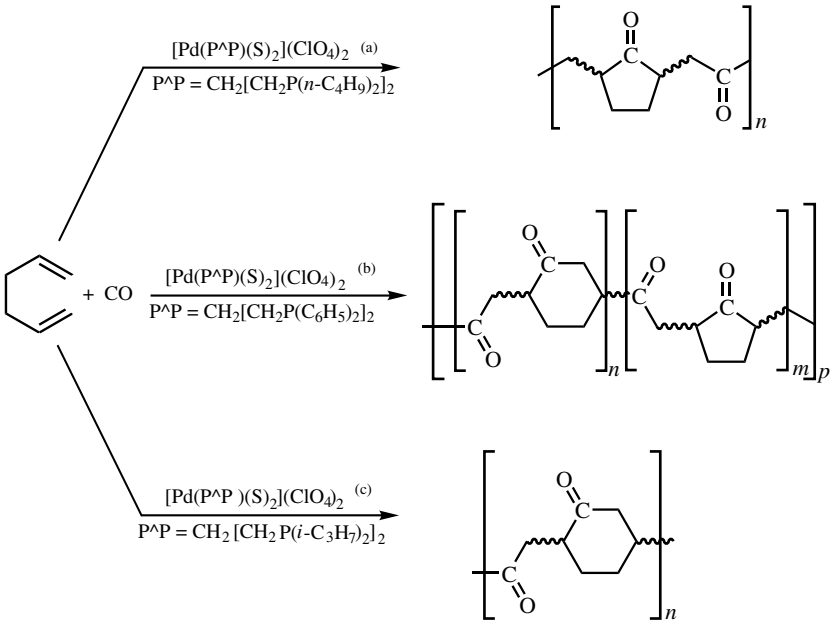
Remarkably, the catalytic systems formed by palladium(II) acetate and boron trifluoride, modified by the same ligands, give stereoirregular materials, independent of ligand chirality. As shown in **Scheme 16**, stereorandomization can be caused by migration of the metal on the cyclopentene ring. Therefore, formation of atactic copolymers might be a consequence of the unsaturated nature of the catalytic species and of a more rapid β-hydrogen elimination and readdition with respect to carbon monoxide insertion.

D.iv. Cyclocopolymerization of α,ω-Dienes with Carbon Monoxide

Under conditions of high dilution, α,ω-dienes were observed to cyclocopolymerize; only a very small number of unreacted double bonds remained in the polymeric material.[82] Starting with 1,5-hexadiene and using systems formed *in situ* in methanol from palladium acetate, the diphosphine ligand, and nickel perchlorate (as the source of the perchlorate anion), different microstructures were produced, depending on the ligand (**Scheme 17**).



Scheme 16



(a) CH_3OH as the solvent, 40 bar CO, 50 °C.

(b) CH_3OH as the solvent, 40 bar CO, 25 °C.

(c) $CHCl_3$ as the solvent in the presence of CH_3OH, ~35 bar CO, 25 °C.

Scheme 17

The cyclohexanone structure obtained with the dippp ligand was assumed to form as a result of two primary insertions of the two double bonds of the substrate. This and the absence of regularity observed with homologous phenyl-substituted ligands are in keeping with the results obtained for propene as the substrate reported above. Based on that similarity, the cyclopentanone structure reported for the dnbppp-containing catalytic system is surprising.[83] However, that structure is not supported by experimental data. Analogous to the catalyst containing the dippp ligand, the [((*R,S*)-BINAPHOS)Pd(CH_3)(CH_3CN)](X) catalyst precursor produced the cyclohexanone structure.[84] However, whereas the latter system gave no diastereoselectivity (*cis/trans* = ~1), with the former system the diastereomeric ratio was close to 3, most probably in favor of the *cis*-form. The (*R*,*S*)-BINAPHOS modified catalyst could also cyclocopolymerize 1,4-pentadiene regioselectively to the corresponding cyclopentanone structure. Again the diastereoselectivity for the insertion of the second double bond was very low (56:44).

E. FINAL REMARKS

The carbonylation of ethene to linear poly(1-oxo-1,3-propanediyl) was developed for commercial application by the identification of cationic palladium complexes modified by diphosphine ligands having high catalytic activity. The identification of such systems and their subsequent manipulation by changing the ligands have enabled the synthesis of copolymers of substituted ethenes with many possible microstructures, that is, regio regular and regioirregular as well as stereoregular and stereoirregular. The steric control in the carbonylation processes to polymeric materials is apparently more efficient than that to low molecular weight carbonylation products such as aldehydes, esters, and diesters. A still missing structure for the aliphatic olefin copolymers is that corresponding to a prevailingly *u*-enchainment. In addition, other substrates such as functionalized alkenes,[85] allenes (e.g., 3-methyl-1,2-butadiene),[86] cyclopentadiene,[87] and phenylacetylene[88] could be copolymerized and, in some cases, terpolymerized.[86],[89]

Unfortunately, stereoregular polyketones are not very stable from an optical point of view; epimerization is rather rapid in the melt.[14],[62] However, the very high enantioface discrimination obtained by means of copolymerization and the intriguing possibility of transforming these materials by a Baeyer–Villiger oxidation[90] or by oximation[91],[92] followed by Beckmann rearrangement might open an interesting method of synthesizing optically active polyhydroxyalkanoates and poly-α-amino acids starting from 1-olefins and carbon monoxide.

The catalytic systems used still require improvement with respect to stability, activity, and molecular weight control. New modifying ligands have already been proposed[93]–[97] and less conventional aqueous media have been applied in conjunction with water-soluble ligands.[98]–[100] Most important, however, appears the search for less expensive nickel catalysts.[101],[102]

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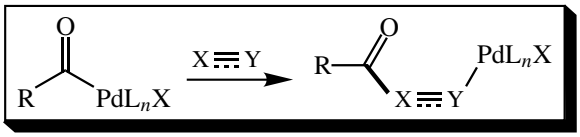

VI.4.3 Other Intermolecular Acylpalladation

CHRISTOPHE COPÉRET

A. INTRODUCTION

The intermolecular acylpalladation corresponds to the addition of an acyl–palladium bond onto a π-bond system of another molecule; this elementary step can also be referred to as an insertion (**Scheme 1**). This produces another organopalladium complex, which can in principle participate in subsequent propagation or termination reactions. This excludes processes that involve alkoxycarbonylation (R— = R′O—) and hydrocarbonylation (R— = H—). This section will focus on nonpolymeric intermolecular reactions of acylpalladium complexes with different π-bond systems (alkenes, imines, dienes, and alkynes).

B. ACYLPALLADATION OF ALKENES

Its stoichiometric version has been widely studied since it corresponds to the insertion of an olefin into an acylpalladium complex, the key step of the copolymerization of CO and ethylene (see **Sect. VI.4.2**).[1]

On the other hand, there are only a few reports of catalytic nonpolymeric reactions that involve the intermolecular reaction of an alkene with an acylpalladium complex. The first example was reported in 1968 while studying the decarbonylation of acyl chlorides in the presence of various palladium salts.[2] For example, phenylpropionyl chloride gave styrene (53%) along with 1,5-diphenyl-1-penten-3-one (10%) in the presence of catalytic amounts of $PdCl_2$. The latter compound was probably formed via reaction of the acylpalladium complex, generated via oxidative addition in the acyl–chloride bond, with styrene itself formed via decarbonylation of the acylpalladium complex followed by β-elimination (**Scheme 2**).

The complexity of this reaction scheme already points out the necessary time-balance between oxidative addition, CO insertion versus deinsertion (decarbonylation), acylpalladation, carbopalladation, and dehydropalladation events to have a selective acylpalladation-type reaction. This has been more recently addressed by selecting acyl chlorides that could not readily undergo dehydropalladation, hence stabilizing the organopalladium intermediates to favor their intramolecular reaction with alkenes. For instance, $Pd(OAc)_2$ catalyzes the reaction of benzoyl chloride derivatives with enol ethers (R = OEt, **Scheme 3**) to give the corresponding acylpalladation products typically in 40–77% yields.[3],[4]

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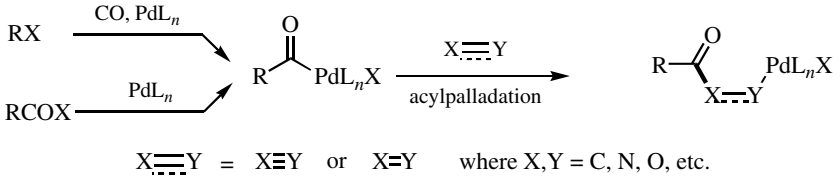
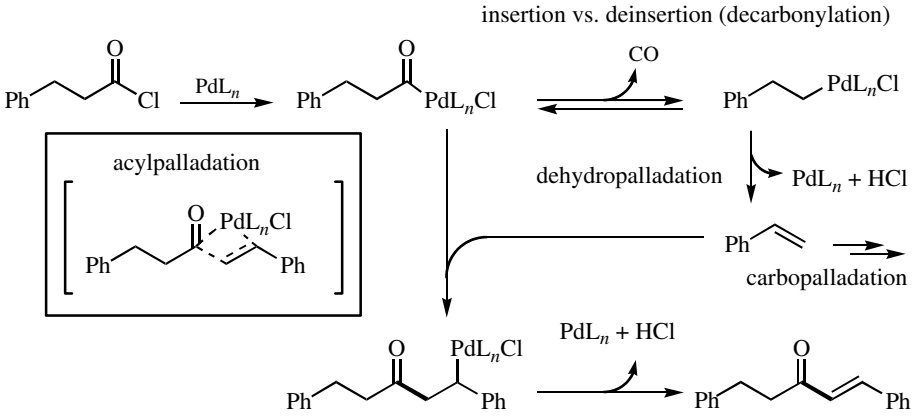
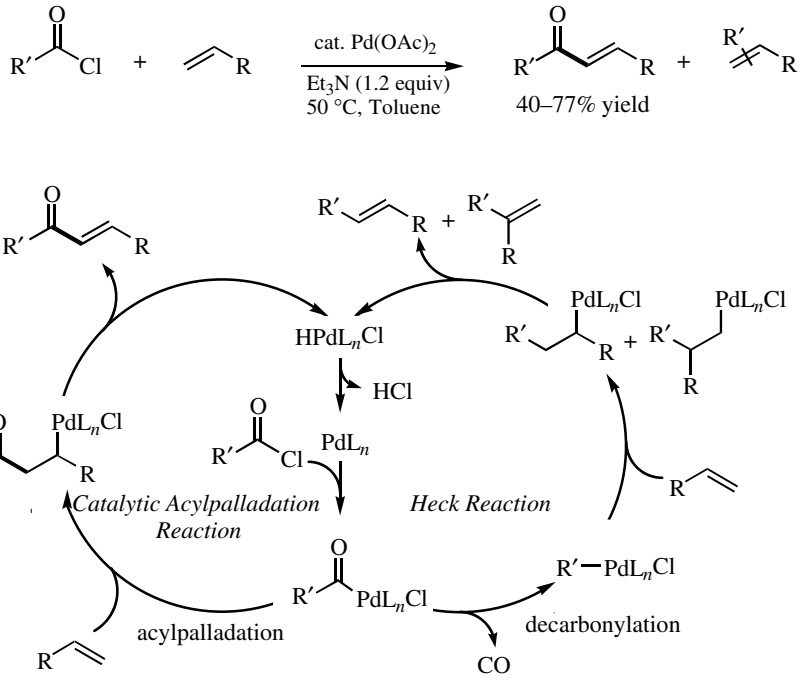


Scheme 1



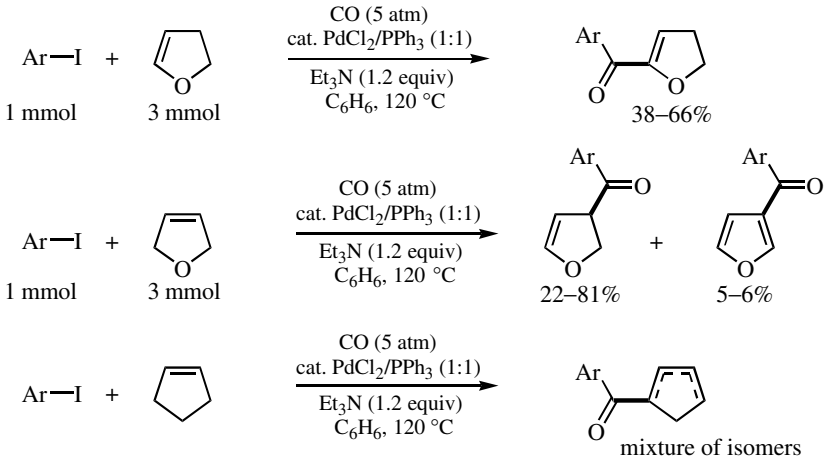
Scheme 2



Scheme 3

This reaction proceeds well under ligandless conditions ($PdCl_2$, $Pd(OAc)_2$, $PdCl_2(RCN)_2$). In fact, addition of small amounts of PPh_3 seems detrimental to this process. It is usually limited to electron-rich alkenes, mainly enol ethers, since other alkenes, like methyl acrylate or styrene, give very low yields of these acylpalladation products. Electron-withdrawing substituents on the aromatic ring of the benzoyl chloride derivatives decreased the yield of benzoylated products by favoring decarbonylation, hence the Heck reaction products. It is noteworthy that acylpalladation is regiospecific, while the corresponding Heck reaction gives a 1:1 mixture of both regioisomers under these conditions.

More recently, Miura and co-workers have investigated the reaction of 2,3- and 2,5-dihydrofuran derivatives with aryl iodides under carbonylative conditions.[5] The former exclusively gives 5-aroyl-2,3-dihydrofuran derivatives (38–66% yields), while the latter gives 3-aroyl-2,3-dihydrofuran derivatives (22–81% yields) along with small amounts of 3-aroylfuran derivatives (5–6%) (**Scheme 4**). In sharp contrast, cyclopentene gave a mixture of all potential isomers, showing the importance of the oxygen atom for the selectivity of this reaction.



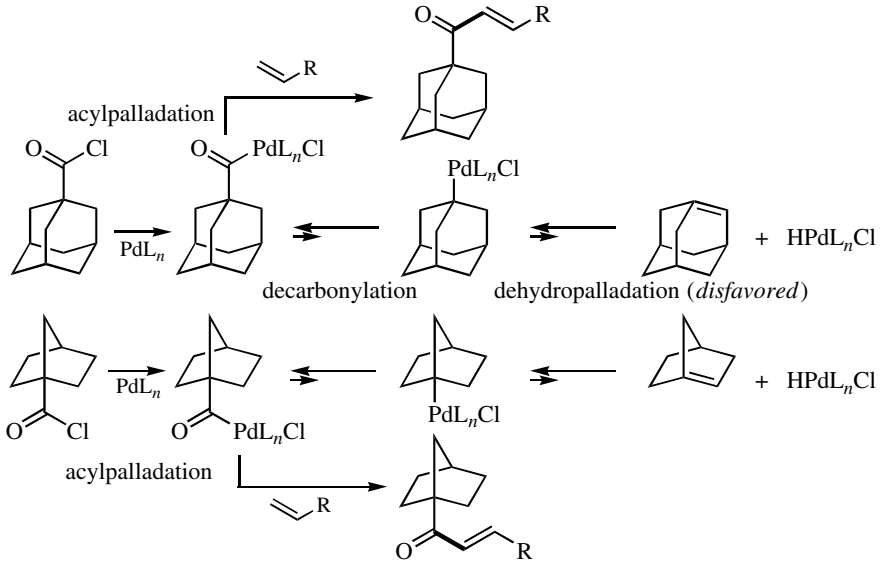
Scheme 4

Another example is the use of 1-adamantane- and 1-norbornanecarbonyl chlorides, which can also generate stable acylpalladium intermediates since both decarbonylation and dehydropalladation are disfavored (**Scheme 5**).[6] This allows the use of a wider range of alkenes (R = CN, CO_2R', Ph, $CONR'_2$) and gives acylpalladation products in 30–65% yields.

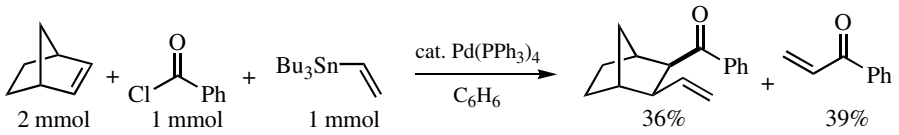
In all of these examples, the terminating step involves dehydropalladation, as in the Heck reaction. Organopalladium intermediates are known to participate in different termination steps, and therefore in tandem reactions.[7] This has been achieved in the case of a tandem acylpalladation/cross-coupling reaction. It requires an alkene, which is both very reactive and capable of generating a palladium intermediate that cannot readily undergo dehydropalladation (e.g., norbornene), and an alkenyltin reagent, that is, a slow cross-coupling agent to favor acylpalladation prior to cross-coupling (**Scheme 6**).[8]

In conclusion, the intermolecular acylpalladation of alkenes is, so far, limited to specific substrates, and this is mainly due to certain strict requirements, that is, (i) acylpalladation faster than decarbonylation and (ii) a termination step faster than polymeric pathway, and yet slower than acylpalladion itself. Attempts to control this reaction by

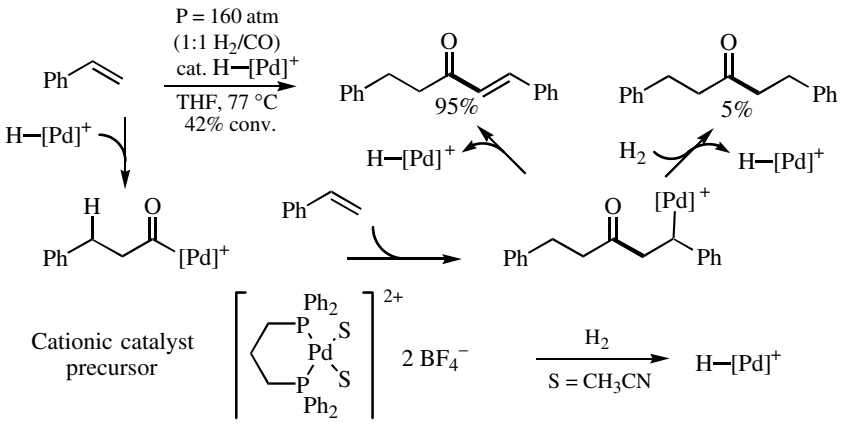
using external parameters like ligands have been usually unsuccessful due to their strong inhibiting effects. However, recent reports on a cationic palladium complex containing phosphine ligands showed promising selectivities for acylpalladation even under hydroformylation conditions (**Scheme 7**).[9],[10] The importance of carbonyl compounds in organic syntheses and the development of coordination chemistry will probably lead to the development of new selective reactions involving acylpalladation as a key step.



Scheme 5



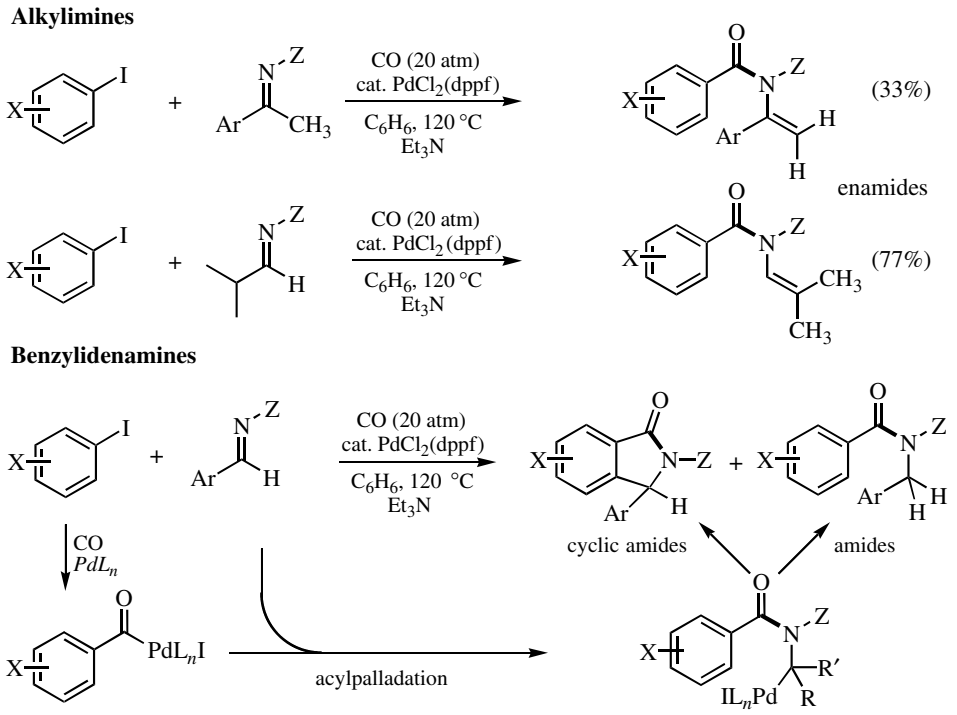
Scheme 6



Scheme 7

C. ACYLPALLADATION OF IMINES

Imines also react with aryl iodides under carbonylative conditions to yield amides or enamides depending on their substituents (**Scheme 8**).[11] Alkyl-substituted imines containing α-protons ($R' = CHR_1R_2$) give enamides, while the benzylidenamines give cyclic amides in 30–55% yields along with the corresponding benzamides formed in 18–40% yields. Both processes can involve acylpalladation of the imine moiety.

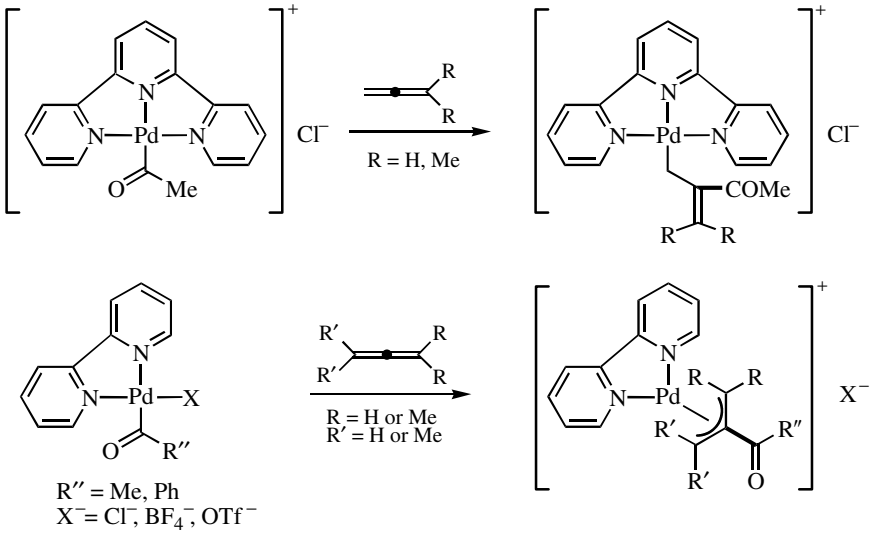


Scheme 8

Allyl phosphates also react with imines under similar carbonylative conditions to yield lactams, but the reaction mechanism involves a [2 + 2] cycloaddition of the imine and a ketene generated by decomposition of an acylpalladation intermediate (for this type of reaction, *vide infra*, **Sect. VI.5.2**).[12],[13]

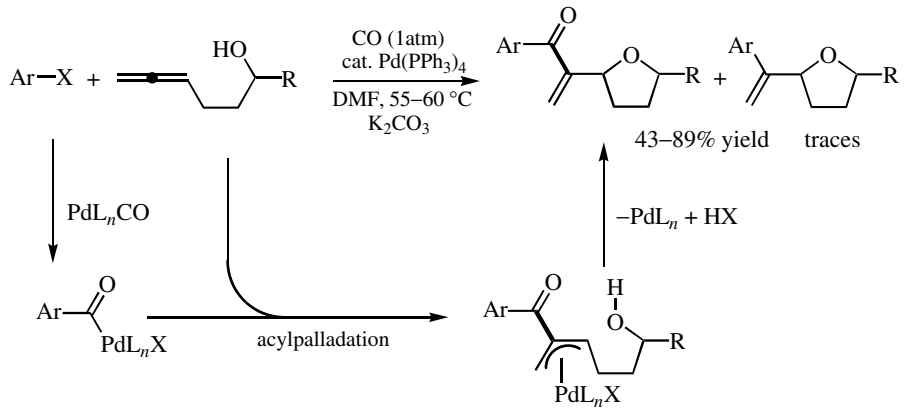
D. ACYLPALLADATION OF DIENES

The first example of acylpalladation of dienes appeared in 1993. It involved a stoichiometric reaction of 1,2-dienes (allenes) with acetylpalladium complexes containing nitrogen ligands (**Scheme 9**).[14] For example, bipyridine (Bipy) or terpyridine (Terpy) cationic acetylpalladium complexes readily react with allenes to form π-allylpalladium complexes in quantitative yields. Terpy, a tridentate ligand, favors η^1-complexes, while Bipy, a bidentate ligand, favors η^3-complexes.



Scheme 9

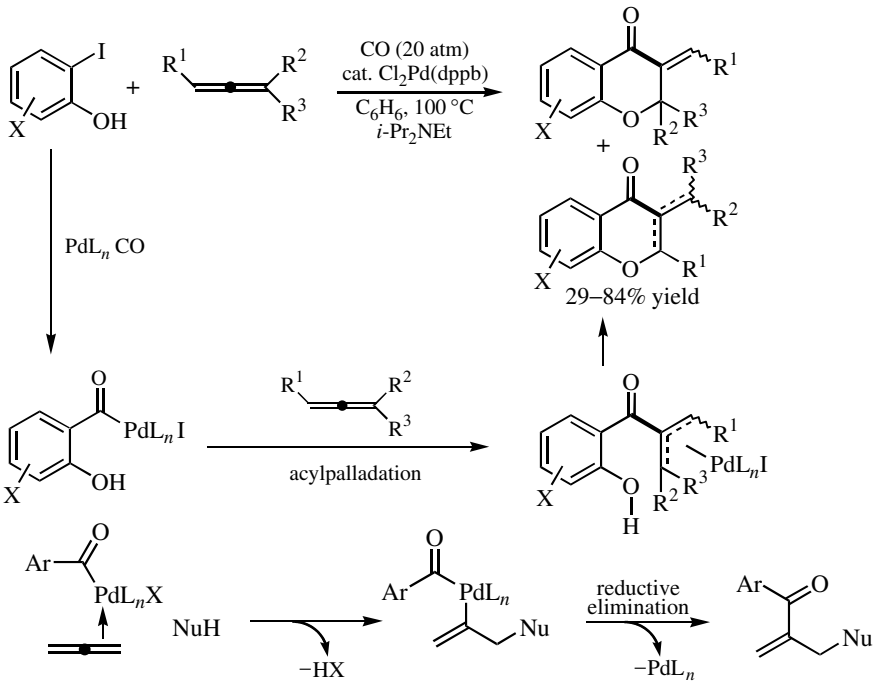
The π-allyl complex thus generated is of prime interest since its reactivity toward nucleophiles can provide a catalytic route to a whole class of molecules. This feature was essential for the discovery of catalytic reactions involving the acylpalladation of allenes as a key step. First, γ-allenyl alcohols react with aryl halides under carbonylative conditions at 65 °C to form furans in a 24–89% yield range, typically 50–89% yields (**Scheme 10**).[15],[16]



Scheme 10

This probably proceeds via (i) oxidative addition followed by CO insertion, (ii) acylpalladation of the allene moiety to generate a π-allylpalladium complex, followed by (iii) its reaction with the OH group to form the furan ring, while regenerating the Pd catalyst.

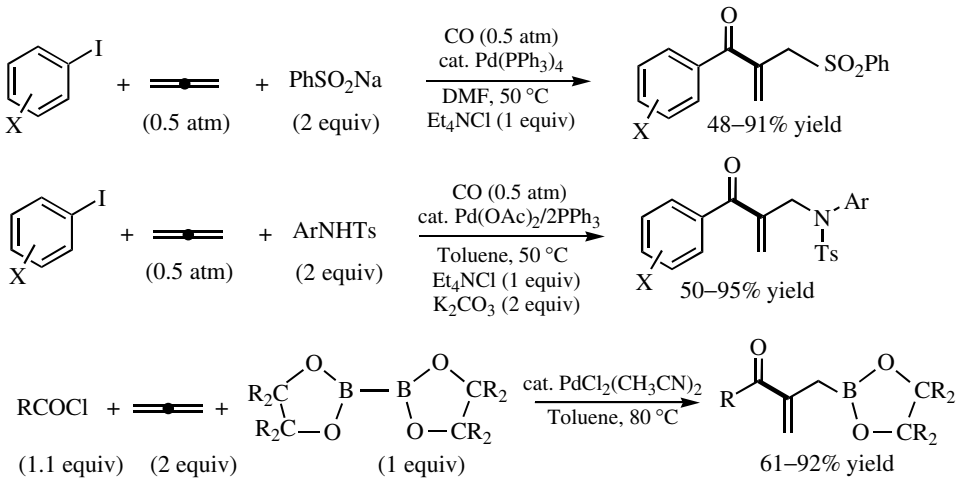
Another example involves the reaction of iodophenol with allenes, where a closely related mechanism can be proposed (**Scheme 11**). This reaction gives usually high yields of pyran derivatives for electron-rich aryl iodides.



Scheme 11

An alternative mechanistic scheme can also be proposed for both reactions, in which the acylpalladium complex activates the allene moiety by coordination, thereby facilitating the nucleophilic attack by the adjacent alcohol or phenol moieties. The product is then formed after reductive elimination.

The fully intermolecular catalytic version was then disclosed using either sulfur- or nitrogen–containing nucleophiles (Ar-NHTs or $ArSO_2Na$)[17] or more recently using boron terminating agents (**Scheme 12**).[18] In the latter case, it readily applies to both

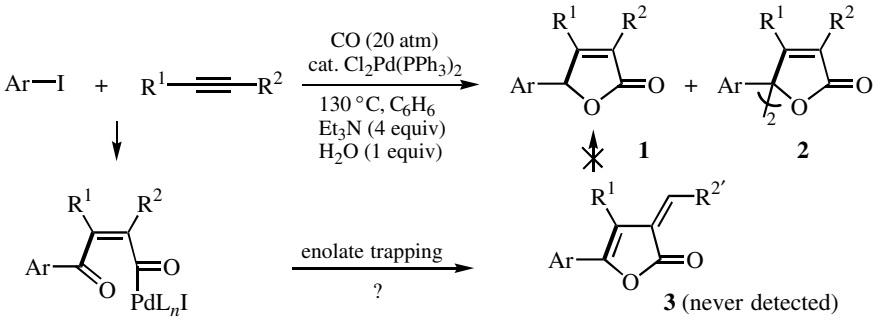


Scheme 12

aromatic or aliphatic acyl chlorides. Finally, it is worth pointing out that there is no report so far on the acylpalladation of 1,3-dienes, while 1,5- and 1,6-dienes do undergo intramolecular acylpalladation (*vide supra*, **Sect. VI.4.1**).[19] Nonetheless, dienes are great potential reagents in combination with various nucleophiles, and more reactions involving this type of tandem processes should appear in the literature in the near future.

E. ACYLPALLADATION OF ALKYNES

Little was known about the intermolecular acylpalladation of alkynes before 1992,[20] and the first general mechanistic study appeared in 1995.[21] The reaction of aryl iodides with internal alkynes under carbonylative conditions gives butenolides **1** *in the presence of water*. It is worth pointing out that **1** contains one extra hydrogen relative to the starting materials (**Scheme 13**). In fact, compound **3** was expected instead of **1** based on the results accumulated in the area of cyclic acylpalladation of alkenes, where enolate trapping is a typical termination step (see **Sect. VI.2.3**). The use of deuterated bases, solvents, and alkynes showed neither incorporation nor scrambling of deuterium in the product **1**, clearly showing that **1** does not arise from **3**.

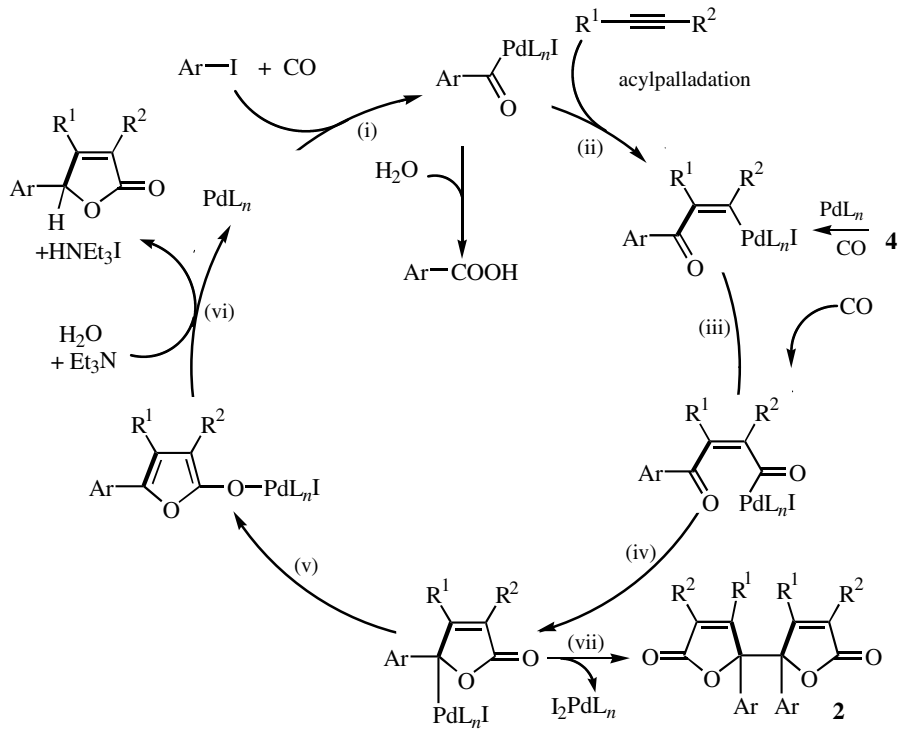


Scheme 13

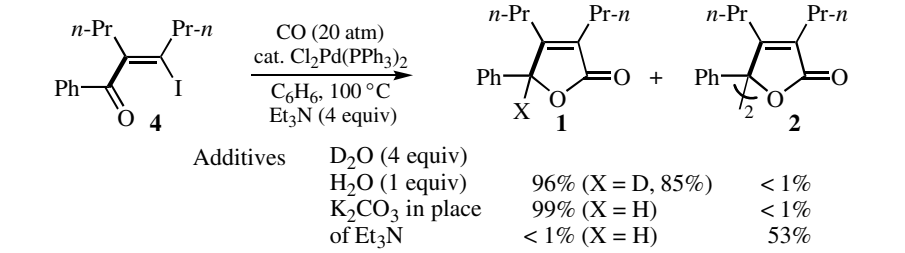
After an arduous mechanistic investigation, the following reaction mechanism was proposed (**Scheme 14**): (i) generation of the acylpalladium complex, (ii) addition to the alkyne (acylpalladation), (iii) insertion of another molecule of CO, (iv) addition of the acylpalladium thus formed to the adjacent ketone, and (v-vi) isomerization into an alkoxypalladium intermediate, which readily hydrolyzes to give the butenolide **1** and regenerate the Pd(0) complex.

This mechanistic scheme was proposed based on the carbonylation of **4**, a precursor to the intermediate generated by acylpalladation (**Scheme 14**, step (ii)). Use of D_2O in place of H_2O yielded the butenolide **1** with one deuterium incorporated in the γ-position, while complete removal of the H source by using an inorganic base such as K_2CO_3 gave the dimer **2** (**Schemes 14**, vii and **15**).

Moreover, the carbonylation of **5** was informative since the dimer was formed exclusively even in the presence of 4 equiv of water (**Scheme 16**). The preferred dimerization pathway, probably due to the need to disrupt aromaticity for hydrolysis, corroborates the final steps in the proposed mechanism, that is step (v) in **Scheme 14**.

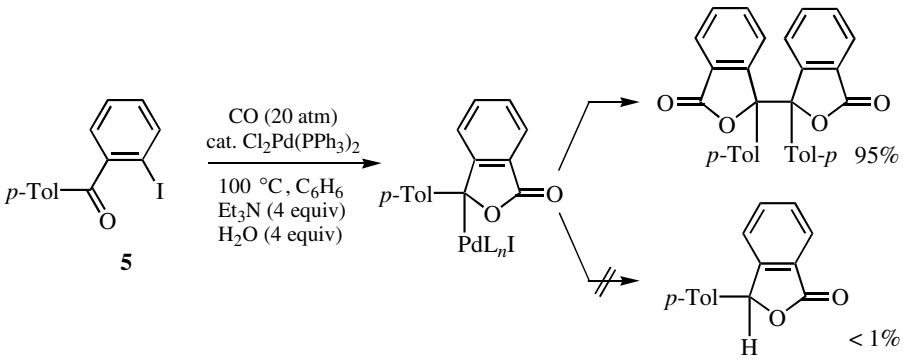


Scheme 14



Additives			
	D_2O (4 equiv)		
	H_2O (1 equiv)	96% (X = D, 85%)	< 1%
	K_2CO_3 in place of Et_3N	99% (X = H)	< 1%
		< 1% (X = H)	53%

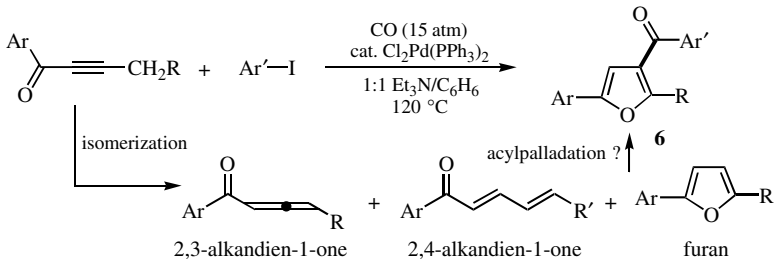
Scheme 15



Scheme 16

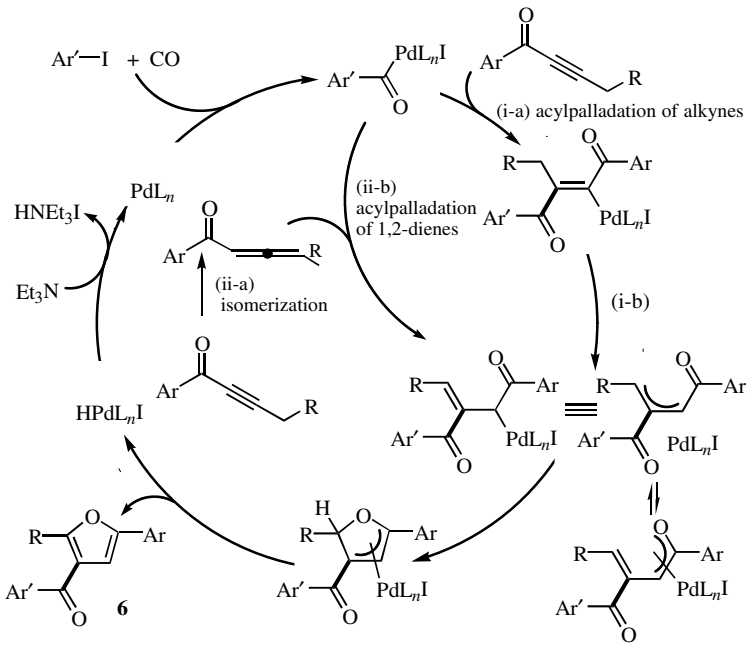
It is also worth pointing out that water is a necessary "evil" since it also converts the aryl iodide into its benzoic acid derivatives, necessitating 4 equiv of ArI to achieve reasonable yields of **1**. Nonetheless, this is a highly efficient method for the synthesis of a wide variety of butenolides in one step starting from readily available materials.

Under similar carbonylative conditions, the reaction of aryl iodides with alkynones gives the furan derivatives **6** (**Scheme 17**).[20]



Scheme 17

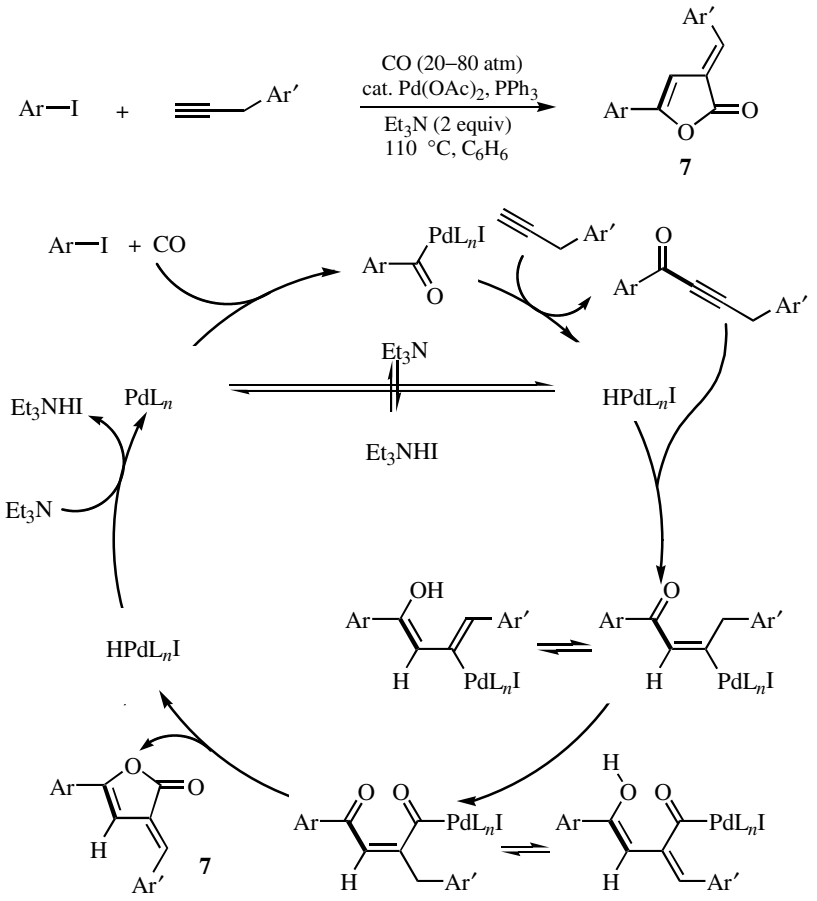
The carbon–carbon bond-forming process also involves an acylpalladation step. Alkynones are known, however, to readily isomerize into 2,3-alkandien-1-one, 2,4-alkandien-1-one, or furan, and it is therefore difficult to know which partner reacted with the acylpalladium intermediate (**Scheme 17**). The latter two were ruled out since their reaction with aryl iodides under carbonylative conditions did not show any sign of the formation of **6**. Even so, there are still two plausible pathways for the carbon–carbon bond formation: either an acylpalladation of the alkynone to give an intermediate complex that isomerizes into a π-allylpalladium complex via tautomerization (**Scheme 18**, pathway (i) as proposed by the



Scheme 18

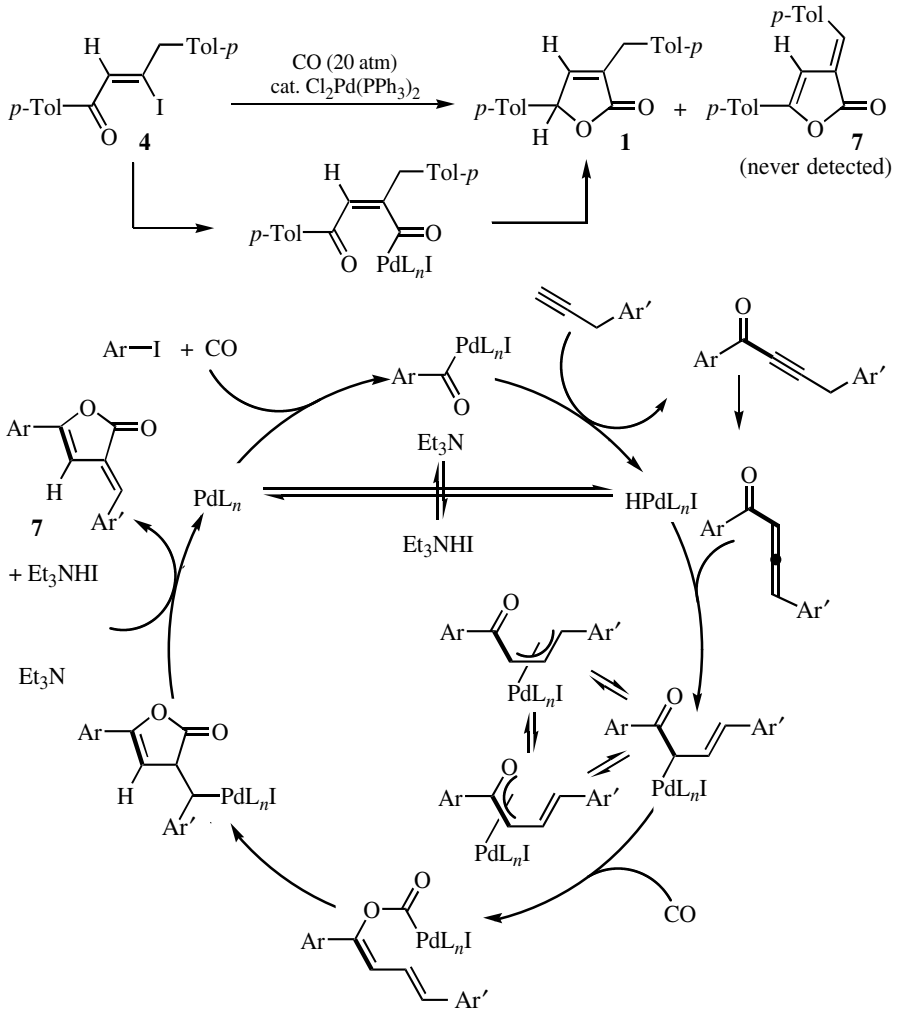
authors) or the formation of this complex via isomerization of the alkynone into a 2,3-alkandien-1-one followed by acylpalladation (**Scheme 18**, pathway (ii); *vide supra*, **Sect. D**). The Pd complex thus formed can readily generate the furan ring via an intramolecular nucleophilic attack followed by β-elimination.

Moreover, replacement of the alkyl group (R) with an aryl group completely changes the course of the reaction (**Scheme 19**). Thus, the reaction of terminal alkynes with aryl iodides or benzoyl chlorides give butenolides (***Z*)-7** (33–88%) as a single isomer under similar carbonylative conditions,[22] whose structure is closely related to **3**. The carbon–carbon bond-forming process probably does not involve acylpalladation, but rather a cross-coupling step. In fact, the synthesis of alkynones using a similar procedure was already reported by Kobayashi and Tanaka in 1981.[23] This was further demonstrated by the treatment of the 1,4-diphenyl-2-butyn-1-one (Ar = Ar′ = Ph) with phenyl iodide in the presence of $HNEt_3Cl$(1 equiv), CO (20 atm), and $Pd(OAc)_2$(cat.), which gave the same butenolide **7** in 50% yield.[24] This is in striking contrast with the carbonylation in the previous examples in which alkynones were converting into furans **6** (**Scheme 18**). The subsequent steps were described to involve hydropalladation of the alkynone followed by an insertion of CO and enolate trapping (**Scheme 19**).



Scheme 19

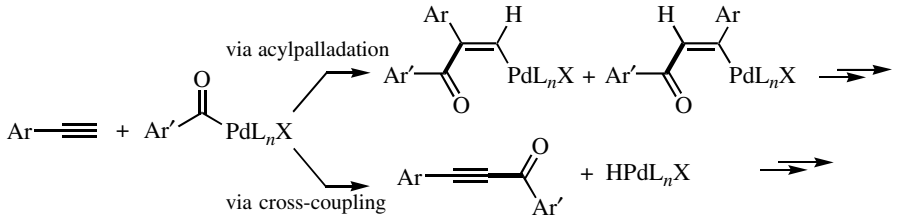
This, however, is unlikely since **4** gave only **1** without traces of **7** (**Scheme 20**). It is therefore probable that the alkynone also isomerized first into an allenone, which would now undergo hydropalladation to form a π-allyl complex in equilibrium with an alkoxypalladium complex. This type of Pd complex is known to readily insert CO and add onto alkenes, thus forming **7** after β-elimination.[25]



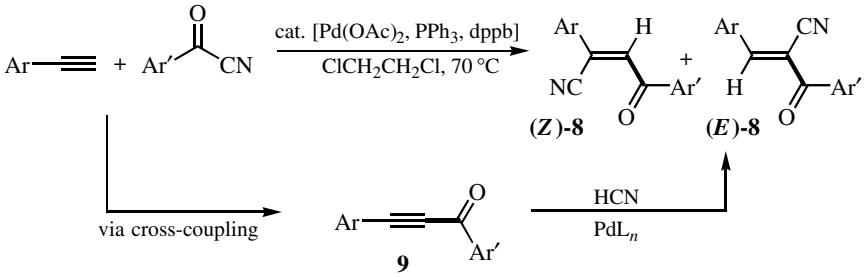
Scheme 20

There are other examples of carbonylation of terminal alkynes, which involve the intermolecular reaction of an acylpalladium complex with an alkyne moiety, but they most probably also involve carbon–carbon bond formations via cross-coupling rather than acylpalladation (**Scheme 21**).

For example, benzoyl cyanides react with arylacetylenes in the presence of a Pd catalyst system (1:1:0.5 $Pd(OAc)_2/PPh_3$/dppb) to form **8** in 55–74% yields in high stereoselectivity (typically >70/1) along with small amounts of the alkynone **9** (1–13%) (**Scheme 22**).[26],[27]



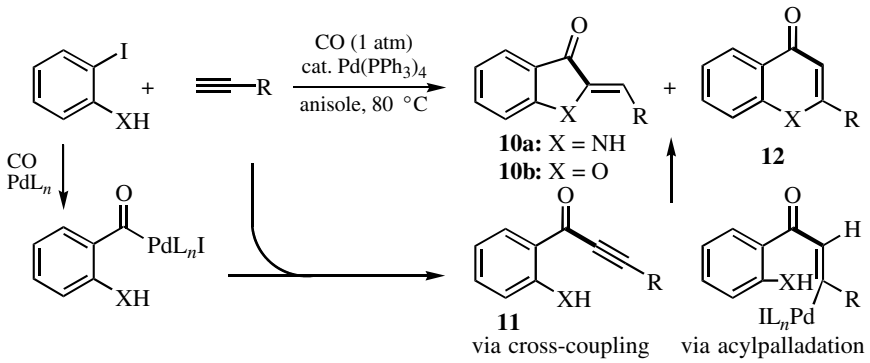
Scheme 21



Scheme 22

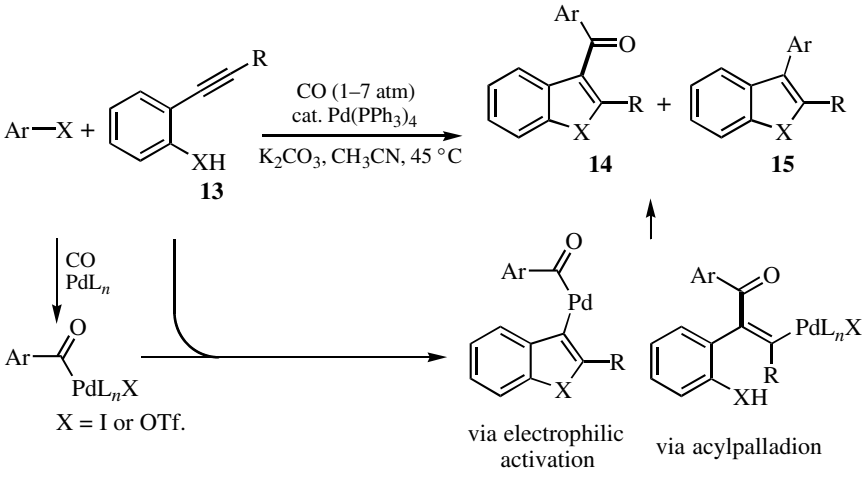
Compound **9** is first produced and is then converted to (**Z**)**-8** in good stereoselectivity. This is in agreement with a reaction that proceeds via cross-coupling followed by hydrocyanation of the resulting alkynone **9**. This is also consistent with the closely related reactivity of benzoyl cyanides and chlorides, the latter only giving **9** under similar reaction conditions (*vide supra*).

Similarly, iodoaniline and iodophenol derivatives react with phenylacetylene under carbonylative conditions to give (**Z**)**-10a** (82%)[28],[29] and (**Z**)**-10b** (77%)[30], respectively, as single stereoisomers (**Scheme 23**). In the case of **10b**, the compound **11b** (X = O) was also isolated in a 15% yield. Moreover, the compound **11a** (X = NH) could readily be converted into **10a** in the presence of palladium complexes, which is also in agreement with cross-coupling as a first step. Additionally, **12** was not observed in either case under these conditions, but small amounts of **12a** (X = NH, 14%) were detected along with **10a** (19%) and **11a** (56%) under ligandless conditions (cat. Pd(dba)$_2$, (C$_8$H$_{17}$)$_3$N) starting from saliciloyl chloride.[31]



Scheme 23

A related example is also worth noting and involves the reaction of aryl iodides or vinyl triflates with **13** under carbonylative conditions to give **14** (43–83% yields) along with small amounts of **15** (**Scheme 24**).[32] This reaction can in principle proceed by either acylpalladation or electrophilic activation of the alkyne moiety. Based on the mechanistic investigation of the noncarbonylative reaction, the electrophilic activation pathway seems to be the most likely mechanism. It is, however, interesting to see that small changes in the substrate can completely change the course of the reaction.



Scheme 24

F. SUMMARY AND FUTURE OUTLOOK

Overall, the carbonylation of alkynes is rather complex, but it is possible to draw a general trend and to divide these processes into three classes depending on the alkyne (i) For most internal alkynes, the carbon–carbon bond-forming process can involve an acylpalladation step whether there is an isomerization or not. (ii) However, some of them may involve an electrophilic activation of the triple bond by the acylpalladium complex followed by nucleophilic attack and reductive elimination. (iii) On the other hand, terminal alkynes appear to undergo mostly cross-coupling for the first carbon–carbon bond formation. Aside from these mechanistic intricacies, it is important to point out that these processes usually involve incorporation of more than one molecule of CO and creation of two to three carbon–carbon bonds in one reaction, and they yield heterocycles in fair to good yields. Other multiple bond systems like alkenes, imines or dienes also provide nice entries to carbo- and heterocycles. The limitations are usually due to the necessary time balance between acylpalladation and the termination step to avoid polymeric or decarbonylation processes.

This section has focused on the intermolecular acylpalladation of π-bond systems and its related chemistry. The diversity of this chemistry and all the potential left if combined with all the regular tools developed in the carbopalladation area promise interesting future developments.

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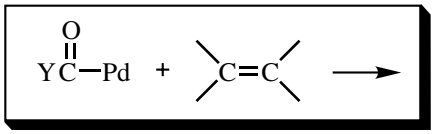


VI.4.4 Carbonylation of Alkenes and Alkynes Initiated by YCO—Pd and YCOO—Pd Bonds (X = N or O Group)

INTRODUCTION

The present section is limited to Pd(II)-catalyzed reactions initiated by nucleophilic attack of RO— (R = H, alkyl, aryl) or R_2N— (R = H, H and alkyl, aryl) groups on carbon monoxide or carbon dioxide followed by attack of the resulting hydroxy-, alkoxy-, aryloxy-, or amino-carbonyl or carboxyl group on double or triple bonds, the process being terminated by H-addition or elimination or continued by a new carbon monoxide addition, followed by other elementary acts leading to termination.

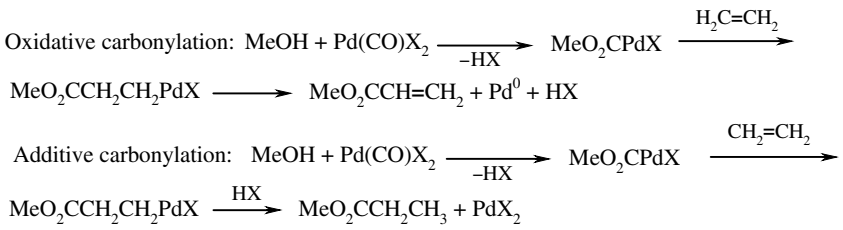
These processes can also involve ring formation. If carbon monoxide becomes part of the ring the reaction will be denoted as cyclocarbonylation.

Section VI.4.4.1 will concern processes not involving carbon monoxide incorporation into a ring.

Section VI.4.4.2 will report on cyclocarbonylation. Reactions in which a ring is formed by attack of the nucleophile itself on double or triple bonds, followed by carbonylation, are treated in **Sect. VI.2.1.3**.

Reactions initiated by attack of H, alkyl, or aryl group on double or triple bonds are treated in **Sect. VI.2** for the reason that they imply different elementary acts, palladium in a low oxidation state being the catalyst. The situation is schematically represented below for the methoxycarbonylation of ethylene.

Initial nucleophilic attack of MeOH on CO



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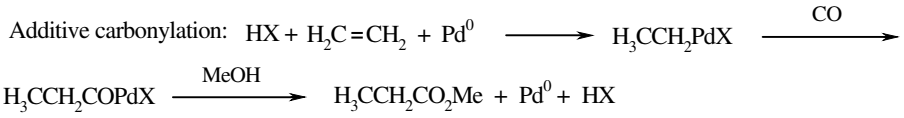
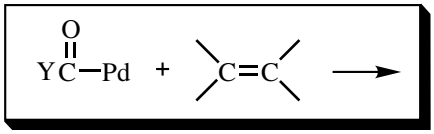
ISBN 0-471-31506-0

Initial protonation or hydride formation



Starting from PdX_2 it is also possible to obtain the relevant H—Pd—X intermediate.

In the case of the processes treated in the present section, which are catalyzed by palladium(II), we shall see that some end up with palladium(0), as in the first example above (therefore requiring reoxidation to palladium(II) to obtain a catalytic cycle) while others maintain the oxidation state (II).



VI.4.4.1 Carbonylation Processes Not Involving CO Incorporation into a Ring

GIAN PAOLO CHIUSOLI and MIRCO COSTA

We shall first consider olefinic substrates (**Sect. A**), then alkynes (**Sect. B**). Reactions with both CO and CO_2 (**Sect. C**) will follow.

A. OLEFINS

The first observation relative to this subject is due to Tsuji, who described a stoichiometric reaction affording β-chloropropionyl chloride from $PdCl_2$, ethylene, and carbon monoxide in benzene at room temperature (r.t.) under 55 atm of carbon monoxide.[1],[2] The product was successively converted by alcohols to the corresponding esters as represented in **Scheme 1**.

The reaction is based on the use of $PdCl_2$ as oxidant and corresponds to what was later called oxidative carbonylation.

It is not clear whether the reaction is initiated by Cl or COCl; however, other processes were found later that were clearly initiated by Pd-coordinated CO_2Alk or CO_2H groups. A simple example is offered by the oxidative dialkoxycarbonylation of ethylene in alcohol leading to dialkyl succinate and alkyl acrylate depending on the CO/C_2H_4 ratio, in the presence of Pd halide and metal ions such as Cu^{2+} or Fe^{2+}, which have an oxidation potential higher than that of Pd halide.[3],[4] **Scheme 2** refers to the synthesis of butyl succinate. Yields over 90% on ethylene can be obtained if an orthoformate is added to counteract the negative effect (CO_2 formation) due to the presence of water.

Heck[5] succeeded in obtaining a dialkoxycarbonylation using alkoxycarbonylmercury chlorides (formed *in situ* from $HgCl_2$ or prepared separately) as transfer agents of the alkoxycarbonyl group to $PdCl_2$. Thus, styrene was carbonylated with $PdCl_2$–$HgCl_2$ (1:1 molar ratio) at 25 °C and 2 atm of CO to obtain dimethyl phenylsuccinate and methyl cinnamate in 86.5% and 11% yield, respectively, based on $PdCl_2$ used. The reaction course was interpreted as shown in **Scheme 3**.

James and Stille[6] established conditions to effect these reactions catalytically using $PdCl_2$ with $CuCl_2$ in excess, in methanol as the solvent at 28 °C (**Scheme 4**). In the presence of a base such as sodium butyrate the diester yield reached 94% with R = Bu.

As shown in **Scheme 4** the cyclic diesters formed starting from cycloolefins are 1,2 or 1,3, both in *cis* configuration. The presence of a base such as sodium acetate or propoxide eliminates the formation of β-methoxy esters (which were found in *trans* configuration).

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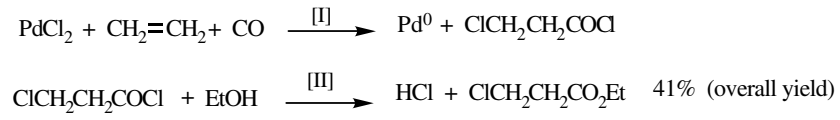
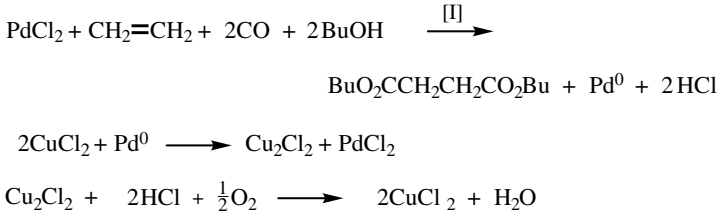
1,3-Diesters and β-methoxyester are not formed in the case of norbornene. The *cis, exo*-diesters are obtained predominantly along with a small quantity of the *cis,exo*-β-chloroester (**Scheme 5**, same conditions [III] as in **Scheme 4**).

The tendency of cyclic olefins to undergo *cis* dicarbonylation rather than *trans* methoxycarbonylation was attributed to their steric strain, which is in the order norbornene > cyclopentene > cycloheptene > cyclooctene > cyclohexene. Steric strain relief would allow a stronger complexation and dicarbonylation. Stille interpreted the



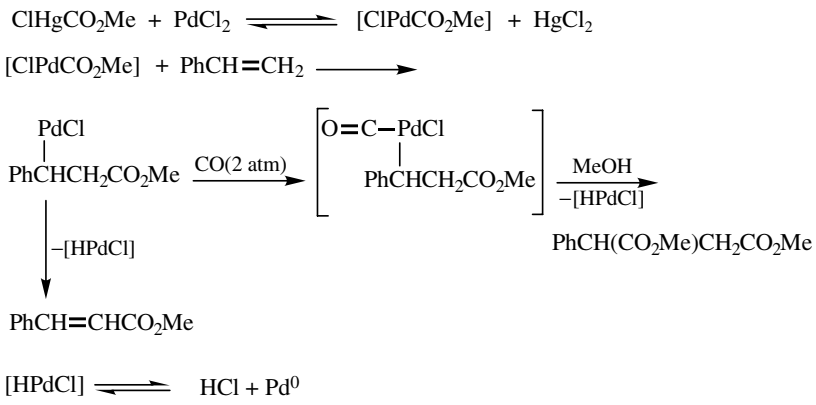
[I] = $PdCl_2$ 10% w/v in benzene, ethylene (55 atm), 5 h, then replacement with CO for several hours, r.t.
[II] = ethanol, 1 h reflux.

Scheme 1

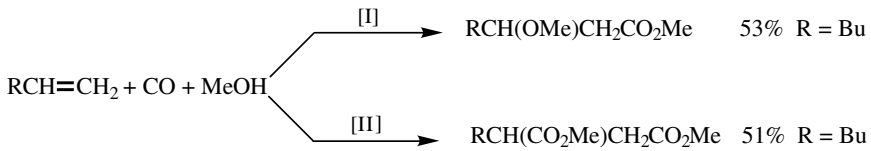


[I] = $PdCl_2$ (5.6 mequiv), $CuCl_2$ (37.3 mequiv), LiCl (117.6 mequiv), $CO/C_2H_4 = 0.67$ (88 atm), BuOH (400 mL), 125–150 °C, 10–15 atm O_2 added in increments.

Scheme 2

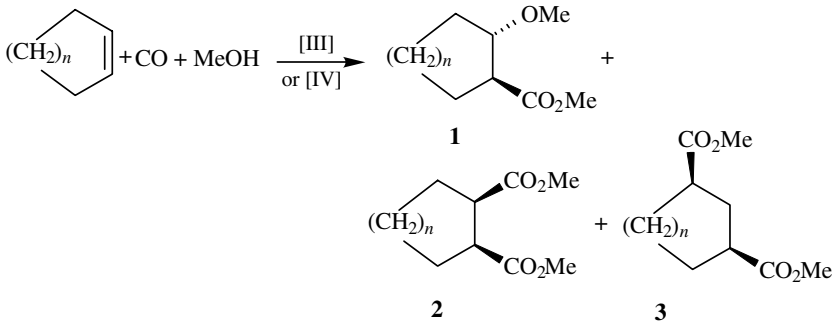


Scheme 3



[I] = $PdCl_2$ (25 mequiv), $CuCl_2$ (100 mequiv), olefin (25 mequiv), MeOH (75 mL), 25 °C, CO (3 atm), 24–72 h.

[II] = as above, with NaOAc (100 mequiv)



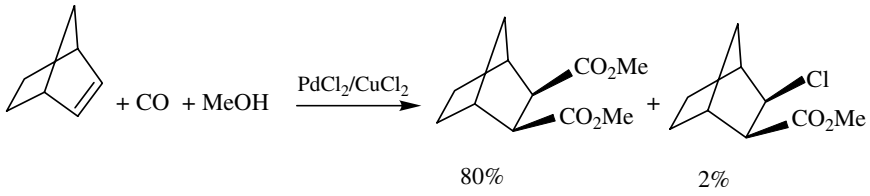
Cycloolefin *n*	Conditions [a]	Conversion [b] (%)	Product Yields (%)		
			1	**2**	**3**
1	III	60	4	68	27
	IV	60		22	78
2	III	17	95	3.5	0.5
	IV	5		80	20
3	III	58	2	34	63
	IV	58		25	75
4	III	10	4	10	85
	IV	30[c]		80	20

[a] [III] = $PdCl_2$ (2.8 mequiv), $CuCl_2$ (100 mequiv), olefin (50 mequiv), MeOH (75 mL), CO (3 atm), 28 °C; [IV] = as in [III] with NaOAc (100 mequiv).

[b] Based on olefin;

[c] Same conditions as [III] except for olefin (25 mequiv).

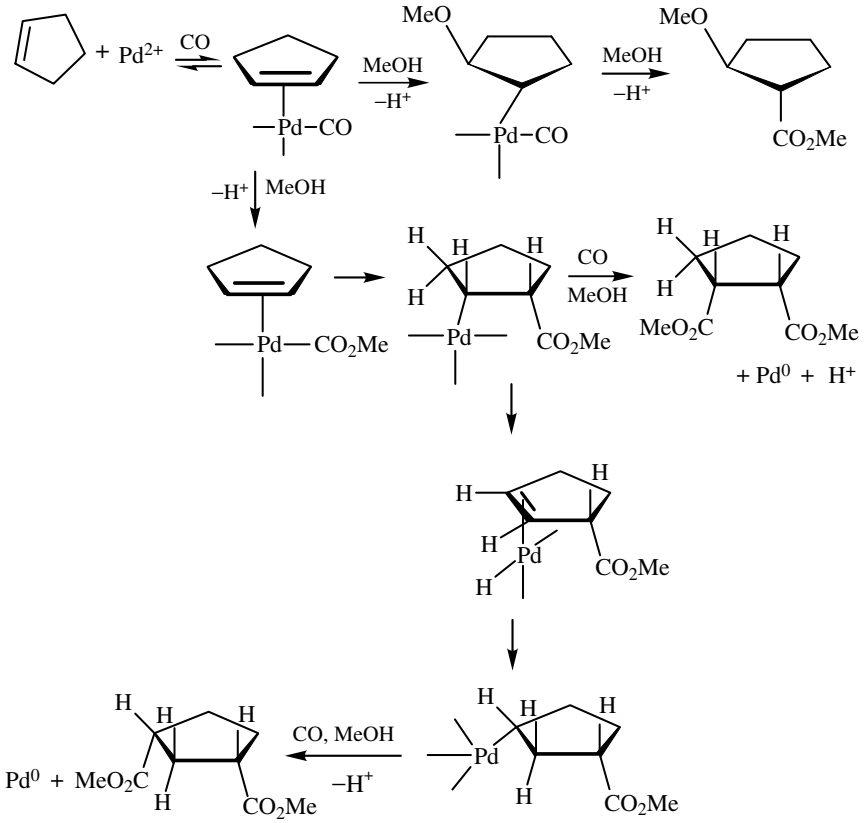
Scheme 4



Scheme 5

course of the reaction of cyclopentene in methanol on the basis of the formation of a Pd—CO_2Me species originating from methanol attack on coordinated carbon monoxide (**Scheme 6**).

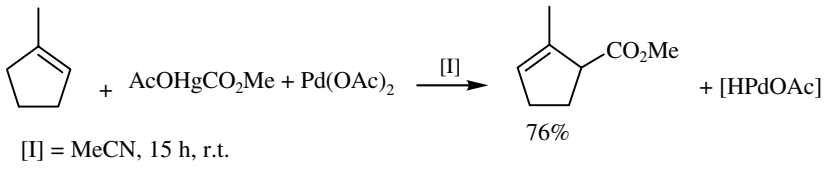
The formation of the 1,3-isomers was attributed to H—Pd elimination and readdition after double bond insertion into the Pd—CO_2Me bond. The ClCuOMe species appears to be a good transport agent of the OMe group. Transferring $OCMe_3$ groups from the corresponding dialkylperoxide is another way to effect oxidative carbonylation of ethylene to succinate.[7]



Scheme 6

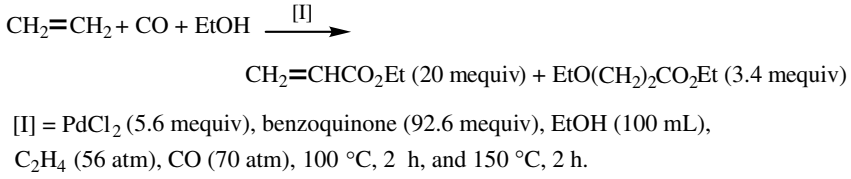
A recent advancement consists of the use of triphenylphosphine sulfide as ligand under conditions of oxidative carbonylation.[8] Thus, styrene could be dicarbonylated to phenylsuccinic dimethyl ester in 80% yield at room temperature and atmospheric pressure. Enantioselection was observed with chiral bisphosphine sulfides.

Reactions leading to unsaturated compounds in place of the dicarboxylated ones can also be obtained. An early example is offered by Heck's finding that methoxycarbonylmercury acetate can carboxylate olefins by methoxycarbonyl transfer to palladium added as acetate,[5],[9] for example (**Scheme 7**).



Scheme 7

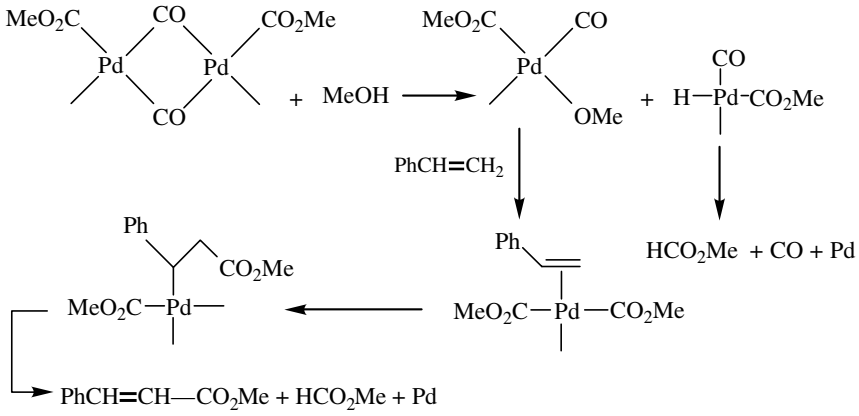
Other examples are the production of methacrylic acid from propylene with $PdCl_2$, $CuCl_2$, LiCl, and LiOAc under CO pressure (20 atm) at 27 °C with addition of oxygen[10] in low yield (of the order of 20%) and that of acrylates from ethylene in the presence of palladium(II) salts and of quinones as reoxidants[11] (**Scheme 8**):



Scheme 8

Conditions for obtaining unsaturated esters rather than the bicarboxylic ones were the subject of much work, most of which was a matter of patents; see, for example, Ref. [12]. Cinnamic methyl ester, previously prepared in low yield from styrene[6],[13] was obtained preferentially[14] when methanol was added to Moiseev's clusters,[15] a tetrameric palladium complex, previously treated with styrene under carbon monoxide atmosphere at 25 °C (**Scheme 9**).

In this case the methoxycarbonyl group was formed by MeOH addition across Pd—CO—Pd bonds and the low concentration of residual carbonyl group prevented further carbonyl insertion after that of styrene. In place of using the cluster, $CuCl_2$, methanol and



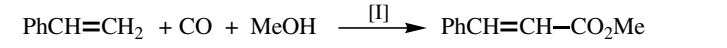
Scheme 9

sodium acetate were used with palladium chloride and an equivalent of magnesium chloride, the latter helping to keep palladium in solution. More than 66 mol of cinnamic methyl ester per mol of catalyst was obtained[14] (**Scheme 10**):

Thus, one important condition for preferential formation of the unsaturated acid is the low concentration of carbon monoxide.

Another condition seems to be the presence of an excess of halide ligand, which could prevent the coordination of a second molecule of carbon monoxide.

Going to the numerous patents that appeared later, one can infer that beneficial conditions can also be obtained using metal acetate salts as additives, particularly $Ba(OAc)_2$, at 100–120 °C (e.g., see Ref. [16]). Cupric tosylate was also used in conjunction with palladium acetate and chloranil as oxidizing agent.[17]



[I] = $PdCl_2$ (0.56 mequiv), $CuCl_2$ (100 mequiv), NaOAc (100 mequiv), $MgCl_2$ (52 mequiv), styrene (100 mequiv), MeOH (100 mL), CO/N_2 = 20:80 atmospheric pressure, 28 °C, 24 h.

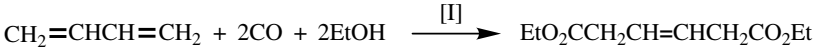
Scheme 10

Butadiene also is a suitable substrate for oxidative carbonylation. Patent literature describes the use of CO in conjunction with Pd–C, $CuCl_2$, and O_2.[18] Another patent uses a quinone as reoxidant system and a compound of Mn or V as cocatalyst. An 89% selectivity of diethyl 3-hexenedioate and diethyl 2-hexenedioate is obtained.[19] (**Scheme 11**):

Molecular sieves have been claimed to improve oxidative carbonylation of butadiene in the presence of $PdCl_2$, $CuCl_2$, and oxygen.[20]

An oxidative carbonylation leading to malonates was effected with ketene[21] (**Scheme 12**).

As stated at the beginning, alkoxycarbonyl- or hydroxycarbonylpalladium species were considered responsible for the initial steps of oxidative carbonylation reactions. Some of these species were isolated as stable complexes by trapping them with phosphorus or nitrogen ligands. The complexes (R = H or alkyl groups) shown below were fully characterized[22]–[31] (X = Cl, $MeCO_2$; R = alkyl, phenyl) (**Scheme 13**).

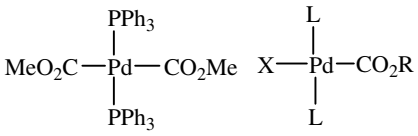


[I] = $Pd(OAc)_2$ (0.1 mequiv), $MnCl_2$ (4 mequiv), chloranil (50 mequiv), butadiene (10 mL), EtOH (15 mL), CO (60 atm), 110 °C, 2 h.

Scheme 11

[I] = $(Ph_3P)_2PdBr_2/SnCl_2/Bu_4N^+Cl^-$(molar ratio 1:2:2), CH_2=CO and CO 24 vol % in N_2, $Me(CH_2)_4ONO$ (569.6 mequiv), PhCl, 90 °C.
[a] 13.5% $AcO(CH_2)_4Me$.

Scheme 12



[22]

X = OAc, R = Me, L = PPh_3 [22]

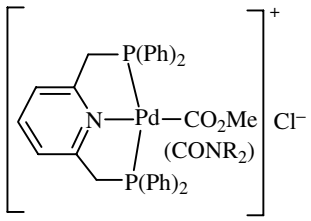
X = Cl, R = Me, Et, *n*-Pr, *iso*-Pr, *n*-Bu, *iso*-Bu *sec*-Bu, cyclopentyl, cyclohexyl; L = PPh_3 [23], [25], [26], [28]

X = Cl; R = Me, Et, CH_2Ph, L = *t*-BuNC [25]

X = Cl, R = Et; L = $P(OPh)_3$ [25]

X = OAc, L = PPh_2Py (Py = 2-pyridyl) [24]

X = Cl, L = PPh_2Py [24]



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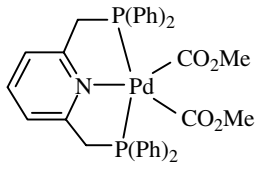

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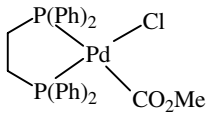

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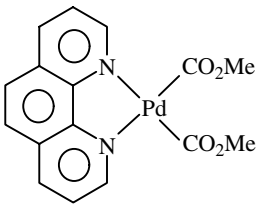

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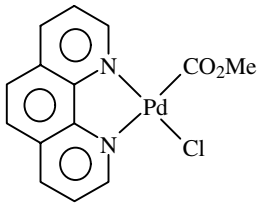
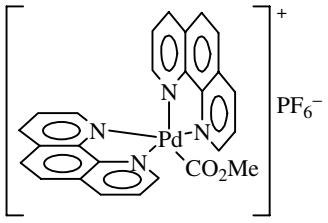
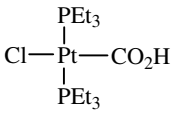


[29]



[30]

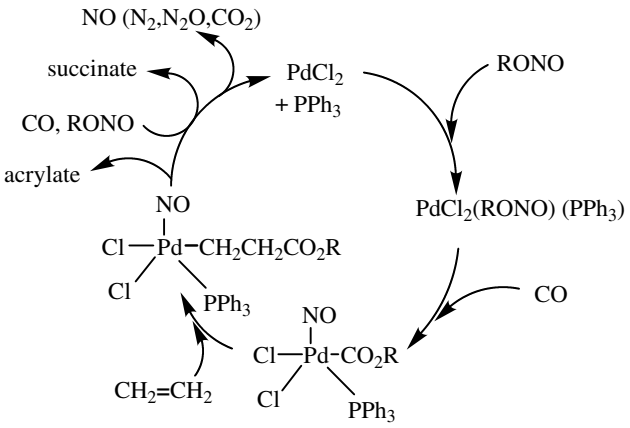


[31]

Scheme 13

The platinum complex is reported here as a model for the corresponding palladium complexes, which have not been isolated. Attack of coordinated or noncoordinated OR or OH groups on a metal carbonyl group was required as a way to form these complexes.[32] The nature and reactivity of the M—CO_2Me bond was discussed.[33] The isolation of a catalytic intermediate in oxidative carbonylation of ethylene and propylene was achieved

by Chauvin and co-workers[34] who studied the carbonylation catalyzed by $PdCl_2(PhCN)_2$ + triphenylphosphine using butyl nitrite as a reoxidant (see also Refs. [35] and [36]) as well as a source of the butoxycarbonyl group and of NO as ligand. The ability of the latter to accept or release charge facilitates the process. The proposed course of the reaction, from which complex $PdCl_2(CO_2Bu)NO(PPh_3)$ was isolated, is shown in **Scheme 14**.



Scheme 14

An interesting variant of oxidative carbonylation was recently achieved by Consiglio and co-workers.[37],[38] In the presence of a cationic palladium complex it was possible to introduce three carbonyl groups in the oxidative carbonylation of ethylene or propylene, one of them under the form of ketone, using $\{Pd(H_2O)_2[(S)$-2,2′-dimethoxy-6,6′-bis(diphenylphosphino)biphenyl]$\}(CF_3SO_3)_2$ as catalyst precursor; **Scheme 15** also shows the proposed mechanism.

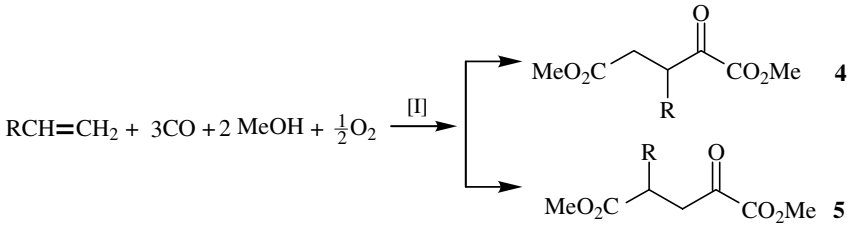
The effect of substituents on the regiochemistry of the reaction was also studied. While the phenyl group (styrene) oriented the CO_2Me attack on the β-position, the regioselectivity was lost with alkyl groups. A satisfactory enantiomeric excess was obtained.

It is also worth mentioning that methyl formate was found to be able to replace carbon monoxide in carbonylation.[39]–[42] It was shown that oxidative carbonylation of alkenes to olefinic esters with the Pd–Cu system can be performed using methyl formate in the presence of carbon monoxide or even in its absence provided that $LiOCH_3$, which favors the decomposition of methyl formate to methanol and CO, is added (**Scheme 16**). A mechanism involving alkoxycarbonylation was proposed.[42]

As anticipated in the Introduction, additive carbonylation of olefins can also be obtained with palladium(II). The hydride mechanism was shown to prevail[2],[43] especially at high CO pressure.[44],[45] We deem it useful, however, to mention here some results that may be interpreted as involving, at least in part, the occurrence of the alkoxycarbonyl (or hydroxycarbonyl) mechanism.

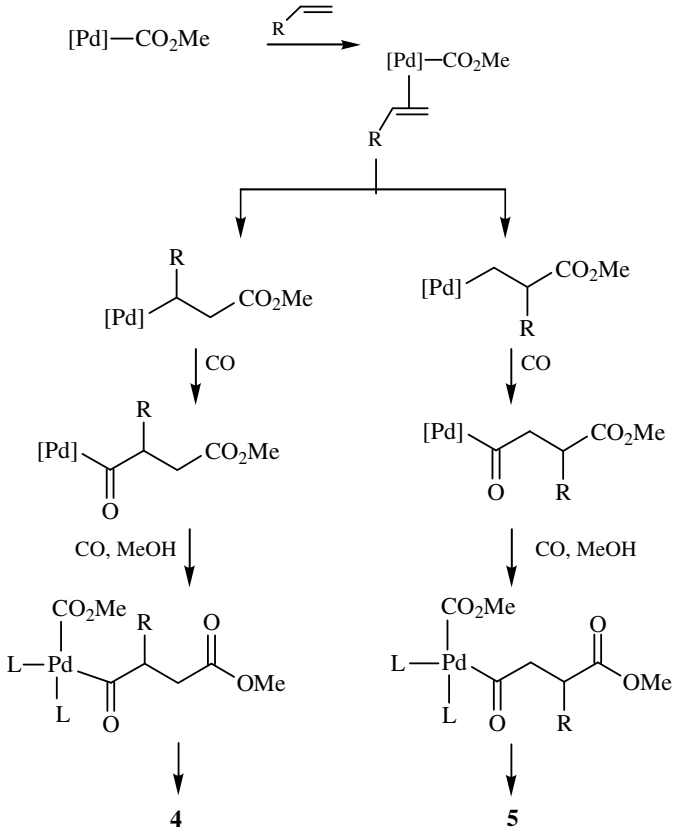
Alper and co-workers[46]–[48] described an efficient process according to which olefins are carbonylated to saturated branched esters or acids (see also Refs. [49] and [50]) rather than to the linear ones using $PdCl_2$, $CuCl_2$, and HCl as catalytic system under mild conditions (**Scheme 17**, R = alkyl, R′ = H, alkyl).

Similar results were obtained using palladium acetate supported on montmorillonite.[51] A palladium hydride-based catalytic cycle was proposed.



RCH=CH$_2$ R	Conversion %	Selectivity **4** + **5** (%)	Regioselectivity **4**/**5** (%)	ee (%)
Ph	80	25	100/0	92
Me	60	5	36/64	59/61
Me_2CHCH_2	13	17	50/50	81/62
$PhCH_2$	5	8	54/46	78/30

[I] = $[PdL_2](CF_3SO_3)$ (0.035 mequiv), benzoquinone (35 mequiv), alkene (35 mequiv), MeOH 25 mL, CO (350 atm), 20 h, 50 °C.



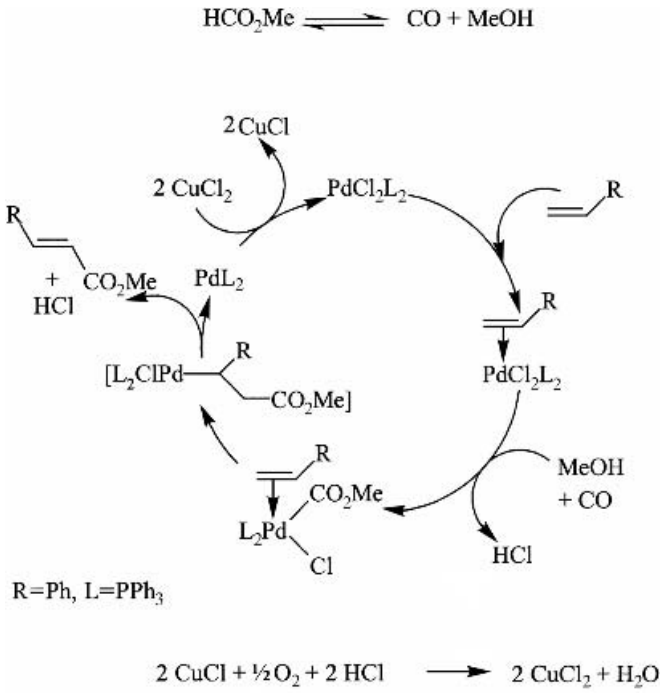
L = ligand, [Pd] = $[PdL_2](CF_3SO_3)$

Scheme 15

$$HCO_2R + R'CH{=}CH_2 \xrightarrow{[I]} R'CH{=}CHCO_2R + R'CH(CO_2R)CH_2CO_2R$$

		6	**7**	
	$R'CH{=}CH_2$	Alkene Conversion	Selectivity (mol %)	
HCO_2R	R' =	(mol %)	**6**	**7**
C_2H_5	Ph	54	59	6
n-C_3H_7	Ph	54	57	9
n-C_4H_9	Ph	53	49	16
CH_3	H	85	85	10
CH_3	CH_3	20	50[a]	40

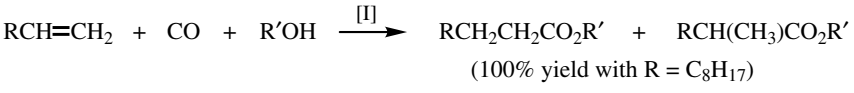
[I] = $PdCl_2(PPh_3)_2$ (0.01 mequiv), $CuCl_2$ (1 mequiv), $LiOCH_3$ (5 mequiv); alkene (45 mequiv except for the last two entries, 62 and 30 mequiv, respectively), HCO_2R (35 mL), 130 °C, 1 h; air addition when P_{CO} = 15 atm; total pressure = 100 atm.
[a] Mixture of isomers.



Scheme 16

Inomata and co-workers[52], however, showed that simply by adding CuCl in place of $CuCl_2$ to the reaction mixture of $PdCl_2(MeCN)_2$, olefin, and CO/O_2 (1:1 atm) in MeOH/THF (1:1) at 25 °C one can obtain bicarboxylic esters instead of the monocarboxylic ones predominantly. The result was interpreted as a consequence of the different medium acidity in the two cases. The authors believe that an initial attack of the methoxycarbonyl group on the olefin is likely.

More recently, the use of a strong acid such as the *p*-toluenesulfonic one in conjunction with phosphorus ligands was shown to lead to high yields and turnovers.[53],[54] The



[I] = 0.78 mequiv $PdCl_2$, conc. HCl (1 mL), $CuCl_2$ in excess, 7.8 mequiv alkene, CO (1 atm), O_2 bubbled at r.t., THF/H_2O (30:1 mL).

Scheme 17

linear to branched acid or ester ratio was shifted toward the branched one. Near room temperature the branched to linear molar ratio of methyl esters deriving from carbonylation of styrene in methanol was 93:7 at 95% yield. Evidence in support of the hydride mechanism was provided.[54]

The occurrence of two cycles, one hydride-based and the other alkoxycarbonyl-based in the $PdCl_2$– $CuCl_2$-catalyzed reactions of olefins with CO and methanol was proposed by Kalck and co-workers,[55] who observed the formation of linear esters in the carbonylation of various allylbenzenes and monoterpenes with $PdCl_2(PPh_3)_2$ or $PdCl_2(PPh_3)_2$ + $SnCl_2 \cdot 2\ H_2O$ as catalyst.

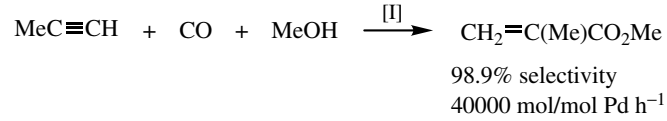
As noted in the Introduction, the hydride-based cycle involves an increase of palladium oxidation state (from 0 to II or, possibly, according to recent suggestions[56,57] from II to IV), while the alkoxycarbonyl-based cycle treated in this section implies a decrease or the preservation of the oxidation state (II).

B. ALKYNES

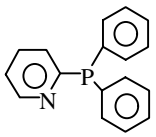
Additive monocarbonylation of alkynes was initially obtained to a limited extent using palladium(II) iodide, a complex mixture of unsaturated and saturated mono and bicarbonylated products being obtained. Thus, acrylic, propionic, maleic, and succinic esters were obtained from acetylene.[58],[59]

A real breakthrough was recently achieved by Drent and co-workers[60] in the additive monocarbonylation of propyne leading to methyl methacrylate (**Scheme 18**).

The success of this procedure is essentially due to the use of the P—N ligand in the presence of a noncoordinating acid. A cationic palladium complex is formed, which can



[I] = $Pd(OAc)_2$ (0.025 mequiv), 2-$PyPPh_2$ (1 mequiv), $MeSO_3H$ (2 mequiv),

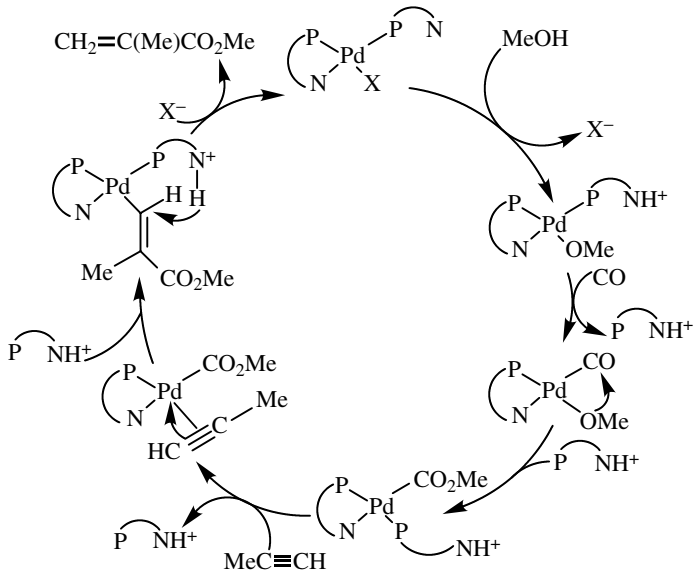
2-$PyPPh_2$ = 

propyne (30 mL), methanol (30 mL), *N*-methylpyrrolidone (30 mL), 45 °C, CO (60 atm).

Scheme 18

readily be attacked by methanol and carbon monoxide. The pyridine nitrogen seems to act as an efficient proton transfer agent. The proposed mechanism is depicted in **Scheme 19**. ($P\frown N$ = 2PyPPh$_2$, X = $MeSO_3^-$). For a different view in favor of the "hydride" mechanism and for other mechanistic observation see Refs. [61] and [24].

Acetylene was selectively dicarbonylated in a stoichiometric oxidative carbonylation reaction leading to the dichloride of maleic acid stereospecifically as reported by Tsuji.[62]



Scheme 19

A much milder catalytic procedure was reported in 1968[63] based on the use of a new catalyst, [Pd(tu)$_4$]Cl$_2$ (tu = thiourea), in methanol at room temperature, with a 25:68:7 mixture of acetylene, carbon monoxide, and air (**Scheme 20**).

Small amounts of dimethyl muconate and dimethyl fumarate accompanied the main product, dimethyl maleate (85% selectivity). Dimethyl muconate could be made to become the major product simply by inverting the C_2H_2/CO ratio. A more efficient system was later found to be PdI_2–tiourea. To the catalytic complex the formula Pd(I)(H$_2$NCSNH$_2$)$_3^+$I$^-$ was assigned.[64]

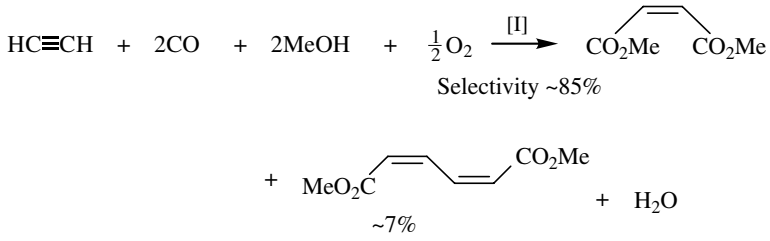
The reaction was extended to several alkynes and dialkynes.[65],[66] Since the former gave lactones in comparable amounts with dicarboxylic esters this subject is treated in **Sect. VI.4.4.2**, dealing with cyclocarbonylation.

With the same catalytic system dialkynes are cyclized without CO incorporation in the ring (R = alkyl, X = NH, NR) in MeOH (**Scheme 21**).

Thus, **8** and **9** (R = Me, X = NH) were obtained in a yield higher than 65% (**8/9** = 2:1 at 20 °C and 1.25 at 13 °C).

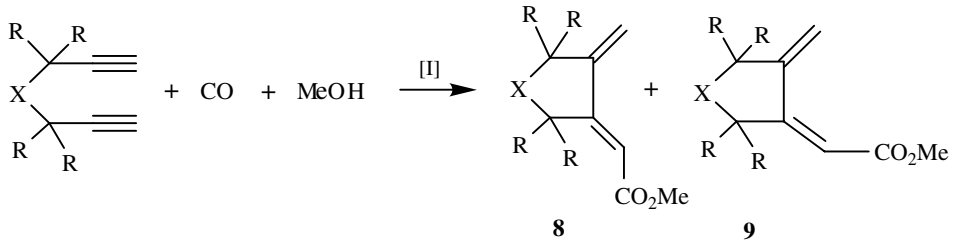
The *trans* isomer of the monocarbonylated product predominated in spite of the fact that the expected stereochemistry must be *cis*. Isomerization at the level of Pd-bonded intermediates was therefore postulated.

Monocarbonylation of diynes corresponds to an additive carbonylation process. It is worth noting that this is not a hydroesterification (i.e., a reaction initiated by H-addition



[I] = $PdCl_2$ (0.51 mequiv), thiourea (1.53 mequiv), methanol (80 mL), 6 L/h of C_2H_2 , CO, air, 40 h.

Scheme 20



[I] = $[Pd(tu)_4]Cl_2$ +0–6 mol tu /mol of Pd), conc. 0.02 M in MeOH, alkyne conc. 2.0 M, CO atmospheric pressure, r.t., 24 h.

Scheme 21

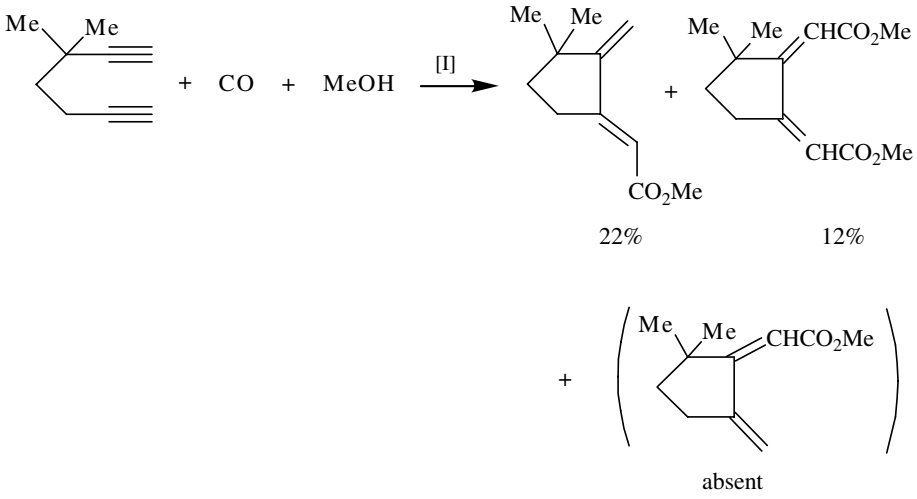
to the triple bond) but an alkoxycarbonylation initiated by the alkoxycarbonyl group. That not only oxidative carbonylation but also additive carbonylation could be initiated by an alkoxycarbonyl group was shown by Norton (see **Sect. VI.4.4.2**) for a reaction with a palladium alkoxycarbonyl complex. In the case of the present catalytic reaction this initiation has clearly been shown to occur because of the lack of an isomer in the reaction of 3,3-dimethyl-1,6-heptadiyne (**Scheme 22**).

In fact, if the reaction had been initiated by protonation there would have been no reason for the lack of the isomer in brackets, while its absence can be justified by the steric hindrance to an initial methoxycarbonyl attack on the triple bond adjacent to the geminal methyl groups.

In **Scheme 22** one can observe that stereoisomeric dicarboxylic acids are also formed (1:2 molar ratio to the monocarboxylic one) through oxidative carbonylation leading to stoichiometric liberation of palladium(0). Their formation is enhanced by the lack of geminal substituents. If oxidative conditions are used ($CO + O_2$), dicarboxylated products become predominant.

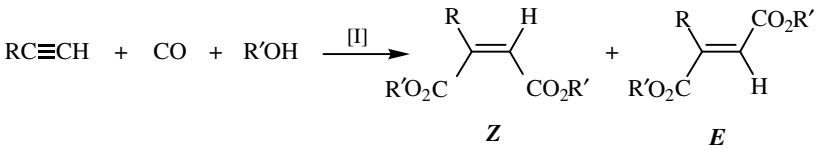
An interesting catalytic system, which operates through a not yet clear mechanism, was described by Alper and co-workers.[67] It consists of the use of $PdCl_2$, $CuCl_2$, and HCl and O_2 to obtain mainly the oxidative bicarbonylation products with terminal alkynes and the additive monocarbonylation products with internal alkynes (**Scheme 23**).

It is worth noting that the same catalytic system has also been employed for the additive carbonylation of olefins,[47] where initial addition of a proton seems to be the most likely mechanism.



[I] conditions as in Scheme 21.

Scheme 22



Alkyne R	Alcohol R′	Product Total Yield (%)	*Z*/*E*
H	Me	100	86:14
C_3H_7	Me	100	78:22
C_4H_9	Me	98	76:22
C_6H_{13}	Me	100	80:20
Cyclohexyl	Me	100	89:11
Cyclohexyl	Et	99	86:13
$PhCH_2CH_2$	Me	100	74:26
EtCHMe	Me	100	84:16

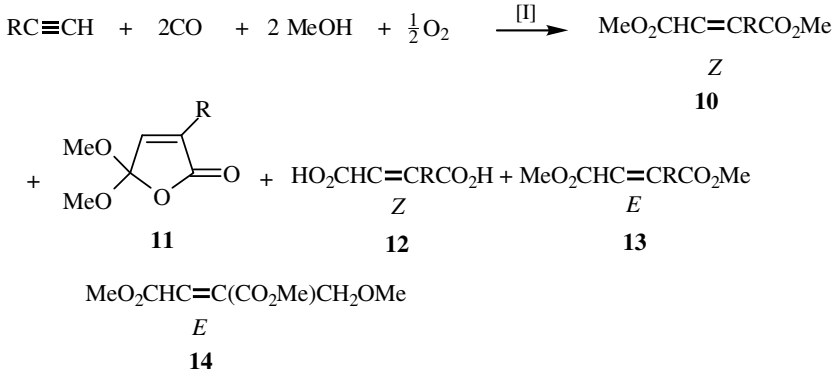
[I] = $PdCl_2$ 1 mequiv, conc. HCl 1 mL, CuCl 5–10 mequiv, alkyne 10–25 mequiv, O_2 1 atm, 2 h, r.t.

Scheme 23

An efficient dicarbonylation of terminal alkynes was achieved using PdI_2 jointly with a tenfold excess of KI in methanol or water.[68] Maleic esters were obtained in satisfactory yields along with their cyclic tautomers (5,5-dialkoxyfuran-2(5*H*)-ones; cf. **Sect. VI.4.4.2**) and small amounts of the corresponding acids and other products (**Scheme 24**). The cyclic

tautomers could readily be converted into the corresponding molecular esters by acid-catalyzed alcoholysis. Up to 4000 mol of product per mol of palladium was obtained.

Adding dimethylacetamide to methanol allows the use of higher alcohols to form the corresponding maleic esters while using a dimethylacetamide–water solution leads to the



[I] = PdI_2 (1 mequiv), KI (10 mequiv), alkyne conc. in MeOH (mol/L) : 0.13 (HC≡CH), 0.70 (BuC≡CH) 0.50 (PhC≡CH); 0.26 ($HOCH_2C{\equiv}CH$) or ($AcOCH_2C{\equiv}CH$), 60 °C, CO/air, 3:1, initial pressure 20 atm at 20 °C, 15 h.

		Yield (%)						mol prod.
R	mequiv of alkyne	**10**	**11**	**12**	**13**	**14**	Total	mol cat.
H	1450	89			3		99[a]	1435
nBu[b]	1000	67	13	8	6		94	940
Ph	3000	46	21	14	6		87	2610
CH_2OH	5000	63				17	80	4000
CH_2OAc[c]	4000	56	34			9	99	3960

[a] 7% dimethylmuconate.
[b] 6 h.
[c] 40 °C.

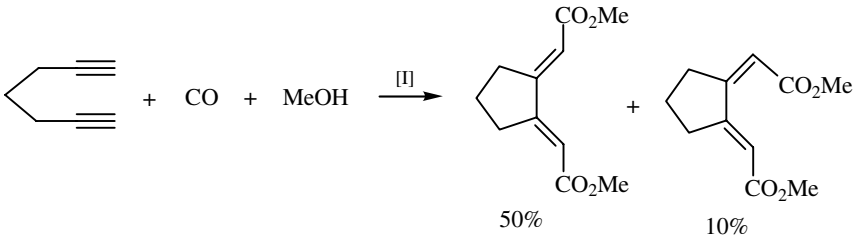
Scheme 24

corresponding acids. Thus, phenylmaleic and phenylfumaric acids (9:1) were obtained with a 75% selectivity at 40% conversion working at 60 °C for 24 h.

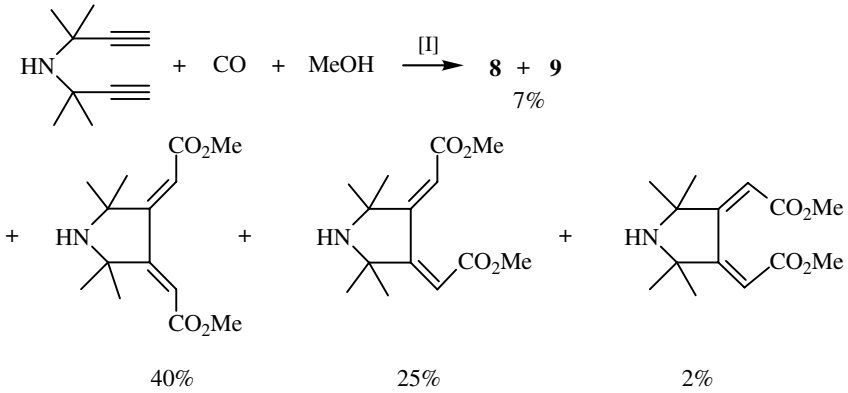
Palladium on carbon (10% Pd–C) with KI can also be used as catalyst.[65],[66] Examples of the utilization of this catalyst for dicarbonylation of dialkynes with a CO/O_2 = 94:6 mixture at atmospheric pressure in methanol at 40 °C are reported in **Scheme 25**.

The proposed mechanism for dialkyne reactions leading to additive or oxidative carbonylation is as follows (**Scheme 26**, X = CH_2, $(CH_2)_2$, R = alkyl).[65],[66]

Other developments of oxidative carbonylation of alkynes refer to the oxidative monocarbonylation described by Tsuji and co-workers[69] (**Scheme 27**). This reaction is likely to consist of the coupling of Pd-bonded alkoxycarbonyl and alkynyl groups.[70]

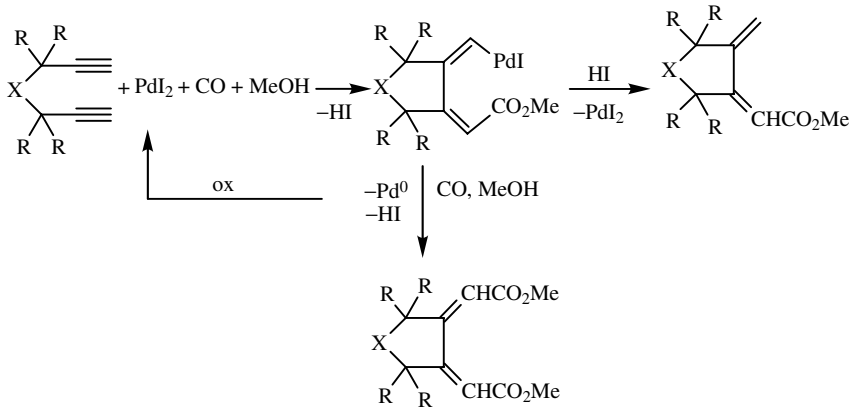


[I] = 10% Pd/C, KI (5 mol/mol Pd); CO_2/O_2 = 94:6 (atmospheric pressure), catalyst conc. 0.02 M in MeOH, substrate/catalyst molar ratio = 30, 40 °C, 20 h; 90% conversion.



[I] = 10% Pd/C, KI(5 mol/mol Pd) CO/O_2 = 94:6 (atmospheric pressure), catalyst conc. 0.02 M in MeOH, substrate/catalyst molar ratio = 20; 40 °C 24 h; 97% conversion.

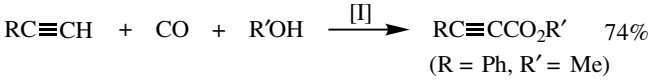
Scheme 25



Scheme 26

The addition of chlorohydroquinone and molybdovanadophosphate has recently been shown to be beneficial.[71]

It is appropriate in this context to note the behavior of acetylenemonocarboxylic and dicarboxylic esters with the same $PdCl_2$ catalyst but under nonoxidative conditions. These compounds were mono- and dicarbonylated; for example, diacetylenedicarboxylic esters



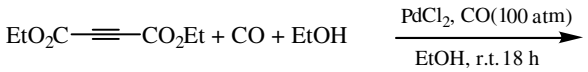
[I] = alkyne (1 mequiv), $PdCl_2$ (0.056 mequiv), $CuCl_2$ (2 mequiv), NaOAc (2 mequiv), methanol (10 mL), r.t.

Scheme 27

could also be carbonylated to tetraesters[72] (**Scheme 28**). HCl addition favored both double carbonylation and hydrogenation.

Propargyl alcohol was triply carbonylated, the first two methoxycarbonyl groups being introduced by oxidative carbonylation and the third one by substitutive carbonylation (**Scheme 29**).[2],[73],[74]

The product, trimethyl ester of aconitic acid, was obtained as a mixture of *Z*- and *E*-stereoisomers.

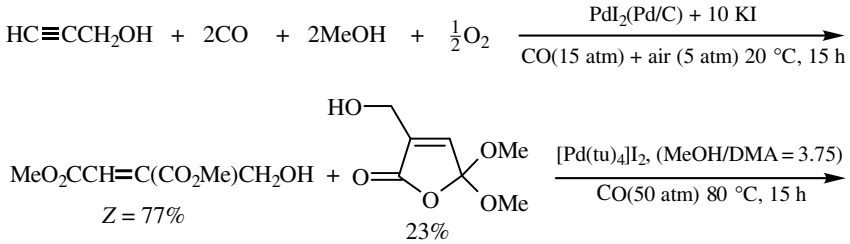


$(EtO_2C)_2C{=}CHCO_2Et + (EtO_2C)_2CHCH_2CO_2Et + (EtO_2C)_2CHCH(CO_2Et)_2$

15 **16** **17**

$PdCl_2$ (mequiv)	$EtO_2CC{\equiv}CCO_2Et$ (mequiv)	Solvent (mL)	Yield (%) **15 + 16**	**17**
5.6	29.4	EtOH (50) 10% HCl	42,5	6,5
11.3	29.4	EtOH (50)	24.3 **(16)**	51

Scheme 28



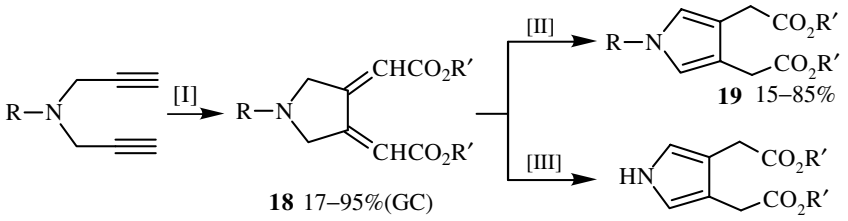
$MeO_2CCH{=}C(CO_2Me)CH_2CO_2Me$ + $MeO_2CCH_2C(CO_2Me){=}CH_2$

62% (*E*/*Z* = 94:6) 19%

Scheme 29

Oxidative carbonylation of dipropargylamines unsubstituted in the methylene groups has special interest because it gave 3,4-bis(alkoxycarbonylmethylene)pyrrolidines in good yields, particularly in the case of the acyl or alkoxycarbonyl-*N*-substituted ones.[75] These pyrrolidines can readily be isomerized to the corresponding pyrrole-3,4-diacetic esters using triethylamine in aprotic solvents. Acyl- or alkoxycarbonyl substituents at nitrogen can also be removed in the same time working in protic solvents. Examples are shown in **Scheme 30**.

Adding dimethylacetamide as cosolvent made it possible to extend the reaction to long chain aliphatic alcohols and to obtain directly the isomerization to 3,4-pyrrolediacetic ester. Saponification of *N*-benzoyl group led to 3,4-pyrrolediacetic esters.[76] Thus, the dimethyl ester could be obtained according to **Scheme 31**.



[I] = 10% Pd–C (0.1 mequiv), amide (R = PhCO) (2.2 mequiv), KI (1.4 mequiv), R′OH (40 mL), CO (4 bar), air (1 atm), 25 °C, 24 h.
[II] = **18** (2.14 mequiv), MeCN or DMSO (10 mL), Et_3N (3.59 mequiv), 50 °C, 6 h.
[III] = **18** (2.08 mequiv), solvent (10 mL), Et_3N (2.87 mequiv), 25 °C, 18 h.

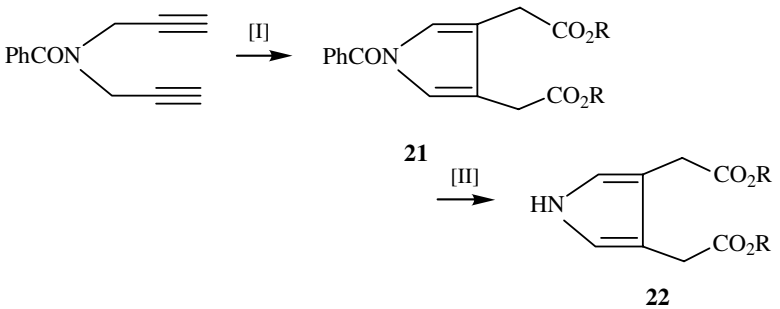
		Step 1		Product[a]	Step 2			Product[a] Yield (%)	
R	R′	Temperature (°C)	Time (h)	Yield (%) **18**	Solvent	Temperature (°C)	Time (h)	**19**	**20**
HCO	Me	25	66	88	DMSO	25	17	80	
	Me				MeOH	25	18		55
MeCO	Me	25	60	89	DMSO	25	70	85	
	Me				MeOH	25	70		81
PhCO	Me	25	24	95	MeCN	25	18	70	
PhCO	nBu	60	44	—	MeOH	25	18		71
	nBu				*n*-BuOH	60	67		64
PhCO	$PhCH_2$	80	70	—	$PhCH_2OH$	60	48		27
PhCO	$MeOCH_2CH_2$	35	64	—	$MeOCH_2CH_2OH$	80	5		49
MeOCO	Me	25	50	58	MeCN	25	20	52	
					MeOH	75	16		40
$PhCH_2OCO$	Me	25	50	90	MeCN	25	20	77	
					MeOH	70	18		55
4-$MeC_6H_4SO_2$	Me	25	40	75	MeCN	50	6	75	
n-Bu	Me	55	60	17	MeCN	25	16	15	
$PhCH_2$	Me	55	65	25	MeCN	70	3	18	
$MeOCOCH_2$	Me	55	72	20	MeCN	25	15	17	

[a] By GLC, based on starting dipropargyl derivative.

Scheme 30

Pyrrolediacetic esters are useful intermediates for the synthesis of octasubstituted porphyrins and for polymers.

Application of the procedure to 4-methoxycarbonyl-4-benzyloxycarbonylheptadiyne led to cyclization to the corresponding bis(methoxycarbonylmethylene)cyclopentane, which is a useful precursor of trisubstituted cyclopentadienes.[77] This compound can be



[I] = 10% Pd/C (0.38 mequiv), KI (7.61 mequiv), dipropargylamide (7.61 mequiv), air (5 atm), CO (20 atm), DMA/ROH (3:2, 60 mL total), 60 °C, 72 h.
[II] = dialkyl pyrrol-3,4-diacetate (2.93 mequiv), NEt_3 (14.06 mequiv), MeOH (25 mL), 14 h, r.t.

R	**21** Yield (%)[a]	**22** Yield (%)[b]
C_3H_7	42	75
C_6H_{13}	45	60
C_8H_{17}	41	74
$C_{10}H_{21}$	43	75
$C_{11}H_{23}$	42	66
$C_{12}H_{25}$	38	75
$C_{14}H_{29}$	33	75

[a] Based on the starting dipropynyl amide, isolated yield.
[b] Based on product **21**, isolated yields.

Scheme 31

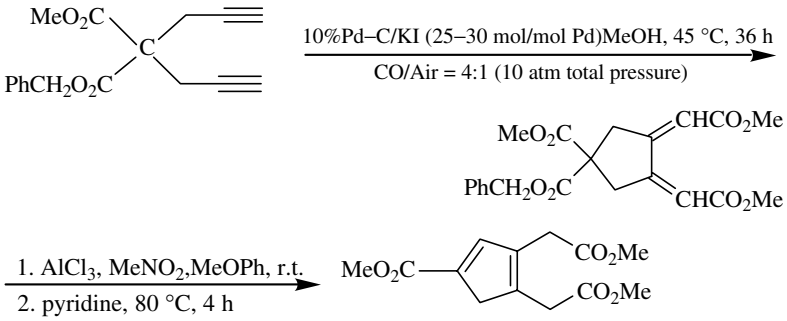
used as ligand for transition metals, where it turns out to be more stable than unsubstituted or methyl-substituted cyclopentadienes (**Scheme 32**).

The procedure of dimethoxycarbonylation of dialkynes was further extended to dipropargyl sulfides to obtain 3,4-disubstituted thiophenes (**Scheme 33**).[78]

The products are useful intermediates for the preparation of conducting polymers.

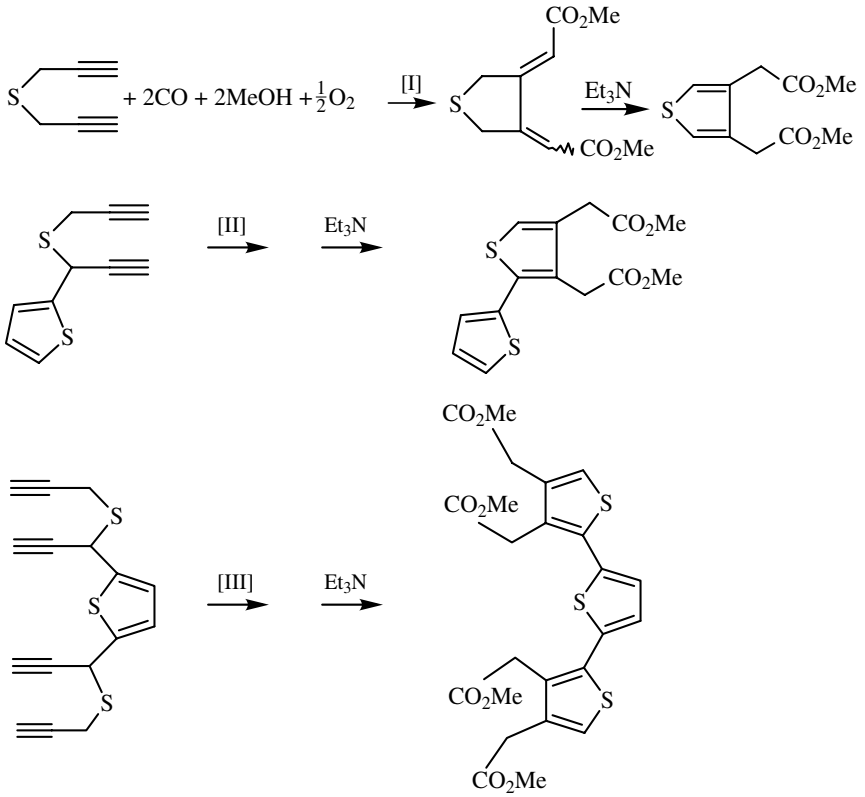
Oxidative carbonylation was coupled with reduction to afford catalytic carbonylation (see also **Sect. VI.4.4.2**). Thus, the diethylacetal of 2-propynal was carbonylated in a 65% yield by combining oxidative dicarbonylation and reductive splitting of an ethoxy group[79] (**Scheme 34**).

Scheme 35 shows the proposed course of the reaction. Reductive splitting of the OEt group is likely to imply a chelating species from which the OEt group is cleaved with



40% based on starting dipropynyl derivate

Scheme 32

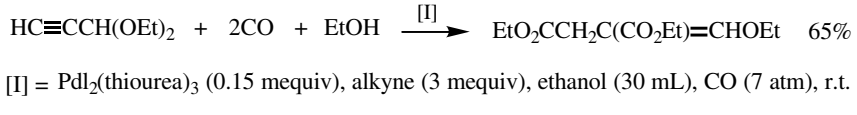


[I] = PdI_2 (0.056 mequiv), KI (0.56 mequiv), alkyne (11.1 mequiv), methanol (22 mL), CO (15 atm), air (5 atm), 40 °C, 5 h.

[II] = PdI_2 (0.194 mequiv), KI (1.95 mequiv), alkyne (5.8 mequiv), methanol (58 mL), CO (15 atm), air (5 atm), 70 °C, 2 h.

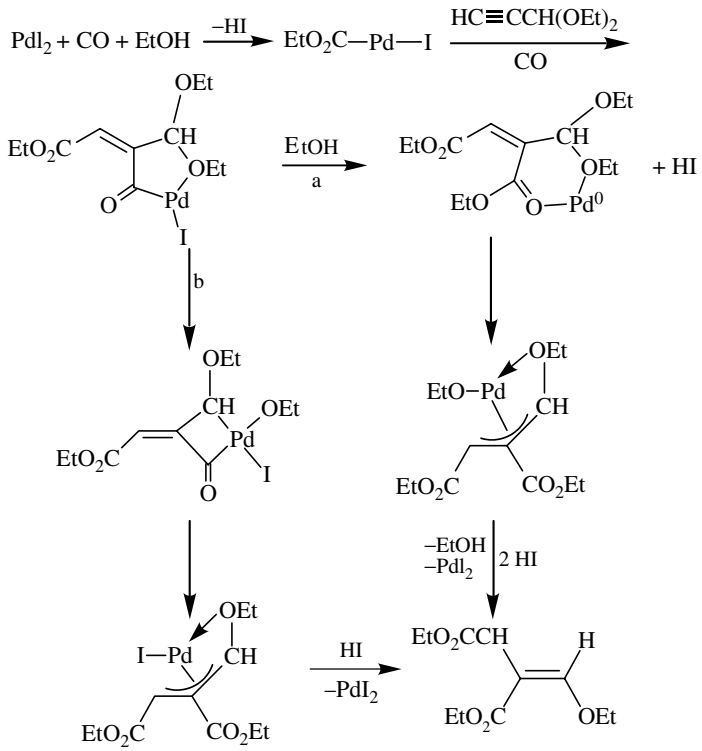
[III] = PdI_2 (0.50 mequiv),KI (5.0 mequiv), alkyne (2.5 mequiv), methanol-1, 2-dimethoxyethane 1:1 (50 mL), CO (15 atm), air (5 atm), 70 °C, 15 h.

Scheme 33



Scheme 34

formation of an intermediate allylic complex of palladium(II) (path a) or through the intermediacy of a palladium(IV) complex (path b).

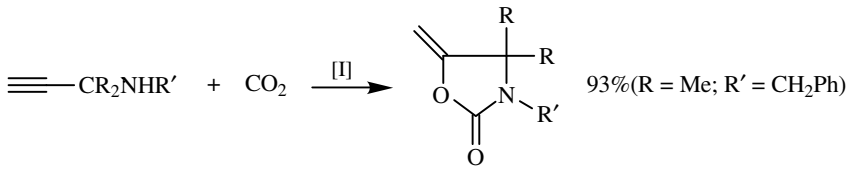


Scheme 35

C. REACTIONS OF ACETYLENIC AMINES WITH CARBON DIOXIDE AND CARBON MONOXIDE

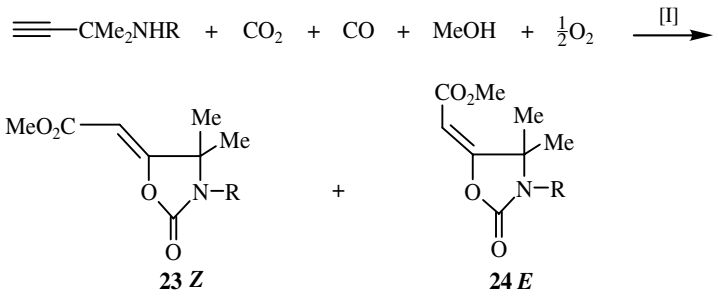
Amino groups can readily attack carbon dioxide to form carbamic acids. The latter can be stabilized by organic bases such as guanidines (**Sect. B**). If a triple bond is present in a suitable position of the amine it can be attacked by the carbamate, giving rise to oxazolidinones[80],[81] (**Scheme 36**).

It was found, however, that if palladium iodide is used in place of the base under oxidative conditions under CO + CO_2 pressure the following reaction occurs[82] (**Scheme 37**).



[I] = alkyne (2.4 mequiv), MeCN (2 mL), 7-methyl-1,5,7-triazabicyclo[4.4.0] dec-2-ene (0.24 mequiv), 80 °C, CO_2 (6 atm), 6 h.

Scheme 36



R	Yield % 23	24
Bu	62	21
Bz	59	30

[I] = PdI_2 or Pd–C (10%) (0.03 mequiv), KI (0.3 mequiv), alkyne (3 mequiv), MeOH (20 mL), 53 °C, CO (5 atm), CO_2(40 atm), air (5 atm), 50 h.

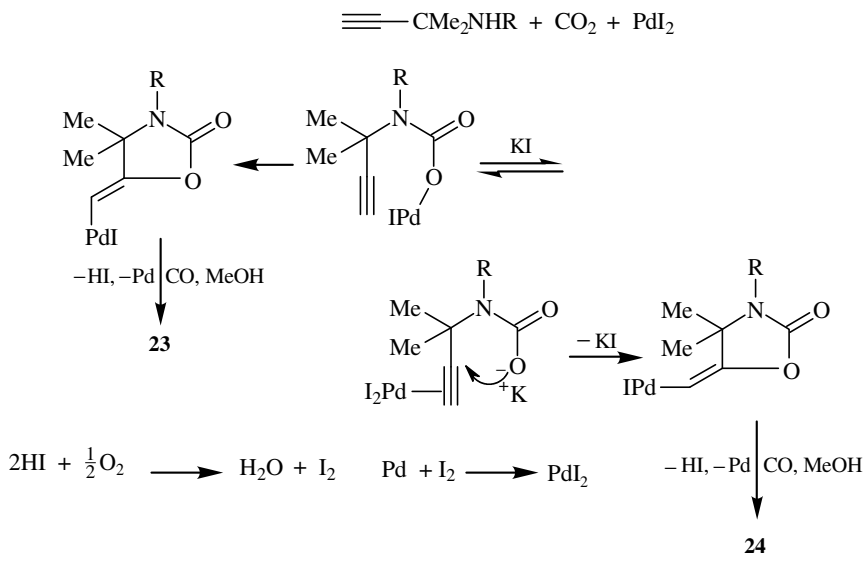
Scheme 37

Apparently, a palladium carbamate is formed that is able to attack the triple bond, thus forming a vinylpalladium bond that undergoes carbonylation in the presence of carbon monoxide.[83] The main product is an oxazolidinone containing a *cis*-(methoxycarbonyl)methylene chain. The product is accompanied by a secondary compound, which is the *trans* isomer. This has been traced to partial attack on the triple bond by the carbamate anion, noncoordinated to palladium, which occurs with opposite stereochemistry[83] (**Scheme 38**).

Some cyclocarbonylation compounds are formed as by-products and are treated in **Sect. VI.4.4.2**, where some condensed products obtained from primary propargylamines are also reported. These products give rise to ureas, which in their turn are cyclocarbonylated. The reaction course was further documented by the use of carbamic esters as a source of the carbamate anion (**Scheme 39**).

With most esters the reaction leads to *E*-products according to a sort of iodolactonization reaction (**Scheme 40**).

With the allylic ester, however, which is expected to give rise to a more stable allylpalladium complex, the reaction product is mainly *Z* (**Scheme 41**). This confirms the interpretation given in **Scheme 38**.



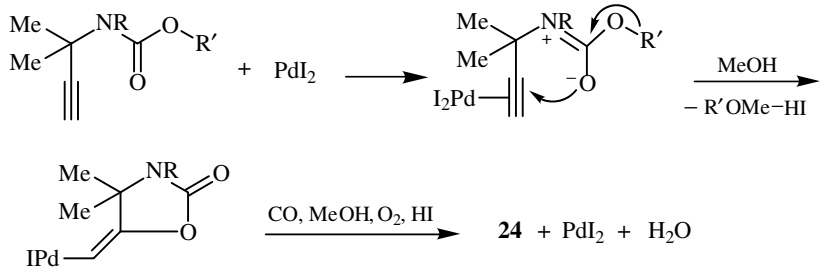
Scheme 38

$$R'O_2CNRCMe_2C{\equiv}CH + CO + MeOH \xrightarrow{[I]} \mathbf{23} + \mathbf{24} + R'OMe$$

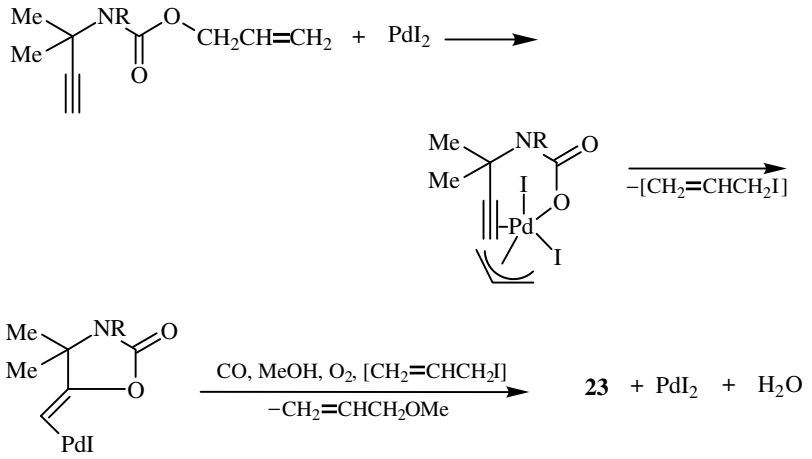
		Yield (%)	
R	R′	**23**	**24**
H	$PhCH_2$	—	36
n-Bu	$PhCH_2$	—	69
$PhCH_2$	$PhCH_2$	<1	64
n-Bu	$PhCH_2$	<0.5	21
n-Bu	$CH_2{=}CHCH_2$	50	25
n-Bu	*t*-Bu	—	94
n-Bu	*n*-Bu	<1	85

[I] = Pdl_2 (0.03 mequiv), KI (0.3 mequiv), alkyne (3 mequiv), MeOH (20 mL), 52 °C, CO (16 atm), air (6 atm), 45 h.

Scheme 39



Scheme 40



Scheme 41

D. SUMMARY

1. It has been shown that a variety of nucleophilic species able to attack Pd-coordinated carbon monoxide provide an efficient way to initiate insertion steps, which can be terminated by H-addition, H-elimination, or attack by nucleophilic species. At the end of the catalytic cycle palladium is found in the same oxidation state as at the beginning of the process or in the reduced state and in this case a reoxidation is needed to reestablish the initial oxidation state. Several olefinic and acetylenic substrates can undergo these processes. Carbonylation and bicarbonylation products can be prepared under mild conditions.

2. The use of oxygen in conjunction with palladium catalysts helps to drive the reaction toward the desired products in high yields (oxidative carbonylation). Ring formation without CO incorporation results in a series of pyrroles, thiophenes, and cyclopentadiene derivatives.

3. The initial nucleophilic species can also be a carbamate, which attacks a triple bond intramolecularly, thus forming a vinylpalladium bond able to insert carbon monoxide. Reactions in which carbon dioxide and carbon monoxide intervene in the same reaction are now in their initial stage of development but are expected to offer wide potentialities.

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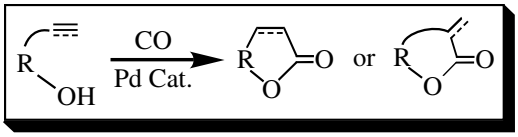

VI.4.4.2 Cyclocarbonylation

BARTOLO GABRIELE and GIUSEPPE SALERNO

A. INTRODUCTION

Palladium-catalyzed cyclocarbonylation of unsaturated compounds is a powerful methodology that allows direct preparation of cyclic compounds containing a carbonyl group in the ring starting from readily available substrates. As anticipated in the introductory remarks at the beginning of **Sect. VI.4.4**, the present section will focus only on cyclocarbonylation processes initiated by X—Pd—(CO)Y species, generated *in situ* from attack of a nucleophile (Y^-) on carbon monoxide coordinated to Pd(II). Cyclocarbonylation reactions following different mechanistic pathways are treated elsewhere in this Handbook. It is necessary to point out, however, that since experimental evidences supporting a particular mechanistic route are often not definitive, a classification of cyclocarbonylations based on mechanistic grounds may result in some cases not entirely appropriate and should be regarded as a formal one.

It is convenient to distinguish between cyclocarbonylations of simple unsaturated substrates carried out in the presence of a nucleophile and cyclocarbonylations of unsaturated substrates incorporating a nucleophilic function. In the latter case, a further distinction may be made between processes effected in the absence of external nucleophiles and processes that take place in the presence of an external nucleophile (**Scheme 1**).

B. CYCLOCARBONYLATION OF UNSATURATED SUBSTRATES IN THE PRESENCE OF NUCLEOPHILES

1,5-Cyclooctadiene was reported to undergo oxidative cyclocarbonylation in the presence of $PdCl_2$ (0.018 equiv), AcONa (0.84 equiv), and $CuCl_2$ (0.84 equiv) in CH_2Cl_2/MeOH (17:1, v/v) at 100 °C and 4.17 atm of CO for 24 h to afford 2-(methoxycarbonyl)bicyclo[3.3.1]non-6-en-9-one as the major product in moderate yield (30%, **Scheme 2**).[1] Even though the authors invoke an H—Pd—Cl species as the key intermediate for this process, the possibility that the reaction is initiated by insertion of a (methoxycarbonyl)palladium complex on the double bond followed by CO insertion, ring closure, and β-hydrogen elimination cannot be ruled out.

Pd-catalyzed carbonylation of simple alkynes carried out in nonnucleophilic solvents in the presence of small amount of H_2O can afford cyclic anhydrides. Depending on the

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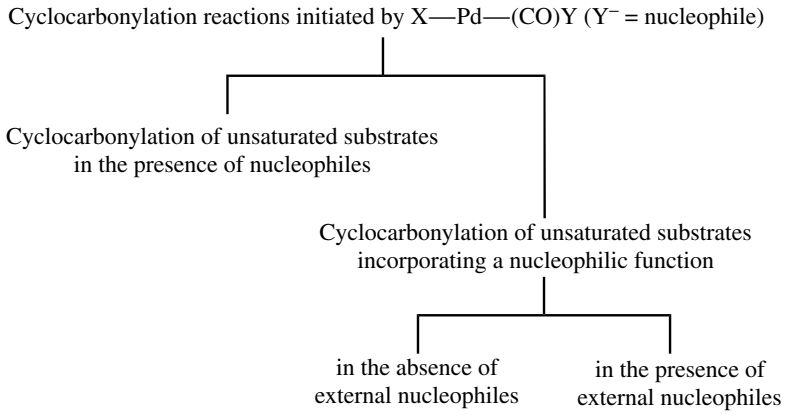
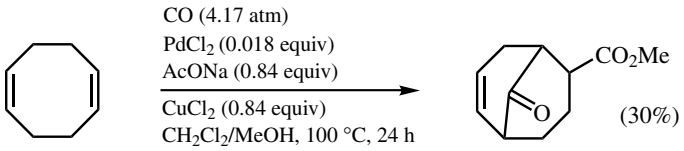


Scheme 1

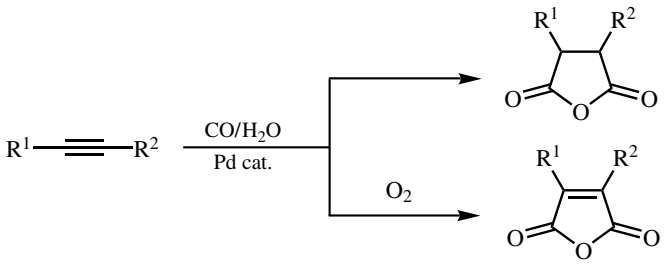


Scheme 2

catalytic system and reaction conditions, either maleic or succinic anhydrides can be obtained (**Scheme 3**).

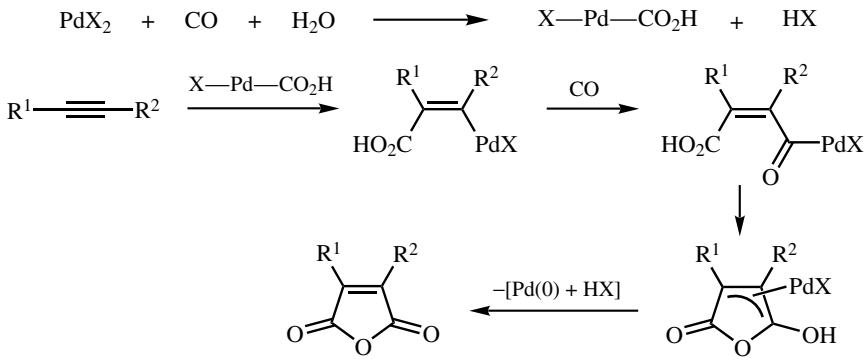
These reactions are likely to be initiated by Pd—CO_2H species, formed by H_2O attack on coordinated CO (**Scheme 4**).[2] Formation of the maleic anhydrides corresponds to oxidative dicarbonylation and occurs with elimination of Pd(0), so the presence of an external oxidant such as O_2 is required to make the process catalytic. On the other hand, a Pd—H species [in equilibrium with Pd(0) + H^+] may be responsible for double bond reduction leading to succinic anhydrides.

Carbonylation of acetylene carried out in the presence of catalytic amounts of $PdBr_2$, LiBr, and H_2O (H_2O/LiBr/$PdBr_2$ molar ratio = 10:2:1) in CH_3CN at 40 °C and 1 atm of total pressure [$p(CO)/p(C_2H_2) = 2.5$] afforded succinic anhydride in 70% yield.[3] Working in the presence of oxygen, maleic anhydride was obtained as the main product.

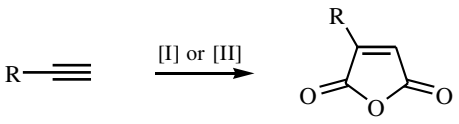


Scheme 3

Formation of phenylmaleic anhydride (24% yield) by carbonylation of phenylacetylene (3.6 equiv) in the presence of $PdCl_2$ (1 equiv) and $HgCl_2$ (1 equiv) in acetone/H_2O (9:1, v/v) under 2 atm pressure of CO at 25 °C for 15 h was reported many years ago.[4] More recently, maleic anhydrides were obtained with good selectivities by oxidative carbonylation of alk-1-ynes in the presence of $PdCl_2$ in conjunction with $CuCl_2$, HCO_2H, and O_2.[5] $CuCl_2$ is believed to act essentially as a cocatalyst, for example, by promoting the formation of heterometallic Pd/Cu complexes, which are supposed to be more active than simple chloropalladium species. A halide-free catalytic system, consisting of $Pd(OAc)_2$ in conjunction with chlorohydroquinone (HQ-Cl), molybdovanadophosphate (NPMoV), and CH_3SO_3H, has also been developed (**Scheme 5**).[6]



Scheme 4



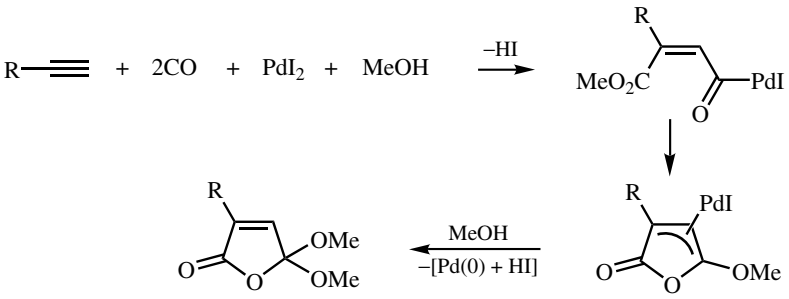
R	Conditions	Yield (%)
Ph	[I]	75
Ph	[II]	62
p-$CH_3C_6H_4$	[II]	63
p-ClC_6H_4	[II]	36
Bu	[I]	35
t-Bu	[I]	47

[I] = CO (9 mL/min), O_2 (3 mL/min), $PdCl_2$ (0.1 equiv), $CuCl_2$ (0.1–0.2 equiv), 90% HCO_2H (1.5–2.0 equiv), THF, 25 °C, 3–8 h.
[II] = CO (20 atm), O_2 (1 atm), $Pd(OAc)_2$ (0.05 equiv), HQ-Cl (0.2 equiv), NPMoV (~0.01 equiv), CH_3SO_3H (0.1 equiv), dioxane, 25 °C, 15 h.

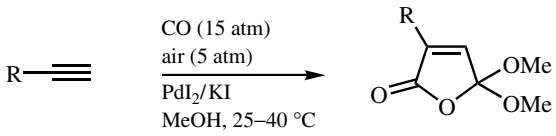
Scheme 5

Although the PdI_2/KI-catalyzed dialkoxycarbonylation of alk-1-ynes mainly afforded maleic diesters (cf. **Sect. VI.4.4.1**), significant amounts of 5,5-dialkoxyfuran-2(5*H*)-ones were also obtained (**Scheme 6**).[7]

Formation of the latter products, which can be regarded as cyclic isomers of maleates, was favored at low temperatures (25–40 °C, Scheme 7). They readily converted into dialkyl maleates working at higher temperatures (60–80 °C) or by acid-catalyzed alcoholysis.



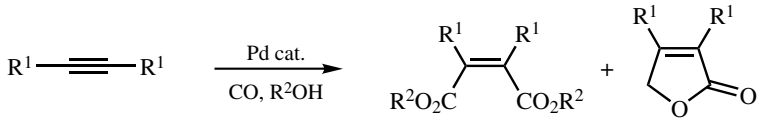
Scheme 6



R	PdI_2(%)	KI (%)	T (°C)	*t* (h)	Yield (%)
Bu	0.33	3.3	40	15	20
Ph	0.50	5.0	25	15	45
CH_2OH	0.033	0.33	25	15	23
CH_2OAc	0.1	1.0	25	5	44

Scheme 7

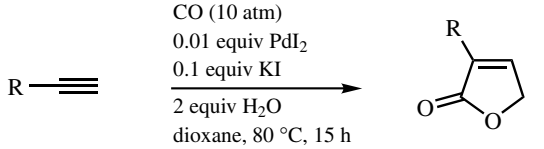
Pd-catalyzed cyclocarbonylation of alkynes can also afford furan-2(5*H*)-ones. The stoichiometry of the process clearly requires a reducing agent. In the earlier examples reported in the literature,[8]–[10] the alkyne itself simultaneously underwent reductive dicarbonylation to furanone and oxidative dialkoxycarbonylation to maleic diester, so the overall process corresponded to that represented in **Scheme 8**.



Scheme 8

Thus, the $PdCl_2$/HCl-catalyzed carbonylation of diphenylacetylene carried out in methanol at 100 °C and 100 atm of CO afforded dimethyl 2,3-diphenylbut-2-enedioate (34% yield) together with 3,4-diphenylfuran-2(5*H*)-one (60%).[8] In a closely related reaction, 3-phenylfuran-2(5*H*)-one (34%) and dimethyl phenylmaleate (32%) were formed from phenylacetylene working in the presence of complex $[Pd(tu)_4]Cl_2$ (tu = thiourea) at room temperature and atmospheric pressure of CO.[9] The latter reaction was subsequently generalized to both aryl- and alkylacetylenes using a slightly modified catalyst, consisting of PdI_2 in conjunction with 3 equiv of thiourea and formally corresponding to the ionic formula $[Pd(tu)_3I]I$.[10]

Although the above reaction is undoubtedly interesting from a conceptual point of view, formation of maleic diesters in addition to lactones does not appear synthetically convenient. This drawback was recently overcome by reacting alk-1-ynes with CO in dioxane at 80 °C in the presence of PdI_2, KI, and H_2O.[11] The reductive carbonylation process leading to furanones occurs in this case at the expense of CO, which is oxidized to CO_2, rather than of starting alk-1-yne (**Scheme 9**). A palladium hydride complex I—Pd—H resulting from decarboxylation of an I—Pd—CO_2H intermediate is probably involved in the reductive pathway leading to furanones.[2]



R	Yield (%)
Bu	77
t-Bu	60
Ph	67
p-$MeOC_6H_4$	65
p-BrC_6H_4	51

Scheme 9

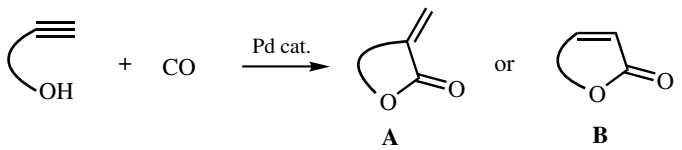
A conceptually very interesting effect was obtained when the reaction was carried out in the presence of added CO_2 (40 atm). Under these conditions, product distribution changed in favor of maleic anhydrides (34–47%), lactones, however, still being formed (30–42%).[2] This result shows that a large excess of CO_2 may allow the oxidative dicarbonylation cycle to run even in the absence of added oxidants.

C. CYCLOCARBONYLATION OF UNSATURATED SUBSTRATES INCORPORATING A NUCLEOPHILIC FUNCTION IN THE ABSENCE OF EXTERNAL NUCLEOPHILES

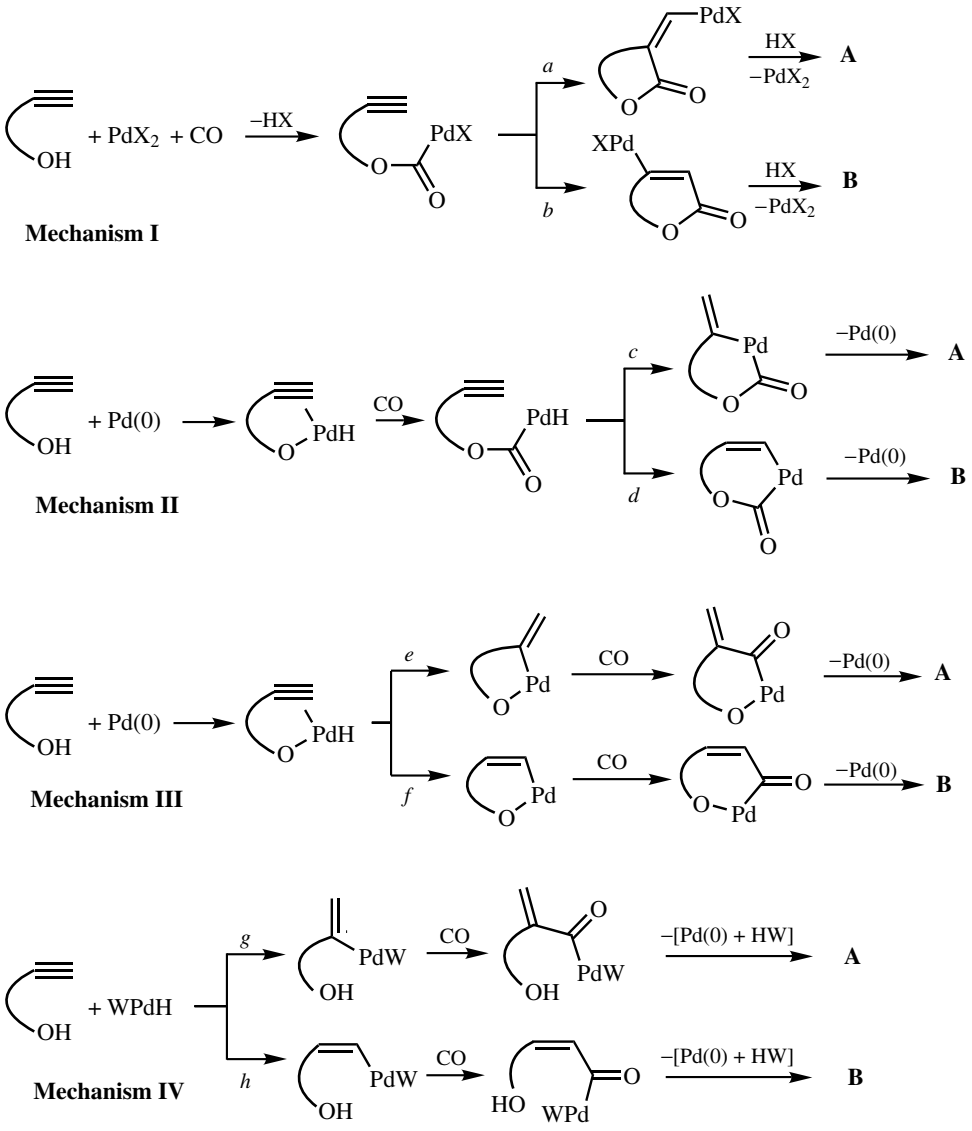
Pd-catalyzed carbonylation of unsaturated substrates incorporating a nucleophilic function in a suitable position may result in ring formation with CO incorporation into the ring (cyclocarbonylation). In the absence of external nucleophiles, the cyclocarbonylation process usually results in intramolecular hydroalkoxycarbonylation of the unsaturated bond, both *exo* and *endo* cyclization modes being possible, as shown in **Scheme 10** for a generic alkynol.

At least four main mechanistic pathways are in principle possible, exemplified in **Scheme 11**.

When Pd(II) is used as catalyst, the reaction can be initiated by an (alkoxycarbonyl)palladium species deriving from attack of the nucleophilic function of the substrate on carbon monoxide coordinated to palladium. This species then inserts the unsaturated



Scheme 10



Scheme 11

bond with formation of an alkyl- or alkenylpalladium intermediate, which undergoes protonolysis of the Pd—C bond to give the final product (**Mechanism I**). An (alkoxycarbonyl)palladium species, however, can also be formed starting from Pd(0), since oxidative addition of the O—H bond to Pd(0) is possible with formation of an alkoxypalladium hydride intermediate, which then inserts CO into the Pd—OR bond. The catalytic cycle is then completed by double or triple bond insertion into the Pd—H bond and reductive elimination (**Mechanism II**). Alternative sequences involving double or triple bond insertion into a Pd—H bond before CO insertion must be considered as well. The palladium hydride complex may be formed *in situ* by oxidative addition to Pd(0) of the RO—H bond of the substrate (**Mechanism III**) or by oxidative addition to Pd(0) of an HW species (W = H, X, etc.) present in the reaction mixture (**Mechanism IV**).

The elementary steps implicated in **Mechanism I** were extensively studied by Norton and co-workers, who were able to independently synthesize, isolate, and characterize all the organopalladium intermediates involved.[12],[13] This elegant and thorough work unequivocally showed that intramolecular insertion of the (alkoxycarbonyl)palladium species on the unsaturated bond in 3-en-1-ols, 3-yn-1-ols, and 4-yn-1-ols occurs exclusively in a *syn-exo* fashion (path *a*). It is important to point out, however, that in a catalytic reaction Pd(0)-initiated mechanisms like II–IV cannot be ruled out. Clearly, in the model system used by Norton there was no alternative to **Mechanism I**, since an alkoxycarbonylpalladium complex was synthesized first and the proton was added at the end of the sequence.

Since **Sect. VI.4.4** concerns carbonylations initiated by X—Pd—(CO)Y species, only processes that can possibly follow **Mechanisms I** and **II** will be treated here, while reactions that were rationalized according to different pathways (such as **III** and **IV**) are discussed elsewhere.

3-En-1-ols and 4-en-1-ols were reported to afford tetrahydrofuran-2-ones or tetrahydropyran-2-ones, respectively, by *exo-trig* cyclocarbonylation carried out in THF at $T = 25$ °C and $P = 1$ atm in the presence of $PdCl_2$, $CuCl_2$, HCl, and O_2.[14] Under the same conditions, 2-en-1-ols afforded tetrahydrofuran-2-ones by an *endo-trig* process (**Scheme 12**).[15]

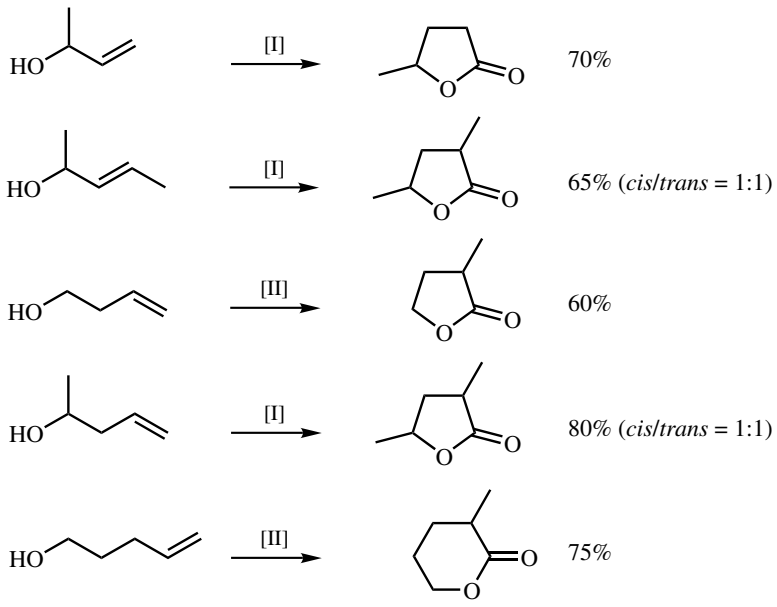
The understanding of the reaction mechanism appears quite difficult, owing to the complexity of the catalytic system. It is, for example, rather curious that an additive carbonylation is obtained in spite of the oxidative conditions employed. **Mechanism I** (**Scheme 11**), however, is not incompatible with the experimental results. The reaction of but-2-en-1-ol to give 3-methylfuran-2-one was also made enantioselective (ee up to 61%) by adding poly-L-leucine as nonracemic ligand.[16] It is worth noting that in this case a Pd—H intermediate has been proposed as the most likely intermediate, according to Mechanism IV, path *h* (**Scheme 11**).[16]

Pd-catalyzed *endo-trig* cyclocarbonylation of 2-en-1-ols, bearing a terminal double bond and a secondary or tertiary alcoholic group, has also been carried out under neutral conditions, using $Pd(dba)_2$/dppb as the catalytic system in DME at $T = 190$ °C and under 40 atm of CO (**Scheme 13**).[17]

Under slightly milder conditions [$T = 150$ °C, $P(CO) = 20$ atm], tertiary 2-yn-1-ols bearing a terminal triple bond afforded substituted furan-2(5*H*)-ones in good yields (**Scheme 14**).[17] **Mechanism II**, path *d* (**Scheme 11**), was proposed for lactone formation in these reactions.

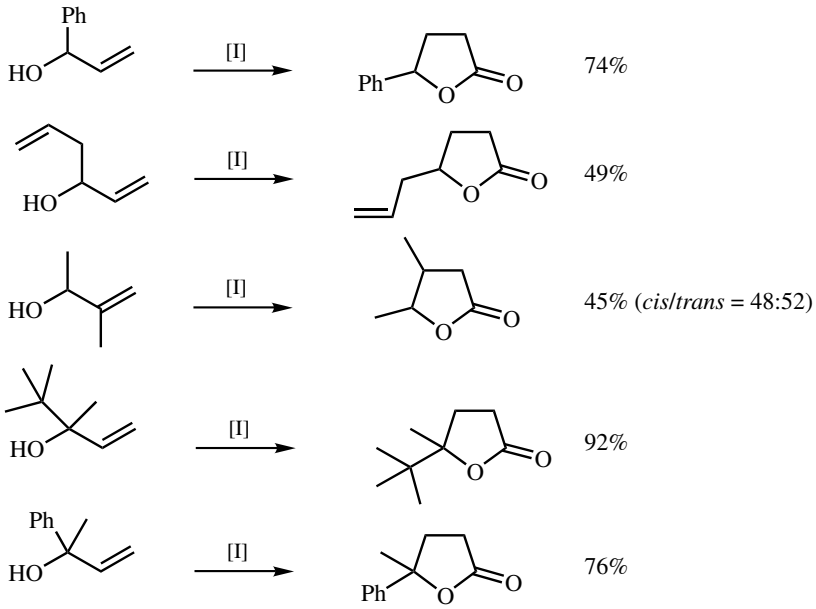
This methodology was subsequently improved by working under 54 atm of a 3:1 mixture of CO and H_2 at 95 °C in CH_2Cl_2 as the solvent. The latter conditions ensured better yields in furan-2(5*H*)-ones and were also suitable for 2-yn-1-ols with a secondary alcoholic group and/or an internal triple bond (**Scheme 14**).[18] The cyclocarbonylation process was shown to occur stereospecifically, since almost complete retention of configuration was observed when (*R*)-1-(*p*-tolyl)pent-1-yn-3-ol was transformed into (*R*)-3-(*p*-tolyl)-5-ethylfuran-2(5*H*)-one [(*R*)-incrustoporin, an antibiotic].[19]

This stereochemical outcome was not in agreement with a mechanism starting with the oxidative addition of the alcoholic function of the substrate to Pd(0), which should have led to the opposite result (inversion of configuration). Accordingly, a mechanism involving direct formation of an H—Pd—(CO)OR intermediate by reaction between the alkynol and a $Pd^0(CO)$ species followed by *endo* triple bond insertion and reductive elimination has been suggested,[19] in contrast with the originally proposed **Mechanism III**, path *f* (**Scheme 11**).[18]



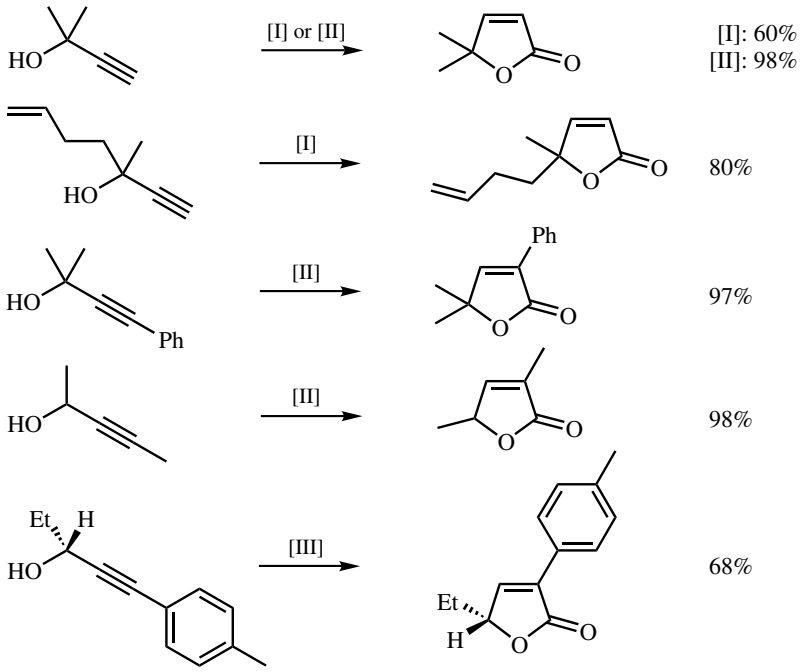
[I] = CO/O_2 (1 atm), $PdCl_2$ (0.1 equiv), $CuCl_2$ (0.2 equiv), HCl (0.75 equiv), THF, 25 °C, 15–18 h.
[II] = CO/O_2 (1 atm), $PdCl_2$ (0.1 equiv), $CuCl_2$, (0.8 equiv), HCl (0.75 equiv), THF, 25 °C, overnight.

Scheme 12



[I] = CO (40 atm), 4% $Pd(dba)_2$, 4% dppb, DME, 190 °C, 48 h.

Scheme 13



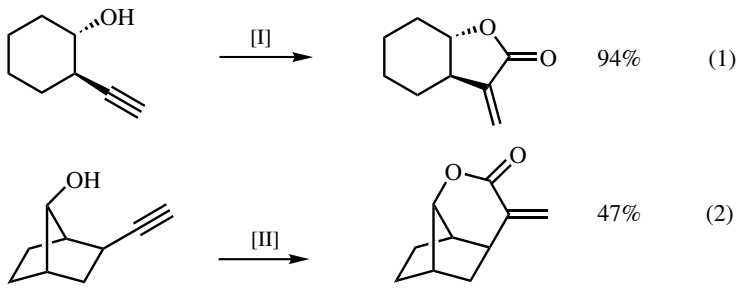
[I] = CO (20 atm), 4% $Pd(dba)_2$, 4% dppb, DME, 150 °C, 48 h.
[II] = CO (40.8 atm), H_2 (13.6 atm), 4% $Pd_2(dba)_3 \cdot CHCl_3$, 8% dppb, CH_2Cl_2, 95 °C, 36 h.
[III] = CO (40.8 atm), H_2 (13.6 atm), 8% $Pd(dba)_2$, 8% dppb, CH_2Cl_2, 95 °C, 48 h.

Scheme 14

α-Methylene lactones were synthesized in good yields by carbonylation of 3-yn-1-ols carried out under mild conditions in the presence of $PdCl_2$ and thiourea in acetone as the solvent (Eq. 1 of **Scheme 15**).[20] Under similar conditions, 4-yn-1-ols afforded the corresponding α-methylene-δ-lactones only when the ethynyl and hydroxyl groups were fixed in the proper geometry and using a stoichiometric amount of $PdCl_2$ (Eq. 2 of **Scheme 15**).[21]

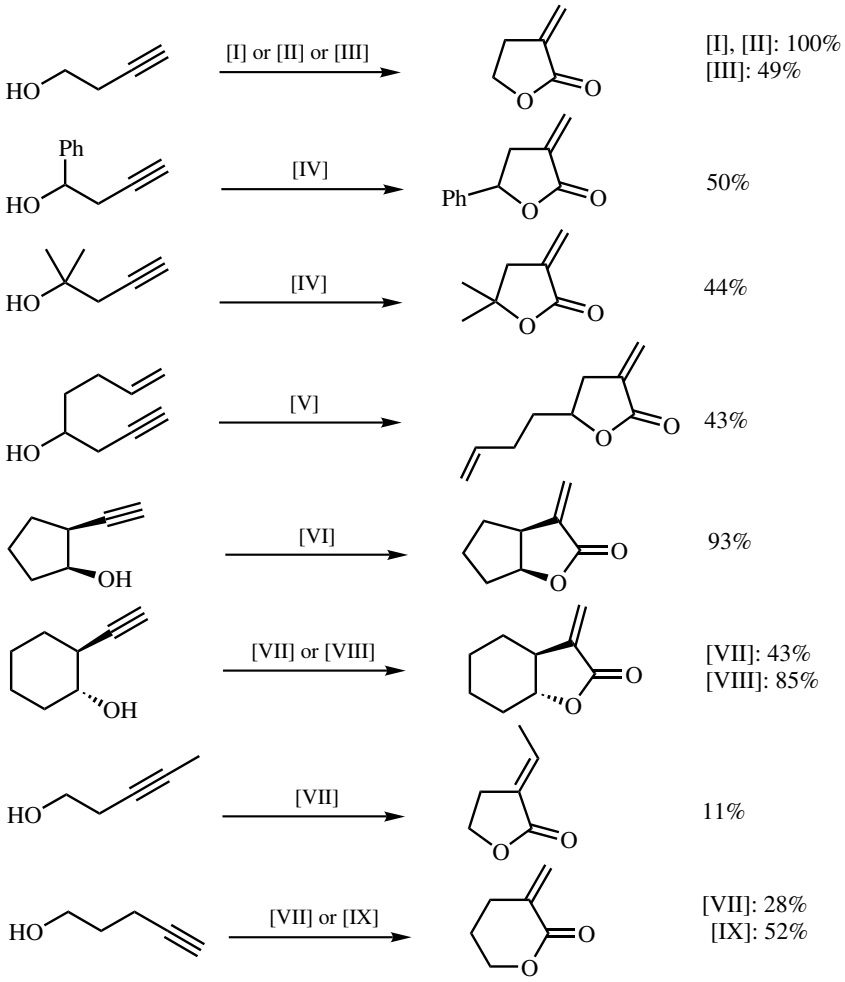
These reactions are thought to proceed according to **Mechanism I**, path *a* (**Scheme 11**). In the course of the investigation of the reaction mechanism,[12] the catalytic system was subsequently improved. The best catalyst was found to be $PdCl_2$ in conjunction with a tertiary phosphine (2 equiv) and $SnCl_2$ (1 equiv) in anhydrous CH_3CN as the solvent. This new catalytic system not only ensured higher yields and more satisfactory catalytic efficiencies but was also suitable for the cyclocarbonylation of simple pent-4-yn-1-ol (**Scheme 16**).[22]

Recently, an extremely efficient catalytic system, based on a cationic Pd(II) species in conjunction with a bidentate ligand containing a 2-pyridylphosphine moiety, has been developed for the additive monocarbonylation of alk-1-ynes.[23] This catalyst was also applied to the cyclocarbonylation of but-3-yn-1-ol. Thus, by reacting the latter in toluene at 60 °C and 60 atm of CO in the presence of $Pd(OAc)_2$, diphenyl-[(6-methyl)-2-pyridyl]phosphine [dp(6-mpy)p] as ligand, TsOH, and traces of hydroquinone (to prevent polymerization), 3-methylenetetrahydrofuran-2-one was obtained in almost quantitative yield.[24] Another useful catalyst for the cyclocarbonylation of 3-yn-1-ols proved to be $[Pd(PPh_3)_2(CH_3CN)_2](BF_4)_2$ in DMF at 80 °C and 20 atm of CO (**Scheme 16**).[25]



[I] = CO (3.4 atm), $PdCI_2$ (0.13 equiv), thiourea (0.13 equiv), acetone, 50 °C, 15 h.
[II] = CO (3.4 atm), $PdCI_2$ (1 equiv), thiourea (1 equiv), acetone, 50 °C, 48 h.

Scheme 15



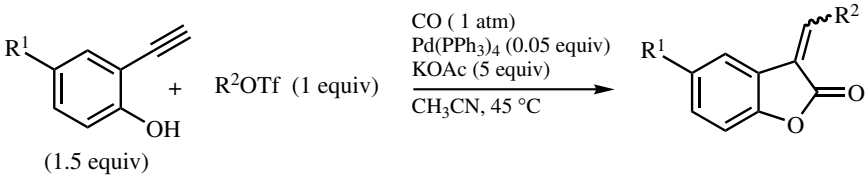
Scheme 16

[I] = CO (7.8 atm), $PdCl_2$ (0.07 equiv), $SnCl_2$ (0.07 equiv), PPh_3 (0.14 equiv), 75 °C, 10 h.
[II] = CO (60 atm), $Pd(OAc)_2$ (7×10^{-4} equiv), dp(6-mpy)p (0.02 equiv) TsOH (0.02 equiv), hydroquinone (traces), toluene, 60 °C, < 12 min.
[III] = CO (20 atm), 2% $[Pd(PPh_3)_2(CH_3CN)_2](BF_4)_2$, DMF, 80 °C, 3 h.
[IV] = CO (20 atm), 2% $[Pd(PPh_3)_2(CH_3CN)_2](BF_4)_2$, DMF, 80 °C, 20 h.
[V] = CO (7.8 atm), $PdCl_2$ (0.27 equiv), $SnCl_2$ (0.27 equiv), PPh_3 (0.54 equiv), 75 °C, 1.5 h.
[VI] = CO (5.7 atm), $PdCl_2$ (0.11 equiv), $SnCl_2$ (0.11 equiv), PPh_3 (0.22 equiv), 65 °C, 1.5 h.
[VII] = CO (20 atm), 2% $[Pd(PPh_3)_2(CH_3CN)_2](BF_4)_2$, DMF, 80 °C, 10 h.
[VIII] = CO (7.8 atm), $PdCl_2$ (0.38 equiv), $SnCl_2$ (0.38 equiv), PBu_3 (0.75 equiv), 75 °C, 6 h.
[IX] = CO (5.1 atm), $PdCl_2$ (0.014 equiv), $SnCl_2$ (0.014 equiv), PPh_3 (0.21 equiv), 75 °C, 23 h.

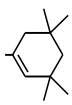
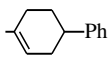
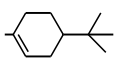
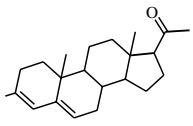
Scheme 16 (*Continued*)

3-Alkylidene-2-coumaranones were obtained in good yields by reacting 2-ethynylphenols, vinyl triflates, and CO in the presence of $Pd(PPh_3)_4$ and a base (AcOK or K_2CO_3) in CH_3CN at 45 °C and 1 atm of CO (**Scheme 17**).[26]

The reaction is believed to proceed as in Mechanism I, path *a* (**Scheme 11**), with two important differences: an R—Pd—X species [generated by oxidative addition of ROTf to Pd(0), X = OTf or OAc] rather than PdX_2 is involved in the first step, and a reductive coupling, rather than a protonolysis, occurs in the last step. This allows to combine a cyclocarbonylation process with the formation of an additional C—C bond.



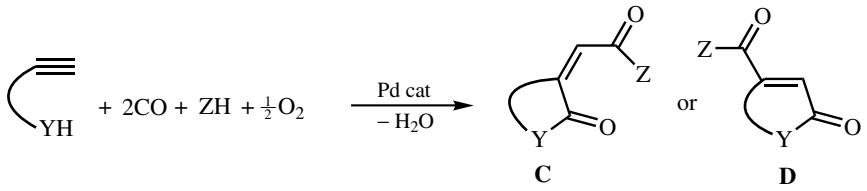
(1.5 equiv)

R^1	R^2	*t* (h)	Yield (%)	*E/Z*
H		4	64	85:15
H		8	52	80:20
Me		4	40	90:10
		8	70	20:80

Scheme 17

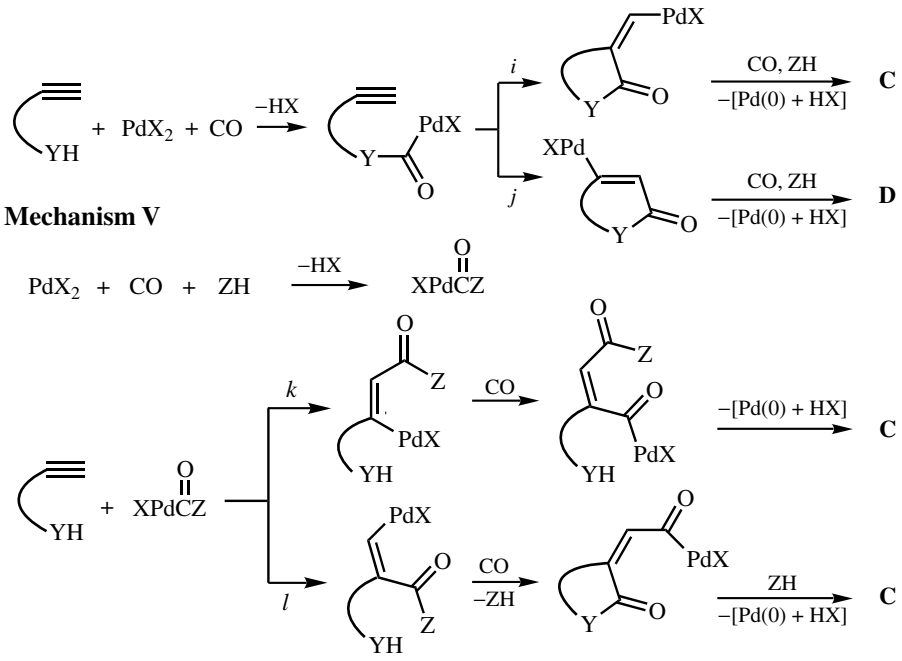
D. CYCLOCARBONYLATION OF UNSATURATED SUBSTRATES INCORPORATING A NUCLEOPHILIC FUNCTION IN THE PRESENCE OF EXTERNAL NUCLEOPHILES

Cyclocarbonylation of unsaturated substrates incorporating a nucleophilic function (—YH) in a suitable position can also be effected in the presence of external nucleophiles (ZH) such as alcohols. These reactions usually result in oxidative dicarbonylation of the unsaturated bond and are promoted by Pd(II) species. As ensuing dicarbonylation Pd(II) is reduced to Pd(0), the presence of an oxidant is needed in order to make the process catalytic, as exemplified in Scheme 18 in the case of triple bond.

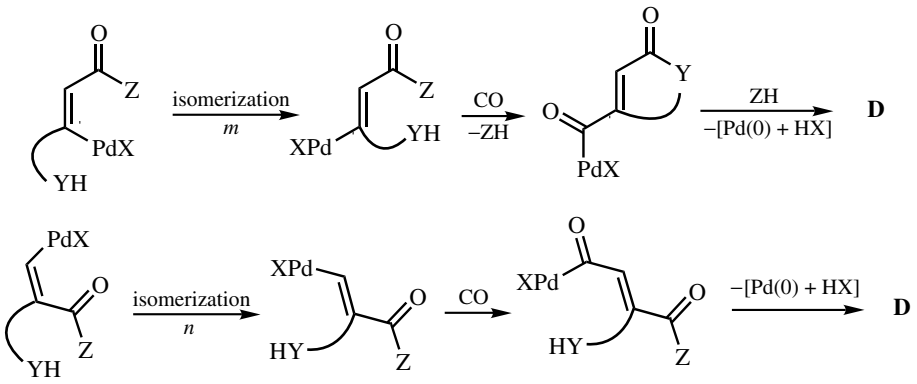


Scheme 18

In principle, two main reaction pathways have to be considered for this process (**Scheme 19**). Cyclocarbonylation may occur first followed by alkoxycarbonylation (**Scheme 19**, **Mechanism V**), or vice versa (**Scheme 19**, **Mechanism VI**). In both cases different regiochemistries and isomerization processes may influence the final outcome. In any case, an X—Pd—(CO)Y or X—Pd—(CO)Z intermediate is involved.



Scheme 19



Mechanism VI

Scheme 19 (*Continued*)

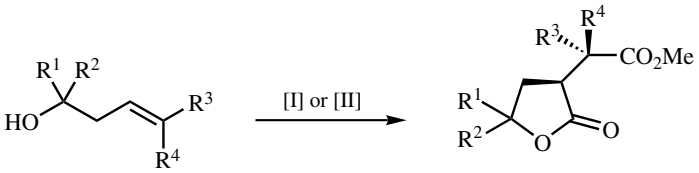
3-En-1-ols were reported to undergo oxidative *syn-exo-trig* cyclocarbonylation–alkoxycarbonylation in the presence of $PdCl_2$, $CuCl_2$, propylene oxide, and $MeC(OEt)_3$ in $MeOH/CH_2Cl_2$ at room temperature and under an atmospheric pressure of CO.[27] Propylene oxide was believed to act mainly as base, necessary for maintaining the reaction mixture neutral by quenching the HCl resulting from the dicarbonylation process, while the use of a dehydrating agent such as $MeC(OEt)_3$ ensured better yields. **Mechanism V**, path *i* (**Scheme 19**), has been proposed for these reactions. Dicarbonylation of 3-en-1-ols bearing a terminal double bond to give 3-[(methoxycarbonyl)methyl]tetrahydrofuran-2-ones was also successfully achieved using a 1:1 mixture of CO/O_2 (total pressure 1 atm) in MeOH at 25 °C in the presence of $PdCl_2$ and CuCl.[28] The use of CuCl was essential for the occurrence of a dicarbonylation process, and both Pd-CO_2Me and Cu-CO_2Me species were thought to be involved as active intermediates. Some representative examples based on both the methodologies are reported in **Scheme 20**.

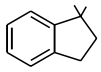
The $PdCl_2$/CuCl-catalyzed reaction was made enantioselective (ee = 19–65%) using allylpalladium chloride dimer, $(C_3H_5PdCl)_2$, and copper(I) triflate, $CuOTf(C_6H_6)_{0.5}$, in the presence of a nonracemic bis-oxazoline ligand, (*S*,*S*)-4,4′-dibenzyl-4,4′,5,5′-tetrahydro-2,2′-bis-oxazole.[29]

The $PdCl_2/CuCl_2$/propylene oxide/$MeC(OEt)_3$ methodology was also applied to internal 3-yn-1-ols. In this case, however, the expected cyclocarbonylation–alkoxycarbonylation process occurred only when the substituent at C-4 was a $SiMe_3$ group (**Scheme 21**). With alkyl or aryl substitution at C-4 the reaction course changed completely, with formation of (*E*)-3-[(methoxy)methylene]tetrahydrofuran-2-ones.[27]

Quite interestingly, pent-3-yn-1-ol afforded the dicarbonylation product, (*Z*)-3-[1-(methoxycarbonyl)ethylidene]tetrahydrofuran-2-one (67% yield), when reacted in MeOH for 2 h using a stoichiometric amount of $PdCl_2$ in conjunction with propylene oxide (5 equiv) and $MeC(OEt)_3$ (0.4 equiv) and in the absence of $CuCl_2$. The latter result seemed to suggest that, in the catalytic reactions, $CuCl_2$ not only acted as the oxidant of Pd(0) but also played an important role in the reaction course (cf. **Sect. B**).

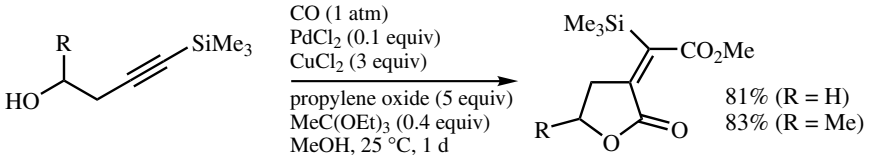
Pd(II)-catalyzed cyclocarbonylation–alkoxycarbonylation of external 3-yn-1-ols to give (*Z*)-3-[(methoxycarbonyl)methylene]tetrahydrofuran-2-ones was achieved in excellent yields and catalytic efficiencies by using a copper-free catalyst based on



R^1	R^2	R^3	R^4	Conditions	*t*	Yield (%)
H	H	H	H	[I]	1 d	76
H	H	H	H	[II]	16 h	76
Me	H	H	H	[I]	1 d	82
$PhCH_2CH_2$	H	H	H	[I]	1 d	97
$PhCH_2CH_2$	H	H	H	[II]	23 h	90
Me	Me	H	H	[I]	1 d	72
H	H	Me	H	[I]	1 d	55
H	H	H	Me	[I]	1 d	56
$—(CH_2)_4—$		H	H	[II]	18 h	86
		H	H	[II]	2 d	80

[I] = $PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), propylene oxide (5 equiv), $MeC(OEt)_3$ (0.4 equiv); P(CO) = 1 atm, $MeOH/CH_2Cl_2$ (3:6, v/v), 25 °C.
[II] = $PdCl_2$ (0.1 equiv), CuCl (1.5 equiv); P(CO) = 0.5 atm, $P(O_2)$ = 0.5 atm, MeOH, 25 °C.

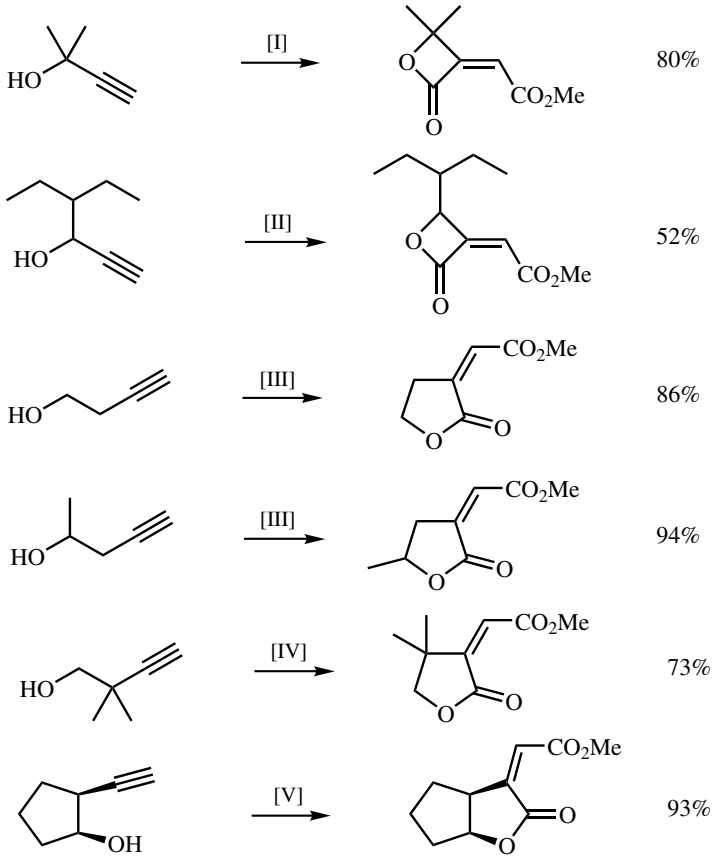
Scheme 20



Scheme 21

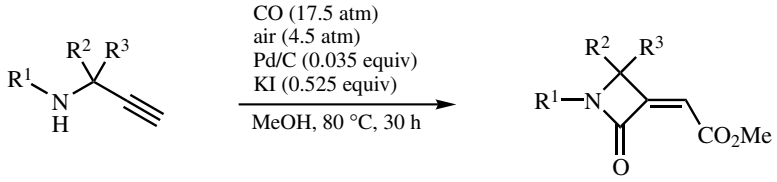
$[PdI_4]^{2-}$ anion (generated *in situ* from PdI_2 in an excess of KI) at 70–80 °C and under 20 atm of a 3:1 mixture of CO and air.[30] **Mechanism V**, path *i* (**Scheme 19**), has been proposed to explain product formation. The same catalyst proved to be effective for the conversion of 2-yn-1-ols (α,α-dialkylsubstituted, or α-monoalkylsubstituted with a sufficiently bulky alkyl group) into (*Z*)-3-[(alkoxycarbonyl)methylene]oxacyclobutan-2-ones with good selectivities (**Scheme 22**).[30] **Mechanism VI**, path *k* (**Scheme 19**), was considered to be the most likely in this case, with the *gem*-dialkyl effect promoting the cyclization step (maleic diesters were mainly obtained from simple propynyl alcohol and but-3-yn-2-ol).

The latter methodology was applied to secondary α,α-dialkylsubstituted 2-yn-1-amines to give α-[(alkoxycarbonyl)methylene]-β-lactams in good yield. Pd/C–KI could also be used in place of PdI_2–KI in these reactions (**Scheme 23**).[31]



[I] = CO (15 atm), air (5 atm), PdI_2 (2×10^{-3} equiv), KI (0.02 equiv), MeOH, 70 °C, 3 h.
[II] = CO (15 atm), air (5 atm), PdI_2 (2×10^{-3} equiv), KI (0.02 equiv), MeOH, 70 °C, 4 h.
[III] = CO (15 atm), air (5 atm), PdI_2 (2×10^{-3} equiv), KI (0.02 equiv), MeOH, 70 °C, 12 h.
[IV] = CO (15 atm), air (5 atm), PdI_2 (2×10^{-3} equiv), KI (0.02 equiv), MeOH, 80 °C, 24 h.
[V] = CO (15 atm), air (5 atm), PdI_2 (2×10^{-3} equiv), KI (0.02 equiv), MeOH, 70 °C, 15 h.

Scheme 22

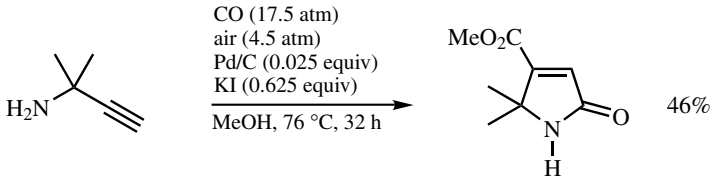


R^1	R^2	R^3	Yield (%)
Bn	Me	Me	71
Bn	Et	Me	80
Bu	Me	Me	40

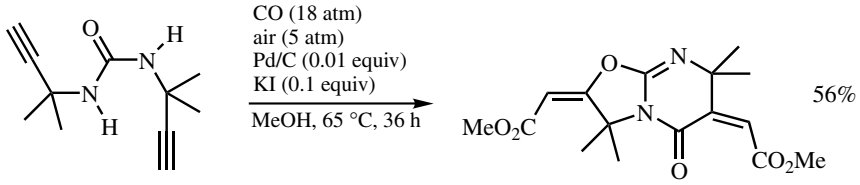
Scheme 23

With a primary amino group, the reaction afforded γ-lactam derivatives (**Scheme 24**), probably via **Mechanism V**, path *j* (**Scheme 19**).[31]

An interesting double cyclization reaction was observed in the Pd/C-KI-catalyzed oxidative carbonylation of *N*,*N*′-bis(1,1-dimethylpropynyl)urea carried out in MeOH at 65 °C and 23 atm of a 3.6:1 mixture of CO and air (**Scheme 25**).[32]



Scheme 24

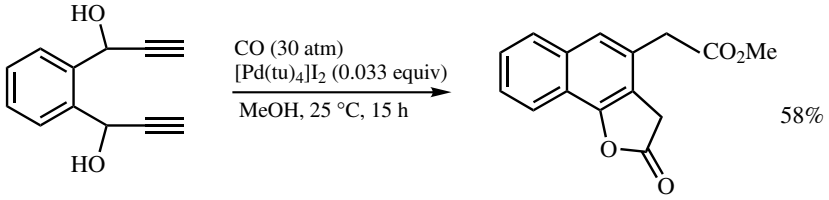


Scheme 25

Product formation has been rationalized according to the following steps: (i) oxygen attack on coordinated triple bond followed by alkoxycarbonylation[31] generates the oxazoline ring; (ii) insertion of the triple bond of the second propargyl group into the Pd—CO_2Me bond followed by CO insertion[7] leads to an acylpalladium intermediate; (iii) the latter then undergoes intramolecular nucleophilic attack by the nitrogen of the oxazoline ring.[32]

Another interesting double cyclization process was reported to occur from the carbonylation of *o*-bis(1-hydroxy-2-propynyl)benzene in the presence of complex $[Pd(tu)_4]I_2$ (tu = thiourea) at 25 °C and 30 atm of CO, with selective formation of a naphthofuranoneacetic ester (**Scheme 26**).[33] In this case, the process may be viewed as a combination of oxidative dialkoxycarbonylation and reduction of one of the hydroxyl group, the net result being additive dicarbonylation.

It is well known that Pd(II)-promoted cyclization–alkoxycarbonylation of 4-en-1-ols and 5-en-1-ols in MeOH to give 2-[(methoxycarbonyl)methyl]tetrahydrofuran or

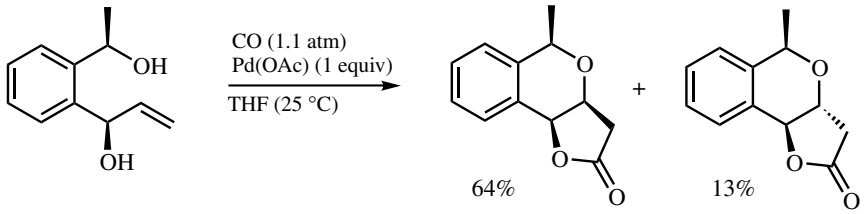


Scheme 26

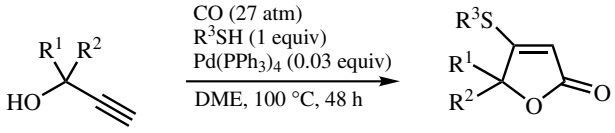
2-[(methoxycarbonyl)methyl]tetrahydropyran derivatives, respectively, almost certainly implies nucleophilic attack on coordinated double bond followed by alkoxycarbonylation.[34] However, the reverse sequence seems to be involved when an additional hydroxyl group is present α to the double bond (**Scheme 27**). This is suggested by the fact that *cis* stereochemistry of ring junction was obtained preferentially in the latter case, while very low stereoselectivity was observed in the "normal" process, which takes place when the hydroxyl group is blocked as methyl ether.[35]

An interesting thiocyclocarbonylation of secondary or tertiary 2-yn-1-ols was reported to occur in DME at 100 °C and 27 atm of CO in the presence of thiols and $Pd(PPh_3)_4$ as the catalyst (**Scheme 28**).[36]

The reaction mechanism is unknown at the present, although an RO(CO)Pd—X intermediate may reasonably be involved.



Scheme 27



R^1	R^2	R^3	Yield (%)
Me	H	Ph	88
Me	Me	Ph	67
Me	Me	n-C_8H_{17}	74
—$(CH_2)_5$—		Ph	85

Scheme 28

E. SUMMARY

1. Nucleophilic addition to Pd-coordinated carbon monoxide can be utilized to form rings containing carbon monoxide itself as a carbonyl group. Cyclic ketones, cyclic anhydrides, and lactones are advantageously prepared in this way using alkenes and alkynes as substrates. Carbon dioxide has been found to exert an important role in the carbonylation of alk-1-ynes under water shift conditions by causing the formation of unsaturated lactones to shift toward maleic anhydrides.

2. The reaction of alkenols and alkynols with carbon monoxide in the absence of external nucleophiles results in additive cyclocarbonylation and has been employed for

the synthesis of γ- and δ-lactones. Depending on the catalytic system and reaction conditions employed, both *endo* and *exo* cyclization modes are possible.

3. Oxidative cyclocarbonylation–alkoxycarbonylation is usually observed when the reaction of alkenols and alkynols is carried out in the presence of external nucleophiles such as alcohols. β-Lactones and β-lactams bearing an exocyclic (Z)-(alkoxycarbonyl)methylene moiety can be prepared according to a very simple oxidative technique starting from propynyl alcohols or amines. Geminal groups have been found to exert a powerful effect on cyclization.

4. When acetylenic ureas are used as substrates under oxidative conditions in methanol, formation of condensed heterocycles takes place under mild conditions.

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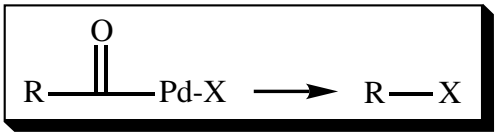

VI.5 Other Reactions of Acylpalladium Derivatives

VI.5.1 Palladium-Catalyzed Decarbonylation of Acyl Halides and Aldehydes

JIRO TSUJI

A. BACKGROUND

The term decarbonylation encompasses all methods of removing carbon monoxide from carbonyl compounds, and several methods of decarbonylation are known. Transition-metal-catalyzed decarbonylation is one of them.[1]

Pd is an efficient catalyst for carbonylation of olefinic and acetylenic compounds and aryl halides to form various saturated and unsaturated carboxylic acids, their esters, and lactones. Also, aldehydes are obtained using Pd catalysts. For a long time, Pd has been known as an efficient catalyst for decarbonylation of aldehydes. Acyl halides are also decarbonylated with Pd catalysts. Now it is well-established that Pd is the efficient catalyst for both carbonylation and decarbonylation as reversible processes.

From mechanistic studies of carbonylation, it has become apparent that an important step in carbonylation is the insertion of carbon monoxide to aryl- and alkylpalladium bonds to form acylpalladium bonds (so-called alkyl–acyl rearrangement). The reverse reaction, namely, decarbonylation of acylpalladium bonds, proceeds under certain conditions. In fact, efficient Pd-catalyzed decarbonylation reactions of aldehydes and acyl halides at high temperature are known (**Scheme 1**).

In addition to Pd-catalyzed decarbonylation, rhodium complexes catalyze the decarbonylation efficiently.[2] In this section, decarbonylation of acyl halides and aldehydes using palladium catalysts is surveyed.[3]

B. PALLADIUM-CATALYZED DECARBONYLATION OF ACYL HALIDES AND ACID ANHYDRIDES

Hydrocarbonylation of alkenes in alcohol is catalyzed by Pd(0) to give esters, and the reaction is expected to proceed via acylpalladium intermediates.[4] Also, the acylpalladium

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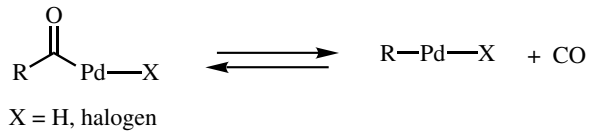
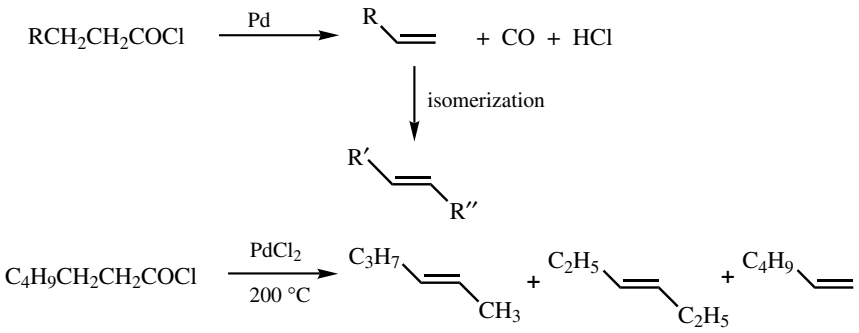


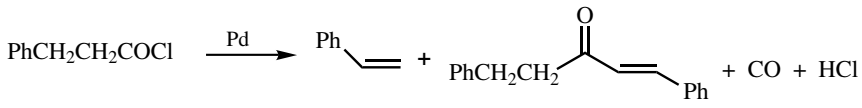
Scheme 1

intermediate is generated by the oxidative addition of acyl halides and undergoes the acyl–alkyl rearrangement as a reverse process of the alkyl–acyl rearrangement. Thus, the acyl halides of aliphatic acids undergo Pd-catalyzed decarbonylation to give alkenes.[3],[5] When heated at 200 °C or above, higher aliphatic acyl halides are decarbonylated in high yields to give alkenes having one less carbon atom. The product is a mixture of isomeric internal alkenes, even when it is distilled from the reaction mixture as soon as it is formed. For example, when decanoyl chloride is heated with a catalytic amount of Pd on carbon or $PdCl_2$ at 200 °C in a distilling flask, rapid evolution of CO and HCl stops after 1 h, during which time a mixture of nonene isomers is distilled off in high yields. The isomerization of the double bond catalyzed by Pd(0) is very fast. Hexenes obtained by decarbonylation of heptanoyl bromide consisted of 1-hexene (7.5%) and a mixture of 2- and 3-hexenes (92.5%) (**Scheme 2**).



Scheme 2

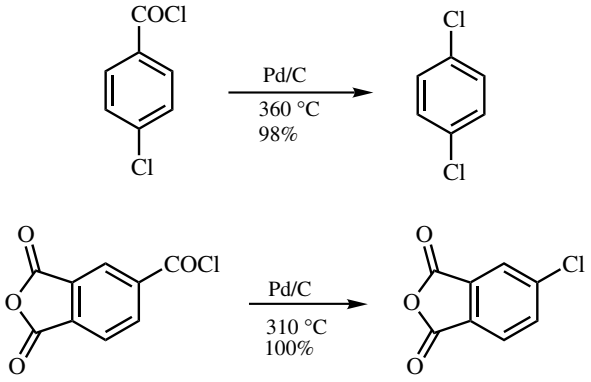
When the double bond migration of alkenes produced by the decarbonylation is impossible, other products are formed in addition to alkenes. When phenylpropionyl chloride was decarbonylated, the main product was styrene (53%), and 1,5-diphenyl-1-penten-3-one was obtained in 10% with a small amount of unidentified products.[3] Benzyl chloride and some unidentified products were obtained from phenylacetyl chloride (**Scheme 3**).



Scheme 3

In contrast to aliphatic acyl halides, which give alkenes in good yields, halides of aromatic acids (aroyl halides) are not decarbonylated satisfactorily below 250 °C. Smooth

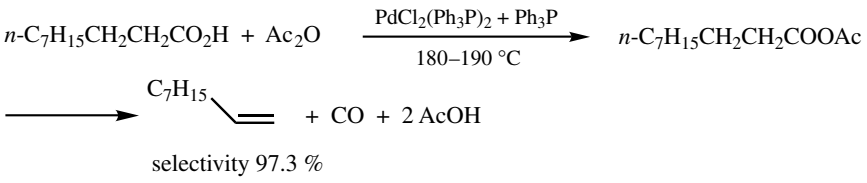
decarbonylation of aroyl chlorides to afford aryl chlorides proceeds above 300 °C in a gas phase or in melt condition using 1 mol % of 5% Pd on carbon.[6] For example, *p*-chlorobenzoyl chloride was converted to *p*-dichlorobenzene in 98% yield at 360 °C in the gas phase. Treatment of trimellitic anhydride acid chloride in the melt with 5% Pd on carbon at 310 °C afforded 4-chlorophthalic anhydride in nearly quantitative yield. Interestingly, no decarbonylation of anhydride occurred, although there is a possibility of oxidative addition and decarbonylation of aromatic acid anhydrides. Poor results were obtained with aroyl chlorides bearing electron-donating groups (**Scheme 4**).



Scheme 4

Rh complexes are good catalytsts for the decarbonylation of aroyl halides under milder conditions.[2]

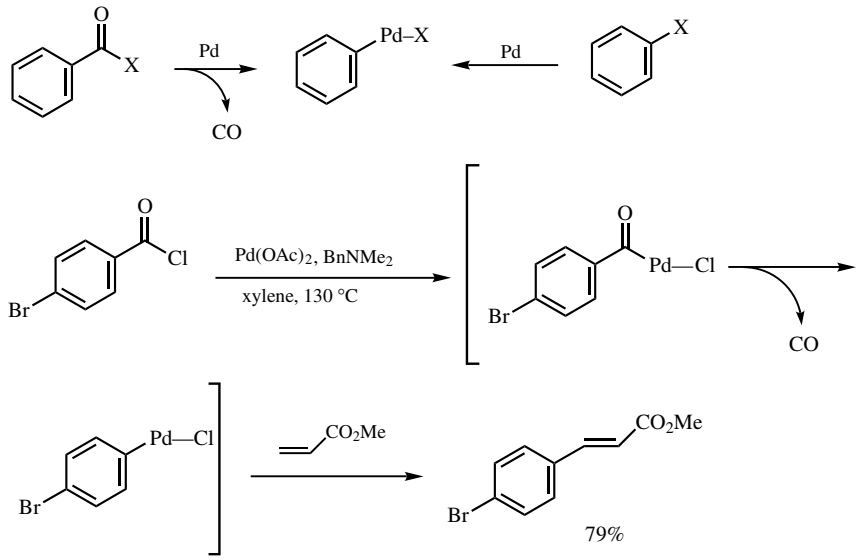
Aliphatic carboxylic acids undergo decarbonylation–dehydration to afford 1-alkenes of one less carbon atom in high yields with surprisingly high selectivity by the treatment of an equimolar mixture of a carboxylic acid and acetic anhydride at 250 °C (bath temperature). It was confirmed that the mixed anhydride is the intermediate of the reaction.[7] The decarbonylation–dehydration occurred by heating an equimolar mixture of decanoic acid and acetic anhydride in the presence of $PdCl_2(Ph_3P)_2$ (0.01 mol %) and excess Ph_3P (50 equiv relative to the Pd catalyst) to afford 1-nonene with a selectivity of 97.3% and a catalyst turnover number (TON) of 12370. It seems likely that Pd(0) coordinated by Ph_3P does not catalyze isomerization of double bonds (**Scheme 5**).



Scheme 5

Under certain conditions in the presence of other substrates, particularly of bases, facile decarbonylation of the aroylpalladium halides occurs to form arylpalladium halides as intermediates, which are usually prepared directly by oxidative addition of aryl

halides. Decarbonylation of aroyl halides via aroylpalladium halides occurs under surprisingly mild conditions. In the presence of other substrates, arylpalladium halides produced from aroyl halides undergo further reactions without forming aryl halides and are used for synthetic purpose. For example, insertion of alkenes occurs smoothly. Thus, the Heck reaction proceeds by the reaction of aroyl chlorides with alkenes in the presence of bases in boiling xylene. $Pd(OAc)_2$ is used as a catalyst without adding Ph_3P.[8] Methyl 4-bromocinnamate was obtained in 79% yield by the reaction of 4-bromobenzoyl chloride with methyl acrylate in the presence of *N*-benzyldimethylamine as the base at 130 °C. The reaction was chemoselective in the absence of Ph_3P, showing that aroyl chloride is more reactive than aryl bromide (**Scheme 6**).[9]

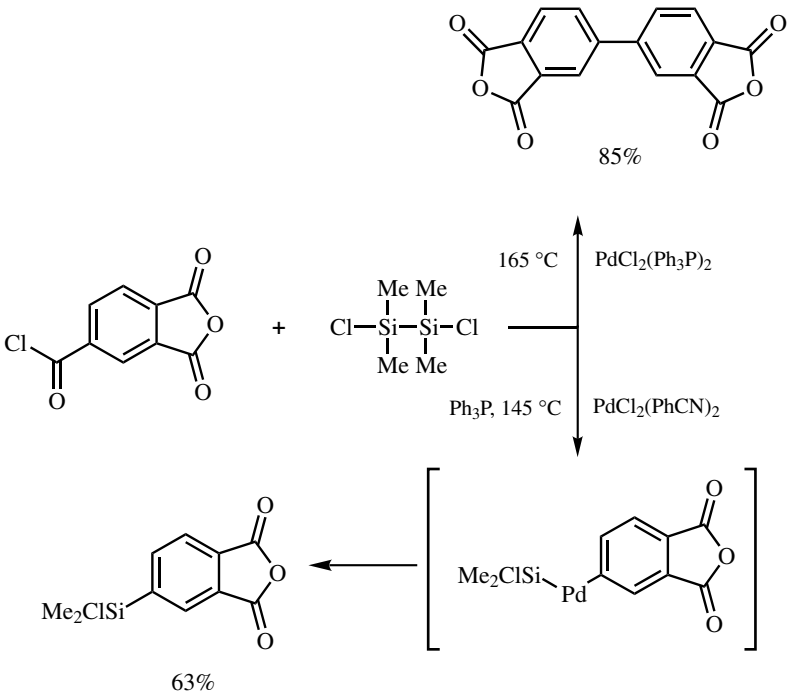


Scheme 6

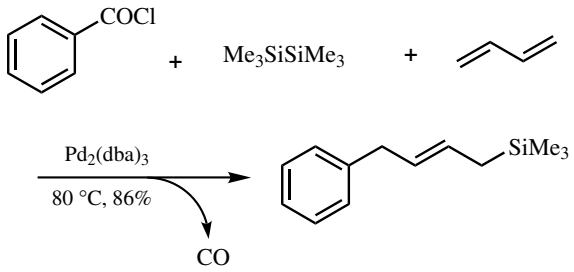
Aroyl chlorides undergo silylative decarbonylation to give arylsilanes by the reaction of disilanes. Oxidative addition of aroyl chlorides and decarbonylation are followed by transmetallation with disilane to generate (aryl)silylpalladium, and its reductive elimination gives arylsilanes. For example, neat trimellitic anhydride acid chloride reacted with dichlorotetramethyldisilane at 145 °C to afford 4-(chlorodimethylsilyl)phthalic anhydride by decarbonylation and reductive elimination.[10] Also, trimellitic anhydride acid chloride was converted to biphenyltetracarboxylic anhydride at 165 °C in refluxing mesitylene by reaction of the disilane. Thus, decarbonylation–coupling of aroyl chlorides offers a good synthetic method of biaryls (**Scheme 7**).[11]

In the presence of conjugated dienes, 1,4-arylsilylation of 1,3-dienes occurs by the reaction of aroyl chloride, 1,3-diene, and disilane in the presence of a Pd(0) catalyst. (4-Phenyl-2-butenyl)trimethylsilane was obtained by the reaction of benzoyl chloride, butadiene, and haxamethyldisilane at 80 °C (**Scheme 8**).[12]

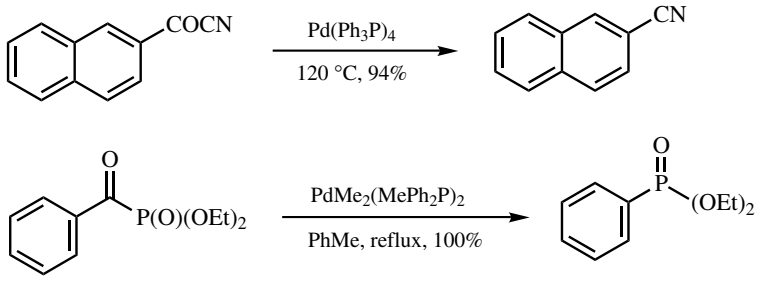
Some aroyl pseudohalides undergo decarbonylation. For example, cyanoketones are converted to nitriles by heating at 120 °C with $Pd(Ph_3P)_4$.[13]Also α-ketophosphonates are decarbonylated smoothly with a Pd–phosphine complex to give phosphonates (**Scheme 9**).[14]



Scheme 7



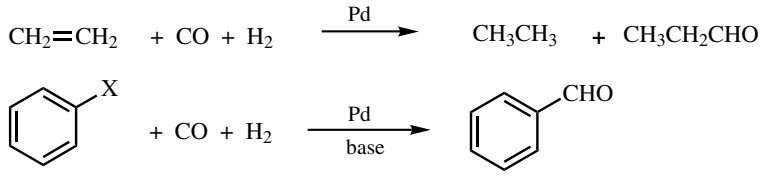
Scheme 8



Scheme 9

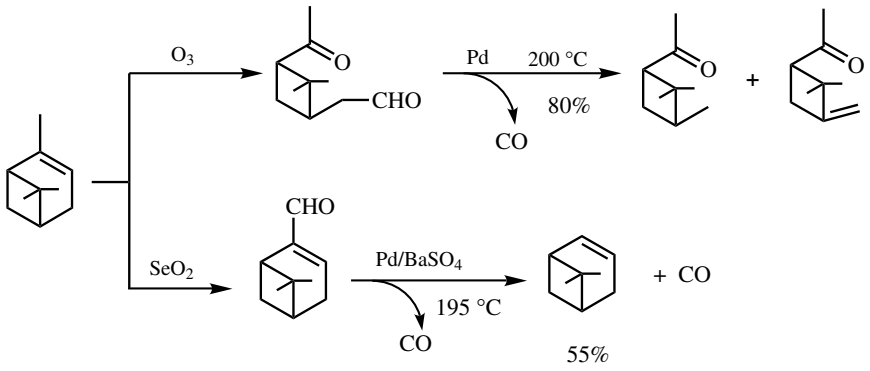
C. PALLADIUM-CATALYZED DECARBONYLATION OF ALDEHYDES

Pd-catalyzed decarbonylation of aldehydes has been well-known. Also, Pd-catalyzed hydroformylation of alkenes to form aldehydes was reported, although the major reaction was hydrogenation to give alkanes.[15] Aromatic aldehydes are prepared by the carbonylation of aryl halides in the presence of H_2 or other hydrides.[16] Thus, Pd catalyzes both formation and decarbonylation of aldehydes (**Scheme 10**).



Scheme 10

Both aliphatic and aromatic aldehydes can be decarbonylated catalytically when heated above 180 °C in the presence of metallic Pd and other hydrogenation catalysts. Considerable work has been carried out on the Pd-catalyzed decarbonylation of aldehydes from both mechanistic and synthetic viewpoints. Products of the decarbonylation are alkenes and the corresponding alkanes. Since the Pd-catalyzed decarbonylation of aldehydes proceeds smoothly in high yields, it has considerable synthetic use. For example, in the five-step irone synthesis from α-pinene, at first *cis*-pinonic aldehyde was prepared by ozonization. Then the Pd-catalyzed decarbonylation afforded pinonone and pinonenone in 80% yield.[17],[18]Another synthetic application is the two-step preparation of apopinene from the readily available α-pinene. The methyl group of α-pinene was oxidized to a formyl group with SeO_2 to form myrtenal, which was decarbonylated with Pd on $BaSO_4$ at 195 °C to give apopinene in an overall yield of 55% (**Scheme 11**).[18]

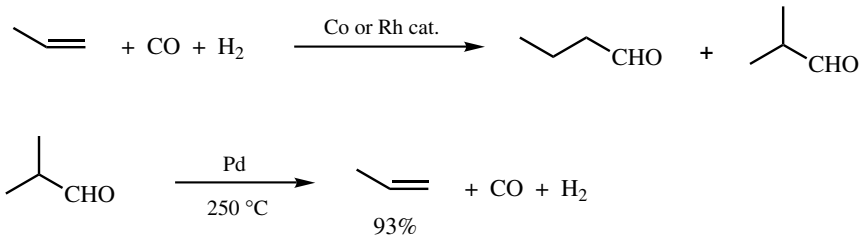


Scheme 11

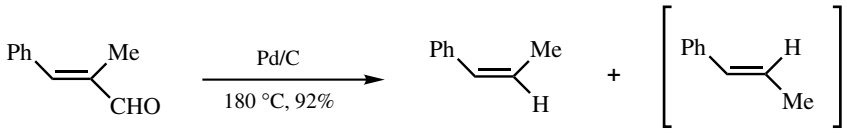
Lower boiling aldehydes can be decarbonylated in a gas phase. Kinetic studies were carried out on the decarbonylation of butyraldehyde over Pd film to give propene and propane.[19] Commercial hydroformylation of propene catalyzed by either Co or Rh

carbonyl complexes affords butyraldehyde and isobutyraldehyde. The less useful isobutyraldehyde is converted to propene, CO, and H_2 by Pd-catalyzed decarbonylation, and propene can be recycled (**Scheme 12**).[20]

[*Z*]-1-Propenylbenzene was obtained as the major product of the decarbonylation of [*E*]-α- methylcinnamaldehyde, when the product was distilled out as it was formed.[21],[22] From this result, it is clear that the initial product of the decarbonylation is largely, if not completely, the [*Z*]-form (**Scheme 13**).



Scheme 12



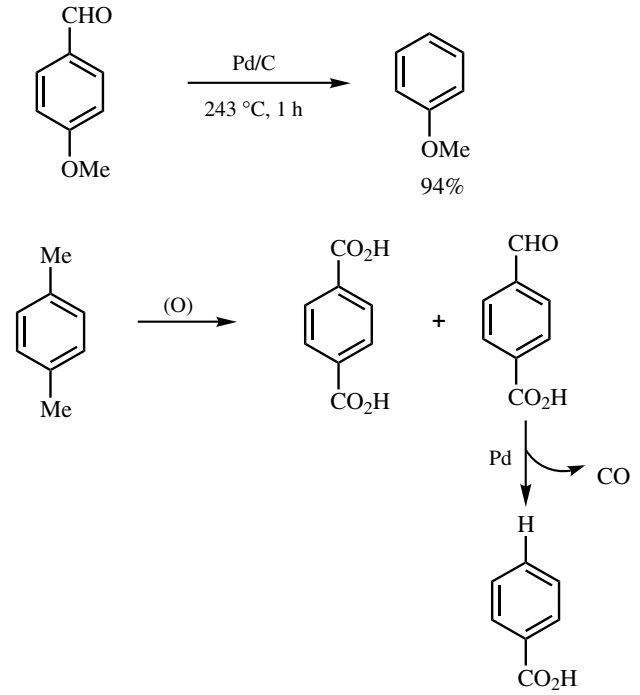
Scheme 13

The decarbonylation of aromatic aldehydes catalyzed by Pd on carbon seems to be fairly general. Anisole was obtained in 94% yield by the treatment of *p*-methoxybenzaldehyde at 243 °C for 1 h using 1% Pd on carbon.[23] In order to remove *p*-formylbenzoic acid formed in a small amount in the oxidation of *p*-xylene to terephthalic acid, the oxidation product containing the aldehyde is subjected to Pd-catalyzed decarbonylation and formylbenzoic acid is converted to benzoic acid, which can be separated from terephthalic acid easily (**Scheme 14**).

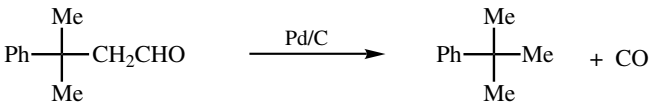
Several exceptions to the decarbonylation of aromatic aldehydes are known. 1-Naphthaldehyde readily lost CO at 210 °C, but 2-naphthaldehyde cannot be decarbonylated even at 250 °C.[23]

Extensive rearrangement of carbon skeletons is observed in the free-radical decarbonylation of some aldehydes such as tetralin-2-carboxaldehyde, β-phenylisovaleraldehyde, and 3,3-dimethyl-4-phenylbutyraldehyde. On the other hand, no rearrangement occurred in the Pd-catalyzed decarbonylation of these aldehydes.[24]–[27] *tert*-Butylbenzene was obtained cleanly in 84% yield by the decarbonylation of β-phenylisovaleraldehyde with Pd on carbon at 160 °C (**Scheme 15**).[26],[27]

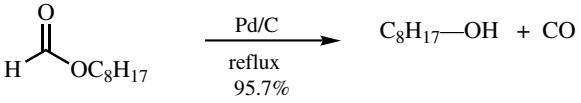
Formates can be regarded as having an aldehyde group, and its decarbonylation is expected. For example, octyl formate was converted to 1-octanol in 95.7% by heating with Pd on carbon at 200 °C.[28] The decarbonylation is dependent on the structure of the formates. Thus, benzyl formate was converted to toluene and CO_2, rather than CO (**Scheme 16**).



Scheme 14



Scheme 15

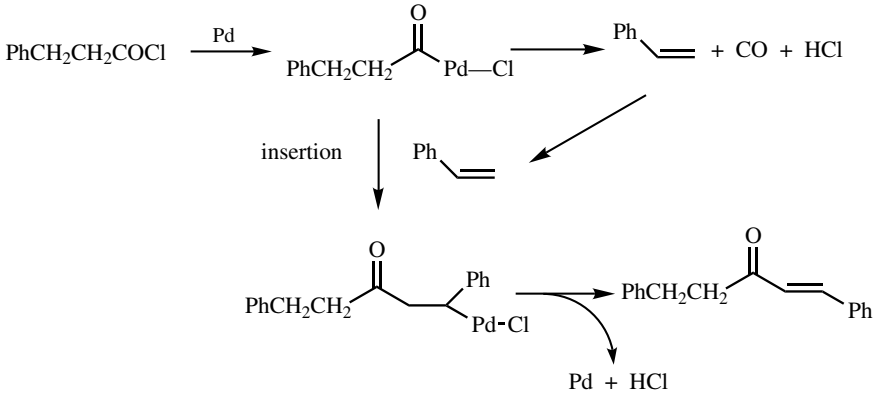


Scheme 16

D. MECHANISM OF PALLADIUM-CATALYZED DECARBONYLATION OF ALDEHYDES AND ACYL HALIDES, AND ITS RELATION WITH ROSENMUND REDUCTION

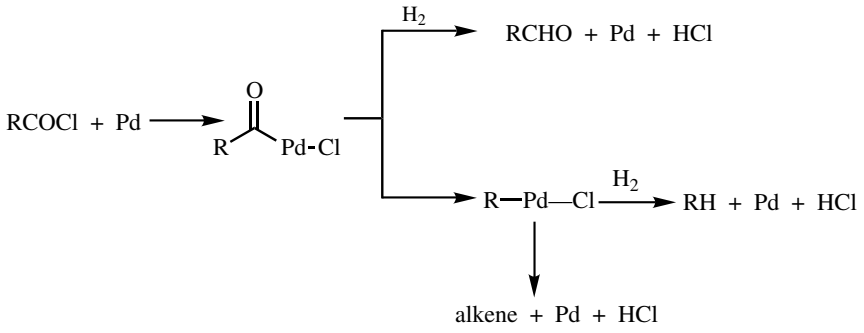
The first step of the decarbonylation of acyl halides is their oxidative addition to form acylpalladium halides, which undergo acyl–alkyl rearrangement to form aryl- or alkylpalladium halides. Finally, elimination of β-hydrogen affords alkenes and HCl. When β-phenylpropionyl chloride was heated at 200 °C with Pd catalyst, styrene was formed as the main product, accompanied by a small amount of 1,5-diphenyl-1-penten-3-one.[3] The

formation of the ketone can be rationalized by insertion of styrene formed by decarbonylation to the intermediary acylpalladium bond. The decarbonylation of aldehydes also seems to proceed by oxidative addition to form acylpalladium hydride. The acyl–alkyl rearrangement generates alkylpalladium hydride, which is converted to either alkene by elimination of β-hydrogen or alkane by reductive elimination (**Scheme 17**).



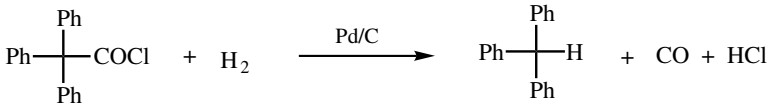
Scheme 17

In connection with the interaction of Pd with acyl halides, it is worthwhile to consider the mechanism of the well-known Rosenmund reduction, by which aldehydes are prepared by bubbling hydrogen gas through a refluxing solution of acyl chlorides in toluene in the presence of Pd catalyst.[29] The first step of the reduction seems to be the formation of acylpalladium chloride by oxidative addition. No decarbonylation of the acylpalladium chloride occurs at the refluxing temperature of toluene. The acylpalladium chloride is converted to aldehyde by the coordination of hydrogen, followed by reductive elimination. Thus, the following mechanism was proposed for the Rosenmund reduction.[30] In the main path of the reaction, hydrogenolysis of the acylpalladium chloride by hydrogen takes place to form aldehydes and HCl. At the same time, as a minor path, the acyl–alkyl rearrangement occurs to form alkylpalladium chloride. Hydrogenolysis of the alkylpalladium chloride gives either alkene or alkane (**Scheme 18**).



Scheme 18

The acyl–alkyl rearrangement becomes a main path with some acyl halides. Actually, formation of the decarbonylation product has been reported in several cases as an abnormal reaction of the Rosenmund reduction. Sterically hindered acyl halides such as diphenylacetyl and triphenylacetyl chlorides and naphthoyl chloride undergo decarbonylation in attempted Rosenmund reduction (**Scheme 19**).[31],[32]



Scheme 19

E. SUMMARY

Pd-catalyzed decarbonylation of acyl halides and aldehydes is summarized. The decarbonylation proceeds mainly using Pd on carbon as a catalyst at high temperature.

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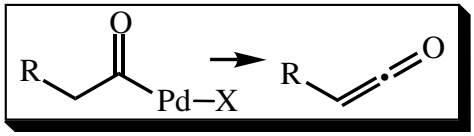

VI.5.2 Formation and Reactions of Ketenes Generated via Acylpalladium Derivatives

HIROSHI OKUMOTO

A. INTRODUCTION

A common reaction path of acylpalladium is to undergo attack of the nucleophile. In spite of the reverse polarity between C—Pd and C—Cl based on simple comparison of the electronegativity of carbon, palladium, and chlorine atoms, the palladium atom of acylpalladium behaves as a leaving group, being very similar to chlorine of acyl chloride. The analogy suggests the possibility of other reaction paths for acylpalladium. One is ketene formation and the other is electrophilic substitution such as Friedel–Crafts reaction. Since the Friedel–Crafts-type reaction is discussed in the other section regarding acylpalladation, it is not mentioned in this section although the possibility to assume ketene as an intermediate cannot be excluded.

If the α-proton of acylpalladium is acidic enough to be deprotonated, ketene or its equivalent could be formed. Otherwise, displacement of the Pd atom of acylpalladium with an appropriate nucleophile, being capable of turning into a good leaving group, could lead to an activated carboxylic acid derivative, giving rise to ketene (**Scheme 1**).

This section deals with a juvenile but interesting field of acylpalladium, generation of ketene, to which little attention has been paid.

B. β-LACTAM SYNTHESIS BY CARBONYLATION OF ALLYL PHOSPHATES

The most prominent use of ketenes is for [2 + 2] cycloaddition with imine for the construction of β-lactam skeleton.[1],[2] When the Y group in **Scheme 1** is vinyl or aryl group, the deprotonation of the activated α-proton is highly facilitated. In this context, the carbonylation of some allylic derivatives, for example, allyl bromide, allyl acetate, allyl phenyl ether, allyl methyl carbonate, allyl phenyl sulfone, and allyl phosphate, documented to form π-allylpalladium intermediates is examined. It is interesting to note that only phosphate undergoes the cycloaddition to produce β-lactam. The characteristic dependency of the stereochemistry on the reaction conditions, being contrary to the results in the usual base-induced cycloaddition is also intriguing. **Scheme 2** presents the

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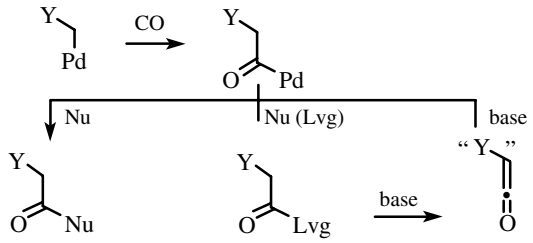
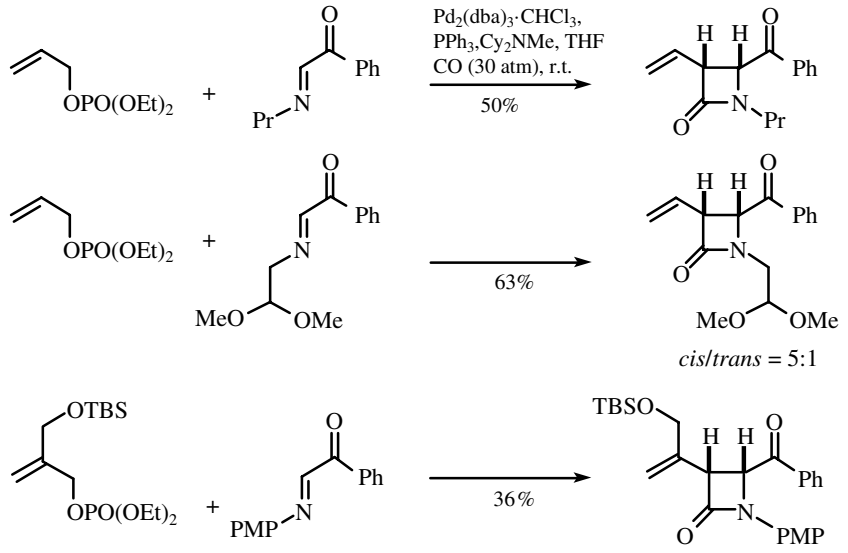


Scheme 1



Scheme 2

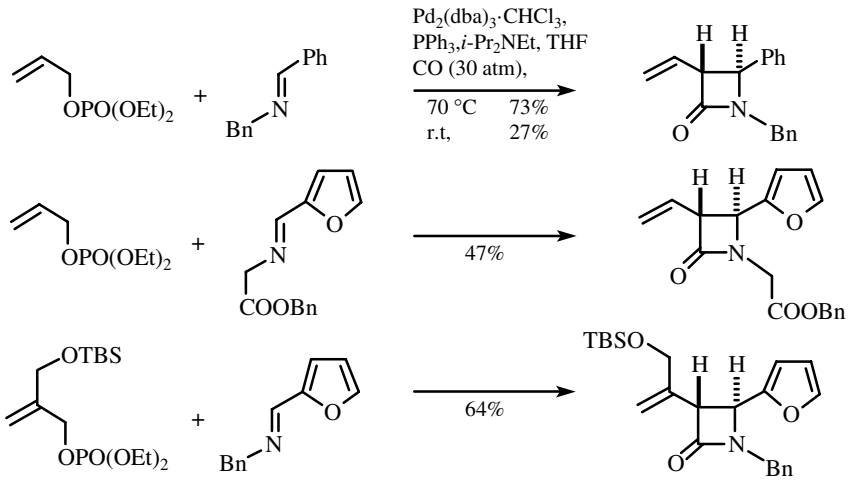
results of the reaction with imines conjugated with a carbonyl. Lactams are prepared from ketoimines at room temperature (r.t.) in good yields.

Presence of an electron-rich substituent, PMP, on the nitrogen atom retards the reaction to some extent. The carbonylative cycloaddition of imines derived from both aliphatic and aromatic amines affords *cis*-β-lactams with high stereoselectivity in spite of their susceptibility to epimerization.

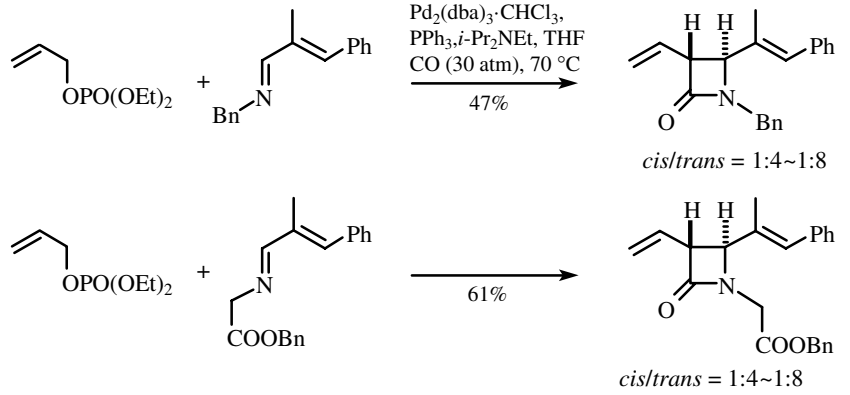
In sharp contrast to the above results, the cycloaddition employing imines, which are not conjugated with a carbonyl, results in the predominant formation of *trans*-β-lactams (**Scheme 3**). The corresponding *cis*-isomers are not detected, even though the reaction is carried out at room temperature.

Some contamination by the *cis*-isomer is observed in the reactions of imines homologated with olefin (**Scheme 4**).

The imines derived from vicinal dicarbonyl substances afford *cis*-lactams (**Scheme 2**), whereas the imines prepared from aryl and alkenyl aldehydes yield *trans*-lactams (**Schemes 3** and **4**). The different basis for the stereoselection in the carbonylative cycloaddition from that of the usual base-induced process is worthy of emphasis. The mechanism of this carbonylative formal [2 + 2] cycloaddition is discussed in comparison with the results of the base-induced ketene–imine cycloaddition.[2]



Scheme 3



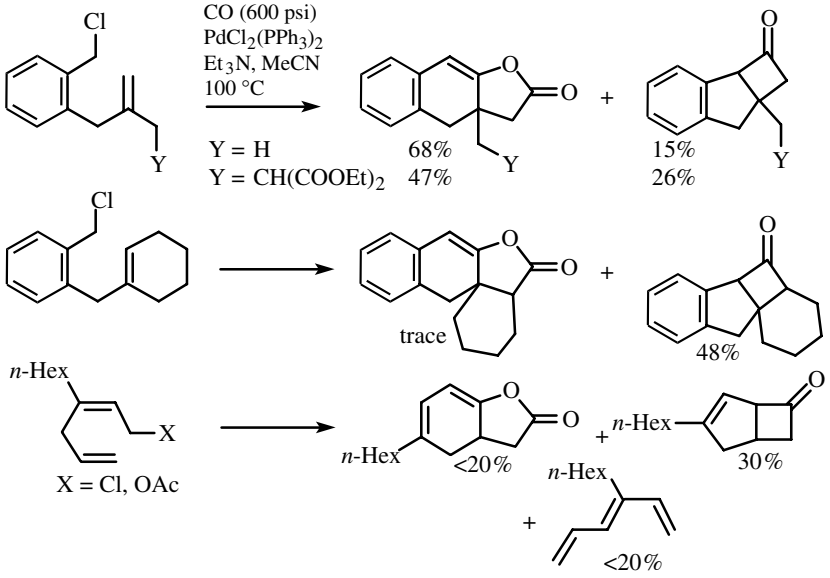
Scheme 4

The catalytic carbonylation of allyl phosphate, a new ketene equivalent, provides a convenient route to a series of β-lactams bearing useful substituents at the positions relevant for further structural modifications with unique stereocontrol.

C. FORMATION OF CYCLOBUTANONE

Another synthetic utility of ketene is for the preparation of cyclobutanone. In the course of the study concerning the acylpalladation onto olefin, carbonylation of benzylic chloride involving an olefin at a proper position is found to accompany cyclobutanone (**Scheme 5**).[3]

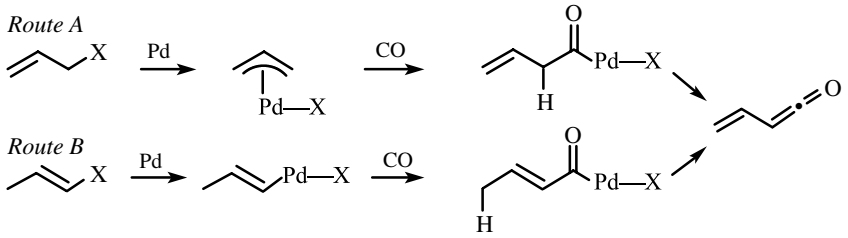
The removal of the α-proton of acylpalladium must be facilitated by the use of aryl substituent (**Scheme 1**, Y = aryl) instead of allylacylpalladium (**Scheme 1**, Y = vinyl). However, insertion of olefin is faster than the ketene formation. Employment of trisubstituted olefin retards the insertion reaction to provide the cyclobutanone as a main product.



Scheme 5

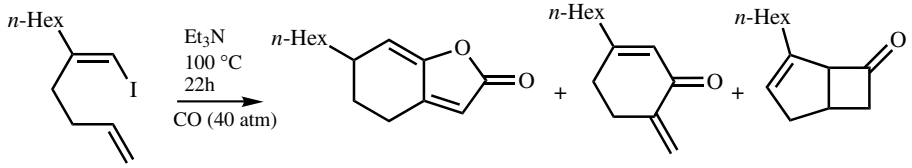
As described in the preceding subsection, the carbonylation of allyl phosphate forms vinyl ketene or its equivalent by the removal of α-proton of allylacylpalladium (**Scheme 6**, **Route A**). The same reactive species should be released by the deprotonation of γ-proton of vinylacylpalladium intermediate (**Route B**).

The carbonylation of vinyl iodide leading to cyclobutanone according to such a route is achieved in a restricted structure under specific conditions (**Table 1**).[4],[5] Use of



Scheme 6

Table 1. Carbonylation of Vinyl Iodides



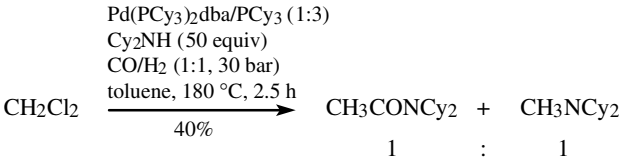
Catalyst	Solvent	Yield (%)		
$Pd(OAc)_2$	MeCN	<2	<2	36
$PdCl_2(PPh_3)_2$	Benzene	<5	<2	<2

$Pd(OAc)_2$ as a catalyst is indispensable to suppress the acylpalladation. Since the intramolecular acylpalladation usually predominates over ketene generation, formation of some side products is inevitable and the yield of the cyclobutanone is unsatisfactory.

D. FORMATION OF KETENE BY CARBONYLATION OF *gem*-DIHALIDE

Transition metal ketene complexes have been derived from various metals through the study of CO reduction relating to the Fischer–Tropsch synthesis. The old preparative method for the ketene–metal complex is carbonylation of carbene complex, in which *gem*-dibromide is used as a common source of carbene. The reaction is carried out in the presence of Zn powder as a reducing agent. Among the examined metals such as Pd, Ni, Pt, and Co, Pd catalyst is shown to be inferior to the other metals, especially Co complex. Some typical examples using Pd catalyst are summarized in **Table 2**.[6]

Relatively inactive methylene chloride is also submitted to carbonylation (**Scheme 7**).[7] Use of PCy_3 is essential for the activation of chloride. In order to recycle the generated Pd(II) species to Pd(0), H_2 gas is employed in place of Zn.

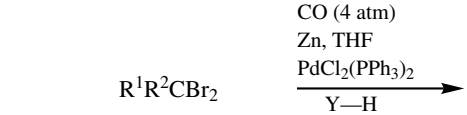


Scheme 7

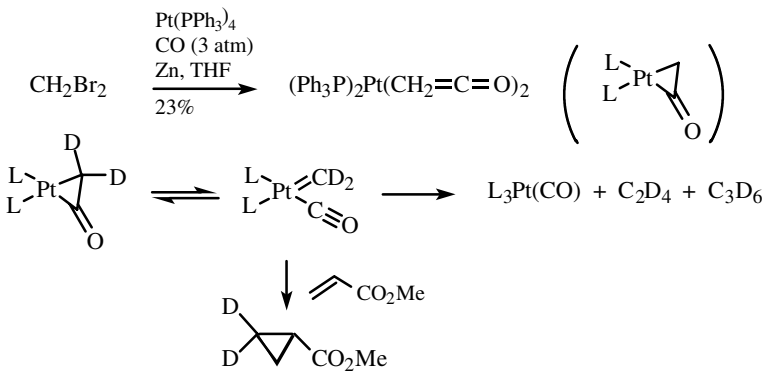
Recently, the activation of chloride (e.g., aryl chloride and vinyl chloride) has become a hot topic in Pd-catalyzed reactions. Some characteristic phosphine ligands and specific conditions have been explored and exploited. Such newly developed reaction media might improve this carbonylation.

Isolation and characterization of the intermediary ketene complexes via carbene are executed by use of Pt and Ni compounds and their fundamental reactions are investigated. For instance, $(PPh_3)_2Pt(ketene)_2$ is isolated and fully characterized (**Scheme 8**).[8] The ketene complex proved to be η^2-C,C and to decompose into original carbene complex, which was corroborated by the isolation of hydrocarbons upon heating and formation of cyclopropane carboxylate in the presence of methyl acrylate.

Table 2. Carbonylation of *gem*-Dibromides



Y—H = MeOH			Y—H = Et_2NH
R^1, R^2 H , H	R^1, R^2 H , CH_3	R^1, R^2 CH_3, CH_3	R^1, R^2 H , H
26%	2%	26%	4%

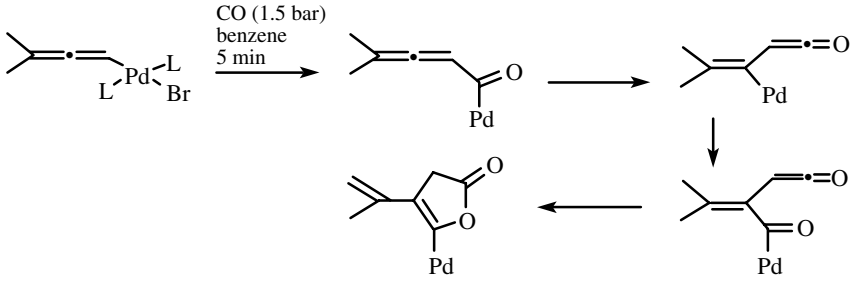


Scheme 8

Ni–ketene complexes are also studied on the carbonylation of nickelacyclobutane[9] and diazo compound.[10]

E. OTHER APPROACHES TO KETENE

A completely different but interesting reaction via ketene is known (**Scheme 9**).[11] Allenylpalladium complex undergoes CO insertion in the usual manner. The Pd atom of the resulting allenylacylpalladium species migrates into sp carbon, the center of the cumulenic bond, giving rise to ketene together with vinylpalladium. The intermediate again catches CO to provide a final lactone–palladium complex. The occurrence of the ketene is detected by IR spectrum.

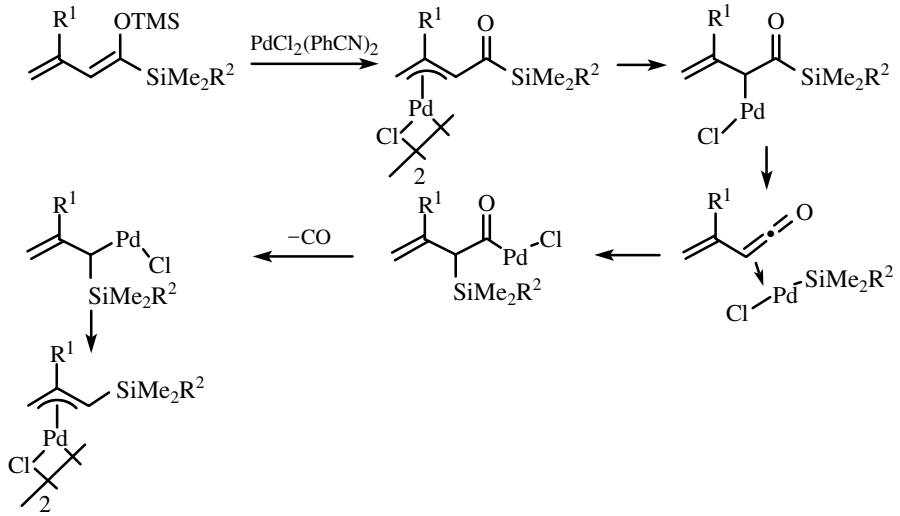


Scheme 9

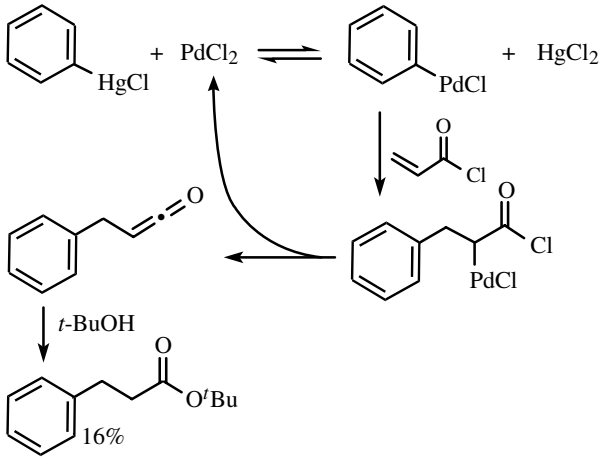
β-Elimination of Pd(II) species containing the substituent on acyl carbon is demonstrated to proceed through ketene as an intermediate. Treatment of 1-silyl-1-siloxybutadiene with $PdCl_2(PhCN)_2$ gives π-allylpalladium complex, from which Si—Pd—Cl is eliminated through σ-Pd form by picking up the silyl group on the acyl carbon (**Scheme 10**).[12],[13] The Si—Pd—Cl complex again adds to the generated ketene in the reverse direction leading to π-allylpalladium complex with loss of CO.

The other example of ketene formation by β-elimination is shown in **Scheme 11**.[14] Phenylpalladium chloride, prepared *in situ* by the transmetallation of phenylmercuric chloride with $PdCl_2$, reacts with acryloyl chloride to provide an insertion product.

β-Elimination of $PdCl_2$ produces ketene; otherwise a usual Heck-type reaction yields cinnamoyl chloride. Upon treatment of the reaction mixture with alcohol, saturated ester is obtained. The reaction sequence does not involve an acylpalladium intermediate; however, the reaction course is very interesting, because these examples show that the candidate of the β-elimination partner of Pd species can be extended from H to other elements.



Scheme 10



Scheme 11

F. SUMMARY

1. Only limited examples for ketene generation have been reported.

2. Eligible partners of the palladium for the β-elimination generating ketene are H, Si, and Cl.

3. The [2 + 2] process for cyclobutanone synthesis is a companion path in the insertion (acylpalladation) process. The utility has been demonstrated in β-lactam synthesis.

4. This field has not been thoroughly investigated; however, the carbonylative approach is a promising possibility as a new use of the Pd-catalyzed reaction.

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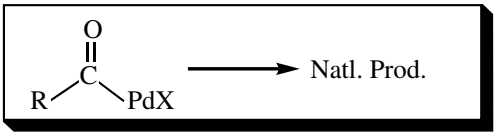

VI.6 Synthesis of Natural Products via Palladium-Catalyzed Carbonylation

MIWAKO MORI

A. INTRODUCTION

Recent advances in organometallic chemistry have led to development of various novel methods in synthetic organic chemistry. A Pd-catalyzed reaction has been a particularly useful method. In these reactions, Pd-catalyzed carbonylation is a very attractive method because one carbon is elongated from various functional groups, such as aryl halide, alkyl halide, allyl acetates, allyl carbonates, and even the keto-carbonyl groups, to form esters, amides, and unsaturated ketones (**Scheme 1**).

Since the reaction proceeds under an atmosphere of carbon monoxide in the usual cases, we can use a balloon that is filled with carbon monoxide and is connected to the top of the reaction vessel. If compounds have these functional groups and the hydroxyl and amino groups or organometallic complexes in a tether, lactams, lactones, and cyclized ketones are produced. Pd-catalyzed reactions can be classified into two types: Pd(0)-catalyzed reactions and Pd(II)-mediated or -catalyzed reactions. In each case, we can obtain the desired esters and amides. In the former reaction, a catalytic amount of palladium catalyst is required. In the latter reactions, a stoichiometric amount of palladium complex is required, but the reaction proceeds by a catalytic amount of Pd(II) complex in the presence of oxidizing agents such as $CuCl_2$ or benzoquinone.

In recent natural product syntheses, a Pd-catalyzed reaction has been used in almost all cases. In this section, total syntheses of natural products using Pd-catalyzed carbonylation are described according to **Scheme 1**.

B. SYNTHESIS OF NATURAL PRODUCTS USING Pd(0)-CATALYZED CARBONYLATION

B.i. Palladium-Catalyzed Carbonylation of Aryl or Vinyl Halide

It is known that the oxidative addition of aryl or vinyl halides to a low-valent palladium complex produces an aryl- or vinylpalladium complex, which reacts with carbon monoxide to afford an acylpalladium complex. If alcohol and amine are added to this reaction system, we can obtain ester or amide.[1]–[4] Intramolecular reactions of aryl or

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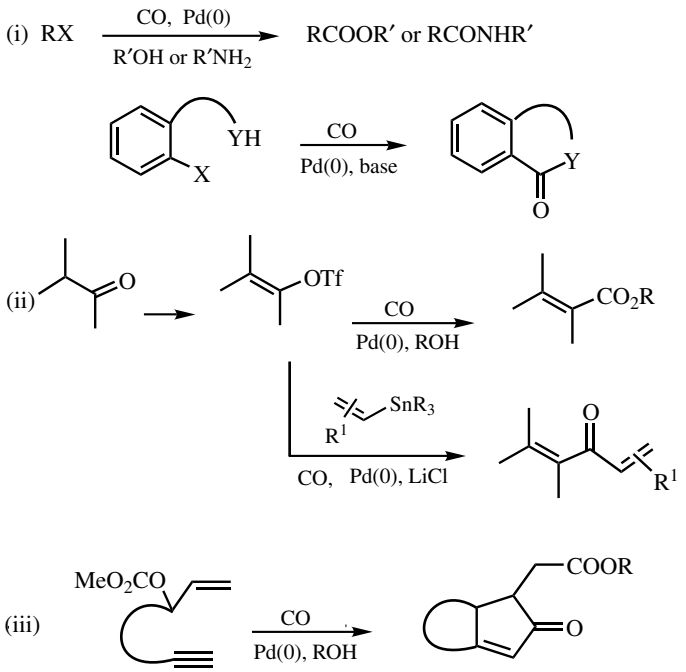
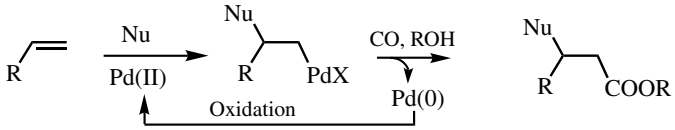
A. Pd(0)-catalyzed carbonylation

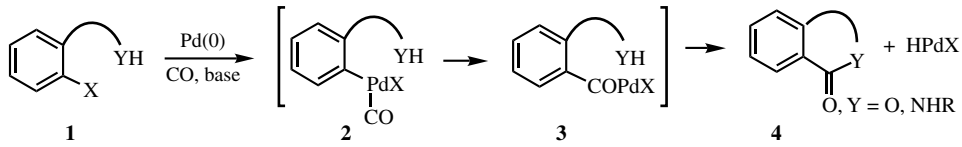


B. Pd(II)-catalyzed or -promoted carbonylation



Scheme 1

vinyl halide having the hydroxyl or amino group in a tether are very attractive methods because these reactions afford lactams[5],[6] and lactones.[5]–[9] Such a reaction would proceed via arylpalladium complex **2**, which is produced from aryl halide having the hydroxyl or amino group in a tether. Migration of the aryl group on palladium into carbon monoxide gives acylpalladium complex **3**, which reacts with the amino group or the hydroxyl group intramolecularly to give lactams and lactones, as shown in **Scheme 2**.



Scheme 2. Synthesis of lactams and lactones.

Mori and Ban reported the novel syntheses of benzolactams[5],[6] and lactones[7] from *o*-haloarylalkylamines and -alcohols using $Pd(OAc)_2$ and PPh_3 in the presence of Bu_3N under carbon monoxide. As an application of this methodology, they succeeded in the total synthesis of sendaverine (**7**, **Scheme 3**) by very short steps.[10] The key step is the formation of isoquinolone **6a** by Pd-catalyzed carbonylation of aryl bromide **5a**. Pandey later reported the synthesis of benzyl-tetrahydroisoquinolines using a similar procedure.[11] This procedure was also used for the total synthesis of protoberberine alkaloids.[12]

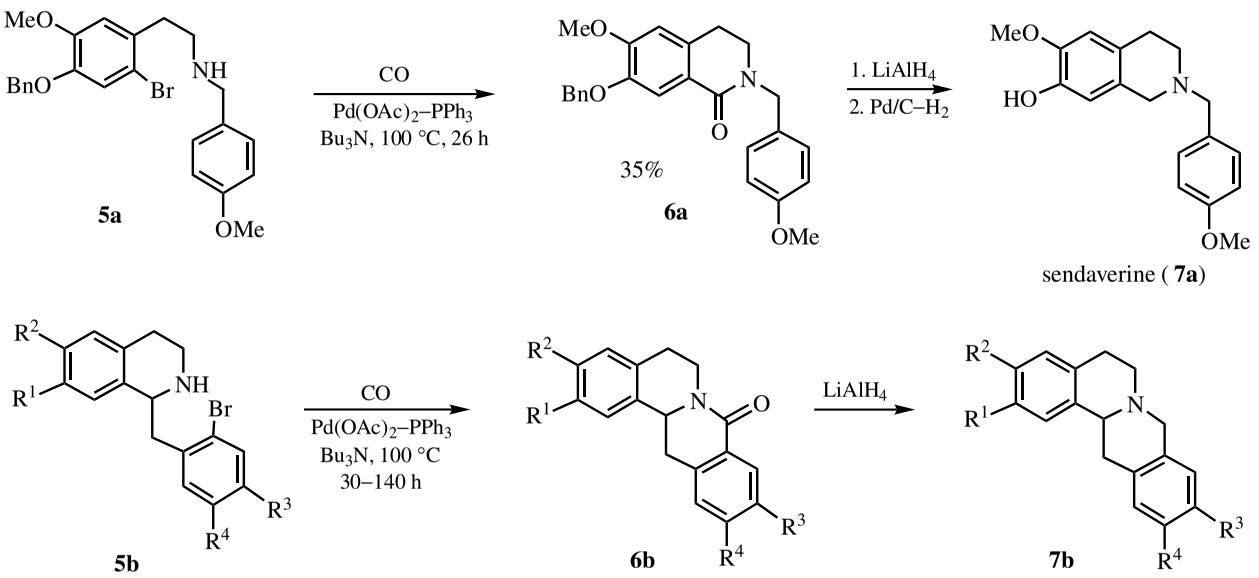
Mori and Ban then reported a novel synthesis of benzodiazepine derivatives by Pd-catalyzed carbonylation of *o*-haloaniline derivatives **10**, which was prepared from *o*-haloanilines **8** (**Scheme 4**) and amino acid derivatives **9**.[13] They succeeded in the total synthesis of many benzodiazepine antitumor antibiotics. A toluene solution of *o*-bromoaniline derivative **10a**, which was prepared from 2-bromo-4-methoxy-5-tosyloxyaniline and 4-hydroxy-*l*-proline, $Pd(OAc)_2$, PPh_3, and Bu_3N, was heated at 110 °C for 48 h under carbon monoxide (5 atm) to produce benzodiazepine derivative **11a**. Compound **11a** was converted into **12**, which was a key intermediate for the synthesis of anthramycin (**13a**).[14] Using a similar procedure, they succeeded in the total synthesis of tomaymycin (**13b**),[15] prothracarcin (**13c**),[15] pretomaymycin (**13d**),[15] neothramycin (**13e**)[16] and SEN 215 (**13f**).[15]

Carbonylation of aryl halide having the amide group in a tether gave imide in good yield.[18] This procedure was further extended to the synthesis of vasicinone (**16**, **Scheme 5**) and rutecarpine (**19**).[19] The carbonylation reaction of *o*-iodoaniline **8a** with amide nitrogen of **14** gave imide, whose carbonyl group reacted with the amino group of **8a** intramolecularly to give **15**. From this compound **15**, vasicinone **16** was obtained in very short step sequences. In a similar manner, ruthecarpine (**19**) was synthesized by two steps from *o*-iodoaniline derivative **8b** by Pd-catalyzed carbonylation as a key step. The reaction of **8b** with tryptamine **17** under carbon monoxide in the presence of $Pd(OAc)_2$ and PPh_3 gave amide, which reacted with the amide carbonyl group intramolecularly to give **18** in high yield. Treatment of **18** with $POCl_3$ gave ruthecarpine (**19**).

When vinyl halide having the amino or the hydroxyl group in a tether was treated in a similar manner, mono- or bicyclic lactams and lactones could be synthesized.[6] This method was further extended to the synthesis of β-lactams **21** from 2-bromoallylamine derivatives **20** (**Scheme 6**).[20] Using this novel β-lactam synthesis, 3-aminonocardicinic acid (3-ANA, **23**), which is a core part of a monocyclic β-lactam antibiotic, nocardicin A (**22**), could be synthesized from **24**.[21],[22]

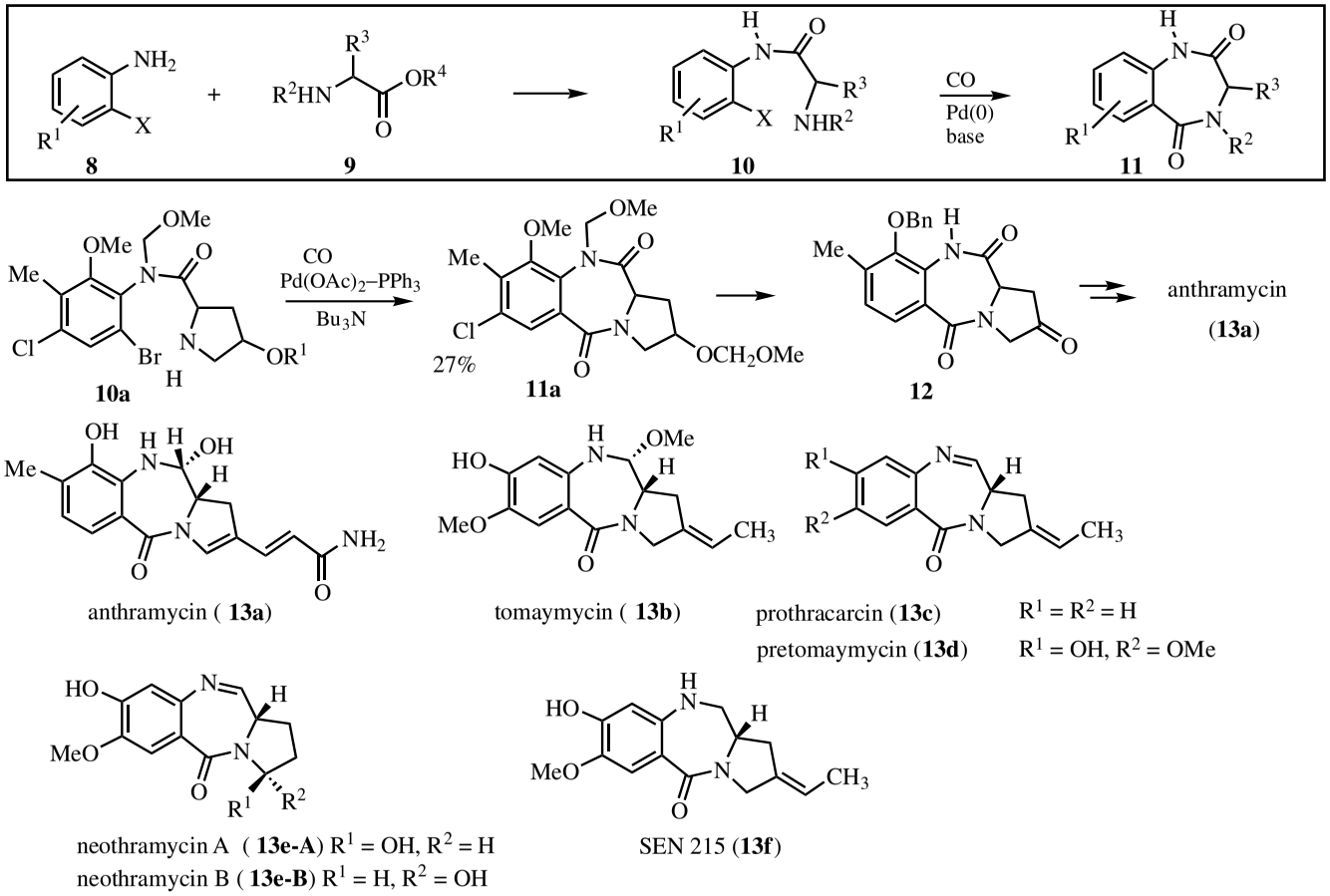
On the other hand, Tsuji reported a total synthesis of zearalenone (**30**, **Scheme 7**) using Pd-catalyzed carbonylation.[23] The reaction of 1-iodo-2-phenylthiomethyl-4,6-dimethoxybenzene (**27a**) with 10-iodo-6,2′-[1,3]dioxolane-2-decanol (**28a**) was carried out under carbon monoxide (12 atm) to afford the corresponding ω-iodoalkyl ester of 2-phenylthiomethyl-4,6-dimethoxybenzoate (**29a**) in 70% yield, which was converted into zearalenone (**30a**) prepared already by the same group.[24],[25] In a similar manner, curvularin (**30b**) was also synthesized.[26]

Recently, Kibayashi reported the total synthesis of (+)-homopumiliotoxin 223G (**31a**, **Scheme 8**).[27] *N*-CbZ-L-Pipecolinic acid was converted into compound **32**, which was treated with Ph_3SiH in the presence of Et_3B to afford vinylstannanes **33a** and **33b** in a ratio of 3.6:1. Treatment of vinylstannane **33a** with NIS gave vinyl iodide **34**, which was subjected to Pd-catalyzed lactonization to give lactone **35** in quantitative yield. From this compound, they succeeded in the total synthesis of homopumiliotoxine 223G (**31a**).

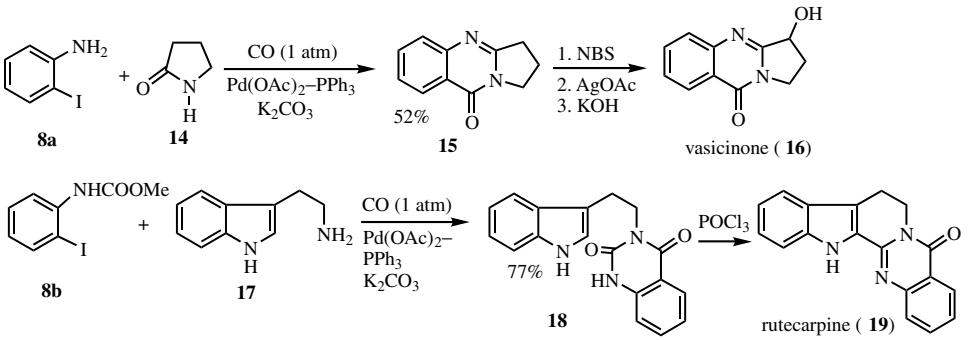


		$LiAlH_4$	
$R^1 = R^2 = R^3 = R^4 = H$	43%	51%	
$R^1 = R^2 = R^3 = R^4 = OMe$	50%	49%	(±)-xylopinine
$R^1 = R^2 = OMe$, $R^3 + R^4 = OCH_2O$	71%	71%	(±)-pseudoepitetrahydroberberine

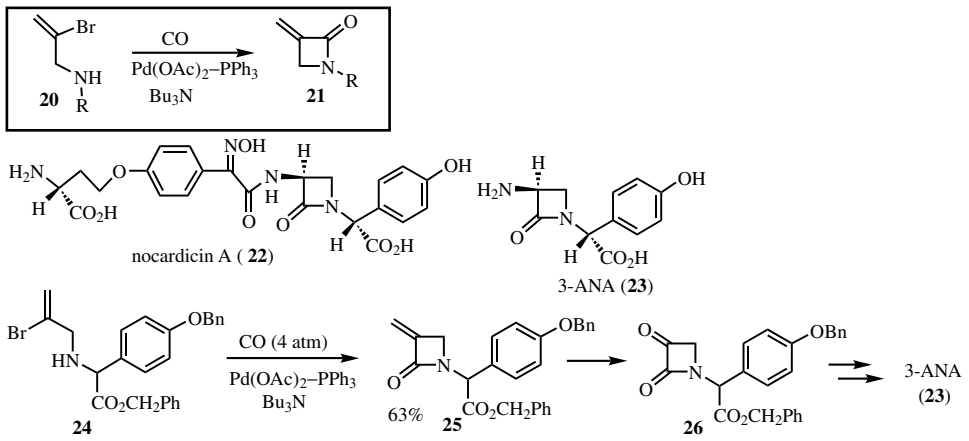
Scheme 3. Synthesis of sendaverine and berberine analogue.



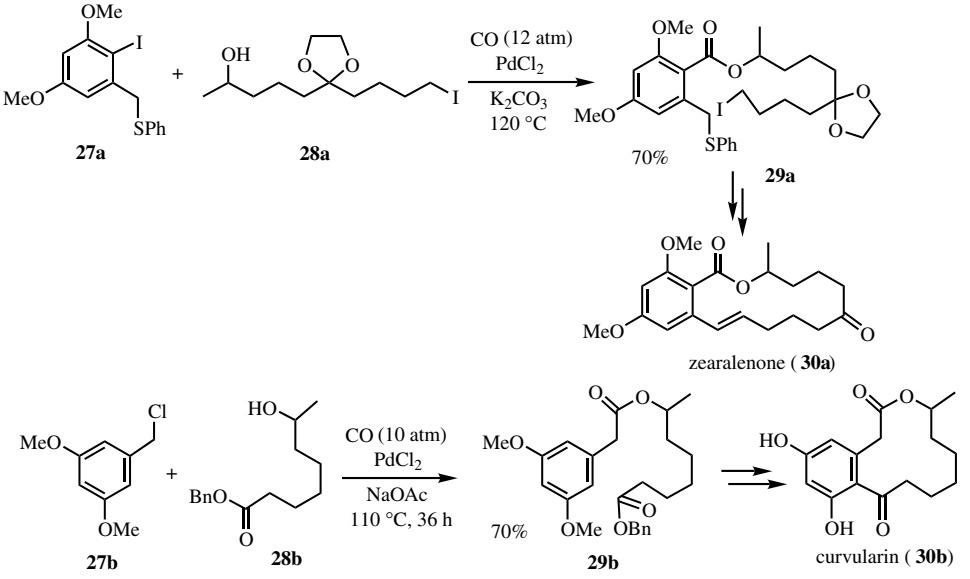
Scheme 4. Synthesis of benzodiazepine derivatives.



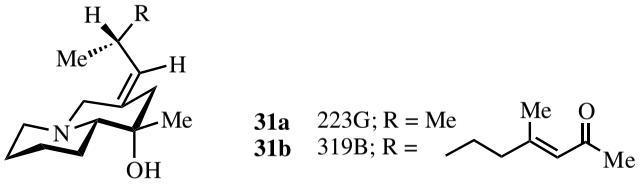
Scheme 5. Synthesis of vasicinone and rutecarpines.



Scheme 6. Synthesis of β-lactams.

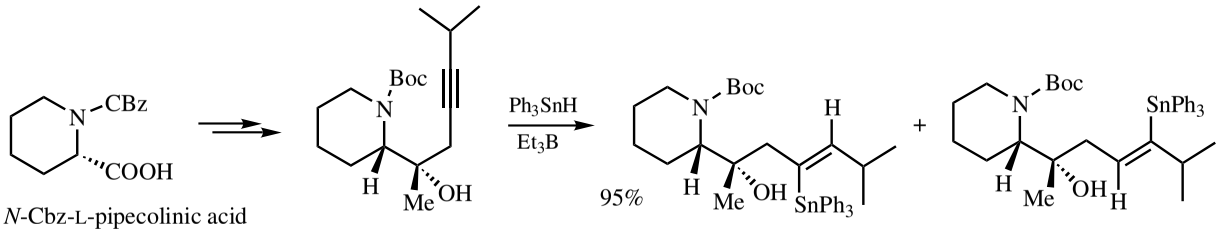


Scheme 7. Synthesis of cuvularin and zearalenone.



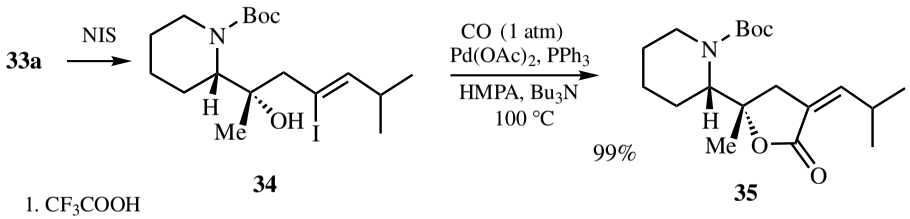
31a 223G; R = Me
31b 319B; R =

homopumiliotoxins (**31**)



N-Cbz-L-pipecolinic acid

32 **33a** **33b**



34 **35**

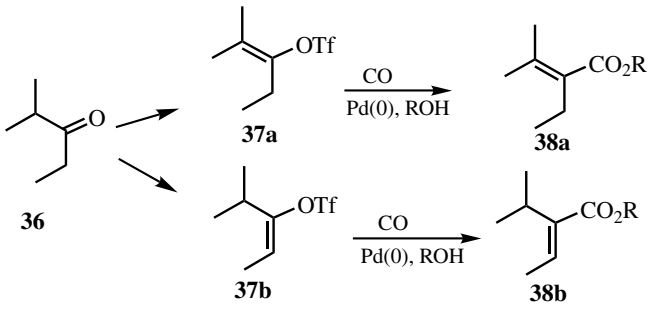
(+)-homopumiliotoxin 223G (**31a**)

Scheme 8. Synthesis of (+)-homopumiliotoxin 223G.

B.ii. Palladium-Catalyzed Carbonylation of Enol Triflate

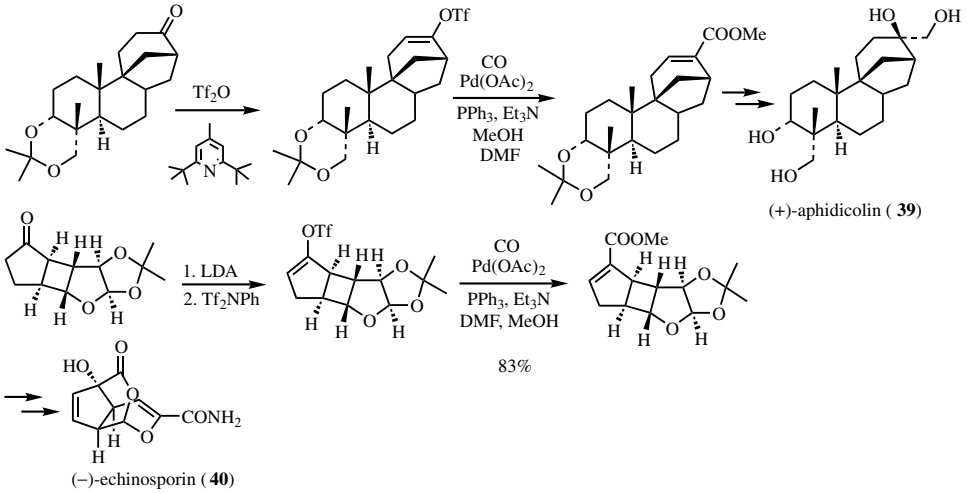
Stille[28] and Ortar[30] independently reported that enol triflate could be oxidatively added to a low-valent palladium complex to give vinylpalladium complex. Since enol triflate is easily prepared from a keto-carbonyl group by treatment with Tf_2O or $PhNTf_2$ in the presence of a base, this means that a new carbon–carbon bond formation can be achieved on the carbonyl carbon using a palladium catalyst.

From the keto-carbonyl group, the desired enol triflates **37a** or **37b** (**Scheme 9**) can be synthesized regioselectively under various conditions. If the carbonylation reaction of enol triflate is carried out using low-valent palladium catalyst in the presence of alcohol, we can prepare α,β-unsaturated ester.[28]–[30]

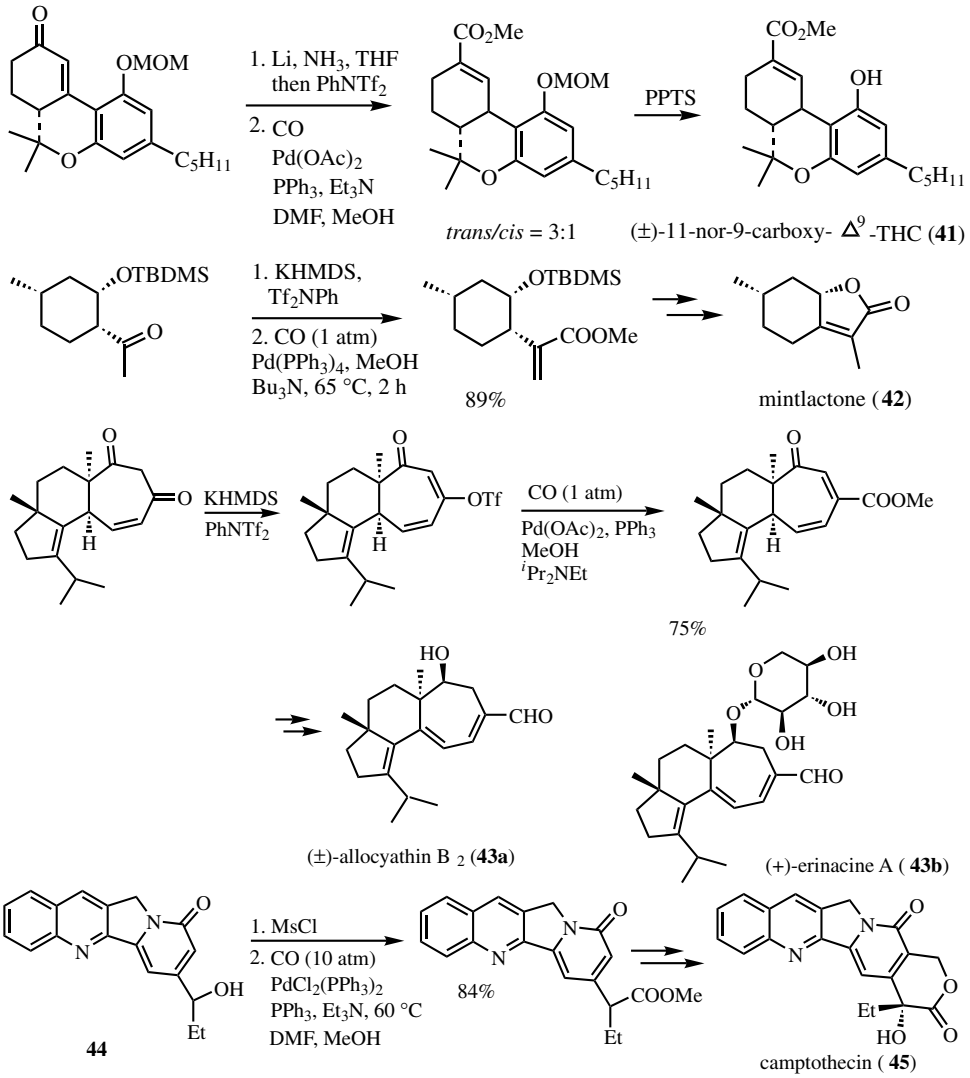


Scheme 9. Construction of ester on the carbonyl carbon.

In the total syntheses of various natural products, Pd-catalyzed carbonylation of enol triflate has been used for one carbon elongation on the keto-carbonyl carbon. There are various examples of ester formation on carbonyl carbon by conversion of the carbonyl group to enol triflate on the total syntheses of natural products. For example, in the total syntheses of (+)-aphidicolin (**39**, Scheme 10),[31] (−)-echinosporin (**40**),[32] (±)-11-nor-9-carboxy-$\triangle^9$-THC (**41**),[33] mintlactone (**42**),[34] (±)-allocyathin B_2 (**43a**),[35] and



Scheme 10. Synthesis of natural product from enol triflate. (*Continued*)

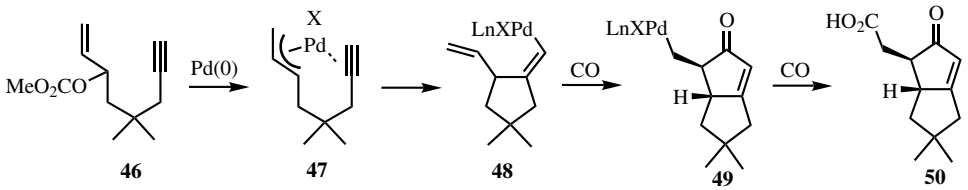


Scheme 10. Synthesis of natural product from enol triflate.

(+)-erinacine A (**43b**),[35] we can see the formation of α,β-unsaturated ester from enol triflates. Furthermore, using Pd-catalyzed carbonylation of mesylate of **44**, formal total synthesis of camptothecin (**45**) could be achieved.[36]

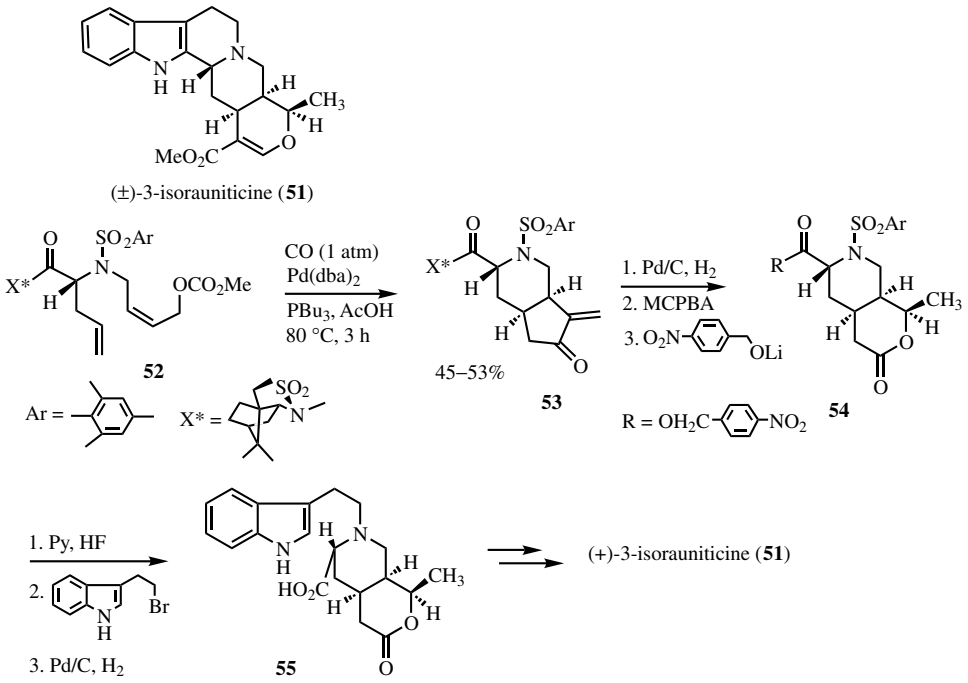
B.iii. Palladium-Catalyzed Carbonylation of Allyl Acetate

A combination of palladium-ene cyclization with carbonylation reactions is particularly attractive since it permits the stereoselective formation of four carbon–carbon bonds in a single process. In this reaction, π-allylpalladium complex **47** (**Scheme 11**) is formed from allyl carbonate **46** and Pd(0), and it is then converted into vinylpalladium complex **48** via palladium-ene cyclization. Carbonylation of **48** gives bicyclic compound **49**, which is further reacted with carbon monoxide to give carboxylic acid **50**.



Scheme 11. Carbonylation via *p*-allylpalladium complex.

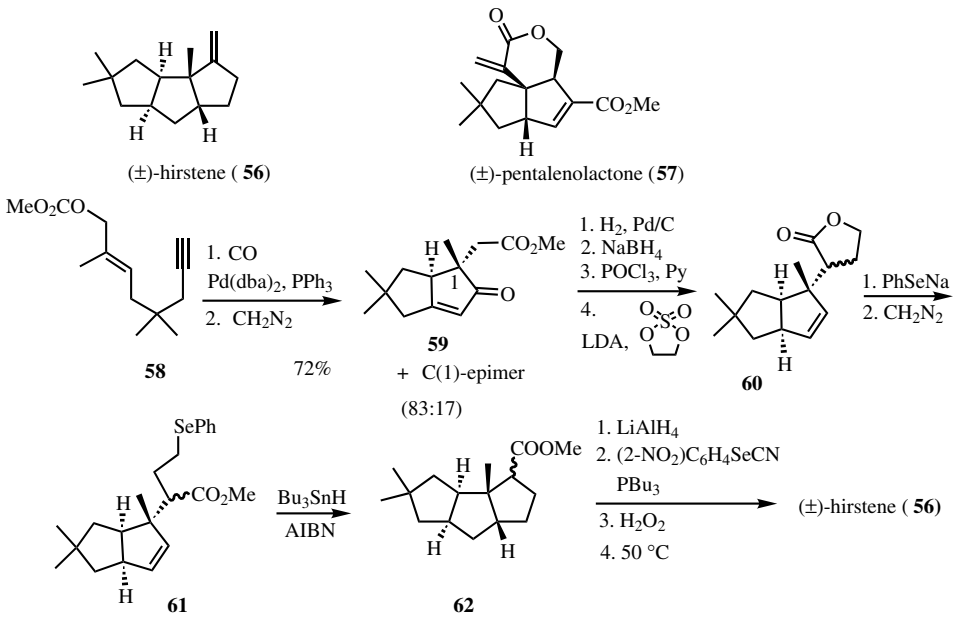
This reaction was developed by Oppolzer and he succeeded in the total synthesis of (±)-pentalenolactone E (**57**).[37] He also succeeded in the first total synthesis (+)-3-isorauniticine (**51**) using sultam-directed asymmetric alkylation and a transition-metal-catalyzed carbometalation/carbonylation reaction.[38] An AcOH solution of carbonate **52**, $Pd(dba)_2$, and Bu_3P was stirred at 80 °C for 3 h under carbon monoxide (1 atm), giving a 67:22:11 mixture of cyclized compound **53** (45–53%) and two stereoisomers. Hydrogenation of compound **53** followed by treatment with MCPBA and then with *p*-nitrobenzyl lithium afforded **54**, which was converted into (+)-isorauniticine (**51**).



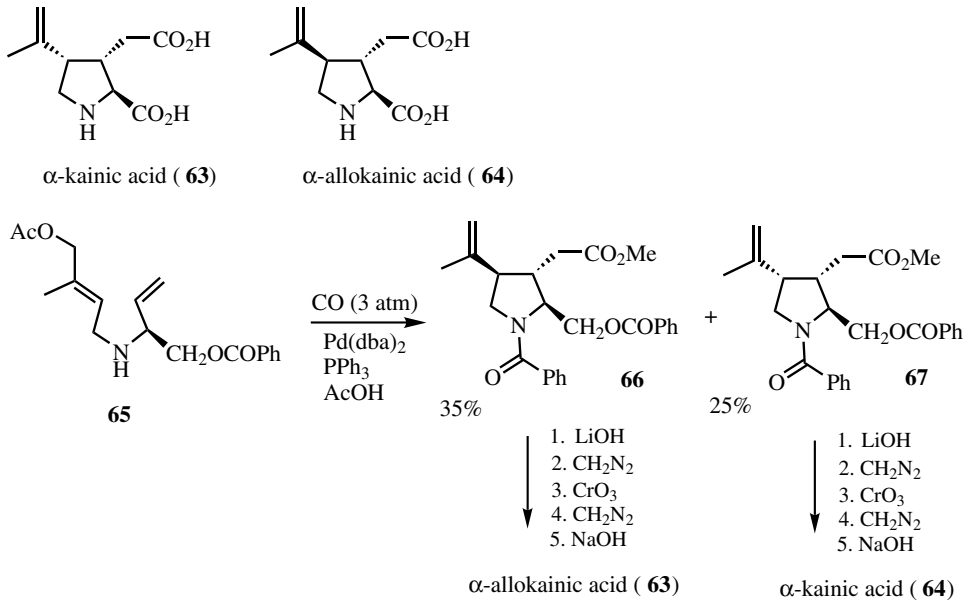
Scheme 12. Total synthesis of (+)-3-isorauniticine.

Oppolzer also synthesized (±)-hirstene (**56**, **Scheme 13**) using this method.[39] Stirring acyclic enynyl carbonate **58** with $Pd(dba)_2$ and PPh_3 in AcOH at 40 °C under carbon monoxide (1 atm) followed by treatment with CH_2N_2 gave epimeric bicyclooctenones **59** and C(1)-epimer of **59** in a 83:17 ratio (78% yield), which was then converted into hirstene (**56**) after several steps.

Yoo achieved the syntheses of α-kainic acid (**63**) and α-allokainic acid (**64**) using Pd-ene cyclization with carbonylation (**Scheme 14**).[40] Cyclization of **65** with $Pd(dba)_2$,



Scheme 13. Total synthesis of (±)-hirstene.

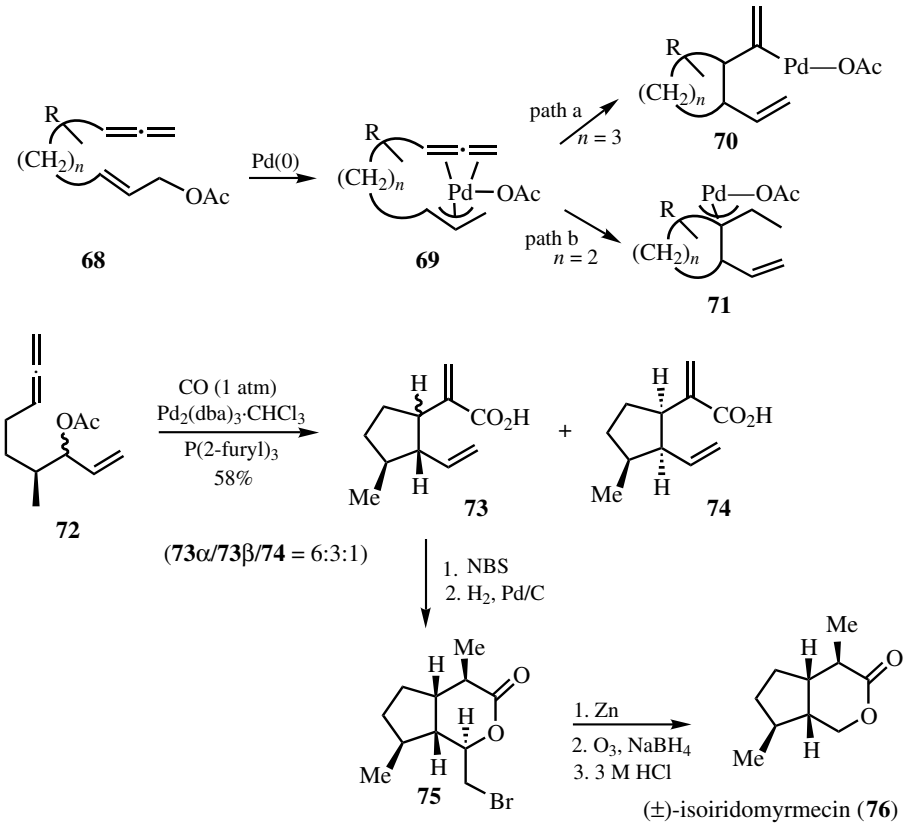


Scheme 14. Synthesis of α–kainic acid.

PPh_3, and CO (3 atm) in AcOH at 80 °C was followed by treatment with CH_2N_2 to give two products, **66** and **67**, in 35% and 25% yields, respectively. Transformation of each compound afforded α-kainic acid (**63**) or α-allokainic acid (**64**), respectively.

Takahashi reported a novel Pd-catalyzed cyclization of allylic acetate and allenic moiety.[41] The reaction is discriminated by the number of tethered carbon chains, as

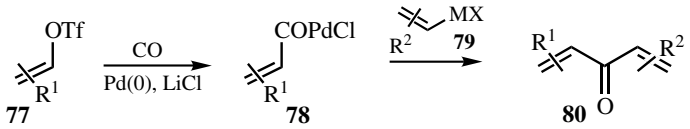
shown in **Scheme 15**. As an application of the example of path a, they synthesized iridoidomonoterpene, isoiridomyrmecin (**76**). Treatment of allene **72** with $Pd_2(dba)_3{\cdot}CHCl_3$ and P(2-furyl)$_3$ in AcOH at 45 °C under carbon monoxide (1 atm) provided the cyclized products **73** (β-H), **73** (α-H), and its *cis*-isomer **74** (6:3:1) in 58% yield. Halolactonization of **73** (β-H) followed by hydrogenation afforded **75**, which was then converted into (±)-isoiridomyrmecin (**76**).



Scheme 15. Synthesis of (±)-isoiridomyrmecin.

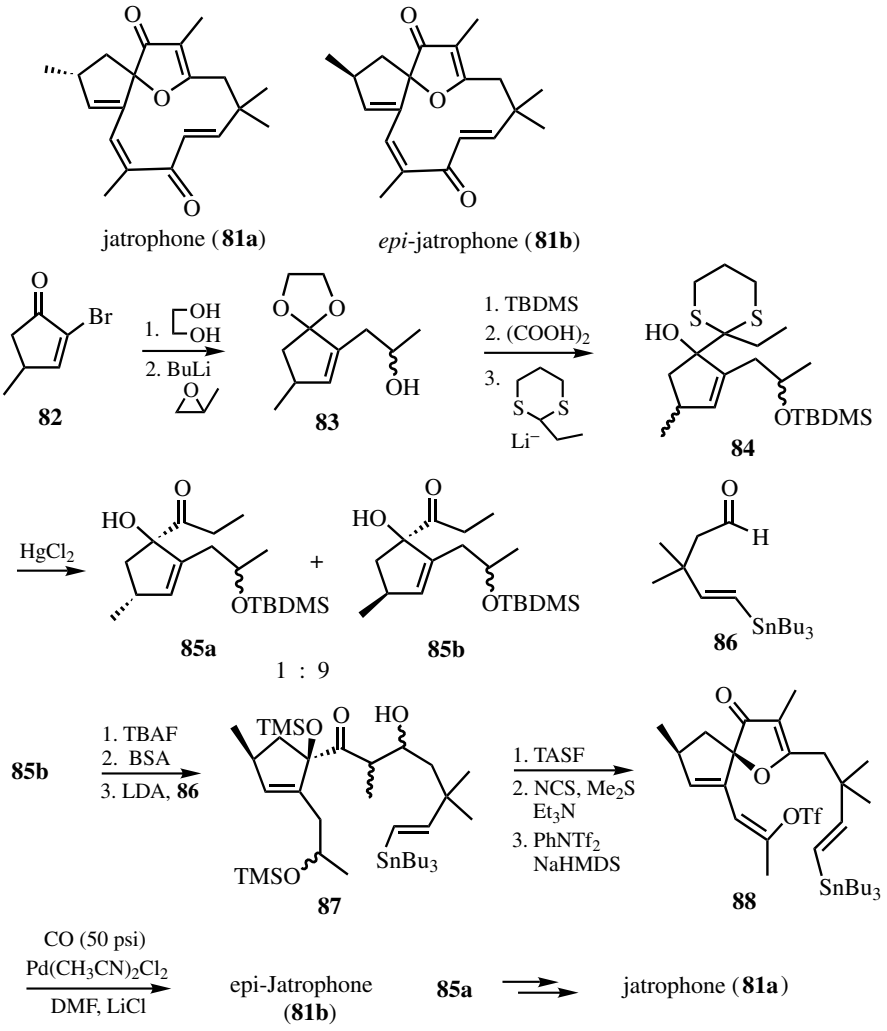
B.iv. Carbonylation Via Transmetalation

Since Migita and Stille independently reported transmetalation of alkylstannane to palladium complex,[42],[43] transmetalation has been considered to be a useful method for the formation of a novel carbon–carbon bond. For the transmetalation reaction, various transition metals are now used. Enol triflate **77** (**Scheme 16**), which is prepared from the keto-carbonyl group, affords a vinylpalladium complex. It converts into acylpalladium complex **78** under carbon monoxide. If an organometallic complex **79** is added to this reaction system, transmetalation would occur to give unsaturated ketone **80**. Stille developed an efficient carbonylative coupling of vinylic triflate with organostannane.[28],[29] The reaction takes place under mild conditions and tolerates a variety of functional groups on both coupling partners.



Scheme 16. Carbonylation via transmetalation.

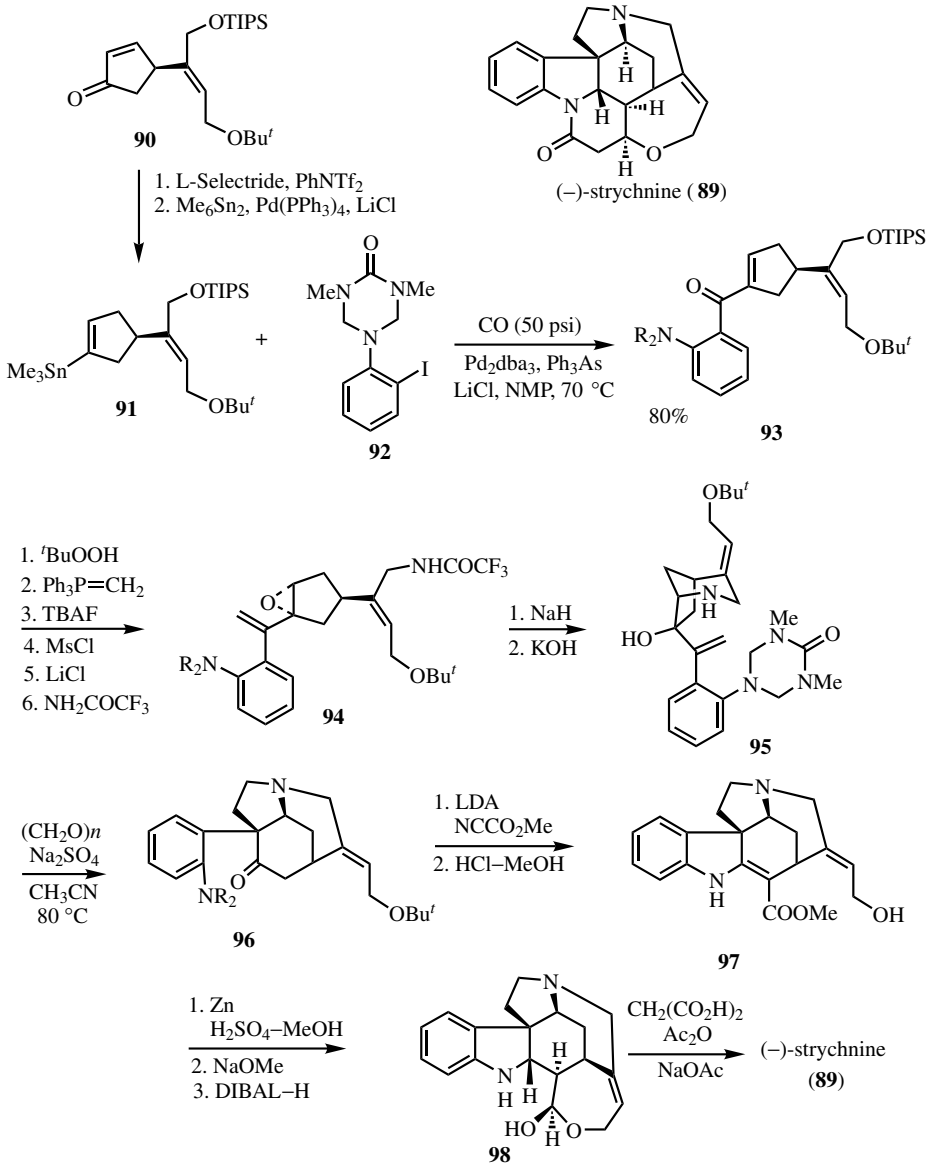
They tried to synthesize (±)-epi-jatrophone (**81b**, **Scheme 17**)[44] and (±)-jatrophone (**81a**)[44] using this method, and carbonylative coupling of vinylic triflate with organostannanes was used for the formation of a macrocycle. Compound **82** was converted into **85a** and **85b** in a ratio of 1:9 as shown in **Scheme 17**. The major isomer **85b** was condensed with compound **86** to give **87**, which was converted into enol triflate **88**. Macrocyclization of compound **88** was carried out by treatment with $Pd(CH_3CN)_2(Cl_2)_2$ and LiCl in DMF



Scheme 17. Total synthesis of jatrophone and *epi*-jatrophone.

at room temperature under 50 psi of carbon monoxide to give epi-jatrophone (**81b**) in 53% yield. From the minor product **85a**, (±)-jatrophone (**81a**) could be synthesized in a similar manner.

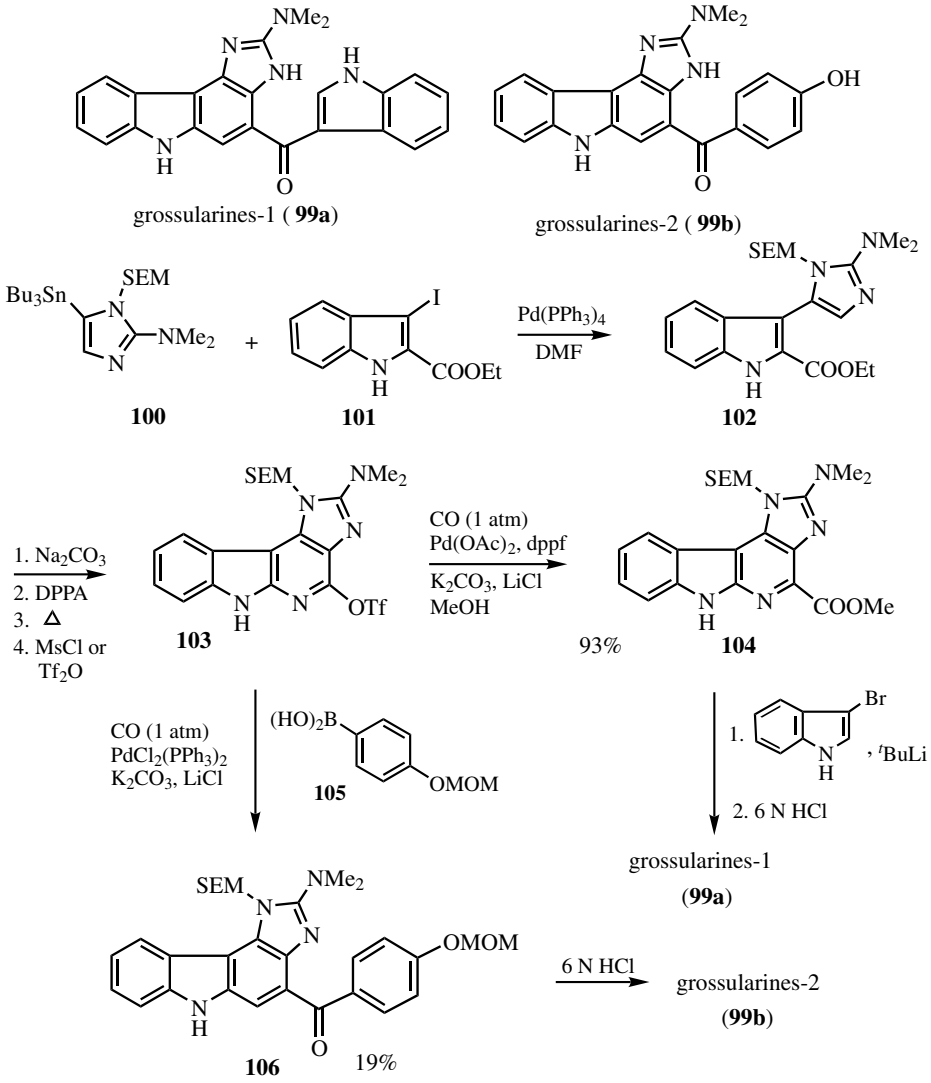
Strychnine is the most challenging target molecule in the total synthesis of alkaloids because it has seven rings in spite of the 24 skeletal atoms. The first total synthesis of (−)-strychnine (**89**, **Scheme 18**) was achieved by Woodward in 1954. After about 40 years, the second total synthesis was reported by Magnus. Several groups then reported unique and elegant total syntheses of strychnine by utilization of organometallic complexes. One



Scheme 18. Total synthesis of (–)-strychinine.

example of the total synthesis of (−)-strychnine was reported by Overman.[45],[46] For this synthesis, he used the aza-Cope–Mannich reaction, which he developed,[47] and Pd-catalyzed reactions. In the early stage of this total synthesis, the reaction of vinyl stannane **91**, which was synthesized from cyclopentenone **90**, with aryl iodide **92** was carried out in the presence of Pd_2dba_3 and Ph_3As under carbon monoxide (50 psi). They obtained coupling product **93** in 80% yield, and then **93** was converted into **95** via several steps. The aza-Cope–Mannich reaction of **95** gave **96** in quantitative yield. From this compound **96**, the total synthesis of (−)-strychnine (**89**) was realized.

The first total syntheses of grossularines-1 (**99a**, **Scheme 19**) and grossularines-2 (**99b**) were achieved by Hibino.[48] In these total syntheses, the key compound is triflate **103**, which was reacted with carbon monoxide in the presence of MeOH to give ester **104** in

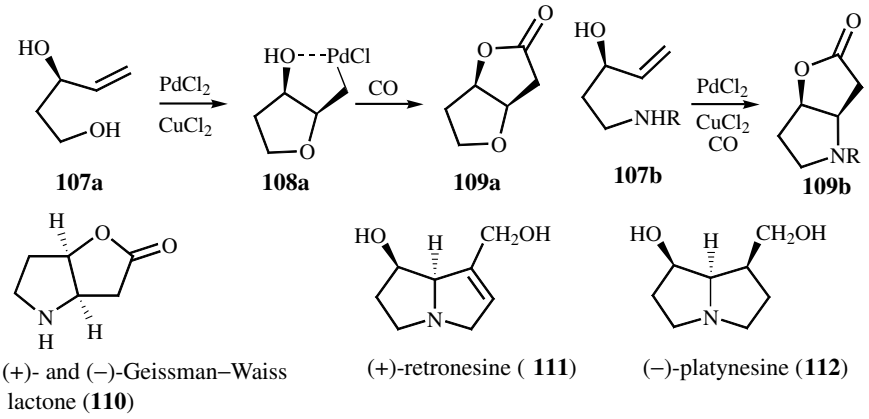


Scheme 19. Total synthesis of grossularines-1 and grossularines-2.

high yield. Condensation of **104** with 3-lithioindole followed by acid treatment gave grossularines-1 (**99a**). On the other hand, a three-component coupling reaction of **103**, arylboronic acid **105**, and carbon monoxide gave **106** in 19% yield, followed by hydrolysis to afford grossularines-2 (**99b**).

C. SYNTHESIS OF NATURAL PRODUCTS USING Pd(II)-PROMOTED OR -CATALYZED CARBONYLATION

It was shown that a nucleophile can react with olefins coordinated by Pd(II), and now this reaction is widely used in synthetic organic chemistry. However, in these reactions, a stoichiometric amount of Pd(II) is required because of the conversion of Pd(0) generated to Pd(II). Thus, in usual cases, an oxidizing agent such as $CuCl_2$ or hydroquinone is required when a catalytic amount of Pd(II) is used. An elegant Pd(II)-mediated bicyclization of 1,3-dihydroxypentene or *N*-toluenesulfonyl- or *N*-methoxycarbonyl-3-hydroxy-4-pentenylamine, has been reported by Tamaru.[49],[50] Using this method, (+)- and (−)-Geissman–Waiss lactones (**110**, **Scheme 20**) were synthesized.[51] These compounds are useful precursors for the synthesis of optically pure (+)-retronesine (**111**) or (−)-platynesine (**112**).

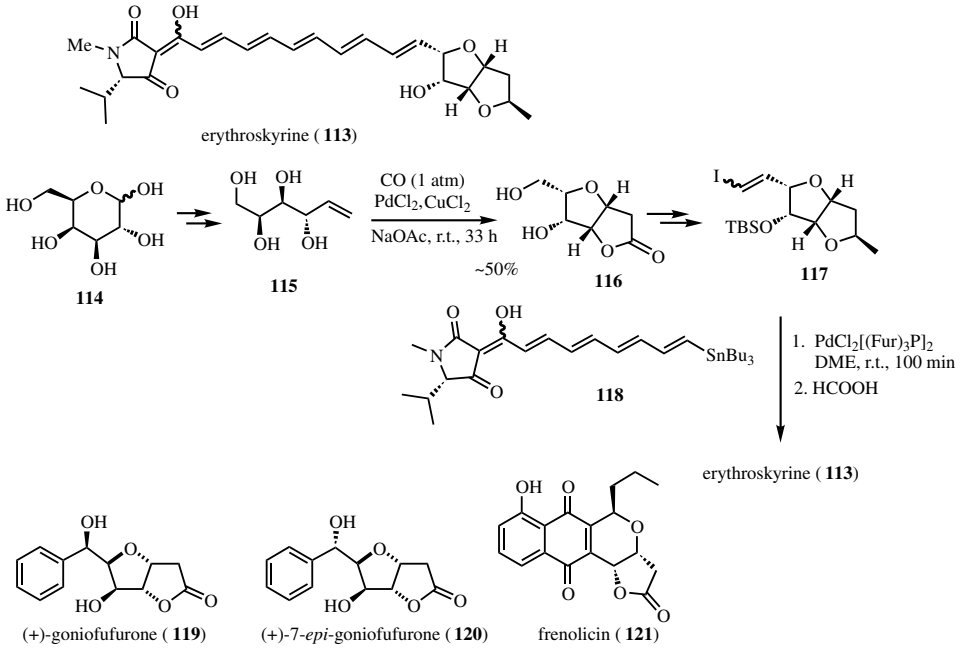


Scheme 20. Synthesis of Geissman–Waiss lactone.

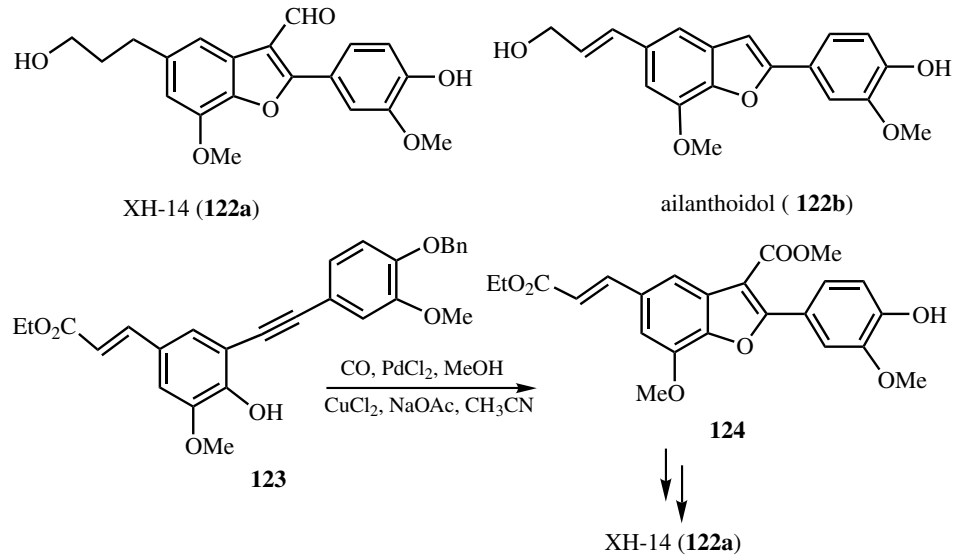
The first total synthesis of erythroskyrine (**113**, **Scheme 21**) was achieved using this coupling reaction.[52] Tetraol **115**, which was prepared from commercially available D-galactose, was subjected to a Pd(II)-catalyzed oxacarbonylation reaction, affording the desired bicyclic compound **116**, which was then converted into vinyl iodide **117** via several steps.

Condensation of **117** with vinylstannane **118** proceeded smoothly using $[P(Fur)_3]PdCl_2$ in DMF at room temperature, followed by desilylation to give erythroskyrine (**113**).

Using this Pd(II)-catalyzed oxacarbonylation, (+)-goniofufurone (**119**),[53] (+)-7-epi-goniofufurone (**120**),[53] and frenolicin (**121**)[54] could be synthesized. In each case, $CuCl_2$ was used as the oxidizing agent. This procedure was extended to the synthesis of a benzofurane skeleton, and Scammells synthesized the natural products XH-14 (**122a**) and ailanthoidol (**122b**, **Scheme 22**).[55]



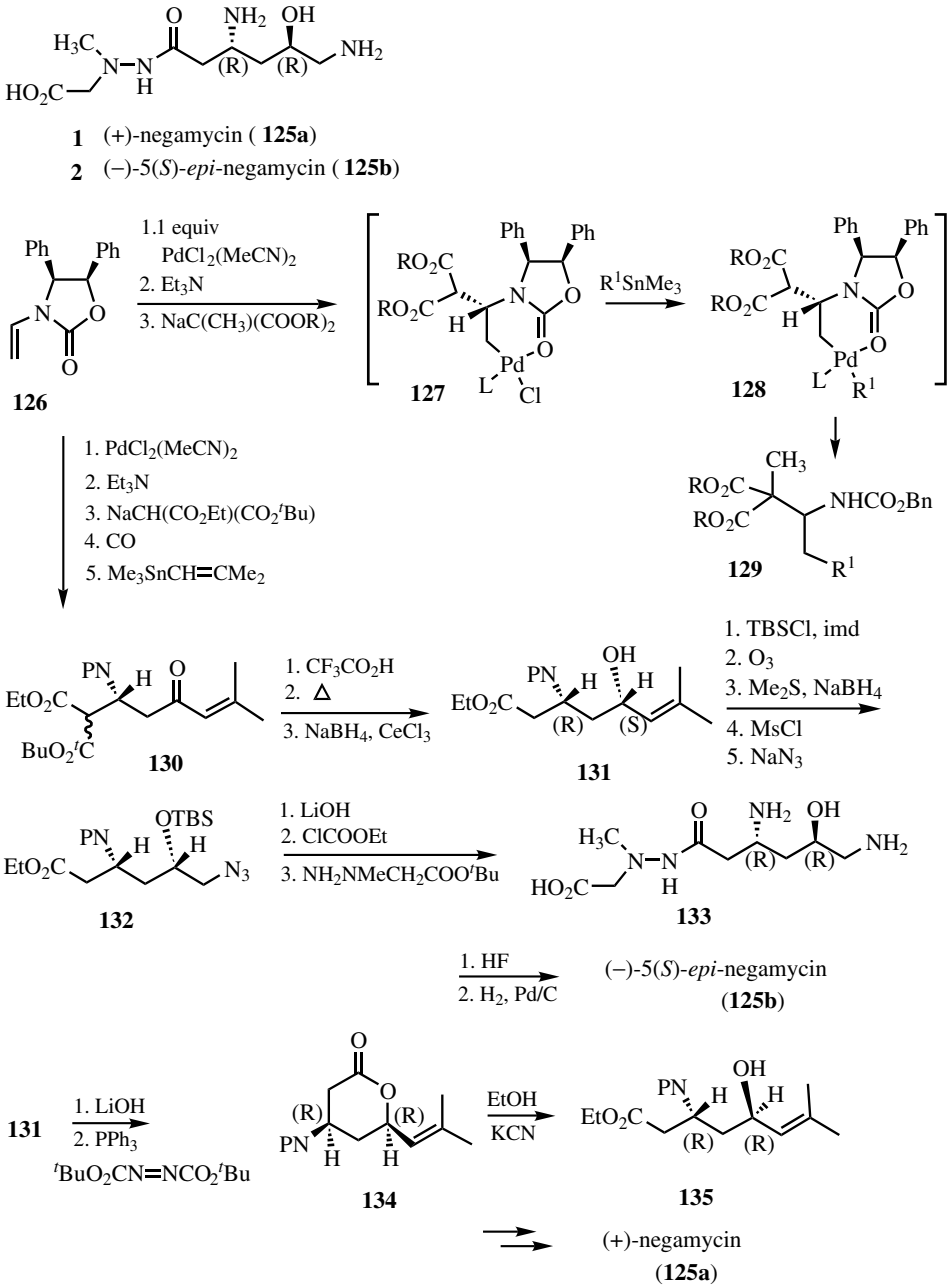
Scheme 21. Synthesis of erythroskyrine.



Scheme 22. Synthesis of XH-14.

Usually, σ-alkylpalladium(II) complex is unstable to β-hydrogen elimination and it is difficult to isolate. However, Hegedus reported that σ-alkylpalladium(II) complex **127** could easily be prepared by the attack of nucleophiles on π-olefinpalladium(II) complex of **126**.[56] Treatment of these complexes with alkylstannanes provided coupling product **129**. In this process, transmetalation of **127** with alkylstannane gave σ-alkylpalladium(II)

complex **128**, and then reductive elimination of **128** occurred. If this reaction is carried out under carbon monoxide, ketone would be formed. Using this procedure, Hegedus succeeded in the total syntheses of (−)-5(*S*)-*epi*-negamycin (**125b**) and (+)-negamycin (**125a**) (**Scheme 23**).[57] A THF solution of ene-carbamate **126**, $PdCl_2(MeCN)_2$, NEt_3, and sodium salt of *tert*-butyl ethyl malonate was stirred at −85 °C for 15 h. In this reaction, a



Scheme 23. Synthesis of (+)-negamycin and (−)-5(*S*)-*epi*-negamycin.

stoichiometric amount of palladium catalyst was used. The mixture was placed in a −30 °C bath and the reaction vessel was evacuated. The atmosphere was replaced with carbon monoxide (1 atm), and the solution was stirred for 1.5 h. The resulting black slurry was treated with isobutenyltrimethylstannane, and the solution was allowed to stand at room temperature and was then stirred for 4 h to afford **130** in good yield (68–77%). This was then converted into (−)-5(*S*)-*epi*-negamycin (**125b**) in overall yield of 20% from **126**. On the other hand, **131** was converted into **135** via **134**, and the total synthesis of (+)-negamycin (**125a**) was realized from **135**.

D. OUTLOOK

Pd-catalyzed carbonylation is a very attractive method because one carbon can be elongated from various functional groups. At first, this method was used for ester or amide formation from aryl or vinyl halide. Then enol triflate could be used as the functional group and we could obtain α,β-unsaturated ester from the keto-carbonyl group. Furthermore, using transmetallation from an organometallic complex to a palladium complex and carbonylation, we can synthesize ketone. Combination of transmetalation with carbonylation provided various methods for novel carbon–carbon bond formation. Now we can find many total syntheses of natural products, using a Pd-catalyzed reaction, such as the Heck reaction, Pd-catalyzed carbonylation, transmetalation of organometallic complex, and reaction via π-allylpalladium complex. Further various elegant total syntheses of natural products are expected to be reported in the near future.

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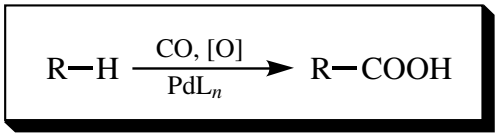

VI.7 Palladium-Catalyzed Carbonylative Oxidation

VI.7.1 Palladium-Catalyzed Carbonylative Oxidation of Arenes, Alkanes, and Other Hydrocarbons

YUZO FUJIWARA and CHENGGUO JIA

A. INTRODUCTION

As described in **Sect. VIII.2.2**, the Pd-catalyzed coupling reaction of arenes and olefins proceeds via σ-aryl-Palladium complex intermediates to give aryl-substituted olefins (**Scheme 1**).

During the development of this arylation reaction, it was found that the σ-aryl-Palladium complexes reacted with CO to give aromatic acids, when AcOH was used as a solvent (**Scheme 2**).[1],[2]

This carboxylation reaction of arenes with CO proceeds catalytically with respect to Pd at room temperature under atmospheric pressure of CO, when $K_2S_2O_8$ is added as an oxidant and trifluoroacetic acid (TFA) is employed as a solvent (**Scheme 3**).[3]–[5]

Alkanes such as methane, ethane, propane, and cyclohexane also undergo carboxylation with CO. The first example of carboxylation of alkanes was performed on cyclohexane using a $Pd(OAc)_2/K_2S_2O_8$/TFA catalyst system (**Scheme 4**).[6]

The reaction was extended to the gaseous alkanes such as methane, ethane, and propane (**Scheme 5**).[7],[8]

Thus, in 1992 acetic acid (AcOH) was first synthesized from methane and CO catalyzed by Pd-based catalysts in low conversion yield.[7] Recently, it has been found that V catalysts such as $VO(acac)_2$ convert methane and CO to AcOH almost quantitatively.[9]

The carbonylative oxidation of olefins was first reported by Tsuji and co-workers (**Scheme 6**).[10] Numerous studies have been carried out on the carbonylation of olefins after Tsuji reported the reaction.[11]

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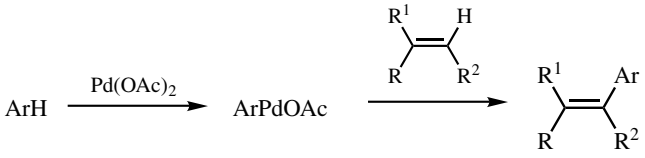
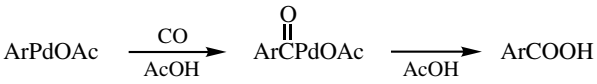
B. PALLADIUM-CATALYZED CARBOXYLATION OF ARENES WITH CO

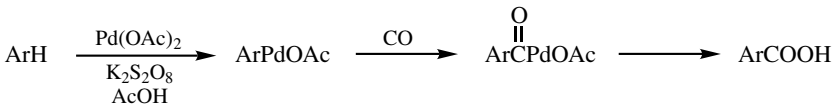
The carboxylation of arenes with CO proceeds easily under very mild conditions (room temperature (r.t.), 1 atm CO) (**Table 1**). The carboxylation of benzene proceeds quantitatively when 1 mmol of benzene, 2.5 mmol of $K_2S_2O_8$, and 1 mL of TFA are employed in the presence of 10 mol% of $Pd(OAc)_2$ as catalyst.[3],[4] Similarly,



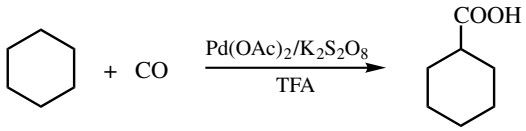
Scheme 1



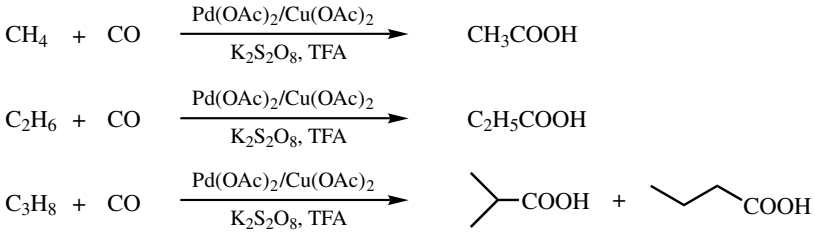
Scheme 2



Scheme 3



Scheme 4



Scheme 5

Scheme 6

TABLE 1. Pd-Catalyzed Carboxylation of Arenes with CO [a]

Arene	Product	Yield (%) [b]	Ratio
Benzene	Benzoic acid	1420	—
Toluene	Toluic acid	800 [c]	26/6/67 [d]
Chlorobenzene	Chlorobenzoic acid	1700	19/27/54 [d]
Anisole	Anisic acid	1200	33/0/67 [d]
Naphthalene	Naphthoic acid	3300	66/34 [e]

[a] The reaction was carried out at 1 atm of CO using 0.1 mmol of $Pd(OAc)_2$, 56 mmol of arene, and 5 mmol of $K_2S_2O_8$ in 5 mL of TFA at r.t. for 20 h.

[b] Isolated yield based on Pd.

[c] Bitolyl-type coupling products formed in considerable amounts.

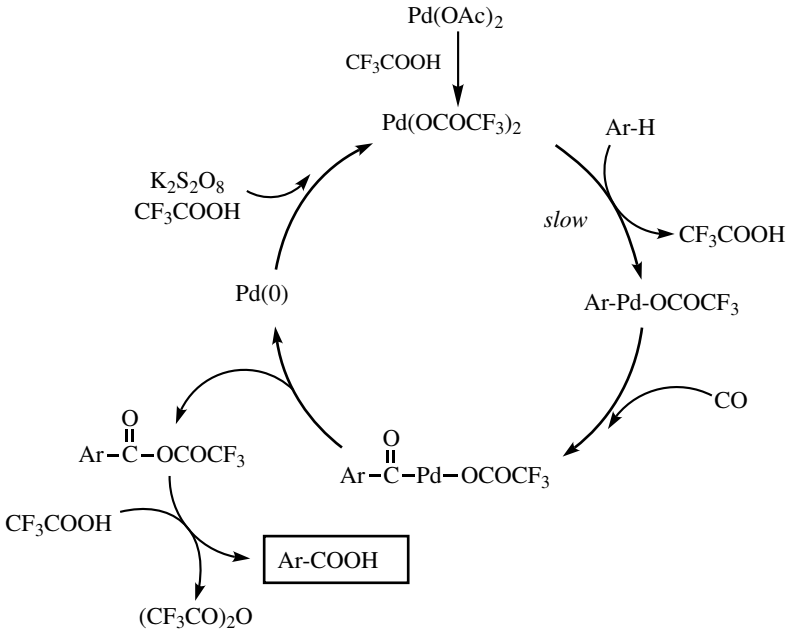
[d] *o;m;p*-Isomer ratio.

[e] α,β-Isomer ratio.

chlorobenzene is converted to a mixture of chlorobenzoic acids in quantitative yield. Toluic and anisic acids are obtained in 67% and 60% yields based on the arenes, respectively.

The reaction of naphthalene gives a mixture of α- and β-naphthoic acids in a ratio of 66:34. β-Naphthoic acid is obtained in 92% selectivity from the reaction of naphthalene and CO by the $Pd(OAc)_2/O_2$/Phen/AcOH/cyclohexane catalyst system.[3]

The reaction proceeds via electrophilic attack of cationic $^+Pd(OCOCF_3)$ species on the benzene ring to give σ-arylPalladium(II) complexes, which undergo insertion of CO to afford aroylPalladium(II) complexes (**Scheme 7**). The subsequent reductive elimination gives Pd(0) and the acid anhydride, which reacts with TFA to give ArCOOH and $(CF_3CO)_2O$. Pd(0) is reoxidized by $K_2S_2O_8$ to Pd(II).

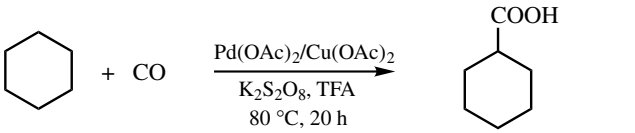


Scheme 7

Since this reaction is direct carboxylation of arenes via C—H bond activation under mild conditions, the process has great potential to be industrialized.

C. PALLADIUM-CATALYZED CARBOXYLATION OF ALKANES WITH CO

Alkanes have been found to react with CO in the presence of Pd-based catalysts. Cyclohexane gives cyclohexanecarboxylic acid in 1981% yield based on Pd (4.3% based on cyclohexane) when reacted with CO with the $Pd(OAc)_2/Cu(OAc)_2/K_2S_2O_8$/TFA catalytic system (**Scheme 8**). [8]

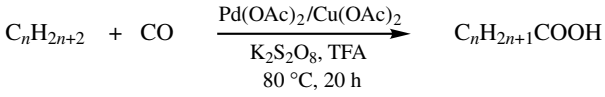


1981% on Pd
4.3% on cyclohexane

Scheme 8

Gaseous alkanes such as methane, ethane, and propane also react with CO to give the corresponding acids (**Scheme 9**, **Table 2**).[8]

As can be seen in **Table 2**, ethane and propane are best carboxylated by the Wacker-type $Pd(OAc)_2/Cu(OAc)_2$ catalytic system, the same as in the carboxylation of cyclohexane. In the reaction of methane, the copper catalyst $Cu(OAc)_2$ shows superior



Scheme 9

TABLE 2. Carboxylation of Methane, Ethane, and Propane by Various Catalyst Systems[a]

		Catalyst and Yield (%)[b]		
Alkane	Product	Pd(II)–Cu(II)	Pd(II)	Cu(II)
Methane	Acetic acid	1300	100	2960
		(0.4)	(0.03)	(0.9)
Ethane	Propionic acid	7600	440	700
		(2.1)	(0.2)	(0.3)
Propane	Butyric acids[c]	7100	1760	1900
		(8.7)	(2.1)	(2.2)

[a] C_3H_8 10 atm, C_2H_6 30 atm, CH_4 40 atm, $Pd(OAc)_2$ and $Cu(OAc)_2$ 0.05 mmol each, $K_2S_2O_8$ mmol, TFA 5 mL, CO 20 atm.

[b] Based on the catalyst (on the alkane).

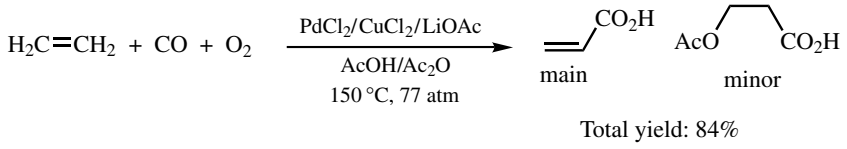
[c] A mixture of isobutyric and butyric acids (4:1).

activity to the mixed catalyst $Pd(OAc)_2/Cu(OAc)_2$. As described in **Sect. A**, the $VO(acac)_2/K_2S_2O_8$/TFA catalyst has recently been found to convert methane and CO to AcOH almost quantitatively.[9]

The Pd-catalyzed reaction proceeds by a similar mechanism to the carboxlation of arenes in Sect. B (**Scheme 7**), involving an electrophilic attack of cationic $^+Pd(OCOCF_3)$ to alkane (RH) to give $RPdOCOCF_3$ species.

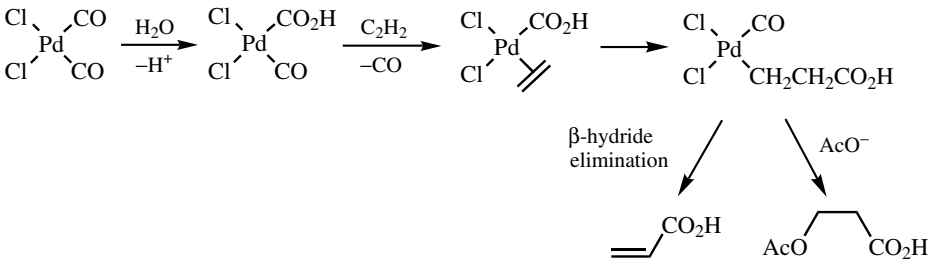
D. CARBONYLATIVE OXIDATION OF ALKENES

The carbonylative oxidation of alkenes catalyzed by palladium catalysts has been extensively studied owing to its industrial importance.[12],[13] The conversion of ethylene to acrylic acid has been developed into a commercial process by Union Oil (**Scheme 10**).[14] The reaction is performed in a mixed solvent of acetic acid and acetic anhydride in the presence of a Wacker catalyst under high pressure of ethylene.



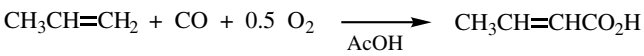
Scheme 10

The suggested mechanism (**Scheme 11**) involves migratory insertion of coordinated ethylene into a palladium–carboxyl bond formed by the reaction of the Pd—CO species with water. Acrylic acid results from β-hydride elimination of the carboxypalladation intermediate, whereas oxidative cleavage by AcOH results in the formation of β-acetoxypropionic acid.[15]

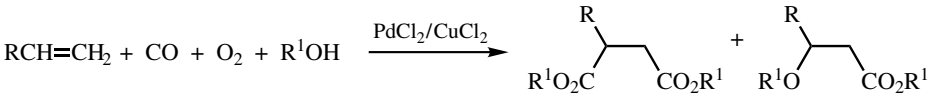


Scheme 11

The carbonylative oxidation of propene under the same conditions affords crotonic acid as the major product rather than the more valuable methacrylic acid (**Scheme 12**). When the reaction of ethylene or terminal alkenes is carried out in alcoholic solvents instead of AcOH, dialkyl succinates and β-alkoxy esters become the major products (**Scheme 13**).[16],[17]



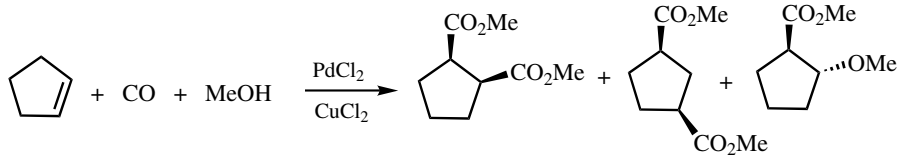
Scheme 12



Scheme 13

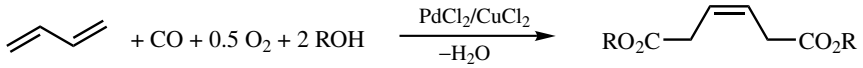
The dicarbonylation takes place as the main reaction in the carbonylative oxidation of cyclic olefins such as cyclopentene with the stoichiometric amount of $CuCl_2$ and a catalytic amount of $PdCl_2$, giving favorably *cis*-1,2- and 1,3-diesters (**Scheme 14**).[17]–[19]

The synthesis of dialkyl hex-3-en-1,6-dioate from butadiene in an alcoholic solvent and in the presence of a Wacker catalyst $PdCl_2/CuCl_2$ and a dehydrating agent such as trimethyl orthoformate provides an economically attractive route for the synthesis of adipic acid (**Scheme 15**).[20]



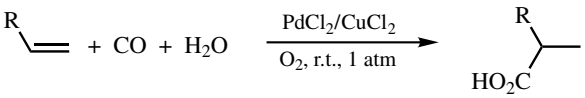
(68:27:4)

Scheme 14



Scheme 15

Nonoxidative hydrocarboxylation of alkenes to carboxylic acids with CO and water catalyzed by Pd catalysts is greatly improved in the presence of oxygen (**Scheme 16**). Almost quantitative yields of mono- and dicarboxylic acids were obtained from the corresponding terminal alkenes and terminal dialkenes, respectively, under atmospheric pressure at room temperature.[21]



Scheme 16

In summary, the carbonylative oxidation of arenes, alkanes, and alkenes can be carried out in the presence of a catalytic amount of a palladium catalyst and an oxidant. The various carbonyl compounds can be prepared directly from simple hydrocarbons by these reactions.

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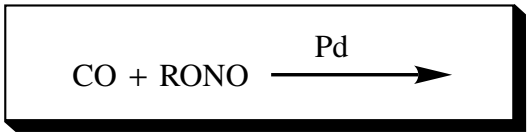

VI.7.2 Palladium-Catalyzed Carbonylative Oxidation Other than Those Involving Migratory Insertion

SHIN-ICHIRO UCHIUMI and KIKUO ATAKA

A. INTRODUCTION

This section deals with the Pd-catalyzed carbonylative oxidation (oxidative carbonylation) reaction, especially the reaction of carbon monoxide and oxygen- or nitrogen- based nucleophiles (**Scheme 1**).

The carbonylative oxidation reaction is most effectively catalyzed by palladium. Many industrial processes have been developed and it became one of the major industrial reactions known to be catalyzed by palladium besides the olefin oxidation.[1]–[3]

The reoxidation of Pd(0) to Pd(II) in carbonylative oxidation reactions is performed in the same manner as the Wacker and related processes,[4],[5] but it has drawbacks such as corrosive damage to normal industrial reactors because of excess usage of $CuCl_2$.

Recently, the processes utilizing alkyl nitrites (RONO, **1**, **a**: R = Me, **b**: R = Et, **c**: R = *n*-Bu) in Pd-catalyzed carbonylative oxidation have been developed and successfully applied to the industrial production of dialkyl oxalates ($(COOR)_2$, **2**, **a**: R = Me, **b**: R = Et, **c**: R = *n*-Bu) and dialkyl carbonates ($(RO)_2CO$, **3**, **a**: R = Me, **b**: R = Et, **c**: R = *n*-Bu).[6]–[9]

In this section, we mainly present industrial production of dialkyl oxalates, dialkyl carbonates, and related processes developed by Ube Industries.

B. OXALATE SYNTHESIS BY CARBONYLATIVE OXIDATION

B.i. Synthesis of Oxalates in Liquid Phase

The synthesis of diethyl oxalate **2b** by carbonylative oxidation of ethanol with O_2 in the presence of $PdCl_2$–$CuCl_2$ catalyst was originally discovered by Fenton and Steinwand.[10] Utilizing triphenylphosphine and cobalt acetate(II) as additives, dimethyl oxalate **2a** was obtained in high yield (**Scheme 2**).[11] Oxalate **2b** was not formed in the presence of water, so this reaction was carried out with a considerable excess of orthoformate **4** as the dehydrating agent in order to maintain anhydrous conditions in the system.

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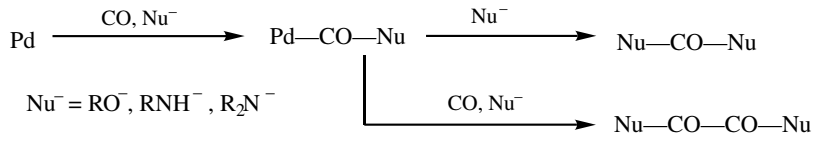
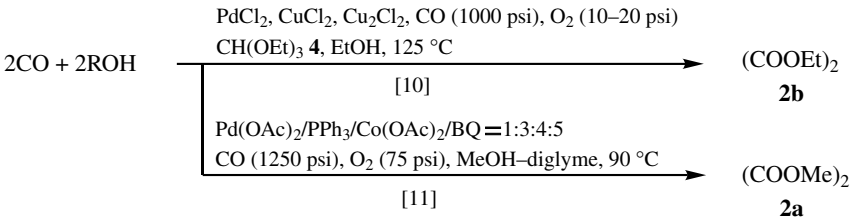


Scheme 1

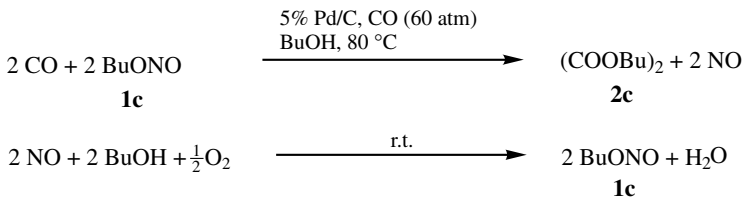


Scheme 2

Ube's research for the development of a new industrial process without using expensive orthoformate as the dehydrating agent revealed that the following catalytic systems afforded oxalate **2** even in the presence of water (**Table 1**).[12] Among these, the catalytic systems such as (5) and (6) showed high reactivities, long catalyst lives, and good selectivities. Further investigation of the fate of the nitrogen compounds in the system showed that nitric oxide and nitric acid were converted to alkyl nitrite **1**. A dramatic improvement of the reaction efficiency was observed when butyl nitrite **1c** was used instead of HNO3 or NO. By this modification, dibutyl oxalate **2c** was obtained even under low CO pressure and at lower temperature.[13]

The elementary reactions of dibutyl oxalate formation in the liquid phase are shown in **Scheme 3**.[12],[14]

In addition to **2c**, a small amount of dibutyl carbonate **3c** and carbon dioxide were obtained as by-products. Ratio of the products **2c** and **3c** was largely influenced by the reaction temperature, the concentration of butanol, and CO pressure. The selectivity for oxalate **2c** increased (i) at the lower reaction temperature, (ii) at lower concentration of butanol, and (iii) under the higher CO pressure.[12]



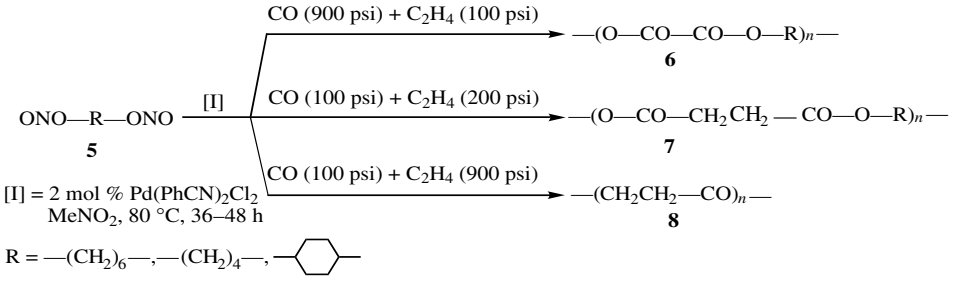
Scheme 3

TABLE 1. Catalyst Systems for Dialkyl Oxalate Synthesis (Liquid Phase)

(1) $PdCl_2$–$CuCl_2$–K_2CO_3	(2) $PdCl_2$–$CuCl_2$–R_3N
(3) $Pd(NO_3)_2$–HNO_3	(4) $PdCl_2$–NO
(5) Pd(0)/activated carbon–HNO_3	(6)Pd(0)/activated carbon–NO

In industrial production, palladium metal supported on activated carbon was the catalyst of choice to prevent loss of palladium and to maintain an adequate suspended state. Ube's first plant for the production of dibutyl oxalate **2c** became operational in 1978.

Recently, polyoxalates **6** have been synthesized from dinitrite **5** (**Scheme 4**).[15],[16] However, TOF (mol/molPd·h) was 2–3, showing quite lower activity. In this reaction system, polyoxalate **6** is the only product under high CO pressure even in the presence of ethylene. Polysuccinate **7** can be obtained as the main product only under low CO pressure. Polyketone **8** becomes the main product under the low CO pressure combined with high ethylene pressure.

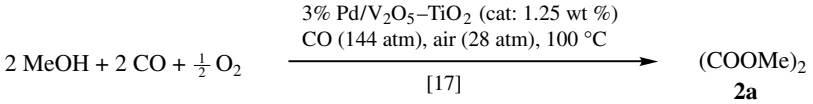


Scheme 4

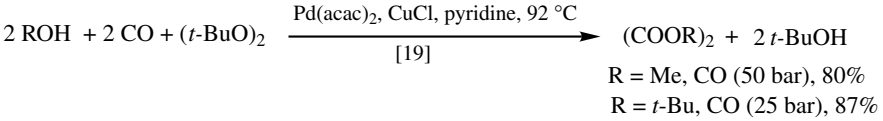
As a heterogeneous liquid phase reaction system, processes utilizing molecular oxygen as an oxidant and metal oxide of vanadium, titanium, and manganese as cocatalysts were reported (**Scheme 5**).[17],[18]

Kinetic studies were carried out in this system and it was confirmed that the rate of dialkyl oxalate formation was first order to the CO pressure.

There is another example that employs dialkyl peroxides as oxidant (**Scheme 6**).[19]

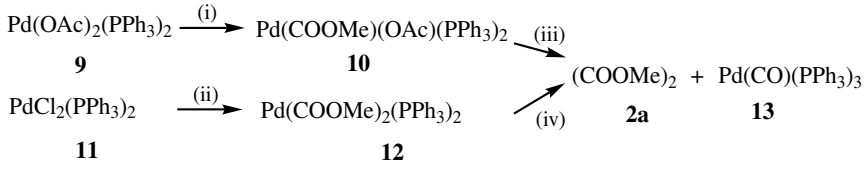


Scheme 5



Scheme 6

For all these oxalate syntheses, reaction intermediates are generally considered as palladium biscarboalkoxy complexes, since the reaction of PdX_2L_2 and CO in the presence of an alcohol and a base was known to give biscarboalkoxy palladium complex **12**, which was thermally decomposed to give dimethyl oxalate **2a** (**Scheme 7**).[20]–[22]



(i) CO (20–50 atm), MeOH, r.t. (ii) CO (2–3 atm), NaOMe, MeOH, 0 °C, 4–5 h.
(iii) CO, Ph_3P, MeOH, 50 °C. (iv) CO (1 atm), MeOH, 50 °C.

Scheme 7

B.ii. Synthesis of Oxalates in Gas Phase

Ube's continuous research revealed that oxalates **2** were formed even in the gas phase at atmospheric pressure. Pd(0) on solid support was used for the production of **2a** (**Table 2**).[9],[23],[24]

According to the large number of patents, catalyst supports based on alumina are most widely used and the effects of additives have also been studied extensively.[26]–[28]

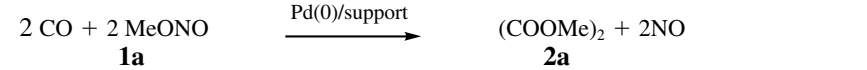
C. CARBONATE SYNTHESIS BY CARBONYLATIVE OXIDATION

C.i. Synthesis of Dialkyl Carbonate by Carbonylative Oxidation

It has been known that the reaction of $PdCl_2$ and CO in EtOH generates diethyl carbonate.[29] Cyclic carbonates **15** were obtained by using *vic*-diol **14** as reaction substrates (**Scheme 8**).[15],[30]

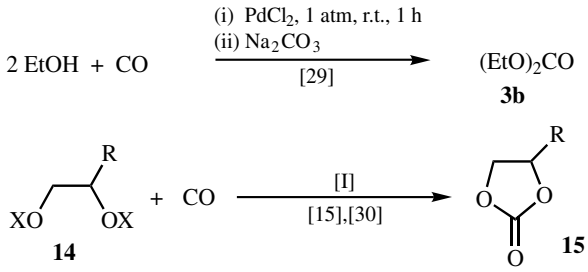
The formation of dialkyl carbonates was observed in every case of the dialky oxalate synthesis that we discussed in the previous section. Generally, it is accepted that higher CO pressure favors dialkyl oxalate formation and lower pressure favors dialkyl carbonate formation. But in the palladium–alkyl nitrite system, we confirmed the oxidation state of

TABLE 2. Effect of Solid Supports on $(COOMe)_2$ Synthesis[a]



Support[b]	Space–Time Yield (g/L-cat.·h)		
	2a	**3a** $(MeO)_2CO$	MF[c]
Activated carbon	286	12	2
Silica	255	13	4
Activated alumina	114	7	3
α-Alumina	489	11	1
NaY zeolite[d]	58	3	4
Si–Al–O(silica alumina)	112	11	5

[a]Reaction conditions: 110 °C, atmospheric pressure, GHSV 2000 h^{-1}.
Inlet gas composition: 10% CO, 10% **1a**, N_2 base.
[b]Catalyst component: 0.5 wt % Pd/support.
[c]Methyl formate.
[d]See Ref. [25].



14a: X = H, R = Ph, [I] = $PdCl_2$,$CuCl_2$, NaOAc, CO (3 atm), r.t., 3–4 day, quant.
14b: X = NO, R = Et, [I] = 1.2 mol % $Pd(acac)_2$, CO (1000 psi), $CHCl_3$, 100 °C, 24 h, quant.

Scheme 8

palladium had more decisive effect on the product selectivity.[8] The key to the selective formation of dialkyl carbonate was to maintain the oxidation state of Pd at +2.[8],[9]

Palladium metal catalyst supported on the activated carbon affords dimethyl oxalate **2a** selectively. On the other hand, dimethyl carbonate **3a** is selectively formed when the same catalyst is treated with methyl nitrite **1a** and HCl. This may be due to the oxidation of the Pd(0) to Pd(II) by **1a** and HCl (Table 3). To keep the oxidation state of palladium at +2, the presence of halogen ion like Cl^- and Br^- is important for the formation of **3a** in the gas phase reaction.

In the palladium–alkyl nitrite system, the gas phase synthesis of dialkyl carbonates has mainly been studied[31] and not many examples are known concerning the liquid phase variants. [32] For catalyst supports, alumina,[33],[34] activated carbon,[35] and Li–Al–O(spinel)[36] were successfully utilized in dimethyl carbonate synthesis (**Table 4**).

Ube Industries constructed a plant for dimethyl carbonate **3a** production with a capacity of 3000 t/y in 1993 and the current capacity has been doubled.

Other than the palladium–alkyl nitrite system, the usual Wacker-type catalyst, which utilizes molecular oxygen as stoichiometric oxidant, is commonly employed.[37] It has superior catalyst efficiency but shows lower productivity than that of the nitrite system.

TABLE 3. Change of the Catalytic Activity by Reoxidation Treatment[a]

Starting Catalyst	Treatment	Valance (XPS)	Catalyst Activities(mol/L-cat.·h)	
			2a $(COOMe)_2$	**3a** $(MeO)_2CO$
Pd–Cl/AC[b]		Pd^{2+}	0.05	2.21
	↓ H_2 (200 °C, 1 h)	Pd^0	2.14	0.60
	↓ **1a** + HCl (200 °C)	Pd^{2+}	0.13	2.17

[a]Reaction conditions: 120 °C, 0.1 MPa, GHSV 8000 h^{-1}. Inlet gas composition: 8% CO, 8% **1a**, N_2 base.
[b]Catalyst component: 1 wt % Pd.

TABLE 4. Effect of Solid Supports on $(MeO)_2CO$ Synthesis[a]

$$CO + 2\ MeONO \xrightarrow{Pd(II)\text{–}Cu/support} (MeO)_2CO + 2\ NO$$

1a → **3a**

	Space–Time Yield (g/L-cat.·h)		
Support[b]	**2a** $(COOMe)_2$	**3a**	MF[c]
Activated carbon	29	553	3
Silica	Trace	58	2
Activated alumina	7	246	2
NaY zeolite[d]	0	210	56
Li–Al–O(spinel)	9	670	Trace

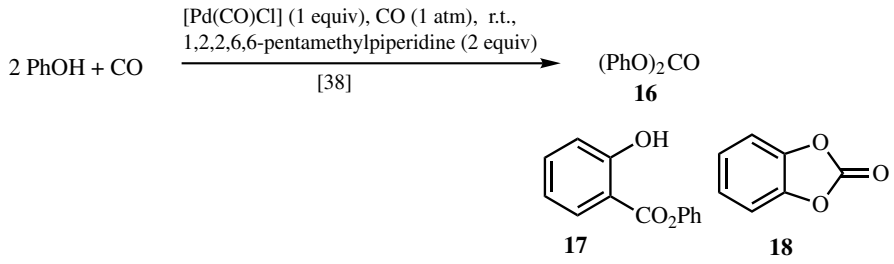
[a] Reaction conditions: 120 °C, 0.4 MPa, GHSV 4000 h−1.
Inlet gas composition: 20 % CO, 10% **1a**, 100 ppm HCl, N_2base.
[b] Catalyst component: 1 wt % Pd–1.2 wt % Cu–2.0 wt % Cl/support.
[c] Methyl formate.
[d] Contains no chloride ion. See Ref. [25].

C.ii. Synthesis of Diaryl Carbonate by Carbonylative Oxidation

Attempts to employ phenol instead of alkanols in the oxidative carbonylation reaction have been widely conducted to synthesize diphenyl carbonate (DPC, **16**). But various side reactions due to low nucleophilicity and facile oxidation of phenol prevent successful application to industrial production.

Stoichiometric use of [Pd(CO)X] produced DPC in moderate yield based on palladium (**Scheme 9**).[38] Phenyl salicylate **17** and *o*-phenylenecarbonate **18** are typical by-products in DPC synthesis, but formation of diphenyl oxalate has not been reported.

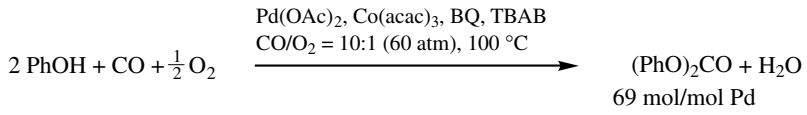
Catalytic variants of this reaction have also been widely studied. Molecular oxygen is the most commonly used oxidant. The presence of cocatalysts is essential to the reaction and various transition metal salts were employed such as Co,[39],[40] Mn,[41] Cu,[42],[43]



Scheme 9

Sn,[44] Pb,[45] and Ce.[46],[47] Benzoquinone (BQ) could be used as a reoxidant instead of molecular oxygen,[48] but in some cases BQ or hydroquinone was used as an organic redox co-catalyst (**Scheme 10**).[40],[42]

Most of the patents applied for concerned combinations of these cocatalysts and in almost all cases, the use of tetrabutylammonium bromide (TBAB) was indispensable. In

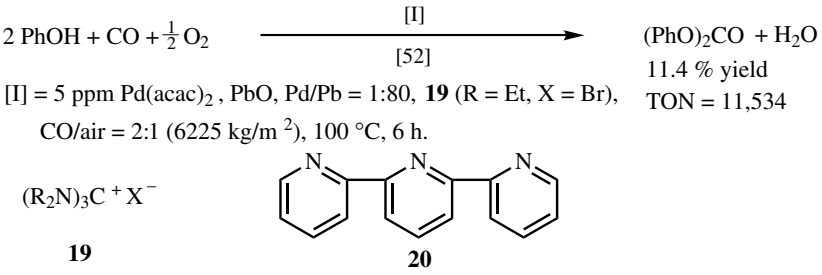


Scheme 10

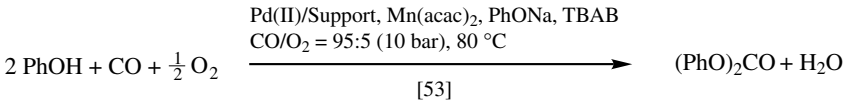
cases utilizing hexaalkylguanidinium halide **19**[49] or terpyridine **20**[50] instead of TBAB, a TON (mol DPC/mol Pd) of more than 10,000 has been achieved (**Scheme 11**).[51],[52]

In heterogeneous systems, palladium has been used as the main catalyst and various metal oxides have been utilized as catalyst supports (**Scheme 12**).[53]–[55] The reaction system is somehow complicated due to the addition of Mn ,TBAB, and NaOPh, but the selectivity of DPC based on phenol is more than 99% and the TOF (mol/molPd·h) is supposed to be around a few hundred.

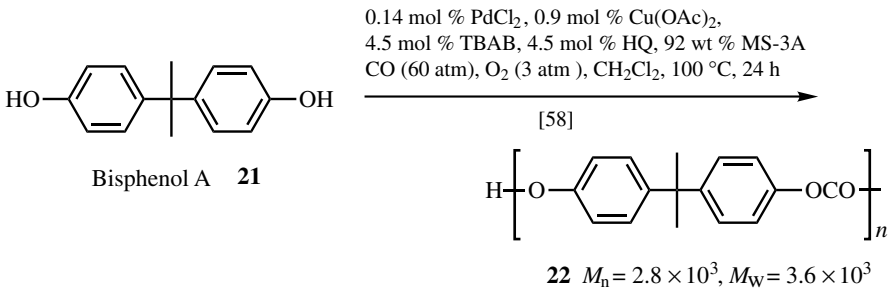
Direct production of polycarbonate **22** from bisphenol A **21** has been reported, but the M_n of the obtained polycarbonate was less than 3000 (**Scheme 13**).[56]–[58]



Scheme 11



Scheme 12

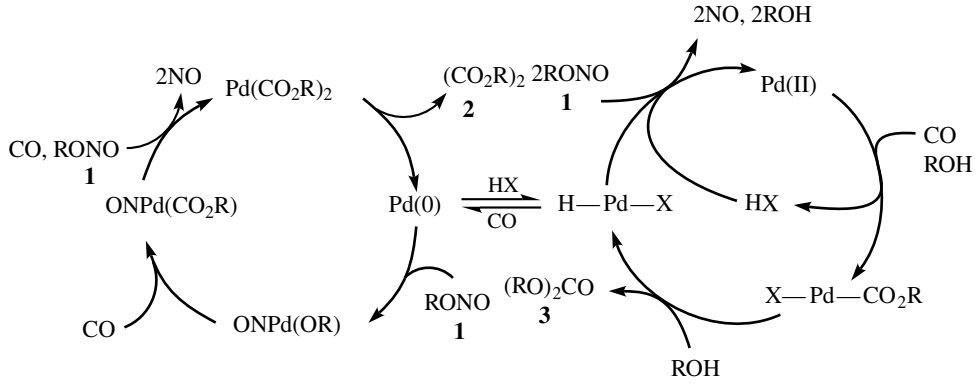


Scheme 13

D. KINETICS AND REACTION MECHANISMS

The reaction mechanism for the palladium–alkyl nitrite system has been established mainly based on kinetics studies. In the liquid phase, the rate of oxalate formation was first order to the CO pressure; on the other hand, the rate of carbonate formation was independent of CO pressure. Based on these findings, the following reaction mechanism has been proposed (**Scheme 14**).[6]

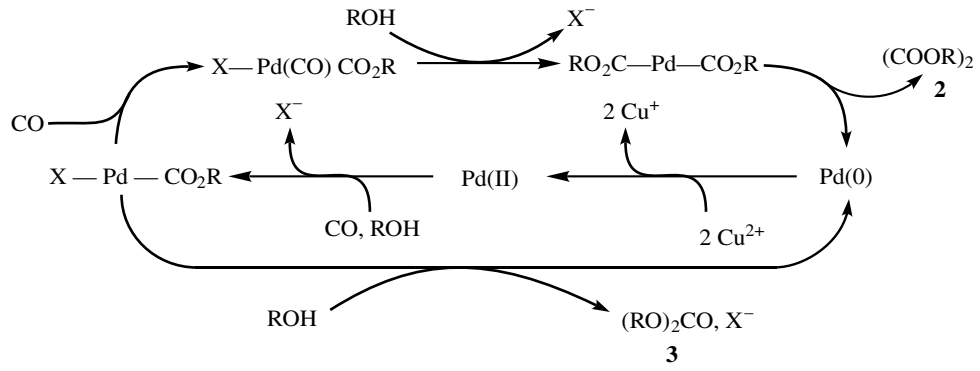
In the gas phase reaction, CO pressure, the concentration of alkyl nitrite, and the concentration of NO showed different effects on the rates of oxalate and/or carbonate formation from those observed in the liquid phase reaction; thus the detail of the reaction mechanism is still unclear.



Scheme 14

In Pd-catalyzed oxalate synthesis other than the palladium–alkyl nitrite system, an intramolecular coupling shown in **Scheme 7** was proposed as a reaction mechanism for oxalate formation. It has been observed that the rate of oxalate formation is first order to the CO pressure in other Wacker-type reactions as well as the palladium–alkyl nitrite system.

Following is the proposed mechanism for the Pd–Cu catalyst system based on the reported data to date (**Scheme 15**).[20]–[22]



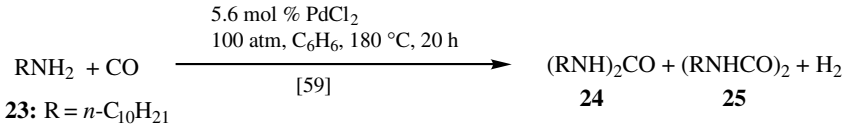
Scheme 15

The most obvious difference in the mechanisms between the palladium–alkyl nitrite system and the Wacker-type system (i.e., Pd–Cu system) is the oxidation state of active palladium species for oxalate formation, which is Pd(0) for the nitrite system and Pd(II) for the Wacker–type system.

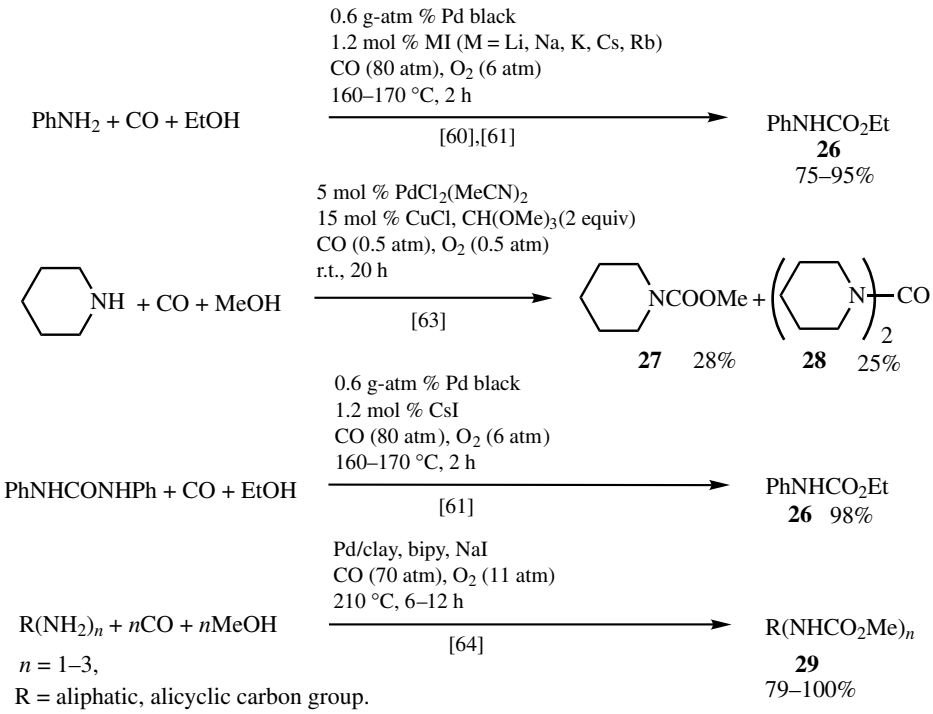
E. SYNTHESIS OF UREAS AND OXAMIDES BY CARBONYLATIVE OXIDATION UTILIZING NITROGEN-BASED NUCLEOPHILES

Urea **24** and oxamide **25** were formed by the reaction of carbon monoxide and amines **23** in the presence of $PdCl_2$, but metallic palladium seemed to be the true catalyst (**Scheme 16**).[59]

Carbamates **26** and **27** were readily synthesized in the presence of iodides in alkanol solvents (**Scheme 17**). [60]–[63] Urea was further alkoxycarbonylated to give carbamates in



Scheme 16



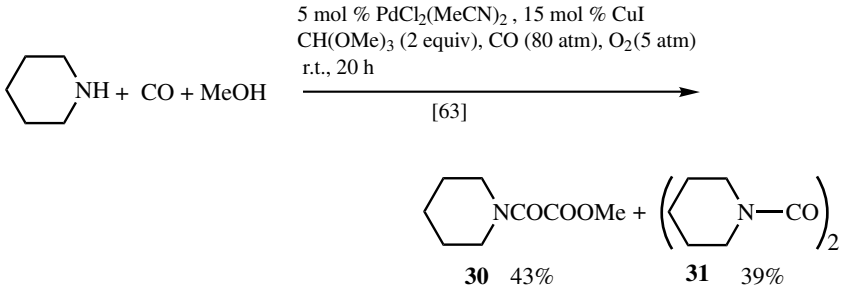
Scheme 17

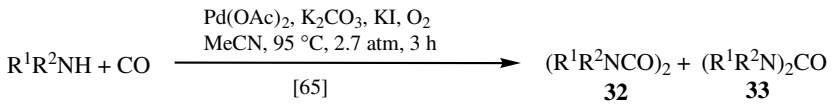
this reaction system.[61] Aliphatic and alicyclic mono-, di-, and triurethanes **29** were prepared from corresponding amines using Pd–clay as a catalyst in the presence of NaI and 2,2′-bipyridine. [64]

Oxamate **30** and oxamides **31** and **32** were obtained by similar reaction conditions (**Scheme 18**).[62],[63],[65]

These reactions also readily proceeded under Wacker-type reaction conditions (**Scheme 19**).[66]–[68]

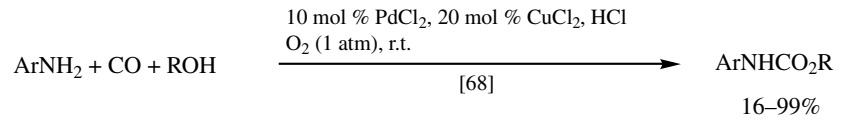
Cyclic carbamates **35**[30],[63] and oxamates **36**[30],[62],[63] were obtained from β-aminoalcohols (**Table 5**). The reaction mechanism for these reactions is considered a Pd(II)–Pd(0) redox system (**Scheme 20**).[30],[63]





R^1	R^2	**32** (%)	**33** (%)
Me	Me	68	0
—$(CH_2)_5$—		98	0
Et	H	12	71
n-Pr	H	12	87

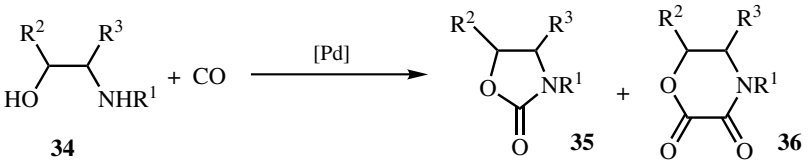
Scheme 18



Ar = *p*-MeC_6H_4, Ph, *p*-ClC_6H_4, *m*-$MeCOC_6H_4$, 2,5-$Me_2C_6H_3$, 3,5-$Me_2C_6H_3$, 2,6-$Me_2C_6H_3$
R = Me, Et

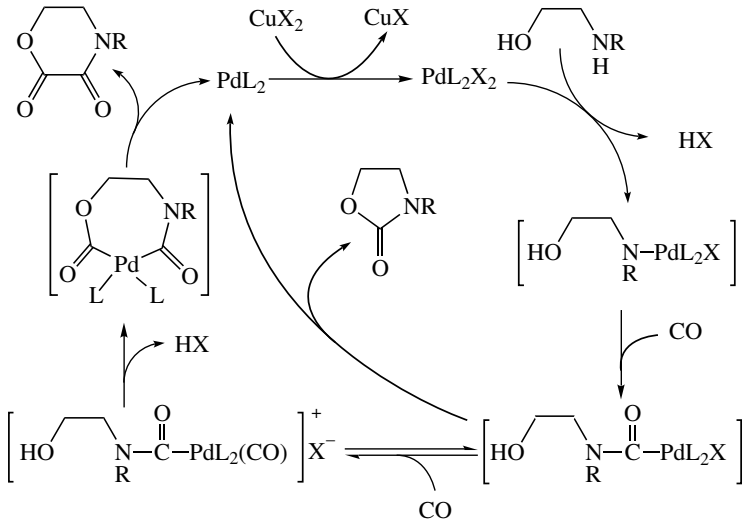
Scheme 19

TABLE 5. Pd-Catalyzed Carbonylative Oxidation of β-Aminoaalcohols



Carbon Number	β-Aminoalcohol **34**	R^1	R^2	R^3	Reaction Condition[a]	Yield(%) **35**		Yield(%) **36**	
2	**a**	H	H	H	A	**a**	65		
3	**b**	Me	H	H	B	**b**	77		
	b	Me	H	H	C	**b**	0–13	**b**	45–57
	b	Me	H	H	D	**b**	78	**b**	11
	b	Me	H	H	E	**b**	77		
	b	Me	H	H	F			**b**	95
4	**c**	H	H	(*R*)-Et	A	**c**	75		
	d	Et	H	H	E	**d**	76		
	d	Et	H	H	F			**d**	86
5	**e**	H	H	(*S*)-*i*-Pr	A	**e**	72		
	f	Me	H	(*R*)-Et	E	**f**	64		
	f	Me	H	(*R*)-Et	F			**f**	85
6	**g**	*n*-Bu	Me	H	B	**g**	95		
8	**h**	Ph	H	H	C	**h**	100		
9	**i**	Bn	H	H	F			**i**	85
	j	Me	Ph	H	F			**j**	82
	k	Me	H	(*S*)-Ph	F			**k**	83
12	**l**	*n*-Bu	Ph	H	B	**l**	94		
	m	*t*-Bu	Ph	H	B	**m**	83		

[a]Reaction conditions. A : 5 mol % $PdCl_2$ $(MeCN)_2$,25 mol % CuI, CO (80 atm), O_2 (5 atm), r.t., 6 h, MeCN.[63]
B : 4–10 mol % $PdCl_2$, $CuCl_2$(2 equiv), AcONa (2 equiv), CO (3 atm), 80 °C, overnight, DME.[30]
C : $PdCl_2$ (1 equiv), AcONa (2 equiv), CO(3 atm), r.t., overnight, DME.[30]
D : $PdCl_2$ (1 equiv), AcONa (2 equiv), CO(3 atm), 80 °C, overnight, DME.[30]
E : 5 mol % $PdCl_2(MeCN)_2$, CuI(1 equiv), CO and O_2 (1 atm), 50 °C, 20 h, MeCN.[63]
F : 5 mol % $PdCl_2$ $(MeCN)_2$, 25 mol % CuI, CO (80 atm), O_2 (5 atm), r.t., 20 h, MeCN.[63]



Scheme 20

F. SUMMARY

Since its discovery in the 1960s, the Pd-catalyzed oxidative carbonylation reaction has been widely studied and belongs to a category of "old" reactions. As we described in the present section, the development of the palladium–alkyl nitrite system widely extended its potential and applications.

From the viewpoint of green chemistry, this reaction has been studied continuously in order to solve environmental problems. For instance, DPC may be produced without methylene chloride by taking advantage of this oxidation. Carbonylative oxidation has the potential to be an indispensable chemical reaction, which will produce various chemicals in the future, because the raw materials, such as CO and methanol, can be produced from nonpetroleum resources.

The Pd-catalyzed oxidative carbonylation reaction is indeed an "old" reaction, but it keeps extending the areas of its practical application. In this sense, this reaction can be truly regarded as a "contemporary" reaction.

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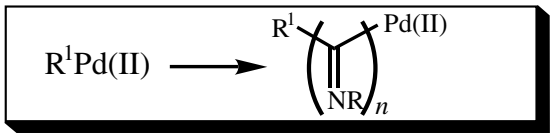

VI.8 Synthesis of Oligomeric and Polymeric Materials via Palladium-Catalyzed Successive Migratory Insertion of Isonitriles

YOSHIHIKO ITO and MICHINORI SUGINOME

Carbon monoxide and isonitrile, which have an isoelectronic structure and serve as π-acid ligand on transition metals, form various stable transition metal complexes. One of the most fundamental and important reactions with carbon monoxide and isonitrile in organometallic chemistry is their insertion into the carbon–metal bond of organometallic compounds (**Scheme 1**).

However, unlike carbon monoxide, isonitriles undergo multiple and successive insertion with some organotransition metal compounds to give poly(isonitrile)s, that is, poly(*N*-substituted iminomethylene)s. The polymerization of isonitriles was first reported with $Ni(CO)_4$ and $CO_2(CO)_8$ catalysts by a Japanese group,[1] followed by a Dutch group with Ni salts as catalysts.[2] Due to the restricted rotation around the polymer main chain, the poly(isonitrile)s have rigid helical structure, whose right-handed and left-handed helical conformations are established by optical resolution.[3],[4] The optically active, helical poly(isonitrile)s were also prepared by polymerization of optically active isonitrile monomers.[5] Moreover, screw-sense selective polymerization of achiral *tert*-butyl isonitrile was achieved by using Ni(II) catalysts complexed with optically active amines.[6] More recently, screw-sense selective living polymerization of achiral isonitriles has also been reported by use of (*R*)- or (*S*)-$[\eta^3$-$C_3H_5)Ni(OCOC(OCH_3)(C_6H_5)CF_3)]_2$ (**1**) (**Scheme 2**).[7]

Multiple, successive insertion of isonitriles into the palladium–carbon σ-bond has also been found with organopalladium(II)bis(phosphine) complexes. However, unlike the Ni- catalyzed polymerization, only single, double, and triple insertion reactions of isonitriles have been reported for Pd-mediated reactions. For instance, reaction of methylpalladium(II) complex **2** with cyclohexyl isonitrile in ratios of 1:1, 1:2, and 1:3 afforded selectively single (**3**), double (**4**), and triple (**5**) insertion products, respectively (**Scheme 3**).[8] However, no further insertion of cyclohexyl isonitrile to **5** took place. No reactivity of the triple insertion complex **5** was explained by the intramolecular coordination of the nitrogen atom of the third imino group, which formed a stable five-membered chelating palladium complex.

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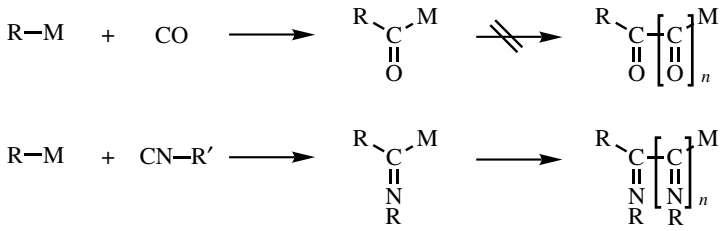
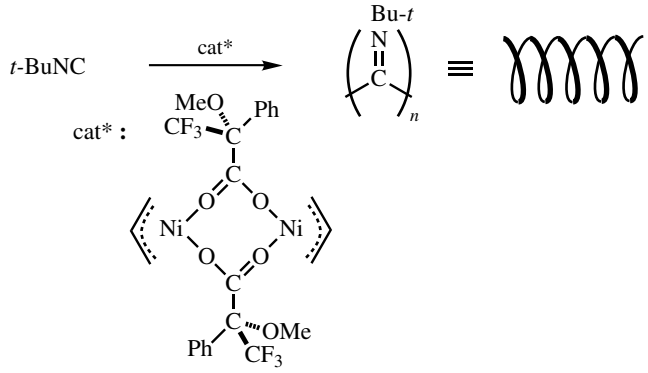


Scheme 1



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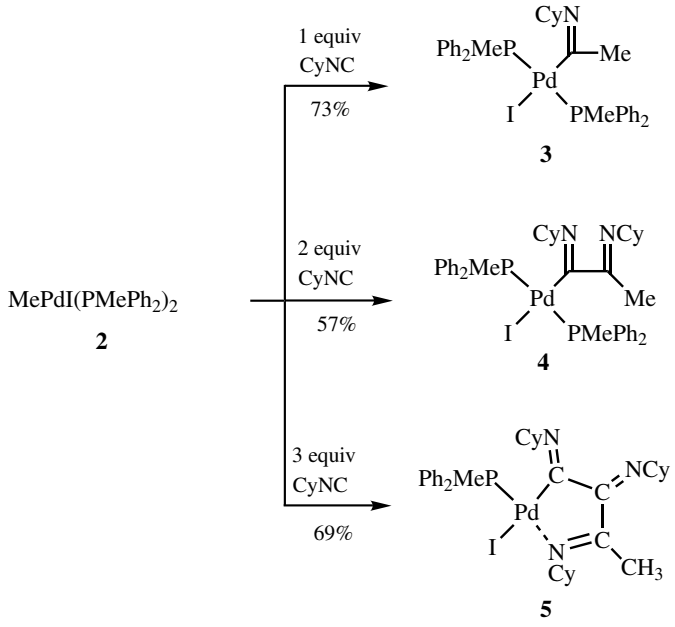
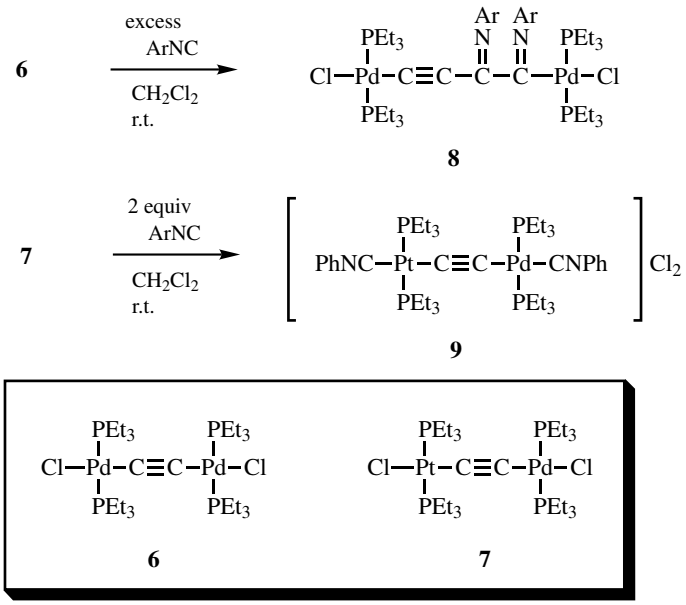
Scheme 2



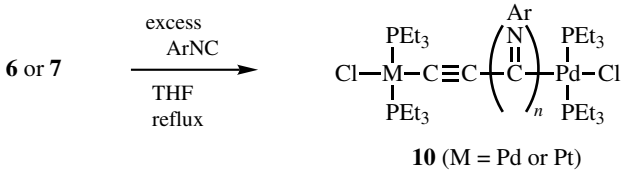
Scheme 3

Recent progress in polymerization of isonitriles with organopalladium(II) complexes is shown below. Although reactions of aryl isonitriles with μ-ethynediyl–dipalladium(II) **6** and a related Pd–Pt heterodinuclear complex **7** at room temperature (r.t.) did not afford poly(isonitrile)s, selective double insertion of the isonitrile into the Pd—C bond (giving **8**) or coordination of the isonitrile to the metal (giving **9**) occurred (**Scheme 4**).[9]–[11] Polymerization of the aryl isonitrile proceeded in the presence of those complexes in THF under reflux to give **10** with narrow molecular weight dispersion (**Scheme 5**). It should be noted that the μ-ethynediyl–bimetallic structure is crucial for attaining high catalytic activity and that the isonitriles insert into only the Pd—C bond with another metal–carbon bond left intact. In fact, structurally related alkynylpalladium complexes **11** and **12** completely failed to promote the polymerization reaction but gave the corresponding monoisonitrile insertion product selectively (**Scheme 6**). This method was successfully applied to the synthesis of block copolymers by virtue of the living nature of the polymerization, which involved isolable organopalladium intermediates.

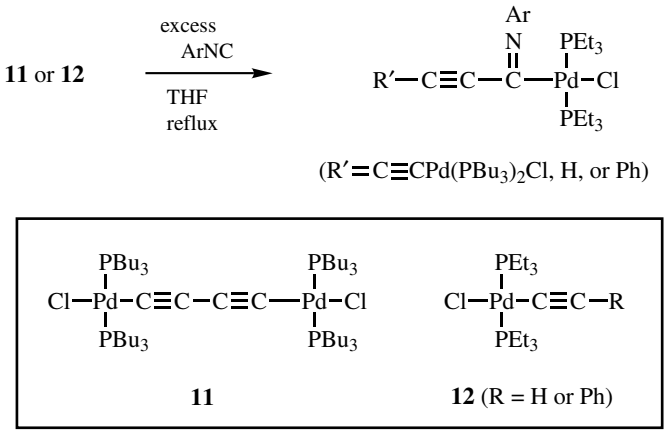
In the Pd-catalyzed polymerization of aryl isonitriles, the screw-sense of the helical structure was controlled by chiral groups introduced to the aryl moiety of the isonitriles.[12],[13] Thus, polymerization of (L)-menthyl ester of *p*- or *m*-isocyanobenzoic acid (**13**)



Scheme 4

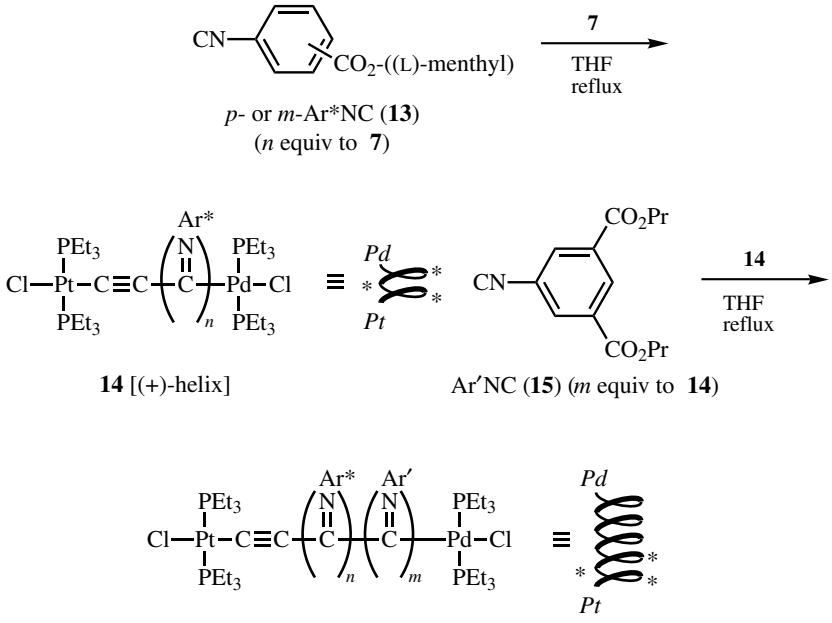


Scheme 5



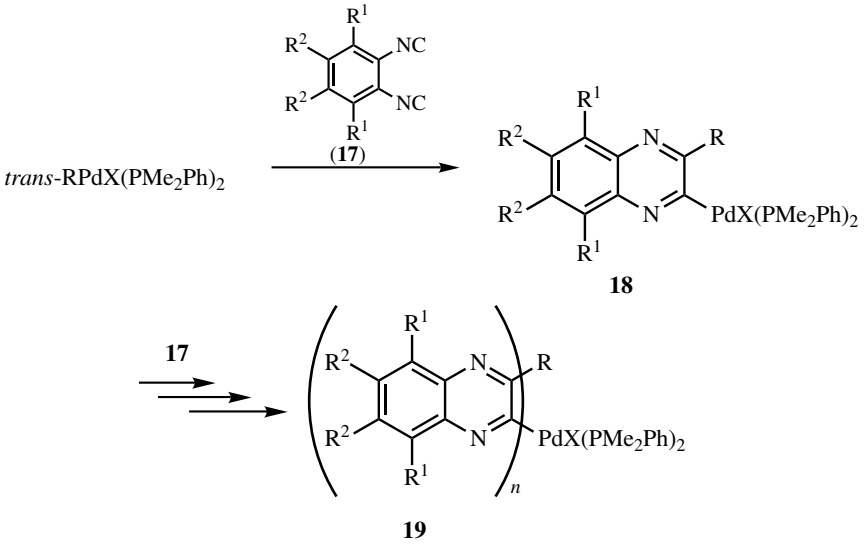
Scheme 6

afforded optically active poly(isonitriles) **14**, which exhibited positive optical rotations (**Scheme 7**). The specific rotation increased proportionally to the polymerization degree and reached a constant value at about 30 mer. The helical, living oligomers higher than 30 mer once isolated were able to promote the polymerization of achiral isonitriles, for example, diisopropyl 5-isocyano-1,3-benzenedicarboxylate (**15**), giving **16**. The optical rotation as well as circular dichroism measurements established that the screw-sense was maintained during the polymerization of the achiral monomer.



Scheme 7

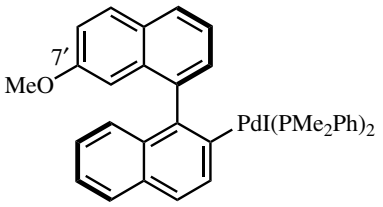
A similar successive insertion of isonitriles into a palladium–carbon bond is involved in Pd-catalyzed aromatizing polymerization of 1,2-diisocyanobenzenes.[14],[15] Repetition of the successive insertion of the two isocyano groups of 1,2-diisocyanobenzenes into the growing [oligoquinoxalinyl]palladium(II) leads to the formation of poly(quinoxalin-2,3-diyl)s, which has a palladium group at the polymer terminus of **19** (**Scheme 8**). The living palladium terminus can be utilized for either further polymerization or introduction of functionalities at the terminus of the polymer. *trans*-Organopalladium(II)bis(dimethylphenylphosphine) complex was the catalyst of choice for the polymerization of 3,6-disubstituted 1,2-diisocyanobenzenes **17′**.



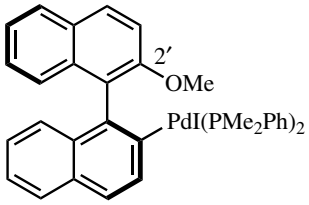
Scheme 8

The helical structure of (oligoquinoxalinyl)palladium(II) complexes was confirmed by optical resolution of a diastereomeric mixture of pentameric and hexameric 5,8-di-*p*-tolylquinoxaline oligomers **20**, which were produced by oligomerization of 3,6-di-*p*-tolyl-1,2-diisocyanobenzene **17′** with methylpalladium(II)bromide complex with chiral bis((*S*)-2-methylbutyl)phenylphosphine (**Scheme 9**).[16],[17] The right-handed and left-handed (oligoquinoxalinyl)palladium(II)bis(phosphine) complexes (*P*)-**21** and (*M*)-**21** thus prepared promoted polymerization of substituted 1,2-diisocyanobenzenes **17** with retention of the screw-sense of the respective initiating oligomers.

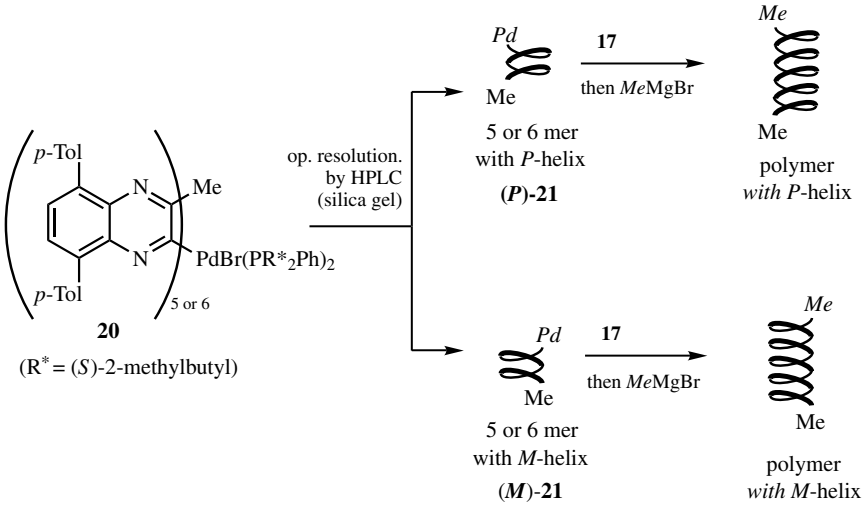
Highly screw-sense selective polymerization of 1,2-diisocyanobenzenes was accomplished by use of enantiomerically pure bis(phosphine)(1,1′-binaphth-2-yl)palladium(II) complexes **22** as initiators.[18],[19] The binaphthyl group that stays at the polymer end opposite to the living palladium terminus can control the screw-sense of the whole poly(quinoxalin-2,3-diyl) molecule. It should be remarked that the screw-sense selectivity crucially depended on substituents on the binaphthyl group of the initiator. For instance, 7′-methoxy derivative **22a** achieved almost complete screw-sense selectivity in the polymerization of **17**, whereas the 2′-methoxy derivative **22b** resulted in $<20\%$ selectivities.



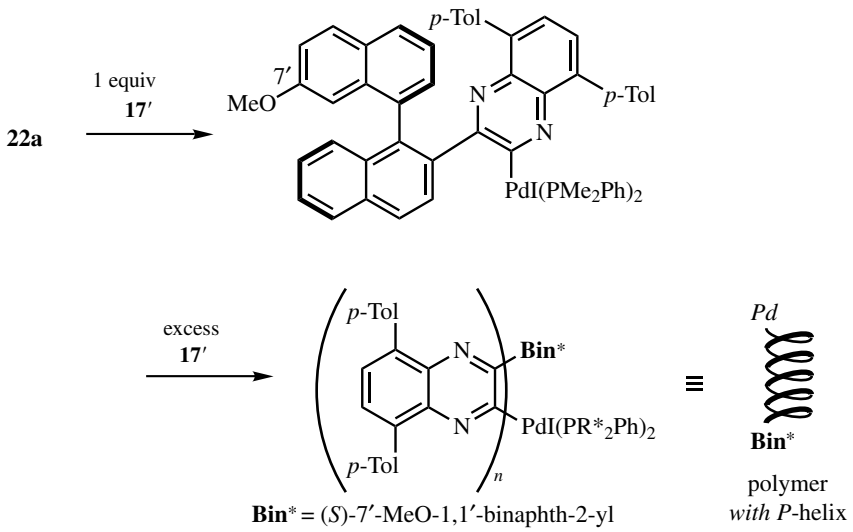
22a



22b

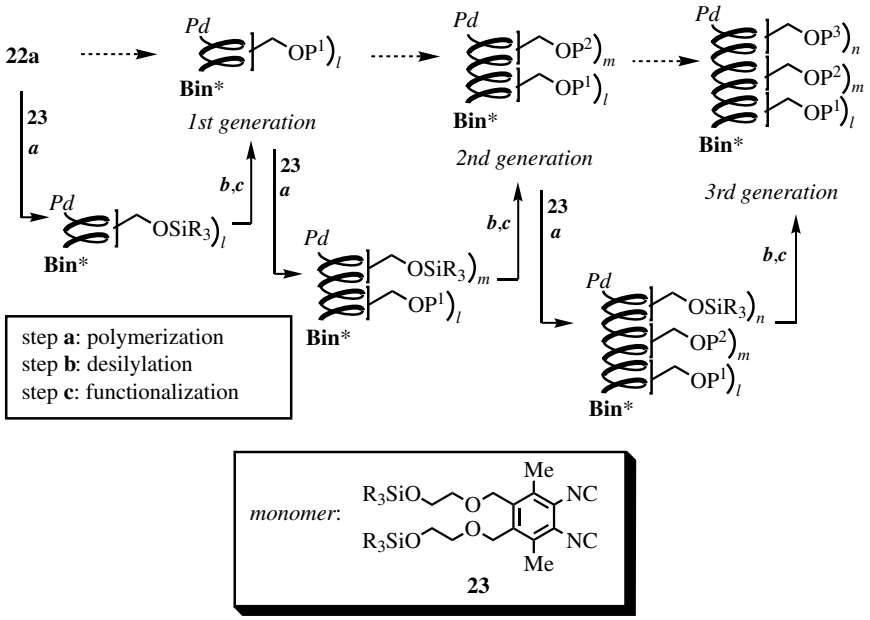


Scheme 9



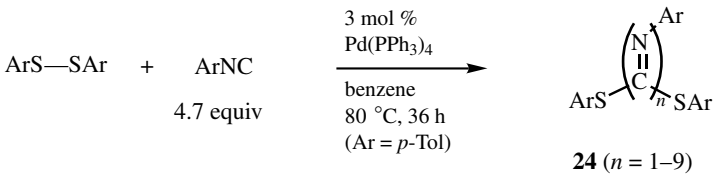
Scheme 10

The living polymerization was applied to the synthesis of amphiphilic block copolymers bearing hydrophobic as well as hydrophilic side chains.[20] Furthermore, by virtue of high stability of the living palladium intermediate, structural modification of the side chain on the quinoxaline monomer units was successfully carried out without any deterioration of the growing palladium moiety (**Scheme 11**).[21] This finding permitted the preparation of helical di- and tri-block copolymers from a sole monomer **23**, which possessed silyl-protected hydroxyalkyl side chains, through repetition of a sequence of polymerization, silyl-deprotection, and introduction of a variety of functionalities onto the hydroxy group.



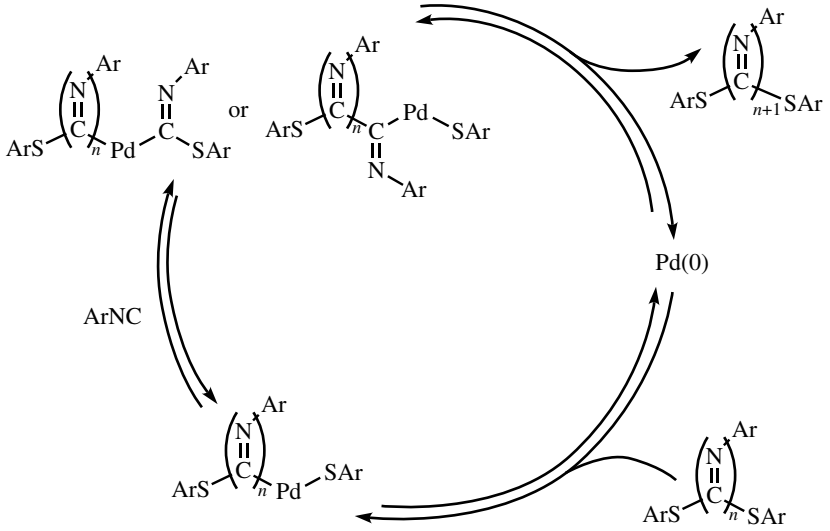
Scheme 11

Besides the above-mentioned living polymerizations mediated by the organopalladium(II) halides, successive insertion of isonitriles into sulfur–sulfur bonds catalyzed by palladium complexes was recently reported (**Scheme 12**).[22] Thus, in the presence of $Pd(PPh_3)_4$, reaction of di-*p*-tolyldisulfide with 4.7 equiv of *p*-tolyl isonitrile afforded a mixture of $ArS(C{=}N{-}Ar)_nSAr$ (Ar = *p*-Tol, *n* = 1–9) in good combined yield. Mechanistic investigations revealed that the oligomerization may involve a reversible oxidative addition of S—S or S—C bonds onto the palladium, followed by insertion of isonitriles into the resultant S—Pd or C—Pd bond, and subsequent reductive elimination(**Scheme 13**).



24 (*n* = 1–9)

Scheme 12



Scheme 13

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PART VII
Catalytic Hydrogenation and Other Palladium-Catalyzed Reactions via Hydropalladation, Metallopalladation, and Other Related *Syn* Addition Reactions without Carbon–Carbon Bond Formation or Cleavage

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VII.1 Background for Part VII

EI-ICHI NEGISHI

Oxidation and reduction are two of the most important chemical terms. At the same time, they are two of the most confusing. The most widely applicable definitions of oxidation and reduction are loss and gain of electrons, respectively. However, all chemical processes are "zero-sum games" with electrons, and no net reduction or oxidation is involved in a sense that, as some chemicals are oxidized, some others in the reaction system must be reduced to the same extent. Thus, in the reductive elimination of diorganylpalladium derivatives to produce the corresponding coupling products, the two organic groups to be coupled are collectively oxidized by two electrons, while Pd is reduced from an FOS (formal oxidation state) of $+2$ to 0. Traditionally, inorganic chemists have focused their attention more on metals, whereas metals are often mere extraneous reagents or catalysts for some organic chemists. In this sense, reductive elimination is primarily an inorganic chemist's term usually involving reduction of metals, such as Pd. This must, however, be counterbalanced by oxidation of some ligands, which is a main concern for synthetic organic chemists. It is essential to establish a clear and solid platform on which to deal with these often confusing terminologies.

In the oxidative addition reaction of $Pd(0)L_n$ with H_2 shown in **Scheme 1**, Pd is oxidized from an FOS of 0 to $+2$, while H_2, which serves, at least in this step, as an oxidant (!), is reduced by two elections. Specifically, each H atom is reduced from an FOS of 0 to -1. In the hydropalladation step, an olefin is reduced by two electrons (0 to -2), which is counterbalanced by two-electron oxidation of one H atom. In the reductive elimination step, the other H is oxidized by 2 electrons, while Pd is reduced from an FOS of $+2$ to 0 (**Scheme 1**).

In the rigid, if formal, analysis detailed above, one clearly sees that H is first *reduced* by Pd before it *reduces* olefins and hence gets *oxidized*. This simple analysis also clearly indicates that Pd can be regenerated in the original form and oxidation state. Thus, one readily sees that the overall process can, in principle, be catalytic in Pd, as it often is. It is advisable to apply the simple FOS analysis not only to minimize confusion associated with oxidation and reduction but also to gain some rational interpretations and, perhaps more importantly, ability to make some useful predictions. Although the FOS analysis is a mere formalism, which even permits variations in some grey zones, it nonetheless provides a logically sound rationalism by virtue of cancellation of ambiguities on both sides of an equation, that is, starting materials and products. In most instances, it is all that is

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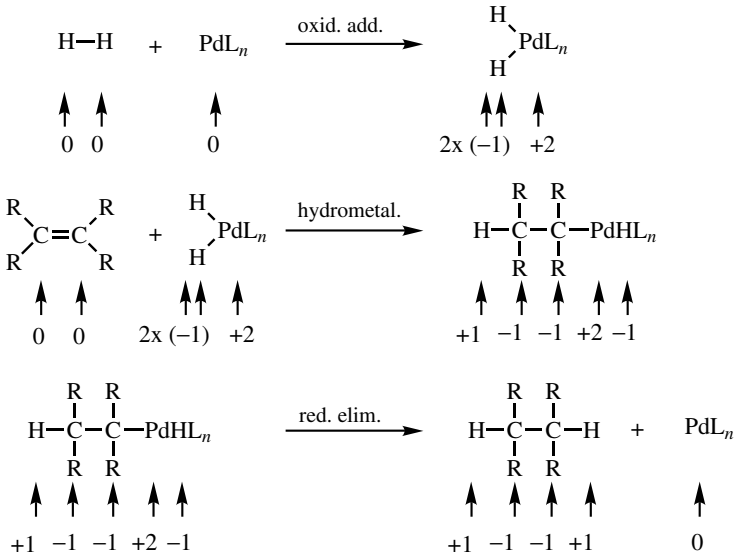
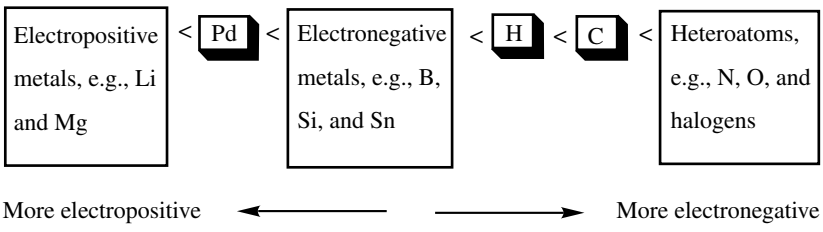


Note: In determining the FOS numbers for C atoms, it is assumed that R is a C group.

Scheme 1

needed for the purpose of organic synthesis. Just as a reminder, the FOS of any atom or group may be determined by merely considering the bond polarity of all bonds to the atom or group in consideration. In this Handbook the following somewhat arbitrary relative order of electronegativity is assumed (**Scheme 2**). As mentioned above, the arbitrariness has no serious consequences, although reasonable assignments of relative electronegativity values are desirable.

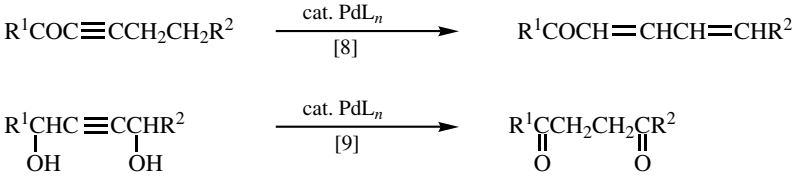


Scheme 2

Heterogeneous hydrogenation with H_2 and Pd catalysts is most probably the oldest application of Pd in organic synthesis, and it is still one of the most important Pd-catalyzed processes. Even though many aspects of heterogeneous Pd-catalyzed hydrogenation still remain unclear, it is nonetheless a mature field from the viewpoint of organic synthesis, which has been extensively reviewed and discussed.[1]–[4] So, a relatively concise discussion is presented in **Sect. VII.2.1**. Somewhat puzzlingly, its homogeneous counterpart has not received much attention from chemists,[5]–[7] especially in comparison with its

counterparts involving Rh and Ru. So, its discussion in **Sect. VII.2.2.1** is also brief. If one considers numerous possibilities for fine-tuning various parameters of Pd-catalyzed homogeneous hydrogenation, however, it is likely that this topic will receive a significantly increased level of attention in the future. One of the recent developments in this area is the use of hydrides and proton sources for effecting hydrogenation equivalents (**Sect. VII.2.2.2**). In general, such processes may be more expensive than hydrogenation with H_2. In many cases, however, they are expected to display some synthetic advantages in terms of selectivity, specificity, and so on. 1,4-Reduction or conjugate reduction of α,β-unsaturated carbonyl and related compounds may be viewed as a special class of hydrogenation in which carbonyl and related functional groups usually play significant roles. In view of its special significance in organic synthesis, it is discussed separately in **Sect. VII.2.3**.

One of the significant side reactions of hydrogenation is isomerization of organic substrates, such as alkenes and alkynes, which may or may not be accompanied by other processes, such as skeletal rearrangement and elimination. Although isomerization is often an unwanted side reaction, it can also be a synthetically useful process, as exemplified by the reactions shown in **Scheme 3**.[8],[9] Those cases that do not involve skeletal rearrangements are discussed in **Sect. VII.3**, while those involving skeletal rearrangements are discussed in **Part IX**.



Scheme 3

One of the recent trends in this area is to separate the hydropalladation step from the reductive elimination step. By so doing, one can now make use of organopalladium intermediates generated via hydropalladation in many subsequent processes of synthetic usefulness, as discussed throughout this Handbook. In these cases, hydride sources other than H_2 are usually needed. Practically all kinds of H-containing compounds have served as hydride sources. They include not only more obvious metal hydrides, such as $LiAlH_4$ and Bu_3SnH, but also organometals, such as *i*-Bu_3Al, hydrocarbons, such as alkynes and alkenes, active H compounds, such as alcohols and amines, and even some compounds that are normally viewed as proton sources, such as HOAc.

One obvious application is to use hydropalladation as a means of catalyzing other stoichiometric hydrometallation processes involving various metals, such as B, Al, Si, Sn, and even Zr. In addition to hydrometallation with respective metal hydrides, hydrogen transfer hydrometallation can be promoted by Pd catalysts, as discussed in **Sect. VII.4**.

As might be expected from simple MO considerations, the great majority, if not all, of known hydropalladation processes appear to involve strict syn addition, even though subsequent *cis-trans* isomerization may be observed. The scope of concerted *syn* addition involving Pd has been significantly expanded by the recognition and observation that many Pd–metal bonds including Pd—Si and Pd—Sn bonds can undergo similar addition reactions. Interestingly, in Pd-catalyzed hydrosilation, the crucial addition step may involve silylpalladation rather than hydropalladation, and the Pd—H bond may merely participate

in the reductive elimination step. Metallopalladation also permits stoichiometric introduction of two metals, which may be the same or different, as well as one metal and one carbon or heteroatom, as discussed in **Sect. VII.5**.

Finally, addition of Pd–heteroatom bonds to π-compounds is extensively discussed in **Part V**. With halogens, O, and N as heteroatoms, *anti* addition is often observed. However, *syn* addition is also possible and has, in fact, been observed. Those Pd–heteroatom addition reactions that are not discussed in earlier sections are discussed in **Sect. VII.6**.

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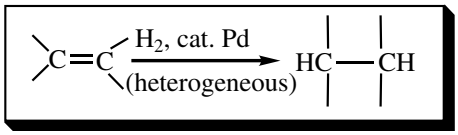

VII.2 Palladium-Catalyzed Hydrogenation

VII.2.1 Palladium-Catalyzed Heterogeneous Hydrogenation

ANTHONY O. KING, ROBERT D. LARSEN, and EI-ICHI NEGISHI

A. INTRODUCTION

A.i. General

As amply demonstrated in earlier parts (**Parts III–VI**), Pd-catalyzed reactions can tolerate a wide variety of functional groups, such as most of the carbonyl compounds including aldehydes and ketones, imines, nitriles, and nitro compounds. Many of them can be carried out in the presence of large excesses of solvent molecules, such as acetonitrile, EtOAc, and acetic acid. This, however, does not mean that Pd and its complexes are inert to those compounds containing various function groups. As discussed in **Sect. I.2**, Pd and its complexes are capable of reacting with essentially any class of organic and inorganic compounds including all of the heterofunctional groups mentioned above and all types of hydrocarbons. The latter includes even alkanes. One should be reminded here again that it is a matter of relative rates, structure of Pd and its complexes, reaction conditions, and so on. Under various conditions of catalytic hydrogenation using H_2 and either Pd metal on a support (heterogeneous hydrogenation) or soluble Pd complexes (homogeneous hydrogenation), a wide variety of organic compounds can indeed be reduced. In fact, Pd-catalyzed heterogeneous hydrogenation represents the first use of Pd in organic synthesis (**Sect. I.1**). It is quite striking and puzzling that, whereas Pd is probably the most widely used metal in heterogeneous catalytic hydrogenation, it currently is far less widely used than Rh or Ru in homogeneous catalytic hydrogenation. Since development of homogeneous catalytic hydrogenation in general is of relatively short history, future investigations may prove its Pd-catalyzed version to be much more widely applicable and useful than presently known.

As both heterogeneous and homogeneous catalytic hydrogenation and related reductions have been extensively and repeatedly reviewed,[1]–[11] their full-fledged discussion is not intended here. In this section, a brief summary of heterogeneous Pd-catalyzed hydrogenation and various specific examples reported mainly during the last decade are

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presented. Readers should also be reminded of the following sections on related topics in addition to other pertinent sections in **Part VII**.

A.ii. Brief Summary of Palladium-Catalyzed Heterogeneous Hydrogenation

A.ii.a. ***Scope with Respect to Substrates and Selection of Transition Metal Catalysts.*** Pd-catalyzed catalytic hydrogenation can be observed with a wide variety of carbon–carbon and other unsaturated bonds. The widely used substrates may be divided into the following three groups of compounds: (i) alkynes, alkenes including dienes and higher polyenes, and arenes; (ii) carbonyl compounds including acyl halides, aldehydes, ketones, carboxylic acids, esters, and amides; and (iii) nitrogen-containing multiple bonds, such as nitriles, imines, and nitro and nitroso compounds. In many of these cases, Pd is either the most satisfactory or one of the most satisfactory catalysts. There are, however, at least four other transition metals—Pt, Rh, Ru, and Ni—which not only have been widely used but also are superior to Pd in some cases. In yet other cases, Pd is practically ineffective, and other catalysts must therefore be used. For example, most esters and amides are not readily reduced to alcohols and amines, respectively, with Pd catalysts, and other catalysts, such as $CuCrO_4$, are typically employed. The information summarized in **Table 1** is intended to provide some guidelines for selecting a suitable catalyst in serious cases. It should be emphasized, however, that many exceptions and variations exist so that the final catalyst selection may require experimental optimization.

TABLE 1. Scope and Limitations of Pd-Catalyzed Heterogeneous Hydrogenation and Alternatives

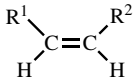
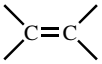
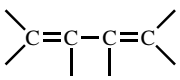
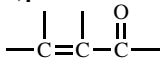
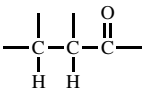
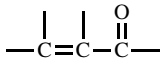
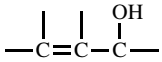
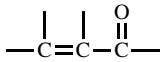
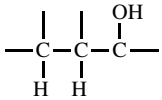
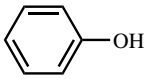
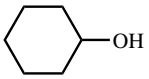
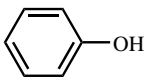
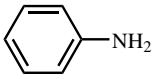
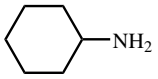
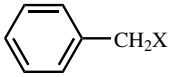
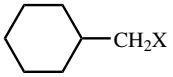
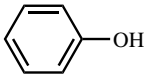
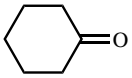
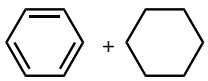
Section Number	Substrates	Products	Heterogeneous Catalysts[a]	
			Pd	Other Metals
B	Alkynes			
	$R^1C{\equiv}CR^2$		Generally satisfactory (Lindlar cat.)	
	$R^1C{\equiv}CR^2$	$R^1CH_2CH_2R^2$	Generally satisfactory	Pt, Rh, Ru
C	Alkenes			
			Generally satisfactory	Pt, Rh, Ru Ni, Ir
		Alkanes	Generally satisfactory	Pt, Rh, Ru Ni, Ir

TABLE 1. (*Continued*)

Section Number	Substrates	Products	Heterogeneous Catalysts: Pd	Heterogeneous Catalysts: Other Metals
	α,β-Unsaturated CO Derivtives			
			Generally satisfactory (**Sect. VII.2.3**)	
			Ineffective	Pt, etc.
			Ineffective	Pt, etc.
I.	**Arenes (Hydrogenation)**			
			Can be used	Pt, Ru, Ni, etc.
			Can be used	Rh, etc.
			Ineffective	Pt, Ir, etc.
			Ineffective	Rh, Ru, etc.
			Ineffective	Rh, Ru, Pt, etc.
			Can be used	
	Arenes (Dehydrogenation)			
			Generally satisfactory	
			Generally satisfactory	Pt, etc.

(*Continued*)

TABLE 1. (*Continued*)

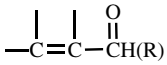
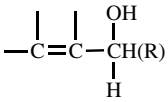
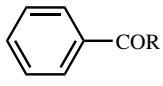
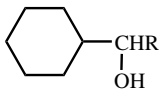
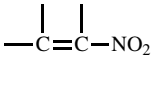
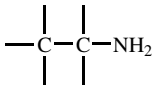
Section Number	Substrates	Products	Heterogeneous Catalysts: Pd	Heterogeneous Catalysts: Other Metals
D.	**Carbonyl Compounds**			
	RCOCl	RCHO	Generally satisfactory **Sect. VI.2.4** (Rosenmund red.)	
	RCHO (R = alkyl)	RCH_2OH	Ineffective	Ru, Pt, etc.
			Ineffective	Pt, etc.
	ArCHO	$ArCH_2OH$	Generally satisfactory	
	ArCHO	$ArCH_3$	Generally satisfactory (use of HOAc)	
	$R^1R^2C{=}O$ (R^1, R^2 = alkyl)	R^1R^2CHOH	Ineffective	Ru, Rh, Pt, etc.
	ArCOR		Generally satisfactory	
			Ineffective	Rh, etc.
	R^1COOR^2	R^1CH_2OH	Ineffective	$CuCrO_4$, etc.
	R^1CONR_2	$R^1CH_2NR_2$	Ineffective	$CuCrO_4$, etc.

TABLE 1. (*Continued*)

Section Number	Substrates	Products	Heterogeneous Catalysts: Pd	Heterogeneous Catalysts: Other Metals
F.	**Nitriles**			
	RCN (R = alkyl)	RCH_2NH_2	Generally satisfactory	Rh, Pt, etc.
	ArCN	$ArCH_2NH_2$	Generally satisfactory	Pt, Ni, etc.
	ArCN	ArCHO	Can be used	
E.	**Imines**			
	$R^1R^2C{=}NR$	R^1R^2CHNHR	Generally satisfactory (reductive alkylation)	Pt, etc.
G.	**Oximes**			
	$R^1R^2C{=}NOH$	$R^1R^2CHNHOH$	Generally satisfactory	Rh, etc.
	$R^1R^2C{=}NOH$	$R^1R^2CHNH_2$	Can be used	Rh, etc.
H.	**Nitro and Nitroso Compounds**			
	RNO_2 (R = alkyl)	$R^1R^2CHNHOH$	Generally satisfactory	Pt, Rh, etc.
	$ArNO_2$	$ArNH_2$	Generally satisfactory	Pt, etc.
			Generally satisfactory	

(*Continued*)

TABLE 1. (*Continued*)

Section Number	Substrates	Products	Heterogeneous Catalysts	
			Pd	Other Metals
	$ArNO_2$	ArNHOH	Can be used	Pt, Ir, etc.
	ArNO	$ArNH_2$	Generally satisfactory	Pt, etc.
	R^1R^2CHNO	$R^1R^2CHNH_2$	Generally satisfactory	Pt, etc.

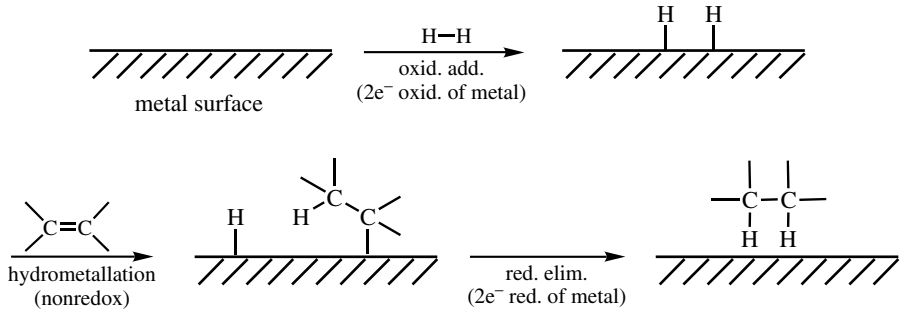
[a]Highlighted boxes indicate the preferred catalysts.

A.ii.b. ***Selection of Supports, Additives, Solvents, and Other Parameters.*** In most cases of Pd-catalyzed heterogeneous hydrogenation, catalysts are used as mixtures of Pd and supports. In some cases, they may be further mixed with some additives. To attain a high catalytic activity, Pd must be used as a dispersion on fine particles of a support. As summarized in **Sect. II.2.1**, activated carbon, alumina, silica, and alkaline earth metal carbonates and sulfates are some of the most commonly used support materials. Many preformulated mixtures of Pd on these supports are commercially available in different particle sizes and Pd contents ranging from about 1 to 30 wt %. Activated carbon generally provides the largest surface areas per weight, leading to high catalyst activities. In principle, when a high catalyst activity is desired, Pd on activated carbon of small particle sizes and high C/Pd ratios may be recommended. In reality, however, some other factors, such as acidity, basicity, and other chemical properties of support materials, catalyst attrition resistance, and other technical aspects, such as ease of filtration and so on, must also be considered. In many cases, selectivity is a more significant factor than reactivity. In such cases, the use of other support materials, such as alumina and alkaline earth metal carbonates, becomes important. Further suppression of catalyst reactivity may be necessary in some cases. Poisoning with additives as in the case of Lindlar's catalyst (Pd on $CaCO_3$ with Pb),[12] the use of sulfided carbon as a support, and the use of amine bases, such as quinoline and pyridine, have been shown to be effective to this end.

Pd-catalyzed heterogeneous hydrogenation may be carried out without any solvent. In many cases, however, the use of solvents is desirable or even necessary. A wide range of solvents ranging from nonpolar hydrocarbons, (e.g., hexane) to highly polar water, HOAc, MeOH, EtOH, and DMF as well as various others of intermediate polarity, such as THF, dioxane, EtOAc, acetone, and MeCN, have been used.

In selecting various factors and parameters, it is useful to recall that reduction involves acquisition of electrons by substrates. Consequently, any electron-withdrawing

influences on substrates should, in principle, promote reduction, and the opposite should be true with electron-donating influences. The resistance to reduction of carboxylate anions and rate-decreasing effects of bases may readily be explained by resorting to this simple principle. Likewise, interaction of substrates with acids should generally accelerate reduction, and the use of HOAc, for example, may be associated with such favorable effects among others. It should be pointed out, however, that Pd-catalyzed hydrogenation, like most of the other Pd-catalyzed reactions, involves a series of reductive and oxidative microsteps, which add up to overall reduction of the substrates at the expense of H_2, which is oxidized in the process. Depending on which of the microsteps is rate determining and/or of critical importance, the effects of various factors may manifest themselves in either direction. It is clearly desirable to be able to predict the effects of various factors and parameters based on satisfactory understanding of mechanistic details including both kinetics and thermodynamics. In reality, many detailed aspects of the mechanism of heterogeneous catalytic hydrogenation are still unclear. Even so, it is generally accepted that the mechanism involves the following three microsteps: (i) The metal (e.g., Pd) undergoes oxidative addition with H_2, that is, oxidation of the metal or reduction of H_2. (ii) The metal–H bond undergoes hydrometallation with the substrates to generate organometallic intermediates (nonredox process). (iii) Reductive elimination of organometallic intermediates releases the reduction products with concomitant regeneration of the catalyst, that is, reduction of the metal.[1]–[11] These microsteps are schematically shown in **Scheme 1**. This scheme lacks many detailed aspects. Nonetheless, it provides a crude and yet potentially useful basis for rational thinking and predictions.

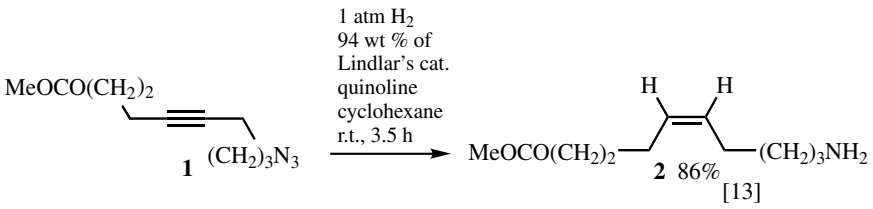


Scheme 1

B. HYDROGENATION OF ALKYNES

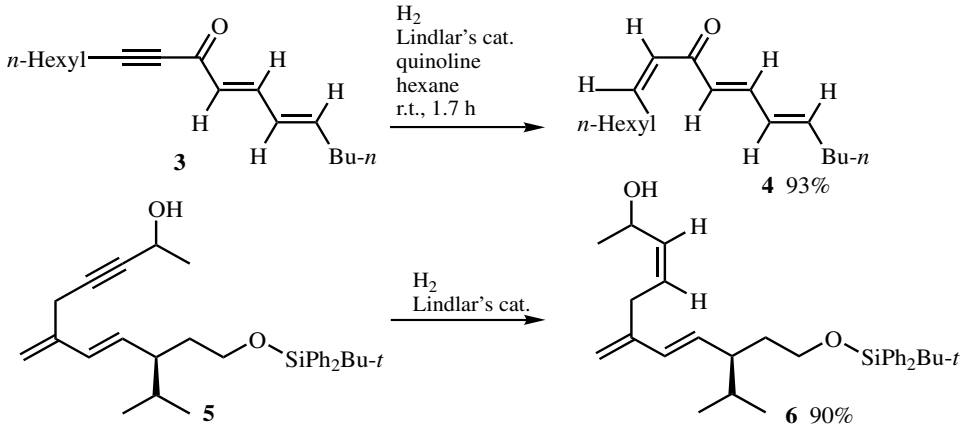
Heterogeneous Pd catalysts are well suited for the hydrogenation of alkynes to either *cis*-olefins or -alkanes. The selective reduction of alkynes to *cis*-olefins can generally be carried out using the well-known Lindlar's catalyst (Pb-doped $Pd/CaCO_3$)[12] in the presence or absence of a nitrogen- or sulfur-containing additive such as quinoline or thiophene. The reduction is quite mild and selective, and therefore many different functional groups can be tolerated. However, the reaction still must be stopped at about 1 equiv of H_2 uptake in order to minimize over-reduction. Even with careful monitoring of the reaction, the hydrogenation of an alkyne may still generate small amounts of the

trans-olefin and over-reduced products. Even with the low reactivity of Lindlar's catalyst, one functional group that reduces as readily as the alkyne function is the azide group. Thus, the azide and alkyne functional groups in **1** were reduced concomitantly (**Scheme 2**).[13]

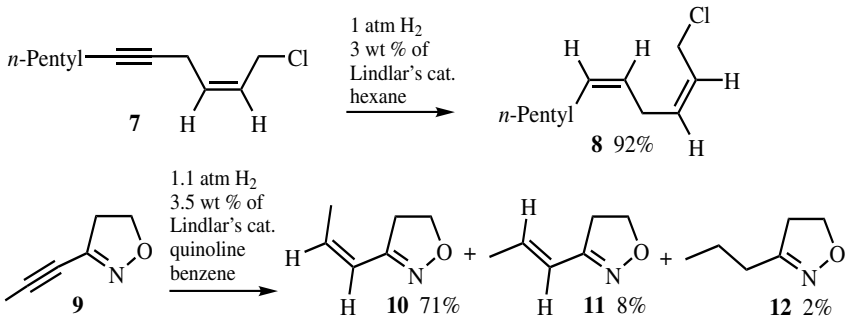


Scheme 2

The conjugated diene moieties in **3** and **5** were not reduced (**Scheme 3**).[14] Many heteroatom functional groups can be tolerated in this reduction. Thus, for example, allylic chlorides, such as **7**, are not competitively reduced.[15],[16] Even the comparatively labile imine and N—O bonds in **9** were not hydrogenated (**Scheme 4**).[17]



Scheme 3



Scheme 4

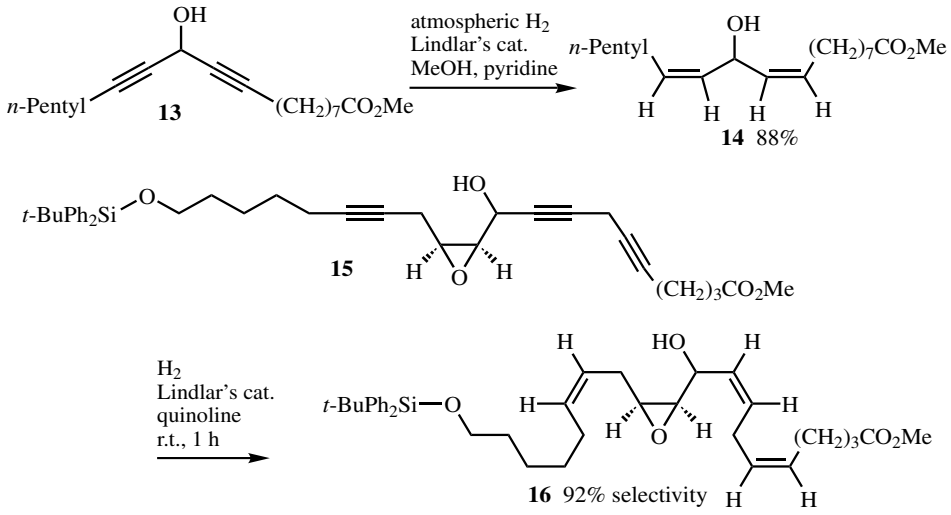
The reduction of substrates carrying multiple triple bonds provided products with multiple *cis* double bonds (**Scheme 5**).[18],[19]

Conjugated diene and triene could also be prepared from the corresponding enyne and dienyne, respectively (**Scheme 6**).[20],[21]

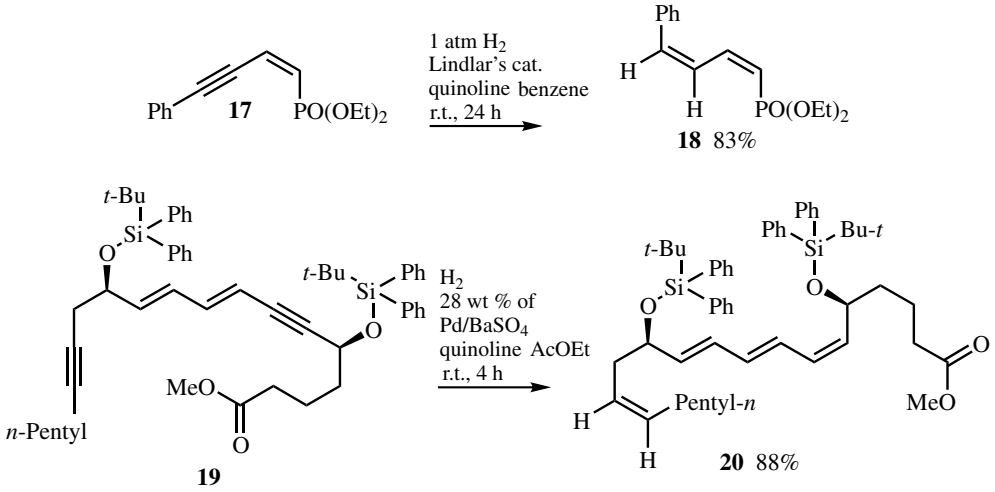
Reduction of aryl alkynes provided styrene derivatives (**Scheme 7**).[22] When the hydroxy group in **21** was protected with a *t*-$BuMe_2Si$ group, the use of $Pd/BaSO_4$ as the catalyst gave even better yield of the *cis* product.

Further shown in **Scheme 8** are examples that utilized $Pd/BaSO_4$ as the catalyst.[23]–[25]

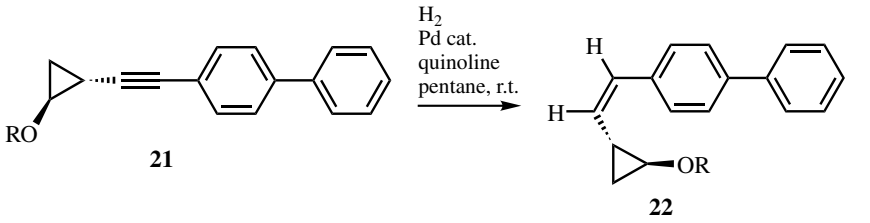
Other less frequently used supports include Al_2O_3[26] or SiO_2 doped with Hg[27] (**Scheme 9**).



Scheme 5



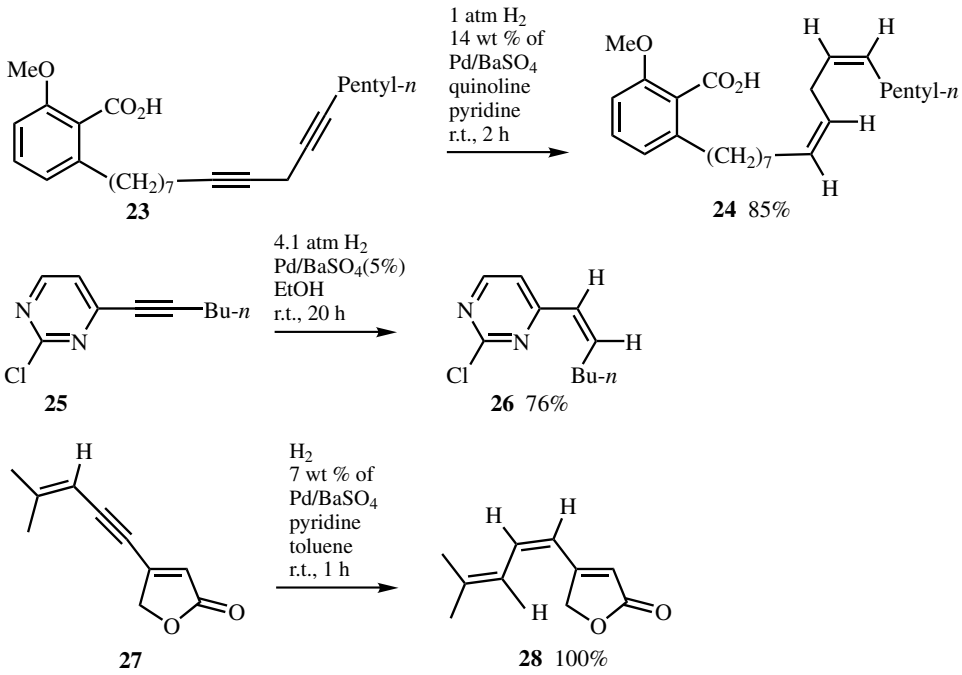
Scheme 6



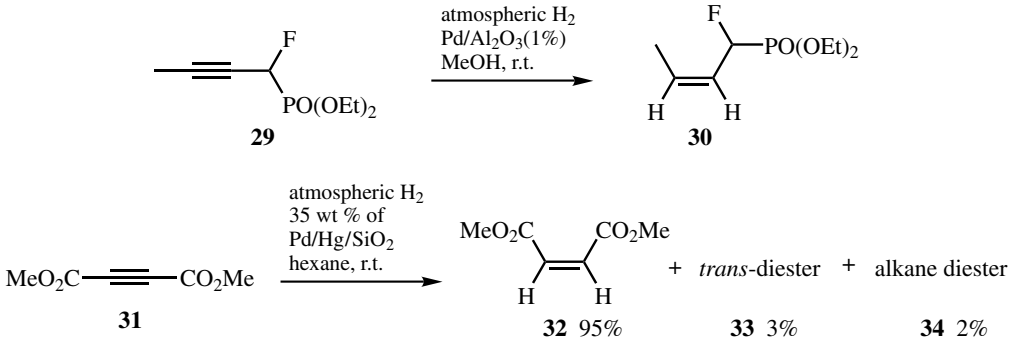
R = Et 76% yield with Lindlar's catalyst

R = $SiMe_2Bu$-*t* 93% yield with $Pd/BaSO_4$

Scheme 7



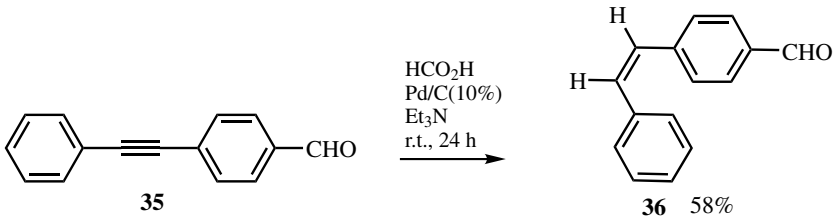
Scheme 8



Scheme 9

Pd metal deposited on borohydride exchange resin (BER) has been used as a catalyst to reduce various alkynes to alkenes in essentially quantitative yields.[28] Ultrasound was also reported to benefit the selective hydrogenation of alkynes to alkenes by decreasing the reduction times from 8–20 h to 0.5–4 h.[29]

Under transfer hydrogenation conditions with formic acid, the reduction of alkyne **35** gave *cis*-olefin **36** in moderate yield (**Scheme 10**).[30] Overhydrogenation is a problem under these reaction conditions with many substrates.

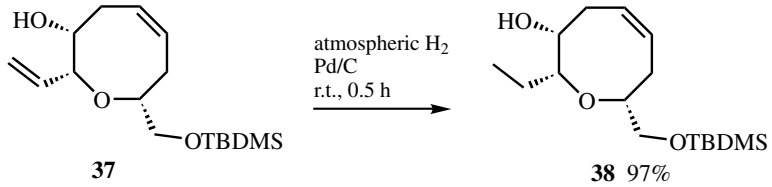


35 **36** 58%

Scheme 10

C. HYDROGENATION OF ALKENES

The hydrogenation of an alkene to an alkane can be accomplished with heterogeneous Pd catalyst under a variety of conditions. Less substituted double bonds are hydrogenated more rapidly (**Scheme 11**).[31] Alcoholic solvents[32],[33] are used often, but many nonpolar aprotic solvents, such as EtOAc and THF, are also common[34],[35] (**Scheme 12**).



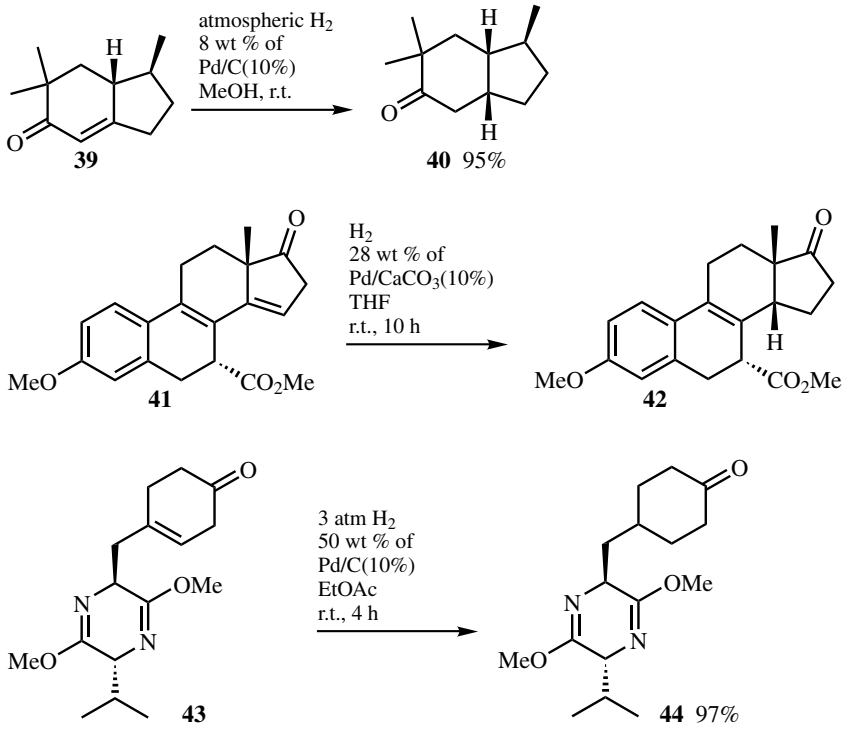
37 **38** 97%

Scheme 11

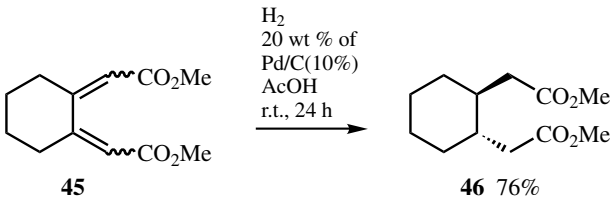
In limited cases the use of polar aprotic solvents, such as DMF, has also been described.[36] In AcOH the reduction of the exocyclic diene **45** gave the *trans*-substituted cyclohexane **46** in 76% yield (**Scheme 13**).[37]

Unlike **45**, the hydrogenation of the dienyl anhydride **47** gave the 1,4-reduction product **48** instead (**Scheme 14**).[38] Product **48** resisted further hydrogenation under a variety of reaction conditions. The olefin was reduced only after converting it to its diester. The hydrogenation of a 1,3-diene can sometimes lead to a mixture of monoolefins, which may not be desirable.

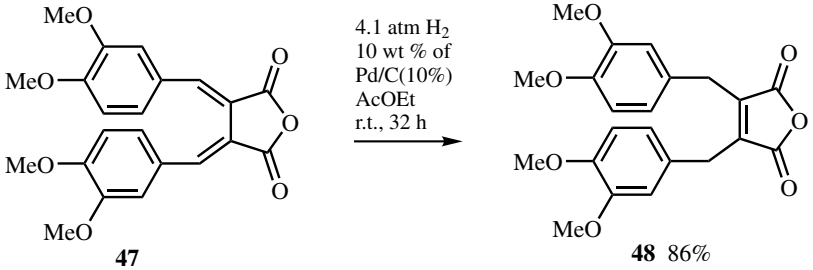
Although hydrogenation of a tetrasubstituted olefin can be carried out selectively in a *cis* fashion,[39] isomerization of the double bond prior to hydrogenation is also common especially with hindered olefins (**Scheme 15**).[40],[41] Thus, hydrogenation of both **51** and **54** gave substantial amounts of the *trans*-substituted products.



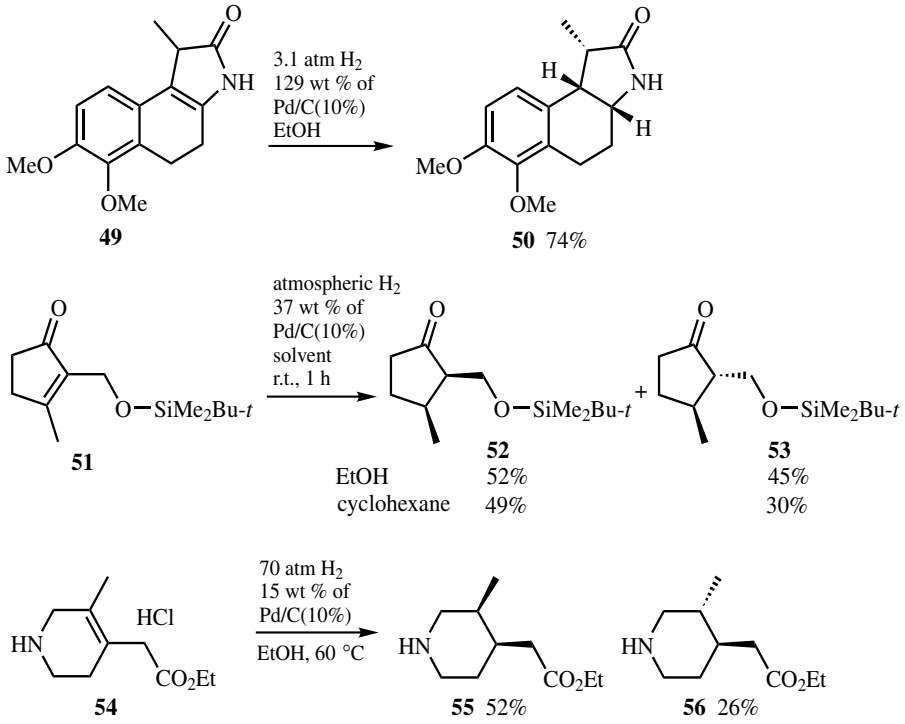
Scheme 12



Scheme 13



Scheme 14

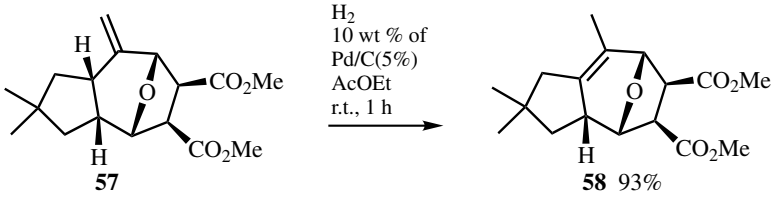


Scheme 15

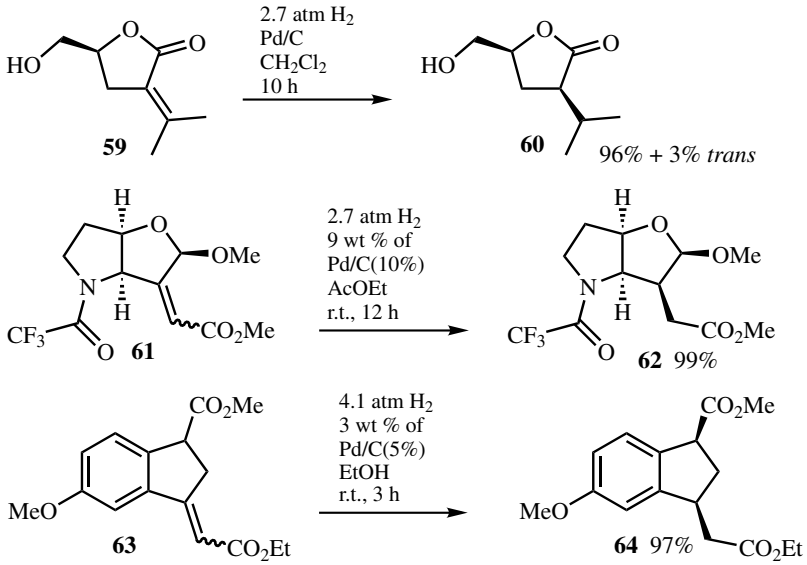
Some olefins may isomerize under the hydrogenation conditions to a less catalyst-accessible position, resulting only in rearrangement with no reduction. Thus, the olefin in **57** isomerized to **58** with Pd/C, and **58** was reduced only when Pt/C catalyst was used (**Scheme 16**).[42]

Diastereoselective hydrogenation of double bonds has been utilized to prepare many chiral substrates. The examples in **Scheme 17** show three of the many reactions in the literature.[43]–[45]

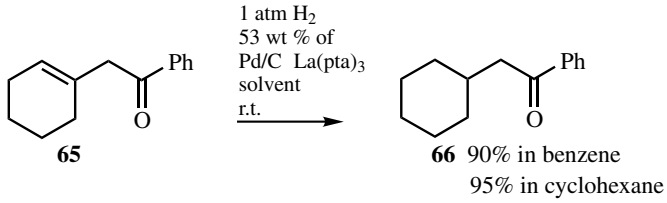
The use of lanthanide *tris*-β-diketonates as additives to inhibit the reduction of aryl ketone functional group was reported (**Scheme 18**).[46] In the presence of the La complex, the trisubstituted cyclohexenyl olefin **65** was reduced selectively in 90–95% yield. Without La(pta)$_3$ the alcohol was obtained as the major product.



Scheme 16



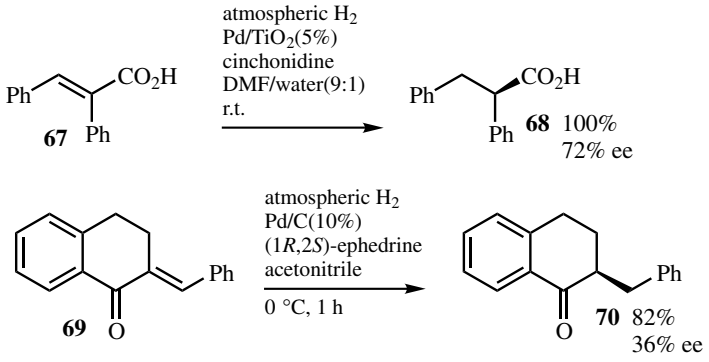
Scheme 17



Scheme 18

The use of a chiral modifier, such as cinchonidine or ephedrine, with Pd/C gives modest asymmetric induction in a few cases (**Scheme 19**).[47],[48]

Also, the use of enoate reductase in conjunction with Pd/C modified with a fluorine-containing surfactant (such as Zonyl^{R}-FSC) was reported for the asymmetric hydrogenation

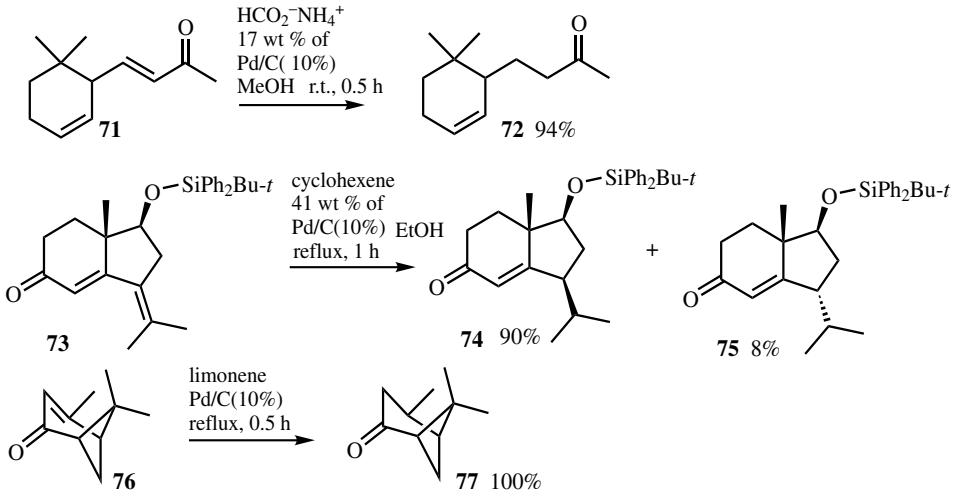


Scheme 19

of tiglic acid in excellent yield and >96% ee.[49] When this hydrogenation method was used on 4-methyl-2-oxopentanoic acid, 95% ee of the α-hydroxy acid was obtained.

A heterogeneous catalyst prepared by the deposition of Pd on crosslinked poly(ethyleneimine) polymer has shown interesting properties. This catalyst could mediate the hydrogenation of 2-pentyne to *cis*-2-pentene. Interestingly, when benzonitrile was added to complex with the Pd on the support, *trans*-2-pentene was produced selectively instead. This complete reversal of selectivity has never been observed with other catalysts.[50],[51]

The transfer hydrogenation of an olefin can be carried out using a variety of hydrogen donors including formate,[52],[53] cyclohexene,[54] and limonene[55] (**Scheme 20**).



Scheme 20

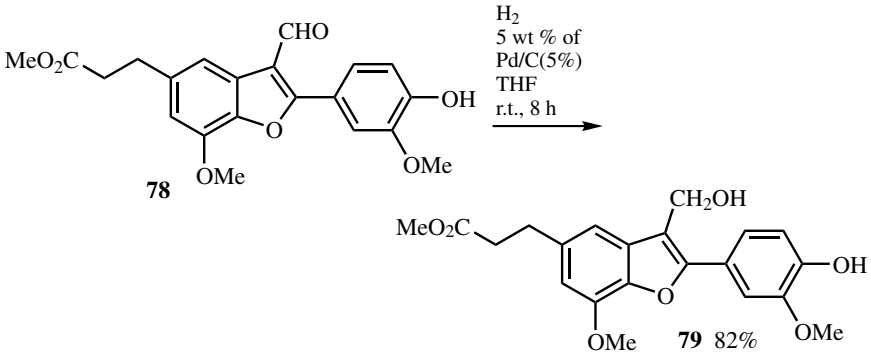
The selective reduction of the conjugated enone olefin was observed with **71** to give unconjugated enone **72** in excellent yield. The conjugated dienone **73** was only reduced at the γ,δ double bond with good stereoselectivity using cyclohexene as the hydrogen donor. Similar selectivity was observed in the reduction of the steroidal 4,6-dien-3-one system to give the conjugated 4-en-3-one in 95% yield.[56] Enone **76** was reduced to ketone **77** in quantitative yield with limonene as the hydrogen donor.

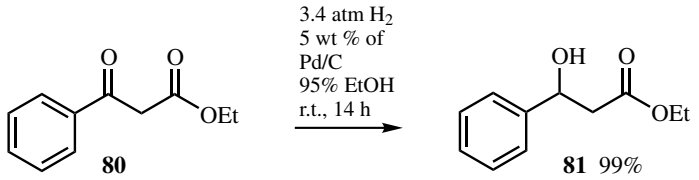
D. HYDROGENATION OF ALDEHYDES AND KETONES

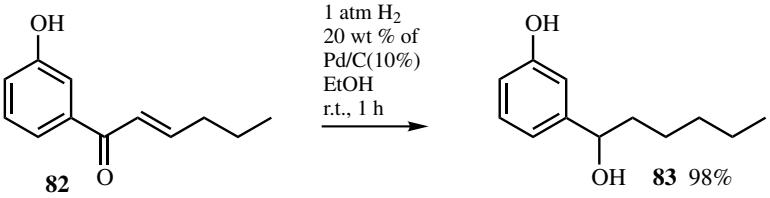
Aromatic aldehydes and ketones can readily be hydrogenated to benzylic alcohols or even hydrogenolyzed to aryl alkanes with Pd catalysts under an atmosphere of hydrogen (**Scheme 21**).[57]–[60]

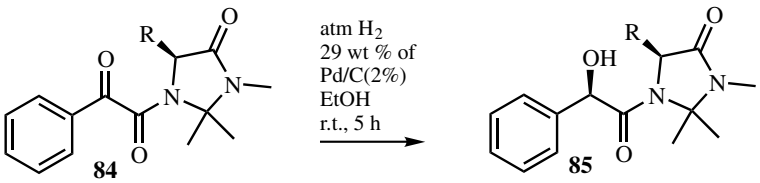
The hydrogenation of alkyl aldehydes or ketones is generally very sluggish but certain conjugated enones and α-keto acids could be reduced to the alcohols (**Scheme 22**).[61]–[65]

Hydrogenation of an alkyl aldehyde or ketone in the presence of an alcohol can lead to a dialkyl ether (**Scheme 23**).[66] In the presence of a primary or secondary amine or amide, the hydrogenation of alkyl ketones resulted in reductive amination.



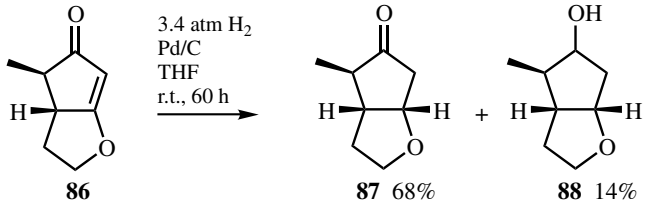




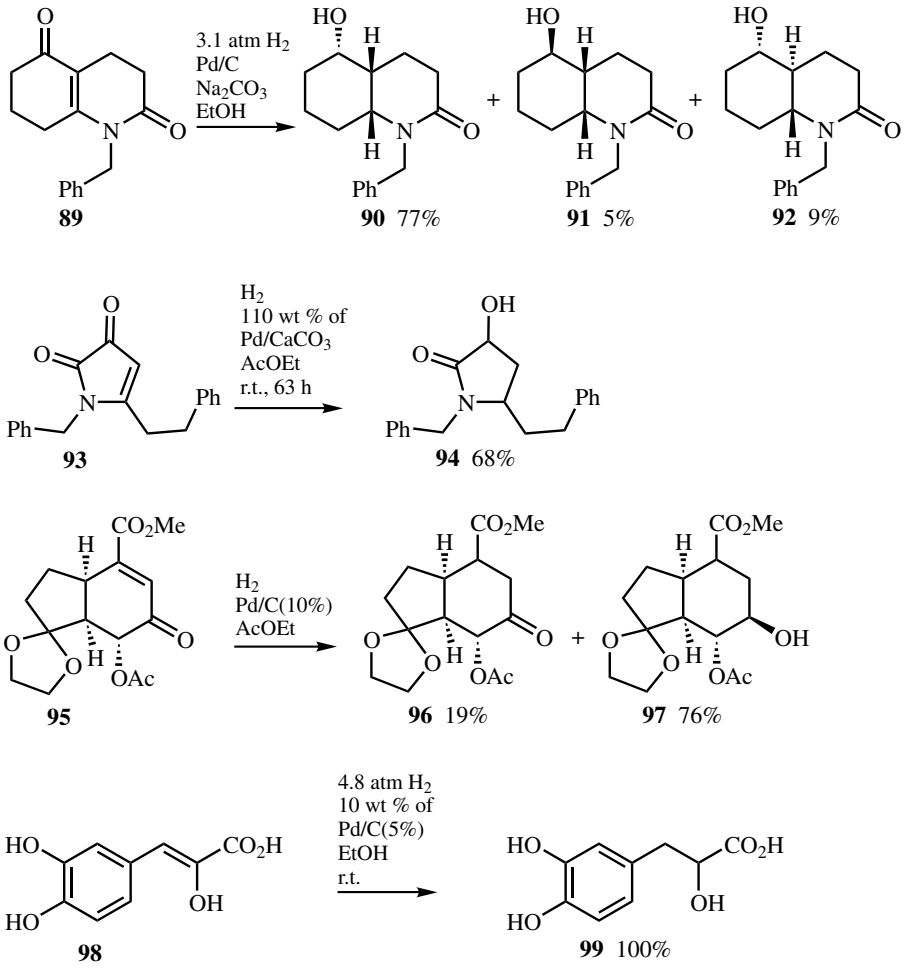


	% de	% Yield
R = —CH_2CHMe_2	96%	95%
R = —Me	86%	96%
R = —CH_2Ph	74%	91%

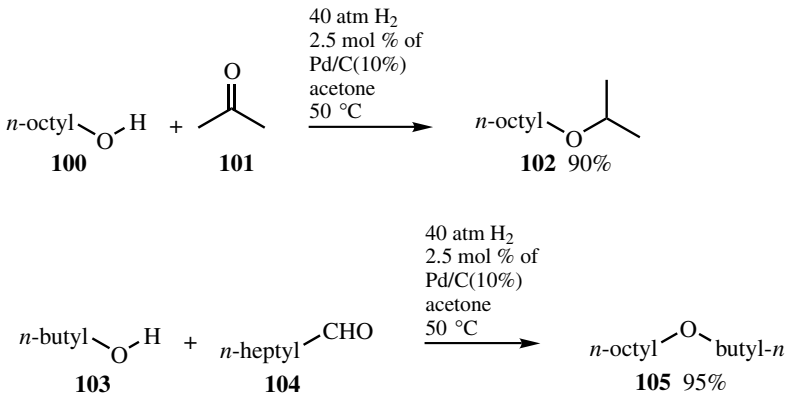
Scheme 21



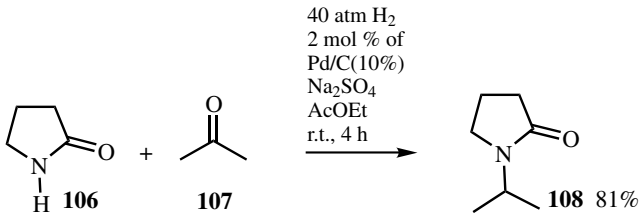
Scheme 22



Scheme 22 (*Continued*)

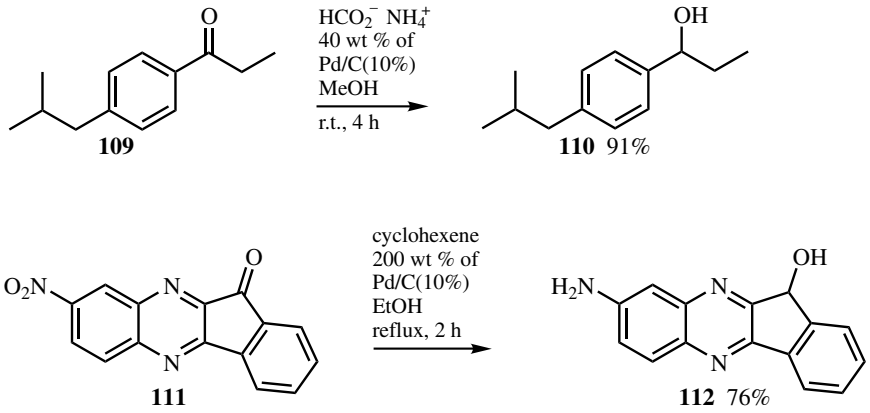


Scheme 23 (*Continued*)



Scheme 23

Benzylic ketone can be reduced with ammonium formate or cyclohexene in the presence of Pd/C. Thus, ketone **109** gave benzylic alcohol **110** in excellent yield (**Scheme 24**).[67],[68] Transfer hydrogenation of **111** with fresh catalyst gave **112** in 76% yield. Interestingly, when the catalyst was reused, only the nitro group of **111** was reduced in 80% yield.



Scheme 24

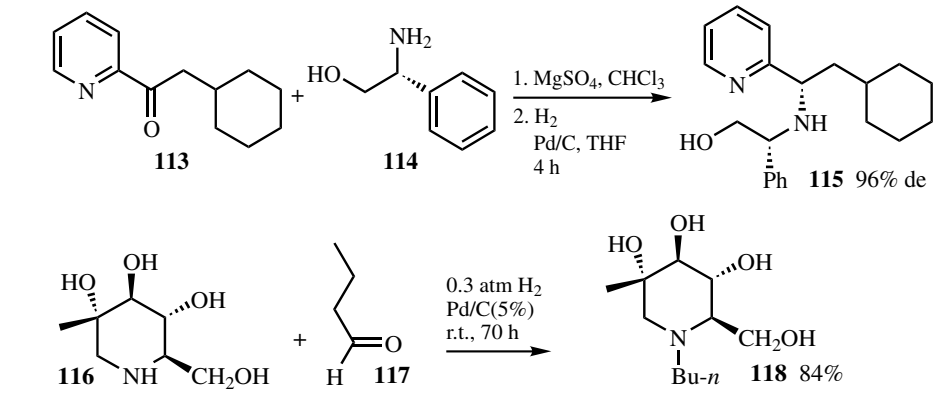
E. REDUCTIVE ALKYLATION

The *in situ* condensation of an amine with a carbonyl compound followed by hydrogenation of the imine intermediate is referred to as a reductive alkylation reaction. Both 1°- and 2°-amines can participate in this reaction (**Scheme 25**).[69],[70]

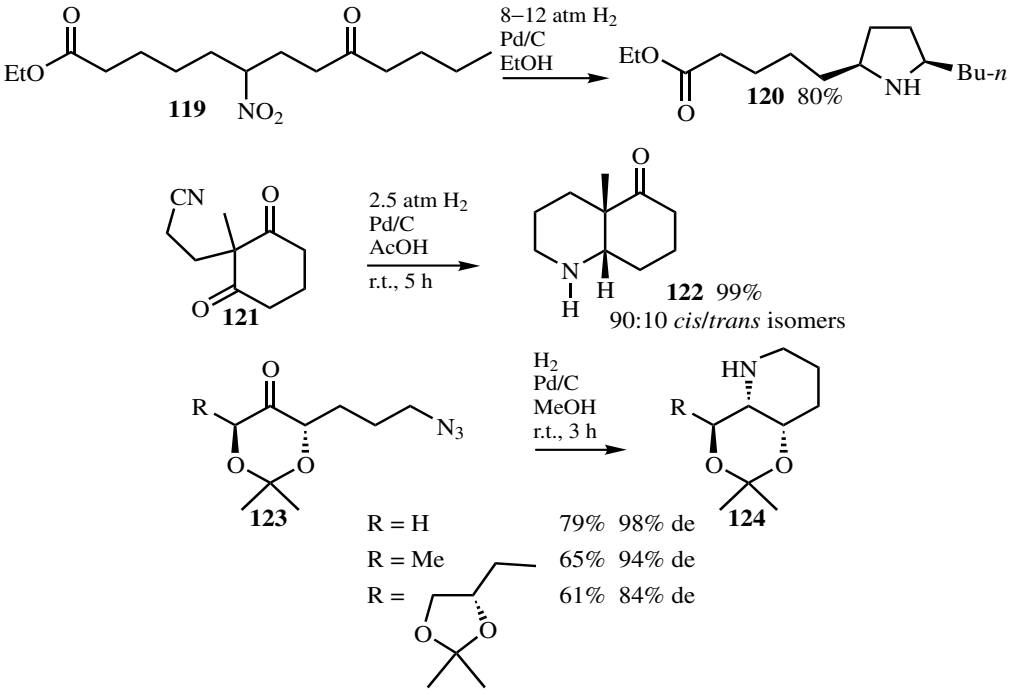
Amine precursors, such as nitro, nitrile, and azido compounds, which can be converted to amines under the hydrogenation reaction conditions, can also be used in the reductive alkylation reaction (**Scheme 26**).[71]–[73]

N-protected amines, which can be deprotected *in situ*, have also been extensively utilized for the preparation of dialkylamines (**Scheme 27**).[74]

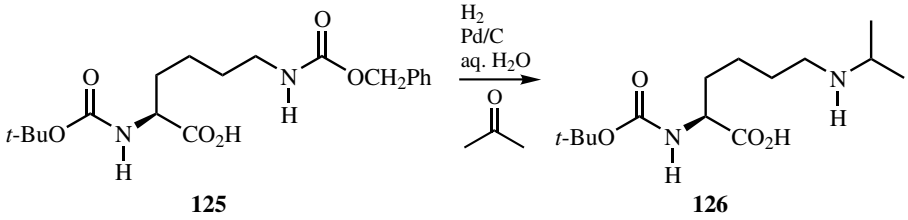
As described previously, primary amides undergo reductive alkylation quite readily. Similarly, secondary cyclic amides will participate in this reaction (**Scheme 28**).[66],[75]



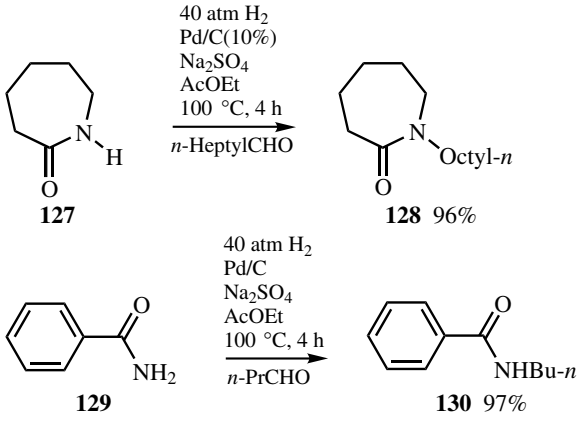
Scheme 25



Scheme 26



Scheme 27

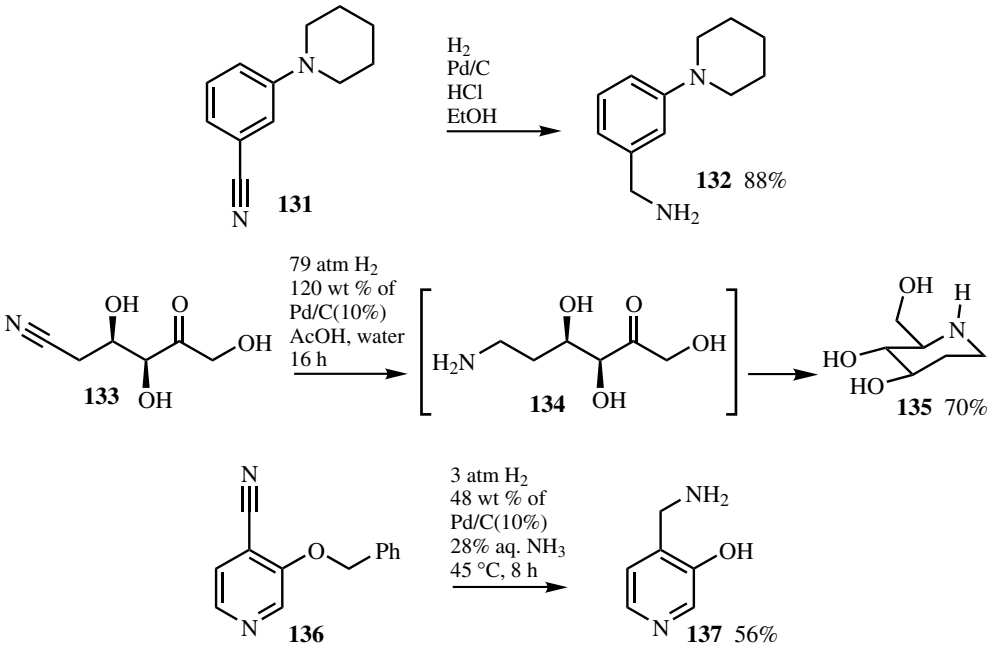


Scheme 28

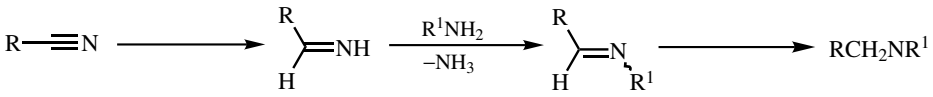
F. HYDROGENATION OF NITRILES

Pd-catalyzed hydrogenation of nitriles generally requires the use of acidic conditions or the addition of ammonia to minimize the formation of dialkyl and trialkyl amines (**Scheme 29**).[76]–[78]

The formation of *secondary* and *tertiary* amines results from the reaction of the amine product with the intermediate imine formed from the half-hydrogenated nitrile followed by further reduction (**Scheme 30**).



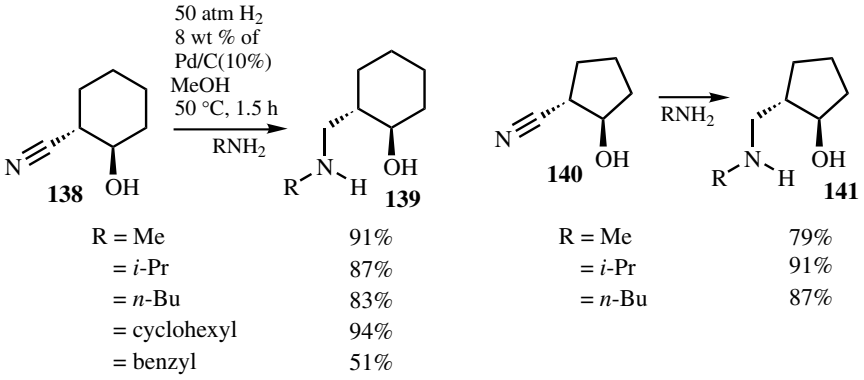
Scheme 29



Scheme 30

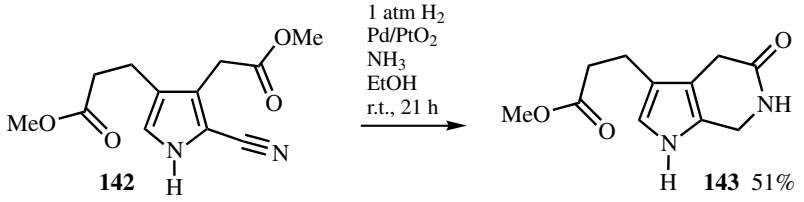
Under acidic conditions, the desired amine formed is immediately protonated to give an ammonium salt, which is inhibited from participating in the amine exchange reaction. With added ammonia the intermediate imine will only participate in the exchange of nitrogen with the excess ammonia until its ultimate reduction to the primary amine. It is therefore possible to prepare mixed alkylamines by the addition of another amine prior to hydrogenation (**Scheme 31**).[79]

In the presence of acetic anhydride, for example, *in situ* acylation of the amine product is another method used to prevent dialkylamine and trialkylamine formation. This is especially useful if the amide is the desired product. Intramolecular lactam formation can also occur with a suitably positioned ester group (**Scheme 32**).[80]



R = Me	91%	R = Me	79%
= *i*-Pr	87%	= *i*-Pr	91%
= *n*-Bu	83%	= *n*-Bu	87%
= cyclohexyl	94%		
= benzyl	51%		

Scheme 31

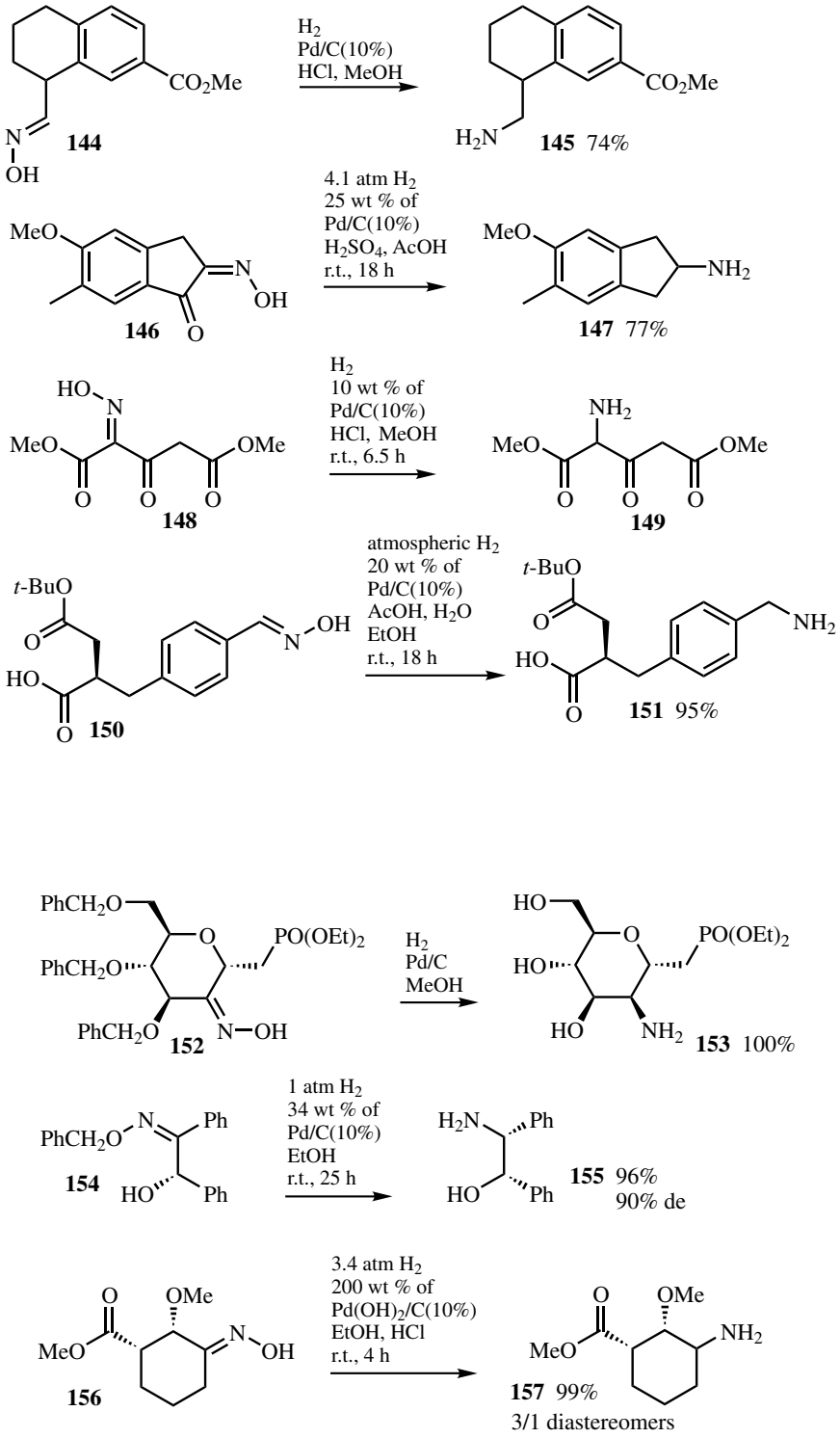


Scheme 32

G. HYDROGENATION OF OXIMES

Similarly, precautions taken for the hydrogenation of a nitrile to a primary amine apply to the reduction of an oxime. Several examples of structurally diverse oximes and reaction conditions are shown in **Scheme 33**.[81]–[84]

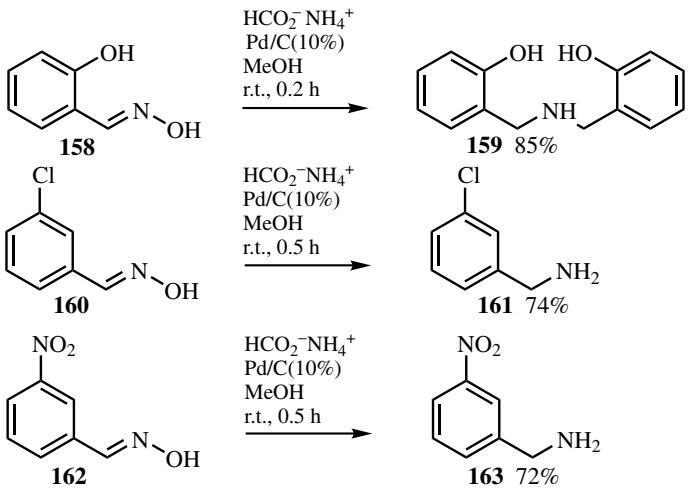
In cases where the oximes or *O*-alkyl oximes are sterically hindered, acidic conditions may not be necessary (**Scheme 34**).[85]–[87] Excellent diastereoselectivities were observed


H2
Pd/C(10%)
HCl, MeOH
CO2Me
N
OH
144
H2N
145 74%
4.1 atm H2
25 wt % of
Pd/C(10%)
H2SO4, AcOH
r.t., 18 h
MeO
N
OH
O
146
NH2
147 77%
H2
10 wt % of
Pd/C(10%)
HCl, MeOH
r.t., 6.5 h
HO
OMe
148
149
atmospheric H2
20 wt % of
Pd/C(10%)
AcOH, H2O
EtOH
r.t., 18 h
t-BuO
150
151 95%
PhCH2O
PO(OEt)2
N–OH
152
HO
NH2
153 100%
1 atm H2
34 wt % of
Pd/C(10%)
EtOH
r.t., 25 h
Ph
154
155 96%
90% de
OMe
156
157 99%
3/1 diastereomers

Scheme 34

for the reduction of oxime **152** and *O*-benzyl oxime **154**, while a 3:1 ratio of diastereomers was obtained from **156**.

Transfer hydrogenation of oxime **158** derived from salicylaldehyde with ammonium formate produced the dialkylamine in good yield instead of the primary amine, but primary amines were produced from other substrates under identical reaction conditions. Thus, *m*-chlorobenzylamine was produced in 74% yield and, more surprising, the nitro group in **162** was slower to reduce than the oxime to give *m*-nitrobenzylamine in good yield (**Scheme 35**).[88]



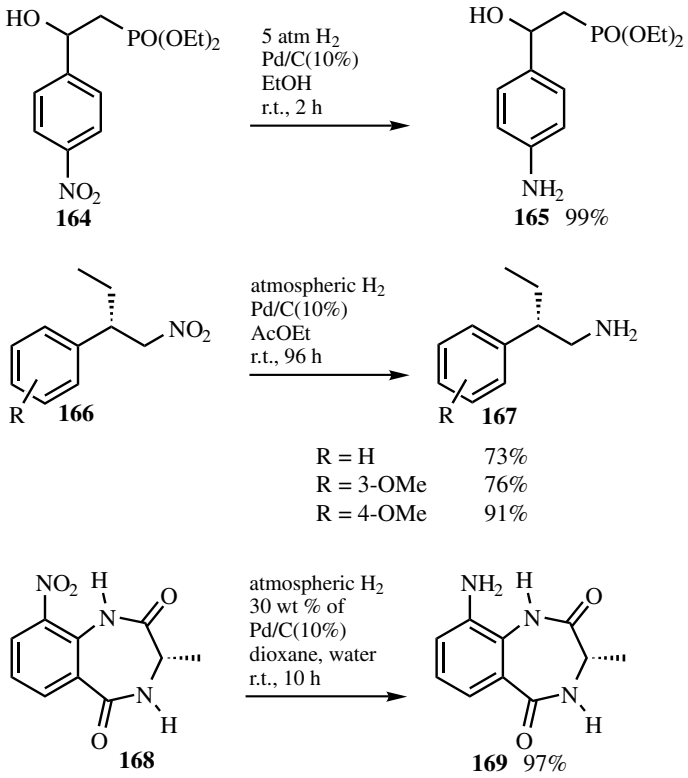
Scheme 35

H. REDUCTION OF NITRO COMPOUNDS

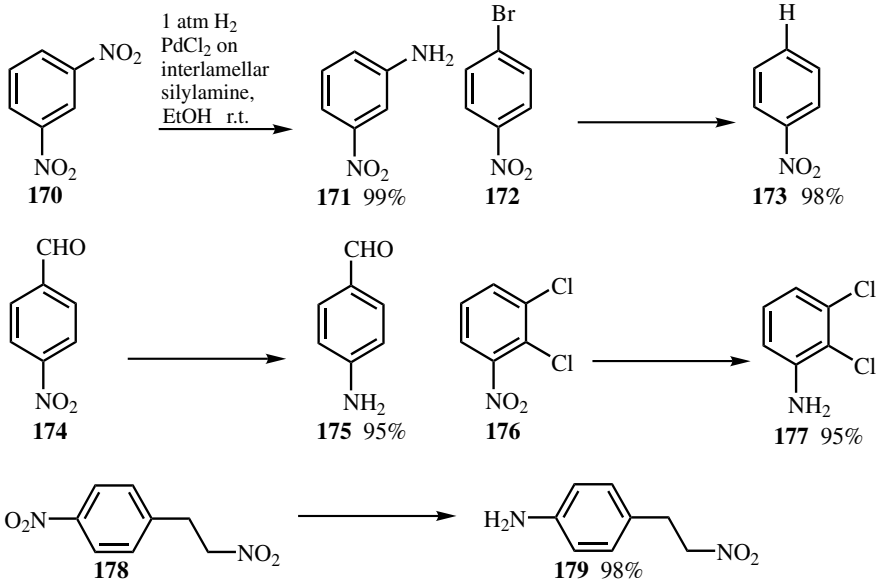
Hydrogenation of the nitro group is one of the most exothermic reduction reactions. Especially with aromatic nitro compounds, care must be taken to ensure the proper amount of catalyst is used and the reaction is not starved of hydrogen. Too high a catalyst loading may create a runaway reaction resulting from the heat released. If the system is starved of hydrogen, the concentration of potentially explosive intermediates, such as azo, azoxy, and hydrazo compounds, may increase to a dangerous level. Aliphatic nitro compounds are much less reactive; therefore, higher catalyst loading and longer reaction times are sometimes required.

Besides the usual alcoholic solvents, other aprotic solvents such as AcOEt and dioxane have been used for the hydrogenation of nitro groups. With Pd as the catalyst, the reduction is generally carried out at room temperature and low hydrogen pressure. Some examples are illustrated in **Scheme 36**.[89]–[91]

The deposition of $PdCl_2$ on interlamellar silylamine afforded a catalyst that catalyzed the selective hydrogenation of only one nitro group of dinitrobenzene **170** to nitroaniline **171** (**Scheme 37**).[92] Exclusive hydrodebromination was observed with *p*-bromonitrobenzene to give nitrobenzene, but only nitro reduction was observed with dichloronitrobenzene **176**. The formyl group of **174** was stable under the reaction conditions. The catalyst was only



Scheme 36

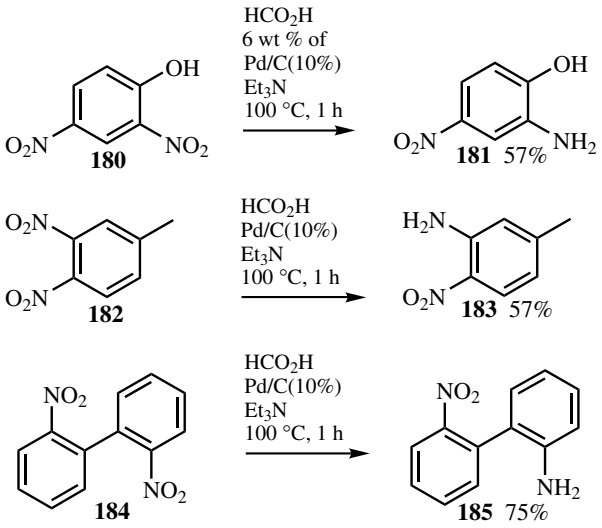


Scheme 37

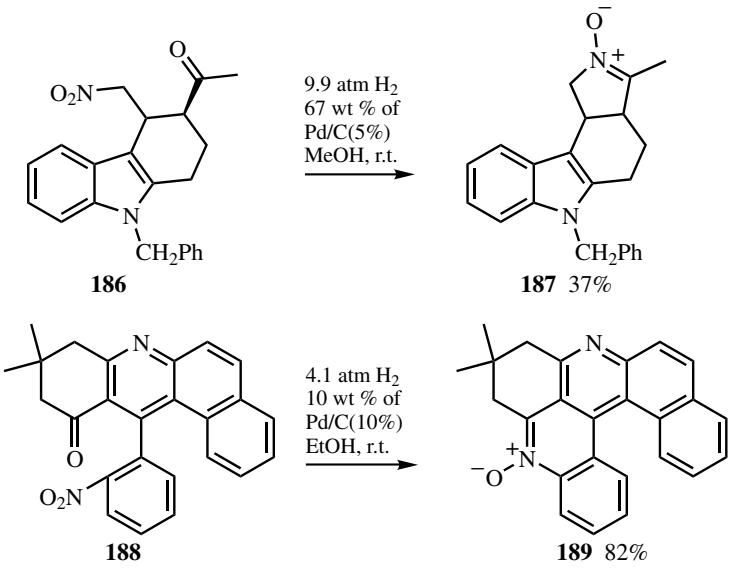
active toward the hydrogenation of the aromatic nitro group and inert for the aliphatic group of **178**.

Transfer hydrogenation ultilizing formic acid and Pd/C gave fair to good yields of mononitro products from dinitro substrates (**Scheme 38**).[93]

If a keto group is situated nearby, the hydrogenation of a nitro group provides a nitrone derivative. Thus, nitrone **187** was formed from **186** and quinoline *N*-oxide **189** was prepared from **188** (**Scheme 39**).[94],[95]



Scheme 38



Scheme 39

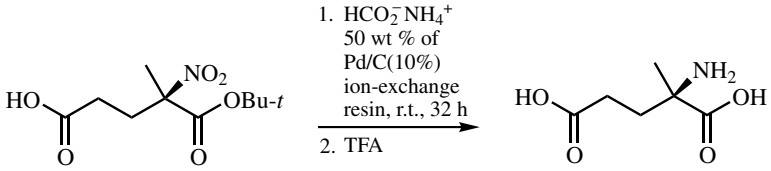
The preparation of nitrones from aliphatic nitro ketones can also be carried out under transfer hydrogenation conditions with ammonium formate and Pd/C in 48–78% yields.[96]

Transfer hydrogenation conditions have also been applied to the reduction of *tertiary* nitro groups (**Scheme 40**).[97]

As expected, the nitro group in **192** was reduced faster than the hydrazo function to give a 64% yield of aminohydrazone **193** (**Scheme 41**).[98]

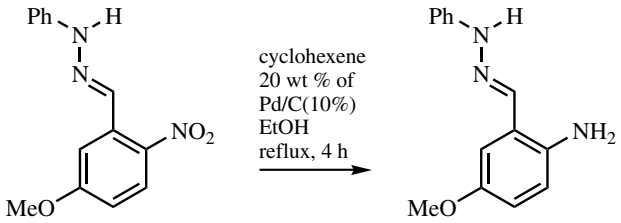
Under the reaction conditions for the nitro group reduction of **194**, the 5-oxytetrazoyl group was hydrogenolyzed concomitantly (**Scheme 42**).[99]

Vinylnitro derivatives gave oximes instead of the expected amines (**Scheme 43**).[100]



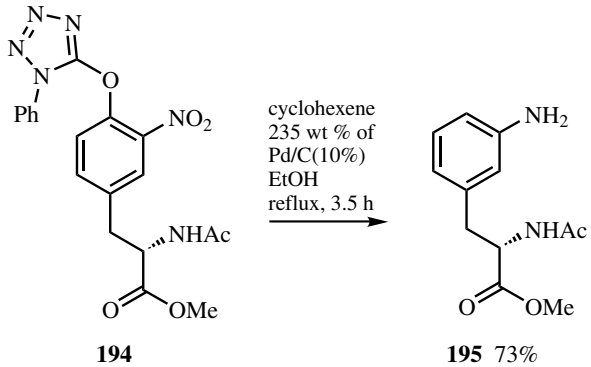
190 **191** 51%

Scheme 40



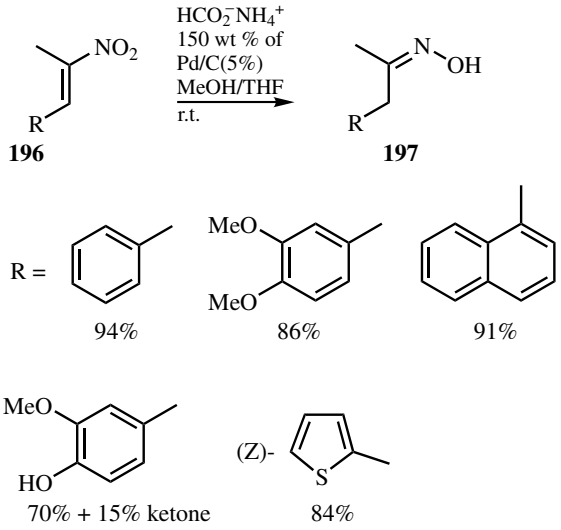
192 **193** 64%

Scheme 41



194 **195** 73%

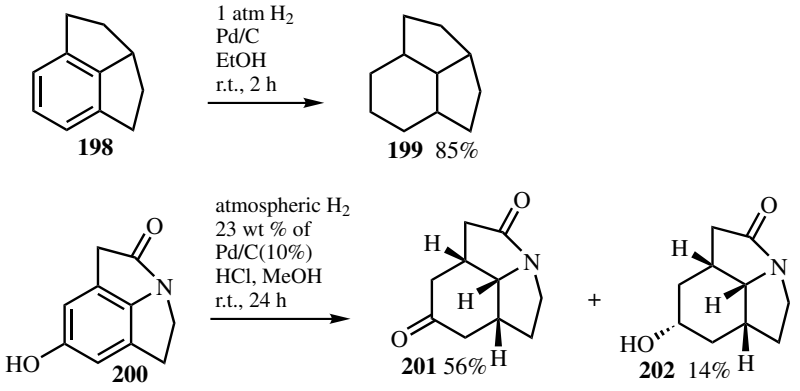
Scheme 42



Scheme 43

I. REDUCTION OF ARENES

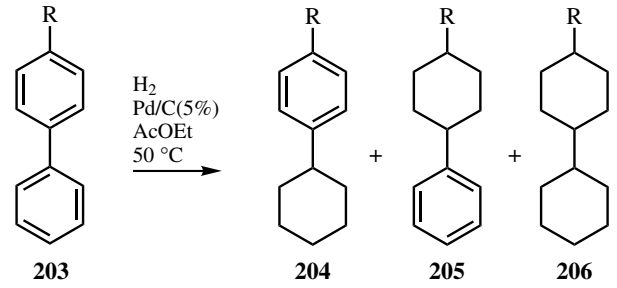
Although the hydrogenation of carbocyclic aromatic compounds with Pd generally requires higher temperatures and pressures than with other metals, such as Pt and Rh, some substrates can be reduced under quite mild conditions. Highly strained ring systems such as **198** and **200** were hydrogenated even at room temperature and 1 atmo of hydrogen pressure (**Scheme 44**).[101],[102]



Scheme 44

The unsubstituted phenyl ring in the biphenyl system was hydrogenated in good selectivity (**Scheme 45**).[103]

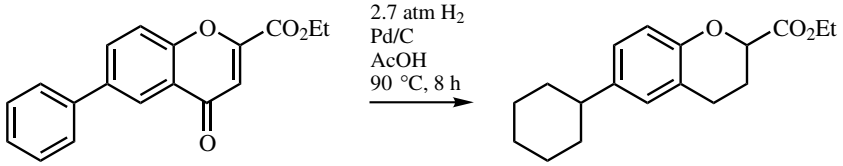
Excellent selectivity was observed with the hydrogenation of chromone ester **207** to give the cyclohexyl product **208** in 80% yield (**Scheme 46**).[104] Doubling the reaction time gave complete saturation of all the rings in 56% yield.



203 **204** **205** **206**

R = OH	89%	2%	2%
R = OMe	87%	10%	3%
R = CH_3	76%	17%	7%

Scheme 45

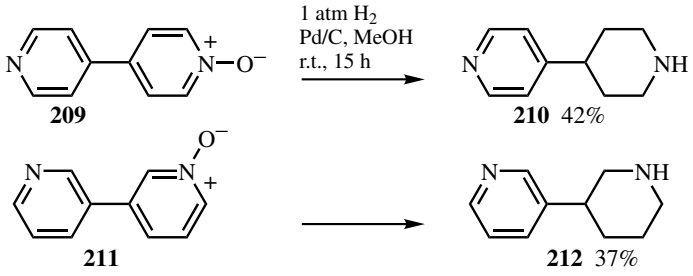


207 **208** 80%

Scheme 46

Nitrosobenzene was reduced to cyclohexylamine under transfer hydrogenation conditions with formic acid in MeOH at room temperature. The reaction temperature was surprisingly low for the ring reduction.[105]

The reaction conditions are generally milder for the Pd-catalyzed hydrogenation of heterocycles. In many instances the use of Pt or Rh catalyst is not as selective as with Pd catalyst. For the bipyridyl mono *N*-oxide system, hydrogenation of the pyridine *N*-oxide ring is preferred over the pyridine ring (**Scheme 47**).[106]



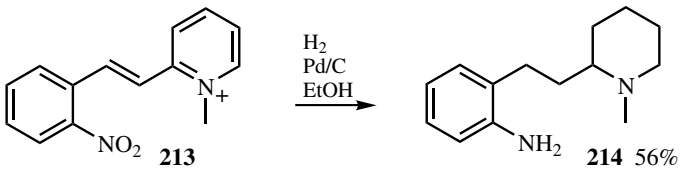
209 **210** 42%

211 **212** 37%

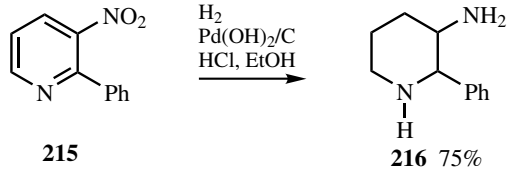
Scheme 47

Pyridinium compound **213** was saturated as readily to give *N*-alkylpiperidine **214** (**Scheme 48**).[107]

The reduction of the pyridine ring is best accomplished under acidic conditions. Phenyl rings are usually not reduced to any significant amount in the process (**Scheme 49**).[108]



Scheme 48



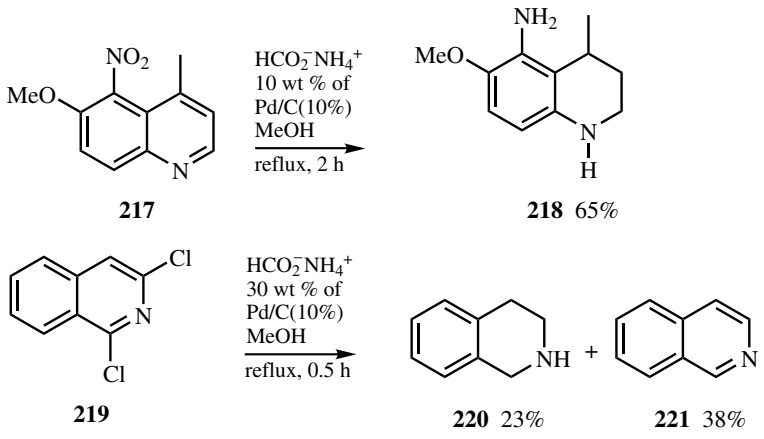
Scheme 49

Transfer hydrogenation has also been used for the reduction of the nitrogen-containing rings in the quinoline and isoquinoline systems (**Scheme 50**).[109]

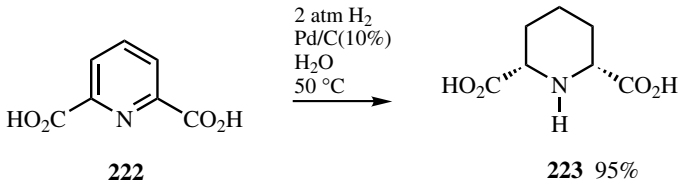
Diacid **222** required no added acid for the reduction to proceed (**Scheme 51**).[110] The reduction provided *cis*-piperidin-2,6-dicarboxylic acid in 95% yield.

Furans and benzofurans are also reduced readily with Pd catalyst under mild conditions (**Scheme 52**).[111],[112]

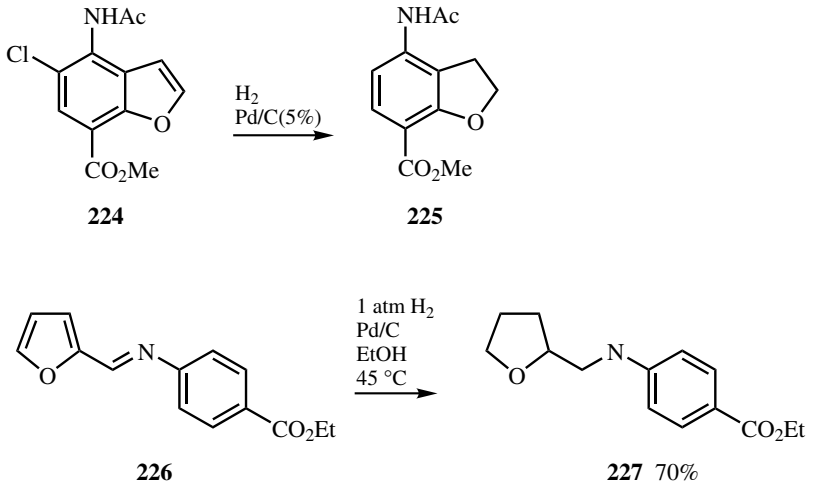
Pyrroles and indoles can also be hydrogenated (**Scheme 53**).[113]–[116]



Scheme 50



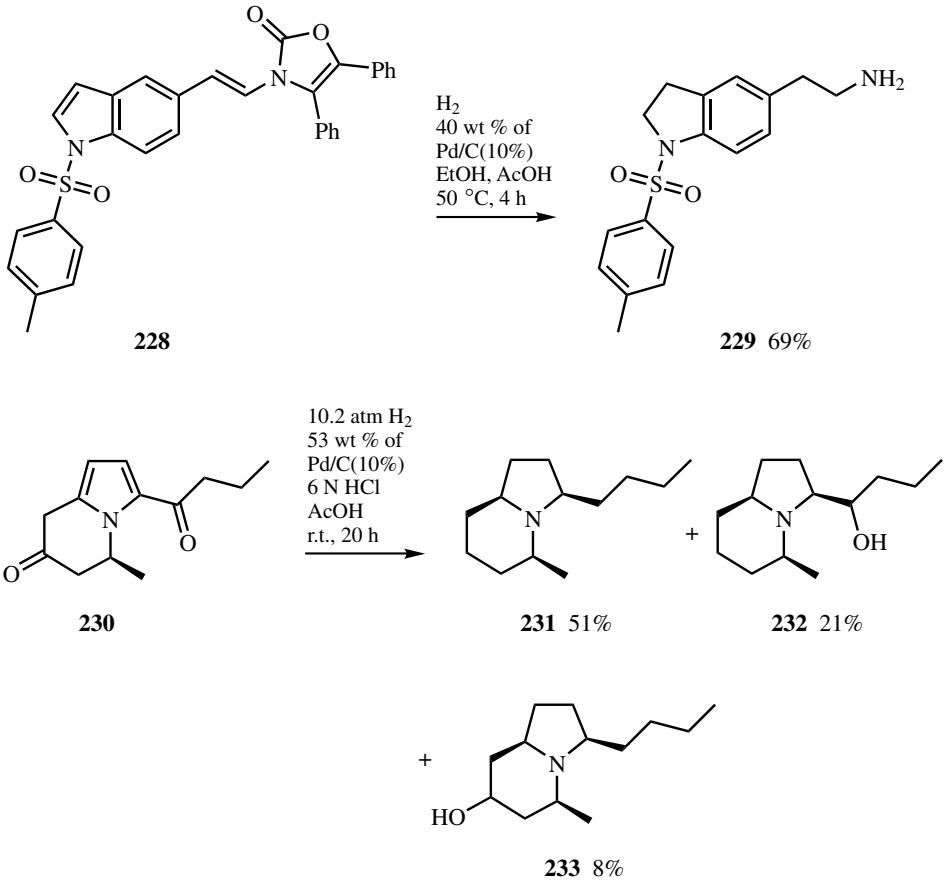
Scheme 51



224 **225**

226 **227** 70%

Scheme 52

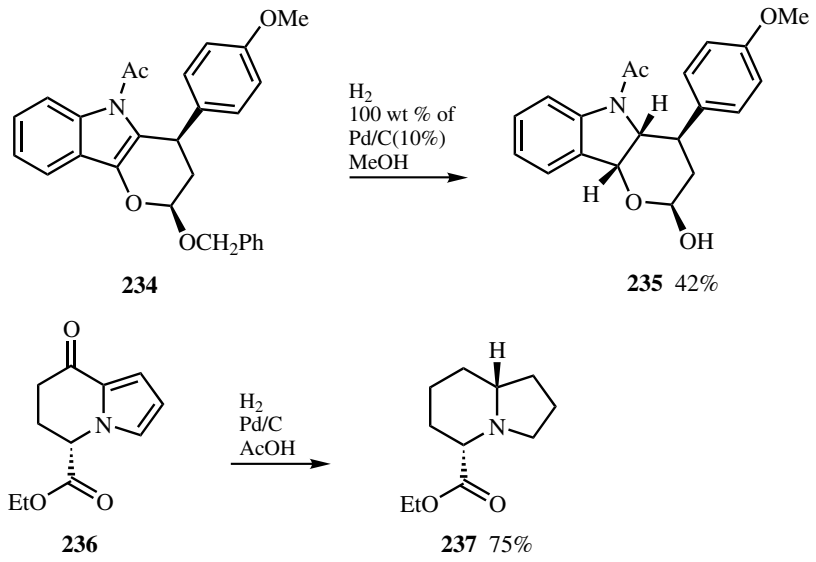


228 **229** 69%

230 **231** 51% **232** 21%

233 8%

Scheme 53



Scheme 53

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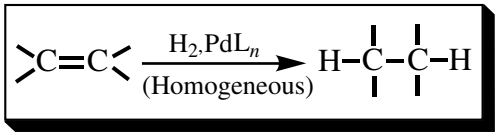

VII.2.2 Palladium-Catalyzed Homogeneous Hydrogenation

VII.2.2.1 Palladium-Catalyzed Homogeneous Hydrogenation with Dihydrogen and Related Hydrogen Transfer Reactions

ANTHONY O. KING

A. HOMOGENEOUS HYDROGENATION WITH DIHYDROGEN

Although many Pd-catalyzed heterogeneous hydrogenation reactions have been described (see **Sect. VII.2.1**), very few Pd-catalyzed homogeneous hydrogenation reactions with dihydrogen have been reported. In certain cases, such as the homogeneous hydrodehalogenation reaction, the reaction conditions are more severe when compared to conditions with heterogeneous catalysts, but the former provides chemical selectivities that may be difficult to attain under heterogeneous conditions. Even at the high temperature needed for this Pd-catalyzed homogeneous hydrodehalogenation reaction, the reduction-sensitive nitro, aldehyde, and ketone functional groups were not hydrogenated (**Scheme 1**).[1] Primary amine, hydroxy, and ether groups were also tolerated.

The direct hydrogenation of carboxylic acids to alcohols is still a very difficult reaction to accomplish, requiring high temperature and pressure. The hydrogenation is much easier if the reduction is carried out on acid chlorides instead. More recently a high-yielding one-pot procedure for the hydrogenation of carboxylic acids to aldehydes was reported (**Scheme 2**).[2],[3] The procedure does not reduce the carboxylic acid directly but involves the *in situ* generation of an anhydride with pivalic anhydride, which is then hydrogenated to the aldehyde.

Both olefin and nitrile groups were shown to be stable under the reaction conditions. Aromatic ring systems were also inert to hydrogenation. Isophthalic acid was converted to isophthalaldehyde in excellent yield. With *ortho*-substituted benzoic acid, such as *o*-toluic acid, the hydrogenation provided only 30% yield of the aldehyde. The reaction is therefore unsuitable for *o*-substituted benzoic acids.

At 130 °C and 100 atm of H_2, $Pd(PPh_3)_4$ catalyzed the hydrogenolysis of triphenylmethyl phosphonium iodide to give diphenylmethyl phosphine in 96% yield (**Scheme 3**).[4]

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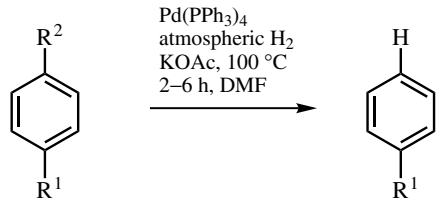
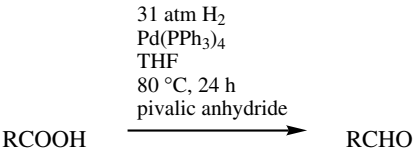


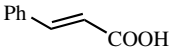
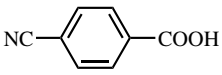
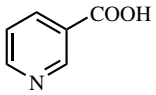
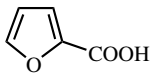
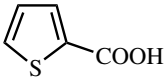
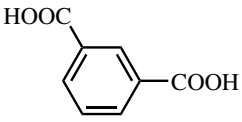
1 **2**

R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
NO_2	Cl	78	NH_2	Br	50
COPh	Cl	96	OH	Br	55
$COCH_3$	Br	81	OMe	Br	60
CHO	Br	76			

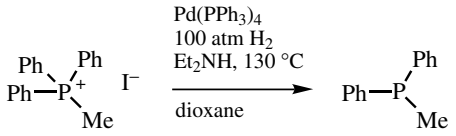
Scheme 1



3 **4**

Carboxylic Acids	(%) Yield of Aldehydes
n-$C_7H_{15}COOH$	98
Oleic acid	99
	84
	99
	99
	87
	72
	94

Scheme 2

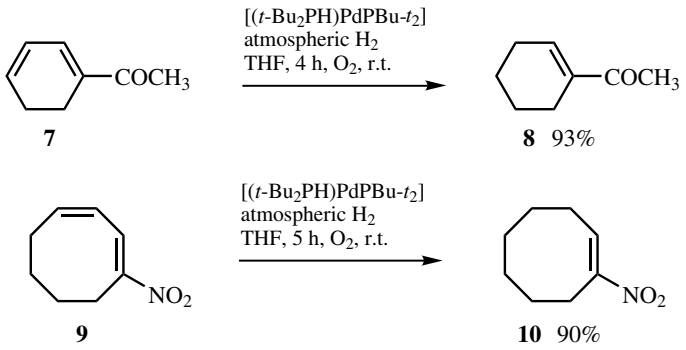


5 **6** 96%

Scheme 3

Ethyltriphenylphosphonium iodide gave only a 30% yield of ethyldiphenylphosphine with even lower yields observed with longer alkyl chains.

With $Pd_2(P(t\text{-}Bu)_2)_2(PH(t\text{-}Bu)_2)_2$ as the catalyst, 1,2-reduction was observed in the hydrogenation of cyclic 1,3-dienes **7** and **9** with the γ,δ-olefins saturated exclusively. Again, both nitro and ketone functions re stable under the reaction conditions (**Scheme 4**).[5] The yields and selectivities for the reduction of acyclic dienes were not as satisfactory and mixtures of the monoene and completely saturated product were observed.



7 **8** 93%

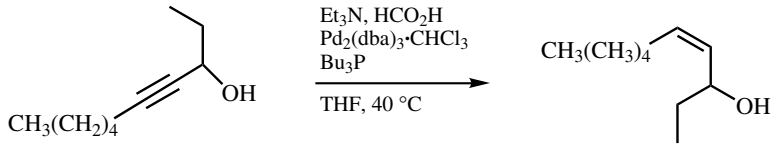
9 **10** 90%

Scheme 4

B. HOMOGENEOUS HYDROGENATION UNDER TRANSFER HYDROGENATION CONDITIONS

Even though phosphine is a severe catalyst poison under Pd-catalyzed heterogeneous hydrogenation conditions (as well as toward other heterogeneous transition metal catalysts such as Pt, Rh, Ru, and Ni), a homogeneous hydrogenation system derived from the combination of phosphine with a palladium compound and formate provides some interesting chemistry not observed even under Pd-catalyzed heterogeneous transfer hydrogenation conditions. Under homogeneous transfer hydrogenation conditions, the reduction of alkenes is generally sluggish. Thus, alkyne **11** could be reduced to give *cis*-olefin **12** in excellent yield (**Scheme 5**).[6] A small amount of the *trans* product was also observed.

A 64% yield was also observed for the hydrogenation of 1-decyne to 1-decene, showing the relative low reactivity of 1-alkenes under these reaction conditions. Methyl 2-octynylcarboxylate was converted to a mixture of *cis/trans*/alkane (98:2:<1). Upon



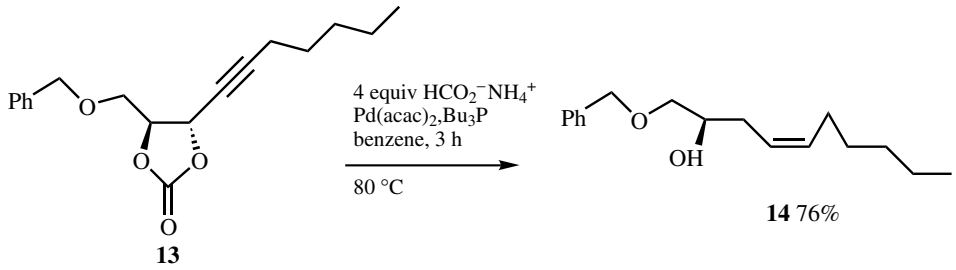
11 **12** 88%
3% *trans*

Scheme 5

extended aging extensive isomerization of the *cis* α,β-unsaturated ester was observed giving a 78:19:3 mixture.[7]

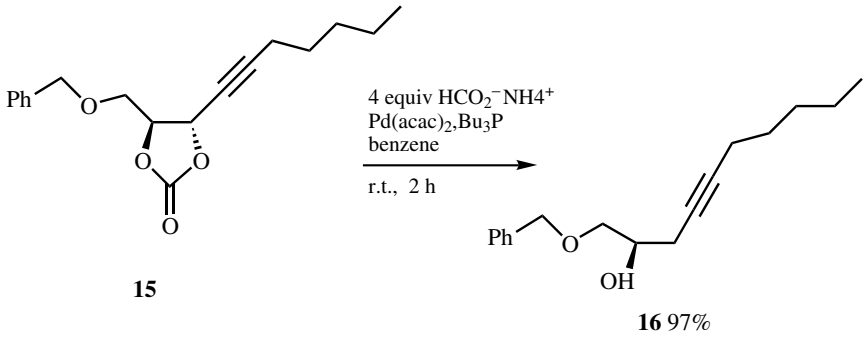
Alkynyl cyclic carbonate **13** underwent hydrogenolysis at the propargylic C—O bond along with the reduction of the alkyne to give *cis*-alkenol **14** (**Scheme 6**).[8]

The benzyl ether remained intact under the seemingly vigorous reaction conditions. The reduction of the alkyne was suppressed when the reaction was carried out at room temperature (r.t.) (**Scheme 7**).



13 **14** 76%

Scheme 6

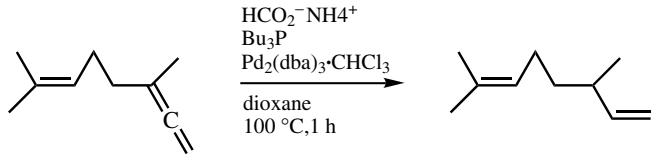


15 **16** 97%

Scheme 7

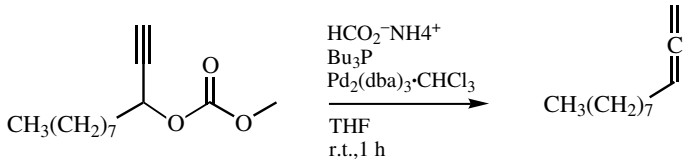
Similar to alkynes, allenes can be converted to alkenes without over-reduction of the olefin. Thus, good yield of terminal olefin **18** was obtained from allene **17** (**Scheme 8**).[9]

Allene **20** could in turn be prepared from propargyl cabonate **19** under slightly modified reaction conditions. For comparison, reactions using the corresponding propargyl acetates were much less satisfactory (**Scheme 9**).



17 **18** 77%

Scheme 8

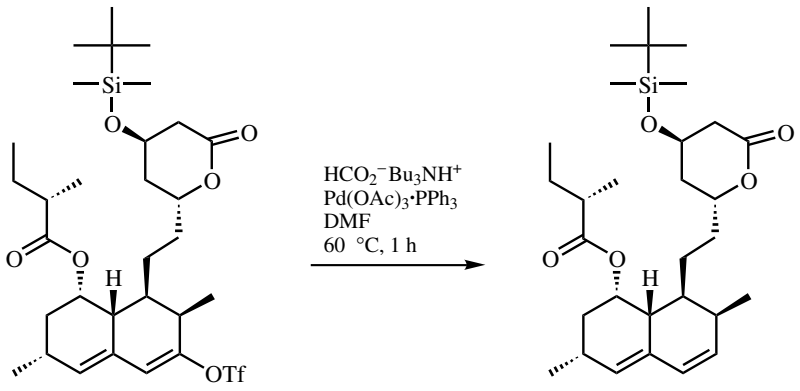


19 **20** 87%

Scheme 9

Other chemical transformations involving allylic substrates utilizing similar transfer hydrogenation conditions are discussed in **Sects. V.2.3.1** and **V.2.3.2**.

Deoxygenation of hydroxy or keto groups can be accomplished under transfer hydrogenation conditions via the corresponding triflates. Thus, dienol triflate **21** was readily hydrogenolyzed to diene **22** in good yield (**Scheme 10**).[10]

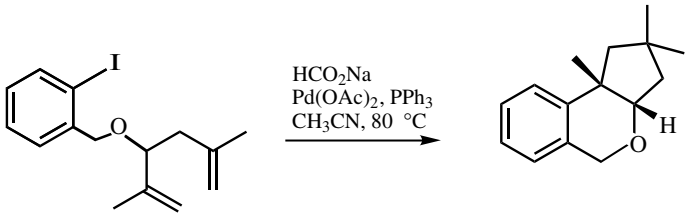


21 **22** 70%

Scheme 10

With many appropriately constructed alkenyl halides, these homogeneous transfer hydrogenation conditions promote the reductive tandem Heck reaction to give polycyclic products. An example is shown in **Scheme 11**.[11] This useful reaction is discussed more extensively in **Sect. IV.2.2**.

Although aryl ketones are generally easy to reduce to benzylic alcohols under heterogeneous conditions and even further hydrogenolyze to aryl alkanes, homogeneous hydrogenation conditions do not promote this reduction. Thus, 4-bromoacetophenone was



23 **24** 70%

Scheme 11

dehalogenated with polymethylhydrosiloxane (PMHS) in the presence of $Pd(PPh_3)_4$ to acetophenone in 98% yield.[12] Even 4-iodonitrobenzene was deiodinated to give nitrobenzene in 75% yield.

C. SUMMARY

It is clear from the limited number of homogeneous Pd-catalyzed hydrogenation reactions with dihydrogen presented above that this area of chemical research is still awaiting a more concerted developmental effort. Homogeneous Pd-catalyzed transfer hydrogenation protocols, on the other hand, have been shown to be more useful up to now. These reactions are discussed in detail in the aforementioned sections.

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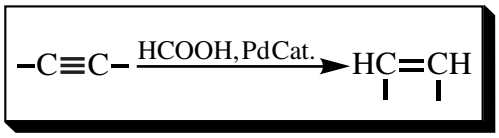

VII.2.2.2 Palladium-Catalyzed Hydrogenation Equivalents

FUMIE SATO

A. INTRODUCTION

Reduction of an unsaturated carbon–carbon bond—conversion of alkenes to alkanes and of alkynes to alkenes—is an important synthetic transformation both in the laboratory and in industry. Apparently, the traditional method for reduction of alkenes and alkynes is hydrogenation using dihydrogen in the presence of a heterogeneous and/or homogeneous transition metal catalyst, including a palladium catalyst. In recent years, however, the transfer hydrogenation, hydrogenation using a hydrogen donor instead of dihydrogen, has been developed.

Hydrogenation using hydrogen donors has the following practical advantages. (i) The use of hydrogen donors obviates difficulties inherent in the use of molecular hydrogen that is highly diffusible and easily ignited, presenting considerable hazards. (ii) The reaction is conveniently carried out; no pressure vessels are needed, and simple stirring of the solution is all that is required. Methods for transformations of this variety have been developed in both heterogeneous and homogeneous palladium catalyses. The former is discussed in **Sect. VII.2.1** and this section describes the latter.

Transfer hydrogenation of alkenes to alkanes catalyzed by a homogeneous palladium catalyst has scarcely been reported except for 1,4-reduction of α,β-unsaturated carbonyl compounds: Nishiguchi and co-workers reported the reduction of 1,4-dienes such as methyl linolate to the corresponding mono-enes using indoline and $(NH_4)_2PdCl_2$ as a hydrogen donor and a catalyst, respectively,[1]–[3] but its synthetic utility has not been elucidated.

In contrast, transfer hydrogenation using a homogeneous palladium catalyst has been accepted as an effective protocol for selective reduction of alkynes to *cis*-alkenes.

B. HYDROGENATION OF ALKYNES USING HYDROSILANES AND ACETIC ACID AS HYDROGEN DONORS

In 1989 Trost and Braslav reported the first semihydrogenation of alkynes using a hydrogen donor in the presence of a homogeneous palladium catalyst.[4] In the presence of 2.5 mol % of $Pd_2(dba)_3$–$CHCl_3$ and 10 mol % of tri-*o*-tolylphosphine, alkynes are reduced smoothly by simple stirring with a mixture of tetramethyldihydrosiloxane (TMDHS) and

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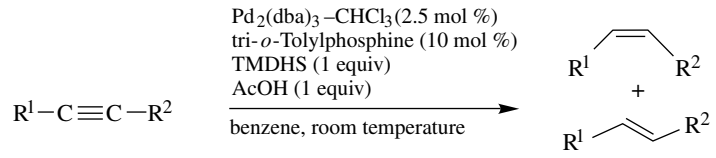
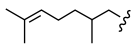
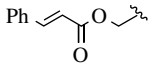
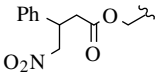
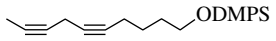
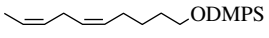
acetic acid in benzene at ambient temperature to afford the corresponding alkenes (**Scheme 1**). As revealed from the table shown in **Scheme 1**, terminal acetylenes undergo effective semireduction to afford the corresponding 1-alkenes in good to excellent yield. The selective formation of *cis*-alkenes from internal alkynes, including poly-ynes, is possible but not general; the *Z*-isomer is initially generated cleanly, but isomerization of the kinetic product occurs during extended reaction times, and/or the process of quenching, work-up, and/or purification. The method attains remarkable chemoselectivity in the reduction of acetylenes having a nitro group or a conjugated double bond, which are among the groups most easily reduced under conditions of heterogeneous catalysis.

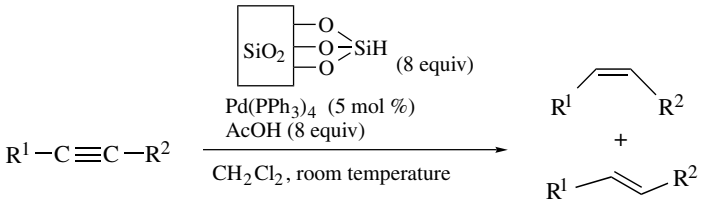


R^1	R^2	Reaction Time	*Z/E*	Yield (%)
$PhOCH_2$	H	6 min	—	95
$DMPSO(CH_2)_4$	H	22 min	—	72
$(CH_3O_2C)_2CHCH_2$	H	1 min (SiO_2 was added)	—	65
Ph	CO_2Me	60 s	*Z* only	87
$PhSCH_2CH_2$	CO_2Me	17 min	*Z* only	81
	CO_2Me	18 min	2.6:1	80
	TMS	84 min	1:2	68
	TMS	114 min	1:3.7	69
		43 min	 *Z,Z*/others = 13.4:1	59

Scheme 1

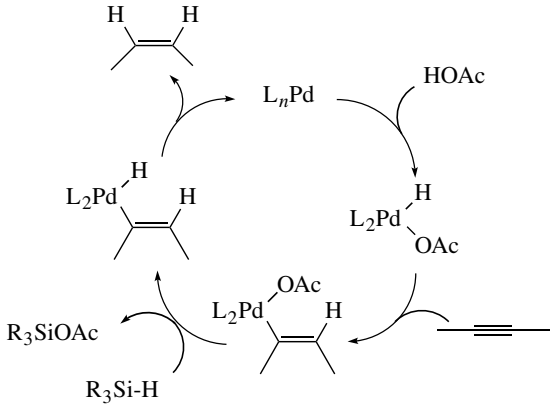
The semihydrogenation can also be carried out by using hydrosilane immobilized on silica gel.[5] Thus, alkynes were treated with such a silane and acetic acid in the presence of a catalytic amount of $Pd(PPh_3)_4$ in CH_2Cl_2 at room temperature to provide the corresponding alkenes in excellent yields (**Scheme 2**). Internal alkynes, including conjugated ones, undergo the selective semihydrogenation to give *cis*-alkenes with high selectivity; however, trimethylsilylacetylenes do not react under the reaction conditions.

The proposed mechanism for these hydrogenation reactions with hydrosilanes includes hydropalladation of an alkyne with acyloxypalladium hydride, generated by the oxidative addition of acetic acid to a Pd(0) species, the formation of alkenylpalladium hydride by exchanging the acetoxy group to hydride, and the following reductive elimination to afford an alkene and regenerate the Pd(0) species. Thus, two olefinic hydrogen atoms in the products came from both silane and acetic acid (**Scheme 3**).



R^1	R^2	Reaction Time	*Z*/*E* (/alkane)	Yield (%)
n-$C_{10}H_{21}$	H	16 h	—	83
n-C_3H_7	*n*-C_3H_7	16 h	11.5:1	97
Ph	CO_2Et	4 h	9:1	96
MeO_2C	CO_2Me	2 h	24:1	98
Ph	Ph	16 h	85:10:5	85
Et	CH_2CH_2OH	3 h	>99:1	96
Ph	$C(C_6H_5)_2OH$	16 h	10:1	84
n-C_4H_9	TMS	16 h	No reaction	

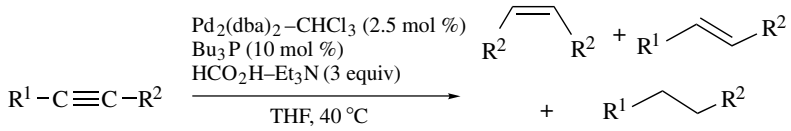
Scheme 2



Scheme 3

C. HYDROGENATION OF ALKYNES USING AMMONIUM FORMATES AS A HYDROGEN DONOR

Transfer hydrogenation of alkynes using HCO_2H–Et_3N as a hydrogen donor is nicely catalyzed by a homogeneous Pd(0) catalyst to afford the corresponding alkenes in good to excellent yields (**Scheme 4**).[6] The method is advantageous in that formic acid is quite inexpensive and is a safe hydrogen donor. The reaction was carried out using 2.5 mol % of $Pd_2(dba)_3$–$CHCl_3$ and 10 mol % of Bu_3P as catalyst. In the presence of this catalyst, the reduction of alkynes can be performed by simple stirring with triethylammonium formate (3 equiv) in THF at 40 °C for the times shown in the table. In general, internal



			Product(s)	
R^1	R^2	Reaction Time	*Z*/*E*/alkane	Total Yield (%)
n-C_8H_{17}	H	1 h	98:—:2	65
n-C_8H_{17}	Me	2 h	97:3: <1	100
		(6 h	97: 3: <1)	
n-C_5H_{11}	CO_2Me	2 h	98:2: <1	95
		(15 h	78:19:3)	
Ph	Et	3 h	89:5:6	100
		(9 h	71:11:18)	
n-C_5H_{11}	CH_2OH	2 h	97.5:2.5: <1	78
Et	$(CH_2)_3OH$	2.5 h	98:2: <1	77
n-C_5H_{11}	CH(OH)Et	3 h	97.5:2.5: <1	90
n-C_5H_{11}	CH_2OTHP	1.5 h	97:3: <1	96
n-C_5H_{11}	CH_2OTBS	2 h	95.5:4.5: <1	92

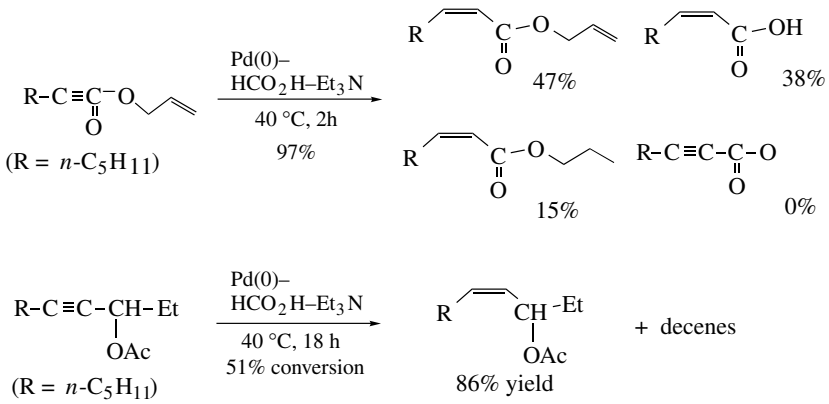
Scheme 4

acetylenes, except for conjugated acetylenes, undergo semihydrogenation with very high *cis*-selectivity, irrespective of the reaction times. Conjugated alkynes such as α,β-unsaturated ester or arylacetylene can also be reduced to give the corresponding *cis*-alkenes predominantly by the reaction for the controlled reaction times; however, elongation of the time causes olefin isomerization from *cis* to *trans* as well as over-reduction. Semihydrogenation of terminal alkynes proceeds smoothly but affords moderate yields due to competitive polymerization under the conditions.

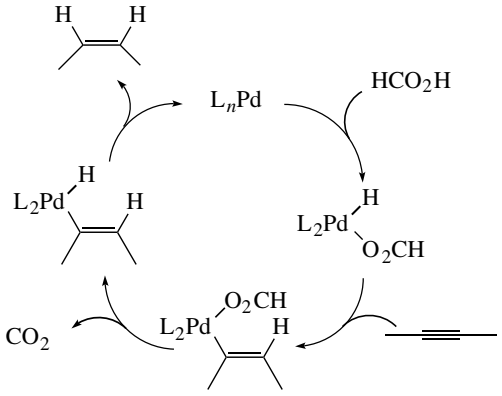
In connection with the finding that a combination of a Pd catalyst and ammonium formates is effective for hydrogenolysis of allyl esters to olefins, and of propargyl carbonates to allenes,[7] the reactions with allyl ester of alkynyl acid and propargyl acetate under the reaction conditions shown in **Scheme 4** were investigated. The results indicate that in both cases reduction of the triple bond takes preference over hydrogenolysis as summarized in **Scheme 5**.

The proposed mechanism for this hydrogenation is shown in **Scheme 6**.

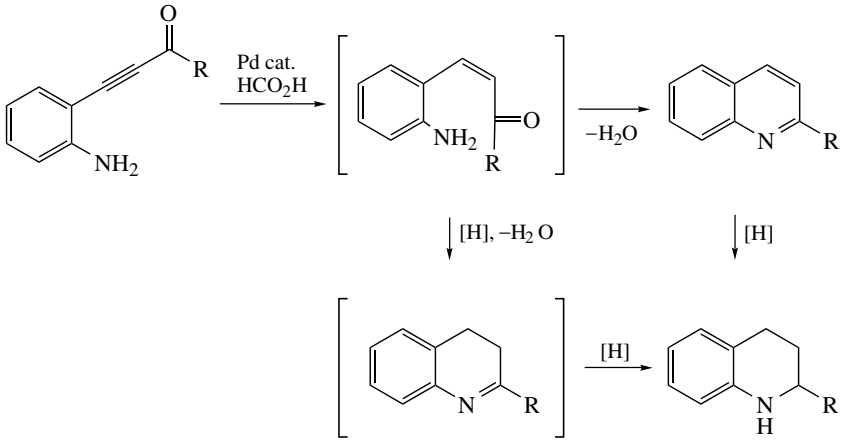
The homogeneous Pd-catalyzed reaction of β-(2-aminophenyl)-α,β-ynones with ammonium formates proceeds through a tandem hydrogenation and heterocyclization reaction to provide 2-substituted quinolines (**Scheme 7**).[8] The table in **Scheme 7** summarizes the results together with those using a heterogeneous catalyst (Pd/C, procedure B shown in the footnote to the table). The homogeneous catalysis gives quinoline selectively in moderate to good yield, while the heterogeneous reaction suffers contamination with tetrahydroquinoline.



Scheme 5



Scheme 6



Scheme 7 (*Continued*)

α,β-Ynone R	Procedure	Time (h)	Yield (%) Quinoline	Yield (%) Tertahydro-quinoline
p-MeO-C_6H_4	A	8	54	
	B	1	67	20
m-Me-C_6H_4	A	2.5	70	
1-Naphthyl	A	24	38	
	B	5	85	Trace
	C	24	46	8
m-F-C_6H_4	A	3.5	60	
	B	1	72	24
m-CF_3-C_6H_4	A	2	61	
	B	1.5	71	12
p-MeCO-C_6H_4	B	3	55	
	C	3	77	
p-MeOOC-C_6H_4	A	20	35	
	B	3.5	73	
p-Cl-C_6H_4	B	2	66	12
	A	2.5	78	
	A	2	55	

Procedure A: ynone/*n*-Bu_3N/HCO_2H/$Pd(OAc)_2(PPh_3)_2$ = 1:5:3.8:0.04, DMF, 70 °C.
Procedure B: ynone/ HCO_2NH_4/Pd/C = 1:3–10:0.1, MeOH, 70 °C.
Procedure C: ynone/HCO_2H/Et_3N/$Pd(OAc)_2$/dppf = 1:3.8– 7.6:4–8:0.05:0.055, DMF, 70 °C.

Scheme 7

D. SUMMARY

The reaction system using a homogeneous palladium catalyst with hydrogen donors is effective for hydrogenation of alkynes to alkenes. The features that make this methodology attractive for organic synthesis are the high selectivity for synthesizing *cis*-alkenes and the ease in which the reaction can be carried out: it is operationally simple and safe and needs only mild reaction conditions (room temperature to 40 °C). In addition, the method achieves the selective semihydrogenation not only of simple dialkyl acetylenes but also of acetylenes having oxygen functionalities such as hydroxy and alkoxy groups, which sometimes cause isomerization and/or over-reduction under the Lindlar reduction conditions.

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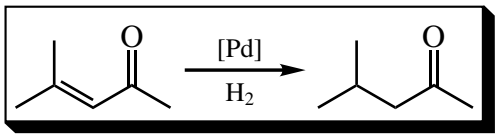

VII.2.3 Palladium-Catalyzed 1,4-Reduction (Conjugate Reduction)

ARIEL HASKEL and EHUD KEINAN

A. INTRODUCTION

A variety of synthetic methods have been developed for the conjugate reduction of α,β-unsaturated carbonyl compounds. This section comprises only those methodologies that involve the use of palladium catalysts. More general reviews that cover a broader spectrum of methods, including those involving metal hydrides, different transition metal catalysts, electron transfer reagents, and biomimetic approaches, have already been published.[1],[2]

There are different reduction modes that can take place in the enone system. The formal addition of a single hydrogen molecule to an enone may form either an allylic alcohol or a saturated carbonyl compound. The addition of two molecules of hydrogen forms the corresponding saturated alcohol. Yet, complete deoxygenation of the substrate would produce either an unsaturated or saturated hydrocarbon. Thus, the issue of regioselectivity, either 1,2- or 1,4-reduction, represents the main consideration in choosing an appropriate reducing method.

In this section we describe only those systems that lead to the 1,4-conjugate reduction mode. Issues of relative and absolute stereoselectivity are also of considerable importance when sp^2 carbon atoms are converted to potentially asymmetric sp^3 centers.

Finally, the value of a specific reducing system reflects its ability to reduce the enone function chemoselectively in the presence of other easily reducible functional groups.

Additional factors that should be taken into consideration are the cost and availability of the catalytic system and the simplicity of the experimental procedures.

This section is divided into three different parts: **Sect.B**, catalytic hydrogenation over palladium catalysts; **Sect.C**, Pd-catalyzed reductions with group 14 metal hydrides; and **Sect.D**, Pd-catalyzed reductions with other hydrogen donors.

B. CATALYTIC HYDROGENATION

The addition of molecular hydrogen to α,β-unsaturated carbonyl compounds has been extensively reviewed.[3]–[8] Enones are reduced to saturated ketones by catalytic hydrogenation, provided that the reaction is interrupted upon the absorption of 1 mole of hydrogen.[9] A number of catalysts were found useful for this transformation, including

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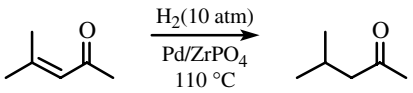
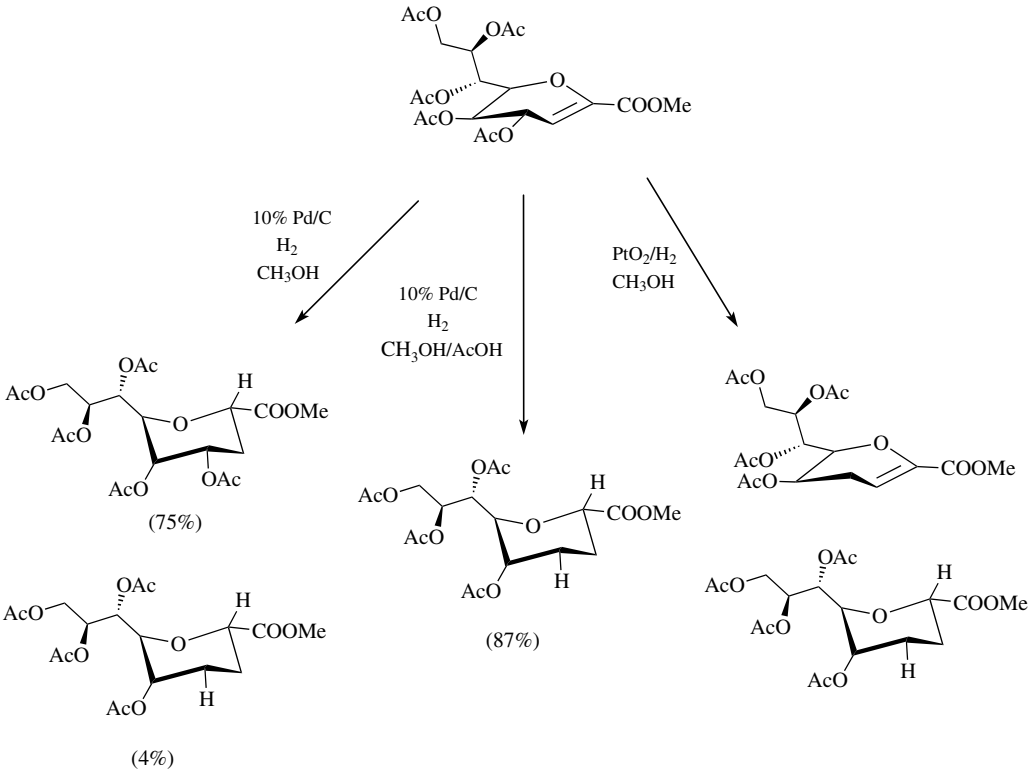
palladium on carbon[10] and the bifunctional catalyst comprised of palladium and zirconium phosphate (**Scheme 1**).[11]



Scheme 1

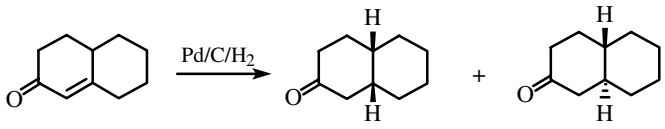
Both the efficiency and the stereochemical course of the hydrogenation of α,β-unsaturated ketones are strongly influenced by the experimental factors, particularly the nature of the solvent and the acidity or basicity of the reaction mixture. It is usually difficult to predict the product distribution in a particular reaction under a given set of conditions. Some efforts have been made to rationalize the effect of the various parameters on the relative proportions of the 1,2- to 1,4-addition products, as well as on the stereochemistry of the reduction.[12]

The influence of the solvent in a conjugate reduction can be exemplified by the synthesis of sialic acid derivatives which are potent inhibitors of the influenza virus surface enzyme sialidase.[13]–[14] A group of potential sialidase inhibitors were obtained by the 1,4-reduction of a galacto-enonate derivative (**Scheme 2**).[15] The catalytic hydrogenation of the enone substrate with 10% Pd/C in methanol afforded the 2-H_{axial} penta-acetylated



Scheme 2

saturated product in 75% yield. Addition of acetic acid to the above, produced exclusively the saturated tetra-acetylated product in 87% yield. On the other hand, catalytic hydrogenation of the same galacto-enonate derivative over PtO_2 in methanol yielded a mixture of the unsaturated and saturated tetra-acetylated products (**Scheme 2**). In the hydrogenation of β-octalone, the product distribution in neutral media is related to the polarity of the solvent and to the solvent being either protic or aprotic. The relative amounts of *cis*-β-decalone decrease steadily with decreasing dielectric constant in aprotic solvents, and with increasing dielectric constant in protic solvents, as exemplified in **Scheme 3** (dielectric constants of the solvents are indicated in parentheses).[16] Similar results were observed in the hydrogenation of cholestenone and testosterone.[17] In polar aprotic solvents the 1,4-addition predominates, whereas in nonpolar aprotic solvents hydrogenation occurs mainly in the 1,2-addition mode.



DMF (38)	79	21
AcOEt (6)	57	43
Et_2O (4.34)	58	42
Hexane (1.89)	48	52
Methanol (33.6)	41	59
Propanol (21.8)	68	32
t-Butyl alcohol (10.9)	91	9

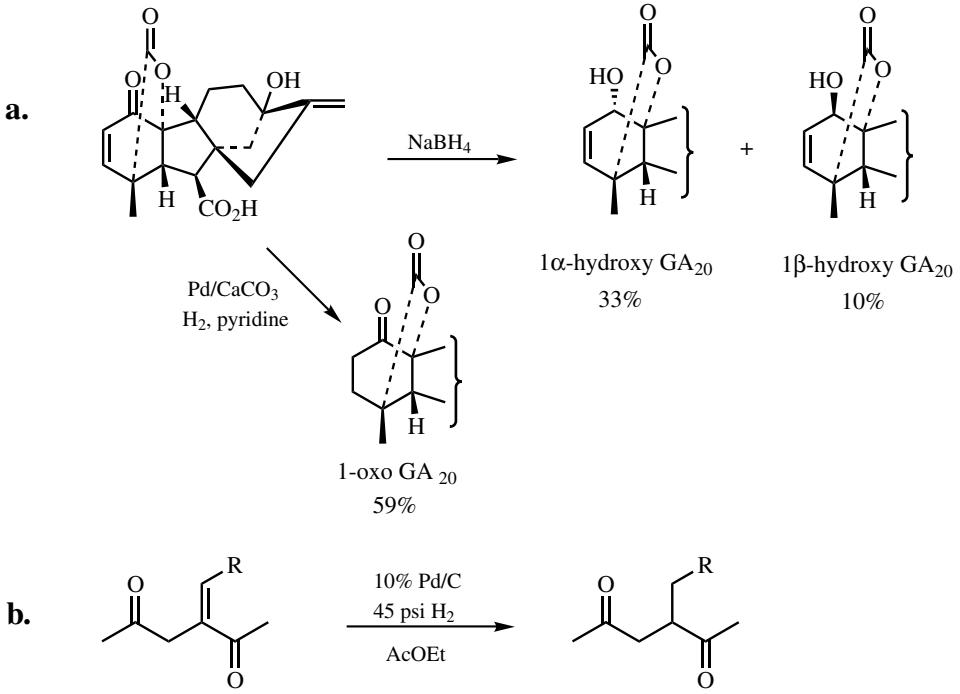
Scheme 3

The regioselectivity of a reaction producing either 1,2- or 1,4-reduction also represents a main consideration in choosing an appropriate reducing method. For example, substituted gibberellins, such as 1α- and 1β-hydroxy GA_5 and GA_{20}, were prepared from a single enone precursor by 1,2-reduction with $NaBH_4$ (**Eq. a**, **Scheme 4**). Conversely, catalytic hydrogenation of the same enone with 10% $Pd/CaCO_3$ in pyridine afforded the 1,4-reduction product, 1-oxo-GA_{20}.

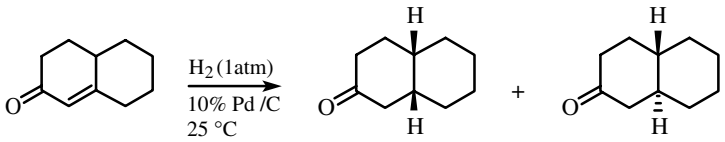
Furthermore, acyclic enones containing an additional non—conjugated carbonyl group were selectively reduced at the double bond under 40 psi with 10% Pd/C in ethyl acetate (**Eq. b**, **Scheme 4**).[18]–[19]

Ring-fused enone systems can be selectively hydrogenated at the double bond in a neutral medium.[20] Acids and bases, however, have a crucial effect on product stereochemistry in hydrogenation of these systems, as illustrated in **Scheme 5**.[21]–[28]

The increased amount of *trans*-fused product obtained under basic conditions was suggested to arise from hydrogenation of the relatively flat enolate ion, which is adsorbed irreversibly onto the catalyst surface. Hydrogenation proceeds by hydride ion transfer



Scheme 4



EtOH	53	47
EtOH, H_2O, HCl	93	7
EtOH, KOH	35–50	65–50

Scheme 5

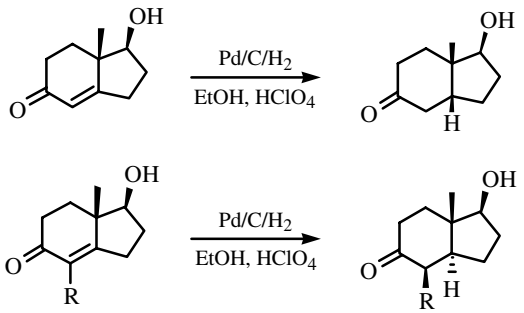
from the metal catalyst, followed by protonation. Conversely, in acidic medium, protonation occurs first and the irreversible adsorption on the catalyst occurs later, followed by transfer of a hydride ion.[11]

Catalytic hydrogenation of an unsaturated ketone was studied by high-pressure kinetic experiments to provide an accurate model for the scale-up of an industrial pilot reactor. The selective reduction of the conjugated double bond was performed in supercritical carbon dioxide as a solvent in the presence of an industrial Pd on alumina catalyst.[29]

Stereochemistry of reduction is also related to the catalyst activity, catalyst concentration, pressure, and even stirring rate, as they all affect the hydrogen availability at the catalyst

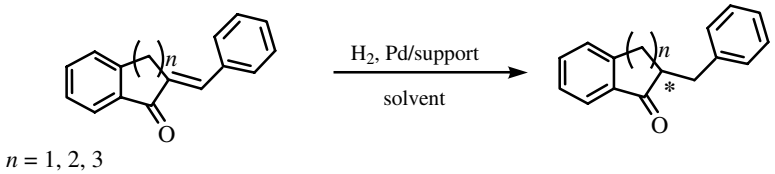
surface. Under conditions of low hydrogen availability, a reversible adsorption becomes significant, and therefore the product stereochemistry is determined by the relative stability of the *cis*- and *trans*-adsorbed species. However, under conditions of high hydrogen availability, product stereochemistry is determined mainly by the nature of the initial adsorption.[11],[12]

Substrate structure has an important influence on stereoselectivity of hydrogenation. For example, hydrogenation of hydrindanone having a trisubstituted double bond gives mainly the *cis*-product (**Scheme 6**),[30] whereas similar compounds with a tetrasubstituted double bond tend to produce the *trans*-isomer. This phenomenon has been rationalized in terms of preferred conformation of the adsorbed enone, which suffers minimal steric interactions.[21]–[28],[31]



Scheme 6

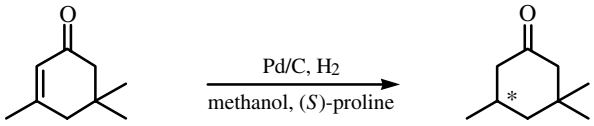
The selective catalytic hydrogenation of exocyclic α,β-unsaturated ketones was successfully utilized in the assymetric synthesis process of the chiral building blocks, α-hydroxy acids.[32] The influence of the catalyst support, solvent and additives in the selective 1,4-reduction was studied in a series of exocyclic enone systems (**Scheme 7**).[33] The best conditions for the selective reduction of the exocyclic double bond were obtained in an apolar solvent like toluene over a range of Pd-supported catalysts (Pd black, Pd/TiO_2, Pd/Al_2O_3, Pd/SiO_2, Pd/C). The usage of polar solvents like methanol and DMF decreased the selectivity dramatically but addition of triethyl amine, pyridine or potassium acetate to the reaction mixtures revert this result successfully.



n = 1, 2, 3

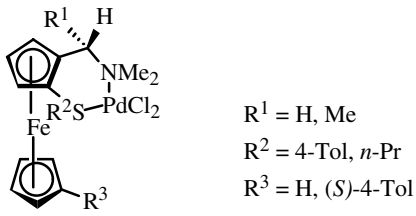
Scheme 7

The enantioselective reduction of a prochiral substrate to produce a nonracemic chiral product is of crucial importance in organic synthesis. One way to achieve this goal is by using an asymmetric catalyst. For example, the asymmetric hydrogenation of isophorone was achieved in 80% ee by using (*S*)-proline as a chiral ligand. Thus, the enantioselective reduction of isophorone was achieved in the presence of Pd/C with stoichiometric amounts of the chiral ligand in methanol at room temperature (**Scheme 8**).[34],[35]



Scheme 8

A different type of catalyst for the selective reduction of enones with molecular hydrogen consists of a series of palladium(II) ferrocenylamine sulfide complexes (**Scheme 9**). These palladium complexes are synthesized in a few steps from inexpensive starting materials.[36]–[38] They are air and moisture stable and active at room temperature under mild hydrogen pressure (80 psi).[39] For example, using this method, cyclohexenone was selectively reduced to cyclohexanone in 100% yield. In comparison, other transition metal catalytic systems, such as $Mo(CO)_6/PhSiH_3$,[40] $Co(CO)_6(PBu_3)_2/H_2$,[41] and $K_3[Co(CN)_5H]$[42] gave the hydrogenation product in 25%, 86%, and 75% yield, respectively. The selective reduction of carbon–carbon double bonds conjugated to carbonyl compounds, such as carboxylic acids, esters, amides, and lactone groups can be completed quantitatively within 0.25–12 h using the ferrocene-based catalyst. The rate of the reduction of double bonds conjugated to more basic carbonyl functionalities, such as amides, was shown to be faster than with those conjugated to more electron-withdrawing groups (i.e., carboxylic acids). Also, the reaction rate is faster with flexible enones that can adopt either cisoid or transoid conformation than with those in a frozen conformation. That could indicate that the Pd catalyst interacts with the carbonyl and double bond simultaneously as was suggested for the $Mo(CO)_6/PhSiH_3$ system.[36]–[38]

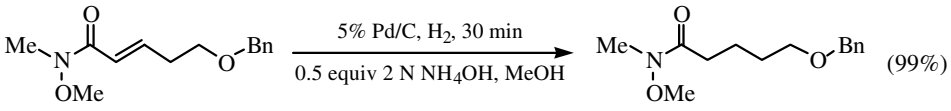


Scheme 9

An additional binuclear complex which effectively catalyzes, at lower hydrogen pressures (1–10 psi), the selective reduction of the conjugated double bond in enones is formed by the reaction of $[(^tBu_2PH)PdP^tBu_2]_2$ with oxygen.[43]–[44]

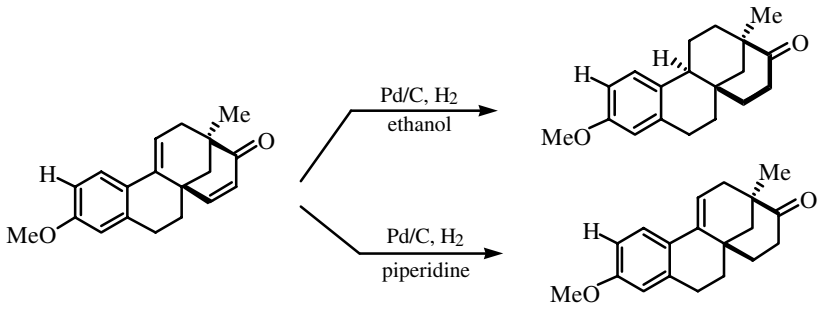
Chemoselective reduction of enones without cleavage of protecting groups is highly desirable in organic synthesis. An attractive catalytic system that addresses this issue is based on the Lindlar catalyst (i.e., 5% palladium on calcium carbonate, poisoned with lead),[45] which can reduce α,β-unsaturated carbonyl compounds at room temperature in methanol. The selectivity and product yields are comparable to the above-described $Pd/C/H_2$ system as well to Pd/C–ammonium formate[46] and Pd/C–methanol-triethylamine.[47] The method is highly chemoselective and compatible with protecting groups like acetonide, *tert*-butyldimethylsilyl (TBDMS), and benzyl, which are left intact under the reaction conditions. Moreover, chemoselective conjugate reduction of α,β-unsaturated carbonyl compounds can

be achieved even in the presence of an *O*-benzyl protecting group using 5% Pd/C, 1 atm H_2, and 0.5 equiv 2 N NH_4OH in methanol at room temperature (**Scheme 10**).[48] Control experiments indicated that in the absence of NH_4OH the benzyl protecting group was completely removed. Another convenient method for the conjugate reduction of enones in the presence of the protecting group PMB (4-methoxybenzyl) utilizes a Pd/C–pyridine combination.[49]



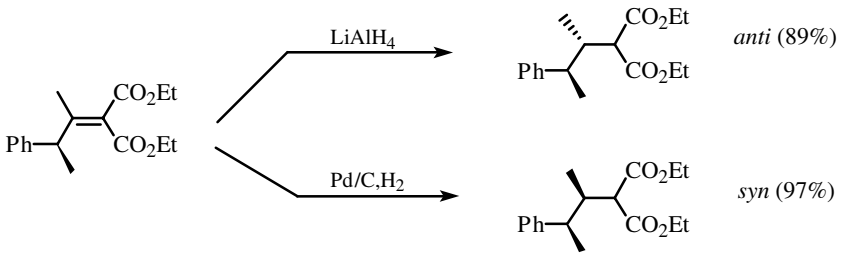
Scheme 10

The selective reduction of polyfunctional molecules is of continuous interest in organic synthesis, especially in the field of natural products. Tetracyclic systems like styrenoid ketones have been found to be attractive precursors for the synthesis of cardiac glycosides.[50] When the styrenoid bond in the enone was hydrogenated over 10% Pd/C in ethanol, at 1 atm of hydrogen and room temperature, the double hydrogenated saturated ketone was formed (**Scheme 11**). However, the conjugated double bond in the unsaturated ketone was selectively reduced when the reaction was performed in piperidine (**Scheme 11**).



Scheme 11

Diastereofacial selection in the conjugate reduction of γ-alkyl-α,β-unsaturated carbonyl derivatives was shown to proceed differently depending on the reagent used.[51] For example, ethylidene malonate was reduced with LAH to produce predominantly the *anti*-product, while catalytic hydrogenation on Pd/C affords the *syn*-product (**Scheme 12**).

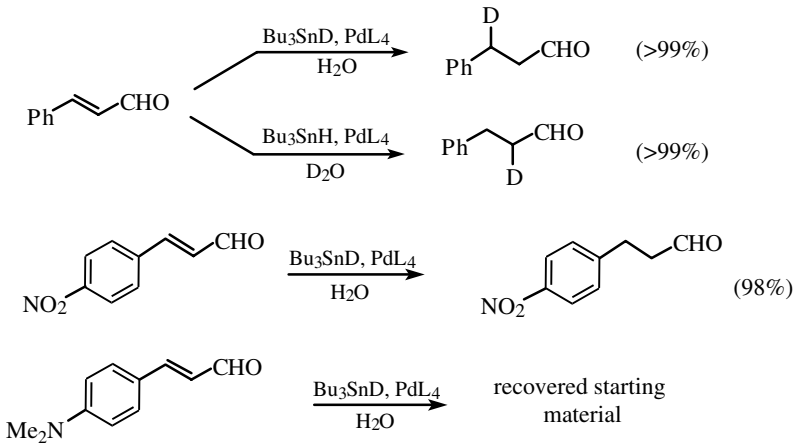


Scheme 12

This significant difference in diastereoselectivity may be due to the palladium metal interaction with the π-electrons of both the aromatic ring and the double bond.

C. PALLADIUM-CATALYZED REDUCTIONS WITH GROUP 14 METAL HYDRIDES

Group 14 metal hydrides, especially those of silicon and tin, are satisfactory unreactive hydride donors as compared with other metal hydrides. They are, generally, poor reducing agents in the absence of a catalyst. Transition metal complexes are attractive transfer agents because they insert readily into Si—H or Sn—H bonds and they also bind specifically to various functional groups. Indeed, a combination of tributyltin hydride, Pd(0) catalyst, and a weak acid, such as ammonium chloride, forms an effective, yet mild tool for conjugate reduction of α,β-unsaturated aldehydes and ketones. With this system, reductions occur with high regioselectivity. Thus, the use of either tributyltin deuteride or D_2O provides a useful approach for deuterium incorporation into either the β- or the α-position, respectively (**Scheme 13**).[52] Similar results are obtained with other acidic cocatalysts, such as zinc chloride, acetic acid, and tributyltin triflate.[53],[54]

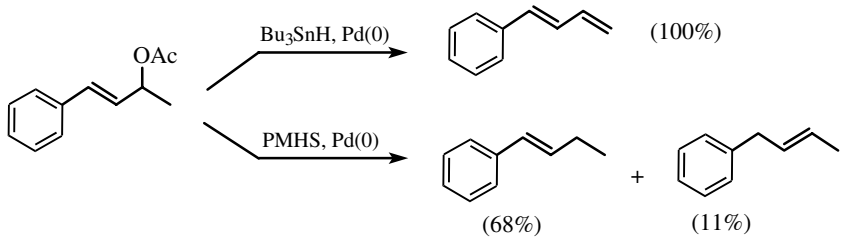


Scheme 13

The sensitivity of the above-described reducing system to the electronic density at the double bond has great potential in terms of chemoselectivity. In addition, this system also allows chemoselective reductive cleavage of allylic heterosubstituents even in the presence of aldehydes, benzylic acetate, and benzylic chloride groups. Benzylic functions are normally as reactive as their allylic analogs when using standard hydride reducing agents.[55]

The use of a Pd(0) catalyst and polymethylhydrosiloxane[56] (PMHS) as a hydride donor offers greater advantages[57]–[59] in comparison with the tributyltin hydride–palladium system described above.[35],[47],[60] Although, in general, PMHS is a much weaker reducing agent than tributyltin hydride, when it is used to reduce π-allylpalladium intermediates it operates with equal efficiency, giving rise to reductive cleavage of allylic heterosubstituents. The stability, nontoxicity, and low cost of PMHS makes it a more convenient reagent than Bu_3SnH. Moreover, PMHS is added to a reaction mixture in a single portion, and products are easily separated from the resultant polysiloxane by-products by filtration or distillation.

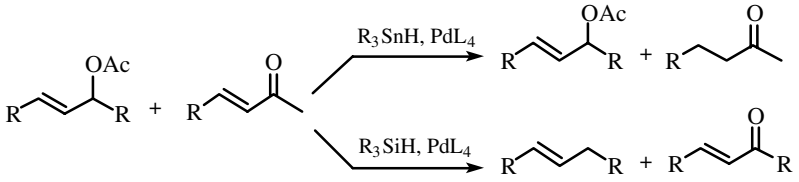
A study that compares the hydride donor characteristics of PMHS and Bu_3SnH has shown remarkable differences between the two.[39] As mentioned before, Bu_3SnH is capable of reducing a large variety of polyfunctional allylic heterosubstituents. However, its reaction with compounds possessing a relatively acidic hydrogen α to the allylic unit leads to subsequent β-hydride elimination from the π-allylpalladium intermediate to yield the corresponding diene. Conversely, when PMHS was employed no β-hydride elimination side products interfered with the allylic reduction reaction (**Scheme 14**).



Scheme 14

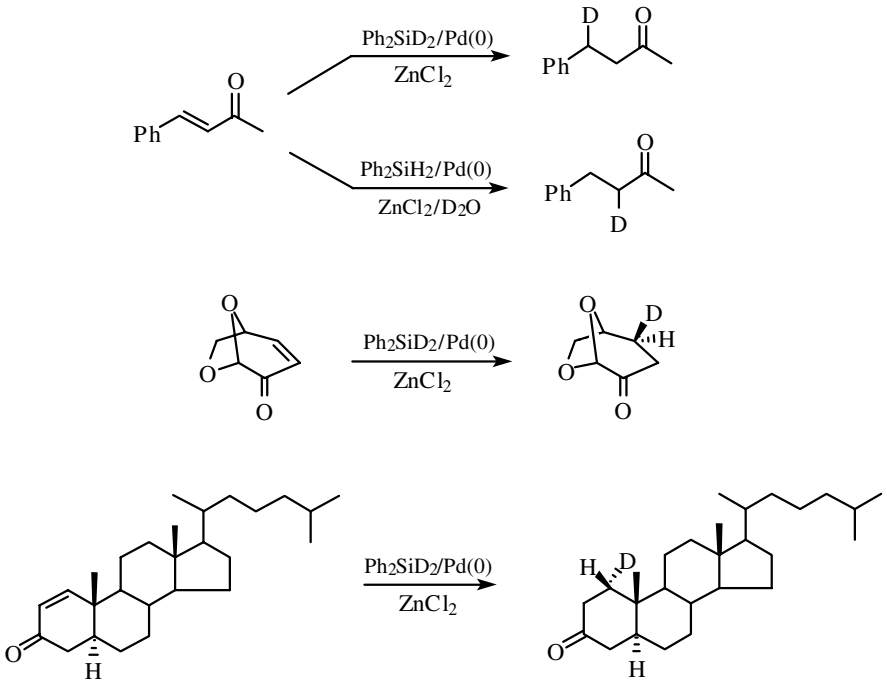
An additional advantage of using the silicon rather than the tin hydride system is manifested by the fact that decomposition of the latter becomes significant when formation of the π-allylpalladium intermediate is slow.

Moreover, the reactivity differences between the tin and silicon hydrides can be exploited for functional-group differentiation. For example, in the presence of Pd(0), tributyltin hydride reduces α,β-unsaturated aldehydes and ketones rapidly but silicon hydrides are unable to do so. Thus, the treatment of a mixture of an allylic acetate and an unsaturated ketone with tin hydride and Pd(0) catalyst results in total conjugate reduction of the latter and unreacted allylic acetate. In contrast, employment of silicon hydride provides complementary chemoselectivity: allylic reduction was completed before any reduction of the Michael acceptor could be detected (**Scheme 15**).



Scheme 15

Even in the presence of other silicon reagents like Ph_2SiH_2, Michael acceptors are totally unaffected. The addition of catalytic amounts of zinc chloride to the Pd(0)/silane system, however, creates a three-component mixture that allows rapid conjugate reduction of α,β-unsaturated aldehydes and ketones. The conjugate reduction was shown to be both regio- and stereoselective. The use of dideuterodiphenylsilane in the reduction of unsaturated ketones yielded saturated ketones containing one deuterium atom at the β-position. On the other hand, when traces of D_2O were added to the nondeuterated mixture, incorporation of deuterium occurred in the α-position (**Scheme 16**).[61],[62]

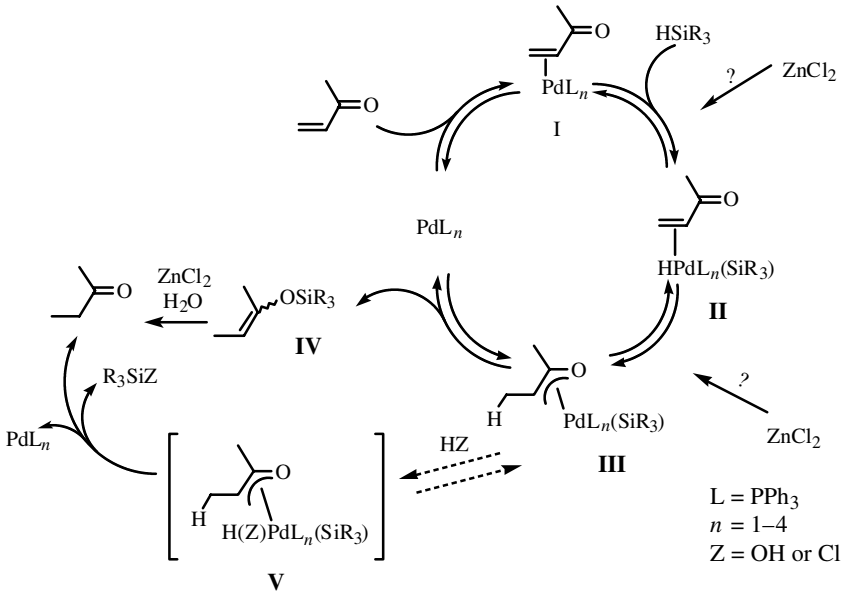


Scheme 16

In conjugate reduction of enones with other transition metals such as chromium, the rates of reduction were shown to be dependent on the conformation of the substrate, with faster reactions being observed with the cisoid forms as compared with the transoid ones.[63] However, with the Pd/Si/Zn system, the rigid transoid enone of cyclohexenone and the flexible enone of acetylcyclohexene are both reduced in comparable rates. This indicates that palladium interacts exclusively with the olefinic part of the enone without significant participation of the carbonyl. Interestingly, this method is highly selective for unsaturated ketones and aldehydes, as the reduction of corresponding α,β-unsaturated carboxylic acid derivatives, such as esters, amides, and nitriles, is very slow under the conditions used. Thus, benzylideneacetone is selectively and cleanly reduced in the presence of methyl cinnamate, cinnamonitrile, or cinnamamide.[40]

The proposed catalytic cycle for the above-described conjugate reduction is outlined in **Scheme 17**. Initial coordination of the nucleophilic Pd(0)–phosphine complex to the electron-deficient olefin to form complex **I** is a reversible process that occurs rapidly at room temperature. Oxidative addition of the silicon hydride moiety to complex **I** would result in the hydrido olefin complex **II**. Migratory insertion of the hydride ligand into the electrophilic β-carbon of the coordinated olefin can result in the palladium enolate intermediate **III**. Reductive elimination of the silicon moiety and the enolate completes the catalytic cycle and forms the silyl enol ether **IV**. The latter is prone to acid-catalyzed hydrolysis to produce the saturated ketone.[40]

The role of the Lewis acid cocatalyst, in addition to its obvious role in catalyzing hydrolysis of the silyl enol ether, is probably that of polarizing the substrate, thereby facilitating migratory insertion of hydride into the olefin (**II** to **III** in **Scheme 17**).



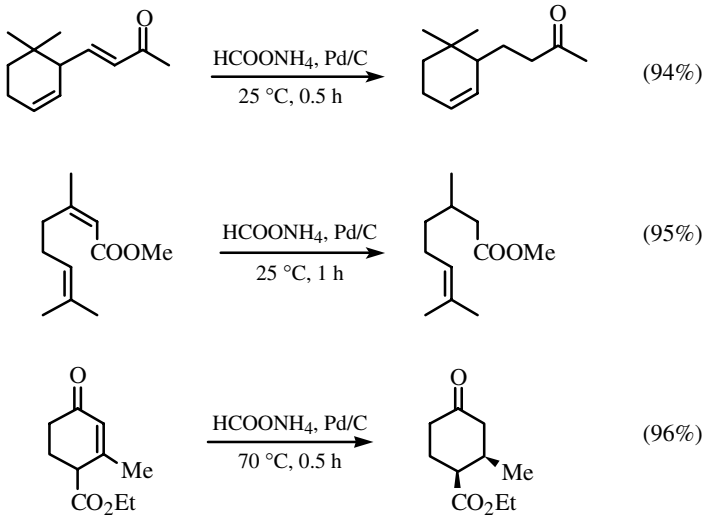
Scheme 17

A possible alternative pathway for the transformation of **III** to a saturated ketone, one that circumvents the formation of silyl enol ether **IV**, involves the protonolysis of the palladium enolate **III** via oxidative addition of a proton donor ZH (Z = OH or Cl). The resultant Pd(IV) intermediate, **V**, undergoes double reductive elimination to produce the saturated carbonyl and R_3SiZ, along with regeneration the Pd(0) catalyst.

The generality of the Pd/Si/Zn method, the mild reaction conditions used, and the simple and convenient experimental procedure make it a method of choice for conjugate reduction of enones.

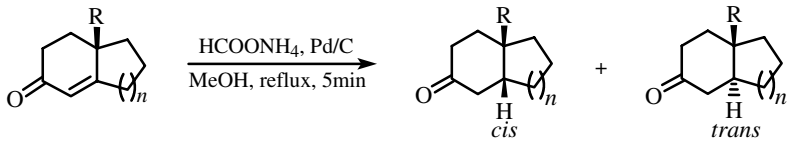
D. PALLADIUM-CATALYZED REDUCTIONS WITH OTHER HYDROGEN DONORS

Trialkylammonium formate and catalytic amounts of palladium on carbon form a convenient reducing system for reduction of a number of organic functional groups, including α,β-unsaturated aldehydes, ketones, and esters.[64] Typical reductions are carried out at 100 °C with 10% excess formic acid, 30% excess triethyl or tributylamine, and Pd/C (10%). The disadvantage of this procedure is the long reaction time required. For example, regioselective reduction of citral and β-ionone is completed after 44 and 20 h, respectively.[45] Shorter reaction time periods of 8–20 minutes were obtained at 110 °C by utilizing ammonium formate in acetic acid as a hydrogen source[65],[66]. A milder experimental procedure consists of the simple stirring of the conjugate carbonyl compound (1 mmol), ammonium formate (6 mmol), and 10% Pd/C in methanol for 0.5–4 h at 25 or 70 °C depending on the substrate.[34] Conjugated aldehydes, ketones, carboxylic acids, and esters are found to undergo exclusive hydrogenation of the conjugated double bond, leaving other functional groups in the molecule unaffected. The reductions are fairly fast and the yields are almost quantitative. Some examples are given in **Scheme 18**.



Scheme 18

The ammonium formate–Pd/C (10%) system was shown to reduce cyclic α, β-unsaturated ketones to the corresponding saturated ketones under reflux in methanol within 5 min.[67] The procedure was exemplified with bicyclo[4.3.0]nonenones and bicyclo[4.4.0]-decalenones as substrates because of their importance in steroid and terpenoid fields (**Scheme 19**). The observed stereoselectivity with some of the substrates is different from the stereochemistry of the conventional hydrogenation reaction (ratios in parentheses, **Scheme 19**), indicating that the mechanism of these transfer hydrogenation reactions is different from that of a standard catalytic hydrogenation with hydrogen gas.[68]



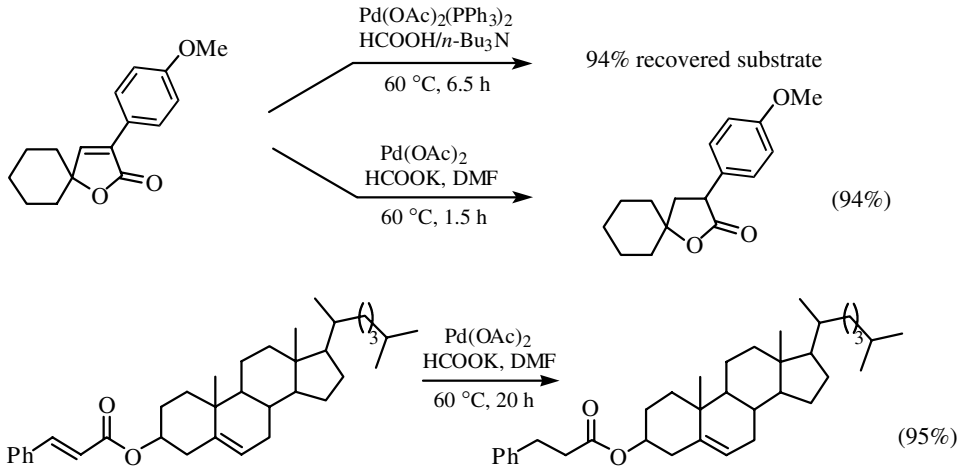
Enone	Yield (%)	*cis*/*trans*[a]
n = 1, R = H	85	90:10 (100:0)
n = 1, R = Me	80	100:0 (100:0)
n = 2, R = H	92	76:24 (43:57)
n = 2, R = Me	86	100:0 (100:0)
n = 2, R = COOEt	76	77:23 (<5:>95)

[a] The ratios in parenthesis are those for conventional hydrogenation.

Scheme 19

Substituted γ-butyrolactones are attractive synthetic targets because of their importance as neurological drugs[69]–[71] as well as synthetic intermediates.[72]–[77] Selective reduction of trisubstituted butenolides may represent a convenient entry into substituted γ-butyrolactones. Since treatment of a butenolide with an excess of HCOOH/n-Bu_3N in the presence of

$Pd(OAc)_2(PPh_3)_2$ does not lead to conjugate reduction (**Scheme 20**),[78] a new approach was developed using potassium formate. A typical procedure involves simple addition of $Pd(OAc)_2$ (0.098 mmol) to a DMF solution of the substrate (2.0 mmol) under inert atmosphere. Addition of potassium formate and heating the mixture to 60 °C for a period of 1.5–20 h, depending on the substrate, produces the desired butyrolactone (**Scheme 20**).

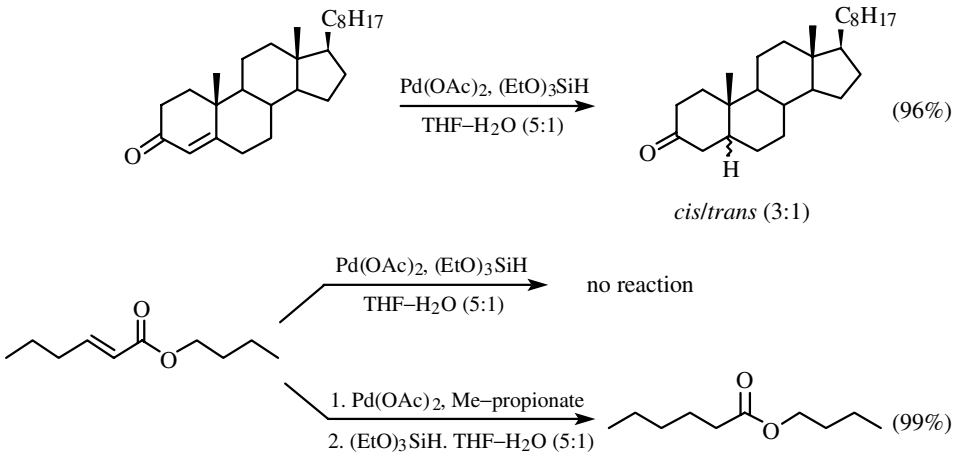


Scheme 20

An additional methodology for the selective reduction of unsaturated acyclic and cyclic carbonyl compounds is composed of refluxing for 15–45 minutes a mixture of limonene and the enone substrate in the presence of 10% Pd/C.[79] For example, the reduction of β-octalone afforded the *cis* isomer in 83% selectivity, which is comparable to the results obtained with hydrogen (**Scheme 3** and **5**) and ammonium formate (**Scheme 19**). The high yields and selectivity as well as the no need for an acid or basic medium makes this method very convenient.

Although heterogeneous catalysts are often simple and convenient to use, they are usually less selective than the homogeneous systems. A highly chemoselective and stereoselective heterogeneous hydrogenation catalyst consists of palladium metal dispersed in a siloxane polymer matrix.[80] The reduction process simply involves the addition of triethylsiloxane (2.5 equiv) to a solution of the α,β-unsaturated carbonyl compound (1 equiv) and palladium acetate (0.05 equiv) in a mixture of THF and water (5:1) at room temperature for 0.5–5 h. Interestingly, water must be present in the reaction medium. No external source of hydrogen is needed as the hydrogen gas is generated *in situ*. The molecular hydrogen is probably produced in the hydrolysis of the Si—H bonds. It is known that R_3Si—H compounds react with HOR′ species in the presence of metal salts to form R_3Si—OR′ and H_2.[81] The isolation of the products involves a very simple procedure of filtration, drying, and removal of the solvent. Although this method shows high chemoselectivity for some unsaturated carbonyl compounds, others, like (*E*)-butyl 2-hexenoate, were totally unreactive (**Scheme 21**). Surprisingly, addition to the reaction solution of methyl propyonate (1 equiv or 10 mol %) prior to the introduction of triethoxysilane creates a more powerful catalyst that readily reduces the unreacted compounds mentioned above (**Scheme 21**). It was shown that

soluble palladium complexes can be formed by the reaction of Pd-black with acetylenes. Therefore, the improved reactivity may arise from the formation of a more reactive soluble Pd–methyl propionate species.



Scheme 21

E. SUMMARY

This section outlines three main approaches to the conjugate reduction of α,β-unsaturated carbonyl compounds utilizing palladium catalysts.

The first approach consists of those systems that utilize molecular hydrogen as the reducing agent. The reaction conditions, such as solvent, acidity/basicity, catalyst type and concentration, hydrogen pressure, and stirring rate have a great effect on the efficiency, stereochemistry, and chemoselectivity of these hydrogenation reactions.

The second strategy involves addition of a group 14 metal hydride to palladium. For example, a combination of either tributyltin hydride or various silicon hydrides and palladium catalyst are efficient systems that affect the conjugate reduction of enones with high chemoselectivity and regioselectivity.

Finally, the use of other hydrogen donors, including various formate salts, are convenient reducing reagents for the Pd-catalyzed reduction of α,β-unsaturated carbonyl compounds.

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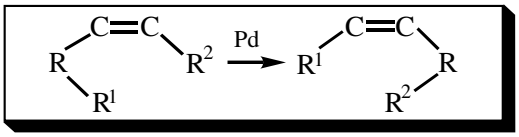

VII.3 Palladium-Catalyzed Isomerization of Alkenes, Alkynes, and Related Compounds without Skeletal Rearrangements

EI-ICHI NEGISHI

A. INTRODUCTION

The ability of Pd to participate in both hydrometallation and dehydrometallation suggests that Pd and its complexes can serve as catalysts for isomerization of alkenes and alkynes via a series of hydropalladation–dehydropalladation, that is 1,2-H shift. On the other hand, Pd-induced allylic rearrangement provides a mechanism whereby alkenes can isomerize via 1,3-shift. In either of these processes, the crucial requirement is the presence or ready availability of an empty coordination site. As amply demonstrated throughout this Handbook, Pd is imminently capable of serving as the catalyst center for isomerization of alkenes and alkynes.

Of various types of Pd-catalyzed isomerization reactions, allylic rearrangements represented by **Scheme 1** are ubiquitous and extensively discussed in **Part V**. These reactions are therefore excluded from this section.

Aside from the allylic rearrangements, however, relatively little has been reported on Pd-catalyzed alkene and alkyne isomerization *per se*, even though many scattered examples of isomerization have been discussed as side reactions, which are mostly unwanted.[1]–[3]

In this section, attention is focused primarily on selective alkene and alkyne isomerization reactions of synthetic interest. A limited number of studies on the Pd-catalyzed isomerization of monoenes including its mechanistic aspects will also be discussed.

B. SELECTIVE ISOMERIZATION OF ALKENES AND ALKYNES

B.i. Isomerization of Isolated Dienes to Conjugated Dienes

1, 5-Cyclooctadiene can be isomerized to 1,3-cyclooctadiene in essentially quantitative yield in the presence of a catalytic amount of $Cl_2Pd(PhCN)_2$[4] (**Scheme 2**).

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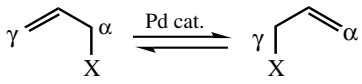
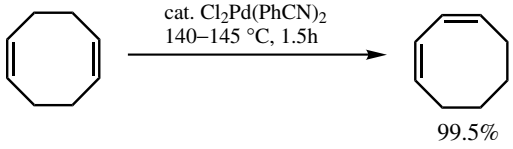


Scheme 1

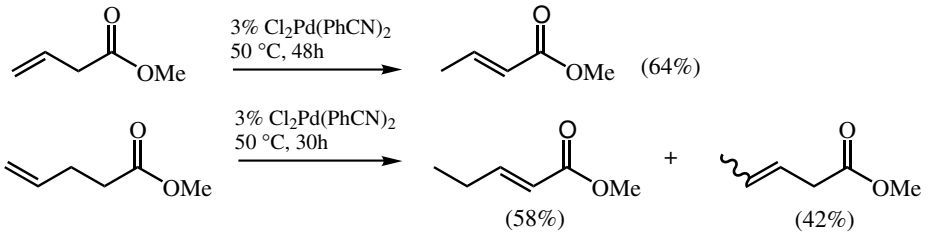


Scheme 2

This reaction, reported in 1968, represents one of the earliest (if not the earliest) examples of Pd-catalyzed highly selective isomerization reactions. Curiously, this study[4] also represents an isolated investigation of this class of isomerization reaction.

B.ii. Isomerization of ω-Carbonyl Alkenes to α, β-Unsaturated Carbonyl Derivatives

The Pd- or Ni-catalyzed isomerization reaction of ω-carbonyl alkenes shown in **Scheme 3** was recently reported.[5] This is another thermodynamically favorable process. The results obtained with methyl 4-pentenoate appear to represent a case of an incomplete reaction. Further development of the reaction is desirable.



Scheme 3

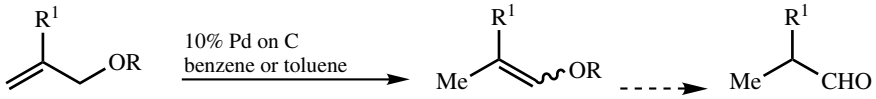
B.iii. Isomerization of Allyl Ethers to Vinyl Ethers

Isomerization of allyl ethers to vinyl ethers is yet another thermodynamically favorable C═C bond isomerization process.[6],[7] The results shown in **Table 1**[6] clearly indicate that it must be a generally favorable reaction of considerable synthetic promise. It should also be noted that the vinyl ether products should readily be convertible to the corresponding aldehydes. Other late transition metals, such as Rh,[8] have also been shown to be effective in catalyzing related alkene isomerization reactions. At present, however, their relative merits and demerits are not clear. Also unclear is whether C═C double bonds more remote than in allyl ethers can also be isomerized.

B.iv. Isomerization of α, β-Unsaturated Ynones and Propargyl Alcohols

Isomerization of α, β-unsaturated ynones into $\alpha,\beta,\gamma,\delta$-unsaturated dienones in the presence of a Pd–PPh_3 complex[9] promises to be of considerable synthetic utility. Some representative results are summarized in **Table 2**.[9] Curiously, however, the same research

TABLE 1. Pd-Catalyzed Isomerization of Allyl Ethers to Vinyl Ethers



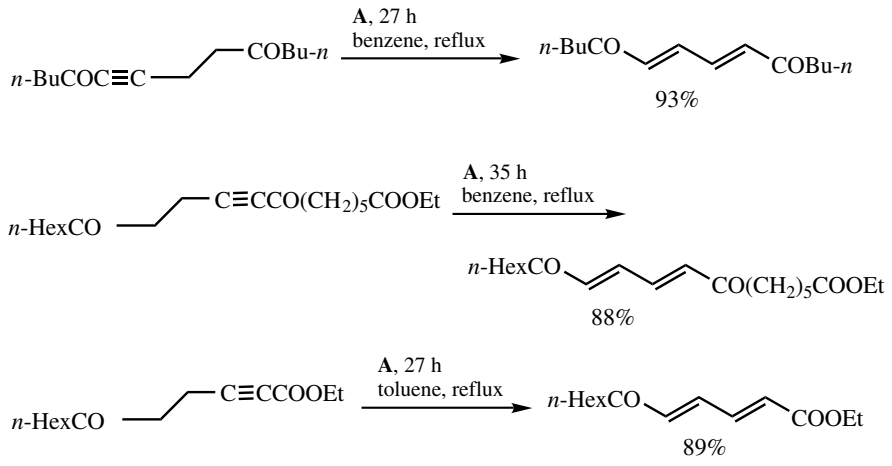
R	R^1	Time (h)	Yield (%)	*cis/trans*
CH_2CH_2CHO	Me	8	95	—
CH_2CH_2COMe	H	17	93	76:24
	Me	18	97	—
n-Bu	H	5	75	64:36
	Me	5	95	—
Ph	H	60	97	69:31
	Me	140	80	—
$CH_2CH\text{-}CH_2$ (O)	H	12	93	77:23
$CH_2CH_2CH(OH)Me$	Me	17	65	—

TABLE 2. Pd-Catalyzed Isomerization of α,β-Unsaturated Ynones to Dienones

$RCOC\equiv C(CH_2)_2R^1$			Time	Yield (%) of RCO(allyl)R	
R	R^1	Catalyst	(h)		Comment
t-Bu	Me	$Pd(OAc)_2$, PPh_3	22	73	A minor amount of the *E,Z*-isomer
Cy	H	$Pd(OAc)_2$, dppb	21	73	
Cy	Et	$Pd(OAc)_2$, PPh_3	2	90	
Ph	Et	$Pd(OAc)_2$, PPh_3	0.75	82	
	Et	$Pd(OAc)_2$, PPh_3	4.5	74	
Ph 	Et	$Pd_2(dba)_3 \cdot CHCl_3$ dppb	1.25	83	

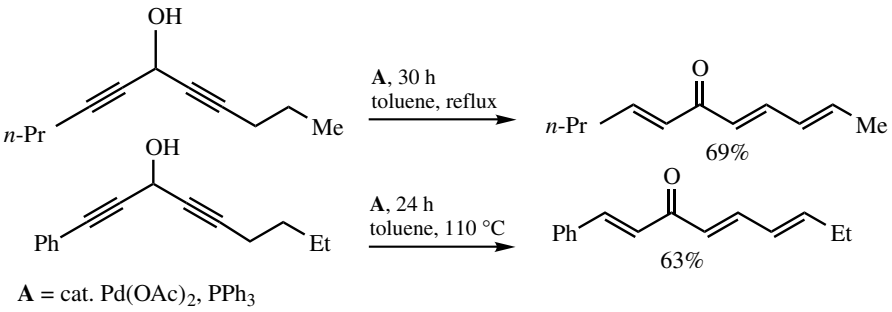
group[10] reported later that PPh_3 alone in the absence of Pd would induce the same isomerization in comparable yields at comparable temperatures (60–140 °C) without clarification of the role of Pd complexes in the reactions shown in **Table 2**.

Some additional examples of the allegedly Pd-catalyzed isomerization reactions were also reported, as shown in **Schemes 4**[11] and **5**.[12]



A = cat. $Pd(OAc)_2$, PPh_3

Scheme 4



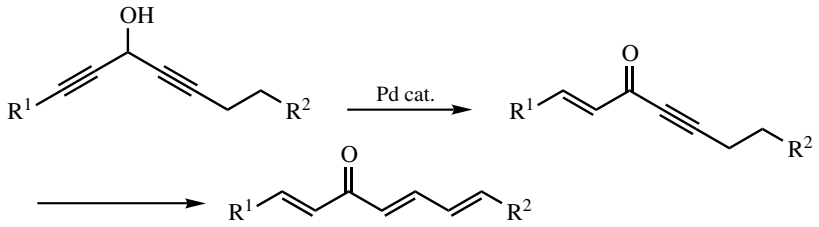
A = cat. $Pd(OAc)_2$, PPh_3

Scheme 5

As propargylic alcohols can be isomerized to α,β-unsaturated enones under Pd-catalyzed conditions,[13] the isomerization reaction of 1,4-diyn-3-ols shown in **Scheme 5** likely proceeds via enynone intermediates, as shown in **Scheme 6**. In view of the same transformation catalyzed by PPh_3 without Pd,[10] it is very desirable to firmly establish the necessity for Pd.

B.v. Isomerization of Monoenes and Its Mechanistic Details

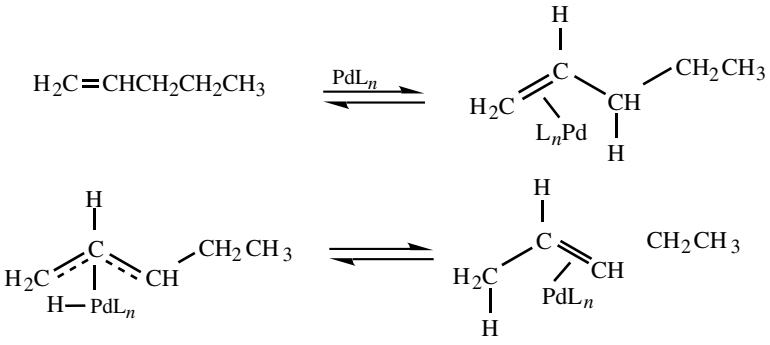
Aside from the formation of stereoisomeric mixtures, those isomerization reactions discussed above are generally highly selective because of significant resonance stabilization effects exerted by π-bonds and filled nonbonding orbitals. In the absence of such



Scheme 6

favorable effects, isomerization of either terminal or internal alkenes would produce mixtures of internal alkenes. In general, such reactions would be of little synthetic interest. They would indeed represent unwanted side reactions to be avoided.

Isomerization of 1-pentene in the presence of $Cl_2Pd(PhCN)_2$ in benzene was reported to give a roughly 75:25 mixture of *trans*- and *cis*-2-pentenes.[14] Examination of deuterium distribution in the isomerization of 1,2-dideuterio-1-pentene indicated that the reaction proceeded by the intramolecular transfer of H and D. The same catalyst was not effective in redistributing D in *trans*-1,2-dideuterioethylene. These results support the 1,3-H shift mechanism (**Scheme 7**) in preference to the 1,2-H shift mechanism.

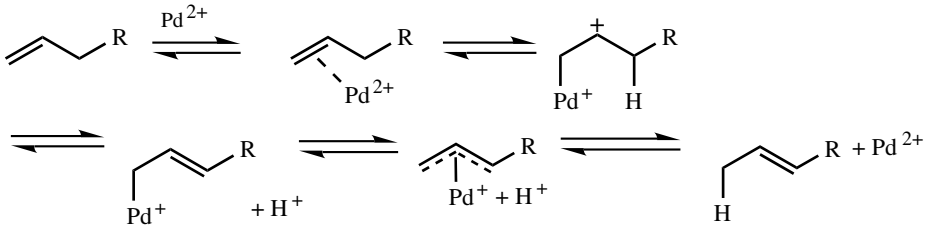


Scheme 7

In a more recent study,[15] 1-octene was isomerized to produce a mixture containing *trans*-2-octene (~50%), *trans*-3-octene (~20%), *cis*-2-octene (~10%), *trans*-4-octene (~10%), and smaller amounts of the other isomers. Interestingly, the catalytic activity of Pd–phosphine complexes was shown to be significantly elevated by Et_2AlCl in PhCl but not by Et_2AlOEt or Et_3Al.

Although the 1,3-H shift mechanism was favored over the 1,2-H shift mechanism in one study,[15] the latter mechanism has also been suggested[9],[13] and supported.[16]

For the isomerization of 1-butene and 2,3-dimethyl-1-butene catalyzed by cationic Pd complexes, such as $Pd(MeCN)_2(BF_4)_2$, an alternate mechanism involving carbocationic intermediates shown in **Scheme 8** has been proposed and experimentally supported.[17],[18] While the modified mechanism appears to be plausible for the reactions studied, it is not clear how generally observable this mechanism might be. It seems reasonable to retain both 1,2- and 1,3-H shift mechanisms for other isomerization reactions.



Scheme 8

C. SUMMARY

1. Palladium catalysis has been shown to be effective in inducing thermodynamically favorable and selective alkene and alkyne isomerization reactions. Aside from the formation of stereoisomeric mixtures, these reactions can be both selective and high-yielding and hence synthetically useful.

2. The synthetic usefulness of Pd-catalyzed isomerization of monoenes has not yet been well demonstrated. Nor have the mechanistic details of the reaction been well delineated. As the reaction must undoubtedly be occurring as side reactions in the Pd-catalyzed hydrogenation and other reactions, further clarification of mechanistic details is desirable.

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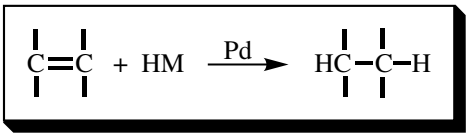

VII.4 Palladium-Catalyzed Hydrometallation

HIDEFUMI MAKABE and EI-ICHI NEGISHI

A. INTRODUCTION

Hydrometallation may be defined as *a process of addition of hydrogen–metal bonds to alkenes, alkynes, and related* π-bonds (**Scheme 1**). Generally, it is a thermodynamically favorable process, primarily because two σ-bonds are formed at the expense of one each of σ- and π-bonds. In most cases, difficulty, if any, is therefore kinetic in nature. In this respect, one should recall a generally applicable and useful guiding principle that, besides the obvious thermodynamic requirements, essentially the only key requirement for a facile hydrometallation is the existence or ready availability of one valence-shell empty orbital for concerted and synergistic frontier orbital interactions briefly discussed in **Sect. II.3.1** (**Scheme 2**). Such concerted hydrometallation processes may also involve strict *syn*-addition, as has often been observed. It is nonetheless important to recall also that the term *hydrometallation* does not imply any specific mechanism, as it merely represents a starting material–product relationship and that hydrometallation can proceed by other mechanisms including polar and radical processes. In such cases, however, facile and highly stereoselective hydrometallation may not generally be observed.

It is well known that, among the main group metals, the group 13 metals, such as B[1] and Al,[2] can undergo facile and highly stereoselective hydrometallation processes, provided that their six-electron hydrido species, that is, HBX_2 and $HAlX_2$, where X represent two identical or different ligands, are available. On the other hand, eight-electron species containing B and Al, such as $NaBH_4$ and $LiAlH_4$, do not readily undergo hydrometallation in accordance with the general discussion presented above. Hydroalumination with $LiAlH_4$ may be observed at high temperatures (>100 °C), but it mostly involves *anti*-addition of H—Al bonds.[3]

Similarly, hydridosilanes, essentially all of which are eight-electron species, do not readily undergo hydrosilation. Hydrostannanes do undergo hydrostannation typically at elevated temperatures, but it must involve various processes including polar and radical processes, as might be suggested by their capricious stereo- and regioselectivity features.[4]

Over the past few decades, Pd complexes have been shown to be effective catalysts for hydrometallation reactions involving both main group and transition metals. Not surprisingly, most of the investigations have dealt with hydrometallation reactions of group 14 metals including Si, Ge, and Sn, which are discussed in **Sects. B** and **C**.

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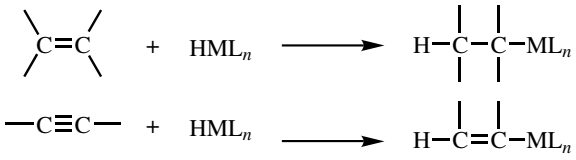
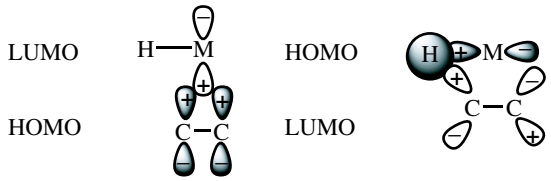


Scheme 1



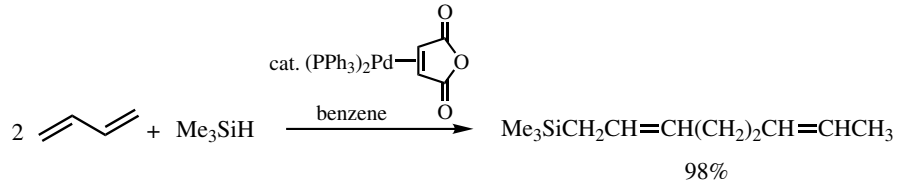
Scheme 2

More recently, however, catalysis by Pd has been shown to be effective in promoting even generally facile hydrometallation reactions, such as hydroboration, hydroalumination, and hydrozirconation.[5] In such cases, objectives may lie in seeking novel regiochemistry, chemoselectivity, enantioselectivity, and so on that are different from those observed under uncatalyzed conditions. In the case of hydroalumination, however, the reaction with alkenes has been surprisingly sluggish even with six-electron hydridoalanes,[2] presumably due to the formation of stable hydridoalane dimers. So, catalysis merely for the sake of kinetic acceleration alone has been very desirable. Those reactions involving B, Al, and Zr are discussed in **Sects. D** and **E**. At present, the scope of Pd-catalyzed hydrometallation appears to be essentially limited to those reactions involving Si, Ge, Sn, B, Al, and Zr.

B. PALLADIUM-CATALYZED HYDROSILATION

B.i. Scope with Respect to π-Substrates

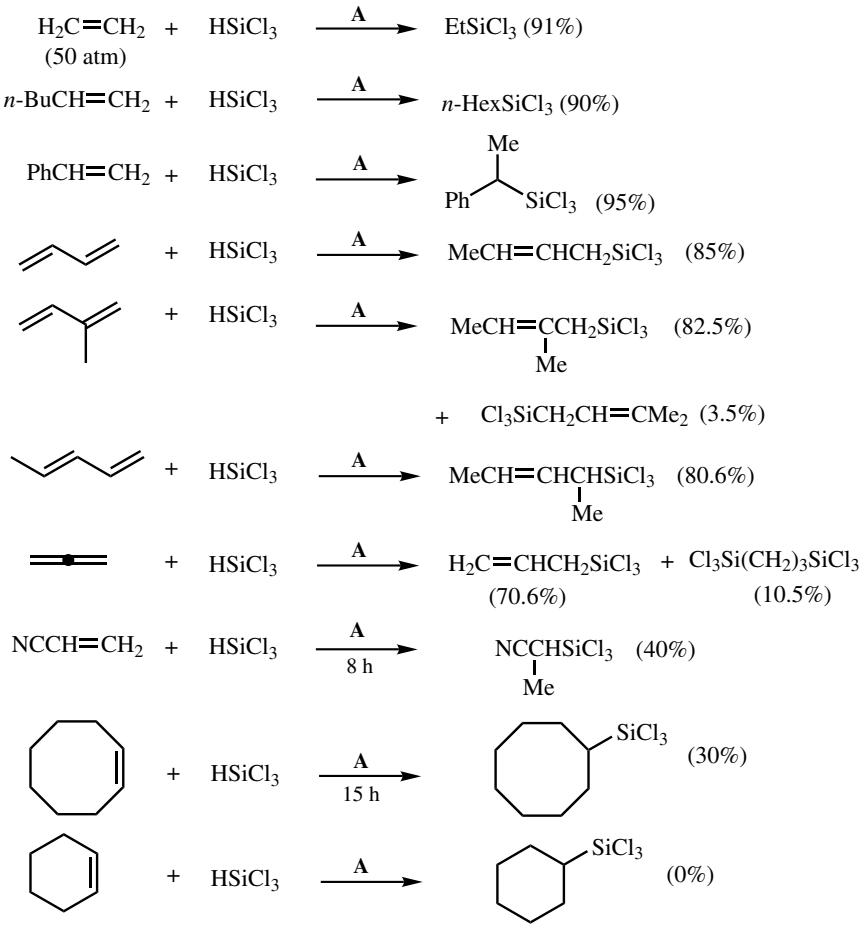
One of the earliest, if not the earliest, reports on Pd-catalyzed hydrosilation is on the reaction of 1,3-butadiene with Me_3SiH in the presence of a catalytic amount of bis(triphenylphosphine)(maleic anhydride)palladium to give a 2:1 adduct in 98% yield reported by Takahashi, Shibano, and Hagihara in 1969[6] (**Scheme 3**). In the same study, the use of $HSiCl_3$ and $HSiMe_2Ph$ was reported to give the more usual 1:1 adduct without specifying structural details.



Scheme 3

Since the transition-metal-catalyzed hydrosilation has been most widely and successfully achieved by using Rh and other transition metal complexes,[7] relatively little attention has been paid to the investigation of Pd-catalyzed hydrosilation. Even so, a couple of dozens of papers published mostly in the 1970s and 1980s have delineated the current scope of Pd-catalyzed hydrosilation, as detailed below.

B.i.a. ***Palladium-Catalyzed Hydrosilation of Alkenes.*** Aside from the above-mentioned study by Takahashi and co-workers[6] and an isolated example of Pd-catalyzed hydrosilation of styrene with $HSiCl_3$ by Kiso, Yamamoto, Tamao, and Kumada,[8] the first systematic study of Pd-catalyzed hydrosilation of alkenes most probably was that by Tsuji and co-workers reported in 1974.[9] In this study, the scope of Pd-catalyzed hydrosilation with respect to (i) substrate structural type, (ii) silanes, and (iii) catalysts including phosphines was delineated for the first time. Some representative results obtained by using $HSiCl_3$ and $Pd(PPh_3)_4$ are shown in **Scheme 4**, which indicate that not

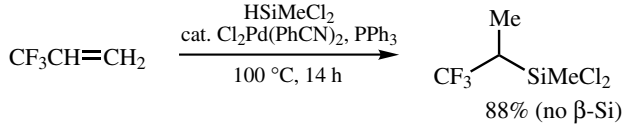


A = 0.1 g of $Pd(PPh_3)_4$ per 0.1 mol each of an olefin and $HSiCl_3$, 100–120 °C, 5–6 h, unless otherwise mentioned.

Scheme 4

only styrene and conjugated dienes reported earlier[6],[8] but also more usual alkenes, such as ethylene and 1-hexene, as well as allenes participate in the reaction at 100–120 °C to give the corresponding hydrosilation products in high yields. However, poor product yields were observed with cyclooctene (30%) and acrylonitrile (40%), and cyclohexene gave no hydrosilation product.[9]

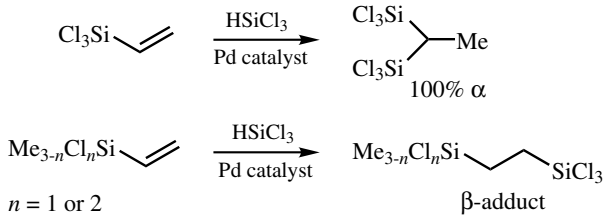
The Pd-catalyzed hydrosilation of heterosubstituted alkenes has led to some noteworthy results. Thus, for example, the reaction of perfluoroalkyl-substituted ethylenes with $HSiMeCl_2$ in the presence of $Cl_2Pd(PhCN)_2$ and PPh_3 produces α-silated derivatives with no sign of β-silation[10] (**Scheme 5**). In sharp contrast, the corresponding reaction catalyzed by $Ru_3(CO)_{12}$ gives a mixture of β-silated alkyl- and alkenylsilanes, and similar results have also been obtained with Rh catalysts.[10] So, the Pd-catalyzed reaction appears to be unique and potentially useful.



$HSiX_3$	(I)(%)	(II)(%)
$HSiMeCl_2$	9	2
$HSiMe_2Cl$	14	75
$HSiMe_2Et$	2	87
$HSi(OEt)_3$	52	0

Scheme 5

In the Pd-catalyzed hydrosilation of silyl-substituted ethylenes with $HSiCl_3$, the α/β silation ratio was shown to depend significantly on the nature of the silyl substituent, as shown in **Scheme 6**.[11] The use of $Ph_2PCH_2PPh_2$(dpm) was reported to be a useful ligand for the preparation of 1,1-bis(trichlorosilyl)ethane.[12]



Pd Catalyst	Yield (%)
$Cl_2Pd(PPh_3)_2$	96
$Pd(PPh_3)_4$	70

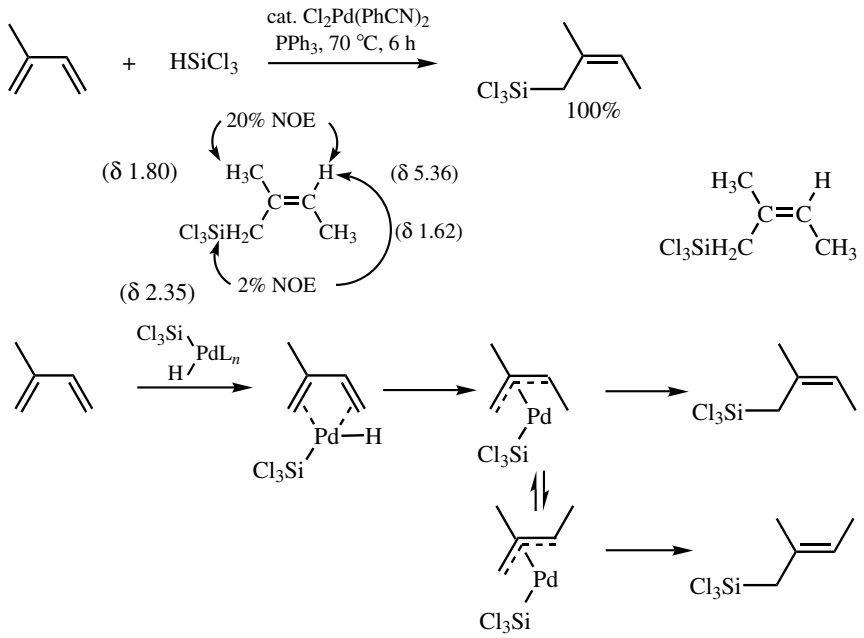
Scheme 6

B.i.b. ***Palladium-Catalyzed Hydrosilation of Conjugated Dienes and Allenes.*** As reported earlier,[6] $HSiCl_3$ underwent hydrosilation of butadiene to give the 1:1 product,

while $HSiEt_3$ gives exclusively the 2:1 product. The use of $HSiMeCl_2$ led to the formation of a mixture of the 1:1 and 2:1 products. The regiochemistry of the reaction of conjugated dienes is conveniently explained by preferential attack of the less hindered C═C bond so as to produce allylpalladium species leading to the formation of allylsilanes. Of the two possible allylic positions, the sterically less hindered of the two ends up bonded to Si.

Various Pd(0) and Pd(II) complexes, such as $Pd(PPh_3)_4$ (85%), $Cl_2Pd(PPh_3)_2$ (90%), $Br_2Pd(PEt_3)_2$ (65%), $I_2Pd(PEt_3)_2$ (61%), and $Pd(OAc)_2 + PBu_3$ (76%), serve as satisfactory catalysts, as indicated by the yields of *n*-$OctSiCl_3$ shown in parentheses. Generally, the relative order of reactivity of phosphines is $PPh_3 > PEt_3 > PBu_3 > PCy_3 > P(OPh)_3$.

Although the stereochemistry of acyclic conjugated dienes remained unestablished, the *Z*-geometry was assigned later by Ojima[13] on the basis of detailed NMR analyses (**Scheme 7**). One reasonable but speculative mechanistic scenario for explaining the observed stereochemistry involves the intermediacy of *s-cis*-isoprene–Pd complex, which is to undergo hydropalladation with the vinyl group so as to produce π-allypalladium species. This species is then converted to the observed product at a rate much faster than stereoisomerization.[13]

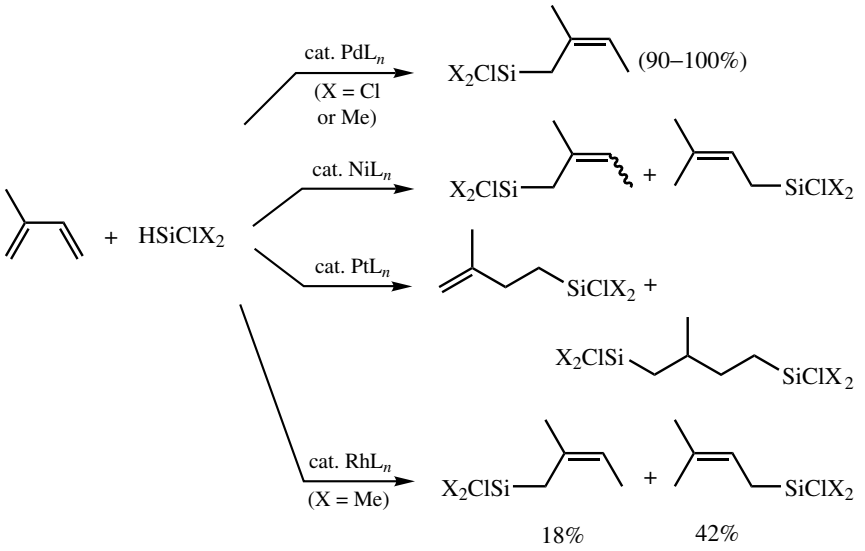


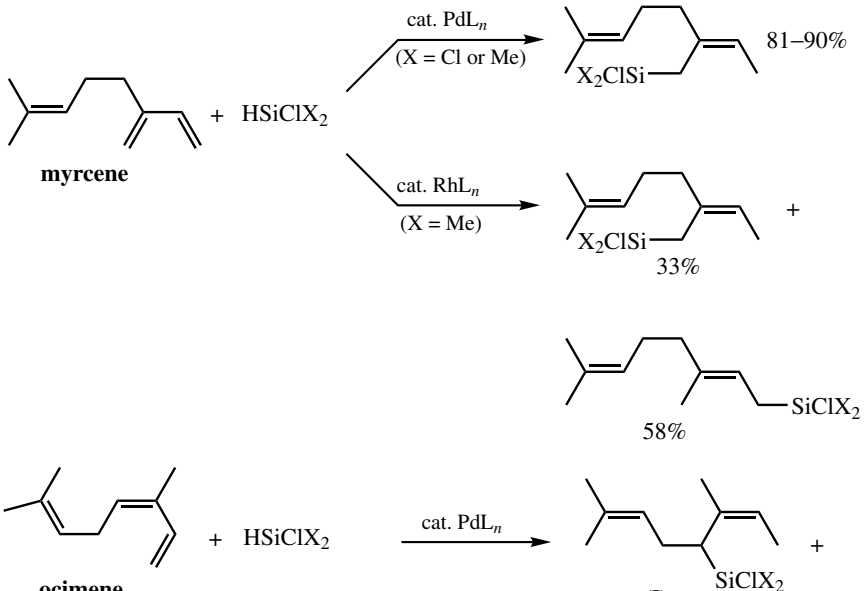
Scheme 7

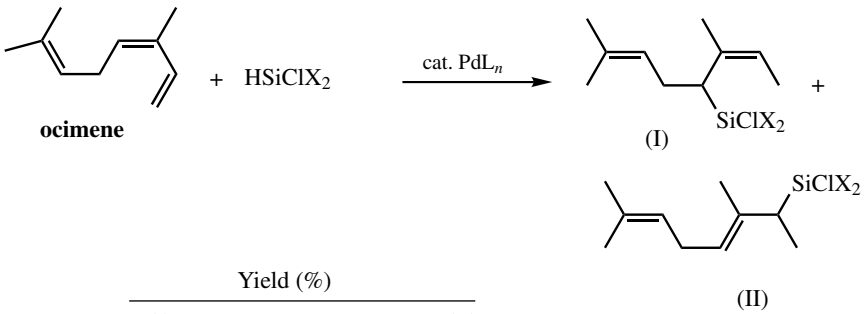
The regio- and stereochemistries observed with isoprene indicated in **Scheme 7** have been shown to be generally observable by using Pd catalysts, and these features are distinct from those observed with other late transition-metal-containing catalysts, as shown in **Scheme 8**.[14]

The synthetic scope of the Pd-catalyzed hydrosilation of conjugated dienes has further been expanded by the development of the stereoselective synthesis of (*Z*)-α-alkylidenecycloalkanols shown in **Scheme 9**.[15]

There have also been many additional examples of Pd-catalyzed hydrosilation of conjugated dienes,[16] which include those employing chiral phosphines, as discussed later.

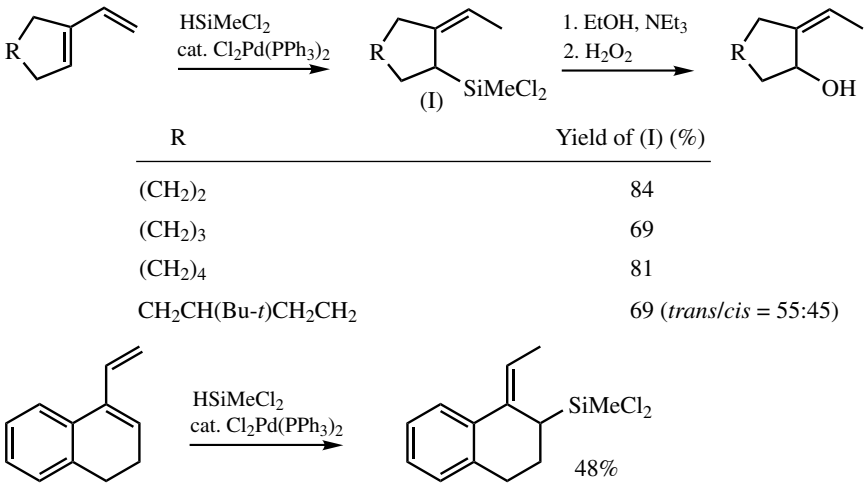






X	Yield (%) (I)	(II)
Cl	42	58
Me	77	0

Scheme 8

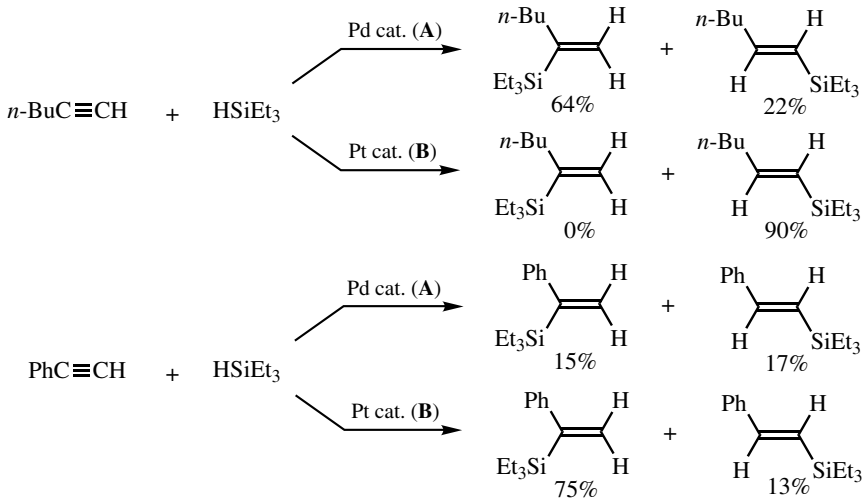


R	Yield of (I) (%)
$(CH_2)_2$	84
$(CH_2)_3$	69
$(CH_2)_4$	81
$CH_2CH(Bu\text{-}t)CH_2CH_2$	69 (*trans*/*cis* = 55:45)

Scheme 9

Aside from the Pd-catalyzed hydrosilation of allene itself shown in **Scheme 4**, few additional examples of Pd-catalyzed hydrosilation of allenes appear to have been reported, even though the corresponding hydrostannation has extensively been investigated, as detailed in **Sect. C**.

B.i.c. ***Palladium-Catalyzed Hydrosilation of Alkynes.*** Relatively little has been reported on the Pd-catalyzed hydrosilation of alkynes. This is in sharp contrast with the corresponding hydrostannation of alkynes discussed later in **Sect. C**. The reaction of terminal alkynes with $HSiEt_3$ in the presence of polyborane-containing Pd and Pt complexes yielded the results summarized in **Scheme 10**,[17] which indicate that Pd and Pt catalysts

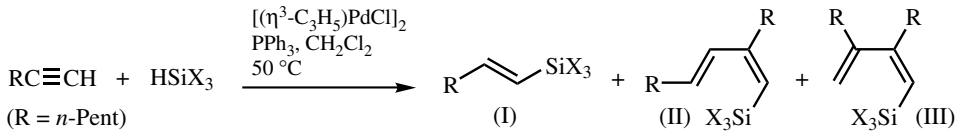


(**A**) = $[(Ph_3P)_3PdCl]_2B_{12}Cl_{12}$ (**B**) = $[(Ph_3P)_3PtCl]_2B_{12}Cl_{12}$

Scheme 10

can lead to significantly different regioselectivity profiles. With 1-hexene, Pd complexes favor α-silation, while highly selective β-silation can be achieved with Pt catalysts. With styrene, however, Pd catalysts give nearly 1:1 mixtures in low yields, while Pt catalysts can produce the α-silyl-substituted products in high yields in 85–89% selectivity.

In a recent study of the reaction of 1-heptyne with $HSiX_3$, where X = Cl and/or Me, in the presence of a Pd–phosphine complex, either 1:1 or 2:1 reaction products were shown to be formed selectively, depending on the structure of silanes[18] (**Scheme 11**). Interestingly, the results closely parallel those observed with butadiene.[6]



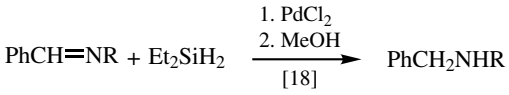
	Yield (%)		
$HSiX_3$	(I)	(II)	(III)
$HSiCl_3$	9	76	15
$HSiMe_2Cl$	97 (β/α = 5.9)	3	—

Scheme 11

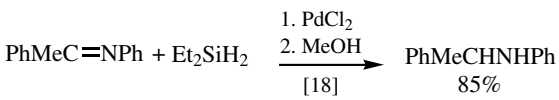
B.i.d. ***Palladium-Catalyzed Hydrosilation of Heteroatom-Containing π-Compounds.*** In a series of studies published in the 1970s, Ojima and co-workers[19]–[21] demonstrated that hydrosilation of imines, isocyanates, and carbodiimides could be catalyzed by Pd complexes, as shown in **Scheme 12**. A related study of the enantioselective reduction of acetophenone with Ph_2SiH_2 was also reported.[22]

B.ii. Palladium-Catalyzed Asymmetric Hydrosilation

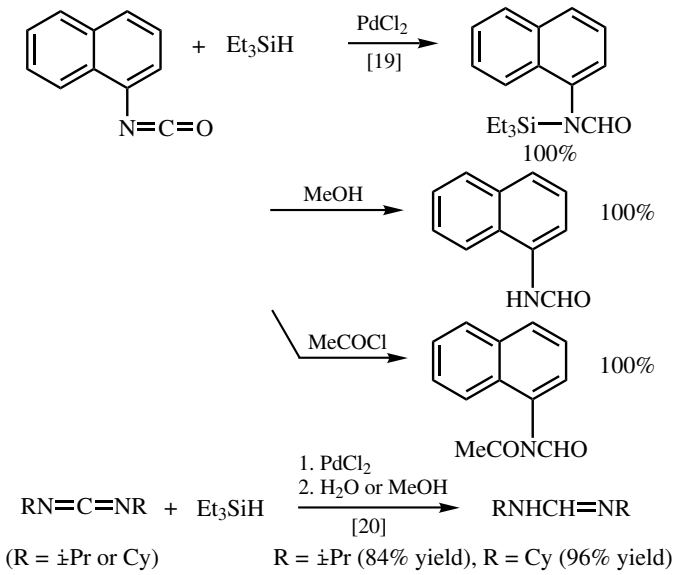
The Pd-catalyzed asymmetric hydrosilation of styrene and conjugated cyclic dienes was investigated as early as 1972, but the observed ee figures were <10%.[8] Since then, a series of attempts have been made to observe Pd-catalyzed asymmetric hydrosilation of high ee by Kumada and co-workers,[23],[24] Hayashi and co-workers,[25],[26] and Achiwa and co-workers.[27],[28] Despite significant improvements made during the 1970s and 1980s, essentially all ee figures observed during this period were below 80%, as indicated by some representative results summarized in **Scheme 13**. Some additional related studies reporting ee figures of <80% have also been published more recently by Marinetti and Ricard,[29],[30] and Hiyama and co-workers.[31],[32]



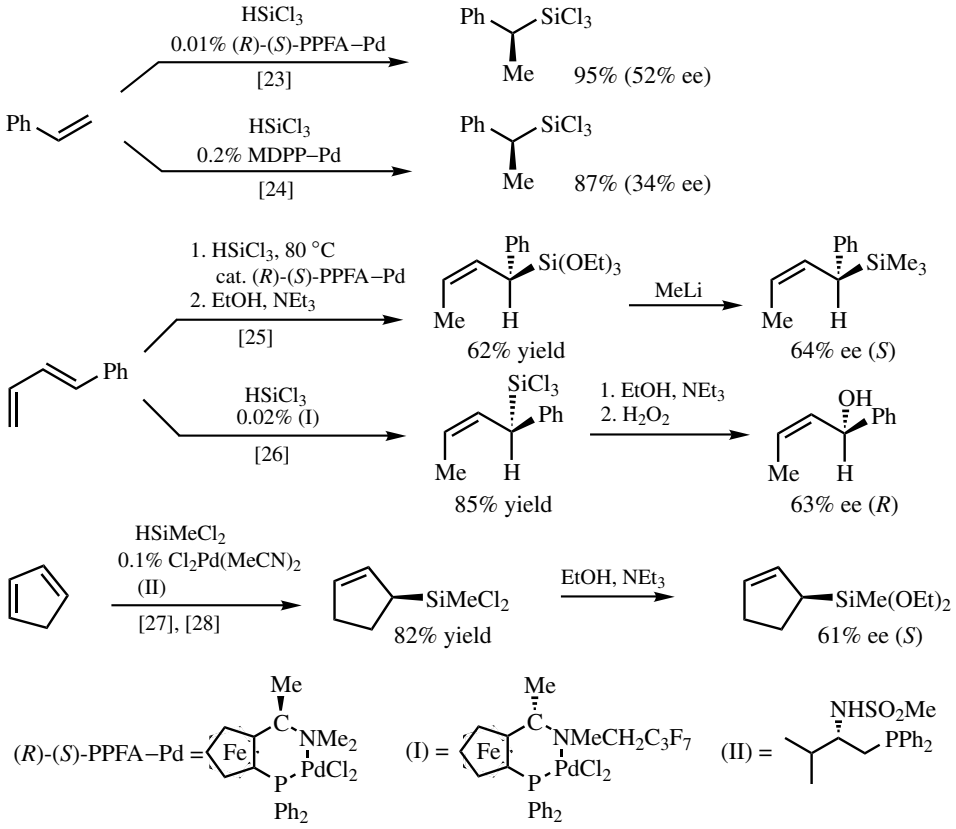
R = Me (95% yield), R = Ph (96% yield).



Scheme 12

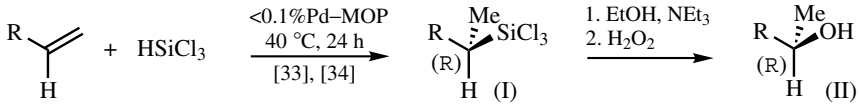


Scheme 12 (*Continued*)

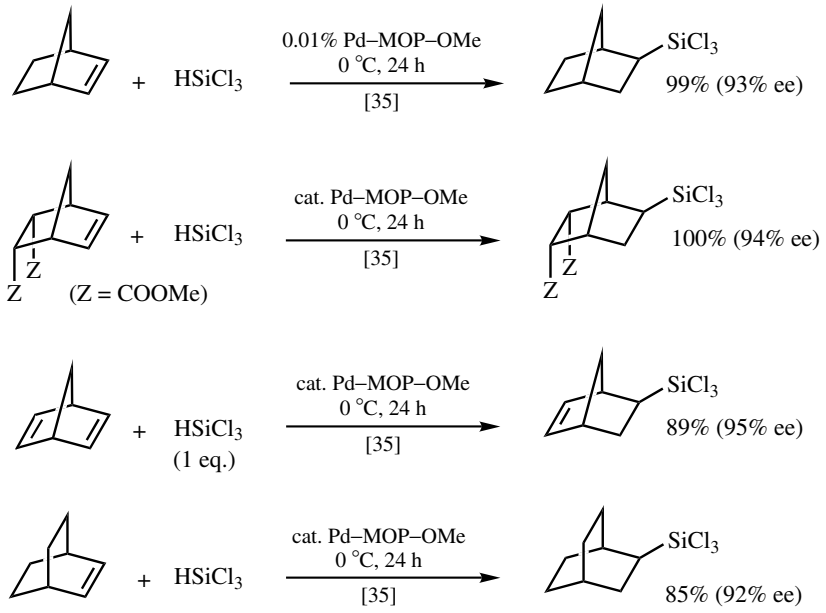


Scheme 13

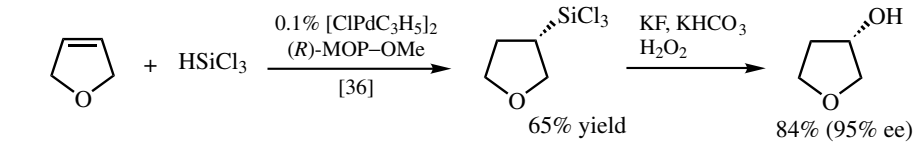
A significant breakthrough in this area was made by Uozumi and Hayashi in 1991,[33] when they reported >90% ee figures for Pd-catalyzed hydrosilation of ordinary 1-alkenes through the development and use of MOP ligands. This method has since been shown to be highly effective in asymmetric hydrosilation of various monoalkenes including 1-alkenes mentioned above,[33],[34] norbornene,[35] dihydrofurans,[36] and styrenes.[37],[38] Some representative results are summarized in **Scheme 14**. Satisfactory but somewhat lower ee figures of 70–80% were observed with cyclopentadiene, but the corresponding reaction of 1,3-cyclohexadiene led to ee figures only up to 51%.[39] Clearly, further development in this area is desirable. For further details of this methodology, the readers are referred to reviews by Hayashi and Uozumi.[40],[41]

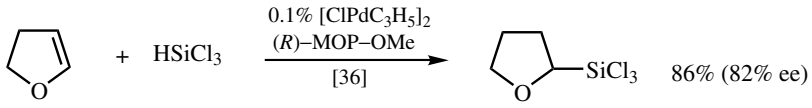


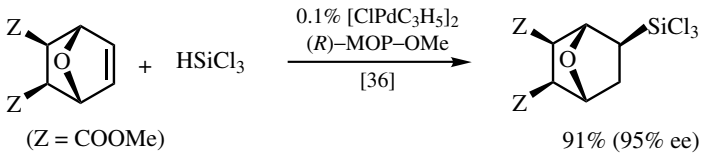
R	MOP–X	Yield of (I) (%)	Regioselectivity (%)	ee of (II) (%)
n-Hex	MOP–OMe	83	93	95 (R)
n-Hex	MOP–OPr-i	88	90	91 (R)
n-Hex	MOP–OBn	85	80	95 (R)
n-Hex	MOP–Et	80	90	93 (R)
$PhCH_2CH_2$	MOP–OMe	90	81	97 (R)
Cy	MOP–OMe	100	66	96 (R)

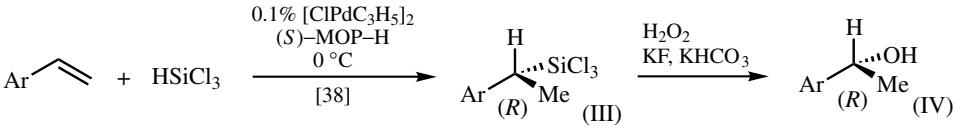


Scheme 14

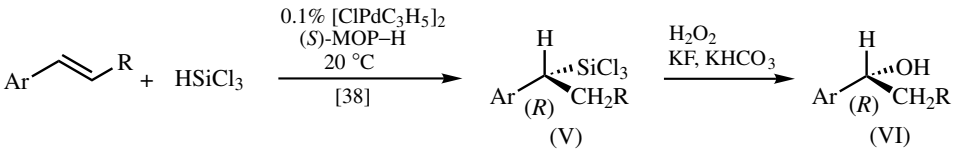




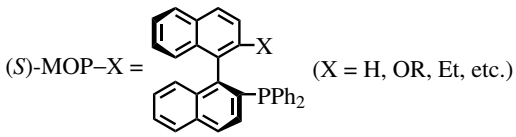




Ar	Yield of (III) (%)	ee of (IV) (%)
Ph	100	93 (*R*)
p-Tol	94	89 (*R*)
p-$CF_3C_6H_4$	98	96 (*R*)
m-ClC_6H_4	68	95 (*R*)
p-ClC_6H_4	80	94 (*R*)



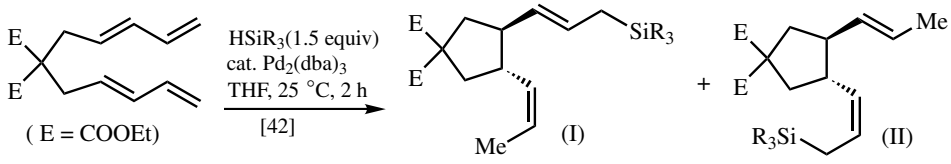
Ar	R	Yield of (V) (%)	ee of (VI) (%)
Ph	Me	95	89 (*R*)
Ph	Bu-*n*	89	92 (*R*)



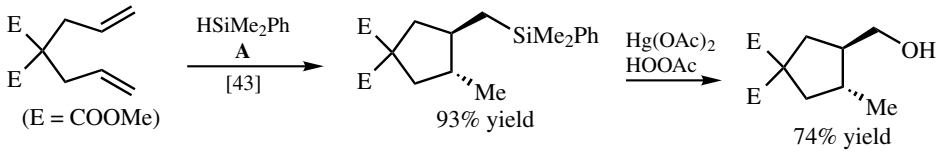
Scheme 14 (*Continued*)

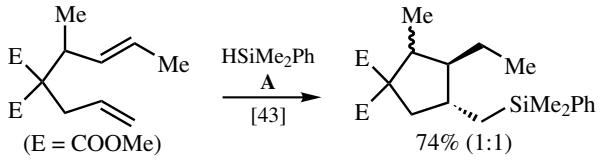
B.iii. Palladium-Catalyzed Cyclization Reactions Via Hydrosilation–Cyclic Carbopalladation

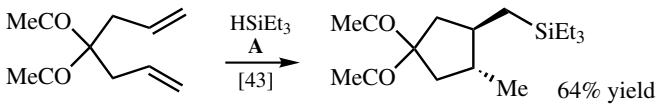
Cyclic carbopalladation discussed in **Sect. IV.3** can be initiated by various reactions generating organopalladium species, such as oxidative addition and hydrometallation. A combination of a silane and a Pd complex capable of inducing hydrosilation has provided yet another method of generating organopalladium species that can undergo cyclic carbopalladation, as indicated by the results shown in **Scheme 15**.[42]–[44] The overall cascade process involves both cyclization and incorporation of a silane. The

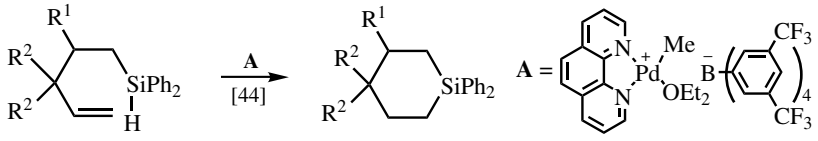


R	Yield (%) (I)	(II)
Ph	80	14
Et	76	13









R^1	R^2	Yield (%)
H	H	86
Me	H	43
H	Me	80

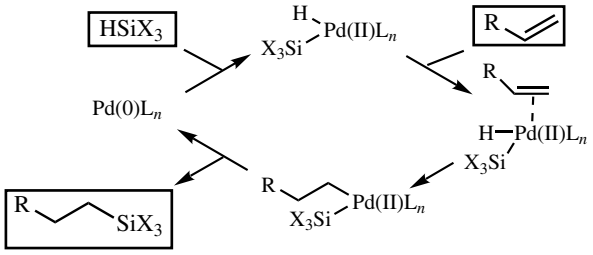
Scheme 15

latter can be achieved either by initial hydropalladation followed later by incorporation of a silyl group[42] or by initial silylpalladation followed later by incorporation of H.[43],[44] Both have been suggested, but this point does not appear to have been firmly established, as discussed in the following subsection.

B.iv. Mechanism of Palladium-Catalyzed Hydrosilation

Until recently, it was generally thought that Pd-catalyzed hydrosilation might proceed via (i) formation of H—Pd—Si species by oxidative addition of Pd(0) complexes to H—Si bonded species, (ii) hydropalladation of π-compounds, and (iii) reductive elimination leading to the formation of C—Si bonds (the Chalk–Harrod mechanism shown in **Scheme 16**).[45] More recently, however, the nonredox metathesis (or transmetallation) routes to metal hydrides and M—Si bonded species have been recognized as reasonable alternatives to oxidative addition and/or reductive elimination in many cases. Furthermore, silylmetallation has also been recognized as a competitive alternative to hydrometallation. Indeed, silylpalladation is a topic of discussion in **Sect. VII.5**.

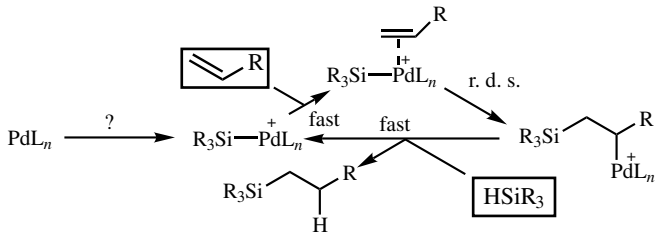
Chalk–Harrod–type mechanism for hydrosilation



Scheme 16

The first detailed and rigorous mechanistic study was reported by Brookhart and co-workers[45] a few years ago by using a cationic Pd complex, that is, $[(phen)PdMe(L)]^+B[3,5\text{-}(CF_3)_2C_6H_3]_4^-$, as a catalyst. For the reaction investigated, a mechanism consisting of (i) silylpalladation and (ii) metathetical formation of the desired hydrosilation product and the Si—Pd bonded species for silylpalladation appears to be plausible (**Scheme 17**). The crucial silylpalladation step is thought to be rate determining.

Brookhart mechanism for Pd-catalyzed hydrosilation



Scheme 17

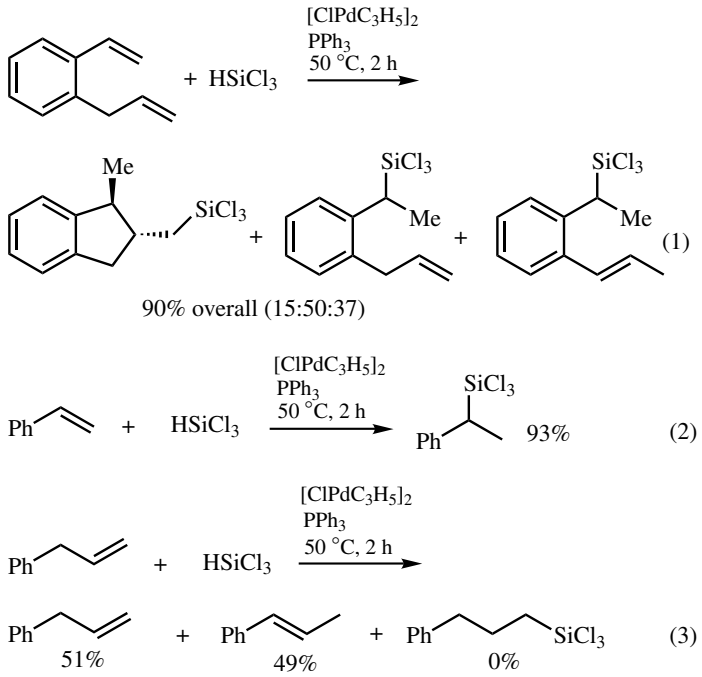
On the other hand, the hydrosilation of styrenes with $HSiCl_3$ in the presence of a Pd–phosphine complex has been shown to proceed via hydropalladation rather than silylpalladation.[46] Specifically, the following set of results were obtained.

1. *o*-Allylstyrene gave a mixture of three products in 90% overall yield, as shown in Eq. 1 in **Scheme 18**.

2. Under the same reaction conditions, styrene was shown to undergo rapidly the expected hydrosilation to give α-trichlorosilylethylbenzene in 93% yield, whereas allylbenzene did not produce any hydrosilation product, the only product being (*E*)-β-methylstyrene (49%) (Eqs. 2 and 3).

3. Whereas monodentate phosphines, (e.g., PPh_3) were effective, bidentate phosphines (e.g., dppe and BINAP) were totally incapable of inducing the desired hydrosilation, suggesting the formation of Pd–monophosphine complexes as reactive species, which are to undergo oxidative addition with hydridosilanes.

The results summarized under the headings 1 and 2 rather conclusively indicate that, under the conditions used, the reaction must proceed via hydropalladation. For the other steps, a combination of oxidative addition and reductive elimination, as in the Chalk–Harrod mechanism, is plausible, but other possibilities involving metathetical processes may not be ruled out. It should be noted that the two reactions employed by Brookhart and co-workers[45] and Hayashi and co-workers[46] are substantially different. It is therefore very likely that the mechanistic conclusions made in their studies are both fundamentally correct and that, as in many other reactions of organopalladium compounds, more than one mechanism operates for a given type or class of organopalladium reactions.



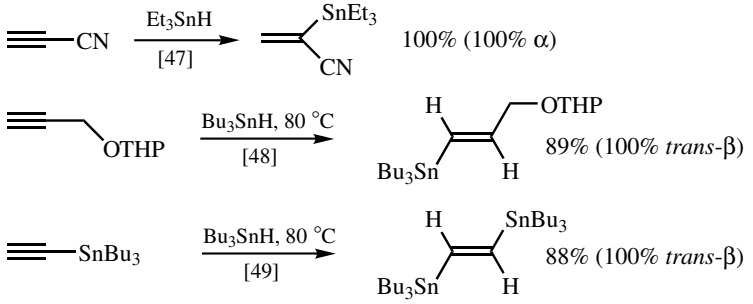
Scheme 18

C. PALLADIUM-CATALYZED HYDROSTANNATION AND HYDROGERMATION

C.i. Background

Unlike hydrosilation discussed in the preceding subsection, which requires catalysis in essentially all cases, hydrostannation can be observed typically at or above 50 °C under thermal conditions. Under such conditions, however, the reaction tends to be capricious and unpredictable. Thus, for example, the reaction of terminal alkynes with $HSnMe_3$, $HSnBu_3$, and other triorganylstannanes tends to produce mixtures of α-, *cis*-β-, and *trans*-β-stannyl-substituted alkenes[47] except for some special cases, such as those shown in **Scheme 19**.[47]–[49]

Although catalysis by transition metal complexes was an obvious approach to solving problems associated with both reactivity and selectivity issues, it was not until 1987 that the Pd-catalyzed hydrostannation and hydrogermation were reported by using alkynes[50] as substrates. This was soon followed by a related study with allenes published in 1988.[51] Since then, Pd-catalyzed hydrostannation has been investigated primarily with the goal of synthesizing alkenyl- and allylstannanes from alkynes, allenes, and conjugated dienes for use in the Stille coupling.[52] Since little has been done to clarify the mechanism of Pd-catalyzed hydrostannation and hydrogermation, it is not clear if the reaction proceeds either via initial hydrometallation followed by Sn incorporation or via initial stannylmetallation followed by H incorporation. Both have been suggested. In this connection, it should be mentioned that the following section (**Sect. VII.5**) discusses metallopalladation.



Scheme 19

C.ii. Palladium-Catalyzed Hydrostannation of Alkynes

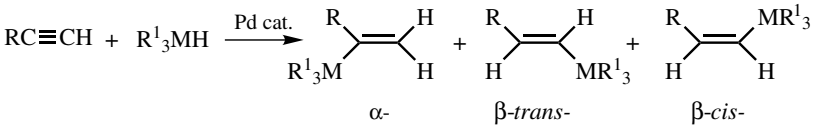
Since the first work reported in 1987,[50] more than a dozen papers on Pd-catalyzed hydrostannation of alkynes have been reported. As detailed below, Pd catalysts significantly accelerate hydrostannation and hydrogermation of alkynes. Thus, the reaction now proceeds at or below room temperatures. However, the selectivity aspects remain unpredictable and often problematical, with three isomers—α, β-*trans*, and β-*cis*—being formed in a capricious manner. The isomer profiles for Pd-catalyzed hydrostannation are often substantially different from those observed under either uncatalyzed or radical-initiated conditions. When all of the seemingly random results are sorted out, however, the following potentially useful generalizations may be presented as a set of guidelines.

1. Besides being considerably faster and facile, the Pd-catalyzed hydrostannation is significantly more stereoselective involving a predominant or exclusive *syn*-addition of H—Sn bonds to alkynes. Even so, the stereoselectivity often is below 90%.

2. Proximal heteroatoms, such as Si, N, O, S, and halogens, can exert significant effects on some critical aspects of the reaction such as the regio- and stereochemistries. With some groups that contain Si, S, and Br as well as alkoxycarbonyl, exclusive formation of α-stannylated alkenes may be achieved.

Some of the representative results observed with nonheterofunctional terminal alkynes are summarized in **Table 1**. Also shown in **Table 2** are the results of hydrostannation of PhC≡CH with a variety of transition metal catalysts. Although the β-*trans*-stannylalkenes are the major isomer in cases where Pd catalysts are used, competitive formation of α-stannylalkenes is a significant side reaction. In fact, there have been very few nonheterofunctional alkynes that have been selectively hydrostannated, although some conjugated alkynes, such as PhC≡CMe,[54]–[56] enynes,[57] and diynes[56] have been selectively hydrostannated (**Scheme 20**). At present, there does not appear to be any procedure, catalyzed or uncatalyzed, that permits highly selective synthesis of one particular isomer of alkenylstannanes derivable from "ordinary" and nonheterofunctional alkynes.

TABLE 1. Pd-Catalyzed Hydrostannation and Hydrogermation of Nonheterofunctional Alkynes



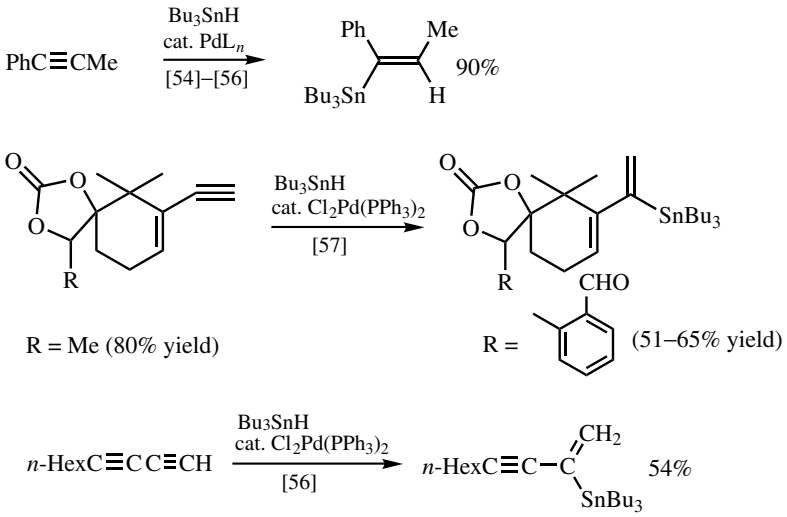
R of RC≡CH	$R^1{}_3MH$	Pd Catalyst	Reaction Conditions	Product Yield (%) α-	β-*trans*-	β-*cis*-	Reference
n-$C_{10}H_{21}$	Ph_3SnH	$Pd(PPh_3)_4$	CH_2Cl_2, 25 °C	9	63	5	[50]
n-$C_{10}H_{21}$	Ph_3GeH	$Pd(PPh_3)_4$	THF, 25 °C	14	83	0	[50]
Ph	Ph_3SnH	$Pd(PPh_3)_4$	CH_2Cl_2, 25 °C	7	44	10	[50]
Ph	Ph_3GeH	$Pd(PPh_3)_4$	THF, 25 °C	8	81	0	[50]
Ph	Bu_3SnH	$Cl_2Pd(PPh_3)_2$	0 °C	38	50	0	[53]
Ph	Bu_3SnH	$Pd(PPh_3)_4$	benzene, r.t.	48	48	0	[54]

TABLE 2. Transition-Metal-Catalyzed Hydrostannation of PhC≡CH with *n*-Bu_3SnH

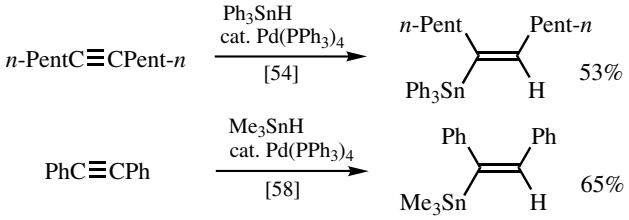
Catalyst	Temperature (°C)	Time (h)	Product Yield (%) α-	β-*trans*-	β-*cis*	Reference
None	60	11	0	34	37	[53]
AIBN	60	20	0	54	27	[53]
$Cl_2Co(PPh_3)_2$	0	4	17	19	4	[53]
$Cl_2Ni(PPh_3)_2$	r.t.	0.2	36	40	4	[53]
$Cl_2Ru(PPh_3)_3$	r.t.	68	9	33	37	[53]
$ClRh(PPh_3)_3$	r.t.	0.5	76	10	0	[53]
$Cl_2Pd(PPh_3)_2$	0	0.5	38	50	0	[53]
$Cl_2Pt(PPh_3)_2$	r.t.	0.2	25	40	8	[53]

In this connection, it should be noted, however, that symmetrical internal alkynes can be stereoselectively hydrostannated (**Scheme 21**).

In more recent investigations, attention has been focused on finding heterofunctional substituents permitting both high yields and high selectivity for use in the selective synthesis of natural products and related compounds. Some representative results of highly selective hydrostannation of heterofunctional alkynes are summarized in **Tables 3** and **4** and **Schemes 22–26**.



Scheme 20



Scheme 21

TABLE 3. Pd-Catalyzed Selective Hydrostannation of Heterofunctional Terminal Alkynes

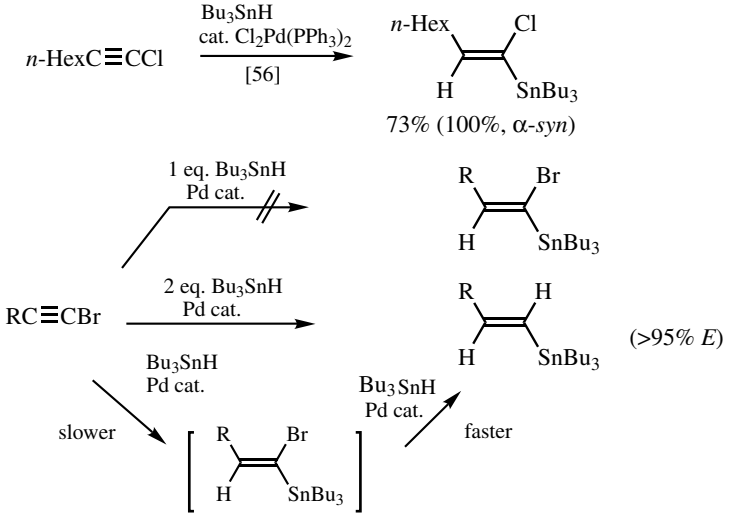
$R^1C{\equiv}CH$	R of R_3SnH	Catalyst	Reaction Conditions	Product (%)		Reference
				α-	*β-trans*-	
$Me_3SiC{\equiv}CH$	Ph	$Pd(PPh_3)_4$	CH_2Cl_2, 25 °C	0	69	[50]
$Me_3SiC{\equiv}CH$	Ph_3GeH	$Pd(PPh_3)_4$	THF, 25 °C	0	98	[50]
$HO(Me)_2CC{\equiv}CH$	Bu	$Cl_2Pd(PPh_3)_2$	THF, r.t.	0	85	[56]
$EtOOCC{\equiv}CH$	Bu	$Pd(PPh_3)_4$	r.t.	83	0	[54]
$MeOOCC{\equiv}CH$	Bu	$Cl_2Pd(PPh_3)_2$	25 °C	94	0	[56]
$MeOCC{\equiv}CH$	Me	$Pd(PPh_3)_4$	THF	51	0	[58]
$PhSC{\equiv}CH$	Bu	$Pd(PPh_3)_4$	Benzene	87	0	[59]

TABLE 4. Pd-Catalyzed Hydrostannation of S-Substituted Internal Alkynes with Bu_3SnH in the Presence of $Pd(PPh_3)_4$

Substrate	Yield (%) of α-*syn*-Adduct	α-Selectivity	Reference
PhSC≡CMe	79	95	[59]
PhSC≡CPh	75	94	[59]
PhSC≡C$SiMe_3$	85	100	[59]
PhSC≡CCH_2OH	84	100	[59]
PhSC≡CCH_2OTBS	90	100	[59]
p-TolOSC≡CBu-*n*	86	98	[60]
p-TolOSC≡C$(CH_2)_4$OPMB[a]	83	100	[60]

[a] PMB = *p*-methoxybenzyl.

Even with internal alkynes, highly regio- and stereoselective hydrostannation can be observed with certain heterosubstituted alkynes. Proximal S[59],[60] (**Table 4**) and halogens,[56],[61] for example, Br and Cl (**Scheme 22**), have led to the formation of single isomers in many cases. The reaction of bromoalkynes with 2 equiv of Bu_3SnH provides a selective route to (*E*)-1-alkenylstannanes.[56],[61]



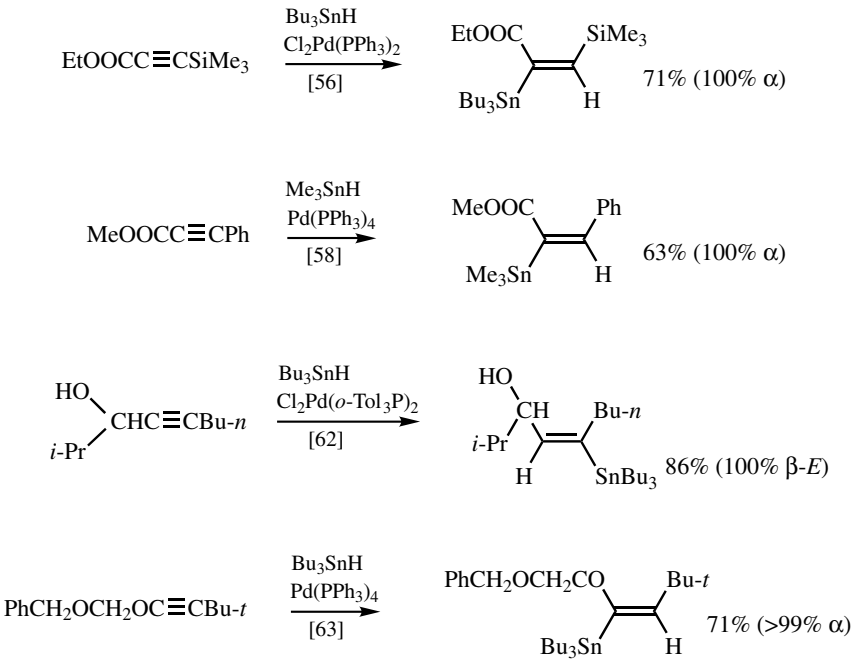
R: Bu (85%),[56] CH_2OTHP (70%),[56] $SiMe_3$ (62%),[56] $Ph(CH_2)_2$ (82%),[61] BnO(Me)CH (80%),[61] $BnO(CH_2)_2$ (72%),[61] $THPO(CH_2)_3$ (74%),[61] $(i\text{-Pr})_3SiO(CH_2)_3$ (86%),[61] *p*-Tol$CH_2O(CH_2)_4$ (77%).[61]

Scheme 22

Unfortunately, proximally oxygenated alkynes, such as alcohols, ethers, ketones, and esters, tend to produce mixtures of isomers, as indicated by the results summarized in **Table 5**, although some highly selective examples, such as those highlighted in **Scheme 23**, are also known. Clearly, further development is desirable.

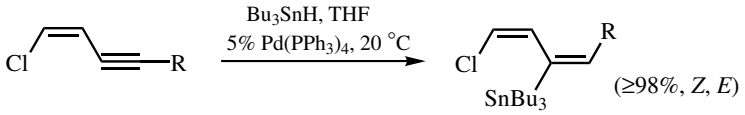
TABLE 5. Pd-Catalyzed Hydrostannation of Proximally Oxygenated Alkynes

Substrate	R of R_3SnH	Catalyst	Product Yield (%) α-	β-*trans*	β-*cis*	Reference
		Alcohol and Ethers				
$HOCH_2C{\equiv}CH$	Bu	$Pd(PPh_3)_4$	58	37	—	[54]
$HOCH_2C{\equiv}CH$	Bu	$Cl_2Pd(PPh_3)_2$	23	18	—	[56]
$PhOCH_2C{\equiv}CH$	Bu	$Cl_2Pd(PPh_3)_2$	77	8	—	[56]
$PhOCH_2C{\equiv}CH$	Bu	$Pd(PPh_3)_4$	62	33	—	[54]
$THPOCH_2C{\equiv}CH$	Bu	$Pd(PPh_3)_4$	46	22	—	[54]
$HO(Me)CHC{\equiv}CH$	Bu	$Pd(PPh_3)_4$	28	66	—	[54]
$TBSO(n\text{-Pent})CHC{\equiv}CH$	Bu	$Pd(PPh_3)_4$	26	68	—	[54]
$Me_2NCH_2C{\equiv}CH$	Bu	$Pd(PPh_3)_4$	19	41	—	[54]
$HOCH_2C{\equiv}CMe$	Bu	$Pd(PPh_3)_4$	74	14	—	[54]
$HO(Ph)CHC{\equiv}CBu\text{-}n$	Bu	$Cl_2Pd(o\text{-}Tol_3P)_2$	21	67	—	[62]
$HO(2\text{-Furyl})CHC{\equiv}CBu\text{-}n$	Bu	$Cl_2Pd(o\text{-}Tol_3P)_2$	8	64	—	[62]
$HO(CH_2)_2C{\equiv}CH$	Bu	$Pd(PPh_3)_4$	44	50	—	[54]
$BnO(CH_2)_2C{\equiv}CH$	Ph	$Pd(PPh_3)_4$	21	53	8	[50]
$BnOCH_2OC{\equiv}CBu\text{-}n$	Bu	$Pd(PPh_3)_4$	30	16	—	[63]
$THPOC{\equiv}CBu\text{-}s$	Bu	$Pd(PPh_3)_4$	55	13	—	[63]
		Ketones and Esters				
$MeOCC{\equiv}CH$	Bu	$Cl_2Pd(PPh_3)_2$	53	12	—	[56]
$MeOOCC{\equiv}CMe$	Me	$Pd(PPh_3)_4$	56	11	—	[58]
$EtOOCC{\equiv}CBu\text{-}n$	Bu	$Cl_2Pd(PPh_3)_2$	62	21	—	[56]

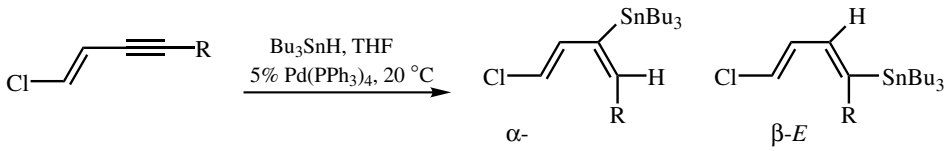


Scheme 23

The Pd-catalyzed hydrostannation of conjugated enynes has revealed some interesting effects of both conjugated alkenyl groups and proximal heteroatoms, such as Cl and OH. Thus, for example, the reaction of (*Z*)-*β*-chlorovinylenynes is highly selective, whereas that of the (*E*)-isomers is not[64] (**Scheme 24**). The results suggest that Cl can exert a significant chelation effect in the reaction. More difficult to interpret and predict are the reactions of oxygenated enynes shown in **Scheme 25**.[64] The observed results cannot readily be explained by invoking a chelation effect. The conjugated (*Z*)-enyne framework itself must be responsible for the high selectivity observed with the (*Z*)-isomers. Whatever the precise reason might be, the Pd-catalyzed hydrostannation of conjugated (*Z*)-enynes promises to provide an efficient and selective route to complex organic compounds, such as *neocarzinostatin* and related compounds.[65]

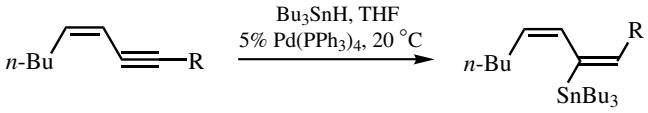


R: Pent-*n* (91%), Ph (93%), CH_2OH (92%)
CH_2OEt (68%), CH_2NMe_2 (85%), CH_2CH_2OH (85%).

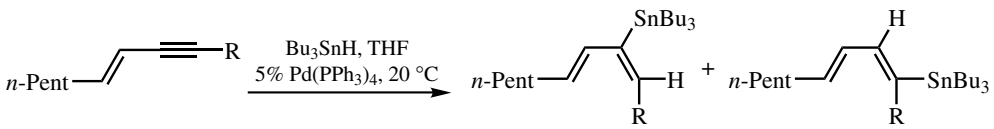


R	Yield (%) α-	Yield (%) β-*E*	R	Yield (%) α-	Yield (%) β-*E*
n-Pent	86	0	CH_2OEt	62	15
Ph	71	12	CH_2NMe_2	89	0
CH_2OH	62	19	CH_2CH_2OH	70	16

Scheme 24



R: CH_2OH (83% and 8% of β-*E*), CH(OH)Pent-*n* (92%), CH_2CH_2OH (55%).

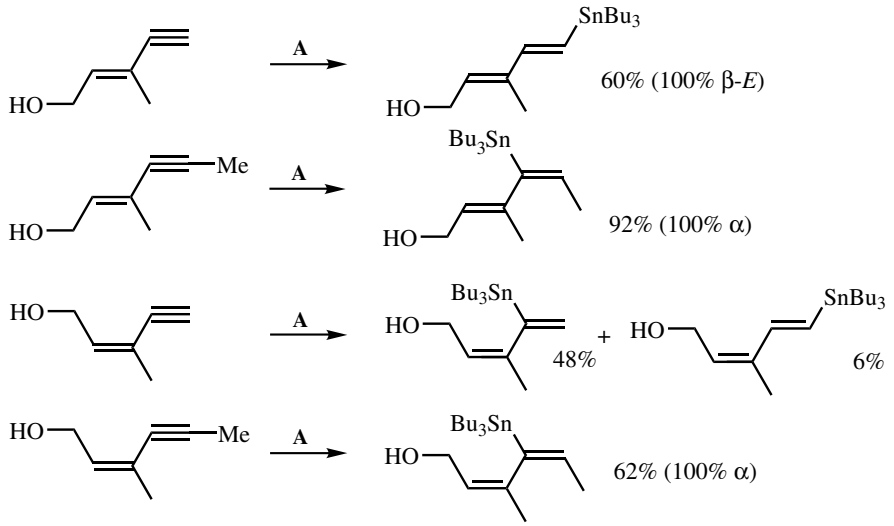


R	α-	β-*E*
CH_2OH	17	33
CH_2CH_2OH	24	41

Scheme 25

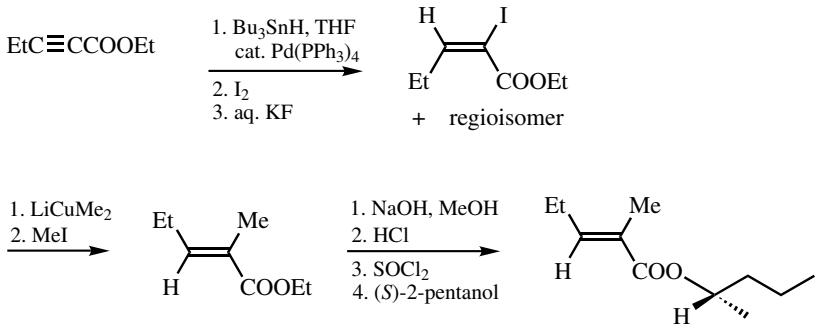
The regio- and stereoselective hydrostannation of enynols shown in **Scheme 26**[57] is also noteworthy.

Few applications of the Pd-catalyzed hydrostannation of alkynes to the synthesis of natural products have been reported. The synthesis of an aggregation pheromone shown in **Scheme 27**[66] is interesting, but more straightforward and efficient alternatives appear to be readily available.



A = Bu_3SnH, 2% $Cl_2Pd(PPh_3)_2$, THF, 20 °C.

Scheme 26

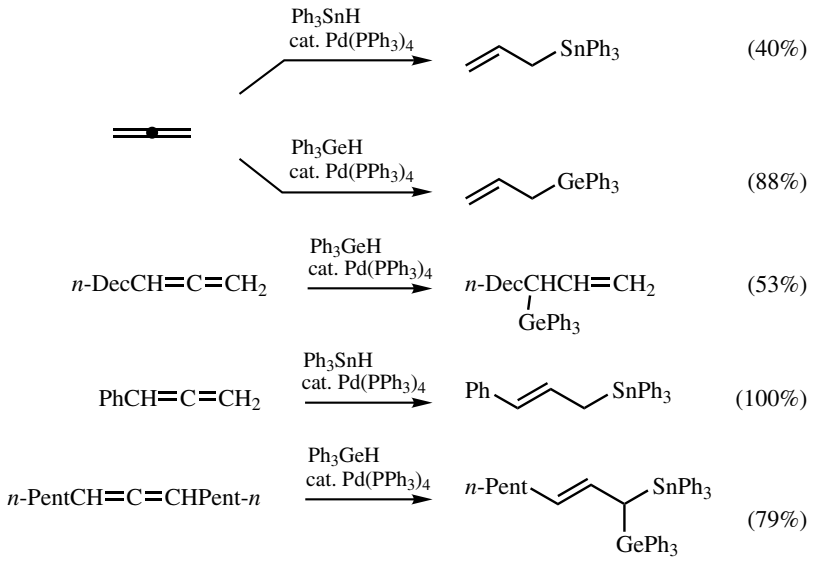


Scheme 27

C.iii. Palladium-Catalyzed Hydrostannation of Allenes

Only a small number of investigations of Pd-catalyzed hydrostannation of allenes have been reported. In 1988, Oshima and co-workers[51] reported what appears to be the first investigation of this topic together with a related study of hydrogermation (**Scheme 28**).

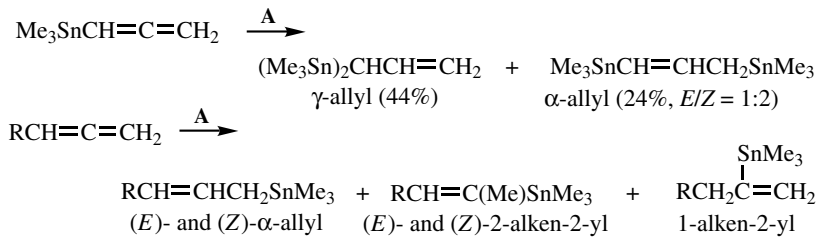
A more recent study[67] has shown that the Pd-catalyzed hydrostannation of terminal allenes can and does indeed produce all of the six readily conceivable products shown in

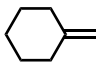


Scheme 28

Scheme 29, even though the formation of the γ-allyl isomer has been limited to the reaction of $Me_3SnCH{=}C{=}CH_2$. Nonetheless, the (*E*)- and (*Z*)-α-allyl isomers usually are the dominant products, accounting for more than 80%, typically ≥90%, of the products.

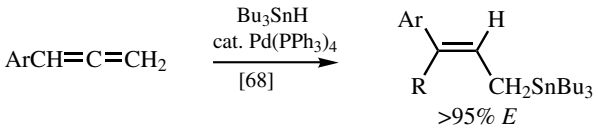
Arylated allenes usually give >95% (*E*)-allylstannanes, whereas alkyl- and alkoxy-substituted allenes tend to produce predominantly (*Z*)-isomers [68],[69] (**Scheme 30**).



R	(*E*)- and (*Z*)-α-Allyl (%)	(*E*)- and (*Z*)-2-Alken-2-yl (%)	1-Alken-2-yl (%)
n-Bu	28 and 44	7 and 4	5
Ph	58 and 9	2 and 0	1
	17 and 40	3 and 3	1
MeO	9 and 57	9 and 0	0
	76	0	0

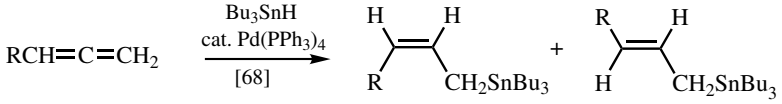
A = Me_3SnH, THF, cat. $Pd(PPh_3)_4$, r.t., 48 h.

Scheme 29



>95% *E*

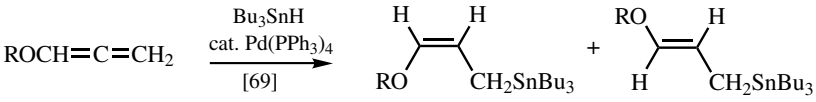
Ar: Ph (60%), *p*-Tol (62%), *p*-FC_6H_4 (77%), *p*-$MeOC_6H_4$ (75%).



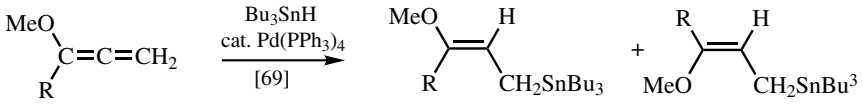
R: *n*-Oct (78%, *Z*/*E* = 67:33),  (52%, *Z*/*E* = 82:18)

$PhCH_2$ (66%, *Z*/*E* = 62:38), MeO (69%, *Z*/*E* = 81:19),

TIPSO (73%, *Z*/*E* = 71:29).



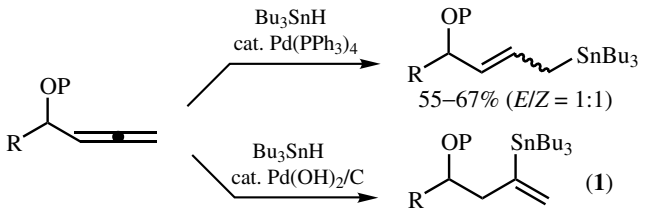
RO: MeO (72%, *Z*/*E* = 75:25), TBSO (70%, *Z*/*E* = 87:13).



R: Bu (45%, *Z*/*E* = 55:45), MeS (52%, *Z*/*E* = 53:47),
Me_3Si (82%, 100% *Z*).

Scheme 30

Another noteworthy recent development is that the use of $Pd(OH)_2$ on charcoal selectively gives β-alkylidene isomers[70] in those cases that would give predominantly mixtures of the (*E*)- and (*Z*)-α-allyl isomers under more usual conditions using $Pd(PPh_3)_4$ as a catalyst (**Scheme 31**).[70]



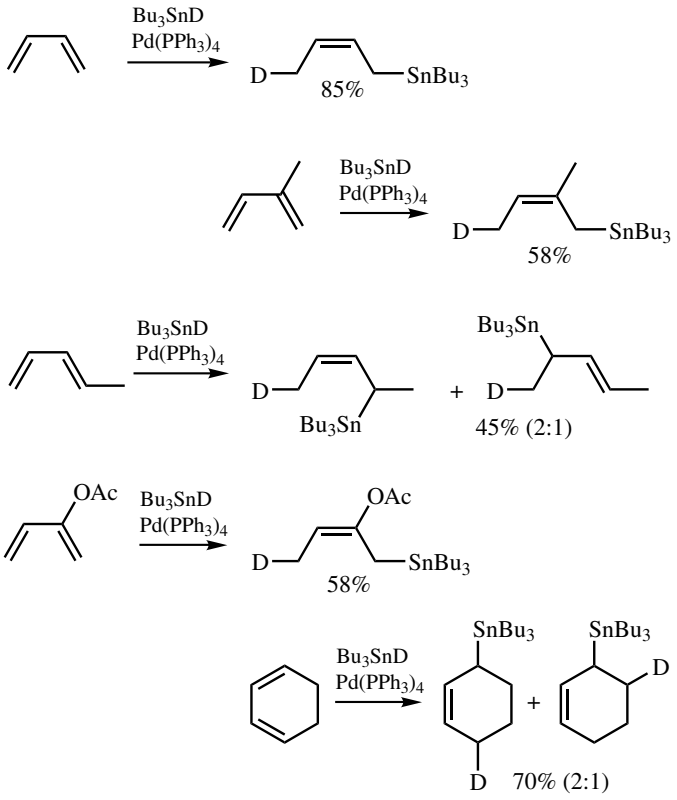
R	P	Yield of **1** (%)
Ph	H	58
	H	57
n-Hept	H	57

R	P	Yield of **1** (%)
	TBDPS	55
	MEM	57

Scheme 31

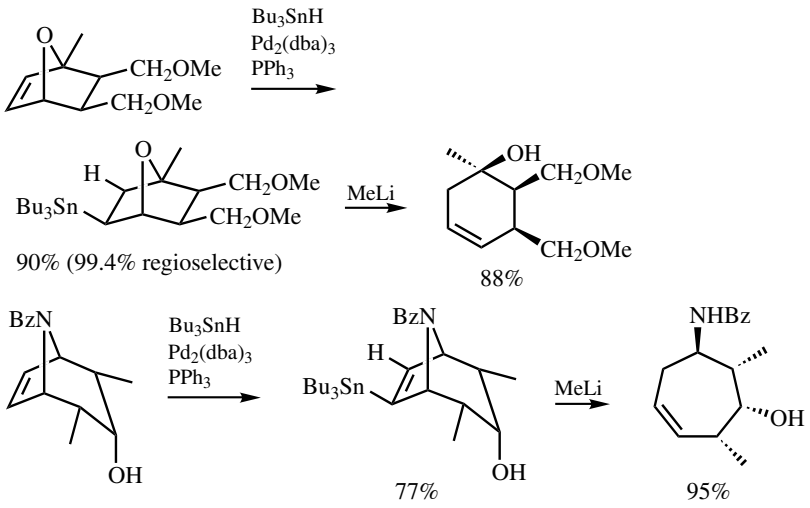
C.iv. Palladium-Catalyzed Hydrostannation of Other π-Compounds

In contrast with the Pd-catalyzed hydrosilation of conjugated dienes discussed in **Sect. B**, the corresponding hydrostannation has not been extensively studied. In a pair of reports published in 1992, Miyake and Yamamura,[71],[72] described the results obtained with several representative conjugated dienes. By using Bu_3SnD, the position of hydride or deuteride incorporation has also been established (**Scheme 32**). The selective formation of (*Z*)-1-stannyl-2-alkenes closely parallels the regio- and stereochemical profiles observed in the Pd-catalyzed hydrosilation (**Sect. B**). Further delineation of the scope, limitations, and other aspects of the reaction is very desirable.



Scheme 32

In a rare investigation of the Pd-catalyzed hydrostannation of unconjugated monoalkenes, Lautens and Klute[73] have demonstrated that unsymmetrically substituted oxa- and azabicyclic alkenes undergo Pd-catalyzed hydrostannation in a highly regioselective manner. The resultant β-oxy- and β-aminostannanes can undergo selective β-elimination to give multiply substituted six- and seven-membered carbocycles (**Scheme 33**). The regioselectivity under the Pd-catalyzed conditions can be significantly higher than that observed under radical conditions. If appropriate applications of this reaction to the synthesis of complex natural products and related organic compounds can be demonstrated, the entire transformation would become an attractive synthetic methodology.



Scheme 33

D. PALLADIUM-CATALYZED HYDROBORATION, HYDROALUMINATION, AND OTHER HYDROMETALLATION REACTIONS OF MAIN GROUP METALS

D.i. Background

In contrast with the extensive investigations on the Pd-catalyzed hydrometallation reactions of Si and Sn, those involving other main group metals have hardly been investigated. For example, about ten papers on Pd-catalyzed hydroboration have been found in the literature. Since hydroboration[1] is generally a facile process of general applicability occurring at or even well below room temperature, there has been relatively little incentive for exploring catalytic hydroboration. As the significance of boronic acids and their derivatives (RBX_2) has increased in conjunction with their Pd-catalyzed cross-coupling (**Sect. III.2**), however, direct synthesis of boronic acids and esters has become increasingly desirable, and transition-metal-catalyzed hydroboration has consequently been more and more extensively investigated. However, the great majority of these studies have employed Rh complexes as catalysts[74],[75] with little attention paid to Pd complexes.

Of the currently known three major stoichiometric hydrometallation reactions with B, Al, and Zr, hydroalumination, especially of alkenes, is of the most limited scope.[2],[76],[77] So there is need for developing transition-metal-catalyzed hydroalumination. Ni-catalyzed hydroalumination[76]–[78] has long been known, but it has not been extensively developed for use in organic synthesis. Pd-catalyzed hydroalumination of alkenes has just been developed.[79] Interestingly, strongly reducing aluminum hydrides, such as *i*-Bu_2AlH (DIBAH) and $LiAlH_4$, are not readily compatible with Pd catalysts, which provides an explanation for a long delay in the development in this area. On the other hand, nonhydridic alanes, such as *i*-Bu_3Al (TIBA), that are not so strongly reducing as DIBAH and $LiAlH_4$, are compatible with apparently nonredox Pd(II) catalysis. Although the synthetic significance of such methodology is not yet clear, this may represent the beginning of the development of *nonredox catalytic hydrogen transfer hydrometallation reactions*, which might be predicted

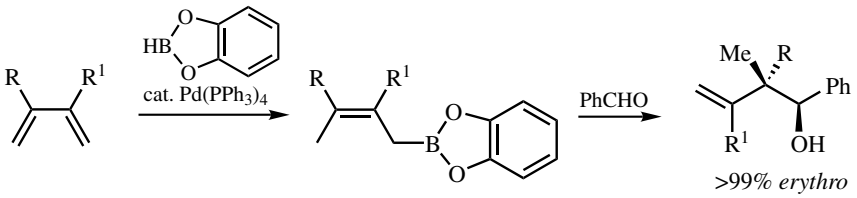
to be useful in dealing with relatively electropositive metals. Although no other Pd-catalyzed hydrometallation reactions of main group metals appear to be currently known, it is likely that some of them, in particular Zn, will receive due attention in the near future.

The *nonredox catalytic hydrogen transfer hydrometallation* protocol should also be widely applicable to those involving transition metals. Indeed, the Pd-catalyzed hydrogen transfer hydrozirconation discussed in Sect. E appears to represent a prototypical example of this class of reactions.

D.ii. Palladium-Catalyzed Hydroboration

In 1989, Suzuki and co-workers[80] reported the reaction of conjugated dienes, such as isoprene, with catecholborane in the presence of Pd and Rh complexes. In this reaction, Pd complexes were significantly more effective than Rh complexes (**Table 6**).

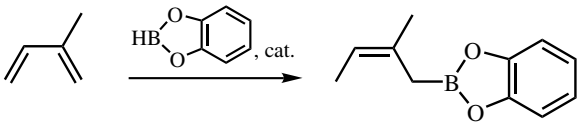
Stereo- and regiodefined allylcatecholboranes thus obtained react with aldehydes to give selectively the corresponding homoallyl alcohols[80] (**Scheme 34**). The regio- and stereochemical profiles of the Pd-catalyzed hydroboration of conjugated dienes closely parallel those observed with silanes.



R	R^1	Yield of Alcohol (%)
H	H	81
H	Me	89
H	$CH_3CH_2CH{=}CMe_2$	77
Me	Me	81

Scheme 34

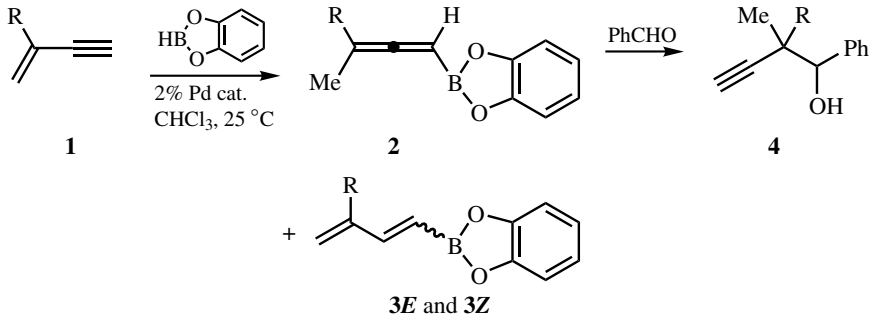
TABLE 6. Pd- or Rh-Catalyzed Hydroboration of Isoprene with Catecholborane



Catalyst	Solvent	Product Yield (%)
$Pd(PPh_3)_4$	Benzene	89
$Pd(PPh_3)_4$	THF	77
$Cl_2Pd(PPh_3)_2$	Benzene	81
$ClRh(PPh_3)_3$	Benzene	2
$ClRh(CO)(PPh_3)_2$	Benzene	19

It was also reported in the same paper[80] that conjugated enynes give allenylboranes, which can then be reacted with PhCHO to provide the corresponding homopropargyl alcohols. This reaction was further investigated in greater detail.[81] As summarized in **Scheme 35**, the reaction was shown to give not only allenylboranes but also (*E*)- and (*Z*)-dienylboranes, in which the (*Z*)-isomers usually dominate. The results further indicate that Pd complexes containing bidentate phosphines, such as dppb and dppf exclusively give (*E*)-dienylboranes, while a catalyst generated from $Pd_2(dba)_3{\cdot}CHCl_3$ and either 3 equiv of PPh_3, (*i.e.*, Pd/P = 1:1.5) or 4 equiv of $PPh_2C_6F_5$ lead to the highest yields of allenylboranes.

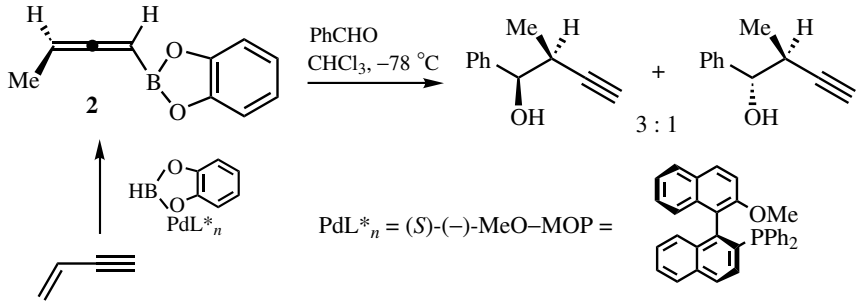
The use of MeO–MOP in place of PPh_3 or $PPh_2C_6F_5$ leads to the formation of optically active allenylboranes, which gives 3-butynyl alcohols of up to 61% ee[82] (**Scheme 36**).



R of **1**–**4**	Catalyst	**2** + **3** (%)	Composition (%)		
			2	**3*Z***	**3*E***
Me	[Pd] + dppb	61	0	0	100
Me	[Pd] + dppf	89	0	0	100
Me	$Pd(PPh_3)_4$	75	60	34	6
Me	[Pd] + 1.5 PPh_3	63	84	16	0
Me	[Pd] + 2$PPh_2C_6F_5$	73	83	17	0
n-Pent	[Pd] + 2$PPh_2C_6F_5$	74	88	12	0
t-Bu	[Pd] + 2$PPh_2C_6F_5$	89	83	4	13

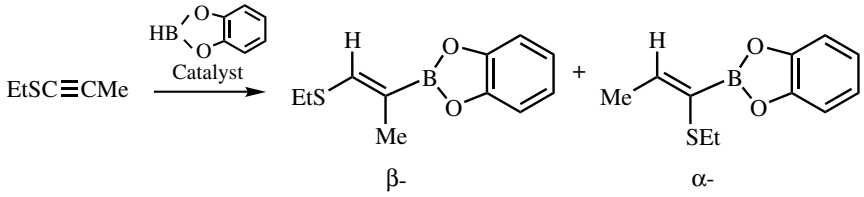
[Pd] = $Pd_2(dba)_3 \cdot CHCl_3$

Scheme 35



Scheme 36

The reaction of 1-thioalkynes with catecholborane can produce mixtures of α- and β-thioalkenylboranes in which the β-isomers predominate[83] (**Scheme 37**). Although Pd complexes are more effective and selective than Rh complexes, they are not as effective and selective as Ni complexes. On the other hand, the cross-coupling reaction of *B*-alkenylcatecholboranes thus generated is not readily catalyzed by Ni complexes. So, the hydroboration–cross-coupling tandem processes are most effectively carried out by using Pd complexes[84] (**Scheme 38**).



Catalyst	Total Yield (%)	β/α
None	20	50:50
$Pd(PPh_3)_4$	54	98:2
$Cl_2Pd(PPh_3)_2$	29	66:34
$Cl_2Pd(dppf)$	69	96:4

Catalyst	Total Yield (%)	β/α
$ClRh(PPh_3)_3$	40	58:42
$HRh(CO)(PPh_3)_2$	46	59:41
$Cl_2Ni(PPh_3)_2$	19	52:48
$Cl_2Ni(dppe)$	100	>99:1

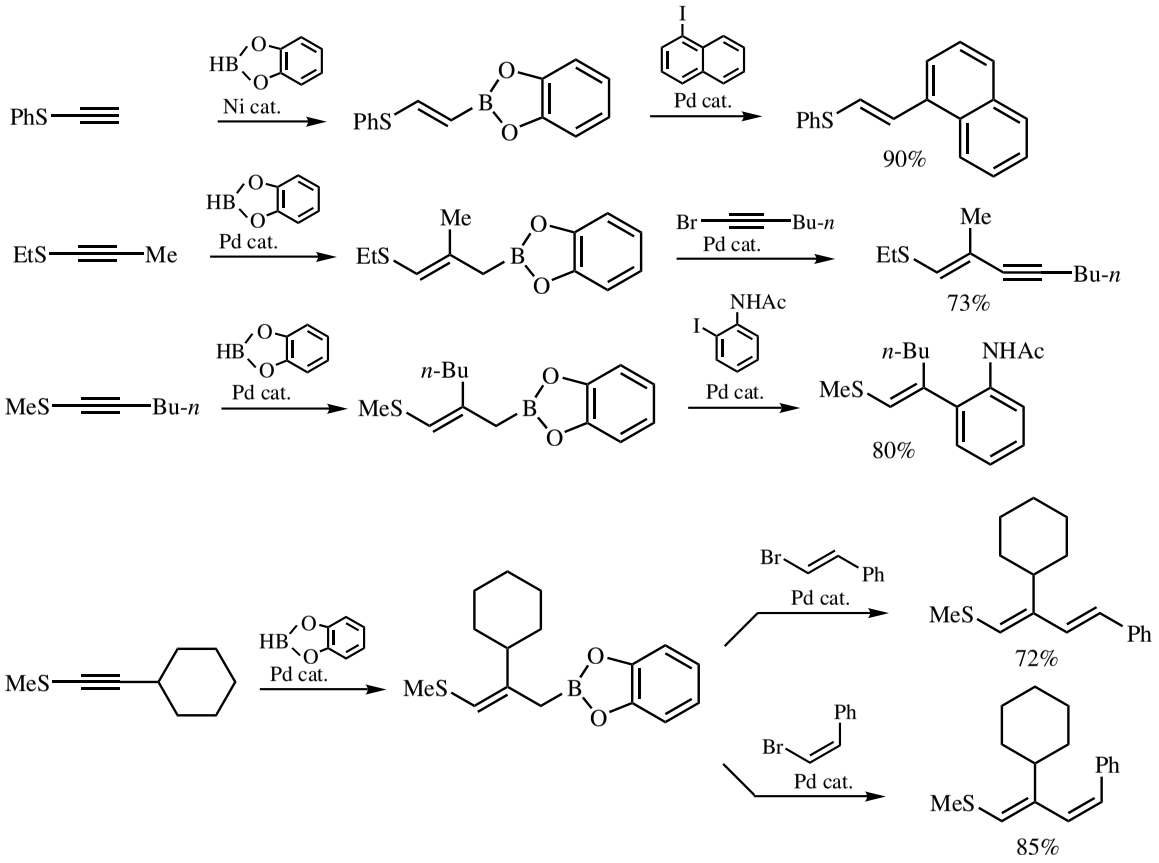
Scheme 37

Little is known about the mechanism of the Pd-catalyzed hydroboration. However, the available data suggest that the reaction might share some common mechanistic features and mechanistic ambiguities as the Pd-catalyzed silation discussed in **Sect. B**. On the other hand, it appears to be mechanistically discrete from the Pd-catalyzed hydroalumination discussed below. Further investigation is needed to clarify its mechanistic details.

D.iii. Palladium-Catalyzed Hydroalumination

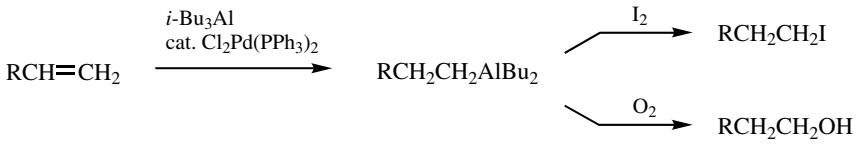
It was recently reported by Negishi and co-workers[79] that the reaction of terminal alkenes with 1.1 molar equiv of *i*-Bu_3Al (TIBA) in the presence of 2.5–5 mol % of chlorine-containing late transition metal complexes of Pd, Pt, Ni, Co, and Rh leads to hydrogen transfer hydroalumination of alkenes. Since alkenes do not readily hydroaluminate in the absence of catalysts, this protocol along with some previously developed transition-metal-catalyzed procedures[76]–[78],[85] promises to significantly widen the synthetic scope and utility of hydroalumination of alkenes. Some representative results of hydroalumination of 1-alkenes with TIBA catalyzed by $Cl_2Pd(PPh_3)_2$ are summarized in **Table 7**.

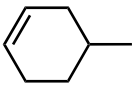
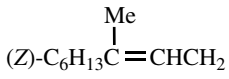
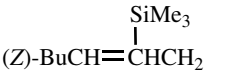
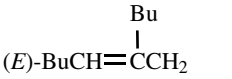
Of various late transition metal complexes tested, $Cl_2Pd(PPh_3)_2$ (90%), Li_2PdCl_4 (78–86%), and K_2PtCl_6 (86%) led to the most satisfactory results, the yields of 1-iodo-


PhS
HB
O
O
Ni cat.
PhS
B
O
O
I
Pd cat.
PhS
90%
EtS
Me
HB
O
O
Pd cat.
EtS
Me
B
O
O
Br
Bu-n
Pd cat.
EtS
Me
Bu-n
73%
MeS
Bu-n
HB
O
O
Pd cat.
MeS
n-Bu
B
O
O
I
NHAc
Pd cat.
MeS
n-Bu
NHAc
80%
MeS
HB
O
O
Pd cat.
MeS
B
O
O
Br
Ph
Pd cat.
MeS
Ph
72%
Br
Ph
Pd cat.
MeS
Ph
85%

Scheme 38

TABLE 7. Hydroalumination of 1-Alkenes with TIBa Catalyzed by $Cl_2Pd(PPh_3)_2$[a]



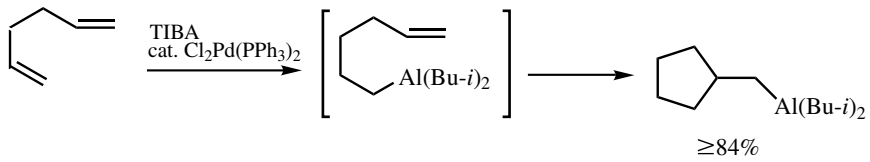
R of $RCH{=}CH_2$	Reaction Time (h)	Product Yield[b](%) RCH_2CH_2I	Product Yield[b](%) RCH_2CH_2OH	Unreacted Alkene (%)	Reduction Product (%)
n-C_8H_{17}	0.5	90 (85)	—	0	0
Cyclohexyl	1	—	73 (70)	0	0
Benzyl	1	—	77 (75)	0	0
$Cl(CH_2)_9$	0.5	88	—	5	0
$Br(CH_2)_9$	1	81	—	10	0
$PhS(CH_2)_3$	12	<5	—	90	—[c]
$PhS(CH_2)_3$	6[d]	—	75	0	0
	0.5	79	—	0	0
(*Z*)- 	5	—	86 (80)	<8	—[c]
(*Z*)- 	6	—	81 (75)	8	4
(*E*)- 	12	—	53	28	14
(*E*)-$C_6H_{13}CH{=}CHCH_2$	5	—	49	35	16
$Me_2C{=}CH(CH_2)_6$	12	—	80	0	0

[a] Unless otherwise mentioned, the reaction was carried out with 1.1 equiv of TIBA and 2.5 mol% of $Cl_2Pd(PPh_3)_2$ at 25 °C in CH_2Cl_2.
[b] By NMR or GLC. The numbers in parentheses are isolated yields.
[c] Unreacted alkene and reduction product were not distinguishable on the GLC trace.
[d] 2.3 equiv of TIBA used.

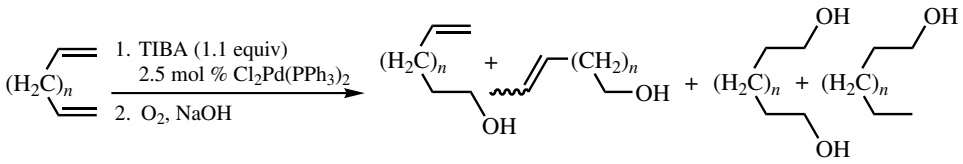
decane obtained from 1-decene being indicated in parentheses. Several other complexes indicated below also led to moderately satisfactory yields of 1-iododecane shown in parentheses: $Cl_2Ni(PPh_3)_2$ (65%), $ClCo(PPh_3)_3$ (76%), and $ClRh(PPh_3)_3$ (79%). On the other hand, nonhalogenated complexes, such as $Pd(OAc)_2$, led to no reaction with >90%

of 1-decene remaining unreacted. Although it is highly speculative, it is tempting to suggest that bimetallic activation[86] involving Al—Cl—Pd bonding might be important. Another significant finding is that either the use of preformed Pd(0) complexes, such as $Pd(PPh_3)_4$ (25%), or that of strongly reducing hydride sources, such as DIBAH (25%) and $LiAlH_4$ (<5%), that can readily convert Pd(II) complexes to Pd(0) complexes in place of TIBA leads to very low yields of hydroalumination indicated in parentheses after the catalysts or hydride reagents. It now seems reasonably clear that the desired hydroalumination is catalyzed by halogenated Pd(II) complexes but not Pd(0) complexes and that reduction of Pd(II) complexes is to be avoided. This nicely explains why strongly reducing aluminum hydrides, such as DIBAH and $LiAlH_4$, are ineffective. Furthermore, it points to the potential significance of hydrogen transfer hydroalumination catalyzed by transition metal complexes.

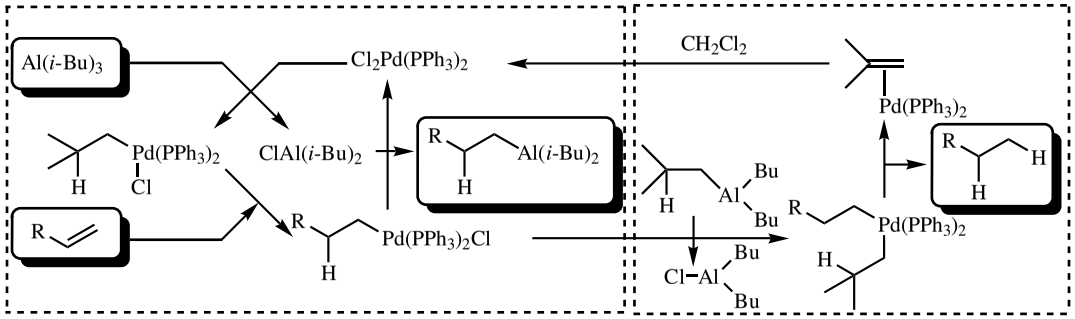
Along with the favorable results presented in **Table 7**, some limitations have also been noted. Thus, some functionally substituted alkenes containing those functional groups that can strongly interact with Pd can lead to either no reaction or some complications. For example, 4-bromo-1-butene, 11-iodo-1-undecene, allyl phenyl ether, allyl benzyl ether, and (3*E*)-1,3-decadiene fail to undergo the desired hydroalumination. Unconjugated di- and trisubstituted alkenyl groups can be tolerated, but α,ω-dienes containing two vinyl groups lead to various complications. 1,5-Hexadiene has been the only α,ω-diene that undergoes the expected hydroalumination–cyclic carboalumination tandem process (**Scheme 39**). Longer α,ω-dienes give mixtures of acyclic products (**Scheme 40**), indicating that, once hydroalumination has occurred at one end of a diene, the course of the reaction at the other double bond is significantly affected by the alkylaluminum group introduced in the first hydroalumination. Although synthetically not very attractive, these results shed considerable light on mechanistic details. One plausible mechanism shown in **Scheme 41** consists of two catalytic cycles, one consisting of the desired cycle that must be a nonredox process catalyzed by Pd(II) complexes and the other undesirable redox process leading to the formation of reduced alkanes. Reoxidation of Pd(0) species generated in the latter process is thought to be effected by CH_2Cl_2, which has been the only effective solvent among others including THF, ether, and even 1,2-dichloroethane.



Scheme 39



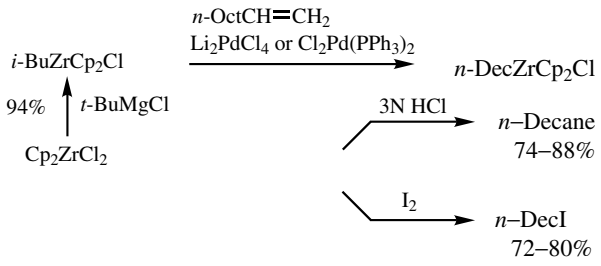
Scheme 40


Al(i-Bu)3
Cl2Pd(PPh3)2
CH2Cl2
Pd(PPh3)2
Pd(PPh3)2
Cl
ClAl(i-Bu)2
R
Al(i-Bu)2
H
R
H
Bu
Al
Bu
H
R
Pd(PPh3)2Cl
R
H
Pd(PPh3)2
H
Cl–Al
Bu
Bu
H
Desired nonredox catalytic cycle
Formation of alkanes by a redox process

Scheme 41

E. PALLADIUM-CATALYZED HYDROMETALLATION INVOLVING TRANSITION METAL COMPLEXES AS HYDRIDE SOURCES

In an extensive search for catalytic hydrogen transfer hydrozirconation of alkenes with *i*-BuZrCp$_2$Cl readily generated *in situ* by treating Cp$_2$ZrCl$_2$ with *t*-BuMgCl, Pd(II) complexes, such as Li$_2$PdCl$_4$ and Cl$_2$Pd(PPh$_3$)$_2$, were found to be among the most satisfactory catalysts along with AlCl$_3$, ZnCl$_2$, AgBF$_4$, and Me$_3$SiI (**Scheme 42**).[87] This procedure promises to be not only more convenient than the preparation and use of HZrCp$_2$Cl but also more chemoselective than the conventional reaction. Furthermore, various features of the Pd-catalyzed hydrogen transfer hydroalumination and hydrozirconation closely resemble each other, suggesting that similar protocols may be developed with other early transition metals including lanthanides, such as Zn, Ti, Hf, Sc, Y, and La.



Scheme 42

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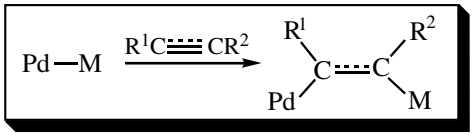

VII.5 Metallopalladation

KOICHIRO OSHIMA

A. INTRODUCTION

In view of the facile reactions of hydropalladium derivative with carbon–carbon multiple bonds, it might readily be expected that metalpalladium complexes should react with alkynes or alkenes to give the corresponding metallopalladation products (**Scheme 1**).

Palladium complexes such as $PdCl_2(PPh_3)_2$ have enabled the activation of metal–metal bonds that consist of different metals.[1] For instance, in 1983, it was reported that the silyl group and metal easily add to acetylenes with regioselectivity using $PhMe_2SiLi$ and several metal compounds such as MeMgl, Et_2AlCl, and $ZnBr_2$ in the presence of palladium catalyst (**Scheme 2**).

In contrast, it is difficult to activate silicon–silicon bonds by palladium complexes because Si—Si bonds are nonpolarized, thermally stable σ-bonds with a dissociation energy of ca. 300 kJ/mol. However, very recently, the addition of Si—Si compounds to C—C unsaturated bonds have been extensively studied. The results are described in several reviews.[2],[3] In this section, bis-silylation, silylboration, and borylstannation of alkynes and alkenes will be reviewed.

B. PALLADIUM-CATALYZED ADDITION REACTIONS OF DISILANES

B.i. Bis-silylation of Acetylenes

In 1975, Kumada and co-workers[4] and Sakurai and co-workers[5] reported that in the presence of a catalytic amount of palladium complexes, disilanes of the type $Me_nSi_2X_{6-n}$ (n = 1–6; X = H and F) or 1,2-disilacycloalkanes add to various acetylenic compounds to give double silylation products. Nagai and co-workers[6] developed the reaction and found that the double silylation of acetylenic compounds occurs not only with disilanes of special substituents but also with other common disilanes such as methoxymethylsilanes and hexamethyldisilane (**Scheme 3**).

The disilylation product could be formed as follows (**Scheme 4**): (i) oxidative addition of the disilane to Pd(0) species, (ii) formation of a π-complex with the acetylene by the coordination of π-electrons to Pd, (iii) insertion of the acetylene to produce silylpalladation adduct, and (iv) reductive elimination of the disilylalkene product.

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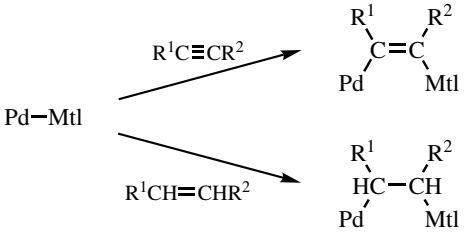
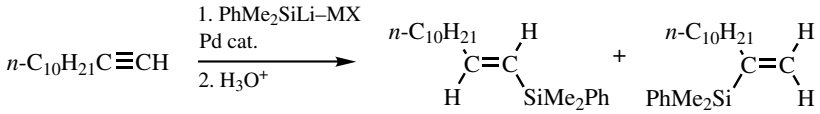


Scheme 1



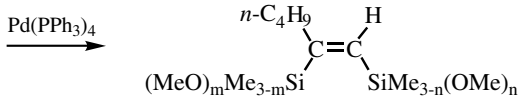
MX	Pd Catalyst	Yield (%)	Ratio
MeMgI	$PdCl_2(PPh_3)_2$	90	>99:1
Et_2AlCl	$PdCl_2(P(o\text{-tolyl})_3)_2$	85	15:85
$ZnBr_2$	$PdCl_2(PPh_3)_2$	71	30:70

Acetylene (1.0 equiv), $PhMe_2SiLi$–MX (2.0 equiv), Pd catalyst (0.01 equiv) THF, 25 °C, 1 h.

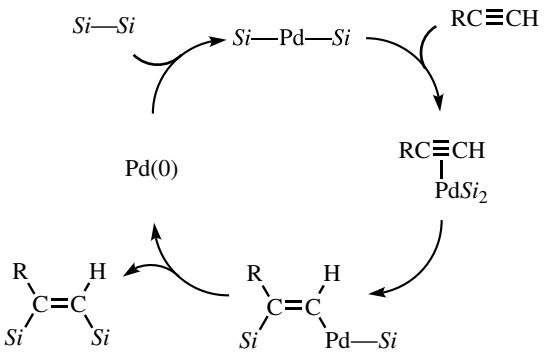
Scheme 2

$(MeO)_mMe_{3-m}SiMe_{3-n}(OMe)_n + n\text{-}C_4H_9C{\equiv}CH$

m = n = 1: 76% m = 1, n = 2: 50% m = n = 2: 54%

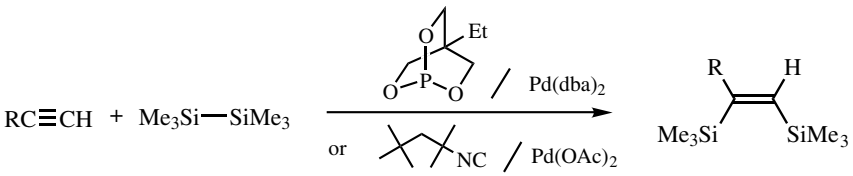


Scheme 3

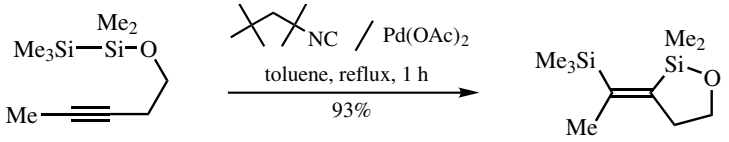


Scheme 4

Two groups have reported that new classes of ligands enable bis-silylation with hexaalkyldisilanes, which have been regarded as much less reactive than the activated disilanes of type $Me_nSi_2X_{6-n}$. Yamashita, Catellani, and Tanaka[7] have introduced bicyclic phosphate as a ligand of palladium. Ito, Suginome, and Murakami[8] have reported that palladium(II) acetate-*tert*-alkyl isocyanate also catalyzes the addition of simple alkyldisilanes to acetylenes. Hexamethyldisilane reacts with terminal acetylenes to give the disilylation products in good to excellent yields (**Scheme 5**). Whereas terminal acetylenes react, internal acetylenes are unreactive unless the disilane and acetylene are tethered together by a two- or three-atom tether to force an intramolecular disilylation (**Scheme 6**).

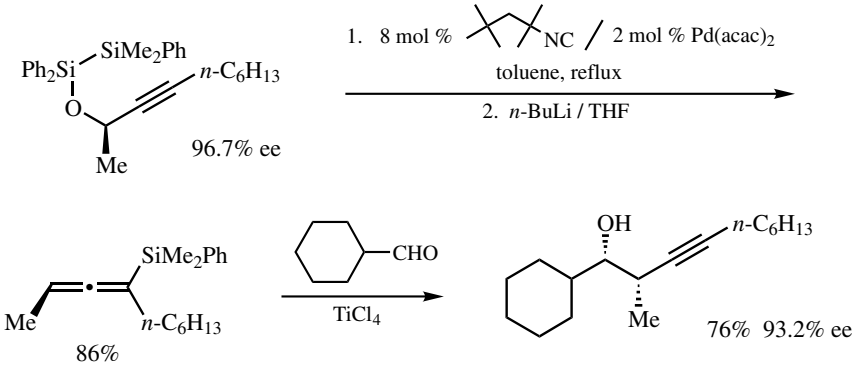


Scheme 5



Scheme 6

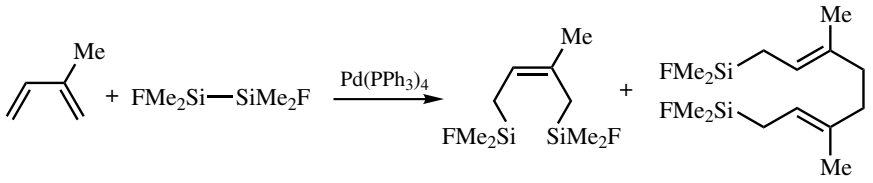
The combination of the Pd-catalyzed bis-silylation and subsequent Peterson-type elimination was applied to the synthesis of allenylsilanes from propargylic ethers.[9] **Scheme 7** shows a preparation of optically active allenylsilane and its use in the synthesis of *syn*-homopropargylic alcohol. Use of the palladium–isonitrile catalyst is crucial to promote the bis-silylation effectively.



Scheme 7

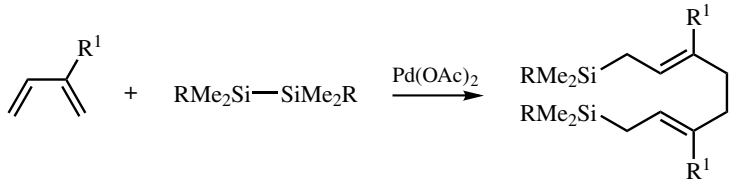
B.ii. Bis-silylation of Dienes

Palladium–phosphine complexes catalyze 1,4-bis-silation with the activated disilanes. Fluoro- and chlorodisilanes provide 1,4-adducts in good yield with high stereoselectivity giving (*Z*)-alkenes.[10],[11] For instance, treatment of isoprene with fluorinated disilane in the presence of palladium–PPh_3 complex gives 1,4-adduct in good yield. A minor amount of 1:2-adduct, which arises from regioselective head-to-head coupling of the isoprene, is produced (**Scheme 8**).



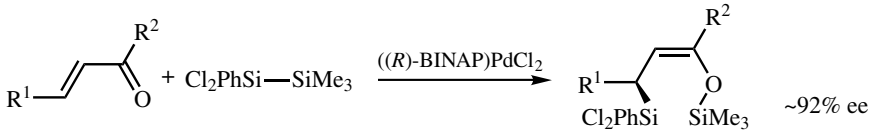
Scheme 8

In sharp contrast to the predominant formation of 1:1-adducts, reactions of 1,3-dienes with various disilanes in the presence of phosphine-free palladium catalyst provide bis-silylative dimerization product in high yield (**Scheme 9**).[12],[13]



Scheme 9

Bis-silylation of various α,β-unsaturated ketones with $Cl_2PhSiSiMe_3$ was reported to be promoted by the phosphine–palladium catalyst.[14] Use of BINAP ligand as an optically active ligand on palladium successfully induces asymmetric bis-silylation (**Scheme 10**).[15]

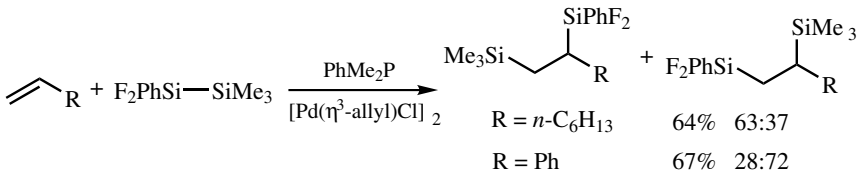


Scheme 10

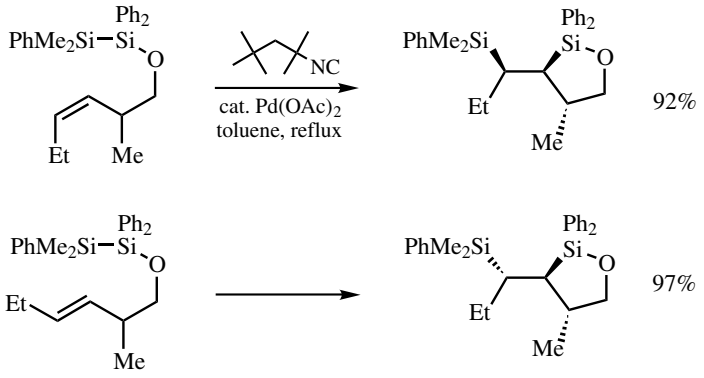
B.iii. Bis-silylation of Alkenes

Recently, bis-silylation of simple alkenes has been achieved. For instance, bis-silylation of terminal alkenes such as 1-octene and styrene with $F_2PhSiSiMe_3$ proceeds in moderate yields in the presence of palladium complex having two basic, sterically less demanding phosphine ligands such as $PPhMe_2$ and PMe_3 (**Scheme 11**).[16] Two regioisomers are produced. The combination of the phosphine ligands and the unsymmetrical fluorinated disilane is essential to attain satisfactory yields for the success of the bis-silylation.

As in the case of bis-silylation of acetylenes, intramolecular bis-silylation of alkenes is more effectively performed compared to the intermolecular reactions. The isonitrile–palladium catalyst provides 5-*exo* cyclization products stereospecifically from (*Z*)- and (*E*)-alkenes tethered to disilanyl groups by ether linkage (**Scheme 12**).[17],[18]



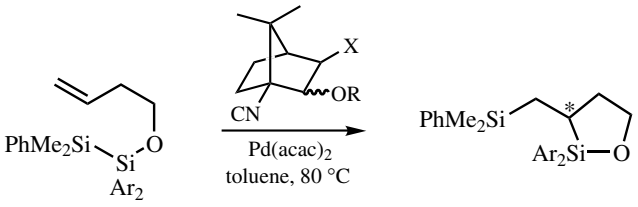
Scheme 11



Scheme 12

Enantioselective intramolecular bis-silylation of homoallylic alcohols has been achieved in the presence of a catalyst prepared from $Pd(acac)_2$ and optically active isonitriles. The bulky substituents of the substrate on the silicon atom proximal to the ether oxygen are crucial to attain good enantioselectivity (**Scheme 13** and **Table 1**).[19]

Diastereoselective intramolecular bis-silylation was applied to the synthesis of highly enantio-enriched allylsilanes (**Scheme 14** and **Table 2**).[20],[21]



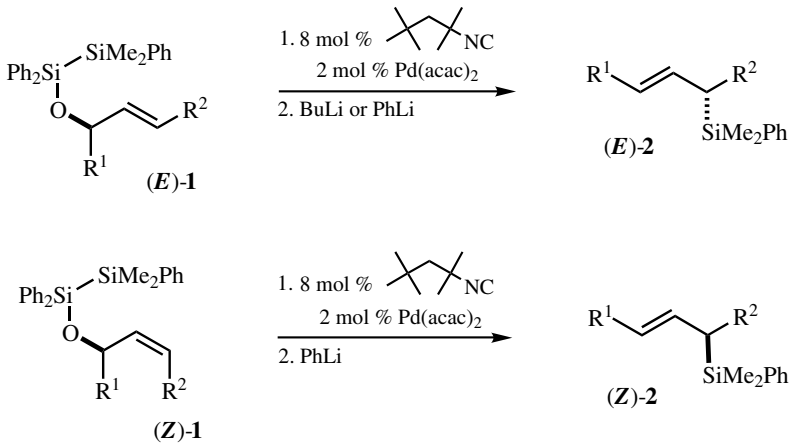
Scheme 13

TABLE 1. Pd-Catalyzed Enantioselective Bis-silylation of Carbon–Carbon Double Bonds in the Presence of Chiral Isonitriles

Substrate (Ar)	Isonitrile (R)	Yield (%)	% ee
Ph	*exo*-Me	79	14(*S*)
Ph	*exo*-Et	85	20(*S*)
Ph	*exo*-$SiMe_3$	83	33(*S*)
Ph	*endo*-$SiMe_3$	76	7(*R*)
o-tol	*exo*-$SiMe_3$	74	55(*S*)
o-tol	R = $SiMe_3$, X = $OSiMe_3$	87	64(*S*)

TABLE 2. Synthesis of Enantiomerically Enriched (*E*)-Allylsilanes

1 (% ee)	R^1	R^2	**2** Yield (%)	% ee
(*R*)-(*E*)-**1a** (99.7)	Me	*n*-Hex	(*S*)-**2a** (87)	97.3
(*R*)-(*Z*)-**1a** (96.0)	Me	*n*-Hex	(*R*)-**2a** (84)	95.4
(*S*)-(*E*)-**1f** (>99)	Ph	*n*-Hex	(*S*)-**2f** (95)	96.3
(*R*)-(*E*)-**1g** (99.8)	*c*-Hex	*n*-Hex	(*S*)-**2g** (96)	98.0
(*R*)-(*E*)-**1h** (98.2)	Me	Ph	(*R*)-**2h** (85)	94.8



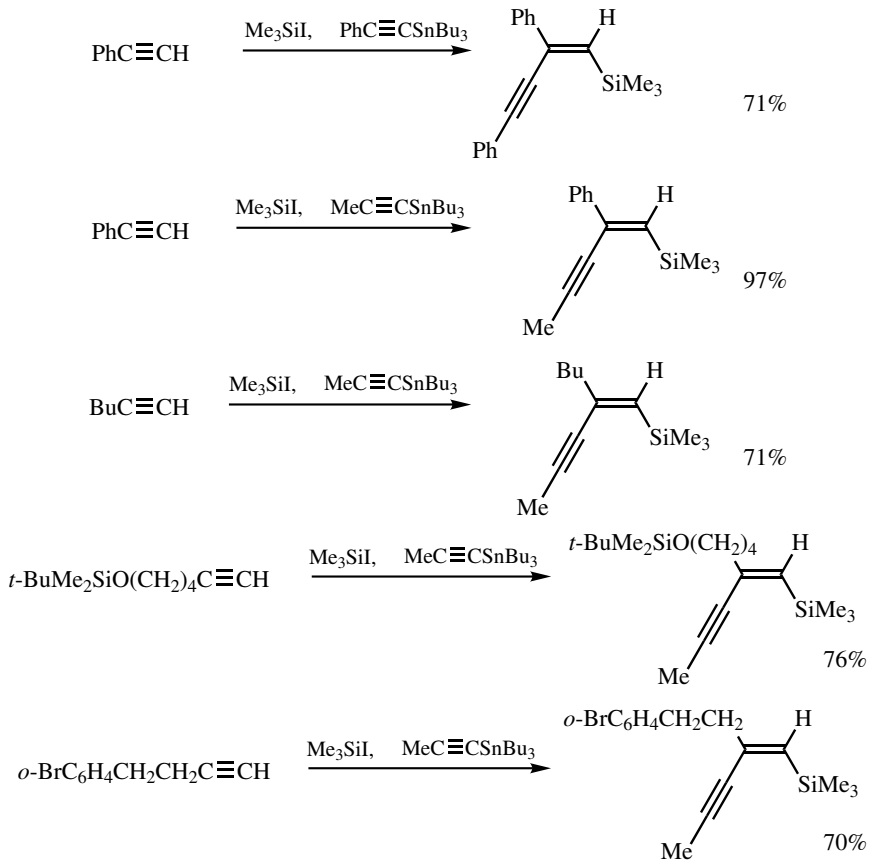
Scheme 14

C. REACTIONS OF TRIMETHYLSILYL IODIDE WITH ACETYLENES

The Pd-catalyzed three-component coupling reaction of acetylenes, iodotrimethylsilane, and acetylenic tin reagents has been reported by Chatani, Amishiro, and Murai (**Scheme 15**).[22] The proposed reaction mechanism is as follows (**Scheme 16**): (i) oxidative addition of Me_3SiI to the palladium catalyst to give silylpalladium iodide; (ii) silylpalladation of acetylene with silylpalladium iodide provides vinylpalladium species; and (iii) transmetallation of an organostannane followed by reductive elimination gives the three-component coupling product, regenerating the palladium(0) catalyst.

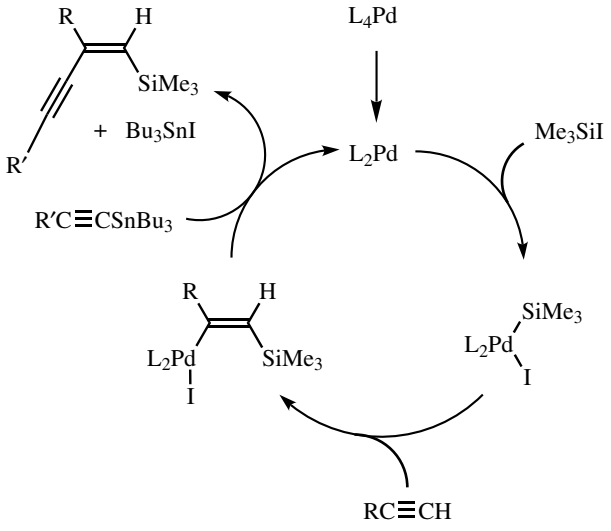
D. PALLADIUM-CATALYZED REACTION OF TRIMETHYLSILYL CYANIDE WITH ACETYLENE

Trimethylsilyl cyanide has widely been used synthetically as a reagent for cyanation. With respect to the Pd-catalyzed reaction, only a few reactions are known. The reaction of substituted iodobenzenes with trimethylsilyl cyanide in the presence of $Pd(PPh_3)_4$ provides good yields of the corresponding benzonitriles. The $PdCl_2$/pyridine-catalyzed reaction of phenylacetylene and substituted phenylacetylenes with trimethylsilyl cyanide



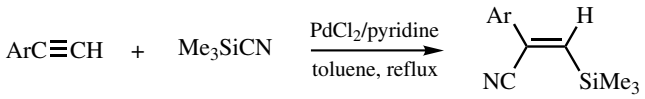
Acetylene (2.5 mmol), Me_3SiI (5 mmol), organostannane (3.5 mmol), $Pd(PPh_3)_4$ (0.05 mmol), dioxane (5 mL), 60 °C, 2–3.5 h

Scheme 15

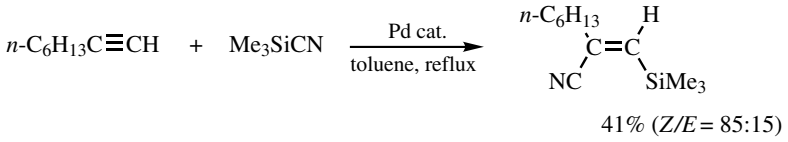


Scheme 16

resulted in the addition of trimethylsilyl cyanide to the carbon–carbon triple bonds to give cyano-substituted vinylsilanes in good to high yields with high regio- and stereoselectivities.[23] The addition was established to be predominantly a *syn*-addition with *Z*/*E* product ratios being in the range of 95:5 (**Scheme 17**). The trimethylsilyl group attaches to the terminal, unsubstituted carbon. Typical examples are shown in **Table 3**. A number of Pd(II) catalysts [$Pd(OAc)_2$, $PdBr_2$, $PdCl_2$ $(PhCN)_2$] are effective, but Pd/C and $PdCl_2$/DIBAL were ineffective. Terminal aliphatic acetylenes gave the corresponding vinylsilanes in good yields. For instance, 1-octyne reacted with trimethylsilyl cyanide to give a stereoisomeric mixture of vinylsilane in which the CN moiety was attached at the internal position (**Scheme 18**). In contrast to the terminal acetylenes, internal acetylenes react more slowly.

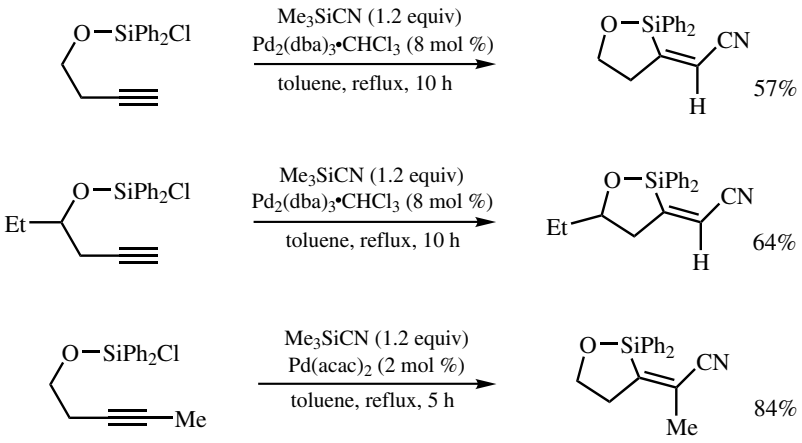


Scheme 17

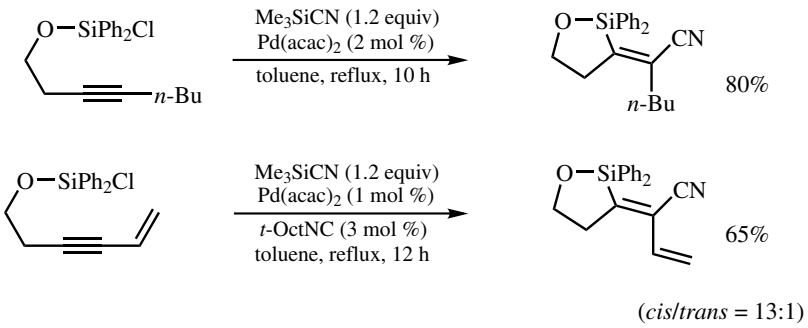


Scheme 18

Intramolecular cyanosilylation was achieved by the reaction of chlorodiphenylsilyl ether of homopropargylic alcohols with trimethylsilyl cyanide in the presence of palladium catalyst.[24] The reaction proceeded regio- and stereoselectively to give (*Z*)-3-(1-cyanoalkylidene)-2-silatetrahydrofurans (**Scheme 19**). It may be presumed that cyano–chloro exchange between starting chlorodiphenylsilyl compound and trimethylsilyl cyanide took place prior to the Pd-catalyzed intramolecular cyanosilylation to carbon–carbon triple bond. Among palladium catalysts examined, $Pd(acac)_2$ and $Pd_2(dba)_3CHCl_3$ were the most effective, but $PdCl_2$/pyridine catalyst, which was employed for the intermolecular cyanosilylation, showed low activity.

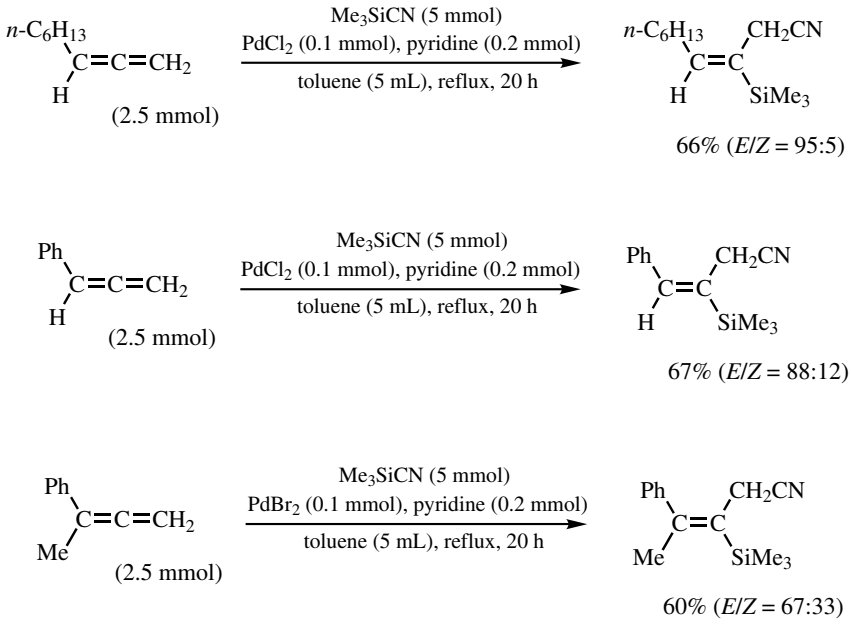


Scheme 19



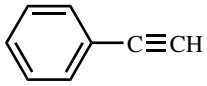
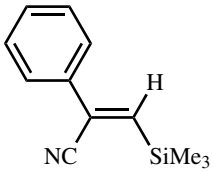
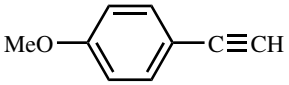
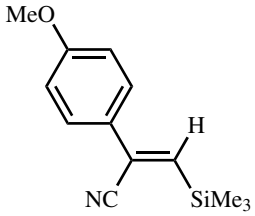
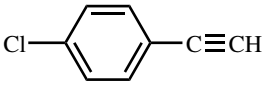
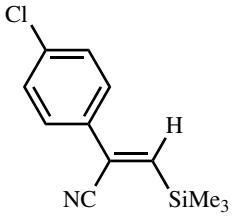
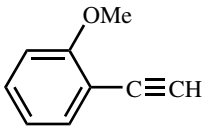
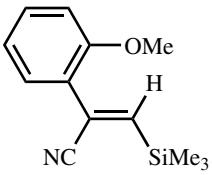
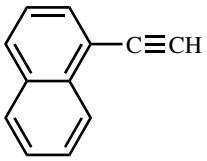
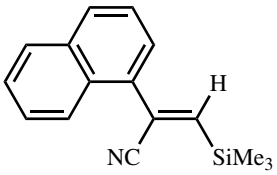
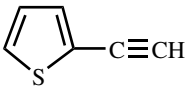
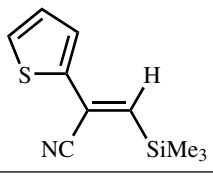
Scheme 19 (*Continued*)

$PdCl_2$ also catalyzes the addition of trimethylsilyl cyanide to allenes.[25] The addition proceeds with high regioselectivity to provide the vinylsilane as the predominant product. The nitrile group is located at the terminal carbon and the trimethylsilyl group at the interior position. For instance, treatment of phenylallene with trimethylsilyl cyanide in the presence of $PdCl_2$/pyridine catalyst in toluene at reflux for 20 h provided 3-phenyl-2-trimethylsilylpropenitrile in 67% yield as a stereoisomeric mixture (*E*/*Z* = 88:12) (**Scheme 20**).



Scheme 20

TABLE 3. Addition of Me_3SiCN to Arylacetylene[a]

Arylacetylene	Product	Yield (%)	*Z*/*E*
		90	95:5
		90	95:5
		47	94:6
		85	83:17
		68	71:29
		39	—

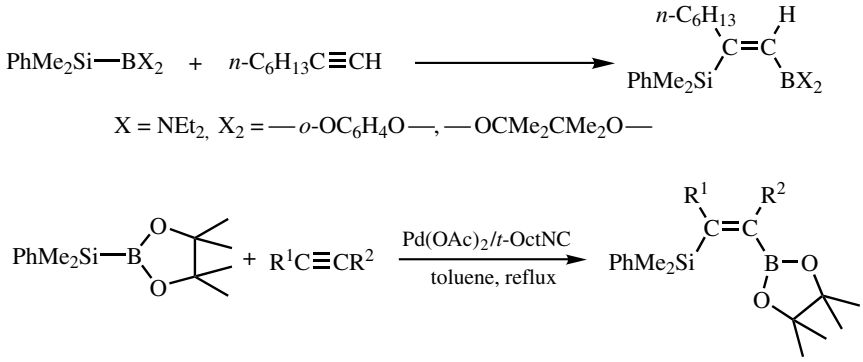
[a] Arylacetylene (5 mmol), Me_3SiCN (10 mmol), $PdCl_2$ (0.2 mmol), pyridine (0.4 mmol), toluene (10 mL), reflux, 20 h.

E. METALLOBORATION WITH DIMETAL COMPOUNDS SUCH AS SILYLBORANE, STANNYLBORANE, AND DIDORANE

E.i. Silaboration of Acetylene with Silylboranes

In spite of the fact that compounds having Si—B bonds (silylboranes) were already prepared in the early 1960s,[26],[27] somewhat surprisingly, transition-metal-catalyzed reaction of the silylboration had not been reported until 1996. Suginome, Nakamura, and Ito[28] have found that silaboration of acetylenes proceeds smoothly in the presence of a catalyst $Pd(OAc)_2$/*t*-octyl NC. Under reflux in toluene, addition of the Si—B bonds across the carbon–carbon triple bond of 1-octyne took place in the presence of the catalyst prepared from 2 mol % of $Pd(OAc)_2$ and 30 mol % of 1,1,3,3-tetramethylbutyl isocyanide (**Scheme 21**).

With the palladium–isonitrile catalyst, terminal alkynes with a variety of substituents and internal alkynes were subjected to the silaboration with 2-silyl-1,3,2-dioxaborolane in refluxing toluene (**Table 4**).[29] The reaction proceeded not only with high yields but also



Scheme 21

TABLE 4. Silaboration of Terminal and Internal Alkynes with Silyldioxaborolane in the Presence of Palladium–Isonitrile Catalyst[a]

Alkyne		Yield	Regioisomeric	Stereoisomeric
R^1	R^2	(%)	Ratio	Ratio
$ClCH_2CH_2CH_2$	H	87	>99:1	>99:1
$NCCH_2CH_2CH_2$	H	77	>99:1	>99:1
t-$BuMe_2SiOCH_2$	H	83	>99:1	>99:1
$THPOCH_2CH_2$	H	88	>99:1	>99:1
$HOCH_2CH_2$	H	77	>99:1	>99:1
Ph	H	82	>99:1	>99:1
EtOCO	H	77	>99:1	>99:1
CH_3CO	H	88	>99:1	>99:1
Me_3Si	H	76	>99:1	96:4
H	H	91	—	90:10
Ph	Ph	74	—	>99:1
Ph	Me	85	93:7	>99:1
n-Bu	*n*-Bu	24	—	>99:1

[a] Silylborane, alkyne (1.5 equiv), $Pd(OAc)_2$ (0.02 equiv), *t*-OctNC (0.30 equiv), toluene, reflux, 1–4 h.

with nearly complete regio- and stereoselectivities to give (*Z*)-alkenes with the boryl groups attached to the terminal sp^2 carbon in the case of terminal alkynes. Complete *cis*-addition of the Si—B bond across the carbon–carbon triple bond of diphenylacetylene and 1-phenyl-1-propyne has been observed. In the latter case, the silyl group attacked α to the phenyl group with good regioselectivity (93:7).

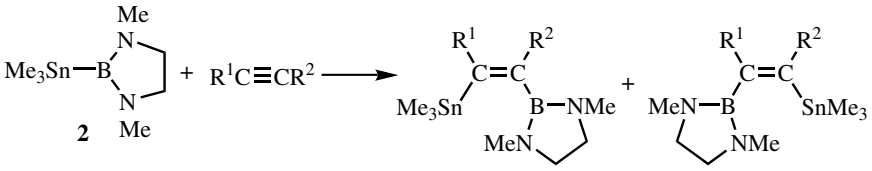
A possible catalytic cycle for the silaboration mediated by palladium catalyst involves an oxidative addition of the Si—B bond onto the Pd(0), followed by regioselective insertion of the carbon–carbon triple bond and subsequent reductive elimination of the product.

E.ii. Borylstannation of Acetylenes and 1,3-Dienes

cis-Addition of the borylstannanes $Me_3SnB[NMe(CH_2CH_2)NMe]$ and $Me_3SnB(NEt_2)_2$ across alkynes was efficiently catalyzed at room temperature or 80 °C by $Pd(PPh_3)_4$, $Pd(dba)_2$, $Cl_2Pd(PPh_3)_2$, or $Me_2Pd[PMe_2(CH_2CH_2)PMe_2]$ to give (β-stannylalkenyl)-boranes in good yields.[30] For instance, stirring a benzene solution of 1,3-dimethyl-2-(trimethylstannyl)-2-bora-1,3-diazacyclopentane (**2**) and 1-octyne in the presence of $Pd(PPh_3)_4$ (1 mol %) at room temperature (r.t.) provided 1,3-dimethyl-2-(2-(*Z*)-(trimethylstannyl)-1-octen-1-yl)-2-bora-1,3-diazacyclopentane in 98% yield (**Scheme 22**).

Internal alkynes such as diphenylacetylene and phenylpropyne were less reactive, but the borylstannation proceeded smoothly at 80 °C to give the corresponding *cis*-addition products. The borylstannane $Me_3SnB(NEt_2)_2$ also reacted with various alkynes very similarly to **2**. However, the resulting adducts were somewhat thermally unstable and attempted isolation by distillation resulted in deterioration of the products. The catalysis is envisioned to be triggered by oxidative addition of the B—Sn bond. X-ray structure of the complex derived from **2** and $Me_2Pd(dmpe)$ has been determined and the complex was found to react with 1-octyne to afford the borylstannation product (see **Sect. II.2.6**).

Regio- and stereoselective 1,4-addition of borylstannane **2** to 1,3-dienes smoothly proceeds in the presence of catalytic amounts of $Pd_2(dba)_3$ and $P(OCH_2)_3CEt$ to provide

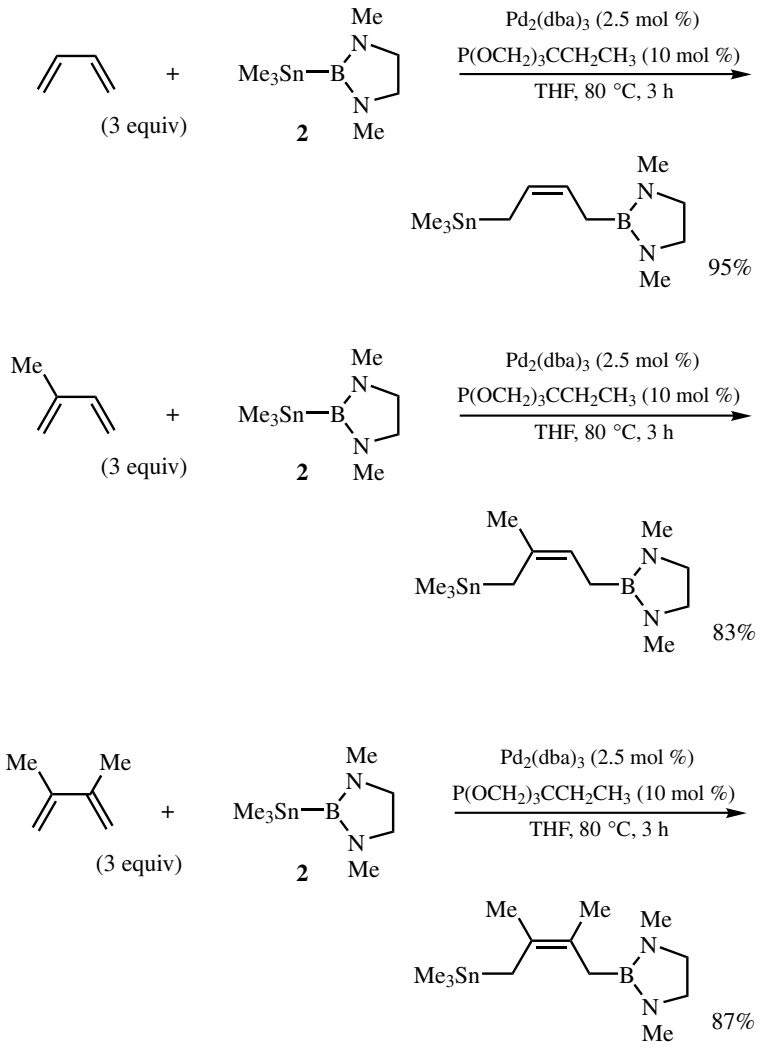


Alkyne		Temperature	Yield (%)	Regioisomeric Ratio
R^1	R^2			
n-C_6H_{13}	H	r. t.	98	>99:1
Ph	H	r. t.	97	>99:1
Ph	Ph	80 °C	97	—
Ph	Me	80 °C	97	85:15

Borylstannane (1.1 equiv), alkyne (1.0 equiv), $Pd(PPh_3)_4$ (0.01 equiv), benzene, 1 h.

Scheme 22

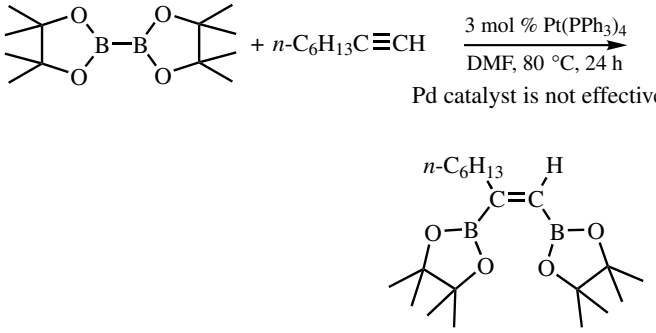
(*Z*)-1-boryl-4-stannyl-2-butenes in high yields.[31] Isoprene afforded 4-boryl-2-methyl-1-stannyl-2-butene exclusively without contamination by the other regioisomer (**Scheme 23**).



Scheme 23

E.iii. Diboration of Alkynes

The additions of bimetallic reagents such as the silicon–metal and tin–metal compounds to the carbon–carbon multiple bonds have been extensively studied; however, there are few reports concerning the metal–boron compounds as shown above. Miyaura and co-workers[32] have examined the addition reaction of tetraalkoxydiboron to alkynes and found that only the platinum complexes such as $Pt(PPh_3)_4$ exhibited excellent catalytic activity (**Scheme 24**). $Pd(PPh_3)_4$ and $Pd(OAc)_2$–isocyanide complexes, which have been the best catalysts for the silyl- and stannylmetallation, were ineffective because their oxidative addition to palladium(0)–phosphine complexes is very slow.[33]



Scheme 24

F. SUMMARY

1. Development of two new classes of ligands has enabled bis-silylation of acetylenes with conventional hexaalkyldisilanes.

2. Internal alkynes are less reactive than terminal ones toward Pd-catalyzed bis-silylation. However, the substrates, with which the disilane and acetylenic moiety are tethered together, provide bis-silylation products in good to excellent yields.

3. Intramolecular bis-silulation of alkenes has also been achieved more effectively than intermolecular reactions. The use of optically active isonitrile ligand on palladium catalyst provides us with a synthetic method for an enantioselective intramolecular bis-silylation of homoallylic alcohols. The method has successfully been applied to the synthesis of highly enantio-enriched allylsilanes.

4. Addition of trimethylsilyl cyanide to carbon–carbon triple bonds proceeds effectively in the presence of palladium catalyst to give cyano-substituted alkenylsilanes in good yields. Reaction of trimethylsilyl iodide with alkynes under the coexistence of acetylenic tin compounds gives three-component coupling products effectively.

5. Silylboration and borylstannation of acetylenes have also been achieved easily in the presence of a catalyst of palladium complexes. In contrast, palladium complexes such as $Pd(PPh_3)_4$ or $Pd(OAc)_2$–isocyanide were ineffective for diboration of alkynes. However, the development of another new ligand will solve this difficulty in the future.

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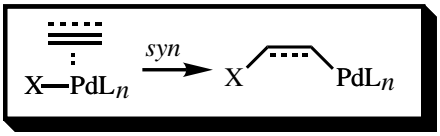

VII.6 Palladium-Catalyzed *Syn*-Addition Reactions of X—Pd Bonds (X = Group 15, 16, and 17 Elements)

AKIYA OGAWA

A. INTRODUCTION

Palladium-catalyzed addition of heteroatom compounds bearing heteroatom–heteroatom bond (X—X) or heteroatom–hydrogen bond (X—H) to carbon–carbon unsaturated bonds, such as alkynes, alkenes, and allenes, is one of the most useful methods for introducing heteroatom functions into organic molecules. The reaction may involve the formation of the species bearing a heteroatom–palladium bond as a key intermediate and proceed via heteropalladation of unsaturated compounds (or alternatively via hydropalladation by a palladium hydride species (H—Pd—X) formed *in situ*). The following two processes can be operative for the heteropalladation (**Scheme 1**). While the former process, that is, *anti*-addition process, proceeds by the attack of the heteroatom nucleophile (X^-) to the unsaturated bond coordinated by palladium, the later process involves the *syn*-addition of X—PdL_n to the unsaturated bonds. Whereas the *anti*-addition process is widely known, *syn*-heteropalladation has been rare.

This section deals with the *syn*-heteropalladation of carbon–carbon unsaturated compounds with group 15, 16, and 17 heteroatom compounds. The *anti*-process including Wacker-type oxy-, amino-, and other related heteropalladation processes are discussed in **Part V**.

B. PALLADIUM-CATALYZED *SYN* ADDITION REACTIONS OF Cl—Pd BONDS

In general, chloropalladation of alkynes is known to proceed with competing *anti*- and *syn*-additions, and examples of selective *syn*-chloropalladation are limited to a few cases.[1]–[3] For example, Kaneda and co-workers report that codimerization of substituted alkynes and allyl chloride proceeds predominantly via *syn*-chloropalladation in the presence of the $PdCl_2(PhCN)_2$ catalyst (**Scheme 2**).[1]

A dienylpalladium complex (**1**) is isolated from the $PdCl_2$-induced dimerization of *t*-butylacetylene and is characterized by X-ray structure analysis (**Scheme 3**).[4] The result

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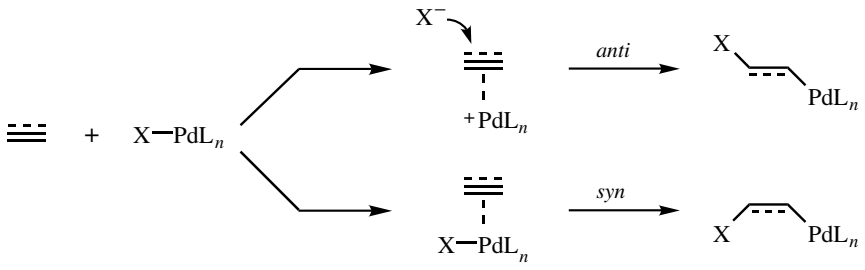
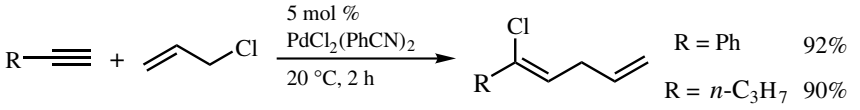
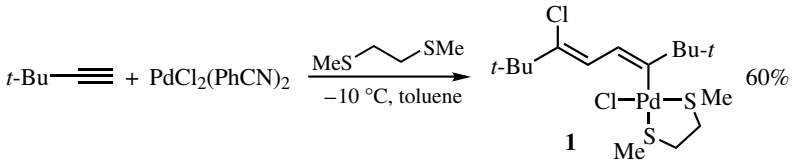


Scheme 1



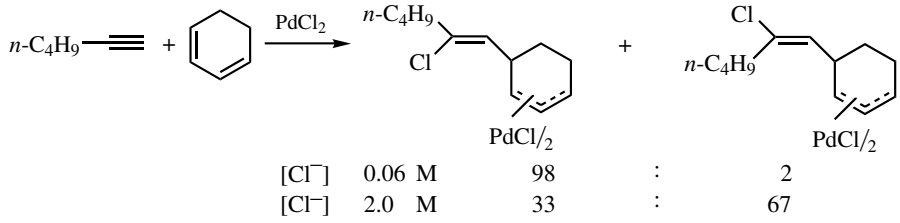
Scheme 2



Scheme 3

strongly suggests that the first step is a *cis*-chloropalladation and the second a *cis*-vinylpalladation of the coordinated alkyne.

Bäckvall and co-workers investigated precisely the stereochemistry and mechanism of chloropalladation of alkynes; namely, chloropalladation adducts from terminal alkynes are trapped *in situ* by either allyl chloride or 1,3-cyclohexadiene (**Scheme 4**).[5] As a result, the stereochemistry of the chloropalladation is found to be dependent on the chloride ion concentration: *cis*-chloropalladation predominates at a low chloride concentration, whereas at a high chloride concentration *trans*-chloropalladation is preferential.

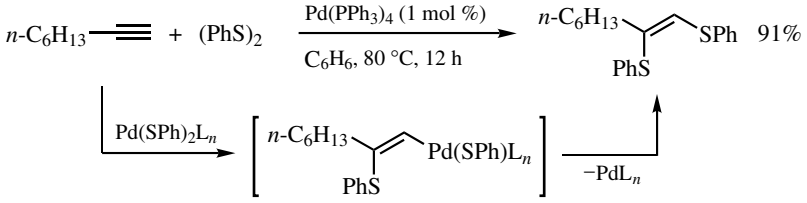


Scheme 4

C. PALLADIUM-CATALYZED *SYN*-ADDITION REACTIONS OF S—Pd AND Se—Pd BONDS

Although organic sulfur and selenium compounds have widely been employed as the sources of ligands for various transition metals, the transition-metal-catalyzed reactions

using them as substrates have scarcely been developed. This is partly due to the widespread belief that organic sulfur and selenium compounds often bind strongly to the catalysts, thus poisoning them and making catalytic reactions ineffective. During the last decade, however, several useful catalytic reactions of organic sulfur and selenium compounds have been reported, some of which includes the *syn*-addition process of S—Pd and Se—Pd bonds to carbon–carbon unsaturated bonds. For example, diaryl disulfides add to a variety of alkynes in the presence of a palladium(0) complex like $Pd(PPh_3)_4$, giving the corresponding vicinal (*Z*)-bis(arylthio)alkenes, stereoselectively (**Scheme 5**).[6]



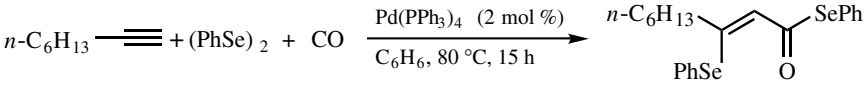
Scheme 5

The stoichiometric reaction of diphenyl disulfide with $Pd(PPh_3)_4$ provides the complex ($[Pd(SPh)_2(PPh_3)]_2$) formulated as a dimer bearing both terminal and bridged sulfide groups,[7] which reacts with alkynes to give the corresponding (*Z*)-*vic*-bis(arylthio)alkenes in good yields. These results suggest that the reaction proceeds via *syn*-thiopalladation of alkynes. Similarly, organic diselenides also add to alkynes smoothly, giving the corresponding vicinal diselenoalkenes in good yields.[6]

On the other hand, similar reactions using dialkyl disulfides in place of diaryl ones result in lower yield of the desired adducts. Thus, the improved method is developed: the Pd-catalyzed addition of bis(triisopropylsilyl) disulfide (i-$Pr_3SiSSSi(Pr$-$i)_3$) to alkynes to give (*Z*)-*vic*-bis(silylthio)alkenes, followed by desilylation with tetrabutylammonium fluoride (TBAF) and quenching of the thus formed thiolate anions with methyl iodide successfully leads to the corresponding (*Z*)-*vic*-bis(methylthio)alkenes in good yields, stereoselectively.[8] Although $Pd(PPh_3)_4$ exhibits no catalytic activity toward the addition of disulfides to alkenes, Cp*RuCl(cod) was reported very recently to work as an excellent catalyst for the vicinal dithiolation of alkenes.[9]

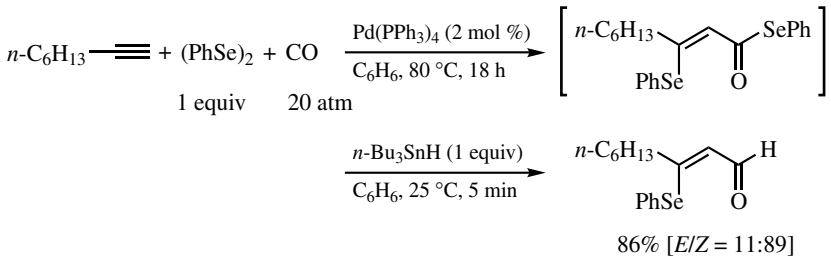
The $Pd(PPh_3)_4$-catalyzed reaction of terminal alkynes with diaryl disulfide or diaryl diselenide under pressurized carbon monoxide is found to lead to the regioselective introduction of carbon monoxide to the terminal position of the alkynes with excellent stereoselectivity, as shown in **Scheme 6**.[6]

$PdCl_2(PPh_3)_2$ is an excellent catalyst for the carbonylative addition of $(PhS)_2$ to alkynes at lower CO pressures. The obtained carbonylative addition products (β-thio-α,β-unsaturated thioesters or β-seleno-α,β-unsaturated selenoesters) can be converted to the corresponding aldehydes chemoselectively, upon treatment with tributyltin hydride in the



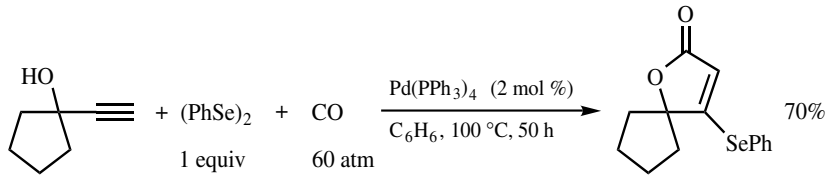
Scheme 6

presence of $Pd(PPh_3)_4$ catalyst.[10],[11] Thus, the Pd-catalyzed carbonylative addition of $(PhSe)_2$ to terminal alkynes and the subsequent reduction with *n*-Bu_3SnH without the isolation of thus formed selenoesters attains a novel selenoformylation of alkynes with $(PhSe)_2$ and CO (**Scheme 7**).[11]



Scheme 7

When the Pd-catalyzed carbonylation with diaryl dichalcogenides and CO is applied to propargyl alcohols, carbonylative lactonization occurs under higher CO pressure giving β-(arylchalcogeno)-α,β-unsaturated γ-lactones in good yields (**Scheme 8**).[12]



Scheme 8

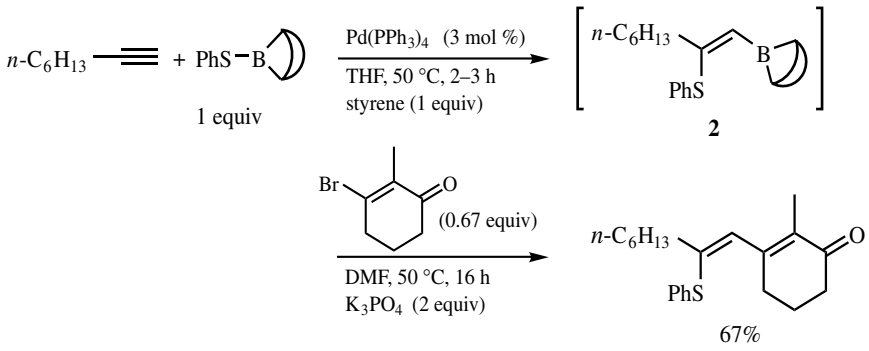
One of the most interesting applications of transition-metal-catalyzed addition of heteroatom–heteroatom linkage to carbon–carbon unsaturated bonds is the simultaneous introduction of two different heteroatoms into unsaturated compounds.[13] For example, 9-(phenylthio)-9-borabicyclo[3.3.1]nonanes, which has a group 16–group 13 interelement linkage, adds to terminal alkynes in the presence of $Pd(PPh_3)_4$, providing the corresponding β-phenylthio-substituted vinylboranes (**2**) regio- and stereoselectively. The present thioboration may proceed via *syn*-addition of the palladium sulfide species ($PhS–PdBX_2$) to alkynes. The combination of this Pd-catalyzed thioboration and the Pd-catalyzed cross-coupling of the thus formed vinylboranes with organic halides leads to the regio- and stereoselective synthesis of vinyl sulfides (**Scheme 9**).[14]

The regio- and stereoselective addition of a group 16–group 14 interelement linkage such as $PhSeSiMe_3$,[15] $PhSeGeMe_3$,[15] $Mes_2Ge\text{-}S\text{-}GeMes_2$,[16] and $Mes_2Ge\text{-}S\text{-}GeMes_2$[16] to alkynes ($RC{\equiv}CH$) is also catalyzed by $Pd(PPh_3)_4$, but the yields of the adducts are relatively low (e.g., (*Z*)-$R(PhSe)C{=}CH(GeMe_3)$, 35%(R = Ph))

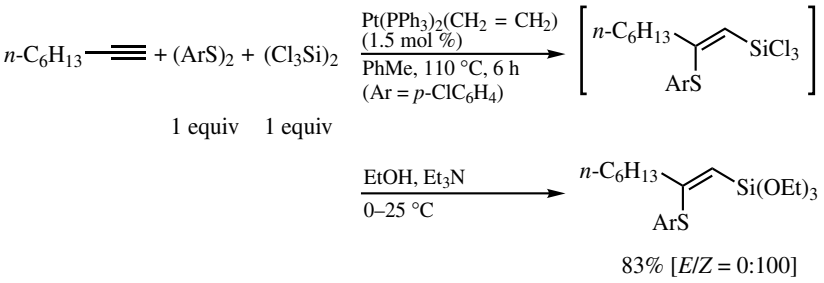
Very recently, a zerovalent platinum catalyst such as $Pt(PPh_3)_2(CH_2{=}CH_2)$ was shown to exhibit an excellent catalytic activity toward the regio- and stereoselective thiosilylation of alkynes by using a novel mixed system of $(ArS)_2$ and $(Cl_3Si)_2$ (**Scheme 10**).[17]

Furthermore, heteroatom compounds bearing a group 16–group 15 element linkage, for example, $PhS–P(O)(OPh)_2$,[18] and $PhSe–P(O)(OPh)_2$,[19] undergo insertion of alkynes regio- and stereoselectively in the presence of $Pd(PPh_3)_4$ (**Scheme 11**). Besides $Pd(PPh_3)_4$, *cis*-$PdMe_2(PPh_2Me)_2$ (76% yield) and *cis*-$PdEt_2(PPh_2Me)_2$ (82% yield) also catalyze the

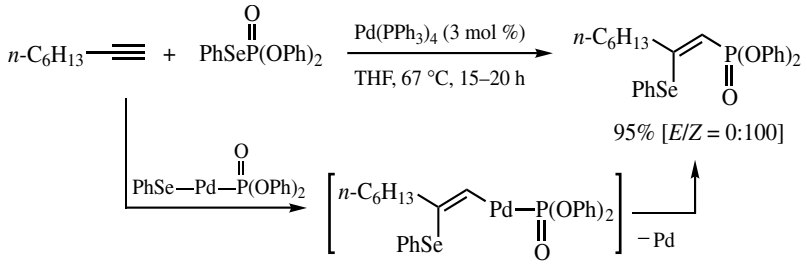
reaction under identical conditions, whereas platinum complexes such as $Pt(PPh_3)_4$, $Pt(PEt_3)_3$, and $Pt(PPh_3)_2(CH_2{=}CH_2)$ do not indicate any catalytic activity under similar reaction conditions.



Scheme 9

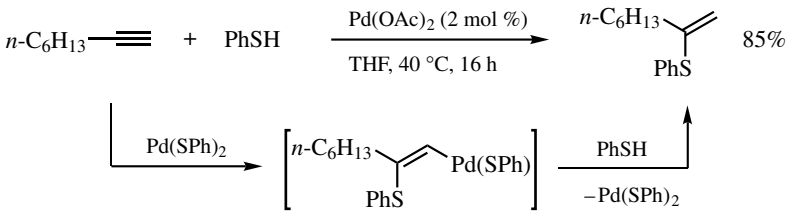


Scheme 10



Scheme 11

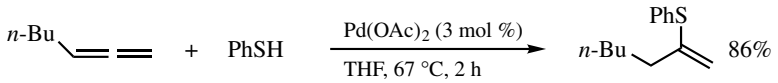
It is well-known that organic thiols add to alkynes regioselectively under radical conditions to afford *anti*-Markovnikov-type vinylic sulfides as a stereoisomeric mixture. In contrast, the addition of arenethiols to terminal alkynes in the presence of palladium acetate is revealed to proceed with a different regioselectivity to give the corresponding Markovnikov-type adducts in high yields (**Scheme 12**).[20]



Scheme 12

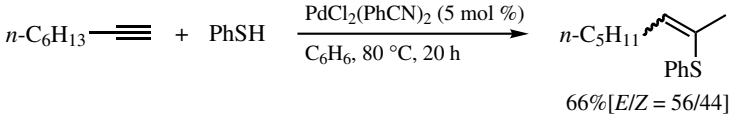
Similar conditions can be employed with benzeneselenol, affording Markovnikov-type vinylic selenides.[21] A possible catalytic pathway involves a ligand-exchange reaction between $Pd(OAc)_2$ and PhSH to generate palladium sulfide species ($[Pd(SPh)_2]_n$), followed by regioselective *syn*-thiopalladation of alkynes to give the corresponding vinylic palladium intermediate as a key intermediate leading to the Markovnikov-type adducts.

The $Pd(OAc)_2$-catalyzed hydrothiolation procedure can be applied to the regioselective addition of thiols and selenols to conjugated enynes[22] and allenes,[23],[24] which provides a useful method for the synthesis of vinylic sulfides and selenides (**Scheme 13**).



Scheme 13

When bis(benzonitrile)dichloropalladium(II) is employed instead of $Pd(OAc)_2$, terminal alkynes undergo Markovnikov addition of benzenethiol and double-bond isomerization sequentially to provide the corresponding internal vinylic sulfides in good yields (**Scheme 14**).[25]



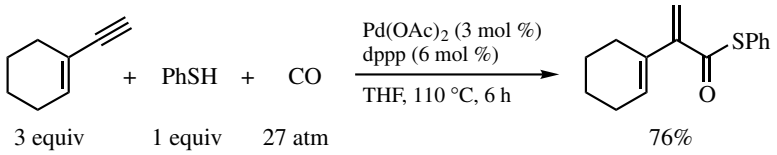
Scheme 14

The stoichiometric reaction of $PdCl_2(PhCN)_2$ with PhSH (2 equiv) provides PdCl(SPh)(PhSH), which shows a high catalytic activity toward both Markovnikov-type hydrothiolation and double-bond isomerization reactions.

In addition, switching the catalyst simply from $Pd(OAc)_2$ to $RhCl(PPh_3)_3$ leads to a sharp reversal of regioselectivity in the addition of PhSH to alkynes, providing *anti*-Markovnikov-type vinylic sulfides with the *trans* configuration.[25] In this reaction, a *syn*-hydrorhodation process (not *syn*-thiorhodation process) is operative.

Several examples of the transition-metal-catalyzed carbonylative thiolation of alkynes and allenes with carbon monoxide were reported recently. While thioformylation products (R(PhS)C═CCHO) are obtained regioselectively by the $RhH(CO)(PPh_3)_3$-catalyzed reaction of alkynes (RC≡CH) with PhSH and CO,[26] the use of $Pt(PPh_3)_4$ as the catalyst

leads to different regioselectivity of CO introduction, affording hydrothiocarbonylation products ($R(PhSC(O))C{=}CH_2$) selectively.[27] The latter reaction—hydrothiocarbonylation—can also proceed by using a palladium catalyst, when conjugated enynes are employed as the substrates (**Scheme 15**).[28] A possible pathway for this carbonylation may involve regioselective thiocarboxypalladation of enynes with $PhSC(O)–PdL_n–H$.



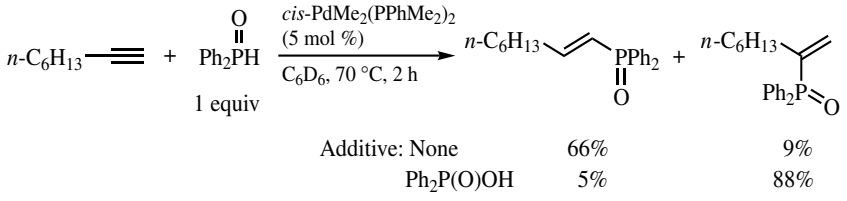
Scheme 15

Although some other examples of the transition-metal-catalyzed carbonylation reaction of carbon–carbon unsaturated compounds with thiols and CO have been reported,[29]–[32] it is unclear whether these reactions involve the *syn*-thiometallation process.

D. PALLADIUM-CATALYZED *SYN* ADDITION REACTIONS OF P—Pd BONDS

Palladium catalysts such as *cis*-$PdMe_2(PPh_2Me)_2$ are reported to catalyze the Markovnikov-type addition of hydrogen phosphonates ($(RO)_2P(O)H$) to alkynes ($RC{\equiv}CH$) to afford a variety of vinylphosphonates ($R\{(RO)_2P(O)\}C{=}CH_2$) in good yields.[33] On the other hand, diphenylphosphine oxide ($Ar_2P(O)H$) adds to alkynes in the presence of palladium catalyst like *cis*-$PdMe_2(PPhMe_2)_2$ giving *anti*-Markovnikov adducts preferentially (**Scheme 16**).[34] The reaction to give *anti*-Markovnikov adducts may proceed through insertion of alkynes into the H—Pd bond of $H–PdL_n–P(O)Ar_2$.

Interestingly, the regioselectivity is reversed, producing Markovnikov products through *syn*-addition when the same reaction is repeated in the presence of trace amounts of diphenylphosphinic acid (**Scheme 16**).[35]



Scheme 16

The reaction involves the formation of $Ph_2P(O)–PdL_n–OP(O)Ph_2$ (**3**) by the reaction of $PdMe_2L_n$ with $Ph_2P(O)H$ and $Ph_2P(O)OH$, and the subsequent insertion of alkynes into the $Ph_2P(O)$—Pd bond of **3**. Some other related reports are known, which include the Pt-catalyzed hydrophosphination of acrylonitrile via carbon–carbon double bond insertion into a Pt—P bond.[36]–[38]

E. SUMMARY

1. Chloropalladation of alkynes usually proceeds by competing *anti*- and *syn*-additions, and its stereochemistry is dependent on the chloride ion concentration. *Syn*-chloropalladation predominates at a low chloride concentration.

2. Thio- and selenopalladation of alkynes generally proceeds by a *syn*-addition process. The addition of RS–SR, RSe–SeR, R_2B–SR, R_3Si–SR, Cl_3Si–SeR, R_3Ge–SeR, and $(RO)_2P(O)$–SR to alkynes proceeds regio- and stereoselectively to give the corresponding *cis*-adducts, most probably via *syn*-thiopalladation or *syn*-selenopalladation. The Pd(OAc)-catalyzed addition of thiols and selenols to alkynes provides the corresponding *syn*-addition products at the initial stage of the reaction. However, stereochemical isomerization of double bond takes place gradually probably by the action of palladium hydride species[39].

3. Heteroatom compounds bearing a P—H linkage such as $(RO)_2P(O)H$ and $R_2P(O)H$ also add to alkynes in the presence of palladium catalyst. When the Markovnikov-type addition to alkynes takes place selectively, the *syn*-addition process is operative.

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PART VIII
Palladium-Catalyzed Oxidation Reactions That Have not Been Discussed in Earlier Parts

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
ISBN 0-471-31506-0

Pd-Cat. Oxid.

VIII.1 Background for Part VIII

EI-ICHI NEGISHI

The definitions of oxidation and reduction and potential sources of confusion associated with them are discussed in **Sect. VII.1**. Some chemists mistakenly think that hydration of ethylene to give ethanol is an oxidation process, but no net oxidation or reduction takes place in hydration of ethylene. On the other hand, hydration of ethylene–palladium complexes to give acetaldehyde (the Wacker oxidation) (**Sect. V.3.1**) is a genuine two-electron oxidation reaction. If one determines the formal oxidation states (FOS) of the participating atoms (i.e., C and Pd) in the examples shown in **Scheme 1**, the difference between simple alkene hydration and the Wacker oxidation (**Sect. V.3.1.1**) is very clear. The formal oxidation states of the other atoms in these reactions do not change.

It should be unmistakably clear that Pd-promoted oxidation by Pd must involve reduction of Pd. Since the great majority of the currently known organopalladium reactions involve Pd(0) and Pd(II) species, *oxidation with the use of Pd generally requires reduction of Pd(II) species to Pd(0) species in elementary processes*. Such processes themselves are only stoichiometric in Pd, because they do not involve regeneration of Pd species in the original form and state. Thus, such processes must be combined with some oxidation processes permitting regeneration of the original Pd species. In cases where organic halides and related electrophiles as well as carboxylic acids, alcohols, and other active hydrogen compounds are used as starting compounds, their oxidative addition oxidizes Pd. If none of the starting compounds oxidizes Pd, it must then be oxidized by some external reagents. In the Wacker oxidation, Pd(0) species are commonly oxidized with $CuCl_2$ and O_2 (**Sect. V.3.1.1**). A number of other oxidants, such as hydrogen peroxide, *m*-chloroperbenzoic acid, quinones, bromine, NBS, alkyl nitrites, and even some externally added organic halides, as well as just air or O_2, have been used for this purpose.

As stated above, Pd-promoted oxidation of organic compounds generally involves, at one stage or another, two-electron reduction of Pd(II) to Pd(0). Of various patterns of elementary organopalladium transformations listed in **Table 3** of **Sect. I.2**, reductive elimination is the predominant process of reduction of Pd, reductive displacement being its close relative. In reductive elimination, two ligands R^1 and R^2 are collectively two-electron oxidized from a FOS of -2 to 0 (**Scheme 2**). And yet, the Pd-catalyzed cross-coupling discussed in Part III does not involve net oxidation as indicated in **Scheme 2**. On the other hand, dimerization of hydrocarbons (e.g., arenes) or organometals promoted by Pd(II) complexes oxidizes them by overall two electrons, while related dimerization of organic halides requiring Pd(0) complexes reduces these halides (**Scheme 2**). Thus, these three different but

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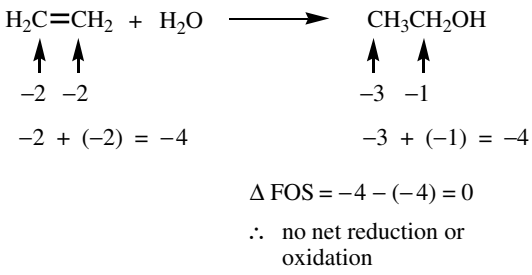
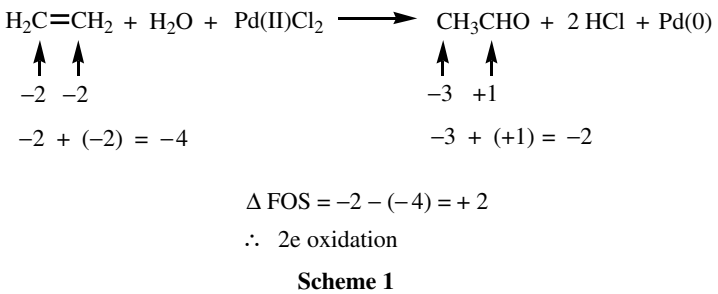
Hydration

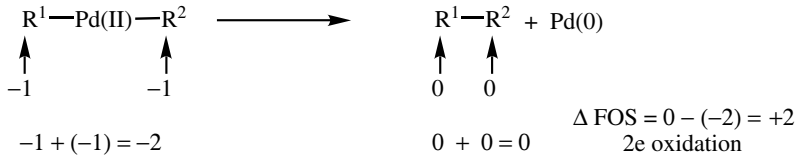


Wacker oxidation

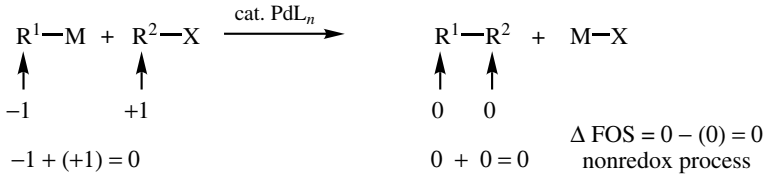


Scheme 1

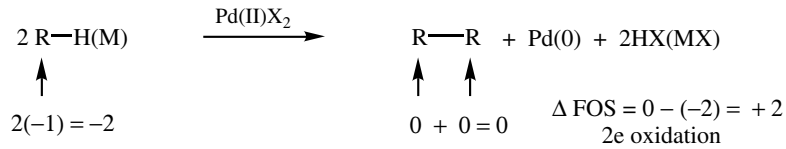
Reductive elimination (2e oxidation of ligands)



Cross-coupling (overall nonredox process)

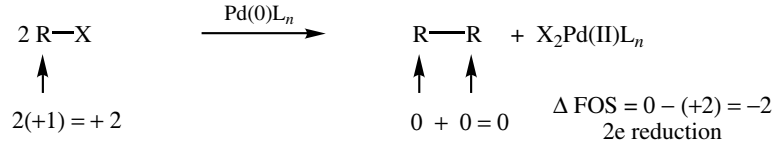


Hydrocarbon or organometallic dimerization (2e oxidation)



Scheme 2

Organic halide dimerization (2e reduction)



Scheme 2 (*Continued*)

related reactions involve overall nonredox processes, oxidation, and reduction, respectively, but the reductive elimination step, which may be operative in all three transformations, oxidizes two ligands. To avoid confusion and misunderstanding, it is therefore advisable to examine overall as well as detailed aspects of these reactions through careful determination of formal oxidation states. Oxidative organometallic dimerization reactions are synthetically closely related to cross-coupling reactions. So, they are discussed in **Sect. III.2.20**. However, related oxidative dimerization reactions of hydrocarbons cannot readily fit into **Part III**, even though they can produce the same dimeric products. These reactions are therefore discussed in **Sect. VIII.2**.

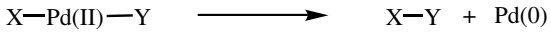
Although reductive elimination (**Pattern 1** for oxidation by Pd in **Scheme 3**) is the key process for oxidation by Pd, it is often preceded or accompanied by various β-elimination processes in a more typically organic sense. Several such processes, that is, **Patterns 2.1** through **2.4**, are listed in **Scheme 3**. β-Elimination and reduction of Pd may occur either synchronously or in two or more steps. In addition, their vinylogous analogues proceeding via 1,4-elimination have also been observed (**Patterns 3.1** through **3.4**). It should also be noted that allylic substitution (**Pattern 4**) is a vinylogue of the reductive elimination process represented by **Pattern 1**. These patterns are summarized in **Scheme 3**.

Various oxidation reactions represented by **Patterns 2** and **3** in **Scheme 3** are discussed in **Sect. VIII.3**. However, the Wacker oxidation and related reactions, in which nucleophilic attack on Pd–alkene π-complexes plays an important role, are discussed in **Sect. V.3**. Most of the allylic substitution reactions represented by **Pattern 4** are generally preceded by reduction of allylic electrophiles (via oxidative addition). Consequently, the overall processes do not generally involve net oxidation or reduction. So, they are discussed in **Sect. V.II**.

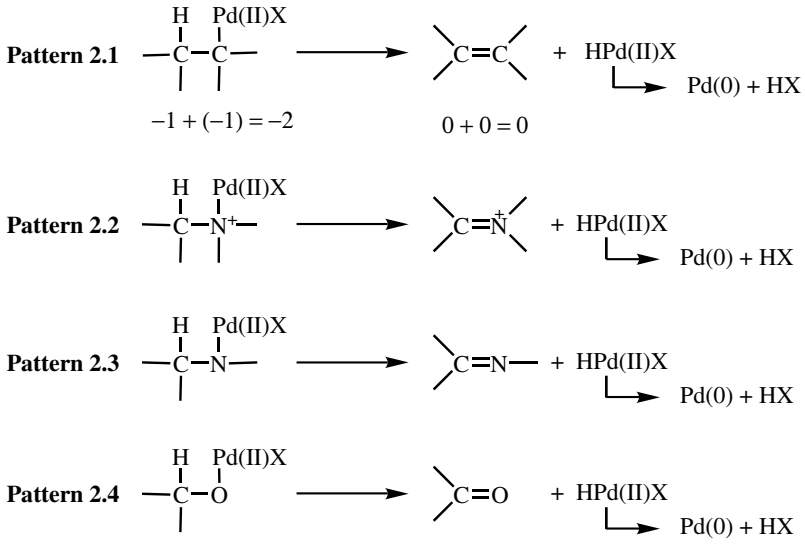
Carbonylation offers yet another opportunity for oxidation. In CO the formal oxidation state (FOS) of the carbon atom is +2. In cases where the carbonylation products are carboxylic acids and their derivatives, the FOS of the carbonyl carbon atom is +3. If they are carbonates and related derivatives, it is +4. These changes in the FOS, that is, +2 → +3 and +4, do not necessarily mean that carbonylation reactions in question involve net oxidation. In fact, most of the Pd-catalyzed carbonylation reactions discussed in **Part VI** do not involve net oxidation. In such reactions, one or more of the reactants serve as oxidants. Two representative examples are shown in **Scheme 4**. *In principle, if no external oxidant or reductant is required, any Pd-catalyzed reaction must be an overall nonredox process*.

On the other hand, the carbonylation reactions discussed in **Sect. VI.7** generally require external oxidants. In some reactions, however, reactants are derivatized such that they can serve as internal oxidants. Conversion of alcohols into nitrites prior to carbonylation is a representative example. In such cases, the question of redox versus nonredox is a matter of precisely what chemical equation one deals with. For example, carbonylation

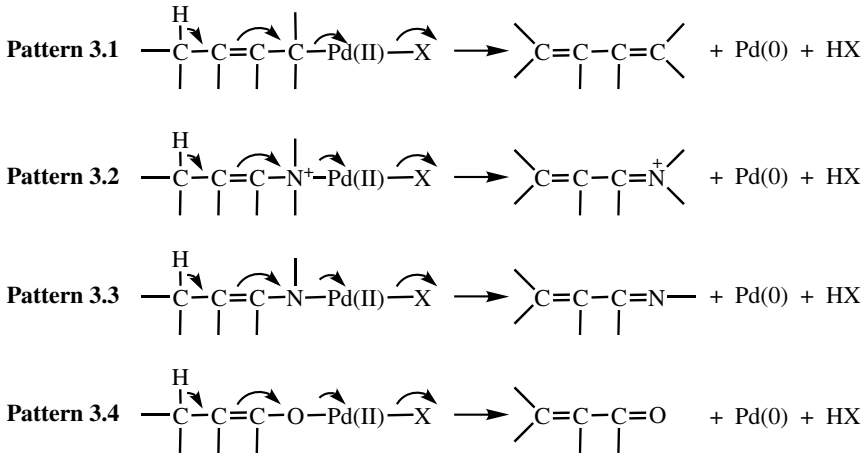
Pattern 1 for oxidation by Pd (reductive elimination)



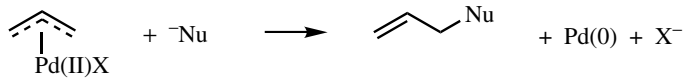
Patterns 2.1 through 2.4 for oxidation by Pd (β-elimination + reductive elimination)



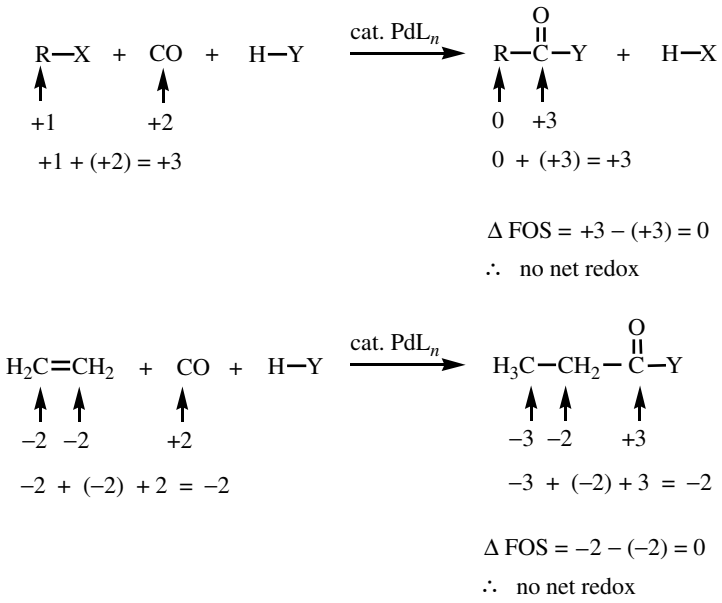
Patterns 3.1 through 3.4 for oxidation by Pd (1,4-elimination + reductive elimination)



Pattern 4 for oxidation by Pd (allylic substitution)



Scheme 3

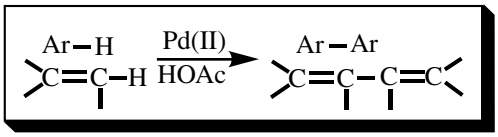


Scheme 4

reactions of alkyl nitrites *per se* may be net nonredox processes that are catalytic in Pd. On the other hand, if one considers the corresponding alcohols as reactants, the overall process may then become oxidative. One should always be reminded that *all chemical processes are after all "zero-sum" games with respect to electrons*. Furthermore, as repeatedly stated in this Handbook, any Pd-catalyzed reactions must be net nonredox processes in an overall sense, whether or not some such reactions are conveniently called oxidation or reduction reactions.

Mainly for the sake of convenience, all Pd-catalyzed carbonylative oxidation reactions are discussed in **Part VI** (**Sect. VI.7**).

The ability of Pd to undergo facile and reversible two-electron redox transformation, often uncomplicated by one-electron processes, offers a large number of opportunities for achieving both oxidation and reduction of organic compounds. Despite extensive developments over the last three to four decades, it may be predicted that many more synthetically useful oxidation reactions can be and will be developed in the near future.



VIII.2 Oxidation via Reductive Elimination of Pd(II) and Pd(IV) Complexes

VIII.2.1 Homodimerization of Hydrocarbons via Palladium-Promoted C—H Activation

YUZO FUJIWARA and CHENGGUO JIA

A. INTRODUCTION

A very important series of reactions are those in which two hydrocarbons such as arenes and alkenes are homocoupled with loss of two hydrogens in the presence of a stoichiometric amount of palladium(II) compounds such as $PdCl_2$ and $Pd(OAc)_2$, or more usefully with a catalytic amount of palladium catalysts and a stoichiometric amount of oxidants.[1],[2] The palladium(II)-promoted coupling reaction was first reported by Hüttel and Bechter in 1959, who found that α-substituted styrenes were coupled by $PdCl_2$ in acetic acid in the presence of NaOAc (**Scheme 1**).[3]

The oxidative coupling of arenes to biaryls in the presence of $PdCl_2$ and sodium acetate was disclosed by van Helden and Verberg afterward.[4] Two similar mechanisms have been proposed for these two reactions (**Schemes 2** and **3**), which involve (i) the electrophilic substitution of a vinylic or aryl hydrogen by palladium through the formation of first a π- and then a σ-bonded vinyl– or aryl–Pd(II) complex; (ii) coordination of another molecular olefin or arene to the palladium complex, and *syn*-insertion to the double bond of the coordinated molecule; and (iii) followed by elimination of HPdOAc and formation of the corresponding diene or biaryl at the same time.[5],[6] The rate-determining step is considered to be the formation of a σ-bonded vinyl– or aryl–Pd(II) complex. The precise mechanism is still uncertain.

B. OXIDATIVE COUPLING OF ARENES

The construction of a single bond between two aromatic rings, either inter- or intramolecularly, is a challenge to organic chemists. The direct coupling of two arenes to form a biaryl or biaryl isomers is economically more attractive than other methods, although

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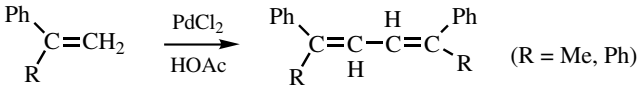
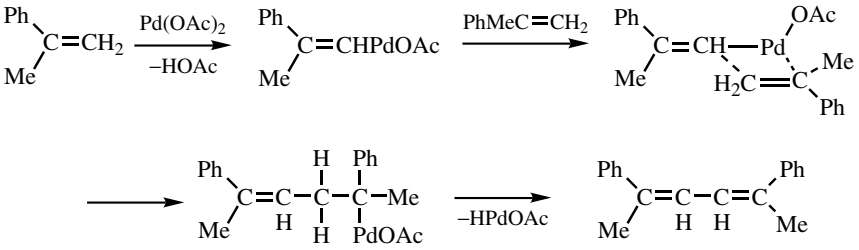
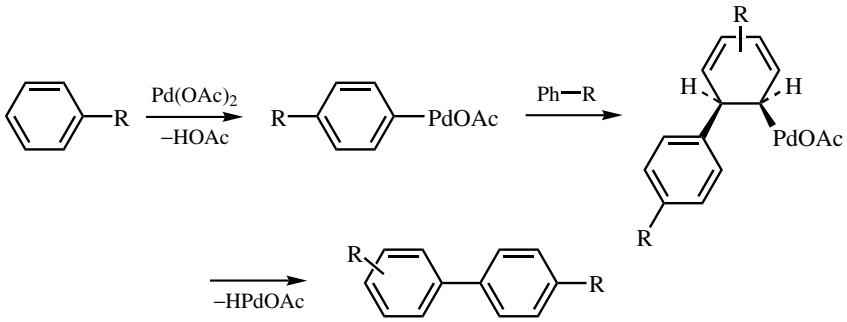


Scheme 1



Scheme 2

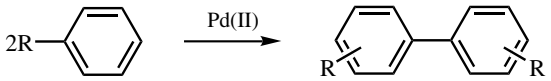


Scheme 3

more selective procedures for the preparation of biaryls such as Pd-mediated Suzuki coupling[7],[8] between aryl bromide and aromatic boronic acid are available.

The reaction of benzene with $PdCl_2$ in the presence of NaOAc gives biphenyl in 81% yield (**Scheme 4**) (based on Pd). As the reaction proceeds Pd metal is deposited, but no coupling occurs unless acetate ion is present.[9] The rate-determining step as mentioned earlier is considered to be the formation of a σ-bonded aryl–Pd(II) complex, followed by a fast breakdown of the complex. The latter is possibly initiated by attack of acetate anion. The yield is improved to 99% (based on Pd) when $[Pd(C_2H_4)Cl_2]_2$ and $AgNO_3$ are employed.[10] The reaction can be made catalytic to palladium when the reaction is carried out under oxygen pressure either with benzene or substituted benzenes.[11],[12],[14],[15] The coupling of the substituted benzenes follows the usual orientation pattern expected for electrophilic attack.[16] The total reaction is extremely rapid either in TFA solution[14] or in the presence of strong acids such as $HClO_4$.[12] Thus, a high turnover number is obtained (**Scheme 4**) for the coupling of benzene in the presence of $HClO_4$. A reasonable explanation of the effect of strong acid is that the electrophilic substitution of Pd^{2+} on aromatic compounds is assisted by the presence on the metal of weakly bonded ligands such as trifluoroacetate.

A new catalyst system composed of $Pd(OAc)_2$ and dialkyl sulfide was reported recently as an effective system for the oxidative coupling of benzene.[11],[13] Also, the



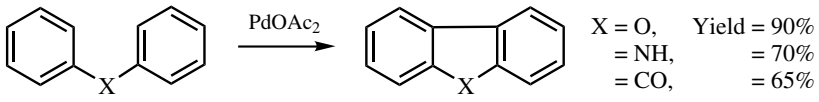
	Reagent	Yield(%)[a]	Reference
R = H,	$PdCl_2$ + NaOAC in HOAc	81	[9]
R = H,	$[Pd(C_2H_4)Cl_2]_2$ + $AgNO_3$ in HOAc	99	[10]
R = H,	Catalyst : $Pd(ClO_4)_2/Fe(ClO_4)_3$, in HOAc under O_2	5660	[12]
R = H,	Catalyst : $Pd(OAc)_2$–$(Me_2CH)_2S$, under O_2 at 70 °C	66[b]	[11],[13]
R = H,	Catalyst : Pd/Faujasite or Pd/Beta, under 1:1 N_2/O_2 7 kg/cm^2, at 150 °C	3[b]	[14]
R = Me,	Catalyst : $Pd(OAc)_2$, under O_2	2000	[15]

[a] Yield based on Pd.
[b] Yield based on the starting aromatic compound.

Scheme 4

manufacture of biphenyl is made possible using zeolite-supported Pd catalysts under oxygen, which has been disclosed in a patent.[14]

The homocoupling of heterocycles such as 2-substituted furan[17],[18] and thiophene[19] in the presence of $Pd(OAc)_2$ affords mainly the corresponding 2,2-bifuran and dithienyl in fair to good yields. Intramolecular couplings are in general much more successful; for example, the cyclization in **Scheme 5** gives the corresponding cyclic compounds in good yields.[20]

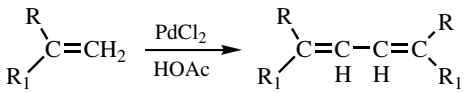


Scheme 5

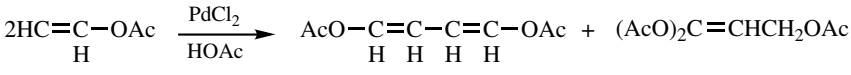
C. OXIDATIVE COUPLING OF ALKENES

Compared with the oxidative coupling of aromatics, less information on the generality of this coupling is available. Terminal olefins having a substitution at the 2-position are coupled by the action of stoichiometric Pd(OAc) or $PdCl_2$ in the presence of NaOAc to form 1,1,4,4-tetrasubstituted 1,3-butadienes (**Scheme 6**).[3],[21],[22] Reaction of isobutylene, 2-phenyl propene, 1,1-diphenyl ethylene, and methyl methacrylate are typical examples.

1,4-Diphenyl butadiene as a main product is obtained in the oxidation of styrene with $Pd(OAc)_2$. Oxidative coupling of vinyl acetate using $Pd(OAc)_2$ gave 1,4-diacetoxyl-1,3-butadiene with several side products, and the reaction could be made catalytic using $Cu(OAc)_2$ as the oxidant[4] (**Scheme 7**).



Scheme 6



Scheme 7

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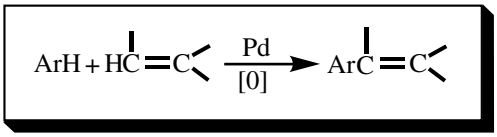


VIII.2.2 Palladium-Promoted Alkene–Arene Coupling via C—H Activation

YUZO FUJIWARA

A. INTRODUCTION

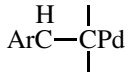
In 1967 the coupling reaction of olefins and benzenes to give arylated olefins was first discovered (**Scheme 1**).[1] This reaction is the beginning of Pd-catalyzed alkene–arene coupling via C—H activation and it was found that $Pd(OAc)_2$ is best at bringing about the reaction.[2]

$Pd(OAc)_2$-promoted coupling of olefins and aromatic compounds proceeds in the homogeneous phase of the olefin and $Pd(OAc)_2$ (1:1 molar ratio) in a solution of a large excess of the aromatic compound and AcOH (**Scheme 2**).

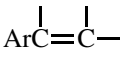
The solution is stirred in the presence of air for a time varying between a few minutes and several hours (usually 8 h) to give the arylated product in 10–95% yield, reduced metallic Pd, and a very small amount of acetates. Not only benzenoid but also nonbenzenoid aromatic compounds such as ferrocene, furan, thiophen, or uracil react readily with a wide range of olefins to give aromatic-substituted olefins.

Pd(II) is reduced to metallic Pd by the reaction; however, addition of oxidants such as $Cu(OAc)_2$, AgOAc, $K_2S_2O_8$, *t*-BuOOH, or O_2 makes the reaction catalytic with respect to palladium.[3]–[7]

The reaction proceeds via electrophilic attack of Pd^+OAc to an aromatic compound (ArH) to form ArPdOAc, which adds to an olefin to give an



species. Subsequent reductive elimination gives an arylated olefin



and Pd(0), which is reoxidized by an oxidant to form Pd(II) again. Thus, the catalytic cycle is completed (**Scheme 3**).[3] The mechanism is proved by isolation of the intermediate ArPd σ-complex, which gives the arylated olefin, carboxylic acid, and phenol when reacted with the olefin, CO, and O_2, respectively (**Scheme 4**).[8]

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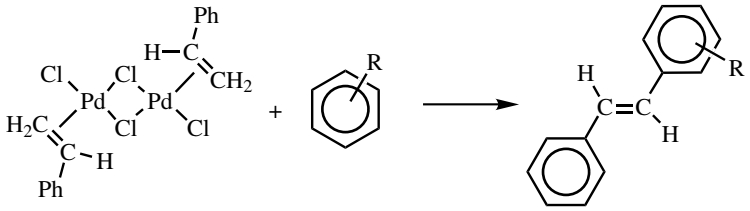
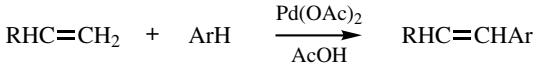
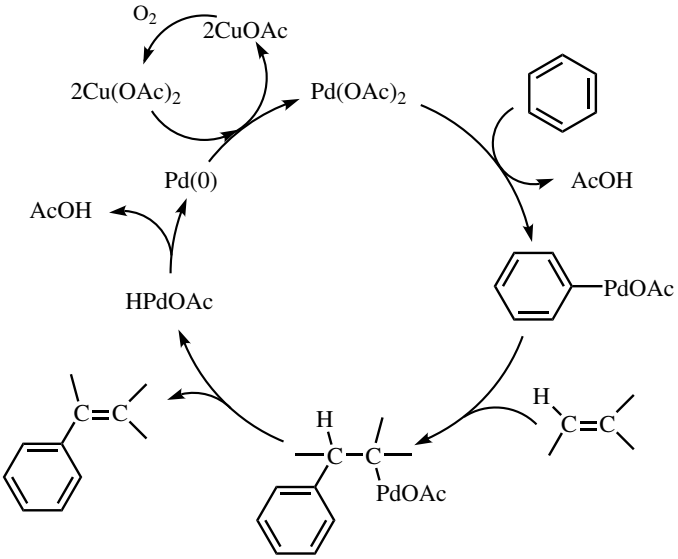


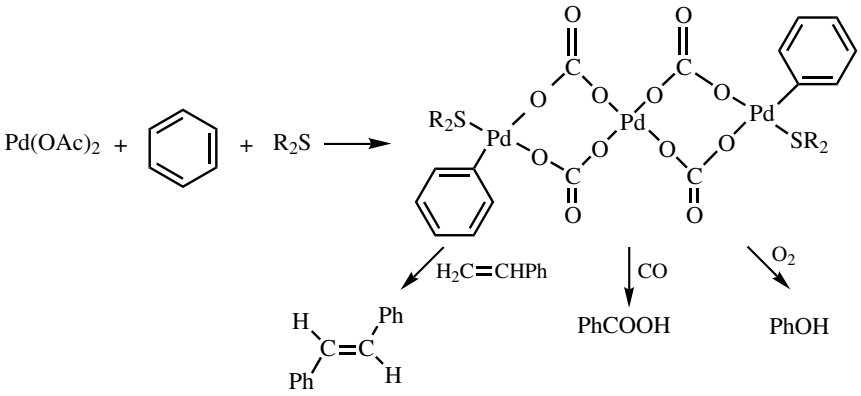
Scheme 1



Scheme 2



Scheme 3

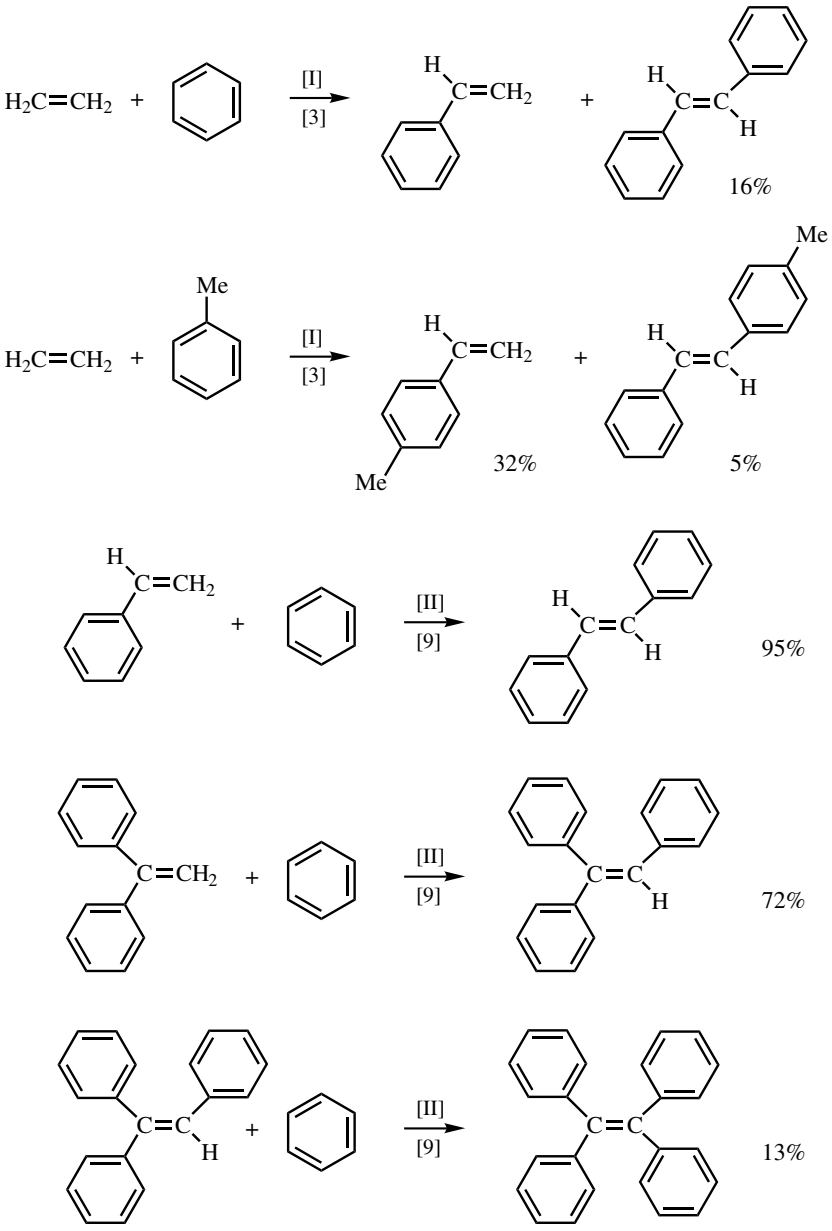


Scheme 4

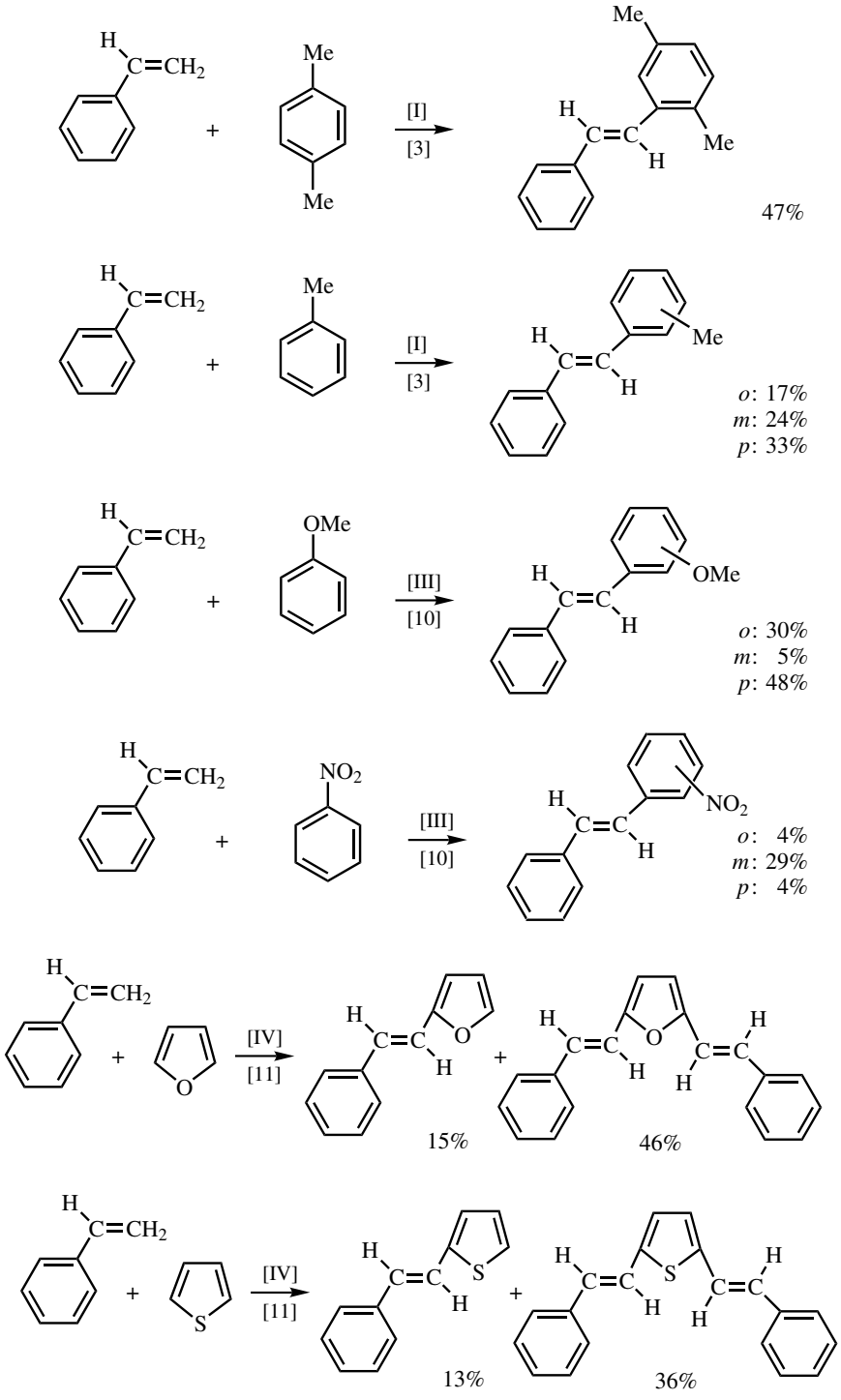
B. PALLADIUM-PROMOTED ALKENE–ARENE COUPLING

$Pd(OAc)_2$-promoted coupling of olefins and aromatic compounds gives the arylated olefins in one step. The typical examples are shown in **Scheme 5**.[3],[9]–[15]

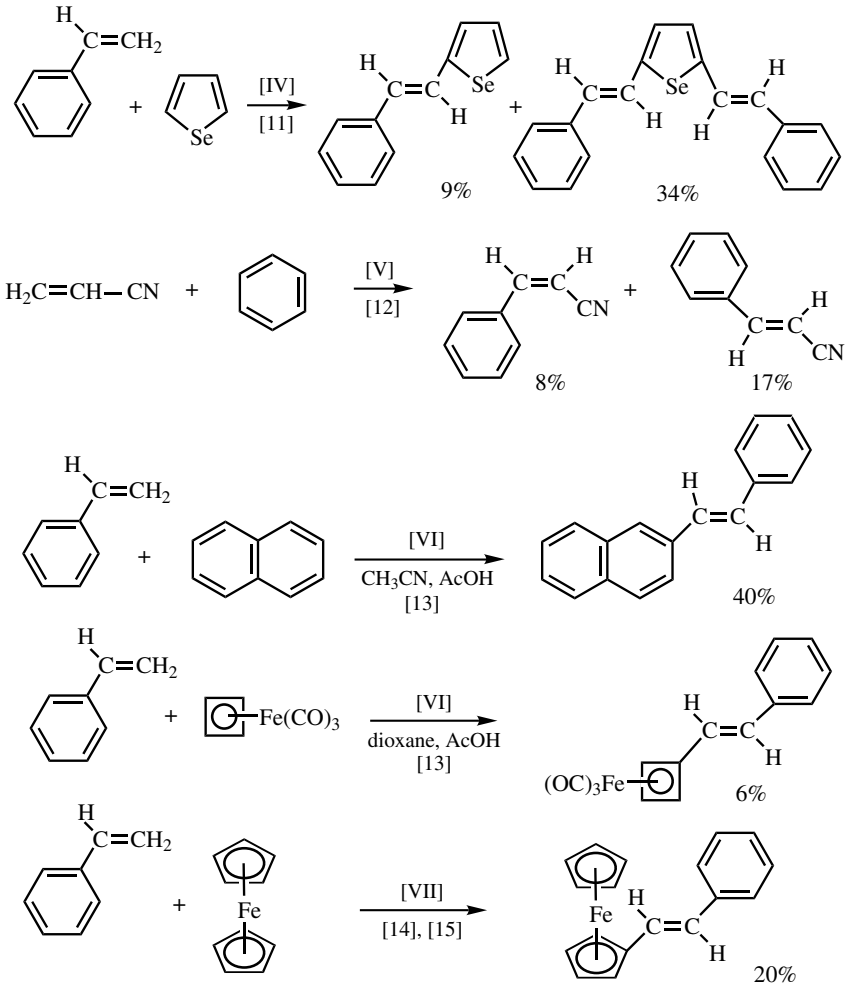
An interesting application of this coupling reaction is the intramolecular version (**Scheme 6**).[16],[17]



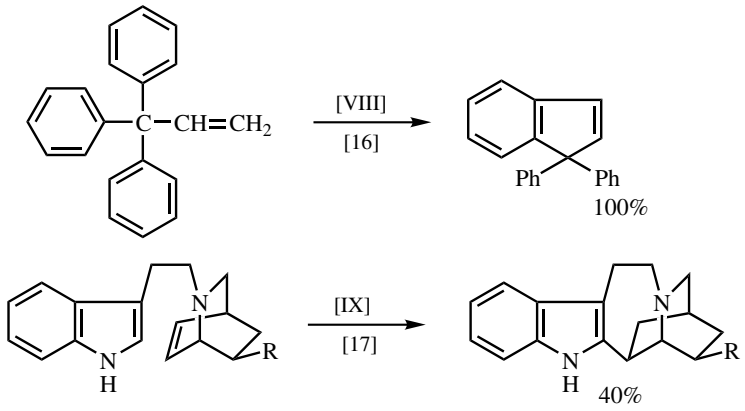
Scheme 5 (*Continued*)


[I]
[3]
47%
[I]
[3]
o: 17%
m: 24%
p: 33%
[III]
[10]
o: 30%
m: 5%
p: 48%
[III]
[10]
o: 4%
m: 29%
p: 4%
[IV]
[11]
15%
46%
[IV]
[11]
13%
36%

Scheme 5



Scheme 5 (*Continued*)



Scheme 6 (*Continued*)

[I] = $Pd(OAc)_2$ (32–50 mmol), ethylene (1 atm) or styrene (1 equiv), benzene, toluene, or *p*-xylene, AcOH, reflux.
[II] = $Pd(OAc)_2$ (16 mmol), olefin (1 equiv), benzene, AcOH, reflux.
[III] = $Pd(OAc)_2$ (16 mmol), styrene (1 equiv), anisole, toluene, or nitrobenzene, AcOH, 110 °C.
[IV] = $Pd(OAc)_2$ (15 mmol), styrene (1 equiv), furan, thiophene or selenophene (1 equiv), dioxane, AcOH, reflux.
[V] = $Pd(OAc)_2$ (28.8 mmol), acrylonitrile (1 equiv), benzene, AcOH, 80 °C.
[VI] = $Pd(OAc)_2$ (10–20 mmol), styrene (1 equiv), naphthalene (1 equiv) or tricarbonyl(η-cyclobutadiene)iron(0) (0.5 equiv), dioxane, AcOH, CH_3CN, reflux.
[VII] = $Pd(OAc)_2$ (15 mmol), styrene (1 equiv), ferrocene (1 equiv), dioxane, AcOH, reflux.
[VIII] = $Pd(OAc)_2$ (0.15 mmol), 3,3,3-triphenyl-1-propene (1 equiv), AcOH, 80 °C.
[IX] = $(CH_3CN)_2PdCl_2$, $AgBF_4$, $NaBH_4$, isoquinuclidine, CH_3CN, 70 °C

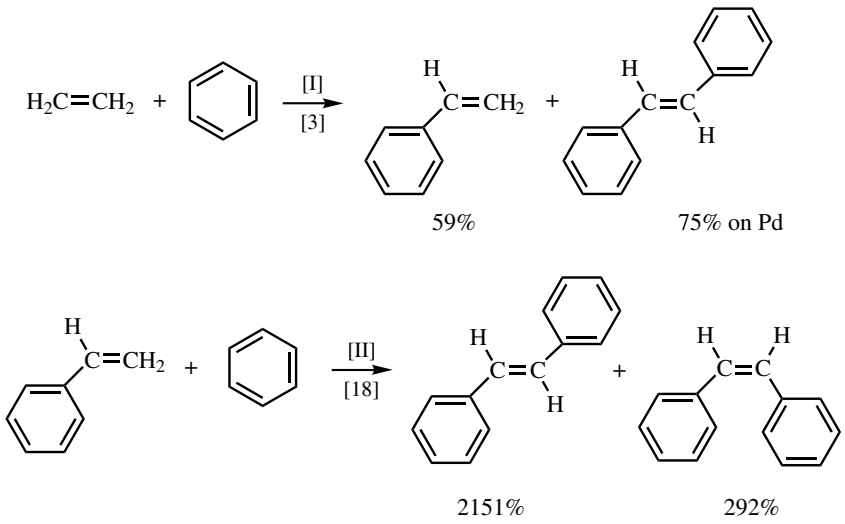
Scheme 6

C. PALLADIUM-CATALYZED ALKENE–ARENE COUPLING

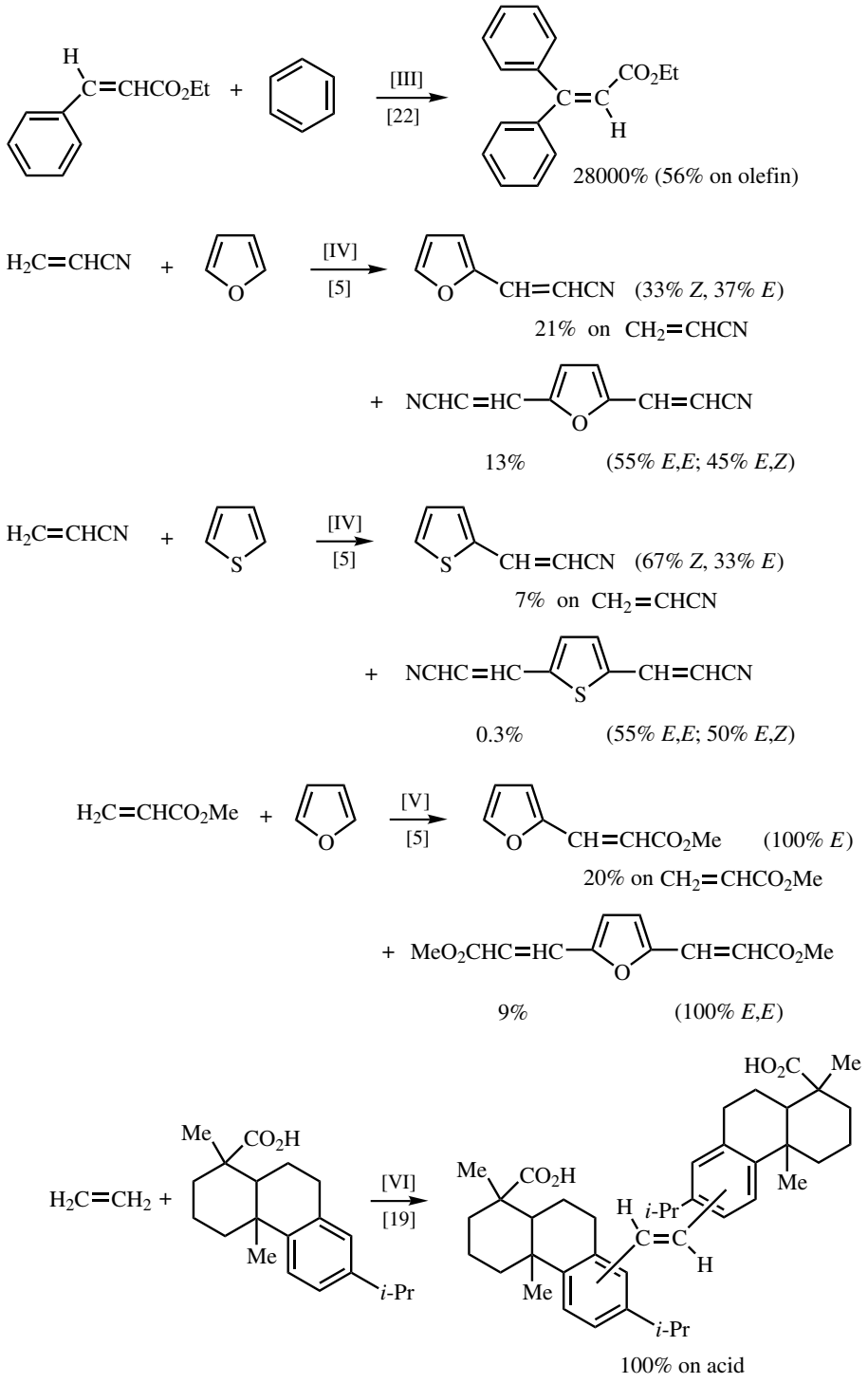
Pd(II)-catalyzed coupling of olefins and aromatic compounds occurs between a wide variety of olefins and aromatics not only benzenoid but also nonbenzenoid. The reaction has the following features. (i) With unsymmetrical olefins the aryl group is generally introduced to the carbon atom of the double bond, which bears fewer substituents because of steric hindrance. (ii) Electron-withdrawing groups on olefinic carbon atoms increase the yield. The examples are shown in **Scheme 7**.[3],[18]–[20]

Asymmetric arylation of olefins is also possible by using cyclic olefins and chiral ligands (**Scheme 8**).[21]

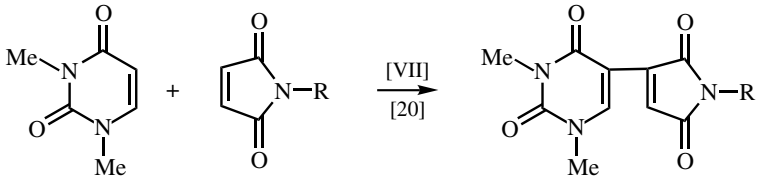
After the finding of the coupling reaction via C—H activation, the coupling of olefins and aromatic halides by palladium catalysts was found as described in **Part IV**; thus, these reactions are known as the Fujiwara arylation[22] or the Fujiwara–Heck reaction.[22],[23]



Scheme 7



Scheme 7 (*Continued*)

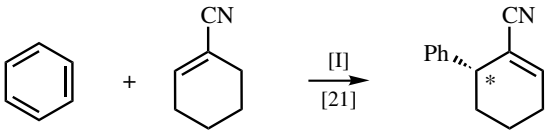


R	Yield (%)[a]
Me	72
Ph	70
CH_2Ph	48

[a] Based on 1,3-dimethyluracil.

[I] = $Pd(OAc)_2$ (10 mmol), AgOAc (10 equiv), air (1 atm), ethylene (1 atm), benzene, AcOH, reflux, 8 h.
[II] = $Pd(OAc)_2$ (0.05 mmol), $AgOCOC_6H_5$ (200 equiv), styrene (160 equiv), benzene, AcOH, reflux, 8 h.
[III] = $Pd(OAc)_2$ (0.055 mmol), benzoquinone (15 equiv), *t*-BuOOH (800 equiv), ethyl cinnamate (500 equiv), benzene (500 equiv), AcOH (35 mL), $(AcO)_2O$ (5 mL) reflux, 8 h.
[IV] = $Pd(OAc)_2$ (2 mol %), $Cu(OAc)_2$ (100 equiv), air (1 atm), acrylonitrile (2 mmol), furan (2 mmol), or thiophen dioxane, AcOH, 100 °C, 8 h.
[V] = $Pd(OAc)_2$ (2 mol %), $Cu(OAc)_2$ (100 equiv), O_2 (1 atm), methyl acrylate (2 mmol), furan (2 mmol), dioxane, AcOH, 100 °C, 8 h.
[VI] = $Pd(OAc)_2$ (0.01 mol), AgOAc (10 equiv), ethylene (1 atm), dehydroabiatic acid (0.02 mol), *n*-heptane, AcOH, 89 °C, 8 h.
[VII] = $Pd(OAc)_2$ (0.2 mmol), AgOAc (2 mmol), uracil (1 mmol), *N*-alkylmaleimide (1 mmol), AcOH (70 mL), reflux, 17 h.

Scheme 7



25% (44% ee)

[I] = $Pd(OAc)_2$ (10 mol %), chiral sulfonylamino-oxazoline (0.1 mmol), *t*-butyl perbenzoate (1.0 mmol), cyclohexenecarbonitrile (1.0 mmol), benzene, 100 °C, 9 h.

Scheme 8

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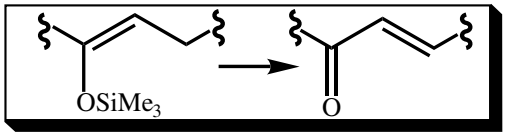

VIII.3 Palladium-Catalyzed or -Promoted Oxidation via 1,2- or 1,4- Elimination

VIII.3.1 Oxidation of Silyl Enol Ethers and Related Enol Derivatives to α,β-Unsaturated Enones and Other Carbonyl Compounds

YOSHIHIKO ITO and MICHINORI SUGINOME

Main group metal enolates such as lithium and magnesium enolates are readily generated and widely utilized for carbon–carbon formation in organic synthesis. Metal exchange of the main group metal with transition metal salts generates the corresponding transition metal enolate intermediates, which are not generally stable in solution even at low temperature. For instance, copper(II) enolates thus generated undergo rapid oxidative coupling to afford the corresponding 1,4-diketones and 1,2-dicarboxylates (**Scheme 1**).[1],[2]

Regioselective oxidative dimerization of ketones was first achieved by use of silyl enol ethers, which are prepared regioselectively from unsymmetrical ketones. The silyl enol ethers undergo silicon–silver exchange by heating with Ag_2O in DMSO, resulting in regioselective formation of 1,4-diketones (**Scheme 2**).[3]

Unlike Ag(I) and Cu(II), palladium(II) salts, which may serve as two-electron oxidant, promote direct dehydrogenation of ketones or ketone enolates to provide the corresponding α,β-unsaturated ketones instead of the oxidative ketone dimerization. Cyclohexanone undergoes dehydrogenation by $PdCl_2$ in air to give 2-cyclohexenone in moderate yield (**Scheme 3**).[4]

The dehydrogenation of ketones may involve the corresponding σ-(2-oxoalkyl)palladium(II) complex, which is in equilibrium with palladium(II) enolate complex, as a key intermediate, followed by β-elimination of palladium hydride. Related direct dehydrogenation of unsymmetrical ketone with $Pd(II)Cl_2$ in *t*-BuOH gives the corresponding α,β-unsaturated ketones as a mixture of regioisomers.[5]

Synthetically useful Pd(II)-catalyzed oxidation of ketones and aldehydes is presented by regioselective synthesis of α,β-unsaturated carbonyl compounds via their silyl enol ethers. The Pd(II)-catalyzed dehydrosilylation for regioselective preparation of α,β-unsaturated carbonyl compounds is carried out simply by treatment with $Pd(II)(OAc)_2$ of silyl enol

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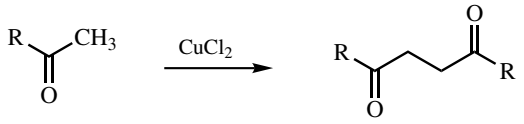
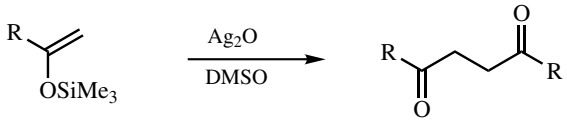
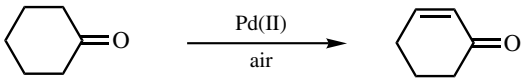


Scheme 1



Scheme 2

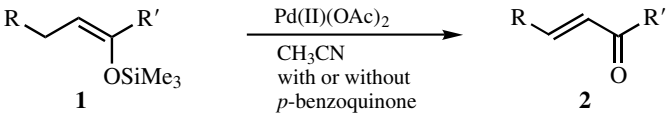


Scheme 3

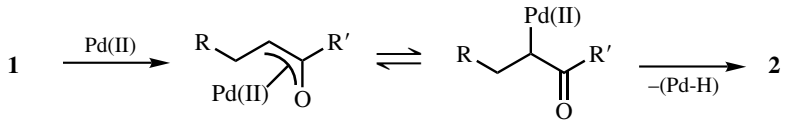
ethers generated regioselectively in the presence of *p*-benzoquinone as re-oxidant in acetonitrile (**Scheme 4**).[6]

The palladium(II) induced dehydrosilylation of silyl enol ether may involve an oxa-π-allylpalladium(II) intermediate, which subsequently undergoes β-elimination of palladium hydride to furnish α,β-unsaturated ketone or aldehyde (**Scheme 5**).

Some synthetic modification for Pd(II)-catalyzed oxidation of silyl enol ethers is also developed. Silyl enol ethers prepared from aldehydes and ketones are converted to the corresponding α,β-unsaturated carbonyl compound in good yields by 10 mol % of palladium(II) acetate in the presence of 1 atm pressure of O_2 in DMSO as solvent (**Scheme 6**).[7]



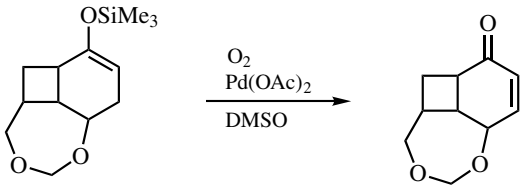
Scheme 4



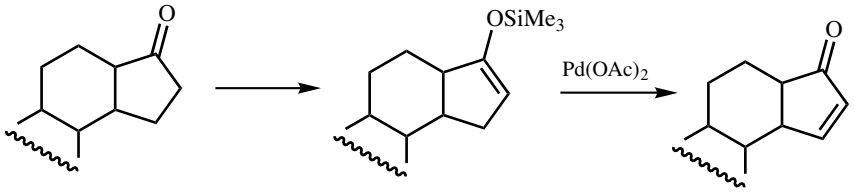
Scheme 5

The simple and convenient methodology for regioselective introduction of α,β-carbon–carbon double bond on unsymmetrical saturated ketones has found various synthetic applications in organic synthesis. Especially, the Pd(II)-catalyzed oxidation methodology has successfully been utilized as key steps in many total syntheses of natural products. Representative synthetic uses are summarized in the following schemes.

1. Dehydrosilylation of silyl enol ethers prepared from unsymmetrical polyfunctionalized ketones gives the corresponding acyclic[8]–[12] and five-,[13]–[28] six-,[29]–[61] seven-,[62]–[65] and eight-membered[66],[67] cyclic α,β-unsaturated ketones and lactones (**Scheme 7**).



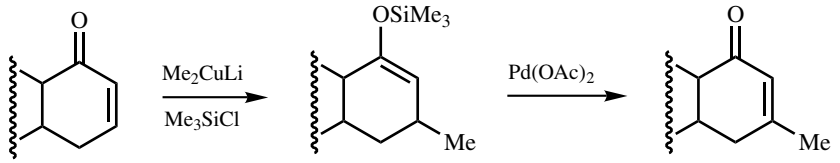
Scheme 6



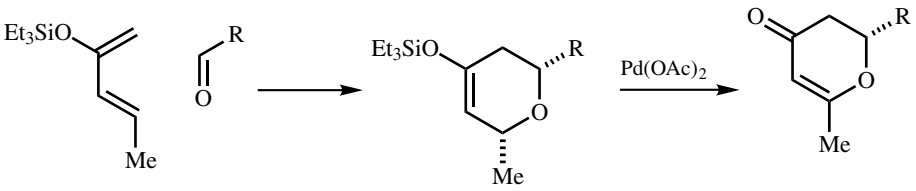
Scheme 7

2. Dehydrosilylation coupled with conjugate addition of organocuprate to α,β-unsaturated ketones in the presence of trimethylchlorosilane provides five-[68],[69] and six-membered[70]–[75] cyclic enones (**Scheme 8**).

3. Dehydrosilylation of Diels–Alder adducts prepared from Danishefsky diene affords six-membered α,β-unsaturated ketones (**Scheme 9**).[76]–[79]



Scheme 8

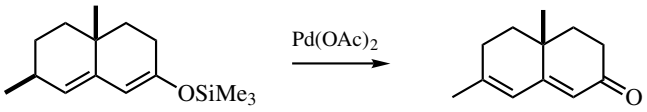


Scheme 9

4. Dehydrosilylation of dienol silyl ethers gives dienones regioselectively (**Scheme 10**).[80]–[82]

5. Dehydrosilylation coupled with miscellaneous synthesis of silyl enol ethers via rearrangement of 1-siloxy-1-alkenylcyclopropane,[83] reactions of γ-siloxyallylmetals with electrophiles,[84],[85] and rearrangement of α-silylketones[86],[87] gives the corresponding ketones.

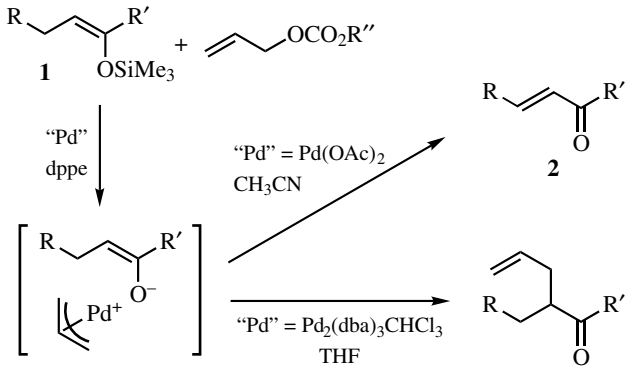
Palladium(II) enolate complex intermediates are also generated by the silicon–palladium exchange reaction of silyl enol ethers with π-allylpalladium(II) alkoxide intermediate, which is formed *in situ* from allyl carbonate with palladium–phosphine complex.[88] With a catalytic amount of $Pd(OAc)_2$ and dppe (diphenylphosphinoethane) in acetonitrile, silyl



Scheme 10

enol ethers of ketone and aldehyde undergo the dehydrosilylation in the presence of allyl carbonate to give the α,β-unsaturated ketones and aldehydes in high yields (**Scheme 11**).

Intermediacy of π-allylpalladium(II) enolate is proposed for β-elimination of palladium hydride, which leads to the formation of α,β-unsaturated ketones. Competitive allylation of ketones is favored by use of palladium(0)$(dba)_2$ (dba: dibenzylideneacetone) in THF.

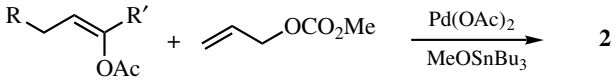


Scheme 11

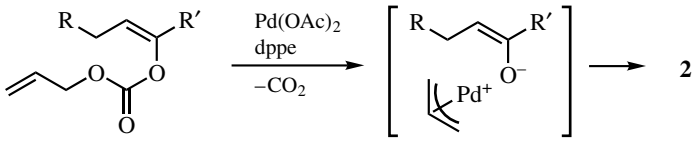
Not only silyl enol ethers but also enol acetates prepared from saturated ketones give α,β-unsaturated ketones by heating with allyl methyl carbonate in the presence of Pd(II)$(OAc)_2$ and dppe with tributyltin methoxide as a bimetallic catalyst (**Scheme 12**).[89]

Regioselective generation of palladium(II) enolate intermediate is simply carried out by treatment of allyl enol carbonates, which are prepared by trapping of ketone enolates with chloroformate, with Pd(II)$(OAc)_2$ in the presence of dppe (**Scheme 13**). π-Allylpalladium(II) enolates thus generated provide α,β-unsaturated ketones.

Some palladium(II) enolate complexes have been prepared and isolated in the reaction of silyl enol ethers lacking a hydrogen, which may be eliminated as palladium(II) hydride via the corresponding σ-(2-oxoalkyl)palladium. As expected, palladium(II) enolate



Scheme 12

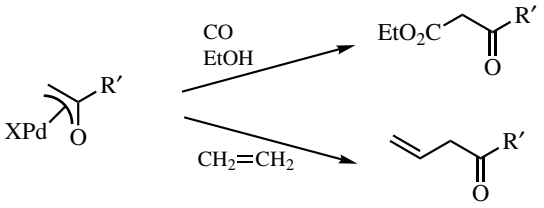


Scheme 13

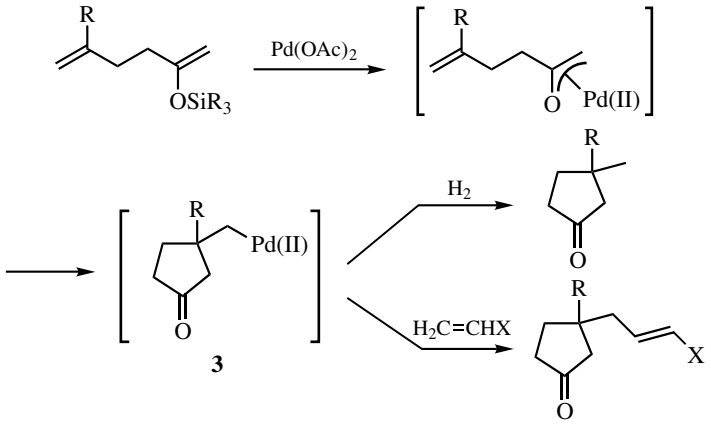
complexes isolated undergo α-carboxylation with CO in ethanol and vinylation with ethylene gas (**Scheme 14**).[90]

Intramolecular olefin insertion of oxa-π-allylpalladium(II) complex proceeds with *exo*-cyclization, giving cyclopentenone derivatives preferably (**Scheme 15**).[91],[92]

Organopalladium(II) intermediate (**3**) thus generated via the *exo*-cyclization is isolable in high yields, when no β-hydrogen is available for elimination, and utilizable for carbon–carbon bond formation.



Scheme 14



Scheme 15

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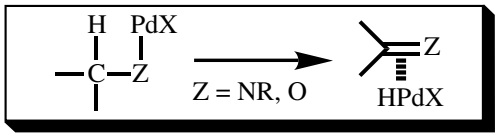

VIII.3.2 Oxidation of Amines, Alcohols, and Related Compounds

SHUN-ICHI MURAHASHI and NARUYOSHI KOMIYA

A. INTRODUCTION

Amines and alcohols are oxidized to the corresponding imine (or iminium ion) and carbonyl compounds, respectively, with palladium catalysts. Coordination of heteroatom to palladium, insertion of palladium into hydrogen–heteroatom bonds, and β-elimination of palladium hydride species are involved in these reactions.

B. OXIDATION OF AMINES

Activation of amines with low-valent palladium catalysts gives two types of intermediates. One is the reaction of primary and secondary amines bearing N—H bonds with palladium to give imine metal complexes **1** (**Scheme 1**).[1]–[3] The other is the reaction of tertiary amines bearing no N—H bond to give iminium ion complexes **2**. Intermediates **1** and **2** are formed when one uses either heterogeneous or homogeneous transition metals and metal complex catalysts. Activation of amines with palladium catalyst leads to discovery of catalytic transalkylation of amines via intermediates **1** or **2**.[1]–[3] Palladium-black is an excellent catalyst.

Pd-catalyzed reactions of amines provide convenient methods for the synthesis of tertiary amines, diamines, polyamines, and heterocyclic amines. Typically, the Pd-catalyzed reaction of *N*-methylbenzylamine with *N*-methylbutylamine gives *N*-butyl-*N*-methylbenzylamine (95%) along with methylamine (**Scheme 2**). The treatment of azetidine (**3**) with the palladium catalyst in the presence of 1,3-propanediamine (**4**) at 120 °C gives *N*-(3-aminopropyl)-1,3-propanediamine (**5**), which undergoes further Pd-catalyzed reaction with **3** to give the tetramine **6** (75%) (**Scheme 3**).

Apparently, 1,*n*-diamines ($n = 2,3$) are less reactive than azetidine toward palladium, because of stabilization by bidentate chelation. Furthermore, convenient processes for the synthesis of heterocyclic compounds can be explored. For example, the Pd-catalyzed reaction of **4** with allylamine at 25 °C gives 2-ethylhexahydropyrimidine (**7**) (95%) (**Scheme 4**), which is a highly efficient hydrogen donor for selective hydrogenations.[4]

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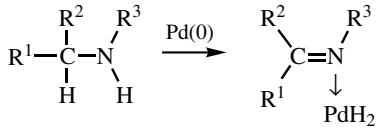

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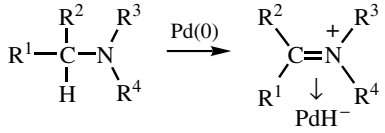

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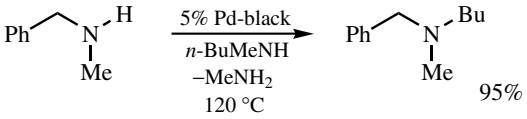
Scheme 1



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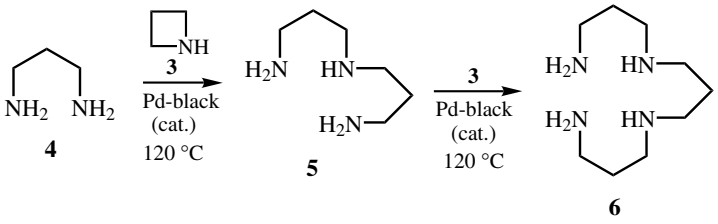

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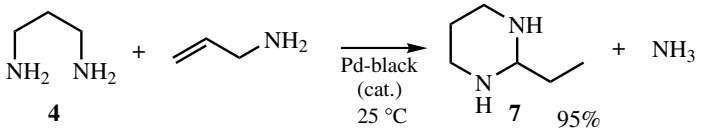
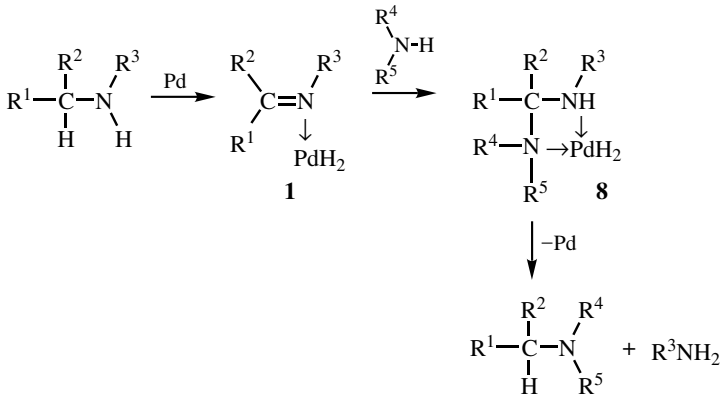


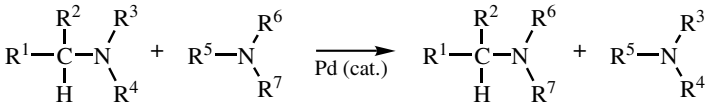
Scheme 4

The key intermediate of the reaction is an imine hydride complex **1**, which is derived from the oxidative addition of low-valent palladium into the N—H bond and subsequent β-palladium hydride elimination (**Scheme 5**). Nucleophilic addition of a second molecule of amine to **1** gives **8**, and intramolecular reductive cleavage of **8** with the metal hydride gives amines.

Tertiary amines can also be activated via iminium ion palladium hydride complex **2**. Thus, the Pd-catalyzed amine exchange reaction of tertiary amines occurs with high efficiency (**Scheme 6**).[5] Typically, the Pd-catalyzed reaction of dibutylhexylamine at 200 °C gave a mixture of tributylamine (26%), dibutylhexylamine (37%), butyldihexylamine (24%), and trihexylamine (3%); the alkyl groups are distributed statistically in

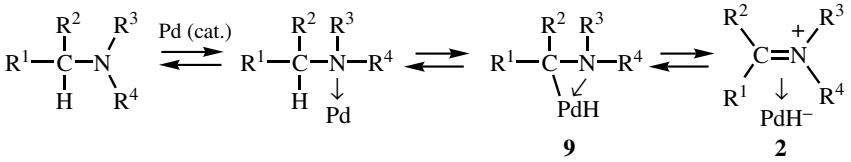


Scheme 5



Scheme 6

these tertiary amines. This process may provide a convenient method for the synthesis of unsymmetrical tertiary amines. This reaction can be rationalized by assuming a mechanism that involves an iminium ion palladium complex **2**. Palladium coordinates to nitrogen and inserts into the adjacent C—H bond to give **9**, which is in equilibrium with a key intermediate, the iminium ion complex **2** (**Scheme 7**). Nucleophilic attack of a second molecule of tertiary amine to extremely electrophilic **2** and subsequent reductive cleavage give the product.

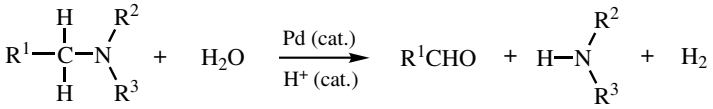


Scheme 7

The Rh-catalyzed asymmetric isomerization of diethylgeranylamine to the enamine, which is a key step of the industrial synthesis of menthol, is similarly initiated by C—H activation of the amine to form iminium–rhodium hydride π-complex.[6]

The iminium ion metal complex **2** can be trapped with an external nucleophile. Thus, Pd-catalyzed hydrolysis of tertiary amines can be performed upon treatment with Palladium black in the presence of water (**Scheme 8**).[7] The reaction proceeds via nucleophilic attack of water on **2** followed by cleavage.

Similar catalytic reactions occur in the presence of the homogeneous ruthenium and rhodium cluster catalysts.[8]–[10] (η^1-Ylide)palladium complexes[11] and unusual

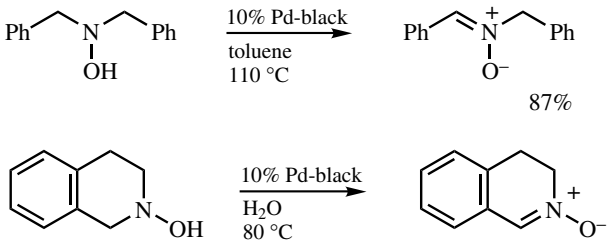


Scheme 8

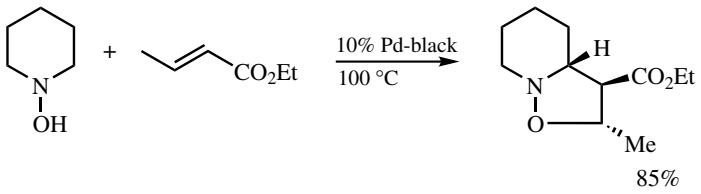
amino-carbene palladium cluster complexes[12] have been isolated as key intermediates of these reactions.

When a Pd-catalyzed dehydrogenation process is applied to *N*,*N*-disubstituted hydroxylamines, the corresponding nitrones, which are valuable intermediates to construct various biologically active nitrogen compounds, are formed highly efficiently (**Scheme 9**).[13] This method will replace conventional methods, which use stoichiometric amounts of oxidants such as HgO and $K_3[Fe(CN)_6]$.[14],[15] Although recently direct catalytic conversion of secondary amines to nitrones has been explored, the preparative methods of nitrones from *N*-hydroxylamines are limited to a few reactions.[16]–[19] The present Pd-catalyzed reaction is useful for the synthesis of cyclic nitrones, which cannot be obtained by the conventional method catalytically.

The Pd-catalyzed reaction of cyclic hydroxylamines in the presence of alkenes gives 1,3-dipolar cycloadducts in high yields.[13] Typically, the Pd-catalyzed reaction of *N*-hydroxypiperidine with ethyl crotonate gave 2-methyl-3-ethoxycarbonylhexahydropyridinoisoxazole stereoselectively in 85% yield (**Scheme 10**).



Scheme 9



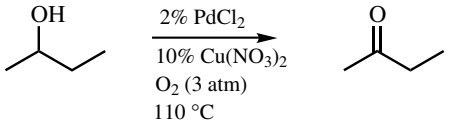
Scheme 10

C. OXIDATION OF ALCOHOLS

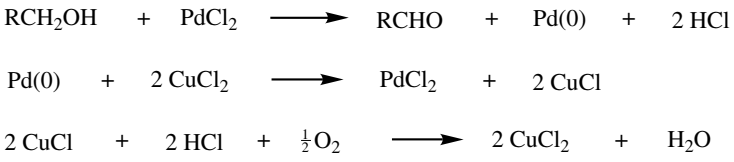
The oxidation of alcohol with palladium(II) salts was first reported in 1828, where the reduction of palladium from wet ethanolic solution of K_2PdCl_4 took place.[20] In order to construct a catalytic process for the oxidation of alcohols, study has focused on the

reoxidation of reduced palladium(0) to active palladium(II). For this purpose, oxidants such as copper salts, organic halides, and molecular oxygen have been used.

The sluggish reoxidation of atomic palladium(0) by molecular oxygen is greatly facilitated by addition of a reoxidant of copper salt (**Scheme 11**).[21] The mechanism of the oxidation can be rationalized by assuming **Scheme 12**. Complexation of alcohol to Pd(II) catalyst forms Pd(II) alkoxide, which undergoes β-palladiumhydride elimination to give a carbonyl compound. Since palladium catalyst is reduced to Pd(0) by reductive elimination, catalytic reaction must include a combined process, where the Pd(0) species is oxidized to the Pd(II) species (**Scheme 12**).



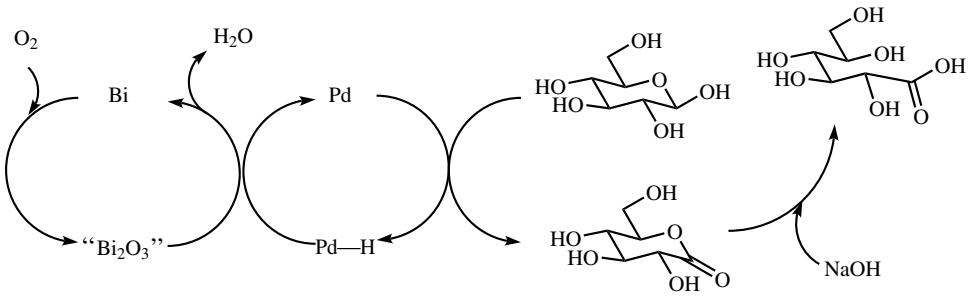
Scheme 11



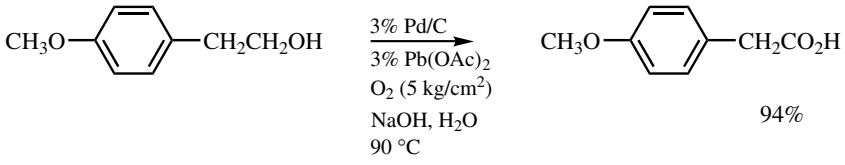
Scheme 12

Bimetallic Pd–Bi catalyst can be used for aerobic oxidations.[22]–[27] Catalytic oxidation of glucose with Pd–Bi/C catalyst gives high yields of gluconate (99%) (**Scheme 13**). Bismuth seems to prevent oxygen poisoning of the palladium surface by acting as a cocatalyst in the oxidative dehydrogenation mechanism.[22] The Pd/C–$Pb(OAc)_2$ system catalyzes selective aerobic oxidation of 2-arylethanol without formation of benzoic acid (**Scheme 14**).[28] There are several reports using multicomponent catalysts such as Bi–Se–Pd/C,[29] Te–Pd/C,[30] Pb–Pd/C,[31] and Co–Cd–Pd/C[32] systems for oxidation of alcohols.

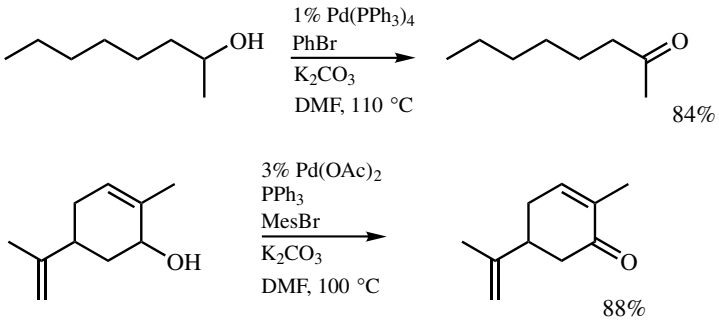
The catalytic oxidation of alcohols can be performed in the presence of organic halides. Saturated and unsaturated secondary alcohols can be converted to the corresponding ketones upon treatment with palladium(0) in the presence of aryl halide and base (**Scheme 15**).[33]–[36]



Scheme 13



Scheme 14



Scheme 15

The oxidation can be rationalized by assuming the mechanism shown in **Scheme 16**. Oxidative addition of Pd(0) species to aryl bromide gives **10**, which reacts with alcohols to give alkoxypalladium species **11**. β-Elimination of palladium hydride species **12** gives ketones and arylhydridopalladium species **12**, which undergoes reductive elimination of ArH to give Pd(0). This system can be applied to solid–liquid phase transfer conditions using NBu_4Cl.[37]

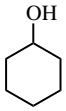
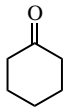
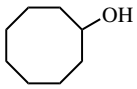
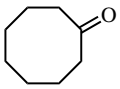
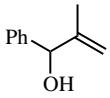
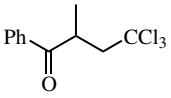
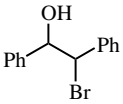
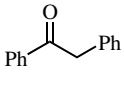
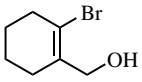
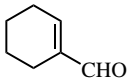
Chlorinated hydrocarbons such as CCl_4[38],[39] and 1,2-dichloroethane[40] work not only as an oxidant of Pd(0) but also as a solvent. Primary alcohols are oxidized to give esters, while secondary alcohols are oxidized to ketones. CCl_4 and 1,2-dichloroethane are converted to $CHCl_3$ and ethylene, respectively (**Table 1**, entries 1 and 2). In the presence of CCl_4 or $CBrCl_3$, allyl alcohols are converted to γ-trichloroketones (entry 3).[41] The reaction proceeds via carbopalladation product **13** (**Scheme 17**), which undergoes β-palladium hydride elimination. The Pd-catalyzed oxidation of halohydrins gives ketones (entry 4).[42] 3-Bromoallylic alcohols can be converted to the corresponding dehalogenated α,β-unsaturated carbonyl compounds (entry 5).[43]

The reaction can be applied to the synthesis of lactone from 1,ω-diols.[35] Unsymmetrical primary–primary diols bearing bulky substituents are oxidized at the sterically hindered position, although the chemoselectivity is modest (**Scheme 18**). It is noteworthy that the regioselectivity of the Ru-catalyzed reaction of unsymmetrical primary–primary diols to lactones is opposite to the Pd-catalyzed reaction.[44],[45]

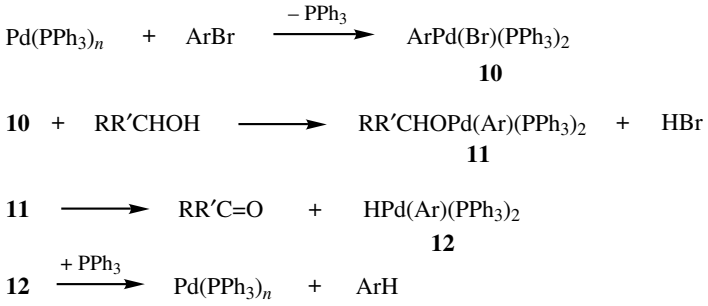
Pd(0)- or Ru(II)-catalyzed amination reactions of alcohols can be performed highly efficiently.[46]–[48] The Pd-catalyzed reaction of 1,4-butenediol with amines gives pyrrole derivatives in excellent yields (**Scheme 19**). When the $RuH_2(PPh_3)_4$-catalyzed reaction of alcohol **14** is performed, cyclization product **15** was obtained in 81% yield (**Scheme 20**).

The Pd-catalyzed oxidations of β-hydroxyenamine and *o*-(2-hydroxyethyl)aniline afford the corresponding pyrroles and indoles (**Scheme 21**).[49]

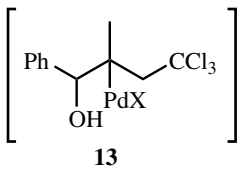
TABLE 1. Pd-Catalyzed Oxidation of Alcohols in the Presence of Organic Halide

Entry	Catalyst (mol %)	Halide	Substrate	Product	Yield (%)	Reference
1	$PdCl_2$[a] (2)	CCl_4			63	[38,39]
2	$PdCl_2$[b] (5)	$ClCH_2CH_2Cl$			83	[40]
3	$Pd(OAc)_2$[c] (1) $P(o\text{-tol})_3$ (2)	$CBrCl_3$			87	[41]
4	$Pd(OAc)_2$[d] (1) $P(o\text{-tol})_3$ (2)	—			63	[42]
5	$Pd(OAc)_2$[d] (9) PPh_3 (15)	—			85	[43]

[a]In the presence of K_2CO_3 at 80 °C. [b]In the presence of Na_2CO_3 and Adogen 464 under reflux.
[c]In the presence of K_2CO_3 in C_6H_6 at 110 °C.
[d]In the presence of K_2CO_3 in C_6H_6 under reflux.



Scheme 16



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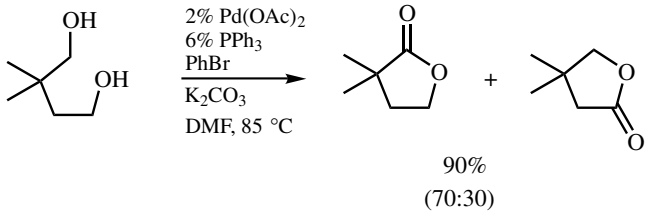
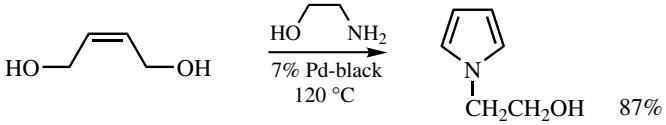
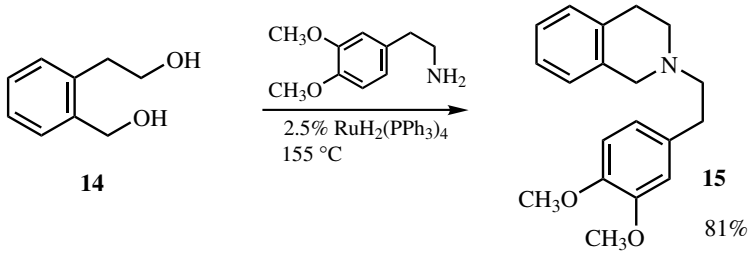
Scheme 17



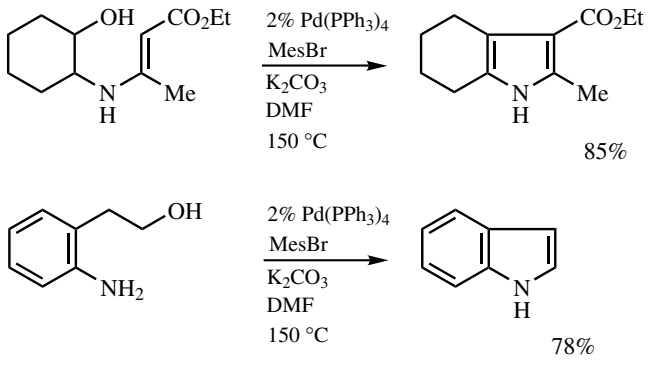
Scheme 18



Scheme 19



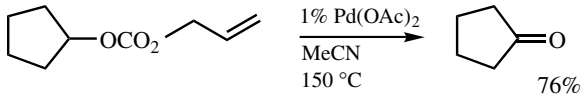
Scheme 20



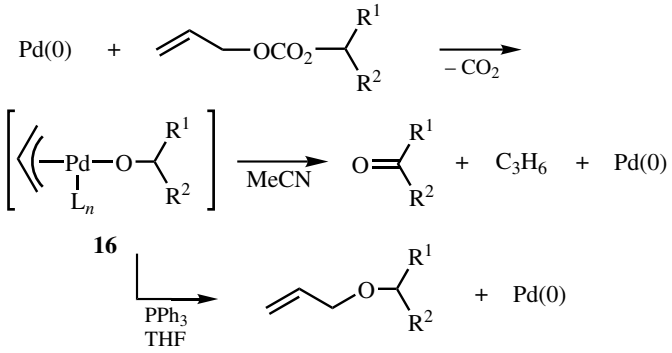
Scheme 21

Allylic carbonate derivatives of alcohols are oxidized to ketones upon treatment with $Pd(OAc)_2$ catalyst in MeCN (**Scheme 22**).[50],[51] This reaction can be accounted for in terms of elimination of β-hydrogen from π-allyl alkoxide complex **16** (**Scheme 23**). Propene and CO_2 are produced, and hence the reaction is clean. It is noteworthy that in the presence of triphenylphosphine reductive coupling occurs to give allyl ether.

Pd-catalyzed aerobic oxidation of alcohols was first reported by Blackburn and Schwartz in 1977. The $PdCl_2$-catalyzed oxidation of cyclopentanol in the presence of NaOAc in



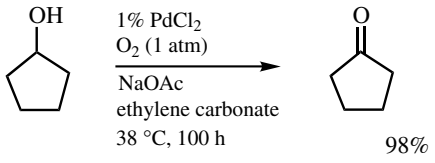
Scheme 22



Scheme 23

ethylene carbonate gave cyclopentanone (**Scheme 24**).[52] The mechanism seems to involve regeneration of actiove Pd(II) species by oxidation with molecular oxygen.

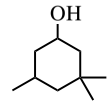
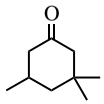
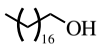
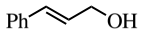
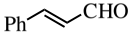
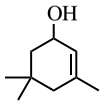
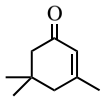
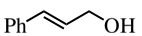
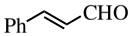
This finding led to the development of a practical method for the aerobic oxidation of alcohols. Several systems have been reported as shown in **Table 2**. Primary and secondary aliphatic alcohols can be converted to the corresponding aldehydes and ketones, respectively, upon treatment with $Pd(OAc)_2$ catalyst in the presence of pyridine and MS3A in toluene (entries 2 and 3).[53] Various benzyl alcohols are also oxidized under the same conditions (entries 12 and 13).[53]

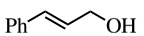
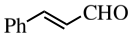
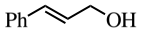
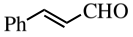
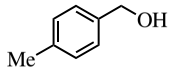
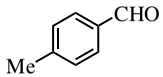
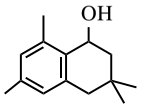
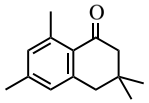
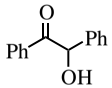
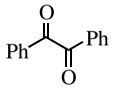
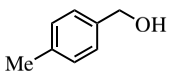
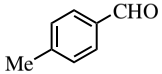


Scheme 24

Oxidation with $Pd(OAc)_2$ catalyst in dimethyl sulfoxide with molecular oxygen is also a general and efficient method.[54] The oxidation of primary and secondary allylic (entries 4 and 5) and benzylic alcohols (entries 9–11) gives aldehydes and ketones, respectively. Palladium–phosphine complex such as $Pd(PPh_3)_4$ can be used for the oxidation of allylic alcohol in the presence of NH_4PF_6 (entry 6).[55] The yield of α,β-unsaturated aldehyde is dependent on the substrate. Palladium cluster $Pd_4phen_2(CO)(OAc)_4$ and giant palladium cluster $Pd_{561}phen_{60}(OAc)180$, prepared upon treatment of $Pd(OAc)_2$ with 1,10-phenanthroline (phen), show high catalytic activity for the aerobic oxidative transformation of allylic alcohols to α,β-unsaturated aldehydes (entries 7 and 8).[56],[57] Heterogeneous oxidation can be performed with giant palladium cluster anchored on TiO_2, which is easily

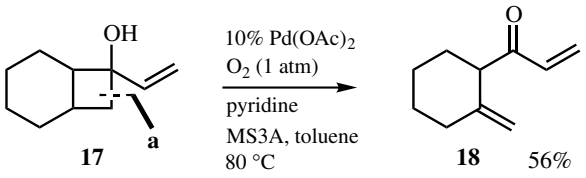
TABLE 2 Palladium-Catalyzed Aerobic Oxidation of Alcohols.

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Substrate	Product	Yield (%)	Reference
	aliphatic alcohol							
1	10% $PdCl_2$ NaOAc	ethylene carbonate	38	54			98	[52]
2	5% $Pd(OAc)_2$ pyridine	toluene MS3A	80	2			97	[53]
3	5% $Pd(OAc)_2$ pyridine	toluene MS3A	80	2			95	[53]
	allyl alcohol							
4	5% $Pd(OAc)_2$	DMSO	80	36			69	[54]
5	5% $Pd(OAc)_2$	DMSO $NaHCO_3$	80	48			67	[54]
6	10% $Pd(PPh_3)_4$ NH_4PF_6	toluene	110				90	[55]

7	3% $Pd_{561}phen_{60}(OAc)_{180}$	C_6H_6	60	24			97	[56]
8	3% $Pd_4phen_2(CO)(OAc)_4$	C_6H_6	50	24			93	[57]
	benzyl alcohol							
9	5% $Pd(OAc)_2$	DMSO	80	24			92	[54]
10	5% $Pd(OAc)_2$	DMSO $NaHCO_3$	80	168			96	[54]
11	5% $Pd(OAc)_2$	DMSO $NaHCO_3$	80	24			83	[54]
12	5% $Pd(OAc)_2$ pyridine	toluene MS3A	80	2			95	[53]
13	5% $Pd(OAc)_2$ pyridine	toluene MS3A	80	2			94	[53]

separated from the reaction mixture and reusable. Similarly, aerobic oxidation of alcohols with palladium catalysts supported on a polyphenylene polymer and K-L Zeolite can be used.[58]–[60] Recently, it was reported that a water-soluble palladium(II) bathophenanthroline complex is a stable recyclable catalyst for the selective aerobic oxidation of alcohols in a biphasic water–alcohol system.[61]

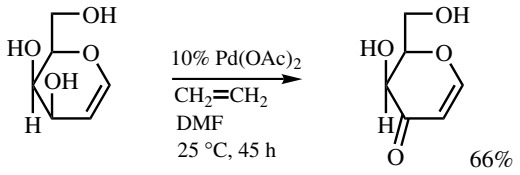
The Pd-catalyzed reaction of *tert*-cyclobutanols in the presence of pyridine gives the ring-opening products.[62],[63] For example, 7-vinylbicyclo[4.2.0]octan-7-ol (**17**) was converted to 1-(2-methylenecyclohexane-1-yl)-2-propen-1-one (**18**) in 56% yield upon treatment with $Pd(OAc)_2$, pyridine, and MS3A under O_2 atmosphere (**Scheme 25**). The reaction seems to involve β-carbon cleavage (bond **a** breaking) from the palladium alkoxide intermediate.



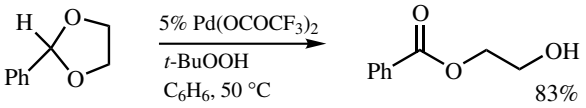
Scheme 25

An alternative method for the oxidation of alcohol is the hydrogen transfer reaction to a hydrogen acceptor, which undergoes hydrogenation during the course of the reaction. Oxidation of D-glycals with a catalytic amount of $Pd(OAc)_2$ under ethylene atmosphere gave 1,5-anhydrohex-1-en-3-ulose (**Scheme 26**).[64] In the absence of ethylene, the allyl alcohol part of the substrate works as a hydrogen acceptor, and the saturated alcohol was obtained.

The oxidative ring opening of five- and six-membered acetals can be performed efficiently to give monoester of diol selectively upon treatment with *t*-BuOOH in the presence of $Pd(OCOCF_3)_2$ catalyst (**Scheme 27**).[65]



Scheme 26



Scheme 27

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VIII.3.3 Other Palladium-Catalyzed or -Promoted Oxidation Reactions via 1,2- or 1,4-Elimination

YUZO FUJIWARA and EI-ICHI NEGISHI

A. INTRODUCTION

As amply indicated in **Part V**, the Wacker oxidation involves (i) alkene π-complexation with Pd, (ii) nucleophilic attack by oxygen nucleophiles, such as H_2O, and (iii) β-dehydropalladation (**Schemes 2** and **3** in **Sect. V.1**). In addition to these three critical steps, oxidation of Pd(0) to Pd(II) is necessary for recycling Pd complexes as catalysts. In this reaction, C—H bond participation occurs in the β-elimination or 1,2-elimination of the oxypalladated intermediate.

There are other Pd-catalyzed or -promoted oxidation reactions of various hydrocarbons under similar reaction conditions. These reactions also involve C—H activation, which may proceed via 1,2-elimination. However, the overall mechanism may be different from that of the Wacker oxidation. For example, oxidation of benzene to phenol with O_2 and $Pd(OAc)_2$ may appear to be an arene version of the Wacker oxidation. However, as discussed later in this section, it must proceed via phenylpalladium acetate.[1],[2] For β-elimination leading to C—H activation, two limiting mechanisms, one ionic and the other concerted, may be considered (**Scheme 1**). The concerted path (path b) is particularly attractive, as it also readily provides a plausible mechanism for widely observed benzylic, allylic, and propargylic C—H activation via 1,2-elimination as well as for alkynyl C—H activation (**Scheme 2**).

Despite the plausibility of the mechanisms shown in **Schemes 1** and **2**, palladation of arenes and other C—H compounds can also be and may have to be interpreted differently. As in the mechanistic discussion of oxidative addition in **Sect. II.3.1** (**Scheme 6**), the crucial requirements in the activation of a σ-bond by Pd may just be a combination of (i) binding of Pd via π- or σ-complexation and (ii) oxidative addition of a proximal σ-bond, specifically C—H bond here. Such mechanisms for benzyl and alkynyl C—H activation are shown in **Scheme 3**. The critical difference between **Schemes 2** and **3** is that, in the latter, there is no element of β-elimination. A wide variety of *o*-palladation reactions observed with heterosubstituted arenes, such as those shown in **Scheme 4**, are more readily explained by the mechanism shown in **Scheme 3** than that in **Scheme 2**.

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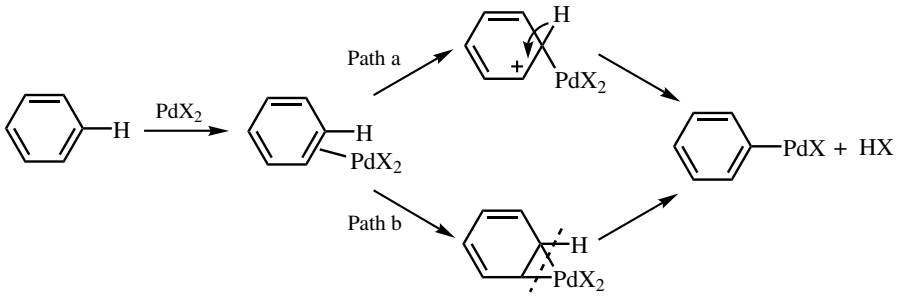
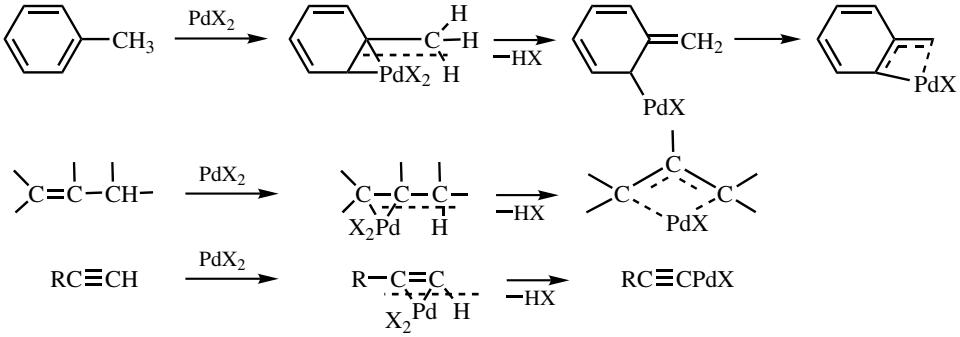
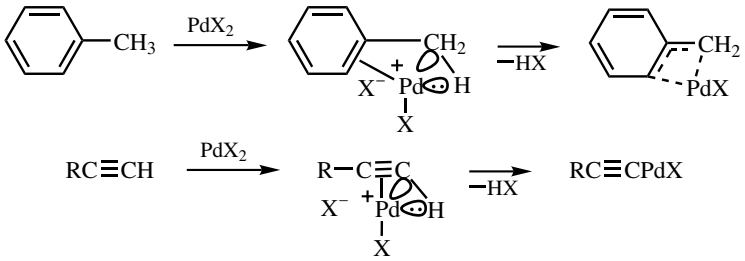


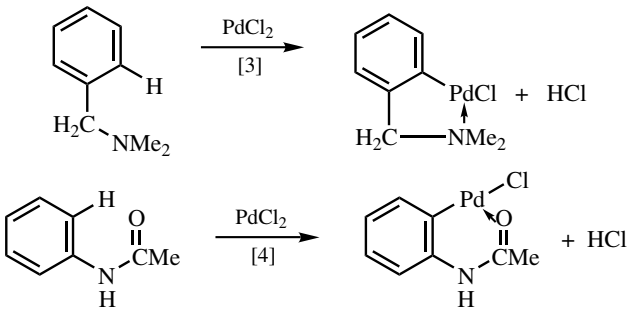
Scheme 1



Scheme 2



Scheme 3

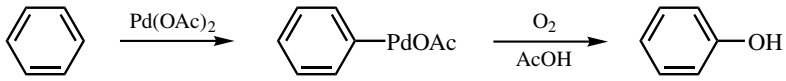


Scheme 4

Somewhat arbitrarily, those cases that can be considered to involve β-elimination, that is, vinyl, aryl, alkynyl, allyl, benzyl, and propargyl σ-bond assisted C—H activation, are discussed in **Sect. VIII.3.3**, and the others are discussed in **Sect. VIII.4**.

B. PALLADIUM-CATALYZED DIRECT PHENOL SYNTHESIS FROM BENZENE

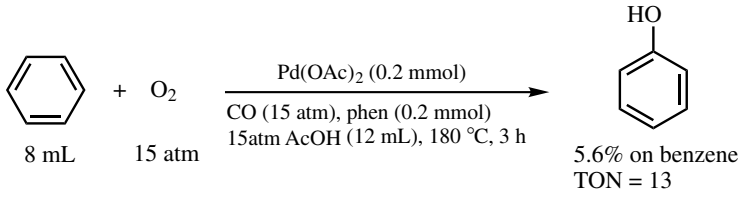
As described in **Sects. VIII.2.2** and **VI.7.1**, the reaction of arenes (ArH) with $Pd(OAc)_2$ gives ArPdOAc, which reacts with olefins and CO. After further investigation of these reactions, it has been found that the phenyl–Pd σ-complex also reacts with O_2 to give phenol (**Scheme 5**).[1],[2]



Scheme 5

Direct synthesis of phenol from benzene and O_2 has been achieved using the $Pd(OAc)_2$/1,10-phenanthroline(phen)/CO/AcOH system at 180 °C (**Scheme 6**).

Both CO and phen are essential to bring about selective phenol synthesis with more than 90% selectivity, along with phenyl acetate formed by a by-product. The yield of phenol was 5.6% based on the benzene corresponding to the turnover number (TON) of 13, when 15 atm of O_2 and CO gases were supplied three times after removal of the residual gases at 1 h intervals. The phenolic oxygen was shown to be derived from O_2, not from the solvent AcOH, on the basis of $^{18}O_2$ isotope experiments, and CO acted as a reducing agent of O_2 to give CO_2.



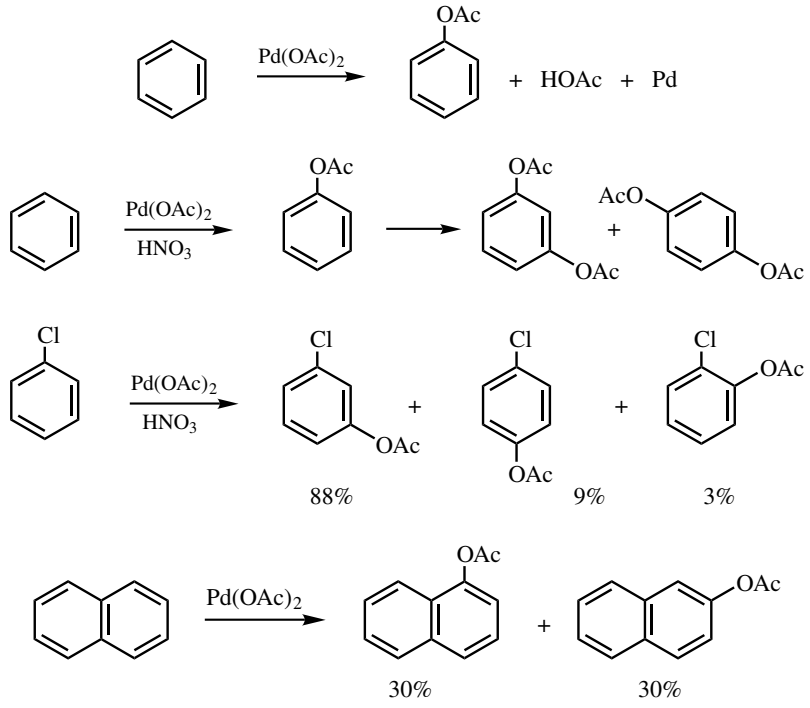
Scheme 6

Similarly, methyl benzoate gave *o*-, *m*-, and *p*-carbomethoxyphenols in 648%, 432%, and 1080% yields based on Pd, respectively. Commercially, phenol has been produced mainly by the cumene process, but this process suffers from disadvantages because it is an indirect method using benzene and propene and it gives acetone as a by-product. Thus, the reaction discussed above is potentially attractive as a candidate for an industrial synthesis of phenol, even though a significantly higher turnover number must be attained.

C. PALLADIUM-CATALYZED OR -PROMOTED OXIDATION OF ARENES PRODUCING ACETOXYARENES

It has long been known that the reaction of benzene with $Pd(OAc)_2$ gives acetoxybenzene.[5]–[8] As such, the reaction is only stoichiometric in Pd. So, many efforts have been made to develop catalytic procedures of high turnover numbers through the use of oxidants, such as O_2 and Cu(II) salts, HNO_3, and potassium peroxydisulfate.[9]–[12]

As might be expected, the acetoxybenzene produced reacts further to give a mixture of *m*- and *p*-bisacetoxybenzene in which the meta isomer predominates. Chlorobenzene gives *m*-chloroacetoxybenzene to the extent of 88% of the product, the relative amounts of the *o*- and *p*-isomers being 3% and 9%, respectively.[11] Naphthalene gives a nearly 1:1 mixture of α- and β-acetoxynaphthalenes in 60% yield[12] (**Scheme 7**).

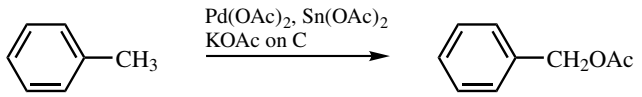


Scheme 7

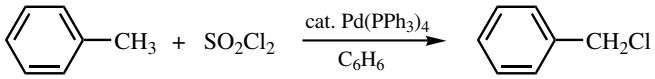
D. PALLADIUM-CATALYZED OR -PROMOTED BENZYLIC OXYGENATION OF ARENES

Oxidation of toluene with $Pd(OAc)_2$ can give (i) acetoxytoluenes as discussed in the preceding section, (ii) bitolyls as discussed in **Sect. VIII.2.1**, and (iii) benzyl ace tate.[5],[8],[11],[13],[14] The use of a catalyst prepared from $Pd(OAc)_2$, $Sn(OAc)_2$, and KOAc and supported on C appears to be effective[14] (**Scheme 8**).

Another synthetically useful example of Pd-catalyzed benzylic oxidation is the selective monochlorination of toluene to give benzyl chloride by the action of SO_2Cl_2 and a



Scheme 8



Scheme 9

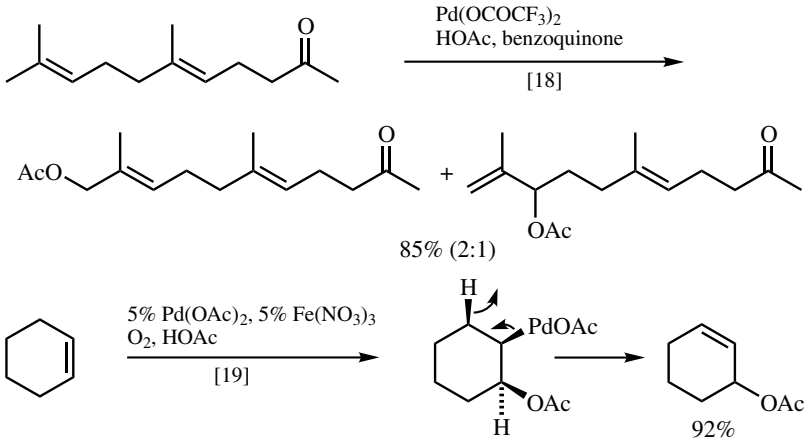
catalytic amount of $Pd(PPh_3)_4$ in benzene[15] (**Scheme 9**). The extent of the formation of benzylidene chloride is 2%.

E. PALLADIUM-CATALYZED OR -PROMOTED ALLYLIC OXYGENATION AND OXIDATIVE DEHYDROGENATION OF ALKENES

Various alkenes including mono-, 1,1-di-, 1,2-di-, and trisubstituted alkenes can be stoichiometrically converted to π-allylpalladium derivatives by the action of Pd(II) reagents, such as a reagent combination consisting of $PdCl_2$, NaOAc, $CuCl_2$, NaCl, HOAc, or Ac_2O and more reactive $Pd(OCOCF_3)_2$ followed by additions of Bu_4NCl.[16],[17] Several representative examples are summarized in **Table 1**.

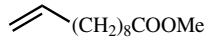
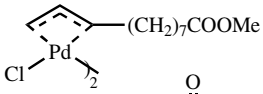
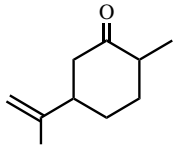
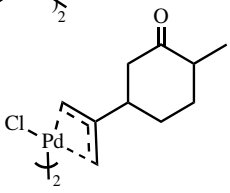
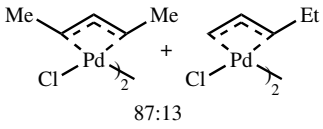
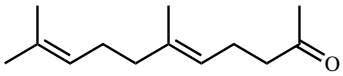
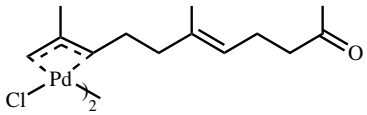
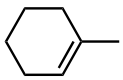
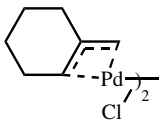
In the presence of oxidants, such as benzoquinone, allylic acetates can be obtained using only catalytic quantities of Pd complexes, as shown in **Scheme 10**. The reactions of cycloalkenes may not involve π-allylpalladium intermediates, and they may merely be examples of the Wacker-type oxidation.

The reaction of propene with HOAc and $Pd(OAc)_2$ can produce 1-, 2-, and 3-acetoxypropenes.[20] This reaction can be made chemo- and regioselective to give preferentially allyl acetate. Similarly, the gas-phase oxidation of isoburylene can be chemoselectively converted to methallyl acetate and the bisacetoxylated derivative[21] (**Scheme 11**).

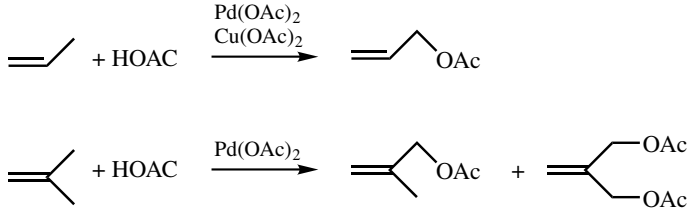


Scheme 10

TABLE 1. Conversion of Alkenes into π-Allylpalladium Chlorides

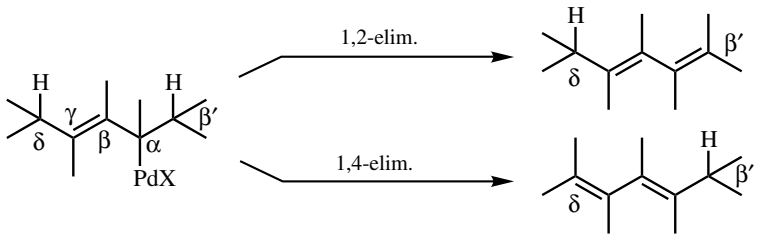
Alkene	Reagent[a]	π-Allylpalladium Chloride	Yield (%)	Reference
	I		68	[16]
	I		66	[16]
	II	 87:13	87	[17]
	I		83	[16]
	II		92	[17]

[a] I=(i) $Pd(OCOCF_3)_2$ in acetone. (ii) Bu_4NCl in acetone.
II=$PdCl_2$, NaOAc, Nacl, $CuCl_2$, HOAc, Ac_2O.

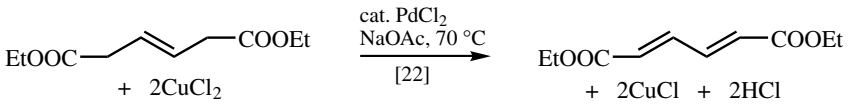


Scheme 11

Allylpalladium derivatives are known to give conjugated dienes via 1,2- or 1,4-elimination (**Sect. V.2.5.1**) (**Scheme 12**). In cases where allylpalladium derivatives are derived from allylic electrophiles via oxidative addition, the overall transformation amounts to nonredox 1,2- or 1,4-elimination. On the other hand, in cases where allylpalladium derivatives are derived from monoalkenes, the overall transformation involves 2 e^- oxidation. For a Pd-catalyzed process, an external oxidant is required, as in an example shown in **Scheme 13**.[22]



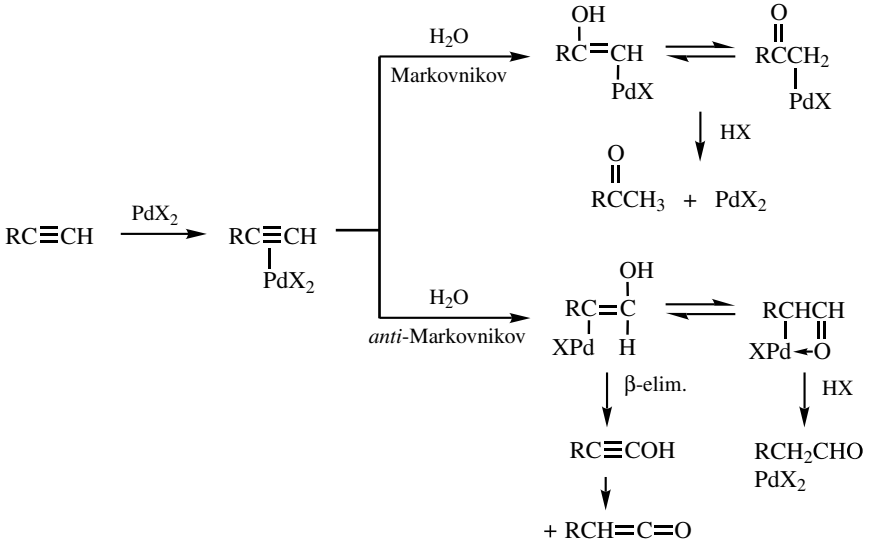
Scheme 12



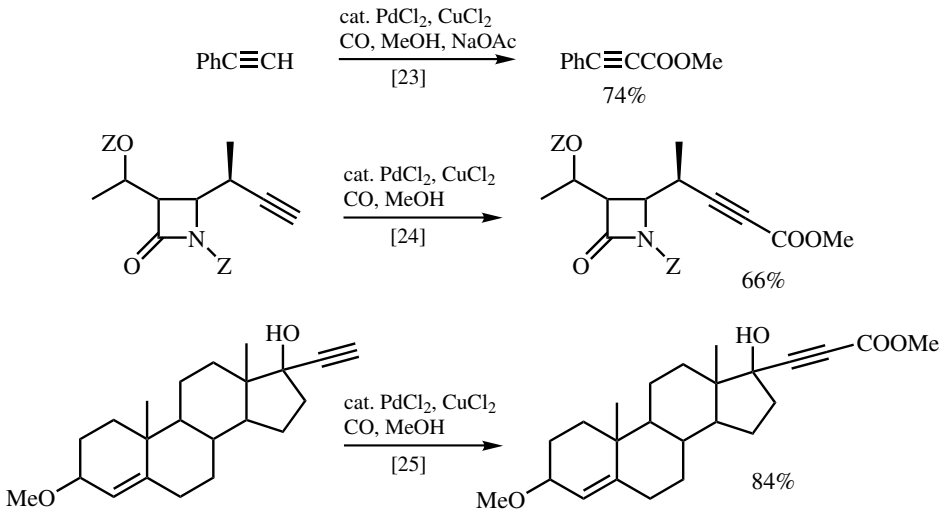
Scheme 13

F. PALLADIUM-CATALYZED OR -PROMOTED OXIDATION OF ALKYNES

Unlike the cases of alkenes, Wacker-type intermolecular oxypalladation reactions of alkynes have not been extensively investigated, although their intramolecular cyclization reactions have been developed into synthetically useful procedures (**Sects. V.3.2**). In principle, they can proceed by a few alternative paths shown for the cases of terminal alkynes in **Scheme 14**. In reality, however, alkynyl C—H activation by Pd to give alkynylpalladium derivatives shown in **Scheme 3** may well be the dominant path, as suggested by the carbonylative oxidation of terminal alkynes to give alkynoic acid esters[23]–[25] shown in **Scheme 15**. Oxidative dimerization of alkynes is a potentially serious side reaction. Further systematic investigation of this fundamentally important process appears to be highly desirable.



Scheme 14



Scheme 15

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VIII.4 Other Miscellaneous Palladium-Catalyzed or -Promoted Oxidation Reactions

EI-ICHI NEGISHI

A. INTRODUCTION

In addition to various Pd-catalyzed or -promoted oxidation reactions discussed in earlier parts, for example, **Part V**, and the preceding sections in this part, there are many other types of oxidation reactions. Some may be related to those discussed earlier. And yet, they display some notably different features. In this section, several different types of such oxidation reactions are discussed in no particular order. Moreover, the following discussion is by no means exhaustive, and it is very likely that many additional types of oxidation reactions, which do not belong to any group of oxidation reactions discussed in this Handbook, will be discovered in the future:

1. Oxidation via chelation-assisted arene C—H activation.
2. Oxidation involving unassisted alkane C—H activation.
3. Wacker-type oxidation reactions involving rearrangements.
4. Oxidation involving C—C bond cleavage and formation other than coupling of organometals (**Sect. III.2.20**) or hydrocarbons (**Sect. VIII.2**).

B. PALLADIUM-CATALYZED OR -PROMOTED OXIDATION OF ARENES VIA CHELATION-ASSISTED ARENE C—H ACTIVATION

The strictly regioselective palladation to give palladacycles shown in **Scheme 4** of the preceding section (**Sect. VIII.3.3**) must undoubtedly be chelation-assisted. Although it is not fully clear whether the reaction additionally involves π-complexation as shown in **Scheme 3** of **Sect. VIII.3.3**, such an interaction would involve considerable strain and hence is unlikely besides being unnecessary. One may therefore consider that the chelation-assisted C—H activation is a process involving, in the main, only σ-bonds.

A variety of Lewis-basic nonbonding electron donors including amino, imino, azo, amido, phosphino, and sufido groups readily participate in the arene palladation, as indicated by the results shown in **Scheme 1**.[1]–[12] Ethers and other oxygenated groups

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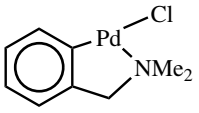
Amino groups



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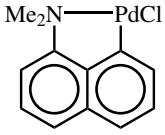

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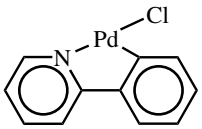

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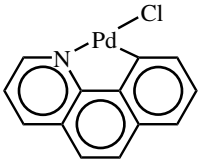

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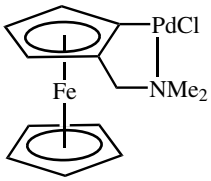

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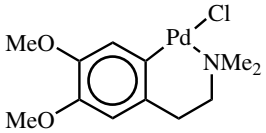
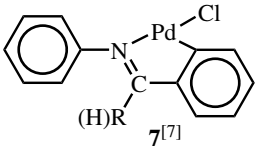


6[6]

Imino and azo groups



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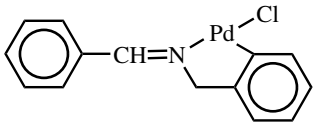

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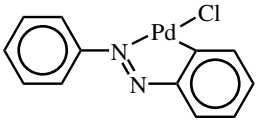

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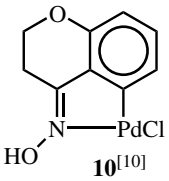
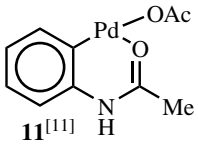


10[10]

O, P, and S groups



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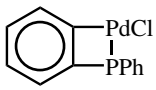

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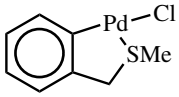


13[13]

Scheme 1

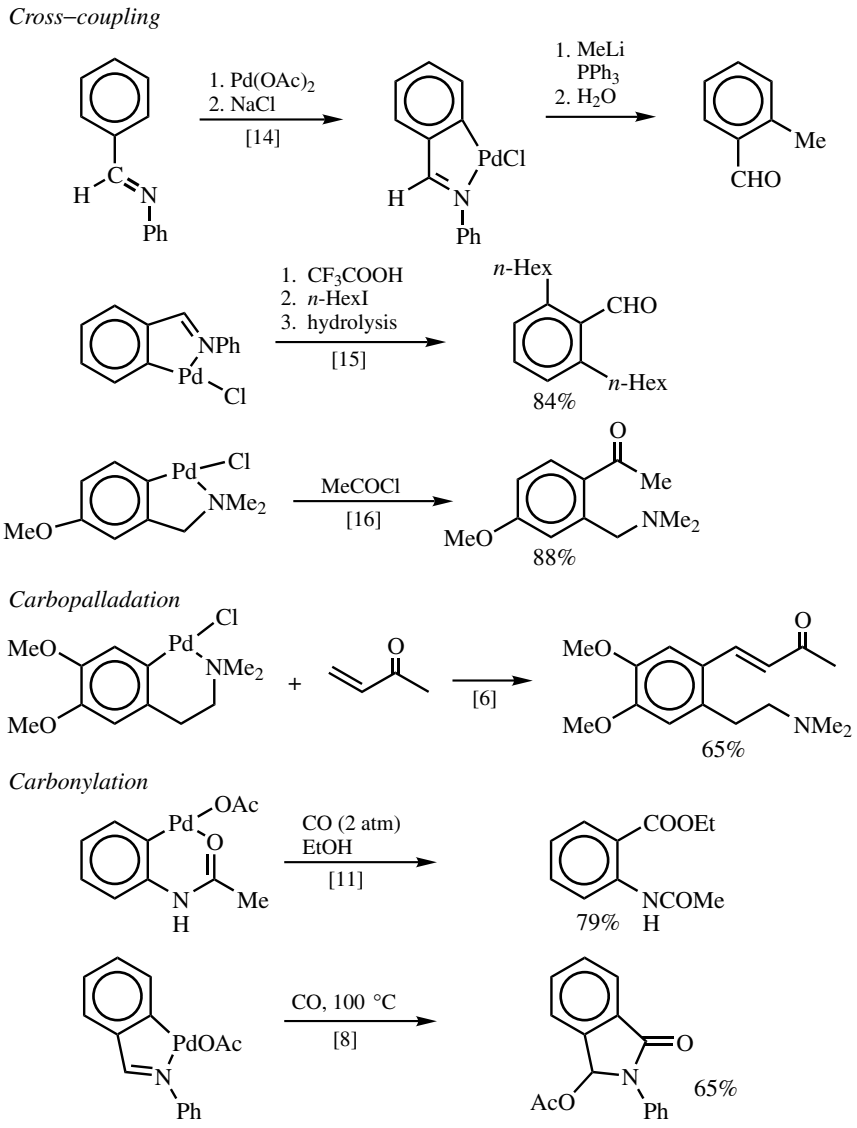
must be less effective. Formation of five-membered palladacycles must be especially favorable, although examples of six-membered rings[6],[10] are known. Interestingly, examples of P-containing four-membered palladacycles are known.[11] Nonetheless, four-membered palladacycles are still rare. Also rare at best are seven-membered and large palladacycles.

Palladation by substitution of H with Pd is as such a nonredox process. However, subsequent transformations leading to the formation of C—C and C–heteroatom bonds can lead to oxidation of organic compounds with concomitant reduction of Pd. Some representative examples of oxidative cross-coupling, carbopalladation, and carbonylation are shown in **Scheme 2**. Cross-coupling can be achieved with either organometals or organic halides.

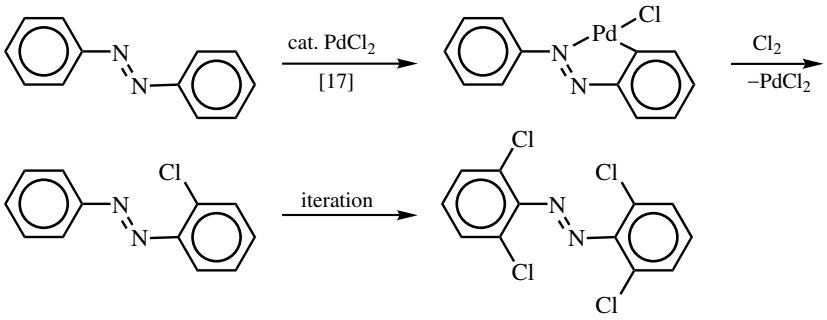
One major drawback of these reactions is that they are, in most cases, stoichiometric not only because Pd(II) is reduced to Pd(0) but also because palladacycles are often thermally too stable to be readily transformed into organic products under mild

conditions and hence are reluctant to participate in catalytic cycles. In cases where difficulties associated with the above-mentioned features can be overcome, such reactions become catalytic in Pd. Selective *o*-chlorination of azobenzene shown in **Scheme 3** is a representative example.[17]

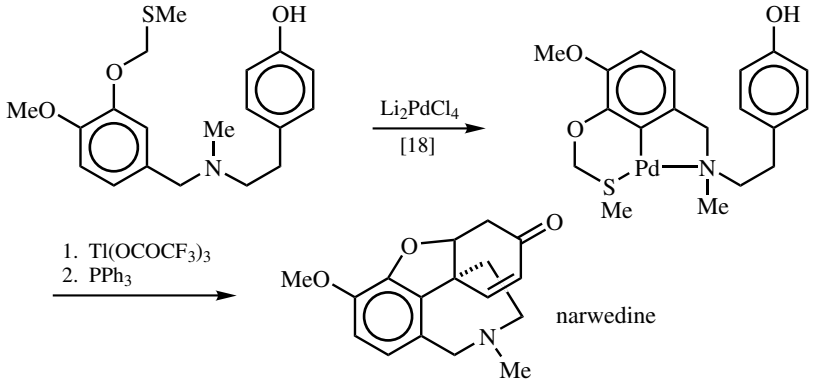
In a remarkable biomimetic synthesis of narwedine shown in **Scheme 4**,[19] a doubly chelated arylpalladium intermediate must undergo a Tl-induced C—C bond formation. Even though it is only stoichiometric in Pd, the high efficiency and selectivity associated with this synthesis might well justify the stoichiometric use of Pd at least on a recycling basis.



Scheme 2



Scheme 3

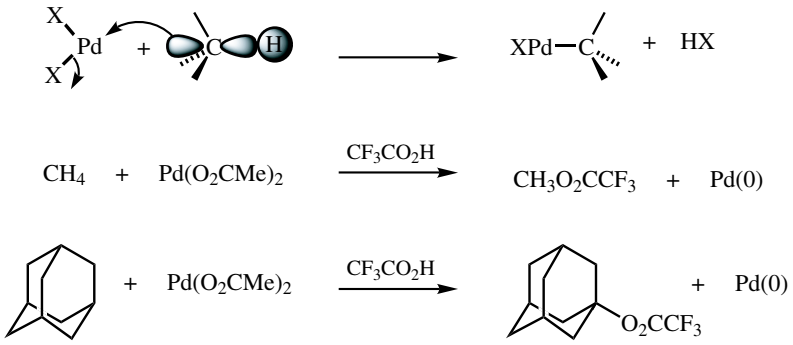


Scheme 4

C. PALLADIUM-CATALYZED OR -PROMOTED OXIDATION OF UNACTIVATED ALKANES VIA UNASSISTED C—H ACTIVATION

As discussed in **Sect. I.2**, Pd is both selective and versatile. In the absence of any other more reactive functional groups, even alkanes, such as methane,[19] cyclohexane,[20]–[22] and adamantane,[19] can undergo palladation via C—H activation. As in the other palladation reactions via C—H activation, it is as such a stoichiometric process. In addition to the concerted perpendicular interaction of Pd with the C—H bond shown in **Schemes 3** and **4** in **Sect. VIII.3.3**, the collinear electrophilic substitution reaction of Pd with the C—H bond, as shown in **Scheme 5**, has been suggested.[19] However, this mechanism appears to be incompatible with the results observed with adamantane, and this point needs to be clarified further.

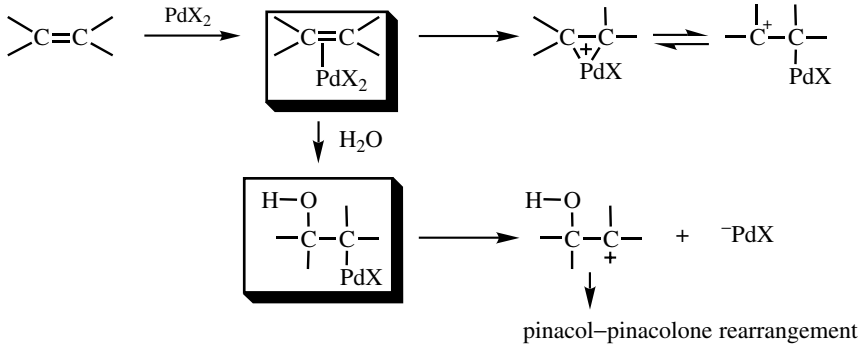
At present, only a small number of examples of Pd-catalyzed reactions of this class are known. One such reaction is the conversion of alkanes into the corresponding carboxylic acids via carbonylation discussed in **Sect. VI.7.1**. Although very promising, the observed turnover numbers are still less than 10–20. One general difficulty is that most of the reagents and the functionalized products are generally more reactive toward Pd than alkanes. Aside from this difficulty, the C—H bond of alkanes is intrinsically unreactive toward Pd. Despite these difficulties, the currently available data point to the feasibility of Pd-catalyzed functionalization of alkanes, and many more favorable results may be obtained in the future.



Scheme 5

D. WACKER-TYPE OXIDATION INVOLVING REARRANGEMENTS

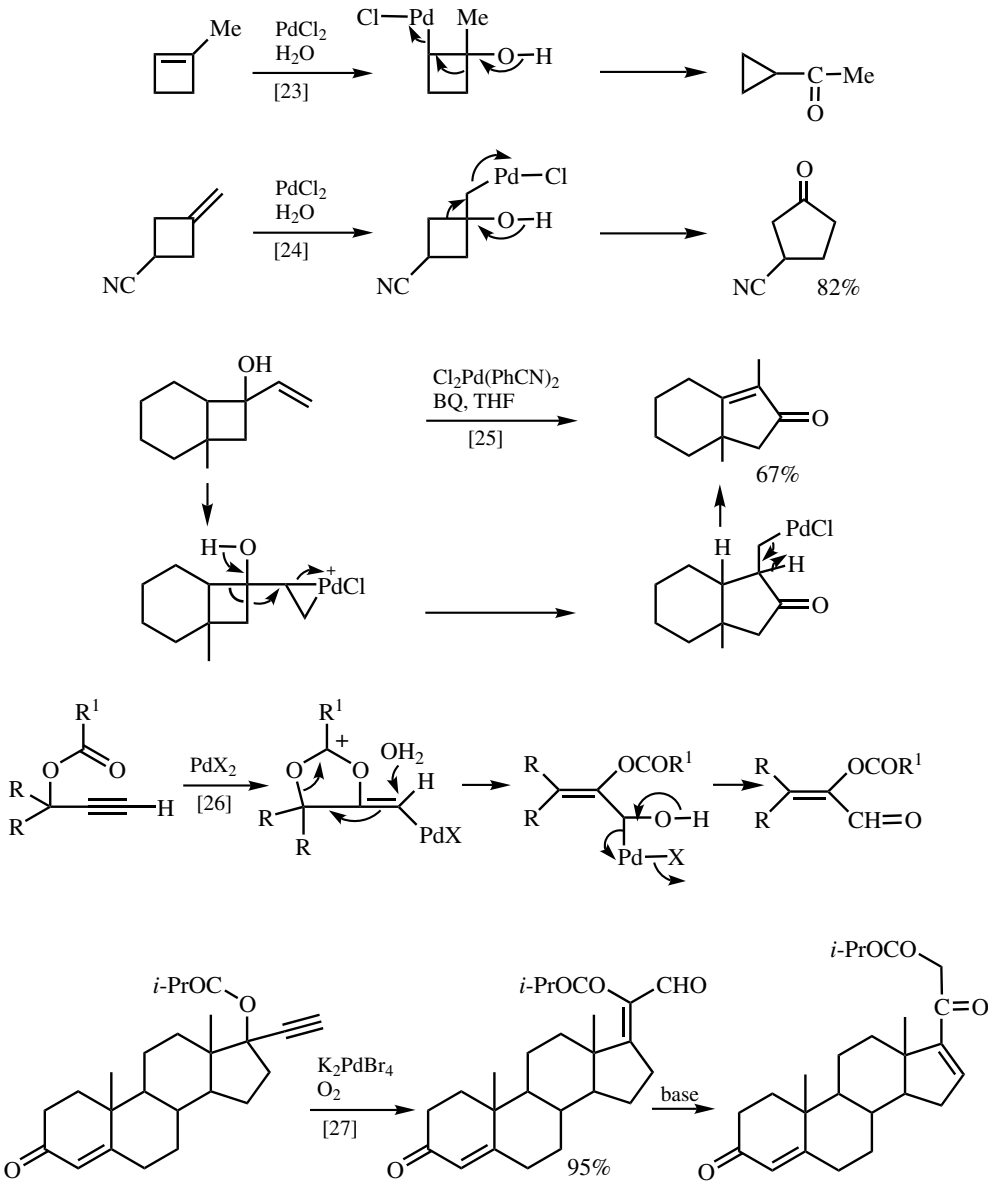
Organopalladium derivatives containing Pd(II) can serve as sources of carbocationic species. Both alkene–Pd π-complexes and oxypalladated intermediates in the Wacker oxidation reactions can therefore generate carbocationic intermediates, which may then undergo anionotropic rearrangements (**Scheme 6**). In fact, it is rather remarkable that, despite the well-known involvement of alkene–Pd π-complexes and oxypalladated intermediates, the Wacker-type oxidation of alkenes is relatively free from various possible rearrangement reactions.



Scheme 6

Some representative examples of Pd-induced pinacol–pinacolone-type rearrangement are shown in **Scheme 7**.[23]–[27] It should be mentioned here that all of these reactions involve both rearrangements and oxidation. Other related rearrangement reactions, which do not involve oxidation or reduction, are discussed in **Sect. IX.2.1.2**.

In addition to anionotropic rearrangements of carbocationic species, organopalladium intermediates in the Wacker-type reactions can also undergo other organopalladium interconversion reactions leading to rearrangements. Carbopalladation and migratory insertion can offer opportunities for such organopalladium interconversion processes. Some representative examples of the oxypalladation–carbopalladation–dehydropalladation cascade processes are shown in **Scheme 8**.

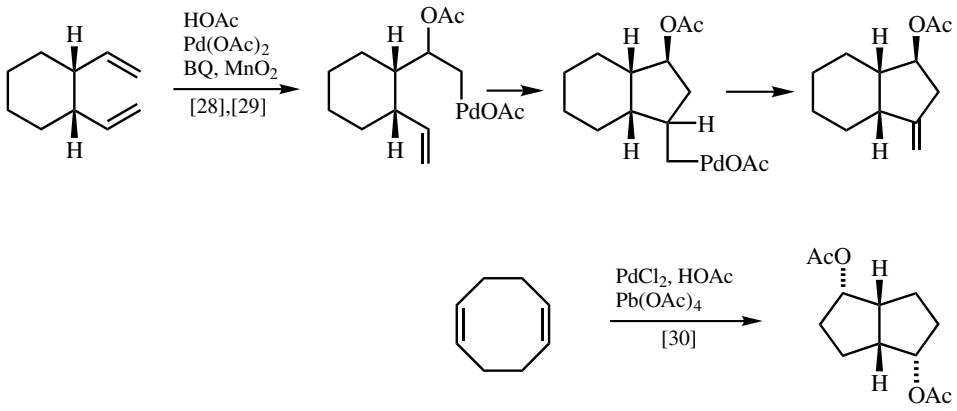


Scheme 7

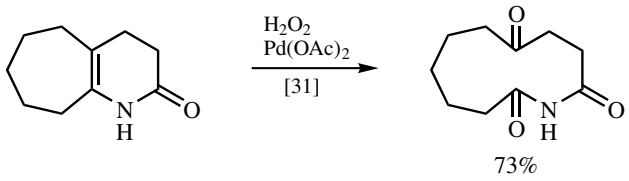
E. PALLADIUM-CATALYZED OR -PROMOTED OXIDATION INVOLVING C—C CLEAVAGE AND FORMATION THAT WERE NOT PREVIOUSLY DISCUSSED

Many Pd-catalyzed or -promoted oxidative C—C bond formation reactions have already been discussed in earlier parts and earlier sections in this handbook. In the oxidative rearrangements discussed above, both formation and cleavage of skeleton-constructing

bonds occur. Although still rare, there are other Pd-catalyzed or -promoted oxidation reactions that involve cleavage of C—C bonds, as indicated by the example in **Scheme 9**.[31]



Scheme 8



Scheme 9

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PART IX
Rearrangement and Other Miscellaneous Reactions Catalyzed by Palladium

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IX.1 Background for Part IX

EI-ICHI NEGISHI

Rearrangement refers to any intramolecular processes leading to net isomerization. Some rearrangements involve C skeletal changes, while others do not. In fact, many of the intramolecular versions of the reactions discussed in **Parts III–VIII** do fit this definition and are therefore rearrangement reactions. Since it is more appropriate and convenient to discuss them as the intramolecular versions of various reactions that can also proceed intermolecularly, they are discussed in the respective earlier parts. They include the following reactions, and their representative examples are shown in **Scheme 1**:

- Rearrangement via cyclic carbopalladation and decarbopalladation (many sections in **Part IV**)
- Intramolecular allylic substitution (**Sect. V.2**)
- Rearrangement of allylpalladium and related derivatives (**Sect. V.2.5.3**)
- Intramolecular oxypalladation and aminopalladation (**Sect. V.3**)
- Isomerization of alkenes, alkynes, and related compounds (**Sect. VII.3**)
- Oxidation involving [1,2]-shift and related processes (**Sect. VIII.4**)

In this part, some other rearrangement reactions displaying certain features that are either not discussed or not emphasized in the previous parts will be presented, and they include the following.

1. Various [3,3] rearrangements including Cope and Claisen rearrangements catalyzed by Pd complexes (**Sect. IX.2.1.1**) involve cleavage and formation of C—C and C–heteroatom σ-bonds. As detailed later, there have been indications that these reactions most likely proceed via dipolar species, and that Pd complexes serve primarily as Lewis acidic catalysts.

2. Involvement of Pd-induced formation of dipolar intermediates has also been implicated in other Pd-catalyzed rearrangements. The dipolar intermediates in these reactions often contain carbocationic centers, which can participate in skeletal rearrangements. Those involving net oxidation are presented in **Sects. V.3** and **VIII.4**, while those that lead to net isomerization are discussed in **Sect. IX.2.1.2**.

3. Oxidative complexation and oxidative addition of Pd to strained carbon–carbon bonds can lead to various C skeletal rearrangements. Relief of strain in the starting compounds may be attained by various processes. However, carbopalladation and

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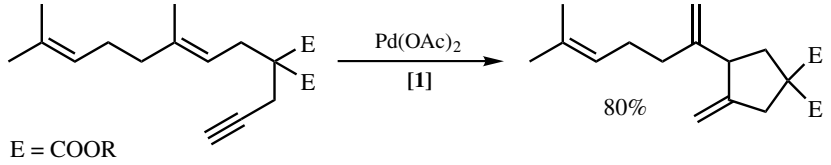
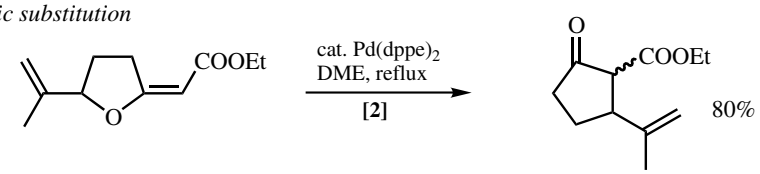
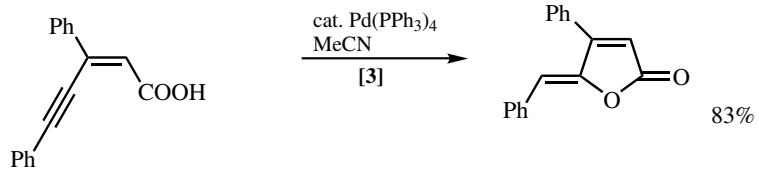
Cyclic carbopalladation



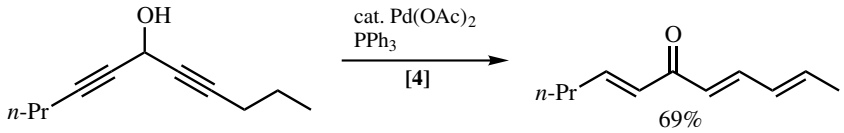
Allylic substitution



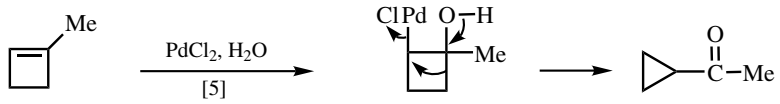
Intramolecular oxypalladation



Isomerization of Alkynes



Oxidative [1,2]-shift (not isomerization but oxidation accompanied by a rearrangement)



Scheme 1

decarbopalladation including allylic rearrangement, homoallyl-cyclopropylcarbinyl rearrangement, and related processes can often provide low activation energy paths. These reactions are also discussed in **Sect. IX.2.1.2**.

4. Yet another group of rearrangement reactions induced by oxidative addition and oxidative complexation of Pd to O—O and other weak bonds may not involve C skeletal rearrangements, although cleavage of O—O and related bonds does lead to changes in overall skeletons, as discussed in **Sect. IX.2.2**.

In principle, there can be many other Pd-catalyzed rearrangement reactions. At present, however, the overall scope of Pd-catalyzed rearrangement reactions is still rather limited. In one sense, lack of skeletal rearrangements in some Pd-catalyzed reactions, such as Wacker processes, where cationic species may be implicated as transient species, is considered to be a very desirable feature of organopalladium chemistry. On the other

hand, one should recall the very versatile nature of Pd and its complexes and their ability to boost their reactivity in many of those cases where an elevated level of reactivity is required (**Sect. I.2**). This property of Pd should enable us to find and develop many additional rearrangement reactions of synthetic utility by tuning various reaction parameters and conditions.

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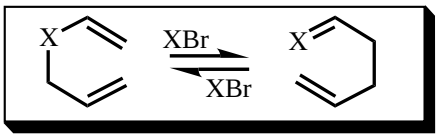

IX.2 Rearrangement Reactions Catalyzed by Palladium

IX.2.1 Palladium-Catalyzed Carbon Skeletal Rearrangements

IX.2.1.1 Cope, Claisen, and Other [3,3] Rearrangements

HIROYUKI NAKAMURA and YOSHINORI YAMAMOTO

A. INTRODUCTION

[3,3] Sigmatropic rearrangements are of importance in view of synthetic and mechanistic aspects and have been utilized for various synthetic strategies. Generally, the rearrangements require high temperatures (~200 °C). The finding that palladium catalysts accelerate the rearrangements under lower temperatures (generally at ambient temperature) has enhanced the synthetic utility of the reaction.[1],[2] The first example of a Pd(II)-*promoted* Cope rearrangement was reported by Jonassen and co-workers[3] in 1966, who described the preparation of the palladium(II) chloride complex of *cis*-1,2-divinylcyclohexane **2** from the reaction of *cis,trans*-1,5-cyclodecadiene **1** with $PdCl_2(PhCN)_2$ (**Scheme 1**). The treatment of **2** with aqueous potassium cyanide afforded *cis*-1,2-divinylcyclohexane **3**, the product of thermal Cope rearrangement of **1**. The rearrangement of a variety of substituted *cis,trans*-1,5-cyclodecadienes was subsequently studied by Heimbach and Morin.[4] The related transformation of the germacratriene **4** to the palladium(II) chloride complex of the corresponding triene of γ-elemene has also been described (**Scheme 2**).[5] A detailed study of the rearrangement of a variety of *cis*-1,2-divinylcyclobutanes to Pd(II) chloride complexes of *cis*,*cis*-1,5-cyclooctadienes has also been reported.[6] The stereochemistry of the reaction is quite complex and the rearrangements promoted by palladium(II) chloride often occurred with less stereoselectivity than the corresponding thermal rearrangements. Thermal rearrangement of **5** gave only cyclooctadiene **6**, while the Pd(II)-mediated reaction afforded a nearly 1:1 mixture of the two diastereomeric palladium(II) complexes (**Scheme 3**).[6]

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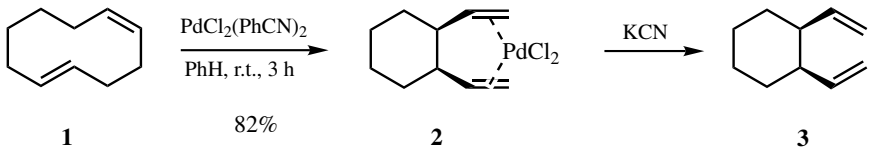
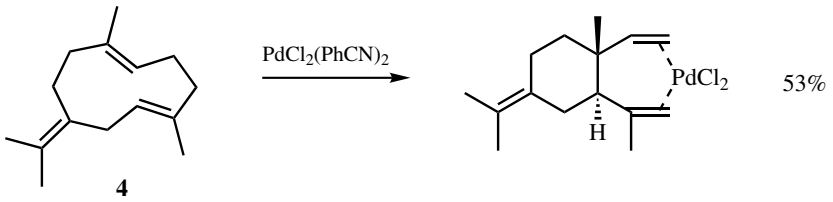
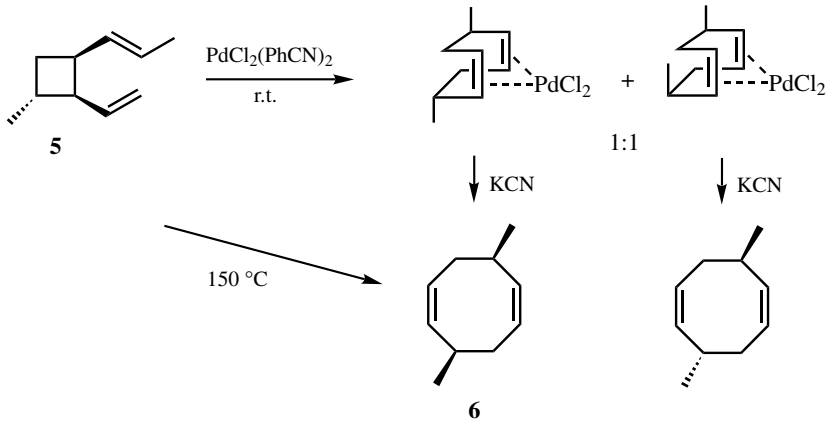


Scheme 1



Scheme 2

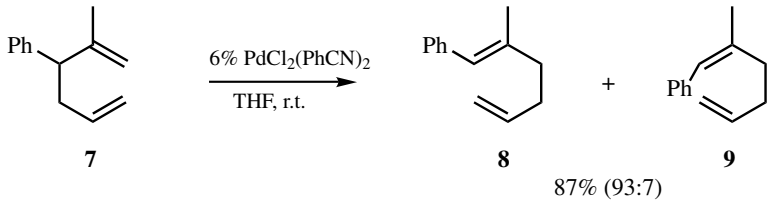


Scheme 3

In 1980, Overman and Knoll[7] reported for the first time that the Cope rearrangement could be conducted catalytically using $PdCl_2$. Since this finding, a large number of diverse [3,3] sigmatropic rearrangements, which form a variety of C—X bonds (C—O, C—N, C—S, C—C), have been investigated extensively.

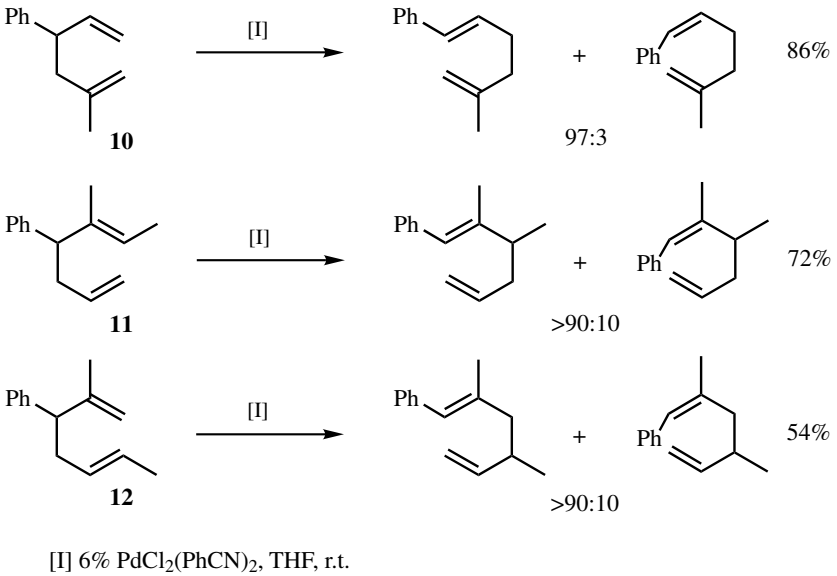
B. PALLADIUM(II)-CATALYZED COPE REARRANGEMENT

The first example of Pd(II)-*catalyzed* Cope rearrangement is shown in **Scheme 4**.[7] The treatment of 2-methyl-3-phenyl-1,5-hexadiene **7** with 6% $PdCl_2(PhCN)_2$ in THF at room temperature (r.t.) produced a 93:7 mixture of the rearranged dienes **8** and **9** in 87% yield. In contrast, the thermal Cope rearrangement of the diene **7** required elevated temperature ($t_{1/2}$ = 13 h at 177 °C) and proceeded with less stereoselectivity, to yield a 3:1 mixture of **8** and **9**. There are significant structural limitations to the $PdCl_2(PhCN)_2$-catalyzed Cope rearrangement under these conditions.

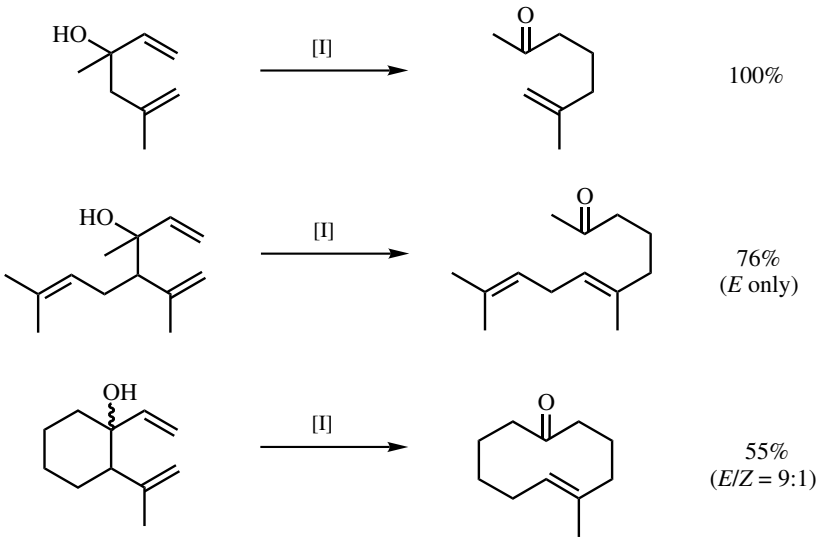


Scheme 4

The rearrangements of 5-methyl-3-phenyl-1,5-hexadiene **10**, 5-methyl-4-phenyl-1,5-heptadiene **11**, and 2-methyl-3-phenyl-1,5-heptadiene **12** proceeded readily under $PdCl_2(PhCN)_2$-catalyzed conditions. However, no rearrangement occurred in the case of 3-phenyl-1,5-hexadiene **13**, 4-phenyl-1,5-heptadiene **14**, and 3-phenyl-1,5-heptadiene **15**. Thus, the $PdCl_2(PhCN)_2$-catalyzed Cope rearrangement requires a substituent at either C-2 or C-5 (**Scheme 5**).[7] Various unstrained, conformationally flexible, acyclic 1,5-dienes underwent Cope rearrangement in the presence of palladium(II) catalyst. For example, the 1,5-hexadienes having a hydroxy group at C-3 underwent the oxy-Cope rearrangement to afford the corresponding ketones in good to high yields (**Scheme 6**).[8] The Pd(II)-catalyzed rearrangement also took place for the 2-methyl-1,5-dienes



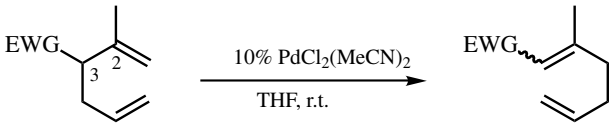
Scheme 5



[I] 10% $PdCl_2(PhCN)_2$, THF, r.t.

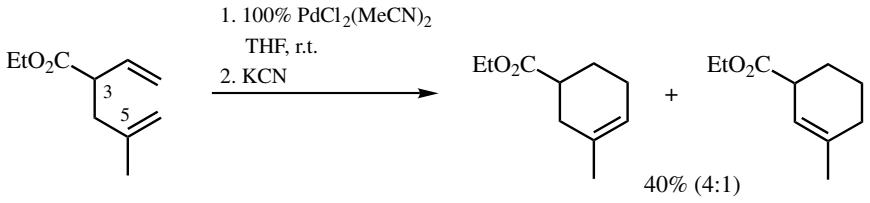
Scheme 6

attached to an electron-withdrawing group, such as ester, ketone, nitrile, and carboxylic acid, at the C-3 position (**Scheme 7**).[9] However, the diene without a substituent at C-2 did not undergo the Pd(II)-catalyzed rearrangement but underwent cyclization in the presence of a stoichiometric amount of $PdCl_2(MeCN)_2$ to produce the cyclohexene derivatives upon treatment with KCN (**Scheme 8**).[10] The similar cyclization was observed in the reaction of compound **16** with an equivalent amount of Pd(II) complex. The thermal rearrangement of **16** gave the [3,3] sigmatropic rearrangement product **18**, whereas the Pd(II)-catalyzed reaction afforded a mixture of **18** and the cyclization product **17** (**Scheme 9**).[11]

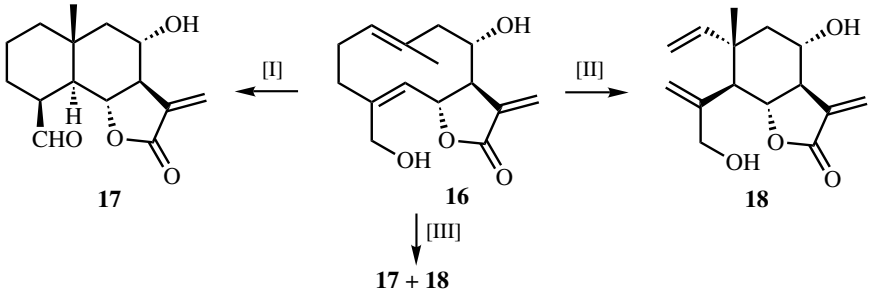


EWG	Yield (%)	*E/Z*
CO_2Et	83	65:35
COMe	93	68:32
CN	77	75:25
CO_2H	64	65:35
	No Reaction	

Scheme 7



Scheme 8

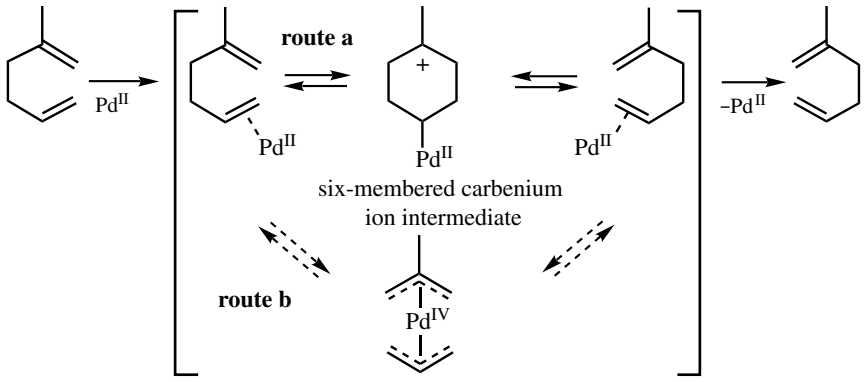


[I] 100% $PdCl_2(PhCN)_2$, toluene, reflux, 1 h. [II] Toluene reflux, 5 h.
[III] 2% $PdCl_2(PhCN)_2$, toluene, reflux, 1 h.

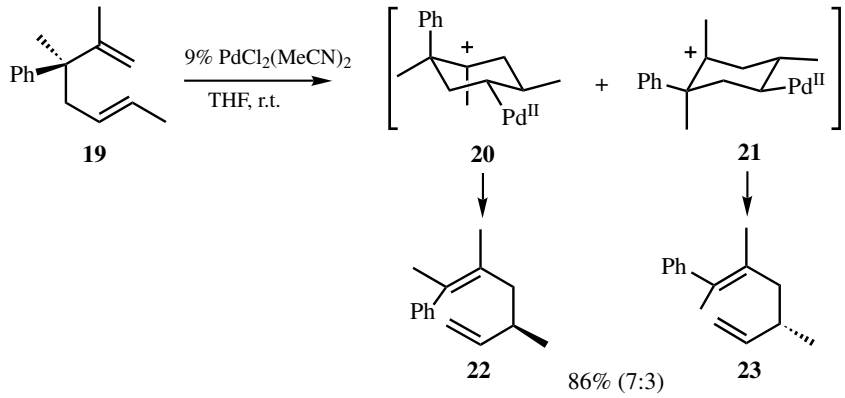
Scheme 9

C. MECHANISM OF THE PALLADIUM-CATALYZED COPE REARRANGEMENT

The Pd(II)-catalyzed Cope rearrangement most probably proceeds through a Pd-bound six-membered carbenium ion intermediate (**route a** in **Scheme 10**). Preferential Pd(II) complexation with the least substituted double bond would be followed by cyclization to a cyclohexyl cation, if a donor substitutent was present at C-2. The C—C bond cleavage followed by depalladation produces the rearranged 1,5-hexadiene. As an alternative mechanism, it was proposed that a palladium(II)–diene complex underwent oxidative addition of the allylic C—C bond to form a bis(π-allyl)palladium(IV) intermediate, which reductively eliminated to give Pd(II) and the Cope product (**route b** in **Scheme 10**). The reaction of 1,5-hexadinene with a stream of excess oxygen produced acetone in the presence of a Wacker catalyst consisting of $PdCl_2(PhCN)_2$, $CuCl_2$, and CuCl in aqueous solution at 60 °C.[12] It was considered that acetone might be produced from the oxidation of the bis(π-allyl)palladium(IV) chloride complex, which was generated via **route b** in **Scheme 10**. However, this proposed mechanism was not operative in Pd(II)-catalyzed Cope rearrangement due to the lack of products of [1,3] rearrangement. Actually, the Cope rearrangement of (*3R,5E*)-2,3-dimethyl-3-phenyl-1,5-heptadiene **19** occurred with virtually complete chirality transfer to afford a 7:3 mixture of the *2Z,5R* and *2E,5S* Cope products **22** and **23** in 86% yield (**Scheme 11**).[13] This observation proved that Cope rearrangements of acyclic dienes catalyzed by palladium(II) complexes occurred preferentially through the six-membered carbenium ion complexes **20** and **21** with the same chair topology as thermal Cope rearrangements. Moreover, the generation of cyclic products from 1,5-dienes, which is shown in **Schemes 8** and **9**,[10],[11] and the experimental evidence that



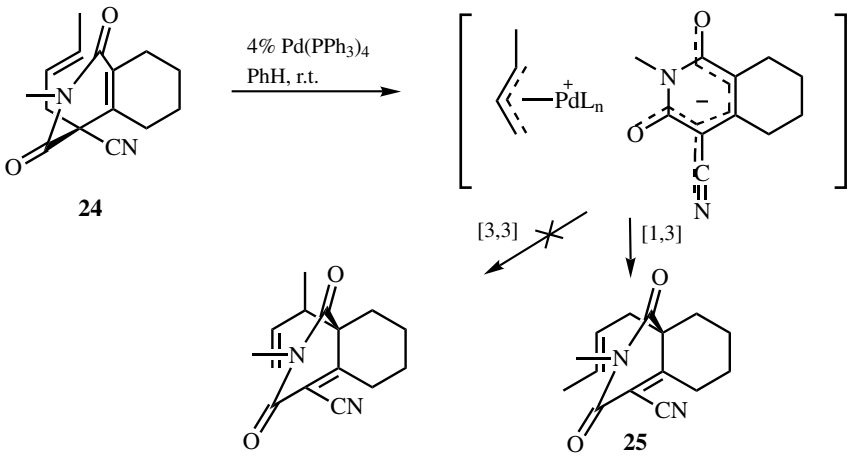
Scheme 10



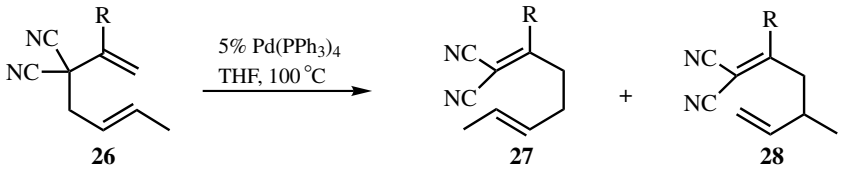
Scheme 11

significant electron deficiency at C-2 is consistent with the rate-limiting step of a cyclization-induced rearrangement mechanism[14] are also strong evidences for the formation of the six-membered carbenium ion intermediate.

On the other hand, the [1,3] rearranged product, whose generation process cannot be explained by the above mechanism (**route a** in **Scheme 10**), is observed in the reaction of **24** with palladium(0) catalyst (**Scheme 12**).[15] The crotyl derivative **24** underwent the Cope rearrangement in the presence of $Pd(PPh_3)_4$ catalyst to afford the [1,3] rearranged product **25**, exclusively. Furthermore, the reaction of 3,3-dicyano-1,5-heptadiene derivatives **26** proceeded in the presence of $Pd(PPh_3)_4$ catalyst to afford the [1,3] rearrangement products **27** as a major product along with the ordinal Cope rearrangement products **28** (**Scheme 13**).[16] In the absence of the catalyst, the thermal Cope reaction of **26** gave **28**, exclusively. Accordingly, it can be summarized that there are two types of mechanism in the Pd-catalyzed Cope rearrangement: (i) the Pd(II)-catalyzed [3,3] rearrangements through a Pd-bound six-membered carbenium ion intermediate as shown in **Scheme 10** (**route a**) and (ii) the Pd(0)-catalyzed [1,3] and [3,3] rearrangements through a bis(π-allyl)palladium(II) intermediate as shown in **Scheme 14**. In the latter case, the electron-withdrawing groups substituted at the allylic carbon of the dienes are essential for the [1,3] rearrangement in order to stabilize the bis(π-allyl)palladium(II) intermediates.

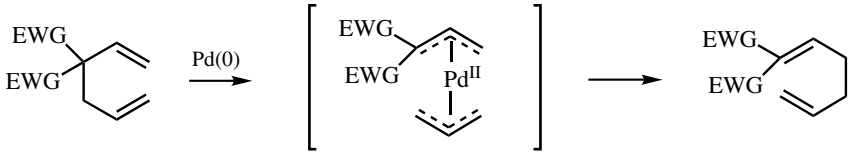


Scheme 12



R	**27** (%)	**28** (%)
Ph	23	10
4-MeC_6H_4	44	28
4-$MeOC_6H_4$	41	29
2-naphthyl	52	30
t-Bu	66	14

Scheme 13

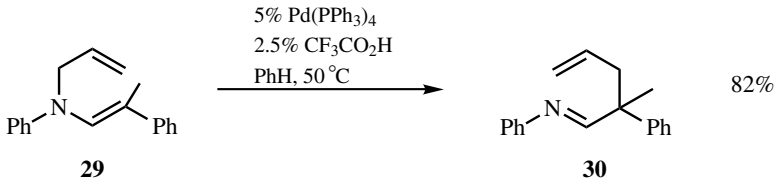


bis(π-allyl)Pd(II)
intermediate

Scheme 14

D. PALLADIUM-CATALYZED AZA-COPE REARRANGEMENT

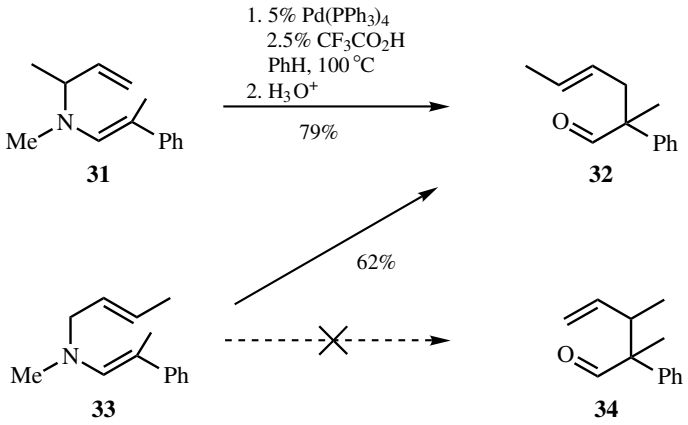
Aza-Cope rearrangement of *N*-allylenamines proceeds under mild reaction conditions in the presence of Pd(0)–protic acid catalyst to give the corresponding imines in good to high yields. *N*-Allyl-*N*-phenyl-2-phenyl-1-propenylamine **29** underwent aza-Cope rearrangement in the presence of $Pd(PPh_3)_4$–trifluoroacetic acid catalyst to give the corresponding γ,δ-unsaturated imine **30** in 82% yield (**Scheme 15**).[17],[18] The reaction



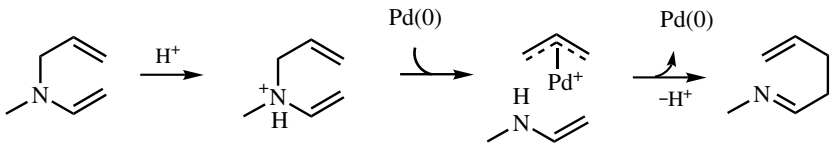
Scheme 15

did not proceed in the presence of $Pd(PPh_3)_4$ catalyst alone. Furthermore, the rearrangement of *N*-methyl-*N*-(1-methylallyl)-2-phenyl-1-propenylamine **31** gave [3,3] rearranged 2-methyl-2-phenyl-4-hexenal **32** after hydrolysis, while that of *N*-2-butyl-*N*-methyl-2-phenyl-1-propenylamine **33** also produced the same product **32** through [1,3] rearrangement: the regioisomeric 2,3-dimethyl-2-phenyl-4-pentenal **34** was not obtained in the latter case (**Scheme 16**). A plausible mechanism is shown in **Scheme 17**. Oxidative addition of a palladium(0) species to the carbon–nitrogen bond of the allylenammonium ion would give a π-allylpalladium complex and an enamine. Nucleophilic reaction of the enamine would give the rearranged imine. The role of the acid catalyst is to form the reactive substrate *N*-allylenammonium ion. It is known that oxidative addition of palladium(0) species to quaternary salts of the corresponding allylamines proceeds faster than that to allylamines.[19]

Stereoselective allylation can be accomplished using *in situ* aza-Cope rearrangement. The bicyclic compound **35**, which is a precursor of Madangamine A, was treated with

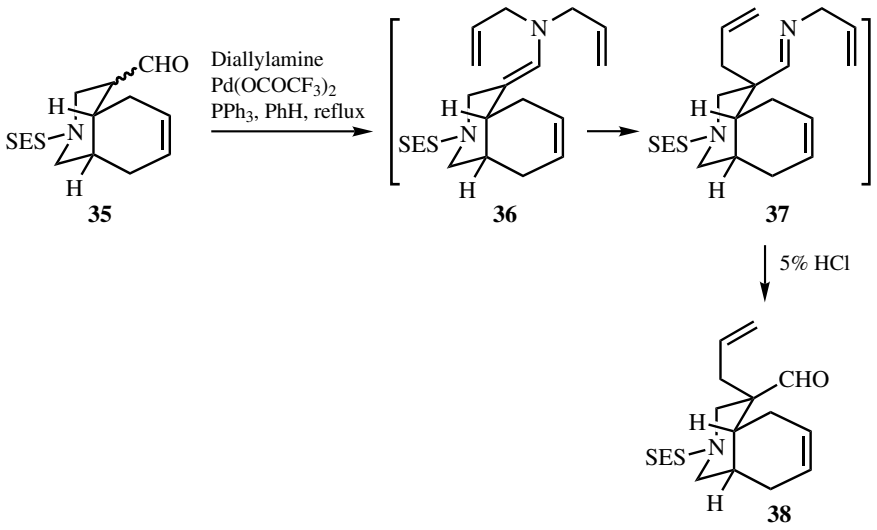


Scheme 16



Scheme 17

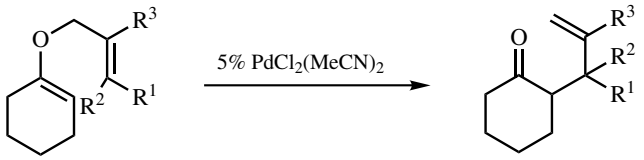
diallylamine in the presence of $Pd(O_2CCF_3)_2$–PPh_3 catalyst to initially generate the enamine **36**, which underwent stereospecific [3,3] sigmatropic rearrangement from the less congested face of the molecule to afford the imine **37**. Acidic hydrolysis of **37** gave a single stereoisomeric aldehyde **38** in 68% yield (**Scheme 18**).[20]



Scheme 18

E. PALLADIUM(II)-CATALYZED CLAISEN REARRANGEMENT

Claisen rearrangement of allyl vinyl ethers is catalyzed by palladium(II). Treatment of *E*-2-buten-1-yl 1-cyclohexenyl ether ($R^1 = CH_3$, $R^2 = R^3 = H$) with 5% $PdCl_2(MeCN)_2$ at room temperature produced 2-(1-methyl-2-propenyl)cyclohexanone in 71% yield. Allyl 1-cyclohexenyl ether ($R^1 = R^2 = R^3 = H$) also underwent the rearrangement smoothly in benzene. However, the rearrangement of 2-methallyl 1-cyclohexenyl ether ($R^1 = R^2 = H$, $R^3 = CH_3$) and prenyl 1-cyclohexenyl ether ($R^1 = R^2 = CH_3$, $R^3 = H$) gave only traces of the rearranged products under the above conditions (**Scheme 19**).[21] The Pd(II)-catalyzed

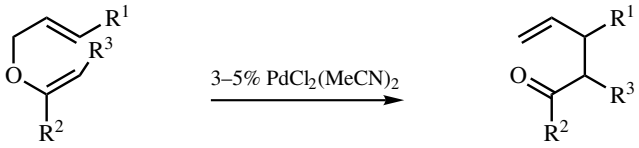


R^1	R^2	R^3	Solvent	Yield (%)
CH_3	H	H	THF	71
H	H	H	PhH	65
H	H	CH_3	PhH	<2
CH_3	CH_3	H	PhH	<5

Scheme 19

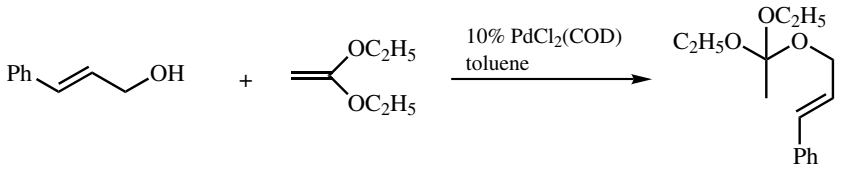
Claisen rearrangement also proceeded in the case of conformationally flexible, acyclic allyl vinyl ethers (**Scheme 20**).[21],[22] However, the chemical yield was highly dependent on the position of substituents at the double bonds.

The ortho ester **41**, which was prepared from cinnamyl alcohol **39** and diethyl ketene acetal **40** in the presence of $PdCl_2$(COD), gave *in situ* the allyl vinyl ether **42** via the elimination of ethanol and the resulting Claisen rearrangement in the presence of 10 mol % $PdCl_2(PPh_3)_2$ in *p*-xylene under reflux condition to give the rearranged product **43** (**Scheme 21**). However, it is not necessarily clear whether the rearrangement was accelerated really by palladium(II) catalyst or not, since thermal Claisen rearrangement generally proceeds under such high temperatures.[23]

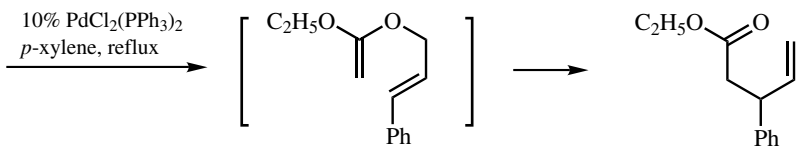


R^1	R^2	R^3	Solvent	Temperature	Yield (%)
CH_3	H	H	PhH	r.t.	<2
H	CH_3	H	PhH	r.t.	<2
CH_3	H	CH_3	PhH	r.t.	18
H	C_2H_5	CH_3	THF	r.t.	71
CH_3	C_2H_5	CH_3	THF	r.t.	93
CH_3	Ph	H	THF	r.t.	67
n-C_3H_7	Ph	H	THF	40 °C	60
$PhCH_2CH_2$	Ph	H	THF	40 °C	41

Scheme 20



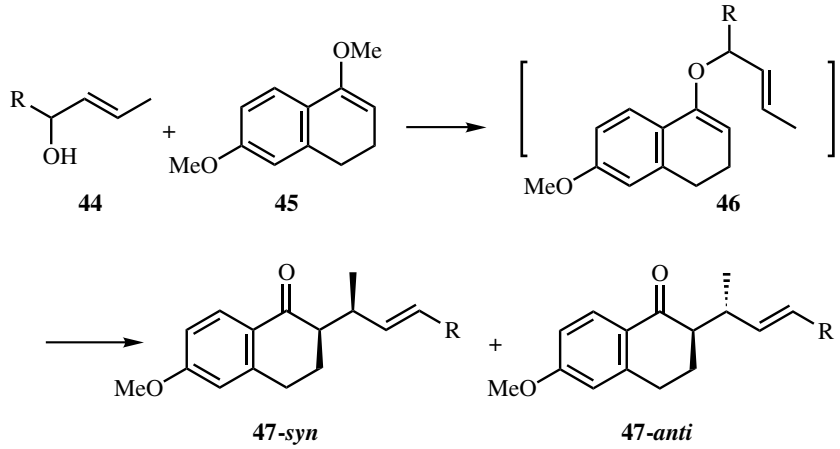
39 **40** **41**



42 **43**

Scheme 21

Highly stereoselective formation of either **47**-*syn* or **47**-*anti* is accomplished by means of the choice of the catalyst employed. The reaction of the *E*-crotyl alcohols **44** and the cyclic enol ether **45** initially produced the allyl vinyl ethers **46**, which underwent the thermal Claisen rearrangement at 100 °C in the presence of 2,6-dimethylphenol (DMP) catalyst to give **47**-*syn*, selectively (**Scheme 22**). On the contrary, the allyl vinyl ethers **46** underwent Claisen rearrangement at room temperature in the presence of $PdCl_2(PPh_3)_2$ catalyst to afford **47**-*anti*, selectively.[24],[25] The *E*⟶*syn* selectivity of the DMP-catalyzed thermal rearrangement[25] is easily visualized by the chair-like transition state **48**, whereas the *E*⟶*anti* selectivity of the Pd(II)-catalyzed rearrangement can be explained by the boat-like transition state **49**, where the diene moiety may act as a bidentate ligand (**Scheme 23**).

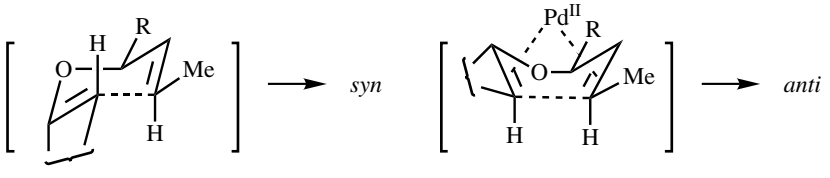


44 **45** **46**

47-*syn* **47-*anti***

R	Catalyst (10%)	Temperature	Yield (%)	**47**-*syn*	**47**-*anti*
H	DMP	100 °C	94	94:6	
H	$PdCl_2(PhCN)_2$	r.t.	>95	13:87	
i-Bu	DMP	100 °C	>95	>98:2	
i-Bu	$PdCl_2(PhCN)_2$	r.t.	>95	2:>98	

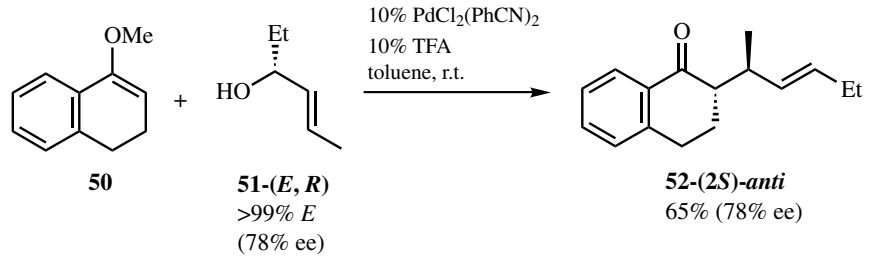
Scheme 22



48 **49**

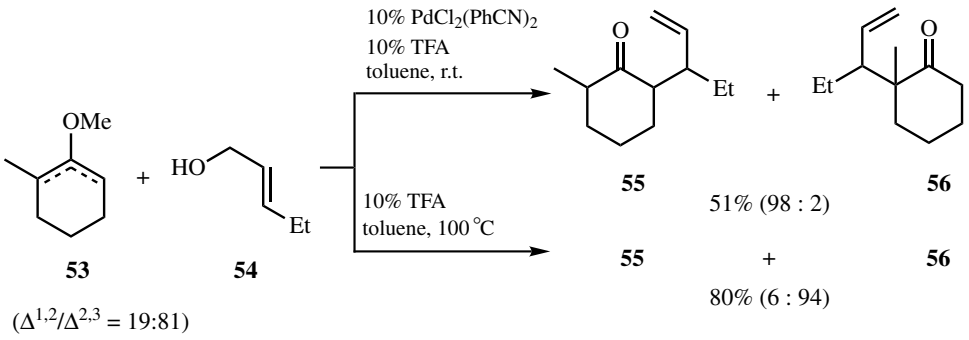
Scheme 23

Asymmetric transmission is achieved using a chiral allylic alcohol.[26] The reaction of the enol **50** with **51-**(*E,R*) proceeded with complete asymmetric transmission to provide **52-**(*2S*)-*anti* in the same enantiomeric excess as that of **51** (**Scheme 24**). This observation strongly supports the boat-like transition state for the Pd(II)-catalyzed Claisen rearrangement. The regioselective Claisen rearrangement of a 19:81 regioisomeric mixture of the enol ether **53** and (*E*)-allylic alcohol **54** was observed in both the Pd(II)-catalyzed and trifluoroacetic acid (TFA)-catalyzed conditions (**Scheme 25**).[27] The Pd(II)–TFA-catalyzed process at room temperature provided the ketone **55** as an essentially single regioisomer, whereas the TFA-catalyzed rearrangement at 100 °C gave the regioisomeric ketone **56** very predominantly.



50 **51-(*E*, *R*)** >99% *E* (78% ee) **52-(2*S*)-*anti*** 65% (78% ee)

Scheme 24



53 **54** **55** 51% (98 : 2) **56**

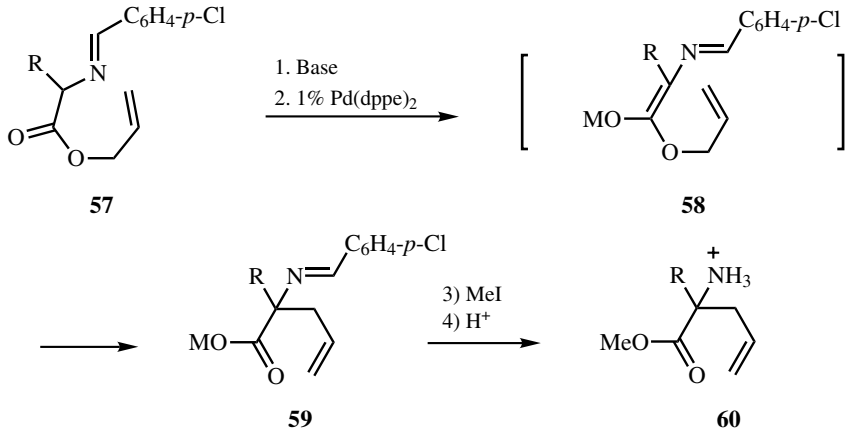
($\Delta^{1,2}/\Delta^{2,3}$ = 19:81) **55** + **56**

80% (6 : 94)

Scheme 25

F. PALLADIUM(II)-CATALYZED IRELAND–CLAISEN REARRANGEMENT

The allyl esters **57**, which were readily prepared from various α-amino acids, rearranged cleanly to **59** via the ketene acetals **58** in the presence of $Pd(dppe)_2$ in THF at room temperature as shown in **Scheme 26**. Esterification followed by hydrolysis of **59** afforded the α-amino methyl esters **60** as a stable form. The bases had no obvious influence on the yield of **60** for the glycine (R = H) and alanine ($R = CH_3$) derivatives. *t*-BuOK was an efficient base for the sterically hindered compounds **57** at the α-carbon atom of carbonyl groups.[28]



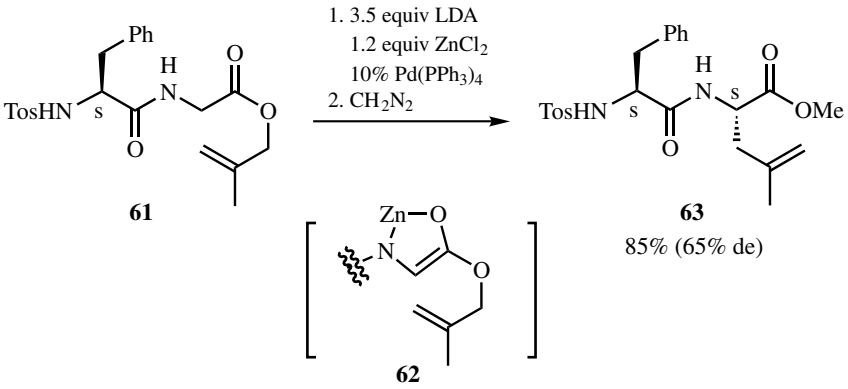
57 **58** **59** **60**

R	Base	Yield (%)
H	LDA	90
H	*t*-BuOK	80
CH_3	NaH	88
CH_3	*t*-BuOK	70
$(CH_3)_2CH$	*t*-BuOK	80
C_6H_5	*t*-BuOK	87
$C_6H_5CH_2$	*t*-BuOK	72

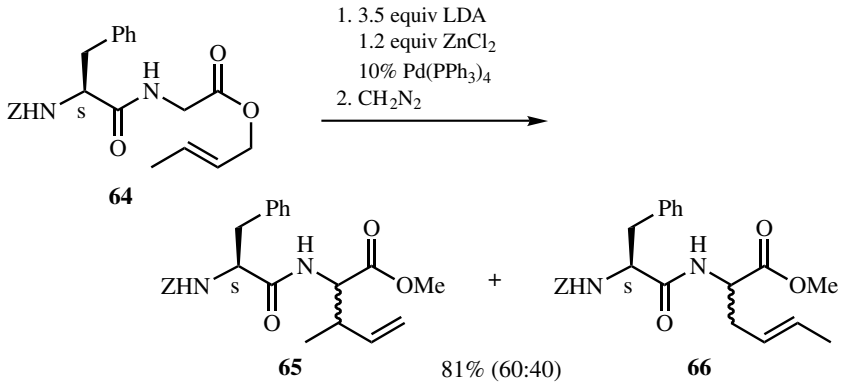
Scheme 26

In contrast to the lithium and potassium enolates, the chelated zinc enolates are quite stable with fixed enolate geometry; thus, Ireland–Claisen rearrangement can proceed in the presence of palladium(0) catalyst with a high degree of diastereoselectivity. Deprotonation of the N-protected glycine methallyl ester **61** with LDA at −78 °C and subsequent addition of $ZnCl_2$ presumably resulted in the formation of a chelated zinc enolate **62**, which underwent Ireland–Claisen rearrangement with $Pd(PPh_3)_4$ catalyst (**Scheme 27**). Subsequent esterification of the rearrangement product with diazomethane afforded the dipeptide **63** in 85% yield with 65% diastereomeric excess.[29] In the case of the crotylester **64**, a 60:40 mixture of sigmatropic rearrangement products **65** and **66** was formed in 81% yield (**Scheme 28**). This result indicates that the reaction proceeds in both fashions—a [3,3] sigmatropic rearrangement via a six-membered cyclic transition state and an intermolecular allylic alkylation via a π-allylpalladium intermediate.

The sequential Michael addition/Ireland–Claisen reactions proceed with high diastereoselectivity in one pot. Preparation of the lithium enolate **68** with LDA in THF at −78 °C followed by the addition of the allylic ester acceptor **67** leads to the smooth conjugate addition, whose stereoselectivity was more than 98% diastereomeric excess. The ketene silyl acetal **70**, which was formed by the trapping of the Michael addition intermediate **69** with TMSCl, underwent Ireland–Claisen rearrangement in the presence of $PdCl_2(PhCN)_2$



Scheme 27



Scheme 28

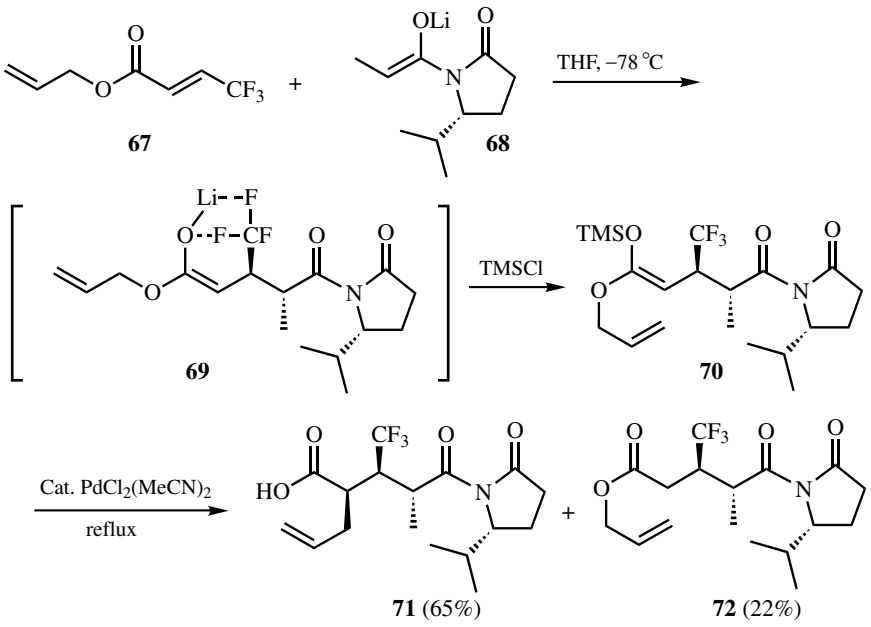
catalyst to give the rearranged product **71** as a single stereoisomer along with the unrearranged Michael adduct **72** (**Scheme 29**).[30]

The cyclopropane σ-bond behaves as a π-component in the Pd(II)-catalyzed Ireland–Claisen-type rearrangement, since the strained σ-bond of cyclopropane has the high *p*-character in hybridization. 1-Allyloxy-1-siloxycyclopropane **73** smoothly rearranged in the presence of $PdCl_2(PhCN)_2$ catalyst at room temperature. The products after hydrolysis were **74** (59%), **75** (34%), and **76** (4%) (**Scheme 30**).[31] However, **73** did not undergo the thermal rearrangement even after heating at 150–160 °C for several hours.

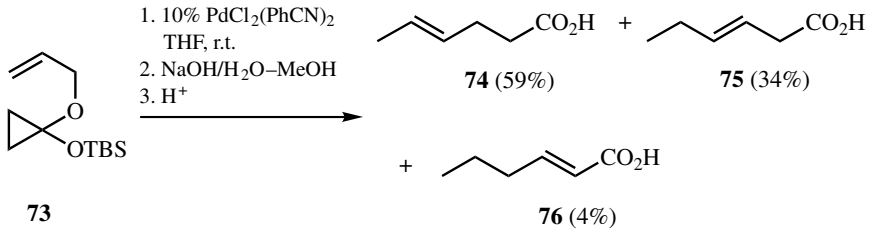
G. SUMMARY

1. 1,5-Dienes undergo Cope rearrangement in the presence of palladium catalysts.

2. Pd(II)-catalyzed Cope rearrangement most probably proceeds through a Pd-bound six-membered carbenium ion intermediate to afford the [3,3] rearranged products. A donor substituent is required at either C-2 or C-5 of 1,5-dienes for the rearrangement in order to stabilize the carbenium cation.



Scheme 29



Scheme 30

3. Pd(0)-catalyzed Cope rearrangement proceeds through a bis(π-allyl)palladium(II) intermediate to afford the [1,3] and [3,3] rearranged products. The electron-withdrawing groups are required at the allylic position of 1,5-dienes to stabilize the bis(π-allyl)palladium(II) intermediate, which is generated by the oxidative insertion of Pd(0) into the C—C σ-bond.

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IX.2.1.2 Palladium-Catalyzed Carbon Skeletal Rearrangements Other than [3,3] Rearrangements

EI-ICHI NEGISHI

A. CARBON SKELETAL REARRANGEMENTS VIA 1,2-ANIONOTROPIC SHIFTS OF ORGANOPALLADIUMS CONTAINING CARBOCATIONIC CENTERS

In Wacker-type oxypalladation processes, potentially carbocationic organopalladium species containing β-oxy or β-amino groups are generated as transient species. In cases where β-dehydropalladation is facile, it provides a preferred mode of cleavage of C—Pd bonds. In view of the electrophilic nature of the Pd-bound C atoms, anionotropic 1,2-shifts in a manner of the pinacol–pinacolone rearrangement should also be expected, and many such reactions have indeed been observed (**Scheme 1**). In most cases, the overall process involves net oxidation, and such reactions are discussed in **Sects. V.3** and **VIII.4**. In some cases where the starting compounds are appropriately oxygenated, net isomerization may result, as exemplified by the results shown in **Scheme 2**.[1] Even though the number of examples is very limited at present, this might prove to be a widely observable phenomenon, especially with strained allylic and propargylic alcohols.

The carbon skeletal rearrangement shown in **Scheme 3**[2] is an oxygen analog of the allylic rearrangement discussed in **Sect. V.2.5.3**. This oxa-allylpalladium rearrangement reaction is followed by β-elimination.

B. PALLADIUM-CATALYZED VALENCE BOND ISOMERIZATION

Treatment of highly strained hydrocarbons with Pd complexes has been shown to induce valence bond isomerization. Some representative examples are shown in **Scheme 4**. The mechanisms of these reactions are not clear in most cases. However, a mechanism involving oxidative complexation, allylic rearrangement, and reductive decomplexation may be proposed for the Dewar benzene-to-benzene rearrangement.

Although the overall process does not represent a rearrangement, a cubyl-to-cyclooctatetraenyl rearrangement observed in the Sonogashira coupling of iodocubane with 1-hexyne[7] is interesting in that the rearrangement observed in this reaction (**Scheme 5**) is different from that of cubane itself shown in **Scheme 4**.

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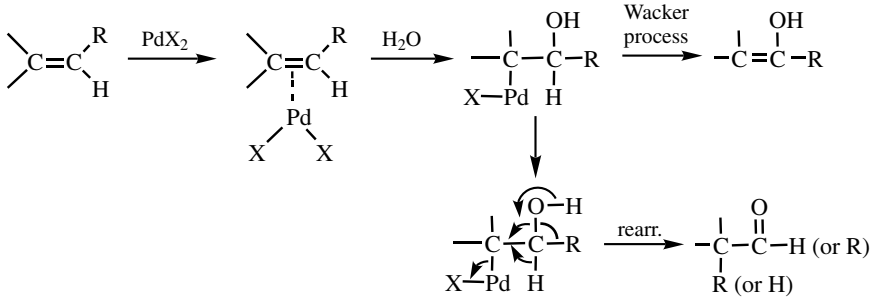
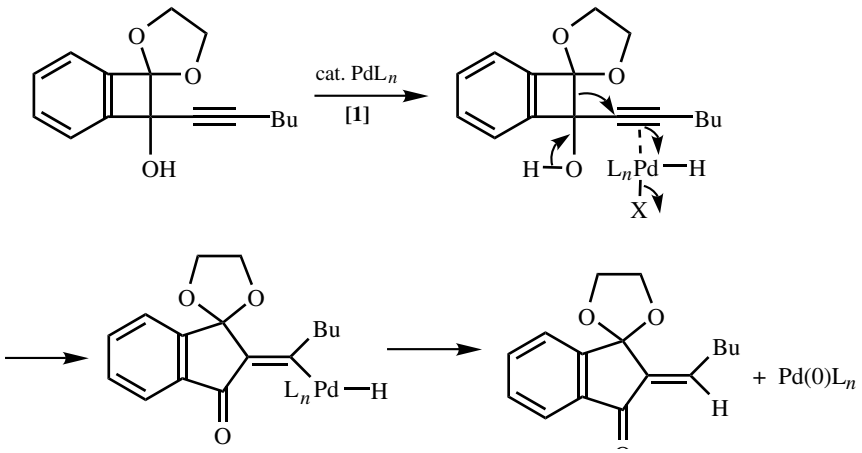
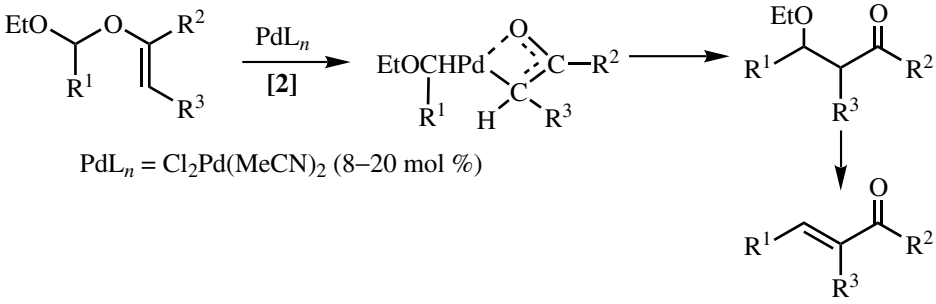


Scheme 1



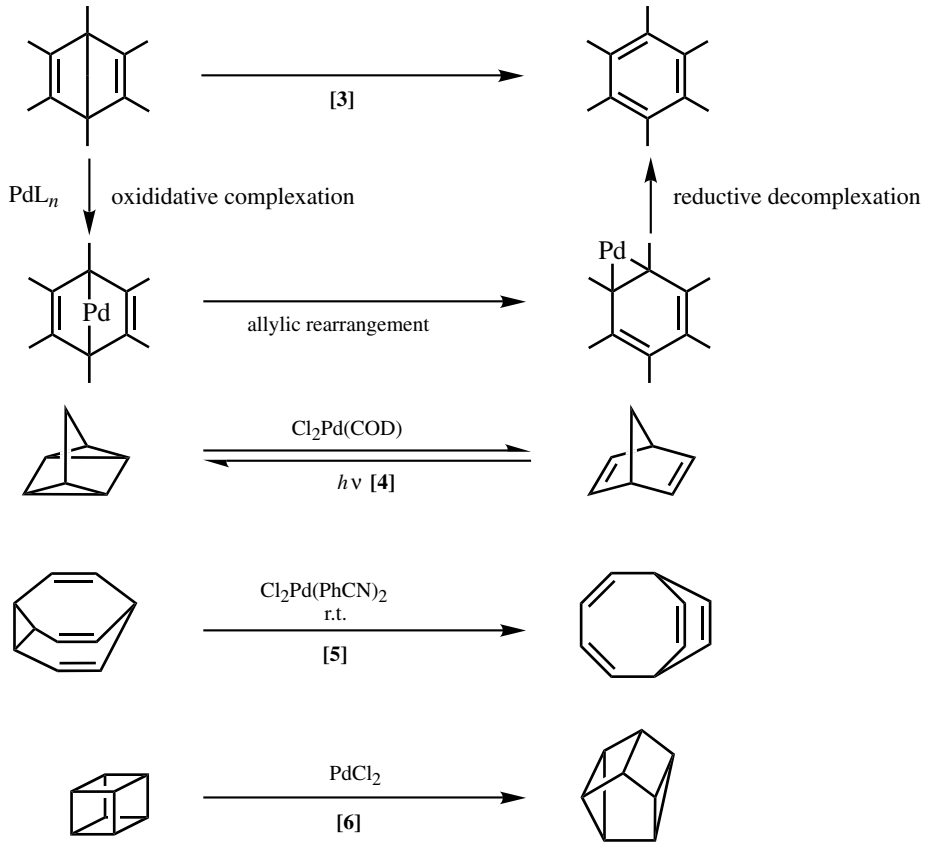
Scheme 2



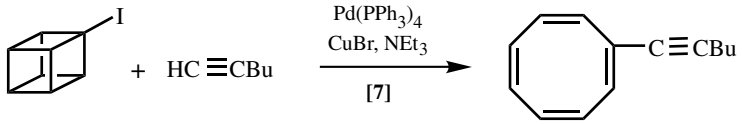
$PdL_n = Cl_2Pd(MeCN)_2$ (8–20 mol %)

R^1	R^2	R^3	Enone (%)
Me	H	Me	80
Et	H	Me	82
Pr	H	Me	86
Et	Me	Me	84
Me	Et	Et	87

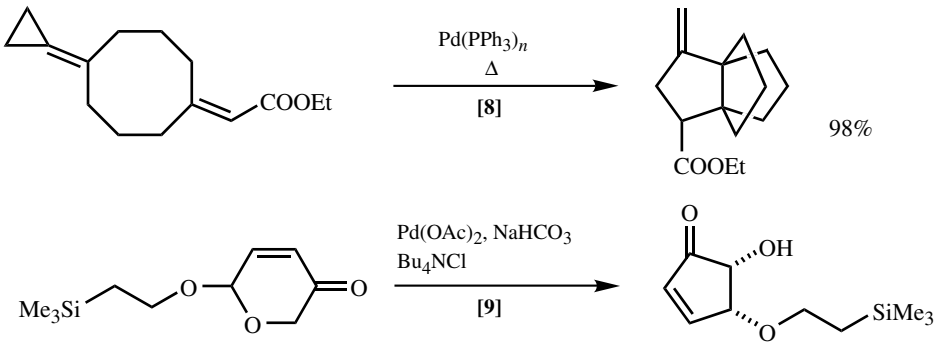
Scheme 3



Scheme 4



Scheme 5



Scheme 6

C. OTHER CARBON SKELETAL REARRANGEMENTS

Although many other Pd-catalyzed reactions will be found in the future, the number of currently known examples appears to be still limited. **Scheme 6** shows some examples of other Pd-catalyzed carbon skeletal rearrangements.

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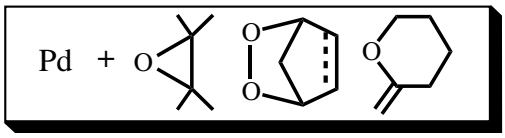
[9] B. Mucha and H. M. R. Hoffmann, *Tetrahedron Lett.*, **1989**, *30*, 4489.



IX.2.2 Palladium-Catalyzed Rearrangements of Oxygen Functions

MASAAKI SUZUKI, TAKAMITSU HOSOYA, and RYOJI NOYORI

A. INTRODUCTION

In this section are collected the Pd-catalyzed rearrangements of epoxides, epiperoxides, and enol ethers. Such skillful manipulations of oxygen functions are important in view of the site-specific oxygenation of carbon skeletons mimicking biosynthesis. The *in situ* generated palladium intermediates are further utilized for carbon–carbon bond-forming reactions under mild conditions, realizing an elegant organic synthesis (see **Sect. V.2.1.5**).

B. PALLADIUM(0)-CATALYZED REACTION OF EPOXIDES AND EPIPEROXIDES

B.i. Palladium(0)-Catalyzed Reaction of 1,3-Diene Epoxides

Three types (A–C) of rearrangement of 1,3-diene epoxides are realized by a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in dichloromethane, benzene, or ethereal solvents (**Scheme 1**).[1] The course of the Pd(0)-catalyzed reaction of the epoxides appeared to be highly dependent on the substitution pattern of the substrates.

The diene epoxides having a transferable hydrogen atom in the C-2 alkyl substituent undergo type A reaction by hydrogen migration reaction. Some examples are shown in **Scheme 2**.

The reactions in **Scheme 3** exemplify the general reaction that involves transfer of a C-5 hydrogen atom. The propensity to undergo this type B reaction is characteristic of open-chain substrates, which lack alkyl substituents at the C-2 position. The stereospecificity is not observed in this reaction.

Monoepoxides derived from simple cyclic 1,3-dienes possessing ordinary ring size (five- to eight-membered ring) give the corresponding β,γ-unsaturated ketones as the sole product as shown in **Scheme 4**. The reaction of a 12-membered ring epoxide produces a mixture of 3-cyclododecenone and the dienol. The latter is possibly formed from the type B reaction. The Pd(0)-catalyzed reaction of terminal 1,3-diene epoxides affords α,β-unsaturated aldehydes predominantly (**Scheme 5**).[2]–[5]

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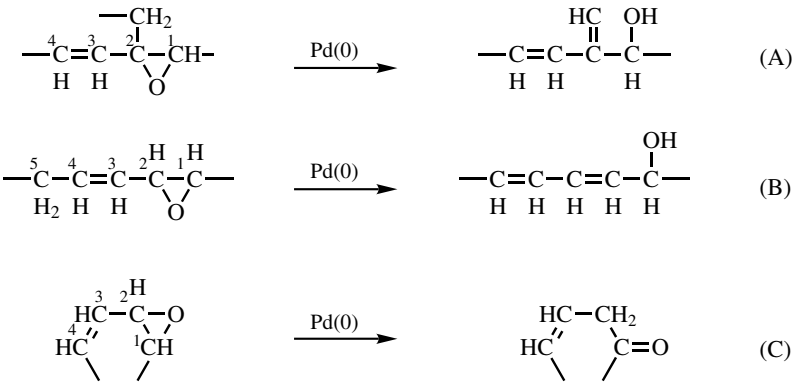
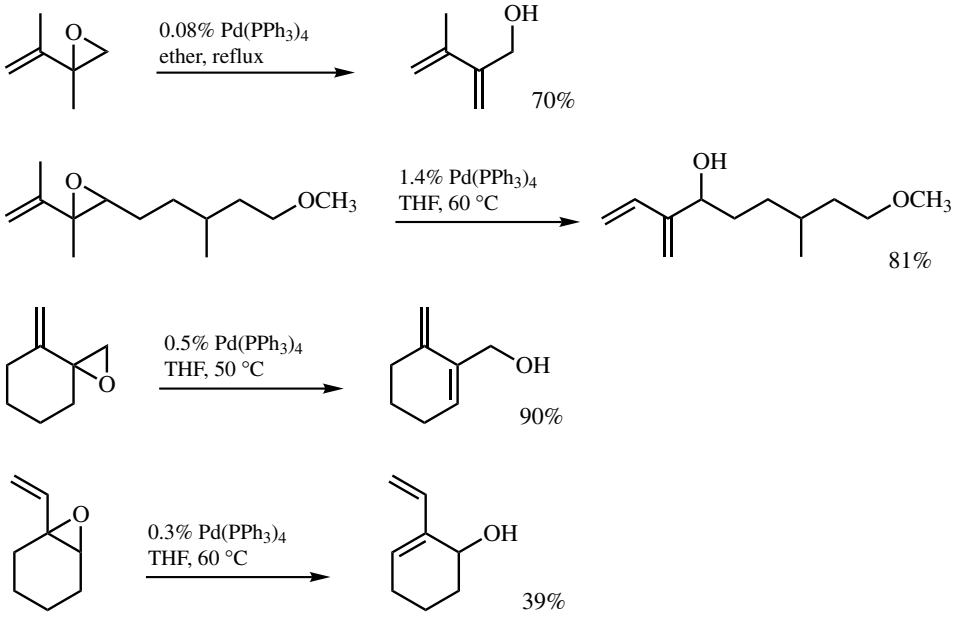
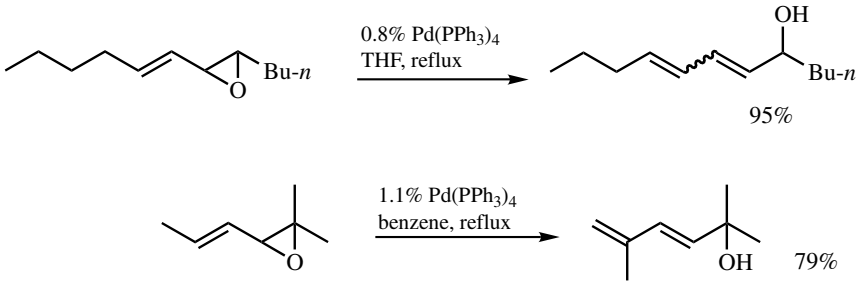


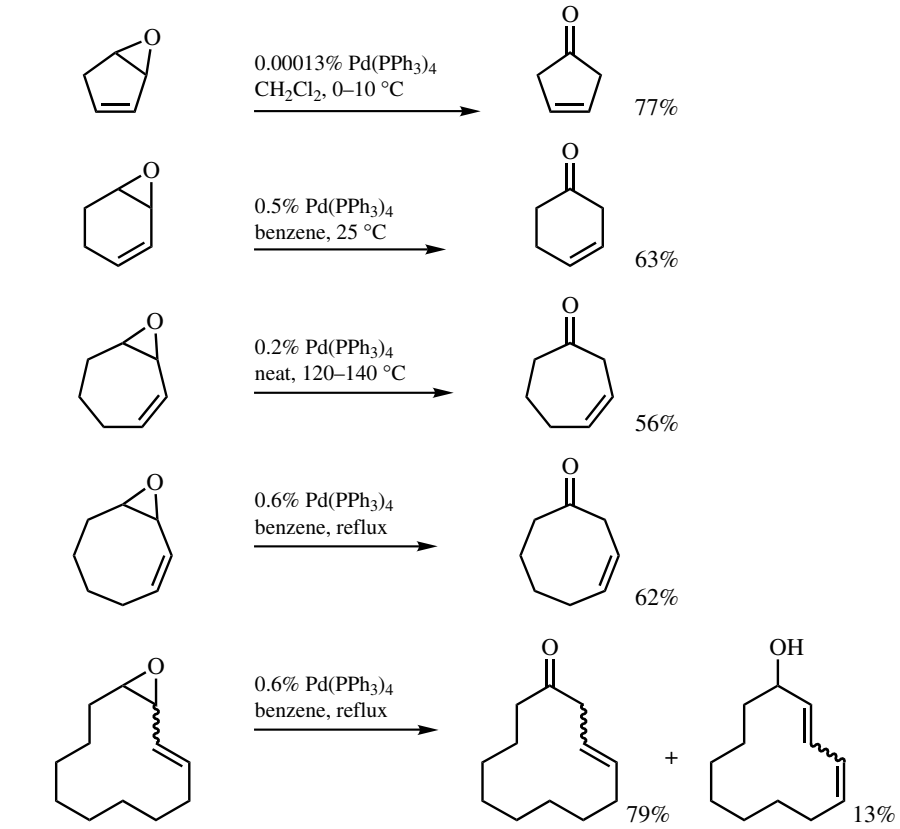
Scheme 1



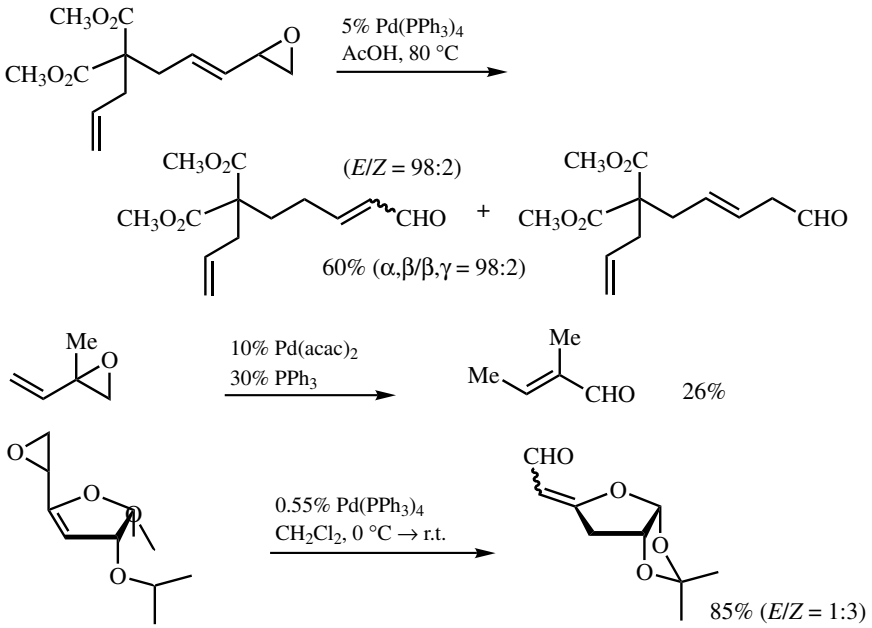
Scheme 2



Scheme 3

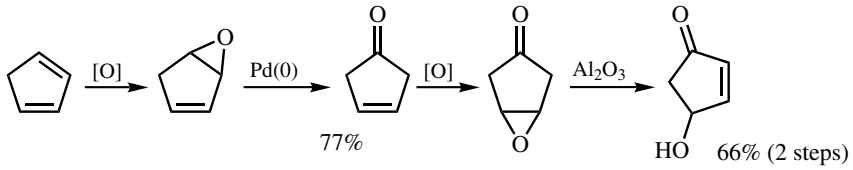


Scheme 4



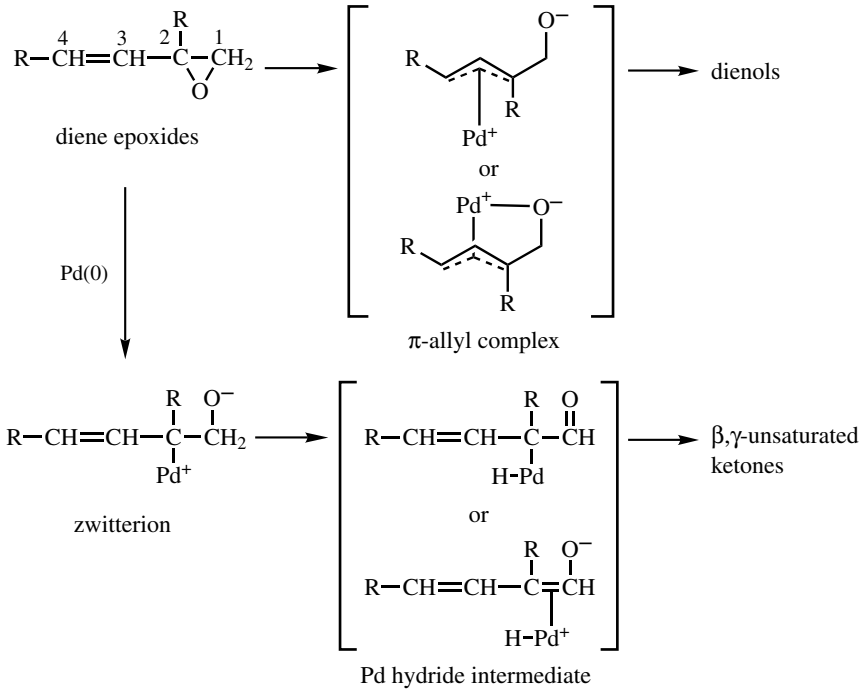
Scheme 5

The important application of the type C rearrangement is demonstrated by the synthesis of 4-hydroxy-2-cyclopentenone, a prostaglandin intermediate, starting from cyclopentadiene (**Scheme 6**).[1]



Scheme 6

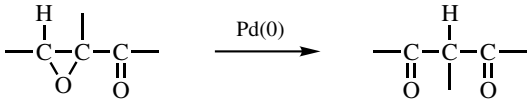
The efficiency of these catalytic reactions of epoxides is ascribed to the eminent nucleophilic character of the Pd(0) catalyst and hydrogen-carrying ability of Pd(II) species.[1] In principle, the diene epoxide is susceptible to Pd(0) attack at C-2 (S_N2-type reaction), C-4 (S_N2'-type reaction), or C-3–C-4 double bond. β,γ-Unsaturated ketone would form via zwitterion and Pd hydride intermediate, while, alternatively, the epoxide can isomerize to dienols through the π-allyl complex (**Scheme 7**). The π-allyl complex is facilely scavenged with hydride, alkoxides, amides, and carboanion nucleophiles to enhance the synthetic utility (see **Sect. V.2.1.5**).



Scheme 7

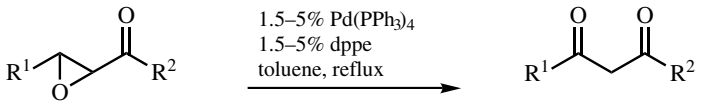
B.ii. Palladium(0)-Catalyzed Isomerization of α,β-Epoxy Ketones to β-Diketones

A straightforward approach to β-diketones under entirely neutral and aprotic conditions is realized by simply heating α,β-epoxy ketones in toluene in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(0) and 1,2 bis(diphenylphosphino)ethane (**Scheme 8**).[6],[7]



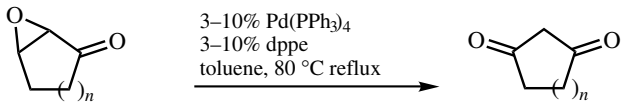
Scheme 8

Some examples are given in **Schemes 9** and **10**. A series of open-chain (**Scheme 9**) and cyclic substrates (**Scheme 10**) facilely undergo the isomerization to the corresponding β-diketones. Epoxy ketone possessing an α-alkyl group reacts only sluggishly (**Scheme 11**). Particularly noteworthy is the efficient synthesis of 1,3-cyclopentanedione, a prized compound, from readily accessible 2,3-epoxycyclopentanone. The most probable reaction mechanism is outlined in **Scheme 12** where the catalysis would be initiated by an S_N2-type nucleophilic, backside attack of Pd(0) species at the epoxy α-carbon. This reaction is applied to the convenient synthesis of dialkyl (2,4-dioxoalkyl)phosphonates (**Scheme 13**)[8] and is also used in the synthesis of 6-azasteroids, potent dual inhibitors of type 1 and 2 steroidal 5α-reductase (**Scheme 14**).[9]



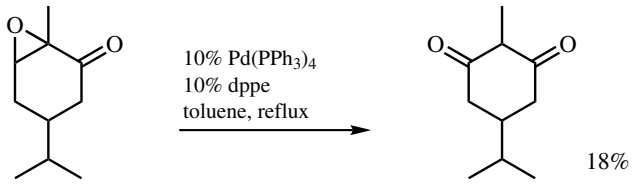
R^1	R^2	Yield (%)
Me	Me	81
i-Pr	Me	80
n-Pr	*n*-Heptyl	90
Ph	*n*-Hexyl	82
Ph	Ph	84

Scheme 9

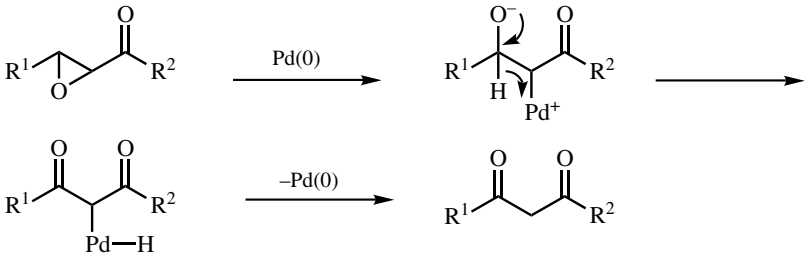


n	Yield (%)
1	94
2	62
3	60
4	52
8	54

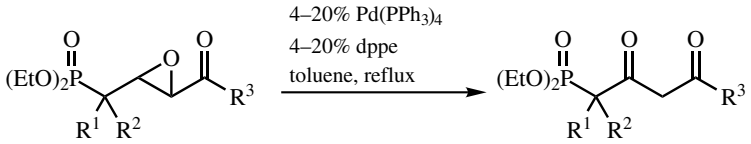
Scheme 10



Scheme 11

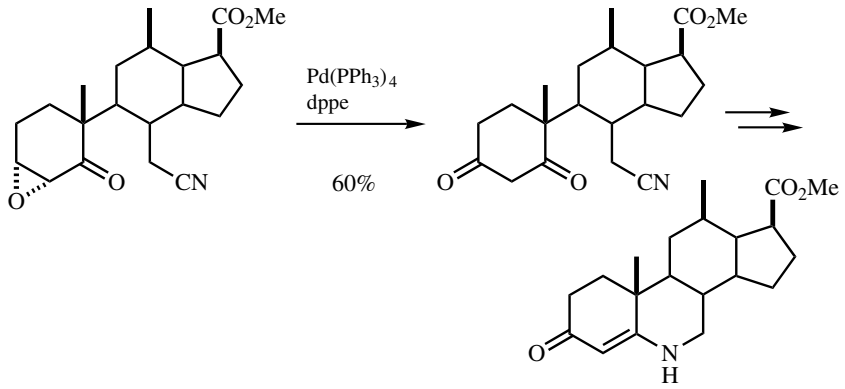


Scheme 12



R^1	R^2	R^3	Yield (%)
H	H	Me	68
H	H	Et	63
H	H	*i*-Pr	66
H	H	*t*-Bu	61
H	H	Ph	81
H	Me	Me	54
Me	Me	Me	49

Scheme 13

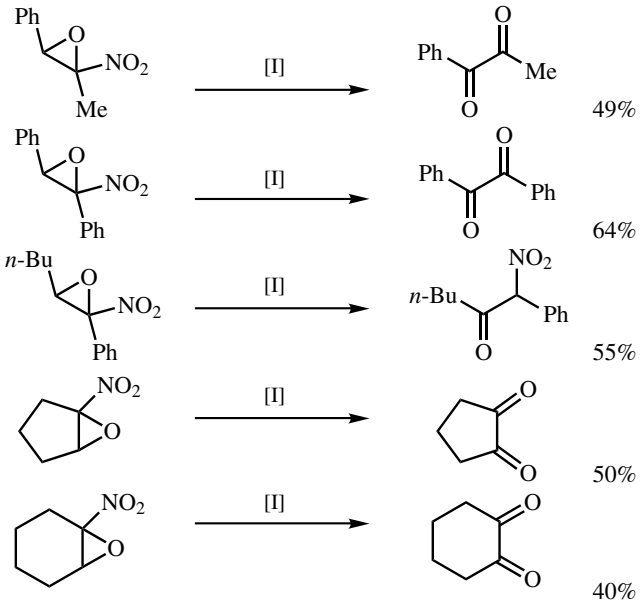


Scheme 14

B.iii. Palladium(0)-Catalyzed Reaction of Various Epoxy Substrates

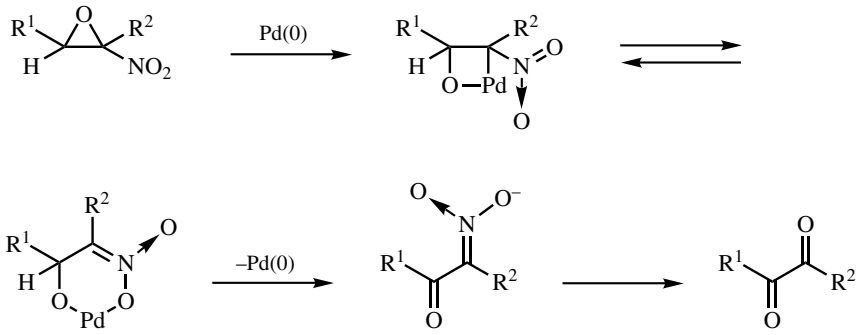
A variety of α-nitroepoxides undergo conversion to the corresponding 1,2-diketones or, in some cases, α-nitroketones with tetrakis(triphenylphosphine)palladium(0) (**Scheme 15**).[10],[11] Proposed reaction mechanism is shown in **Scheme 16**. 2,3-Epoxy alcohols also undergo the Pd(0)-catalyzed reaction to be isomerized to α- or β-hydroxy ketones or both, depending on the nature of the substituents on the phenyl ring (**Scheme 17**).[12]

Pd(0)–tertiary phosphine complexes catalyze the chemo- and regioselective isomerization of simple epoxides to corresponding carbonyl compounds efficiently (**Schemes 18** and **19**).[13],[14] Not only aliphatic substituted epoxides but also aryl-substituted ones undergo this isomerization in excellent yields.



[I] = 5% $Pd(PPh_3)_4$, NEt_3 (1 equiv), benzene, reflux.

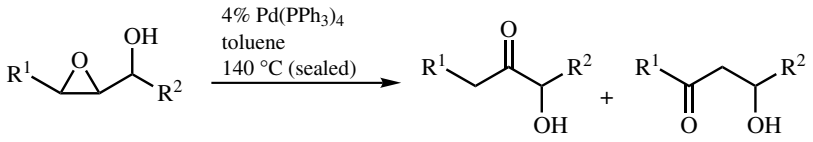
Scheme 15



Scheme 16

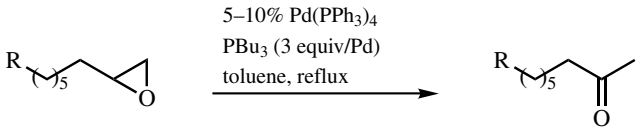
B.iv. Palladium(0)-Catalyzed Reaction of 1,4-Epiperoxides

1,4-Epiperoxides (endoperoxides) serve as key substances in a variety of chemical and biological transformations. The O—O bond undergoes either homolytic or heterolytic cleavage depending on the reaction conditions. The 2,3-saturated and 2,3-unsaturated 1,4-epiperoxides undergo interesting reactions with a Pd(0) catalyst.[15]–[17] The former is converted to the corresponding 4-hydroxy ketones and 1,4-diols as the major products and the latter affords corresponding 4-hydroxy enones, *syn*-1,2;3,4-diepoxides, and



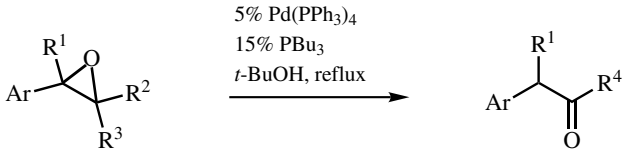
R^1	R^2	Yield (%)	
Ph	H	62	—
Ph	Me	60	—
Ph	Ph	50	32
4-MeC_6H_4—	Ph	38	42
4-$NO_2C_6H_4$—	Ph	59	39
4-$MeOC_6H_4$—	Ph	—	—

Scheme 17



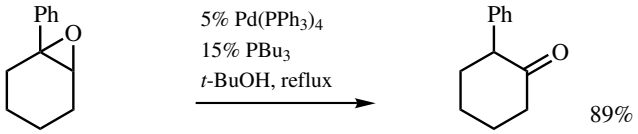
R	Yield (%)
n-Bu	88
—$(CH_2)_3OH$	85
—(*E*)-$(CH_2)_2CH{=}CHCO_2Et$	90
—$(CH_2)_3CN$	96

Scheme 18

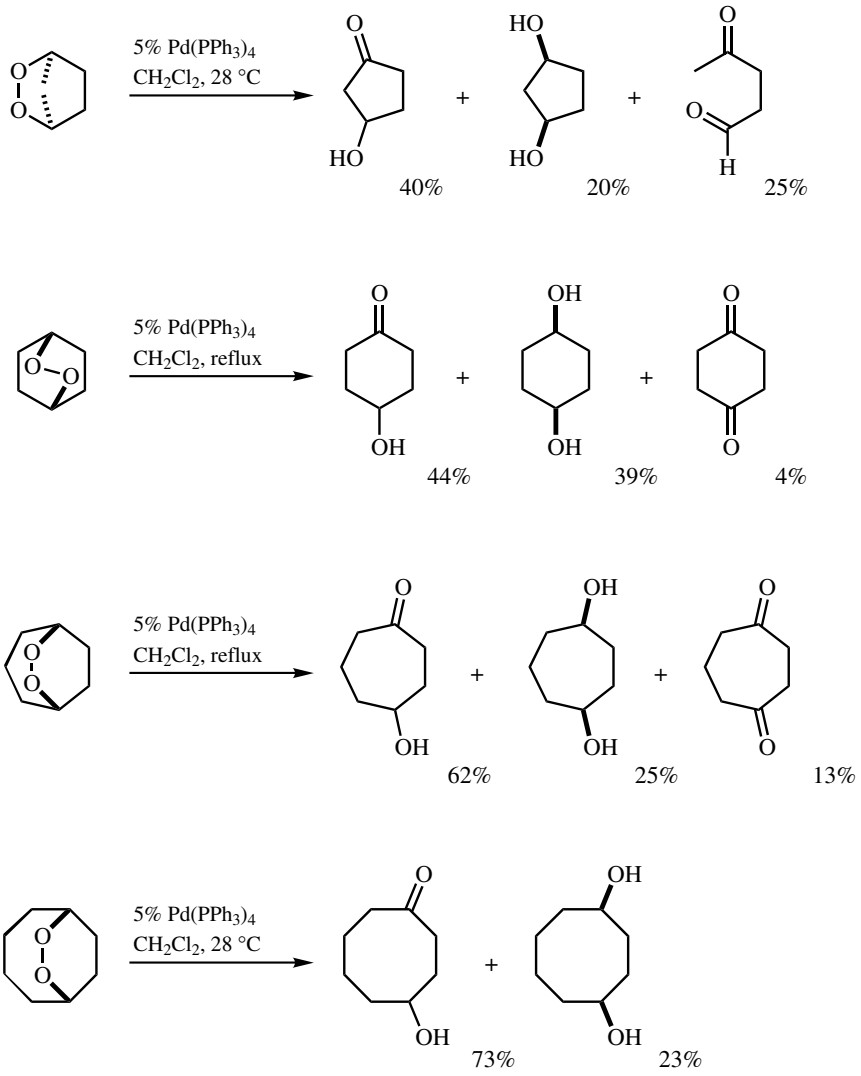


Ar	R^1	R^2	R^3	R^4	Yield (%)
2-Naphtyl	H	H	H	H	98
2-Naphtyl	H	Me	H	Me	96
2-Naphtyl	Me	H	H	H	99
2-Naphtyl	Me	Me	H	Me	96
2-Naphtyl	H	Me	Me	—	No reaction
2-Naphtyl	Me	Me	Me	—	No reaction
Ph	H	Ph	H	Ph	84
Ph	H	H	Ph	Ph	97
Ph	Ph	H	H	H	3

Scheme 19



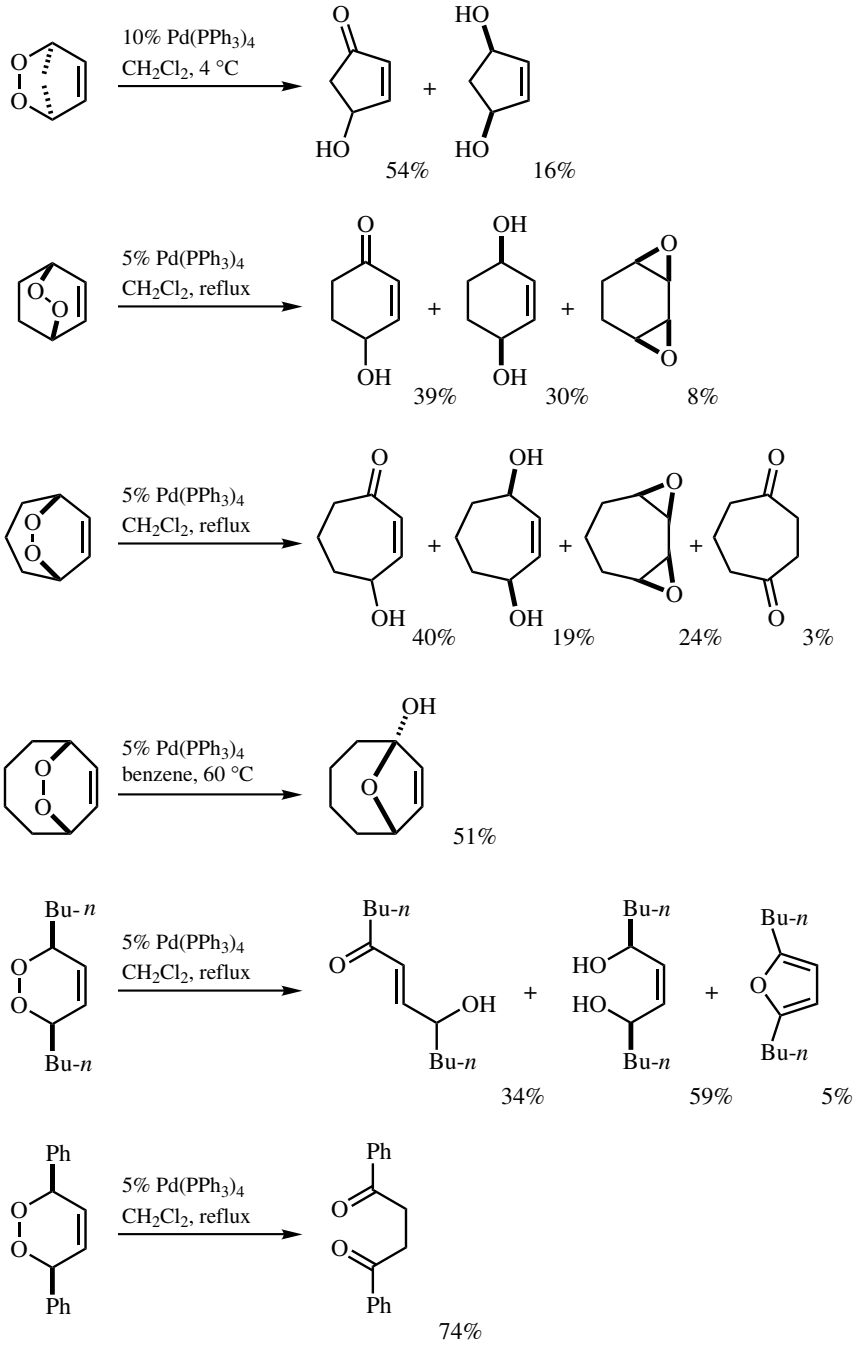
Scheme 19 (*Continued*)



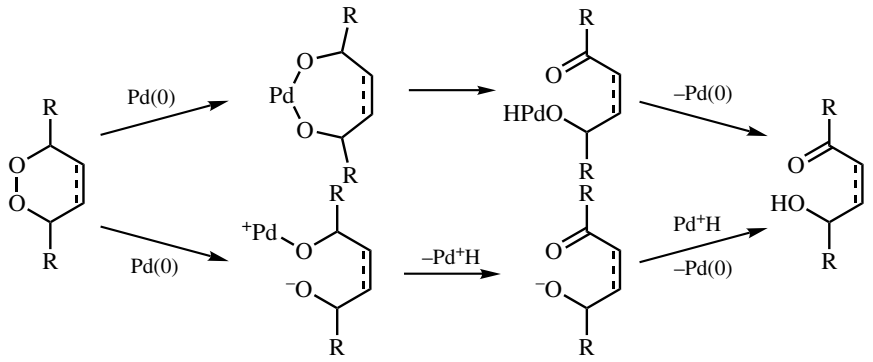
Scheme 20

1,4-diols. Some examples are shown in **Schemes 20** and **21**, respectively. The reactivity of the substrates is dependent on the ring systems.

The epiperoxides-to-hydroxy enones conversion is best accounted for in terms of a competing Pd(0)/Pd(II) redox mechanism (**Scheme 22**). On the other hand, the formation of diols, diepoxides, and hydroxy enones from monocyclic substrates involves radical

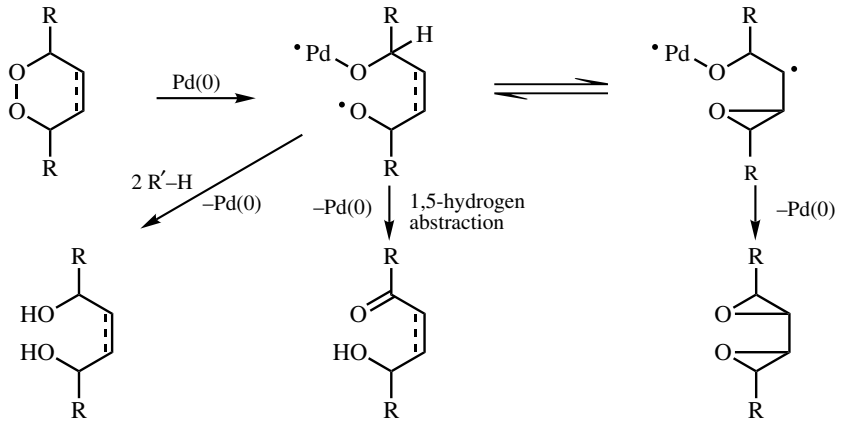

10% Pd(PPh3)4
CH2Cl2, 4 °C
54%
16%
5% Pd(PPh3)4
CH2Cl2, reflux
39%
30%
8%
5% Pd(PPh3)4
CH2Cl2, reflux
40%
19%
24%
3%
5% Pd(PPh3)4
benzene, 60 °C
51%
5% Pd(PPh3)4
CH2Cl2, reflux
34%
59%
5%
5% Pd(PPh3)4
CH2Cl2, reflux
74%

Scheme 21

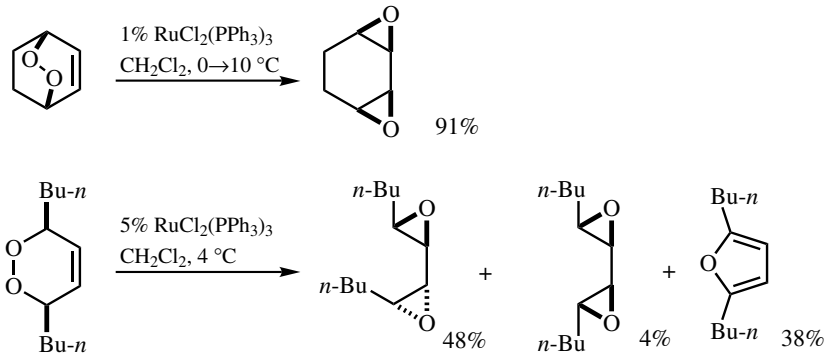


Scheme 22

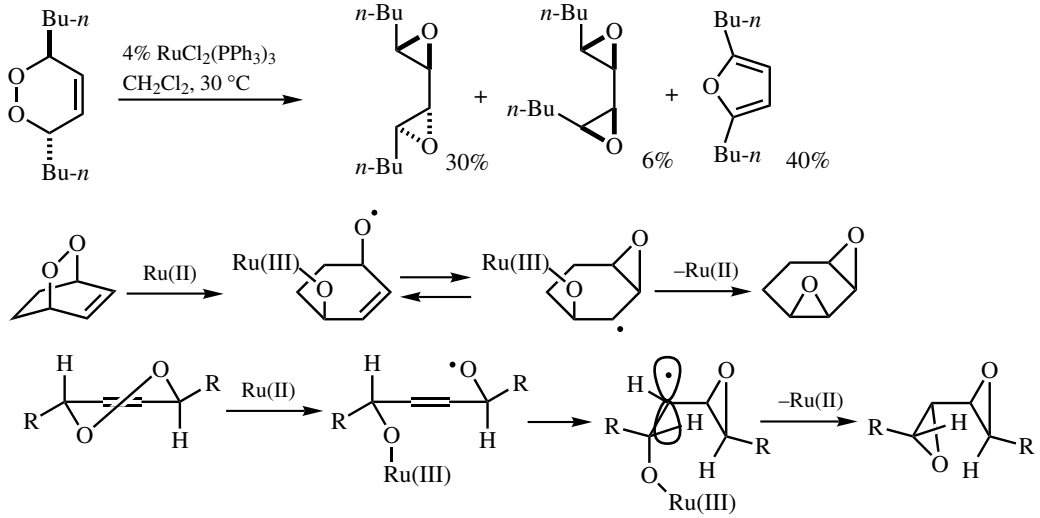
intermediates, which can be explained by a mechanism based on Pd(0)/Pd(I) one-electron exchange (**Scheme 23**). Here, the Pd(0)-catalyzed reaction is compared with that by a Ru(II) catalyst. Interestingly, the reaction of 2,3-unsaturated 1,4-epiperoxides with a Ru(II) catalyst selectively affords diepoxides (**Scheme 24**).[18],[19] This reaction probably proceeds via inner-sphere radical pathways and the stereochemical outcome of the epoxide formation reflects ground-state geometry of the epiperoxide substrates.



Scheme 23

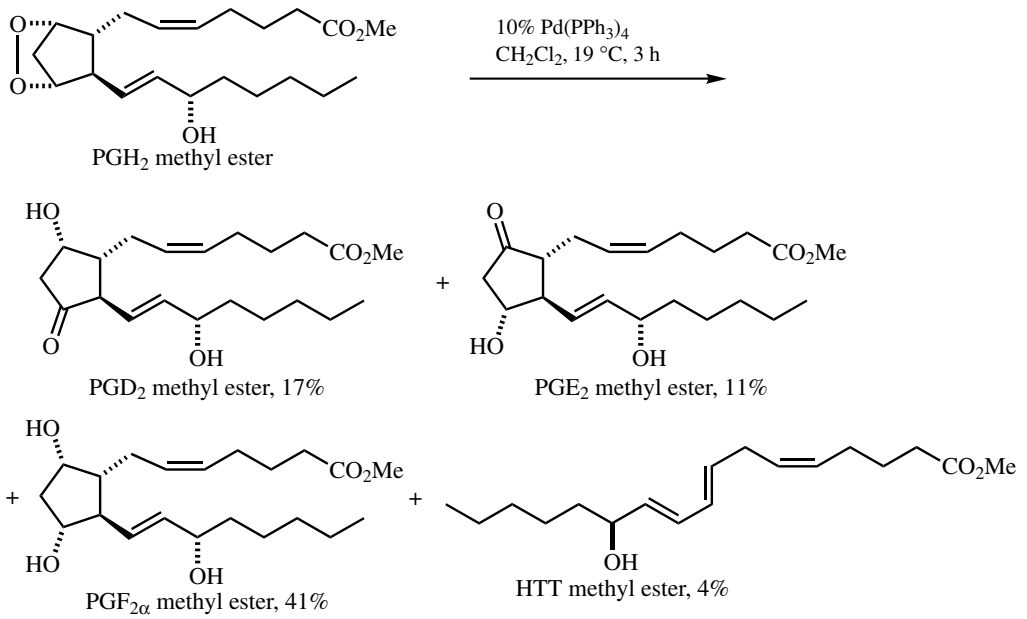


Scheme 24 (*Continued*)

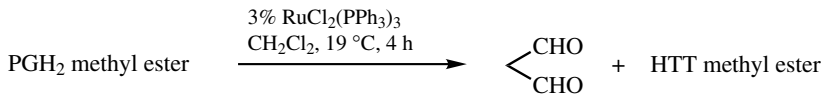


Scheme 24

The catalytic production of the hydroxy ketones and diols from 2,3-saturated 1,4-epiperoxides is formally related to the biogenetic conversion of prostaglandin (PG) endoperoxides (PGGs and PGHs) to primary PG derivatives. Thus, the reaction of PGH_2 methyl ester is exposed to 10% tetrakis(triphenylphosphine)palladium(0) (CH_2Cl_2, 19 °C, 3 h) to give a mixture of PGD_2 (17%), PGE_2 (11%), $PGF_{2\alpha}$ (41%), and (5*Z*,8*E*,10*E*,12*S*)-12-hydroxy-5,8,10-heptadecatrienoic acid (HTT) methyl ester (4%) (**Scheme 25**).[15],[17] This reaction pattern is markedly different from that observed with the reaction catalyzed by Ru(II), giving the HTT methyl ester exclusively.[18],[19]



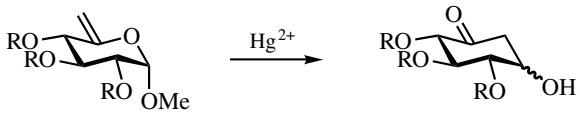
Scheme 25



Scheme 25 (*Continued*)

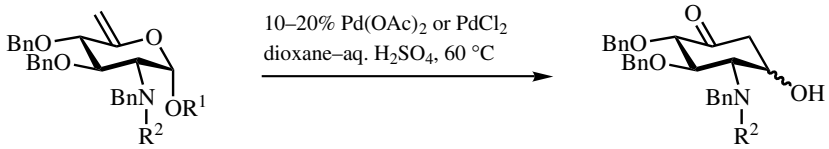
C. PALLADIUM(II)-CATALYZED FERRIER(II) REARRANGEMENT

Highly functionalized cyclohexanes are useful intermediates for the synthesis of natural products and chemical probe compounds having six-membered ring systems. Among preparations of chiral-substituted cyclohexanes, one of the most efficient and intriguing approaches is the conversion of 6-deoxyhex-5-enopyranosides into cyclohexanones, which is known as the Ferrier(II) rearrangement (**Scheme 26**).[20],[21] Although a stoichiometric amount of $HgCl_2$ is used in the original Ferrier(II) rearrangement, the modified reaction conditions are realized by a catalytic amount of Hg(II) salt as an effective promoter.



Scheme 26

An attractive alternative in the similar carbocyclization of amino-6-deoxyhex-5-enopyranoside derivative is reported using $PdCl_2$ or $Pd(OAc)_2$ in the presence of aqueous sulfuric acid instead of poisonous Hg(II) salt (**Scheme 27**).[22]–[24]



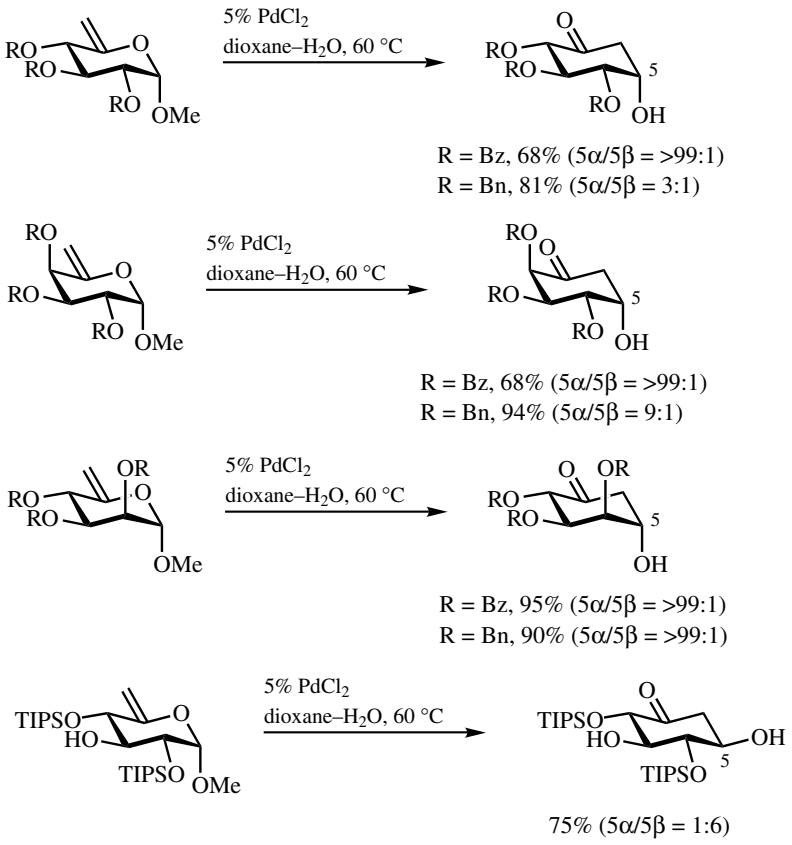
R_1 = Me, R_2 = Cbz or R_1 = Bn, R_2 = Ac

60–80%

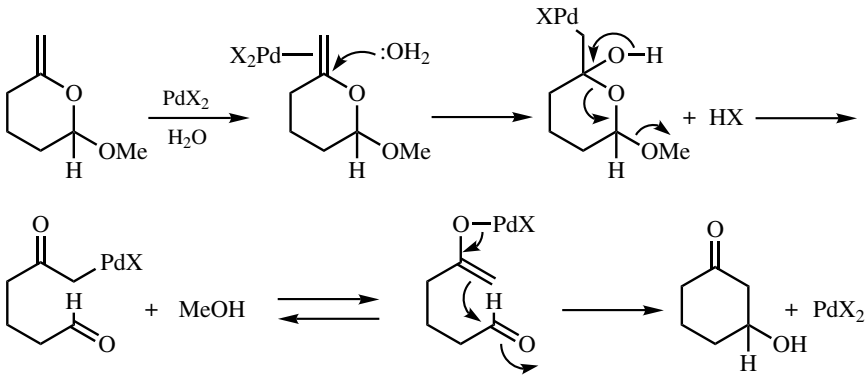
Scheme 27

Systematic investigation of Pd(II)-mediated Ferrier(II) rearrangement for a variety of 6-deoxyhex-5-enopyranosides was reported later, establishing the optimized conditions consisting of the use of 5% $PdCl_2$ in aqueous dioxane solution at 60 °C (**Scheme 28**).[25]

A possible reaction mechanism is shown in **Scheme 29**. All the reactions of benzoyl- and benzyl-protected *gluco*-, *galacto*-, and *manno*-hexenopyranosides under these conditions proceed smoothly to give the corresponding cyclohexanones in excellent yields with high α-stereoselectivities at newly generated C-5 chiral centers. The benzoyl-protected substrates exclusively afford α-anomer. In contrast, 2,4-bis-*O*-triisopropylsilyl-*gluco*-hexenopyranoside shows the opposite β-selectivity. These stereoselectivities are rationally explained by chair-like conformations obtained by molecular calculations.

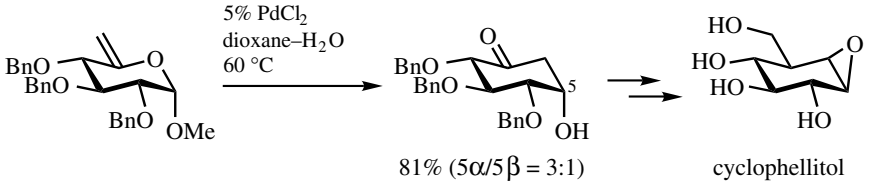


Scheme 28

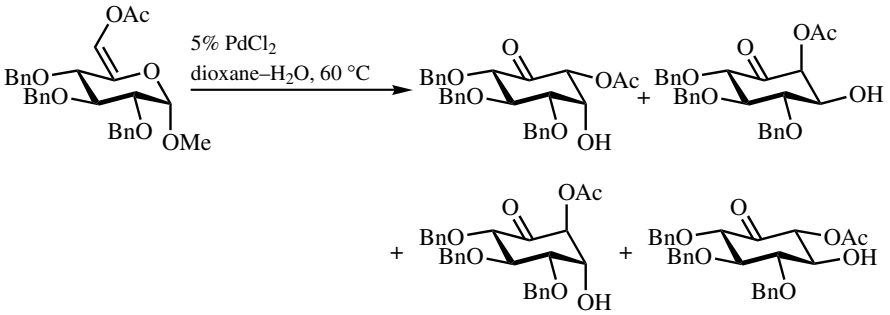


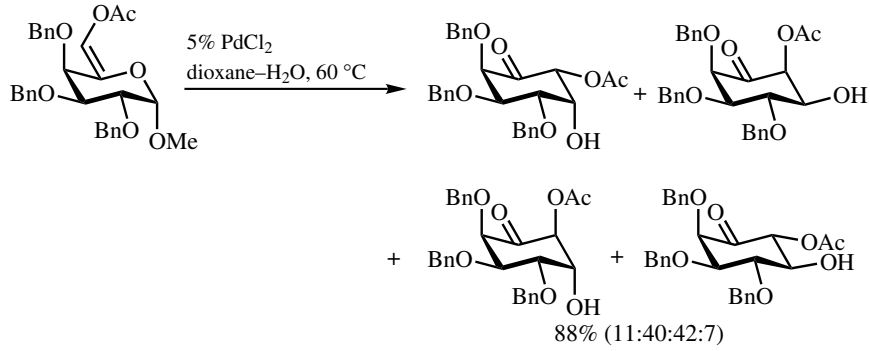
Scheme 29

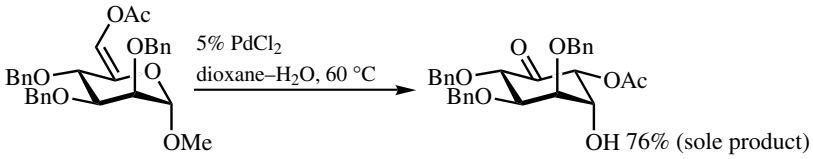
The efficient synthesis of cyclophellitol, a potent β-glucosidase inhibitor, is accomplished by using this method as a key step (**Scheme 30**).[26] Furthermore, this methodology is extended to 6-*O*-acetyl-5-enopyranosides, enabling the conversion to fully oxygenated cyclohexanones (**Scheme 31**).[27] Although glucose- and galactose-derived 6-*O*-acetyl-5-enopyranosides give four diastereomeric mixtures under the above-



Scheme 30







Scheme 31

mentioned conditions, a mannose-derived substrate notably affords a single isomer as a sole product. The synthetic utility of this reaction is demonstrated by the application to the synthesis of D-*myo*-inositol 1,4,5-tris(phosphate) (IP_3) and all stereoisomers of natural inositols.[28]

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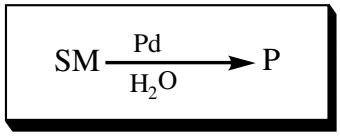
PART X
Technological Developments in Organopalladium Chemistry

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
ISBN 0-471-31506-0



X.1 Aqueous Palladium Catalysis

IRINA P. BELETSKAYA and ANDREI V. CHEPRAKOV

A. INTRODUCTION

The use of water in Pd-catalyzed reactions can be traced to the early research in this field of chemistry. Although unintentionally, it has steadily been developing into a group of methods addressing different challenges including both industrial implementation and applications in fine organic synthesis. This section attempts to comprehensively review the instances of the use of water in palladium catalysts and to elucidate the functions of water.

B. ROLES AND FUNCTIONS OF WATER IN PALLADIUM CATALYSIS

B.i. Water as Solvent

It is a matter of common belief that water is a unique solvent. The reasons for this are multifold. First of all, water is the "solvent of nature." As all biochemical processes are run in aqueous environments, the use of water as solvent in common chemistry may be regarded as biomimetic and biocompatible. Broad implementation of aqueous techniques will reduce the use of toxic and hazardous organic solvents. Therefore, aqueous procedures are often referred to as *green, environmentally friendly,* or *benign*. Besides, such procedures bring in a higher level of technological and occupational safety. Water is a highly polar liquid with polarity unmatched by any other commonly used solvent. Water is amphoteric, capable of lending both electrophilic and nucleophilic assistance, supporting acid or base catalysis.

Water divides everything into the hydrophobic and the hydrophilic manifolds, and places a special sort of matter (surfactants or amphiphiles) as a gate between the immiscible. Thus, water spawns interfacial (e.g., micellar) phenomena, solubilization, encapsulation, and so on, and at the high end the biomembranes.

At last, technical grade water is an economical solvent—cheap, easily available, and recyclable.

Water is compatible with a lot of major organic reactions, including most of the known Pd-catalyzed reactions. The only problem is negligible solubility of a majority of organic compounds in water. This is addressed by using (i) aqueous organic solvents, (ii) phase transfer, and (iii) solubilization. On the other hand, the immiscibility of organic

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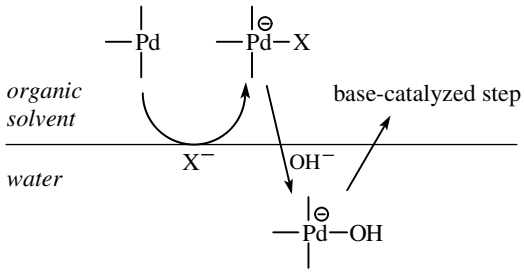
compounds with water is regarded as an advantage in the development of recyclable phase-separation techniques.

B.i.a. ***Aqueous Organic Solvents.*** Mixtures of water with polar organic solvents are often used as media in palladium catalysis. Two things must be borne in mind when analyzing such results. First, organic solvents considered as infinitely miscible with water (MeCN, THF, DME, dioxane, acetone, etc.) may not be miscible with aqueous solutions of electrolytes, as are many bases used in catalytic procedures. For example, while alkali metal acetates unless taken in huge amounts do not cause phase separation, carbonates are well known to do so even at modest concentrations. So, it is not always possible to decide whether a given published procedure involves a homogeneous aqueous organic solvent or a biphasic system.

Second, due to the low molar volume of water, the volume fraction, which is the parameter commonly used for the characterization of mixed solvents, may be misleading if used as a tentative estimate of actual water content in given media. Thus, for example, as low as 5 vol % of water in DMF actually corresponds to as much as 20 mol %, and 20 vol % of water in DMF gives a 1:1 DMF–water mixture. Moreover, the properties of mixtures of water with other solvents are not incremental, since small quantities of water cause dramatic change of properties, while further addition has a milder effect.

B.i.b. ***Phase Transfer.*** Pd-catalyzed reactions involving anionic nucleophiles or inorganic bases are sensitive to phase-transfer catalysis by quaternary ammonium salts and other PTC agents. Besides well-understood explicit phase-transfer phenomena, heterozphasic aqueous Pd-catalyzed reactions often run well in the absence of deliberately added phase-transfer agents. Thus, such reactions may involve implicit phase transfer due to (i) formation of PTC agents from amines, if used as bases, and (ii) amphiphilicity of intermediates of the catalytic cycles. Thus, hydrophobic neutral palladium complexes with regular phosphine ligands may bind halide ions to give charged complexes traveling between phases and engaged in ligand exchange equilibria (**Scheme 1**).



Scheme 1

The addition of agents that, being soluble in water, can extract reagents from the organic phase is sometimes referred to as *reverse phase transfer*, though this phenomenon is a particular case of solubilization. The difference is subtle as the former is associated with binding by large molecules (macrocycles, dendrimers), while the latter is effected by supramolecular aggregates (micelles and more complex unions of molecules). The relatively inexpensive cyclodextrins and their derivatives have been tried to

improve the performance of biphasic systems to help process highly hydrophobic substrates.

B.i.c. ***Solubilization.*** Solubilization is caused by surfactants added in concentrations above the *cmc* (critical micelle concentration) level, which are for common surfactants in the range 10^{-3}–10^{-2} M. When added in concentrations not far exceeding the *cmc* level, the surfactants form micelles either in aqueous phase (normal micelles, formed by strongly hydrophilic surfactants, solubilize organic compounds) or in organic phase (reversed micelles, formed by less hydrophilic surfactants, solubilize water and salts). At the interfacial layer of micelles hydrophobic and hydrophilic components meet and can react. Unfortunately, this phenomenon (micellar catalysis) is of limited practical utility, because the solubilization capacity of micelles is very small (several molecules of solubilizate per micelle composed of hundreds of surfactant molecules).

Also, the addition of surfactants leads to the decrease of surface tension, and thus to an increase of the interfacial area at intense stirring of the mixture. Such a forced dispersion may greatly facilitate mass transfer between phases, which is likely to be the most important factor accounting for the effect of surfactants in heterogeneous process. However, depending on the choice of surfactant the emulsification may ensue, which may strongly interfere with workup of reaction mixtures.

The addition of surfactants in amounts far exceeding the *cmc* leads to the formation of complex systems (gels, liquid crystalline phases, etc.), which are not suitable as media for reactions. However, by the addition of small amphiphilic molecules such as C_2–C_5 alcohols and electrolytes the systems with high content of surfactant transform into stable *microemulsions*, which are transparent nonviscous liquids capable of solubilization of large amounts of hydrophobic matter (1 M and higher), thus resembling regular solvents. Such media do not require the use of special ligands and were shown to be suitable for various Pd-catalyzed reactions (*vide infra*).

B.i.d. ***Recyclable Systems.*** Palladium is an expensive metal, the price of which is subject to unpredictable changes. Thus, any industrial or large-scale laboratory application of palladium depends on the possibility of cutting costs, which can either be done by increasing the catalytic efficiency (TON) or by recycling. It should be noted that these two approaches are equivalent: from the economic viewpoint, the same end is achieved by using a single reaction with 0.01 mol % Pd or a recyclable reaction with 1 mol % Pd and 1% leaching. A real recyclable process is always a compromise between the rate and the extent of leaching.

Recycling is achieved by anchoring the catalyst to a different phase than the phase that holds the main products of reaction. Liquid–liquid or solid–liquid systems are possible.

Biphasic liquid–liquid systems require the use of strongly bonded hydrophilic ligands to hold the palladium in the aqueous phase. The discussion of such ligands can be found in **Sect. C**.

The major drawback of biphasic systems is the slow mass transfer between immiscible phases. The actual processes in such systems usually take place in the aqueous layer, where the catalyst resides. Thus, organic reagents must possess a certain solubility in water, otherwise the rate would be negligible. In order to overcome this restriction, mass transfer is facilitated by (i) solubilization or reverse phase transfer (cf. above) by addition of surfactants or macrocyclic hosts or (ii) increasing the area of contact between phases by supporting a thin layer of the aqueous phase over a solid support. The latter concept is

referred to as *supported aqueous phase catalysis* (SAPC). The difference between SAPC and common supported catalysts is that in the former there is always a liquid phase layer of measurable thickness on the surface of the support, so the molecules dissoved in this liquid retain a certain degree of mobility.

Hydrophilic phosphines can also be used to form palladium complexes, which can be absorbed on the surfaces of hydrophilic supports, such as silica. In this case, the catalyst is fully immobilized, though not chemically bonded, so it can easily leach to any polar solvent. Such an approach is referred to as *glass bead technology*.[1] Here water is used only in the process of preparation of the catalyst, which is impregnated onto the support in aqueous solution.

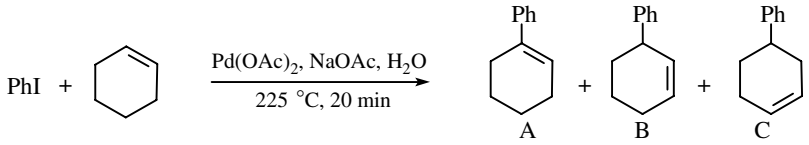
Recyclable processes can also be designed when aqueous media are used with catalysts chemically bonded to hydrophilic supports. The examples of such can be found in **Sect. C.v**.

At last, it should also be noted that activated charcoal is a support compatible with aqueous media. Wettability of charcoal is accounted for by residual carboxylic groups present at its surface.[2] So, Pd/C makes a good recyclable phosphine-free catalyst applicable to aqueous chemistry.

B.i.e. ***Hydrophobic Effect.*** Hydrophobic organic molecules are prone to fold inside to populate more compact conformations when put into aqueous environments. The same can be said about the transition states. Thus, water may have an effect similar to the effect of high pressure, so that it may accelerate those steps in catalytic cycles that have a negative entropy of activation (oxidative addition, insertion, etc.), particularly in intramolecular cyclization reactions. Currently, it is not clear what the actual contribution of the hydrophobic effect is in the positive influence of water noted in many Pd-catalyzed reactions. This problem deserves a separate study.

B.i.f. ***Modification of Biomolecules.*** One of the rationales for developing aqueous variants of Pd-catalyzed reactions is the elaboration of methods suitable for the modification of naturally occurring compounds in media resembling their native environments. This approach allows one to avoid costly derivatization of natural molecules aimed at rendering them soluble in common organic solvents.

B.i.g. ***Supercritical and Subcritical Water.*** On heating water to the critical point (373 °C, 221 bar) it turns into a nonpolar liquid miscible with hydrophobic organic compounds. Such a solvent could be useful for organic reactions if it were not for the fact that water at such a temperature is a very aggressive reagent itself. Therefore, though some reactions including the Heck arylation have been realized in overheated water, the selectivity of such processes is too low for practical applications.[3],[4] More practical might be overheated water far below the critical point. At 225 °C the dielectrical constant of water is close to that of common polar aprotic solvents like MeCN. At this temperature the Heck reaction of iodoarenes with cycloalkenes, usually considered as hard substrates for Heck chemistry, went smoothly to yield mixtures of arylcycloalkenes with all possible positions of the double bond, though the exposure should be kept short to avoid the products being destroyed by hot water.[5] The addition of tetrabutylammonium chloride had a strong influence on yield and regioselectivity (**Scheme 2**). Anyway, this work is a promising achievement in the development of truly *green* media, as it shows that a good selectivity and conversion can be achieved in pure water in the absence of any cosolvents or solubilizing additives.



	Yield	Ratio A/B/C
Without additives	21%	8:30:62
With 1 equiv Bu_4NCl	40%	67:13:20

Scheme 2

B.ii. Water as Reagent

Water is a moderately reactive nucleophile involved in several well-known catalytic cycles, such as hydroxycarbonylation and Wacker oxidation of olefins. Besides these, palladium, as many other late transition metals, is reactive in the *water gas shift reaction* (WGS reaction) (**Scheme 3**), which is a source of metal hydride complexes. Further transformations triggered by the WGS reaction are versatile.

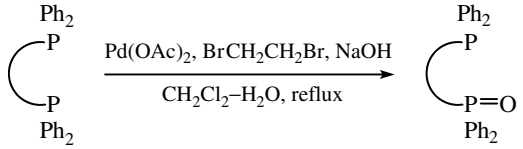
Scheme 3

As water is almost never added to reaction mixtures in stoichiometric amounts, such reactions are usually carried out in the presence of excess water, which at the same time plays the role of solvent or cosolvent.

B.iii. Assistance in the Reduction of Palladium(II)

Water is known to take part in the generation of Pd(0) species in phosphine-assisted processes. Pd(II) is reduced by phosphine giving phosphine oxide, the oxygen atom of which comes from the water molecule. This is particularly important in reactions in the presence of water-soluble phosphines, such as TPPTS.[6]–[9] It is likely that this process is suppressed in acidic solutions, which allows one to use diphosphines, considered as highly sensitive to oxidation, as ligands for oxidation of olefins in oxygen atmosphere.[10]

The water-assisted reduction of Pd(II) by phosphines has been utilized for the development of an expeditious catalytic procedure for the selective oxidation of bidentate diphosphines to monooxides (**Scheme 4**).[11]

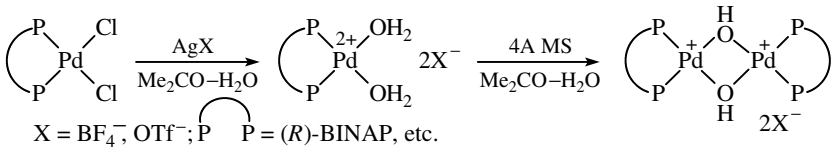


diphosphine = DPPM, DPPE, DPPP, DPPF, BINAP

Scheme 4

B.iv. Water as Ligand

Water is a very strongly bonded but kinetically labile ligand for palladium, at least in the (+2) oxidation state.[12] Even in trace amounts it is preferentially bonded by cationic palladium complexes.[13] Halide ligands can be exchanged for water by the action of silver salts with nonnucleophilic anions in wet solvents.[14],[15] Aquocomplexes are transformed either spontaneously[16]–[19] or in the presence of molecular sieves or alkalies to μ-hydroxocomplexes (**Scheme 5**).[14]

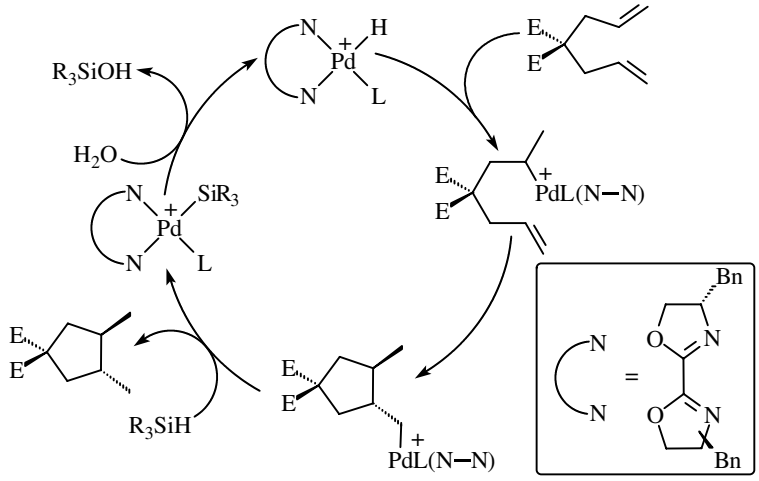


Scheme 5

Both aquo- and bridged hydroxocomplexes are believed to be important intermediates in such catalytic processes as the WGS reaction and the like.[20],[21]

High bonding constant and kinetic lability may account for the major role played by water in reactivation of catalytic species, particularly in phosphine-free reactions. Such species as halide ions and olefins, present in reaction mixtures either as reagents or as by-products, are bonded by palladium to occupy sites in the coordination sphere of the metal, which are required for catalytic activity. Palladium catalyst is thus inhibited by substrates or by-products. Water, being present in huge excess over palladium catalyst, displaces such ligands but is itself displaced by the ligands engaged in catalytic activity, and thus may serve as a placeholder ligand.

An interesting example of the participation of water at the reactivation step of the catalytic cycle has been discovered recently for enantioselective reductive cyclization of diallylmalonate in the presence of chiral bisoxazoline complexes of palladium[22] (**Scheme 6**).



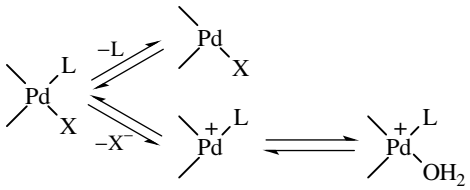
Scheme 6

An entirely different mode of interaction of electron-rich cyclopalladated Pd(II) complexes with water has been described, involving the oxidation of Pd(IV) species through oxidative addition of water to Pd(II) with subsequent elimination of dihydrogen.[23] It is not clear whether this process, proved for Pd complex with a very specific coordination sphere, may have a relation to a hypothetical involvement of Pd(II)/Pd(IV) catalytic cycles in the reactions generally considered as Pd(0)/Pd(II) processes (Heck reaction, cross-coupling, etc.), particularly in those involving palladacycles as catalysts.[24]

There is no direct evidence on the interaction of Pd(0) with water. By analogy with Pt(0) and according to indirect evidence on the reactivity, the oxidative addition of Pd(0) to the water molecule with the formation of PdH species can be hypothesized.[25]–[27]

B.v. Water and Phosphine-Free Catalysis

Ligand exchange equilibria are necessarily involved in catalytic cycles. It is generally believed that for palladium chemistry the dissociation–association mechanism of ligand exchange is more probable than the association–dissociation mechanism involving a pyramidal 5-coordinate intermediate. Two distinct possibilities exist for the former—dissociation of neutral ligand giving 3-coordinate neutral complex, or dissociation of negative ion giving 3-coordinate positively charged complex (**Scheme 7**). The first *neutral* pathway is the major mechanism operating in the proceses catalyzed by complexes with monodentate phosphine ligands, while the second *cationic* pathway is believed to be operative in reactions catalyzed by strongly bonded bidentate ligands.[28]–[30] It is evident that the cationic route is the only mechanism possible for reactions catalyzed by palladium complexes lacking phosphine or other strongly bonded ligands (*phosphine-free* catalysis). Moreover, the cationic route (a typical S_N1 reaction) should be strongly facilitated by polar protic solvents, in the first place by water, which solvates the leaving anion and may form aquocomplex engaged in further ligand-exchange equilibria belonging to a given catalytic cycle. Thus, it is likely that aqueous systems are best suited for phosphine-free catalysis, and numerous examples discussed below speak in favor of this hypothesis.



Scheme 7

B.vi. Postaqueous Techniques

The success of aqueous techniques in catalysis initiated approaches that mimic their advantageous features while resolving immanent flaws of aqueous chemistry. Polyols (ethylene glycol, glycerol, etc.) and formamide resemble water in many aspects including solvent properties, immiscibility with hydrophobic liquids, and ability to support micellization and solubilization phenomena. Such liquids (e.g., ethylene glycol) are often used as a substitute for water in phase-separation techniques (biphasic, supported liquid phase,

glass bead technology, etc.) using exactly the same approaches, for example, the same hydrophilic ligands.

New phase-separation systems are sought by substituting water for other liquids possessing specific solvent properties reminiscent of those of water. A few include perfluoroorganic liquids (*fluorous* = *fluor*ine + aque*ous* catalysis)[31] and supercritical CO_2.[32],[33] Both require the use of special (fluorophilic) ligands and catalysts having a specific affinity for such liquids.

The so called nonaqueous ionic liquids (molten salts) (Ref. [34] and references therein) were developed as highly polar media resembling water in the ability to accelerate processes involving polar steps (e.g., phosphine-free Pd-catalyzed reactions).

All these approaches may be collectively referred to as postaqueous catalysis.

C. HYDROPHILIC LIGANDS

The transfer of the phosphine-assisted catalytic processes to aqueous media prompts the development of specific hydrophilic ligands. The most important rationale for the application of such ligands is the development of phase-separation techniques. In the biphasic liquid–liquid technique, the hydrophilic phosphine works as an effective extractor of palladium to the aqueous phase. However, numerous recent works coming primarily from Genêt's group (*vide infra*) show that many important Pd-catalyzed reactions can be made to run under very mild conditions in homogeneous aqueous media if carried out in the presence of hydrophilic phosphines—essentially *aqueous phosphine-assisted catalysis*.

Phosphines are hydrophilized by the introduction of either ionic groups (anionic: sulfonate, carboxylate, phopshonate, etc.; or cationic, such as quaternized nitrogen) or nonionic groups that strongly interact with water, such as multiple hydroxyls, carbohydrate, or polyoxyethylene residues. Early results on the preparation and application of hydrophilic phosphines were reviewed.[35] It should be noted that only a few of the numerous ligands listed below have so far been tried in Pd-catalyzed reactions. However, because no theory can predict which is the best catalyst or ligand for a given reaction, random screening of a large manifold and a good assortment of already available structures can help.

C.i. Anionic Phosphines with Sulfo Groups

Before discussing the ligands themselves, we note that the behavior of catalytic systems containing ionic hydrophilic phosphines may depend on ionic strength, the type of counterion, and other such factors, which are usually overlooked in organic and organometallic chemistry. Such effects were noted for Rh/TPPTS-catalyzed hydroformylation[36]–[38] but were never explicitly investigated for Pd-catalyzed reactions.

Among the family of hydrophilic phosphines, the sulfonated triphenylphosphines are the most important. Such molecules can be obtained either by sulfonation of phosphines bearing aromatic rings or by substitutive methods.

The sulfonation of aromatic rings attached directly to phosphorus requires the use of oleum due to deactivation of the ring by protonated phosphorus atom. The sulfo group enters the *meta*-position. A certain degree of care must be taken when comparing results obtained with sulfonated ligands from different sources, as the sulfonation of even the

simplest phosphines actually gives mixtures of structures with different degrees of sulfonation, plus the respective phosphine oxides in variable ratios.

Depending on conditions, the sulfonation of Ph_3P leads to three possible products: $Ph_xP(m\text{-}C_6H_4SO_3Na)_{3-x}$ ($x = 2$, TPPMS[39]; $x = 1$, TPPDS[40]; $x = 0$, TPPTS[41]–[43]). TPPTS is a strongly hydrophilic ligand possessing a huge solubility in water (up to 1100 g/L). TPPMS is sparingly soluble in water (80 g/L) and behaves more like an amphiphile; thus, in the solid state the packaging of its molecules[39] resembles a typical bilayer, which is the mode of aggregation of surfactant molecules. Otherwise, practically nothing is known about the difference of these three ligands in various reactions. TPPMS is often preferred simply because it is more easily accessible. The procedure for the preparation of TPPTS is sophisticated and poorly reproducible. TPPDS ligand has recently been proposed as it is believed to closely match TPPTS but can be obtained by a reproducible and reliable procedure.[40] A direct comparison of sulfonated triphenylphosphines in a biphasic Heck reaction of PhI with methylacrylate has shown that the performance of all three ligands is almost identical. However, this model reaction is too easily catalyzed by virtually any Pd-containing material to serve as a truly rigorous test.[40]

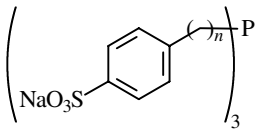
The sulfonation of tris(4-fluorophenyl)phosphine achieved by a prolonged exposure to 25% oleum leads to disulfonated derivative. The ligand is claimed to possess an enhanced π-acidity.[44] Sulfonation of bidentate phosphines DPPE (tetrasulfonated ligand DPPETS)[45] and DPPP (tetrasulfonated ligand DPPPTS),[46],[47] as well as such chiral ligands as (*S*,*S*)-cyclobutaneDIOP, (*S*,*S*)-BDPP, (*S*,*S*)-CHIRAPHOS, and (*R*)-PROPHOS[46],[48],[49] leads to complex mixtures of products with variable degrees of sulfonation. Sulfonation of (*R*)-TolBINAP has been reported to give a pure tetrasulfonated product with sulfo groups being attached to tolyl residues.[10] Though scarce data are available on enantioselectivity of reactions with chiral sulfonated phosphines, a rule of thumb is that it is degraded with the degree of sulfonation, possibly because sulfonated ligands are less strongly bonded to metal, thus enabling partial dechelation and loss of asymmetric configuration.

The sulfonation of phosphines in which aryl rings are not directly bonded to phosphorus runs much faster and smoother, giving mostly *para*-substituted molecules. Such ligands include the hydrophilized analogs of highly σ-donor trialkylphosphines **1**,[50] tetrasulfonated bis-diphenylphosphinopropane DPPPTS,[51] the sulfonated ligand with chiral methyl pendant **2**,[52] tridentate ligand SULPHOS,[53] phosphanorbornadiene derivative NORBOS,[54] and a selection of ligands bearing sulfonated benzofuranyl residues including an analog of chiral ligand MeOBIPHEP[55] (**Scheme 8**).

Among other sulfonated chelating phosphines are ligands BISBIS,[56] BINAS, and highly hydrophilic exhaustively sulfonated BINAS-6[57]–[59] (**Scheme 9**).

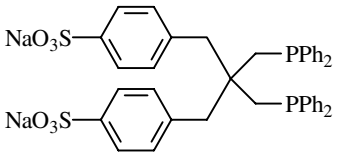
Besides electrophilic sulfonation, sulfonated phosphines can be produced by nucleophilic substitution reactions using PH_3, primary or secondary phosphines, and fluoroarenes in superbasic media. This method has been applied for the synthesis of *para*-isomer of TPPTS (*p*-TPPTS) (**Scheme 10**)[60] as well as dozens of other interesting ligands including chelating, chiral, and amphiphilic phosphines (a selection is in **Scheme 11**).[61]

The properties of *p*-TPPTS ligand were shown to be closer to those of unsubstituted Ph_3P than to TPPTS with *meta*-sulfonato groups. The cone angle of *p*-TPPTS ligand turned out to be smaller than that of TPPTS, and close to that of Ph_3P. Thus, a skewed position of sulfonato groups in TPPTS is indeed the main factor defining a large steric bulk of this ligand, since charged groups with their hydration shell are engaged in internal rotation and each sulfonatophenyl residue occupies a wide cone, repulsing two other residues.

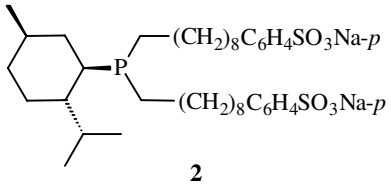


n = 1, 2, 3, 6

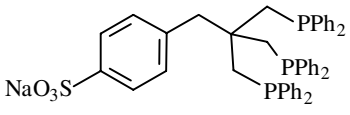
1



DPPPDS



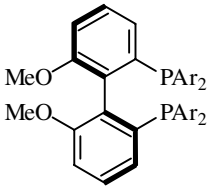
2

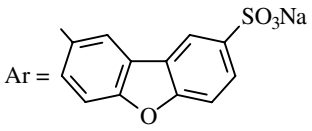


SULPHOS

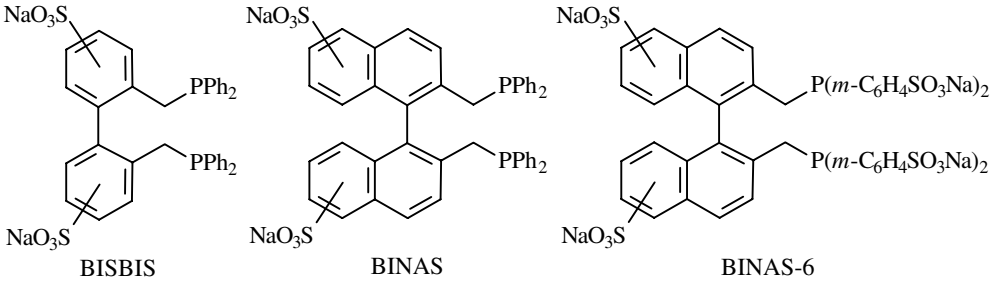
Ph_nPAr_{3-n}

n = 0–2

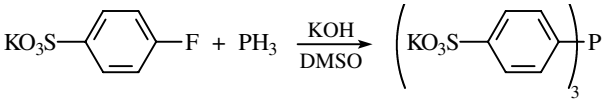




Scheme 8



Scheme 9

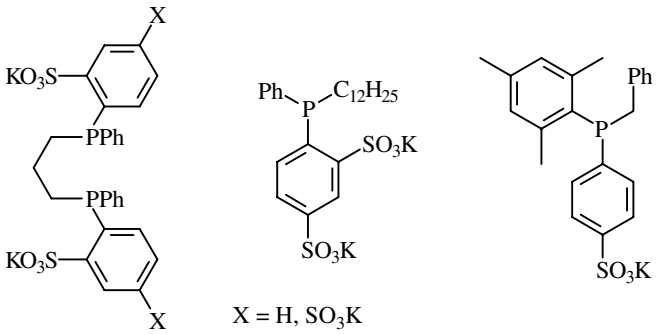


Scheme 10

Aliphatic phosphines with sulfo group in a side chain $Cy_2P(CH_2)_2SO_3Na$[62] and $Ph_2P(CH_2)_nSO_3Na$ (n = 2, 3, 4)[63],[64] have been prepared. The first may have a certain value as a hydrophilized electron-rich bulky ligand.

C.ii. Other Anionic Phosphines

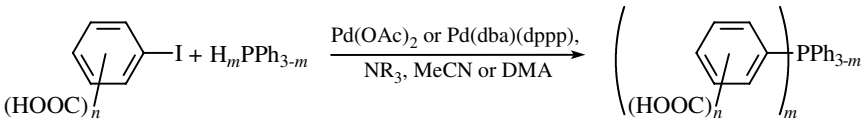
A vast number of phosphine ligands bearing carboxylic groups were described, including the industrially important ligand Ph_2PCH_2COONa,[65] and a series of derivatives of triphenylphosphine with one, two, or three carboxyphenyl groups.[66] The most general



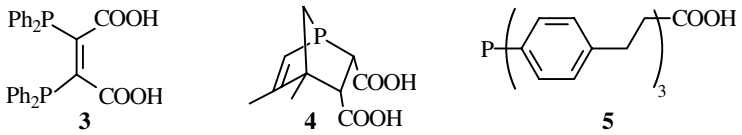
Scheme 11

methods leading to this group of ligands are a cross-coupling of haloarenes with phosphines (**Scheme 12**)[67],[68] or free-radical addition of primary or secondary phosphines to unsaturated acids.[69],[70]

Several other interesting ligands of this series have been published as **3**,[71] **4**,[72] and **5**[73] (**Scheme 13**).



Scheme 12



Scheme 13

Unlike sulfonated phosphines, which retain water solubility at any pH of the reaction mixture, carboxylated phosphines can be used only in alkaline solutions.

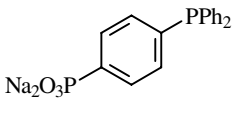
Examples of phosphines bearing anionic phosphonato groups include the derivatives of triphenylphosphine: *p*-TPPMP,[74],[75] two isomers of TPPDP,[76] and the derivatives of phosphanorbornadiene **6** and **7** (**Scheme 14**).[54]

A simple and convenient method leading to tris-phosphonatophenylphosphine *p*-TPPTP ligand has been proposed only very recently, making this ligand one of the most easily available choices for research in aqueous catalysis (**Scheme 15**).[77]

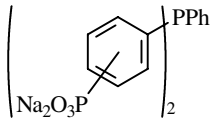
All these phosphines are readily soluble in water, the most hydrophilic being not TPPTP but *p*-TPPDP, the solubility of which matches the solubility of TPPTS.

C.iii. Cationic Phosphines

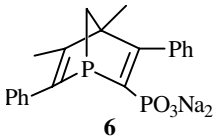
So far, hydrophilic phosphines with cationic groups have received scarce attention in the area of palladium catalysis. However, such ligands may have serious advantages over the



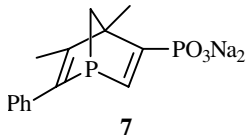
p-TPPMP



meta: *m*-TPPDP; *para*: *p*-TPPDP



6



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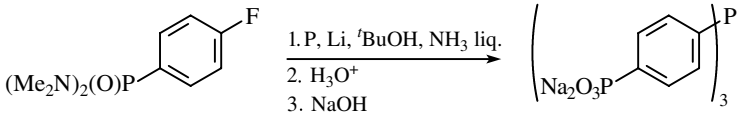
Scheme 14

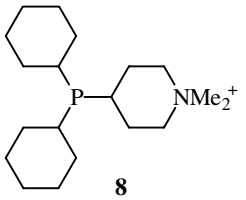


Scheme 15

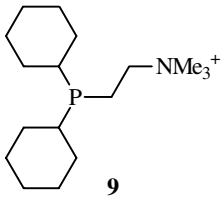
sulfonated phosphines. There are indications that the introduction of cationic groups makes both the ligands and catalytic systems based on them less sensitive to oxidation by air.[78],[79] The hydrophilicity (amphiphilicity) of such molecules can be controlled by variation of acidity or counterion.

A number of cationic phosphines containing quaternized nitrogen or phosphorus atoms has been examined; among them are $Me_3N^+–(CH_2)_2–PPh_2$ (AMPHOS)[80]; $R_3N^+–(CH_2)_m–PH_2$ (R = Me, *n*-Bu, etc.; *m* = 2, 3, 6, 10, 11)[78]; $Ph_2P(CH_2)_nPMe_3^+$, (PHOPHOS, *n* = 2, 3, 6, 10)[81],[82]; aliphatic phosphines **8** and **9** structurally similar to PCy_3[62]; and chiral bisphosphine **10**[83] (**Scheme 16**).

Several ligands modified with guanidyl residues have been obtained, including ligands **13–15**, which are structurally similar to sulfonated triphenylphosphines (**Scheme 17**) [79],[84],[85]



8



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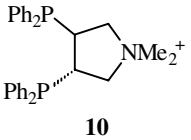
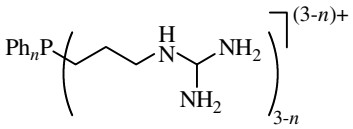
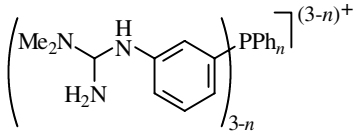


10

Scheme 16



11 (*n* = 1); 12 (*n* = 2)

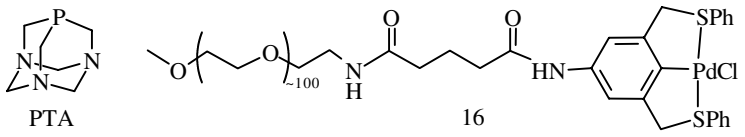


13 (*n* = 0); 14 (*n* = 1); 15 (*n* = 2)

Scheme 17

Due to the high basicity of guanidyl residue, the ligands are not deprotonated in aqueous alkaline solutions. However, the solubility of such ligands depends on the counterion: large anions like I^- or PF_6^- may precipitate poorly soluble salts.

Less basic neutral nitrogen-containing ligands have been developed in order to make ligands capable of dual behavior: in the presence of acids such ligands and their complexes reside in the aqueous phase, while on the addition of stronger base the ligands may be extracted to organic solvents, thus furnishing recyclable systems with controllable amphiphilicity. Examples of such ligands include aminoalkylphosphines,[86],[87] monodentate phosphines with pyridyl or aminophenyl residues,[88],[89], and chelating phosphines analogous to BISBI with such residues.[90] A very interesting neutral nitrogen-containing ligand is 1,3,5-triaza-7-phosphaadamantane (PTA) (**Scheme 18**), easily obtained by a reaction of trihydroxymethylphosphine with hexamethylenetetramine.[91],[92] PTA, which is soluble in water and renders its complexes hydrophilic, is reported to be stable to oxidation.



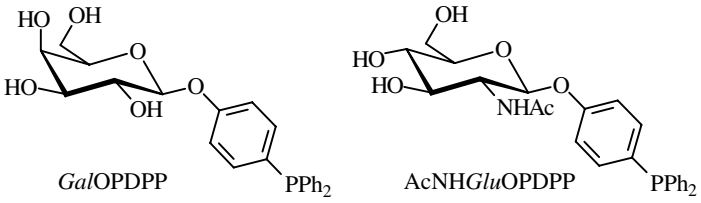
Scheme 18

C.iv. Neutral Amphiphilic Ligands

Besides ionic or ionizable groups the hydrophilicity can be imparted by such strongly hydrated residues as multiple hydroxy groups or polyoxyethylene tails of considerable length. According to rough empirical correlations used in surfactant theory to predict the hydrophile–lipophile balance of a given molecule, the hydrophilicity of a typical ionic group (sulfonate, carboxylate, etc.) is approximately an order of magnitude higher than that of a hydroxy group, and two orders of magnitude higher than the hydrophilicity of a structural unit CH_2CH_2O of polyethylene glycol (PEG). As a result, the ligands bearing such nonionic residues are usually less hydrophilic than ionic ligands and are partitioned between aqueous and organic phases. The main advantage of such ligands is that their hydrophilicity is variable and can be controlled.

Recycling of ligands or catalysts based on nonionic hydrophilic residues can be effective because the dehydration (desolvation) of such molecules leads to their precipitation into a separate phase soluble in nonpolar liquids. Desolvation is easily effected by heating (thermomorphicity) or addition of agent (e.g., ether), which competes for the molecules of the solvation shell.[93] An example of such a catalyst is the PEG-bound SCS-palladacycle **16** (**Scheme 18**), successfully used in the recyclable Heck reaction.[94]

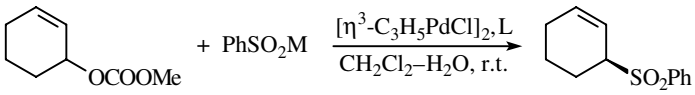
Besides recycling, the variation of hydrophilicity of a thermomorphic ligand with temperature can be used for boosting the catalytic efficiency of a biphasic reaction. At elevated temperature of reaction, the catalyst goes to the organic phase, where the reaction takes place, thus lifting the solubility limitations. On cooling, the catalyst returns to the aqueous phase for recycling. An example of such a process has been reported with phosphine ligands attached to natural carbohydrates D-galactose or D-*N*-acetylglucosamine (**Scheme 19**). A tenfold increase of TON was obtained in a biphasic Heck reaction with these ligands as compared to the same reaction in the presence of TPPTS ligand.[95]



Scheme 19

The attachment of phosphines to carbohydrate residues can give not only recyclable but also enantioselective catalysts, in which chirality transfer occurs not from the phosphine part but from the carbohydrate. An example of such a ligand—the disaccharide trehalose modified with two diphenylphosphine residues to give a bidentate phosphine—has been published, though so far it has been used only for Rh-catalyzed recyclable enantioselective hydrogenation.[96] This approach may be fruitful if tested for palladium catalysis.

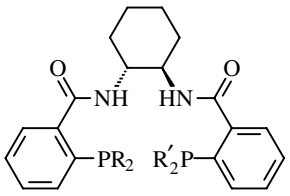
In some cases the modification pursued other goals, for example, to impart not only hydrophilicity but also phase-transfer properties due to the ability to bind alkali metal or other cations, as in the case of PEG or crown ether-substituted phosphines.[97]–[99] The behavior of such catalytic systems can reveal very fine effects, such as those associated with the preferential bonding of countercations. Thus, in an enantioselective allylic substitution catalyzed by chiral bidentate phosphines **L1**–**L3** in a biphasic system, high yields and ee were obtained only with ligands **L2** and **L3** modified with a short polyether residue, while the parent hydrophobic ligand **L1** failed (**Scheme 20**). A strong dependence of the performance of the catalytic system on the nature of the countercation was observed, by far the best being Na, which is the most strongly bonded cation by open-chain polyethers. Thus, the polyether-modified ligands served as ion pumps, delivering ionic reagent from the aqueous to the organic phase.[100]

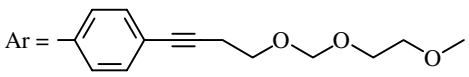


M = Li, Na, K, NH_4; L = **L1**–**L3**

L	Time	Conversion
L1	180 min	15%
L2	<10 min	50%

M	Time	L	Yield (%)
Li			40
Na	1 h	L2	90
K			10
NH_4			5

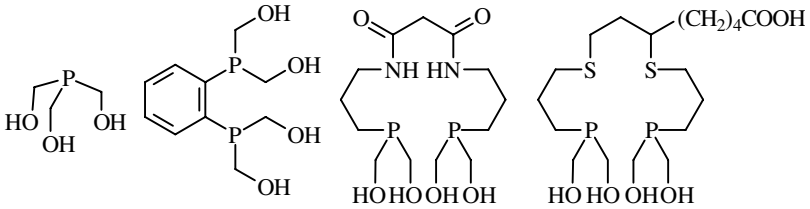




L1: R, R′ = Ph
L2: R = Ph; R′ = Ar
L3: R′ = Ar

Scheme 20

The most general way to attach phosphine residues to carbohydrates, polyols, or PEG is allylation with subsequent free-radical addition of primary or secondary phosphines.[69],[70] The hydroxymethylation of PH bonds is the other general method of preparation of a large number of interesting hydrophilic phosphines, some examples of which are given in **Scheme 21**, which were recently obtained and characterized, though they have not yet found their place in catalysis.[101]



Scheme 21

C.v. Immobilized Hydrophilic Ligands

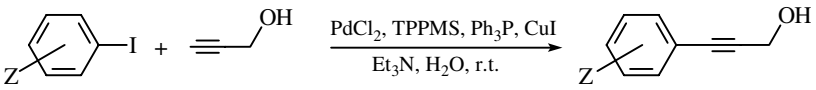
Phosphines can be tailored to hydrophilic polymers such as polyacrylic acid or polyethyleneimine[102] to give water-soluble polyligands, the advantages of which over monomeric ligands are not clear. More practical are amphiphilic block-copolymer supports, consisting of a hydrophobic resin such as polystyrene, to which hydrophilic polymer endcapped with phosphine is grafted. The beads of such a polymer are wettable by aqueous solvents and so can expose their phosphine centers as ligands for immobilized recyclable catalysts (*vide infra* **Scheme 49**).[103]–[105] Another solution for designing a recyclable polymeric support is thermomorphic polymer, such as polyacrylamide, part of a hydrophilic amido groups that are modified with hydrophobic alkyl residues. The resulting polymer is amphiphilic with hydrophile–lipophile balance depending on temperature, which makes it suitable, after attaching phosphine residues, to serve as a recyclable thermomorphic ligand in aqueous reactions.[93],[106]

D. WATER IN VARIOUS PALLADIUM-CATALYZED REACTIONS

D.i. The Sonogashira Reaction and Other sp–sp^x Couplings

Pd-catalyzed cross-coupling of aryl (vinyl) halides or triflates with terminal acetylenes is commonly performed in anhydrous solvents in the presence of tertiary amines in the presence of CuI or other Cu(I) salts as cocatalysts. The main problem in optimizing the conditions for cross-coupling reactions with acetylenes is the relatively high reactivity of triple bond toward palladium activation, which results in an excessive formation of by-products (usually formed via nonselective oligomerization pathways) without the involvement of organic halide. As shown below, aqueous techniques often help to eliminate this obstacle and to achieve selective cross-coupling, giving high yields of target products.

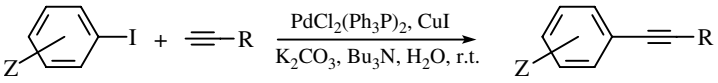
The reaction of both water-soluble and water-insoluble aryl iodides and hydrophilic propargyl alcohol can be performed in water in the presence of either TPPMS or Ph_3P ligands, and CuI. Thus, this process actually runs in a heterogeneous system (**Scheme 22**).[107]



Z = *p*-COOH, *m*-COOH, *p*-NO_2, *p*-MeCO

Scheme 22

The participation of hydrophilic phosphine ligand is not necessary. The reaction can be catalyzed by water-insoluble complex $PdCl_2(PPh_3)_2$ in the presence of a stoichiometric amount of inorganic base K_2CO_3 and a substoichiometric amount of Bu_3N, which apparently performs the role of phase-transfer agent (**Scheme 23**).[108] Alternatively, the reaction can be run in aqueous microemulsion.[109]

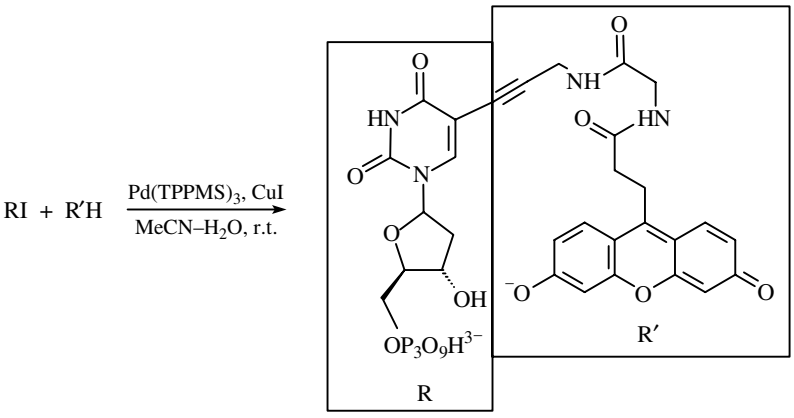


Z = H, NO_2, CN, MeCO;
R = Ph, *n*-C_5H_{11}, *p*-$C_9H_{19}C_6H_4$

Scheme 23

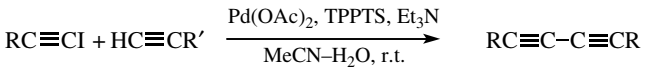
The reaction can be performed with acetylene generated *in situ* from CaC_2. A similar reaction was reported later with acetylene gas in aqueous MeCN, giving symmetrical tolanes.[110]

TPPMS complex of palladium complex is an excellent catalyst for the cross-coupling of acetylenes with iododerivatives in aqueous acetonitrile solvent under very mild conditions (room temperature or gentle heating) applicable to the derivatization of complex and fragile natural compounds. Thus, the method was applied for the convergent synthesis of a chain-terminating nucleotide reagent carrying a fluorescent dye unit (**Scheme 24**). Both the triphosphate residue and the dye fragment tolerated the reaction conditions, in sharp contrast with the commonly used processes in organic solvents, in which such fragile groups have no chance of survival.[39]



Scheme 24

TPPTS ligand is also very efficient in homogeneous aqueous media. The reactions are performed at room temperature, either with or without copper salts.[111] The absence of copper salts is very important if the reaction is to be made recyclable, though this has not been further investigated. Mild conditions allow one to use this method for the cross-coupling of iodoacetylenes with terminal acetylenes to afford diynes,[112] which could not endure the elevated temperatures and strong bases used in standard nonaqueous procedures (**Scheme 25**).

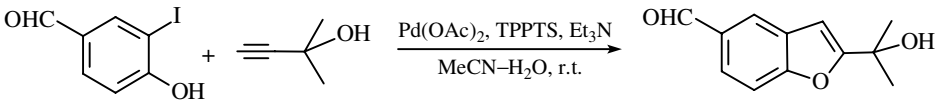


R = ^{n}Bu, R′ = CMe_2OH; R = Me_3Si, R′ = $CH(OH)CH_2{}^nBu$;
R = Me_3Si, R′ = CMe_2OH; R = CEt_2NH_2, R′ = $CH(OH)CH_2{}^nBu$;
R = ^{n}Bu, R′ = Ph.

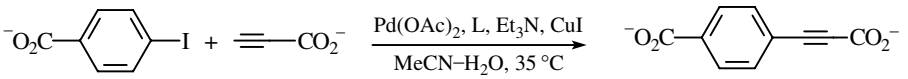
Scheme 25

The same catalytic system was used for cross-coupling of terminal acetylenes with *o*-iodophenols and anilines giving the cyclization products, 2-substituted furanes and indoles, in high yields (**Scheme 26**).[112]

Later, cationic phosphines with guanidinium groups **11**–**15** were used as ligands for aqueous cross-coupling of water-soluble acetylenes and aryl iodides.[79],[84],[85] The structural analog of TPPTS ligand **13** outperformed the former, giving higher conversions in less time (**Scheme 27**). However, it should be noted that the amount of this expensive ligand (25 mol %) required for reaction is prohibitively high, as the recycling of the catalyst from the reaction mixture described seems impossible.



Scheme 26



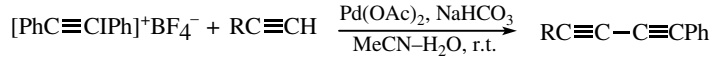
L	Time	Yield (%)
TPPTS		48
13	30 min	95
14		30

Scheme 27

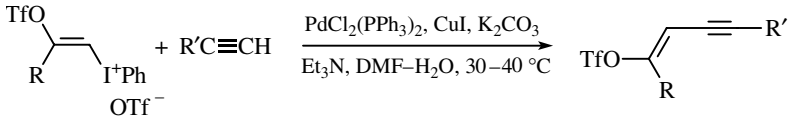
Aqueous media are often used for reactions with hypervalent iodine compounds. A number of mild and selective methods for arylation of acetylenes by diaryliodonium salts have been published. In neat water the reaction is run at room temperature in a heterogeneous system ($PdCl_2(PPh_3)_2$, CuI, K_2CO_3, 10 mol % Bu_3N) and must be assisted by amine base, which possibly additionally serves as PTC agent.[113]

Iodonium salts with alkenyl or alkynyl groups are cross-coupled with acetylenes in homogeneous aqueous solution by phosphine-free catalyst to give diynes and enynes (**Scheme 28**).[114]

The remarkable selectivity of this method allowed one to engage the alkenyliodonium salt bearing an additional triflate group, which remained intact in the product.[115]



Scheme 28



R = H, CH_2OMe, Ph, ^nBu; R′ = Ph, CH_2OMe, $SiMe_3$, CH_2Cl, etc.

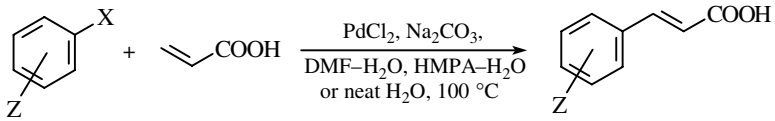
Scheme 29

D.ii. Heck Reaction

The Heck reaction can be accomplished under phase-transfer conditions with inorganic carbonates as bases under very mild conditions even at room temperature. The reactions were carried out in a liquid–liquid system composed of aqueous solution of base and organic reagents without organic solvent.[116] Later, this method was developed into a common-purpose Jeffery–Larock protocol. It has been shown that, depending on substrates and base, the phase-transfer Heck reaction can be accomplished in either an aqueous liquid–liquid or a nonaqueous solid–liquid system,[117]–[119] though the actual choice between these two techniques is often a matter of taste.

The presence of phase-transfer agents is, however, unnecessary. The addition of water to the organic solvent has often been noted to have a strong accelerating influence on Heck reactions. This influence is more strongly pronounced in phosphine-free reactions, though phosphine-assisted processes are also often notably facilitated.

Water and aqueous organic solvents can successfully be used for carrying out the Heck reaction with acrylic acid or acrylonitrile in the aqueous phase catalyzed by phosphine-free palladium salts for aryl iodides or P(*o*-Tol)$_3$ complex of palladium for aryl bromides in the presence of inorganic bases K_2CO_3, Na_2CO_3, $NaHCO_3$, or KOH (**Scheme 30**).[120]



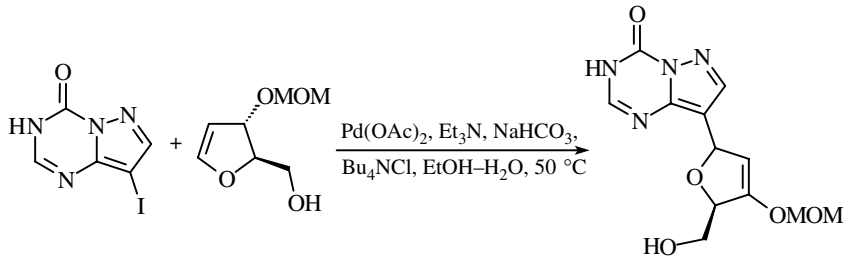
X = I, Br;
Z = H, *p*-Cl, *p*-MeO, *p*-Me, *p*-NO_2, *p*-CHO, *p*-OH, *m*-COOH

Scheme 30

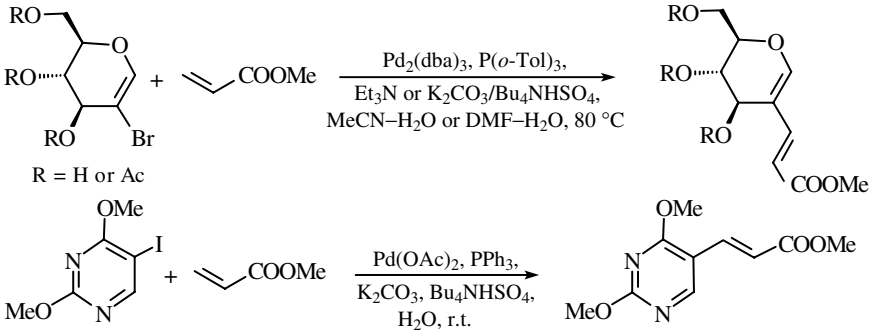
The accelerating effect of water on the rate of the phosphine-free Heck reaction of PhI with methyl acrylate in *N*-methylpyrrolidone solvent has recently been examined to reveal that the addition of water promotes the formation of stable palladium nanoparticles serving as a source of catalyst.[121]

A positive effect of water was observed in Heck reactions of 2,3-dihydrofuranes (e.g., glycals) with iodo- and bromoderivatives of pyrimidines and other nitrogen-containing heterocycles (**Scheme 31**). In several cases the reactions that could not be achieved using a standard method (in anhydrous DMF with Et_3N and NaOAc as base) took place in aqueous ethanol (1:1, v/v) with $NaHCO_3$–Et_3N mixture in the presence of Bu_4NCl with suppression of double bond migration.[122]

Another example of the use of aqueous media for modification of naturally occurring molecules involves a phosphine-assisted Heck reaction (**Scheme 32**).[123],[124]



Scheme 31

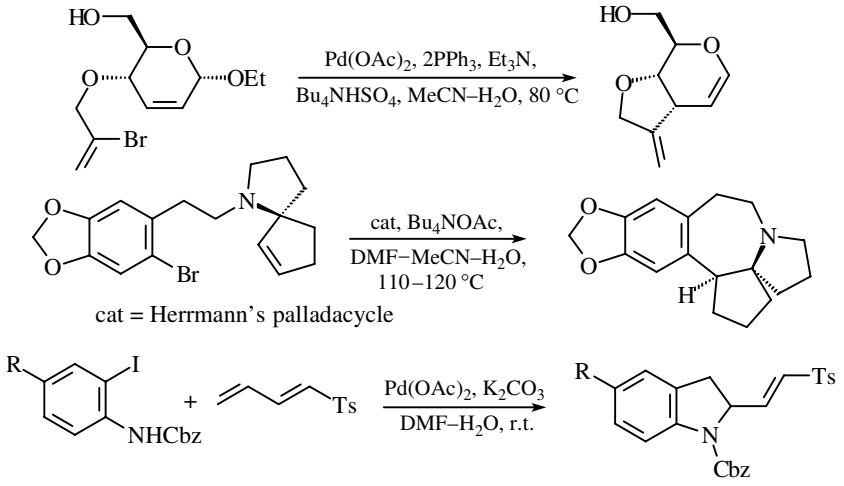


Scheme 32

The aqueous protocol has been applied to combinatorial Heck reactions with resin-bonded iodoarenes,[125] though in such cases water can have a detrimental effect,[126] which is likely due to folding of hydrophobic polymeric support.

Several intramolecular Heck reactions in aqueous media have been published (**Scheme 33**),[127]–[131] though no systematic investigation on the possible effects of water on Pd-catalyzed cyclizations has been done, so it can only be guessed if the hydrophobic effect is responsible.

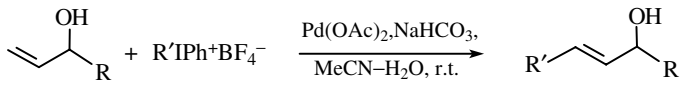
The reactions in neat water without organic cosolvent are restricted to water-soluble reagents or are run in heterogeneous phase-transfer assisted systems. In search of a general approach to process all sorts of substrates—hydrophilic and hydrophobic—in



Scheme 33

aqueous media with high water content but excluding expensive and toxic organic solvents or quaternary ammonium salts, the application of aqueous microemulsions has been proposed for Heck reactions. Solvent properties of such systems were shown to be close to those of aqueous DMF.[132]

Besides iodo- and bromoderivatives, the Heck reaction has been applied to diazonium and iodonium salts, always in phosphine-free processes. The former are usually processed in alcoholic solutions, sometimes in the presence of water.[133] The reactions of aryl and alkenyliodonium salts are done under very mild conditions in aqueous solvents,[134]–[140] which allows one to use this method for selective arylation (alkenylation) of allylic alcohols (**Scheme 34**).



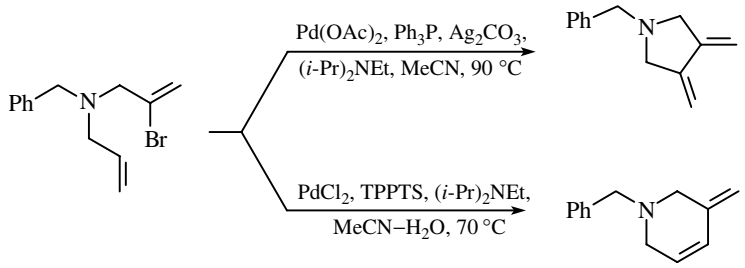
R = H, *n*-C_5H_{11}, $CH(OH)CH_2OBn$

R′ = Ph, $PhCH{=}CH_2$

Scheme 34

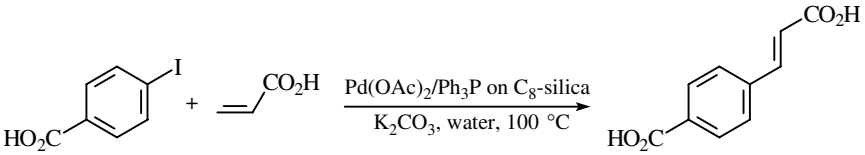
The use of hydrophilic sulfonated phosphines TPPMS[39] and particularly TPPTS[111] allowed development of a very mild procedure for Heck reactions of iodoarenes and iodoalkenes, though this protocol requires a large amount of expensive catalyst, which makes this scheme unsuitable for large-scale reactions. The method showed unusual selectivity trends; for example, in the reactions with cycloalkenes no migration of double bond was reported.[111] Also, a very rare *endo-trig*-mode of cyclization is favored in the aqueous phosphine-assisted method compared to the normal *exo-trig*-mode observed in nonaqueous methods (**Scheme 35**).[141],[142]

Efficient recyclable aqueous systems for the Heck reaction are yet to be discovered. Several biphasic and supported liquid phase systems using ethylene glycol as a substitute



Scheme 35

for water have been described.[143],[144] An interesting supported catalyst for use in aqueous solutions has been developed. $Pd(OAc)_2$ and Ph_3P were impregnated on chromatographic reversed phase sorbent C_8-silica, widely used in HPLC. Such a catalyst is effective in the Heck reaction and allylic substitution with water-soluble and water-insoluble substrates in water and organic solvents and is reusable without appreciable loss of activity (**Scheme 36**).[145]



Scheme 36

D.iii. Suzuki–Miyaura Reaction

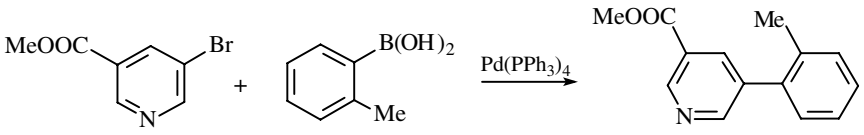
Unlike other cross-coupling reactions, the reaction with boronic acids and other organoboron compounds requires the presence of bases, the role of which is to form an electron-rich intermediate with tetracoordinate boron atom. Inorganic bases (alkali hydoxides, carbonates, phosphates, etc.) are most conveniently used as aqueous solutions, which is not a problem because organoboron compounds are tolerant to protolytic decomposition by water. Therefore, a standard technique of performing the Suzuki reaction[146] is the use of either aqueous solvents or heterogeneous biphasic systems, depending on the miscibility of a given organic solvent with aqueous solutions of inorganic salts. With the first reports, the use of water in this reaction has commonly been unintentional, as no specific advantages had then been sought. Later, it was shown that the presence of water may be an important factor, which has led to the development of aqueous phosphine-free and biphasic phosphine-assisted techniques.

D.iii.a. ***Standard Phosphine-Assisted Protocol.*** The process is done with palladium complexes with hydrophobic phosphine ligands and aqueous solution or a slurry of inorganic base in a biphasic system in which benzene or toluene is the most frequently used solvent. Therefore, it is evident that the process should involve phase transfer, because the precatalyst and organic halide reside in the organic phase, while boronate must be extracted to the aqueous phase. The most probable answer to the question of how the

reaction may proceed in the absence of deliberately added phase-transfer agents is likely to be a certain amphiphilicity of boronates $RB(OH)_3^-$, which may to a small extent be partitioned into the organic phase to sustain the catalytic process. As soon as the feed of boronate into the organic phase is poor, net catalytic efficiency is rather low and ample amounts of phosphine ligands are required to keep palladium species from decomposition to palladium black.

Still, the use of anhydrous organic solvents in the Suzuki reaction often brings no noticeable advantages. In this case it becomes necessary either to use organic bases like Et_3N or to add phase-transfer salts and carry out the reaction in solid–liquid PTC mode.

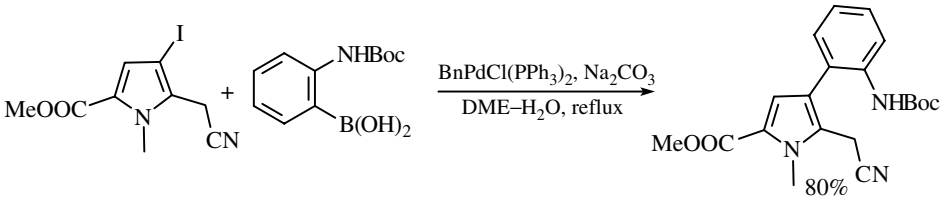
A drawback of the aqueous protocol in the Suzuki reaction is the possibility of protonolysis, which sometimes happens with sterically hindered boronic acids, in which case the rate of cross-coupling reaction may become lower than the rate of side reactions.[147] Thus, in the reaction of methyl 5-bromonicotinate with sterically hindered *o*-tolylboronic acid, the use of a biphasic technique with Na_2CO_3 as a base gave poor results in comparison with the reaction in anhydrous DMF in the presence of Et_3N (**Scheme 37**).[148]



Conditions	Yield (%)
Na_2CO_3, PhH–H_2O	12
Et_3N, DMF	81

Scheme 37

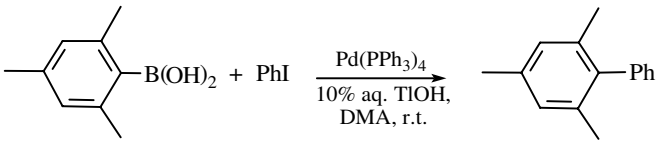
However, this rule is not without exceptions. For example, a cross-coupling of Boc-protected *o*-aminophenylboronic acid, the substrate that must readily be protolyzable, with bulky iodopyrroles gave excellent yields of the target products in aqueous solvents (**Scheme 38**).[149]



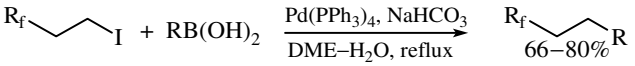
Scheme 38

The use of aqueous TlOH can also be helpful to minimize side reactions for protolyzable boronic acids (**Scheme 39**).[150]

The standard method has proved its usefulness in such exotic applications as cross-coupling of saturated iodides bearing perfluoroalkyl groups with boronic acids, which has been performed in aqueous DME (**Scheme 40**).[151]



Scheme 39

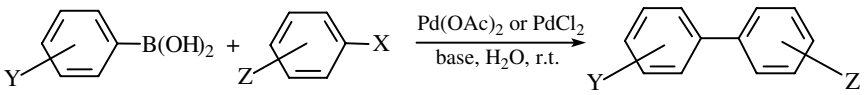


R = Ph, ZC_6H_4 (Z = *p*-Cl, *p*-F, *p*-OEt, *m*-OPh), 3-thienyl, etc.
$R_f = C_nF_{2n-1}$ (n = 4, 6, 10)

Scheme 40

D.iii.b. ***Aqueous Phosphine-Free Method.*** The use of palladium catalysts without the addition of phosphine ligands for cross-coupling with organoboron compounds in aqueous media allows a dramatic increase in catalyst efficiency, with the reaction being performed under milder conditions.

The reaction of arylboronic acids with water-soluble organic halides can be performed at room temperature in the presence of simple palladium salts ($PdCl_2$, $Pd(OAc)_2$, etc.) and inorganic bases (NaOH, Na_2CO_3, K_2CO_3, K_3PO_4, etc.). The yields of products are in most cases near quantitative (**Scheme 41**).[152]



X = Br, I; Y = H, *p*-F, *p*-(4-n-amylcyclohexyl); Z = *m*-, *p*-OH; *o*-, *m*-, *p*-COOH.

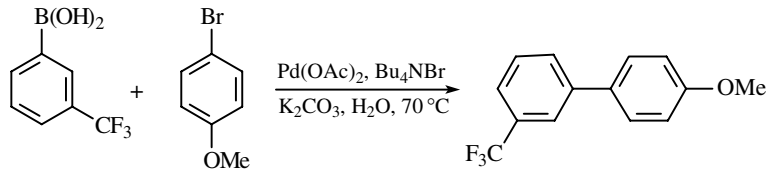
Scheme 41

Esters of arylboronic acids can be used in place of free acids. The addition of phosphine ligands often leads to a substantial drop of catalytic efficiency, and even to the formation of by-products.[153],[154] In the case when arylboronic acid is sterically hindered, the reaction in organic solvents in the presence of Ph_3P may lead to the transfer of a phenyl group from phosphine.

Inhibition of the Suzuki reaction by phosphine ligands was also noted when catalyst precursors were either $Pd_2(DBA)_3 \cdot PhH$ or (η^3-allylPdCl)$_2$. In the case when phosphines were absent from the reaction mixtures, higher turnover numbers were observed at milder conditions. The reactions were also accelerated at higher pH values, which is consistent with the hypothesis that the reactive form of organoboron compound is anionic tetrahedral complex.[155]

Another useful variation of the phosphine-free Suzuki reaction uses a heterogeneous system with neat water as solvent and tetrabutylammonium chloride as promoter and phase-transfer catalyst (**Scheme 42**). Aryl bromides were shown to give higher yields than aryl iodides, because of inhibition of phase-transfer by the liberated iodide ion.[156]

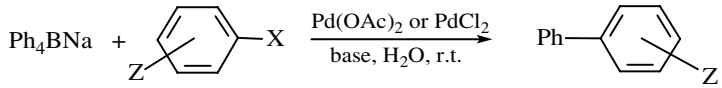
Tetraarylborate salts and readily available sodium tetraphenylborate can be used in cross-coupling with aromatic halides. All four aryl groups are transferred if the reaction is carried



Scheme 42

out in aqueous media in the presence of inorganic bases, in sharp contrast with the standard phosphine-assisted method, in which it is usually possible to use only one aryl group.

Water-soluble aryl halides readily react in neat water, giving the respective biaryl in high yields at room temperature (**Scheme 43**). Water-insoluble aryl halides can also be made to react, though in this case the addition of organic cosolvent like DMF or acetone helps to accelerate the process.[157]

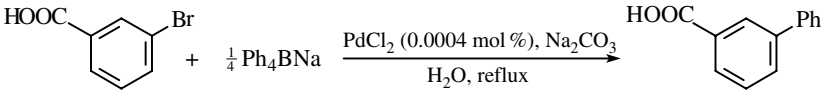


X = Br, I; Z = *m*-, *p*-OH; *m*-, *p*-COOH; *p*-CHO; *m*-, *p*-NO_2, etc.

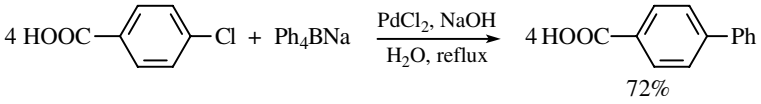
Scheme 43

Reactions with sodium tetraphenylborate showed very high catalytic efficiency. So, the reaction of *m*-bromobenzoic acid gives a quantitative yield of phenylated product even if the initial load of $PdCl_2$ is as low as 0.0004 mol %, which corresponds to a turnover number of 250,000 (**Scheme 44**).

The efficiency of this catalytic system is so high that some water-soluble aryl chlorides, such as *p*-chlorobenzoic acid, readily react (**Scheme 45**).[158]



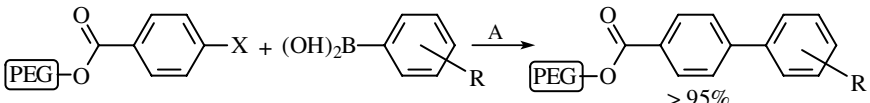
Scheme 44



Scheme 45

The attachment of PEG residues renders the solubility in water. Such substrates were found to readily take part in cross-coupling with boronic acids in water when heated by microwave irradiation in a domestic oven. Iodides, triflates, and nonafluorobutanesulfonates (nonaflates) were used as substrates to give nearly quantitative yields of biaryls (**Scheme 46**).[159]

Water-insoluble iodoarenes react with boronic acids in water in the presence of PEG-6000 as phase-transfer agent, giving biaryls in good yields.[159]



A: $Pd(OAc)_2$, K_2CO_3, water, μW, l–5 min
X = I, OTf, ONf;
R = H, *p*-CHO, *m*-OMe, 3,5-$(CF_3)_2$, etc.

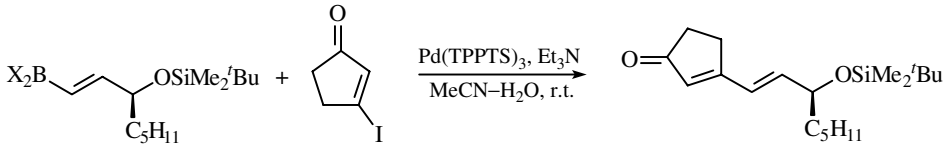
Scheme 46

D.iii.c. ***Hydrophilic Phosphine-Assisted Method.*** The use of hydrophilic phosphines allows either the resolution of the heterogeneity problem of the reaction in the presence of inorganic salts or the design of a biphasic phase-separable technique.

The method in which palladium complexes with hydrophilic phosphines are used in a biphasic system of water–organic solvent can be considered complementary to the standard protocol. In this case, boronate and palladium catalyst reside in the aqueous phase, while halide substrate is in the organic phase. In order for the reaction to run, the latter should be partitioned into the aqueous phase. Alternatively, oxidative addition may occur at the interface. Due to the low efficiency of both methods, high loads of palladium catalyst and phosphine are required. Recycling is possible but is hampered by the accumulation of inorganic salts (halide, borate) in the aqueous layer.

The first reported reaction with the assistance of hydrophilic phosphine used TPPMS ligand in aqueous organic media or neat water. The process required prolonged heating at 80 °C, thus giving no specific advantages over the standard protocol.[39]

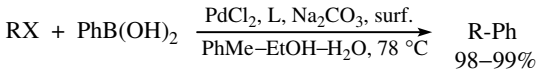
The use of TPPTS ligand achieved a new mild and selective method suitable both for common needs and for complex synthetic tasks and reactions with fragile substrates (**Scheme 47**). The reaction can be run at room temperature with amines as bases, which are notoriously ineffective in the standard method.[111],[160]



Scheme 47

Similar results were obtained with sulfonated benzofuranylphosphine ligands.[55]

The main problem with the hydrophilic phosphine-assisted protocol is a need for high loads of catalyst and ligand. Recent results show that this requirement is most likely accounted for by ineffective mass transfer in biphasic media. The addition of surfactants results in a serious increase in catalytic efficiency and allows one to decrease the amount of catalyst to 0.01 mol % without appreciable loss of reaction rate and yield (**Scheme 48**).[161] Any type of surfactants (cationic, anionic, betains, or nonionic) are equally useful, provided that the amount of surfactant in the system is high. Though the authors of this are silent about the nature of the system formed, the data of the composition of the reaction media (alcohol as cosolvent, molar ratio of surfactant, water, alcohol, and electrolyte are the factors typical for such systems) prompt a conclusion that it is

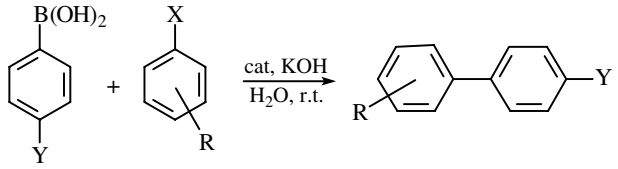


L = $Ph_2P(CH_2)_4SO_3K$, TPPMS, TPPTS
R = allyl; C_6H_4Z (Z = H, *o*-, *m*-, *p*-Me; *p*-NO_2, *p*-OMe, *p*-OH, *p*-NH_2, etc.)
X = Br, I; RX = $PhCH_2Cl$

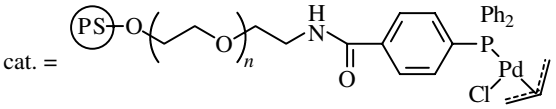
Scheme 48

most likely the so-called Winsor II solubilized system (inverted microemulsion in equilibrium with aqueous solution of base to make a biphasic system similar to two immiscible liquids), in which all reagents are solubilized in the microemulsion phase, and thus no mass transfer restrictions apply.

Bonding of palladium to a block-copolymer consisting of a hydrophobic polystyrene region and a hydrophilic PEG region may mimic the operation of a biphasic system, if the latter is supposed to work mainly in the interfacial layer. Palladium centers in such a resin are actually located at a sort of interfacial layer composed of highly hydrated polyoxyethylene tails. The area of contact and the extent of exposure of catalytic centers in the immobilized catalyst would be higher than in a liquid–liquid biphasic system. The performance of immobilized catalyst in the aqueous Suzuki reaction (**Scheme 49**) has been shown to be higher than the performance of Pd/TPPTS catalyst under similar conditions.[105]



Y = H, Me, OMe; R = H, *o*-, *p*-Me; X = Br, I

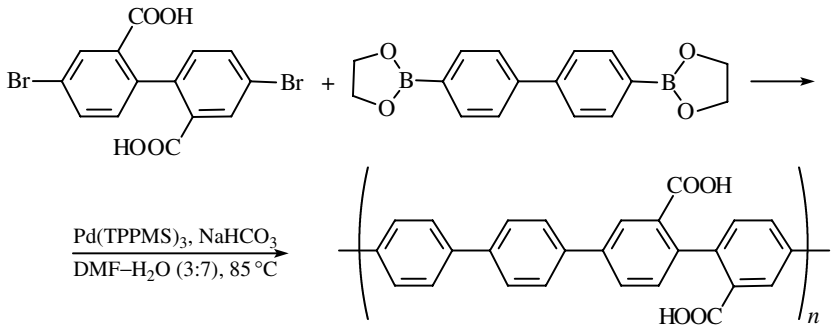


Scheme 49

D.iii.d. ***Miscellaneous.*** The Suzuki reaction in the presence of either TPPMS ligand or phosphine-free mode has successfully been applied for the preparation of water-soluble polyphenylenes containing carboxylic (**Scheme 50**)[162],[163] or sulfonato[164] groups.

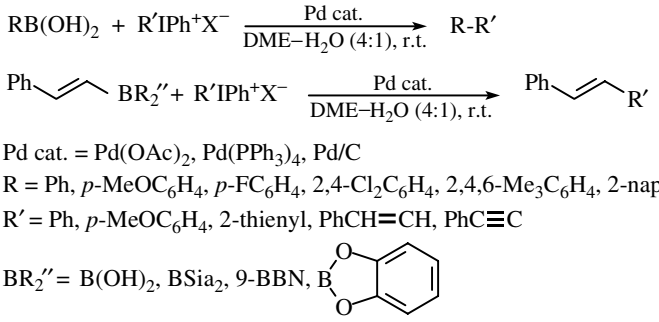
Since the polyphenylene materials are manufactured for electroluminescent devices, it is essential that the chains be uniform and not include alien fragments that may come, for example, from participation of aryl groups of phosphine ligands in the cross-coupling. Therefore, a phosphine-free protocol eliminating this problem is a valuable method in this area.

Diaryliodonium salts can be used in cross-coupling with boronic acids or sodium tetraphenylborate in place of aryl halides. This reaction can be performed in water in the presence of catalytic amounts of $PdCl_2$.[165]



Scheme 50

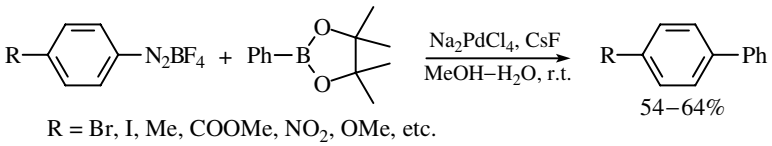
Later it was shown that a wide range of organoboron compounds, including boronic acids, boronates, and acetylene hydroboration products, readily react with such hypervalent iodine compounds as iodonium salts and Koser's or Zefirov's iodinanes in aqueous solvents in the absence of base, giving near quantitative yields of the coupling products (**Scheme 51**).[166] Phosphine-free and phosphine-assisted catalysis were equally effective.



Scheme 51

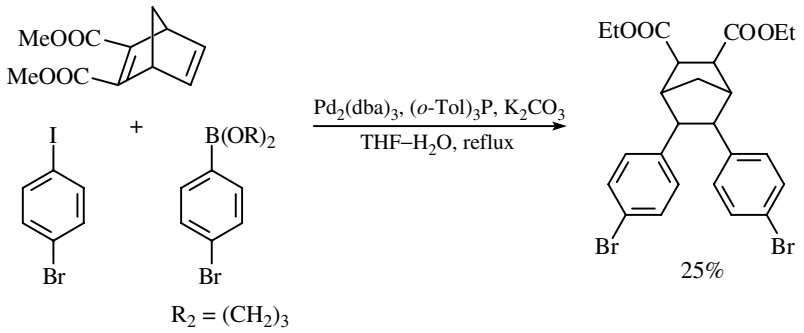
Phosphine-free catalysis can be applied as well for cross-coupling of arylboronic acids and arenediazonium salts, though in this case the application of aqueous media gave no distinct advantages over anhydrous organic solvents.[167] However, in the case of cross-coupling with arylboronates aqueous media turned out to be the best solvent (**Scheme 52**).[168]

Aqueous conditions are suitable for more complex multistep reactions. Thus, a tandem Heck–Suzuki process has been realized in a heterogeneous system with high content of water[169] (**Scheme 53**).



R = Br, I, Me, COOMe, NO_2, OMe, etc.

Scheme 52



Scheme 53

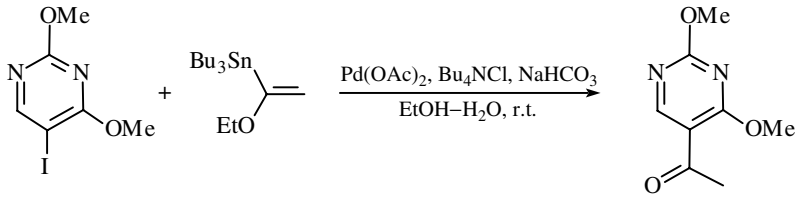
D.iv. Cross-Coupling with Organotin Compounds

The basic technique for carrying out the Stille reaction requires palladium complexes with phosphine ligands in anhydrous organic solvents like DMSO and HMPA, often at elevated temperatures. However, there is nothing in the Stille reaction that cannot tolerate water. However, due to formation of tin-containing products, which are likely to accumulate in the aqueous phase, the perspective for an effective recyclable biphasic protocol for Stille reactions is obscure.

The Stille reaction in some cases (reactions with reactive iodoarenes, etc.) benefits from phosphine-free catalysis. The use of phosphine-free complexes, such as $Pd(dba)_2$, $PdCl_2(MeCN)_2$, $[(\eta^3\text{-allyl})PdCl]_2$, or even simple palladium salts, allows one to perform the reactions under milder conditions, at lower temperatures, in less polar solvents (acetone, THF, ether, benzene), and with lower amounts of catalyst to achieve higher TON values.

The addition of small amounts of water helps to increase the selectivity and yield in cross-coupling of vinyloxiranes with $PhSnMe_3$ by favoring allylic rearrangement over direct substitution.[170]

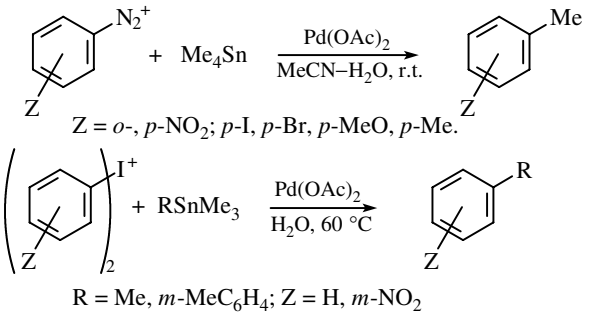
The cross-coupling of α-stannylated enol ether with 2,4-dimethoxy-5-iodopyrimidine in aqueous ethanol yielded 5-acetyl derivative (**Scheme 54**).[122]



Scheme 54

The use of monosubstituted stannanes $RSnX_3$ in aqueous systems allows a dramatic reduction of toxicity hazards associated with volatile organotins. The compounds $RSnCl_3$ dissolved in aqueous alkali to give stannates $[RSn(OH)_{3+n}]^{n-}$ has been shown to be useful in cross-coupling reactions with water-soluble aryl halides either in a phosphine-free system or in the presence of TPPMS ligand.[171],[172]

Arenediazonium and aryliodonium salts are cross-coupled with organotin compounds in neat water or aqueous solvents (**Scheme 55**). The former can be used as prepared *in*

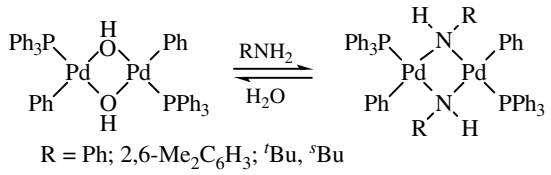


Scheme 55

situ from anilines to react with Me_4Sn in acidic aqueous acetonitrile in the presence of 1 mol % $Pd(OAc)_2$.[173] The latter are reactive in neat water at neutral pH.[174] Koser's and Zefirov's hypervalent iodine reagents were also used for cross-coupling with organotin compounds in aqueous systems.[175]

D.v. Carbon–Heteroatom Bond-Formation Cross-Coupling Reactions

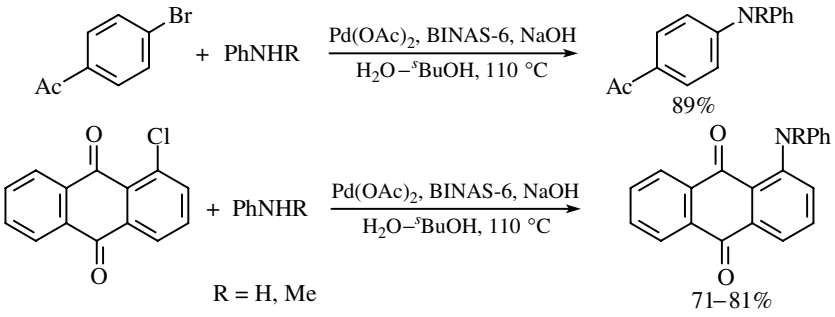
D.v.a. ***Formation of C—N Bonds.*** Though Pd-catalyzed amination—the Hartwig–Buchwald reaction—is normally performed in anhydrous media in the presence of strong bases, no steps of the mechanism of this reaction strictly require the absence of water. Moreover, it has been shown that amido complexes of Pd, the key intermediates of this reaction, can easily form by ligand exchange of water or hydroxyl (**Scheme 56**).[176]



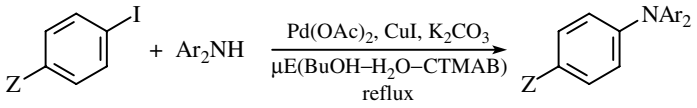
Scheme 56

The realization of a recyclable protocol for amination is particularly important, as very expensive bidentate phosphines are used, and the load of catalyst is usually rather high, limiting broader use of this indispensable reaction. Indeed, the amination has been performed in a biphasic system of water–*sec*-butanol, using a highly hydrophilic bidentate BINAS-6 ligand and NaOH as the base (**Scheme 57**).[177] The choice of organic solvent is rather interesting: it is known that C_3–C_4 alcohols may in the absence of any surfactant form microheterogeneous systems with water resembling microemulsions, thus being capable of solubilization of significant amounts of hydrophobic organic matter.

Besides the Hartwig–Buchwald reaction, amination can be achieved by a Pd-catalyzed variant of the Ullmann reaction in the presence of copper salts. Though the scope of this reaction is much narrower, it does not require expensive phosphine ligands and thus is more economical. The arylation of diphenylamine with water-insoluble aryl iodides can be achieved in aqueous microemulsions in the presence of phosphine-free palladium catalyst and copper(I) iodide (**Scheme 58**).[178]



Scheme 57

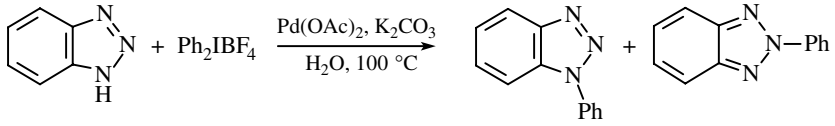


μE = microemulsion; CTMAB = $C_{16}H_{33}NMe_3Br$
Ar_2NH = Ph_2NH, carbazole

Scheme 58

This method has successfully been applied for the arylation of amino acids.[179]

Iodonium salts can be used for the arylation of heterocycles such as benzotriazole. The reaction can be run in neat water, in which both substrates are soluble in the presence of base, and does not require copper cocatalyst (**Scheme 59**).[180]

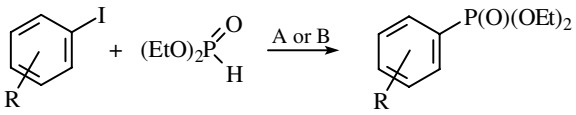


Scheme 59

D.v.b. ***Formation of C—P Bonds.*** Cross-coupling with phosphorus-containing nucleophiles, a convenient method for the preparation of phosphines, can also be performed using various aqueous techniques. The arylation of diethylphosphite can be carried out in a biphasic system of benzene–water in the presence of NaOH, Bu_4NCl, and TPPMS ligand (**Scheme 60**). It should be noted that large ions Bu_4N^+ and $Ph_2P(C_6H_4SO_3)^-$ should readily form a lipophilic ion pair, and thus the reaction is most likely to take place in the organic phase. Alternatively, the reaction can be run in homogeneous aqueous solution under very mild conditions.[181] The arylation by aryl bromides requires elevated temperatures.[182]

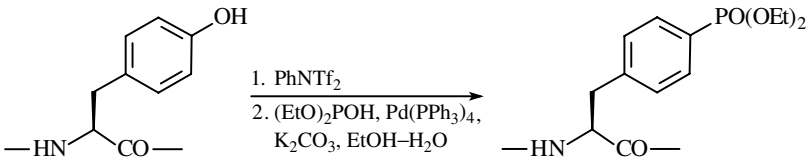
Water plays an essential role as a cosolvent, as the decrease of water content from 50% to 10% (v/v) with all other parameters kept invariant leads to a sharp decrease of the yield (e.g., for reaction with PhI, from quantitative to a meager 30%).

An aqueous technique allows modification of hydrophilic natural molecules, as in the example of substitution of hydroxy groups of tyrosine residues of peptides (**Scheme 61**).[183]



A: $Pd(OAc)_2$, TPPMS, NaOH, Bu_4NCl, $PhH–H_2O$, 60 °C.
B: $Pd(OAc)_2$, TPPMS, Et_3N, $MeCN–H_2O$, r.t.

Scheme 60



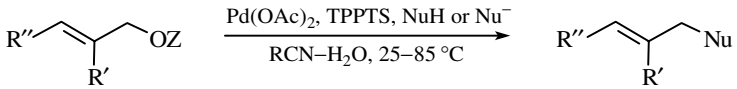
Scheme 61

D.v.c. ***Formation of C—S Bonds.*** Hydrosulfination of olefins by an SO_2/H_2 mixture catalyzed by cationic complexes of palladium such as $[Pd(MeCN)_2(DPPE)](BF_4)_2$ can be realized in aqueous solutions.[184]

D.vi. Allylic Substitution

Allylic substitution (the Tsuji–Trost reaction) is among the most synthetically useful processes in palladium catalysis. As the catalytic efficiency of allylic substitution is often moderate (5–10 mol % of Pd catalyst are usually used), and phosphine-free systems are generally inefficient, the recycling of catalyst is the only feasible way to make the process more economical. Various phase-separation techniques have been tried for this reaction. In what concerns the rate of reaction and catalytic efficiency, such ligands as TPPTS are likely to be less effective compared to Ph_3P.[185] Thus, the main reason for the use of hydrophilic ligands in allylic substitution is the design of recyclable systems.

Allylacetate reacts with various N- and C-nucleophiles in aqueous MeCN (10% H_2O, v/v) in the presence of $Pd(OAc)_2$ and TPPTS, giving substitution products in moderate to high yields.[111] Because this reaction is carried out in a homogeneous solution containing only a small amount of water, the role of highly hydrophilic TPPTS ligand is unclear. However, the use of water-insoluble nitrile solvents, such as benzonitrile or valeronitrile, in place of MeCN makes the system biphasic, and the application of TPPTS in this case allows an easy separation of catalyst, which may be crucial as typically very high loads of catalyst (up to 4 mol % of palladium acetate) and up to 20 mol % of expensive TPPTS ligand are introduced (**Scheme 62**).[111],[186]

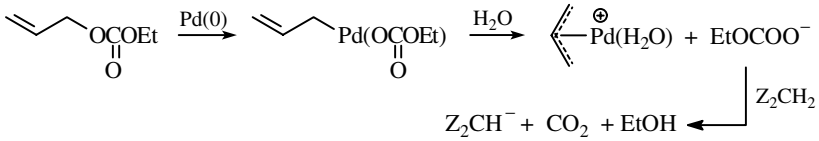


R = Me, Pr, Ph; R′ = H, Me; R″ = H, Ph; Z = Ac, COOEt.

Scheme 62

The reaction was extensively studied for cinnamyl esters (acetate and carbonate) as allylic substrates, with some examples given for allyl acetate and its homologues, and a wide range of nucleophiles including N-nucleophiles (primary and secondary amines, hydroxylamine and its derivatives, and sodium azide), C-nucleophiles (malonates, ethyl acetoacetate, acetylacetone, sodium tetraphenylborate), and S-nucleophile sodium *p*-toluenesulfinate.

It is interesting to note that in the case of reaction with allylic carbonates, CH acids are introduced as such, and the reaction is run in the absence of base. This may be accounted for by the possibility that carbonate leaving group may itself be a source of basicity in strongly polar aqueous media (**Scheme 63**).

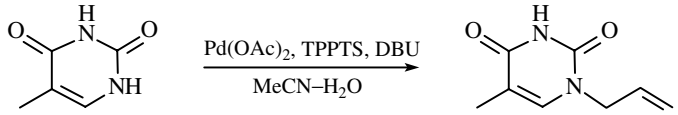


Scheme 63

Vinyl oxiranes may serve as substrates for allylic substitution in aqueous media and also in the absence of base.[111],[186]

An aqueous layer containing the catalyst can be reused twice without noticeable decrease of catalytic activity, while in further attempts of reuse a gradual decrease of activity takes place.

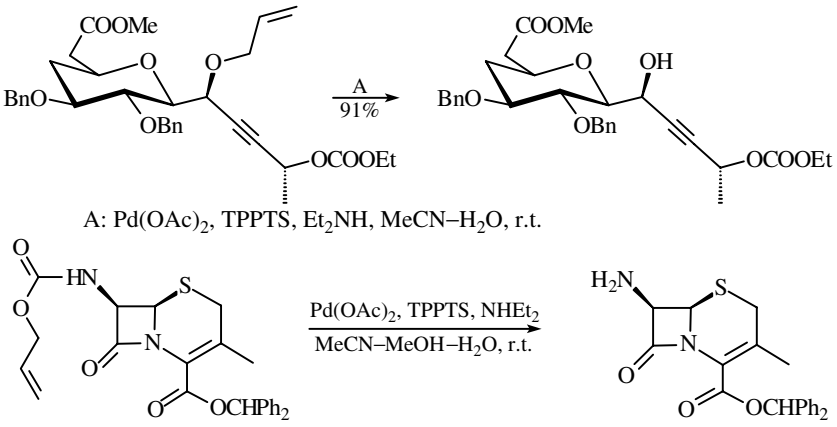
A dramatic enhancement of selectivity has been noted for the allylation of uracils and thiouracils. In DMSO or dioxane the reaction in the presence of $Pd(OAc)_2$–Ph_3P gave a mixture of substitution products at N-1 and N-3, while the reactions in aqueous MeCN catalyzed by TPPTS complex of palladium gave selectively 1-*N*-allyluracils and *S*-allylthiouracils (**Scheme 64**).[187]



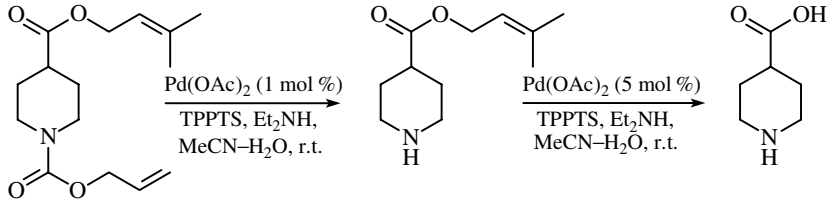
Scheme 64

An ingenious application of an aqueous biphasic and monophasic methodology described above was suggested for the selective deprotection of primary and secondary amines and alcohols protected by allyloxycarbonyl (Alloc) group.[188]–[190] Using diethylamine as an acceptor of allyl, the reaction proceeds very smoothly under mild conditions and is characterized by a formidable chemoselectivity, which can be seen from the example in **Scheme 65**.

Removal of *alloc* protection under such conditions leaves intact other protective groups, which would have been attacked if the deprotection were done by conventional techniques based on hydrogenolysis or solvolysis. Moreover, the conditions can be finely adjusted to allow selective differential deprotection of similar protective groups, differing only by steric bulk (**Scheme 66**). This technique has been applied for peptide synthesis.[191]



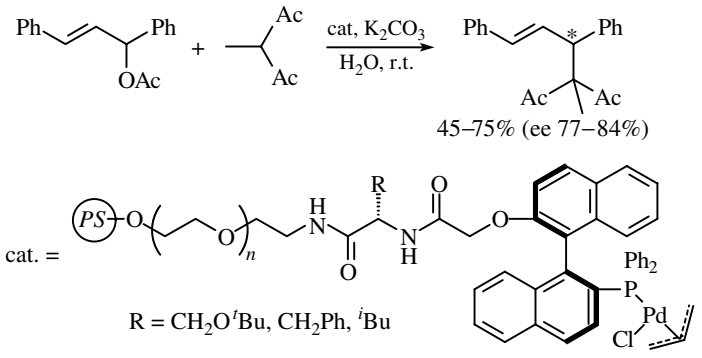
Scheme 65



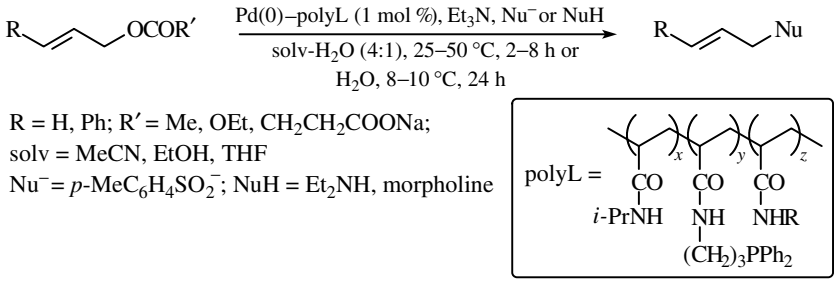
Scheme 66

Palladium bound to polymeric support has been employed for allylic substitution. Amphiphilic resins based on block PS–PEG-bearing phosphine residues (cf. **Scheme 49**) were used for allylic substitution in aqueous media both in achiral and in enantioselective reactions. In the latter, MOP-type ligand has been tethered by a chiral link containing a residue of natural amino acid to the amphiphilic block-copolymer (**Scheme 67**).[103],[104],[192]

Thermomorphic polymeric ligands based on poly (*N*-isopropyl)acrylamide resin were tested in the reaction in aqueous organic solvent, as well as neat water (**Scheme 68**).[106]



Scheme 67



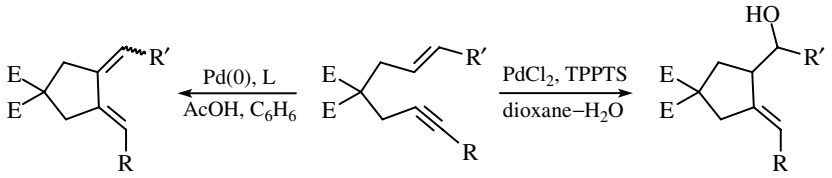
Scheme 68

Recycling of the catalyst is achieved by either sedimentation of polymer by hexane from aqueous organic solvent, or heating of reaction mixture above room temperature for the reactions in neat water. As the hydrophile–lipophile balance of the polymer varies with temperature, the increase of temperature renders the material less hydrophilic. Catalyst activity is reported not to be degraded after as much as 10 reuses. This is one of the most spectacular durability records set so far in recyclable Pd-catalyzed processes.

A supported aqueous phase system has been developed for allylic substitution. Coabsorption of $Pd(OAc)_2$ and TPPTS onto both mesoporous and nonporous silicas gave catalysts active for the reaction of cinnamyl ethyl carbonate with ethyl acetoacetate.[193] The activity of supported catalyst depends on the amount of water used to form a layer on the surface of silica. In the absence of water the catalyst is inactive. The supported catalyst possesses activity close to the activity of $Pd(OAc)_2$–TPPTS catalyst in a biphasic system, though it is more stable, as even on prolonged reaction times no tokens of catalyst decomposition leading to the formation of Pd-black was noted for the former. Still, the recycled SAPC catalyst possesses lower activity than the one freshly prepared. Another report on glass bead technology applied to allylic substitution has been published.[144]

D.vii. 1,6-Enyne Cyclization

In aqueous media and in the presence of TPPTS ligand the cyclization of 1,6-enynes gives not a diene, as in the well-known Trost reaction performed in nonaqueous solvents in the presence of carboxylic acids, but instead a homoallylic alcohol (**Scheme 69**).[194]



Scheme 69

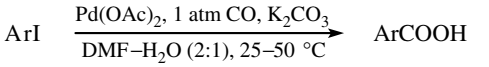
The mechanism of this process is unclear. Particularly, the source of the PdH species remains obscure (cf. **Sect. B.iv**), the addition of which to the triple bond must have triggered the whole process. This process may have a relation to industrially important Pd-catalyzed dimerization of butadiene in the presence of water giving octadienols.[195]

D.viii. Hydroxycarbonylation

In the hydroxycarbonylation reaction, water performs the role of nucleophilic reagent, which cleaves acylpalladium intermediate to yield carboxylic acids. This type of reaction may benefit from all kinds of aqueous techniques.

The hydroxycarbonylation of organic halides (haloarenes, benzyl and allyl halides) requires the presence of base, and thus it is facilitated by phase-transfer conditions in reactions performed in the presence of phase-transfer agents.[196],[197]

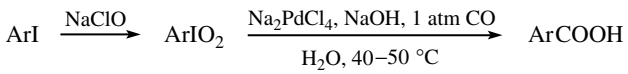
Homogeneous aqueous media and phosphine-free conditions are well suited for the carbonylation of aryl iodides. The process is realized under very mild conditions in aqueous DMF solvent in the presence of inorganic bases such as alkali metal hydroxides, carbonates, and acetates and any available palladium salt ($Pd(OAc)_2$, K_2PdCl_4, $Pd(NH_3)_4Cl_2$, etc.) (**Scheme 70**). Phosphine ligands retard the reaction.[198]



Ar = *p*-ZC_6H_4 (Z = NO_2, Cl, CN, Me, NH_2, etc.);
2-$C_{10}H_7$, 2-thienyl.

Scheme 70

With water-soluble aryl iodides the carbonylation can be run in neat water.[198] Water-insoluble aryl iodides can be processed in neat water if preoxidized by bleach to iodyl derivatives. The latter, due to either slightly enhanced solubility in water or higher reactivity toward oxidative addition, readily react under very mild conditions (**Scheme 71**).[199]

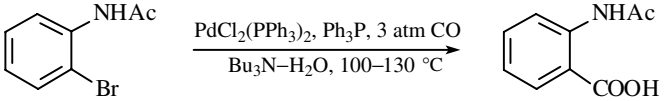


Scheme 71

In aqueous media Pd(II) salts are rapidly reduced by CO to give inactive Pd-black, and thus very reactive substrates are required to trap Pd(0), such as aryl iodides or phosphine ligands, which form stable complexes of Pd(0). Thus, in most cases less reactive aryl bromides cannot be processed in the absence of phosphine ligands.

O-Bromoacetamides can be carbonylated in a biphasic system of Bu_3N–water in a process apparently involving phase transfer (**Scheme 72**).[200]

Water-insoluble aryl iodides can be hydroxycarbonylated directly using solubilized media, such as canonical microemulsions or Shinoda's swollen micelles. Microemulsions formed by cationic and anionic surfactants can be used for both liquid and solid aryl



Scheme 72

iodides, giving high yields of benzoic acids in the presence of palladium salts in phosphine-free mode. Though the microemulsions always contain aliphatic alcohols used to adjust the hydrophile–lipophile balance of the surfactant system, the formation of esters was never observed.[201]

Because carbonylation is a process of high practical importance, considerable work has been done on developing a recyclable biphasic protocol. Carbonylation is a hard challenge for this task, because, similar to the case of the Heck reaction, this process leads to the formation of salts, which irreversibly change the composition of the aqueous catalyst-containing layer and lead to its degradation. Besides, the products of hydroxycarbonylation, the carboxylates, are soluble in water and must be recovered from alkaline solution. Acidification leads to the formation of an additional amount of salt. Therefore, in spite of extensive research, the recyclability of the systems developed so far is only modest. Rarely can more than a single reuse be achieved.

The carbonylation of bromobenzene in a biphasic system of toluene–water takes place under harsh conditions (**Scheme 73**). In order to overcome the degradation of catalyst at high temperature, it is necessary to apply a huge (more than 12-fold) excess of ligand. Key intermediates of the catalytic cycle, $PhPdBr(TPPTS)_2$ and $PhCOPdBr(TPPTS)_2$, were obtained and characterized, each being highly hydrophilic, thus furnishing direct evidence that the whole catalytic cycle runs in the aqueous phase.

$$\mathrm{PhBr} \xrightarrow[\mathrm{Et_3N,\ toluene{-}H_2O,\ 150\ ^\circ C}]{\mathrm{Pd(OAc)_2,\ TPPTS,\ 15\ atm\ CO}} \mathrm{PhCOOH}$$

Scheme 73

In a comparative study of the carbonylation of water-insoluble bromo- and iodoarenes in biphasic systems, it has been shown that trivial hydrophobic phosphines may be more effective than hydrophilic ones.[202]

A very interesting example of biphasic carbonylation of chloroarenes apparently involving an implicit phase transfer was described.[203] In this method chloroarene itself is used as an organic phase in the system containing aqueous alkali and palladium salt in the presence of Cy_3P without any phase transfer or solubilizing agents.

The catalyst supported on amphiphilic PS–PEG resin (same as in **Scheme 49**) has been used for carbonylation of water-insoluble iodoarenes in water at room temperature to give near to quantitative conversions. The catalyst survived as many as 30 reuses without loss of activity, which makes it one of the most durable supported catalysts described so far.[204]

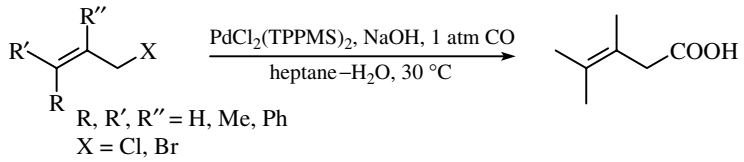
Unlike bromobenzene, benzyl chloride can be carbonylated in a biphasic system of heptane–water (**Scheme 74**) under very mild conditions. Both hydrophobic triphenylphosphine and amphiphilic TPPMS can serve as ligands for the process, which may mean that the reaction in this case may actually run at the interface. A strong acceleration of the reaction by anionic surfactants $n\text{-}C_7H_{15}SO_3Na$ or $n\text{-}C_7H_{15}COONa$ is evidence in favor of this hypothesis.[205]

$$\mathrm{PhCH_2Cl} \xrightarrow[\mathrm{heptane{-}H_2O,\ 50\ ^\circ C}]{\mathrm{PdCl_2(TPPMS)_2,\ NaOH,\ 1\ atm\ CO}} \mathrm{PhCH_2COOH}$$

Scheme 74

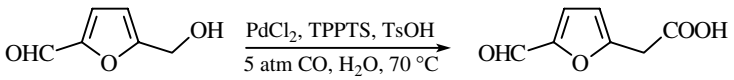
The amphiphilic ligand TPPMS does not allow recycling of the aqueous catalytic solution, because upon acidification it is partitioned between phases, leading to a huge leaching. Carbonylation of benzyl chloride in the presence of strongly hydrophilic ligands TPPTS or BINAS is almost as facile, but additionally allows for recycling, though even in this case the performance of reused catalyst drops.[206] A comparative study of the carbonylation of benzyl chloride in biphasic systems with phase-transfer and phase-separation techniques has been published.[207]

Similar to benzyl chloride, allylic halides are carbonylated (**Scheme 75**).[208],[209] The reaction in a biphasic system is markedly more facile than carbonylation in homogeneous organic media.



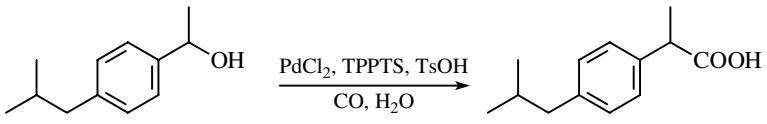
Scheme 75

The use of aqueous media allows benzylic alcohols to serve as substrates for hydroxycarbonylation, which in this case is run in the presence of strong acids to enable oxidative addition to the C—O bond. Thus, 5-hydroxymethylfurfural, considered as a renewable source of organic matter not depending on fossils, has been transformed to (5-formylfuryl-2)acetic acid using a water-soluble palladium complex with TPPTS ligand (**Scheme 76**).[210],[211]



Scheme 76

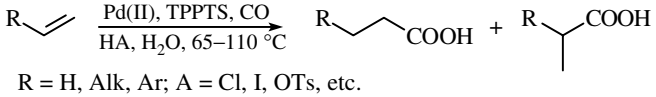
The carbonylation of benzyl chloride to phenylacetic acid in a similar system requires more harsh conditions (100 °C, 60 atm CO).[212] This process has been applied for development of a new process of manufacturing of a very popular anti-inflammatory drug, *ibuprofen* (**Scheme 77**).[213]



Scheme 77

Alternatively, this reaction can be performed in the presence of heterogeneous catalyst Pd on montmorillonite in aqueous Et_2CO in the presence of HCl and PPh_3. The catalyst in this case can be recycled without loss of activity.[214] The presence of water in the reaction mixture is a critical parameter in defining the selectivity of carbonylation.[215]

Hydroxycarbonylation of olefins can take place in acidic solutions via a route similar to that accounting for the carbonylation of alcohols. This process has been realized in a biphasic system (**Scheme 78**).[216],[217] The catalytic efficiency and selectivity are usually rather low even with fresh catalyst, though a promising advance in the optimization of this industrially important process has been made.[218]



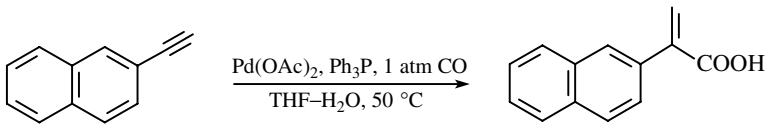
R = H, Alk, Ar; A = Cl, I, OTs, etc.

Scheme 78

In aqueous carbonylation, water (hydroxide ion) is not necessarily the sole nucleophilic agent at the product-forming step of the catalytic cycle. Reactions in the presence of boronic acids may yield ketones,[219] and amines are stronger nucleophiles to give amides,[220] though in both reactions acids are formed as by-products.

The reductive carbonylation of acetylenes proceeds via a different mechanism compared to the carbonylation of olefins, but through the addition of palladium hydride species to the triple bond. The most probable source of PdH is the WGS reaction, so water is required at two key steps of this catalytic cycle. Depending on conditions, the nature of the catalyst, and promoter additives, the carbonylation of acetylenes can lead to different products. An important role of cationic palladium complexes that readily form in the presence of water has been disclosed.[221]

Carbonylation of naphthylacetylenes can be run under very mild conditions, thus opening a convenient approach to *naproxen* (**Scheme 79**).[222]

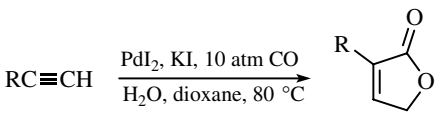


Scheme 79

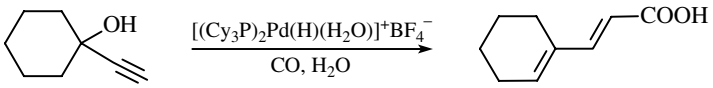
Regiospecific reductive phopshine-free carbonylation of acetylenes in the presence of PdI_2 under modest pressure of CO gave furan-2(5*H*)-ones in good yield (**Scheme 80**).[223] Similar results were obtained in a biphasic system.[224]

Reductive carbonylation of readily available alkynols in the presence of cationic hydride complex of palladium and water yields dienoic acids (**Scheme 81**).[225] A similar reaction has been achieved with allenic alcohols.[226]

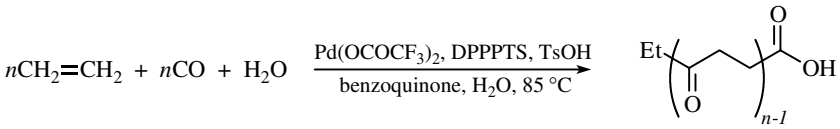
Either WGS reaction or reversible protonation of $Pd(TPPTS)_3$ complex is believed to trigger the copolymerization of CO and ethylene in water (**Scheme 82**).[47],[51],[218],[227],[228]



Scheme 80



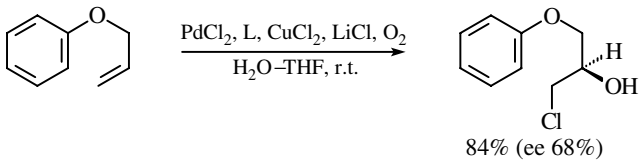
Scheme 81



Scheme 82

D.ix. Oxidations

Wacker oxidation of olefins by palladium complexes involves water as the nucleophilic reagent. Depending on conditions, the oxidation of olefins by Pd(II) salts in the presence of water gives ketones[229] or chlorohydrins. The enantioselective procedure leading to the latter involves chiral bidentate phosphines, either sulfonated or nonsulfonated (**Scheme 83**, L = sulfonated (*R*)-TolBINAP).[10]



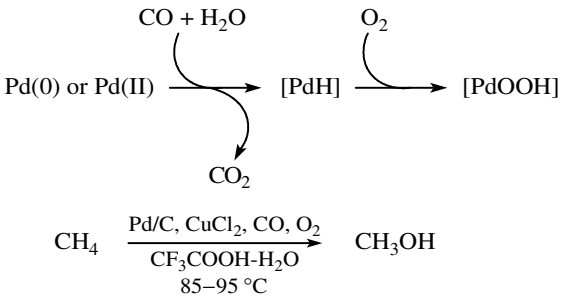
Scheme 83

A useful method of deprotection applied to *O*-allyl derivatives of carbohydrates and natural polyols under aqueous conditions employs Wacker-type oxidation-assisted hydrolysis of unsaturated group using the system $PdCl_2$–CuCl–O_2 in aqeous DMF.[230] A recyclable supported aqueous phase system for Wacker oxidation has been described.[231]

In the presence of oxygen, palladium hydride gives peroxide complexes and further on hydrogen peroxide. A conjunction of the WGS catalytic cycle with the hydrogen peroxide-producing cycle has been discovered to afford several interesting catalytic systems for the oxidation of alkanes into carboxylic acids,[232] a highly effective conversion of methane to methanol (**Scheme 84**),[233] and deep oxidation of organic compounds including toxic chloroorganic and organophosphorus pollutants.[234] The latter process is reported to be a unique broad-scope method of detoxification of wastes and polluted waters.

D.x. Reductions (Hydrogenolysis, Hydrogenation, Homocoupling)

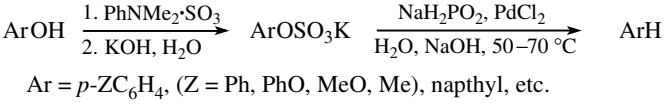
Hydrogenolysis of carbon–heteroatom bonds is not only of synthetic but also of great practical importance, as it is one of the ways to detoxify hazardous chloroorganic pollutants. For the latter purpose, the development of effective aqueous procedures is highly desirable.



Scheme 84

Hydrogenolysis of C—X bonds is effected in catalytic processes with the participation of PdH species, generated by the action of various reductants. The use of water allows one to employ an inexpensive reducing agent, such as NaH_2PO_2.[235]–[237]. In homogeneous alkaline solutions NaH_2PO_2 is a very efficient reductant in the process catalyzed by $PdCl_2$ at 50–70 °C. The reaction can be applied for chloroarenes possessing at least some solubility in water, such as chlorophenols, chlorobenzoates, and chloroanilines.

The same reducing agent can be used for the removal of the phenolic hydroxy group via prior transformation into monoarylsulfates by reaction with the complex of sulfur trioxide with dimethylaniline (**Scheme 85**).[238]



Ar = *p*-ZC_6H_4, (Z = Ph, PhO, MeO, Me), napthyl, etc.

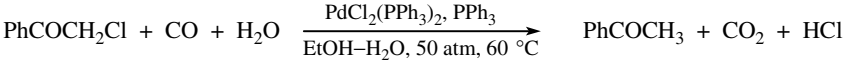
Scheme 85

Formic acid and formates are excellent sources of PdH species in *transfer hydrogenation/hydrogenolysis*.

The reduction of allylic halides or acetates, as well as benzyl halides, can be achieved by the Pd-catalyzed reaction with formate ions[239] in the biphasic system of toluene–water or heptane–water in the presence of hydrophilic phosphine ligands TPPMS, sodium 3-(diphenylphosphino)benzoate, and PEG-modified trialkylphosphine. The process is accelerated by the addition of PEG.[240]

Hydrogenolysis of water-insoluble aryl halides in neat water can also be aided by such solubilizing agents as cyclodextrins.[241] An electrocatalytic process of dechlorination of chloroorganic pollutants in the presence of supported Pd in water has been described.[242]

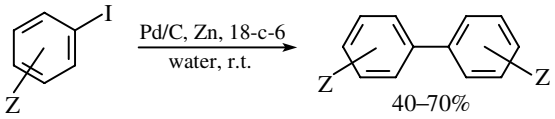
The WGS reaction can be used as a source of PdH species for various reductions including the hydrogenation of the double bond[243] and hydrogenolysis of the hydroxylic group in α-hydroxyacids[244] or chlorine atom in α-chloroketones (**Scheme 86**) or α-chloroacids.[245]



Scheme 86

Though the hydrogenation of the double bond is one of the basic catalytic reactions in Pd chemistry, little has been published on aqueous variants of this process. Hydrogenation of α,β-unsaturated aldehydes in recyclable biphasic systems in the presence of TPPTS complex of palladium has been studied.[246],[247] Also, a biphasic hydrogenation of nitrocompounds in the presence of $PdCl_2$ and TPPTS under mild conditions has been reported.[248]

Room temperature homocoupling of aryl iodides was achieved in neat water or water–acetone mixture in the presence of Pd/C or $Pd(OAc)_2$, and Zn dust (**Scheme 87**). The addition of 18-crown-6 was required for the reaction in neat water. The reactions are run under aerobic conditions. The effect of phosphine is negative.[249],[250]



Z = H; *m*-, *p*-Me; *o*-, *p*-OMe; *p*-Cl; *p*-F; etc.

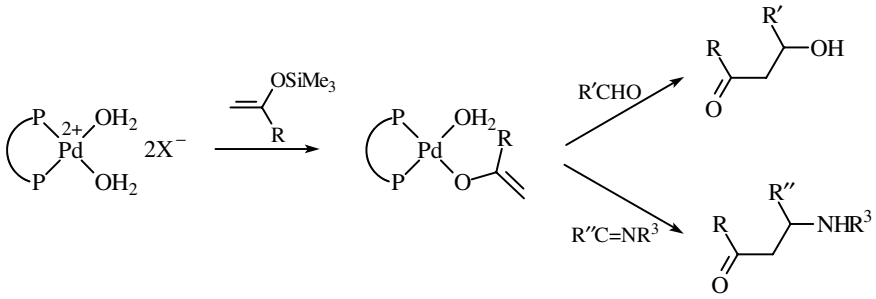
Scheme 87

Later, it was shown that this method is applicable to chloroarenes. The presence of water is declared to be critical for the reductive coupling to take place.[251]

D.xi. Soft Electrophilic Catalysis

Cationic palladium complexes are soft electrophiles and can take part in a number of reactions requiring electrophilic catalysis. So far, such reactions have been poorly studied, but several published examples show that this chemistry may be very important, particularly in aqueous media.

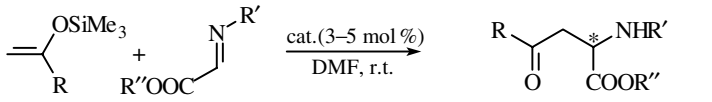
Both mononuclear aquo- and binuclear μ-hydroxocomplexes of palladium react with silyl enol ethers to give *O*-enolate complexes, which may take part in the aldol[15],[252] and Mannich reactions (**Scheme 88**).[14],[253]



Scheme 88

The reactions are highly enantioselective (**Scheme 89**).

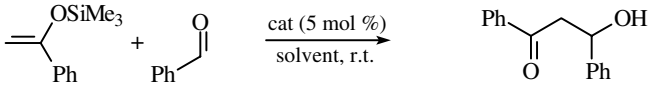
Recyclable diaquocomplexes of palladium with BINAP tailored to a polymeric support were used for enantioselective aldol (**Scheme 90**) and Mannich reactions.[254] Chemical yield of the aldol reaction is strongly improved by the addition of water to the solvent.

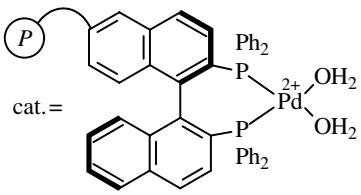


60–95% (ee 67–90%)

cat.= $LPd(H_2O)_2(BF_4)_2$; $[LPd(\mu\text{-}OH)_2PdL](BF_4)_2$
L = (*R*)-BINAP; (*R*)-Tol-BINAP
R = Me, Ph, *o*-$MeOC_6H_4$, *m*-$O_2NC_6H_4$, 2-naphthyl, etc.
R′ = Me, *i*-Pr; R″ = Ph, p-$MeOC_6H_4$

Scheme 89





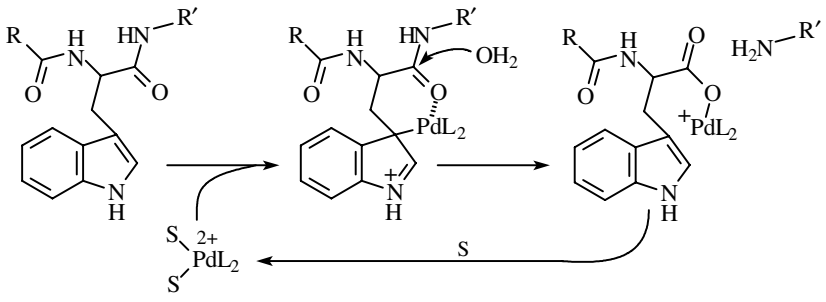
cat.=

Solvent	Yield (%)	ee (%)
DMF	35	76
DMF–H_2O	94	74
DMF–H_2O	81	71

Scheme 90

Aquocomplex of palladium with chiral bis-oxazoline ligand has been used to perform the enantioselective Michael reaction.[255]

D.xi.a. ***Hydrolysis and Hydration.*** The electrophilicity of cationic palladium(II) complexes has been taken advantage of in an interesting biomimetic method of selective cleavage of peptide bonds at histidine, methionine, or tryptophane residues.[256]–[258] Further discrimination is possible as peptides with two former amino acids are cleaved in aqueous solution but not cleaved in acetone, while those with tryptophane are cleaved only in acetone in the presence of water. The mechanism of cleavage at tryptophane is particularly interesting as it involves the electrophilic *ipso*-palladation of indole ring, while the remaining coordination site of Pd in the *spiro*-cyclopalladated complex is used for the electrophilic activation of carbonyl (**Scheme 91**).



S = H_2O, Me_2CO; R, R′ = peptide residues; L_2 = bidentate ligand.

Scheme 91

Catalytic hydration of activated double bond, for example, in the transformation of maleate to malate, is a rare process belonging to the same type of chemistry.[259]

E. SUMMARY

Water has numerous functions difficult to decouple in a particular reaction. However, among hundreds of examples of both intentional and unintentional use of water in palladium catalysis, three major protocols can be traced.

1. Aqueous phosphine-free methods use palladium salts without phosphine ligands in neat water or aqueous organic solvents. Reaction in neat water are not restricted to water-soluble reagents but may be run in heterogeneous reaction mixtures with the aid of phase-transfer agents or may involve implicit phase transfer likely due to the ability of palladium complexes to cross phase boundaries. Aqueous phosphine-free methods, applicable mostly to reactive substrates in reactions involving oxidative addition to the carbon–halogen bond, show very high catalytic efficiency and thus are economical. Very high TON values compensate for the impossibility of realizing a recyclable process.

2. Aqueous phosphine-assisted methods use hydrophilic phosphine ligands in aqueous organic solvents. The processes are very mild and selective but use high loads of catalysts and are not recyclable. This protocol is targeted at sophisticated organic synthesis, often involving hydrophilic biomolecules, where economic issues are not of primary importance.

3. Recyclable phase-separation methods use heterogeneous systems with aqueous phase holding the catalyst, and hydrophobic organic phase holding the stock of substrates and receiving the products of the reaction. Palladium catalyst is held in the aqueous phase by strongly bonded hydrophilic ligands, mostly phosphines. The reactions are believed to take place in the aqueous phase, thus placing severe restrictions on the substrates, which must possess a measurable solubility in water for the reaction to run at a reasonable rate. Mass-transfer limitations can partially be overcome by increasing the area of interface (supporting aqueous phase or catalysts themselves over hydrophilic solids, addition of surfactants for lowering surface tension, etc.) or using solubilizing agents that transfer the reagents across the interface. The methods are hardly applicable for small-scale laboratory synthesis, as each case requires careful optimization to arrive at the best compromise between rate, loss of catalyst, and durability.

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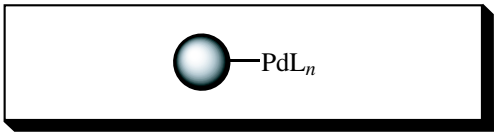

X.2 Palladium Catalysts Immobilized on Polymeric Supports

TONY Y. ZHANG

A. INTRODUCTION

Immobilizing palladium on polymeric supports is a rapidly evolving field as ever more Pd-catalyzed processes have been discovered and developed, becoming routine tools in the arsenal for synthetic chemists in both industry and academia. A major driving force for the recent surge of progress in immobilized catalysts is the advent of solid-phase synthesis in the context of combinatorial chemistry, which has brought forward many new synthetic methodologies directly applicable to solid-bound ligand preparation. Immobilized catalysts also facilitate the high throughput screening effort for new reactions, improved reactivity, and selectivity. Additionally, the rapid rise of palladium prices in recent years driven by a combination of factors including popularity of palladium in the use of automobile catalytic converters, which created huge demand for this precious metal by its sheer market size, provided economic incentive for the recycling and reuse of palladium catalysts. Extraction of palladium from the ores is currently economically sensible only in limited areas on the earth, with political and governmental policy changes in the palladium-producing regions only making the supply more erratic.

We will attempt to cover the recent progress in the chemistry of solid-bound Pd-catalyzed processes, with a focus on those customarily carried out in a homogeneous system, especially carbon—carbon bond-forming reactions. The relatively mature field of heterogeneous Pd-catalyzed processes, such as hydrogenation and dehydrogenation under the influence of Pd/C and Pd/Al_2O_3, either in condensed or gas phase, will not be included in this review as many others are available already. In addition, since the same polymeric ligands, especially phosphorus-based ones, can be used to anchor many other transition metals for different and useful chemistry, support systems for other metals such as rhodium will also be discussed.

This review will consist of three parts: (i) rationale and need for immobilizing palladium on a solid support, (ii) comparison of various palladium immobilization systems; and (iii) applications of these solid-bound palladium catalysts in organic chemistry. Some personal speculations about the future of this burgeoning field will also be included for the sole purpose of eliciting further interest and discussion. The term solid support will be

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used liberally, for lack of better ones, to take account of soluble polymers, which may exist as liquid at ambient temperature.

B. NEED FOR SOLID-BOUND CATALYSTS

A major impetus for the development of solid-supported palladium catalyst has been the cost of this precious metal. As alluded to previously, palladium metal prices have surpassed that of gold and platinum recently.[1] For industrial chemical processes, an expensive reagent like palladium is used in one the following circumstances. (i) The process adds so much value that a stoichiometric amount of palladium can be justified. In such cases the spent palladium is usually collected and sent back to the original manufacture for reclamation. (ii) The palladium catalyst commands such a high activity and turnover number that a minimum amount of the metal is used and the spent catalysts are disposed of along with other reaction waste. (iii) The palladium reagent or catalyst is used in a continuous process for extended periods of time and is recovered. (iv) The palladium catalyst or reagent is used, recycled on site, and reused. In all these cases, immobilization of palladium will facilitate the separation of the metal from the product stream, enabling the chemists and engineers with more choices in designing the synthetic process. Despite the popularity of homogeneous catalysts in recent years, heterogeneous palladium catalysts such as Pd/C still command a dominant share of catalyst sold by volume, ease of recovery being no small factor. In addition, catalyst immobilization enables the utilization of novel continuous reactor designs such as polymeric hollow fiber catalytic membrane reactors.[2]–[4]

The second driver for immobilizing palladium is the savings realized from reusable ligands. This is especially true for those designer chiral ligands that may take multiple elaborate steps to prepare. Attachment of ligands onto a solid support also simplifies the tedious task of separating the product stream from residual ligands such as phosphines and their oxides.

An often underappreciated advantage of immobilized palladium catalysts over their free counterparts is the control of residual palladium in the final products. This is especially relevant to pharmaceutical manufacturing processes. While not extremely toxic ($LD_{50} = 25$ mg/kg, rat oral, chloride), palladium at higher intakes is poisonous.[5]–[10] However, the carcinogenic potential of the palladium ion is still unclear. Although there is some evidence that it is capable of acting as a mutagen, other research has concluded that evidence for palladium genotoxicity seems to be low in mammalian and bacterial cells.[11] Nonetheless, strict regulations have to be followed to maintain a minimum amount of residual palladium in drug products. This can be a formidable task as virtually all marketed drug molecules are polar compounds having various coordination sites with an affinity for soluble transition metals. Complexing palladium by a solid support has proved to be an efficient way of removing even trace amounts of palladium from product solutions.[12] Even more, immobilization of the ligand and palladium onto a solid support greatly facilitates the workup and purification of the products as tedious extractions are reduced to a simple filtration. Another practical aspect is the dramatically reduced odor and toxicity and increased chemical stability of the immobilized ligands on a polymeric support in comparison to their free counterparts. This is especially true for ligands with air-sensitive moieties such as alkyl phosphines.

An intellectually more intriguing aspect of immobilized catalysts, other than the aforementioned practical benefits related to better handling properties, is their ability to offer improved activities and selectivities. Site isolation of catalytic centers on a polymer network prevents catalyst deactivation through internuclear interaction. This is especially pertinent to palladium catalyst since Pd(0)-black precipitation has been the primary pathway for catalyst deactivation in most homogeneous Pd-catalyzed processes. In addition, the ability to introduce into the polymer matrix a second active site, though not directly participating in the reaction, offers great opportunity of fine-tuning the activity of the catalytic center. Polymer-supported palladium complexes have been demonstrated to afford a higher level (10×) of catalytic activity than their structurally analogous monomeric counterparts in the Heck arylation of methyl acrylate by iodobenzene. This higher catalytic activity of the polymeric catalyst was attributed to its resistance toward deactivation via aggregation of the reactive complex to insoluble Pd metal clusters or by disproportionation to a sterically blocked and coordinatively saturated species.[13] Much progress has been made in the application of the molecular imprinting concept in the fabrication of catalysts,[14]–[26] and if the current trend continues, those tailor-made catalysts with superior activities and selectivity for a specific chemical process will come to fruition in the near future. Already several polymeric ligands are commercially available and the choices are expanding.

C. NATURE OF SOLID SUPPORT

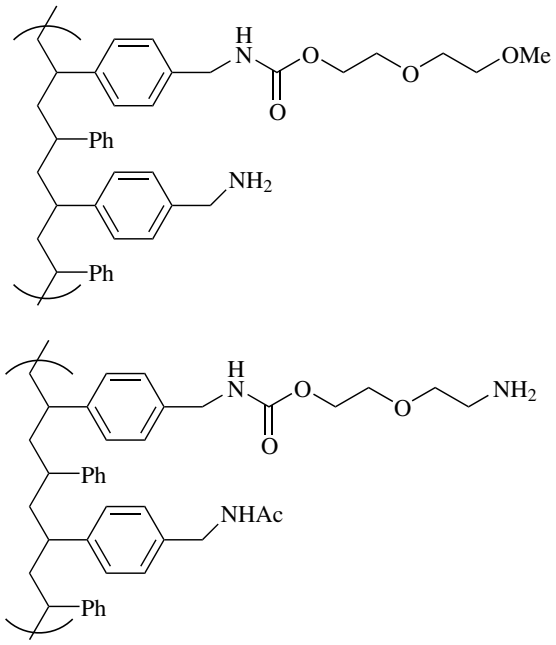
C.i. General Overview

The solid support for catalyst serves three purposes: (i) a site for the attachment of ligands to bind palladium, or any other metals, to create the catalytic center; (ii) an environment to facilitate the diffusion of substrate and product to and from the active sites; and (iii) a phase differentiation mechanism to enable the separation of the support with the bound catalyst from solvents, products, and by-products alike. To play these roles, the support system should remain inert during the reaction conditions; be permeable to reagents, substrates, and products; and maintain reasonable mechanical integrity. Several factors must be considered in choosing a suitable support for a particular catalytic reaction. These include the choice of ligands attached, swelling properties of the support, loading capacities for the ligands, and stability toward air, moisture, solvents, and other chemicals during the reaction and workup. Mechanical vulnerability toward agitation and recycling is also a major contributing factor with regard to leaching of either ligand, metal, or both from the support. Many of these issues are interrelated, such as mechanical strength and swelling properties, making the search for a *universal* catalyst support suitable for all occasions a formidable, if not an impossible, task.

C.ii. Types of Polymers

Resin type plays the most crucial role in its suitability as a solid support for catalyst. Consideration must be given to the cost, availability, functionlization, and chemical stability of the polymer under the given reaction conditions. Modification of existing resins by introducing linkers or side chains to the polymeric backbone can improve resin performance significantly. For example, incorporation of a PEG chain either as a linker between the primary amino group and the polystyrene backbone or as a side chain improved

swelling property and solid-phase synthetic efficiency appreciably (**Scheme 1**),[27] indicating the main role of PEG as a swelling behavior modifier. Intense research activities in solid-phase synthesis have led to the development of a repertoire of analytical methods to assess the synthetic efficiency of a particular support[27]–[29] and distribution of functional groups across the resin bead diameter[30],[31] by FT-IR, gel phase NMR, and fluorescence labeling, all of which can be applied directly to polymer-supported catalyst research.

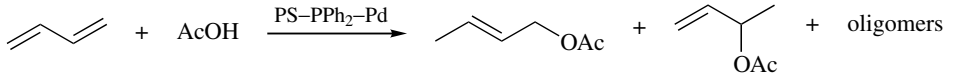


Scheme 1

C.ii.a. ***Polystyrenes.*** Polystyrene (PS) resins are among the earliest polymer supports for both solid-phase synthesis and catalytic reactions, starting from the Merrifield peptide synthesis. Polystyrene resins still command a dominating lead in solid-phase synthesis over other polymers for their low cost and inertness under most reaction conditions. The lack of ligating lone-pair electrons on the backbone offers a unique advantage for metal catalysis over polar polymers such as acrylates, especially if undiscriminating coordination is not desired. Their major drawback is poor accessibility for low crosslinked resins in protic solvents such as water and alcohols. Attaching polar chains to the polymer backbone, not necessarily directly as a linker to the functional groups, improves general swellability considerably. However, loading capacity suffers drastically as these chains increase molecular weight.

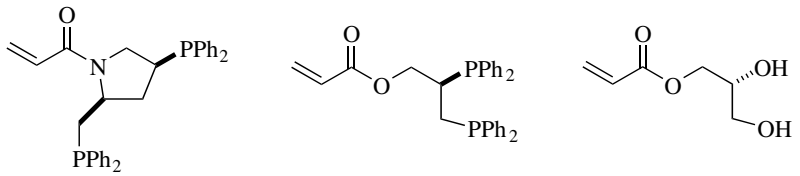
One of the earliest examples of polystyrene-bound palladium was reported by Terasawa and co-workers in 1975,[32] when such a system was used for hydrogenation of olefins and acetylenes and isomerization of double bonds. However, it is not clear if the high activity exhibited by resin-bound catalysts toward hydrogenation was due to the reduced heterogeneous palladium deposited on the resin. Pittman et al.[33] in 1976 prepared a series of diphenylphosphinated PS-based palladium catalysts and studied their behavior

over butadiene oligomerization with acetic acid to give acetoxylated alkenes (**Scheme 2**). These initial studies ruled out a mechanism involving a bridged bimetallic intermediate and established the validity of catalytic site isolation on the polymer matrix. The leaching of Pd from the resin was a serious problem with $PdCl_2$ and $Pd(PPh_3)_4$ as a palladium source, but to a lesser extent when $Pd(OAc)_2$ was used, suggesting a ligand disproportion leaching pathway.



Scheme 2

C.ii.b. ***Polyacrylates.*** Various acrylic acid derivatives are easily prepared and widely available, with the carboxylic group as a convenient pivoting point for attaching ligands. Stille's group has polymerized a number of these functionalized olefin monomers and used them for the preparation of polymers with chiral phosphines (**Scheme 3**).[34]–[36]



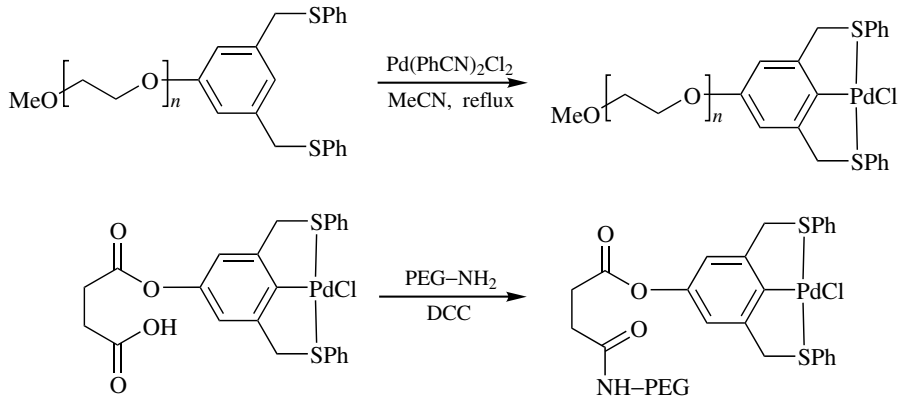
Scheme 3

Bergbreiter and co-workers[37]–[42] have pioneered the area of so-called smart catalysts, taking advantage of the temperature-dependent solubility differences of *N*-isopropylacrylamides. These polymers are soluble below their lower critical solution temperature (LCST), but precipitate upon being heated above the LCST, thus providing a unique mechanism for catalysts separation and recovery. The polymeric catalyst is soluble in aqueous or mixed aqueous/organic media and has high activity in nucleophilic allylic substitution and in Sunogashira–Castro–Stevens cross-coupling of alkynes with aryl iodides. The catalyst can be recycled efficiently by solvent or thermal precipitation methods. Advantages of polyacrylates include ease in the preparation of functionalized monomers, high loading capacity, and good accessibility in polar solvent. Existence of labile, polar groups and relatively acidic protons on the polymer backbone become a liability in some applications.

C.ii.c. ***Polyethers.*** Polyethers encompass a very diverse collection of polymers ranging from the very flexible polyethylene glycol (PEG) to the highly rigid polyphenylene ethers. As a group they tend to possess a high degree of inertness toward a variety of chemical conditions. A major drawback of these polymers is the low loading level, especially for PEGs. Poly(2,6-diphenyl-1,4-phenylene oxide) containing cyclopentadienyl ligands has been made by direct lithiation of the parent polymer followed by reaction with 2-norbornen-7-one and an ensuing retro Diels–Alder reaction. The resulting polymer served as a ligand for cobalt, titanium, and rhodium.[43] This type of polymer exhibits better thermal stability than typical polystyrene-based ones. The Co

and Rh complexes prepared as such proved to be effective hydroformylation catalysts, while the immobilized titanocene hydrogenated cyclohexene 10–70 times faster than its homogeneous analogs.

Janda's group[44]–[47] have advocated the use of soluble polyethylene glycol (PEG resin) as a platform for catalysis as well as for combinatorial synthesis, for the advantages of being able to conduct reactions in a homogeneous solution with soluble PEG resin in polar solvents, and easy recyclability via precipitation upon decreasing solvent polarity. While homogeneous Pd-catalyzed transformations have been used routinely on PEG-bound substrate in parallel synthesis,[44], [48]–[50] very little has been reported on the pure PEG-bound palladium catalysts. A notable exception is that from Bergbreiter's group (**Scheme 4**),[51] who described a new pincer-type SCS ligand containing Pd(II) as a simple, robust catalyst for the Heck reaction with a variety of alkene acceptors and aryl iodides. These ligands were synthesized and attached to polyethylene glycol of a mean molecular weight around 5000 via ether or amide linkages. Compared with the analogous PCP-type catalysts reported by Milstein and co-workers,[52] these SCS catalysts are less active toward inserting into aryl halide bonds but avoid the requirement of an air-sensitive phosphine synthesis. They can readily be recycled upon the completion of each cycle by pouring the DMF reaction solution into diethyl ether to precipitate the catalyst. This is one of the first examples of palladium immobilized through a metal–carbon bond. Soluble PEG-bound arylphosphines have been prepared and used in the Staudinger and Mitsunobu reactions,[46] while the use of these phosphines as ligands for catalysis has yet to be reported.



Scheme 4

C.ii.d. ***Polyethylene.*** Bergbreiter and weatherford[53] have reported the use of diphenylphosphine-terminated ethylene oligomers as ligands for Pd(0) and Pd(II). The ligand is made simply by living polymerization of ethylene with butyllithium followed by capture of the long-chained alkyllithium with $ClPPh_2$ to give a soluble polymer with low molecular weight (1400–2000). Homogeneous reactions including allylation of amines, β-ketoesters, and cyanoacetate were carried out with essentially complete recovery of the Pd catalyst in the first cycle. One major limitation is the stability of the electron-rich phosphine toward air oxidation, which hampers its recyclability. In general, use of polyethylene as a solid support is restricted by its inherent low loading capacity, which diminished precipitously with

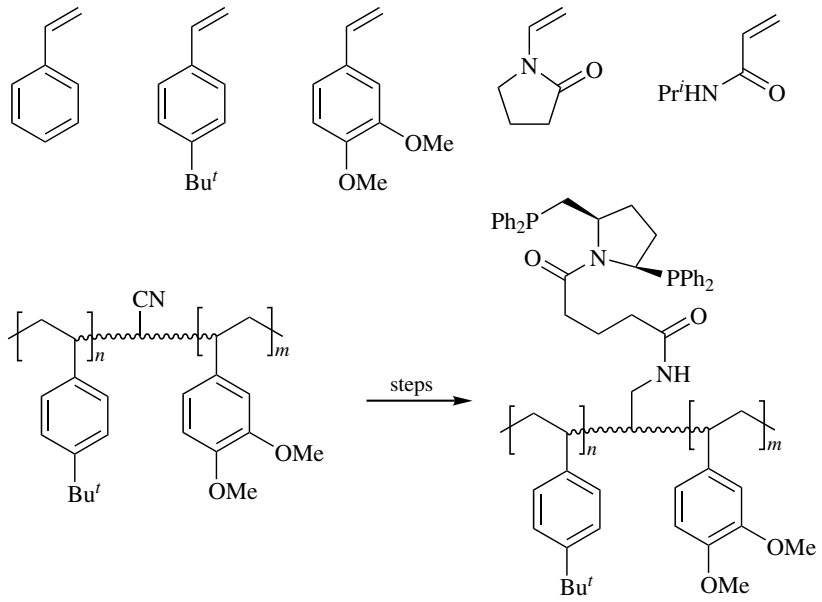
increasing molecular weight and limited swelling profiles. Though some work has been carried out using surface etching methods such as plasma oxidation as a means of introducing functional groups onto the surface, nonetheless its poor swelling characteristics and low effective loading severely limited its application as a catalyst carrier.

C.ii.e. ***Ion Exchange Resins.*** Various strong cation exchange resins such as Amberlyst-15 (crosslinked PS-bound sulfonate) have long been used for the extraction and recovery of transition metals from aqueous solution. Due to the high loading of the sulfonic acid residue, chelation is inevitable on such polymer matrixes. Application of these resin-based catalysts has been limited to hydrogenations[54]–[58]and other transformations characteristic of heterogeneous metal–palladium-mediated processes.[59],[60] The nature of these supported catalysts has not been well characterized, with some evidence lending support to the existence of a metal colloid. However, Heck reaction of aryl iodides has been carried out using a Pd(II) catalyst in the form of $PdCl_2$ supported on anion exchange resin, which can be recovered and reused several times.[61] Cation exchange resin has also been used as a carrier for Rh-catalyzed hydroformylation reactions.[62] Oxidation of naphthalenes to naphthoquinone[63] and ethylene to acetic acid[64] has been achieved using palladium deposited on ion exchange resin with H_2O_2 and O_2, respectively. Palladium(II) salts absorbed on polymer-bound tertiary amines (Amberlyst A-21) have been used as catalysts for ester interchange,[64] with palladium presumably playing a Lewis acid catalyst.

C.ii.f. ***Grafting Polymers, Copolymers, and Other Novel Support Structures.*** Incorporation of hydrophilic chains such as PEG enhances the swelling property, and hence reagent accessibility of polystyrene resin in a polar media. Commercially available resins of this type include Argogel® and Tentagel®, made from lightly crosslinked polystyrene backbone with PEG as linkers to the functional groups. Mechanical stability, loading level, and handling properties are some of the challenges to overcome when considering these resins as a catalyst support. Macroporous polystyrene with grafted PEG chain[65] has proved to be generally applicable in a wide range of solvents including water. A high degree of crosslinking and internal surface area provided both mechanical stability and free access of reagents to the reaction center. Since reagents and substrates diffuse to reaction centers through the pore structures rather than swollen gel matrices, reaction can be carried out without the limitation of swelling solvents as for gel-type resins. High crosslinking also makes these resins suitable for repeated uses as catalyst carriers.

By applying a sequential normal/living free-radical polymerization strategy, Janda and co-workers[66],[67] have produced libraries of linear block polymers with a nitrile group from the radical initiator embedded in each polymer chain using various vinyl monomers (**Scheme 5**). The nitrile group can be reduced to amino groups, which become the anchoring point for attaching chiral phosphines.[66] The catalyst prepared from this support has been successfully employed in the enantioselective hydrogenation of dehydroamino acids. This methodology affords a rapid access to a library of polymers with different solubility profiles for screening. A major drawback of this type of block polymers is the inherent problem of low loading capacity, each polymer chain having only one ligand attached. However, further exploration of the potential of monomer-based functionalization, rather than that of an initiator-based one, would likely solve this problem.[68],[69]

Notable among the new polymer types are those polymers derived from enantiopure binaphthol[70] with chiral BINAP attached. While application to Pd-catalyzed processes has not been reported, they represent rare examples of the cooperative effect of the



Scheme 5

polymer environment with the ligands. Polyolefins have been prepared by ring-opening metathesis polymerization (ROMP) to give a linear polymer bearing carboxyl groups as anchoring point for catalysts.[71] Free-radical-mediated living polymerization provided another very powerful route for fabricating grafting polymer with dense and yet accessible functional group distribution.[69]

C.ii.g. ***Inorganic Support.*** Silica- bound catalyst can easily be prepared either by surface modification or a sol-gel process.[72]–[78] Palladium catalyst prepared from such a support was used for hydrosilylation in the early 1970s.[79] A novel bimetallic system consisting a well-defined Rh species coordinated via a isocyanide tether to silica deposited with heterogeneous palladium was reported to offer superior activity to either metal catalyst alone.[80] Major drawbacks of this class of support are the instability toward basic aqueous media and the prevalence of free hydroxyl groups on the gel surface, which are not compatible with many reactions.

Inert metals such as platinum have been used as a support for palladium catalyst through a putative metal–metal bond resembling those present in metal clusters.[81] There have been numerous reports concerning the use of various zeolites as support for palladium catalysts.[79],[82],[83] Palladium complexes entrapped into zeolite cages have been reported to be reusable catalyst for the Heck reaction, without the difficulties associated with cage diffusion problems.[84]

C.iii. Degree of Cross-linking

The level of crosslinking of a polymer is the single most crucial factor in determining its suitability as a catalyst support after the backbone composition.[85] Linear polymers tend to have better solubility and swellability, and hence offer better accessibility to the

catalytic centers, as diffusion is usually not a problem with these polymers in suitable solvents. Reactions conducted in these environments are analogous to those in a homogeneous medium. However, one must also consider the major drawbacks of these linear polymers as catalyst carriers. First, their applications are strongly solvent dependent on their swellability. Second, they tend to cause more problems during the reactions and workup as a consequence of gelling up, making separation of the polymers from the low molecular weight components difficult. Third, linear polymers generally possess inferior mechanical stability when compared with their more crosslinked counterpart. While the first two problems can be alleviated to a certain degree by judicious choice of solvents and other means, poor mechanical strength is difficult to ameliorate, limiting their ability to be recycled and reused. However, soluble polymers do possess a unique dimension in their applicability, as changing the composition of solvent would enable one to selectively separate the polymer from the rest of the reaction system.[45]

In contrast, crosslinked polymers, being insoluble in all solvents, provided the best handling properties when produced as free-flowing spherical beads. By controlling the degree of crosslinking, useful levels of swelling can be obtained for reactant accessibility. Separation normally involves a simple filtration and washing with appropriate solvents to remove small molecules. Superior mechanical strength also makes them desirable in chemical processes involving agitation. The most widely used polymer in solid-phase synthesis has been 1–2% crosslinked polystyrene, which swells substantially in aprotic solvents such as CH_2Cl_2 and THF. On the other hand, diffusion of substrates into highly crosslinked polymer can be a problem, and in those cases controlling porosity of the resin during polymerization becomes critical in ensuring accessibility. Polystyrene with a higher degree of crosslinking (5–20% divinylbenzene), generally referred to as macroreticular resins, can be prepared with different pore size distributions by the deployment of porogens, that is, solvents or small molecular weight polymers, during the suspension polymerization process. Since substrates can reach only to catalytic sites either on the bead surface or within larger pores in highly crosslinked polymers, distribution of pore sizes and surface area will directly affect the effectiveness of the catalysts.[54],[86],[87] In practice, 1–2% crosslinked polystyrene has been the polymer carrier of choice as it retains much of a soluble polymer's accessibility, while possessing a crosslinked polymer's virtues in separation and handling. However, recent advances in macroporous polymers with improved accessibility and loading level will likely change the landscape of the playing field.

C.iv. Loading Capacity

Loading capacity refers to the extent of polymer functionalization that can be used for the attachment of reagents, substrate, ligand, or metals. For some polymers, such as polyvinylpyridines, essentially every repeating pyridine unit can be considered as a functionalized ligand. Loading can reach 9 mmol/g, limited by the molecular weight of the repeating monomers, barring the presence of crosslinking comonomers (e.g., divinylbenzene). For others, such as Merrifield resin (chloromethylated polystyrene of 1–2% crosslinking), loading capacity is limited by the method of polymer preparation. For those prepared via postpolymerization Friedel–Crafts chloromethylation (e.g., $MeOCH_2Cl$, $SnCl_4$ as catalyst), useful loading levels of 1–3 mmol/g can be achieved, depending on the effectiveness in loading, which is directly related to catalysts used, site, and accessibility. An advantage of this method[88] is that the functional groups are generally accessible for

later use given the right solvents, with effective loading reflected by the polymer composition. This is quite intuitive since if a particular site can be functionalized, the resulting group is likely to be as accessible. However, postpolymerization modification tends to give large variations in loading level, and changes in swelling characteristics further limit the chemistry that can be performed on a given polymer. To address these concerns, copolymerization of prefunctionalized monomers has been used widely. This method offers the benefits of high loading and better reproducibility. However, differences in activity of various monomers toward polymerization may lead to heterogeneity in functional group distribution, resulting in some of them being embedded inside the core and becoming inaccessible. This problem can be alleviated to some extent by grafting[86] and living polymerization,[69],[89] affording tailored polymer beads having nonfunctional cores populated with functionalized chains. As a result, these polymers have the advantage of high mechanical strength and accessibility, uniform distribution of functional groups, and high loading. While the commercial availability of functionalized styrene derivatives is very limited, other vinyl monomers such as acrylates are widely accessible for the preparation of these engineered catalyst carriers.

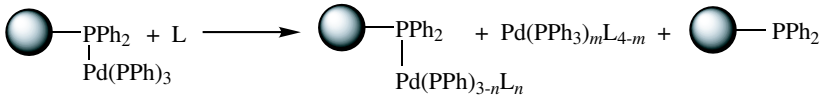
C.v. Choice of Ligands

Choice of suitable ligands for a particular reaction can be based on homogeneous catalysis data when accessibility of the polymeric environment is taken into consideration. Phosphines remain the most popular ligands in palladium chemistry for well-known reasons including appropriate stereoelectronic properties for catalyst turnover, numerous applications in metal catalysts, and commercial availability of a wide choice of phosphinic reagents with varying degree of electron density and steric bulk. The atomic radius of a phosphorus atom seems to be a perfect match for that of palladium as far as orbital overlap is concerned. Phosphines also possess the desired dynamic behaviors to allow dissociative pathways to operate, displaying a colorful array of catalytic activities. Due to a rich history of phosphine coordination chemistry, most work in polymer-supported palladium catalysts, especially earlier ones, focused on the use of these ligands.[32],[33],[90] Recent advances in chiral phosphines further fueled the pace of discovery toward a recyclable version of these expensive chiral ligands, which often required multistep synthesis. Chiral BINAP, as the golden standard of the class, has been attached to various supports by different linkers,[70],[91]–[99] along with DIOP[34],[100]–[103] and other popular chiral manifolds.[104]–[109] A polysiloxane-based phosphine prepared via the sol-gel process from $(MeO)_3Si(CH_2)_3(Ph)PCH_2CH_2OMe$ has been used as a ligand for palladium in hydrogenation reactions.[110],[111]

The major drawback of phosphine-based ligands is their instability toward air oxidation, which is suspected to be the major cause for catalyst deactivation and metal leaching from the support. For triarylphosphines, such as $Ph_2PC_6H_4CH_2$–PS, the problem is not as pronounced as their alkyldiaryl, dialkylaryl, or trialkyl analogs. Attachment of these ligands to a polymeric matrix does seem to attenuate their susceptibility toward air oxidation considerably, and the polymeric ligands can be handled in air briefly for most practical purposes. Moreover, commercial availability of polystyrene-bound triarylphosphines from several sources will undoubtedly stimulate the use of this class of polymeric ligands in the area.

Another factor contributing to the leaching of palladium from phosphine-based support is the cleavage of C—P bond under certain circumstances,[112]–[115] presumably

through quarternization. However, exchange with free ligand through a disproportionation mechanism is a far more serious problem, especially when free phosphines are used during the reaction (**Scheme 6**).



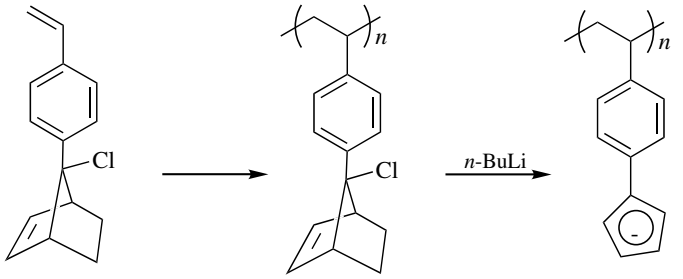
Scheme 6

Nitrogen as a ligating atom for palladium in a polymeric system has received widespread application. Chiral oxazolines with an acrylate group attached have been polymerized with various vinyl monomers to afford chiral polymers primarily used as chromatographic medium.[116] Similar polymeric oxazolines have been immobilized on modified silica gel as chiral stationary phases for chromatography.[117] Transition metal salts, including those of palladium, have been incorporated into organic–inorganic polymer hybrids by the acid-catalyzed sol-gel reaction of tetraethoxysilane in the presence of poly(2-methyl-2-oxazoline).[118] Interestingly, application of these homogeneous polymer hybrids containing transition metal salts involve pyrolysis to remove organic components, resulting in a porous silica-supported catalyst with high surface area. Dimethylaminated polystyrene-anchored $PdCl_2$ complexes have been reported as olefin hydrogenation catalysts with appreciable selectivity with regard to steric hindrance around the double bond.[119],[120] Palladium anchored by *N*-phenylanthranilic acid or anthranilic acid attached to chloromethylated polystyrene beads was found to be effective in the hydrogenation of alkenes, aryls, PhCN, and $PhNO_2$.[121] Polymer-anchored Pd(II) complex catalyst was synthesized by sequential attachment of 1,2-diaminopropane as a ligand to the chloromethylated styrene–divinylbenzene copolymer. However, application of these *N*-ligated palladiums on polymeric support has been limited to recyclable hydrogenation catalysts.[122] Functionalization of the polystyrene surface via oxygen or ammonia plasma treatment proved to be a novel way to achieve palladium anchorage through the creation of oxygenated or nitrogenated functional groups on the polymer surface.[123] Polythiourea derived from chiral diamines has been found to reduce phenyl ethyl ketone via transfer hydrogenation to afford (*R*)-phenylethanol with ee of 70%. Polyvinylpyridines of various crosslinking degrees are commercially available. These polymers, either alone or fabricated with silica, have been studied extensively as carriers for palladium and other group VIII metals as hydrogenation catalysts.[124]–[129] Polymer-bound phenanthroline has been found to be an efficient carrier for palladium in the Heck reaction of aryl iodides and acrylamide.[130]

Poly(*N*-vinyl-2-pyrrolidone) has been studied as a carrier for palladium in the hydrogenation of olefins[131],[132] and nitroaromatics,[133] hydrodehalogenation of organic halides,[134]–[136] and carbonylation of allyl halides.[137],[138] In these cases PVP mostly likely played the role of supporting *in situ* formed colloidal Pd, rather than that of a well-defined ligand.

Stille and co-workers devised an elegant method for attaching cyclopentadienyl ligand onto polystyrenes. Thus, reaction of *p*-styryl-MgBr with norbornen-7-one gave *syn*-7-(*p*-styryl)norborn-2-en-7-ol, which was converted into 7-chloro-7-(*p*-styryl)norborn-2-ene. Polymerization of this compound with styrene and divinylbenzene gave polymers

containing 10 mol % norbornyl derivative. Treatment of the copolymer with BuLi gave polymer-bound cyclopentadienyl anions that could be converted to polymer bound rhodium or cobalt catalysts and used for hydroformylation of 1-hexene (**Scheme 7**).[43],[139]

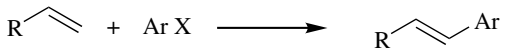


Scheme 7

D. REACTIONS CATALYZED BY IMMOBILIZED CATALYSTS

D.i. Heck Reactions (Scheme 8)

The Heck reaction (**Scheme 8**) using polystyrene-bound phosphines has been studied extensively.[140] The ratio of Pd/P appeared to be crucial in these cases, as low activity was observed with a Pd/P ratio of 1:5, while during the same time a ratio of 1:1 gave full conversion. The Heck reaction of aryl iodides and acrylamide has been carried out in the presence of polymer-supported phenanthroline-bound palladium. This method proved to be a very efficient for two-carbon functionalization of aryl halides when combined with a Hoffmann degradation.[141],[142] The use of Davisil 300, hydrophobically modified controlled-pore glass beads, commonly employed as reverse phase column packing, has been used to anchor $(Ph_3P)_2Pd(OAc)_2$ as a catalyst for Heck and allylic substitution reactions with a low level of leaching, and in the latter case, a high enantiomeric excess.[143] In a similar note, palladium absorbed on glass beads modified with guanidinium phosphine ($P[C_6H_4$-3-$C(NMe_2){=}NH]_3$) exhibits high activity and low metal leaching.[144] Palladium complexes on silica as well as on functionalized styrene–divinylbenzene crosslinked resins with bidentate ligands such as acetylacetonate and 1,3-bis(diphenylphosphino)propane moieties have been used in the catalytic telomerization of 1,3-butadiene with methanol. Their performances were studied in terms of activity and selectivity in formation of telomers.[145] While the catalyst resulting from acetylacetonate appeared to be labile during the catalytic cycle, the polymer–diphosphine-based ligand displayed activity and selectivity comparable with those of the corresponding homogeneous counterparts, without appreciable metal leaching to the solution. As mentioned before, the pincer-type, tridentate, sulfur–carbon– sulfur ligated palladium system attached to polyethylene glycol via ether or amide linkages proved to be an effective catalyst for the Heck reaction[51] with remarkable air stability and recyclability. An engineered solid-supported Heck vinylation catalyst has been

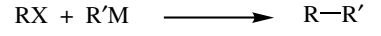


Scheme 8

developed taking advantage of the water-soluble phosphine ligand TPPTS (triphenylphosphine trisulfonate sodium salt)[146] immobilized on polyethylene glycol film on silica support. Miraculously, the complicated system is stable enough for several recycles without the leaching of Pd at high temperature, despite the fact that the phosphine was attached to the support without a covalent bond.[147] A silica-supported polymercaptopropylsiloxane palladium complex was reported to be easily prepared from mercaptopropyltriethoxysilane and silica via hydrolysis, followed by treatment with palladium chloride in acetone. The resulting surfur-ligated palladium was found to be an efficient catalyst for Heck arylation of acrylamide and butyl acrylate for several cycles without noticeable loss of activity.[148],[149] Analogous aminopropylsiloxane has also been applied as a support for palladium in Heck reactions.[150] Merrifield resin-derived arylphosphine-bound palladium has been used to catalyze the coupling of allylic alcohols with hypervalent iodonium salts.[151] A totally inorganic support such as zeolite has been used to trap palladium complexes and for the Heck reaction. It is noteworthy that except for very large complexes, no limitation to the diffusion of products in the zeolite cages was observed and the catalysts proved to be active even for aryl chlorides under standard reaction conditions.[84] Along a similar line, palladium impregnated in mesoporous molecular sieves such as MCM-41 offers great interest for its large (>20 Å) and uniform pore sizes and hence the ability to allow facile diffusion of substrate to internal active sites.[152] Modified silica-supported catalysts of the type SiO_2–X–$(NH)_2$-Pd–L_2 (L = $P(C_6H_5)_3$ or C_6H_5CN and X = Sn, Al or Ti) were studied for the Heck reaction of iodobenzene with methyl acrylate. The catalysts were stable and could be reused several times in normal atmosphere without appreciable loss of catalytic activity.[153]

D.ii. Cross-Coupling Reaction (Scheme 9)

Suzuki coupling[154] of organic boronic aicds with aryl or alkenyl electrophiles is widely used in the construction of functionalized aromatic compounds and stereoselective synthesis of substituted alkenes. The reaction has the advantages of being remarkably chemo-, regio-, and stereoselective, and can be carried out under mild reaction conditions, compatible with a wide variety of functional groups. High reaction efficiency, stability of the organoboronates toward air and moisture, and simple workup and waste treatment procedures further underscore the popularity of this Pd-catalyzed process. Suzuki coupling also happens to be one of the most forgiving Pd-catalyzed C—C bond-forming processes when it comes to ligand choice.[155] Jang[156] and Fenger and Le Drian[157] have reported the use of polystyrene-attached phosphines as a catalyst carrier for Suzuki coupling, where the catalyst was recycled over 10 times with minimal loss of activity. Zhang and Allen[158] have reported the use of a novel polysiloxane-bound thiourea as a carrier for palladium in Suzuki couplings for repeated usage. A graft polymer of PEG and polystyrene has been attached to triarylphosphines and successfully used for Suzuki coupling reactions in aqueous solutions.[159] A water-soluble polymer-bound Pd(0)–phosphine catalyst based on polyacrylamide[38] has been applied to the coupling of aryl iodides with terminal alkynes. The catalyst can be recycled efficiently by either solvent or thermal precipitation methods.



Scheme 9

Cross-couplings between organotin (Stille type), Grignard reagent (Kumada type), and aryl halide have been carried out using palladium over silica support.[160]

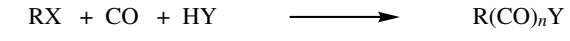
D.iii. Carbonylation and Hydroformylation (Scheme 10)

Examples of solid-bound Pd-catalyzed carbonylation of aryl and alkenyl halide, allyl alcohol, and derivatives are abundant in the literature. Polyketones have been obtained via carbonylation of ethylene and carbon monoxide catalyzed by palladium complexes of polysiloxane-bound phosphine[161]–[165] or Pd(dppp) absorbed on alumina.[166]–[168] Similar processes can also be carried out by catalyst formed simply by absorbing $Pd(O_2CNEt_2)_2(NHEt_2)_2$ onto silica gel.[169] Polyphosphine-bound palladium has been used to prepare ethyl hexanoate from 1-pentene, CO, and ethanol.[170] Similar esterification of styrene has been achieved using a bimetallic system involving palladium and nickel immobilized on poly(*N*-vinyl-2-pyrrolidone).[171]

Carboxylic acids have been prepared from carbonylation of allyl bromide over palladium catalysts supported by polyphenol,[172] polyvinylpyrrolidone,[173],[174] polyacrylamide (PAA), modified poly(2,6-dimethyl-1,4-phenylene oxide), and polysulfone.[2],[137],[175] It is unclear under these reducing conditions if gel form metal cluster is involved as the active catalyst. Palladium acetate immobilized on the clay montmorillonite has proved to be an effective catalyst for the carbonylation of secondary allylic alcohols, affording α,β-unsaturated carboxylic acids in moderate yields. However, triphenylphosphine was needed for the activivation of the catalyst.[176] Palladium catalyst bound to a platinum cluster has been used up to three times for allylic alkylation without a significant loss of its activity.[81] Preliminary study indicated that the Pd—Pt bond remains intact during the catalytic cycle.

Linear, phosphinated polystyrenes have been synthesized from low molecular weight chloromethylated polymer (MW = 1200 and 45,000). The palladium complex prepared from this polymer became soluble and acted as a homogeneous catalyst over 150 °C, and separated as solid precipiate from the reaction mixture upon cooling after the reaction. Counterintuitively, the activity of palladium catalyst for the ethoxycarbonylation of 4,4′-dibromobiphenyl increased with decreased ratio of benzene in the solvent, with maximum activity observed in ethanol. Such an activity difference cannot be solely accounted for by the kinetics as a similar solvent effect was not observed in the reaction with Ph_3P–Pd catalyst. The reaction was also inhibited by the presence of toluene, hexane, THF, and pyridine.[177] Butyloxycarbonylation of aryl bromide has been reported on sulfur-containing polysiloxane.[178] Recently, a commercially available aminopolymer ArgoGel® has been used to anchor triarylphosphine as an amphiphilic ligand for Pd-catalyzed hydroxycarbonylation of aryl halides to give arylcarboxylic acids.[179]

A detailed study on the selectivity of polymer-bound catalysts versus their homogeneous counterparts has been conducted on the Pd(0)-catalyzed alkoxycarbonylation of alkenes[180],[181] with mixed results. Generally, catalyst prepared from diphenylphosphonated polystyrene (1% crosslinked) catalysts gave high selectivity for terminal ester formation, but lower than their homogeneous analogs.[181] Very high turnover was obtained for the same reaction when palladium was immobilized on perfluorinated ion exchange polymer.[182]



Scheme 10

Polymer-bound palladium complexes [polystyrylphosphine–palladium(0) complexes, poly-2-vinylpyridine–palladium(II) complexes, and poly-2-*N*-vinylpyrrolidine–palladium(II) complexes] were prepared and tested as catalysts for a double carbonylation reaction. For example, double carbonylation of PhI in the presence of $HNEt_2$ gave 81% of $PhCOCONEt_2$.[183] Similar transformations have also been reported using polystyrylmercapto–palladium (0) complexes with the catalyst being easily recovered and reused.[184] The double carbonylation of phenyl iodide catalyzed by palladium supported on silica–polytitanazane[185] or polyaluminazane[186] is reported to give $PhCOCONEt_2$ with high yield and selectivity.

Nitroaromatics have been reductively converted into aryl carbamate with methanol under CO atmosphere catalyzed by palladium(II) anchored onto montmorillonite clay.[187] Conversely, the same carbamates can also be obtained via oxidative carbonylation of amines with carbon monoxide and oxygen in the presence of a bimetallic catalyst $PdCl_2$–$MnCl_2$ supported on poly(*N*-vinyl-2-pyrrolidone).[188]

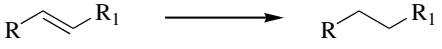
Silica prepared via the sol-gel process has proved to be an excellent support for transition metal (Rh, Ru, and Co) catalyzed processes involving CO.[189] Oswald and Murrell have disclosed a novel chlorosilylalkylphosphine, $Ph_2P(CH_2)_8SiCl_3$, prepared easily from hydrophosphinylation of silylalkene, serving as a ligand for Rh-catalyzed hydroformylation. Polysiloxane-bound phosphine prepared from this ligand via the sol-gel process also proved to be a useful catalyst for hydrogenation and hydroformylation.[190],[191] On a separate note, carbonylation of organic halides using polymer-anchored palladium afforded esters in reasonable yields under solid–liquid solid-phase transfer conditions.[192]

D.iv. Hydrogenation (Scheme 11)

Hydrogenation is the most well studied area among immobilized palladium catalysis. While a great majority of the applications focused on the use of support such as alumina and activated carbon, a great diversity of novel support systems have been reported in recent years, aimed at finding a catalyst with a well-characterized coordination sphere and tailor-made activity. Pd(0) catalysts dispersed on crosslinked styrene–divinylbenzene copolymers have been prepared by impregnation of lipophilic complexes followed by reduction with hydrazine. It was found that the functional groups in the polymer as well as polymer particle sizes had a major effect on catalyst activity.[37], [40], [193]–[195]

Much activity in this field, however, focuses on Ru- or Rh-catalyzed asymmetric hydrogenation of acylaminoacrylate with polymer-bound chiral phosphines to afford chiral amino acids. As early as 1976, Stille reported asymmetric catalytic hydrogenations of these compounds using an acrylate–styrene copolymer-bound DIOP [2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphine)butane] and other chiral phosphines.[34],[35],[108],[109],[196]–[198]

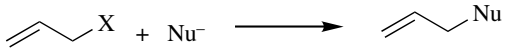
In recent years, other support systems have been reported with mixed results, including cyclodextrin.[199] Anchoring anthralinic acid (*o*-$H_2NC_6H_4CO_2H$) to chloromethylated polystyrene beads followed by treatment with $PdCl_2$ gave a catalyst that is effective for hydrogenating alkenes, dienes, and even benzene. The catalyst is air stable and has a lifetime of 10,000 catalytic cycles per Pd atom.[200]



Scheme 11

D.v. Allylic Activation (Scheme 12)

Palladium supported on silica was found to be an effective catalyst for the α-allylation of cycloketones via their silyl enol ether using diallyl carbonate.[201] An early example of allylic substitution by soft nucleophile (α-ketoester and cyanoacetates) using polymer-supported catalyst involved the use of diphenylphosphine-terminated ethylene oligomers as ligands.[53],[195] Similar transformations were also facilitated by palladium dispersed in an insoluble, crosslinked polystyrene resin.[202] The same group also pioneered the use of polyacrylamide-bound phosphine–palladium complexes in allylic substitution reactions,[38] where the catalyst can be recovered using either solvent or temperature-dependent solubility differences. Allyl chloride or allyl acetate can be activated by $SnCl_2$ in the presence of palladium immobilized on cyanopropylsiloxane-modified silica to add to ketones or aldehydes in a 1,2-fashion.[203] A similar type of support has also been applied to Truji–Trost-type allylic substitutions.[204],[205] Palladium catalyst prepared from triarylphosphines attached onto polyethylene glycol–polystyrene graft copolymer (PEG–PS) catalyzed the substitution of allylic acetates of various carbon (1,3-dicarbonyl), nitrogen (NaN_3), and sulfur (sulfinate) compounds in high yields and, remarkably, using water as a solvent.[206] The same transformation can be achieved by catalysts deposited on the surface of mesoporous silica from $Pd(OAc)_2$ and water-soluble sulfonated phosphines.[207],[208]

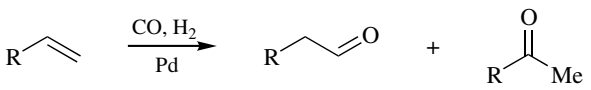


Scheme 12

D.vi. Wacker Oxidation (Scheme 13)

A unique class of polymer, polyquinone-bearing sulfonic acid functional groups, when combined with Pd(II), displayed activities for the oxidation of alkenes to aldehyde, without the need for a cocatalyst such as $CuCl_2$.[209] Here the polymer matrix serves both as a catalyst carrier and a redox mediator. A remarkable solvent effect on the selectivities of a polymer-bound palladium catalyst was observed with the oxidation of 2-octene, affording 97% 2-octayne in EtOH–H_2O and 89% 2-octanone when EtOH was replaced with dixoane.[210] Oxidation of 2-methylnaphthalene to 2-methyl-1,4-naphthoquinone (vitamin K_3) can be effected by palladium absorbed on ion exchanged resin with aqueous H_2O_2.

Wacker reactions using palladium compounds immobilized on several polymeric backbones, including polybenzimidazole, polystyrene, and polyacrylonitrile were investigated.[211],[212] Interestingly, the most active catalyst appeared to be the highly rigid *N*-cyanomethylated polybenzimidazole system with the cyano groups as the ligands.[213] The polymer-supported species exhibited remarkable stability toward high temperature and repeated use and seemed to avert the most common problem encountered in Wacker oxidation, that is, irreversible precipitation of metallic palladium, a phenomenon attributed to the site isolation of metal centers on the support, which prevents aggregation.

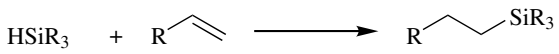


Scheme 13

Cyanomethylated polystyrene[214] and polyimide[215] have also been investigated as Wacker catalyst carriers. A thorough review on polymer-supported metal complexes as oxidation catalyst is available.[216]

D.vii. Hydrosilylation (Scheme 14)

Pd complexes of polymeric diphenylphosphinyl ferrocene are effective catalysts for the hydrosilylation of styrene and 1-hexene by $SiHCl_3$. They can be recycled with no loss of activity.[217] Nitrile groups on macroporous copolymers of acrylonitrile/divinylbenzene/styrene are effective ligands for the immobilization of Rh(I), Pt(II), and Pd(II) complexes, which can be used as hydrosilylation catalysts, with their effectiveness closely related to the morphology of the polymer matrix.[218] Similar transformation was also effected by platinum catalyst immobilized by mercaptan groups over polysiloxane.[219]



Scheme 14

D.viii. Miscellaneous Reactions

Codimerization of acetylenes and allyl halides to give 1,4-pentadiene derivatives can be carried out using polymer-supported palladium(II) chloride catalyst.[220],[221] $Pd(OAc)_2$ bound to diphenylphosphinated styrene–divinylbenzene polymer has been applied to the oligomerization of butadiene to give 1,7-octadiene and higher oligomers.[222],[223]

F. SUMMARY

Much progress has been made in the last three decades on polymer-bound catalysts. A common theme of this field of research, like the huge body of work of combinatorial chemistry, is the focus on *separation*. Combinatorial and high throughput parallel synthesis are based on the invention and adoption of efficient methods for separating the compound of interest (reaction products) from excess reagents or substrates (which are needed to achieve high reaction efficiency so as to minimize impurity levels), solvent, and by-products. Ways to achieve such a high-efficiency separation include bonding substrates to solid supports, bonding reagents to solid supports,[224]–[227] solid-supported reagents to extract products, solid-supports to scavenge excess reagents,[228],[229] selective precipitation of one from the others, and layer separation using either aqueous, organic, or fluorous media.[230] When one considers a specific metal-centered catalyst as just another reagent, many of these methods in parallel synthesis can be applied directly to the separation of catalyst, provided the caveat of catalysts being recycled and reused is taken into consideration. However, most of the current examples of immobilized catalyst development focused on the support system being a mere carrier for the catalyst, striving to achieve similar activities as the homogeneous counterpart with the added advantage of separation. Except for a few isolated cases, these immobilized catalysts in general have not exhibited drastically improved activities and specificities over their free counterparts. The potential of exploiting the power of high throughput synthesis in the discovery of

novel catalysts will undoubtedly accelerate the endeavor of finding immobilized catalyst with vastly improved activities and selectivities. This and the search for new polymers with high mechanical stability, high loading, and general applicability in a wide range of solvents will likely occupy the minds of catalyst researchers for the early part of the new millennium.

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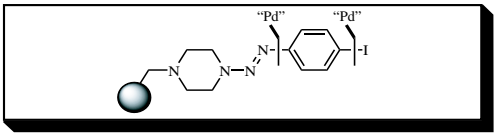

X.3 Organopalladium Reactions in Combinatorial Chemistry

STEFAN BRÄSE, JOHANNES KÖBBERLING, and NILS GRIEBENOW

A. INTRODUCTION AND GENERAL REMARKS

Certain features of organic transformations being performed on a solid support facilitate their use in automated multiple parallel syntheses in a combinatorial way, which have emerged as an indispensable tool to speed up drug discovery in modern life sciences. Therefore, many techniques that were originally developed for the liquid phase have been adapted to be carried out on solid support. The advantages of solid phase transformations such as the avoidance of tedious workup procedures are also particularly valuable for Pd-catalyzed homogeneous reactions, because the soluble palladium catalyst can easily be removed by washing processes. A quasi high-dilution effect and the noninterference of various functionalities in the building blocks on solid support are additional benefits of solid phase chemistry. Thus, in recent of years an increasing number of reports on well-established Pd-catalyzed and Pd-mediated processes being performed on solid phases have been published. This section provides an extensive overview on the use of Pd-catalyzed and Pd-mediated reactions in solid phase combinatorial chemistry and parallel synthesis. While reactions involving immobilized catalysts or solid-phase-bound reagents are covered in **Sect. X.2**, reactions on soluble polymers such a MeO–PEG (polyethylene glycol) and some modern separation techniques (e.g. fluorous phase developments) are covered in this section, which is divided into three parts.

The first part will discuss Pd-catalyzed and Pd-mediated transformations on solid support without cleaving off any higher molecular weight compound from the support. Techniques for the attachment of building blocks and simple group transformations, such as hydrogenation reactions, are also included. In the second part, cleavage reactions that give rise to soluble products as well as transformations that occur right after the cleavage step (derivatization by cleavage) will be covered. Finally, new separation techniques that enhance the throughput for automated parallel synthesis are reviewed.

Throughout this section, the specific type of resin used will always be stated since several reactions can only be carried out on certain supports. If not otherwise stated, the resin bead logo symbolizes the terminal part of the aromatic substructure (see **Figure 1**), and all mentioned polymers are crosslinked (in general 1–2% divinylbenzene). This survey includes available literature up to September 2000. No reference is made to reactions that were carried out only in the liquid phase without any combinatorial aspect.

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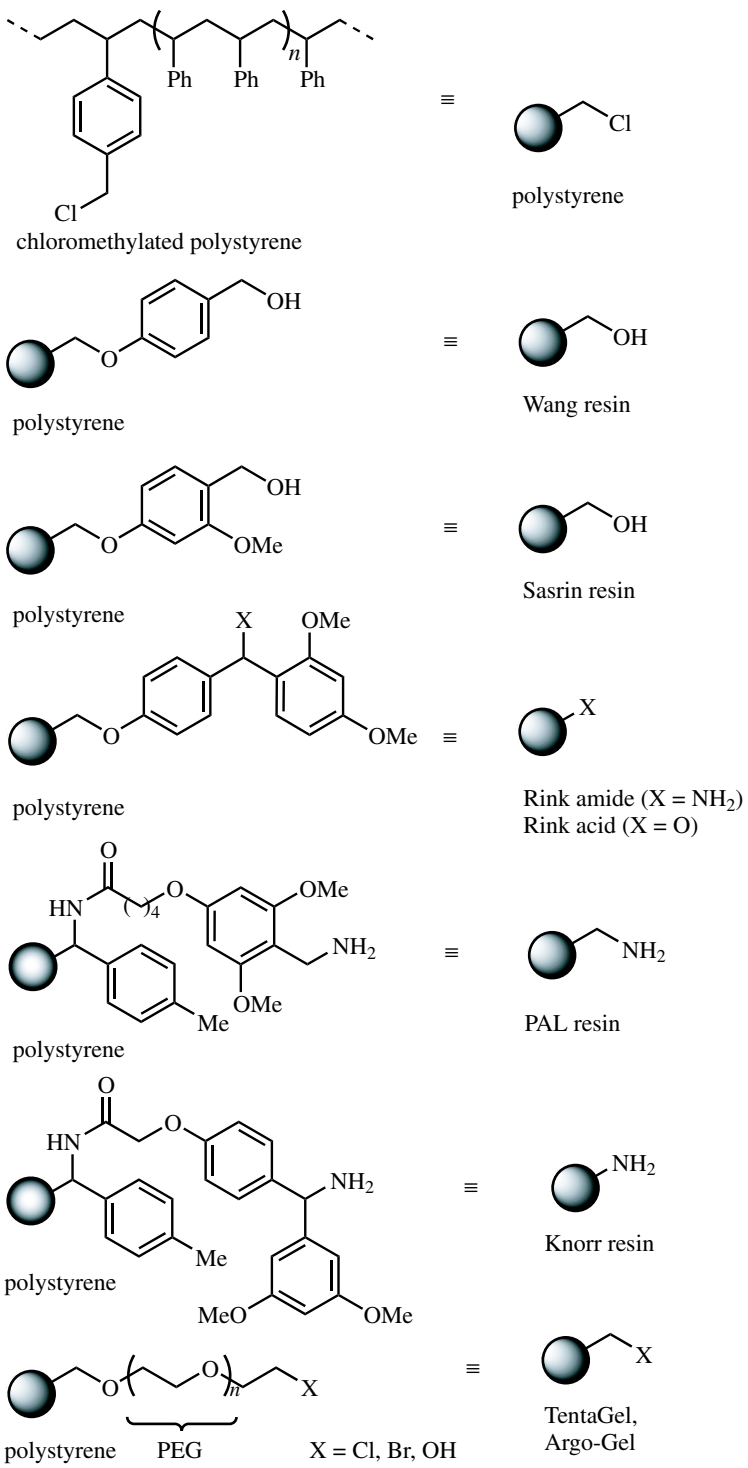


Figure 1. Types of functionalized polystyrene resins used for Pd-Catalyzed and Pd-mediated reactions on solid support (for reviews and explanations, see Ref. [1]).

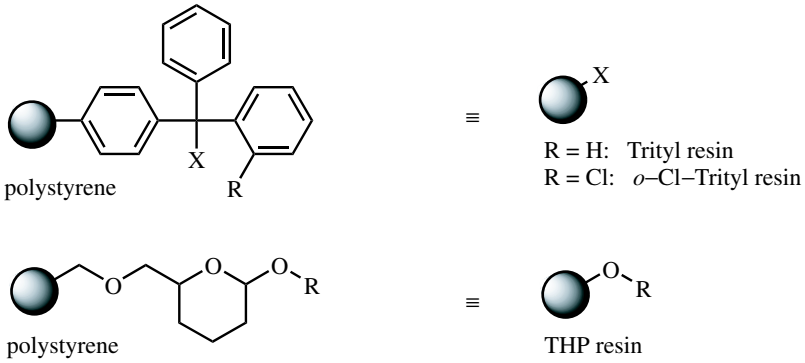


Figure 1. (*Continued*)

Tables 1 and **2** are organized in the order of publication year to acknowledge the originality of the respective disclosure. Whenever no details of the reaction conditions are indicated in the table or scheme, the original publication did not provide this information. The yields and purities refer to those of the final product, when cleavage conditions are mentioned. The number of examples refers to the number of different compounds obtained. Throughout this section "Ar" refers to carbocyclic arenes, whereas "hetaryl" refers to furyl, thienyl, pyridyl, and other heteroaromatic compounds.

B. PALLADIUM-CATALYZED COUPLING REACTIONS AND TRANSFORMATIONS ON SOLID SUPPORTS

B.i. General Remarks

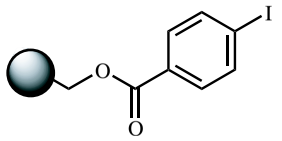
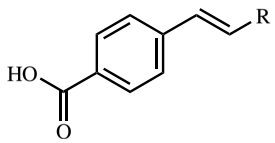
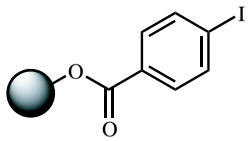
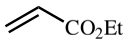
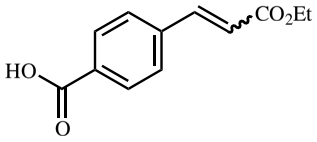
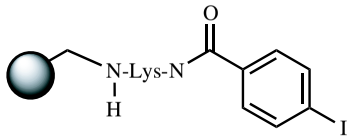
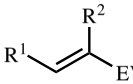
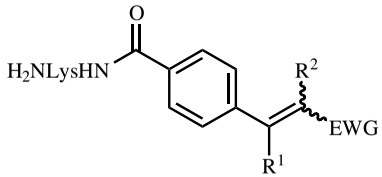
Since the coupling of a suitable starting material to a solid support as well as the design of an appropriate linker are often the keys to successful solid phase synthesis, it is not surprising that considerable efforts have been put into the development of alternative methods to the standard peptide coupling protocols that were the first to be adapted for solid phase transformations. Among these new methods there is also a range of Pd-catalyzed reactions such as cross-couplings, [2]–[4] substitutions, and hydrogenations. It is noteworthy that almost every linker type used in solid phase chemistry has found its application in Pd-catalyzed and Pd-mediated reactions.

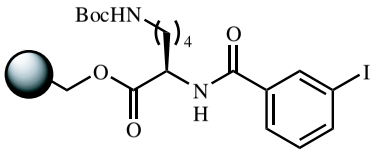
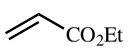
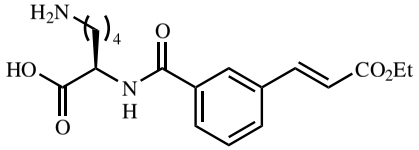
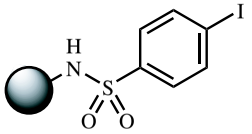
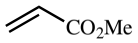
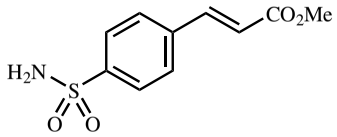
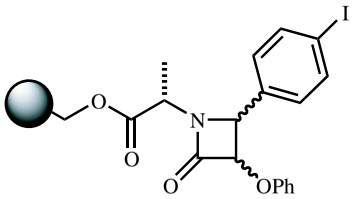
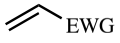
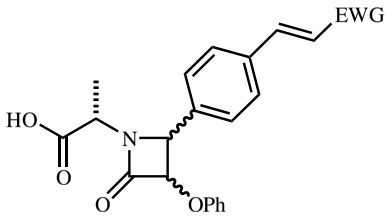
B.ii. The Heck Reaction on Solid Support

The Heck reaction is one of the most efficient tools for C—C bond connection in the liquid as well as on the solid phase. Various aspects of this reaction are discussed in **Part IV** of this handbook.

B.ii.a. ***Intermolecular Heck Reactions.*** Heck reactions on solid support are extensively used due to the easy accessibility of starting materials such as haloalkenes or haloarenes and alkenes. The reaction conditions used may be divided into the standard Heck conditions [$Pd(OAc)_2$, PPh_3 or P(*o*-Tol)$_3$, DMF, 80–100 °C, 2–24 h][5] or the protocol developed by Jeffery [$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, DMF, 20–80 °C][6] The yields

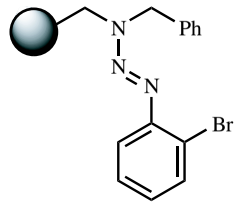
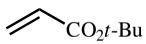
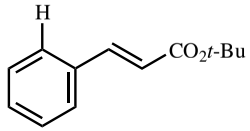
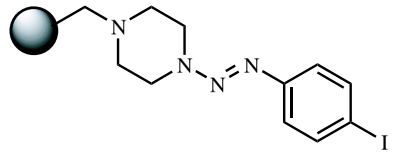
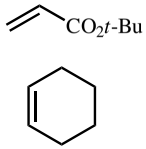
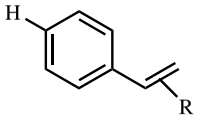
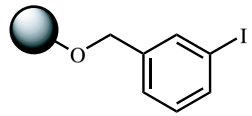
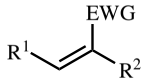
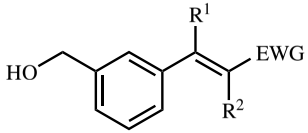
TABLE 1. Intermolecular Heck Reactions on Solid Support: Polymer-Bound Aryl Iodides and Related Compounds

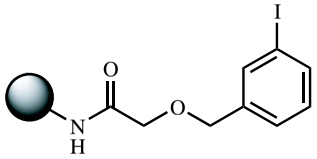
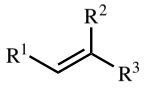
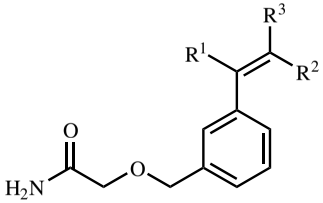
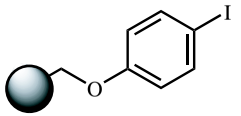
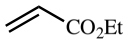
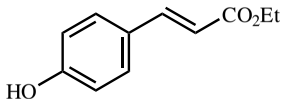
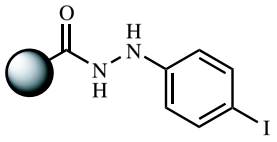
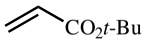
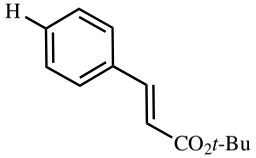
Entry	Starting Material	Alkenes Used	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
1	 Wang resin	 R = *p*-$C_6H_4CO_2Me$ or CO_2Et	 Cleav.: 90% TFA, CH_2Cl_2, r.t., 1 h	$Pd(OAc)_2$, Et_3N, *n*-Bu_4NCl, DMF, 80–90 °C, 16 h	(2) 90–91	[8]
2	 TentaGel–OH		 Cleav.: TFA/CH_2Cl_2/PhOMe (50:47:3), r.t., 30 min	$Pd(OAc)_2$, PPh_3, Bu_4NCl, sat. K_2CO_3, DMF/H_2O (9:1), 37 °C, 4 h	>95 conv.	[9]
3	 Millipore PS–PEG–PAL	 EWG = $CONH_2$, CN; R^1 = H, Ph; R^2 = H, Me	 Cleav.: TFA/CH_2Cl_2/PhOMe (50:47:3), r.t., 30 min	$Pd(OAc)_2$, PPh_3, Bu_4NCl, sat. K_2CO_3, DMF/H_2O (9:1), 37 °C,	(6) 54 to >95	[9]

4	 Wang		 Cleav.: 90% TFA, CH_2Cl_2, 4h	$Pd(OAc)_2$, $P(o\text{-}Tol)_3$, Et_3N, DMF, 60 °C, 19 h	43	[10]
5	 Rink amide		 Cleav.: 20% TFA, CH_2Cl_2	$Pd(OAc)_2$, Bu_4NCl, Et_3N, 90 °C, 18 h	(1)	[11]
6	 Sasrin resin or Argo-Gel–MB–OH	 EWG = $CONH_2$, CN, CO_2Et, $CONMe_2$	 Cleav.: 3–10% TFA, CH_2Cl_2	$PdCl_2$ (dppf), Et_3N, Bu_4NI, DMF/H_2O (9:1), 40 °C	(4) 60–91	[12]

(*Continued*)

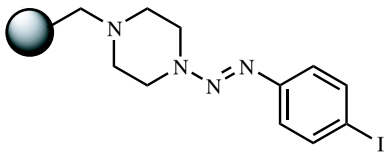
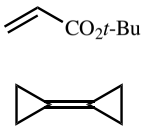
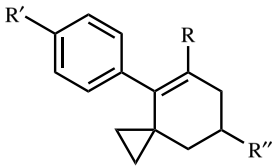
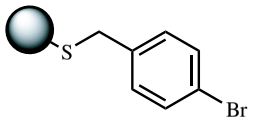
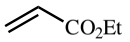
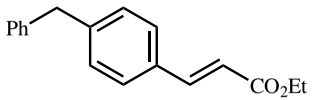
TABLE 1. (*Continued*)

Entry	Starting Material	Alkenes Used	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
7	 polystyrene		 Cleav.: HCl, THF, ultrasound, 50 °C, 5 min	$Pd(OAc)_2$, PPh_3, Et_3N, DMF, ultrasound, 80 °C, 24 h	(2)	[13]
8	 polystyrene		 Cleav.: HCl, THF, ultrasound, 50 °C, 5 min or $HSiCl_3$, CH_2Cl_2, 32 °C, 10 min	$Pd(OAc)_2$, PPh_3, Et_3N, DMF, ultrasound, 80 °C, 24 h	(2)	[13],[14]
9	 polystyrene with base-labile linker	 R^1 = H, Me; EWG = CO_2t-Bu, CO_2Me, CN, COEt, $CONMe_2$, SO_2Ph; R^2 = H, Me	 Cleav.: NaOMe, MeOH/dioxane, r.t., 24 h	$Pd(OAc)_2$, NaOAc, Bu_4NCl, DMA, 100 °C, 24 h	(7) 48–96	[15]

10	 Rink resin	 R^1 = H, Me, CO_2Me, Ph; R^2 = H, Me, CO_2Me, CN, Ph, $P(O)(OMe)_2$, COEt, $CONMe_2$; R^3 = H, Me, NHAc, COMe, CH_2CO_2Me, CN	 Cleav.: 20% TFA, CH_2Cl_2, r.t., 5 min	$Pd(OAc)_2$, NaOAc, Bu_4NCl, DMA, 100 °C, 24 h	(11) 40–96	[15]
11	 Wang resin		 Cleav.: 20% TFA, CH_2Cl_2	$Pd_2(dba)_3 \bullet CHCl_3$, $P(o\text{-Tol})_3$ DMF, 110 °C, 24 h	(1) >90	[7]
12	 polystyrene or TentaGel or ArgoPore		 Cleav.: $Cu(OAc)_2$, MeOH, pyr, r.t., 2h	$Pd(OAc)_2$, NaOAc, Bu_4NBr, DMA, 100 °C, 24 h	(1) 83–96	[16]

(*Continued*)

TABLE 1. (*Continued*)

Entry	Starting Material	Alkenes Used	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
13				$Pd(OAc)_2$, PPh_3, Et_3N, DMF, 80 °C, 24 h	(2)	[17]
	polystyrene		Multicomponent reactions; see **Scheme 2**			
14				$Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 70 °C, 14 h	(1) 57	[18]
	polysyrene with linker (see also **Scheme 39**)		Cleav.: (1) $Et_3O^+ BF_4^-$; (2) $PhB(OH)_2$, $PdCl_2(dppf)$, K_2CO_3, THF, 60 °C, 14 h			

obtained under Jeffery conditions were frequently enhanced by the addition of 10% of water to the reaction mixture. In some cases $Pd_2(dba)_3$ was found to be far more effective than $Pd(OAc)_2$.[7]

The Heck reaction was performed on immobilized aryl halides, mostly iodides, or iodonium salts with soluble alkenes (**Table 1**) or on immobilized alkenes with soluble aryl halides (**Table 2**). When performed on the same type of resin and with the same catalyst system, the immobilization of aryl iodides appears to be more beneficial than that of alkenes.[8]

B.ii.b. ***Multi component Reactions on Solid Supports.*** Multicomponent reactions (MCRs) are particularly feasible for combinatorial synthesis. The advantage of conducting a MCR on solid support lies in the ease of removal of non-polymer-bound components and excess building blocks. The three-component reaction developed by Larock using an aryl halide, a nonconjugated diene, and an appropriate nucleophile (mostly an amines) to highly diverse compounds has been carried on a solid phase using immobilized amines (**Scheme 1**).[22] The advantage of this procedure in comparison with the use of immobilized aryl halides is that any possible by-products formed from aryl halides, such as simple Heck coupling products, stay in solution and can be removed by washing processes. The yields of this three-component reaction are quite good and the purities of the obtained products are moderate to good. The flexibility of this approach using different starting materials (11 different aryl halides and 5 different resins) make this approach very attractive.

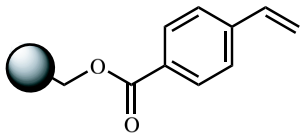
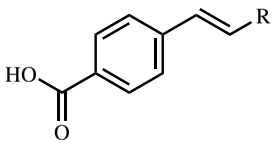
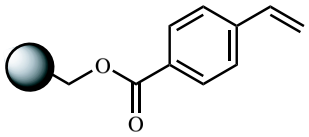
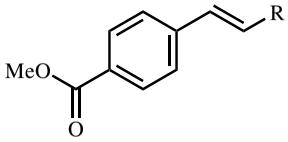
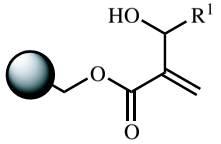
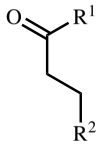
The reactions of bicyclopropylidene with aryl halides under Heck conditions give rise to the formation of allylidenecyclopropanes, which in turn can react with dienophiles in a Diels–Alder reaction. This new three-component reaction has also been conducted on a solid support using the versatile triazene T1 linker (**Scheme 2**).[17],[24] Heck coupling of an immobilized iodoarene **I** with bicyclopropylidene in the presence of an acrylate forms a polymer-bound spirooctene **II**. Alternatively, the iodoarene **I** could first be transformed into a polymer-bound cinnamate **IV** by Pd-catalyzed coupling with an acrylate. The cinnamate can then act as the dienophile for the Heck coupling products of bicyclopropylidene and aryl iodides to give the polymer-bound spirooctenes like **V**. The latter transformation was conducted under high pressure, which facilitates both the Heck coupling and the Diels–Alder reaction. The triazene moieties could be cleaved to diazonium salts, which in turn act as precursors for Heck reactions with various alkenes to give the spirooctenes **III** and **VI** in good yields and excellent purities. By applying palladium on charcoal for this transformation, the same catalyst may also be used in a subsequent catalytic hydrogenation of the double bond in the coupled alkene (see also **Scheme 36**).[24]

B.ii.c. ***Intramolecular Heck Reactions.*** The main advantage of intramolecular Heck reactions on solid support is the pseudodilution of the starting material leading to an increase of the yield. The first use of this was reported in 1995 for the synthesis of 20- to 24-membered macrocyclic ring systems (**Scheme 3**).[25]

Similarly, a 20-membered ring was formed and released from a 2-chlorotrityl linker (**Scheme 4**).

Besides the preparation of macrocycles, the cyclization to give heteroatom-containing five-, six-, and seven-membered rings has been investigated (**Table 3**). Thus, the construction of indoles, benzofurans, dihydroisoquinolines, and benzazepines has been reported. Starting from aryl iodides with an appropriate alkenyl or, under reductive conditions, alkynyl tether, smooth cyclizations occur under standard conditions.

TABLE 2. Intermolecular-Heck Reactions on Solid Support: Polymer-Bound Alkenes

Entry	Starting Material	Aryl Halide or Iodonium Salt	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
1	 Wang resin	RX = PhI, 2-Naphthyl-Br, 2-Thienyl-Br, 3-Pyridyl-Br,	 Cleav.: 20% TFA, CH_2Cl_2, r.t., 1 h	$Pd_2(dba)_3$, P(*o*-Tol)$_3$, Et_3N, DMF, 100 °C, 20 h or $Pd(OAc)_2$, Et_3N, *n*-Bu_4NCl, DMF, 80–90 °C, 16 h	(4) 64–81	[8]
2	 polystyrene	$Ph_2I^+ BF_4^-$; *p*-$(MeOC_6H_4)_2$ $I^+ BF_4^-$; (2-Thienyl)$_2I^+ BF_4^-$;	 Cleav.: NaOMe, MeOH/THF (1:4), reflux, 20 h	$Pd_2(dba)_3$•$CHCl_3$, P(*o*-Tol)$_3$, $NaHCO_3$, DMF, 40 °C, 20 h	(3) 55–80 (6) 54 to >95	[19] [9]
3	 Wang resin; R^1 = aryl, hetaryl, alkyl	R^2Br; R^2 = aryl, hetaryl	 Cleav.: 75% TFA, CH_2Cl_2, r.t., 1 h	$Pd_2(dba)_3$,P(*o*-Tol)$_3$, Et_3N, DMF, 100 °C, 24 h	(21) 0–49	[20]

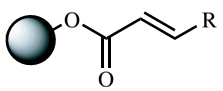
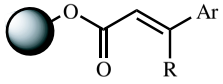
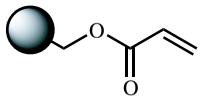
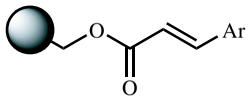
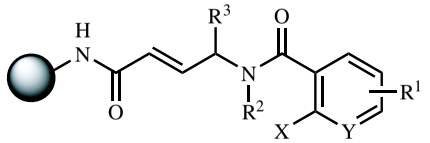
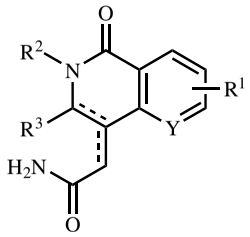
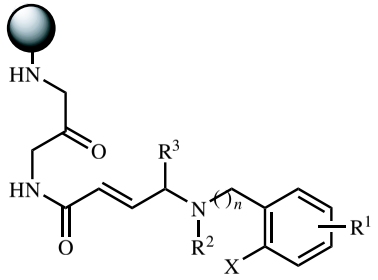
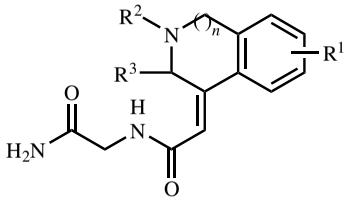
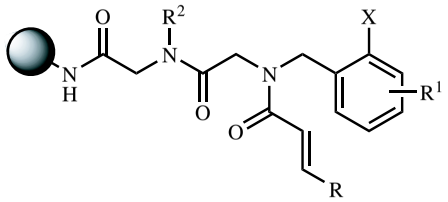
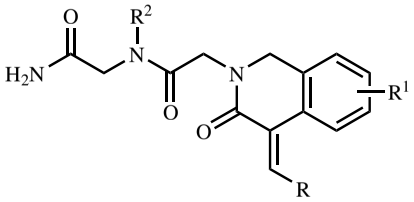
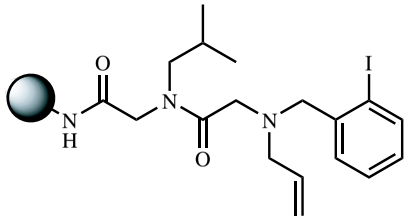
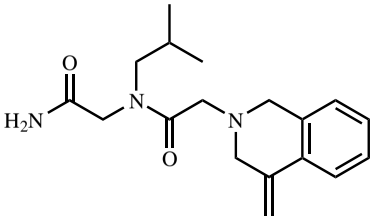
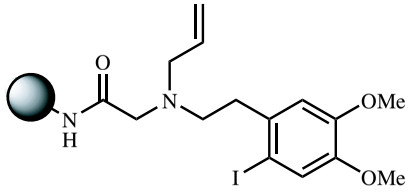
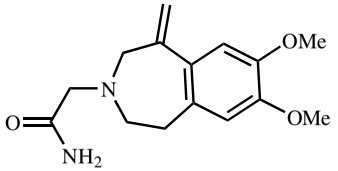
4	 MeO-PEG 5000 R = *o*-$MeOC_6H_4$, 1-Naphthyl, *o*-Tol, 2,4-$Cl_2C_6H_3$, 4-Pyr, *c*Pr	ArI; Ar = *p*-Tol, *p*-BuC_6H_4, *p*-MeO C_6H_4	 *Z*/*E* = <1:99 to > 99:1	$Pd(OAc)_2$, $NaHCO_3$, DMF, 145 °C, 20 h	(14) 82–95	[21]
5	See Scheme 1					[22]
6		ArX; Ar = Ph, *o*-H_2N-C_6H_4, *o*-HOC_6H_4		$Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, DMF, 40–100 °C, 20 h	(4) 49–76 after cleavage	[23]

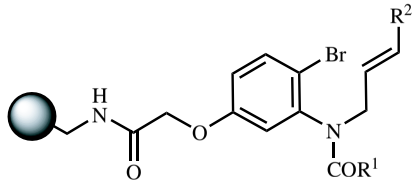
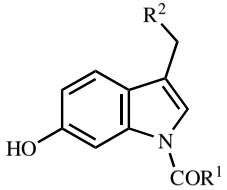
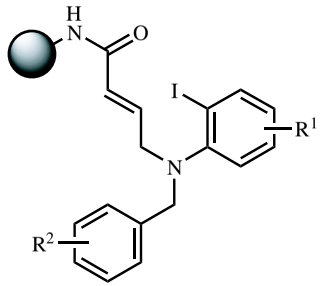
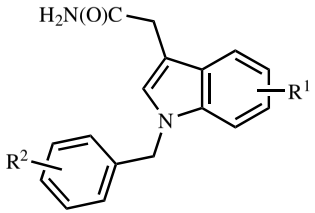
TABLE 3. Synthesis of Indoles, Benzofuranes, Dihydroisoquinolines, and Benzazepines by Heck Reactions on Solid Support

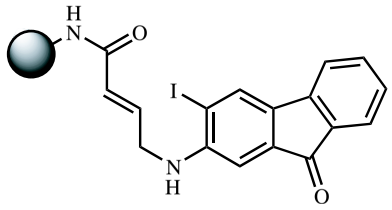
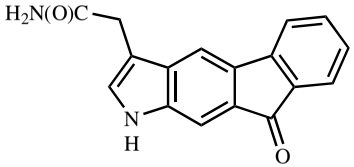
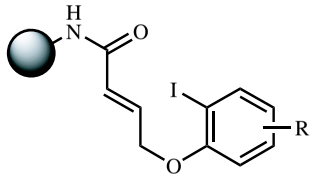
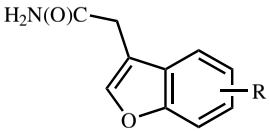
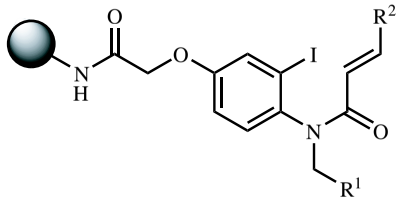
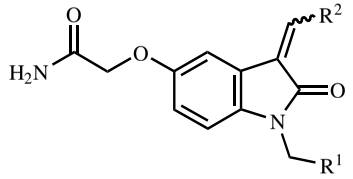
Entry	Starting Material	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
1			$Pd(PPh_3)_4$, PPh_3 NaOAc, DMA, 85 °C, 5 h	(9) 65–92	[27],[28]
	Rink amide; X = Br, I; Y = CH, N; R^1 = Me, F, $(OMe)_2$, Cl, OMe; R^2 = *i*-Bu, CHCH Ph, Ph; R^3 = H, Me	Mixture of double bond isomers; cleav.: TFA/H_2O (95:5), r.t., 20 min			
2				(Several claimed)	[28]
	Rink amide	*n* = 1–3; cleav.: TFA/H_2O (95:5), r.t., 20 min			

3	 Rink amide	 Cleav.: TFA/H_2O(95:5), r.t., 20 min		(Several claimed)	[28]
4	 Rink amide	 Cleav.: TFA/H_2O (95:5), r.t., 20 min	$Pd(PPh_3)_4$, PPh_3, NaOAc, DMA, 90–95 °C, 8 h		[28]
5	 Rink amide	 Cleav.: TFA/H_2O (95:5), r.t., 20 min	$Pd(PPh_3)_4$, PPh_3, NaOAc, DMA, 90–95 °C, 7.5 h		[28]

(*Continued*)

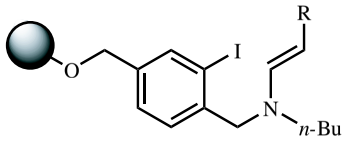
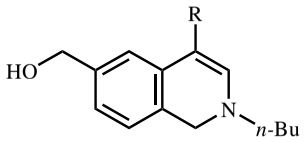
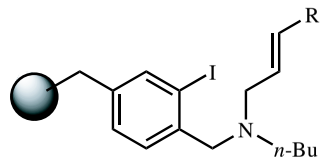
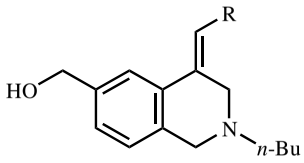
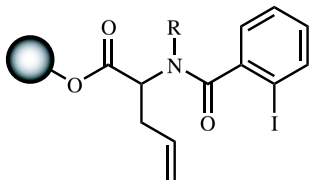
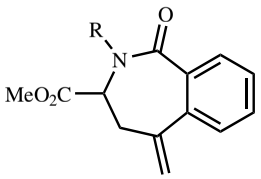
TABLE 3. (*Continued*)

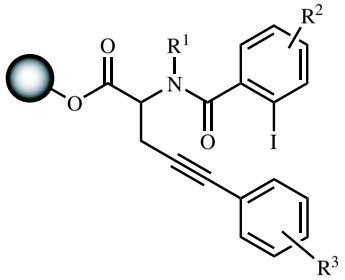
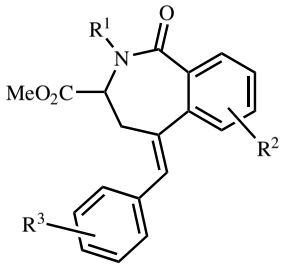
Entry	Starting Material	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
6	 TentaGel S	 R^1 = Et, *i*-Pr, Ph, *m*-$MeOC_6H_4$; R^2 = H, Me, Ph; cleav.: TFA (neat)	$Pd(PPh_3)_4$, PPh_3, Et_3N, DMA, 85 °C, 5 h	(8) 65–94	[29]
7	 Rink amide AM or Rink amide resin	 R^1 = H, 6-OMe, 5-CO_2Me; R^2 = 4-F, 4-CF_3, 4-F, 2-Cl, 4-OCF_3, H; cleav.: 30% TFA, CH_2Cl_2	$Pd_2(dba)_3$•$CHCl_3$, P(*o*-Tol)$_3$, $NaHCO_3$, DMF, 40 °C, 24 h	(12) 67–88	[30]

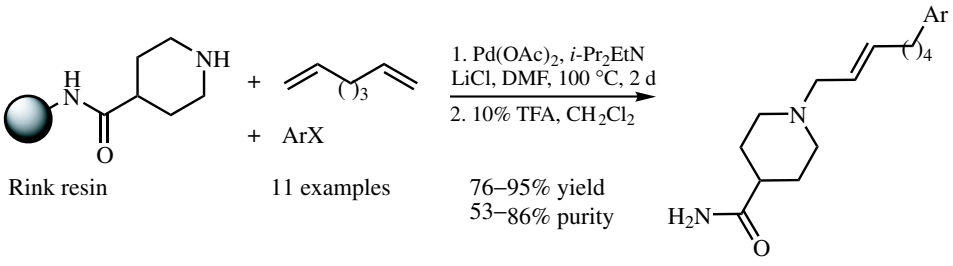
8			$Pd_2(dba)_3{\bullet}CHCl_3$, $P(o\text{-Tol})_3$, $NaHCO_3$, DMF, 40 °C 24 h	(1) 76	[30]
	Rink amide AM or Rink amide resin	Cleav.: 30% TFA, CH_2Cl_2			
9			$Pd_2(dba)_3{\bullet}CHCl_3$, $P(o\text{-Tol})_3$, $NaHCO_3$, DMF, 40 °C, 20 h	(2) 81–83	[30]
	Rink amide AM or Rink amide resin	R = H, 5, 7-$(Cl)_2$;cleav.: 30% TFA, CH_2Cl_2			
10			$Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF, 100 °C, 16 h	(9) 65–92;*E/Z* 2.7:1–5.9:1	[31]
	R^1 = H,CH_2*c*-Hex, *i*-Bu; R^2 = H, CH_3, Ph	Cleav.: 25% TFA, CH_2Cl_2, 25 °C, 16 h			

(*Continued*)

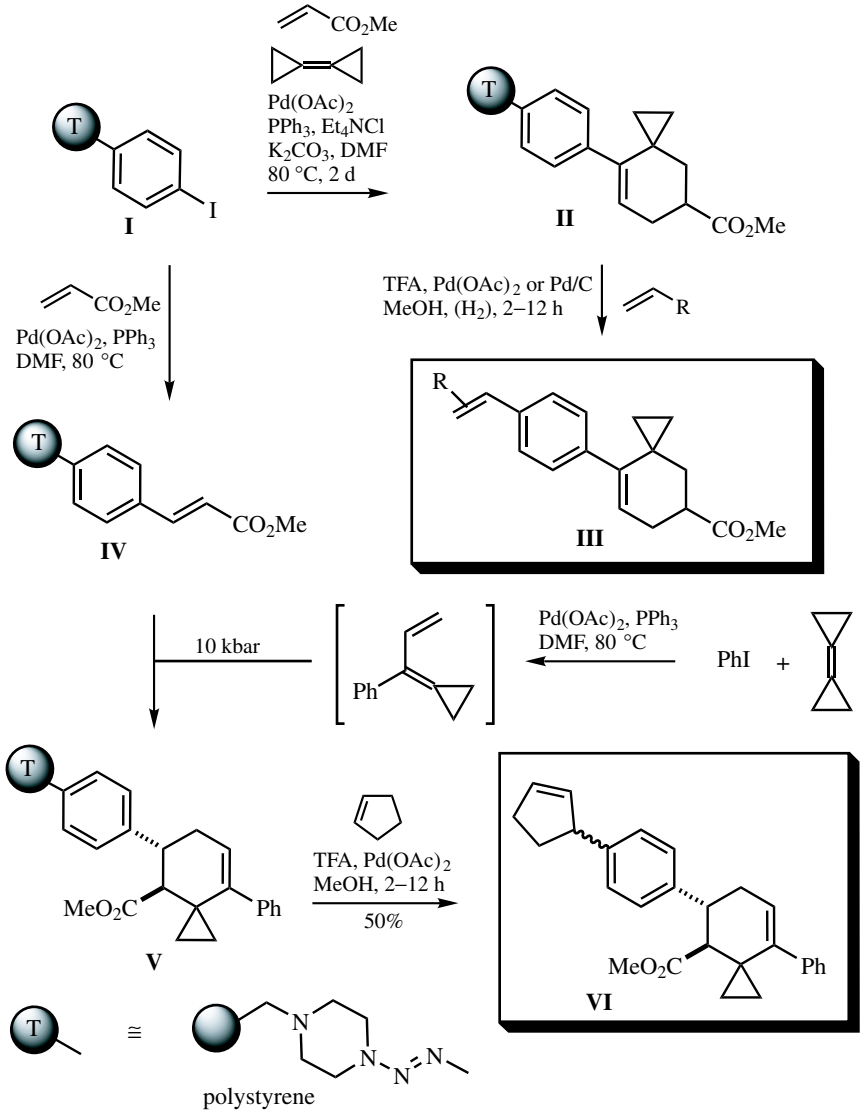
TABLE 3. (*Continued*)

Entry	Starting Material	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
11			$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, 100 °C, 24 h	(3) 95–100	[32]
	polystyrene with additional base-labile linker; R = CO_2Me, Ts, Ac	Cleav.: NaoMe, MeOH/dioxane (1:4), r.t., 24 h			
12			$Pd(OAc)_2$,PPh_3, Bu_4NCl, K_2CO_3, 100 °C, 24 h	(2) 90–100	[32]
	polystyrene with additional base-labile linker; R = CO_2Me, Ts, Ac	Cleav.: MeONa, MeOH/dioxane (1:4), r.t., 24 h			
13			$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, 70 °C	(2)	[33]
	Wang resin; R = Me, Bn	Cleav.: 50% TFA, CH_2Cl_2			

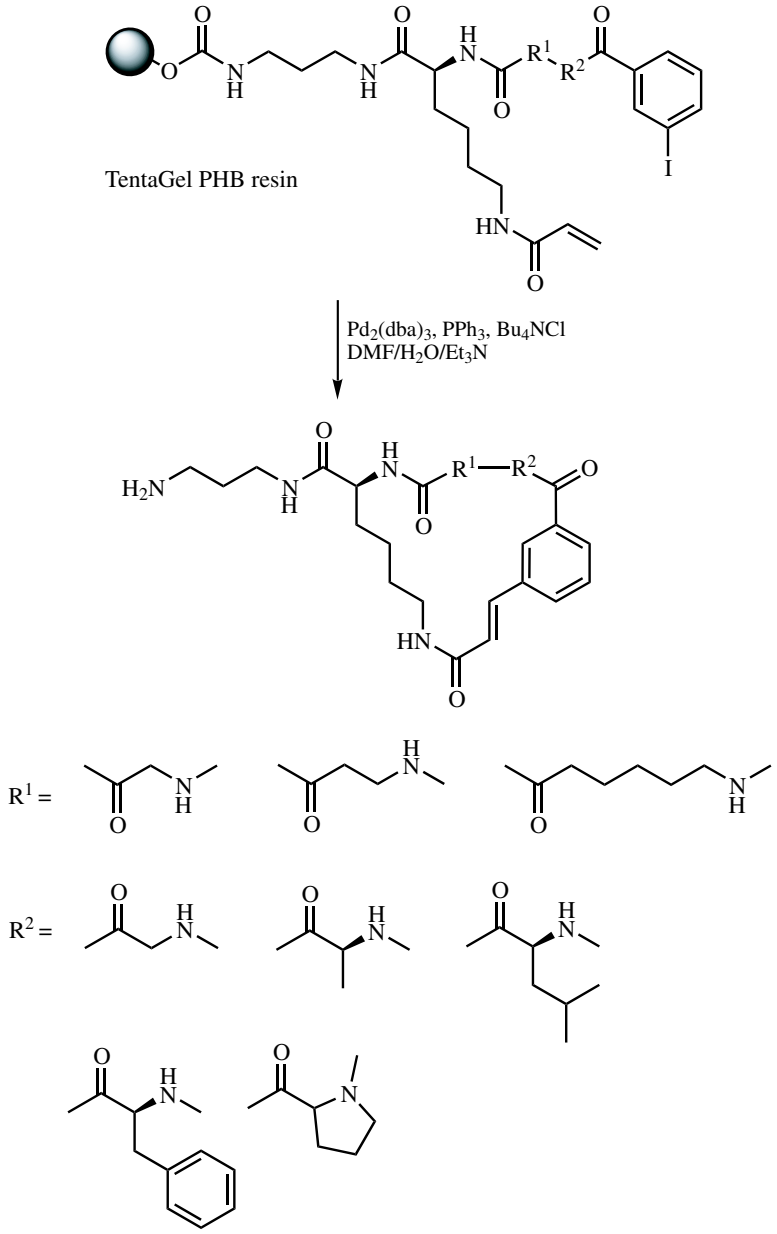
14			$Pd(OAc)_2$, PPh_3, Bu_4NCl, KOAc or HCO_2Na 70 °C	(7)	[33]
	Wang resin; R^1 = Ph, CH_2CH_2Ph; R^2 = H, 7-Cl, 7,8-diOMe; R^3 = H, 4-CONHBu, 3-CF_3	Cleav.: (a) 50% TFA, CH_2Cl_2; (b) CH_2N_2			



Scheme 1. Couplings of a solid-supported piperidine with 1,5-hexadiene and aryl halides.[22]



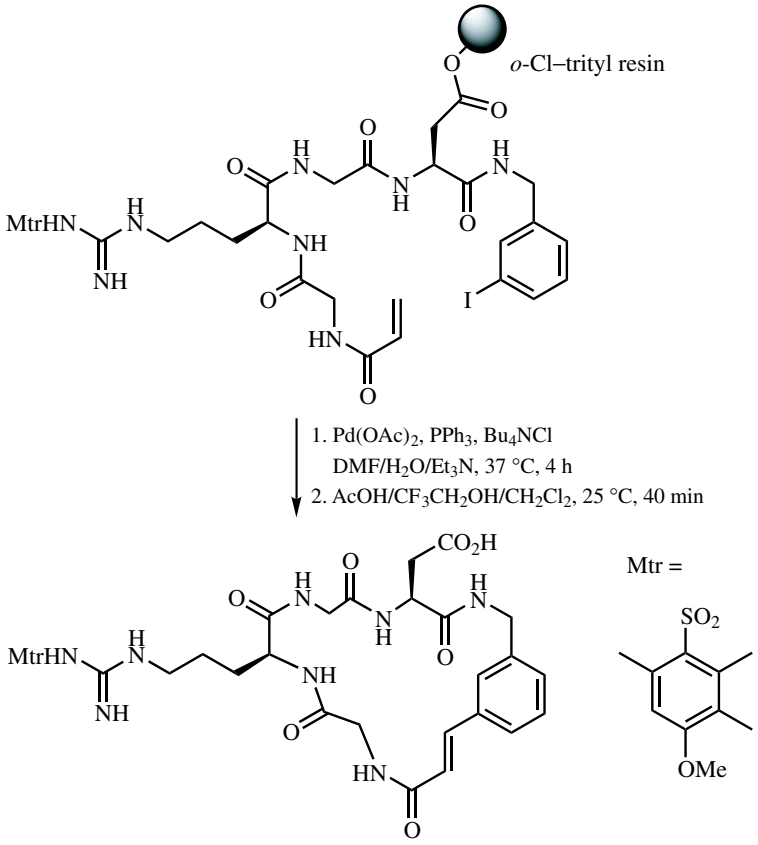
Scheme 2. Three-component Heck–Diels–Alder reactions on a solid support.[17]



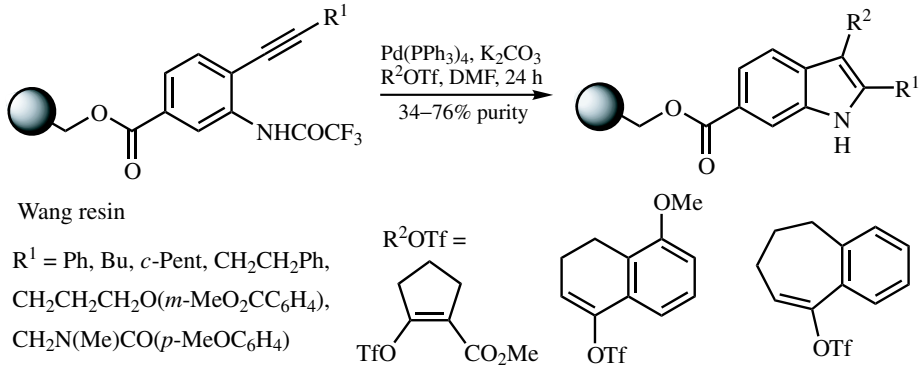
Scheme 3. Intermolecular Heck reaction for the synthesis of macrocycles.[25]

Intermolecular carbometallation of a triple bond by an organylpalladium triflate and subsequent intramolecular nucleophilic attack gives rise to indoles (**Scheme 5**).[34] The major advantage of this approach is based on the fact that the triflate may be varied over a wide range.

An interesting sequential reaction consisting of an intermolecular alkene carbometallation and subsequent intermolecular alkyne cross-coupling has been reported by

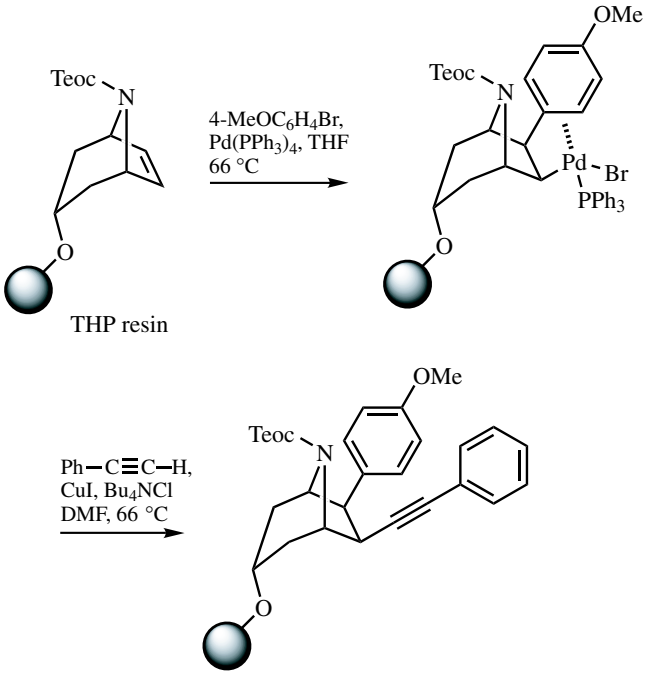


Scheme 4. Interamolecular Heck reaction for the synthesis of a macrocycle.[26]



Scheme 5. Carbometallation and cylization of *o*-alkynylaniline derivative.[34]

Koh and Ellman (**Scheme 6**).[35] Starting from an immobilized tropane framework, stoichiometric carbopalladation yields a stable organopalladium intermediate, which in the presence of added copper(I) iodide underwent coupling with added terminal acetylene.



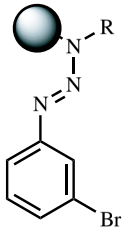
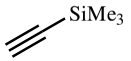
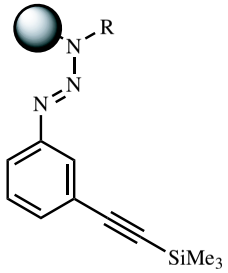
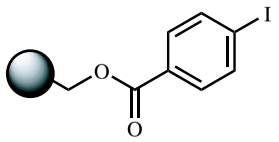
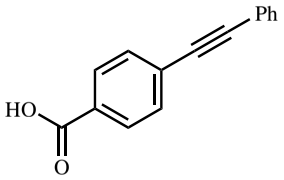
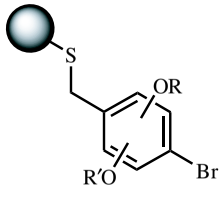
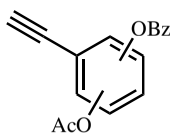
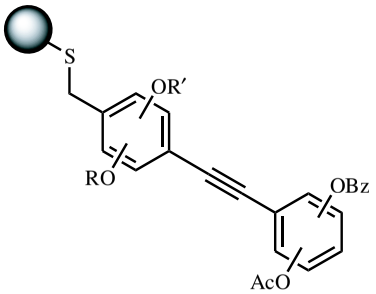
Scheme 6. Carbometallation on the tropane framework.[35]

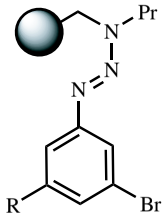
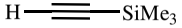
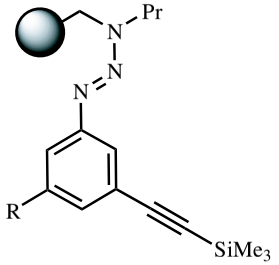
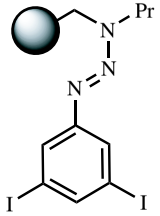
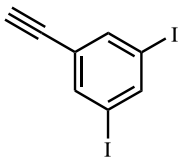
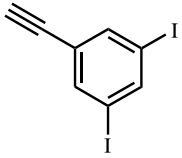
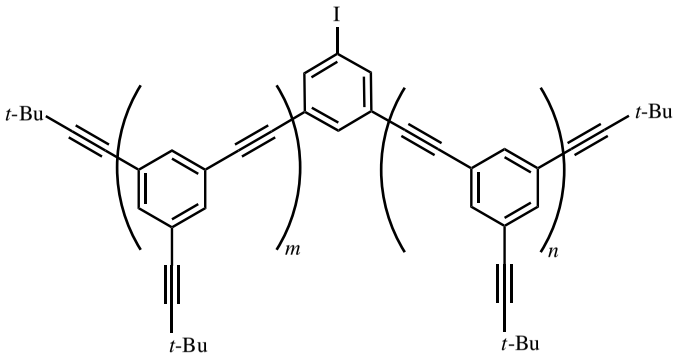
B.iii. Arylations and Alkenylations of Terminal Alkynes: Sonogashira-Type Coupling Reactions

The arylation of terminal alkynes (so-called Sonogashira coupling, but sometimes also referred to as the Heck reaction) has quite frequently been used in solid phase organic synthesis. Since the C,C triple bond can be converted into various new functionalities or simply act as a spacer, any straightforward access to substituted alkynes is a valuable process. An advantage of the Sonogashira coupling performed on solid support is the facile removal of by-products such as the diynes formed by homocoupling of the alkynes. Most terminal alkynes are suitable; however, propiolic ester has failed so far.[8] Moore and co-workers reported one of the first alkyne couplings on solid support utilizing the versatile triazene linkage (**Table 4**, entry 1).[36] The repetitive coupling, deprotection sequence allowed the synthesis of arylacetylene oligomers. Using a triazene-linked iodoarene as a starting point, hyperbranched polymers with a narrow size distribution were built up on solid support with (3,5-diiodophenyl)acetylene as a monomer.[37] Prior to detachment, capping with 3,5-di-*tert*-butylphenylethyne under palladium catalysis was performed to enhance the solubility. The resulting polymer had a molecular weight range of 5–25 kDa. With an alkynyl group being attached *ortho* to a triazene linker, and the latter upon cleavage yielding a diazonium ion moiety, cyclization to form a cinnoline may occur (**Table 4**, entry 16).[38] Alternatively to the attachment of aryl halides, alkynes have been also immobilized to solid support (**Table 5**).

B.iii.a. ***Carbometallations with Subsequent Nucleophilic Attack.*** The heteroannelation of aryl iodides containing a potentially *ortho*-nucleophilic substituent (amino or hydroxy)

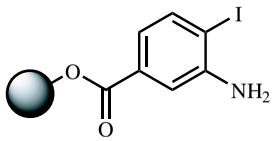
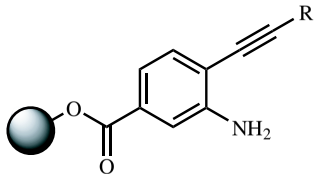
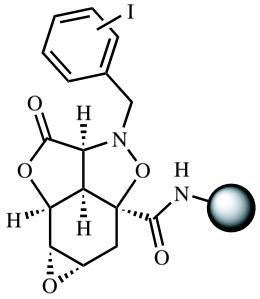
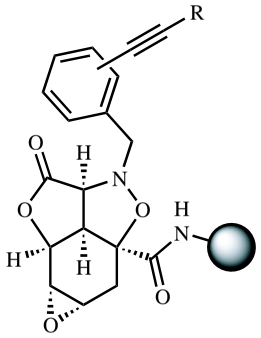
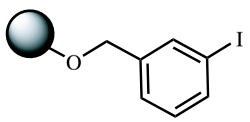
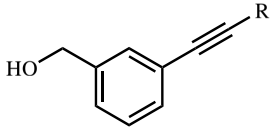
TABLE 4. Arylation of Terminal Alkynes: Immobilization of the Aryl Halide

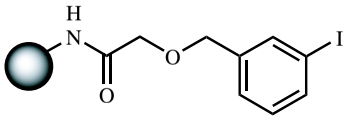
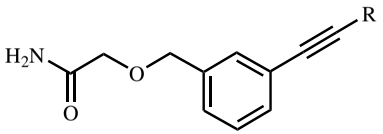
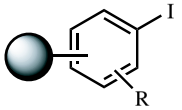
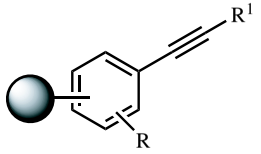
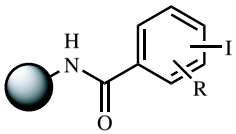
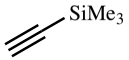
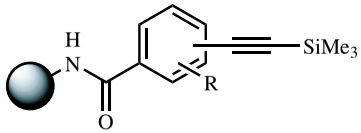
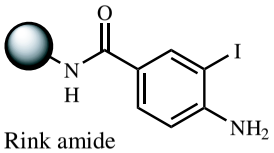
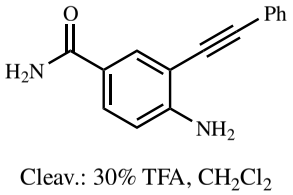
Entry	Starting Material	Alkyne	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
1				$Pd_2(dba)_3$, PPh_3, CuI, DMF, 65 °C, 24 h	(3)	[36]
2				$Pd_2(dba)_3$, $P(o\text{-Tol})_3$, Et_3N, DMF, 100 °C, 20 h	(1) 90%	[8]
3				$Pd(OAc)_2$, Et_3N, reflux, 4 h	(>1)	[39]

4	 polystyrene; R = OC_6H_{13}, $CO_2C_6H_{13}$, CN			$Pd_2(dba)_3$, PPh_3, CuI, DMF, 65 °C, 12 h	(3) [40]
5	 polystyrene	(a)  (b) capping with 		$Pd_2(dba)_3$, PPh_3, CuI, DMF, piperidine, r.t., 12 h	(>18) [37]

(*Continued*)

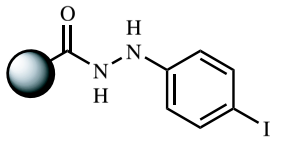
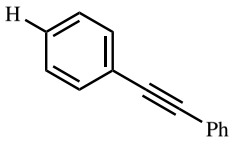
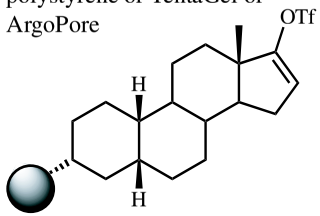
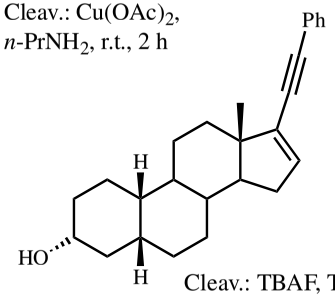
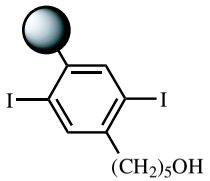
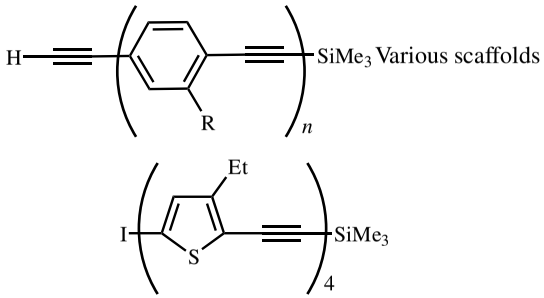
TABLE 4. (*Continued*)

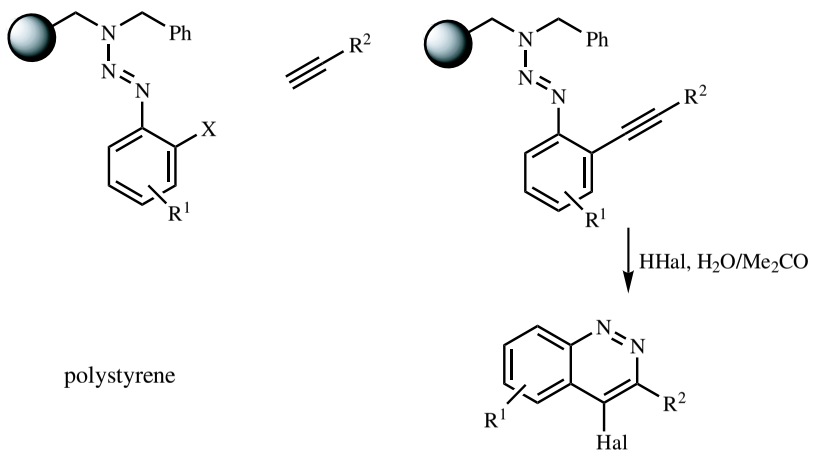
Entry	Starting Material	Alkyne	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
6	 Wang resin	 R = Ph, Bu, c-Pent, CH_2CH_2Ph, $CH_2CH_2CH_2O(m\text{-}MeO_2CC_6H_4)$, $CH_2N(Me)CO(p\text{-}MeOC_6H_4)$		$Pd(PPh_3)_2$, CuI, Et_2NH, DMF, 2 h	(6)	[34]
7	 TentaGel S NH_2	 31 different alkynes		$Pd(PPh_3)_2,Cl_2$ CuI, $i\text{-}Pr_2EtN$, DMF, r.t., 15–45 min	(ca. 100)	[41]
8	 Resin with base-labile linker	 R = *t*-Bu, CH_2OH, CH(Me)OH, BuPh, CMe_2OH, CH_2NHBoc	 Cleav.: NaOMe, MeOH/dioxane, r.t., 24 h	$Pd(OAc)_2$, NaOAc, Bu_4NCl, DMA 100 °C, 24 h	(7) 77–96	[15]

9	 Rink resin	 R = various Ar or HetAr	 Cleav.: 20% TFA, CH_2Cl_2, r.t., 5 min	$Pd(PPh_3)_2$, Cl_2 CuI, Et_3N or *i*-Pr_2EtN, dioxane, r.t. to 50 °C, 24 h	(7) 79–95	[42]
10	 various scaffolds	 R^1 = *t*-Bu, *n*-Bu, $CH(OH)CH_3$, $CH(OTfa)CH_3$, Ph, CH_2OH		$Pd(PPh_3)_2$, Cl_2 CuI, Et_3N, dioxane, r.t. 24–30 h	(14) 52–97	[42]
11	 PS or PS–PEG with Rink linker; R = H, Me			$Pd(PPh_3)_4$, CuCl, THF/Et_3N (1:1), r.t., 40 h	(3)	[43]
12	 Rink amide		 Cleav.: 30% TFA, CH_2Cl_2	$Pd(PPh_3)Cl_2$ CuI, Et_3N/DMF, (1:5), 80 °C, 5–16 h	(1) 96% pur.	[44]

(*Continued*)

TABLE 4. (*Continued*)

Entry	Starting Material	Alkyne	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
13	 polystyrene or TentaGel or ArgoPore		 Cleav.: $Cu(OAc)_2$, *n*-$PrNH_2$, r.t., 2 h	$Pd(PPh_3)Cl_2$ CuI, Et_3N/dioxane (2:1), r.t., 24 h	(1) 52–92	[16]
14	 polystyrene with fluoride-labile linker		 Cleav.: TBAF, TMU, 100 °C, 1 h	$Pd(OAc)_2$, PPh_3, Bu_3N, DMF, 80 °C 2 h	(1) 46	[45]
15	 polystyrene with THP link		 repetitive coupling, deprotection, up to *n* = 17	$Pd_2(dba)_3$, PPh_3, CuI, Et_2NH/THF (1:4)	Various experiments	[46]



16

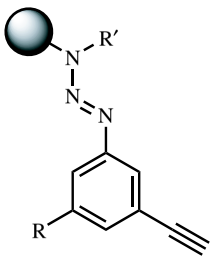
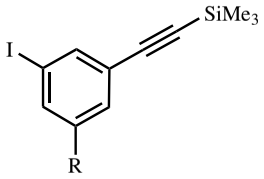
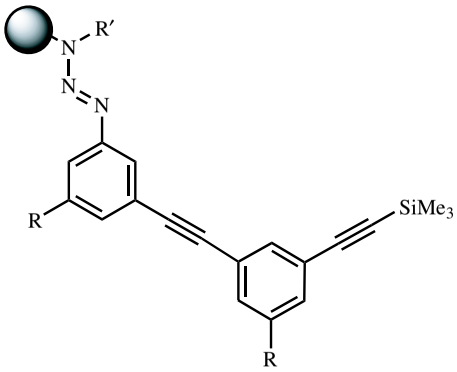
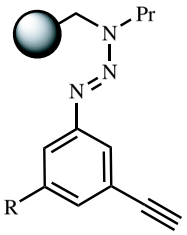
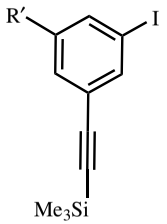
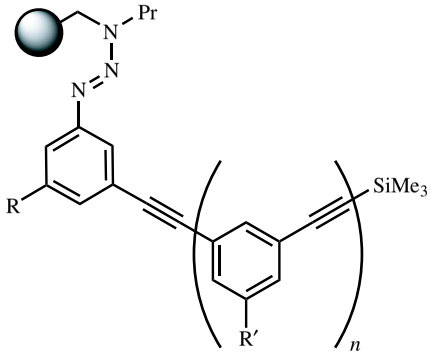
polystyrene

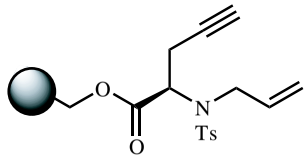
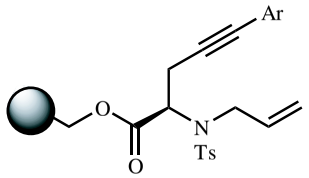
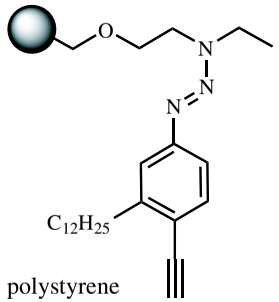
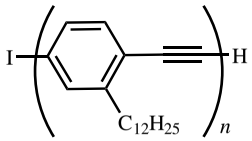
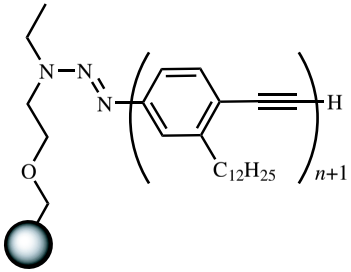
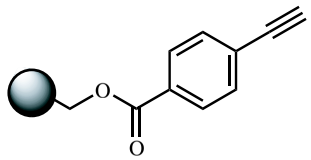
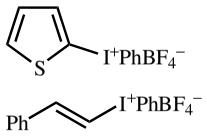
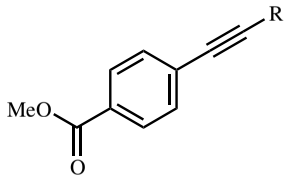
$Pd(OAc)_2$, PPh_3, Et_3N, DMF, 80 °C,12–18 h

(20) >80

[38]

TABLE 5. Arylation and Alkenylation of Terminal Alkynes: Immobilization of the Alkyne

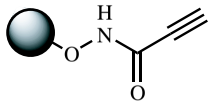
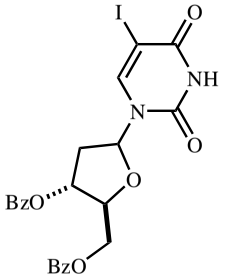
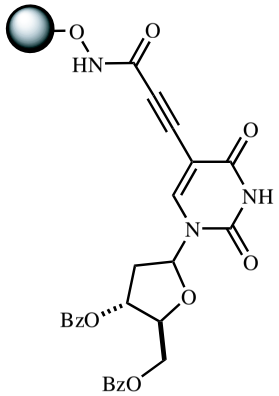
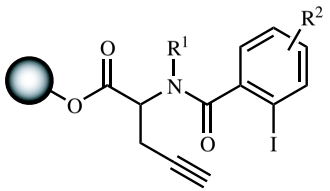
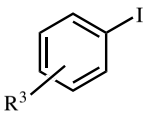
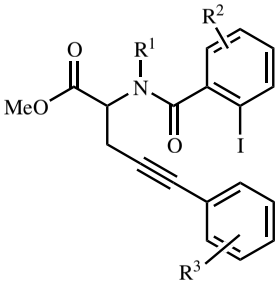
Entry	Starting Material	Aryl Halide	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
1	 polystyrene with linker			$Pd_2(dba)_3$, PPh_3, CuI, DMF, 65 °C, 24 h; 5 iterations (after deprotection)	(61)	[36]
2	 polystyrene; R= OC_6H_{13}, $CO_2C_6H_{13}$, CN	 Repetitive coupling and deprotection; up to n=5		$Pd_2(dba)_3$, PPh_3, CuI, DMF, 65 °C, 12 h	(Several described)	[40]

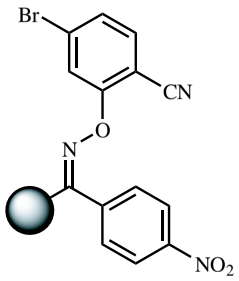
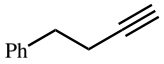
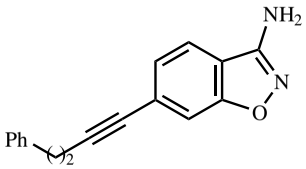
3	 Wang resin	ArI; Ar=Ph, *p*-$MeOC_6H_4$ *p*-ClC_6H_4, *p*-$MeO_2CC_6H_4$		$PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_2Cl_2, r.t., 18 h	(4)	[47]
4	 polystyrene	 repetitive coupling, deprotection, up to $n = 15$		$Pd_2(dba)_3$, PPh_3, CuI, DMF, *i*-$PrNH_2$/THF, (1:5)	(Various)	[48]
5	 polystyrene	$RPhI^+BF^-$= $Ph_2I^+BF_4^-$ *p*-$MeOC_6H_4I^+Ph\ BF_4^-$ 		$Pd(PPh_3)_4$, CuI, $NaHCO_3$, DMF, 40 °C, 20 h	(4) 50–75	[19]

Cleav.: NaOMe, MeOH/THF (1:4), reflux, 20 h

(*Continued*)

TABLE 5. (*Continued*)

Entry	Starting Material	Aryl Halide	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
6	 polystyrene with 2-chlorotrityl linker			$Pd(PPh_3)_4$, CuI, Et_3N, DMF, 25 °C	(1) >89	[49]
7	 Wang resin		 R^1 = Ph, CH_2CH_2Ph, Me, R^2 = H, 7-Cl, 7,8-$(OMe)_2$; R^3 = H, 4-CONHBu, 3-CF_3 Cleav.: (a) 50% TFA, CH_2Cl_2; (b) CH_2N_2	$Pd(PPh_3)_4$, CuI, Et_3N, CH_2Cl_2	(7) 39–73	[33]

8	See **Table 4**, entry 15					[46]
9	 Polystyrene		 Cleav.: TFA/5 N aq. HCl (4:1), 55 °C, 2 h	$Pd(PPh_3)_4$, CuI, Et_3N, THF, 55 °C, 36 h	(1) 58 93% pur.	[50]

with alkynes provides an elegant and straightforward access to substituted indoles and benzofurans (for a review see Ref. [51]). This sequential reaction involving a carbometallation of a triple bond and subsequent nucleophilic displacement of the metal has frequently been used, and various reaction conditions have been reported (**Table 6**). In addition to terminal alkynes even internal alkynes can successfully be applied for indole synthesis. While terminal alkynes were mostly coupled in the presence of a copper cocatalyst (**Table 6**, entries 1–3), internal alkynes were successfully converted under copper-free conditions (**Table 6**, entry 4,[52] entry 6[53]). In most cases, the more sterically demanding group on the triple bond (*t*-Bu, $SiMe_3$ > Ph > CO_2Et, Et, CH_2CH_2R, Me) will be found in the 2-position of the indole or benzofuran; thus, the substitution pattern in the product can be predicted. Since trimethylsilyl substituents are readily cleavable from the indole core, trimethylsilylalkynes serve as synthons for terminal alkynes; however, they produce the opposite regiochemistry.[52],[53] The nitrogen atom of the iodoaniline may either be unprotected (**Table 6**, entries 1 and 4), acylated (**Table 6**, entries 2 and 4),[52] or even attached as an aminal to solid support (**Table 6**, entry 6).[53] The coupling of 1,3- and 1,4-dienes with aryl halides having an *ortho*-nucleophilic group such as amino or hydroxyl groups was developed in the liquid phase by Larock and is one of the most versatile carboannelation reactions. Similarly, the reaction of an immobilized aminoiodoarene on a solid support with 1,3-butadienes (**Table 6**, entries 7–9 and 11) or 1,4-pentadienes (**Table 6**, entries 10 and 12) led to the formation of dihydroindoles, dihydrobenzofurans, tetrahydroquinolines, and tetrahydrobenzopyranes, respectively.

Recently, the reaction of polymer-bound aryl halides with 2,4-disubstituted allene-carboxylic acids leading to polymer-bound butenolides was reported (**Scheme 7**). After removal from the polymer, the substituted butenolides can serve as important building blocks for natural product synthesis.[60]

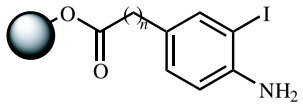
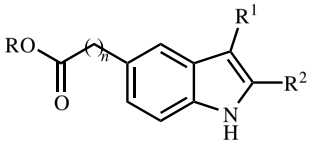
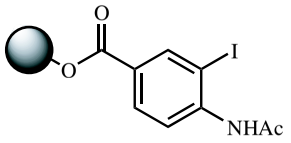
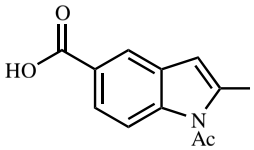
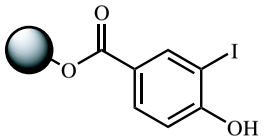
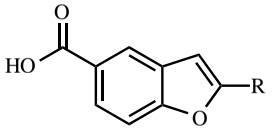
B.iv. Cross-Coupling Reactions on Solid Support

Cross-coupling reactions are extremely valuable tools for the construction of complex structures also on solid support. The accessibility of appropriate building blocks, in former times the bottleneck of library syntheses, has improved since a wide variety of alkenyl-, aryl-substituted stannanes or boranes can now be purchased from commercial suppliers in a broad variety.

B.iv.a. ***Stille Reactions.*** The Stille reaction, described in detail in **Sect. III.2.3.**, was one of the first cross-coupling reactions performed on solid support.[61] The reaction conditions employed were chosen in analogy to the liquid phase procedures and often feature an arsine or trifurylphosphine as an added ligand. Immobilized aryl halides have been coupled with aryl- and alkenylstannanes to a large extent (**Table 7**). Stannanes attached to a solid support have been used less frequently for Stille reactions (**Table 8**); however, they have been used in Ellman's benzodiazepine synthesis (**Scheme 8**).[62]

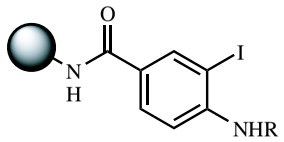
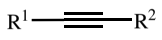
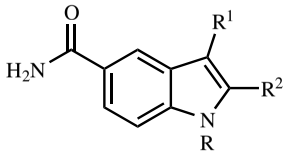
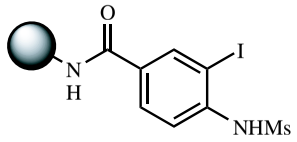
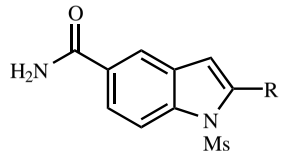
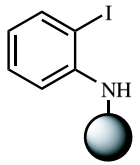
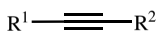
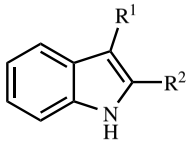
Various aryl bromides and iodides are suitable for this reaction. The reaction conditions may include microwave irradiation (**Table 7**, entry 6). It is interesting to note that a Stille coupling can be performed on a polymer-bound halobenzyl ester, which subsequently was cleaved by Pd-catalyzed hydrogenation to give the corresponding substituted methylarenes in the liquid phase (**Table 7**, entry 8).

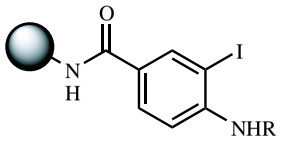
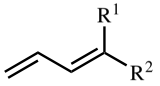
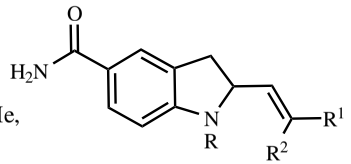
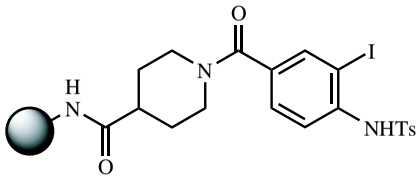
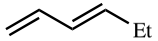
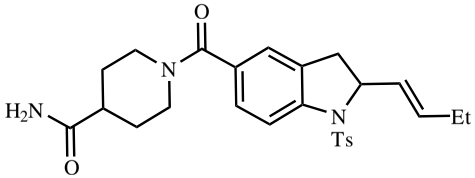
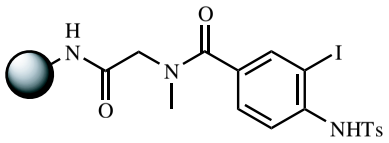
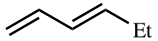
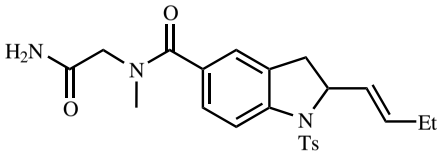
TABLE 6. Carboannelation of Amino Iodoarenes

Entry	Starting Material	Aryl Halide	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
1	 TentaGel; n = 0,1	 R^1 = H, Me, Ph, CO_2Et; R^2 = Me, C_6H_{13}, Ph, 2-Pyridyl, 2-(6-MeONaphthyl), CH_2c-Pent, p-Tol, p-$MeOC_6H_4$, $(CH_2)_3$, Cl, p-ClC_6H_4, CH_2NMe_2, $(CH_2)_4OH$, n-Bu	 Cleav.: R = H: i-PrOH/H_2O, 2N NaOH, 40–50 °C, 5 h; R = Me: MeOH/H_2O; R = Et: EtOH/H_2O	$Pd_2(PPh_3)_2Cl_2$ CuI, TMG, dioxane, 80–90 °C, 24 h	(Several described)	[54]
2	 TentaGel; S–OH	 R = Ph, p-ClC_6H_4, p-$MeOC_6H_4$, p-$PrC_6H_4(CH_2)_3OH$, SPh, i-Bu	 Cleav.: 0.03 M NaOH/i-PrOH, 50 °C, 5 h	$Pd(PPh_3)_2$, CuI, TMG, dioxane, 90 °C, 18 h	(7) 78–90% pur.	[55],[56]
3	 TentaGel; S–OH	 R = Hex, t-Bu, Ph, $(CH_2)_3Cl$, CMe_2OH, CH_2NH_2, CH_2NEt_2, $CH_2NHCONH$ t-Bu, CH_2NHCO_2t-Bu	 Cleav.: NaOH (aq.)/i-PrOH	$Pd(PPh_3)_4$, CuI, TMG, dioxane, 50 °C, 16 h	(10) 42–65%	[57]

(*Continued*)

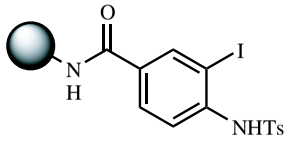
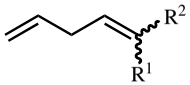
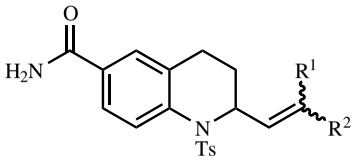
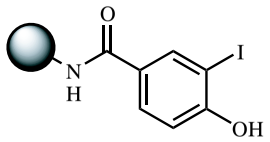
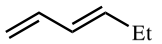
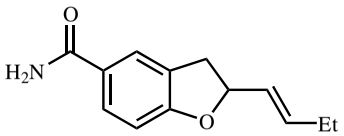
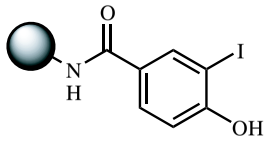
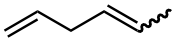
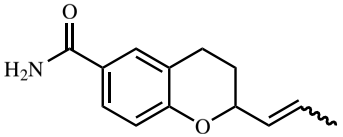
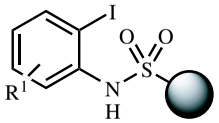
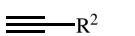
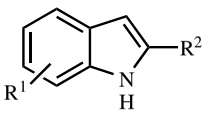
TABLE 6. (*Continued*)

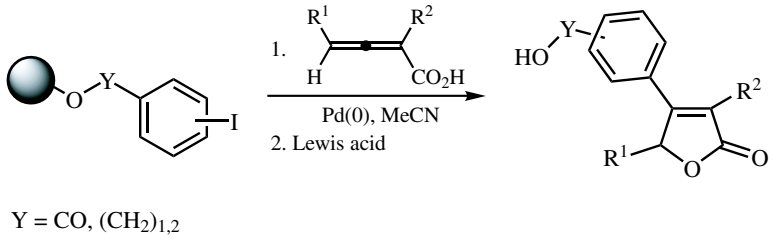
Entry	Starting Material	Aryl Halide	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
4	 R = H, Ac, CO -Pr Rink amide AM resin	 R^1 = Me, Pr, Ph, CO_2Et, CH_2CH_2OH, CH_2CH_2Cl, CH_2CH_2(m-$MeOC_6H_4$), $CH_2NC_4H_8$); R_2 = Pr, *t*-Bu, Ph, $SiMe_3$	 Cleav.: 30% TFA, CH_2Cl_2, 1 h	$Pd(OAc)_2$, PPh_3, LiCl or Bu_4NCl, K_2CO_3, or Na_2CO_3 or KOAc, DMF, 80 °C, 7–120 h	(15) 38–100 53–92% pur.	[52]
5	 Rink amide	 R = Ph, Bn, C_5H_{11}, CH_2NMe_2	 Cleav.: 30% TFA, CH_2Cl_2	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N/DMF (1:5), 80 °C, 5–16 h	(4) 87–96 79–98% pur.	[44]
6	 polystyrene with THP linker	 R^1 = Me, Et, Pr, Ph, CH_2CH_2OH; R^2 = Pr, *t*-Bu, Ph, $SiMe_3$	 Cleav.: 10% TFA, CH_2Cl_2	$Pd(PPh_3)_2Cl_2$, TMG, DMF, 110 °C, 21 h	(6) 63–97	[53]

7	 Rink amide; R = SO_2Ar, COAr	 R^1 = H, Me; R^2 = Me, Et, CO_2Me, OAC	 Cleav.: 30% TFA, CH_2Cl_2	$Pd(OAc)_2$, LiCl, *i*-Pr_2EtN, DMF, 100 °C	(12) 87–96 79–98% pur.	[58]
8	 Rink amide		 Cleav.: 10% TFA, CH_2Cl_2	$Pd(OAc)_2$, LiCl, *i*-Pr_2EtN, DMF, 100 °C	(1) 81 86% pur.	[58]
9	 Rink amide R = SO_2Ar, COAr		 Cleav.: 10% TFA, CH_2Cl_2	$Pd(OAc)_2$, LiCl, *i*-Pr_2EtN, DMF, 100 °C	(1) 69 85% pur.	[58]

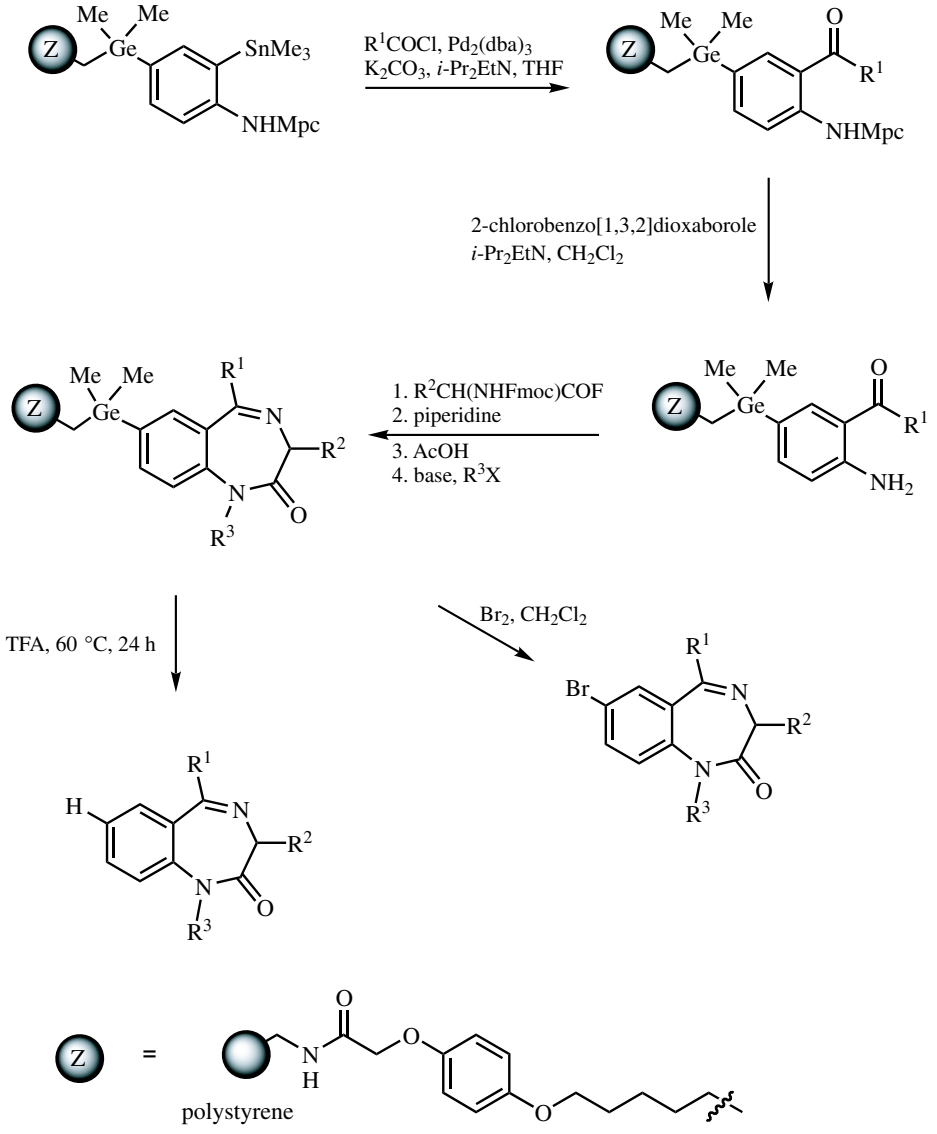
(*Continued*)

TABLE 6. (*Continued*)

Entry	Starting Material	Aryl Halide	Product(s)	Reaction Conditions	(Number of Examples); Yield (%)	Reference
10	 Rink amide	 R^1 = H, Me; R^2 = Me, Et, CO_2Me, OAc	 Cleav.: 30% TFA, CH_2Cl_2	$Pd(OAc)_2$, LiCl, *i*-Pr_2EtN, DMF, 100 °C	(12) 87–96 79 to >90% pur.	[58]
11	 Rink amide		 Cleav.: 30% TFA, CH_2Cl_2	$Pd(OAc)_2$, LiCl, *i*-Pr_2EtN, DMF, 100 °C	(1) 90 88% pur.	[58]
12			 Cleav.: 30% TFA, CH_2Cl_2	$Pd(OAc)_2$, LiCl, *i*-Pr_2EtN, DMF, 100 °C	(1) 84 88% pur.	[58]
13	 polystyrene; R^1 = H, F, MeO, CO_2Me	 R^2 = aryl, alkyl		$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 70 °C	(17) 65–100	[59]

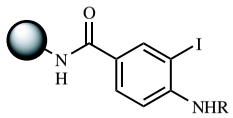
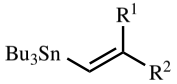
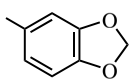
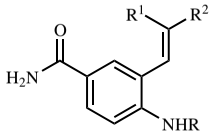
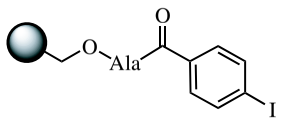
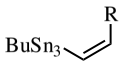
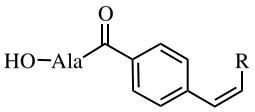
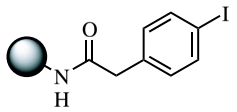
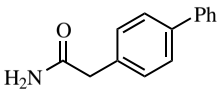


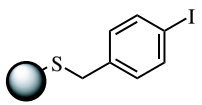
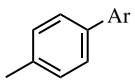
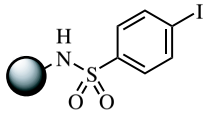
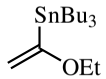
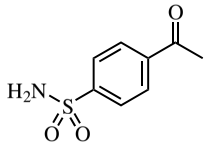
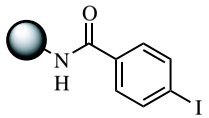
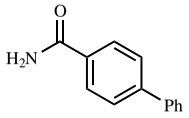
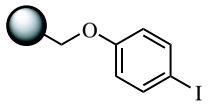
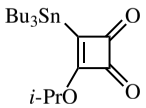
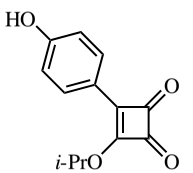
Scheme 7. Synthesis of butenolides.[60]



Scheme 8. Synthesis of benzodiazepines.[62]

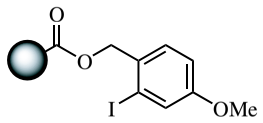
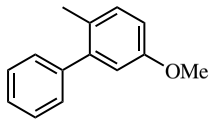
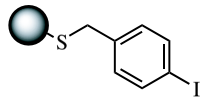
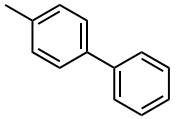
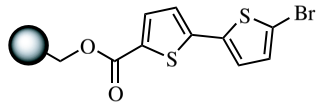
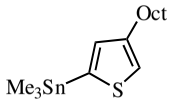
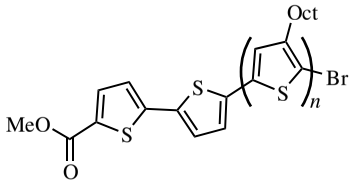
TABLE 7. Stille Reactions with Immobilized Aryl Halides

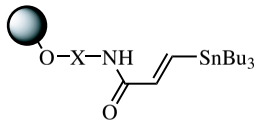
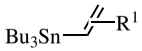
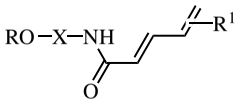
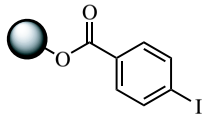
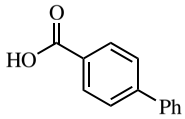
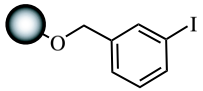
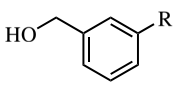
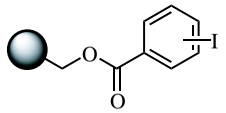
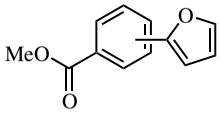
Entry	Starting Material	Stannane	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)	Reference
1	 Rink amide	 R^1 = H, Me; R^2 = H Me, Ph, or Me_3Sn 	 Cleav.: 5% TFA, CH_2Cl_2	$Pd_2(dba)_3$, $AsPh_3$, NMP, 45 °C, overnight	(5) 85–91 >90% pur.	[61]
2	 Wang resin	 R = H, Me	 Cleav.: 95% TFA, CH_2Cl_2	$Pd_2(dba)_3$, $AsPh_3$, NMP, 45 °C, overnight	(2) 88–92 >90% pur.	[61]
3	 Rink resin	Bu_3SnPh	 Cleav.: 5% TFA, CH_2Cl_2	$Pd_2(dba)_3$, TFP[a], LiCl, NMP, r.t., 12 h	(33) ca. 90% pur.	[63]

4	 Rink amide with NpSSMpact linker	Me_3SnAr = Ph, *m*-$AcOC_6H_4$	 Cleav.: *hν* (350 nm), MeCN	$Pd_2(dba)_3$, TFP, LiCl, NMP, r.t., 12 h	21–27 ca. 80–90% pur.	[63]
5	 Rink amide		 Cleav.: 20% TFA, CH_2CL_2	$Pd_2(dba)_3$, $AsPh_3$, NMP, r.t., 15 h	(1)	[11]
6	 Rink amide TentaGel	Bu_3SnPh	 Cleav.: 99% aq. TFA, 1 h	$Pd_2(dba)_3$, $AsPh_3$, NMP, microwave irradiation (3.8 min, 40 W)	(1) 85 >99% conv.	[64]
7	 Wang resin		 Cleav.: 20% TFA, CH_2Cl_2, r.t., 20 min	$PdCl_2(PPh_3)_2$, CuI, DMF, r.t., 30 h	(1)	[65]

(*Continued*)

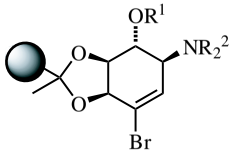
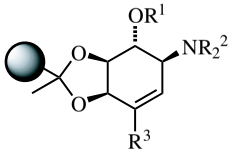
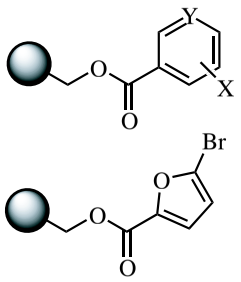
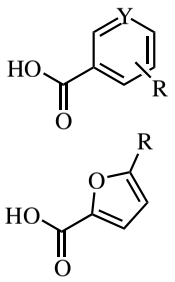
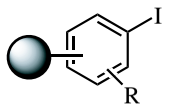
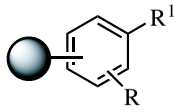
TABLE 7. (*Continued*)

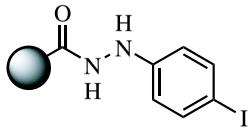
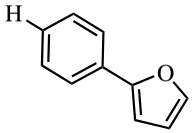
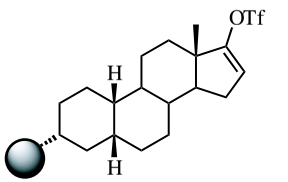
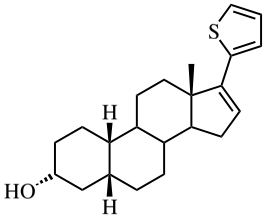
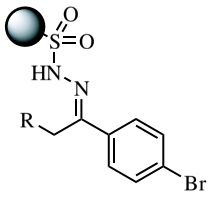
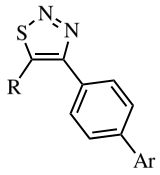
Entry	Starting Material	Stannane	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)	Reference
8	 polystyrene with magnetite core	Me_3SnPh	 Cleav.: $Pd(OAc)_2$, NH_4HCO_2, DMF, 65 °C, 20 h	$Pd_2(dba)_3$, TFP, LiCl, NMP, 65 °C, 22 h	(1)	[66]
9	 polystyrene with thio linker and with magnetite core	Me_3SnPh	 Cleav.: *hν* (350 nm), DMF, 6 h	$Pd_2(dba)_3$, TFP, LiCl, NMP, microwave irradiation, 2 h	(1) 8.5	[66]
10	 polystyrene		 Repetitive coupling and bromination; $n = 1$ to 3; cleav.: NaOMe, THF, reflux, then MeI, 18-c-6, reflux, 3 h	$PdCl_2(PPh_3)_2$, LiCl, DMF, 80 °C	(5) (trimer to tetramer), 89–95% pur.	[67]

11	 Wang or PEG; X = Gly, Phe, AlaAca, Arg(Pbf)-Aca	 Various substituents	 Cleav.: R = H: TFA/CH_2Cl_2/H_2O (80:15:5), r.t., 1 h; R = Me: CH_2Cl_2, MeOH, DBU, r.t., overnight	$Pd_2(dba)_3$, $AsPh_3$, NMP, r.t., overnight	>60	[68]
12	 TantaGel S with photocleavable linker	Bu_3SnPh	 Cleav.: *h*v (Hg pressure, >320 nm)	$Pd_2(dba)_3$, $AsPh_3$, NMP, 50 °C, 42 h	(1) 50 93% pur.	[69]
13	 polystyrene with base-labile linker	Bu_3SnR; R = aryl, hetaryl or alkenyl	 Cleav.: 6 equiv. NaOMe, MeOH/dioxane (1:4), r.t., 24 h	$Pd_2(dba)_3$, $AsPh_3$, dioxane, 50 °C, 24 h (preferentially) or $Pd(PPh_3)_4$, dioxane, 100 °C, 24 h	49–95	[70]
14	 polystyrene on SynPhase crown	Bu_3Sn (2-Furyl)	 Cleav.: 0.1 M NaOMe, THF/MeOH (4:1), r.t., 20 h	$Pd_2(dba)_3$, $AsPh_3$, THF	(2) quant 75 to >90% pur.	[71]

(*Continued*)

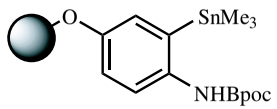
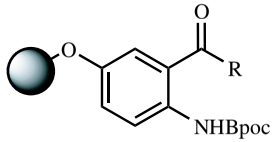
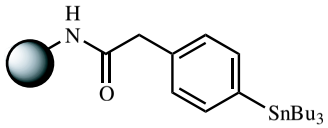
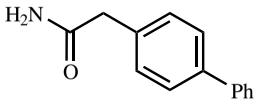
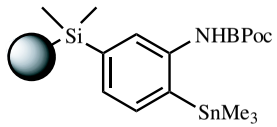
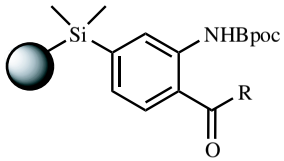
TABLE 7. (*Continued*)

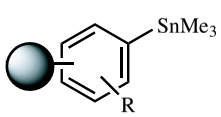
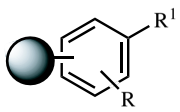
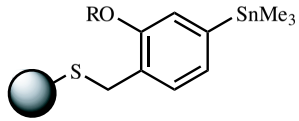
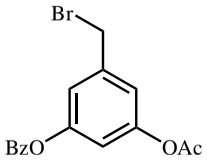
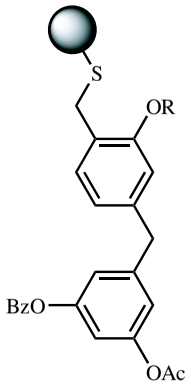
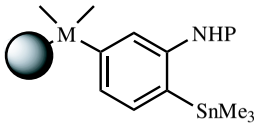
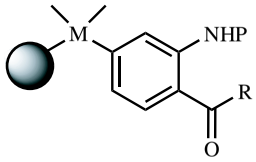
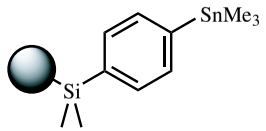
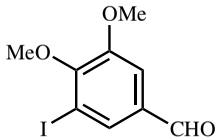
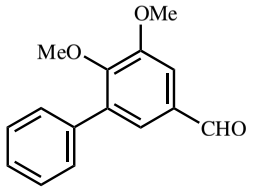
Entry	Starting Material	Stannane	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)	Reference
15	 Wang-type diol linker	Bu_3SnR^3; R^3 = various alkenyl groups		$Pd(PPh_3)_4$, dioxane, 100 °C, 24 h	(11)	[72]
16	 polystyrene; Y=CH, N	Bu_3SnR; R = Ph, Ethenyl, 2-Furyl, 2-Thienyl, *o*-$Et_2NC(O)C_6H_4$, *o*-$Et_2NC(O)OC_6H_4$	 Cleav.: $LiOH/H_2O$/MeOH/THF	$Pd(PPh_3)_4$, DMF, 60 °C, 24–48 h	(22) 71 to >95	[73]
17	 various scaffolds	R^1SnBu_3: R^1 = 2-Furyl, 2-Thienyl 2-Pyridyl, 3-Pyridyl, Ethenyl		$Pd_2(dba)_3$, $AsPh_3$, dioxane, 50 °C, 24 h	(9) 37–95	[42]

18		Bu_3Sn(2-Furyl)		$Pd_2(dba)_3$, $AsPh_3$, dioxane, 60 °C, 24 h	(1) 50–90	[16]
	polystyrene or TentaGel or ArgoPore		Cleav.: $Cu(OAc)_2$, MeOH, pyr, r.t., 2 h			
19		Bu_3Sn(2-Thienyl)		$Pd(PPh_3)_4$, LiCl, DMF, 110 °C, 3 h	(1) 38	[45]
	polystyrene with fluoride-labile		Cleav.: TBAF, TMU, 100 °C, 1 h			
20		Bu_3SnAr; Ar = Ph, *p*-F-C_6H_4		$PdCl_2(PPh_3)_2$, DMF, 90 °C, 24 h	(3) 76–80	[74]
	polystyrene		Cleav.: $SOCl_2$, DCE, 60 °C, 5 h			

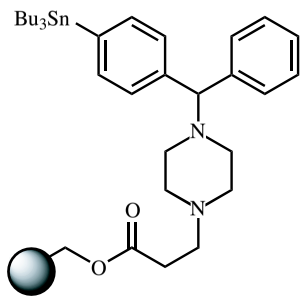
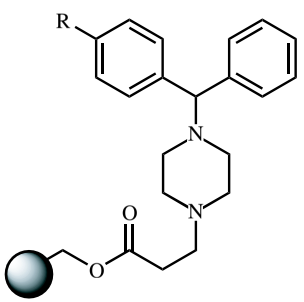
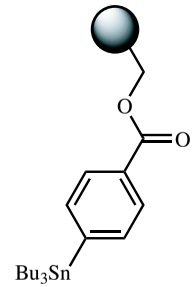
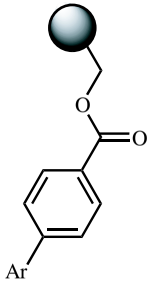
[a] TFP = Trifurylphosphine.

TABLE 8. Stille Reactions with Polymer-Bound Stannanes

Entry	Starting Material	Electrophile	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)	Reference
1	 polystyrene with linker	RCOCl; R = *o*,*m*, *p*-$MeOC_6H_4$, *c*Hex, 2-Me–5-NCC_6H_4 *m*-$CF_3C_6H_4$, *p*-(*t*-BuC_6H_4), *o*-ClC_6H_4, 1-(*p*-ClPh)*c*-Pent, $CH_2CH_2CO_2Me$, Thienyl, 2-Furyl, 1-Adamantyl, 3-(1,2-methylenedioxo) C_6H_3, 2-Naphthyl		$Pd_2(dba)_3 \bullet CHCl_3$, K_2CO_3, THF, r.t.	52–82 >80% pur.	[75],[76]
2	 Rink amide	PhI or PhOTf	 Cleav.: 5% TFA, CH_2Cl_2	$Pd_2(dba)_3$, TFP, LiCl, NMP, r.t., 12 h	PhI: 15 PhOTf: 3	[63]
3	 polystyrene with linker	RCOCl; R = *m*, *p*-$MeOC_6H_4$, 1-Adamantyl, Ph		$Pd_2(dba)_3 \bullet CHCl_3$, K_2CO_3, THF, *i*-Pr_2NH, r.t., 1 h	>50	[62]

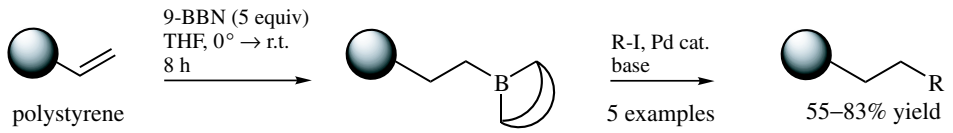
4		R^1X; R^1X = ArOTf, $ArCH_2Br$		$PdCl_2(PPh_3)_2$, LiCl, DMF, 120 °C, 2–8 h	(Several claimed)	[39] (p. 32)
5	 TentaGel			$Pd(PPh_3)_4$, Et_3N, reflux, 4 h	(several claimed)	[39]
6	 M = Si, P = Bpoc or M = Ge, P = Mpc	RCOCl; R = *m*, *p*-$MeOC_6H_4$, 1-Adamantyl, 3-(1,2-methylenedioxo) C_6H_3, 2-Naphthyl		$Pd_2(dba)_3 \cdot CHCl_3$, K_2CO_3, THF, r.t., 1 h	>58	[77]
7	 R = H, OMe polystyrene with linker		 Cleav.: 50% TFA, CH_2Cl_2	$Pd(PPh_3)_4$, aq. Na_2CO_3, DME, reflux, 12 h	(1)	[78]

(*Continued*)

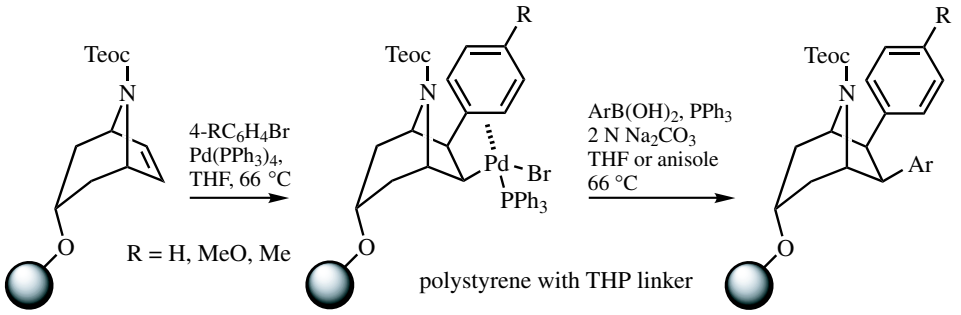
8	 polystyrene	RBr; R = 2,3-Pyridyl, Ph, 2-Thienyl and other hetaryl		$Pd(PPh_3)_4$, LiCl, DMF, 100 °C	(10) [79]
9		ArX; X = Br, I		Palladacycle, LiCl NMP, 90 °C	(6) 80 to >95 [80]

B.iv.b. ***Suzuki Coupling Reactions.*** The cross-coupling of organoboron derivatives with carbon electrophiles, the so-called Suzuki reaction (see **Sect. III.2.2**; for a review see Ref. [81]), has been conducted in various instances on a solid support. The mild reaction conditions, the compatibility with most functional groups, and the ready availability of starting material (boronic acids) have made this transformation a powerful tool in solid phase organic synthesis.

Starting from a vinyl-substituted resin, hydroboration with 9-BBN yields a homobenzylborane (**Scheme 9**). This intermediate can be coupled with various functionalized aryl iodides as well as vinyl and alkyl iodides giving rise to resins with amide, ester, or protected hydroxy functionalities.[82] Similarly, bromostyrene could be coupled with functionalized boranes for the attachment of preformed handles, for example, for the construction of the silicon traceless linker.[83] The carbometallation of certain alkenes such as tropanes and the subsequent treatment with aryl boronic acid gives rise to two new C—C bonds (**Scheme 10**).



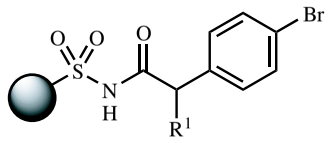
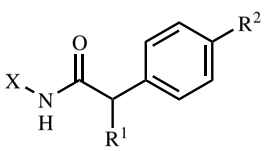
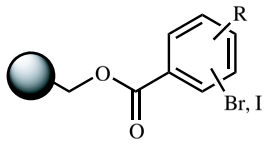
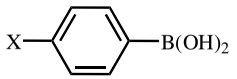
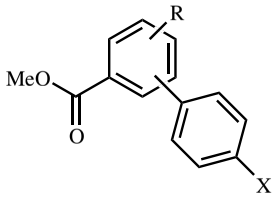
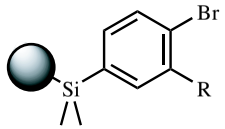
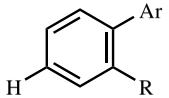
Scheme 9. Derivatization of a borane.[82]

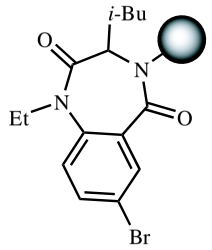
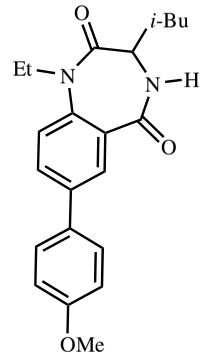
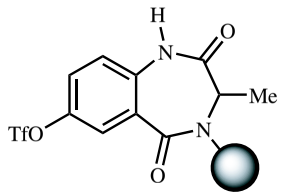
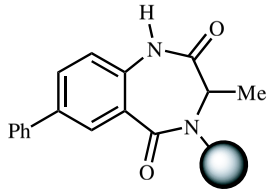


Scheme 10. Carbometallation on the tropane framework.[35]

In the case of aromatic iodides, the couplings were performed using $Pd(OAc)_2$ (0.3 equiv), PPh_3 (0.9 equiv), NaOH (3 equiv), a phase transfer agent (Triton B, 1.5 equiv), and the iodide (4 equiv) in DMF at 85 °C for 14 h. The alkenyl and alkyl iodides were coupled using $PdCl_2$(dppf) as a catalyst and K_2CO_3 as a base. Microwave-assisted coupling of aryl- and heteroarylboronic acids with polymer-bound bromo- and iodobenzoic acids proceeds under quite mild condition within short reaction times (4 min, 40 W).[64] The yields were between 55% (alkyl) and 85% (aryl iodides) as determined by quantitative IR analysis of representative carbonyl bands. Synthetically interesting is the conversion of aryl halides into the corresponding boronates. Thus, treatment of polymer-bound aryl iodides with a pinacol ester of diboron under palladium catalysis gave the corresponding polymer-bound boronates (**Table 9**, entries 13 and15). The Suzuki coupling reaction was then carried out using a variety of aryl halides. Cleavage from the solid support delivered diverse biaryl libraries in good yields with high purities of the individual compounds (**Table 10**, entries 4 and 9).

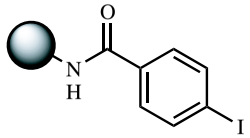
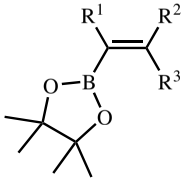
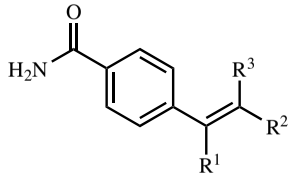
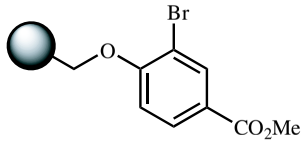
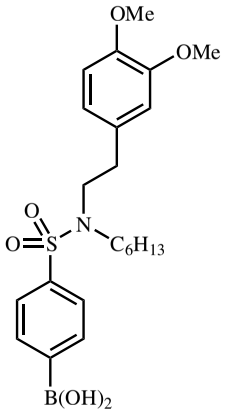
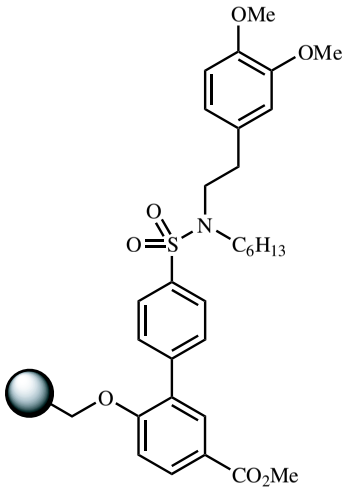
TABLE 9. Suzuki Reactions with Immobilized Aryl, Alkenyl Halides and Triflates

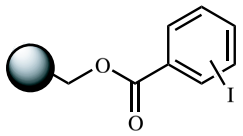
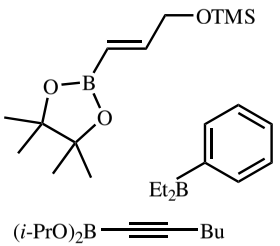
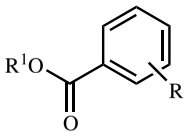
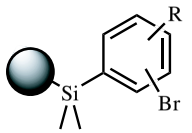
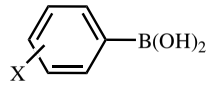
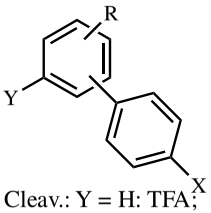
Entry	Starting Material	Aryl- and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
1	 polystyrene with linker; R^1 = H, Me, Et, *i*-Pr, Bn	$R^2B(OH)_2$ or *i*-Bu–9BBN; R^2 = Ph, *p*-$F_3CC_6H_4$, *p*-$MeOC_6H_4$, 2,6-$Cl_2C_6H_3$,	 Cleav.: (1) CH_2N_2; (2) OH^- (X = OH) or amine ($X = NR^3_2$)	$Pd(PPh_3)_4$, Na_2CO_3, THF, 65 °C	(10) 87–100	[85]
2	 polystyrene; R = H, Me, OMe	 X = H, OMe, Me, NO_2	 Cleav.: 0.2 equiv NaOMe	$Pd(PPh_3)_4$, (optimum) or $Pd(PPh_3)_2Cl_2$ or $Pd(C_3H_5)_2Cl_2$/ PPh_3 or $PdBn(PPh_3)_2Cl$		
3	 R = H, CN Wang resin with linker	$ArB(OH)_2$; Ar = Ph, *p*-HOC_6H_4	 Cleav.: TFA	$Pd(PPh_3)_4$, aq. 2 M Na_2CO_3, EtoH, 90 °C 16–24 h	(2)	[87],[88]

4	 polystyrene with PAL-type linker	*p*-$MeOC_6H_4B(OH)_2$	 Cleav.: TFA/Me_2S/H_2O (90:5:5), 36 h	Pd $(PPh_3)_4$, 2 M aq. K_2CO_3, THF, reflux, 18 h	(1) 62	[89]
5	 polystyrene with additional linker	$C_6HB(OH)_2$	 Cleav.: 30% TFA, CH_2Cl_2	Pd $(PPh_3)_4$, K_3PO_3, dioxane, 80 °C, 8.5 h	(1)	[90]

(*Continued*)

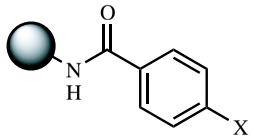
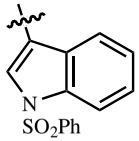
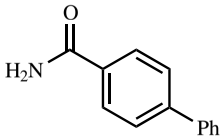
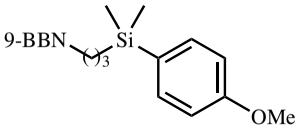
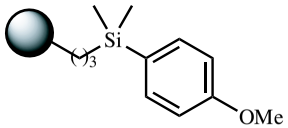
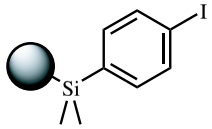
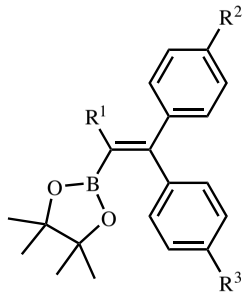
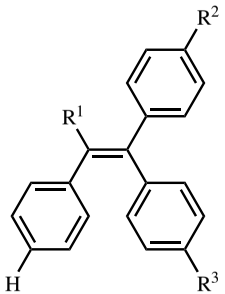
TABLE 9. (*Continued*)

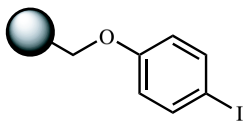
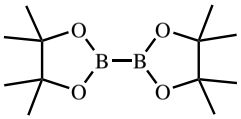
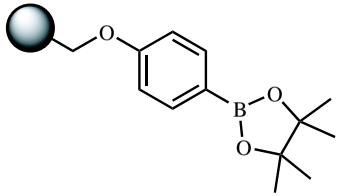
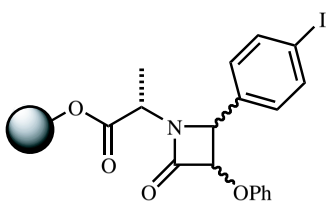
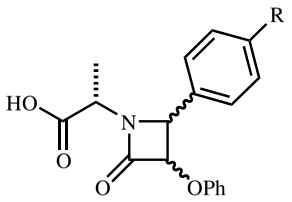
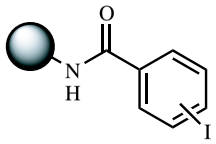
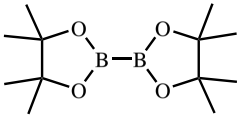
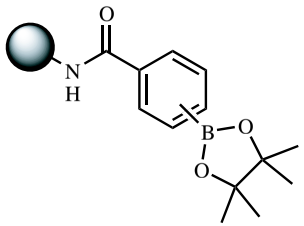
Entry	Starting Material	Aryl- and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
6	 Rink amide		 Cleav.: 30% TFA, CH_2Cl_2	$Pd(PPh_3)_2,Cl_2$, 3 M KOH, DME, 80 °C	(10) 75 to >95	[91]
7	 polystyrene			$Pd(PPh_3)_4$, 2 M aq. Na_2CO_3, EtOH, 80 °C 25 h	(1) detection by MAS ^1H NMR	[92]

8	 Sasrin or Wang resin	$R—B(OH)_2$ R = Ph, 2-Thienyl Bu_3B 	 Cleav.: R^1 = H: TFA, CH_2Cl_2, r.t., 30 min; R^1 = Me: 3 equiv NaOMe, MeOH, THF, 1 h	$Pd(PPh_3)_4$, or $Pd(dppf)_2Cl_2$, or $Pd_2(dba)_3$ (optimum); K_2CO_3, DMF, r.t.	(6) 50–91 100% conv.	[93]
9	 Wang resin with linker; R = H, OMe	 X = H, 4-Me, 4-MeO, 4-$HOCH_2$, 4-Cl, 3-NO_2	 Cleav.: Y = H: TFA; Y = I: ICl; Y = Br: Br_2/pyr	$Pd(PPh_3)_4$, Na_2CO_3, DME, reflux or $Pd(PPh_3)_4$, Et_3N/DMF reflux, 24 h	(22) 36–99	[94]

(*Continued*)

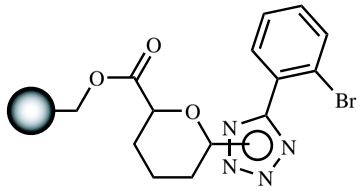
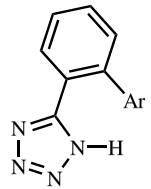
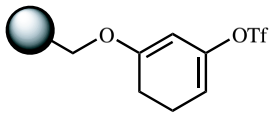
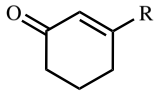
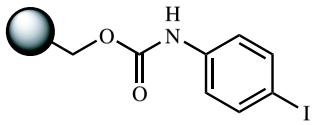
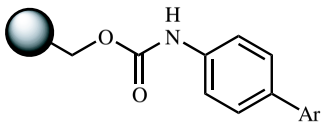
TABLE 9. (*Conitinued*)

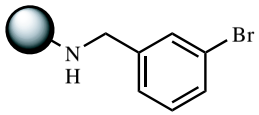
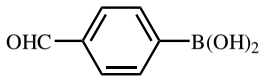
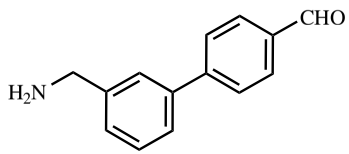
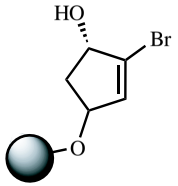
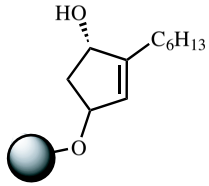
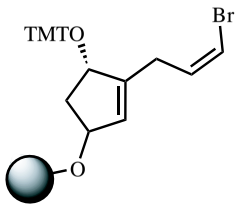
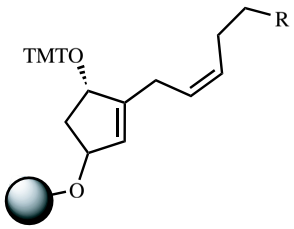
Entry	Starting Material	Aryl- and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
10	 Rink amide TentaGel; X = I, Br	$RB(OH)_2$; R = Ph, 2-Naphthyl, 2-Thienyl, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *o*-$MeOC_6H_4$, *m*-$NO_2C_6H_4$, 	 Cleav.: 99% aq. TFA, 1 h	$Pd(PPh_3)_4$, Na_2CO_3, H_2O, EtOH, DME, microwave irradiation (3.8 min, 40 W)	(8) 93–99	[64]
11	 polystyrene			$Pd(PPh_3)_4$, Na_2CO_3, DME, 80 °C 24 h	(1)	[83]
12	 ArgoGel amine with linker	 (generated *in situ*) R^1 = Me, Et, Pr; R^2 = H, OMe, R^1 = various substituents	 Cleav.: 30% TFA, CH_2Cl_2	$Pd(dppf)Cl_2$, KOH, DME, 25 °C, 18 h	13–59; 1–4 isomers each	[95]

13	 Wang resin			Pd(0). KOAc, DMSO, 80 °C, 2 h	(1)	[65]
14	 Sasrin resin or ArgoGel–MB–OH	$RB(OH)_2$; R = Ph, *o*,*m*-$MeOC_6H_4$, *m*-$NO_2OC_6H_4$, *m*-$(MeCONH)C_6H_4$, 2-Thienyl		$PdCl_2$(dppf), Et_3N, DMF, 65 °C, 12–24 h	(7) 65–83	[12]
15				$PdCl_2$(dppf), KOAc, DMF, 80 °C, 16 h	(1) >99% conv.	[96]

(*Continued*)

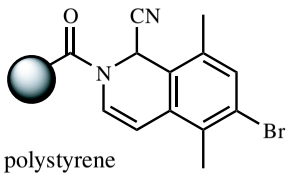
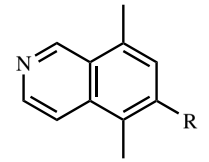
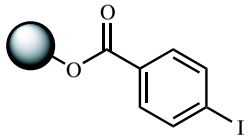
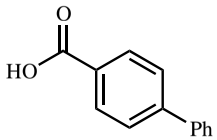
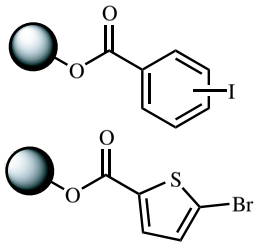
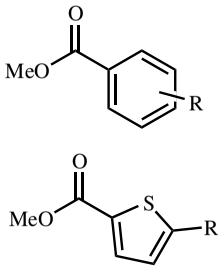
TABLE 9. (*Conitinued*)

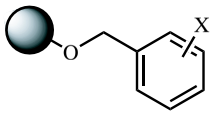
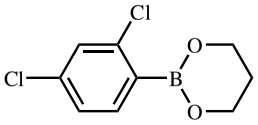
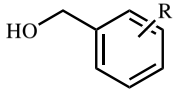
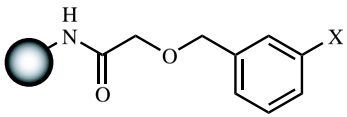
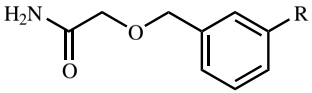
Entry	Starting Material	Aryl- and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
16	 polystyrene	$ArB(OH)_2$; Ar = Ph, Tol	 Cleav.: 99% aq. TFA, 1 h	$Pd(PPh_3)_4$, Na_2CO_3, DME, 80 °C, 24 h	(2) 53–57	[97]
17	 Rink resin	$RB(OH)_2$; R = aryl or Thienyl	 Cleav.: 5% TFA, Me_2CO	$Pd(PPh_3)_4$, aq. 2 M, Na_2CO_3, dioxane, 90 °C, 2.5 h	(9) 28–47 >95% pur.	[98]
18	 Wang resin	$ArB(OH)_2$; Ar = Tol, *p*-$MeOC_6H_4$		$Pd(PPh_3)_4$, Na_2CO_3, DME, 90 °C, 24 h	(2) 32–33 92–94% pur.	[99]

19	 Rink resin		 Cleav: 5% TFA, CH_2Cl_2	Pd(0), aq. K_2CO_3, EtOH, xylene	(1) 60	[100]
20	 (presumably polystyrene) with dibutylsilyl linker	C_6H_{13}–9-BBN		$Pd(PPh_3)_4$, THF, Na_2CO_3, 65 °C	(1)	[101]
21	 (presumably polystyrene) with dibutylsilyl linker	RC_2H_4–9-BBN; R = $(CH_2)_2OMe$, Bu, $NHSO_2Ph$, NHBn, OEt, OMe, O*i*-Pr		$Pd(PPh_3)_4$, THF, Na_2CO_3, 65 °C	(7)	[101]

(*Continued*)

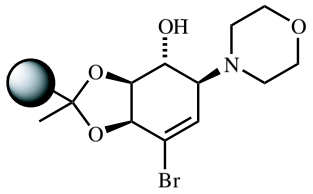
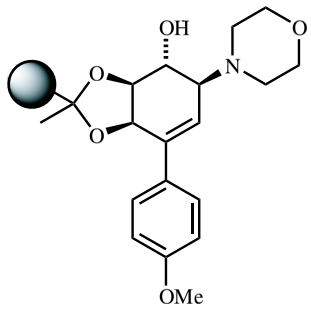
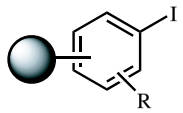
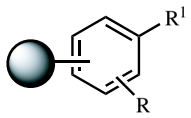
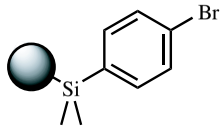
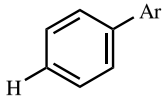
TABLE 9. (*Conitinued*)

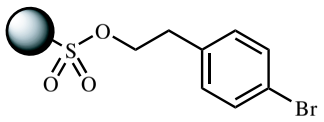
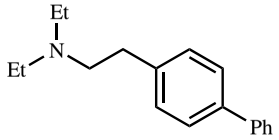
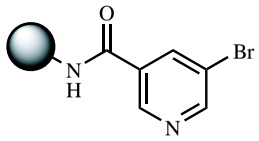
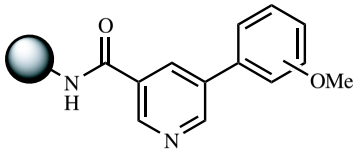
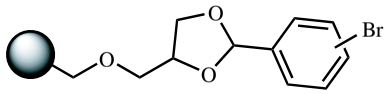
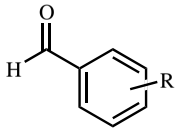
Entry	Starting Material	Aryl- and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
22	 polystyrene	$RB(OH)_2$; R = Ph, 3-Thienyl	 Cleav.: 1 M aq. KOH	$Pd(PPh_3)_4$, DME, Na_2CO_3, 80 °C, 36 h	(2) 17–19	[102]
23	 TentaGel S with photocleavable linker	$PhB(OH)_2$	 Cleav.: *hv* (Hg high-pressure lamp, >320 nm)	$PdCl_2(dppf)$, Et_3N, DMF, 65 °C, 18 h	(1) 72 93% pur.	[69]
24	 MeO–PEG 4000, 5000, or 6000	$RB(OH)_2$; R = aryl and hetaryl	 Cleav.: Et_3N, MeOH	$Pd(PPh_3)_4$, 2 M Na_2CO_3, DMF, 110 °C, 10 h	(18) 46–93	[103]

25	 polystyrene with base-labile linker; X = Br, I	 $RB(OH)_2$ (various substituted aromatic and heteroaromatic structures); C_6H_{13}–9-BBN	 Cleav.: 6 equiv NaOMe, MeOH/dioxane (1:4), r.t., 24 h	$Pd(OAc)_2$, K_2CO_3, dioxane/H_2O (6:1), 100 °C, 24 h	(21) 51–97	[70]
26	 polystyrene with Rink linker	*p*-$OHCC_6H_4B(OH)_2$, *o*-$MeC_6H_4B(OH)_2$	 Cleav.: 20% TFA, CH_2Cl_2, r.t., 5 min	$Pd(OAc)_2$, K_2CO_3, dioxane/H_2O (6:1), 100 °C, 24 h	(2) 40–89	[70]

(*Continued*)

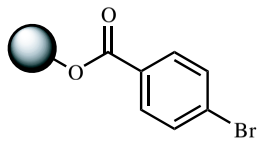
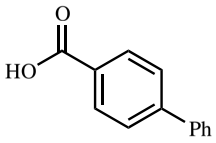
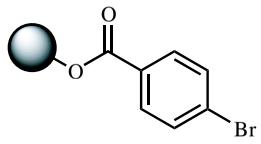
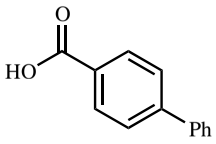
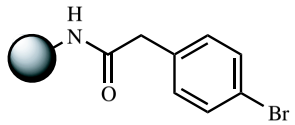
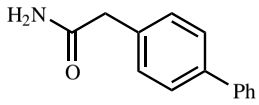
TABLE 9. (*Conitinued*)

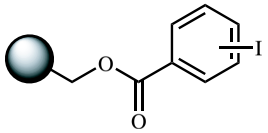
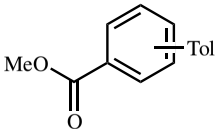
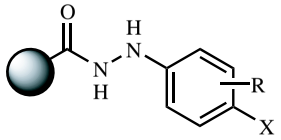
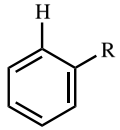
Entry	Starting Material	Aryl- and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
27	 polystyrene with Wang-type linker	*p*-$MeOC_6H_4B(OH)_2$		$Pd(OAc)_2$, dioxane/H_2O (6:1), 100 °C, 24 h; double coupling	(1)	[72]
28	 various scaffolds	$R^1B(OH)_2$; R^1= aryl, hetaryl		$Pd_2(dba)_3$, $AsPh_3$, dioxane, 50 °C, 24 h	(>10) 37–95	[42]
29	 R = H, OMe polystyrene with linker	$ArB(OH)_2$; Ar = Ph, 1-Naphthyl, Tol, $(OHC)(MeO)C_6H_3$	 Cleav.: 50% TFA, CH_2Cl_2	$Pd(PPh_3)_4$, aq. Na_2CO_3, DME, reflux, 12 h	(7) + a 100 cpd library	[78]

30	 polystyrene with links	*p*-$MeC_6H_3B(OH)_2$	 Cleav.: Et_2NH, 60 °C, 18 h	$Pd(PPh_3)_4$, Na_2CO_3, toluene, EtOH, 90 °C, 20 h	(1) 23 90% pur.	[104]
31	 Rink amide	*o,p*-$MeC_6H_4B(OH)_2$		$Pd(PPh_3)_4$, Na_2CO_3, toluene, EtOH, 90 °C, 20 h	(2) >25	[105]
32	 polystyrene	$RB(OH)_2$; R = aryl or hetaryl	 Cleav.: 3 M HCl/dioxane (1:1)	$Pd(PPh_3)_4$, Na_2CO_3, DME, reflux, 24–48 h	(15) 45 to >95	[106]

(*Continued*)

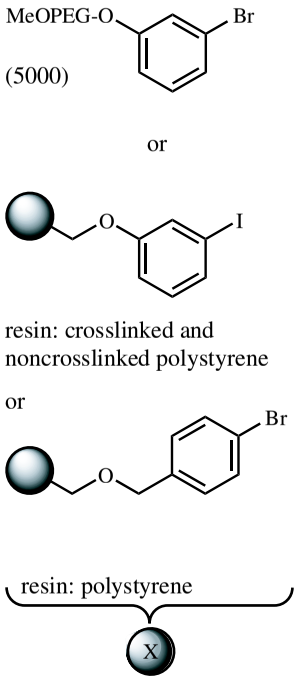
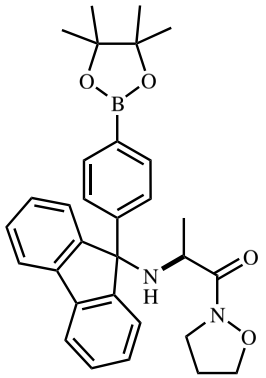
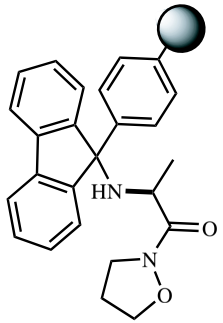
TABLE 9. (*Continued*)

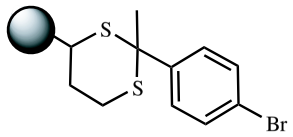
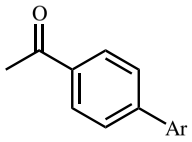
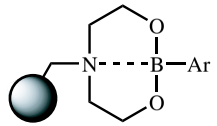
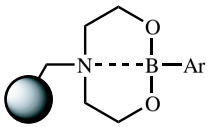
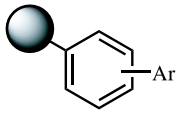
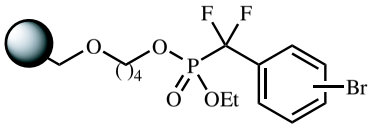
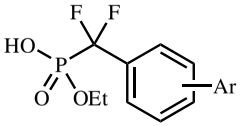
Entry	Starting Material	Aryl-and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
33	 polysterene with 9-phenylfluorenyl–9-yl linker (PhFI)	$PhB(OH)_2$	 Cleav.: 20% TFA, CH_2Cl_2/MeOH (9:1)	$Pd(PPh_3)_4$, Na_2CO_3, DME, 80 °C, 16 h	(1) 68 >95% pur.	[107]
34	 polystyrene with 9-phenylfluorenyl-9-yl linker (PhFI acetic acid)	$PhB(OH)_2$	 Cleav.; 20% TFA, CH_2Cl_2/MeOH (9:1), 2 h	$Pd(PPh_3)_4$, Na_2CO_3, DME, 80 °C, 16 h	(1) 72 >95% pur.	[108]
35	 polystyrene with Knorr linker	$PhB(OH)_2$	 Cleav.; TFA, CH_2Cl_2 2 h	$Pd(PPh_3)_4$, Na_2CO_3, THF/ H_2O (4:1), 60 °C, 2 d	(1) 72 >95% pur; reaction in MicroTube™	[109]

36	 polystyrene on SynPhase crown	*p*-TolB(OH)$_2$	 Cleav.: 0.1 M NaOMe, THF/MeOH (4:1), r.t., 20	$Pd(OAc)_2$, K_2CO_3, THF/H_2O (6:1), 60 °C, 2 d	(2) quant; 83–94% pur.	[71]
37	 polystyrene or TentaGel or Argopore X = Br, I; R = H, Me, F	RB(OH)$_2$; R = *p*-MeOC$_6$H$_4$, *p*-OHCC$_6$H$_4$, 2-Thienyl	 Cleav.: Cu(OAc)$_2$, *n*-PrNH$_2$, r.t., 2 h	$Pd(PPh_3)_2,Cl_2$ or $Pd(PPh_3)_4$	(5) 60–93	[16]

(*Continued*)

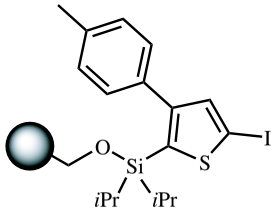
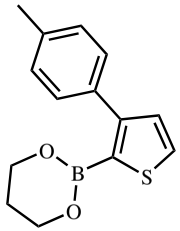
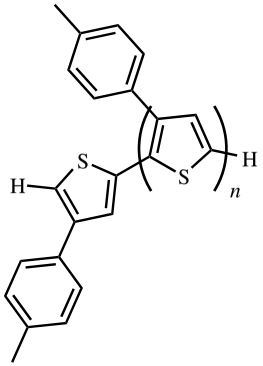
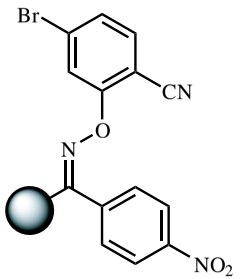
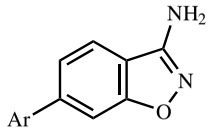
TABLE 9. (*Continued*)

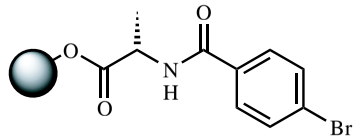
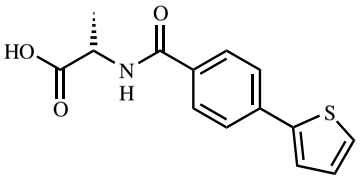
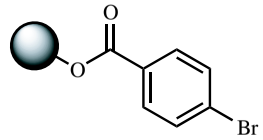
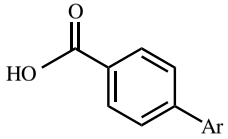
Entry	Starting Material	Aryl-and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
38				$PdCl_2$(dppf), aq. 2M Na_2CO_3, DMF, 80 °C, overnight	(4) 50–90	[110]

39	 polystyrene	$ArB(OH)_2$; Ar = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$	 Cleav.: 2.5 equiv $PhI(Tfa)_2$, $CH_2Cl_2/EtOH/H_2O$ (4.5:4.5:1), r.t., 30 min	$Pd(PPh_3)_4$, Na_2CO_3, DMF, DME, 80 °C, overnight; repeat coupling	(3) 28–33	[111]
40	 various linker	 polystyrene		$Pd(PPh_3)_4$, various cond.	(3) 25–100	
41	 noncrosslinked polystyrene	$ArB(OH)_2$	 Cleav.: 4 equiv Me_3SiI, CH_2Cl_2, r.t., 4h	$PdCl_2(PhCN)_2$, K_2CO_3, DMF, rt., 24 h	(28) 43–90	[112]

(*Continued*)

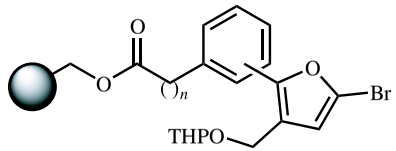
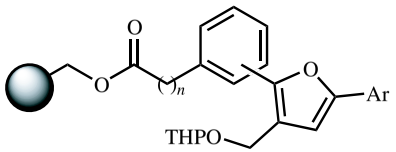
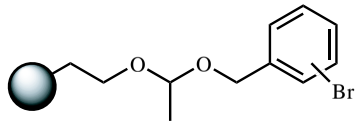
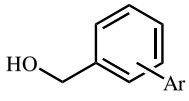
TABLE 9. (*Continued*)

Entry	Starting Material	Aryl-and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
42	 polystyrene		 Repetitive coupling and iodination; n =1–3; cleav.: TBAF, THF	$Pd(PPh_3)_4$, $NaHCO_3$, THF, reflux, 8 h	(5) (dimer to tetramer), 48–87	[113]
43	 polystyrene	$ArB(OH)_2$; Ar = Ph, 3,5-$(Cl)_2C_6H_3$, 3,5-$(CF_3)_2C_6H_3$, *p*-$OHCC_6H_4$	 Cleav.: TFA/5 N aq. HCl (4:1), 55 °C, 2h	$Pd(PPh_3)_4$, THF, 55 °C, 36 h	(4) 41–54 81 to >96% pur.	[50]

44	 polystyrene with Rink-type linker	(2-Thienyl)B(OH)$_2$	 Cleav.: 1% TFA, CH_2Cl_2 75 min	$Pd(PPh_3)_4$, aq. Na_2CO_3, DMF, 80 °C, 24 h	(1) >90 >90% pur.	[114]
45	 MeO–PEG 5000	$ArB(OH)_2$; Ar = Ph, *p*-FC_6H_4, *m*-$O_2NC_6H_4$, *p*-EthenylC_6H_4	 Cleav.: (a) 1 N NaOH; (b) 12 NCl	$Pd(PPh_3)_4$, 2 M K_2CO_3, DMF, 70–80 °C, 3–4 h	(3) 55–60	[115]

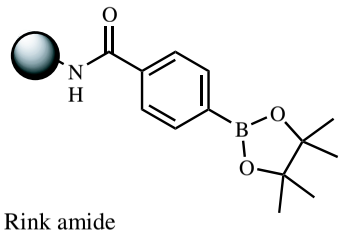
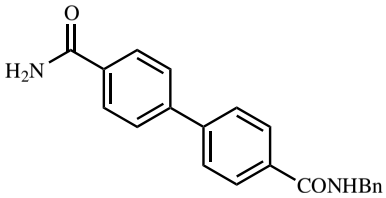
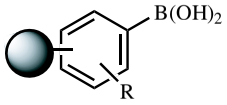
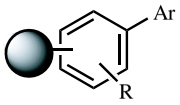
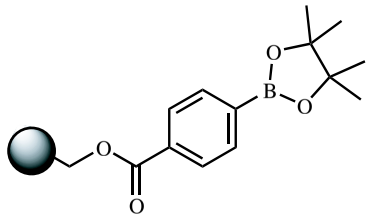
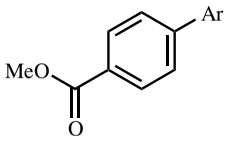
(*Continued*)

TABLE 9. (*Continued*)

Entry	Starting Material	Aryl-and Alkyl-Borane/Boronic Acid	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)[a]	Reference
46	 Wang resin; n = 0,1	$ArB(OH)_2$; Ar = m-$O_2NC_6H_4$, m,p-ClC_6H_4, m-$MeOC_6H_4$, p-(t-$BuNHSO_2C_6H_4$)		$Pd(OAc)_2$, PPh_3, 2 M Na_2CO_3, DME 85–90 °C,	(7)	[116]
47	 Wang with linker	$ArB(OH)_2$; Ar = PH, p-MeC_6H_4		$Pd(PPh_3)_4$, Na_2CO_3, DME, 80 °C, 24 h	(4) 60–68	[117]

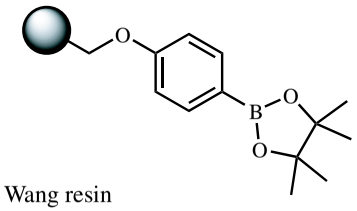
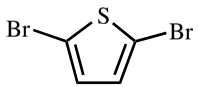
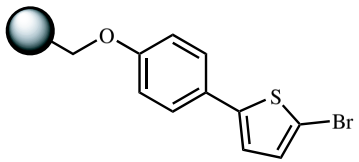
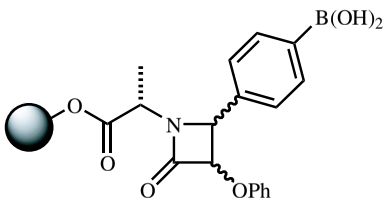
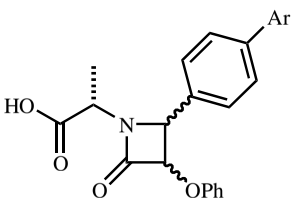
[a] Yield in parentheses refers to the bromobenzamide as starting material.

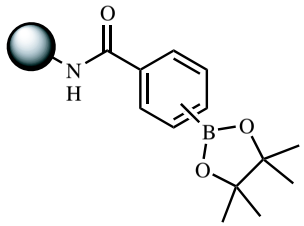
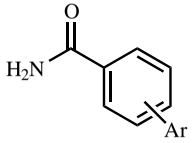
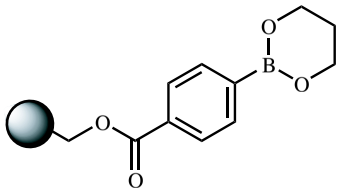
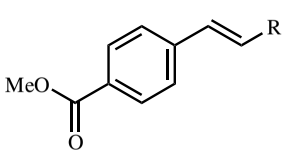
TABLE 10. Suzuki Reactions with Polymer-Bound Aryl and Alkyl Boranes

Entry	Starting Material	Aryl Halide	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)	Referemce
1	 Rink amide	*p*-IC_6H_4CONH-Bn	 Cleav.: TFA, CH_2Cl_2	$Pd(PPh_3)_4$, DMF, 80 °C	(10) 75 to >95	[91]
2		ArI		$Pd(PPh_3)_4$, EtOH, K_2CO_3, toluene, reflux, 12 h	(Various examples claimed)	[39] (p. 29)
3	 Wang resin	ArX; Ar = Ph, *o*-$O_2NC_6H_4$, *m*-$MeOC_6H_4$, *o*-NCC_6H_4	 Cleav.: (a) 50% TFA, CH_2Cl_2, 30 min; (b) Me_3SiCHN_2, $CHCl_3$, MeOH	$Pd(PPh_3)_4$, K_2CO_3, DMF	(4) 43–77% conv.	[93]

(*Continued*)

TABLE 10. (*Continued*)

Entry	Starting Material	Aryl Halide	Product(s)	Reaction Conditions	(Number of Examples) Yield (%)	Referemce
4	 Wang resin			Pd(0), aq. KOH, DME, 80 °C, 2 h	(1)	[65]
5	 Sasrin resin or ArgoGel–MB–OH	ArI; Ar = Ph, *m*-$NO_2C_6H_4$, *p*-$MeOC_6H_4$,	 Cleav.: 3–10% TFA, CH_2Cl_2	$PdCl_2$(dppf), Et_3N, H_2O, DMF, 40 °C, 12–24 h	(3) 100% conv.; 60–86	[12]

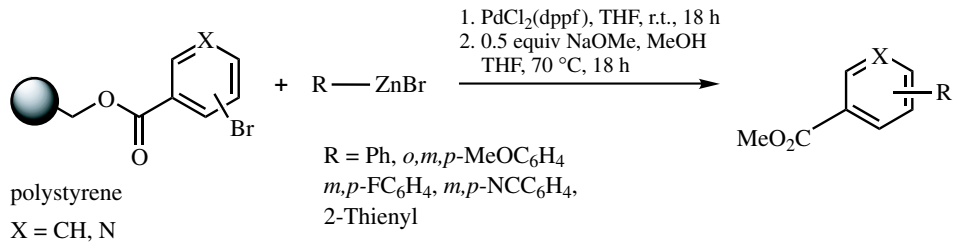
6	 Rink amide TentaGel	ArX; X = Br, I; Ar = Ph, 2-Naphthyl, *p*-NCC_6H_4, *m*-NCC_6H_4, 6-MeO–Tropolonyl, *p*-$CF_3C_6H_4$2-(8-MeO) Naphthyl	 Cleav.: 20% TFA, CH_2Cl_2	$Pd(PPh_3)_4$, K_3PO_4 DMF 80 °C, 2.5–20 h	(9) 26–95	[96]
7	 polystyrene	$Ph_2I^+BF_4^-$; *p*-$MeOC_6H_4I^+BF_4^-$; 2-Thienyl$I^+BF_4^-$; (E)-PhCH═CH—$I^+BF_4^-$;	 Cleav.: NaOMe, MeOH/THF (1:4), reflux, 20 h	$Pd(PPh_3)_4$, Na_2CO_3, DMF, r.t., 20 h	(4) 60–86	[19]
8	See **Scheme 9**					[82]

In general, Suzuki reactions with immobilized aryl halides (**Table 9**) appear to be more successful then with polymer-bound boronic acids (**Table 10**). A recent report describes the use of solid-supported arylboronic acids in a resin-to-resin Suzuki coupling (RRTR Suzuki strategy) (**Table 9**, entry 40).[84]

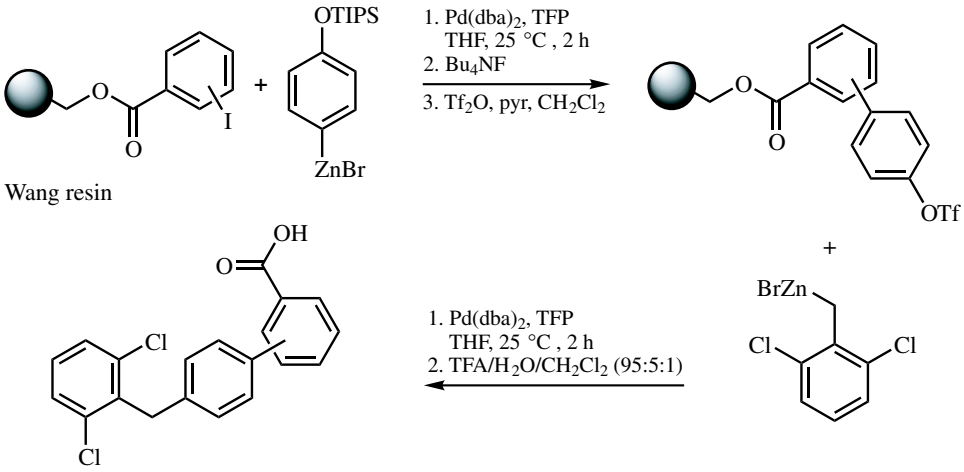
B.iv.c. ***Cross-Coupling Reactions Involving Zincates (Negishi Couplings).*** The cross-coupling between (het)arylzincates and aryl halides (Negishi coupling) provides a general access to (het)biaryls (see **Sect. III.2.1**). Since zincates leave quite a large number of functional groups unaffected and are readily available from Grignard reagents or aryllithium compounds, this approach is very appealing. Hence, polymer-bound aryl bromides (**Scheme 11**), iodides, and triflates (**Scheme 12**) have been coupled with various zincates. Recently, the coupling of an immobilized arylzincate, prepared *in situ* from the corresponding aryl iodide and *tert*-butylzincate, was reported. However, the coupling of a nonpolymer-bound zincate turned out to be more effective (**Scheme 13**).

In addition to benzyl zincates, thymidine derivatives bearing carbonyl functionalities were successfully employed in this reaction.[120] However, according to a recent report, nickel catalysis might be superior to palladium catalysis for such coupling reactions.[121]

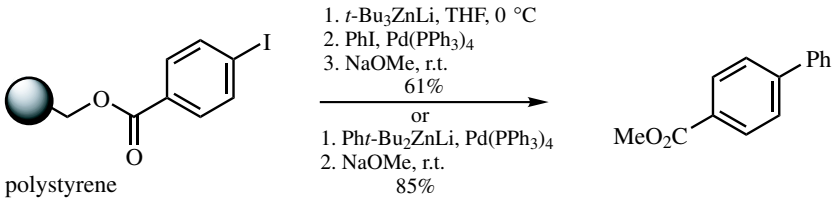
The same kind of resin was used for the solid phase synthesis of 2-furylarenes, which were further elaborated in a Suzuki coupling (**Table 9**, entry 46).[116]



Scheme 11. Aryl–aryl cross-coupling reactions with polymer-bound aryl bromides.[118]



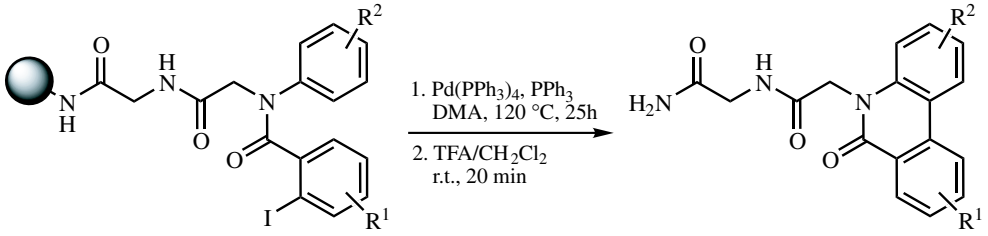
Scheme 12. Aryl–aryl cross-coupling reactions with polymer-bound aryl iodides and triflates.[119]



Scheme 13. Aryl–aryl cross-coupling reactions with polymer-bound arylzincates.[122]

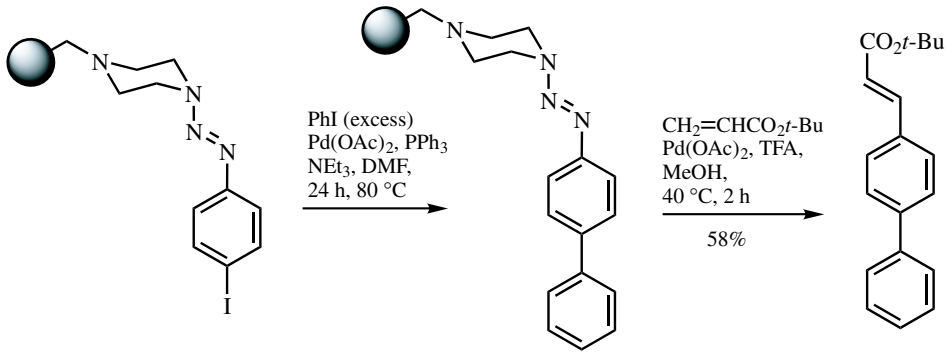
B.iv.d. ***Cross-Coupling Reactions Involving Silicon Compounds.*** A very recent example is reported for the cross-coupling of aryl(fluoro)silanes with aryl iodides attached to solid support.[123]

B.iv.e. ***Biaryl Synthesis by Arylation of Arenes.*** The intramolecular arylation of arenes on a polymer support to produce a library of phenanthridones has been described in a patent (**Scheme 14**).[28]



Scheme 14. Dimerization leading to biaryls.[28]

B.iv.f. ***Reductive Coupling of Aryl Halides Leading to Biaryls.*** The reductive coupling of iodobenzene to a triazene T1 linker-bound iodoarene has been reported (**Scheme 15**).[13] The resulting biaryl was cleaved off the resin using another Heck coupling of the immediate diazonium salt with acrylate giving rise to a cinnamonic acid derivative (**Sect. C.ii.a**, **Scheme 36**).[24]

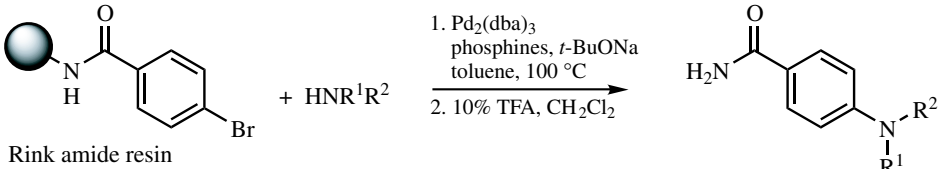


Scheme 15. Reductive coupling of aryl halides leading to biaryls.[24]

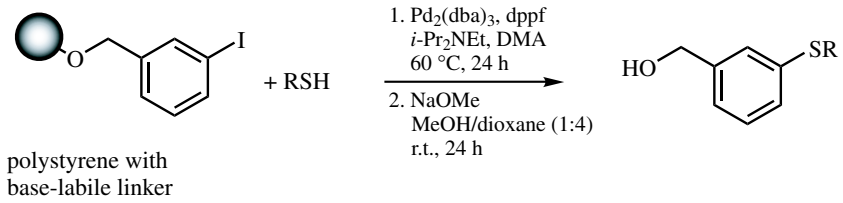
B.v. Arylations of Amines, Alcohols, and Thiols

The heterofunctionalization of haloarenes on a solid support is a versatile method to create small-molecule libraries of high diversity. Starting with simple resins, aryl amines can be prepared in good to excellent yield by amination of polymer-bound aryl halides employing either the Hartwig or the Buchwald protocol (BINAP or P(*o*-Tol)$_3$, *t*-BuONa (**Scheme 16**); for a review see Ref. [124]).[125],[126] Primary and secondary alkylamines and anilines can be employed; in the case of cyclic amines, BINAP was found to be the optimal ligand for the arylation.[126]

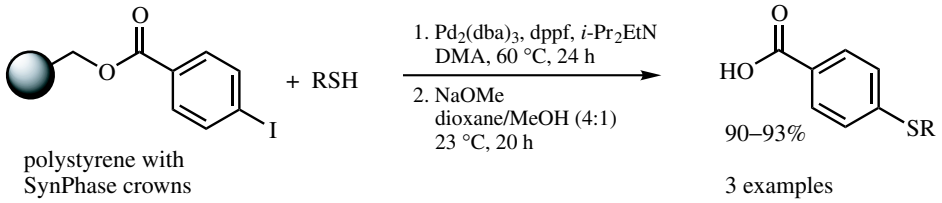
The arylation of thiols has also been investigated. Starting from immobilized aryl iodides, smooth reaction occurs with various thiols using dppf as the preferred ligand (**Schemes 17** and **18**).[70],[71]



Scheme 16. Amination of polymer-bound aryl halides.[125]



Scheme 17. Coupling between thiols and resin-bound aryl iodides.[70]



Scheme 18. Coupling on SynPhase crowns.[71]

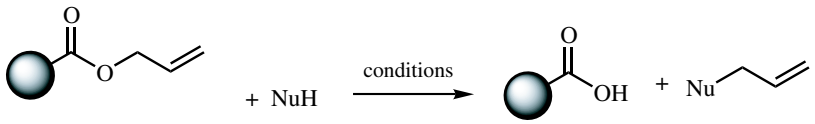
B.vi. Reactions Involving π-Allyl Complexes

The chemistry of π-allyl complexes on a solid could be divided into protecting group/linker chemistry and C–C/C–heteroatom bond-forming reaction.

B.vi.a. ***Deprotection of Allyl Esters.*** The deprotection of allyl esters under palladium catalysis has frequently been employed in various syntheses of pharmaceutically

relevant molecules, peptides, or carbohydrates. Among others, Kunz and co-workers [127]–[129] and Guibé and co-workers[130] have developed this deprotection of allyl esters on a solid support with the aid of a palladium catalyst.[131] The mild reaction conditions are suitable for enantiomerically pure compounds that are prone to undergo racemization. The allyloxy-based protecting group is completely orthogonal to *t*-butyloxy and fluorenyloxy groups (Boc, Fmoc). The removal of traces of palladium can be accomplished by treatment with sodium diethyldithiocarbamate in DMF.[132] It is noteworthy, though, that in general stoichiometric amounts of the palladium complex have been used. While there is agreement that $Pd(PPh_3)_4$ is usually the best catalyst, the choice of the nucleophile may be crucial for the success of the reaction (see **Scheme 19**)[108],[130],[132]–[146]; for trimethylsilyl azide as a nucleophile see Ref. [147]. Especially the Fmoc group may also be removed if morpholine is used as the nucleophile. In this case, phenyltrihydrosilane[148],[149] or dimethylamine/borane [150] should be used as neutral group scavengers.

Allyloxycarbonyls (Alloc or AOC) are useful protecting groups especially for primary amines (for a review see Ref. [131]). As they are easily cleaved-off in the presence of a suitable palladium catalyst,[151] they have found widespread interest in peptide, oligonucleotide, and glucopeptide synthesis ever since they were introduced. Various sources for the nucleophile have been reported. They might consist of tin hydride,[130],[144] formic acid salts,[163]



Resin	Nucleophile[a]	Conditions	Yield (%)	Reference
Polystyrene	PhNHMe	$Pd(PPh_3)_4$, DMSO, THF, aq. HCl	n.r.[b]	[133]
PEG–PS	Morpholine	$Pd(PPh_3)_4$, DMSO, THF, aq. HCl	n.r.	[134]
PEG–PS	NMM	$Pd(PPh_3)_4$, $CHCl_3$	n.r.	[132]
n.r.	Morpholine	$Pd(PPh_3)_4$, DMSO, THF, aq. HCl	n.r.	[135]
Polystyrene	Dimedone	$Pd(PPh_3)_4$, CH_2Cl_2/THF (1:1), 18 h	n.r.	[139]
PAC–PS	NMM, AcOH	$Pd(PPh_3)_4$, $CHCl_3$	n.r.	[136]
Rink amide	NMM, AcOH	$Pd(PPh_3)_4$, $CHCl_3$	n.r.	[137]
2-ClTrityl	$TMSN_3$	$Pd(PPh_3)_4$, $ClCH_2CH_2CCl2$	n.r.	[143]
Wang type	Dimedone	Pd(0), CH_2Cl_2	98%[c](57%)	[138]
	DMBA	$Pd(PPh_3)_4$, THF	n.r.	[142]
Wang	HOBt	$Pd(PPh_3)_4$, CH_2Cl_2, DMF, PPh_3	n.r.	[161]
PhFl on PS	Morpholine	$Pd(PPh_3)_4$, CH_2Cl_2	n.r.	[108]
Wang	PhNHMe	$Pd(PPh_3)_4$, DMSO/DMF (1:1)	n.r.	[140]
Trityl	NMM, AcOH	$Pd(PPh_3)_4$, $CHCl_3$	n.r.	[141]

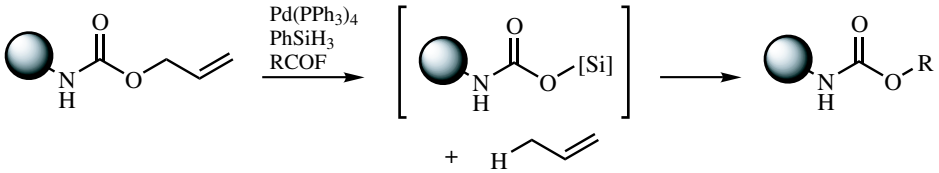
[a] NMM = *N*-methylmorpholine; DMBA = dimethylbarbituric acid.
[b] n. r. = not reported.
[c] Crude yield, yield of the pure product 57%.

Scheme 19. Deprotection of allyl esters on solid support (recent examples).

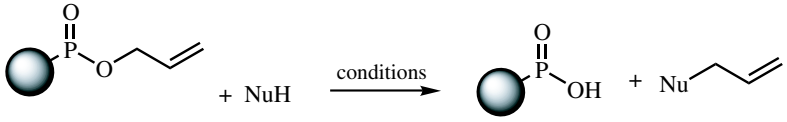
azides,[152],[153] *N*-methylaniline,[154] acetates,[155],[156] dimedone,[151],[157] morpholine,[158] *N*-methylmorpholine,[159] pentamethylsilylamine/trimethylsilyl trifluoroacetate,[160] or HOBt (*N*-hydroxybenzotriazole).[161] In addition, a one-pot deprotection/peptide coupling strategy was investigated consisting of a silyl hydride as the nucleophile, which also gives rise to an intermediate silyl ester (**Scheme 20**).[162]

The Alloc deprotection is also applicable to automated solid phase synthesis of oligonucleotides[163] as well as linear and cyclic peptides.[164]

Similar to carboxylic acid derivatives, allylphosphonates can be cleaved under mild conditions (**Scheme 21**).[165]–[167]



Scheme 20. *In situ* deprotection and peptide coupling with Alloc-protected amines.[162]



Resin	Nucleophile	Conditions	Yield (%)	Reference
Wang	Morpholine	$Pd(PPh_3)_4$, DMF	n.r.	[167]
Wang	$BuNH_2$, HCO_2H	$Pd(PPh_3)_4$, THF	100[a]	[165]
Wang	NMM, AcOH	$Pd(PPh_3)_4$, $CHCl_3$	n.r.	[166]

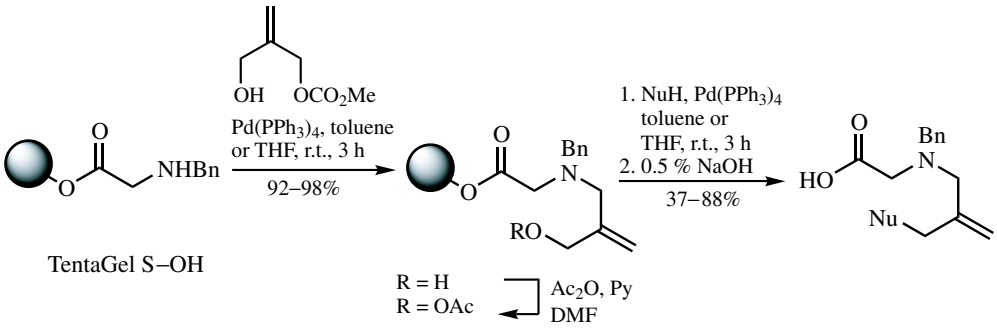
[a]Conversion

Scheme 21. Deprotection of allylphosphonates.

Benzylphosphonates can be deprotected with palladium acetate under increased hydrogen pressure with simultaneous cleavage from the support.[168]

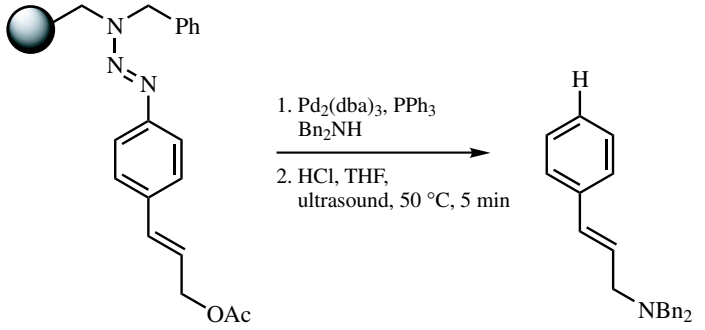
B.vi.b. ***Coupling of Building Block to Solid Support Via π-Allylpalladium Complexes.*** The reactions of immobilized nucleophiles with π-allylpalladium precursors have been described for various combinations.[13],[169]–[172] A double allylation reaction has been shown using an immobilized nitrogen nucleophile with 2-hydroxymethylallyl methyl carbonate. After the first allylic substitution, acylation and a subsequent coupling with various nucleophiles provided access to substituted glycine derivatives (**Scheme 22**).[169]

The versatile triazene T1 linker has been applied to create a template for an allylic substitution with dibenzylamine on an immobilized cinnamyl acetate. Traceless cleavage furnished the tertiary amine in good yield and purity (**Scheme 23**).[13]



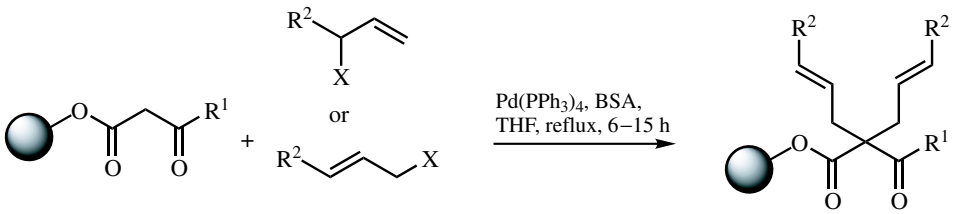
Nu = various primary and secondary amines, sulfinates, and thiols

Scheme 22. A synthesis applying bisallylic building blocks.[169]



Scheme 23. Allylic substitution on a triazene-linked cinnamyl acetate.[13]

Starting from oxygen-linked 1,3-dicarbonyl compounds (malonates or acetoacetates), Tietze and co-workers have demonstrated an allylic substitution at the α-position of various substrates (allyl acetates, carbonates, and chlorides).[170] Under the conditions employed, bisalkylation was observed in all cases. Since the acetoacetates could be alkylated by hard electrophiles at the γ-position, a broad spectrum of compounds might be obtained. The cleavage from the resin was performed using DIBAL-H to obtain the corresponding diols (**Scheme 24**).

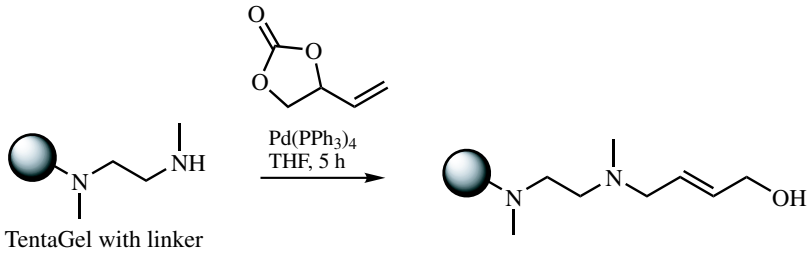


Scheme 24. Allylic substitution with polymer-bound nucleophiles.[170]

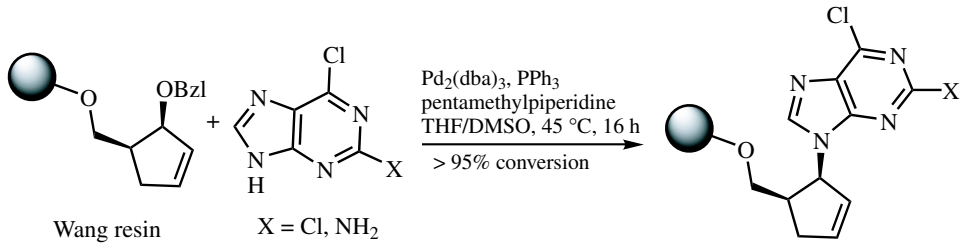
A chain elongation of a polymer-bound secondary amino functionality was achieved by Pd-catalyzed allylic substitution on a vinyl dioxolanone (**Scheme 25**). This carbonate provides neutral conditions for the alkylation reaction.

Allyl benzoates have been used in the synthesis of carbocyclic nucleoside analogs. Both 2,6-dichloropurine and 2-amino-6-chloropurine were effective nucleophiles in the presence of a bulky tertiary base and the palladium catalyst (**Scheme 26**).[172]

Recently, N-allylation of an *o*-nosyl-protected N-terminus of a peptide with allyl methyl carbonate has been reported.[173]



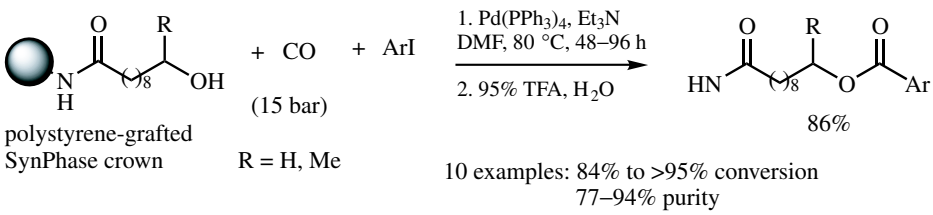
Scheme 25. Allylation of a polymer-bound amine with vinyldioxolane under palladium catalysis.[171]



Scheme 26. Synthesis of carbocyclic nucleoside analogs.[172]

B.vii. Carbonylative Coupling and Cyanation Reactions

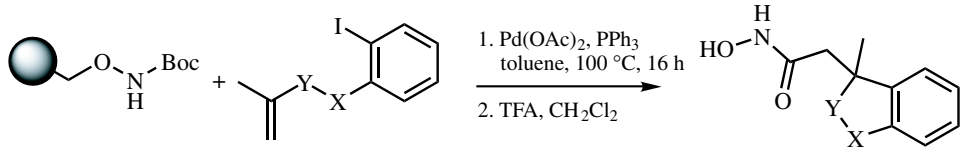
The carbonylation of aryl halides in the presence of suitable nucleophiles such as alcohols and amines offers an attractive approach to benzoic acid derivatives. Hence, the reaction of polymer-supported primary and secondary alcohols with aryl iodides under a carbon monoxide atmosphere was investigated. Under the reported reaction conditions, this three-component reaction proceeded in good yields and after cleavage; the products were obtained in moderate to good purities (**Scheme 27**).[174]



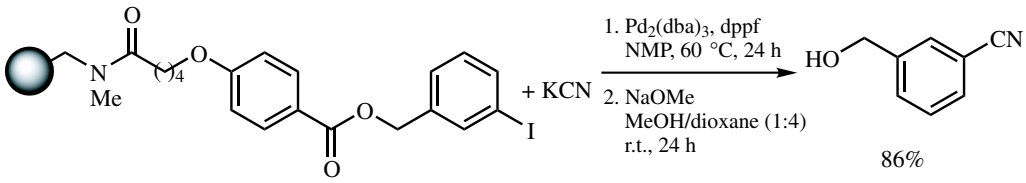
Scheme 27. Carbonylative coupling reaction on solid support.[174]

Grigg and co-workers recently demonstrated a cascade consisting of an intramolecular carbopalladation, carbonylation, and nucleophilic attack by an immobilized hydroxamic acid ester (**Scheme 28**).[175]

The coupling of immobilized aryl iodides with potassium cyanide has been found to yield the corresponding nitrile in good yield (**Scheme 29**).[15]



Scheme 28. Carbonylation cascade reaction on solid support.[175]

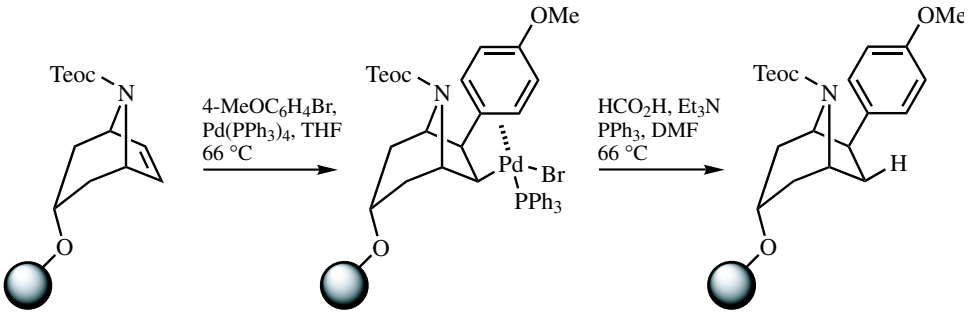


Scheme 29. Coupling between cyanide and resin-bound aryl iodides.[15]

B.viii. Hydrogenation Reaction

The various types of hydrogenation reactions that have been performed on solid support consist of hydrodepalladations, σ-organyl complexes, and hydrogenations of double and hydrogenolytic triple bonds as well as hydrogenolytic removal of benzyl-type protecting groups.

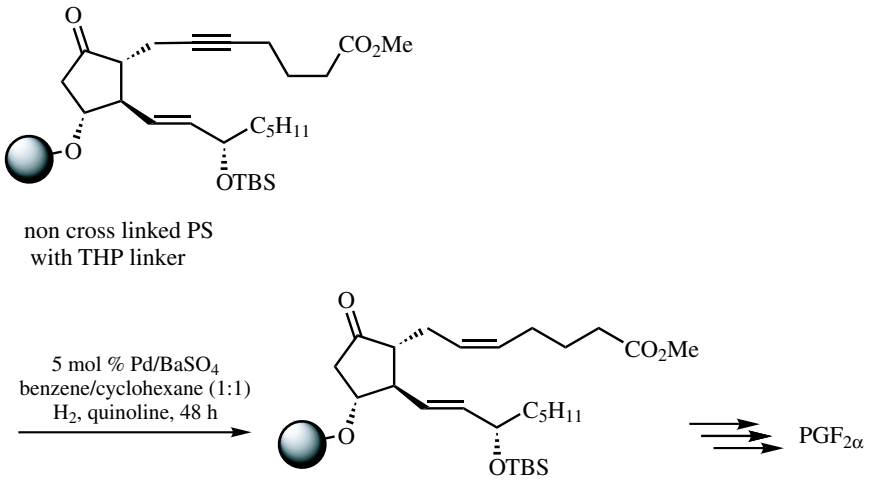
B.viii.a. ***Hydrodepalladations of σ-Organylpalladium.*** The formal reduction of σ-organylpalladium replacing a C—Pd by a new C—H bond can, for example, be brought about by formic acid.[35] The intermediate σ-complexes usually arise by carbopalladation of a multiple bond (**Scheme 30**).



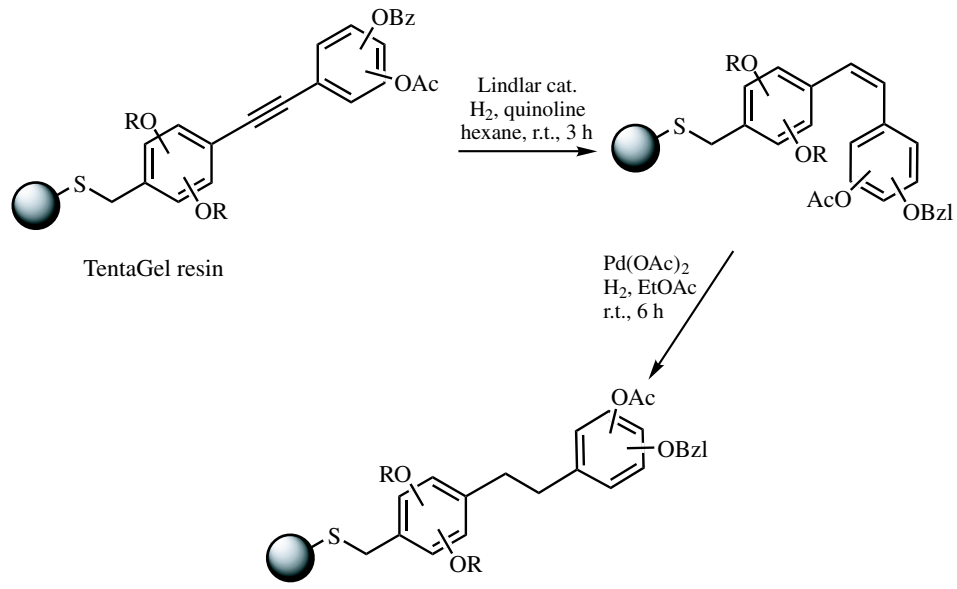
Scheme 30. Carbometallation on the tropane framework.[35]

B.viii.b. ***Catalytic Hydrogenation of Triple and Double Bonds.*** The catalytic hydrogenation of a triple to a double bond has been performed on noncrosslinked polystyrene,[176] which demonstrates the suitability of this support.[177],[178] This transformation has been adopted to the polymer-bound version of the classical prostaglandin synthesis (**Scheme 31**).[177]

On the other hand, even crosslinked polystyrene was used in the reduction of immobilized alkynes with the Lindlar catalyst.[39] The subsequent further hydrogenation to the alkane was achieved with palladium acetate as a precatalyst (**Scheme 32**).[39]

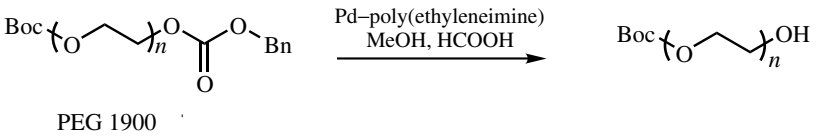


Scheme 31. Prostaglandin synthesis on solid support.[177]



Scheme 32. Hydrogenation on solid support.[39]

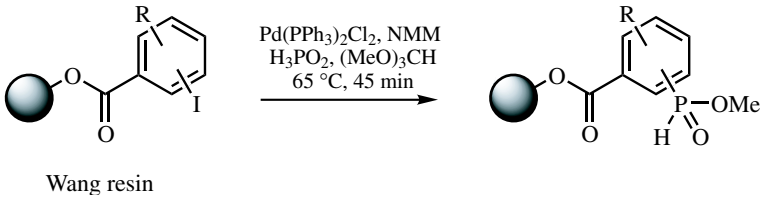
B.viii.c. ***Deprotection of Benzyl Ethers.*** Benzyl ether and benyloxycarbonyl groups (Cbz or Z) in compounds on a PEG support could be cleaved by catalytic hydrogenation with a heterogeneous palladium catalyst [179],[180] or with homogeneous palladium acetate.[181] In some cases, palladium–poly(ethyleneimine) has been found to be more effective than palladium black (**Scheme 33**).[182]



Scheme 33. Benzyl ether deprotection on PEG.[182]

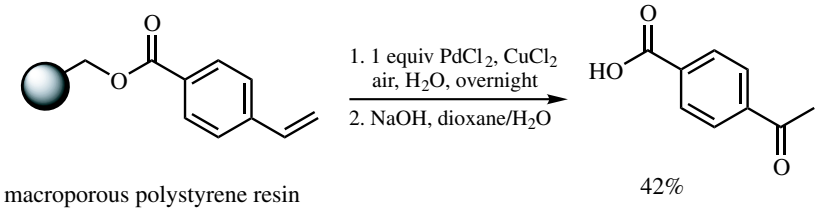
B.ix. Miscellaneous Reactions

The coupling of aryl iodides on solid support with hydrophosphoric acid in the presence of trimethyl orthoformate has been described in detail in a recent patent.[183] The resulting polymer-bound methyl arylphosphonates were subsequently derivatized (**Scheme 34**).



Scheme 34. Synthesis of arylphosphinic acid derivatives.[183]

B.ix.a. ***Wacker-Type Reactions.*** The Wacker oxidation of an alkene bound to a macroporous polystyrene resin yielded the expected methylketone whereas an alkene bound to a low-crosslinked Merrifield resin gave no product (**Scheme 35**). The results correlate with the relative permeability of each of these resins toward the aqueous solvent employed.[184] It is interesting to note that the catalytic version of this process gave nearly the same yield as the stoichiometric reaction.



Scheme 35. Wacker-type oxidations on a solid support.[184]

C. PALLADIUM-CATALYZED CLEAVAGE OFF THE SOLID SUPPORT AND CONCOMITANT DERIVATIZATION

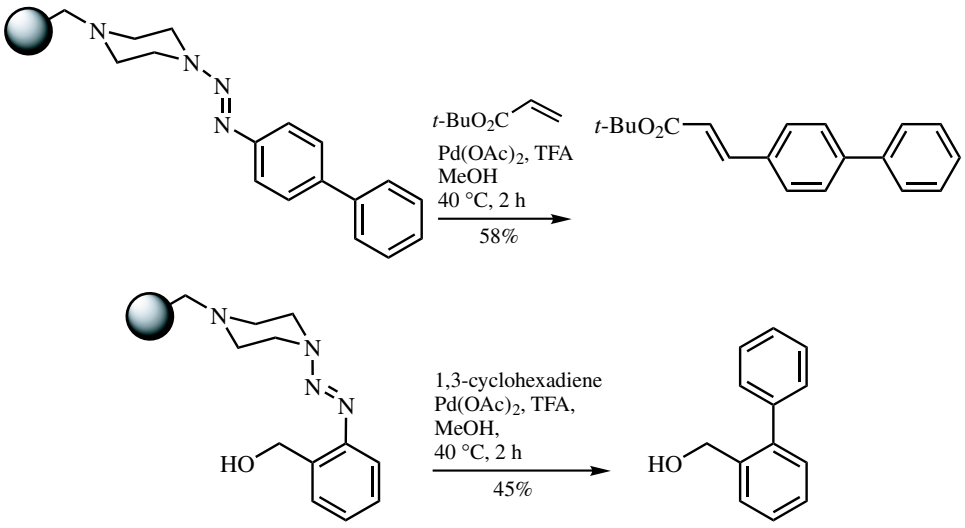
C.i. General Remarks

The cleavage of substrates from a solid support using Pd-promoted or Pd-catalyzed reactions has some advantages over other cleavage methods. Since most protecting groups and functionalities are resistant toward palladium complexes, a selective surgical cutoff is frequently possible. In addition, intermediate π-allyl- and σ-arylpalladium complexes can in principle be used for further derivatization with the use of appropriately versatile linker types.

C.ii. Cleavage with Ensuing Cross-Coupling Reactions on Solid Support

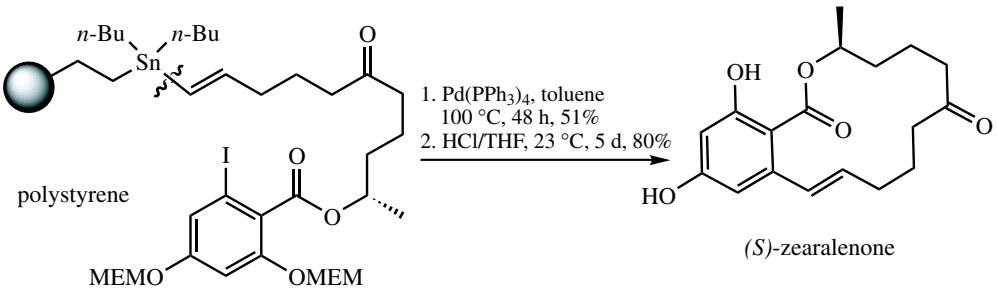
C.ii.a. ***Heck Reactions.*** A cleavage with an ensuing Heck reaction was developed utilizing the T1 triazene linker. Upon cleavage with trifluoroacetic acid, a diazonium ion is first formed and this can couple with an added alkene under palladium catalysis. The coupling works well with simple terminal alkenes and styrenes as well as di- and even trisubstituted alkenes.[24] The coupling with 1,3-cyclohexadiene eventually yields a biaryl, apparently by a facile dehydrogenation of the primary coupling product (**Scheme 36**).[24] The advantage of this process is clearly the possibility of using volatile alkenes (and alkynes) without contamination of any salt or other less volatile by-products.

C.ii.b. ***Stille Couplings.*** A polymer-bound tin hydride has been used to hydrostannylate alkynes under palladium catalysis hydrostannylation to give polymer-bound alkenylstannanes.[185] Alternatively, the latter could be prepared from a polymer-bound tin chloride and an alkenyllithium or -magnesium halide reagent. These alkenylstannanes were employed in intermolecular as well intramolecular Stille reactions. The intermolecular reactions provided the coupling products in good yields. In addition, the



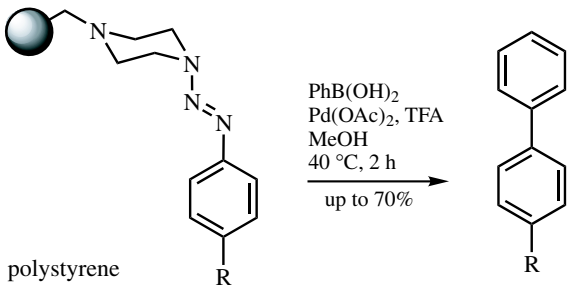
Scheme 36. Cleavage with ensuing Heck coupling using the triazene linker.[24]

stannylated resin produced in the cleavage–coupling could be recycled. Although the obtained products were not contaminated by any stannane, they had to be separated from an excess of the reactive electrophiles that had to be applied in the cleavage–coupling step. The intramolecular variant that was used by Nicolaou and co-workers to produce macrocyclic ring systems such as the natural product (*S*)-zearalenone does not have this drawback (**Scheme 37**).[186]



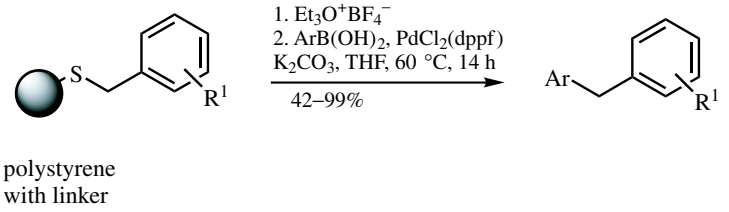
Scheme 37. Cleavage Stille strategies using stannane linker.[186]

C.ii.c. ***Suzuki Couplings.*** Suzuki couplings ensuing a cleavage reaction are potentially applicable in a multidirectional sense. However, due to the tendency of the boronic acid derivative to give homocoupling products, the necessity in general to apply additional ligands, and the low volatility of the boronic acid derivative, a more or less tedious workup is required after these types of transformations. A few studies have proved that certain functionalities when generated during cleavage may act as the leaving groups for a subsequent Suzuki reaction (**Scheme 38**). One of these is the diazonium group, which can be generated by cleavage of the triazene T1 linker (**Schemes 2**, **15**, **23**, **36**, and **41**). While the Heck-type coupling with alkenes gave good yields of the desired products (**Scheme 36**), the analogous reaction with phenylboronic acid appeared to be difficult due to workup problems.[24]



Scheme 38. Cleavage with subsequent Suzuki coupling.[24]

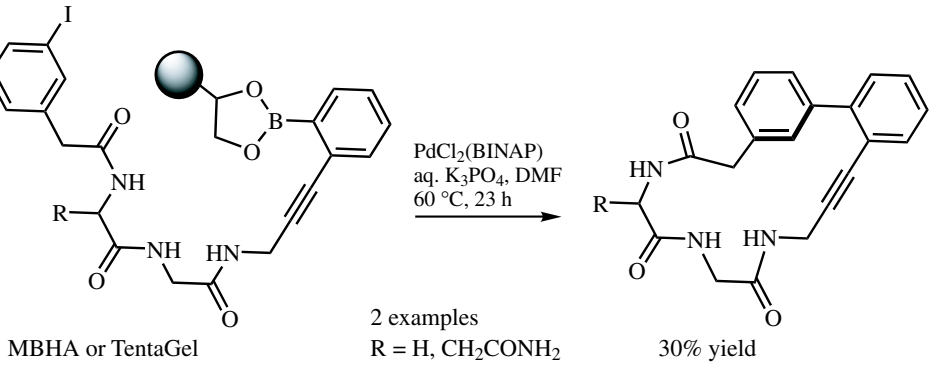
Arylmethyl(homobenzyl)ethylsulfonium salts are also appropriate substrates for Suzuki-type coupling reactions (**Scheme 39**). In this reaction performed on a polymer-bound sulfonium tetrafluoroborate, the benzyl fragment on the sulfur was transferred to



Scheme 39. Cleavage Suzuki coupling approach using sulfonium salts.[18]

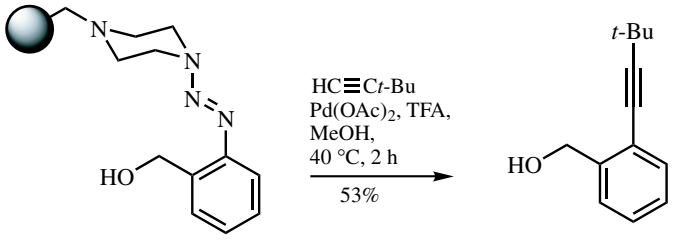
the boronic acid residue. The sulfonium salt was prepared from an alkylthiol resin by alkylation with a substituted benzyl halide and subsequent alkylation with triethyloxonium tetrafluoroborate; the final product of its reaction with the presence a boronic acid derivative was a diaryl methane.[18]

A boronic acid ester, which contains an aryl iodide moiety attached by an appropriate tether, can act as an intramolecular arylation agent. Thus, Li and Burgess developed a polymer-bound precursor, which by a biaryl coupling ensuing cleavage furnished a macrocyclic constrained β-turn peptide mimic (**Scheme 40**).[187]



Scheme 40. Intramolecular cleavage–Suzuki coupling.[187]

C.ii.d. ***Sonogashira-Type Couplings.*** The coupling of alkynes with diazonium salts has been reported in the context of the T1 linker. In this case the product was isolated in moderate yield and it had to be separated by chromatography from alkyne homodimers and trimers (**Scheme 41**).[24]



Scheme 41. Sonogashira coupling associated with the cleavage.[24]

C.iii. Reactions Involving π-Allyl Complexes

C.iii.a. ***Deprotection of Allyl Esters: Allylic Linkers for Solid Phase Synthesis.*** The advantages of linker cleavage under palladium catalysis are the mild reaction conditions[131] and their orthogonality to various protecting groups. Kunz et al.[188]–[190] developed the first and simplest linker to use the π-allyl detachment strategy. Starting from 2-bromocrotonic acid, attachment to an amino group on a resin and further reaction with the cesium salt of an appropriate protected amino acid or peptidic structure yield the HYCRAM (hydroxycrotonylamide) resin (**Figure 2**).[191] The allylic cleavage proceeds with $Pd(PPh_3)_4$ and morpholine or hydroxybenzotriazole.[192] The readily available

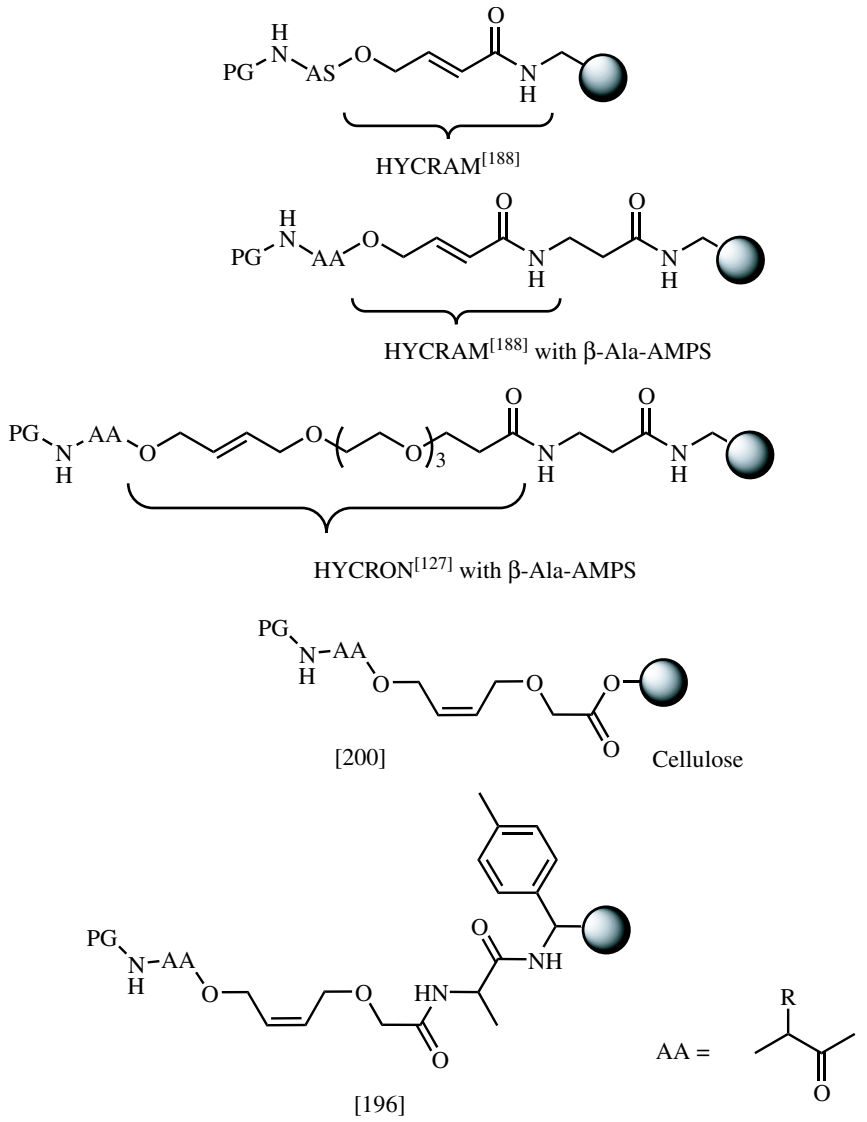
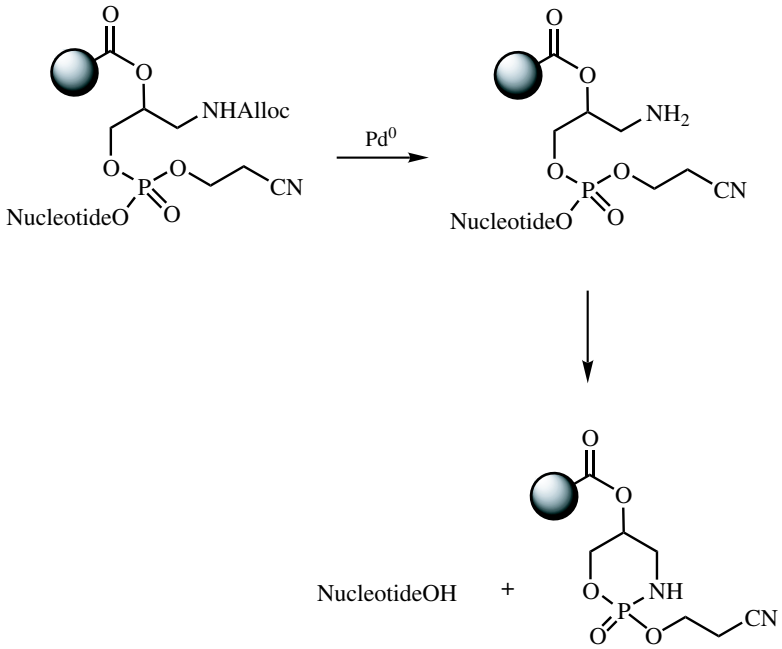


Figure 2. Allylic alcohol linkers.[131]

HYCRON linker[127],[193]–[195] is based on a similar concept; however, in this case, a handle comprising an amino acid and a preformed linker has been used to minimize the risk of racemization upon cleavage. A higher stability toward unwanted nucleophilic cleavage was achieved in comparison with the HYCRAM linker. The incorporation of β-alanine facilitates monitoring the reaction. Several other, but similar constructs have been used for comparable purposes.[196]–[202] Recently, the semisynthesis of vancomycin on solid support was accomplished using an allylic anchor.[146]

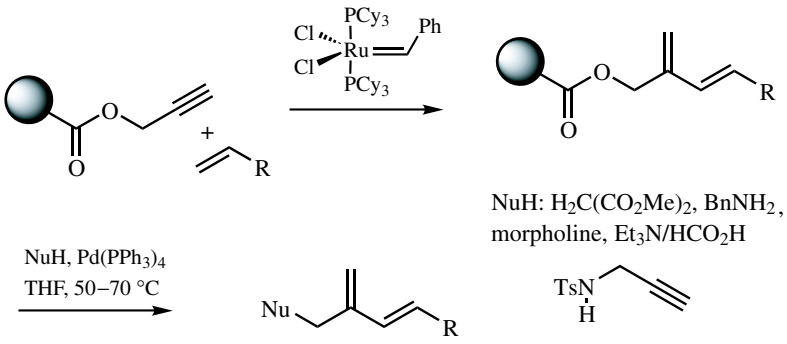
An indirectly (= safety catch) π-allyl cleavable linker was developed for the synthesis of DNAs on solid support (**Scheme 42**). Starting from a linker that has an Alloc-protected amino group, conventional phosphoramidite chemistry was carried out to build up the desired nucleotide. Removal of the Alloc group under palladium catalysis and neutral conditions then produces molecules with a free amino group that can intramolecularly attack the activated phosphonates and liberate the nucleotide form the solid support.



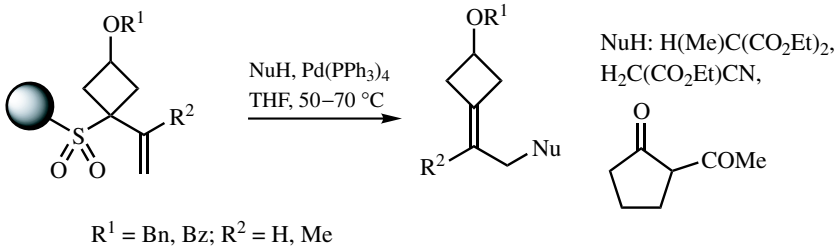
Scheme 42. A safety-catch Pd-activated linker.[155],[156]

C.iii.b. ***Functionalization During Cleavage.*** The cleavage of polymer-bound allyl esters with palladium catalysts provides a general access to π-allyl complexes, which in turn may react with various nucleophiles. Schürer and Blechert used an ene-yne cross metathesis and a subsequent cleavage in the presence of various nucleophiles to yield corresponding functionalized dienes (**Scheme 43**).[203]

Similarly, solid-bound 1-alkenylcyclobutylsulfone were cleaved from a resin in the presence of suitable nucleophiles to give substituted cyclobutylidene derivatives (**Scheme 44**).[204]



Scheme 43. Cleavage with formation of π-allyl intermediates.[203]



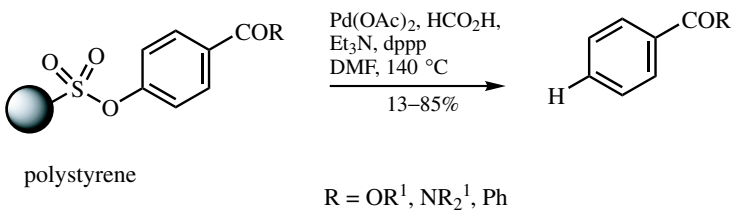
R^1 = Bn, Bz; R^2 = H, Me

Scheme 44. Cleavage with formation of π-allyl intermediates.[204]

C.iv. Hydrogenolytic Cleavage

Hydrogenolytic removal of substrates from solid support is important as they cleave the substrate with a hydrogen at the former site of the polymer binding. These types of linkers are also called traceless linkers, reflecting the memory of the point of attachment.[205]

C.iv.a. ***Hydrogenation of Sulfonates.*** The detachment of substituted arylsulfonates in the presence of a reducing agent such as formic acid provides a traceless cleavage. In this case it is important that the arene core is substituted with electron-withdrawing substituents to enhance the yields significantly (**Scheme 45**).[206] This approach has been described (without experimental details) quite early in a patent including the possible derivatization of the intermediate σ-arylpalladium–aryl complex.[207]

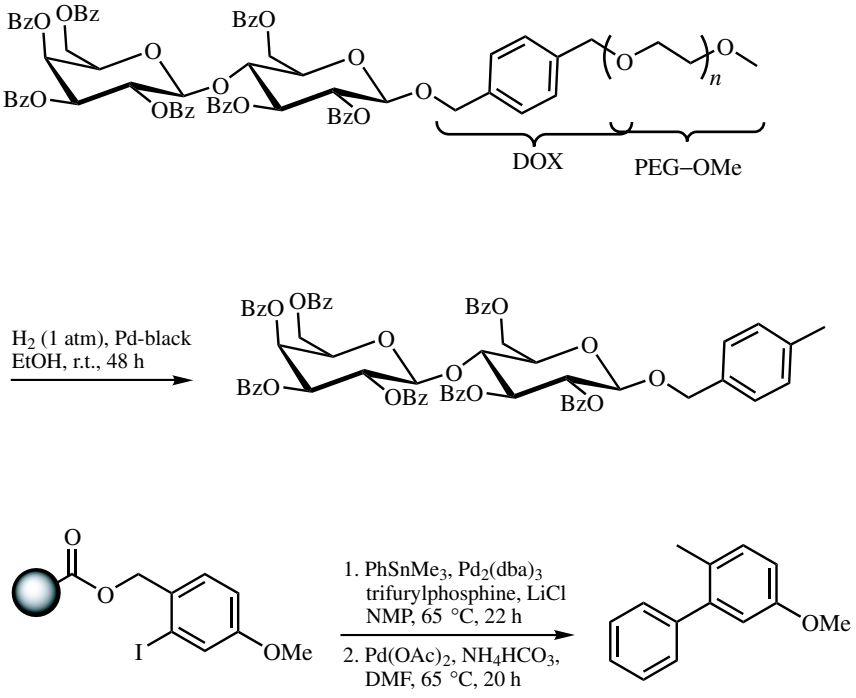


polystyrene

R = OR^1, NR_2^1, Ph

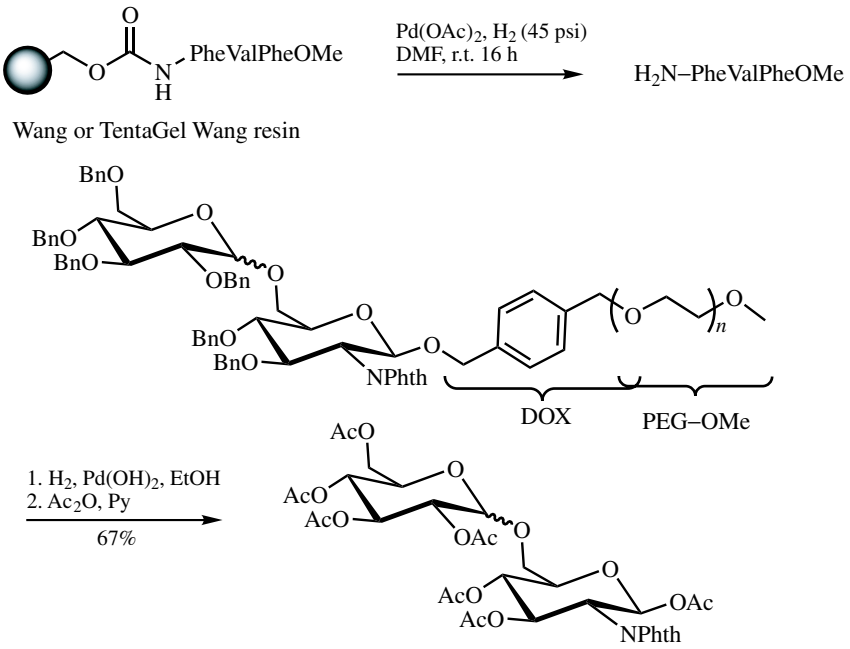
Scheme 45. Hydrogenolytic cleavage of a polymer-bound substrate.[206]

C.iv.b. ***Deprotection of Benzyl Ethers and Esters.*** The cleavage of specially designed polymeric benzyl-type protecting groups has been achieved using heterogeneous palladium black. In these cases, the catalytic hydrogenation furnishes methyl-substituted arenes as side products or targets (**Scheme 46**). An early example takes advantage of the properties of the MeO–PEG-type support for the synthesis of di- and oligosaccharides. It is interesting to note that the DOX linker enables the cleavage of the PEG structure leaving the *p*-methylbenzyl (TM) group attached under certain conditions [208] (but cf. **Scheme 47**).[209] Similarly, the cleavage for polystyrene resin was achieved using homogeneous palladium catalysts (palladium acetate) with either formate reduction[66] or under an atmosphere of hydrogen.[39]



Scheme 46. Syntheses of methylarenes on solid support.[208]

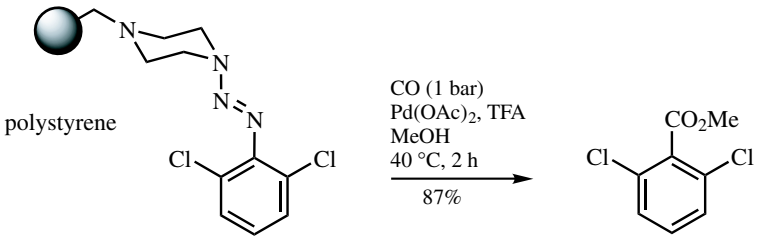
Alternatively, the benzyl group was attached to the solid support, and hydrogenolytic cleavage was used to detach the molecules, which then usually are left with an oxygen or nitrogen functionality (cleavage of C—O Bn and C—N Bn, respectively).[181],[209]–[211] The polymer in these cases are formally immobilized Z or Cbz groups. Interestingly, TentaGel and polystyrene are providing the products in comparable yields under identical conditions. Benzylic linkers can also advantageously be used in the presence of other benzylic protecting groups, since they can be removed in the same step.[181],[209] Pd-catalyzed removal of the Cbz group was also conducted after (non-Pd-catalyzed) detachment from the solid support.[212]



Scheme 47. Detachment from polymeric benzyl-type protecting groups.[209]

C.v. Carbonylative Cleavage

Cleavage with ensuing carbonylation has been conducted with the T1 linker system in methanolic trifluoroacetic acid to generate methyl esters in good yields (**Scheme 48**).[24] This overall process constitutes a transformation of an aniline to the corresponding methyl carboxylate.



Scheme 48. Detachment/carbonylation reaction.[24]

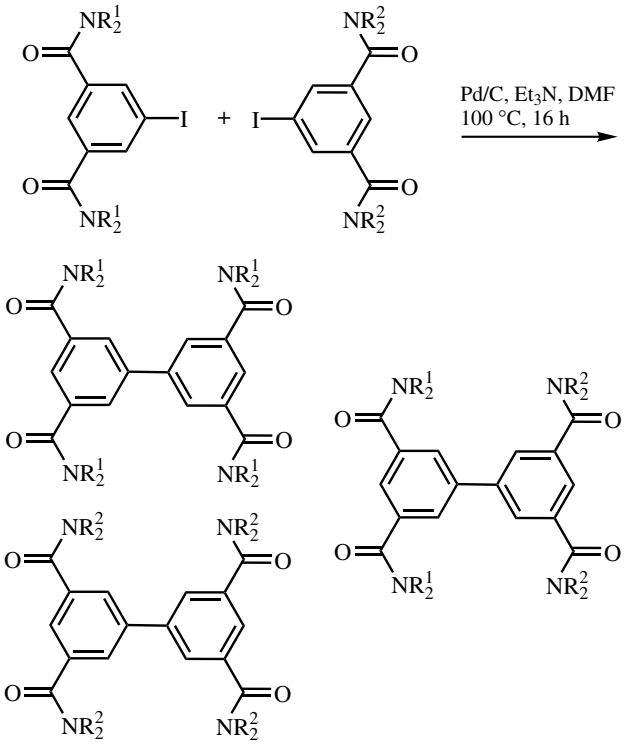
D. NEW DEVELOPMENTS IN COMBINATORIAL CHEMISTRY APPLYING PALLADIUM-CATALYZED REACTIONS

D.i. Liquid Phase Combinatorial Synthesis

Although interesting with respect to diversity, liquid phase combinatorial chemistry has scarcely been tapped. An interesting example was provided by Boger and co-workers.

Starting from a mixture of iodoarenes, reductive dimerization in the presence of palladium on charcoal gave access to a library of biaryl derivatives. By using five different iodoarenes, a mixture of 15 biaryls was produced, which were identified clearly by means of HPLC traces (**Scheme 49**).[213] A novel core suitable for use in solution-phase combinatorial has been prepared using the Stille reaction.[214]

A multicomponent parallel Suzuki coupling was reported to produce a library of heterobiaryls (nine examples).[215]



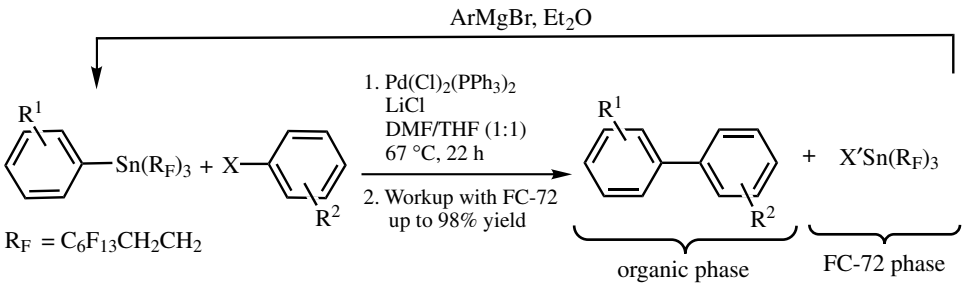
Scheme 49. Liquid phase reductive aryl–aryl coupling.[213]

D.ii. Fluorous Phase Chemistry

The application of the "fluorous liquid phase" as a third liquid phase (besides organic or aqueous phase) facilitates workup and thus purification of a target compound after an organic synthesis (for a review see Ref. [216]). This concept, for example, has been applied in the fluorous phase Stille coupling,[217] which was facilitated by microwave irradiation (**Scheme 50**).[218]

An example for liquid phase chemistry with solid phase workup has recently been published. In this case, a quinoline–carboxylic ester was transesterified with an appropriate bromobenzyl alcohol. The Suzuki coupling with a boronic acid derivative proceeded smoothly and the quinoline handle was cleaved off. The advantage of this method lies in the ease of purification since the quinoline could be sequestered from the reaction mixture by protonation with sulfuric acid and recrystallization.[220]

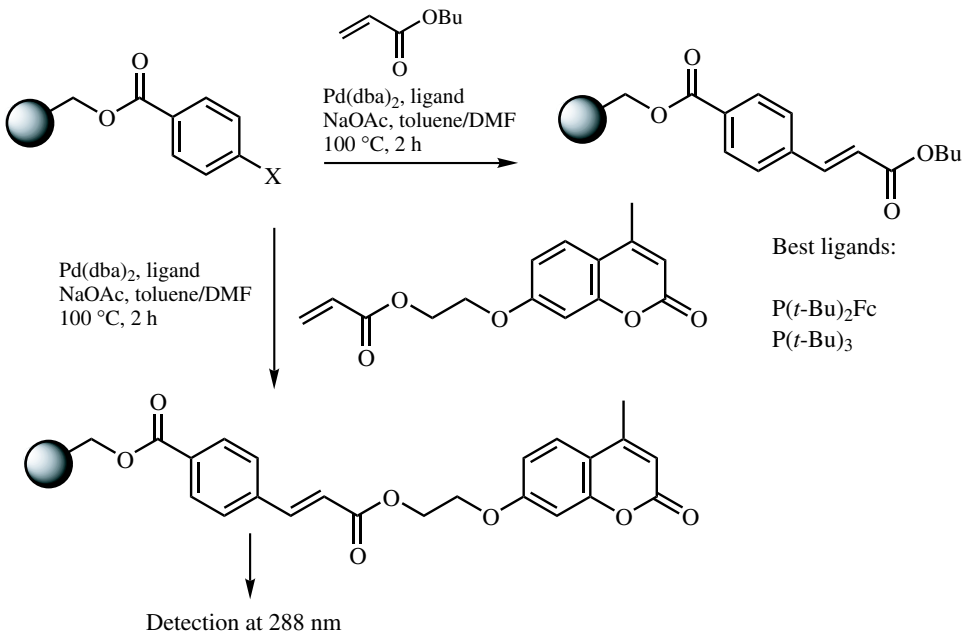
Besides these technologies, the application of polymer-bound or immobilized palladium catalysts has found widespread interest (see **Sect. X.2**).



Scheme 50. Stille couplings with fluorous tin reactants.[219]

D.iii. Combinatorial/High Throughput Palladium Catalysis

Combinatorial catalysis is a young and rapidly emerging field in chemical research. The unparallelized rational search for new catalysts is a tedious, time-consuming process, which may take several years and hundreds or more reactions. Therefore, the rapid screening for new systems is an interesting goal. While catalysis with other metals has been investigated, there are only a few reports to date that deal with palladium catalysis. A group at SYMYX investigated polymer-bound ethylediiminepalladium complexes in the polymerization of ethylene. Since the resin beads grow in size due to the polymerization, the largest beads were those with the most active catalysts. Recently, Hartwig and co-workers have shown that reaction of an immobilized aryl halide with a fluorescent marker dye in the presence of various ligand systems is indeed a fast way to determine the most active catalyst system (**Scheme 51**).[221]



Scheme 51. Fluorscence-based assay for high-throughput screening of ligands for the Heck reactions.[221]

Burgess and co-workers have developed a library of oxazoline ligands applicable for Pd-catalyzed allylic substitution.[222]

E. CONCLUSION

Due to the mild reaction conditions, the good selectivities, and the generally high yields associated with Pd-catalyzed reactions, they are commonly used in solid phase organic synthesis (SPOS). Since virtually every Pd-catalyzed reaction can be applied beneficially in SPOS, this section is in some ways a miniaturizing mirror of the major part of this Handbook. Especially C—C bond formations are of great importance for the efficient buildup of pharmaceutically important molecules from simple starting materials. Pd-catalyzed cross-coupling reactions are by far the dominating family of transformations applied in SPOS for this purpose.

In general, the catalyst is easily removed by simply washing the resin. This can be extremely important since transition metals often interfere with high throughput screening assays to be performed with the final products.

The possible functionalizations during cleavage are gaining increasing importance as they add yet another dimension of diversity. When soluble supports are used, the removal of the catalyst and excess may not be as trivial. This problem may be solved by the use of immobilized palladium catalysts in association with volatile reagents. Another option, which has not yet been pursued, is to use efficient scavenger resins to sequester the catalyst. This possibility will also give some new impulses to liquid phase combinatorial chemistry.

Some other aspects of catalysis like control of stereochemistry with chiral ligands have not yet been widely explored in solid phase organic synthesis. Up to now most compound libraries simply contained racemates and frequently even mixtures of diastereomers. For sure, to address stereoselectivity will be one of the next challenges in combinatorial solid phase synthesis.

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PART R
References

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
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R.1 General Guidelines for References Pertaining to Palladium and Organopalladium Chemistry

EI-ICHI NEGISHI

A. GENERAL REFERENCE SOURCES (AS OF 1999)

In addition to general abstracts such as *Chemical Abstracts*, *Beilstein*, and *Science Citation Index*, as well as computerized reference sources, such as *CAS on Line*, *SciFinder*, and *Web of Science*, the following general reference sources contain references, discussions, and other information pertaining to organopalladium chemistry. Their acronyms and abbreviations are shown and may be used throughout this Handbook. Many of these reference sources, such as *Comp. Org. Synth.* and *Houben-Weyl*, contain independent reviews, and those reviews that are pertinent to the Handbook are separately listed in the list of reviews (Sect. R.3).

A.i. Dictionaries and Encyclopedias

DIC	*Dictionary of Inorganic Compounds (Dic. Inorg. Comp.)*, 5 Vols. Plus Supplement Vols. J. E. Macintyre, Ed., Chapman and Hall, London, **1993**–, Vol. 5, pp. 568–574 lists Pd-containing compounds.
DOCV	*Dictionary of Organic Compounds* (*Dic. Org. Comp.*), 5th ed., 7 Vols. (**1982**) plus Supplement Vols. (**1983**–).
DOMC II	*Dictionary of Organometallic Compounds* (*Dic. Organomet. Comp. II*), 2nd ed., 5 Vols., Chapman and Hall, London, **1995**. Vol. 3, pp. 2881–2990 lists most of the well-characterized organopalladium compounds.
EIC	*Encyclopedia of Inorganic Chemistry* (*Encycl. Inorg. Chem.*), 8 Vols., R. B. King, Ed., Wiley, New York, **1994**.
EROS	*Encyclopedia of Reagents for Organic Syntheses* (*Encycl. Reag. Org. Synth.*), 8 Vols., L. A. Paquette, Ed., Wiley, New York, **1995**.
ROS	*Reagents for Organic Synthesis* (*Reag. Org. Synth.*), M. Fieser and L. F. Fieser, Eds. (Vols. 1–7); M. Fieser, Ed. (Vols. 8–16), Wiley, New York, **1967–1992**.

A.ii. Pergamon's Comprehensive Chemistry Series

Note: Authored chapters in these compilations are cited as if they are reviews in review journals. For example,

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
ISBN 0-471-31506-0

1991COS(5)1185 Metal-Catalyzed Cycloaddition of Small Ring Compounds. T. Ohta and H. Takaya, *Comp. Org. Synth.*, **1991**, *5*, 1185–1205.

CCC *Comprehensive Coordination Chemistry* (*Comp. Coord. Chem.*), 7 Vols., G. Wilkinson, R. D. Gillard, and J. A. McCleverty, Eds., Pergamon Press, Oxford, **1987**.

CHCH *Comprehensive Heterocyclic Chemistry* (*Comp. Heterocycl. Chem.*), 8 Vols., A. R. Katritzky and C. W. Rees, Eds., Pergamon Press, Oxford, **1984**.

CHCH II *Comprehensive Heterocyclic Chemistry II* (*Comp. Heterocycl. Chem. II*), 11 Vols., A. R. Katritzky, C. W. Rees, and E. F. W. Scriven, Eds., Pergamon Press, Oxford, **1996**.

COC *Comprehensive Organic Chemistry* (*Comp. Org. Chem.*), 6 Vols., D. Barton and W. D. Ollis, Eds., Pergamon Press, Oxford, **1979.**

COMC *Comprehensive Organometallic Chemistry* (*Comp. Organomet. Chem.*), 9 Vols., G. Wilkinson, F. G. A. Stone, and E. W. Abel, Eds., Pergamon Press, Oxford, **1982**.

COMCII *Comprehensive Organometallic Chemistry II* (*Comp. Organomet. Chem. II*), 14 Vols., E. W. Abel, F. G. A. Stone, and G. Wilkinson, Eds., Pergamon Press, Oxford, **1995**.

COS *Comprehensive Organic Synthesis* (*Comp. Org. Synth.*), 9 Vols., B. M. Trost and I. Fleming, Eds., Pergamon Press, Oxford, **1991**.

A.iii. Other Comprehensive Compilations

CMCB *The Chemistry of the Metal–Carbon Bond* (*Chem. Met. Carbon Bond*), F. R. Hartley and S. Patai, Eds., Wiley, New York, *1* (**1982**), *2* (**1985**), *3* (**1985**), *4* (**1987**), *5* (**1989**).

COT R. C. Larock, *Comprehensive Organic Transformations* (*Comp. Org. Transform.*), Wiley-VCH, Weinheim, **1989**, 1160 pp. 2nd ed., **1999**, 2583 pp.

GHIC *Gmelin Handbook of Inorganic Chemistry* (*Gmelins' Handbuch der Anorganischen Chemie, Gmelin)*, Springer-Verlag, Berlin.

HW *Houben-Weyl Methoden der Organischen Chemie* (*Houben-Weil*), G. Thieme Verlag, Stuttgart.

MELL J. W. Mellor, *A Comprehensive Treatise on Inorganic and Theoretical Chemistry* (*Mellor Comp. Treat. Inorg. Theo. Chem.*), 16 Vols., Longmans, Green and Co., London, **1922–1937**. Chapter 71 in Vol. F15, pp. 592–685 is entitled "Palladium."

A.iv. Annual and Periodical Surveys

AROS *Annual Reports in Organic Synthesis* (*Ann. Rep. Org. Synth.*) (**1971**–), Academic Press, New York.

ARPC *Annual Reports on the Progress of Chemistry* (*Ann. Rep. Prog. Chem.*), Part A: Inorganic Chemistry; Part B: Organic and Organometallic Chemistry; Part C: Physical Chemistry; The Royal Society of Chemistry, Cambridge, UK.

COSM **Note**: Vol. 93 (**1997**).

CUCR *Compendium of Organic Synthetic Methods* (*Comp. Org. Synth. Methods*) (**1971**–), Wiley, New York, *1* (**1971**), *2* (**1974**), *3* (**1977**), *4* (**1980**), *5* (**1984**), *6* (**1988**), *7* (**1992**), *8* (**1995**).

THLH *Current Chemical Reactions* (*Curr. Chem. React.*), (**1979**–), ISI, Inc., Philadelphia.

Theilheimer's Synthetic Methods of Organic Chemistry (*Theilheimer*) (**1948**–), Vol. 52 in **1997**, Karger, Basel.

A.v. Selected Review Series Containing Chapters on Palladium Chemistry

Note: Authored chapters in these compilations are cited as if they are reviews in review journals.

AICR	*Advances in Inorganic Chemistry and Radiochemistry* (*Adv. Inorg. Chem. Radiochem.*)
AOMC	*Advances in Organometallic Chemistry* (*Adv. Organomet. Chem.*)
CCR	*Coordination Chemistry Reviews* (*Coord. Chem. Rev.*)
OR	*Organic Reactions* (*Org. React.*), Wiley, New York, **1942**– . **Note**: Vol. 52 (**1998**).
OSOM	*Organic Synthesis via Organometallics* (*Org. Synth. Organomet.*), Springer-Verlag, Weinheim and Vierweg, Braunschweig. *1* (**1987**); *2* (**1989**); *3* (**1991**).
PIC	*Progress in Inorganic Chemistry* (*Prog. Inorg. Chem.*).

A.vi. Collections of Experimental Procedures

Note: Authored experimental procedures in these compilations are cited as if they are publications in primary journals.

IS	*Inorganic Syntheses* (*Inorg. Synth.*), Wiley, New York, **1939**– . **Note**: Vol. 32 (**1998**).
OMS	*Organometallic Syntheses* (*Organomet. Synth.*), J. J. Eisch and R. B. King, Eds., Academic Press, New York, and Elsevier, Amsterdam. *1* (**1965**); *2* (**1981**); *3* (**1986**); *4* (**1988**).
OS	*Organic Syntheses* (*Org. Synth.*), Wiley, New York, **1921**– . **Note**: Vol. 75 (**1998**).
OSCV	*Organic Synthesis Collective Volumes* (*Org. Synth. Coll. Vol.*), Wiley, New York, *1* (**1941**), *2* (**1943**), *3* (**1955**), *4* (**1963**), *5* (**1973**), *6* (**1988**), *7* (**1990**), *8* (**1993**).

A.vii. Chemical Catalogs

Among a large number of chemical catalogs, the following contain classified listings of palladium and those heteroatoms that occupy the key position in ligands.

Inorganics & Organometallics from Aldrich
Aldrich Chemical Co., Milwaukee (1998–1999 ed.) Palladium, pp. 273–279; Nitrogen, pp. 245–267; Oxygen, pp. 270–272; Phosphorus, pp. 280–307; Selenium, pp. 348–350; Sulfur, pp. 421–424.

Strem Chemicals, Inc., Catalog
(Catalog No. 17 for 1997–1999), Strem Chemicals, Inc., Newburyport, MA. Palladium, pp. 160–165; Nitrogen, pp. 146–157; Oxygen, pp. 158–160; Phosphorus pp. 165–189; Selenium, pp. 221–223; Sulfur, pp. 248.

B. PUBLICATION ACRONYMS AND ABBREVIATIONS

Primary Journals and Review Journals. The acronyms for *primary journals* and *review journals* are listed below. This list also includes acronyms for some *dictionaries* and *encyclopedias* (Sect. A.i), *Pergamon's Comprehensive Chemistry Series* (**Sect. A.ii**),

other comprehensive compilations (Sect. A.iii), *annual and periodical surveys* (Sect. A.iv), *selected review series containing chapters on palladium chemistry* (Sect. A.v), and *collections of experimental procedures* (Sect. A.vi). The other *books*, *patents*, and other miscellaneous references are given the following reference codes.

Books. The acronym for a book consists of BK for book and the first and last initials of the first author or editor.

Patents. The reference code for a patent consists of (i) year, (ii) PTXY where XY is the country code as shown in the list below, and (iii) patent number.
Note: For patents issued in any other countries, PTMS is used.

Country Code	Country Adjective	Country Code	Country Adjective
AT	Austrian	IL	Israeli
BE	Belg.	IN	Indian
BR	Braz. Pedido PI	JP	Jpn.
CA	Can.	LT	Lith.
CH	Switz.	LV	Latv.
CN	Chinese	NL	Neth.
CS	Czech	NO	Norw.
CZ	Czech Rep.	PL	Pol.
DD	East Ger.	Ro	Rom.
DE	Ger.	RU	Russ.
DK	Dan.	SE	Swed.
EP	Eur. Pat.	SK	Slovakia
ES	Span.	SU	U.S.S.R.
FI	Finn.	US	U.S.
FR	Fr.	WO	PCT Int.
HU	Hung.	ZA	S.African

Dissertations (Theses). As a rule, Ph.D. dissertations are not referenced. If it is desirable to cite them, they are handled as miscellaneous publications.

Miscellaneous References. Original papers and reviews published in journals not listed below and any other publications that cannot be coded by the system presented above including Ph.D. dissertations are coded using MSXY, where X and Y correspond to the first and last initials of the first author or editor.

LIST OF PUBLICATION ACRONYMS AND ABBREVIATIONS

Acronym	Abbreviation
ACA	*Aldrichim. Acta*
ACIE	*Angew. Chem. Int. Ed. Engl.*
ACR	*Acc. Chem. Res.*
ACRY	*Acta Crystallogr.*
ACS	*Adv. Chem. Ser.*
ACSC	*Acta Chem. Scand.*
AICR	*Adv. Inorg. Chem. Radiochem.*

AJC	*Aust. J. Chem.*
ANY	*Ann. N. Y. Acad. Sci.*
AOMC	*Adv. Organomet. Chem.*
AP	*Arch. Pharm.* (*Weinheim, Ger.*)
APOC	*Adv. Phys. Org. Chem.*
AROS	*Ann. Rep. Org. Synth.*
BAPS	*Bull. Acad. Pol. Sci. Ser. Sci. Chim.*
BASR (cf. IZV)	
BCSJ	*Bull. Chem. Soc. Jpn.*
BKCS	*Bull. Korean Chem. Soc.*
BMCL	*Bioorg. Med. Chem. Lett.*
BSCB	*Bull. Soc. Chim. Belg.*
BSCF	*Bull. Soc. Chim. Fr.*
CB	*Chem. Ber.*
CBR	*Chem. Br.*
CC	*Chem. Commun.*
CCA	*Croatia Chim. Acta*
CCC	*Comp. Coord. Chem.*
CCCC	*Collect. Czech. Chem. Commun.*
CCR	*Coord. Chem. Rev.*
CEJ	*Chem. Eur. J.*
CHC	*Chem. Heterocycl. Compd.*
CHCH	*Comp. Heterocycl. Chem.*
CHCHII	*Comp. Heterocycl. Chem. II*
CHIM	*Chimia*
CIC	*Comp. Inorg. Chem.*
CIL	*Chem. Ind.* (*London*)
CJC	*Can. J. Chem.*
CL	*Chem. Lett.*
CMC	*Comp. Med. Chem.*
CMCB	*Chem. Met. Carbon Bond*
COC	*Comp. Org. Chem.*
COMC	*Comp. Organomet. Chem.*
COMCII	*Comp. Organomet. Chem. II*
COS	*Comp. Org. Synth.*
COSM	*Comp. Org. Synth. Methods*
COT	*Comp. Org. Transform.*
CPB	*Chem. Pharm. Bull.*
CPS	*Comp. Polymer Sci.*
CR	*Chem. Rev.*
CRH	*C. R. Hebd. Seances Acad. Sci.*
CRHC	*C. R. Hebd. Seances Acad. Sci. Ser. C.*
CS	*Chem. Scr.*
CSR	*Chem. Soc. Rev.*
CUCR	*Curr. Chem. React.*
CZ	*Chem.-Ztg.*
DAN (cf. DCR)	*Dokl. Akad. Nauk SSSR*
DCR (cf. DAN)	

DOC	*Dic. Org. Comp.*
DOMCII	*Dic. Organomet. Comp. II*
EIC	*Encycl. Inorg. Chem.*
EJIC	*Eur. J. Inorg. Chem.*
EJOC	*Eur. J. Org. Chem.*
EPJ	*Eur. Polym. J.*
EROS	*Encycl. Reag. Org. Synth.*
EXP	*Experientia*
FCF	*Fortschr. Chem. Forsch.*
FCON	*Fortschr. Chem. Org. Naturst.*
GCI	*Gazz. Chim. Ital.*
GHIC	*Gmelin*
HCA	*Helv. Chim. Acta*
HET	*Heterocycles*
HW	*Houben-Weyl*
IC	*Inorg. Chem.*
ICA	*Inorg. Chim. Acta*
IECR	*Ind. Eng. Chem. Res.*
IJC	*Indian J. Chem.*
IJCB	*Indian J. Chem. Sect. B*
IS	*Inorg. Synth.*
ISJC	*Israel J. Chem.*
IZV (cf. BASR)	*Izv. Akad. Nauk SSR Ser. Khim.*
JACS	*J. Am. Chem. Soc.*
JC	*J. Catal.*
JCR	*J. Chem. Res.*
JCS	*J. Chem. Soc.* (for older *J. Chem. Soc.* that was not divided)
JCSC	*J. Chem. Soc. C*
JCSD	*J. Chem. Soc. Dalton Trans.*
JCSF	*J. Chem. Soc. Faraday Trans.*
JCSPI	*J. Chem. Soc. Perkin Trans. 1*
JCSPII	*J. Chem. Soc., Perkin Trans. 2*
JFC	*J. Flourine Chem.*
JGC (cf. ZOBK)	*J. Gen. Chem. USSR* (*Engl. Transl.*)
JHC	*J. Heterocycl. Chem.*
JICS	*J. Indian Chem. Soc.*
JMEC	*J. Med. Chem.*
JMC	*J. Mol. Catal.*
JOC	*J. Org. Chem.*
JOCR (cf. ZOK)	*J. Org. Chem. USSR* (*Engl. Transl.*)
JOMC	*J. Organomet. Chem.*
JPC	*J. Prakt. Chem.*
JPHS	*J. Pharm. Sci.*
JPOS	*J. Polym. Sci.*
KST	*Kunststoffe*
LAC	*Liebigs Ann. Chem.*
MACM	*Macromolecules*
MC	*Monatsch. Chem.*

MCP	*Macromol. Chem. Phys.*
MEND	*Mendeleev Commun.*
MKC	*Makromol. Chem.*
MRC	*Macromol. Rapid Commun.*
NAT	*Nature*
NATW	*Naturwissenschaften*
NJC	*Nouv. J. Chim.* (*New J. Chem.*)
OL	*Org. Lett.*
OM	*Organometallics*
OMR	*Organomet. React.*
OMS	*Organomet. Synth.*
OPPI	*Org. Prep. Proc. Int.*
OR	*Org. React.*
OS	*Org. Synth.*
OSCV	*Org. Synth. Coll. Vol.*
OSOM	*Org. Synth. Organomet.*
PAC	*Pure Appl. Chem.*
PC	*Phytochemistry*
PH	*Polyhedron*
PIC	*Prog. Inorg. Chem.*
PL	*Polym. Lett.*
PMSE	*Polym. Mater. Sci. Eng.*
PNAS	*Proc. Natl. Acad. Sci. USA*
POJ	*Polym. J.*
PTUS	Patent, Country, Number
QR	*Quant. Rev. Chem. Soc.*
RCR	*Russ. Chem. Rev.* (*Engl. Transl.*)
RJN	*Recuil*: *J. R. Netherlands Chem. Soc.*
RTC	*Recl. Trav. Chim. Pays-Bas*
SCI	*Science*
STE	*Steroids*
SYN	*Synthesis*
SYNC	*Synth. Commun.*
SYNL	*Synlett*
TA	*Tetrahedron*: *Asymmetry*
TCC	*Top. Curr. Chem.*
TET`	*Tetrahedron*
THLH	*Theilheimer*
TL	*Tetrahedron Lett.*
TOM	*Top. Organomet. Chem.*
ZAAC	*Z. Anorg. Allg. Chem.*
ZC	*Z. Chem.*
ZNF	*Z. Naturforsch.*
ZNFB	*Z. Naturforsch. B*
ZOBK (cf. JGC)	
ZOK (cf. JOCR)	*Zh. Org. Khim.*
ZOKL	*Zh. Obsch. Khim. Lett.*

R.2 Books (Monographs)

EI-ICHI NEGISHI

There are a large number of books on organometallic chemistry, and no attempts are made to list all of them here. Only some selected books on organotransition metal chemistry in general published since 1980 (Sect. A) and those that are primarily dedicated to palladium (Sect. B) are listed below.
Note: The acronym for a book consists of BK for book and the initials of the first and last names of the first author.

A. BOOKS PUBLISHED SINCE 1980 PERTAINING TO ORGANOTRANSITION METAL CHEMISTRY IN GENERAL

1982BKSD411p	S. G. Davies, *Organotransition Metal Chemistry: Applications to Organic Synthesis*, Pergamon Press, Oxford, **1982**, 411 pp.
1985BKAP398p	A. J. Pearson, *Metallo-Organic Chemistry*, Wiley, New York, **1985**, 398 pp.
1985BKCL447p	C. M. Lukehart, *Fundamental Transition Metal Organometallic Chemistry*, Brooks/Cole Publishing Co., Monterey, CA, **1985**, 447 pp.
1986BKAY455p	A. Yamamoto, *Organotransition Metal Chemistry*, Wiley, New York, **1986**, 455 pp.
1987BKJC989p	J. P. Collman, L. S. Hegedus, J. R. Norton, and R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, **1987**, 989 pp.
1988BKRC422p	R. E. Crabtree, *The Organometallic Chemistry of the Transition Metals*, Wiley, New York, **1988**, 422 pp.
1988BKFC784p	F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry, 4th ed., Wiley, New York*, **1988**, 784 pp.
1991BKRW965p	R. G. Wilkins, *Kinetics and Mechanism of Reactions of Transition Metal Complexes*, 2nd ed., VCH, Weinheim, **1991**, 465 pp.
1990BKPH484p	P. J. Harrington, *Transition Metals in Total Synthesis*, Wiley, New York, **1990**, 484 pp.
1992BKCF495p	C. Elschenbroich and A. Salzer, *Organometallics*, 2nd ed., VCH, Weinheim, **1992**, 495 pp.
1994BKMS603p	M. Schlosser, Ed., *Organometallics in Synthesis*, Wiley, New York, **1994**, 603 pp.
1998BKI0518p	I. Omae, *Applications of Organometallic Compounds*, Wiley, New York, **1998**, 518 pp.
1998BKMB[I]595p	M. Beller and C. Bolm, Eds., *Transition Metals for Organic Synthesis, Vol. 1*, Wiley-VCH, Weinheim, **1998**, 595 pp.

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
ISBN 0-471-31506-0

1998BKMB(2)967p M. Beller and C. Bolm, Eds., *Transition Metals for Organic Synthesis, Vol. 2*, Wiley-VCH, Weinheim, **1998**, 467 pp.

B. BOOKS ON ORGANOPALLADIUM CHEMISTRY

1971BKPM319p P. M. Maitlis, *The Organic Chemistry of Palladium*, 2 Vols., Academic Press, New York, **1971**, Vol. 1: *Metal Complexes*, 319 pp. Vol. 2: *Catalytic Reactions*, 216 pp.

1973BKFH544p F. R. Hartley, *The Chemistry of Platinum and Palladium*, Wiley, New York, **1973**, 544 pp.

1980BKPH435p P. M. Henry, *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Reide l, Dordrecht, **1980**, 435 pp.

1980BKJT207p J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer-Verlag, Berlin, **1980**, 207 pp.

1985BKRH461p R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York, **1985**, 461 pp.

1995BKJT560p J. Tsuji, *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*, Wiley, New York, **1995**, 560 pp.

1997BKJM304p J. L. Malleron, J. C. Fiaud, and J. Y. Legros, *Handbook of Palladium-Catalyzed Organic Reactions*, Academic Press, New York, **1997**, 304 pp.

1999BKJT323p J. Tsuji, Ed., *Perspectives in Organopalladium Chemistry for the 21st Century*, Elsevier, Amsterdam, **1999**, 323 pp.

2000BKJL432p J. J. Li and G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Elsevier, Amsterdam, **2000**, 432 pp.

R.3 Reviews and Accounts on Organopalladium Chemistry (as of September 1999)

EI-ICHI NEGISHI and FANG LIU

Reviews and accounts are listed (i) in chronological order, (ii) in alphabetical order of publication acronyms, and (iii) in increasing order of page numbers. Efforts have been made to include those reviews published in comprehensive compilations, review series, and others as independent reviews in which the author names are clearly indicated.

The number of the pertaining part is indicated to facilitate the selection of appropriate reviews.

For additional reviews, the following review indexes may be consulted.

1972AOMC274	M. I. Bruce, *Adv. Organomet. Chem.*, **1972**, *10*, 274. Guides to the Literature: Organotransition-Metal Chemistry, 1950–1970.
1973AOMC448	M. I. Bruce, *Adv. Organomet. Chem.*, **1973**, *11*, 448. Guides to the Literature: Organotransition-Metal Chemistry, 1971.
1974AOMC380	M. I. Bruce, *Adv. Organomet. Chem.*, **1974**, *12*, 380. Guides to the Literature: Organotransition-Metal Chemistry, 1972.
1982COMC(9)1521	G. B. Young, in *Comp. Organomet. Chem.*, G. Wilkinson, F. G. A. Stone, and E. W. Abel, Eds. Pergamon Press, Oxford, **1982**, *9*, 1521–1570. Index of Review Articles and Specialist Texts on Organometallic Chemistry (1970–1981).
IROC	*Index of Reviews in Organic Chemistry* (*Ind. Rev. Org. Chem.*), D. A. Lewsi, Ed. (**1971–1981**), S. J. A. Jones, Ed. (**1983–1988**), Royal Society of Chemistry, London.
ISR	*Index to Scientific Reviews*, ISI, Inc., Philadelphia, **1991**– .

LIST OF REVIEWS AND ACCOUNTS

1942GHIC435p	-E. Pietsch, *Gmelin Handbook Inorg. Chem.*, **1942**, *65*, 435 pp.	**Part II**
1948OR362R	E. Mosettig and M. Mozingo, *Org. React.*, **1948**, *4*, 362–377. The Rosenmund Reduction of Acid Chlorides to Aldehydes.	**VII**
1953OR263R	W. H. Hartung and R. Simonoff, *Org. React.*, **1953**, *7*, 263–326. Hydrogenolysis of Benzyl Group Attached to Oxygen, Nitrogen, or Sulfur.	**VII**

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
ISBN 0-471-31506-0

1967AOMC321R	A. Aguilo, *Adv. Organomet. Chem.*, **1967**, *5*, 321–352. Olefin Oxidation with Palladium(II) Catalyst in Solution.	**VIII**
1967MSND83R	N. R. Davies, *Rev. Pure Appl. Chem.*, **1967**, *17*, 83–93. Isomerization of Olefins Catalyzed by Palladium and Other Transition-Metal Complexes.	**IX**
1968CCR319R	R. Ugo, *Coord. Chem. Rev.*, **1968**, *3*, 319–344. The Coordinative Reactivity of Phosphine Complexes of Platinum(0), Palladium(0), and Nickel(0).	**II**
1969ACR10R	R. F. Heck, *Acc. Chem. Res.*, **1969**, *2*, 10–16. Addition Reactions of Transition Metal Compounds.	**II**
1969ACR144R	J. Tsuji, *Acc. Chem. Res.*, **1969**, *2*, 144–152. Carbon–Carbon Bond Formation Via Palladium Complexes.	**III**, **IV**, **V**, **VI**
1969MSJT109R	J. Tsuji, *Adv. Org. Chem.*, **1969**, *6*, 109–255. Organic Syntheses by Means of Noble Metal Compounds.	**General**
1969MSJT149R	J. Tsuji, *Platinum Metals Rev.*, **1969**, *13*, 149–150. Palladium Compounds in Organic Synthesis. Carbonylation of Unsaturated Molecules.	**VI**
1969SYN157R	J. Tsuji, *Synthesis*, **1969**, 157–169. Decarbonylation Reactions Using Transition Metal Compounds.	**VI**
1971ANY483R	P. M. Henry, *Ann. N. Y. Acad. Sci.*, **1971**, *172*, 483–506. Mechanisms of Palladium(II)-Catalyzed Reactions.	**General**
1971ANY516R	E. W. Stern, *Ann. N. Y. Acad. Sci.*, **1971**, *172*, 516–622. Homogeneous Catalysis. Applications and Implications.	**General**
1971MSPH41R	P. M. Henry, *Trans. N. Y. Acad. Sci.*, **1971**, *33*, 41–64. Mechanisms of Palladium(II)-Catalyzed Reactions.	**General**
1971MSRH221R	R. F. Heck, *Fortschr. Chem. Forsch.*, **1971**, *16*, 221–242. Addition–Elimination Reactions of Palladium Compounds with Olefins.	**III**, **IV**
1971PAC107R	J. Tsuji, *Pure Appl. Chem.*, **1971**, *2*, 107–119. Organic Synthesis by Means of Transition Metal Compounds.	**General**
1972FCF41R	J. Tsuji, *Fortschr. Chem. Forsch.*, **1972**, 41–84. Organic Synthesis by Means of Transition-Metal Complexes. General Patterns.	**General**
1972OMR319R	W. Kitching, *Organomet. React.*, **1972**, *3*, 319–398. Oxymetallation.	**V**
1972OMR1R	R. Jira and W. Freielsleben, *Organomet. React.*, **1972**, *3*, 1–190. Olefin Oxidation and Related Reactions with Group VIII Noble Metal Compounds.	**V**, **VIII**
1973ACR8R	J. Tsuji, *Acc. Chem. Res.*, **1973**, *6*, 8–15. Addition Reactions of Butadiene Catalyzed by Palladium Complexes.	**IV**
1973AOMC87R	A. Wojcicki, *Adv. Organomet. Chem.*, **1973**, *11*, 87–145. Insertion Reactions of Transition Metal–Carbon σ-Bonded Compounds I: Carbon Monoxide Insertion.	**VI**
1973CIC(4)781R	B. L. Shaw and N. I. Tucker, *Comp. Inorg. Chem.*, **1973**, *4*, 781–994. Organo-Transition Metal Compounds and Related Aspects of Homogeneous Catalysis.	**General**
1973CCR123R	A. Peloso, *Coord. Chem. Rev.*, **1973**, *10*, 123–181. Kinetics of Nickel, Palladium, and Platinum Complexes.	**II**

1973PAC489R	P. M. Maitlis, *Pure Appl. Chem.* **1973**, *33*, 489–512. Organo-transition Metal Chemistry Without Phosphines. Palladium Catalyzed Cyclotrimerization of Acetylenes.	**IV**
1973SYN524R	I. Moritani and Y. Fujiwara, *Synthesis*, **1973**, 524–533. Aromatic Substitution of Olefins by Palladium Salts.	**IV**, **V**, **VIII**
1974ACS90R	J. K. Stille, L. F. Hines, R. W. Fries, P. K. Wong, D. E. James, and K. Lau, *Adv. Chem. Ser.*, **1974**, 90–110. Synthesis and Reactions of Palladium–Carbon σ-Bonded Compounds II.	**General**
1974ANY114R	Y. Ishii, *Ann. N. Y. Acad. Sci.*, **1974**, *239*, 114–128. Preparation and Reactions of Palladium(0)–Dibenzylideneacetone Complexes.	**II**
1974MSRH53R	R. F. Heck, *Proc. Robert A. Welch Found. Conf. Chem. Res.*, **1974**, *17*, 53–98. Synthesis and Reactions of Palladium–Carbon Compounds.	**II**
1975AOMC273R	D. M. Roundhill, *Adv. Organomet. Chem.*, **1975**, *13*, 273–361. Organometallic Reactions Involving Hydrido-Nickel, -Palladium, and -Platinum Complexes.	**II**, **VII**
1975AOMC363R	P. M. Henry, *Adv. Organomet. Chem.*, **1975**, *13*, 363–452. Palladium-Catalyzed Organic Reactions.	**General**
1975CCR35R	M. Graziani, M. Lenarda, R. Ros, and U. Belluco, *Coord. Chem. Rev.*, **1975**, *16*, 35–50. Reactions of Platinum(0) and Palladium(0) Complexes with Electronegatively Activated Small Rings.	**IV**
1975MSIM273R	I. Moritani, T. Hosokawa, and S. I. Murahashi, in *Organotransition-Metal Chemistry*, Y. Ishii and M. Tsutsui, Eds., Plenum Press, New York, **1975**, 273–279. The Palladium Catalyzed Reactions for Synthesis of Amines and Benzofurans.	**V**
1976ACR93R	P. M. Maitlis, *Acc. Chem. Res.*, **1976**, *9*, 93–96. The Palladium(II)-Induced Oligomerization of Acetylenes: An Organometallic Detective Story.	**IV**
1976MSLH329R	L. S. Hegedus, *J. Organomet. Chem. Libr.*, **1976**, *1*, 329–359. Application of π-Allyl Transition Metal Complexes in Organic Synthesis.	**V**
1976OR1R	A. J. Birch and D. H. Williamson, *Org. React.*, **1976**, *24*, 1–186. Homogeneous Hydrogenation Catalysts in Organic Solvents.	**VII**
1977ANY52R	J. K. Stille, *Ann. N. Y. Acad. Sci.*, **1977**, *295*, 52–58. Mechanism of Oxidative Addition of Organic Halides to Group VIII Transition Metal Complexes.	**IV**
1977ANY201R	Richard F. Heck, *Ann. N. Y. Acad. Sci.*, **1977**, *295*, 201–224. Catalytic Applications of Palladium in Organic Syntheses.	**General**
1977BKIW595R	J. Tsuji, in *Organic Synth. Met. Carbonyls*, I. Wender and P. Pino, Eds., Wiley, New York, **1977**, 595–654. Decarbonylation Reactions Using Transition Metal Compounds.	**VI**
1977MSRH323R	R. F. Heck, *Adv. Catal.*, **1977**, *26*, 323–349. Transition Metal-Catalyzed Reactions of Organic Halides with Carbon Monoxide, Olefins, and Acetylenes.	**IV**

1977TET2615R	B. M. Trost, *Tetrahedron*, **1977**, *33*, 2615–2649. Organopalladium Intermediates in Organic Synthesis.	**General**
1978BKJB285R	E. Negishi, in *Aspects of Mechanism and Organometallic Chemistry*, J. H. Brewster, Ed., Plenum Press, New York, **1978**, 285–317. Selective Carbon–Carbon Bond Formation Via Transition Metal Catalysis: Is Nickel or Palladium Better than Copper?	**III**
1978CCR89R	V. I. Sokolov and O. A. Reutov, *Coord. Chem. Rev.*, **1978**, *27*, 89–107. Reactions of Zerovalent Platinum and Palladium Complexes with Organometallic Compounds of Nontransition Metals.	**General**
1978MSAY161R	A. Yamamoto and T. Yamamoto, *Macromol. Rev.*, **1978**, *13*, 161–218. Coordination Polymerization by Transition-Metal Alkyls and Hydrides.	**VI**
1979ACR146R	R. F. Heck, *Acc. Chem. Res.*, **1979**, *12*, 146–151. Palladium-Catalyzed Reactions of Organic Halides with Olefins.	**IV**
1979AOMC141R	J. Tsuji, *Adv. Organomet. Chem.*, **1979**, *17*, 141–193. Palladium-Catalyzed Reactions of Butadiene and Isoprene.	**IV**
1979PAC1235R	J. Tsuji, *Pure Appl. Chem.*, **1979**, *51*, 1235–1241. Palladium Catalysts in Natural Products Synthesis.	**General**
1980ACR385R	B. M. Trost, *Acc. Chem. Res.*, **1980**, *13*, 385–393. New Rules of Selectivity: Allylic Alkylations Catalyzed by Palladium.	**V**
1980ANY250R	J. Tsuji, *Ann. N. Y. Acad. Sci.*, **1980**, *333*, 250–263. Applications of Palladium Catalysts to Natural Product Syntheses.	**General**
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