Palladium Reagents and Catalysts

Palladium Reagents and Catalysts—New Perspectives for the 21st Century J. Tsuji
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New Perspectives for the 21st Century

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Contents

Preface

Organopalladium chemistry has changed remarkably since I wrote the book *Palladium Reagents and Catalysts, Innovations in Organic Synthesis* in 1995. This is the main reason why I undertook the difficult task of writing a new book on organopalladium chemistry. Several reactions which had long been regarded as impossible, are now known to proceed smoothly with Pd catalysts, and several dreams have become reality. For example, no one believed, only 5 years ago, that cyclohexanone could be arylated easily by a Pd-catalyzed reaction of chlorobenzene to afford 2-phenylcyclohexanone. Aryl chlorides, which had been regarded as totally inactive in catalytic reactions, are now known to undergo facile Pd-catalyzed reactions, giving a potentially big impact to practical applications. It is not an exaggeration to say that the recent development of organopalladium chemistry is revolutionary. It is widely recognized that palladium is the most versatile metal in promoting or catalyzing reactions, particularly those involving carbon–carbon bond formation, many of which are not always easy to achieve with other transition metal catalysts.

In 1981, I wrote *Organic Synthesis with Palladium Compounds* citing about 1000 references which had appeared before 1978. I wrote a larger book (560 pages) in 1995, entitled *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*. Mention should also be made of *Handbook of Organopalladium Chemistry*, edited by E. Negishi in 2002, which is 3279 pages long, and is an excellent encyclopedia covering all fields of organopalladium chemistry, and includes ample experimental data.

Considering the explosive and remarkable growth in organopalladium chemistry, particularly in the last 5 years, I now feel that another comprehensive book is needed to summarize the newer aspects of organopalladium chemistry. My primary purpose in writing this book is to give new perspectives on the synthetic usefulness of contemporary organopalladium chemistry for synthetic organic chemists. I wrote this book on the assumption that my old book *Palladium Reagents and Catalysts, Innovations in Organic Synthesis* is accessible to readers, and I tried, as much as possible, to avoid repetitions or overlaps. I believe that, together, the two books cover the whole of organopalladium chemistry, from the past to the present.

The proper classification of all Pd-catalyzed reactions is important, and there are several possibilities. The classification I chose tries to achieve easy understanding by synthetic organic chemists. It is different from the classification used by Negishi which is based mainly on organometallic chemistry.

The many references that are given in this book were selected from a much larger number which I have collected over the years. I have tried to be as comprehensive

as possible in selecting those references of evident synthetic utility in papers published before the middle of 2003. The overall task of selecting which references to include, based on my own interests, was very difficult. I can only hope that not too many researchers will feel that their important papers were not cited.

It may be a hopeless venture for a single author to write a book covering the rapidly progressing field of modern organopalladium chemistry. I took great care writing this book. Many errors and incorrect citations must, however, inevitably be present. These are my sole responsibility, and readers are advised to keep in mind that statements, data, illustrations, or other items may, inadvertently, be inaccurate.

I want to express my appreciation to Dr M. Miura (Associate Professor, Osaka University) for reading all chapters and correcting errors. I thank Professor H. Nozaki (Emeritus, Kyoto University) for his pertinent comments on the manuscript. The following chemists read various chapters of the crude manuscript and gave me valuable advice which I appreciated very much: M. Catellani (Professor, Parma University) T. Hiyama (Professor, Kyoto University), K. Mikami (Associate Professor, Tokyo Institute of Technology), M. Nishiyama (Tosoh Corporation), A. Suzuki (Emeritus Professor, Hokkaido University), Y. Tamaru (Professor, Nagasaki University), K. Yamamoto (Professor, Science University of Tokyo in Yamaguchi), and Y. Yamamoto (Professor, Tohoku University). Also, I want to thank T. Ikariya (Professor, Tokyo Institute of Technology) for designing the cover illustration.

As one who has devoted most of his research life to the development of organopalladium chemistry, I will be very happy if this book stimulates, in any way, the further development of organopalladium chemistry.

J. Tsuji
October 2003
Kamakura, Japan

Abbreviations

Ac	acetyl
acac	acetylacetonato
Ar	aryl
atm	atmospheric pressure
BBEDA	*N*,*N*′-bis(benzylidene)ethylenediamine
9-BBN	9-borabicyclo[3. 3. 1]nonanyl
9-BBNH	9-borabicyclo[3. 3. 1]nonane
Bn	benzyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′binaphthyl
BPPFA	1-[1,2-bis(diphenylphosphino)ferrocenyl]ethyldimethylamine
bpy	2,2′-bipyridyl
Boc	*t*-butoxycarbonyl
BQ	1,4-benzoquinone
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bz	benzoyl
CDT	1,5,9-cyclododecatriene
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
DBA	dibenzylideneacetone
DBU	1,8-diazabicyclo[5. 4. 0]undec-7-ene
DCHPE	bis(dicyclohexylphosphino)ethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIPPP	bis(diisopropylphosphino)propane
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAD	dimethyl acetylenedicarboxylate
DMI	1,3-dimethylimidazolidin-2-one
DPMSPP	diphenyl(*m*-sulfophenyl)phosphine
DPPB	bis(diphenylphosphino)butane
DPPE	bis(diphenylphosphino)ethane
DPPF	1,1′-bis(diphenylphosphino)ferrocene
DPPP	bis(diphenylphosphino)propane
EWG	electron-withdrawing group
KHMDS	potassium hexamethyldisilazane, potassium bis(trimethylsilyl)amide
LHMDS	lithium hexamethyldisilazane, lithium bis(trimethylsilyl)amide

MA	maleic anhydride
MOM	methoxymethyl
MOP	monodentate optically active phosphine
NaHMDS	sodium hexamethyldisilazane, sodium bis(trimethylsilyl)amide
Nf	nonaflate, nonafluorobutanesulfonate
Nu	nucleophile
PEG	poly(ethylene glycol)
phen	1,10-phenanthroline
PhMe	toluene
PHMS	poly(hydromethylsiloxane)
PMP	1,2,2,6,6-pentamethylpiperidine
PPFA	*N*,*N*-dimethyl-1,2-(diphenylphosphino)ferrocenylethylamine
py	pyridine
TASF	tris(diethylamino)sulfonium difluoro(trimethyl)silicate
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TCPC	2,3,4,5-tetrakis(methoxycarbonyl)palladacyclopentadiene
TDMPP	tri(2,6-dimethoxyphenyl)phosphine
Tf	trifluoromethylsulfonyl (triflyl)
TFA	trifluoroacetic acid
TFP	tri(2-furyl)phosphine
TMG	tetramethylguanidine
TMPP	trimethylolpropane phosphite or 4-ethyl-2,6,7-trioxa-1-phosphobicyclo[2. 2. 2]octane
TMS	trimethylsilyl
Tol	tolyl
TON	turnover numbers
TOF	turnover frequencies
TPPTS	(II-2) tri(*m*-sulfophenyl)phosphine; CA Index name, 3,3′,3″-phosphinidynetrisbenzenesulfonic acid
TPPMS	(II-1) (*m*-sulfophenyl)diphenylphosphine, diphenyl(3-sulfophenyl)phosphine; CA Index name, 3-(diphenylphosphino)benzenesulfonic acid
Ts	tosyl
TsOH	*p*-toluenesulfonic acid
TTMPP	tri(2,4,6-trimethoxyphenyl)phosphine

Chapter 1

The Basic Chemistry of Organopalladium Compounds

1.1 Characteristic Features of Pd-Promoted or -Catalyzed Reactions

There are several features which make reactions involving Pd catalysts and reagents particularly useful and versatile among many transition metals used for organic synthesis. Most importantly, Pd catalysts offer an abundance of possibilities of carbon–carbon bond formation. Importance of the carbon–carbon bond formation in organic synthesis needs no explanation. No other transition metals can offer such versatile methods of the carbon–carbon bond formations as Pd. Tolerance of Pd catalysts and reagents to many functional groups such as carbonyl and hydroxy groups is the second important feature. Pd-catalyzed reactions can be carried out without protection of these functional groups. Although reactions involving Pd should be carried out carefully, Pd reagents and catalysts are not very sensitive to oxygen and moisture, and even to acid in many reactions catalyzed by Pd–phosphine complexes. It is enough to apply precautions to avoid oxidation of coordinated phosphines, and this can be done easily. On the other hand, the Ni(0) complex is extremely sensitive to oxygen.

Of course, Pd is a noble metal and expensive. Its price frequently fluctuates drastically. A few years ago, Pd was more expensive than Pt and Au but cheaper than Rh. As of October 2003, the comparative prices of the noble metals were: Pd (1), Au (1.8), Rh (2.8), Pt (3.3), Ru (0.2). Recently the price of Pd has dropped dramatically, and Pt is currently the most expensive noble metal.

Also, the toxicity of Pd has posed no serious problem so far. The fact that a number of industrial processes, particularly for the production of fine chemicals based on Pd-catalyzed reactions, have been developed and are currently being operated, reflects the advantages of using Pd catalysts commercially.

1.2 Palladium Compounds, Complexes, and Ligands Widely Used in Organic Synthesis

In organic synthesis, two kinds of Pd compounds, namely Pd(II) salts and Pd(0) complexes, are used. Pd(II) compounds are mainly used as oxidizing reagents, or catalysts for a few reactions. Pd(0) complexes are always used as catalysts. Pd(II)

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compounds such as $PdCl_2$ and $Pd(OAc)_2$ are stable, and commercially available. They can be used in two ways: as unique stoichiometric oxidizing agents; and as precursors of Pd(0) complexes.

$PdCl_2$ is stable, but its solubility in water and organic solvents is low. It is soluble in dilute HCl and becomes soluble in organic solvents by forming a $PdCl_2(PhCN)_2$ complex. M_2PdCl_4 (M = Li, Na, K) are soluble in water, lower alcohols and some organic solvents. $Pd(OAc)_2$ is commercially available. It is stable and soluble in organic solvents.

Pd(II) salts can be used as a source of Pd(0). Most conveniently phosphines can be used as reducing agents. For example, when $Pd(OAc)_2$ is treated with PPh_3, Pd(0) species and phosphine oxide are formed slowly [1]. A highly active Pd(0) catalyst can be prepared by a rapid reaction of $Pd(OAc)_2$ with P(*n*-Bu)$_3$ in 1 : 1 ratio in THF or benzene [2]. P(*n*-Bu)$_3$ is oxidized rapidly to phosphine oxide and a phosphine-free Pd(0) species is formed besides Ac_2O. This catalyst is very active, but not stable and must be used immediately; black Pd metal begins to precipitate after 30 min if no substrate is added. The *in situ* generation of Pd(0) species using *n*-PBu_3 as a reducing agent is very convenient preparative method for Pd(0) catalysts.

$$Pd(OAc)_2 + PPh_3 + H_2O \longrightarrow Pd(0) + Ph_3PO + 2\,AcOH$$

$$Pd(OAc)_2 + P(n\text{-}Bu_3) \longrightarrow Pd(0) \cdots O{=}PBu_3 + Ac_2O$$

Commercially available $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$-$CHCl_3$ and (η^3-allyl-PdCl)$_2$ are generally used as precursors of Pd(0) catalysts with or without addition of phosphine ligands. However, it should be mentioned that catalytic activities of Pd(0) catalysts generated *in situ* from these Pd compounds are not always the same, and it is advisable to test all of them in order to achieve efficient catalytic reactions.

$Pd(PPh_3)_4$ is light-sensitive, unstable in air, yellowish green crystals and a coordinatively saturated Pd(0) complex. Sometimes, $Pd(PPh_3)_4$ is less active as a catalyst, because it is overligated and has too many ligands to allow the coordination of some reactants. Recently bulky and electron-rich P(*t*-Bu)$_3$ has been attracting attention as an important ligand. Interestingly, highly coordinatively unsaturated Pd(*t*-$Bu_3P)_2$ is a stable Pd(0) complex in solid state [3] and commercially available. The stability of this unsaturated phosphine complex is certainly due to bulkiness of the ligand. This complex is a very active catalyst in some reactions, particularly for aryl chlorides [4].

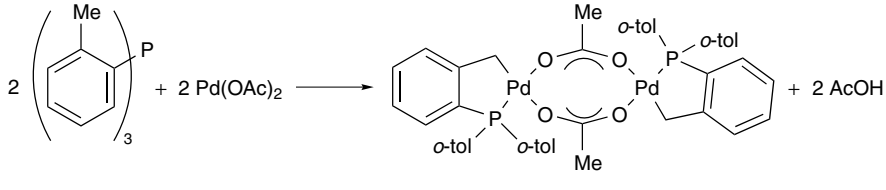
$Pd_2(dba)_3$-$CHCl_3$ (dba = dibenzylideneacetone) is another commercially available Pd(0) complex in the form of purple needles which contain one molecule of $CHCl_3$ when $Pd(dba)_2$, initially formed in the process of preparation, is recrystallized from $CHCl_3$, where $Pd(dba)_2$ corresponds to $Pd_2(dba)_3$-dba. In literature, researchers use both $Pd_2(dba)_3$ and $Pd(dba)_2$ in their research papers. In this book both complexes are taken directly from original papers as complexes of the same nature. The molecule of dba is not a chelating ligand. One of the dba molecules in $Pd_2(dba)_3$-dba does not coordinate to Pd and is displaced by $CHCl_3$ to form $Pd_2(dba)_3$-$CHCl_3$, when it is recrystallized from $CHCl_3$. In $Pd_2(dba)_3$, dba behaves as two monodentate ligands, but not one bidentate ligand, and each Pd

is coordinated with three double bonds of three molecules of dba, forming a 16-electron complex. It is an air-stable complex, prepared by the reaction of $PdCl_2$ with dba and recrystallization from $CHCl_3$ [5]. $Pd_2(dba)_3$ itself without phosphine is an active catalyst in some reactions. As a ligand, dba is comparable to, or better than monodentate phosphines.

Pd on carbon in the presence of PPh_3 may be used for reactive substrates as an active catalyst similar to $Pd(PPh_3)_n$.

Recently colloidal Pd nanoparticles protected with tetraalkylammonium salts have been attracting attention as active catalysts. They are used for Heck and Suzuki–Miyaura reactions without phosphine ligands [6,7]. Most simply, $Pd(OAc)_2$ is used without a ligand, forming some kind of colloidal or soluble Pd(0) species *in situ* in reactions of active substrates such as aryl iodides and diazonium salts. Pd on carbon without phosphine is active for some Heck and other reactions, but not always. These Pd(0) catalysts without ligands are believed to behave as homogeneous catalysts [8].

A number of phosphine ligands are used. Phosphines used frequently in Pd-catalyzed reactions are listed in Tables 1.1–1.18. Most of them are commercially available [9]. Among them, PPh_3 is by far the most widely used. Any contaminating phosphine oxide is readily removed by recrystallization from ethanol. Bulky tri(*o*-tolyl)phosphine is an especially effective ligand, and was used by Heck for the first time [10]. The Pd complex of this phosphine is not only active, but also its catalytic life is longer. This is explained by formation of the palladacycle **1**, called the Herrmann complex, which is stable to air and moisture and commercially available [11]. It is an excellent precursor of underligated single phosphine Pd(0) catalyst. But this catalyst is not active at low temperature, and active above 110 °C. Also a number of palladacycles (Table 1.18) are prepared as precursors of catalysts and show high catalytic activity and turnover numbers.



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In some catalytic reactions, more electron-donating alkylphosphines such as $P(n\text{-}Bu)_3$ and tricyclohexylphosphine, and arylphosphines such as tri(2,4,6-trimethoxyphenyl)phosphine (TTMPP) and tri(2,6-dimethoxyphenyl)phosphine (TDMPP), are used successfully. These electron-rich phosphines accelerate the 'oxidative addition' step. Furthermore, $P(t\text{-}Bu)_3$ was found to be a very important ligand particularly for reactions of aryl chlorides. It is a very bulky and electron-rich phosphine, and has been neglected for a long time and has not been used as a ligand, because it is believed that the bulkiness inhibits coordination of reactants. Now it is understandable that strongly electron-donating $t\text{-}Bu_3P$ accelerates the 'oxidative addition' step of aryl chlorides, because oxidative addition is nucleophilic in nature. Also, the bulkiness assists facile reductive elimination. The following pK_a

values of conjugate acids of phosphines support the high basicity of P(*t*-Bu)$_3$, which is more basic than P(*n*-Bu)$_3$:

$$P(t\text{-Bu})_3\ (11.4),\ PCy_3\ (9.7),\ P(n\text{-Bu})_3\ (8.4),\ PPh_3\ (2.7)$$

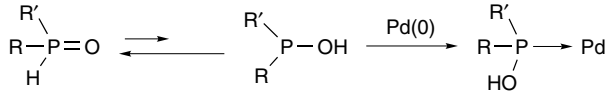
Since the first report on the use of P(*t*-Bu)$_3$ in Pd-catalyzed amination of aryl chlorides by Koie and co-workers appeared in 1998 [12], syntheses and uses of a number of bulky and electron-rich phosphines related to P(*t*-Bu)$_3$ (Tables 1.4–1.6) have been reported [13]. These di- and trialkylphosphines are somewhat air-sensitive. However, their phosphonium salts are air-stable, from which phosphines are liberated by the treatment with bases and conveniently used for catalytic processes [14].

Sulfonated triphenylphosphine [TPPTS (triphenylphosphine, *m*-trisulfonated); tri(*m*-sulfophenyl)phosphine] (**II-1**) and monosulfonated triphenylphosphine [TPPMS (triphenylphosphine, monosulfonated); 3-(diphenylphosphino)benzenesulfonic acid] (**II-2**) are commercially available ligands and their sodium salts are water-soluble [15]. The Na salt of the ligand TPPTS is very soluble and may be too soluble in water, hence moderately soluble TPPMS is preferred. Another water-soluble phosphine is 2-(diphenylphosphinoethyl)trimethyl ammonium halide (**II-11**) [16]. A number of other water-soluble phosphines are now known (Table 1.2). Pd complexes, coordinated by these phosphines, are soluble in water, and Pd-catalyzed reactions can be carried out in water, which is said to have an accelerating effect in some catalytic reactions.

Bidentate phosphines such as DPPE, DPPP and DPPB[1] play important roles in some reactions. Another bidentate phosphine is DPPF (**XI-1**), which is different from other bidentate phosphines, showing its own characteristic activity. The tetrapodal phosphine ligand, *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)-cyclopentane (Tedicyp) (**X-1**) was found to be a good ligand, and its Pd complex gives high turnover numbers [17].

Phosphites, such as triisopropyl phosphite and triphenyl phosphite, are weaker electron donors than the corresponding phosphines, but they are used in some reactions because of their greater π-acceptor ability. The cyclic phosphite [trimethylolpropane phosphite (TMPP) or 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]-octane] (**III-2**), which has a small cone angle and small steric hindrance, shows high catalytic activity in some reactions. It is not commercially available, but can be prepared easily [18].

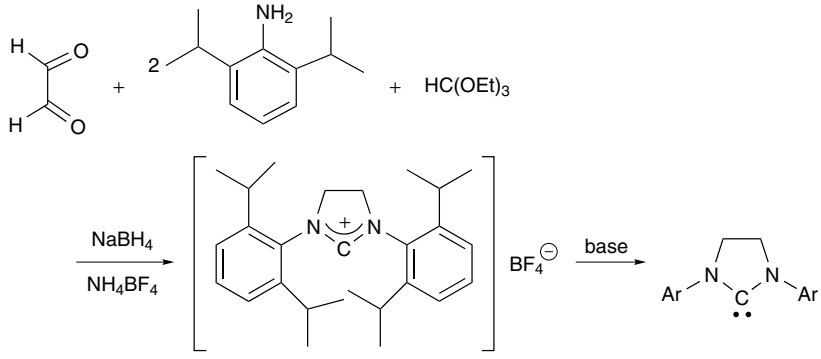
Recently Li reported that air stable phosphine oxides **2a** [RR′P(O)H] in the presence of transition metals undergo tautomerization to the less stable phosphinous acids **2b** [RR′POH], which subsequently coordinate to Pd centers through phosphorus atoms to form Pd phosphinous acid complexes **2c**, which behave as active catalysts for unactivated aryl chlorides [19]. Their Pd complexes **XVIII-4** (POPd), **-5** (POPd1) and **-6** (POPd2) are commercially available (Table 1.18).



2a **2b** **2c**

[1] According to IUPAC nomenclature, abbreviations of ligands themselves are written in capital letters, for example, DPPE, DPPF, BINAP, DBA are used, but the ligands in complexes are written with small letters like $PdCl_2$[dppe]Cl_2, $Pd_2(dba)_3$, although this rule is neglected in many cases.

Heterocyclic carbene ligands are now attracting attention as new ligands (Table 1.16). Carbenes are reactive and unstable species, which are difficult to isolate. It is well-known that they can be stabilized and isolated by coordinating to metal complexes of W, Mo and Cr. Recently Ardeuengo found that imidazol-2-ylidenes with large substituents on nitrogens are stable carbenes and can be isolated [20,21]. They are good ligands of transition metal complexes, and called 'phosphine mimics', which are bulky and electron-rich, and hence active for the reactions of aryl chlorides [22]. The carbenes can be generated from dihydroimidazolium salts, which are prepared easily from glyoxal, primary amine and ortho-formate. Research on reactions catalyzed by Pd–carbene complexes is expanding rapidly including asymmetric catalysis. It should be mentioned that alkyl-substituted imidazolium salts are ionic liquids, used extensively as unique solvents for various reactions, including Pd-catalyzed reactions [23].



dihydroimidazolium salt

Coordinated phosphines do not directly participate in catalytic reactions, and hence they are called 'spectator' or 'innocent' ligands. Roles of phosphines are not entirely understood and their performance is not always predictable [24]. Therefore, in surveying optimum conditions of catalytic reactions, it is advisable to test the activity of important types of phosphines and phosphites, which have both different steric effects and electron donating properties as much as possible.

Ratios of Pd to ligands are also important. In the presence of an excess ligand, the concentration of active catalytic species is decreased, and hence the catalytic process may be inhibited. Some Pd(0)-catalyzed reactions proceed without phosphine ligands, and a phosphine-free catalyst is an ideal one, because phosphines are expensive and difficult to recover.

Pd is an expensive metal. In Pd(0) or Pd(II)-catalyzed reactions, particularly in commercial processes, repeated uses of Pd catalysts are required. When products are low-boiling, they can be separated from the catalyst by distillation. The Wacker process for the production of acetaldehyde is an example. In order to separate from less volatile products, there are several approaches for the economical use of Pd catalysts. Active Pd complexes covalently bound to a polymer chain are frequently used. After the reaction, the supported catalyst can be recovered by filtration and reused several times. Polymers such as the Merrifield resin [25], amphiphilic poly(ethylene glycol)-polystyrene copolymer [26] and polyethylene [27] are typical examples. Also polymer-supported microencapsulated Pd is used as a reusable

catalyst [28]. When a water-soluble phosphine is used, the Pd catalyst always stays in an aqueous phase and can be separated from products in an organic phase, and is used repeatedly. An N-containing 15-membered macrocyclic triolefin (**XVII-1**) is a good ligand for cross coupling [29]. Solid phase synthesis has been extensively applied to Pd-catalyzed reactions as an efficient synthetic method [30].

Recovery of Pd after reactions is important in commercial processes, but it is not always easy to collect Pd from solutions [31]. Pd can be recovered as insoluble complexes such as the dimethylglyoxime complex or $PdCl_2(PPh_3)_2$ by treatment with HCl and PPh_3. Removal of a very small amount of Pd, remaining in a solution, or purification of reaction products contaminated with a trace of Pd, can be done by treating the solution with active charcoal, polyamines, polymer-anchored phosphines and $P(n\text{-Bu})_3$ [32]. The Pd can be collected in solution by coordination or absorption.

3-(Diethylenetriamino)propyl-functionalized silica gel, commercially available from Aldrich, is used to scavenge Pd in a solution at a low concentration.

1.3 Fundamental Reactions of Pd Compounds

The following six fundamental reactions of Pd complexes are briefly explained in order to understand how reactions either promoted or catalyzed by Pd proceed [32a]. In schemes used for explanation, 'spectator' or 'innocent' phosphine ligands are omitted for simplicity. First, a brief explanation of the chemical terms specific to organopalladium chemistry is given:

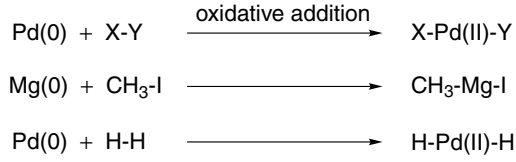
1. Oxidative addition (OA);
2. Insertion (IS);
3. Transmetallation (TM);
4. Reductive elimination (RE);
5. β-H elimination;
6. Elimination of β-heteroatom groups and β-carbon.

It should be noted that sometimes different terms are used for the same process. This situation arises from the fact that chemical terms specific to organometallic chemistry originate from inorganic chemistry, and these terms differ from the ones originating from organic chemistry.

1.3.1 'Oxidative' Addition

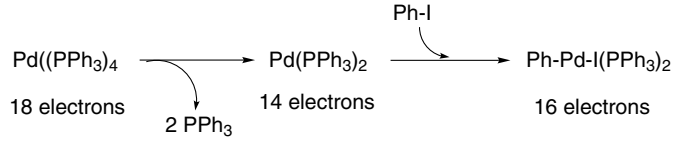
The term 'oxidative' may sound strange for organic chemists who are not familiar with organometallic chemistry. The term 'oxidative' used in organometallic chemistry has a different meaning to 'oxidation' used in organic chemistry, such as oxidation of secondary alcohols to ketones. The 'oxidative' addition is the addition of a molecule X—Y to Pd(0) with cleavage of its covalent bond, forming two new bonds. Since the two previously nonbonding electrons of Pd are involved in bonding, the Pd increases its formal oxidation state by two units, namely, Pd(0) is oxidized to Pd(II). This process is similar to the formation of Grignard reagents from alkyl halides and Mg(0). In the preparation of Grignard reagents, Mg(0) is oxidized to Mg(II) by the 'oxidative' addition of alkyl halides to form two covalent

bonds. Another example, which clearly shows the difference between 'oxidation' in organic chemistry and 'oxidative' addition in organometallic chemistry, is the 'oxidative' addition of H_2 to Pd(0) to form Pd(II) hydride. In other words, Pd(0) is 'oxidized' to Pd(II) by H_2. This sounds strange to organic chemists, because H_2 is a reducing agent in organic chemistry.



According to the 18-electron rule, a stable Pd(0) complex with an electron configuration of the next highest noble gas is obtained when the sum of d electrons of Pd and electrons donated from ligands equals eighteen. Complexes which obey the 18-electron rule are said to be coordinatively saturated. Pd(0) forms complexes using d^{10} electrons ($4d^8$ and $5s^2$). Coordinatively saturated complexes are formed by donation of electrons from the ligands until the total number of electrons reaches eighteen. This means that four ligands which donate two electrons each can coordinate Pd(0) to form a coordinatively saturated Pd(0) complex. In other words, the coordination number of Pd(0) is four.

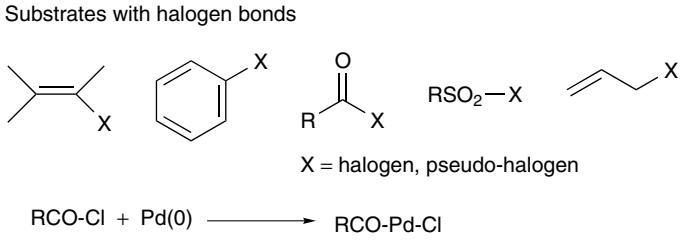
The oxidative addition occurs with coordinatively unsaturated complexes. As a typical example, the saturated Pd(0) complex, $Pd(PPh_3)_4$ (four-coordinate, 18 electrons) undergoes reversible dissociation *in situ* in a solution to give the unsaturated 14-electron species $Pd(PPh_3)_2$, which is capable of undergoing oxidative addition. Various σ-bonded Pd complexes are formed by oxidative addition. In many cases, dissociation of ligands to supply vacant coordination sites is the first step of catalytic reactions.



Oxidative addition is facilitated by higher electron density of Pd, and in general, σ-donor ligands such as R_3P attached to Pd facilitate oxidative addition. On the other hand, π-acceptor ligands such as CO and alkenes tend to suppress oxidative addition. A number of different polar and nonpolar covalent bonds are capable of undergoing the oxidative addition to Pd(0). The widely known substrates are C—X (X = halogen and pseudohalogen). Most frequently observed is the oxidative addition of organic halides of sp^2 carbons, and the rate of the addition decreases in the following order; C-I > C-Br >>> C-Cl >>> F. Aryl fluorides are almost inert [33]. For a long time this order has been thought to be correct. Recently a breakthrough has occurred in the discovery of facile oxidative addition of sp^2 C-Cl bonds by using electron-rich ligands such as P(*t*-Bu)$_3$ or *N*-heterocyclic carbene ligands. Alkenyl, aryl halides, acyl halides and sulfonyl halides undergo oxidative

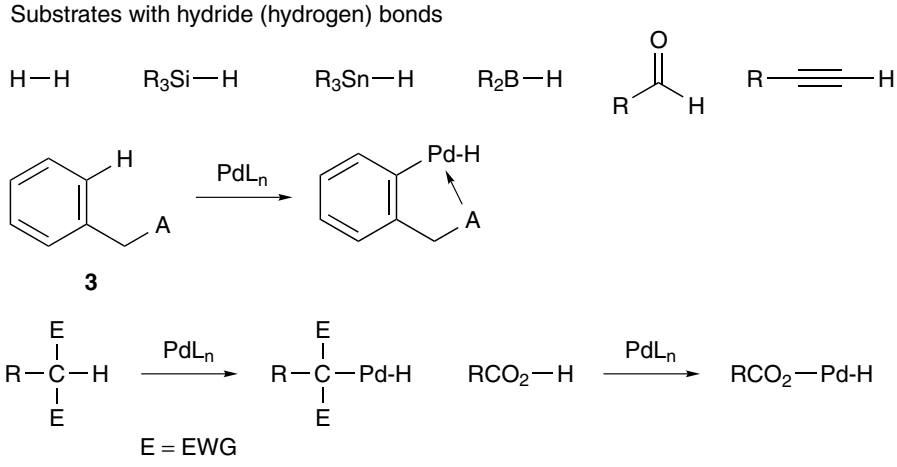
addition. Diazonium salts and triflates, which undergo facile oxidative addition, are treated as pseudohalides in this book.

It should be pointed out that some Pd-catalyzed reactions of alkyl halides, and even alkyl chlorides are emerging, indicating that facile oxidative addition of alkyl halides is occurring.



The following compounds with H-C and H-M′ bonds undergo oxidative addition to form Pd hydrides. Reactions of terminal alkynes and aldehydes are known to start by the oxidative addition of their C-H bonds. The reaction, called '*ortho*-palladation', occurs on the aromatic C—H bond in **3** at an *ortho* position of such donor atoms as N, S, O and P to form a Pd—H bond and palladacycles. Formation of aromatic palladacycles is key in the C—H bond activation in a number of Pd-catalyzed reactions of aromatic compounds. Some reactions of carboxylic acids and active methylene compounds are described as starting by oxidative addition of their acidic O—H and C—H bonds.

Hydrogen ligands on transition metals, formed by oxidative additions, are traditionally, and exclusively, called 'hydrides', whether they display any hydridic behavior or not. Thus Pd(0) is oxidized to H-Pd(II)-H by the oxidative addition of H_2.



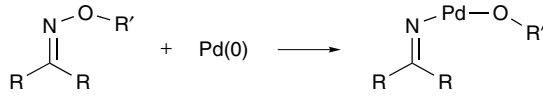
Metal–metal bonds M′-M′, such as R_2B-BR_2 and R_3Si-SiR_3, undergo oxidative addition by cleaving the M′-M′ bond (where M′ represents a main group metal).

Substrates with metal–metal bonds

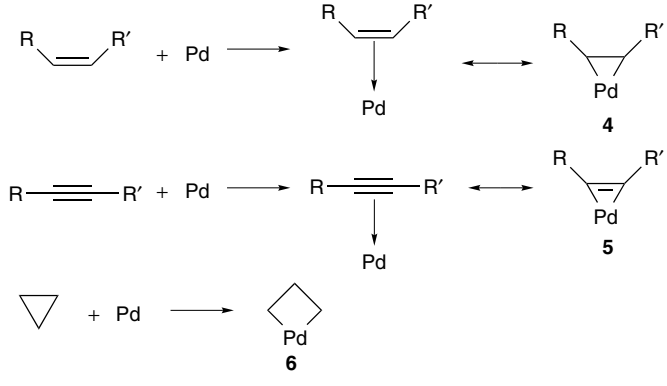
$R_3Si\text{-}SiR_3$ $R_3Sn\text{-}SnR_3$ $R_2B\text{-}BR_2$ $R_3Sn\text{-}SiR_3$ etc.

$$RM'\text{—}M'R + Pd \xrightarrow{\text{oxidative addition}} RM'\text{-}Pd\text{-}M'R$$

An N-O bond in oxime derivatives undergoes oxidative addition to form a Pd-imino bond. New Pd-catalyzed reactions of oximes, such as the amino Heck reaction, have been discovered (see Chapter 3.2.10) [34].



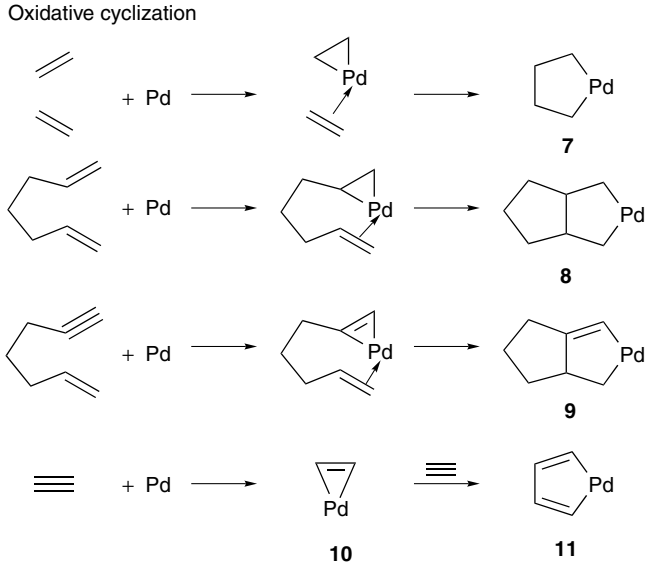
Oxidative addition involves cleavage of the covalent bonds as described above. In addition, oxidative addition of a broader sense occurs without bond cleavage. For example, π-complexes of alkenes and alkynes are considered to form η^2 complexes[2] by oxidative addition. Two distinct Pd—C bonds are formed, and the resulting alkene complexes are more appropriately described as the palladacyclopropane **4** and the alkyne complex may be regarded as the palladacyclopropene **5**. Thus the coordination of the alkene and alkyne results in formal oxidation of Pd. The palladacyclobutane **6** is formed by the oxidative addition of cyclopropane with bond cleavage.



Oxidative cyclization is another type of oxidative addition without bond cleavage. Two molecules of ethylene undergo Pd-catalyzed addition reactions. Intermolecular reaction is initiated by π-complexation of the two double bonds, followed by cyclization to form the palladacyclopentane **7**. This is called oxidative cyclization. The oxidative cyclization of 1,6-diene affords the palladacyclopentane **8**, which undergoes further transformations. Similarly, the oxidative cyclization of α,ω-enyne affords the palladacyclopentene **9**. Formation of these five-membered rings occurs stepwise and can be understood in terms of the formation of either palladacyclopropene or palladacyclopropane. Then the inter- and intramolecular

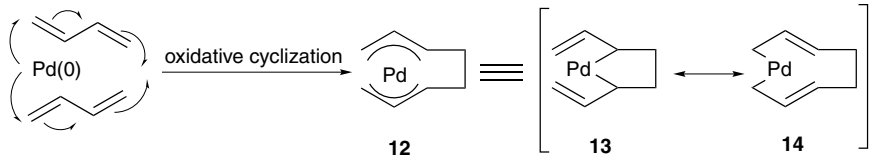
[2] The prefix η^n (hapto n) is used in front of the ligand formula to imply bonding to n carbons and to specify the number of carbon atoms that interact with the Pd center.

insertions of alkene to the three-membered rings produces the palladacyclopentane **7** and palladacyclopentene **9**. In the reaction of acetylene with Pd(0), palladacyclopropene **10** is generated and subsequent intermolecular insertion of acetylene provides palladacyclopentadiene **11**.



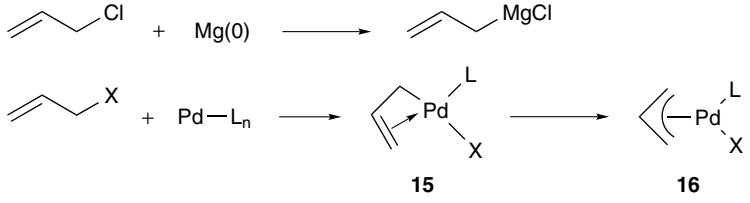
The term oxidative cyclization is based on the fact that two-electron oxidation of Pd(0) occurs by cyclization. The same reaction is sometimes called 'reductive cyclization', which may be a source of confusion. This term comes from organic chemistry and is based on the formal change in alkene or alkyne bonds, since the alkene double bond is 'reduced' to the alkane bond, and the alkyne bond is 'reduced' to the alkene bond by the cyclization. A number of Pd-catalyzed cyclizations of alkynes and alkenes are known and they proceed by oxidative cyclization. Thus both 'oxidative' and 'reductive' cyclizations are used for the same process.

In cyclization of conjugated dienes, typically butadiene, coordination of two molecules of butadiene gives rise to the bis-π-allyl complexe **12.** The distance between the terminals of two molecules of butadiene becomes closer by π-coordination to Pd(0), and the oxidative cyclization is thought to generate either the 1-pallada-2,5-divinylcyclopentane **13** or 1-pallada-3,7-cyclononadiene **14**.



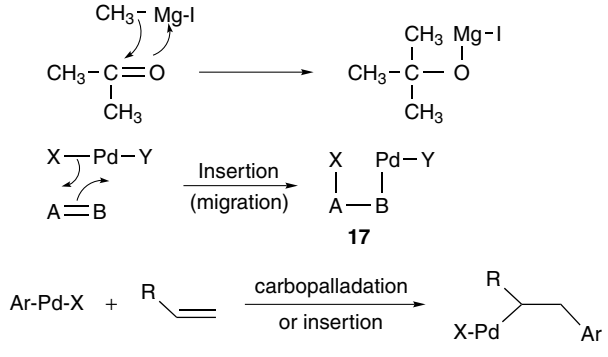
Similar to the formation of allylmagnesium halide, the oxidative addition of allyl halides to Pd(0) complexes generates allylpalladium complexes **15**. However, in the latter case, the π-bond is formed by the donation of π-electrons of the double bond, and resonance of the σ-allyl and π-allyl bonds in **15** generates the π-allyl complex **16** or η^3-allyl complex. The carbon–carbon bond in the π-allyl

complexes is the same length as that in benzene. The allyl Grignard reagent is prepared by reaction of an allyl halide with Mg metal. However, π-allylpalladium complexes are prepared by oxidative addition of not only allylic halides, but also esters of allylic alcohols (carboxylates, carbonates, phosphates), allyl aryl ethers and allyl nitro compounds. Typically, the π-allylpalladium complex is formed by the oxidative addition of allyl acetate to Pd(0) complex.



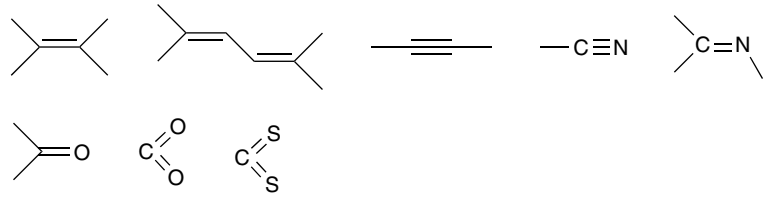
1.3.2 Insertion

Reaction of Grignard reagents with carbonyl groups can be understood as an insertion of an unsaturated C=O bond of the carbonyl groups into the Mg–carbon bond to form Mg alkoxide. Similarly, various unsaturated ligands such as alkenes, alkynes and CO formally insert into an adjacent Pd–ligand bond in Pd complexes to give **17**. The term 'insertion' is somewhat misleading. The insertion should be understood as the migration of the adjacent ligand from the Pd to the Pd-bound unsaturated ligand. The reaction below is called 'insertion' of an alkene to a Ar-PdX bond mainly by inorganic chemists. Some organic chemists prefer to use the term 'carbopalladation' of alkenes.

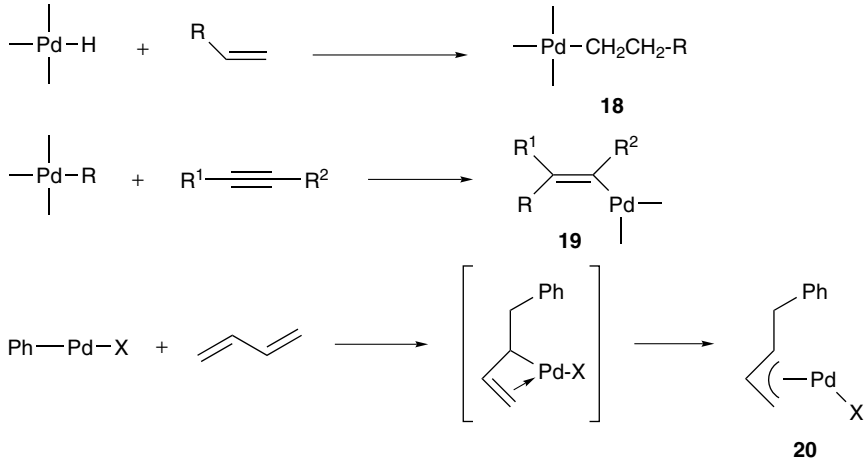


The insertion is reversible. Two types of the insertion are known. They are α,β-(or 1,2-) and α,α-(or 1,1-) insertions. Most widely observed is the α,β-insertion of unsaturated bonds such as alkenes and alkynes. The following unsaturated bonds undergo α,β-insertion:

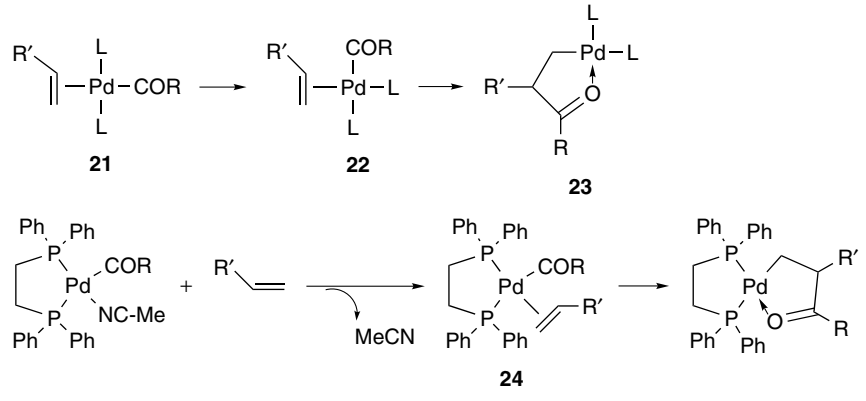
The insertion of alkene to Pd-H, which is called 'hydropalladation' of an alkene, affords the alkylpalladium complex **18**, and insertion of alkyne to Pd-R bonds



forms the vinylpalladium complex **19**. The reaction can be understood as the '*cis*-carbopalladation' of alkynes. The π-allyl complex is formed by the reaction of conjugated dienes with Pd complexes. The insertion of one of the double bonds of butadiene to the Ph-Pd bond leads to the π-allylpalladium complex **20**.

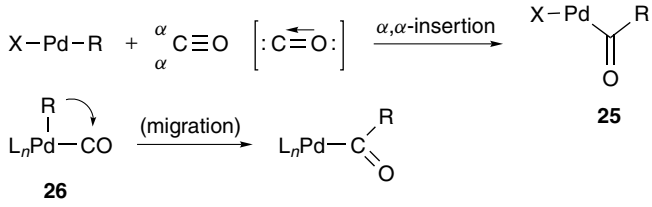


Rates of insertion are controlled by several factors. Firstly, the insertion of an alkene to a Pd complex is faster when a cationic complex is used. The addition of a Ag salt to a chloro complex generates a cationic complex and hence the insertion is accelerated probably owing to facile coordination of the alkene. For insertion (migration), *cis* coordination is necessary. Thus the *trans*-acyl-alkene complex **21** must be isomerized to a rather unstable *cis* complex **22** to give the insertion product **23**. Secondly coordination of a bidentate ligand forms the *cis* complex **24**

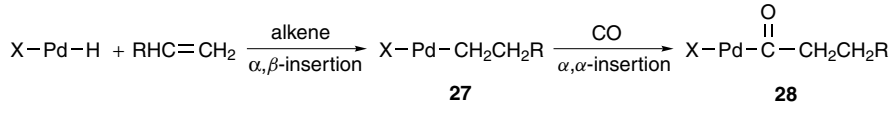


by chelation, and the insertion is possible without *trans* to *cis* isomerization. This effect explains partly an accelerating effect of bidentate ligands, which force the *cis* coordination of reacting molecules.

CO is a representative species which undergoes the α,α-insertion. Its insertion to a Pd-carbon bond affords the acylpalladium complexes **25**. The CO insertion is understood to occur by migration of an alkyl ligand in **26** to a coordinated CO. Mechanistically the CO insertion is regarded as 1,2-alkyl migration to the *cis*-bound CO (migratory insertion). The migration is reversible and an important step in carbonylation. SO_2, isonitriles and carbenes are other species that undergo α,α-insertion.

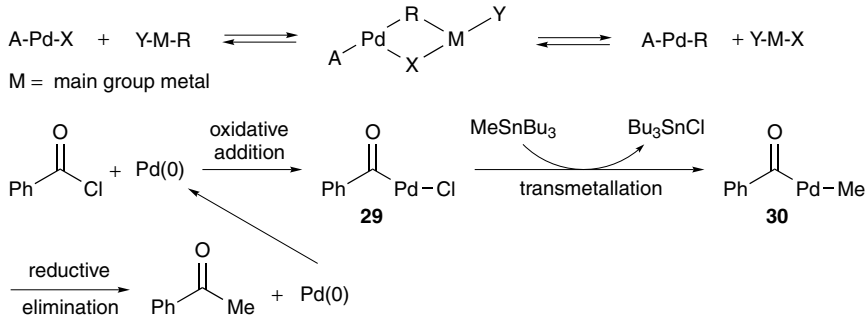


Both Mg and Pd complexes similarly undergo oxidative addition and insertion. Whereas the main reaction path of Grignard reagents is insertion of a carbonyl group, the Pd complexes can undergo both oxidative addition and insertion with a variety of π-bonds. In addition, it should be emphasized that the insertion can occur sequentially several times. For example, insertion of an alkene to a Pd-C or Pd-H bond affords the alkyl complex **27,** and is followed by CO insertion to generate the acyl complex **28**. Sometimes, further insertions of alkene and CO take place. Particularly useful is the formation of polycyclic compounds by sequential intramolecular insertions of several alkenyl and alkynyl bonds. Several C-C bonds are formed without adding other reagents and changing reaction conditions. These reactions are called either domino, cascade or tandem reactions. Among these terms, 'domino' is most common [35].



1.3.3 Transmetallation

Organometallic compounds M′-R and hydrides M′-H of main group metals (M′ = Mg, Zn, B, Al, Sn, Si, Hg) react with Pd complexes (A-Pd-X) formed by oxidative addition, and the organic group or hydride is transferred to Pd by substituting X with R or H. In other words, alkylation of Pd or hydride formation takes place and this process is called transmetallation. The driving force of transmetallation is ascribed to the difference in electronegativity of two metals, and the main group metal M′ must be more electropositive than Pd for transmetallation to occur. The oxidative addition–transmetallation sequence is widely known. Reaction of benzoyl chloride with Pd(0) gives benzoylpalladium chloride (**29**), and subsequent

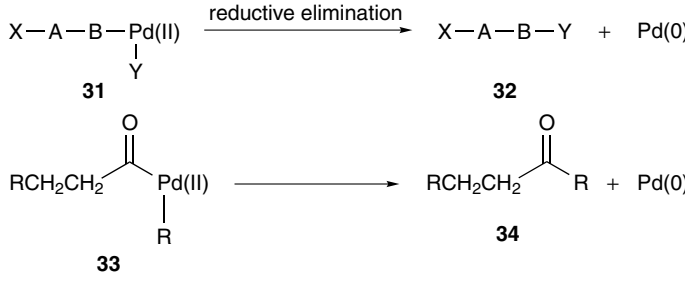


transmetallation with methyltributyltin generates benzoylmethylpalladium (**30**). Formation of acetophenone by the reductive elimination of **30** is a typical example.

1.3.4 Reductive Elimination

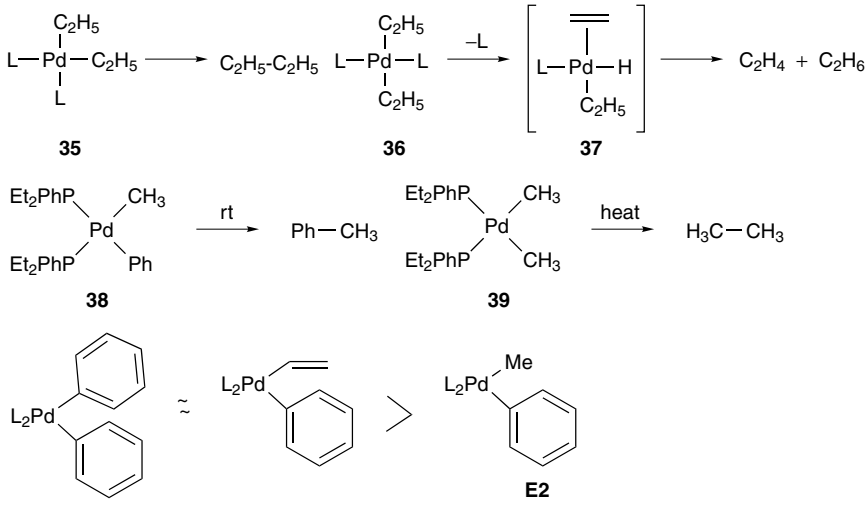
Similar to 'oxidative', the term 'reductive' used in organometallic chemistry has a different meaning from reduction in organic chemistry. Reductive elimination is a unimolecular decomposition pathway, and the reverse of oxidative addition. Reductive elimination (or reductive coupling) involves loss of two ligands of *cis* configuration from the Pd center in **31**, and their combination gives rise to a single elimination product **32**. In other words, coupling of two groups coordinated to Pd liberates the product **32** in the last step of a catalytic cycle. By reductive elimination, both the coordination number and the formal oxidation state of Pd(II) are reduced by two units to generate Pd(0), and hence the reaction is named 'reductive' elimination. The regenerated Pd(0) species undergo oxidative addition again. In this way, a catalytic cycle is completed by a reductive elimination step. No reductive elimination occurs in Grignard reactions. Without reductive elimination, the reaction ends as a stoichiometric one. This is a decisive difference between the reactions of Pd complexes and main group metal compounds.

For example, in a carbonylation reaction, the acylpalladium complex **33**, formed by the insertion of CO, undergoes reductive elimination to give ketone **34** as a product, and Pd(0) as a catalytic species is regenerated.



The reductive elimination of A-B proceeds if A and B are mutually *cis*. In other words, reductive elimination is possible from *cis*-complexes. If groups to be eliminated are *trans* oriented, they must first rearrange to *cis*. The *cis*-diethyl complex

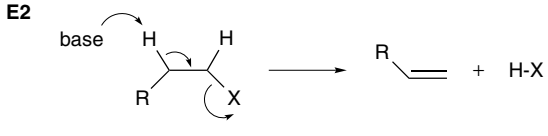
35 gives butane, whereas ethylene and ethane are formed from the *trans*-diethyl complex **36** via β-H elimination to generate the Pd hydride **37**, and lead to its reductive elimination [36]. It is understandable that bidentate ligands of large bite angles help favor reductive elimination. Reductive elimination of the Pd-C(sp^2) bond is faster than that of the Pd-C(sp^3) bond. Thus the reductive elimination of *cis*-PdMe(Ph)(PEt_2Ph)$_2$ (**38**) proceeds rapidly at room temperature, whereas heating is necessary for the generation of ethane from *cis*-$PdMe_2(PEt_2Ph)_2$ (**39**). Reduced electron density of Pd promotes reductive elimination, and addition of strong π-accepter ligands, such as CO and electron deficient alkenes, promotes reductive elimination. Also bulky ligands facilitate reductive elimination.



1.3.5 β-H Elimination (β-Elimination, Dehydropalladation)

Another termination step in a catalytic cycle is *syn* elimination of hydrogen from carbon at β-position to Pd in alkylpalladium complexes to give rise to Pd hydride (H-Pd-X) and an alkene. This process is called either 'β-hydride elimination' or 'β-hydrogen elimination'. Most frequently used is 'β-hydride elimination', because the β-H is eliminated as the Pd-hydride (H-Pd-X). The proper and unambiguous term of this process is 'dehydropalladation' in a *cis* manner. This is somewhat similar to a E1 or E2 reaction in organic chemistry, althought it is *anti* elimination.

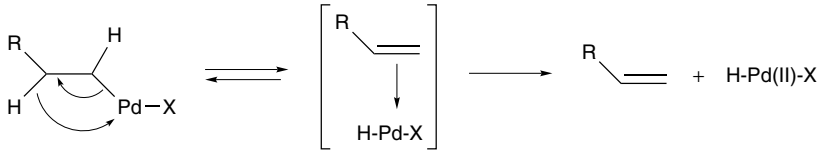
Organic chemists, particularly synthetic organic chemists including myself, prefer to use arrows in mechanistic discussion of organic reactions to show formation and fission of bonds. When arrows are used, the direction of the arrow is important. An E1 or E2 reaction may be simply stated. Dehydropalladation may be explained similarly, because Pd-X is regarded as a leaving group.



However, we must consider 'dehydropalladation' from a different point of view, although it may cause some confusion. The β-H is eliminated as a hydride by

dehydropalladation to form H-Pd(II)-X (Pd hydride) and an alkene, the latter being in coordination to the Pd center to form **40**. A hydrogen ligand on Pd is traditionally called a 'hydride'. This is the reason why the reaction is called 'β-hydride elimination'. Finally H-Pd(II)-X affords Pd(0) and HX by reductive elimination in the presence of a base. Thus the β-H elimination is expressed by an equation, in which arrows show different directions. If H-Pd-X is not scavenged quickly by a base, the reverse insertion of alkene to give alkylpalladium may occur. In this book, β-H elimination, or simply β-elimination is used.

Insertion of alkene to a Pd hydride to form alkylpalladium and elimination of β-H from the alkylpalladium are reversible steps. The β-H elimination generates an alkene. Both the hydride and the alkene coordinate to Pd as shown by **40**, increasing the coordination number of Pd by one. Therefore, the β-H elimination requires coordinative unsaturation of Pd complexes. The β-H to be eliminated should be *cis* to Pd.



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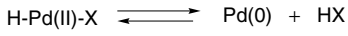
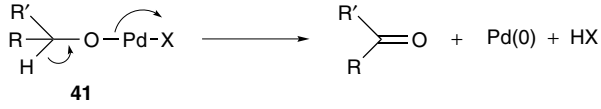


Alcohols are oxidized by Pd(II) species. In this case, carbonyl compounds are formed by the β-H elimination from the Pd alkoxides **41**, and the reactions may be expressed by either **41** or **41a**.



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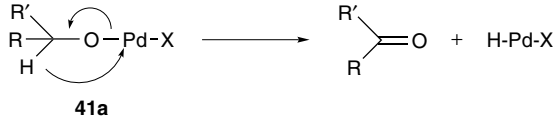
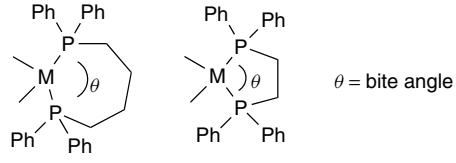


41a

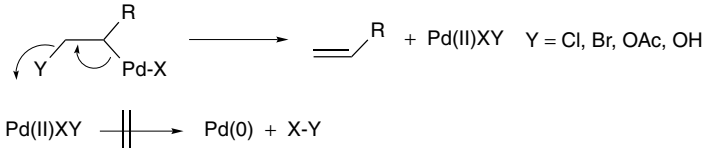
The reductive elimination and the β-H elimination are competitive. The β-H elimination takes place with *trans* dialkylpalladium complexes such as **36**. The reductive elimination is favored by coordination of bidentate phosphine ligands which have larger bite angles (for the effect of bite angles, see van Leeuwen *et al*. [24]) to force other mutually *cis* ligands closer. Thus bidentate ligands of



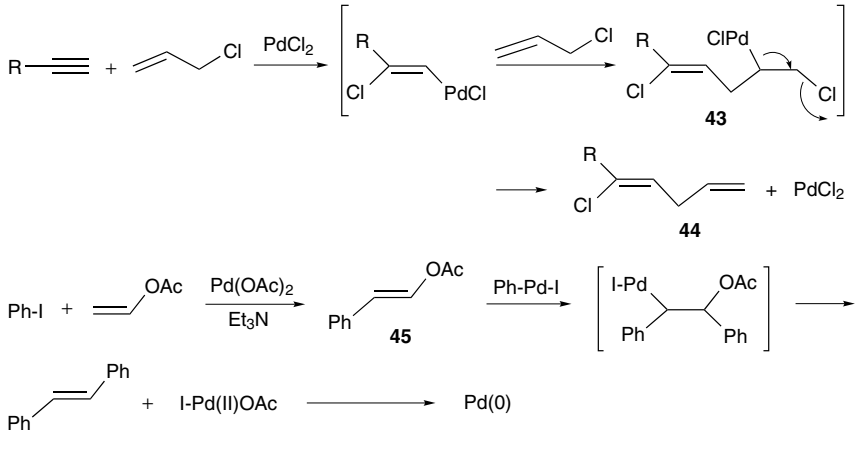
large bite angles, such as DPPF and DPPB and very bulky P(*t*-Bu)$_3$, accelerate the reductive elimination more easily than the bidentate DPPE and monodentate PPh_3.

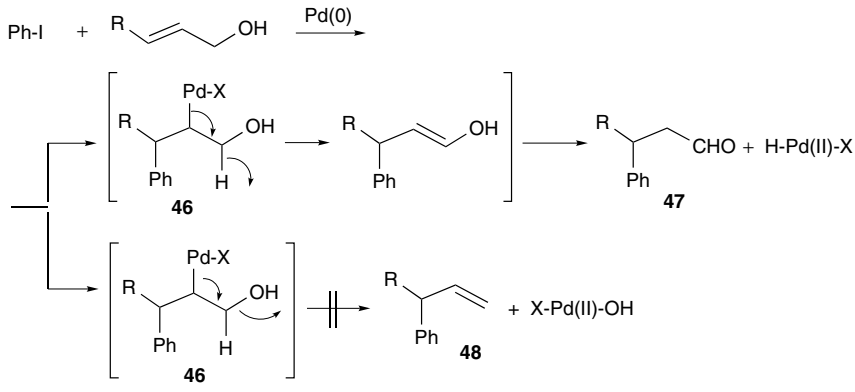
1.3.6 Elimination of β-Heteroatom Groups and β-Carbon

In addition to β-H, β-heteroatoms and even β-carbon are eliminated, although they are observed less extensively. Elimination of β-heteroatoms seems to be specific to Pd(II) complexes. When heteroatom groups (Cl, Br, OAc, OH, etc.) are present on β-carbon to Pd, their elimination with PdX takes place. Most importantly the Pd(II) species is generated by the elimination of the heteroatom groups. Thus Pd(II)-catalyzed oxidative reactions become possible. For example, HO-Pd-X, which is a Pd(II) species, is formed by the elimination of β-OH. No reductive elimination to give Pd(0) and HO-X occurs. Usually elimination of β-heteroatoms is faster than that of β-H.

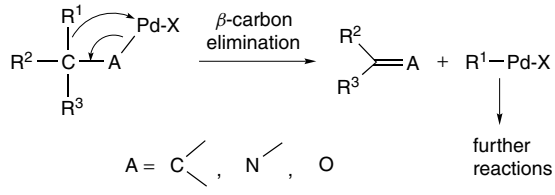


$PdCl_2$-catalyzed addition reaction of allyl chloride to alkynes is explained by chloropalladation of a triple bond, followed by insertion of the double bond of allyl chloride to generate **43**. No π-allyl complex is formed from allyl chloride and $PdCl_2$. The final step is elimination of β-Cl to afford 1-chloro-1,4-diene **44** with regeneration of Pd(II) [37]. As another example, the Pd(0)-catalyzed Heck reaction of vinyl acetate affords stilbene; in this reaction, the primary product is β-phenylvinyl acetate (**45**), which reacts again with iodobenzene, and the last step is elimination of β-OAc to give stilbene. At the same time, Pd(II) is generated, which is reduced to Pd(0) *in situ* [38]. However, elimination of β-heteroatoms is not always faster than that of β-H. For example, the Heck reaction of allyl alcohol with iodobenzene proceeds by preferential elimination of β-H from the insertion product **46** to afford aldehyde **47**, and no elimination of β-OH from the same carbon occurs to give the alkene **48** [39,40].

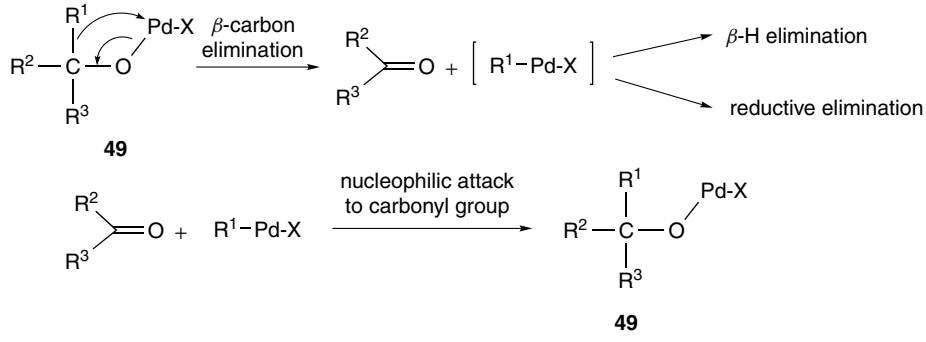


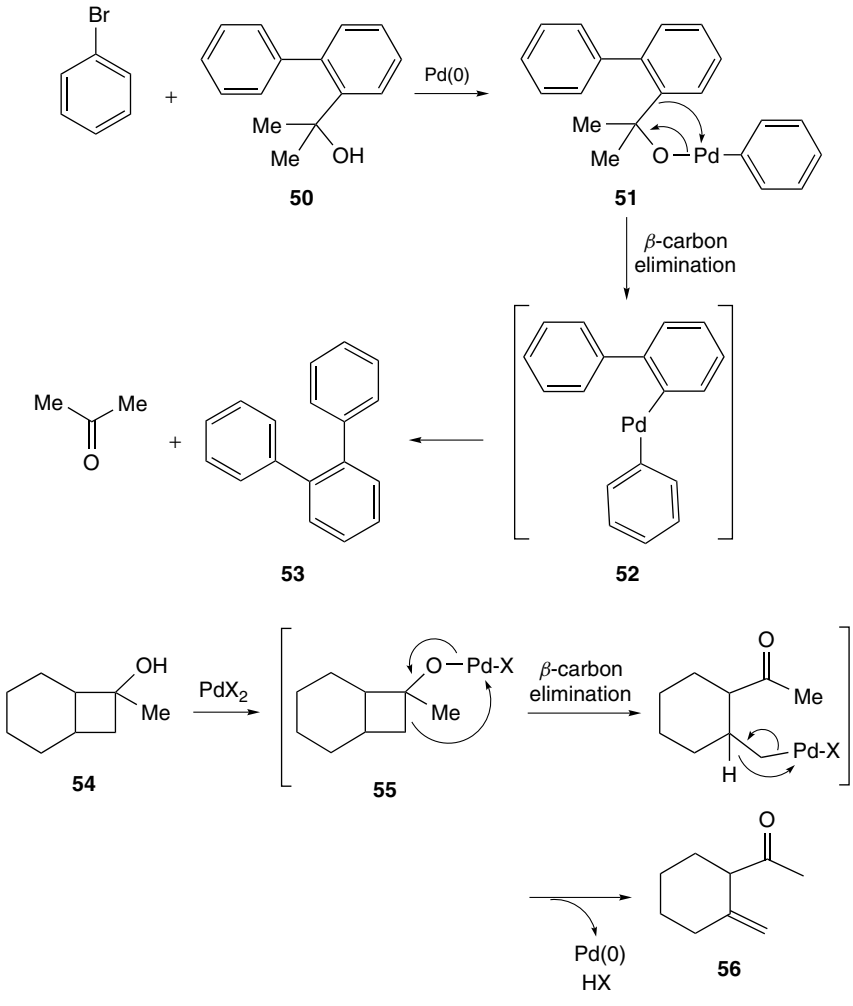


Elimination of β-carbon is less common, but its examples are increasing (see Chapter 3.8.2). β-Carbon elimination can be expressed by the following general scheme:



In the following, examples of β-carbon elimination when A = O are shown. The reaction is observed in the Pd-catalyzed reaction of *tert*-alcohols. Conversion of *tert*-alcohols to ketones occurs via their Pd-alkoxides **49** and the reaction can be understood by elimination of β-carbon. Fission of a carbon–carbon bond occurs. It should be noted that β-carbon elimination can be regarded as a reverse process of nucleophilic attack to the carbonyl group by R-Pd-X (see Chapter 3.7.2). As an example, Pd-catalyzed reaction of α,α-dimethylarylmethanol **50** with bromobenzene is explained by elimination of β-carbon of the arylpalladium alkoxide **51** to generate the diarylpalladium intermediate **52**. Its reductive elimination affords 2-phenylbiphenyl (**53**) and acetone [41]. Similarly, Pd(II)-promoted reaction of the cyclobutanol **54** to give the unsaturated ketone **56** can be understood by elimination of β-carbon from **55** and subsequent β-H elimination [42].

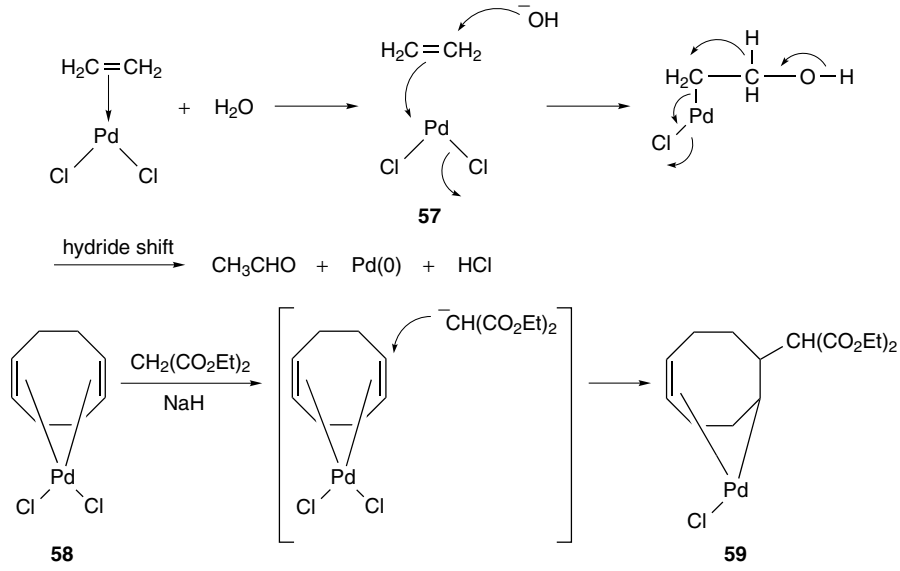




1.3.7 Electrophilic Attack by Organopalladium Species

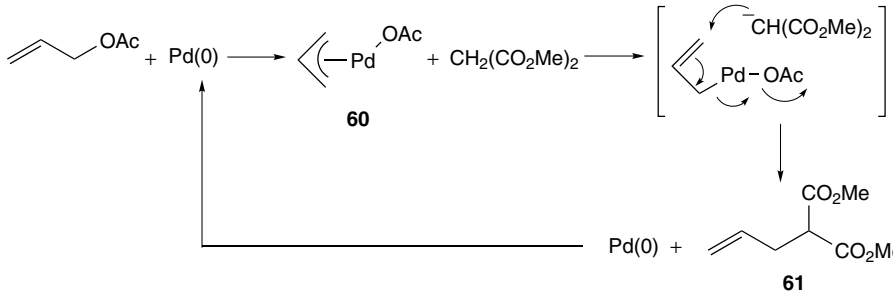
Many useful reactions which are entirely different from ordinary organic reactions can be achieved by using Pd complexes. Effect of the coordination is remarkable. Unsaturated organic compounds such as CO, alkenes and alkynes are rather unreactive towards nucleophiles because they are electron rich. However, their reactivity is inverted when these unsaturated molecules coordinate to electron deficient Pd. This is a noteworthy effect of the coordination. Reaction of nucleophiles with the coordinated unsaturated bonds is one of the most characteristic and useful reactions of Pd complexes. Particularly complexes having strong π-acceptor ligands typically CO or cationic complexes are highly electrophilic and accept nucleophiles. Mechanistically, some nucleophiles attack the ligand after coordination to the metal, and the process is understood as the insertion of the ligand. Also, direct attack of nucleophiles on the ligand is possible.

Various nucleophiles attack coordinated alkenes. Typically attack of the OH anion on ethylene coordinated to Pd(II), as shown by **57**, takes place in the Wacker process to afford acetaldehyde [43]. Also, the COD complex of $PdCl_2$ **58** was

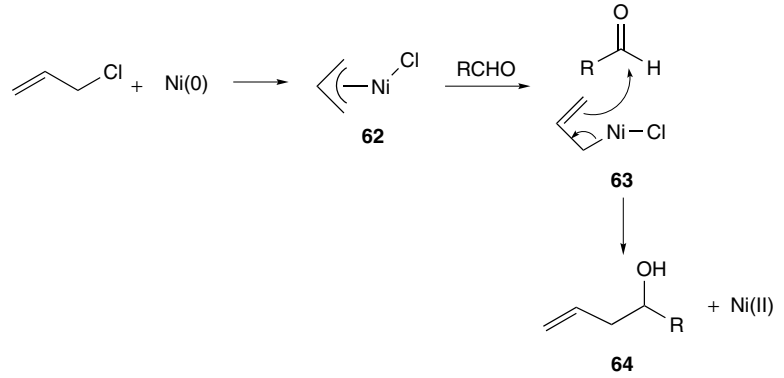


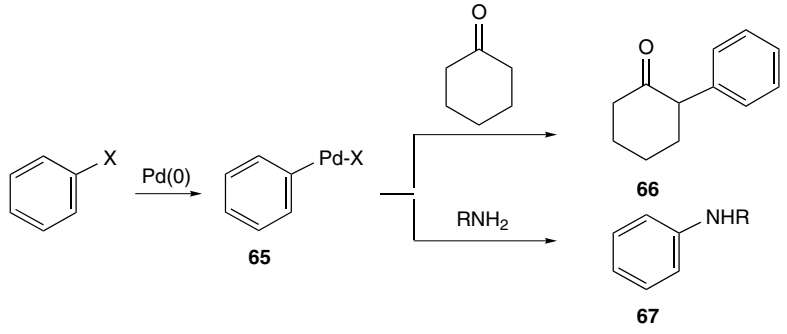
shown to be attacked by carbon nucleophiles such as malonate anion to give **59**. This reaction is the first example of carbopalladation of coordinated alkenes [44].

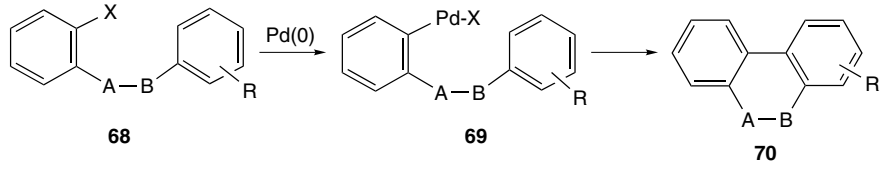
Attack of carbon nucleophiles such as malonate anion to π-allylpalladium **60** to give allylmalonate **61** is well-known [45]. Pd in the π-allyl complex **60** accepts two electrons by the nucleophilic attack, and is reduced to Pd(0) directly or indirectly. Generation of Pd(0) offers a chance to undergo oxidative addition again. The reduction of Pd(II) to Pd(0) is an essential step for catalytic cycles. Pd is a noble metal and Pd(0) is more stable than Pd(II). In this respect, Pd is very unique. In contrast, the attack of an electrophile such as aldehyde **63** on allyl compounds of Mg or Ni complex **62** proceeds to give homoallyl alcohol **64** and to generate oxidized metal ions Mg(II) or Ni(II), which cannot constitute catalytic cycles.



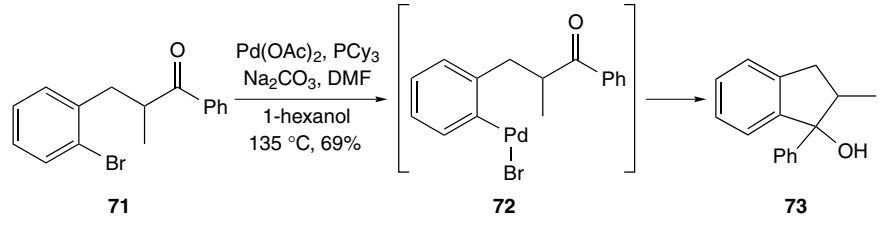
Recently Pd-catalyzed reactions of aryl halides, which can be formally understood as electrophilic attacks by arylpalladium halides **65,** are rapidly emerging. Arylation of cyclohexanone to afford 2-phenylcyclohexanone (**66**) (see Chapter 3.7.1) and formation of arylamines **67** (see Chapter 3.7.2) are typical examples. One explanation of intramolecular attack on an aromatic ring in **68** to form biaryl **70** is electrophilic attack of **69** on an aromatic ring, although the mechanism may not be so simple. A detailed discussion is given in Chapter 3.3.







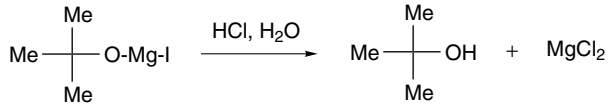
Recently Yamamoto reported Pd-catalyzed intramolecular nucleophilic addition of the arylpalladium bromide **72** formed from **71** to ketone to give the alcohol **73** using PCy_3 as a ligand and an excess of 1-hexanol. This is the first example of a Pd-catalyzed Grignard-type reaction [46].



1.3.8 Termination of Pd-Catalyzed or -Promoted Reactions and a Catalytic Cycle

Grignard reactions proceed via oxidative addition and insertion. The reaction product **75** is isolated after hydrolysis of the insertion product **74** with dilute aqueous HCl, giving $MgCl_2$, and it is practically impossible to reduce the generated Mg(II)

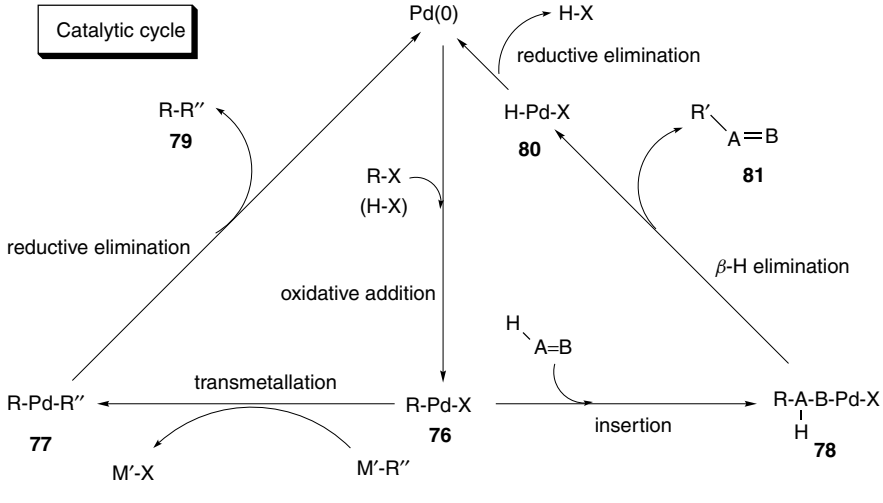
to Mg(0) *in situ*, and hence the Grignard reaction is stoichiometric. In other words, Mg(0) is oxidized to Mg(II) by the Grignard reaction. However, the reactions involving Pd(0) complexes proceed with a catalytic amount of Pd(0) compounds in many cases whenever they are attacked by nucleophiles.



74 **75**

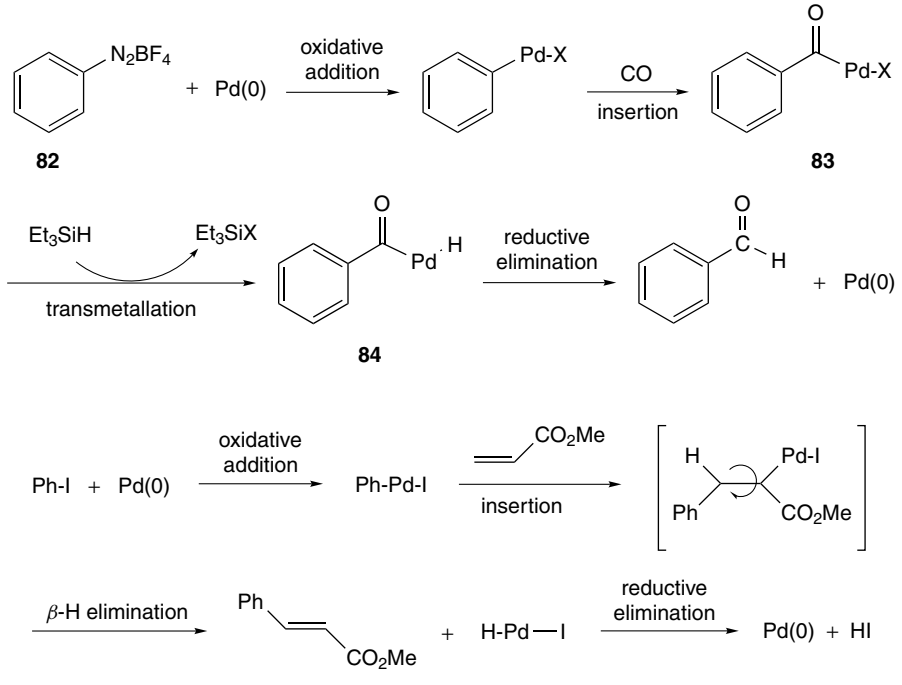
The catalytic reactions which can be carried out with a small amount of expensive Pd complexes is the most useful feature of synthetic reactions involving Pd complexes. In the catalytic reactions, an active catalytic species must be regenerated in the last step of the reactions. Reductive elimination and β-H elimination are two key reactions that regenerate the catalytic species, making the whole reaction catalytic.

As shown in the following general scheme, the catalytic cycle of the Pd(0) catalyst is understood by a combination of the aforementioned unit reactions. The oxidative addition of R-X affords **76** which undergoes either transmetallation to give **77** or insertion to generate **78**. The reductive elimination of the reaction product **79** from **77** occurs and regenerates Pd(0), which undergoes oxidative addition to afford **76** and starts the new catalytic cycle, then subsequent insertion gives **78** or transmetallation affords **77**. The β-H elimination of the product **81** from **78** gives H-Pd-X **80**, from which the Pd(0) catalytic species is formed. The Pd hydride **80** itself also serves as a catalytic species through insertion of alkenes. The ability of Pd to undergo facile shuttling between two oxidation states contributes to make the reactions catalytic.



As a typical example of the catalytic cycle, phenyldiazonium salt **82** undergoes oxidative addition, followed by CO insertion to afford the acylpalladium intermediate **83**. Then transmetallation with triethylsilane generates **84** and benzaldehyde

is obtained by reductive elimination [47]. Another example is the reaction of iodobenzene with acrylate to give cinnamate via oxidative addition, insertion and β-H elimination (Heck reaction).



1.3.9 Reactions Involving Pd(II) Compounds and Pd(0) Complexes

Organic reactions involving Pd are classified into oxidative reactions with Pd(II) salts and catalytic reactions with Pd(0) complexes. Pd(II) salts [$PdCl_2$, $Pd(OAc)_2$] are unique oxidizing or dehydrogenating reagents. The reactions promoted by

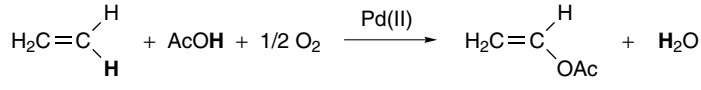
Oxidative (dehydrogenative) reactions with Pd(II) compounds

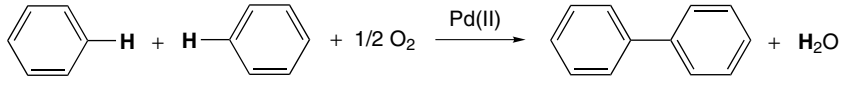
$$\text{A-H} + \text{B-H} + PdX_2 \longrightarrow \text{A-B} + Pd(0) + 2\,HX$$

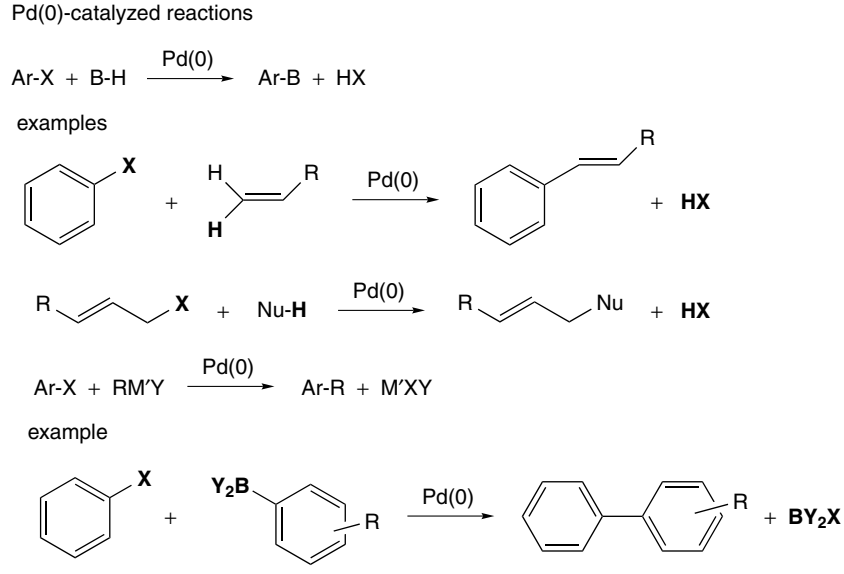
$$Pd(0) + 2\,HX + 1/2\,O_2 \xrightarrow{[OX]} PdX_2 + H_2O$$

$$\text{A-H} + \text{B-H} + 1/2\,O_2 \xrightarrow[[OX]]{PdX_2} \text{A-B} + H_2O$$

examples







Pd(II) can be expressed by the following general schemes. As a whole, two hydrogens are abstracted from two substrates A-H and B-H, generating Pd(0) and the product A-B. This reaction is stoichiometric with Pd(II), but the reaction becomes catalytic when Pd(0) is oxidized *in situ* to Pd(II) with appropriate oxidants (OX), and the whole reaction can be summarized by a third equation. For example, formation of vinyl acetate from ethylene and oxidative coupling of benzene can be understood formally as dehydrogenation reactions. These oxidative reactions using Pd(II) are considered in Chapter 2.

The Pd(0)-catalyzed reactions of Ar-X and B-H (or B-Y) can be expressed by the following general equations, which involve no oxidation. The Mizoroki–Heck reaction, allylation of nucleophiles, and cross-couplings are typical reactions of this type. They are treated in Chapters 3–8.

A clear understanding that these two types of reactions involving Pd(II) and Pd(0) are mechanistically quite different is required before studying organopalladium chemistry.

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Books[3]

A number of books and monographs treating organopalladium chemistry have been published as listed below. Particularly, there is an excellent encyclopedia of organopalladium chemistry, edited by E. Negishi, which was published in 2002 [9]. The book is 3279 pages long, covering all reactions either catalyzed or promoted by Pd(0) and Pd(II) compounds reported before 2000 and including ample experimental data and references. The Handbook is not only useful but also monumental in organopalladium chemistry.

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3 These book references are not cited in the text.

Chapter 2

Oxidative Reactions with Pd(II) Compounds

2.1 Introduction

Pd(II) salts, typically $PdCl_2$ and $Pd(OAc)_2$, are unique oxidizing reagents, and there are many useful oxidation reactions (dehydrogenation reactions) specific to Pd(II) salts. After the oxidation of organic substrates with Pd(II) is completed, Pd(II) is reduced to Pd(0). If a stoichiometric amount of expensive Pd(II) salts is consumed, the reaction can not be a truly useful synthetic method. It is possible to make the reaction catalytic with respect to Pd(II) by oxidizing Pd(0) efficiently *in situ* to Pd(II) with some oxidants. There are several ways to regenerate Pd(II) *in situ*. The first example of the oxidation of an organic compound catalyzed by Pd(II) was achieved in 1959 by the Wacker process [1]. This is a commercial process to oxidize ethylene to acetaldehyde using $PdCl_2$ and $CuCl_2$ as catalysts in aqueous HCl. The process involves three unit reactions (Equations 2.1–2.3). The essence of the Wacker process is the invention of an ingenious catalytic cycle, in which reduced Pd(0) is reoxidized *in situ* to Pd(II) with $CuCl_2$ (Equation 2.2). It is ingenious because the oxidation of Pd(0), a noble metal, with $CuCl_2$, a base metal salt, is expected to be very difficult. The CuCl is easily reoxidized to $CuCl_2$ with oxygen (Equation 2.3).

$$CH_2{=}CH_2 + H_2O + PdCl_2 \longrightarrow CH_3CHO + 2\,HCl + Pd(0) \quad (2.1)$$

$$Pd(0) + 2\,CuCl_2 \longrightarrow PdCl_2 + 2\,CuCl \quad (2.2)$$

$$2\,CuCl + 2\,HCl + 1/2\,O_2 \longrightarrow 2\,CuCl_2 + H_2O \quad (2.3)$$

$$CH_2{=}CH_2 + 1/2\,O_2 \xrightarrow[CuCl_2]{PdCl_2} CH_3CHO \quad (2.4)$$

In this way, ethylene (or other organic compounds) is oxidized indirectly with oxygen without consuming $PdCl_2$ and $CuCl_2$ by the combination of these redox reactions. The catalytic oxidation of organic compounds with Pd(II) and an oxidant can be regarded formally as a dehydrogenation reaction as summarized in the schemes shown in Equations (2.5–2.7). In this dehydrogenation reaction, two hydrogens are abstracted from ethylene and water in the Wacker reaction

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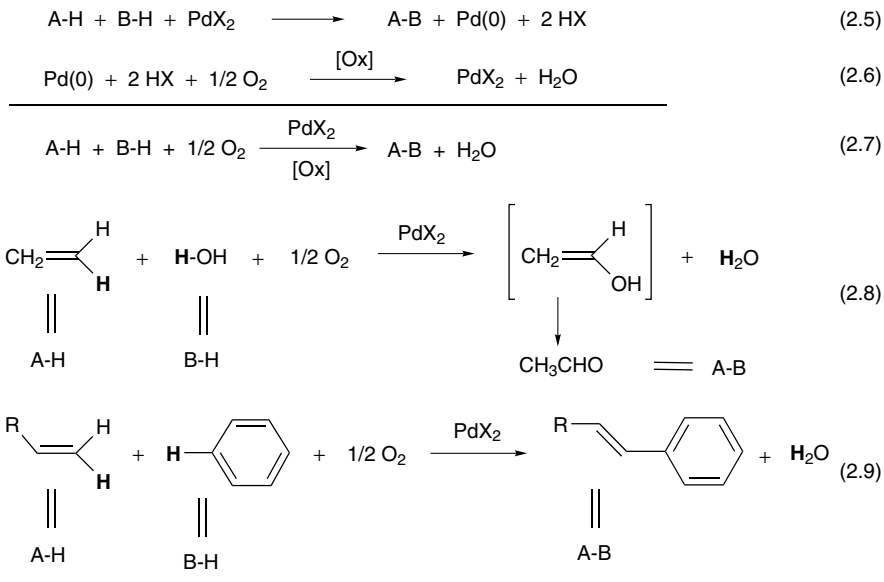
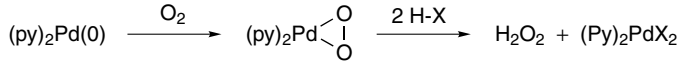


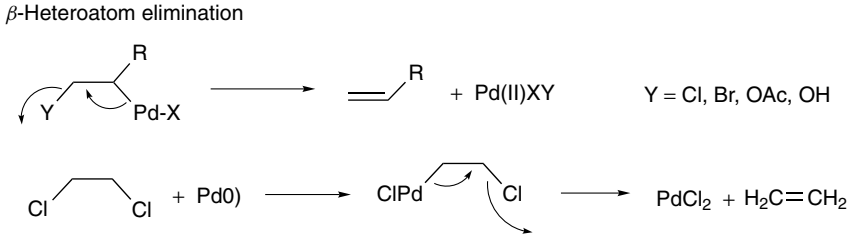
(Equation 2.8). Similarly oxidative coupling of an alkene with benzene can be understood as the dehydrogenation reaction (Equation 2.9).

In addition to $CuCl_2$, several inorganic compounds such as $Cu(OAc)_2$, HNO_3 and MnO_2 are used as oxidants of Pd(0). Also benzoquinone (BQ), hydrogen peroxide and some organic peroxides are used. Alkyl nitrites are unique oxidants which are used in some industrial processes [2]. Efficient reoxidation of Pd(0) in some oxidation reactions with O_2 alone without other reoxidants is possible in DMSO [3–5]. It was found that Pd(0) species formed *in situ* from Pd(II) in the presence of O_2 are stabilized by DMSO as a ligand and easily oxidized to Pd(II) with oxygen [6]. DMSO is a favorable ligand and ligand-promoted direct oxidation of Pd(0) with oxygen takes place [7]. $Pd(OAc)_2$–pyridine (1 : 2) is a simple and efficient catalyst system, and some oxidative reactions proceed under oxygen without using other oxidants [8]. The oxidation of Pd(0) is explained by the following mechanism [9]. Oxygenation of a pyridine–Pd(0) complex produces the peroxopalladium(II) complex, which is converted to a Pd(II) complex and hydrogen peroxide by protonation.

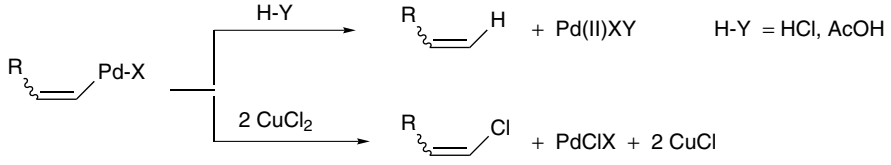


An important Pd(II)-generation step in Pd(II)-catalyzed reactions is the elimination of heteroatom groups such as Cl, Br, OAc and OH at β-position to Pd, and Pd(II) species are generated after the elimination. Elimination of heteroatom groups is faster than that of hydrogen. No reoxidant is required for this efficient catalytic reaction. Based on this reaction, 1,2-dichloro- and dibromoethane derivatives [10], α-halo ketones such as chloroacetone and desyl chloride are used for Pd(II) generation [11,12].

Another important Pd(II)-generation step is protonolysis with acids. For example, alkenylpalladium intermediates formed by palladation of alkynes with



Pd(II) are living species, because there is no possibility of β-H elimination. So Pd(II)X_2 is generated from these Pd intermediates by protonolysis with HX, or oxidative halogenation with CuX_2. In such a case, the reaction proceeds with a catalytic amount of Pd(II) salt without reoxidants.



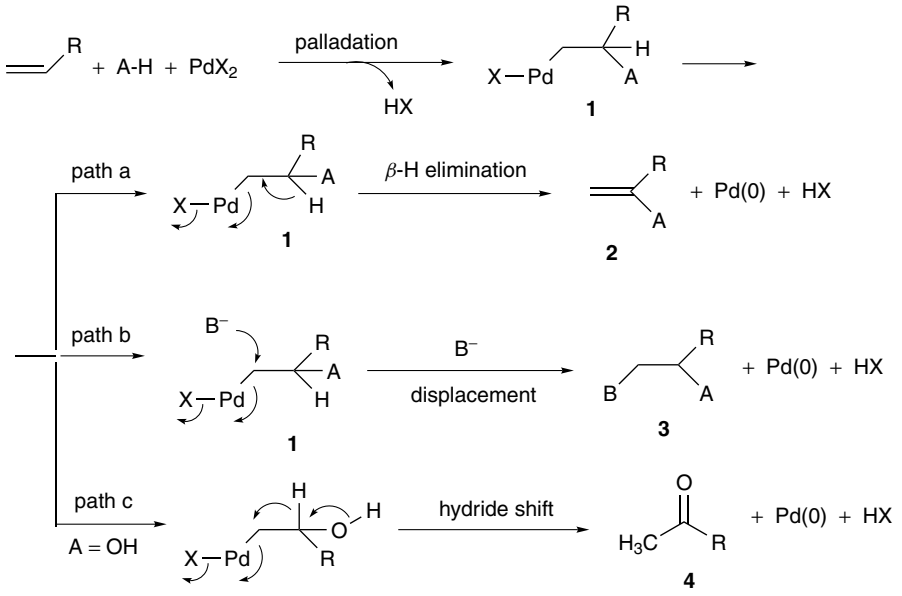
One important method for the oxidation reaction using Pd(II) is a gas phase reaction using a solid Pd catalyst supported on active carbon or alumina. Actually vinyl acetate and allyl acetate are produced commercially in a gas phase by using the supported Pd catalyst. It is assumed that Pd(0) is oxidized efficiently to Pd(II) with oxygen on the surface of the support.

Oxidative reactions of various organic compounds with Pd(II) are surveyed by further subdivisions based on substrates.

2.2 Reactions of Alkenes

2.2.1 Introduction

Alkenes coordinate to Pd(II) compounds to form π-complexes. Roughly speaking, a decrease in electron density of alkenes by the coordination to electrophilic Pd(II) permits attack by various nucleophiles to the coordinated alkenes. In contrast, electrophilic attack is commonly observed with uncomplexed alkenes. Pd(II) is highly electrophilic and behaves as a very expensive and selective proton equivalent toward alkenes. The attack of nucleophiles with concomitant formation of a carbon—palladium σ-bond **1** is called palladation of alkenes. This reaction is similar to the mercuration reaction. However, unlike the mercuration products, which are stable and isolable, the product **1** of the palladation is usually unstable and undergoes rapid decomposition. The palladation reaction is followed by three reactions. Pd-X in **1** is a good leaving group. The β-H elimination from **1** to form the vinyl compounds **2** is one reaction path, resulting in the nucleophilic substitution of olefinic proton (path a). When the displacement of Pd-X in **1** with another nucleophile takes place, the nucleophilic addition to alkenes occurs to give **3** (path b). Another possibility is 1,2-hydride shift. When the nucleophile is the OH anion, the carbonyl group **4** is generated via hydride shift (path c). Depending on



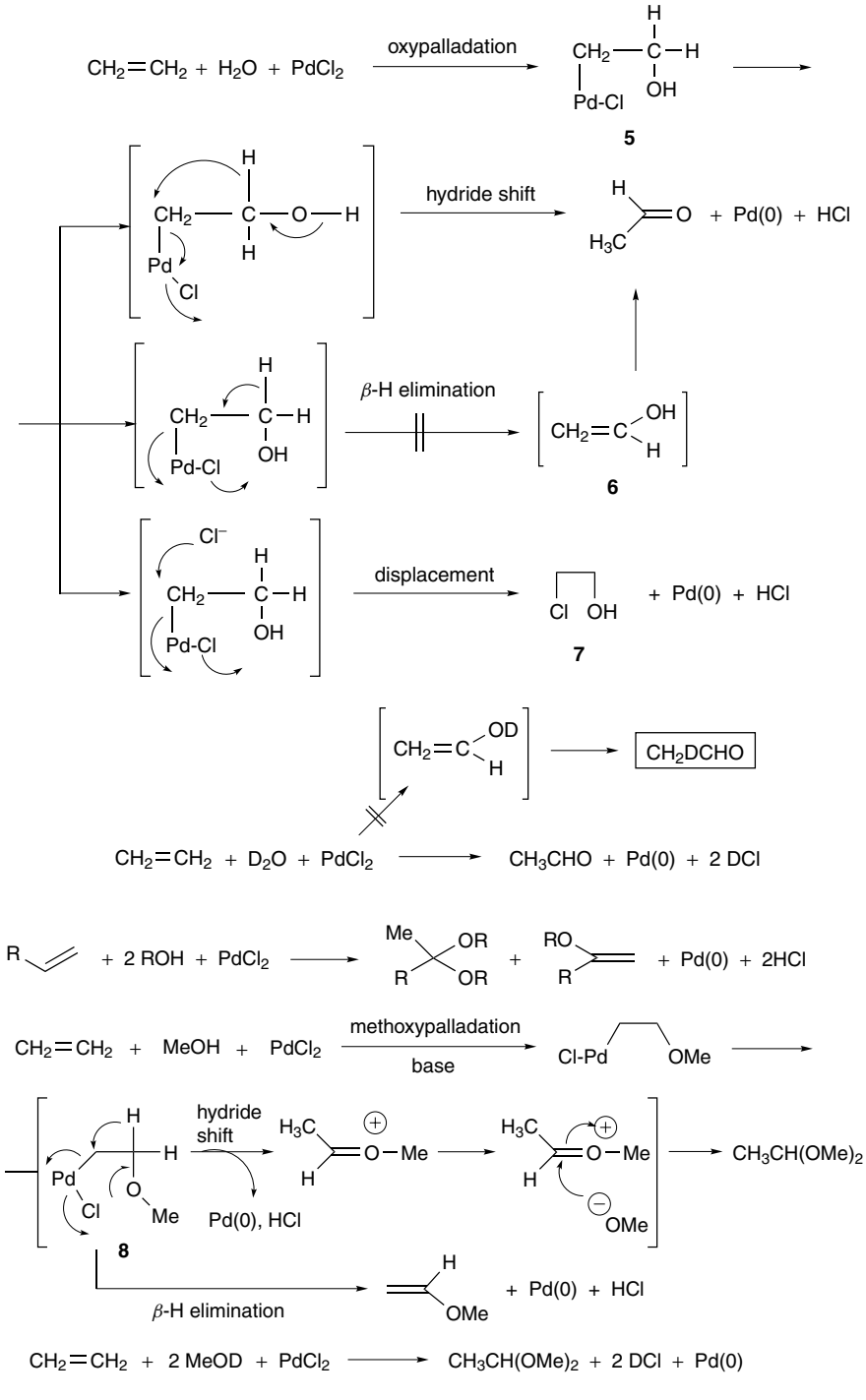
AH, BH = nucleophiles, H_2O, ROH, RCO_2H, RNH_2, CH_2E_2
(E = electron-withdrawing group)

reactants and conditions, either nucleophilic substitution of alkenes or nucleophilic addition to alkenes takes place with or without hydride shift.

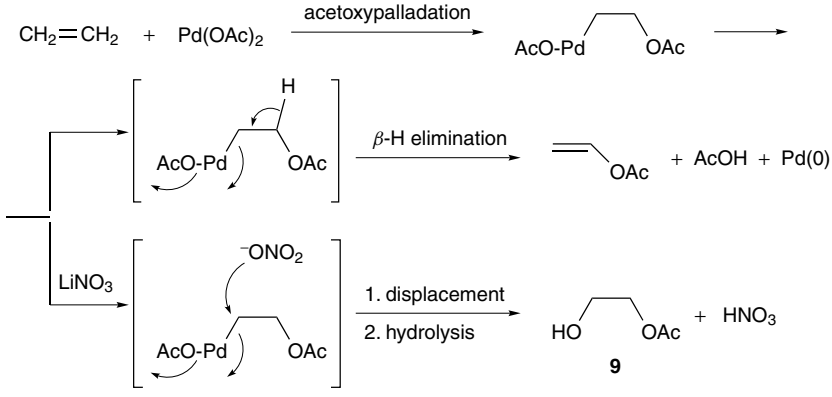
The reactions of water, alcohols and carboxylic acids with alkenes are explained by these three reaction paths. Formation of acetaldehyde from ethylene, water and $PdCl_2$ is understood by the sequence of hydroxypalladation to form **5**, followed by hydride shift. It has been confirmed that no incorporation of deuterium occurs by the reaction of ethylene with $PdCl_2$ carried out in D_2O, and the four hydrogens in ethylene are retained in acetaldehyde, indicating that hydride shift occurs (path c) [1]. Therefore, free vinyl alcohol (**6**), expected to be formed by β-H elimination (path a), is not an intermediate (path c). In the presence of LiCl, 2-chloroethanol (**7**) is obtained by path b.

Oxidation of ethylene in alcohol with $PdCl_2$ in the presence of a base gives the acetal of acetaldehyde as a major product and vinyl ether as a minor product. Methoxypalladation is the first step. Then hydride shift is followed by attack of methoxy anion to form the acetal of acetaldehyde. No deuterium incorporation is observed in the acetal formed from ethylene and MeOD, indicating that the hydride shift takes place as shown by **8** (path c). Formation of methyl vinyl ether can be understood by β-H elimination. The β-H elimination is a main path with higher alkenes.

Formation of vinyl acetate by the reaction of ethylene with $Pd(OAc)_2$ can be understood by the acetoxypalladation and β-H elimination (path a). No hydride shift occurs because the acetoxy group is electron-attracting. In addition, ethylene glycol monoacetate (**9**) is formed as a nucleophilic addition product in the presence of nitrate anion (path b) [13]. Formation of glycol monoacetate is explained by the displacement of Pd-OAc with a nitrate anion, followed by hydrolysis of the nitrate ester.



Typical nucleophiles known to react with the coordinated alkenes are water, alcohols, carboxylic acids, ammonia, amines, enamines and active methylene compounds [14]. The intramolecular version is particularly useful for syntheses of various heterocyclic compounds [15,16]. CO and aromatics also react with alkenes.



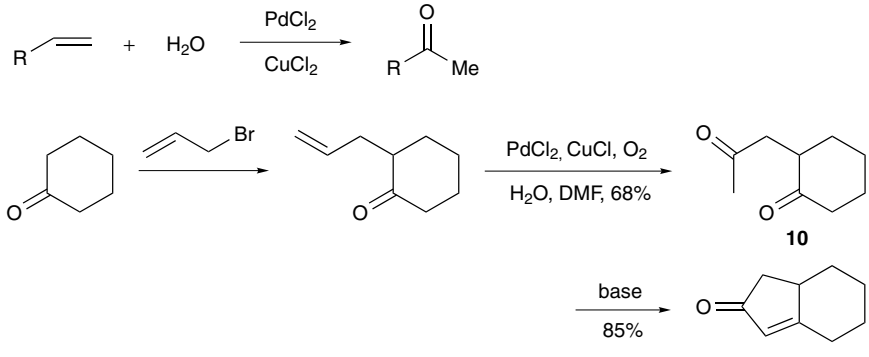
2.2.2 Reaction with Water

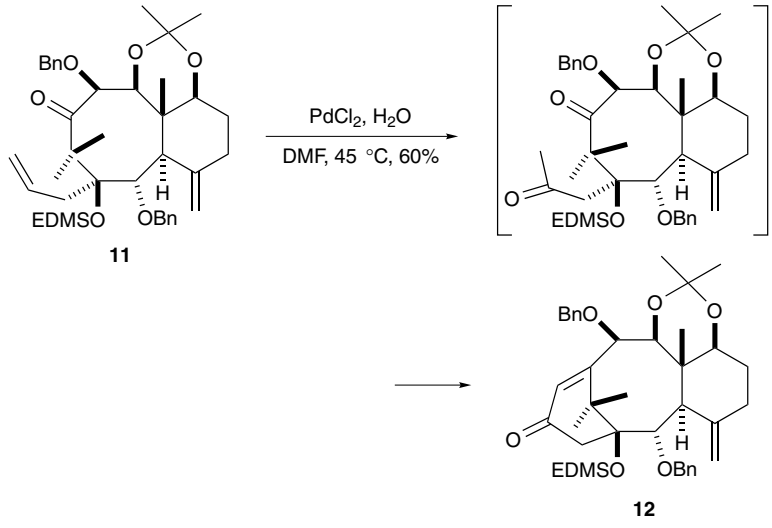
Formation of acetaldehyde and metallic Pd by passing ethylene into an aqueous solution of $PdCl_2$ was reported by Phillips in 1894 [17] and used for a quantitative analysis of Pd(II) [18]. The reaction was highlighted after the industrial process of acetaldehyde production from ethylene based on this reaction had been developed [1].

The Wacker process is carried out in aqueous HCl solution and low-boiling acetaldehyde is removed continuously by distillation. However, the oxidation of higher alkenes is carried out in organic solvents which can mix both alkenes and water. DMF is widely used as a solvent for this purpose. The oxidation is a useful synthetic method of producing ketones from alkenes and is used extensively [19]. Some organic compounds are used as stoichiometric oxidants. Benzoquinone is most widely used.

The oxidation of higher alkenes in organic solvents proceeds under almost neutral conditions, and hence many functional groups such as ester or lactone, sulfonate, aldehyde, acetal and MOM ether are tolerated.

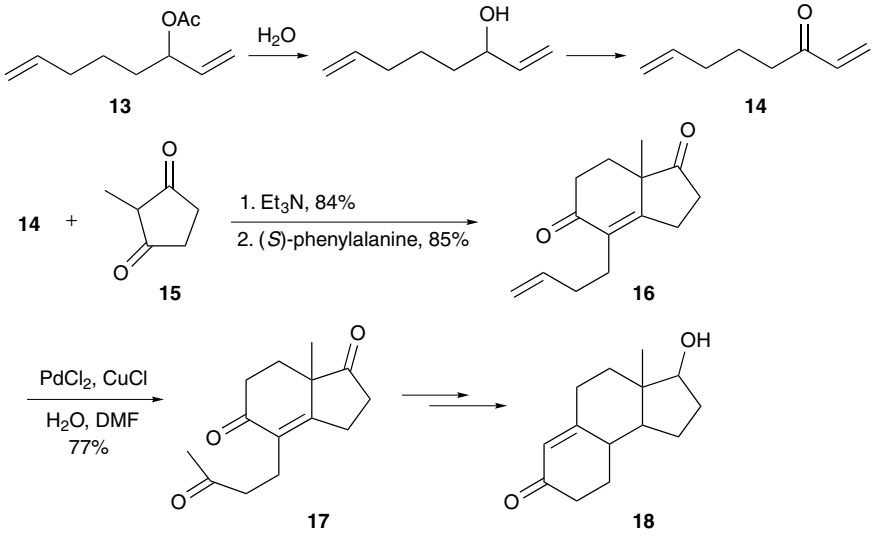
The attack of OH obeys the Markovnikov rule. Higher alkenes are oxidized to ketones and this unique oxidation of alkenes has extensive synthetic applications [19]. The oxidation of terminal alkenes affords methyl ketones, which have widespread uses in organic synthesis. Based on this reaction, the terminal alkenes, which are stable to acids, bases and nucleophiles, can be regarded as masked methyl ketones. Several 1,4-dicarbonyl compounds are prepared based on this oxidation. Typically, the 1,4-diketone **10** can be prepared by the allylation

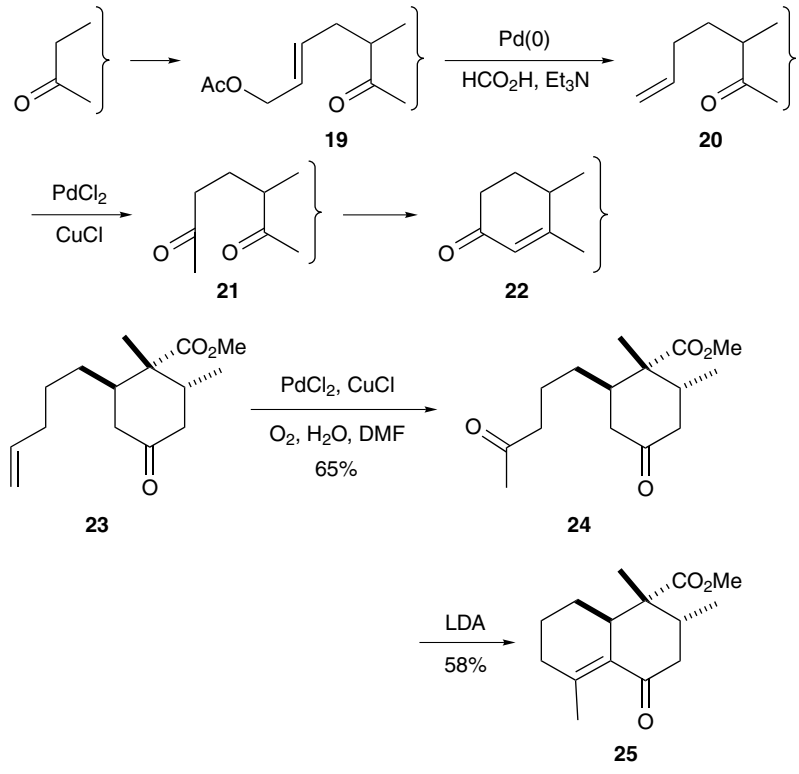




of ketones followed by oxidation [20]. The reaction was successfully applied to a multifunctionalized complex skeleton of a taxoid. Oxidation of the allyl group in **11** is followed by *in situ* aldol condensation to afford the cyclohexenone **12** in 60 % yield [21].

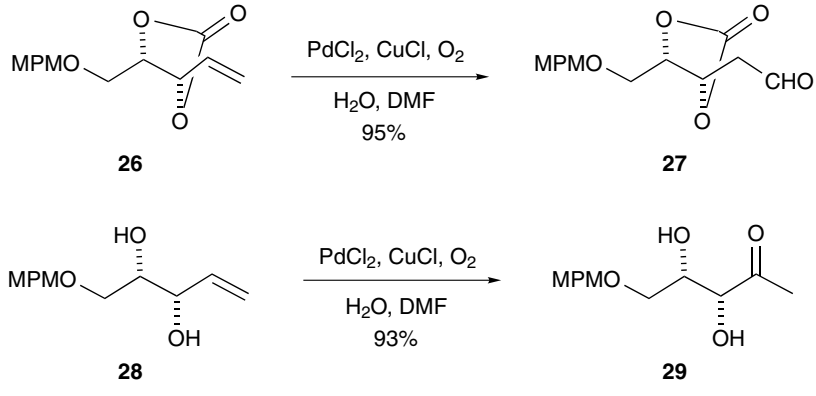
3-Acetoxy-1,7-octadiene (**13**), obtained by Pd-catalyzed telomerization of butadiene (see Chapter 5.1), is converted to 1,7-octadien-3-one (**14**) by hydrolysis and oxidation. The compound **14** is a useful bis-annulation reagent. Bis-annulation to form two fused six-membered ketones is a synthetic application of the enone **14** [22]. The Michael addition of 2-methyl-1,3-cyclopentanedione (**15**) to **14** and asymmetric aldol condensation using (*S*)-phenylalanine afford the optically active diketone **16**. The terminal double bond is oxidized with $PdCl_2$-CuCl-O_2 to give the methyl ketone **17** (76 % optical purity) in 77 % yield. Finally reduction of the double bond and aldol condensation produce the important intermediate **18** of steroid synthesis in optically pure form after recrystallization several times.



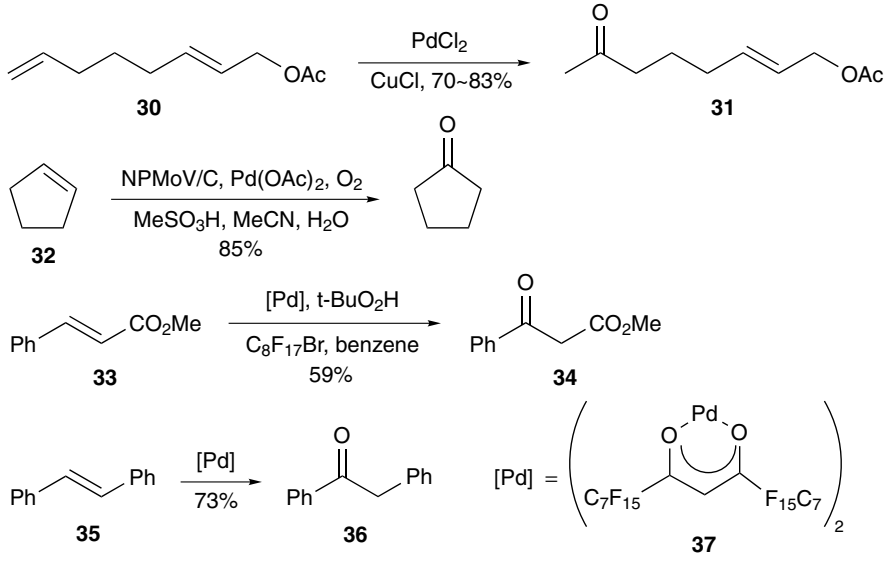


The 1,5-diketone **21** is prepared by 3-butenylation of ketones to give **20** via Pd-catalyzed hydrogenolysis of the allylic acetate **19**, followed by Pd-catalyzed oxidation, and is used for annulation to form the cyclohexenone **22** [19]. In this method, the 3-butenyl group is a masked methyl vinyl ketone. Preparation of the 1,7-diketone **24** was performed by oxidation of **23**, and applied to the synthesis of dysidiolide (**25**) [23].

In some cases where there is a neighboring group participation, aldehydes are formed from terminal olefins. The aldehyde **27** was obtained cleanly by participation of the cyclic carbonate of allylic diol **26**, but the normal oxidation to afford the methyl ketone **29** occurred with the unprotected diol **28** [24].



The oxidation of simple internal alkenes is very slow. Clean selective oxidation of the terminal double bond in **30** in the presence of an internal double bond to yield **31** is possible under normal conditions [25]. Oxidation of cyclic alkenes is difficult, but can be carried out under selected conditions. Addition of strong mineral acids such as $HClO_4$, H_2SO_4 and HBF_4 accelerates the oxidation of cyclohexene and cyclopentene [26]. Heteropoly acids (NPMoV) supported on carbon and $Pd(OAc)_2$ are good catalyst systems to oxidize cyclopentene (**32**) in the presence of CH_3SO_3H to cycloptentanone [27]. Internal double bonds in methyl cinnamate (**33**) and stilbene (**35**) were oxidized to **34** and **36** using Pd(II) perfluorinated bis(diketonate) complex **37** as a catalyst in benzene using *t*-butyl hydroperoxide in fluorous biphasic system, which facilitates the isolation of products from the catalyst [28].

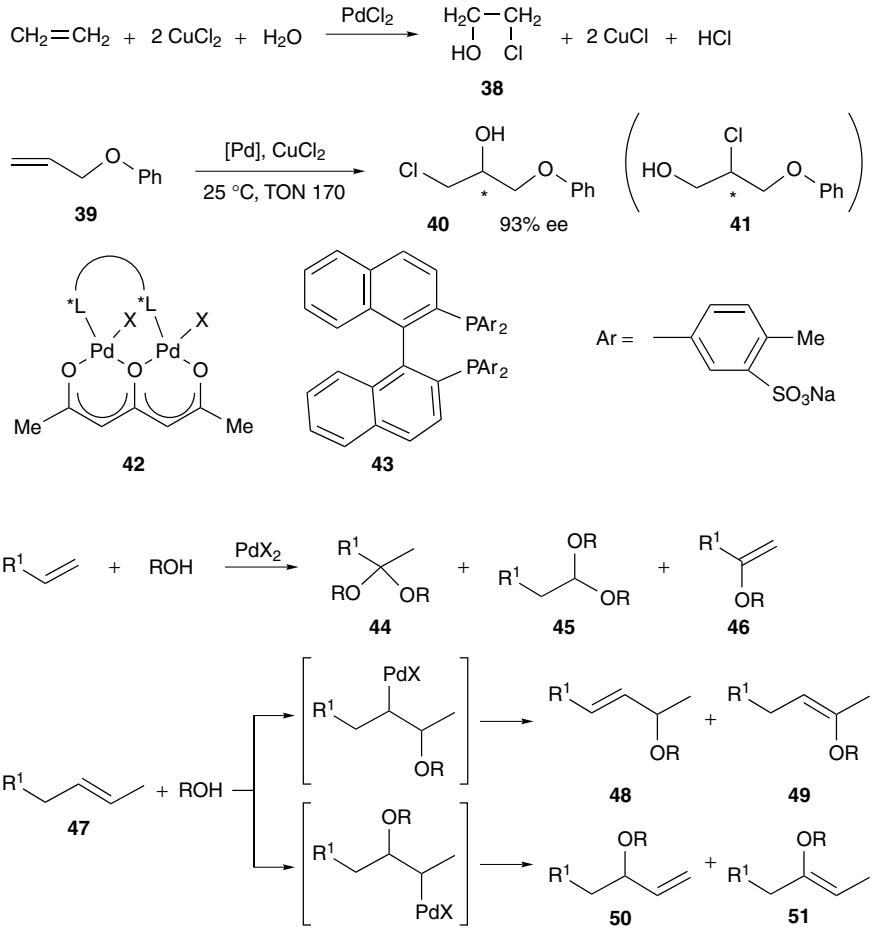


Ethylene chlorohydrin (**38**) is formed in the Wacker process as a byproduct. Chlorohydrins are obtained as main products when $PdCl_3(pyridine)^-$ is used [29]. The optically active chlorohydrin **40** with high ee was obtained without forming the regioisomer **41** from allyl phenyl ether (**39**) and other substituted alkenes when the bimetallic Pd complex **42** coordinated by water soluble chiral BINAP-based ligand **43** (**II-9**) was used [30].

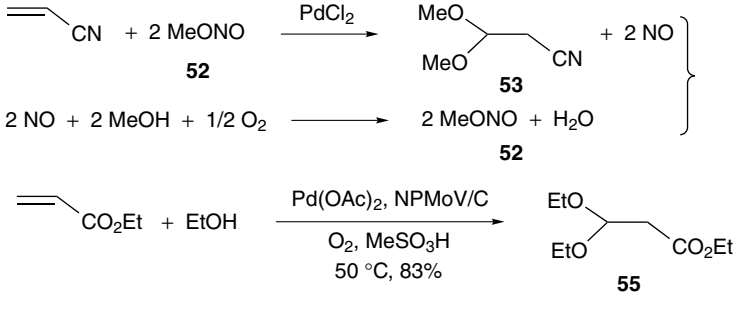
2.2.3 Reactions with Alcohols and Phenols

Oxidation of ethylene in alcohol with $PdCl_2$ in the presence of a base gives acetal and vinyl ether. Reaction of terminal alkenes in alcohols affords regioisomers of the acetals **44** and **45** and vinyl ethers **46** depending on the structure of the alkenes. Internal alkenes **47** and alcohols give allylic ethers **48** and **50** and vinyl ethers **49** and **51** depending on which hydrogen is eliminated.

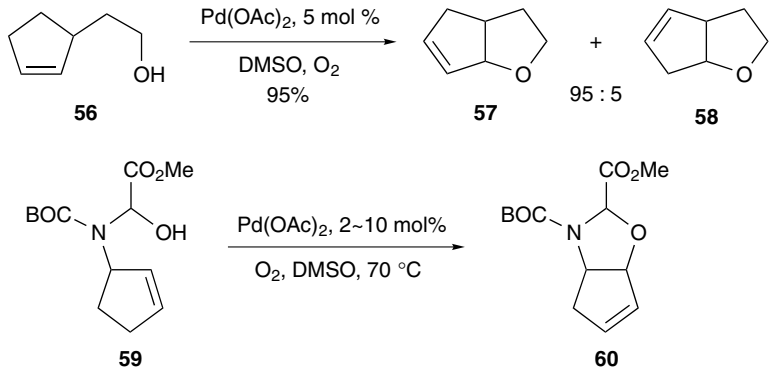
Oxidation of terminal alkenes bearing an EWG in alcohols or ethylene glycol affords acetals of aldehydes chemoselectively. 3,3-Dimethoxypropionitrile (**53**) is produced commercially in MeOH from acrylonitrile by use of methyl nitrite (**52**) as



a unique reoxidant of Pd(0). Methyl nitrite (**52**) is regenerated by oxidation of NO with oxygen in MeOH. Methyl nitrite is a gas, which can be separated easily from the water formed by the oxidation [2]. Ethyl acrylate was converted to the terminal acetal **55** in high yield using $Pd(OAc)_2$, combined with molybdovanadophosphate (NPMoV), supported on carbon, under oxygen atmosphere [31].

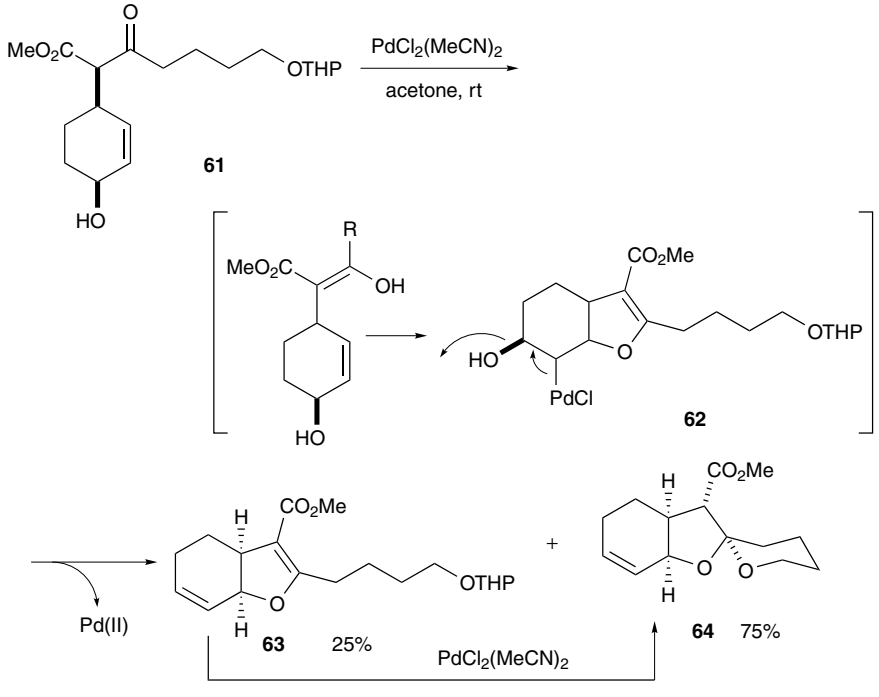


$Pd(OAc)_2$-catalyzed cyclization of **56** gave the tetrahydrofurans **57** and **58** using molecular oxygen as reoxidant in DMSO [32]. Formation of the oxazole **60** from



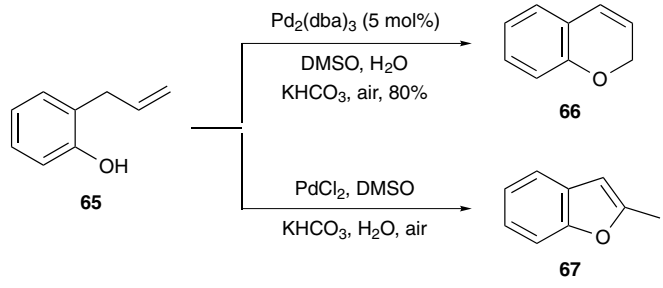
59 was carried out with a catalytic amount of $Pd(OAc)_2$ in DMSO under oxygen (1 atm) [6].

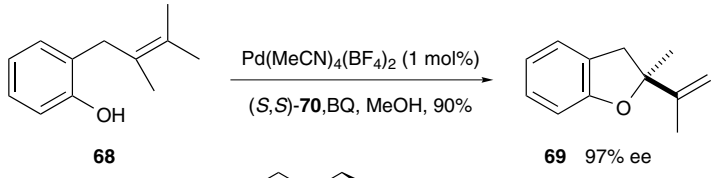
A reaction of unsaturated diols, in which one of the OH groups is allylic, offers an example of elimination of β-heteroatom (in this case OH) and generation of Pd(II). For example, in the cyclization of the 2-cyclohexenol bearing the β-keto ester side chain **61**, the enolate undergoes oxypalladation to form **62**, and subsequent elimination of β-OH with PdCl in **62** gave the dihydrofuran **63** and the tricyclic spiroacetal **64** with generation of Pd(II) in one-pot using 5 mol% $PdCl_2$ without reoxidant [33].

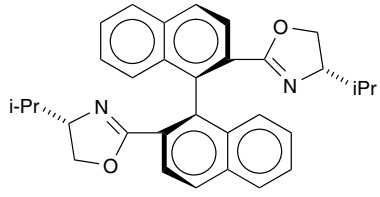


A phenolic oxygen participates in facile oxypalladation [16]. Different chemoselectivity is observed depending on the catalytic species. The 2H-1-benzopyran **66** was formed cleanly from 2-allylphenol (**65**) by *endo* cyclization with $Pd_2(dba)_3$ or

$Pd(OAc)_2$, but the benzofuran **67** was obtained by *exo* cyclization with $PdCl_2$ [34]. Catalytic asymmetric cyclization of 2-(2,3-dimethyl-2-butenyl)phenol (**68**) using the binaphthyl-based chiral ligand **70**, called (*S*,*S*)-ip-boxax afforded the furan **69** with high ee (97 %) [35].

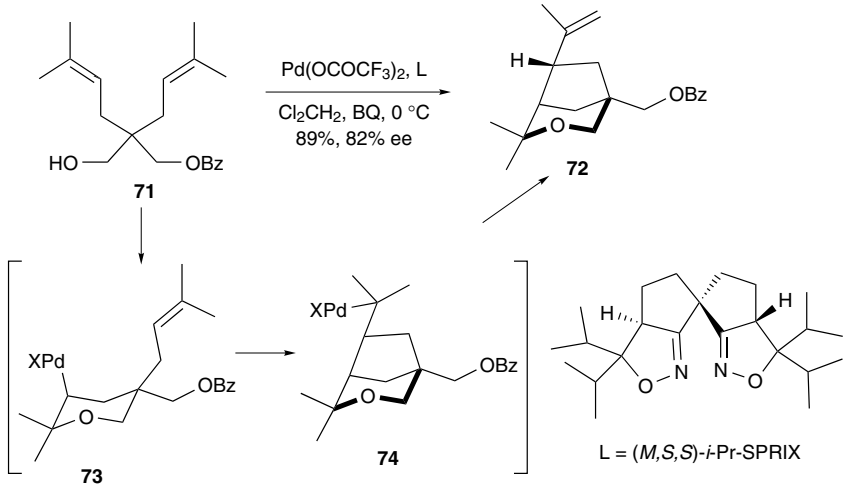






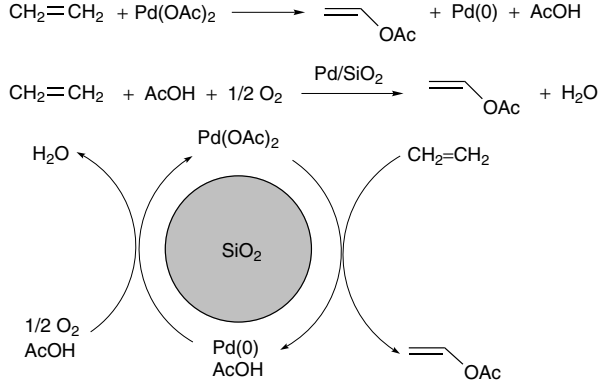
(*S*,*S*)-**70**

Asymmetric domino cyclization of the unsaturated alcohol **71** proceeded smoothly to give the bicyclic compound **72** with 82 % ee in 89 % yield as a single diastereomer using a spiro bis(oxazoline) ligand which has a chiral spiro skeleton and two oxazoline rings. The reaction proceeds via the formation of **73** and **74** as oxypalladation products. BQ was used as a reoxidant [36].



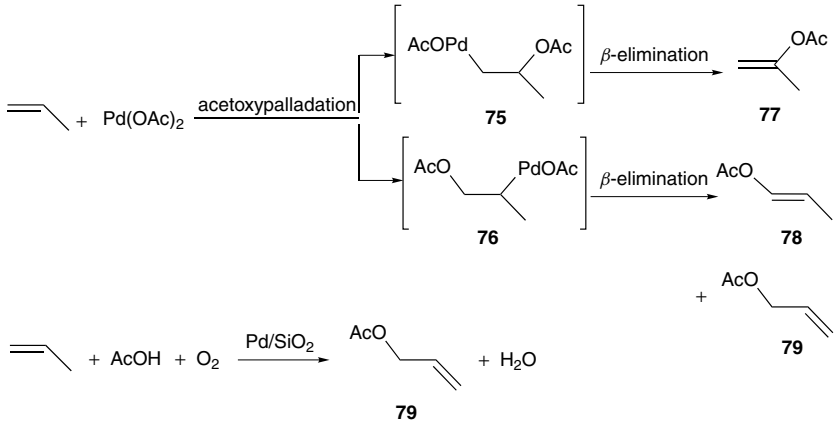
2.2.4 Reactions with Carboxylic Acids

Formation of vinyl acetate by the reaction of ethylene with $Pd(OAc)_2$ via acetoxypalladation of ethylene and β-H elimination was discovered by Moiseev in 1960 [37]. Attempted industrial production of vinyl acetate from ethylene and AcOH using the Pd(II) and Cu(II) redox system in a liquid phase was abandoned due to corrosion of reactors by AcOH. Instead, an interesting commercial process in the gas phase using a supported Pd catalyst was developed by Kuraray in Japan [38]. At present, vinyl acetate is produced commercially from ethylene, AcOH and O_2 in the gas phase using Pd supported on silica or alumina as a catalyst. It is assumed that rapid conversion of Pd(0) to $Pd(OAc)_2$ with AcOH and O_2 is repeated efficiently on the surface of the support at high temperature. Discovery of efficient conversion of Pd(0) to Pd(II) on the surface of the support is a big technical innovation and is applied to other processes.



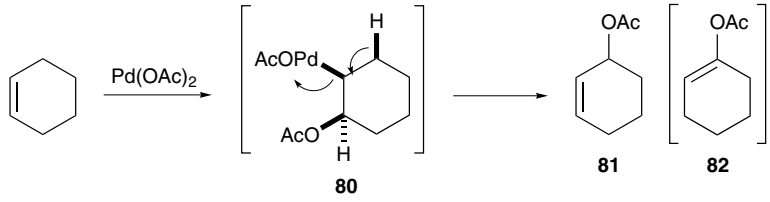
1,2-Dioxygenation by nucleophilic addition to alkenes takes place in the presence of the nitrate anion. The reaction of ethylene with $Pd(OAc)_2$ in the presence of $LiNO_3$ affords ethylene glycol monoacetate (**9**) [13].

From higher alkenes, three kinds of products, namely alkenyl acetates, allylic acetates and dioxygenated products, are obtained. Reaction of propylene gives two propenyl acetates **77** and **78** and allyl acetate (**79**) by acetoxypalladation to form two intermediates **75** and **76**, followed by elimination of different β-hydrogens.

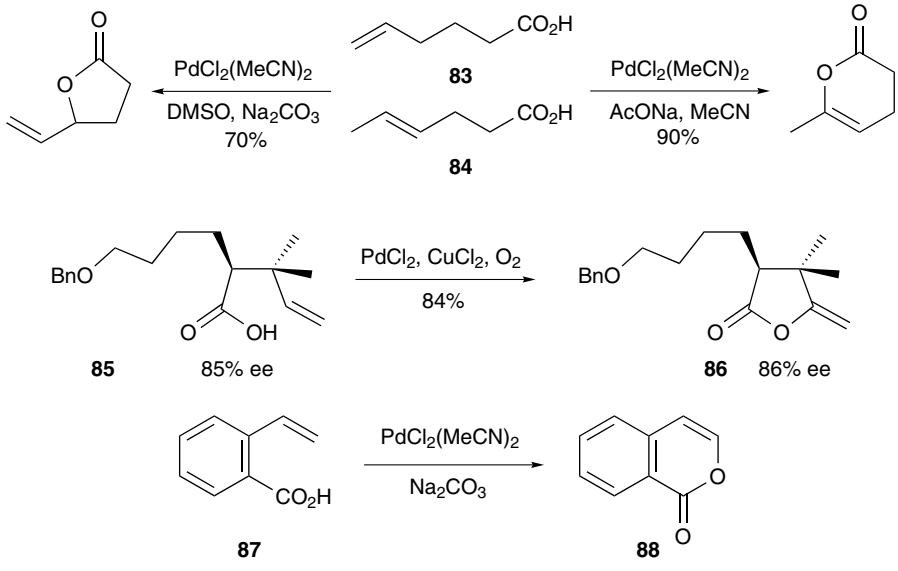


The chemoselective formation of allyl acetate (**79**) by a gas phase reaction using a supported Pd catalyst has been developed as a commercial process by Showadenko Ltd in Japan.

The oxidation of cycloalkenes to cyclic ketones with $PdCl_2$ is difficult under usual conditions, but allylic oxidation proceeds smoothly. Reaction of cyclohexene with $Pd(OAc)_2$ gives 3-acetoxycyclohexene (**81**); 1-acetoxycyclohexene (**82**) is not formed, because no β-H *syn* to Pd is available on the acetoxy-bearing carbon, and *syn* β-H elimination yields the allylic acetate **81** as shown by **80** [39].

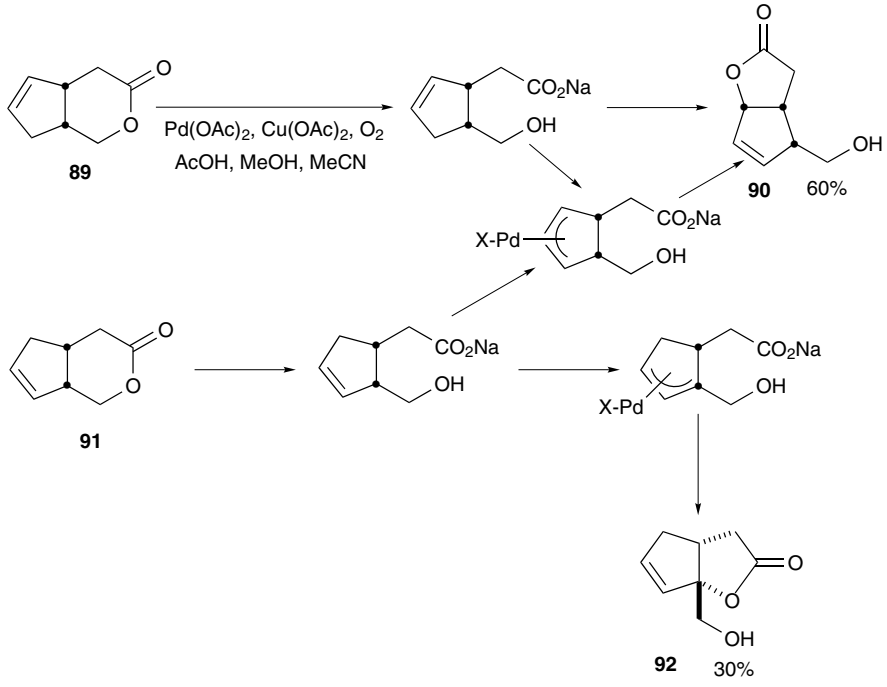


The intramolecular reaction of alkenes with various O and N functional groups offers useful synthetic methods for heterocycles [15,16,40]. Reaction of unsaturated carboxylic acids affords lactones by either *exo* or *endo* cyclization depending on the positions of the double bond. Both 5-hexenoic acid (**83**) and 4-hexenoic acid (**84**) were converted to five- or six-membered lactones depending on the solvents and bases [41,42]. Oxidative cyclization of the optically active 4-pentenoic acid derivative **85** (85 % ee) using O_2 as an oxidant afforded the γ-lactone **86** with 86 % ee in 84 % yield [43]. 2-Vinylbenzoic acid (**87**) was converted to isocoumarin (**88**), but not to the five-membered lactone [41,44].



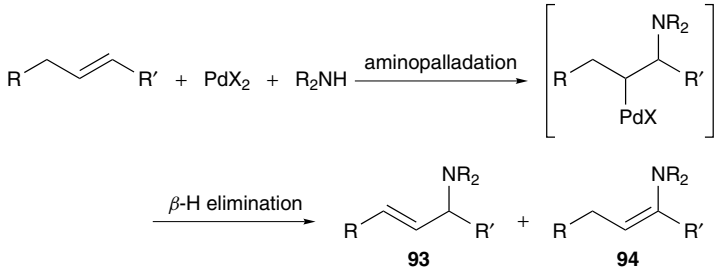
Treatment of an equimolar mixture of the sodium salts, derived from the lactones **89** and **91**, with $Pd(OAc)_2$, $Cu(OAc)_2$, and O_2 afforded two lactones **90** (60 %) and

92 (39 %). Formation of the lactone **90** from **89** is explained by the intramolecular acyloxypalladation mechanism. On the other hand, the lactones **90** and **92** are formed by two paths. Two different mechanisms cooperate to form the desired lactone **90** in 60 % yield and **92** in 30 % yield. The formation of **90** and **92** can be rationalized by generation of the π-allylpalladium intermediates by allylic C—H bond activation as an alternative pathway [45].



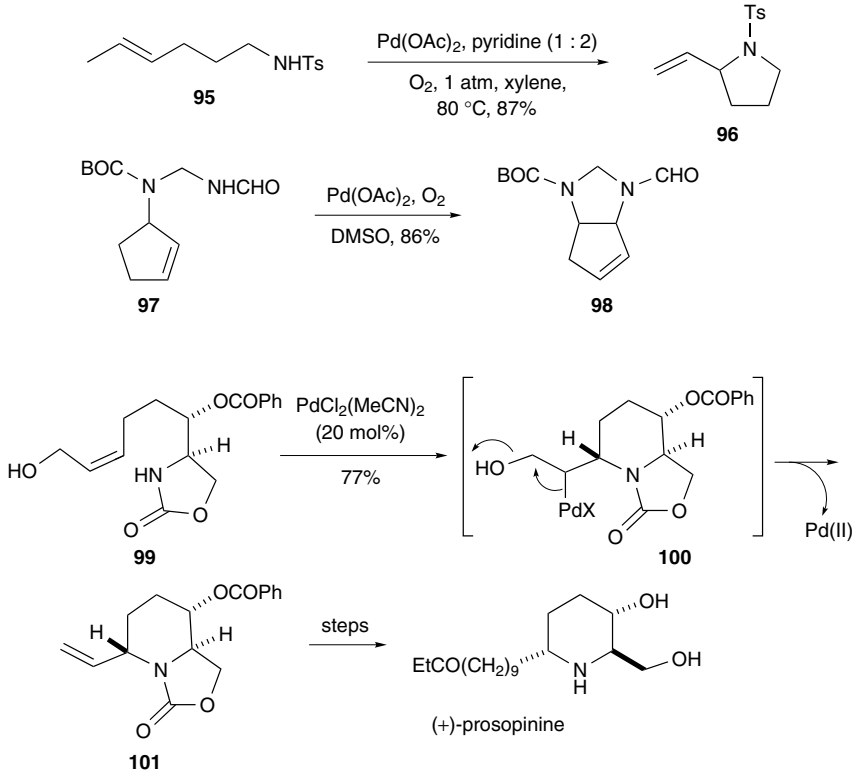
2.2.5 Reactions with Amines

Formation of allylic amines **93** and enamines **94** is expected by oxidative amination of alkenes via aminopalladation and β-H elimination using Pd(II) salts. Formation of allylic amines is favored.



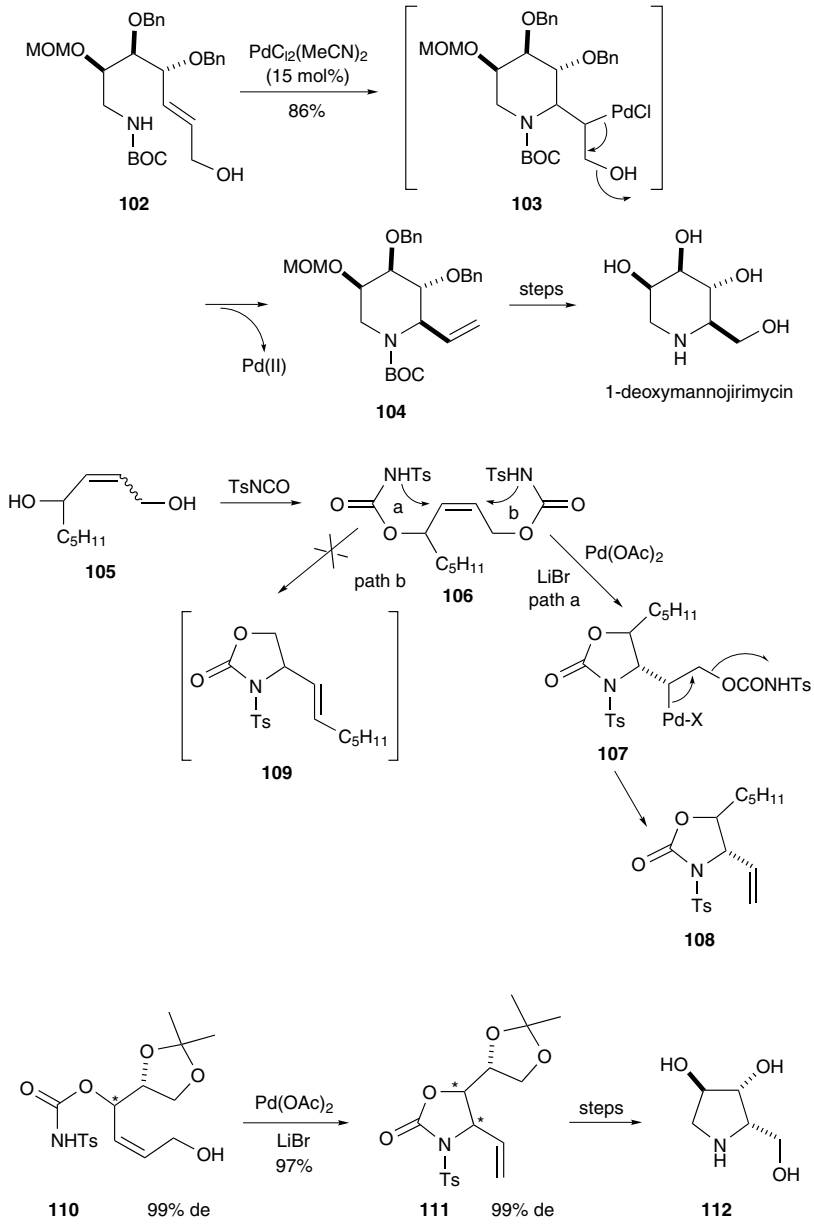
Aliphatic amines coordinate to electrophilic Pd(II) too strongly to undergo aminopalladation, and the aminopalladation is possible only in a special case. On the other hand, amides such as tosylamide, acetamide, and carbamates react more easily than free amines, because amidation reduces electron density and

the complexing ability of amines. Intermolecular reactions are rather difficult, but intramolecular ones proceed smoothly and are extensively applied to syntheses of N-containing heterocycles [15,16,40]. For example, 5-*exo* cyclization of 4-hexenyltosylamide (**95**) using $Pd(OAc)_2$-pyridine (1 : 2) and oxygen gave the 2-vinylpyrrolidine (**96**) smoothly. No other oxidant is necessary [8]. Cyclization of the formamide **97** with a catalytic system of $Pd(OAc)_2$–DMSO-O_2 afforded **98** [46]. Intramolecular aminopalladation of the allylic alcohol **99** is followed by elimination of β-OH to generate Pd(II) as shown by **100**, and hence the cyclization proceeds with a catalytic amount of $PdCl_2$ with no oxidant to give **101**, and (+)-prosopinine was synthesized by this method [47].

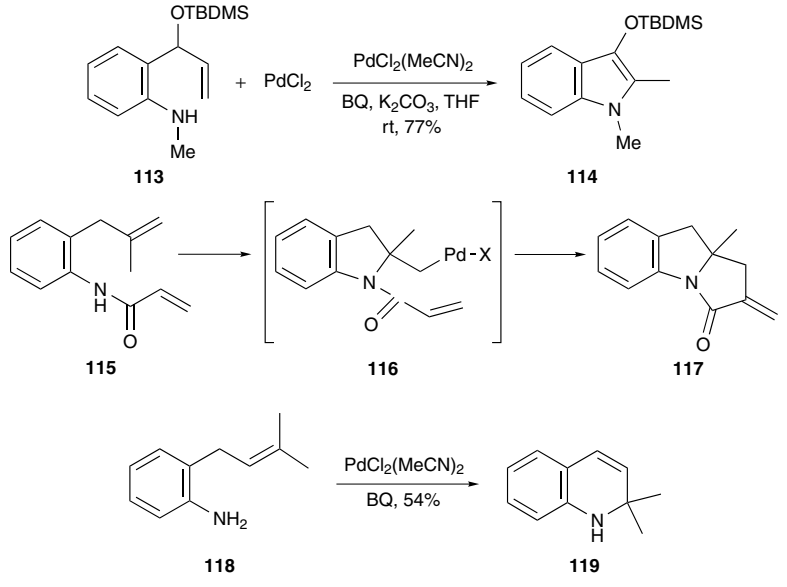


Similarly, $PdCl_2$-catalyzed cyclization of the ureathane **102**, derived from D-mannitol, proceeded with elimination of OH as shown by **103** to afford **104** with excellent diastereoselectivity, from which 1-deoxymannojirimycin was synthesized [48].

Treatment of the diallylic alcohol **105** with TsNCO gave the *N*-tosyldicarbamate **106**. Interestingly, Pd-catalyzed cyclization of **106** gave the 4-vinyl-2-oxazolidinone **108** (path a) regioselectively by elimination of the carbamate group as shown by **107** without forming the isomeric oxazolidinone **109** (path b). Addition of Li salt is essential, without which no reaction takes place. Cyclization of the chiral allylic alcohol **110** produced the highly optically pure 4-vinyl-2-oxazolidinone **111**, which was converted to **112** [49].

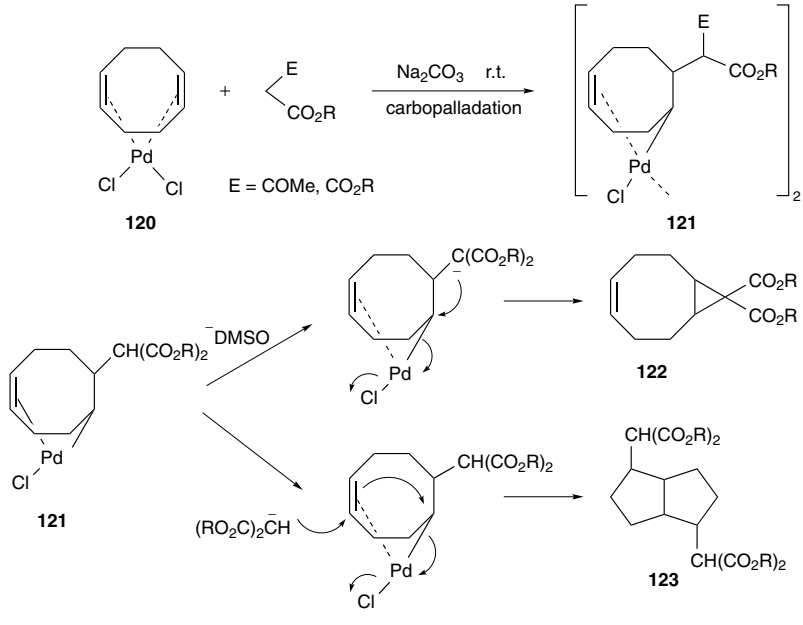


Oxidative amination of aromatic amines which are less basic than aliphatic amines proceeds smoothly without protection of amines. The intramolecular reaction of aniline derivatives offers good synthetic methods for heterocycles. 2-Methylindole is obtained by 5-*exo* amination of 2-allylaniline [50]. As an application, *N*-methyl-2-methyl-3-siloxyindole **114** was prepared from *N*-methyl-2-(1-siloxyallyl)aniline **113**. Without silyl protection, no reaction occurred [51]. If there is another olefinic bond in the same molecule, the aminopalladation product **116** of the amide **115** undergoes olefin insertion to give the tricyclic compound **117** [50]. 2,2-Dimethyl-1,2-dihydroquinoline (**119**) was obtained by 6-*endo* cyclization of 2-(3,3-dimethylallyl)aniline (**118**).

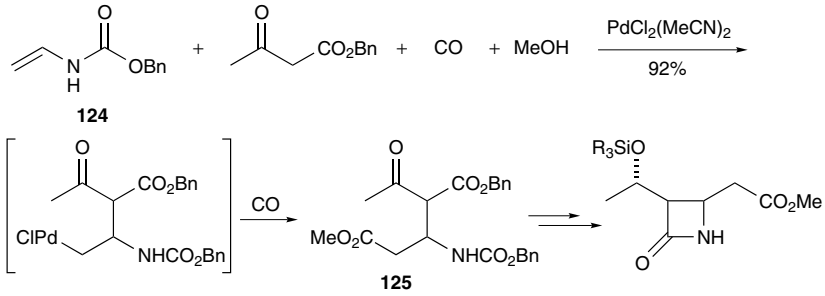


2.2.6 Reactions with Carbon Nucleophiles

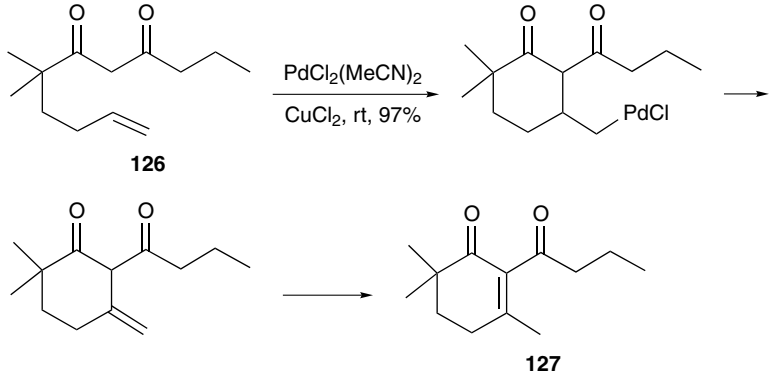
When the stable complex of COD **120** was treated with malonate or acetoacetate in ether at room temperature in the presence of Na_2CO_3, a facile carbopalladation occurred to give the new and stable complex **121**. This reaction is the first example of carbopalladation of alkenes in Pd chemistry. The Pd–carbon σ-bond in the carbopalladation product **121** is stabilized by coordination of π-olefin bond. By the treatment of the new complex **121** with a base, the generated malonate anion attacked the Pd–carbon σ-bond, affording the bicyclo[6.1.0]nonane **122**. Also treatment of the complex **121** with another molecule of malonate afforded the bicyclo[3.3.0]octane **123** by transannulation to the π-olefin bond [14,52].



Carbopalladation of the double bond of the benzyl *N*-vinylcarbamate **124** with benzyl acetoacetate, and subsequent carbonylation affords the amino ester **125**, which was converted to a β-lactam [53].

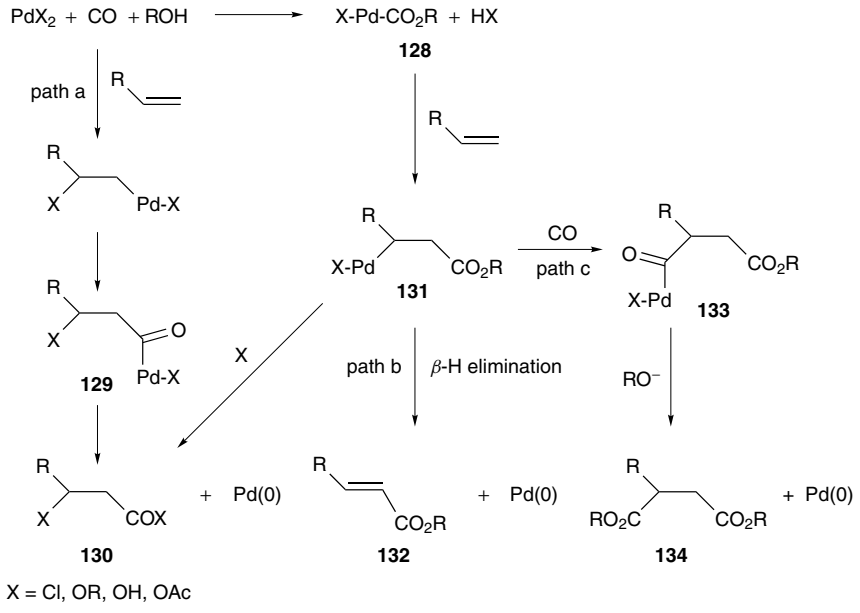


Intramolecular carbopalladation of the unsaturated β-diketone **126** catalyzed by the combination of $PdCl_2$ with $CuCl_2$ at room temperature provided the cyclohexenone **127** in very high yield (97 %). In other words, facile oxidative alkylation of an unactivated alkene with a carbon nucleophile took place [54].



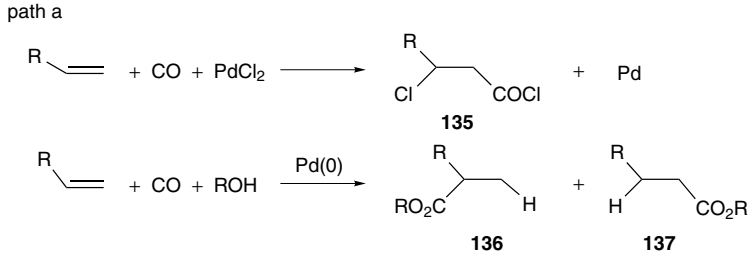
2.2.7 Oxidative Carbonylation

Oxidative carbonylation of alkenes is a unique reaction of Pd(II). Three types of oxidative carbonylation to give β-substituted acid derivatives **130**, α,β-unsaturated esters **132** and succinate derivatives **134** are known, which can be understood by the following mechanism. Palladation of alkenes with PdX_2, followed by CO insertion, generates the acylpalladium intermediate **129** whose reductive elimination affords β-substituted carboxylic acid derivatives **130** (path a). Reaction in alcohol in the presence of a base starts by the formation of the alkoxycarbonylpalladium **128.** Carbopalladation of alkene with **128** generates **131**. Then β-H elimination of the intermediate **131** yields the α,β-unsaturated ester **132** (path b). Further CO insertion to **131** gives the acylpalladium intermediate **133** and its alcoholysis yields the succinate derivative **134** (path c). Formation of the β-alkoxy ester **130** (X-OR) is regarded as nucleophilic substitution of Pd-X in **131** with alcohols.

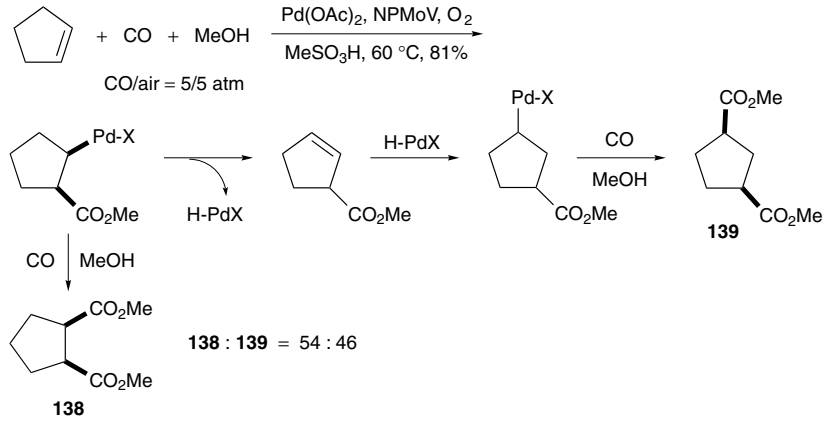


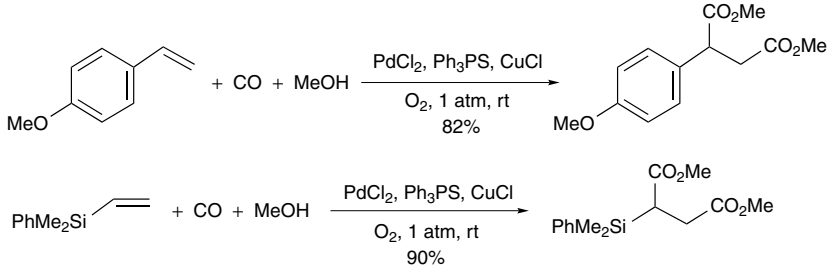
The first report of the oxidative carbonylation is reaction of alkenes with CO in benzene in the presence of $PdCl_2$ to afford the β-chloroacyl chloride **135** (path a) [14,55].

Hydrocarbonylation of alkenes to give the saturated esters **136** and **137** is catalyzed by Pd(0) (see Chapter 8.1) [56]. It should be pointed out that the hydrocarbonylation is clearly different mechanistically from the oxidative carbonylation, which is promoted by Pd(II) to produce **130, 132** and **134**.

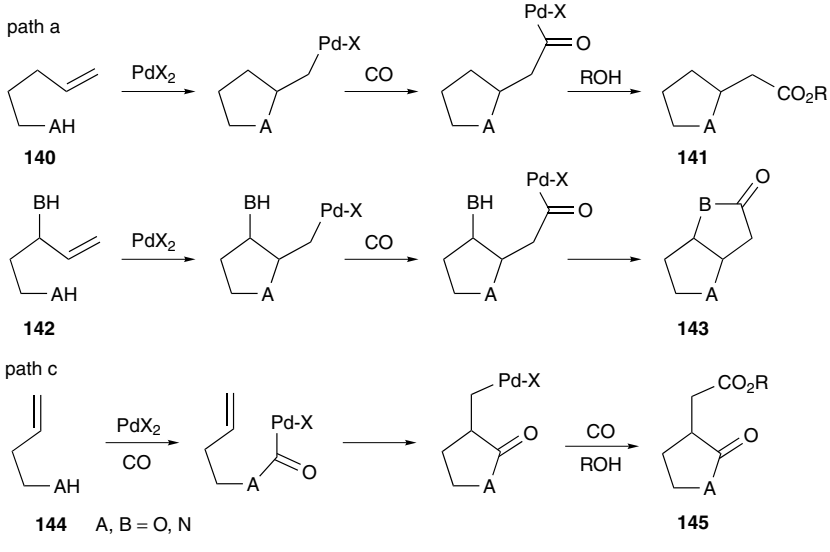


Extensive studies have been carried out on oxidative carbonylation [57]. Oxidative dicarbonylation of cyclopentene to give the diester **138** and **139** (path c) proceeds with good yields using a catalytic amount of $Pd(OAc)_2$ and heteropoly acid (NPMoV) under pressure of CO and air (5 atm each). Formation of the diester **139** is explained by dehydropalladation after monocarbonylation, followed by hydropalladation in a different direction [58]. Saigo and co-workers reported that phosphine sulfide (Ph_3PS) is an effective ligand for oxidative dicarbonylation of alkenes [59]. Aromatic alkenes such as *p*-methoystyrene and vinylsilane were converted to succinate derivatives in 82 % and 92 % yields, respectively, in the presence of Ph_3PS and CuCl at room temperature and under 1 atm of CO and O_2. The yield in carbonylation of styrene in the absence of phosphine sulfide was 36 %. Phosphine oxide is somewhat less effective (60 % yield) than Ph_3PS.

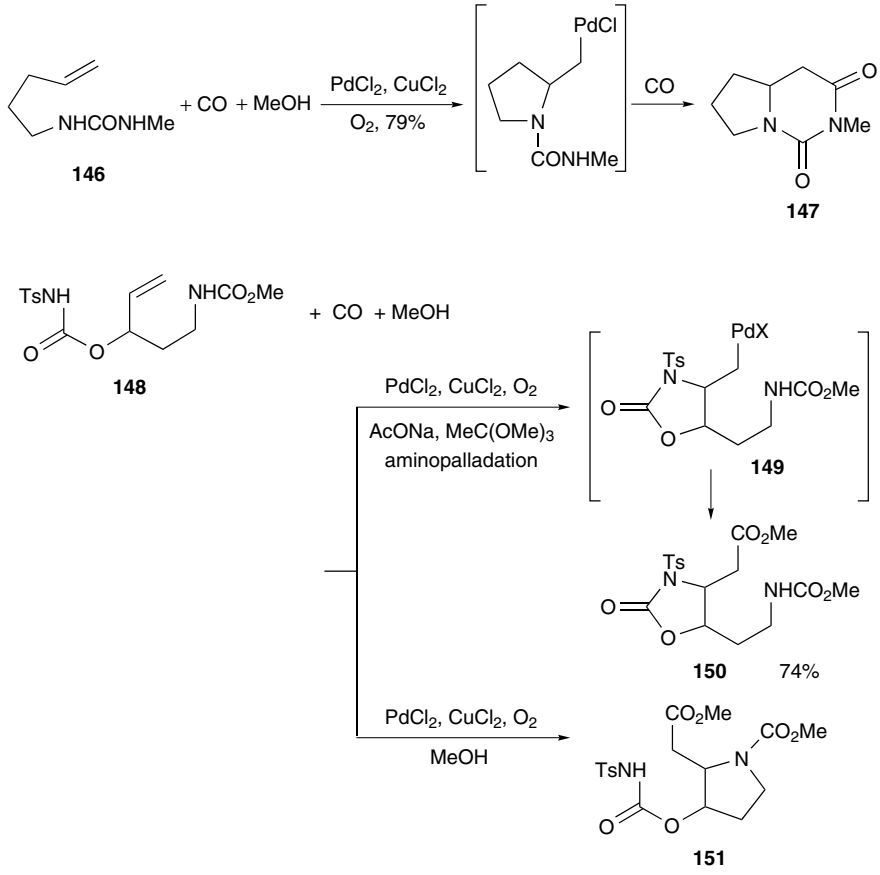




Carbonylation of alkenes having an amino or hydroxy group (AH or BH = OH or NHR) **140, 142** and **144** offers interesting synthetic methods for cyclic compounds. The 4-pentenylamine or alcohol **140** is converted to **141** via amino or oxypalladation, followed by carbonylation. The amino alcohol **142** gives **143** by palladation and carbonylation by path a. The homoallylic amine or alcohol **144** is converted to lactone or lactam ester **145** by path c [60].

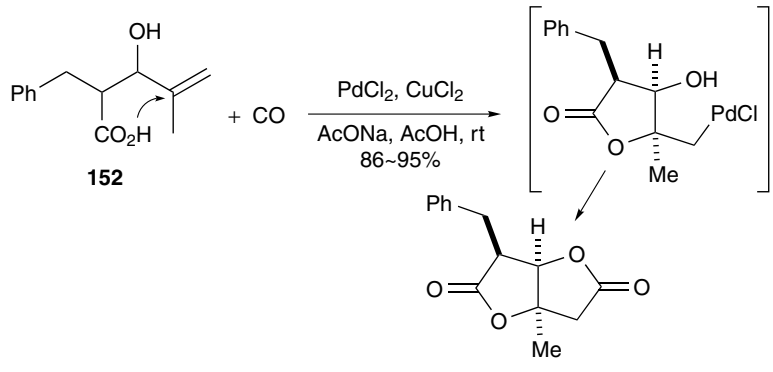


Aminocarbonylation of *N*-4-pentenyl-*N′*-methylurea (**146**) gave **147** smoothly in the presence of $PdCl_2$, $CuCl_2$ and O_2 [61]. Aminocarbonylation of the unsaturated diamine derivative **148** is chemoselective. In the presence of sodium acetate and methyl orthoformate, aminopalladation of the tosylamide took place selectively to afford **150** via **149**. On the other hand, selective reaction of the carbamate occurred to give **151** in the absence of sodium acetate [62].

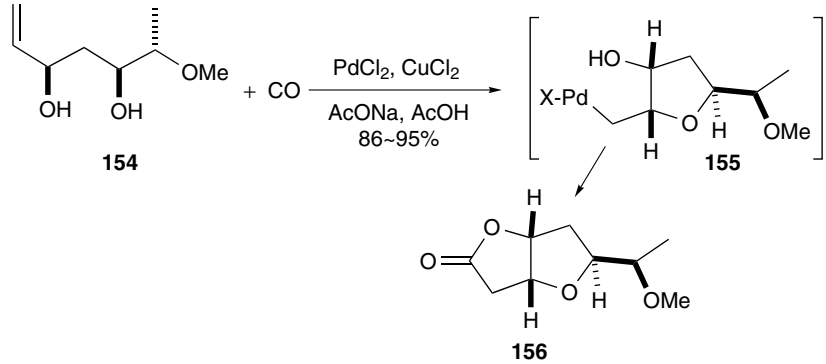


The unsaturated hydroxy carboxylic acid **152** was converted to the dilactone **153** via domino oxypalladation and carbonylation [63]. The γ-lactone **156** was prepared by intramolecular oxycarbonylation of the alkenediol **154**. The intermediate **155** is formed by the oxypalladation, and subsequent intramolecular carbonylation affords the lactone **156**. The reaction was applied to the synthesis of tetronomycin [64]. The oxycarbonylations of alkenol and alkanediol can be carried out with a catalytic amount of $PdCl_2$ and a stoichiometric amount of $CuCl_2$, and have been applied to syntheses of a number of natural products.

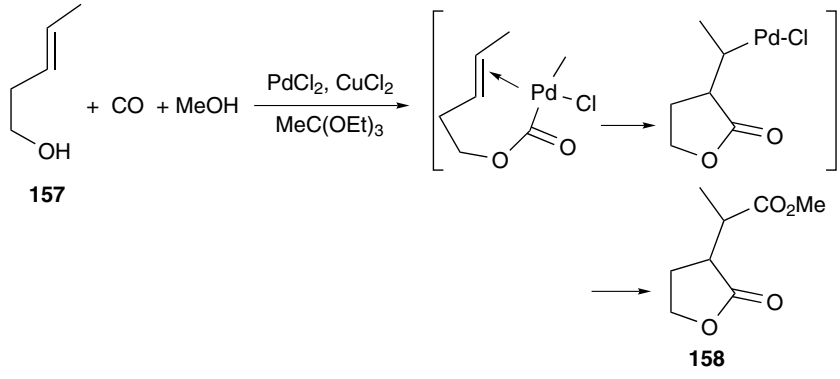
Oxidative carbonylation of 3-penten-1-ol (**157**) in the presence of ethyl orthoformate gave the lactonic ester **158** smoothly by dicarbonylation under mild conditions (path c) [65]. Dicarbonylation of the homoallylic alcohol **159** carried out using the chiral bioxazolidine as a ligand **161** gave the chiral lactone **160** in 57 % yield with 65 % ee [66].



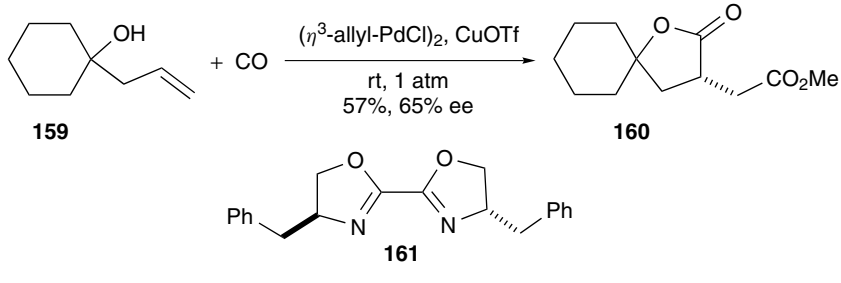
152 **153**



154 **155** **156**



157 **158**



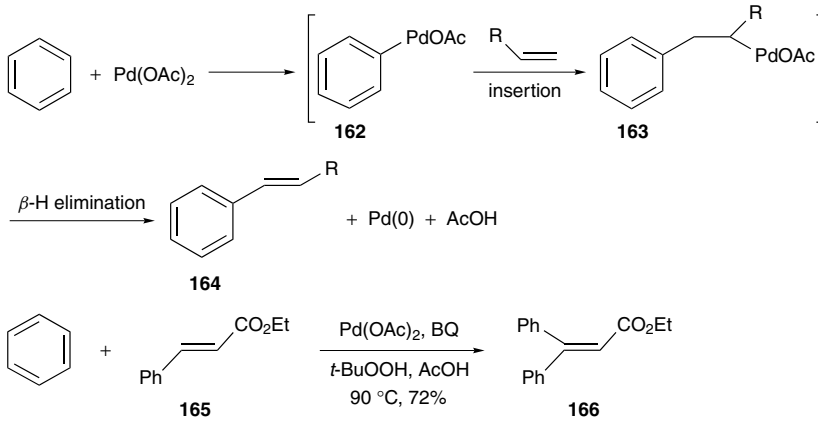
159 **160** **161**

2.2.8 Reactions with Aromatic Compounds

Similar to mercuration, $Pd(OAc)_2$ undergoes facile palladation of aromatic compounds. The palladation product **162** is an unstable intermediate. It can be isolated only when stabilized by chelation. The palladation products of aromatics as reactive intermediates undergo three reactions. The reaction with alkenes to afford styrene derivatives **164** is the first one. Pd(II)-promoted alkenylation of aromatic compounds, discovered by Fujiwara, is a stoichiometric Heck reaction. The second one is homocoupling to form biaryls. The acetoxylation of aromatic rings is the third reaction. These latter two reactions are treated in Chapter 2.7.

The Pd(II)-mediated reaction of benzene with alkenes affords styrene derivatives **164**. The reaction can be understood by palladation, insertion of olefin to give **163**, and β-H elimination [67,68]. In addition to benzene and naphthalene derivatives, electron-rich heteroaromatic compounds such as ferrocene, furan and thiophene react with alkenes to give vinyl heterocycles. The effect of substituents in this reaction is similar to that observed in the electrophilic aromatic substitution [69].

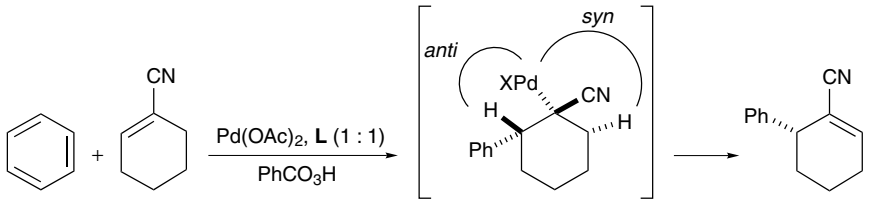
Oxidative coupling of arenes with alkenes consumes a stoichiometric amount of Pd(II). Efficient catalytic reaction of cinnamate (**165**) with benzene to afford **166** was carried out using BQ and *t*-butyl hydroperoxide as oxidant in AcOH [70]. The coupling proceeds smoothly in the presence of catalytic amounts of $Pd(OAc)_2$ and molybdovanadophosphoric acid (HPMoV) under oxygen (1 atm) in AcOH [71].



Asymmetric oxidative coupling of benzene with cyclohexenecarbonitrile (**167**) using the chiral diamine **170** as a ligand is based on the expectation that β-H elimination from the opposite side to the phenyl group as shown by **168** should generate a chiral alkene. $Pd(OAc)_2$ (10 mol %), the chiral sulfonylaminophenyloxazoline ligand **170** (1 : 1) and *t*-butyl perbenzoate as an oxidant were used, and 6-phenylcyclohexenecarbonitrile (**169**) with 30 % ee was obtained [72].

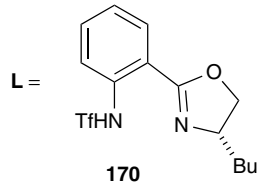
Intramolecular oxidative coupling of the benzene ring with 1,2-benzoquinone to yield **171** was applied to total synthesis of carbazoquinostatin A [73]. Cyclization of 2-arylamino-1,4-quinones was carried out using $Pd(OAc)_2$ and $Sn(OAc)_2$ (5 mol% each) in AcOH under oxygen [74].

In the enantioselective total synthesis of okaramine N, Corey carried out intramolecular oxidative coupling of congested trisubstituted alkene at C-2 of indole in a complex molecule to give **172** in 44 % yield using $Pd(OAc)_2$ (1 equiv.) at room

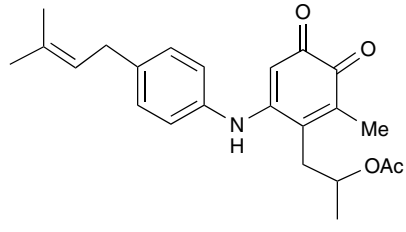


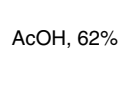
167 **168** **169**

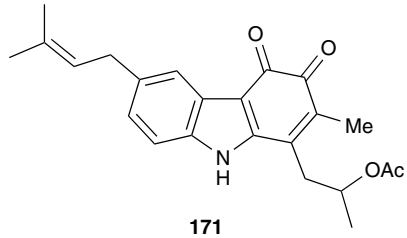
30%, 30% ee



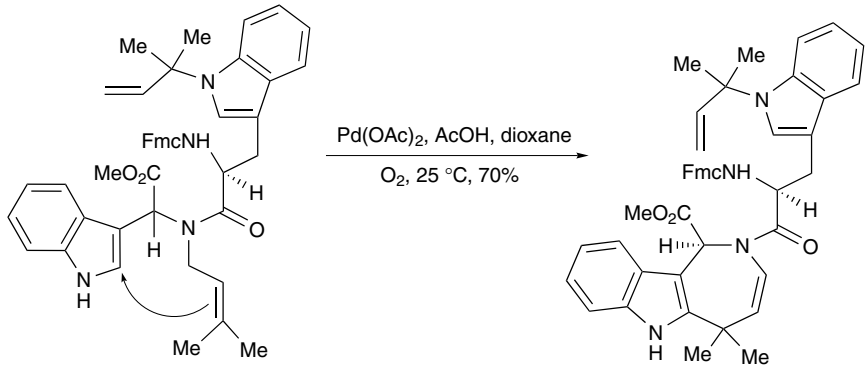
170







171

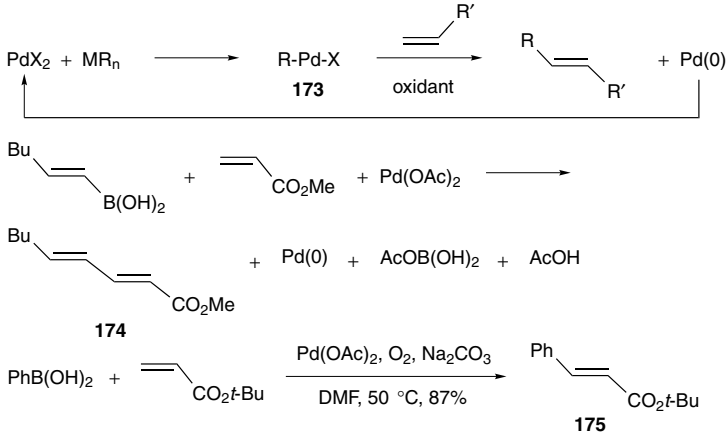


172

temperature under O_2 atmosphere. The reaction seems to occur via palladation at C-2 of the indole ring [75].

2.2.9 Coupling of Alkenes with Organometallic Compounds

Coupling of organometallic compounds of B, Sn and Si with alkenes as a halogen-free oxidative Heck-type reaction proceeds with Pd(II) compounds catalytically in the presence of oxidants. The reaction can be understood by alkylation (or arylation and alkenylation) of $Pd(II)X_2$ with main group metal compounds $M'R_n$ to generate R-Pd-X **173**, which is a species similar to an intermediate formed in the Heck reaction. Subsequent alkene insertion and β-H elimination provide the coupling products and Pd(0). Reoxidation of Pd(0) with an oxidant to Pd(II) makes the reaction catalytic. Coupling of 1-hexenylboronic acid with acrylate promoted by $Pd(OAc)_2$ to give methyl 2,4-nonadienoate (**174**) was reported by Dieck and Heck in 1975 [76]. Reaction of acrylate with phenylboronic acid in the presence of $Pd(OAc)_2$ under O_2 afforded cinnamate (**175**) in 87 % yield [77,78].

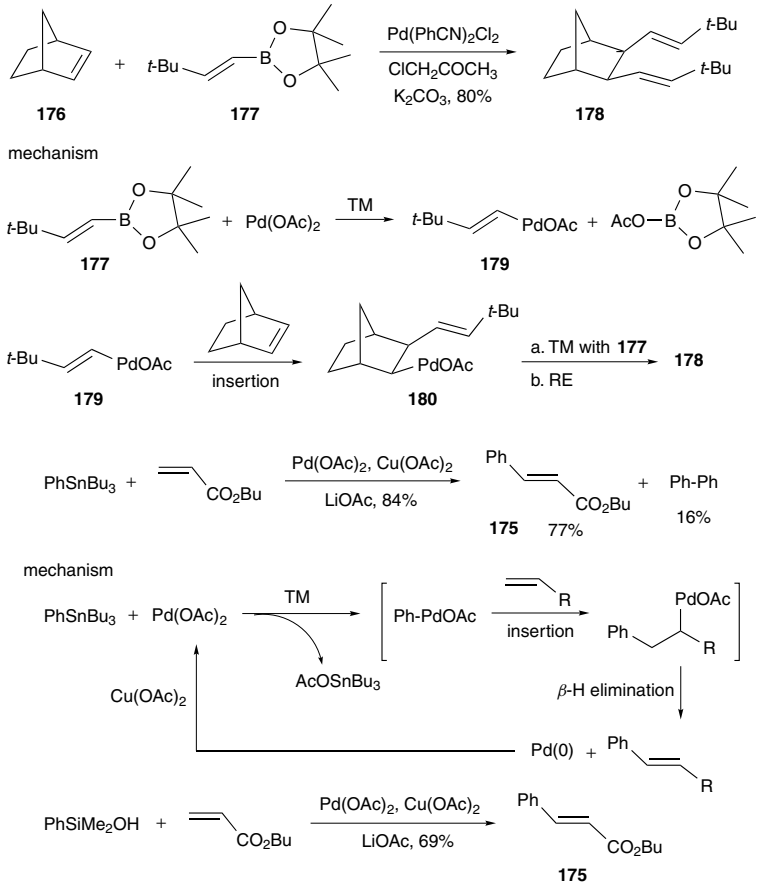


Reaction of norbornene (**176**) with the organoborane **177** afforded the doubly alkenylated product **178**. Although no mechanism was given, the first step seems to be the alkenylation of $Pd(OAc)_2$ with **177**, or transmetallation of **177** with $Pd(OAc)_2$ to give **179** (which corresponds to **173**). Then insertion of norbornene took place to afford **180**. Since there is no β-H *syn* to Pd, β-H elimination is impossible. Therefore transmetallation with **177** and reductive elimination occur to give rise to the doubly alkenylated product **178**. Chloroacetone was used as a good oxidant of Pd(0), since Cu(II) salts gave poor results in this reaction [11].

Reaction of phenylstannane with acrylate gave cinnamate (**175**) using $Pd(OAc)_2$ and $Cu(OAc)_2$. The reaction is explained by phenylation of $Pd(OAc)_2$, insertion of alkene and β-H elimination. The generated Pd(0) is reoxidized to Pd(II) with Cu(II) salt [78,79]. Coupling of arylstannanes and alkenes proceeds smoothly using $Pd(OAc)_2$ and pure O_2 as an oxidant. Uses of DMF or NMP as a solvent and AcONa as a base are important [80].

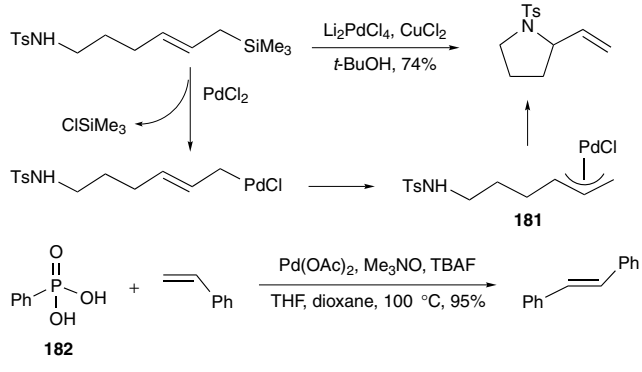
Aryl and alkenyl silanols react smoothly with alkenes. The presence of the OH group on silicon is important and silanols are reactive without activation by

fluorides. Phenyldimethylsilanol reacts with acrylate to give cinnamate (**175**) using $Pd(OAc)_2$ and $Cu(OAc)_2$ [79,81].



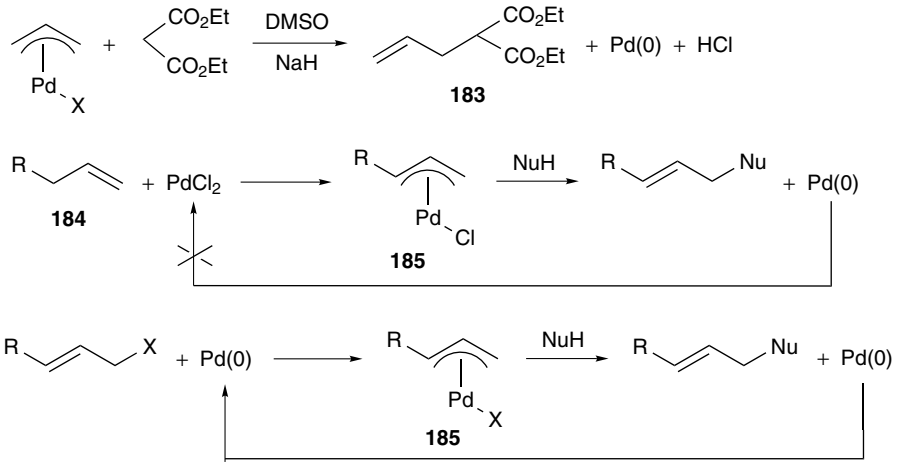
π-Allylpalladium **181** is formed by a stoichiometric reaction of allylic trimethylsilane with $PdCl_2$, and undergoes intramolecular amination. Overall, Pd-catalyzed cyclization of allylsilanes by nucleophilic displacement of the silyl group occurred in the presence of $CuCl_2$ [82].

Also oxidative arylation of alkenes can be carried out by the reaction of phenylphosphonic acid **182** with alkenes [83].



2.3 Stoichiometric Reactions of π-Allyl Complexes

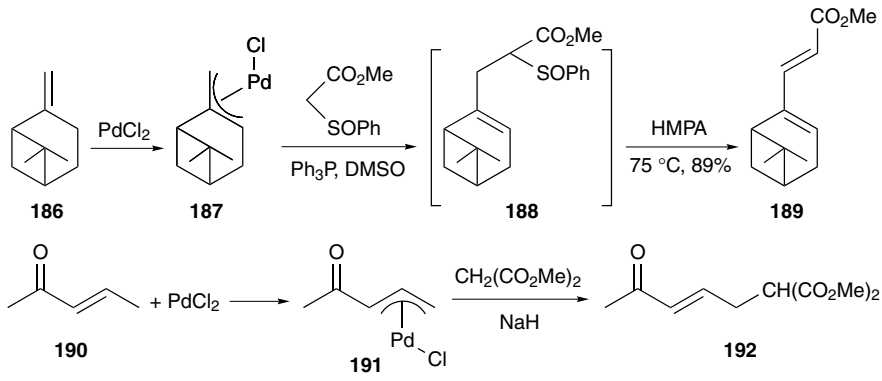
Reaction of π-allylpalladium chloride with a soft carbon nucleophile such as malonate and acetoacetate in DMSO as a coordinating solvent to give the allylated product **183** was reported in 1965 [14,84]. This reaction constitutes the basis of stoichiometric as well as catalytic π-allylpalladium chemistry. Depending on how π-allylpalladium complexes are prepared, the reaction becomes stoichiometric or catalytic. Preparation of π-allyl complexes **185** from alkenes **184** requires Pd(II) salts, and subsequent reaction with a nucleophile generates Pd(0). The whole process consumes a stoichiometric amount of Pd(II), because *in situ* regeneration of Pd(II) is hardly attainable. These reactions are treated in this section. On the other hand, *in situ* formation of the π-allylpalladium complexes **185** by oxidative addition of Pd(0) to various allylic compounds (esters, carbonates, etc.), and their reactions with nucleophiles are catalytic, because Pd(0) is regenerated after the reaction with the nucleophile, and reacts again with allylic compounds. These catalytic reactions are treated in Chapter 4.



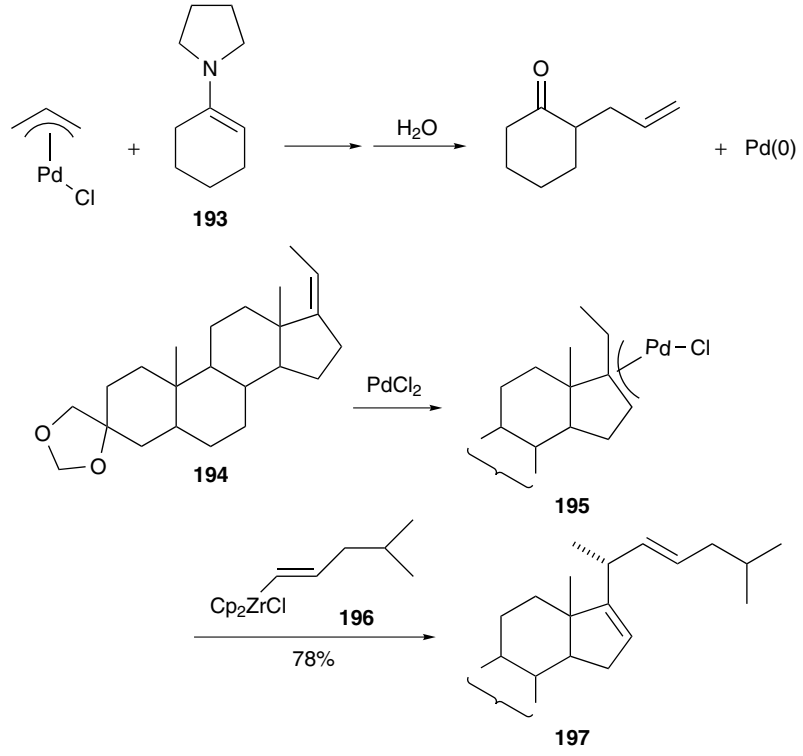
X = OAc, OCO_2Me, etc.

Formation of π-allylpalladium complexes from alkenes and $PdCl_2$, and the reaction of the complexes with carbon nucleophiles constitutes alkylation of alkenes with carbon nucleophiles via π-allylpalladium complexes as a stoichiometric reaction, offering a method of oxidative functionalization of alkenes, and can be applied to syntheses of a number of natural products [85]. For example, functionalization of pinene (**186**) was carried out via the reaction of the π-allylpalladium **187** with a phenylsulfinyl group to give **188**, and converted to the pinene derivative **189** [86]. π-Allyl complex formation takes place particularly easily from the α,β- or β,γ-unsaturated carbonyl compounds. The reaction of the complex **191**, formed from 3-penten-2-one (**190**), with a carbon nucleophile to lead to **192** is an example of γ-alkylation of α,β-unsaturated ketones or esters [87].

The enamine **193** as a carbon nucleophile reacts with π-allylpalladium chloride to give 2-allylcyclohexanone after hydrolysis [84]. Hard carbon nucleophiles of organometallic compounds also react with π-allylpalladium complexes. A steroidal side chain was introduced to **194** to afford **197** regio- and stereoselectively by the

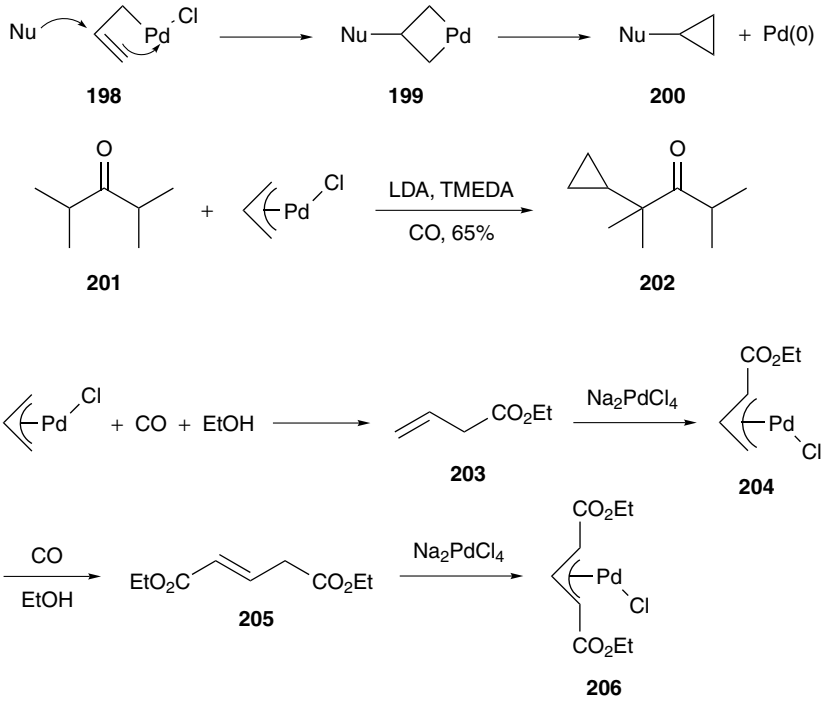


reaction of the steroidal π-allylpalladium complex **195** with the alkenylzirconium compound **196** [88].



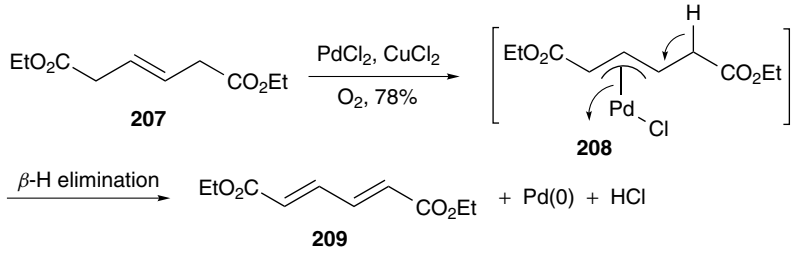
Interestingly, some nucleophiles attack the central carbon of the π-allyl system **198** to form the palladacyclobutane **199** and reductive elimination produces the cyclopropanes **200**. Li enolates of carboxylic acids are such nucleophiles for the cyclopropanation [89,90]. The Li enolate of the ketone **201** reacts with π-allylpalladium chloride to afford the α-cyclopropyl ketone **202** in the presence of TMEDA under CO atmosphere [91].

Treatment of π-allylpalladium chloride with CO in EtOH afforded ethyl 3-butenoate (**203**) [92], which was easily converted to 1-carboethoxy-π-allylpalladium chloride (**204**) by treatment with Na_2PdCl_4 in EtOH. Then the repeated



carbonylation of **204** gave ethyl 2-pentenedioate (**205**), which was converted further to the 1,3-dicarboethoxy-π-allylpalladium complex **206** [93].

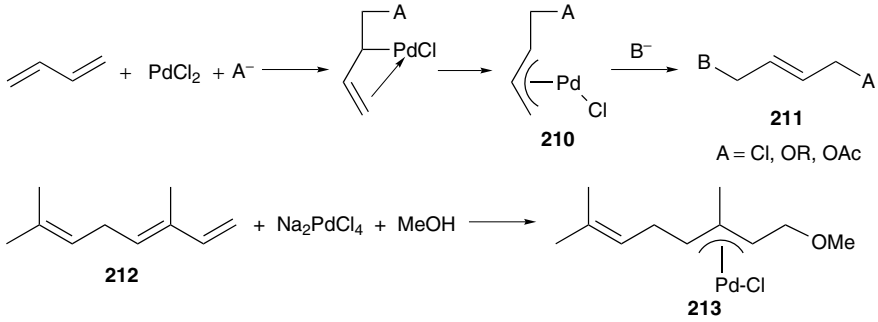
Conjugated dienes are formed by β-H elimination of π-allylpalladium complexes. Catalytic oxidative dehydrogenation of ethyl 3-butenedicarboxylate (**207**) to afford butadienedicarboxylate (muconate) (**209**) proceeded in high yield using $PdCl_2$ and $CuCl_2$ under an oxygen atmosphere in AcOH containing sodium acetate [94]. The reaction proceeds via the π-allylpalladium complex **208** and subsequent β-H elimination.



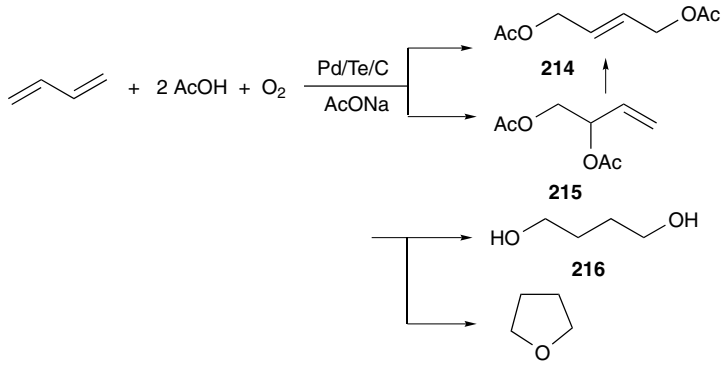
2.4 Reactions of Conjugated Dienes

When butadiene is treated with $PdCl_2$, the 1-chloromethyl-π-allylpalladium complex **210** (A = Cl) is formed by chloropalladation of one of the double bonds. In the presence of pronucleophiles AH, the substituted π-methallylpalladium complex **210** (A = nucleophile) is formed. In this way, the nucleophile can be introduced at the terminal carbon of conjugated diene systems. For example,

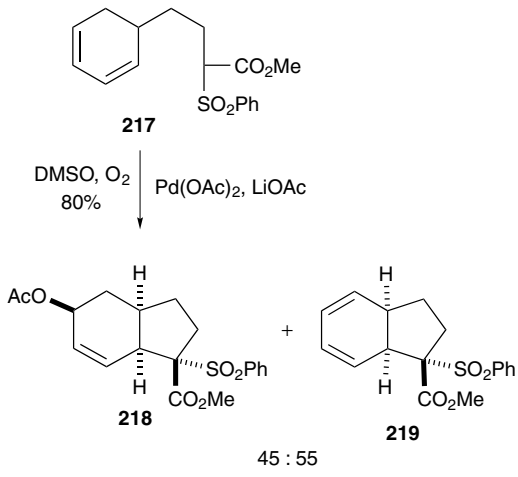
a methoxy group is introduced at the terminal carbon of 3,7-dimethyl-1,3,6-octatriene (**212**) to give the π-allylpalladium complex **213**. The π-allylpalladium complexes formed from conjugated dienes are reactive and react further with nucleophiles to give the 1,4-difunctionalized products **211**. Based on this reaction, various nucleophiles are introduced to conjugated dienes to form 1,4-difunctionalized 2-alkenes **211**. In this way, acetoxy, alkoxy, halo, amino groups, carbon nucleophiles and CO are introduced to dienes. This is the basis of the synthetic application of Pd(II)-promoted oxidative difunctionalization of conjugated dienes [95]. The reaction itself is stoichiometric with respect to Pd(II) salts, but it can be made catalytic by the use of reoxidants of Pd(0).



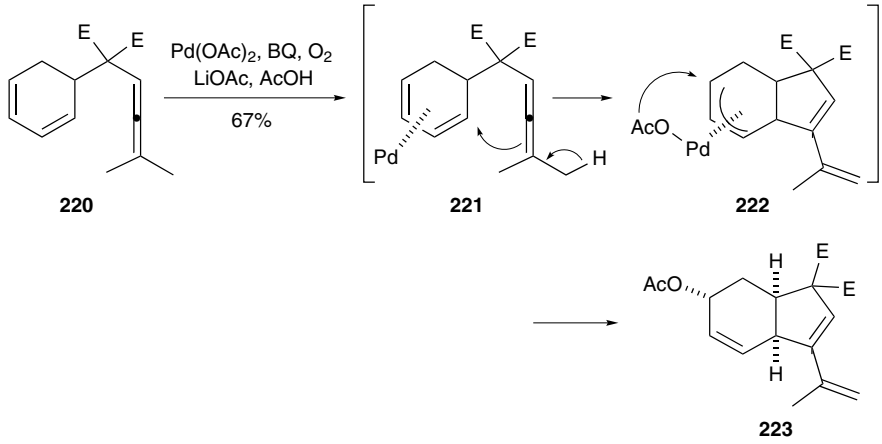
The oxidative diacetoxylation of butadiene with $Pd(OAc)_2$ affords 1,4-diacetoxy-2-butene (**214**) and 3,4-diacetoxy-1-butene (**215**). The latter can be isomerized to the former. The commercial process for 1,4-diacetoxy-2-butene (**214**) was developed in AcOH using a Pd catalyst, which contains Te supported on carbon. Importantly, the Pd stays on carbon without dissolving into AcOH. 1,4-Butanediol (**216**) and THF are produced commercially from **214** [96].



Some synthetic applications of 1,4-difunctionalization of various 1,4-dienes are cited here. Stereoselective 1,4-difunctionalization of the 1,3-cyclohexadiene **217** using $Pd(OAc)_2$ and O_2 in DMSO afforded nearly equal amounts of 1,4-adduct **218** and addition–elimination product **219** [97]. Pd(II)-promoted intramolecular reaction of the allene-substituted 1,3-cyclohexadiene **220** gave the triene **223** regio- and stereoselectively. The reaction may be explained by nucleophilic attack of the



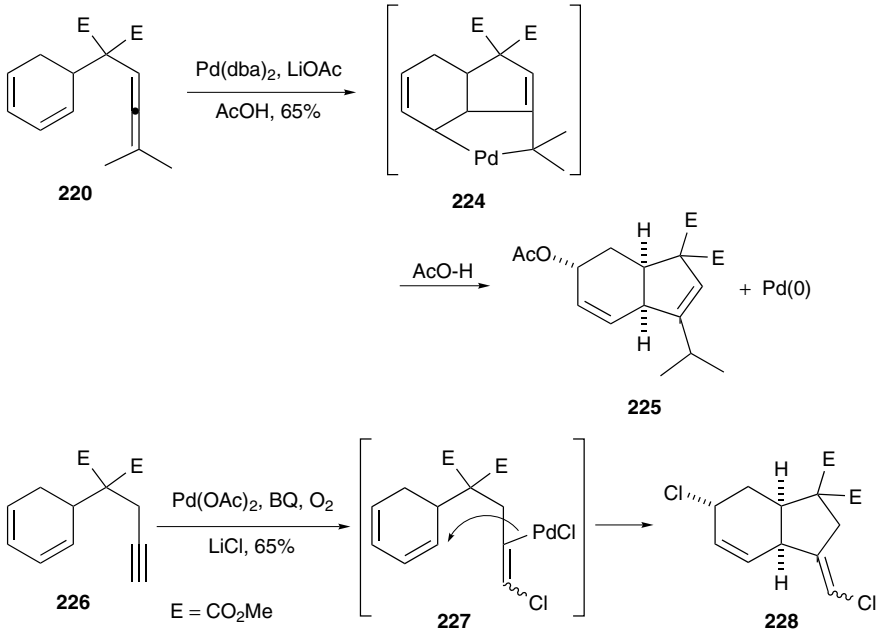
allene to the 1,3-cyclohexadiene, followed by acetoxylation of the π-allylpalladium system as shown by **221** and **222** to give **223**.



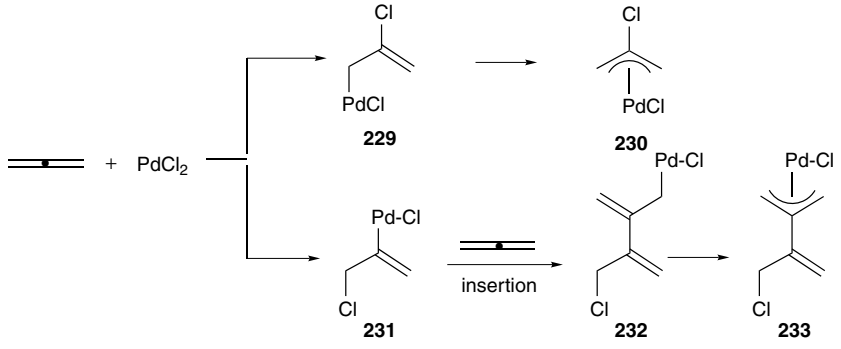
It is worth mentioning that the diene **225** was obtained by the Pd(0)-catalyzed reaction of the same substrate **220** by a different mechanism, namely oxidative cyclization of **220** to generate palladacyclopentane **224** and addition of AcO-H to **224** to give **225** [98]. Also reaction of the alkyne-substituted 1,3-cyclohexadiene **226** using $Pd(OAc)_2$ and BQ in the presence of LiCl starts by chloropalladation of the triple bond, followed by attack to the diene as shown by **227** to give the dichloro compound **228** [99].

2.5 Reactions of Allenes

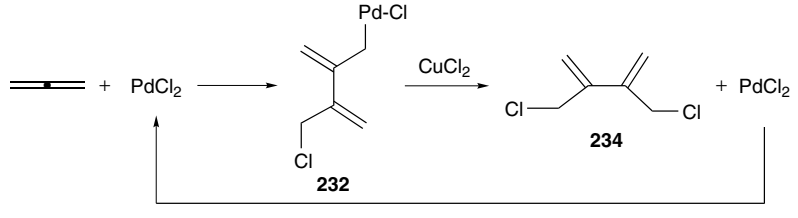
Allenes react with Pd(II) salts in two ways, giving monomeric and dimeric π-allylpalladium complexes **230** and **233** [100,101]. Chloropalladation of allene occurs in two directions depending on attack on the central carbon of allene either by Cl or PdCl. The complex **230** is obtained by the attack of PdCl on the terminal carbon



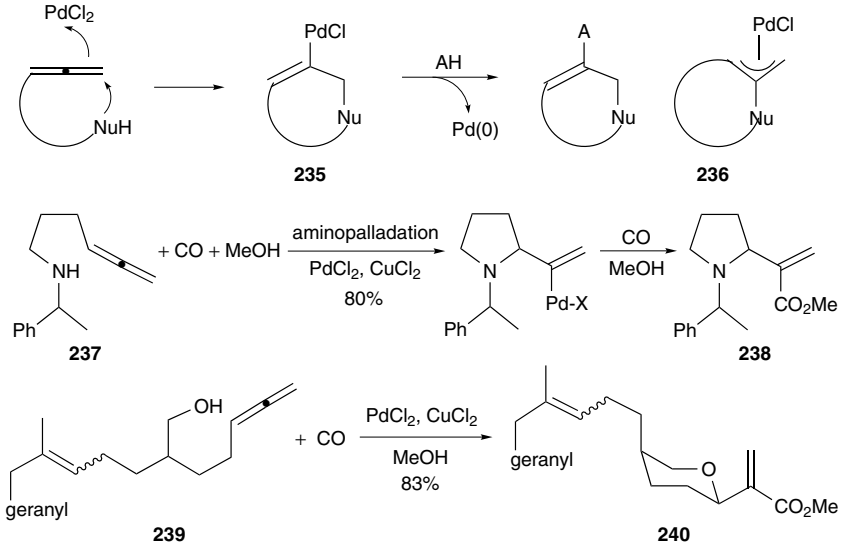
via **229**. Chloropalladation in a different direction generates **231**, and insertion of allene to **231** affords the dimeric complex **233** via **232**.



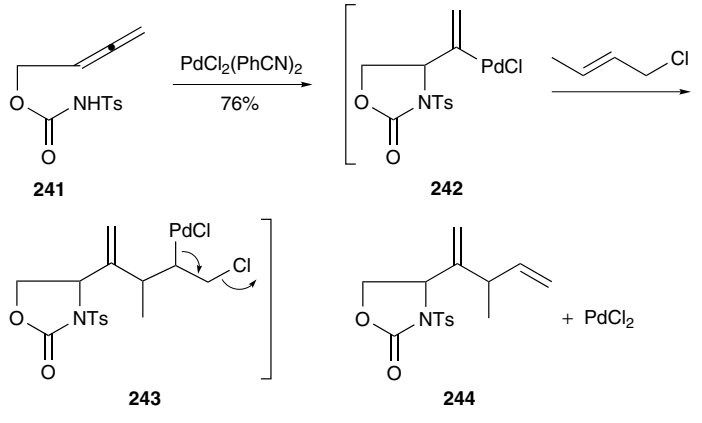
Treatment of **232** with $CuCl_2$ affords 2,3-bis(chloromethyl)-1,3-butadiene (**234**) and regenerates $PdCl_2$. Thus preparation of this interesting dimerization product **234** can be carried out with a catalytic amount of $PdCl_2$ and 2 equivalents of $CuCl_2$ in MeCN [102].

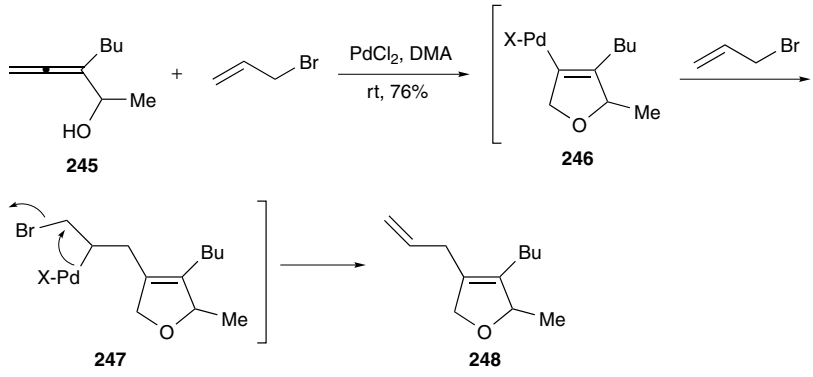


Intramolecular reaction of allenes is known to proceed mainly by palladation at the central carbon to generate alkenylpalladium **235**, which undergoes further reactions. Also π-allylpalladium **236** is formed when a nucleophile attacks the central carbon. The intramolecular aminopalladation of the 6-aminoallene **237**, followed by CO insertion, afforded the unsaturated amino ester **238**. The reaction has been applied to the enantioselective synthesis of pumiliotoxin [103]. Oxycarbonylation of the allenyl alcohol **239** afforded the unsaturated ester **240** in 83 % yield using a catalytic amount of $PdCl_2$ and 3 equivalents of $CuCl_2$ in MeOH and is used for the synthesis of rhopaloic acid [104].

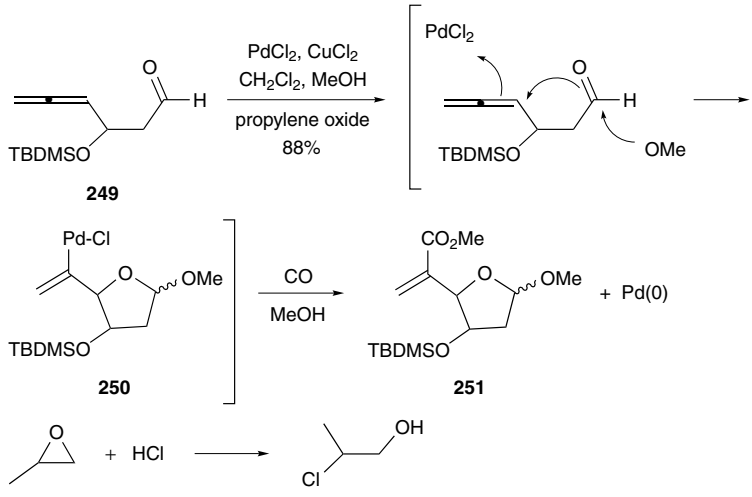


Aminopalladation of the carbamate **241** generates **242** and subsequent insertion of allylic chloride and dechloropalladation as shown by **243** as a Pd(II)-generation step affords the diene **244** and generates $PdCl_2$. Therefore the reaction proceeds with a catalytic amount of $PdCl_2$ without a reoxidant [105]. Similarly, oxypalladation of the 2,3-allenol **245** generates **246**. Reaction of allyl bromide and debromopalladation as shown by **247** produced 4-allyl-2,5-dihydrofuran **248** using 5 mol% of $PdCl_2$ [106].





Intramolecular oxypalladation of the allenyl aldehyde **249** generates the intermediary alkenylpalladium complex **250**, and subsequent carbonylation affords the unsaturated ester **251** in 88 % yield. Propylene oxide is added as a scavenger of HCl [107].

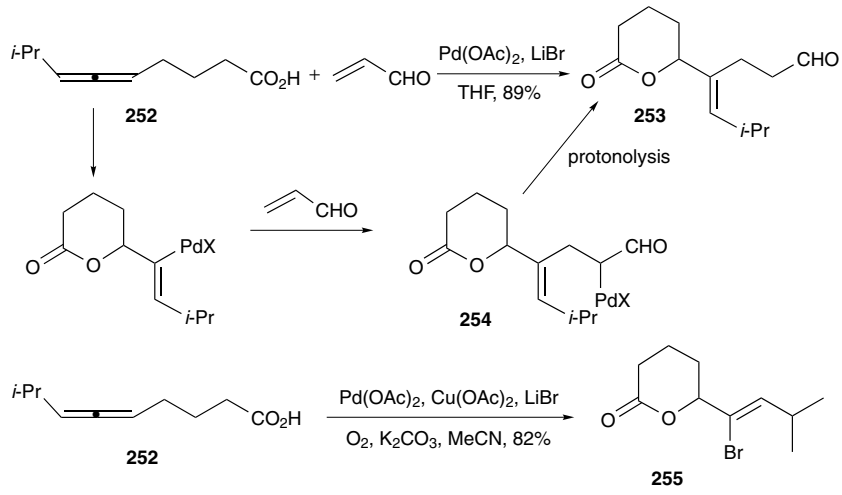


Intramolecular oxypalladation of 5,6-dienoic acid **252** is followed by acrolein insertion to generate **254**, which undergoes protonolysis to produce the aldehyde **253** without giving β-H elimination product as a Heck-type reaction. The reaction proceeds with a catalytic amount of $Pd(OAc)_2$ in the presence of LiBr, which plays an important role in inhibiting β-H elimination in **254** [108]. Reaction of **252** in the presence of $Pd(OAc)_2$, Cu(OAc), LiBr and O_2 in MeCN provided alkenyl bromide **255** [109].

2.6 Reaction of Alkynes

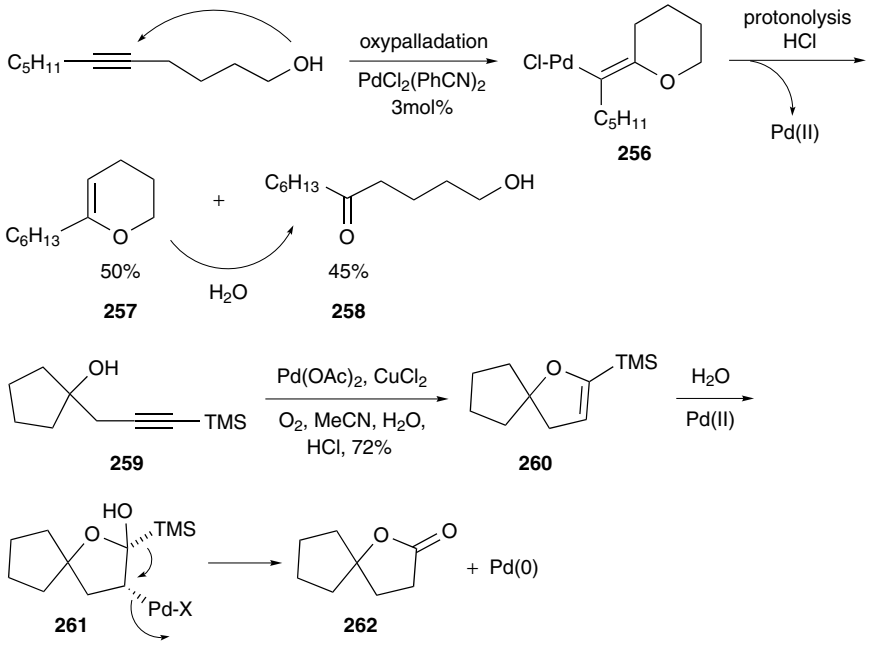
Alkynes undergo several Pd(II)-promoted stoichiometric oxidative reactions via facile palladation. However, in some cases, reactions proceed with a catalytic amount of Pd(II) via *in situ* regeneration of Pd(II) by protonolysis.

Various heterocyclic compounds can be synthesized by Pd(II)-catalyzed reaction of alkynoic alcohols, carboxylic acids and amines via oxy- or aminopalladation

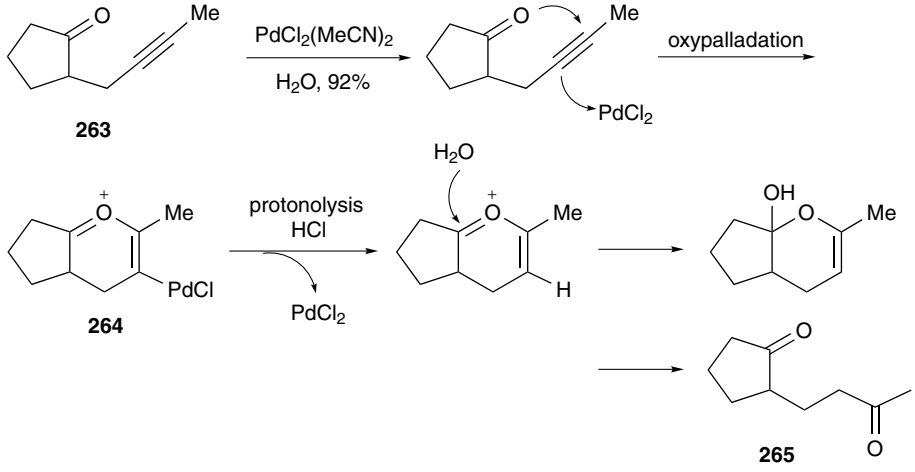


of triple bonds. Intramolecular oxypalladation of 5-undecyn-1-ol with a catalytic amount of $PdCl_2(PhCN)_2$ generates the vinylpalladium **256**. The dihydropyran **257** and the keto alcohol **258** are produced by protonolysis of the oxypalladation product **256** as the Pd(II)-generation step. The reaction shows the possibility of regioselective hydration of alkynes [110].

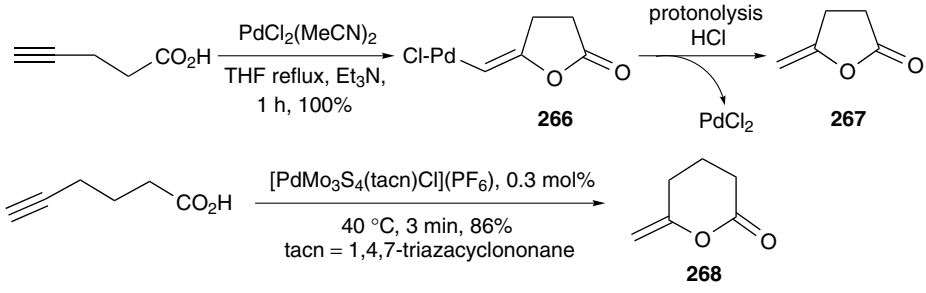
γ-Lactone **262** was obtained by the treatment of 4-(trimethylsilyl)-3-butyn-1-ol **259** with $Pd(OAc)_2$ and $CuCl_2$ under oxygen. Oxypalladation of **259** and protonolysis give **260**. Then hydroxypalladation of **260**, followed by desilylpalladation affords **262** and Pd(0), which is oxidized *in situ* to Pd(II) with $CuCl_2$ [111]. The reaction shows that the silylacetylene is a synthetic equivalent of (—CH_2CO_2H).



Regioselective hydration of the alkynyl ketone **263** is also catalyzed by $PdCl_2$ to afford the 1,5-diketone **265** under mild conditions. Protonolysis of the oxypalladation product **264** generates Pd(II), and the 1,5-diketone **265** is formed by hydration of the intermediate [112].

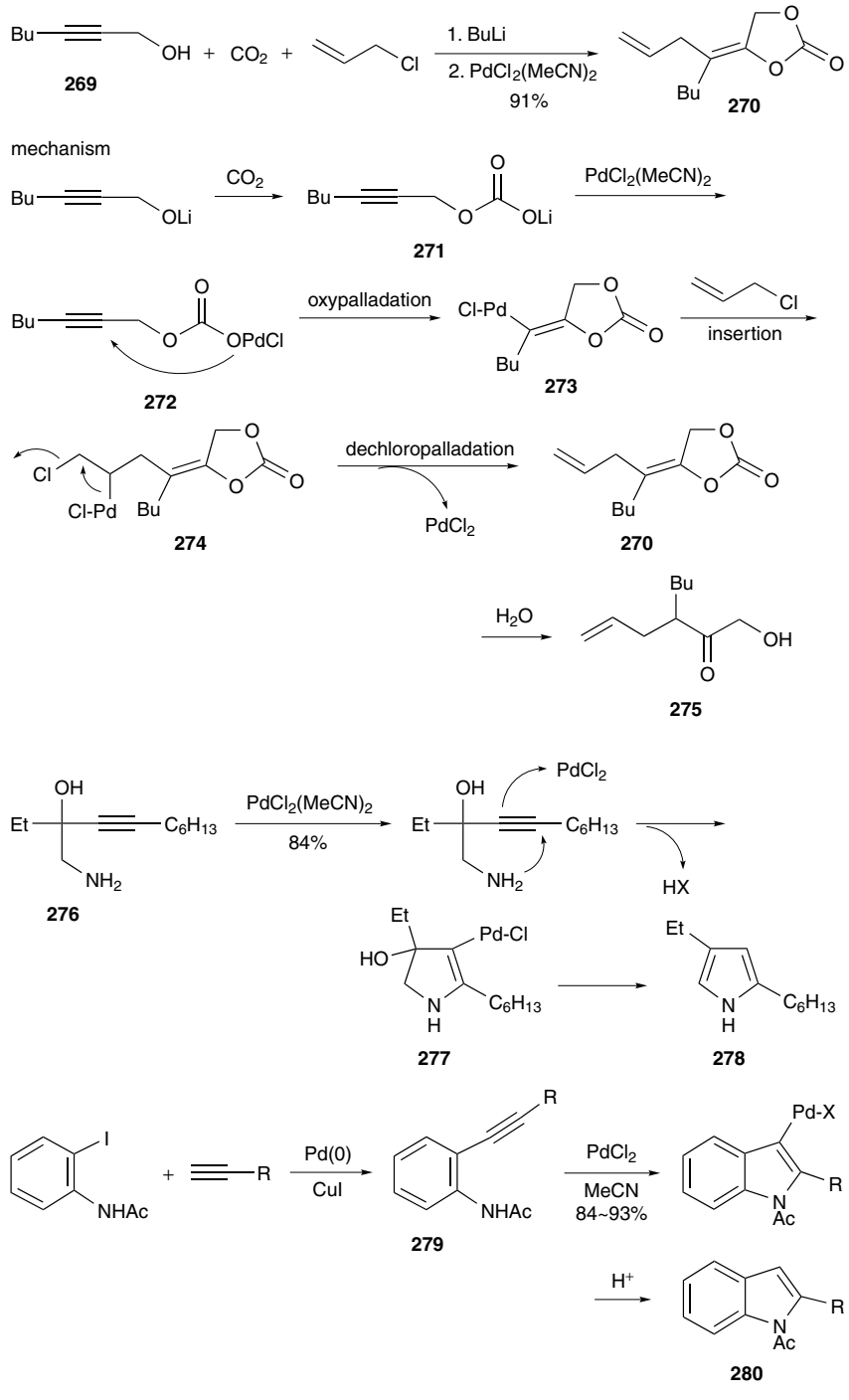


$PdCl_2$-catalyzed oxypalladation of 4-pentynoic acid generates the γ-lactonic alkenylpalladium **266**, and its protonolysis affords the γ-methylene-γ-lactone **267** with regeneration of Pd(II) [113]. A palladium cluster is a very active catalyst of the cyclization, and the δ-methylene-δ-lactone **268** was obtained from 5-hexynoic acid in high yield at 40 °C in a few minutes [114].

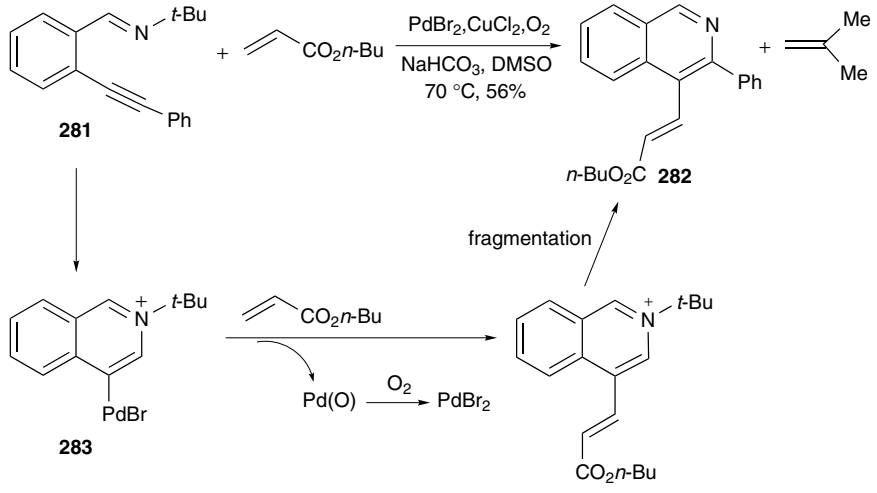


The $PdCl_2$-catalyzed reaction of propargylic alcohol **269**, CO_2 and allyl chloride yields the cyclic carbonate **270** in the presence of BuLi. In this reaction, lithium 2-alkynyl carbonate **271** undergoes oxypalladation as shown by **272** to generate the cyclic carbonate **273**. Insertion of allyl chloride gives **274**, which undergoes dechloropalladation as shown by **274** to give the cyclic carbonate **270** and $PdCl_2$. Hydrolysis of the carbonate affords the 2-oxo-3-butyl-5-hexen-1-ol (**275**) [115].

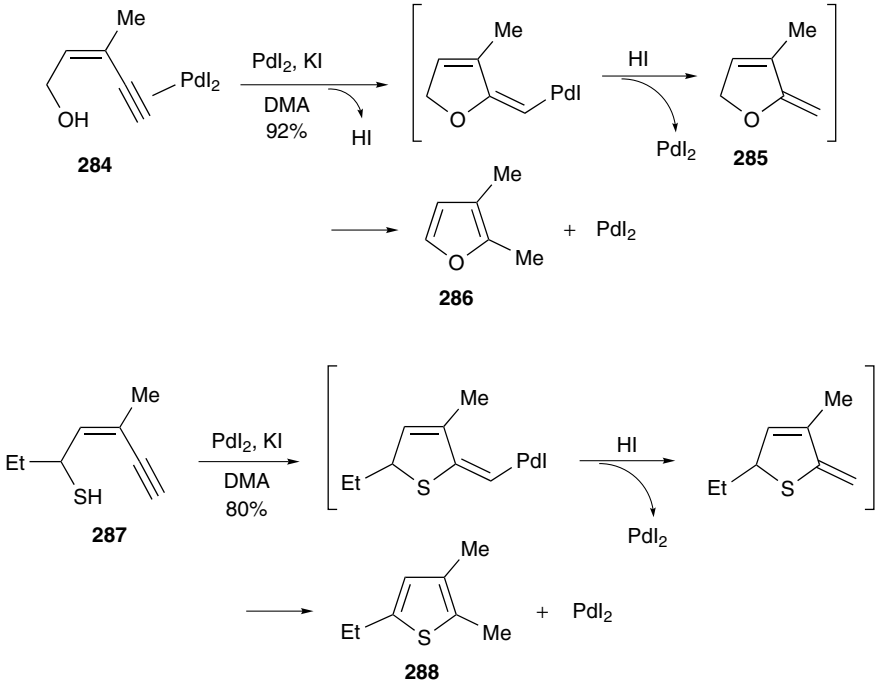
Formation of the pyrrole **278** from 1-amino-3-alkyn-2-ol **276** is catalyzed by $PdCl_2$. The reaction can be understood as aminopalladation to generate **277**, followed by protonolysis and dehydration [116]. Indoles are prepared from *o*-alkynyl aromatic amines. The required alkynyl amine **279** is prepared from *o*-iodoacetanilide. Aminopalladation of **279** and protonolysis affords **280** [117].



4-(1-Alkenyl)isoquinoline **282** was obtained by the reaction of 2-(1-alkynylphenyl)aldimine **281** with acrylate in DMSO. Cyclization of benzaldimine by $PdBr_2$ generates **283**, and insertion of acrylate, followed by β-H elimination gave **282** and Pd(0), which was oxidized to Pd(II) with $CuCl_2$ and O_2. Finally the isoquinoline **282** was formed by fragmentation [118].

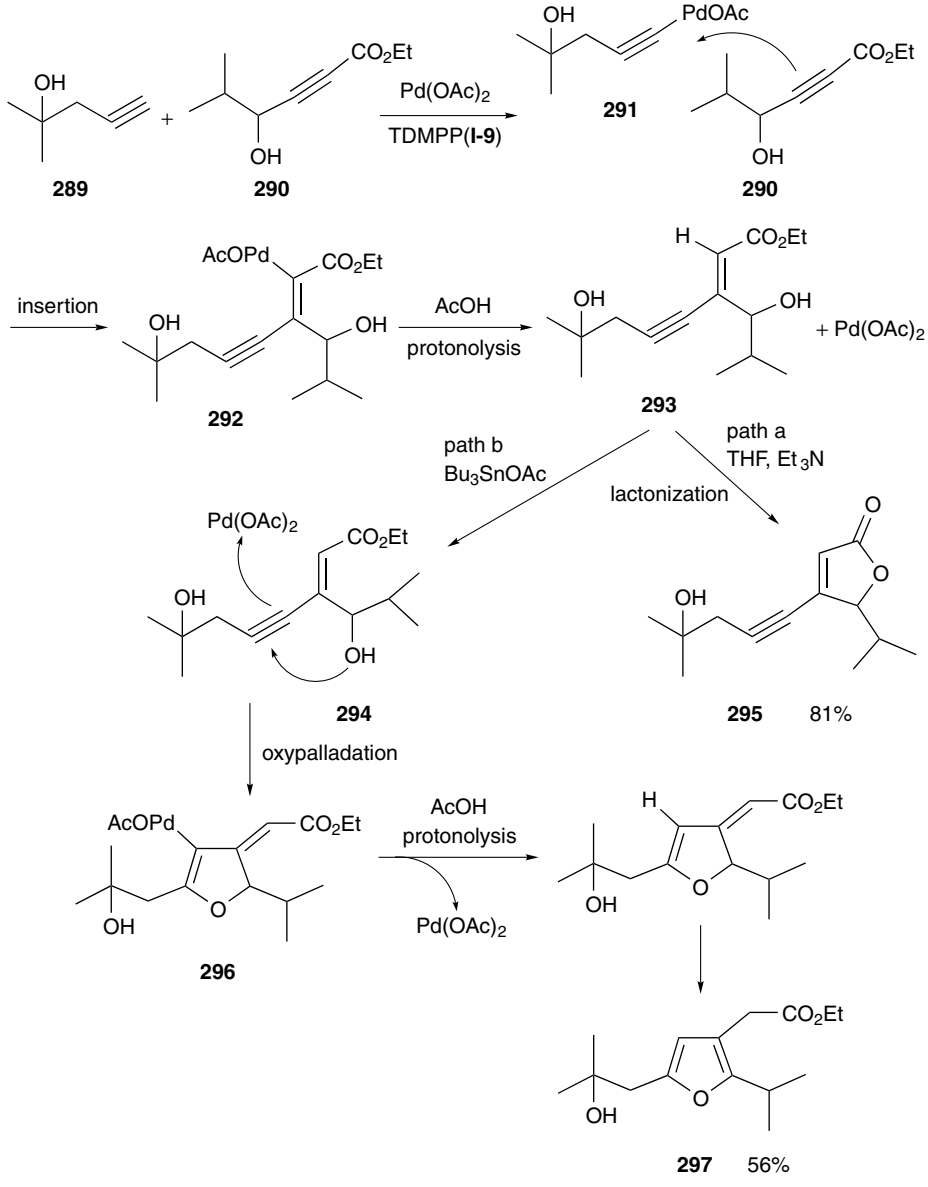


Treatment of (*Z*)-pent-2-en-4-yn-1-ol **284** with PdI_2 and KI afforded furan **286** via oxypalladation, followed by protonolysis to give **285** and regeneration of PdI_2. KI is added to make PdI_2 soluble [119]. The corresponding thiol **287** undergoes a similar cyclization to form the thiophene **288** [120].



An enyne system **292**, which can be generated by Pd-catalyzed domino reactions of the terminal alkyne **289** with the alkynoate **290**, undergoes cyclization to give the furan **297** and the butenolide **295** under different conditions [121]. The reaction of the terminal alkyne **289** with $Pd(OAc)_2$ using TDMPP (**I-9**) as a ligand

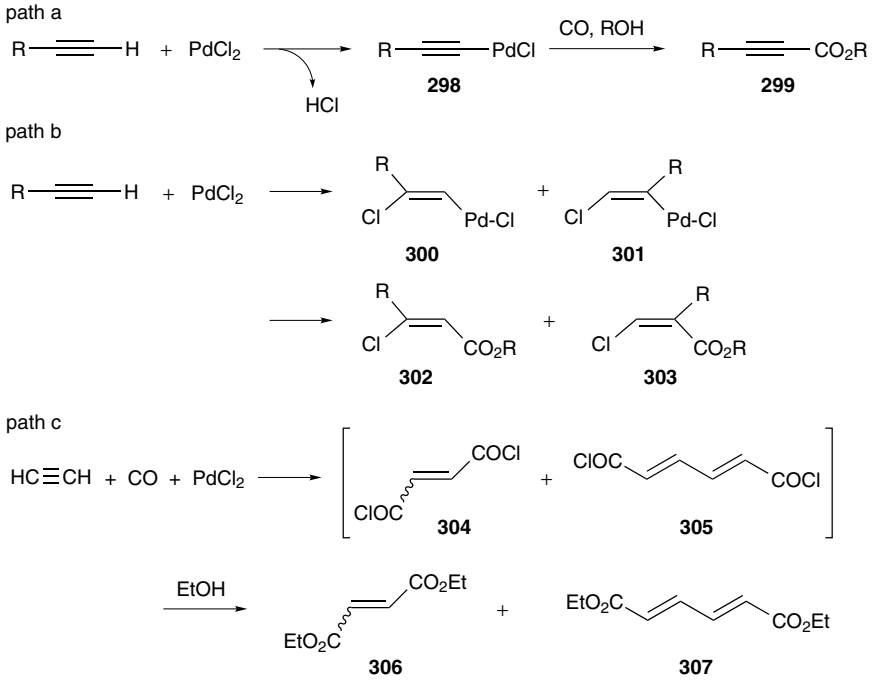
generates alkynylpalladium **291**. Insertion of **290** to **291** gives **292**. The enyne system **293** is formed by protonolysis of **292**. In the presence of triethylamine, lactonization of **293** takes place to afford the butenolide **295** in 81 % yield. On the other hand, the furan **297** is obtained in the presence of tributyltin acetate. In these reactions, protonolysis of **292** and **296** with AcOH generates $Pd(OAc)_2$ and hence the oxidative reaction proceeds with a catalytic amount of $Pd(OAc)_2$.



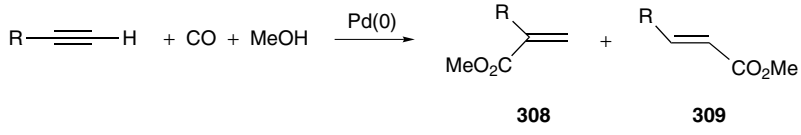
Oxidative carbonylation is another useful reaction. The following three types of oxidative carbonylation of alkynes are known. The first one is the synthesis of the acetylene carboxylates **299** via formation of the alkynylpalladium intermediate **298** from terminal alkynes (path a) [122].

The second type of carbonylation starts by *cis* chloropalladation of triple bonds to generate **300** and **301**, and CO insertion gives the unsaturated β-chloro esters **302** and **303** (path b).

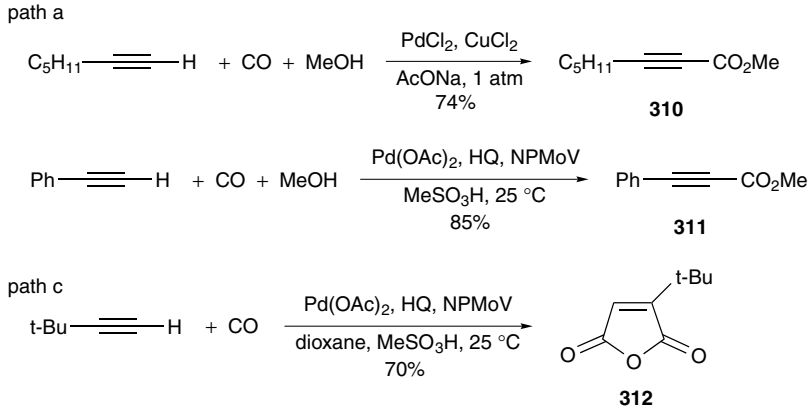
In the third type, oxidative dicarbonylation of alkyne gives maleate, fumarate and muconate derivatives **304** and **305** by dimerization and dicarbonylation, which are then converted to the corresponding esters **306** and **307** (path c) [123]. Methyl muconate was obtained as a main product in MeOH containing thiourea and a catalytic amount of $PdCl_2$ by using acetylene and oxygen [124].



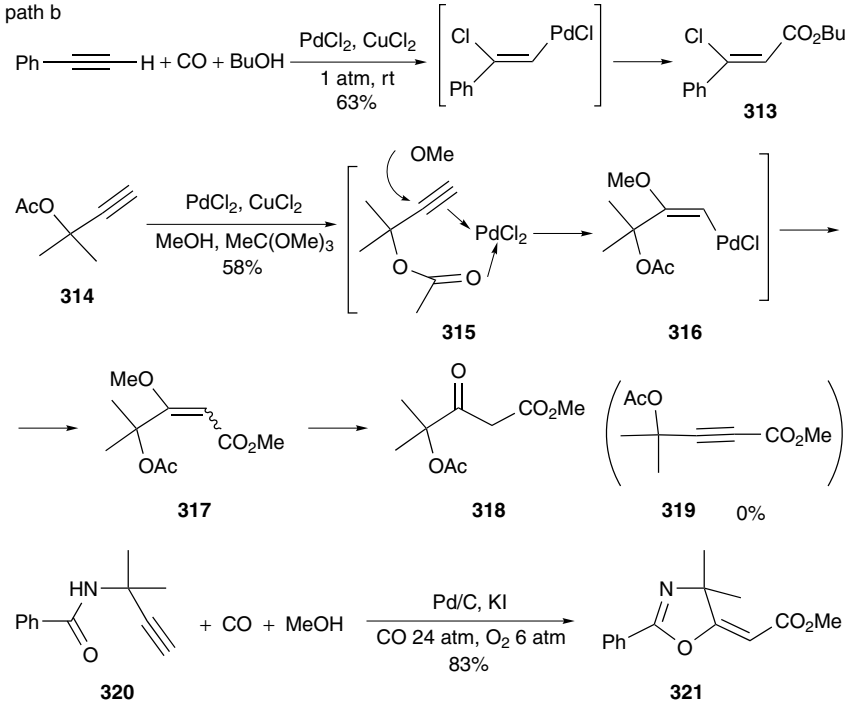
Hydrocarbonylation of alkynes to give the unsaturated esters **308** and **309**, catalyzed by Pd(0), is clearly different from the oxidative carbonylation, and this process is treated in Chapter 7.11.



Reaction of various terminal alkynes using $PdCl_2$ and $CuCl_2$ in the presence of a base affords the alkynic esters **310** in satisfactory yields (path a) [122]. Carbonylation of terminal alkynes proceeds smoothly using $Pd(OAc)_2$, hydroquinone and heteropolyacid (molybdovanadophosphate, NPMoV) in the presence of $MeSO_3H$ under oxygen at room temperature. Different products are obtained depending on the solvents. In MeOH, the acetylenic ester **311** was obtained (path a), but α-alkylmaleic anhydride **312** was obtained in dioxane (path c) [125].

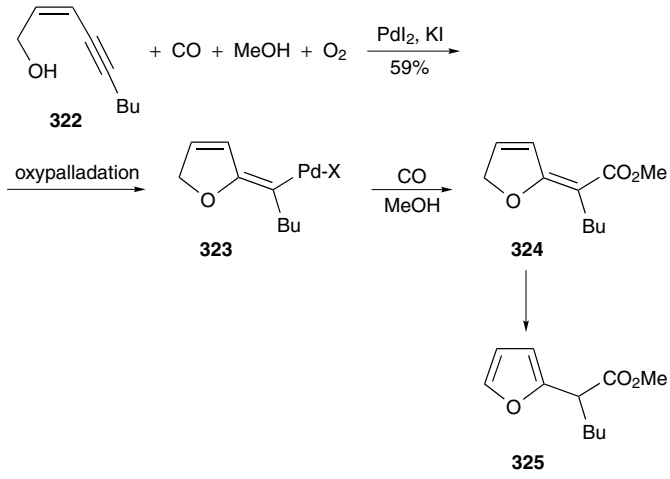


An example of path b-type reaction is regioselective chlorocarbonylation of phenylacetylene using $PdCl_2$ and $CuCl_2$ to give the 3-chloro-3-phenylacrylate (**313**). The reaction is understood by chloropalladation of alkynes, followed by CO insertion [126]. As a related reaction, oxidative carbonylation of the terminal propargylic acetate **314** gives γ-acetoxy-β-methoxy-α,β-unsaturated ester **317**, which is hydrolyzed to give the β-keto ester **318**. The reaction proceeds via regioselective methoxypalladation of the triple bond as shown by **315** and **316** [127]. It should be pointed out that these path b carbonylations of terminal alkynes are carried out without addition of bases, and no path a-type carbonylation to give acetylene carboxylates **319** is observed. 5-(Methoxycarbonyl)methylene-3-oxazoline **321** is obtained by oxidative carbonylation of the benzamide **320** using

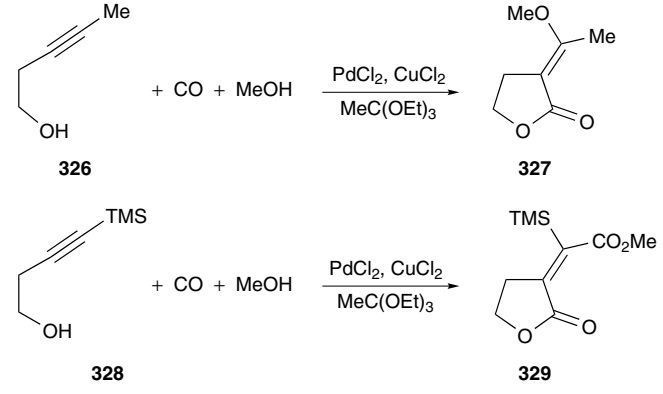


Pd on carbon as a catalyst, and O_2 and KI as oxidants. *anti*-Attack to the triple bond takes place to give the *E*-product stereoselectively [128].

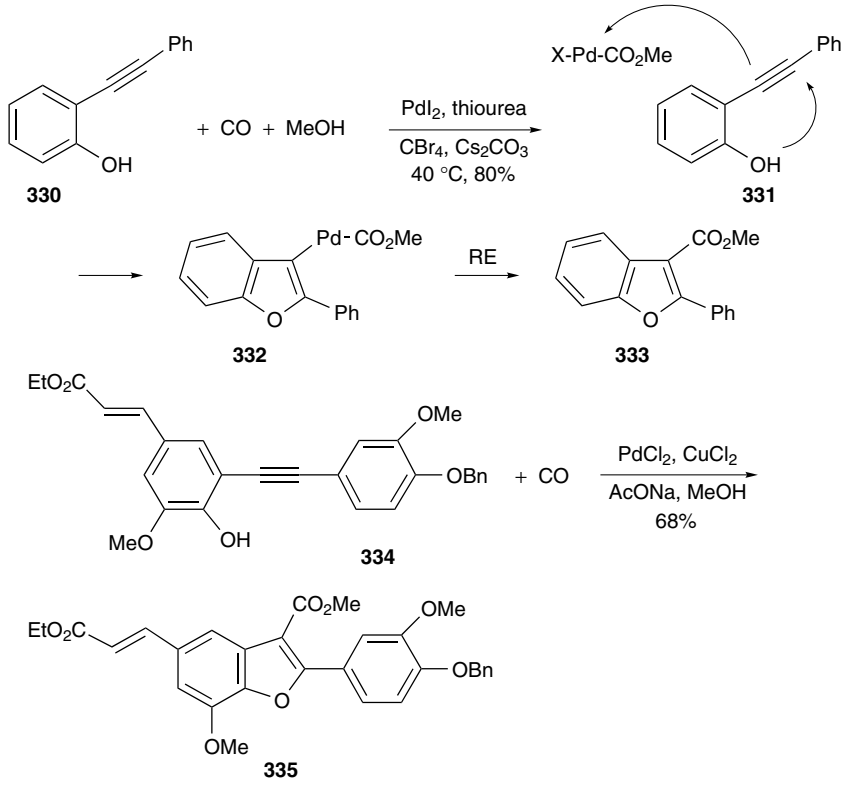
Intramolecular path b-type reaction of (*Z*)-alk-2-en-4-yn-1-ols **322**, catalyzed by PdI_2 and KI, produced the furan-2-acetic ester **325** by efficient oxidative carbonylation. The reaction is explained by intramolecular oxypalladation of the triple bond to generate **323**, followed by CO insertion to give **324** and double bond isomerization [129].



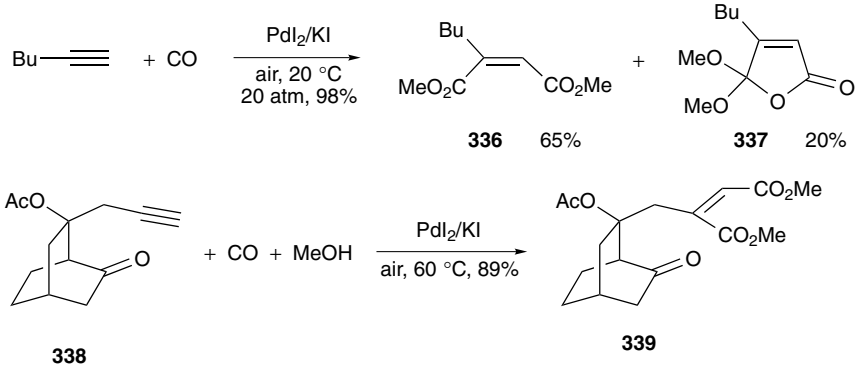
Carbonylation of the 3-butyn-1-ols under mild conditions gives different products depending on substituents. The lactone **327** was obtained from 3-pentyn-1-ol (**326**) by path b-type reaction. The lactonic ester **329** was obtained by path c-type reaction from **328** which has a TMS group at the alkyne terminus [65].



Similarly, *o*-hydroxyphenylacetylene **330** underwent carbonylative cyclization to give benzofuran-3-carboxylate **333**. As catalysts, PdI_2–thiourea–CBr_4 [130] or $PdCl_2$–$CuCl_2$ [131] are used. As a mechanistic explanation, the reaction proceeds by carbopalladation of methoxycarbonylpalladium as shown by **331** to give **332** and its reductive elimination. The reaction of *o*-hydroxyphenylacetylene **334** catalyzed by $PdCl_2$ and BQ afforded the benzo[*b*]furan-3-carboxylate derivative **335** [132].

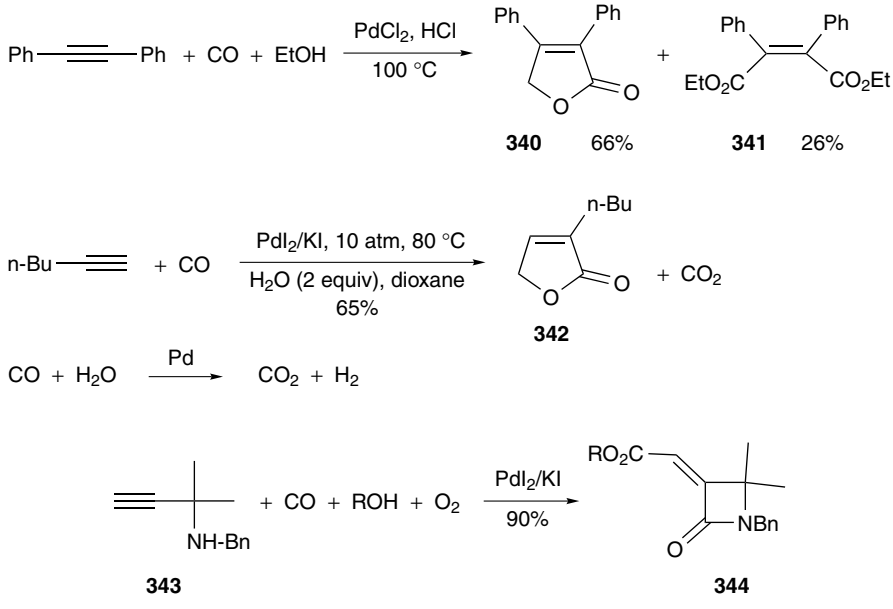


An efficient and selective dicarbonylation of terminal alkynes mainly to *E* form can be carried out under mild conditions using PdI_2 and KI under pressure of CO and air. From 1-hexyne, dimethyl butylmaleate (**336**) was obtained as a main product and the acetal of butylmaleic anhydride **337** as a minor product [133]. Iodine is an oxidant. The usefulness of this reaction was demonstrated by the smooth preparation of a synthetic intermediate of CP-263,114 **339** from the terminal alkyne **338** in high yield [134].

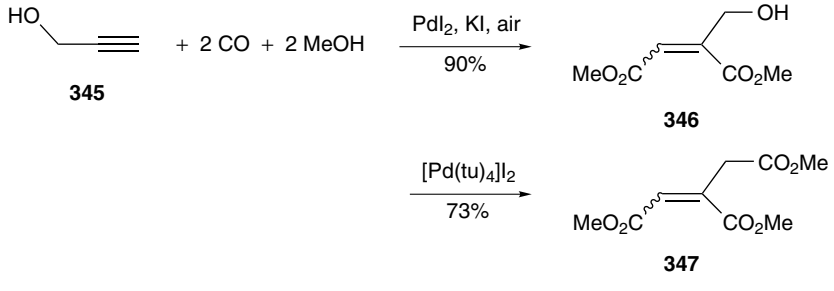


In some cases, oxidative carbonylation proceeds even in the absence of any oxidant. As an example, diphenylcrotonolactone (**340**) was obtained unexpectedly

as a major product by the carbonylation of diphenylacetylene in EtOH together with diethyl diphenylmaleate (**341**) using $PdCl_2$ and HCl. In this oxidative carbonylation, reduction of an anhydride to a lactone occurred [135]. The unsaturated lactone [3-substituted furan-2(5*H*)-one] **342** was obtained from 1-hexyne using PdI_2 and KI under milder conditions. The presence of water is essential. Formation of CO_2 was observed showing that the reduction occurred with H_2 generated from CO and water [136]. Under similar conditions, oxidative dicarbonylation of the propargylamine **343** affords the β-lactam **344**. Also γ-lactams and oxazolines were obtained depending on the protecting groups of the amine [137].

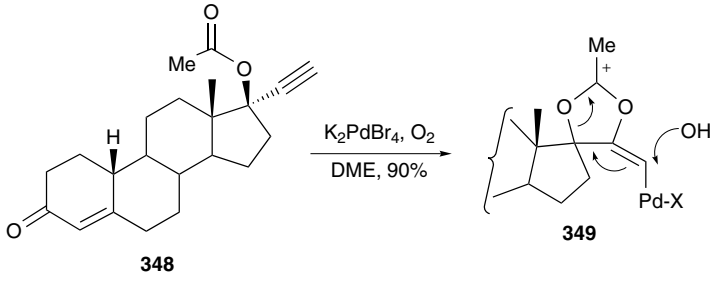


Several products are obtained by Pd-catalyzed carbonylation of propargyl alcohol (**345**). As one example, aconitate is obtained as a minor product in the carbonylation of propargyl alcohol [138]. However, trimethyl aconitate (**347**) was obtained in 70 % overall yield from **345** in two steps. The first step is the oxidative carbonylation under CO and air using PdI_2 and KI to give dimethyl hydroxymethylbutenedioate (**346**), which is carbonylated further to give **347** using $[Pd(tu)_4]I_2$ (tu = thiourea) as a catalyst [139].

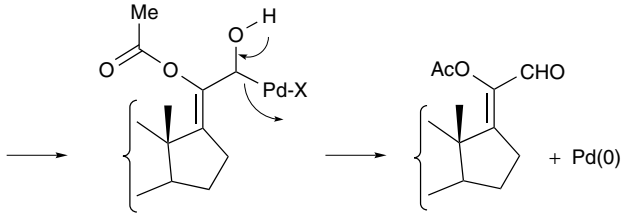


Propargyl ester **348** undergoes an interesting oxidative rearrangement by using a catalytic amount of $PdBr_2$ under an oxygen atmosphere to form the α-acetoxy-α,β-unsaturated aldehyde **351** [140]. The first step is oxypalladation to form **349**, and subsequent hydration as shown by **349** and **350** gives rise to the aldehyde **351**. Interestingly, reoxidation of Pd(0) takes place smoothly under oxygen without using other reoxidants. Since it is known that the aldehyde **351** can be converted to **352** with a base, the reaction offers an efficient synthetic method for corticosteroids from 17-keto steroids [141,142]. The internal alkyne **353** undergoes similar rearrangement to give the α-acetoxy-α,β-unsaturated ketone **354**. No reaction takes place in the absence of water and oxygen. The ketone **354** is hydrolyzed to give the α-diketone **355**. The reaction offers a synthetic method for α-diketones [143].

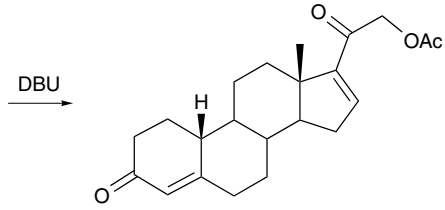
Pd(0)-catalyzed hydrocarbonylation of propargyl alcohols is treated in Chapter 6.3.



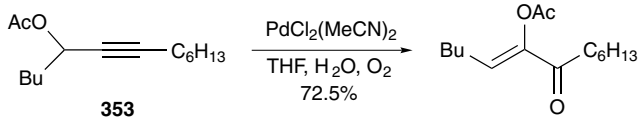
348 **349**



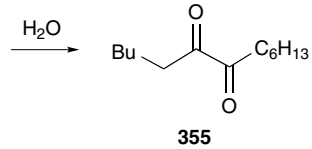
350 **351**



352

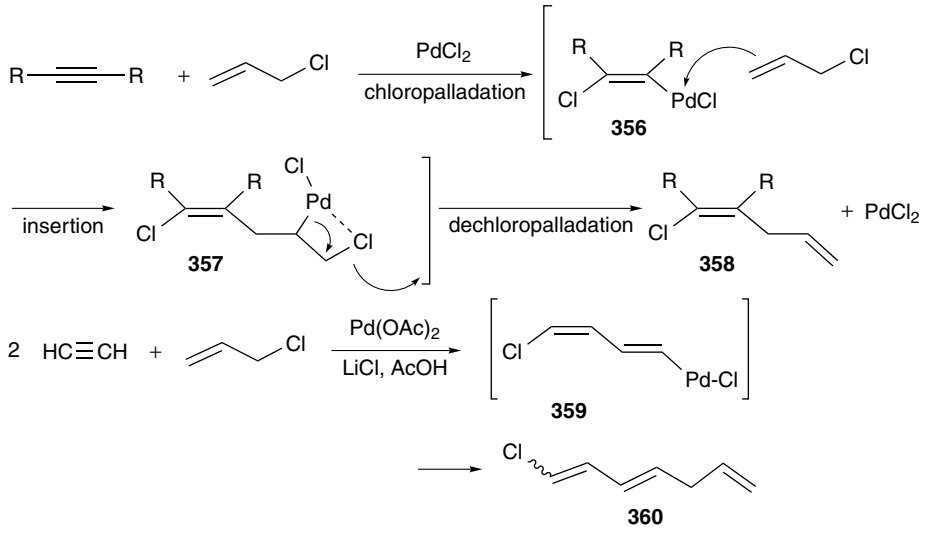


353 **354**

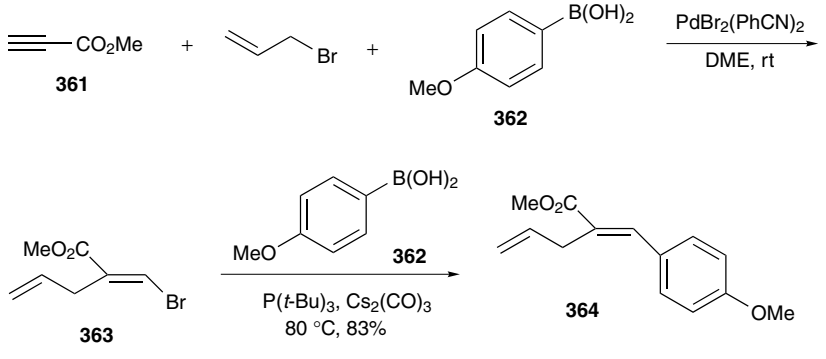


355

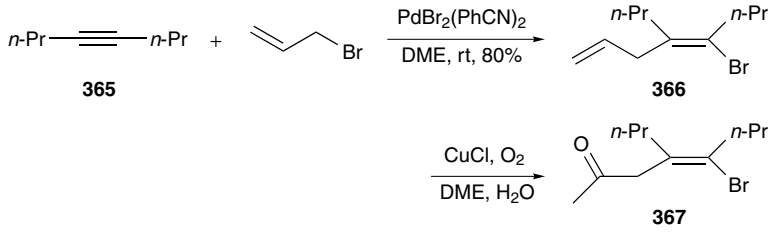
The chloroallylation of alkynes with allyl chlorides affords 1-chloro-1,4-dienes **358** using $PdCl_2$ as a catalyst. The reaction can be understood by chloropalladation of alkyne to generate **356**, followed by insertion of the double bond of allyl chloride to give **357**. The last step is the well-established dechloropalladation to afford the chlorodiene **358** as the Pd(II)-generation step. In this case, no β-H elimination occurs. Interaction of Pd-Cl plays a role [144]. $Pd(OAc)_2$-catalyzed reaction of acetylene and allyl chloride in the presence of LiCl affords an *E*, *Z*-mixture of the 1-chloro-1,3,6-heptariene (**360**). In this case, first insertion of acetylene occurs to give **359**, and then the insertion of allyl chloride follows [145].



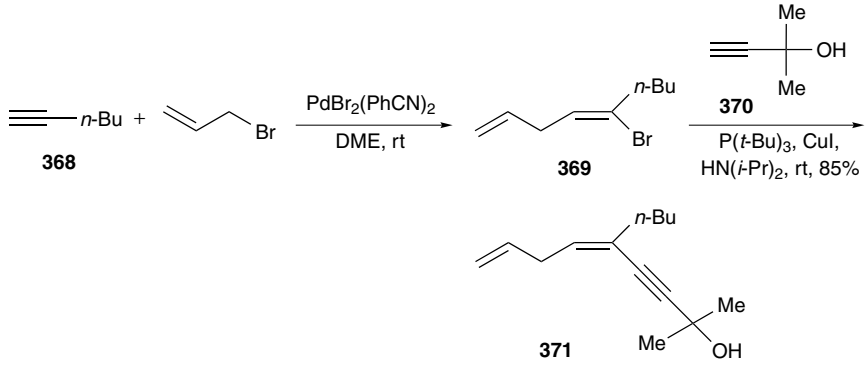
The bromoallylation product **363** of the alkyne **361** was converted to the 1-aryl-1,4-pentadiene **364** in 83 % yield by adding the the organoborane **362**, $P(t\text{-}Bu)_3$ and Cs_2CO_3. Thus the haloallylation products, obtained by the reaction shown above, are reactive alkenyl halides and further Pd-catalyzed conversion is possible as a two-step, one-pot reaction [146].



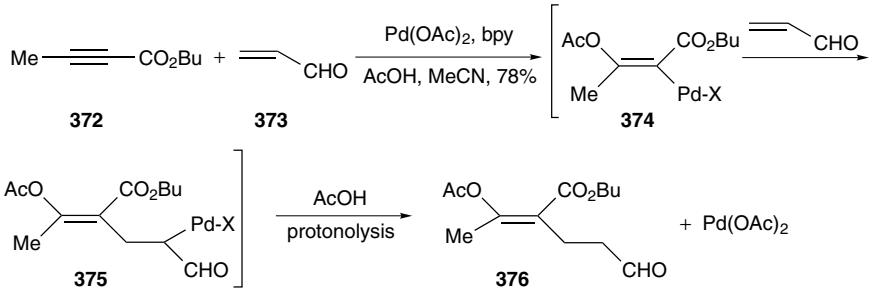
The ketone **367** was obtained in one pot by oxidation of the terminal double bond of the bromoallylation product **366** of the alkyne **365** by adding CuCl and H_2O under O_2 atmosphere [146].



Preparation of hepta-2,6-dien-2-yne **371** is possible by combination with the Sonogashira reaction. The dienyne **371** was obtained by Sonogashira coupling of the bromoallylation product **369** with the alkyne **370** at room temperature using CuI and P(*t*-Bu)$_3$ [147].

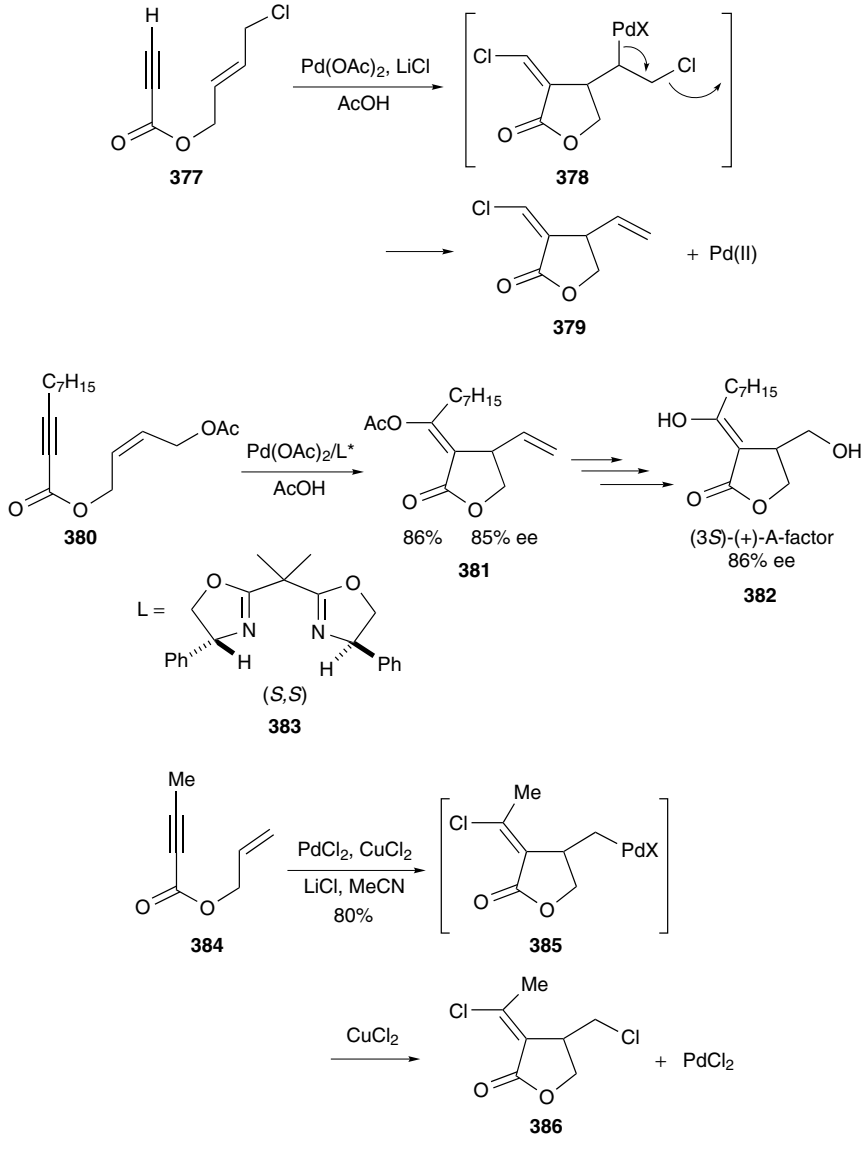


γ,δ-Unsaturated carbonyl compounds are obtained by the domino reaction of alkynes with acrolein or methyl vinyl ketone. Treatment of the alkyne **372** and acrolein (**373**) with Pd(OAc)$_2$ (5 mol%) generates the acetoxylpalladation product **374**, and insertion of acrolein to **374** gives **375**, which is converted to the aldehyde **376** by protonolysis with AcOH, and Pd(OAc)$_2$ is regenerated. The use of bpy (6 mol%) or phenanthroline as a ligand is important. The ligand plays a crucial role in inhibiting β-H elimination and assisting protonolysis [148].

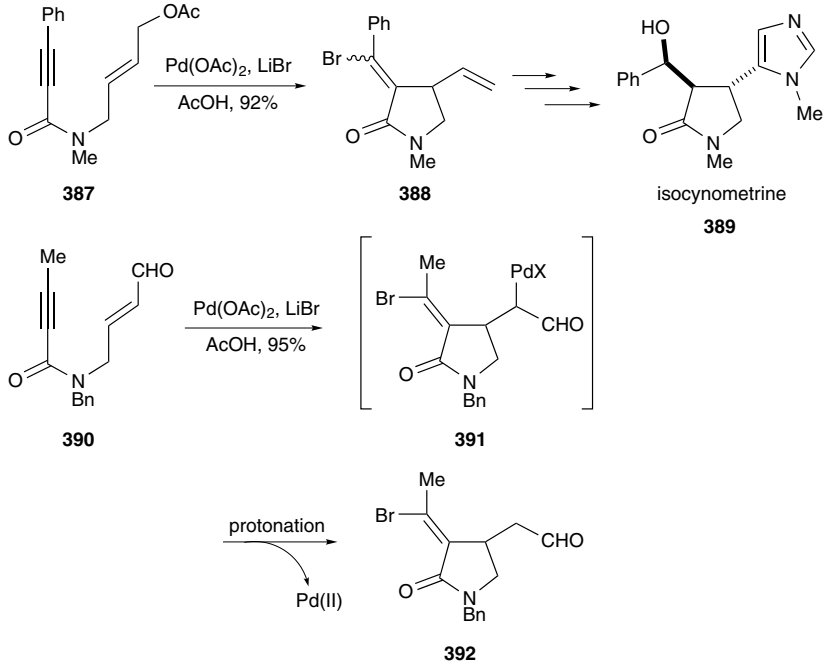


An interesting and useful synthetic method of γ-lactones has been developed by Lu and co-workers based on an intramolecular version of the haloallylation reactions [149]. $PdCl_2$ or Pd(OAc)$_2$-LiCl-catalyzed reaction of the 3′-(chloromethyl)-2′-alkenyl 2-alkynoates **377** affords the α-alkylidene-β-vinyl-γ-butyrolactones **379**. The first step is chloropalladation of the triple bond, followed by

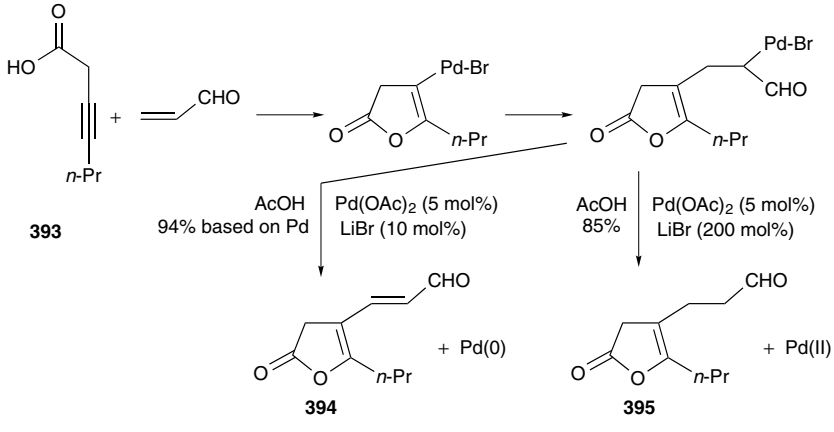
insertion of the double bond to generate **378**. The last step is dechloropalladation of the insertion product **378** to give the vinyl group **379** without undergoing β-H elimination. The reaction of the 2-alkynoate bearing an allylic acetate moiety **380** using $Pd(OAc)_2$ and the chiral bisoxazoline ligand **383** afforded the β-vinylbutyrolactone **381** in 85 % ee. In this reaction, acetoxypalladation of the triple bond is followed by insertion of olefin bond, and deacetoxypalladation is the last step, and A-factor **382** (86 % ee) was synthesized from **381** [150]. The cyclization was extended to the allyl 2-alkynoates **384** without 4′-heteroatom [151]. In this case, the insertion products must be quenched by oxidative cleavage to generate Pd(II). Thus different products are obtained depending on methods of quenching the insertion products. In the presence of $CuCl_2$, oxidative chlorination of the insertion product **385** takes place to give the β-chloromethyllactones **386**. Quenching is also possible by protonolysis and carbonylation [152].



Similarly, γ-lactams are prepared from 2-alkynamides bearing an allyl acetate moiety on nitrogen. The last step is deacetoxypalladation to generate Pd(II) [153]. The α-alkylidene-γ-butyrolactam **388** was obtained by cyclization of the *N*-allylic 2-alkynamide **387** using $Pd(OAc)_2$ and LiBr, and the reaction has been applied to the synthesis of isocynometrine (**389**) [154]. The aldehyde **392** was obtained by cyclization of the alkynic α,β-unsaturated aldehyde **390**, followed by protonolysis of the insertion product **391** with AcOH [155].



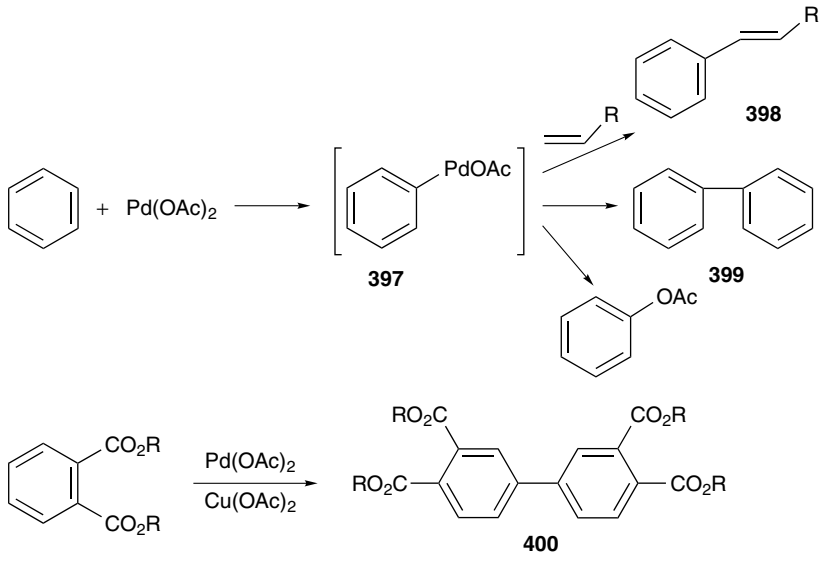
In the reactions shown above, preferential β-heteroatom elimination occurs rather than β-H elimination. Lu reported that the presence of a halide ligand effectively blocks β-H elimination. Thus the different products were obtained depending on the amounts of added LiBr in the reaction of 3-heptynoic acid (**393**) with acrolein. In the presence of 200 mol% LiBr in AcOH, protonolysis occurs to give **395** and Pd(II), while the unsaturated aldehyde **394** was obtained by a



Heck-type reaction in 94 % yield based on $Pd(OAc)_2$ when 10 mol% of LiBr was used [156].

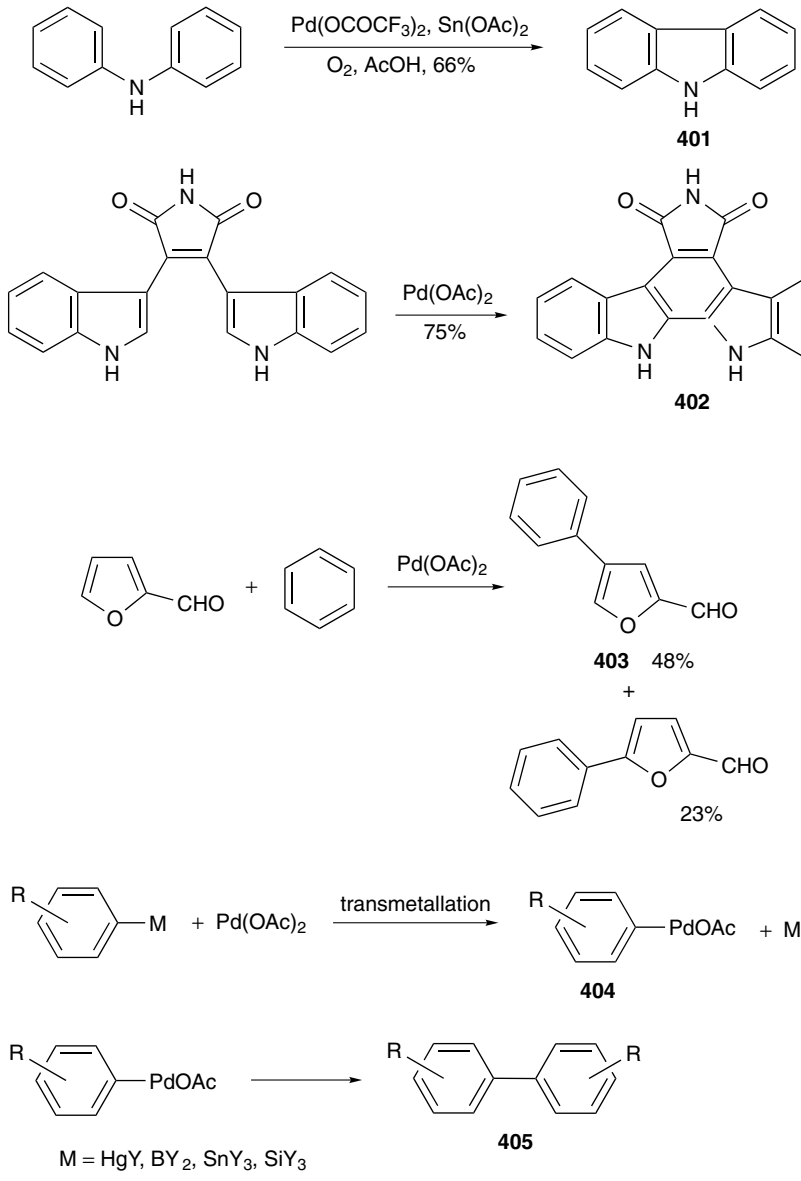
2.7 Homocoupling and Oxidative Substitution Reactions of Aromatic Compounds

Three oxidative reactions of benzene with $Pd(OAc)_2$ via reactive phenylpalladium acetate (**397**) are known. The insertion of alkenes and β-H elimination afford arylalkenes **398**. This topic is treated in Section 2.2.8. Two other reactions, oxidative homocoupling [157,158] and acetoxylation [159] are treated in this section. The palladation of aromatic compounds is possible only with $Pd(OAc)_2$. No reaction takes place with $PdCl_2$. The oxidative homocoupling of benzene with $Pd(OAc)_2$ affords biphenyl (**399**). The scope of the homocoupling reaction has been studied [160,161]. The reaction was applied to commercial production of biphenyltetracarboxylate (**400**) by coupling of dimethyl phthalate using $Pd(OAc)_2$ and $Cu(OAc)_2$. Addition of phenanthroline is important for the regioselective formation of the most important 3,4,3′4′-isomer [162].



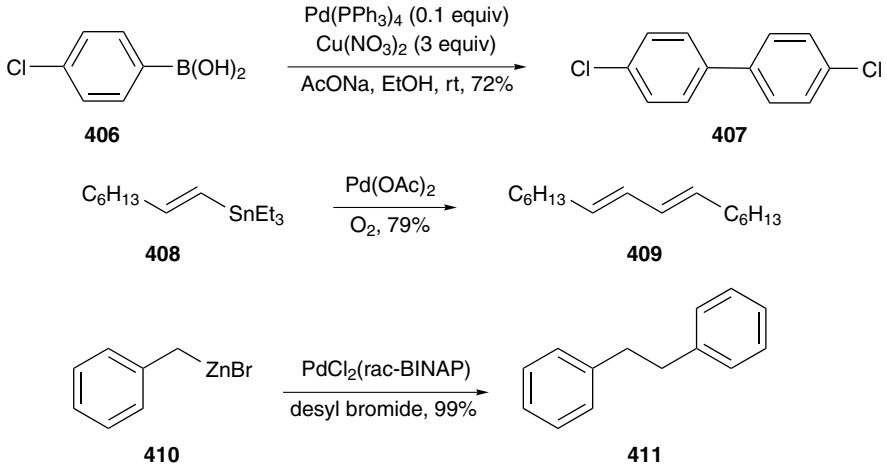
In addition to benzene derivatives, the coupling can be extended to heteroaromatic compounds. Akermark found that preparation of carbazole (**401**) can be carried out using $Pd(TFA)_2$ and $Sn(OAc)_2$ under oxygen in AcOH [74]. Staurosporine aglycone **402** was prepared by the intramolecular coupling of indole rings [163]. The coupling of thiophene, furan and pyrrole [164,165] has been carried out. The oxidative cross-coupling of furans and thiophenes with benzene is possible. 4-Phenylfurfural (**403**) is a main product of the cross-coupling of furfural and benzene [166].

Biaryls are also prepared by oxidative coupling of organometallic compounds. Transmetallation of various organometallic compounds (Hg, Tl, Sn, B, Si, etc.) with Pd(II) generates *in situ* the reactive σ-arylpalladium intermediates **404**, which undergo oxidative homocoupling to afford **405** (similar to formation of **399** from **397**).

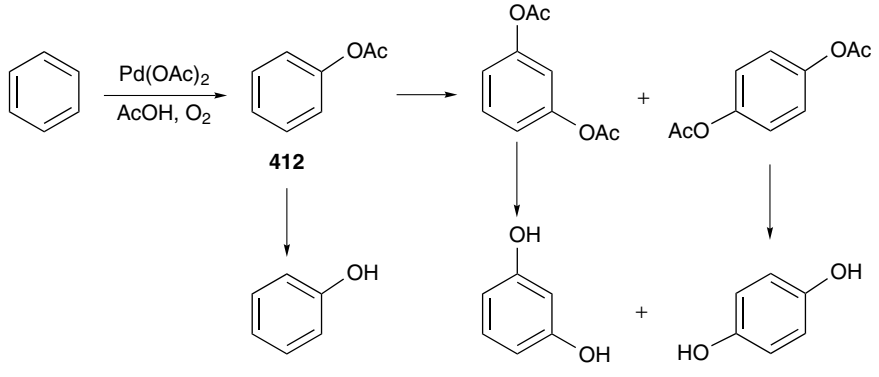


Biaryls are prepared also by homocoupling of arylmetal compounds using several oxidants. Arylbronic acids undergo efficient oxidative coupling [167]. 4,4′-Dichlorobiphenyl (**407**) was obtained in 72 % yield from 4-chlorophenylboronic acid (**406**) using $Cu(NO_3)_2$ as an oxidant [168].

Homocoupling of the alkenylstannane **408** was carried out with $Pd(OAc)_2$ and O_2 to give the conjugated diene **409** [169,170]. Alkyl–alkyl coupling of alkylboranes and alkylzinc compounds promoted by Pd(II) was carried out. Benzylzinc bromide (**410**) was coupled to give **411** in high yield by the treatment with $PdCl_2$(*rac*)-BINAP as a catalyst. In this reaction, desyl bromide (2-bromo-2-phenylacetophenone) or desyl chloride is used as an oxidant of Pd(0) [12]. Also *N*-chlorosuccinimde can be used as the oxidant in arylzinc coupling [171].



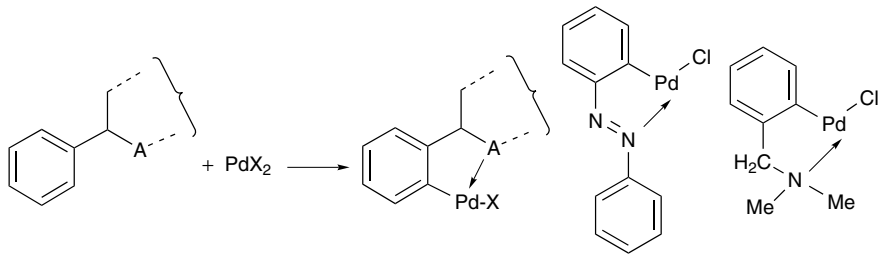
Acetoxybenzene (**412**) is prepared by the reaction of benzene with $Pd(OAc)_2$ [158,172]. This reaction is regarded as a potentially useful method for phenol production from benzene, if carried out with only a catalytic amount of $Pd(OAc)_2$. Further reaction of acetoxybenzene produces 1,3- and 1,4-diacetoxybenzenes.



2.8 Regioselective Reactions Based on Chelation and Participation of Heteroatoms

Unactivated aromatic and alkyl groups can be functionalized by formation of chelate Pd complexes and interesting applications have been published, although most of them are stoichiometric reactions.

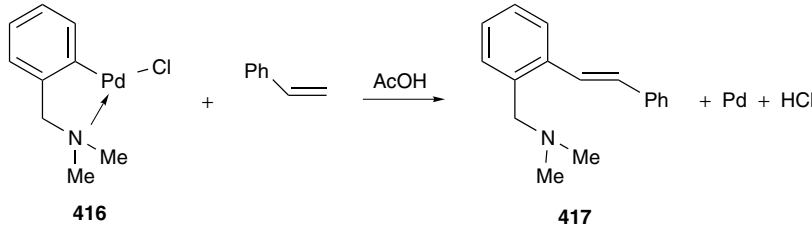
Aromatic compounds **413**, bearing hetero atom-containing groups at positions suitable for forming mainly five-membered or sometimes six-membered chelating rings, undergo cyclopalladation at an *ortho*-position to form a σ-arylpalladium bond as in **414** by virtue of the stabilization due to the chelation of these hetero atoms. The *ortho*-palladation products **414** are stable and can be isolated [173]. After the first report on the preparation of the azobenzene and *N*,*N*-dimethylbenzylamine complexes **415** and **416** [174], numerous complexes have been prepared.



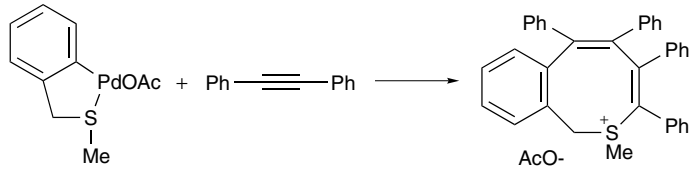
413 **414** **415** **416**

The σ-arylpalladium bonds in these complexes are reactive and undergo insertion and substitution reactions, and the reactions offer useful methods for the regiospecific functionalization of the aromatic rings. Alkenes, alkynes and CO insert under certain conditions. Some classical examples are cited in the following.

The first example is insertion of styrene to *N*,*N*-dimethylbenzylamine complex (**416**) to form the stilbene derivative **417**, which takes place smoothly at room temperature in AcOH [14]. Alkynes insert smoothly. Two moles of diphenylacetylene insert into the benzyl methyl sulfide complex **418** to afford the eight-membered heterocycle **419** [175].



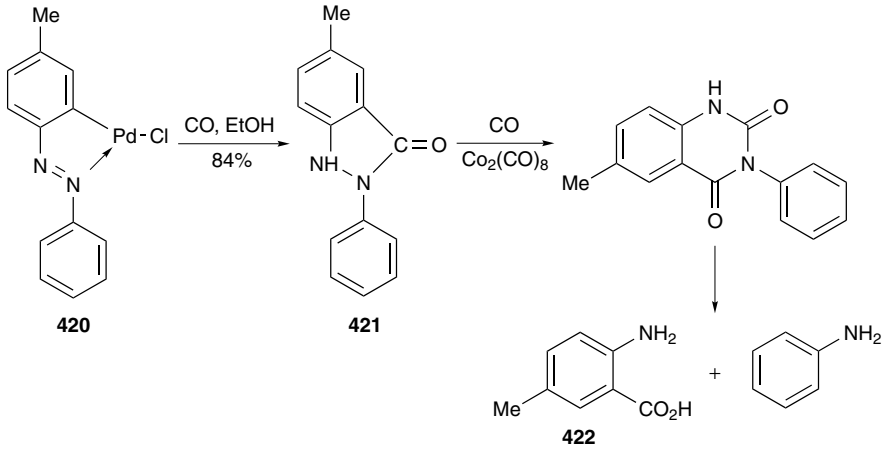
416 **417**



418 **419**

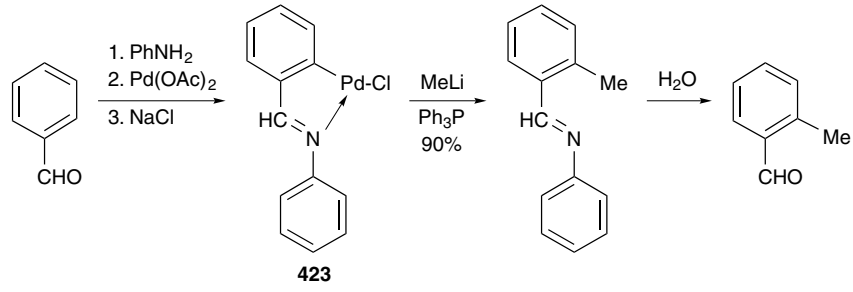
Facile insertion of CO takes place, and the reaction offers a synthetic method of *ortho*-substituted benzoic acid derivatives. The 2-aryl-3-indazolone **421** was obtained in high yield by carbonylation of 4-methylazobenzene complex **420** in alcohol or water [176]. Cobalt-catalyzed carbonylation of **421** and subsequent hydrolysis afforded aniline and 5-methylanthranilic acid (**422**). The results show that the σ-bond formation is an electrophilic substitution of $PdCl_2$ on the benzene ring [176,177].

The alkylation at the *ortho* carbon is possible by the reaction of chelate complexes with Grignard reagents, organolithium reagents in the presence of PPh_3, or alkyl halides. *o*-Methylbenzaldehyde was prepared via the formation of a Schiff base complex **423** and its reaction with MeLi [178]. The *ortho* alkylation is possible even with alkyl halides. Treatment of acetanilide (**424**) with 3 equivalents of

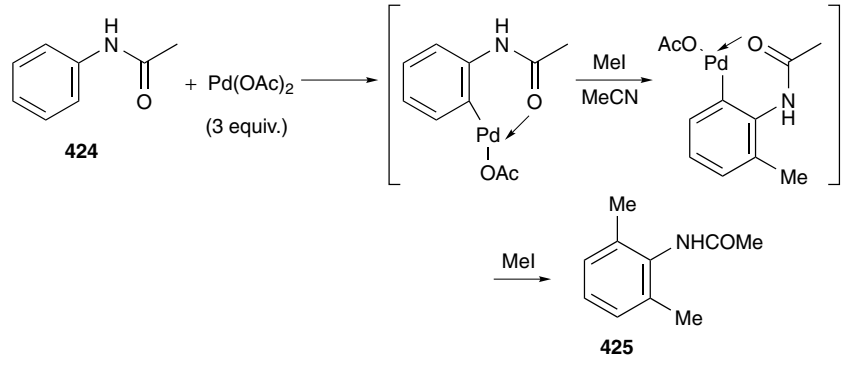


420 **421** **422**

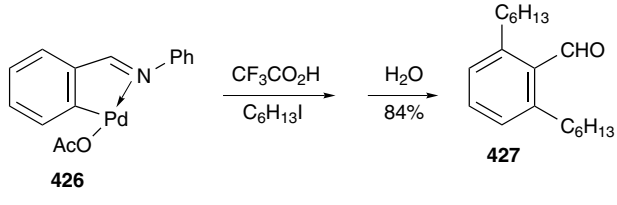
$Pd(OAc)_2$ and an excess of MeI afforded 2,6-dimethylacetanilide (**425**) by stepwise *ortho*-palladation and methylation twice [179]. However, treatment of the Schiff base complex **426** with trifluoroacetic acid and alkyl iodide produced the 2,6-dialkylbenzaldehyde **427** after hydrolysis. This reaction can be made semicatalytic [180].



423

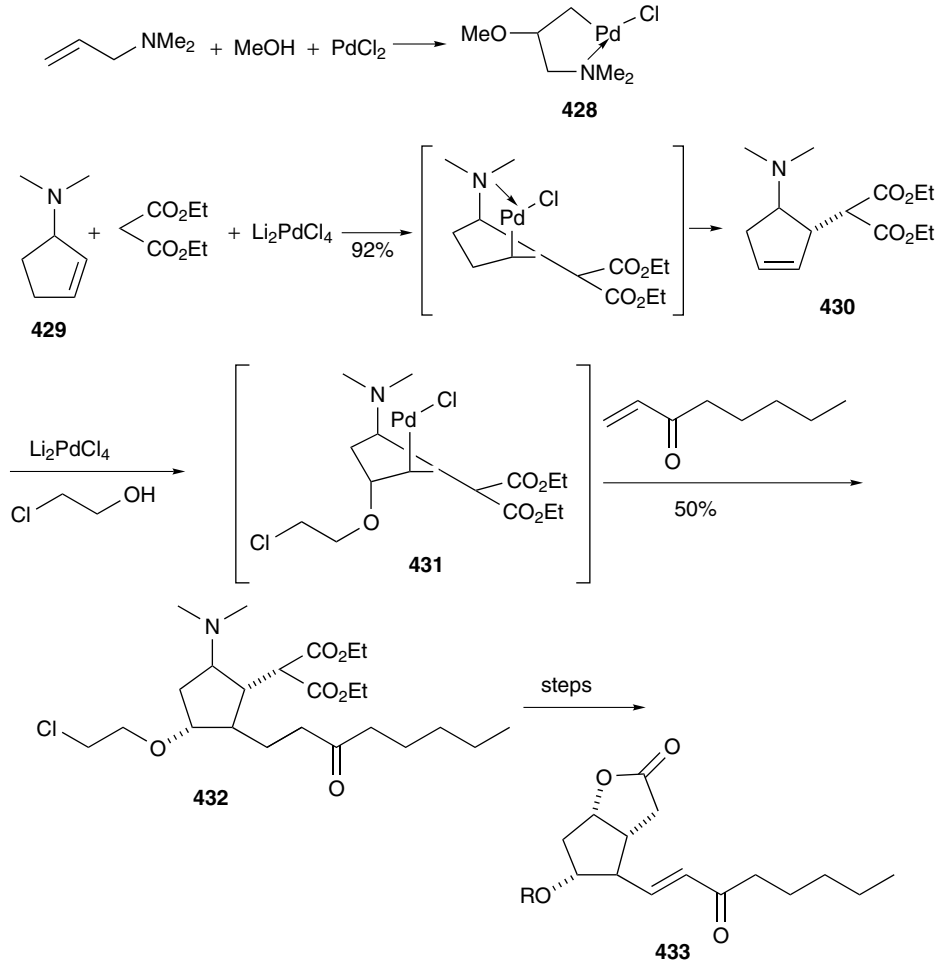


424 **425**



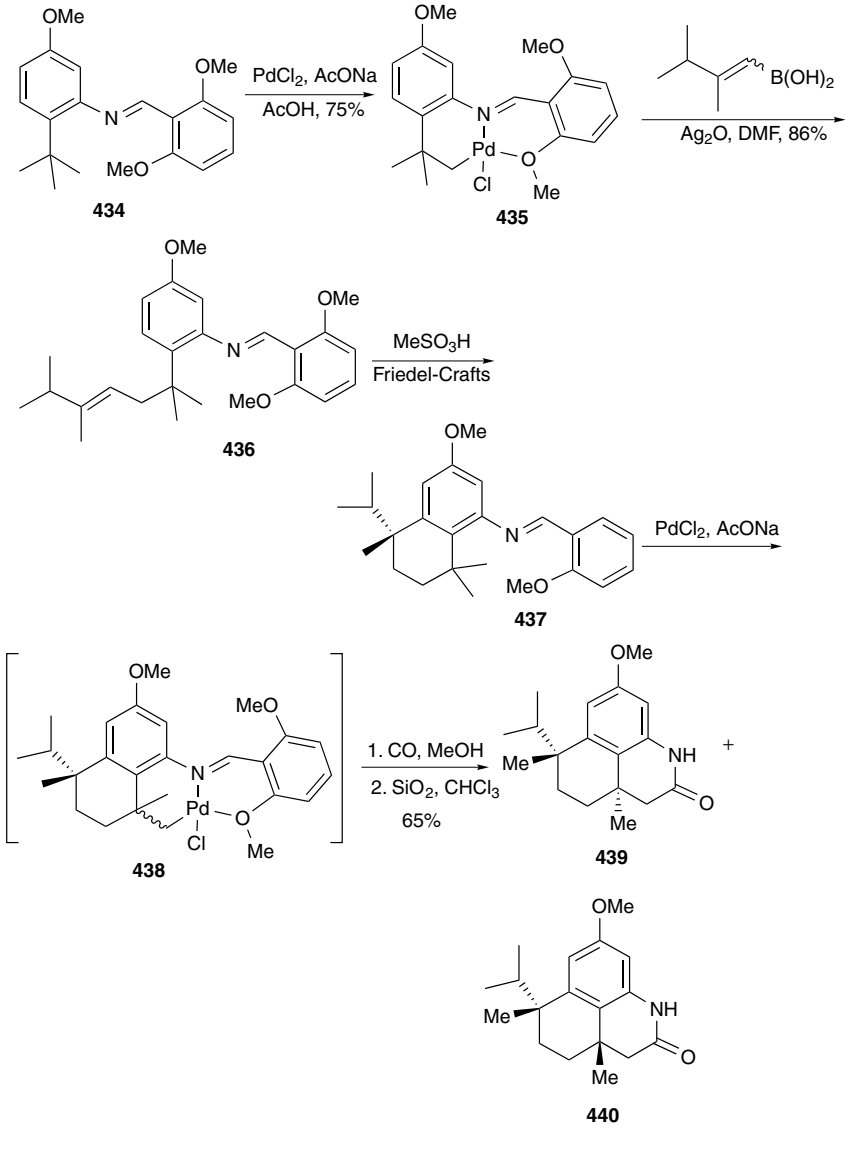
426 **427**

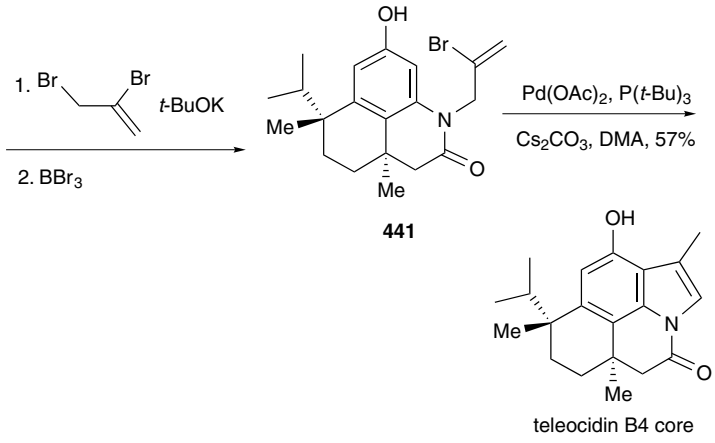
Due to the chelating effect of nitrogen, facile cyclopalladation of allylamines occurs to form **428** which undergoes insertion reactions [180]. The first classical application is the ingenious synthesis by Holton of a prostaglandin derivative starting from 3-(dimethylamino)cyclopentene (**429**), utilizing facile palladation by the chelating effect of allylic amines [181]. The key steps in the synthesis are the facile and stereoselective introductions of a carbanion and an oxy anion into the cyclopentene ring by virtue of the stabilizing chelating effect of the amino group, and the alkene insertion to the Pd–carbon σ-bond. The first step is the stereo-defined carbopalladation with malonate and the subsequent β-H elimination to form the 3-substituted 4-aminocyclopentene **430** in 92 % yield. The attack of the malonate is *anti* to the amino group. Further treatment of the amino ester **430** with Li_2PdCl_4, 2-chloroethanol and diisopropylethylamine in DMSO gave rise to the oxypalladation product **431**, which was immediately treated with pentyl vinyl ketone. Insertion of the alkene afforded the desired enone **432** in 50 % yield. The enone **432** was converted to an important intermediate **433** for prostaglandin synthesis.



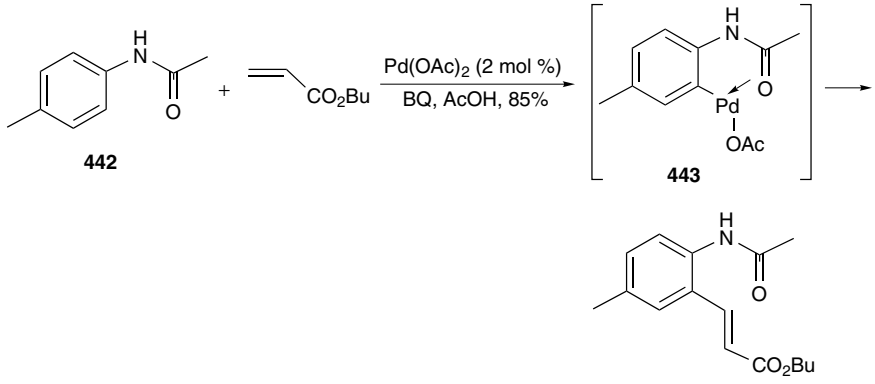
As a recent elegant application of coordination-directed C—H activation and subsequent C—C bond formation, Sames synthesized the core of teleocidin B4 [182].

The key step is the selective C—H bond activation of two methyl groups of an *ortho-tert*-butyl in the Schiff base **434**. Treatment of **434** with $Pd(OAc)_2$ afforded the palladacycle **435** in 75 % yield by the help of rather strong coordination to N and O functions. The first functionalization was achieved by the reaction with the alkenylboronic acid to yield the alkylated product **436** in 86 % yield, which was converted to **437** by the Friedel-Crafts reaction. Then the second palladacycle formation from **437** provided two diastereomers **438**, which were, without isolation, subjected to carbonylation (40 atm) at room temperature. Treatment of crude reaction mixture with silica gel cleaved the Schiff base and spontaneous lactonization occurred to give a mixture of the lactones **439** and **440** (6 : 1). The main product was N-alkylated to yield **441**. Finally, the fourth ring was constructed by a Heck-type reaction on the aromatic ring to give the desired compound.



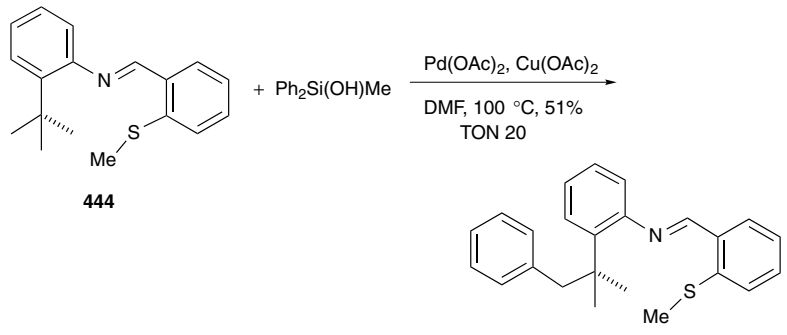


Synthetic reactions utilizing the stable chelate complexes cited above are mostly stoichiometric. However, studies on catalytic reactions involving chelate complexes are attracting attention as more useful synthetic methods. The amide carbonyl of acetanilide (**442**) is capable of forming a six-membered chelate ring **443**, and undergoes alkene insertion [183]. Importantly, the reaction of the acetanilide **442** with butyl acrylate via the complex **443** can be carried out in AcOH with a catalytic amount of $Pd(OAc)_2$ (2 mol%) and BQ as an oxidant to give the coupling product in 85 % yield [184].



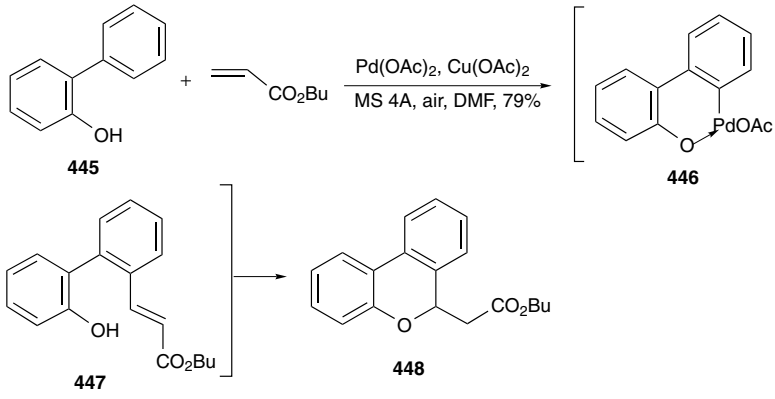
Similarly, the catalytic functionalization *t*-butyl group has been investigated. Using 2-thiobenzylidene Schiff base **444**, phenylation of the methyl group with $Ph_2Si(OH)Me$ was carried out in the presence of $Pd(OAc)_2$ (2.5 mol%) and $Cu(OAc)_2$ (2 equiv.) in DMF, and the phenylated product was obtained in 51 % yield with TON 20. Although the reaction is not efficient, further improvement is expected [185].

Recently, regioselective oxidative coupling of alkenes with aromatics as useful synthetic methods has been developed based on participation of some functional groups such as OH and amino present in suitable positions of aromatic rings, even though no stable chelate complex is isolated. Oxidative coupling of 2-phenylphenol (**445**) with acrylate using $Pd(OAc)_2$ and $Cu(OAc)_2$ in the presence of MS 4A under air occurred regioselectively at the 2′ carbon due to coordination



444

of phenolic oxygen to Pd(II) species as shown by **446** to give **447** as a primary product. Subsequent Michael-type addition afforded 6*H*-dibenzo[*b*,*d*]pyran-6-acetate **448** in 69 % yield [186]. Sulfonamide in biphenyl **449** is a good coordinating group, and regioselective coupling of acrylate at 2′ carbon occurred to give **450**, and subsequent Michael-type addition afforded ethyl 5,6-dihydro-5-(benzenesulfonyl)phenanthridine-6-acetate (**451**).



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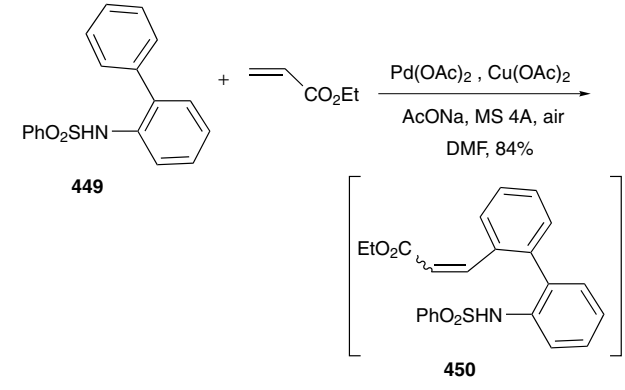

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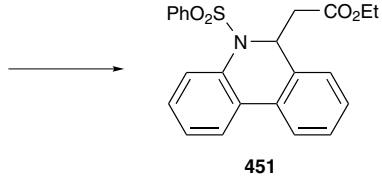
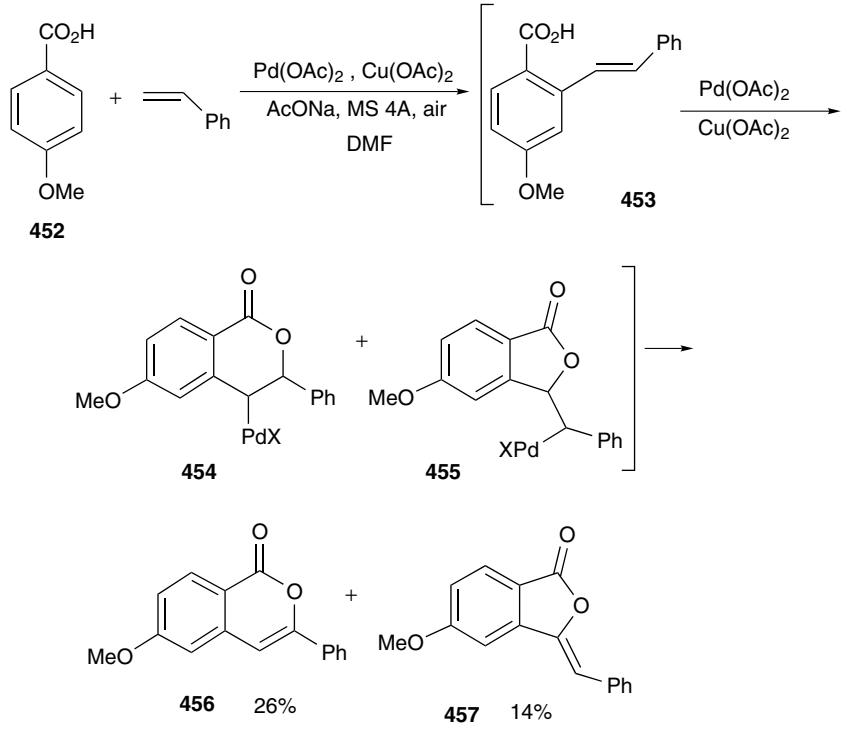


451

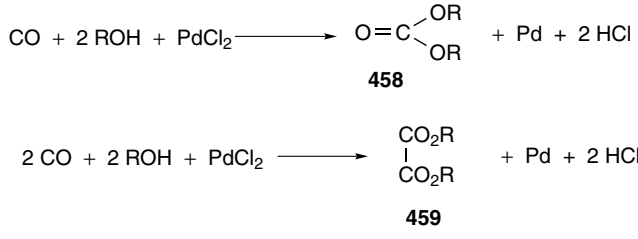
Furthermore, regioselective reaction of styrene at the *ortho* position of *p*-methoxybenzoic acid (**452**) gave **453** as a primary product. Subsequent oxypalladation of **453** to give **454** and **455**, and β-H elimination produced two lactones **456** and **457** [187].

Clean regiocontrol by weak coordination of Pd to OH, NHR and COOH groups is remarkable.



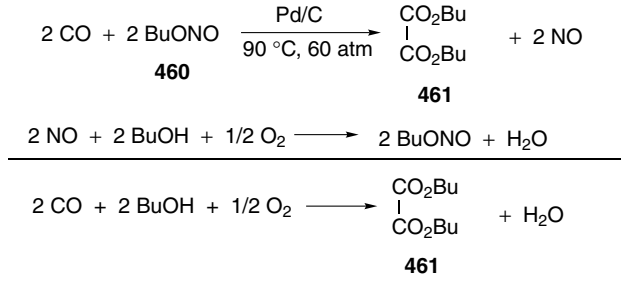
2.9 Oxidative Carbonylation of Alcohols and Amines

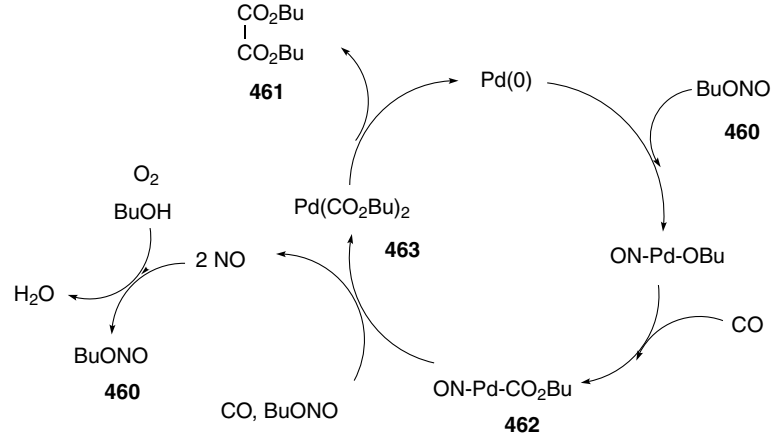
Oxidative carbonylation of alcohols using $PdCl_2$ affords the carbonate **458** and the oxalate **459** [188,189]. Selectivity of the mono- and dicarbonylation depends on CO pressure and reaction conditions.



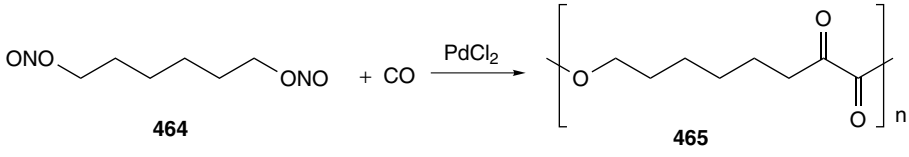
Industrial processes for dialkyl oxalate and dimethyl carbonate from CO, alcohol and oxygen catalyzed by Pd have been developed by Ube Industries in Japan [2].

Production of *n*-butyl oxalate (**461**) is carried out in 1-butanol containing *n*-butyl nitrite (**460**) using Pd on carbon as a catalyst under CO pressure. The most ingenious invention in this process is the use of *n*-butyl nitrite as an efficient oxidant of Pd(0). Formally Pd(0) is oxidized to Pd(II) easily with *n*-butyl nitrite **460**, then oxidative carbonylation proceeds to give di-*n*-butyl oxalate (**461**) and Pd(0). NO gas is generated after oxalate formation. In turn, NO is reconverted to **460** by the reaction with oxygen and 1-butanol. Most important from the standpoint of a commercial process is easy azeotropic separation of H_2O, formed by the oxidation, from 1-butanol. Otherwise water reacts with CO to produce CO_2 in the presence of a Pd catalyst. The mechanism of this interesting catalytic cycle is explained in the following. Oxidative addition of alkyl nitrite **460** to Pd(0) is followed by CO insertion to generate **462**, which is converted to **463** by the reaction of CO and butyl nitrite. Finally, reductive elimination of **463** affords the oxalate **461** and Pd(0).

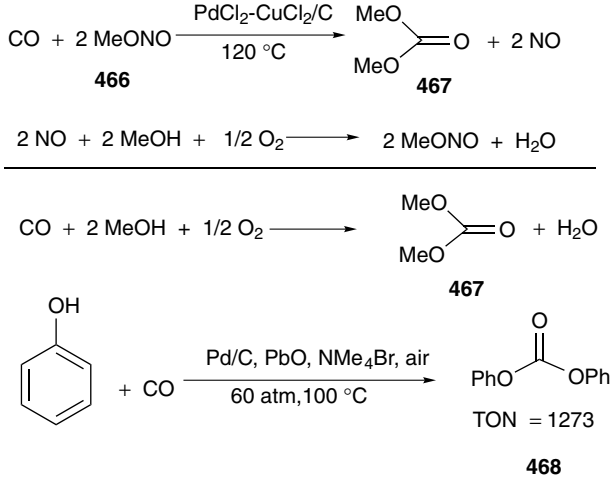




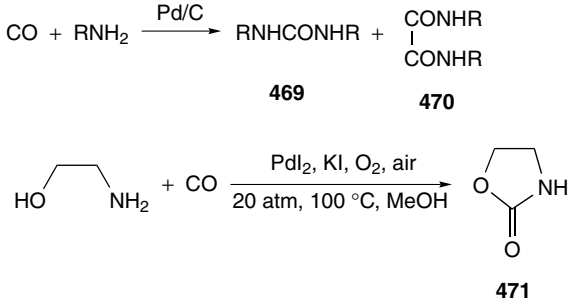
As an application, the polyoxalate **465** has been synthesized from dinitrite **464** using Pd-phosphine complex as a catalyst [190].



Dimethyl carbonate (**467**) is produced under low pressure CO. Dimethyl carbonate is now produced commercially by Ube industries based on the oxidative carbonylation of MeOH in the gas phase using methyl nitrite (**466**) as an oxidant as shown below. Another promising reaction is the preparation of commercially important diphenyl carbonate (**468**) by the oxidative carbonylation of phenol. So far the technology developed in many industrial laboratories is far from commercialization [191].

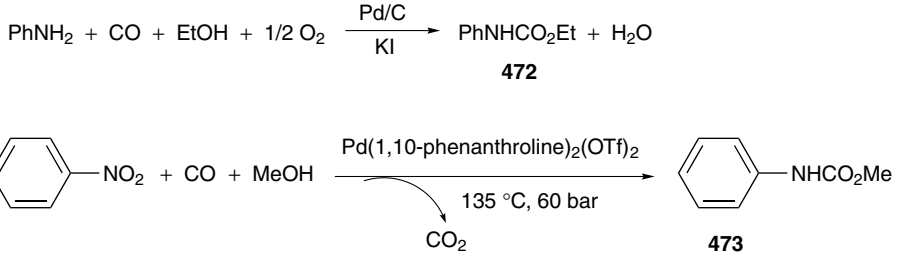


Oxidative carbonylation of amines affords alkylurea **469** and oxamide **470** [192]. Substituted ureas were prepared efficiently in the presence of PdI_2 and KI under CO and CO_2 pressure (total 60 atm) [193]. Synthesis of 2-oxazolidinone (**471**) by the carbonylation of 2-aminoethanol was carried out efficiently using a catalytic system of PdI_2–KI [194].

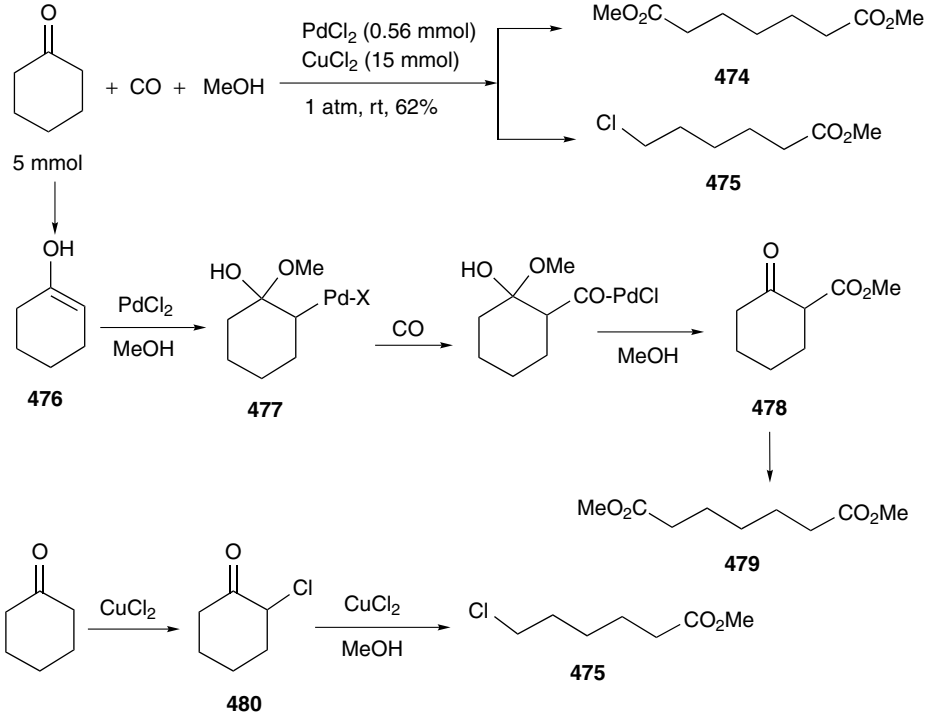


Carbamates are produced by the oxidative carbonylation of amines in alcohol, and active research on the commercial production of alkyl carbamate as a precursor of isocyanates based on this reaction has been carried out. As an example, ethyl phenylcarbamate (**472**) was produced in a high yield (95 %) with a selectivity higher than 97 % by the reaction of aniline with CO in EtOH at 150 °C

and 50 atm. Pd on carbon is the catalyst and KI is added as a promoter [195]. Furthermore, methyl phenylcarbamate (**473**) is obtained by reductive carbonylation of nitrobenzene directly. Pd(II) coordinated by phenanthroline is used as a catalyst [196].

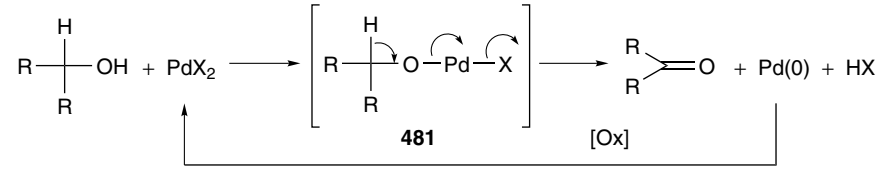


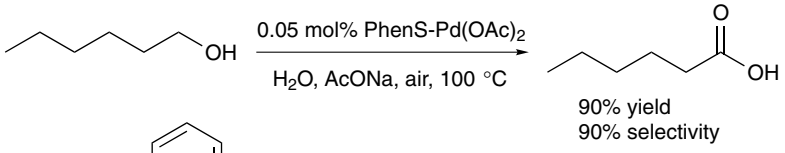
Interestingly ketones can be carbonylated. Reaction of cyclohexanone with CO in MeOH using $PdCl_2$ and $CuCl_2$ as catalysts under mild conditions afforded dimethyl pimelate (**474**) and methyl 6-chlorohexanoate (**475**) in good yields. Mechanism of the carbonylation is not clear. Dimethyl pimelate (**474**) is formed by methanolysis (retro-Dieckmann reaction) of methyl cyclohexanonecarboxylate (**478**) promoted by $CuCl_2$ and acid. Methyl cyclohexanonecarboxylate (**478**) may be formed by methoxypalladation of the enolate **476** to form Pd enolate **477**, followed by CO insertion. Chlorination of cyclohexanone with $CuCl_2$ gives 2-chlorocyclohexanone **480** which is converted to **475** [197].

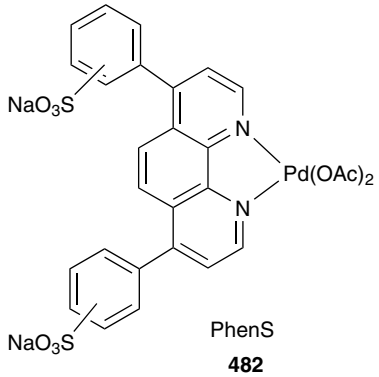


2.10 Oxidation of Alcohols

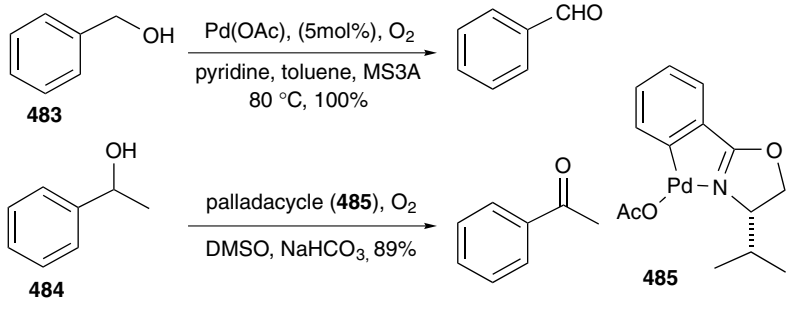
Alcohols are oxidized slowly with $PdCl_2$ or $Pd(OAc)_2$. The reaction is explained by formation of Pd-alkoxide **481**, followed by β-H elimination. More efficient methods of oxidation using palladium catalysts and O_2 as an oxidant have been reported by several groups. Primary alcohols are oxidized to carboxylic acids using Pd-phenanthroline **482** as a catalyst, which can be recycled [198].



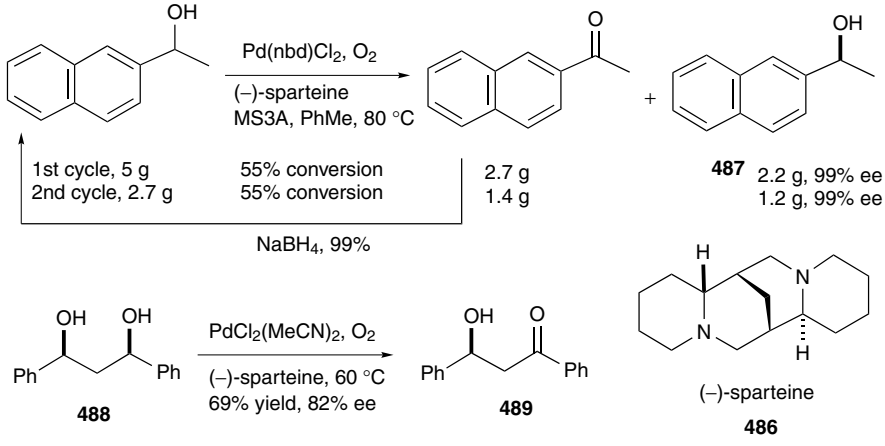




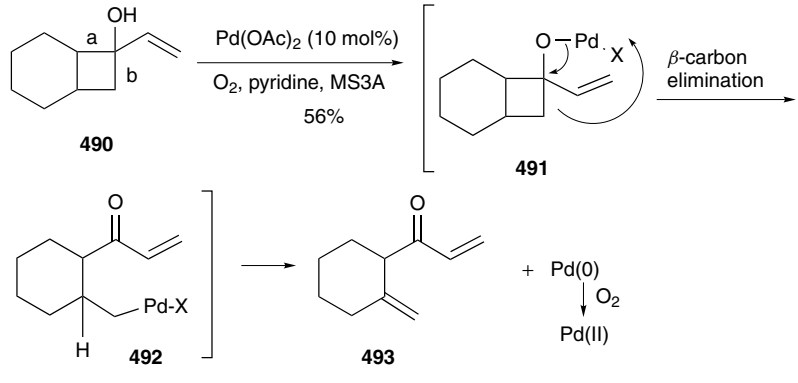
Primary and secondary alcohols such as benzyl alcohol (**483**) and 1-phenylethanol (**484**) are oxidized with O_2 efficiently to benzaldehyde and acetophenone using $Pd(OAc)_2$, complexed with pyridine, as a catalyst in the presence of a molecular sieve [199] or supported on hydrotalcite [200]. Also, the palladacycle of 4,5-dihydro-1,3-oxazole **485** is a good catalyst for oxidation of alcohols in DMSO under oxygen [201].



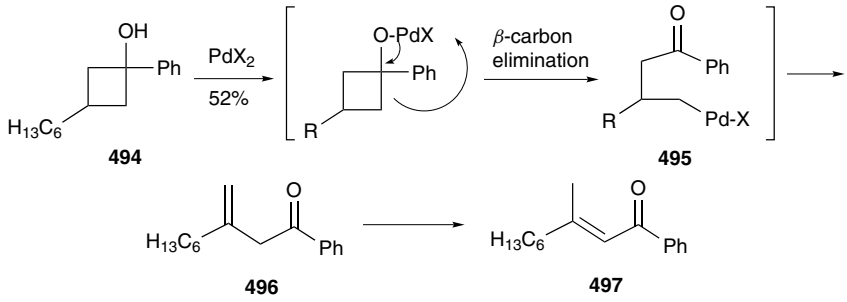
More importantly, asymmetric synthesis is possible using an optically active alkaloid as a ligand. Pd-catalyzed oxidative kinetic resolution of secondary alcohols with molecular oxygen was achieved using $Pd(OAc)_2$-(−)-sparteine complex. Optically enriched (−)-1-(2-naphthyl)ethanol (99 % ee) (**487**) was recovered in 44 % yield by the oxidation of a racemic mixture of 1-(2-naphthyl)ethanol. Quantitative reduction of the ketone provides an opportunity for the preparation of chiral alcohols in >50 % overall yield from the racemic mixture via multistep oxidative kinetic resolution [202]. $Pd(MeCN)_2Cl_2$ complexed with (−)-sparteine (**486**) can be used similarly. It is concluded that (−)-sparteine plays a dual role in the oxidative kinetic resolution of alcohols, as a ligand on Pd and an exogenous base [203,204]. Efficient enantio-selective oxidation of 1,3-*meso*-diol **488** resulted in an oxidative desymmetrization to provide **489** with 82 % ee in 69 % yield [204,205]. *tert*-Butyl alcohol was found to be a good solvent for the oxidation of benzylic, allylic and aliphatic alcohols [204].



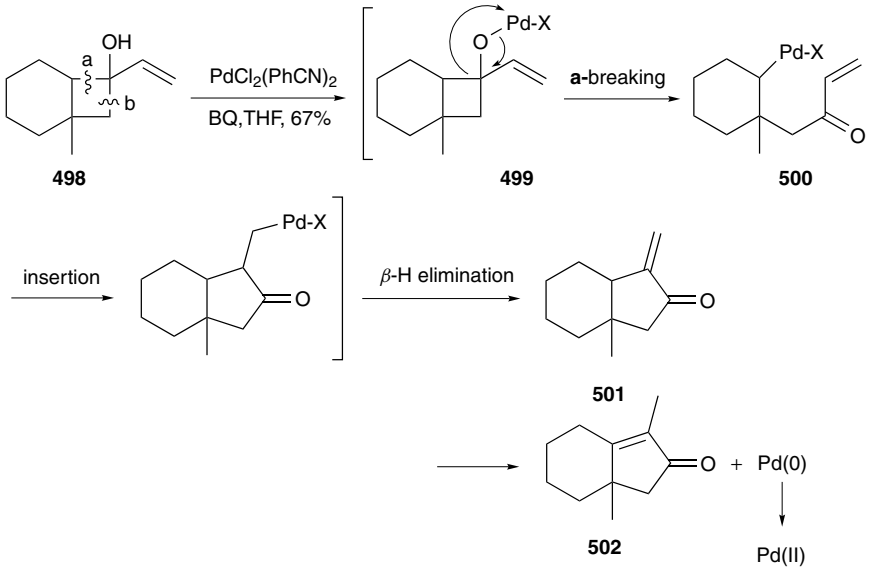
Oxidative rearrangement and ring expansion of strained molecules of *tert*-cyclobutanols are known [206]. Recently it has been claimed that the reaction can be explained more reasonably by elimination of β-carbon (see Chapter 3.8.2) [207]. Conversion of the vinylcyclobutanol **490** to the ring-opened product **493** by relief of the ring strain under oxidative conditions is explained by β-carbon elimination as shown by **491** to generate **492**, followed by β-H elimination. In this case,



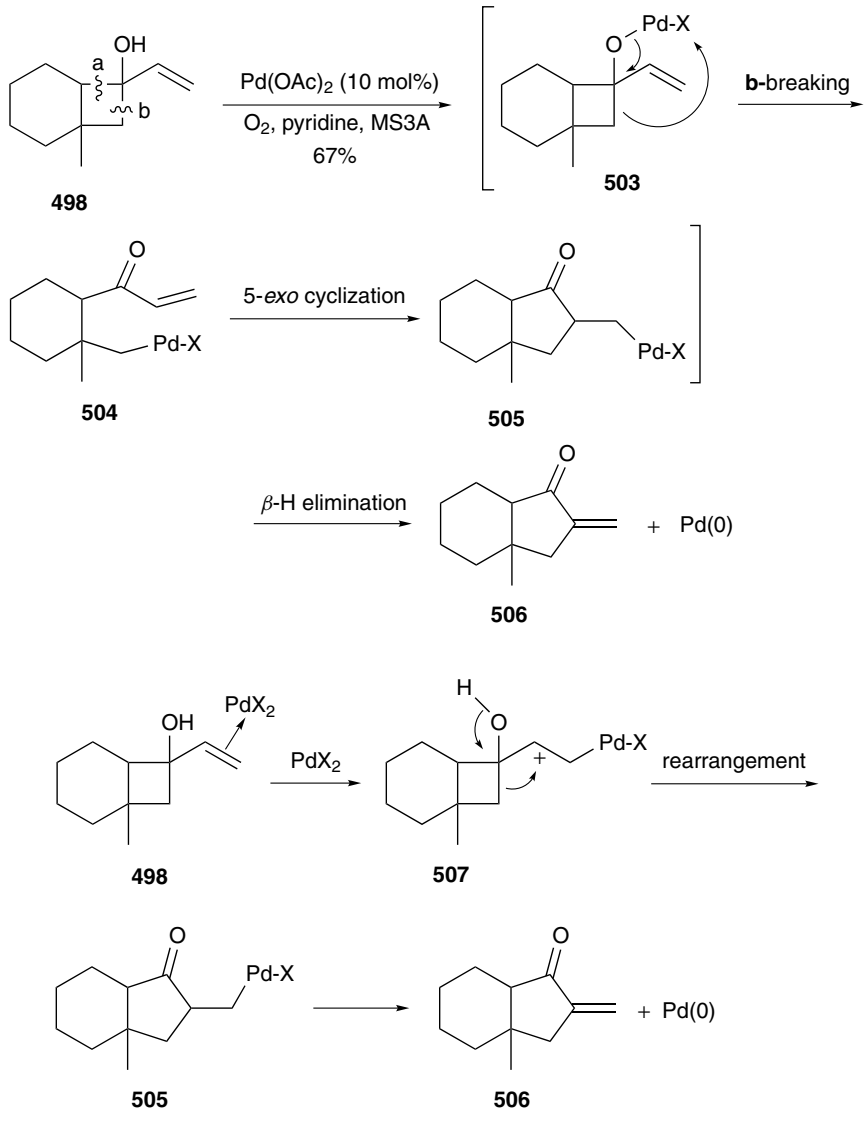
formation of the alkoxypalladium **491**, instead of pre-coordination of π-bond with Pd, is a crucial step. Also the β-carbon elimination occurs selectively from the less substituted bond (bond b). Similarly cleavage of the *tert*-cyclobutanol ring **494** occurs to generate **495**, and β-H elimination affords **496**. Finally, **497** is obtained after isomerization [207].



The presence of an angular methyl as in **498** makes a difference. Bond cleavage occurs in two ways (**a** and **b**). The cleavage of bond **a** as shown by **499** is followed by 5-*exo* cyclization of the intermediate **500** and β-H elimination to afford the cyclopentanone **501** and then **502** [205]. Using $Pd(OAc)_2$ (10 mol%), pyridine and molecular sieve under oxygen, the different cyclopentanone **506** was obtained selectively by cleavage of bond **b** in **498** as shown by **503** [207]. Unlike **502**, the β-H elimination in **504** is impossible in the presence of the angular methyl, and 5-*exo* cyclization occurs to generate **505**, and then **506** is formed.



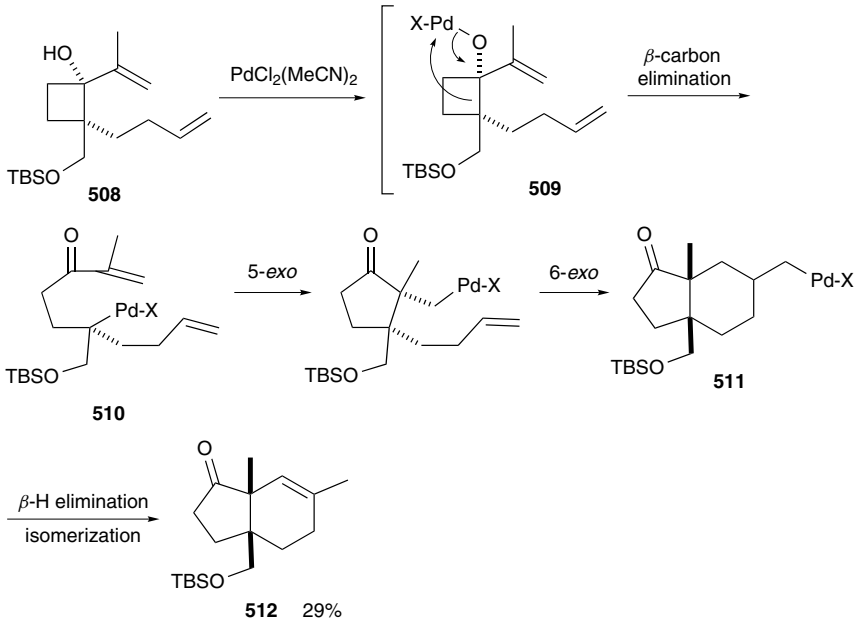
As another possibility, the reaction is explained by precoordination of PdX_2 to the double bond. Then palladation occurs with concomitant rearrangement and ring expansion as shown by **507** to generate **505** and then **506**.

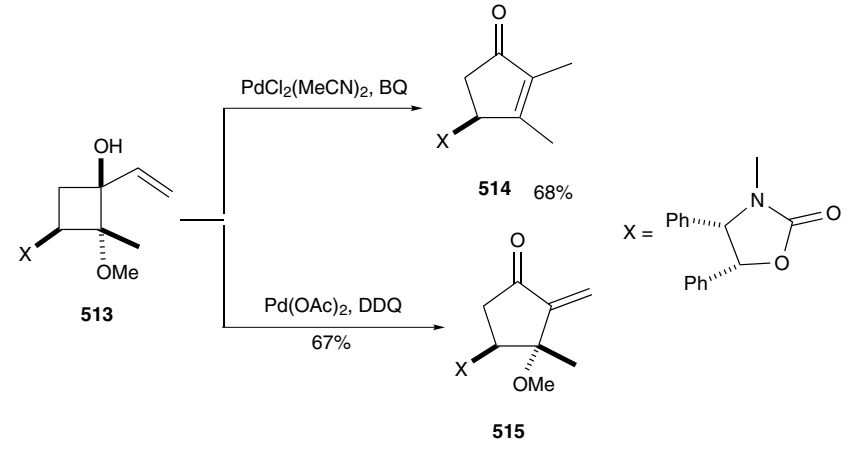


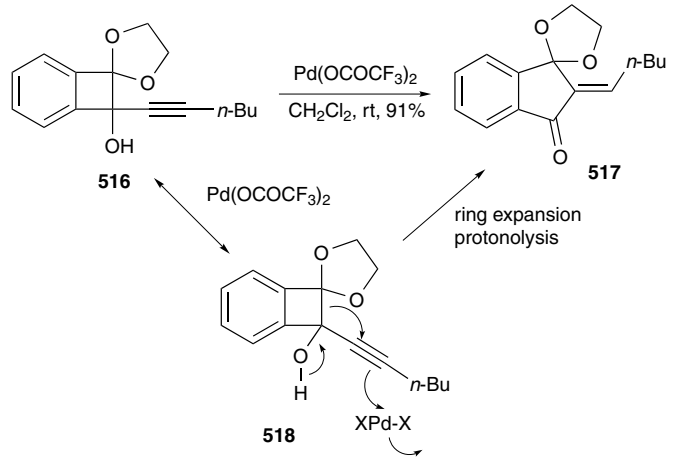
Treatment of the 1-isopropenyl-2-(3-butenyl)cyclobutanol **508** with Pd(II) afforded the bicyclo[4.3.0]nonane **512**. The reaction can be understood by domino β-carbon elimination as shown by **509**, followed by 5-*exo* and 6-*exo* cyclizations of **510** to give **511**, and β-H elimination and isomerization afforded **512** [208]. A different mechanism based on ring expansion was given before.

The vinylcyclobutanol **513**, bearing a β-methoxy group, was converted to two products **514** and **515** with or without elimination of the methyl group when $PdCl_2$ and BQ, or $Pd(OAc)_2$ and DDQ were used [209].

Palladation of alkyne **516** and ring expansion occurred as shown by **518** to give the cyclopentanone **517** in 91 % yield at room temperature using $Pd(TFA)_2$ [210].

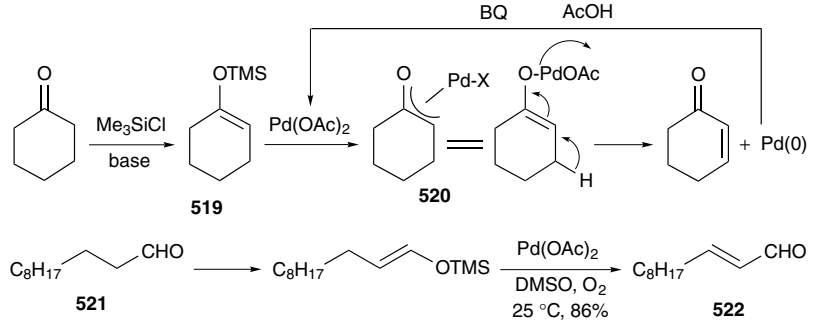

HO
TBSO
508
$PdCl_2(MeCN)_2$
X-Pd
O
TBSO
509
β-carbon elimination
O
Pd-X
TBSO
510
5-*exo*
O
Pd-X
TBSO
6-*exo*
O
Pd-X
TBSO
511
β-H elimination
isomerization
O
TBSO
512 29%


$PdCl_2(MeCN)_2$, BQ
OH
X
OMe
513
O
X
514 68%
X =
Ph
N
O
O
Ph
$Pd(OAc)_2$, DDQ
67%
O
X
OMe
515

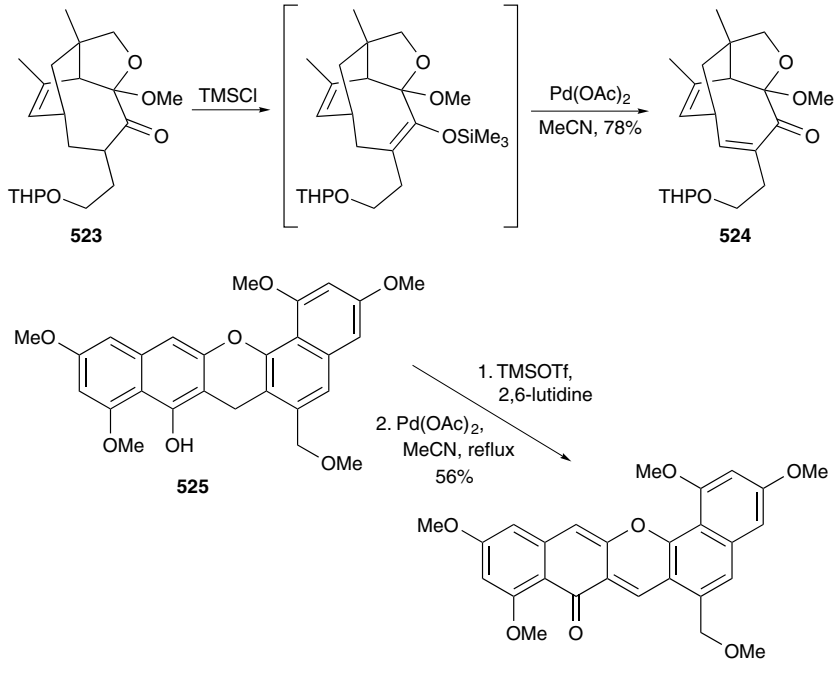

O
O
n-Bu
OH
516
$Pd(OCOCF_3)_2$
CH_2Cl_2, rt, 91%
O
O
n-Bu
O
517
$Pd(OCOCF_3)_2$
ring expansion
protonolysis
O
O
O
H
n-Bu
XPd-X
518

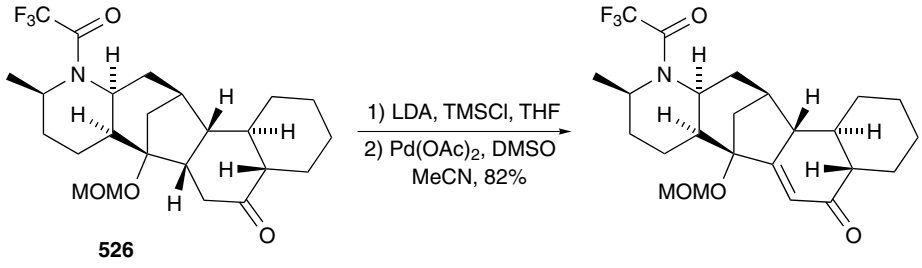
2.11 Enone Formation from Ketones and Cycloalkenylation

Preparation of enones from saturated ketones by Pd(II)-promoted dehydrosilylation via silyl enol ethers was reported by Ito. Transmetallation of the silyl enol ether of cyclohexanone **519** with $Pd(OAc)_2$ gives the oxo-π-allylpalladium complex **520** (Pd enolate), which undergoes β-H elimination to afford cyclohexenone. BQ is used as an oxidant of Pd(0) [211]. However, the enone formation can be carried out using a catalytic amount of $Pd(OAc)_2$ in DMSO under oxygen without other oxidants at room temperature. Also aldehyde **521** is converted to unsaturated aldehyde **522** via silyl ether in DMSO [4].



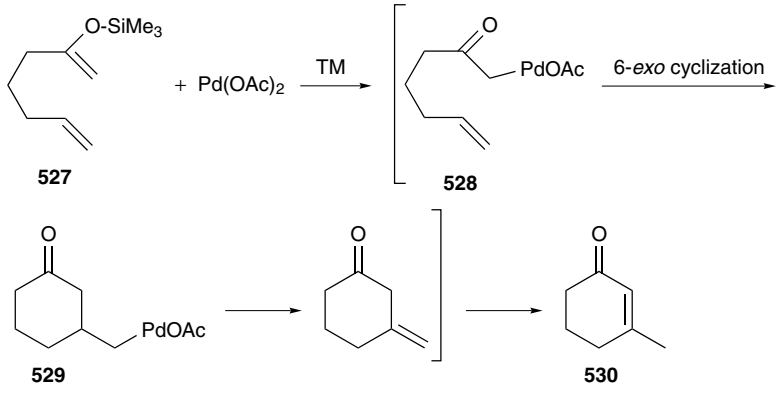
The enone formation has been applied to a number of natural product syntheses. The enone **524** was prepared from the complex molecule **523** and successfully applied to the total synthesis of pallescensin [212]. Even the phenolic OH in **525** was converted to the conjugated ketone. The reaction was utilized as a key step in hypoxyxylerone synthesis [213]. In the total synthesis of galbulimima alkaloid GB 13, Mander converted a cyclohexanone in the complicated molecule **526** to the corresponding cyclohexenone via silyl enol ether in 82 % yield [214].





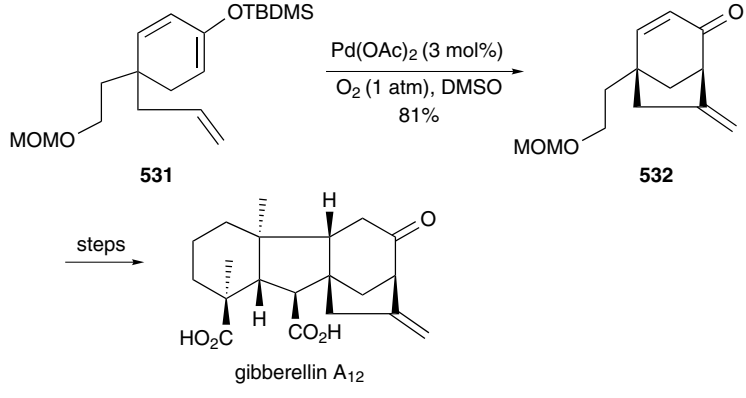
526

In the presence of a double bond, its intramolecular insertion to Pd enolate in **528** takes place. For example, the silyl enol ether **527** undergoes transmetallation with $Pd(OAc)_2$ to give the Pd enolate **528**, or the oxy-π-allylpalladium, which undergoes 6-*exo* cyclization to generate **529**. The subsequent β-H elimination gives the 3-methylcyclohexenone (**530**) [215]. The reaction is called 'cycloalkenylation' [216].



527 **528** **529** **530**

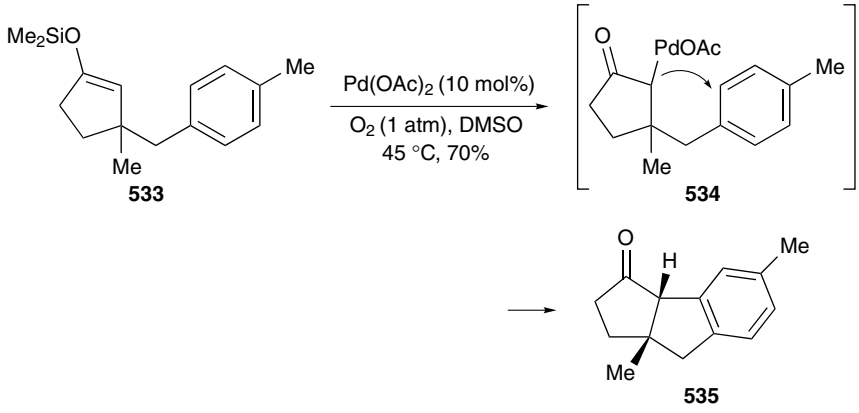
Five- and six-membered rings can be prepared by this reaction [217], and the reaction has been applied to syntheses of natural products. Now the cycloalkenylation can be carried out with a catalytic amount of $Pd(OAc)_2$ in DMSO under O_2. The bicyclo[3.2.1]octenone **532**, a partial skeleton of gibberellin, was obtained in 81 % yield by the cycloalkenylation of the silyl dienol ether **531** in DMSO using



531 **532**

gibberellin A_{12}

3 mol% of $Pd(OAc)_2$ under O_2. Use of TBDMS gave higher yields than TMS group [218,219]. Furthermore, the reaction has been extended to coupling with an aromatic ring. Treatment of **533** with $Pd(OAc)_2$ in DMSO under O_2 generates the Pd enolate **534**, which has no possibility of β-H elimination and attacks the aromatic ring to afford the benzo-fused bicyclo[3.3.0]octane **535** [220].



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Chapter 3

Pd(0)-Catalyzed Reactions of sp^2 Organic Halides and Pseudohalides

3.1 Introduction

Among many substrates used for Pd(0)-catalyzed reactions, organic halides are most widely used. In Grignard reactions, Mg(0) metal reacts with organic halides of sp^3 carbons (alkyl halides) more easily than halides of sp^2 carbons (aryl and alkenyl halides). On the other hand, Pd(0) complexes react more easily with halides attached to sp^2 carbons, namely aryl and alkenyl halides. In addition, several pseudohalides are used as well. They undergo facile oxidative addition to Pd(0) to form Pd complexes which have σ-Pd–carbon bonds. Scheme 3.1 summarizes the oxidative addition of phenyl halides and pseudohalides to form phenylpalladium halides. Aryl iodides and bromides have been used widely.

Until recently use of aryl chlorides for catalytic reactions has been neglected due to low reactivity, despite the fact that chlorides are cheaply and easily available. Remarkable progress has been achieved since 1998 in developing Pd-catalyzed reactions of aryl chlorides. A review of Pd-catalyzed reactions of aryl chlorides has been published by Littke and Fu [1]. Facile Pd-catalyzed reactions of aryl chlorides occur by using electron-rich and bulky ligands and proper bases. P(*t*-Bu)$_3$, biphenylyl(di-*t*-butyl)phosphine and heterocyclic carbenes are the most effective ligands. As measures of basicity and bulkiness, the pK_a and cone angles of some phosphines are cited:

$$\text{p}K_a: \quad \text{P}(t\text{-Bu})_3 = 11.40, \quad \text{PCy}_3 = 9.7, \quad \text{P}(2,4,6\text{-}(\text{OMe})_3\text{C}_6\text{H}_3)_3 = 11.0$$

$$\text{Cone angle}: \quad \text{P}(t\text{-Bu})_3 = 182^\circ, \quad \text{PCy}_3 = 170^\circ,$$
$$\text{P}(2,4,6\text{-}(\text{OMe})_3\text{C}_6\text{H}_3)_3 = 184^\circ$$

It is instructive to compare these values with those of PPh_3 and P(*n*-Bu)$_3$:

$$PPh_3: \quad \text{p}K_a = 2.73, \quad \text{cone angle} = 145^\circ; \quad \text{P}(n\text{-Bu})_3, \quad \text{p}K_a = 8.4$$

Consideration of the order of reactivity of several kinds of chlorides is also important:

heteroaryl chlorides > electron-deficient chlorides (activated chlorides)
> neutral or electron-rich chlorides

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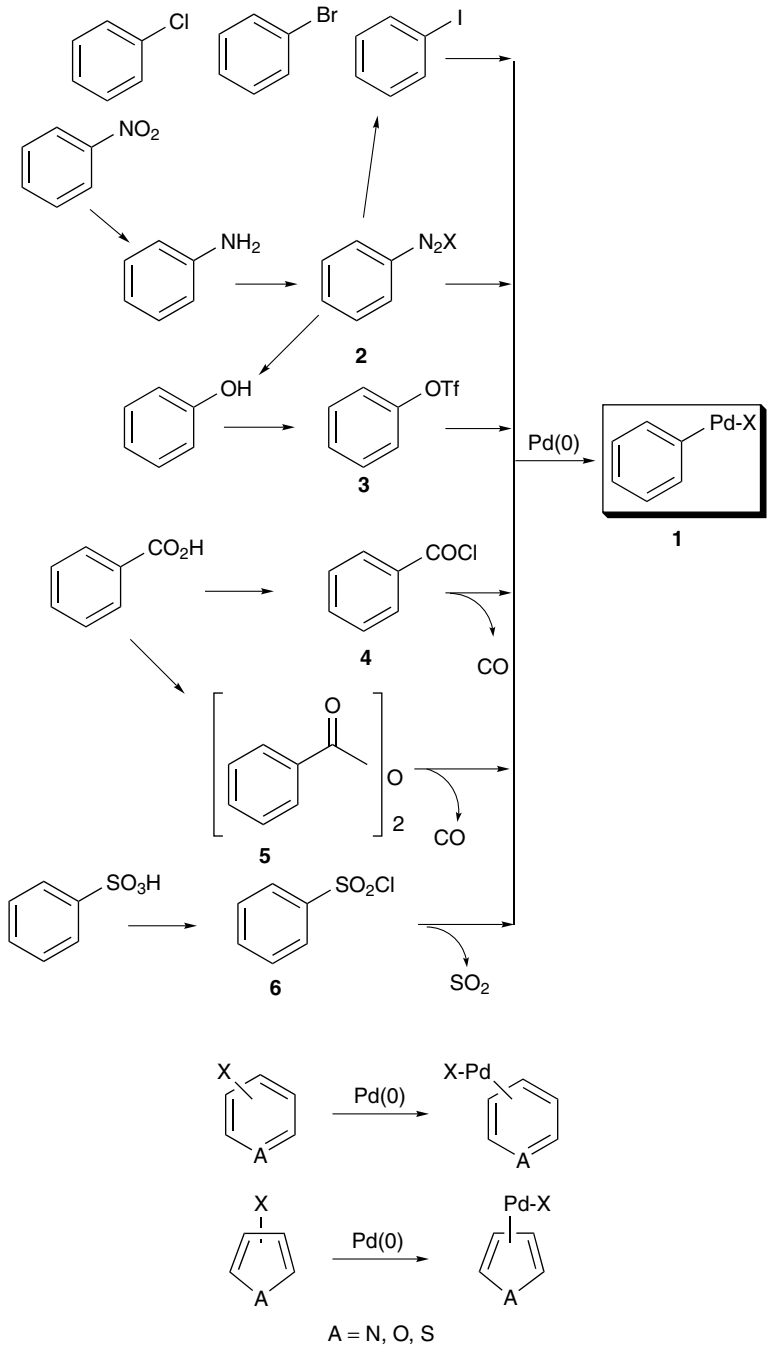
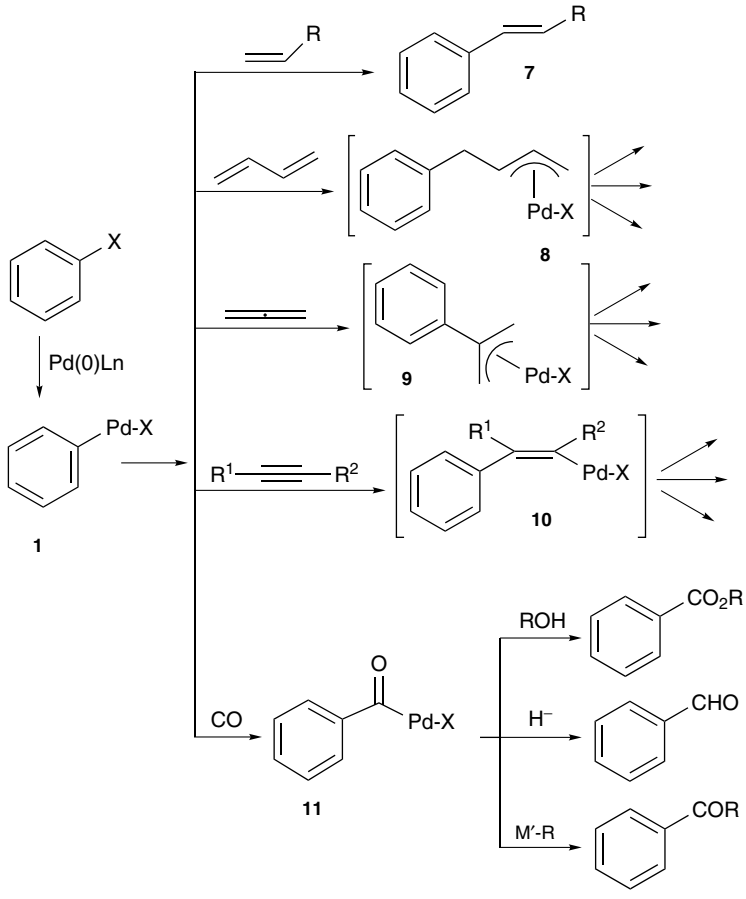


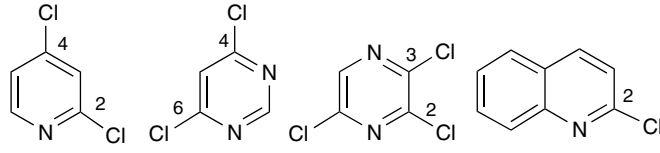
Scheme 3.1 Formation of phenylpalladium intermediates from organic halides and pseudohalides by oxidative addition.

Many papers reporting 'best ligand' or 'most active catalyst for the coupling of aryl chlorides' have appeared, but some of them are active only for activated aryl chlorides, and not necessarily effective for electron-rich chlorides, sometimes poor catalysts. Chlorides of some nitrogen-containing heterocycles are reactive under



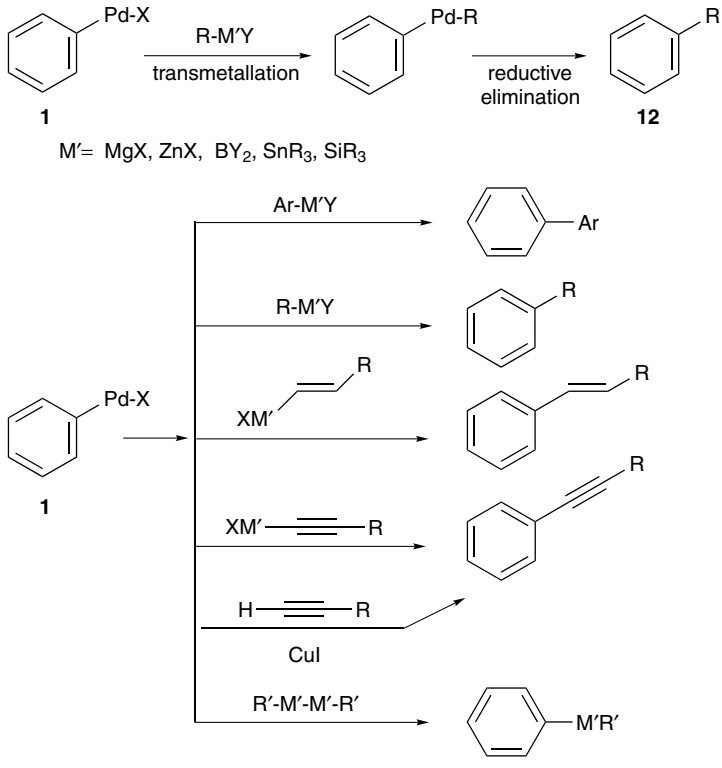
Scheme 3.2 Insertion to phenylpalladium intermediates.

usual conditions. For example, Pd-catalyzed reactions of 2- and 4-chloropyridines, 4- and 6-chloropyrimidines, 2-chloroquinolines, and 2- and 3-chloropyrazines proceed in the presence of PPh_3 and are extensively applied to their functionalization.



Several reactive pseudohalides are available for catalytic reactions. Diazonium salts **2** derived from anilines, and phenyl triflates **3** and nonaflates (nonafluorobutanesulfonates) derived from phenols are highly reactive substrates. In addition, acyl chlorides **4**, anhydrides **5**, and sulfonyl chlorides **6** are also used.

The phenylpalladium halides **1** are 'living' species and undergo several further transformations before termination. Insertion of unsaturated bonds is one of them, as summarized in Scheme 3.2. Alkene insertion is followed by β-H elimination to yield arylalkenes **7**. Insertion of 1,2- and 1,3-dienes generates the π-allylpalladium



Scheme 3.3 Transmetallation of phenylpalladium intermediates **1**.

intermediates **8** and **9**. Alkyne insertion gives rise to the alkenylpalladiums **10**. These species **8, 9** and **10** undergo further reactions before termination. The acylpalladium **11** is formed by CO insertion, from which esters, aldehydes and ketones are produced.

Cross-coupling proceeds by transmetallation of **1** with organometallic compounds of main group metals (Mg, Zn, B, Al, Sn, Si) and reductive elimination to give **12** as summarized in Scheme 3.3.

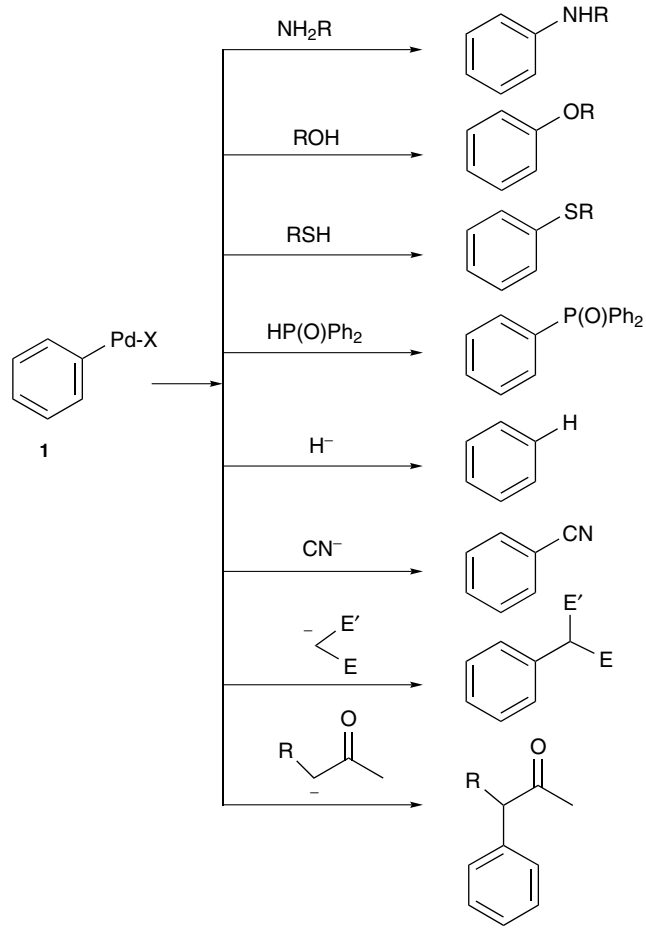
Trapping of phenylpalladium **1** with several anions or nucleophiles produces a variety of aromatic substitution products as shown in Scheme 3.4.

By considering Schemes 3.1–3.4, we can easily see the wide versatility and high synthetic value of the new and rich aromatic chemistry involving Pd-catalyzed reactions of aryl halides. These reactions offer unique methods for carbon–carbon bond formation, which are impossible or difficult to achieve by conventional means. A revolution and large expansion occurred in aromatic substitution reactions on the discovery of these aryl halide reactions.

Alkenyl halides undergo similar transformations. In addition to alkenyl halides **13**, alkenyl triflates **15** and phosphates **16**, derived from aldehydes and ketones, are useful pseudohalides, that undergo oxidative addition to form alkenylpalladium intermediates **14**. Typical examples of insertion of unsaturated bonds to **14** are shown in Scheme 3.5.

Transformations of the alkenylpalladium **11** via transmetallation and trapping with anions are summarized in Scheme 3.6.

All the reactions summarized in Schemes 3.1–3.6 are treated in this chapter.

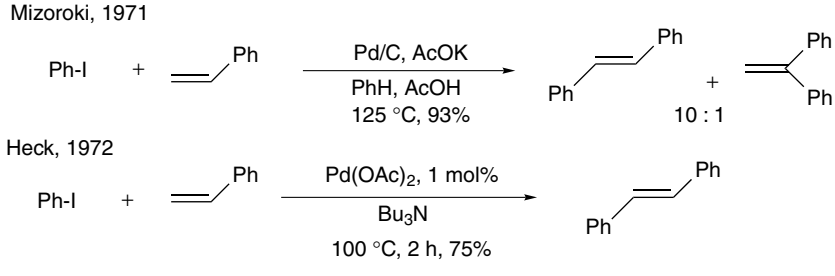


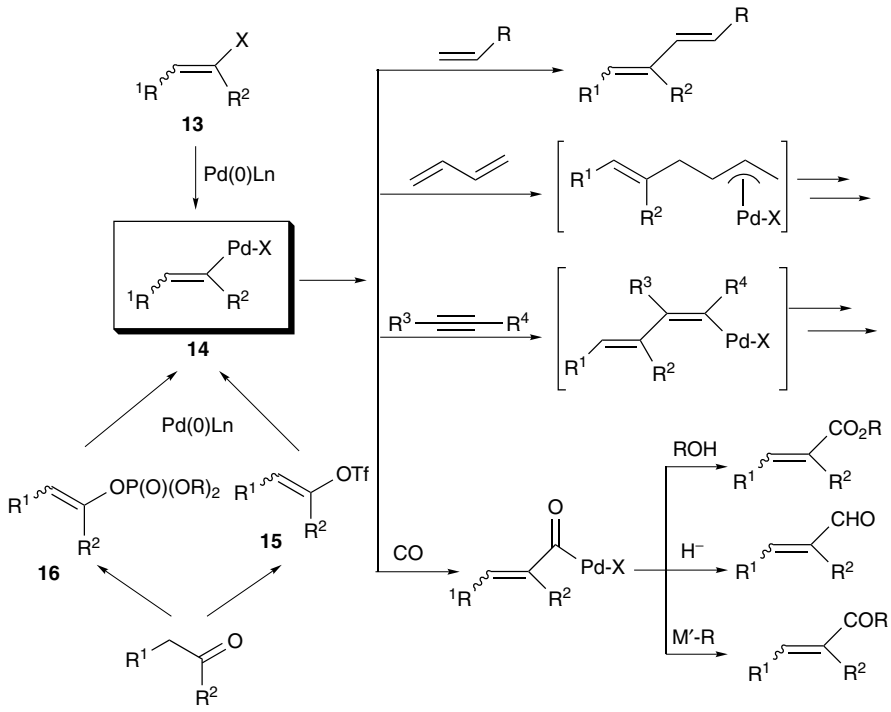
Scheme 3.4 Trapping of phenylpalladium intermediate **1** with anions and nucleophiles.

3.2 Reactions with Alkenes (Mizoroki–Heck Reaction)

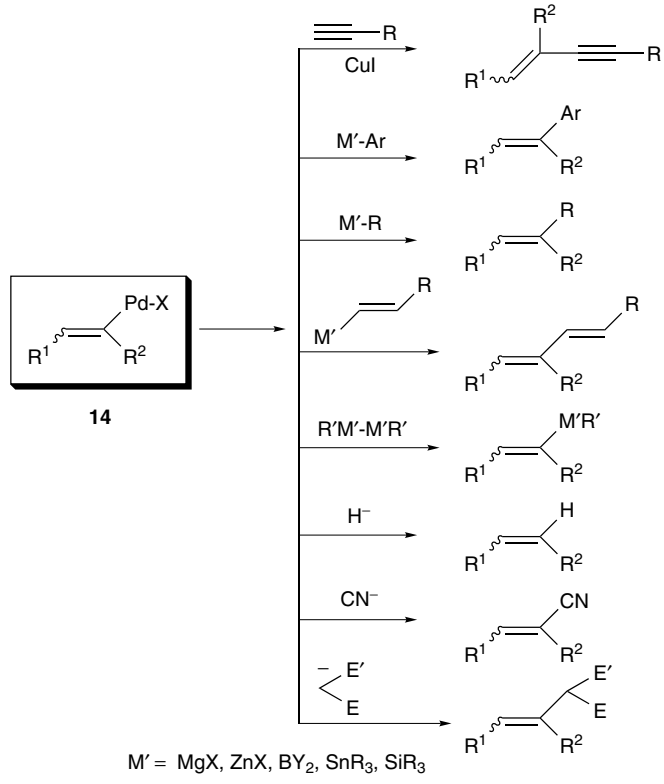
3.2.1 Introduction

Direct alkenylation of benzene derivatives with alkenes was reported by Fujiwara in 1967 and via mercuration by Heck in 1968 using a stoichiometric amount of Pd(II) salts [2]. Then, inspired by the discovery of oxidative addition of iodobenzene to $Pd(PPh_3)_4$ to generate Ph-Pd-I by Fitton in 1968 [3], Mizoroki and Heck independently reported the alkenylation of benzene derivatives by the reaction of





Scheme 3.5 Insertion to alkenylpalladium intermediates **14**.



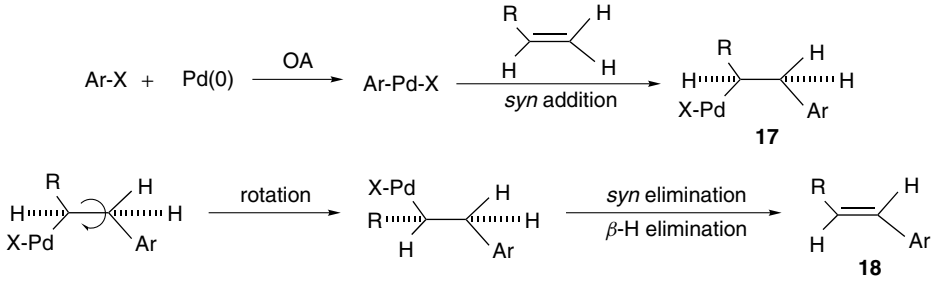
Scheme 3.6 Transmetallation and trapping of alkenylpalladium intermediates **14** with anions.

aryl iodides with various alkenes, typically acrylate and styrene using Pd on carbon or $Pd(OAc)_2$ as a catalyst without a phosphine in the presence of bases. Sadly Mizoroki died after publishing only a few papers on the reaction [4,5].

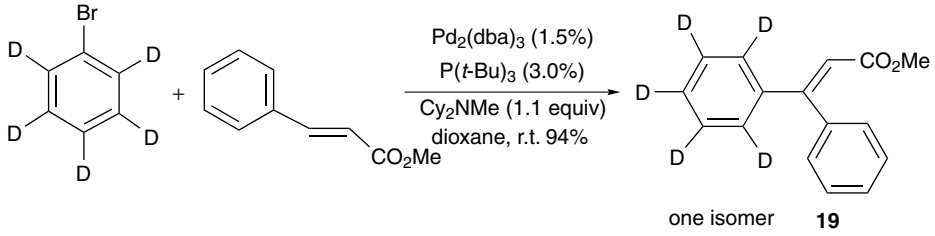
This hitherto unknown reaction has attracted attention as a potentially important method for carbon–carbon bond formation. Now all reactions which proceed via insertion of alkenes and also alkynes to the arylpalladium intermediates **1** (Scheme 3.1) and the alkenylpalladium **14** (Scheme 3.5) are called Mizoroki–Heck reactions or Heck reactions (abbreviated to HR in this chapter). A number of reviews have already been published [6]. The reaction is certainly the most useful and versatile method of carbon–carbon bond formation involving sp^2 carbons.

HR consists of three elemental reactions: (1) oxidative addition of an organic halide to form arylpalladium halides; (2) insertion of an alkene to form the alkylpalladium **17** (or carbopalladation of alkene); and (3) dehydropalladation (β-H elimination) to give the arylalkenes **18** or conjugated dienes.

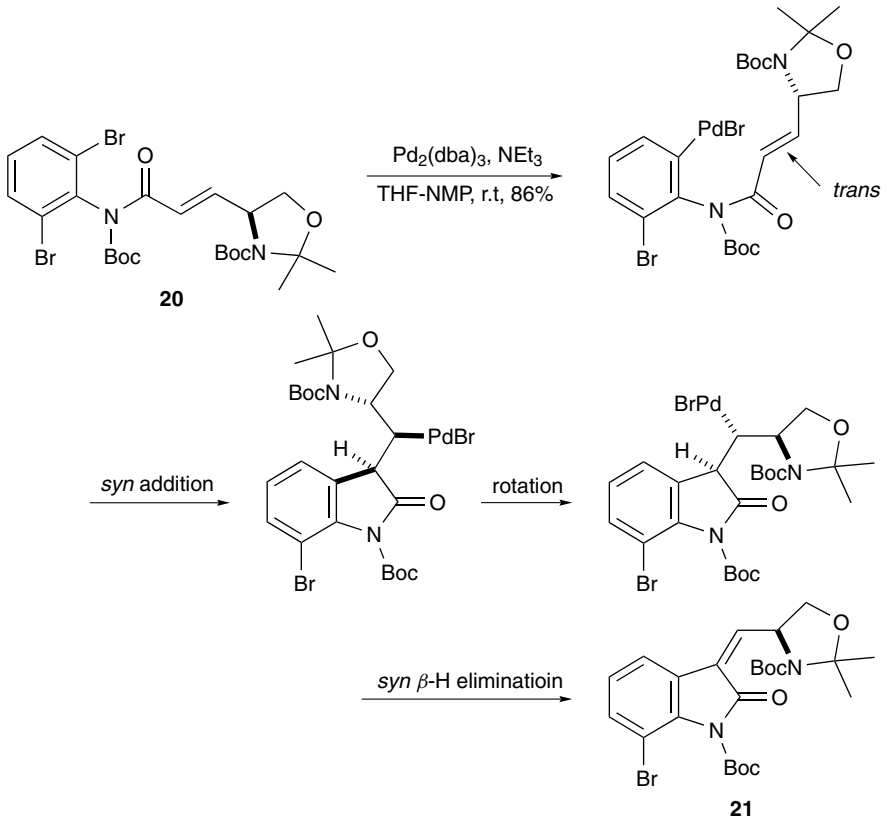
The stereochemistry of the insertion (carbopalladation) is *syn* addition. The *syn* addition of Ar-PdX to an alkene generates σ-(β-aryl)alkylpalladiums **17**. Then internal rotation around the former double bond occurs, making the *syn* β-H elimination possible to give the *trans*-alkenes **18**.



As supporting evidence of the *syn* addition, the *syn* elimination mechanism, Fu obtained only the *E*-isomer **19** as a kinetic product of the reaction of methyl *trans*-cinnamate with deuterated bromobenzene at room temperature using $Pd_2(dba)_3$ and P(*t*-Bu)$_3$. Under thermodynamic control at 120 °C, an *E*, *Z*-mixture (1 : 1) was formed [7].

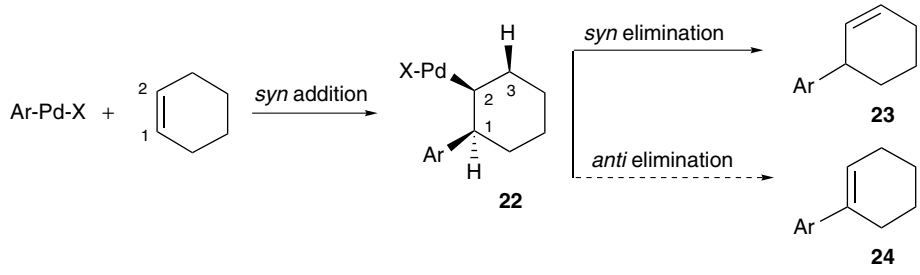


The *syn* addition, rotation, and *syn* elimination rule is valid even for reaction of congested molecules. Hirama applied HR of **20** to the stereocontrolled synthesis of the northern part of a potent proteasome inhibitor TMC-95A, and found that the *Z* isomer of the cyclized product **21** was obtained selectively in 86 % yield

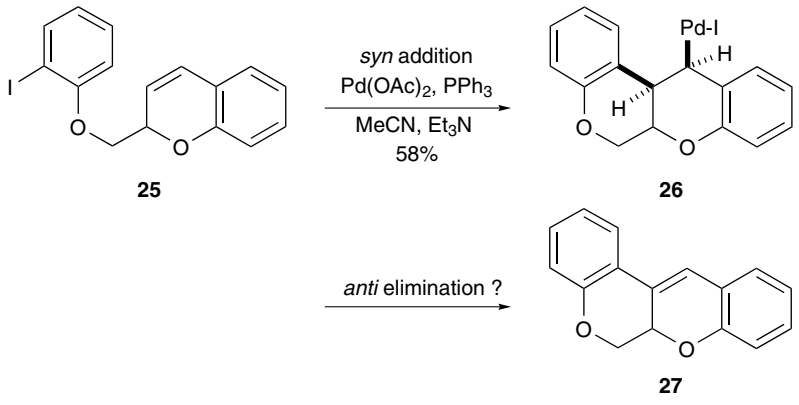


using $Pd_2(dba)_3$ without phosphine ligand in the presence of Et_3N [8]. Selective formation of the *Z* isomer can be understood by the *syn* addition, rotation, and *syn* elimination rule. The selection of conditions is critical for effective cyclization. Under different conditions, the yield of the cyclized product was low [9].

On the other hand, rotation of the intermediate **22** formed from cyclic alkenes is impossible and the *syn* β-H elimination from carbon C3 gives 3-arylalkene **23**, rather than 1-substituted alkene **24**, because β-H at carbon 1 is *anti* to PdX.



Furthermore, attention should be paid to the fact that direct *syn* β-H elimination is not possible in an intramolecular reaction. For example, *syn* carbopalladation of **25** generates the intermediate **26** and formal *anti* β-H elimination occurs to afford the cyclic alkene **27**. As one explanation, stereomutation may occur to allow *syn*



elimination, because Pd is on a benzylic carbon [10]. There are a number of examples of formal *anti* elimination, and there is no definite answer at present as to whether this is direct *anti* elimination or *syn* elimination after stereomutation.

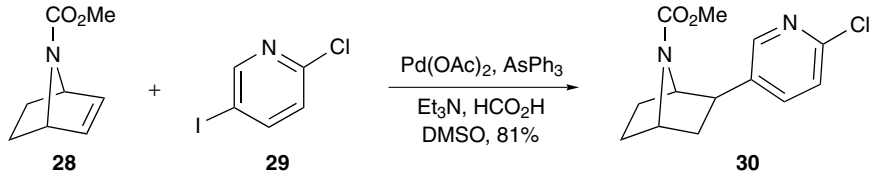
The following factors are variable in HR, and careful qualitative and quantitative optimization of these factors are essential to achieve successful reactions: halides; alkenes; ligands; solvents; bases; additives; and temperature. In order to find optimum conditions of reactions, a careful survey of these factors is crucial. In the literature, numerous recipes of optimum reactions have been reported, in which high turnover numbers (TON) and TOF have been reported. However, in many cases, these results have been obtained under a narrow range of conditions from specific reactants in small scale experiments, and the results can not always be retraced. At present, it is difficult to find clear-cut recipes for many kinds of reactions from data reported in the literature. In the following sections, some controlling factors are surveyed.

3.2.2 Catalysts and Ligands

HR are catalyzed by Pd(0) complexes of phosphines. Mainly commercially available $Pd(PPh_3)_4$, $Pd_2(dba)_3$ and $Pd(OAc)_2$ are used as precursors of Pd(0) catalysts with or without phosphines. When overligated $Pd(PPh_3)_4$ is used, reactions of congested molecules may be slow due to the presence of too many ligands, which inhibit coordination of reactants. $Pd(OAc)_2$, $Pd(dba)_2$ and even Pd on carbon are used with phosphines.

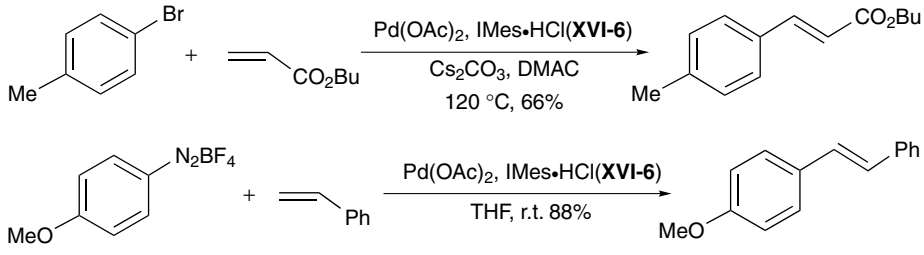
Bulky tri(*o*-tolyl)phosphine was used first by Heck [11]. A palladacycle obtained from it is known as the Herrmann complex (**XVIII-1**) and is used extensively in HR [12]. Also, palladacycles **XVIII-7** [13] and **XVIII-2** [14] are high performance catalysts. Turnover numbers as high as 630–8900 were achieved by tetraphosphine Tedicyp (**X-1**) [15]. Recently, the remarkable effect of electron-rich and bulky phosphines, typically P(*t*-Bu)$_3$ and other phosphines shown in Tables 1.4, 1.5 and 1.6, have been unveiled. Smooth reactions of aryl chlorides using these ligands are treated later. Electron-rich ligands accelerate oxidative addition of aryl chlorides, and reductive elimination is accelerated by bulky ligands. HR can be carried out in an aqueous solution by use of a water-soluble sulfonated phosphine (TPPMS, **II-2**) [16].

Sometimes, $AsPh_3$ shows better effect than PPh_3. In the synthesis of epibatidine (**30**) by hydroarylation of the azabicyclic alkene **28** with 2-chloro-5-iodopyridine (**29**) in the presence of formic acid, the best result was obtained using $AsPh_3$ [17].



28 **29** **30**

In addition, electron-rich and bulky heterocyclic carbenes are attracting attention as effective phosphine mimics [18]. Using carbene ligand **XVI-6**, HR of aryl bromides proceeds at 120 °C [19] and that of diazonium salts **31** at room temperature [20]. A new phosphine-imidazolium salt (**XVI-14**) was found to catalyze HR efficiently [21].



31

Occasionally reactions proceed with phosphine-free Pd(0) catalysts. Some phosphines are more expensive than Pd and more difficult to recover than Pd. Therefore, an ideal catalyst is a phosphine-free Pd(0) catalyst. Reactions of reactive halides and pseudohalides such as aryl iodides, diazonium salts and acyl chlorides proceed under phosphine-free conditions.

Supported heterogeneous Pd catalyst can be used with or without phosphine. Köhler reported that ligandless Pd/C (product of Degusa AG) is highly active; TON up to 36 000 was obtained in the reaction of bromobenzene with styrene in NMP at 140 °C [22].

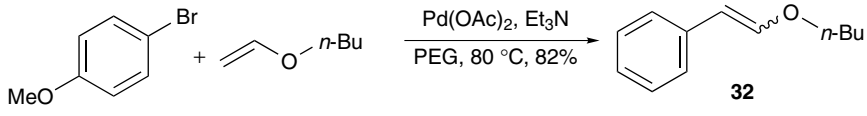
Some reactions catalyzed by ligand-free Pd catalysts in the presence of various additives proceed smoothly, and are treated in the next section.

3.2.3 Reaction Conditions (Bases, Solvents, and Additives)

Since strong acids are formed, the reaction must be carried out in the presence of bases. Coordinating and polar solvents, such as DMF, MeCN, NMP and DMSO, are preferable solvents. DMF is the most widely used. Water, a highly polar liquid, has been found to accelerate some reactions, which are carried out smoothly in aqueous solvents using water-soluble ligands.

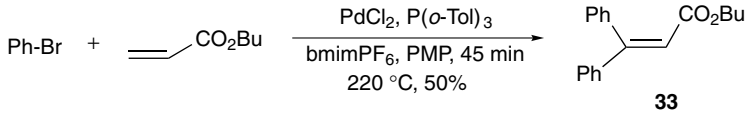
Poly(ethylene glycol) (PEG) having molecular weight 2000 (or lower) has been used as a good biphasic solvent for regioselective reaction of *n*-butyl vinyl ether

to give a single isomer **32** cleanly. It is known that a mixture of regioisomers is formed in other solvents. Furthermore, after the reaction, products can be isolated with dry ether. Pd catalyst always stays in the PEG layer and is recycled easily [22a]. HR proceeds rapidly in ionic liquids and catalysts can be recycled [18,23,24]. Double HR of bromobenzene with butyl acrylate occurred rapidly under microwave irradiation in bmim PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate) to give β,β-diphenylacrylate (**33**) [24]. In addition to the use of the ionic solvent, addition of 1,2,2,6,6-pentamethylpiperidine (PMP) as a base is important for the double HR.



32

E : *Z* = 7 : 3



33

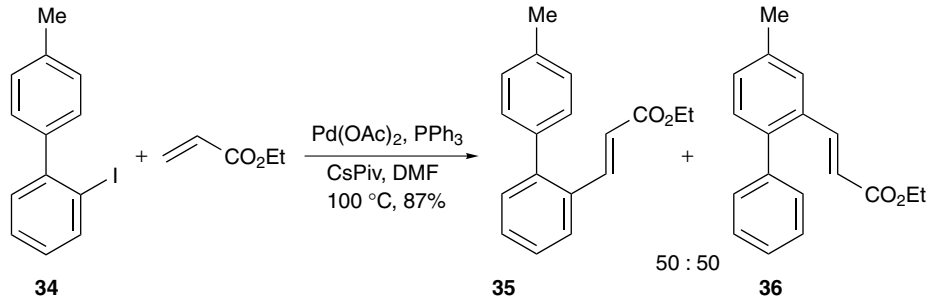
Uses of some additives are recommended. Addition of Ag_2CO_3 cleanly suppresses double bond isomerization in products. In addition, Ag salts accelerate reactions, possibly by removing halide ions strongly attached to Pd from a coordination sphere to generate a cationic Pd catalyst, making the insertion easier. Thallium salts also accelerate reactions, and suppress the double bond isomerization. A favorable effect of some alkali halides, such as LiCl and KBr, on the reaction is known [25].

Selection of bases is also important. Trialkylamines and inorganic bases such as K_2CO_3 and KOAc are commonly used. An unusually good effect of Cs_2CO_3 in some reactions is now well-known. It behaves as a base better than K_2CO_3 due to partly better solubility in organic solvents and higher basicity, and is used frequently. Buchwald reported that a bulky amine, Cy_2NMe, is a very effective base [26].

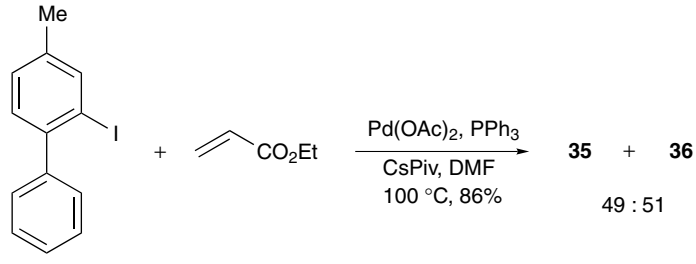
Larock found that the reaction of 2-iodo-4-methylbiphenyl (**34**) with acrylate provided two products **35** and **36** in equal amounts using cesium pivalate as a base. Of course, **35** is an expected product [27]. Also the reaction of **37** afforded the mixture of **35** and **36**. Gallagher also discovered a similar migration using 3-bromo-4-phenylpyridine (**38**) and acrylate to afford **39** and **40** [28]. Although the mechanism of the migration process to form the crossover products is not clear, certainly a reversible 1,4-Pd shift of arylpalladium intermediates **41** and **43** via the palladacycle **42** is occurring.

Reetz reported that a highly active ligandless Pd catalyst for HR of aryl bromides can be generated by combining $Pd(OAc)_2$ or $PdCl_2(PhCN)_2$ with *N*,*N*-dimethylglycine (DMG), and TON 106 700 was obtained with this catalyst in the reaction of bromobenzene with styrene, although the reaction was slow [29,30].

Jeffery made the important observation that a large rate acceleration in HR of aryl iodides occurs by addition of more than equimolar amounts of tetraalkylammonium salts as a phase-transfer catalyst and solid bases without ligands. The



34 **35** **36**



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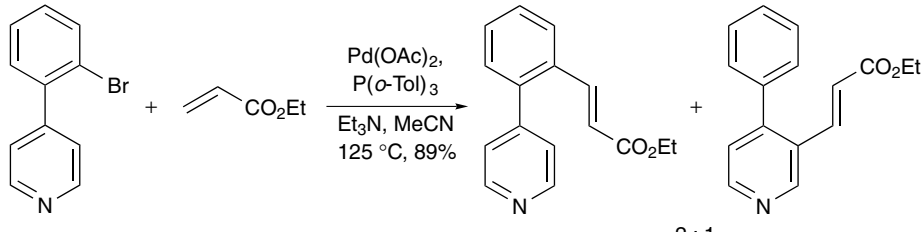
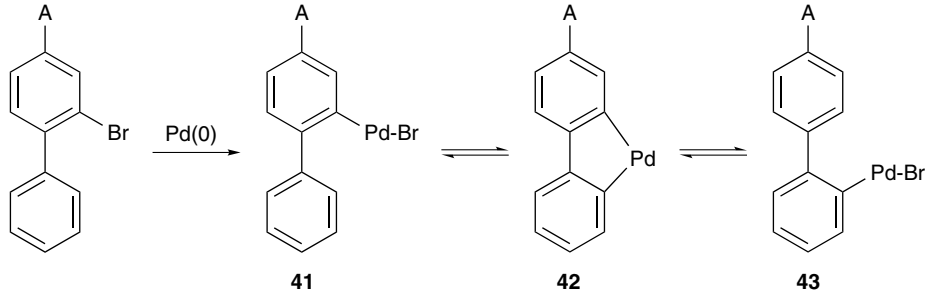


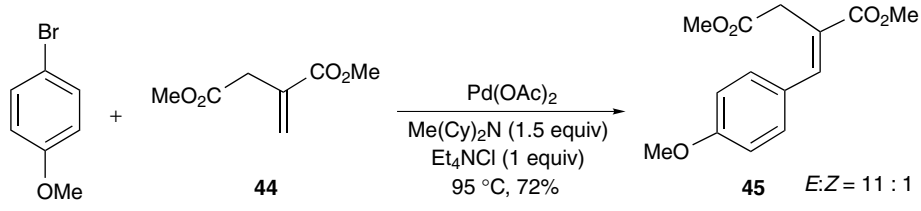
38 **39** **40**



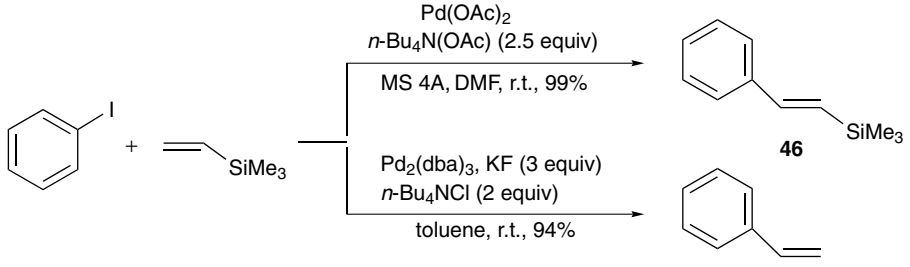
41 **42** **43**

conditions are called 'Jeffery's ligandless conditions'. Reactions of aryl and alkenyl iodides proceed smoothly by the addition of $KHCO_3$ and Bu_4NCl in DMF at room temperature [31]. Detailed studies have shown that careful selection of the kinds and amounts of Pd catalysts, bases, solvents, water and particularly tetraalkylammonium salts, are important to find optimum conditions [32]. As one explanation of the effect of tetraalkylammonium salts, Reetz found using transmission electron microscopy that $R_4N^+X^-$-stabilized Pd colloids are formed under Jeffery's ligandless conditions and function as active catalysts [33].

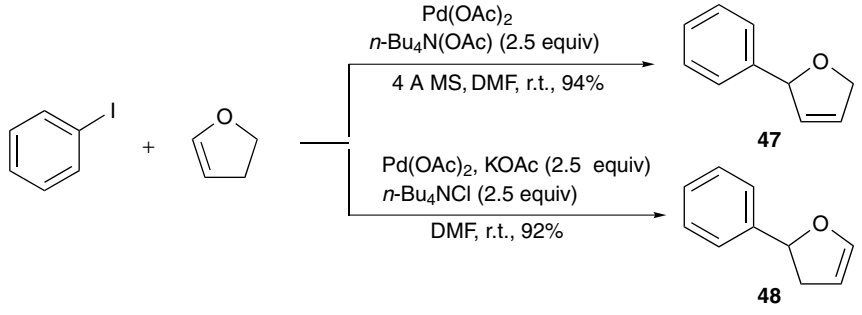
As a recent example, HR of the disubstituted alkenes **44** gave **45** with high stereoselectivity using a ligandless catalyst. In this case, selection of bases is crucial and combined use of methyl(dicyclohexyl)amine and a phase transfer catalyst gave the best results [26].



It is known that HR of vinyltrimethylsilane with aryl halides affords styrene derivatives by desilylation–arylation. In the presence of Ag salt, normal products are obtained [34]. Jeffery reported that either the normal product **46** or styrene, the desilylation product, from iodobenzene and vinyltrimethylsilane are obtained selectively under mild conditions by slight modification of conditions. In the presence of Bu_4NOAc and molecular sieve in DMF, 2-trimethylsilylstyrene (**46**) is obtained as expected. On the other hand, styrene is obtained selectively as an abnormal product in toluene in the presence of 3 equivalents of KF. Formation of styrene is explained by the combination of three reactions, namely β-H elimination, reverse readdition of H-Pd-X, and subsequent desilylpalladation. Whatever the mechanism, the presence of a large amount of KF, which strongly activates the TMS group, must play an important role [35].

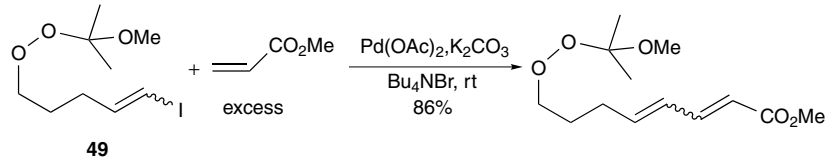


As another example of a delicate effect of tetraalkylammonium salts, either 2-phenyl-2,5-dihydrofuran (**47**) or 2-phenyl-2,3-dihydrofuran (**48**) was obtained selectively in the arylation of 2,3-dihydrofuran with a slight change of additives [36].



Jeffery's conditions are so mild that reaction of an alkenyl iodide containing a very unstable peroxide group **49** proceeded smoothly without decomposition of the peroxide under the conditions at room temperature [37].

Cyclization of the quinoxaline chloride **50** to prepare pyrrolo[2,3-*b*]quinoxaline under usual conditions is slow and the yield is low, because the aminoquinoxalines are strong chelating agents and poison Pd catalysts. However, the locked Pd catalyst is released and the reaction proceeds smoothly under Jeffery's ligandless conditions to give the pyrrolo[2,3-*b*]quinoxaline **51** in 67 % yield [38].



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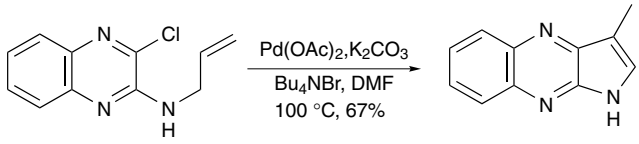
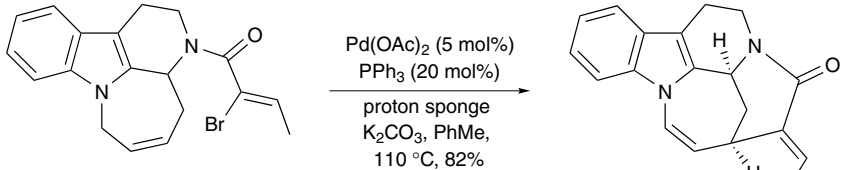


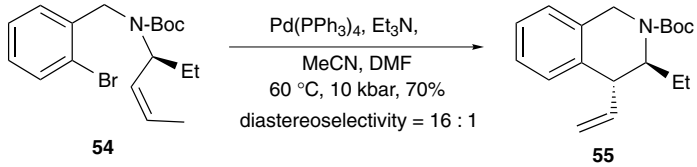
50 **51**

Many successful applications of Jeffery's conditions have been reported. However, Rawal reported in his alkaloid synthesis that Jeffery's conditions were not suitable for the attempted cyclization of the iodide corresponding to **52** (Br → I), and the cyclization of the vinyl bromide **52** proceeded cleanly under a 'nonpolar' set of conditions; $Pd(OAc)_2$, PPh_3, proton sponge in toluene at 100 °C to give **53** in 82 % yield [39].



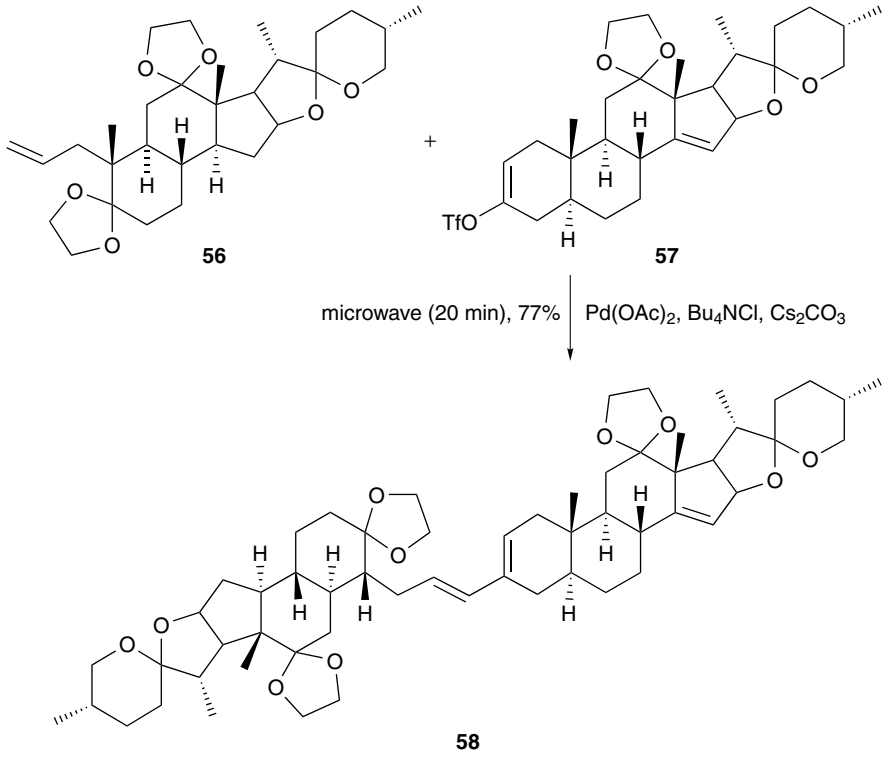
52 **53**

A remarkable effect on rate enhancement under high pressure is known [40]. The enantiomerically pure isoquinoline **55** was obtained from the bromide **54** in 70 % yield and with high diastereoselectivity (16 : 1) under pressure (10 kbar). The yield was lower than 10 % under normal pressure and even under Jeffery's conditions [41].



54 **55**

Also acceleration is observed by microwave irradiation in a solvent-free reaction [24,42]. HR of the steroidal triflate **57** with alkene **56** is a key reaction in practical synthesis of the complex bis-steroidal diene intermediate **58**. The best yield



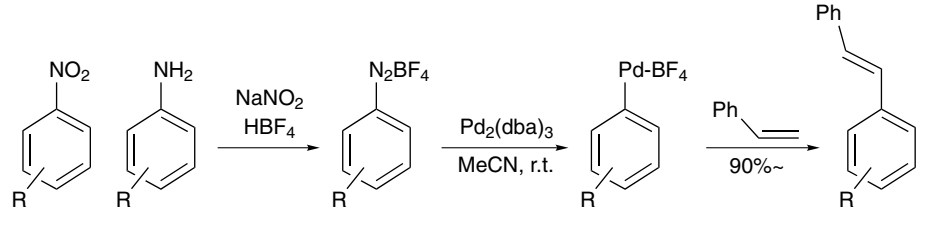
(77 %) was obtained under Jeffery's ligandless conditions and microwave irradiation. Cs_2CO_3 was found to be more effective than K_2CO_3 [43].

3.2.4 Halides and Pseudohalides

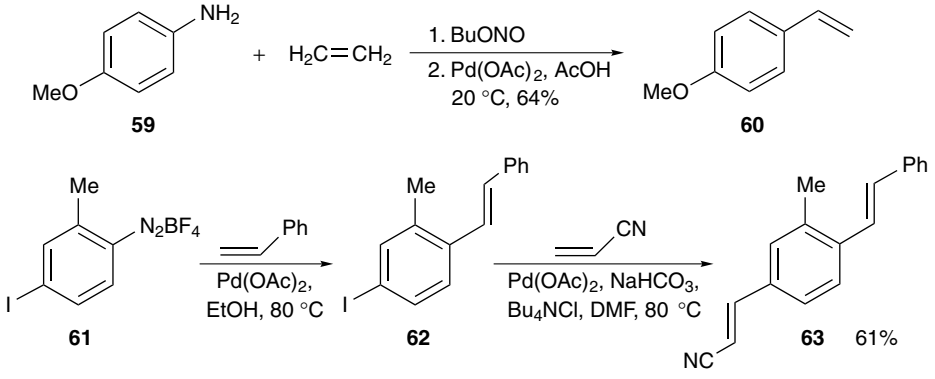
The halides and pseudohalides given in Scheme 3.1 show different reactivities, which are summarized briefly in the following.

3.2.4.1 Diazonium Salts

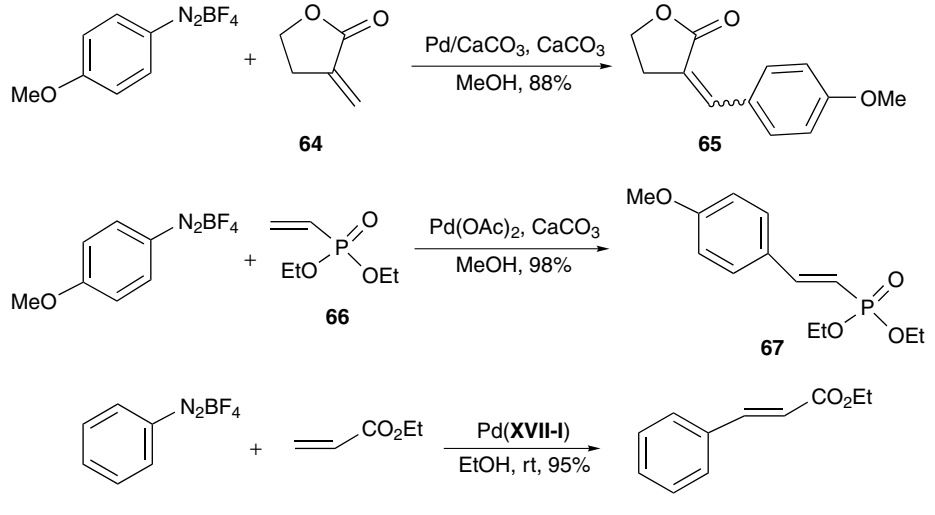
Diazonium salts are the most reactive source of arylpalladium species and the reaction can be carried out at room temperature using $Pd_2(dba)_3$ as a catalyst in the absence of both phosphine ligand and base [44]. The reaction of diazonium salts means indirect substitution reaction of an amino group of anilines or aromatic nitro group with an alkene. The use of diazonium salts is synthetically more convenient than the use of aryl halides, because many aryl halides, particularly iodides, are prepared from diazonium salts.



p-Methoxystyrene (**60**) and other styrene derivatives are prepared from *p*-methoxyaniline (**59**) via diazotization with butyl nitrite in AcOH and reaction under ethylene [45]. The highly reactive diazonium group in the iodoaryldiazonium salt **61** was selectively displaced with styrene at 80 °C in EtOH using $Pd(OAc)_2$ to give **62** and then the remaining iodo group was displaced with acrylonitrile in the presence of Bu_4NCl in DMF at 80 °C to afford **63** [46].

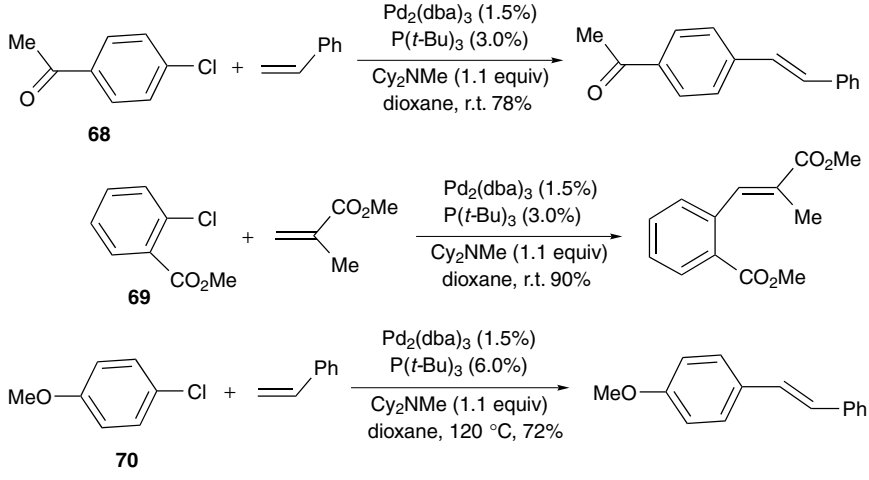


Usually the reaction of diazonium salts is carried out in the absence of bases, and the reaction medium becomes acidic with progress of the reaction, and some undesirable reactions may occur. This problem can be solved by adding $CaCO_3$ as a heterogeneous base. The α-benzylidene-γ-butyrolactone **65** was prepared by arylation of the very labile α-methylenebutyrolactone (**64**) using Pd on $CaCO_3$ as a catalyst and $CaCO_3$ as the solid base in MeOH [47]. Vinylphosphonates such as **67** are prepared by the reaction of aryldiazonium salts with diethyl vinylphosphonate (**66**) using $CaCO_3$ as the base. The reaction, followed by hydrogenation, offers a good synthetic method for Wadsworth–Emmons reagents [48]. The Pd(0) complex of 15-membered macrocyclic triolefins containing different aryl units (**XVII-1**) is an air- and moisture-stable phosphine-free complex, and can be used as a highly active catalyst for HR of diazonium tetrafluoroborates at room temperature [49].

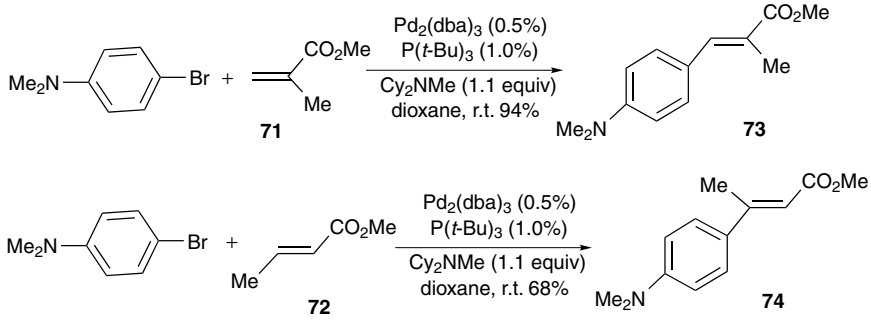


3.2.4.2 Halides

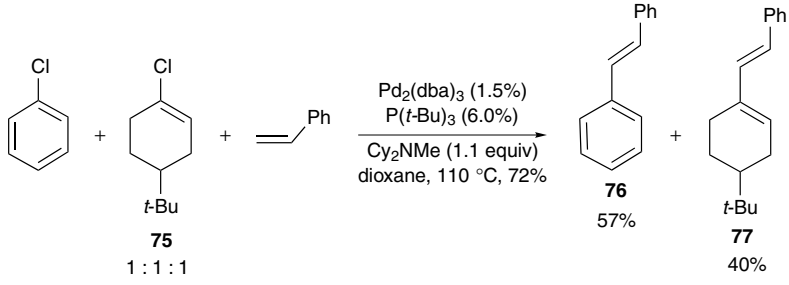
The oxidative addition of aryl halides to Pd(0) is a disfavored step when powerful electron donors such as OH and NH_2 reside on aromatic rings. Iodides react smoothly even in the absence of a ligand, and bromides in the presence or absence of a phosphine ligand. For a long time, iodides and bromides have been used as reactive halides. Recently remarkably smooth reactions of aryl chlorides have been achieved by proper selection of ligands and bases; electron-rich and bulky phosphines, typically P(*t*-Bu)$_3$, are effective. Littke and Fu reported that HR of aryl chlorides proceeds smoothly using $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cs_2CO_3 [50]. Furthermore, the combination of $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe gives a versatile catalyst for reactions of aryl chlorides under mild conditions [7]. The unusual effectiveness of Cy_2NMe was reported by Gürtler and Buchwald [26]. Reactions of aryl chlorides **68** and **69** activated by EWGs proceed at room temperature. A higher temperature (120 °C) is required for the reaction of *p*-chloroanisole (**70**) under these conditions. Reetz *et al.* reported that the combination of $Pd(OAc)_2$ or $PdCl_2$ with Ph_4PX(X = Cl, Br, I) in a ratio of 1 : 6 generates an active catalyst for HR of aryl chlorides in the presence of sodium acetate in DMF or NMP at 120–150 °C. In addition, *N*,*N*-dimethylglycine is an excellent additive to improve regioselectivity [30].



HR of electron-rich aryl bromides with 1,1- or 1,2-disubstituted alkenes such as methyl methacrylate (**71**) and crotonate (**72**) proceeds at room temperature in dioxane with the same catalyst to provide **73** and **74** [26].



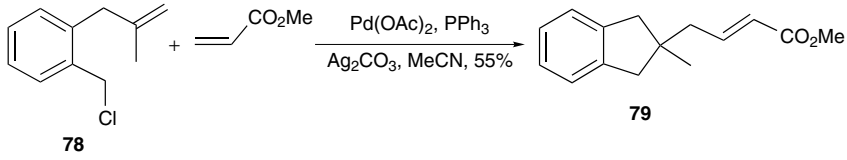
Unlike aryl chlorides, unactivated alkenyl chlorides react more smoothly. It is generally recognized that alkenyl chlorides are much more reactive than aryl chlorides. However, curiously somewhat higher reactivity of chlorobenzene than the alkenyl chloride **75** was observed by the use of this catalyst in the following competitive reaction. The yield of **76** was higher than that of **77**.



Littke and Fu reported an interesting and important suggestion that commercially available $Pd[P(t\text{-}Bu)_3]_2$ is a resting state of the system in the HR, and not a catalytically active species. Change of the ratio of Pd to phosphine from 1 : 1 to 1 : 2 leads to a marked decrease in the rate of reactions, and the Pd monophosphine adduct $PdP(t\text{-}Bu)_3$ is the active catalyst. The combination of $Pd[P(t\text{-}Bu)_3]_2$ and a phosphine-free Pd complex generates *in situ* the active 1 : 1 adduct [7].

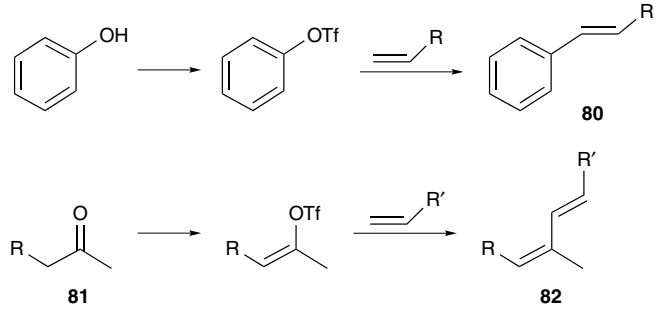
Also diadamantyl(*t*-butyl)phosphine (**I-20**) is a good ligand for HR of aryl bromides at room temperature [51].

Benzyl chlorides are reactive partners of HR. For example, intra- and intermolecular reactions of the benzyl chloride **78** with methyl acrylate afford the indane ester **79** [52].



3.2.4.3 Triflates

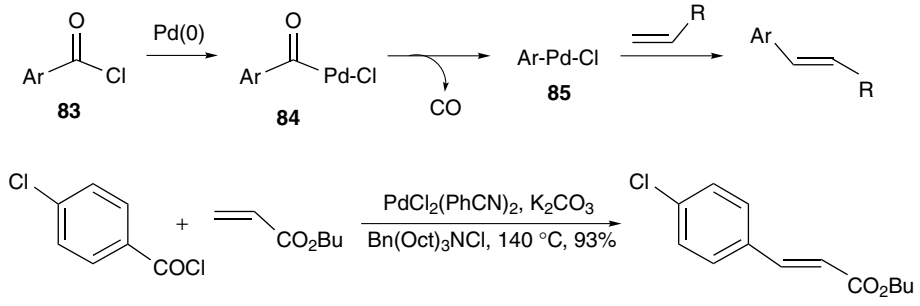
Aryl and alkenyl triflates prepared from phenols and carbonyl compounds are reactive substrates which undergo facile oxidative addition. Reactivity of triflates is between that of iodides and bromides. Pd-catalyzed reactions of triflates mean indirect displacement of the phenolic OH group to afford **80** and transformation of carbonyl compounds **81** to the substituted alkenes **82**. In classical organic chem-



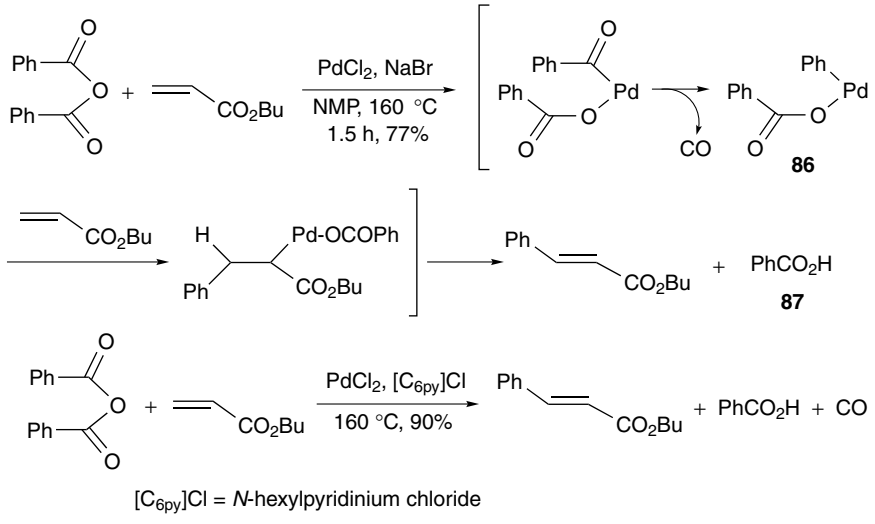
istry, displacement of the phenolic OH group is practically impossible. Nonaflates (nonafluorobutanesulfonates) are also active reaction partners.

3.2.4.4 Acyl Halides, Carboxylic Acid Anhydrides, and Aldehydes

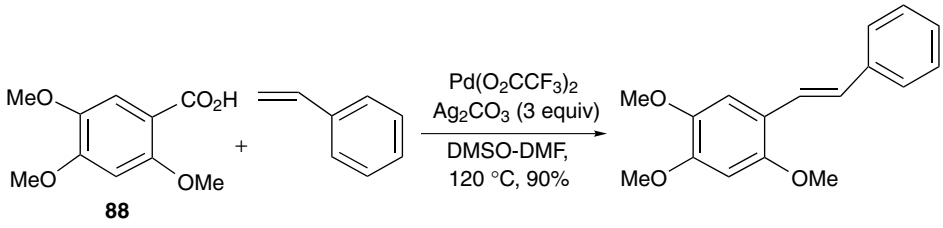
The acylpalladium halide complex **84** is an intermediate of catalytic decarbonylation of aroyl halides **83** [53]. The decarbonylation of **84** generates the arylpalladium intermediate **85** at higher temperature which undergoes facile alkene insertion. Therefore, similar to aryl halides, acyl halides can be used for the alkene insertion. The reaction is carried out with a phosphine-free Pd catalyst in the presence of tertiary amines [54]. Higher yields were obtained by using a mixture of K_2CO_3 and benzyltrioctylammonium chloride [55].



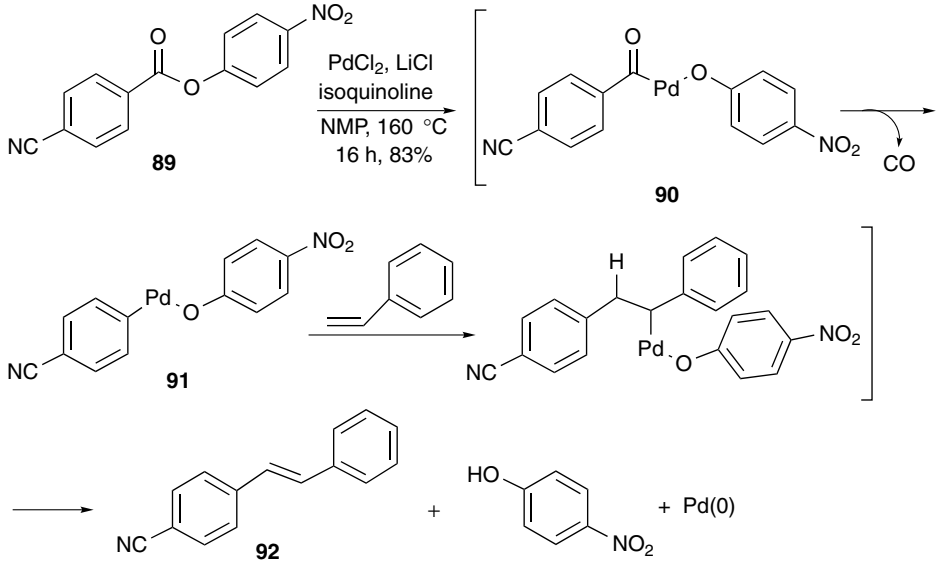
Anhydrides of aromatic acids undergo facile oxidative addition, followed by decarbonylation to generate arylpalladium intermediates **86**. HR of anhydrides was carried out using catalytic amounts of $PdCl_2$ and NaBr in NMP at 160 °C in the absence of ligands. Higher temperature is required for the decarbonylation. It should be mentioned that addition of bases is not necessary (of course, bases react with anhydrides). In this base-free reaction, only the free acid **87** is formed as a byproduct [56]. Also the reaction proceeds in an ionic liquid (*N*-hexylpyridinium chloride) using $PdCl_2$ as a catalyst at 160 °C. Facile recycle of the catalyst and the ionic liquid is possible [57].



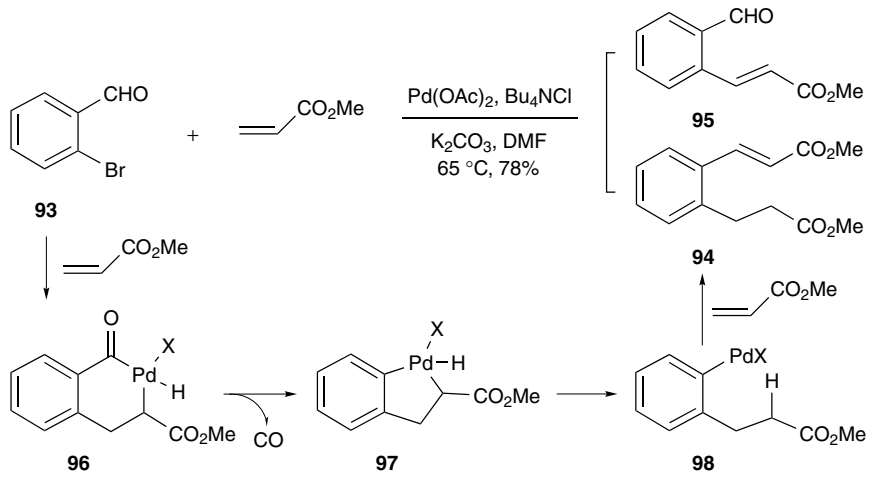
Meyers *et al*. reported that arylpalladium intermediates are generated from electron-rich aromatic acids **88** by decarboxylation and undergo HR in 5 % DMSO–DMF when palladium trifluoroacetate was used. However, addition of 3 equivalents of Ag_2CO_3, which may accelerate the decarboxylation, is necessary [58].



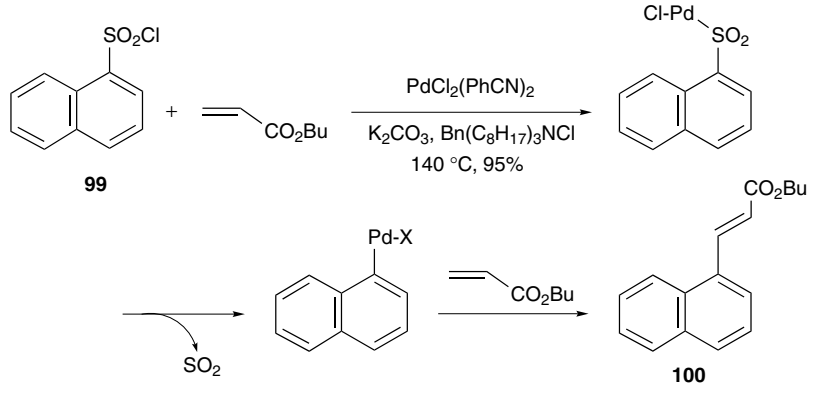
Esters are usually inert for oxidative addition. Exceptionally, *p*-nitrophenyl esters of aromatic acids **89** undergo oxidative addition to generate the acylpalladium **90**, and its decarbonylation generates the arylpalladium intermediate **91**. Insertion of alkene and β-H elimination give the coupled product **92**. The base-free HR of the esters proceeds by using $PdCl_2$ as a catalyst and isoquinoline as a ligand in the presence of LiCl at 160 °C in NMP. Phosphine inhibits the reaction [59].



Interestingly, HR of *o*-bromobenzaldehyde (**93**) with acrylate gave the doubly substituted product **94** and the expected product **95** under Jeffery's ligandless conditions [60]. Formation of **94** is explained by the following mechanism. Insertion of acrylate to **93**, followed by oxidative addition of aldehyde generates **96**. The palladacycle **97** is formed by decarbonylation, and its reductive elimination gives **98**. The final product **94** is obtained by HR of **98** with acrylate.



Oxidative addition of the sulfonyl chlorides **99** is followed by facile generation of SO_2 to form the arylpalladium complexes, which undergo alkene insertion and β-H elimination to give **100** [55].

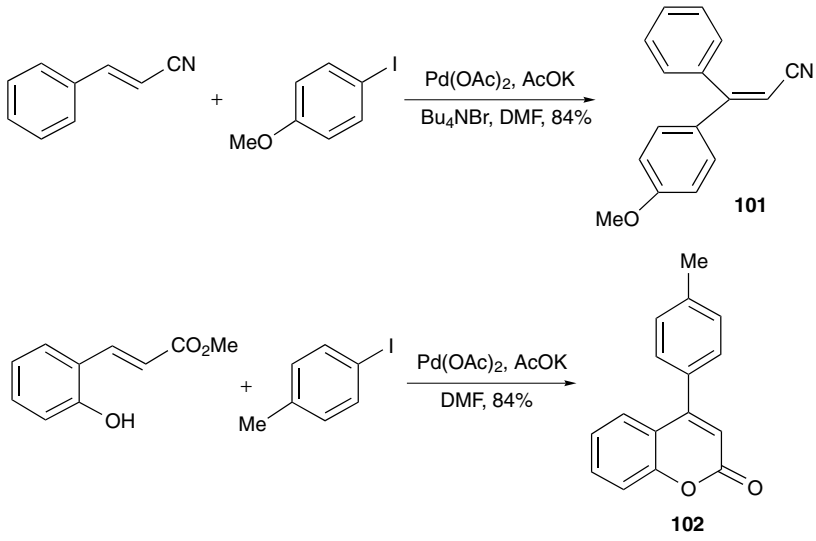


3.2.5 Alkenes

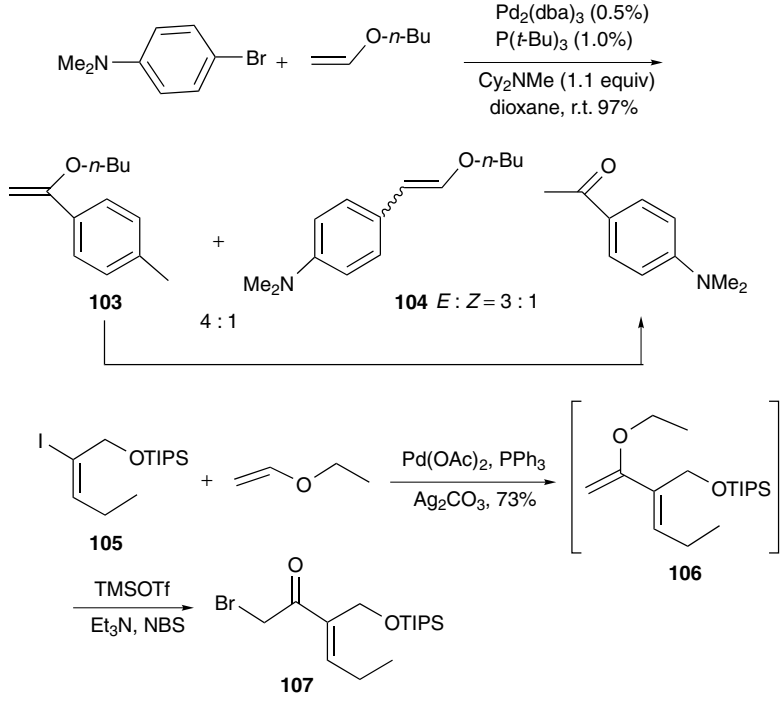
Characteristic behaviors of several functionalized alkenes in HR are summarized as follows. HR of monosubstituted alkenes usually proceeds satisfactorily. Intermolecular HR is sensitive to steric factors of alkenes, and reactions of 1,1- and 1,2-disubstituted alkenes are slower than those of monosubstituted alkenes. Although intermolecular reactions of congested double bonds are slow, intramolecular reactions of even very hindered double bonds proceed smoothly.

Although examples are few, stereospecific HR of 1,2-disubstituted alkenes such as cinnamate under controlled conditions is known [7,26]. As another example, (*E*)-3,3-diarylacrylonitrile **101** was obtained selectively by the reaction of (*E*)-3-phenylacrylonitrile with *p*-iodoanisole [61]. HR of methyl *o*-hydroxycinnamate with *p*-iodotoluene afforded the coumarin **102**, showing that the tolyl and ester groups are *trans* as expected [62].

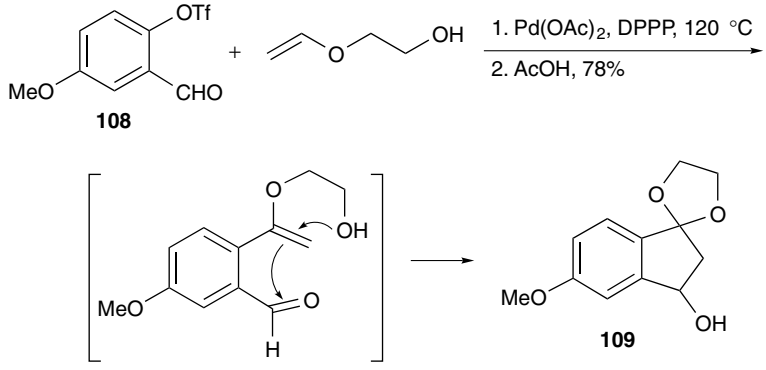
Alkenes bearing EWGs are most reactive. Reactivity of alkenes bearing electron-donating groups such as vinyl ethers, vinyl esters, enamides, and enamines, is lower



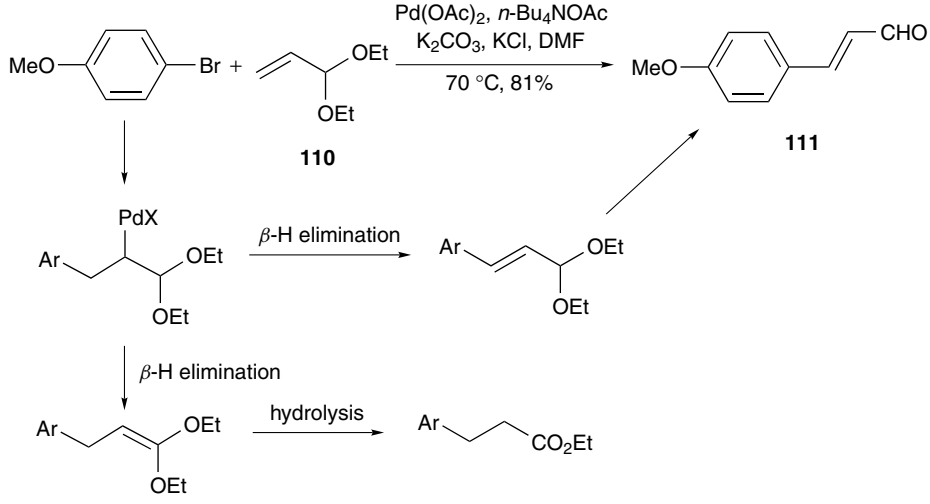
than that of alkenes with EWGs. In addition, their reactions give two regioisomers depending on substrates and reaction conditions. As a recent example, reaction of *n*-butyl vinyl ether with *p*-*N*,*N*-dimethylaminophenyl bromide afforded the isomers **103** as a major product together with **104**. The reaction occurs at room temperature when electron-rich P(*t*-Bu)$_3$ is used as a ligand [7]. Aryl or vinyl methyl ketones are prepared by α-selective reaction of methyl or ethyl vinyl ethers with aryl or vinyl halides, followed by hydrolysis [63]. Also HR of ethyl vinyl ether with the vinyl iodide **105** proceeded regioselectively in the presence of Ag_2CO_3, and the product **106** was converted to the bromomethyl ketone **107** [64].



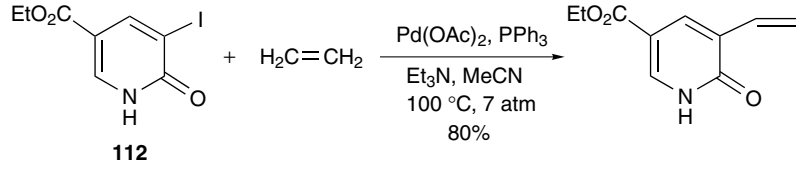
The protected indanone **109** was obtained by the Pd-catalyzed one-pot reaction of the triflate of salicylic aldehyde **108** with 2-hydroxyethyl vinyl ether and addition of AcOH [65]. In this case, selective α-arylation is followed by annulation promoted by Pd and AcOH to give **109**.



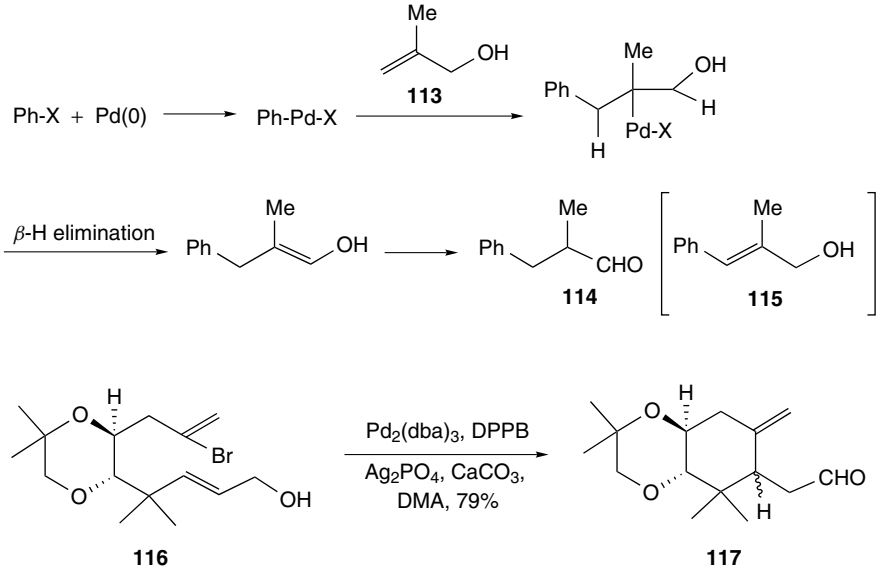
Cinnamaldehydes **111** are prepared by the reaction of acrolein diethyl acetal (**110**) with aryl halides and hydrolysis of the coupling product. Formation of saturated esters (3-arylpropionates) is competitive, and cinnamaldehydes were obtained with high selectivity in the presence of $Pd(OAc)_2$, Bu_4NOAc, K_2CO_3, and KCl in DMF at 90 °C [66].



Reaction of ethylene with aryl iodide can be carried out under pressure. The vinylpyridone was prepared in 80 % yield from the 3-iodopyridone **112** under pressure (7 atm) [67].

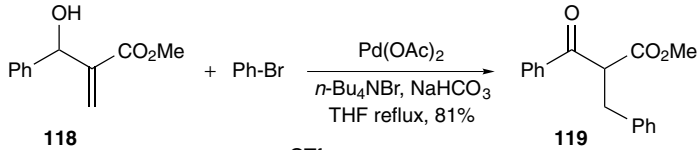


When allylic alcohols are used as an alkene component in HR, β-H elimination occurs from an oxygen-bearing carbon, and aldehydes or ketones are obtained, rather than β-arylated allylic alcohols [68,69]. The reaction of methallyl alcohol (**113**) with a halobenzene is a good synthetic method for dihydro-2-methylcinnamaldehyde, an important fragrant compound **114**. The allylic alcohol **115** is not formed. An intramolecular version of the aldehyde formation was applied to the preparation of the key intermediate **117** from **116** in the total synthesis of saponaceolide [70].

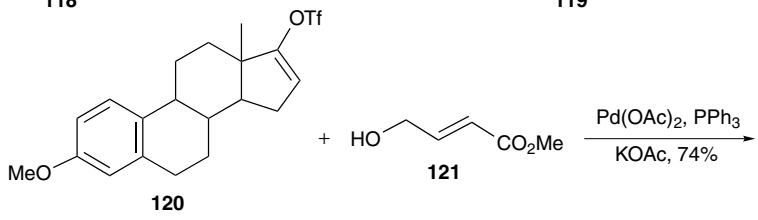


Arylation of the easily available Baylis–Hillman adduct **118** under Jeffery's conditions gave the keto ester (**119**) in good yield [71]. On the other hand, some allylic alcohols behave differently. The β-substituted butenolide **123** was obtained by the reaction of the steroidal vinyl triflate **120** with methyl 4-hydroxy-2-butenoate (**121**). In this case, 3-substituted 4-hydroxy-2-butenoate **122** is a primary product, rather than an aldehyde [72]. In addition to allylic alcohols, other unsaturated alcohols react with aryl halides to give carbonyl compounds. For example, although the reaction was slow (3 days), undecen-1-ol (**124**) reacted with iodobenzene to afford the aldehydes **125** and**126**. In this reaction, reversible and efficient elimination of H-Pd-I and its readdition (reinsertion) in reverse regiochemistry are repeated several times until irreversible elimination of H-Pd-I from the oxygen-bearing carbon in **124** occurs, finally giving **125** as a main product in a surprisingly high yield and **126** as a minor product. Efficient Pd migration occurs [73].

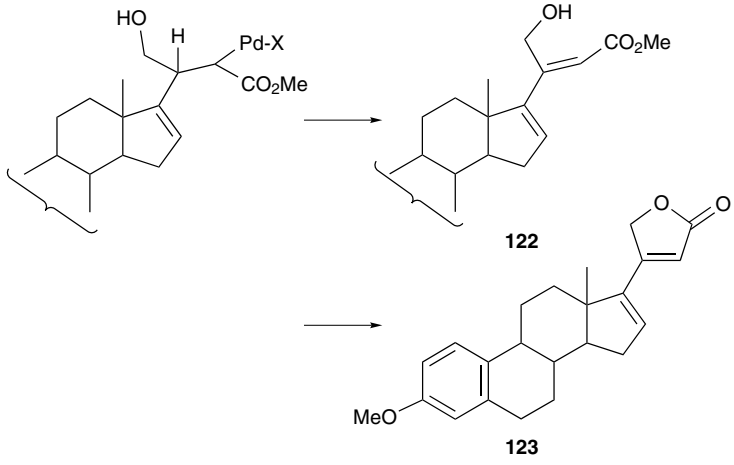
In the reaction of allylic ethers with aryl halides, elimination of β-alkoxy group occurs in some cases. Intramolecular reaction of the glycal **127** afforded the *cis*-fused pyrano[2,3-*c*]pyran **129** via deoxypalladation as shown by **128** [74]. On the other hand, ring cleavage of **130** occurs by deoxypalladation to give **132** via **131** [75]. Furthermore, the *bis*-annulated pyranoside **134** was obtained by domino HR without elimination of the allyl ether group in **133** [76].



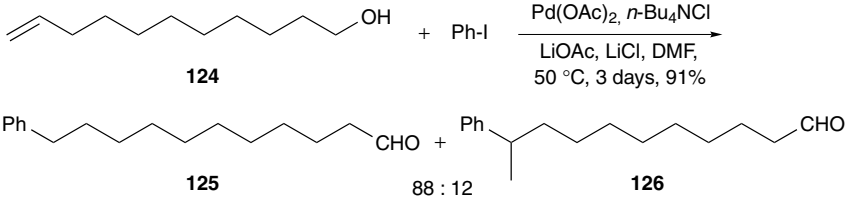
118 **119**



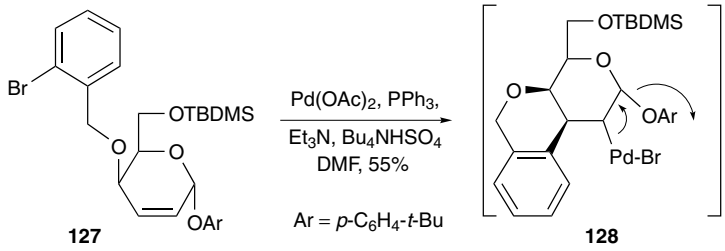
120 **121**



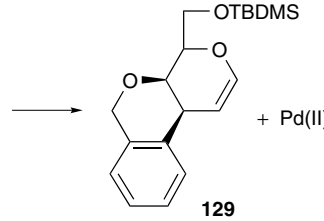
122 **123**



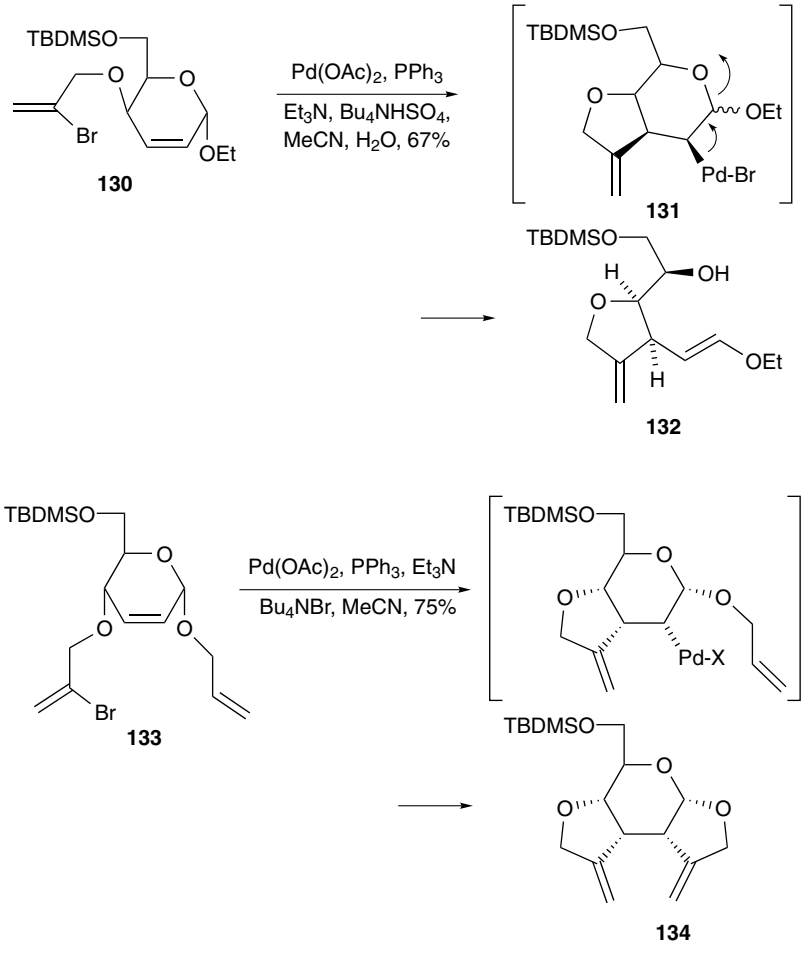
124 **125** 88 : 12 **126**



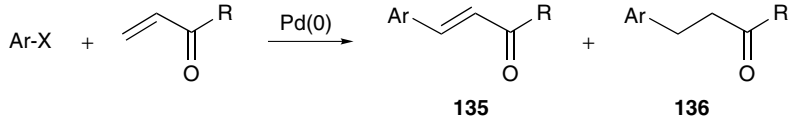
127 **128**



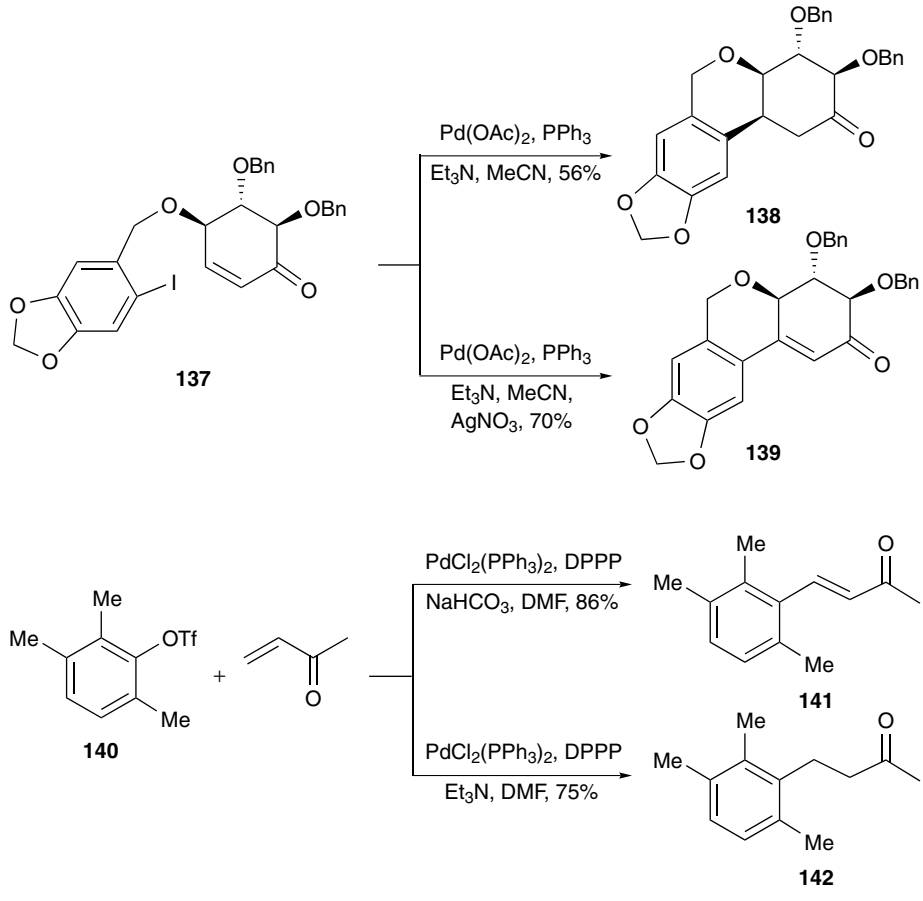
129



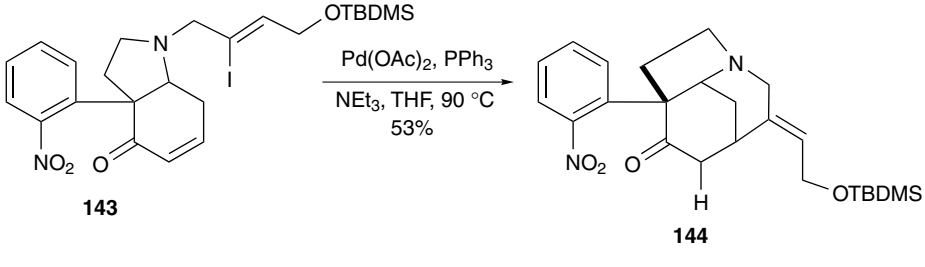
Single products are obtained by the HR of unsaturated esters such as acrylate. On the other hand, two reactions occur in HR of α,β-unsaturated ketones depending on substrates and reaction conditions. One of them is normal HR to give substituted products **135** formed via β-H elimination. In addition, 1,4-conjugated addition to give the Michael addition-type products **136** by reduction of alkylpalladium

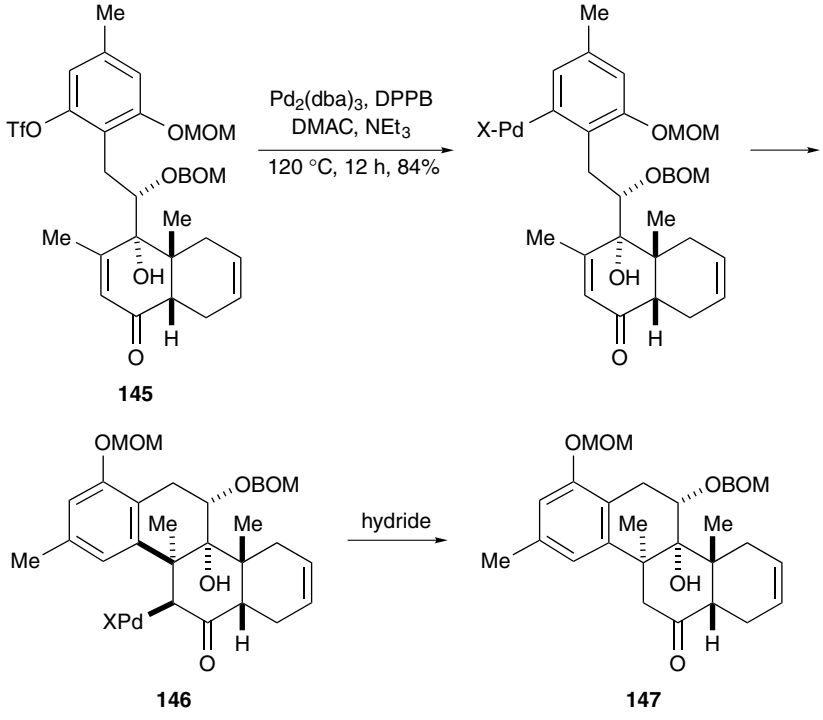


intermediates is observed. Intramolecular reaction of the enone **137** afforded the reduced product **138** under usual conditions and the unsaturated ketone **139** in the presence of $AgNO_3$ [77]. Chemoselectivity of the reaction of the aryl triflate **140** with methyl vinyl ketone depends on bases. The unsaturated product **141** was obtained in the presence of $NaHCO_3$, and the saturated ketone **142** was obtained when Et_3N was used as the base [78].

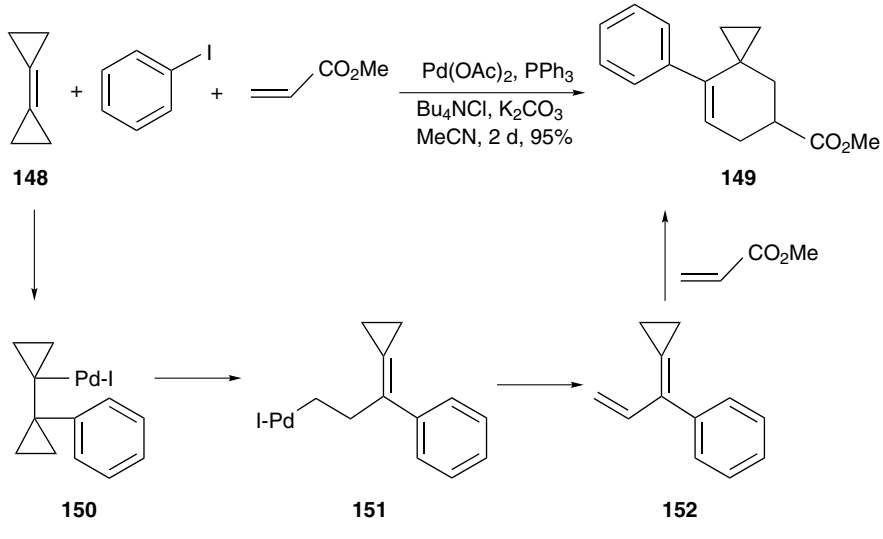


As an example of 1,4-conjugated addition, the intramolecular reaction of **143**, carried out in the total synthesis of strychnine by Bonjoch, gave the unexpected reduced product **144**. Et_3N may be a hydride source [79]. In the stereocontrolled synthesis of zoanthenol by the Hirama group, the benzylic quaternary center was constructed in 84 % yield by HR of the very congested β,β-disubstituted enone **145** using DPPB as a ligand in the presence of Et_3N. The Pd-enolate **146**, formed by intramolecular insertion, is an intermediate, and the saturated ketone **147** was obtained by attack of the hydride supplied possibly from Et_3N or protonolysis of the enolate. Direct hydrogenolysis of the triflate group in **145** occurred before olefin insertion when HCO_2H was added as a hydride source [80].





Bicyclopropylidene (**148**) undergoes HR with ring cleavage. Carbopalladation of **148** generates **150**. Then **151** is formed by β-carbon elimination. This intermediate undergoes several transformations with other substrates. In one case, it is converted to 1,3-diene **152**, and its Diels-Alder reaction with acrylate affords the spirocyclopropane **149** [81].



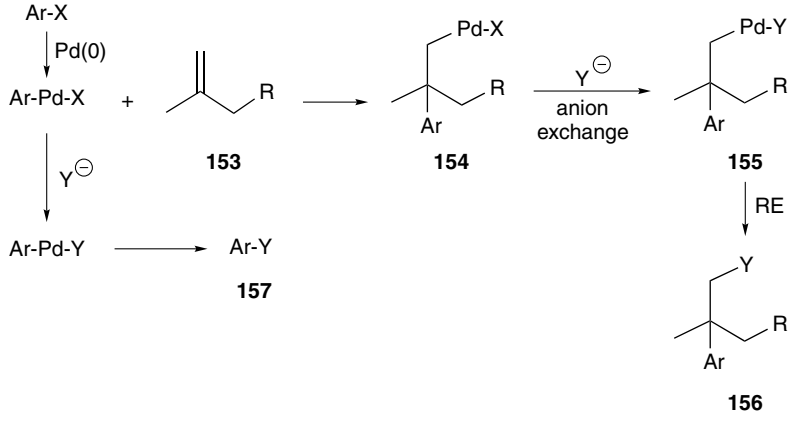
3.2.6 Formation of Neopentylpalladium and its Termination by Anion Capture

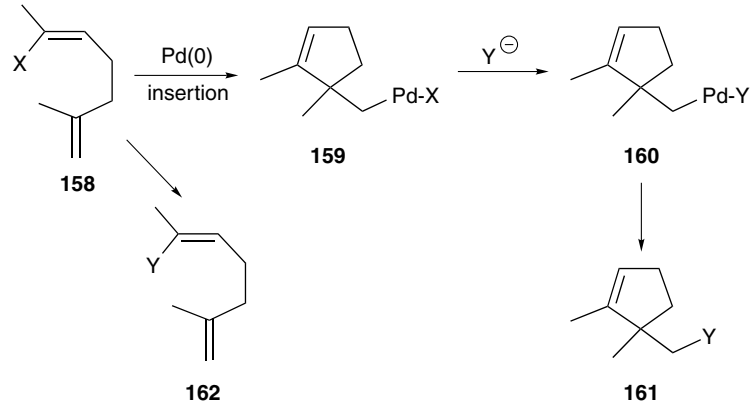
The carbopalladation of the 1,1-disubstituted alkenes **153** generates the neopentylpalladium **154** which is a living species, because there is no β-H to be eliminated in **154**, and the reactions are terminated only by exchanging Pd—X with anions or nucleophiles to afford **155**, and the product **156** is formed by reductive elimination. As an intramolecular version, the cyclized product **161** was obtained from halo dienes **158** by exchange of the neopentylpalladium intermediate **159** with anions to give **160**. As a side reaction, direct displacement of Ar—X with anions occurs to give **157** or **162**. Usually carbopalladation is faster than the direct anion exchange process to give **162**.

Anionic : ^{-}H, ^{-}OAc, $^{-}N_3$, $^{-}CH(CO_2R)_2$, $^{-}SO_2Ph$, RCO_2^{-}.

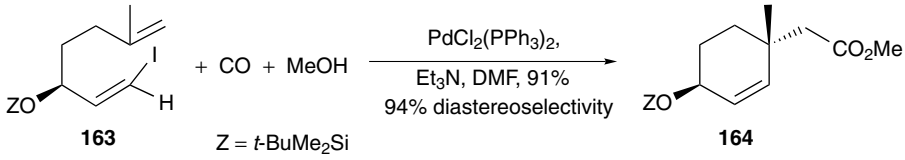
Neutral : NHR_2, ROH, CO-ROH.

Organometallic RM : M = Mg, Zn, B, Sn.

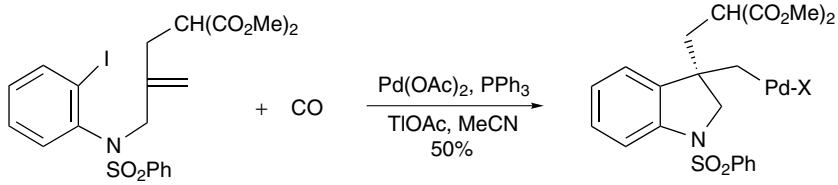




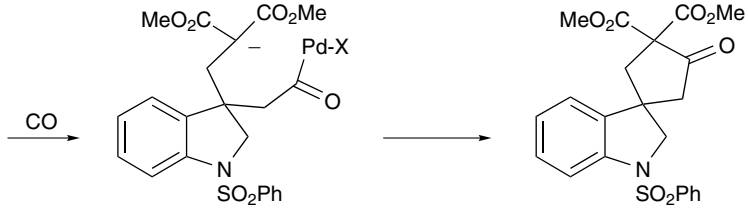
Some examples of termination by anion capture are as follows. Reactions are terminated by carbonylation. Domino carbopalladation and carbonylation of the iododiene **163** under 1 atm of CO via a neopentylpalladium intermediate gave the cyclized ester **164** with high yield and diastereoselectivity [82]. The iodide **165** underwent 5-*exo* cyclization to generate the neopentylpalladium **166** and its carbonylation gave the acylpalladium **167**. Intramolecular attack by malonate anion affords **168** [83].



163 **164**

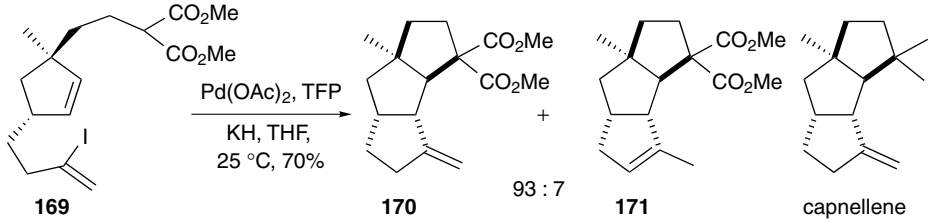


165 **166**



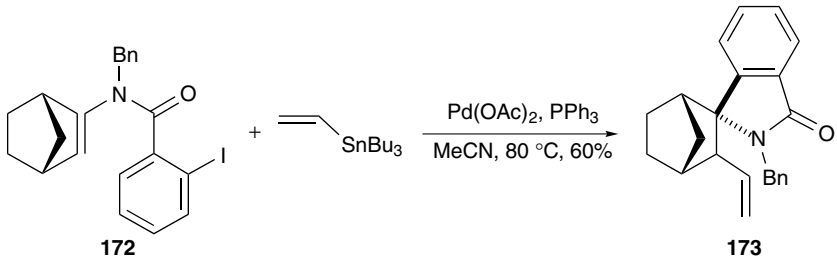
167 **168**

Total synthesis of capnellene has been achieved by *bis*-cyclization of the cyclopentene **169**. The tricyclic compounds **170** and **171** were prepared by the attack of malonate anion using TFP as a ligand, and capnellene was synthesized from **170** [84].



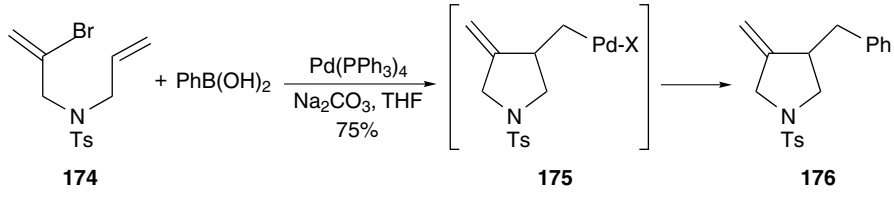
169 **170** **171** capnellene

Termination occurs by transmetallation with organometallic compounds of B and Sn, followed by reductive elimination. The aryl iodide **172** underwent 5-*exo* cyclization. Transmetallation of the alkylpalladium with vinyltin reagent, followed by reductive elimination, afforded **173** [85]. The anion trap is not limited to the

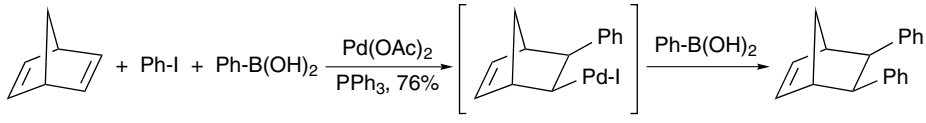


172 **173**

neopentylpalladium intermediate. The domino reaction of the bromodiene **174** was terminated with phenylboronic acid to afford **176**. In this case, transmetallation occurs preferentially in **175** with suppression of β-H elimination [86]. Similarly the domino Heck–Suzuki coupling of norbornadiene, iodobenzene and phenylboronic acid afforded the diphenylnorbornene **178**. In this case, *syn* β-H elimination from **177** is not possible on steric grounds [87].

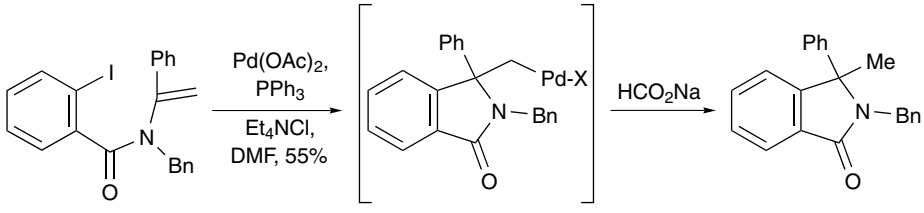


174 **175** **176**



177 **178**

Hydroarylation of olefins by attack of hydride derived from formic acid is frequently used. Cyclization of **179** generates the neopentylpalladium **180**, which is trapped with the hydride to yield the hydroarylation product **181** [88].



179 **180** **181**

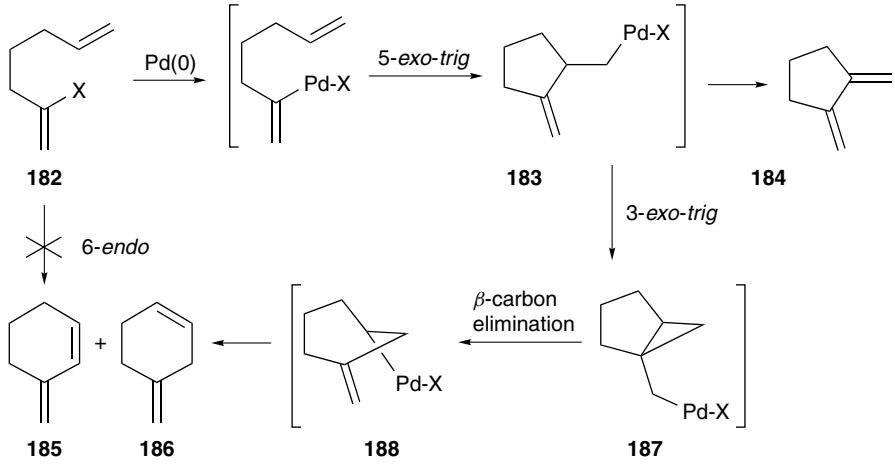
3.2.7 Intramolecular Reactions

3.2.7.1 Introduction

Many intramolecular versions and domino reactions involving halides as a starter and alkenes and alkynes as a relay offer a variety of useful synthetic methods of unique heterocycles and carbocycles. Few other methods can compete with

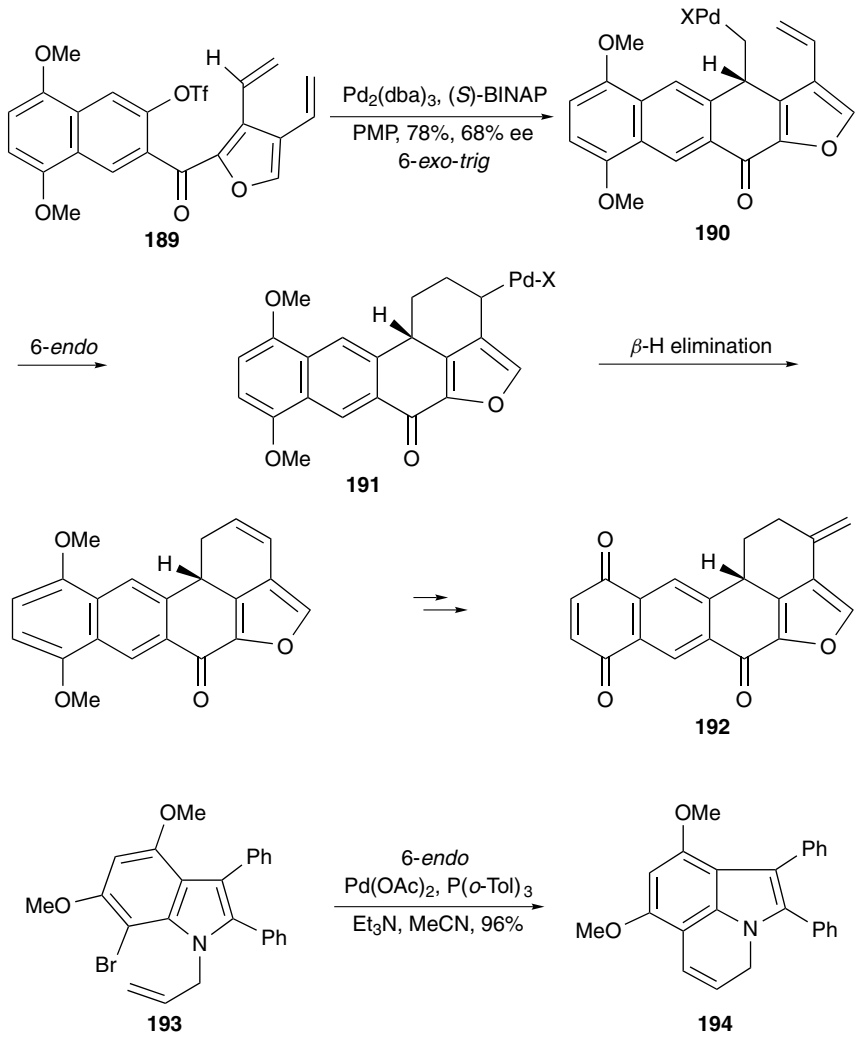
these Pd-catalyzed cyclizations. Negishi *et al*. gave a review of cyclic carbopalladation [6f]. Although many reports and a number of excellent reviews have been published [6], an understanding of the high potentiality of these somewhat complicated cyclization methods in organic synthesis is becoming increasingly difficult. Also complete coverage of the chemistry is nearly impossible. Therefore, in order to improve understanding, the cyclization methods are classified into several patterns and the types and are explained with pertinent examples.

There are two modes of cyclization, namely *exo* and *endo*. Extensive studies on the selectivity between *exo* and *endo* cyclizations have been carried out by Grigg *et al*. [89]. *Exo* cyclization is the favored path, and *endo* cyclization is less likely for the formation of smaller than six-membered rings. *Endo* cyclization becomes the main path when carbon chains are more flexible in forming rings of larger sizes. Cyclization of 2-halo-1,6-heptadiene **182** gives rise to the five-membered ring **184** by 5-*exo-trig* cyclization, and the six-membered rings **185** and **186** by *endo* cyclization. Although formation of the six-membered ring **185** may be understood by direct 6-*endo-trig* cyclization, an accepted explanation for its formation is 5-*exo-trig* to generate **183** and its 3-*exo-trig* cyclization to give the cyclopropane **187**. Subsequent cyclopropylcarbinyl-homoallyl rearrangement, which is β-carbon elimination, to afford **188** and β-H elimination afford the six-membered rings **185** and **186**. Ratios of *exo* and *endo* cyclizations may change by size and conformation of rings, substituents, and reaction conditions as shown in following examples.



The total synthesis of xestoquinone **192** was carried out based on domino 6-*exo-trig* and 6-*endo-trig* cyclizations of **189**. In this case, the selective 6-*endo-trig* cyclization of **190** to give **191** seems to be favored by smaller ring strain of the six-membered ring than that of the five-membered ring presumably formed by 5-*exo-trig* cyclization [90]. Similarly, exclusive *endo* cyclization of *N*-allylindole **193** to give **194** is understandable by smaller ring strain of the product [91].

The following example shows that ratio of 6-*endo* to 5-*exo* in the cyclization of **195** changes dramatically from 99 : 1 to 4 : 96 by slight modification of the catalyst systems [89,92,93]. The effect of the addition of HCO_2H as a hydride source to afford the 5-*exo* product **198** is understandable. The *exo* cyclization generates

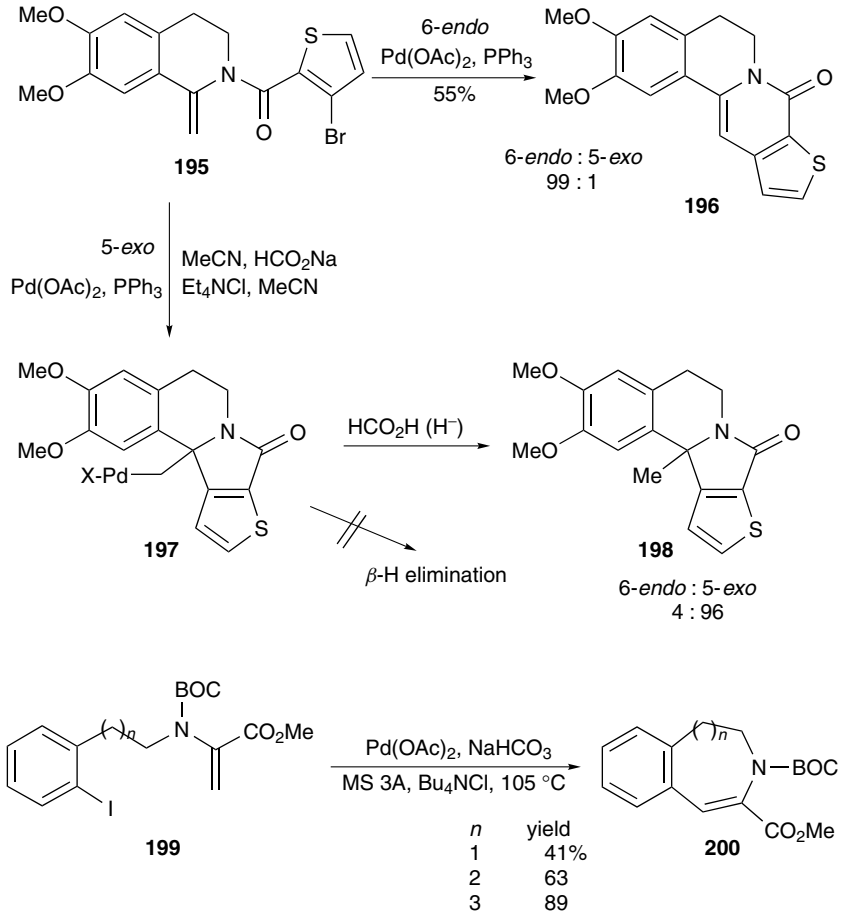


the neopentylpalladium **197**, and termination by itself is difficult. The reaction can be terminated smoothly to give **198** by hydride capture in the presence of HCO_2Na. Exclusive *endo* cyclization occurs to give **196** in the absence of anions. Thus generally speaking, *exo* cyclization is more favored than *endo* cyclization whenever the situation allows in five- and six-membered ring formations.

Yields of *endo* cyclization products of the iodo enamine **199** to give the heterocycles **200** steadily increase with longer chain lengths under Jeffery's conditions. It is surprising that the medium-sized (eight- and nine-membered) rings were obtained in high yields [94].

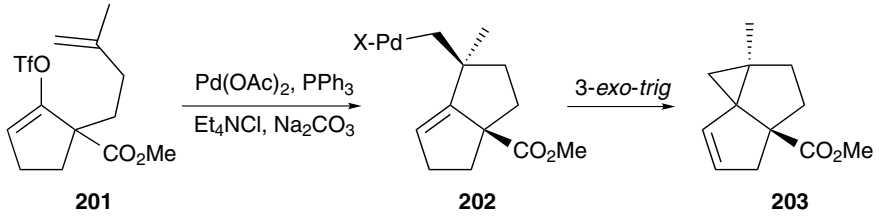
3.2.7.2 Formation of Three- and Four-Membered Rings

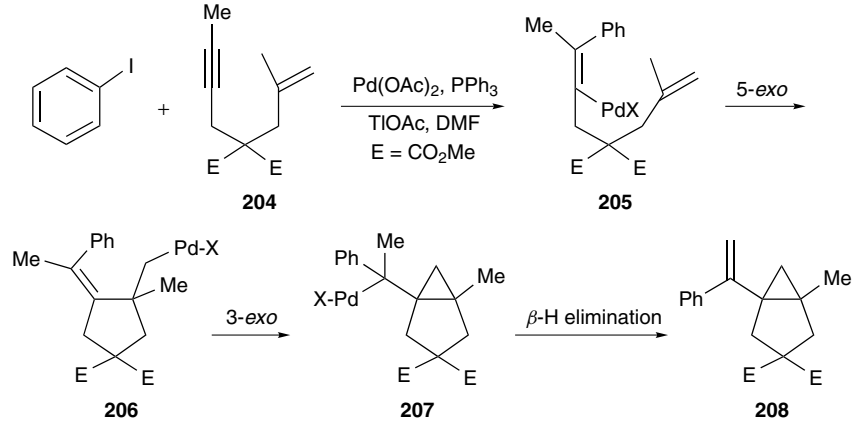
Intramolecular HR has been utilized as a simple construction method for complex skeletons of natural products. Many elegant and efficient total syntheses of natural products with interesting structures have been achieved, showing that HR is a



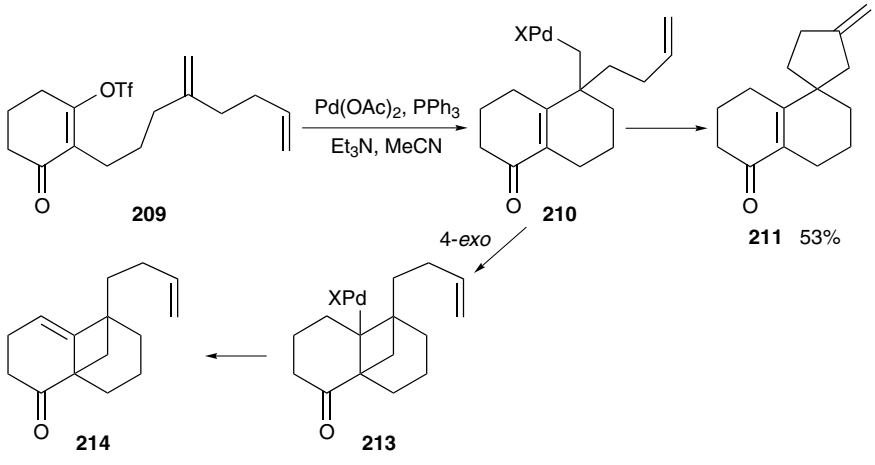
powerful tool for the cyclization based on carbon–carbon bond formation. Some examples are shown in the following.

Numerous carbo- and heterocyclic compounds of various sizes have been prepared by HR-type monocyclization. Cyclopropanes are formed only when neopentylpalladium intermediates are formed in the absence of anions. Intramolecular carbopalladation of the alkenyl triflate **201** generates the neopentylpalladium **202**, and its 3-*exo* cyclization and β-H elimination afford the cyclopropane **203** [95]. Intermolecular carbopalladation of the alkyne **204** generates **205**. Its 5-*exo* cyclization provides the neopentylpalladium **206**, which undergoes 3-*exo* cyclization to construct the three-membered ring **207**. Finally β-H elimination gives rise to the cyclopropane **208** [96].



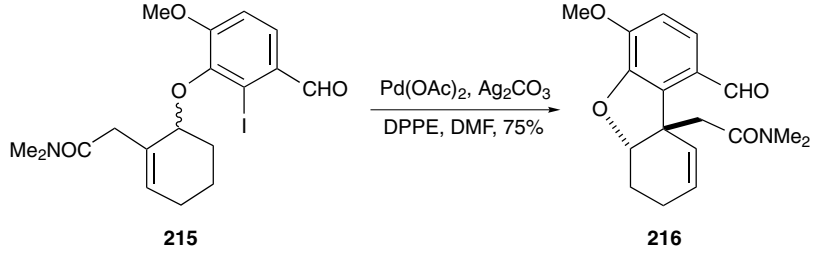


Formation of cyclobutanes is not common. As a rare example, Overman reported that *bis*-cyclization of the triflate **209** afforded the spirocycle **211** as a major product via **210**. At the same time, construction of the cyclobutane **213** by 4-*exo* cyclization of **210** occurred and **214** was detected in 5 % yield [97].

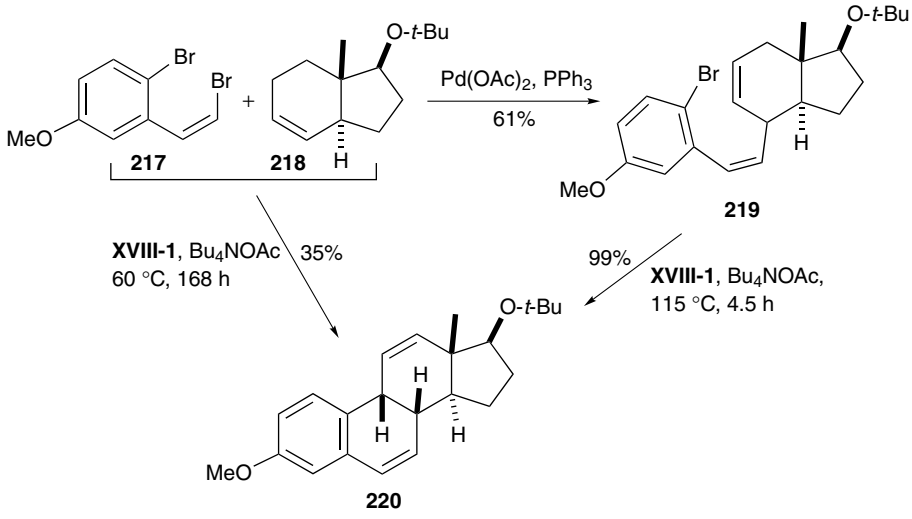


3.2.7.3 Formation of Five- and Six-Membered Rings in Natural Product Syntheses

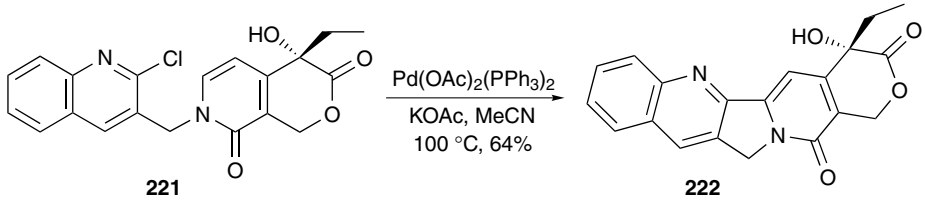
Facile formation of five- and six-membered rings has wide application in natural product syntheses. The tricyclic synthetic intermediate of the galantamine alkaloid **216** was prepared by intramolecular HR of **215**. A single double bond isomer was obtained in the presence of Ag_2CO_3 as a weak base [98,99].



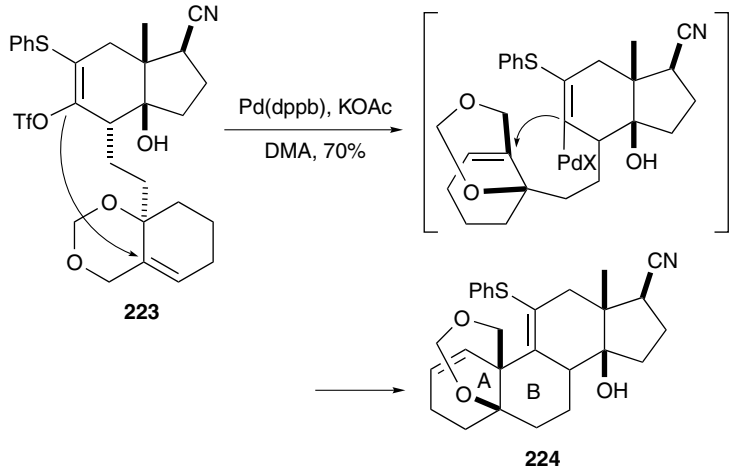
An interesting example which shows different catalysts are required for HR of a vinyl bromide and an aryl bromide was observed in enantiopure synthesis of estrone by double HR [100]. The vinyl bromide in **217** preferentially reacted with **218** to give **219** selectively in 61 % yield without giving a double bond isomer using $Pd(OAc)_2$ and PPh_3. Then **219** was converted to **220** in 99 % yield under Jeffery's conditions using the Herrmann complex (**XVIII-1**) as a catalyst. On the other hand, the one-pot domino reaction of **217** with **218** under the same conditions afforded **220** in 35 % yield.

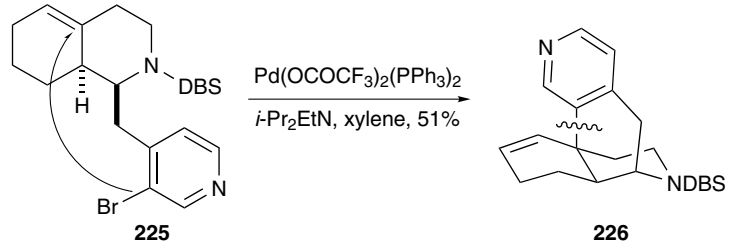


A practical six-step synthesis of (*S*)-camptothecin has been achieved utilizing HR as a key reaction. Intramolecular reaction of the optically pure quinoline chloride **221** with the enamide moiety gave pure (*S*)-camptothecin (**222**) after recrystallization in 64 % yield under usual conditions [101]. It should be added that chlorides of heterocyclic compounds such as pyridines and quinolines are activated by electron-attracting nitrogens and react smoothly without using electron-rich ligands.

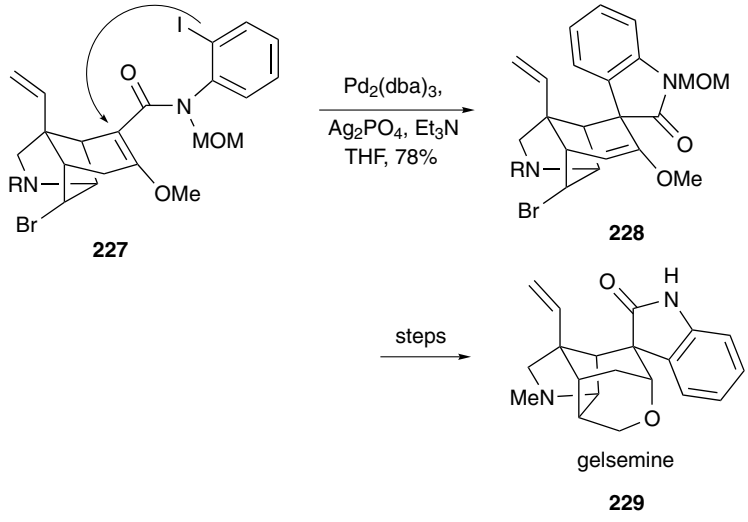


In the enantioselective synthesis of a cardenolide precursor, the congested quaternary carbon center and the *cis*-AB ring fusion in the steroid skeleton **224** were constructed by cyclization of the alkenyl triflate **223** [102]. Similarly critical quaternary carbon–aryl bond formation took place by the cyclization of the bromopyridine **225** to afford the pyridinomorphinan **226** using 60 mol% Pd trifluoroacetate and PPh_3 [103].

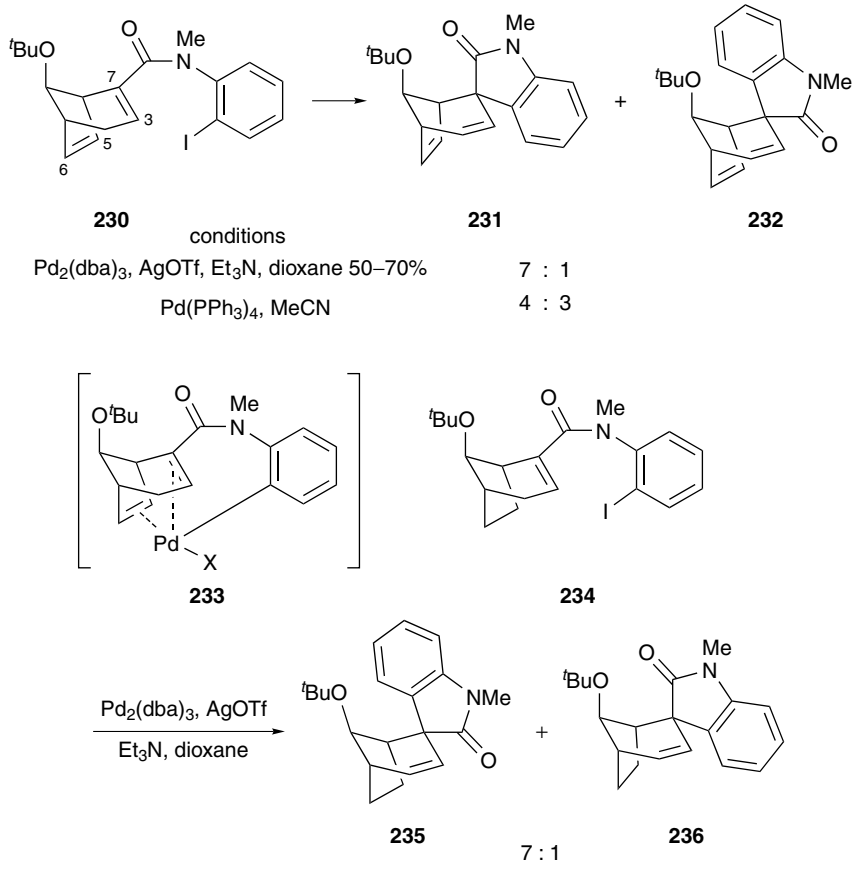




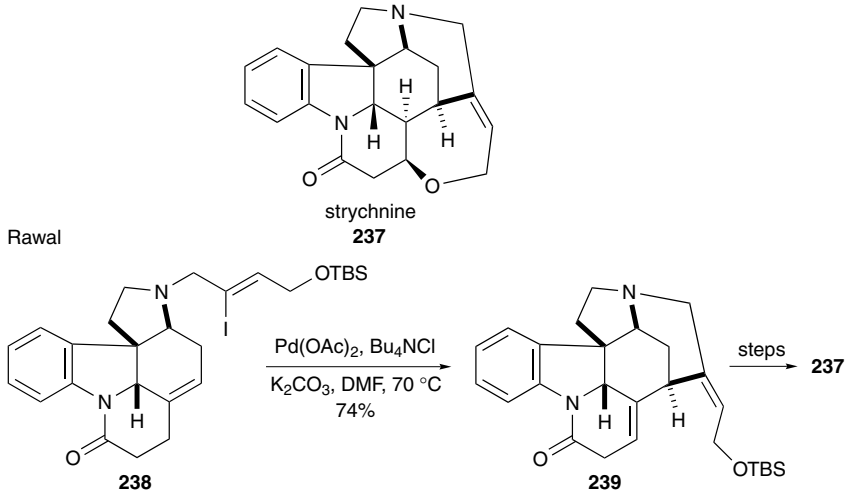
In the total synthesis of gelsemine achieved by Overman, carbopalladation of a very congested tetrasubstituted double bond of a vinylogous carbamate in **227** was successfully carried out under cationic Heck conditions adding silver phosphate to give the spirooxindole **228** as the major product in 61–78 % yield, which had the opposite configuration of the spirooxindole as that found in gelsemine. After epimerization, total synthesis of gelsemine (**229**) has been completed [104].



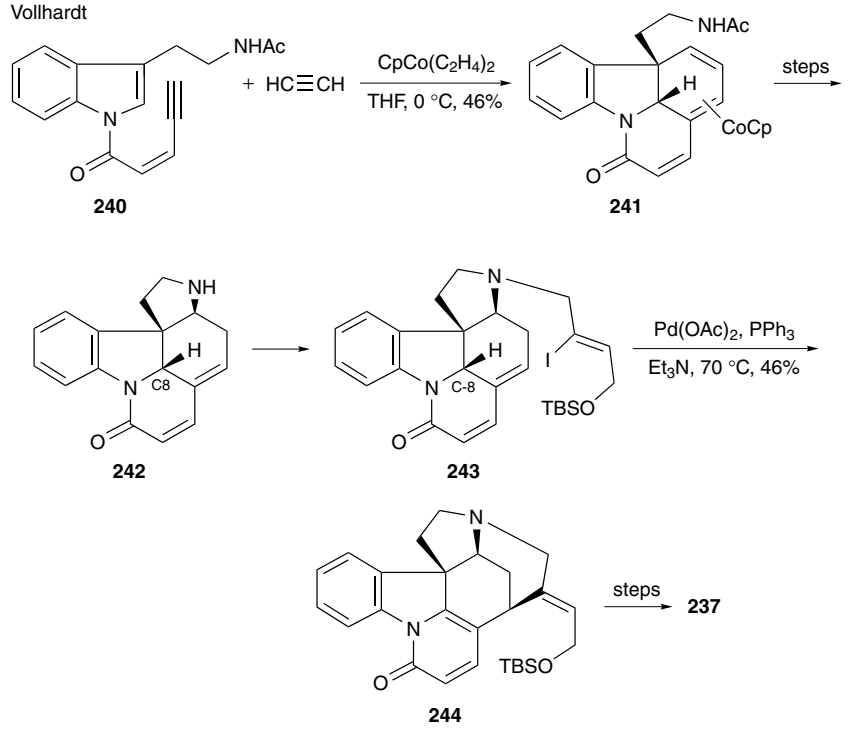
In the studies of gelsemine synthesis, Danishefsky studied stereochemical control in intramolecular HR of **230** [105]. In this case, carbopalladation of C3—C7 double bond occurs preferentially from the α face due to coordination of Pd to both double bonds as shown by **233** using a ligandless catalyst and AgOTf to give the desired oxindole **231** as a major isomer (7 : 1), which has the correct configuration for gelsemine synthesis. When $Pd(PPh_3)_4$ is used, both isomers were obtained in 4 : 3 ratio, because a few molecules of PPh_3 coordinate to Pd, inhibiting coordination of Pd to the C5—C6 double bond. When the C5—C6 double bond is reduced as **234**, there is no possibility of fixing Pd species in the α side, and hence the carbopalladation occurs from the less congested β side to give the major isomer **235** and the minor product **236** in a ratio of 7 : 1.



Total syntheses of the complex molecule of strychnine have been carried out by several groups applying intramolecular HR as key reactions. The first elegant Pd-based total synthesis of strychnine (**237**) has been achieved by Rawal. An intramolecular Diels-Alder reaction and HR were key reactions. The Pd-catalyzed cyclization of the pentacyclic lactam **238** under Jeffery's conditions gave isostrychnine **239** in 74 % yield. Conversion of **239** to **237** is known [106].

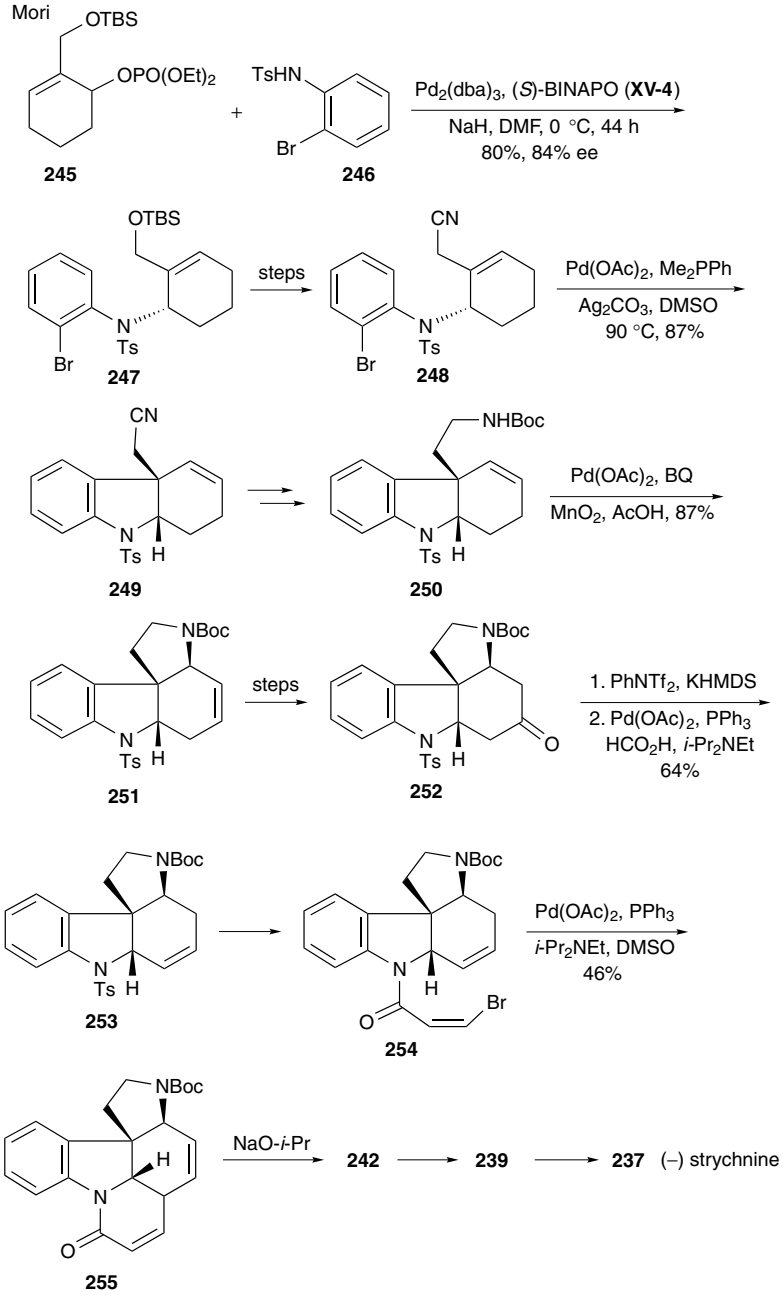


The Vollhardt's synthesis utilizes [2 + 2 + 2]cycloaddition of **240** with acetylene mediated by a Co–acetylene complex to yield **241** and an intramolecular HR of **243** to afford **244** as the key reactions. The intramolecular HR of the conjugated dienone **243** under usual conditions affords the pyridone **244** via β-H elimination from C8 [107].



HR of a similar type is utilized in the total synthesis of optically active strychnine by Mori's group [108]. Their method can be said to be a truly Pd-based

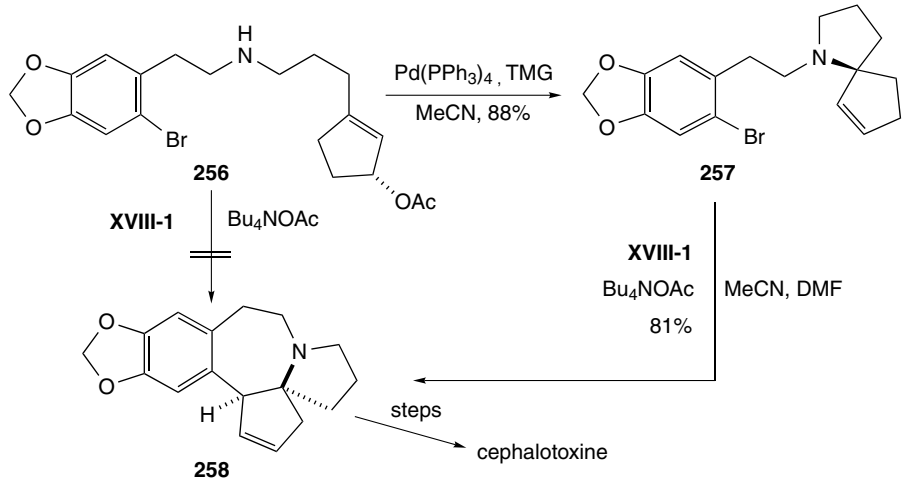
synthesis because the total synthesis has been achieved by applying six-different Pd-catalyzed reactions. At first asymmetric allylation of **246** with the allylic phosphate **245** using (*S*)-BINAPO (**XV-4**) afforded **247** with 84 % ee. Intramolecular HR of **248** using Me_2PPh as a ligand yielded **249** with 99 % ee after recrystallization. $Pd(OAc)_2$-promoted intramolecular aminopalladation of **250** in the presence of BQ and MnO_2 as oxidants of Pd(0) gave **251**. The ketone **252** was converted to an enol triflate, which was subjected to Pd-catalyzed hydrogenolysis with HCO_2H to give the olefin **253**. Again, intramolecular HR of **254** gave **255**, and subsequent



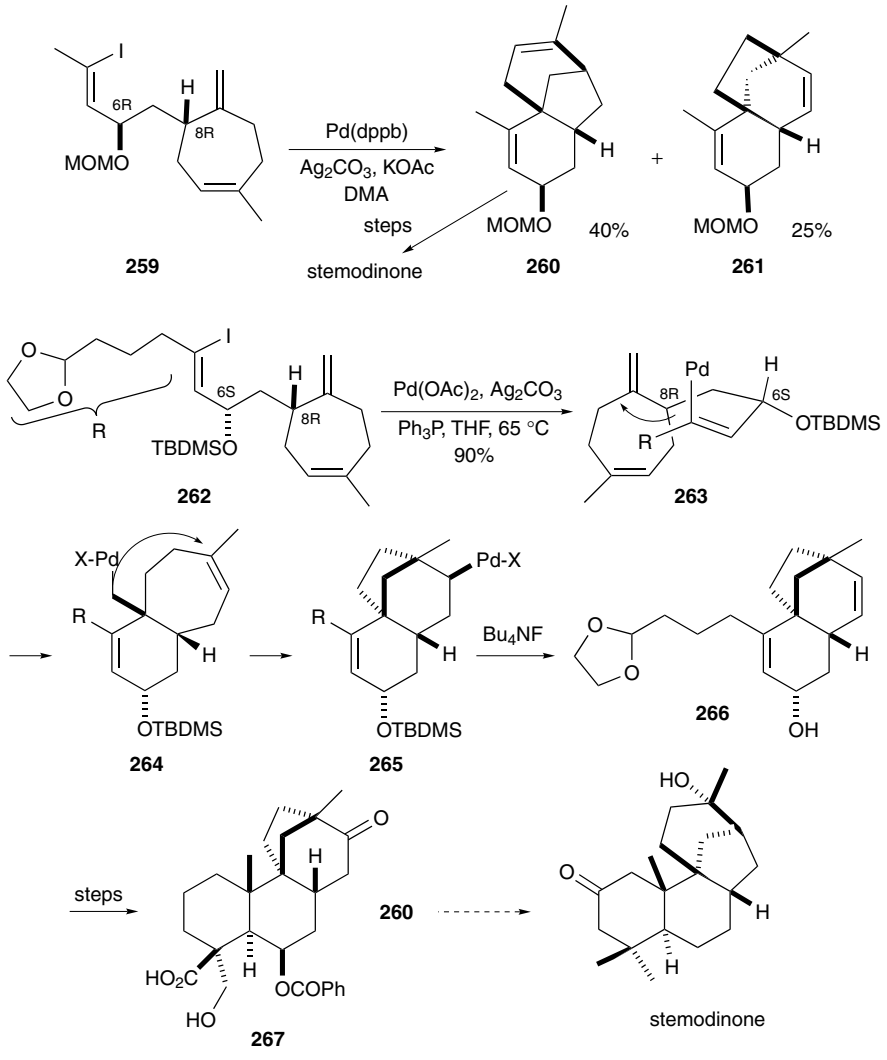
isomerization of the double bond in **255** gave the conjugated dienone **242**, which is the same intermediate in Vollhardt's synthesis, thus completing the chiral total synthesis of strychnine (**237**).

3.2.7.4 Syntheses of Medium to Large Rings and Applications to Natural Product Syntheses

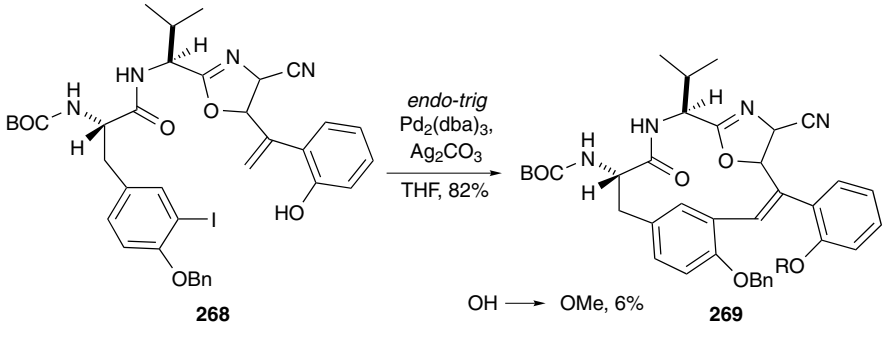
Two Pd-catalyzed cyclizations were used for the enantioselective synthesis of (−)-cephalotoxine [109]. One-pot Pd-catalyzed domino reactions, namely intramolecular allylation of amine and HR of **256**, seem to be the best path for the desired synthesis. However, attempted direct conversion of **256** to **258** with the Herrmann complex was unsuccessful. Then selective intramolecular aminoallylation with the chiral cyclopentyl acetate occurred smoothly to give the spiro amine **257** in 88 % yield when $Pd(PPh_3)_4$ and TMG (tetramethylguanidine) as a base were used. The cyclization proceeded with retention of stereochemistry without racemization. The next HR reaction of **257** gave the seven-membered compound **258** in 81 % yield under Jeffery's conditions using the Herrmann complex as a catalyst. No transformation of **257** to **258** occurred when $Pd(PPh_3)_4$ was used. The results show that the best catalysts for the allylation and HR are different.



The *bis*-Heck cyclization of trienyl iodides has been applied as a key reaction by Overman to total syntheses of stemodane diterpenes and scopadulcic acid. Treatment of the 6*R*, 8*R* epimer of the trienyl iodide intermediate **259** with Pd(dppb) in the presence of Ag_2CO_3 in DMA provided two tricyclic products **260** (40 %) and **261** (25 %). The major product **260** has the stemodane skeleton [110]. On the other hand, *bis*-cyclization of the 6*S*, 8*R* epimer of the trienyl iodide **262** proceeded with complete stereo- and regioselectivity as shown by **263** and **264** to afford the tricycle of the scopadulan skeleton **266**, from which total synthesis of scopadulcic acid A (**267**) was achieved. In the second cyclization as shown by **264**, generation of the cyclohexylpalladium intermediate **265**, having Pd attached to the secondary carbon center is favored to give **266** selectively. Formation of a stemodane skeleton is expected from the 6*R*, 8*R* epimer [111].

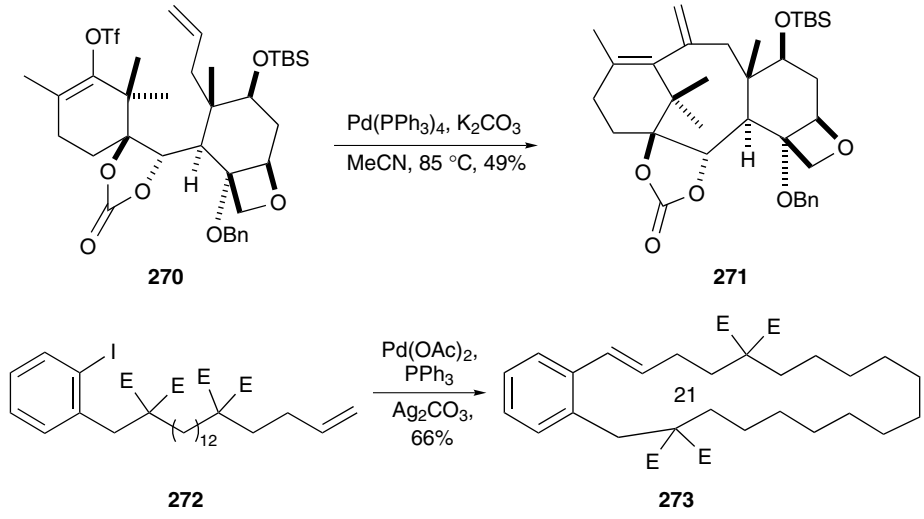


For the total synthesis of macrocyclic compound 'diazonamide A', Harran's group tried intramolecular HR of highly functionalized iodide **268**, although they found the proposed structure to be wrong. Selective *endo* cyclization took place to give the macrocycle **269** in 82 % yield when $Pd_2(dba)_3$, Ag_3CO_3, and biphenylyl-



(di-*t*-butyl)phosphine (**IV-1**) were used [112]. Participation of the phenolic OH group near the double bond by forming Pd phenoxide seems to be crucial for the smooth cyclization. When OH was methylated, the yield of the cyclization was only 6 %.

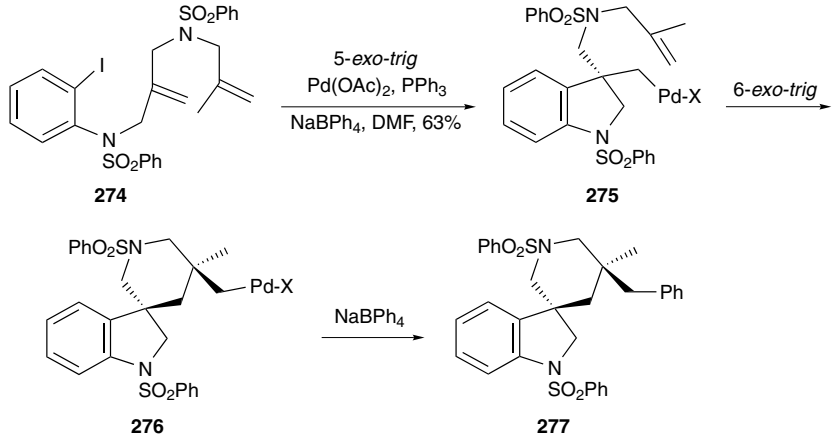
The eight-membered ring of baccatin III skeleton **271** was constructed by 8-*exo* HR of the enol triflate **270** [113]. The 21-membered ring **273** was obtained in surprisingly high yield (66 %) from **272**. In similar cyclizations, rings larger than 13 members are obtained under high dilution conditions [114]. Interestingly, exclusive *endo* cyclizations occur in the formation of large rings.



3.2.7.5 Domino cyclization to form polycycles

Polycyclic compounds are prepared by domino polycyclization of suitably designed polyenynes, in which a starter (halide), a relay (alkene or alkyne), and a terminator (alkene or alkyne) are tethered in such a way to induce efficient domino reactions. The alkyne insertion produces the thermally stable alkenylpalladium species as living species, which can not be terminated by themselves, and further transformations are required in order to terminate reactions and to regenerate Pd(0) species for catalytic recycling. While alkynes play the role of the relay to pass the ability of carbon–carbon bond formation to other groups, alkene insertion is followed by facile dehydropalladation whenever there is a β-H, and generation of Pd(0) catalytic species. In order to play the role of the relay, the alkenes must be 1,1-disubstituted, and its insertion generates neopentylpalladiums as the living species. These living species undergo further insertion of alkenes and alkynes, and the reactions are terminated by capturing the anionic species as described before.

Grigg has shown a number of possibilities of polycyclizations. As an early example, the 1,6-diene **274** underwent 5-*exo* cyclization to generate the neopentylpalladium **275**, and 6-*exo* cyclization of **275** yields the neopentylpalladium **276**, which was captured by $NaBPh_4$ to afford the spiro compound **277** as a single diastereomer [115].

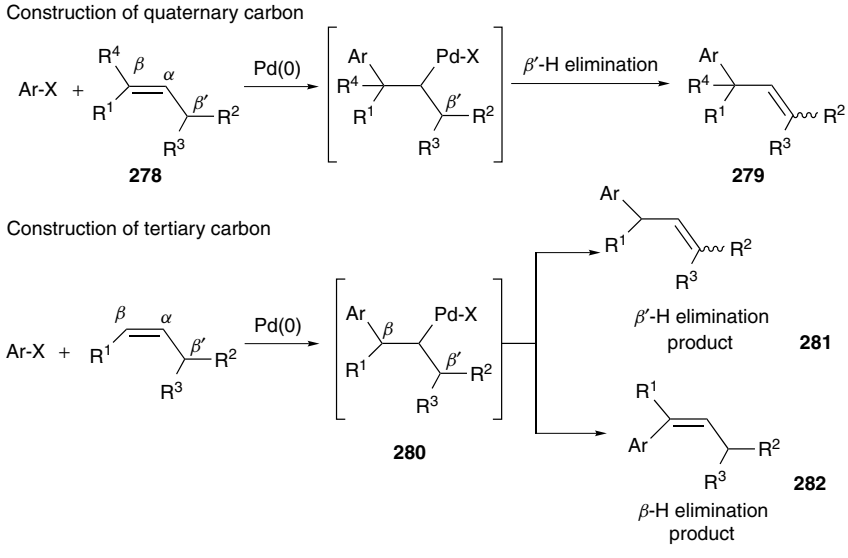


3.2.8. Asymmetric Reactions

Compared to very extensive studies on Heck reactions, examples of successful asymmetric Heck reactions (abbreviated to AHR in this section) are rather limited, showing that AHRs are not easy to carry out, and careful tuning of conditions is crucial. Most of the HRs proceed by using monodentate ligands. On the other hand, chiral bidentate ligands are mainly required for AHRs. This may be a reason for the difficulty in achieving efficient AHRs. The ligands most extensively used are BINAP, its derivatives, and phosphinooxazolines [116].

Construction of racemic tertiary and quaternary carbon centers by HR has been studied extensively, suggesting the potential of asymmetric syntheses. Actually AHRs have been achieved by constructing quaternary and tertiary carbon centers. The quaternary carbon centers **279** are introduced at β-carbons by H elimination from β'-carbon in **278**.

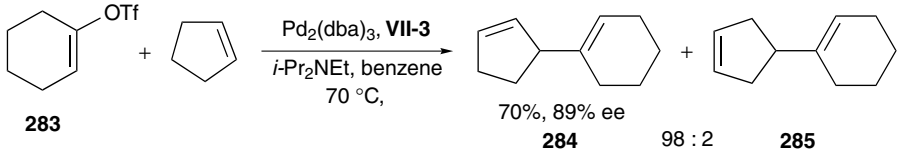
On the other hand, construction of tertiary carbon centers **281** is more challenging, because there is a possibility of β-H elimination to provide **282** as a competitive path, which destroys the newly formed carbon center in **280**. Thus



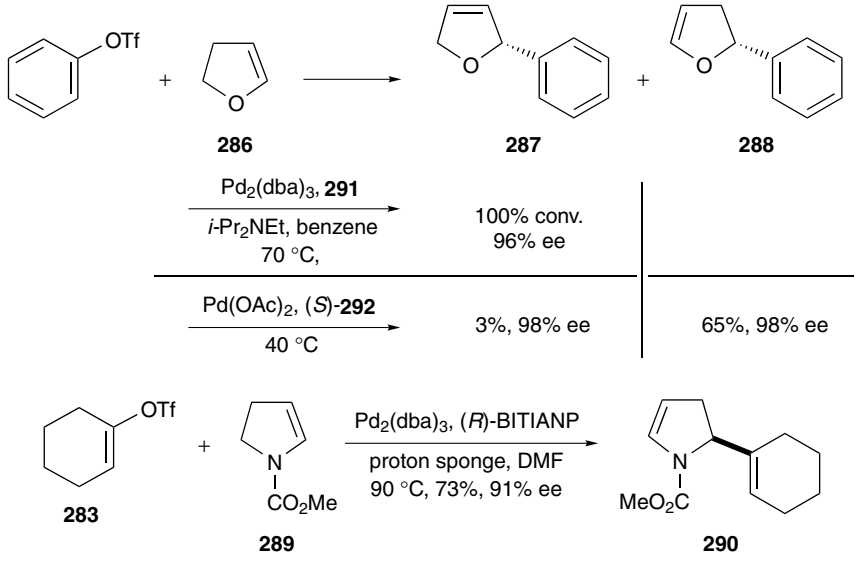
how to achieve β'-H elimination selectively, rather than β-H elimination, is a crucial problem for successful AHR, and several methods have been reported. As one solution, Ag or Tl salts are added in order to generate cationic Pd catalysts. It is generally accepted that double bond migration is suppressed by the use of the cationic Pd catalysts.

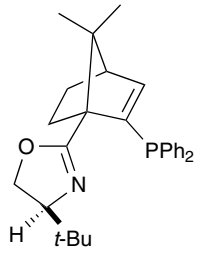
3.2.8.1 Intermolecular AHR

Successful intermolecular AHR has been studied much less than intramolecular AHR. After pioneering work by Hayashi *et al*. on intermolecular AHR of 2,3-dihydrofuran (**286**) with phenyl triflate using (*R*)-BINAP to afford 2-phenyl-2,3-dihydrofuran (**288**) with 96 % ee [117], a number of AHR using related substrates have been reported. Pfaltz carried out successful AHR of cyclopentene with cyclohexenyl triflate (**283**) using phosphinooxazoline (**VII-3**) as a ligand and obtained selectively the coupled product **284** with 89 % ee in 70 % yield. A small amount of the isomer **285** was formed [118]. This ligand is effective to suppress double bond migration. Under similar conditions using BINAP, a mixture of double bond isomers was obtained.



Further studies on AHR of 2,3-dihydrofuran (**286**) with phenyl triflate afforded different products with high % ee depending on the ligands used. The isomer **287** with 96 % ee was obtained selectively when the phosphine—oxazoline ligand **291** was used [119]. On the other hand, the isomer (**288**) with 98 % ee was the major product when (*S*)-MeO-BIPHEP (**292**) was used [120]. AHR of **283** with **289** using (*R*)-BITIANP (**293, XV-7**) in the presence of proton sponge afforded the coupling product **290** with 91 % ee selectively [121].





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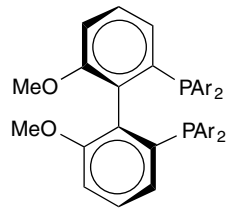
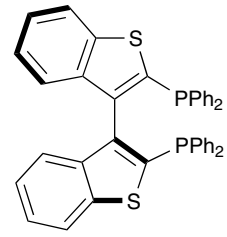


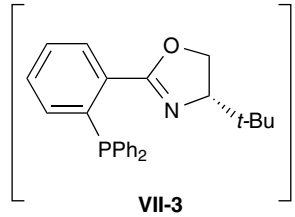
Ar = 3,5(*t*-Bu)$_2$C$_6$H$_3$

292



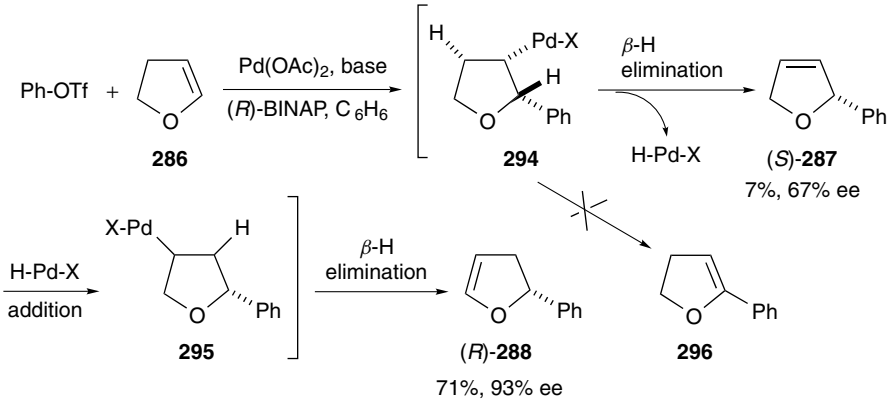
293 (*R*)-BITIANP

(**XV-7**)



VII-3

According to Hayashi *et al*. [117], formation of **287** and **288** can be understood by the following mechanism; carbopalladation to form the intermediate **294**, followed by β-H elimination gives the primary product **287**. Inverse addition of the resulting H-Pd-X to **287** gives another intermediate **295**, and β-H elimination affords the dihydrofuran **288** [117]. It should be noted that the β-H elimination from **294** to give 2-phenyl-4,5-dihydrofuran (**296**) is not possible because there is no H at C-1 *syn* to Pd, and H at C-4 is eliminated to give **287**. This situation is one reason why AHR by creating *tert*-carbon centers is possible in rigid cyclic systems.

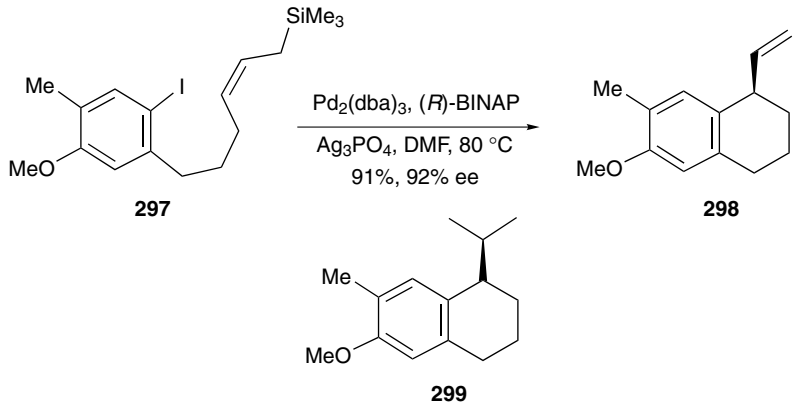


286 **294** (*S*)-**287** 7%, 67% ee

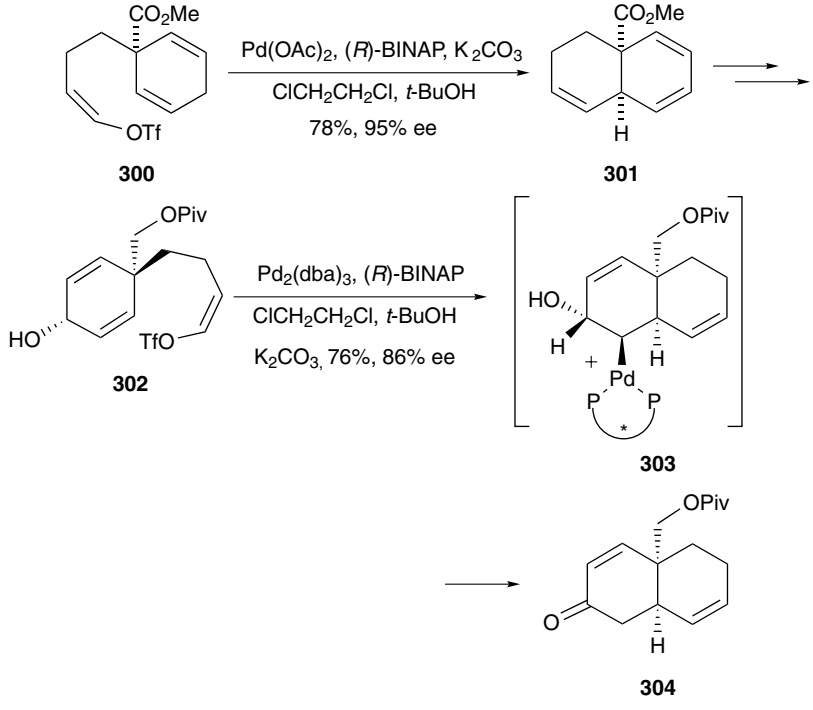
295 (*R*)-**288** 71%, 93% ee **296**

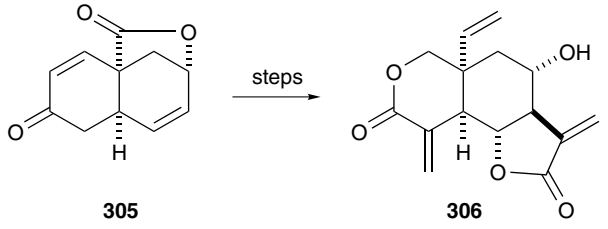
3.2.8.2 Construction of Tertiary Carbon Centers by Intramolecular AHR

Intramolecular AHR is a useful tool for total syntheses of optically active natural products [121a]. Tietze has shown that regiochemistry of β-H elimination can be controlled by employing an allyltrimethylsilane moiety in directing the elimination as in **297**, and the product **298** with 92 % ee was obtained from **297** in 92 % yield. Then **298** was converted to the calamenene derivative **299** [122].



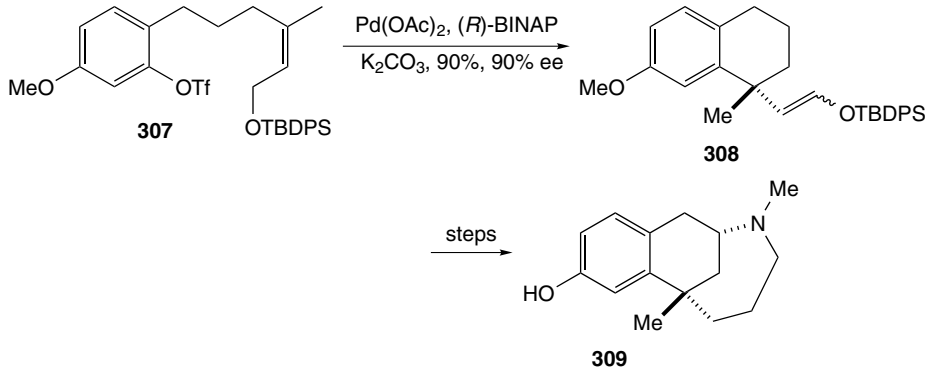
The first examples of intramolecular AHRs were reported by Shibasaki *et al*. [123] and Overman *et al*. [124] in 1989. The Shibasaki group carried out cyclization of achiral alkenyl iodide or triflate **300** to give the chiral tetrahydronaphthalene system **301** by differentiation of enantiotopic C=C double bonds using (*R*)-BINAP without using a silver salt [123]. Subsequently, the reaction has been improved [125]. The chiral hexahydronaphthalene system **304** with 86 % ee was obtained by AHR of the bisallylic alcohol **302** via *syn* β-H elimination from the intermediate **303**, and **304** was converted to the key intermediate **305** in the synthesis of vernolepin (**306**). Use of a mixed solvent of 1,2-dichloroethane and *t*-BuOH is important [126].





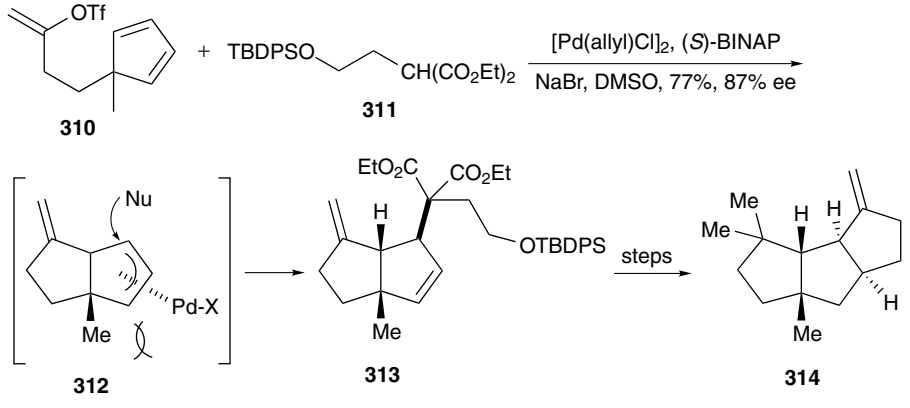
305 **306**

In the total synthesis of (−)-eptazocine (**309**), the benzylic quaternary center with 90 % ee in **308** was constructed by AHR of the triflate **307** using (*R*)-BINAP [127].



307 **308** **309**

Differentiation of the prochiral cyclopentadienyl system in **310** by intramolecular AHR generates π-allylpalladium **312**, which was trapped intermolecularly with the malonate **311** in regio- and stereoselective manner to provide the bicyclic system **313** with 87 % ee in the presence of NaBr in DMSO. The regio- and stereoselective anion capture can be understood by considering the steric effect as shown by **312**. The total synthesis of capnellene **314** has been achieved from **313** [128].

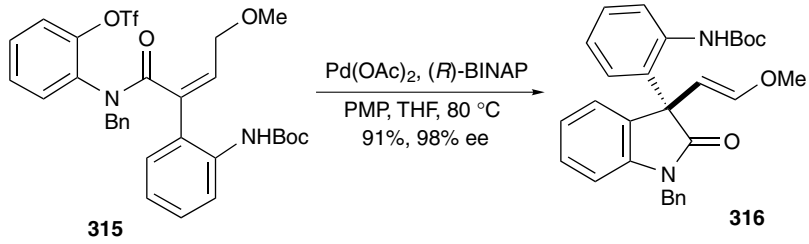


310 **311** **312** **313** **314**

3.2.8.3 Construction of Quaternary Carbon Centers by Intramolecular AHR

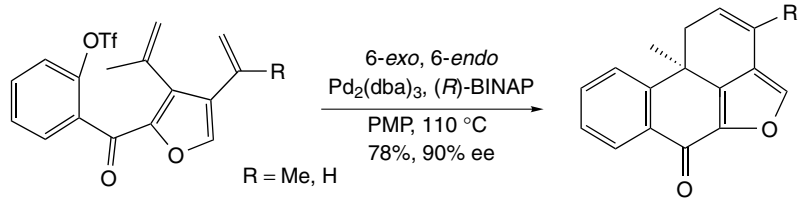
Overman and co-workers have carried out pioneering and extensive studies on AHR to synthesize quaternary carbons bearing two aryl substituents. Aiming at the

enantioselective syntheses of naturally occurring indole alkaloides, they obtained 3-alkyl-3-aryloxindole moiety, and several related indole alkaloids [129]. Construction of the quaternary carbon in **316** was achieved with high enantioselectivity (98 % ee) in high yield (91 %) by AHR of the triflate **315** using (*R*)-BINAP as a ligand and PMP as a base.



315 **316**

High % ee was obtained by domino AHR of the diene **317**. The AHR of the diene **317** (R = Me) afforded the tetracyclic compound **318** in 91 % yield with high ee (90 % ee). Unexpected 6-*endo* cyclization, rather than 5-*exo* cyclization occurred to produce the six-membered ring in the second cyclization. It was found that ee was 71 % when R = H. The results show that the remote substituent gave a profound effect on the ee in the polyene cyclization [130].

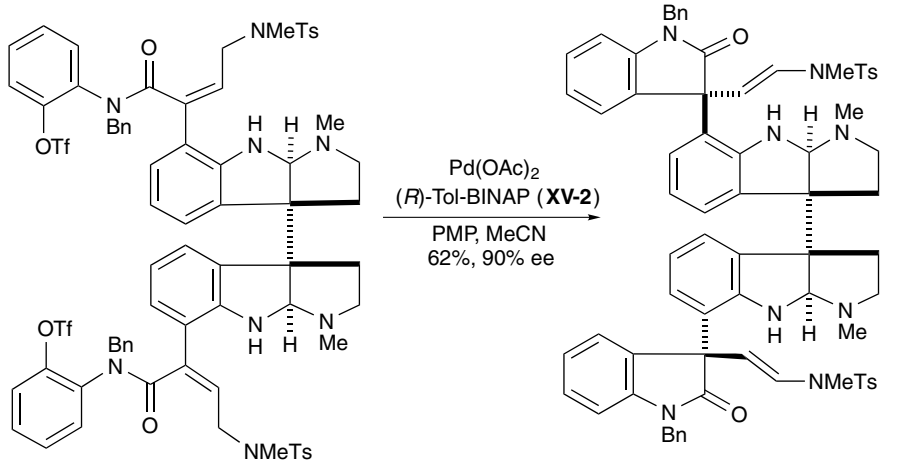


317 (*R*)-**318**

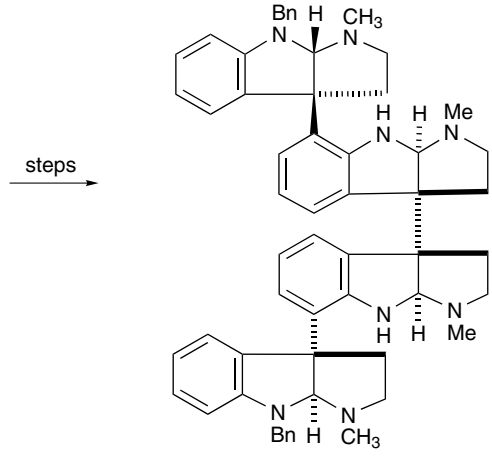
Elegant enantioselective total syntheses of quadrigemine C (**321**) and psycholeine have been achieved by Overman [131]. The key step is the desymmetrization of the *meso* intermediate **319** by asymmetric double Heck cyclization using (*R*)-Tol-BINAP as a chiral ligand and PMP as a base to provide the C_1-symmetric dioxindole **320** in 62 % yield with 90 % ee, installing the two peripheral quaternary stereocenters.

A highly enantioselective intramolecular AHR of the cyclohexadienone **322** to give **324** with 96 % ee in 100 % conversion was carried out using the chiral phosphoamidite-type ligand (**III-10**), which is monodentate. The stereogenic center was not created at the site of C—C bond formation, but instead the cyclohexadienone was desymmetrized. The use of Cy_2MeN as a base gave the best result. It should be added that the carbopalladation product **323** has no β-H *syn* to Pd, and hence the cyclized product **324** was formed by *syn* β-H elimination after epimerization [132].

As another approach to AHR, an efficient AHR can be achieved based on the remarkable diastereoselectivity, which is caused by chiral auxiliaries. Coupling of the chiral prolinol vinyl ether **325**, which contains a prochiral double bond, with *o*-iodoanisole using ligandless $Pd(OAc)_2$ in aqueous DMF, afforded the product



319 **320**



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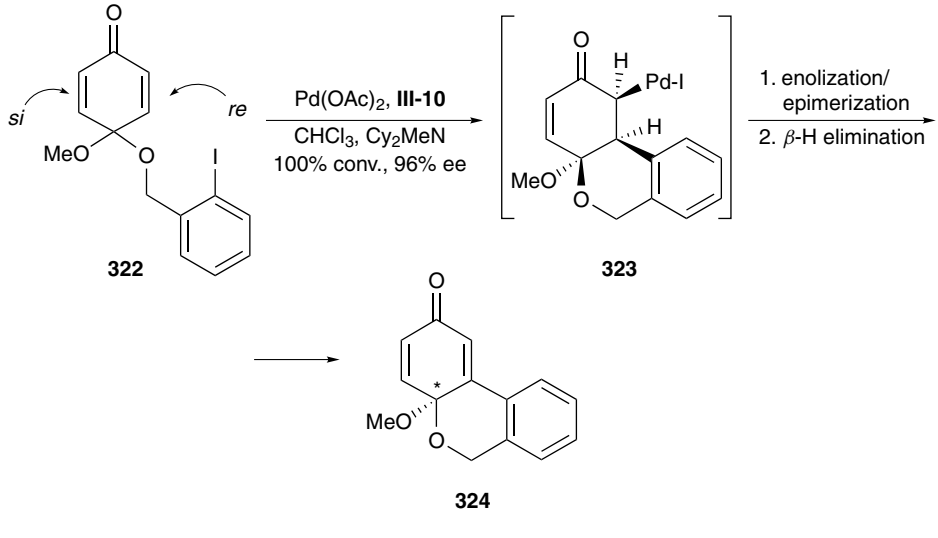
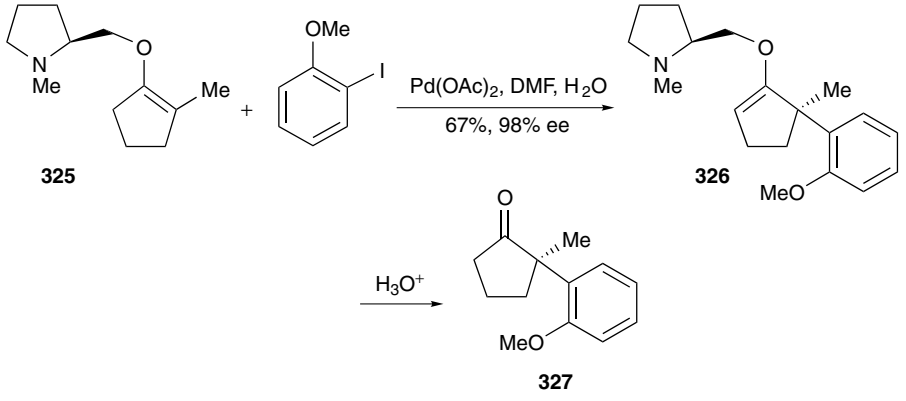
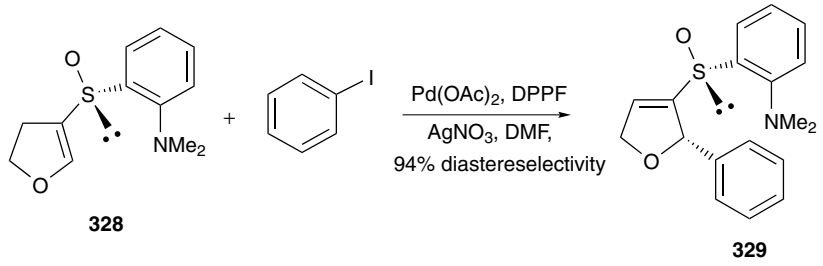


322 **323** **324**

326, creating the quaternary carbon with 98 % ee. Effect of the chiral auxiliary amine is remarkable [133]. Hydrolysis of **326** provided the chiral 2,2-disubstituted cyclopentanone **327**. In this way, asymmetric α-arylation of cyclopentanones can be achieved in three steps.



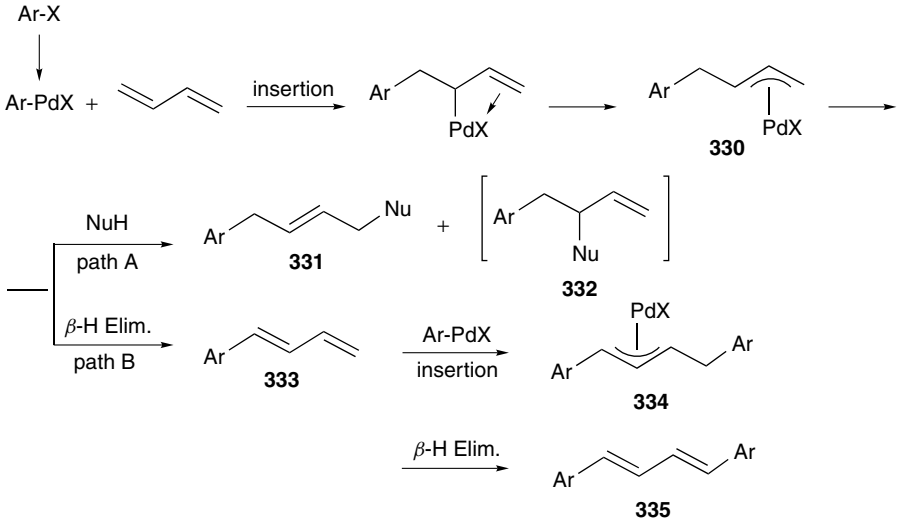
Also HR of 4,5-dihydrofuran, attached to the chiral *o*-dimethylaminophenyl-sulfoxide **328**, with iodobenzene afforded the coupling product **329** with 94 % diastereoselectivity [134]. The efficient asymmetric induction occurred by the coordination of Ph-Pd-I to the amino group. A similar effect of the chiral sulfoxide was observed in the intramolecular HR [135].



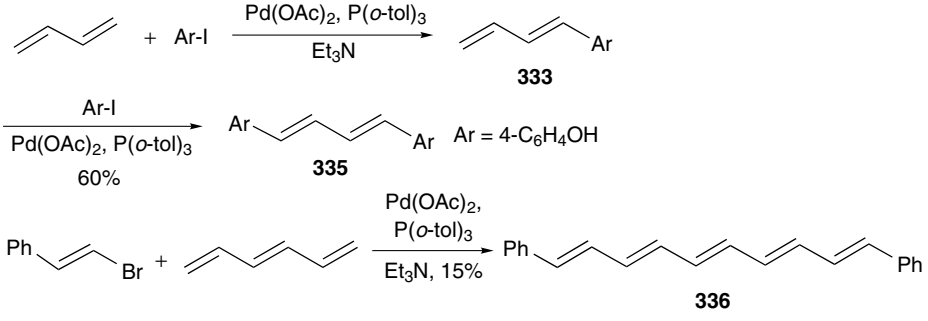
3.2.9 Reactions with 1,2-, 1,3-, and 1,4-Dienes

3.2.9.1 Reactions of 1,3- and 1,4-Dienes

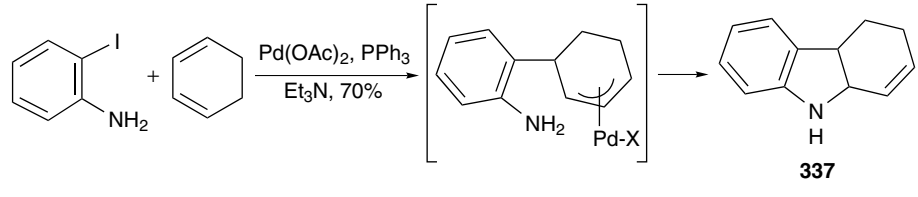
Reaction of conjugated dienes with aryl and alkenyl halides can be explained by the following mechanism. Insertion of a conjugated 1,3-diene into an aryl or alkenylpalladium bond gives the π-allylpalladium complex **330** as an intermediate, which reacts further in two ways. As expected, nucleophiles such as carbon nucleophiles, amines, and alcohols attack the π-allylpalladium intermediate to form the 1,4-addition product **331** and 1,2-addition product **332**. In the absence of the nucleophiles, β-H elimination occurs to afford the substituted 1,3-diene **333**. In some cases, the substituted 1,3-diene **333** reacts again with aryl halide to form the π -allylpalladium **334**. Subsequent elimination affords the 1,4-diarylated 1,3-diene **335**.



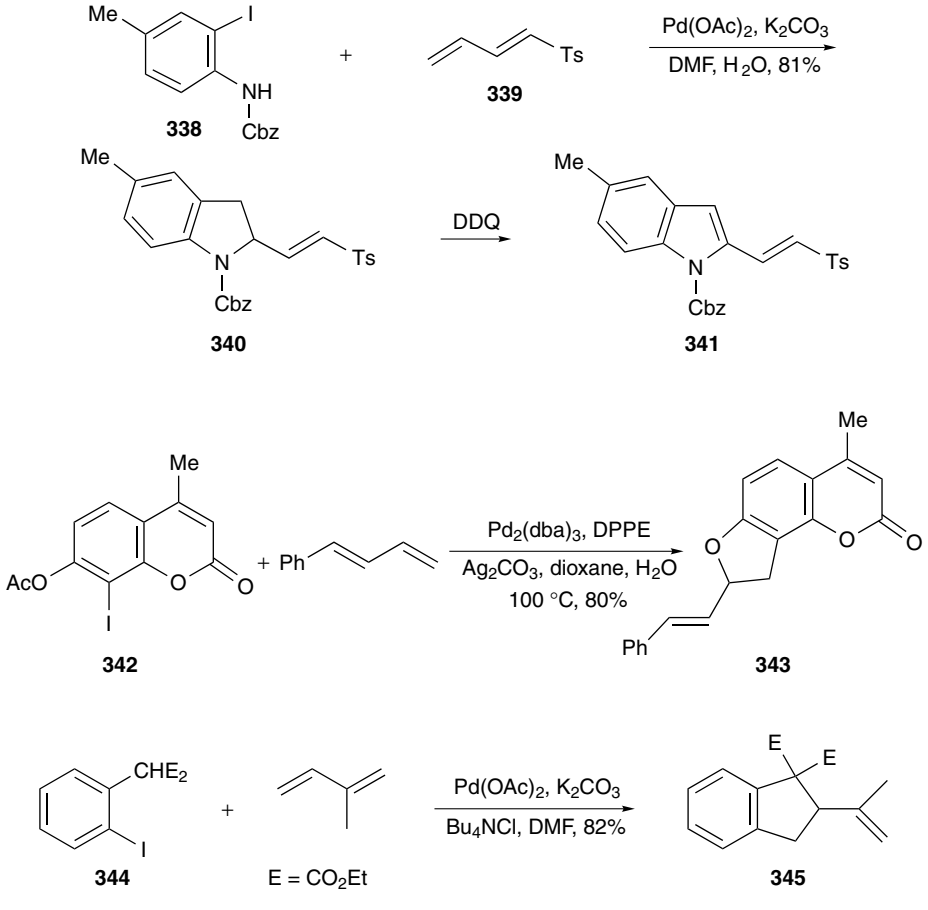
As early examples, Heck prepared the arylated conjugated dienes **333** and the 1,4-diarylated dienes **335**. Also reaction of 2-phenylvinyl bromide with hexatriene afforded 1,10-diphenyl-1,3,5,7,9-decapentaene (**336**), although yield was low [136].



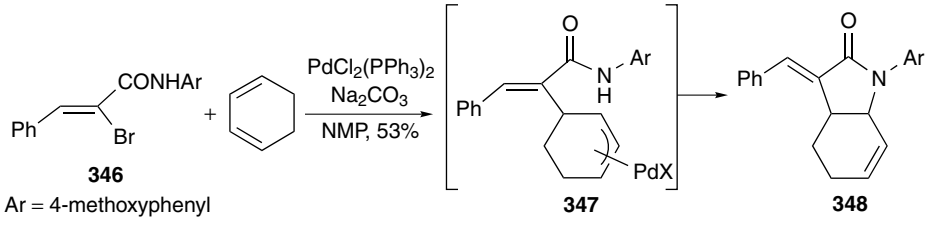
Dieck reported preparation of the tetrahydrocarbazole **337** by heteroannulation of *o*-iodoaniline with 1,3-cyclohexadiene [137]. As a recent example, heteroannulation of the *o*-iodoaniline derivative **338** with the conjugate dienyl sulfone **339** afforded the vinylogous 2-sulfonylindoline **340**, which was converted to the indole derivative **341** by oxidative dehydrogenation [138]. Pd-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxycoumain **342** offers a synthetic method for dihydrofurocoumarins. The dihydrofurocoumarin **343** was obtained by the reaction of **342** with 1-phenylbutadiene in 80 % yield. After optimization, the uses of $Pd(OAc)_2$,



DPPE, Ag_2CO_3 in a mixture of dioxane and water provided good results [139]. Carboannulation of diethyl *o*-iodophenylmalonate (**344**) with isoprene afforded **345** by 1,2-addition [140].

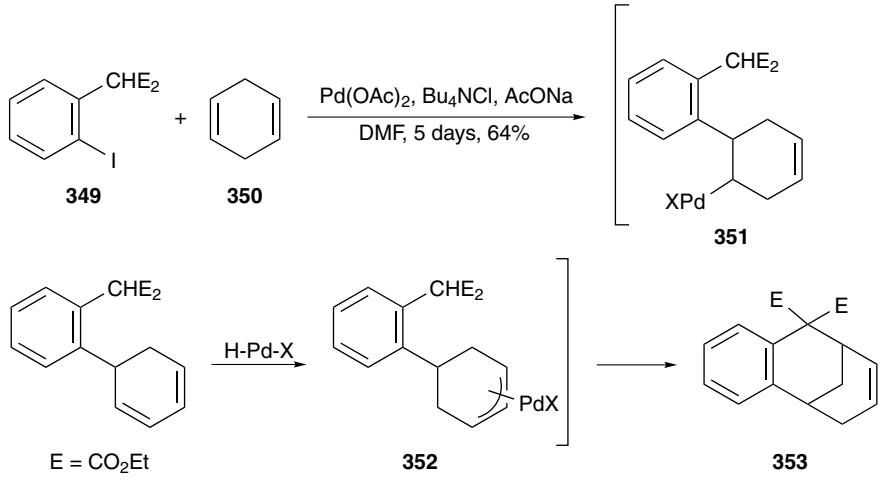


γ-Lactams are prepared by the reaction of α-bromoacrylamides with dienes. The bicyclic lactam **348** was obtained by treatment of 1,3-cyclohexadiene with **346**. The reaction is considered to proceed via the π-allylpalladium intermediate **347** [141].

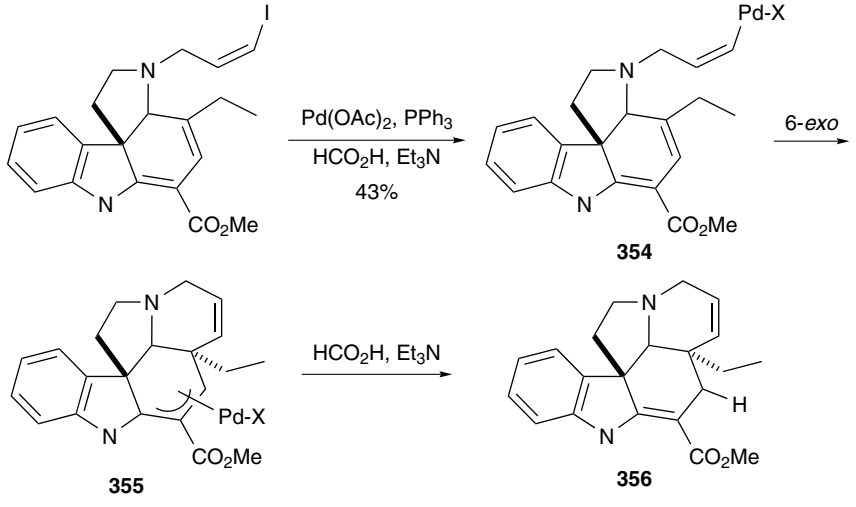


Unconjugated 1,4-cyclohexadiene (**350**) undergoes heteroannulation. Reaction of **350** with **349** is explained by carbopalladation to give **351**. Dehydropalladation

and readdition of H-Pd-X in the opposite direction generate the π-allylpalladium **352**, and intramolecular nucleophilic attack of the malonate provides **353** [142].

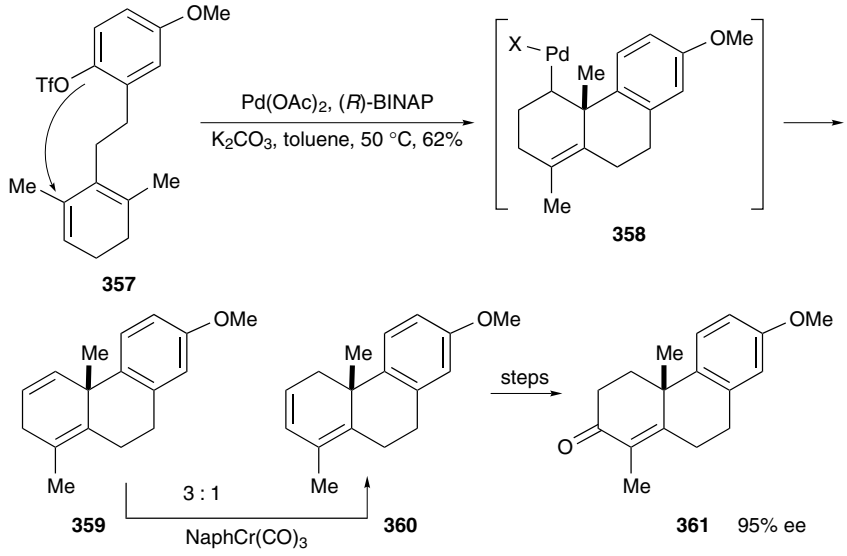


Intramolecular reaction is useful for construction of complex molecules. Annulation of the congested 1,3-diene system to construct a quaternary carbon was applied to several total syntheses of natural products. In the total synthesis of tabersonine **356**, the key step is the intramolecular reaction of the vinylpalladium to the conjugated diene in **354** to generate π-allylpalladium intermediate **355**, which is trapped by hydride from formic acid to afford **356** [143].

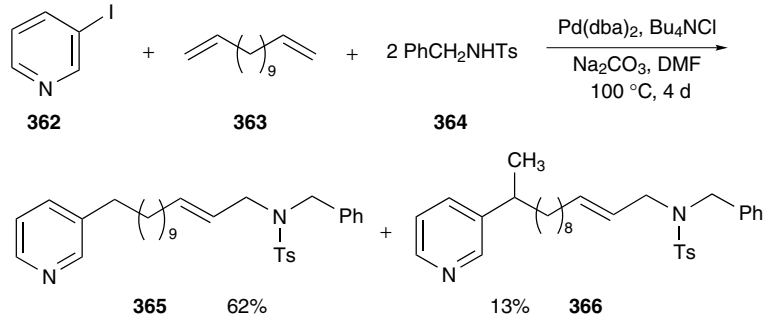


Among several possibilities in the cyclization of the 1,3-cyclohexadiene **357**, 6-*exo* cyclization to the olefin moiety to generate **358** is expected to be the most favorable, and asymmetric cyclization of the 1,3-diene **357** using BINAP as a chiral ligand constructed a quaternary carbon, and subsequent β-H elimination gives a mixture of the 1,4- and 1,3-dienes **359** and **360**. The best results were obtained at

50 °C. The 1,4-diene **359** was converted to the 1,3-diene **360** using naphthalene-$Cr(CO)_3$ as a catalyst, and then to the synthetic intermediate of diterpene **361** [144].



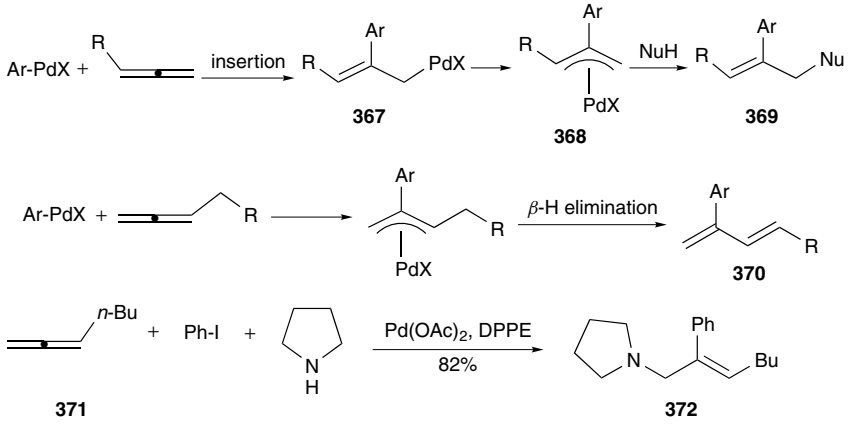
Interestingly, reaction of aryl halides with long chain α,ω-dienes proceeds efficiently via Pd migration and formation of π-allylpalladium intermediates, which are trapped by nucleophiles. Treatment of 3-iodopyridine (**362**) with 1,12-tridecadiene (**363**) in the presence of amine **364** produced a mixture of **365** (62 %) and **366** (13 %). The reaction took 4 days showing that the elimination and readdition of H-Pd-X occurred back and forth many times along the long carbon chain, and was terminated by the formation of the π-allylpalladium intermediate [145].



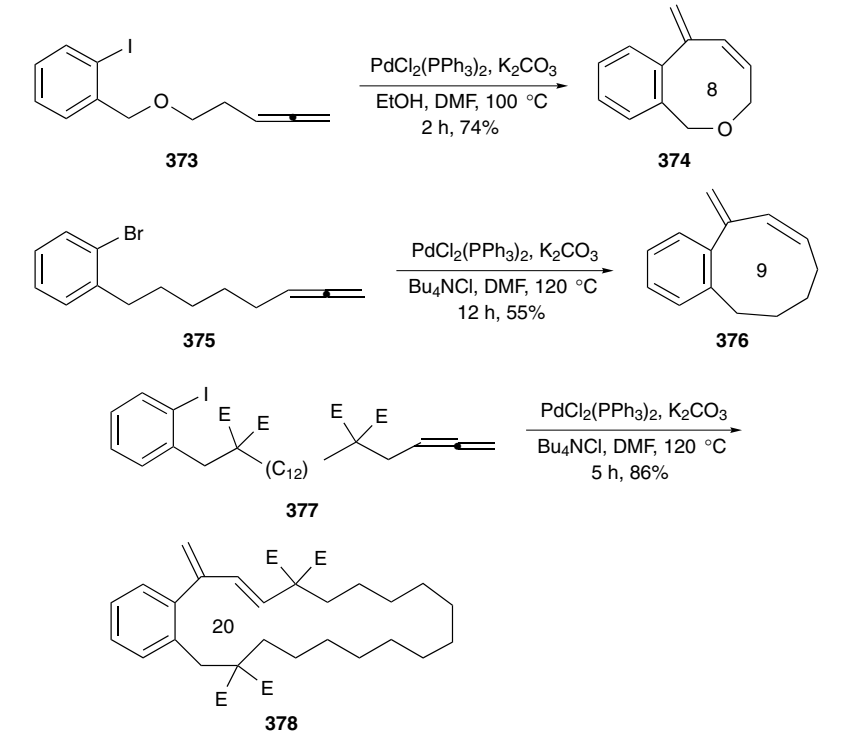
3.2.9.2 Reactions of 1,2-Dienes

Allenes undergo facile carbopalladation and are used extensively in organic synthesis. The general reaction patterns of allenes with aryl halides are as follows. In carbopalladation of allene, an Ar group attacks the central sp carbon of the allene system to generate **367** and then the π-allylpalladium **368** as an intermediate. Then the attack of a nucleophile mainly on a less substituted terminus yields the alkene **369**. Thus 1,2-addition to one of the double bonds in the allene occurs. In the absence of nucleophiles, β-H elimination gives 2-substituted 1,3-dienes

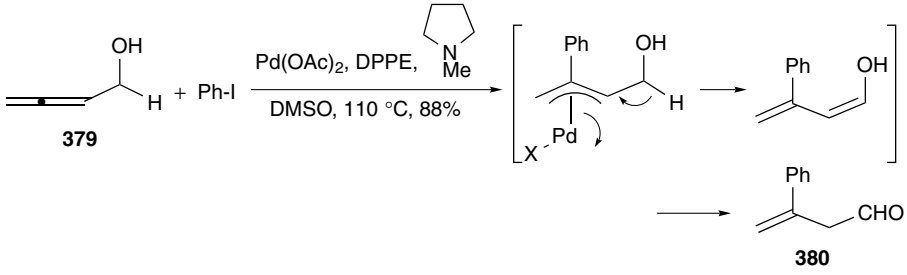
370. As an early example, reaction of 1,2-hexadiene (**371**) with iodobenzene and pyrrolidine afforded the allylic amine **372** [146].



Allenes are extensively used for synthetic purposes due to high reactivity for carbopalladation. They are more reactive than alkenes. Ma and Negishi have shown that common, medium, and large ring compounds can be prepared efficiently by cyclization of ω-(2-halophenyl)allenes, **373, 375**, and **377**. Carbon–carbon bond formation takes place at the central carbon of the allenes to give *exo*-methylene groups under Jeffery conditions. In addition to efficient formation of eight- and nine-membered rings **374** and **376**, the 20-membered ring **378** was constructed from **377** in 86 % yield in 5 h. This is a remarkably high yield for such a large ring achieved in a short reaction time [147].

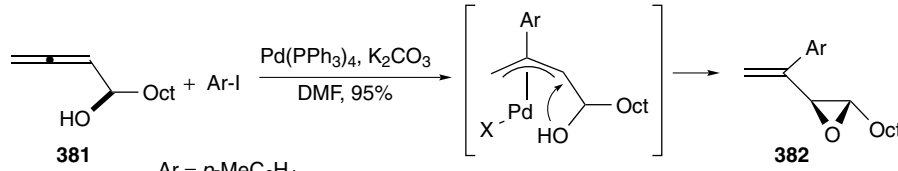


A main reaction path of the 2,3-butadien-1-ols **379** with aryl and alkenyl halides in DMSO using DPPE is β-H elimination, and β,γ-unsaturated aldehyde **380** or ketones are obtained [148]. However, allenes bearing nucleophilic centers undergo heterocyclization under different conditions and numerous applications have been reported.



379 **380**

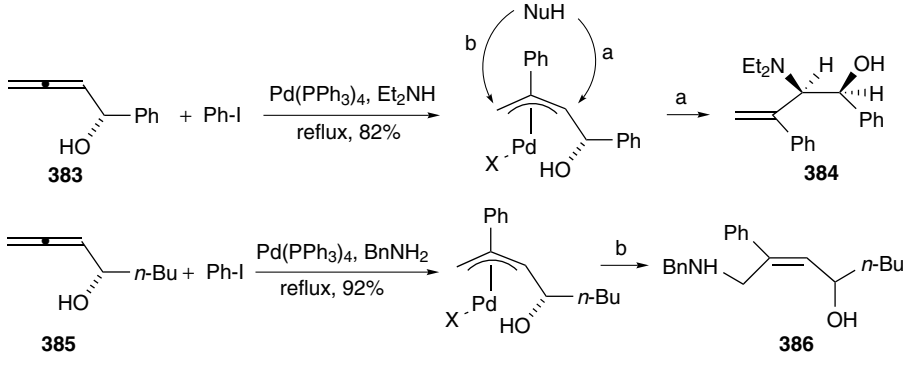
For example, allenyl alcohols are extensively used for heteroannulation. The alkenyloxirane **382** was obtained with high ee and in high yield by the cyclization of the chiral 1-substituted 2,3-butadien-1-ol **381**. The reaction is highly diastereoselective and the *trans*-alkenyloxirane was obtained with no racemization and without forming a dihydrofuran [149].



381 **382**

95% ee Ar = *p*-MeC$_6$H$_4$ 98% ee

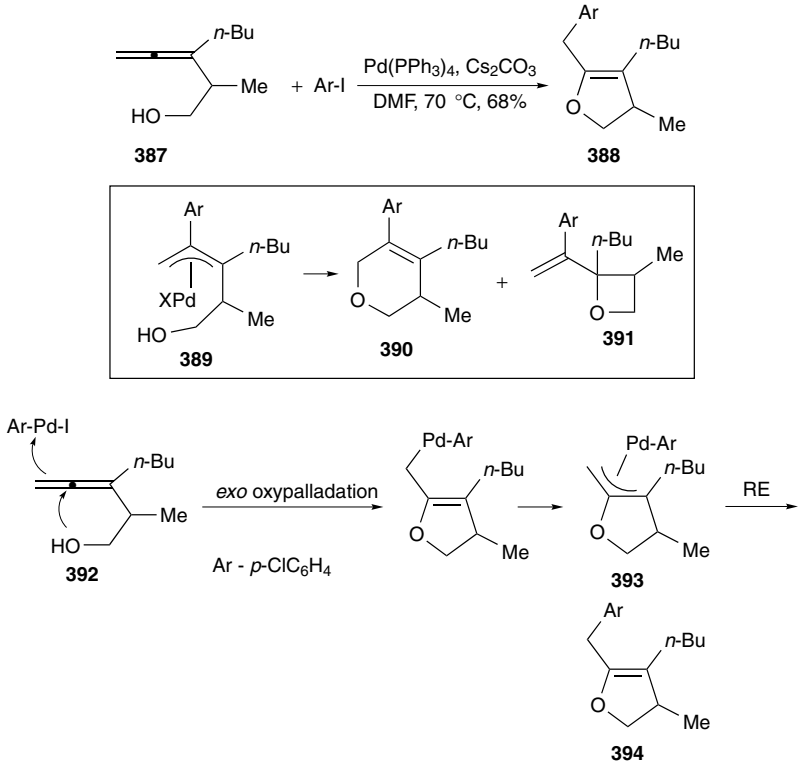
The remarkable effect of substituents on regioselectivity was observed in the intermolecular reaction of 1-substituted 2,3-butadien-1-ols with nucleophiles giving different regioisomers depending on the kind of 1-substituents. 1-Phenyl-2,3-butadien-1-ol (**383**) reacts with diethylamine to afford 2-amino-1,3-diphenyl-3-buten-1-ol **384** regio- and stereoselectively. On the other hand, reaction of 1-alkyl-2,3-butadien-1-ol **385** yields the 4-amino-2(*E*)-alken-1-ol **386**. These reactions offer efficient synthetic methods for 2- or 4-amino alken-1-ols with high regio- and stereoselectivity [150].



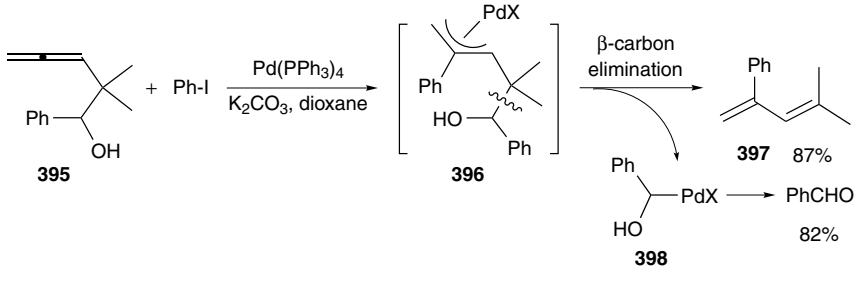
383 **384**

385 **386**

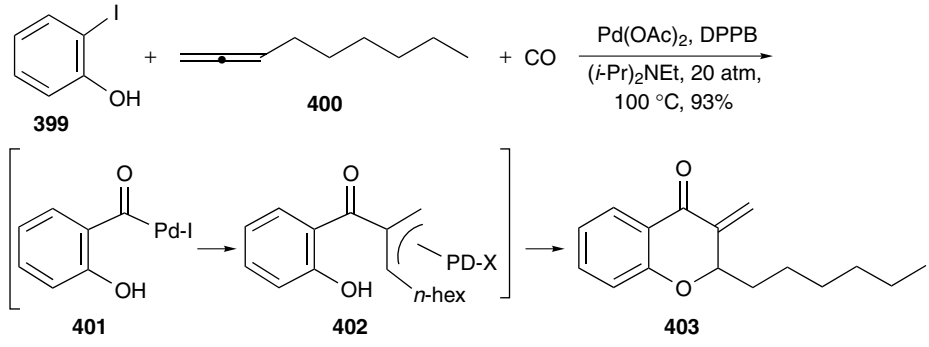
Different regioselectivities were observed in the reaction of 3,4-pentadien-1-ols **387** with aryl iodides. The expected products **390** and **391** from the π-allylpalladium intermediates **389** were not formed [151]. Exclusive formation of the dihydrofuran **388** is explained by concerted inter- and intramolecular *exo*-oxypalladation as shown by **392** to give π-allylpalladium **393**, and reductive elimination gives rise to the dihydrofuran **394**, showing that the intramolecular oxypalladation is faster than the intermolecular carbopalladation with Ar-Pd-I.



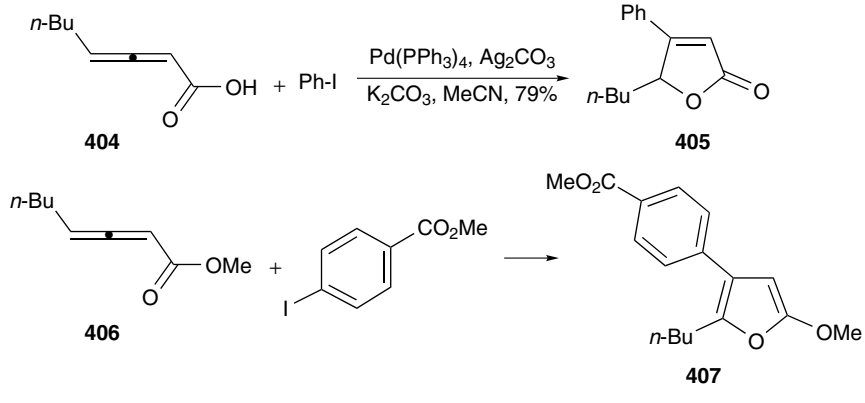
Unusual Pd-catalyzed fragmentation occurred in the reaction of 1-phenyl-2,2-dimethyl-3,4-pentadien-1-ol (**395**) with iodobenzene. The arylated diene **397** and benzaldehyde were obtained in high yields. In this reaction, phenylpalladium attacked the central carbon to generate the π-allylpalladium intermediate **396**. Then decarbopalladation (β-carbon elimination) occurred to provide the arylated diene **397** and α-hydroxybenzylpalladium **398**, which collapsed to benzaldehyde and Pd(0) [152].



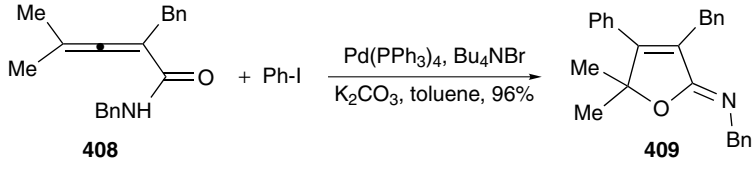
In the presence of CO, insertion of CO is faster than that of allenes. In the reaction of *o*-iodophenol (**399**) with 1,2-nonadiene (**400**) under CO pressure (20 atm) by use of DPPB as a ligand, CO insertion generates the acylpalladium **401**, to which insertion of the allene occurs to give the π-allylpalladium intermediate **402**, and nucleophilic attack of phenolic OH yields **403** in high yield [153].



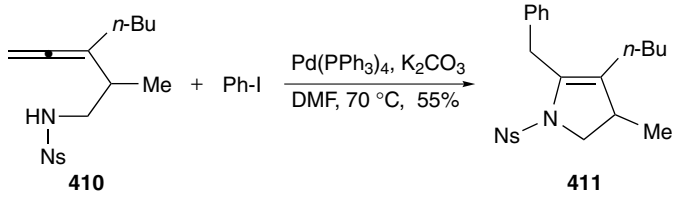
Butenolides are obtained by the reaction of 2,3-alkadienoic acids catalyzed by Pd(0) in the presence of Ag_2CO_3 as shown by the transformation of **404** to **405** [154]. The butenolide formation proceeds even in the absence of Ag salt [155]. The furan **407** was obtained directly by the reaction of methyl 2,3-alkadienoate **406** [156].



Unexpected O-attack, rather than N-attack, occurred in the cyclization of 2,4,4-trisubstituted 2,3-butadienamide **408** to afford the iminolactone **409** in high yield [157].

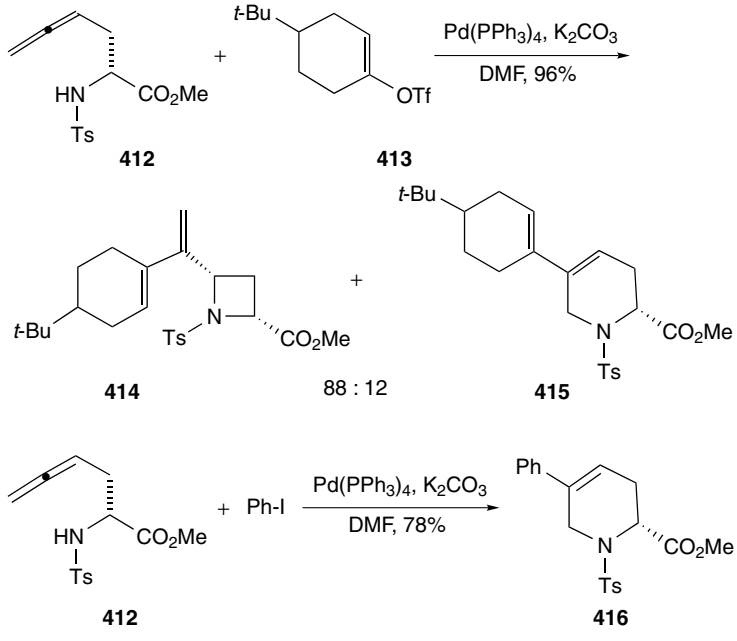


The 2,3-disubstituted 3,4-pentadienylamine derivative **410** underwent *exo*-cyclization to produce the dihydropyrrole **411** as a major product [158].



410 **411**

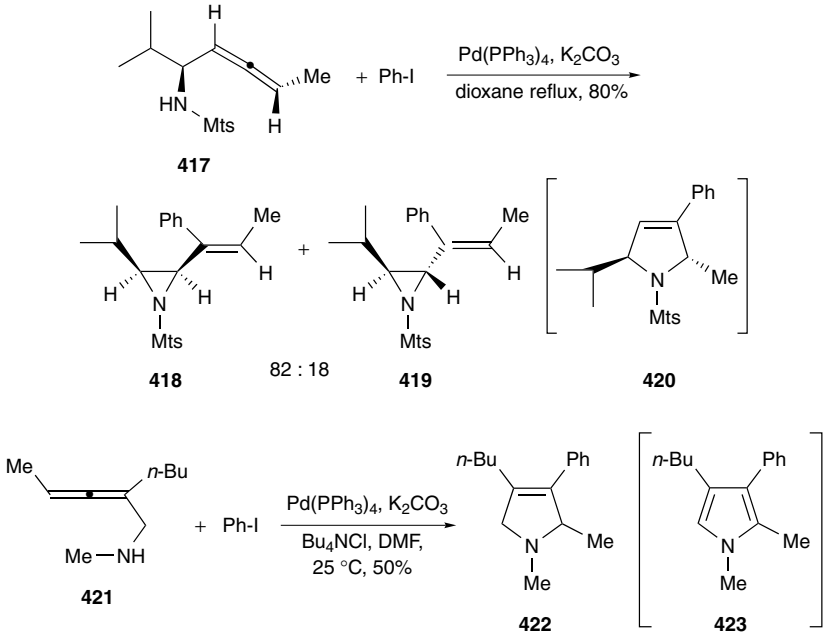
Formation of azetidines and tetrahydropyridines is expected by the reaction of 3,4-pentadienylamines with alkenyl halides. The ratio of the two products was found to change depending on the substrates. The reaction of the amino acid ester **412** with the triflate **413** afforded the azetidine **414** with high selectivity and the six-membered ring **415** as the minor product. On the other hand, the pipecolic ester **416** was obtained as the sole product of the reaction of **412** with iodobenzene [159].



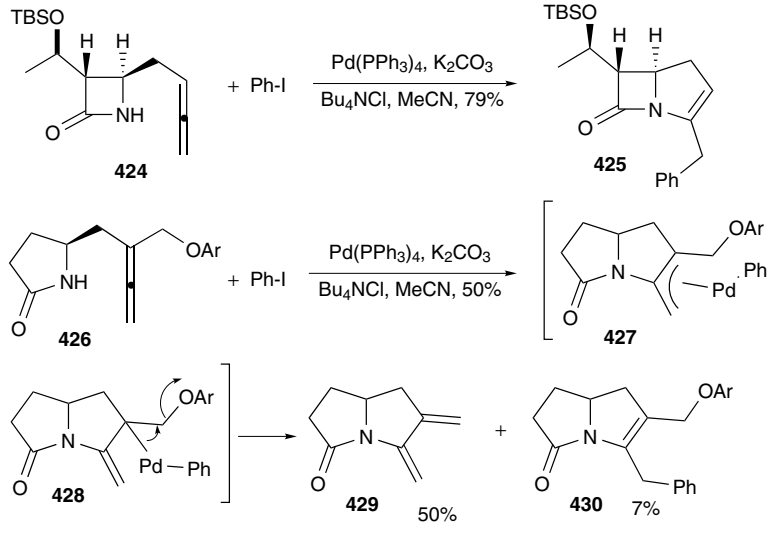
412 **413** **414** **415** **412** **416**

Reaction of the 2,3-butadienylamine **417** with aryl iodides affords three- and five-membered rings. The regioselectivity depends on reaction conditions. Particularly solvents play an important role. Dioxane is a solvent of choice for the aziridine formation. The chiral aziridine **418** as a main product and **419** as the minor product were obtained from 2,3-butadenylamine **417** without racemization in dioxane. The five-membered ring **420** was not obtained in this case [160].

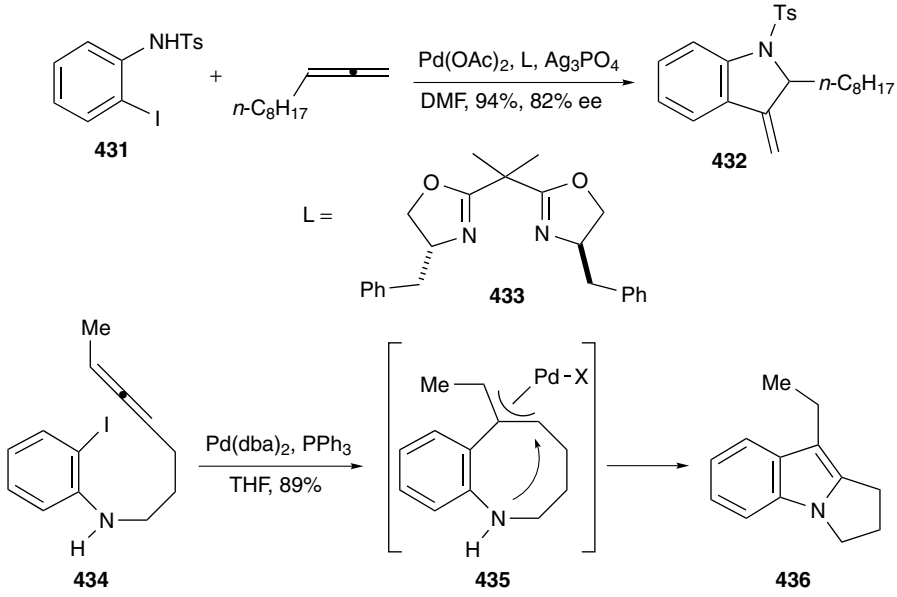
The 2,5-dihydropyrrole **422** was obtained by the reaction of the 2,3-pentadienylamine **421** under Jeffery conditions. In the absence of Bu_4NCl, the pyrrole **423** was the sole product [161].



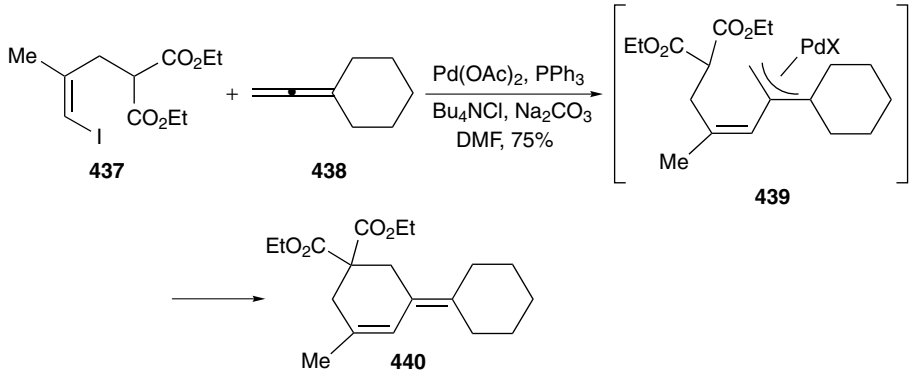
Unexpected nucleophilic attack of the amino group in the β-lactam **424** at the central carbon of the allene system occurred in the intramolecular reaction of the β-lactam bearing the terminal allene to give the carbapenem **425** under Jeffery conditions without giving an expected six-membered ring [162]. The cyclization of the γ-lactam **426** afforded again the unexpected product **429** as the main product, and **430** as the minor product formed by the attack of the amino group at the central carbon. Formation of **429** can be understood by generation of a different type of π-allylpalladium intermediate **427** by aminopalladation of **426**. Deoxypalladation (β-acetoxy elimination) as shown by **428** gives rise to the diene **429** [163]. The unexpected reaction shows that the aminopalladation is more favorable and faster than the intermolecular carbopalladation.



Reaction of the *o*-iodoaniline derivative **431** with 1,2-decadiene in the presence of the chiral bisoxazoline **433** as a ligand and Ag salt provided the indoline **432** with 80 % ee [164]. Construction of indole skeletons was carried out by intramolecular carbopalladation of allenes followed by amination. The π-allylpalladium intermediate **435** was formed from *o*-iodoaniline derivative **434**, and intramolecular amination afforded the indole **436** in 89 % yield [165].



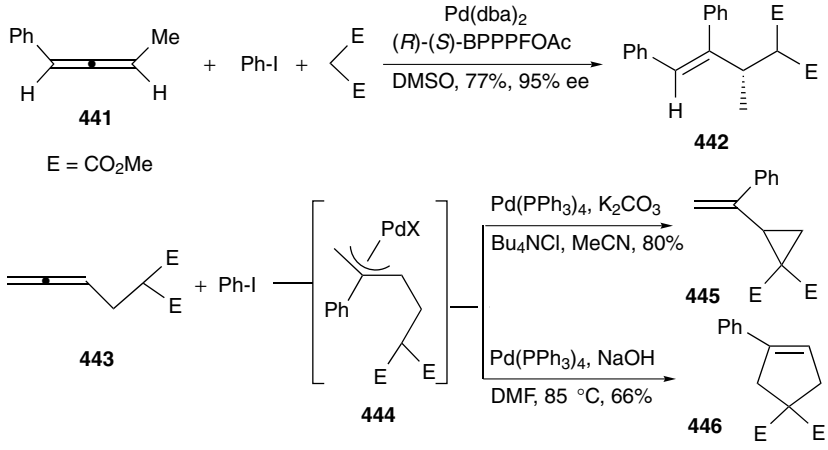
The intermediate formed by the reaction of the vinyl iodide **437** with the allene **438** was trapped by the malonate as shown by **439** to yield **440** [166].



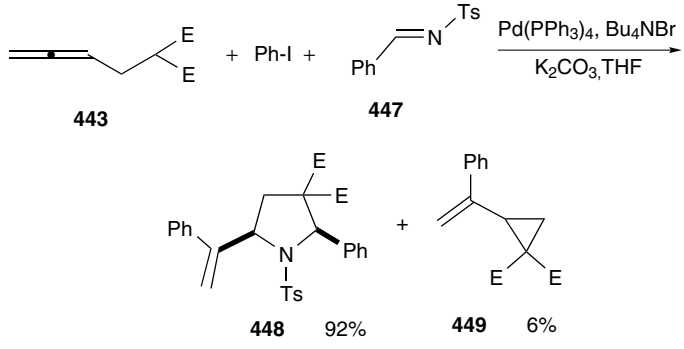
Efficient asymmetric carbopalladation occurred in the reaction of the racemic allene **441** with iodobenzene and malonate using BPPFOAc (**XI-14**) as a chiral ligand. The chiral malonate derivative **442** with 95 % ee was obtained in 77 % yield [167].

Cyclization of dimethyl 2,3-butadienylmalonate (**443**) yielded mainly the five-membered ring, rather than the three-membered ring via the intermediate

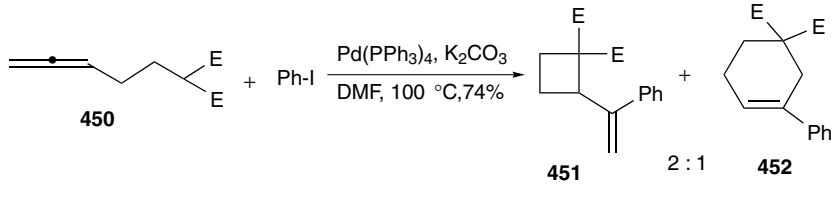
444 [168]. Recently however, Ma found that regioselectivity to give the three-membered ring **445** and the five-membered ring **446** can be controlled; while the three-membered ring **445** was obtained selectively by the addition of a catalytic amount of Bu_4NCl, the five-membered ring **446** was the main product when NaOH was used as a base [169].



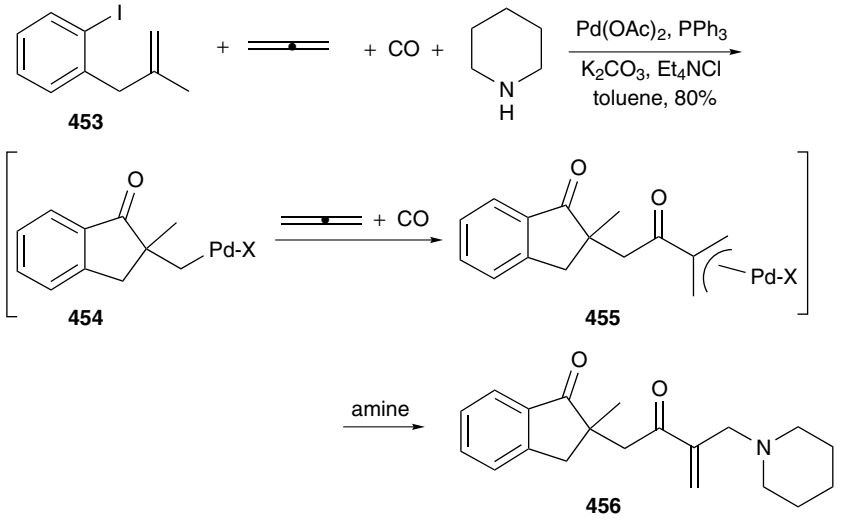
In the presence of an imine, a three-component cyclization occurred to produce pyrrolidine. Reaction of the allene **443**, the imine **447**, and iodobenzene catalyzed by $Pd(PPh_3)_4$ in the presence of Bu_4NBr gave the *cis*-pyrrolidine **448** in 92 % yield. The pyrrolidine **448** was formed by the reaction of the intermediate **444** with the imine before the cyclization. The product **449**, obtained by the two-component reaction, was the minor product [170].



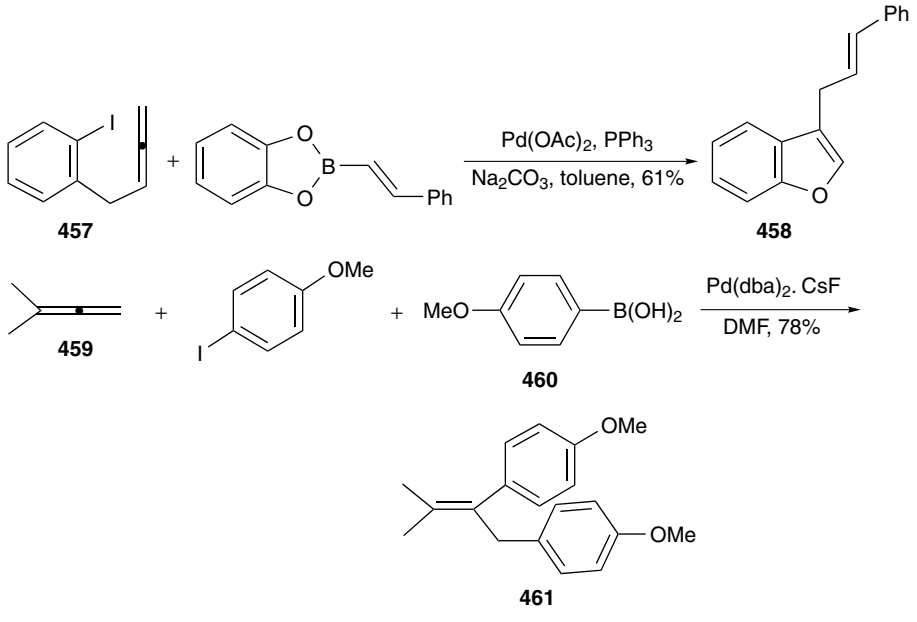
Interestingly, the four-membered ring **451** was obtained from allenylmalonate **450** as the major product, and the six-membered ring **452** was the minor product [171].



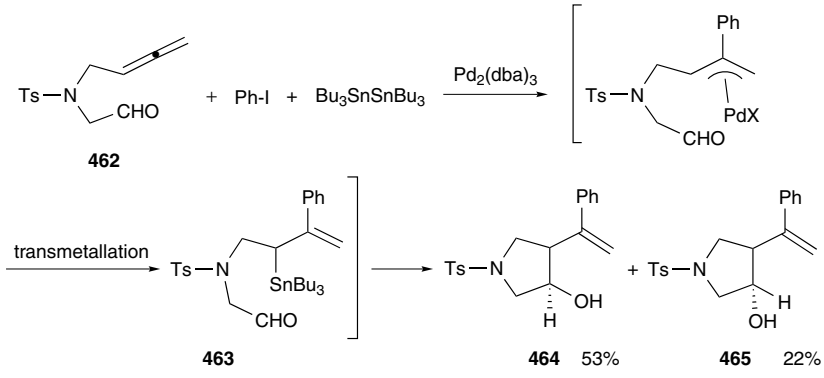
Efficient domino reactions of the alkenyl iodide **453** with CO, allene, and piperidine proceeded to give **456** in very high yield (80 %) after six-step reactions [172]. CO is the most reactive, and CO insertion is followed by olefin insertion to generate **454**. Then allene insertion occurs after the second CO insertion. Finally, the π-allylpalladium intermediate **455** is trapped by the amine to yield **456**.



Reactions of allenes with halides are terminated by attack of organometallic compounds. The reaction of the 2-(2,3-butadienyl)iodobenzene (**457**) was terminated with alkenyl borane to give **458** [173]. 3-Methyl-1,2-butadiene (**459**) reacts with ary iodide, and the reaction is terminated by the attack of arylboronic acid **460** to afford **461** [174].

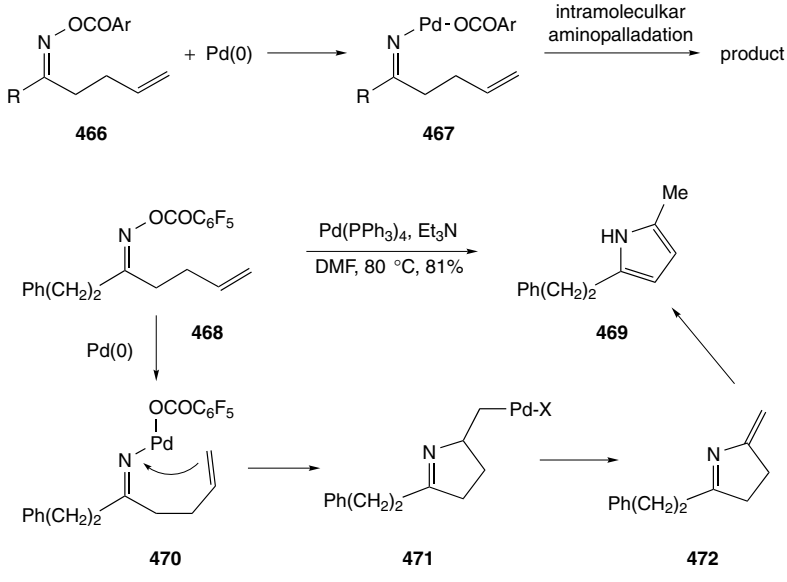


'Umpolung' occurs by transmetallation of the π-allylpalladium intermediate, formed from the allene **462** and iodobenzene, with hexabutyldistannane, and the generated the allylstannane intermediate **463** reacts with aldehyde intramolecularly to yield the cyclopentanols **464** and **465** [175]. A similar 'umpolung' reaction was carried out using indium [176,177].

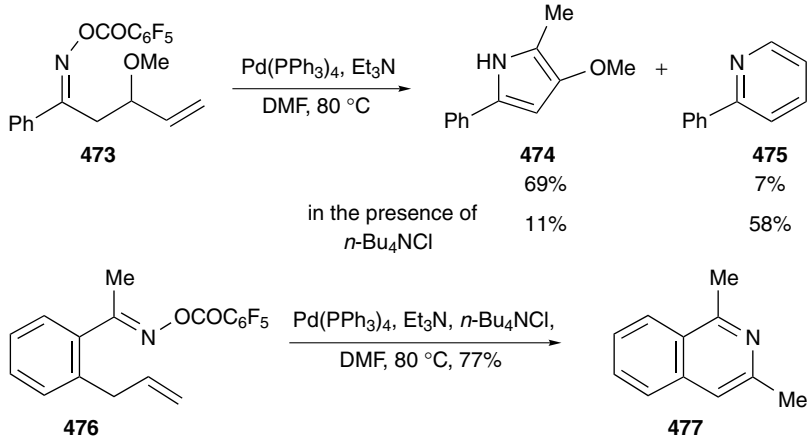


3.2.10 Amino Heck Reactions of Oximes

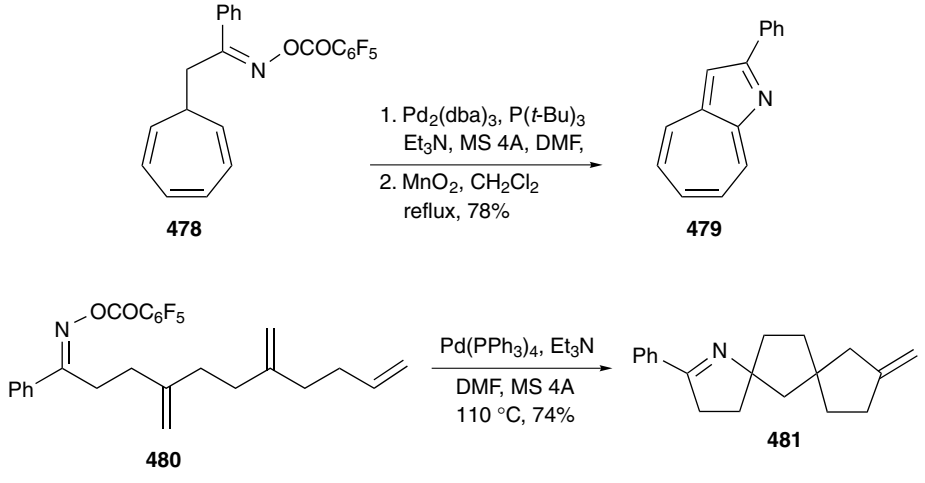
Narasaka found that an N—O bond in oxime undergoes oxidative addition to Pd(0). Based on this reaction, his group developed a new synthetic method of N-heterocycles. Oxidative addition of some unsaturated ketone oximes **466** generates **467**, which undergoes intramolecular aminopalladation. Particularly, facile oxidative addition of *O*-pentafluorobenzoyloxime **468** occurs to provide **470**. When the oxime of γ, δ-unsaturated ketone **468** is treated with $Pd(PPh_3)_4$ in the presence of a base in DMF, intramolecular Heck-type amination of alkene takes place to give rise to the the pyrrole **469**. The reaction can be understood by sequences of oxidative addition to give alkylideneaminopalladium **470**, double bond insertion to form the cyclized intermediate **471**, β-H elimination to form the cyclic imine **472**, and double bond isomerization [178].



Pyridines and quinolines are similarly prepared. The pyrrole **474** was obtained by 5-*exo* cyclization of 3-methoxy-1-phenyl-4-penten-1-one (*E*)-*O*-pentarfluorobenzoyloxime **473** under usual conditions. On the other hand, 2-phenylpyridine (**475**) was obtained by 6-*endo* cyclization as the main product in the presence of *n*-Bu_4NCl. Isoquinoline **477** was prepared in 77 % yield by 6-*exo* cyclization of the oxime **476** [179].

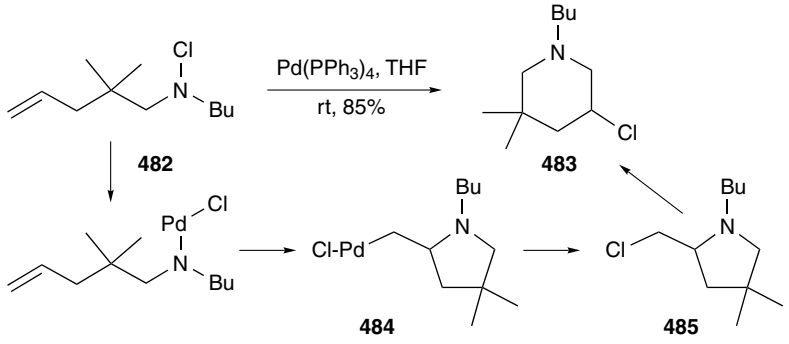


Substituted azaazulene **479** was prepared from cycloheptatrienylmethyl ketone *O*-pentafluorobenzyloxime **478** by Pd-P(*t*-Bu)$_3$-catalyzed cyclization, followed by treatment with MnO_2 [180]. As observed in the Heck reaction, the domino insertion of olefins occurred to produce the polycyclic imine **481** when the trienyloxime **480** was subjected to the Pd-catalyzed reaction [181].



As a related reaction, an N-Cl bond in unsaturated *N*-chloroamine undergoes oxidative addition to Pd(0) and cyclization. In the treatment of *N*-chloro-2,2-dimethyl-4-pentenylamine **482** with $Pd(PPh_3)_4$ in the absence of a base, oxidative

addition is followed by double bond insertion to give the alkylpalladium chloride **484**, which is converted to the 2-chloromethylpyrroridine **485** by reductive elimination, without undergoing β-H elimination in the absence of a base. Then isomerization of the less stable **485** to the more stable 3-chloropiperidine **483** occurs. The presence of 2,2-dimethyl groups is important for the smooth reaction; the yield was low without them [182].



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3.3 Reactions of Aromatics and Heteroaromatics

Aryl–aryl coupling is an important synthetic reaction. Efficient aryl–aryl coupling is possible by Pd-catalyzed cross couplings of aryl halides with aryl metal (Mg, Zn, B, Sn, Si) compounds, and the methods have wide applications. On the other hand, a simple Pd-catalyzed arylation of arenes with aryl halides has been known. Although less attention has been paid, the importance of the reaction is increasing as more efficient methods of aryl–aryl bond formation become available. The arylation of arenes with aryl halides is treated in this section.

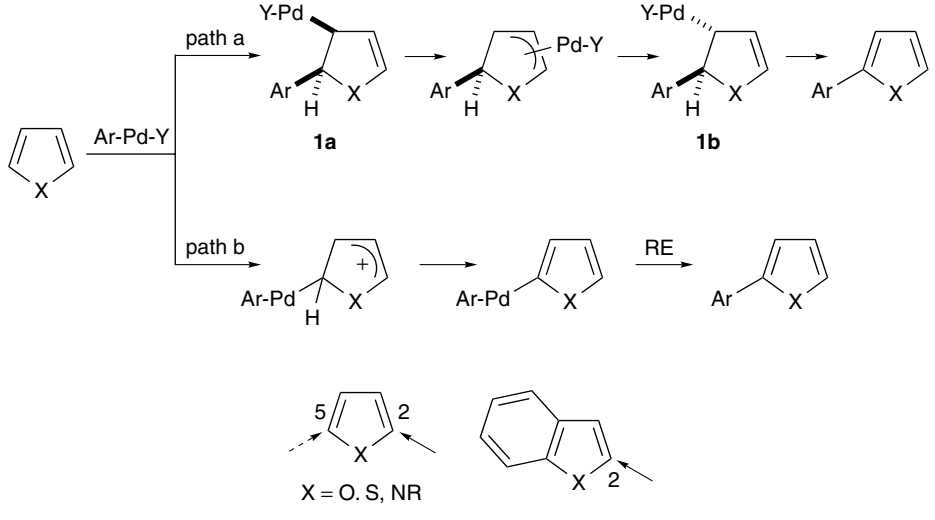
In contrast to facile reactions of aryl halides with alkenes and alkynes, reactions of aromatic compounds with aryl halides have received less attention. Only intramolecular arylation of benzene derivatives, except phenols, is known [1]. On the other hand, electron-rich heterocycles such as furans, thiophenes, pyrroles, oxazoles, imidazoles, and thiazoles undergo facile inter- and intramolecular arylation with aryl halides. These are called 'heteroaryl Heck reactions' [2].

3.3.1 Arylation of Heterocycles

Some heterocycles undergo facile inter- and intramolecular arylations. Two mechanistic explanations of the arylation are possible. The Heck-type reaction is one of them. Carbopalladation of one of two double bonds with Ar-Pd-X gives **1a**, which is stabilized by π-allylpalladium formation. Pd and β-H is *anti* in **1a** and hence *syn* β-H elimination is not possible. Therefore, in stereoisomerization from *anti* **1a** to *syn* **1b** a relationship between Pd and β-hydrogen occurs, and *syn* β-H elimination from **1b** affords the arylation product (path a). Another explanation is electrophilic substitution with Ar-Pd-X. Since arylations occur mainly at electron-rich carbons of heterocycles, they can be understood as electrophilic substitutions (path b). In some cases, a Heck-type mechanism seems to be more reasonable. Certainly arylations proceed by one of these mechanisms depending on the electronic nature of the substrates and reaction conditions, and hence further mechanistic studies are necessary.

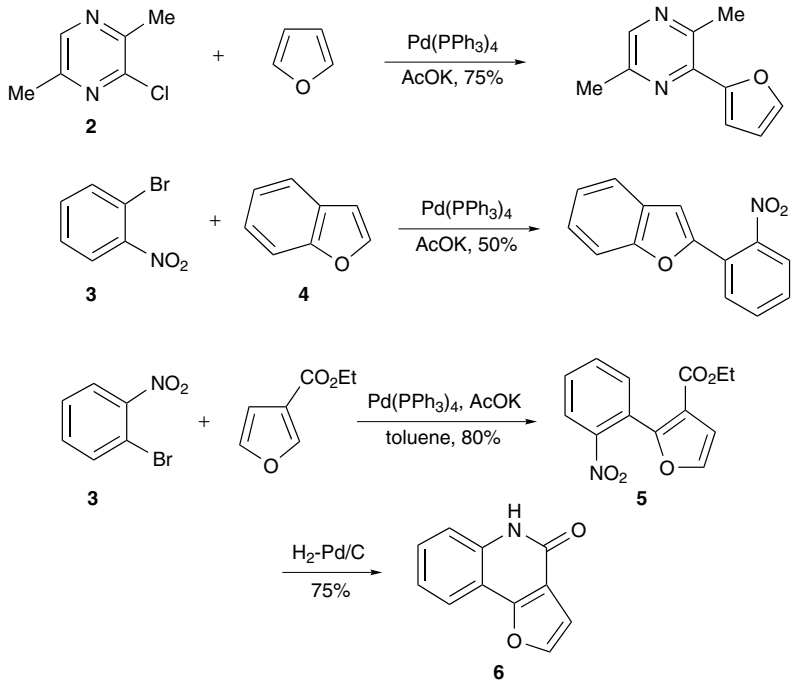
Furans, thiophenes, and pyrroles are arylated at the electron-rich C-2 positions. Further arylation occurs at C-5. Similarly, arylations at C-2 positions of benzofurans, benzothiophenes, and indoles take place preferentially.

Ohta and co-workers carried out extensive studies on intermolecular arylation of various heterocycles (furan, thiophene, pyrrole, oxazole, thiazole, *N*-methylimidazole, benz[*b*]oxazole, benzo[*b*]furan, and benzo[*b*]thiophene) with mainly chloropyrazines as heteroaryl halides using $Pd(PPh_3)_4$ and AcOK [3].

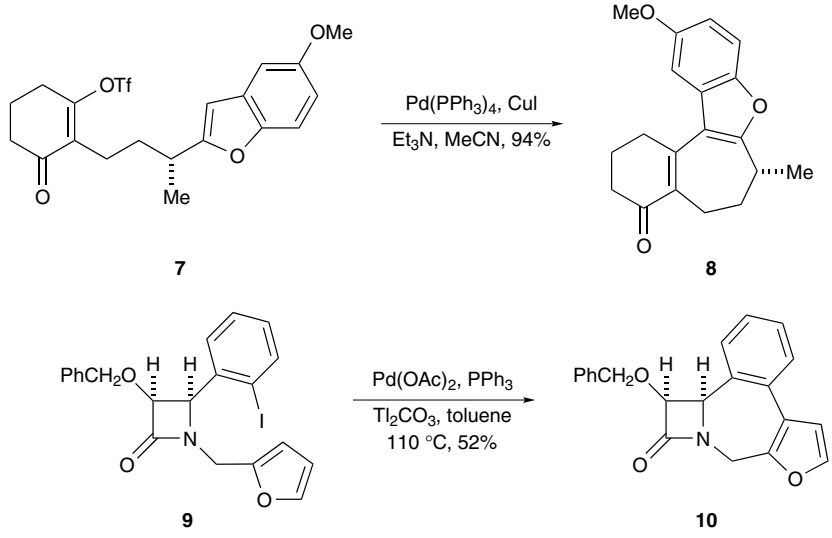


3.3.1.1 Furan and Benzofuran

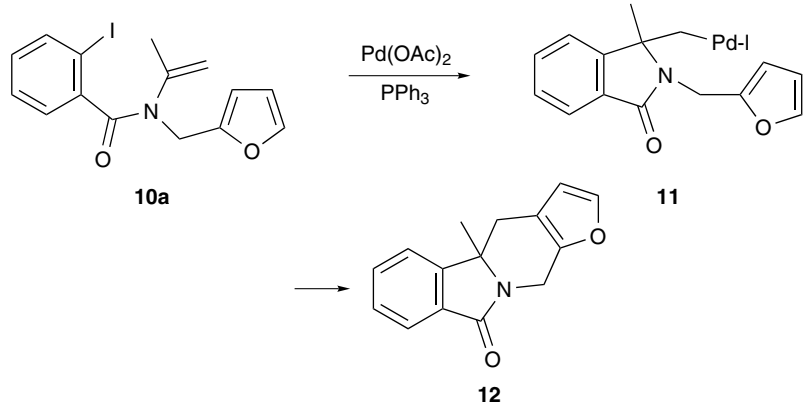
Reaction of the chloropyrazine **2** with furan afforded the 2-arylfuran. 2-Arylation of benzo[*b*]furan (**4**) occurs with *o*-bromonitrobenzene (**3**) [3b]. Regioselective 2-arylation of ethyl 3-furancarboxylate with **3** occurred to give **5** in 80 % yield when $Pd(PPh_3)_4$ and AcOK were used in toluene. 5-Arylation was the main path when ligandless Pd/C was used in the polar solvent NMP. The furo[3,2-*c*]quinolinone **6** was obtained after hydrogenation of the nitro group [4].



Intramolecular reaction of the vinyl triflate with benzo[*b*]furan in **7** is a key step in the preparation of the synthetic intermediate **8** of (−)-frondosin A [5]. Intramolecular reaction of the iodide with furan in **9** gave the tetracyclic β-lactam **10** containing furan ring in the presence of Tl_2CO_3 as a base. The rather unusual C-3 substitution occurs in the reactions of **7** and **9**, because the C-2′ positions are blocked [6]. If the cyclizations of **7** and **9** proceed similar to Heck-type carbopalladation and β-H elimination, direct *syn* β-H elimination is not possible, and isomerization from *anti* to *syn*, followed by *syn* β-H elimination should occur. Therefore, direct electrophilic substitution may be a better explanation.

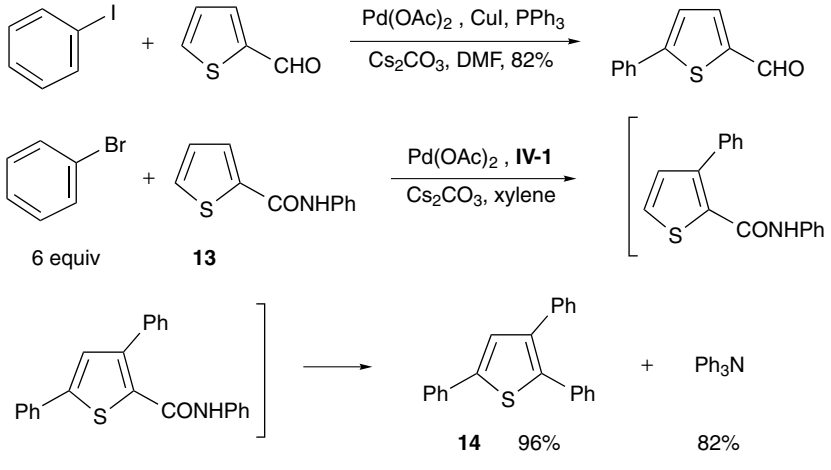


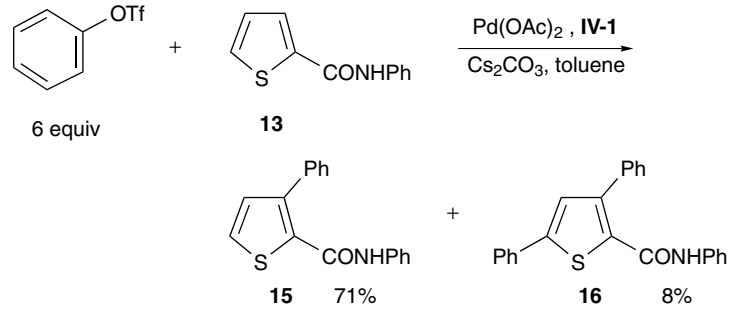
Arylation is not limited to aryl halides. Alkenylpalladium intermediates, formed *in situ* in domino reactions of polyenynes, attack aromatic rings. The intermediate **11** is generated by 5-*exo* cyclization of the iodide **10a**. Then cyclization occurs to give **12** by attack of the alkylpalladium species on furan in **11**, because the alkylpalladium has no possibility of β-H elimination [7].



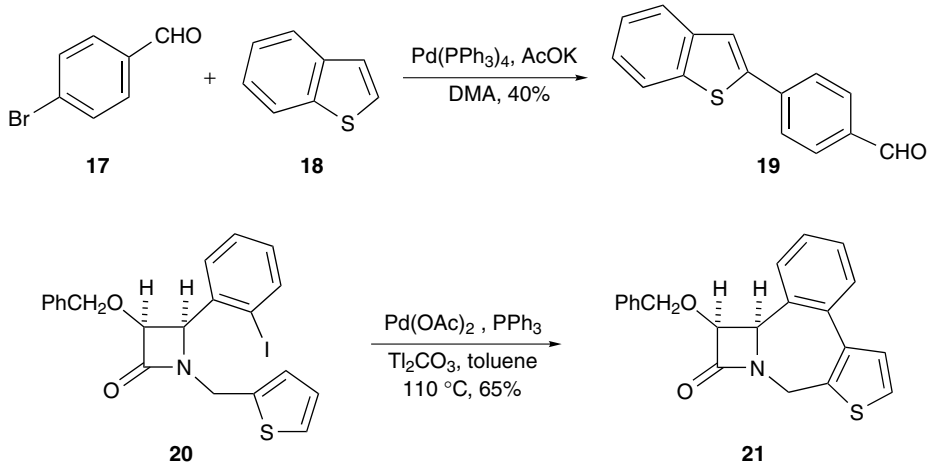
3.3.1.2 Thiophene and Benzothiophene

5-Arylation of 2-thiophenecarbaldehyde, catalyzed by $Pd(OAc)_2$ and CuI, took place with iodobenzene to give 5-phenyl-2-thiophenecarbaldehyde in high yield. Although the role of CuI is not clear, coordination of sulfur to CuI may enhance the deprotonation at C-2 [8]. Reaction of an excess of bromobenzene with 2-thiophenecarboxamide **13** afforded 2,3,5-triphenylthiophene (**14**) in 96 % yield. (Biphenyl-2-yl)(di-*t*-butyl)phosphine (**IV-1**) and Cs_2CO_3 were used in the reaction. The reaction involves unusual decarbamoylation and C—C bond cleavage via 3-phenyl- and 3,5-diphenyl-2-thiophenecarboxamides. Ph_3N was obtained in 82 % yield as the byproduct. Reaction of phenyl triflate with the thiophene **13** afforded the 3-phenyl and 3,5-diphenylthiophenes **15** and **16**, showing that the phenylation proceeds successively at the C-3 and C-5 positions. The C-3 substitution is rather unusual [9].



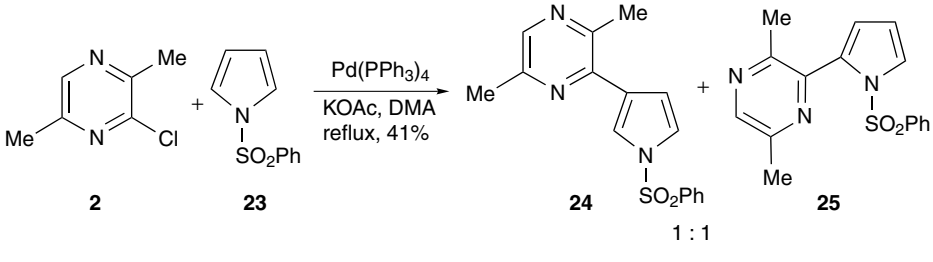


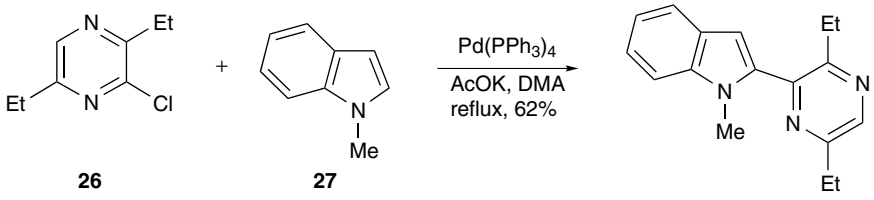
Benzo[*b*]thiophene (**18**) is arylated with the aryl bromide **17** as expected at C-2 to afford **19** [3b]. Intramolecular 3-arylation of the thiophene in **20** gave the tetracyclic β-lactam **21** containing thiophene in the presence of Tl_2CO_3 as a base [6].



3.3.1.3 Pyrrole and indole

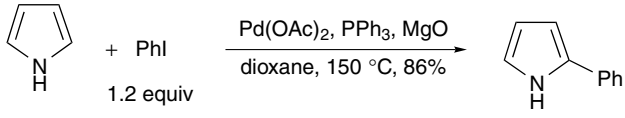
The 2- and 3-substitution products **24** and **25** were obtained in 1 : 1 ratio by the reaction of the chloropyrazine **2** with *N*-phenylsulfonylpyrrole (**23**). Since reaction of **2** with pyrrole itself occurs only at the C-2 position, the $PhSO_2$ group seems to enhance the reactivity at C-3. Indole (**27**) is intermolecularly arylated with **26** at C-2 as expected [3a].



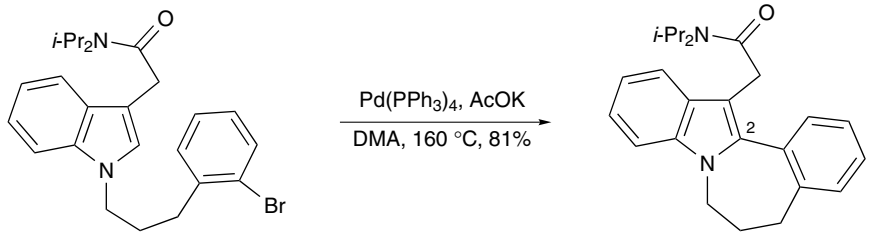


26 **27**

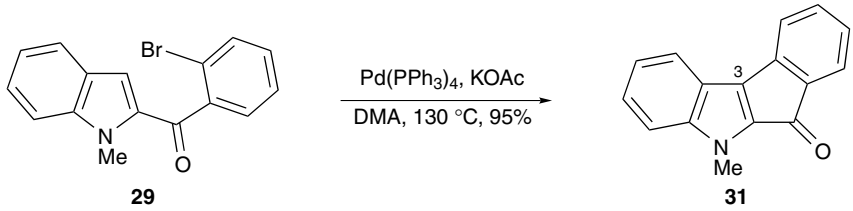
C-arylations of azoles proceed smoothly when N-protected azoles (pyrrole, indole, and imidazole) are used. N-free pyrrole, imidazole, and indole are poor substrates for C-arylation. However, Sezen and Sames reported an interesting effect of MgO as an additive [10]. 2-Phenylpyrrole was obtained cleanly in 86 % yield by the reaction of unprotected pyrrole with iodobenzene in the presence of MgO (1.2 equiv.). No N-arylation occurred. MgO seems to be bound to nitrogen strongly, and not only protects the nitrogen, but also increases the nucleophilicity of heteroarene nucleus.



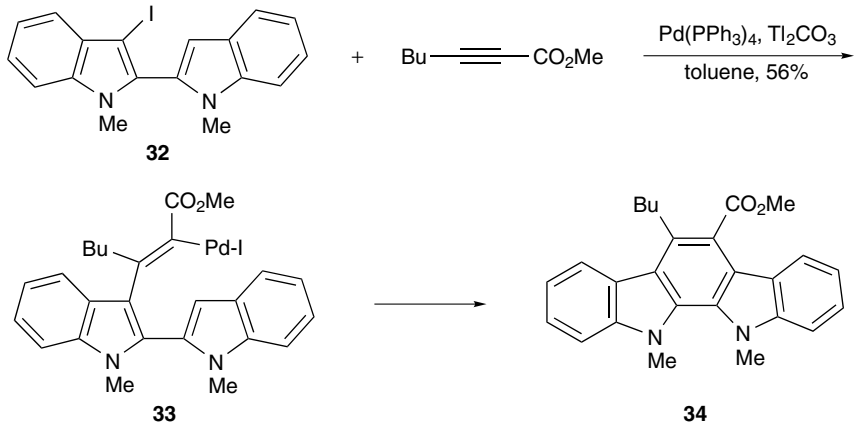
Intramolecular arylation of **28** and **29** occurred at either C-2 or C-3 to give **30** and **31** when the C-3 or C-2 position is substituted [11]. The alkenylpalladium intermediate **33**, generated by the reaction of the bis-indole **32** with an alkyne as a relay, attacks the indole to give **34** [12].



28 **30**



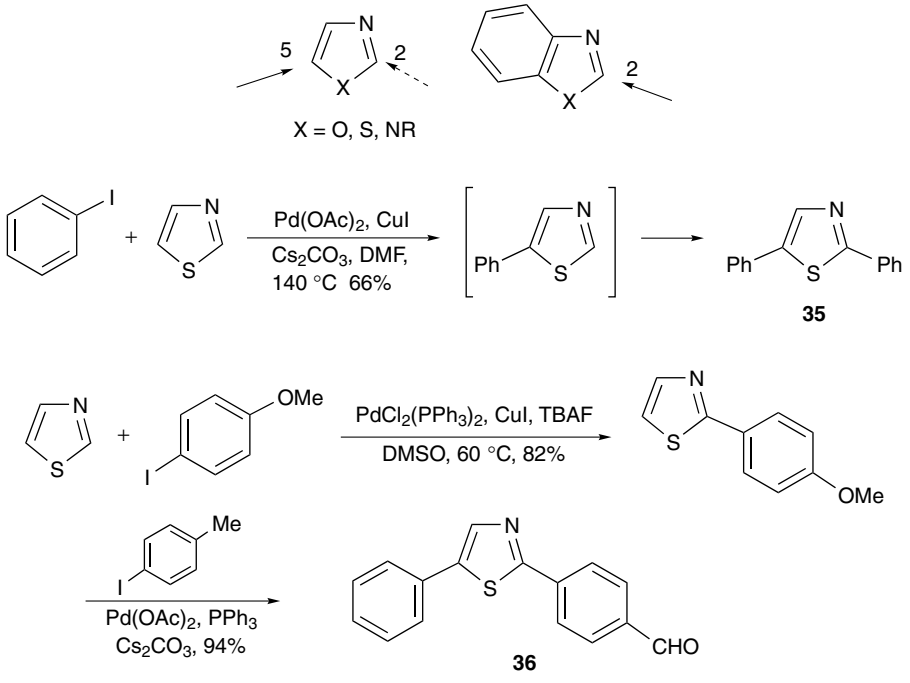
29 **31**

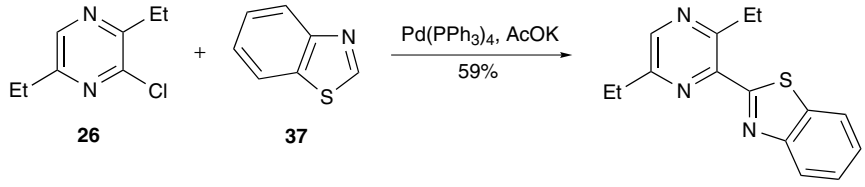


3.3.1.4 Thiazole and Benzo[b]thiazole

Most reactive sites in thiazoles, oxazoles, and imidazoles are electron-rich C-5 positions. If C-5 positions are blocked, less reactive C-2 positions are arylated. Also arylation of their benzo derivatives occurs at C-2.

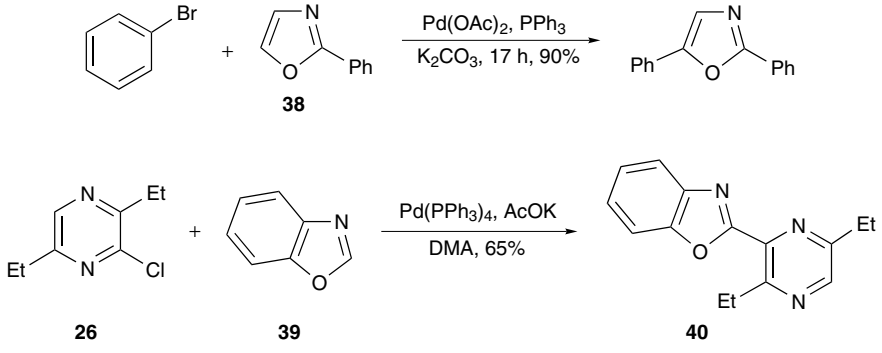
Phenylation of thiazole with iodobenzene at C-5 gave 5-phenylthiazole and further reaction afforded 2,5-diphenylthiazole (**35**) when $Pd(OAc)_2$, PPh_3, and Cs_2CO_3 were used. Addition of CuI gives a favorable effect [8]. Regioselectivity of mono- and diarylation of thiazole can be controlled. 2-Arylation with 4-iodoanisole took place cleanly when $PdCl_2(PPh_3)_2$ and CuI were used in the presence of TBAF in DMSO at 60 °C. Further arylation in the presence of $Pd(OAc)_2(PPh_3)_2$ and Cs_2CO_3 in DMF at 140 °C afforded 2,5-diarylthiazole **36** [13]. Arylation of benzothiazole (**37**) with the 2-chloropyrazine **26** occurred regioselectively at C-2 [3].





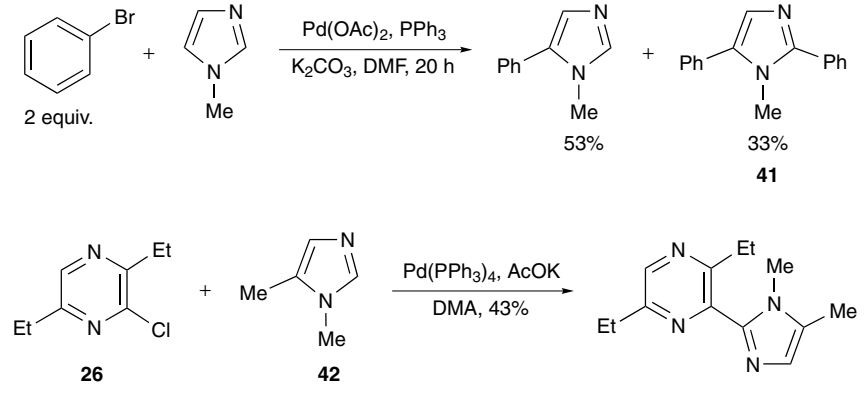
3.3.1.5 Oxazole and Benz[b]oxazole

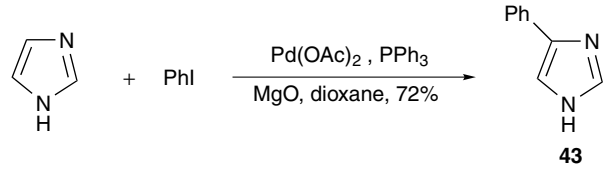
2-Phenyloxazole (**38**) is regioselectively phenylated at C-5 to afford 2,5-diphenyloxazole with bromobenzene, and arylation of benz[*b*]oxazole (**39**) with **26** gives the C-2 arylation product **40** as expected [3].

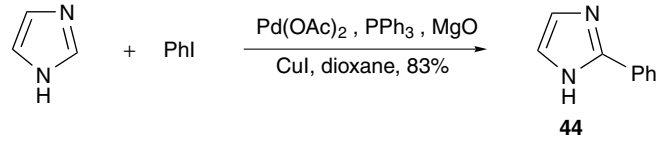


3.3.1.6 Imidazole and 1H-benzimidazole

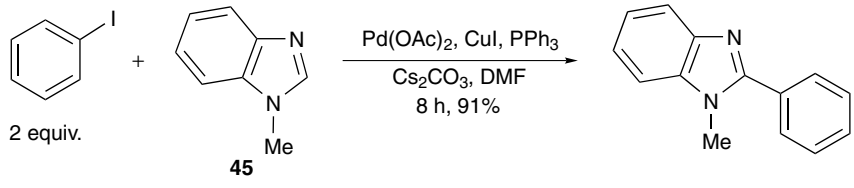
Phenylation of 1-methylimidazole with bromobenzene occurred at the most electron-rich C-5. Weak bases such as K_2CO_3 were used. At the same time, the electron-poor C-2 position is also phenylated further to give **41**. The results suggest different mechanisms for the phenylations at C-5 and C-2 [9]. 1,5-Dimethylimidazole (**42**) is arylated at C-2 with chloropyrazine **26** [3]. Sezen and Sames found that the regiochemistry of C-phenylation of N-unprotected imidazole can be controlled by additives without giving the N-phenylation product. 4-Phenylimidazole **43** was obtained from imidazole in 72 % yield by the addition of MgO (1.2 equiv.). Furthermore, exclusive 2-phenylation occurred to provide **44** in 83 % yield when CuI (2 equiv.) was added to the Pd–PPh_3–MgO system [10].

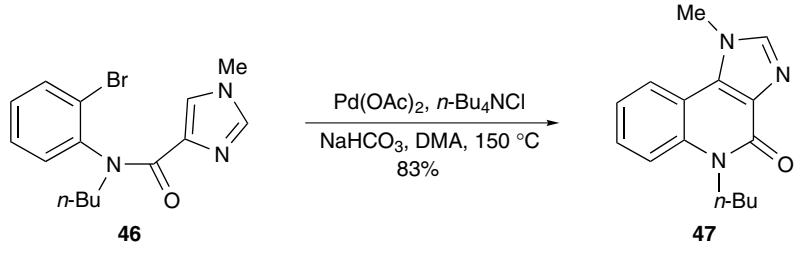






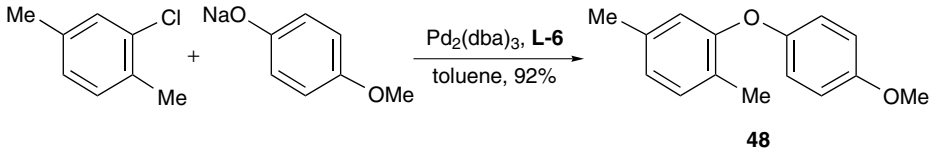
1H-Benz[*b*]imidazole (**45**) is phenylated at the electron-poor C-2 in very low yield (2 %). However, the reaction proceeds effectively in the presence of CuI as a promoter [8]. Intramolecular arylation of the 1-methylimidazole moiety **46** gave the C-5 arylation product **47** under ligandless Jeffery conditions [14].

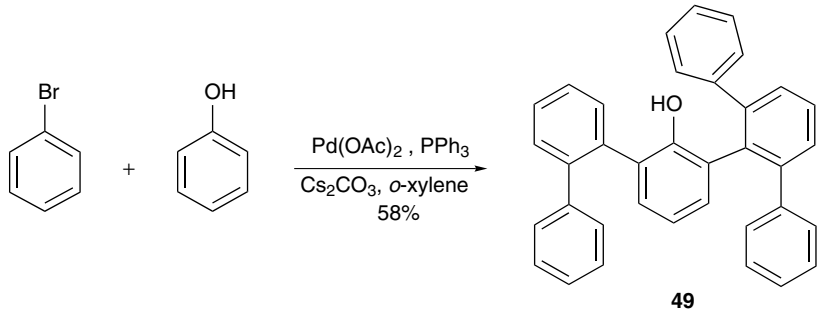




3.3.2 Intermolecular Arylation of Phenols

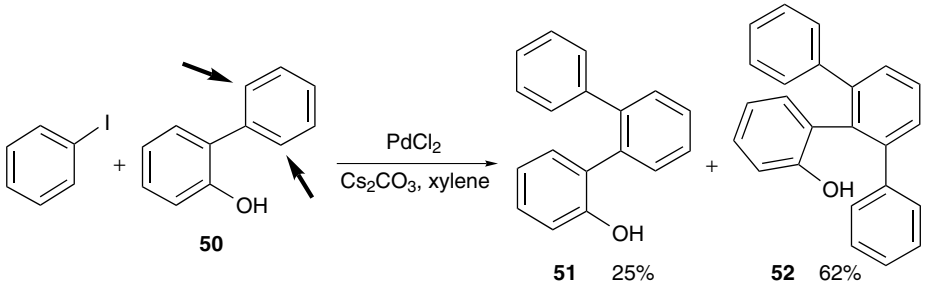
Intermolecular arylation of carbocyclic arenes are rare. Exceptionally, phenols are easily arylated. As treated in Chapter 3.7.4, the aryl ether **48** is formed by reaction of aryl halides with hydroquinone monomethyl ether when bulky and electron-rich phosphines are used, which accelerate reductive elimination. Miura and co-workers found new completely different reactions of phenol with bromobenzene by using $Pd(OAc)_2$, PPh_3 and Cs_2CO_3 to give the unexpected pentaphenylated product **49** in 58 % yield [1b,15].



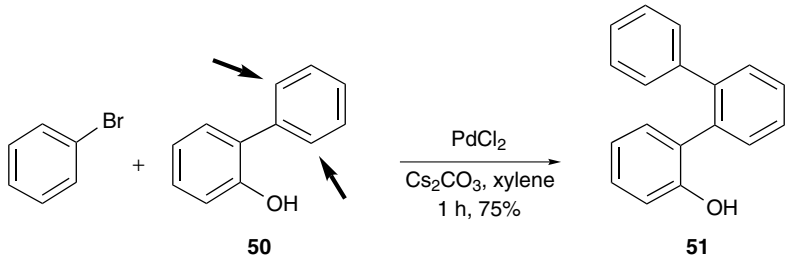


49

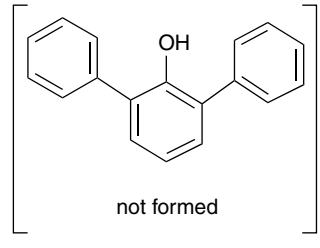
The first product of the interesting pentaphenylation is *o*-phenylphenol (**50**). It was found that *o*-phenylphenol (**50**) undergoes not only monophenylation, but also diphenylation on treatment with iodobenzene at the C-2′ positions to give **51** and **52** by the use of $PdCl_2$ and Cs_2CO_3. The fact that the monoarylated product **51** (25 %) and the diarylated product **52** (62 %) were obtained by the treatment of 2-phenylphenol (**50**) with 4 equivalents of iodobenzene shows that the arylation of benzene ring is faster than the arylation of *ortho* carbon of phenol under these conditions [16]. Similarly, when the reaction of bromobenzene with **50** in xylene was stopped after a short time, 2-(biphenyl-2-yl)phenol (**51**) was obtained in high yield, but 2,6-diphenylphenol was not formed [15].



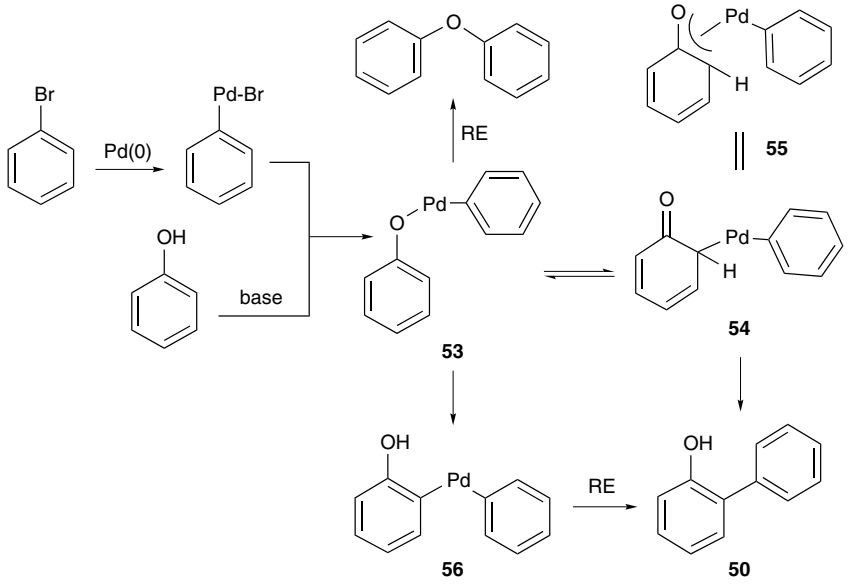
50 **51** 25% **52** 62%



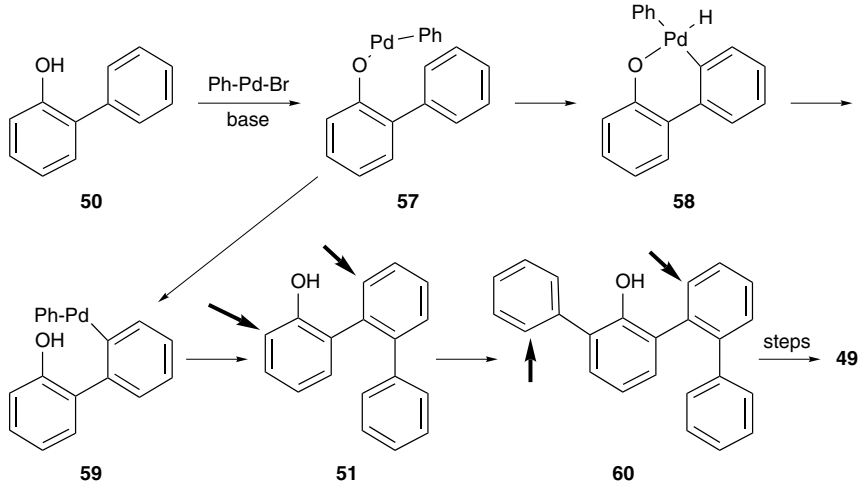
50 **51**



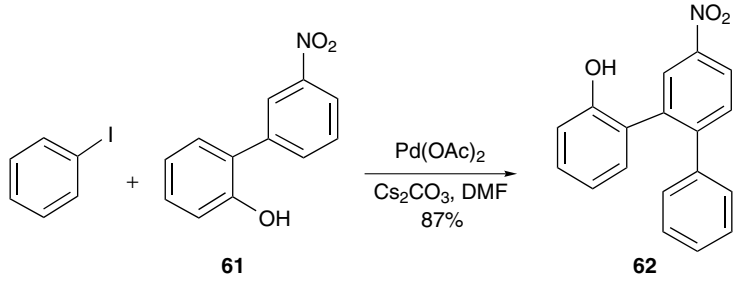
Formation of **50** may be understood in terms of arylation of phenol via the keto form **54** which is stabilized as the oxa-π-allylpalladium **55** as one possibility. This reaction path is similar to arylation of cyclohexanone. Electrophilic attack of **53** at *ortho* carbon to give **56** and reductive elimination are another explanation.



Formation of 2(biphenyl-2-yl)phenol (**51**) from **50** is explained by electrophilic attack of **57** to form **59** and its reductive elimination. As another explanation, oxidative addition of aromatic *ortho* C—H bond to **57** generates the palladacycle **58** and its reductive elimination affords **59**. Domino arylations by a similar sequence of the reactions via **60** finally give rise to the pentaphenylated product **49** in 58 % yield. Certainly the reaction occurs by strong participation of OH group. It is surprising that efficient polyarylation of phenol with bromobenzene proceeds smoothly in the presence of Cs_2CO_3 which is sparingly soluble in xylene and since it is difficult to abstract protons from phenol.

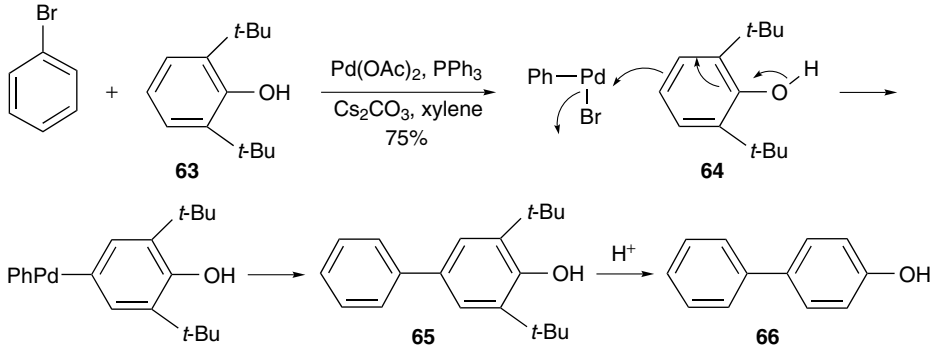


Phenylation of *o*-(2-nitrophenyl)phenol (**61**) with iodobenzene occurred at C-6′ of the electron-deficient nitrobenzene to give **62** in 87 % yield, suggesting that the phenylation is not a simple electrophilic substitution [17].

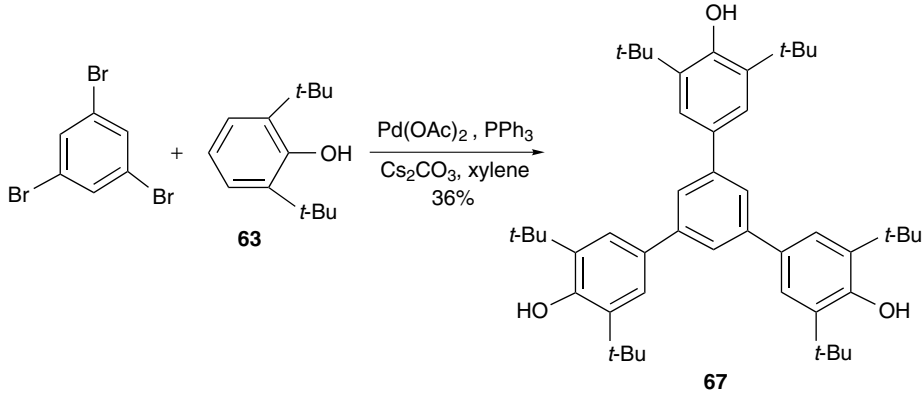


61 **62**

Interestingly 2,6-di-*t*-butylphenol (**63**), which has no possibility of oxa-π-allylpalladium formation, undergoes *p*-phenylation with bromobenzene as shown by **64** to afford **65** when PPh_3 and Cs_2CO_3 are used [18]. The reaction is understandable as electrophilic substitution. Commercially important 4-hydroxybiphenyl (**66**) is produced from **65** by removal of the *t*-butyl groups. Reaction of the phenol **63** with 1,3,5-tribromobenzene afforded the 1,3,5-tri(4-hydroxyphenyl)benzene **67**.

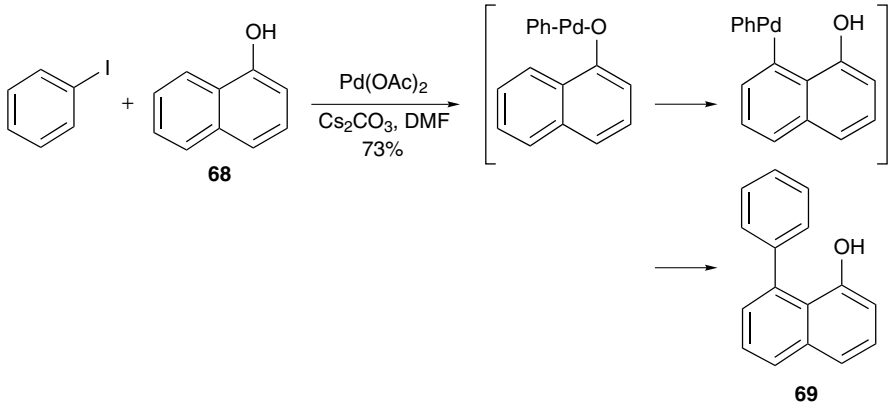


63 **64** **65** **66**

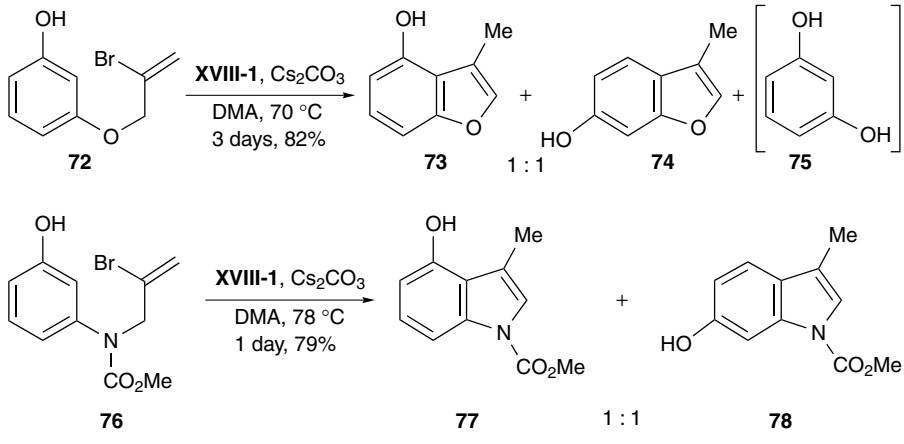


63 **67**

Arylation of 1-naphthol (**68**) with iodobenzene, catalyzed by ligandless $Pd(OAc)_2$, gave 8-phenyl-1-naphthol (**69**). The expected 2-phenylnaphthol was not obtained. Iodobenzene gave better results than bromobenzene. On the other hand, 1-(biphenyl-2-yl)-2-naphthol (**71**) was obtained by the reaction of 2-naphthol (**70**) with bromobenzene by the use of $Pd(OAc)_2$, PPh_3 and Cs_2CO_3 [16,17].

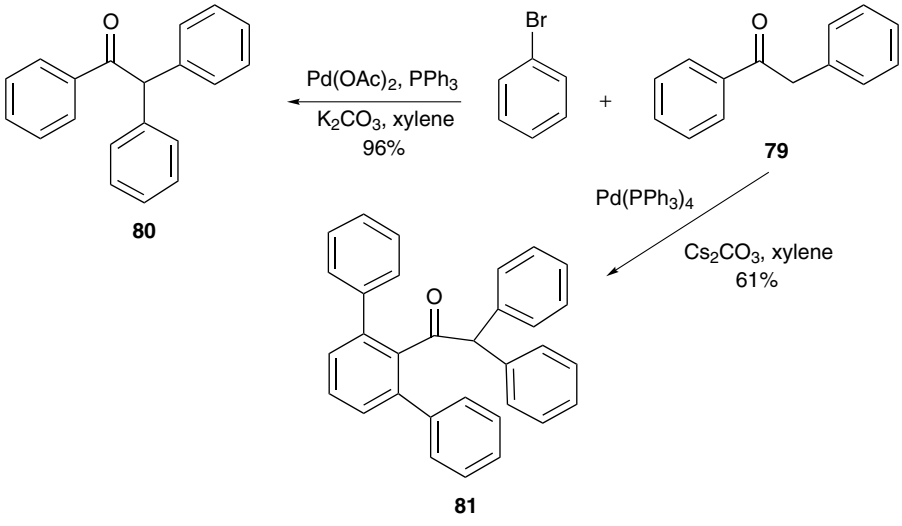


As a related reaction, Rawal carried out intramolecular vinylation of 2-bromoallyl ether of electron-rich resorcinol **72** and obtained the benzofurans **73** and **74** in equal amounts by *ortho* and *para* substitutions when the Herrmann catalyst (**XVIII-1**) was used. Cleavage of the allyl ether to give resorcinol (**75**) is a side reaction, whose amount increases when $Pd(PPh_3)_4$ is used as a catalyst. Similarly the indoles **77** and **78** were synthesized in 1 : 1 ratio from **76** [19].

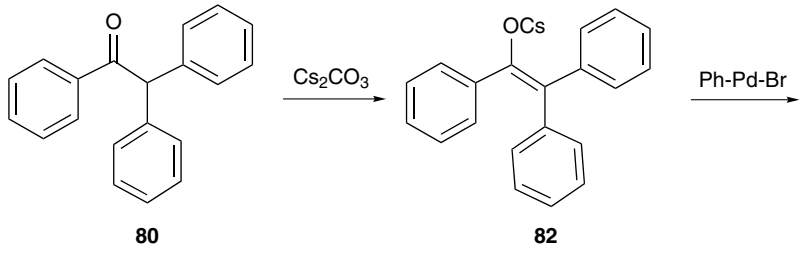


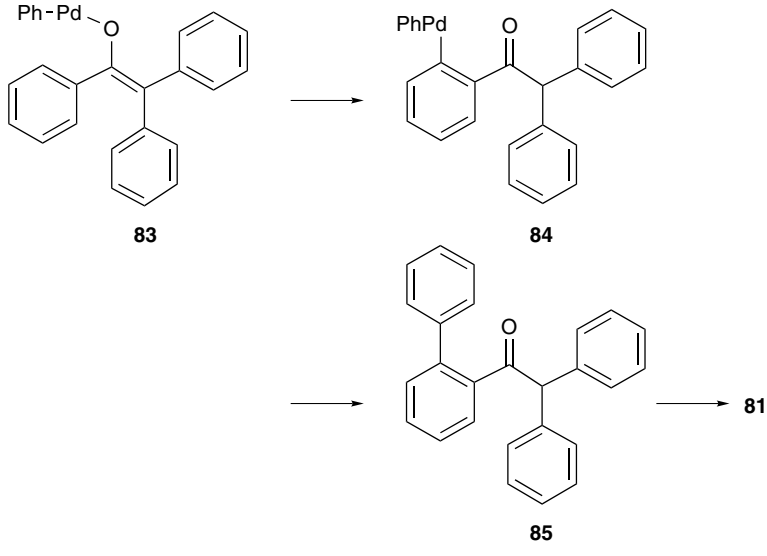
3.3.3 Intermolecular Polyarylation of Ketones

An interesting arylation (aryl–aryl coupling) was discovered by Miura's group during their studies on arylation of ketones as described in Chapter 3.7.1.2 [1b]. An attempted arylation of benzyl phenyl ketone (**79**) with bromobenzene produced the α-monoarylated ketone **80** in high yield when K_2CO_3 was used as a base and $Pd(OAc)_2$-PPh_3 as a catalyst. Unexpectedly they obtained the polyarylated product **81** when Cs_2CO_3 and $Pd(PPh_3)_4$ were used. Different effects of K_2CO_3 and Cs_2CO_3 on the reaction path are noteworthy [20,21]. This interesting polyarylated product **81** was obtained by *ortho–ortho*' diarylation of the phenyl ring of **80**. It is difficult to stop the reaction after α-monoarylation to form **80** when Cs_2CO_3 is used as the base.



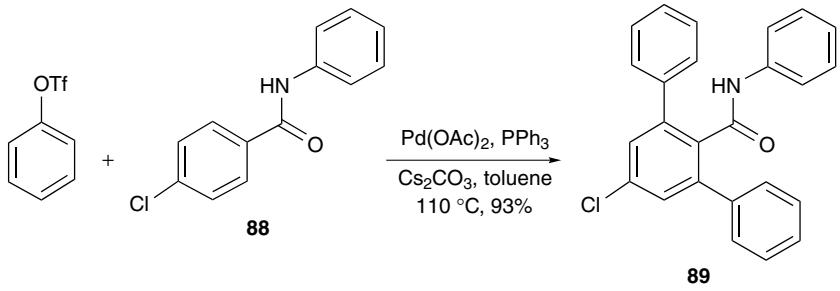
This reaction is explained by the following mechanism. The first step is α-arylation of the ketone to give **80**. Then stepwise mono- and diarylations of both *ortho* carbons in the phenyl ring in **80** take place by neighboring carbonyl group participation. Transmetallation of Cs enolate **82** with Ph-Pd-Br generates the Pd-O-enolate **83**, and the phenyl-Pd-aryl species **84** is generated by electrophilic attack at the *ortho* carbon. Finally reductive elimination affords the diarylated product **85**. The triarylated product **81** is obtained from **85** by a similar sequence of reactions. Anthrone (**86**) was triphenylated at C-1, C-8, and C-10 positions to give **87**. The mechanism of the unexpected hydroxylation at the C-10 position is unknown.





83 **84** **85** **86** **87**

A similar efficient *ortho–ortho* diarylation of the *N*-phenylbenzanilide **88** with phenyl triflate took place to give **89** in 95 % yield in the presence of PPh_3 as a ligand and Cs_2CO_3 as a base. Certainly, participation of the amide carbonyl group plays an important role [22].

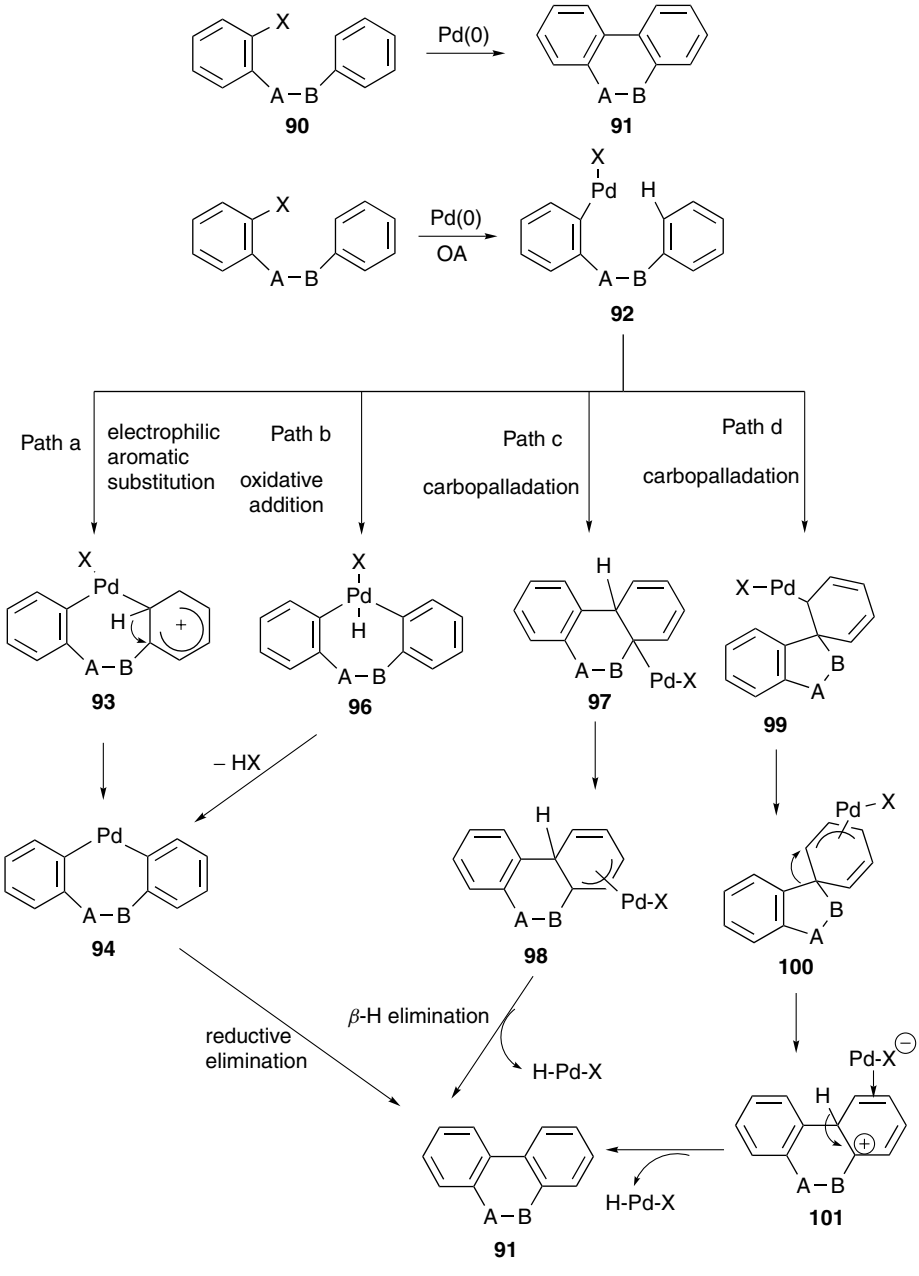


88 **89**

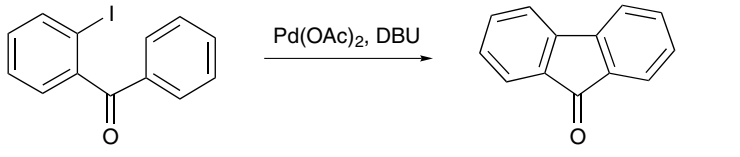
3.3.4 Intramolecular Arylation of Aromatics

Pd-catalyzed intramolecular arylation of some aromatics proceeds smoothly, offering a useful method of aryl–aryl coupling. However, the reaction is not mechanistically simple [1a], and several mechanisms (paths a, b, c, and d) for the arylation

of aromatics **90** to give **91** are possible. Intramolecular electrophilic substitution via **93** generates the palladacycle **94** and its reductive elimination affords **91**. This mechanism is applicable to arylation of electron-rich aromatics (path a). Oxidative addition of an *ortho* C—H bond in **92** affords the Pd(IV) species **96**, which is converted to **94** (path b). Similar to a Heck-type reaction, carbopalladation of **92** to give **97** and the π-allylpalladium **98** is another possibility. After stereoisomerization via the π-allylpalladium intermediate **98**, *syn* β-H elimination affords **91** (path c). Carbopalladation to form the spiro ring **99** and rearrangement as shown by **100** gives **101**, and subsequent *syn* β-H elimination yields **91** (path d).



The Pd-catalyzed intramolecular coupling of aryl halides or triflates with aromatic rings to give biaryl compounds offers useful synthetic methods. Intramolecular arylation of benzene derivatives was reported first by Ames. Cyclization of **102**, catalyzed by $Pd(OAc)_2$ in the presence of DBU, is an example [23]. Pyrimido[4,5-*b*]indole was prepared by intramolecular arylation of 4-anilino-5-iodopyrimidine **103** in 86 % yield in the presence of $Pd(OAc)_2$, PPh_3 and AcONa in DMF [24]. Cyclization of the monobrominated diarylpyrazole **104** afforded pyrazolo[1,5-*f*]phenanthridine in 65 % yield in the presence of phosphine-free $Pd(OAc)_2$, Bu_4NBr, LiCl and K_2CO_3 in DMF at 110 °C [25].



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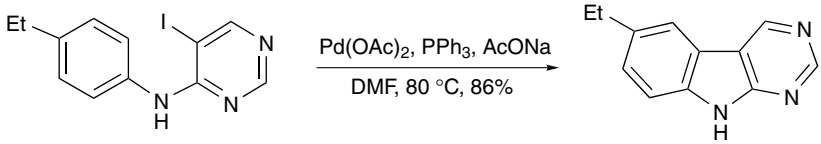

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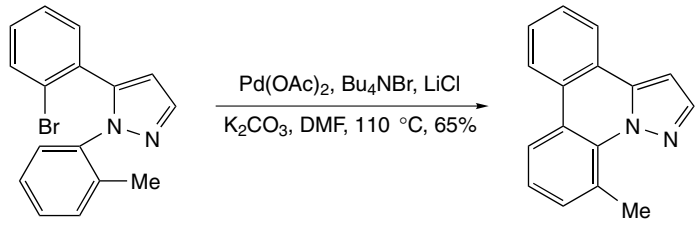
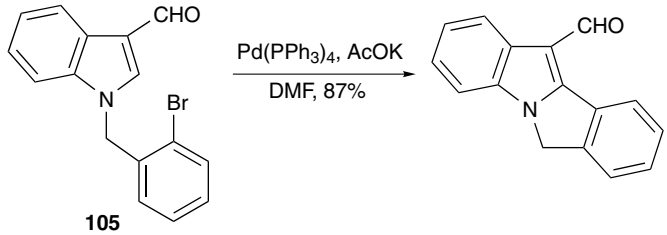


104

In intramolecular arylation of the indole **105**, the C-2 arylation product of the pyrrole ring was obtained preferentially without attacking the benzene ring. On the other hand, when the C-2 position is blocked, arylation of **106** occurs in the benzene ring to give **107**, showing that pyrrole is more reactive than benzene [26].



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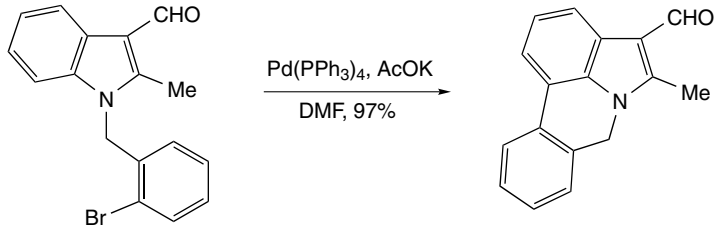
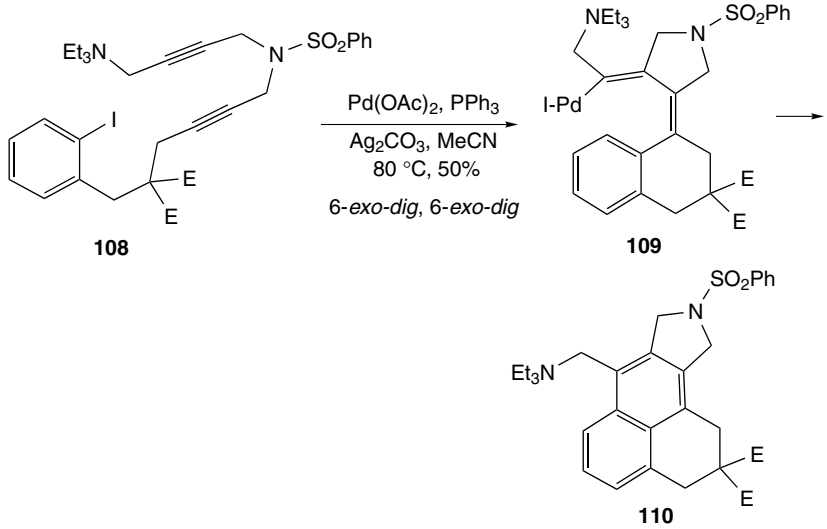


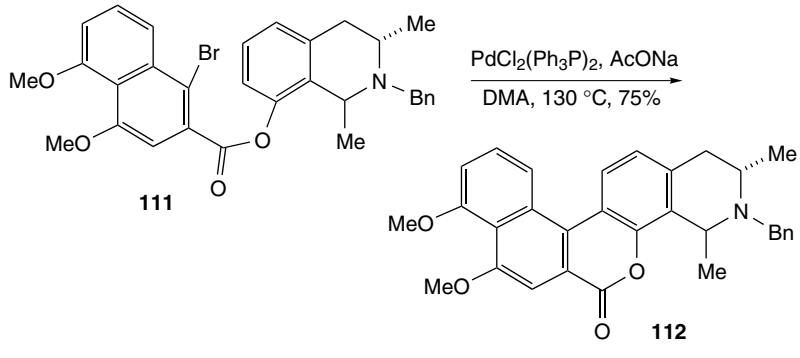
106 **107**

The alkenylpalladium **109** formed as an intermediate of two domino 6-*exo-dig* cyclizations of **108** undergoes vinylation to the benzene ring to give the naphthalene ring **110**. This type of reaction is observed frequently as a termination step of domino cyclization of polyenynes [27].

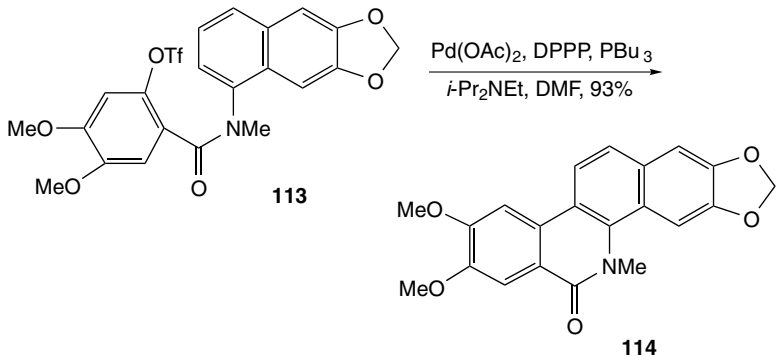


108 **109** **110**

A number of synthetic applications have been published. The synthesis of the naphthylisoquinoline alkaloid **112** from **111** is an early example [28]. The reaction has been applied to the synthesis of gilvocarcin M [29,30]. A recent example is the synthesis of benzo[*c*]phenanthridine alkaloids **114** by cyclization of the triflate **113**. High yields were obtained by combined use of DPPP and *n*-Bu_3P [31].

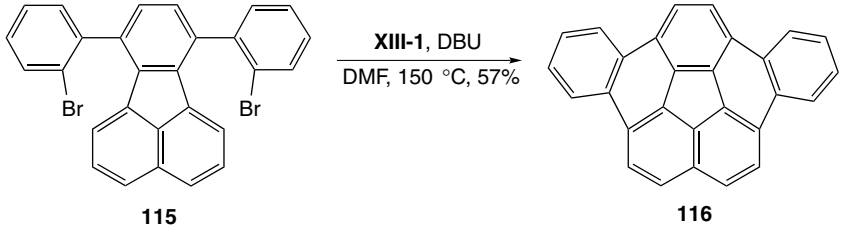


111 **112**

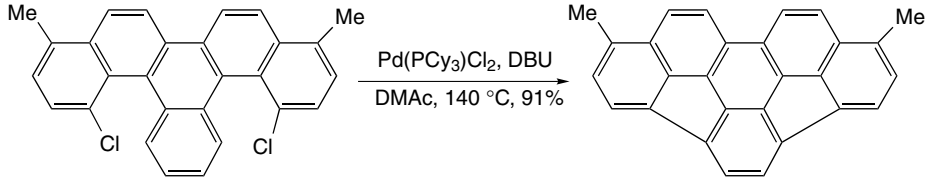


113 **114**

Dibenzo[*a*, *g*]corannulene (**116**), a fullerene fragment, was obtained by cyclization of 7,10-di(2-bromophenyl)fluoranthene (**115**). A Herrmann palladacycle (**XVIII-1**) as a catalyst and excess DBU as a base were used under rather severe conditions (150 °C, 72 h) [32]. Also the *as*-indaceneo[3.2.1.8.7.6-pqrstuv]picene derivative **118** was prepared from the dichloride **117** in 91 % yield. PCy_3 and DBU were used for activation of the less reactive dichloride **117** [33].

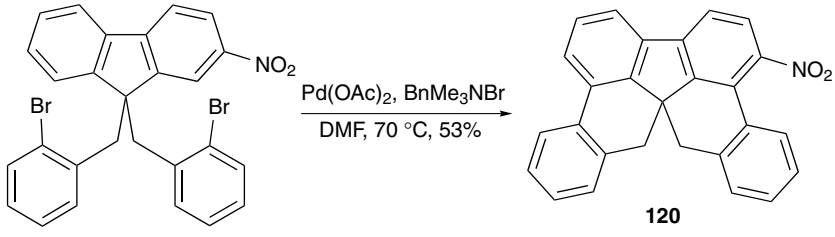


115 **116**



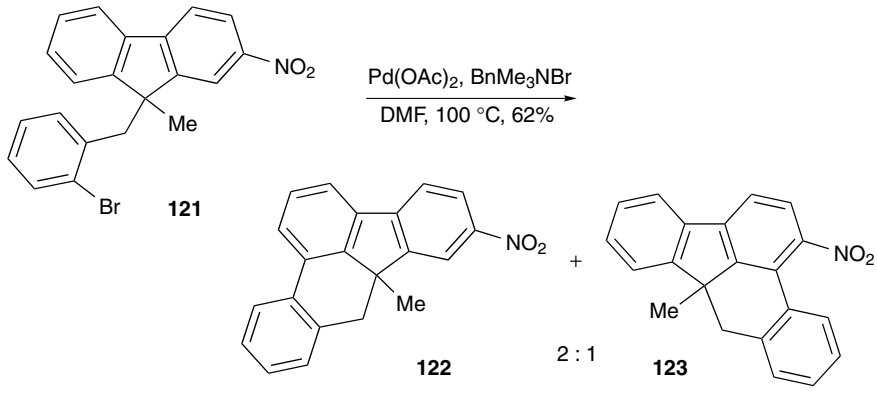
117 **118**

The spiro-polycyclic aromatic compound **120** was prepared from the nitro dibromide **119** under ligandless Jeffery conditions. In addition, reaction of the nitro monobromide **121** under similar conditions afforded **122** and **123** in a ratio of

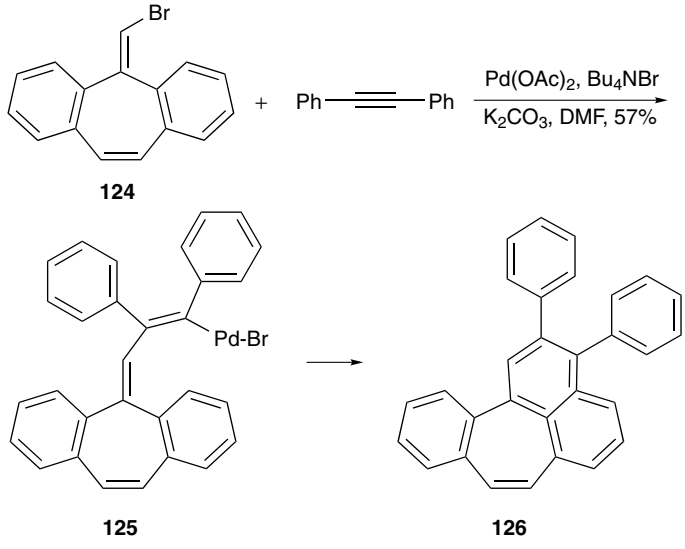


119 **120**

2 : 1. The fact that the arylation occurs on the deactivated nitro group-bearing benzene rings in **119** and **121** indicates that the reaction is not a simple electrophilic substitution [34].

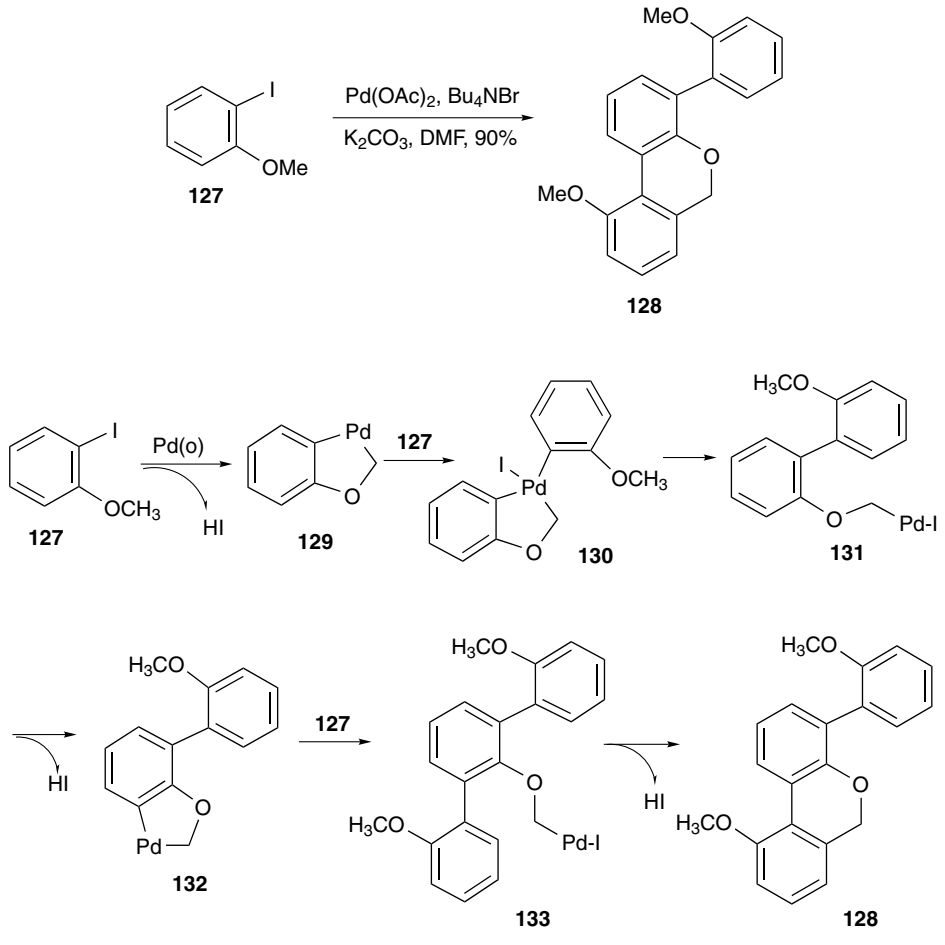


Reaction of the alkenyl bromide **124** with diphenylacetylene generates the alkenylpalladium intermediate **125**, which undergoes intramolecular alkenylation to give **126** by using a ligandless catalyst [35].

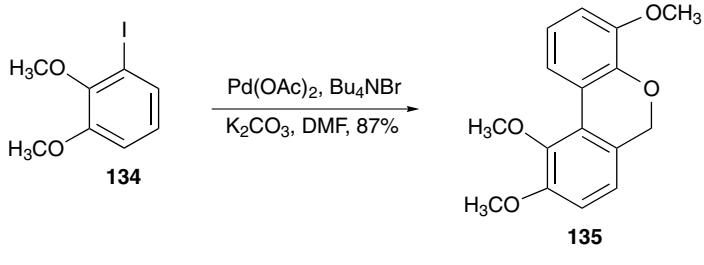


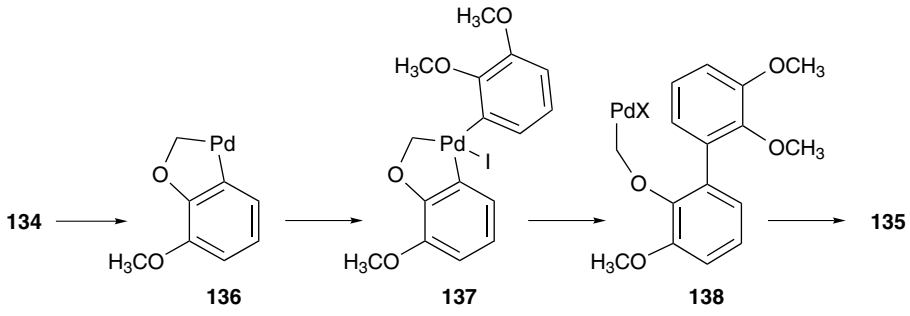
Dyker has developed novel domino reactions, which involve facile formation of palladacycles. He reported very interesting domino reactions of three molecules of 2-iodoanisole (**127**) to give the 6H-dibenzo[*b*, *d*]pyran **128** in high yield (90 %) after several steps in one pot under ligandless Jeffery conditions [36]. The key step of the reaction is the formation of the five-membered palladacycles **129** and **132** by *ortho*-palladation (cyclopalladation) involving sp^3 C—H activation of the methoxy group. The oxidative addition of **127** to the palladacycle **129** generates **130**, and its reductive elimination gives the arylated product **131**. Then the palladacycle **132** is formed from **131**. A similar sequence of reactions from **132** via **133** yields

128. It is important to mention that no reductive elimination of the five-membered palladacycle **129** to form four-membered ether occurs. Instead, oxidative addition of **127** to **129** takes place to form **130**.

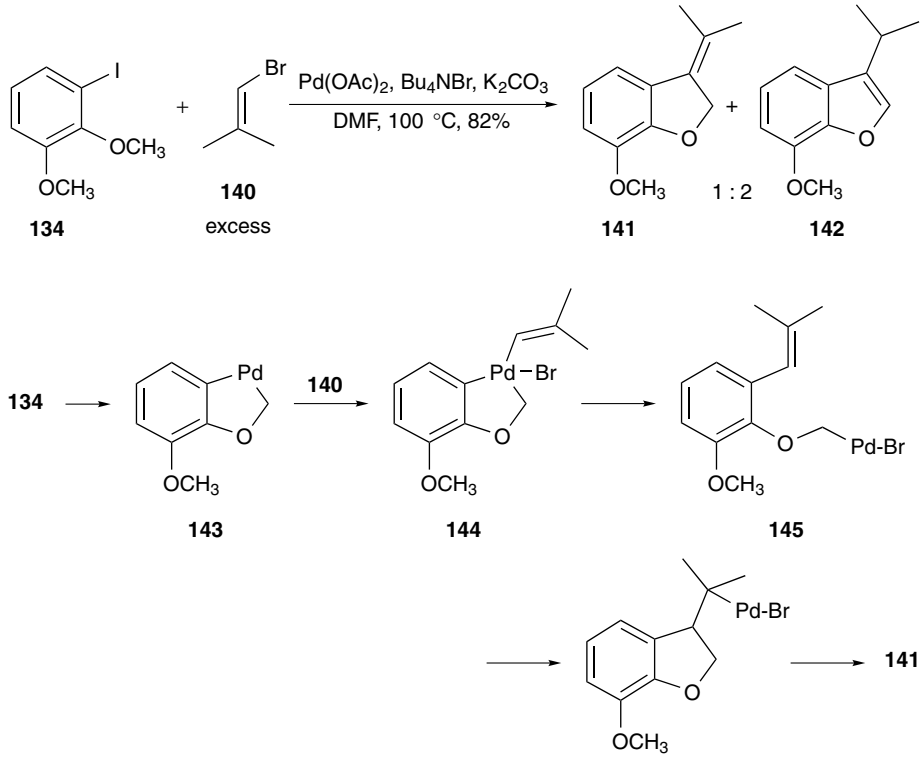


Domino reactions of two molecules of 1-iodo-2,3-dimethoxybenzene (**134**), in which the position for the second cyclopalladation is blocked, gave **135**. The reaction proceeds via formation of the palladacycle **136**. Oxidative addition of **134** to **136** generates **137**. Reductive elimination of **137** gives **138**. Then cyclopalladation of **138** and reductive elimination afford the ether ring **135**.



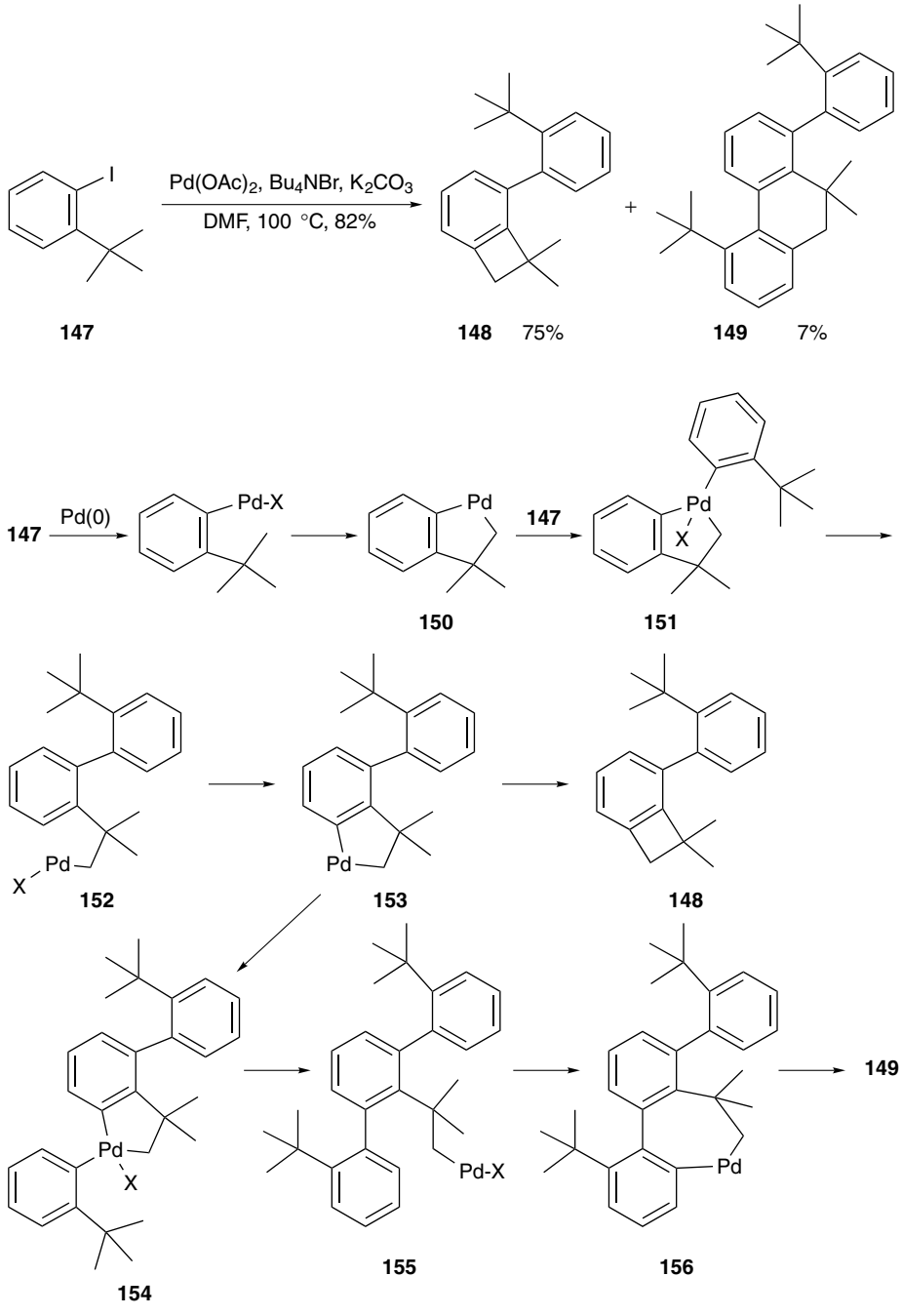


Intermolecular reaction of 1-iodo-2,3-dimethoxybenzene (**134**) with the vinyl bromide **140** (10 equiv.) gave a mixture of **141** and **142** [37]. In this reaction, oxidative addition of **140** to the palladacycle **143** generates **144**, and the coupled product **145** is formed by reductive elimination. Finally 5-*exo* cyclization of **145** and β-H elimination afford **141**.



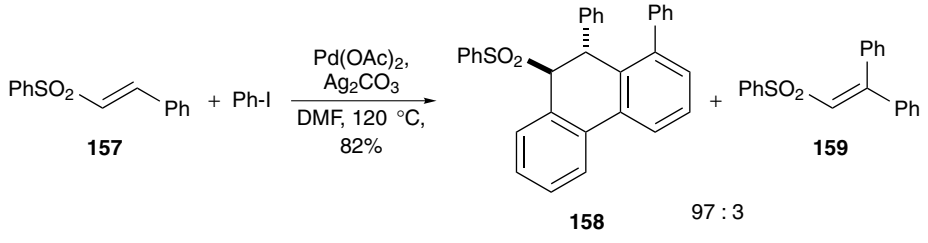
Furthermore, Dyker reported the Pd-catalyzed reaction of 2-*t*-butyliodobenzene (**147**) gave the benzocyclobutane **148** and the trimer **149** [38]. Key steps are facile formation of the palladacycles **150**, **153**, and **156** by C—H activation of the methyl group. Oxidative addition of **147** to the five-membered palladacycle **150** to generate **151** and reductive elimination gives **152**. In this case, the palladacycle **153** undergoes very unusual reductive elimination to give the strained benzocyclobutane **148** in 75 % yield. Further reaction of **153** via **154** and **155** yields again the

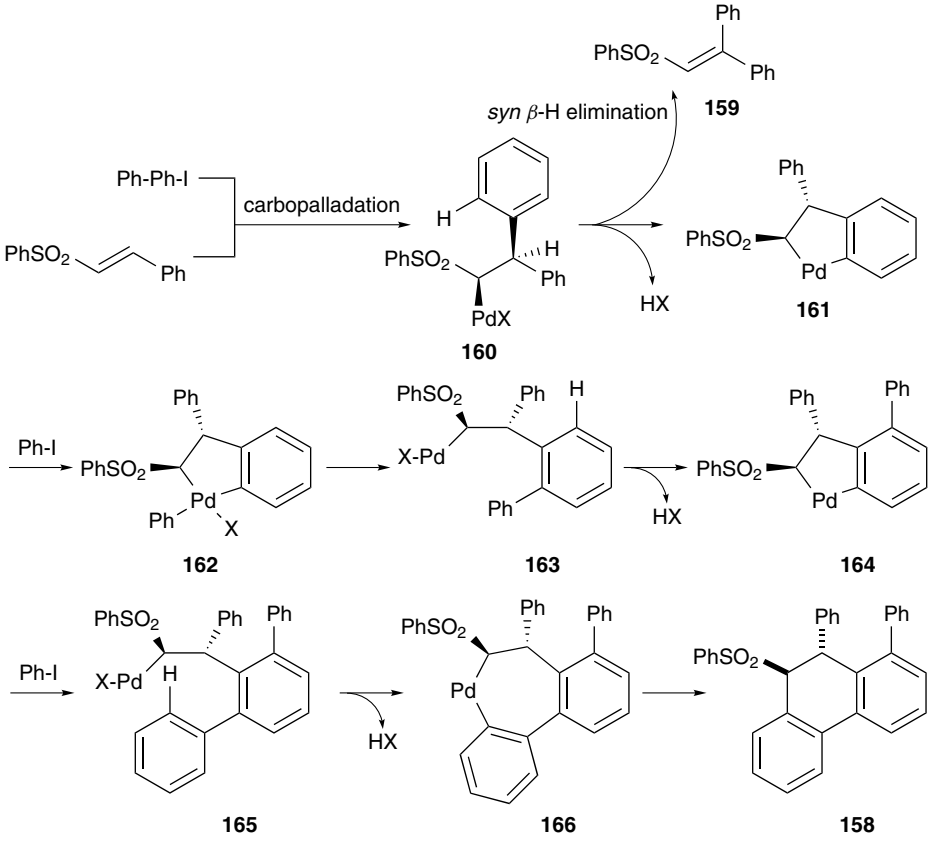
unusual seven-membered palladacycle **156**. The cyclohexane **149** is obtained by its reductive elimination, although yield was low (7 %).



Unexpected annulation occurred in an attempted Heck reaction of the α,β-unsaturated sulfone **157** with an excess of iodobenzene to give **158** in high yield. The use of Ag_2CO_3 as a base is important [39]. The expected Heck product **159**

was a minor one under the conditions. The reaction is explained by the following mechanism. Formation of the Heck product **159** by carbopalladation to generate **160**, followed by β-H elimination is understandable. However, formation of the palladacycle **161** from **160** occurs as the main path. Oxidative addition of Ph—I to **161** affords **162**, and its reductive elimination gives the *o*-phenylated product **163**. Similar sequences via **164** and **165** yield the palladacycle **166**, and **158** is obtained by reductive elimination.





It seems likely that facile formation of palladacycles as intermediates will play an important role in developing new Pd-catalyzed reactions of aromatic compounds.

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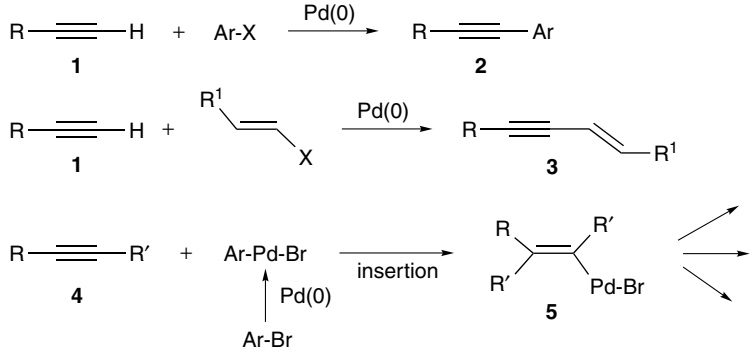
3.4 Reactions with Alkynes

3.4.1 Introduction

Pd-catalyzed coupling reactions of terminal and internal alkynes **1** and **4** with halides are surveyed in this section. Reactions of alkynes with aryl and alkenyl halides are classified in to two types. The first one is the preparation of arylalkynes **2** and alkenylalkynes (1,3-enynes) **3** by the reactions of terminal alkynes **1** with aryl and alkenyl halides in the presence of Pd(0) and CuI as catalysts (section 3.4.2). The second one is insertion of internal alkynes **4** to aryl- and alkenylpalladium bonds formed by oxidative addition of halides, generating alkenylpalladiums **5**, which are living species and undergo further transformations before termination. Terminal alkynes also undergo the insertion in the absence of CuI catalyst (section 3.4.3)

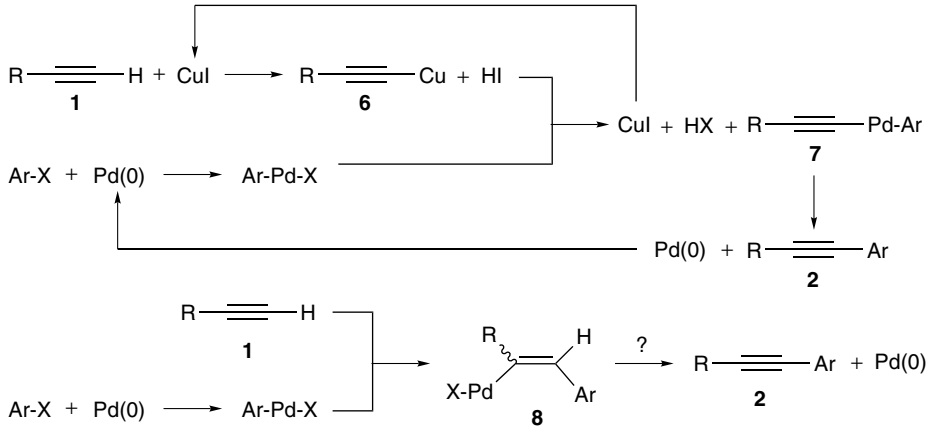


3.4.2 Reactions of Terminal Alkynes to Form Aryl- and Alkenylalkynes (Sonogashira Coupling)

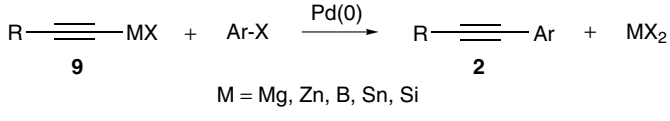
Direct introduction of sp^2 carbon to alkynes by the reaction of Cu acetylides with aryl and alkenyl halides to form arylalkynes and alkenylalkynes is known as the Castro reaction [1]. Later it was found that coupling of terminal alkynes (1-alkynes) with halides proceeds more smoothly by using Pd catalysts. There are two methods of Pd-catalyzed coupling. In 1975 direct coupling of 1-alkynes catalyzed by a phosphine-Pd(0) complex in the presence of amines was reported by Heck and Cassar as an extension of the Heck reaction to 1-alkynes [2,3]. In the same year, Sonogashira and Hagihara found that the addition of CuI as a co-catalyst gave better results, and the Pd(0)-CuI-catalyzed reaction is called the

Sonogashira reaction [4,5]. A comprehensive review on Pd-catalyzed alkynylation was published recently by Negishi and Anastasia [6]. Facile Pd(0)-CuI-catalyzed coupling of aryl and alkenyl halides with 1-alkynes is used extensively for the preparation of arylalkynes or enynes.

The reaction is explained by the following mechanism. At first, CuI activates 1-alkynes **1** by forming the Cu acetylides **6**, which undergo transmetallation with arylpalladium halides to form the alkynylarylpalladium species **7**, and reductive elimination to give **2** is the final step. However, the coupling proceeds even in the absence of CuI under certain conditions, and it may be possible to form the alkynylarylpalladium species **7** directly from 1-alkynes. As another less likely possibility, carbopalladation of a triple bond with Ar-Pd-X (or insertion of the triple bond to Ar-Pd-X) generates the alkenylpalladium **8** which undergoes dehydropalladation to afford disubstituted alkynes **2**. In this mechanism, CuI plays no role. The mechanism of β-H elimination of alkenylpalladium to form alkynes is not clearly known.

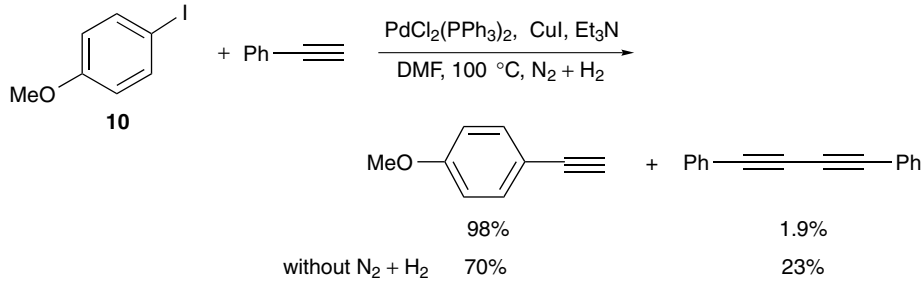


Coupling catalyzed by Pd(0) and CuI proceeds via *in situ* generation of Cu acetylides **6**. Later acetylides of main group metals such as Mg, Zn, Sn, and B have been found to be good partners of the coupling. This is the second preparative method of arylalkynes. Coupling of metal acetylides **9** of 1-alkynes with halides proceeds without CuI. In an exact sense, Pd-catalyzed couplings of metal acetylides with halides are different from the Sonogashira reaction. Coupling of Zn acetylides is regarded as a Negishi reaction, and that of Sn acetylides may be called a Kosugi–Migita–Stille reaction. These couplings with metal acetylides are treated in this section for the sake of convenience, rather than in section 3.6, because the same products are obtained by this method and the Sonogashira reaction.

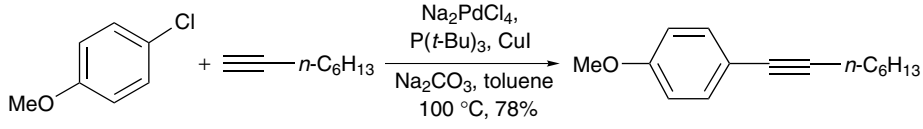


3.4.2.1 Aryl–Alkynyl Coupling (Sonogashira Reaction): Reaction Conditions and Catalysts

Various results are obtained in Sonogashira coupling depending on the substrates used and the reaction conditions. Homocoupling and decomposition of alkynes are serious competitive reactions, and poor results are obtained sometimes due to these side reactions in the Sonogashira reaction particularly when less reactive electron-rich aryl halides are used. It is well known that CuI catalyzes oxidative homocoupling of 1-alkynes in O_2 atmosphere (Glaser reaction). Also Pd(II) promotes the homocoupling. Therefore the reaction should be carried out with strict exclusion of O_2. Homocoupling in the Sonogashira reaction can be decreased by slow addition of alkynes in THF [7] and use of phase-transfer agent (n-Bu_4NI) in H_2O–toluene [8]. Ho *et al*. reported that the homocoupling of phenylacetylene with 4-iodoanisole (**10**) can be reduced drastically by carrying out the reaction in an atmosphere of H_2 diluted with N_2 or argon [9].

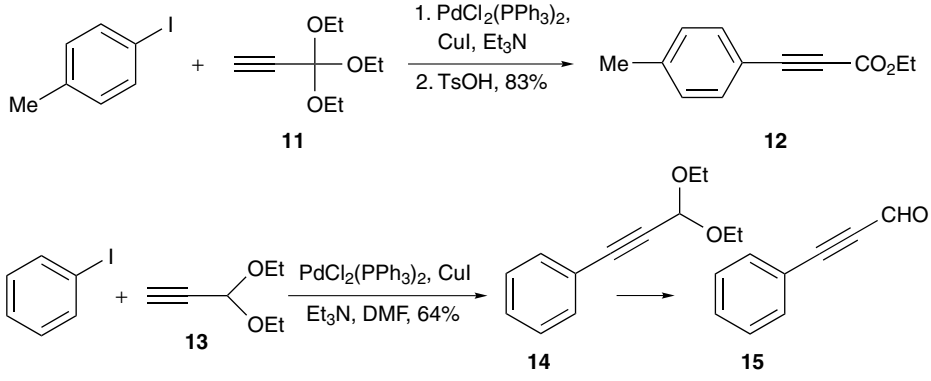


Phenylacetylene is an exceptionally reactive alkyne, and it is true that coupling of some electron-rich aryl halides proceeds smoothly only with phenylacetylene. In many papers, the coupling of phenylacetylene alone is reported. Good results are not always obtained in reactions of other alkynes with electron-rich aryl halides under similar conditions. Aryl iodides, bromides, and triflates are used for the coupling. Curiously, it is generally believed that Sonogashira coupling of aryl chlorides is difficult, and only a few reports on Sonogashira coupling of activated chlorides have been published. Plenio found a versatile catalyst for the Sonogashira coupling of various aryl chlorides. As a ligand, bulky and electron-rich P(t-Bu)$_3$ or (1-Ad)$_2$P(n-Bu) is the most effective. Na_2PdCl_4/PR_3/CuI was found to be a precursor of the efficient catalyst system, and the coupling proceeds in toluene or DMSO at 100 °C [10].

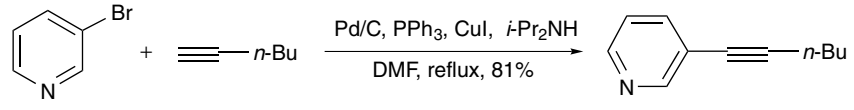


Alkynes with EWGs such as propiolate are poor substrates for the coupling with halides. Therefore, instead of inactive propiolate, triethyl orthopropiolate (**11**) is used for the coupling with aryl halides to prepare the arylpropiolate **12**. The

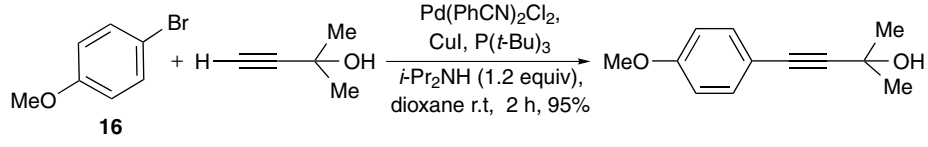
coupling product **14** obtained from 3,3-diethoxy-1-propyne (**13**) and aryl halides is a precursor of the arylalkynal **15** [11].



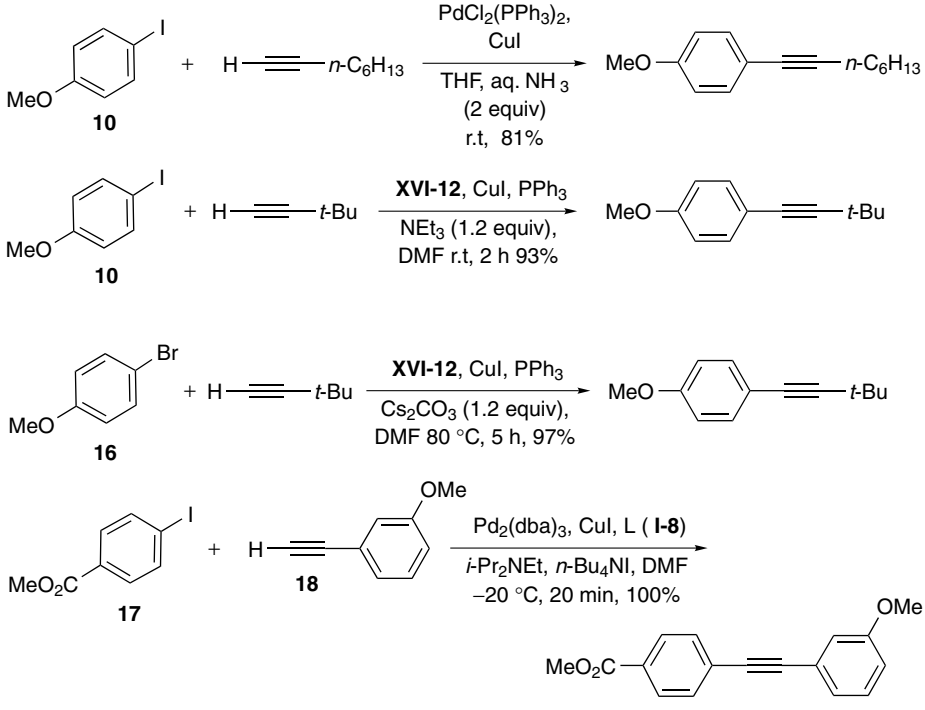
The Sonogashira reaction is usually carried out at about 80 °C. $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ are used in the presence of excess amine in most cases. It should be added that these Pd compounds as precursors do not always show the same behavior and sometimes show different activity. At this temperature, decomposition of some labile alkynes tends to occur. Therefore, the reaction should be carried out under milder conditions as far as possible to prevent the side reaction. Pd on charcoal acts as an efficient catalyst for the coupling of aryl bromides such as 3-bromopyridine in the presence of CuI, PPh_3, and i-Pr_2NH in DMA–H_2O [12].



Thorand and Krause claimed that THF is a very good solvent [7], but Ho *et al*. reported that THF is a poor solvent in their reaction [9]. One drawback of the Sonogashira reaction is the use of a large excess of amines almost as a solvent. Buchwald and Fu *et al*. reported that coupling of inactivated 4-bromoanisole (**16**) can be carried out at room temperature by using $Pd(PhCN)_2Cl_2$ as a catalyst, P(t-Bu)$_3$ as a ligand, and only 1.2 equivalents of diisopropylamine. Poor results are obtained when PPh_3, PCy_3, P(o-Tol)$_3$ and DPPF are used instead of P(t-Bu)$_3$ under similar conditions [13].

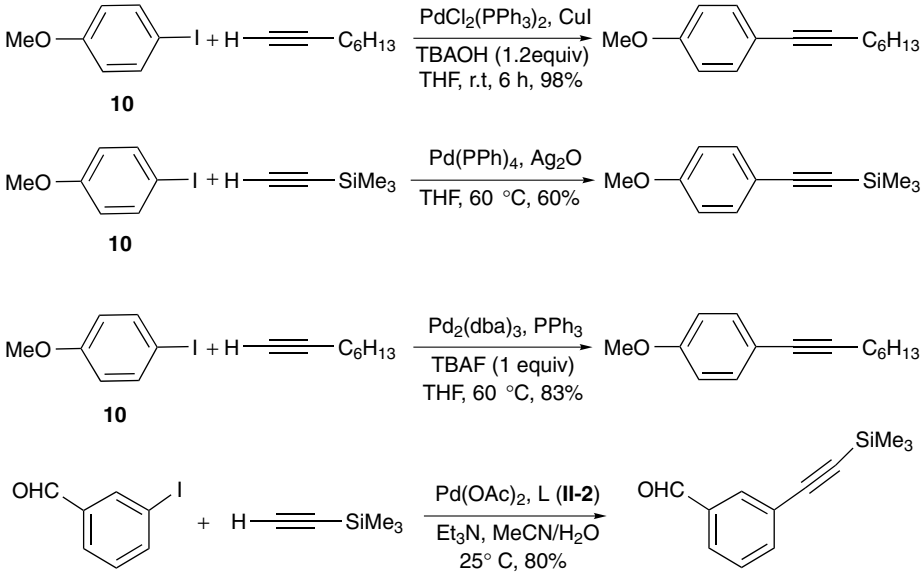


Beletskaya *et al*. reported that the reaction of arylalkynes proceeds smoothly at room temperature in water using only 10 mol% of Bu_3N and excess K_2CO_3. $PdCl_2(PPh_3)_2$ and CuI are catalysts [14]. Mori and co-workers discovered a convenient and useful procedure for Sonogashira coupling. They found that the coupling of aryl iodides such as electron-rich *p*-iodoanisole (**10**) can be carried out smoothly at room temperature using only 2 equivalents of aq. NH_3 (0.5 M) in THF [15]. Room temperature coupling of aryl iodides **10** is possible in the presence of carbamoyl-substituted N-heterocyclic carbene complex (**XVI-12**) with the coexistence of PPh_3 (1 mol%) and Et_3N (1.2 equiv.) in DMF. Reaction of electron-rich aryl bromide **16** proceeds at 80 °C with the same catalyst and Cs_2CO_3 as the best base [16]. Reaction of the reactive aromatic alkyne **18** with the reactive electron-deficient aryl iodide **17** proceeds even at −20 °C in a quantitative yield. Tri(2,4,6-trimethylphenyl)phosphine (**I-8**) was used as a ligand [17].

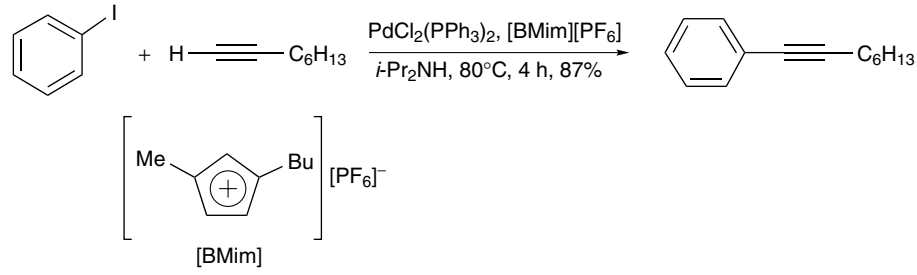


Room temperature reaction of *p*-iodoanisole (**10**) also takes place in the presence of Bu_4NF (TBAF) or hydroxide (TBAOH) without addition of other amines. $PdCl_2(PPh_3)_2$ and CuI are catalysts [18]. Ag_2O, instead of CuI, can be used for the coupling at 60 °C [19]. Furthermore, the coupling proceeds without CuI or Ag_2O in the presence of a stoichiometric amount of TBAF [20]. Sonogashira reaction proceeds in aqueous media ($MeCN/H_2O$) at room temperature by the use of the water-soluble sulfonated phosphine ligand **II-2** without CuI [21]. Also coupling of triple bonds in peptides with aryl iodides was carried out in water in the presence

of **II-2** as a ligand [22]. Synthesis of the 65-membered cyclic peptide containing triple bonds was achieved via 'on resin' Sonogashira coupling [23].

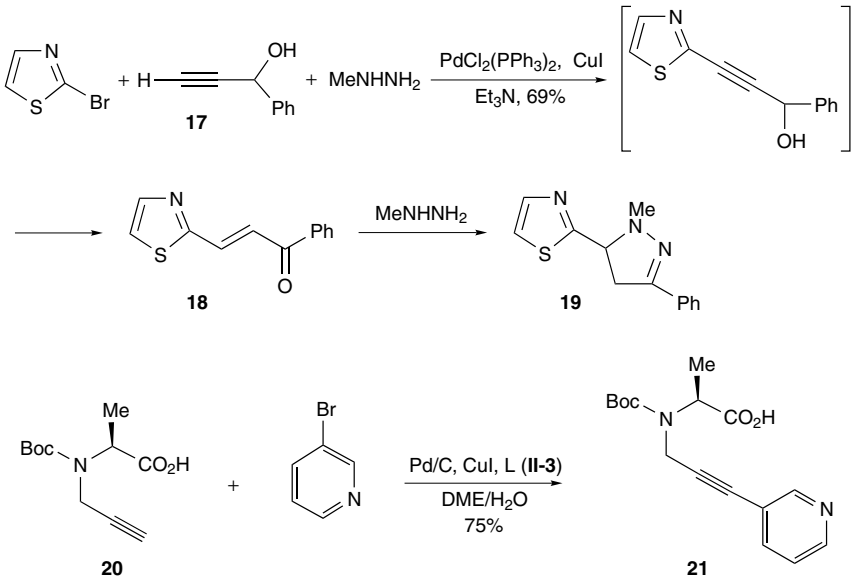


The coupling proceeds in an ionic liquid BMim (1-butyl-3-methylimidazolium hexafluorophosphate) in the absence of CuI. In this medium, the facile separation and recycling of the catalyst are possible [24].



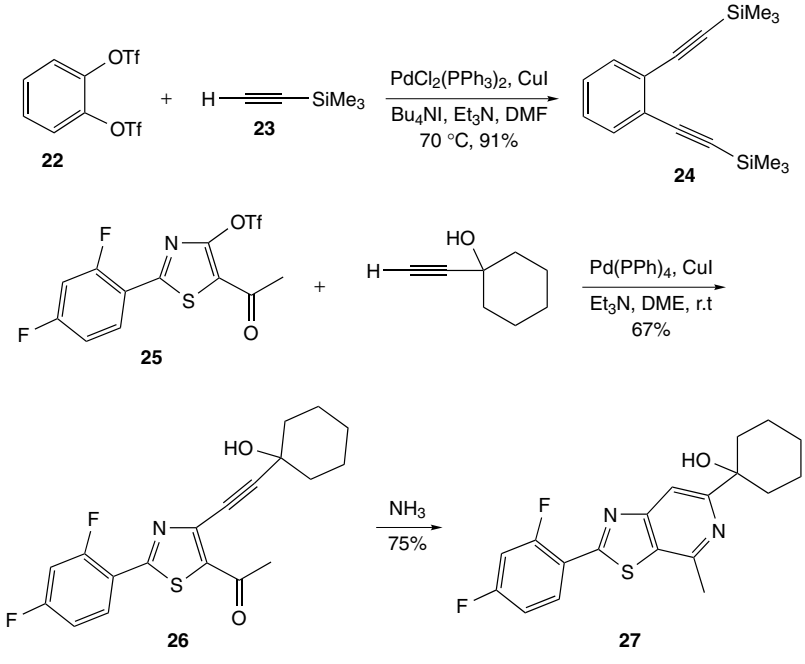
Isomerization of the coupling products of 1-arylpropargyl alcohols with electron-deficient halides generate α,β-unsaturated aryl ketones, which undergo further condensation to afford heterocycles such as pyrroles and pyrimidines [25]. For example, domino coupling–isomerization–condensation reactions of 1-phenylpropargyl alcohol (**17**), 2-bromothiazole, and methylhydrazine generated the enone **18**, and the pyrazoline **19** was obtained by the reaction of methylhydrazine [25].

Pd on carbon and CuI, combined with phosphine ligands, are used as good catalysts in some cases. The coupling of *N*-propargylamino acid **20** with 3-bromopyridine proceeded in an aqueous phase to give **21**. Pd on carbon and water-soluble diphenylphosphinobenzoic acid (**II-3**) were used [26].

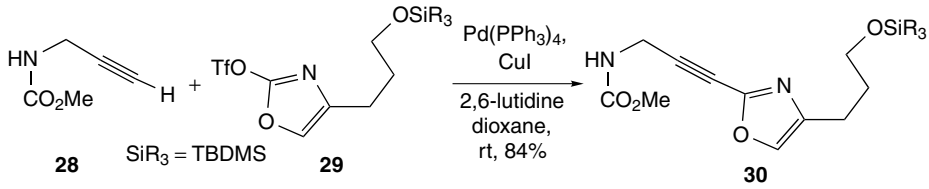


17 **18** **19** **20** **21**

Aryl and alkenyl triflates are reactive partners. Coupling of ditriflate of catechol (**22**) with the alkyne **23** gave the 1,2-dialkynylbenzene **24** in good yield in the presence of *n*-Bu_4NI (300 mol %) [27]. Functionalization of some heterocycles is possible by the reaction of their triflates. Coupling of the 5-acetyl-4-thiazolyl triflate **25** proceeded at room temperature in the presence of $Pd(PPh_3)_4$ and CuI, and the product **26** was converted to the pyrido[3.4-*c*]thiazole **27** by treatment with ammonia [28]. The triflate **29** was prepared from the corresponding oxazolone, and its Sonogashira reaction with methyl *N*-propargylcarbamate (**28**) afforded the 2-alkynyloxazole **30** in 84 % yield [29].

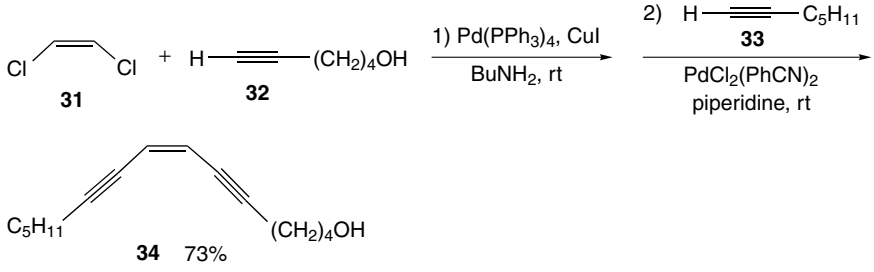


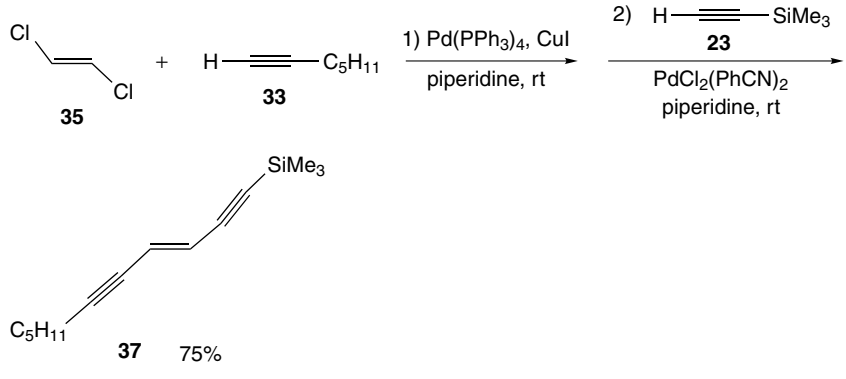
22 **23** **24** **25** **26** **27**



3.4.2.2 Alkenyl–Alkynyl Coupling (Sonogashira Reaction)

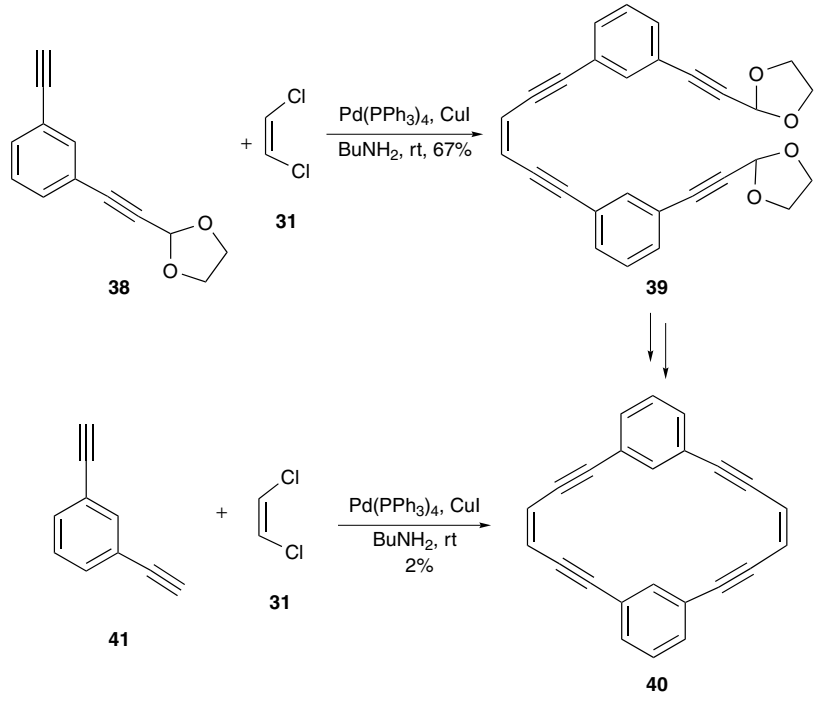
Aryl iodides, bromides, and triflates are used for Sonogashira coupling. But so far few smooth reactions of aryl chlorides with alkynes have been reported. On the other hand, smooth coupling takes place with alkenyl chlorides. The Pd-catalyzed reaction of 1-alkynes with alkenyl chlorides, which are inert in many other Pd-catalyzed reactions, proceeds smoothly without special activation of the chlorides. For example, *cis*-1,2-dichloroethylene (**31**) can be coupled with 1-alkynes smoothly, and the coupling has wide synthetic applications, particularly for the synthesis of enediyne structures [30]. The reaction of **31** with two different 1-alkynes is extensively used for construction of highly strained enediyne structures present in naturally occurring anticancer antibiotics such as espermicin and calichemicin [31,32]. The asymmetric (*Z*)-enediyne **34** can be prepared by a one-pot reaction of **31** with two different 1-alkynes **32** and **33**. Similarly the asymmetric (*E*)-enediyne **37** was obtained in a one-pot reaction of 1-alkynes **33** and **23** with *trans*-1,2-dichloroethylene **35**.



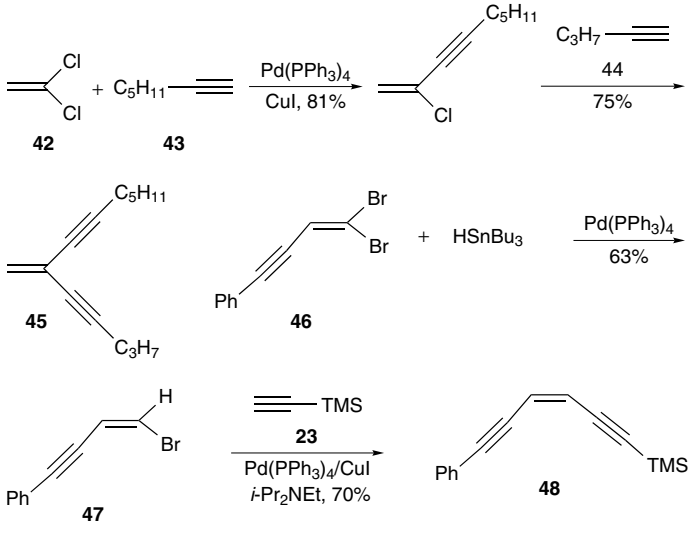


The novel [6.6]metacyclophane **40** was prepared by coupling **31** with 1-alkynes as a key reaction. The shortest way to **40** is the coupling of *m*-diethynylbenzene (**41**)

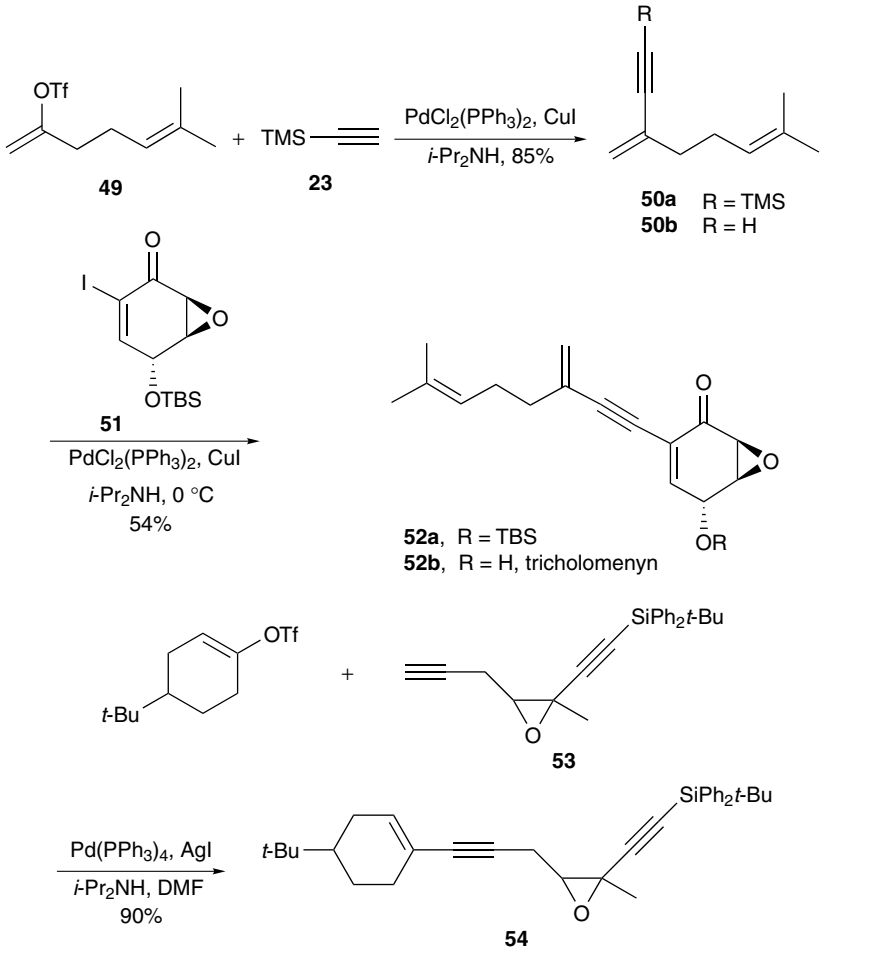
with **31**. The yield of the attempted reaction was only 2 %. Then **39** was prepared in 67 % yield by coupling **38** with **31**, from which **40** was obtained by Ti-mediated intramolecular coupling of aldehydes [33].



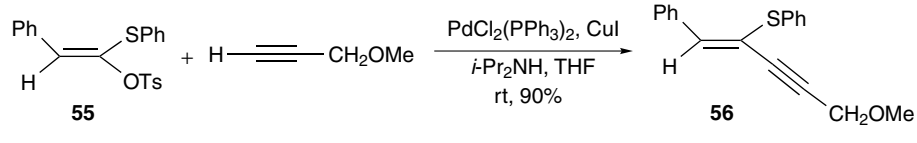
Both chlorines of 1,1-dichloroethylene (**42**) react stepwise with different 1-alkynes **43** and **44** to form the asymmetric enediyne **45** [34]. The enediyne system **48** was prepared by Pd-catalyzed stereoselective hydrogenolysis of the 1,1-dibromo-1-alkene **46** with tin hydride to give **47**, followed by coupling with 1-alkyne **23** in a one-pot reaction [35].



Alkenyl triflates are reactive partners. In the total synthesis of (−)-tricholomenyn (**52b**), coupling of the vinyl triflate **49** with **23** gave the enyne **50a**, and reaction of the vinyl iodide **51** with the deprotected 1-alkyne **50b** afforded **52a**. Combined use of $PdCl_2(PPh_3)_2$, CuI, and *i*-Pr_2NH gave the best results in this case. The reaction in THF and di-isopropylamine at 0 °C is important. Under usual conditions of the Sonogashira reaction, no product was obtained [36]. Coupling of ethynyloxirane **53** with alkenyl triflate afforded the epoxyenediyne **54** in high yield without attacking the labile epoxyalkyne system. AgI is a better cocatalyst than CuI in this reaction [37].

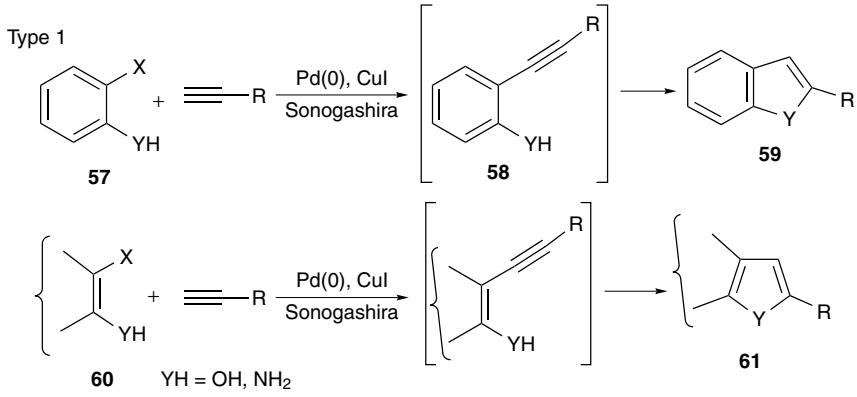


Vinyl tosylates are also used. Coupling of the vinyl tosylate **55** with an 1-alkyne afforded the enyne **56**. Only the use of $PdCl_2(PPh_3)_2$, CuI, and *i*-Pr_2NH gave satisfactory results [38].



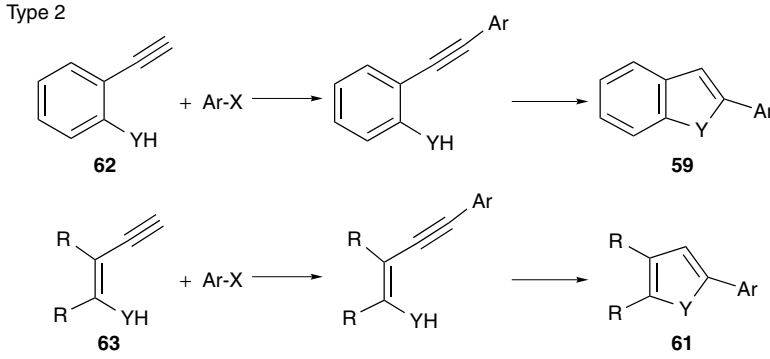
3.4.2.3 Coupling and cyclization

Coupling of 1-alkynes with aryl halides having a nucleophilic group at an *ortho* position and subsequent cyclization offer useful synthetic methods of heterocycles [39]. Two types are known. In type 1, the halides **57** react with 1-alkynes to generate **58**, which undergo cyclization to afford 2-substituted heterocycles **59**. β-Substituted alkenyl halides **60** behave similarly to give 2-substituted heterocycles **61**.



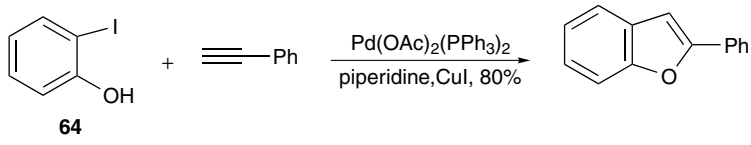
In type **2**, the ethynyl derivatives **62** and **63** react with aryl halides to generate disubstituted alkynes, which cyclize to afford **59** and **61**.

These reactions are used extensively for the preparation of heterocycles **59** and **61** such as benzo[*b*]furans, butenolides, and indoles. In some cases, cyclization proceeds spontaneously to give **59** in a one-pot reaction.



Furan derivatives are prepared by reaction of *o*-iodophenols. 2-Phenylbenzo-[*b*]furan was prepared by the reaction of *o*-iodophenol (**64**) with 1-alkyne in one step [40]. It should be noted that similar 2-arylbenzo[*b*]furan formation occurred by the use of Pd-free, copper-phosphine complex [41]. Similarly 2-substituted furo[3.2-*b*]pyridine **66** was prepared from 2-iodo-3-pyridinol (**65**) in a one-pot reaction [42]. Naturally occurring ailanthoidol was synthesized by the reaction of **67** and **68** to give the cyclized product **69** [43].

The deoxynucleoside **72** was prepared in two steps by coupling the 5-iodo nucleoside **70** with 1-dodecyne, and CuI-catalyzed cyclization of **71** [44].



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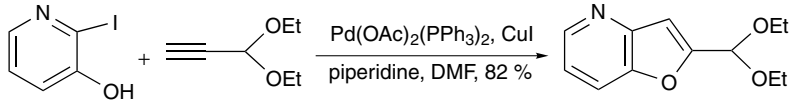
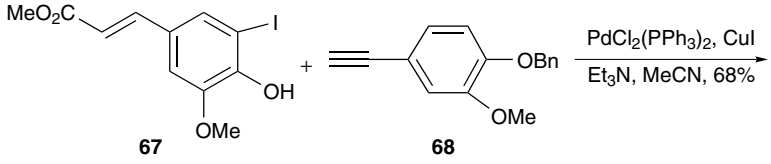
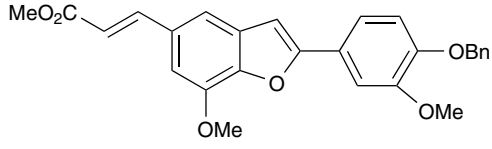


65 **66**



67 **68**



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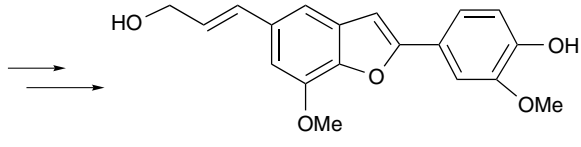
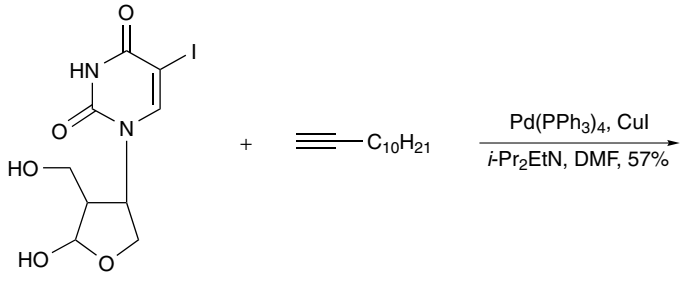


ailanthoidol



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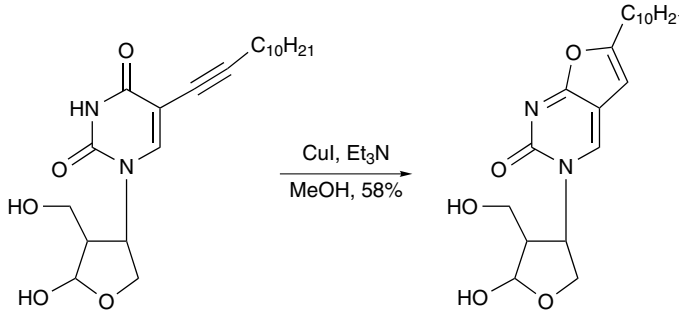
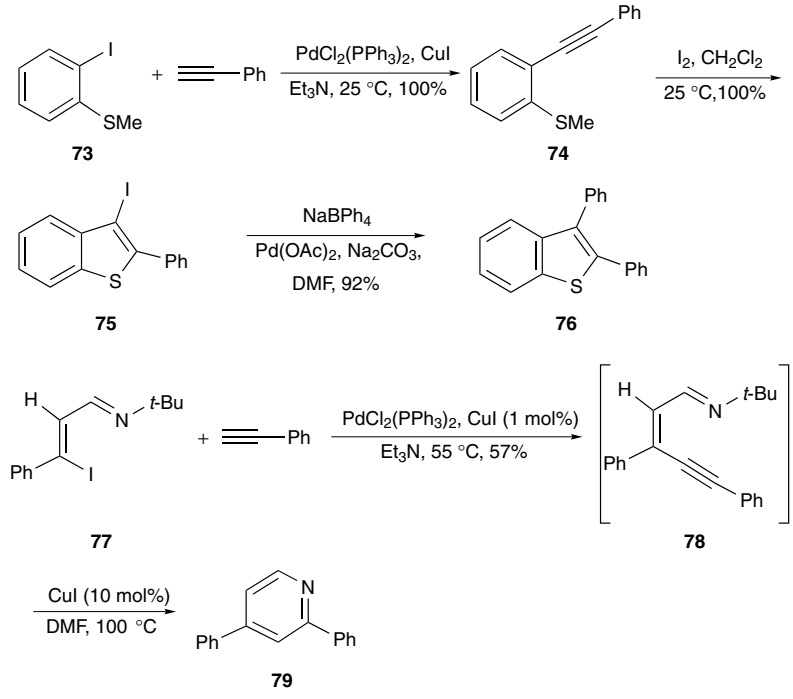


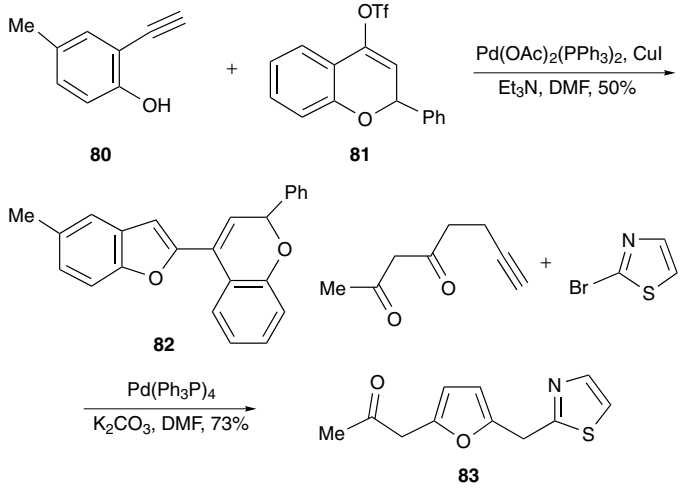
71 **72**

Sonogashira coupling of *o*-iodothioanisole (**73**) with phenylacetylene affords *o*-(1-alkynyl)thioanisole **74**, which cyclizes to give 2-substituted 3-iodobenzothiophene **75** by the treatment with iodine. Furthermore, Suzuki coupling of **75** affords the 2,3-disubstituted benzothiophene **76** [45]. The iminoalkyne **78** is prepared by Sonogashira coupling of the alkenyl iodide **77**, and the substituted pyridine **79** is obtained by the CuI-catalyzed cyclization [46].



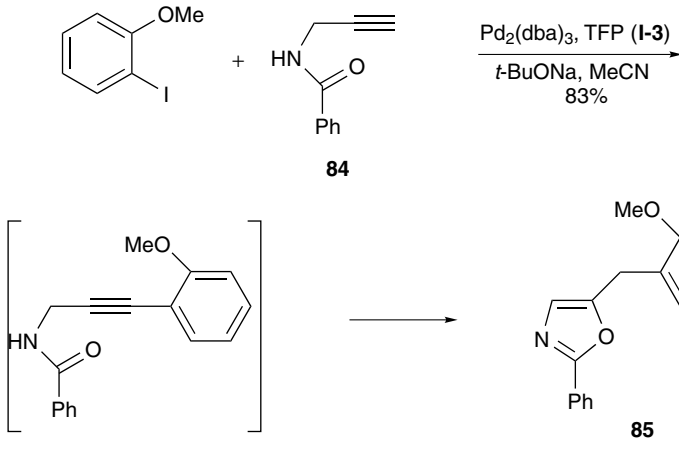
73 **74** **75** **76** **77** **78** **79**

As an alternative procedure (type 2 reaction), coupling of the *o*-ethynylphenol **80** with the alkenyl triflate **81** proceeds smoothly to yield the benzofuran **82** [40]. Coupling of 2-bromothiazole with an enolate of 1,3-dicarbonyl compound was used for preparation of 2,5-disubstituted furan **83** [47]. Coupling of 2-iodoanisole



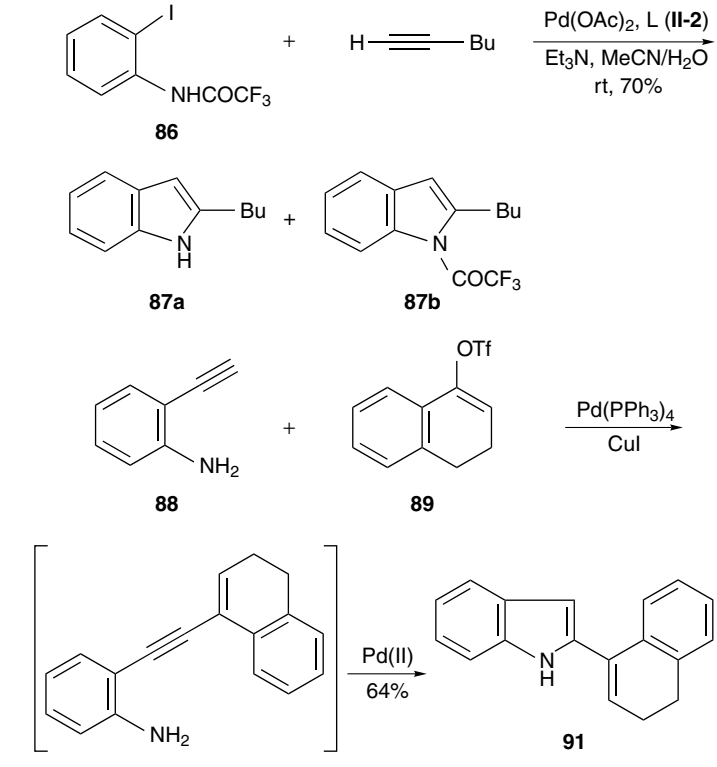
80 **81** **82** **83**

with *N*-propargylbenzamide (**84**) generated the coupling product in the presence of *t*-BuONa, which underwent base-catalyzed *in situ* cyclization to yield 2,5-disubstituted oxazole **85** [48].



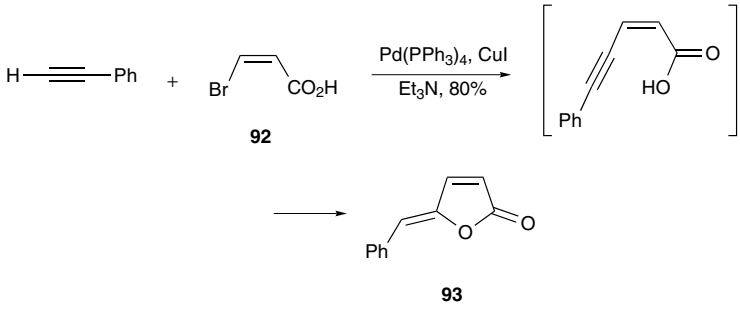
84 **85**

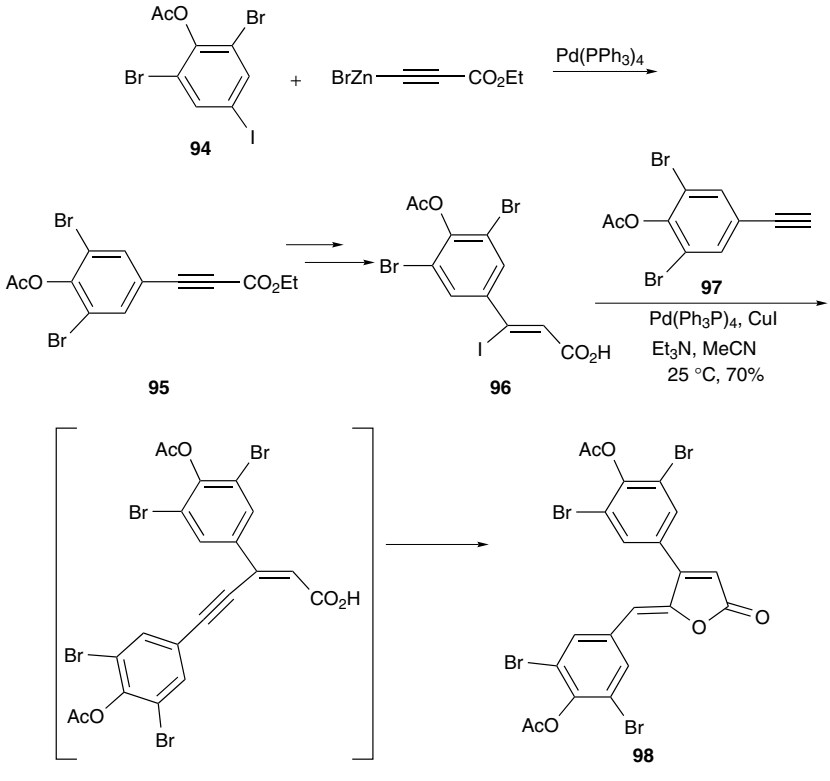
The coupling of the *o*-iodoaniline derivative **86** with 1-alkynes in aqueous media at room temperature by the use of the water soluble ligand **II-2**, followed by intramolecular amination gave the indoles **87a** and **87b** [49]. As a type 2 reaction, the indole **91** was obtained by coupling 2-ethynylaniline (**88**) with the triflate **89** and cyclization [50].



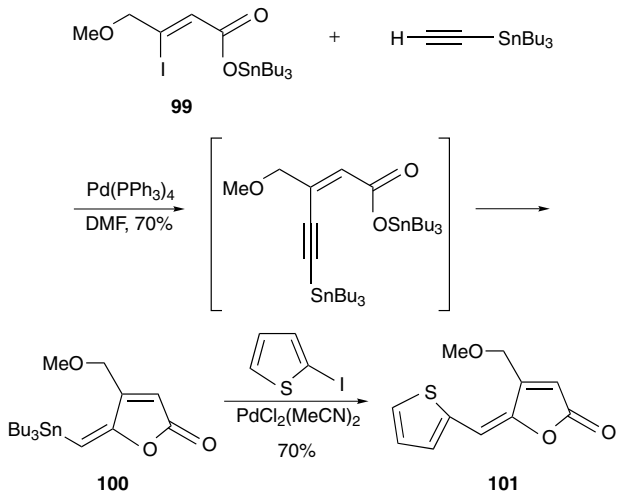
86 **87a** **87b** **88** **89** **91**

The γ-alkylidenebutenolide **93** was prepared by domino coupling of (*Z*)-3-bromoacrylic acid (**92**) with 1-alkynes to generate an enyne acid, followed by lactonization [51]. Negishi synthesized γ-alkylidenebutenolide **98** by the coupling–lactonization reaction [52]. The 3-aryl-3-iodocinnamic acid **96**, a coupling partner, was prepared by the coupling of Zn acetylide of ethyl propiolate with **95**, followed by hydroiodination. As described earlier, Sonogashira coupling of propiolate itself is very difficult. The coupling–lactonization of **96** with the 1-alkyne **97** afforded the acetate of rubrolide (**98**) in 70 % yield via lactonization.



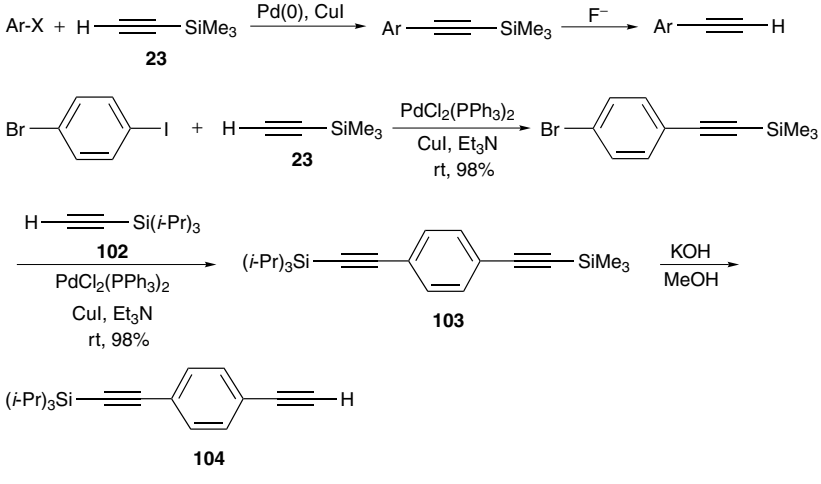


Stereoselective preparation of (*E*)-5-stannyl-γ-alkylidenebutenolide **100** was achieved by the reaction of tin acetylide with tributylstannyl 3-iodopropenoate derivative **99**, and the arylbutenolide **101** was obtained by the Migita–Kosugi–Stille reaction of **100** [53].

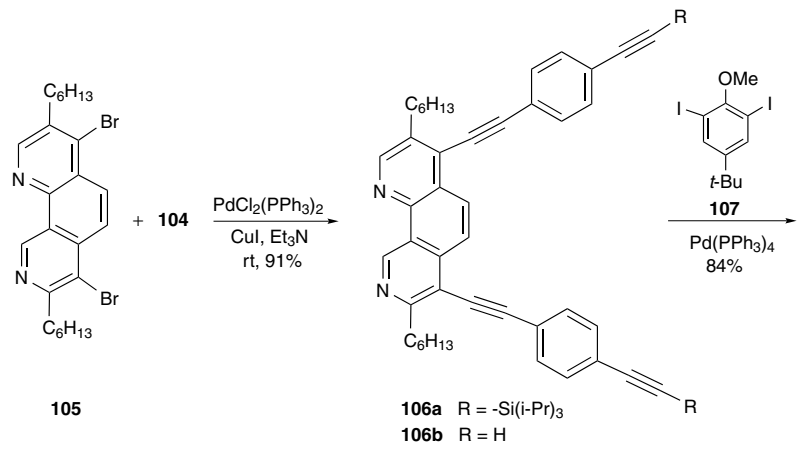


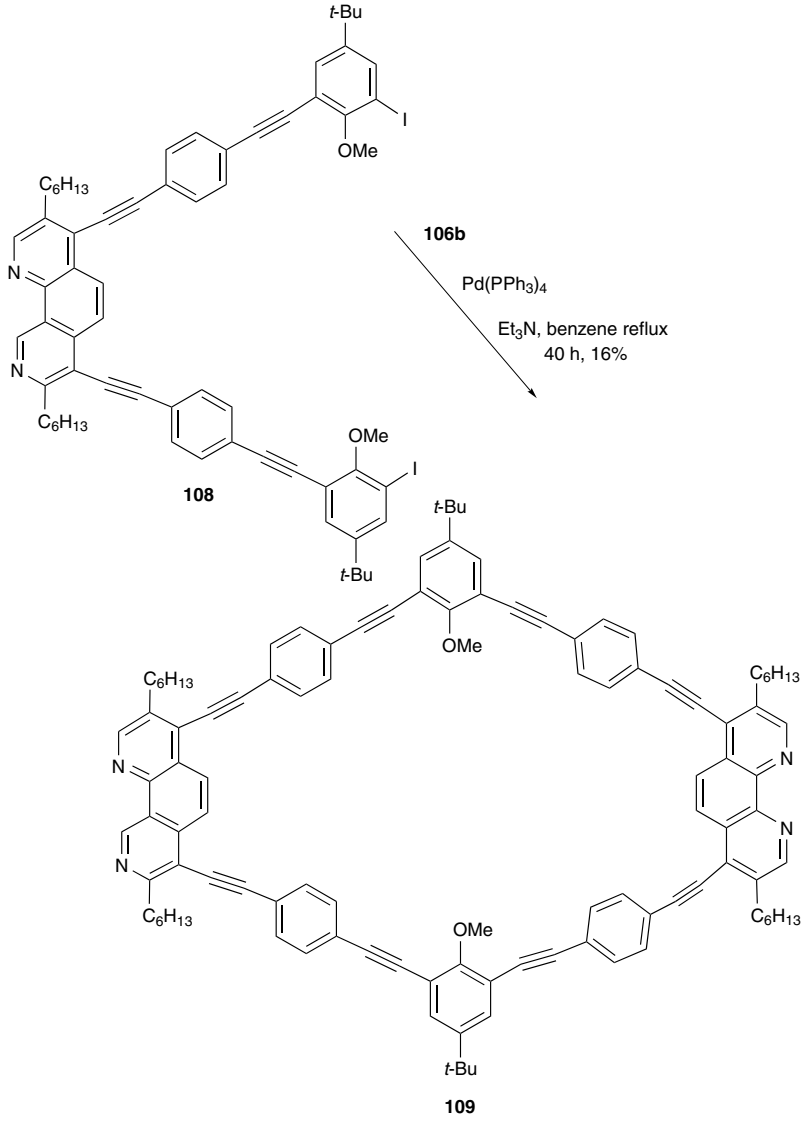
3.4.2.4 Acetylene Surrogates

Selective monosubstitution of acetylene to prepare 1-alkynes is not easy. It can be done by the use of protected acetylenes. As one method, trimethylsilylacetylene (TMS-acetylene) (**23**) is used. After its coupling with halides, the TMS group is removed by treatment with a base or fluoride anion to give 1-alkynes. Among numerous examples, an application to synthesize a rigid macrocycle with two exotopic phenanthroline binding sites is cited. In this synthesis, TMS-acetylene (**23**) and triisopropylsilylacetylene (**102**) are used as protected acetylenes [54]. At first the dialkynes **103**, protected with TMS and triisopropylsilyl groups, were prepared from *p*-bromoiodobenzene in high yield, and the TMS group in **103** was selectively removed to give **104**, which undergoes coupling with the dibromophenanthroline

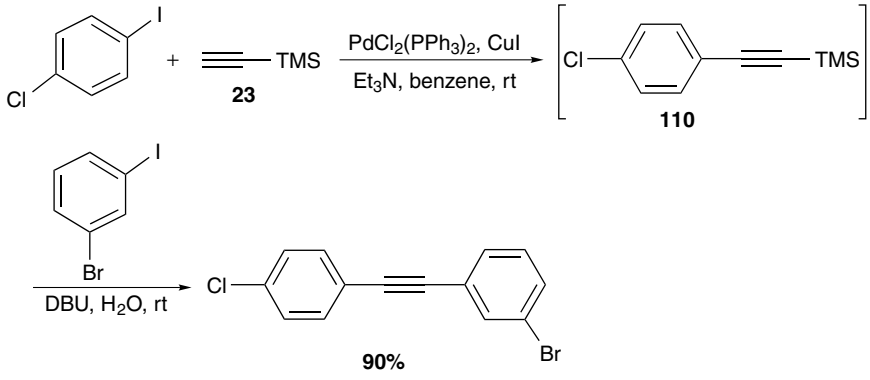


105 to give **106a** in 91 % yield. Deprotection of **106a** afforded the diyne **106b**. Coupling of **106b** with two molecules of the 1,3-diiodobenzene **107** afforded **108** in 84 % yield. Finally the macrocycle **109** was obtained by the coupling of **108** with **106b** in 16 % yield.

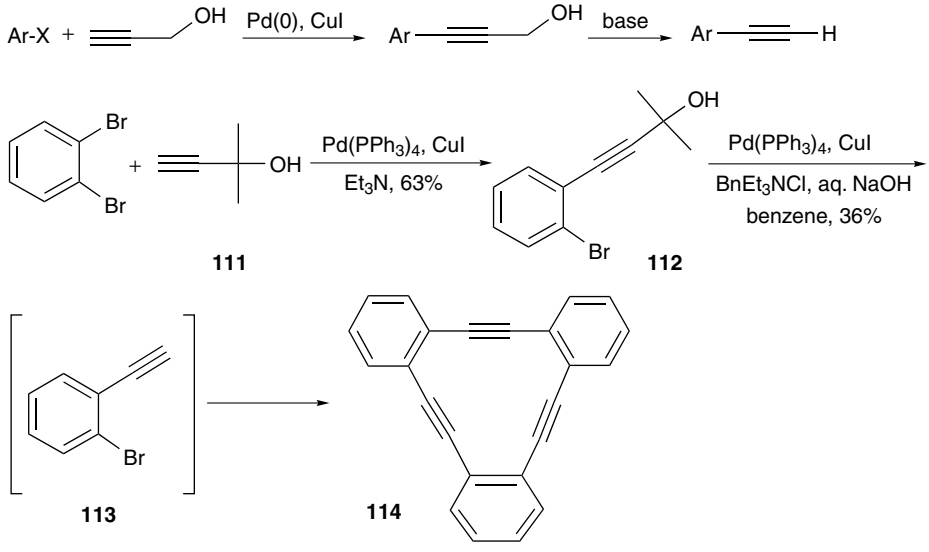

C6H13
Br
N
N
Br
C6H13
+ 104
PdCl2(PPh3)2
CuI, Et3N
rt, 91%
R
OMe
I
I
t-Bu
107
Pd(PPh3)4
84%
105
106a R = -Si(i-Pr)3
106b R = H


t-Bu
I
OMe
C6H13
N
N
C6H13
106b
Pd(PPh3)4
Et3N, benzene reflux
40 h, 16%
OMe
I
108
t-Bu
t-Bu
OMe
C6H13
C6H13
N
N
N
C6H13
C6H13
OMe
t-Bu
109

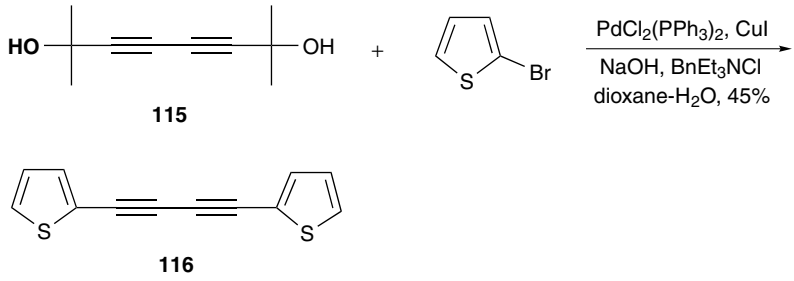
One-pot synthesis of symmetric and asymmetric biarylacetylenes was carried out from **23** at room temperature. The TMS group in the coupling product **110** of *p*-chloroiodobenzene was removed *in situ* by addition of DBU (6 equiv.) and water (40 mol%). Then *m*-bromoiodobenzene was added to give asymmetric diarylacetylene in 90 % yield [55].



Another protected acetylene is propargyl alcohol and 2-methyl-3-butyn-2-ol (**111**). After coupling with halides, deprotection by alkaline hydrolysis gives 1-alkynes. Dehydro[12]annulenes **114** was synthesized from **111** as the protected acetylene. Monocoupling of *o*-dibromobenzene with **111** afforded the protected alkyne **112**. Treatment of **112** with Pd(0)-CuI catalyst, NaOH, and quaternary ammonium chloride generates the deprotected 1-alkyne **113** *in situ*. Subsequent homocoupling of three molecules of **113** afforded the annulene **114** in 36 %

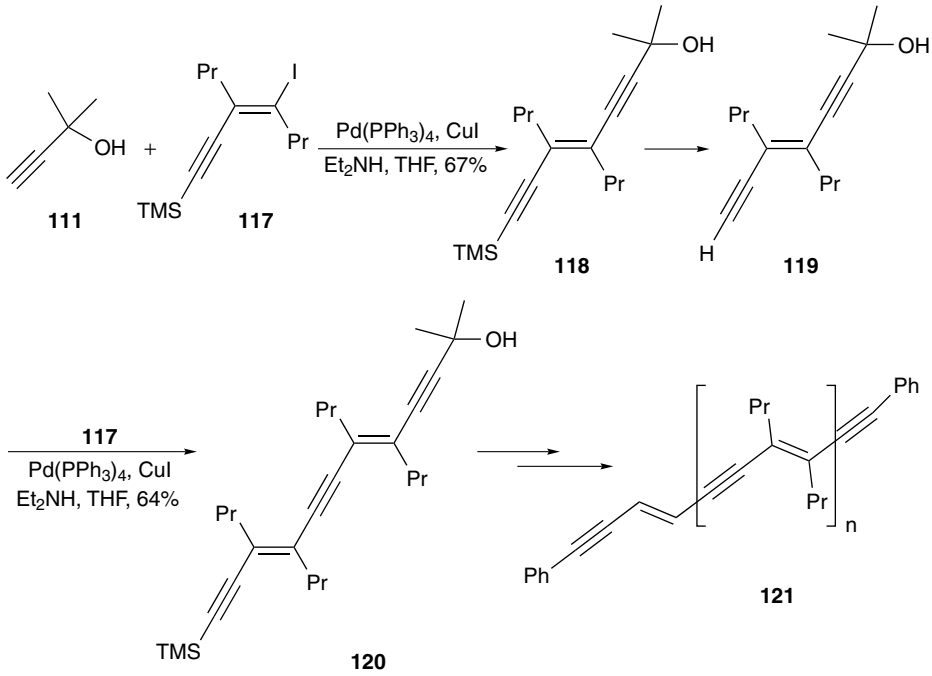


yield [56]. Deprotection of the diyne **115** *in situ*, followed by coupling with 2-bromothiophene in a basic solution, provided the coupled product **116** [57]. As an improved procedure of the deprotection, the coupled products were heated



in paraffin oil with a catalytic amount of powdered KOH *in vacuo* and volatile 1-alkynes were collected by distillation [58].

The protected acetylene **111** was used for the synthesis of the oligoenynes **121**. Coupling of **111** with alkenyl iodide **117** afforded **118** which was deprotected to give **119**. The conjugated dienetriyne **120** was obtained by further coupling of the terminal alkyne **119** with **117**. After repeating the same sequence of reactions, namely deprotection and Sonogashira coupling, the oligoenyne **121** was obtained [59].



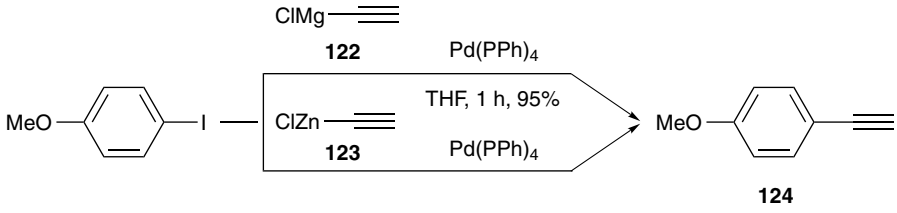
Ethynyl Grignard reagent **122** and ethynylzinc halide **123** are good protected acetylenes as described in the next section.

3.4.2.5 Coupling of Metal Acetylides

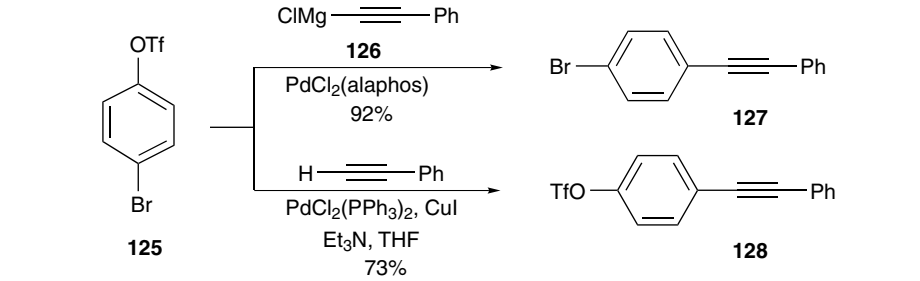
In addition to Sonogashira coupling via Cu acetylides generated *in situ* as mentioned in sections 3.4.2.2–3.4.2.4, coupling of 1-alkynes has been carried out smoothly using acetylides of main group metals as an alternative method of

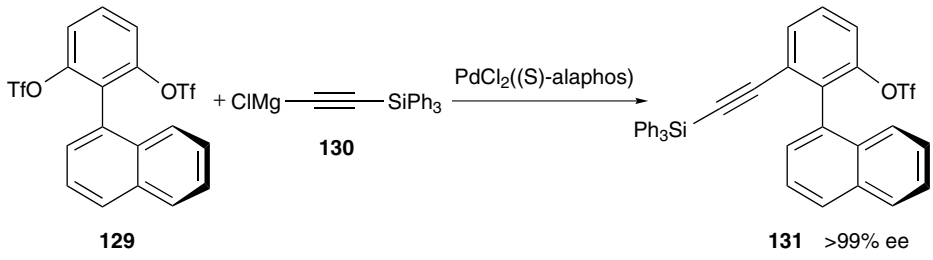
arylation and alkenylation of 1-alkynes. Mg, Zn, and Sn acetylides are used frequently as activated alkynes and the coupling with aryl and alkenyl halides proceeds without using CuI. This method often gives better results than the Pd(0)/CuI-catalyzed Sonogashira coupling of free 1-alkynes, but not always.

Mg acetylides are easily prepared and used for coupling. A good preparative method of 1-alkynes is the coupling of commercially available ethynylmagnesium chloride (**122**) or ethynylzinc chloride (**123**) as acetylene surrogates with aryl or alkenyl halides. Their couplings with halides directly afford the 1-alkynes **124**. No deprotection is necessary [60].



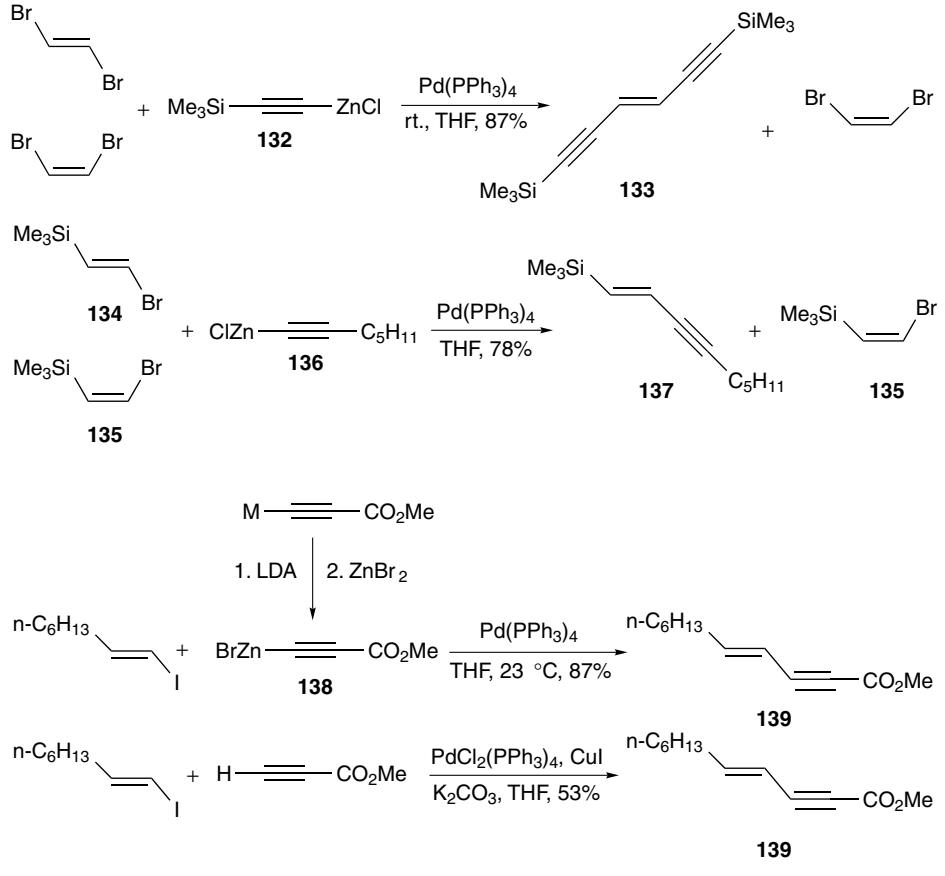
Smooth chemoselective coupling of triflate group in *p*-bromophenyl triflate (**125**) with the Mg acetylide **126** at room temperature in the presence of an aminophosphine named alaphos (**VII-6**) and $PdCl_2$ gave **127** [61]. This aminophosphine ligand is superior to DPPF, DPPP and PPh_3. On the other hand, the bromo group in **125** reacted chemoselectively with free phenylacetylene to afford the triflate **128** when $PdCl_2(PPh_3)_2$ and CuI were used. Asymmetric monocoupling of the prochiral biaryl ditriflate **129** with the Mg acetylide **130** in the presence of LiBr and chiral $PdCl_2$(alaphos) gave the axially chiral monoalkynylated product **131** with 99 % ee. In this reaction, addition of LiBr is essential [62].





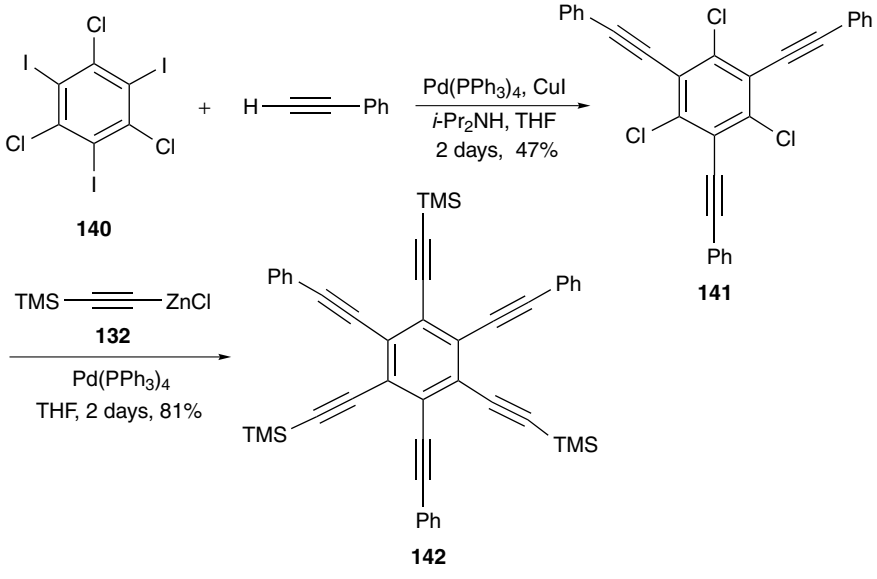
Zn acetylides, prepared *in situ* by the treatment of Li acetylides with $ZnCl_2$, are widely used. Both *trans*- and *cis*-1,2-dibromo-ethylenes react with metal acetylides

with different reactivity. Competitive reactions of *trans*- and *cis*-1, 2-dibromoethylenes with the Zn acetylide **132** showed that the *trans* isomer is more reactive than the *cis* isomer to give **133** with high selectivity [63,64]. Also the competitive reactions of *trans*-(**134**) and *cis*-vinyl bromides (**135**) with the Zn acetylide **136** showed that the *trans*-vinyl bromide **134** is more reactive than the *cis* isomer **135**, giving **137** selectively and keeping the *cis*-bromide **135** intact [65]. Negishi and coworkers have demonstrated that the coupling of alkynylzincs is more satisfactory than the Sonogashira reaction under various conditions, as shown by the following examples. The coupling of the alkynylzinc **138**, formed from methyl propiolate which is an EWG, with alkenyl iodides proceeded well at room temperature to give conjugated enyne **139** in 87 % yield. The yield of **139** by the corresponding Sonogashira reaction was 53 % [66].

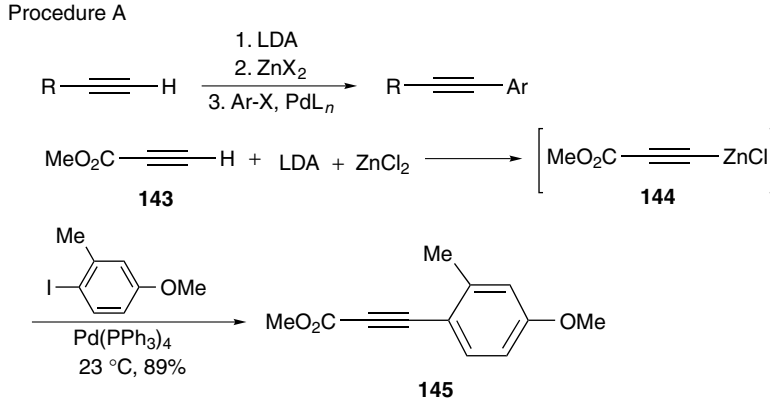


Differently substituted hexaethynylbenzenes were prepared by domino Sonogashira and Negishi couplings of trichlorotriiodobenzene **140** [67]. The Sonogashira coupling of **140** with phenylacetylene afforded **141** chemoselectively in 47 % yield. Then Negishi coupling of **141** with the Zn acetylide **132** catalyzed by $Pd(PPh_3)_4$ yielded the differently substituted hexaethynylbenzene **142** in 81 % yield. It is surprising that **142** was obtained in such a high yield by the coupling of less reactive chlorides. This is a rare example of the coupling of 1-alkynes with aryl

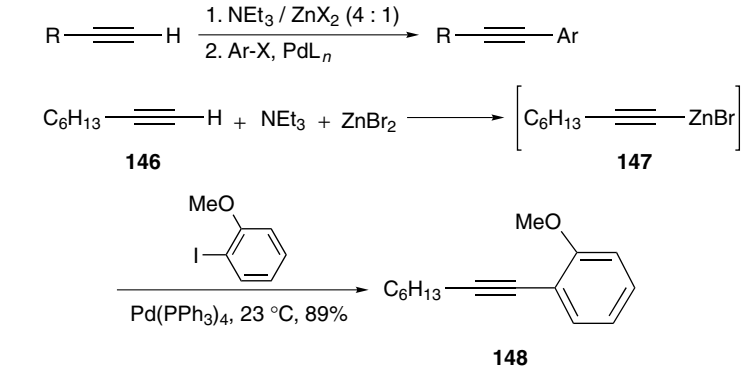
chlorides. In this case, electron-attracting ethynyl groups activate (though weakly) the C—Cl bonds toward oxidative addition to Pd(0).



Negishi reported improved procedures (A and B) of coupling with aryl halides by generating Zn acetylide derivatives *in situ* [68]. In procedure A, alkynylzinc halides are generated by the treatment of 1-alkynes with LDA and then ZnX_2, and are directly used for the coupling with aryl halides. This method is valuable for electron-deficient alkynes, and methyl propiolate (**143**) can be coupled via the Zn acetylide **144** to afford **145** in 89 % yield. As described earlier in this section, coupling of propiolate is less satisfactory under Sonogashira conditions. An amine as a base and $ZnBr_2$ are used in procedure B to generate the Zn acetylide **147** from **146**, and its reaction with aryl bromide gives **148**. Therefore procedure B is operationally simple.

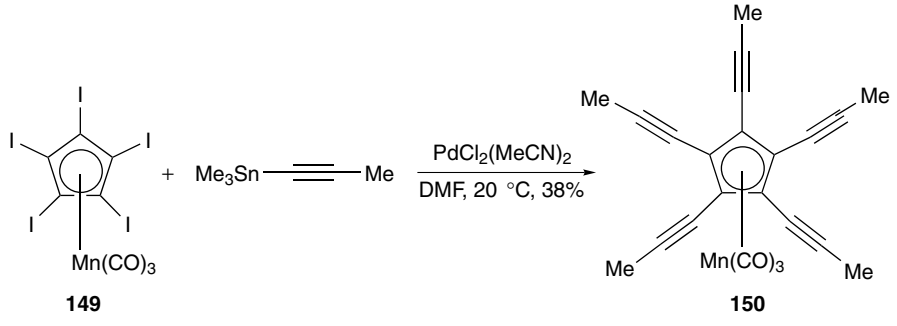


Procedure B

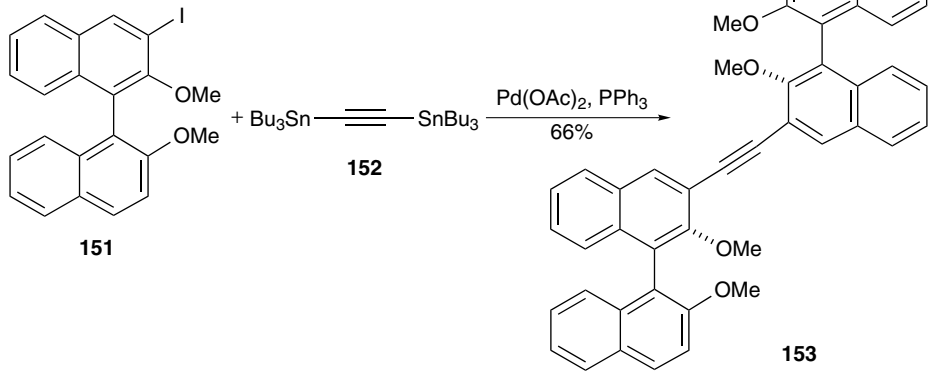


146 **147** **148**

Sn acetylides are frequently used for coupling. Coupling of Mn tricarbonyl complex of pentaiodocyclopentadiene (**149**) with trimethylpropynyltin afforded the pentapropynyl derivative **150** at room temperature [69]. Symmetrically disubstituted alkynes can be prepared by coupling of bis(tributylstannyl)ethyne (**152**). The bis(binaphthol) derivative **153** was prepared by the reaction of **152** with the iodide **151** [70].

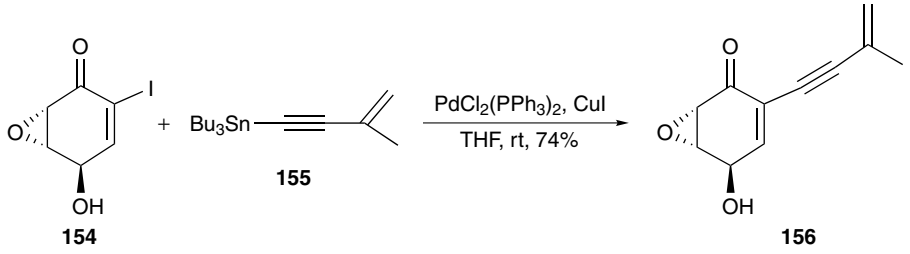


149 **150**



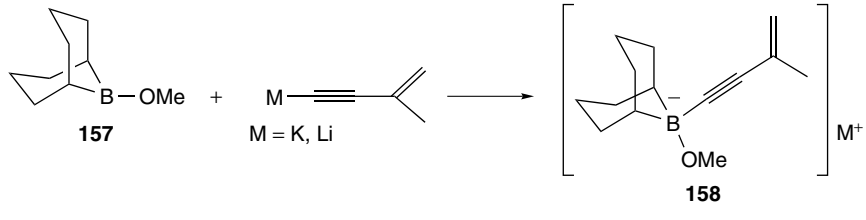
151 **152** **153**

In the synthesis of tricholomenyn (**52b**), Sonogashira coupling of vinyl iodide was carried out in 54 % yield under the carefully controlled conditions as described before [36]. Ogasawara and Taylor reported that the reaction gave poor yields under usual conditions of Sonogashira coupling. They obtained the model compound **156** in 74 % yield by coupling the Sn acetylide **155** with the iodide **154** [71].

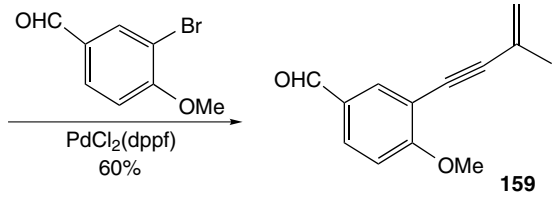


154 **155** **156**

A few studies have been carried out on coupling of alkynyl borones. The stable methoxy(alkynyl)borate complex **158** was prepared *in situ* by the treatment of B-methoxy-9-borabicyclo[3.3.1]nonane (**157**) with alkynyllithiums or potassium reagents, and used directly for the coupling with halides to afford a variety of the disubstituted alkynes such as **159** [72,73].

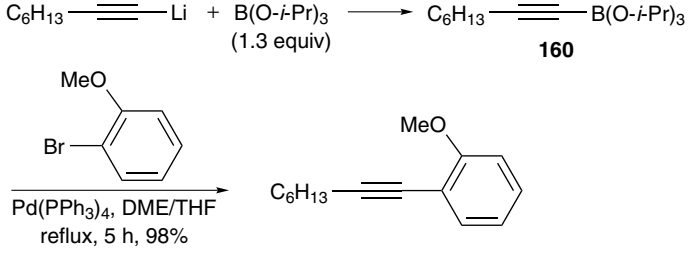


157 **158**



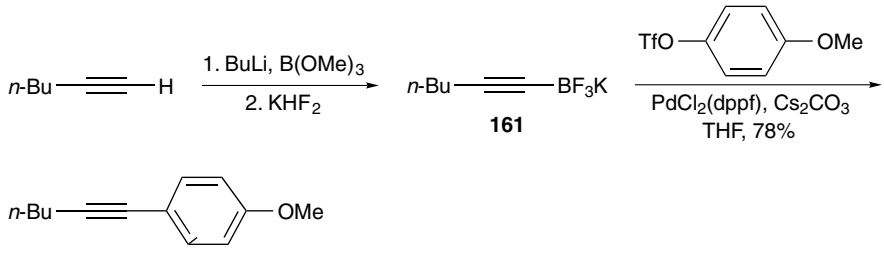
159

As an efficient coupling partner, the alkynylboronate **160** was generated *in situ* from alkynyllithium and triisopropoxyborane, and used for the coupling as a one-pot reaction [74]. The method is simple and particularly useful for the coupling of

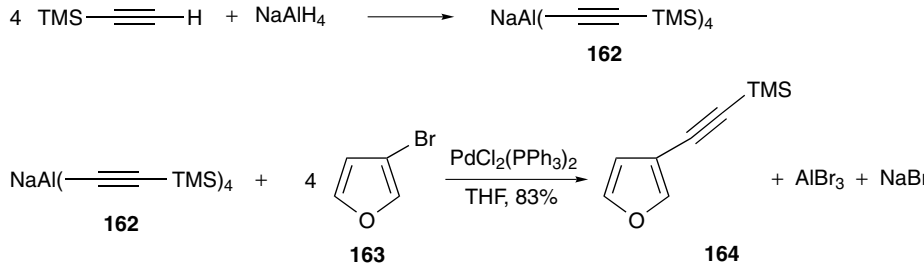


160

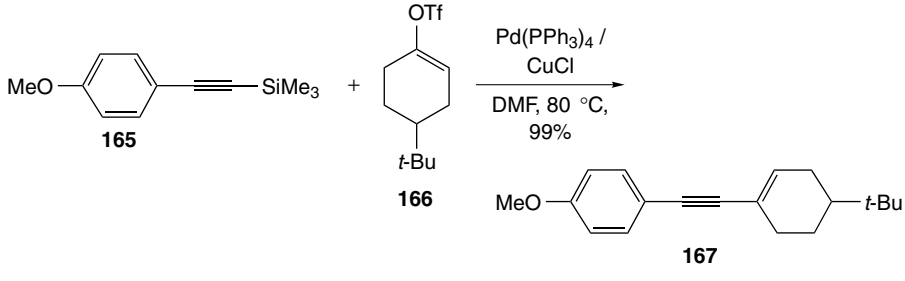
unactivated and *ortho*-substituted aryl halides such as *o*-bromoanisole to give the arylalkyne in high yield. Air- and moisture-stable potassium alkynyltrifluoroborate **161** is a convenient coupling partner with aryl halides or triflates [75].



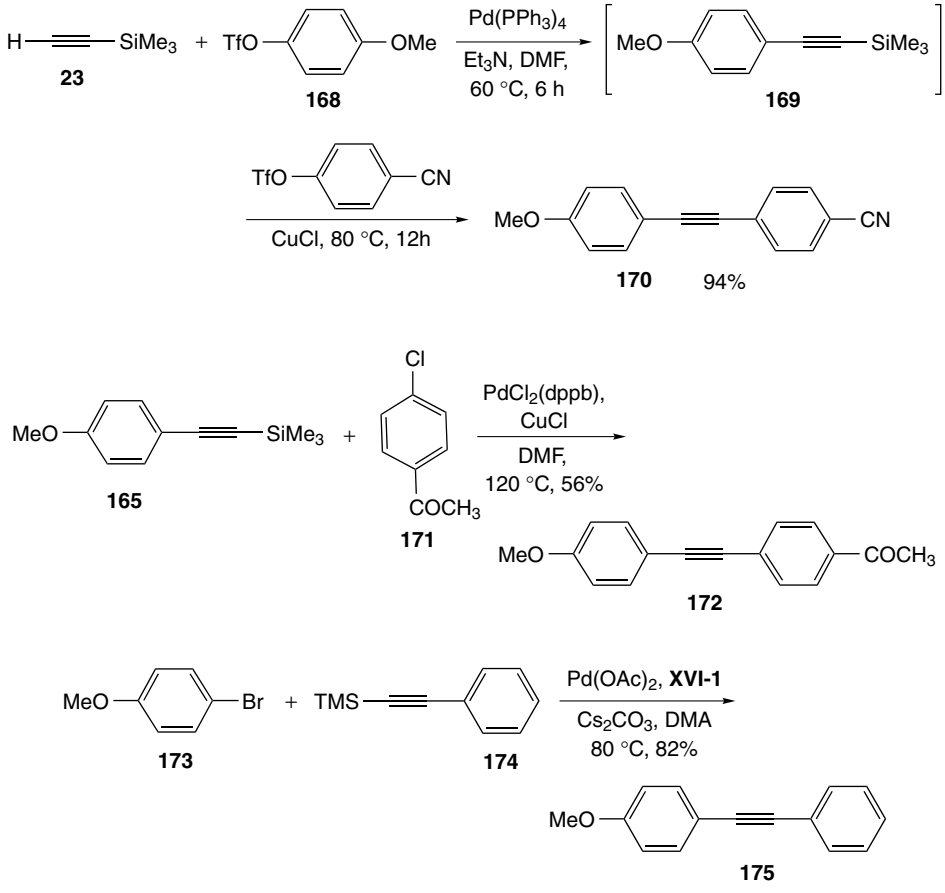
Sodium tetralkynylaluminates **162**, prepared from $NaAlH_4$ and terminal alkynes, are used for the coupling with aryl halides such as 3-bromofuran (**163**) to give the coupled product **164** cleanly in high yield. Most importantly, all four alkynyl moieties can be utilized for the coupling [76].



As described before, trimethylsilylacetylene (**23**) is used as a protected acetylene, because no Pd-catalyzed coupling reaction occurs with the TMS group. Interestingly, however, Hiyama discovered that alkynylsilanes can be used for the coupling with aryl and alkenyl triflates using Pd(0)-CuCl as catalysts [77,78]. For example, coupling of the trimethylsilylalkyne **165** with the alkenyl triflate **166** using Pd(0)-CuCl as the catalyst in DMF gave the diarylalkyne **167** in nearly quantitative yield. The asymmetric diarylalkyne **170** was prepared in one pot from **23** and two different aryl triflates. The first coupling of the aryl triflate **168** with **23** produced the silylalkyne **169** using Pd(0) and Et_3N. Without isolation, the silylalkyne **169** was coupled with another aryl triflate by addition of CuCl as the cocatalyst to afford



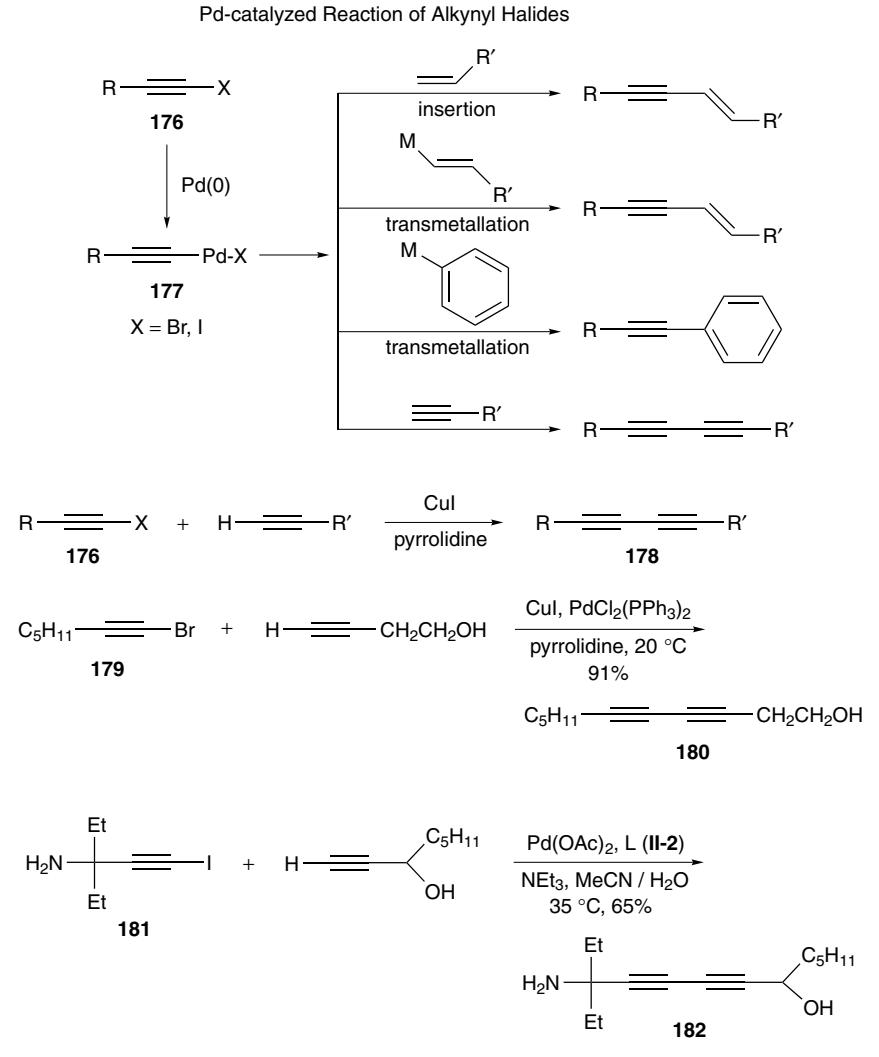
the asymmetric diarylalkyne **170**. Aryl chlorides bearing an EWG **171** can be coupled with trimethylsilylalkyne **165** to give **172**. $PdCl_2$(dppb) is a good catalyst. No efficient coupling takes place with electron-rich aryl chlorides. Coupling of 4-bromoanisole (**173**) with alkynylsilane **174** to give **175** occurred when $Pd(OAc)_2$, carbene ligand **XVI-1**, and Cs_2CO_3 with or without CuI are used [79].



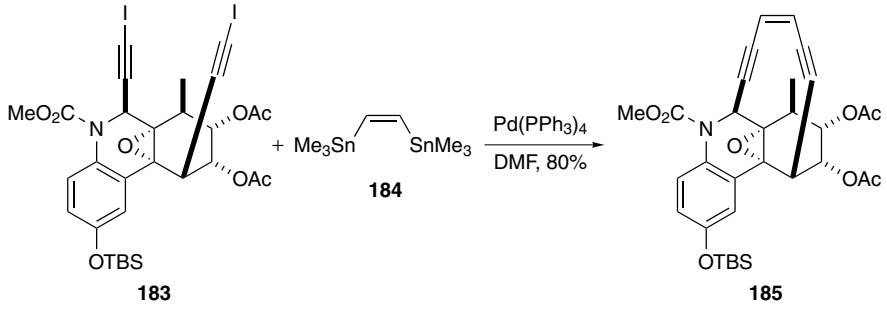
3.4.2.6 Homo- and Cross-couplings of 1-Haloalkynes

1-Haloalkynes **176** behave as reactive halides and palladium acetylides **177** are generated by oxidative addition, which undergo various coupling reactions as expected.

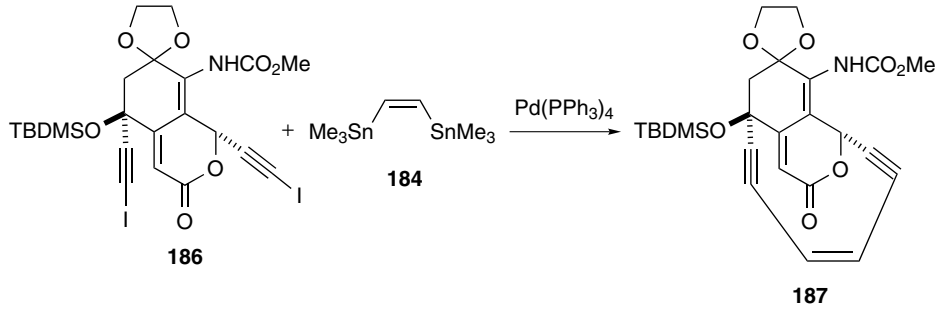
Coupling of 1-haloalkynes **176** with 1-alkynes catalyzed by CuI in the presence of aliphatic amines to give asymmetric 1,4-diynes **178** is known as the Cadiot–Chodkiewicz reaction. Efficient coupling takes place with 1-iodoalkynes. Better results are obtained by the addition of a Pd complex [80]. The 1,3-diyne **180** was obtained by the coupling of the 1-bromoalkyne **179** in 91 % yield when both $PdCl_2(PPh_3)_2$ and CuI were used. The yield was 74 % when CuI alone was used [81]. Coupling of 1-iodoalkyne **181** with 1-alkyne in aqueous media using water-soluble phosphine ligand gave **182** smoothly. $Pd(OAc)_2$ and ligand (**II-2**) are used in the absence of CuI [21].



As an alternative preparative method of enynes, the highly strained cyclic enediyne moiety **185** was constructed by coupling the dialkynyl diiodide **183** with (*Z*)-1,2-distannylethylene (**184**) in 80 % yield in the total synthesis of dyenemicin A [82]. The presence of the epoxide in **183** is important. No coupling took place



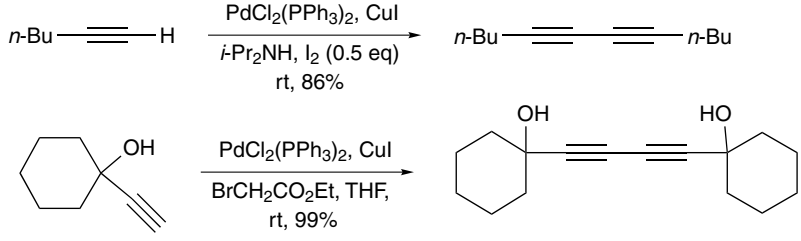
when there is a double bond instead of the epoxide. By a similar method, the cyclic enediyne structure **187** was constructed by coupling the dialkynyl diiodide **186** with **184** as a key step in the total synthesis of calicheamicinone [83].



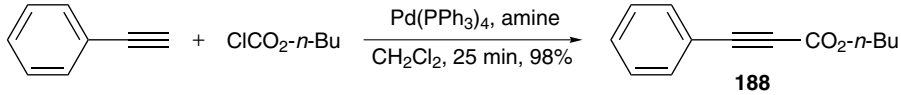
186 **184** **187**

3.4.2.7 Miscellaneous Reactions

Although no halides are involved, homocoupling of alkynes are cited here as a related reaction. Homocoupling (oxidative coupling) of 1-alkynes is catalyzed by CuCl in pyridine under oxygen, and is called Glaser coupling. The coupling also proceeds in the presence of $PdCl_2(PPh_3)_2$ and CuI in aliphatic amines. This oxidative coupling requires Pd(II), which is reduced to Pd(0), and some oxidizing agents are necessary to regenerate Pd(II). For this purpose, chloroacetone [84], bromoacetate [85], and iodine [86] are added as shown by the following examples. It is known that Pd(0) is oxidized to Pd(II) by oxidative addition to these halides.



Henkelmann and co-workers found that chloroformates are good coupling partners of 1-alkynes, and the reaction offers a useful synthetic method for arylpropiolates [87]. Reaction of *n*-butyl chloroformate with phenylacetylene in the presence of 1,2,2,6,6-pentamethylpiperidine as a hindered base and a small amount of *N*,*N*-dimethylaminopyridine afforded *n*-butyl phenylpropiolate (**188**) in 98 % yield within 25 min in refluxing dichloromethane.



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amine = 1,2,2,6,6-pentamethylpiperidine, dimethylaminopyridine

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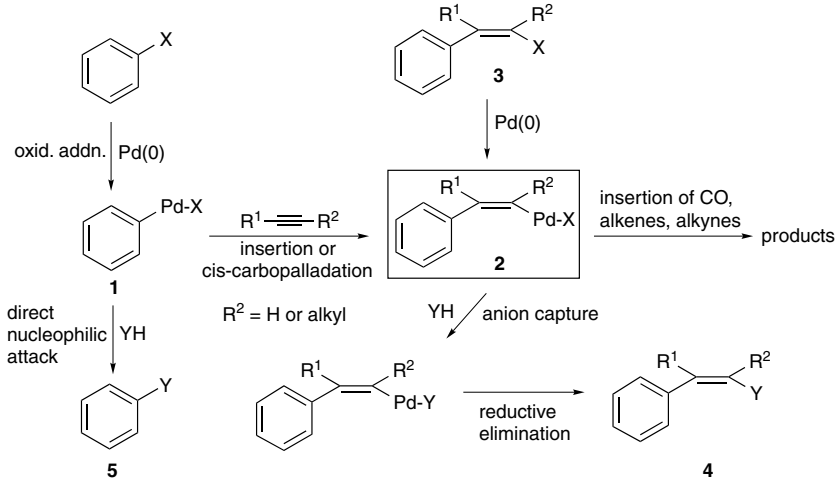
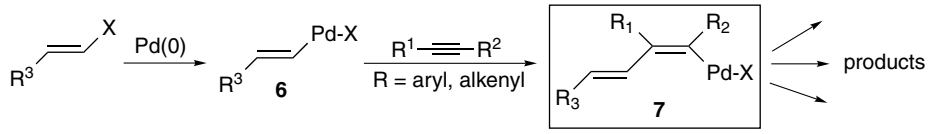
3.4.3 Reactions of Internal and Terminal Alkynes with Aryl and Alkenyl Halides via Insertion

3.4.3.1 Classification of Reactions

Alkynes are more reactive than alkenes in carbopalladation. Facile insertion of internal alkynes to some Pd—C bonds (carbopalladation of alkynes) generates the alkenylpalladiums **2** and **7** by mainly selective *syn* addition of organopalladium species **1** and **6** to alkynes. Formally the species **2** can be generated by oxidative addition of appropriately substituted alkenyl halides **3** to Pd(0).

Terminal alkynes react with aryl halides to form arylalkynes and enynes in the presence of CuI as described in section 3.4.2. Insertion of terminal alkynes also occurs in the absence of CuI, and the alkenylpalladium species **2** and **7** are formed and undergo further reactions (Scheme 3.6). The reactions of internal and terminal alkynes via insertion are treated in this section.

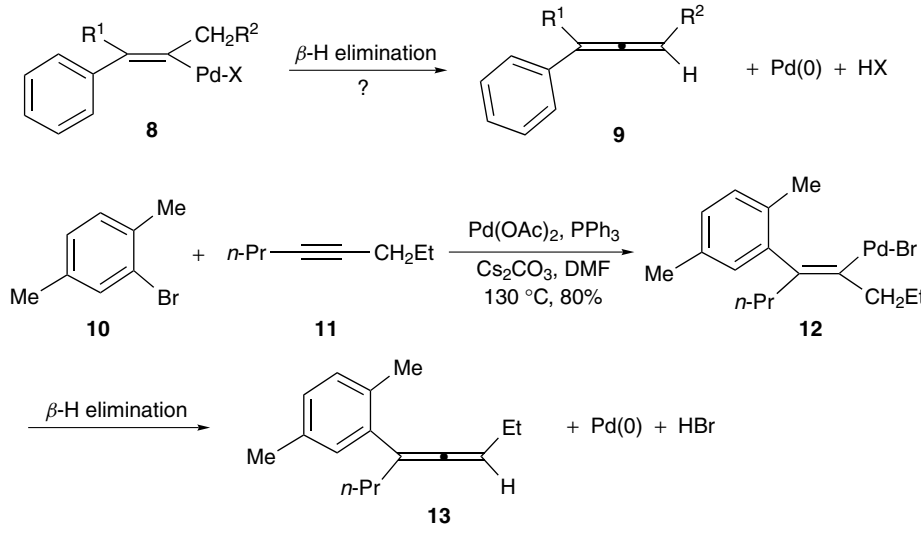




Scheme 3.6 Reactions of alkynes with aryl and alkenyl halides and further transformation.

Whereas alkene insertion is followed by facile dehydropalladation whenever there is a β-hydrogen to afford alkenes and Pd(0) catalytic species, the alkyne insertion produces the thermally stable alkenylpalladium species **2** and **7**, which can not be terminated by themselves and further transformations are required in order to terminate the reactions and to regenerate Pd(0) species for catalytic recycling. In other words, it is generally believed that the reaction of generated alkenylpalladium species **2** and **7** can not be terminated, because the β-H elimination (formation of alkynes or allenes) even in the presence of a β-hydrogen is not possible. Therefore the carbopalladation of alkynes is a 'living' process, in which alkynes play a role of 'relay' to pass the ability of carbon–carbon bond formation to other reactants.

However, there have appeared a few reports on the formation of allenes **9** from **8** by the reaction of alkynes with halides. As one example, clean and selective formation of the allene **13** in good yield by the reaction of the aryl bromide **10** with 4-octyne (**11**) was reported. It is important to use *ortho*-substituted bromides for the allene formation [1]. The reaction can be understood by β-H elimination from the alkenylpalladium species **12**. Similar allene forming reactions have been reported [2–4]. At present, the allene formation has been observed only in reactions using dialkylacetylenes, and should be regarded as an exceptional process.



In this section, transformations of **2** and **7** are classified and explained by citing proper examples. The formation of **2** is competitive with direct coupling of aryl halides with anions or nucleophiles as a side reaction to give **5**. Yields of desired

products of domino coupling reaction formed via **2** and **7** are sometimes low due to this side reaction.

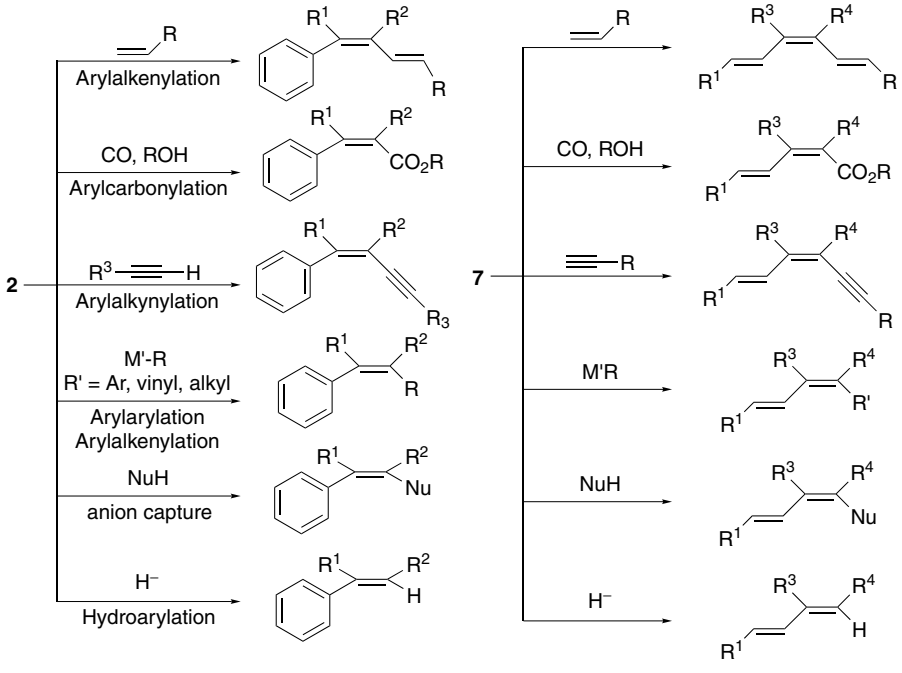
3.4.3.2 Intermolecular Reactions

The alkenylpalladium species **2** and **7** are capable of undergoing further insertion or anion trap before termination as summarized in Scheme 3.7. The following species trap the alkenylpalladium species **2** and **7**.

Anionic: H, OAc, N_3, $CH(CO_2R)_2$, SO_2Ph, RCO_2

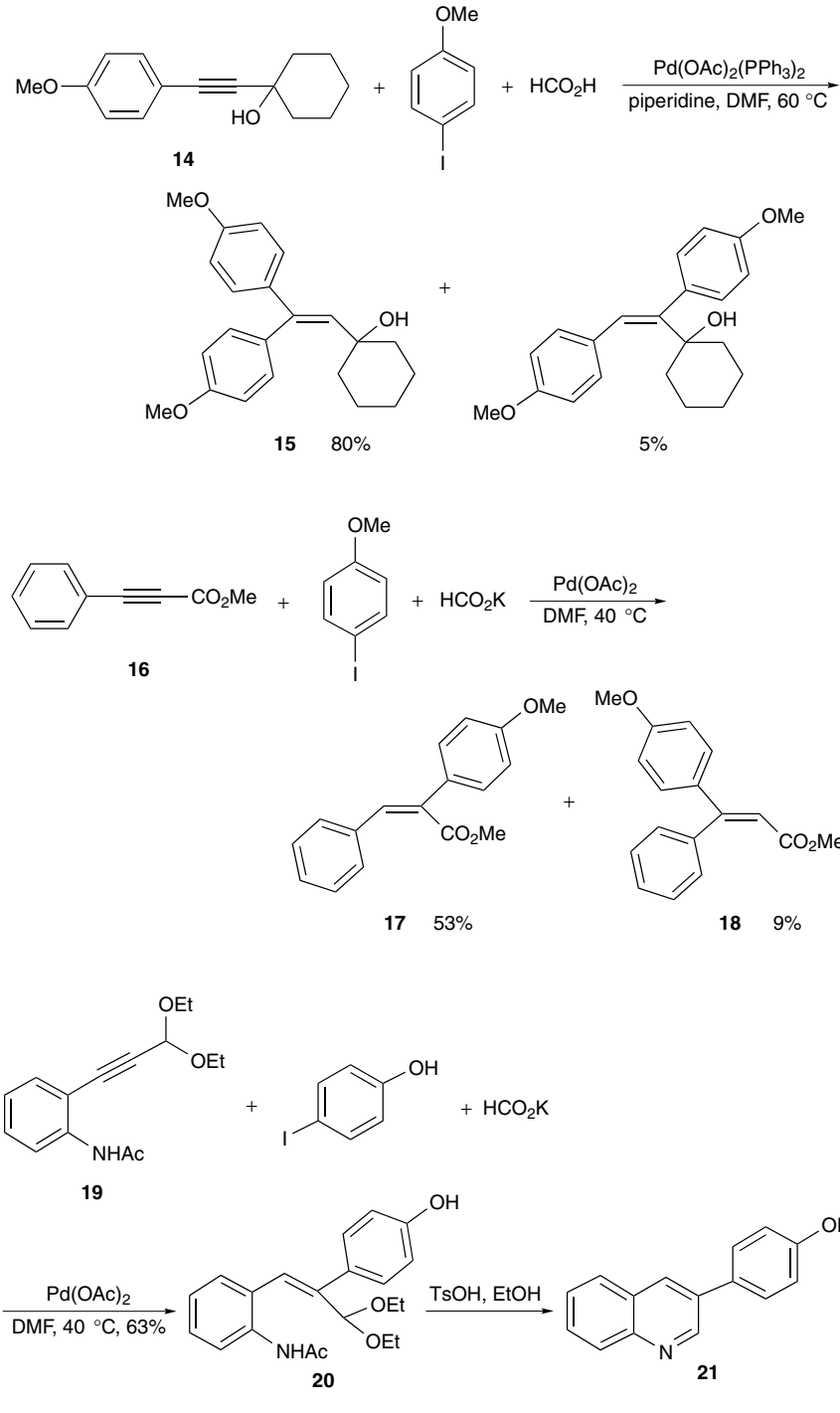
Neutral: NHR_2, ROH, CO-ROH

Organometallic RM: M = Zn, B, Sn.

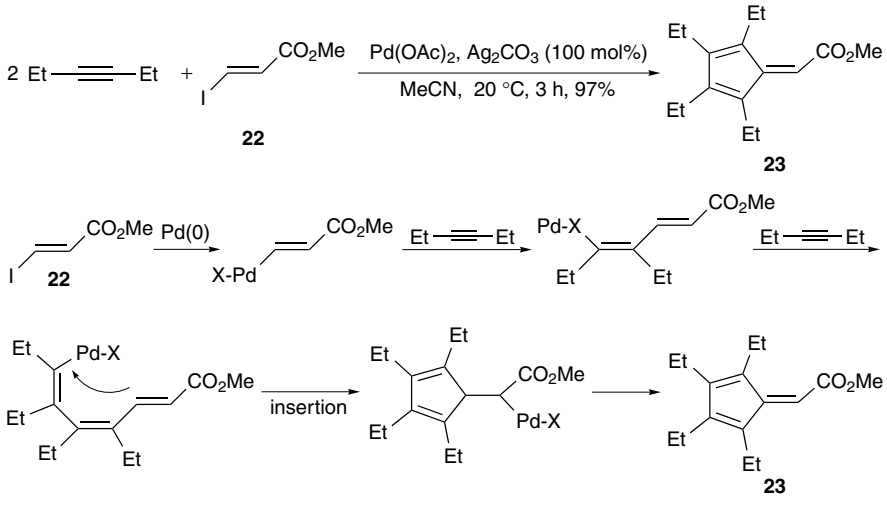


Scheme 3.7 Intermolecular transformations of aryl- and alkenylpalladium intermediates **2** and **7**.

As a typical intermolecular carbopalladation and termination, hydroarylation of alkynes are carried out extensively in the presence of HCO_2H as a hydride source. Formation of regioisomers is observed in the reaction of asymmetric alkynes, and ratios depend on the nature of the substituents. High regioselectivity was observed in the reaction of the tertiary propargylic alcohol **14** to give **15** as a major product [5]. The (*Z*)-2-arylcinnamates **17**, rather than 3-arylcinnamate **18**, was obtained by the hydroarylation of methyl phenylpropiolate (**16**) [6]. 3-Substituted quinoline **21** was prepared by the regioselective hydroarylation of **19**, followed by treatment of **20** with an acid without isolation [6].



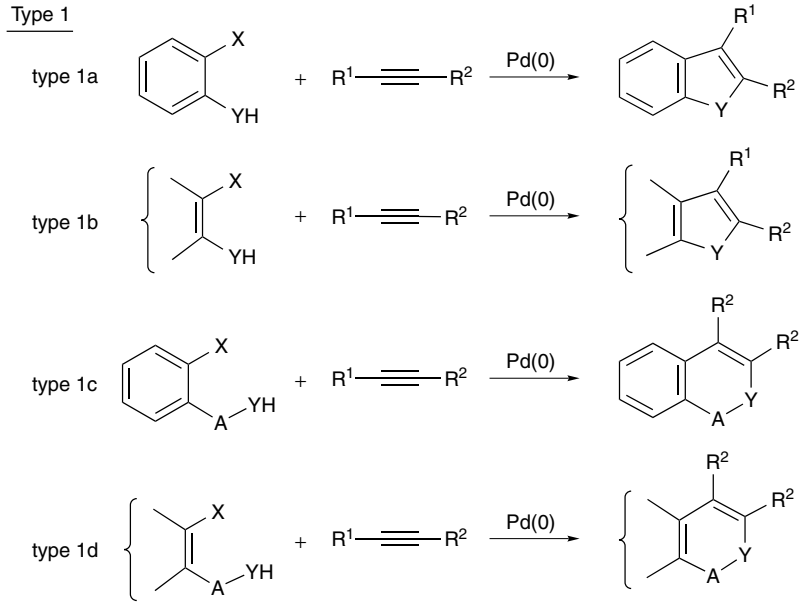
Fulvenes are obtained by the Pd-catalyzed reaction of alkenyl iodides with two alkynes [7,8]. The pentasubstituted fulvene **23** was obtained in good yield from two molecules of 3-hexyne and the alkenyl iodide **22** in the presence of an equimolar amount of silver carbonate without phosphine [9]. In this reaction,



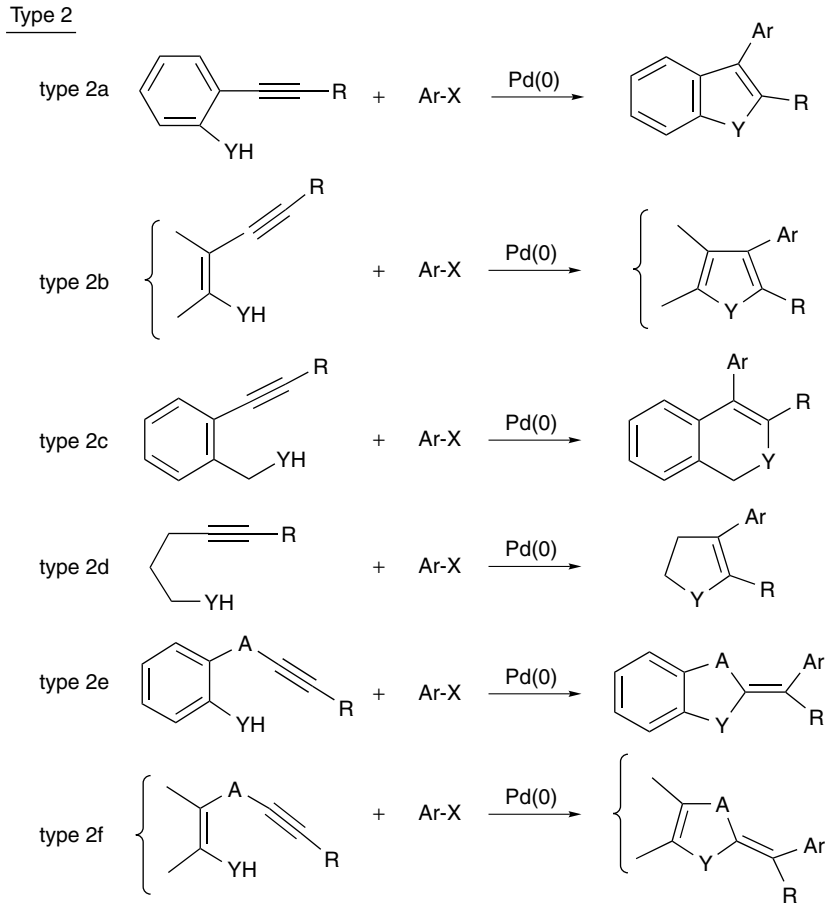
the alkenylpalladium undergoes intermolecular insertion of 3-hexyne twice, and intramolecular Heck-type reaction affords the fulvene **23**.

3.4.3.3 Intramolecular Reactions; General Patterns of Cyclization

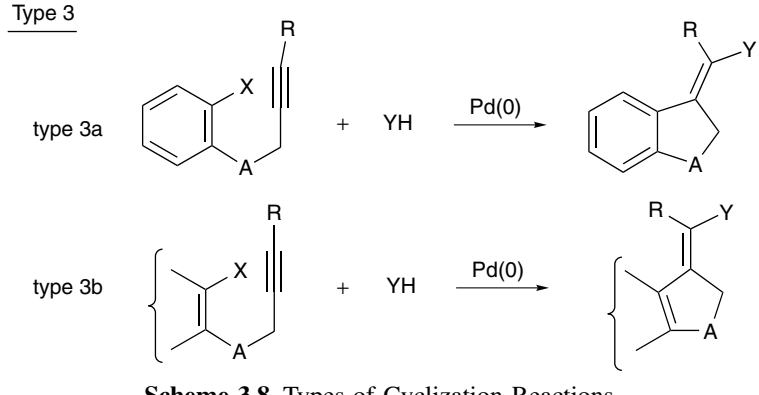
Intramolecular versions and domino reactions involving appropriately functionalized aryl halides and alkynes offer useful synthetic methods for a variety of heterocycles and carbocycles. Few other methods can compete with these Pd-catalyzed cyclizations in versatility. Numerous reports and a number of excellent reviews covering the carbo- and heteroannulations have been published [10]. In order to aid understanding of this somewhat complex chemistry, the cyclizations are classified in to three types (Scheme 3.8).



Scheme 3.8



Scheme 3.8

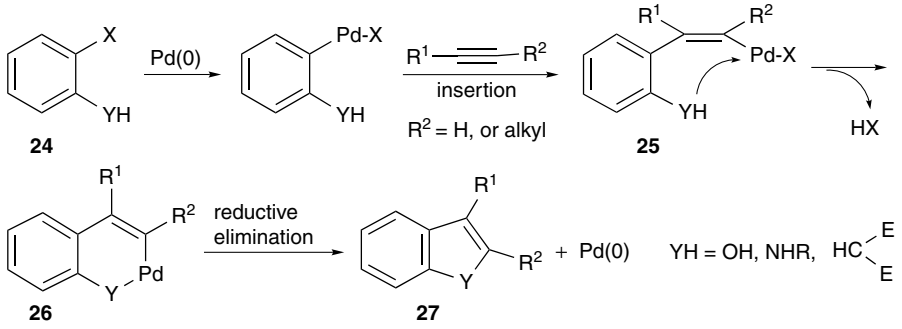


Scheme 3.8 Types of Cyclization Reactions.

3.4.3.4 Cyclization Type 1

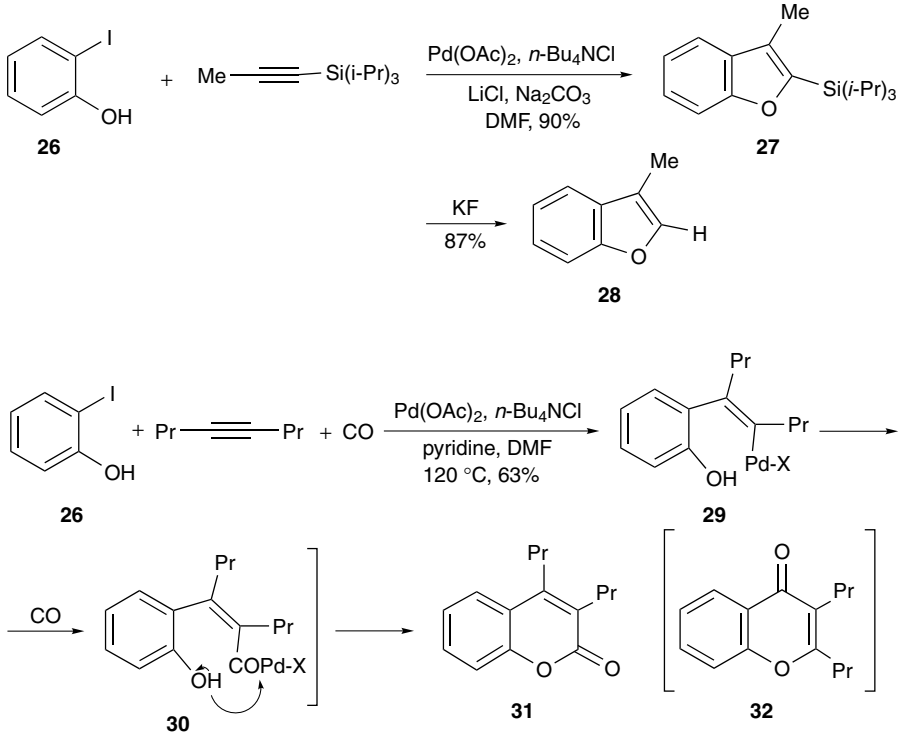
At first, syntheses of heterocycles and carbocycles by the reaction of internal alkynes with *ortho*-functionalized aryl halides **24** are surveyed (Scheme 3.9). The

cyclization proceeds by carbopalladation of alkyne to generate the alkenylpalladium **25**, followed by attack of a nucleophile YH to form the palladacycle **26.** Reductive elimination produces the cyclic compound **27**. Overall *cis* addition to alkyne occurs.

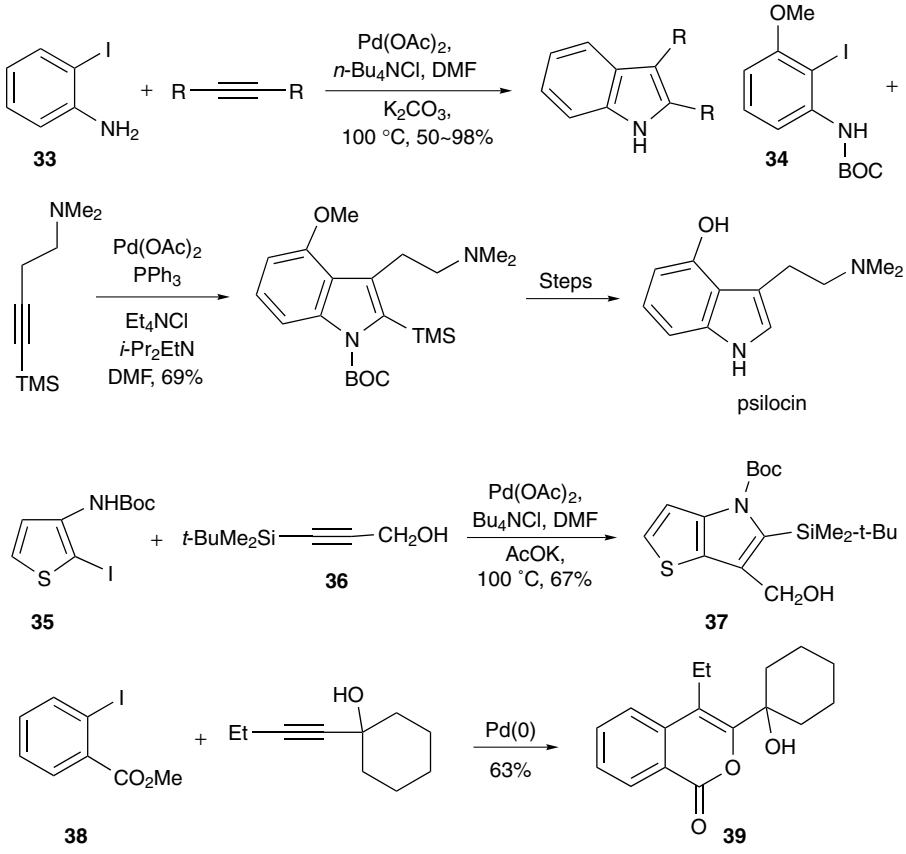


Scheme 3.9

Pd-catalyzed reaction of *o*-iodophenol (**26**) with alkynes offers a good synthetic method of functionalized benzofurans **27**. The silyl group in the benzofuran **27**, obtained from tri-isopropylsilylalkyne, can be used for electrophilic substitution or desilylation to yield **28** [11]. In the reaction of **26** under CO atmosphere (1 atm), the insertion of 4-octyne occurs in preference to the insertion of CO to generate the alkenylpalladium **29**, to which CO insertion occurs to afford the acylpalladium **30**. Finally, intramolecular reaction of **30** yields the coumarin **31**. The chromone **32** is not obtained [12].



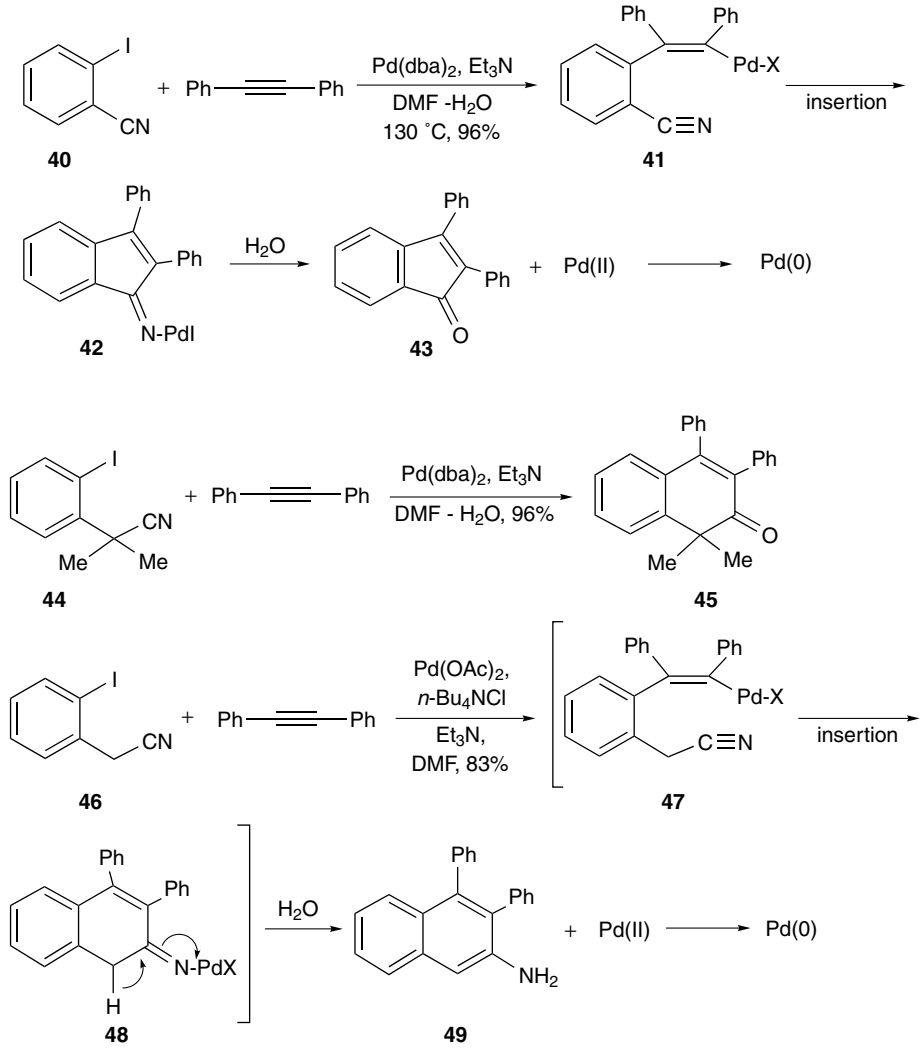
Reaction of *o*-iodoaniline (**33**) with internal alkynes offers a good synthetic method of substituted indoles [13]. A practical synthesis of psilocin was carried out by utilizing the reaction of the iodoaniline derivative **34** with internal alkyne to form an indole derivative as a key reaction [14]. The thieno[3.2-*b*]pyrrole **37** was obtained by the reaction of 2-iodo-3-aminothiophene (**35**) with the alkyne **36** [15]. These reactions of aryl iodides proceed in the absence of phosphine ligands. The isocoumarin **39** was obtained by the reaction of methyl *o*-iodobenzoate (**38**). Poor yield was obtained when the free acid was used [11].



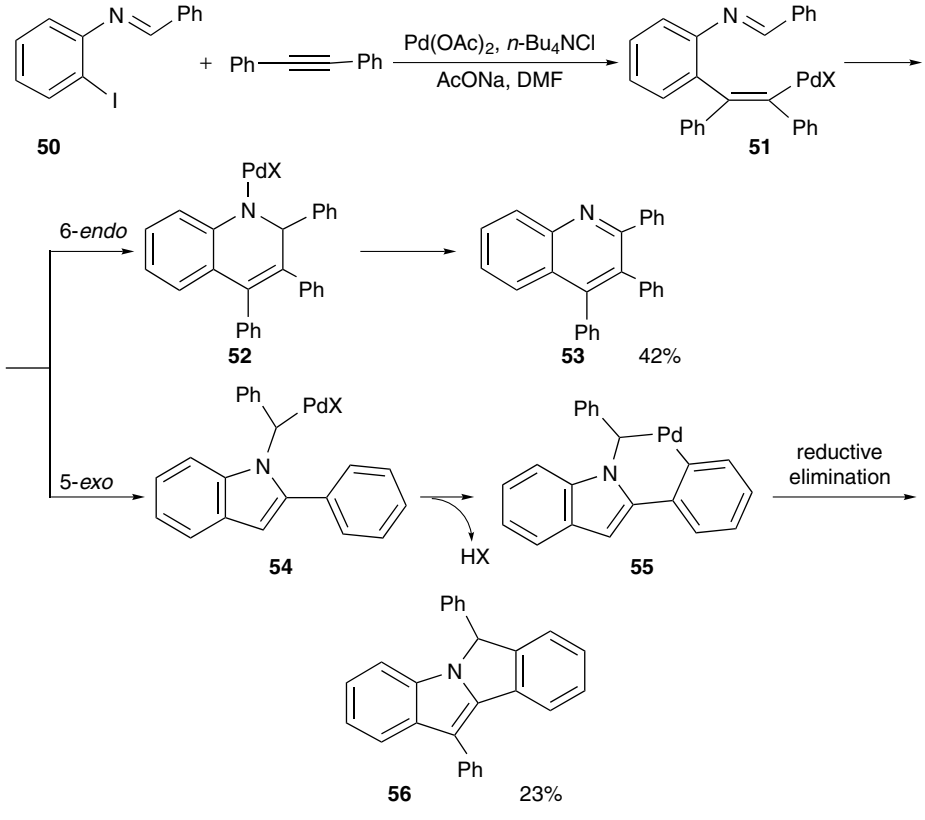
MeCN is a good and inert solvent used in various Pd-catalyzed reactions. However, nitriles participate in Pd-catalyzed intramolecular reactions. The indenone **43** was obtained by the reaction of *o*-iodobenzonitrile (**40**) with alkynes. The reaction can be understood by insertion of a nitrile bond to alkenylpalladium intermediate **41** or 5-*exo* cyclization to give the iminopalladium **42**, hydrolysis of which affords the indenone **43** and Pd(II), which is reduced to Pd(0) [4].

Similarly, the six-membered ketone **45** was obtained from 2-(*o*-iodophenyl)-2-methylpropanenitrile (**44**). However, the reaction of *o*-iodophenylacetonitrile (**46**) afforded the β-naphthylamine **49**, not a ketone. Presumably, 6-*exo* cyclization of **47** yields the iminopalladium **48**. Tautomerization (aromatization) of **48** occurs

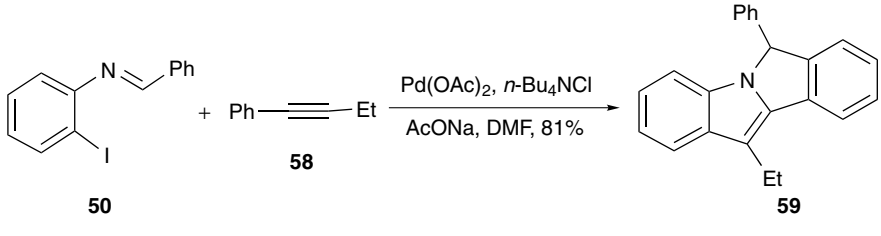
to form the amino group **49** in the final step, rather than hydrolysis to give the ketone [16,17].



Reaction of the imine **50**, derived from *o*-iodoaniline and benzaldehyde, with diphenylacetylene afforded a mixture of the quinoline **53** and the isoindolo[2.1-*a*]indole **56**. Formation of the quinoline can be understood by insertion of the C=N bond in **51**, which is regarded as 6-*endo* cyclization of the intermediate **51** to generate **52**, followed by β-H elimination to yield the quinoline **53**. On the other hand, the isoindolo[2.1-*a*]indole **56** is formed by 5-*exo* cyclization of **51** to produce **54**. The final step is the electrophilic palladation of the σ-palladium intermediate **54** to the adjacent aromatic ring to give **55**, and reductive elimination gives rise to **56** [18]. The isoindolo[2.1-*a*]indole **59** was obtained in high yield from alkylarylacetylene **58** and the imine **50** [19].

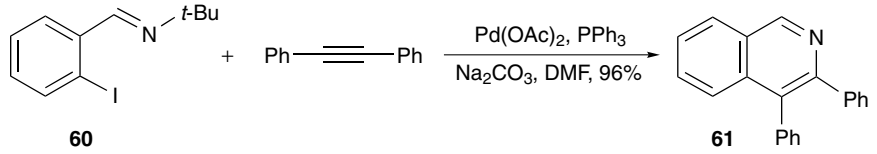


50 **51** **52** **53** **54** **55** **56**

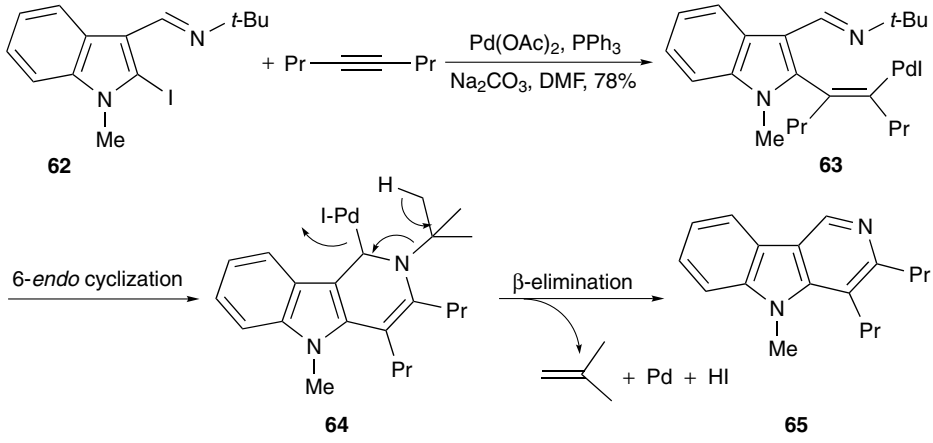


50 **58** **59**

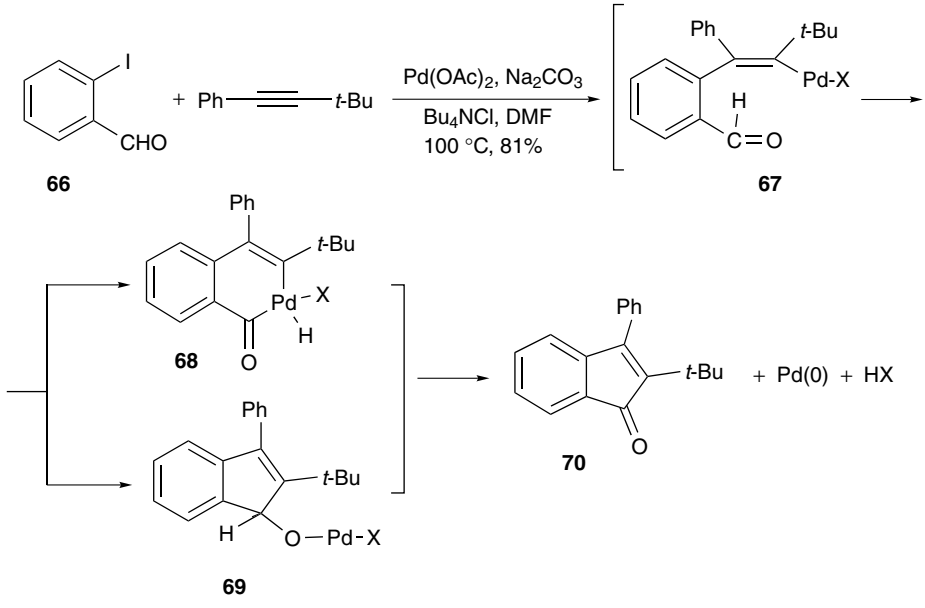
The isoquinoline **61** was obtained by the reaction of *t*-butylimine **60** of *o*-iodobenzaldehyde with internal alkyne [20]. The reaction was extended to synthesis of the γ-carboline **65** from the *t*-butylimine of *N*-methyl-2-iodoindole-3-carboxaldehyde **62** [21]. The reaction is explained by 6-*endo* cyclization of the alkenylpalladium intermediate **63**, followed by elimination of β-*t*-butyl group as isobutylene as shown by **64**. This mechanism explains the importance of *t*-butylimine in this cyclization.



60 **61**

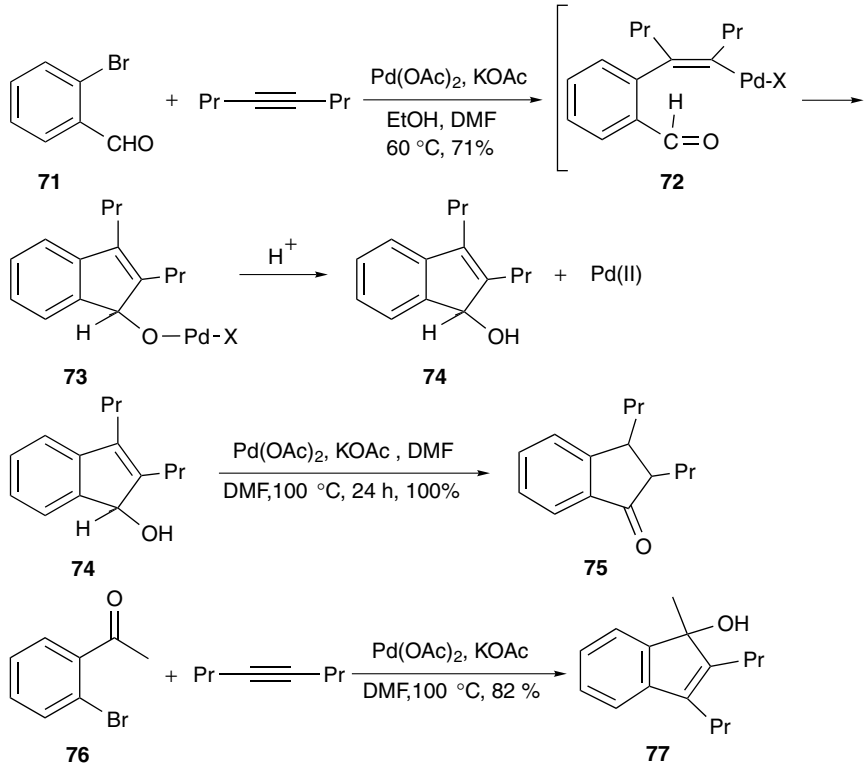


The indenone **70** is obtained by the reaction of *o*-iodobenzaldehyde (**66**) with alkyne [22,23]. Two mechanisms are suggested. One of them involves the formation of Pd(IV) species **68** from **67** by oxidative addition of aldehyde, and its reductive elimination affords the indenone **70**. Another possibility is the insertion of carbonyl group (or nucleophilic attack) to form the indenyloxypalladium **69**, and β-H elimination gives the indenone **70**.

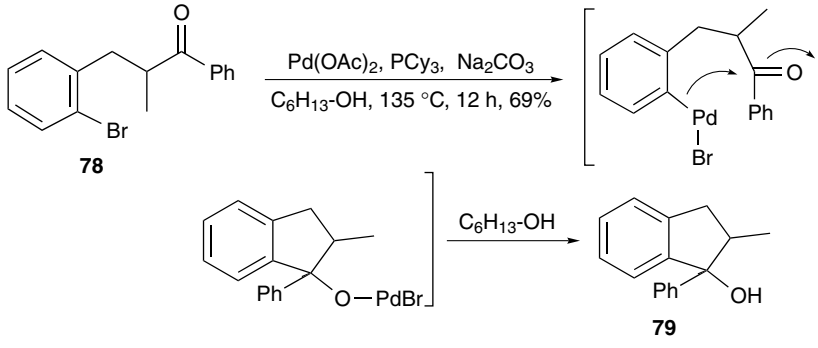


On the other hand, Yamamoto and co-workers observed that the Pd-catalyzed reaction of *o*-bromobenzaldehyde (**71**) with 4-octyne in DMF using $Pd(OAc)_2$ gave rise to the indenol **74** in 71 % yield. Also it was confirmed that the indenol **74**, once formed, was isomerized to the indanone **75** quantitatively in the presence of $Pd(OAc)_2$ and AcOK [24]. Furthermore, reaction of *o*-bromoacetophenone (**76**) with 4-octyne afforded the substituted indenol **77** in 82 % yield, which has no

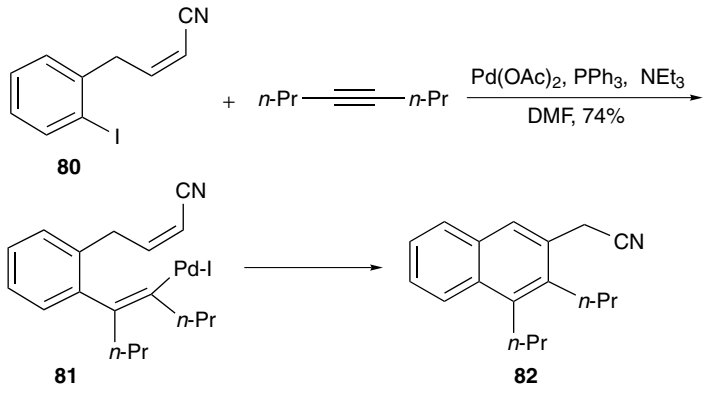
possibility of isomerization. Yamamoto proposed that the indenols **74** and **77** are formed by intramolecular nucleophilic attack of the vinylpalladium species **72** to the carbonyl group to form the Pd alkoxide **73**; namely, a hitherto unknown catalytic Grignard-type reaction occurred. However, the formation of **73** may be explained by insertion of a carbonyl group, followed by protonolysis to afford **74** and Pd(II) [25].



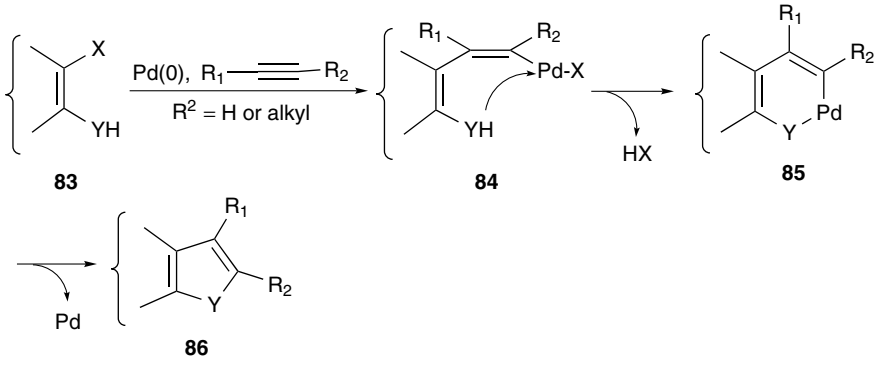
Furthermore, as a related reaction, they obtained the cyclopentanol **79** by the Grignard-type reaction of 1-methyl-2-(*o*-bromophenyl)ethyl phenyl ketone (**78**) without alkynes in the presence of $Pd(OAc)_2$, PCy_3, Na_2CO_3 and 1-hexanol. It was confirmed that the addition of 1-hexanol was crucial [26]. These reactions are mechanistically interesting. A similar catalytic reaction has been reported by Vicente. These reactions are considered again in Chapter 3.7.2 [27].



The substituted naphthalene **82** was produced from the *o*-(3-cyano-2-propenyl)-iodobenzene (**80**) by carbopalladation of 4-octyne, followed by Heck reaction of **81** [28].

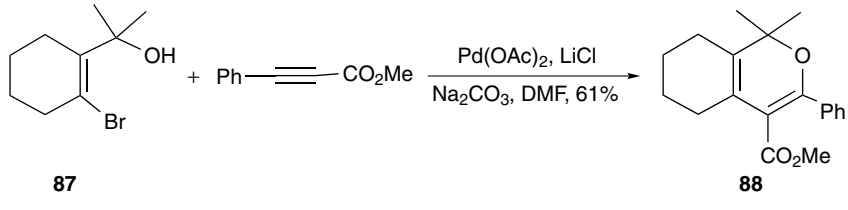


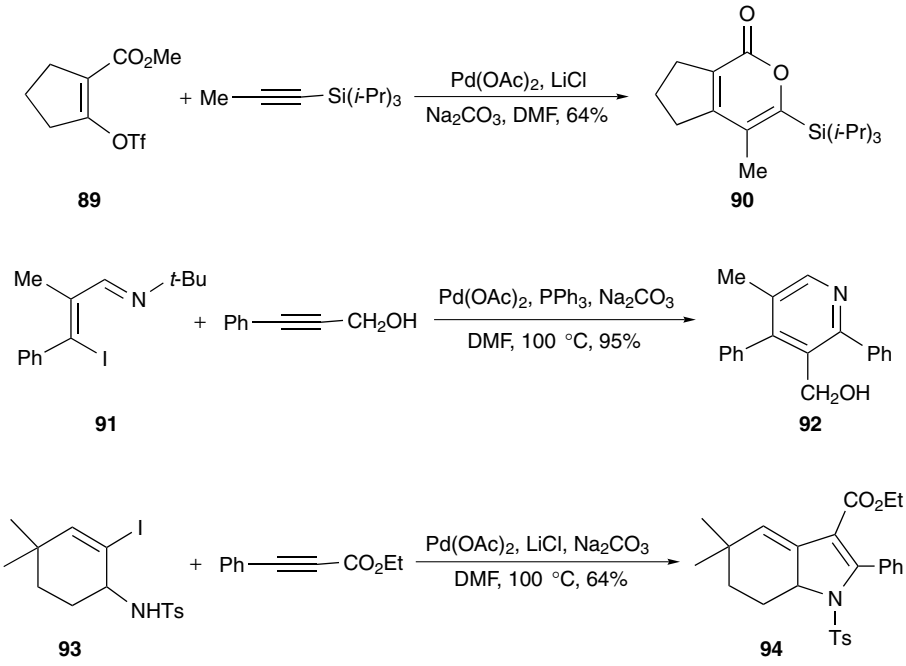
The *cis*-heteroannulation of alkyne extended to alkenyl halides **83** containing a proximate nucleophilic center to yield the heterocycles **86** by the reactions via **84** and **85** similar to those summarized in Scheme 3.9 (Scheme 3.10).



Scheme 3.10

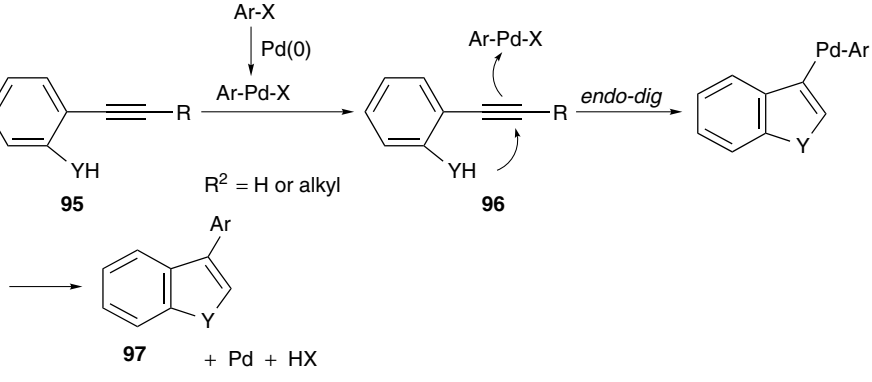
The pyran **88** and α-pyrone **90** are prepared from the vinyl bromide **87** and the vinyl triflate **89** by intramolecular trapping of the alkenylpalladium intermediates with alcohol and ester [29,30]. The pyridine **92** was prepared by the iminoannulation of the iminoalkenyl iodide **91** [31]. The 2-iodo-3-tosylaminocyclohexene **93** underwent *cis*-carboamination of ethyl phenylpropiolate to give **94** [32].





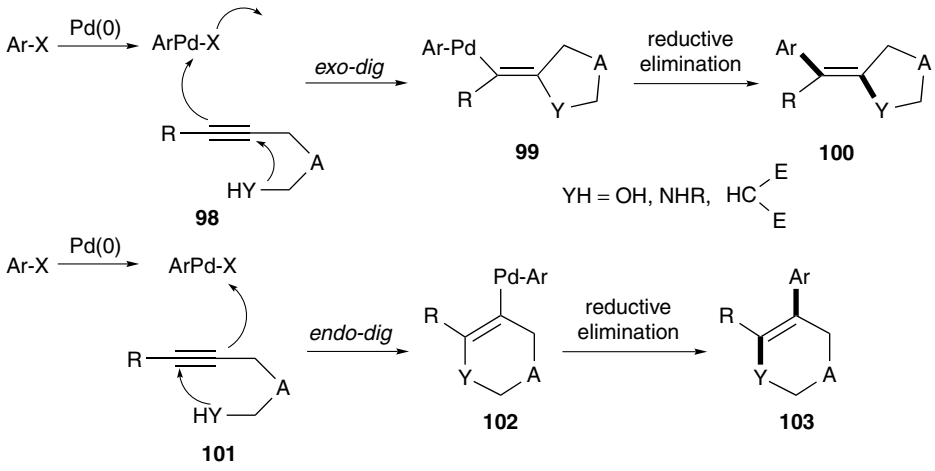
3.4.3.5 Cyclization Type 2

Another heteroannulation is combination of aryl and alkenyl halides with *ortho*-functionalized phenylalkynes **95** to give heterocycles **97** such as benzofurans and indoles (Scheme 3.11). In this reaction, *trans* addition of Ar-Pd to a triple bond and *endo* cyclization, as shown by **96**, occur.



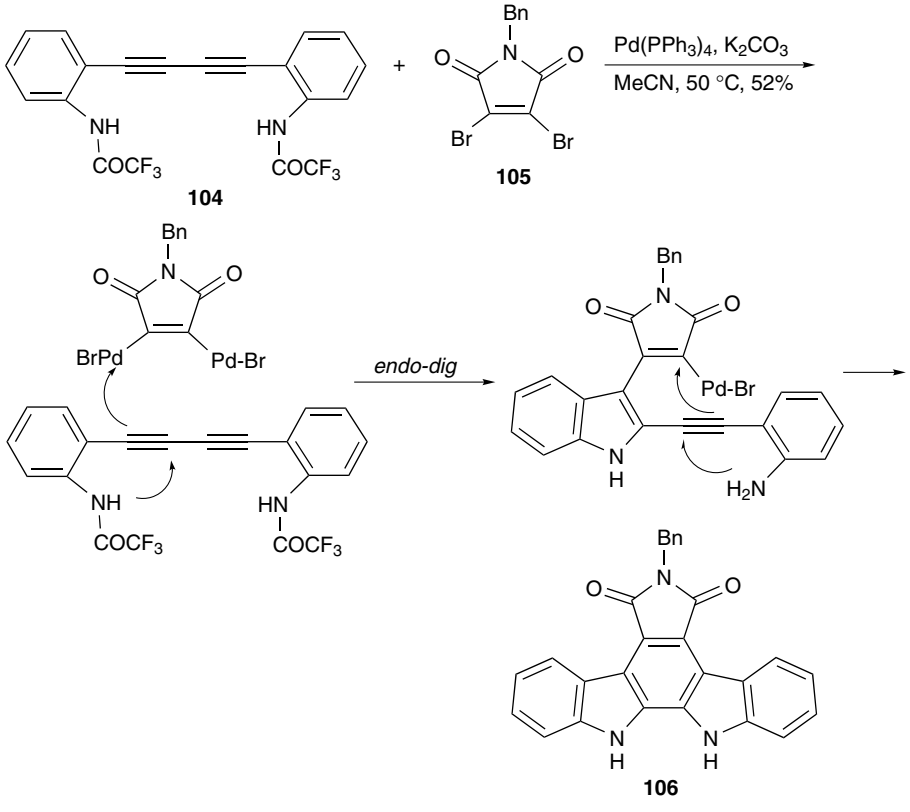
Scheme 3.11

The alkynes containing proximate nucleophiles (YH) undergo *trans* addition of the nucleophile and organopalladium species, as shown by **98** and **101**, to generate **99** and **102**, and reductive elimination produces the cyclized *trans* addition products **100** and **103**. In this cyclization, either *exo-dig* or *endo-dig* cyclizations take place depending on the number of carbon atoms between the triple bond and the nucleophilic center to give **100** and **103** (Scheme 3.12).



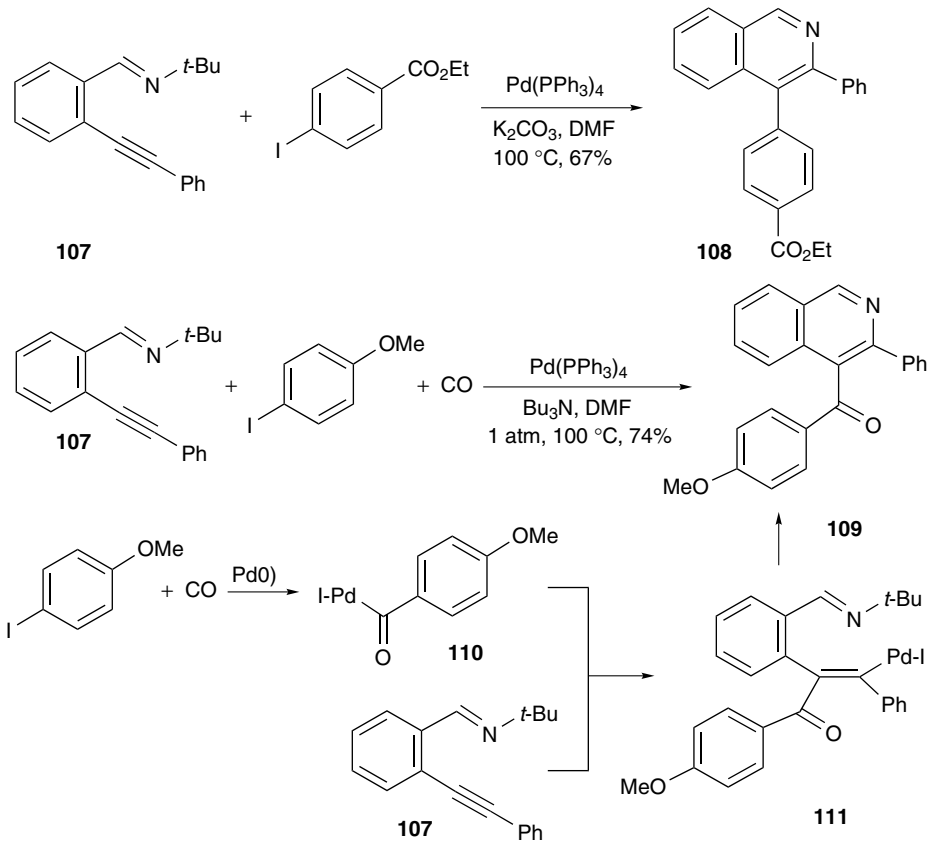
Scheme 3.12

The indole synthesis was extended to an elegant synthesis of indolo[2.3-*a*]carbazole **106** by bis-annulation of the diacetylene **104** with the dibromomaleimide **105** [33].



The isoquinoline **108** is prepared from the imine **107** as a variation of the iminoannulation [34]. When the iminoannulation of **107** is carried out under CO

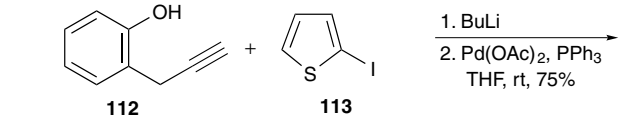
atmosphere (1 atm), CO reacts with *p*-iodoanisole to generate the acylpalladium **110**, which undergoes acylpalladation of the triple bond of **107** to afford the 4-aroylisoquinoline **109** via **111** [35].



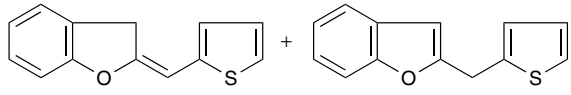
Reaction of *o*-2-propynylphenol (**112**) with 2-iodothiophene (**113**) gave the 2-alkylidenedihydrobenzofuran **114** and the benzofuran **115** [36]. The reaction of a nitrogen analog **116** afforded the pyrrolidine derivative **117** [37]. The propargyl tosylcarbamate **118** underwent *trans* carboamination with cyclohexenyl triflate to give the oxazolidinone **119** in the presence of TFP as a ligand and benzyltriethylammonium chloride [38,39].

The 1-(1-alkynyl)cyclobutanol **120** was expanded by Pd-catalyzed reaction with aryl- and alkenyl halides to produce the 2-(2-arylidene)cyclopentanones **123**. The reaction can be understood formally by carbopalladation to give **121**, and migration of an electron-rich carbon to Pd to form the palladacyclohexanone **122**, and the cyclopentanone **123** is obtained by reductive elimination of **122** (see Chapter 3.8.2) [40].

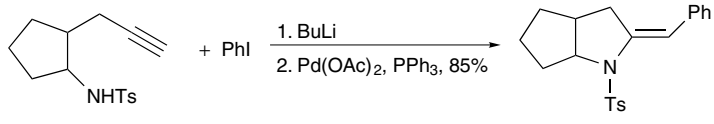
A useful precursor **126** was prepared by coupling the triflate **124**, derived from a γ-lactam, with the alkynyl amine **125**. The *cis* addition product **128** was formed in this case via intramolecular amination as shown by **127** [41].



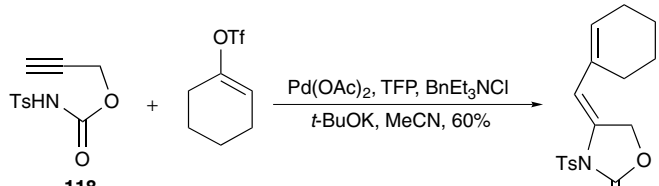
112 **113**



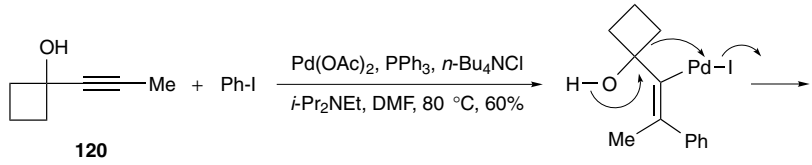
114 3 : 1 **115**



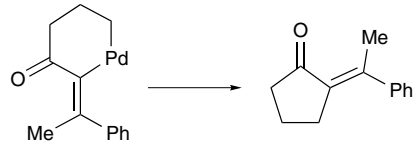
116 **117**



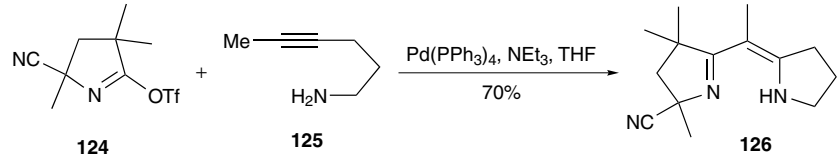
118 **119**



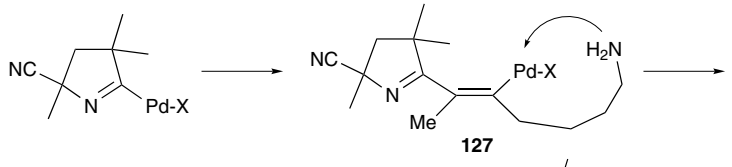
120 **121**



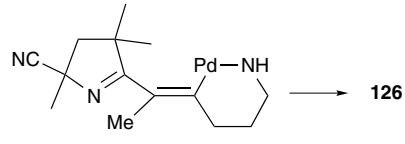
122 **123**



124 **125** **126**



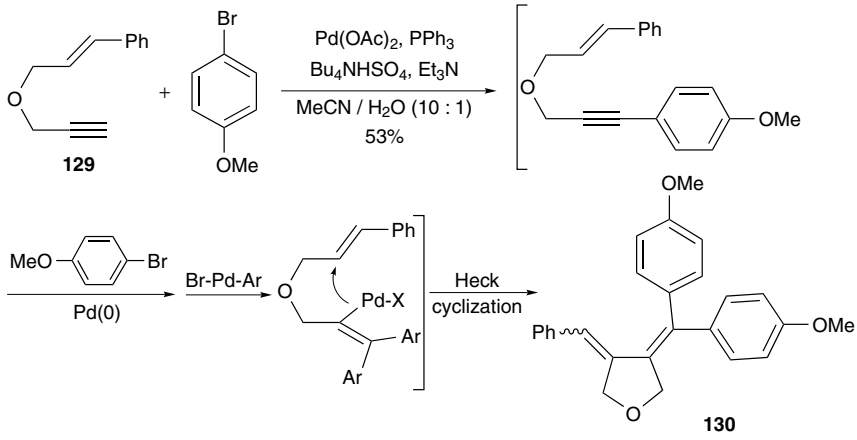
127



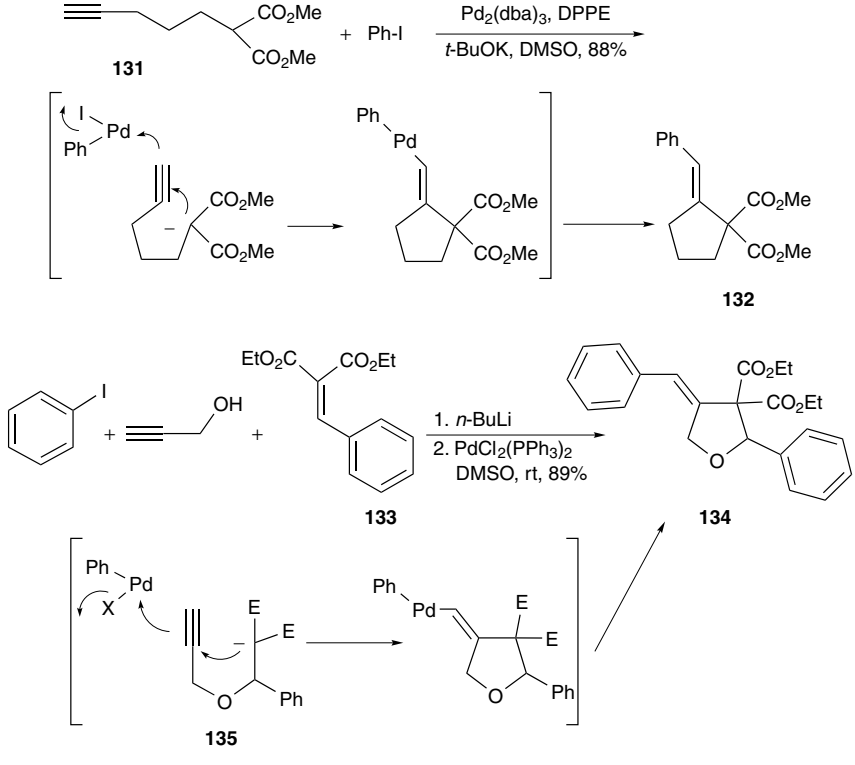
126

128

Reaction of the enyne **129** with *p*-bromoanisole gave the furan **130** smoothly in 53 % yield via Sonogashira coupling and carbopalladation of the triple bond, followed by intramolecular insertion of the double bond (Heck-type reaction) [42].

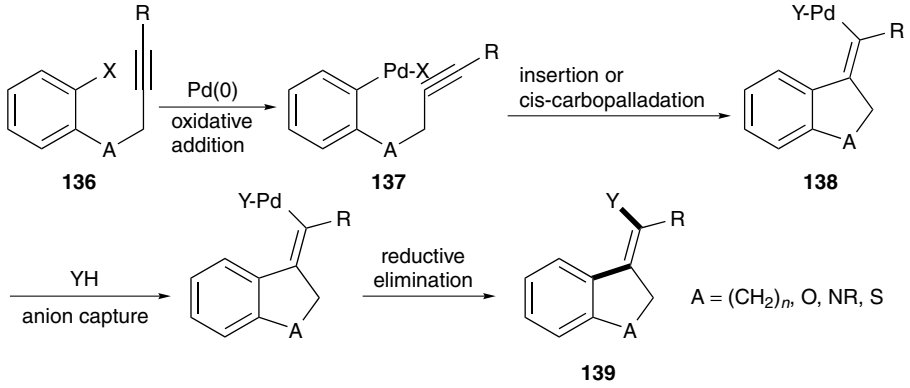


The stereo-defined benzylidenecyclopentane **132** was obtained by *trans* addition of a phenyl group and a carbanion to the terminal alkyne **131.** The cyclization proceeds via *trans* carbopalladation [43]. As a related reaction, stereo-defined 3-arylidenetetrahydrofuran **134** was prepared by the reaction of iodobenzene, propargyl alcohol, and Michael acceptor **133**. The reaction is understood in terms of Michael addition of propargyl alcohol to **133**, followed by carbopalladation of the triple bond as shown by **135** [44].



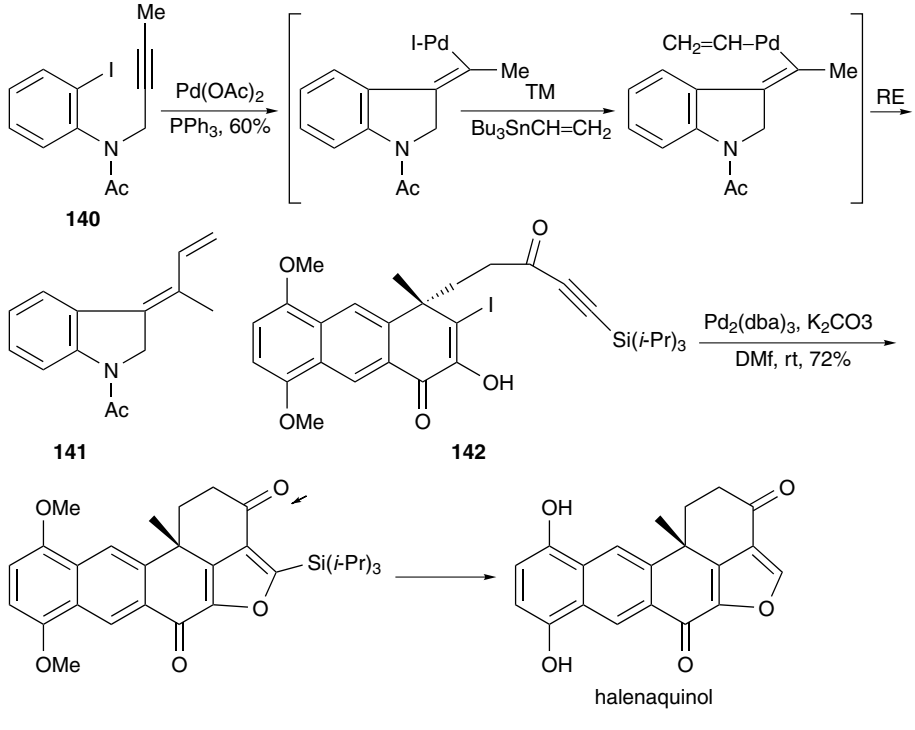
3.4.3.6 Cyclization Type 3

In type 3 cyclization, the aryl halides **136** having an alkyne side chain at *ortho* position undergo *cis* carbopalladation of **137** to generate **138**, which is trapped by a nucleophile YH to give the cyclized product **139**. In this cyclization, *cis* addition to triple bonds occurs (Scheme 3.13).

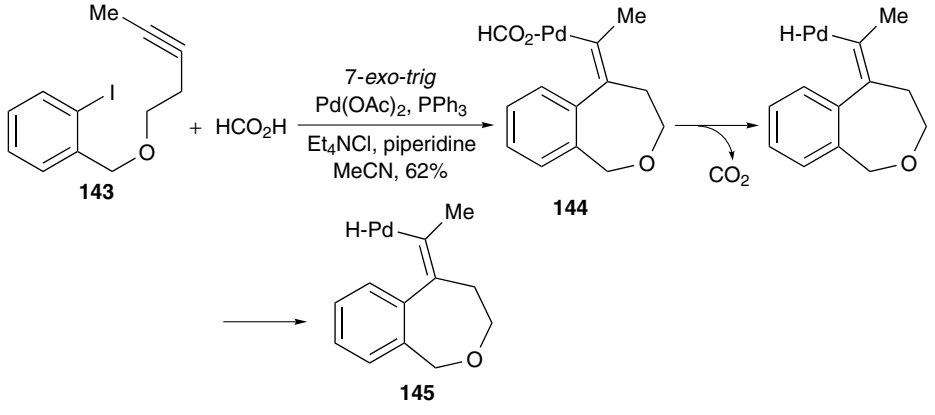


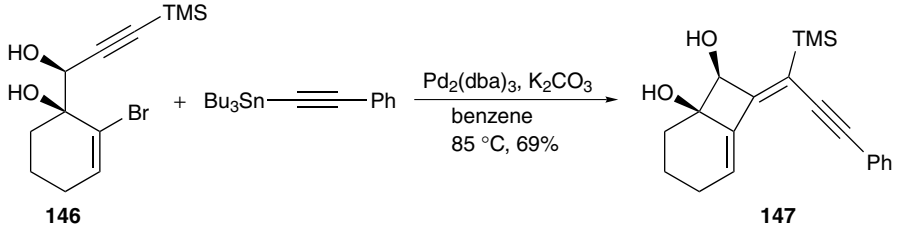
Scheme 3.13

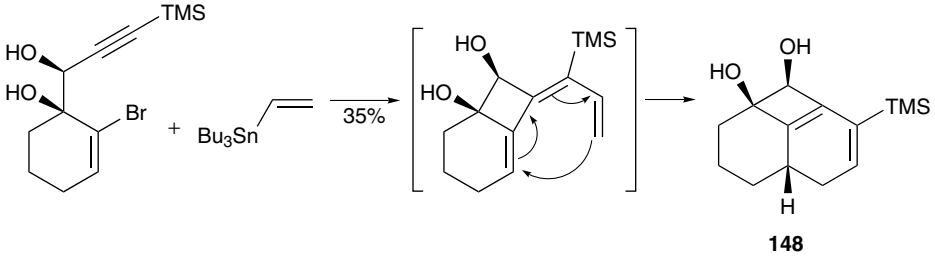
Reaction of **140** with vinyltin reagent yields the cyclized product **141**. The conversion can be understood by *cis* carbopalladation, transmetallation with the Sn reagent, and reductive elimination [45,46]. This reaction is overall *cis* addition to the triple bond. The intramolecular version of furan synthesis was applied to the preparation of the key intermediate of halenaquinone and halenaquinol syntheses from **142** [47].



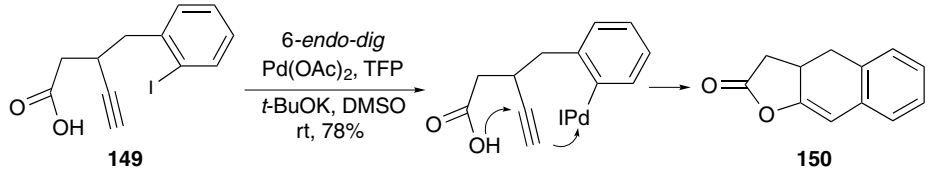
The homopropargylic ether **143** undergoes 7-*exo-dig* cyclization in the presence of formic acid to generate the Pd formate **144**, which is converted to the Pd hydride. Reductive elimination gives the *cis* hydroarylation product **145** [48]. Cyclobutane was formed by a rare unfavored 4-*exo-dig* cyclization of the γ-bromopropargylic diol **146** and trapped with an alkynyltin reagent to yield the cyclobutanediol **147** in 69 % yield. When a vinyltin reagent was used for the trapping, the unusual strained tricyclic system **148** was obtained in 35 % yield by 6π-electrocyclization of an intermediate [49].



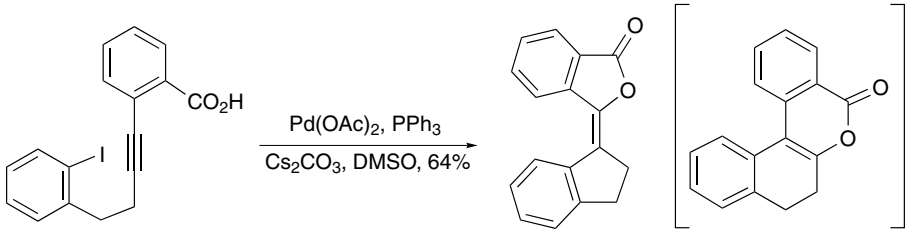




The 3-substituted pentynoic acid **149** underwent 6-*endo-dig* cyclization to give rise to the γ-arylidenebutyrolactone **150** using TFP as a ligand [50]. On the other

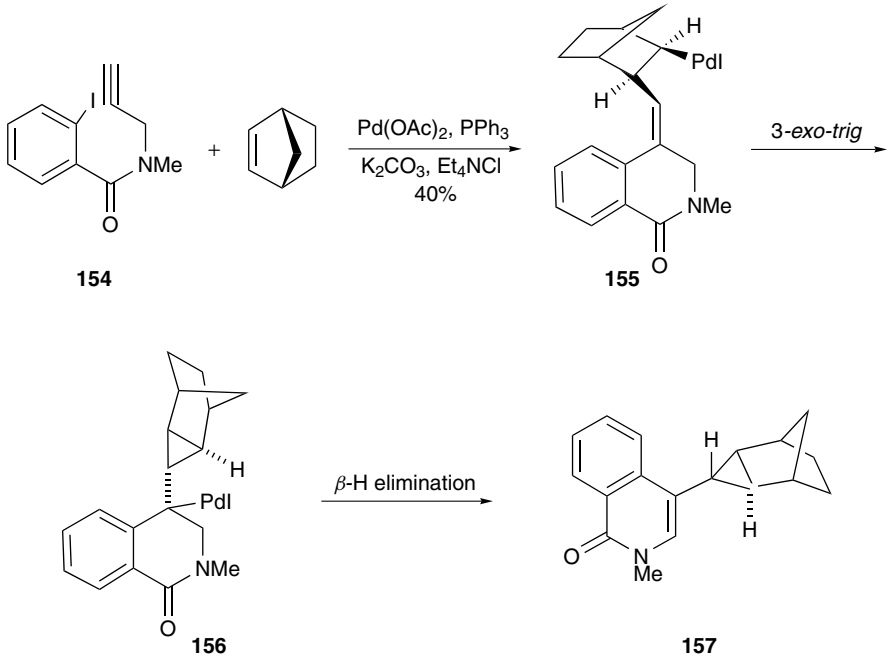


hand, *o*-alkynylbenzoic acid **151** underwent 5-*exo-dig* cyclization to yield the γ-arylidenebutyrolactone **152** using Cs_2CO_3 as a base in DMSO. The product of 6-*endo-dig* cyclization **153** was obtained as a byproduct depending on reaction conditions [51].



151 **152** **153**

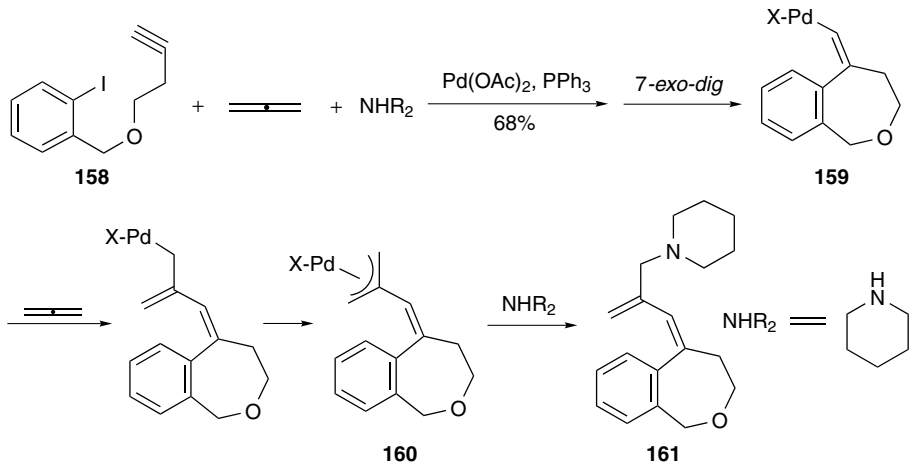
The reaction of the alkyne **154** in the presence of norbornene as a relay generates **155** by insertion of norbornene. The cyclopropane **156** is formed by 3-*exo-trig* cyclization, and the lactam **157** was obtained by β-H elimination [52].



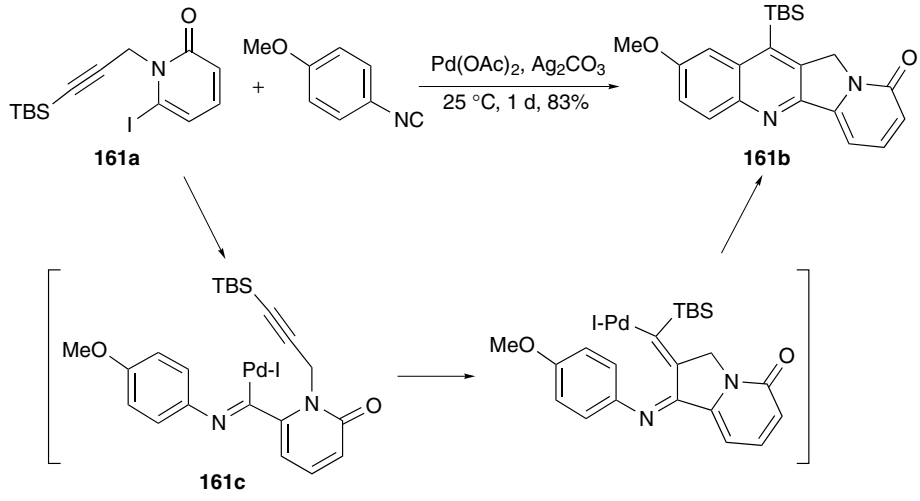
154 **155** **156** **157**

Allene can be used as a relay switch to generate a π-allylpalladium, which can be trapped by a nucleophile. The reaction of **158** with allene and an amine afforded **161**. The 7-*exo-dig* cyclization of **158** gives **159**, which is converted to the π-allylpalladium **160** by insertion of allene. The reaction is terminated by amination of **160** to yield **161** [53].

Curran reported an interesting synthetic method of skeletons of camptotecin analog [53a]. Reaction of 6-iodo-*N*-propargylpyridone **161a** with an electron-rich aryl



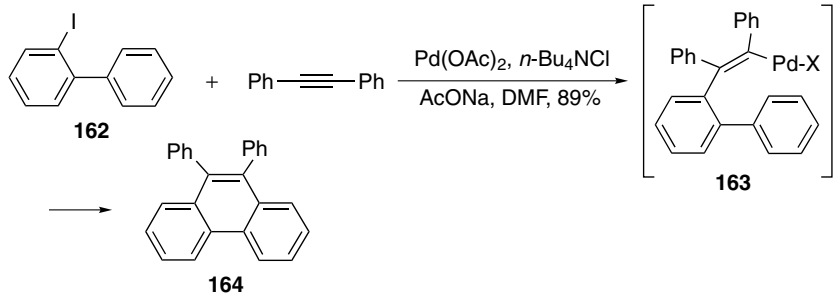
isonitrile in the presence of $Pd(OAc)_2$ and Ag_2CO_3 provided 11*H*-indolizino[1.2-*b*]quinoline-9-one **161b** in 83 % yield. The reaction is understood by insertion of the isonitrile to arylpalladium to generate **161c** as the first step. It is known that isonitrile behaves similar to CO and undergoes insertion. Subsequent insertion of the triple bond and attack on the aromatic ring give rise to **161b**.



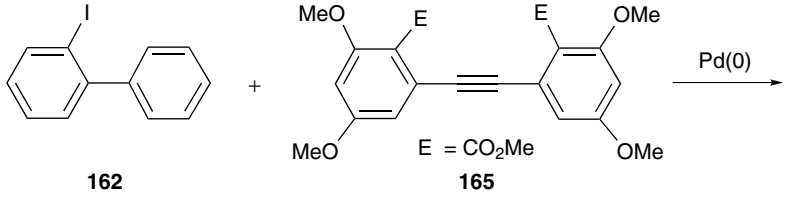
3.4.3.7 Cyclization Involving Attack on Aromatic Rings

Termination by attack on an aromatic ring is discussed in Chapter 3.3.4. Similar termination occurs frequently in the reaction of alkynes with halides.

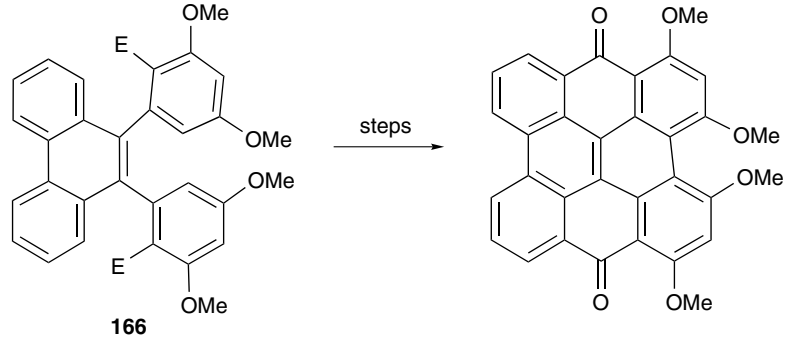
The reaction of 2-iodobiphenyl (**162**) with alkynes offers a good synthetic method of 9,10-disubstituted phenanthrenes **164**. The intermediate **163** undergoes attack on an aromatic ring as one possibility [54]. The reaction of functionalized diarylacetylene **165** with **162** was applied to the syntheses of an analog of antiviral agent hypericin **167** via **166** [55]. Also the indolocarbazole **169** was prepared from 3-iodobiindole **168** by attack on the indole ring [56].



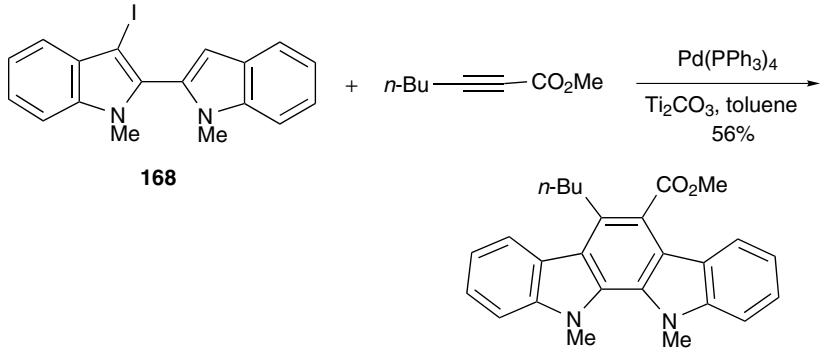
162 **163** **164**



162 **165**

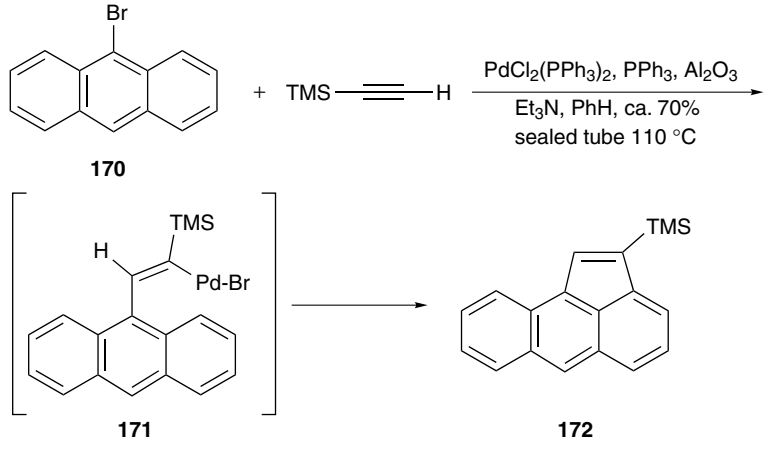


166 **167**

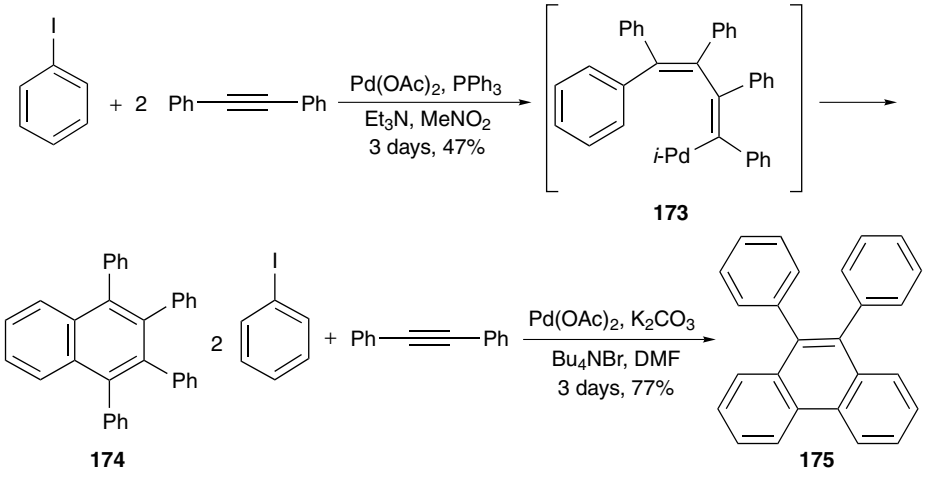


168 **169**

Regioselective carbopalladation of 1-alkynes substituted by bulky groups such as TMS with 9-bromoanthracene (**170**) generates **171**, which attacks the aromatic ring to afford the 2-substituted aceanthrylene **172**. The reaction offers a good synthetic method for this cyclic system [57].

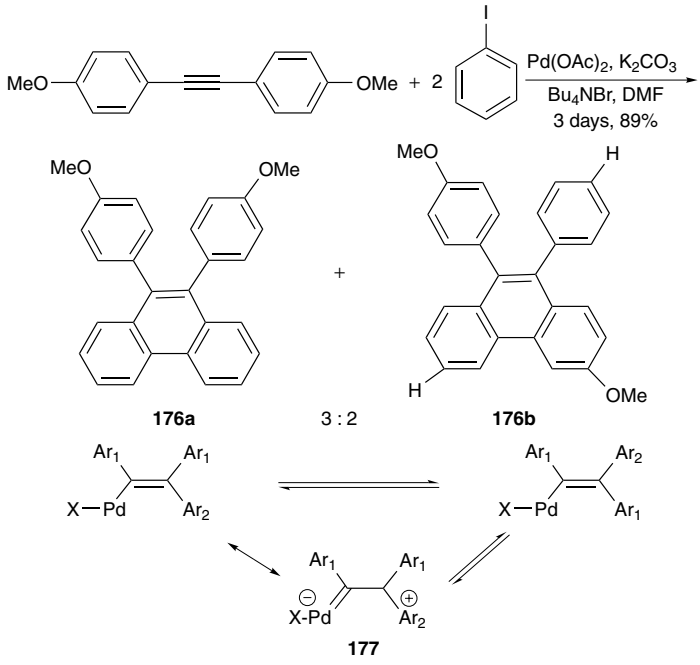


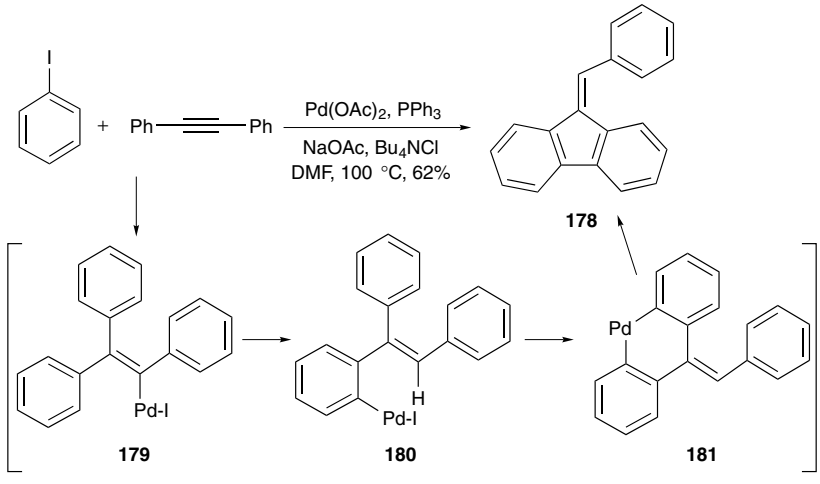
Reactions of diarylacetylenes with aryl iodides give different cyclic products under different conditions. 1,2,3,4-Tetraphenylnaphthalene **174** was obtained by the reaction of two molecules of diphenylacetylene with iodobenzene in nitromethane. In this reaction, the intermediate **173** attacks the benzene ring [22]. In the absence of PPh_3 in DMF, 9,10-diphenylphenanthrene (**175**) was formed.



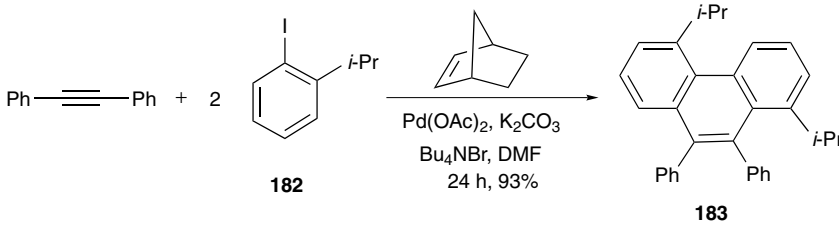
However, reaction of dianisylacetylene under similar conditions afforded a mixture of the regioisomers **176a** and **176b**. The result shows that *cis–trans* isomerization of the alkenylpalladium intermediate becomes possible due to the contribution of **177** which can rotate [58].

Furthermore, the reaction of diphenylacetylene with iodobenzene under Jeffery conditions gave rise to 9-alkylidene-9H-fluorene **178**. The reaction is explained by a novel migration of the alkenylpalladium intermediate **179** to the arylpalladium species **180**. Finally **178** is formed via the palladacycle **181** and reductive elimination [59].





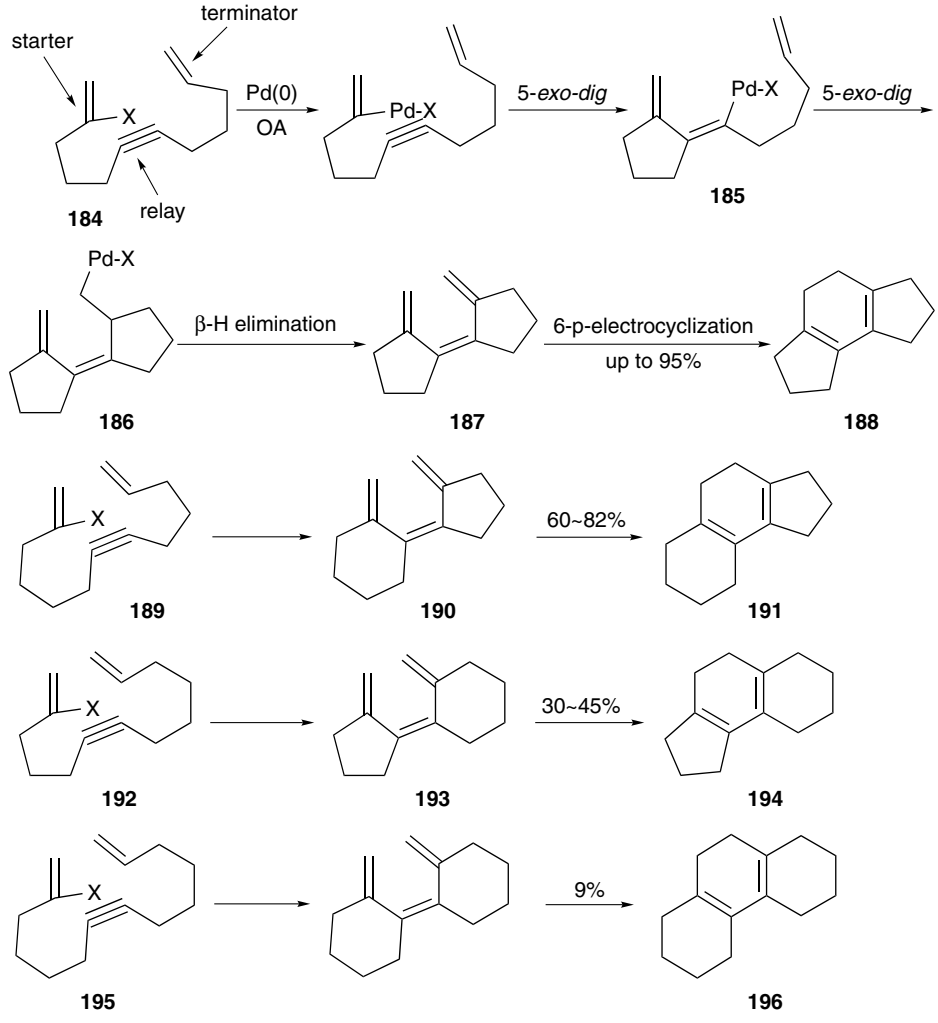
Catellani reported that reaction of diphenylacetylene with the *ortho*-substituted phenyl iodide **182** in the presence of norbornene in a less than equivalent amount afforded the 1,5-disubstituted 9,10-diphenylphenanthrene **183** selectively [60]. The



role of norbornene as a 'catalyst' in this interesting conversion can be explained similarly as observed by Catellani in the reaction of alkenes with iodobenzene (see Chapter 3.8.1).

3.4.3.8 Formation of Tricycles from Halo Dienynes

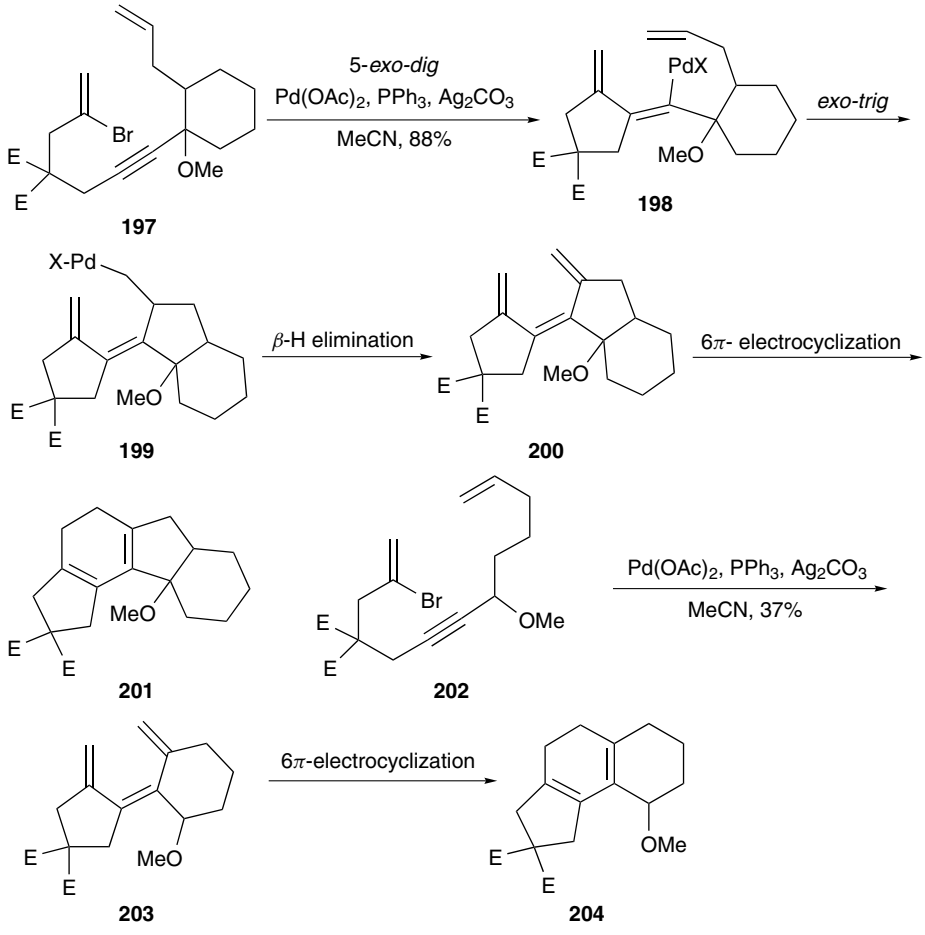
Domino cyclizations of various types of polyenynes offer powerful synthetic tools for efficient syntheses of polycyclic compounds. Among many possibilities, several representative patterns are cited here. A fully intramolecular version of a three-step domino reaction of 2-bromododeca-1,11-dien–6-yne **184** and 2-bromotrideca-1,12-dien-7-yne **189** offers a useful synthetic method of the tricycles **188** and **191** with a central cyclohexa-1,3-diene moiety. In these compounds **184** and **189**, an alkenyl bromide starter, an alkynyl relay, and an alkenyl terminator are all tethered as summarized by **184** in Scheme 3.14. The final step is facile 6-π-electrocyclization of **187** and **190** to give rise to **188** and **191** [61].



Scheme 3.14 Cyclization of 2-halo dienynes.

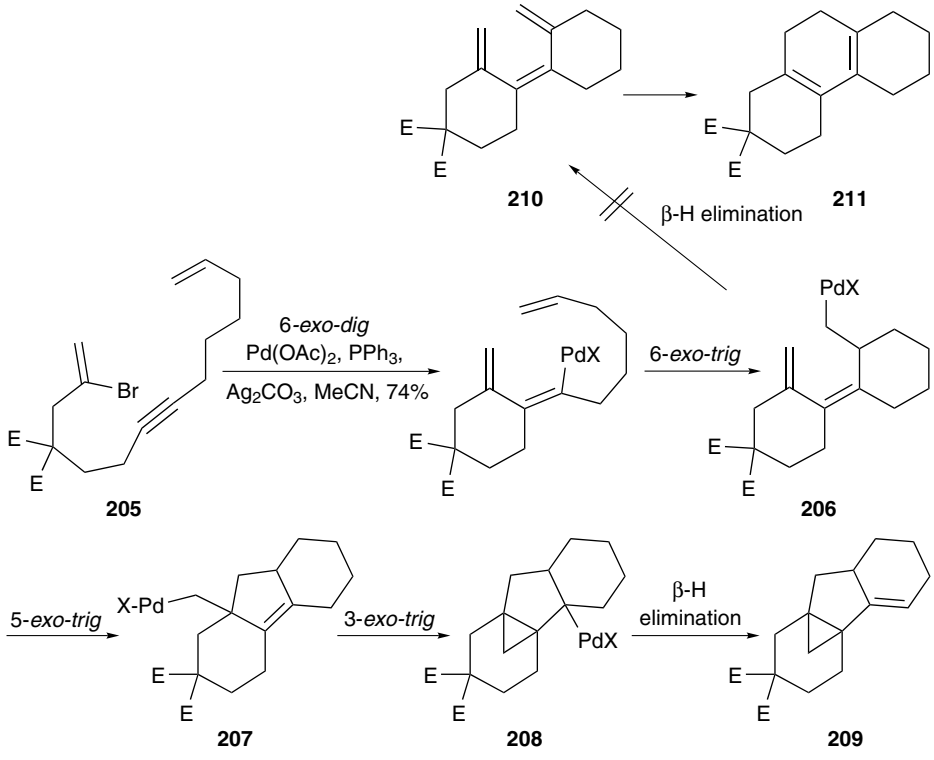
The reaction of the dienyne **184** proceeds by oxidative addition of the alkenyl bromide, followed by 5-*exo-dig* cyclization to generate **185**. Then 5-*exo-trig* cyclization of **185** gives the favored five-membered ring **186**, and then generates the hexatriene system **187**, which undergoes thermal 6-π-electrocyclization to give the 1,3-cyclohexadiene **188** [62]. Good yields are obtained when only five-membered rings are formed by Pd-catalyzed cyclizations involving alkynes and alkenes. Formation of six-membered or larger rings **194** and **196** is less favorable.

For example, reaction of the dienyne **197** proceeds at 80 °C by oxidative addition of the alkenyl bromide, followed by 5-*exo-dig* cyclization to generate **198**. Then 5-*exo-trig* cyclization of **198** gives the favored five-membered ring **199**, and then generates the hexatriene system **200**, which undergoes thermal 6-π-electrocyclization at this temperature to give the 1,3-cyclohexadiene moiety **201** [62]. Lower yields are obtained when one of the Pd-catalyzed cyclizations leads to a six-membered ring. For example, the cyclization of **202** gave the hexatriene **203**, and its 6-π-electrocyclization produced **204** in 37 % yield. Similarly, the tricycle **196** was obtained from the dienyne **195** in 9 % yield.



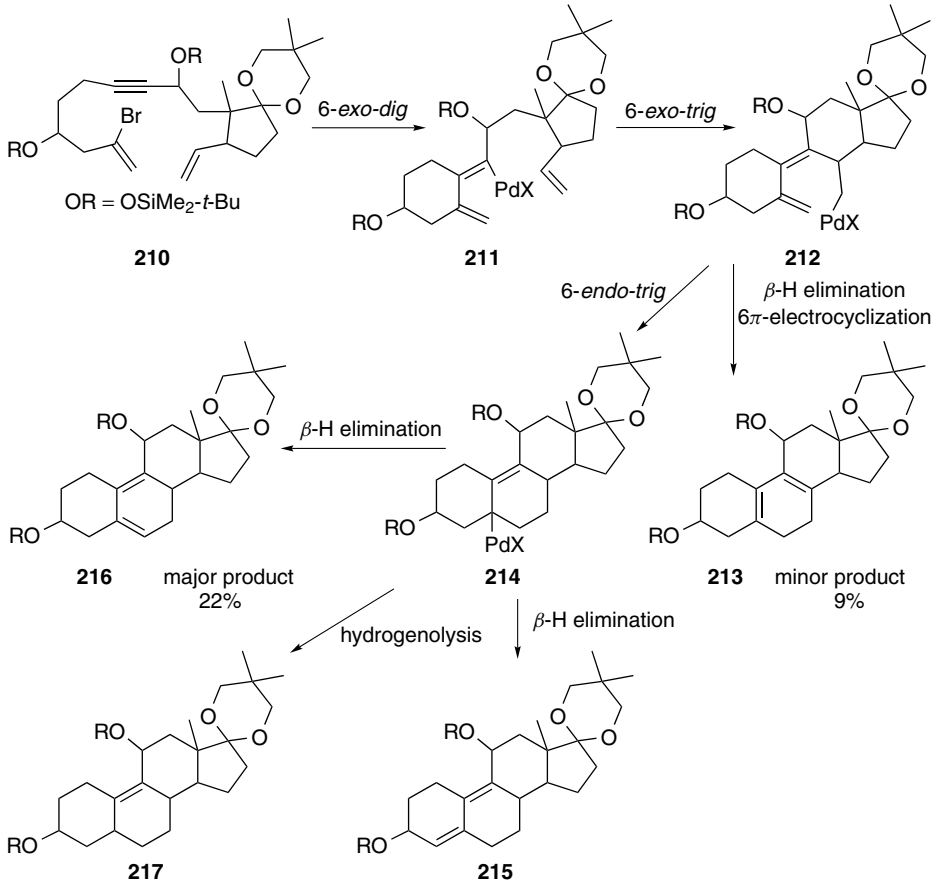
In the cyclization of 2-bromotetradeca-1,13-diene-7-yne (**205**), which is expected to lead eventually to the three six-membered rings **211**, an interesting

transformation was observed to give the tetracyclic system **209** containing a bridging cyclopropane ring. The intermediate **206** undergoes 5-*exo-trig* to give **207** and its 3-*exo-trig* cyclization yields the cyclopropane **208**. Thus the tetracyclic system **209** was formed in 74 % yield. In this cyclization, 5-*exo-trig* cyclization of **206** to give **207** is faster than β-H elimination to generate the hexatriene system **210**, and the expected tricyclic system **211** is not formed [63].



The cyclization discussed above offers attractive synthetic methods of steroid skeletons. Efficiency and selectivity of the cyclization of bromodienynes heavily depend on substituents. As an example, the attempted cyclization of the bromodienyne **210** with all functionalities essential for the synthesis of desired steroid skeletons is explained here. Formation of the intermediates **211** and **212** is straightforward. The expected β-H elimination of **212** and subsequent 6-π-electrocyclization to afford the cyclohexadiene system **213** are minor paths. Rather unusual 6-*endo-trig* cyclization of **212** is faster than the β-H elimination. The generated intermediate **214** is converted to a mixture of the steroid skeletons **215**, **216**, and **217** which have double bonds in different places.

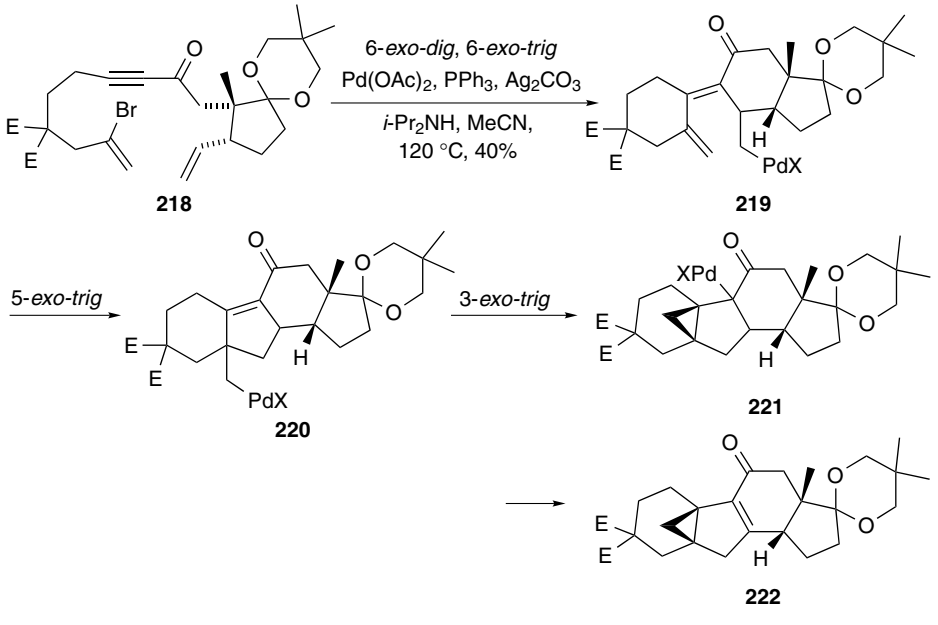
On the other hand, the slightly different bromo keto dienyne **218** was converted to the unexpected pentacyclic non-steroidal system **222**. In this case, 5-*exo-trig* cyclization of **219** gives **220** and its 3-*exo-trig* cyclization produces the cyclopropane **221** [63].



210 **211** **212**

216 major product 22% **214** **213** minor product 9%

217 **215**

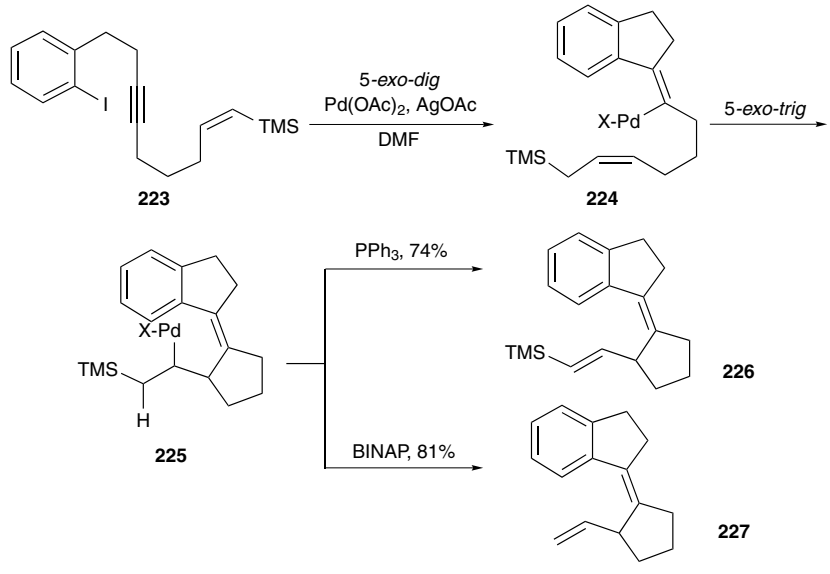


218 **219**

220 **221**

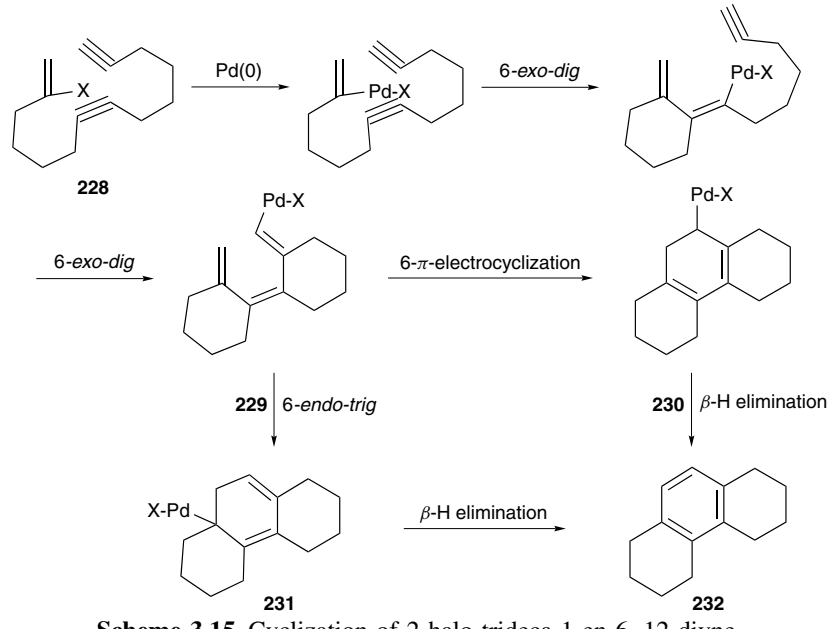
222

The enyne system **223** with an *o*-iodophenyl starter and a vinylsilyl group terminator underwent 5-*exo-dig* and 5-*exo-trig* cyclizations to yield **225**. No further cyclization of **225** took place. Instead the β-H elimination gave the vinylsilane **226** as the final product when PPh_3 was used. No 6π-electrocyclization of **226** occurred. Also the reaction was terminated by elimination of the β-TMS group to give the olefin **227**, when BINAP, which suppresses β-H elimination, was used [64].



3.4.3.9 Formation of Tricycles from Halo Enediynes

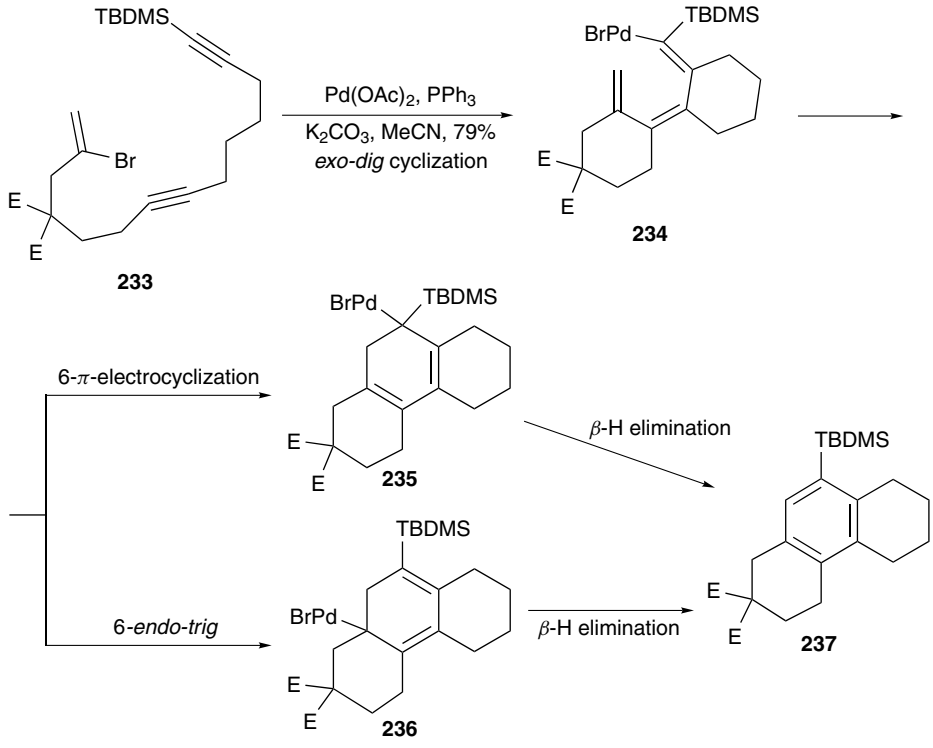
The bisannulated benzene derivative **232** is expected to be formed by the cyclization of the haloenediyne system **228** (Scheme 3.15). The formation of **232** is



Scheme 3.15 Cyclization of 2-halo-trideca-1-en-6, 12-diyne.

explained either by 6π-electrocyclization of **229** to form the cyclohexadiene **230**, and subsequent β-H elimination, or 6-*endo-trig* cyclization of **229** to give the cyclohexadiene **231**, followed by β-H elimination [65].

For example, the octahydrophenanthrene skeleton **237** was obtained from the 2-bromotetradeca-1-ene-7,13-diyne **233** when the triple bond was terminally substituted by a trialkylsilyl group. Formation of the benzene rings **237** at the last step can be understood either in terms of 6π-electrocyclization of the intermediate **234** to yield **235**, followed by β-H elimination, or 6-*endo-trig* cyclization of **234** to produce **236** and β-H elimination.

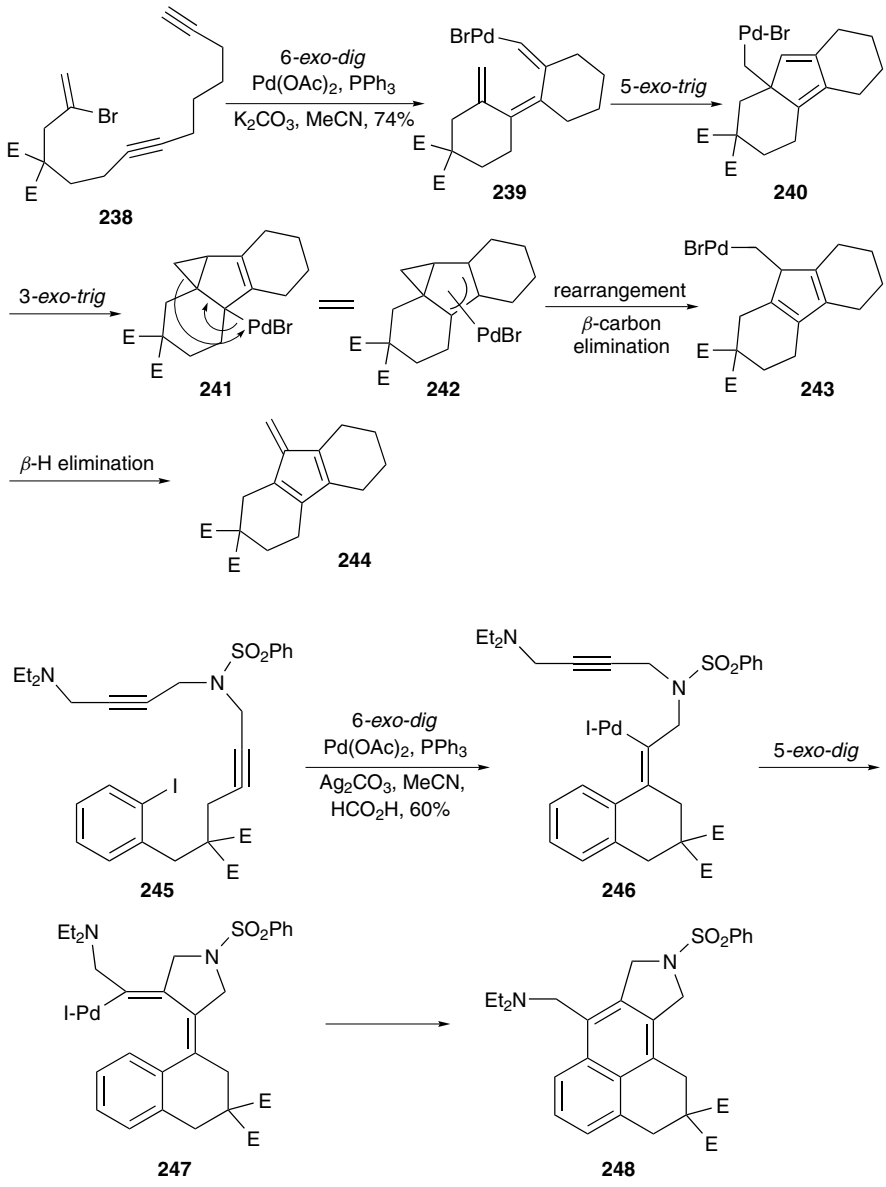


On the other hand, the terminally unsubstituted bromoenediyne **238** undergoes 5-*exo-trig* cyclization, instead of 6-*endo-trig*, of **239** to generate the neopentylpalladium **240**, and subsequent 3-*exo-trig* carbopalladation gives the cyclopropane **241**, which is stabilized by the formation of π-allylpalladium **242**. Then β-carbon elimination of **241** afforded the homoallylpalladium **243**, and β-H elimination yields the fulvene **244** [66].

The 1,6-diyne system **245** with an iodophenyl starter was converted to the tetracycle **248**. Carbopalladation of **245** generates **246** and subsequent 5-*exo-dig* cyclization affords **247**. The last step is attack on the aromatic ring to give the tetracycle **248** [67].

3.4.3.10 Formation of Polycycles

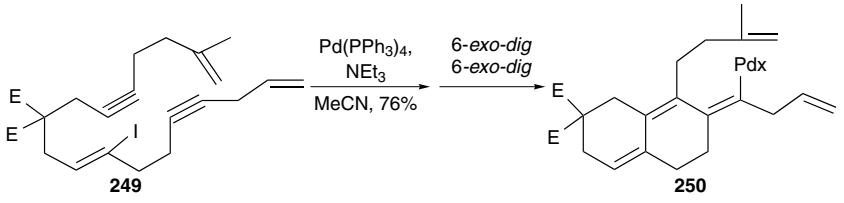
The steroid skeleton **253** was constructed very efficiently by domino cyclization of the trienediyne **249**. The vinyl iodide is a starter and two 6-*exo-dig* cyclizations



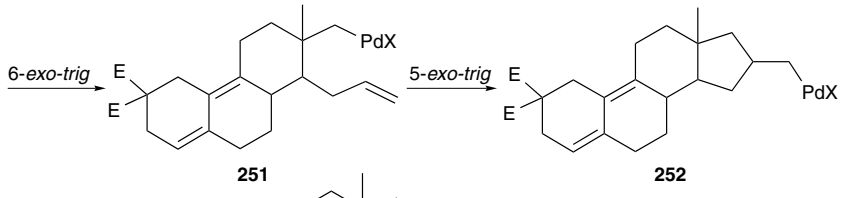
afford **250**, and subsequent 6-*exo-trig* cyclization generates the neopentylpalladium **251**, and its 5-*exo-trig* cyclization yields **252**. The reaction is terminated by β-H elimination to give **253** [68].

In the Pd-catalyzed reaction of the enetetrayne alcohol **254** under CO atmosphere, 6-*exo-dig* cyclization occurs four times to generate **255**, which then undergoes carbonylation to give the lactone **256** in 66 % yield [69].

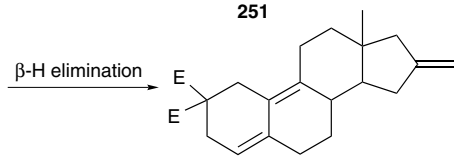
The cyclization of the enetriyne **257** was carried out in the presence of allene and piperidine. Two 6-*exo-dig* cyclizations of **257** afford **258**, and then 6-*exo-dig* cyclization gives the vinylpalladium **259**. Insertion of allene to **259** occurs after these steps to generate the π-allylpalladium intermediate **260**, and the reaction is terminated by amination of **260** to produce **261** [70].



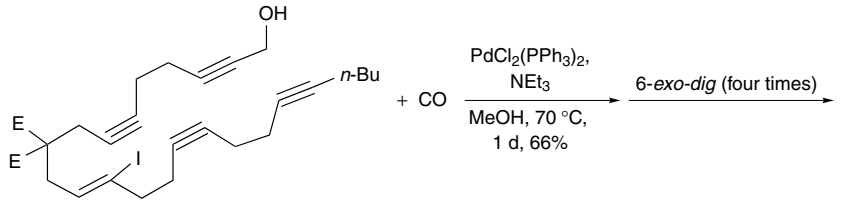
249 **250**



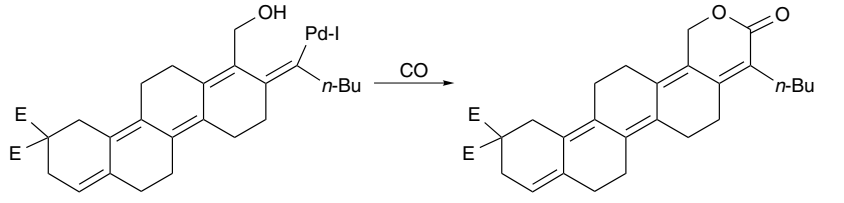
251 **252**



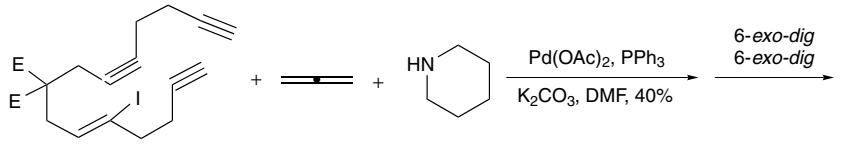
253



254



255 **256**



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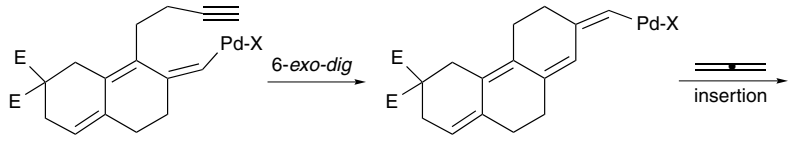

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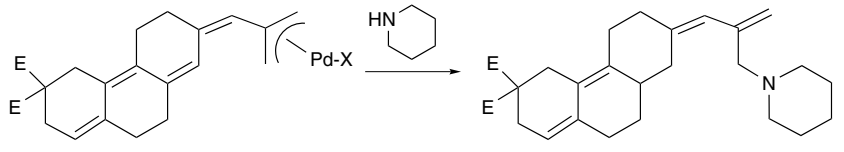

260 **261**

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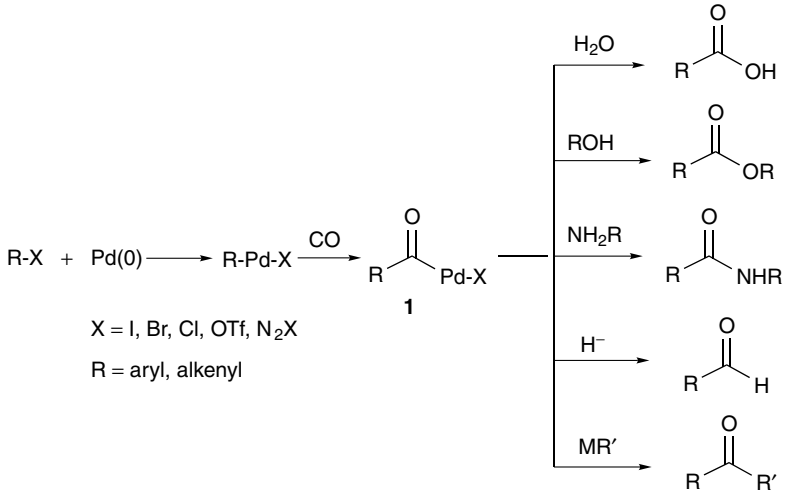
3.5 Carbonylation and Reactions of Acyl Chlorides

3.5.1 Introduction

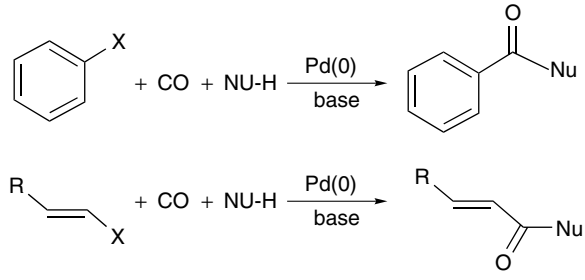
Aryl and alkenyl halides and triflates undergo Pd-catalyzed carbonylation, offering useful synthetic methods for carboxylic acids, esters, amides, aldehydes and ketones. Facile CO insertion into aryl- or alkenylpalladium complexes generates acylpalladium intermediates **1**. The intermediates are attacked by several

nucleophiles, affording different products. The nucleophilic attack of alcohol or water affords esters or carboxylic acids. Aldehydes are produced by the reaction of hydrides. Transmetallation with main group organometallic compounds, followed by reductive elimination yields ketones. In general, iodides and triflates are most reactive substrates for the carbonylation. Bromides are moderately reactive. Although a number of smooth Pd-catalyzed reactions of aryl chlorides such as Heck and Suzuki couplings are known, aryl chlorides are regarded to be relatively inert for carbonylation except for a few chlorides which are highly activated with strong EWGs. Perhaps CO is a strong ligand and decreases the effectiveness of bulky and electron-rich ligands which are used satisfactorily for other reactions of chlorides.



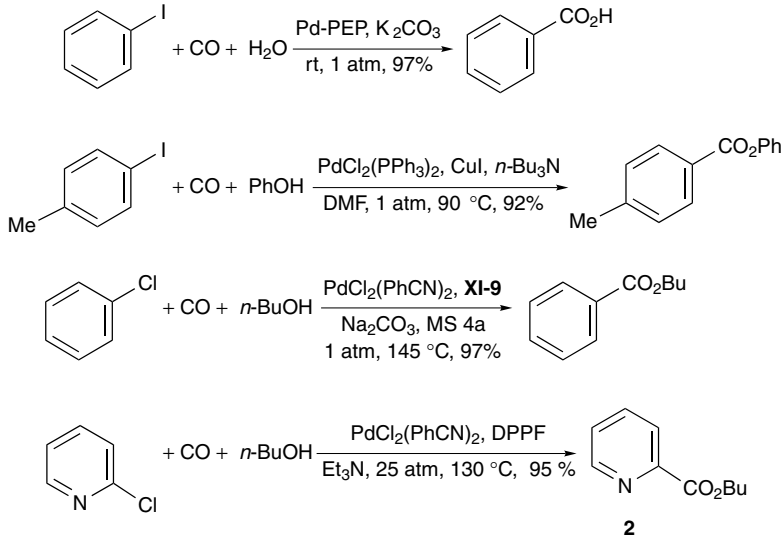
3.5.2 Formation of Carboxylic Acids, Esters, and Amides

Aromatic and α,β-unsaturated carboxylic acids and esters are prepared from aryl and alkenyl halides.



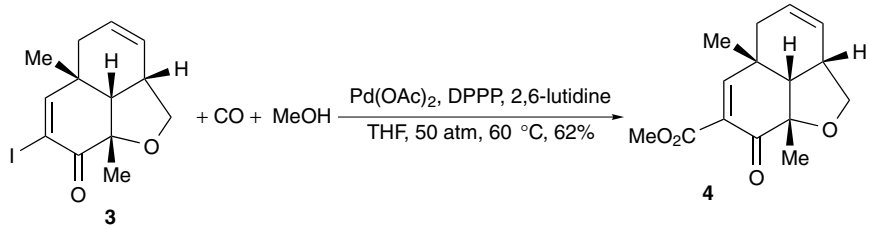
Carbonylation of reactive iodides proceeds using $PdCl_2(PPh_3)_2$ as a standard catalyst under mild conditions in the presence of a base. Several modified catalyst systems have been reported. For example, ligandless Pd charcoal is an active catalyst at 140 °C [1]. Uozumi reported that the amphiphilic phosphine-Pd complex (Pd-PEP) bound to PEG-PS resin is a very active and useful catalyst. Carbonylation

of iodobenzene proceeded in H_2O without an organic solvent at room temperature and under atmospheric pressure of CO in the presence of Pd-PEP and K_2CO_3 to give benzoic acid in 97 % yield. No reaction occurred when Pd-PPh_3, instead of Pd-PEP, was used under similar conditions. The catalyst can be recycled [2]. Pd-complex immobilized on PAMAM (polyamino amido) dendrimers supported on silica was found to be an active catalyst for efficient carbonylation of iodobenzene in MeOH at 100 °C and 7 atm to produce methyl benzoate and the catalyst was recycled four to five times without loss of activity [2a]. Phenyl benzoate was obtained in high yield from iodobenzene in the presence of phenol in DMF under 1 atm of CO. Addition of CuI accelerated the reaction [3]. Chlorides are difficult to be carbonylated. However, Beller carried out the carbonylation of chlorobenzene using the ferrocenyldicyclohexylphosphine **XI-9** in the presence of Na_2CO_3 at 140 °C in *n*-BuOH, and obtained butyl benzoate in high yield [4]. Chloropyridines are active chlorides and butyl picolinate (**2**) was prepared by carbonylation of 2-chloropyridine at 130 °C. DPPF and DPPB were used as effective ligands [5].

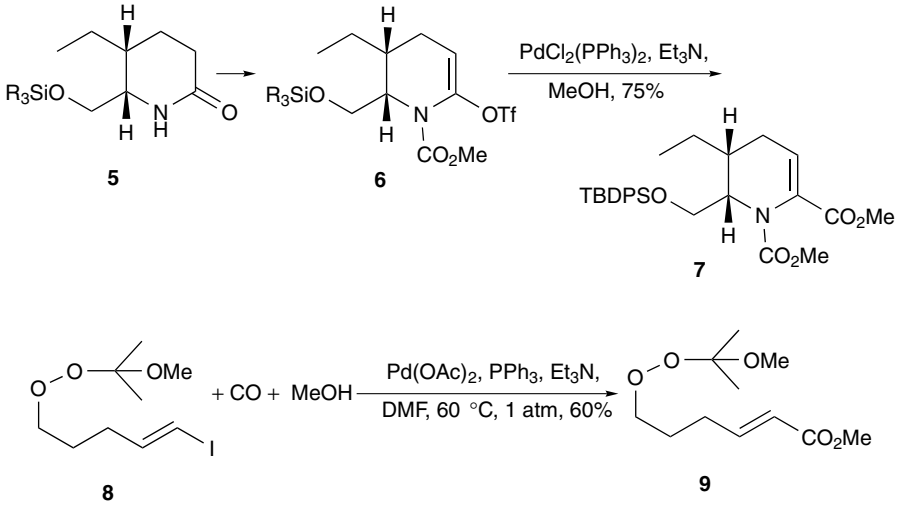


2

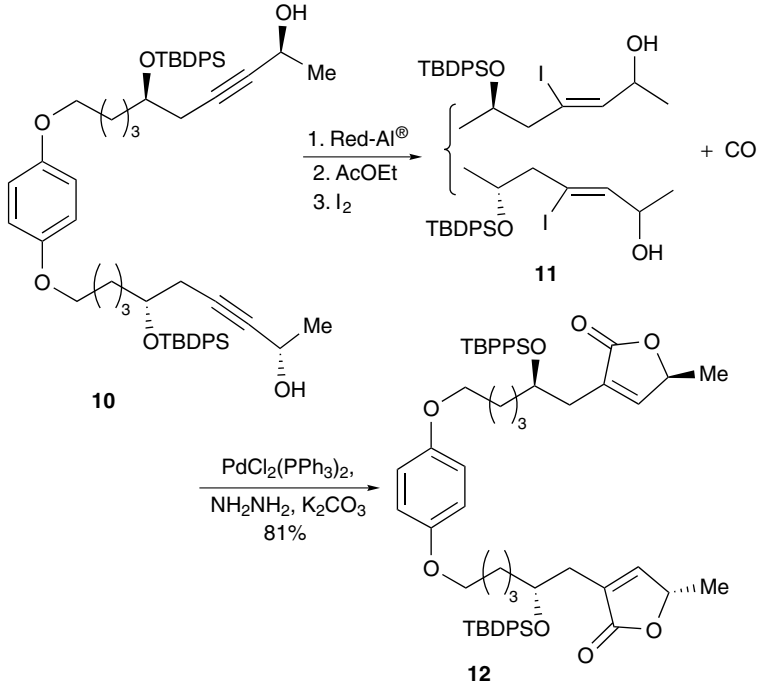
Alkenyl halides and triflates are easily carbonylated. Carbonylation of α-iodo enone **3** proceeded at 60 °C using $Pd(OAc)_2$ and DPPP, and the ester **4** was obtained in 62 % yield [6]. The lactam **5** was converted to the vinyl triflate **6**, which was carbonylated to afford the α,β-unsaturated ester **7** [7]. Carbonylation of the alkenyl iodide **8**, possessing a labile peroxy group proceeded smoothly to give the α,β-unsaturated ester **9** under 1 atm of CO at 60 °C in DMF. The peroxy group remained intact [8].



3 **4**

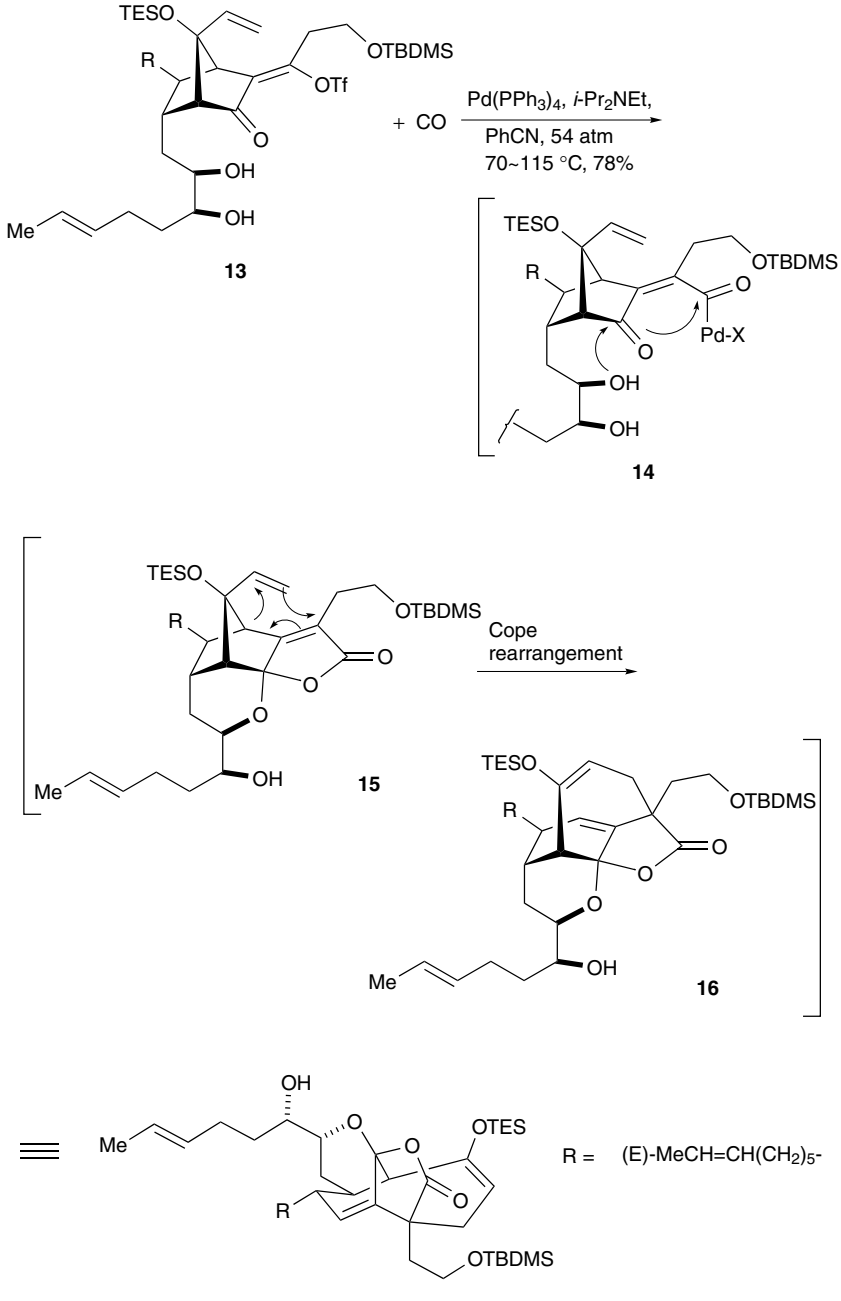


Alkenyl iodides can be generated *in situ* by hydroalumination of alkynes, followed by iodination, and α,β-unsaturated esters are prepared by carbonylation without isolation of the iodide. As an example, the propargylic alcohol **10** was aluminated regio- and stereoselectively and converted to the alkenyl iodide **11**. The intramolecular carbonylation of **11** afforded the dibutenolide **12** in 81 % yield. The reaction is a key step in the total synthesis of (+)-parviflorin [9].

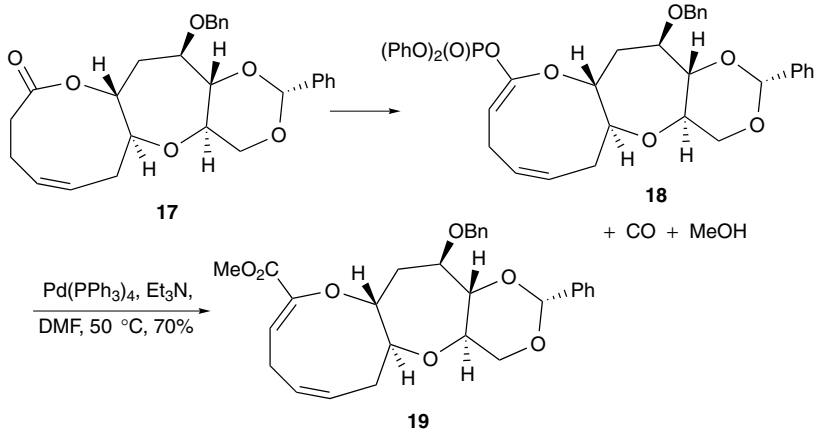


Carbonylation is widely utilized for preparation of complex molecules of natural products. As one example, Leighton constructed the fully elaborated tetracyclic

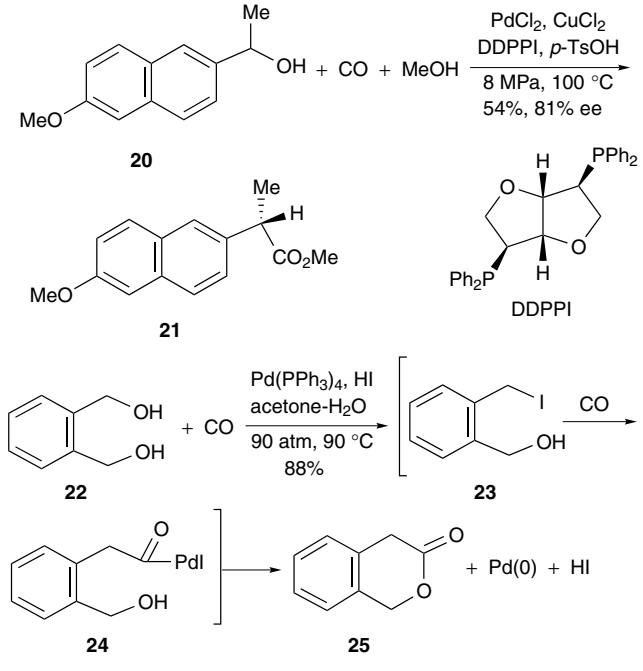
core of phomoiderides **16** efficiently by novel domino carbonylation–Cope rearrangement of the vinyl triflate **13** as a key step [10]. The acylpalladium species **14**, generated by the carbonylation of the alkenyl triflate **13**, was trapped intramolecularly by the hemiketal OH group, which was formed from the hydroxy ketone as shown by **14** to afford the unsaturated lactone **15** at 75 °C. The strained molecule of **15** underwent Cope rearrangement as shown by **15** to give **16** in 78 % yield simply by raising the temperature to 110 °C. Interestingly benzonitrile was used as the best solvent.



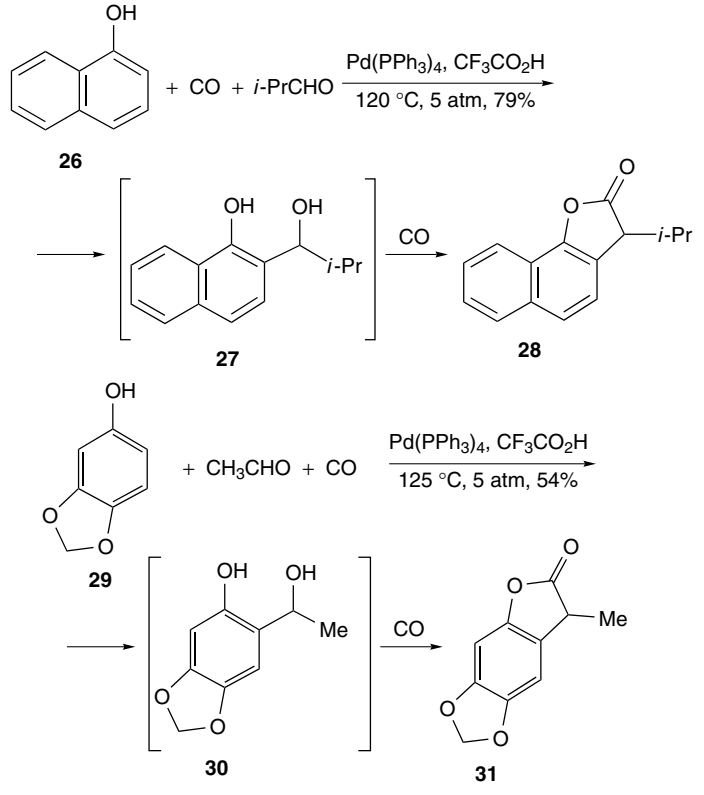
In the total synthesis of ciguatoxins, the enol phosphate **18**, derived from the nine-membered lactone **17**, was carbonylated smoothly to give the unsaturated ester **19** [11].



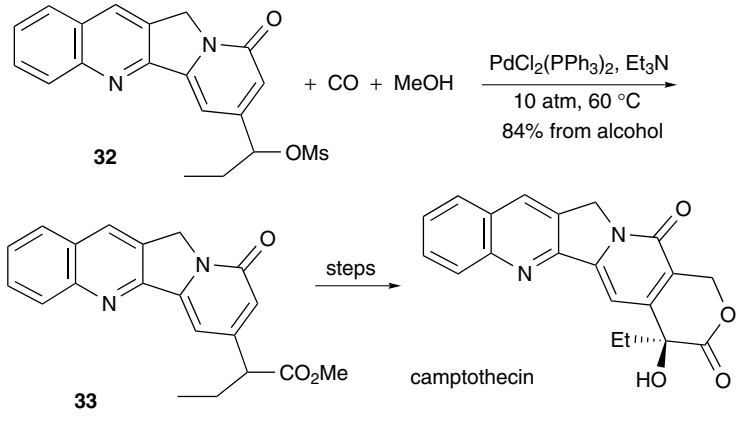
Benzylic alcohols are reactive in the presence of an acid as an activator. Asymmetric carbonylation of 1-(6-methoxy-2-naphthyl)ethanol (**20**) by using DDPPI as a chiral ligand in the presence of $CuCl_2$ and *p*-TsOH as activators afforded the methyl ester of (*S*)-naproxen (**21**) with 81 % ee [12]. Benzyl alcohol was carbonylated to phenylacetic acid under somewhat harsh conditions in the presence of HI. Presumably the carbonylation of benzyl iodide, generated by the reaction of benzyl alcohol with HI, occurred. 1,2-Di(hydroxymethyl)benzene (**22**) was carbonylated to give 3-isochromanone **25** in 88 % yield. In this reaction, one of the benzylic alcohols is converted to benzylic iodide **23** and the lactone **25** was obtained via acylpalladium **24** [13].



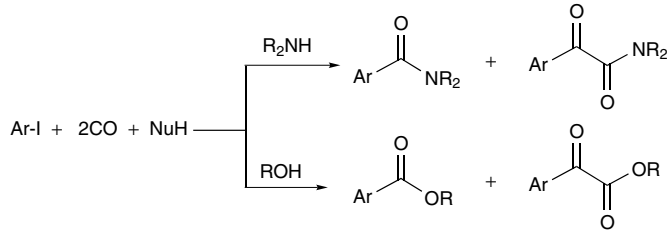
Pd-catalyzed reaction of α-naphthol, isobutyraldehyde, and CO in the presence of CF_3CO_2H afforded naphthofuran-2(3*H*)-one **28** in 79 % yield. The reaction is explained by acid-catalyzed formation of 1-(2-naphthyl)butanol **27**, followed by carbonylation of the benzylic alcohol. Although its reactivity is lower, the phenol derivative **29** reacted with acetaldehyde to generate the benzylic alcohol **30**, which was carbonylated to provide the benzofuranone **31** in 54 % yield [14].



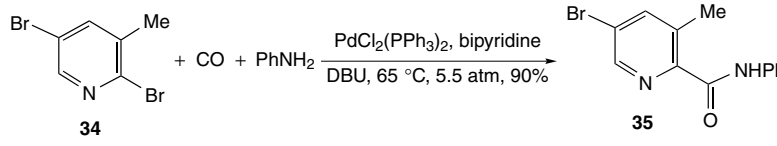
Although it is not a benzylic type, the mesylate **32** was carbonylated under normal conditions to give the methyl ester **33** as a precursor of camptothecin in high yield [15].



Carbonylation in the presence of secondary amines provides either amides or α-keto amides by single and double carbonylations. Also, the corresponding α-keto esters are prepared. It was reported that ratios of single and double carbonylations depend mainly on the nature of the phosphine ligands. It was claimed that $PMePh_2$ or DPPB is a suitable ligand for double carbonylation [16].

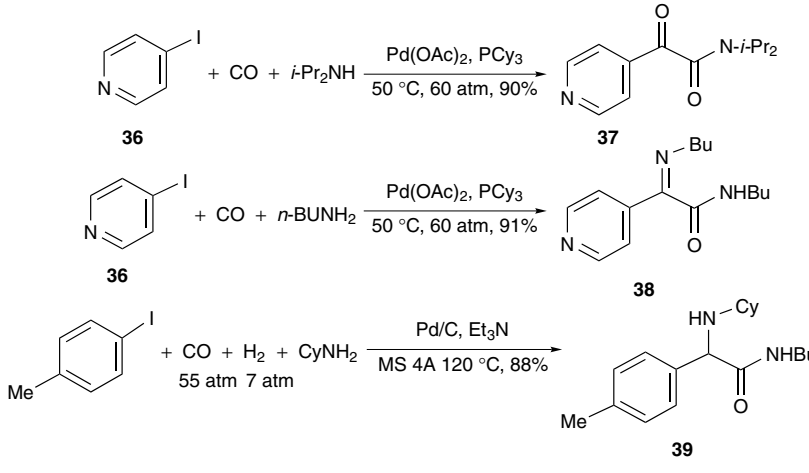


Later several ligands, including PPh_3, were found to be effective depending on the substrate. Carbonylation of 2,5-dibromo-3-methylpyridine (**34**) in the presence of aniline produced the 2-picolinamide **35** regio- and chemoselectively when 2,2-bipyridine was used as a ligand. Poor yield and selectivity were obtained by the use of ubiquitous phosphine ligands. The monoamide **35** was isolated in 82 % yield in a chemical plant in 600 kg scale production [17].

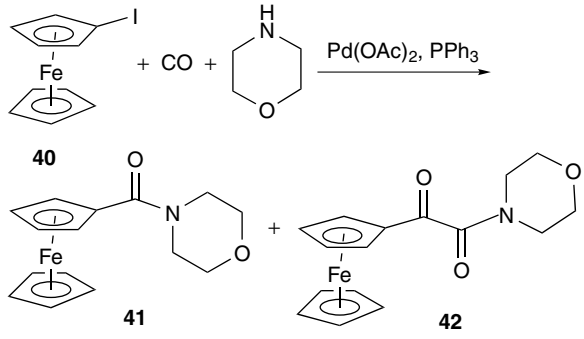


34 **35**

4-Pyridylglyoxamide **37** was prepared by double carbonylation of 4-iodopyridine (**36**). High selectivity and yield of **37** were obtained when PCy_3 and *i*-PrOH were used as a ligand and nucleophile, respectively. When a primary amine, *n*-$BuNH_2$, was used, the Schiff base of keto amide **38** was obtained in high yield [18]. Domino double carbonylation and hydrogenation of the Schiff base occurred in the reaction of *p*-iodotoluene with cyclohexylamine under CO and H_2 pressure using ligandless Pd on charcoal to afford the α-amino amide **39** in high yield [19].

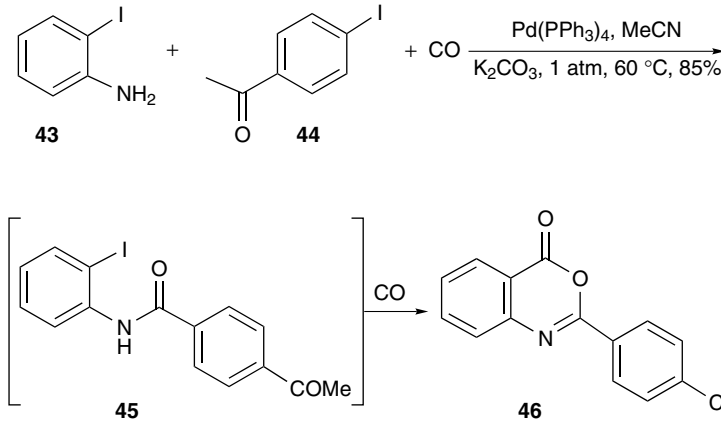


Carbonylation of iodoferrocene **40** in the presence of morpholine gave rise to the amide **41** and the keto amide **42** by using PPh_3 as a ligand [20]. A slight difference in temperature and pressure had a marked influence on the product ratios. The keto amide **42** was obtained as the main product with 80 % selectivity at 60 °C and 50 atm. The amide **41** was obtained as a single product at 100 °C.



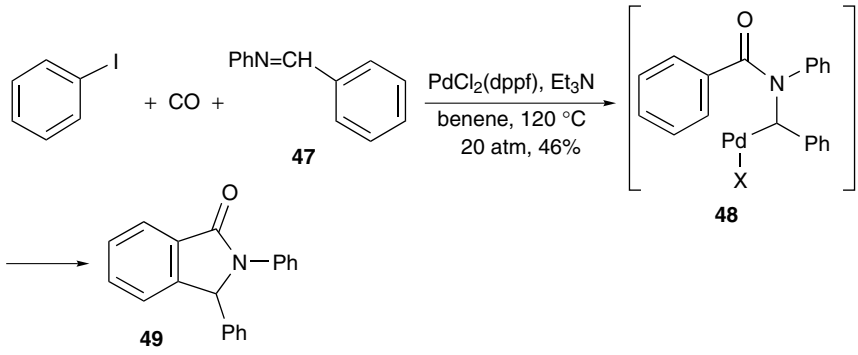
temp.	press. (atm)	conv. %	ratio **41** : **42**
60	50	92	20 : 80
100	40	100	>99 : 1

Carbonylation of a mixture of more reactive *p*-iodoacetophenone (**44**) and *o*-iodoaniline (**43**) occurred stepwise chemoselectively to give the amide **45**, and further carbonylation of **45** afforded 2-aryl-4*H*-3,1-benzoxazolin-4-one **46** [21].

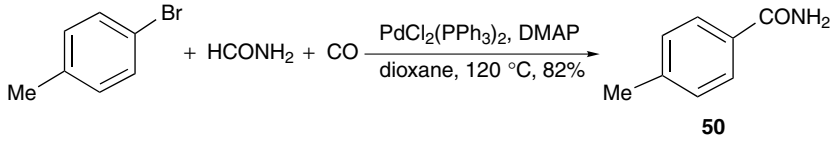


Carbonylation of iodobenzene in the presence of *N*-benzylideneamine **47** using DPPF as a ligand proceeded via formation of amide **48** by insertion of **47** to the acylpalladium bond, and 3-phenyl-2,3-dihydro-1*H*-isoindol-1-one (**49**) was obtained [22].

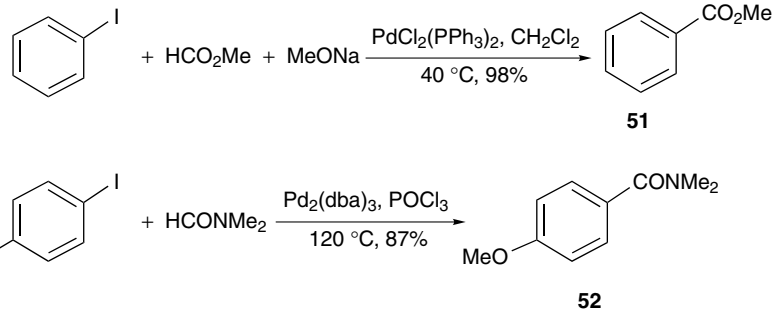
Direct preparation of primary amides by carbonylation in the presence of NH_3 is not easy. As one solution, Indolese carried out carbonylation of *p*-bromotoluene

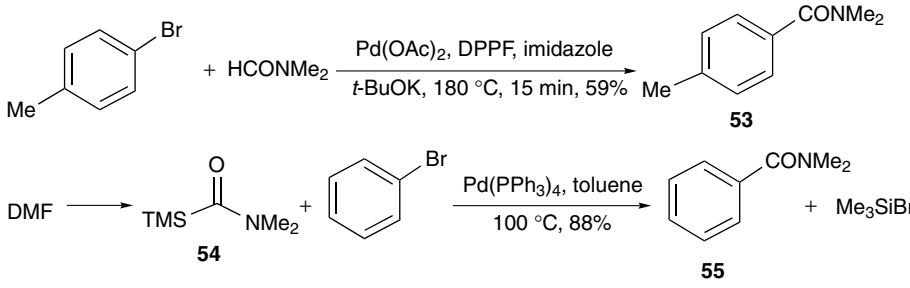


using formamide as an ammonia equivalent in the presence of Lewis bases such as DMAP or imidazole, and obtained toluamide (**50**) in good yield [23].



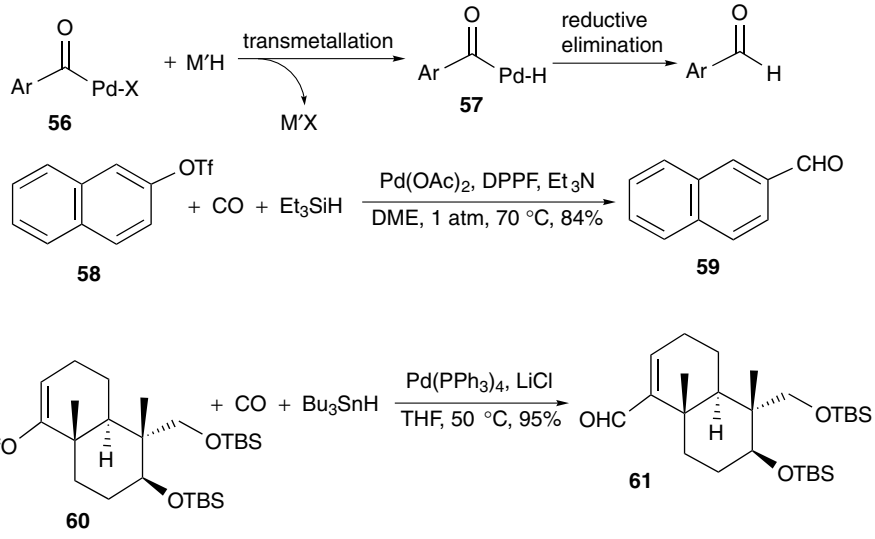
Several attempts to find CO-free preparative methods of esters and amides have been carried out using alkyl formate or formamide as CO sources. Methyl benzoate (**51**) was obtained in 98 % yield by the reaction of iodobenzene with methyl formate in the presence of MeONa [24]. DMF can be used as an amide source. Reaction of aryl iodides with DMF in the presence of 2 equivalents of $POCl_3$ using ligandless Pd catalyst afforded the *N*,*N*-dimethylbenzamide **52**. Formation of a Vilsmeier reagent from DMF and $POCl_3$ is expected and the amide may be formed by Pd-catalyzed reaction of aryl iodide with the Vilsmeier reagent [25]. Aminocarbonylation of aryl bromides with DMF was carried out using Pd-DPPF as a catalyst in the presence of stoichiometric amounts of imidazole and *t*-BuOK to afford *N*,*N*-dimethylbenzamide **53** [26]. Also, *N*,*N*-dimethylbenzamide (**55**) was prepared by the reaction of aryl bromide with carbamoylsilane **54**, which is prepared from DMF [27].





3.5.3 Formation of Aldehydes and Ketones

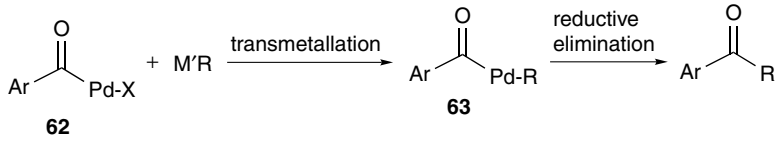
Aldehydes are prepared by carbonylation in the presence of hydride sources. Formation of aldehydes can be understood by transmetallation of acylpalladium **56** with a hydride to give acylpalladium hydride **57**, followed by reductive elimination. Metal hydrides and hydrogen are used for aldehyde synthesis. Hydrosilane is one of the hydrides. Reaction of β-naphthyl triflate (**58**) with Et_3SiH using DPPF as a ligand under mild conditions afforded the aldehyde **59** [28]. Carbonylation of the alkenyl triflate **60** in the presence of tin hydride and LiCl afforded the aldehyde **61** in 95 % yield [29].



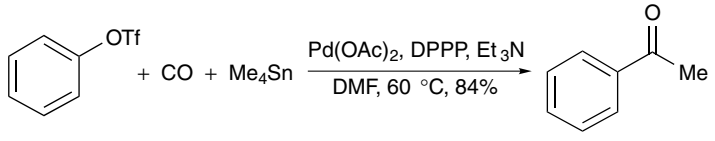
Ketones are prepared by transmetallation of acylpalladium **62** with organometallic reagents. Phenyl triflate was converted to acetophenone (**64**) by carbonylation in the presence of Me_4Sn [30].

In the total synthesis of strychnine, Overman prepared the alkenyl aryl ketone **67** in 80 % yield by the carbonylation of the aryl iodide **65** with the alkenylstannane **66** using $AsPh_3$ as a ligand [31].

Chloroanisole, activated by coordination of electron-attracting Cr carbonyl **68**, reacted with CO and dimethylindium **69** to afford the methyl ketone **70** under mild conditions [32]. Also Bu_3In was used for the preparation of butyl phenyl ketone (**71**) [33].



62 **63**



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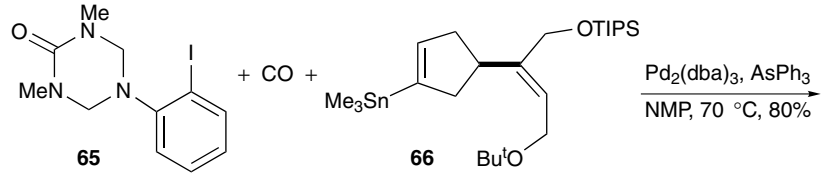
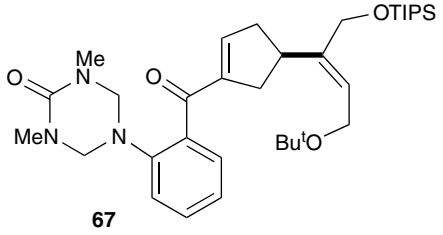


65 **66**



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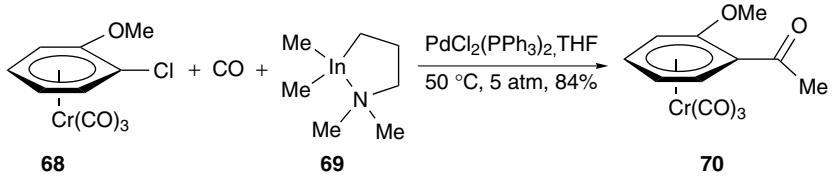
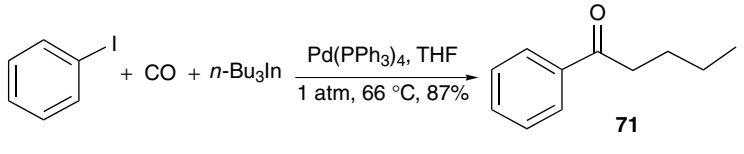
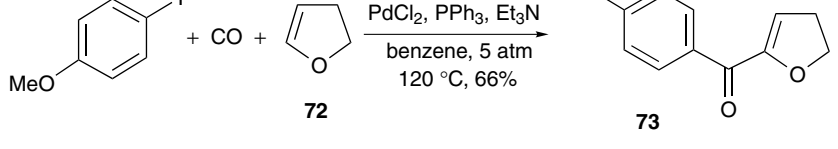


68 **69** **70**



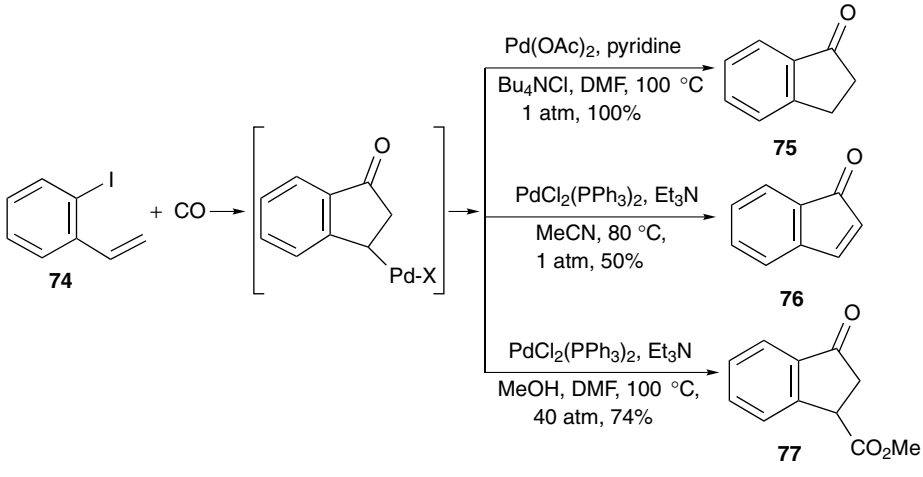
71

Ketones are also prepared by carbonylation in the presence of alkenes. Carbonylation of 4-iodoanisole in the presence of dihydrofuran (**72**) provided the ketone **73** via insertion of the double bond in dihyrofuran to acylpalladium, followed by β-H elimination [34].

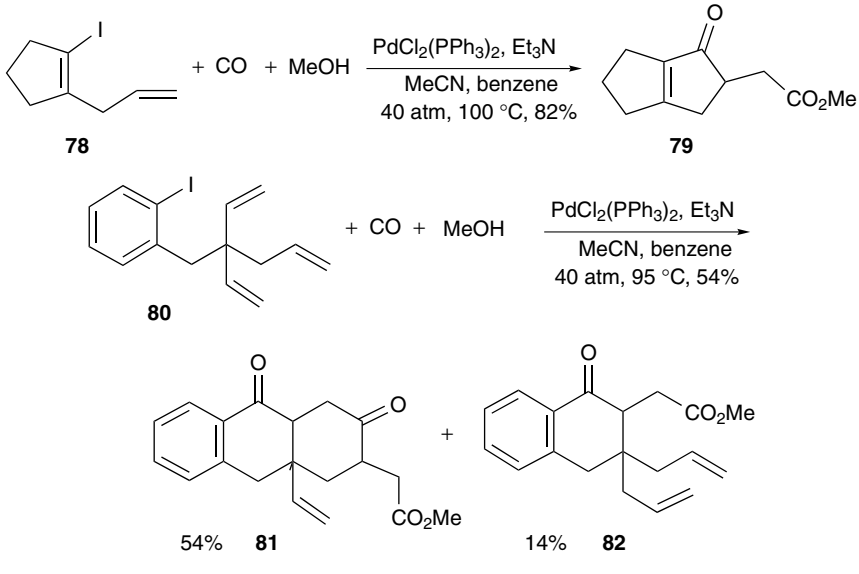


72 **73**

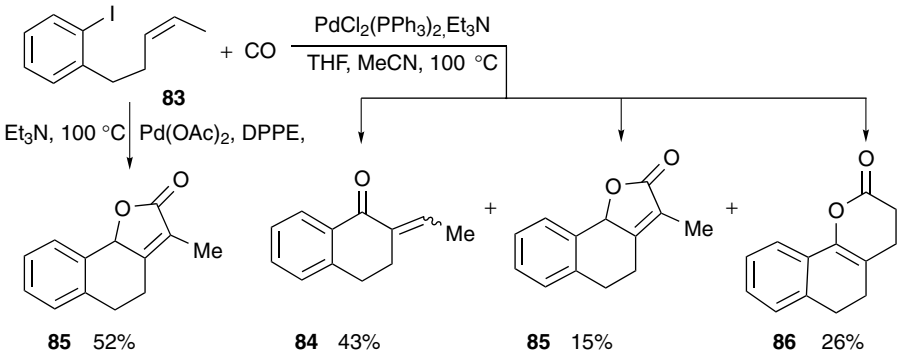
Carbonylation of 2-iodostyrene (**74**) afforded indanone (**75**) and indenone (**76**) via intramolecular acylpalladation of the double bond. In the presence of Bu_4NCl and pyridine, protonation occurred to give indanone (**75**). When Et_3N was used, indenone (**76**) was obtained. Under high pressure CO (40 atm), the keto ester **77** was the main product [35].



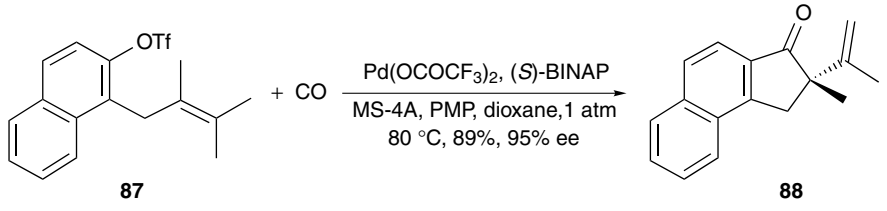
There are several possible reaction paths in the carbonylation of 1-iodo-1,4-, 1,5-, and 1,6-dienes, and chemoselectivity depends on reaction conditions and ligands. For example, the 1-iodo-1,4-diene **78** reacted with two CO molecules to give the keto ester **79** in high yield by domino insertion of CO, alkene, and CO [36]. The diketo ester **81** was obtained from iodotriene **80**. In this reaction, domino insertion of CO, alkene, and CO occurred to give rise to the diketo ester **81** in 54 % yield. The bicyclic monoketo ester **82** was formed in 14 % yield by premature trapping of acylpalladium intermediate with MeOH [37].



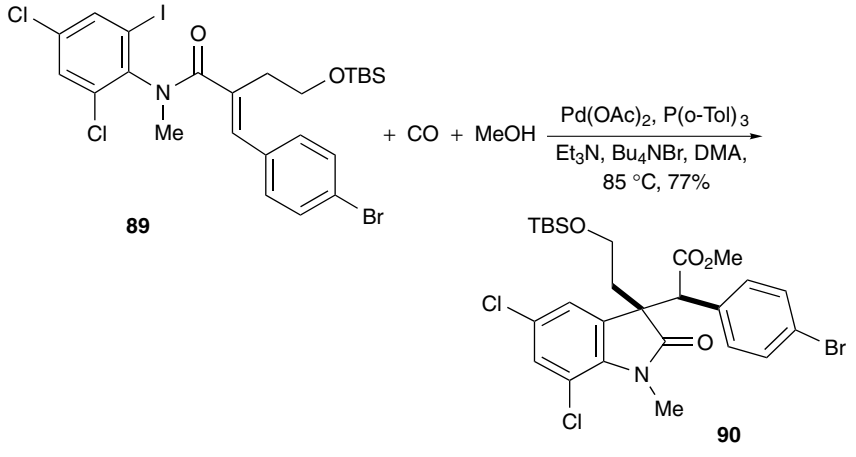
Carbonylation of 2-(3-pentenyl)iodobenzene (**83**) afforded a mixture of the ketone **84**, γ-lactone **85**, and δ-lactone **86**. When DPPE instead of PPh_3 was used, the γ-lactone **85** was obtained as the main product [38].



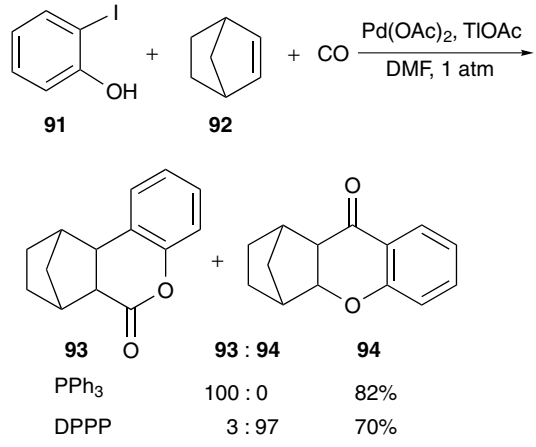
Efficient enantioselective carbonylative cyclization of the *o*-allylphenyl triflate **87** occurred using (*S*)-BINAP, $Pd(OCOCF_3)_2$, and PMP (pentamethylpiperidine) to provide the ketone **88** with 95 % ee [39].



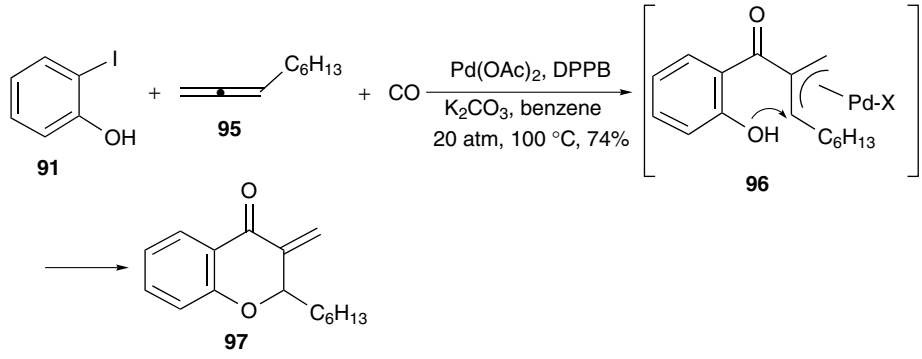
In the carbonylation of the iodo amide **89**, insertion of the sterically hindered double bond in **89** occurred at first, generating a quaternary carbon, and subsequent CO insertion gave the lactam ester **90** in 77 % yield [40].



The three-component reaction of 2-iodophenol (**91**), norbornene (**92**), and CO provided the ketone **94** and the δ-lactone **93** depending on the order of insertions of CO and alkene, which was controlled by ligands [41]. The ketone **94** was produced via insertions of CO and then alkene when DPPP was used. Formation of the lactone **93** occurred via alkene and CO insertions when PPh_3 was used [42].

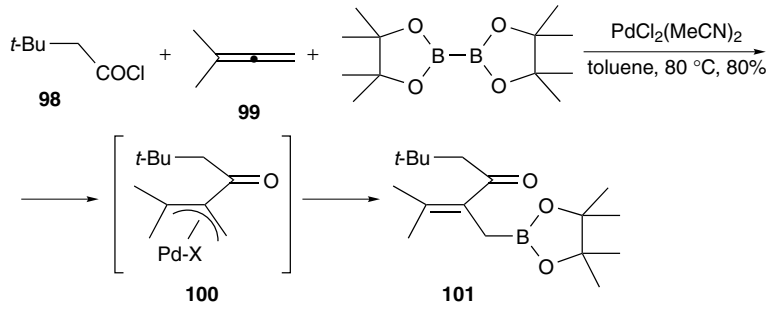


Carbonylation of 2-iodophenol (**91**) in the presence of 1,2-nonadiene (**95**) afforded 2-(*n*-hexyl)-3-methylene-2,3-dihydro-4*H*-1-benzopyran-4-one (**97**) in 74 % yield, showing that selective attack of phenoxy group at the substituted terminus of π-allylpalladium intermediate **96** occurred. Uses of DPPB and K_2CO_3 were important [43].

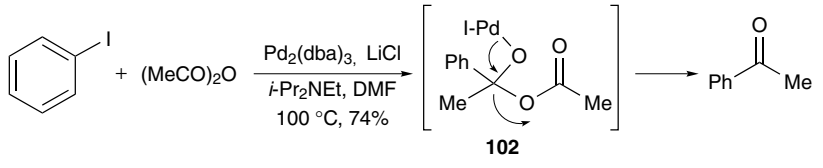


Acylpalladium was generated by the oxidative addition of acyl chloride **98** to Pd(0), and reacted with 1,1-dimethylallene (**99**) to give π-allylpalladium intermediate **100**. Then transmetallation of **100** with diborane and reductive elimination provided 2-acylallylboronate **101**. Thus highly regio- and stereoselective acylboration of allenes occurred using ligandless Pd catalyst [44].

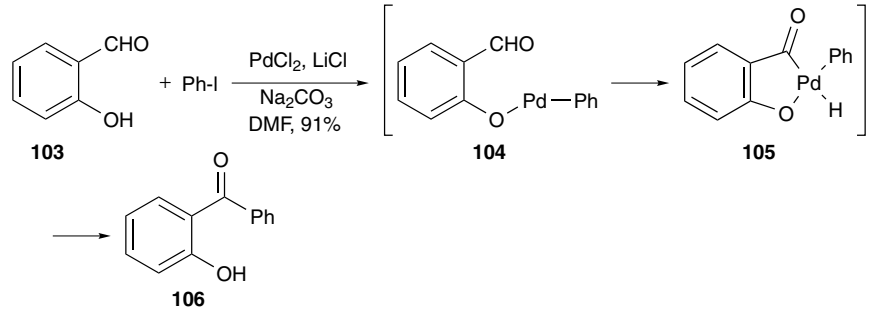
Cacchi found a new and simple CO-free methyl ketone synthesis using acetic anhydride. Acetophenone was obtained in 74 % yield by the reaction of iodobenzene with acetic anhydride using ligand-free Pd catalyst in the presence of



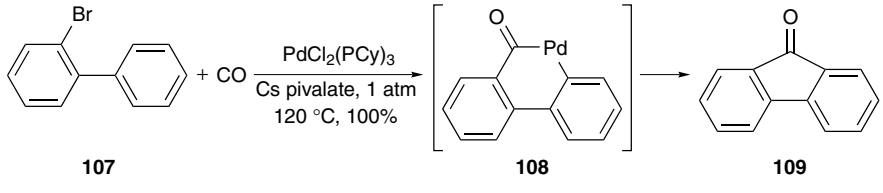
LiCl [45]. As one explanation, insertion of C=O bond to Ph-PdX generates **102**, from which acetophenone is formed.



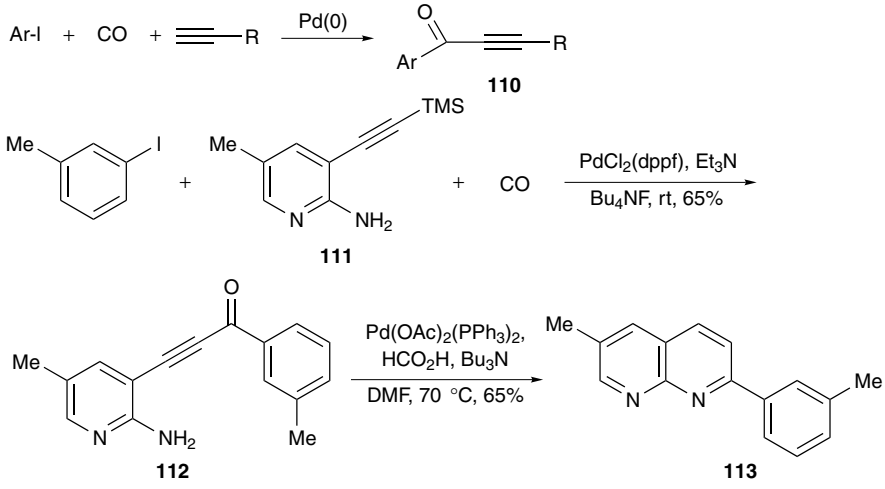
Miura found that the aldehyde group in salicylaldehyde (**103**) can be converted to aryl ketone **106** in high yield by the reaction with aryl iodide using ligandless $PdCl_2$ and LiCl in the presence of Na_2CO_3 in DMF. The reaction is explained by the following mechanism. The first step is formation of phenylpalladium phenoxide **104**. Oxidative addition of the C-H bond of aldehyde to the phenyl(aryloxy)palladium **104** generates Pd(IV) species **105**, which was converted to the ketone **106** by reductive elimination [46].



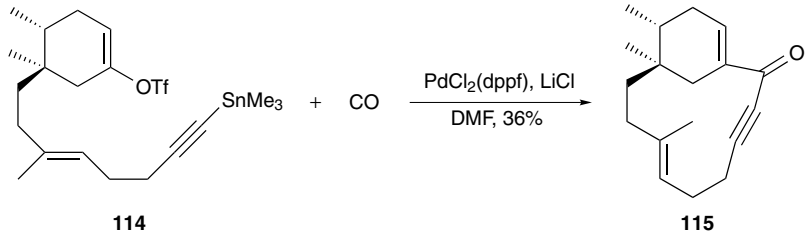
A good synthetic method for substituted fluoren-9-ones is the carbonylation of *o*-halobiaryls [47]. Carbonylation of 2-bromobiphenyl (**107**) in DMF in the presence of cesium pivalate gave rise to fluoren-9-one (**109**) in quantitative yield via the palladacycle **108**. Use of PCy_3 as a ligand is important.



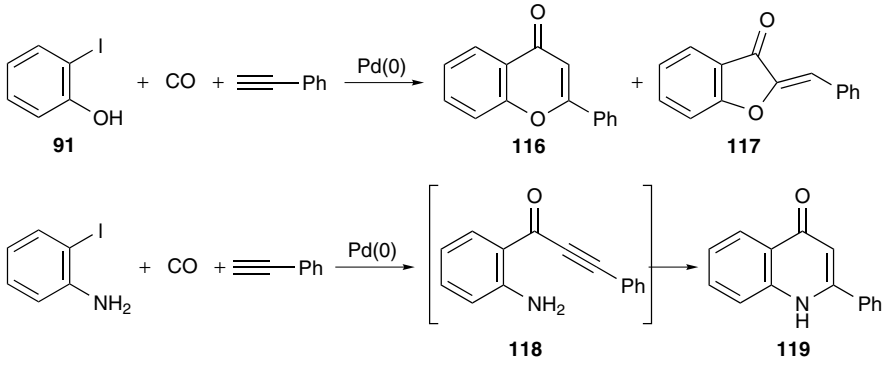
A well-established preparative method of alkynyl ketones **110** is the Sonogashira-type carbonylation of aryl halides in the presence of terminal alkynes. (Trimethylsilyl)pyridylethyne (**111**), deprotected *in situ*, reacted with 3-iodotoluene and CO to give the alkynyl *m*-tolyl ketone **112** using DPPF as a ligand. Pd-catalyzed reductive cyclization of **112** using HCO_2H afforded the 1,8-naphthyridine **113** [48].



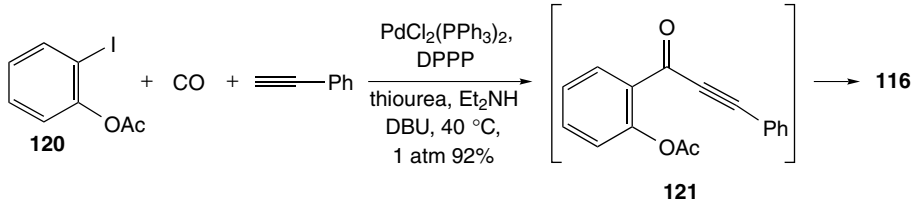
The 12-membered cyclic alkynyl alkenyl ketone **115** was obtained by carbonylative cyclization of the alkenyl triflate with alkynylstannane in **114** [49].



Formation of flavone **116** and aurone **117** by carbonylation of 2-iodophenol (**91**) in the presence of terminal alkyne is known [50]. Also 1,4-dihydro-4-oxoquinoline **119** is obtained by the reaction of 2-iodoaniline with CO and terminal alkynes [51]. These reactions proceed via the formation of the aryl alkynyl ketones **118** as intermediates.

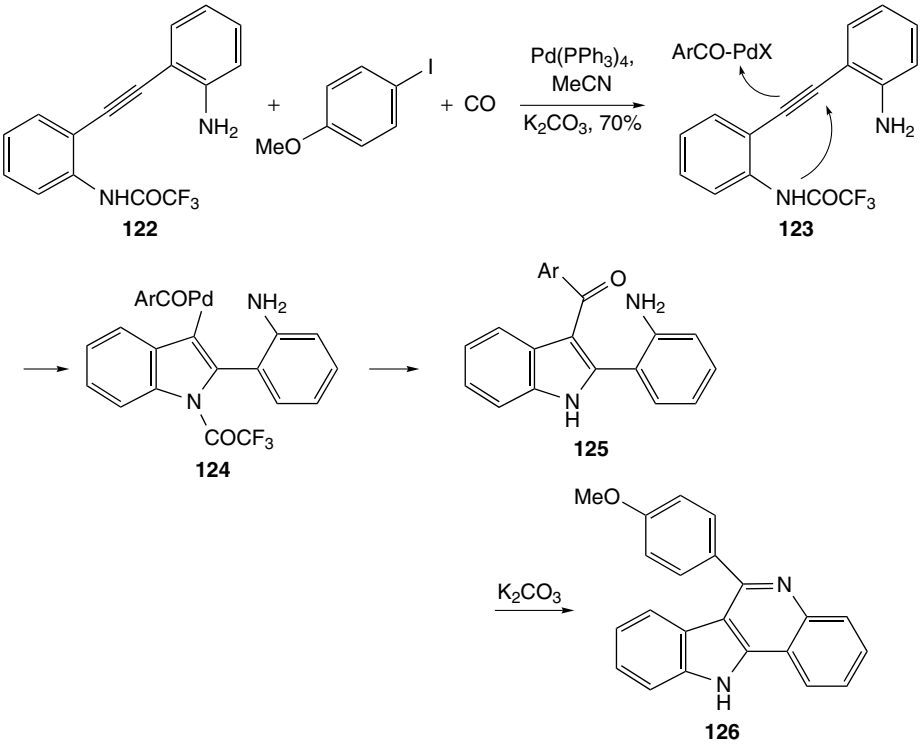


Yang carried out extensive studies on selective formation of the flavones **116**, and found that the acetate of iodophenol **120**, as a latent hydroxy group, was superior to free iodophenol **91** and formation of the aurone **117** was suppressed. As a catalyst, $PdCl_2(PPh_3)_2$, combined with DPPP and thiourea, was found to be the best one. Under these conditions and 1 atm, the flavone **116** was obtained selectively in 92 % yield without isolating the alkynyl ketone **121** [52].



120 **121**

Formation of indole derivative by the reaction of 2-ethynylaniline, aryl halide and CO is known [53]. Cacchi extended the reaction to the synthesis of indolo[3.2-*c*]quinoline. Reaction of 2-(2′-aminophenylethynyl)trifluoroacetanilide **122**, 4-iodoanisole and CO occurred as shown by **123** to provide **124** and then the 3-aroylindole **125**. Treatment of **125** with a base gave the indoloquinoline **126** in 70 % overall yield [54].



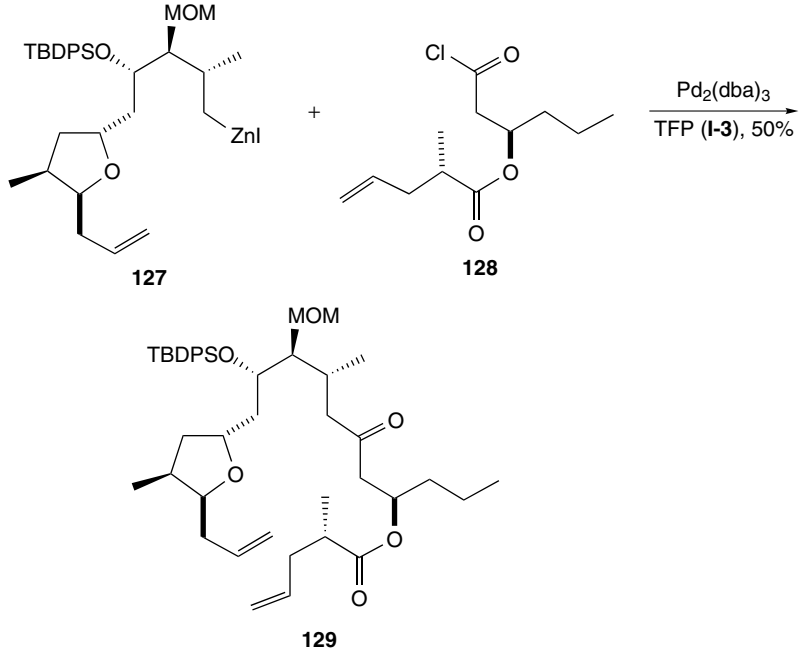
122 **123** **124** **125** **126**

3.5.4 Reactions of Acyl Halides and Related Compounds

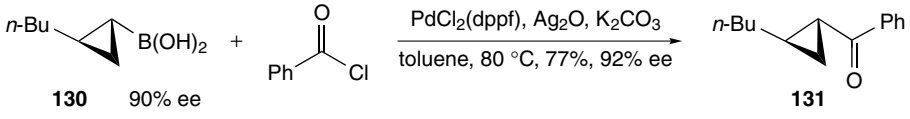
Acylpalladiums are important intermediates of carbonylation reactions. Since similar acylpalladiums can be prepared directly by oxidative addition of acyl halides to

Pd(0), acyl halides and related compounds are useful substrates for the syntheses of various carbonyl compounds without using CO.

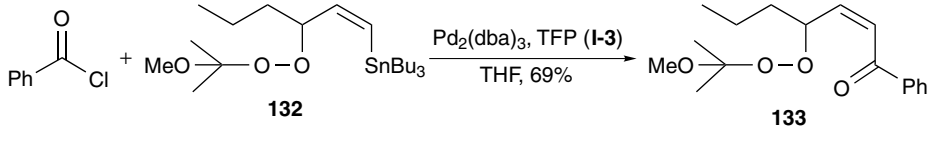
Pd-catalyzed coupling of acyl halides with organometallic reagents is a useful synthetic method of ketones. The alkylzinc reagent **127**, prepared from the corresponding alkyl iodide with Zn/Cu couple, was coupled with the acid chloride **128** to give the ketone **129** in 50 % yield and used for the total synthesis of amphidinolide T14 [55].

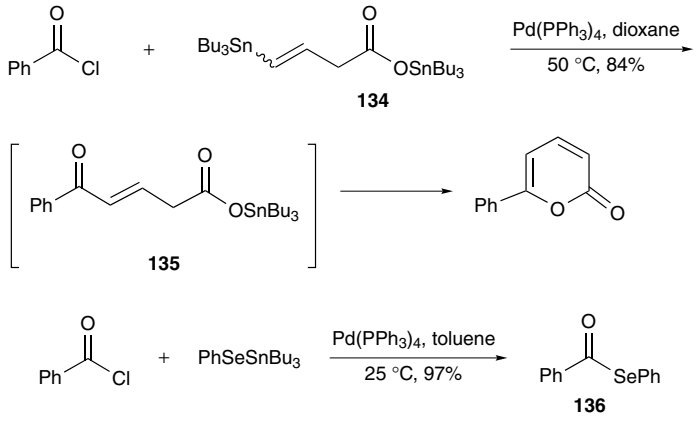


Coupling of chiral cyclopropylboronic acid **130** with benzoyl chloride catalyzed by $PdCl_2$(dppf) was achieved by the combination of Ag_2O and K_2CO_3 as bases to provide the cyclopropyl phenyl ketone **131** with 92 % ee in 77 % yield [56].

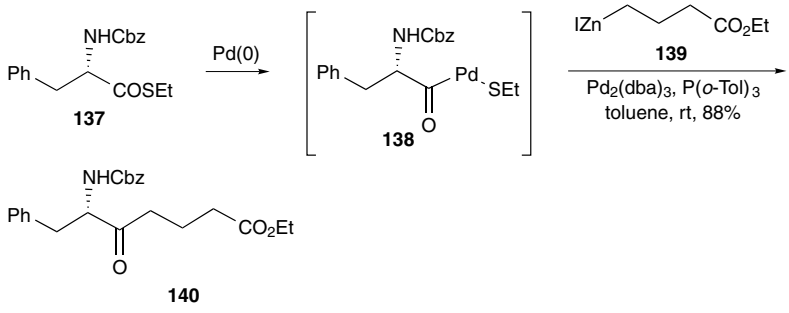


Coupling of the alkenylstannyl peroxyketal **132** with benzoyl chloride proceeded to give the phenyl ketone **133** without affecting the peroxy group using trifurylphoshine as a ligand [8]. Coupling of alkenylstannane **134** with benzoyl chloride afforded the ketone **135**, which was cyclized to 6-phenylpyran-2-one [57]. Phenyl seleno benzoate **136** was prepared in high yield by the reaction of phenyl tributylstannyl selenide with benzolyl chloride at room temperature [58].

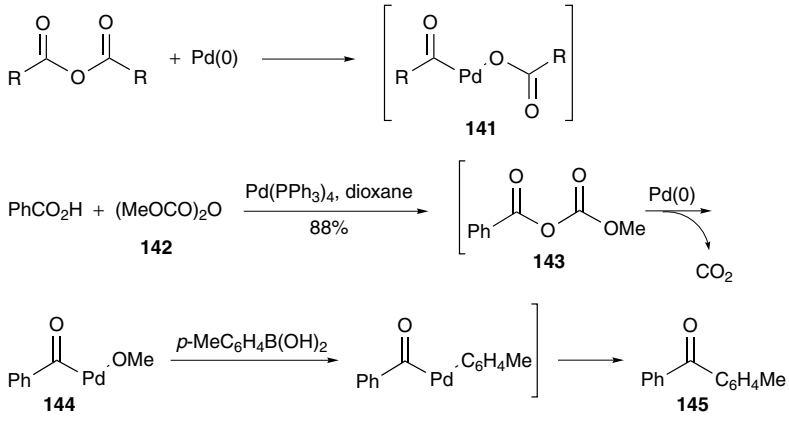




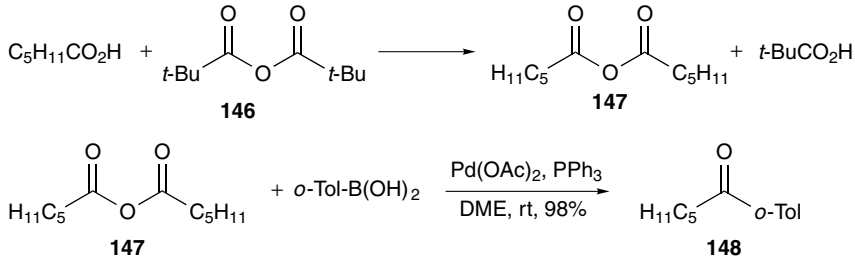
The acylpalladiums such as **138** are generated by oxidative addition of thioesters and used for ketone synthesis as reported by Fukuyama. Coupling of ethyl thioester of phenylalanine **137** with alkylzinc reagent **139** using P(*o*-Tol)$_3$ as a ligand gave **140** in high yield [59]. Phenyl thioesters are also used [60].



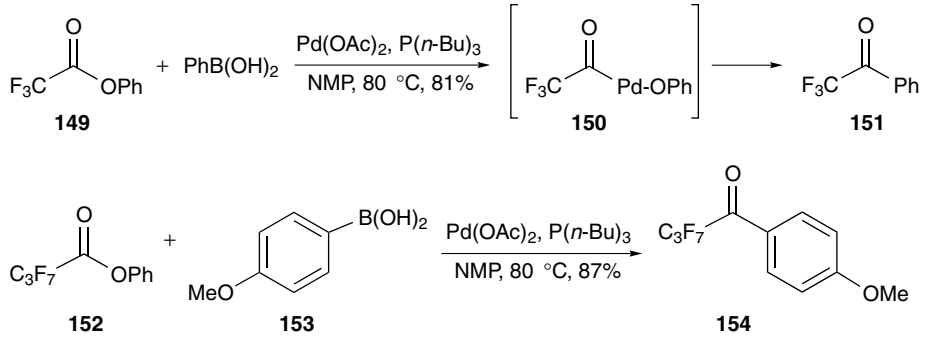
The acylpalladium **141** is formed by oxidative addition of acid anhydride to Pd(0), and can be used for synthetic purposes [61]. The mixed anhydride **143** was prepared *in situ* by the reaction of benzoic acid with dimethyl dicarbonate (**142**), and the benzoylpalladium methoxide **144** is generated by decarboxylative oxidative addition of **143**, and is used for Suzuki coupling with arylboronic acid to yield the diaryl ketone **145** [62].



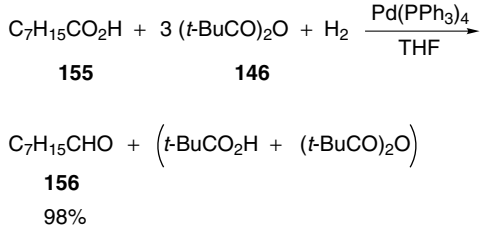
Although less convenient, mixed acid anhydride **147** can be prepared *in situ* by the treatment of carboxylic acid with pivalic anhydride (**146**), and used for Suzuki coupling to afford the ketone **148** [63].



Phenyl trifluoroacetate (**149**) undergoes oxidative addition to generate the acylpalladium **150** [64]. Based on this reaction, trifluoromethyl ketones such as **151** can be prepared by Suzuki coupling with arylboronic acids. Similarly, anisyl heptafluoropropyl ketone (**154**) was prepared by the Suzuki coupling of phenyl heptafluorobutyrate (**152**) with anisylboronic acid **153** [65].

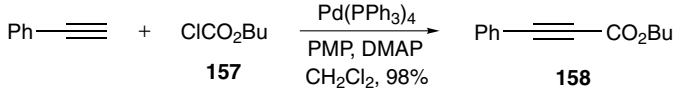


Reduction of carboxylic acids to aldehydes can be carried out via *in situ* formation of acid anhydrides by the treatment of carboxylic acids **155** with an excess of pivalic anhydride (**146**). The acylpalladium intermediate, prepared in this way, is hydrogenolyzed to give aldehyde **156**. Separation of the desired aldehyde **156** from other byproducts is tedious under these conditions [61,66].



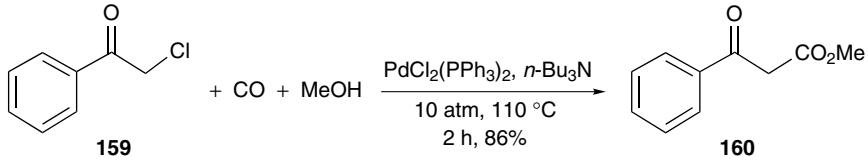
Alkynic esters are prepared by the coupling of terminal alkynes with chloroformate **157**. Butyl chloroformate (**157**) is an unstable compound, and the reaction

should be carried out carefully. Butyl phenylpropiolate (**158**) was prepared in high yield by the reaction of phenylacetylene with butyl chloroformate (**157**) using PMP as a hindered base and a small amount of DMAP in nonpolar solvents such as dichloromethane [67].

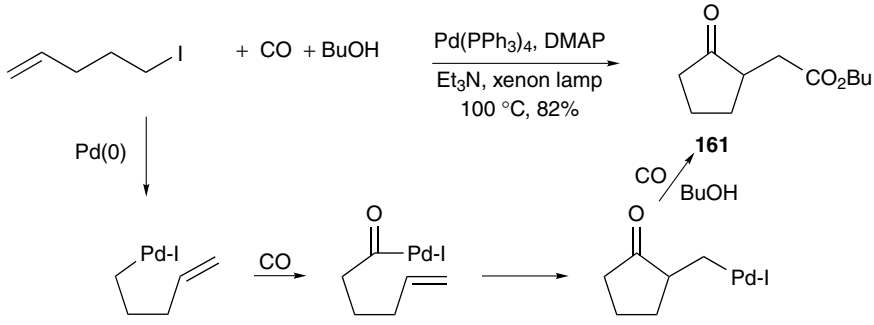


3.5.5 Miscellaneous Reactions

Some halides of sp^3 carbons can be carbonylated. Carbonylation of α-halo ketones and esters is a known reaction [68,69]. β-Keto esters are prepared by the carbonylation of halomethyl ketones [70,71]. Methyl benzoylacetate (**160**) was obtained in 86 % yield by the carbonylation of 2-chloroacetophenone (**159**) in MeOH using $PdCl_2(PPh_3)_2$ as a catalyst at 110 °C and 10 atm in the presence of *n*-Bu_3N [71].



Cyclization and dicarbonylation of 4-pentenyl iodide afforded the keto ester **161** in 82 % yield in benzene in the presence of $Pd(PPh_3)_4$, Et_3N, and DMAP at 100 °C and 40 atm under irradiation with a xenon lamp [72].



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3.6 Cross-Coupling Reactions with Organometallic Compounds of the Main Group Metals via Transmetallation

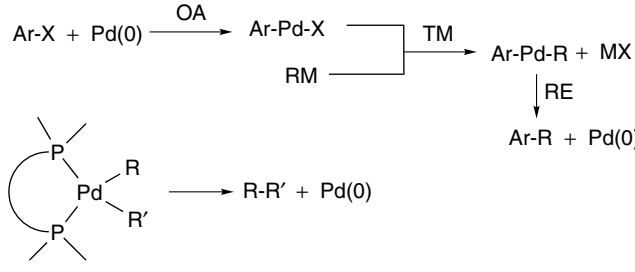
3.6.1 Introduction

A classical synthetic method of biaryls is Cu-promoted coupling of aryl halides, which is known as the Ullmann reaction. An interesting review on aryl–aryl bond formation one century after the discovery of the Ullmann reaction has been published [1]. However, the Ullmann reaction is far from satisfactory. Now Pd-catalyzed coupling reactions are emerging as excellent methods of biaryl formation. Pd-catalyzed cross-couplings of aryl and alkenyl (and some alkyl) halides with organometallic compounds (mainly Mg, Zn, B, Sn, and Si), which include a variety of groups such as aryl, alkenyl, alkynyl, and alkyl to form aryl–aryl, aryl–alkenyl, aryl–alkynyl, aryl–alkyl, alkenyl–alkenyl, alkenyl–alkynyl, alkenyl–alkyl, and alkyl–alkyl bonds, are powerful methods of C—C bond formation [2]. Coupling of aryl and alkenyl halides with alkynylmetal compounds is treated in section 3.4.2. An interesting historical survey on studies of cross-coupling reactions developed from the mid 1970s has been given by Negishi [3]. Recent remarkable progress in

this field, which has been realized by the introduction of electron-rich and bulky ligands, is facile coupling of aryl chlorides. Typically commercially available and air stable $Pd[P(t\text{-}Bu_3)]_2$ is used. An excellent review on Pd-catalyzed reactions of aryl chlorides has appeared [4]. Heterocyclic carbenes are also effective ligands for coupling reactions [5]. Aryl fluorides are considered to be inert. Electron-deficient aryl fluorides can be coupled when PMe_3 [6] or biphenylylphosphines [7] are used.

Organopalladium species formed by the oxidative addition of halides undergo transmetallation with alkyl, aryl, alkenyl, allyl, and benzyl compounds of main group metal elements, and then the carbon–carbon bond formation occurs by reductive elimination as a final step. Couplings of electropositive metals such as Mg and Zn show somewhat different features from those of electronegative elements such as B, Sn, and even Si. Sufficiently reactive Mg, Zn, and Sn reagents undergo transmetallation of R-Pd-X without an additive. On the other hand, transmetallation of B and Si reagents proceeds in the presence of additive or promoter. Facile preparation of stereo- and regiodefined alkyl- and alkenylmetals via hydrometallation or carbometallation of alkenes and alkynes enhances the usefulness of the coupling.

Coupling of alkylmetals with alkyl halides has been regarded as a difficult reaction due to slow oxidative addition of alkyl halides and easy β-H elimination of alkylpalladium intermediates. Recently breakthrough has occurred in this area by using bulky bidentate ligands. Bidentate phosphines and bulky monophosphines, coordinated to Pd catalysts, are expected to help favor reductive elimination by enforcing *cis* geometry of alkyl and other organic groups. In addition, a large bite angle of ligands brings two organic groups closer, promoting the reductive elimination step.

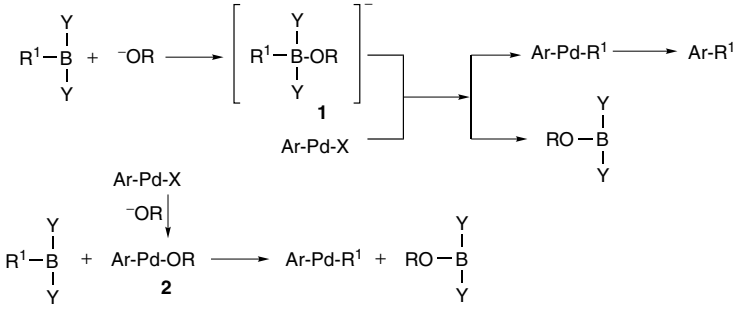


3.6.2 Organoboron Compounds (Suzuki–Miyaura Coupling)

3.6.2.1 Introduction and New Preparative Methods of Organoboranes

Coupling of organoboron compounds with aryl, alkenyl and alkynyl halides is one of the most useful coupling reactions and called Suzuki–Miyaura coupling (abbreviated to S-MC in this section) [8–10]. Due to low nucleophilicity of organic groups R on the B atom, their transmetallation is difficult. The coupling reaction proceeds via transmetallation in the presence of bases [11]. The role of the base is explained by activation of either Pd or boranes. The nucleophilicity of R is enhanced by quaternization of the boron with bases, generating the corresponding 'ate' complexes **1**, which undergo facile transmetallation. Alternatively, the formation of (alkoxo)palladium species Ar-Pd-OR **2** from Ar-Pd-X facilitates the transmetallation with organoboranes. No reaction takes place under neutral

conditions. This is a characteristic feature of organoboron chemistry, which is different from that of other organometallic reagents. Various aryl, alkenyl, and even alkylborane reagents of different reactivity can be used for the coupling with aryl, alkenyl, alkynyl, and some alkyl halides, and the coupling offers very useful synthetic methods.

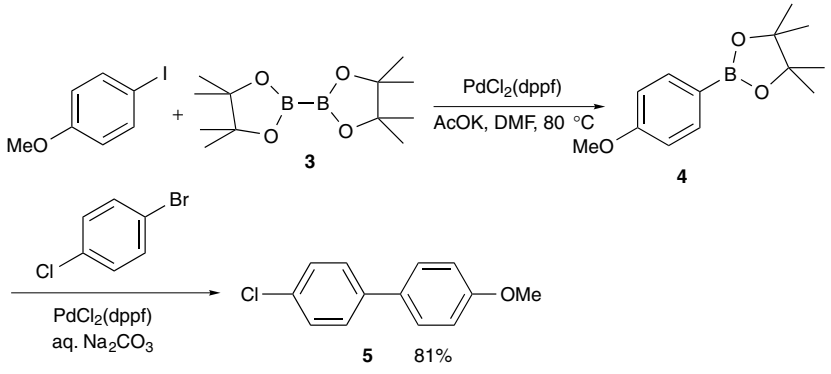


S-MC is the most popular among Pd-catalyzed cross-couplings on account of several advantages:

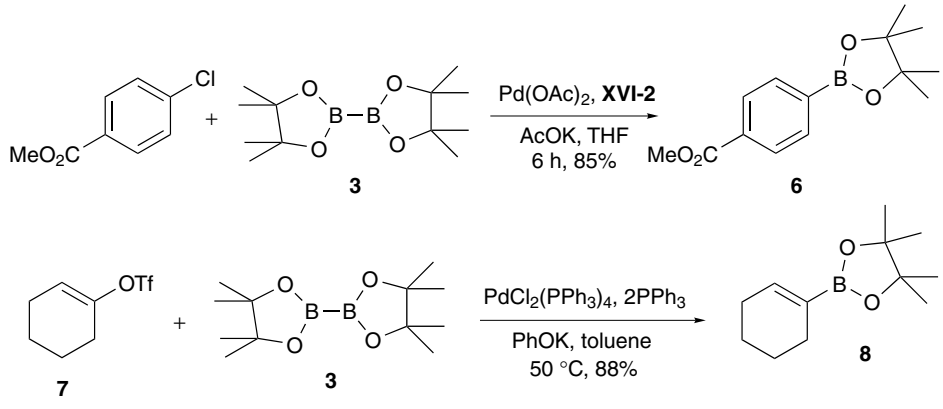
1. Commercial availability of a large number of organoboranes especially boronic acids and their esters.
2. Stability of boronic acids to heat, air, and moisture.
3. Tolerance to a broad range of functional groups.
4. Mild reaction conditions.
5. Low toxicity, but not non-toxicity.
6. Easy separation of inorganic boron from reaction mixture.

Hydroboration of alkenes and alkynes is an established preparative method of alkyl- and alkenylboranes. Arylboranes, arylboronic acids and their esters (boronates) are prepared from aryllithium or Grignard reagents.

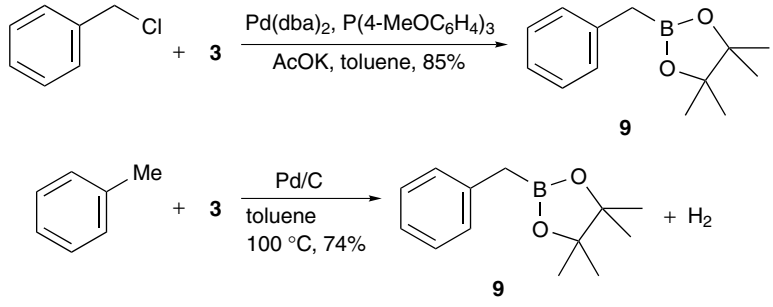
Several new synthetic methods of arylboronates, such as pinacol ester, have been developed. A convenient preparative method of arylboronates **4** is Pd-catalyzed cross-coupling of aryl halides and triflates with bis(pinacolato)diboron (**3**), which can be handled easily in air. The best ligand for the coupling is DPPF [12]. In addition, one-pot biaryl synthesis can be carried out most conveniently without isolation of the boronate **4** to provide **5** [13]. Ligandless $Pd(OAc)_2$ is active for



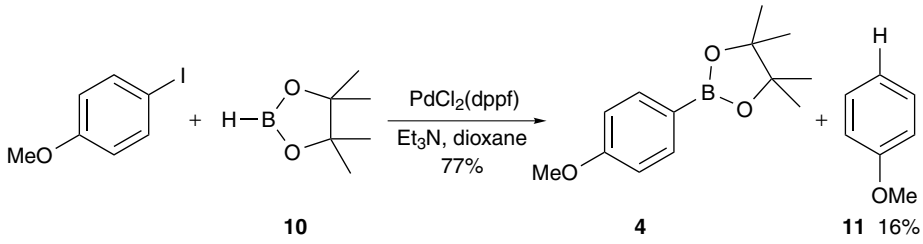
the coupling of aryl bromides having EWG in DMF [14]. The carbene (**XVI-2**) was found to be a good ligand for activated aryl chlorides to afford **6** [15]. Borylation of alkenyl triflate **7** with **3** affords alkenylboronate **8** when $PdCl_2(PPh_3)_2$-2PPh_3 as a catalyst and PhOK as a base are used, and the method is applied to one-pot synthesis of asymmetrical 1,3-dienes and arylalkenes [16].

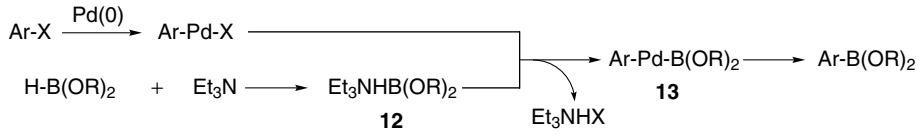


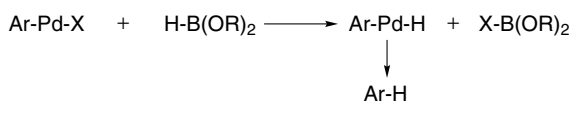
Borylation of benzyl chloride with **3** in toluene in the presence of AcOK, $Pd(dba)_2$, and tri(4-anisyl)phosphine gives pinacol benzylboronate **9** in high yield [17]. More conveniently benzylboronate **9** can be prepared by borylation of toluene with **3** by the use of Pd on carbon as a catalyst [18].

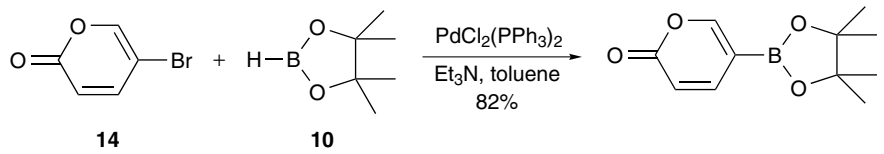


Masuda and co-workers have found a new and mechanistically interesting synthetic method of pinacol arylboronate by the coupling of pinacolborane **10** with aryl triflates and iodides in the presence of DPPF as a ligand and Et_3N as the most effective base in dioxane. In this case, the arylboronate **4** is produced as the main product, and hydrogenolysis of halides with boron hydride to give the reduced arene **11** is the minor path. The reaction mechanism is shown in the following. Transmetallation of **12** to form **13** is a key step. Direct transmetallation of boron hydride to form palladium-hydride is a minor path [19]. Reaction of 5-bromo-2-pyrone (**14**) with **10** provided the pinacolboronate in 82 % yield by using $PdCl_2(PPh_3)_2$ as a catalyst, but a very poor result was obtained when $PdCl_2$(dppf) was used [20]. Triflates are the most reactive.

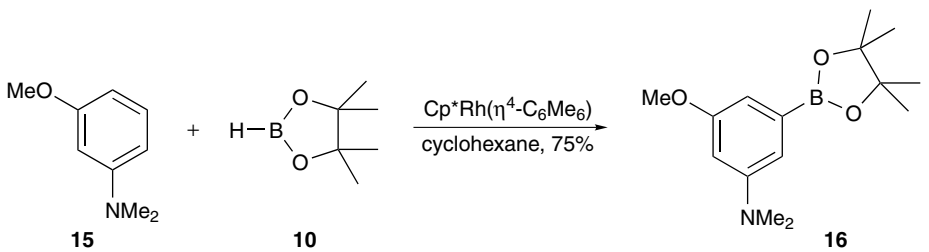






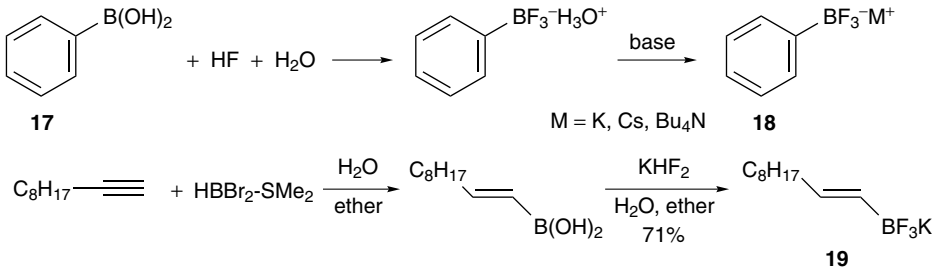


Although this is not a Pd-catalyzed reaction, direct borylation of arenes **15** with pinacolborane **10** to give arylboronate **16** can be achieved using several transition metal complexes as catalysts. Some Rh and Ir catalysts are known to be active [21,22].

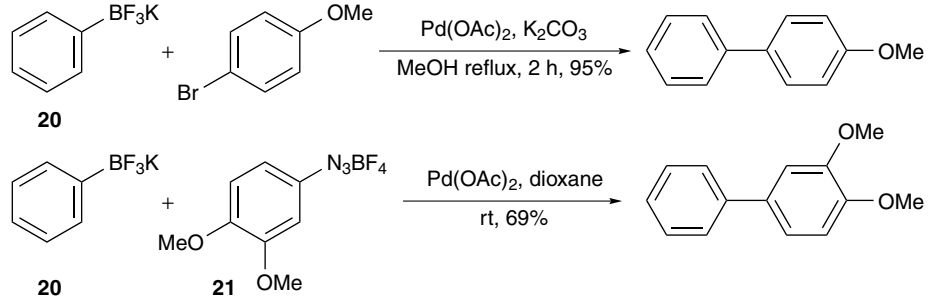


Phenylboronic acid (**17**) and its derivatives are widely used. Boronic acids are sometimes difficult to purify because they undergo cyclotrimerization with loss of water to form boroxines. On the other hand, organotrifluoroborate salts **18** are easily prepared, purified, and handled [23]. Aryltrifluoroborate salts **18** are prepared by the reaction of arylboronic acid with HF and base [24]. Alkenyltrifluoroborates **19** are prepared by hydroboration of 1-alkynes, followed by treatment with KHF_2 [25].

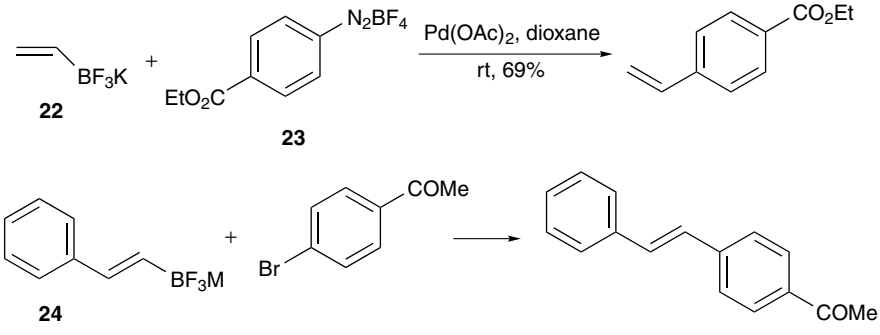
These potassium organotrifluoroborates are good partners of S-MC [26]. Coupling of $PhBF_3K$ (**20**) with deactivated *p*-bromoanisole proceeds with ligandless Pd catalyst in refluxing MeOH in the presence of K_2CO_3 [27]. Reaction of more



reactive diazonium salt **21** with **20** proceeds at room temperature without addition of a base [28].



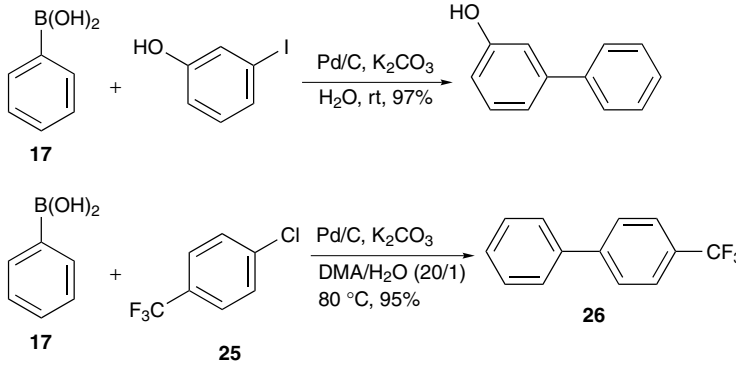
Vinylboronic acid is difficult to purify. On the other hand, coupling of vinyltrifluoroborate **22** with diazonium salt **23** occurs at room temperature in the presence of ligandless Pd without a base [28]. However, use of DPPB or DPPF is necessary for the coupling of K or Bu_4N salt **24** of alkenyltrifluoroborates with aryl bromides [24,25].



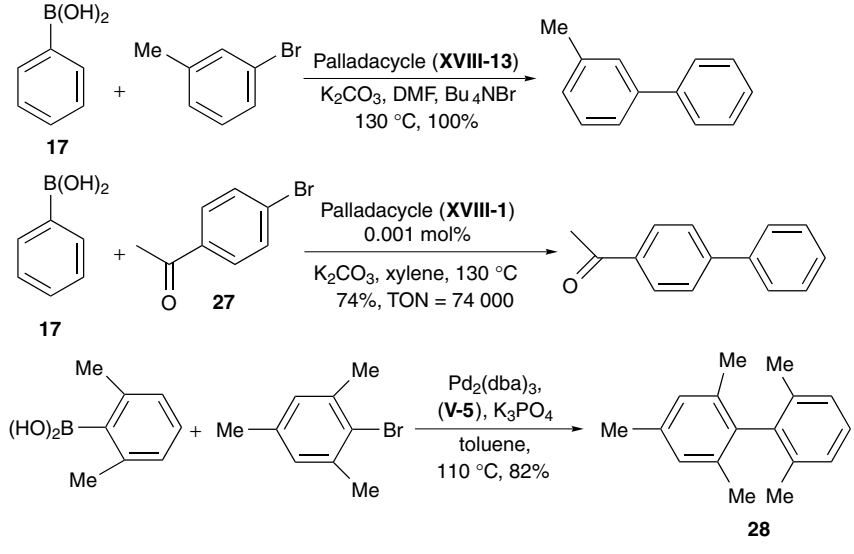
3.6.2.2 Catalysts and Reaction Conditions

A number of papers claiming 'A highly active catalyst for Suzuki coupling', 'Convenient and efficient catalyst for S-MC' or 'Extremely high-activity catalysts' have been published. In some cases, these catalysts seem to be active for only limited substrates, and not appropriate for every substrate.

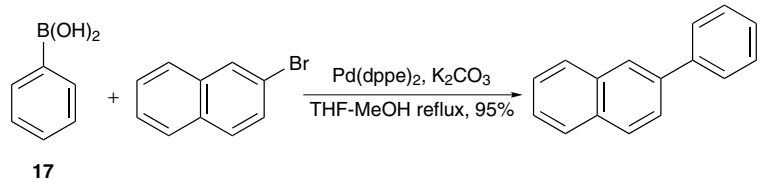
Several types of catalysts are used. From a practical standpoint, ligandless catalysts are most useful. Several reactions for the coupling have been reported. Coupling of phenylboronic acid (**17**) with iodophenol was carried out in the presence of Pd on carbon as a reusable catalyst and K_2CO_3 in water [29]. Coupling of mainly electron-deficient aryl chlorides such as 4-chlorotrifluoromethylbenzene (**25**) catalyzed by Pd on carbon proceeded in DMA/H_2O (20 : 1) to give the coupling product **26** in high yield [30]. Also Pd on carbon and KF were used in MeOH [31]. Coupling of aryl iodides by a similar catalyst supported on alumina proceeds without solvent [32]. Hollow Pd spheres are active catalysts for aryl iodides and bromides in EtOH, and the catalyst was used six times without loss of activity [33]. Reactions catalyzed by Pd nanoparticles are carried out in water [34,35].



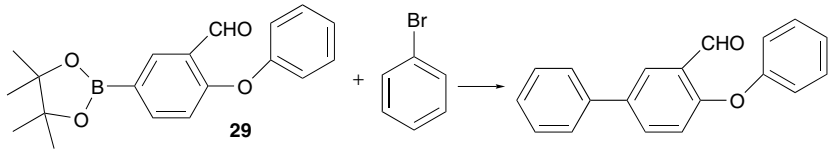
Sulfur-containing palladacycle **XVIII-13** is a precursor of an effective catalyst in the presence of Bu_4NBr [36]. Palladacycle **XVIII-1** is an efficient catalyst, and high TON (74 000) was obtained in the coupling of electron-deficient aryl bromide **27** [37]. Preparation of sterically hindered biaryl **28** was carried out with bulky phenanthrene-based phosphine **V-5** [38].



$Pd(dppe)_2$ with K_2CO_3 in THF–MeOH [39], and combination of diazabutadiene (**XVII-4**) with Cs_2CO_3 or CsF are effective catalysts. No coupling takes place with bases such as Na_2CO_3 and MeONa [40].



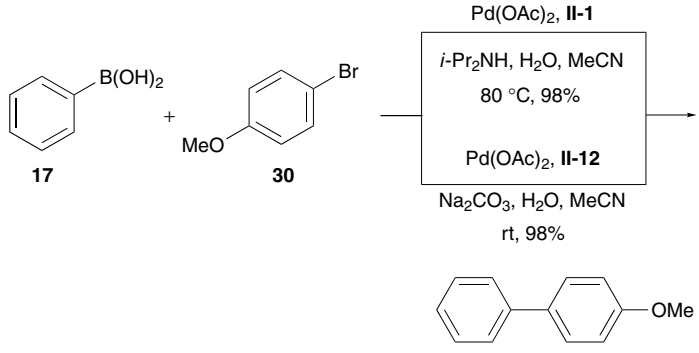
In S-MC, ligands, solvents and bases have critical effects and careful selection is necessary. For example, the following comparative survey has been carried out in the coupling of formylated arylboronate **29**. In this case, Na_2CO_3 seems to be superior to K_2CO_3 [41].



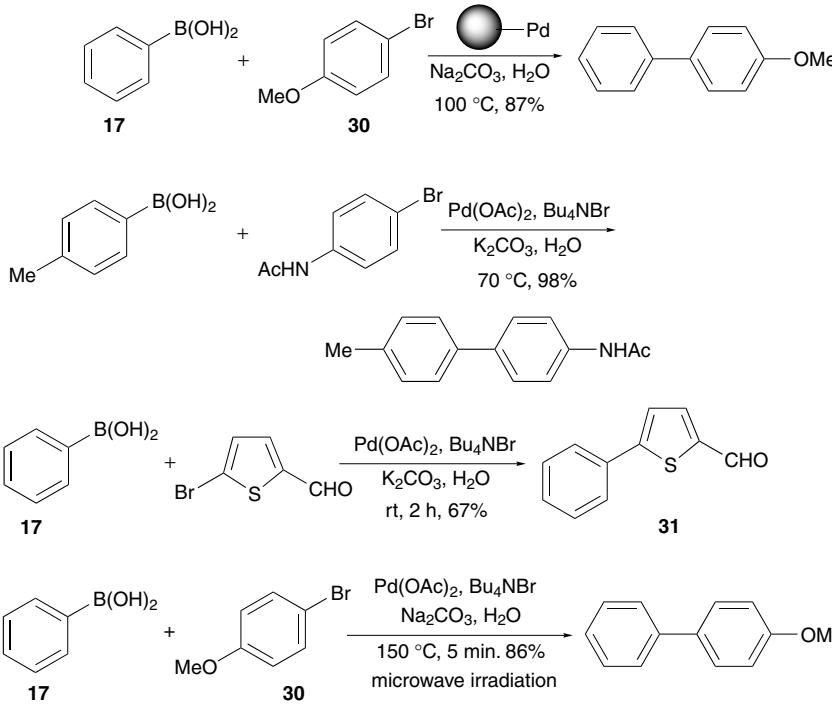
solvent	base	catalyst	temp.	time	yield
xylene	K_2CO_3	**XVIII-1**	130 °C	16	0
THF	KOH	$Pd(PPh_3)_4$	60 °C	16	0
toluene-EtOH	Na_2CO_3	$Pd(PPh_3)_4$	80 °C	2	83%

Water is a good solvent for some S-MC. Reaction proceeds in a mixed solvent in the presence of water-soluble ligands which are listed in Table 1.2. Use of water-soluble sulfonate ligand **II-1** in a mixed solvent of H_2O and MeCN at 80 °C is typical [42]. Coupling of electron-rich bromide **30** with **17** proceeds at room temperature in high yield using di-*t*-butylphosphine, containing the water-soluble trimethylammonium group (**II-12**). The ligand **II-12** gave higher yield than **II-1** in this reaction at room temperature [43].

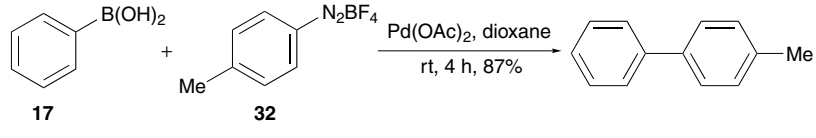
More conveniently, reaction can be carried out in water without a cosolvent under certain conditions. Coupling of substrates insoluble in water such as **30** proceeds with TON up to 20 000 in water when an insoluble and assembled Pd catalyst and a non-cross-linked amphiphilic (amphiphilic) polymer, containing diphenylphosphine group, are used. The catalyst system was used 10 times without any decrease in activity [44]. Also an amphiphilic resin-supported Pd catalyst can be used in water many times giving nearly quantitative yields of coupling products [45].



Furthermore, coupling of aryl bromides proceeds in water in the presence of ligandless $Pd(OAc)_2$ as a precursor and 1 equivalent of Bu_4NBr. Use of 1 equivalent is important. Aryl iodides and triflates are not good substrates under the conditions [46]. 5-Phenylthiophene-2-carboxaldehyde (**31**) was prepared under similar conditions at room temperature [47]. Reaction of **17** with **30** proceeded rapidly in 5–10 min under microwave irradiation at 150 °C [48].

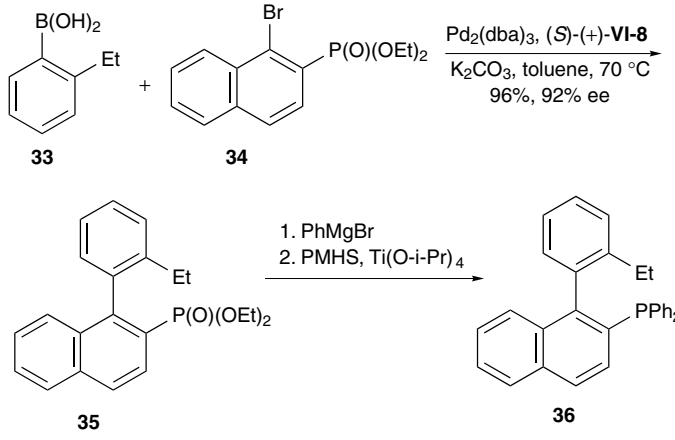


S-MC of diazonium salt **32** proceeds with ligandless Pd at room temperature in dioxane in the absence of a base [49]. $Pd(OAc)_2$ and carbene ligand **XVI-2** are effective for the coupling of aryldiazonium tetrafluoroborates with aryl, alkenyl, and alkyl boronates at room temperature [50].



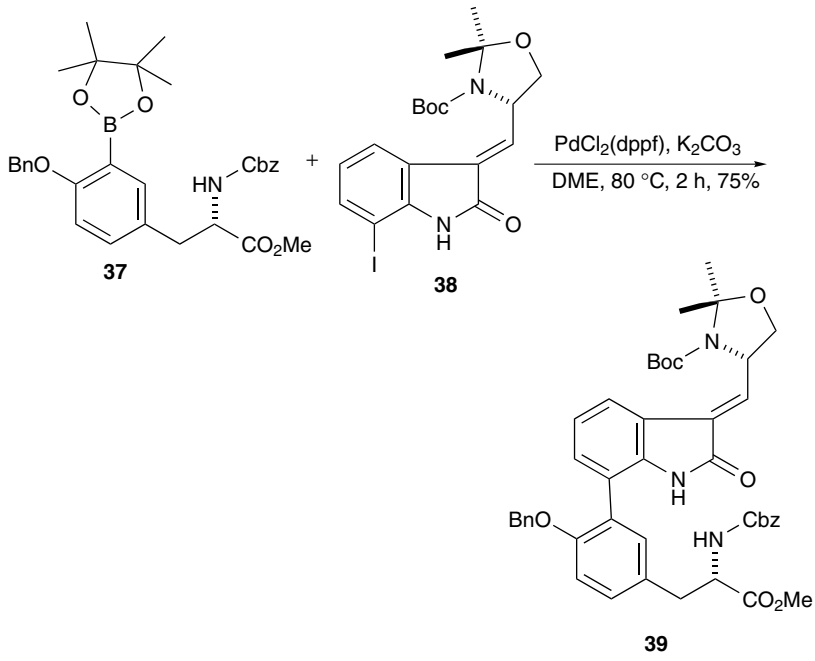
3.6.2.3 Coupling of Arylboranes

Arylboranes with aryl bromides and iodides Coupling of arylboranes with aryl bromides and iodides offers an extremely useful synthetic method for biaryl compounds, and numerous examples are known. Asymmetric S-M aryl–aryl coupling of **33** with **34** in the presence of chiral 2-aminobinaphthyl-based phosphine (S)-**VI-8** afforded the highly enantiomerically enriched biaryl **35** (92 % ee), which was converted to the axially chiral 1-aryl-2-naphthylphosphine **36**. BINAP is not an effective ligand for this asymmetric reaction [51].



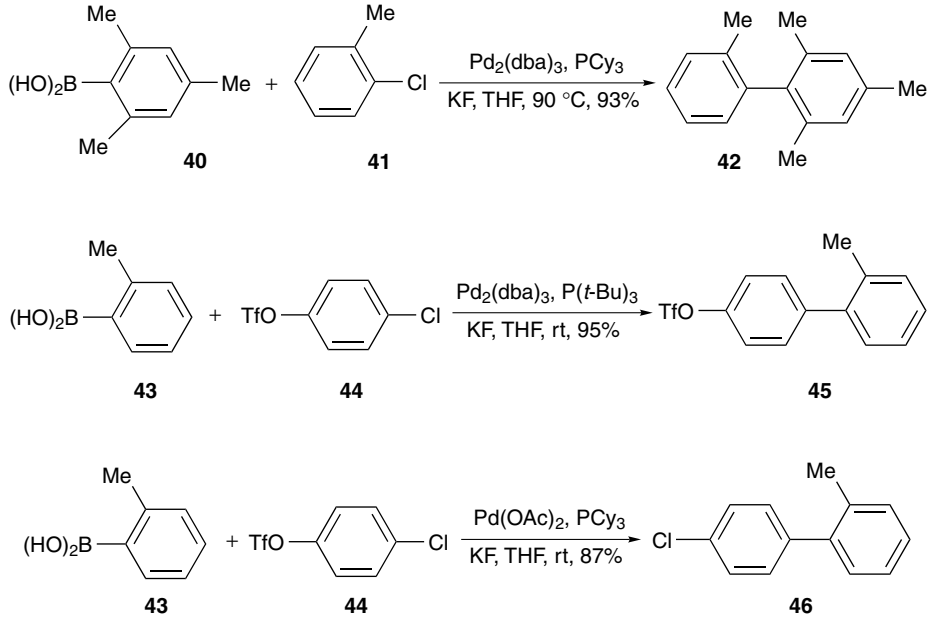
33 **34** **35** **36**

Total synthesis of proteasome inhibitor TMC-95A was achieved by smooth coupling of the functionalized boronate **37** with the iodide **38** without touching labile functional groups to give **39** in 75 % yield in the presence of $PdCl_2$(dppf) as a key reaction [52].

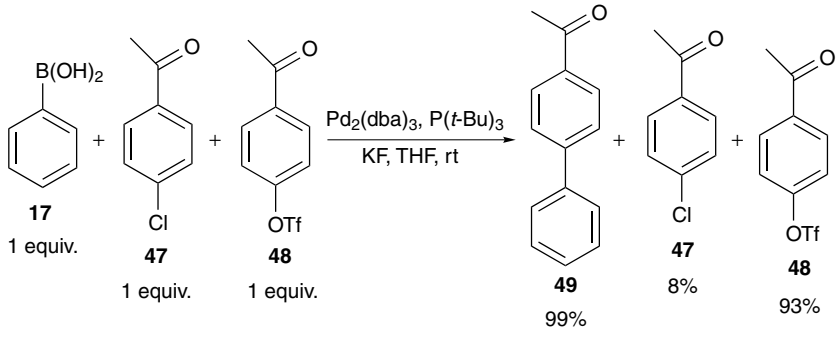


37 **38** **39**

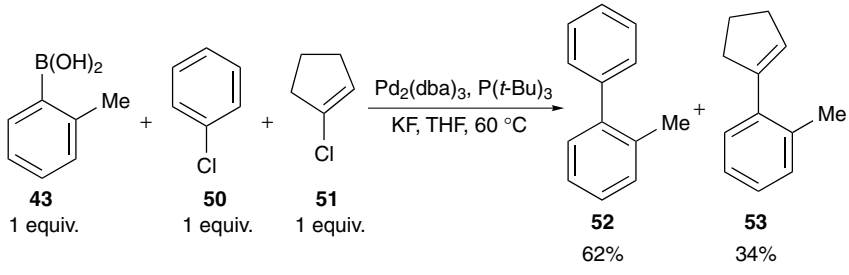
Arylboranes with aryl chlorides and triflates Aryl chlorides are now regarded as good partners of the coupling by the discovery of a number of effective ligands. In this section, mainly coupling of aryl chlorides are surveyed. P(*t*-Bu)$_3$ and PCy$_3$ have been found to be very effective ligands [53]. In the case of S-MC, aryl triflates are known to be less reactive than the corresponding iodides and bromides. Curiously no coupling of aryl triflates took place with the catalyst [Pd/(P(*t*-Bu)$_3$] even at 60 °C. On the other hand, PCy$_3$, which is less bulky and less basic than P(*t*-Bu)$_3$, was found to be an effective ligand for triflates, and coupling of **43** with 4-methoxyphenyl triflate proceeded at room temperature using Pd(OAc)$_2$-PCy$_3$. The sterically hindered biaryl **42** was prepared at 90 °C from **40** and **41** by the use of PCy$_3$. Since reaction of aryl triflates proceeds at room temperature when PCy$_3$ is used, the different behavior of P(*t*-Bu)$_3$ and PCy$_3$ offers interesting chemoselective reactions. The most remarkable is the unprecedented chemoselectivity observed in the reaction of 4-chlorophenyl triflate (**44**) with 2-tolylboronic acid (**43**) at room temperature; chemoselective coupling of aryl chloride took place to give **45** when P(*t*-Bu)$_3$ was used. On the other hand, chemoselective reaction of the triflate group occurred to afford **46** in 87 % yield at room temperature in the presence of PCy$_3$ [54].



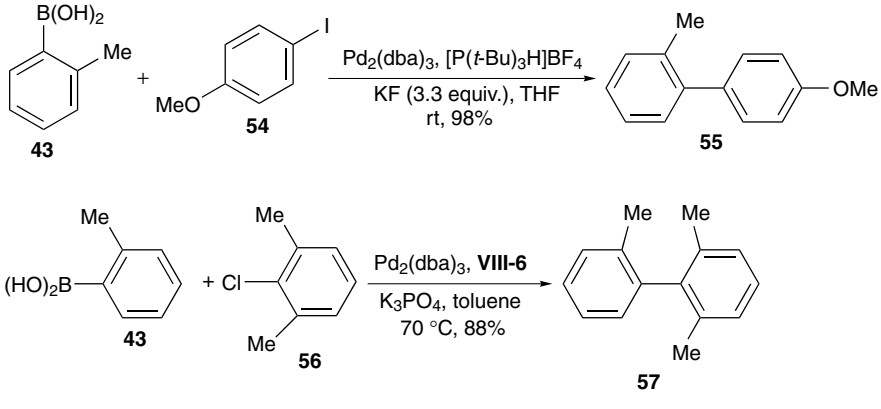
Furthermore higher reactivity of chloride over triflate was demonstrated by intermolecular competitive reaction of the aryl chloride **47** and the triflate **48** with **17**. Reaction at room temperature in the presence of P(*t*-Bu)$_3$ provided the biphenyl **49** with high selectivity. Recovery of the chloride **47** was only 8 %. The catalyst [Pd/(P(*t*-Bu)$_3$] activates the C—Cl bond in preference to the C—OTf bond to afford **49** at room temperature in excellent selectivity and high yield. The chemoselectivity observed shows that the belief that the C—OTf bond is more reactive than the C—Cl bond is no longer valid when Pd/P(*t*-Bu)$_3$ is used.



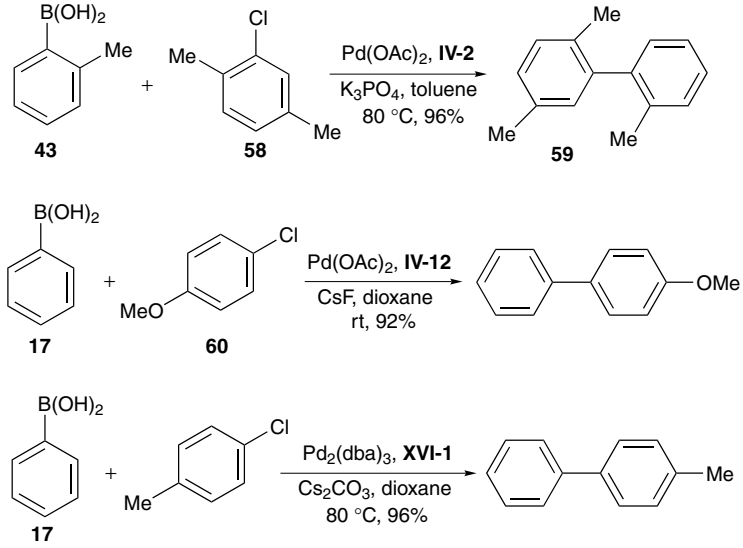
Generally speaking, alkenyl halides are more reactive than aryl halides. An opposite chemoselectivity was observed in the competitive reaction of chlorobenzene (**50**) and 1-cyclopentenyl chloride (**51**) with **43**. A higher yield of **52** (62 %) than that of **53** (34 %) was obtained. The result shows that aryl chloride **50** is more reactive than the alkenyl chloride **51** in the presence of $P(t\text{-Bu})_3$ [54].



$P(t\text{-Bu})_3$ is a remarkable ligand, but it is gradually oxidized. Fu reported that its phosphonium salt $[P(t\text{-Bu})_3H]BF_4$, is air-stable and can be used more conveniently. The salt shows the same reactivity as that of free $P(t\text{-Bu})_3$ in the coupling of **43** with **54** to afford **55** [55]. Triarylphosphines are rather poor ligands for the reactions of aryl chlorides. However, ferrocenylphosphine **VIII-6**, which is a triarylphosphine, was found to be an unexpectedly effective ligand, and coupling of electron-rich and hindered aryl chloride **56** with **43** proceeded at room temperature to afford **57**. The ferrocenyl ligand **VIII-5**, missing the TMS group, is ineffective [56].



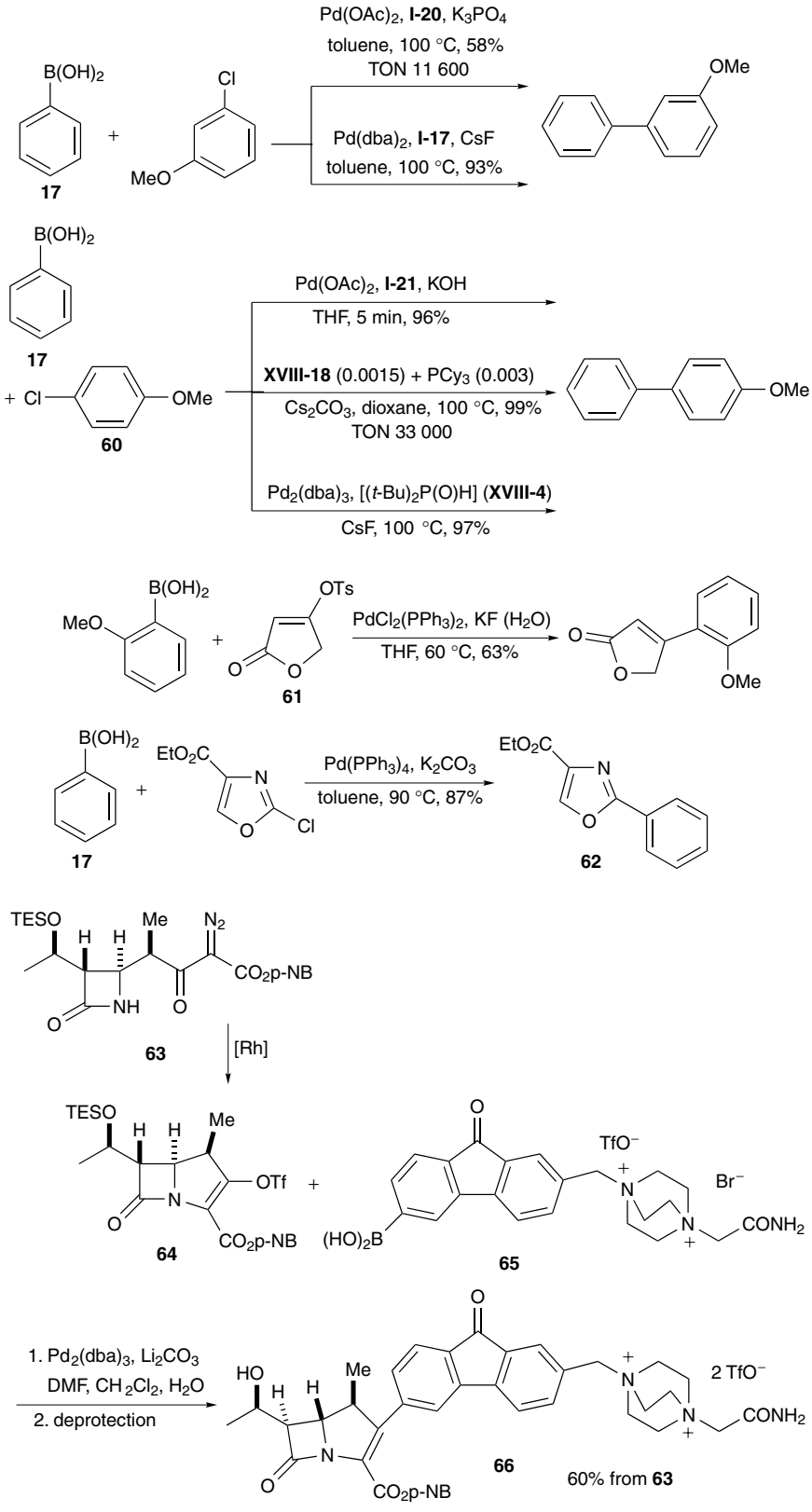
Buchwald group reported biphenylyl(dicyclohexyl)phosphine derivatives such as **IV-2** and **IV-12** are effective for coupling of deactivated aryl chlorides. Reaction of the sterically hindered substrate **58** proceeds at 80 °C, but coupling of 4-chloroanisole (**60**) occurs at room temperature when **IV-12** is used [57]. The polymer-supported ligand is equally active and can be recycled [58]. Carbene **XVI-1** is an excellent ligand, and the most effective base is Cs_2CO_3 (96 % yield). Other bases such as CsF (65 %), K_2CO_3 (53 %), and Na_2CO_3 (6 %) are less effective [59].



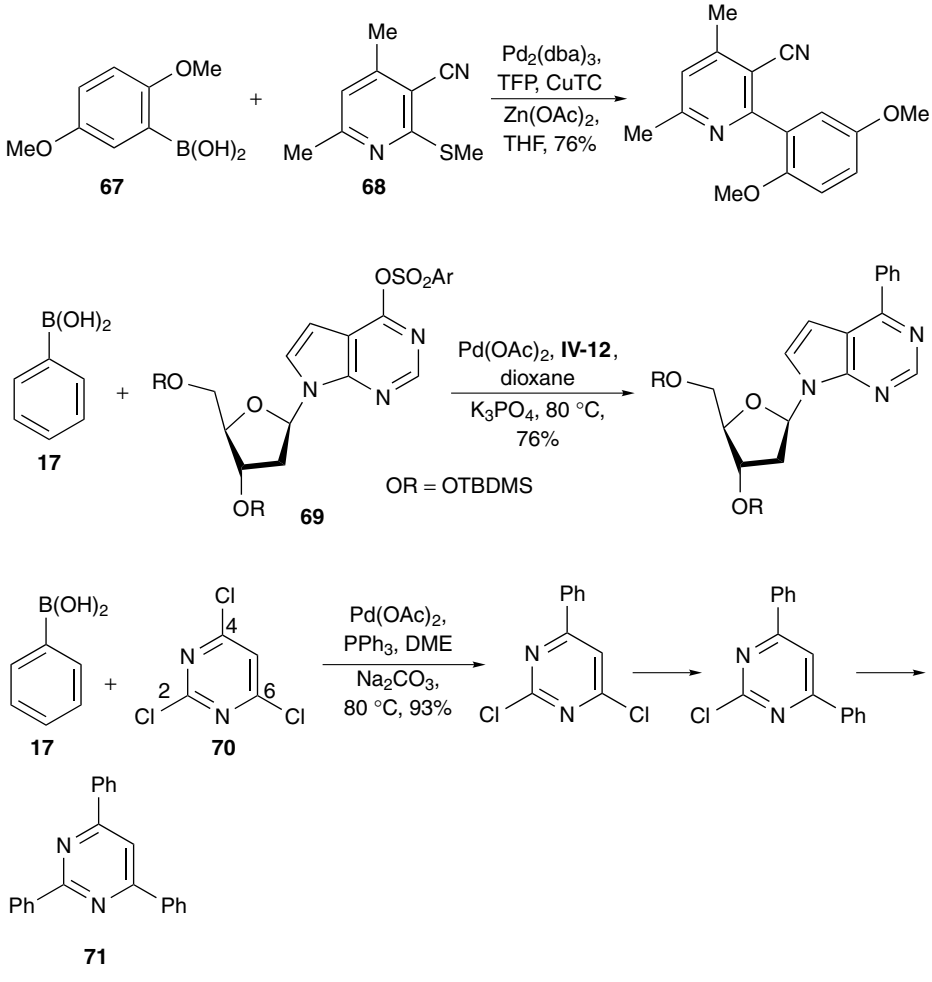
High TON (11 600) was obtained in the reaction of *m*-chloroanisole with **17** in the presence of bulky diadamantyl-*n*-butylphosphine (**I-20**) [60]. Adamantyl(di-*t*-butyl)phosphine (**I-21**) is more effective and coupling of 4-chloroanisole (**60**) with **17** proceeded at room temperature in 5 min, giving 4-methoxybiphenyl in 96 % yield [61]. Aryldicyclohexylphosphine (**I-17**) is also an effective ligand for coupling of 3-chloroanisole [62]. *ortho*-Palladated triaryl phosphite complex (**XVIII-18**) and additional PCy_3, is highly effective and TON as high as 33 000 was obtained. It should be pointed out that the triaryl phosphite alone is not an effective ligand [63]. High yield (97 %) was obtained by using di(*t*-butyl)phosphine oxide (**XVIII-4**) as a precursor of the phosphinous acid ligand [64]. It was claimed that very high TON (6 800 000) was obtained in the coupling of activated aryl chlorides, such as 2-chloro-5-(trifluoromethyl)nitrobenzene, with **17** using the tetraphosphine (**X-1**) [65].

Some heteroaryl halides are good coupling partners, and their reactions offer a versatile method of functionalization of heterocycles. Tosyl as a leaving group can be used for the coupling. 4-Tosyl-2-(5*H*)-furanone (**61**) has been found to undergo facile coupling in the presence of KF [66]. 2-Substituted oxazoles such as **62** were prepared by S-MC of ethyl 2-chloroxazole-4-carboxylate [67].

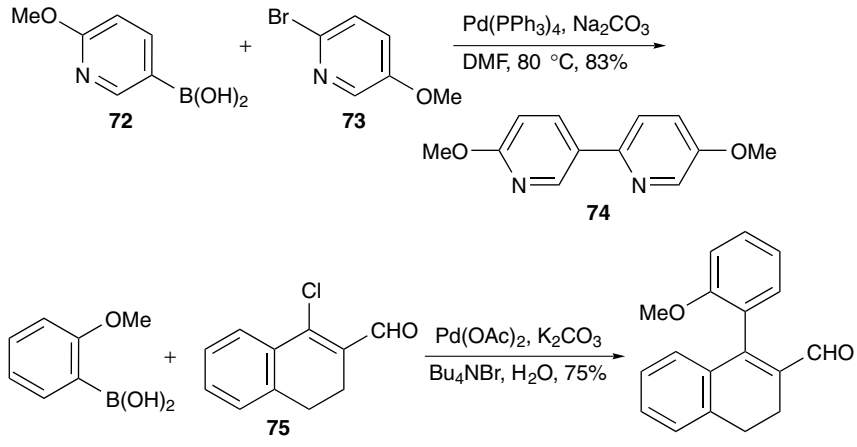
A practical kilogram scale synthesis of carbapenem L-742,728 was carried out by applying the coupling of the doubly quaternarized boronic acid **65** with the triflate **64** under carefully optimized conditions to afford the coupling product **66** after deprotection in a yield of 60 % over the four steps from **63**. Li_2CO_3 was the best base [68].


Pd(OAc)2, I-20, K3PO4
toluene, 100 °C, 58%
TON 11 600
Pd(dba)2, I-17, CsF
toluene, 100 °C, 93%
B(OH)2
Cl
MeO
OMe
17
Pd(OAc)2, I-21, KOH
THF, 5 min, 96%
XVIII-18 (0.0015) + PCy3 (0.003)
Cs2CO3, dioxane, 100 °C, 99%
TON 33 000
Pd2(dba)3, [(t-Bu)2P(O)H] (XVIII-4)
CsF, 100 °C, 97%
60
PdCl2(PPh3)2, KF (H2O)
THF, 60 °C, 63%
OTs
61
Pd(PPh3)4, K2CO3
toluene, 90 °C, 87%
EtO2C
62
TESO
Me
N2
CO2p-NB
NH
63
[Rh]
OTf
64
TfO−
Br−
CONH2
(HO)2B
65
1. Pd2(dba)3, Li2CO3
DMF, CH2Cl2, H2O
2. deprotection
HO
2 TfO−
66
60% from 63

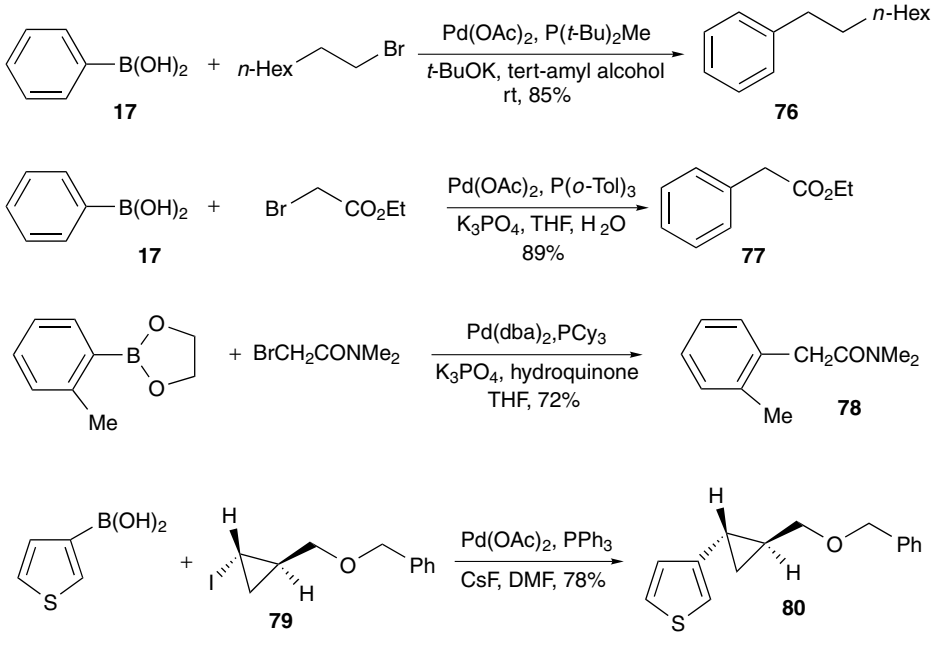
Heteroaromatic methyl thioethers (pyridyl, pyrimidyl, oxazolyl, thiazolyl, thiophenyl, 1,2,4-triazinyl) can be used for the coupling in the presence of 1.2 equivalents of copper thiophene-2-carboxylate (CuTC) and $Zn(OAc)_2$. Congested 2-pyridyl methyl thioether **68** reacts with the boronic acid **67** using TFP [69,70]. 2′-Deoxyguanosine O^6-arylsulfonate **69** underwent facile coupling with **17**. Aminobiphenylylphosphine **IV-12** was the effective ligand [71]. Also 6-chloropurine can be used for the coupling [72]. Three chlorides in 2,4,6-trichloropyrimidine **70** have different reactivity, and couplings proceed step-wise in the order of positions 4 > 6 > 2 to give triphenylpyrimidine **71** in 93 % yield as the final product [73].



The bipyridyl **74** was prepared by the coupling of 3-pyridylboronic acid **72** with 2-bromo-5-methoxypyridine **73** in good yield. Similarly heteroarylpyridines were prepared [74]. Coupling of the β-chloro-α,β-unsaturated aldehyde **75** occurred in water without a co-solvent in the presence of Bu_4NBr [75].

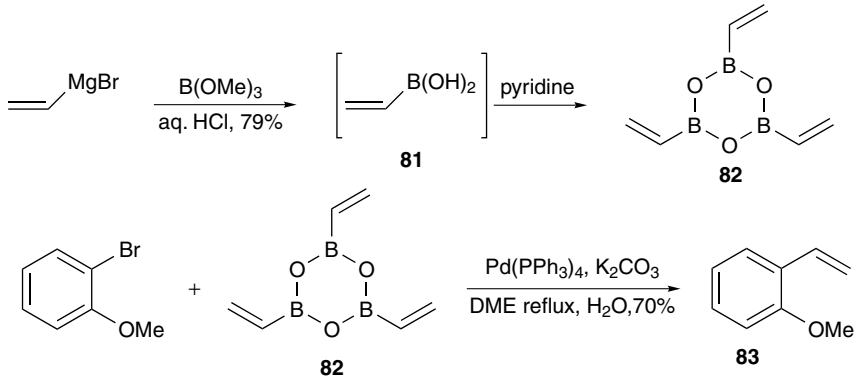


Arylboranes with alkyl halides Interestingly, Fu and co-workers discovered that alkyl halides can be used for the coupling. No β-H elimination occurs. Clearly, reductive elimination takes place before β-H elimination. Reaction of **17** with octyl bromide proceeded smoothly to give octylbenzene (**76**) in 85 % yield in the presence of P(t-Bu)$_2$Me as a ligand and t-BuOK as a base at room temperature [76]. Phenylacetate (**77**) was prepared by coupling **17** with bromoacetate. P(o-Tol)$_3$ is the most effective ligand [77]. N,N-Dimethyltolylacetamide (**78**) was obtained by the coupling of tolyldioxaborolane with 2-bromo-N,N-dimethylacetamide using PCy_3 as a ligand and hydroquinone as a free-radical scavenger [78]. Heteroarylboronic acids are used for coupling. Thiophene-3-boronic acid reacts with iodocyclopropane **79** to give **80** in the presence of CsF as a base. This reaction showed for the first time that cyclopropyl iodide can be used as a coupling partner [79].

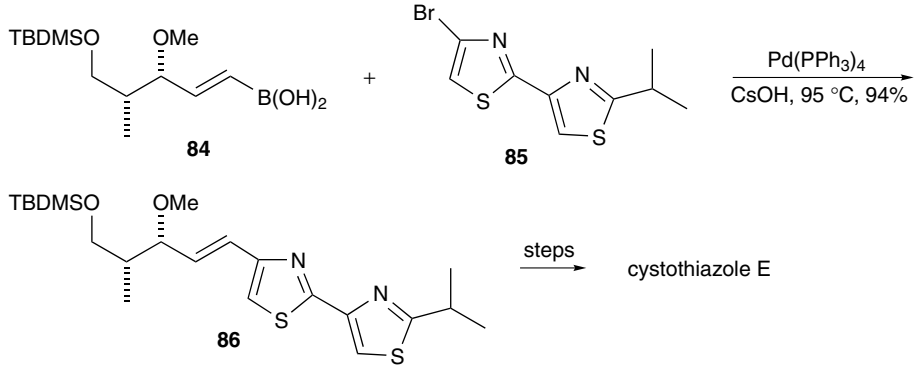


3.6.2.4 Coupling of Alkenylboranes

1-Alkenylboron derivatives are readily available by stereo-defined hydroboration of alkynes and used for the preparation of styrene derivatives by alkenyl–aryl coupling. Vinylboronic acid (**81**), the most simple alkenylboronic acid, is difficult to handle, because it undergoes uncontrollable polymerization. Its anhydride, 2,4,6-trivinylcyclotriboroxane (**82**)-pyridine complex, is stable, and can be used conveniently for the coupling. Vinylation of 2-bromoanisole with **82** proceeds in refluxing DME using K_2CO_3 as a base to provide 2-vinylanisole (**83**) [80].

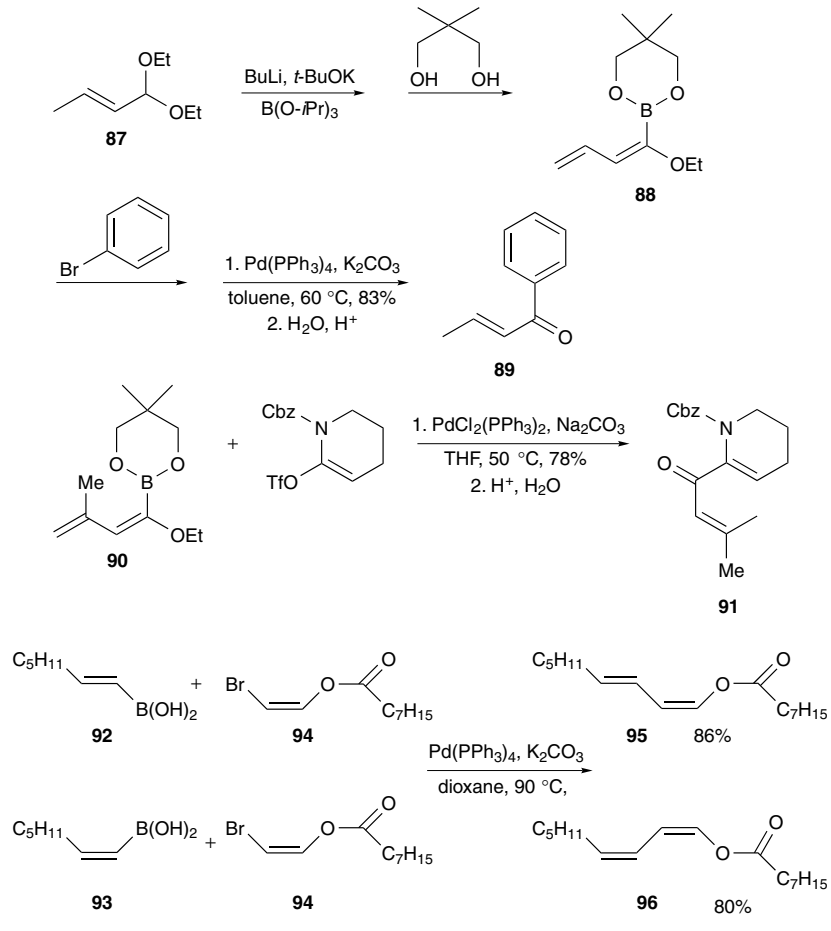


The coupling product **86** of alkenylboronic acid **84** with the bromothiazole **85** in the presence of CsOH as a base has been converted to cystothiazole E [81].

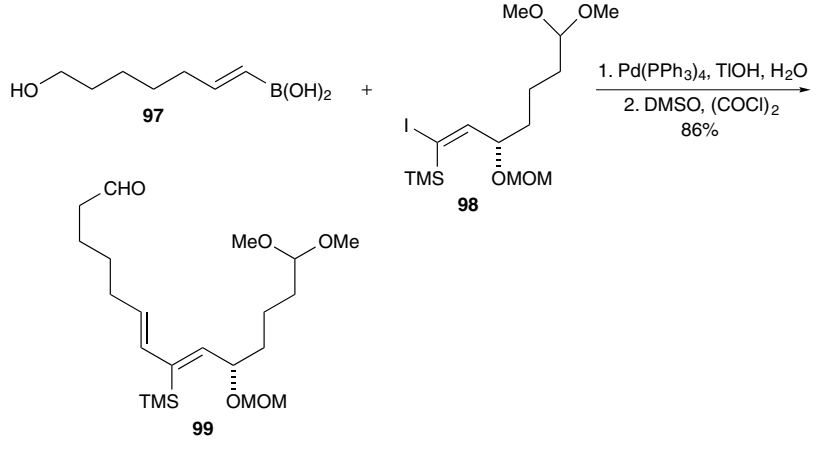


1-Ethoxybutadienylboronate **88** was prepared from α,β-unsaturated acetal **87**, and used for synthesis of phenyl 1-propenyl ketone (**89**) by S-MC and hydrolysis [82]. Similarly the 2-acyl-1,4,5,6-tetrahydropyridine **91** was prepared by the coupling of **90** with an alkenyl triflate, which was derived from the corresponding lactam [83].

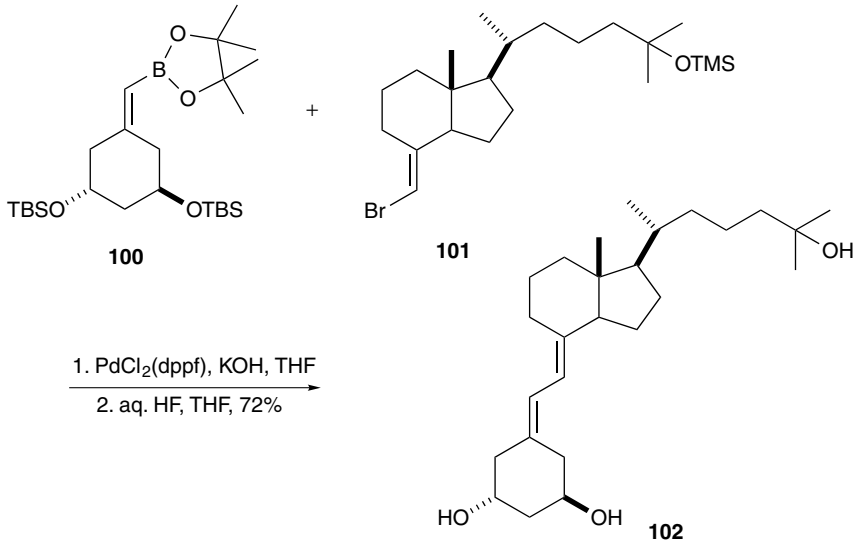
Alkenyl–alkenyl coupling offers a versatile synthetic method of stereo-defined conjugated diene systems. Both (*Z*, *E*)-and (*Z*, *Z*)-conjugated alkadienyl carboxylates **95** and **96**, which are present in a range of natural products, were obtained by coupling (*Z*)-and (*E*)-heptenylboronic acids **92** and **93** with (*Z*)-2-bromovinyl octanoate (**94**) [84].



Coupling of alkenylboronic acid **97** with alkenyl iodide **98** to yield **99** in high yield was utilized in total synthesis of (−)-chlorothricolide [85].



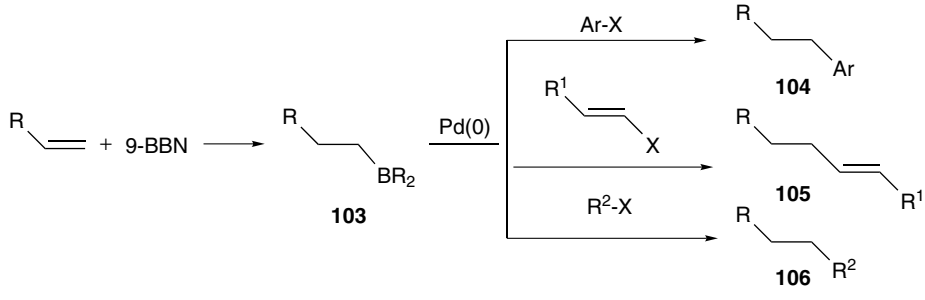
Synthesis of 19-nor-1α,25-dihydroxylvitamin D_3 (**102**) was achieved by coupling the alkenylboronate **100** with the alkenyl bromide **101** in 72 % yield after deprotection [86].



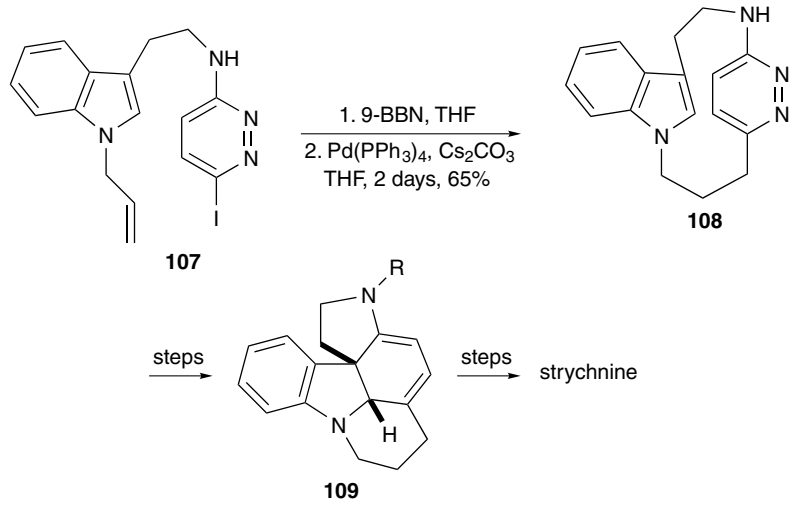
3.6.2.5 Coupling of Alkylboranes

Alkylboranes with aryl and alkenyl halides Coupling of alkylboranes offers an important synthetic method for arylalkanes. It is somewhat surprising that the coupling of alkylboranes with aryl and alkenyl halides proceeds smoothly via reductive elimination without undergoing β-H elimination of alkylpalladium intermediates. Bidentate phosphine ligands play important roles by enforcing a *cis* geometry of alkyl and other organic groups and bringing two organic groups closer to favor the reductive elimination step.

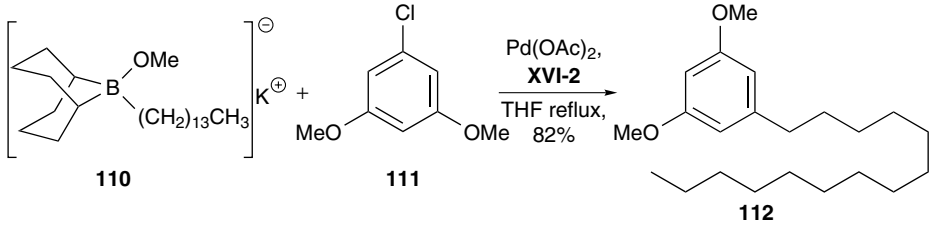
Alkylboranes **103** are easily prepared by hydroboration of 1-alkenes with 9-BBN, and subsequent reactions with aryl, alkenyl, and alkyl halides offer versatile methods of alkylation to afford alkylated products **104**, **105**, and **106**. The 'hydroboration-coupling protocol' has been utilized extensively in natural product syntheses [87].



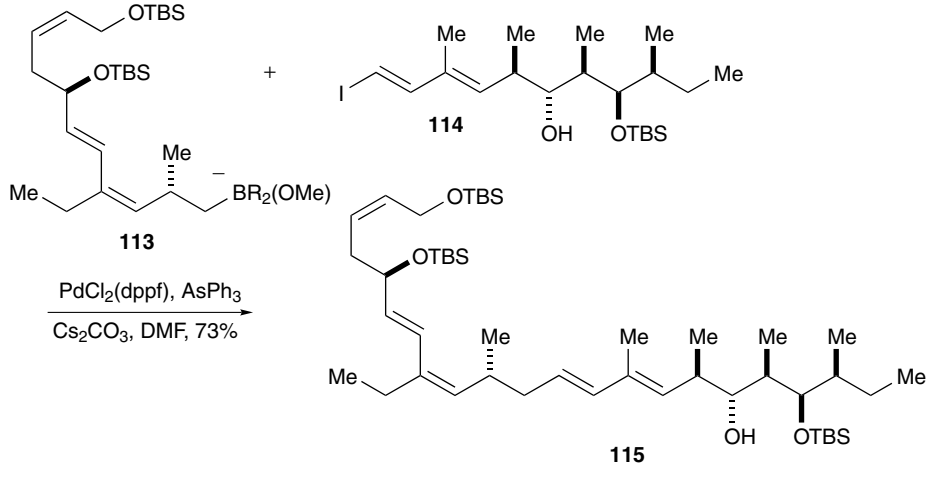
In a concise formal total synthesis of strychnine, the cyclophane **108** was prepared in 65 % yield by applying the hydroboration–intramolecular coupling method to **107** under high dilution conditions, and converted to the pentacycle **109** by transannular inverse-electron-demand Diels-Alder reaction [88].



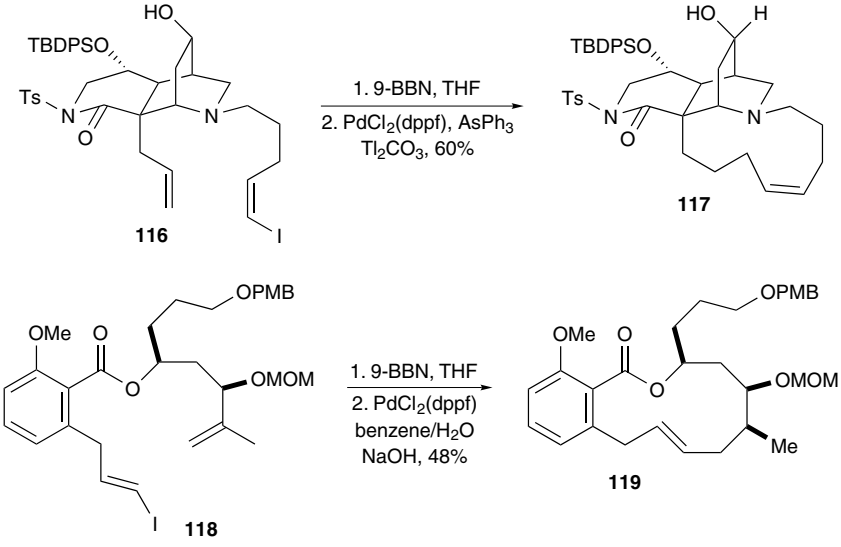
Coupling of 1,3-dimethoxy-5-chlorobenzene (**111**) with 9-tetradecyl-9-BBN derivative **110** proceeded in THF with carbene ligand **XVI-2** to give 1,3-dimethoxy-5-dodecylbenzene (**112**) [89].



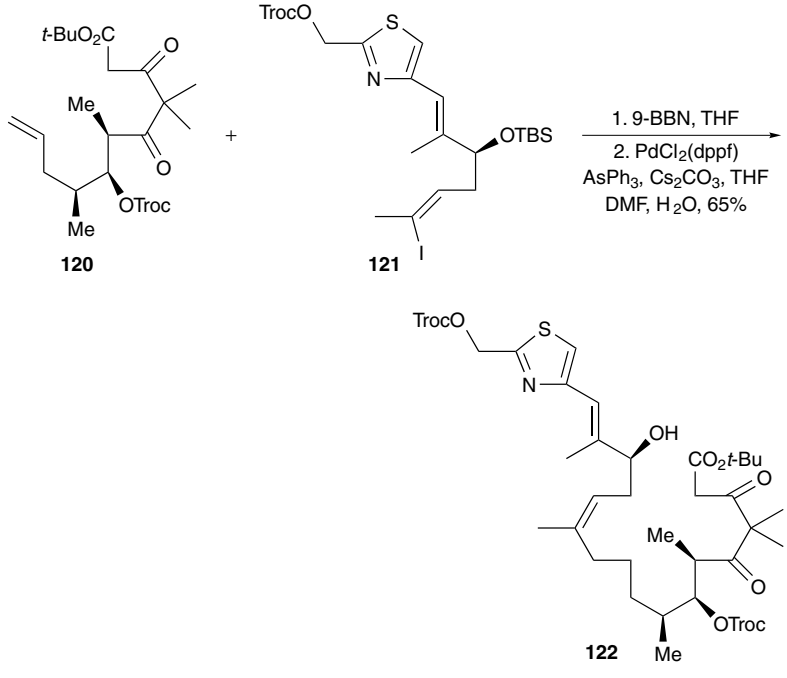
Synthetic intermediate of the cytotoxic ketide callystatin A **115** was prepared by coupling the alkylboronate **113** with the alkenyl iodide **114**. The coupling product **115** was obtained in 73 % yield when $PdCl_2$(dppf), $AsPh_3$, and Cs_2CO_3 were used in aq. DMF [90].



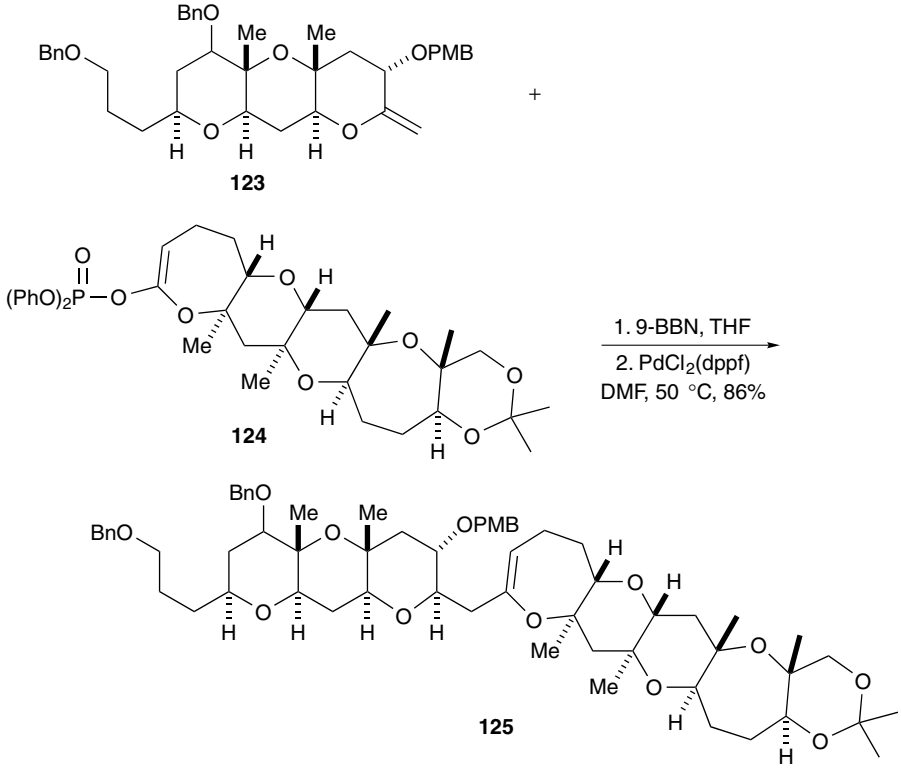
The bridged azadecalin core of xestocyclamine A **117** was constructed in 60 % yield by intramolecular coupling of the alkylborane derived from the terminal alkene **116**. Both DPPF and $AsPh_3$ as ligands and Tl_2CO_3 as a base were used [91]. Similarly, the core structure of salicylihalamide A **119** was prepared under high dilution conditions from the iodoalkene **118**. NaOH was used as a base [92].



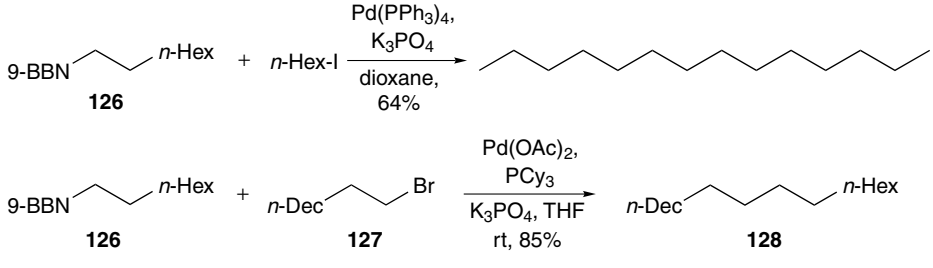
In the total synthesis of epothilone B, intermolecular coupling of multifunctionalized alkylborane derived from **120** with the alkenyl iodide **121** to afford **122** was carried out without affecting the functional groups. Two ligands, DPPF and $AsPh_3$, were used [93,94].



The first total synthesis of (−)-gambierol, a marine polycyclic ether toxin, has been achieved utilizing the coupling of alkylborane, derived by hydroboration of the terminal alkene in **123**, with the enol phosphate **124** to provide **125** in high yield (86 %). Enol phosphates have been shown to be good coupling partners [95]. Ciguatoxin and gymnocin A, related marine polycyclic ether toxins, have been synthesized based on a similar methodology [96].

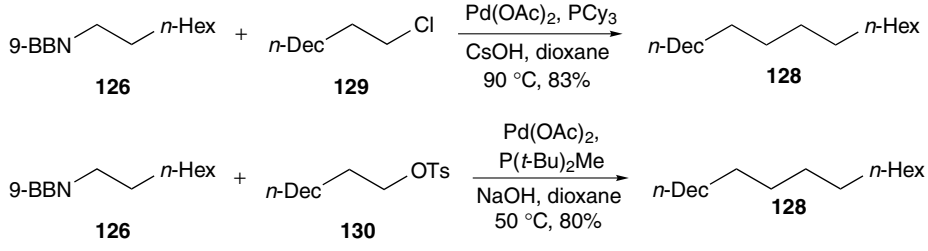


Alkylboranes with alkyl halides Akylborane–alkyl halide coupling has been regarded as a difficult, but challenging reaction. In 1992, Suzuki and Miyaura showed for the first time that the coupling of *n*-octylborane **126** with *n*-hexyl iodide afforded tetradecane in 64 % yield. It should be noted that PPh_3 was used as a ligand [97]. Recently, Fu and co-workers have revived the reaction. They carried out the coupling of dodecyl bromide (**127**) with octylborane **126** at room temperature smoothly to give eicosane (**128**) in 85 % yield. The best ligand is PCy_3.



Interestingly, P(*t*-Bu)$_3$ and PPh_3 are poor ligands, and the yields were $< 2\,\%$ with these ligands [98].

Surprisingly even less-reactive alkyl chlorides undergo the coupling. Reaction of dodecyl chloride (**129**) with octylborane **126** at 90 °C provided eicosane (**128**) in 83 % yield when PCy_3 and CsOH were used [99]. Again P(*t*-Bu)$_3$, PPh_3 and other easily available ligands gave poor results. It has been unexpected that alkyl chlorides undergo oxidative addition so easily. Furthermore, dodecyl tosylate (**130**) undergoes smooth coupling [100]. Interestingly, PCy_3 is a poor ligand in this case. The best yield (80 %) was obtained when P(*t*-Bu)$_2$Me was used as a ligand. The discovery of facile reactions of alkyl chlorides has been a breakthrough in this field, and may yield further developments.



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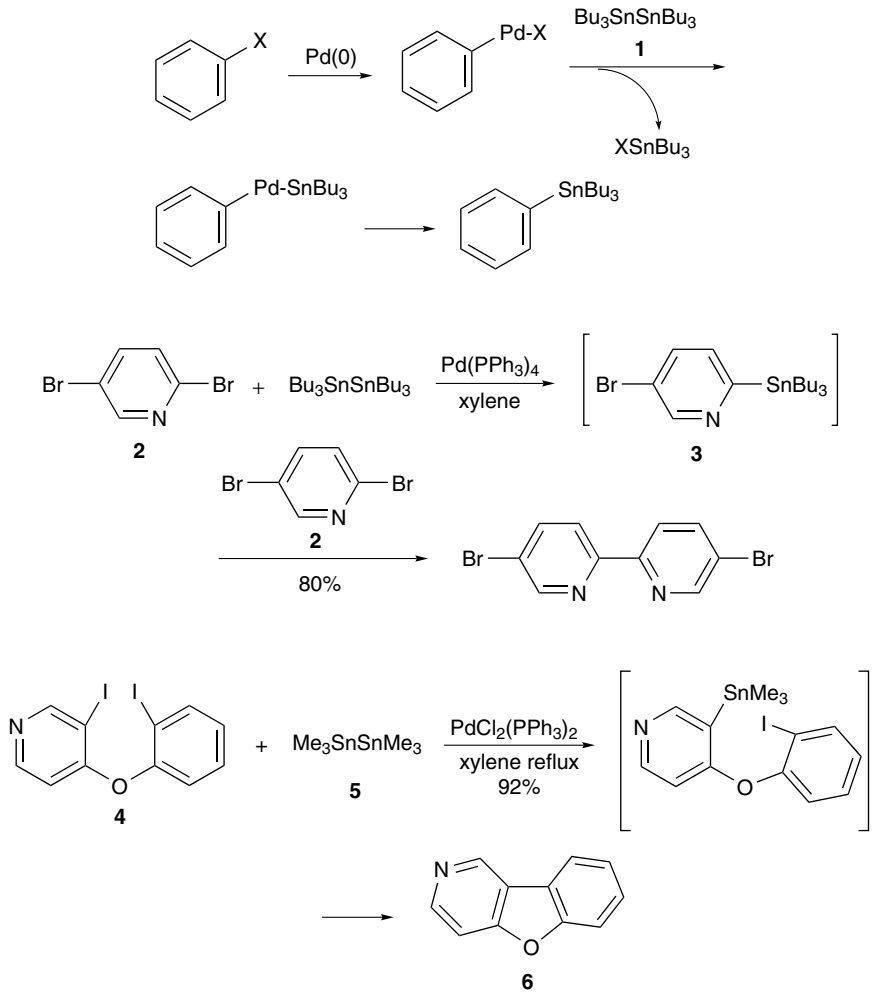
3.6.3 Organostannanes (Kosugi–Migita–Stille Coupling)

3.6.3.1 Introduction and Preparative Methods of Organostannanes

Couplings of organostannanes with halides were discovered by the Kosugi–Migita [1] and Stille groups [2]; the reaction is called the Kosugi–Migita–Stille coupling [3–5]. It is a useful reaction due to air and moisture stability and excellent functional group compatibility of organostannanes, which can be prepared easily. The coupling can be run under neutral conditions. On the other hand, stoichiometric consumption of toxic organostannanes is a drawback, making it unsuitable for large-scale production.

$$RSnBu_3 + Ar\text{-}X \xrightarrow{[Pd]} Ar\text{-}R + XSnBu_3$$

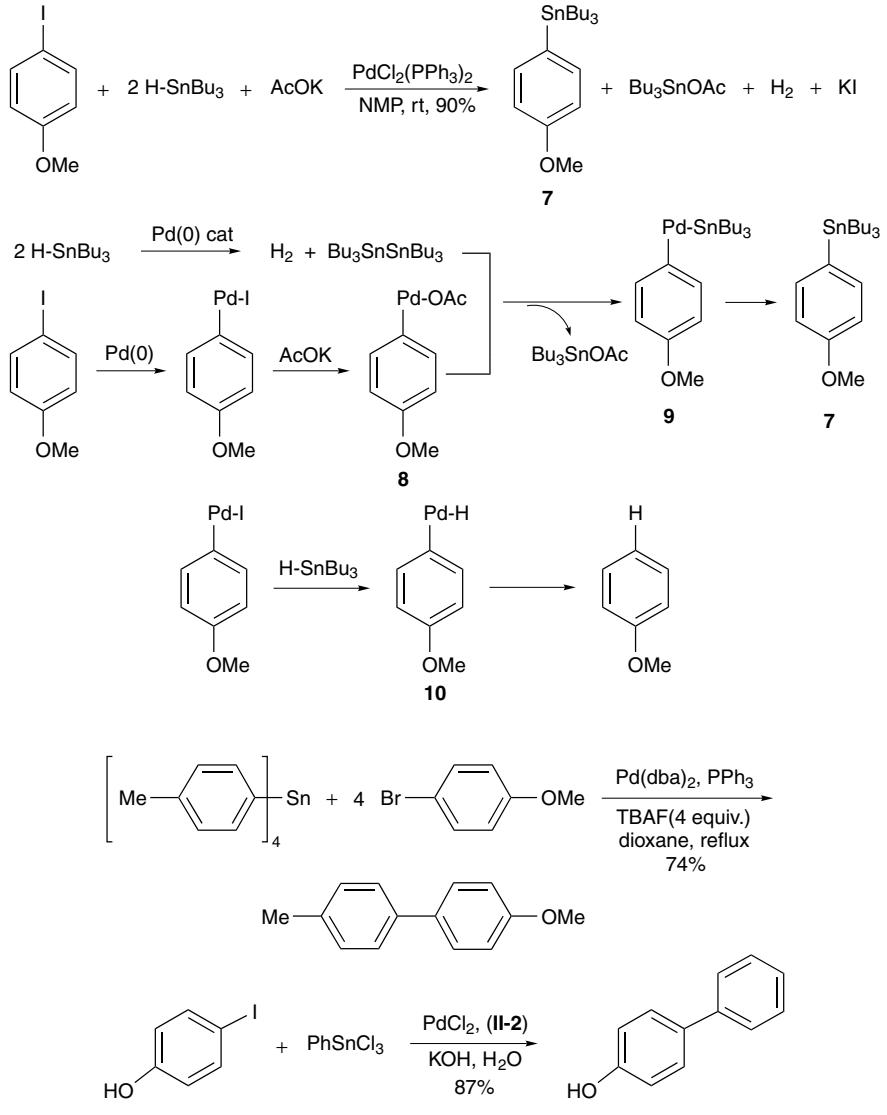
Organostannanes are prepared by several methods. Hydrostannation of alkenes and alkynes is an established synthetic method of alkyl- and alkenylstannanes. Arylstannanes are prepared by the reaction of aryllithiums with R_3SnCl. The Pd-catalyzed reaction of aryl halides with hexa-*n*-butyldistannane (**1**), discovered by Eaborn [6] is a widely used synthetic method of arylstannanes. The method was applied to the preparation of 5, 5′-dibromo-2, 2′-bipyridine from 2,5-dibromopyridine (**2**) [7]. Two bromines in **2** exhibit different reactivity, and 2-bromo is selectively displaced by the tributylstannane group to give **3**, which selectively reacts with **2** to afford 5, 5′-dibromo-2, 2′-bipyridine. Transmetallation of $(Me_3Sn)_2$ is faster than $(Bu_3Sn)_2$. Sometimes, poor results are obtained with $(Bu_3Sn)_2$. In such a case, use of $(Me_3Sn)_2$ is recommended [8]. The direct coupling can be carried out conveniently without isolation of organostannanes. The intramolecular version is a convenient method of cyclization via aryl–aryl coupling [9]. As an application, the synthesis of benzo[4.5]furo[3.2-*c*]pyridine (**6**) was achieved in high yield by the Pd-catalyzed reaction of the heterodiaryl ether **4** with hexamethyldistannane (**5**) [10].



An interesting preparative method of arylstannanes based on the Pd-catalyzed reaction of aryl iodides with tributyltin hydride at room temperature has been reported by Murata *et al*. [11]. Interestingly, the reaction of *p*-iodoanisole with tin hydride generates the Pd—Sn bond **7**, and not anisole by hydrogenolysis. Anisylstannane (**7**) is obtained in good yield, and the amount of anisole is small. The use of AcOK as a base and NMP as a solvent are most effective. Concerning the mechanism of the reaction, facile formation of hexabutyldistannane by Pd-catalyzed reaction of $HSnBu_3$ is known [12]. This is the first step of the reaction, and transmetallation of anisylpalladium **8** with distannane generates **9** and its reductive elimination gives anisylstannane (**7**). From this mechanism, it is understandable that formation of anisole via the palladium hydride **10** is a minor path.

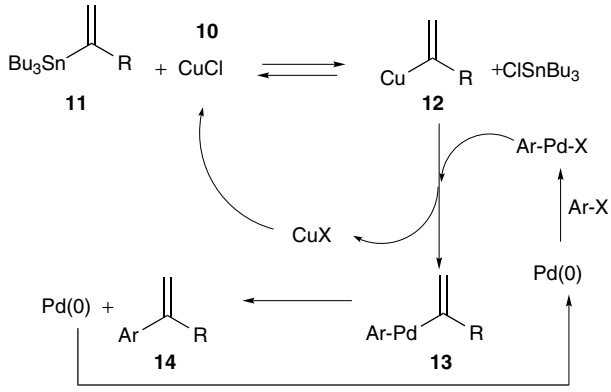
Aryl, alkenyl, and alkynylstannanes, and some alkylstannanes are used for the coupling with aryl and alkenyl halides, pseudohalides and arenediazonium salts. The reaction of allylstannane with aryl iodides is the first example of the Pd-catalyzed cross-coupling of organostannanes [1]. Generally only one of four organic groups on the tin is utilized for the coupling reaction. Kosugi reported

that four aryl groups of tetraarylstannanes can be utilized in the fluoride-assisted coupling in the presence of 4 equivalents of TBAF [13]. $PhSnCl_3$ was used for the coupling with water-soluble ligand **II-2** [14,15].



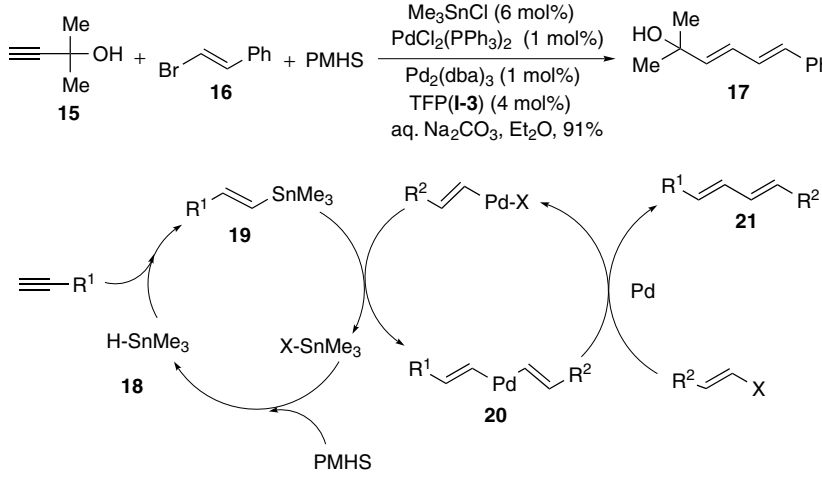
Different groups are transferred from Sn with different selectivities. A simple alkyl group has the lowest transfer rate. Thus asymmetric organostannanes containing three simple alkyl groups (usually methyl or butyl) are chosen, and the fourth group, which undergoes transfer, is usually an alkynyl, alkenyl, aryl, benzyl, or allyl group. The cross-coupling of these groups with aryl, alkenyl, alkynyl, and benzyl halides affords a wide variety of cross-coupled products. Usually PPh_3 is used as a ligand. However, a large acceleration rate is observed in some cases when tri-2-furylphosphine (TFP) (**I-3**) and $AsPh_3$ are used [16]. Also, addition of CuI [17], or CuCl and LiCl in DMSO is recommended [18]. In this case, transmetallation

of alkenylstannane **11** with CuCl takes place at first to generate alkenylcopper **12**, which undergoes transmetallation with arylpalladium to give **13**. Reductive elimination affords the coupled product **14**. The rapid double transmetallation results in acceleration of the coupling reaction.



Mechanistic studies on the Kosugi–Migita–Stille coupling have been carried out [19].

The coupling consumes a stoichiometric amount of organostannanes. Attempting to improve the reaction, Maleczka's group reported a coupling reaction, which is catalytic in Sn [20]. They found that the Pd-catalyzed reaction of terminal alkyne **15**, alkenyl halide **16**, PMHS (polymethylhydrosiloxane) and a catalytic amount of Me_3SnCl affords conjugated diene **17** when two kinds of Pd catalysts [$PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$/TFP, 1 mol % each] are used. PMHS behaves as a reducing agent of Me_3SnX to Me_3SnH. The catalytic process is based on the following steps. At first Me_3SnH (**18**) is generated by reduction of Me_3SnX with PMHS, and alkenylstannane **19** is generated by Pd-catalyzed hydrostannation of alkyne with Me_3SnH. Then Pd-catalyzed cross-coupling of **19** with alkenyl halide affords conjugated diene **21** and Me_3SnX, which is reduced with PMHS. Transmetallation of **19** generates **20** as an intermediate. Two Pd-catalyzed reactions may



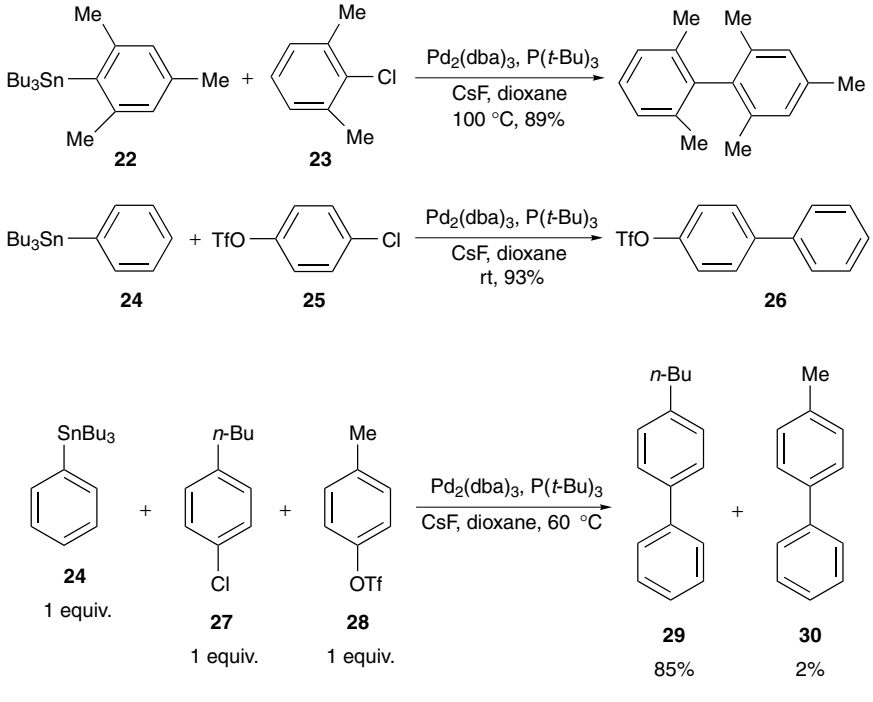
need two kinds of Pd catalyst. In this reaction, only trisubstituted alkynes, typically **15**, are used, because hydrostannylation of alkynes should be regioselective.

The coupling of organostannanes, partly due to functional group compatibility, has been used in efficient syntheses of medicinal compounds and natural products.

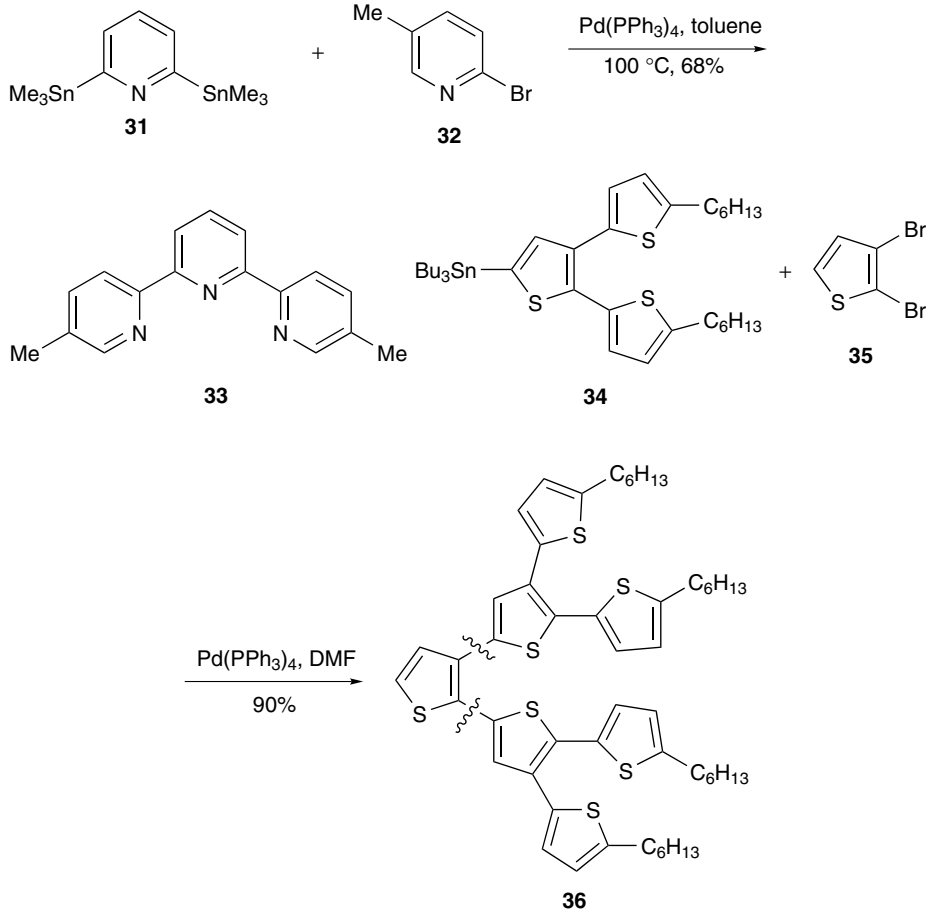
3.6.3.2 Coupling of Aryl- and Heteroarylstannanes

Aryl- and heteroarylstannanes are used extensively for aryl–aryl or aryl–alkenyl coupling. First, examples of aryl–aryl coupling are cited. Several types of catalysts are used. A combination of Pd-P(*t*-Bu)$_3$ is recommended as a mild and general catalyst for the coupling of aryl bromides, chlorides, and triflates with a range of organostannanes [21]. Couplings of congested aryl chloride **23** with the sterically hindered arylstannane **22** proceeded at 100 °C in the presence of CsF as a base. The reaction of the corresponding aryl bromides occurs at room temperature.

The most remarkable is the unprecedented chemoselectivity observed in the reaction of 4-chlorophenyl triflate (**25**) with phenytributylstannane (**24**) to give **26** selectively. Furthermore the higher reactivity of chloride over triflate was demonstrated by intermolecular competitive reaction of the aryl chloride **27** and the triflate **28** with **24** to produce the biphenyl **29** with high selectivity. Yield of the coupling product **30** of the triflate **28** was only 2 %. The catalyst Pd/P(*t*-Bu)$_3$ activates the C—Cl bond in preference to the C—OTf bond to afford **26** and **29** at room temperature in excellent chemoselectivity and high yields. The observed chemoselectivity shows that the belief that the C—OTf bond is more reactive than the C—Cl bond is not valid any more when Pd/P(*t*-Bu)$_3$ is used. Similar chemoselectivity was observed also in the Suzuki–Miyaura coupling of the corresponding compounds (see Chapter 3.6.2.3).

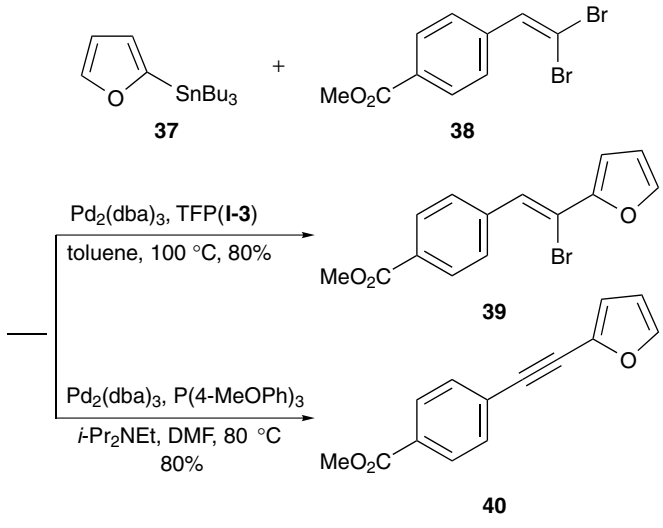


Coupling of heteroarylstannanes with heteroaryl halides proceeds smoothly. The dimethylterpyridine (**33**), a useful pyridine-based ligand, was prepared by the coupling of 2,6-bis(trimethylstannyl)pyridine (**31**) with 6-bromo-3-picoline (**32**) in 68 % yield [22]. A first synthesis of thiophene dendrimers was carried out based on the coupling of the stannylthiophene **34** with both bromides of 2,3-dibromothiophene (**35**) to give **36** in high yield in the presence of $Pd(PPh_3)_4$ in DMF [23].

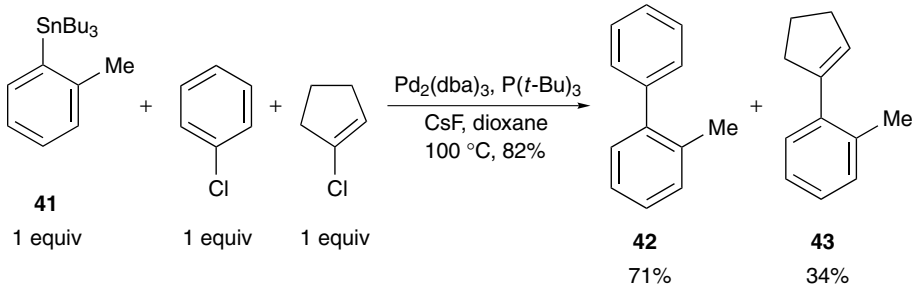


Coupling of *gem*-dibromostyrene derivatives with organostannanes affords two kinds of products depending on the solvents. Reaction of the dibromide **38** with 2-stannylfuran **37** in toluene produced the (*Z*)-bromoalkene **39** stereospecifically. TFP was used as a ligand. Interestingly the internal alkyne **40** was obtained in DMF when an electron-rich triarylphosphine or TFP is used. The solvents (toluene or DMF) used make a difference in chemoselectivity [24].

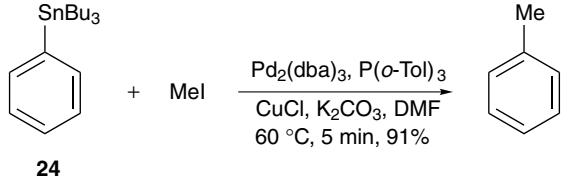
Generally alkenyl halides are more reactive than aryl halides. An opposite chemoselectivity was observed in the competitive reaction of chlorobenzene and



1-cyclopentenyl chloride with the arylstannane **41** in the presence of P(*t*-Bu)$_3$. A larger amount of the aryl–aryl coupling product **42** was obtained than that of the aryl–alkenyl product **43** in the presence of P(*t*-Bu)$_3$, showing that aryl chloride was coupled in preference to alkenyl chloride [21].

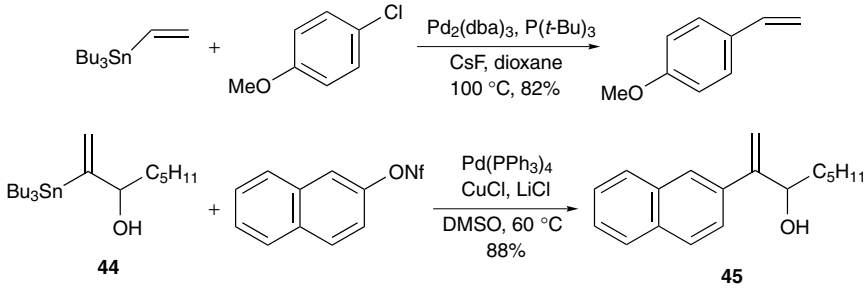


Methylation is possible by the reaction of arylstannane with MeI. In order to find a general protocol for the synthesis of short-lived $^{11}CH_3$-labeled PET (positron emission tomography) tracers for incorporation of radionuclides into bioactive organic compounds, Suzuki and co-workers carried out the coupling of MeI with tributylphenylstannane (**24**) to afford toluene as a model reaction in 91 % yield within 5 min. P(*o*-Tol)$_3$ was used as a ligand, together with CuCl [25].



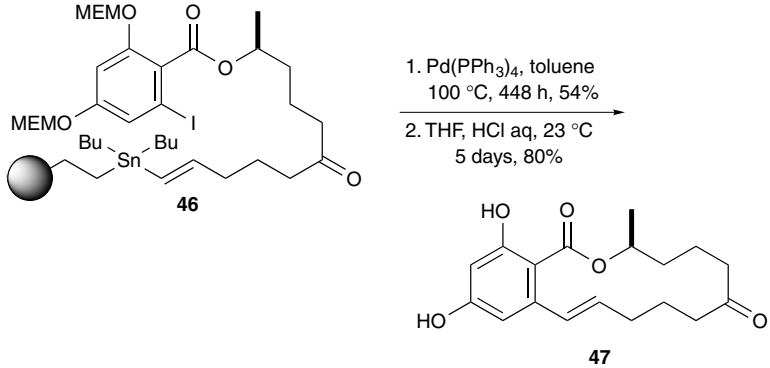
3.6.3.3 Coupling of Alkenylstannanes

Alkenyl–aryl and alkenyl–alkenyl couplings are also widely used. Pd/P(*t*-Bu)$_3$ is an efficient catalyst for the coupling of aryl chlorides with aryl-, alkenyl-, and alkylstannanes [21]. Coupling of 4-chloroanisole with vinylstannane proceeded at 100 °C with the use of CsF as a base. Addition of CuCl and LiCl in DMSO is recommended, which accelerates the transmetallation step in the coupling of sterically congested substrates. Coupling of the alkenylstannane **44** with naphthyl nonaflate proceeded smoothly to give **45** in 88 % yield [18].

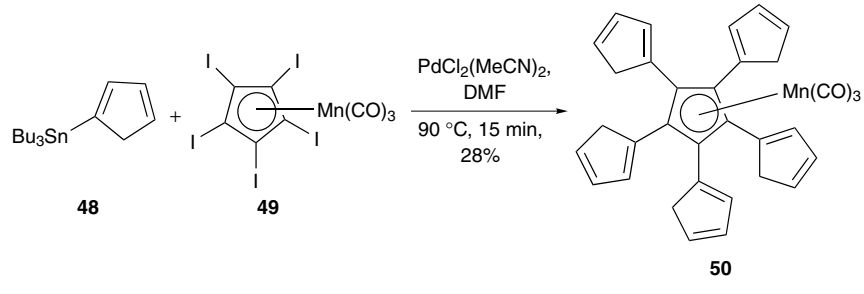


44 **45**

As an example of alkenyl–aryl coupling, solid-phase synthesis of the macrocyclic system of (*S*)-zearalenone (**47**) was achieved based on coupling and cyclorelease strategy. Cyclization of polymer-bound alkenylstannane with aryl iodide moiety proceeded in 54 % yield, and the product was deprotected to give **47** [26]. Aiming at the synthesis of penta(cyclopentadienyl)cyclopentane, Vollhardt prepared pentacyclopentadienylated cyclopentadiene complex **50** by coupling tributylcyclopentadienylstannane (**48**) with tricarbonyl(η^5-pentaiodocyclopentadienyl)manganese (**49**) in one step in 28 % yield [27].



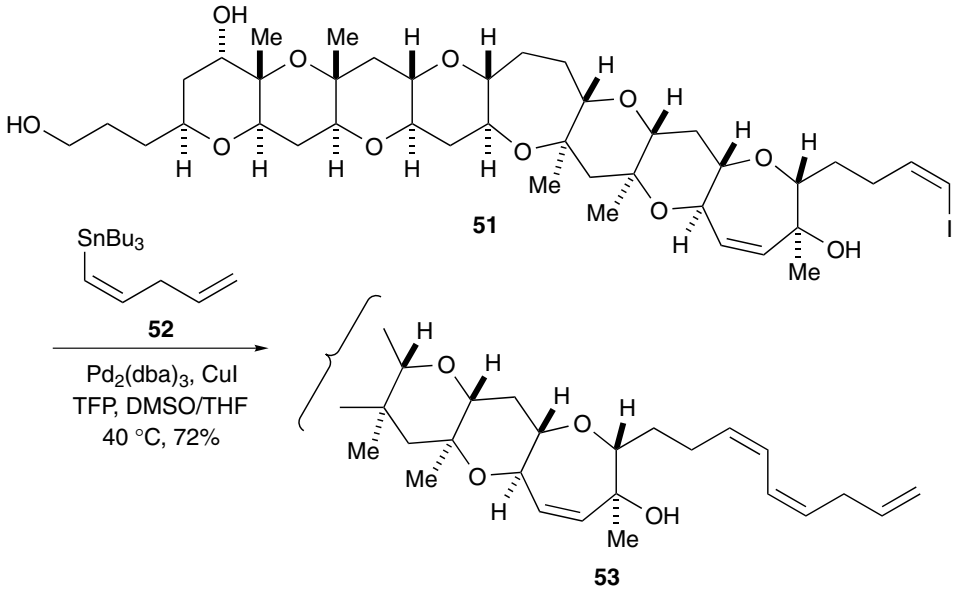
46 **47**



48 **49** **50**

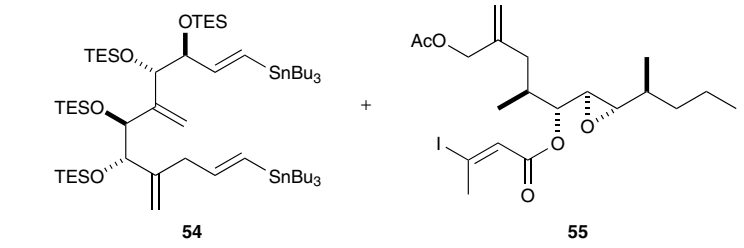
Alkenyl–alkenyl coupling is useful for the preparation of stereo-defined diene or polyenes, and applied extensively to efficient syntheses of natural products partly due to good functional group compatibility.

In the total synthesis of (−)-gambierol, a marine polycyclic ether toxin, by two groups [28,29], the sensitive terminal (*Z*, *Z*)-triene side chain in **53** was constructed as a crucial step by stereoselective coupling of (*Z*)-alkenyl iodide **51** with (*Z*)-1,4-pentadienylstannane **52** in DMSO to afford **53** in 72 % yield without isomerization of the triene system. $Pd_2(dba)_3$ and CuI as catalysts and TFP (**I-3**) as a ligand were used [29]. Similar coupling using the less reactive alkenyl bromide provided **53** in 43 % yield [28].

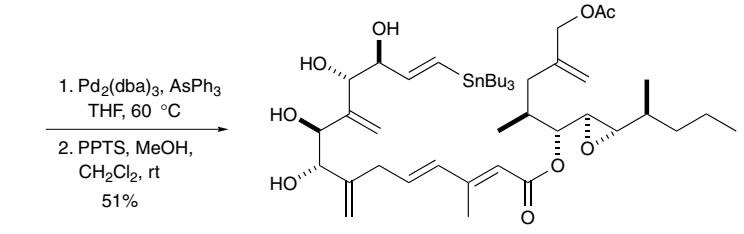


In the total synthesis of amphidinolide A (**57**), a key step is the coupling of di(alkenylstannane) **54** with **55**, which has the alkenyl iodide and allyl acetate moieties as reactive groups. The coupling proceeded in two steps when $AsPh_3$ is used as a ligand. At first, reaction took place chemoselectively with the alkenyl iodide to give **56**. Then cyclization of **56** occurred by the coupling of the allylic acetate moiety with the alkenylstannane in cyclohexane in the presence of LiCl to afford **57** [30].

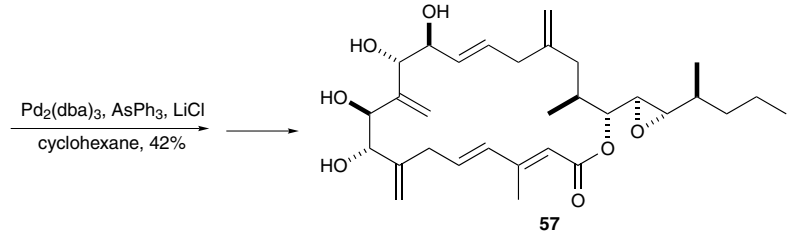
The Sonogashira coupling of the terminal alkyne in **58** with the ditriflate **59** occurred selectively in the presence of Pd-CuI catalyst to give **60**. Then domino coupling/Diels-Alder reaction of **60** occurred to afford **62** via **61** at room temperature. It is interesting that [4 + 2] cyclization of nonactivated diene and dienophile (a triple bond) occurred even at 20 °C, and the result suggests a possible role of the Pd catalyst. The compound **62** was spontaneously transformed completely to the final product **63** through oxidative aromatization [31].



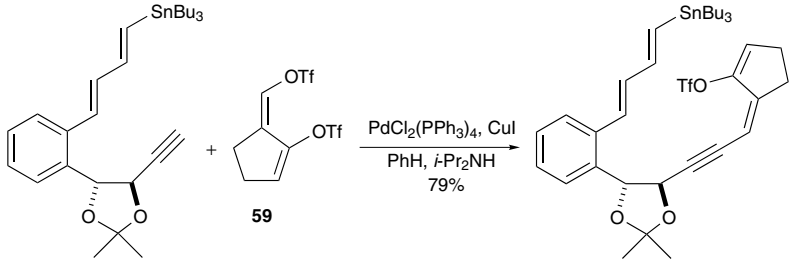
54 **55**



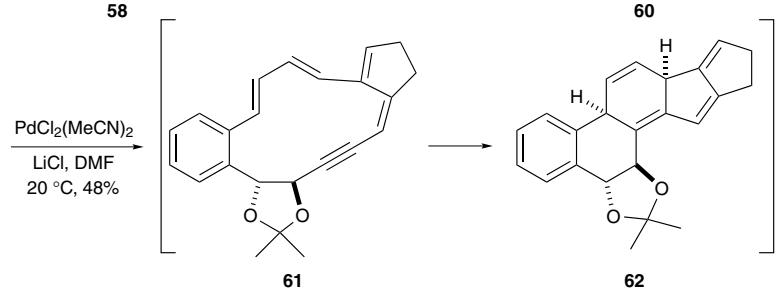
56



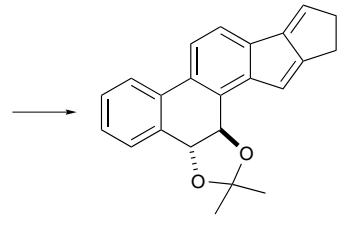
57



58 **59** **60**

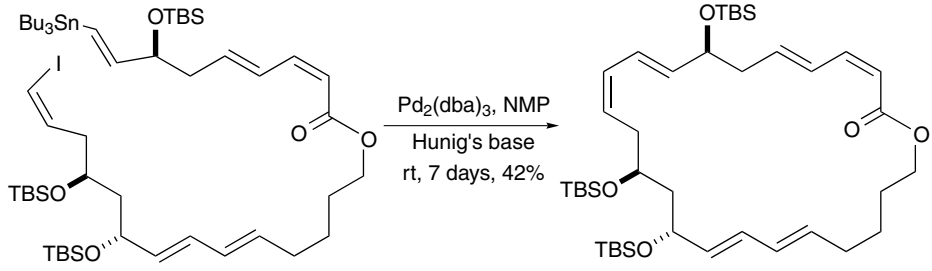


61 **62**



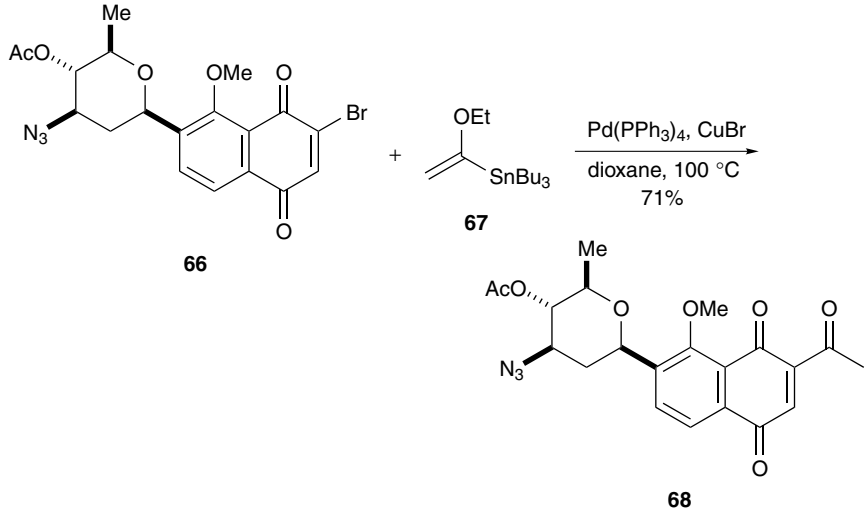
63

Total synthesis of (−)-macrolactin A, a 24-membered macrolide, was achieved based on intramolecular coupling of alkenylstannane with iodide in **64** to afford the macrolide **65** as a key reaction. The cyclization occurred without a phosphine ligand in NMP in 42 % yield [32].



64 **65**

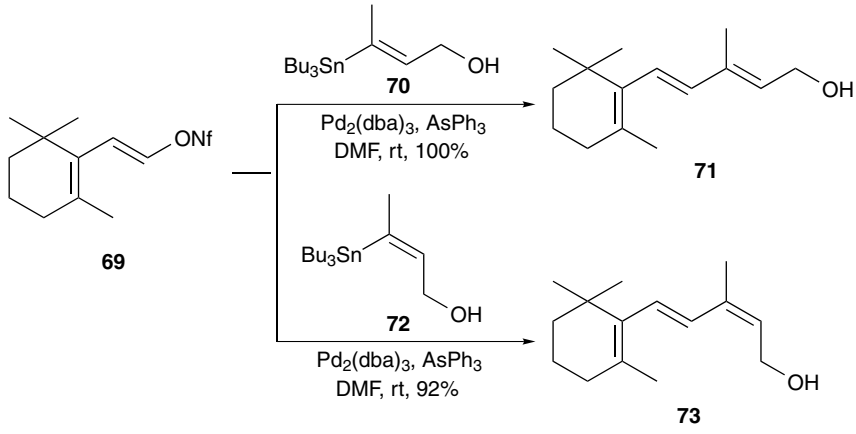
Methyl ketones are prepared by the coupling of 1-ethoxyvinylstannane (**67**) and hydrolysis. The coupling of the bromonaphthoquinone **66** with **67** afforded **68**, and was applied to synthesis of an azido analog of medermycin [33].

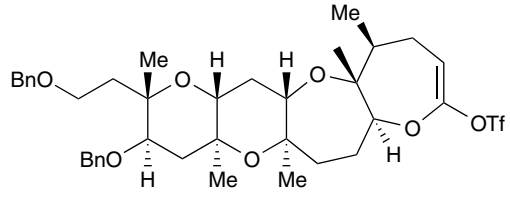


66 **67** **68**

Stereoselective syntheses of the trienes **71** and **73** were carried out in very high yields by the coupling of the dienyl nonaflate **69** with the (*E*)- and (*Z*)-alkenylstannanes **70** and **72** in the presence of $AsPh_3$ as a ligand in DMF at room temperature. The nonaflate was found to be more reactive than the corresponding triflate [34].

The coupling of the enol triflate **74** with the stannyl enol ether **75** proceeded rapidly at room temperature to give **76** in good yield in the presence of CuCl as an additive, which plays a crucial role for the success of the coupling. The reaction has been utilized extensively for the construction of polyether systems of marine natural products such as maitotoxin [35].





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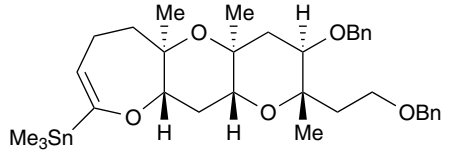
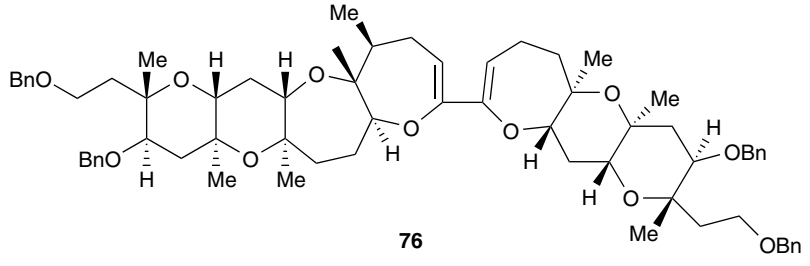
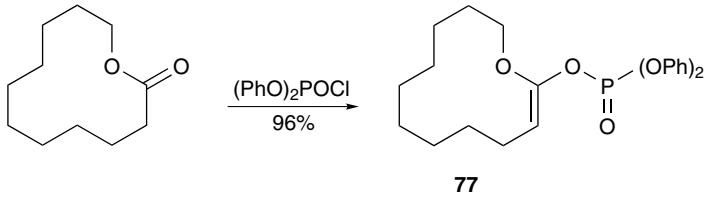




Enol phosphate is a good coupling partner. Coupling of the lactone enol phosphate **77**, derived from 11-undecanolide, with vinylstannane afforded the cyclic enol ether **78** in good yield [36].

The mimetic of brassinolide **81** was prepared in high yield by the coupling of *trans*-bis(tri-*n*-butylstannyl)ethylene (**79**) with the enol triflate **80** [37].

It is known that the reaction of 1,1-dibromo-1-alkenes with organostannanes affords internal alkynes [24]. The (chlorocyclopropyl)dienyne side chain **84** of callipeltoside A was prepared in 95 % yield by the coupling of the 1,3-dienylstannane **82** with the dibromide **83**. The use of DMF is important [38].



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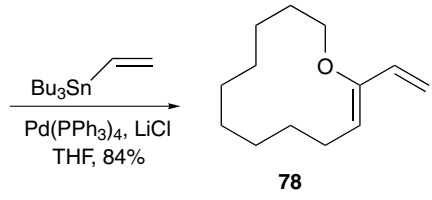

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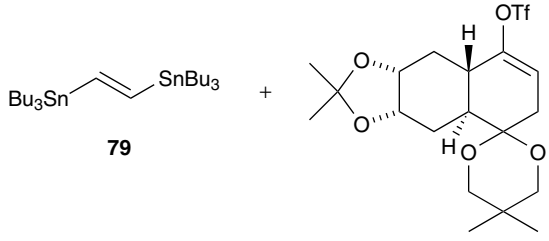
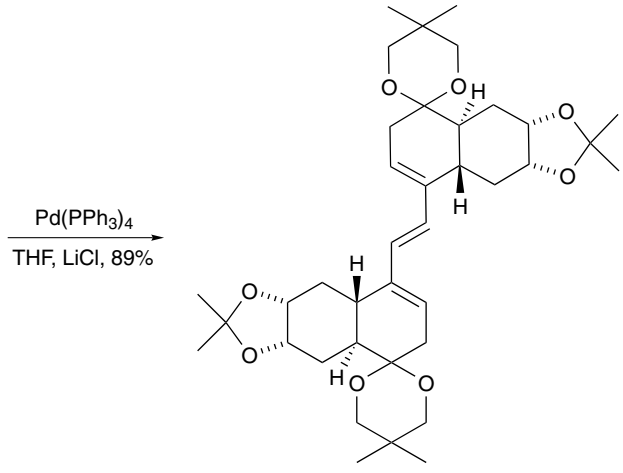


79 **80**



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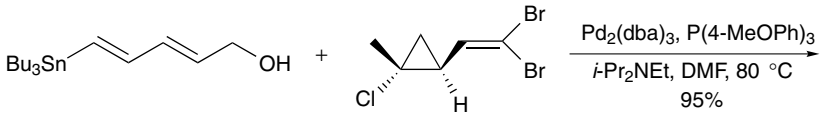
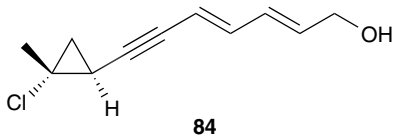
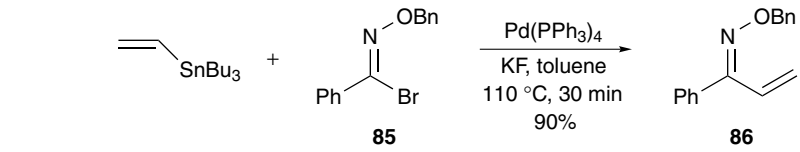


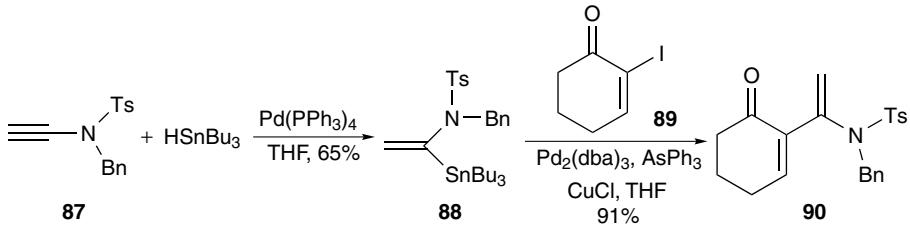
82 **83**



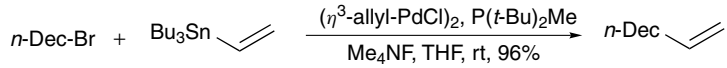
84

The *N*-alkoxyimidoyl bromide **85** is used as an efficient coupling partner with vinylstannane to afford the ketone oxime **86** in the presence of KF as a base [39]. Pd-catalyzed hydrostannation of the enamine **87** provided the *N*-tosyl-α-stannyl enamine **88**. Functionalized α-substituted enamine **90** can be prepared by Pd-catalyzed coupling with alkenyl iodide **89**. $AsPh_3$ was used as a ligand [40].





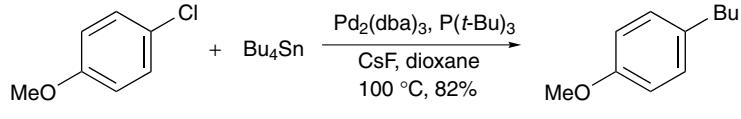
Interestingly coupling of *n*-decyl bromide with alkenylstannane proceeded smoothly at room temperature to afford 1-dodecene in 96% yield. Uses of $P(t\text{-Bu})_2Me$ as a ligand, Me_4NF (1.9 equiv.), and a molecular sieve are important. $P(t\text{-Bu})_3$ is not effective [41]. Similarly, tetradeca-1,6-diene was prepared [41].

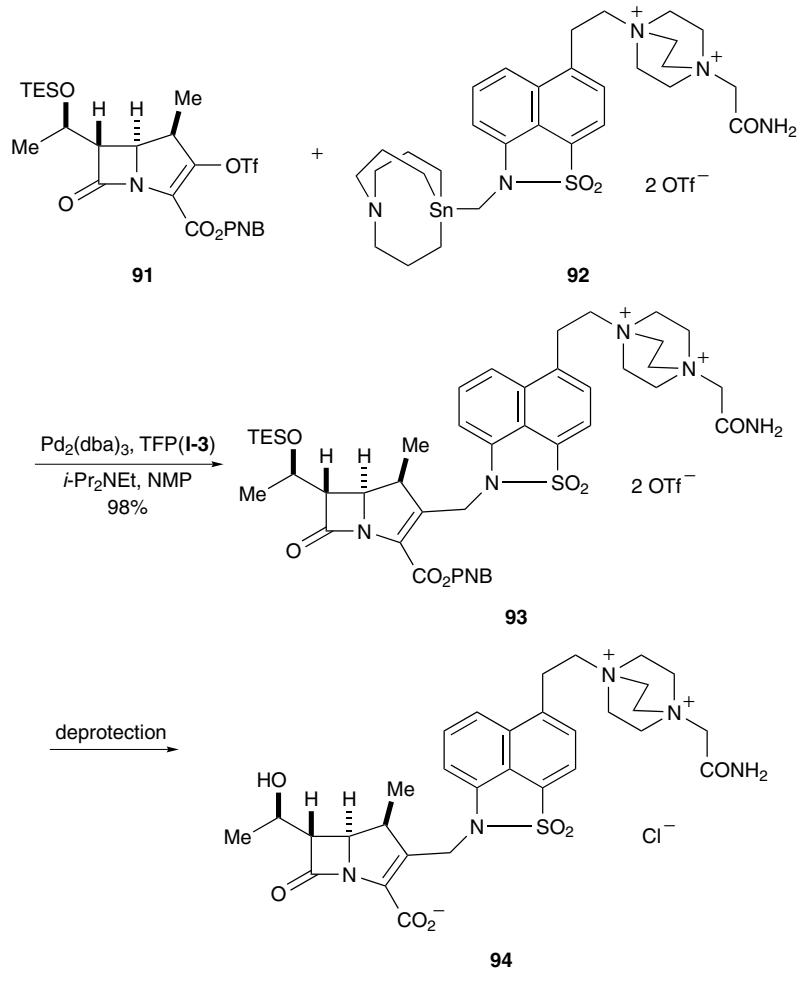


3.6.3.4 Coupling of Alkylstannanes

Alkylstannanes are less reactive, and no reaction of the *n*-Bu group in $RSnBu_3$ is usually observed. Pd-$P(t\text{-Bu})_3$ is a good catalyst for the coupling of 4-chloroanisole with tetra-*n*-butylstannane to give 4-*n*-butylanisole in good yield in the presence of CsF as a base [21].

The protected carbapenem **93** was prepared commercially in high yield by the coupling of the enol triflate **91** with the fully elaborated stannatrane **92** as a coupling partner by the use of TFP in NMP. Deprotection of **93** gave the desired carbapenem **94**. Use of the stannatrane **92** as an organostannane reagent is crucial in this case [42].



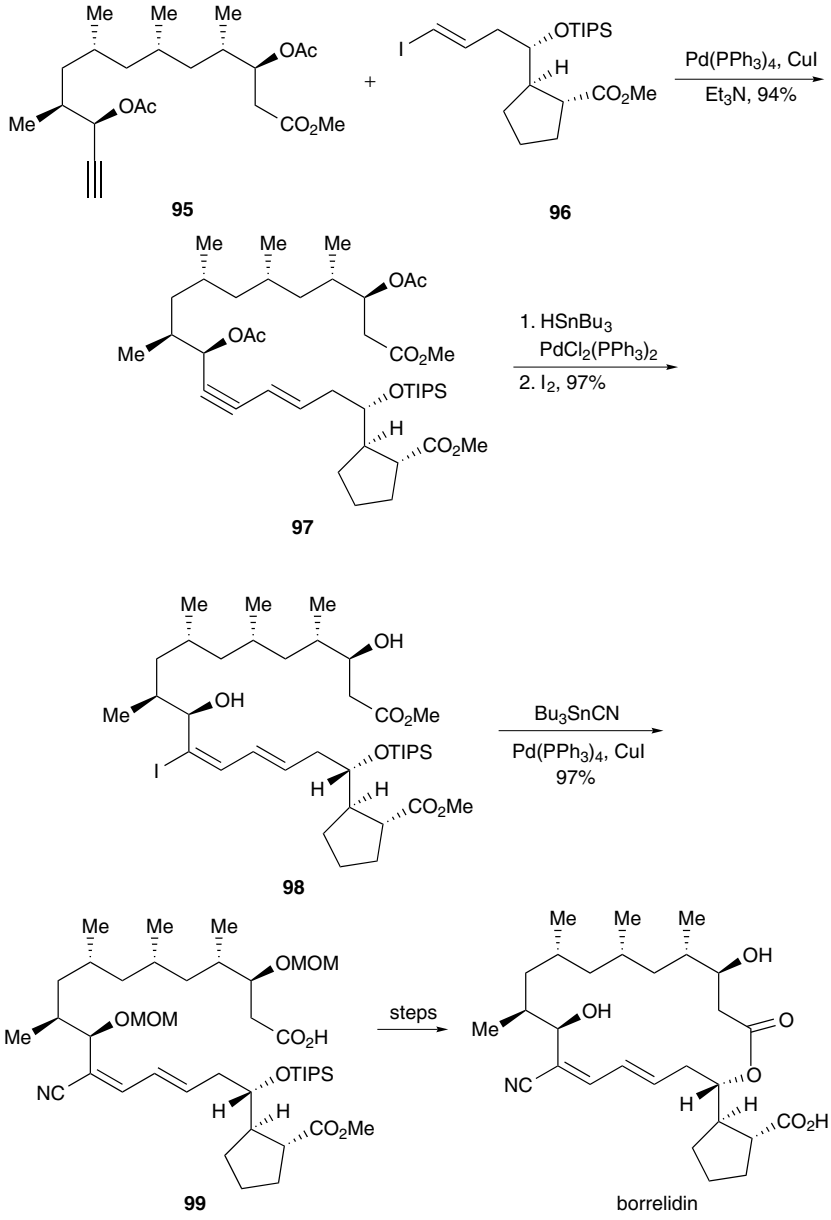


Morken and co-workers have accomplished enantioselective total synthesis of borrelidin, amply demonstrating the usefulness of several Pd-catalyzed reactions. Only a part of their efficient synthetic approach to this multifunctional macrolide is cited here [43]. The Sonogashira coupling of **95** with **96** afforded **97** in 94 % yield. Pd-catalyzed regioselective hydrostannation of the triple bond of **97**, followed by iodination and deacetylation of the resulting alkenylstannane afforded the alkenyl iodide **98**. Pd-catalyzed cyanation of **98** using Bu_3SnCN was carried out in the presence of CuI as a cocatalyst to provide the nitrile **99** in very high yield (97 %).

3.6.4 Organozinc Compounds (Negishi Coupling)

3.6.4.1 Introduction and Preparation of Organozinc Compounds

Cross-coupling of organozinc reagents is called Negishi coupling [44]. Reaction of organozinc reagents (aryl, alkenyl, alkyl) with alkenyl and aryl halides proceeds generally with high yields and tolerates a wide range of functionality. Aryl-, alkenyl-, and alkylzinc reagents are prepared most conveniently *in situ* by the reactions of organolithium, magnesium, and aluminum reagents with $ZnCl_2$, and used without isolation. Gauthier and co-workers suggest that kilogram quantities



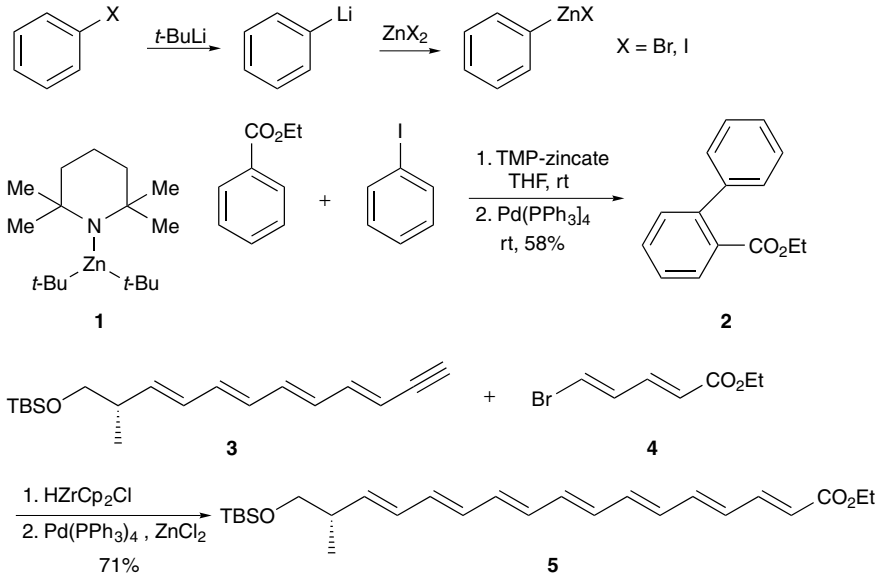
of solid $ZnCl_2$ can be oven dried at 120 °C in vacuum with N_2 purge for 3–5 days. Handling of a THF solution is preferred to the solid, but commercial $ZnCl_2$ solution (THF, Aldrich) contains 0.5 % H_2O as determined by Karl Fisher titration [45].

Tetramethylpiperidine-zincate **1** is a good reagent for directed *ortho* zincation of various functionalized aromatic and heteroaromatic compounds. For example, benzoate was converted to biphenyl-2-carboxylate **2** by zincation with **1**, followed by coupling with iodobenzene [46].

A facile and convenient preparative method of alkylzinc reagents is direct reaction of alkyl iodides with activated Zn/Cu couple [47] or Zn dust [48]. Huo reported an efficient, general preparative method of alkylzincs from unactivated

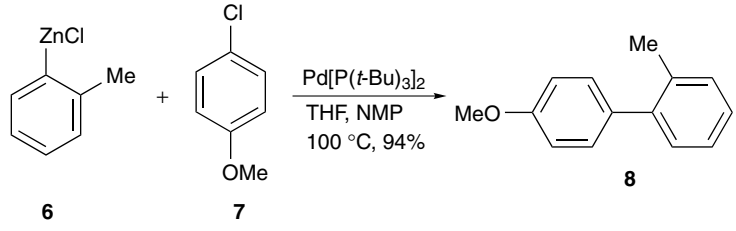
alkyl bromides and chlorides, which relied on activation of Zn dust with 1–5 mol% of iodine [49].

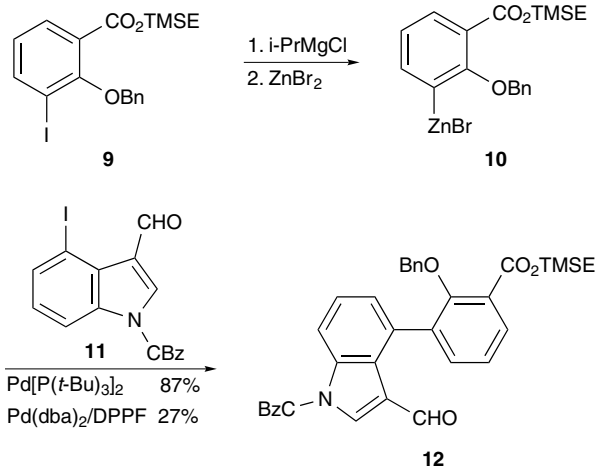
Alkenylzinc reagents are prepared conveniently *in situ* by hydrozirconation of 1-alkyne, followed by transmetallation from Zr to Zn with ZnX_2. Then coupling is carried out without isolation of Zn reagents, and hence a catalytic amount of ZnX_2 is enough. For example, hydrozirconation of 1-alkyne **3**, followed by coupling with the alkenyl bromide **4** to provide the conjugated (all-*E*)-oligoene **5** with retention of stereochemistry, was carried out using both Pd complex and $ZnCl_2$ as catalysts [50].



3.6.4.2 Coupling of Aryl- and Alkenylzinc Reagents

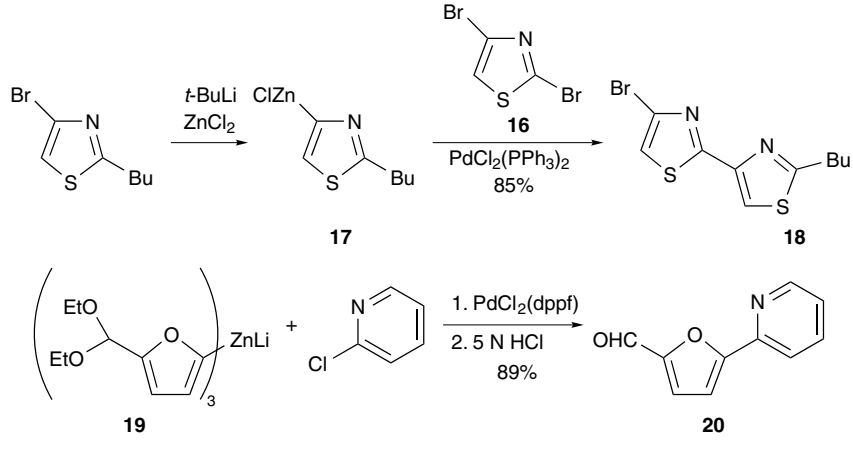
For aryl–aryl coupling, aryl iodides, bromides, and triflates are used. It has been shown that the Negishi coupling of arylzinc reagents with aryl chlorides proceeds smoothly by the use of commercially available, air-stable $Pd[P(t\text{-}Bu_3)]_2$. Coupling of arylzinc chloride **6** with electron-rich 4-chloroanisole (**7**) proceeds smoothly in THF–NMP using $Pd[P(t\text{-}Bu_3)]_2$ as a catalyst to give **8** in high yield [51]. In synthetic studies toward diazonamide, aryl–aryl coupling was employed. Reaction of the arylzinc reagent **10**, derived from the aryl iodide **9** via a Grignard reagent, with 4-iodoindole-3-carboxaldehyde (**11**) to afford **12** proceeded in high yield using $Pd[P(t\text{-}Bu_3)]_2$. The yield was poor when DPPF was used as a ligand [52].



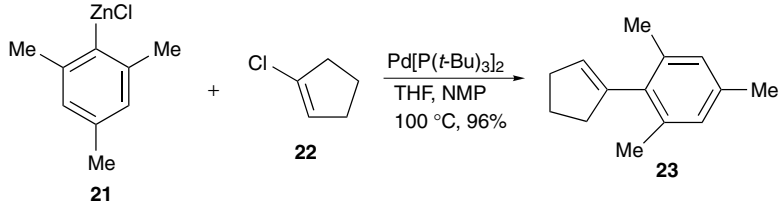


A new ionic phosphine ligand (**I-19**) is effective for the coupling of arylzinc **13** with aryl iodide **14** at room temperature to give **15** in a biphasic system containing toluene, THF, and an ionic liquid [bdmim][BF_4]. The Pd catalyst always stays in the ionic liquid and can be recycled [53].

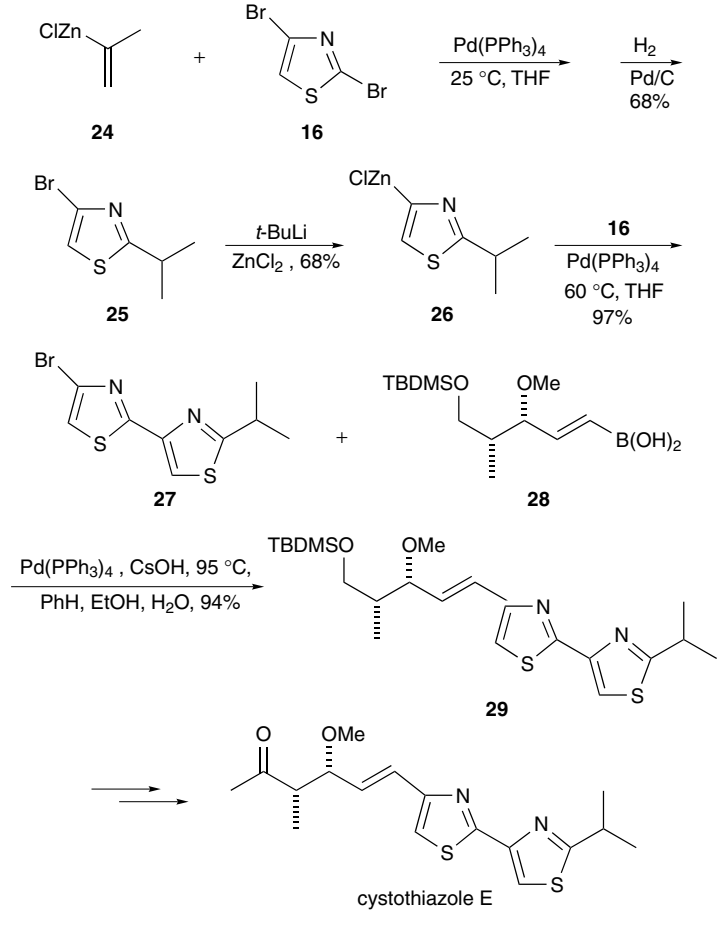
Coupling of heteroarylzinc halides and heteroaryl halides proceeds smoothly. The bithiazole **18** was obtained in 85 % yield by regioselective coupling of the 2-bromo group in 2,4-dibromothiazole (**16**) with the 4-thiazolylzinc chloride **17** [54]. The tri(furylzinc) reagent **19** undergoes smooth coupling with 2-chloropyridine to give the coupling product **20** in the presence of DPPF. All three furyl groups in **19** are utilized for the coupling [45].



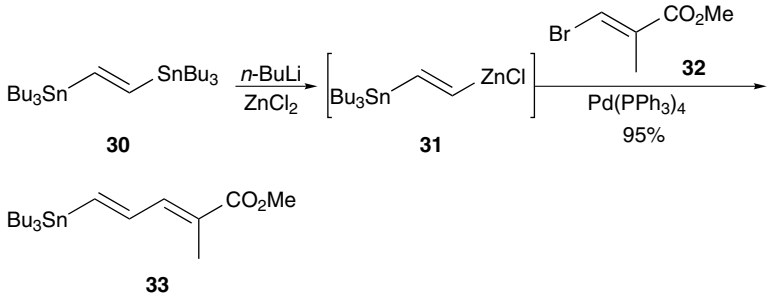
Coupling of the sterically congested arylzinc chloride **21** with 1-cyclopentenyl chloride (**22**) gave **23** in high yield when Pd[P(*t*-Bu$_3$)]$_2$ was used as a catalyst in THF–NMP [51].



Arylalkenes, conjugated dienes, and polyenes are produced by the coupling of alkenylzinc reagents. The first total synthesis of cystothiazole E was achieved by applying the Negishi coupling twice and Suzuki–Miyaura coupling once. Coupling of 2-propenylzinc chloride (**24**) occurred selectively with the 2-bromo group of 2,4-dibromothiazole (**16**), and **25** was obtained after hydrogenation of the coupling product. The 4-thiazolylzinc chloride **26** also reacted selectively with the 2-bromo group of **16** to afford the bromobithiazole **27**. Finally Suzuki–Miyaura coupling of **27** with the alkenylboronic acid **28** provided the coupling product **29**, which was converted to cystothiazole E [55].

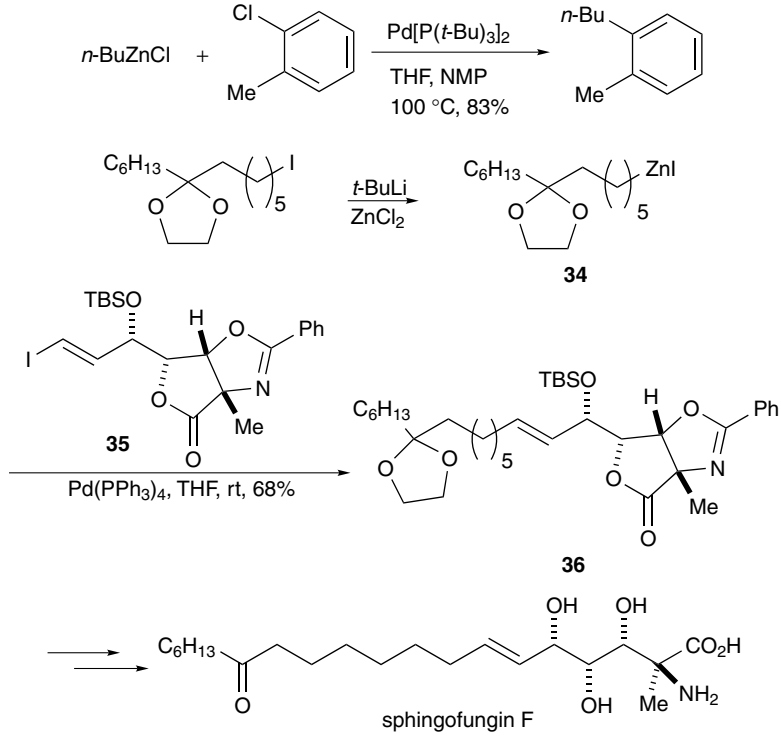


The Negishi coupling was applied as a key reaction to a short synthesis of calyculin. The key building block **33** of the tetraene fragment of calyculin was synthesized from *trans*-bis(tributylstannyl)ethene (**30**) via four consecutive transfer reactions (Sn-Li-Zn-Pd-C). Exchange of Bu_3Sn in **30** with $ZnCl_2$ gave **31**, which underwent chemoselective coupling with the vinyl bromide **32** to give **33** in 95 % yield [56].

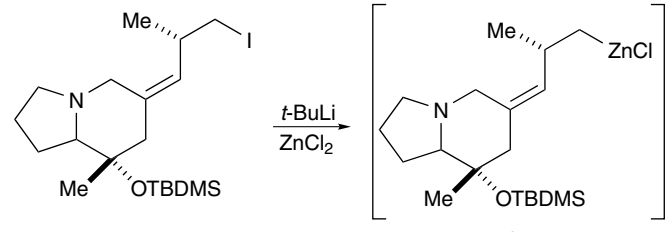


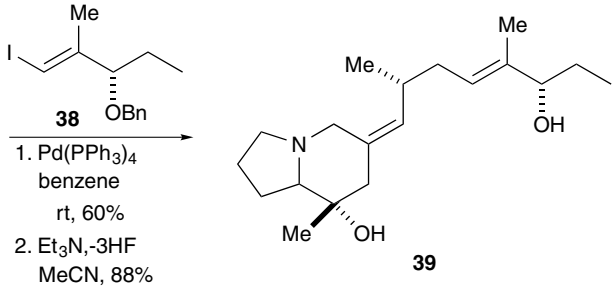
3.6.4.3 Coupling of Alkylzinc Reagents

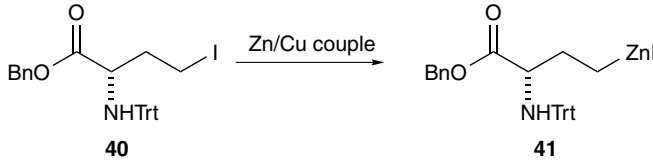
Alkylzinc reagents can be used for the coupling without undergoing β-H elimination. Coupling of *n*-butylzinc chloride with 2-chlorotoluene proceeds smoothly using $Pd[P(t\text{-}Bu_3)]_2$ [51]. In the total synthesis of sphingofungin, the alkylzinc **34** was derived from the long-chain alkyl iodide. Coupling of **34** with the alkenyl iodide **35** afforded **36**, and sphingofungin F has been synthesized from **36** [57].

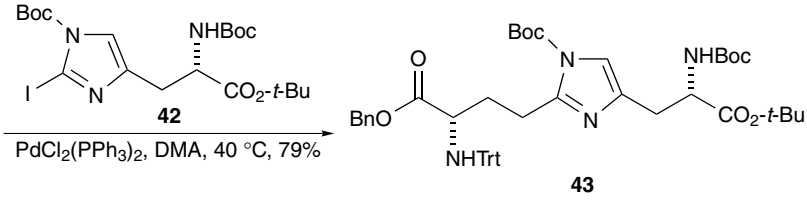


Total synthesis of (+)-pumiliotoxin A (**39**) has been achieved based on the Negishi coupling of the alkylzinc chloride **37**, derived from the alkyl iodide, with the alkenyl iodide **38** at room temperature, and subsequent deprotection [58]. The alkylzinc reagent **41** was prepared conveniently by the reaction of the alkyl iodide **40** with Zn/Cu couple, and treated with 2-iodoimidazole **42** to afford the adduct **43** [47].

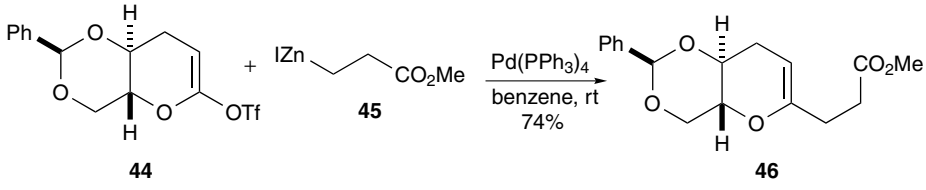


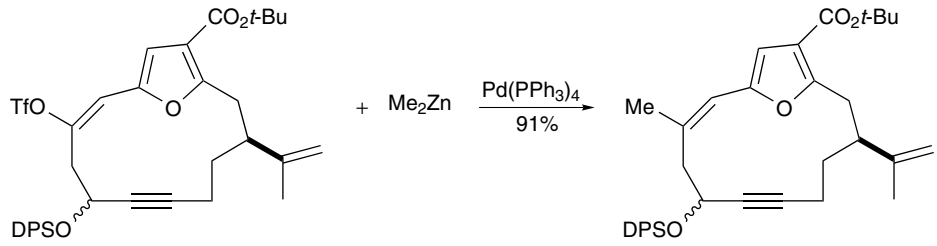






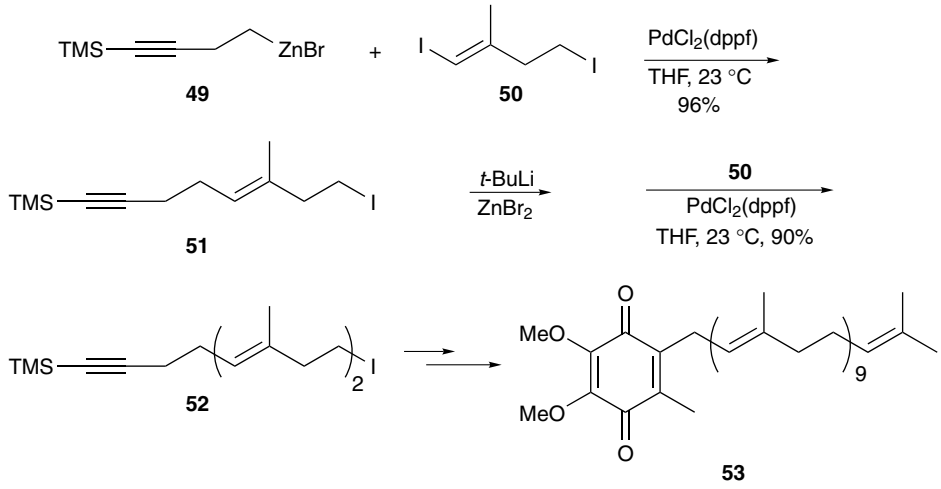
Coupling of the alkenyl triflate **44** with the Zn homoenolate **45** proceeded smoothly to give **46**. The coupling of triflate is the key reaction to construct a cyclic polyether fragment in the total synthesis of gambierol [59]. The methyl group was introduced in high yield by the reaction of the alkenyl triflate **47** with Me_2Zn to afford **48** [60].





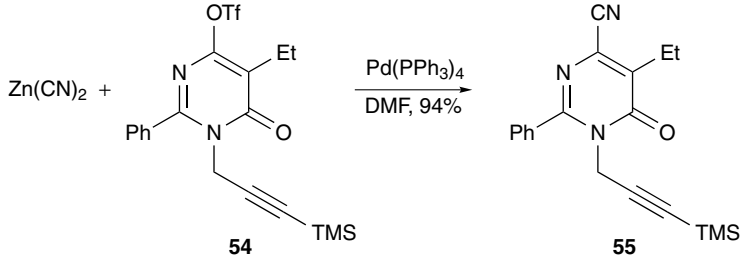
47 **48**

A versatile and regio- and stereoselective synthetic method of terpenoids containing 1,5-diene units has been developed by Negishi. Chemoselective coupling of the alkylzinc bromide **49** with the alkenyl iodide in **50** provided **51**. The alkyl iodide in **51** was converted to alkylzinc bromide, which was coupled again with the alkenyl iodide **50** to provide **52**. Coenzyme Q_{10} (**53**) was synthesized in 26 % overall yield by repeating a similar sequence of the coupling reactions [61].



49 **50** **51** **52** **53**

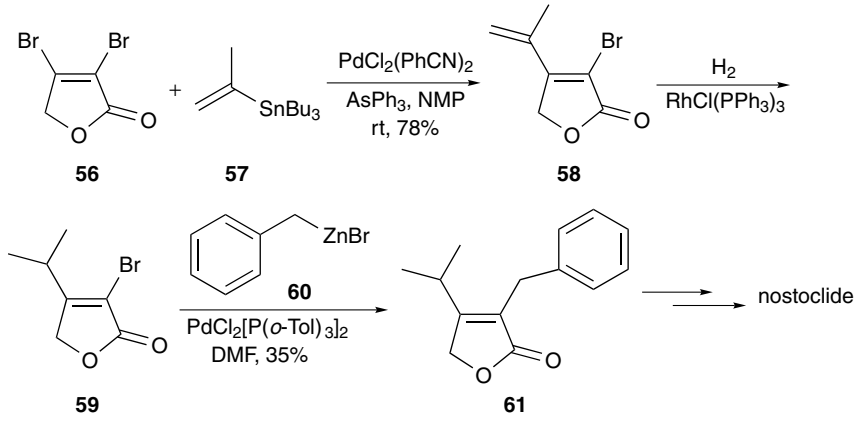
Aryl cyanides can be synthesized by Pd-catalyzed cyanation of halides or pseudohalides with $Zn(CN)_2$. As an example, the triflate group in the pyrimidone **54** was displaced with CN group to afford **55** in high yield [62].



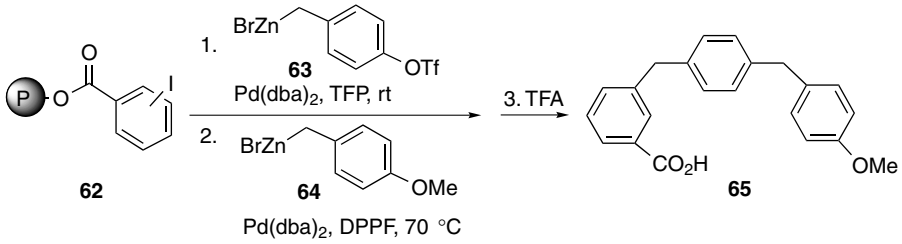
54 **55**

A formal total synthesis of nostoclide has been carried out based on regioselective coupling of 3,4-dibromo-2(5*H*)-furanone (**56**). Coupling of the dibromide

56 with 2-propenyltributylstannane (**57**) afforded **58** regioselectively using $AsPh_3$ as a ligand. Coupling of the corresponding boron and magnesium reagents were unsatisfactory. After hydrogenation of **58**, the key intermediate **61** was obtained by coupling **59** with benzylzinc bromide (**60**). Curiously, attempted coupling of **58** with **60** produced only 1,2-diphenylethane and no desired coupling product was obtained [63].



The benzylzinc bromide **63** reacted preferentially with the polymer-bound aryl iodide **62**, without attacking the triflate. Then the benzylzinc bromide **64** was added to the reaction mixture, and coupling with the triflate occurred to afford **65** after cleaving from the polymer [64].

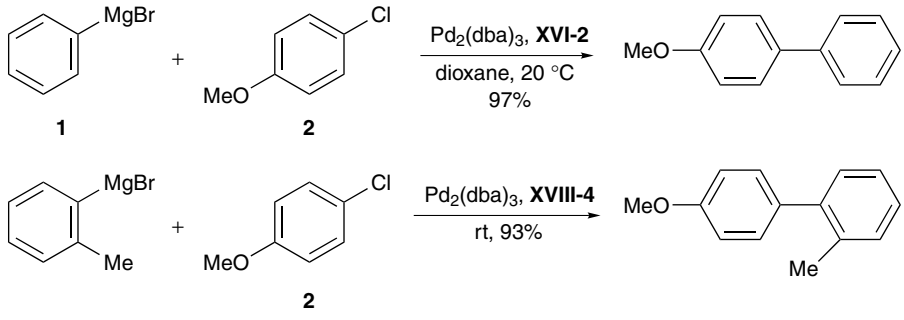


3.6.5 Organomagnesium Compounds

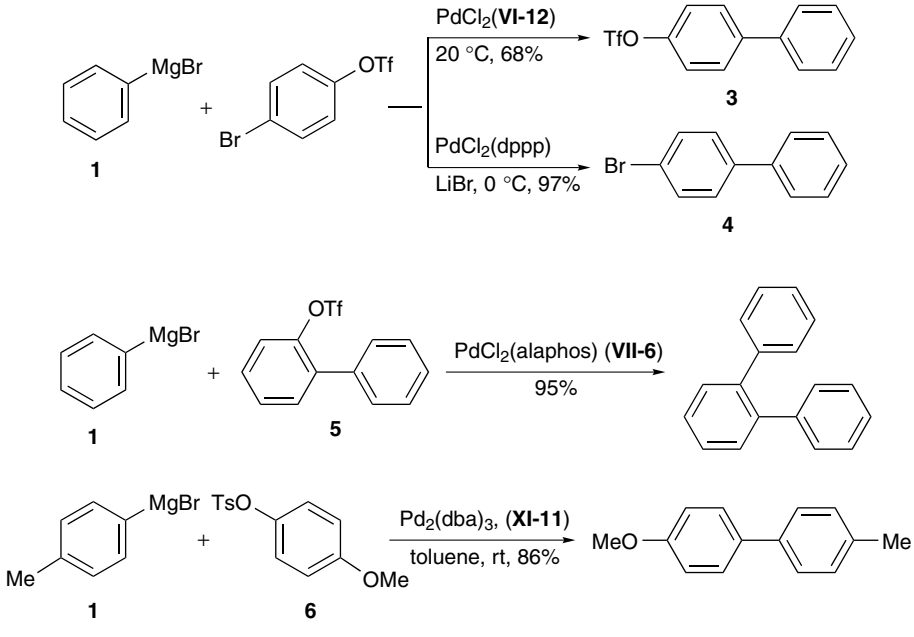
As described in preceding sections, organoboron, tin, and zinc reagents are widely used for couplings. In many cases these reagents are prepared from organolithium or magnesium compounds. Therefore direct couplings of Mg and Li compounds, if they proceed smoothly, are more atom-economical and convenient. Numerous Grignard reagents are commercially available and readily prepared from the corresponding halides. They are reactive partners of coupling. However, a drawback of this method is the intolerance to many functional groups and moisture.

Coupling of arylmagnesium halides takes place with aryl, alkenyl, and alkyl halides. Reaction of electron-rich chlorides can be carried out using carbene ligand **XVI-2**. For example, the coupling product of 4-chloroanisole (**2**) with phenylmagnesium bromide (**1**) was obtained in high yield at room temperature [65]. Also

the coupling of unactivated aryl chlorides such as 4-chloroanisole (**2**) using air-stable phosphine oxide (t-Bu_2P)(O)H) (**XVIII-4**) as a ligand proceeded at room temperature in high yield [66].

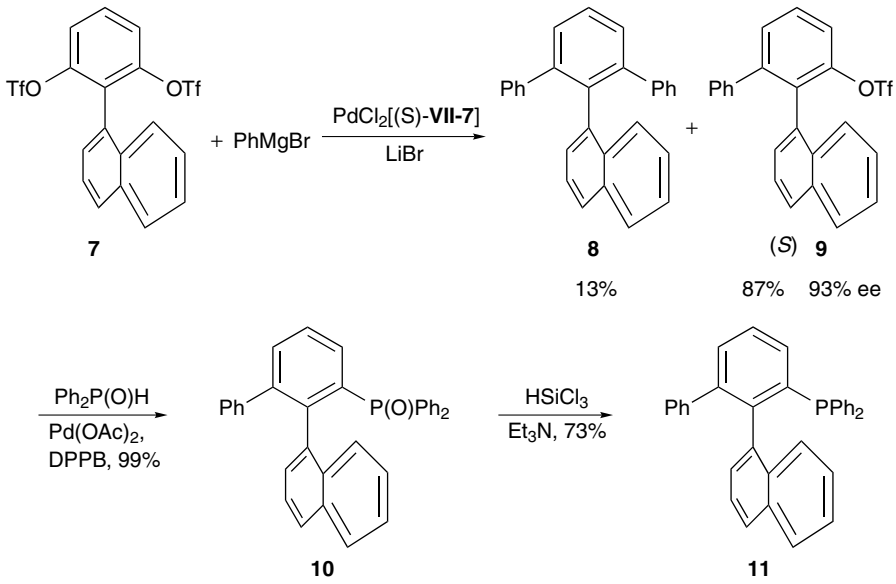


An interesting chemoselectivity between aryl bromides and triflates depending on ligands was observed. In the reaction of 4-bromophenyl triflate, the bromide reacted chemoselectively without attacking the triflate when Pd-MeO-MOP (**VI-12**) complex was used to give **3** in 97 % yield. On the other hand, 4-bromobiphenyl (**4**) was obtained chemoselectively by using Pd-DPPF as a catalyst [67]. For the coupling of congested o-substituted aryl triflate **5**, aminophosphine alaphos (**VII-6**) is an effective ligand [68]. Unactivated aryl tosylate **6** can be coupled at room temperature using P(t-Bu)$_2$ attached to ferrocene **XI-11** as an effective ligand [69].

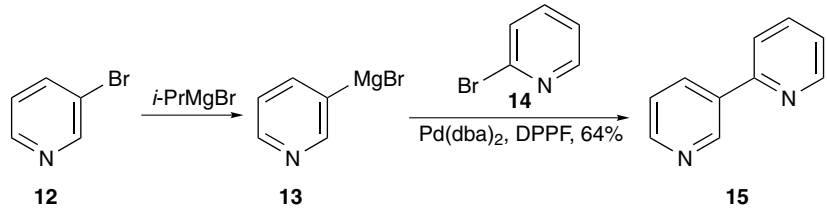


Highly asymmetric coupling of Grignard reagents is possible. The axially chiral (S)-biaryl **9** was prepared with 93 % ee in 87 % yield by the reaction of the bistriflate **7** with PhMgBr. (S)-phephos (**VII-7**) was the best chiral ligand [70]. The

diphenylated product **8** was obtained in 13 % yield. Interestingly, kinetic resolution occurs in the second coupling to give **8**. The (*R*) isomer of **9** undergoes the second phenylation about five times faster than its (*S*) isomer, indicating that the minor (*R*) isomer of **9** is consumed preferentially by the second asymmetric coupling, which causes an increase of the enantiomeric purity of (*S*)-**9** as the amount of **8** increases. The chiral phosphine **11** was prepared by the Pd-catalyzed conversion of the remaining triflate in **9** to **10** using diphenylphosphine oxide, and reduction of **10** with $HSiCl_3$.

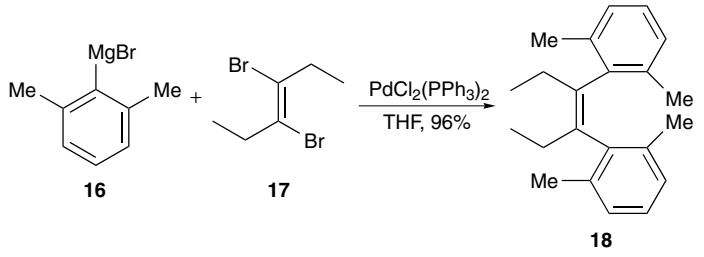


Some heteroaryl halides are electron-deficient and reactive. 3-Pyridylmagnesium chloride (**13**) was prepared efficiently by the treatment of 3-bromopyridine (**12**) with isopropylmagnesium chloride, and 2-(3-pyridyl)pyridine (**15**) was prepared by coupling **13** with 2-bromopyridine (**14**) using DPPF as a ligand [71].



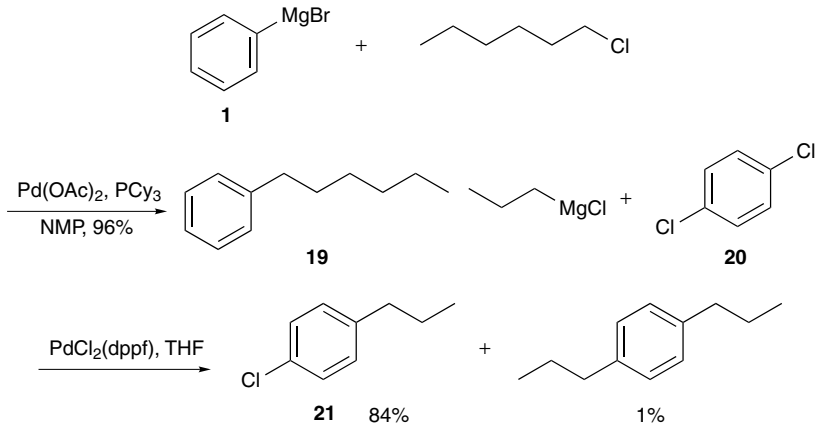
The pure *cis*-stilbene derivative **18** was prepared cleanly in high yield by the reaction of sterically hindered 2,6-dimethylphenylmagnesium bromide (**16**) with *trans*-3,4-dibromo-3-hexene (**17**), which is easier to prepare than the corresponding *cis*-dibromide [72].

Interestingly, alkyl chlorides can be used for the coupling without undergoing β-H elimination. The best ligand for the efficient coupling of 1-chlorohexane is PCy_3, and the reaction in NMP or DMAC as a solvent gives *n*-hexylbenzene (**19**),



16 **17** **18**

which is difficult to synthesize by Friedel-Crafts alkylation [73]. It is remarkable that unusually facile oxidative addition of alkyl chloride to Pd(0) occurs at least in this case. Commercial production of alkylbenzene derivative can be carried out by the reaction of alkylmagnesium halides with aryl halides. For example, reaction of *p*-dichlorobenzene (**20**) (2 equiv.) with propylmagnesium chloride (1 equiv.) afforded *p*-chloropropylbenzene (**21**) cleanly by monosubstitution. Pd-DPPF is used as a catalyst [74].

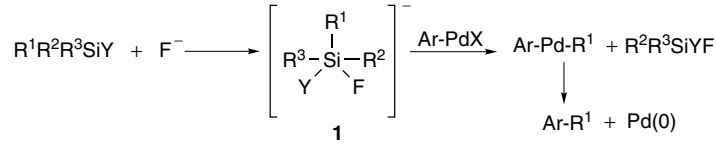


1 **19** **20** **21**

3.6.6 Organosilicon Compounds (Hiyama Coupling)

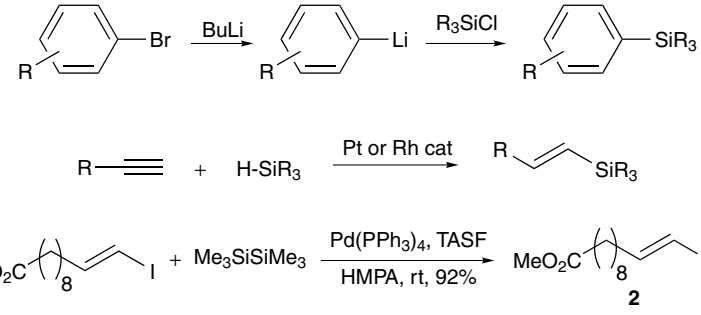
3.6.6.1 Introduction and Preparative Methods of Organosilicon Compounds

In contrast to organometallic reagents of Mg, B, and Sn, organosilicon compounds are inert for transmetallation under normal Pd-catalyzed coupling conditions. Hiyama has discovered that the C—Si bond can be activated by nucleophiles such as F^- and OH^- by forming pentacoordianted silicates **1**, and transmetallation of organosilicon compounds proceeds in the presence of a fluoride anion source as a promoter. Thus, smooth cross-coupling of organosilanes with halides is possible by the addition of a stoichiometric amount of promoters, typically TASF $[(Et_2N)_3S^+(Me_3SiF_2^-)]$ or TBAF $[(n\text{-}Bu)_4NF]$, and the reaction is called Hiyama coupling [75,76]. KF and CsF are effective only in some cases. Recent improvement in the coupling reaction has been reviewed by Denmark and Sweis [77].



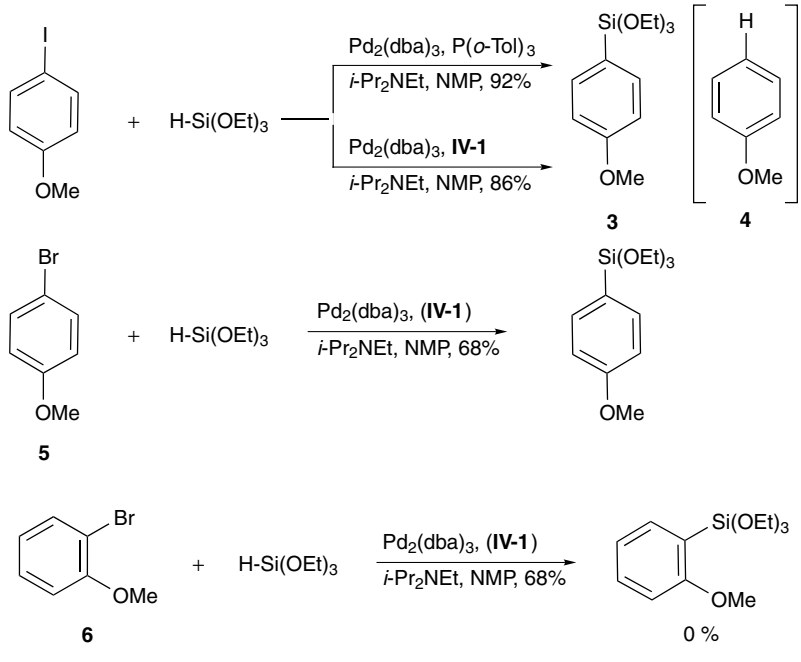
1

An established synthetic method for arylsilanes is lithiation of aryl halides, followed by the reaction with R_3SiCl. Alkenylsilanes are produced by hydrosilylation of 1-alkynes catalyzed by Rh or Pt complexes. Also aryl- and alkenylsilanes **2** are synthesized by Pd-catalyzed reaction of hexamethyldisilane with halides in the presence of TASF [78,79].



2

Masuda and co-workers have discovered a new synthetic method for aryltriethoxysilanes **3**. They found that **3** can be prepared in high yields by Pd-catalyzed silylation of aryl iodides such as 4-iodoanisole and bromides with triethoxysilane using P(*o*-Tol)$_3$ as a ligand in NMP [80]. Of course, the silylation is competitive with hydrogenolysis to form the reduced arene **4**. DeShong and co-workers have studied the scope and limitation of the reaction [81]. They found that biphenylyl(di-*t*-butyl)phosphine **IV-1** is the most effective ligand. Although aryl iodides are the substrates of choice, an acceptable yield of arylsiloxanes may be obtained from the corresponding bromide. Interestingly, satisfactory results were obtained from electron-rich 4-iodoanisole and 4-bromoanisole (**5**). The steric effects on the reaction are serious and no reaction of 2-bromoanisole (**6**) occurs.



3 **4**

5

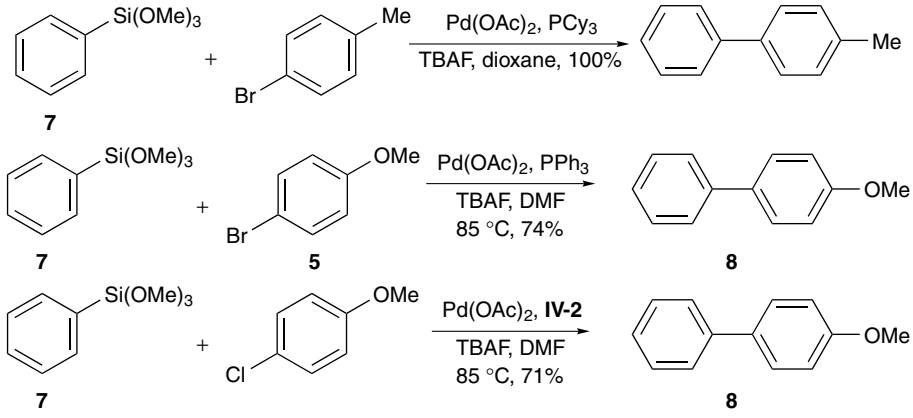
6

0 %

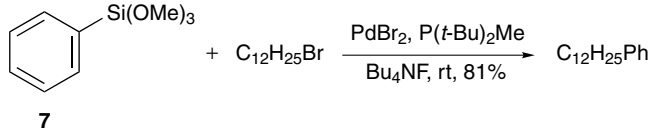
One of the advantages of Hiyama coupling is that silicon is a comparatively environmentally benign element, since organosilicon compounds are oxidized ultimately to inactive silica gel. Better tolerance to functional groups is another advantage. A drawback, however, is consumption of more than stoichiometric amounts of expensive additives. In addition, functional groups protected by silyl groups can not be tolerated, because they are deprotected by a fluoride anion.

3.6.6.2 Couplings of Arylsilanes

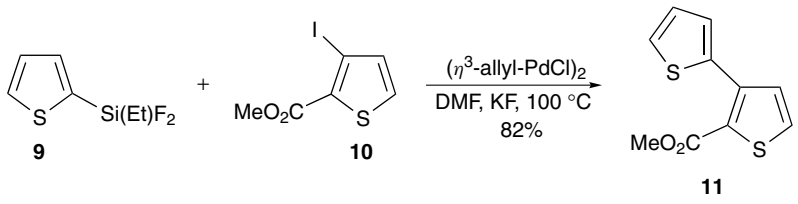
Arylsilanes bearing heteroatoms such as F, Cl, OH, and OR can be used as coupling partners. Of these, OH appears to be most reactive. Easily prepared arylalkoxysilanes are good coupling partners [82,83]. The carbene ligand **XVI-2** is a good ligand for the coupling of phenyltrimethoxysilane (**7**) with activated aryl chlorides. In the coupling of 4-bromotoluene, PCy_3 is more effective than the carbene ligand [84]. Curiously, coupling of **7** with deactivated 4-bromoanisole (**5**) proceeded in DMF to afford **8** even when PPh_3 was used. Furthermore, biphenylyldicyclohexylphosphine **IV-2** is effective for the coupling of 4-chloroanisole with **7** to provide **8** [85].



Lee and Fu reported that coupling of phenyltrimethoxysilane (**7**) with alkyl bromides is possible under selected conditions. 1-Phenyldodecane was obtained in 81 % yield by the reaction of **7** with *n*-dodecyl bromide at room temperature. P(*t*-Bu)$_2$Me as an effective ligand and Bu_4NF (2.4 equiv.) as an activator were used [86].

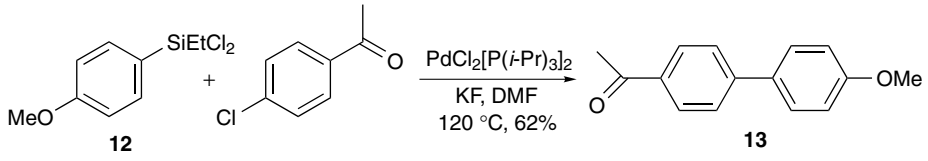


Some halides on silicon are activating groups. Generally two fluorine atoms are required for aryl–aryl coupling. For example, coupling of ethyl(2-thienyl)difluorosilane (**9**) with 3-iodothiophene **10** afforded the bisthiophene **11** using a ligandless Pd catalyst in the presence of KF [87].



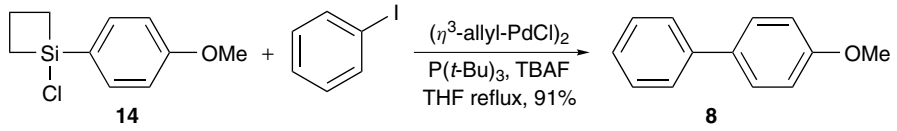
9 **10** **11**

Electron-deficient aryl chlorides can be coupled with organo di- or trichlorosilanes such as aryldichloroethylsilane and aryltrichlorosilane in the presence of KF. In this case, the *in situ* fluorination of chlorosilanes with KF occurs. Electron-rich alkylphosphines such as tri(isopropyl)phosphine or bis(dicyclohexylphosphino)-ethane are effective ligands. For example, coupling of the dichlorosilane **12** with 4-chloroacetophenone at 120 °C in DMF gave **13** in 62 % yield [88].



12 **13**

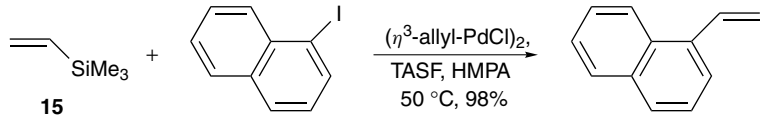
In addition to dichloro groups, some other activating groups are known. Denmark and Wu found that arylchlorosiletanes [aryl(chloro or fluoro)silacyclobutanes] are reactive coupling partners and ascribed the high reactivity at first to 'strain release Lewis acidity' of the siletane, but later to the formation of ring-opened silanol derivatives. The anisylchlorosiletane **14** reacted smoothly with iodobenzene using $P(t\text{-Bu})_3$ as a ligand in the presence of TBAF [89].



14 **8**

3.6.6.3 Couplings of Alkenylsilanes

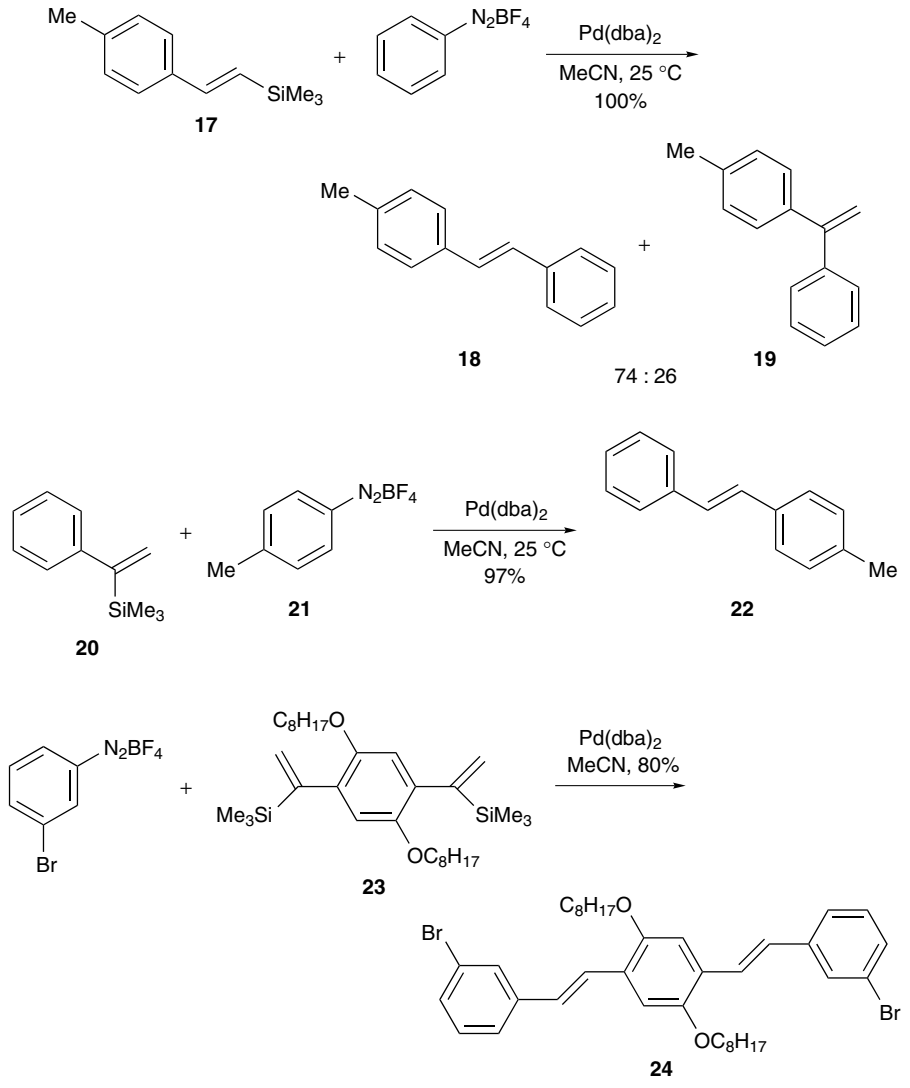
Trimethylsilanes are easily available. Coupling of commercially available trimethylvinylsilane (**15**) with the iodide **16** proceeds most satisfactorily using TASF and ligandless Pd in HMPA [90].



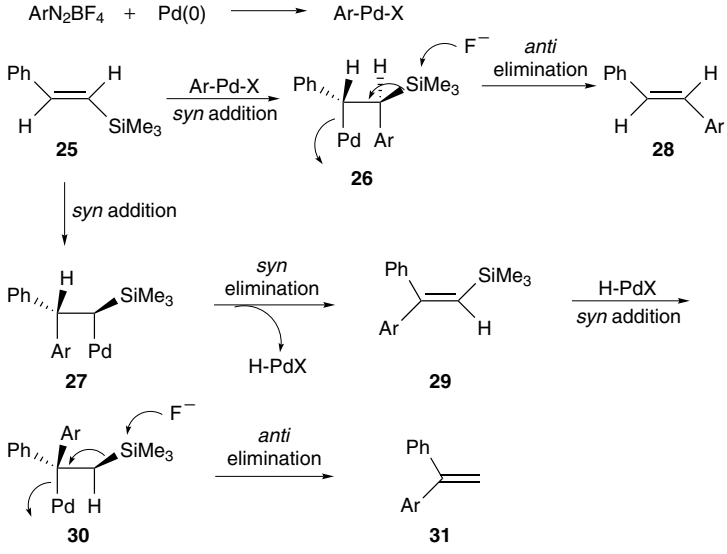
15 **16**

Silanes couple under promoter-free conditions with good electrophiles like aryldiazonium salts. Matsuda and co-workers have discovered that benzenediazonium tetrafluoroborate reacts with β-trimethylsilylstyrene derivative **17** using ligandless

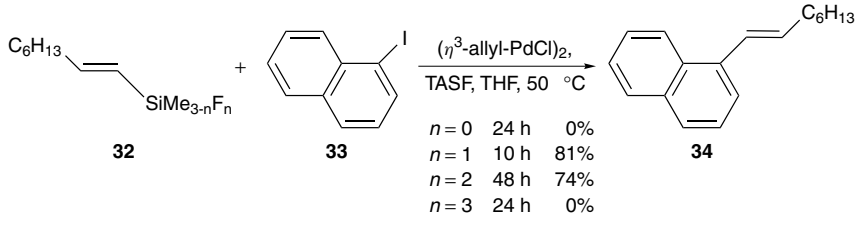
$Pd(dba)_2$ in MeCN at room temperature. Two products, namely the expected *ipso* product **18** and the *cine* product **19**, were obtained [91]. On the other hand, reaction of α-trimethylsilylstyrene **20** with **21** afforded the *cine* product **22** regio- and stereoselectively [92]. An application of the coupling of aryldiazonium salt to α,α'-bis(trimethylsilyl)-1,4-divinylbenzene derivative **23** afforded the (*E*, *E*)-bis(styryl)benzene derivative **24** cleanly [93].



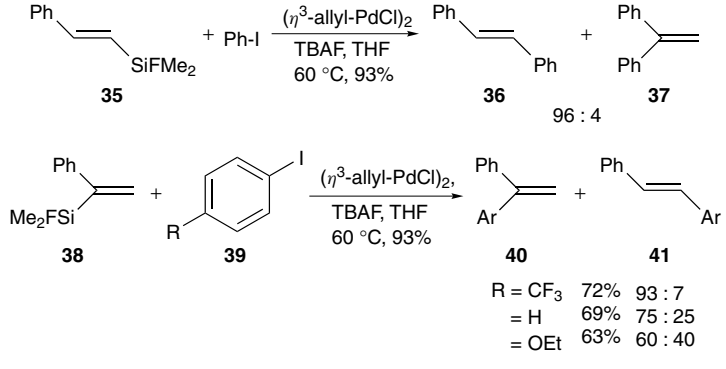
The reaction of **17** (or **25**) to give **19** (or **31**) can not be explained by the 'oxidative addition–transmetallation–reductive elimination' mechanism. In the reaction of **25**, carbopalladation to form **26** and **27** is the first step. Desilylpalladation of **26** affords the expected *ipso* product **28**. On the other hand, the intermediate **27** undergoes *syn* dehydropalladation to give **29**, to which *syn* addition of H-PdX occurs to generate **30**. Then *anti* desilylpalladation provides the *cine* product **31**. This reaction is not completely fluoride-free, because the BF_4^- anion is present.



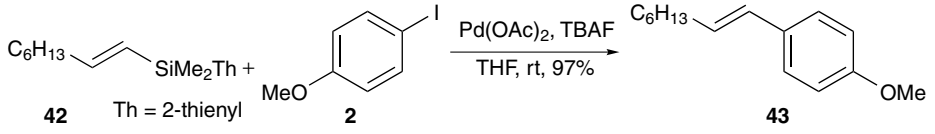
Reactivity of alkenylsilanes changes by replacing one to three methyl groups in **32** with other groups. Introduction of F enhances reactivity as shown by the reaction of 1-silyl-1-octene **32** with 1-naphthyl iodide (**33**) to afford **34**. Introduction of one F gives the highest reactivity possible owing to easy formation of the pentacoordinate silicate from the alkenylsilane without any electron-donating group. No reaction occurs with octenyltrimethylsilane under this condition [94].



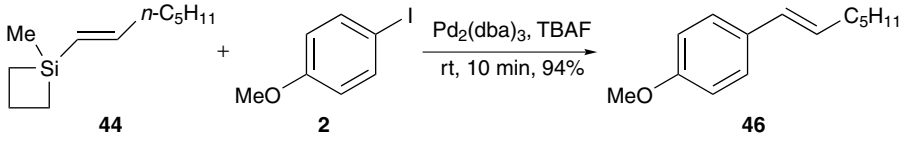
Coupling of the *trans*-styrylsilane **35** with iodobenzene gave rise mainly to *trans*-stilbene (**36**) as the *ipso* product and only a small amount of the *cine* product **37**. Under the same conditions, *cine* product **41** was obtained to some extent from the α-silylstyrene **38** in addition to *ipso* product **40**. The *ipso : cine* ratios change depending on substituents (R) of the aryl iodides **39** [95].



The 2-thienyl (Th) group in the alkenylsilane **42** also promotes the coupling, which occurs at room temperature in the presence of TBAF to provide **43** [96]. The 2-thienyl group is considered to facilitate the formation of pentacoordinate silicate or to be replaced readily by OH.



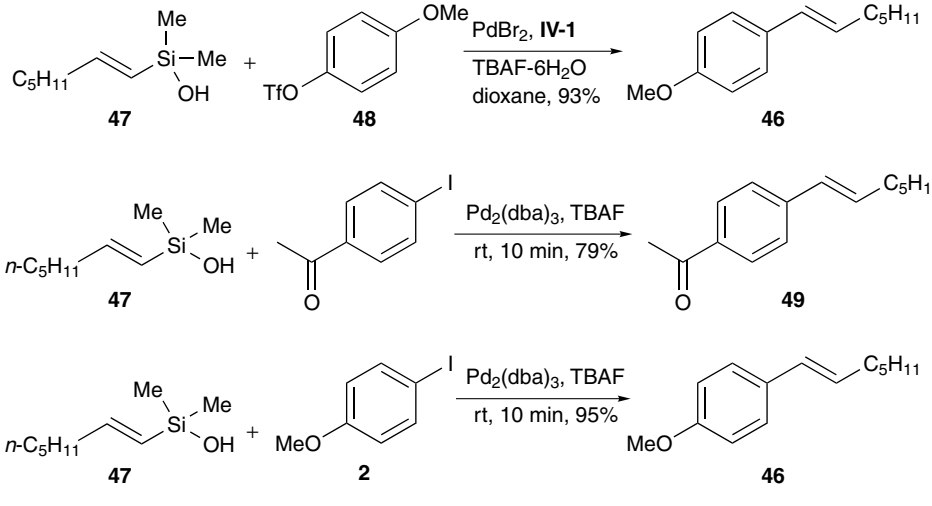
The alkenylsiletane **44** is very reactive and reacts with 4-iodoanisole (**2**) at room temperature with ligandless Pd catalyst in 10 min to give **46** in 94 % yield [97]. Here again **44** is considered to be transformed to a silanol before coupling.



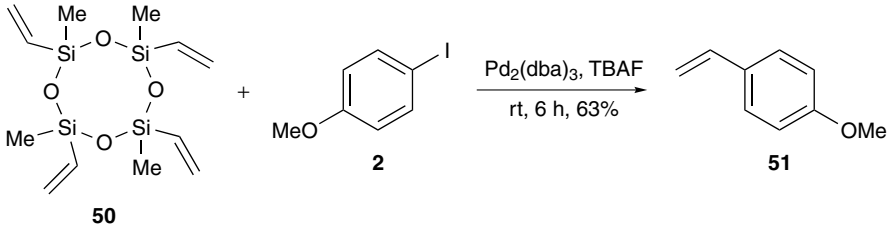
3.6.6.4 Couplings of Aryl- and Alkenylsilanols, and Alkoxysilanes

Silanols are apparently the most effective coupling reagents, which react under mild conditions in the presence of promoters [98]. The coupling of alkenylsilanols with deactivated aryl iodides occurs with ligandless $Pd(dba)_2$ [99]. Reaction of the silanol **47** with the triflate **48** proceeded smoothly in the presence of bulky biphenylylphosphine (**IV-1**). Curiously, $PdBr_2$ was a more active catalyst than $PdCl_2$ and use of TBAF $\cdot$ $6H_2O$ gave better results [100,101].

Coupling of the silanol **47** with electron-deficient 4-iodoacetophenone proceeded at room temperature in 10 min to afford **49** in 79 % yield using ligandless Pd catalyst. Also coupling with the less reactive aryl iodide **2** occurred efficiently with ligandless Pd catalyst [99].

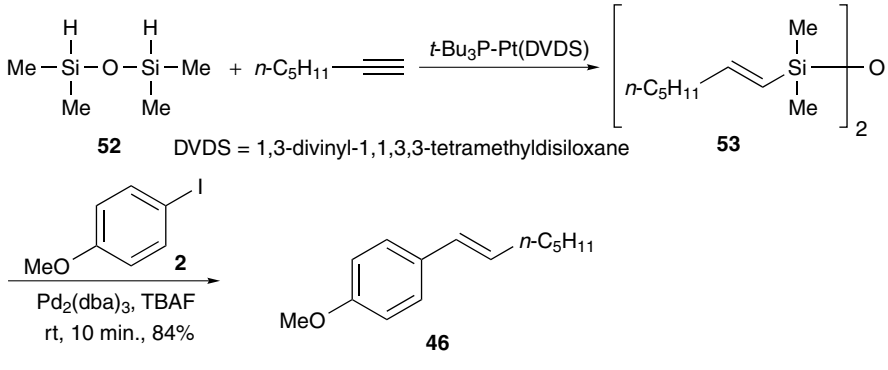


Vinylation of aryl iodides can be carried out using the commercially available cyclooligodisiloxane **50** at room temperature [102].



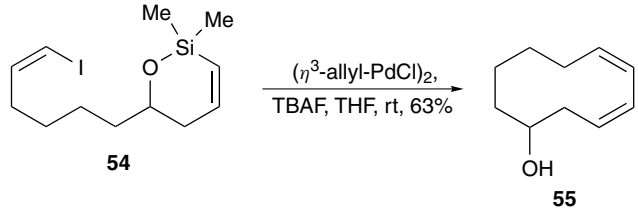
50 **2** **51**

The coupling products are obtained by one-pot hydrosilylation/cross-coupling of alkynes. Pt-catalyzed hydrosilylation of alkyne with tetramethyldisiloxane (**52**) generates the alkenylsilane **53**, which is coupled with 4-iodoanisole (**2**) using ligandless Pd catalyst and TBAF at room temperature to afford **46** in 84 % yield [103].



52 **53** **46**

Coupling of reactive alkoxyalkenylsilanes has been applied to the synthesis of medium-sized rings. The cyclic silyl ether **54** was converted to cyclodeca-3,5-dienol (**55**) at room temperature [104]. In many silane coupling reactions, it has been claimed that ligandless π-allylpalladium chloride is an effective catalyst precursor. Possibly, chloride ion is essential for transmetallation as compared with unreactive $Pd(OAc)_2$.

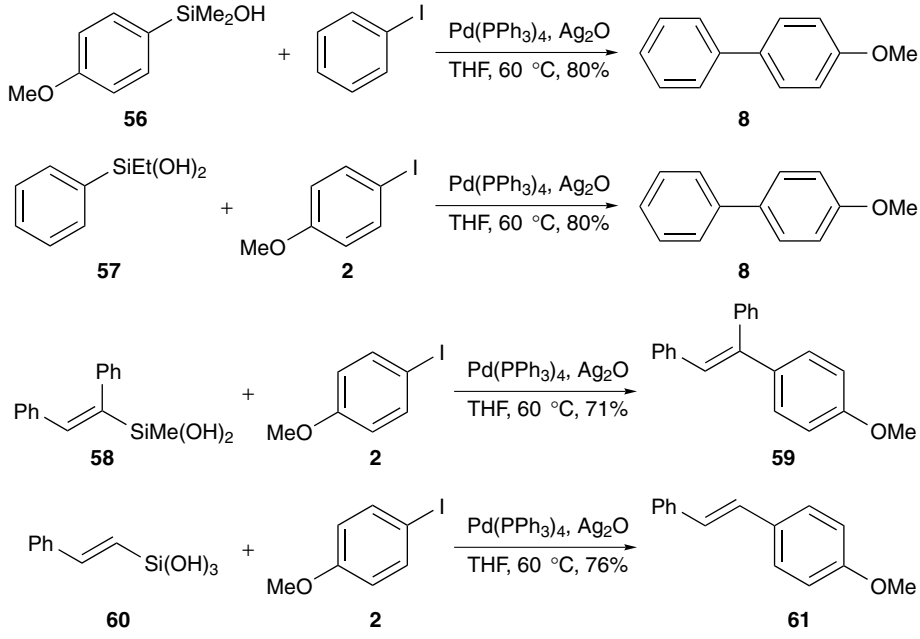


54 **55**

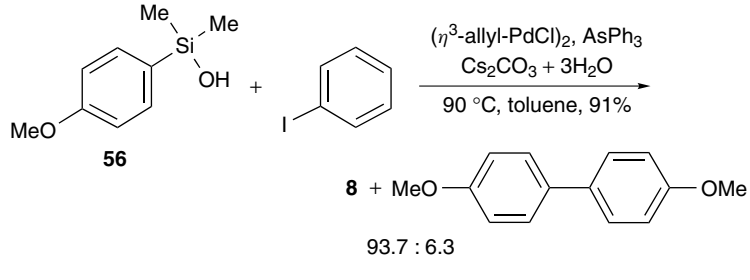
3.6.6.5 Fluoride-Free Procedures

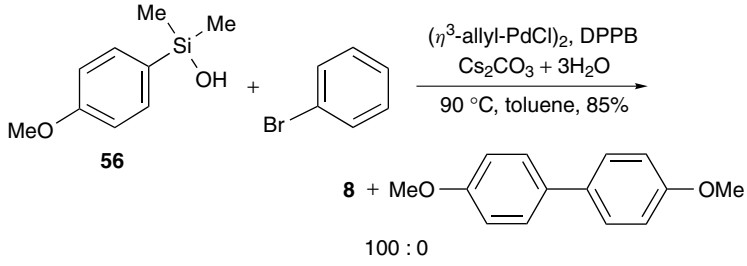
The couplings of organosilanes discussed so far are carried out in the presence of more than equimolar amounts of promoters, typically TBAF, which is expensive.

The promoters preclude wide use of the reaction. Mori and Hiyama discovered that Ag_2O can be used as a promoter for the reaction of silanols [105]. Reaction of the arylsilanol **56** with iodobenzene to give **8** proceeded smoothly in THF in the presence of an equimolar amount of Ag_2O. Interestingly no reaction occurred when $Pd(OAc)_2$, PPh_3, and TBAF were used. Silanediols and silanetriols are more reactive than silanols. Coupling of the arylsilanediol **57**, alkenylsilanediol **58**, and the triol **60** with less reactive 4-iodoanisole (**2**) occurred smoothly to provide **8**, **59** and **61**. These silanols are prepared easily by hydrolysis of the corresponding chlorosilanes and used without isolation.

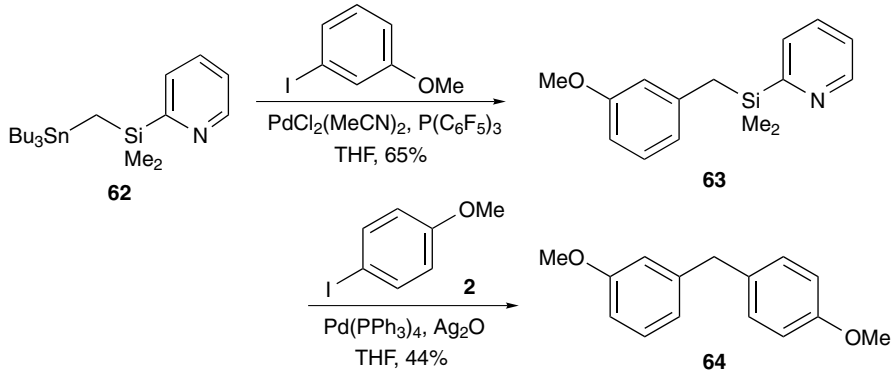


Arylsilanols, although less reactive than alkenylsilanols, can be coupled in the presence of Cs_2CO_3 (2 equiv.) and $AsPh_3$ in toluene. Under these fluoride-free conditions, coupling of *p*-methoxyphenylsilanol **56** with phenyl iodide afforded the coupling product **8** in high yield. Homocoupling occurred to a small extent. Coupling of less reactive phenyl bromide proceeded selectively using DPPB as a ligand. Control of water content in Cs_2CO_3 is important for maximum activity [106].

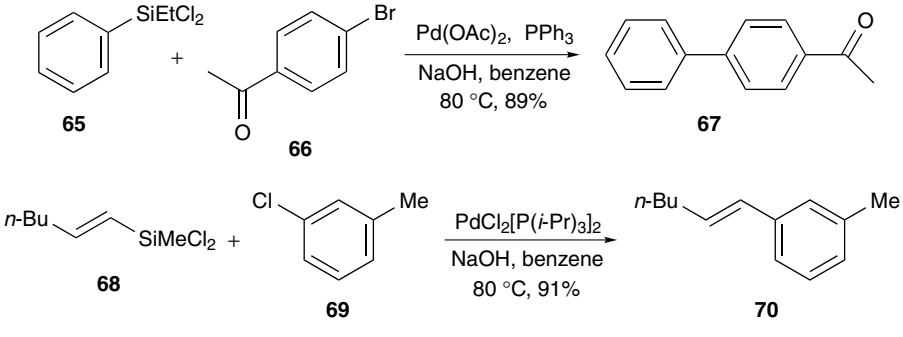




A straightforward route to diarylmethanes is double cross-coupling of (2-pyridyl)-silylmethylstannane **62** with aryl halides. First, chemoselective coupling of alkyl-stannane in **62** with 3-iodoanisole produced **63** using $P(C_6F_5)_3$ as a ligand. Then reaction of 4-iodoanisole (**2**) with the pyridylsilane **63** took place in the presence of Ag_2O to give the diarylmethane **64**. The pyridyl group in **63** seems to activate the silane group for the coupling by coordination to Pd to assist transmetallation [107].

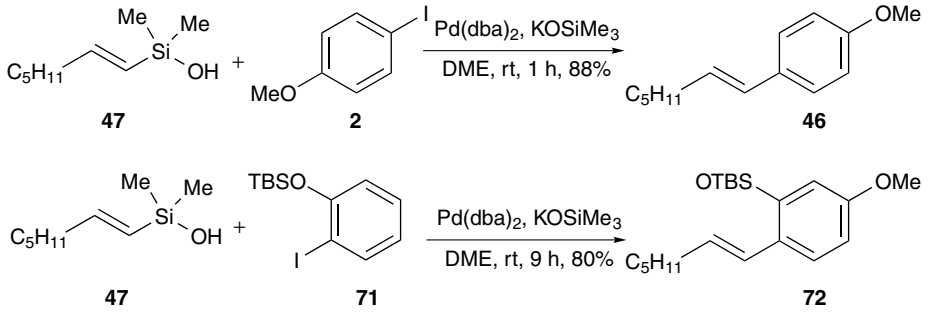


As a more useful fluoride-free process, the Hiyama group reported that coupling of $ArSiRCl_2$ occurs smoothly by the addition of powdered NaOH (6 equiv.) as an activator, instead of fluorides. Coupling of activated aryl bromide **66** with **65** proceeded in refluxing benzene using $Pd(OAc)_2$ and PPh_3 [108]. LiOH, K_2CO_3, and Na_2CO_3 are less effective. Similarly, coupling of alkenyldichlorosilane **68** with 3-chlorotoluene (**69**) took place at 80 °C to give **70**. P(*i*-Pr)$_3$ is an effective ligand.



Another good solution for the desirable fluoride- and silver-free procedure has been demonstrated by the Denmark group. They found that the reaction of the alkenylsilanol **47** with 4-iodoanisole (**2**) to afford **46** proceeded smoothly in the presence of 2 equivalents of $KOSiMe_3$ as a base without other promoters using ligandless $Pd(dba)_2$ as a catalyst in DME at room temperature [109]. Coupling of TBS-protected 2-iodophenol (**71**) with **47** by this method proceeded to afford **72** without cleaving the silyl protection.

Further development of the fluorine-free procedure will certainly promote silane coupling chemistry.



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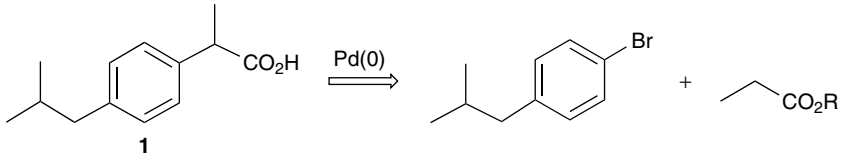
3.7 Arylation and Alkenylation of C, N, O, S, and P Nucleophiles

Arylation and alkenylation of various nucleophiles with aryl and alkenyl halides have been underdeveloped for a long time except for the coupling of halides with organometallic compounds of main group metals via transmetallation. However, recently remarkable progress has occurred by the discovery that Pd catalysts are effective for arylation of C, N, O, S, and P nucleophiles. For example, it is now possible to arylate ketones with aryl chlorides to prepare α-aryl ketones. The progress has led to new innovations in organic synthesis. The new reaction became possible by the selection of the proper ligands and bases. Bulky ligands have been found to accelerate reductive elimination, and a number of effective bulky ligands for arylation have been synthesized.

3.7.1 α-Arylation and α-Alkenylation of Carbon Nucleophiles

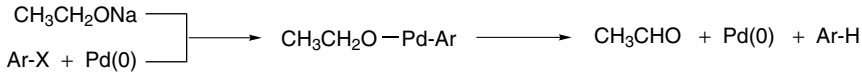
In contrast to facile α-alkylation of carbonyl compounds, α-arylation or alkenylation of carbonyl compounds has been considered to be a difficult reaction. Recently, a big breakthrough has occurred, and methods for the smooth α-arylation or alkenylation of carbonyl compounds have been developed [1]. Active methylene compounds, ketones, aldehydes, esters, amides and nitriles are now α-arylated easily not only with aryl iodides, but also with bromides and even chlorides. These reactions will lead to wide-ranging applications. A typical example of a synthetic application of the innovative reactions is a new preparative method for α-arylated carboxylic acids, such as ibuprofen (**1**) and naproxen, by direct α-arylation of acetate or propionate.



1

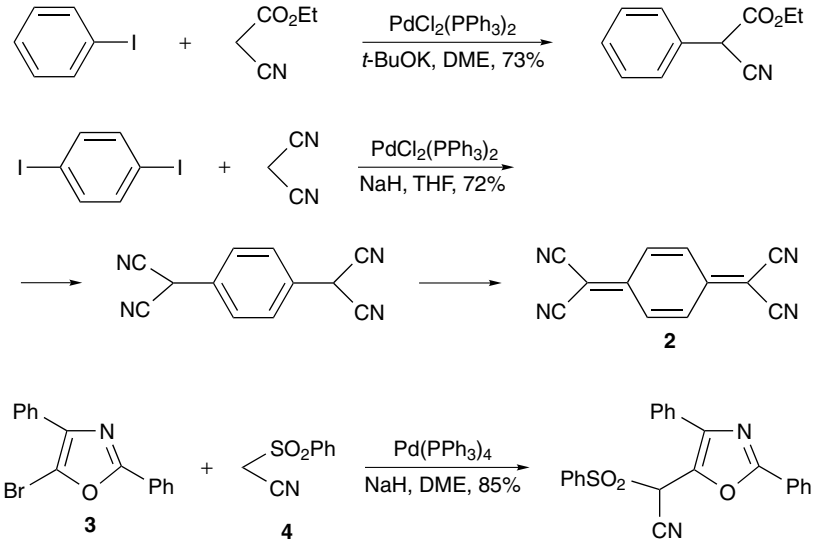
The breakthrough became possible by the emergence of new ligands, particularly bulky and electron-rich ligands. The selection of bases is also important, and stable

bases such as $MN(TMS)_2$ (M = Li, Na, K), NaH, and *t*-BuONa are used. MeONa and EtONa are usually not effective because they are easily oxidized to aldehydes with aryl halides as shown below. Cs_2CO_3 is a unique and very effective base in some reactions.

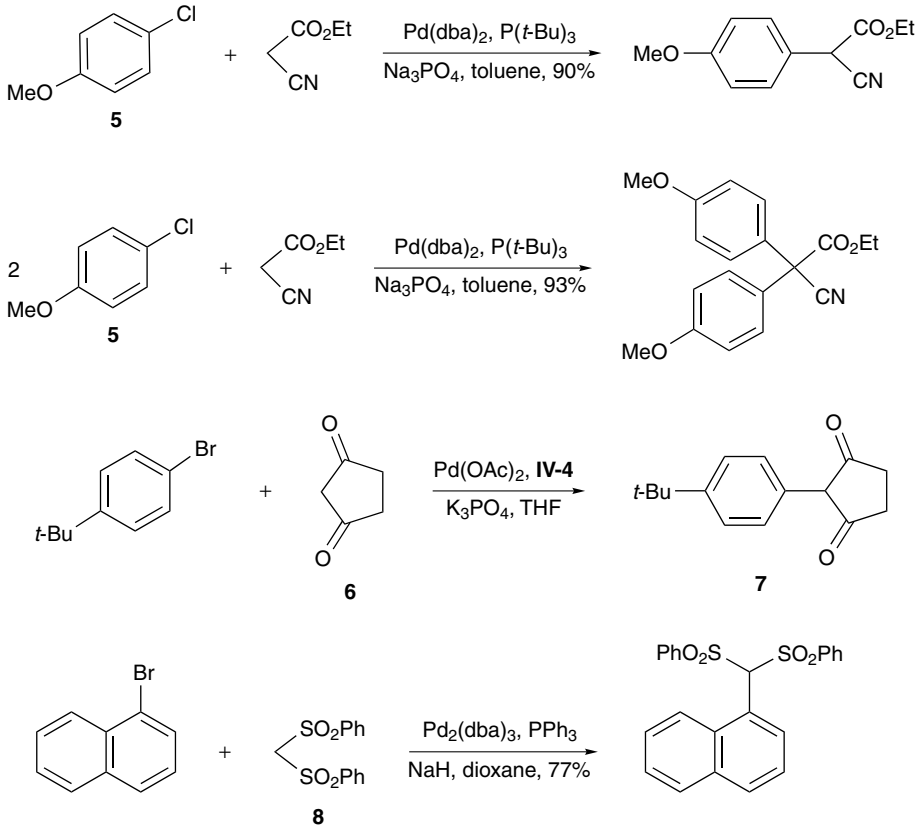


3.7.1.1 Arylation of Active Methylene Compounds

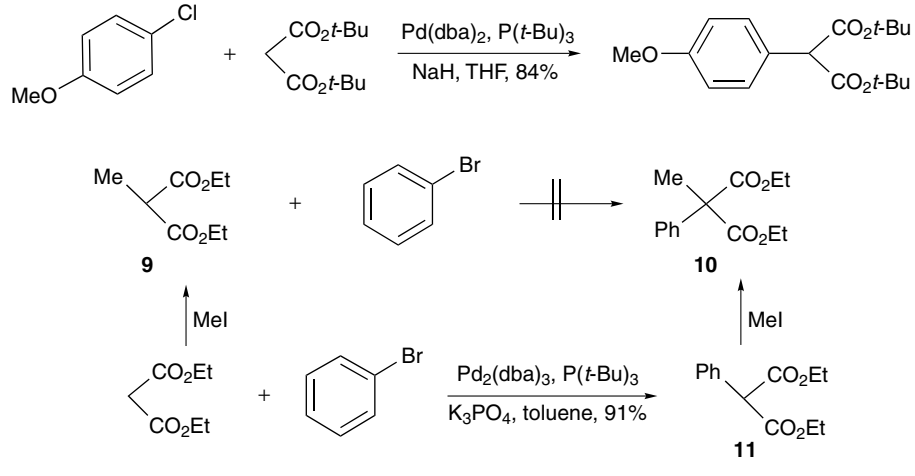
Arylation of active methylene compounds has been carried out using Cu salts as promoters under severe conditions [2]. Recently it was discovered that the reaction can be carried out much more smoothly using Pd catalysts. The first Pd-catalyzed intermolecular arylation of cyanoacetate and malononitrile with aryl iodides was carried out by Takahashi using PPh_3 as a ligand, and was applied to a simple synthesis of tetracyanoquinodimethane (**2**) by the reaction of *p*-diiodobenzene with malononitrile [3]. The intramolecular arylation of malonates and β-diketones with aryl iodides proceeds smoothly. Presence of a cyano group seemed to be important [4,5]. The arylation has been successfully extended to halides of heterocycles, such as pyridine, quinoline and isoquinoline. The reaction of bromoxazole **3** with sulfone **4** is an example [6].

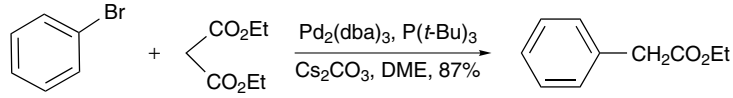


Facile stepwise mono- and diarylations of cyanoacetate took place with aryl bromides and electron-rich *p*-chloroanisole (**5**) [7]. Recently Kawatsura and Hartwig [8] and Fox *et al*. [9] have shown that the presence of the cyano group is not crucial, and β-diketones are monoarylated with aryl bromides when bulky and electron-rich ligands such as P(*t*-Bu)$_3$ are used. For example,1,3-cyclopentanedione (**6**) was arylated intermolecularly to give **7** using biphenyl-type phosphine **IV-4** as a ligand [9]. Arylation of bis(phenylsulfonyl)methane (**8**) with 1-bromonaphthalene proceeded using even PPh_3 as a ligand [10].



Di-*t*-butyl malonate can be arylated with electron-rich aryl chlorides using NaH and P(*t*-Bu)$_3$ [11]. The arylation suffers steric effects, and no arylation takes place with diethyl methylmalonate (**9**). Thus, diethyl methylphenylmalonate (**10**) can be prepared via arylation of malonate to give **11**, followed by methylation as a one-pot reaction. When the arylation of diethyl malonate is carried out at 120 °C, phenylacetate (**12**) is obtained as a one-pot reaction product [12].



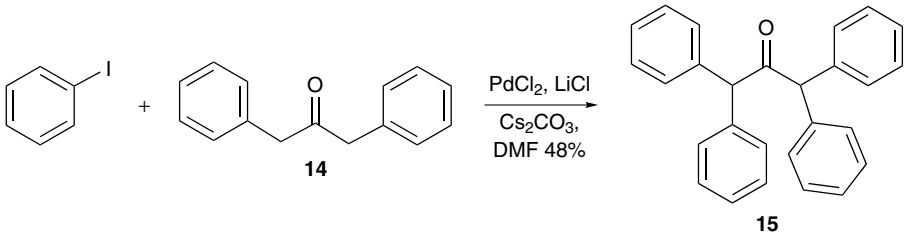


12

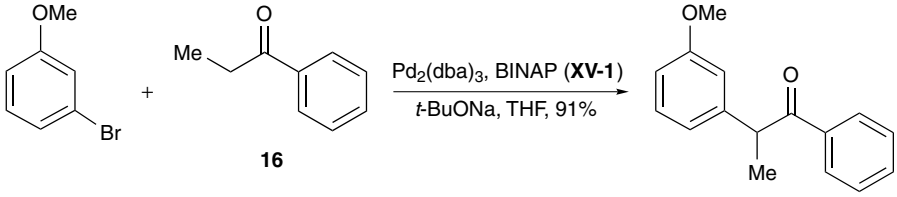
Hartwig and Wolkowski have synthesized arylpalladium complexes of malonates, and have shown that the greater steric hindrance of bulky ligand $FcP(t\text{-}Bu)_2$ (**VIII-2**), relative to that of phenylphosphines, induces reductive elimination from the complexes [13].

3.7.1.2 Arylation of Ketones

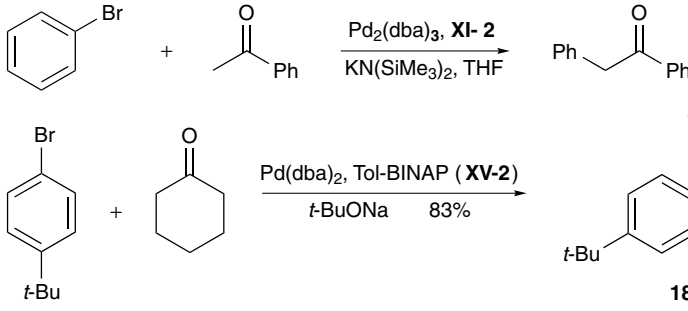
Direct arylation of ketones was a difficult reaction. Arylation of ketones has been carried out by the Pd-catalyzed reaction of tin enolates of ketones, generated *in situ*, with aryl halides [14,15]. Facile direct arylation of ketones has been reported by the groups of Miura, Buchwald, and Hartwig almost simultaneously [16–18], and α-aryl ketones are now easily available by Pd-catalyzed arylation. Miura reported the arylation of dibenzyl ketone (**14**) with iodobenzene using $PdCl_2$ as a catalyst and Cs_2CO_3 as a base without any ligand to give tetraphenylacetone (**15**) [16]. Buchwald and Hartwig reported monoarylation of ketones such as propiophenone (**16**), acetophenone, and cyclohexanone with aryl bromides gave **17** and **18** using BINAP (**XV-1**), Tol-BINAP (**XV-2**), DPPF (**XI-1**), DtBPF (**XI-4**) and Xantphos (**IX-10**) as ligands, and strong bases such as $KN(TMS)_2$ or *t*-BuONa [8,17,18].



14 **15**

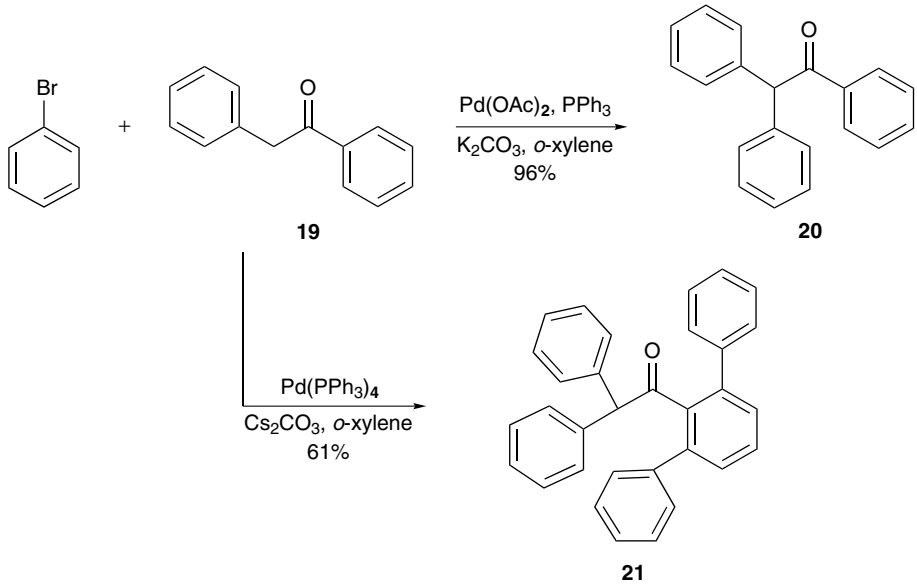


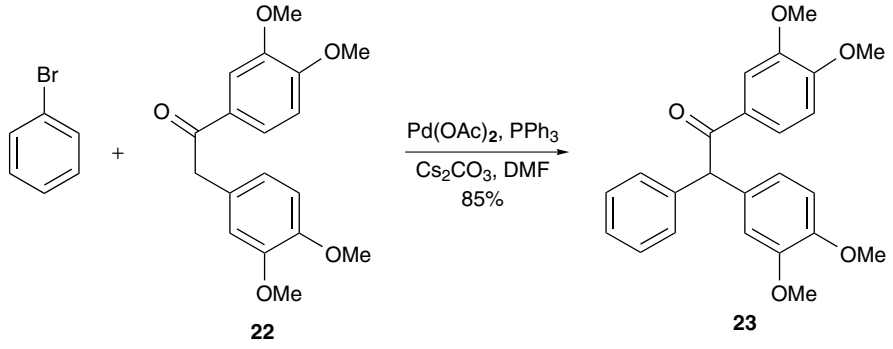
16 **17**



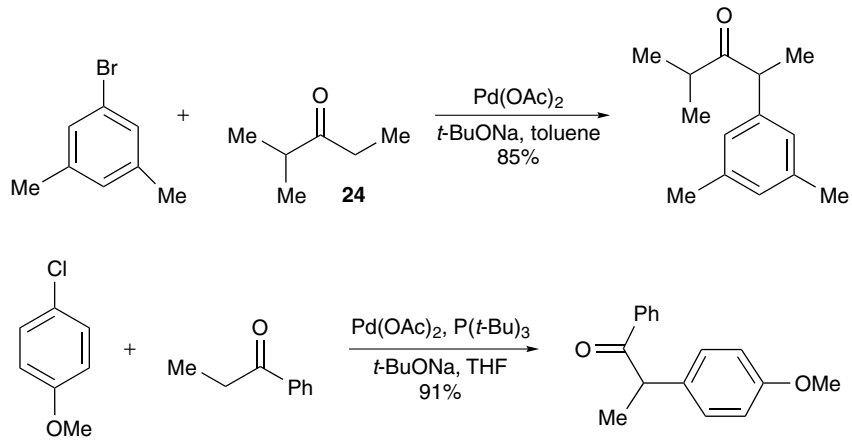
18

Selective and smooth monoarylation of benzyl phenyl ketone (**19**) gave **20** using K_2CO_3 as a base. It should be noted that PPh_3 is an effective ligand [19]. On the other hand, the polyarylated ketone **21** was obtained when Cs_2CO_3 was used. This is an interesting example which shows different actions of two carbonates (K_2CO_3 and Cs_2CO_3) as bases. Formation of **21** and related arylation of phenyl rings are treated in Chapter 3.3.4. Preparation of **20** by selective monoarylation of **19** was applied to the synthesis of the tamoxifen structure **23** from **22** [20].

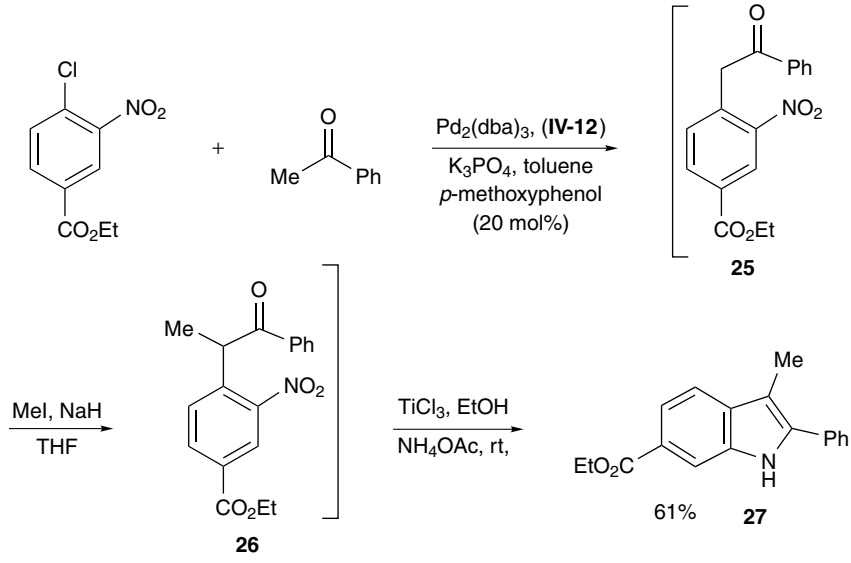




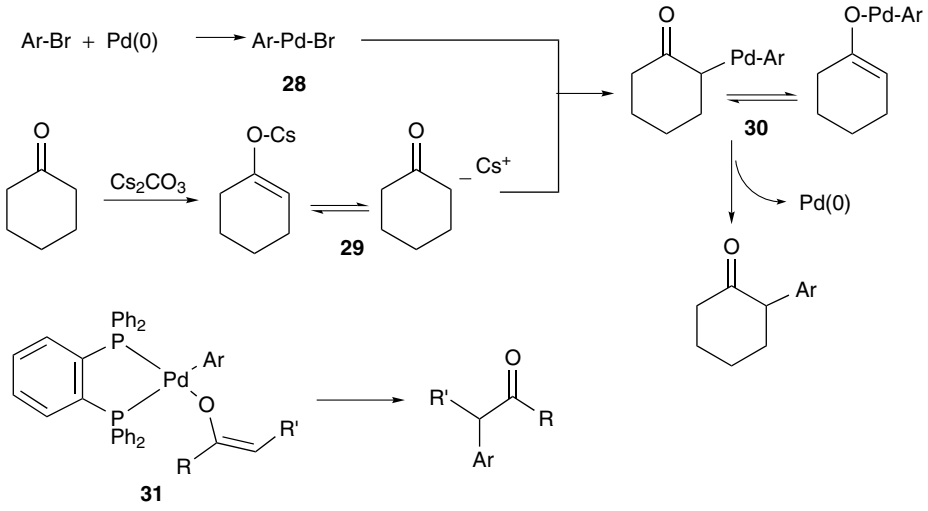
The arylation of the ketone **24** with 3,5-dimethylbromobenzene was carried out even without any phosphine [9]. The arylation with *p*-chloroanisole can be carried out by using P(*t*-Bu)$_3$, PCy_3, and **IV-6** as effective ligands [8,9]. The air-stable carbene complex (**XVI-1**) Pd(allyl)Cl is a good catalyst for the arylation of ketones with unactivated aryl chlorides and triflates [21]. It is still not known which phosphine is most effective for the arylation of individual ketones.



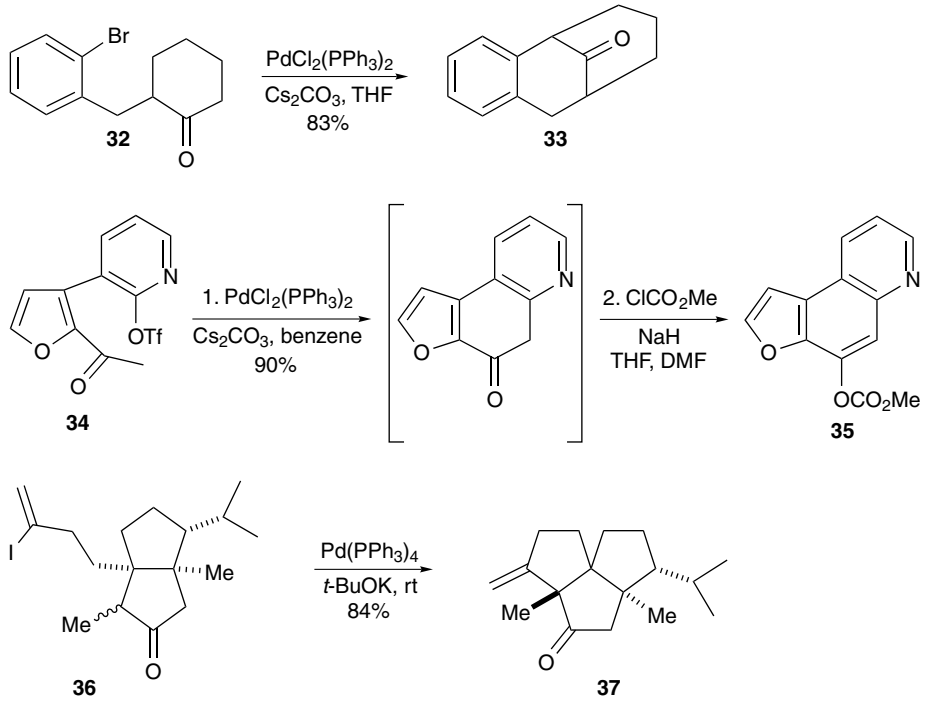
Buchwald and co-workers observed the persistent formation of 2-nitrophenols in an attempted arylation with reactive *o*-chloronitroarenes. They found an unusual effect of phenolic additives, and developed an annulative approach to highly substituted indoles. The arylation of acetophenone with 3-nitro-4-chlorobenzoate proceeded smoothly in the presence of 20 mol% 4-methoxyphenol and K_3PO_4 to give **25**, which was methylated without isolation. Reduction of the methylated ketone **26** with $TiCl_3$ afforded 2,3-disubstituted indole **27** in 61 % overall yield [22].



The arylation is explained by the following mechanism. Arylpalladium halides **28** are formed by oxidative addition of aryl halides. Then the arylpalladium enolates **30** are generated by transmetallation of **28** with alkali enolates of ketones **29**. Finally reductive elimination of the arylpalladium enolates **30** affords α-aryl ketones. Hartwig isolated the arylpalladium enolate complexes **31** of ketones, esters and amides, and confirmed formation of α-arylated products on heating [23].

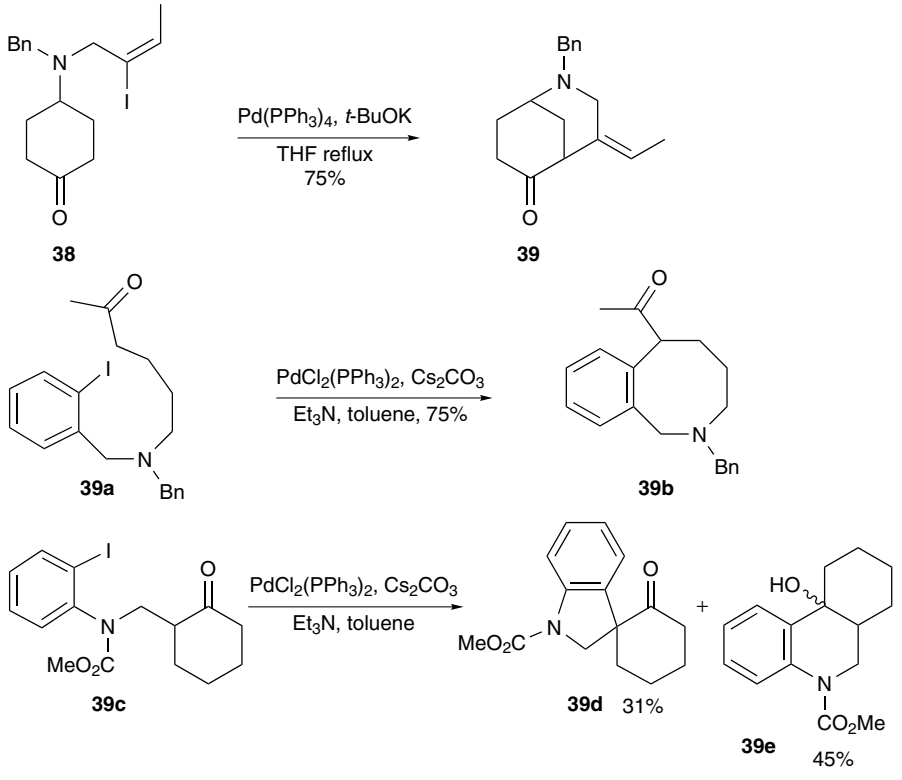


Facile intramolecular arylation using PPh_3 as a ligand was reported in 1988 by Ciufolni *et al*. [24]. Reaction of the bromo ketone **32** afforded the cyclic compound **33** [25]. Intramolecular arylation of the triflate **34** gave the heterocycle **35** [26]. Similarly, a Pd-catalyzed reaction of the ketone with the vinyl iodide in **36** yielded the cyclized product **37** in 84 % yield at room temperature using $Pd(PPh_3)_4$ as a catalyst by slow addition of *t*-BuOK to avoid competing alkyne formation [27].

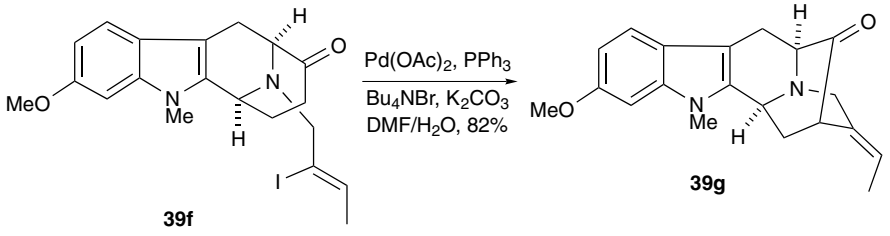


Sole and co-workers constructed the 2-azabicyclo[3.3.1]nonane framework **39** from the keto iodide **38** [28]. The group has observed two reaction paths in the

cyclization of amino-tethered aryl halides and ketones, namely attack to the ketone to give alcohols and the enolate arylation [29]. Cyclization of **39a** using PPh_3 and Cs_2CO_3 afforded the arylated ketone **39b** in 75 % yield in toluene. On the other hand, reaction of **39c** under similar conditions afforded the arylated ketone **39d** in 31 % yield and the alcohol **39e** in 45 % yield. The latter was formed by addition to the ketone. The intramolecular carbonyl attack by aryl halides has been discovered by Yamamoto recently, and the topic is treated separately in Chapter 3.7.2.

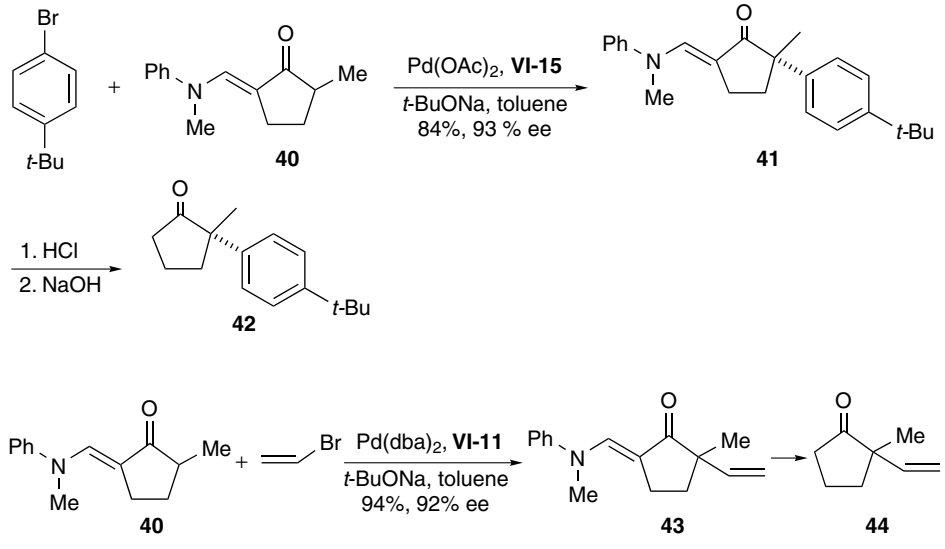


In the total synthesis of complex indole alkaloids, intramolecular alkenylation of the ketone **39f** was carried out successfully by Cook to give **39g** in 82 % yield [30].



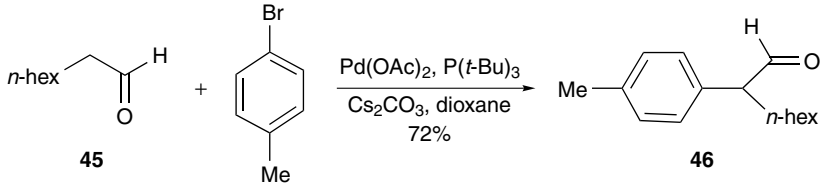
Arylation of the cyclopentanone derivative **40**, in which one of the α-carbons is protected as an enamine, with 4-bromo-*t*-butylbenzene using BINAP as a

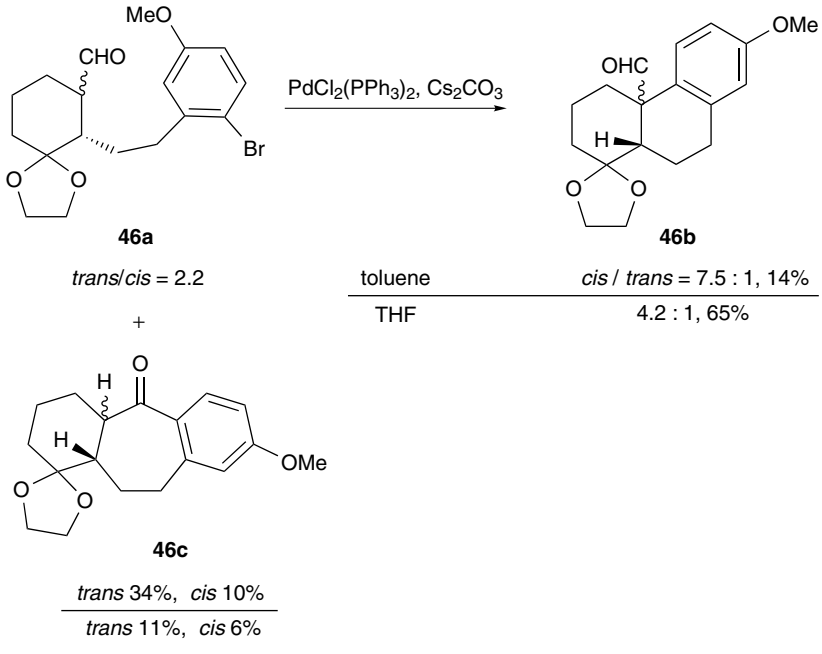
chiral ligand gave **41**. Deprotection of **41** afforded the the chiral α,α-disubstituted cyclopentanone **42** with 89 % ee [31]. The chiral ligand **VI-15** is highly effective and the arylation proceeded at room temperature to give **41** with 93 % ee [32]. Asymmetric α-alkenylation of ketones proceeds similarly. New phosphine ligands possessing both axial chirality and a chirogenic phosphorus center such as **VI-11** were prepared. Asymmetric vinylation of **40** gave **43** with 92 % ee by using **VI-11** as the chiral ligand, and **43** was converted to optically active 2-vinyl-2-methylcyclopentanone (**44**) [33].



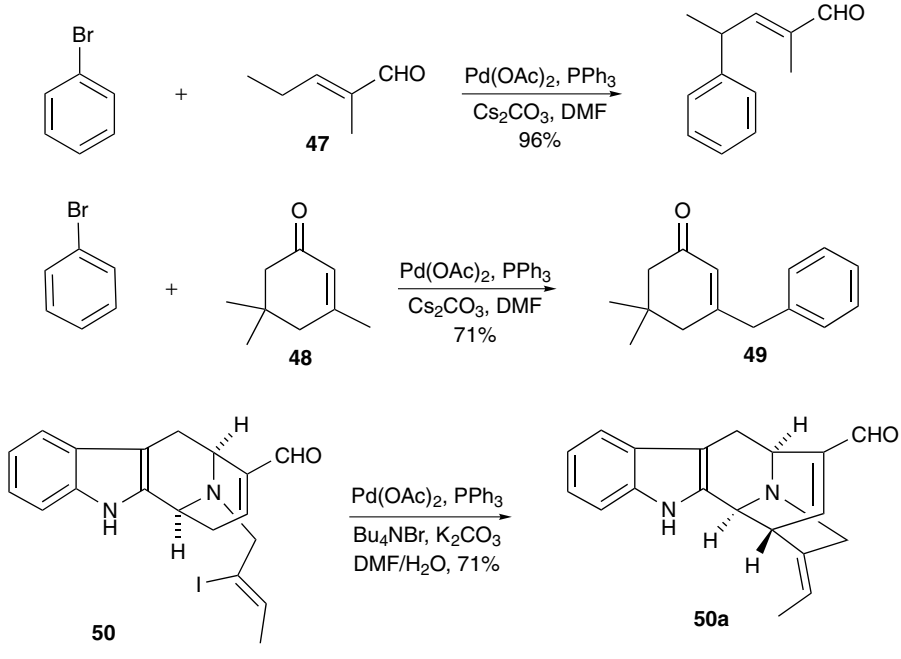
3.7.1.3 Arylation of Aldehydes and α,β-Unsaturated Carbonyl Compounds

Usually aldol condensation occurs first when arylation of aldehydes is carried out using PPh_3 as a ligand, and then γ-arylation of the aldol products takes place. Smooth α-arylation of the aliphatic aldehyde **45** with 4-bromotoluene afforded **46** when P(*t*-Bu)$_3$ as a ligand and Cs_2CO_3 as a base were used in dioxane without undergoing aldol condensation [34]. Intramolecular reaction of the secondary aldehyde **46a** afforded the arylation product **46b** as the main product in polar solvents such as THF, and mainly the ketone **46c** was obtained in toluene as a nonpolar solvent. In this reaction, use of Cs_2CO_3 gives satisfactory results, while Et_3N, NaH, *t*-BuONa, and KN(TMS) are ineffective [35].

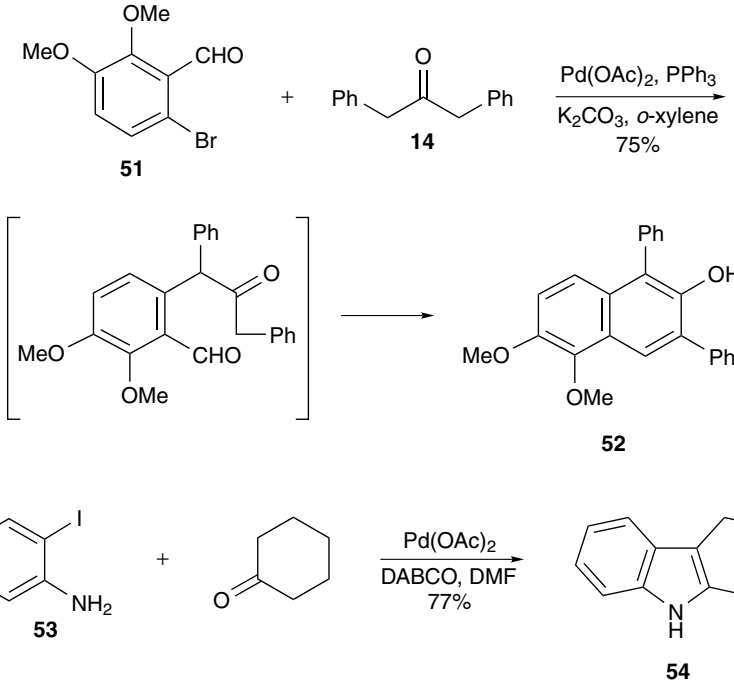




On the other hand, regioselective γ-arylation of the α,β-unsaturated aldehyde **47** and ketone **48** with bromobenzene takes place using PPh_3. For example, one of the methyl groups of isophorone (**48**) was regioselectively γ-arylated to give **49** without attacking the γ-carbon of the ring [36]. γ-Alkenylation of α,β-unsaturated aldehydes was successfully applied to the total synthesis of (+)-vellosimine. The α,β-unsaturated aldehyde **50** was γ-alkenylated intramolecularly and stereospecifically to afford **50a** in 71 % yield [37].

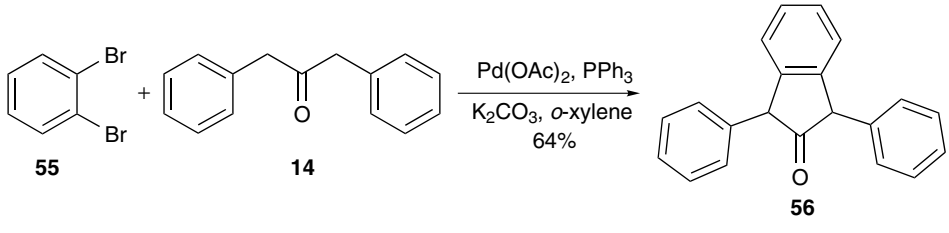


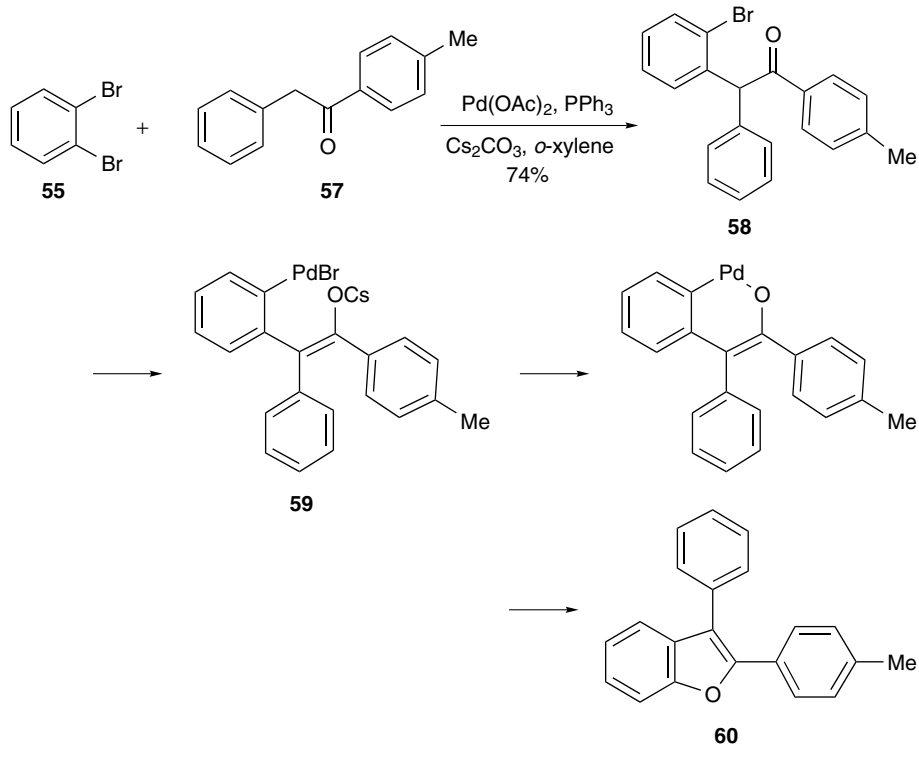
Various cyclic compounds can be prepared by the reaction of ketones with bifunctional aryl halides. The β-naphthol derivative **52** was obtained by α-arylation of dibenzyl ketone (**14**) with *o*-bromobenzaldehyde derivative **51**, followed by aldol condensation [38]. Also the indole derivative **54** was synthesized by the reaction of cyclohexanone with 2-iodoaniline (**53**). Formation of **54** may be explained by enamine formation at first, followed by intramolecular Mizoroki–Heck reaction, rather than via α-arylation [39].



1,2-Dibromobenzene (**55**) is a good building block for cyclic compounds. The indanone **56** was obtained as expected by diarylation of dibenzyl ketone (**14**). On the other hand, α-arylation of benzyl tolyl ketone (**57**) with **55** afforded **58**, and subsequent O-arylation of the enolate **59** gave the furan **60** [40].

By the reaction of α,β-unsaturated carbonyl compounds with the dibromide **55**, cyclization occurs by α-arylation, followed by intramolecular Mizoroki–Heck reaction. For example, reaction of verbenone (**61**) with **55** using PPh_3 generates **62** by γ-arylation of **61**, and subsequent intramolecular Mizoroki–Heck reaction affords the indane **63**. The benzocyclobutane **67** was obtained unexpectedly

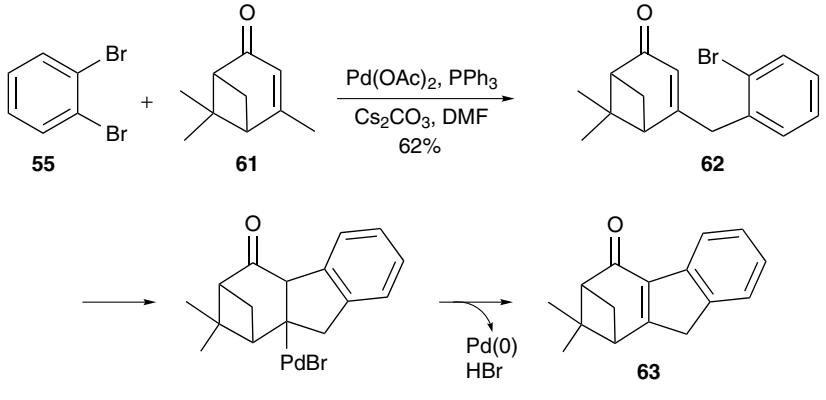


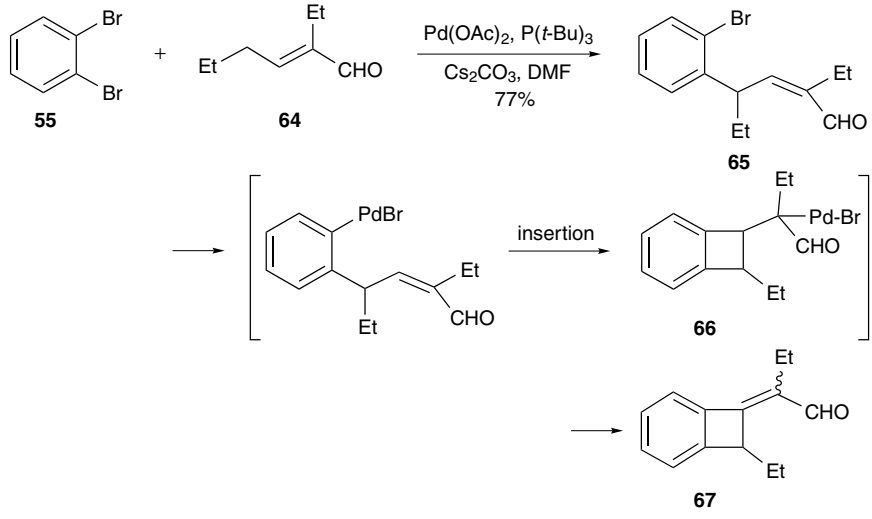


from the α,β-unsaturated aldehyde **64** via γ-arylation, followed by an interesting Mizoroki–Heck reaction to give the strained cyclobutane **67** via **66**, rather than a cyclopentane derivative. For this creation, P(t-Bu)$_3$ is a good ligand [40].

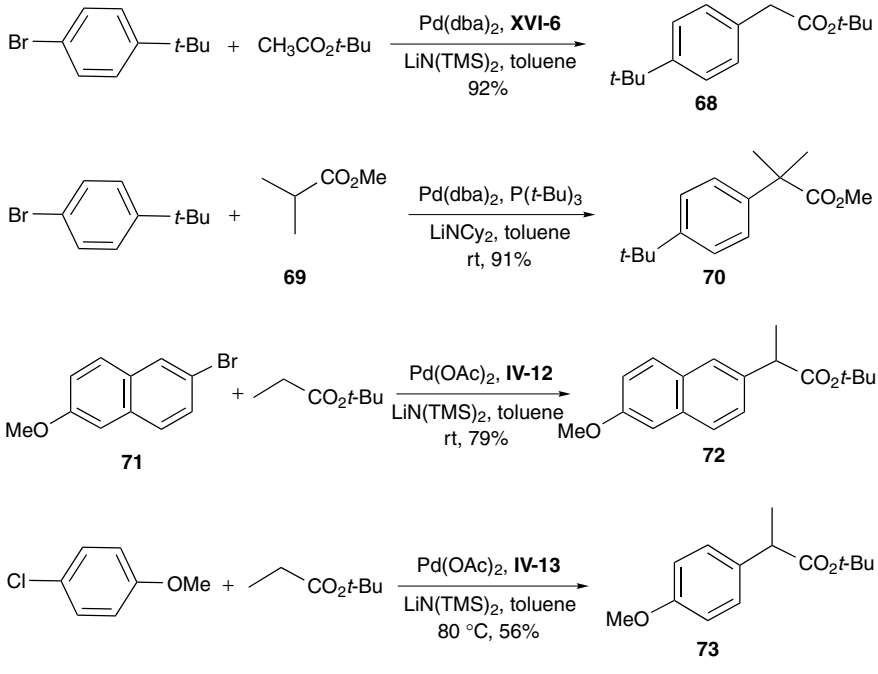
3.7.1.4 Arylation of Esters, Amides, and Nitriles

Direct α-arylation of esters had been regarded as impossible. New methods of facile α-arylation of esters and amides have been developed as useful synthetic methods by selection of appropriate ligands and bases [41]. Bulky and electron-rich ligands such as P(t-Bu)$_3$ and carbene ligand **XVI-6** are suitable, and NaN(TMS)$_2$, LiN(TMS)$_2$ and LiNCy$_2$ are used as bases. Use of t-butyl esters is recommended to minimize a

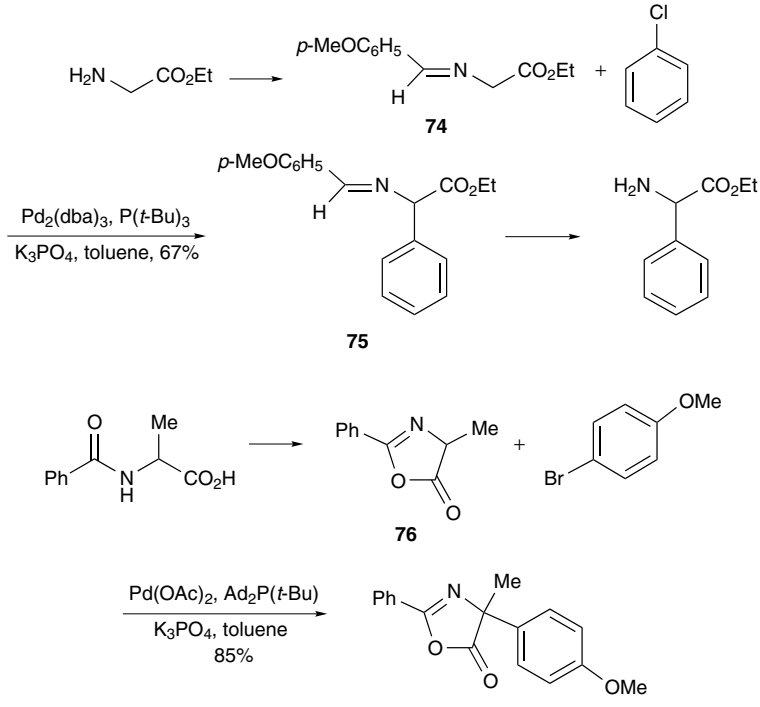




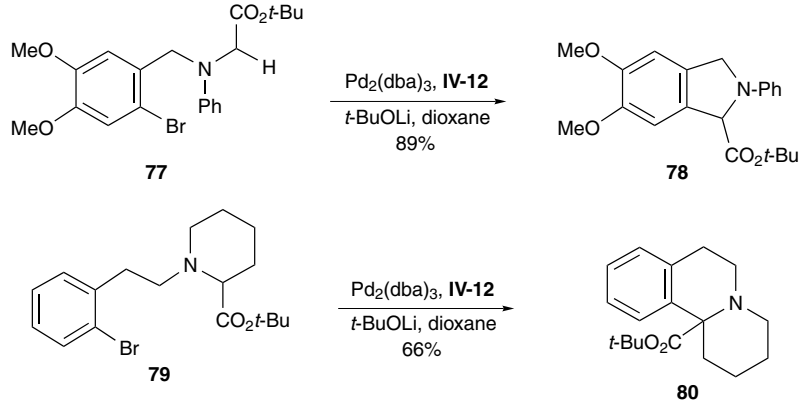
competing Claisen condensation. Arylation of *t*-butyl acetate gives *t*-butyl phenylacetate **68** in 92 % yield using carbene ligand **XVI-6**. Arylation of methyl isobutyrate (**69**) proceeded smoothly using P(*t*-Bu)$_3$ as a ligand and LiNCy$_2$ as a base at room temperature, and the quaternary carbon was constructed in **70** [42]. α-Arylated carboxylic acids (particularly α-arylacetic acid and propionic acid), such as naproxen and ibuprofen, are important medicinal compounds. These acids can be prepared easily by α-arylation of esters, followed by hydrolysis. For example, the naproxen derivative **72** was prepared by the reaction of *t*-butyl propionate with 2-bromo-6-methoxynaphthalene (**71**) using **IV-12** [43] or **XVI-6** as ligands [41]. Similarly, the ibuprofen derivative **73** was obtained by the arylation of *t*-butyl propionate with *p*-chloroanisole using **IV-13** [43].



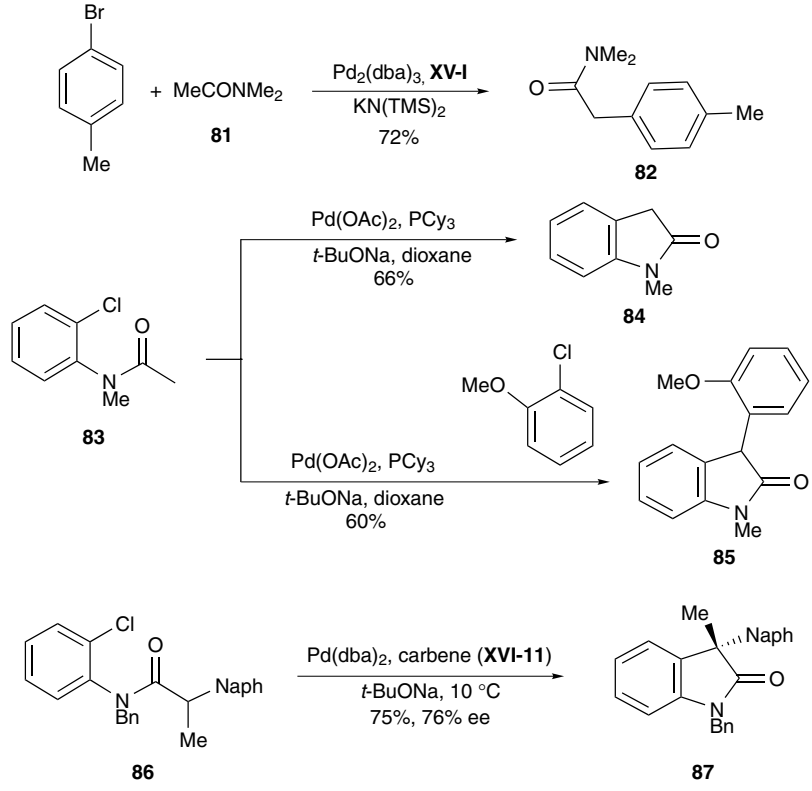
A new synthetic method for physiologically important unnatural α-aryl amino acids has been developed based on α-arylation of N-protected glycine ester. α-Arylation of ethyl glycinate **74**, in which the amino group is protected by benzylidenation, with aryl bromides and aryl chlorides using P(*t*-Bu)$_3$ as a ligand affords **75**. The subsequent hydrolysis gives α-phenylglycinate. No coupling was observed with α-substituted amino acid esters [41]. α-Arylated quaternary amino acids can be prepared by α-arylation of azlactones and hydrolysis. The azlactone **76**, derived from alanine, was arylated with *p*-bromoanisole in 85 % yield using bulky phosphines such as (*t*-butyl)diadamantylphosphine [Ad$_2$P(*t*-Bu)] [44].



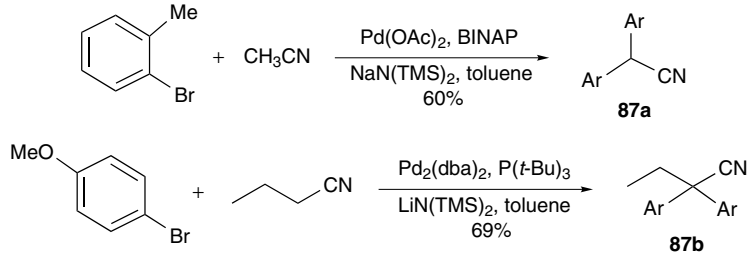
Intramolecular arylation of the amino acid ester **77** afforded the tetrahydroisoindole carboxylate **78**, and the tetrahydroisoquinoline carboxylate **80** was obtained from the amino acid ester **79**. In the cyclizations, ligand **IV-12** was used [45].



N,*N*-dialkylamides can be arylated. Arylation of dimethylacetamide (**81**) using BINAP as a ligand and $KN(TMS)_2$ as a base yields the phenylacetamide derivative **82** [46]. Intramolecular arylation proceeds more smoothly, and the oxindole **84** was prepared by intramolecular arylation of *N*-methyl-2-chloroacetanilide (**83**). For this reaction, PCy_3 as a ligand is superior to BINAP and P(*t*-Bu)$_3$. When the reaction was carried out in the presence of 2-chloroanisole, the 3-aryloxindole **85** was obtained by domino intramolecular and intermolecular arylations. Asymmetric cyclization of the amide **86** using chiral carbene **XVI-11**, derived from (+)-isobornylamine as a chiral ligand, gave the oxindole **87** in 75 % yield with 76 % ee [47].



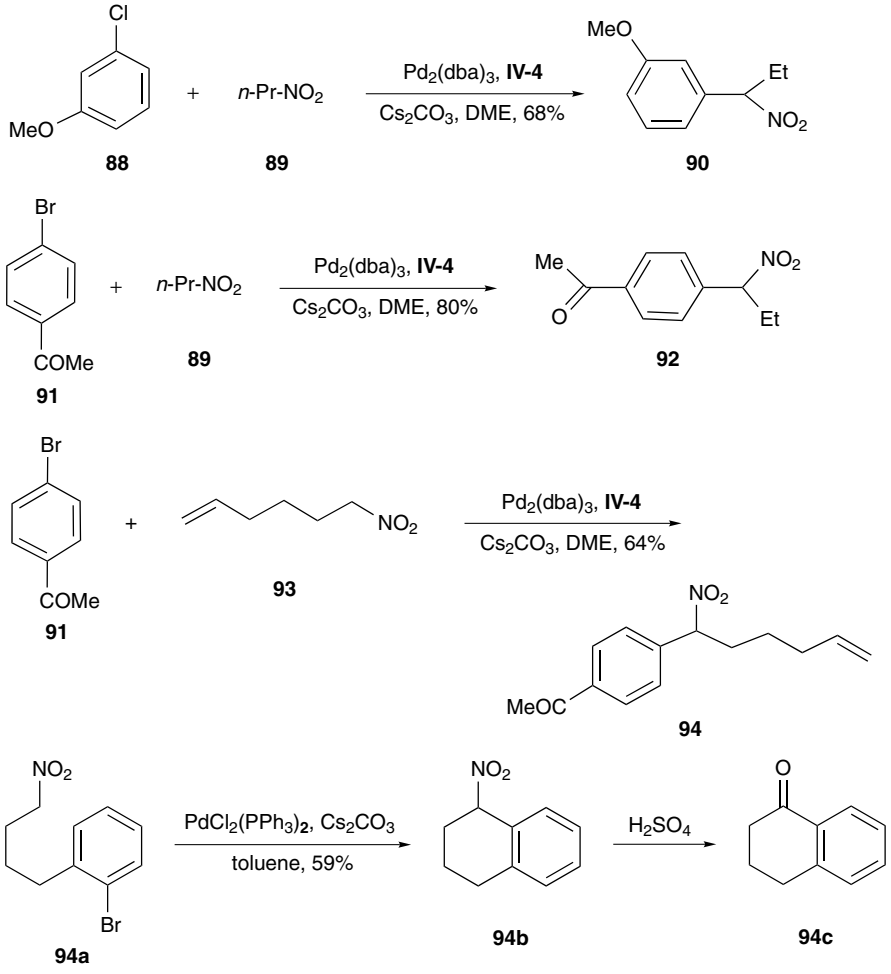
In general, in contrast to high reactivity of malononitrile for arylation, mononitriles are less acidic than ketones and hence less reactive. Hartwig reported, however, that α-arylation of nitriles is possible by using BINAP or P(*t*-Bu)$_3$ as a ligand. Diarylation of butyronitrile and acetonitrile occurred to give **87a** and **87b**



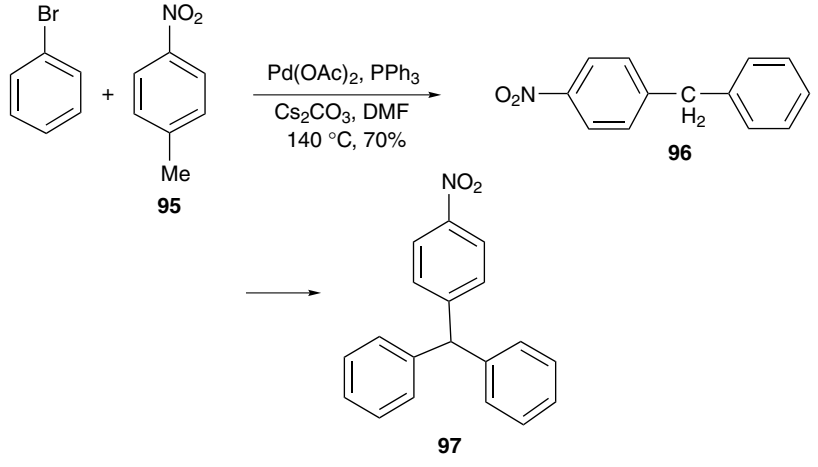
in preference to monoarylation, because monoarylated nitriles are more reactive than simple nitriles [48].

3.7.1.5 Arylation of Other Compounds Bearing Acidic Hydrogens

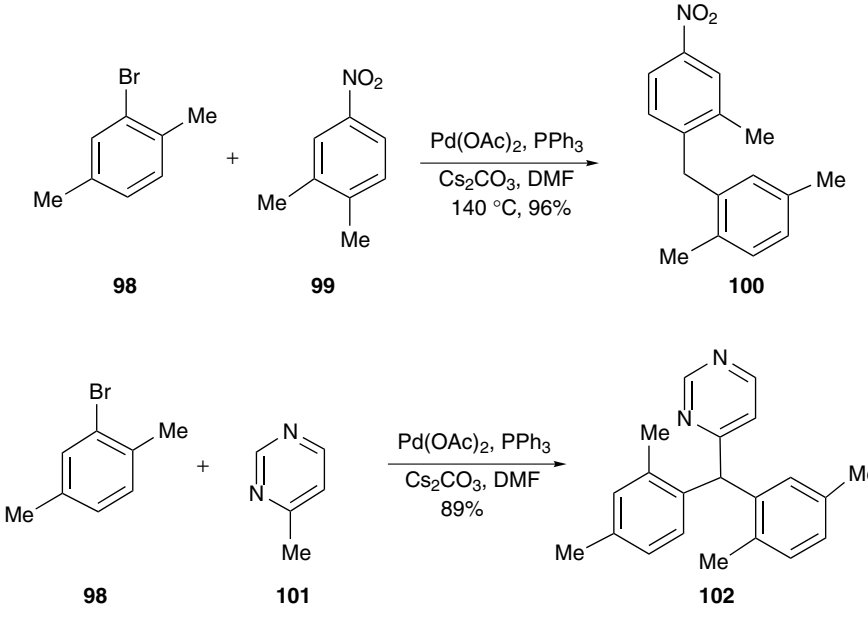
In addition to carbonyl compounds, nitro alkanes which have acidic hydrogens can be arylated with aryl bromides and chlorides using Cs_2CO_3 as a base [49]. Stronger bases are not suitable. It is important to use **IV-4** as a ligand. Interestingly this ligand is less active for the arylation of ketones. Only monoarylation takes place and no diarylation occurs. Reaction of 3-chloroanisole (**88**) and 4-bromoacetophenone (**91**) with nitropropane (**89**) afforded **90** and **92**. Arylation of the nitro alkene **93** with the electron-deficient bromide **91** gave **94** selectively and no Mizoroki–Heck reaction of the olefin occurred under the conditions used. Intramolecular arylation of the nitro alkane **94a**, followed by treatment of the primary product **94b** with sulfuric acid yielded the α-tetralone **94c** [35].



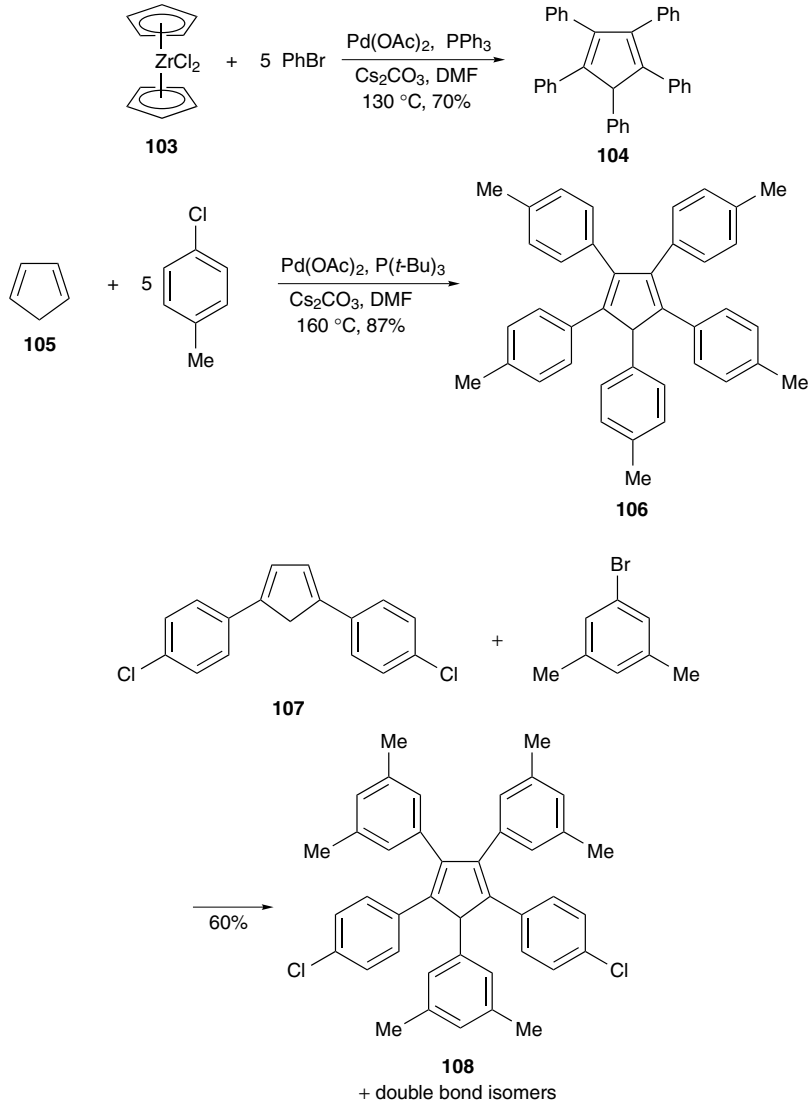
Furthermore, arylation of the methyl group of *p*-nitrotoluene (**95**) with bromobenzene occurs at 140 °C using Cs_2CO_3. As a ligand PPh_3 is effective [50]. Both the monophenylated product **96** and the diarylated one **97** were obtained selectively depending on the reaction conditions.



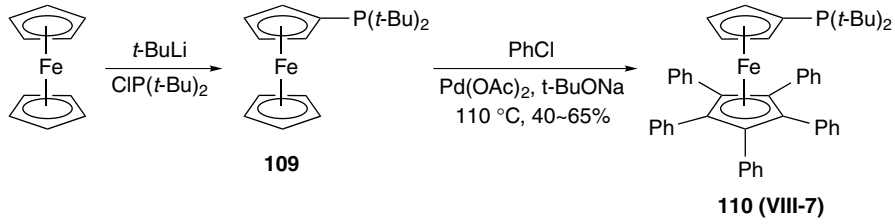
As expected, less activated 3-nitrotoluene was not arylated, and the monoarylated product **100** was obtained selectively from 3,4-dimethylnitrobenzene (**99**) and sterically hindered 2-bromo-1,4-dimethylbenzene (**98**). On the other hand, diarylation of 4-methylpyrimidine (**101**) with 2-bromo-1,4-dimethylbenzene (**98**) gave **102** smoothly. No arylation of 4-methylbenzonitrile occurs.



An interesting and efficient perarylation of metallocenes with aryl bromides has been reported by Miura *et al*. [51]. Typically, pentaphenylcyclopentadiene (**104**) was obtained in 70 % yield by reaction of zirconocene dichloride (**103**) with bromobenzene. Cs_2CO_3 is the best base in this reaction. The first phenylation to give phenylcyclopentadiene seems to proceed via transmetallation. Then, sequential perphenylation of the intermediary cyclopentadienyl anions leads to the product **104**. The pentaarylcyclopentadiene **106** was obtained in 87 % yield by the direct reaction of cyclopentadiene (**105**) with 4-chlorotoluene using *t*-Bu_3P as a ligand at a somewhat higher temperature of 160 °C. Also the 1,3-diarylated cyclopentadiene **107** was triarylated further with 5-bromo-1,3-dimethylbenzene to give the pentaarylated products **108** as a mixture of double bond isomers [52]. The reaction is useful as a simple synthetic method of pentaarylcyclopentadienes, which are used as bulky Cp ligands. The bulky Cp complexes have considerable importance because their catalytic activity is different from non-substituted Cp complexes [53].



Interestingly, di-*t*-butylpentaphenylferrocenylphosphine **110**(**VIII-7**) was prepared via direct pentaphenylation of a ferrocenyl phosphine without decomposition of the complex. First, di-*t*-butylphosphinoferrocene (**109**) was prepared, and its reaction in neat chlorobenzene afforded **110** in 40–65 % yield. The reaction may be explained by arylation via C—H bond activation by Pd coordinated to P(*t*-Bu)$_3$ [54].

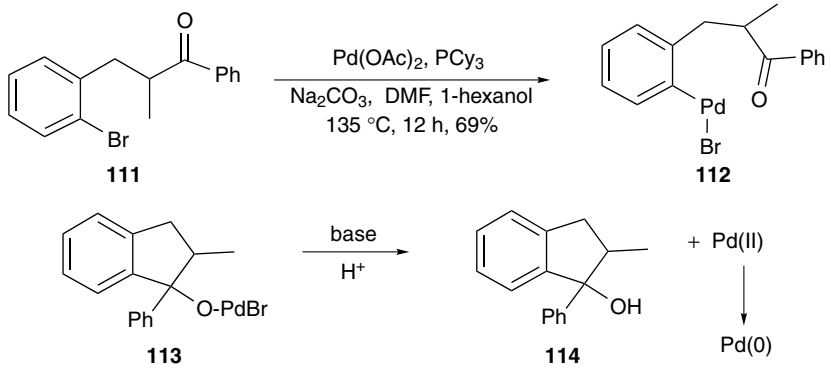


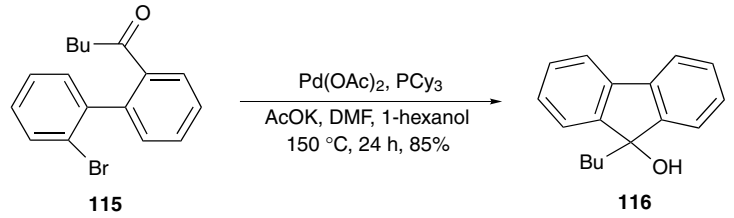
Facile *ortho*-arylation of phenols is known; this is covered in Chapter 3.3.

3.7.2 Intramolecular Attack of Aryl Halides on Carbonyl Groups

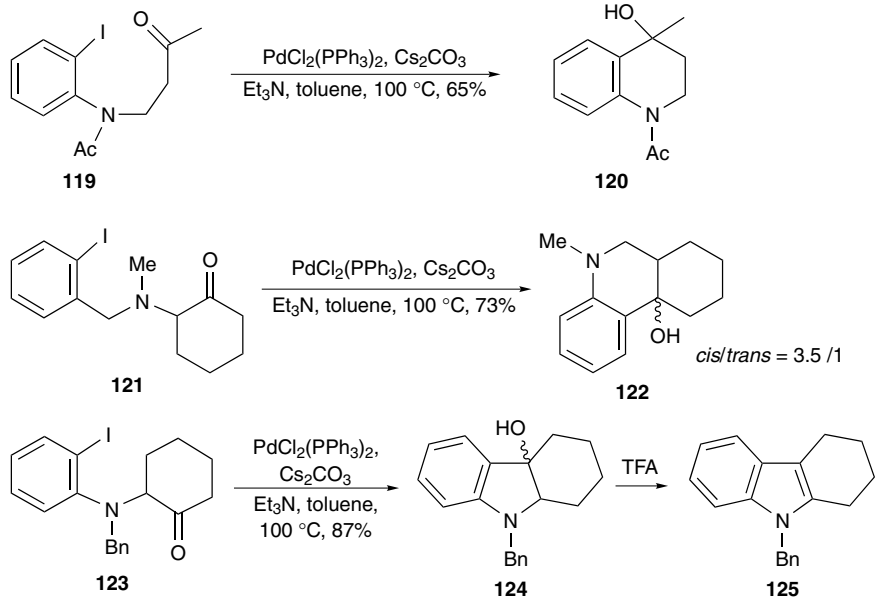
It has been well-established that organopalladium intermediates are electrophilic, and clearly different from other organometallic compounds such as Grignard reagents which are nucleophilic. It is highly desirable to achieve a catalytic version of Grignard reactions. Yamamoto and co-workers reported a 'formal' Pd-catalyzed Grignard-type reaction [55]. They obtained the cyclopentanol **114** in 69 % yield by the reaction of the phenyl ketone **111** in the presence of Pd(OAc)$_2$, PCy$_3$, and Na_2CO_3 in DMF. PPh_3 is not effective. Furthermore, addition of 1-hexanol (5 equiv.) was crucial. The reaction is explained by nucleophilic attack of the Pd intermediate **112** to form **113**, from which the cyclopentanol **114** is provided. At the same time Pd(II) is generated and reduced to Pd(0) probably with 1-hexanol. Similarly the cyclopentanol **116** and the cyclohexanol **118** were obtained from the bromo ketones **115** and **117**.

The reaction proceeds at high temperature (ca. 150 °C). Interestingly no α-arylation of ketones occurred under these conditions. Also, bromides gave better results than iodides.

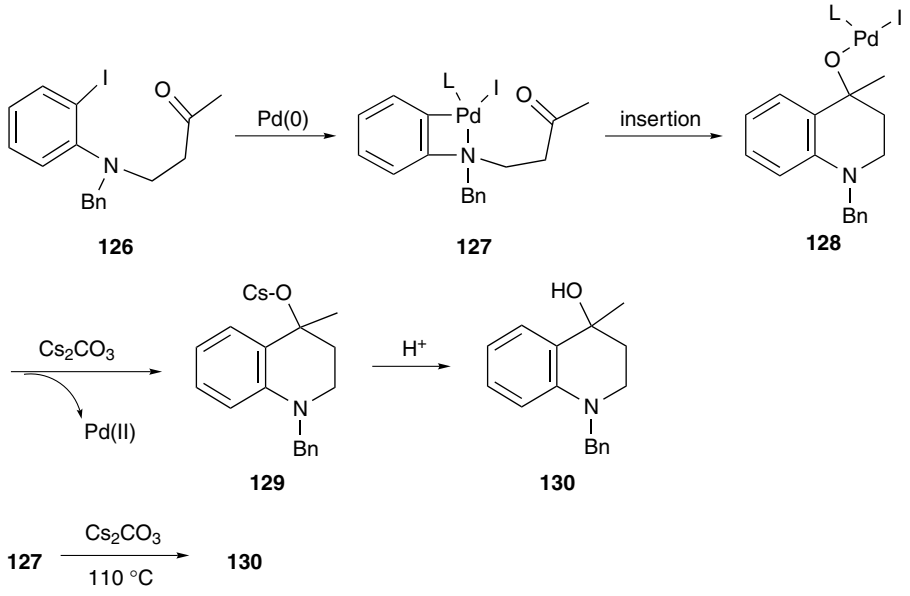




Sole and co-workers found the smooth carbonyl addition reaction of amino-tethered aryl iodides and ketones [29]. Treatment of the 2-iodoanilino ketone **119** with PPh_3, Et_3N and Cs_2CO_3 in toluene afforded the alcohol **120**. The cyclized product **122** was obtained from 2-iodobenzylamino ketone **121**. The cyclized product **124** of the iodo ketone **123** was converted to the indole derivative **125** in high yield by acid-catalyzed dehydration. In these reactions, no α-arylation was observed.



The tethered amino groups seem to play an important role. In the mechanistic studies, the rare four-membered palladacycle **127** was isolated in high yield as a stable compound by treatment of the iodoaniline-derived ketone **126** with $Pd(PPh_3)_4$, and converted to the alcohol **130** in high yield on heating with Cs_2CO_3. The cyclization is explained by the formation of the complex **127**, which makes insertion of the C=O bond (or carbopalladation) to form the Pd alkoxide **128** easier. The alcohol **130** and Pd(II) are generated by the reaction of **128** with Cs_2CO_3 via **129**.



So far, these Pd-catalyzed Grignard-type reactions are limited to intramolecular versions to form five- and six-membered alcohols. Further extension and mechanistic studies are highly desirable.

Also, it should be added that β-carbon elimination is the reverse process of these reactions (see Chapter 3.8.2).

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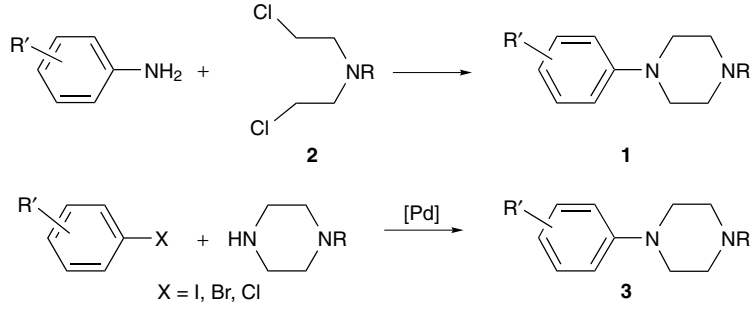
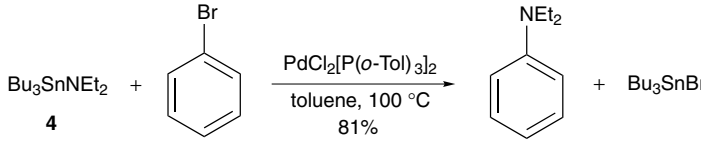
3.7.3 Arylation of Nitrogen Nucleophiles

3.7.3.1 Introduction

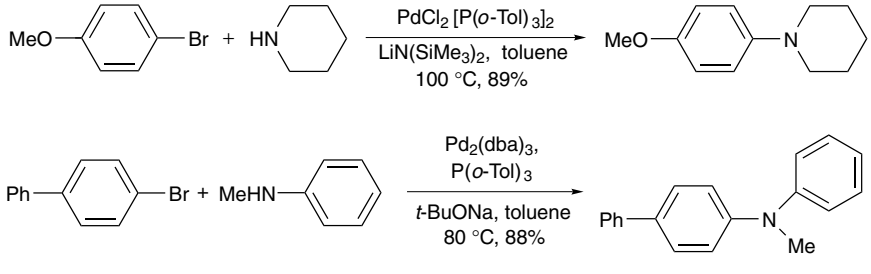
Preparation of aromatic amines by the reaction of aryl halides with aliphatic and aromatic amines has been regarded as a difficult reaction. Recently a facile synthetic method for aromatic amines by amination of aryl halides has been discovered, and rapid progress has occurred in the Pd-catalyzed reaction of amines with aryl halides [1]. One simple example which shows the usefulness of the new method is cited here. The commercially important arylpiperazines **1** have been synthesized by intramoleular N-alkylation of aniline derivatives with *N*,*N*-di-(2-chloroethyl)amine (**2**), which is highly carcinogenic. Now the amines **3** can be prepared efficiently by coupling aryl iodides, bromides or chlorides with N-substituted piperidines. This example provides a big contribution to synthetic chemistry by the new Pd-catalyzed efficient preparative method for arylamines, which are useful in medicinal and material chemistry.



The first report on the Pd-catalyzed preparation of arylamines by the reaction of aryl bromides with *N*,*N*-diethylaminotributyltin (**4**) was given by Kosugi *et al.* in 1983. A poor result was obtained with aryl iodides. In this reaction, bulky P(*o*-Tol)$_3$ was used as the most suitable ligand [2].

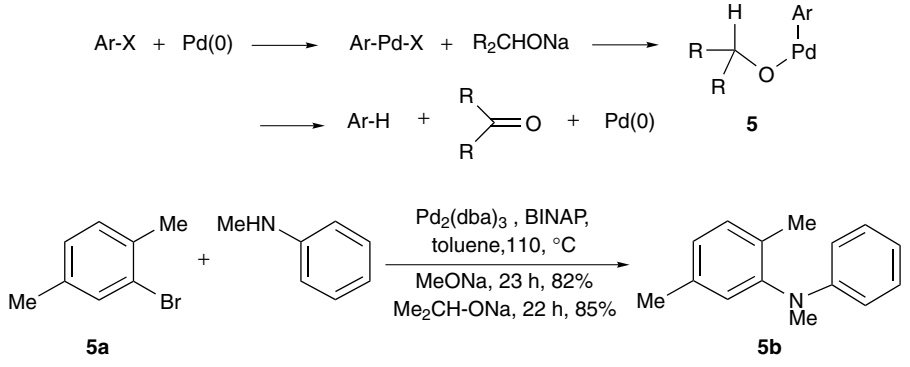


Reinvestigation of the Kosugi and Migita reaction was carried out by the Buchwald and Hartwig groups leading to the discovery of a tin-free synthetic method for arylamines based on the Pd-catalyzed reaction of aryl bromides with amines using P(*o*-Tol)$_3$ as a ligand [3,4].



The success of the new method is due to selection of bases which are stable under the reaction conditions and also the use of bulky phosphine ligands. Later, reductive elimination was found to be crucial in the C—N bond formation, which is accelerated by bulky ligands. As bases, $MN(TMS)_2$ (M = Li, Na, K) and *t*-BuONa give good results. Alkoxides such as MeONa, EtONa, and *n*-BuONa seem to be unsuitable, because oxidation of alcohols and reduction of aryl halides occur via facile β-H elimination of the palladium alkoxide **5**.

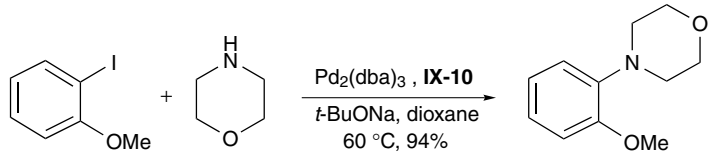
t-BuONa is a good base. Formation of aryl *t*-butyl ether to some extent is competitive with arylamine formation. Reductive elimination of Ar-Pd-O-*t*-Bu to form aryl *t*-butyl ethers is slower, and the amine formation takes place preferentially. But, interestingly Prashad *et al*. reported that β-hydrogen-containing alkoxides such as MeONa and sodium isopropoxide can be used satisfactorily in the amination as a base even at 110 °C [5]. Amination of the bromide **5a** with *N*-methylaniline proceeded smoothly to give the diarylamine **5b** in good yields using MeONa and BINAP as a ligand. Surprisingly even sodium isopropoxide can be used so that easier oxidation to acetone is expected.



5a **5b**

Aryl iodides, bromides, chlorides, triflates and some tosylates are used for the arylamine synthesis. Secondary (dialkyl, alicyclic, alkyl–aryl, and diarylamines) and primary amines (alkyl and arylamines) participate in the reaction with different reactivity. In general, more basic and less bulky amines react faster.

Generally aryl bromides are better substrates than aryl iodides. A disappointing result was obtained in the reaction of aryl iodides when **IV-1** was used as a ligand. Satisfactory results were obtained by using **IV-2, IV-12** and xantphos (**IX-10**). Reaction of *o*-iodoanisole **5c** with morpholine using **IX-10** provided **5d** in 94 % yield [6].

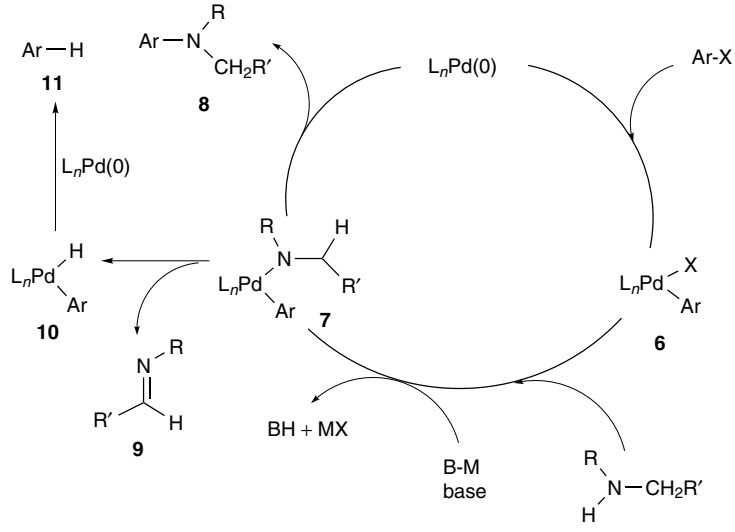


5c **5d**

Also it is important to consider that reactivity of halides is dependent on whether aryl groups are electron-deficient, neutral or electron-rich. Electron-deficient aryl

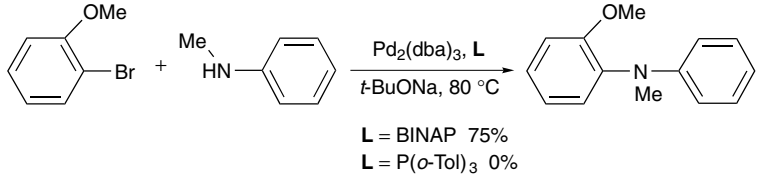
halides have higher reactivity. Less reactive electron-rich aryl halides have considerable practical importance and optimum conditions must be found for the reaction of these aryl substrates. Therefore, proper ligands and bases should be selected carefully for each amine and aryl substrate.

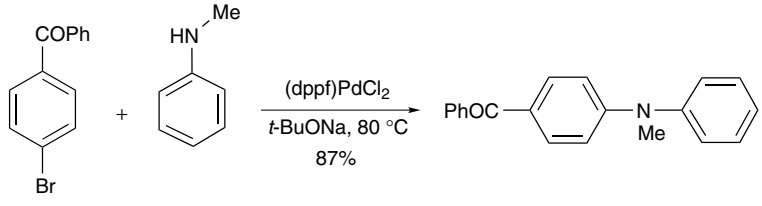
Mechanism of the arylamine formation is the following. Oxidative addition of aryl halide generates the arylpalladium **6**, to which an amine coordinates. Abstraction of proton from the coordinated amine with a base (BM) affords the arylpalladium amide **7**, and its reductive elimination yields the arylamine **8**. Reductive elimination of **7** is a rate-determining step. A path, competitive to the path from **7** to **8**, is β-H elimination to give the imine **9** and the Pd hydride **10**, and the reduced arene **11** is formed by reductive elimination of **10**. This is a serious side reaction. The elimination of β-H may be minimized by the use of chelating ligands.



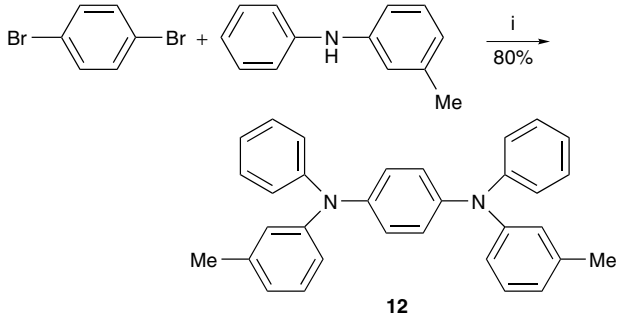
3.7.3.2 Importance of Bulky and Electron-Rich Phosphines

Bidentate phosphine ligands such as BINAP and DPPF were found to give much better results than P(*o*-Tol)$_3$ in the reaction of *N*-methylaniline with electron-rich aryl bromides as shown by the following examples [7,8].





However, the bidentate ligands are not always effective. An important discovery by Koie and co-workers in 1998 that bulky and electron-rich P(*t*-Bu)$_3$ is an excellent ligand for amination of aryl bromides has had a big impact on this research area. More importantly, even aryl chlorides react with amines using this ligand [9]. Preparation of triarylamines **12** and **13** by coupling aryl halides with diarylamines can be carried out smoothly using P(*t*-Bu)$_3$, . Known ligands P(*o*-Tol)$_3$ and BINAP gave poor results in the same reactions. *N*-(3-methylphenyl)diphenylamine (**13**) was prepared in 99 % yield, but the yield was 5 % when P(*o*-Tol)$_3$ was used and 0 % with BINAP. Amination of electron-rich aryl bromides and chlorides was carried out at room temperature with this ligand [10]. Recently, air stable, sterically hindered pentaphenylferrocenyl di-*t*-butylphosphine (**VIII-7**) has been synthesized, which creates a remarkably active catalyst. Triphenylamine was prepared in 86 % yield by coupling chlorobenzene with diphenylamine using this ligand [11].



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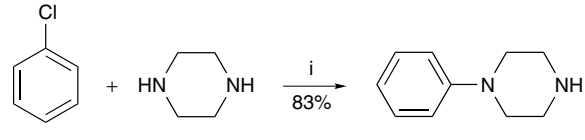
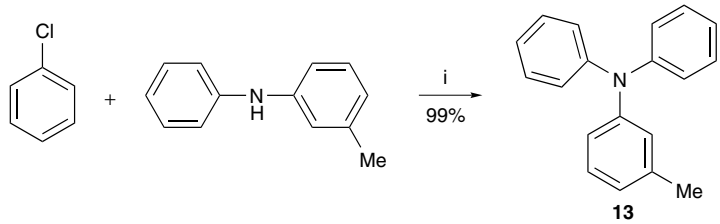
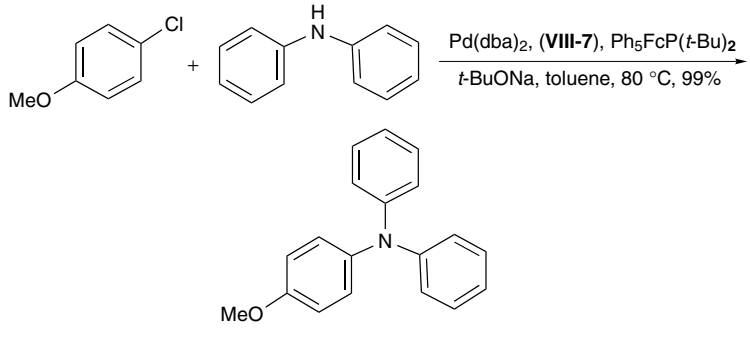




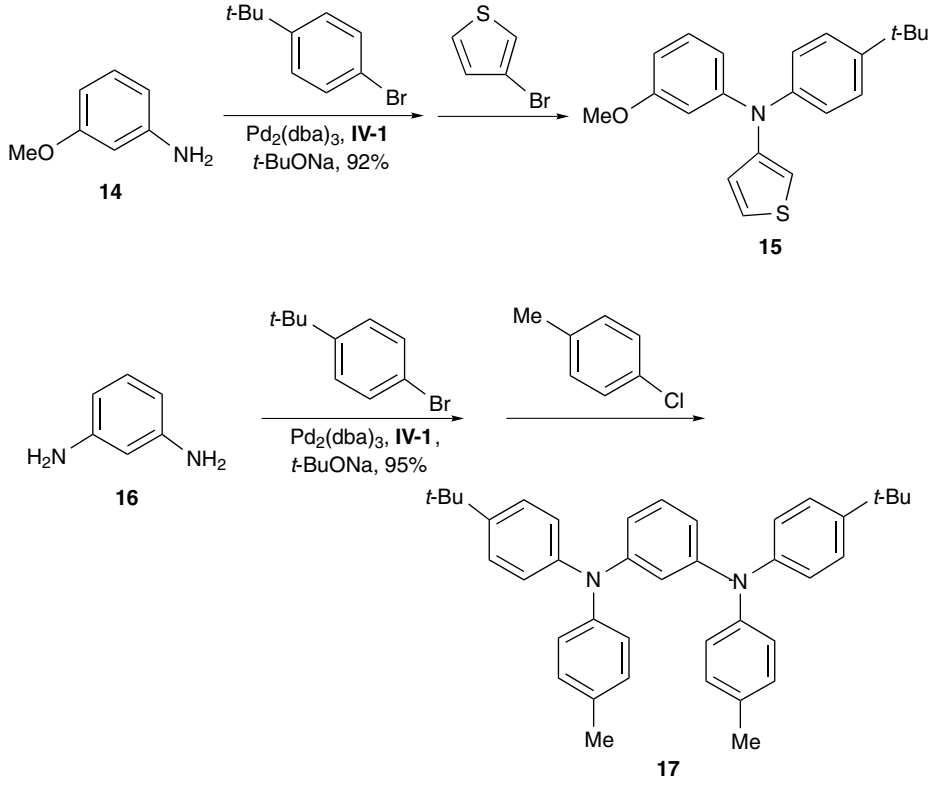
13

i = Pd(OAc)$_2$, P(*t*-Bu)$_3$, *t*-BuONa, xylene, 120 °C

Pd(OAc)$_2$, P(*o*-Tol)$_3$, *t*-BuONa, xylene, 120 °C = 5% yield



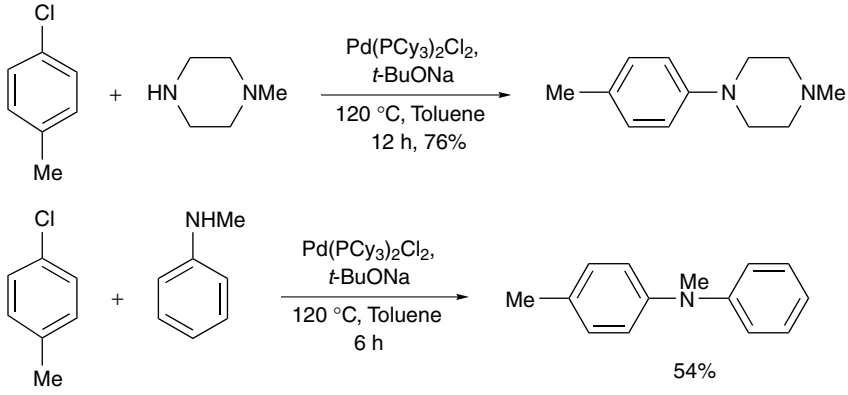
The use of P(*t*-Bu)$_3$ was an important discovery, because this phosphine has scarcely been used as a ligand of active transition metal catalysts. It was believed that P(*t*-Bu)$_3$ is too bulky for stable coordination. It is known that only two molecules of P(*t*-Bu)$_3$ can coordinate to Pd to form the highly coordinatively unsaturated, but stable bis(tri-*t*-butyl)phoshinepalladium complex [12]. This complex is commercially available as a good precursor of active Pd catalysts. Inspired by the discovery that P(*t*-Bu)$_3$ is an important ligand, several researchers have synthesized a number of electron-rich and bulky phosphine ligands. For example, the asymmetric triarylamine **15** was prepared from 3-methoxyaniline (**14**) using the biphenylylphosphine **IV-1** in a one-pot reaction. Similarly, the arylamine **17** was prepared by one-pot, step-wise arylation of *m*-diaminobenzene (**16**) [13].



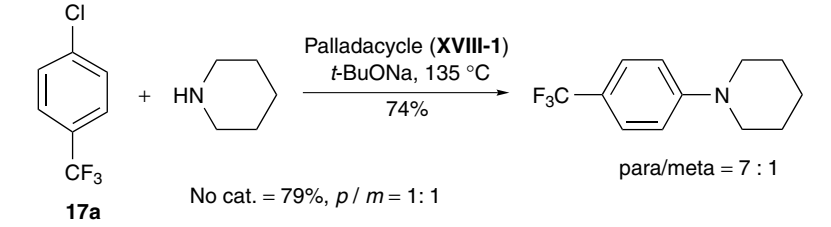
In 1997, Reddy and Tanaka discovered that aryl bromides and even aryl chlorides are aminated using PCy_3 as a ligand [14]. Beller *et al*. found that the palladacyle **XVIII-1** (the Herrmann complex) is active for the amination of electron-deficient aryl chlorides [15].

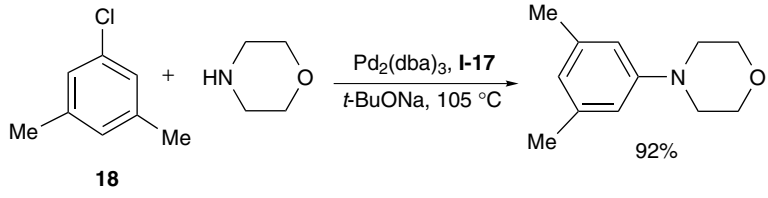
Reaction of *p*-chlorotrifluorobenzene **17a** with piperidine using palladacycle **XVIII-1** was carried out to give the coupled product with high regioselectivity, mainly a *para* isomer as expected. On the other hand, the reaction proceeded without the Pd catalyst, but *para* and *meta* products were obtained in equal amounts presumably via benzyne intermediate.

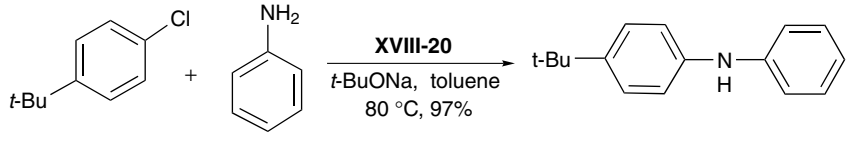
Also aryldicyclohexylphosphine **I-17** with a rigid cyclic acetal catalyzed amination of the aryl chloride **18** [16]. Zim and Buchwald reported that the air and

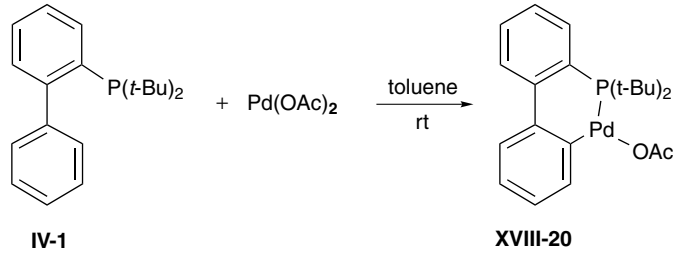


thermally stable palladacycle **XVIII-20**, prepared by the treatment of biphenylylphosphine **IV-1** with $Pd(OAc)_2$, is an active one-component catalyst for the amination of aryl chlorides. The complex is commercially available. More importantly, they found that, in addition to commonly used *t*-BuONa, bases such as MeONa and even KOH are effective bases in the amination of chlorides when this catalyst is used [5,17].







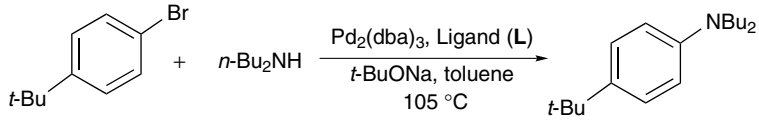


It is interesting to compare cone angles of monophosphines as a measure of their bulkiness [18]:

$$P(n\text{-Bu})_3 = 132^\circ; \quad PPh_3 = 145^\circ; \quad PCy_3 = 170^\circ;$$
$$P(t\text{-Bu})_3 = 182^\circ; \quad P(o\text{-Tol})_3 = 194^\circ.$$

It is commonly recognized that electron-rich phosphines facilitate oxidative addition of aryl chlorides and bromides, and bulky phosphines accelerate reductive elimination. From these considerations, $P(t\text{-Bu})_3$ is one of the best ligands. 'Bulky' and 'electron-rich' are key words in discovering good ligands for active catalysts.

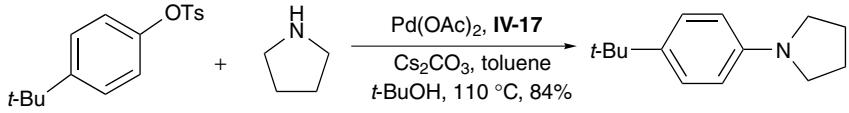
Amination of iodides and bromides proceeds in DME at room temperature using **IV-12** [19,20]. Reaction of *p*-bromo-*t*-butylbenzene (**19**) with dibutylamine, which is relatively less reactive, was carried out to afford **20** using several ligands, and it was found that BINAP, DPPF, and BPPFA are poor ligands. On the other hand, $P(o\text{-Tol})_3$, PPFA (**VIII-9**), and PPF-OMe (**VIII-11**) gave good results [21].

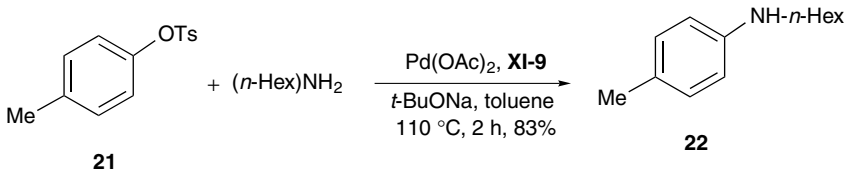


19 **20**

L = P(*o*-Tol)$_3$: 48 h, 83%
L = (*rac*)-PPFA (**VIII-9**) : 24 h, 92%
L = (*rac*) PPF-OMe (**VIII-11**) : 5 h, 97%

Tosylates are not reactive partners of amination. Even $P(t\text{-Bu})_3$ is not effective. Buchwald reported that amination of tosylates and benzene sulfonates with various amines proceeded smoothly by using biphenyl-based phosphine **IV-17** in the presence of Cs_2CO_3 [21a]. Bidentate ferrocenyl ligands, Dt-BPF (**XI-4**), **XI-9**, and **XI-10** are effective not only for aryl chlorides, but also for aryl tosylates **21** to give **22** [22].

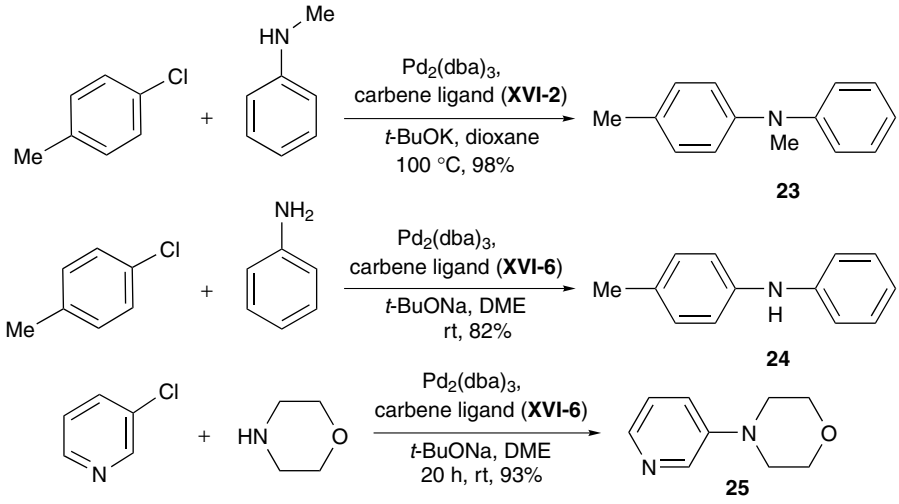




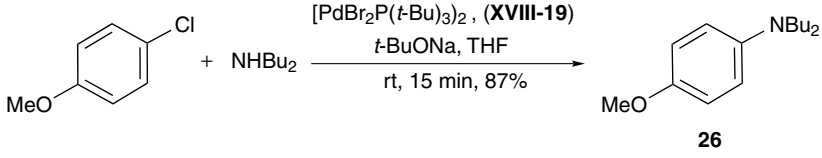
21 **22**

Another good ligand is carbene **XVI-6**, and its derivatives. Synthesis of these carbene ligands is rather simple. Pd–carbene complexes prepared *in situ* are active catalysts. For example, reaction of chlorotoluene with *N*-methylaniline was carried out at 100 °C using the imidazol-2-ylidene complex **XVI-2** to give **23** in

high yield [23]. The Pd complex of **XVI-2** is an air and moisture-stable complex and shows a remarkable insensitivity to oxygen and water. Amination of aryl bromides and chlorides with a variety of amines proceeds under mild conditions by utilizing the complex as a catalyst [24]. The dihydroimidazole carbene complex **XVI-6** is more active and the reaction of chlorotoluene with aniline proceeded even at room temperature to afford 4-methyldiphenylamine (**24**) in 82 % yield [25]. Usually, but not always, reactions of aryl halides with amines proceed at an elevated temperature when phosphine ligands are used. It is claimed that Pd-catalyzed reaction of 3-chloropyridine with amines is very slow when monodentate phosphines are used due to stronger coordination of pyridine to Pd. The reaction with morpholine proceeded smoothly at room temperature by using **XVI-6** to afford **25** in 93 % yield. This means that the carbene ligand coordinates to Pd more strongly than phosphines and pyridine. However, amination of 3-bromo-, 2-chloro-, 4-chloropyridines, and 2-chloropyrimidine with heterocyclic amines has been reported to proceed smoothly using xantphos (**IX-10**) as a ligand and either Na_2CO_3 or Cs_2CO_3 as a base [26].

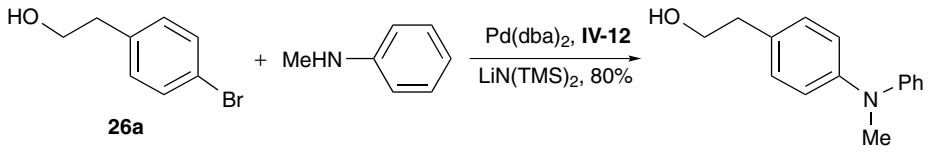


Commercially available and stable monoligated complex **XVIII-19** is a very active catalyst, and coupling of *p*-chloroanisole with dibutylamine proceeded at room temperature in 15 min to give the aminated product **26** in 87 % yield [27]. The catalyst is also active for amination of aryl bromides with hindered N-alkyl-substituted anilines [28].



Amination of aryl halides containing OH, amide, or enolizable keto groups can be carried out without protection of these functional groups by the use of bulky

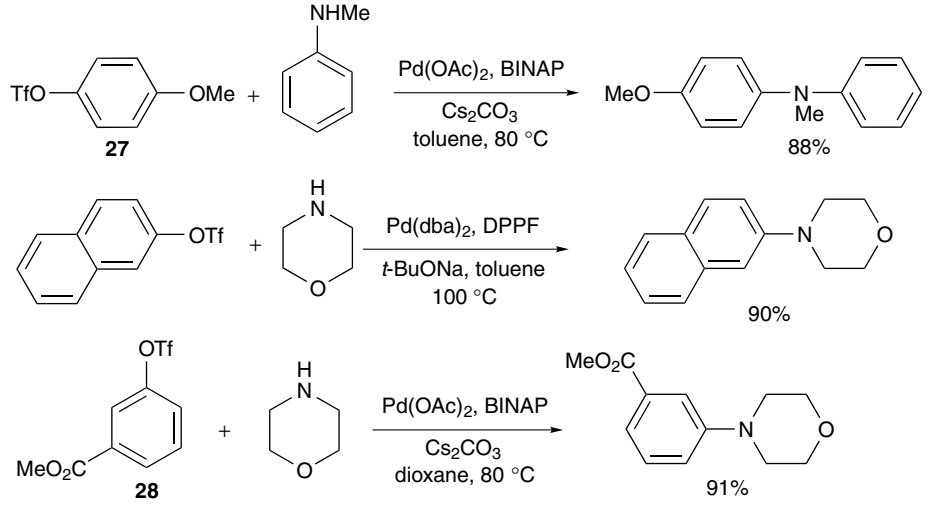
ligand **IV-12** and 2.2 equivalents of $LiN(TMS)_2$ as a base as shown by the reaction of *p*-bromo(2-hydroxyethyl)benzene (**26a**) [29].



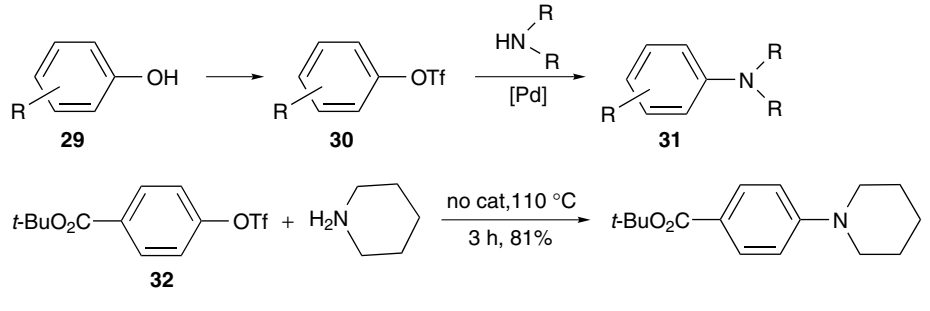
3.7.3.3 Arylation of Various Amines

Aryl chlorides have been regarded as inert substrates in catalytic reactions. Recent developments in facile Pd- and Ni-catalyzed reactions of aryl chlorides, which are cheaper than iodides and bromides, have made a big impact on the chemical industry.

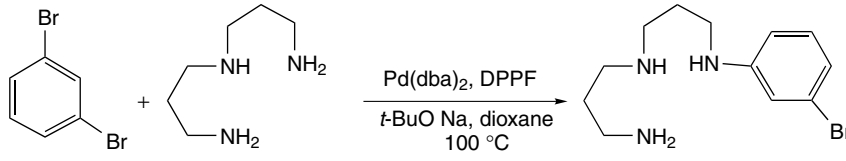
Aryl triflates react with amines using BINAP and DPPF (**XI-1**) as ligands and Cs_2CO_3 as a base. *t*-BuONa can not be used for some reactive triflates **27** and **28**, because they tend to be decomposed with this base [30].



On account of the facile amination of triflates, arylamines **31** can now be prepared from phenols **29** via their triflates **30**. It should be added that electron-deficient aryl triflates **32** can be aminated without a catalyst [31,32].

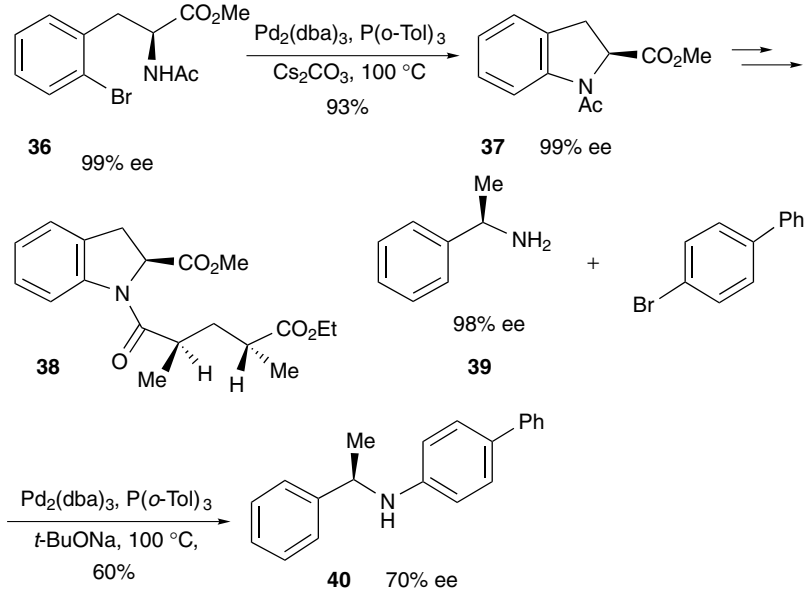


Selective monoamination of *ortho-, para-*, and *meta*-dibromobenzenes **33** with the polyamine **34** took place using DPPF (**XI-1**) as a ligand to give **35** in a reasonable yield even in the presence of an excess of the polyamine without giving the diamination product. In addition, selective monoarylation of the primary amine moiety in the polyamine **34** was observed [33].

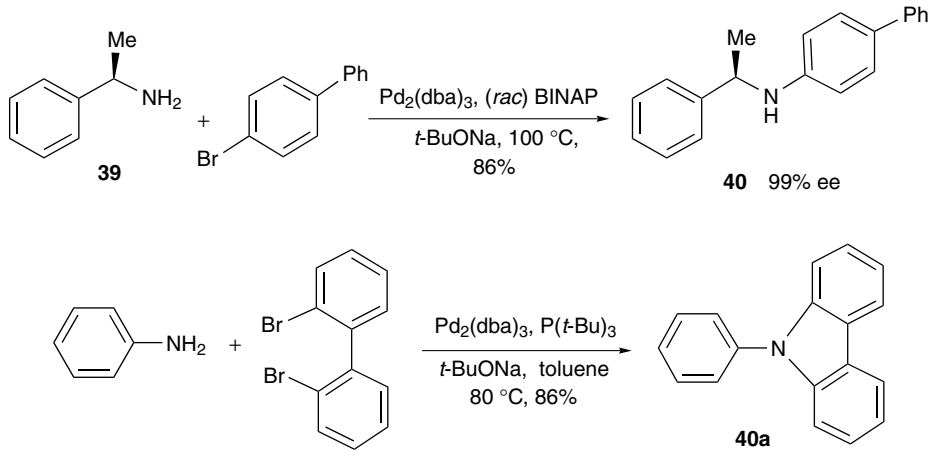


33 1 mmol **34** 3 mmol **35**

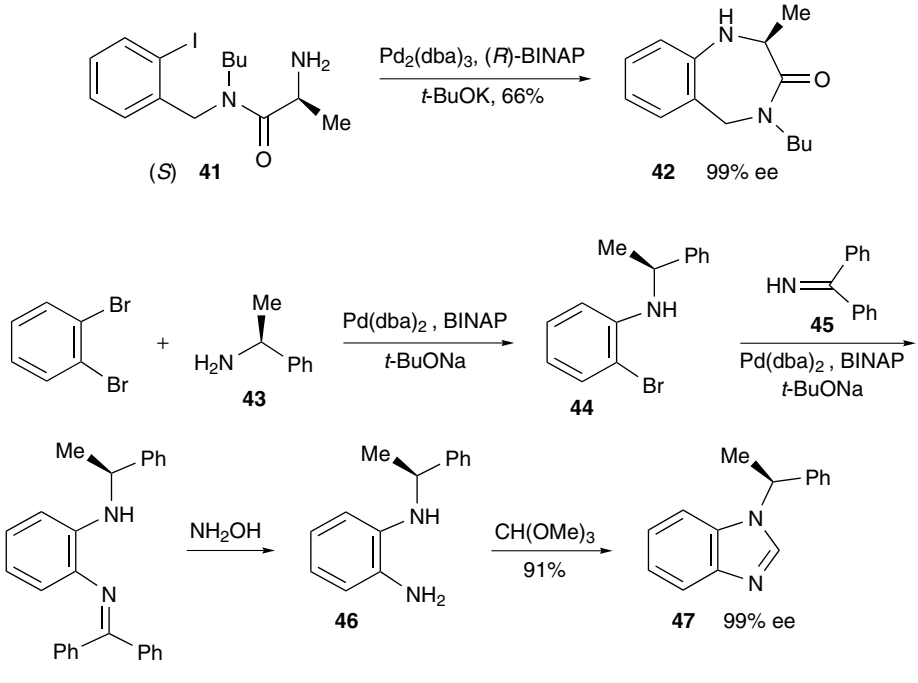
Pd-catalyzed reactions of chiral amines with aryl halides can be carried out without racemization by selection of proper ligands. Intramolecular reaction of the 2-bromophenyalanine derivative **36** using P(*o*-Tol)$_3$ proceeded without racemization to give **37**, which is a key intermediate in the synthesis of ACR inhibitor **38**. On the other hand, racemization was observed to a considerable extent using the same ligand in intermolecular reaction. Reaction of (*R*)-α-methylbenzylamine (**39**) with a bromide afforded the arylated amine **40** with 70 % ee. Racemization is explained by reversible elimination of benzylic hydrogen to form imine. Intermolecular arylation of **39** to give **40** proceeded without racemization when racemic BINAP was used as a ligand [34]. The reaction of aniline with 2, 2′-dibromobiphenyl yielded the carbazole **40a** in good yield. The reaction offers a facile synthetic method for multisubstituted carbazoles [35].



36 99% ee **37** 99% ee **38** **39** 98% ee **40** 70% ee

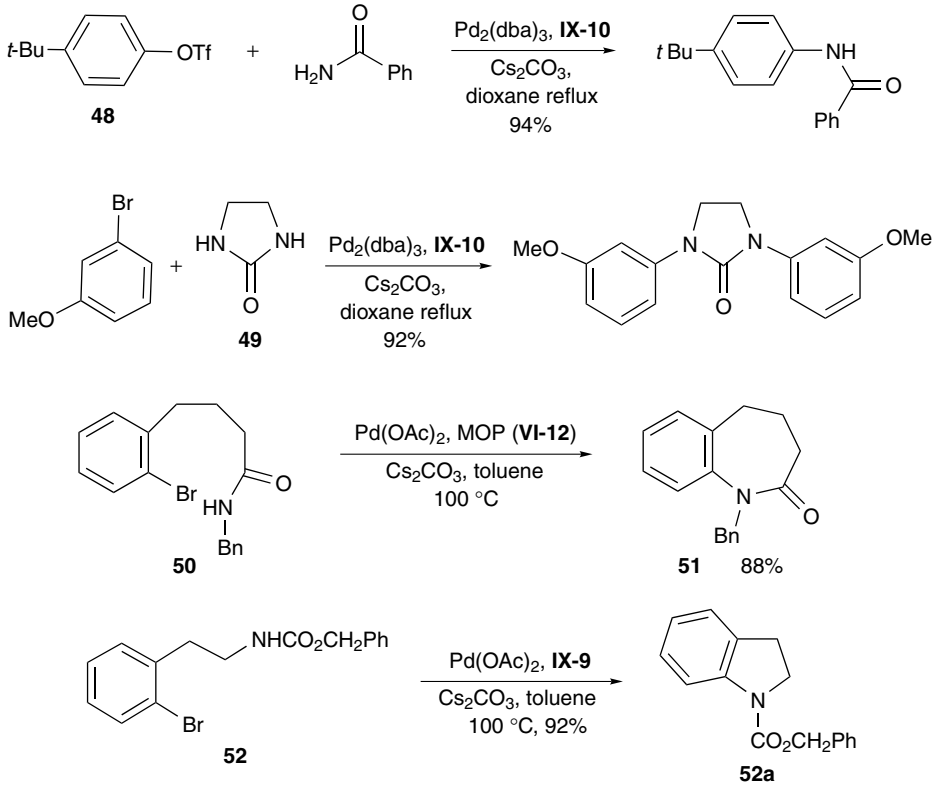


Enantiopure tetrahydrobenzo-1,4-diazepin-3-(3*H*)-one **42** was obtained by intramolecular amination of the aryl iodide **41** using BINAP as a ligand without racemization [36]. The chiral imidazole **47** was prepared by successive Pd-catalyzed amination of the chiral amine **43** with 1,2-dibromobenzene to give **44**, which was iminated with benzophenone imine (**45**). Then deprotection gave **46**, and acid-catalyzed ring closure yielded **47** [37]. The reactions have been applied to the synthesis of various chiral imidazolium salts as precursors of chiral carbene ligands [38]. Amination of aryl bromides proceeds very rapidly by temperature-controlled microwave heating [39].



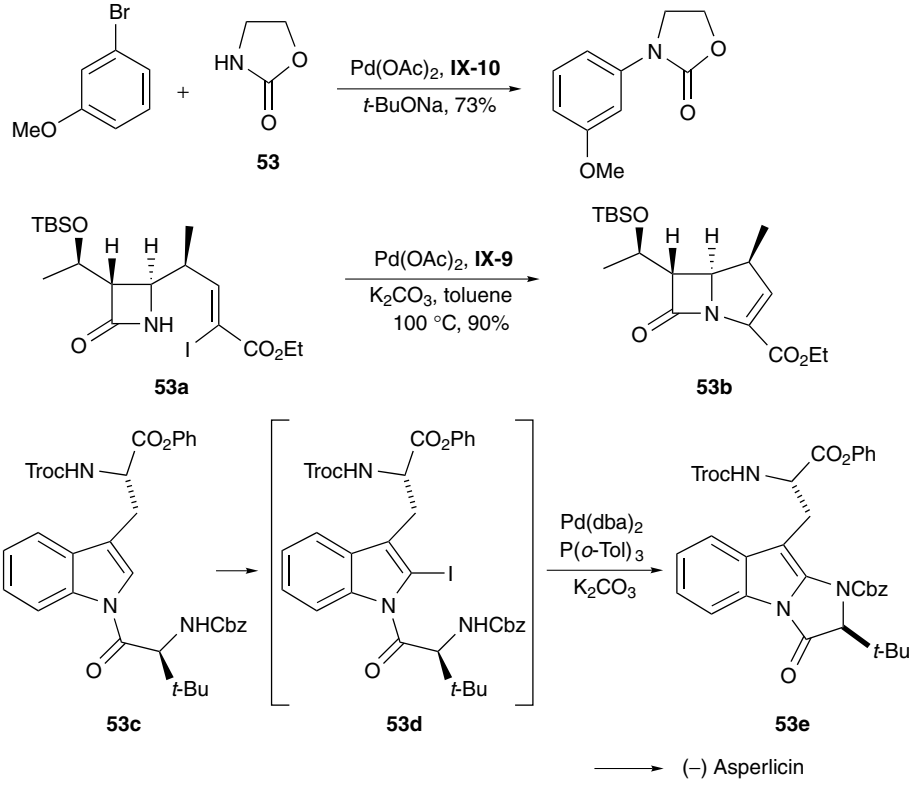
3.7.3.4 Arylation of Amides, Carbamates, and Azoles

In addition to amines, some derivatives of amines can be arylated. Weakly basic amides are arylated, and intermolecular reactions between aryl bromides and triflates **48** with benzamide can be carried out. Combined uses of xantphos (**IX-10**) and Cs_2CO_3 in THF or dioxane gave the most successful results. The cyclic urea **49** was diarylated [40]. Sulfonamides are also arylated [41]. Intramolecular reaction of the secondary amides such as **50** or carbamates offers convenient synthetic methods for five-, six-, and seven-membered lactams like **51**. As ligands, MOP (**VI-12**), DPEphos (**IX-9**), xantphos (**IX-10**), and BINAP are used depending on the size of the rings. As an example, ligand **IX-9** is the most suitable for the preparation of the five-membered *N*-carbobenzyloxy derivative **52a** from **52**, but BINAP was not effective.

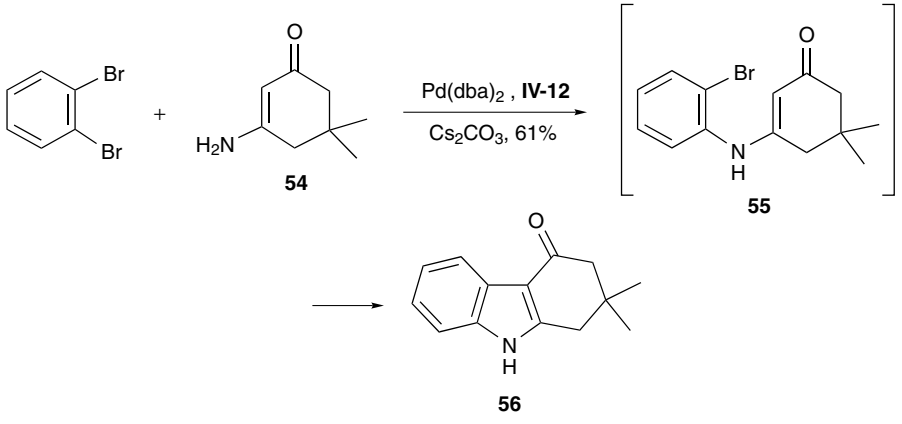


Yang and Buchwald reported that the following preparative method of the catalyst is important. First, a toluene solution of $Pd(OAc)_2$, a ligand and an amine is heated at 100 °C for 2 min in the absence of a base, and the base is added at 0 °C. Good results are obtained for the catalyst prepared in this way [42]. Preparation of DPEphos (**IX-9**) and xantphos (**IX-10**) is easier and cheaper than that of racemic BINAP, and they are used as good bulky bidentate ligands [43]. Also, xantphos (**IX-10**) gave excellent results in arylation of 2-oxazolidinones **53** with aryl bromides [44]. The 1β-methylcarbapenem **53b** was prepared from **53a** by Mori by using **IX-9** as the ligand and K_2CO_3 as the best base. The lactam **53b**

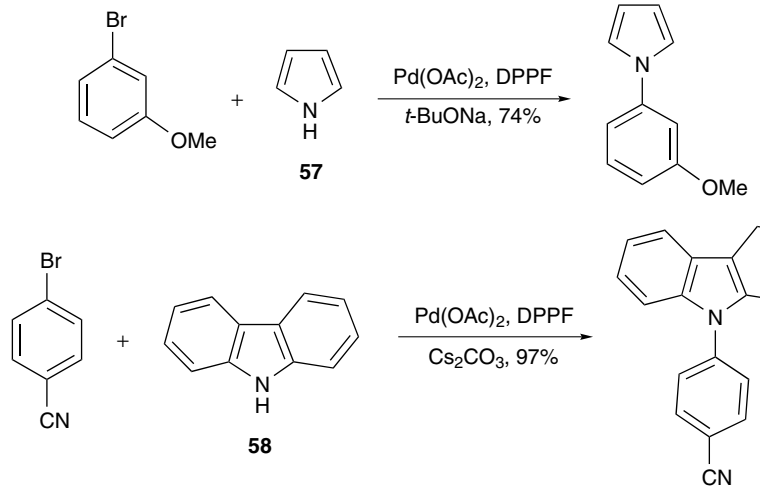
was obtained in 90 % yield when the catalyst was prepared by the Buchwald recipe in the absence of the base [45]. Pd-catalyzed cyclization of the iodide **53d**, prepared from **53c**, was applied to the synthesis of (−)-asperlicin. The iodide **53d** has two amino groups, but the cyclization afforded **53e** chemoselectively. In addition, two epimerizable stereocenters in **53e** were preserved [46].



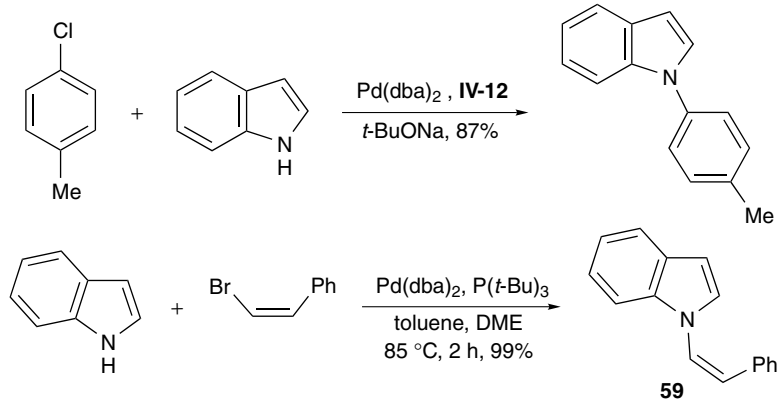
Heterocycles were synthesized by arylation of vinylogous amides, followed by Heck reaction. Monoarylation of the vinylogous amide **54** with 1, 2-dibromobenzene afforded **55**. The indole derivative **56** was obtained by intramolecular Heck reaction of **55** [47].



Azoles such as pyrrole (**57**), carbazole (**58**), and indole can be N-arylated in the presence of DPPF [48]. Various N-arylated indoles were prepared conveniently by N-arylation of indole with aryl iodides, bromides, chlorides, and triflates. Suitable ligands are selected from bulky biphenyl- or binaphthyl-based phosphines **IV-12**, **IV-14**, and **VI-3** depending on the kinds of aryl halides used [49].



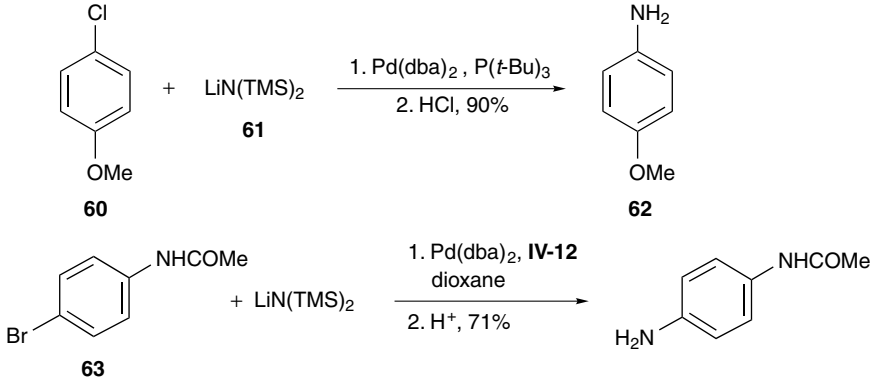
Vinylation of azoles is also possible. The vinylation of indole with *cis*-β-bromostyrene proceeded with retention of configuration to afford **59** in high yield using P(t-Bu)$_3$ as a ligand [50].



3.7.3.5 Arylation of Ammonia Surrogates

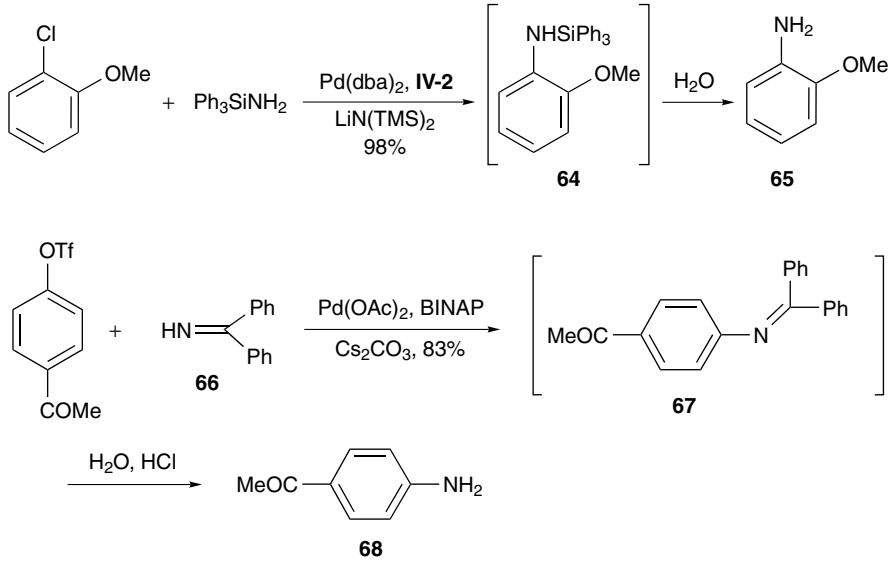
So far no arylation of ammonia has been reported, and it is difficult to prepare aniline derivatives directly by the Pd-catalyzed reaction of aryl halides with ammonia. Aniline derivatives are prepared indirectly by the reaction of ammonia surrogates (ammonia equivalents). The reaction of the ammonia surrogates with aryl halides, followed by deprotection affords aniline derivatives. As one of them, LiN(TMS)$_2$ (**61**) reacts with aryl bromides and chlorides. P(t-Bu)$_3$ is the best ligand, and the coupled products are converted easily to anilines by treatment with aq. HCl.

Synthesis of **62** from **60** is an example [51]. Use of $LiN(TMS)_2$ as the ammonia surrogate is problematic for aryl bromides containing an amide group, but the reaction of *p*-bromoacetanilide (**63**) proceeds smoothly using 2.2 equivalents of **61** [29].



No smooth reaction of $LiN(TMS)_2$ was observed with sterically congested *ortho*-substituted aryl halides. In such a case, Ph_3SiNH_2 can be used as an ammonia surrogate and the coupled product **64** was converted to **65** [52].

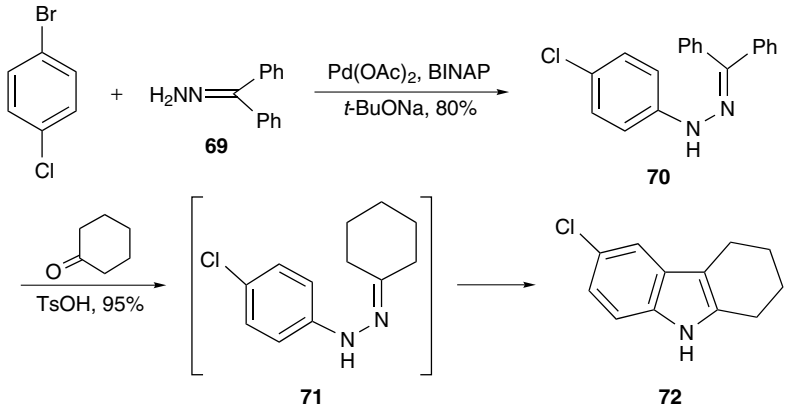
Benzophenone imine (**66**) is another ammonia surrogate. Arylation of the imine **66** is carried out using BINAP and Cs_2CO_3. Hydrolysis of the arylated imine **67** affords the aniline derivative **68** [53].



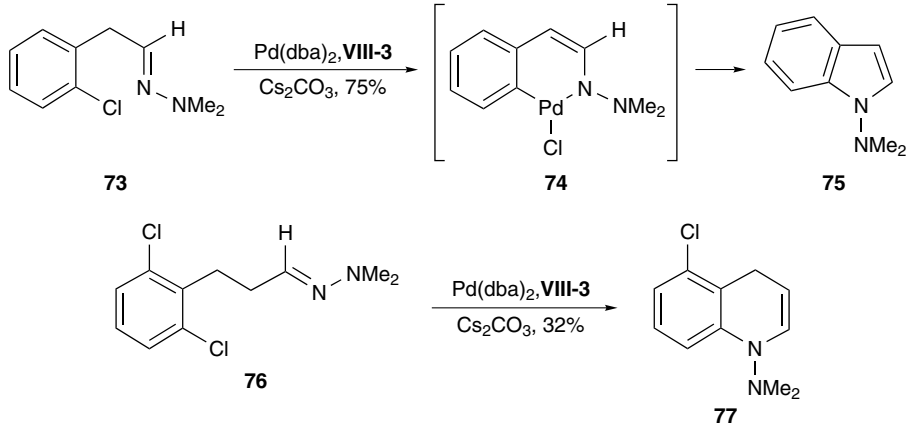
3.7.3.6 Arylation of Other Nitrogen-Containing Compounds

The arylation of imines can be applied to indole synthesis. The Fischer indole synthesis was carried out by Pd-catalyzed arylation of benzophenone hydrazone (**69**) to give *N*-arylbenzophenone hydrazone **70**. The subsequent exchange reaction

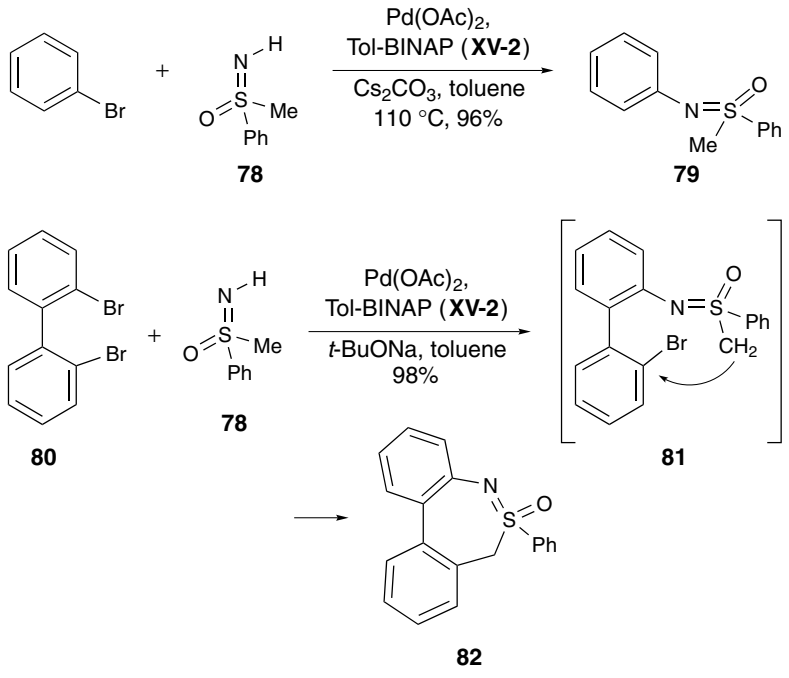
of **70** with cyclohexanone afforded the *N*-arylcyclohexanone hydrazone **71** as a requisite intermediate of the Fischer indole synthesis. The hydrazone **71** was converted to the indole **72** [54].



Intramolecular amination of *N*,*N*-dimethylhydrazone of *o*-chlorophenylacetaldehyde (**73**) offers a facile synthetic method of indoles. 1-Aminoindole **75** was prepared by intramolecular arylation of **73**. For this reaction, (ferrocenyl)aminophosphine **VIII-3** was a better ligand than P(*t*-Bu)$_3$. *N*,*N*-dimethylhydrazones have no hydrogen to be displaced, and the arylation is explained by isomerization to the enamine form **74**. Another possibility may be insertion of C=N bond to Ar-Pd bond, followed by dehydropalladation. Similarly, the quinoline **77** was obtained by intramolecular amination of 2,6-dichlorophenylpropionaldehyde *N*,*N*-dimethylhydrazone (**76**) [55].

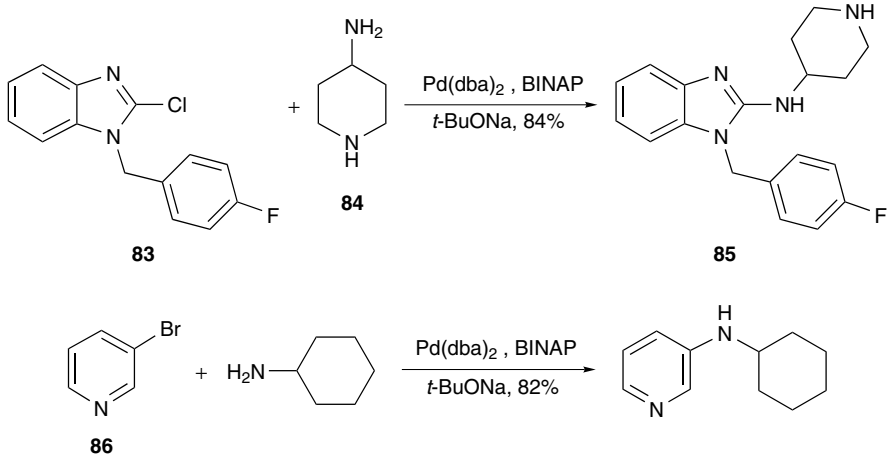


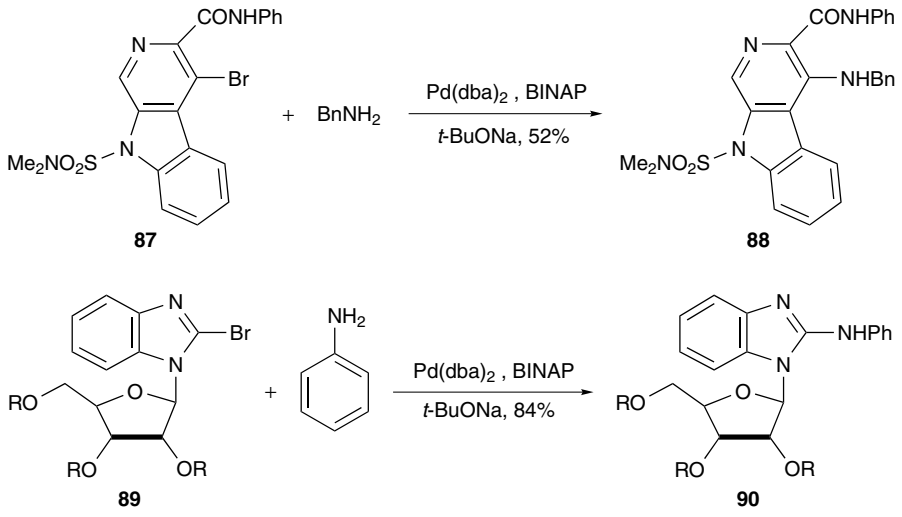
Sulfoximines **78** are N-arylated with aryl iodides and bromides to give **79** using BINAP or Tol-BINAP as a ligand and Cs_2CO_3 as a base [56]. The reaction of **78** with 2, 2′-dibromobiphenyl (**80**) using *rac*-BINAP and *t*-BuONa afforded the seven-membered ring compound **82** by sequential N-arylation and C-arylation as shown by **81**. The reaction shows that a methyl group activated by a sulfoximino group can be arylated as in the reaction of carbonyl compounds [57].



3.7.3.7 Arylation with Nitrogen-Containing Heterocyclic Halides

Arylation with various heterocyclic compounds can be carried out when their reactive halides are available at proper positions. For example, the antihistamine norastemizole derivative **85** was synthesized by the reaction of the chlorobenzimidazole **83** with the diamine **84**. Selective arylation of the primary amine in the diamine **84** proceeded with high selectivity [58]. BINAP is a good ligand for the amination of 3-bromopyridine (**86**) [59]. Similarly benzylamine was introduced to the bromopyridine moiety of the 3-carboxy-β-carbolines **87** to give **88** [60]. Another example is the C-8 aminated adenosine derivative **90** was obtained in a high yield by the amination of **89** [61].





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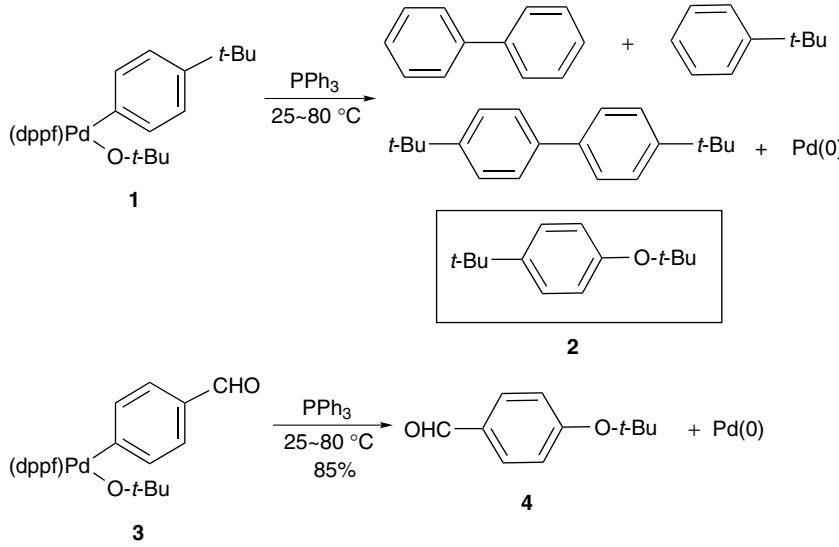
3.7.4 Arylation of Phenols, Alcohols, and Thiols

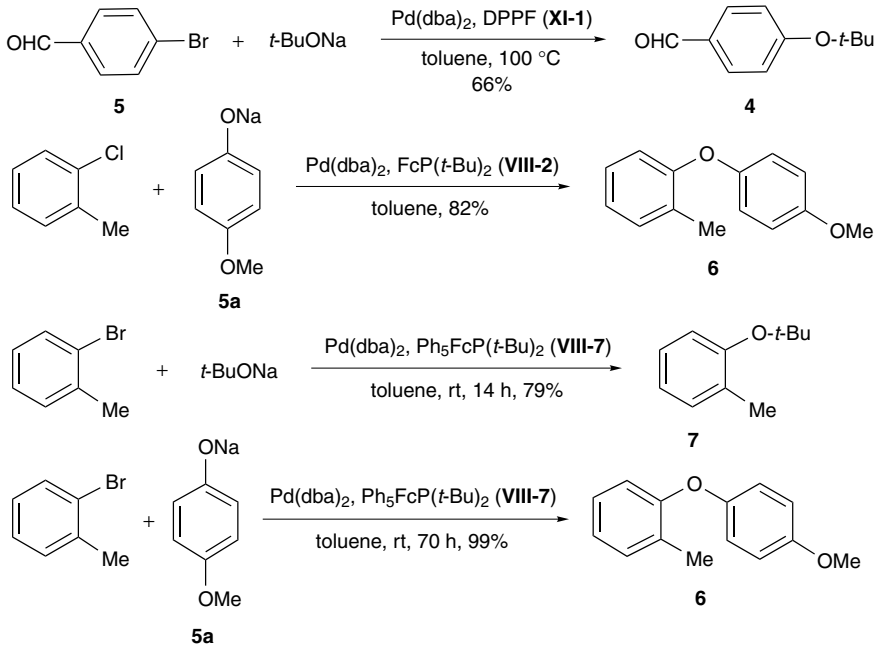
3.7.4.1 O-Arylation of Phenols

Synthesis of diaryl ethers and alkyl aryl ethers by the reactions of aryl halides with phenols and alcohols has been regarded as a difficult reaction. The Pd-catalyzed reaction of aryl halides with phenols and alcohols has been discovered recently and is now attracting attention as a new synthetic method for aryl ethers. Reductive elimination to form the C—O bond as the last step of the ether formation is a rate-determining step. As supporting evidence, Hartwig isolated the DPPF (**XI-1**) complex of arylpalladium *t*-butoxide **1** from electronically neutral *p*-*t*-butylphenyl bromide, and has shown that complex **1** resists reductive elimination to afford the *t*-butyl ether **2**, and gives biaryls and *t*-butylbenzene on heating. On the other hand, the thermally unstable DPPF complex **3** of electron-deficient aryl bromide gives the ether **4** in 85 % yield [1]. Thus a number of bulky and electron-rich ligands which accelerate the reductive elimination are used for successful synthesis of aryl ethers.

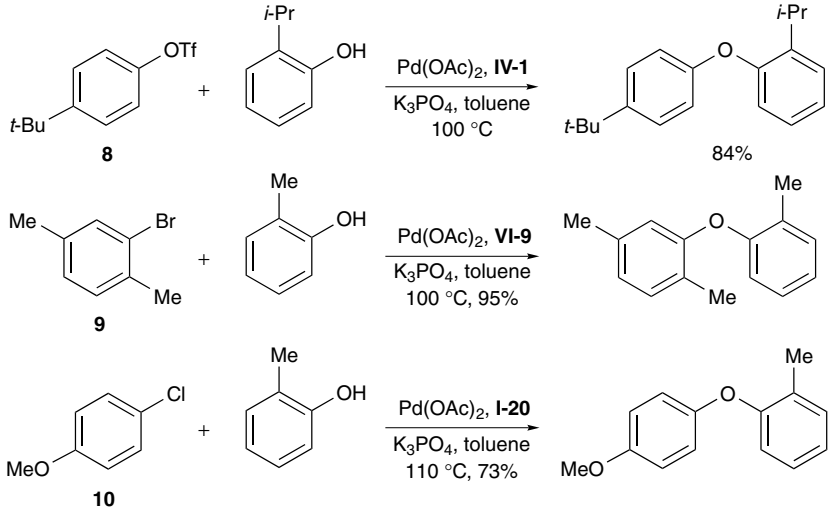
Ring arylation of phenols with aryl halides to produce arylphenols is competitive with aryl ether formation. As discussed in Chapter 3.3.2, it is known that the ring arylation proceeds with Pd(0)-PPh_3 catalyst.



Hartwig and co-workers found that DPPF is a suitable ligand for formation of the ether **4** from *p*-bromobenzaldehyde (**5**) and *t*-BuONa, but this ligand is effective only for electron-deficient aryl bromides [1]. Later they found that reaction of electronically neutral *o*-chlorotoluene with sodium phenoxide **5a** gave **6** in toluene by using monodentate ferrocenylphosphine $FcP(t\text{-}Bu)_2$ (**VIII-2**) as a ligand. Other ligands such as BINAP and DPPF are ineffective [2]. Pentaphenylated ferrocenyl ligand **VIII-7** is a very effective ligand, and the *t*-butyl ether **7** and the diaryl ether **6** were obtained by the reactions of *o*-bromotoluene with *t*-BuONa and the sodium phenoxide **5a** at room temperature [3].

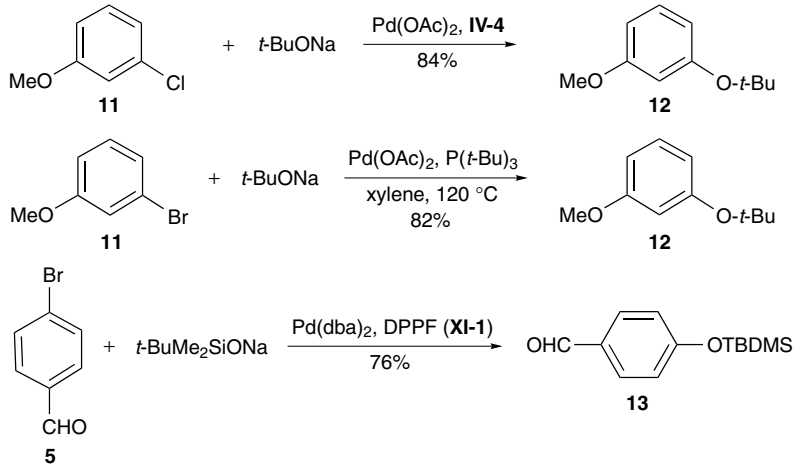


Buchwald expanded the versatility of the ether formation by finding that biphenyl- or binaphthyl-type phosphines (**IV-1, IV-3, IV-4, IV-13**, and **VI-9**) are effective ligands [4]. Reactions of electron-deficient aryl chlorides, bromides, and triflates, and also some electron-neutral halides, and triflates proceed smoothly using these bulky ligands. The triflate **8** reacts smoothly using biphenylylphosphine **IV-1** as a ligand. Good results were obtained in the reactions of electronically neutral or electron-rich aryl bromide **9** by using binaphthyl-based aminophosphine **VI-9**. K_3PO_4 or NaH is a suitable base. Toluene is the only solvent in which efficient reaction proceeds. Other solvents such as THF, DME, and dioxane give poor results. For the reaction of highly electron-rich 4-chloroanisole (**10**), these ligands gave poor results and only diadamantylphosphine **I-20** gave the aryl ether in 73 % yield.

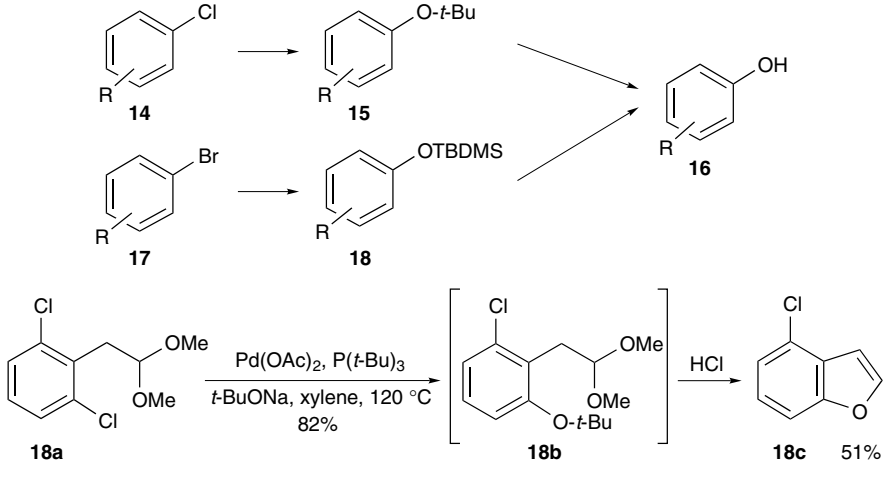


3.7.4.2 Arylation of Alcohols

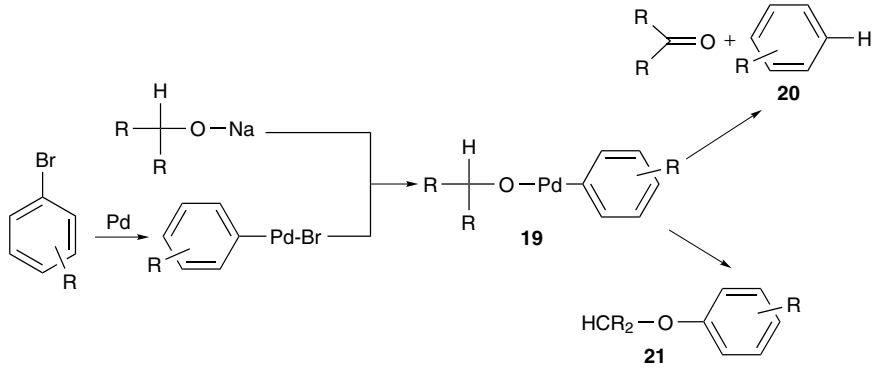
Efficient formation of aryl *t*-butyl ethers from electron-rich chlorides or bromides can be carried out using biphenyl-type monophosphines (**IV-1, IV-4, IV-12**) [5]. The aryl *t*-butyl ether **12** was prepared from electron-rich *m*-chloroanisole (**11**) using **IV-4** as a ligand. The *t*-butyldimethylsilyl ether **13** was obtained from the electron-deficient bromides **5** using DPPF (**XI-1**) [1]. Also *t*-butyl ether formation is carried out by using $P(t\text{-Bu})_3$.



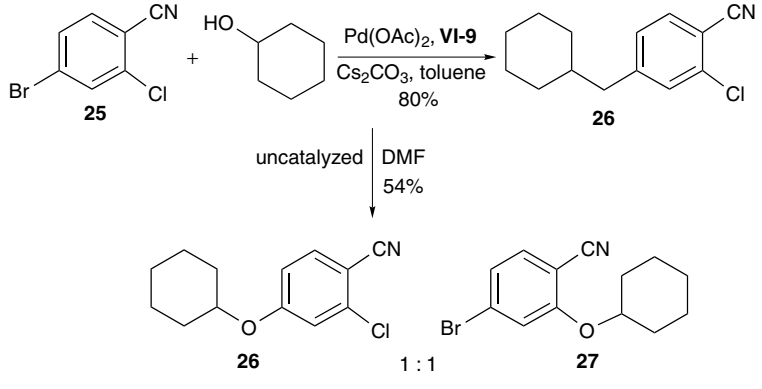
The aryl *t*-butyl ether **15** and silyl ether **18**, prepared by the Pd-catalyzed reaction, can be converted easily to phenols **16**, and these reactions offer convenient synthetic methods for phenols **16** from aryl halides **14** and **17**. Based on this reaction, the first synthesis of 4-chlorobenzofuran (**18c**), which is difficult to synthesize by conventional methods, was carried out. Selective mono-*t*-butoxylation of 2,6-dichloroacetaldehyde dimethylacetal (**18a**) using $P(t\text{-Bu})_3$ as a ligand gave the *t*-butyl ether **18b**, and subsequent treatment with aq. HCl afforded 4-chlorobenzofuran (**18c**) in 51 % overall yield. Further conversion of **18c** to various 4-substituted benzofurans is possible by Pd-catalyzed substitutions of the 4-chloro group in **18c** [6].



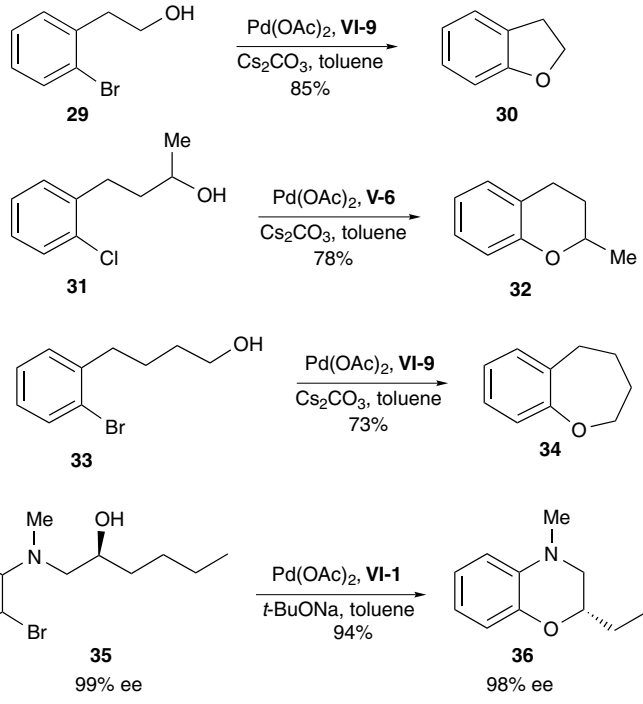
Formation of the alkyl ethers **21** from alcohols, except *t*-BuOH which lacks β-H, is not easy. In this case, the following competing oxidation–reduction reaction of halides with alcohols to afford the arenes **20** as shown by the intermediate **19**, should be suppressed. Ethers from electron-rich aryl halides and primary alcohols such as 1-butanol can be prepared using binaphthyl ligands. Aryl alkyl ethers are prepared by Pd-catalyzed reaction of aryl bromides with secondary alcohols in toluene using Tol-BINAP (**XV-2**) [7]. The alkyl ether **23** and the arene **24** were obtained smoothly from the chloride **22** in a ratio of 8 : 1 from primary alcohols such as 1-butanol by using several biphenyl and binaphthyl-type ligands such as **VI-1** and **VI-9**. Cs_2CO_3 was used as a base [8].



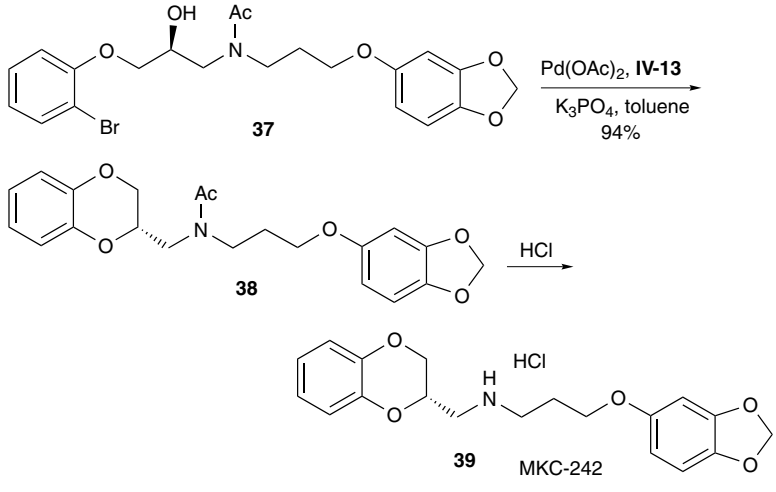
Strongly electron-deficient aryl halides react with alcohols without any catalyst. Catalyzed reaction is sometimes better than uncatalyzed reaction as shown by the reaction of 4-bromo-2-chlorobenzonitrile (**25**) with cyclohexanol. The ether **26** was obtained in 80 % yield using Pd(0)-**VI-9** as a catalyst. On the other hand, the uncatalyzed reaction gave equal amounts of **26** and **27** [7].



Preparation of cyclic ethers by intramolecular reactions of the primary (**29** and **33**) and the secondary alcohols (**31** and **35**) proceeds more easily using Cs_2CO_3 or K_3PO_4, and binaphthyl-based monophosphine ligands **VI-1, VI-9** [9]. The five-, six-, and seven-membered cyclic ethers **30, 32**, and **34** were prepared from the aryl chloride **31** and bromides **29** and **33**. The benzoxazapine **36** was obtained without racemization of chiral alcohol by the cyclization of the optically active bromo alcohol **35**.

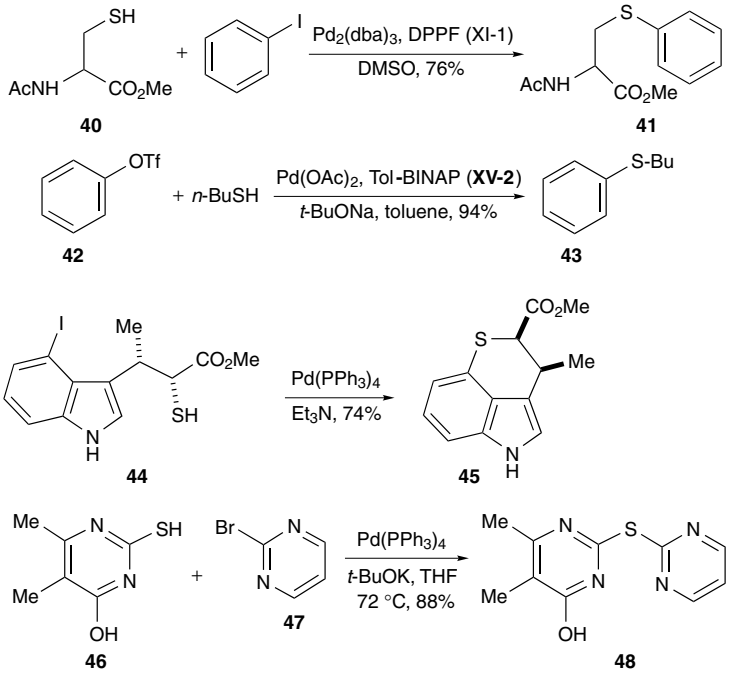


An antidepressant MKC-242 **39** was synthesized by applying the cyclization of the optically active alcohol **37** as a key step to form the benzodioxane **38** using aminobiphenylylphosphine (**IV-13**) as a ligand.

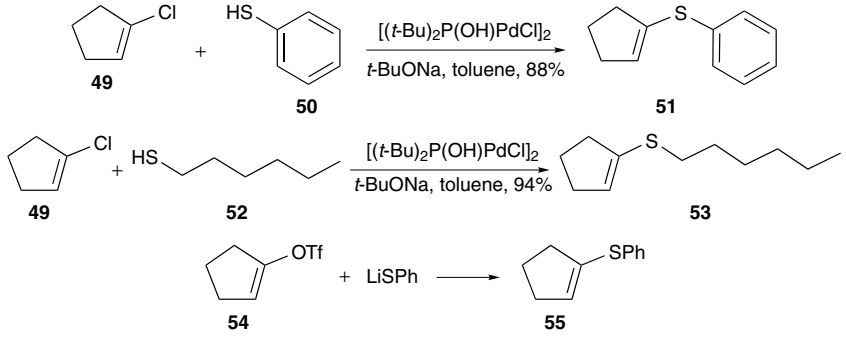


3.7.4.3 Arylation of Thiols

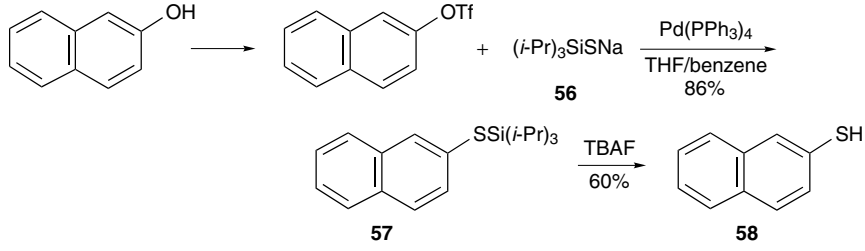
Aryl sulfides (thioethers) are prepared by the reaction of aryl halides with mercaptans or thiophenols in DMSO. Synthesis of the phenyl thioether **41** using the thiol **40** is an example. DPPF is a good ligand [10,11]. Phenyl *n*-butyl thioether (**43**) was prepared by the reaction of triflate **42** with *n*-butylmercaptan. BINAP is an effective ligand, but Tol-BINAP is more effective. *t*-BuONa is used as a base, but interestingly no *t*-butyl phenyl ether is formed in this reaction [12]. Total synthesis of chuangxinmycin (**45**) was carried out by intramolecular reaction of the aryl iodide **44** [13]. The asymmetric bispyrimidine thioether **48** was prepared in high yield by coupling pyrimidine-2-thiol **46** with 2-bromopyrimidine (**47**) [14].



Commercially available, air-stable Pd phosphinous acid complex is an active catalyst for the thioether formation by the reaction of 1-cyclopentenyl chloride (**49**) with thiophenol (**50**) and hexylmercaptan (**52**) to give the thioethers **51** and **53** [15]. 1-Cyclopentenyl phenyl thioether (**55**) was obtained by the reaction of 1-cyclopentenyl triflate (**54**) with lithium phenyl sulfide [16].



As a related reaction, thiophenols are prepared from phenols. For example, the Pd-catalyzed reaction of 2-naphthyl triflate with sodium triisopropylsilane thiolate (**56**) gives the silyl ether of 2-thionaphthol **57**. Deprotection of **57** affords 2-thionaphthol (**58**) [17].



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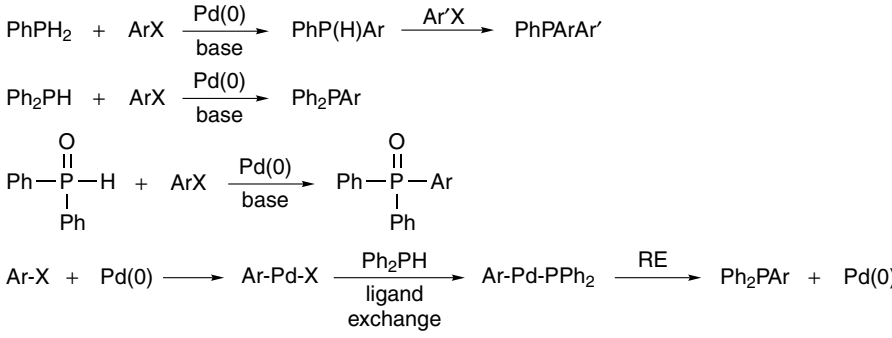
3.7.5 Arylation of Phosphines, Phosphonates, and Phosphinates

Pd-catalyzed arylation of various phosphorus compounds containing P—H bonds with aryl and alkenyl halides, or triflates offers useful methods of C—P bond formation. After pioneering work on Pd-catalyzed arylation and alkenylation of dialkyl phosphonates by Hirao *et al*. [1], extensive studies have been carried out on arylation of various phosphorus compounds. The methods are particularly useful for the synthesis of various chiral phosphines used in Pd-catalyzed asymmetric reactions.

3.7.5.1 Arylation of Phosphines and Phosphine Oxides

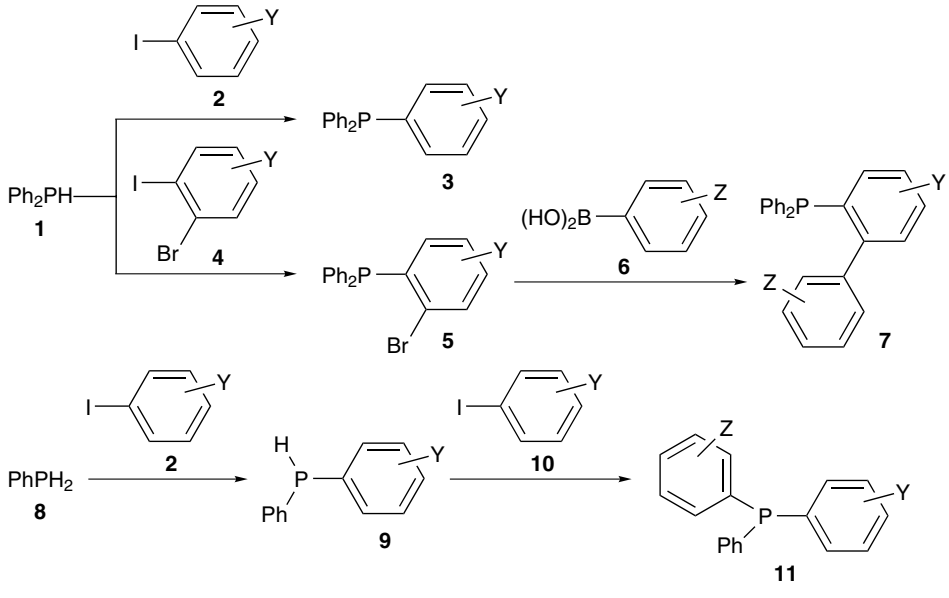
Arylations of phosphines and phosphine oxides are carried out as shown by the following general equations. The reactions are explained by oxidative addition of aryl halides, followed by ligand exchange with Ph_2P-H, which is similar to transmetallation. Finally, reductive elimination affords arylated products.

Arylation of phosphines and phosphine oxides

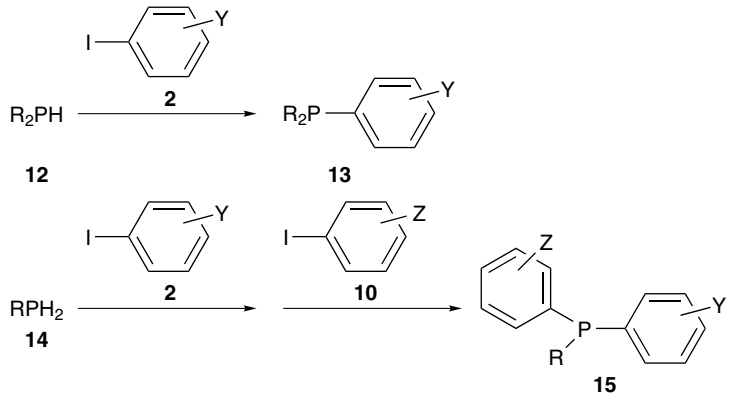


Recently, extensive synthetic studies on multiply functionalized chiral arylphosphines by Pd-catalyzed arylation of primary and secondary phosphines with aryl halides have been carried out by Stelzer [2]. The synthetic methods can be summarized by the following general schemes.

Diphenylarylphosphines **3** are prepared by coupling Ph_2PH (**1**) with aryl iodides **2**. Coupling of Ph_2PH (**1**) with 2-bromoiodobenzene derivatives **4** affords chemoselectively the bromophenylphosphines **5**, and Suzuki coupling with **6** gives the biphenyl-type phosphines **7**. Consecutive displacements of the hydrogen atoms of the primary phosphine **8** with different aryl iodides **2** and **10** yield the multiply



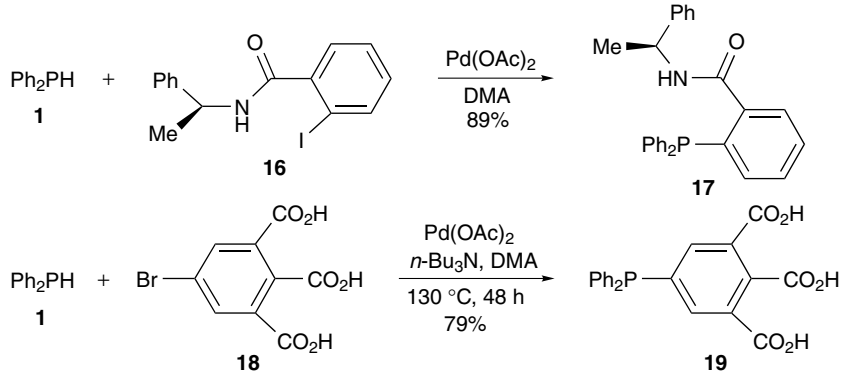
functionalized phosphines **11**. Similarly alkylarylphosphines **13** and **15** are prepared by the coupling of primary and secondary alkylphosphines **12** and **14** with aryl iodides **2** and **10**. Some examples of the syntheses of interesting polyfunctionalized phosphines are cited here.

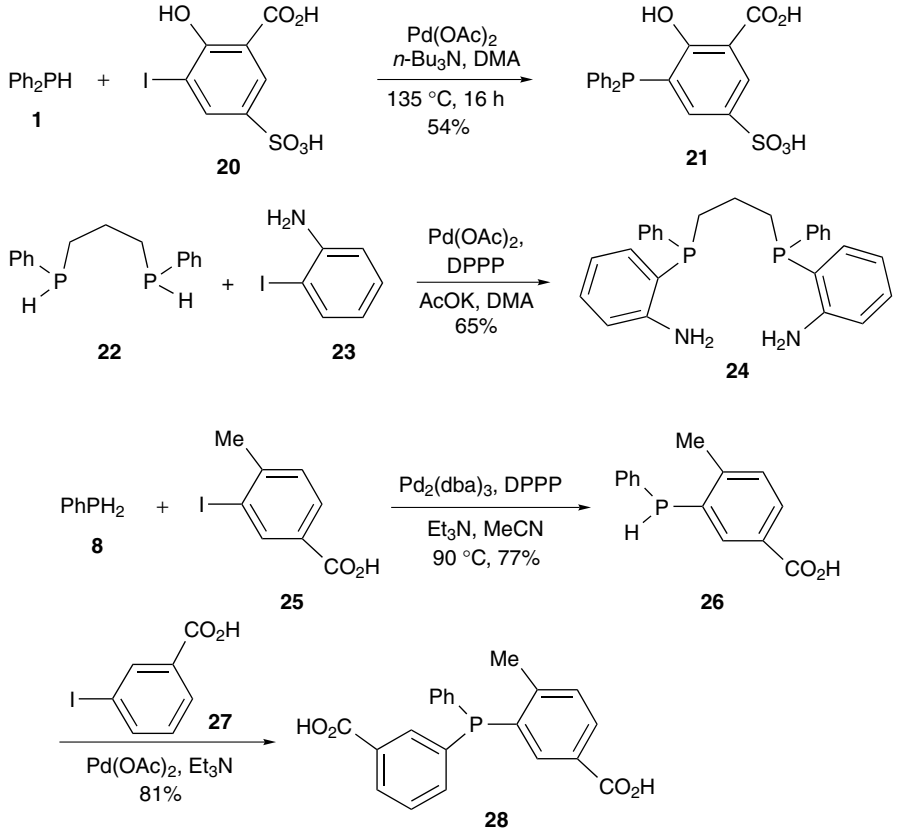


The chiral phosphine ligand **17** was prepared by coupling the congested iodide **16** with Ph_2PH (**1**). 5-Diphenylphosphinobenzene-1,2,3-tricarboxylic acid **19** as a water-soluble ligand (**II-4**) was prepared by smooth coupling of bromobenzenetricarboxylic acid **18**. Similarly the water-soluble phosphine **21** was obtained from **1** and **20**. The bidentate ligand **24** was prepared by smooth reaction of 1,3-bis(phenylphosphino)propane (**22**) with 2-iodoaniline (**23**) using DPPP as a ligand. The ligand **24** was a 1 : 1 mixture of two diastereomers, and enrichment of one of the diastereomers in a ratio of 8 : 3 was achieved by recrystallization from MeOH. It is somewhat surprising that the couplings of aryl iodides, **16**, **18**, and **20**, substituted by highly polar substituents, proceed smoothly.

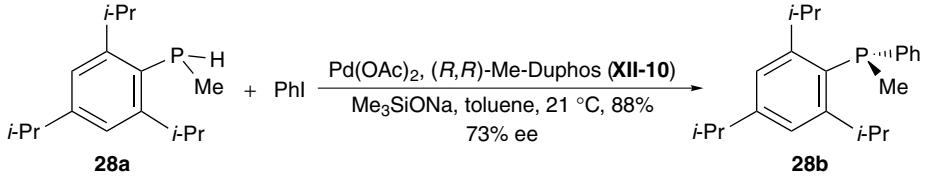
A racemic phosphine **28** was obtained by consecutive displacement of hydrogen atoms of phenylphosphine (**8**) with two different aryl iodides **25** and **27**. For the coupling of diphenylphosphine with aryl iodides, Pd on carbon is a good catalyst in DMF under microwave dielectric heating in DMF [3].

A P-chirogenic phosphine can be synthesized by Pd-catalyzed asymmetric phosphination. Coupling of the racemic phosphine **28a** with iodobenzene afforded the



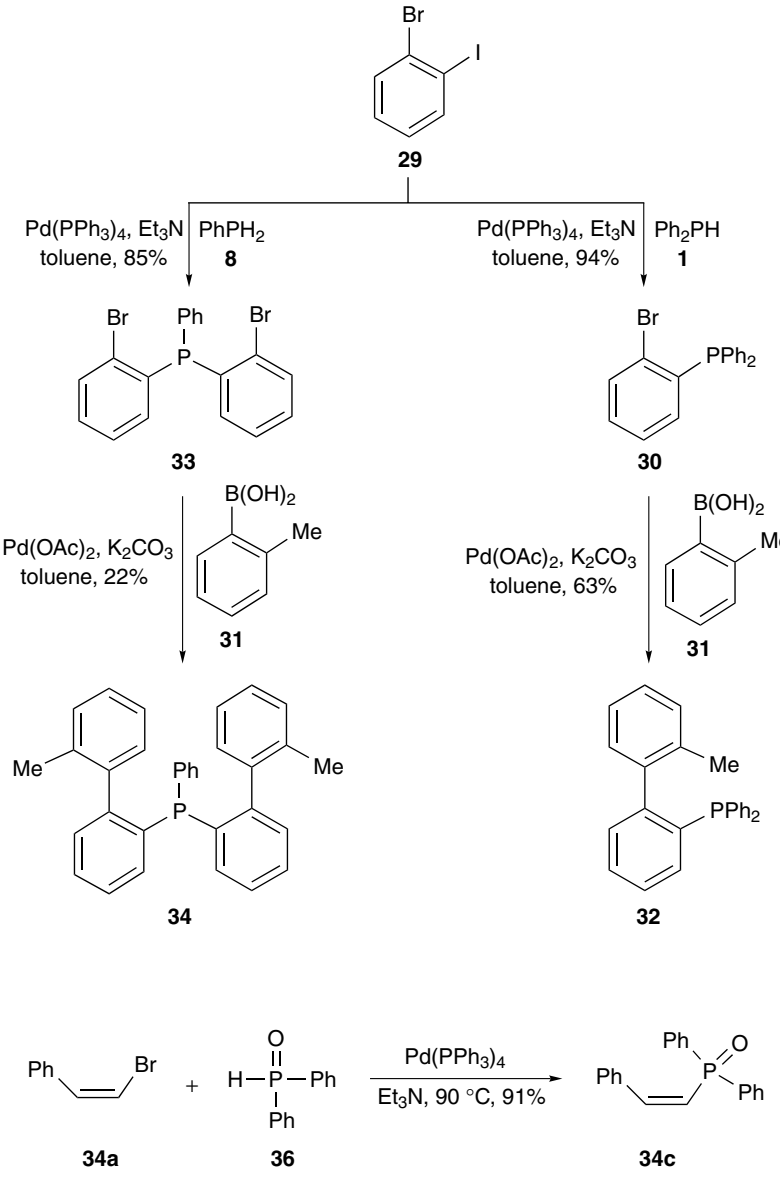


enantio-enriched phosphine **28b** in 88 % yield with 73 % ee. (*R*,*R*)-Me-Duphos (**XII-10**) was used as a chiral ligand [4].

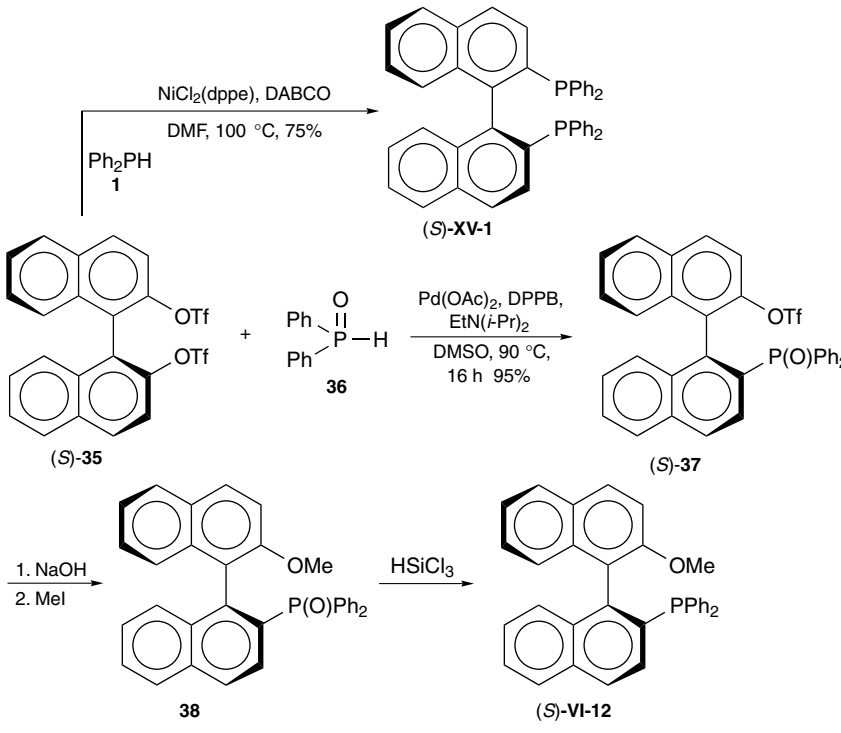


The biphenyl-based phosphine **34** was prepared from 2-bromoiodobenzene (**29**). Chemoselective coupling of the iodide in 2-bromoiodobenzene (**29**) with diphenylphosphine (**1**) gave 2-bromophenyldiphenylphosphine (**30**), and its Suzuki–Miyaura coupling with **31** afforded the biphenylylphosphine **32**. Reaction of **29** with the primary phosphine **8** afforded the di(2-bromophenyl)phenylphosphine (**33**), and bis-biphenylylphosphine derivative **34** was obtained by Suzuki–Miyaura coupling of **33** with **31**, although the yield was not high [2].

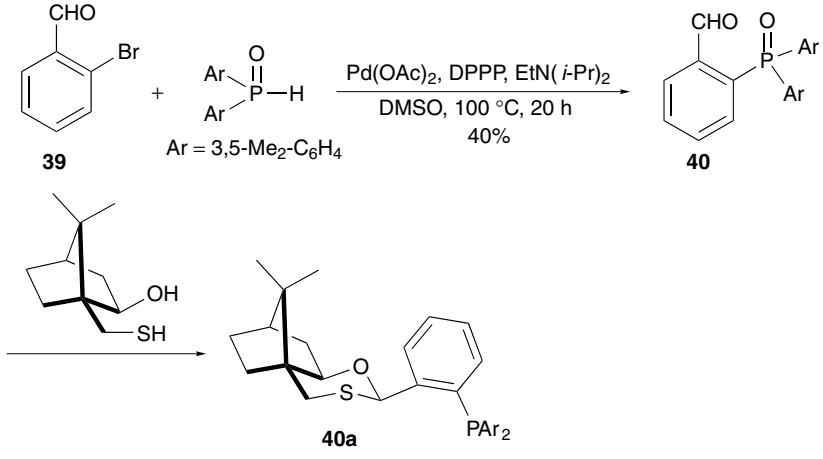
Phosphine oxides are conveniently used for the coupling, because diphenylphosphine oxide (**36**) is more easily handled than Ph_2PH (**1**). Reaction of (*Z*)-alkenyl bromide **34a** with diphenylphosphine oxide (**36**) gave (*Z*)-diphenylvinylphosphine oxide **34c** with complete retention [5].



Triarylphosphine oxides are prepared by coupling aryl halides or triflates with diphenylphosphine oxide (**36**), and they are reduced to triarylphosphine with $HSiCl_3$. Selective monophosphination of 2, 2′-bis-triflate of binaphthol (**35**) with diphenylphosphine oxide occurred to give the optically active phosphine oxide (**37**) using DPPB or DPPP. No bis-substitution was observed [6,7]. The phosphine oxide **37** can be converted to the phosphine by treatment with $HSiCl_3$ and an amine. Various optically active monodentate phosphines such as MeO-MOP (**VI-12**) are prepared from **37** via **38**. On the other hand, bis-substitution of **35** takes place to afford the bis-phosphine when $NiCl_2$(dppe) is utilized as a catalyst, and the reaction is used for the preparation of BINAP (**XV-1**) [8].

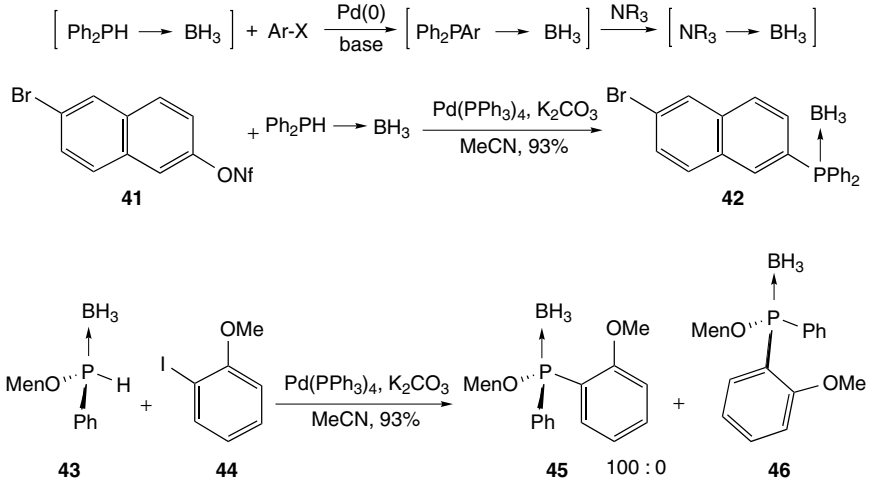


Reaction of 2-bromobenzaldehyde (**39**) with diarylphosphine oxide using $Pd(OAc)_2$ and DPPP afforded the mixed triarylphosphine oxide **40**, which was converted to the chiral phosphine ligand **40a** [9].

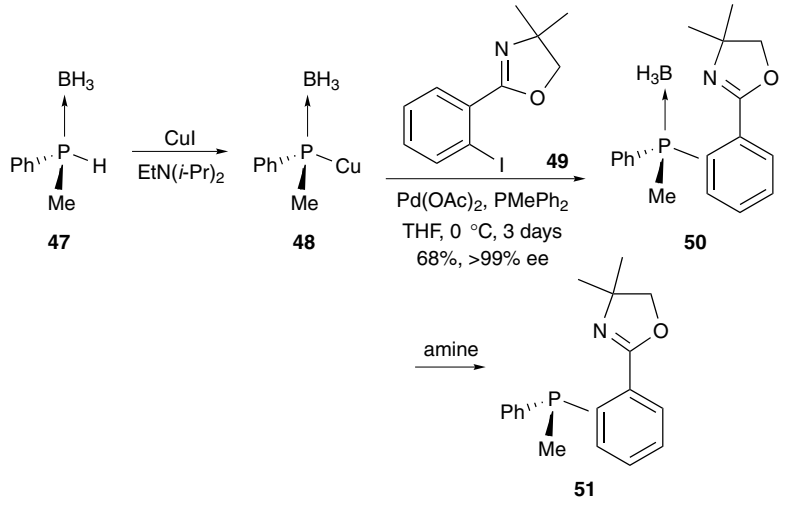


Imamoto reported that Pd-catalyzed coupling of phosphine-borane with aryl halides is useful for preparation of asymmetric phosphines. Phosphines can be easily isolated from phosphine-boranes by exchange reaction with amines such as pyrrolidine and DABCO [10]. Lipshutz found that aryl nonaflates (*Nf = nonafluorobutanesulfonate) and triflates are good substrates for coupling with BH_3-stabilized diarylphosphines. Selective coupling with nonaflate without

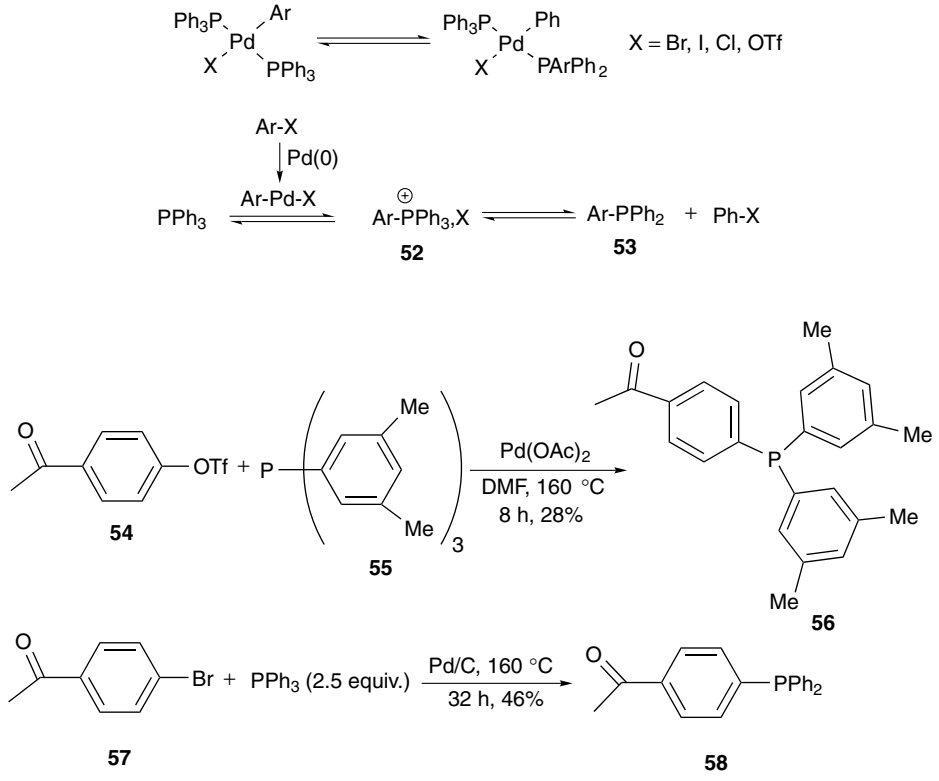
attacking bromide in **41** gave the asymmetric phosphine-borane **42** in MeCN using $Pd(PPh_3)_4$ and K_2CO_3 [11]. In the synthetic studies directed toward P-chiral phosphines, Imamoto disclosed that the reaction of optically active (*S*)-(menthyloxy)phenylphosphine-borane (**43**) with 2-iodoanisole (**44**) gave the phosphine-borane **45** with complete retention of configuration in MeCN using K_2CO_3 as a base. Solvents are crucial and nearly complete inversion was observed to give **46** in THF [12–14].



Phosphorylation of Ar_2PH-BH_3 with aryl halides proceeds under mild conditions using Pd-Cu catalyst and P-chiral phosphine-boranes of high enantiopurity are prepared by this method. As an effective ligand, $MePPh_2$ is used with $Pd(OAc)_2$. The phosphine-borane **50** was prepared in 68 % yield by phosphorylation of optically active (Sp)-methylphenylphosphine-borane (**47**) via **48** with the iodide **49** in the presence of the $Pd(OAc)_2$-$MePPh_2$ catalyst and CuI as a cocatalyst at 0 °C for 3 days. The reaction proceeded with retention of stereochemistry and the asymmetrically substituted phosphine **51** with 99 % ee was obtained [15].



An interesting direct synthetic method of phosphines **53** is an exchange reactions between Ar-Pd-X and PPh_3 via the phosphonium salt **52**. The exchange is frequently observed as a side-reaction in coupling reactions catalyzed by Pd(0)-PPh_3 [16]. The functionalized phosphine **56** was prepared by the Pd-catalyzed exchange reaction between the triflate **54** and the phosphine **55**. $Pd(OAc)_2$ or Pd/C is used as a catalyst. Treatment of either the triflate **54** or bromide **57** wih 2.5 equivalents of PPh_3 for 20–30 h afforded the phosphine **58** in 40–50 % yield. Triflates are more reactive than bromides in the exchange reaction [17].



3.7.5.2 Arylation of Phosphonates and Phosphinates

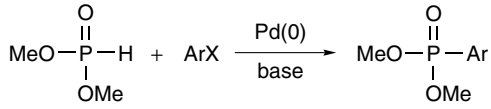
Phosphonates and phosphinates are arylated as shown by the following general schemes.

Hirao *et al*. synthesized diethyl *p*-anisylphosphonate **61** by arylation of diethyl phosphonate (**60**) with *p*-bromoanisole (**59**) [1]. The reaction was applied to the synthesis of the phosphonate **63a** by coupling of the alkenyl bromide **62** with the phosphonate **63** [18].

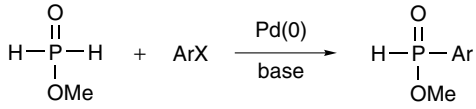
The optically active isopropyl methylvinylphosphinate **65** (97 % ee) was prepared from isopropyl methylphosphinate **64** (97 % ee) with complete retention of stereochemistry [19].

Formation of monoaryl, and symmetric or asymmetric diarylphosphinates is expected by stepwise arylation of methyl phosphinate (**66**). However, methyl phosphinate is a very unstable compound. Lei *et al*. found that its reaction can

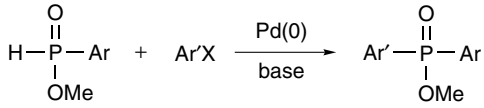
Arylation of dimethyl phosphonate (dimethoxyoxophosphorane)

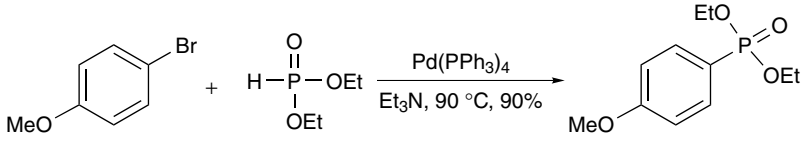


Arylation of methyl phosphinate (methoxyoxophosphorane)

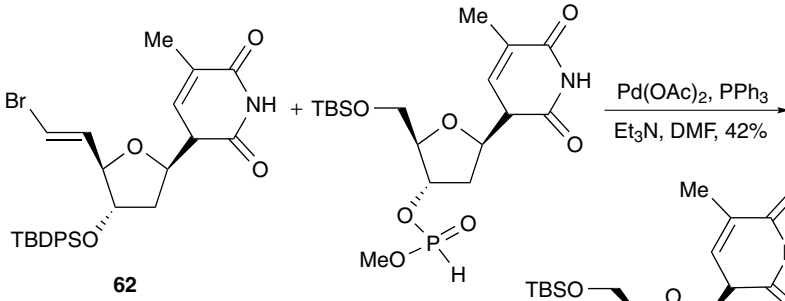


Arylation of methyl arylphosphinate (arylmethoxyoxophosphorane)

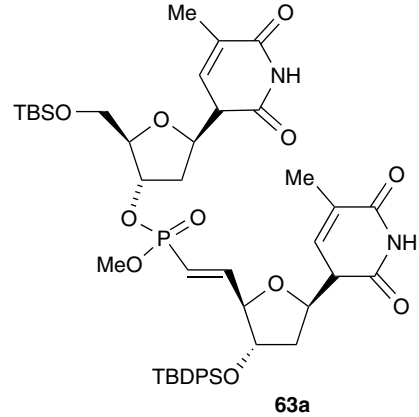




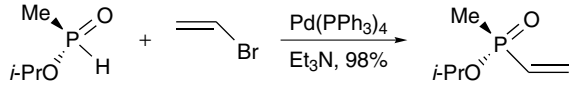
59 **60** **61**



62 **63**

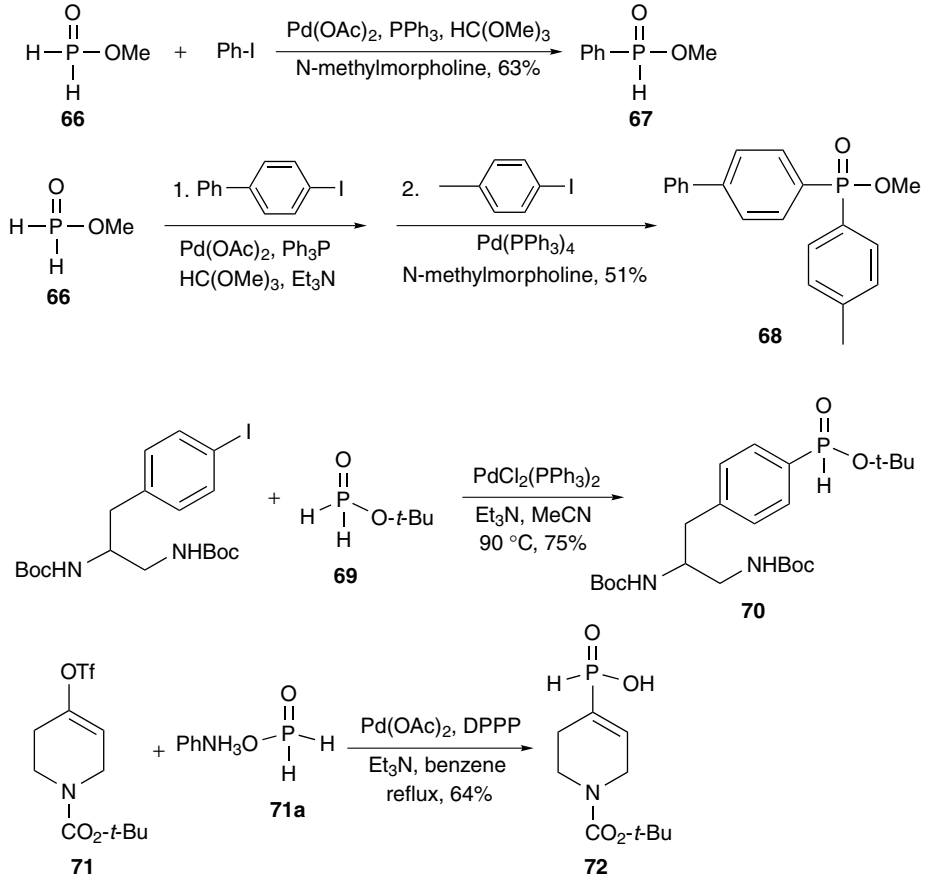


63a

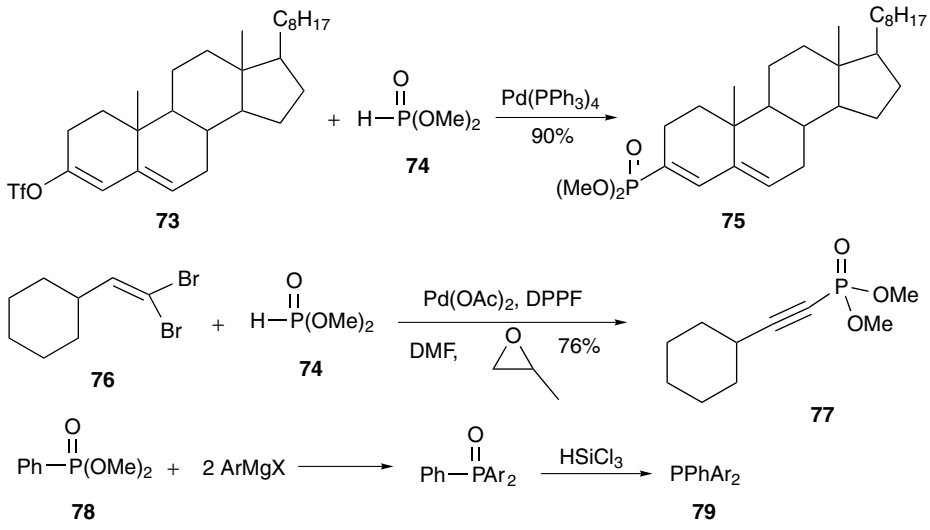


97%ee **64** 97%ee **65**

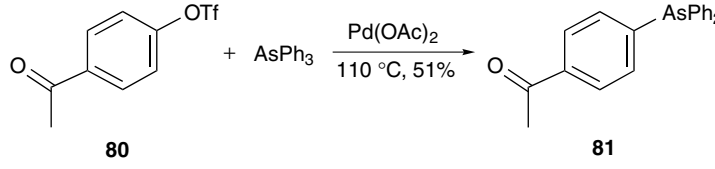
be carried out smoothly in the presence of trimethyl orthoformate [20]. Methyl phenylphosphinate **67** was obtained from **66** in 63 % yield by this method. Asymmetric methyl diarylphosphinate **68** was prepared by stepwise reaction of **66** with two different aryl iodides. Schwabacher and Stefanescu reported that *t*-butyl phosphinate (**69**) is much more stable than the corresponding methyl ester **66** and preparative method of phosphinates can be improved by using *t*-butyl phosphinate (**69**). Actually the functionalized arylphosphinate **70** was prepared in good yield as the *t*-butyl ester [21]. Reaction of anilinium hypophosphite **71a** with alkenyl bromide or triflate **71** afforded the monosubstituted alkenylphosphinic acid **72** without forming the symmetric phosphinic acid by disubstitution. The best ligand is DPPP [22].



Reaction of dimethyl phosphonate (**74**) with the steroidal dienyl triflate **73** gave the dimethyl alkenylphosphonate **75** [23]. Dimethyl alkynylphosphonate (**77**) was produced in one step by the reaction of 1,1-dibromo-1-alkenes **76** with dimethyl phosphonate (**74**) in DMF using $Pd(OAc)_2$-DPPF as a catalyst and propylene oxide as a scavenger of HBr. The expected monocoupling product, bromovinylphosphonate, was not obtained [24]. Phosphonates **78** can be converted to arylphosphines **79** by reaction with aryl Grignard reagents, followed by reduction with $HSiCl_3$ [25].



As a related reaction, functionalized arylarsines **81** can be prepared by the Pd-catalyzed exchange reaction of activated aryl triflates **80** with $AsPh_3$ under solvent-free conditions at 115 °C [26].



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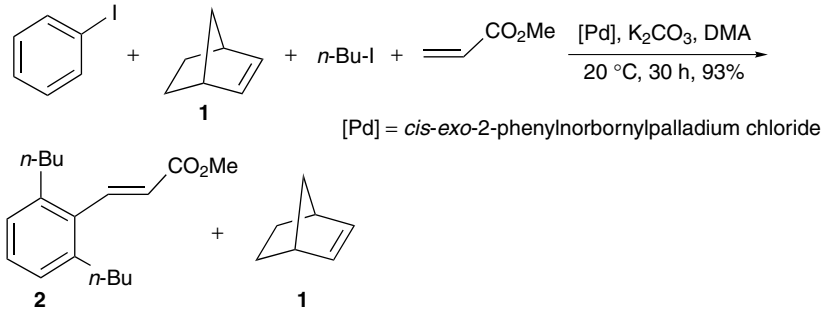
3.8 Miscellaneous Reactions of Aryl Halides

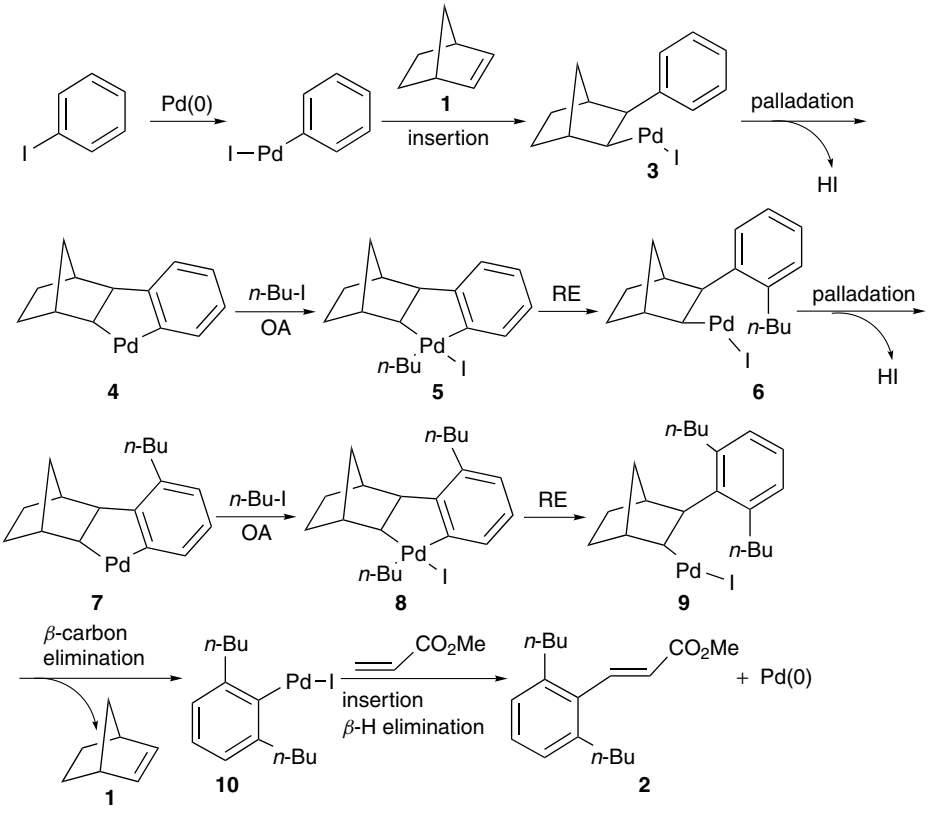
3.8.1 The Catellani Reactions using Norbornene as a Template for *ortho*-Substitution

In continuing studies on Pd-catalyzed reactions of norbornene (**1**), Catellani has discovered very interesting reactions, in which norbornene shows unique behavior [1]. Catellani and co-workers carried out a three-component reaction of iodobenzene, methyl acrylate, and *n*-butyl iodide in the presence of 1 equivalent of norbornene (**1**), and obtained methyl 2,6-di-*n*-butylphenylacrylate (**2**) in 93 % yield using *cis-exo*-2-phenylnorbornylpalladium chloride as a catalyst. Norbornene (**1**) was recovered after the reaction [2]. No direct Heck reaction of iodobenzene with acrylate occurred showing that the strained double bond in norbornene undergoes insertion much faster than that of acrylate. The behavior of norbornene (**1**) is truly remarkable.

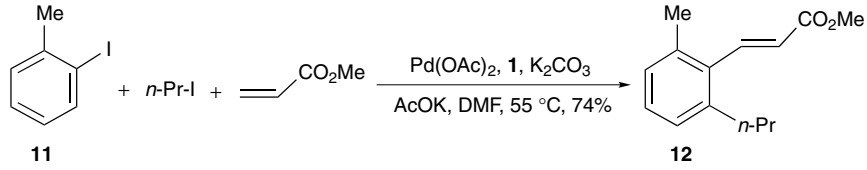


This reaction revealed several very interesting and unexpected (or curious) steps. The mechanistic explanation given by Castellani can be summarized in the following scheme. First, *syn* insertion of **1** to Ph-Pd-I affords the *cis, exo* complex **3**. In this case, *syn* β-H elimination to give phenylnorbornene is impossible due to the rigid *trans* configuration of the Pd atom and β-hydrogen. The

next step is facile formation of the palladacycle **4** under mild conditions mainly by virtue of the coordination of the aromatic ring to Pd. The complex **4** was isolated. The reaction corresponds to activation of an inert aromatic C—H bond. In general, reductive elimination in a five-membered palladacycle **4** to form a cyclobutane is disfavored, and hence unusual oxidative addition of *n*-BuI occurs to give **5**, which is an uncommon Pd(IV) species. The reductive elimination gives the *ortho*-*n*-butylphenylnorbornylpalladium iodide **6** without undergoing β-H elimination of the butyl group. Then similar steps, namely the palladation of **6** to form the palladacycle **7**, the oxidative addition of *n*-BuI to give **8**, and the reductive elimination to afford the 2,6-dibutylphenylnorbornyl complex **9**, are repeated. The 2,6-di-*n*-butylation is explained in this way. Then interestingly, β-carbon elimination of **9** (deinsertion of **1** or decarbopalladation) occurs to yield 2,6-di-*n*-butylphenylpalladium iodide (**10**) and **1** is regenerated. Several further transformations of **10**, such as Heck, Suzuki, and Sonogashira reactions, are possible as expected. Formation of 2,6-di-*n*-butylphenylacrylate (**2**) via insertion of acrylate to **10** and β-H elimination is understandable. The total yields of **2** after multi-step reaction were remarkably high (93 %). The Suzuki and Sonogashira reactions of **10** are shown later. Examples of this type of palladacycle formation by electrophilic attack on benzene rings are increasing (Chapter 3.3.4).



The reaction of *o*-iodotoluene (**11**) with acrylate and a large excess of *n*-PrI in the presence of **1** proceeded more efficiently using ligandless $Pd(OAc)_2$, and 2-methyl-6-*n*-propylphenylacrylate (**12**) was obtained [3].

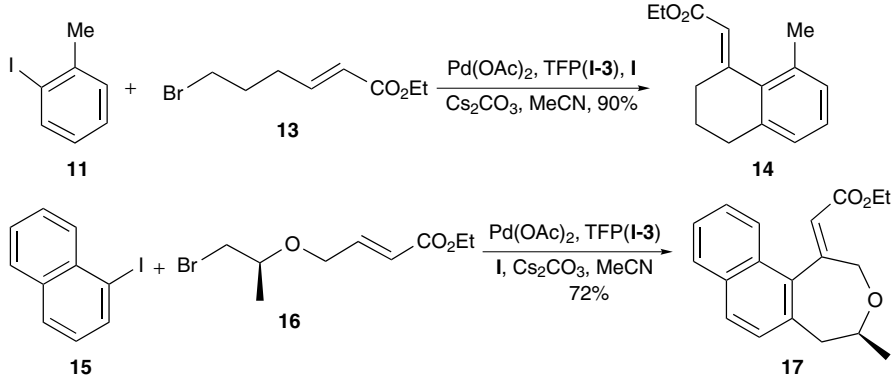


11 **12**

There are several interesting features in this reaction, although they may be understood by high reactivity of the strained double bond in norbornene:

1. Facile selective oxidative addition of alkyl halide to **4**, which is regarded as uncommon.
2. No β-H elimination of *n*-butyl group in **5**.
3. Easy formation of the palladacycles **4** and **7**, which undergo further reactions.
4. Facile β-carbon elimination (deinsertion of **1**) in **9**.
5. No direct Heck reaction and Suzuki coupling of aryl halides occur at all in the three-component reactions of aryl halide, alkyl halide, and alkene (or phenylboronic acid).
6. Smooth reactions with ligandless Pd catalysts. The process shows a new and unique type of 'catalysis' by **1**.

The Catellani's alkylation–alkenylation sequence using norbornene offers a useful synthetic method for 2,6-dialkylated 1-substituted benzenes. Lautens applied the reaction to the synthesis of fused aromatic compounds using *ortho*-substituted iodobenzenes and bromoalkenes. Reaction of *o*-iodotoluene (**11**) with ethyl 6-bromo-2-hexenoate (**13**) afforded the benzocarbocycle **14** via monoalkylation and intramolecular Heck reaction. It is important to use tri-2-furylphosphine (**I-3**) as a ligand [4]. Similarly the 2,5-disubstituted 4-benzoxepine **17** was obtained in 72 % yield by the reaction of 1-iodonaphthalene (**15**) with the unsaturated bromo ester **16** [5].

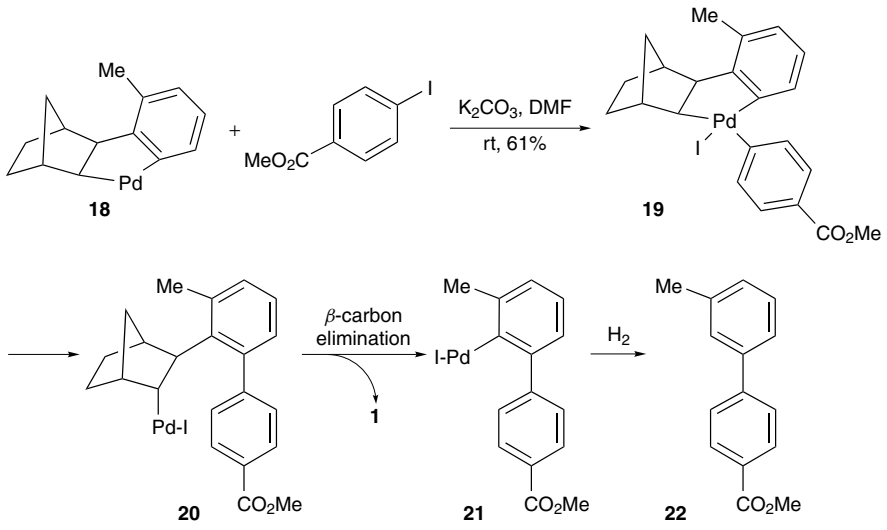


11 **13** **14**

15 **16** **17**

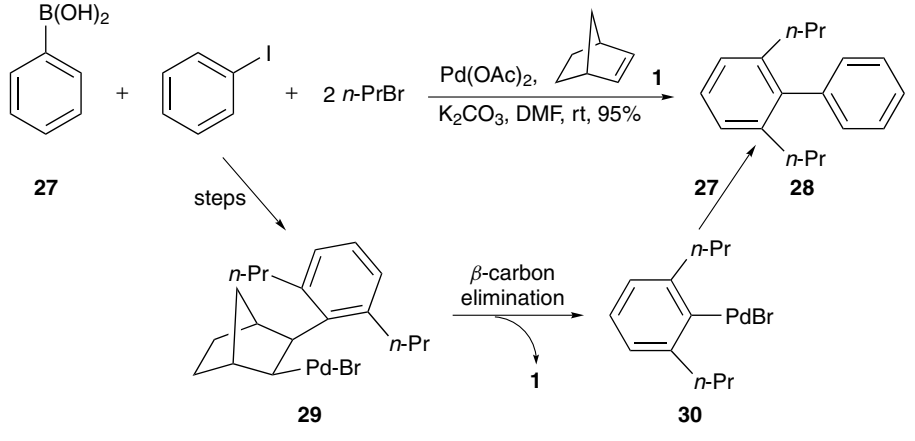
Similar to the formation of the *ortho*-alkylated phenylnorbornyl complex **6**, *ortho* arylation is possible. Reaction of the palladacycle **18**, which has an *ortho* methyl group, with methyl *p*-iodobenzoate afforded the substituted biphenyl **22** [6]. The formation of **22** can be understood by oxidative addition of iodobenzoate to **18** to generate **19**, reductive elimination to form **20** by sp^2–sp^2 C—C bond formation,

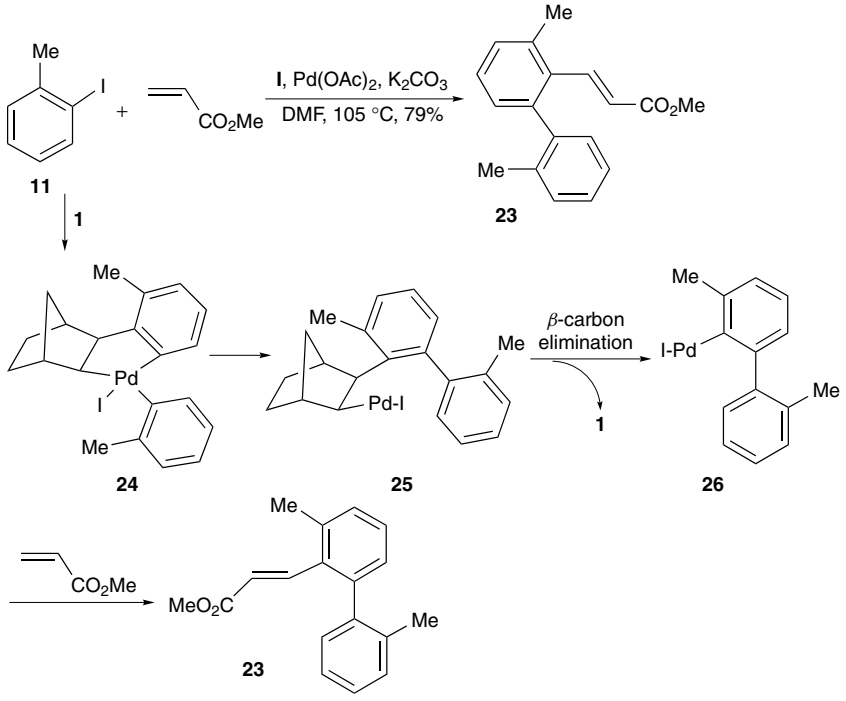
and deinsertion of norbornene from **20** to provide **21**. Treatment of **21** with H_2 produced the *meta*-substituted biphenyl **22**. Although the reaction is stoichiometric, it shows the possibility of *ortho* arylation.



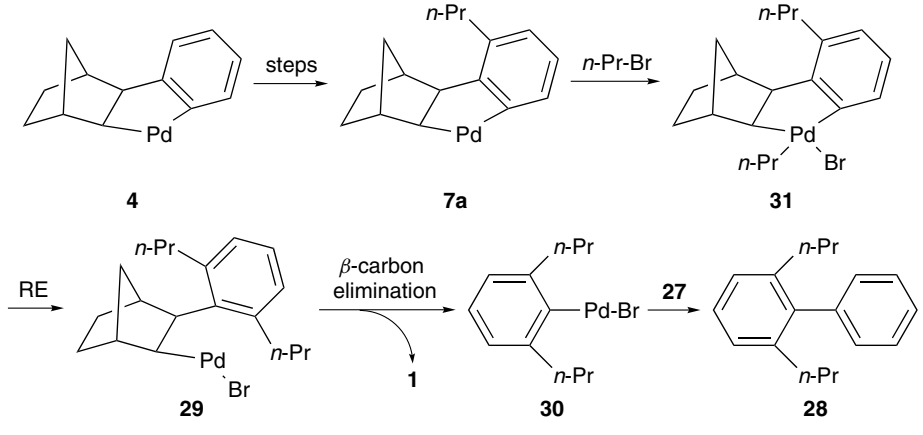
The *ortho* arylation was combined with the Heck reaction. Reaction of *o*-iodotoluene (**11**) with methyl acrylate in the presence of **1** gave rise to the substituted biphenylylacrylate **23** [7]. This Pd-catalyzed reaction is understood by the sequential formation of **24, 25** and **26**. It is very interesting that no direct Heck reaction of **11** with acrylate occurs at all under the conditions due to higher reactivity of norbornene compared with acrylate. The reaction of allyl alcohol provided 3-biphenylylpropanal [7a].

The norbornene-catalyzed reaction has also been extended to synthesis of 2,6-dialkyl-1, 1′-biphenyl **28** by 2,6-dialkylation of aromatic ring via palladacycles and Suzuki–Miyaura coupling. The reaction of phenylboronic acid (**27**), iodobenzene, and *n*-propyl bromide (excess) in the presence of norbornene (**1**) afforded 2,6-di-*n*-propyl-1-biphenyl (**28**) in 95 % yield via **29** and **30**.

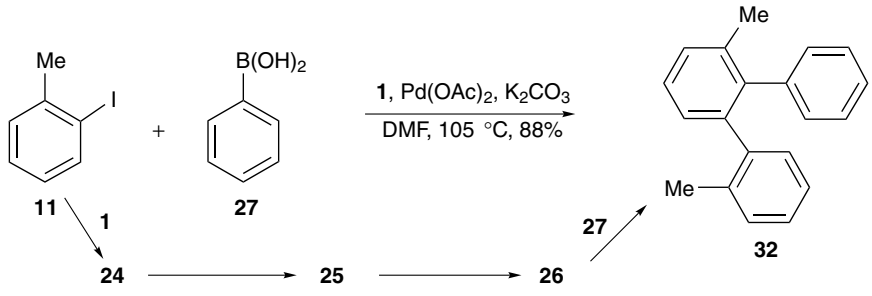




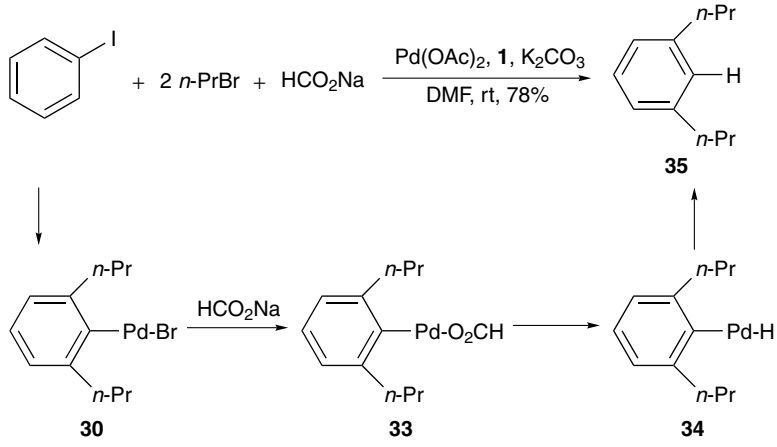
The reaction proceeds via the formation of the palladacycles **4** and **7a**. After the formation of **29** by 6-propylation of **31**, elimination of β-carbon regenerates norbornene (**1**) and 2,6-dipropylphenylpalladium bromide **30**. At the final step, Suzuki coupling of **30** with **27** gives 2,6-di-*n*-propyl-1-biphenyl (**28**) in a surprisingly high yield (95 %) after so many steps [8].



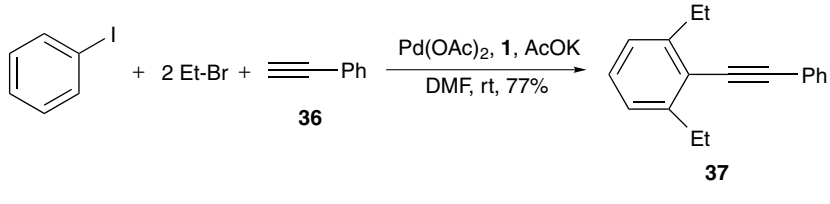
Combination of the *ortho* arylation with Suzuki coupling as a good synthetic method of terphenyls was carried out [9]. Reaction of *o*-iodotoluene (**11**) with phenylboronic acid (**27**) afforded dimethylterphenyl **32** in 88 % yield. The reaction is easily understandable by formation of the biphenylylpalladium **26** via **24** and **25**. The Suzuki coupling of **26** with **27** yields the terphenyl **32** as expected.



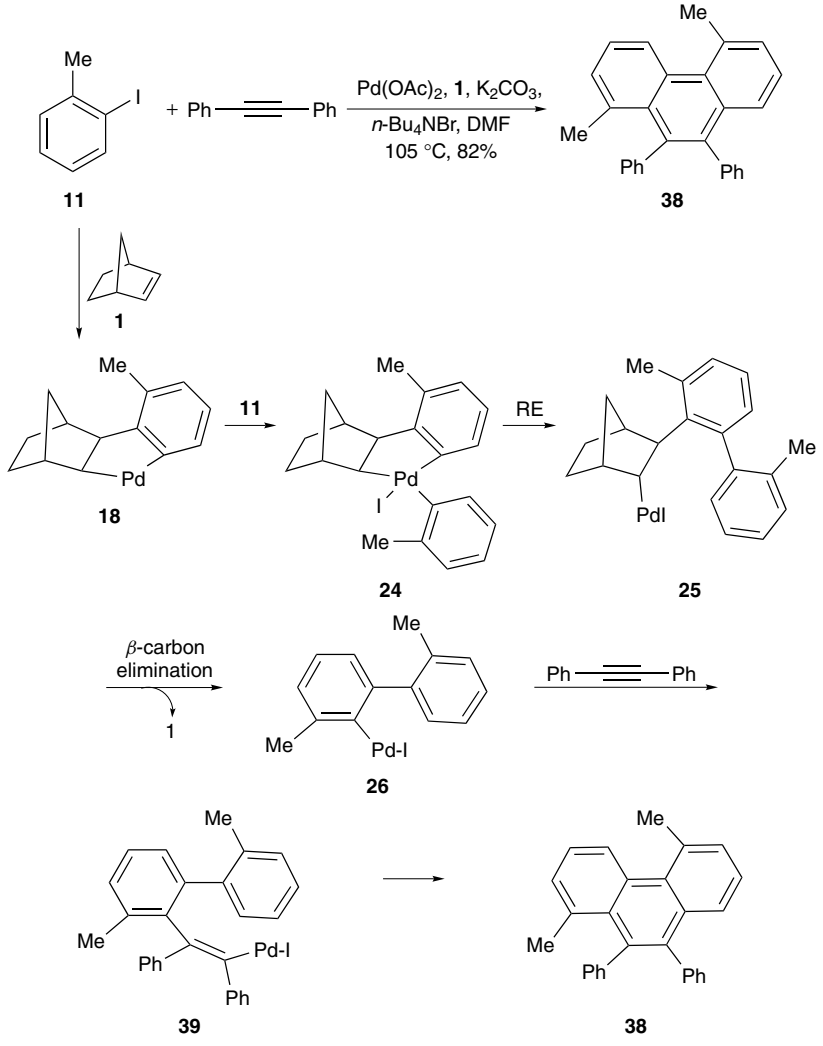
When sodium formate is used as a terminating agent, hydrogenolysis of arylpalladium occurs [10]. Reaction of iodobenzene, *n*-propyl bromide, and sodium formate afforded 1,3-di-*n*-propylbenzene (**35**) in 78 % yield. In this case, the 2,6-di-*n*-propylphenylpalladium **30** was hydrogenolyzed with sodium formate, and **35** was obtained via Pd formate **33** and hydridopalladium **34**. This is not only very interesting, but also useful, because *meta* dialkylation of benzene can be achieved in this way, which is difficult to carry out by conventional methods.



The reaction can be combined with Sonogashira coupling to give *o*, *o*′-dialkylated diphenylacetylenes [11]. Pd-catalyzed reaction of iodobenzene, ethyl bromide, and phenylacetylene (**36**) afforded 2,6-diethyldiphenylacetylene **37** in 78 % yield with remarkable chemoselectivity. In this reaction, CuI as a cocatalyst was not used. The direct Sonogashira coupling of iodobenzene with phenylacetylene (**36**) was suppressed by slow addition of excess ethyl bromide and phenylacetylene at room temperature.



Substituted phenanthrene **38** was prepared by the reaction of *o*-iodotoluene (**11**) with diphenylacetylene in the presence of *n*-Bu_4NCl in 82 % yield [12]. The reaction is explained by insertion of diphenylacetylene to the biphenylyl-palladium **26** to form **39**, which undergoes well-known cyclization to provide the dimethyldiphenylphenanthrene **38**.



Although norbornene is recovered at the end of the reactions, it is used in a large amount, and it is not a true catalyst in the exact sense. However, the remarkably high chemoselectivity of the norbornene 'catalyzed' reactions is impressive.

References

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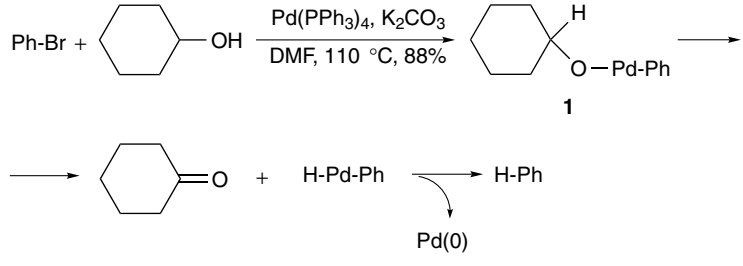
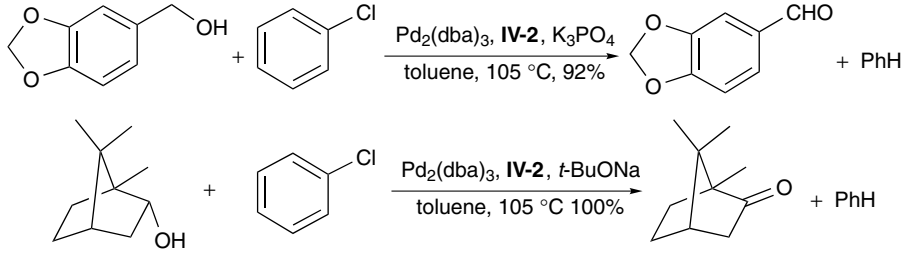
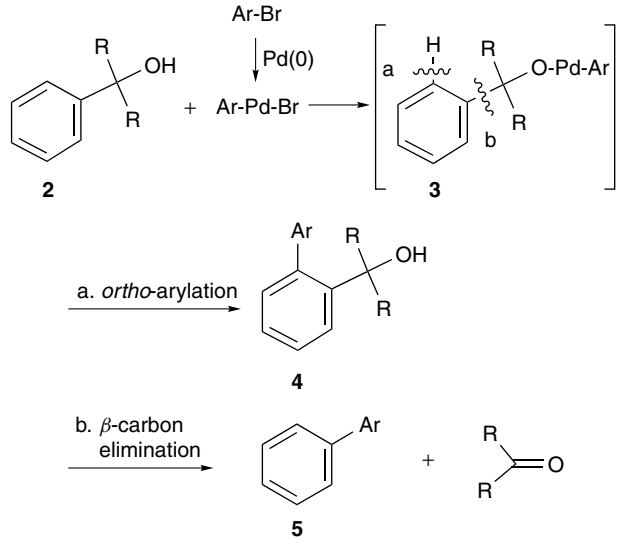
3.8.2 Reactions of Alcohols with Aryl Halides Involving β-Carbon Elimination

A unique method of oxidation of primary and secondary alcohols was found by Tamaru, who reported that the Pd-catalyzed oxidation of alcohols with aryl halides proceeds under basic conditions involving β-H elimination of the alkoxypalladium **1** [1]. Guram *et al*. reported that cheaply available chlorobenzene can be used for the oxidation of benzyl alcohols and some secondary aliphatic alcohols in toluene at 105 °C using biphenylyl(dicyclohexyl)phosphine (**IV-2**) as a ligand. Sterically hindered aliphatic alcohol was oxidized using *t*-BuONa as a base [1a].

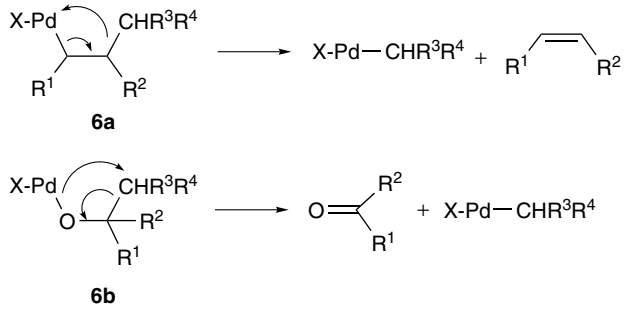




Miura and co-workers made an interesting observation when they treated α,α-disubstituted arylmethanols **2** with aryl halides. In this case, there is no possibility of β-H elimination, and they observed two transformations of the palladium alkoxide **3**: *ortho*-arylation to give biarylyl alcohol **4**; and β-carbon elimination to afford biaryl **5** and ketone [2]. A general aspect of *ortho*-arylation of aromatics is surveyed in Chapter 3.3, and reactions involving β-carbon elimination are treated in this section. Examples of β-carbon elimination are still rare, but numbers are increasing.

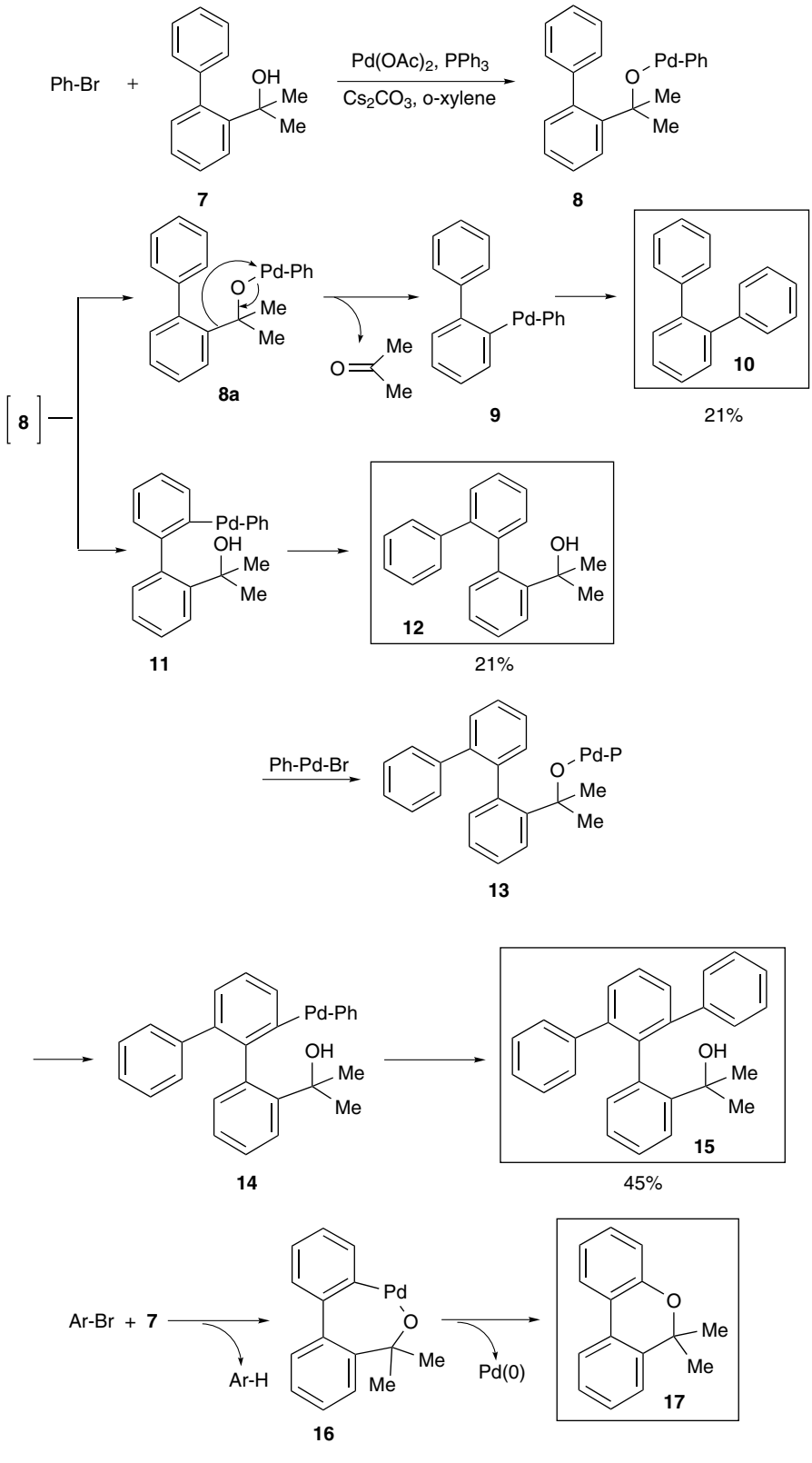


The frequently observed β-carbon elimination is expressed by the following two types. As discussed in Chapter 1.3.5, the directions of arrows as indicated by **6a** and **6b** have no exact mechanistic meaning. The arrows are used in this book in order to help synthetic organic chemists understand the chemical transformations.

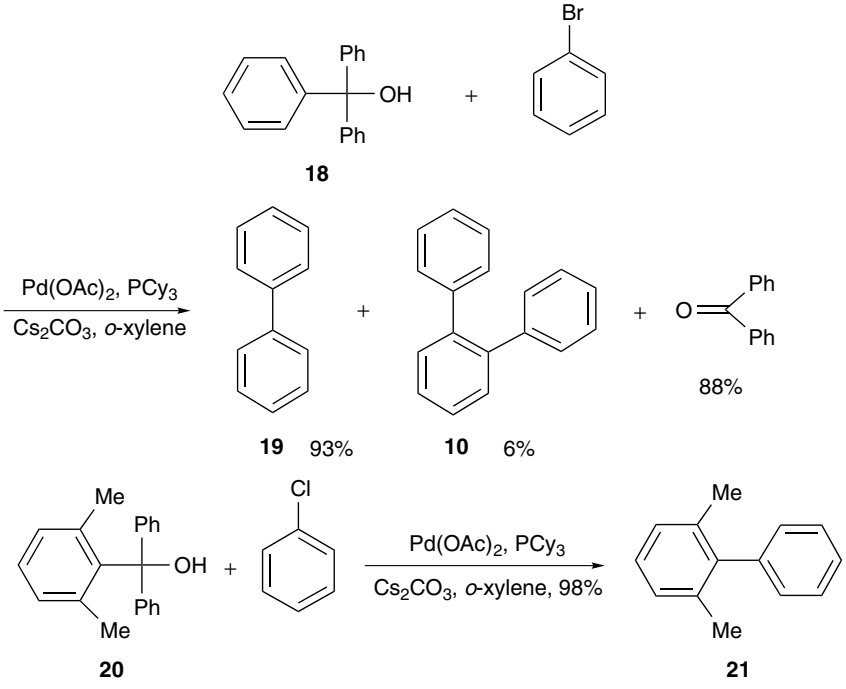


Miura *et al*. carried out extensive studies on the reaction of 2-(biphenyl-2-yl)-2-propanol (**7**) with aryl bromide and related reactions using Cs_2CO_3 as a suitable base [3]. A mechanistic explanation of the whole process is summarized in the following. In the reaction with bromobenzene, first the phenylpalladium alkoxide **8** is formed. They found that *ortho*-arylation to produce **12** (21 %) and **15** (45 %) is the main path when PPh_3 is used as a ligand as indicated by the paths from **8** to **15** via **11,12,13** and **14**. On the other hand, arylative coupling via β-elimination of aryl group as indicated by **8a** occurs to yield *o*-terphenyl (**10**) in 21 % yield. When bulky bromides such as 2-substituted 1-bromonaphthalenes are used, the ether **17** is produced as the major product via the formation of the palladacycle **16**.

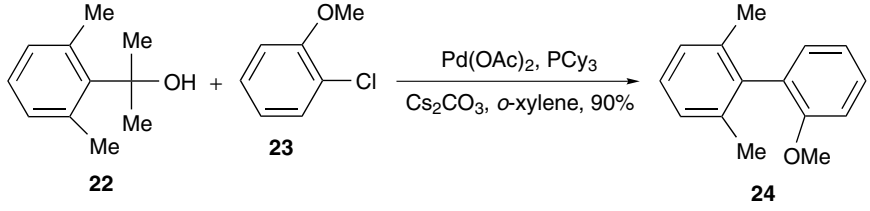
The β-carbon elimination becomes the main path when PCy_3 is used. Reaction of triphenylmethanol (**18**) with bromobenzene gave rise to biphenyl (**19**) in 93 % yield, along with *o*-terphenyl (**10**) in 6 % yield. For the arylation, aryl chlorides can be used as coupling partners. The coupling of 2,6-dimethylphenyl(diphenyl)-methanol (**20**) with chlorobenzene afforded, 2,6-dimethylbiphenyl (**21**) in 98 %


Ph-Br
OH
Me
Me
7
Pd(OAc)2, PPh3
Cs2CO3, o-xylene
O
Pd-Ph
Me
Me
8
[8]
Pd-Ph
O
Me
Me
8a
Me
O
Me
Pd-Ph
9
10
21%
Pd-Ph
OH
Me
Me
11
OH
Me
Me
12
21%
Ph-Pd-Br
O
Pd-P
Me
Me
13
Pd-Ph
OH
Me
Me
14
OH
Me
Me
15
45%
Ar-Br + 7
Ar-H
Pd
O
Me
Me
16
Pd(0)
O
Me
Me
17

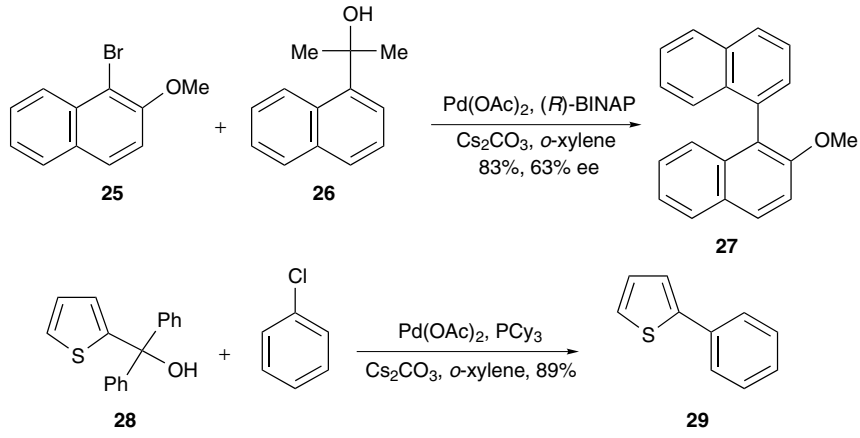
yield without giving biphenyl at all. The result clearly shows that the bond to the bulky aryl group is cleaved preferentially. In other words, the aryl group having one or two *ortho* substituent(s) is selectively eliminated.



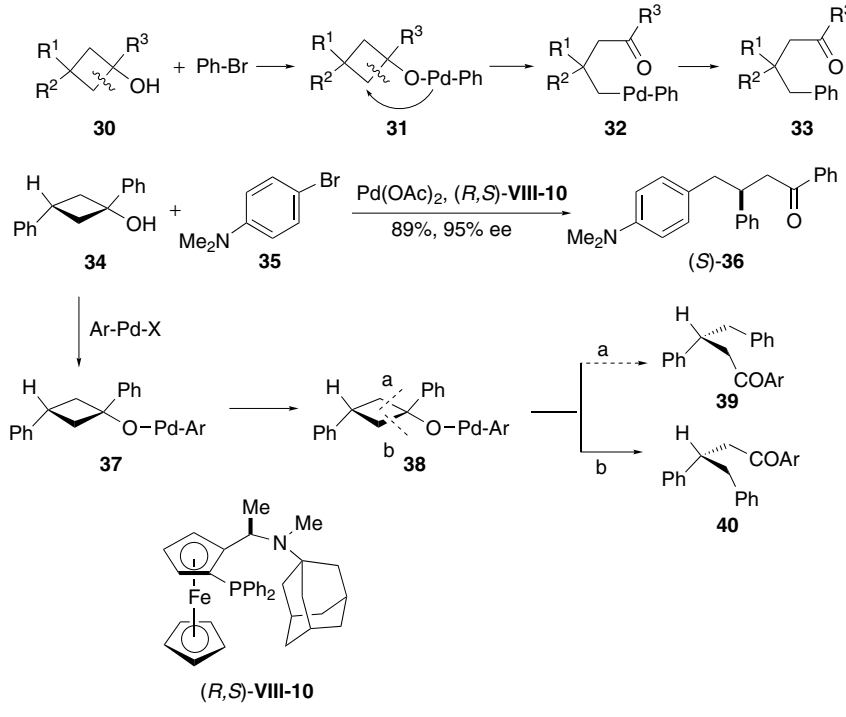
The coupling reaction offers a very useful synthetic method of various biaryls. Coupling of 2-(2,6-dimethylphenyl)-2-propanol (**22**) with 2-chloroanisole (**23**) was carried out and the asymmetric biphenyl **24** was obtained. The smooth coupling of **22** demonstrates a synthetically more useful method than that of **20**, because readily removable acetone is the byproduct.



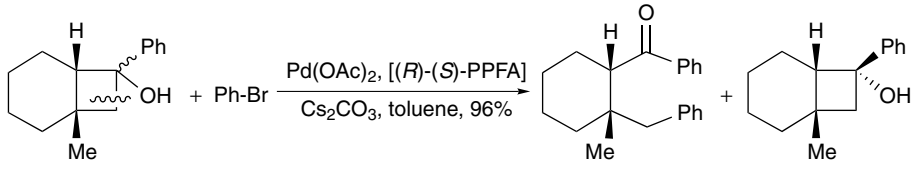
The coupling of the naphthalene derivatives **25** with **26** using (*R*)-BINAP as a chiral ligand provided the (*R*)-enantiomer-enriched binaphthyl **27** with 63 % ee, suggesting a possibility of asymmetric syntheses of substituted chiral binaphthyls. The coupling can be extended further to heteroaryl derivatives. Reaction of (2-thienyl)diphenylmethanol (**28**) with chlorobenzene gave 2-phenylthiophene (**29**) in 89 % yield.



β-Carbon elimination is observed in other systems. Ring-opening of *tert*-cyclobutanols **30** by the reaction with aryl halides has been reported and the reaction is explained to proceed via β-carbon elimination as shown by **31** to generate alkylpalladium **32**, which is converted to **33** [4]. Asymmetric arylation of the cyclobutanol **34** with *N*,*N*-dimethylaminobromobenzene (**35**) using the bulky *N*-adamantyl derivative of (*R*), (*S*)-PPFA **VIII-10** as a chiral ligand afforded the γ-phenylated ketone **36** in 89 % yield with 95 % ee. In this reaction, enantioselective C-C bond cleavage (a or b) as explained by **38** occurs to provide one of the enantiomers **39** and **40**. It was concluded that the b-bond cleavage occurred when the ligand **VIII-10** was used [5].



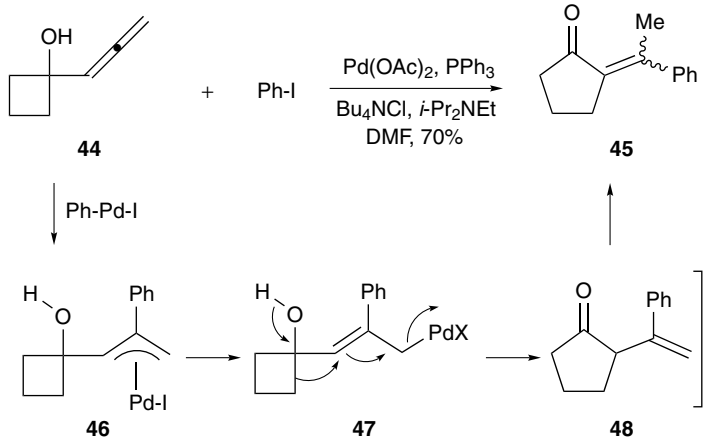
Kinetic resolution of the racemic cyclobutanol **41** occurred by the reaction with bromobenzene using (*R*), (*S*)-PPFA (**VIII-9**) to give the chiral ketone **42** and the recovered cyclobutanol **43** with moderate enantioselectivity [6]. It is noted that in this type reaction, less-substituted carbon is eliminated selectively.



41 **42** **43**

45%, 56% ee 46%, 59% ee

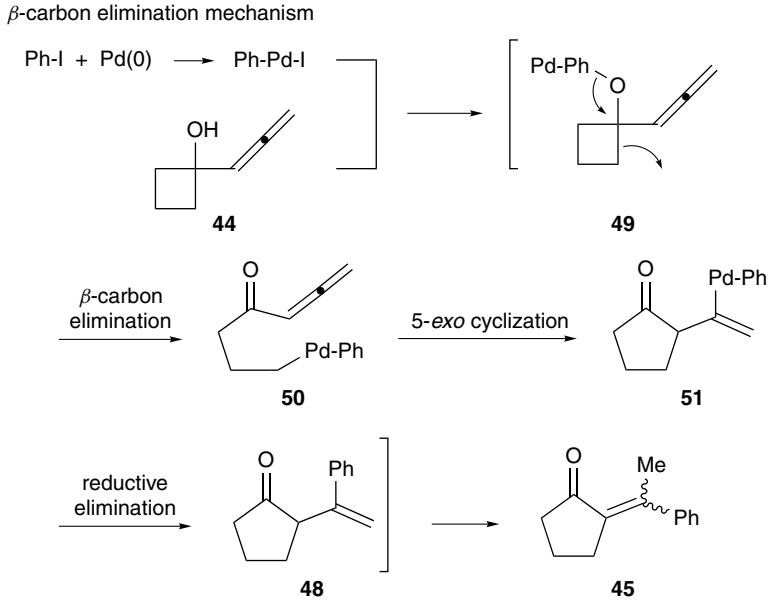
Ring expansion occurs by the reaction of allenylclobutanols with halides to cyclopentanones [7]. Intermolecular reaction of the allenylcyclobutanol **44** with iodobenzene afforded the cyclopentanone **45**. Larock and Reddy explained the reaction by the following mechanism. The carbopalladation of the allene with Ph-Pd-I generates the π-allylpalladium **46**, and the concerted rearrangement and ring expansion as shown by **47** provide **48**, which isomerizes to **45** [8].



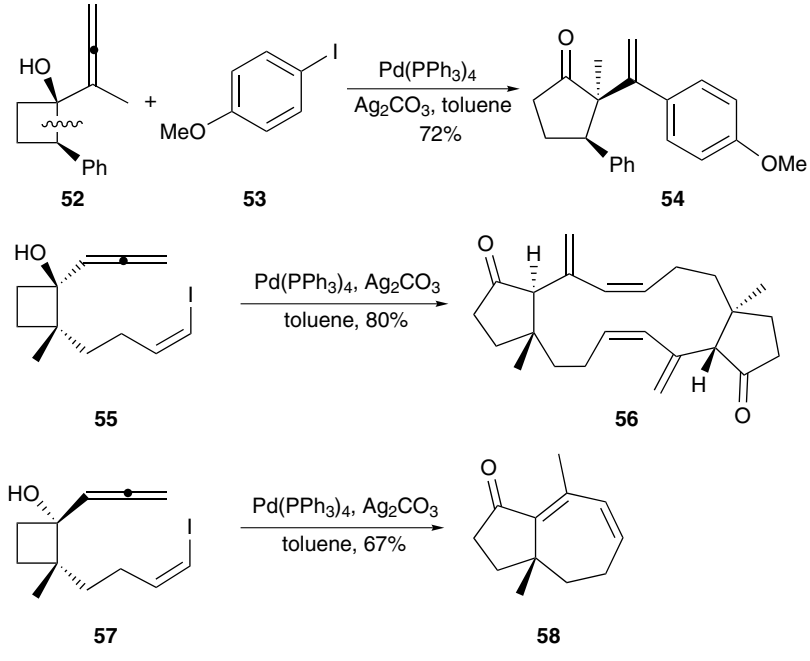
44 **45** **46** **47** **48**

As another possibility, the reaction of **44** might be explained by the formation of palladium alkoxide **49**, followed by β-carbon elimination to afford **50**. Carbopalladation (5-*exo* cyclization) of **50** gives **51**, and reductive elimination produces **45** via **48**. However, this route seems to be less likely, since more substituted carbon migrates in this type of reactions as demonstrated by the following examples [9].

Ihara *et al*. carried out interesting applications of the cyclopentanone formation. Stereoselective synthesis of α-substituted cyclopentanone **54** with a quaternary carbon stereocenter was carried out by the reaction of the allenylcyclobutanol **52** with 4-iodoanisole (**53**) [9]. Intramolecular reactions of the stereoisomers **55** and **57** in the presence of silver salt in toluene afforded different products depending on their stereochemistry. The macrocyclic dimeric product **56** was obtained from

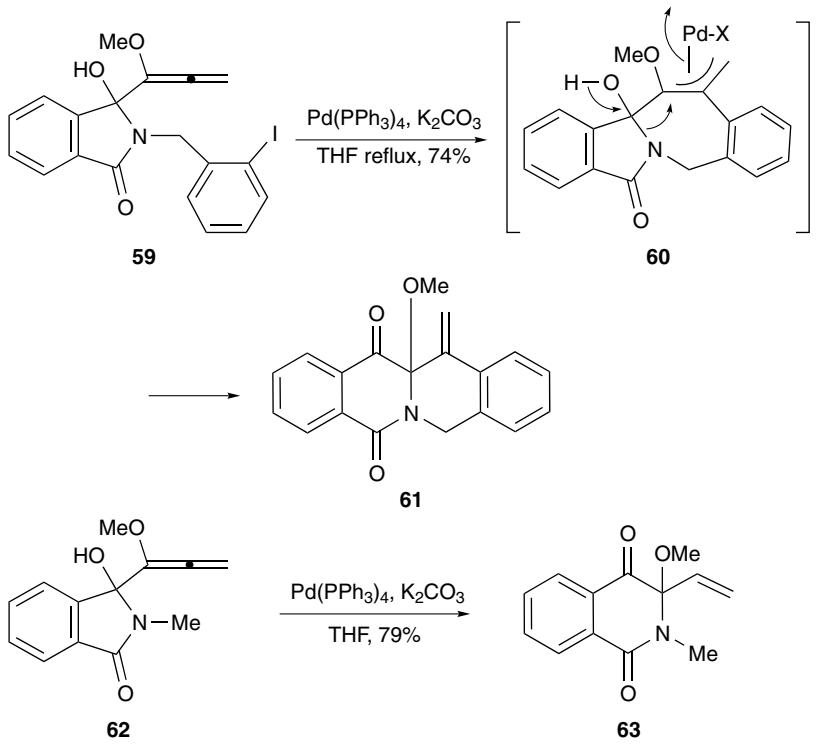


55 in 80 % yield, a surprisingly high yield, and the monomeric product **58** was obtained from **57** [7].



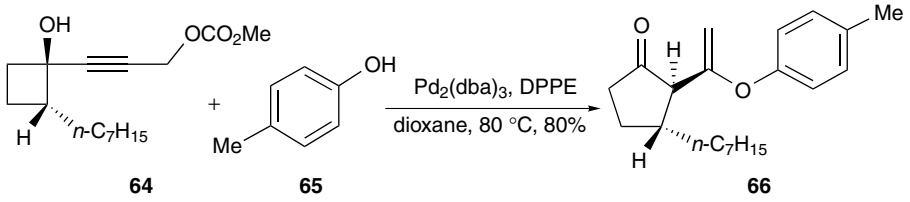
Similar carbopalladation–ring expansion was observed in the Pd-catalyzed reaction of the (hydroxy)- methoxyallenylisoindoline bearing an iodophenyl moiety **59**. In this case, carbopalladation of the allene to form the π-allylpalladium is followed by rearrangement–ring expansion, as shown by **60**, to give the isoquinolinedione

61 [10]. The allenyl alcohol without the iodophenyl moiety **62** alone undergoes the Pd-catalyzed rearrangement–ring expansion to give the isoquinolinedione **63** [11].



59 **60** **61** **62** **63**

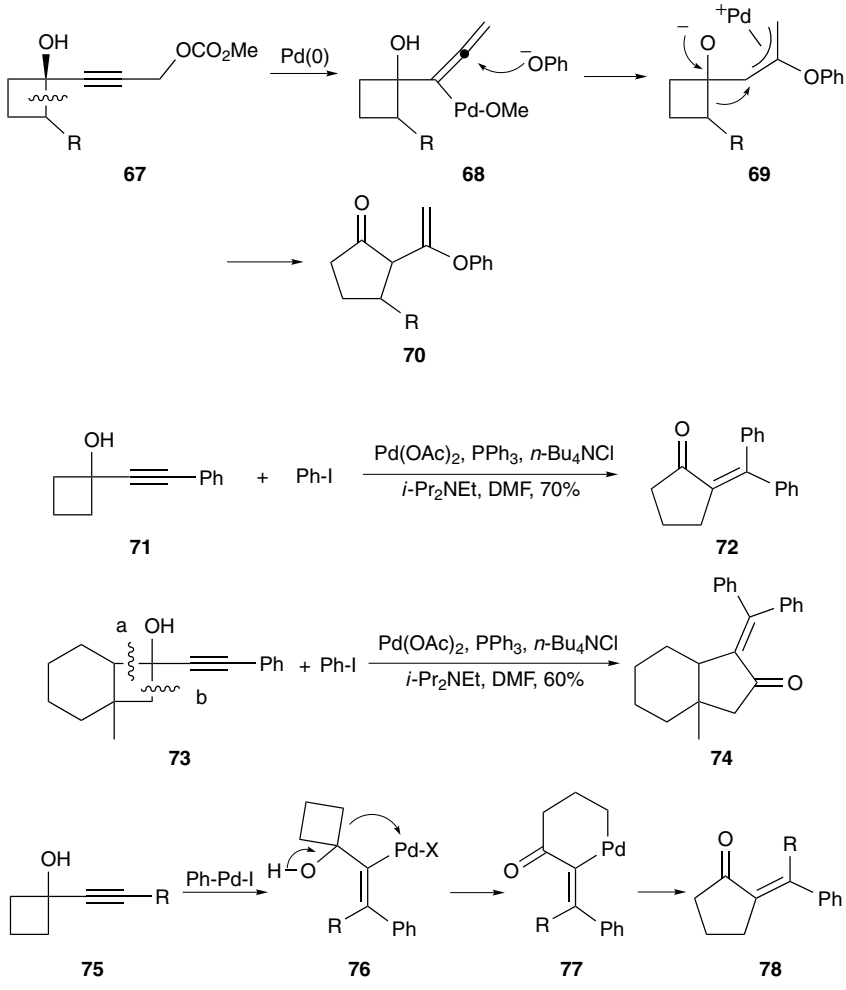
Interestingly, formation of the cyclopentanone **66** from the cyclobutanol having propargyl carbonate moiety **64** occurred by treatment with *p*-cresol (**65**) using DPPE as a ligand.



64 **65** **66**

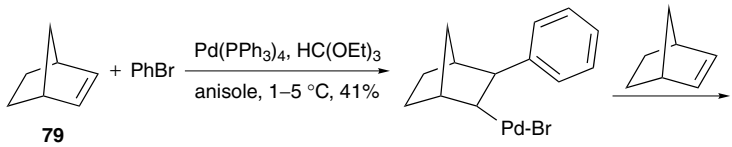
Ihara *et al*. explained the reaction by the formation of the allenylpalladium **68**, which is attacked by phenoxide to form π-allylpalladium intermediate **69**. Finally, ring expansion of **69** gives the cyclopentanone **70** [12].

Larock and Reddy obtained the 2-alkylidenecyclopentanone **72** by the reaction of 1-(1-alkynyl)cyclobutanol **71** with iodobenzene. The bicyclononanone **74** was obtained from **73**. Selective formation of **74** demonstrates that the more substituted bond a in the cyclobutanol **73** undergoes exclusive cleavage (or migration) [8,13]. Larock proposed the mechanism of the reaction of **75** involving ring expansion of **76** to form palladacycle **77** and reductive elimination to give **78**.

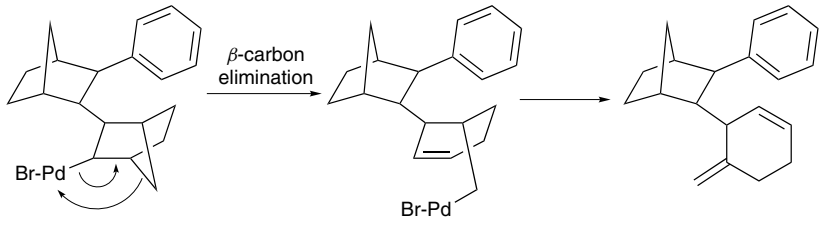


A somewhat different example of β-carbon elimination was observed by Catellani and Chiusoli in 1983 [14]. Reaction of two molecules of norbornene (**79**) with bromobenzene gave rise to **83**. Stepwise carbopalladations of norbornene generate **80** and **81**. Then β-carbon elimination yields the alkylpalladium **82** and β-H elimination affords **83**. As described in Chapter 3.8.1, the deinsertion of norbornene from **84** to generate norbornene (**79**) and arylpalladium **85** is an example of β-carbon elimination.

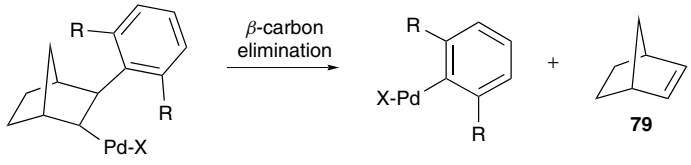
Although no aryl halide is involved, Pd-catalyzed ring cleavage of cyclobutanone oximes **86**, leading to unsaturated nitriles **89** via β-carbon elimination as shown by **87** to give the alkylpalladium **88**, was reported by Nishimura and Uemura [15]. The tricyclic *O*-benzoyloxime **93** was converted to the nitrile **94** by selective bond cleavage. Interestingly the cyclopropanecarbonitrile **99** was obtained from the spiro compound **95**. In this reaction, β-carbon elimination generates the alkylpalladium **97**, which has no possibility of β-H elimination. Under basic conditions, intramolecular nucleophilic attack of the carbanion to the alkylpalladium provides the palladacyclobutane **98**, and the cyclopropanecarbonitrile **99** is formed by reductive elimination.



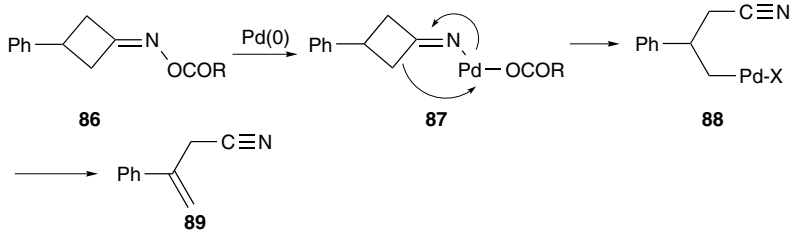
79 **80**



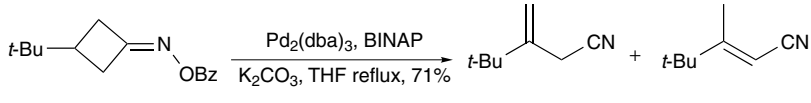
81 **82** **83**



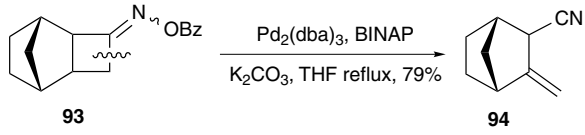
84 **85** **79**



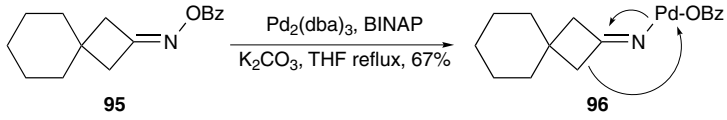
86 **87** **88** **89**



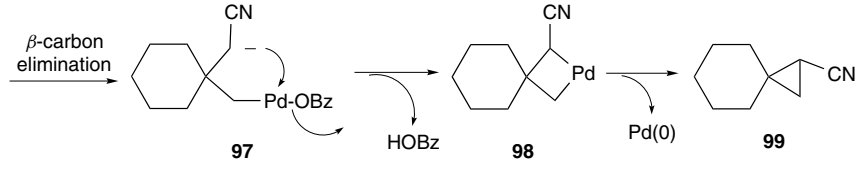
90 **91** 64 : 36 **92**



93 **94**

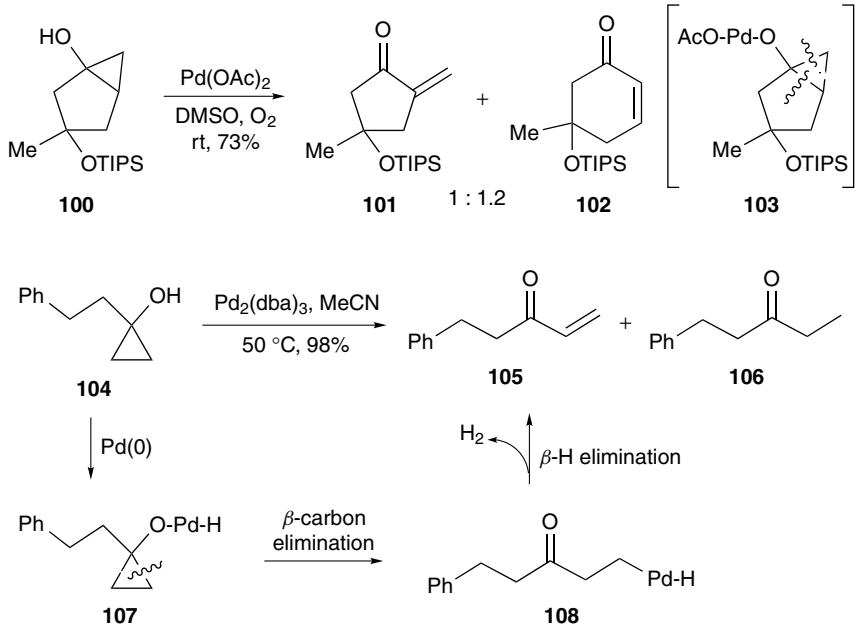


95 **96**



97 **98** **99**

As a related reaction, ring opening of cyclopropyl alcohols was reported by the Uemura and Cha groups using Pd(II). Two products **101** and **102** were obtained in a ratio of 1 : 1.2 by the ring opening of bicyclo[1.0.3]hexane **100** as shown by **103** [16]. $Pd(OAc)_2$ in DMSO under oxygen was used and they claim that the reaction is promoted by Pd(II). On the other hand, Okumoto and co-workers carried out the ring cleavage of **104** using ligandless $Pd_2(dba)_3$ alone to afford the unsaturated ketone **105** and a negligible amount of the saturated ketone **106** [17]. Formation of hydridopalladium alkoxide **107** by oxidative addition of Pd(0) to alcohol and β-H elimination in **108** are assumed in their case.



As described in Chapter 5.3, a number of addition reactions to methylenecyclopropanes are explained by β-carbon elimination.

References

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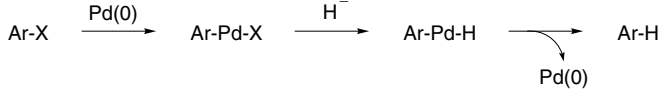
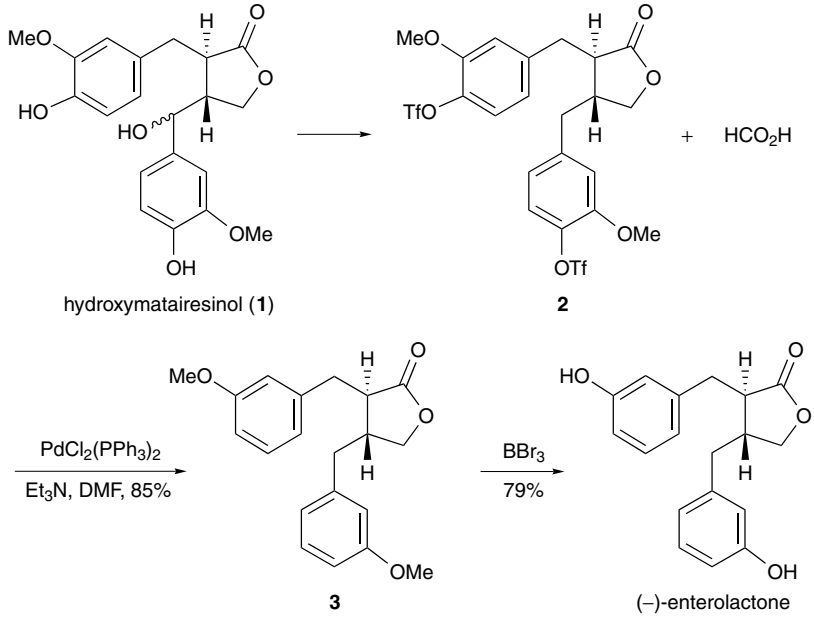
3.8.3 Hydrogenolysis with Various Hydrides

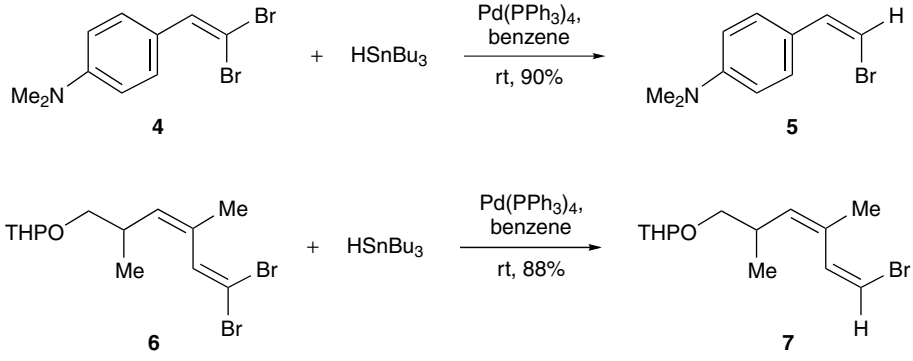
Pd-catalyzed hydrogenolysis of aryl and alkenyl halides and pseudohalides such as triflates using various hydride sources is an established process. The reaction can be explained by the transmetallation with hydride to form palladium hydride, which undergoes reductive elimination. Among several hydride sources, HCO_2H/Et_3N, $HSnBu_3$, and R_3SiH are most extensively used. Typical recent examples of hydrogenolysis using these hydrides are briefly cited in this section.



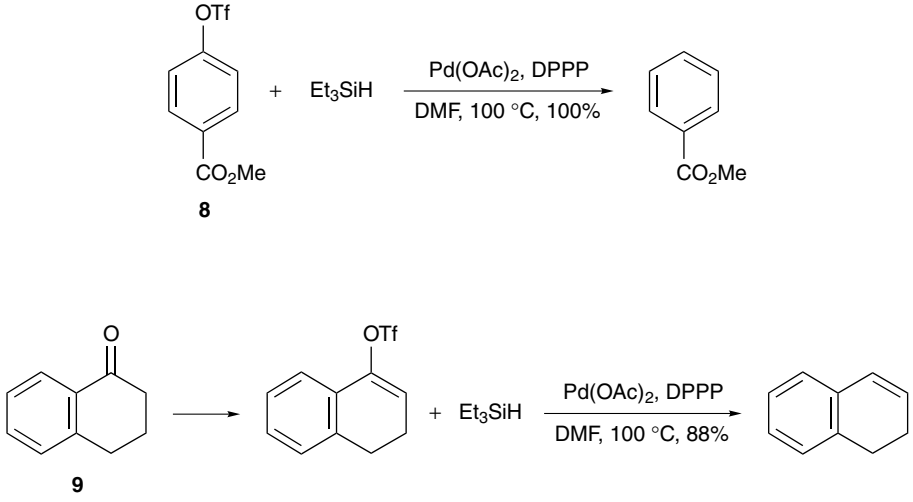
Ammonium formate, typically a mixture of HCO_2H and Et_3N, is soluble in organic solvents and hydrogenolysis proceeds under mild conditions [1]. In the synthesis of (−)-enterolactone from natural lignan hydroxymatairesinol **1**, OH groups were removed by hydrogenolysis of their 4, 4′-bistriflates **2** using HCO_2H and Et_3N to yield 3, 3′-dimethylenterolactone (**3**) in 85 % yield [2].



Stereoselective hydrogenolysis of 1,1-dibromo-1-alkenes with $HSnBu_3$ proceeds at room temperature to afford (*Z*)-1-bromo-1-alkenes [3]. The dibromide **4** was converted to (*Z*)-bromide **5** cleanly. The (*Z*)-bromide **7** was obtained from1,1-dibromo-1,3-diene derivative **6**. PPh_3 as a ligand gave the best results. An unsatisfactory result was obtained when HCO_2H/Et_3N was used. (*Z*)-1-Bromo-1-alkenes are useful to prepare conjugated (*Z*)-alkenyl compounds by Pd-catalyzed reactions.

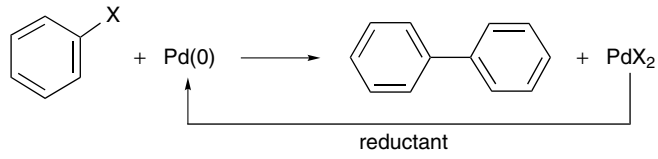


Aryl and alkenyl triflates **8** and **9** were hydrogenolyzed with Et_3SiH in DMF [4].



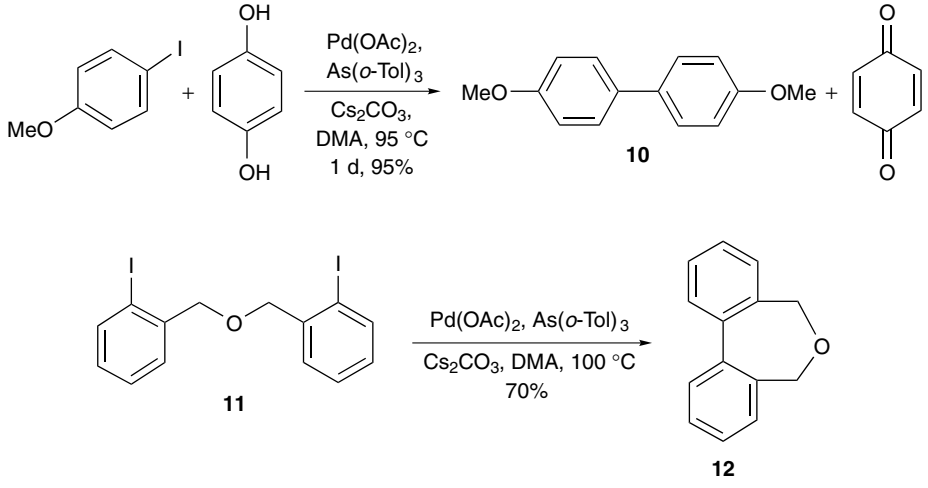
3.8.4 Homocoupling of Organic Halides (Reductive Coupling)

Homocoupling of aryl halides promoted by Cu metal is an old reaction, called the Ullmann reaction. An interesting review on the historical background of Ullmann coupling was published recently [5]. Pd(0) can be used for the coupling. The Ullmann coupling of aryl and alkenyl halides catalyzed by Pd(0) to give symmetrical biphenyl and conjugated dienes proceeds smoothly with proper reductants. Pd(0) species mediate the coupling with concomitant oxidation of Pd(0) to $Pd(II)X_2$, and a reducing agent is required to regenerate Pd(0) from Pd(II) in order to make the reaction catalytic. The reaction is reductive coupling of the halides, which is

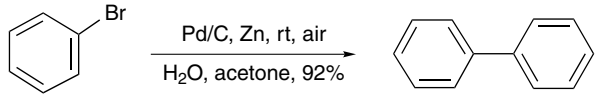


mechanistically different from all the reactions of aryl halides so far discussed. The efficiency of the catalytic reaction depends on the activity of the reductants. A number of reductants are used. Zn or Cu powder are frequently used. Recent reports on the reductive coupling using other reductants are cited in this section.

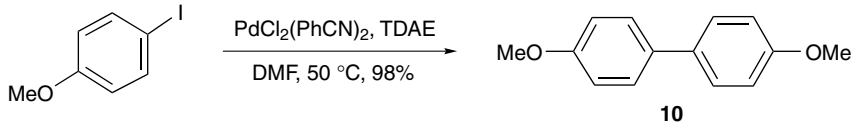
As a convenient process, Rawal used $Pd(OAc)_2$ combined with As(*o*-Tol)$_3$ or P(*o*-Tol)$_3$ as a catalyst, and hydroquinone as a reductant in DMA in the presence of Cs_2CO_3 for the coupling of mainly aryl iodides. The coupling product **10** was obtained in 95 % yield. Intramolecular coupling of the diiodide **11** afforded **12** in 70 % yield [6].



The coupling catalyzed by Pd/C in the presence of Zn powder proceeds smoothly at room temperature in a mixed solvent of acetone and water as the best solvent. Venkatraman and Li carried out the reductive reaction even under an air atmosphere, and claimed that the Pd catalyst is not sensitive to oxygen [7].



Tanaka *et al*. reported that tetrakis(dimethylamino)ethylene (TDAE) (**13**) is an efficient reductant for the coupling of aryl bromides. Ligandless Pd compounds such as $PdCl_2(PhCN)_2$ and $Pd(OAc)_2$ are active catalysts. Phosphine-ligated complexes such as $Pd(PPh_3)_4$ are not effective. The coupling proceeds in DMF at 50 °C to give the coupling product in 98 % yield [8].



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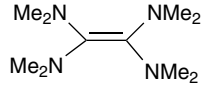
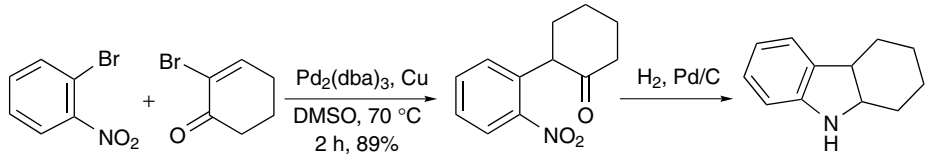


TDAE **13**

Ullmann coupling is homocoupling. Banwell *et al*. reported an interesting cross coupling of *o*-halonitroarenes with α-halo enones [9]. As an example, reaction of *o*-bromonitrobenzene (**14**) with 2-bromocyclohexenone **15** proceeded in the presence of ligandless Pd catalysts such as $Pd_2(dba)_3$ or Pd/C and Cu powder in DMSO to yield the cross coupling product **16** in 89 % yield based on **15**. The homocoupling of bromonitrobenzene (**14**) is a competitive reaction. This unwanted process could be suppressed by slow addition of the aryl bromide **14** in an excess. The indole derivative **17** was produced by Pd/C catalyzed hydrogenation of **16** and condensation.



14 **15** **16** **17**

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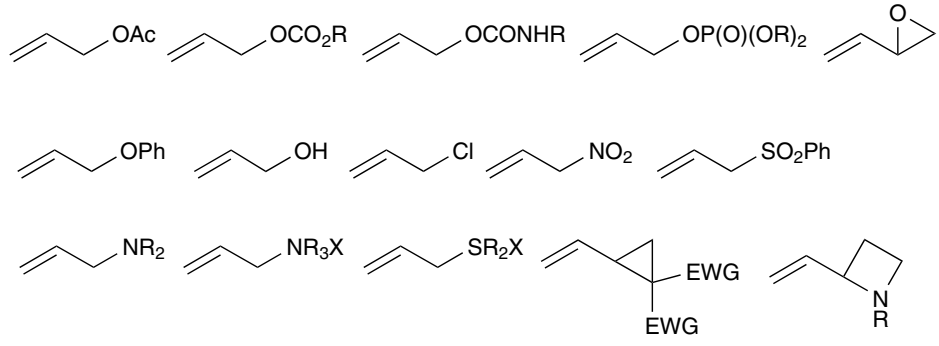
Chapter 4

Pd(0)-Catalyzed Reactions of Allylic Compounds via π-Allylpalladium Complexes

4.1 Introduction and Range of Leaving Groups

Pd-catalyzed reactions of various allylic compounds via the formation of π-allylpalladium complexes offer many synthetically useful methods. The following allylic compounds are known to form π-allylpalladium complexes by oxidative addition.

Allylic compounds used for Pd-catalyzed reactions



In addition, π-allylpalladium complexes **1** and **2** are formed as intermediates in the reactions of organic halides with 1,3- and 1,2-dienes. Usually these π-allylpalladium complexes, without isolation, undergo a variety of transformations as summarized in Scheme 4.1, offering many useful synthetic methods.

Reaction of π-allylpalladium chloride with malonate and acetoacetate was reported in 1965, showing that π-allylpalladium complexes are electrophilic [1]. Most importantly, electrophilic π-allylpalladium complexes react with various kinds of pronucleophiles of carbon, oxygen, and nitrogen. Then Pd(0) is regenerated after the reactions. The generation of Pd(0) offers the possibility of a catalytic process. This is the characteristic feature of π-allylpalladium chemistry.

π-Allyl complexes of other transition metals, typically π-allylnickel complexes are either nucleophilic or electrophilic depending on the nature of the reactants,

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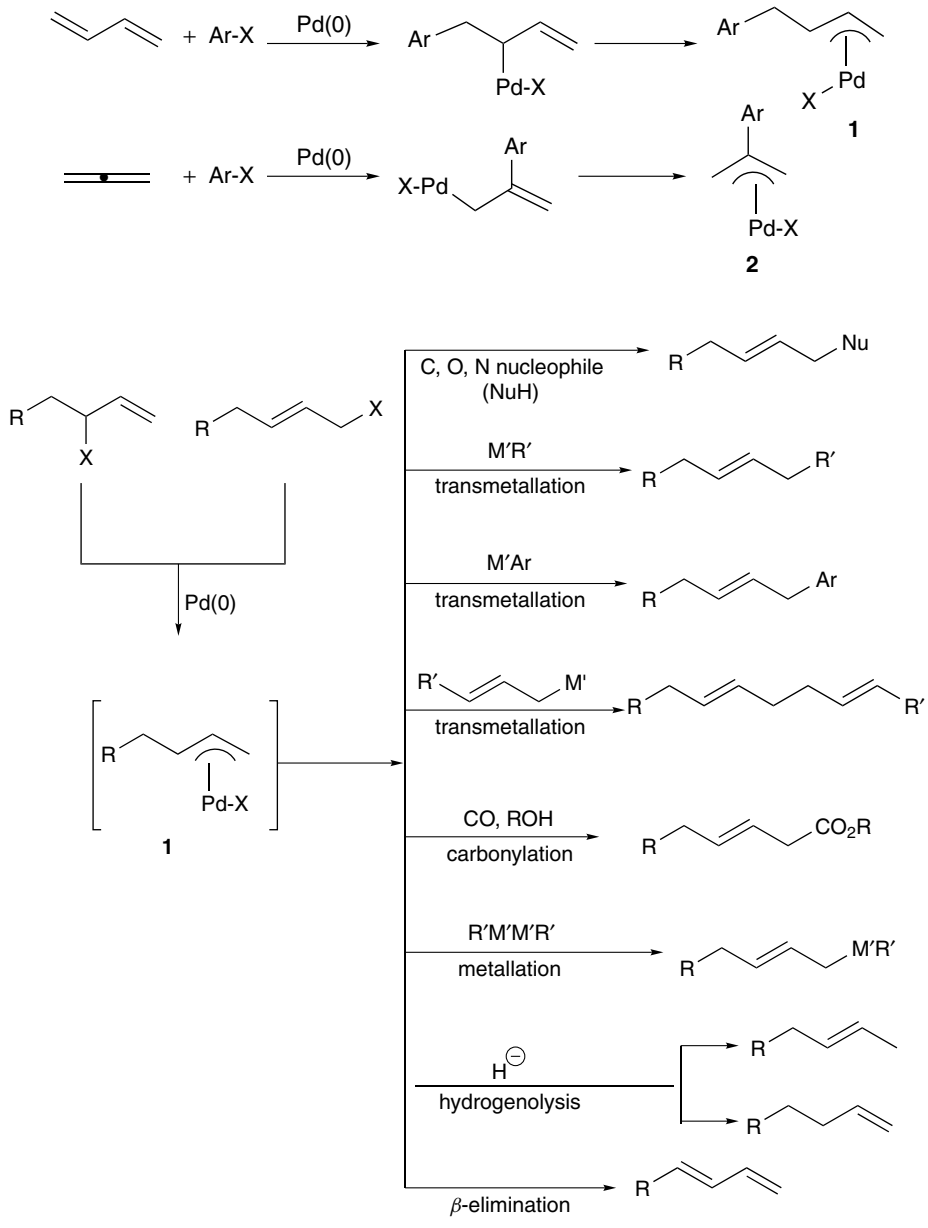
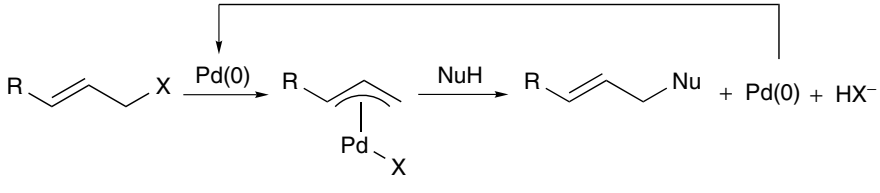
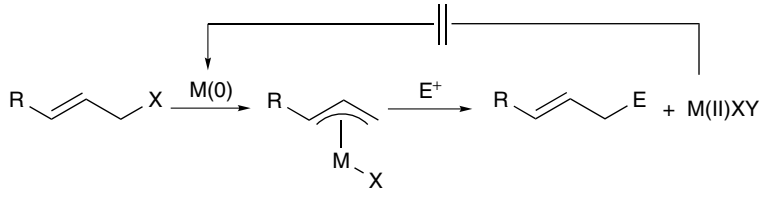


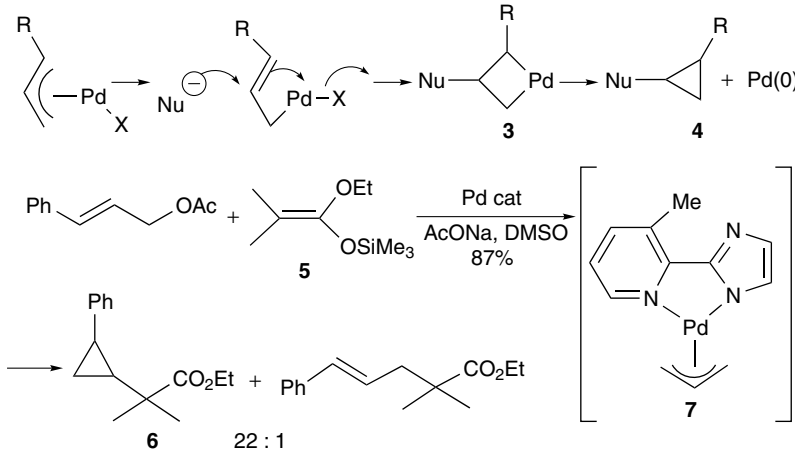
Scheme 4.1 Pd-catalyzed reactions of allylic compounds.



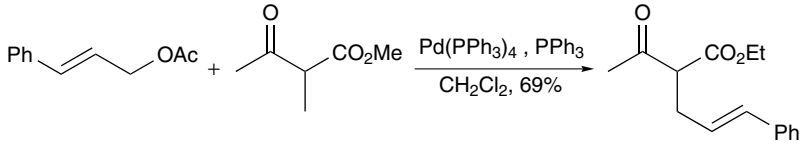
and generate either Ni(II) or Ni(0) after the reaction. When Ni(II) is regenerated, the reaction is stoichiometric.



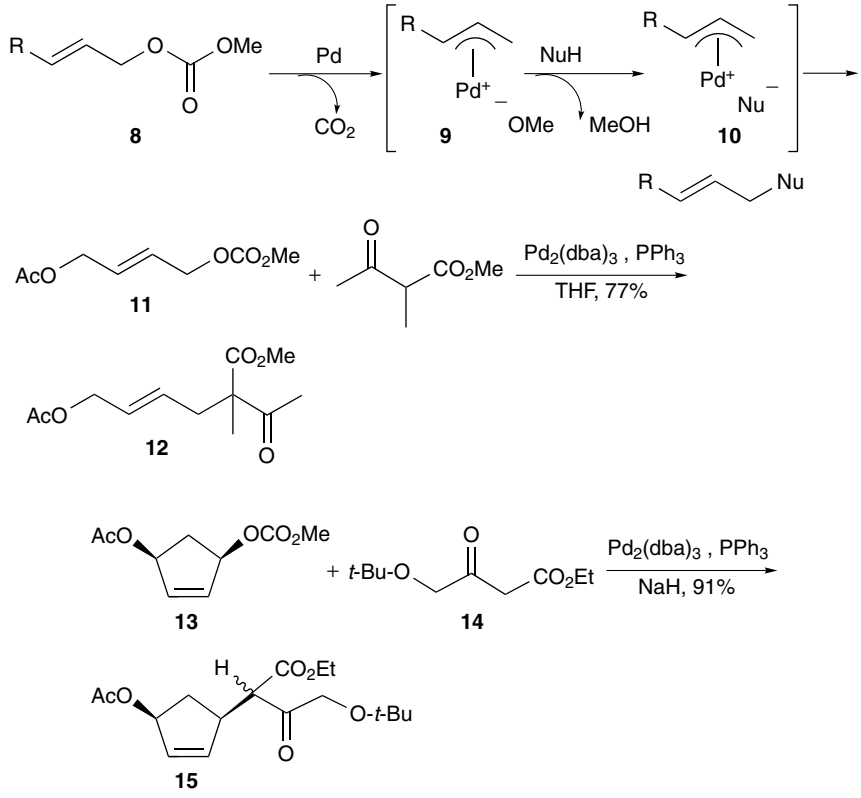
Although it is not a common reaction, some nucleophiles, particularly ester enolates, are known to attack the central sp^2 carbon of π-allyl group in the presence of σ-donor ligands to generate palladacyclobutane **3**, which is converted to the substituted cyclopropanes **4** by reductive elimination [2,3]. Satake *et al*. reported that π-allylpalladium-pyridinylimidazole complex **7** is a very effective catalyst for the cyclopropanation [4]. Ethyl α-cyclopropylisobutyrate (**6**) was obtained in high yield with high chemoselectivity by the reaction of the ketene silyl acetal **5** with cinnamyl acetate using **7** as a catalyst.



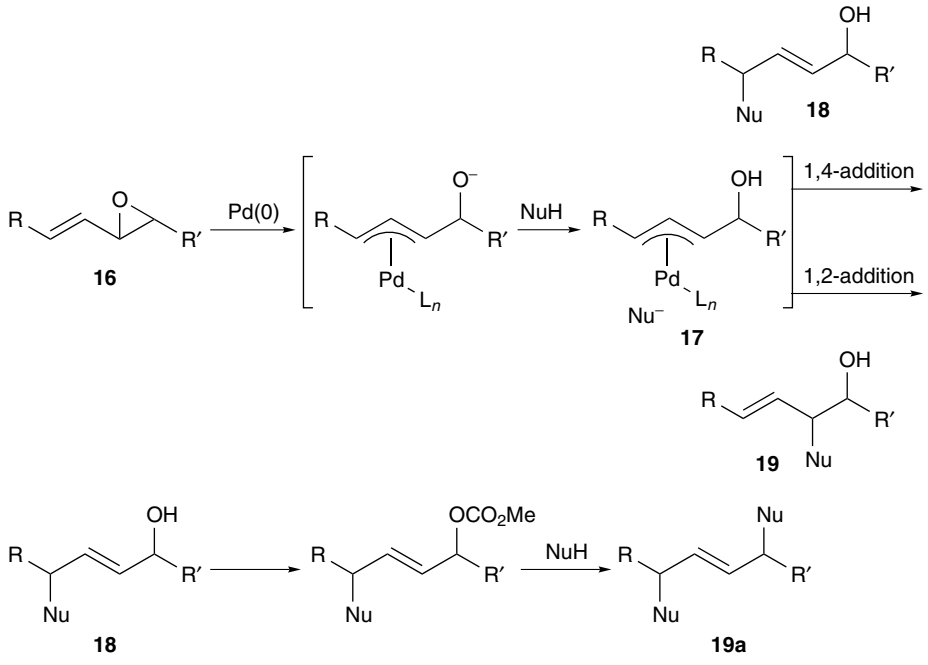
As shown above many allylic compounds can be used for catalytic reactions with different reactivity. Allylic esters such as carbonates, acetates, and phosphates are widely used. Allylic acetates and phosphates react in the presence of bases such as Et_3N and AcONa. However, Giambastiani and Poli reported that allylation of β-keto esters, but not malonates, with allylic acetates can be carried out under neutral conditions, although the reaction is slower [5].



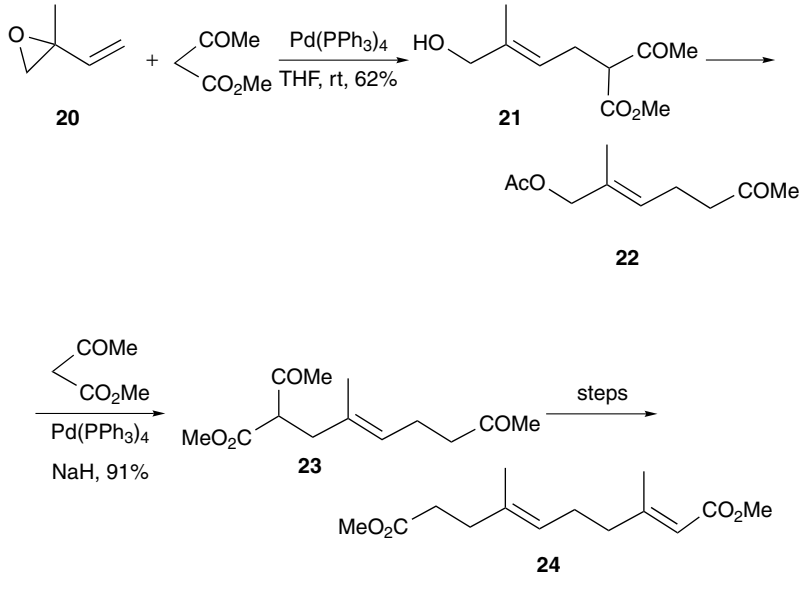
Allylic carbonates are more reactive than acetates. In addition, reaction of carbonates proceeds in the absence of bases [6]. Formation of π-allylpalladium **9** from allyl methyl carbonates **8** proceeds by oxidative addition, followed by decarboxylation, and π-allylpalladium methoxide **9** is generated at the same time, which abstracts a proton from a pronucleophile to form **10**. *In situ* formation of methoxide is a key in the allylation under neutral conditions. Allylation under neutral conditions is useful for the reaction of base-sensitive compounds. For example, exclusive chemoselective reaction of the carbonate group in 4-acetoxy-2-butenyl methyl carbonate (**11**) occurred in the absence of a base to yield **12**. Similar chemoselective reaction of the allyl carbonate group in the chiral cyclopentenyl methyl carbonate **13** with the β-keto ester **14** without attacking the allylic acetate group to give **15** was observed even in the presence of NaH. As expected, retention of stereochemistry (see Chapter 4.2.1) was observed in this substitution [7].

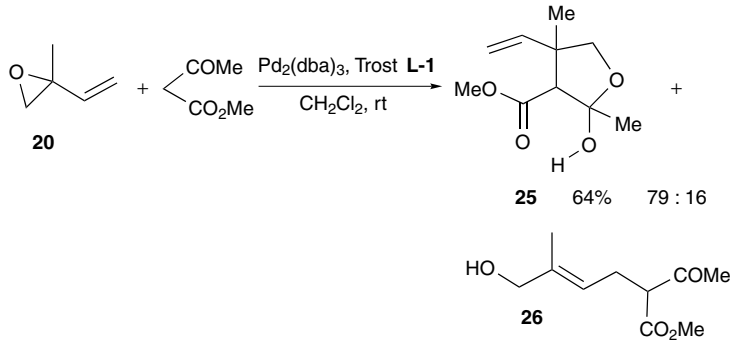


Alkenyloxirans **16** are reactive allylating agents used under neutral conditions. The epoxy ring is opened by Pd(0) to form π-allylpalladium with generation of an alkoxide anion, which abstracts a proton from a pronucleophile to produce the α-hydroxy-π-allylpalladium **17**. Reductive elimination of **17** affords either 1,4-adducts **18** or 1,2-adducts **19** [8,9]. The 1,4-adducts are mainly obtained under usual conditions due to the electronic effect of the epoxide oxygen. The 1,4-adducts **18** are allylic alcohols, and can be used again for the allylation after esterification to yield **19a**.

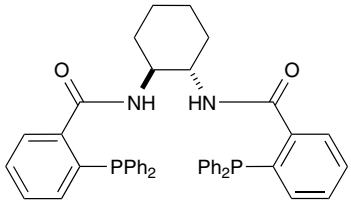


Reaction of isoprene monoepoxide (**20**) with acetoacetate afforded the allylic alcohol **21**. The pheromone **24** was synthesized after second allylation of acetoacetate with **22** to provide **23** [8]. The regioselectivity is controlled by ligands. The 1,4-adducts such as **21** are formed when achiral ligands are used. Interestingly, the same reaction of **20** afforded the 1,2-adduct **25** (64 % yield) and the 1,4-adduct **26** in a ratio of 79 : 16 when Trost **L-1** as a bulky chiral ligand (even racemic) was used [10].

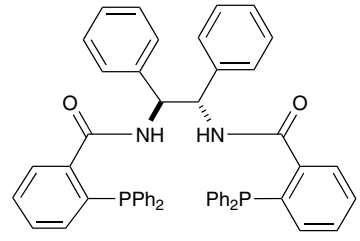




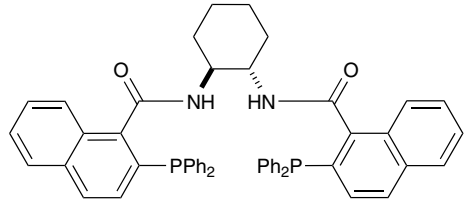
Trost designed chiral diamides of 2-diphenylphosphinobenzoic acid (DPPBA) and 2-diphenylphosphinoaniline (DPPA), and their derivatives (abbreviated as Trost **L-1, L-2, L-3, L-4**, and **L-5**), which are remarkably effective ligands in asymmetric allylations as described later.



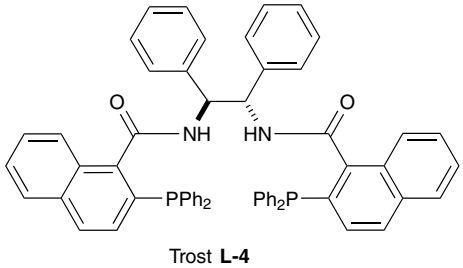
Trost **L-1**
(XIII-1)



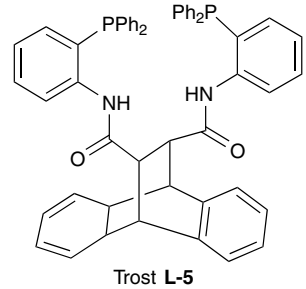
Trost **L-2**
(XIII-2)



Trost **L-3**
(XIII-3)



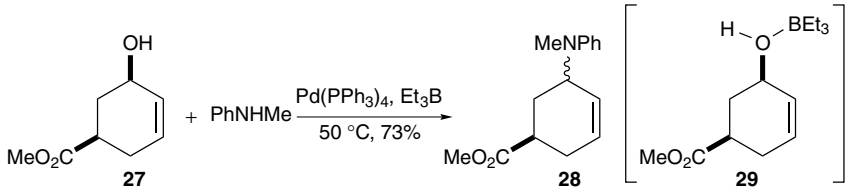
Trost **L-4**
(XIII-4)

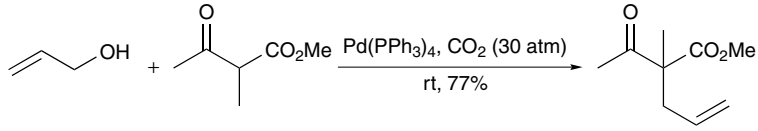


Trost **L-5**
(XIII-5)

Less reactive allylic alcohols can be used in the presence of some activators. Lewis acids are used for this purpose. Allylation of amines and malonates with allyl alcohols was carried out by Ozawa using a sp^2-hybridized bidentate phosphine-Pd

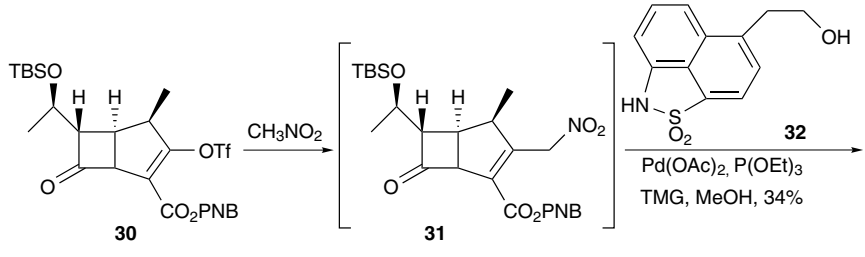
in the presence of pyridine [10a]. Et_3B is one of them, and allyl alcohols behave as good electrophiles in the presence of the borane. Amination of *cis*-5-methoxycarbonylcyclohexen-3-ol (**27**) with *N*-methylaniline proceeded at 50 °C in the presence of 2 equivalents of Et_3B to yield a mixture of *cis*- and *trans*-cyclohexenylamines **28**. The hydroxy group is activated by coordination of Et_3B as shown by **29** [11]. Also Ti(O-*i*-Pr)$_4$ is used for allylation with allylic alcohols in benzene [12]. CO_2 activates allylic alcohols presumably by forming monoallyl carbonate, and amination proceeds under 1 atm of CO_2. Allylation of α-methylacetoacetate with allyl alcohol occurred at room temperature under 30 atm of CO_2 [13].

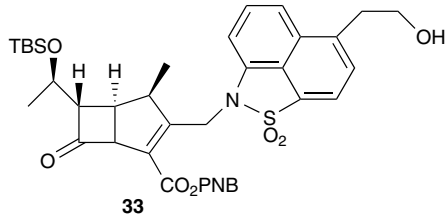




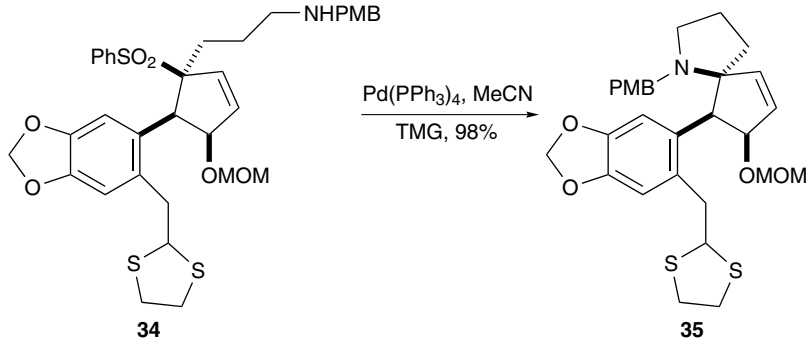
Allylamines are less reactive allylating agents. Bricout *et al*. reported that C and N-allylations with allyldiethylamine occurred using $Pd(OAc)_2$ and DPPB, but Ni catalysts were found to be better [14].

The nitro group is a good leaving group, and allyl nitro compounds are used conveniently for allylation because they can be prepared easily by the reaction of nitromethane with aldehydes and ketones, and used for Pd-catalyzed reactions [15]. As an interesting application, the alkenyl triflate **30** was converted to the allyl nitro derivative **31**, which was, without isolation, subjected to the Pd-catalyzed amination with **32** in the presence of tetramethylguanidine (TMG) as a strong amine base to afford the *anti*-MRS carbapenem intermediate **33** in 34 % overall yield [16].





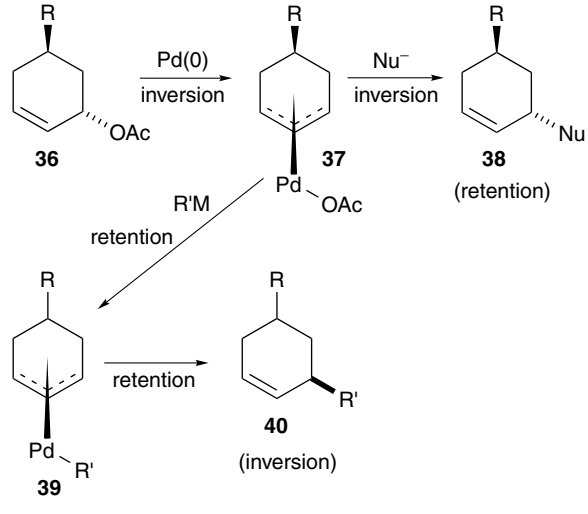
Intramolecular amination of the allyl sulfone **34** proceeded regioselectively in MeCN in the presence of TMG to give cephalotaxine intermediate **35** in 98 % yield. The use of TMG is important. When Et_3N was used, the yield was 64 % [17].



4.2 Allylation

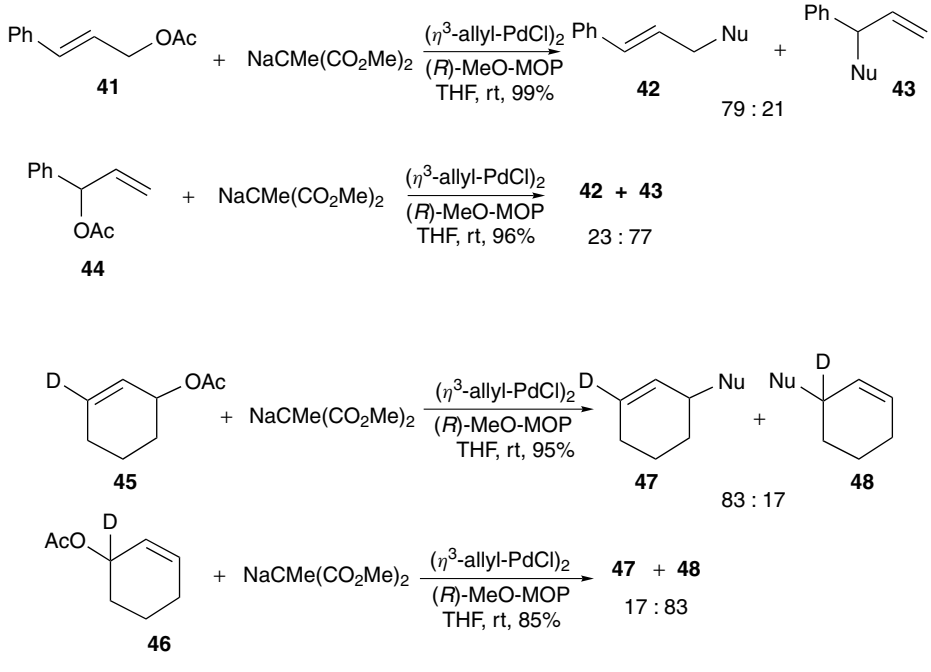
4.2.1 Stereo- and Regiochemistry of Allylation

Stereochemistry of Pd-catalyzed allylation of nucleophiles has been studied extensively. In the first step, formation of π-allylpalladium complexes **37** by the attack of Pd(0) on allylic compounds **36** proceeds with inversion of configuration (*anti* attack). Subsequent reaction of **37** with nucleophiles occurs in different stereochemistry depending on the nature of the nucleophiles. The 'soft' (stabilized) nucleophiles which are derived from conjugate acids with $pK_a < 25$, such as active methylene compounds, attack **37** from the backside of the Pd atom to give **38** with inversion of stereochemistry. Thus overall retention is observed. On the other hand, 'hard' nucleophiles ($pK_a > 25$), typically organometallic compounds of main group metals (Mg, Zn, B, Sn and others) generate **39** by transmetallation, and subsequent reductive elimination affords **40**. Both the transmetallation and

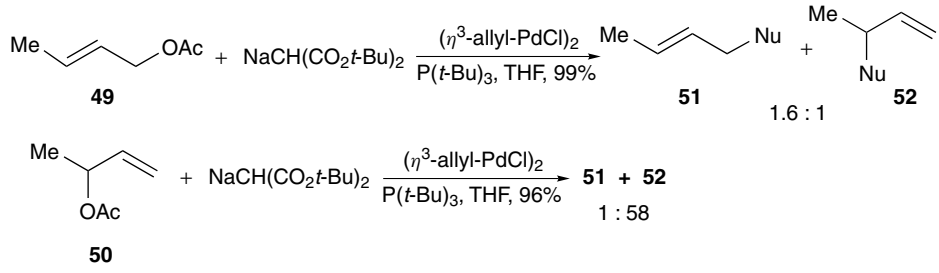


reductive elimination proceed with retention, and hence overall inversion is observed with hard nucleophiles. However, Kurosawa and co-workers observed both inversion and retention of stereochemistry in the oxidative addition of 5-(methoxycarbonyl)-2-cyclohexenyl chloride to Pd(0) depending on the ligands and solvents used [18].

Pd-catalyzed allylation of nucleophiles with substituted π-allyl systems usually occurs at the less substituted allylic terminus with high regioselectivity. Exceptional regioselectivity has been reported depending on the substrates and ligands. Hayashi found that regiochemistry of allylation of $NaCMe(CO_2Me)_2$ with allyl acetates is partially retained in the final products when $(\eta^3\text{-allyl-PdCl})_2$ and bulky ligands are used [19]. For example, attack at the less-substituted terminus of **41** occurred to give the product **42** when bulky (*R*)-MeO-MOP (**VI-12**) was used as a ligand. Substitution took place with preference at the position originally occupied by the leaving acetate group in **41**. On the other hand, substitution of the allyl acetate **44** occurred at the more crowded carbon of **44** to give **43** as the major product. This is known as a memory effect. Similar memory effect of π-allylic ligands was observed by the reaction of the deuterated cyclic allyl acetates **45** and **46**. The substituted cyclohexene **47** was obtained mainly from the acetate **45**, while the acetate **46** afforded **48** as a major product. The results show that the geometrical isomerization of π-allylpalladium intermediates is slow when bulky ligands are used. The original regiochemistry was lost when PPh_3 was used.

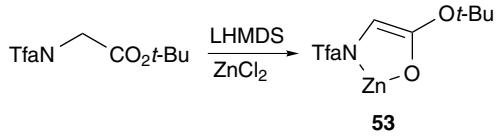


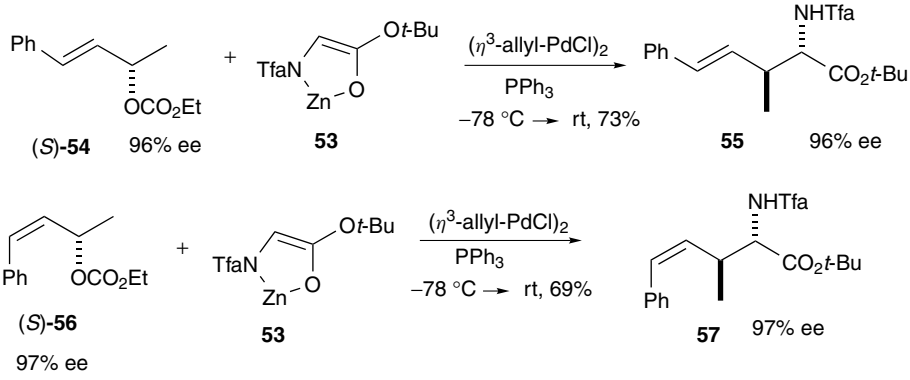
Aremoglu and Williams found a strong memory effect in the reaction of the allylic acetate **50** to give **52** by using bulky aliphatic phosphines, typically PCy_3 [20]. No memory effect was observed in the reaction of the acetate **49**. In these



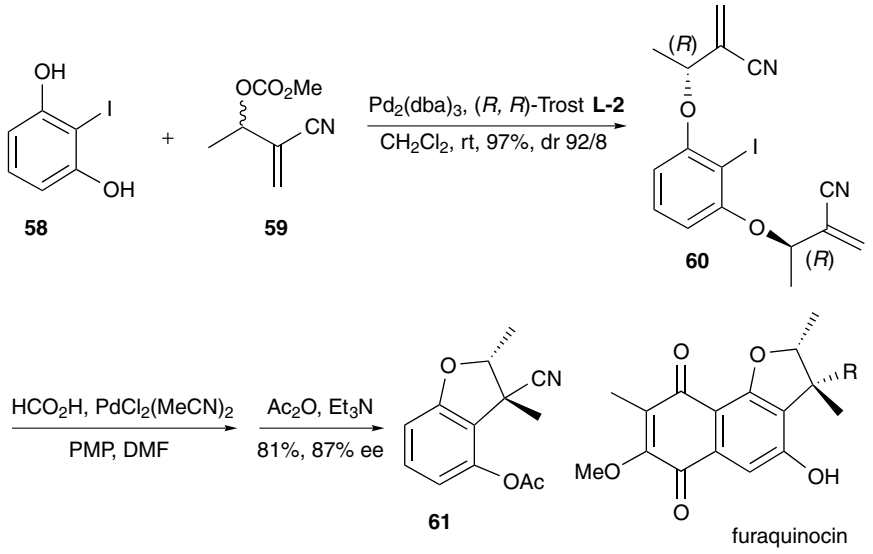
reactions, $P(t\text{-Bu})_3$ is a more effective ligand than PCy_3. Also ferrocenyl phosphines showed large memory effect [21,22].

Retention of geometry, perfect chirality transfer, and high reactivity have been observed by the reaction of the chelated Zn enolate of amino acid ester **53** even when PPh_3 was used [23]. In addition, the non-stabilized enolate **53** was found to be very reactive. Reaction of the allylic carbonates **54** and **56** with the enolate **53** gave **55** and **57** with perfect chirality transfer and high diastereoselectivity. The carbonates and the enolates are highly reactive and the reaction starts even at $-78\,^{\circ}C$. Lower selectivity was observed by the reaction of the corresponding allylic acetate.



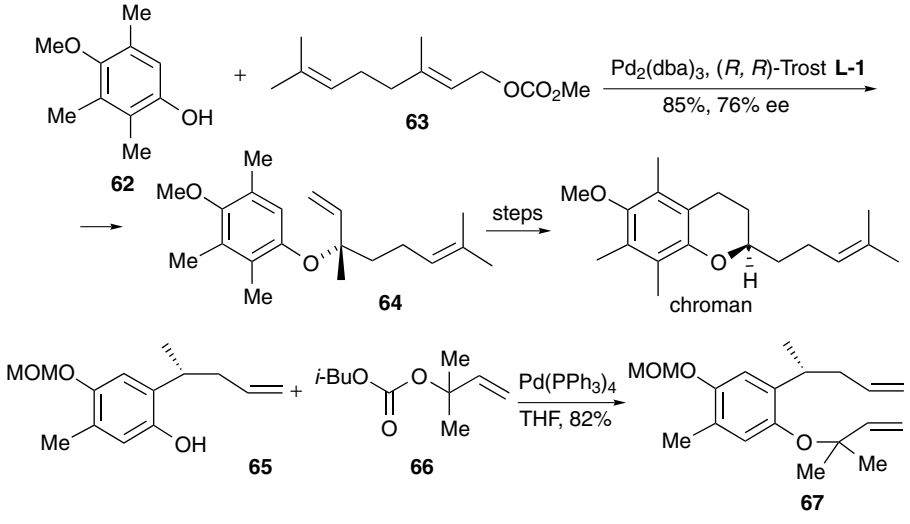


Remarkable control of regioselectivity has been observed by the use of some chiral ligands. For example, the diallylation of 2-iodoresorcinol (**58**) with the allyl carbonate **59** occurred regioselectively at the substituted terminus to give **60** in very high yield (97 %) with a good diastereomeric ratio (dr) (dr = 92/8) using one of the Trost ligands (*R*,*R*)-Trost **L-2** [24]. No attack at the unsubstituted terminus took place. In addition, efficient deracemization of the racemic carbonate **59** occurred. Reductive Heck reaction of **60** using HCO_2H afforded **61** with 87 % ee. Use of the sterically hindered base pentamethylpiperidine (PMP) gave good



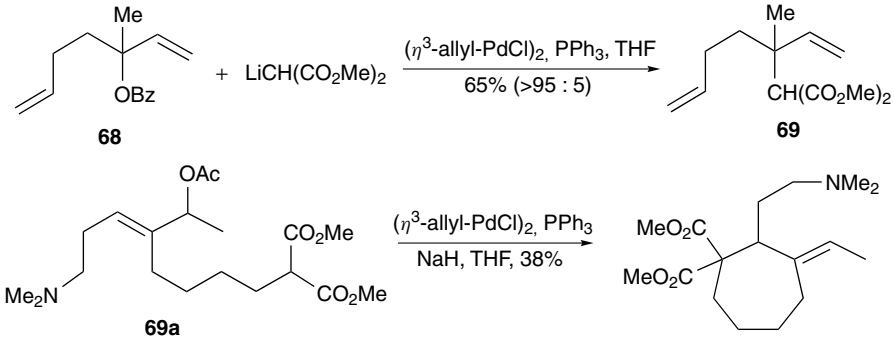
results. Concise total synthesis of furaquinocin has been achieved employing these two Pd-catalyzed reactions in key steps.

Allylation of the phenol **62** with geranyl methyl carbonate (**63**) provided the more congested allyl aryl ether **64** with excellent regioselectivity (92 : 8) and 76 % ee when Trost **L-1** was used. The reaction offers a good synthetic method of chroman [25]. On the other hand, curiously Shishido and co-workers found that the congensted isomer **67** was obtained as a single product in 82 % yield by the allylation of the phenol **65** with the allyl carbonate **66** even when PPh_3 was used. It is puzzling why this unusual regioselective reaction occurred under normal reaction conditions [26].

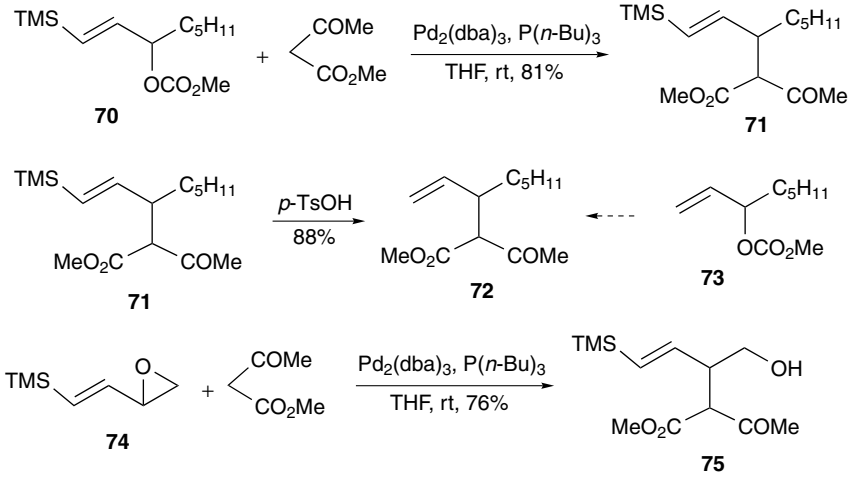


Some tethered alkene affects regioselectivity remarkably. The reaction of the diene **68** with malonate occurred at the more substituted allylic terminus proximal to the tethered alkene to give **69**, having a quaternary stereocenter with

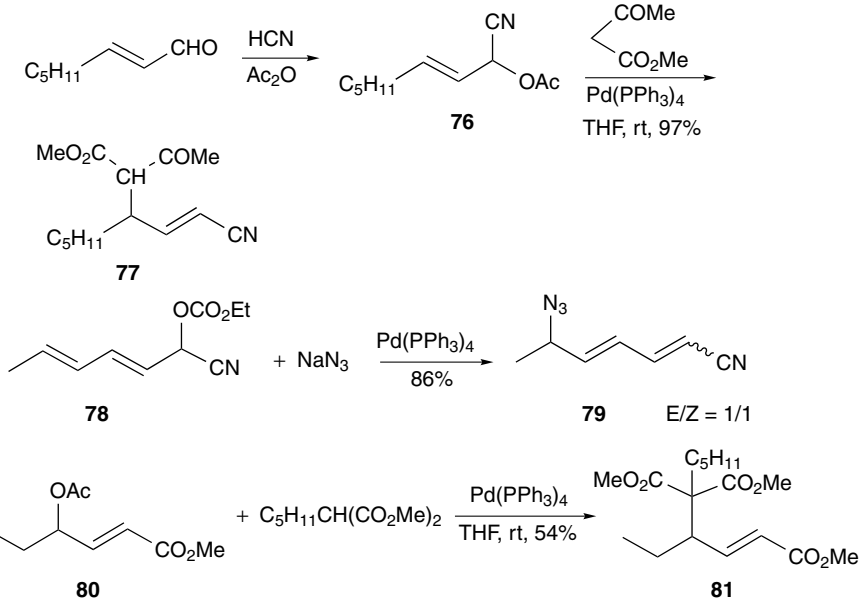
complete regiocontrol. Thus the double bond at this position showed complete regiocontrol [27]. The seven-membered ring was obtained regioselectively as a single product by the cyclization of the asymmetric allylic acetate **69a**. Substitution occurred at the allylic terminus proximal to the amino group [28].



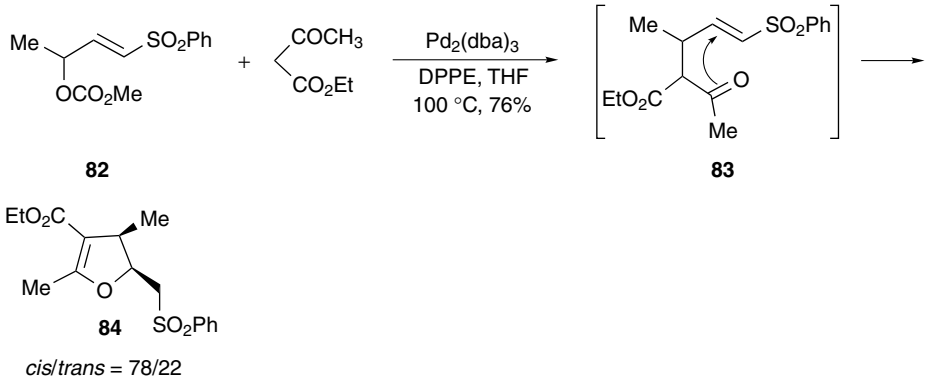
Substituents in allylic systems also control regiochemistry. The TMS group is one of these substituents. The vinylsilane **71** was obtained exclusively by the reaction of TMS-substituted allyl carbonate **70**. Desilylation of **71** afforded **72**. In this way, nucleophilic substitution at the more substituted carbon of **73** can be achieved indirectly by using **70** [29]. Unusual 1,2-addition of a nucleophile to TMS-substituted vinyloxirane **74** was observed to afford vinylsilane **75**.



EWGs show a decisive effect on regioselectivity, and nucleophiles selectively attack the electron deficient side of π-allyl systems as expected. Reaction of α-acetoxy-β,γ-unsaturated nitrile **76** with a nucleophile afforded the γ-substituted α,β-unsaturated nitrile **77** and the ester **81** exclusively by 1,3-transposition. Also the reaction of γ-acetoxy-α,β-unsaturated ester **80** gave **81** regioselectively [30]. Clean 1,5-transposition occurred by the reaction of the dienyl carbonate **78** with NaN_3 to afford **79** [31].



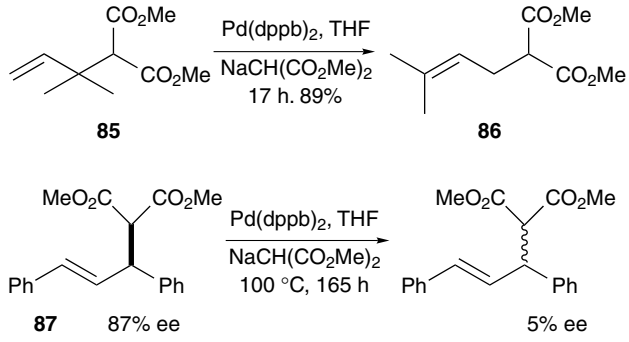
Regioselective reaction of sulfone-substituted allyl carbonate **82** with acetoacetate generated **83**, which underwent Michael-type addition to afford 4-substituted dihydrofuran **84** in one step [32].



4.2.2 Asymmetric Allylation

Asymmetric versions of several Pd-catalyzed reactions have been under active study. Among them, Pd-catalyzed asymmetric allylations have been carried out most extensively with much success. Several types of Pd-catalyzed asymmetric allylation, by which racemic, *meso*, and achiral substrates are converted into enantiomerically enriched compounds, have been extensively studied using a number of chiral ligands [33].

Attention should be paid in the studies on asymmetric allylation to the fact that allylation of malonates is reversible and under thermodynamic control at higher temperature and longer reaction time [34]. For example, the congested malonate



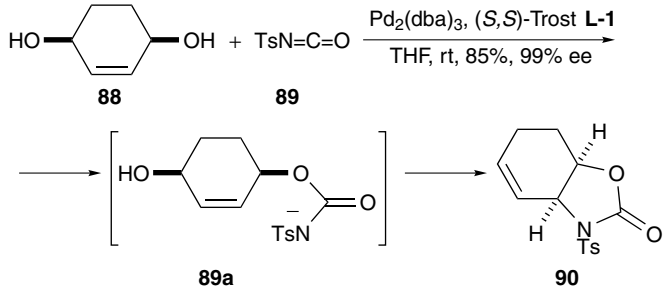
85 rearranged to **86** under catalysis of Pd. Also the chiral malonate **87** (87 % ee) was racemized to 5 % ee after treatment with $Pd(dppb)_2$ for 165 h [35].

A general view of asymmetric allylation is summarized briefly here, and numerous examples of asymmetric syntheses are cited in individual sections. The asymmetric synthesis is classified into the following types based on how the differentiation or enantio-discriminating events occur:

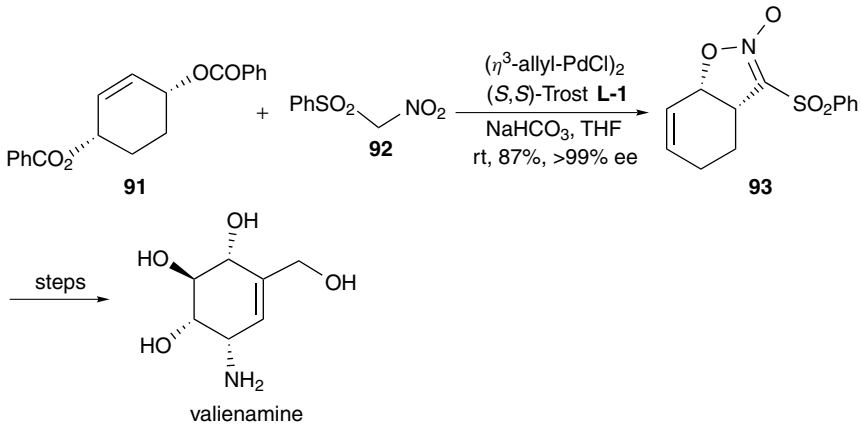
1. differentiation of the enantiotopic leaving groups of *meso* compounds;
2. differentiation of the enantiotopic allylic termini of symmetric intermediates;
3. differentiation of two interconverting intermediates (the enantiotopic faces exchange);
4. differentiation of the enantiotopic face of alkenes;
5. differentiation of the enantiotopic faces of nucleophiles;
6. desymmetrization by differentiation of enantiotopic geminal leaving groups.

These aspects of asymmetric allylation are explained by citing a few typical examples.

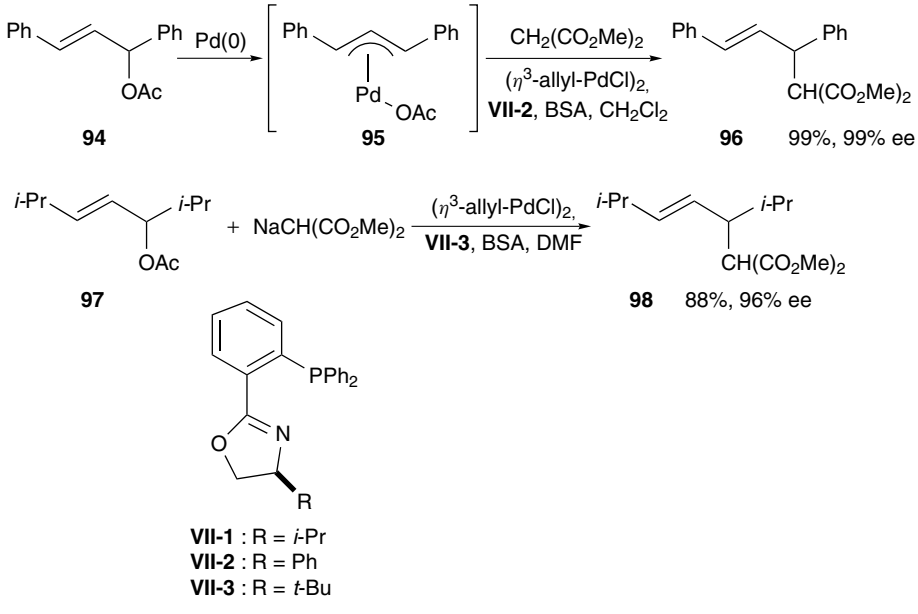
1. Differentiation of the enantiotopic leaving groups of meso compounds. Desymmetrization of *meso* compounds occurs by Pd-catalyzed monosubstitution using a chiral Pd catalyst by differentiating enantiotopic leaving groups. Reaction of *meso*-cyclohexene-3,6-diol (**88**) with *p*-tosyl isocyanate (**89**) afforded the oxazolidin-2-one **90** via ureathane **89a** with 99 % ee using Trost **L-1** as a chiral ligand [36].



Sulfonylnitromethane (**92**) is an interesting nucleophile, which undergoes double substitution. Double C-, and O-allylation of **92** with *meso*-3,6-dibenzoyloxycyclohexene (**91**) provided the enantiomerically pure heterocycle **93** in 87 % yield, and asymmetric synthesis of valienamine was achieved [37].

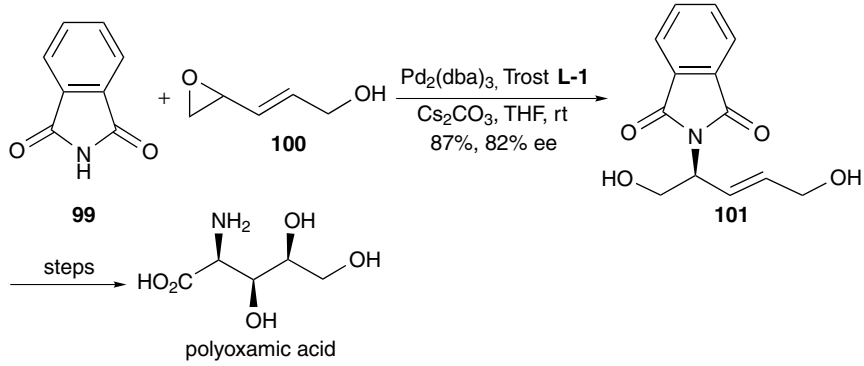


2. Differentiation of the enantiotopic allylic termini of symmetric intermediates. 1,3-Diphenyl-2-propenyl acetate (**94**) as a chiral racemic precursor is a standard compound used for testing effectiveness of chiral ligands, and very extensive studies on asymmetric allylation using **94** to provide the chiral compound **96** have been carried out. π-Allylpalladium intermediate **95**, formed from **94**, is symmetric and differentiation of enantiotopic termini of the π-allyl system occurs. Numerous examples of achieving >95 % ee have been reported. As one example of early studies, high ee of **96** was obtained by using 2-(2-phosphinophenyl)dihydrooxazoles (PHOX)(**VII-2**) as an effective ligand. Desymmetrization of 1,3-diisopropylallyl acetate **97** was carried out to provide **98** successfully using **VII-3** [38]. Interestingly, while a poor result was obtained by the reaction of **94** with malonate when Trost ligands were used, 92 % ee was obtained in 98 % yield by the reaction of 1,3-dimethylallyl acetate with malonate [39].

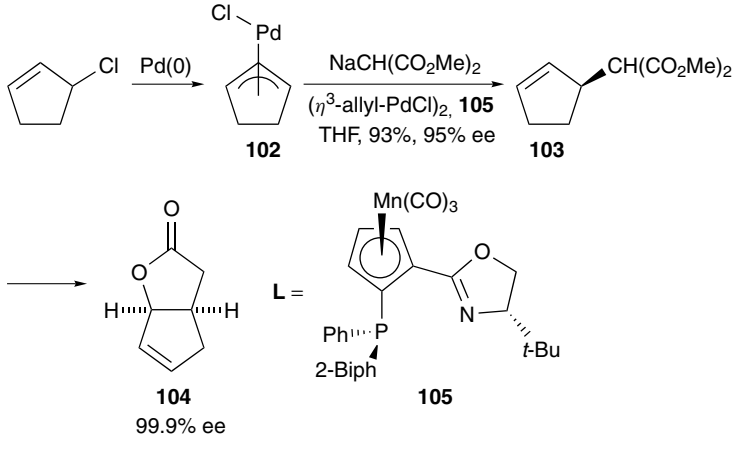


The desymmetrization of 1,3-diphenylallyl esters **94** using malonates has been widely studied with numerous chiral ligands to evaluate their effectiveness. However, it should be noted that the reaction of 1,3-diphenylallyl system is a special case, and thus, effective ligands in the desymmetrization of 1,3-diphenylallyl esters are not necessarily good ligands for other allylic compounds.

The epoxide **100** generated a symmetrical π-allylpalladium intermediate and reacted with phthalimide (**99**) using Trost **L-1** to provide **101** in 87 % yield with 82 % ee, and polyoxamic acid was synthesized from **101** [39].

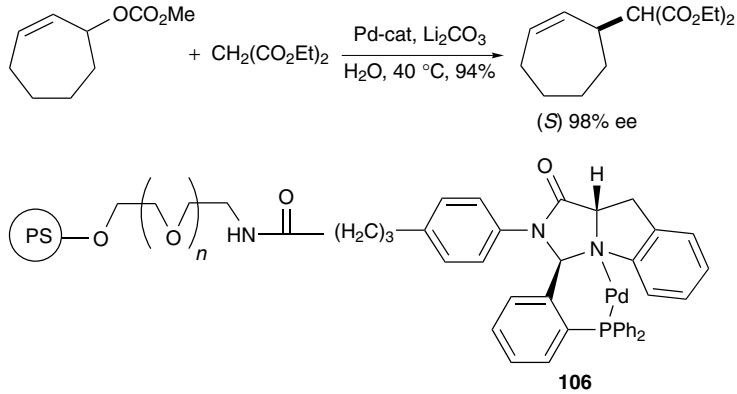


Similar desymmetrization occurs via symmetric intermediate in cyclic allylic compounds. Synthesis of enantiomerically pure jasmonoids has been reported by Helmchen based on this method. The symmetric intermediate complex **102** is generated from 3-chlorocyclopentene. The allylated malonate **103** was obtained with high % ee using the phosphinyloxazoline ligand **105** and converted to the important intermediate **104** with 99 % ee [40].



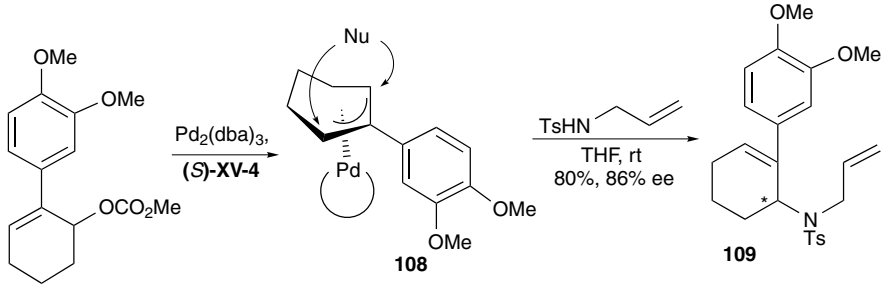
The Uozumi group developed unique recyclable amphiphilic resin-supported triarylphosphines (PEP) attached to polyethylene glycol-polystyrene graft copolymer (PEG-PS), and found that Pd(PEP) is an active catalyst for allylation in water [40a]. They immobilized a chiral amine on PS-PEG-NH_2 resin to give PS-PEG resin-supported chiral P,N-ligand (*R*,*S*) **106**. Asymmetric allylation of diethyl malonate

with 2-cycloheptenyl carbonate was carried out in water in the presence of Li_2CO_3 at 40 °C using the chiral ligand **106**, and diethyl 2-cycloheptenylmalonate with 98 % ee was obtained in 94 % yield [40b].

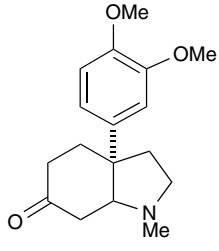


106

In the asymmetric total synthesis of (−)-mesembrane, Mori carried out asymmetric N-allylation of N-tosylallylamine with the 2-substituted cyclohexenyl-3-carbonate **107** using (*S*)-BINAPO (**XV-4**). The allylamine attacked one of the allylic termini of the symmetric intermediate **108** to provide **109** with 86 % ee. Recrystallization from MeOH gave **109** with 99 % ee [41]. A similar method was applied to the total synthesis of (−)-tubifoline [42].

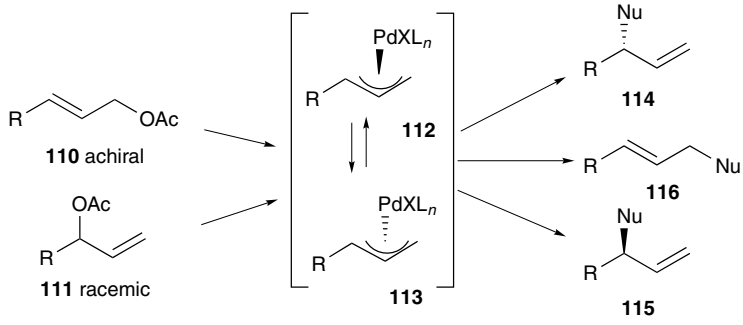


107 **108** **109**



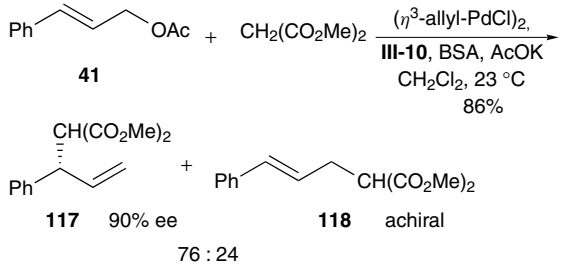
(–)-mesembrane

3. Differentiation of two interconverting intermediates. Reaction of allylic acetates **110** and **111** proceeds via the formation of interconverting π-allyl intermediates **112** and **113** (by enantiotopic faces exchange), and affords **114** and **115** using chiral catalysts. In this case, control of regioselectivity to minimize the

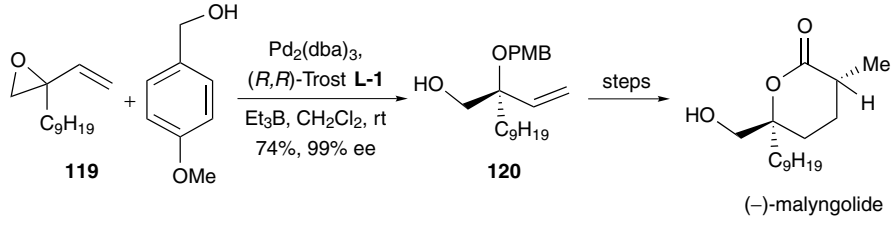


formation of the achiral product **116** is a crucial problem, and selection of ligands is important.

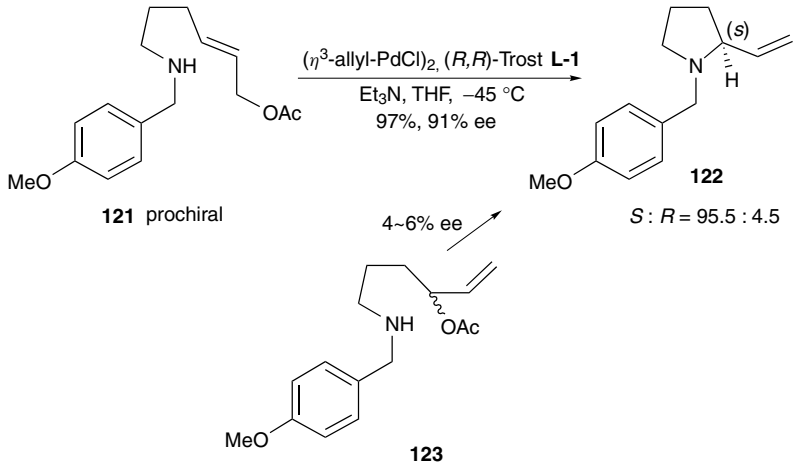
Pfaltz succeeded to achieve high regioselectivity in the allylation of malonate with cinnamyl acetate (**41**) using the ligand **III-10** and obtained **117** with 90 % ee along with achiral **118** [43].



Deracemization of 3-nonyl-3,4-epoxybut-1-ene (**119**) occurred by the Et_3B-assisted reaction with *p*-methoxybenzyl alcohol (PMB) to afford the chiral product **120** with 99 % ee by using (*R*,*R*)-Trost **L-1**. In addition to high enantioselectivity, unusual exclusive 1,2-addition of the alcohol at the more substituted terminus occurred to generate a chiral center. The reaction is a key step in total synthesis of (−)-malyngolide [44].



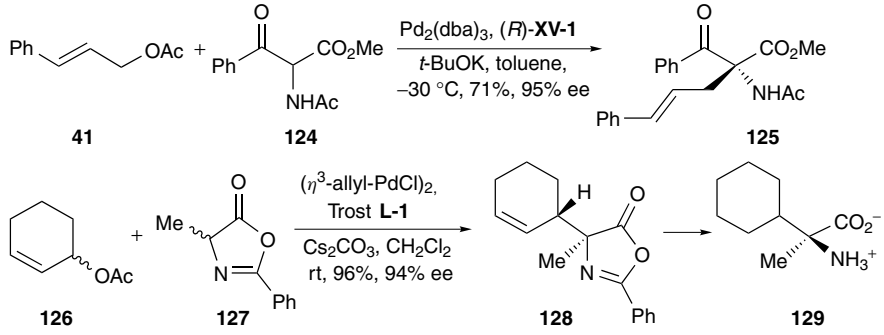
4. Differentiation of the enantiotopic face of alkenes. Asymmetric induction occurs in the allylation of the prochiral allylic acetate **121** via enantiotopic face discrimination of the double bond to afford **122** with high ee using Trost **L-1** as a ligand. Tethering of the nucleophile as in **121** made the reaction regioselective and gave the high ee. On the other hand, the same product **122** was obtained from the chiral racemic allyl acetate **123** with only 4–6 % ee, showing that



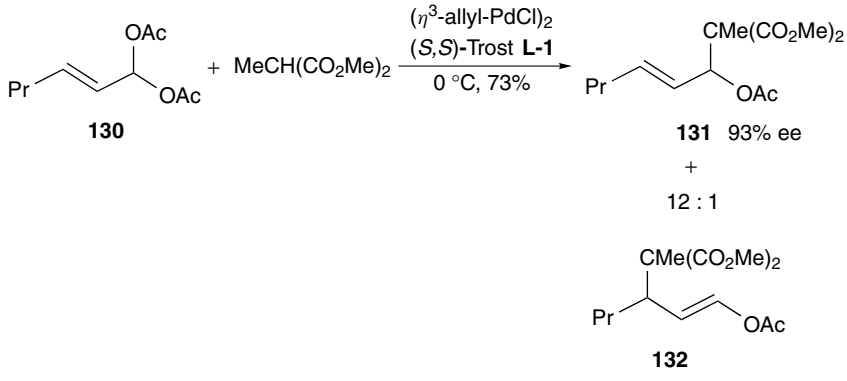
enantiodiscrimination is the ionization event, namely at a π-coordination step of the alkene moiety of the substrate **121** or **123** [45].

5. Differentiation of the enantiotopic faces of nucleophiles. A stereogenic center is generated in a nucleophile by enantioface differentiation of a prochiral nucleophile. Asymmetric allylation of the β-keto ester **124** with cinnamyl acetate (**41**) gave **125** with 95 % ee using (*R*)-BINAP (**XV-1**) as a chiral ligand via differentiation of enantiotopic faces of enolate of **124**, generating the stereogenic center at α-carbon [46].

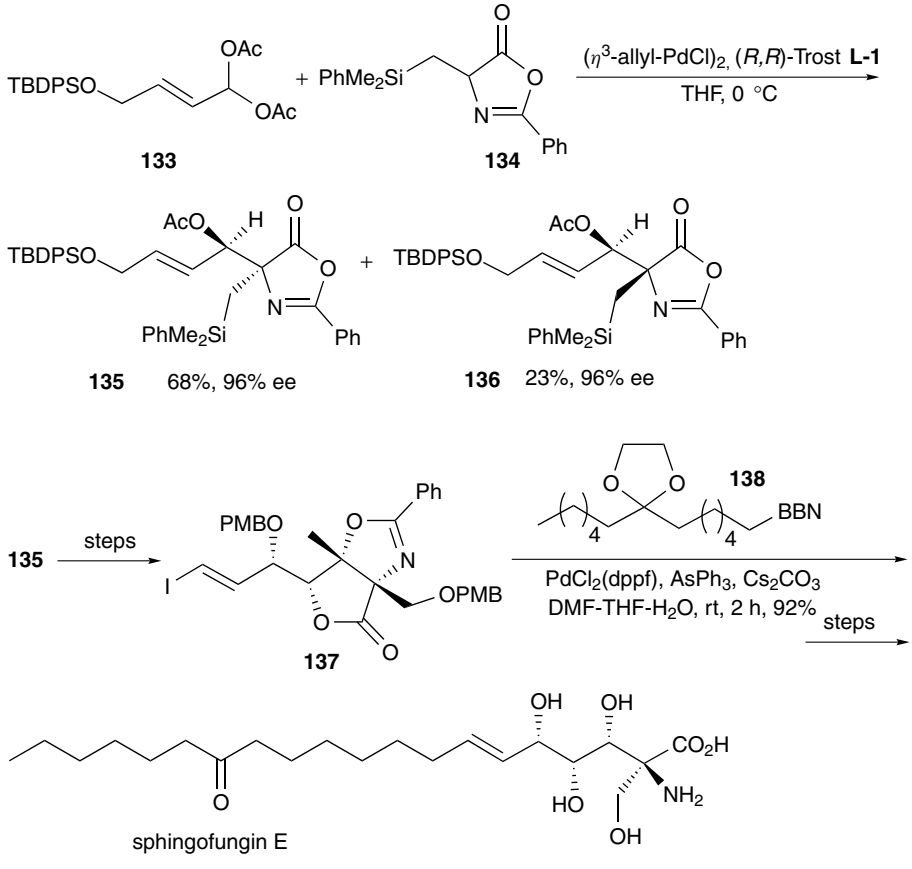
Allylation of the racemic alanine-derived azlactone **127** with racemic 3-acetoxycyclohexene (**126**) using Trost **L-1** as a ligand produced the allylated product **128** in 96 % yield with a 2.5 : 1 diastereomeric ratio. The enantiomeric excesses were 94 % and 92 % for the major and minor diastereomers. The reaction offers a good method of asymmetric synthesis of α-alkylated amino acid **129** [47].



6. Desymmetrization by differentiation of enantiotopic geminal leaving groups. Differentiation of the two enantiotopic leaving groups located on the same carbon atom of an achiral substrate offers a possibility of asymmetric synthesis. Asymmetric monoallylation of malonate with the achiral allylic geminal diacetate **130** afforded **131** with 93 % ee as the major product and the enol acetate **132** as the minor product. Based on this chemoselective monoallylation, these geminal diesters can be regarded as 'prochiral carbonyl surrogates' in Pd-catalyzed asymmetric allylation [48].



Asymmetric allylation of the azlactone **134** with the prochiral *gem*-diester **133** involves differentiations of both enantiotopic geminal leaving groups and enantiotopic faces of the azlactone, and was applied to the elegant total synthesis of sphingofungin E. The reaction of **133** with **134** by using (*R*,*R*)-Trost **L-1** afforded 2.4 : 1 mixture of the diastereomers **135** and **136**. The major isomer **135** (96 % ee) was converted to **137** and the long chain was introduced by Suzuki coupling of **137** with **138**. Asymmetric synthesis of sphingofungin E has been achieved using the product [49].

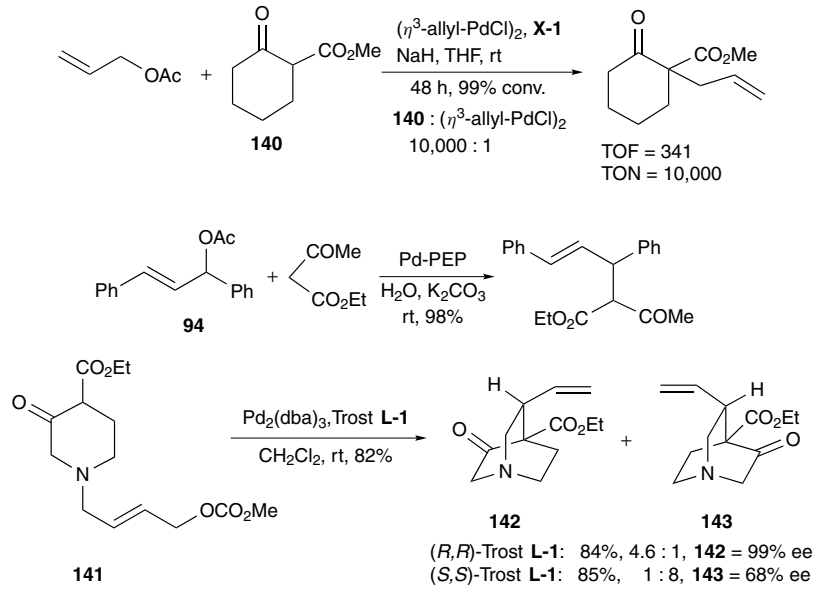


4.2.3 Allylation of Stabilized Carbon Nucleophiles

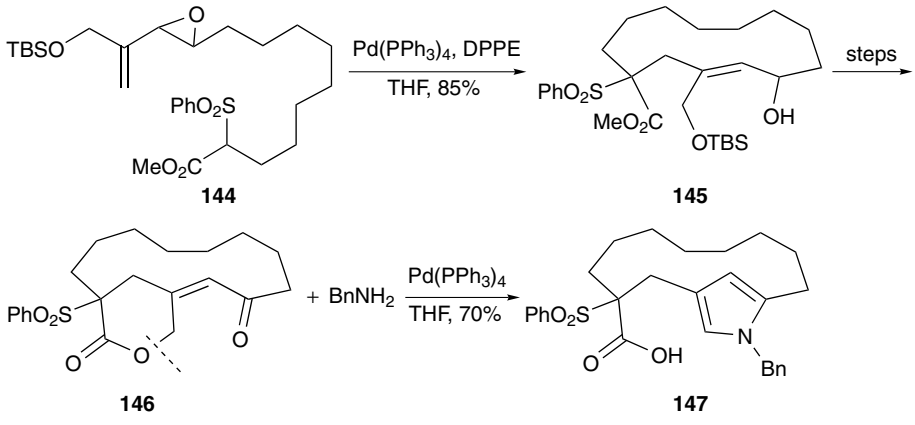
Extensive studies have been devoted to allylation of carbon pronucleophiles as important methods of C—C bond formation. As described before briefly, reactions with allylic carbonates and alkenyloxiranes proceed under neutral conditions due to *in situ* generation of alkoxides which abstract protons from nucleophiles. Also allylation with allyl aryl ethers can be carried out without addition of bases. Reactions of allylic acetates and other allylic compounds are carried out in the presence of bases [5].

Usually presence of two electron-withdrawing groups (EWGs) in carbon pronucleophiles are required for facile allylation. Ketones, CHO, CO_2R, CN, NO_2, SO_2 are effective EWGs. Derivatives of malonates and β-keto esters are most extensively used. Aryl groups are weakly effective. One NO_2 and SO_2 are active enough for the allylation. A number of ligands have been utilized for allylation, showing different activities. Santelli and co-workers reported that tetraphosphine, Tedicyp (**X-1**), combined with (η^3-allyl-PdCl)$_2$ generates a very efficient catalyst. They claimed that TON 10 000 was attained in a typical allylation of β-keto ester **140** with allyl acetate using this catalyst [50]. Uozumi and co-workers prepared amphiphilic resin-supported triarylphosphine (PEP) attached to polyethylene glycol-polystyrene graft polymer, and they found that Pd complexes of PEP [Pd(PEP) and Pd(PEP)$_2$] are recyclable active catalysts for allylation in water. Ethyl acetoacetate was allylated with the allyl acetate **94** in water in the presence of K_2CO_3 at room temperature using Pd(PEP)$_2$ (1 mol%) as a catalyst to give rise to the allylated product in 98 % yield [40a].

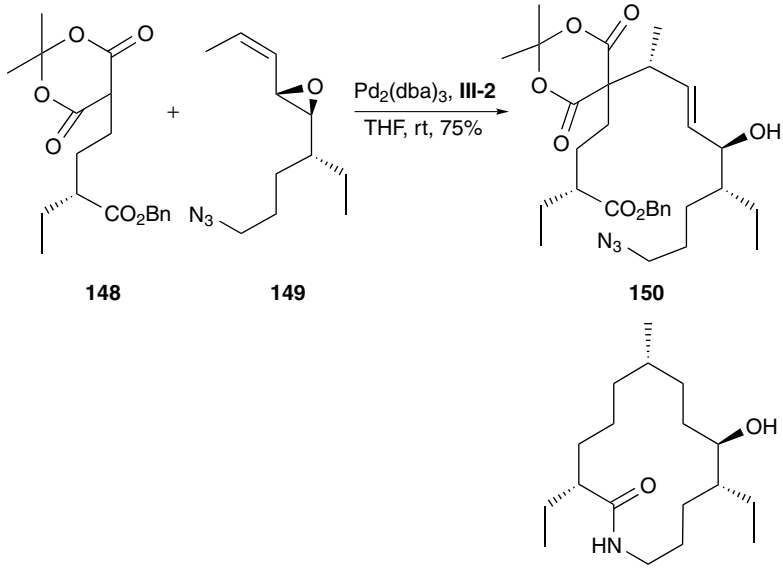
Intramolecular reaction of the cyclic β-keto ester **141** proceeded with high enantio- and diastereoselectivities. When (*R*,*R*)-Trost **L-1** was used, a mixture of the [2.2.2]bicycles **142** (99 % ee) and **143** was obtained in 84 % yield in a ratio of 4.6 : 1. On the other hand, Eu(fod)$_3$ as an additive showed a remarkable effect. The diastereoselectivity was reversed when (*S*,*S*)-Trost **L-1** and Eu(fod)$_3$ were used to give a mixture of **142** and **143** (68 % ee) in a ratio of 1 : 8 in 85 % yield [51].



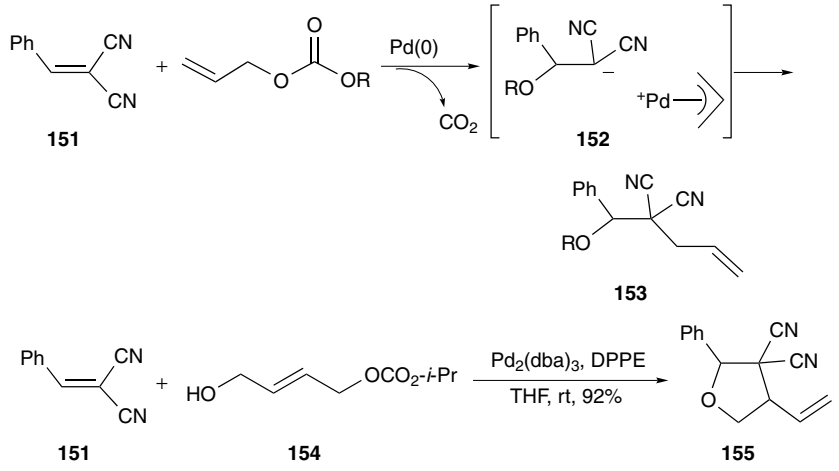
Intramolecular allylation with alkenyloxiranes offers a good method of macrocyclization. In the total synthesis of roseophilin by Fürstner, the alkenyloxirane **144** was cyclized smoothly to yield the 13-membered carbocycle **145** in high yield (85 %) in the presence of two ligands DPPE and PPh_3. Then Pd-catalyzed reaction of the allylic lactone **146** with benzylamine afforded the pyrrole carboxylic acid **147** cleanly in 70 % yield via regioselective allylation of benzylamine at the electron-deficient terminus of the allylic lactone **146** [52].



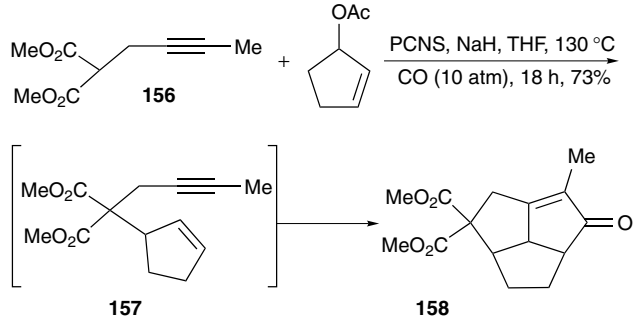
Usually no reaction of alkenyloxiranes bearing a methyl group at the terminus as in **149** takes place; instead isomerization to enone occurs. The reaction of the epoxide **149** with the Meldrum's acid derivative **148** proceeded at room temperature in THF using a precatalyst generated by mixing $Pd_2(dba)_3$ (1.5 mol%) and cyclic phosphite TMPP (**III-2**) (20 mol%) to afford **150** in 75 % yield, and macrolactam aglycon of fluviricin B1 was synthesized [53].



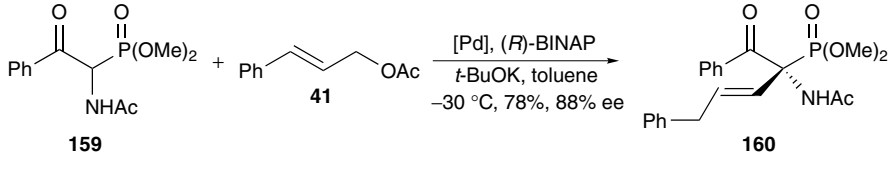
In the reaction of the activated alkene **151** with allyl carbonate, Michael attack of an alkoxide to the alkene occurs at first. Then the generated anion **152** is allylated to afford **153**. The THF derivative **155** was obtained in high yield by the coupling of the alkene **151** with monocarbonate of 2-buten-1,4-diol **154** in the absence of a base [54].



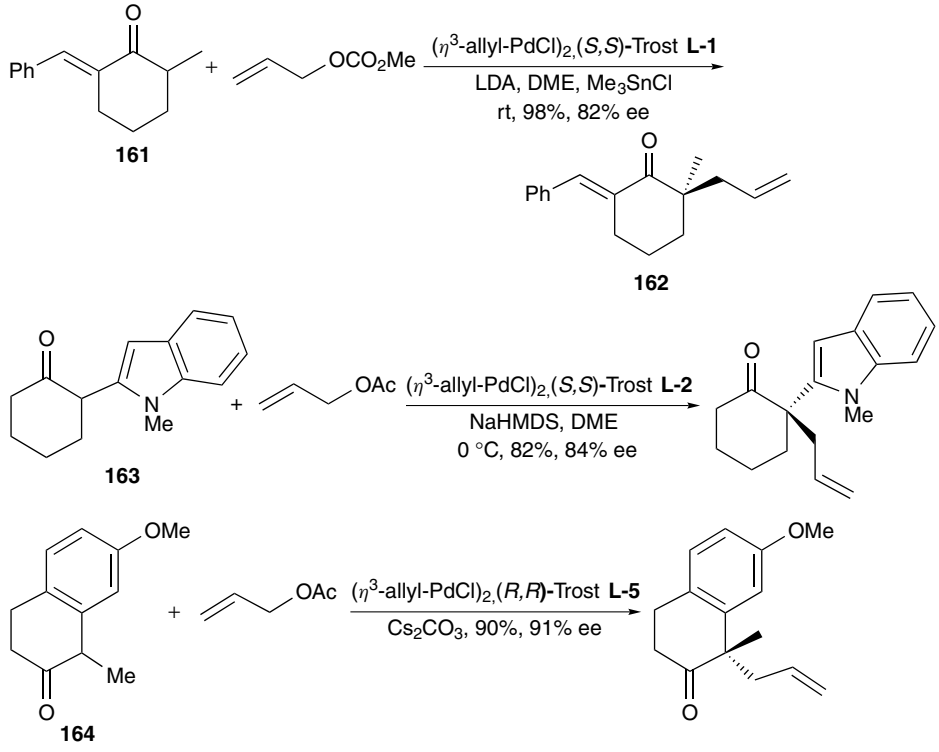
One pot synthesis of tricyclic enone **158** is possible via domino Pd-catalyzed allylation and Co-catalyzed Pauson-Khand reaction. Allylation of the propargylic malonate **156** with 3-acetoxycyclopentene under CO pressure afforded the fused tricyclic compound **158** via **157** in 73 % yield. Bimetallic catalyst PCNS (Pd and Co nanoparticles immobilized on silica) was used as a catalyst [55].



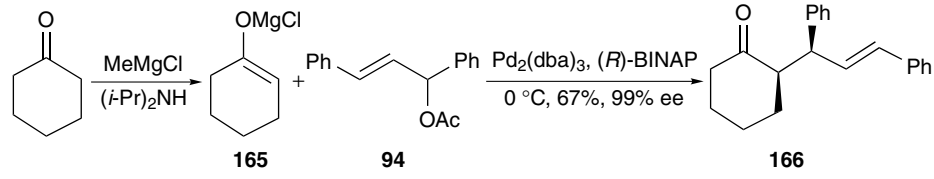
A phosphonate is an activating group. Asymmetric allylation of the chiral racemic α-acetamido-β-keto phosphonate **159** with cinnamyl acetate (**41**) was carried out at $-30\,^{\circ}C$ to afford α-alkyl-α-aminophosphonic acid derivative **160** with 88 % ee in 78 % yield when (*R*)-BINAP was used as a chiral ligand [56].



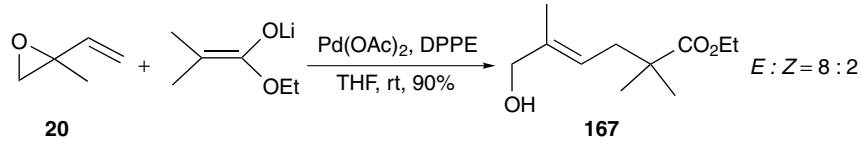
Allylation of simple ketone is not possible under usual conditions, but the reaction can be carried out under selected conditions. Asymmetric allylation of the chiral racemic α-methylcyclohexanone **161** with allyl carbonate proceeded in the presence of LDA as a base with or without Me_3SnCl as a Lewis acid at room temperature to provide the allylated ketone **162** in very high yield with 82 % ee when (*S*,*S*)-Trost **L-1** was used. The choice of base is crucial, and it was claimed that no reaction took place when Na or K bases were used in this reaction [57]. Asymmetric allylation of α-aryl and heteroaryl ketones has been carried out. Asymmetric allylation of 2-indolylcyclohexanone **163** took place at 0 °C to give the the allyl ketone in 82 % yield with 84 % ee. In this reaction, NaHMDS was used as a base and Trost **L-2** as chiral ligand [58]. Asymmetric allylation of the tetralone **164** with allyl acetate was carried out using Trost **L-6** in the presence of Cs_2CO_3 to provide the allylated ketone with 91 % ee in 90 % yield [59].



Non-stabilized ketone enolates are also allylated. The reaction of Mg enolate of cyclohexanone **165** with **94** afforded the chiral ketone **166** with high diastereo- and enantioselectivities by using (*R*)-BINAP [60].

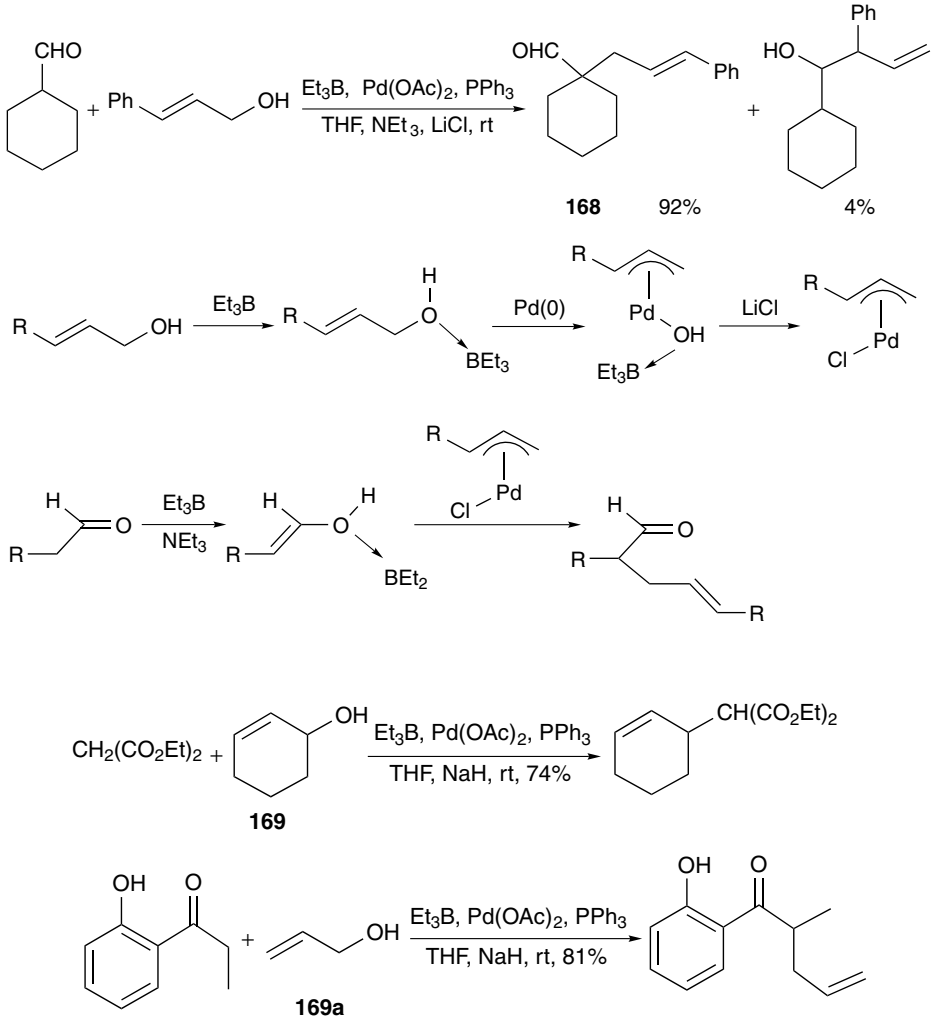


Direct allylation of esters is difficult, but their enolates are allylated. Expected 1,4-addition of Li enolate of ethyl isobutyrate to the isoprene monoxide **20** took place to give **167** at room temperature by using DPPE as a ligand [61].

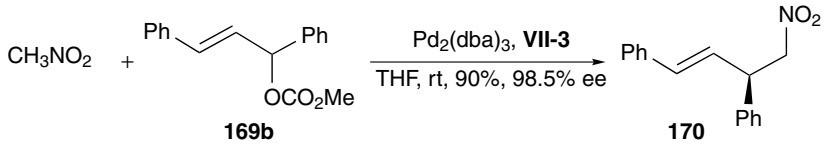


20 **167**

Tamaru reported that Pd-catalyzed α-allylation of aldehydes to afford **168** can be carried out even with allyl alcohols in the presence of a stoichiometric amount of Et_3B, NEt_3, and LiCl. Although the mechanism is not clear, activation of allyl alcohol by Et_3B occurs by coordination to generate π-allylpalladium. In addition, boron enolates are formed by the reaction of aldehydes with Et_3B and Et_3N, and attacked by π-allylpalladium [62]. Similarly allylation of malonates and ketones with allylic alcohols **169** and **169a** were carried out [63].

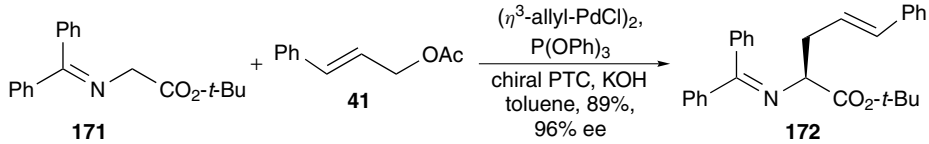


Nitroalkanes are smoothly allylated. Asymmetric allylation of nitromethane with the carbonate **169b** at room temperature afforded **170** in 90 % yield with 98.5 % ee. PHOX derivative **VII-3** was used as a chiral ligand [64].



169b **170**

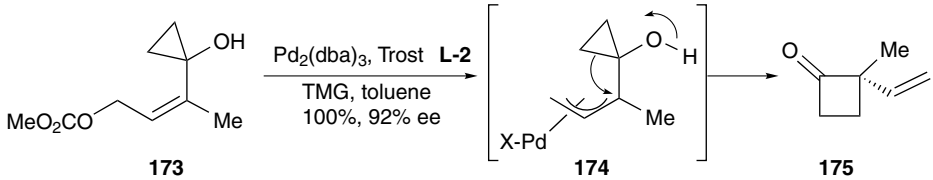
N-(Diphenylmethylene)glycine *t*-butyl ester (*t*-butyl glycinate-benzophenone Schiff base) **(171)** is a reactive prochiral nucleophile and α-allyl-α-amino acids can be prepared by allylation and hydrolysis of the allylated product. Asymmetric allylation of **171** with cinnamyl acetate (**41**) afforded **172** regioselectively with high % ee when the reaction was carried out in presence of achiral phosphite $P(OPh)_3$, and a chiral phase-transfer catalyst of alkaloid [*O*-allyl-(9-anthracenylmethyl)cinchonidinium iodide] [65,66].



171 **41** **172**

PTC = *O*-methyl cinchonidinium iodide

As a different type C-allylation, Trost reported asymmetric ring expansion involving Wagner–Meerwein shift of the allyl carbonate **173** bearing a cyclopropanol group to give the 2-vinylcyclobutanone **175** as shown by **174** in quantitative yield with 92 % ee, when Trost **L-2** as a chiral ligand and TMG as a base were used. Efficient differentiation of the prochiral face of the alkene occurred [67].



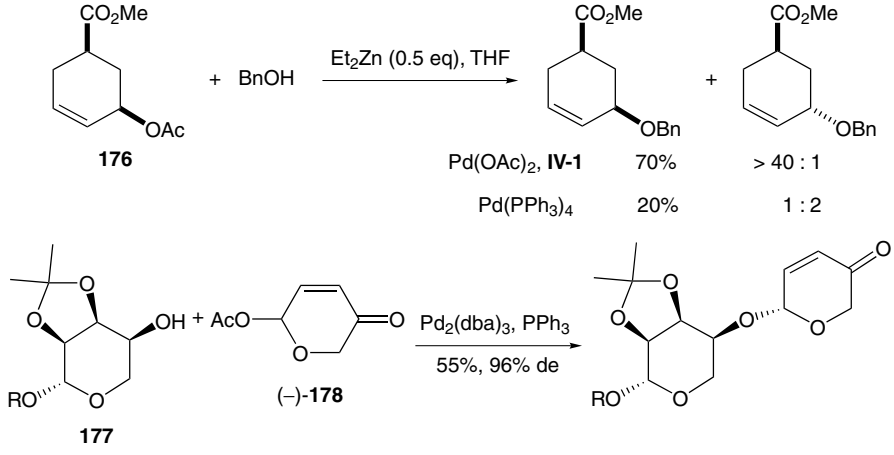
173 **174** **175**

4.2.4 Allylation of Oxygen and Nitrogen Nucleophiles

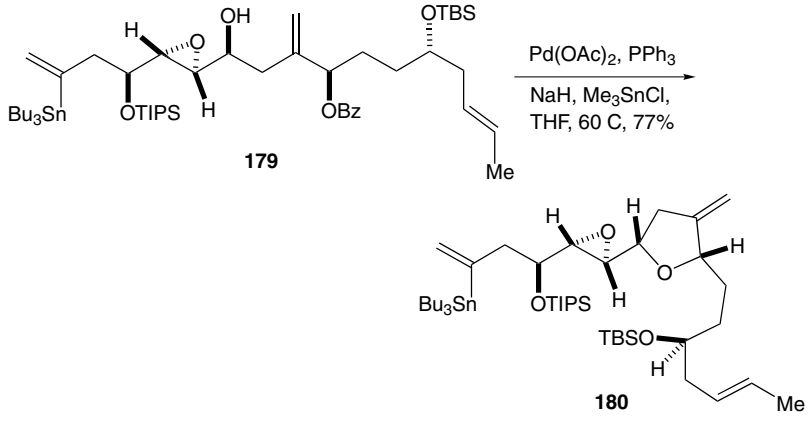
4.2.4.1 Allylation of Oxygen Nucleophiles

Pd-catalyzed O-allylation of aliphatic alcohols is sluggish particularly in the intermolecular version due to poor nucleophilicity of alcohols. As one solution, metal alkoxides are used to make nucleophilicity of alcohols stronger. Lee reported that Zn alkoxides are good coupling partners. Reaction of the cyclic allyl acetate **176** with benzyl alcohol proceeded smoothly at room temperature in the presence of Et_2Zn (0.5 equiv.) using $Pd(OAc)_2$ with bulky biphenyl-based phosphine **IV-1** and gave two ethers with retention of stereochemistry in high yield (70 %) in a ratio

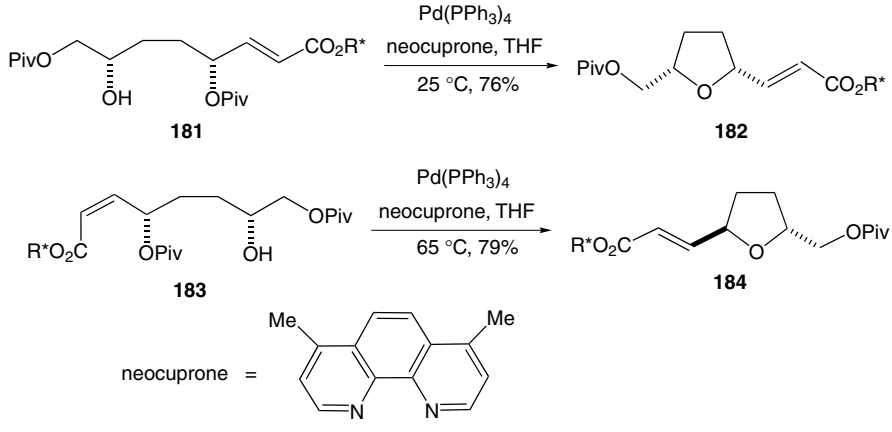
of 40 : 1. On the other hand, inversion occurred to give a ratio of 1 : 2 in low yield (20 %) when PPh_3 was used [68]. Interestingly allylation of OH group in a β-L-ribose **177** with the cyclic allylic acetate **178** proceeded smoothly using $Pd_2(dba)_3$ and PPh_3 in dichloromethane to afford the disaccharide precursor with 96 % de in 55 % yield without activation of OH group [69].



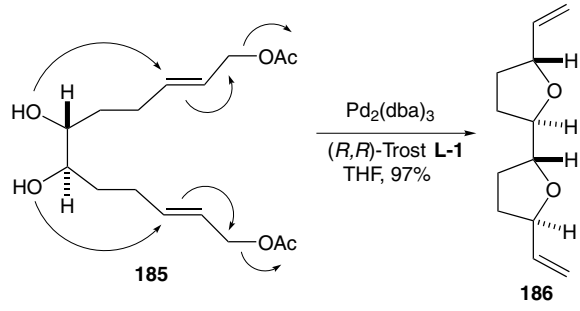
Stereoselective formation of 3-methylenetetrahydrofuran such as **180** by intramolecular allylation of alcohol with allyl benzoate in **179** was utilized in synthetic studies of the core of amphidinolide [70]. Thus treatment of **179** with $Pd(OAc)_2$ and PPh_3 in the presence of Me_3SnCl (1 equiv.) and NaH in THF afforded the *cis*-tetrahydrofuran **180** stereoselectively in 77 % yield. In this reaction, the less reactive hydroxy group was converted to the more reactive tin alkoxide by the reaction of Me_3SnCl (1 equiv.) and NaH.



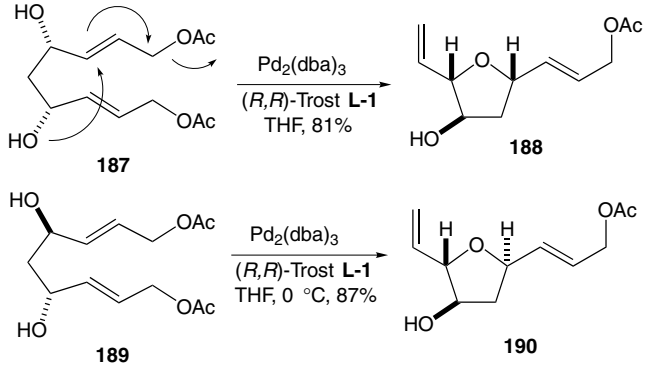
Tetrahydrofuran formation proceeds with high stereocontrol. Cyclization of (*E*)-allylic ester **181** proceeded at room temperature with overall retention of configuration to give the 2,5-*cis*-tetrahydrofuran **182** using $Pd(PPh_3)_4$ in the presence of neocuprone (2,9-dimethyl-1,10-phenanthroline). On the other hand, overall inversion occurred in the reaction of (*Z*)-allylic ester **183** to afford the 2,5-*trans*-tetrahydrofuran **184** with (*E*)-alkene [71].



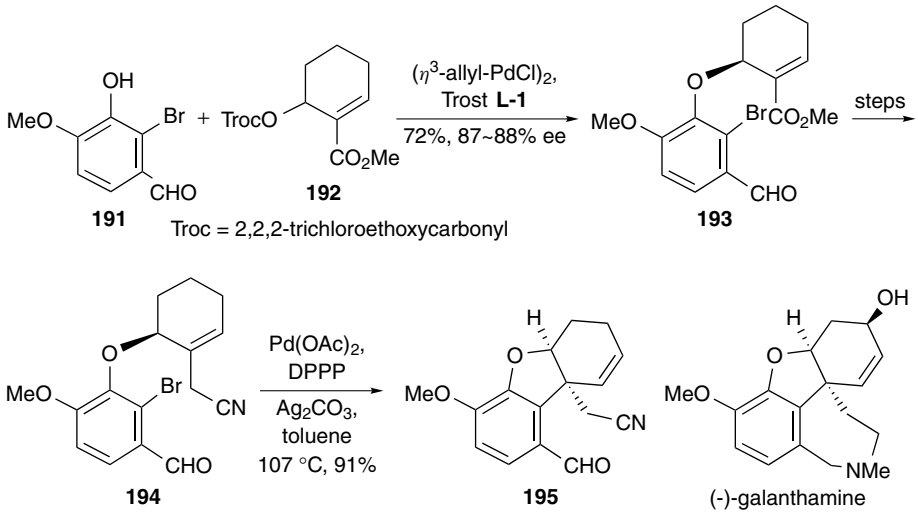
Formal total synthesis of uvaricin was achieved by applying double cyclization of vicinal diol bis(allylic acetate) to afford bis-THF core selectively using chiral ligand Trost **L-1** as a key reaction [72]. Thus the cyclization of **185** afforded the diene **186** with two new stereocenters in 97 % yield as a single diastereomer.



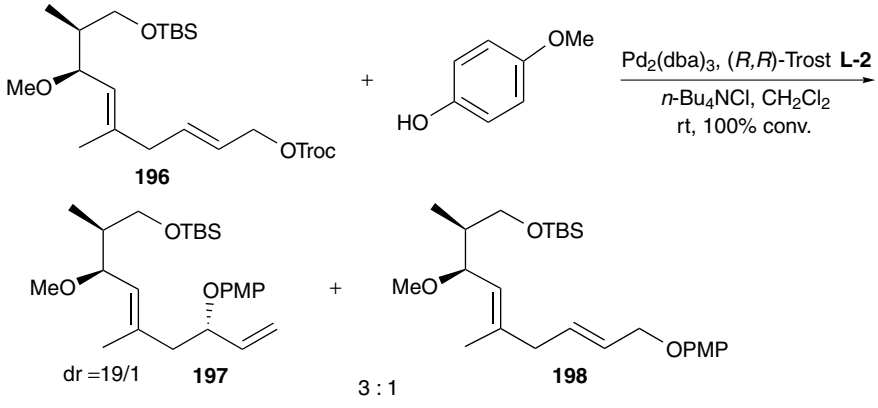
The F-ring of the polyether macrolide halichondrin was constructed by Pd-catalyzed selective monocyclization of **187** and **189**. No dicyclization took place due to steric reasons. Desymmetrization of the *meso*-diol **187** gave the tetrahydrofuran **188** in high yield using Trost **L-1** as a chiral ligand, and cyclization of the C_2 symmetric diacetate **189** afforded the desired diastereoisomeric tetrahydrofuran **190** [73].



In contrast to less efficient allylation of alcohols, allylation of phenols proceeds much more smoothly. In the enantioselective synthesis of (−)-galanthamine by Trost, two Pd-catalyzed reactions were utilized. Asymmetric allylation of the bromovanillin **191** with the cyclic allylic carbonate **192** gave the ether **193** by using $(\eta^3$-allyl-PdCl$)_2$ and chiral Trost **L-2**. Subsequent Heck reaction of **194** afforded **195** in 91 % yield when DPPP was used as a ligand. DPPF and DPPE gave lower yield [74].

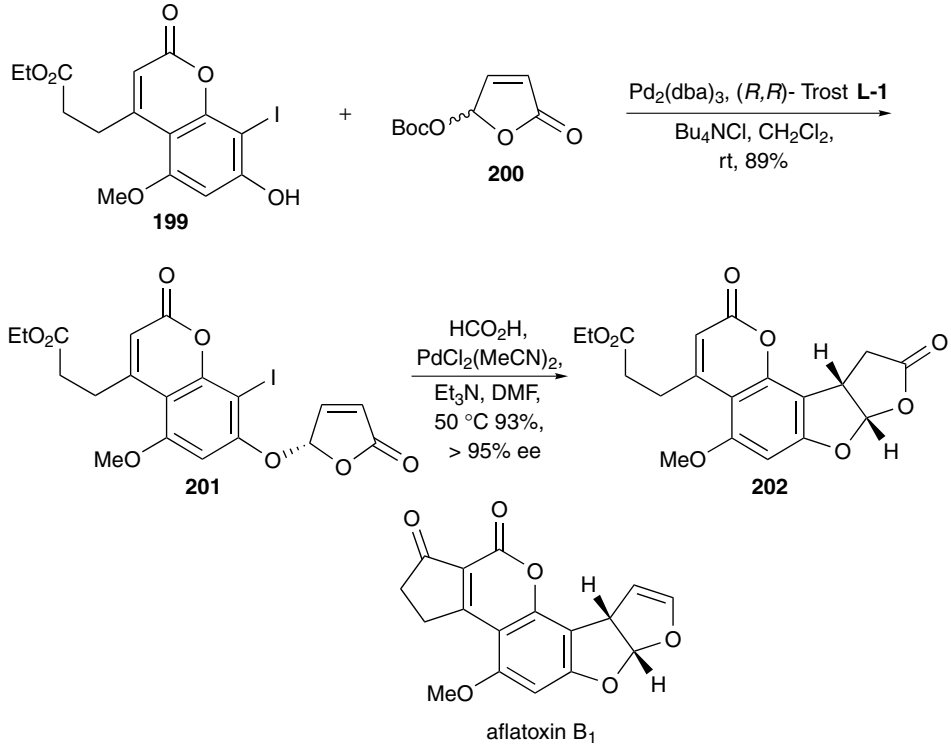


In the total synthesis of callipeltoside, Pd-catalyzed asymmetric allylation of *p*-methoxyphenol with the allylic carbonate **196** was carried out. When chiral ligand (*R*,*R*)-Trost **L-2** was used, a mixture of regioisomers **197** and **198** was obtained in high yield. The regioselectivity to form the branched and linear isomers was 3 : 1, and the diastereomeric ratio was 19 : 1. The branched isomer **197** was the major product [75].

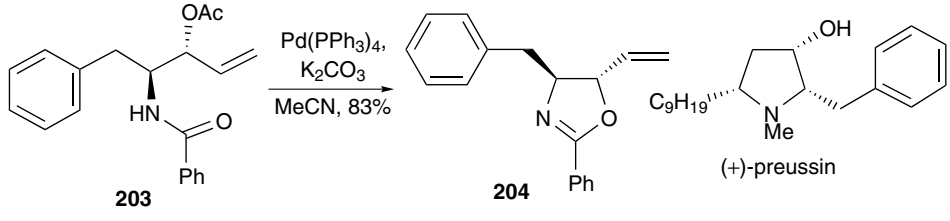


The enantioselective total synthesis of (+)-aflatoxin B_1 has been achieved by O-allylation with γ-acyloxybutenolide and reductive Heck reaction [76]. The coumarin derivative **199** was O-allylated with γ-*O*-Boc-butenolide **200**, which is an

allyl carbonate, to give **201** in 89 % yield in the presence of Bu_4NCl and Trost **L-1**. Reductive Heck reaction of **201** by using ligandless Pd catalyst afforded the coumarin **202** in 93 % yield with higher than 95 % ee, and aflatoxin B_1 was prepared from **202**. Efficient deracemization of the butenolide by differentiation of the enantioface occurred.



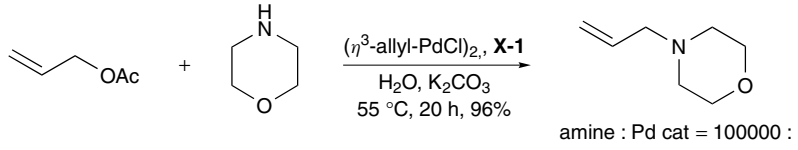
Efficient intramolecular O-allylation of L-*N*-benzoylphenylalaninol derivative **203** to form *trans*-oxazoline **204** with high diastereoselectivity (14 : 1) was utilized for the enantioselective total synthesis of (+)-preussin [77].



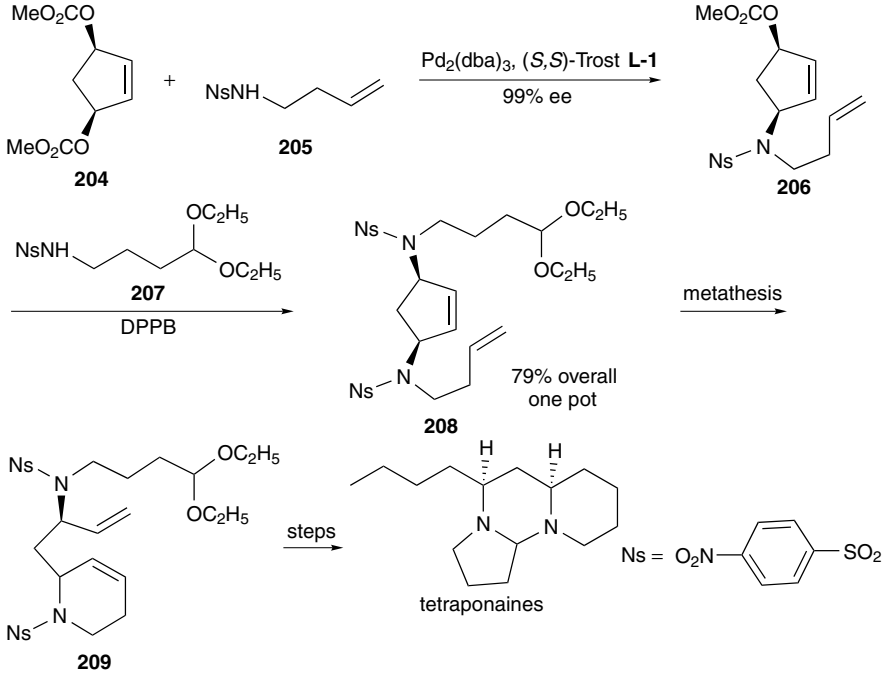
4.2.4.2 Allylation of Nitrogen Nucleophiles

Amines are reactive nucleophiles and allylation of amines proceeds smoothly using various ligands. Santelli reported that amination of allylic acetates proceeds

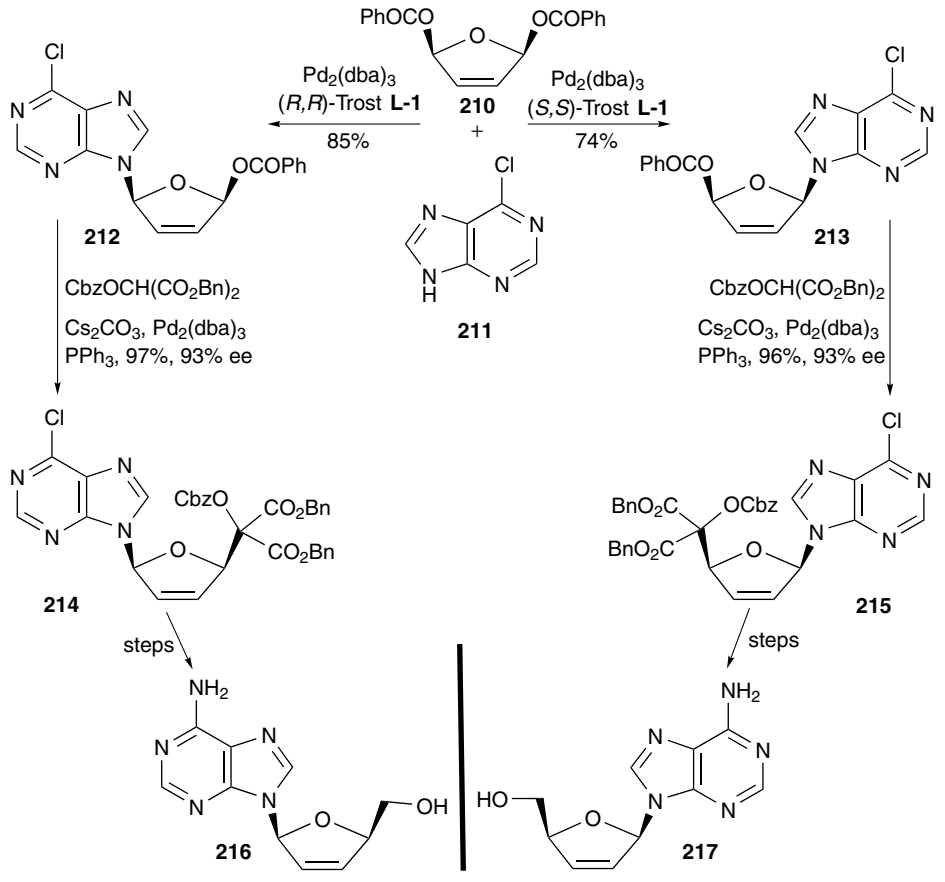
smoothly in water by using tetradentate Tedicyp (**X-1**) as a ligand. Allylmorpholine was obtained in 96 % yield by allylation of morpholine in water alone when the substrate/catalyst ratio of 100 000/1 was used. But 1000/1 was necessary for diallylamine formation from allylamine in 85 % yield. Pd-Tedicyp is soluble in water [78].



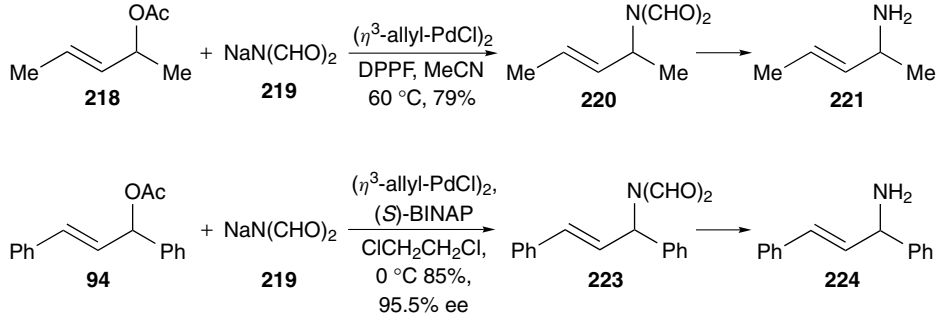
Reaction of *meso*-bis-carbonate **204** with the sulfonamide **205** afforded **206** with 99 % ee. The second regio- and diastereoselective allylation of the amine **207** with **206** gave the diamine **208** using DPPB as a ligand. Ru-catalyzed metathesis of the diene **208** afforded **209** and tetraponaine was synthesized [79].



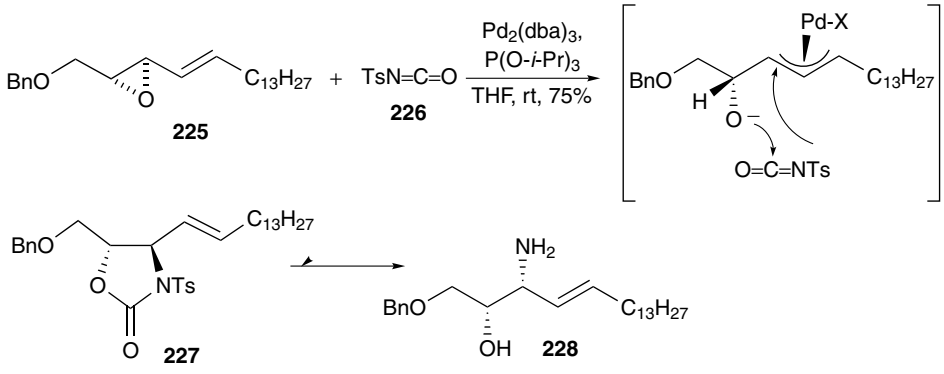
Asymmetric synthesis of nucleoside has been carried out based on desymmetrization of the *meso* form of *cis*-2,5-dibenzoyloxy-2,5-dihydrofuran diester (**210**), which possesses two allylic leaving groups at 2,5-positions with correct stereochemistry. N-allylation of 6-chloropurine (**211**) with **210** using Pd(0)-(*R*,*R*)-Trost **L-1** afforded **212**. Reaction of **212** with a malonate derivative using PPh_3 afforded **214**, which was converted to adenosine **216**. The enantiomeric adenosine **217** was prepared via **213** and **215** simply by using (*S*,*S*)-Trost **L-1** in the first allylation [80].



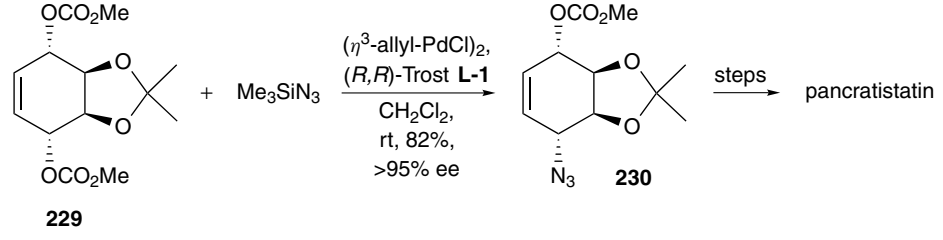
Allylation of ammonia gives a mixture of products, and it is difficult to prepare primary amines from ammonia, and several ammonia surrogates are used. Allylation of sodium diformylamide (**219**) with the allyl acetate **218** proceeded smoothly by using DPPF as a ligand to afford **220**, which was hydrolyzed to provide the primary allylamine **221**. The reaction was sluggish when PPh_3 was used. The primary allylamine **224** with high ee (95.5 %) was obtained from **94** via **223** by the use of (*S*)-BINAP [81].



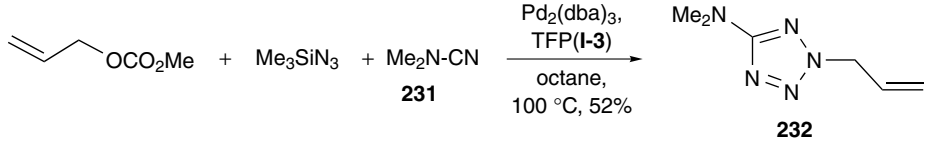
Tosyl isocyanate (**226**) was allylated smoothly with the alkenyloxirane **225** using isopropyl phosphite as a ligand to give the oxazolidinone **227** in 75 % yield, which was converted to the *syn* amino alcohol **228** in high yield. Oxazolidinone formation proceeds with overall retention of configuration, and is used for the synthesis of regioisomers of sphingosine [82].



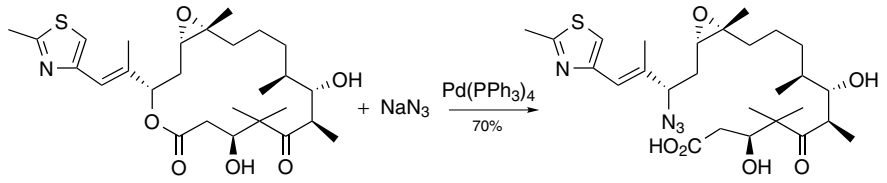
Azide is a reactive nucleophile and is used as an ammonia surrogate. Desymmetrization of the dicarbonate **229** occurred by the reaction with TMS azide to afford azide **230** in 82 % yield with higher than 95 % ee. The reaction is a key step in the asymmetric total synthesis of (+)-pancratistatin [83].



2-Allyltetrazoles are selectively prepared by three-component coupling of allyl carbonate, TMS azide and nitrile. Reaction of dimethylcyanamide (**231**) afforded 2-allyl-4-(dimethylamino)tetrazole **232** using TFP (**1–3**) as a ligand. π-Allylpalladium tetrazole is the proposed intermediate [84].

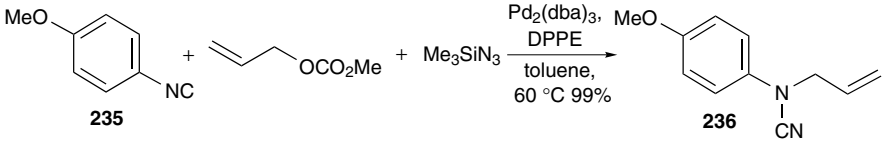


A lactam analog of epothilone has been synthesized by replacing allylic (and lactonic) OH with amino group in epothilone B **233** via Pd-catalyzed reaction of allylic lactone **233** with NaN_3 to provide the azide **234** [85].

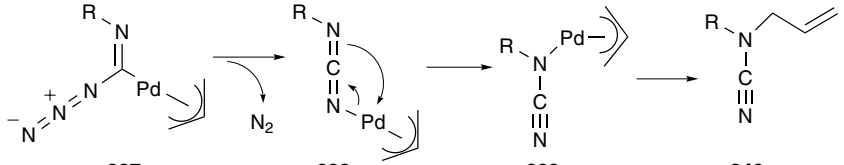


233 **234**

Allyl cyanamide **236** was prepared in good yield by the reaction of aryl isocyanide **235**, allyl carbonate, and TMS azide by using DPPE as a ligand [86]. A proposed mechanism is the following. Insertion of isocyanide to Pd-azide generates π-allylpalladium intermediate **237**. Elimination of N_2 generates the Pd-carbodiimide complex **238**, and 1,3-migration of π-allylpalladium group from the nitrogen to α-nitrogen atom affords the cyanamide complex **239**. It should be noted that the conversion from **237** to **238** is a π-allylpalladium mimic of the Curtius rearrangement. The complex **238** is in equilibrium with the Pd-cyanamide complex **239**. Then reductive elimination provides the allyl cyanamide **240**.

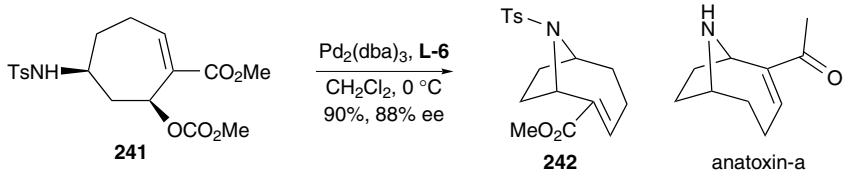


235 **236**

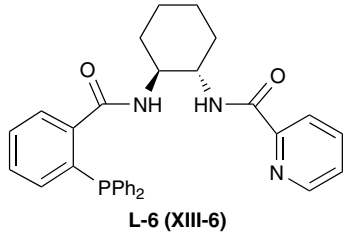


237 **238** **239** **240**

Asymmetric cyclization of the cyclic allyl carbonate **241** is a good synthetic method for 9-azabicyclo[4.2.1]non-2-ene system **242**, which can be converted to



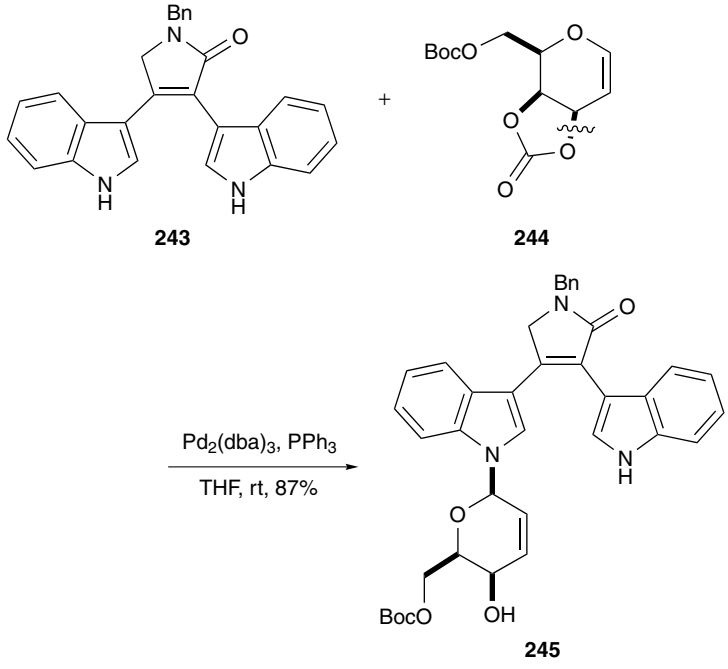
241 **242** anatoxin-a



L-6 (XIII-6)

anatoxin-a [87]. Cyclization of *cis*-amino carbonate **241** was a delicate reaction. No cyclization occurred in DMF using Trost **L-1** as a ligand. Good results (90 % yield, 88 % ee) were obtained using monophosphine ligand Trost **L-6** (**XIII-6**) in dichloromethane. Net retention took place in the cyclization, and no cyclization of the corresponding *trans*-amino carbonate occurred.

Allylation of the bis-indole lactam **243** with fucose-derived glycal (cyclic allyl carbonate) **244** proceeded at room temperature using PPh_3, affording the single regio- and stereoisomer **245** in 87 % yield [88].

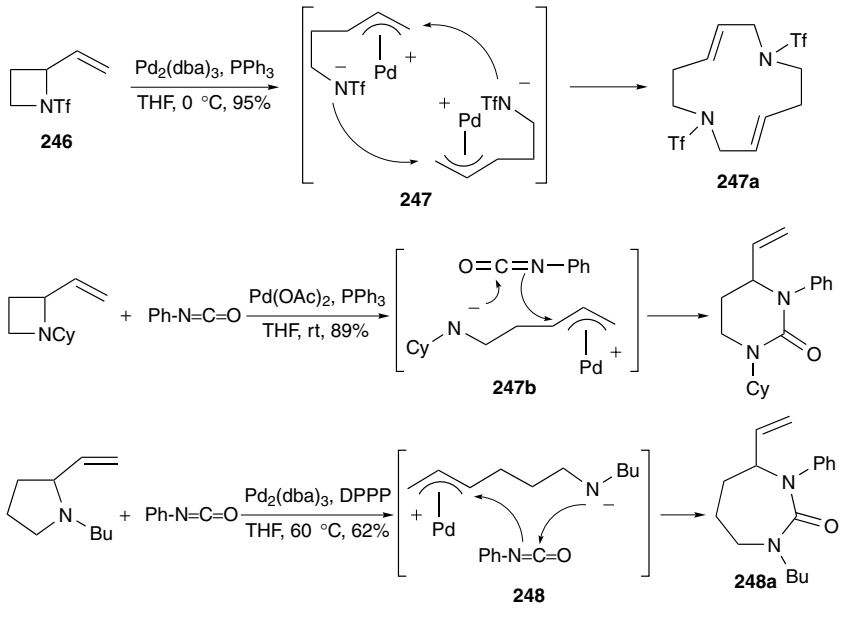


243 **244** **245**

Due to ring strain, π-allylpalladium is generated by ring-opening of 2-vinylazetidine **246**. It undergoes different reactions depending on the substituent on nitrogen. When triflyl group was used as N-protection, N-allylation between two molecules occurred to afford *N*,*N*-1,7-bis(trifluoromethanesulfonyl)-1,7-diazacyclododeca-3,9-diene **247a** as a cyclic dimer in very high yield as shown by **247**. No dimerization occurred when the *N*-tosyl group was used [89].

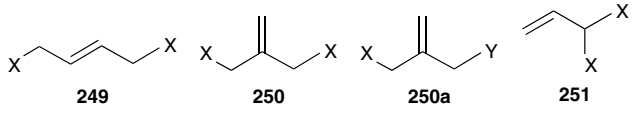
Alper carried out reaction of *N*-cyclohexyl-2-vinylazetidine with phenyl isocyanate at room temperature and obtained the 4-vinyltetrahydropyrimidin-2-one in high yield. Formal insertion of C=N bond of isocyanate occurred as explained by **247b** [90].

Even strain-free 2-vinylpyrrolidine can be cleaved by Pd to generate the π-allylpalladium intermediate, and the 1,3-diazepin-2-one **248a** was obtained by the reaction with phenyl isocyanate as shown by **248**. The use of $Pd_2(dba)_3$ and DPPP is important. When $Pd(OAc)_2$ and PPh_3 were used, conjugated diene was obtained by elimination [91].

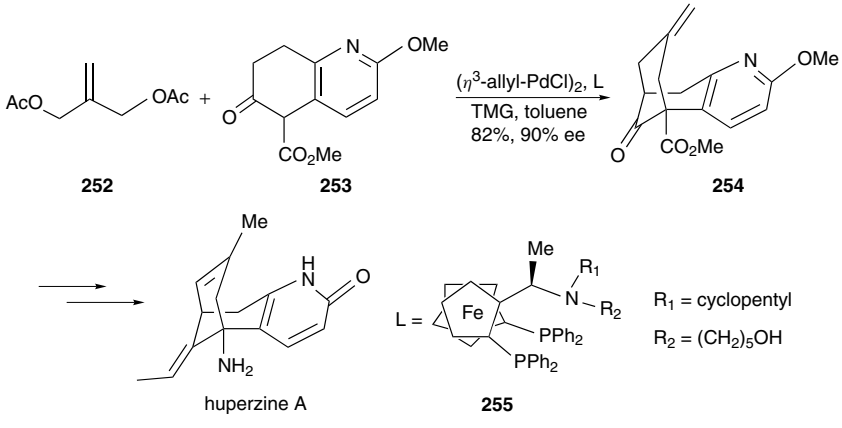


4.2.5 Allylation with Bis-Allylic Compounds and Cycloadditions

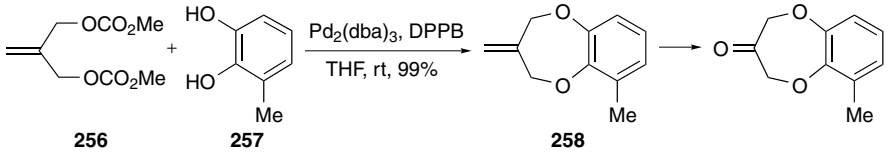
Reactions of the three bis-allylic compounds **249**, **250**, and **251** with various nucleophiles are useful for the preparation of a number of cyclic compounds.



Total synthesis of racemic huperzine was achieved by Kozikowski utilizing bis-allylation of the β-keto ester **253** with 2-methylenepropanediol diacetate (**252**) to give **254** [92], and the enantioselective synthesis of (−)-huperzine has been carried out by Terashima [93] and Bai [94] using BPPFA-type ligands. The derivative **255** of (*R*)-(*S*)-BPPFA (**XI-12**) was found to be the most effective chiral ligand among several known chiral ones (82 % yield, 90 % ee).

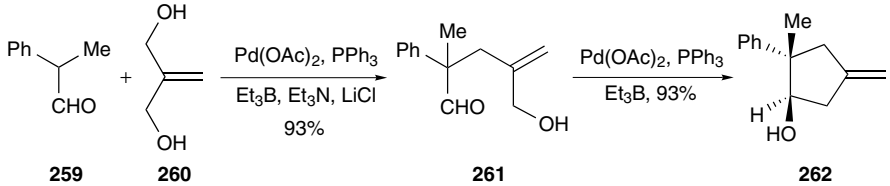


Bis-allylation of 3-methylcatechol (**257**) with the allylic bis-carbonate **256** using $Pd(OAc)_2$ and DPPB offers a facile synthetic method of the substituted 3-methylene-3,4-dihydro-2*H*-1,5-benzodioxepine (**258**). The reaction proceeds at room temperature to give **258** in high yield [95].



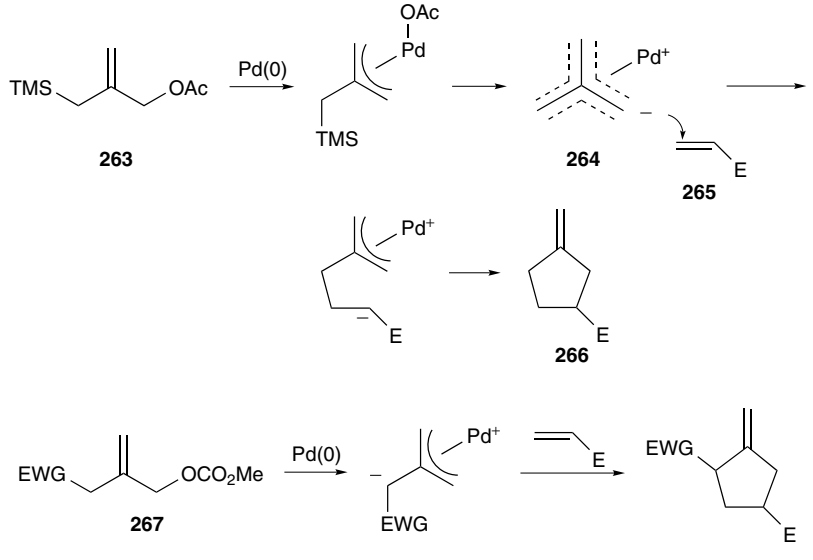
256 **257** **258**

Tamaru discovered that 2-methylenepropane-1,3-diol (**260**) showed a different type of bifunctionality under slightly different conditions in the reaction with the aldehyde **259**. In the presence of Et_3B, Et_3N, and LiCl, electrophilic α-allylation of the aldehyde took place to afford **261** in 93 % yield. Then nucleophilic allylation of the aldehyde **261** in the absence of Et_3N and LiCl occurred to give the homoallylic alcohol **262**. Et_3B plays interesting dual roles; first, it promotes α-allylation of the aldehyde enolate in the presence of amine, and second, umpolung of an allyl alcohol exhibits nucleophilic attack to aldehyde (Chapter 4.3.3) [96].



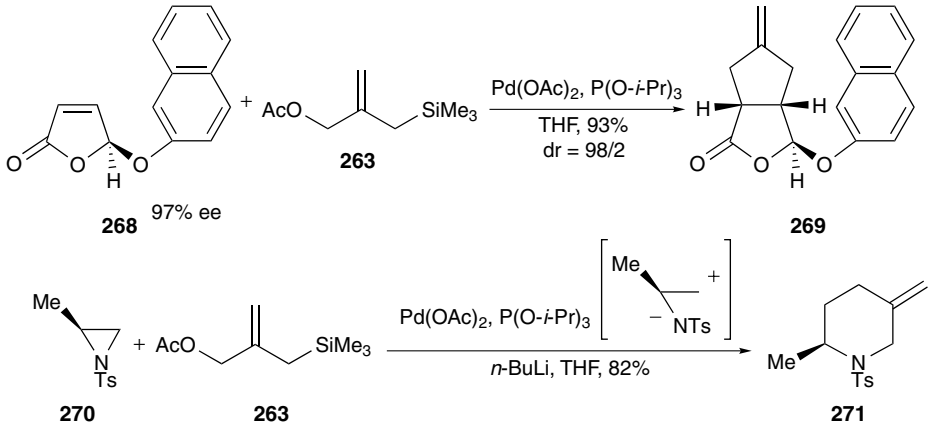
259 **260** **261** **262**

2-(Trimethylsilylmethyl)allyl acetate (**263**) is a useful compound, which generates Pd-trimethylenemethane complex (TTM) **264** and undergoes [3 + 2] cycloadditions with **265** to afford **266**. Also [3 + 3] cycloaddition is possible [97]. The carbonate **267** can be used for similar cycloadditions under neutral conditions [98].

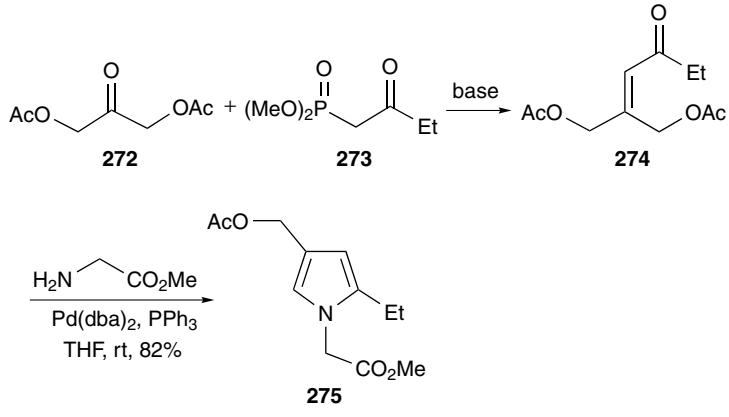


263 **264** **265** **266** **267**

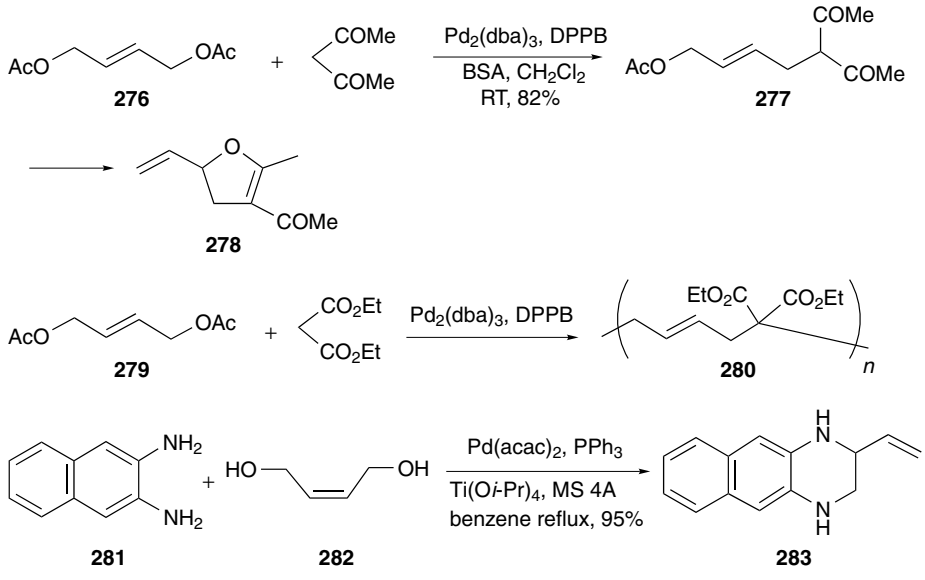
Enantioselective synthesis of brefeldin A was achieved by utilizing [3 + 2] cycloaddition of **263** with the chiral butenolide **268** to provide **269** as a key reaction [99]. Less basic triisopropyl phosphite was used as a suitable ligand. Functionalized piperidine **271** was prepared in an enantiomerically pure form by [3 + 3] cycloaddition of enantiomerically pure aziridine **270** with **263** and the total synthesis of (−)-pseudoconhydrine has been achieved [100].



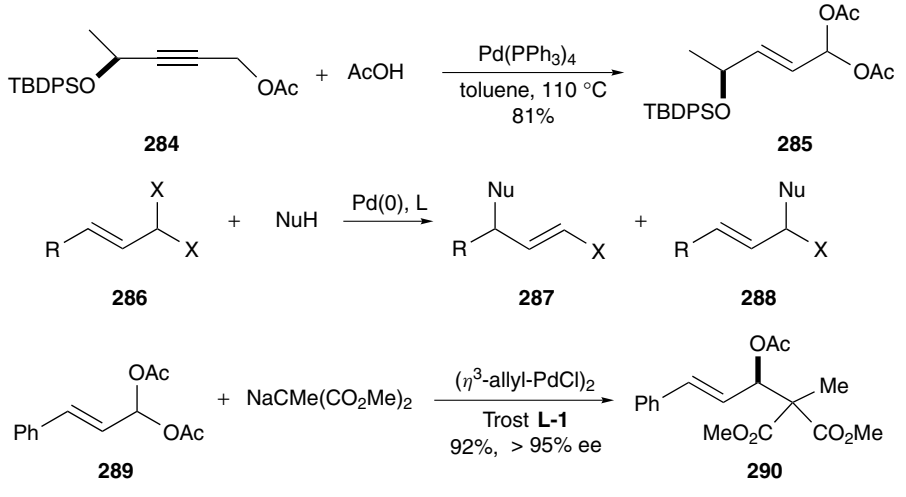
2-(Acylmethylene)propanediol diacetate **274** was prepared by Wadsworth–Emmons olefination reaction of 1,3-diacetoxyacetone (**272**) with β-keto phosphonate **273**, and Pd-catalyzed reaction of **274** with methyl glycinate afforded the trisubstituted pyrrole **275** [101].



Diacetate of 2-butene-1,4-diol (**276**) reacts with nucleophiles in two ways, cyclization and polymerization. Intermolecular reaction of **276** to afford **277**, followed by intramolecular reaction with active methylene compounds using BSA and DPPB afforded the furan derivative **278** [102]. Under different conditions, the polymer **280** was obtained. 1,2,3,4-Tetrahydro-2-vinylbenzo[*g*]quinoxaline **283** was prepared in 95 % yield by diamination of 2-butene-1,4-diol (**282**) with 2,3-diaminonaphthalene (**281**) [103].



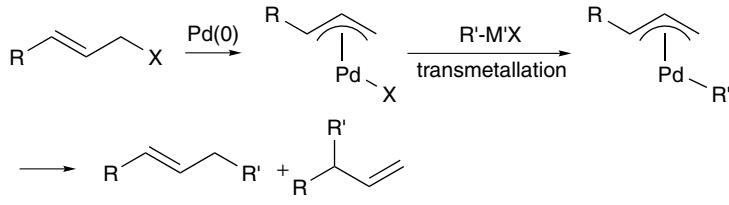
Allylic geminal dicarboxylates **285** are prepared by Pd-catalyzed reaction of propargyl acetate **284** with AcOH [104]. Two products **287** and **288** are obtained from *gem*-allylic compounds **286**, and **288** is an allylic ester and undergoes the second allylation. Several applications to asymmetric syntheses have been reported [48]. Reaction of **289** with dimethyl methylmalonate afforded **290** with 95 % ee.



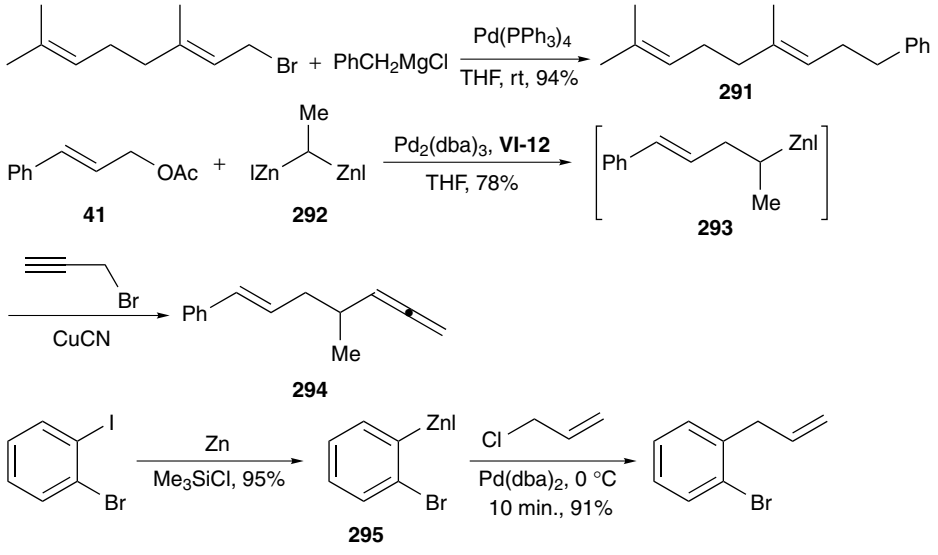
4.3 Reactions with Main Group Organometallic Compounds via Transmetallation

4.3.1 Cross-Coupling with Main Group Organometallic Compounds

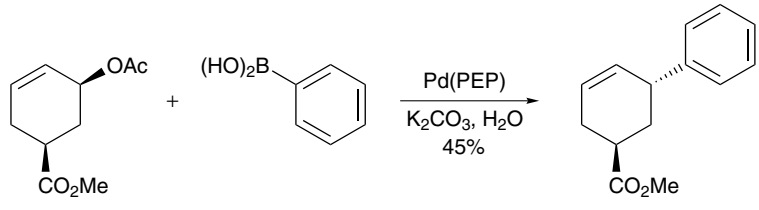
Allylic compounds undergo smooth Pd-catalyzed cross-coupling with main group organometallic compounds as expected. Substitution occurs mainly at less-substituted allylic termini. A few examples are cited here.



Reaction of geranyl bromide with benzyl Grignard reagent proceeded regioselectively to give **291** in high yield [105]. Desymmetrization of *gem*-dizincioethane (**292**) occurred by cross-coupling with cinnamyl acetate (**41**) by using MeO-MOP (**VI-12**) as a chiral ligand to generate the homoallylzinc reagent **293** and Cu-catalyzed cross-coupling of **293** with propargyl bromide afforded the allene **294** in good yield, although % ee was not high (22 %) [106]. 2-Bromophenylzinc iodide (**295**) was prepared from 2-bromoiodobenzene and coupled with allyl chloride using phosphine-free $Pd(dba)_2$ catalyst at room temperature to give 2-bromoallylbenzene [107].

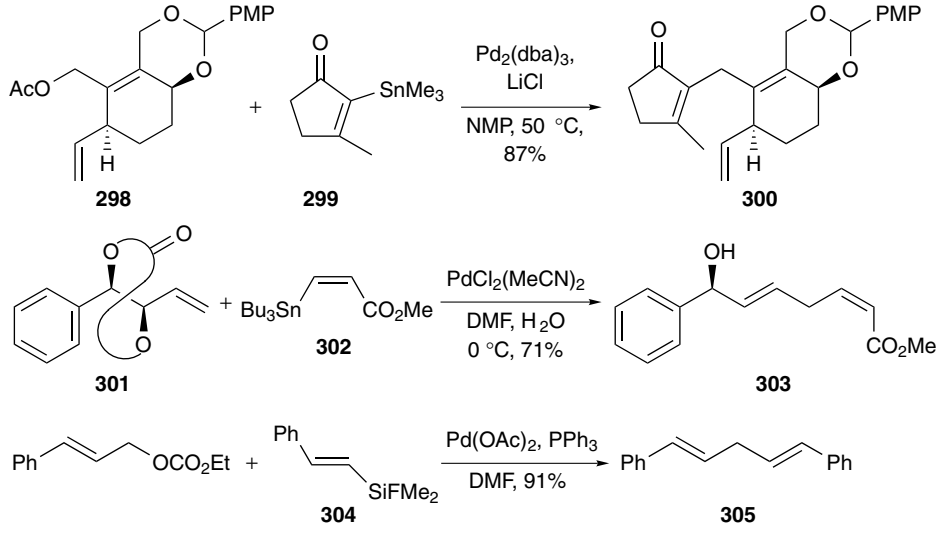


Suzuki coupling of the allyl acetate **296** with phenylboronic acid took place to give **297** as a single diastereomer using polymer-supported Pd, showing that inversion occurred cleanly as expected [108].

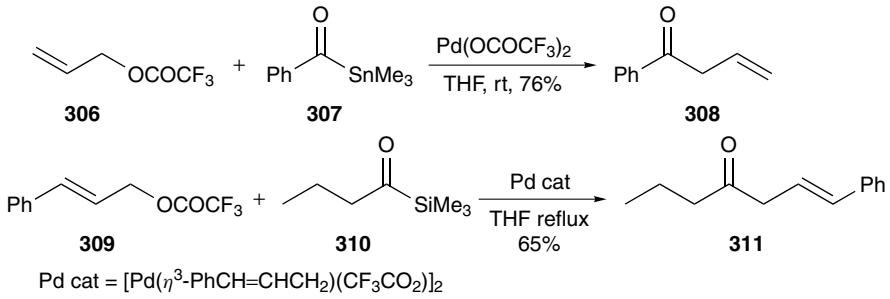


296 PEP = poly(ethylene glycol)-polystyrene graft copolymer **297**

Cross-coupling of the alkenylstannane **299** with the congested allyl acetate **298** has been carried out using ligandless Pd catalyst to give **300** in 87 % yield in convergent synthesis of guanacastepene [109]. The cyclic carbonate **301** reacted with vinylstannane **302** to give the allylic alcohol **303** in good yield using ligandless Pd catalyst [110]. Cross-coupling of the alkenylsilane **304** with cinnamyl ethyl carbonate took place to give 1,4-diene **305** without addition of fluoride as a promoter, because an ethoxide which activates the C—Si bond is generated from the carbonate [111].



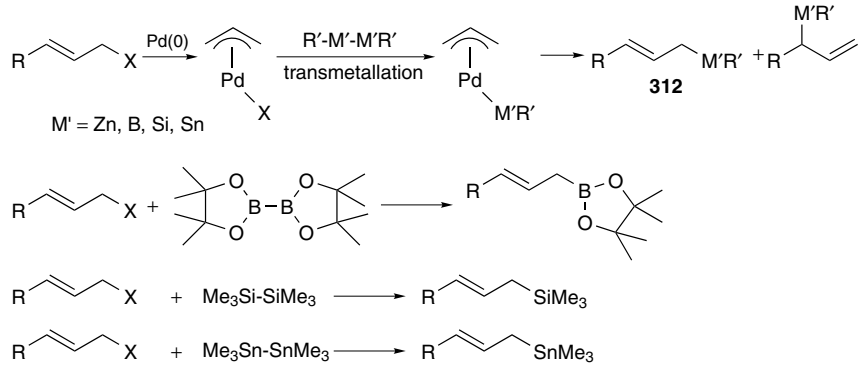
Allyl ketones are prepared by cross-coupling of allyl esters with acyl metals. For the coupling, allyl trifluoroacetate (**306**) and the acylstannane **307** were used to provide the ketone **308** [112]. Similarly, acylsilanes such as **310** are used for the coupling with allyl trifluoroacetate **309** to give **311** [113]. For these couplings, use of allyl trifluoroacetate is important. No reaction occurred with allyl acetate. While ligandless palladium trifluoroacetate is most effective, $Pd(OAc)_2$ shows low activity.



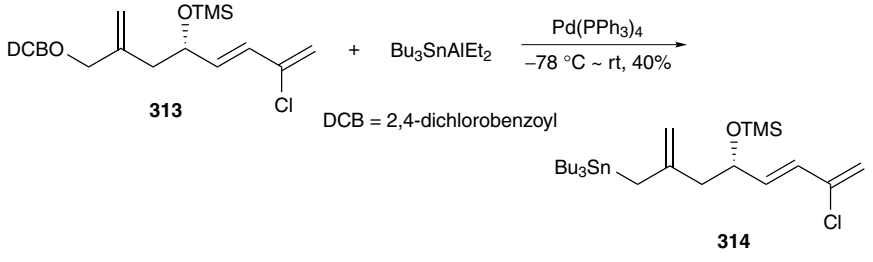
4.3.2 Formation of Allylic Metal Compounds

Allylpalladium compounds are electrophilic. Conversion of allylpalladium to nucleophilic allyl compounds of main group metals **312** is called ‘umpolung’, and offers

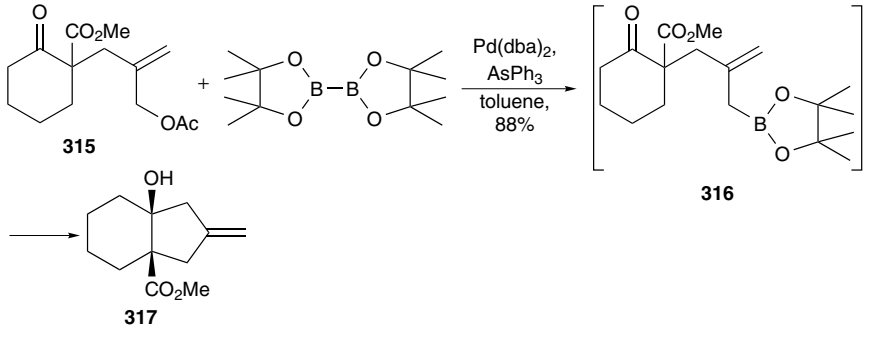
a useful synthetic method. Allyl metal compounds can be prepared and isolated, but in many cases umpolung reactions are carried out via *in situ* formation of nucleophilic allyl compounds. One well-established synthetic method of allylic compounds of main group metals is the Pd-catalyzed reaction of allyl compounds with homodimetal compounds such as $R_2B\text{-}BR_2$, $R_3Si\text{-}SiR_3$, and $R_3Sn\text{-}SnR_3$ as shown by the following general scheme. Also heterodimetals of B, Al, Sn, and Si compounds are used. An excellent review covering Pd-catalyzed syntheses and reactions of allyl metal compounds has been written by Marshall [114].



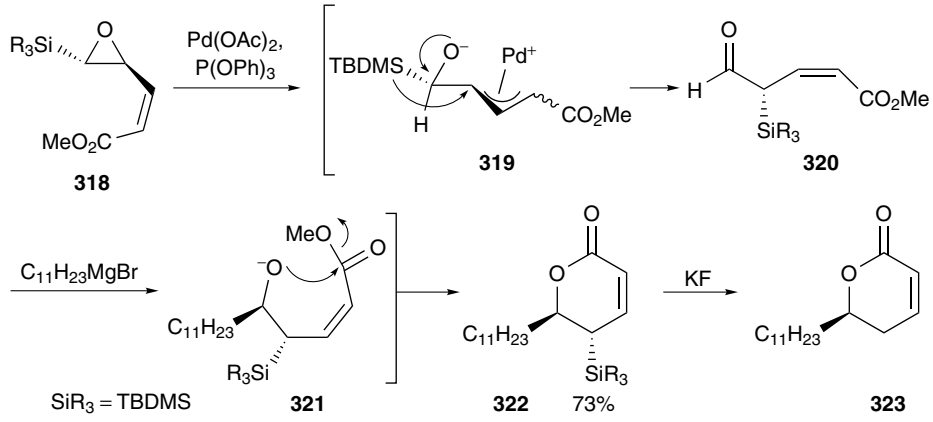
Allylstannane **314** was prepared by the reaction of the allyl ester **313** with the very reactive hetero dimetal compound $Bu_3Sn\text{-}AlEt_2$ [115].



As a typical example of umpolung, domino borylation of the allylic acetate **315** with diborane to generate allylborane **316**, and intramolecular nucleophilic allylation of ketone afforded the cyclic homoallylic alcohol **317** in 88 % yield [116].



α-Silyl-β,γ-unsaturated aldehydes (allylsilanes) are prepared by an interesting stereocontrolled Pd-catalyzed rearrangement of silylated vinyloxiranes [117]. As an synthetic application, treatment of the epoxide **318** with $Pd(OAc)_2$ and $P(OPh)_3$ afforded the α-silyl aldehyde **320** by stereocontrolled rearrangement as shown by **319**. Addition of a Grignard reagent to **320** afforded the unsaturated lactone **322** with high diastereoselectivity. A pheromone **323** was prepared by desilylation [118].



4.3.3 Allylation Involving Umpolung

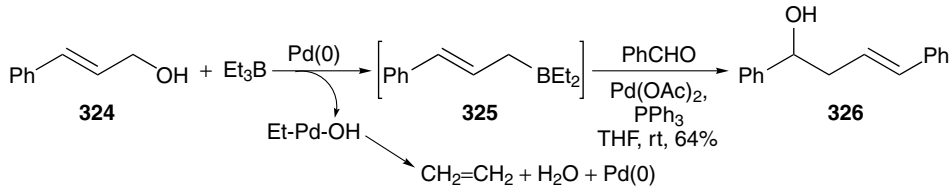
Pd-catalyzed reactions of allyl compounds with carbonyl compounds proceed in the presence of main group organometallic compounds, typically, Et_3B, Et_2Zn, InI, and $SnCl_2$. In these reactions, nucleophilic allylmetal intermediates are generated by transmetallation of electrophilic π-allylpalladium with these metal compounds and react with carbonyl compounds to afford homoallylic alcohols. As a whole, umpolung of π-allylpalladium intermediates occurs. The umpolung occurring with Et_3B and Et_2Zn can be understood by a simple transmetallation mechanism. On the other hand, reductive transmetallation is involved in the reactions with InI and $SnCl_2$.

Tamaru and co-workers have shown that Et_3B displays two distinctive behaviors in Pd-catalyzed reaction of allylic alcohols [118a]:

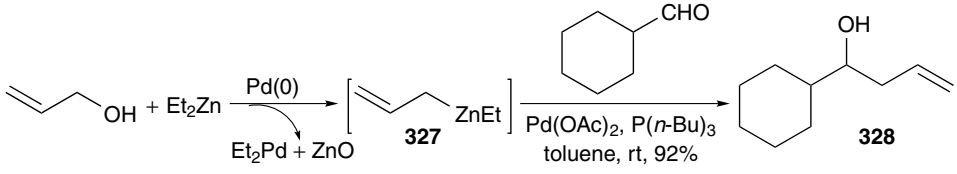
1. activation of allyl alcohols for electrophilic allylation (α-allylation of ketones and aldehydes); and
2. promotion of nucleophilic allylation.

Activation of allyl alcohols is treated in Chapter 4.1. Concerning nucleophilic allylation, it has been shown that cinnamyl alcohol (**324**) reacts smoothly with benzaldehyde in the presence of Pd catalyst and Et_3B as a stoichiometric reagent in THF at room temperature to afford homoallylic alcohol **326** [119]. In this reaction, nucleophilic allylboron **325** is generated by transmetallation of π-allylpalladium with Et_3B and reacts with benzaldehyde.

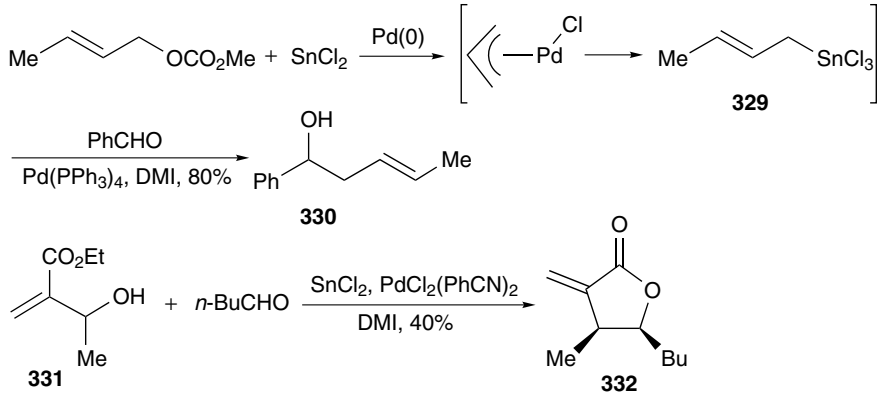
When aliphatic aldehydes are used under similar conditions, α-allylation and aldol condensation of aldehydes occur.



Nucleophilic allylation of aldehydes with allyl alcohol proceeds smoothly in the presence of Et_2Zn via the formation of nucleophilic allylethylzinc **327** to provide the homoallyl alcohol **328** [120].

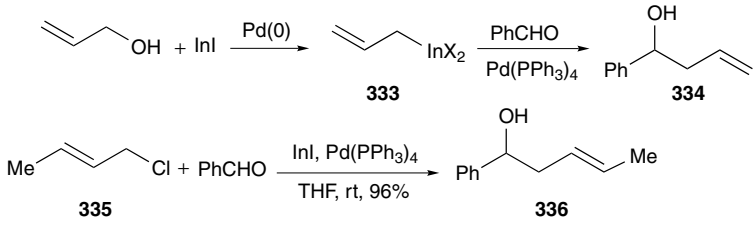


Masuyama and co-workers have shown that nucleophilic allyltrichlorostannanes **329** are generated by the reaction of allyl carbonates with $SnCl_2$ and react with aldehydes to give the homoallyl alcohols **330**. DMI is a good solvent [121]. Also allyl alcohols can be used for the allylation. Formation of the allyltrichlorostannane **329** from allyl alcohol and $SnCl_2$ was confirmed by NMR studies [122]. α-Methylenelactone **332** was obtained by the reaction of ethyl (α-hydroxyethyl)acrylate **331** with pentanal [123].

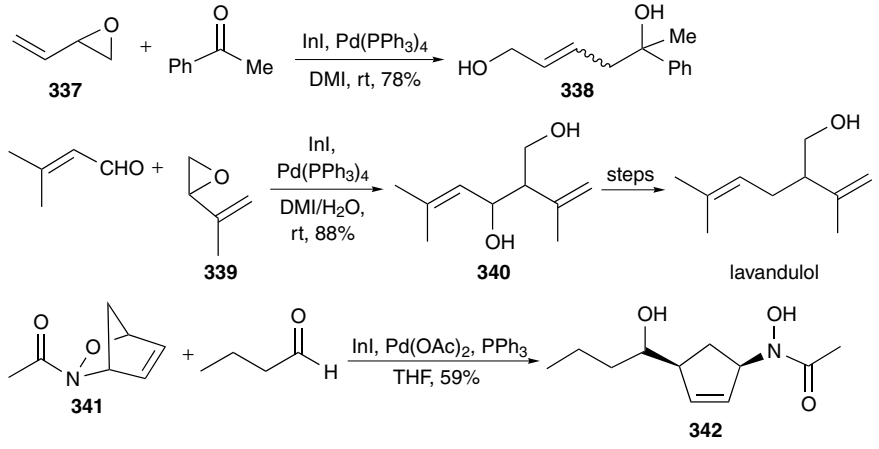


Indium metal or indium iodide as a reducing agent can be used for umpolung of π-allylpalladium. Araki reported that allylic indium(III) reagents **333** are generated *in situ* by reductive transmetallation of π-allylpalladium with indium(I) salts [124]. Based on this reaction, nucleophilic allylation of benzaldehyde with allylic chlorides, alcohols, and esters occurred at room temperature in the presence

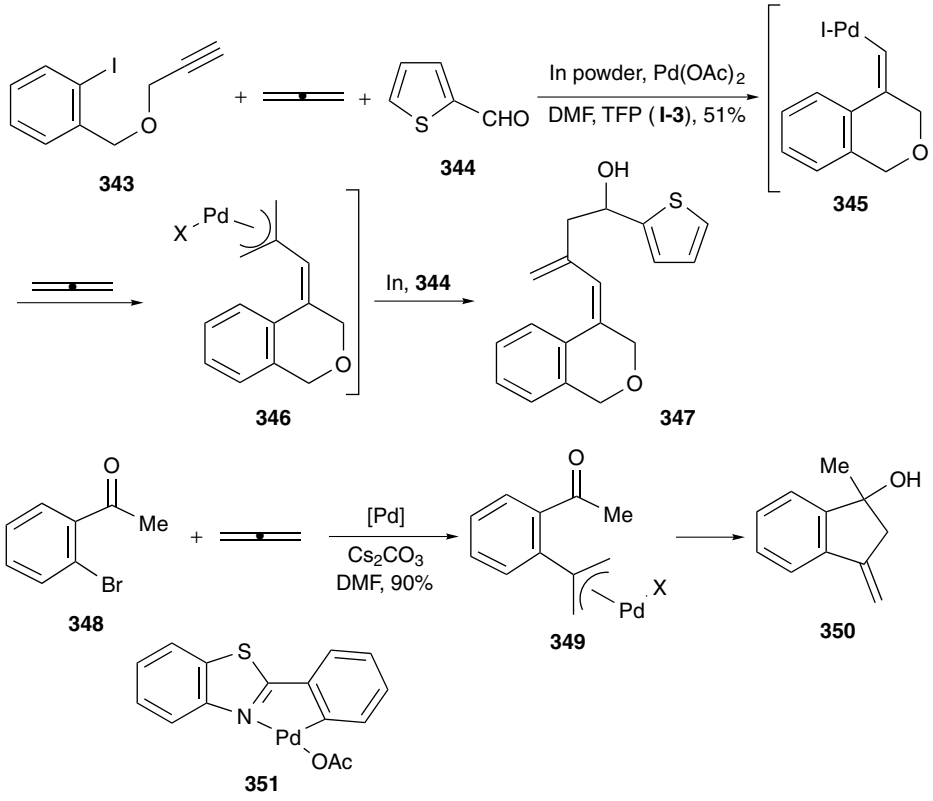
of a stoichiometric amount of In(I) iodide to afford the homoallyl alcohols **334** and **336**. It is known that SmI_2 shows a similar reactivity [124a].



Alkenyloxiranes are more versatile and react with both aldehydes and ketones giving mainly 1,5-diols by 1,4-addition in anhydrous DMI. For example, reaction of the epoxide **337** with acetophenone afforded 5-phenyl-2-hexene-1,5-diol (**338**) [125]. On the other hand, the isoprene monoxide **339** reacted with aldehyde to provide the 1,3-diol **340** regioselectively in aqueous DMI and lavandulol was synthesized [126]. The In-induced umpolung has been applied to the *N*-acylnitroso cycloadduct **341** as an allylic ether, which reacted with aliphatic aldehydes such as butanal and ketones to give the *cis*-1,4 adduct **342** predominantly [127].

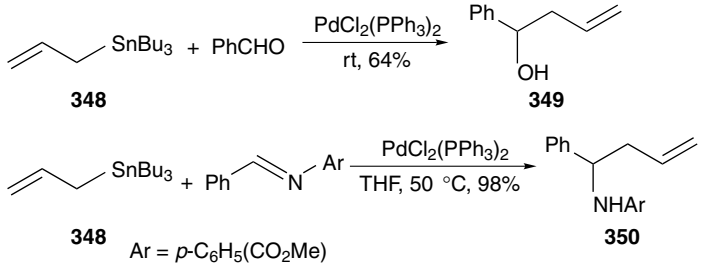


Domino reaction of the alkyne **343** with allene, and 2-thiophenecarboxaldehyde in the presence of TFP as a ligand and indium powder gave the homoallyl alcohol **347**. In this reaction π-allylpalladium **346** was generated by the reaction of **345** with allene. In-induced umpolung of **346** and its nucleophilic allylation of aldehyde provided the homoallyl alcohol **347** [128]. Interestingly, the π-allylpalladium intermediate **349**, generated from 2-bromoacetophenone and allene, attacked the ketone to afford the 3-methyl-1-indanol **350** without addition of any organometallic reagent. The uses of the palladacycle **351** as a catalyst and Cs_2CO_3 as a base are important [129]. Formation of allylindium by the reaction of allyl halides with In metal has been reported [130]. Also In-$InCl_3$ can be used [131].



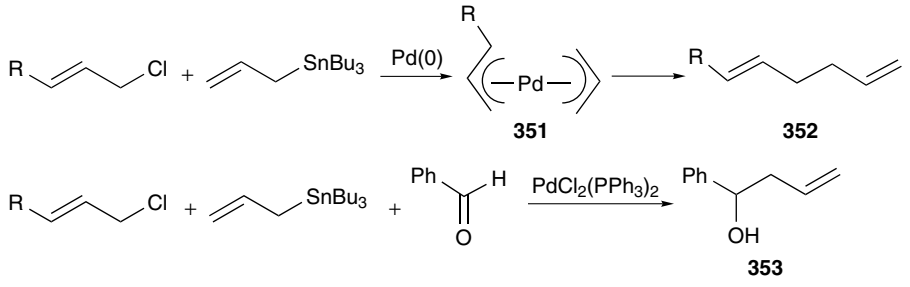
4.3.4 Reactions of Amphiphilic Bis-π-Allylpalladium Compounds

Although bis-π-allylpalladium complexes were not isolated and identified, their formation is assumed in several reactions. Allylation of aldehydes with allylstannane **348** occurs under acidic conditions in the presence of Lewis acid. Yamamoto and co-workers found that the reaction proceeds smoothly under essentially neutral conditions in the presence of Pd catalyst to give homoallyl alcohol **349** [132]. Allylation of imines to produce amines **350** is more facile. Formation of nucleophilic bis-π-allylpalladium as a key intermediate was assumed in these reactions [133].

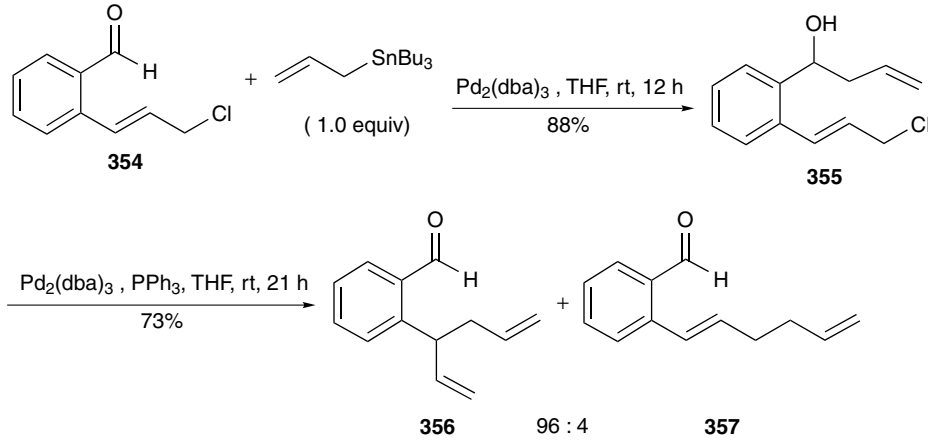


Cross-coupling of allyl halides with allylstannane to form 1,5-hexadiene (**352**) is known [134]. Yamamoto has made an interesting observation that allylation of aldehydes took place to give homoallyl alcohol **353** by the reaction of allyl

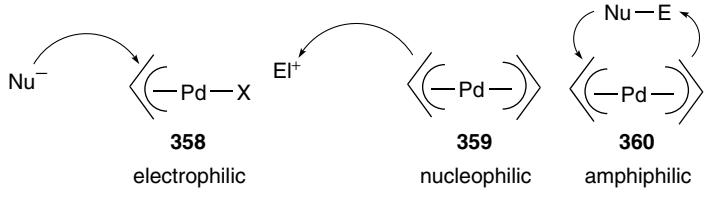
halides, allylstannane, and aldehyde without forming 1,5-hexadiene [135]. These reactions are explained by the formation of bis-π-allylpalladium **351** from Pd(0), allyl halides, and allylstannane [136].



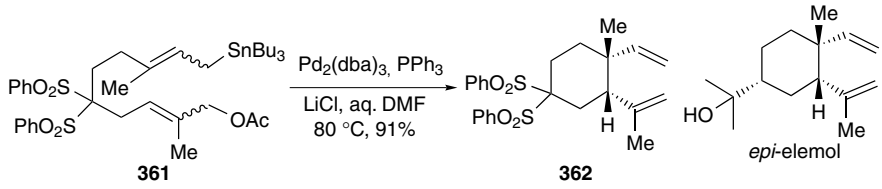
Concerning the possibility of allylation and cross-coupling, Yamamoto and coworkers found that PPh_3 plays a key role in differentiating these reactions. They carried out the reaction of *o*-(3-chloro-1-propenyl)benzaldehyde (**354**) with allylstannane in the presence of $Pd_2(dba)_3$. In the absence of PPh_3, allylation of aldehyde took place to give **355**. On the other hand, cross-coupling took place to afford the biallyls **356** and **357** in the presence of PPh_3 (40 mol%) [135].



From these studies, they proposed the formation of bis-π-allylpalladium **359**, which is nucleophilic. This is in marked contrast to the well-established fact that the π-allylpalladium complex **358** is electrophilic. Also, they assumed that the bis-π-allylpalladium **360** is amphiphilic and reacts with both nucleophilic and electrophilic carbons.

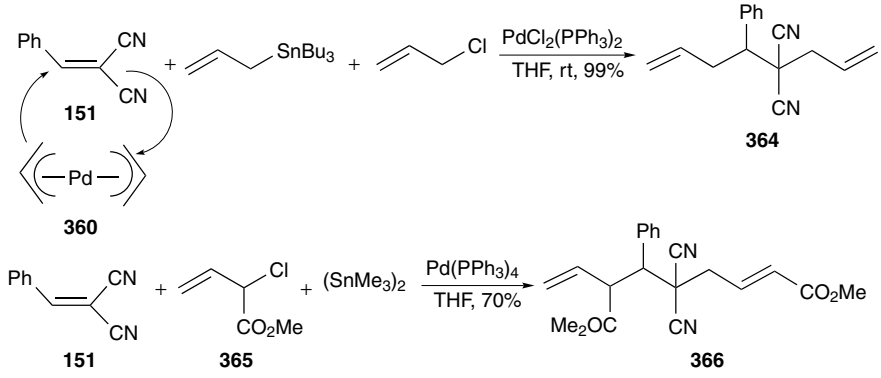


Intramolecular cross-coupling of allyl acetate and allylstannane in **361** via bis-π-allylpalladium was carried out using $Pd_2(dba)_3$ and PPh_3 to give the cyclohexane derivative **362** as a single regio- and stereoisomer. The presence of LiCl and H_2O is essential. The cyclized product **362** was converted to *epi*-elemol [137].

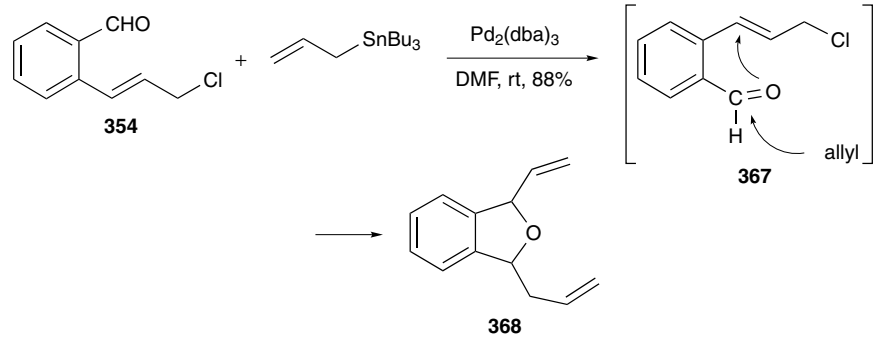


361 **362**

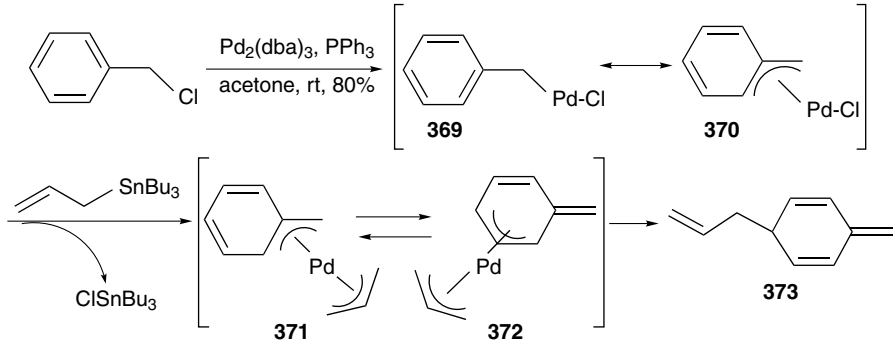
Reaction of benzylidenemalononitrile (**151**) with allyl chloride and allylstannane afforded 1,2-diallylated product **364** in high yield, indicating that bis-π-allylpalladium **360** is an amphiphilic allylating agent [138]. Instead of allylstannane, $(SnMe_3)_2$ can be used for the coupling of the allyl chloride **365** with **151**, and Szabo has shown that nucleophilic allylation occurred at the substituted allyl terminus, and electrophilic allylation took place at the terminal carbon to provide **366** [139].



Heterocyclization of *o*-(3-chloro-1-propenyl)benzaldehyde (**354**) occurred with allylstannane to afford the cyclized product **368**. The reaction is understandable by assuming the amphiphilic allylation of C=O bond of aldehyde as shown by **367** [140]. Amphiphilic allylation of the C=O bond of aldehyde was observed by the reaction of butadiene with aldehyde [141] (Chapter 5.1).

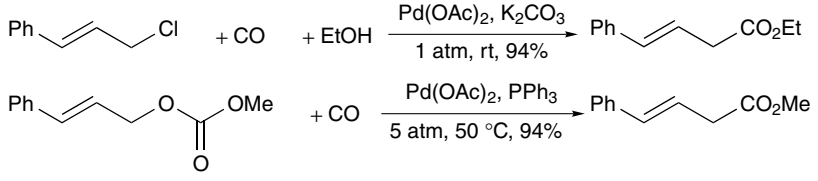


As a related reaction, Yamamoto reported a novel allylative dearomatization to give 6-allyl-3-methylene-1,4-cyclohexadiene (**373**) by the reaction of benzyl chloride and allylstannane under mild conditions. In this reaction, the π-benzylpalladium species **370** is generated from benzylpalladium **369**. The bis-π-allylpalladium species **371** and **372** are generated by the reaction of π-benzylpalladium **370** with allylstannane. Finally the dearomatization product **373** is formed from **372** by reductive elimination. It is surprising that the dearomatization product **373** is rather stable and no isomerization to a benzene derivative was observed at room temperature [142].

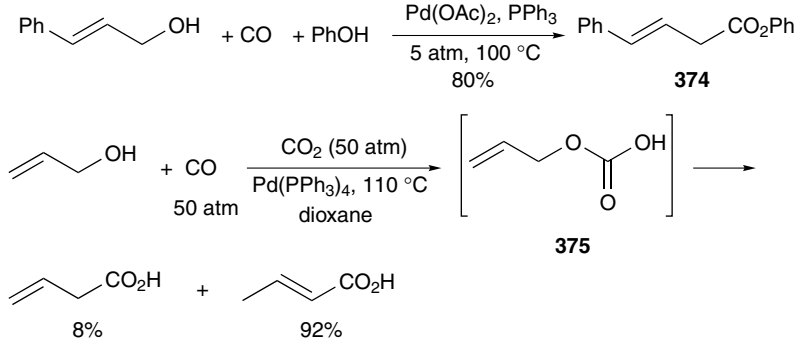


4.4 Carbonylation Reactions

β,γ-Unsaturated esters are prepared by the carbonylation of allylic compounds under various conditions depending on the leaving groups. Carbonylation of allylic chlorides proceeds under two-phase (liquid–solid) and mild conditions (room temperature, 1 atm of CO in the presence of K_2CO_3 in EtOH) using ligandless Pd catalyst. Ethyl 4-phenyl-3-butenoate was obtained from cinnamyl chloride in 94 % yield [143]. Allylic carbonates are reactive and their carbonylation proceeds under mild neutral conditions [144].

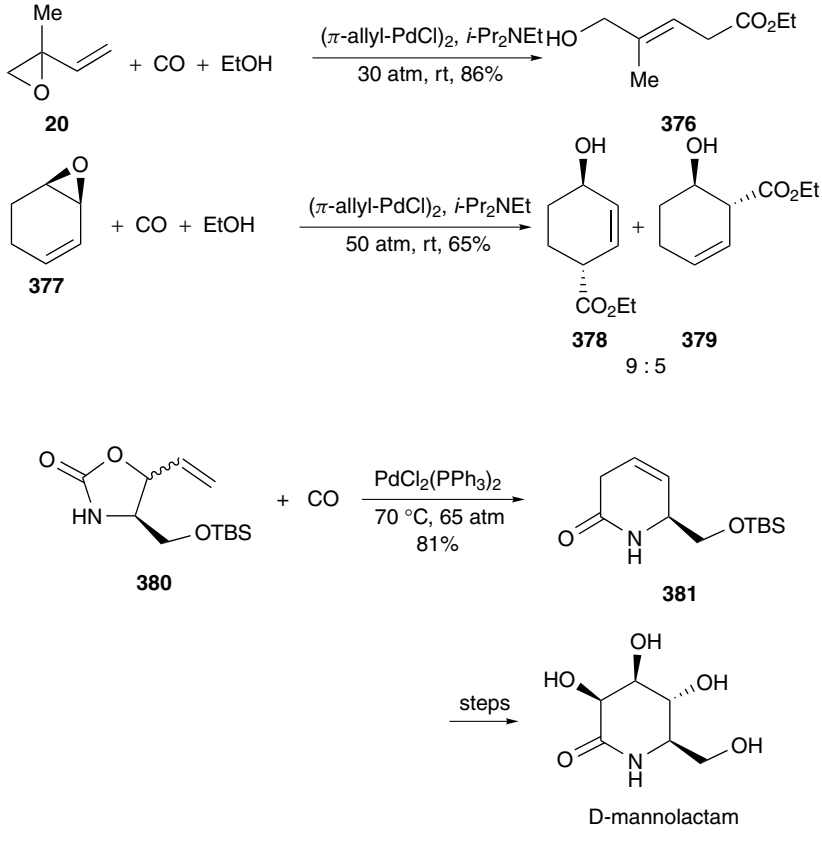


Less reactive allylic alcohols are carbonylated under harsh conditions. However, carbonylation of allylic alcohols proceeds smoothly in the presence of phenol as a nucleophile. Phenyl 4-phenyl-3-butenoate (**374**) was obtained in 80 % yield from cinnamyl alcohol under 5 atm of CO at 100 °C. The carbonylation may proceed by the formation of allyl phenyl ether, which is a reactive compound [145]. Allyl alcohol was carbonylated under high pressure of CO_2 (50 atm) and CO (50 atm) in dioxane to provide 2-butenoic acid as the main product and 3-butenoic acid as the minor product at 110 °C. Presumably monoallyl carbonate **375** is generated from

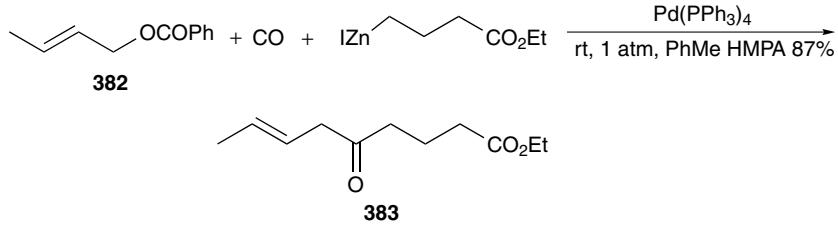


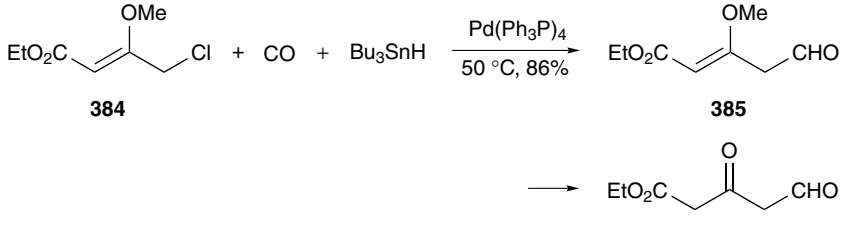
allyl alcohol and CO_2, and carbonylated to give 3-butenoic acid, which isomerized to 2-butenoic acid [146].

β,γ-Unsaturated δ-hydroxyester **376** was obtained by regioselective carbonylation of the isoprene oxide (**20**) in EtOH using ligandless Pd catalyst at room temperature under CO pressure (30 atm). Both regioisomers **378** and **379** were also obtained by carbonylation of cyclohexene oxide **377** [147]. Decarboxylation-carbonylation of the vinyl-substituted cyclic carbamate **380** gave the six-membered unsaturated lactam **381** regioselectively in 81 % yield, and D-mannolactam was synthesized from **381** [148].

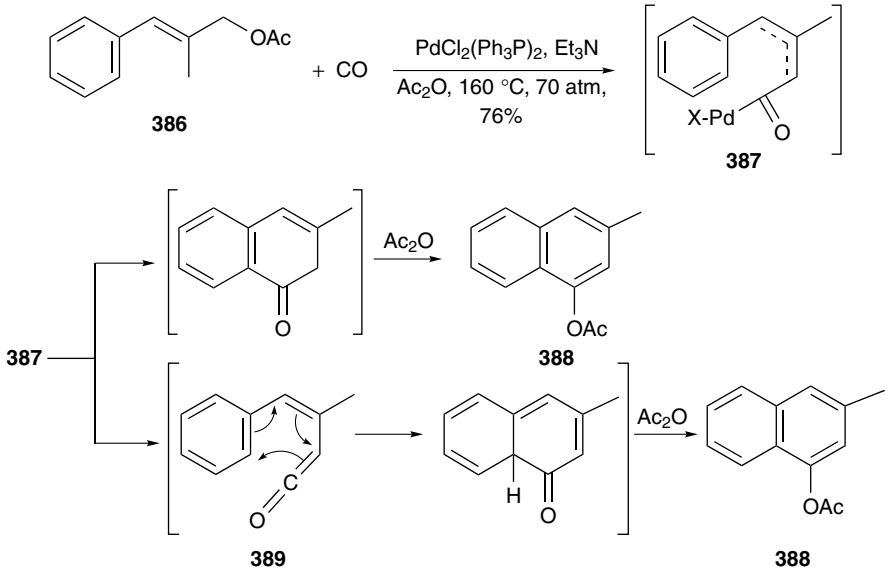


In the presence of main group organometallic compounds, ketones are obtained. Carbonylation of allylic ester **382** with alkylzinc reagent afforded the ketone **383** in high yield [149]. Carbonylation of allyl chloride **384** in the presence of tin hydride afforded the β,γ-unsaturated aldehyde **385** via hydrogenolysis of acylpalladium intermediate [150].

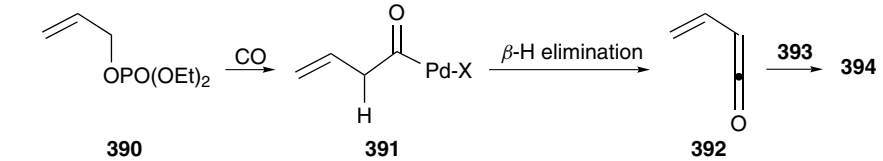


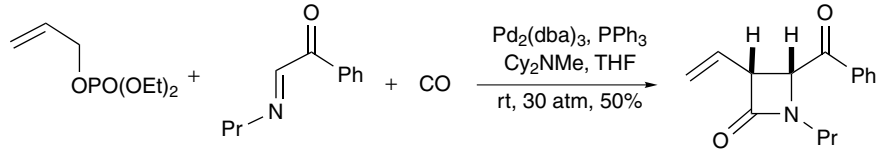


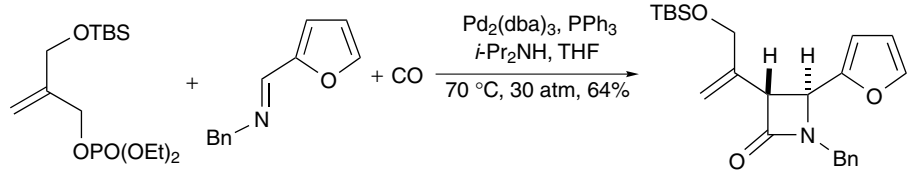
Cyclocarbonylation of 3-phenyl-2-methylallyl acetate **386** afforded 1-naphthyl acetate **388** under harsh conditions (160 °C, 70 atm) in the presence of acetic anhydride and Et_3N. This interesting reaction may be explained by electrophilic attack of the acylpalladium group in the intermediate **387** on the benzene ring. Another possibility is the formation of the ketene **389** and its electrocyclization [151].



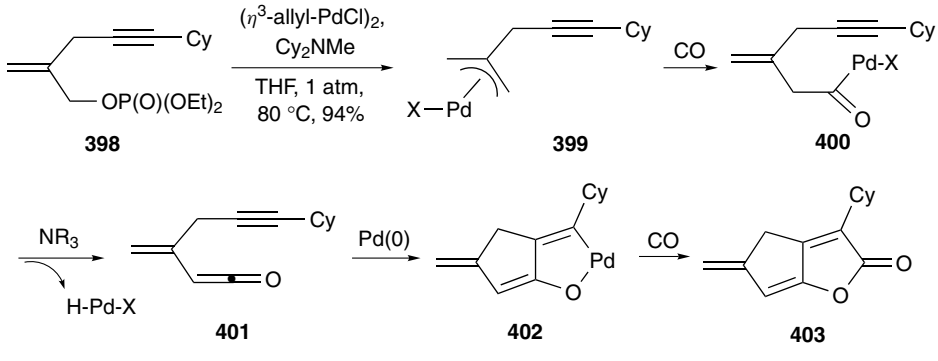
Vinyl ketene (**392**) is generated by the carbonylation of the allyl phosphate **390** in the presence of a base as shown by **391**. A useful application of the ketene formation is the synthesis of β-lactam skeleton by [2 + 2] cycloaddition of the ketene with imines. Thus, reaction of the imine **393**, derived from vicinal dicarbonyl compounds, with the ketene **392** afforded *cis*-lactam **394** [152]. On the other hand, the *trans*-lactam **397** was obtained by the carbonylation of the allyl phosphates **395** in the presence of the imine **396** derived from aldehyde [153].





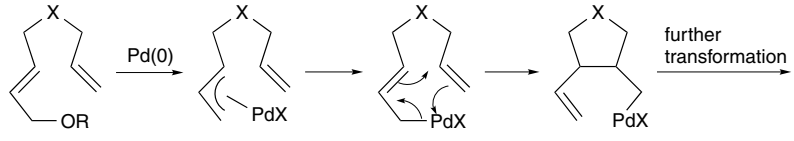


Highly unsaturated lactone **403** was obtained by an intramolecular reaction of 2-(propargyl)allyl phosphate **398** with CO (1 atm) catalyzed by ligandless Pd catalyst in the presence of Cy_2NMe. As an explanation, the acylpalladium **400** is converted to the ketene **401**, and the palladacycle **402** is generated by oxidative cyclization. Insertion of CO to **402** and reductive elimination provide **403** [154].



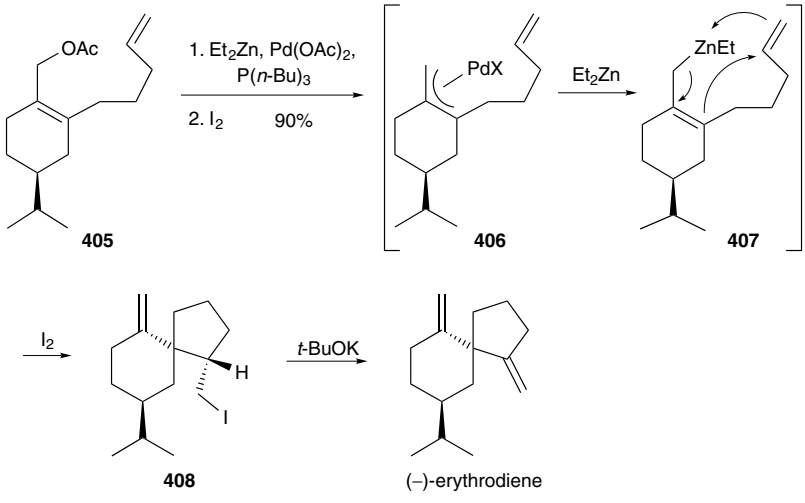
4.5 Intramolecular Reactions with Alkenes and Alkynes

In contrast to a facile intermolecular insertion of alkenes and alkynes to Pd-aryl and Pd-alkenyl bonds as observed in Heck reaction, curiously intermolecular insertion of alkenes and alkynes to Pd-allyl bond in π-allylpalladium is very rare. On the other hand, intramolecular insertion of alkenes and alkynes to π-allylpalladium occurs smoothly to form five- and six-membered rings. Oppolzer and co-workers have developed a useful synthetic method of cyclic compounds by intramolecular insertions of alkenes and alkynes, and they explained the reaction as Pd-ene reaction as shown by **404**. The method has been applied to the syntheses of several natural products and complex cyclic compounds [155,156].



404

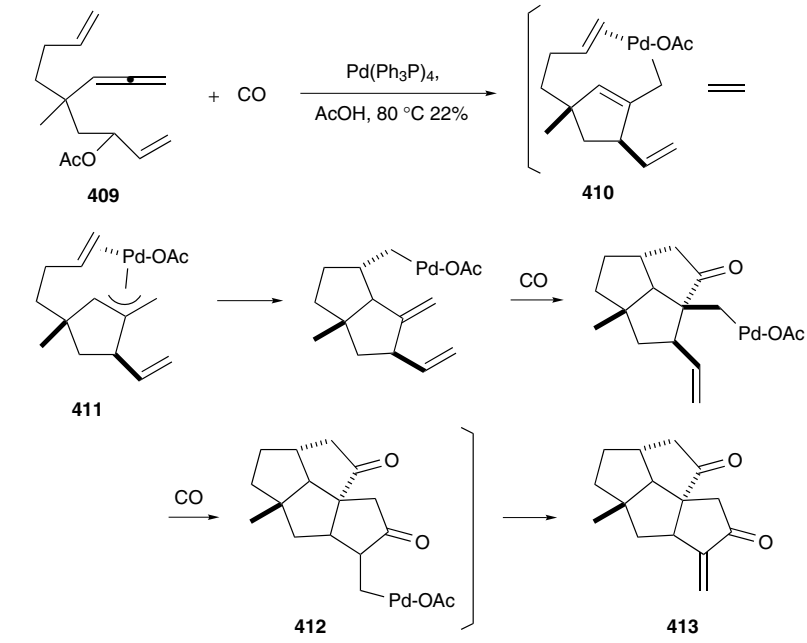
Oppolzer and co-workers achieved highly diastereoselective synthesis of (−)-erythrodiene via Pd-catalyzed Zn-ene reaction as a key step [157]. In the Pd-catalyzed reaction of the allylic acetate **405** using an excess of Et_2Zn, the allylzinc intermediate **407** was generated by transmetallation of π-allylpalladium **406** with Et_2Zn. The Zn-ene reaction as shown by **407**, followed by quenching with iodine, afforded the iodide **408**, which was converted to (−)-erythrodiene. The diastereomeric ratio in the cyclization was 95 : 5 by the directing effect of the resident chiral center C-4. Clean and high-yield cyclization occurred by the use of P(*n*-Bu)$_3$ as a ligand.



405 **406** **407**

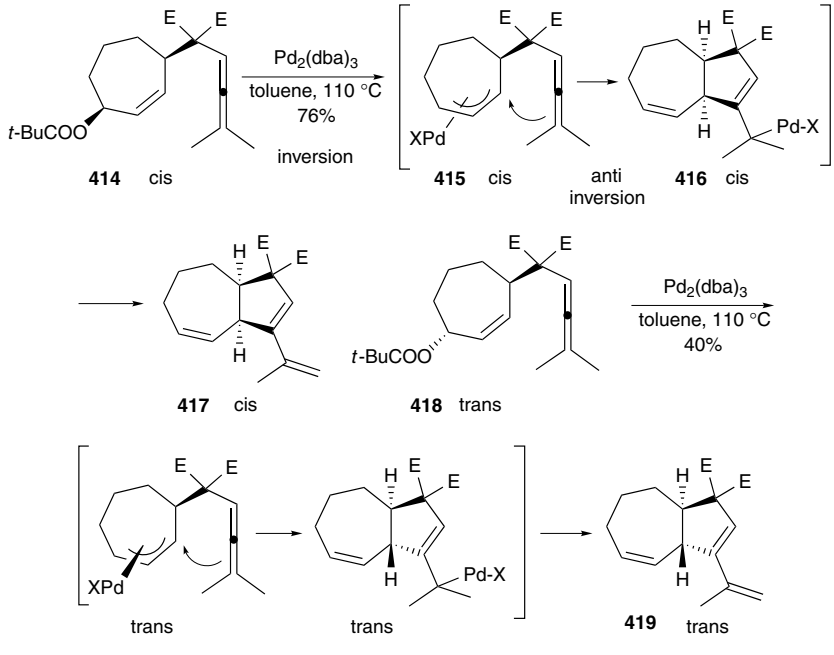
408 (–)-erythrodiene

Efficient domino cyclization of the allyl acetate bearing an allene moiety **409** under CO in AcOH afforded the tetracyclic diketone **413** [158]. The first step is the attack of the π-allyl group at the central carbon of the allene to form **410** (or insertion of one of the allene double bonds), which is a stable π-allylpalladium **411**. Then domino insertion of double bond, CO, double bond, CO, and double



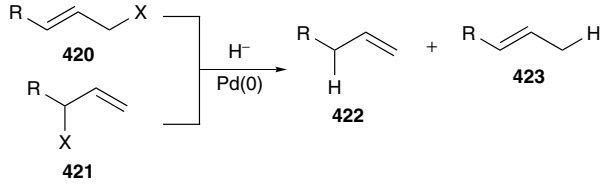
bond occurred to give **412**. Finally **413** was obtained by β-H elimination. The overall yield of six C—C bond formations was 22 %.

Bäckvall and co-workers observed that intramolecular reaction of allyl group with allene in **414** (**415** to **416**) proceeded stereoselectively by an *anti* attack of allene on π-allylpalladium, generated from cyclic *cis*-allylic pivalate **414**. Overall retention occurred in the cyclization to afford **417**. Thus, cyclizations of *cis*-pivalate **414** and *trans*-pivalate **418** afforded *cis* and *trans* products **417** and **419**, respectively [159].



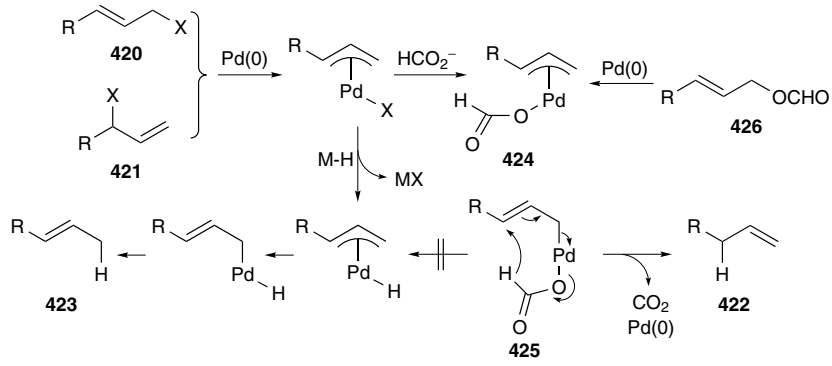
4.6 Hydrogenolysis of Allylic Compounds

Alkenes are obtained by Pd-catalyzed hydrogenolysis of allylic compounds via π-allyl complexes with various hydrides. HCO_2H, R_3SiH, $HSnBu_3$, $LiBHEt_3$, $NaBH_4$, and SmI_2 are used [160]. Hydrogenolysis would be a useful reaction when it is regio- and stereoselective. Hydrogenolysis of terminal allylic compounds **420** and **421** affords either 1- and 2-alkenes **422** and **423** depending on the nature of the hydrides used. Regioselective formation of 1-alkenes from terminal allylic compounds is a useful reaction and most desirable. HCO_2H is particularly important, because 1-alkenes **422** are formed with high regioselectivity by hydrogenolysis only with formate [161]. A mixture, HCO_2H/Et_3N, which is soluble in organic solvents, is used most conveniently. Other hydrides usually give 2-alkenes **423** as major products.

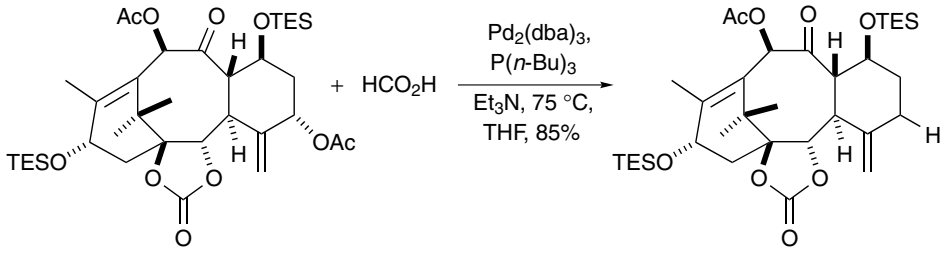


4.6.1 Preparation of 1-Alkenes by Hydrogenolysis with Formates

Various terminal allylic compounds **420** and **421** are converted to 1-alkene **422** by using HCO_2H/Et_3N. When allylic formates **426** are available from allylic alcohols, they are converted to 1-alkenes **422** by the treatment with Pd catalysts. $P(n\text{-}Bu)_3$ is the best ligand to give highest selectivity. Regioselective hydrogenolysis is explained by the formation of π-allylpalladium formate **424** and transfer of hydride to the more substituted side as shown by **425** to give **422**. Hydrogenolysis with other hydrides proceeds by transmetallation to generate π-allylpalladium hydride which undergoes reductive elimination to give **423**. In this case, transfer of hydride occurs to a terminal carbon to form 2-alkene **423**.

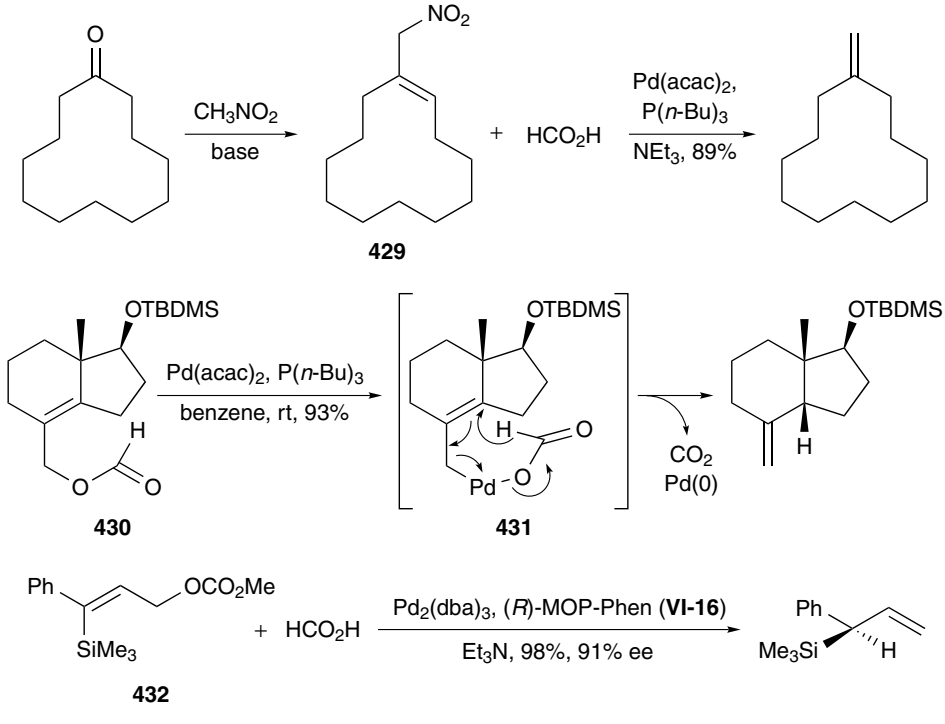


Many applications of 1-alkene formation have been reported. The allylic acetate **427** was converted to *exo* methylene **428** by removal of the acetoxy group [162].



427 **428**

Methylenecyclododecane was prepared by hydrogenolysis of 1-nitromethylcyclododecene (**429**) by formal *anti* thermodynamic isomerization of internal double bond to *exo* position [163]. Treatment of the allylic formate in the hydrindan system **430** with Pd catalyst provided the *exo* methylene regio- and stereoselectively as shown by **431**. In this case, the more stable *cis* ring junction, rather than the more useful *trans* junction, was formed [164]. Optically active allylsilane was obtained in 98 % yield with 91 % ee by enantio- and regioselective hydrogenolysis of the silylated allyl carbonate **432** using (*R*)-MOP-Phen (**VI-16**) as a chiral ligand [165].



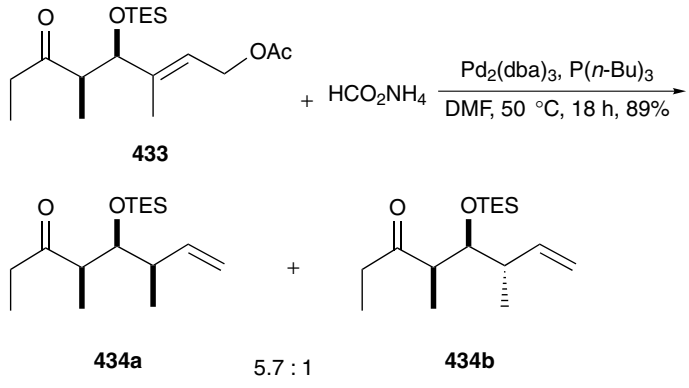
429

430 **431**

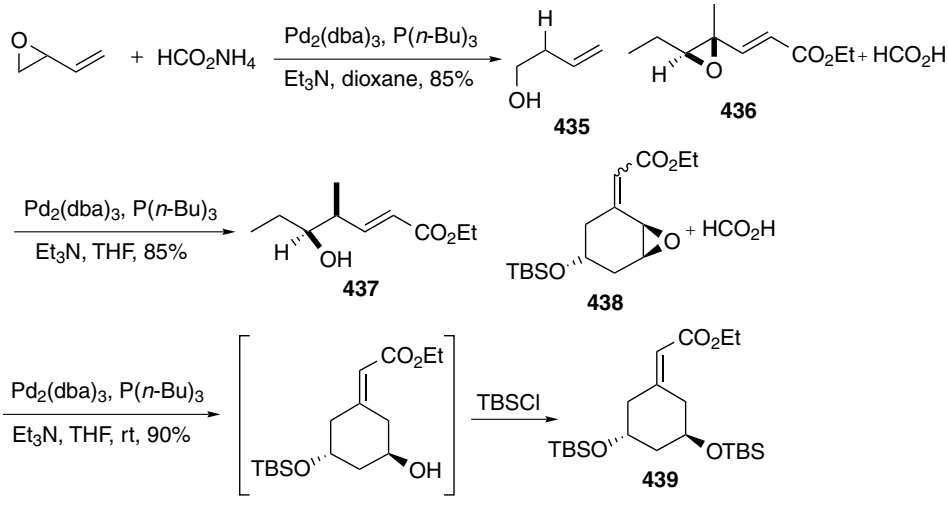
432

Highly regioselective hydrogenolysis of the aldol product **433** proceeded smoothly in DMF to produce the terminal alkenes **434a** and **434b** in high yield

in a ratio of 5.7 : 1. High diastereoselectivity was attained under carefully selected conditions (use of DMF and 1 : 2 ratio of P:Pd) [166].

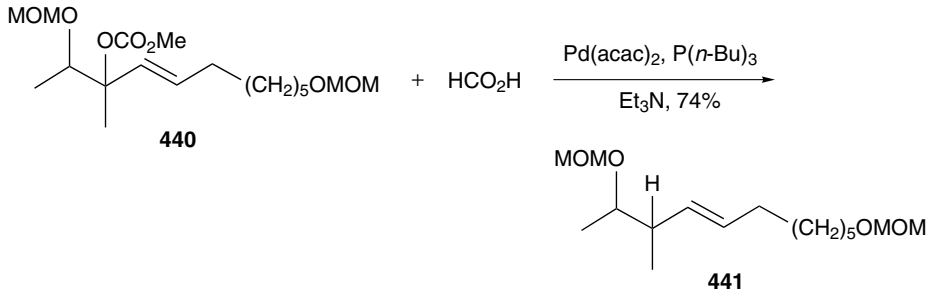


Hydrogenolysis of vinyloxirane is regioselective to give homoallylic alcohol **435**. Hydrogenolysis of the alkenyloxirane **436** is regio- and stereospecific and proceeds by overall inversion of configuration of the allylic C—O bond to afford the homoallylic alcohol **437** [167]. Sato applied the reaction to the synthesis of an A-ring precursor of vitamin D. The protected homoallylic alcohol **439** was obtained at room temperature from the alkenyloxirane **438** in 90 % yield [168].

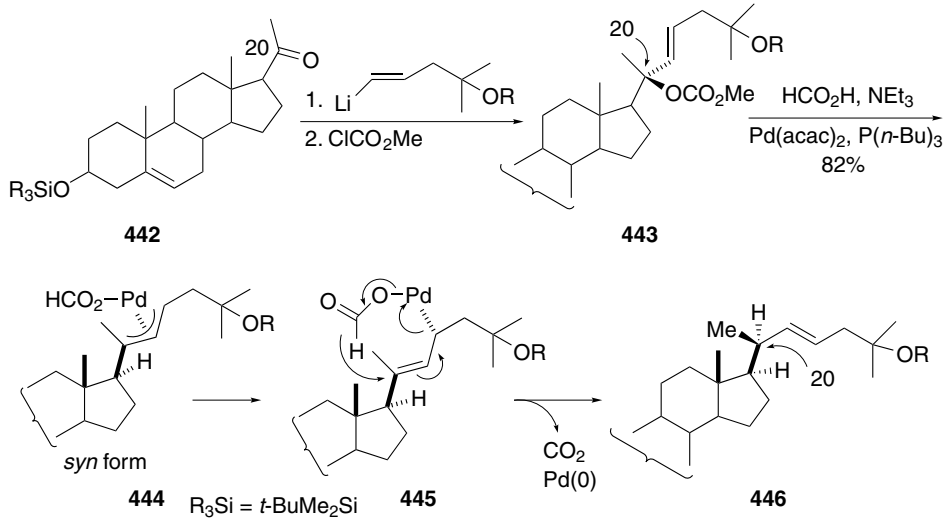


4.6.2 Hydrogenolysis of Internal and Cyclic Allylic Compounds

Regioselectivity in hydrogenolysis of internal allylic systems depends on the bulkiness of substituents. The alkene **441** was obtained regioselectively from *tert*-carbonate **440**. The hydride attacked the congested *tert*-carbon, but not *sec*-carbon [169].

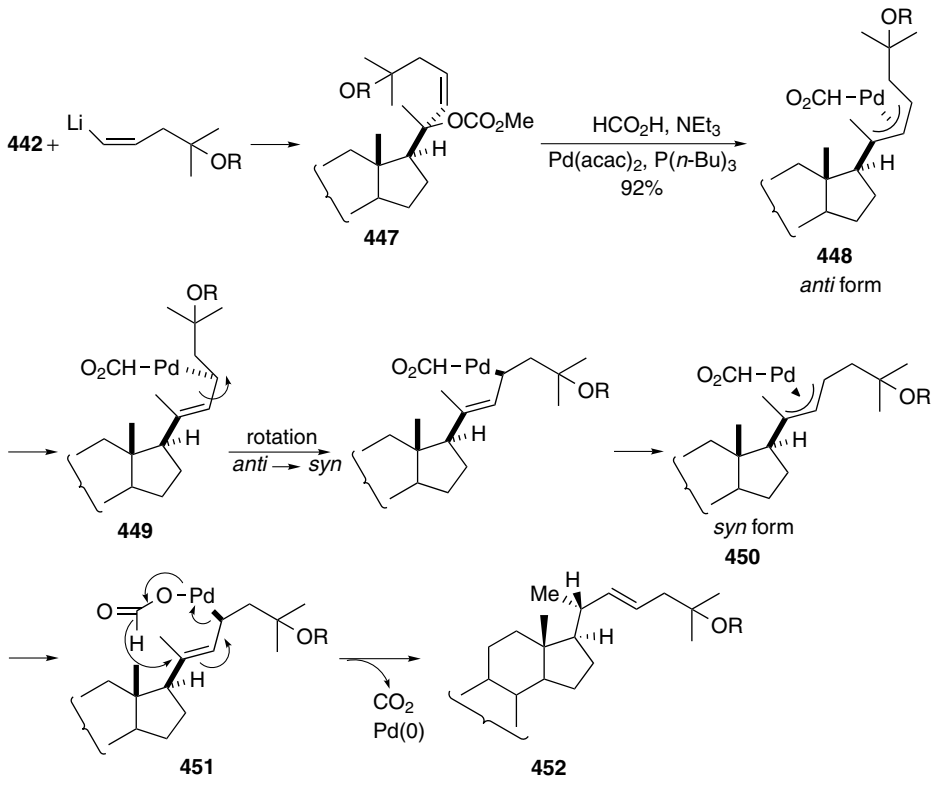


π-Allylpalladium formation proceeds with inversion and hydride transfer from palladium formate proceeds with retention of configuration, and hence stereoselective hydrogenolysis with overall inversion should be possible in rigid systems. Stereocontrolled synthesis of natural and unnatural configurations at C-20 in steroid side chains has been achieved based on the regio- and stereoselective hydrogenolysis of C-20 carbonate [170]. The (*E*)-β-carbonate **443** was prepared by the reaction of the C-20 keto steroid **442** with (*E*)-vinyllithium, and converted to α-oriented π-allylpalladium **444** with inversion, which has a stable *syn* structure. Concerted decarboxylation-hydride transfer as shown by **445** occurred with retention from the α-side to give the unnatural configuration **446**.

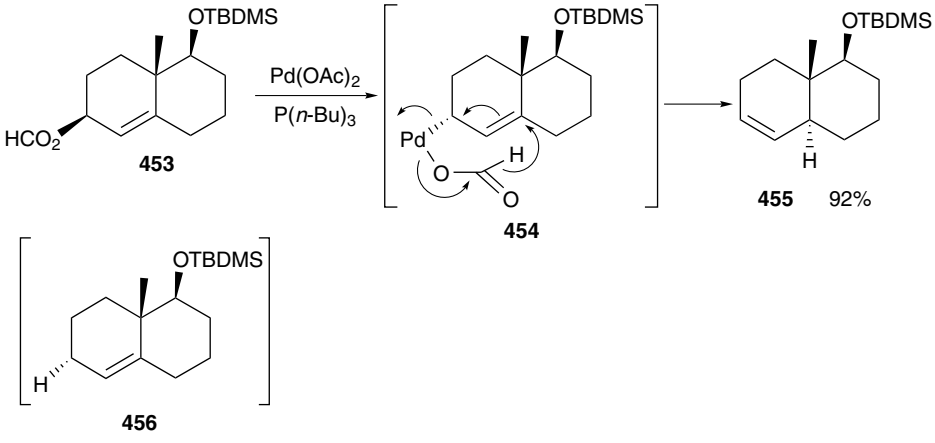


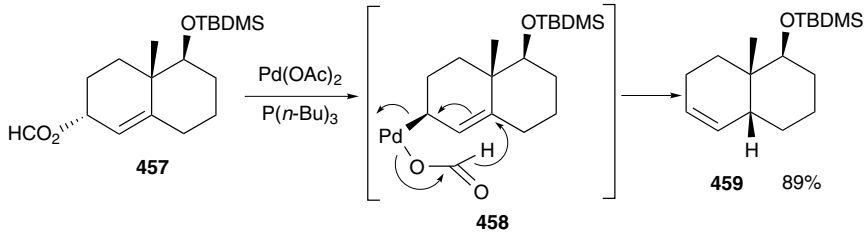
On the other hand, the α-oriented π-allylpalladium **448**, formed from the (*Z*)-β-carbonate **447**, has an unstable *anti* structure, which rotates to form the more stable *syn* structure **450** before decarboxylation. By this rotation, Pd moves from the α-side to β-side as shown by **449**, and hydride transfer occurs from β side as shown by **451**, and the natural configuration **452** was constructed.

Regio- and stereoselective hydrogenolysis of allylic formates in rigid cyclic systems offers a useful method for stereoselective construction of ring junctions. As

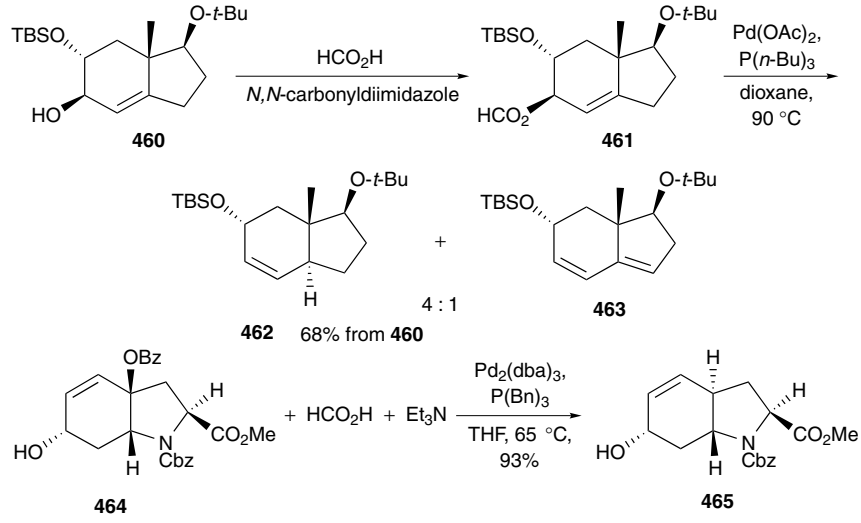


one example, the β-oriented allylic formate **453** was converted to the *trans*-decalin **455**. The hydride attack occurred from the α-side as shown by **454**. In addition, the hydride attacked the congested angular carbon regioselectively without forming the regioisomer **456**. The *cis* junction in **459** was constructed from the α-oriented allylic formate **457** by the hydride attack from the β-side as expressed by **458**. The reaction has been successfully applied to the construction of either AB *cis* or *trans* junction in steroid molecules [171].





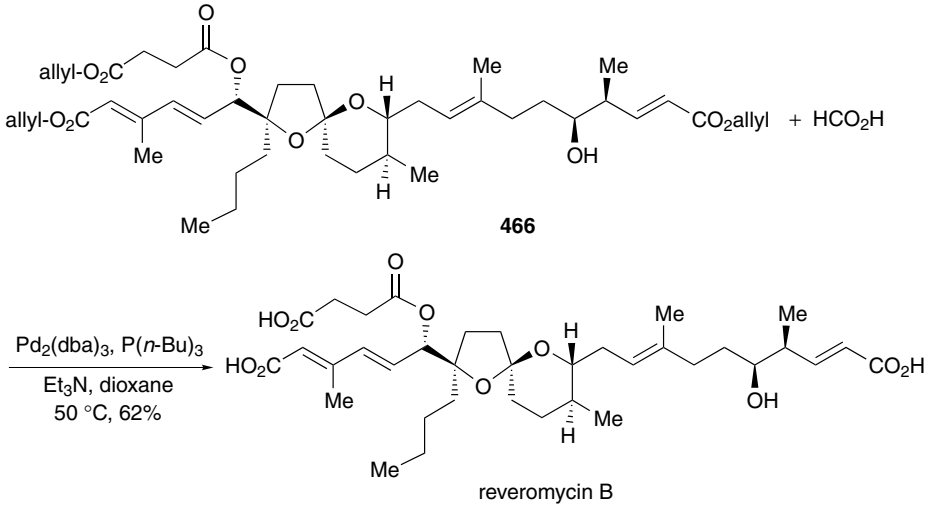
The method was applied to a hydrindane system. The *trans* ring junction **462** was constructed by stereoselective hydrogenolysis of the β-oriented allylic formate **461**, derived from **460**. No attack by Pd-catalyst to the allyl silyl ether group in **462** occurred. Elimination to provide the 1,3-diene **463** is a side reaction [172]. In the total synthesis of (−)-tuberostemonine, regio-, stereo- and chemoselective hydrogenolysis of **464** to provide **465** was utilized. Only β-oriented angular allylic benzoate was hydrogenolyzed to give the *trans* junction with overall inversion. No reaction occurred in the allylic alcohol moiety. In this case, tribenzylphosphine [$P(Bn)_3$] was used as a ligand [173].



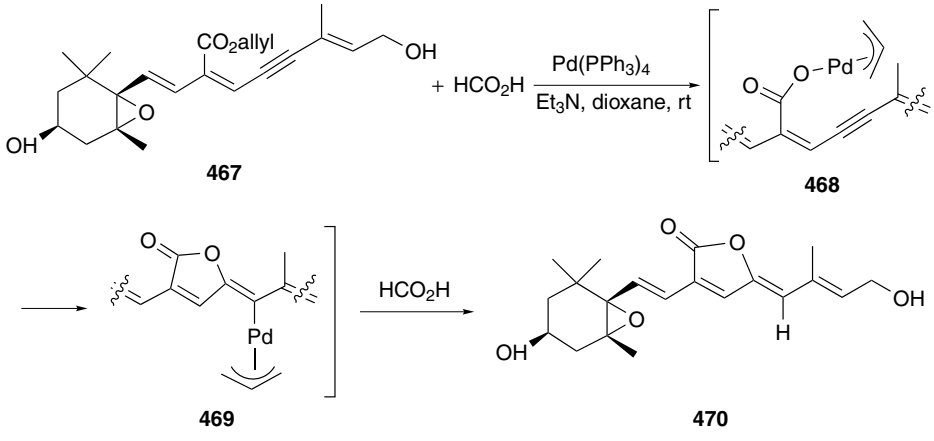
4.7 Allyl Group as a Protecting Group

The allyl group is a good protecting group, because facile deprotection based on the formation of π-allylpalladium intermediates is possible. Carboxylic acids are protected as allyl esters, and alcohols and amines are also protected as allyl carbonates and carbamates, respectively. Deprotection can be carried out in two ways. One method is the Pd-catalyzed hydrogenolysis with hydride sources. HCO_2H/Et_3N is the most suitable reagent for hydrogenolysis, which takes place at room temperature under neutral conditions, and the byproducts are propene and CO_2 [161]. Also $HSnBu_3$ and $HSiR_3$ are used as hydrides. The second method is allyl transfer to other nucleophiles such as amines, carboxylic acids, and active methylene compounds.

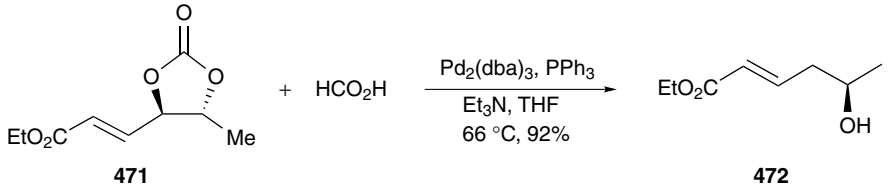
Carboxylic acids are protected as allyl esters. In the final step of the total synthesis of reveromycin B, three allyl ester groups in **466** were removed cleanly with HCO_2H/Et_3N to give reveromycin B in 62 % yield [174].



Deprotection of allyl ester in **467** with HCO_2H/Et_3N was highly chemoselective. In the coexistence of a 2,4-enyne system in **467**, at first π-allylpalladium carboxylate **468**, formed from the allyl ester, attacked the triple bond to form the butenolide **469** without reacting with formate. Hydrogenolysis with formate took place only at the final step to afford **470** chemoselectively. Also, the alkenyloxirane group, which is allylic epoxide, stayed intact [175].

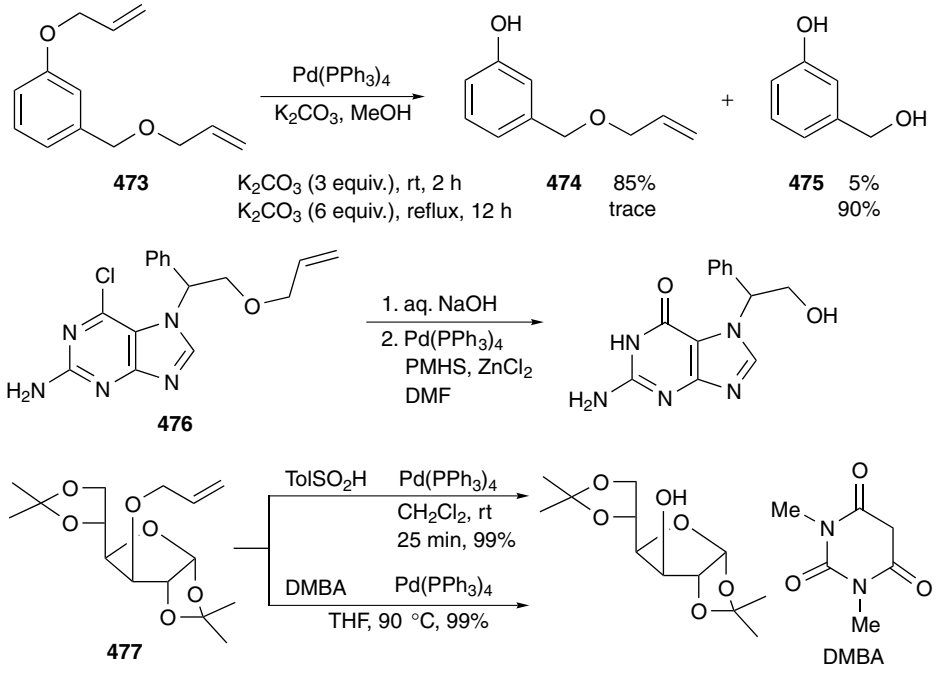


Alkyl allyl ethers are difficult to cleave. Therefore alcohols are protected as allyl carbonate. Deprotection of the cyclic carbonate **471** with HCO_2H/Et_3N proceeded regioselectively at room temperature to afford the δ-hydroxy ester **472**. The electronic effect is crucial in this case and hydride attacked an electron deficient carbon [176].

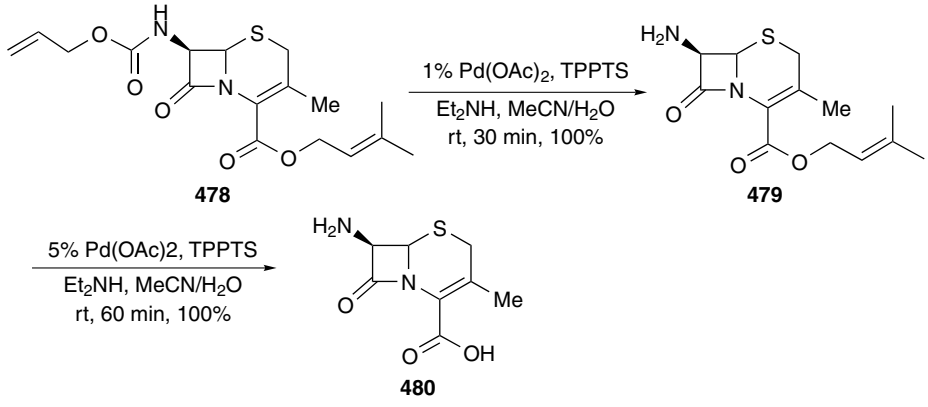


471 **472**

Phenols are protected as allyl aryl ethers, which can be cleaved smoothly. Deprotection of the allyl aryl ether in **473** to give **474** occurred at room temperature in MeOH in the presence of K_2CO_3 using $Pd(PPh_3)_4$. Allyl benzyl ether was deprotected in refluxing MeOH to provide **475** [177]. The alkyl allyl ether in **476** was cleaved with PMHS in the presence of $ZnCl_2$ as an activator in DMF [178]. Benzenesulfinic acid or Na salt is a good scavenger, and it is claimed that better results are obtained with sulfinic acid even when deprotection of protected acids, amines, and alcohols by other scavengers is not satisfactory. The alkyl allyl ether **477** was deprotected smoothly with toluenesulfinic acid at room temperature [179]. Deprotection of **477** is also possible under neutral conditions by using *N*,*N*-dimethylbarbituric acid (DMBA) as the scavenger [180].

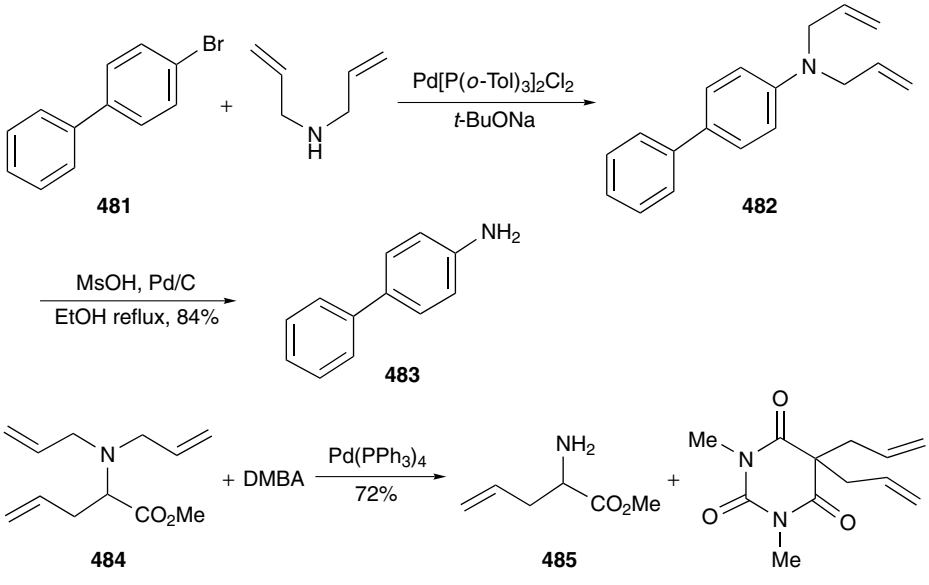


Various water-insoluble substrates are deprotected smoothly in water using water-soluble ligand (TPPTS, **II-1**) in the presence of cyclodextrin [181]. Deprotection of allyl carbonates and carbamates can be carried out in $MeCN/H_2O$ using TPPTS as a ligand and Et_2NH as the scavenger [182]. Chemoselective removal of allyl carbamate in a base-sensitive cephalosporin **478** was achieved with 1 % Pd(0)/TPPTS at room temperature to afford **479**, and then the prenyl carboxylate

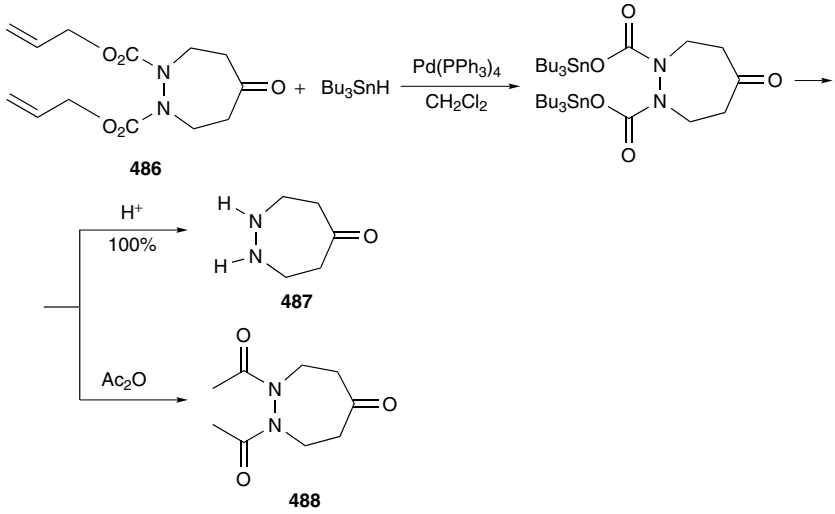


was quantitatively removed using 5 % catalyst to provide **480** [183]. Chemoselective removal of allyl and prenyl groups in aq. MeCN was applied to the synthesis of peptides in solution [184].

Amines are protected as carbamates, which are easily deprotected. Diallylamine can be used as an ammonia equivalent if it is cleaved easily. However, allylamines are difficult to cleave under normal conditions. As an ammonia equivalent, the diallyl groups in **482** were removed in EtOH using Pd/C as a catalyst in the presence of methanesulfonic acid (1 equiv.). Probably diallylamine is activated for Pd-catalyzed cleavage by ammonium salt formation. 4-Aminobiphenyl (**483**) can be prepared by Pd-catalyzed amination of 4-bromobiphenyl (**481**) with diallylamine to give **482**, followed by deprotection [185]. Also allylamines are deprotected with *N*,*N*-dimethylbarbiturate (DMBA) as the scavenger [186]. N-protection in methyl *N*,*N*,α-triallylglycinate **484** was removed to form the primary amine **485** using DMBA as the scavenger of allyl groups [187].

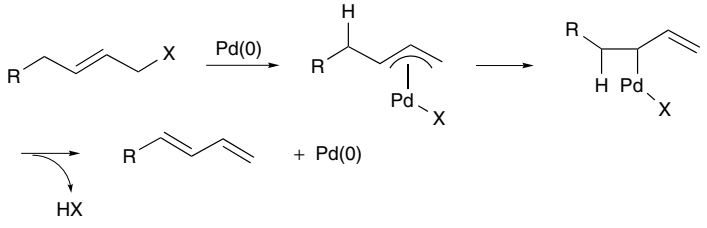


Pd-catalyzed reaction of the diallyl dicarbamate of hydrazine **486** with Bu_3SnH in the absence of a proton source, produced the tin carbamate, which was converted to free hydrazine **487** by protonation, and to the amide **488** by treatment with acetic anhydride. Transprotection from allyl carbamate **486** to the amide **488** was carried out in this way [188].

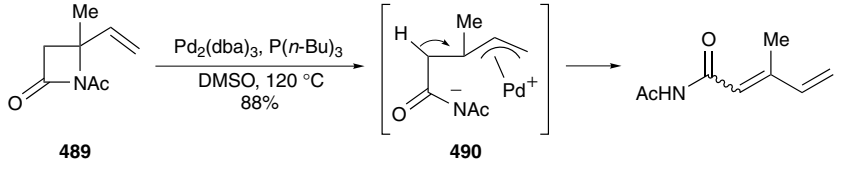


4.8 1,4-Elimination

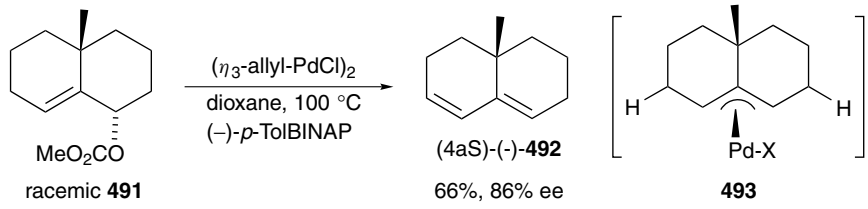
By the treatment of allylic compounds with Pd(0) catalyst in the absence of nucleophiles, conjugated dienes are formed by 1,4-elimination (dehydropalladation). The elimination provides mainly (*E*)-dienes, but not completely selectively. P(*n*-Bu)$_3$ is an effective ligand [189].



π-Allyl complexes are formed from 4-vinylazetidines or 4-vinyl-2-azetidinones when the amino or amide group is protected with an electron-withdrawing group. *N*-acetyl-4-vinyl-2-azetidinone **489** was converted to 2,4-pentadienamide as a 1 : 1 mixture of *E* and *Z* isomers by 1,4-elimination from π-allylpalladium intermediate **490**. No reaction took place with the *N*-benzyl derivative [89].

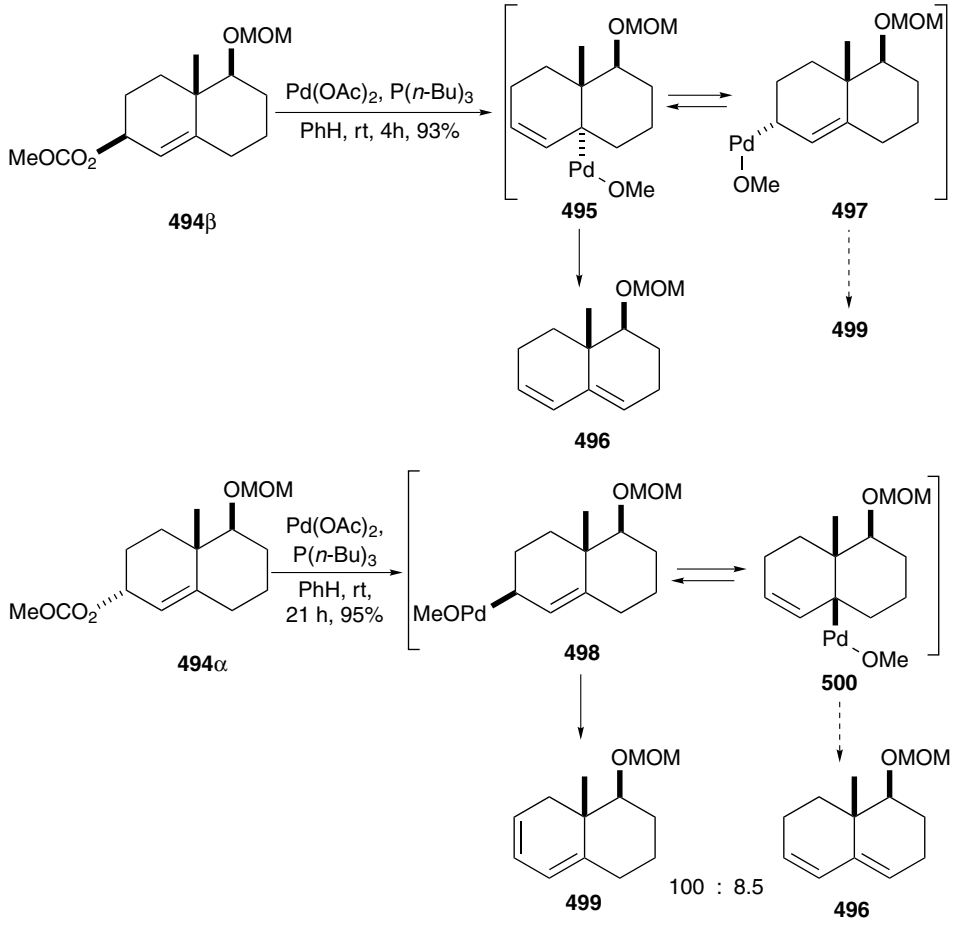


1,4-Elimination in some cyclic systems proceeds regio- and stereoselectively. The Pd-catalyzed reaction of the racemic carbonate **491** afforded the diene **492** with 86 % ee via desymmetrization of the π-allylpalladium intermediate **493** when (−)-TolBINAP was used as a ligand [190].



racemic **491** (4aS)-(-)-**492** 66%, 86% ee **493**

Hetero- or homoannular conjugated dienes are prepared in hydronaphthalene derivatives by the Pd-catalyzed regioselective elimination of allylic carbonates under mild conditions. The heteroannular conjugated diene **496** was obtained selectively by the Pd-catalyzed regioselective elimination of the β-oriented allylic carbonate **494** under mild conditions via the stable intermediate **495**. The homoan-

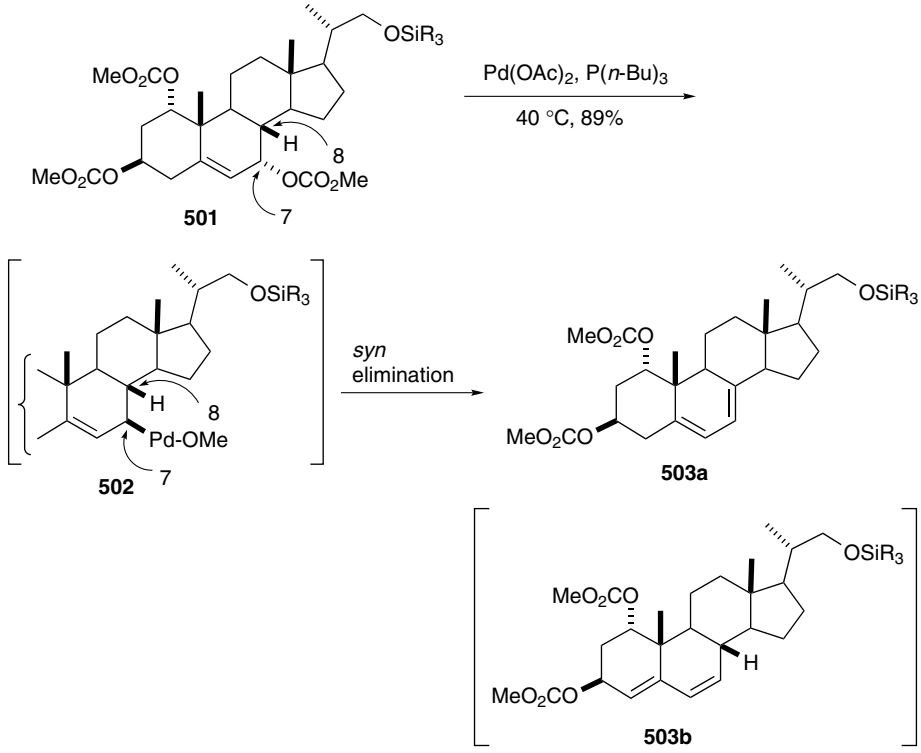


494β **495** **497** **499** **496**

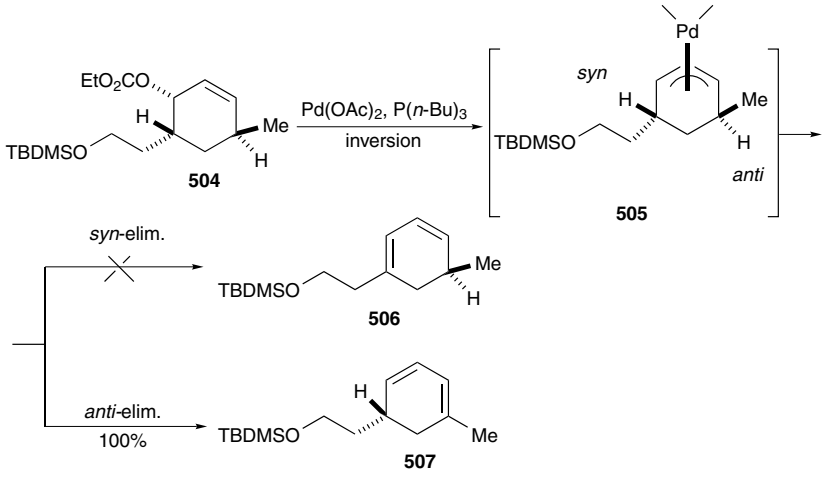
494α **498** **500** **499** **496**

nular diene **499** via **497** was not formed because the rate of elimination from the angularly *trans* tertiary complex **495** is faster than that from the secondary one **497**. On the other hand, the homoannular diene **499** was introduced as the main path by elimination of the α-oriented allylic carbonate **494α**. In this case, formation of the angularly *cis* complex **500** is unfavorable due to repulsion, and elimination occurred from the intermediate **498** [191].

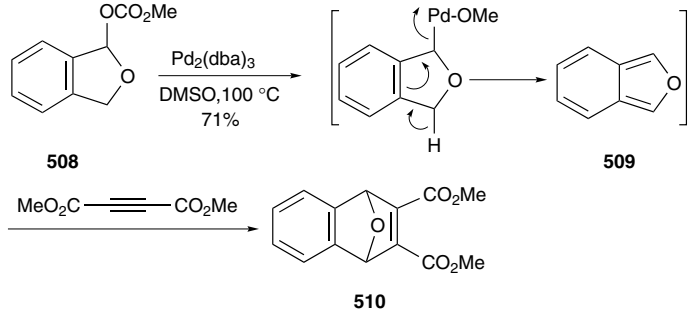
Usually preparation of homoannular conjugate dienes is not easy. The Pd-catalyzed method of selective formation of homoannular dienes was applied to introduction of a homoannular diene system in provitamin D. Treatment of the 7α-carbonate **501** with the Pd catalyst at 40 °C afforded the desired homoannular 5,7-diene **503a** regioselectively in 89 % yield. No heteroannular diene **503b** was detected. In the intermediate complex **502**, the 7σ-allylpalladium is β-oriented and suitable for facile *syn* elimination of 8β-H to afford the 5,7-diene **503a** exclusively [191]. The eliminations proceed smoothly with high selectivity when P(n-Bu)$_3$ is used as a ligand.



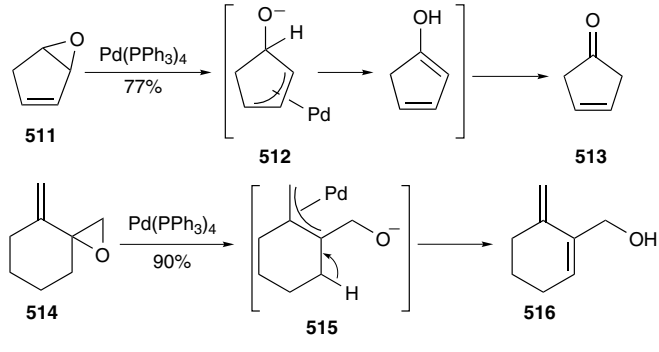
It seems likely that β-H elimination occurs *syn* to Pd. However, Takacs *et al*. have made an interesting observation. When the cyclohexenyl carbonate **504**, which has both *syn* and *anti* hydrogens, was subjected to the elimination, the cyclohexadiene **507** was obtained as a sole product, which should be formed by elimination of H *anti* to Pd in **505**. The diene by *syn* elimination to give **506** was not formed [192].



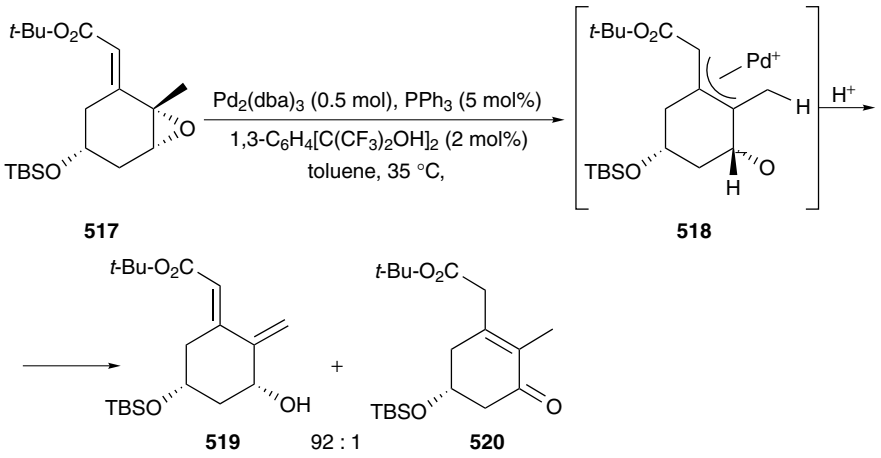
Mikami and Ohmura reported that isobenzofuran (**509**) can be generated by the treatment of the benzylic lactol methyl carbonate **508** with phosphine-free Pd catalyst via 1,4-elimination of π-benzylpalladium at 100 °C under neutral conditions. The isobenzofuran **509** was trapped as a cycloadduct **510** *in situ* with dimethyl acetylenedicarboxylate [193].



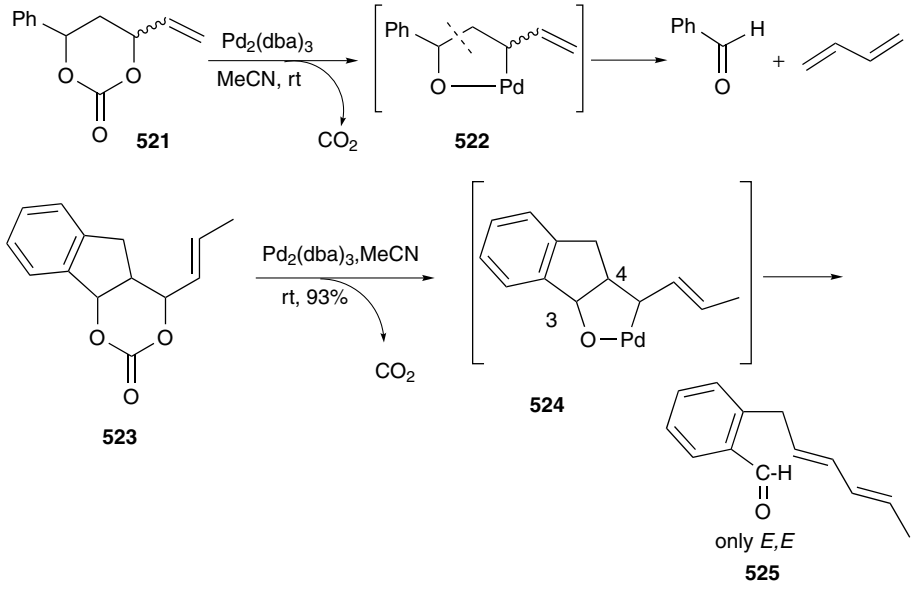
Pd-catalyzed reaction of alkenyloxiranes provides two elimination products, the unsaturated ketones or the dienyl alcohols by elimination of different hydrogens. From cyclopentadiene monoxide (**511**), the unsaturated ketone **513** was obtained as explained by **512**. On the other hand, the dienyl alcohol **516** was obtained from the alkenyloxirane **514** via **515** [194].



A useful building block **519** for vitamin D synthesis was prepared by reaction of the alkenyloxirane **517** [195]. Under usual conditions of the elimination, both the dienyl alcohol **519** and the unsaturated ketone **520** were formed in equal amounts. Radinov and co-workers discovered an interesting and remarkable effect of the addition of fluorinated alcohols, such as 1,3-bis-(1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)benzene or perfluoro-*t*-butyl alcohol as a proton source, on the chemoselectivity, and the desired **519** was obtained with nearly complete chemoselectivity with these additives [195]. They suggest that rapid protonation of the intermediate alkoxide **518** with these alcohols seems to be important.

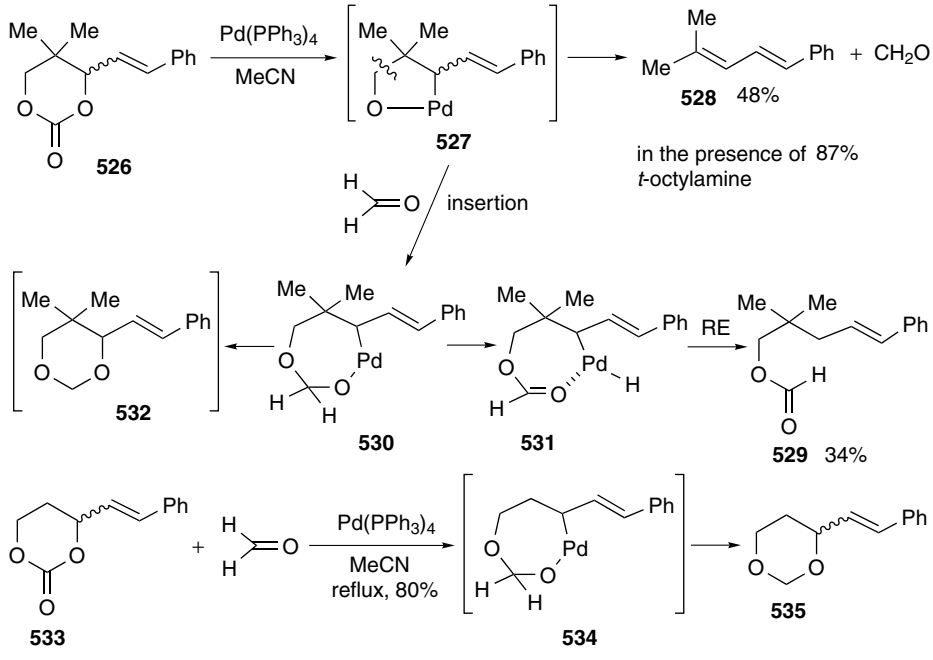


Tamaru and co-workers reported that benzaldehyde and butadiene are formed from 6-phenyl-4-vinyl-1,3-dioxacyclohexan-2-one (**521**) at room temperature using ligandless Pd catalyst. Facile C—C bond cleavage (β-carbon elimination or β-decarbopalladation) in the intermediate palladacycle **522** occurs. As an extension,

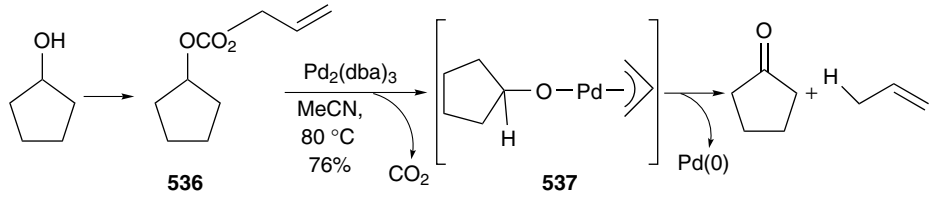


they found that a variety of dienals and dienones are formed by Pd-catalyzed ring opening of mono-, di-, and tricyclic 4-vinyl-1,3-dioxacyclohexan-2-ones involving facile β-decarbopalladation. The carbonate **523** was converted to the dienyl aldehyde **525** in high yield, involving cleavage between the C-3 and C-4 bond in **524** [196].

Different products are obtained depending on substituents. Reaction of **526**, which has no substituent at C-6, afforded the diene **528** (48 %) and the formate **529** (34 %). In this reaction, formaldehyde is generated and inserts to the intermediate **527** to form **530**. The formate **529** was obtained from **530** by β-H elimination to generate **531** and reductive elimination. The diene **528** was obtained in 87 % yield in the presence of *t*-octylamine as a scavenger of formaldehyde. Also the 1,3-dioxane **532** is formed in the presence of formaldehyde. Thus the reaction of the carbonate **533** with formaldehyde afforded the 1,3-dioxane **535** via **534** in high yield [197].



As a related elimination, allyl alkyl carbonates of primary, secondary, allylic, and benzyl alcohols are converted to ketones and aldehydes in MeCN via facile β-H elimination of π-allylpalladium alkoxide **537**, formed from allyl alkyl carbonate **536** [198]. The reaction offers a good method of oxidation of alcohols under neutral conditions without using inorganic oxidants.

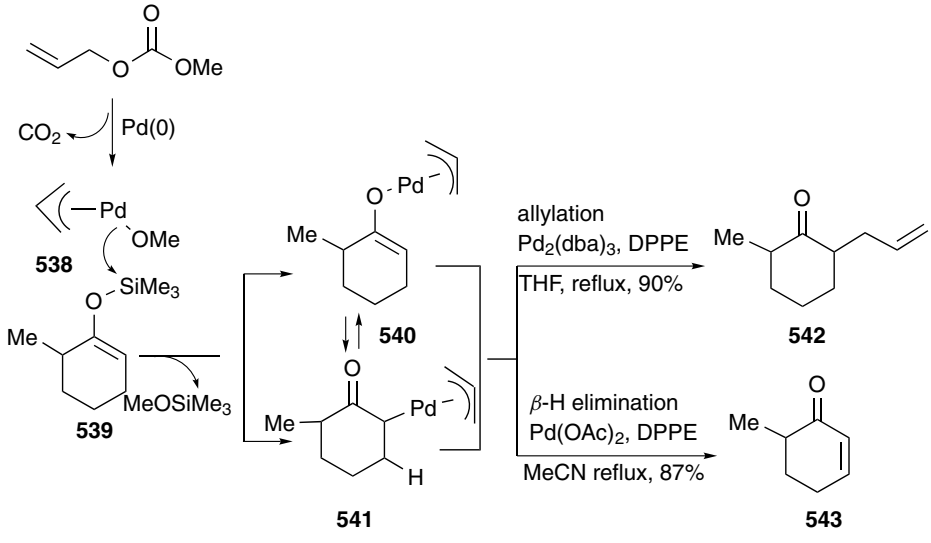


4.9 Reactions via π-Allylpalladium Enolates

Allylation of ketone enolates is treated in Chapter 4.2.3. The chemistry of π-allylpalladium enolates, which is related, but more versatile than that of simple ketone enolates, is treated in this section. π-Allylpalladium enolates are generated in two ways. One is the transmetallation of silyl and tin enolates with π-allylpalladium alkoxide formed from allyl carbonates. The other is Pd-catalyzed reaction of allyl β-keto esters [199].

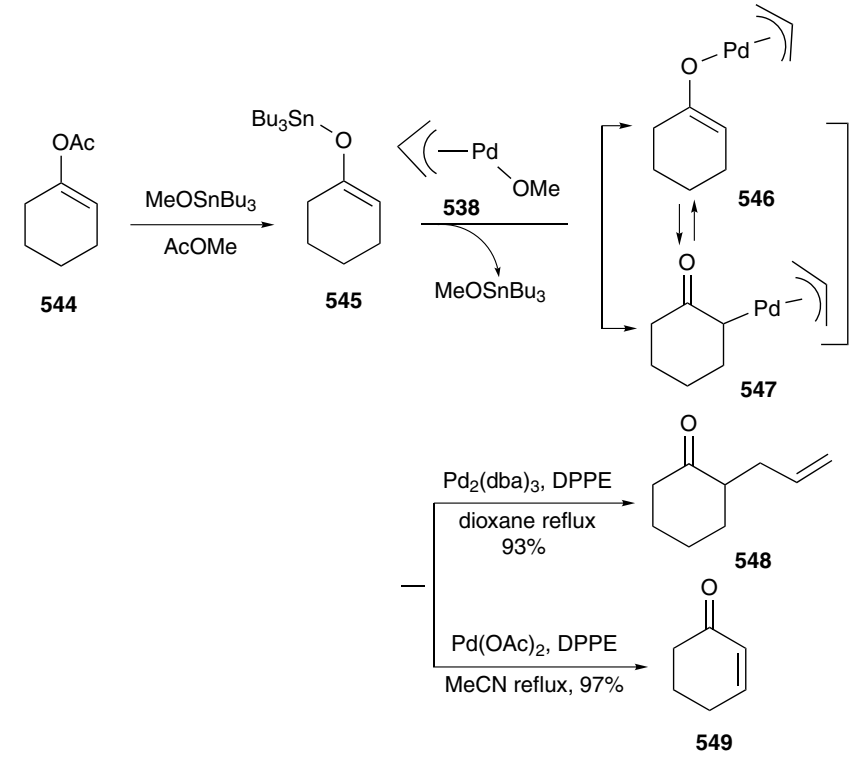
4.9.1 Generation of π-Allylpalladium Enolates from Silyl and Tin Enolates

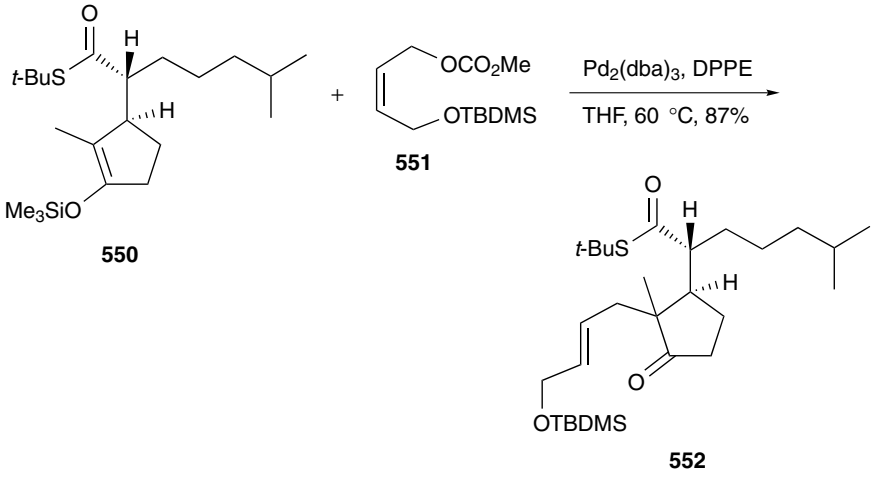
Formation of π-allylpalladium enolates by the reaction of the silyl enolate **539** with allyl carbonate is summarized as follows. The enolate of cyclohexanone is treated as a model compound here. Transmetallation of π-allylpalladium methoxide **538** with the silyl enolate **539** generates either Pd enolates **540** or α-palladaketone **541**. Reductive elimination affords allylcyclohexanone **542** in THF [200]. At higher temperature, cyclohexanone **543** is obtained by β-H elimination using ligandless Pd catalyst in MeCN [201].



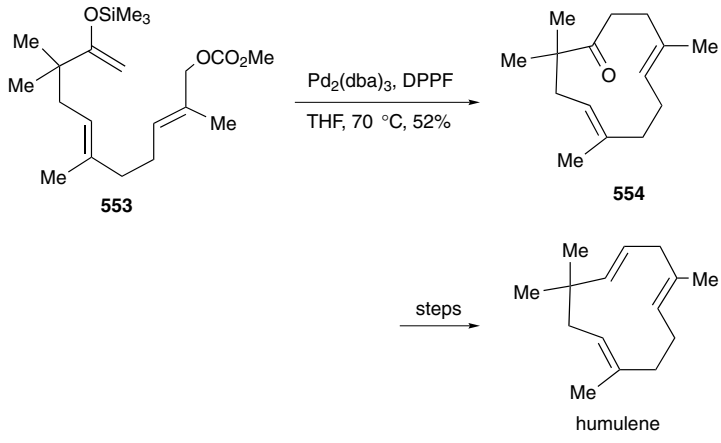
Tin enolate **545** is generated by the reaction of enol acetate with $MeOSnBu_3$. Transmetallation with **538** provides π-allylpalladium intermediates **546** and **547**, and at the same time regenerates $MeOSnBu_3$. Thus, $MeOSnBu_3$ works as a co-catalyst. Then the allyl ketone **548** and the enone **549** are obtained under slightly different conditions.

Applications of these reactions have been reported. Wicha and co-workers prepared the allylated ketone **552** in 87 % yield as a synthetic intermediate of vitamin D by the reaction of the silyl enol ether **550** with the *cis*-allyl carbonate **551** [202].

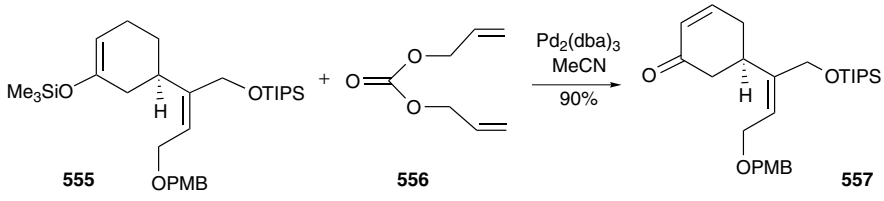




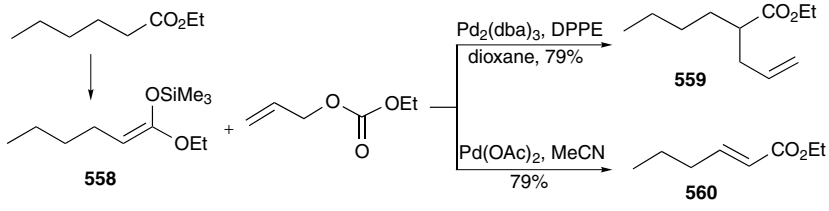
The intramolecular version of the allylation has been carried out by Corey. The 11-membered cyclic ketone **554** was obtained from the silyl enol ether **553** in 52 % yield, and short syntheses of humulene and δ-araneosene have been achieved utilizing the reaction as a key step [203].



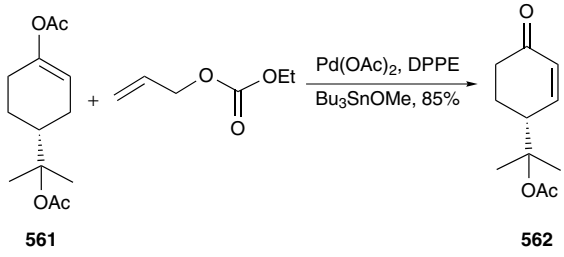
β-H elimination occurs by the treatment of π-allylpalladium enolates in boiling MeCN to give α,β-unsaturated ketones and aldehydes. Shibasaki and co-workers used the enone formation in the total synthesis of strychnine [204]. The silyl enol ether **555** was treated with diallyl carbonate **556** in MeCN and the cyclohexanone **557** was obtained in high yield.



Esters can be converted to either α-allyl ester **559** or α,β-unsaturated esters **560** by the Pd-catalyzed reaction of ketene silyl acetals such as **558** with allyl carbonate under slightly different conditions [205].

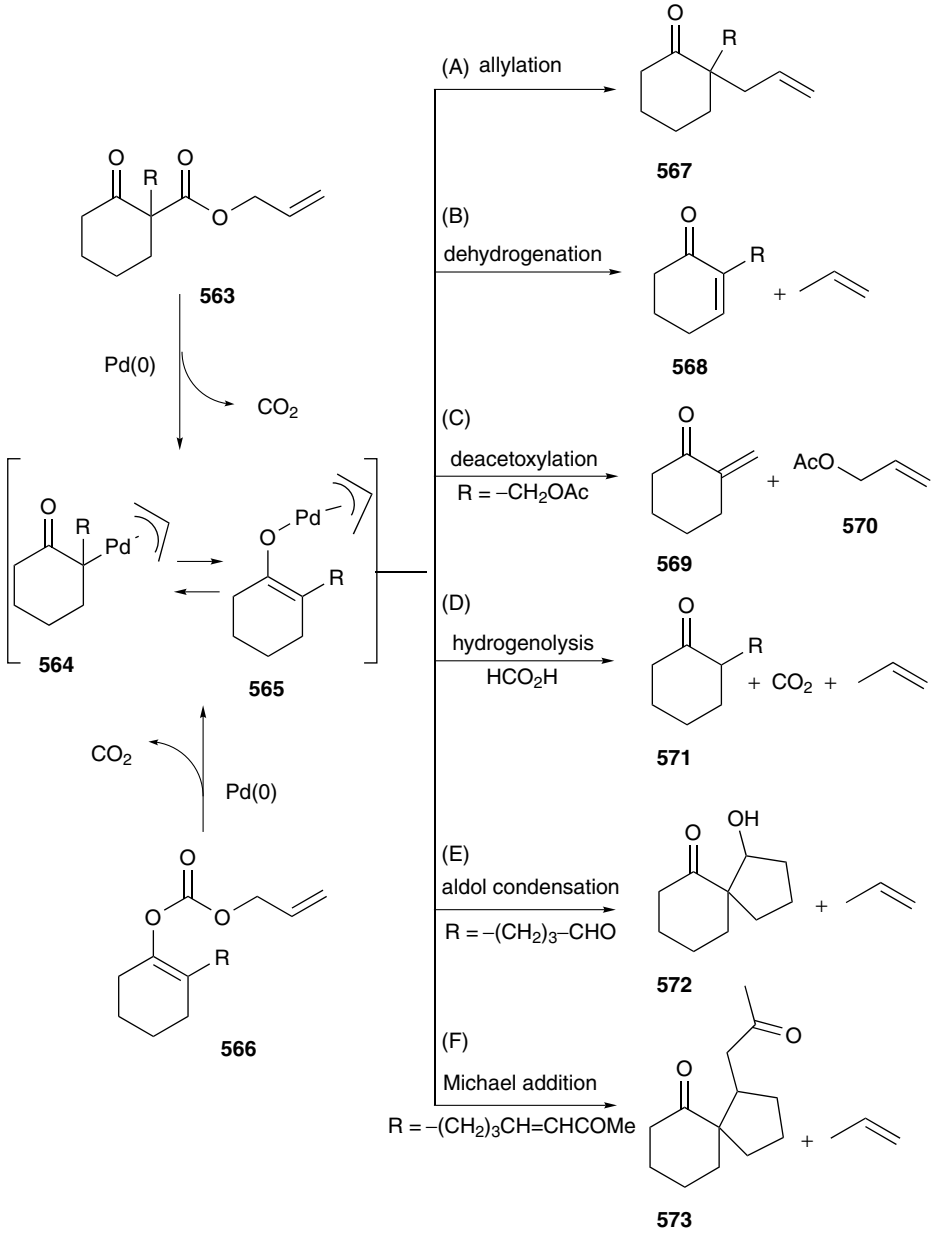


The cyclohexenyl acetate **561** was converted to the cyclohexanone **562** by the reaction of allyl carbonate using $Pd(OAc)_2$ and Bu_3SnOMe as a bimetallic catalyst [206].



4.9.2 Reactions of Allyl β-Keto Carboxylates and Related Compounds

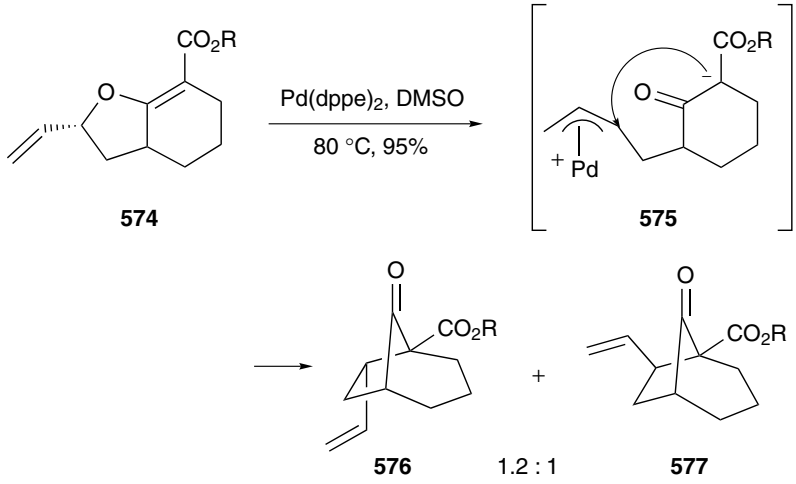
Allyl β-keto carboxylates **563** undergo facile Pd-catalyzed decarboxylation to form either π-allylpalladium enolates **565** or α-palladaketone **564**. Also π-allylpalladium enolates are generated from enol carbonates **566**. As summarized below, several transformations to afford **567**–**573** are possible under different but proper conditions depending on the substituents R [199]. In addition to allyl β-keto carboxylates, other allyl esters such as allyl malonates, cyanoacetates and nitroacetates undergo similar transformations. With these Pd-catalyzed reactions, a new generation of β-keto esters and malonate chemistry has been developed.



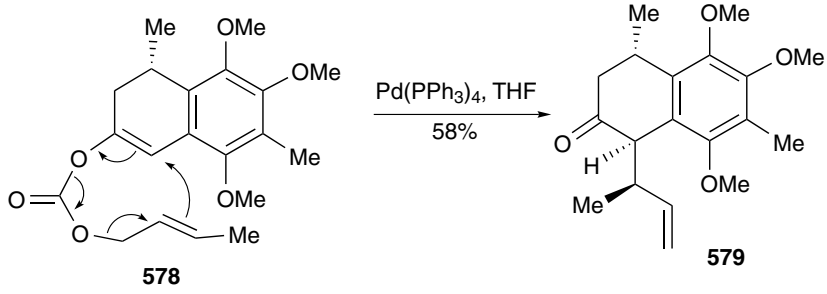
Each reaction is explained briefly by citing synthetic applications.

4.9.2.1 Decarboxylation–Allylation (A)

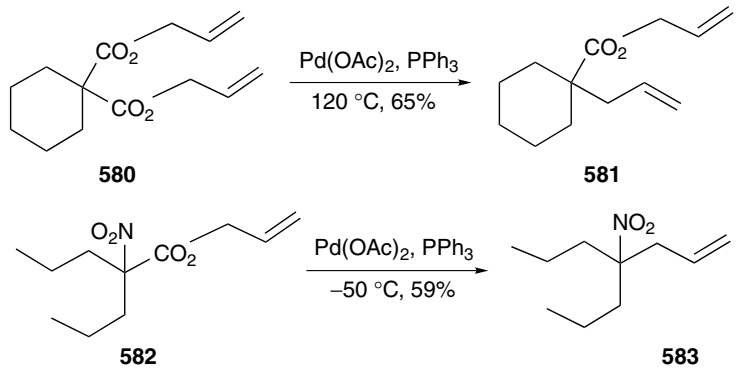
Formation of allylketones **567** from allyl β-keto esters **563** and allyl enol carbonates **566** is the Pd-catalyzed Carroll rearrangement. As a related reaction, Pd-catalyzed regioselective intramolecular allylation of the allyl enol ether of β-keto ester **574** occurred as shown by **575** in DMSO, and afforded a mixture of the *endo*- and *exo*-bicyclo[3.2.1]octane frameworks **576** and **577** using DPPE as a ligand. PPh_3 is not suitable [207].



In order to achieve regio- and stereoselective α-allylation of a cyclohexanone derivative, Paquette and Nicolaou carried out the Pd-catalyzed decarboxylation-allylation of the allyl enol carbonate **578** at room temperature to give the allyl ketone **579** in 58 % yield and a regioisomer (24 %) using PPh_3 [208].

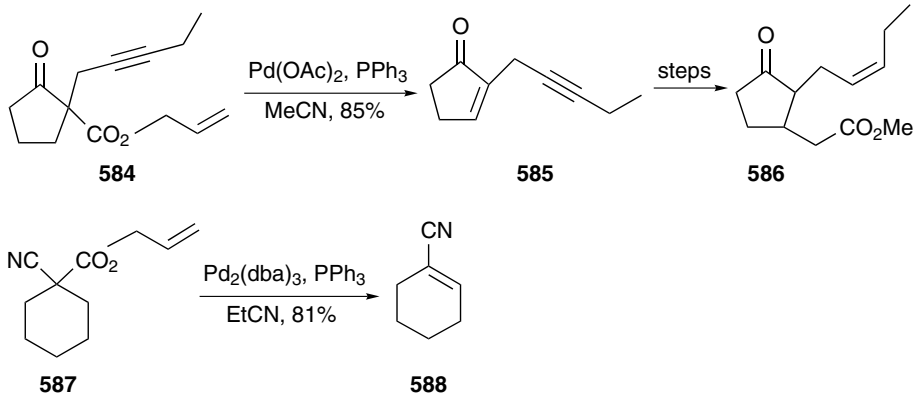


Not only allyl β-keto esters, but also the diallyl malonate derivative **580** underwent decaboxylation-allylation to give allyl α-allylcarboxylate **581**. The nitro ester **582** is very reactive and the allylation proceeded even at $-50\,^{\circ}C$ to give the α-allylnitroalkane **583** [209].



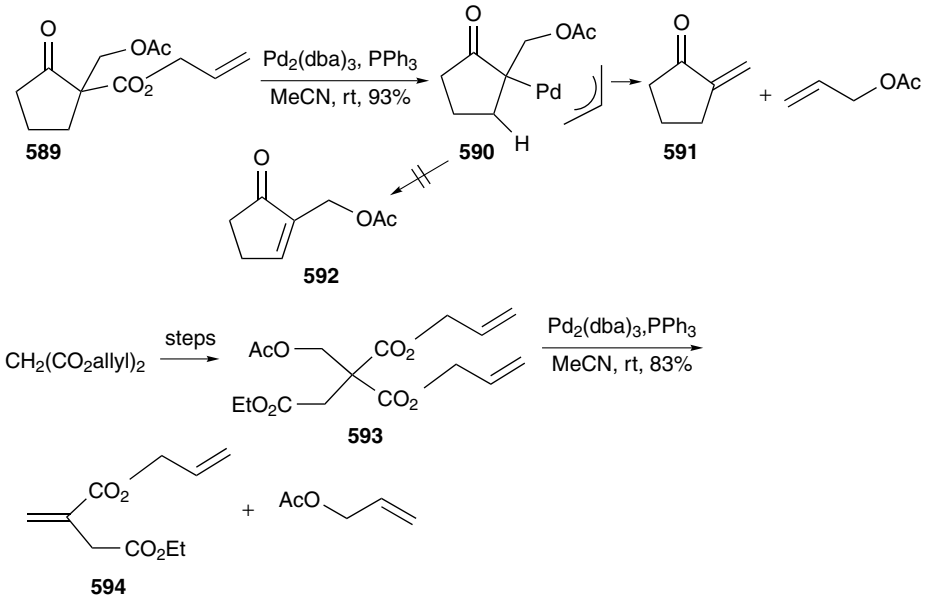
4.9.2.2 Preparation of α,β-Unsaturated Carbonyl Compounds by Decarboxylation–Elimination (B)

π-Allylpalladium enolates undergo β-H elimination to afford α,β-unsaturated ketones in MeCN at high temperature. Preparation of the cyclopentenone **585** from allyl α-2-pentynylcyclopentanone carboxylate (**584**) by β-H elimination is a key step in the commercial production of methyl *cis*-jasmonate (**586**) [210]. α,β-Unsaturated nitrile **588** was prepared from the disubstituted allyl cyanoacetate **587** [211].

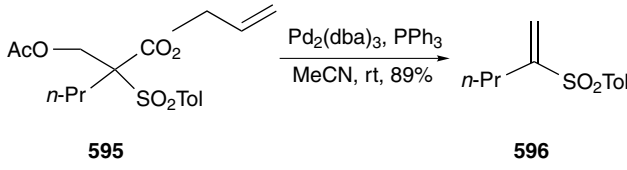


4.9.2.3 Synthesis of α-Methylene Compounds by Decarboxylation–Deacetoxylation (C)

The acetoxymethyl group is introduced at the α-carbon of cyclopentanonecarboxylate by the reaction of formaldehyde followed by acetylation to give **589**, which undergoes facile Pd-catalyzed decarboxylation and deacetoxylation to give α-methylenecyclopentanone **591** [212]. Interestingly, the acetoxy group in **590** is eliminated as allyl acetate more easily than β-H, and the cyclopentenone **592** is not formed. Itaconate **594** was prepared by application to allyl malonate. Treatment of the appropriately substituted ethyl diallyl malonate **593** with Pd catalyst at room temperature provided the allyl ethyl itaconate (**594**) in 83 % yield.

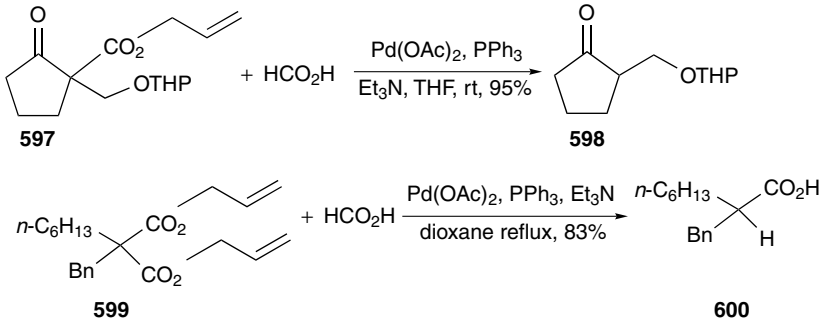


Allyl α-sulfonyl ester **595** underwent a similar reaction to give the vinylsulfone **596**.



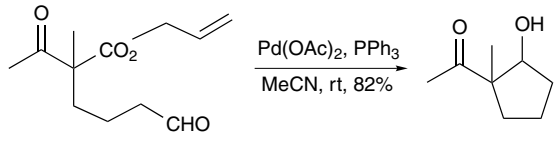
4.9.2.4 Decarboxylation–Hydrogenolysis (D)

Hydrolysis of the dialkylated β-keto esters and malonates is not easy, and usually harsh conditions are required. Also decarboxylation occurs only at high temperature. On the other hand, hydrolysis and decarboxylation reactions of substituted allyl β-keto esters and allyl malonates using Et_3N-HCO_2H proceed at room temperature under neutral conditions. THP-protected allyl β-keto ester **597** was converted to **598** at room temperature without deprotection of THP [213]. The free monocarboxylic acid **600** was obtained smoothly from the disubstituted diallyl malonate **599** [214].



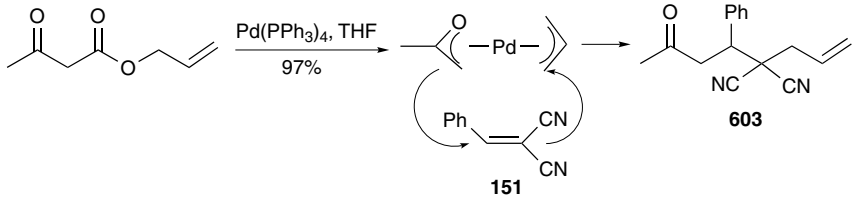
4.9.2.5 Aldol Condensation and Michael Addition (E, F)

Typical reactions of metal enolates are aldol condensation and Michael addition. As expected, Pd enolates undergo these two reactions. So far intramolecular reactions proceed efficiently. Intermolecular reactions are competitive with other reactions. Aldol condensation of the keto aldehyde **601** at room temperature provided the aldol product **602** in 82 % yield [215]



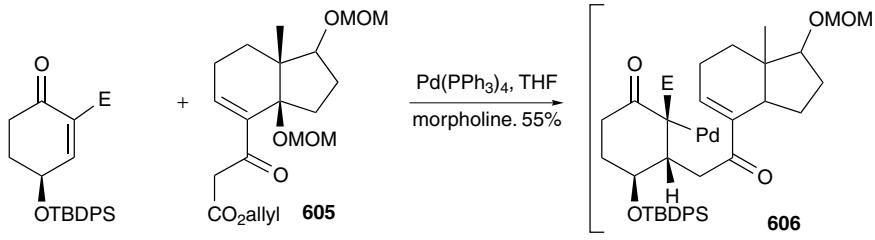
601 **602**

Intramolecular Michael addition occurs under mild conditions [216]. In the Pd-catalyzed reaction of allyl acetoacetate with benzylidenemalononitrile (**151**), the Michael addition of acetone enolate to benzylidenemalononitrile (**151**), followed by electrophilic allylation took place to afford **603** [217].

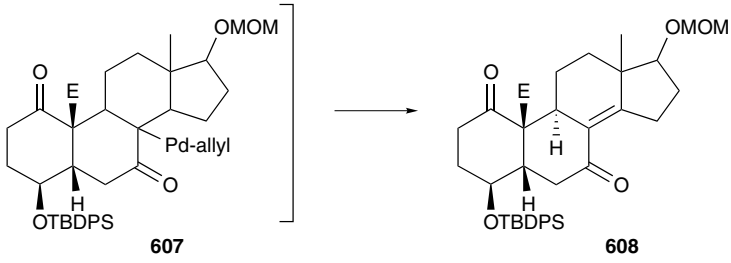


151 **603**

An interesting strategy for convergent steroid synthesis has been reported by Deslongchamps based on Pd-catalyzed decarboxylation–Michael addition of allyl β-keto ester (bicyclic Nazarov reagent) **605** to cyclohexanone **604**. The first intermolecular Michael addition of the Pd-enolate, generated from **605**, to **604** afforded **606**. Further intramolecular Michael addition constructed the steroid skeleton **607**, and the tetracycle **608** was obtained by β-H elimination [218].



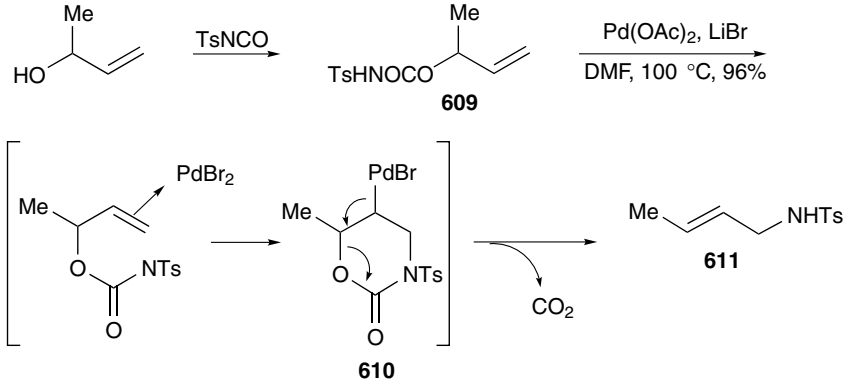
604 E = CO_2Me **605** **606**



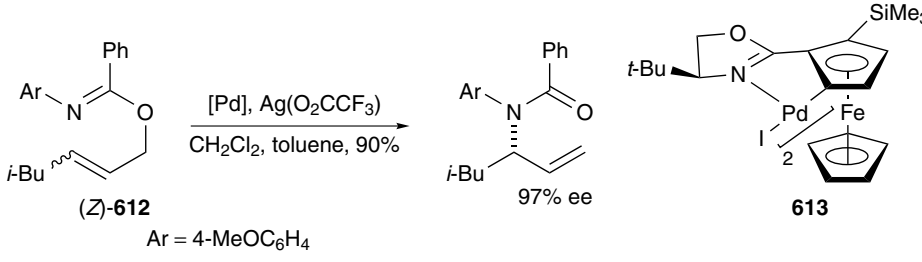
607 **608**

4.10 Pd(0) and Pd(II)-Catalyzed Allylic Rearrangement

[3,3]-Sigmatropic allylic rearrangement of allylic esters is catalyzed by both Pd(II) and Pd(0) by different mechanisms. Pd(II)-catalyzed reaction is explained by formation of cyclic intermediate. *N*-tosylallylamine **611** was prepared regioselectively from allylic alcohol via the allyl carbamate **609** by the Pd-catalyzed aminopalladation and decarboxylation using $Pd(OAc)_2$ in the presence of LiBr. No reaction occurred in the absence of LiBr. Most probably, Pd(II)-mediated aminopalladation of the double bond as shown by **610** generates the cyclic intermediate **610**. Deoxypalladation and decarboxylation give rise to the rearranged product **611** with regeneration of Pd(II) [219].

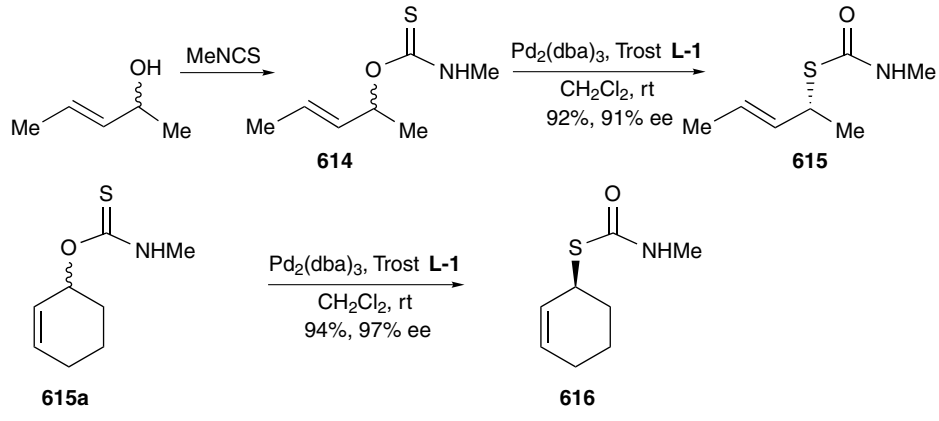


Overman and co-workers carried out extensive studies on Pd(II)-catalyzed asymmetric allylic rearrangement of allylic imidates to form enantioenriched allylic amides. They achieved 97 % ee as the best result by the reaction of the allylic imidate **612** using the cyclopalladated ferrocenyl oxazoline **613** having elements of planar chirality as a catalyst precursor, and discussed the mechanism of the reaction [220].



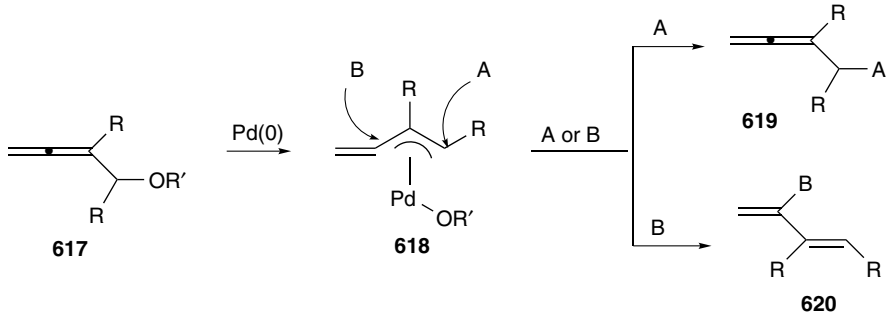
Gais and Böhme reported that Pd(0)-catalyzed enantioselective *O*,*S*-rearrangement of the racemic *O*-allylic thiocarbamate **614** using Pd(0) and Trost **L-1** as a chiral ligand provided the *S*-allylic thiocarbamate **615** in 92 % yield with 91 %

ee. Differentiation of allylic termini of the symmetric intermediate took place. Rearrangement of the cyclohexenyl derivative **615a** proceeded more efficiently and afforded **616** in 94 % yield with 97 % ee [221].

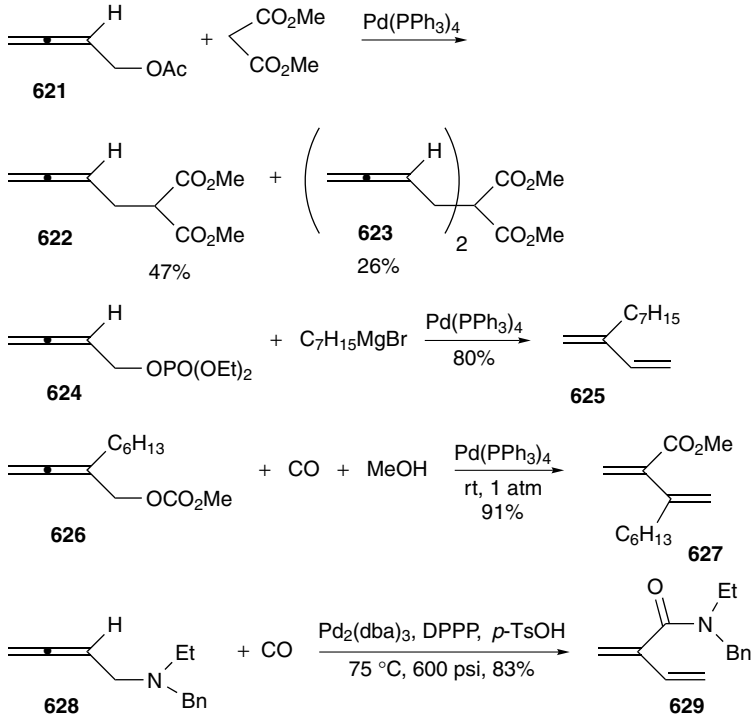


4.11 Reactions of 2,3-Alkadienyl Derivatives via Methylene-π-allylpalladiums

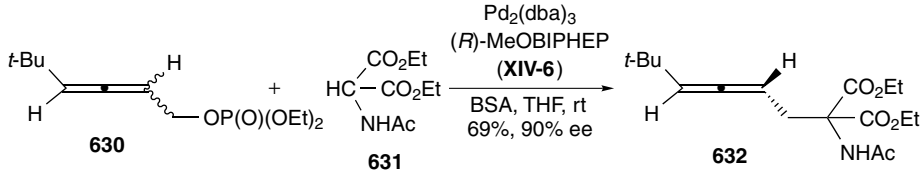
Reactive methylene-π-allylpalladiums **618** are generated from esters of 2,3-alkadienyl alcohols **617**, and react with nucleophiles to afford either 1,2-dienes **619** or 1,3-dienes **620** regioselectively depending on the nature of allyl leaving groups and nucleophiles.



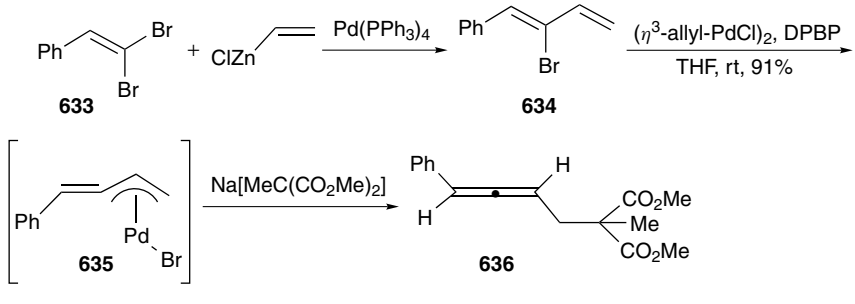
The 1,2-dienes (allenes) **622** and **623** were obtained by the reaction of soft carbon nucleophiles such as malonate [222]. On the other hand, reaction of the phosphate **624** with Grignard reagent provided the 1,3-diene **625** [223]. Carbonylation of the carbonate **626** proceeded smoothly under mild conditions (rt, 1 atm) and 3-alkyl-1,3-butadiene-2-carboxylate **627** was obtained in high yield [224]. The 2,3-dienylamine **628** was carbonylated under harsh conditions to provide the α-vinylacrylamide **629** in the presence of DPPP and TsOH [225].



Murahashi carried out the reaction of the phosphate **630** with the aminomalonate **631** using (*R*)-MeO-BIPHEP (**XIV-6**) as a chiral ligand and obtained the allene **632** with 90 % ee, offering a possibility of asymmetric synthesis of substituted allenes [226].

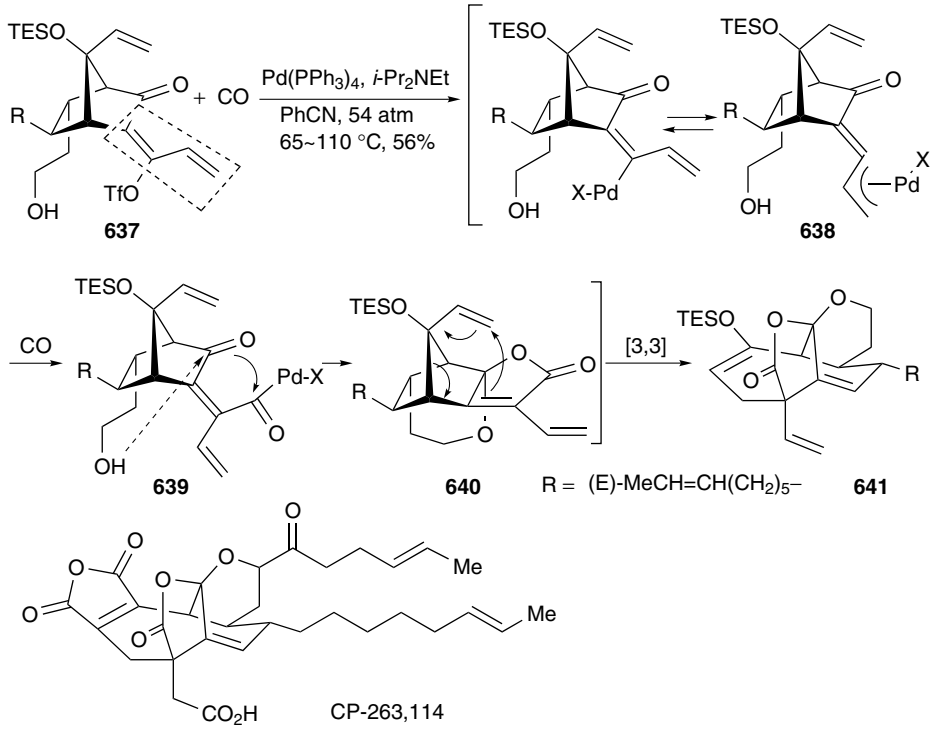


Hayashi found that methylene-π-allylpalladium **635** can be generated from 2-bromo-1,3-diene, which is prepared by the Pd-catalyzed cross-coupling of 1,1-dibromo-1-alkene **633** with vinylzinc reagent. Thus, the reaction of 1-phenyl-2-



bromo-1,3-butadiene (**634**) with malonate afforded the 1,2-diene **636**, presumably via the methylene-π-allylpalladium **635** in 91 % yield by using bisphosphine DPBP (**IX-11**). Other ligands such as DPPE, DPPP, DPPB, DPPF and PPh_3 gave very low yields (<10 %) [227].

Leighton constructed the complex molecule of the CP-263,114 core ring system **641** by elegant application of Pd-catalyzed carbonylation of the 1,3-butadienyl 2-triflate moiety in **637** via the methylene-π-allylpalladium **638** to afford the unsaturated lactone **640**. The lactone was subjected to Cope rearrangement to produce **641** as shown by **640** in 56 % overall yield. Formation of the unsaturated lactone **640** by intramolecular acetalization involving the alcohol, ketone, and acylpalladium as shown by **639**, is a key reaction [228].



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Chapter 5

Pd(0)-Catalyzed Reactions of 1,3-Dienes, 1,2-Dienes (Allenes), and Methylenecyclopropanes

5.1 Reactions of Conjugated Dienes

Several types of Pd-catalyzed or promoted reactions of conjugated dienes via π-allylpalladium complexes are known. The Pd(II)-promoted oxidative difunctionalization of conjugated dienes with various nucleophiles is treated in Chapter 2.4, and Pd(0)-catalyzed couplings of conjugated dienes with aryl and alkenyl halides are summarized in Chapter 3.2.9.1. Other Pd(0)-catalyzed reactions of conjugated dienes are treated in this section.

It is well known that Ni(0) catalyzes the cyclodimerization and cyclotrimerization of butadiene to form COD or CDT. On the other hand no cyclization of butadiene occurs with Pd(0) catalyst. Pd(0)-catalyzed dimerization of butadiene to form 1,3,7-octatriene (**1**) is the main reaction.

All Pd(0)-catalyzed reactions proceed via the formation of π-allylpalladium intermediates, which readily react with various nucleophiles as expected, giving 1 : 1 and 2 : 1 adducts. This is a characteristic feature of Pd(0)-catalyzed reactions of conjugated dienes. The most useful reaction is the dimerization with incorporation of pronucleophiles to give so-called 'butadiene telomers' **2** and **3** as shown by the following general scheme. Pd(0)-PPh_3 is an active catalyst for the dimerization. No dimerization occurred when $PdCl_2$ was used as a catalyst precursor. The 1 : 1 adducts **4** are obtained depending on the nature of the ligands. No dimerization of substituted dienes and cyclic dienes occurs and only 1 : 1 adducts, such as **5**, are formed as described later.

Dimerization of butadiene was studied extensively in the 1970s [1]. Since then, few studies have been reported. Beller and co-workers studied the telomerization of butadiene with MeOH, and found that the Pd-carbene (**XVI-1**) complex was an excellent catalyst and the linear telomer **6** was obtained with 99 % chemoselectivity and 98 % yield at 90 °C. In addition, they claimed that TON = 267 000 was attained with this catalyst. Also they showed that $Pd(OAc)_2/3PPh_3$ is a good catalyst for the telomerization [2]. Telomerization in the presence of water to give 2,7-octadien-1-ol (**7**) proceeded in an ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate) at 70 °C. The reaction mixture separated into two phases when it was cooled. After separation of the product, the ionic liquid phase is recycled [3].

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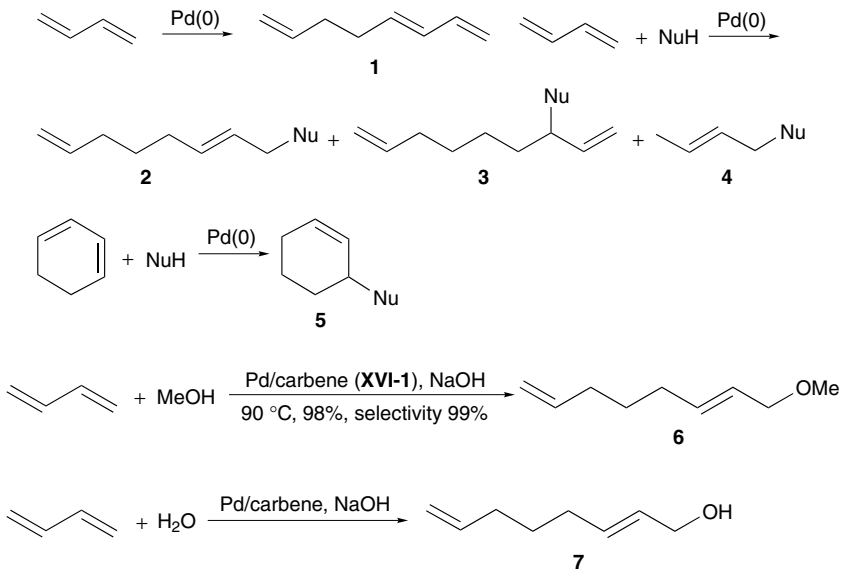
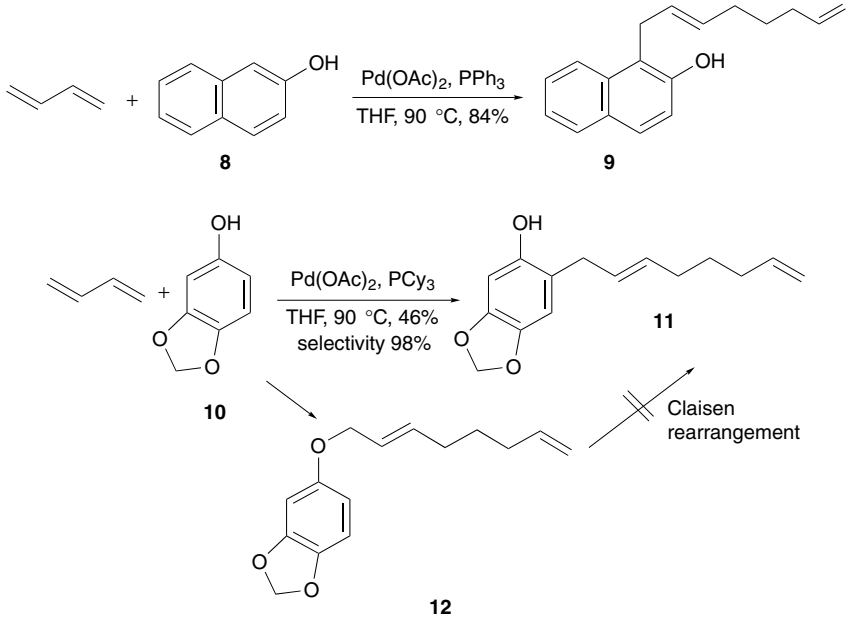
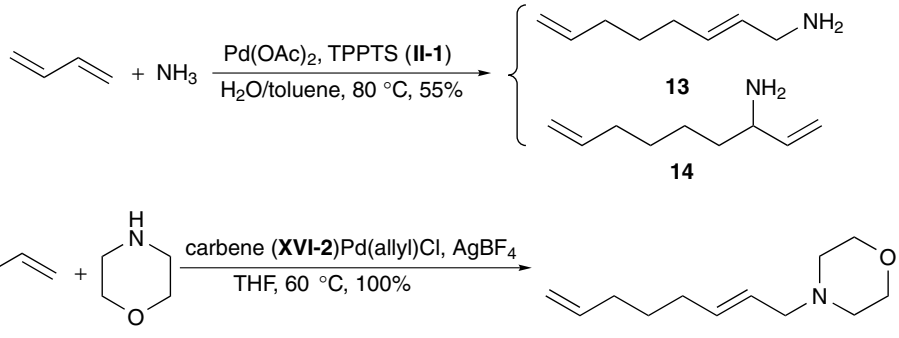


Phenols are reactive substrates and aryl 2,7-octadienyl ethers are obtained in good yield. Beller obtained 1-octadienyl-2-naphthol (**9**) in high yield, instead of the *O*-octadienyl ether, when β-naphthol (**8**) was subjected to telomerization at 90 °C for 16 h using $Pd(OAc)_2$ and PPh_3. Electron-rich phenols, such as 3,4-methylenedioxyphenol (**10**), were converted selectively to **11** without forming the aryl octadienyl ether **12** by using PCy_3 as a ligand. Formation of the octadienyl ether **12** is reversible, and irreversible C-octadienylation occurs due to the ambident character of these phenols. Claisen rearrangement of the ether **12** is one possibility, but it is unlikely because a branched 6-octadienylphenol should be formed from **12**, and not the linear one **11** [4].

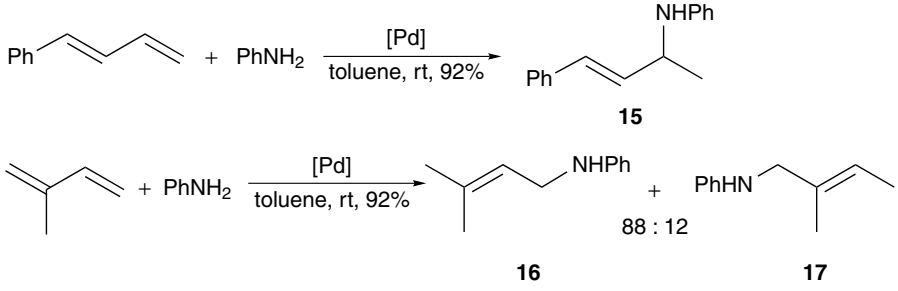


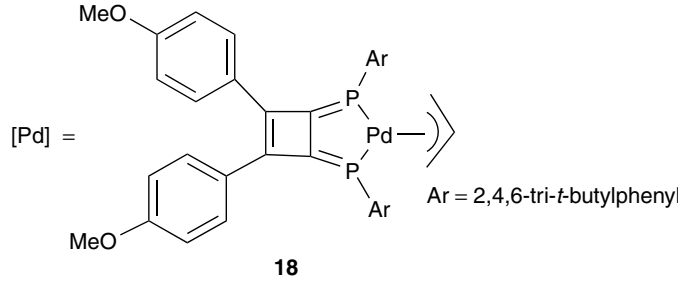
Octadienylamines **13** and **14** are obtained by the reaction of aqueous ammonia. Under usual conditions, these primary amines react further to give a mixture of di(octadienyl)amine isomers. The primary amines were obtained selectively without producing the secondary amines when the reaction was carried out in two phases (H_2O and toluene) using water-soluble TPPTS (**II-1**) as a ligand [5].

Nolan found that cationic Pd complexes of carbene **XVI-2**, coupled with non-coordinating anions such as PF_6 or BF_4, are precursors of active catalysts for telomerization of amines such as morpholine with butadiene. The catalyst is inactive when chloride is used. The telomerization proceeded rapidly even at room temperature in THF or toluene with a catalyst loading of 0.2 mol % [5a].

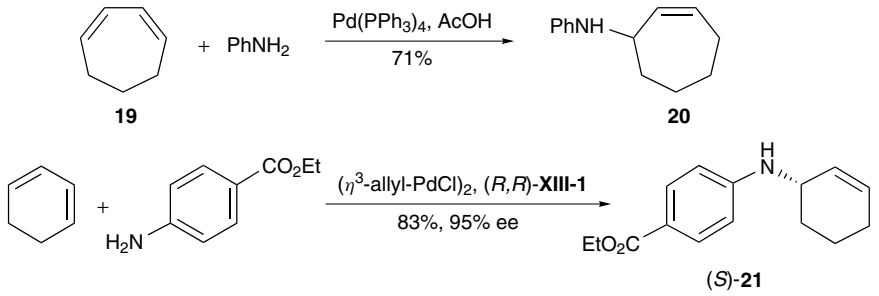


No dimerization of substituted or cyclic dienes occurs by using Pd-PPh_3 as a catalyst under usual conditions, instead the 1 : 1 adducts are formed. For example, dimerization of isoprene using Pd-PPh_3 is slow. 1,2-Hydroamination of 1-phenylbutadiene with aniline proceeded to afford the amine **15**, and two products **16** and **17** were obtained from isoprene when an exotic Pd complex **18** was used as a catalyst [6].

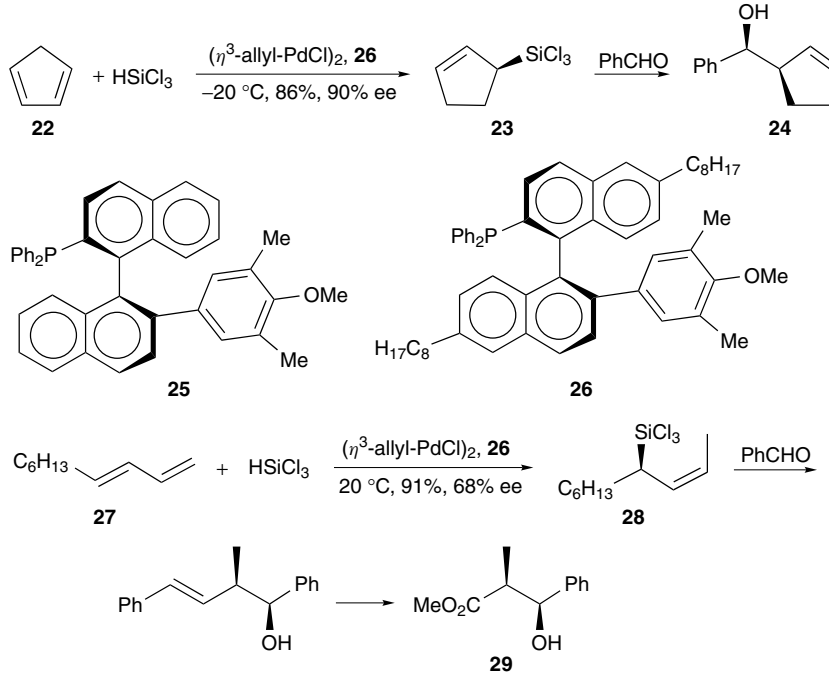




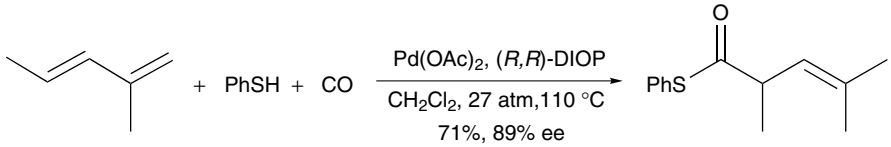
Hydroamination of prochiral cyclic dienes such as 1,3-cycloheptadiene (**19**) with aniline gave rise to 3-(*N*-phenylamino)cycloheptene (**20**) smoothly using Pd-PPh_3. This reaction suggests the possibility of asymmetric amination. Actually Hartwig carried out successful asymmetric hydroamination of 1,3-cyclohexadiene with 4-aminobenzoate using (*R*, *R*)-(**XIII-1**) as a chiral ligand and obtained *N*-(3-cyclohexenyl)-4-aminobenzoate (**21**) in 83 % yield with 95 % ee [7].



It is known that 1-silyl-2,7-octadiene is prepared when $HSiMe_3$ is used in the telomerization of butadiene. However, simple hydrosilylation occurs to give 1-silyl-2-butene by the reaction with $HSiCl_3$. Han and Hayashi have shown that the bulky Ar-MOP **25** is an effective ligand for asymmetric hydrosilylation of prochiral cyclic dienes, but the more bulky monodentate phosphine **26** is more effective. Hydrosilylation of cyclopentadiene (**22**) with $HSiCl_3$ afforded the 3-silylcyclopentene **23** at −20 °C in 86 % yield with 90 % ee. Optical purity was determined by converting **23** to **24**. 1,3-Decadiene (**27**) was converted to (*R*)-(*Z*)-4-(trichlorosilyl)-2-decene (**28**), which was isolated as a single regioisomer in 91 % yield, and ee % was determined as 68 % ee after converting to **29** [8].

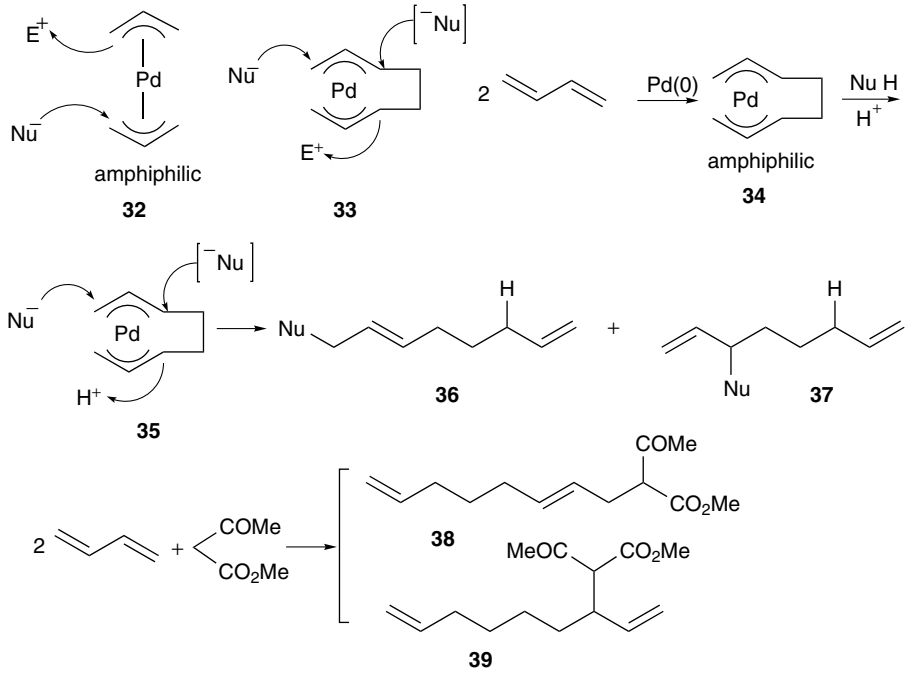


It is well-established that either 3-pentenoate or 3,8-nonadienoate are obtained by the carbonylation of butadiene depending on the nature of the catalysts. So far no successful asymmetric carbonylation of prochiral dienes is known. Alper carried out enantioselective thiocarbonylation of prochiral dienes, such as 2-methyl-1,3-pentadiene (**30**), with thiophenol and obtained the β,γ-unsaturated thioester **31** with 89 % ee in 71 % yield using (*R*, *R*)-DIOP as a chiral ligand [9].



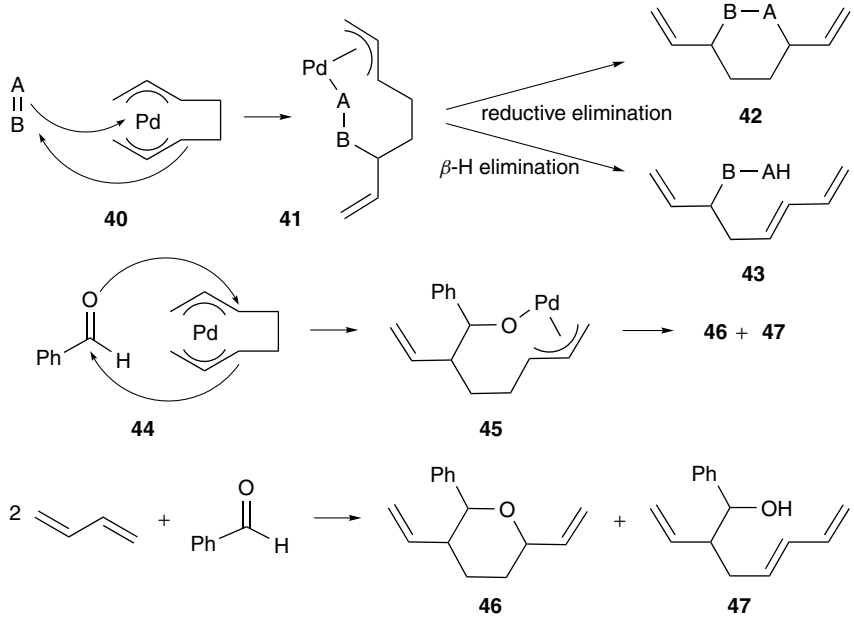
30 **31**

Jolly and co-workers carried out mechanistic studies on Pd-catalyzed telomerization and proposed that the bis-π-allyllic palladium **34** is formed at first [10]. It is known that the bis π-allylpalladium **32** is amphiphilic [11]. Similarly, an amphiphilic reaction of **34** is expected as shown by **33**. In the telomerization with a pronucleophile, protonation occurs at first, followed by electrophilic attack of the π-allylpalladium moiety as illustrated by **35** to produce the telomers **36** and **37**. Thus the reaction of butadiene with malonate gives a mixture of **38** and **39**. It should be noted that the protonation takes place at the congested side of the π-allyl system.

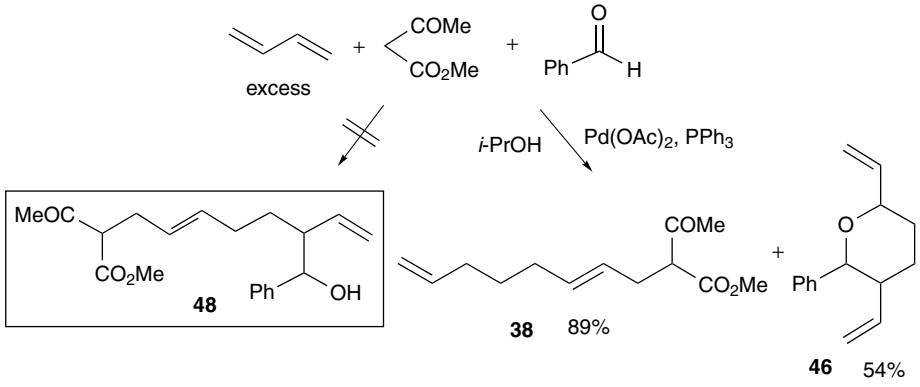


The amphiphilic nature of the bis-π-allyllic palladium was clearly shown by the reaction of the polarized double bond A=B to give either **42** or **43**. In this case, the first nucleophilic attack of one of the π-allylpalladium moieties occurs to generate

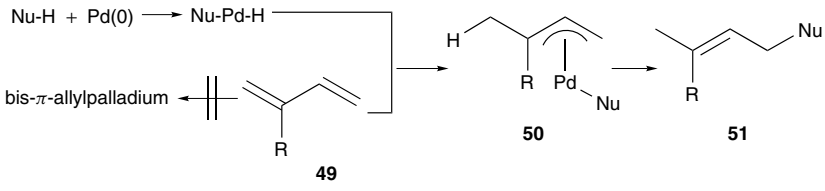
41, from which **42** is formed by reductive elimination, and **43** is obtained by β-H elimination. Actually benzaldehyde reacted with butadiene to give the pyran **46** and unsaturated alcohol **47** via **45** depending on the nature of the Pd catalyst [12]. A similar amphiphilic reaction of phenyl isocyanate afforded divinyl-δ-lactam [13].



Then Kiji and Tsuji attempted the amphiphilic reaction of excess butadiene with acetoacetate and benzaldehyde in one-pot, expecting the formation of the telomer **48**. But the acetoacetate and benzaldehyde behaved separately to yield the telomers **38** and **46**, without giving the desired product **48** [14].



Formation of 1 : 1 adducts from substituted dienes **49** can be understood by the following mechanism. In this case, generation of bis-π-allylic palladium is not possible for steric reasons. Instead, insertion of a diene to H-Pd bond of H-Pd-Nu occurs to afford the π-allylpalladium complex **50**, and nucleophilic attack at the allylic terminus gives **51**.

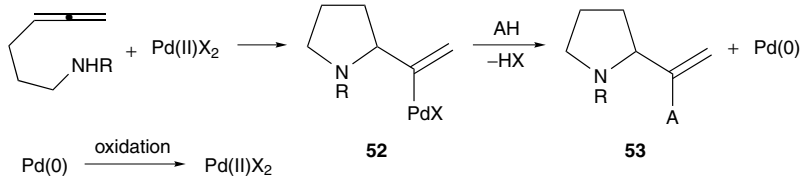


5.2 Reactions of Allenes

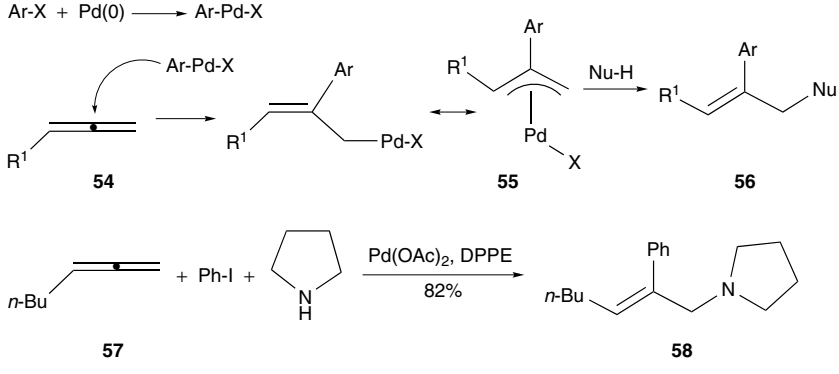
5.2.1 Introduction

Allenes (1,2-dienes) are more reactive than alkenes, and Pd-catalyzed reactions of allenes with carbon and heteroatom nucleophiles proceed mostly via the formation of π-allylpalladium intermediates, and offer useful methods for making carbon–carbon and carbon–heteroatom bonds. The first report on Pd-catalyzed reaction of allenes with amines and malonate was given by Coulson in 1973 [15]. A comprehensive review on Pd-catalyzed reactions of allenes is available [16].

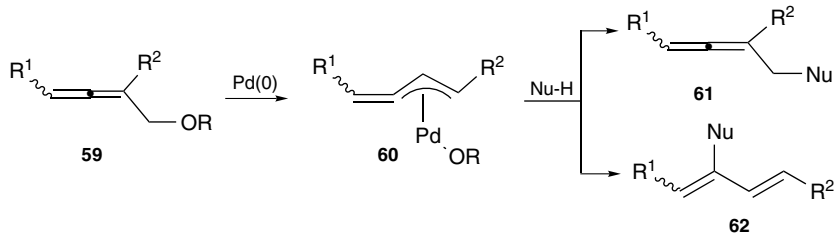
Pd-catalyzed and promoted reactions of allenes can be classified into three groups. The first one is promoted by Pd(II). For example, aminopalladation of hexa-1,2-dienyl-6-amine with Pd(II) generates the alkenylpalladium intermediate **52**, which is converted to functionalized alkene **53** with generation of Pd(0). In order to make the reaction catalytic, Pd(0) has to be oxidized to Pd(II) with some oxidants. This type of reaction is treated in Chapter 2.5.



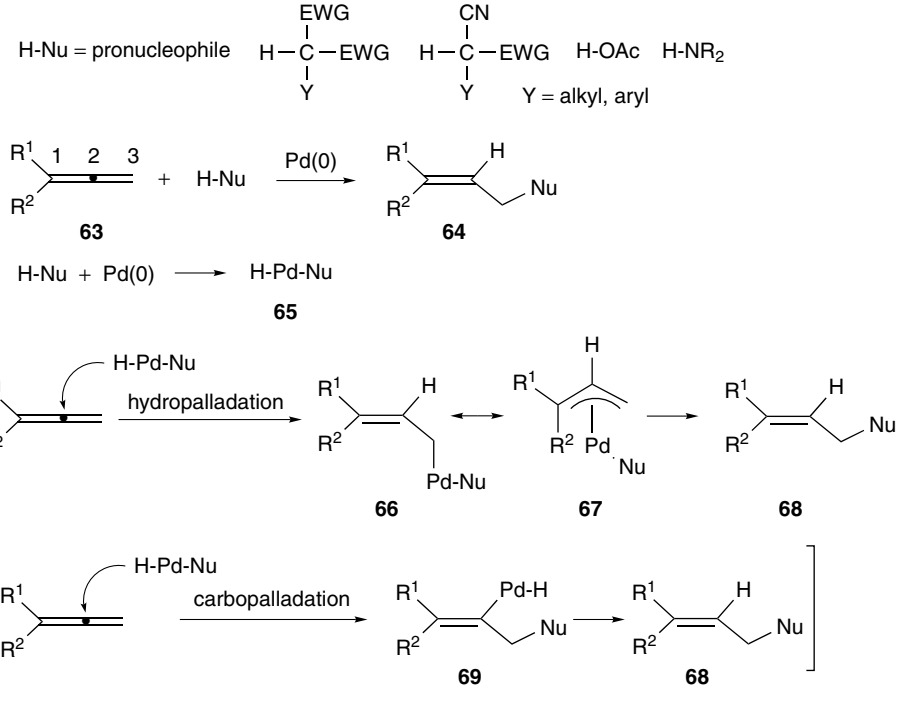
In the Pd(0)-catalyzed reaction of allene **54** with aryl halide, carbopalladation of allene with Ar-Pd-X takes place to give the π-allylpalladium intermediate **55**, which is attacked by a pronucleophile to give **56**. For example, reaction of 1,2-hexadiene (**57**) with iodobenzene and pyrrolidine afforded the allylic amine **58** [17]. The catalytic reactions of this type have been extensively studied. They are surveyed in Chapter 3.2.9.2.



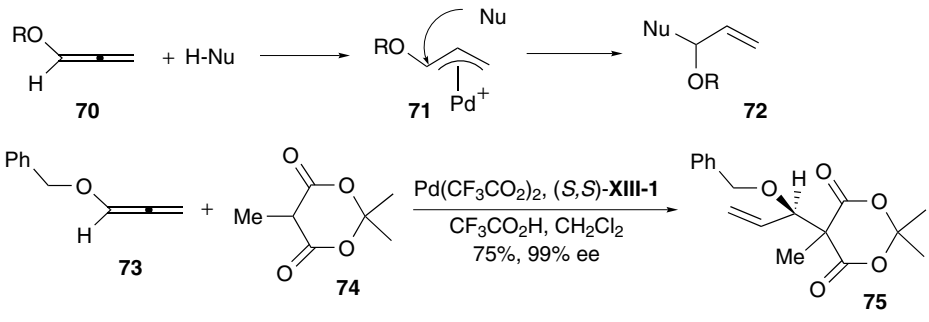
Facile Pd(0)-catalyzed reactions of 2,3-alkadienyl derivatives **59** with nucleophiles occur via the formation of methylene-π-allylpalladium intermediates **60**, from which 1,2- and 1,3-dienes **61** and **62** are formed depending on the nature of the pronucleophiles. These reactions are treated in Chapter 4.11.



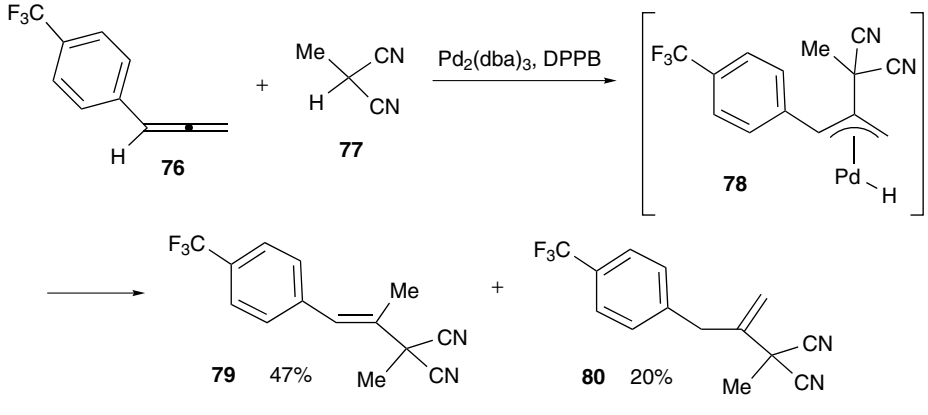
In this section, Pd(0)-catalyzed reactions of allenes with nucleophiles are treated, which are clearly different mechanistically from the reactions explained in the above. Attack of nucleophiles may occur at C-1, C-2, and C-3 carbons of the allenes **63**. Among them, attack at C-3 to give **64** is predominant. Most importantly, reactions of allenes with pronucleophiles start by the oxidative addition of pronucleophiles to Pd(0) to generate H-Pd-Nu **65**. The formation of **64** by hydrocarbonation can be explained in two ways in the case where Nu-H is the carbon pronucleophile. As one possibility, hydropalladation of one of the two double bonds occurs to afford the terminal palladium intermediate **66**, which is stabilized by the formation of π-allyl complex **67**, and reductive elimination provides the C-3 adduct **68**. Another possibility is carbopalladation to generate **69**, and subsequent reductive elimination provides **68**. Of these two possibilities, the hydropalladation mechanism is preferable.



Various reactions of pronucleophiles with allenes has been reviewed by Yamamoto and Radhakrishnan [18]. Regioselectivity in these reactions is controlled by steric and electronic effects. The attack at C-3 is a main path, but several exceptional cases have been reported. Due to electronic bias, the hydrocarbonation of alkoxy- or phenoxyallenes **70** gives allylic ethers as the C-1 adduct **72** either exclusively or predominantly via π-allylpalladium **71** [19]. Trost expanded the regioselective formation of allylic ether to an asymmetric reaction. Addition of the Meldrum's acid **74** to the allenyl ether **73** catalyzed by palladium trifluoroacetate and (*S*, *S*)-**XIII-1** as a chiral ligand in the presence of trifluoroacetic acid afforded the the allylic ether **75** with 99 % ee in 75 % yield [20].



The reaction of the phenylallenes substituted by EWG at *para*-position provides C-2 adducts exclusively or predominantly. A mixture of the C-2 adducts **79** and **80** was obtained regioselectively from *p*-trifluoromethylphenylallene (**76**). The reaction of phenylallene possessing electron-donating groups, such as methoxy, provides the C-3 adduct, and a mixture of the C-2 and C-1 adducts is formed from arylallenes bearing other substituents [21].

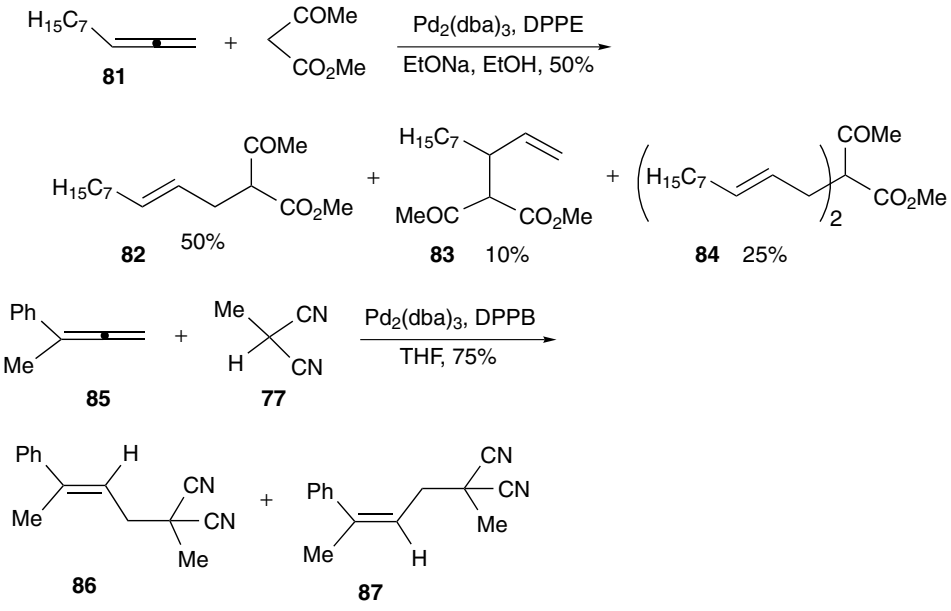


5.2.2 Reactions with Pronucleophiles

5.2.2.1 Reactions with Carbon Pronucleophiles

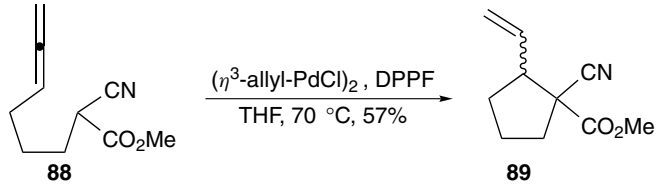
Gore *et al*. carried out the reaction of malonate and acetoacetate with deca-1,2-diene (**81**) under basic conditions using DPPE as a ligand and obtained a mixture

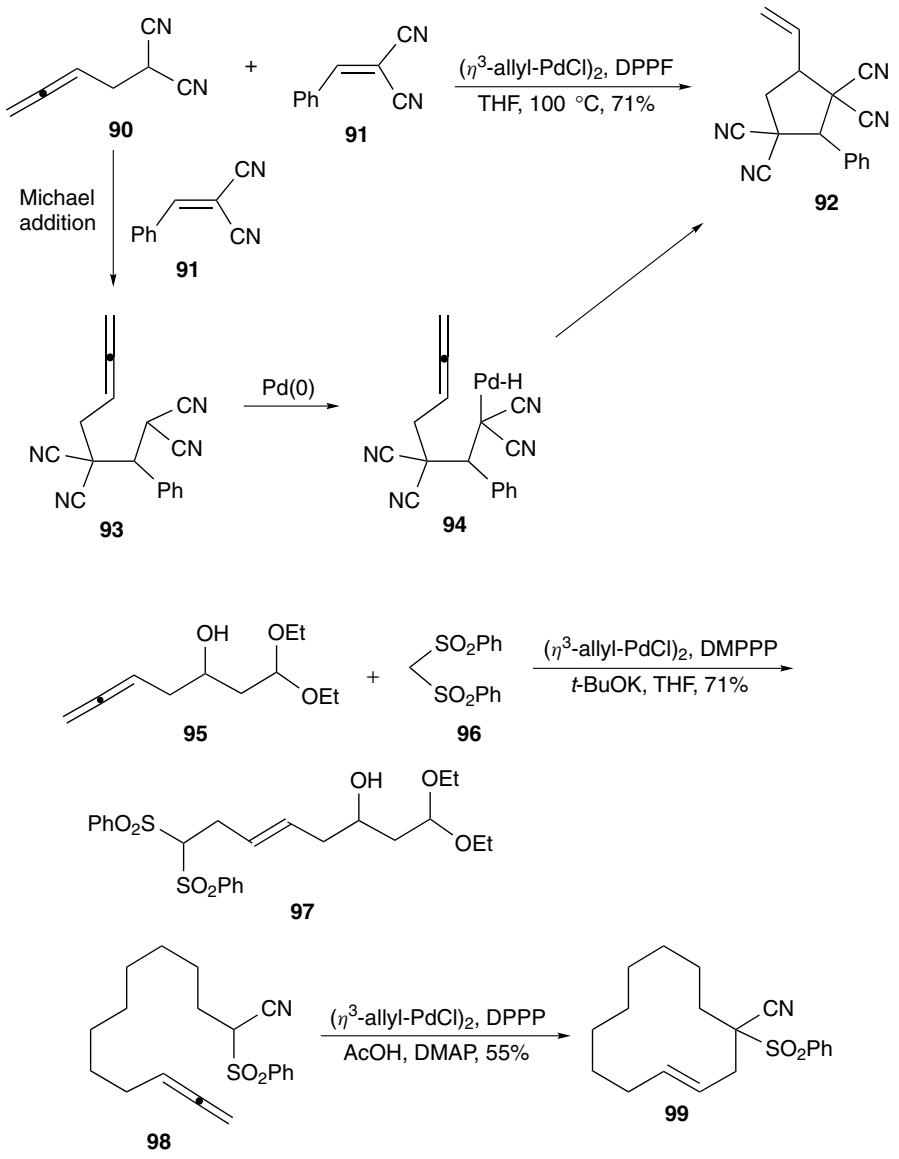
of C-3 adducts **82** and **84** as major products and C-1 adduct **83** as a minor product [22]. Yamamoto *et al*. found methylmalononitrile (**77**) is more reactive. The CN group seems to be more effective to activate pronucleophiles than carbonyl groups, and it is known that malononitrile is more reactive than malonate in some reactions. It should be noted that the addition of **77** to 3-phenyl-1,2-butadiene (**85**) proceeded in the absence of a base to give the C-3 adducts **86** and **87** using DPPB as a ligand. It is remarkable that carbon–carbon bond formation involving pronucleophiles occurs under neutral conditions [23].



As an intramolecular version, the vinylcyclopentane **89** was obtained from methyl 4,5-hexadienylcyanoacetate (**88**) by C-1 attack in 57 % yield using DPPF in the absence of a base [24]. In the intermolecular reaction of 2,3-butadienylmalononitrile (**90**) with the activated alkene **91**, at first Michael-type addition of malononitrile to the alkene occurred to give **93**, which underwent cyclization to give the cyclopentane **92** via the formation of hydridopalladium **94** [25].

Trost carried out the addition of bis(benzenesulfonyl)methane (**96**) to the allene **95** in the presence of *t*-BuOK using DMPPP [di(2-methoxyphenyl)phosphinopropane, **IX-6**] as a ligand to yield **97** [26]. Preparation of medium and large rings has been carried out by intramolecular reaction of various pronucleophiles with 1,2-dienes. The 12-membered ring **99** was obtained from the allene **98** in 55 % yield in the presence of AcOH as an acid and DMAP as a base [27].

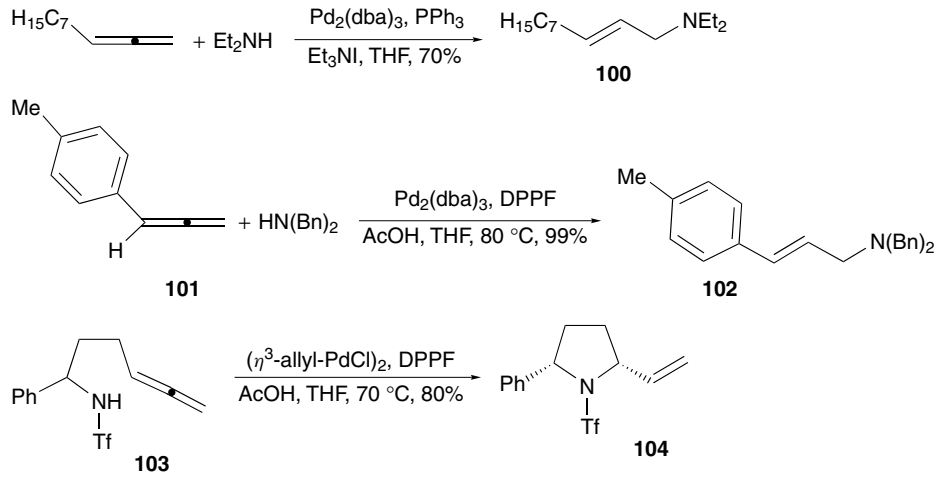




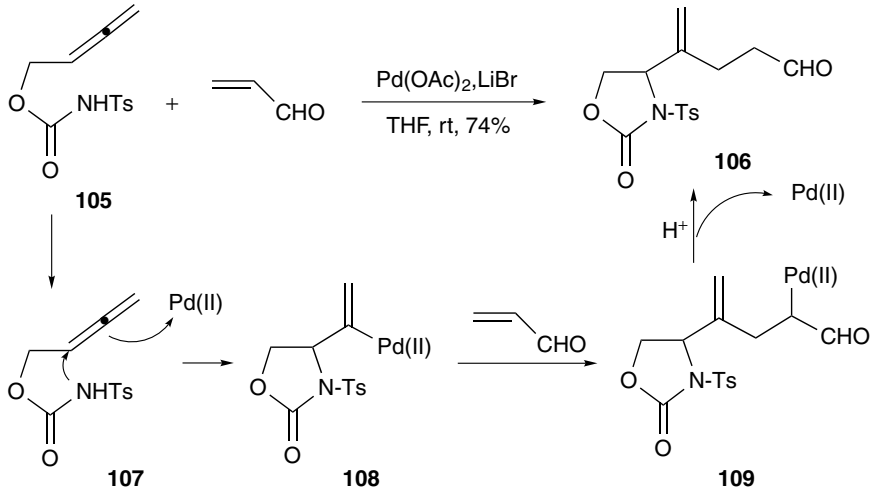
5.2.2.2 Hydroamination

Hydroamination of alkylallene was carried out using PPh_3 as a ligand to give the corresponding allylic amines such as **100** [28]. Similarly, arylallene **101** was aminated at terminus to give the allylic amine **102** in high yield using DPPF as a ligand in the presence of AcOH [29]. Under similar conditions, 2,5-disubstituted pyrrolidine **104** was obtained from the hexa-4,5-dienylamine **103** in 80 % yield [30].

It should be pointed out that some Pd-catalyzed reactions of allenes with nucleophiles proceed by a different mechanism. The mechanistically interesting intramolecular reaction of allenylcarbamate **105** with acrolein afforded the oxazolinone **106** in the presence of $Pd(OAc)_2$ and LiBr. This reaction is promoted by Pd(II), not by Pd(0) [31]. Unlike the Pd(0)-catalyzed reactions surveyed in the above section,



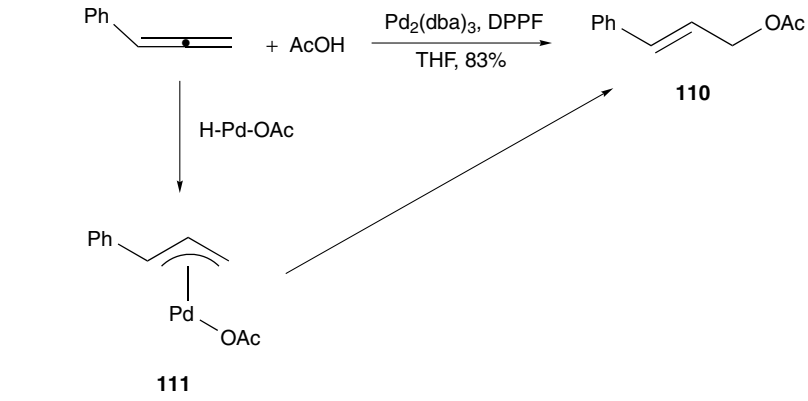
intramolecular aminopalladation as shown by **107** generates alkenylpalladium intermediate **108**, which undergoes insertion of acrolein to give the alkylpalladium **109**. The last step is protonolysis of **109** to provide the saturated aldehyde **106** and regenerates Pd(II), and hence the whole reaction proceeds catalytically with Pd(II). A similar catalytic reaction via oxypalladation using Pd(II) was reported [32] (see Chapter 2.5).

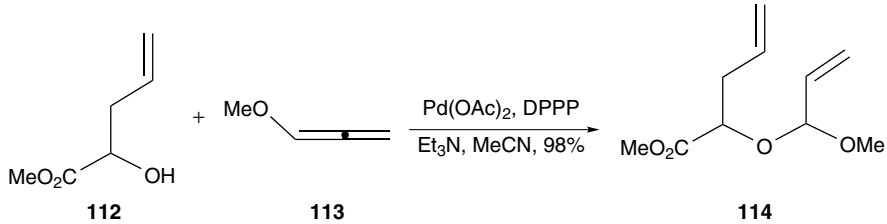


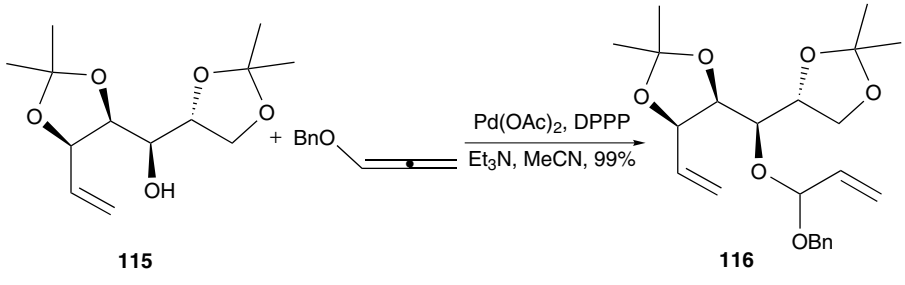
5.2.2.3 Reactions of Oxygen Nucleophiles

Allylic acetate **110** was obtained by regioselective hydroacetoxylation of phenylallene at the terminal double bond. DPPF is the most effective ligand. The reaction is explained by hydropalladation of allene with H-Pd-OAc to form π-allylpalladium acetate **111** and reductive elimination [33].

Addition of secondary alcohol **112** to 1-methoxyallene (**113**) occurred selectively at the C-1 position as expected to form the acetal **114** using $Pd(OAc)_2$ and DPPP [34]. The reaction of the alcohol **115** with benzyloxyallene was applied to the synthesis of highly functionalized acetal **116** [35].

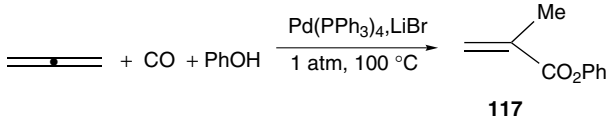


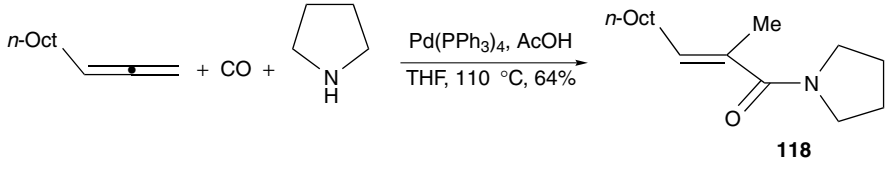




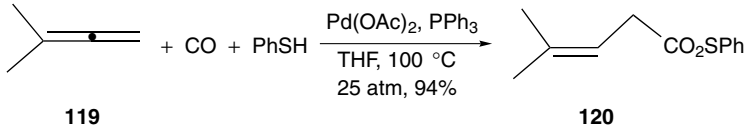
5.2.3 Carbonylation

Few studies on Pd-catalyzed carbonylation of allenes have been reported. Grigg carried out the carbonylation of allene in the presence of phenol under 1 atm at 100 °C and obtained phenyl methacrylate (**117**) by the attack of the central carbon [36]. Carbonylation in the presence of secondary amine and AcOH occurred at the C-2 position to give α,β-unsaturated amides such as **118** [36].

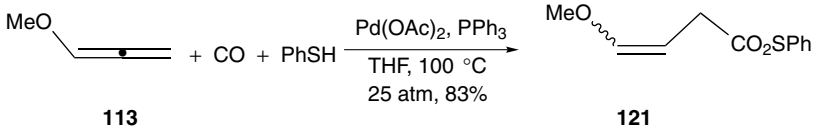




On the other hand, thiocarbonylation of simple allenes such as **119** with benzenethiol afforded the β,γ-unsaturated thioester **120** in good yield. Attack of CO at the terminal carbon occurred. Somewhat unexpectedly, thiocarbonylation of methoxyallene **113** also took place at the C-3 carbon to give the thioester **121** [37].



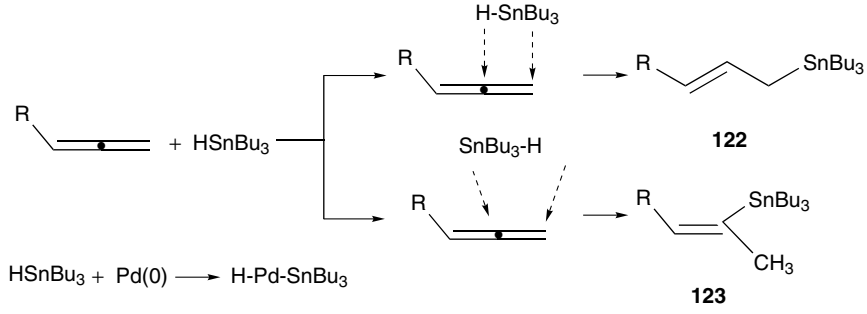
119 **120**



113 **121**

5.2.4 Hydrometallation and Dimetallation

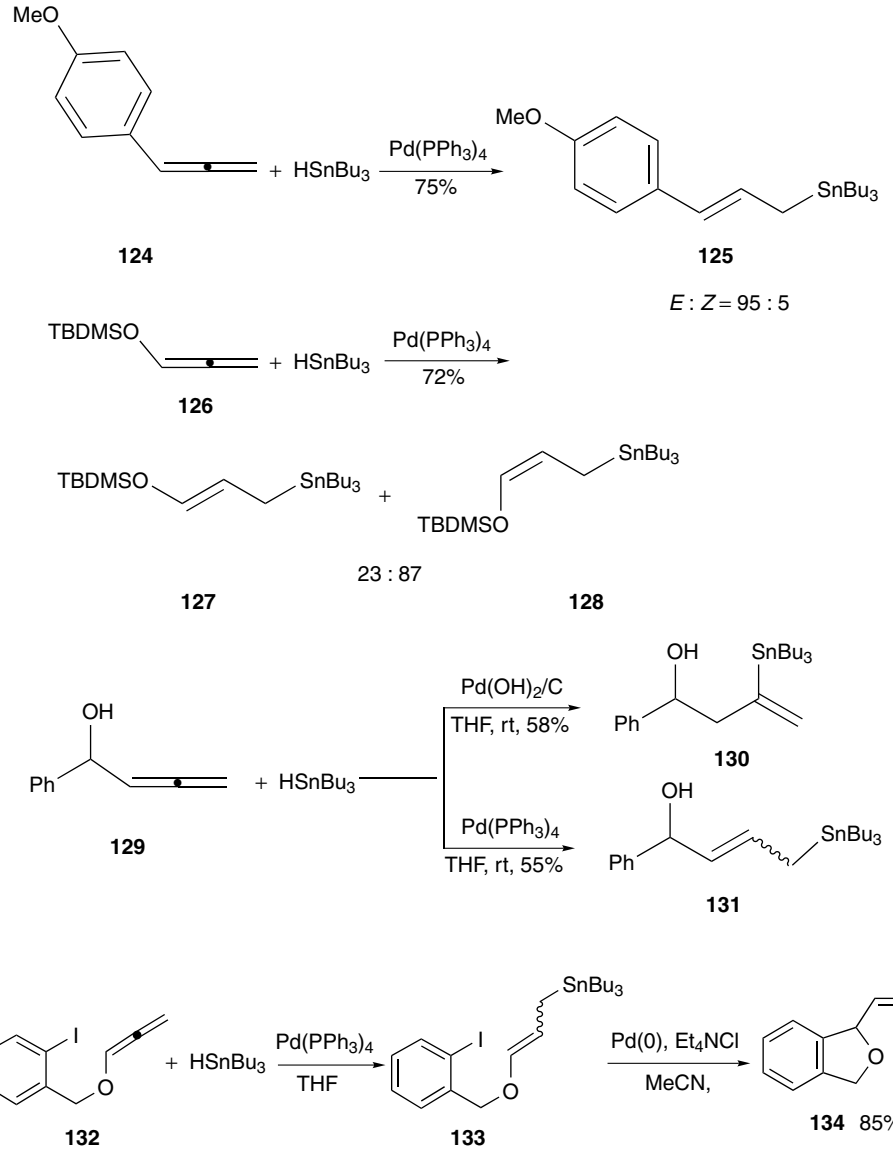
Facile metallation of allenes offers convenient synthetic methods of functionalized alkenes. Pd-catalyzed *cis* hydrostannation of allenes proceeds smoothly via either hydropalladation or stannylpalladation of 1,2-dienes with H-Pd-$SnBu_3$ to produce allylstannanes **122** or vinylstannane **123** [38].



123

Hydrostannation of arylallenes such as **124** proceeded regio- and stereoselectively to provide allylstannane **125** [39]. Reaction of allenyl silyl ethers such as **126** also proceeded regioselectively to produce allylstannanes. A mixture of the stereoisomers **127** and **128** was obtained, but in this case the *Z* isomer **128** was obtained predominantly. As shown above, allylstannanes are obtained by metallation at the terminal carbon [40]. However, Lautens *et al*. reported that the vinylstannane **130** was obtained from alkylallene **129** when ligandless heterogeneous $Pd(OH)_2$ on carbon was used as a catalyst. It was confirmed that the allylstannane **131** was obtained when $Pd(PPh_3)_4$ was used. The catalysts changed the selectivity [41].

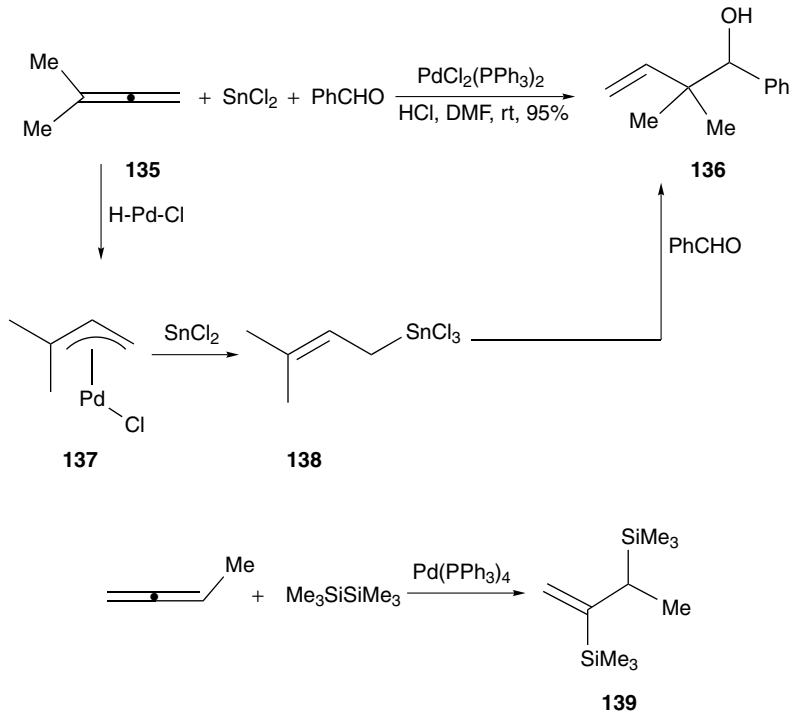
As a synthetic application, Grigg applied the regioselective hydrostannation of alkoxyallene to the hydrostannation–cyclization sequence, and obtained the benzodihydrofuran **134** from the allenyl ether **132** via the allylstannane **133** in one pot [42].



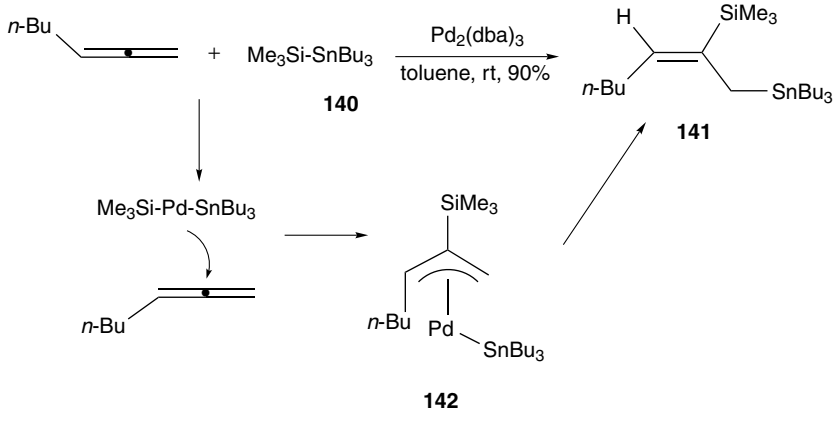
Stereoselective allylation of aldehydes via Pd-catalyzed *in situ* hydrostannation of allenes using $SnCl_2$ was carried out by Chang. In this reaction, the π-allylpalladium **137** is generated by hydropalladation of the alkylallene **135** with H-Pd-Cl, and umpolung of **137** with $SnCl_2$ occurs to give the allylstannane **138**. Then the homoallyl alcohol **136** is formed by the reaction of **138** with aldehyde [43].

Pd-catalyzed dimetallation of allenes with dimetallic reagents has been studied extensively. For example, regioselective 1,2-disilylation of alkylallene gave **139** [44].

Regio- and stereoselectivities in Pd-catalyzed silylstannation (silastannation) of allenes are not always satisfactory. They are markedly improved by the use of phosphine-free Pd catalyst, particularly $Pd_2(dba)_3$. The allylstannane **141** was

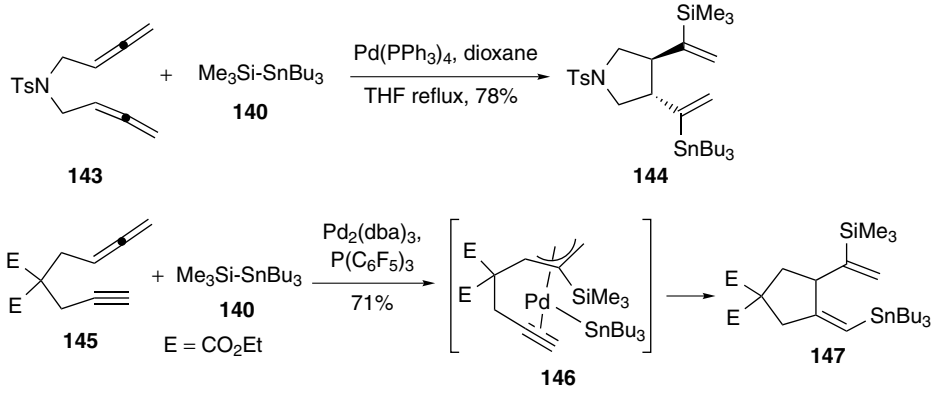


obtained regio- and stereoselectively in high yield by the silylstannation of 1,2-heptadiene with Me_3Si-$SnBu_3$ (**140**). Silylpalladation to form π-allylpalladium **142** is the first step, and reductive elimination gives rise to the 1-stannyl-2-silyl-2-heptene **141** [45]. This regioselective silylstannation is a useful reaction, because selective transformations of the silyl and stannyl groups in **141** to other functional groups are possible.

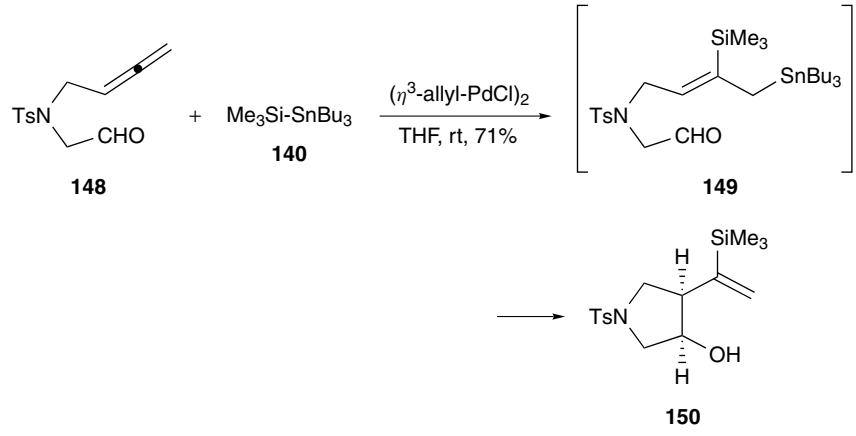


Inter- and intramolecular versions of regioselective silylstannation of allenes with **140** have been utilized for the preparation of functionalized cyclic compounds. Silylstannation–cyclization of 5-aza-nona-1,2,7,8-tetraene (**143**) with **140** using $Pd(PPh_3)_4$ gave *trans*-1,2-(1-silylvinyl)(1-stannylvinyl)cyclopentane

144 [46]. Silylstannation–cyclization of octa-1,2-dien-7-yne (**145**) with **140** proceeded cleanly via π-allylpalladium intermediate **146** to give the cyclized product **147** by using $P(C_6F_5)_3$ as a ligand. It is claimed that $P(C_6F_5)_3$ is a better ligand than PPh_3 [47].

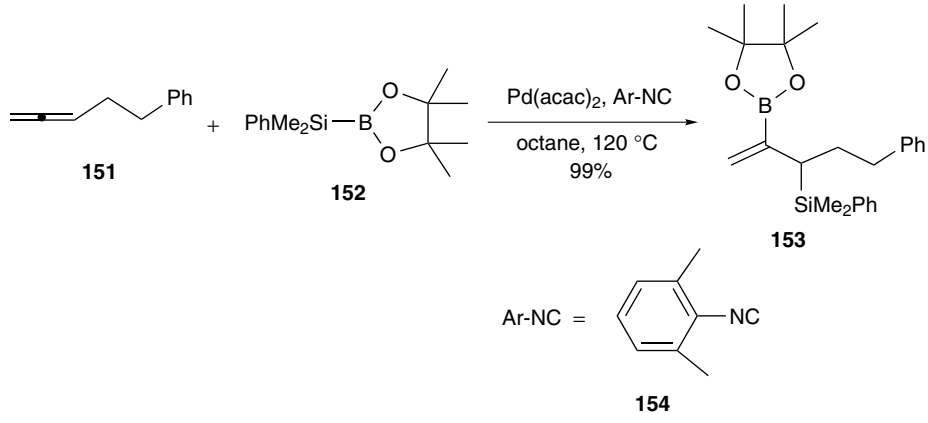


Silylstannation of the allenyl aldehyde **148** with **140** in THF at room temperature generated the allylstannane **149**, which attacked intramolecularly the formyl group to yield the cyclic homoallylic alcohol **150**. Phosphine-free π-allylpalladium chloride was the most effective catalyst [48].



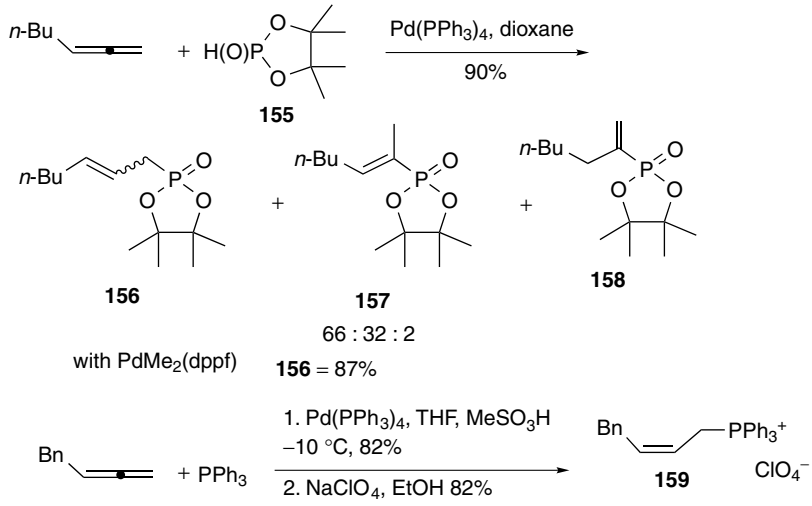
Borylsilylation (borasilylation) of alkylallene **151** with the silylborane **152** provided the 2-boryl-3-silyl-1-alkene **153** regioselectively in 99 % yield. Hindered 2,6-xylyl isocyanide (**154**) was the effective ligand for the reaction [49]. A similarly good result was obtained by using $Pd_2(dba)_3$ in combination with cyclic phosphite (**III-2**) as a catalyst [50].

A mixture of the allylphosphonate **156** and alkenylphosphonates **157** and **158** was obtained by the Pd-catalyzed hydrophosphorylation of 1,2-heptadiene with 4,4,5,5-tetramethyl-1,3,2-dioxaphospholane-2-oxide (**155**) using $Pd(PPh_3)_4$ as a catalyst. When $PdMe_2(dppf)$ was used, the allylphosphonate **156** was obtained regioselectively in 87 % yield [51]. The allylphosphonium salts such as **159** were



151 152 153 154

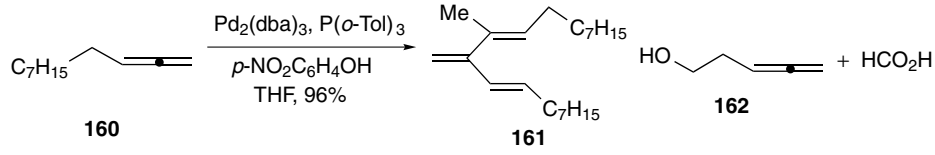
prepared by Pd-catalyzed addition of PPh_3 to allenes in the presence of methanesulfonic acid. Various 1,3-dienes were prepared by a Wittig-type reaction of the salts such as **159** with aldehydes [52].



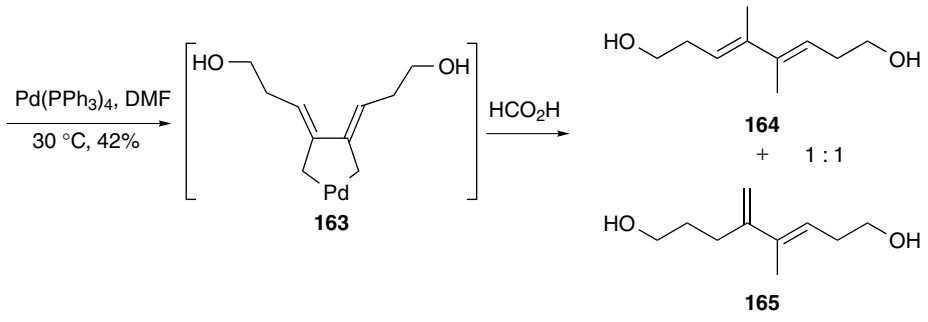
155 156 157 158 159

5.2.5 Miscellaneous Reactions

Dimerization of alkylallene **160** proceeded regioselectively at each C-2 carbon, and the cross-conjugated triene **161** was obtained in high yield using P(*o*-Tol)$_3$ as a ligand and *p*-nitrophenol as an additive [53]. In the presence of formic acid, reductive dimerization at C-2 carbons occurred to give the conjugated dienes **164** and **165**. The dimerization is explained by the formation of the palladacycle **163**, formed by oxidative cyclization, as an intermediate [54].



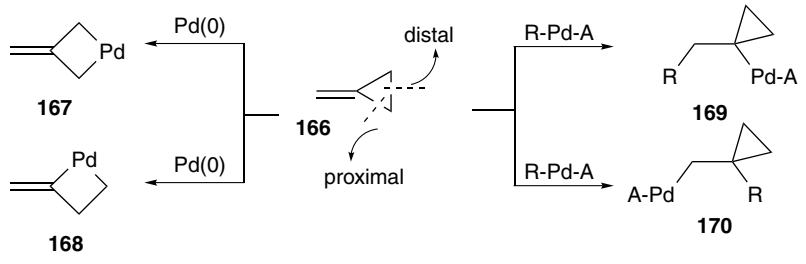
160 161 162



5.3 Reactions of Methylenecyclopropanes

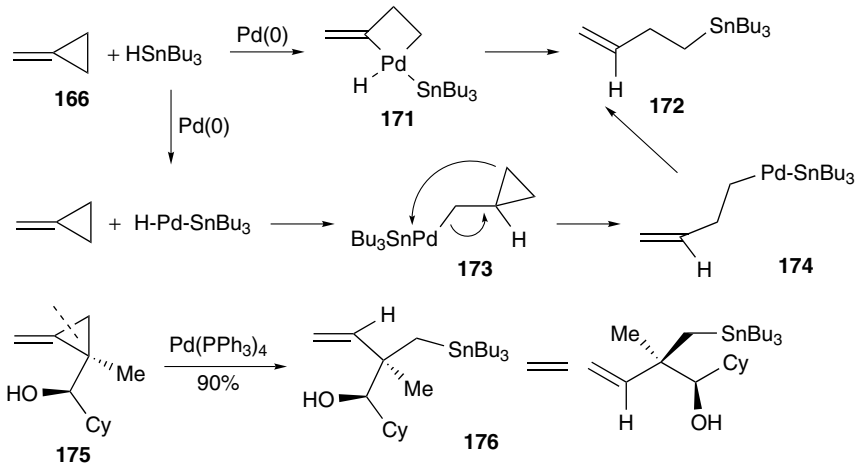
5.3.1 Introduction

Methylenecyclopropanes (MCPs) **166** show unique reactivity mainly due to high strain, and are attracting the attention of synthetic chemists. Many studies have been carried out on their transition metal-catalyzed reactions, particularly cycloadditions with unsaturated polar bonds. A comprehensive review on recent advances in metal-catalyzed reactions of MCPs by Nakamura and Yamamoto is available [55]. In this section, typical Pd-catalyzed addition reactions are mainly surveyed. Although MCPs are rather simple compounds, they undergo a variety of Pd-catalyzed reactions. Different reactions take place depending on the structures of the MCPs, reacting substrates, and catalysts, and some of the reactions are mechanistically complicated and not easily understood. Formally Pd-catalyzed reactions of MCPs may be explained by two palladacycles **167** and **168**, formed by oxidative addition of MCP with cleavage of the distal and proximal bonds. These intermediates are not enough to explain all reactions. In addition, two types of addition patterns of Pd complexes to the exomethylene to provide **169** and **170** should be considered as intermediates.

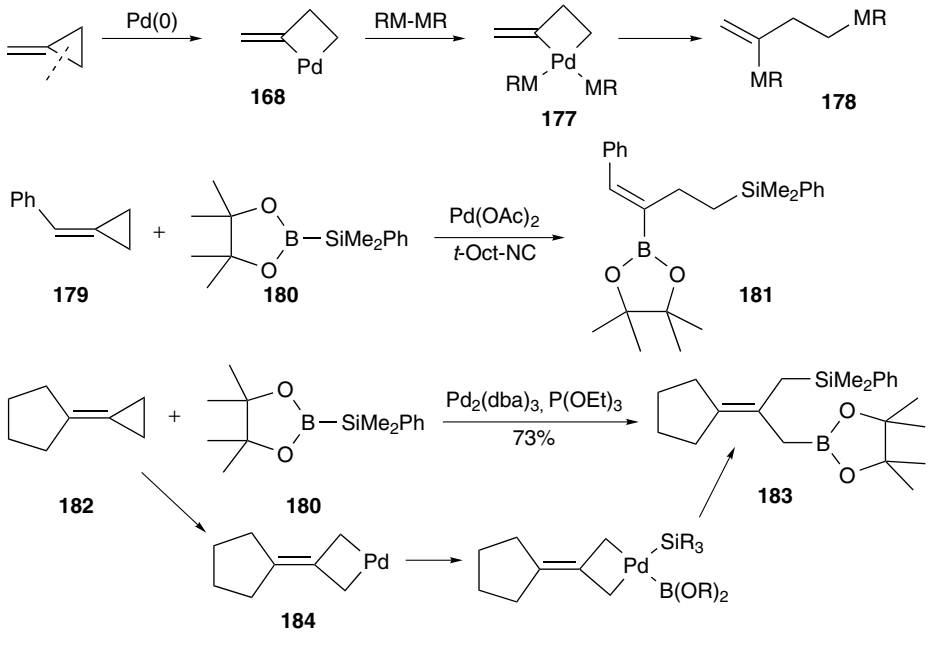


5.3.2 Hydrostannation and Dimetallation

Hydrometallation proceeds by proximal bond cleavage. Addition of $HSnBu_3$ affords the homoallylstannane **172** [56]. The addition may be understood formally by the formation of the palladacycle **171**, but explanation by the formation of the cyclopropylcarbinylpalladium **173** is more appropriate. The intermediate **173** undergoes β-carbon elimination to generate the homoallylpalladium **174**, which then gives rise to **172** by reductive elimination. Addition of $HSnBu_3$ to a substituted MCP **175** to yield **176** can be understood by this mechanism.

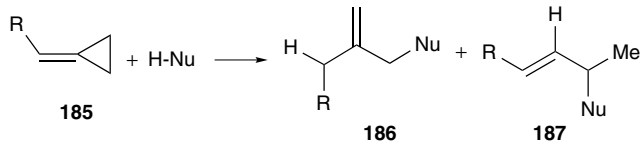


Dimetallation may be understood by participation of both palladacycles **167** and **168**. In general, addition of dimetallic reagents occurs via the palladacycles **177** with cleavage of the proximal bond to provide **178**. For example, borylsilylation of the MCP **179** with **180** gave **181** using a combination of $Pd(OAc)_2$ with *t*-octyl isocyanide (**XVII-6**). On the other hand, addition via the distal bond cleavage was observed in the reaction of the same reagent **180** with the MCP **182**, and the product **183** was obtained via **184** [57].

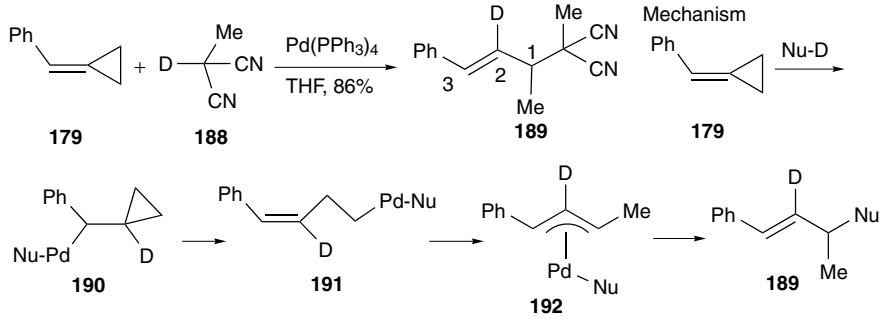


5.3.3 Hydrocarbonation and Hydroamination

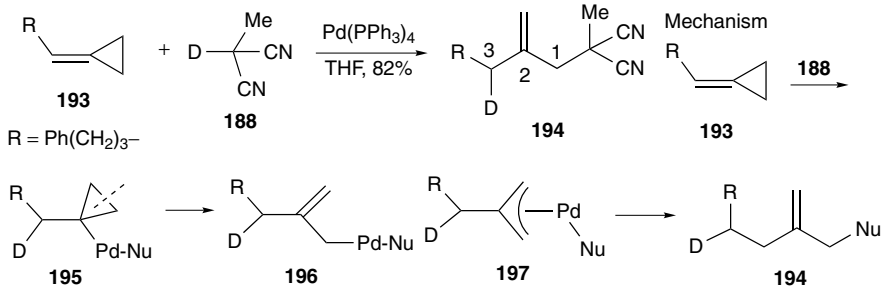
Two products **186** and **187** are obtained by the addition of carbon pronucleophiles (Nu-H) by the cleavage of both distal and proximal bonds in **185**. These reactions look somewhat complicated and their mechanisms are not easily understood.



Reaction of MCP **179** with deuterated methylmalononitrile (**188**) catalyzed by $Pd(PPh_3)_4$ gave rise to the proximal bond cleavage product **189** in 86 % yield, which is deuterated at C-2 exclusively. This product corresponds to **187** [58]. The reaction of **179** with **188** starts by the addition of Nu-Pd-D to the methylene bond to generate the cyclopropylcarbinylpalladium **190**, which is converted to **191** by β-carbon elimination. Then the rather unusual rearrangement of **191** to the π-allylpalladium intermediate **192** takes place. The rearrangement can be understood by elimination of H-Pd-Nu from **191** and readdition. Then reductive elimination provides **189**.

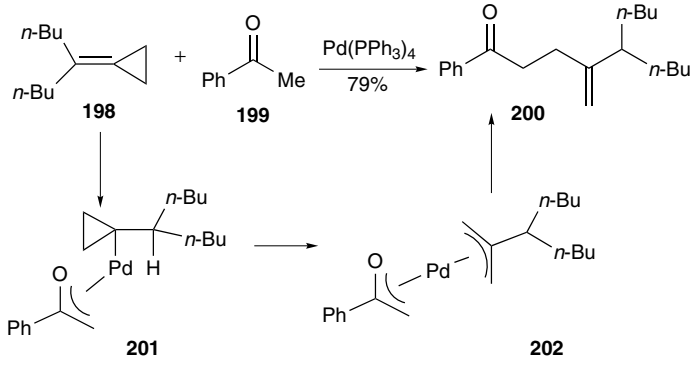


On the other hand, addition of methylmalononitrile (**188**) to the MCP **193** gave the distal bond cleavage product **194** in 82 % yield, which is deuterated at the C-3 position. Obviously, the product **194** corresponds to **186**. The reaction starts from the addition product **195**, which is converted to the allylpalladium **196** by β-carbon elimination, and then to the π-allylpalladium intermediate **197**. The final product **194** is obtained from **197**.

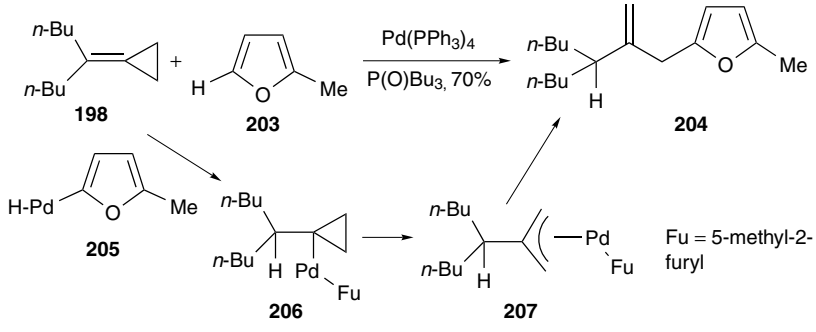


Ketones are allylated with MCPs using $Pd(PPh_3)_4$ as a catalyst under neutral conditions [59]. Reaction of acetophenone (**199**) with MCP **198** afforded the allylated acetophenone **200** in 79 % yield. The reaction is understood by the generation of H-Pd-CH_2COPh under neutral conditions, and the addition to form **201**. The

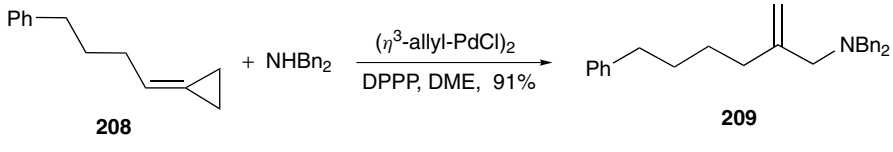
rearrangement of **201** via β-carbon elimination to the π-allylpalladium enolate **202** and reductive elimination provide **200**.

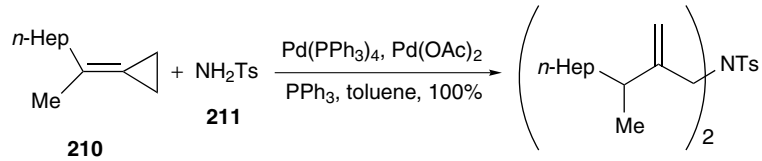


Interesting hydrofurylation of MCP **198** with furans occurs by activation of the CH bond in furans, involving distal bond cleavage [60]. Reaction of the furan **203** with the MCP **198** afforded the 2-allylated furan **204** by using $Pd(PPh_3)_4$. Interestingly the addition of tributylphosphine oxide is important for the smooth reaction. The reaction starts by the oxidative addition of the C-H bond of furan to Pd(0) to form **205**, and the addition to **198** generates **206**. Subsequent rearrangement of **206** to the π-allylpalladium **207** and reductive elimination provide the allylated furan **204**.



The distal bond cleavage occurs in hydroamination. Reaction of MCP **208** with dibenzylamine afforded the allylic amine **209** by using the combination of π-allylpalladium chloride with DPPP as a catalyst [61]. Similarly sulfonamide **211** was allylated with MCP **210** to produce the diallylated amide **212** using a complex mixture of Pd(0), Pd(II), and PPh_3 as a catalyst [62]. The use of Pd(0)-PPh_3 in an appropriate ratio seems to be effective.





210 **211** **212**

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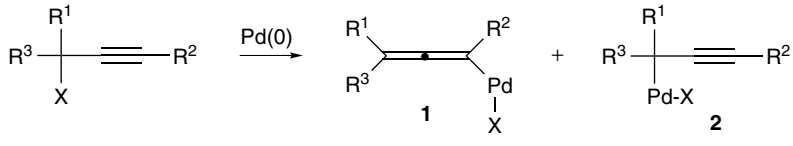
Chapter 6

Pd(0)-Catalyzed Reactions of Propargyl Compounds

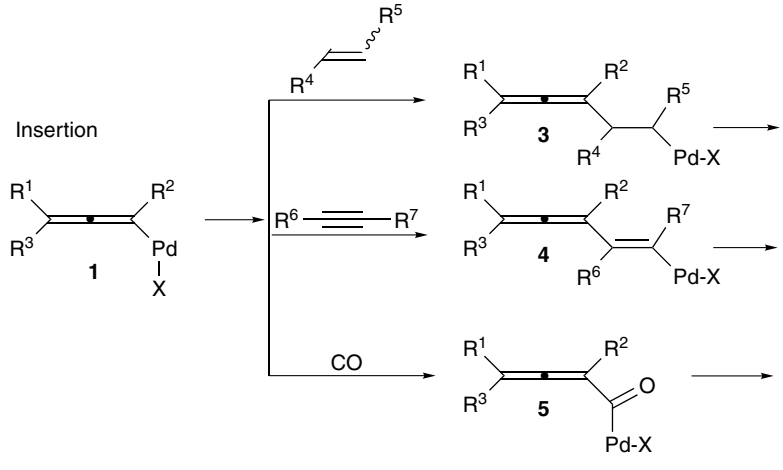
6.1 Introduction and Classification of Reactions

Pd(0)-catalyzed reactions of various propargyl compounds proceed by the formation of either the σ-allenylpalladiums **1** or the propargylpalladiums (or σ-prop-2-ynylpalladiums) **2** as intermediates.



The Pd(0)-catalyzed reactions of propargyl compounds so far discovered can be classified into several types from a mechanistic viewpoint [1]. The σ-allenylpalladium complexes **1** as intermediates undergo three types of transformations depending on reactants.

The first one is insertion of unsaturated bonds to the σ-bond. The insertions of alkenes, alkynes, and CO generate the alkylpalladium **3**, 1,3,4-trienylpalladium **4**, and acylpalladium compounds **5**, respectively. These intermediates undergo further transformations.



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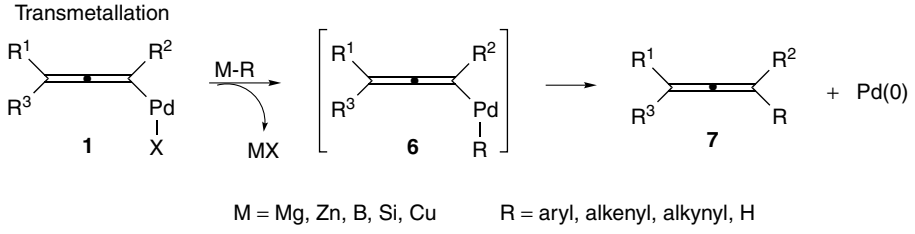
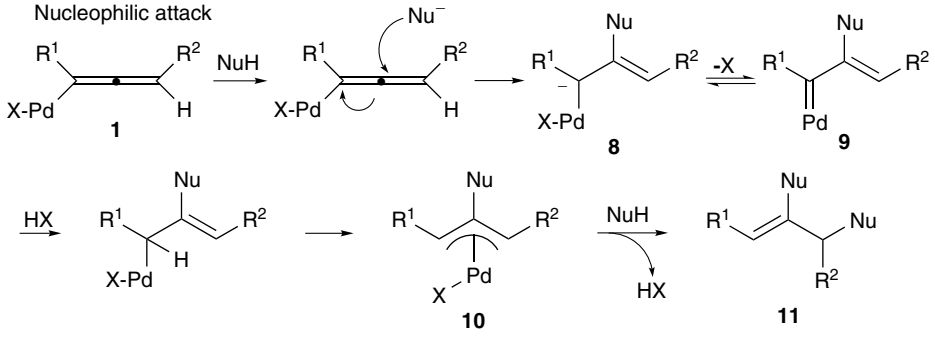
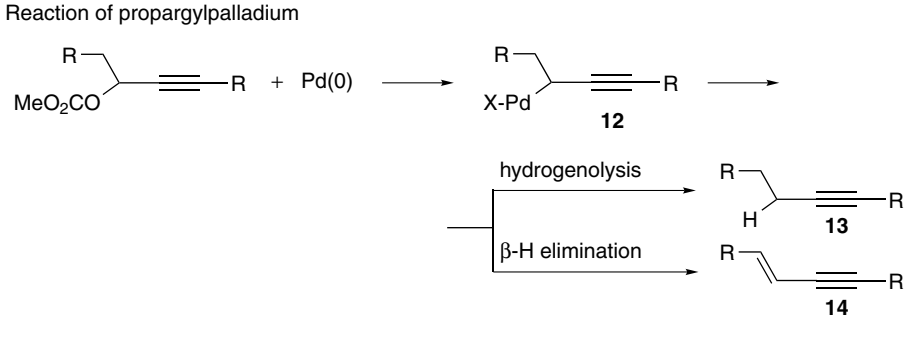
The second type of reactions proceed by transmetallation of the complexes **1**. MR (M = main group metals) and metal hydrides MH undergo the transmetallation with **1** to generate **6**. Subsequent reductive elimination gives the allene derivative **7**. Also reactions of **1** with 1-alkynes in the presence of CuI to afford allenylalkynes belong to this type.



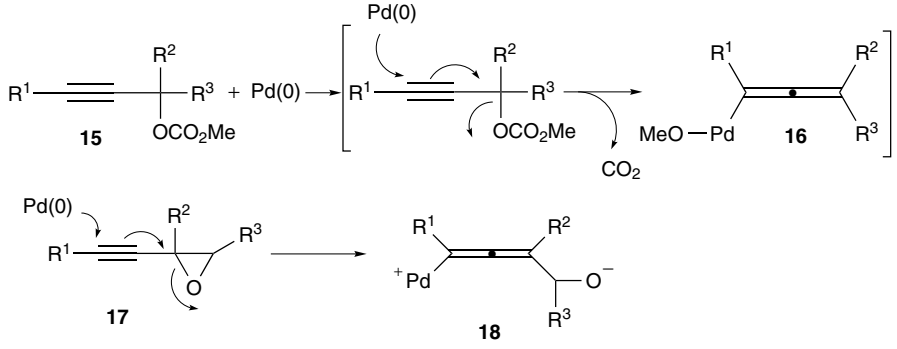
The third type of reactions occur by attack of a nucleophile at the central sp carbon of the allenyl system in **1**. Reactions of soft carbon nucleophiles, as well as oxygen and nitrogen nucleophiles belong to this type. The attack of the nucleophile generates the intermediates **8**, which are regarded as palladium–carbene complexes **9**. The intermediates **8** pick up a proton from the substrate to form the π-allylpalladium complexes **10**, which undergo further reactions with a nucleophile as expected; hence two nucleophiles are introduced to give the alkenes **11**.



Two reactions via the propargylpalladiums **2** (**12**), namely, hydrogenolysis to form alkynes **13** and β-H elimination to give enynes **14**, are known.



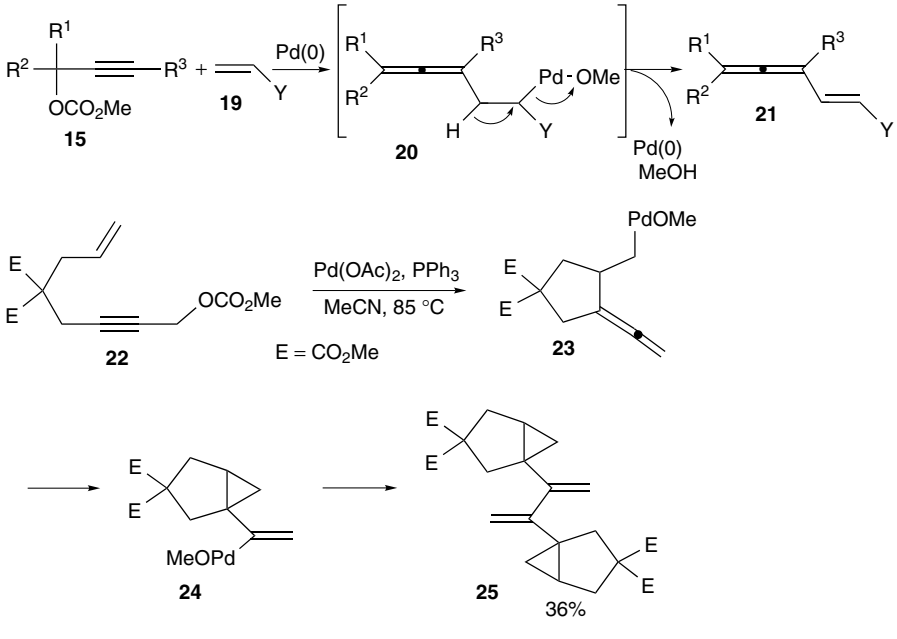
Several propargyl derivatives can be used for the Pd-catalyzed reactions, but they have different reactivities. Although propargyl alcohols are most easily available, they are less reactive substrates. Their esters such as acetates, carbonates, and phosphates are reactive, however. Propargyl carbonates **15** undergo various Pd-catalyzed reactions smoothly, especially under neutral conditions, because the σ-allenyl(methoxy)palladiums **16** are generated, which pick up a proton from pronucleophiles. Also 2-(1-alkynyl)oxiranes **17** undergo facile reactions under neutral conditions by forming the alkoxyallenylpalladium complexes **18** as an intermediate.



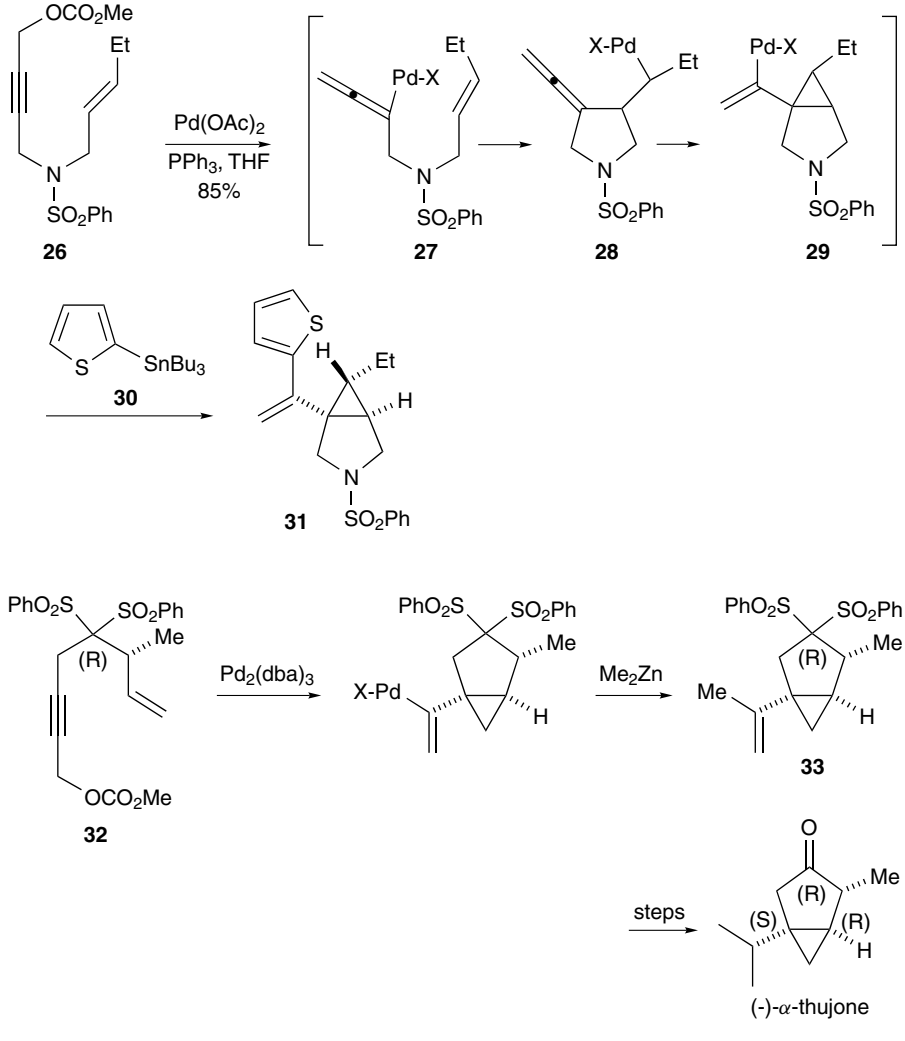
6.2 Reactions via Insertion of Alkenes and Alkynes

Smooth insertion of alkene **19** into the σ-allenylpalladium bond generates **20**, and subsequent β-H elimination affords 1,2,4-trienes **21**.

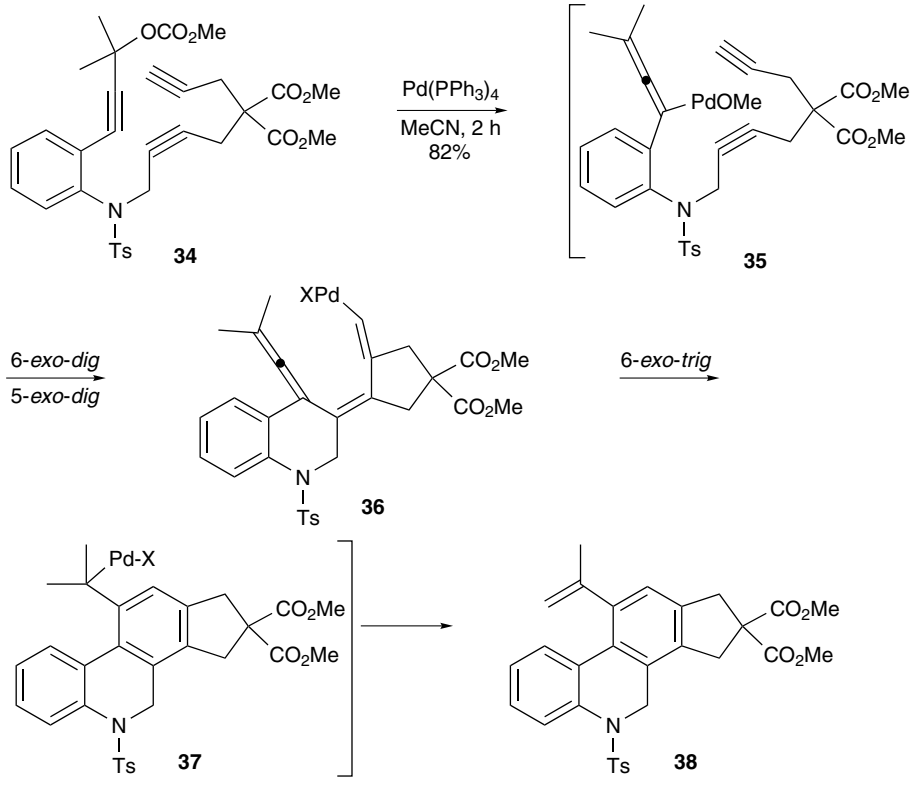
Intramolecular domino reactions proceed smoothly to afford cyclic compounds [2]. Domino 5-*exo* cyclization of the carbonate **22** generated the allenyl intermediate **23**, and 3-*exo* cyclization of **23** gave the cyclopropane **24**, which was converted to a dimeric product **25** [3].



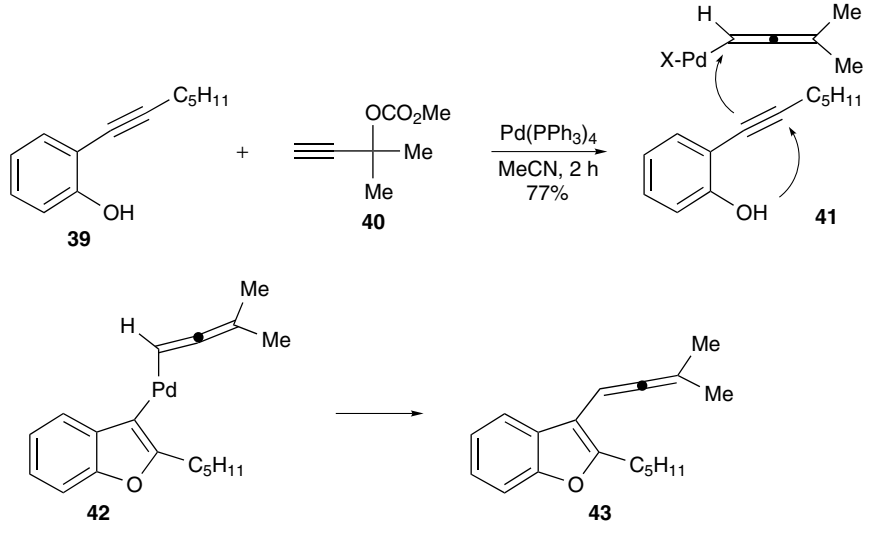
The allenylpalladium **27**, formed from the carbonate **26**, undergoes 5-*exo* cyclization to give **28** and its 3-*exo* cyclization, without β-H elimination, generates the bicyclo[3.1.0]hexane system **29**, which has no β-hydrogen to be eliminated. Thus transmetallation of **29** with the tin reagent **30**, followed by reductive elimination affords the azabicyclo[3.1.0]hexane **31** diastereoselectively [4]. The synthesis of (−)-α-thujone was achieved by diastereoselective domino cyclization of the chiral carbonate **32**, and trapping with dimethylzinc to give **33** as a key reaction [5].



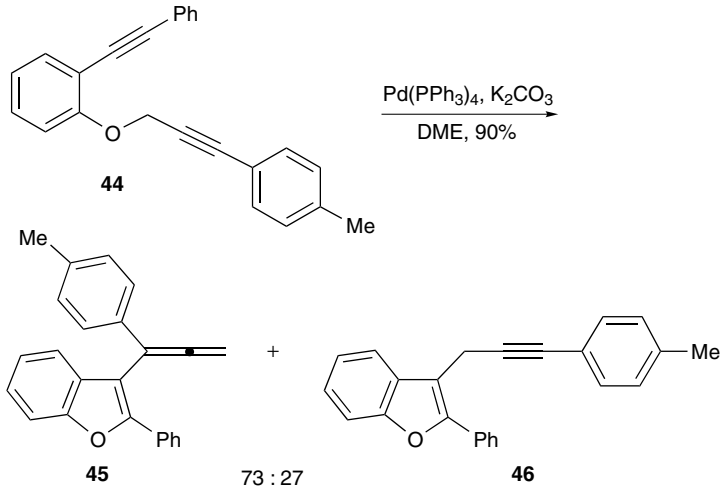
Insertion of triple bonds generates the 1,3,4-trienylpalladium intermediates **4**, which undergo further transformations. Domino cyclizations of the propargyl carbonate **34** with two more triple bonds provided **38** smoothly in surprisingly high yield (82 %). The reaction is understood by 6-*exo-dig* and 5-*exo-dig* cyclizations of **35** to generate **36**, followed by 6-*exo-trig* cyclization to give **37**. The β-H elimination gave rise to **38** [6].



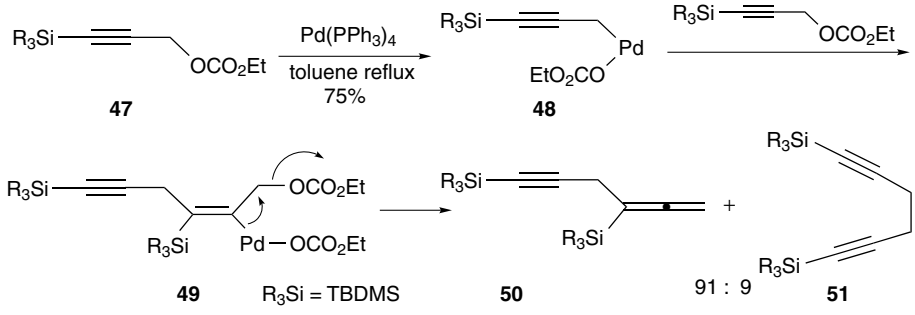
The Pd-catalyzed reaction of *o*-alkynylphenol **39** with tertiaryl propargyl carbonate **40** gave the 2-substituted 3-allenylbenzo[*b*]furan **43** under neutral conditions. Attack of phenoxide anion to the triple bond from the opposite side of σ-allenylpalladium intermediate as shown by **41** generates allenyl(benzofuryl)palladium intermediate **42**, and the coupling product **43** is formed by reductive elimination [7].



Similarly 2-substituted 3-allenylbenzo[*b*]furan **45** was prepared by the Pd-catalyzed reaction of the propargyl *o*-(alkynyl)phenyl ether **44**. The isomer **46** was a minor product [8].

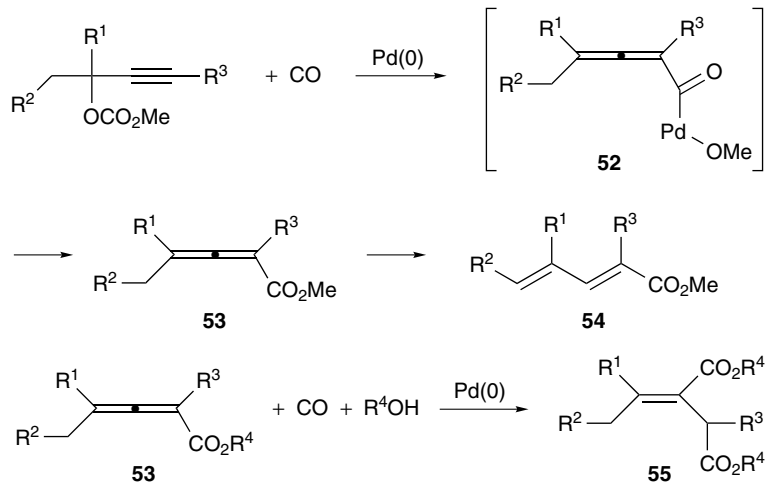


Propargyl ethyl carbonate **47** substituted with bulky TBDMS group underwent an interesting reductive coupling via propargylpalladium intermediate to give the allenylalkyne **50** as a major product and the 1,5-diyne **51** as a minor product. The reaction is explained by insertion of the triple bond of **47** to propargylpalladium **48** to generate **49**, followed by β-carbonate elimination to afford **50** [9].

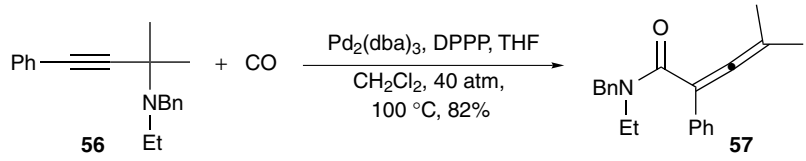


6.3 Carbonylations

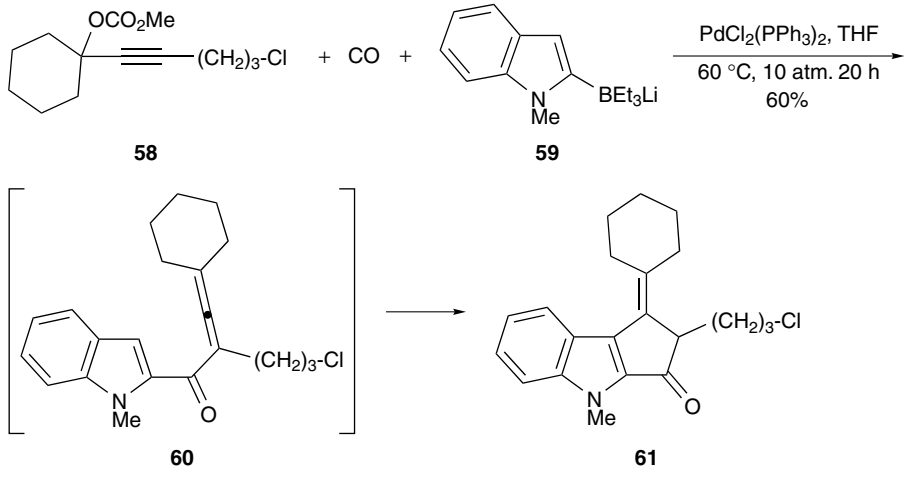
Propargyl compounds undergo facile mono- and dicarbonylations depending on reaction conditions [10]. Monocarbonylation proceeds under mild conditions using propargyl carbonates [11]. Firstly CO insertion into the allenylpalladium intermediate generates the acylpalladium **52**, which reacts with alcohol to give the 2,3-alkadienoate **53**. Under certain conditions, isomerization of **53** to the 2,4-dienoate **54** occurs. Carbonylation of propargyl carbonates under mild conditions stops at this stage. Under a high pressure of CO, or in the presence of an activating group (for example, $R^3 = CO_2R$), further attack of CO at the central sp carbon of the allenyl system in **53** takes place to give the diester **55**.



The carbonylation of the propargylamine **56** in the presence of TsOH gave 2,3-alkadienamides **57** by insertion of CO with cleavage of propargylic C—N bond [12].

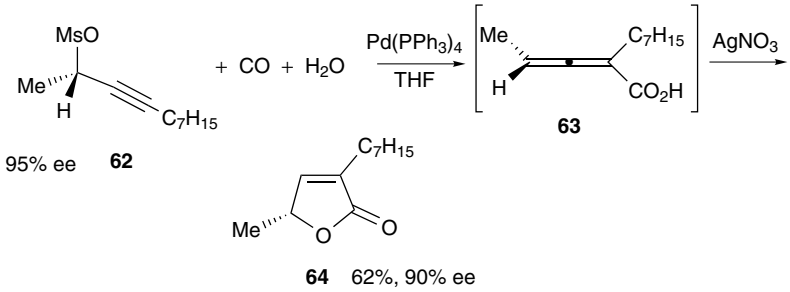


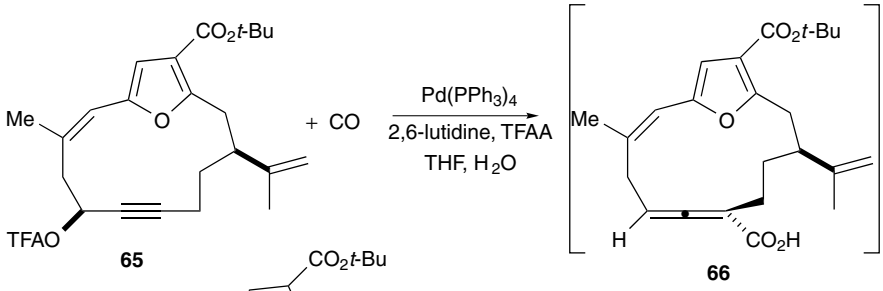
Cross-coupling of the propargyl carbonate **58** with the indolylborate **59** gave the allenyl ketone **60**, which, without isolation, underwent 1,4-addition to the allenyl ketone in **60** to afford the cyclopenta[*b*]indole derivative **61** [13].

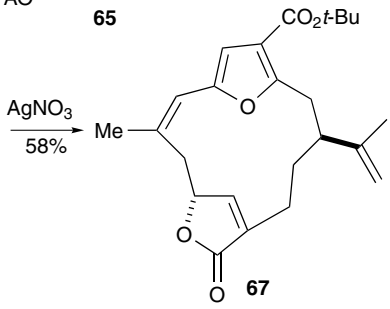


The allenic acid **63**, obtained by the carbonylation of the chiral propargyl mesylate **62**, was converted stereospecifically to the butenolide **64** by treatment with $AgNO_3$ as a catalyst. Racemization occurred by the carbonylation of the

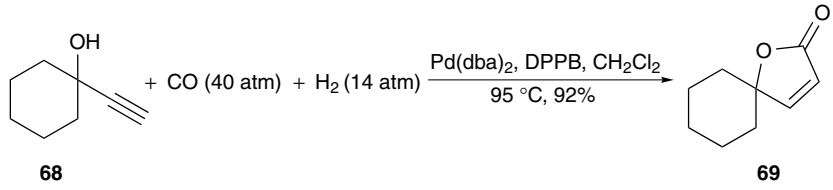
corresponding propargyl carbonate [14]. Carbonylation of the cyclic propargylic trifluoroacetate **65** gave the dienoic acid **66** with net inversion of configuration, which was converted to the butenolide **67** [15].





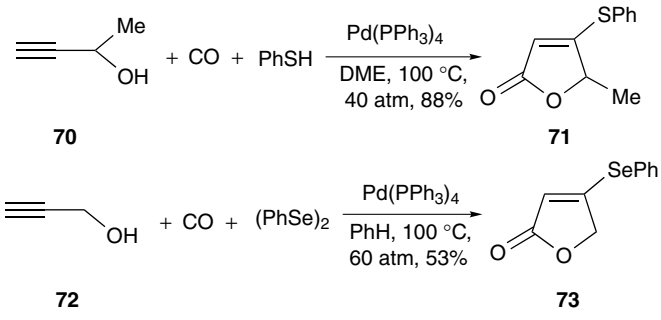


Propargyl alcohols are less reactive than their esters. Carbonylation of the tertiary propargyl alcohol **68** at 95 °C under pressure of CO and H_2 and neutral conditions using DPPB provided the 2(5*H*)-furanone **69**. It was claimed that H_2 was required for this reaction [16].

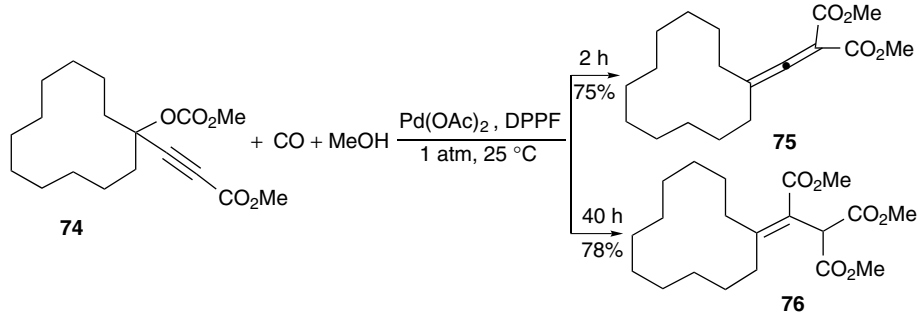


Carbonylation of propargyl alcohol **70** in the presence of thiophenol unexpectedly gave rise to 3-(phenylthio)-2-buten-4-olide **71** in high yield [17]. Similarly, 3-(phenyseleno)-2-buten-4-olide **73** was obtained from propargyl alcohol (**72**) in the presence of diphenyl diselenide [18].

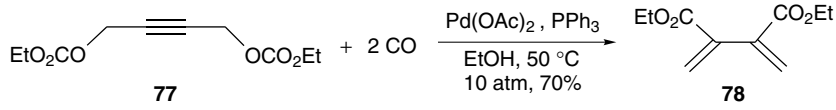
By introduction of an ester group to an acetylenic terminus of propargyl carbonates, facile dicarbonylation becomes a main path. The monocarbonylation product



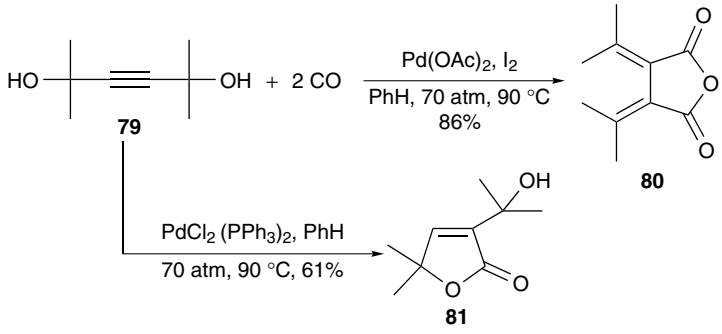
75 of the cyclododecyl derivative **74** was isolated when the reaction was stopped in 1 h. Further carbonylation of the diester **75** for 40 h gave the triester **76**. Bidentate ligands DPPP and DPPF are the most effective for the dicarbonylation [19].



Butyne-1,4-diol derivatives undergo dicarbonylation of different types. A simple synthetic method of bis(methylene)succinate **78** is the carbonylation of the dicarbonate of but-2-yne-1,4-diol (**77**) at 50 °C [20].

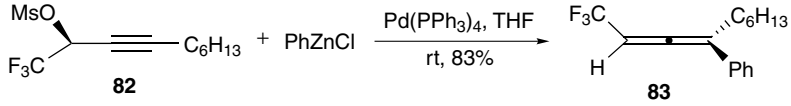


Fulgide (isopropylidenesuccinic anhydride derivative) **80** was obtained from **79** in benzene [21]. The fulgide formation was improved by using $Pd(OAc)_2$ as a catalyst in the presence of iodine. When $PdCl_2(PPh_3)_2$ was used as the catalyst, the furanone **81** was obtained in 61 % yield [22].

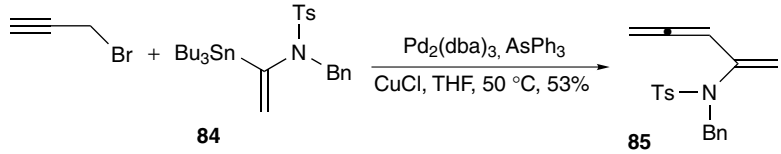


6.4 Reactions of Main Group Metal Compounds

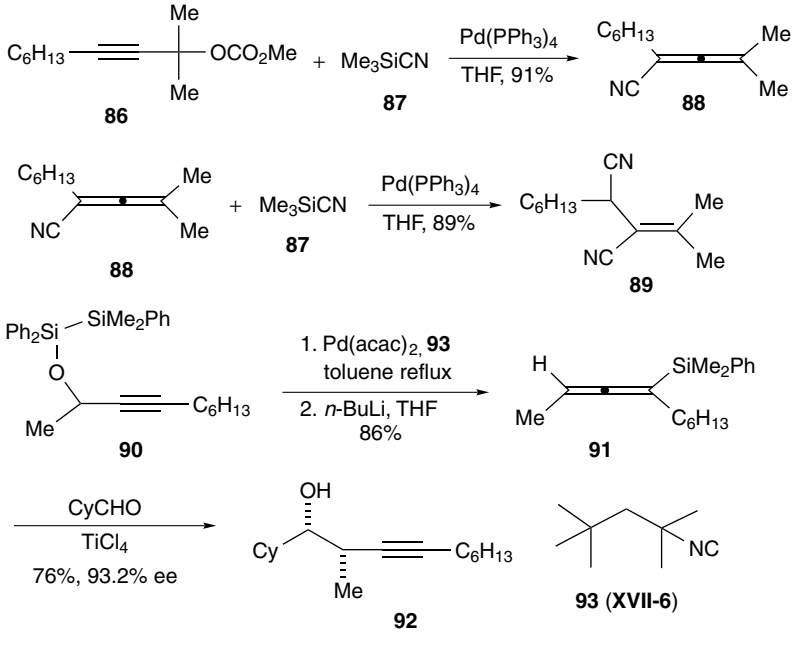
Reactions of propargyl halides, carbonates, acetates, mesylates, and phosphates with hard carbon nucleophiles MR (M = Mg, Zn, B, Si) give allenyl derivatives [23]. Propargyl acetates react with phenylzinc chloride smoothly. The reaction of the chiral propargyl mesylate **82**, bearing 1-trifluoromethyl group, with PhZnCl proceeded with high *anti* selectivity to give **83** [24].



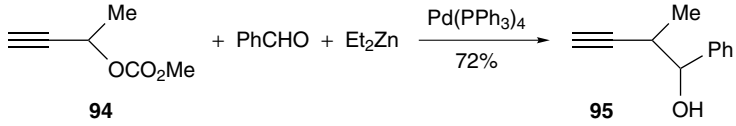
The functionalized enamine **85** was prepared by coupling of propargyl bromide with the α-stannyl enamide **84** using $AsPh_3$ as a ligand and CuCl as an additive [25].



The cyanoallene **88** was prepared by the reaction of the carbonate **86** with trimethylsilyl cyanide (**87**). In the presence of excess **87**, the dicyanated product **89** was obtained in high yield [26]. Treatment of the chiral (*R*)-disilanyl ether **90** with the Pd catalyst coordinated by hindered isonitrile **93** (**XVII-6**) yielded the allenylsilane **91**, which was trapped with cyclohexanecarboxaldehyde to give *syn*-homopropargylic alcohol **92** with 93.3 % ee with high diastereoselectivity [27].

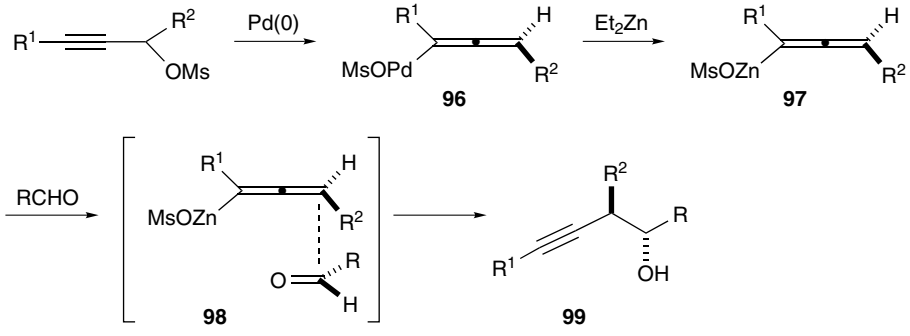


No cross-coupling of propargyl compound **94** with an excess of Et_2Zn occurred. Instead, a nucleophilic propargyl species is generated by 'umpolung' and reacts with benzaldehyde to give **95** [28].

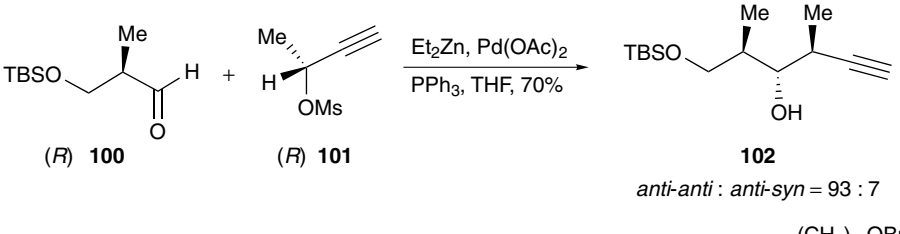


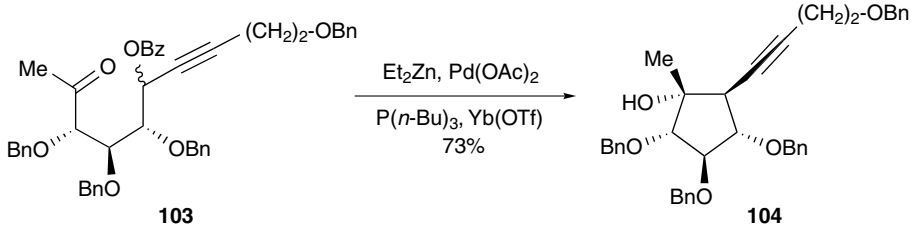
94 **95**

Further studies on the reaction of propargyl compounds with Et_2Zn have been carried out using chiral propargyl mesylates [29]. Treatment of allenylpalladiums **96** with Et_2Zn generates the allenylzinc reagents **97**, which are nucleophilic and attack the carbonyl group to give homopropargyl alcohols **99** with high stereoselectivity as shown by **98**.

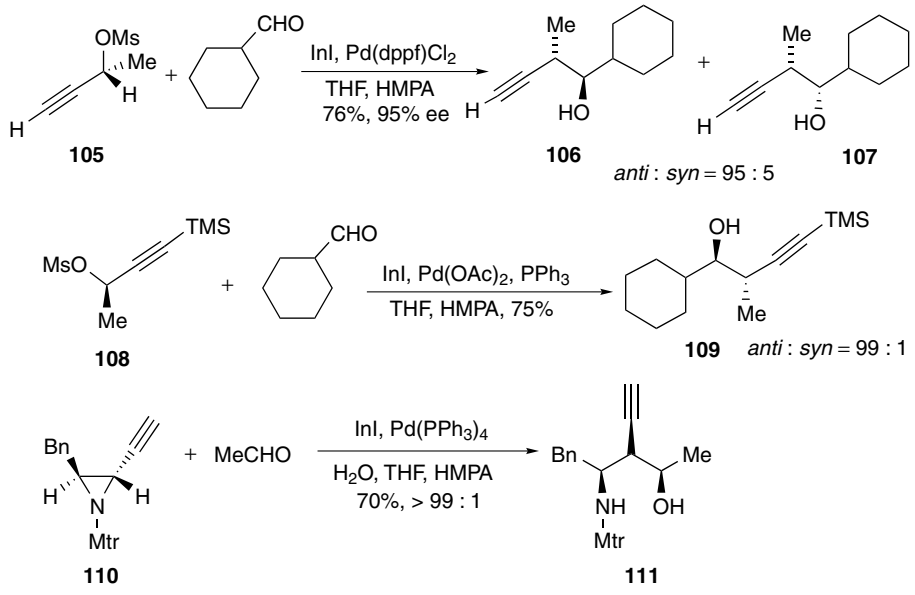


Under carefully controlled conditions, the reaction proceeds with excellent stereocontrol. Addition of the allenylzinc reagent derived from the (*R*)-mesylate **101** to (*R*)-aldehyde **100** proceeded at −20 °C to give the *anti*–*anti* triad **102** in 70 % yield with a small amount of the *anti*–*syn* isomer [30]. As an intramolecular version, the propargyl benzoate **103** attacked the methyl ketone to afford the cyclopentanol **104** using Et_2Zn and an Lewis acid with high stereocontrol. The most effective Lewis acid was $Yb(OTf)_3$. A good catalyst was $Pd(OAc)_2$-P(*n*-Bu)$_3$ [31].



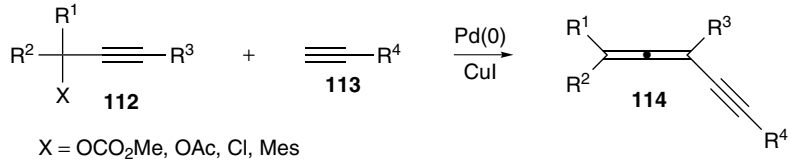


Allenylindiums are prepared by transmetallation of allenylpalladiums with indium iodide and used for the reaction with aldehydes to afford homopropargyl alcohols. Addition of an transient allenylindium reagent derived from the chiral mesylate **105** to cyclohexanecarboxaldehyde produced the *anti* form **106** with high selectivity using $Pd(dppf)Cl_2$ as a catalyst [32], but $Pd(OAc)_2$-PPh_3 was found to be a superior catalyst in the reaction of the mesylate **108** with cyclohexanecarboxaldehyde to give the *anti* form **109** with higher selectivity [33]. An allenylindium reagent bearing a protected amino group was obtained from 3-alkyl-2-ethynylaziridine **110** in high yields, and stereoselective addition of the allenylindium to acetaldehyde afforded the 2-ethynyl-1,3-amino alcohol **111** bearing three chiral centers in good yields [34].



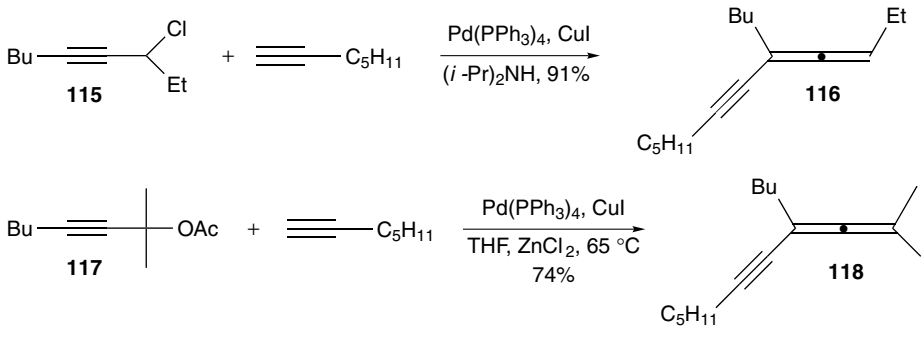
6.5 Reactions of Terminal Alkynes; Formation of 1,2-Alkadien-4-ynes

1,2-Dien-4-ynes (allenylacetylenes) **114** can be prepared in good yields by Pd-catalyzed coupling of terminal alkynes **113** with propargyl compounds **112** such as carbonates, acetates, and halides in the presence of a catalytic amount of CuI as a cocatalyst. The Pd/Cu-catalyzed coupling of propargyl carbonates proceeds rapidly at room temperature [35].



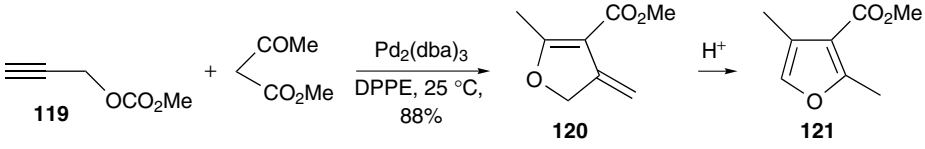
5-Butyldodeca-3,4-dien-6-yne (**116**) was obtained in 91 % yield by the reaction of 3-chloro-4-nonyne (**115**) with 1-heptyne in diisopropylamine. Coupling of the

propargylic acetate **117** with 1-heptyne is possible in the presence of 3 equivalents of zinc chloride with or without using CuI to give the 1,2-alkadien-4-yne **118** [36].

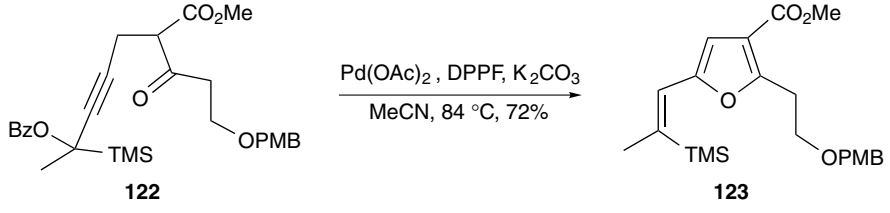


6.6 Reactions of Nucleophiles on Central sp Carbon of Allenylpalladium Intermediates

In contrast to facile Pd(0)-catalyzed reactions of allyl esters with soft carbon nucleophiles via π-allylpalladium intermediate, propargyl esters such as acetate are less reactive toward soft carbon nucleophiles. However, β-keto esters and malonates react under neutral conditions with propargyl carbonates using DPPE as a ligand [37]. Acetoacetate reacts with methyl propargyl carbonate (**119**) in THF at room temperature to afford 4-(methoxycarbonyl)-5-methyl-3-methylene-2,3-dihydrofuran (**120**) in 88 % yield. The furan **121** was obtained by isomerization of the methylenefuran **120** under slightly acidic conditions.

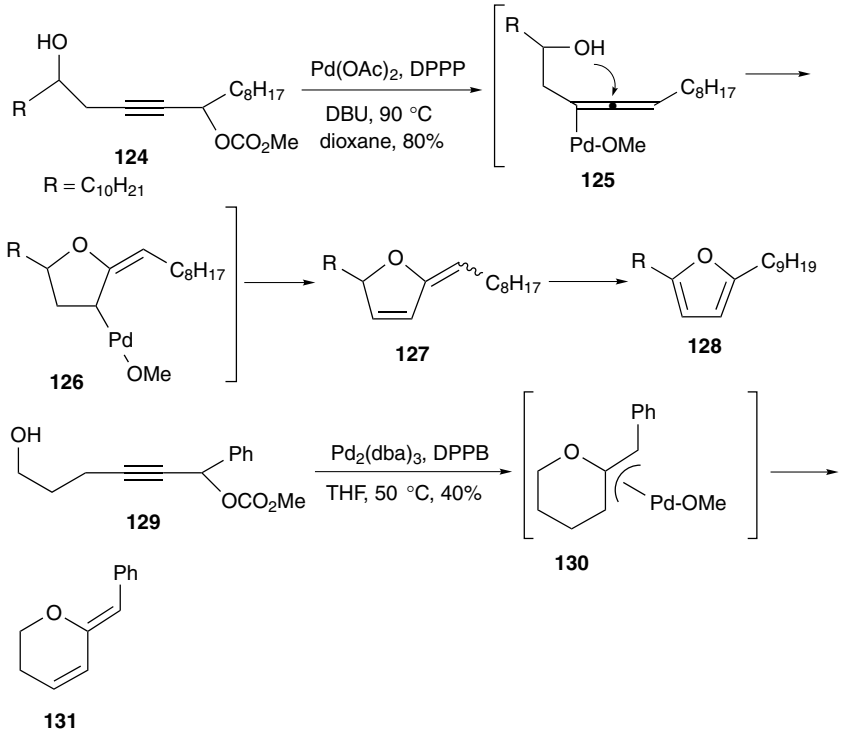


The furan **123** was obtained by intramolecular reaction of the propargyl benzoate with an enolate of the β-keto ester in **122** using DPPF as a ligand, and the reaction was applied to the synthesis of the C(1)-C(18) segment of lophotoxin [38].

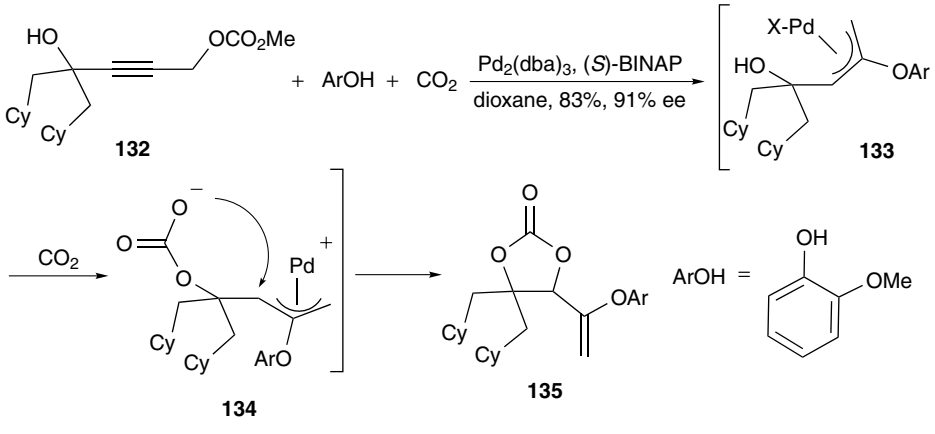


Propargyl carbonate **124** which has a hydroxy group at C-5 undergoes cyclization by attack of the hydroxy group at the central carbon of the allenyl system **125**. The intermediary σ-allylpalladium complex **126** undergoes β-H elimination to give the diene **127**, which is converted to the more stable furan **128** in 80 %

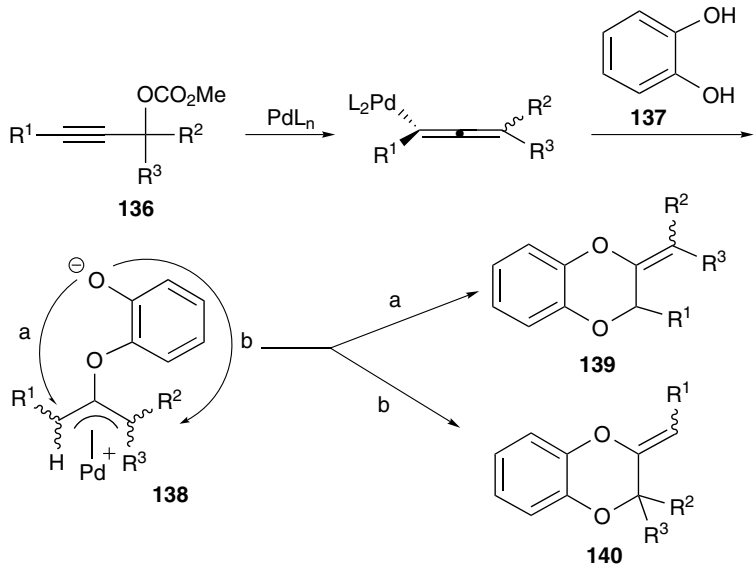
yield using DPPP and DBU [1a, p. 2608]. Similarly, the unsaturated dihydropyran **131** was obtained from 1-phenyl-6-hydroxy-2-hexynyl carbonate (**129**) via the π-allylpalladium intermediate **130** [39].



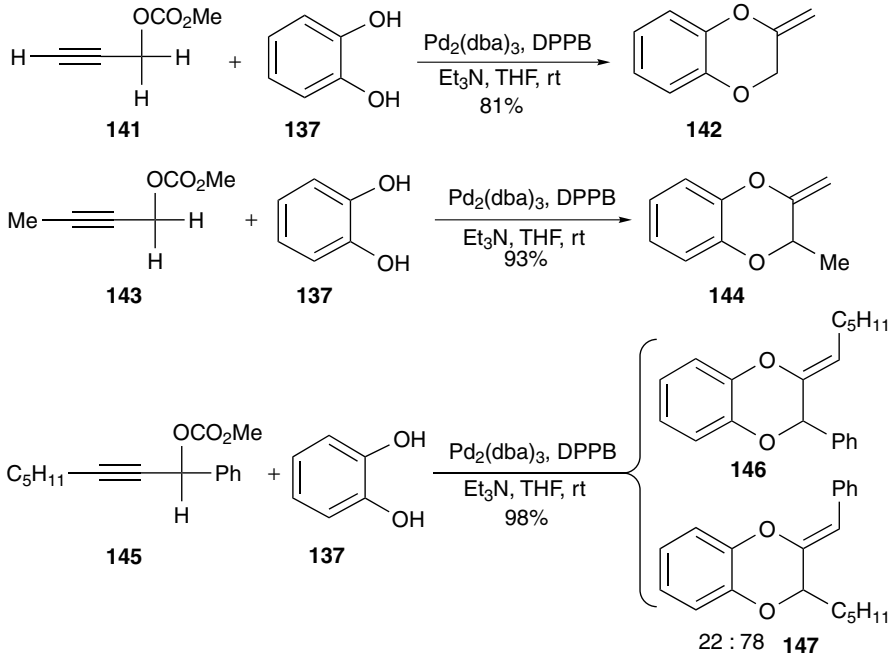
The asymmetric three-component reaction of the carbonate **132** with *o*-methoxyphenol under CO_2 atmosphere afforded the cyclic carbonate **135** in 83 % yield with 91 % ee using (*S*)-BINAP as a chiral ligand. In this reaction, the π-allylpalladium intermediate **133**, formed by the attack of phenol to the allenylpalladium intermediate, reacts with CO_2 to generate the carbonate **134**. Then intramolecular attack of the carbonate anion to the π-allylpalladium terminus provides the cyclic carbonate **135** [40].



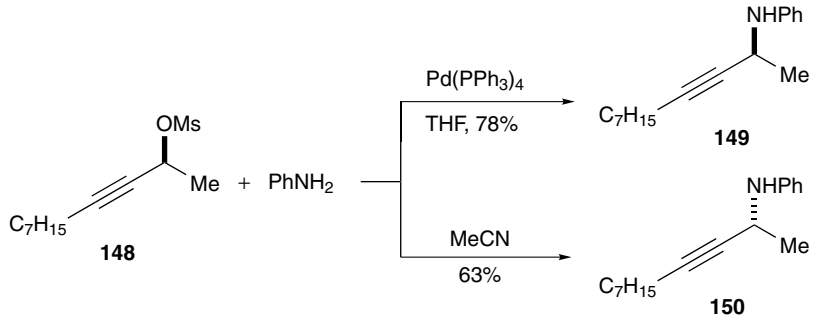
2,3-Dihydro-1,4-benzodioxines **139** and **140** are prepared by the reaction of propargyl carbonates **136** with catechol (**137**) by attacking either terminus of the π-allylpalladium intermediate **138**.



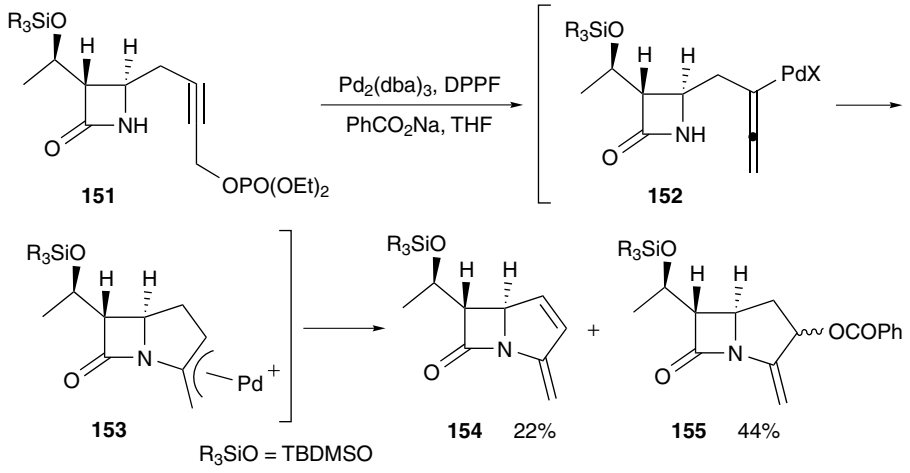
The reaction of propargyl carbonate (**141**) with catechol (**137**) using DPPB gave 2-methylenebenzodioxin **142**. The reaction of methyl-substituted alkynyl carbonate **143** with **137** afforded 3-methylbenzodioxin **144**, and a mixture of **146** and **147** was obtained from **145** in a ratio of 22 : 78 [41].



The reaction of propargylic mesylate **148** with aniline proceeded without a catalyst to afford the propargylamine **150** with inversion of configuration. On the other hand, the Pd-catalyzed reaction of **148** gave **149** with retention of configuration [42].

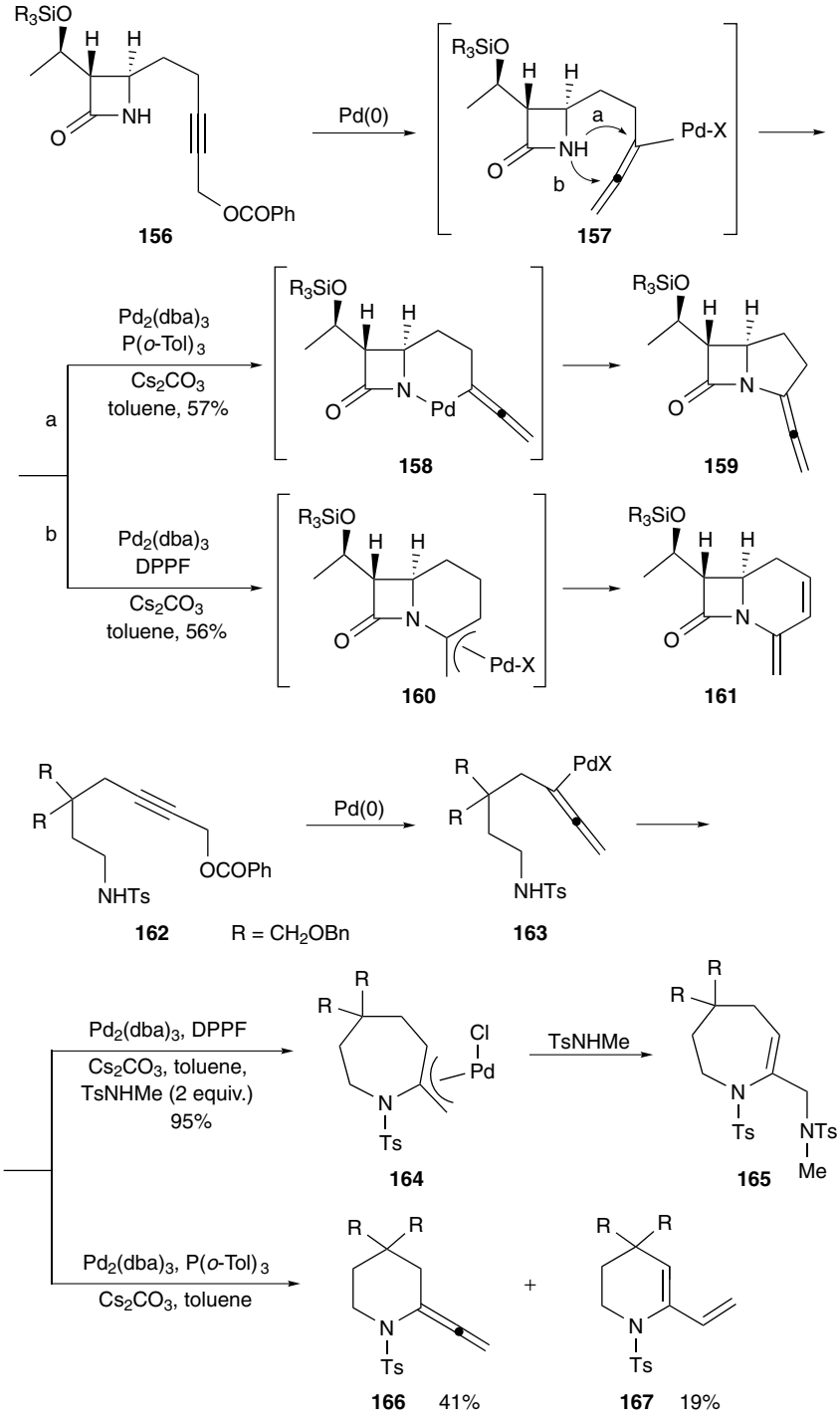


In some intramolecular reactions, the amino group attacks either the sp^2 or sp carbon of σ-allenylpalladium intermediates depending on the monodentate or bidentate ligand being used. Carbapenam skeletons are prepared by intramolecular attack of 6-aminopropargyl compounds. Treatment of the propargyl phosphate **151** having a β-lactam moiety with $Pd_2(dba)_3$ and bidentate ligand (DPPF) afforded the carbapenam skeletons **154** and **155**. In this reaction, the lactam nitrogen attacked the central sp carbon of the σ-allenylpalladium **152** as expected and the π-allylpalladium intermediate **153** was generated.



In the reaction of the propargyl benzoate **156**, attack of the lactam nitrogen occurred in two ways as shown by **157** depending on the ligands used. The carbapenam **159** was formed by attack of the amino nitrogen to Pd-X to form the palladacycle **158**, followed by reductive elimination by using monodentate ligand P(*o*-Tol)$_3$ and Cs_2CO_3. On the other hand, the carbacepham **161** was obtained via the formation of π-allylpalladium **160** when DPPF was used [43].

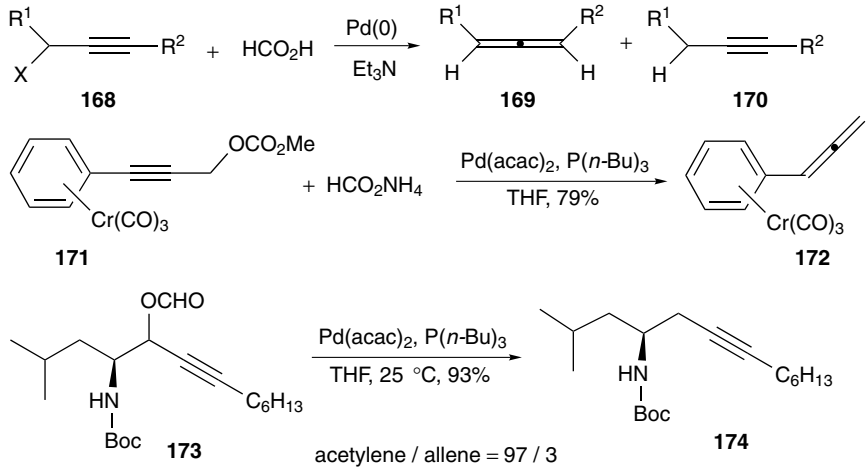
Treatment of the propargyl benzoate **162** with $Pd_2(dba)_3$ and DPPF in the presence of *N*-alkyltosylamide generated the allenylpalladium **163**, and the π-allylpalladium intermediate **164** was generated by the attack of the amino group.



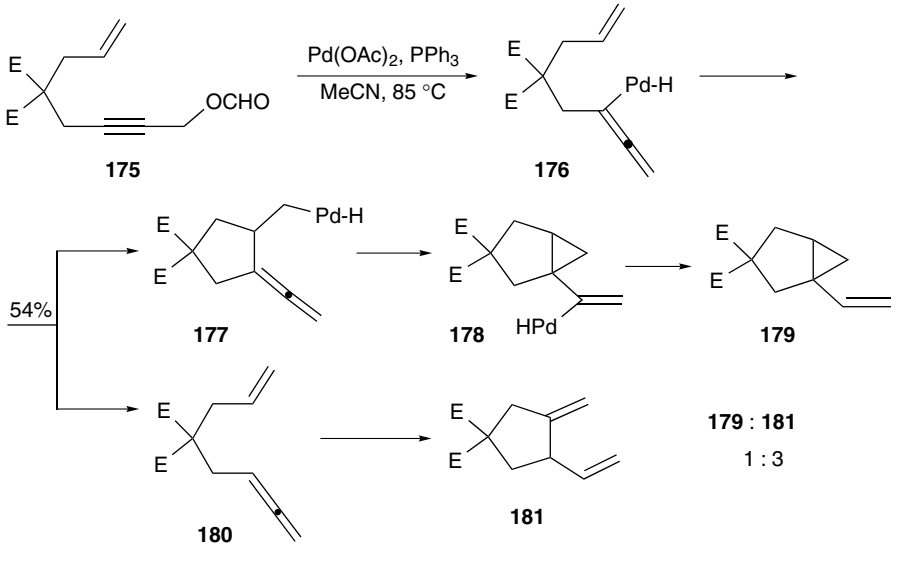
Finally the azepine derivative **165** was obtained in 95 % yield by the attack of *N*-alkyltosylamide to the π-allylpalladium intermediate **164**. On the other hand, the 2-allenyl- and 2-vinylpiperidines **166** and **167** were obtained from **162** when P(*o*-Tol)$_3$ was used [44].

6.7 Hydrogenolysis and Elimination of Propargyl Compounds

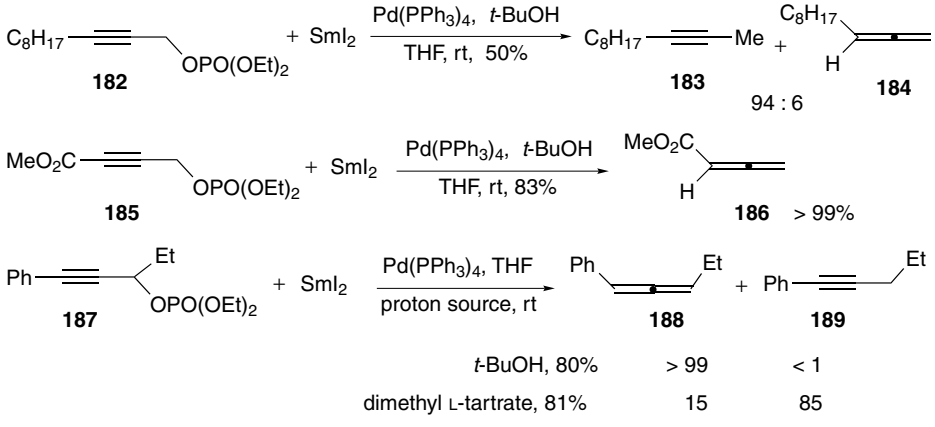
Allenes **169** and alkynes **170** are prepared by hydrogenolysis of propargyl compounds with several hydrides. Triethylammonium formate is used most conveniently under mild conditions [45]. Chromium tricarbonyl-complexed phenylallene **172** was prepared from the carbonate **171** [46]. The alkyne **174** was obtained selectively from the propargyl formate **173** having an amino group [47].



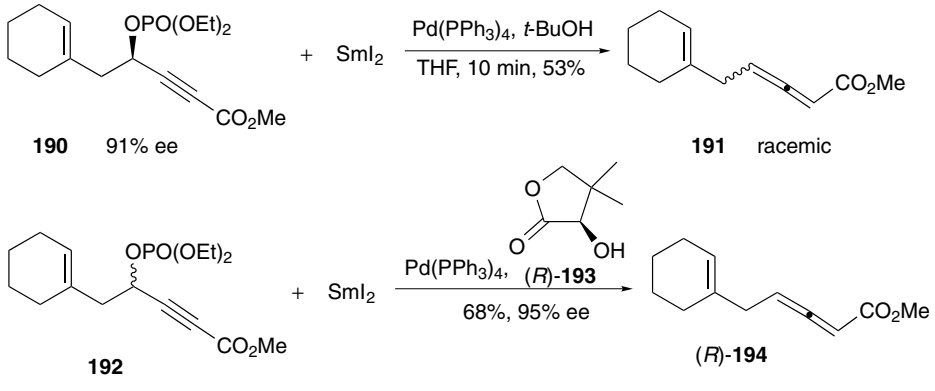
Reaction of propargyl formate **175** affords two products **179** and **181** depending on the kind of intermediates being subjected to hydrogenolysis with formate. When 5-*exo* cyclization of **176** and 3-*exo* cyclization of **177** to give the cyclopropane **178** occurred before the hydrogenolysis, the bicyclo[3.1.0]hexane **179** was obtained. On the other hand, the cyclopentane **181** was formed by hydrogenolysis of **176**, and the cyclopentane **181** was obtained by Pd-catalyzed cyclization of **180** [3].



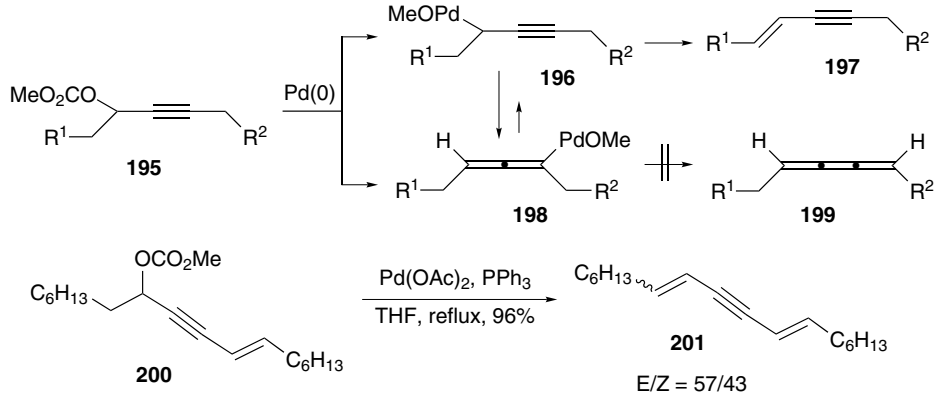
Pd-catalyzed reduction of propargyl compounds with SmI_2 is possible in the presence of proton sources [48]. Yoshida and Mikami reported a dramatic change of chemoselectivity in the reduction of propargyl phosphates with SmI_2 and various proton sources [49]. The alkyne **183** was a main product from the primary propargyl phosphate **182** using *t*-BuOH as a proton source. The allene **184** was a minor product. The propargyl phosphate **185** bearing an ester group gave the allene **186** exclusively. The chemoselectivity of the reduction of secondary phosphate **187** depends on the proton sources. The allene **188** was obtained by the use of *t*-BuOH, and the alkyne **189** was a major product when dimethyl L-tartrate was used.



Furthermore Mikami and Yoshida have studied regio- and enantioselective synthesis of allenic esters by Sm(II)-mediated reduction of propargyl compounds. Attempted chirality transfer by SmI_2 reduction of the optically active propargylic phosphate **190** (91 % ee) provided the racemic compound **191**. Then they carried out dynamic kinetic resolution based on asymmetric protonation using racemic propargyl phosphate **192**. Among several chiral proton sources, (*R*)-pantolactone **193** gave the optically active allenic ester **194** with the highest % ee (95 % ee). Interestingly the yield of **194** was 68 %, which is higher than the maximum yield (50 %) obtained by ordinary kinetic resolution. The efficient asymmetric protonation is attained due to the chelation of the chiral alcohol **193** with Sm (III) intermediate species possessing high Lewis acidity and oxophilicity [50].



When propargyl carbonates **195** are treated with a Pd catalyst in the absence of other reactants, β-H elimination from the propargylpalladium intermediates **196** occurs to give conjugated enynes **197**. Formation of cumulative 1,2,3-alkatrienes **199** from the allenylpalladiums **198** does not take place. Preparation of the conjugated ene–yne–ene system **201** in high yield from the propargyl carbonate **200** is an example [51].



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Chapter 7

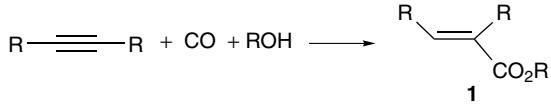
Pd(0)- and Pd(II)-Catalyzed Reactions of Alkynes and Benzynes

7.1 Reactions of Alkynes

Alkynes undergo a variety of reactions using either Pd(II) or Pd(0), and each topic appears in separate chapters. Oxidative reactions of alkynes with Pd(II) are surveyed in Chapter 2.6, and Pd(0)-catalyzed reaction of alkynes with organic halides are summarized in Chapter 3.4, and other typical reactions of alkynes are treated in this chapter. Since benzynes are regarded as reactive alkynes, they are surveyed in this chapter.

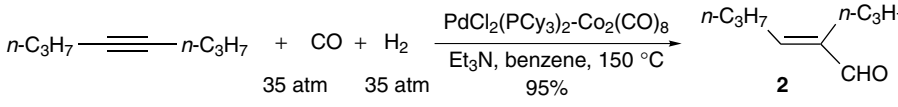
7.1.1 Carbonylation

Hydroesterification of alkynes proceeds smoothly using $PdCl_2(PPh_3)_2$ as a standard catalyst, offering a convenient synthetic method of α,β-unsaturated esters **1**. Carbonylation of 1-alkynes and asymmetric alkynes yields a mixture of regioisomers.



1

In contrast to facile hydroformylation of alkenes, only a few successful examples of hydroformylation of alkynes have been reported. Hidai and co-workers have found that $PdCl_2(PCy_3)_2$ is an effective catalyst for hydroformylation of alkynes. Furthermore, a bimetallic catalyst of $PdCl_2(PCy_3)_2$ and $Co_2(CO)_8$ showed remarkably high catalytic activity. Reaction of 4-octyne under CO and H_2 pressure (35 atm each) at 150 °C in the presence of Et_3N produced the 2-*n*-propyl-2-hexenal (**2**) in 95 % yield [1]. $Co_2(CO)_8$ alone is inactive. Also no hydroformylation of alkenes occurred with this bimetallic catalyst.



2

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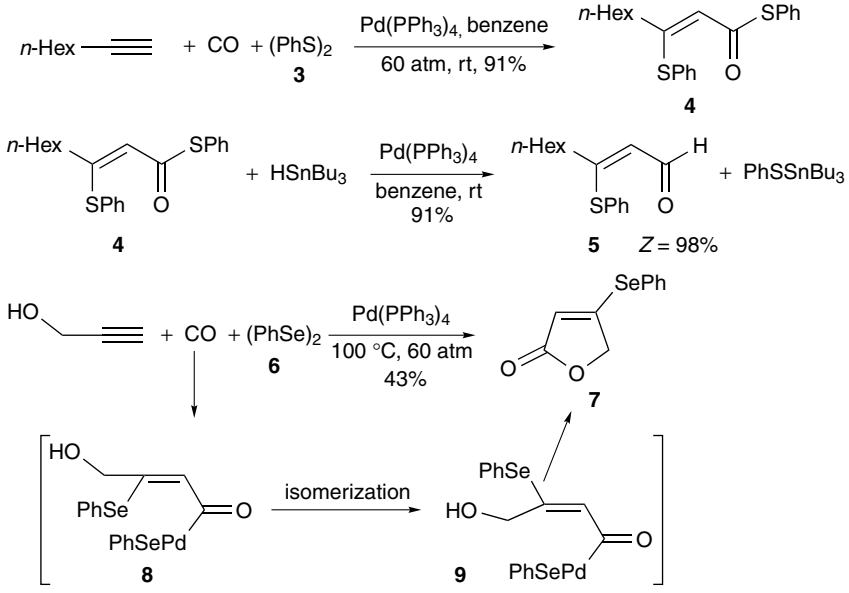
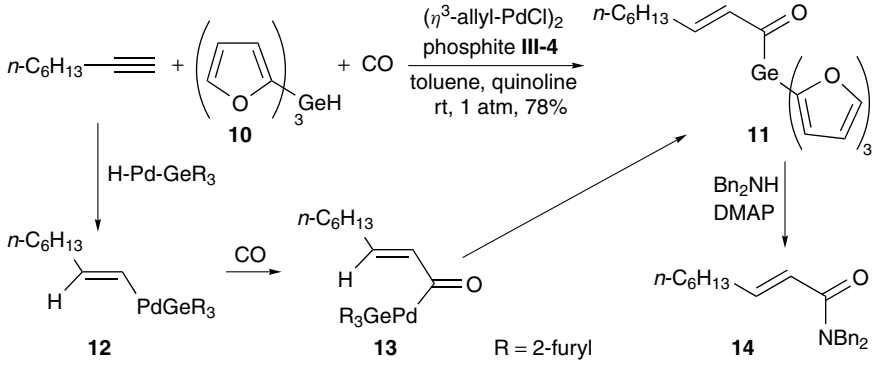
Carbonylation proceeds in the presence of chalcogen compounds without poisoning Pd catalysts. Pd-catalyzed stereo- and regioselective carbonylative double thiolation of 1-octyne with diphenyl disulfide (**3**) afforded the (*Z*)-β-(phenylthio)-α,β-unsaturated thioester **4** [2]. The thioester **4** can be converted to 3-(phenylthio)-2-alkenal **5** by Pd-catalyzed reduction with $HSnBu_3$ under mild conditions [3]. When propargyl alcohol was subjected to the carbonylation in the presence of either diphenyl diselenide (**6**) or disulfide **3**, 3-phenylselenobutenolide **7** or 3-phenylthiobutenolide was obtained. The transformation involves isomerization of the acylpalladium intermediate **8** to **9** [4].

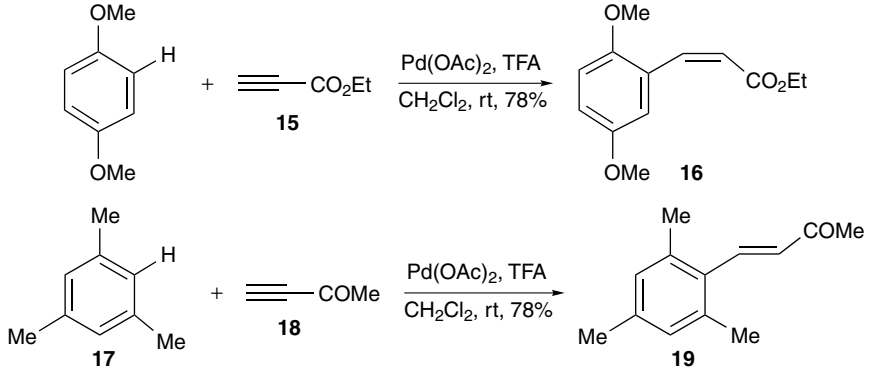


As a related reaction, hydrocarbometallation of alkynes takes place by Pd-catalyzed reaction of 1-alkyne with trifurylgermane (**10**) and CO under mild conditions in the presence of a catalytic amount of quinoline to give the acylgermane **11** using tri(2,4-di-*t*-butylphenyl) phosphite **III-4** as a ligand. The reaction is explained by hydropalladation of alkyne to generate **12**, and the acylpalladium **13** is formed by CO insertion. The 2-nonenamide **14** was prepared by DMAP-catalyzed reaction of **11** with *N*,*N*-dibenzylamine [5].

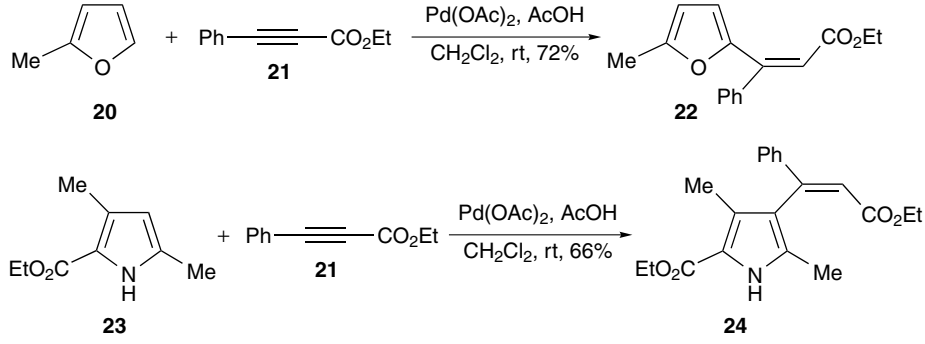


7.1.2 Hydroarylation

Pd-catalyzed hydroarylation of alkynes via aromatic C—H bond activation has been reported by Fujiwara. The reaction offers a good synthetic method of arylalkenes, which are usually prepared by Heck reaction of alkenes. Electron-rich arenes bearing more than one OH, OMe, and alkyl groups react with electron-deficient alkynes [6]. The reaction proceeds with a catalytic amount of $Pd(OAc)_2$ in trifluoroacetic acid (TFA) at room temperature. Hydroarylation of ethyl propiolate (**15**) with *p*-dimethoxybenzene yielded ethyl (*Z*)-3-(2,5-dimethoxyphenyl)-2-propenoate (**16**). Mesitylene (**17**) is an active arene and the reaction of **17** with 3-butyn-2-one (**18**) afforded the unsaturated ketone **19** which has *E*-form [7].

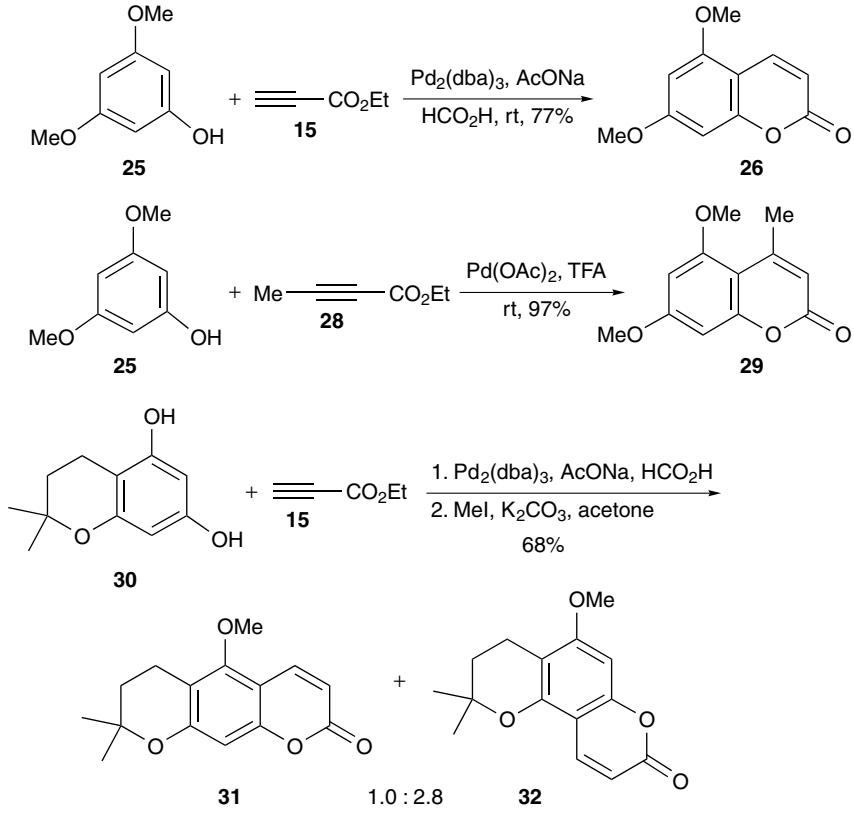


Electron-rich heterocycles such as furans and pyrroles undergo facile reactions. The furan **20** is an active compound and the reaction with ethyl phenylpropiolate (**21**) proceeded at room temperature in dichloromethane in the presence of AcOH, instead of TFA, to give rise to (*Z*)-2-alkenylfuran **22** exclusively [8]. The 3-alkenylpyrrole **24** was obtained by the reaction of the trisubstituted pyrrole **23** with **21** [9].



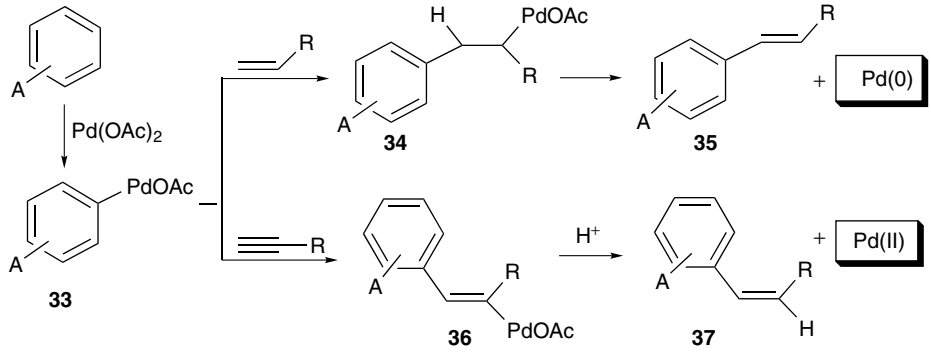
In 1996, Trost and Toste reported a new synthetic method of coumarins by the Pd-catalyzed reaction of electron-rich phenol with propiolate **15** at room temperature using $Pd_2(dba)_3$ in formic acid. 2,5-Dimethoxycoumarin (**26**) was obtained from 3,5-dimethoxyphenol (**25**) [10]. On the other hand, Fujiwara carried out the

preparation of the coumarin **29** from **25** and ethyl methylpropiolate (**28**) using $Pd(OAc)_2$ in trifluoroacetic acid [11]. The hydroarylation of ethyl propiolate (**15**) with the chroman derivative **30** proceeded in HCO_2H using $Pd_2(dba)_3$ and AcONa, and a mixture of **31** and **32** was obtained in a ratio of 1.0 : 2.8 [12]. Two groups, the groups of Fujiwara and Trost, used Pd(II) and Pd(0) catalysts, respectively, and the mechanism of their reactions should be different.

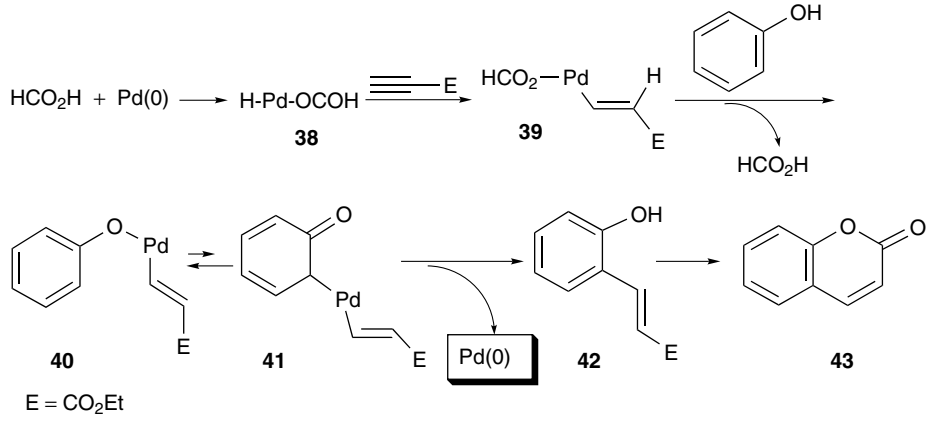


The Pd(II)-catalyzed hydroarylation of alkynes reported by Fujiwara can be explained by the following mechanism [6]. Fujiwara reported previously the oxidative coupling of benzene with alkenes using $Pd(OAc)_2$ and some oxidants in AcOH. In this reaction, phenylpalladium acetate **33** is formed at first, and insertion of alkene to **33** generates the alkylpalladium intermediate **34**. The reaction is terminated by β-H elimination to give **35** with generation of Pd(0). In order to make the reaction catalytic, Pd(0) is oxidized to Pd(II) by oxidants. This Pd(II)-promoted reaction is treated in Chapter 2.2.8. The Pd(II)-catalyzed reaction of arenes with alkynes proceeds by insertion of alkyne to form the alkenylpalladium intermediate **36**, which has no possibility of β-H elimination, and the reaction can be terminated only by protonolysis, giving **37**. At the same time, Pd(II) is regenerated, and hence the reaction proceeds catalytically without addition of oxidants and other reagents.

Trost and Toste explain their Pd(0)-catalyzed reaction by the following mechanism. First, reaction of Pd(0) and HCO_2H generates hydridopalladium **38**, and the vinylpalladium intermediate **39** is formed by insertion of alkyne, and either the

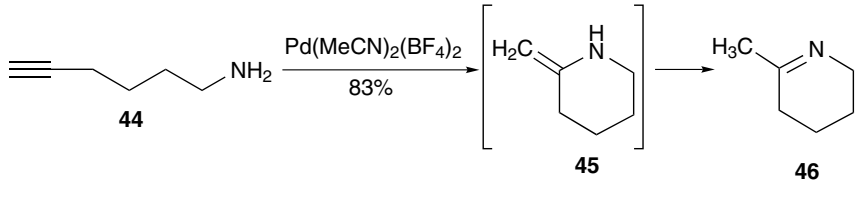


C-bound or O-bound vinylpalladium (**40** or **41**) is formed by the exchange reaction of **39** with phenol. Finally reductive elimination yields the hydroarylation product **42** and then coumarin **43** [12]. The hydroarylation reaction has been carried out with phenolic substrates, and it is interesting to know whether the Pd(0)-catalyzed reaction can be applied to non-phenolic substrates such as mesitylene or not, but so far no example has been given. On the other hand, Pd(II)-catalyzed hydroarylation with mesitylene proceeds smoothly.

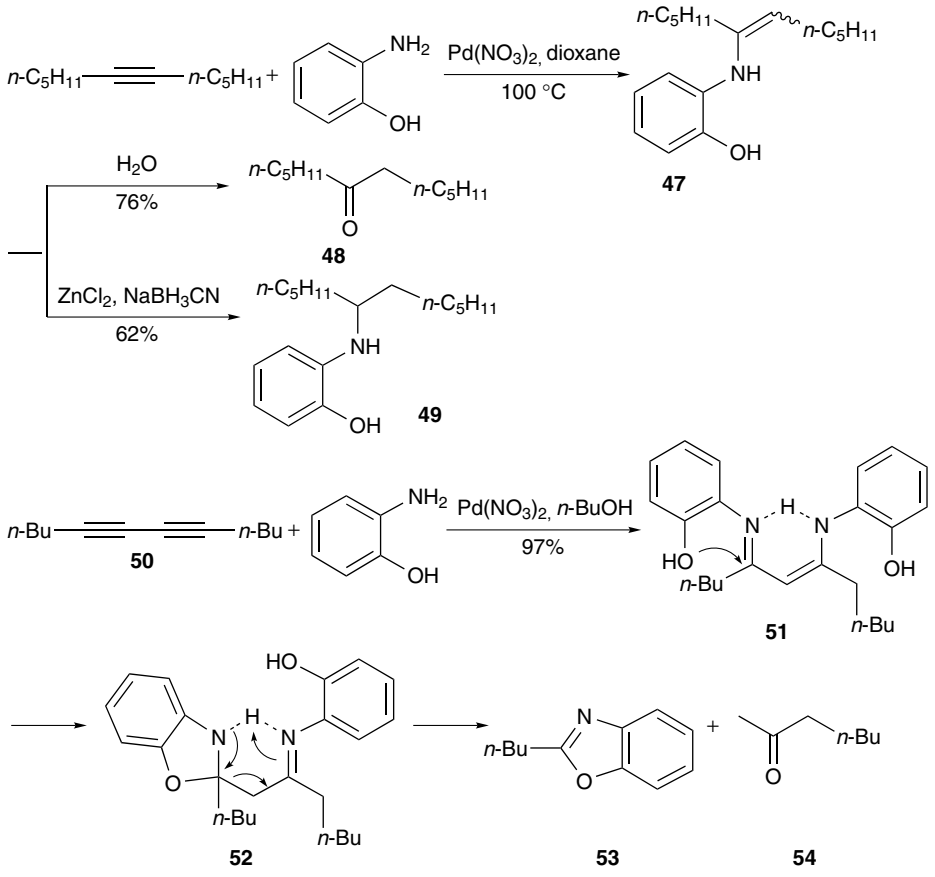


7.1.3 Hydroamination, Hydrocarbonation, and Related Reactions

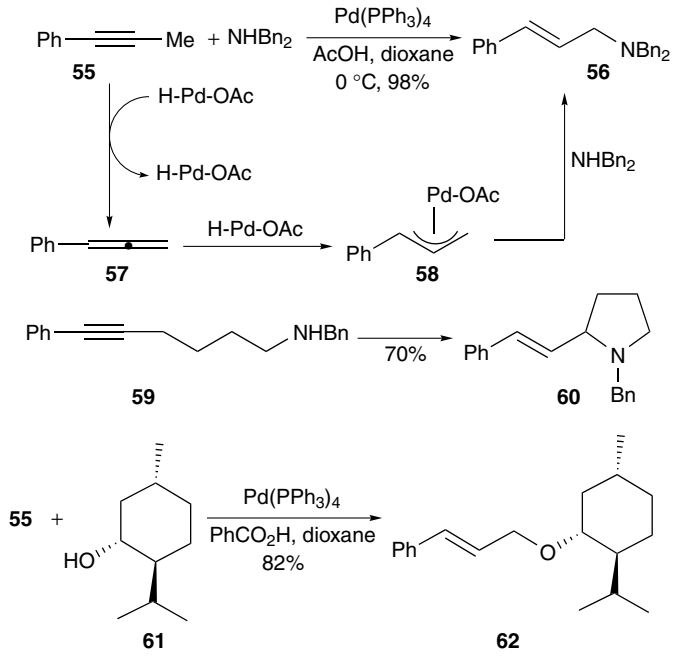
Addition of C, N, and O-pronucleophiles to alkynes is catalyzed by Pd complexes. Pd-catalyzed hydroamination of alkynes is rare. Intramolecular hydroamination of 6-amino-1-hexyne (**44**) was catalyzed by a Pd(II) compound and 2-methyl-1,2-dehydropiperidine (**46**) was obtained as a final product via 2-methylenepiperidine **45** [13].



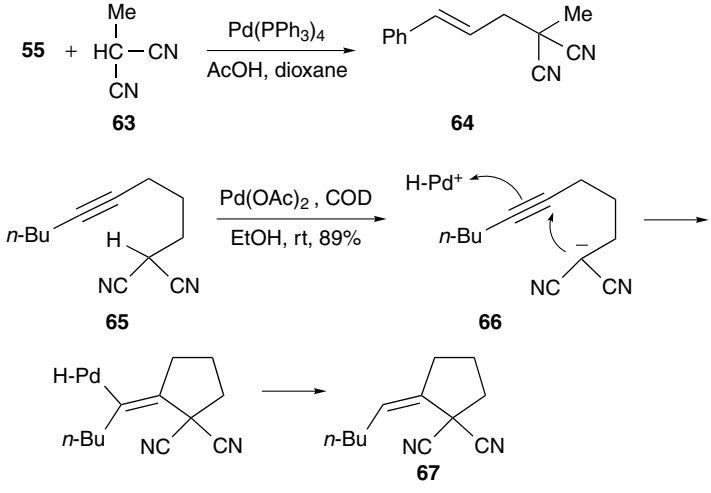
Intermolecular hydroamination of internal alkynes with *o*-aminophenol proceeded smoothly using ligandless $Pd(NO_3)_2$ as a catalyst in dioxane to give the enamine **47** as a product, which was isolated after hydrolysis to the ketone **48** in good yield. The amine **49** was obtained after reduction. Satisfactory hydroamination is possible only with *o*-aminophenol [14]. Hydroamination of the diyne **50** with *o*-aminophenol afforded the 2-substituted benzoxazole **53** and the ketone **54**. The reaction involves carbon–carbon bond cleavage. The intermediate **51** formed by bis-hydroamination undergoes ring formation and bond cleavage as demonstrated by **52**, and 2-butylbenzoxazole (**53**) and the ketone **54** were obtained in high yields [15].

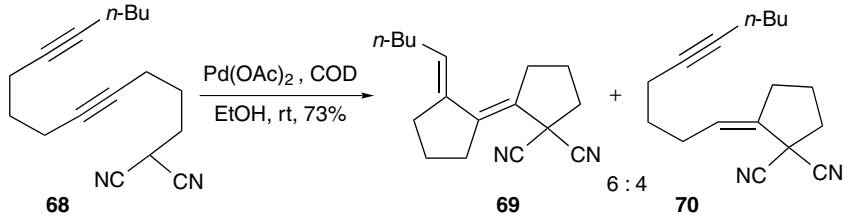


1-Phenyl-1-propyne (**55**) underwent facile formal intermolecular hydroamination, affording the allylic amine **56** in high yield at 0 °C in the presence of AcOH or benzoic acid. In this reaction, at first, Pd-catalyzed isomerization of **55** to phenylallene (**57**) occurs by addition–elimination of H-Pd-OAc to internal alkyne **55**, and then the allene **57** is converted to π-allylpalladium intermediate **58** by hydropalladation. The final step is a well-known amination to produce the allylic amine **56**. As an intramolecular version, 2-(2-phenylpropenyl)pyrrole (**60**) was obtained from 1-phenyl-7-amino-1-hexyne **59** [16,16a]. Similarly Pd/benzoic acid-catalyzed hydroalkoxylation of **55** with (−)-menthol (**61**) afforded the allylic ether **62** [17].

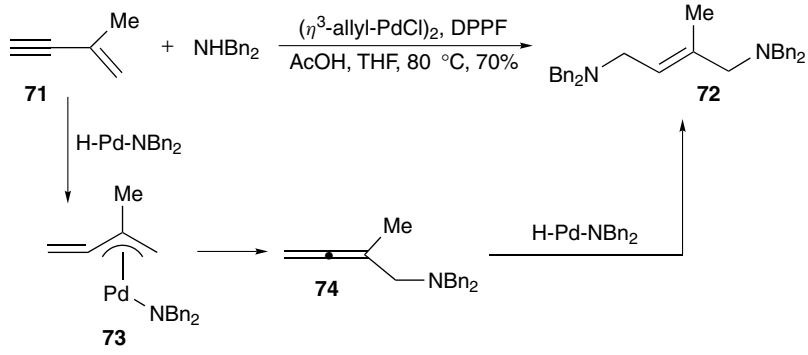


Also hydrocarbonation of **55** with methylmalononitrile (**63**) took place to give **64** [18]. On the other hand, efficient intramolecular hydrocarbonation of the 5-alkynylmalononitrile **65** gave the cyclopentane **67** in 89 % yield using $Pd(OAc)_2$ and COD in ethanol. The use of COD or 1-octene as an additive is important. Formation of the *Z* isomer suggests that the reaction does not proceed through π-allylpalladium intermediate, but involves the coordination of H-Pd^+ to the triple bond and subsequent *trans* carbopalladation as shown by **66**. No reaction occurred with the corresponding malonate and cyanoacetate, and $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ are ineffective. Cyclization of the malononitrile derivative **68** afforded the di- and monocyclization products **69** and **70** suggesting that the reaction proceeds by carbopalladation of alkyne with H-Pd species [19].



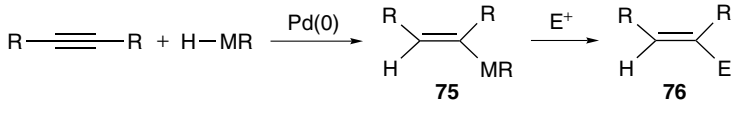


Conjugated enynes are very reactive and show interesting reactivity in the presence of Pd catalysts. Hydroamination of the conjugated enyne **71** in the presence of AcOH afforded 1,4-diamino-2-butene **72**. In this reaction, Pd-catalyzed isomerization of the enyne to allene, followed by generation of the methylene-π-allylpalladium **73** occurs, and amination yields the allenylamine **74**. Further Pd-catalyzed amination of **74** affords the diamine **72**. The reaction took place in the presence of AcOH using DPPF as a ligand [20]. A similar reaction occurred with carbon pronucleophiles [21].



7.1.4 Hydrometallation and Hydro-Heteroatom Addition

Hydrometallations of alkynes with $HSiR_3$, $HSnBu_3$ and HBR_2 are useful reactions, because introduced metal groups MR in **75** are reactive and can be displaced with other functional groups to give the functionalized alkenes **76**. Also hydroheteroatom addition occurs using substrates containing H-S, H-Se, and H-P bonds.

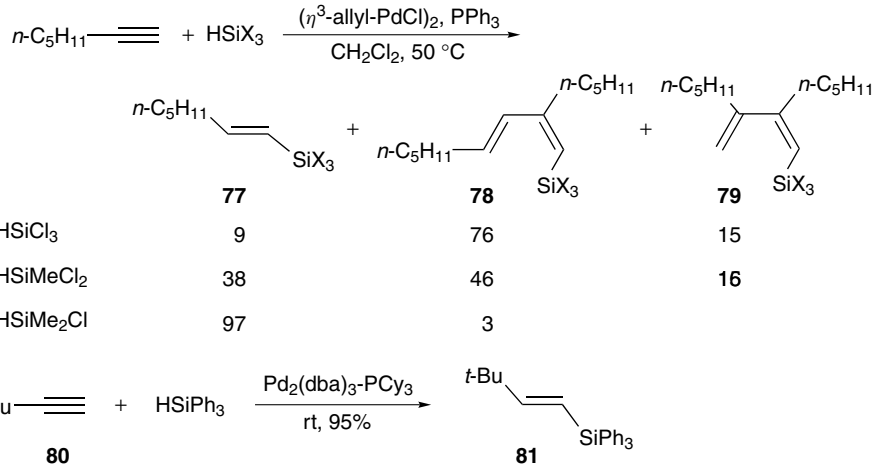


H—MR = H-SiR_3, $HSnBu_3$, H-BR_2 , H-hetero atoms

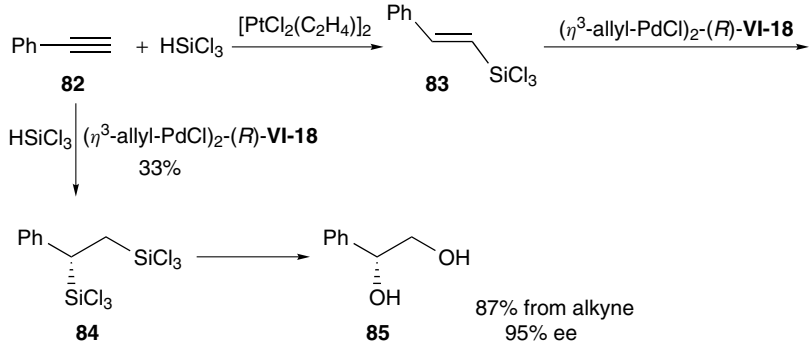
Compared with hydrosilylation of alkenes, less extensive studies have been carried out on hydrosilylation of alkynes. Mono- and dihydrosilylation occur depending on conditions. Yamamoto found concomitant dimerization–hydrosilylation of 1-heptyne catalyzed by Pd-PPh_3 catalyst to give a mixture of products **77**, **78**, and **79**. Their ratios depend on the hydrosilanes used. The head–tail dimer **78** was the main product when $HSiCl_3$ was used. The expected monohydrosilylation

took place to give **77** with $HSiMe_2Cl$. A small amount of tail–tail dimer **79** was obtained with $HSiCl_3$ and $HSiMeCl_2$ [22].

Oshima found that hydrosilylation with less reactive triorganosilanes can be carried out by using electron-rich phosphines. Hydrosilylation of terminal alkyne **80** with $HSiPh_3$ was carried out using PCy_3 as a ligand at room temperature to provide **81** regioselectively in high yield [23].

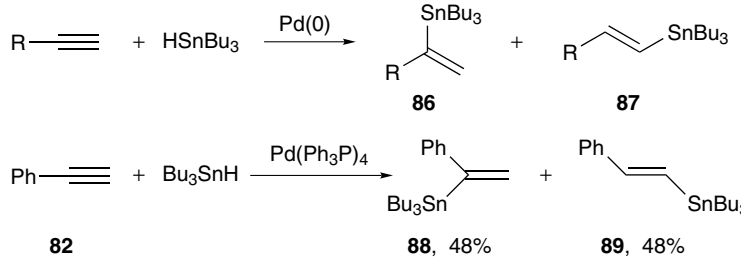


Preparation of chiral benzylic alcohols has been achieved by asymmetric dihydrosilylation of terminal arylalkynes, followed by oxidation [24]. The chiral diol **85** with 95 % ee was obtained by direct Pd-catalyzed asymmetric dihydrosilylation of phenylacetylene (**82**) with $HSiCl_3$ using MOP [(*R*)-**VI-18**], followed by oxidation of 1,2-disilylated product **84**, but the yield of **84** was 33 % (the main product was 1-trichlorosilyl-2,4-diphenyl-1,3-butadiene). Better results were obtained by hydrosilylation using two catalysts. The first Pt-catalyzed monosilylation to give **83** was followed by the second hydrosilylation catalyzed by the chiral Pd catalyst. The diol **85** with 95 % ee was obtained in 87 % overall yield by this method.

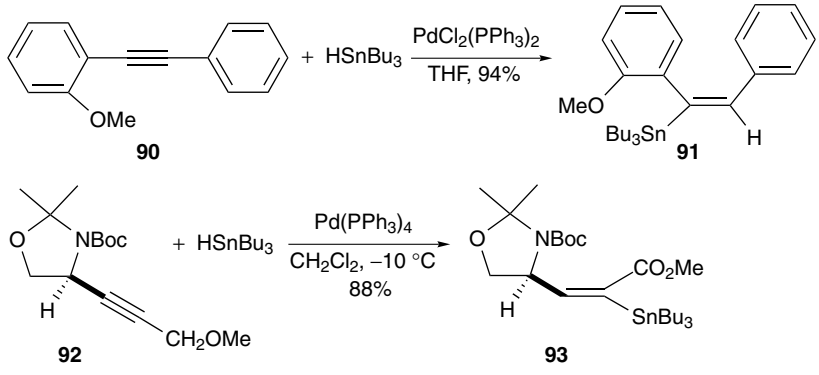


Hydrostannation of alkynes proceeds smoothly to give alkenylstannanes, which are used for further transformations. The reaction is induced by transition metal catalysts and free-radical sources, giving different regioisomers **86** and **87** [25].

Pd complexes are effective catalysts for *cis* addition. Usually a mixture of the regioisomers **86** and **87** is obtained, and the ratio depends on the substituents of the alkynes and ligands. Hydrostannation of **82** afforded equal amounts of the regioisomers **88** and **89**.

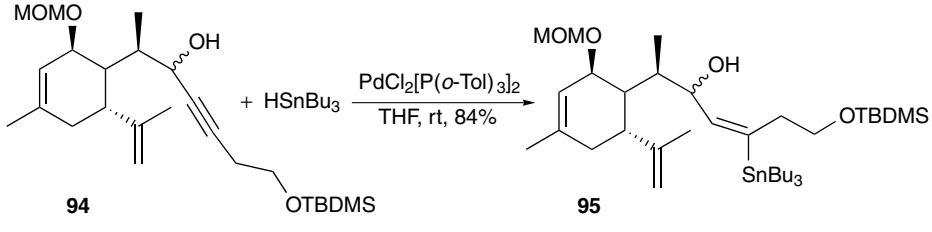


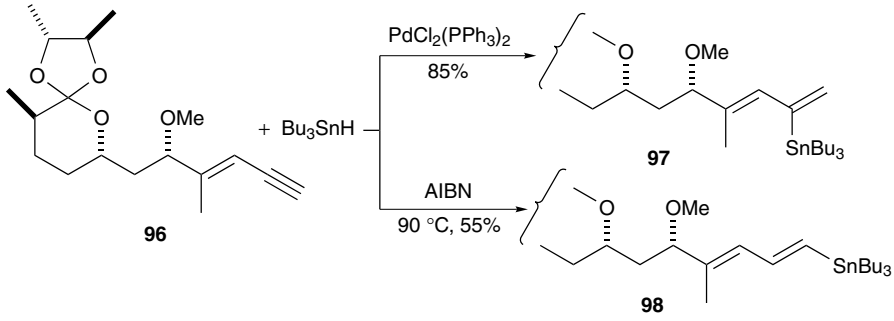
Several reports on regioselective hydrostannation have been published. In hydrostannation of asymmetric diarylacetylene **90**, stannation occurred regioselectively at the carbon close to the *ortho*-substituted benzene to give **91** [26]. Hydrostannation of the serine-derived ynoate **92** at $-10\,^{\circ}C$ afforded the α-stannyl ester **93** with high regioselectivity (16 : 1), and the reaction was applied to the total synthesis of asperazine [27].



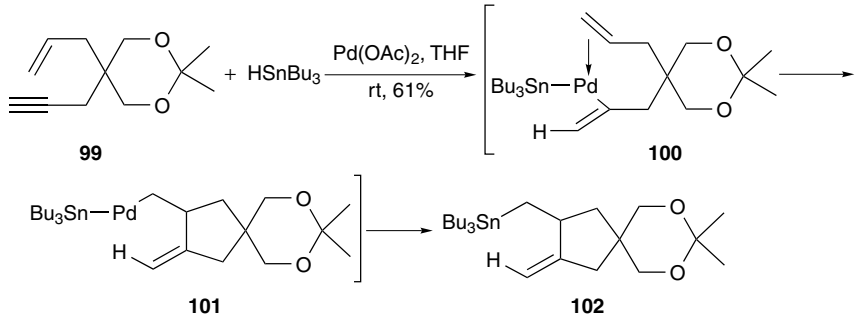
Usually, hydrostannation of propargyl alcohols is not regioselective. However, the β-stannyl alcohol **95** was obtained with complete regioselectivity by hydrostannation of the propargyl alcohol **94** using P(*o*-Tol)$_3$ as a ligand, and the reaction was applied to the total synthesis of zoanthamine [28].

While Pd-catalyzed hydrostannation of the conjugated enyne **96** afforded the alkadienylstannane **97** regioselectively, a radical-initiated reaction provided the terminal adduct **98** [29].

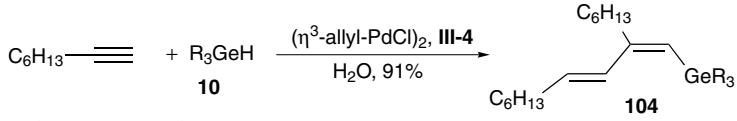




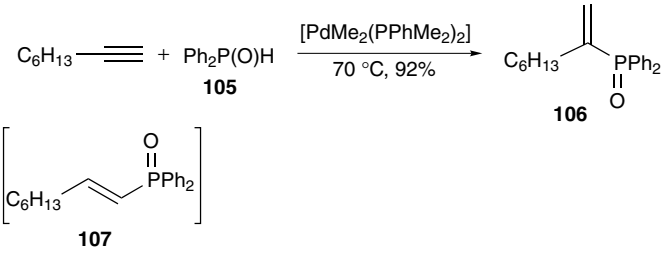
Cyclization of the 1,6-enyne **99** with $HSnBu_3$ provided the cyclopentane **102** at room temperature. Ligandless $Pd(OAc)_2$ was used. In this reaction, regioselective hydropalladation of the alkyne generates **100** at first, and subsequent alkene insertion yields **101**. Finally reductive elimination gives rise to the cyclized product **102** [30].



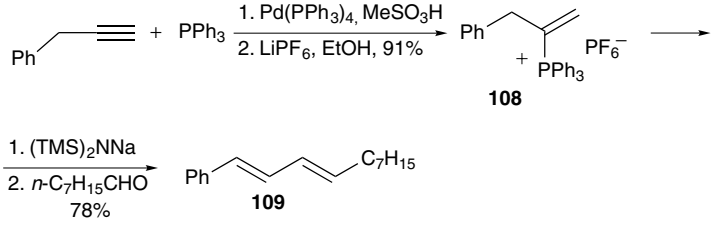
Hydrogermylation of 1-octyne with tri(2-furyl)germane **10** at room temperature in water provided the 1,3-dienylgermane **104** in high yield [31].



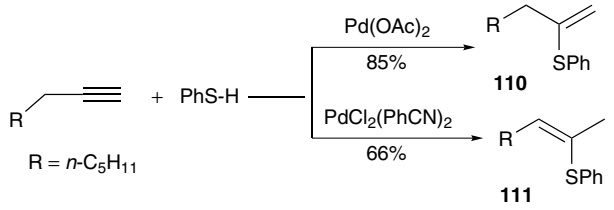
Hydrophosphinylation of 1-octyne with diphenylphosphine oxide (**105**) afforded the alkenylphosphine oxide **106** by internal attack with high regioselectivity. However, addition of a small amount of $Ph_2P(O)OH$ changed the regioselectivity to provide the product **107** by terminal attack [32].



The alkenylphosphonium salt **108** was prepared by the addition of PPh_3 at the internal carbon of 1-alkyne in the presence of methanesulfonic acid. After anion exchange with $LiPF_6$, the conjugated diene **109** was obtained by the reaction of **108** with an aldehyde [33].

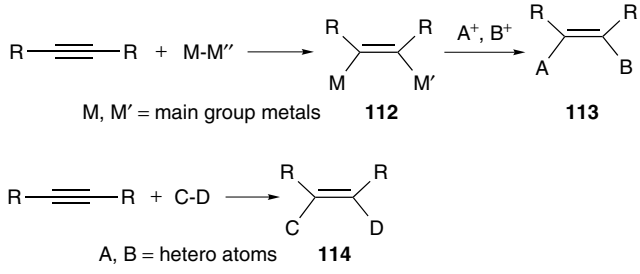


Hydrothiolation of 1-alkynes with thiols gives vinyl sulfides with high regio- and stereoselectivities. Reaction of 1-octyne with benzenethiol catalyzed by $Pd(OAc)_2$ gave the Markonikov-type product **110**. Isomerization of the double bond occurred and the isomer **111** was obtained when $PdCl_2(PhCN)_2$ was used [34].

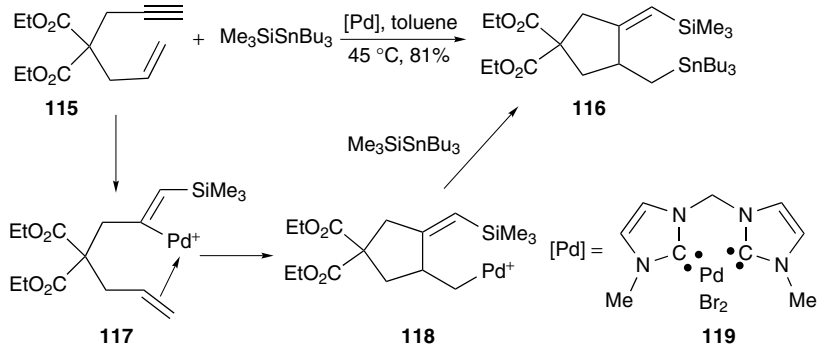


7.1.5 Dimetallation and Related Reactions

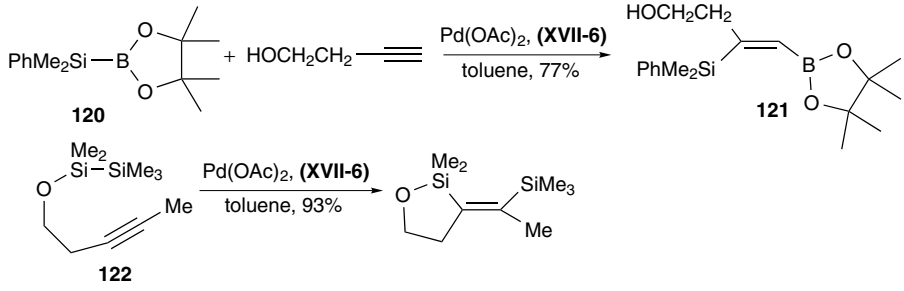
Functionalized alkenes are prepared by the *syn* addition of dimetallic reagents and related compounds. α,β-Dimetallated compounds **112**, easily prepared by the Pd-catalyzed addition of dimetallic reagents (R_nM-$MR_{n'}$) of main group metals to alkynes, are reactive, and can be converted to functionalized alkenes **113**. Also addition of dichalcogen compounds produces the functionalized alkenes **114**. Many examples are known, and some recent examples are cited.



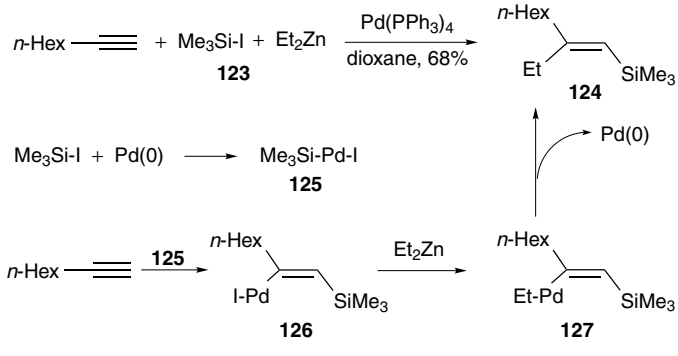
The first step of the Pd-catalyzed silylstannation–cyclization of the 1,6-enyne **115** is silylpalladation of the triple bond to generate alkenylpalladium **117**, and the cyclopentane bearing silylvinyl group **116** was obtained via **118**. The carbene–Pd complex **119** was the most effective catalyst [35].



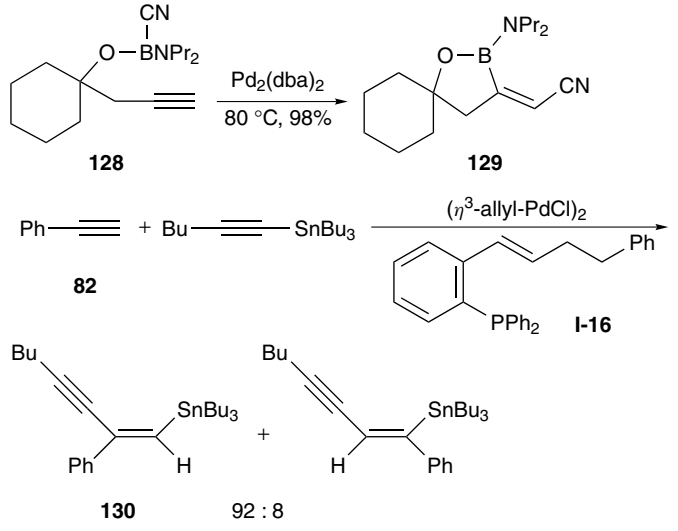
Borylsilylation of 1-octyne with **120** provided the alkenylboronate **121** in high yield using $Pd(OAc)_2$ and bulky isocyanide (1,1,3,3-tetramethylbutyl isocyanide, **XVII-6**) as a ligand. The product **121** was subjected to Suzuki coupling catalyzed by $PdCl_2$(dppf) [36]. Under similar conditions, no intermolecular bis-silylation of internal alkynes took place. However, intramolecular bis-silylation of disilanyl ether of homopropargylic alcohol proceeded smoothly with 5-*exo-dig* cyclization [36a].



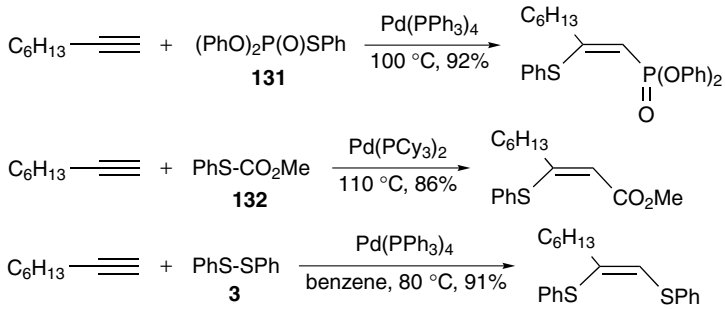
Although mechanistically different, functionalized alkenylsilanes are prepared stereoselectively by the reaction of 1-alkynes with iodotrimethylsilane (**123**) and diethylzinc. At first oxidative addition of **123** to Pd(0) generates **125**. Then insertion of 1-octyne to **125** affords the alkenylpalladium **126**. Transmetallation with Et_2Zn gives **127** and reductive elimination provides the alkenylsilane **124**. The reaction can be regarded as a Heck-type reaction of alkyne with Me_3Si-I, followed by Negishi coupling [37].



Some examples of carbometallation are known. Although intermolecular cyanoboration of alkynes is rather difficult, intramolecular cyanoboration of **128** proceeds smoothly using $Pd_2(dba)_3$ as a catalyst to provide the cyclic alkenylborane **129**, which undergoes Suzuki coupling [38]. Carbostannation of 1-alkyne **82** with alkynylstannane catalyzed by iminophosphine **I-16** gave the enyne **130** as the main product with high regio- and stereoselectivities [39].



Various 1,2-bifunctionalized alkenes containing heteroatoms are prepared by addition to alkynes. Thiophosphorylation of 1-octyne with phosphorothiolate **131** provided (*Z*)-1-(diphenoxyphosphinyl)-2-(phenylthio)-1-octene in good yield [40]. A useful synthetic method for (*Z*)-3-phenylthioacrylate derivative is the Pd-catalyzed thioesterification of 1-alkynes with *O*-methyl *S*-phenyl thiocarbonate (**132**). Addition of **132** to 1-octyne using $Pd(PCy_3)_2$ as a catalyst afforded methyl (*Z*)-3-phenylthio-2-nonenoate in 86 % yield [41]. (*Z*)-1,2-Bis(phenylthio)alkene was prepared in good yield by stereoselective Pd-catalyzed addition of $(PhS)_2$ (**3**) to 1-alkyne [2].

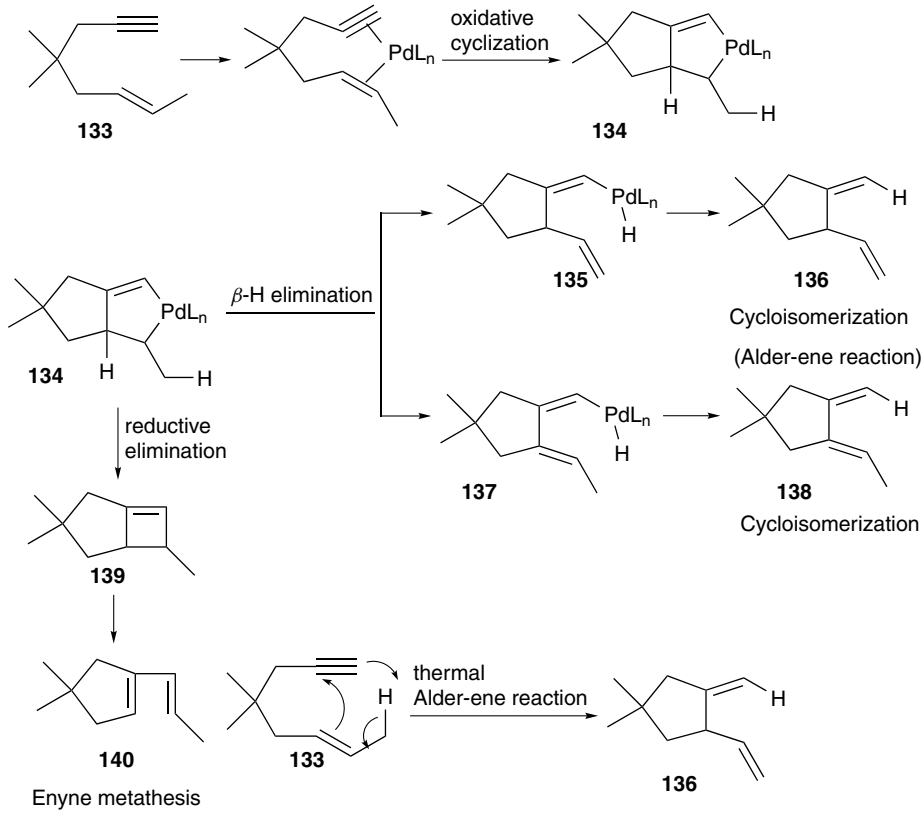


7.1.6 Cyclization of 1,6-Enynes and 1,7-Diynes

Facile Pd-catalyzed cyclizations of 1,6-enyne **133** and diynes is a useful synthetic method for substituted cyclopentanes, and called cycloisomerization. The reactions

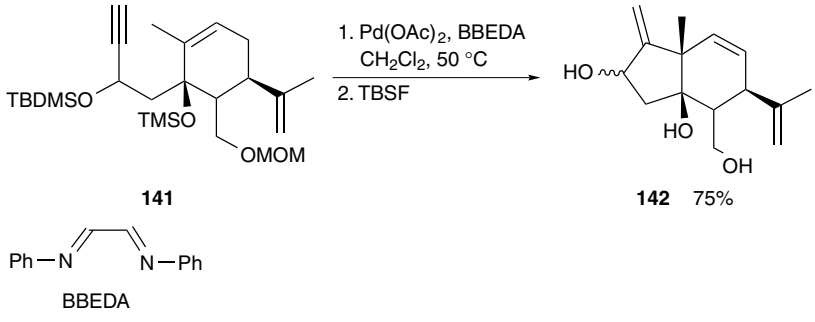
have been studied extensively by Trost [42]. One mechanistic explanation of the reactions is shown by the following scheme (palladacycle mechanism). At first oxidative cyclization of 1,6-enyne **133** generates the palladacycle **134**. Then β-H elimination generates either the alkenylpalladium **135** or **137** depending on which H is eliminated. Finally the diene **136** or **138** is obtained by reductive elimination. The diene **136** is the same product obtained by the thermal Alder-ene reaction of **133** at higher temperature. The conjugated diene **138** can not be obtained by the thermal reaction, but is produced only by the Pd-catalyzed reaction. Another path is reductive elimination of **134** to generate the strained cyclobutene **139**, which undergoes electroisomerization to afford the diene **140**. This path is called enyne metathesis [43].

I. Palladacycle mechanism



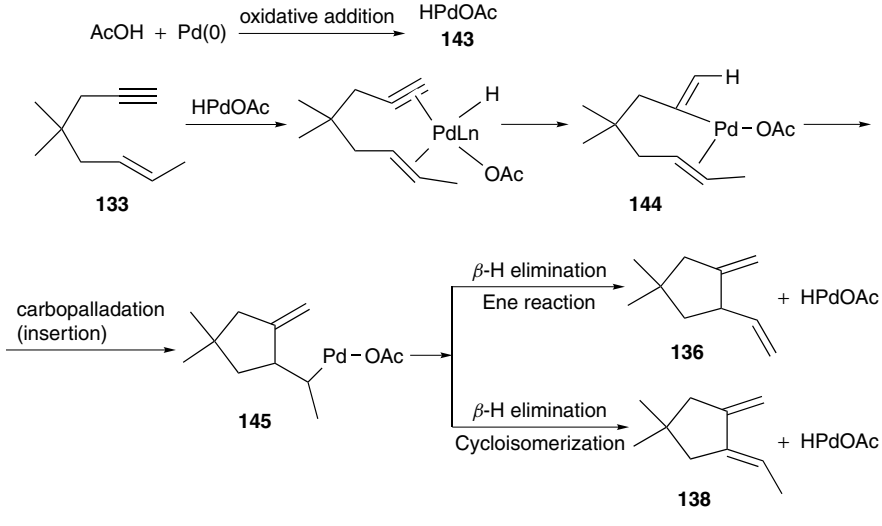
A number of interesting applications of cycloisomerization to natural product syntheses have been carried out by Trost. As an example, total synthesis of picrotoxinin has been achieved based on cycloisomerization (Alder-ene reaction) of the 1,6-enyne system **141** as a key reaction. No satisfactory cyclization of **141** occurred when phosphine ligands such as P(*o*-Tol)$_3$, DPPB, and triisopropyl phosphite were used. However, smooth cyclization took place to give the Alder-ene product in a quantitative yield at 50 °C when *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) was used as a ligand, and the triol **142** was obtained in 75 % yield after

deprotection, and the asymmetric synthesis of picrotoxinin has been carried out. The effect of the BBEDA ligand is remarkable [44].



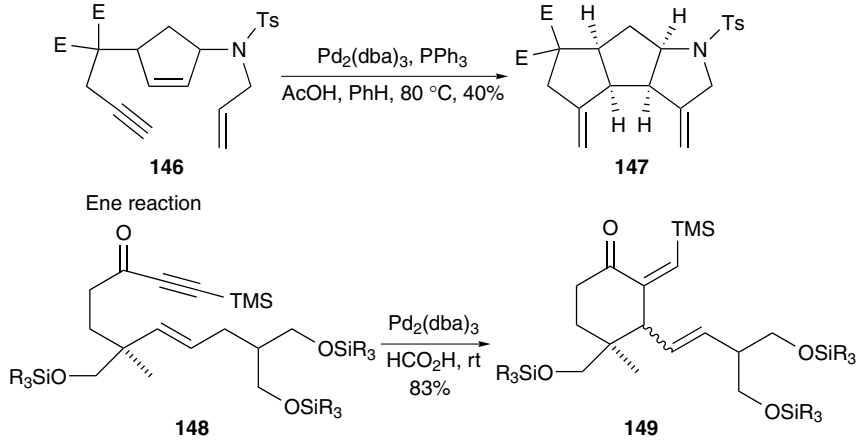
The cycloisomerization of 1,6-enynes proceeds smoothly in the presence of AcOH or HCO_2H and the reaction is explained by the following mechanism (hydridopalladium acetate mechanism) [45]. Most importantly, oxidative addition of AcOH to Pd(0) generates H-Pd-OAc **143**, and the cyclization of 1,6-enynes starts by insertion of the triple bond to **143** to afford the alkenylpalladium **144**. Subsequent intramolecular insertion of the double bond gives the alkylpalladium **145**. The termination step is β-H elimination and either the diene **136** or **138** is formed with regeneration of H-Pd-OAc. It should be noted that the alkenylpalladium **144** is a similar species formed in a Heck reaction by oxidative addition of alkenyl halide to Pd(0). Based on this reaction, alkyne is a useful starter in domino cyclization of polyenynes.

II. Hydridopalladium acetate mechanism

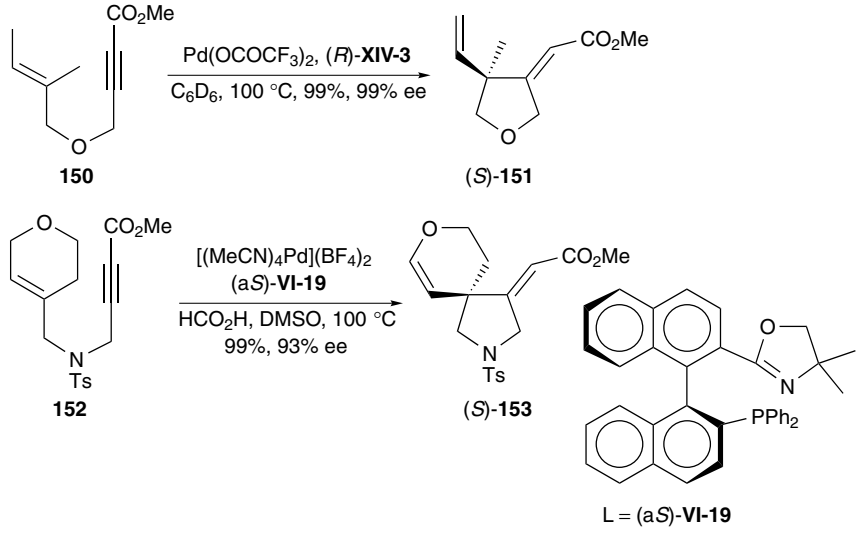


By way of an example, the formation of **147** from **146** in the presence of AcOH is explained by this mechanism [45]. Cycloisomerization of 1,7-enynes is more difficult than that of 1,6-enynes. Seemingly difficult cyclization of 1,7-enyne **148**

bearing a hindered double bond was achieved in the presence of HCO_2H, an acid stronger than AcOH, and in the absence of ligand. The six-membered ring compound **149** was obtained in 83 % yield under the conditions. This reaction is a key step in the total synthesis of cassiol [46].

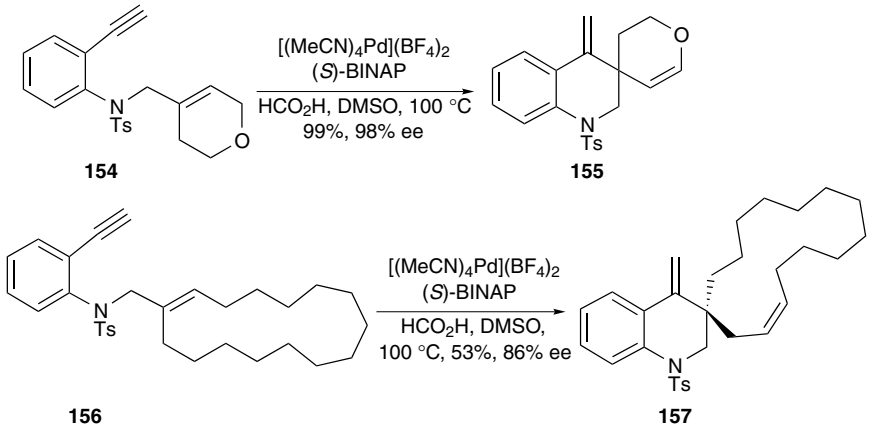


Mikami developed an efficient Pd-catalyzed asymmetric ene reaction of 1,6- and 1,7-enynes. The 1,6-enyne **150** was converted to the tetrahydrofuran (*S*)-**151** with 99 % ee in 99 % yield using $Pd(OCOCF_3)_2$ and (*R*)-SEGPHOS **XIV-3** in C_6D_6 [47]. Similarly the asymmetric ene reaction of 1,6-enyne **152** afforded the (*S*)-spiro compound **153** using a cationic Pd(II) complex in DMSO in the presence of HCO_2H. As a chiral ligand, (a*S*)-binaphthyldiphenylphosphine bearing an 'achiral' *gem*-dimethyl oxazoline unit (**VI-19**) was used [48].

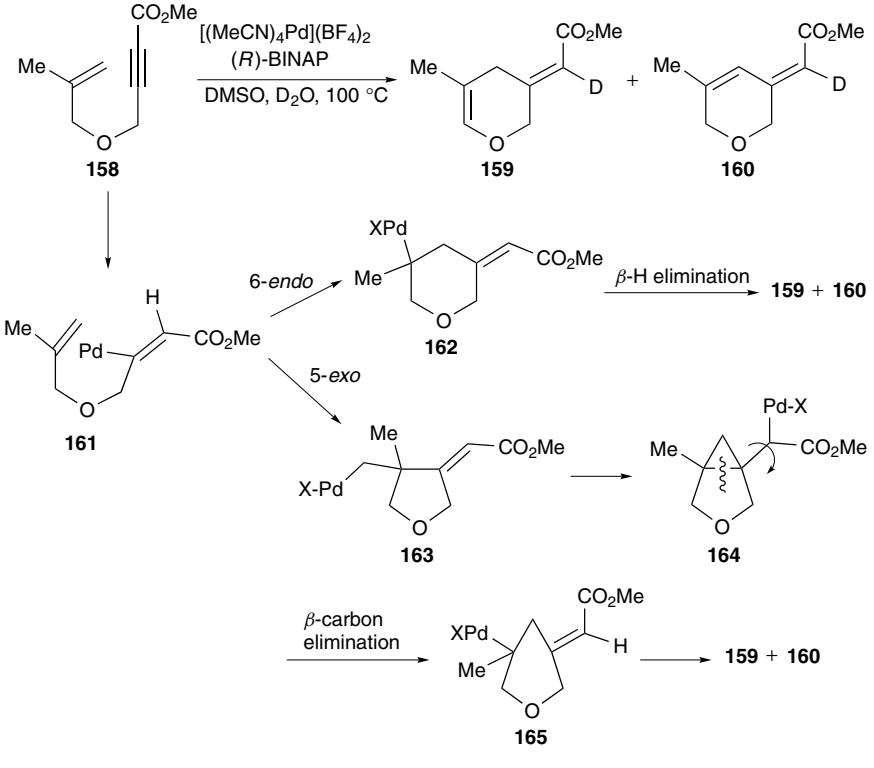


Highly enantioselective synthesis of the quinoline **155** was achieved via ene cyclization of the 1,7-enyne **154** using a cationic Pd(II) complex and (*S*)-BINAP in DMSO in the presence of HCO_2H with very high % ee (98 % ee) and in high

yield (99 %). Also the spiro quinoline bearing a macrocycle **157** with 86 % ee was obtained from the 1,7-enyne **156** [49].

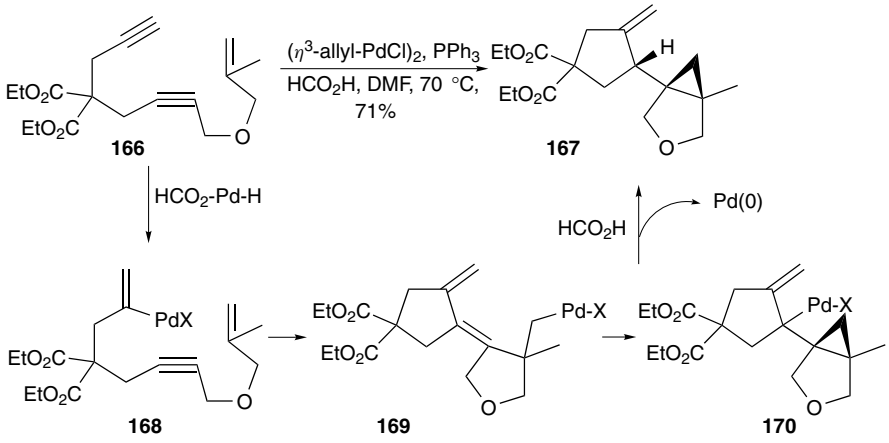


Ene-type cyclization of the 1,6-enyne **158** to provide a five-membered ring is not possible. Instead, the cyclohexenes **159** and **160** were obtained using cationic Pd(II) and (*R*)-BINAP. The reaction can be understood by two reaction paths. The rather unusual 6-*endo* cyclization of **161** to generate **162** is one possibility. The formation of the neopentyl-type palladium intermediate **163** by 5-*exo* cyclization is another possibility. Then the olefin insertion affords the cyclopropane **164**, and subsequent β-carbon elimination provides **165**, from which **159** and **160** are formed by β-H elimination [50].



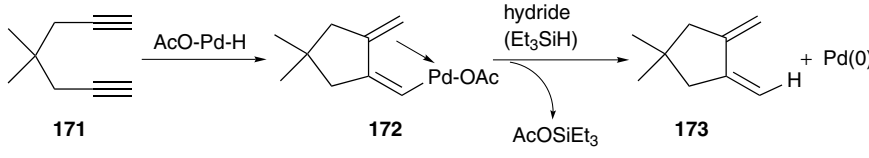
For all these asymmetric ene cyclizations, Mikami proposed a reaction mechanism, in which he claimed that Pd(II) is a real catalytic species, rather than generally accepted Pd(0) species, and stresses the importance of the use of weakly coordinating anions such as BF_4, which stabilize the cationic Pd(II) complex.

The cyclization of the enediyne **166** (1,6-diyne system) in the presence of HCO_2H involved cyclopropanation via **168** and the neopentylpalladium **169**, which provides the cyclopropane **170**. Since β-H elimination hardly takes place, the cyclized product **167** was formed by reduction of alkylpalladium **170** with HCO_2H and Pd(0) is regenerated [51].



The cycloisomerization of 1,6-diyne **171** in the presence of AcOH is terminated by reduction of the alkenylpalladium **172** with hydride such as H-$SiEt_3$ to afford the conjugated diene **173**.

III. Hydropalladation and reductive cyclization

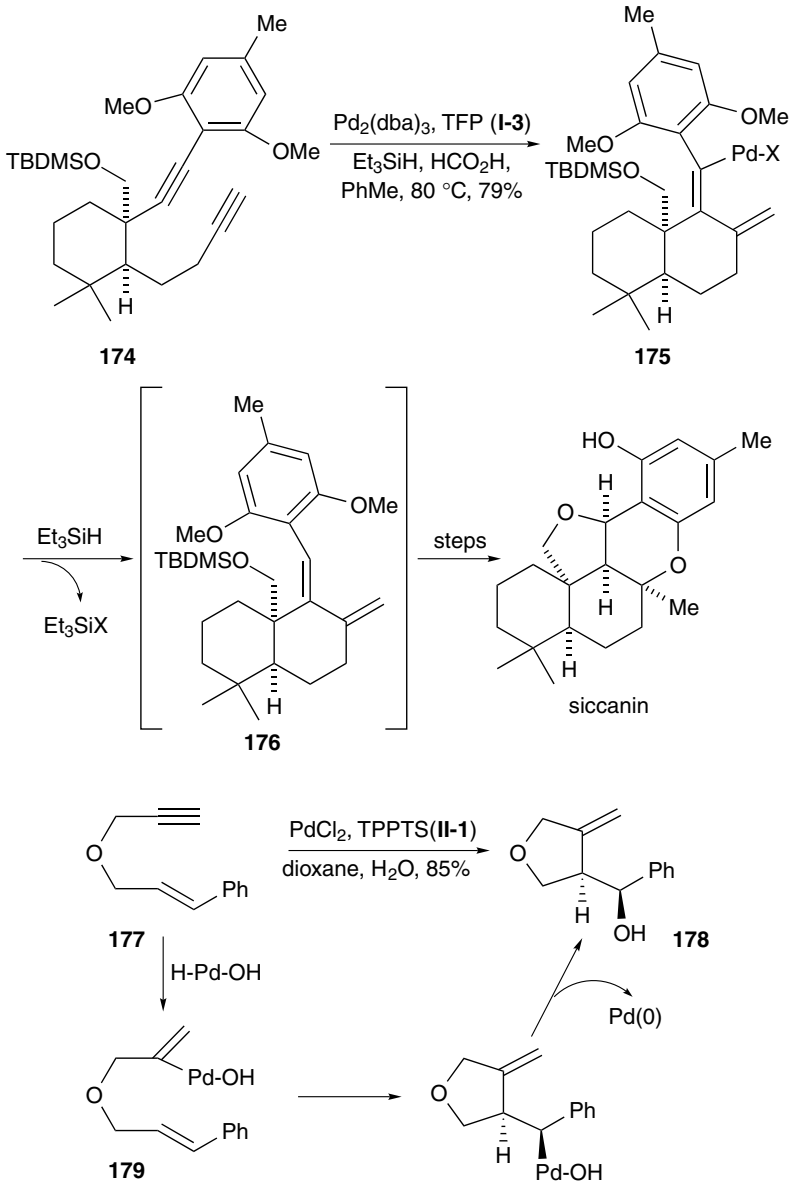


In the total synthesis of siccanin, cyclization of the 1,7-diyne **174** was carried out in the presence of HCO_2H and $HSiEt_3$ using TFP (**I-3**) as a ligand to provide the alkenylpalladium **175**. The reaction can be terminated only by reduction of **175** with hydrosilane to give the 1,3-diene **176** in 79 % yield [52].

Genet *et al*. reported an interesting cyclization of 1,6-enynes in an aqueous solution. Treatment of the 1,6-enyne **177** with $PdCl_2$ in aqueous dioxane afforded the methylenetetrahydrofuran **178** in 85 % yield. The reaction is explained by involvement of H-Pd-OH species, namely, formation of **179** by insertion of the alkyne to H-Pd-OH, followed by cyclization, and reductive elimination [53].

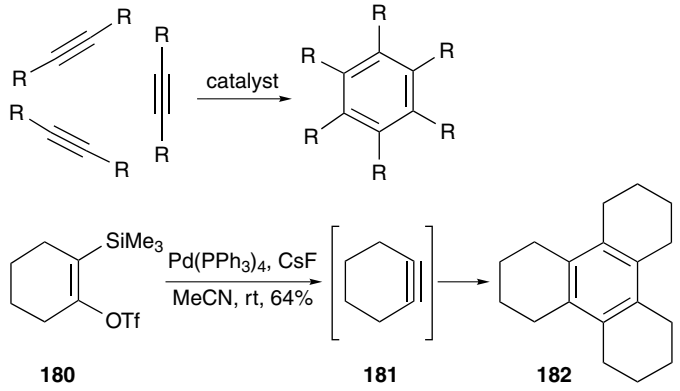
7.1.7 Benzannulation

Cyclotrimerization of substituted alkynes catalyzed by various transition metal complexes to produce benzene derivatives is a well-known reaction. As a recent example,

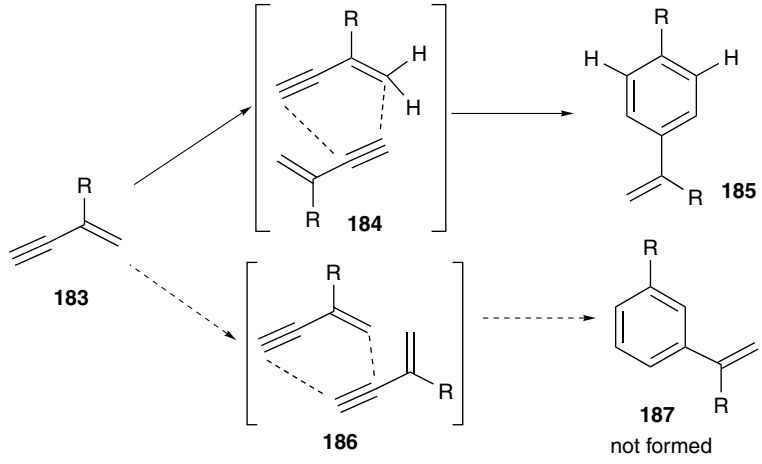


Yokota *et al*. reported quantitative cyclotrimerization of symmetric internal alkynes using a complicated catalyst system of Pd(II)/chlorohydroquinone/NPMoV under oxygen [54]. In addition, regiocontrol to produce a single isomer is one problem inherent in cyclotrimerization of substituted alkynes, and many attempts to achieve regioselective cyclization have been carried out with partial success.

Perez and co-workers reported a novel Pd-catalyzed cyclotrimerization of cycloalkynes. They generated highly strained cyclohexyne (**181**) by the treatment of 2-trimethylsilylcyclohexenyl triflate (**180**) with CsF in the presence of $Pd(PPh_3)_4$. Cyclotrimerization of cyclohexyne (**181**) occurred rapidly as soon as it was generated, and they obtained dodecahydrotriphenylene (**182**) in 62 % yield [55].

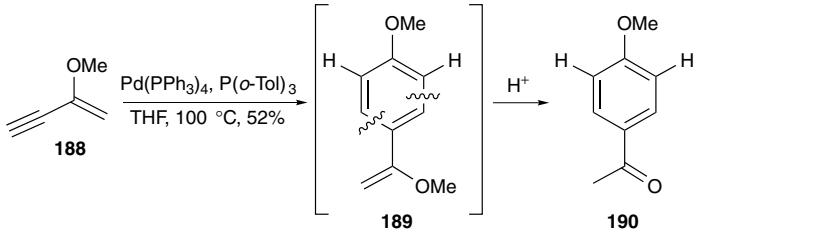


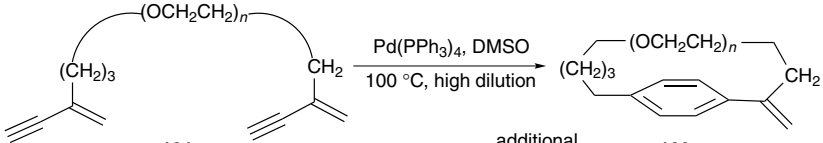
Yamamoto *et al*. have developed novel methods of regioselective syntheses of polysubstituted benzenes based on [4 + 2] addition of an enyne with an alkyne, offering useful synthetic methods of substituted benzenes in short steps [56]. Two types of [4 + 2] addition have been reported. One of them is the homobenzannulation of conjugated enynes **183** catalyzed by $Pd(PPh_3)_4$. The reaction proceeds with remarkably high regioselectivity to give 1,4-disubstituted benzenes **185** as a single isomer via the path as shown by **184**. The isomers **187** via **186** are not formed [57].



The reaction has many synthetic applications. 4-Substituted anisole **189** was obtained from 2-methoxyenyne **188** using $Pd(PPh_3)_4$ and additional $P(o\text{-Tol})_3$, and the product was converted to 4-methoxyacetophenone **190** [58]. The intramolecular reaction is useful for the synthesis of various phane derivatives. Several oxaparacyclophanes **192** have been prepared from **191** using $Pd(PPh_3)_4$ and additional ligands in DMSO in good yields [59].

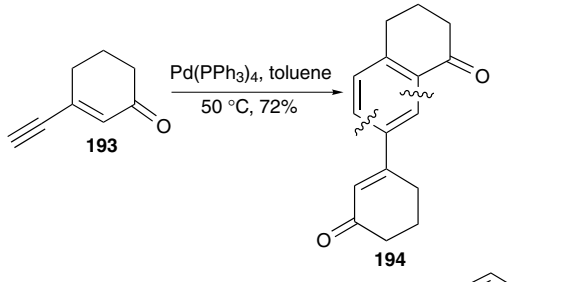
The presence of an EWG in the enynes accelerates the reaction. The conjugated cyclic enynone **193** underwent smooth homobenzannulation to give the diketone **194** at 50 °C [60]. Benzannulation of the highly reactive enyne **195**, possessing an EWG, was carried out in a fluorous biphasic system of perfluorodacalin, toluene, and hexane using perfluoro-tagged triarylphosphine **197**, and the disubstituted

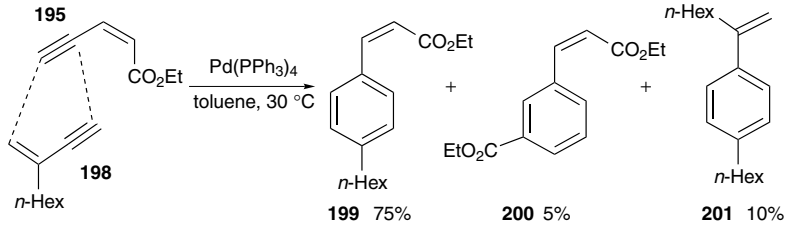




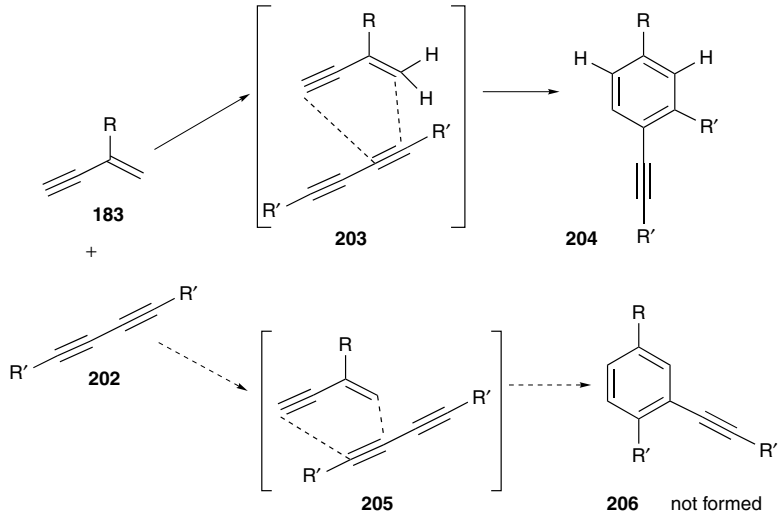
n	yield	additional ligand
1	34	+ PPh_3
2	100	+ PPh_3
3	95	+ P(*o*-Tol)$_3$
4	50	+ P(*o*-Tol)$_3$

benzene **196** was obtained as a single product. The reaction can be carried out several times without loss of catalytic activity [61]. Reactivity-controlled cross-benzannulation of **195** with the enyne **198** was carried out by slow addition of the more reactive enyne **195** (1 equiv.) to a solution of the enyne **198** (1.5 equiv.). In this way, the cross-coupled benzene **199** was obtained in 75 % yield. The isomers **200** and **201** were minor products [62].

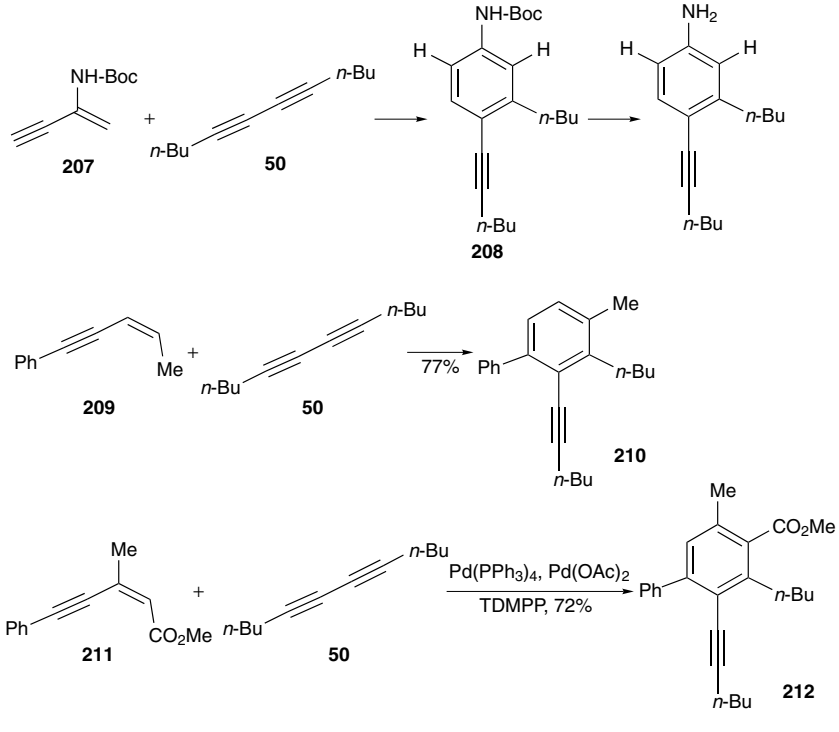




In the second type [4 + 2] addition, the conjugated diynes **202** are used as the partner of the enynes **183**, and the arylalkynes **204** are obtained by the path as shown by **203**. The other expected isomers **206** via **205** are not formed [63].

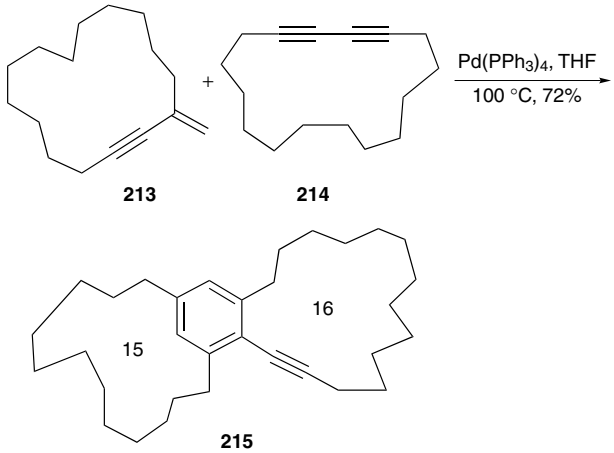


The aniline derivative **208** was obtained by cross-benzannulation of the amino-enyne **207** with dodeca-5,7-diyne (**50**) [64]. Cross-benzannulation of the 1,4-disubstituted enyne **209** with the diyne **50** afforded the 1,2,3,4-tetrasubstituted benzene **210** [63]. Pentasubstituted benzene **212** can be synthesized by the coupling of the trisubstituted 1-buten-3-yne **211** with the diyne **50** [63].

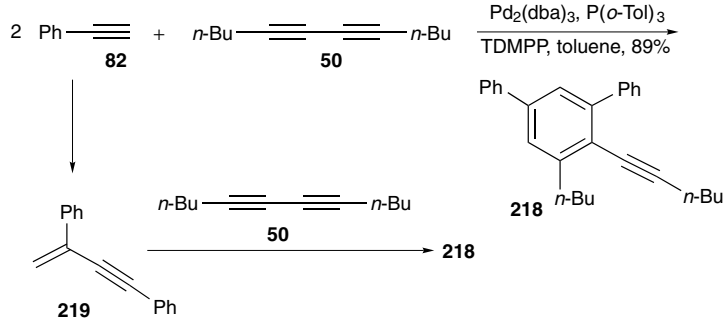


Intermolecular enyne-diyne cross-benzannulation offers a convenient synthetic method for cyclophanes. The cyclic enyne **213** reacted smoothly with 12-carbon-tethered cyclic diyne **214**, and the *meta*-cyclophane having both 15- and 16-membered rings **215** was prepared in high yield (72 %) [65].

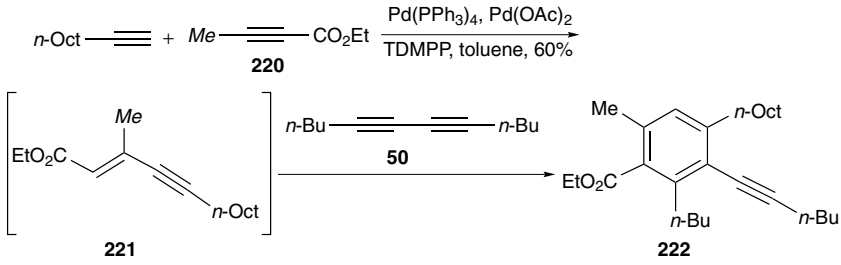
The phthalide **217** was prepared by intramolecular reaction of the highly unsaturated ester **216** using $Pd(PPh_3)_4$ in the presence of DPPF. Similarly 3,4-dihydroisocoumarins were synthesized [66].



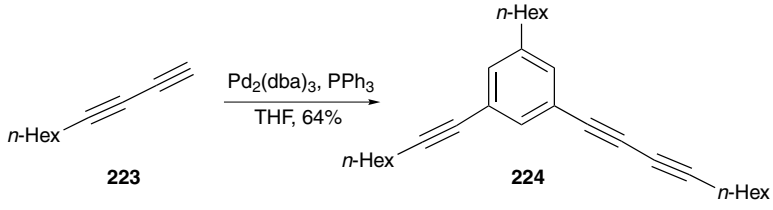
The most desirable aim in benzannulation is selective cyclization of three different alkynes to give a single isomer; Yamamoto offered a solution. Reaction of phenylacetylene (**82**) with 5-dodecadiyne (**50**) using $Pd(PPh_3)_4$ and additional $P(o\text{-Tol})_3$ as a catalyst, afforded the tetrasubstituted benzene **218** as a single product in 89 % yield. In this case, dimerization of phenylacetylene to 1,3-diphenylbut-1-yn-3-ene (**219**) took place.



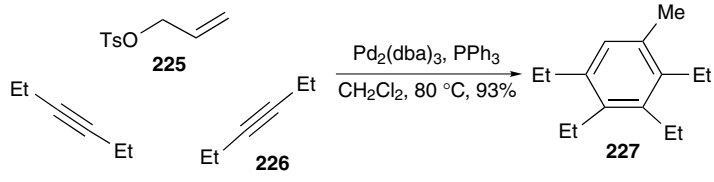
Then selective cyclization of three different alkynes, that is, 1-decyne, an acceptor alkyne **220**, and diyne **50** proceeded selectively to give pentasubstituted benzene **222** as a single product in 60 % yield using $Pd(PPh_3)_4$, $Pd(OAc)_2$ and electron-rich TDMPP [tri(2,6-dimethoxyphenyl)phosphine] (**I-9**). In this case, at first TDMPP accelerates the selective coupling of 1-decyne with the reactive alkyne **220** to give **221**, and the coupling product **221** reacted with diyne **50** to produce the pentasubstituted benzene **222** [67].



The 1,3,5-unsymmetrically substituted benzene **224** was prepared in 64 % yield by intermolecular cyclotrimerization of 1,3-decadiyne (**223**). The reaction was surprisingly regioselective to give **224** as a single product [68].

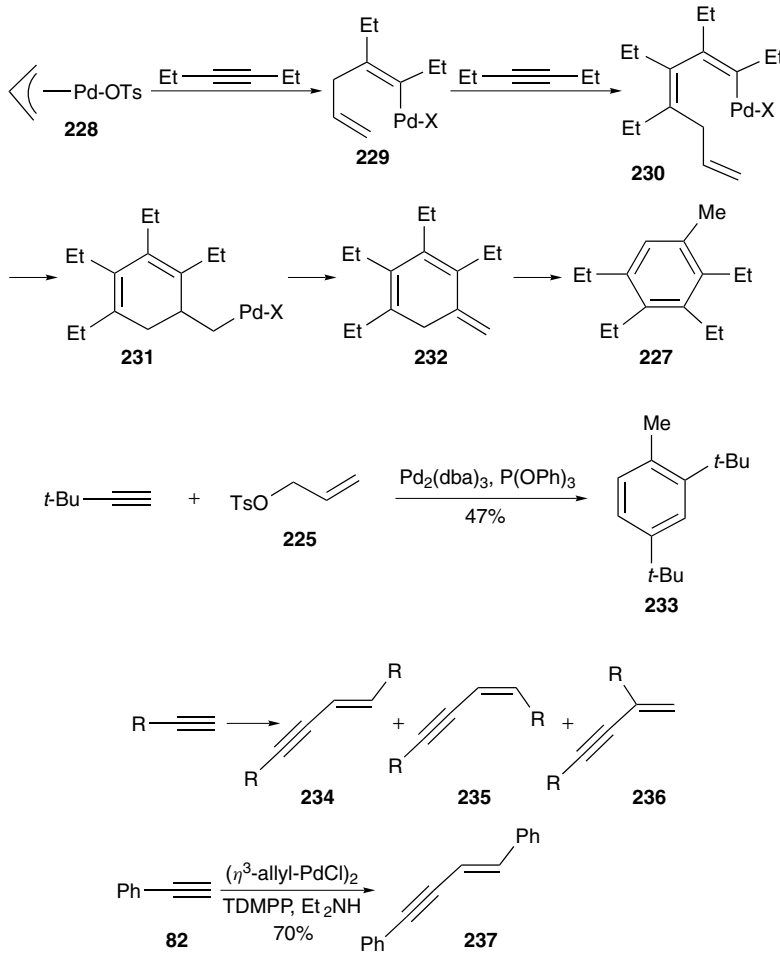


Benzannulation occurred by the reaction of allyl tosylate (**225**) and internal alkynes such as 3-hexyne to give the pentasubstituted benzene **227** in 93 % yield using $Pd_2(dba)_3$ and PPh_3. The reaction is explained by repeated insertion of the triple bond to the π-allylpalladium bond (**228**) to give **229** and **230**. Subsequent intramolecular insertion affords **231**. β-H elimination provides the pentasubstituted benzene **227** via **232**. No reaction occurred when allyl bromide or acetate were used. The trisubstituted benzene **233** was obtained by the reaction of 1-alkyne with allyl tosylate **225** when $P(OPh)_3$ was used as a ligand [69].



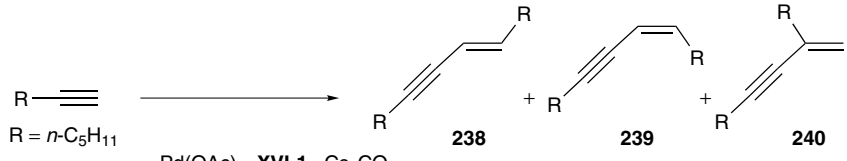
7.1.8 Homo- and Cross-Coupling of Alkynes

Homo-dimerization of terminal alkynes is catalyzed by Pd complexes. Usually control of regio- and stereoselectivities is difficult and a mixture of isomers **234**, **235**

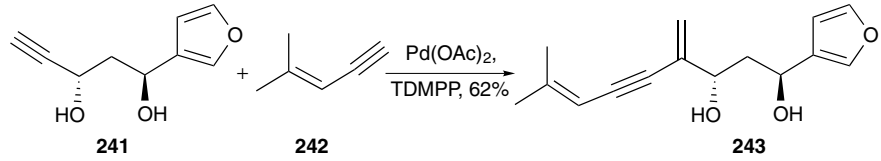


and **236** is obtained. The reaction is selective only under carefully controlled conditions. Head to head dimer **237** of phenylacetylene (**82**) was obtained selectively when (η^3-allyl-PdCl)$_2$ and TDMPP (**I-9**)were used in the presence of Et_2NH [70].

Yang and Nolan carried out dimerization of 1-alkynes using $Pd(OAc)_2$ combined with carbene ligand (**XV-1**). As shown by the examples, use of Cs_2CO_3 and K_2CO_3 changed the ratios of the head-to-head and head-to-tail dimers (**238**, **239** and **240**), showing that the control of regio- and stereoselectivities is a very delicate problem [71].

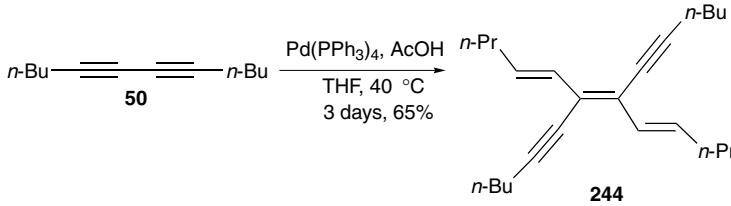


Control of selectivities in cross-dimerization of two alkynes is more difficult. Trost *et al*. carried out selective dimerization of 1-alkynes with acceptor alkynes, possessing an EWG, using TDMPP [72]. Furthermore, Trost and McIntosh succeeded in the selective cross-coupling of 1-alkyne **241** with unactivated alkyne **242**, obtaining the coupled product **243** in 62 % yield [73].



241 **242** **243**

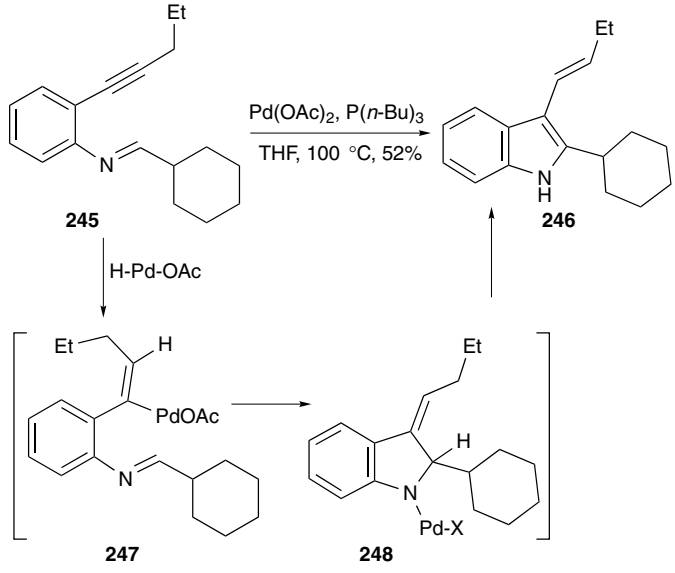
Yamamoto *et al*. reported a new and more complicated dimerization of diynes. $Pd(PPh_3)_4$-catalyzed reaction of dodecadiyne (**50**) in the presence of AcOH afforded (*E*)-1,2-dialkenyl-1,2-dialkynylethylene **244** in 65 % yield [74].



50 **244**

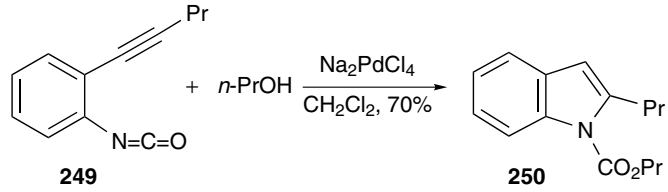
7.1.9 Miscellaneous Reactions

Intramolecular cyclization of alkynes with imines offers a new synthetic method for indoles [75]. Reaction of 2-(1-alkynyl)-*N*-alkylideneaniline **245** catalyzed by $Pd(OAc)_2$ and $P(n\text{-}Bu)_3$ afforded 2-alkyl-3-(1-alkenyl)indole **246**. The reaction starts by insertion of triple bond to H-Pd-OAc to generate **247**, followed by insertion of C=N bond to afford **248**. Finally, β-H elimination provides the indole



245 **246** **247** **248**

246. As another synthetic method for indoles, *N*-(propoxycarbonyl)indole **250** was obtained by the treatment of 2-(alkynyl)phenylisocyanate **249** with Na_2PdCl_4 in 1-propanol [76].

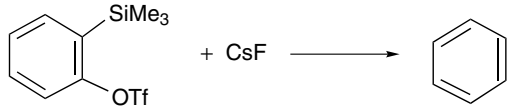


249 **250**

7.2 Reactions of Benzynes

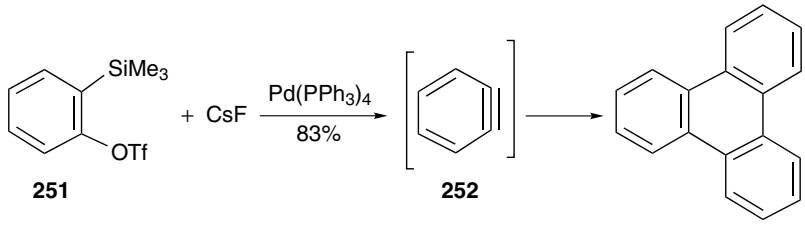
7.2.1 Cyclotrimerization and Cocyclization

Benzyne (**252**), generated by the treatment of 2-trimethylsilylphenyl triflate (**251**) with CsF [77], can be regarded as a very reactive alkyne. Therefore, similar to alkynes, Pd-catalyzed cyclotrimerization and cocyclization of arynes with other unsaturated bonds are expected. Transition metal-catalyzed reactions of benzyne is a newly developing field of research. Benzyne (**252**) is generated by the treatment of **251** with both CsF and Pd(0) complexes in the presence of other reactants and undergoes further reactions as soon as it is generated. Although there is no evidence, the Pd(0) catalyst may accelerate the generation of benzyne from 2-trimethylsilylphenyl triflate (**251**).



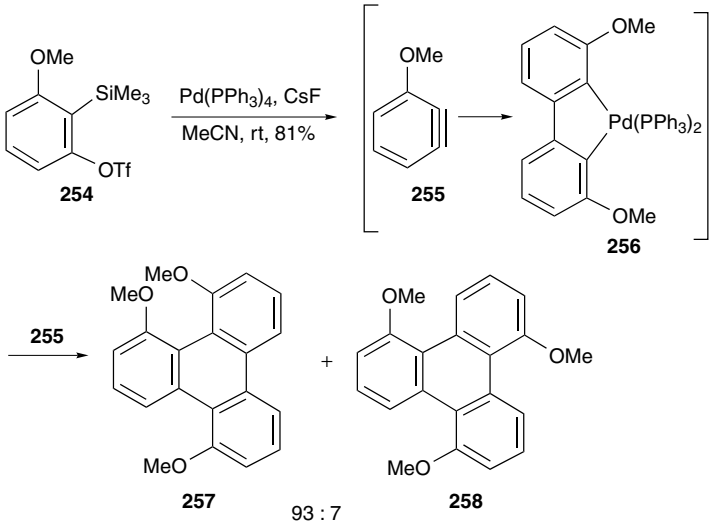
251 **252**

Recently, the Yamamoto group and the Guitian group as pioneers in this field have developed efficient Pd-catalyzed reactions of arynes, particularly cyclotrimerization and cocyclization with alkynes, offering useful synthetic methods for polycyclic aromatic compounds [78]. The Spanish group reported that the cyclotrimerization of benzyne, generated from **251**, occurred *in situ* at room temperature in the presence of $Pd(PPh_3)_4$ in MeCN, and obtained triphenylene (**253**) in 83 % yield [79].

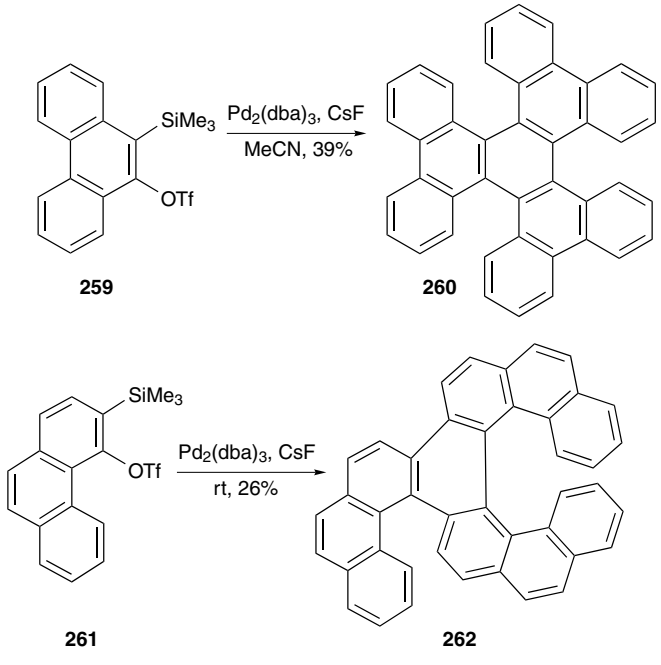


251 **252** **253**

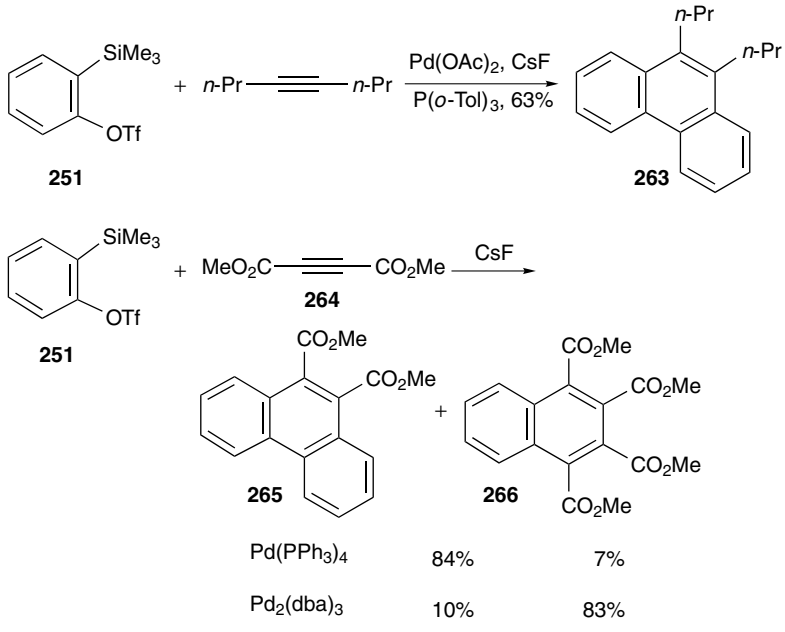
The cyclization of methoxybenzyne (**255**), generated from **254**, proceeded to give trimethoxytriphenylene **257** with high regioselectivity and **258** as a minor product in 81 % total yield. The high regioselectivity of the cyclotrimerization to form **257** is explained by the formation of the palladacycle **256** as an intermediate, which is generated by oxidative cyclization of two benzynes.



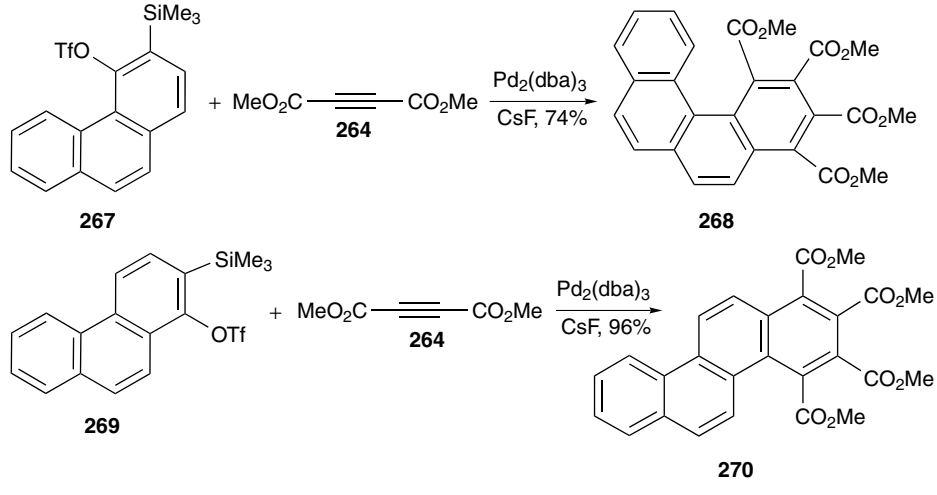
The cyclization of arynes can be applied to the synthesis of various polycyclic aromatics. Hexabenzo[*a,c,g,I,m,o*]triphenylene (**260**) was obtained as a single product in 39 % yield from 9,10-didehydrophenanthrene generated from **259** [80]. Cyclization of 3,4-didehydrophenanthrene **261** gave rise to the polycyclic compound **262**, which has a double helicene structure, in 26 % yield [81].

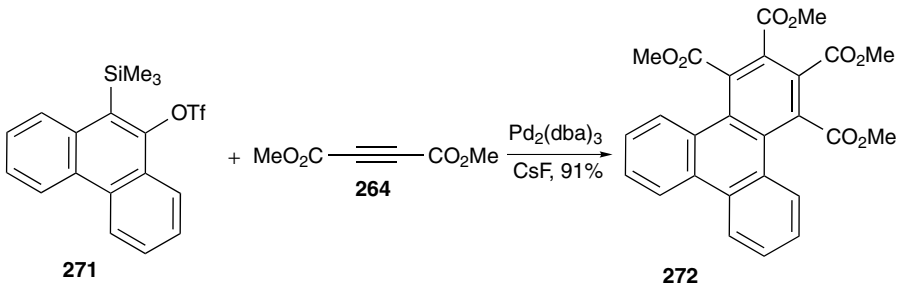


Pd-catalyzed cocyclization of arynes with alkynes also proceeds smoothly. Yamamoto obtained phenanthrene derivatives exclusively in good yield, regardless of the electronic nature of the alkynes using $Pd(OAc)_2$ and P(*o*-Tol)$_3$. The reaction of **251** with 4-octyne gave rise to the phenanthrene **263** [82]. Similarly, Perez carried out the reaction of benzyne with electron-deficient alkynes such as dimethyl acetylenedicarboxylate (DMAD) (**264**), and obtained the phenanthrene **265** as the main product using $Pd(PPh_3)_4$. On the other hand, when $Pd_2(dba)_3$ was used, the naphthalene derivative **266** was the main product [83].

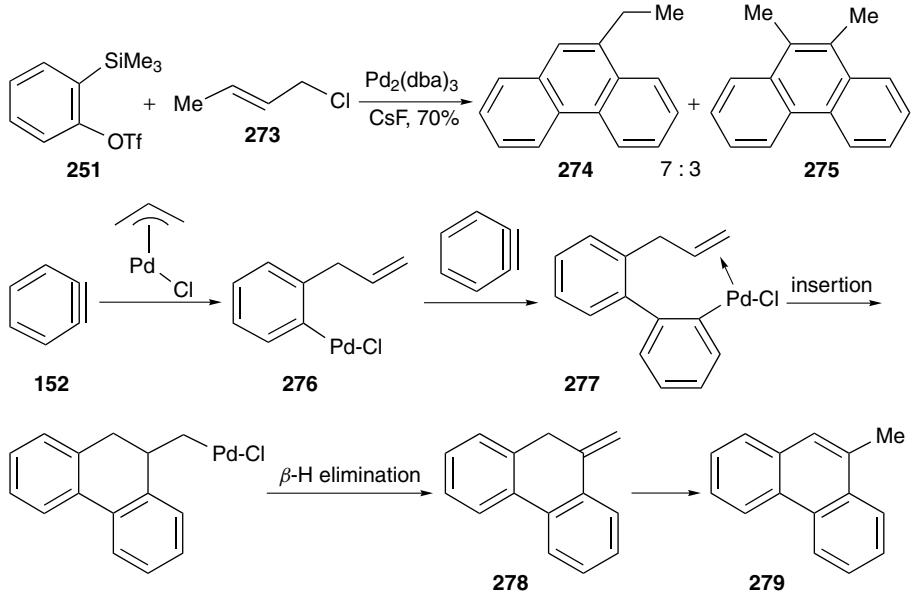


The polycyclic arynes derived from phenanthrenes **267**, **269**, and **271** underwent cocyclization with two molecules of DMAD, giving the tetraesters **268**, **270**, and **272**, respectively, in good yield [84,85].

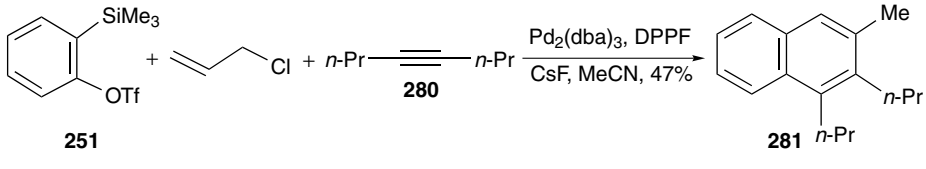




Yamamoto *et al*. found that benzyne and methallyl chloride **273** underwent an interesting 2 : 1 cycloaddition to afford the phenanthrenes **274** and **275** using phosphine-free $Pd_2(dba)_3$ [86]. This novel reaction is explained by the following mechanism. First, insertion of benzyne to π-allylpalladium generates **276**, which undergoes the insertion of benzyne again to give **277**. Subsequent intramolecular alkene insertion, and β-H elimination provide **278**, and then **279**.



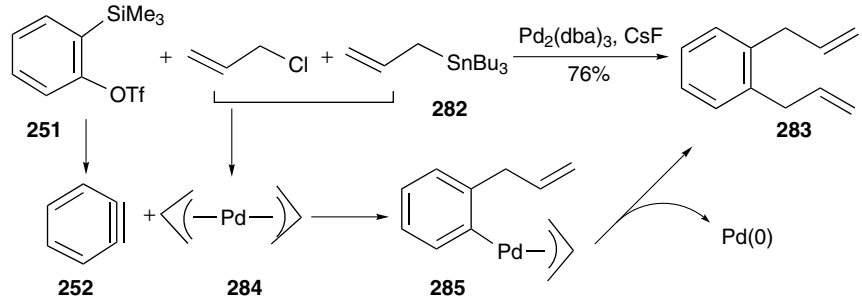
Furthermore, the 1 : 1 : 1 cycloaddition of benzyne generated from **251**, allyl chloride, and alkyne **280** afforded the naphthalene **281** [86].



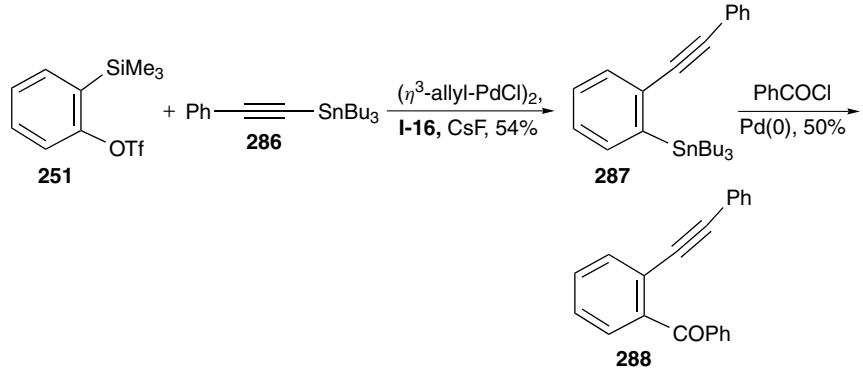
7.2.2 Addition Reactions of Arynes

1,2-Diallylbenzene (**283**) was obtained by the reaction of benzyne (**252**) with allyl chloride and allylstannane **282**. Yamamoto *et al*. reported that Pd-catalyzed

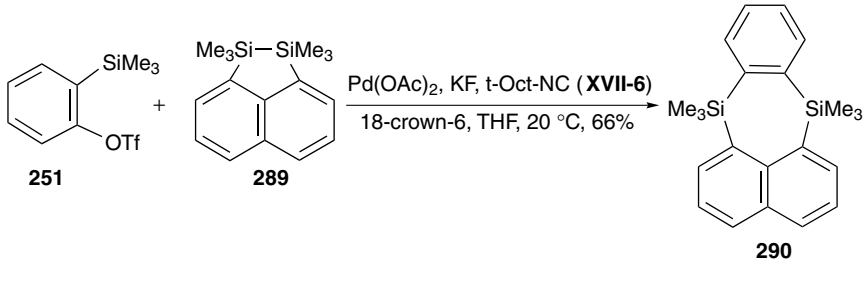
reaction of allyl chloride and allylstannane generates bis-π-allylpalladium (**284**), and insertion of benzyne to **284** affords **285**, and subsequent reductive elimination yields diallylbenzene (**283**) [87].



Carbostannation of arynes with alkynylstannanes such as **286** as well as alkenylstannanes is catalyzed by Pd-iminophosphine (**I-16**) complex to give rise to 2-alkynylphenylstannane **287**, which is convertible to a variety of 1,2-functionalized arenes such as **288** [88].

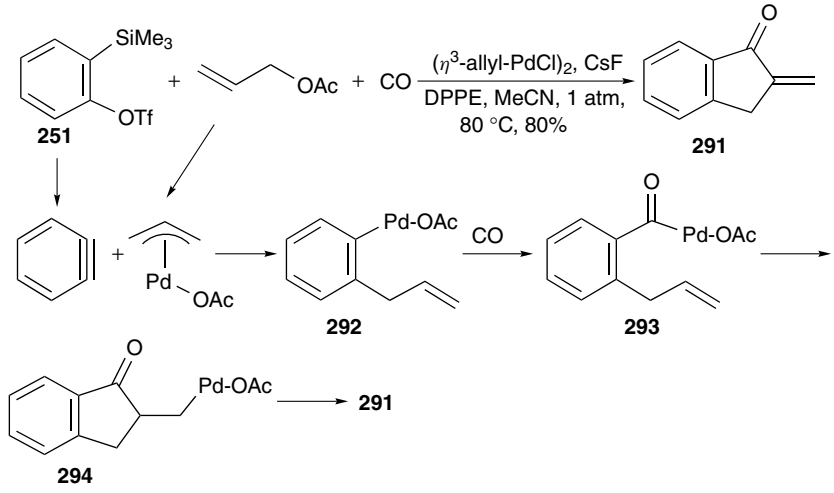


Bis-silylation of benzyne with the disilane **289**, catalyzed by the Pd complex of *t*-octyl isocyanide (**XVII-6**) gave the 1,2-disilylbenzene derivative **290** [89].



Benzyne can be carbonylated in the presence of allyl acetate to give 2-methyleneindanone **291** under atmospheric pressure of CO using DPPE as a ligand [90]. In this reaction, at first the 2-allylphenylpalladium **292** is generated.

CO insertion affords the acylpalladium **293**, and the following intramolecular insertion of alkene to the acylpalladium bond in **293** provides **294**, which is converted to **291** by β-H elimination.



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Chapter 8

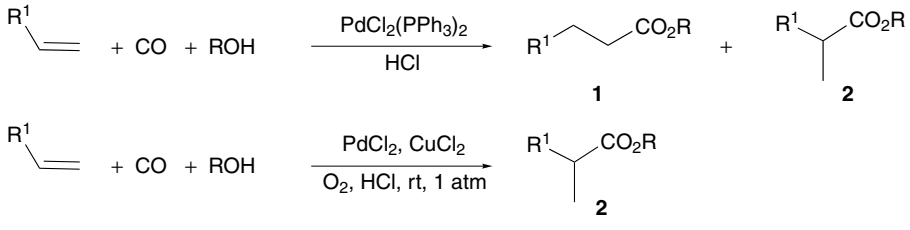
Pd(0)-Catalyzed Reactions of Alkenes

Various reactions of alkenes are surveyed separately in several chapters. Pd(II)-promoted oxidative reactions of alkenes are treated in Chapter 2.2 and Pd(0)-catalyzed reactions of alkenes with organic halides are discussed in Chapter 3.2. Other Pd(0)-catalyzed reactions of alkenes are discussed in this chapter.

8.1 Carbonylation

The oxidative carbonylation of alkenes, which is promoted by Pd(II), is described in Chapter 2.2.7. The Pd(0)-catalyzed carbonylation reactions, which are mechanistically different from the oxidative carbonylation, are treated in this section.

Preparation of carboxylic acids and esters by the reaction of alkenes, CO, and water or alcohols can be carried out under mild conditions. The reaction is called hydrocarboxylation or hydroesterification of alkenes, and $PdCl_2(PPh_3)_2$ as a standard catalyst precursor is used in the presence of acids such as HCl as a proton source [1]. Usually a mixture of linear and branched esters **1** and **2** are obtained. Their ratios depend on the structure of the alkenes and catalytic species, and control of the regioselectivity is an important problem. Carbonylation of 1-alkenes proceeds under mild conditions (room temperature, 1 atm) to give branched esters **2** with high selectivity using $PdCl_2$ in the presence of $CuCl_2$, HCl, and O_2 (Alper recipe) [2]. Interestingly, although the Alper's carbonylation is carried out in the presence of $CuCl_2$ and O_2, no oxidative carbonylation occurs.



Several Pd complexes have been claimed to be highly active catalysts. The linear ester **4** was obtained as the main product along with the branched ester **3** as the minor product by the carbonylation of 1-octene using $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$

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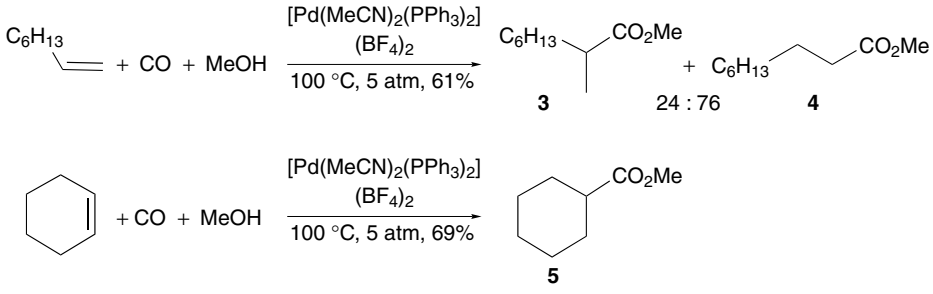
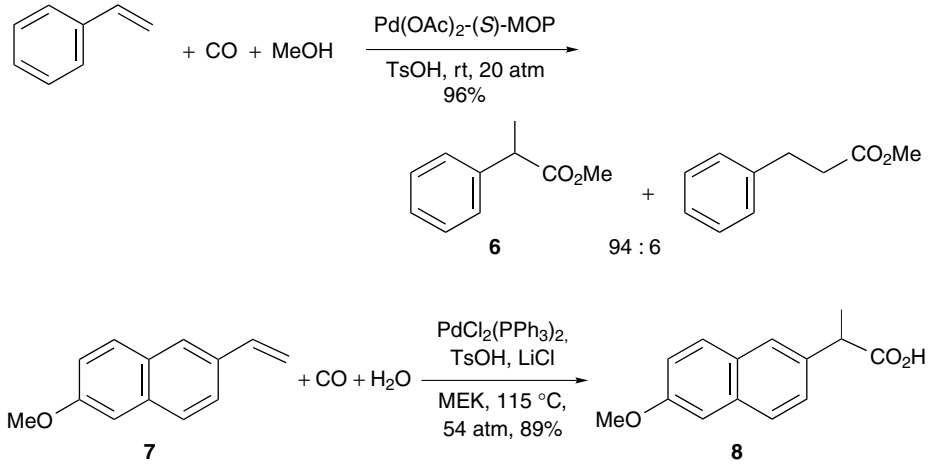


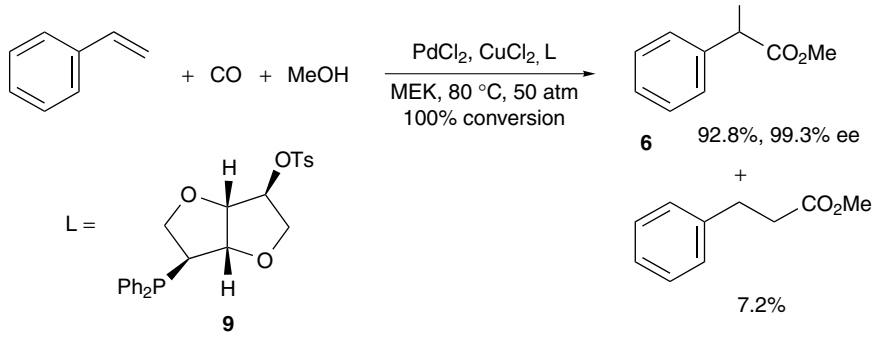
[3]. Also cyclohexene was carbonylated smoothly to afford methyl cyclohexanecarboxyl are (**5**) with this catalyst.

$Pd(OAc)_2$ immobilized on montmorillonite is an active catalyst for carbonylation in MeOH in the presence of PPh_3 to give branched esters [3a]. The branched ester **6** was obtained from styrene in 96 % yield with 94 % selectivity using $Pd(OAc)_2$-(*S*)-MeO-MOP (**VI-12**) in the presence of *p*-TsOH, although % ee was negligible [3]. The commercially important branched ester **8** was obtained in 89 % yield with 97.5 % selectivity from 2-vinyl-6-methoxynaphthalene (**7**) using $PdCl_2(PPh_3)_2$ and *p*-TsOH and LiCl as effective promoters [4]. The Pd complex of pyridine-2-carboxylic acid is an active catalyst for carbonylation of alkenes with alcohols [5]. Carboxylic acids are prepared by the carbonylation in water by the use of water-soluble phosphines such as **II-8** in the presence of *p*-TsOH [5a].

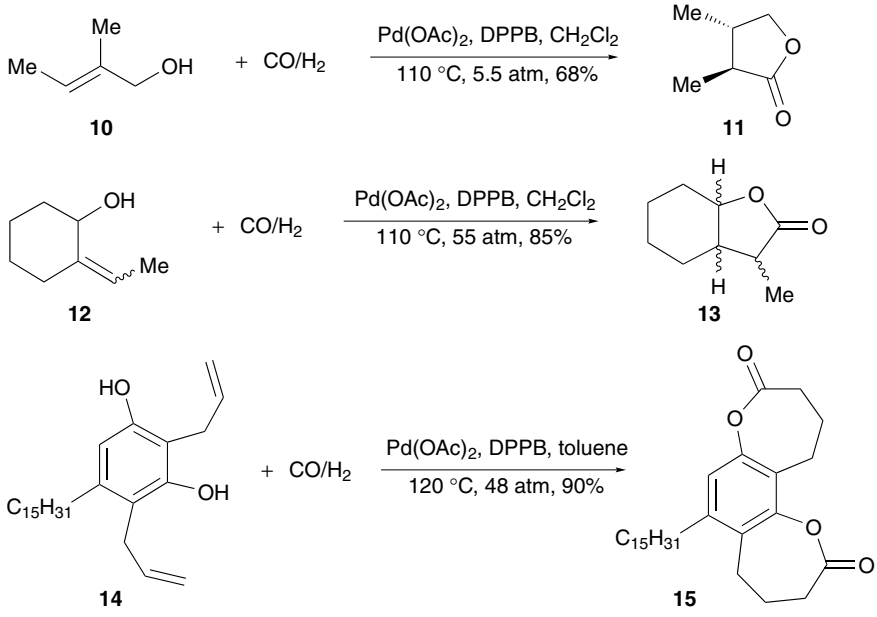


The formation of branched esters suggests the potential for asymmetric carbonylation. Only a few successful asymmetric carbonylations are known. Zhou and co-workers reported the highly successful asymmetric carbonylation of styrene. They obtained the branched ester **6** with 99.3 % ee and high regioselectivity of the branched ester using the Alper catalyst, $PdCl_2$-$CuCl_2$ in the presence of the chiral monophosphine DDPPI **9** in methyl ethyl ketone [6].

Cyclocarbonylation of substituted allylic alcohols to give rise to γ-lactones proceeds regio- and stereoselectively using DPPB as a ligand under pressure of CO and H_2 in dichloromethane. It is claimed that the presence of H_2 is essential

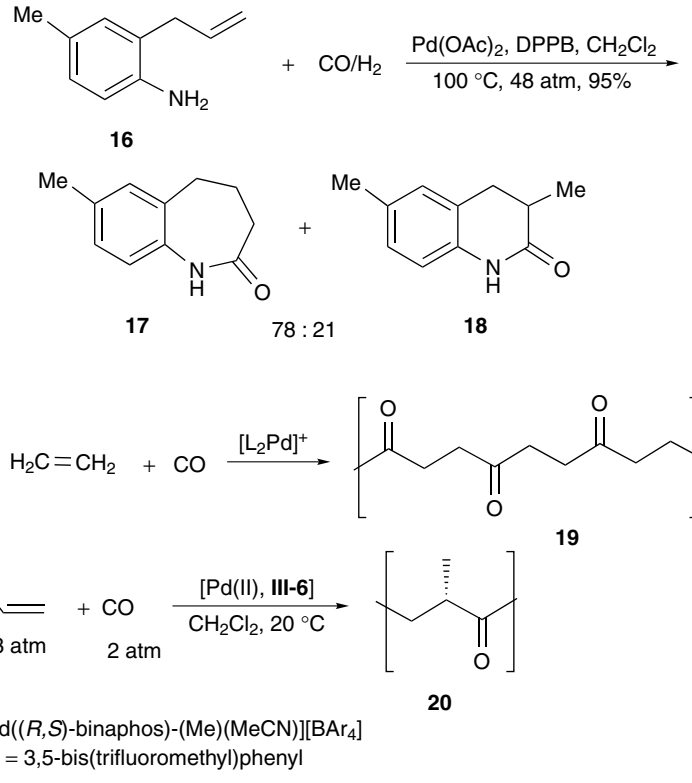


for the lactone formation. Carbonylation of (*E*)-allylic alcohol **10** afforded the *trans*-disubstituted lactone **11**. The 2-alkylidenecyclohexanol **12** was converted to a mixture of stereoisomers, which is known as an insect repellent **13** [7]. Carbonylation of 2-allylphenol in dichloromethane using DPPB gave the seven-membered lactone as a main product (52 %) and six-membered lactone in 21 % yield [8]. As an application, carbonylation of 2,4-diallyl-1,3-dihydroxy-5-alkylbenzene **14** under CO and H_2 pressure using DPPB in toluene afforded the seven-membered lactone **15** regioselectively in 90 % yield [9].



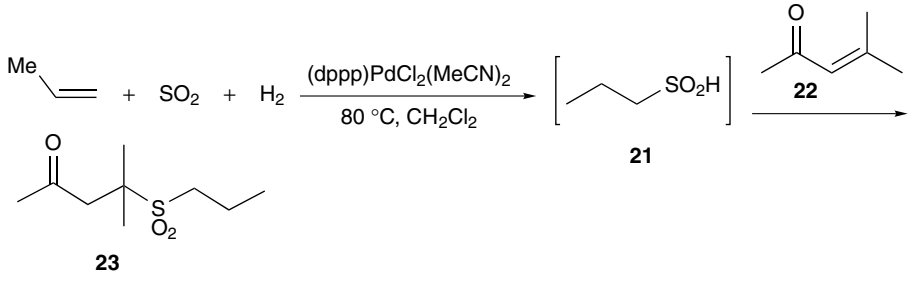
Under similar conditions, 2-allyl-4-toluidine (**16**) was converted to the seven-membered lactam **17** as the main product and the six-membered lactam **18** as the minor product under CO and H_2 pressure in 95 % total yield [8].

Carbonylation of some alkenes catalyzed by a cationic Pd complex yields polyketones, which are alternating copolymers. The polyketone **19** of ethylene or propylene named 'carilon' is produced commercially by Shell [10]. A Chain-transfer mechanism for the alternating copolymerization of CO and ethylene was proposed



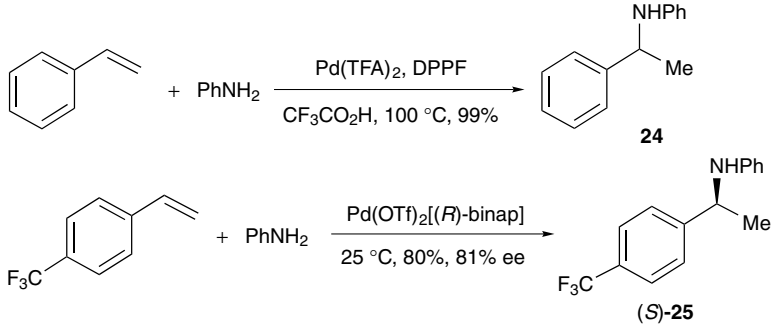
[11]. Nozaki and co-workers prepared the completely isotactic chiral polyketone **20** having (*S*) form and high molecular weight cleanly by copolymerization of CO and propylene at room temperature with very high enantioselectivity by using a cationic Pd complex coordinated by the asymmetric chiral phosphine–phosphite ligand [(*R*,*S*)-BINAPHOS](**III-6**). They showed that the enantioselectivity for the propylene insertion was at least 95 % ee [12]. The high enantioselectivity is explained by the assumption that CO always coordinates at the position *trans* to the phosphine ligand, and propylene coordinates *trans* to the phosphite ligand.

As a related reaction, hydrosulfination of propylene with SO_2 and H_2 gives alkane sufinic acid **21**, which is unstable and trapped *in situ* by Michael addition to α,β-unsaturated ketones such as mesityl oxide (**22**), and the γ-oxo sulfone **23** is isolated in high yields. The hydrosulfination proceeds in CH_2Cl_2 using DPPP as a ligand [13].

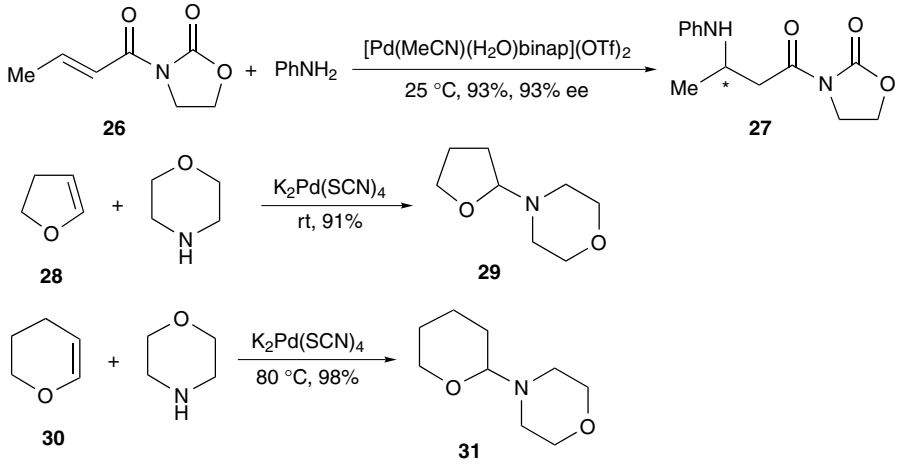


8.2 Hydroamination

Preparation of aliphatic amines by direct hydroamination of alkenes with amines is a highly desirable reaction. However, except for the well-established hydroamination of 1,3-dienes via π-allylpalladiums, no smooth hydroamination of simple alkenes is known. As a breakthrough, Kawatsura and Hartwig reported that the hydroamination of styrene derivatives with aniline is catalyzed by $Pd(TFA)_2$ and DPPF in the presence of trifluoroacetic acid (TFA) or triflic acid as a cocatalyst to afford the branched amine **24** regioselectively in 99 % yield. Formation of the branched amine **24** offers an opportunity of asymmetric amination. They obtained the (*S*)-amine **25** in 80 % yield with 81 % ee using (*R*)-BINAP as a chiral ligand [14]. The reaction is explained by insertion of styrene to the H-Pd bond and nucleophilic attack of amine on an η^3-benzylpalladium complex [15]. Hii and coworkers obtained the amine **24** with 70 % ee in 75 % yield using the dicationic Pd complex, $[Pd(MeCN)(H_2O)(R\text{-BINAP})](OTf)_2$ [16].



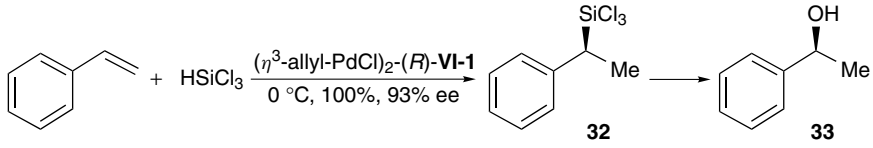
In addition, they carried out enantioselective Michael-type hydroamination of the alkenoyl-*N*-oxazolidinone **26** with aniline and obtained the chiral amine **27** with 93 % ee. Furthermore, they reported hydroamination of dihydrofuran (**28**) and 2,3-dihydropyran (**30**). Reaction of dihydrofuran (**28**) with morpholine proceeded at room temperature to give 2-aminotetrahydrofuran **29** regioselectively in high yield. Hydroamination of 2,3-dihydropyran (**30**) with morpholine proceeded at 80 °C to give 2-morpholinotetrahydropyran (**31**). For this hydroamination, phosphine-free



$K_2Pd(SCN)_4$ was used as an active catalyst. The hydroamination did not appear to be acid-catalyzed since sulfuric and *p*-toluenesulfonic acids failed to induce any reaction even after heating at 60 °C for 24 h [17].

8.3 Hydrometallation

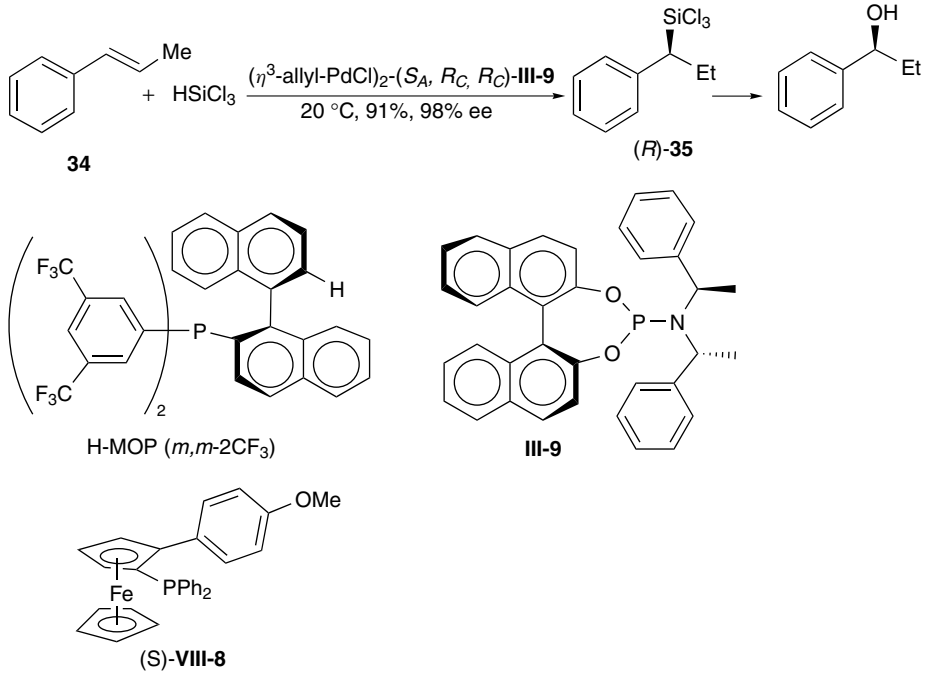
Mainly hydrosilylation has been studied as the hydrometallation of alkenes. Hydrosilylation of 1-alkenes is often carried out using reactive $HSiCl_3$. Triorganosilanes are less reactive. Hydrosilylation of 1-alkenes with $HSiCl_3$ produces terminal silanes as expected when PPh_3 is used. However, Hayashi and co-workers found that regioselectivity changes drastically when bulky ligands are used. The attack of the trichlorosilyl group at an internal carbon of the terminal double bond occurs and offers the possibility of asymmetric hydrosilylation. This is synthetically useful because chiral alcohols can be prepared by the Tamao method, that is, oxidative conversion of silyl groups to alcohols. Successful studies on asymmetric hydrosilylation of simple 1-alkenes, norbornene, and styrene have already been carried out extensively by Hayashi's group mainly by using MeO-MOP (**VI-12**) as a chiral ligand [18,19]. They found that H-MOP (**VI-1**) is more effective than **VI-12** for the hydrosilylation of styrene, and obtained the chiral 1-trichlorosilyl-1-phenylethane (**32**) with 93 % ee, which was converted oxidatively to the chiral alcohol **33**. Further modification of H-MOP ligand improved the efficiency. For example, the highest % ee (98 % yield) was obtained for hydrosilylation of styrene when H-MOP(*m*,*m*-$2CF_3$), which has 3,5-ditrifluoromethylphenyl groups instead of phenyl, was used. While the silane with 97 % ee was obtained by hydrosilylation of 4-methoxystyrene using H-MOP(*m*,*m*-$2CF_3$), it was only 61 % ee when H-MOP was used [20].



32 33

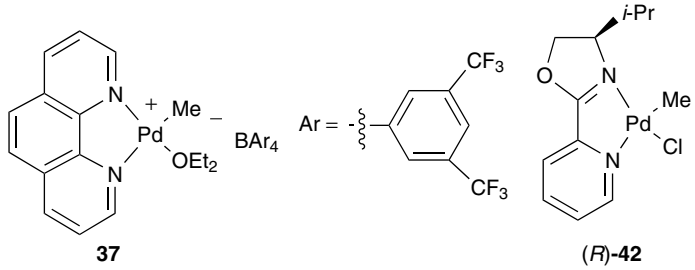
Johannsen and co-workers found that the phosphoramidite of axially chiral BINOL (**III-9**) is an effective chiral ligand, and they obtained **32** with 99 % ee in 87 % yield from styrene. Also they prepared 1-trichlorosilyl-1-phenylpropane (**35**) with 98 % ee in 91 % yield by the hydrosilylation of β-methylstyrene (**34**) with this ligand, and chiral 1-phenyl-1-propanol was prepared from **35** [21]. Furthermore, they claimed that arylmonophosphinoferrocene was an efficient ligand. In particular, the *p*-MeO-Ph-MOPF (**VIII-8**) they synthesized was the most effective ligand for asymmetric hydrosilylation of styrene, and ultrafast asymmetric hydrosilylation occurred with TOF exceeding 180 000 h^{-1} [22].

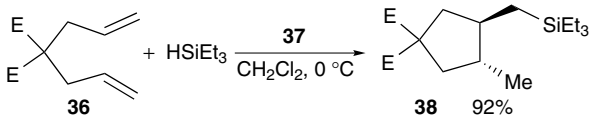
As an extension of hydrosilylation of alkenes, cyclization-hydrosilylation of 1,6-dienes occurs by the reaction with $HSiR_3$ [23]. The cationic complex **37**, generated *in situ* from (phen)Pd(Me)Cl and $NaBAr_4$, is an active catalyst, catalyzing the reaction of dimethyl diallylmalonate (**36**) with $HSiCl_3$ to give the disubstituted cyclopentane **38** with 98 % *trans* selectivity in 92 % yield [24]. A mechanism different from that of usual hydrosilylation, which postulates formation of H-Pd-SiR_3 and hydropalladation of alkene, was proposed by Widenhoefer



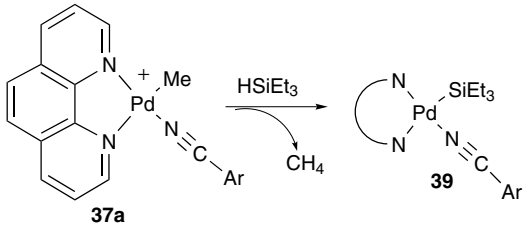
for the cyclization–hydrosilylation. At first, generation of silylpalladium **39** is assumed. Insertion of **36** to the Pd-Si bond in **39** (silylpalladation) provides alkylpalladium **40**. Cyclization of **40** gives **41**, which reacts with $HSiEt_3$ to produce the product **38** and regenerates the catalytic species **39**.

The polycyclic compound **44** was obtained efficiently in 74 % yield by domino cyclization–hydrosilylation of the triene **43** catalyzed by **37** with high diastereoselectivity (20 : 1) [26]. An asymmetric version has been carried out using a chiral catalyst precursor generated from (*N*,*N*)Pd(Me)Cl(*R*)-4-isopropyl-2-(2-pyridyl)-2-oxazoline (**42**) and $NaBAr_4$. Reaction of **36** with $HSiEt_3$ using **42** afforded the (*S*,*S*)-cyclopentane **45** in 82 % yield with 87 % ee [25,27]. The triethylsilyl group in **45**, obtained by hydrosilylation with $HSiEt_3$, can not be oxidized to the corresponding alcohol due to low reactivity. Therefore the cyclization–hydrosilylation of the 1,6-diene **46** was carried out using pentamethyldisiloxane (**47**), and the cyclized product **48** was oxidized smoothly to the alcohol **49** with 76 % ee in 82 % overall yield [27]. Cyclization–hydrosilylation of 1-cyclopropyl-1,6-diene **50** with a siloxane proceeded smoothly using **37** as a catalyst, and the cyclopentane **51** was obtained in 93 % yield [28].

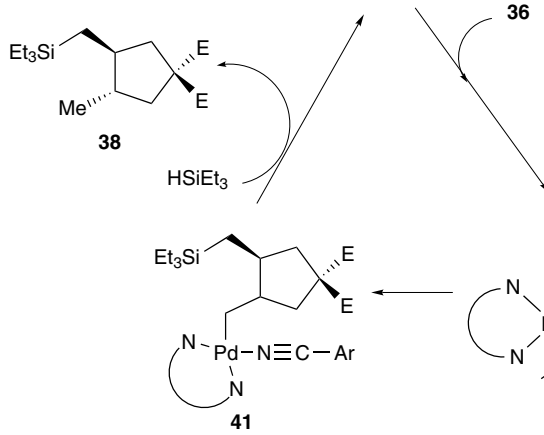


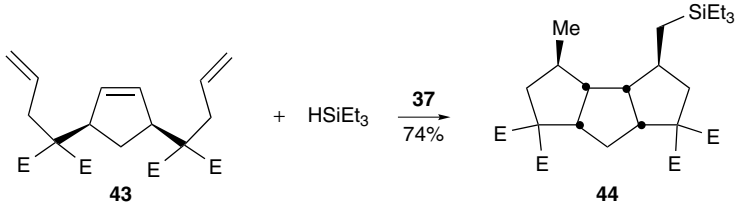


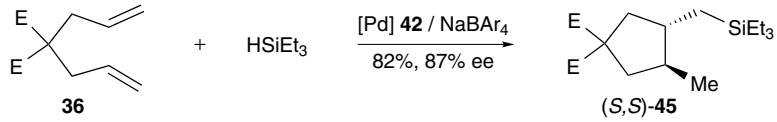
36 **38** 92%

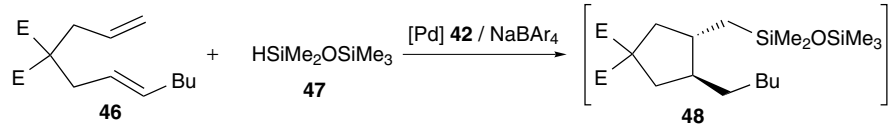


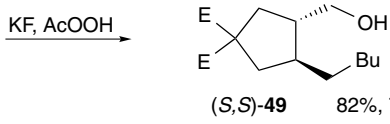
37a **39**

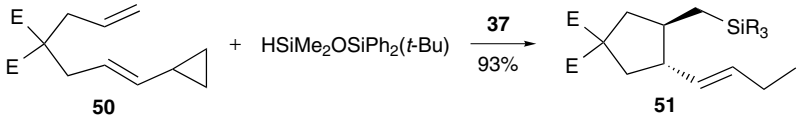




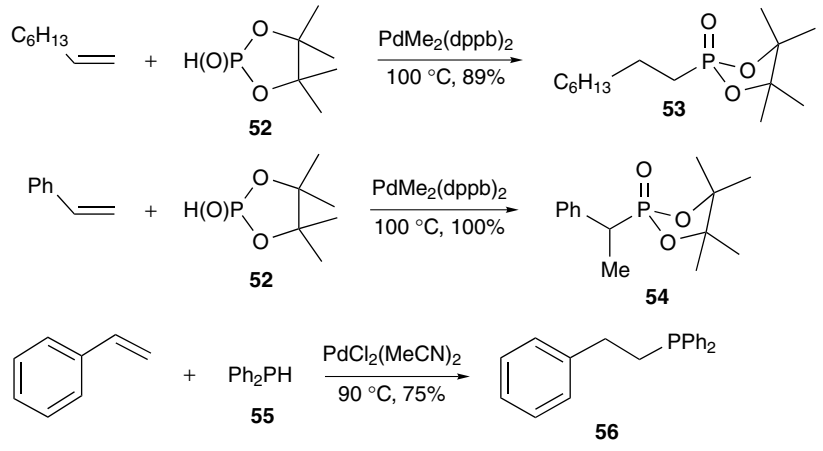






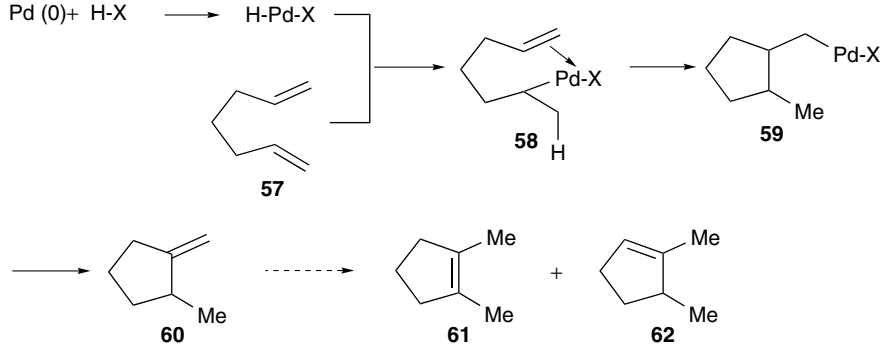


Hydrophosphorylation of alkenes has been regarded as a rather difficult reaction. Tanaka discovered that efficient hydrophosphorylation of simple alkenes and cyclic alkenes is possible by using the five-membered cyclic phosphonate **52**. The reaction of 1-octene with **52** proceeded at 100 °C to afford the linear phosphonate **53** in 89 % yield. Regioselectivity depends on the nature of the alkenes, and the branched phosphonate **54** was formed by the reaction of styrene. DPPB was found to be a suitable ligand [29]. Hydrophosphination of styrene with diphenylphosphine (**55**) proceeded regioselectively by using phosphine-free Pd catalyst to afford 2-phenylethyl(diphenyl)phosphine (**56**) [30].



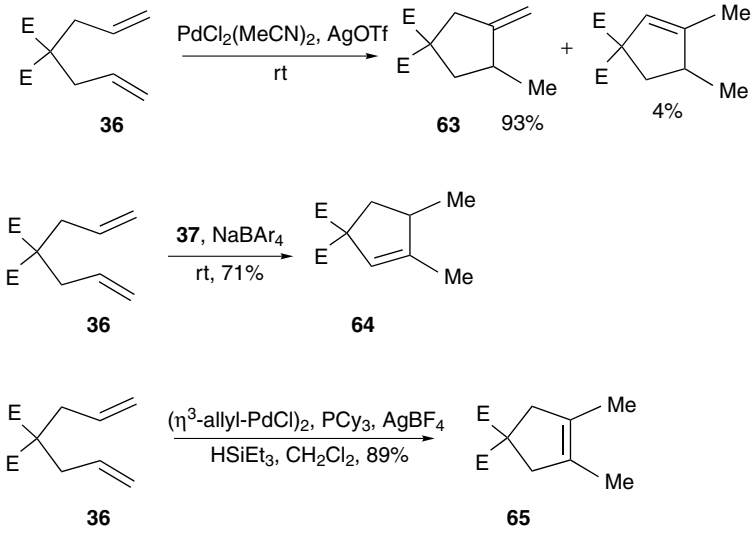
8.4 Miscellaneous Reactions

In the presence of a proton source, 1,6-heptadiene (**57**) undergoes cycloisomerization to afford 1,2-disubstituted cyclopentenes. Insertion of one of the double bonds of **57** to H-Pd-X generates **58**. Further insertion of the double bond in **58** gives **59**, and β-H elimination affords **60**, **61**, and **62** depending on the reaction conditions [23].

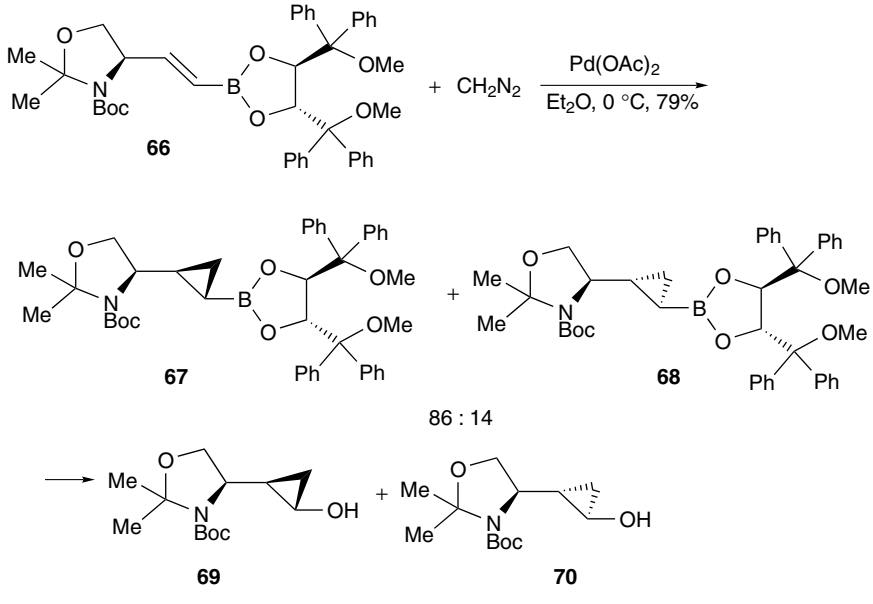


Lewis acids as cocatalysts are effective for Pd-catalyzed cycloisomerization. The reaction of diallylmalonate **36** in the presence of AgOTf afforded **63** with high selectivity [31]. Asymmetric cyclization of 1,6-diene **36** was carried out using $PdCl_2(MeCN)_2$-$AgBF_4$ in the presence of a chiral ligand [32]. Cycloisomerization

of **36** was catalyzed by **37** to afford **64** in 71 % yield [33]. Furthermore, reaction of the 1,6-diene **36** with an equivalent amount of $HSiEt_3$ gave unexpectedly the cycloisomerization product **65** as the major product when π-allylpalladium-PCy_3 and $NaBAr_4$ were used without giving the expected cyclization–hydrosilylation product **45** [34].



The $Pd(OAc)_2$-catalyzed cyclopropanation of alkenes with diazomethane is a good synthetic method for cyclopropanes and has been used extensively. As a recent example, reaction of alkenylboronate **66** with diazomethane afforded two isomeric cyclopropanes **67** and **68** in 79 % yield with a diastereomeric ratio of 86 : 14, and they were converted to cyclopropyl alcohols **69** and **70** [35].



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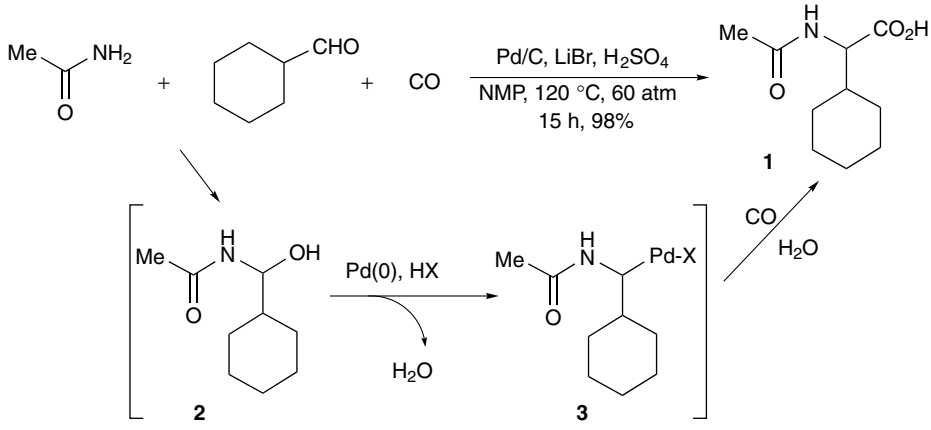
Chapter 9

Pd(0)-Catalyzed Miscellaneous Reactions of Carbon Monoxide

Several Pd(0)-catalyzed reactions which are not covered in Chapters 2–8 are treated in this chapter. A useful preparative method of *N*-acylamino acids by the reaction of amides, aldehydes, and CO is known as amidocarbonylation, and cobalt carbonyl is an active catalyst [1]. Beller *et al*. found that the reaction can be also catalyzed by Pd complexes. Reaction of acetamide, cyclohexanecarboxaldehyde, and CO (60 atm) at 120 °C using ligandless Pd/C as a catalyst in NMP in the presence of LiBr and H_2SO_4 afforded the acylamino acid **1** in 98 % yield [2]. In this reaction, *N*-α-hydroxyalkylamide **2** is formed from amide and aldehyde, and converted to the alkylpalladium complex **3**. Acylamino acid **1** is formed by CO insertion.



Imidazolidine-2,4-diones, generally called hydantoins, are prepared when urea and N-substituted ureas are used instead of amides in the amidocarbonylation. Carbonylation of cyclohexanecarboxaldehyde, and *N*,*N*-dimethylurea (**4**) in NMP using $PdBr_2$ and PPh_3 in the presence of LiBr and H_2SO_2 afforded the hydantoin **5** in 80 % yield [3].

Dghaym *et al*. reported that α-amino acid derived imidazoline **7** can be synthesized by Pd-catalyzed reaction of the imine **6**, CO, and benzoyl chloride using

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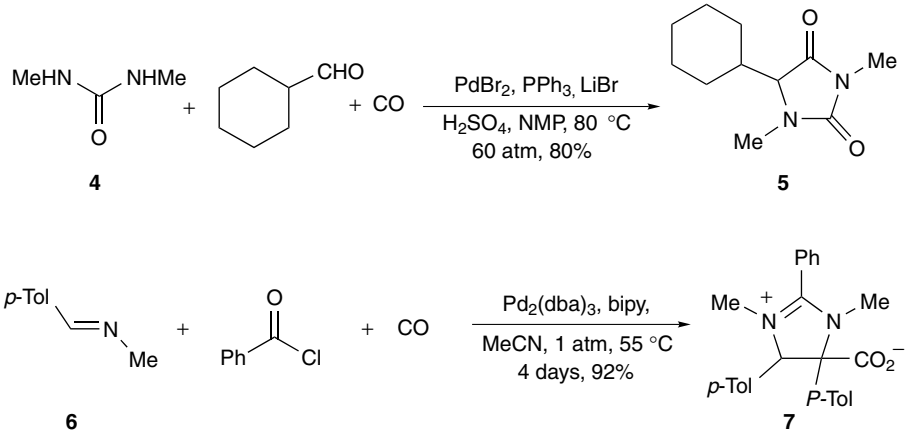
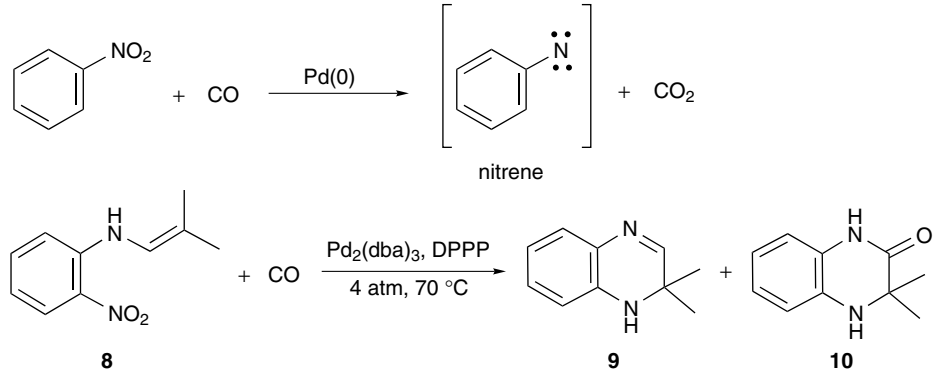


$Pd_2(dba)_3$ and 2,2′-bipyridine as a ligand under atmospheric pressure of CO at 55 °C for 4 days in 92 % yield [4].

It is known that nitrene can be generated by Pd-catalyzed deoxygenation of organic nitro compounds with CO. Based on the nitrene formation, carbonylation of the enamine **8**, derived from 2-nitroaniline and α-substituted aldehyde, was carried out using $Pd(dba)_2$ and DPPP and a mixture of 1,2-dihydroquinoxaline **9** (71 % yield) and 3,4-dihydroquinoxalinone **10** (11 % yield) was obtained [5].



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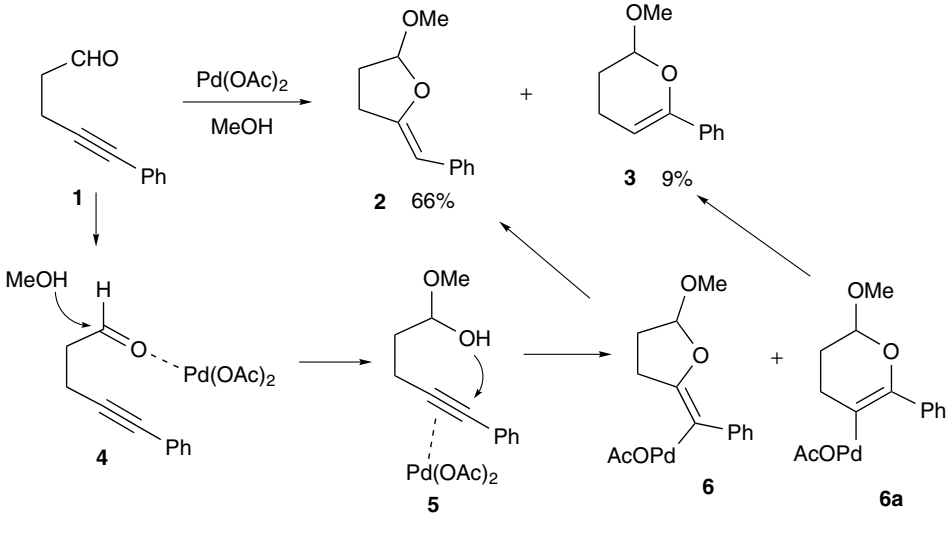
Chapter 10

Miscellaneous Reactions Catalyzed by Chiral and Achiral Pd(II) Complexes

Some Pd(II) compounds are known to behave as moderate, but very efficient Lewis acids, and to catalyze several reactions, which are known to be catalyzed by common Lewis acids under milder conditions. Pd(II) compounds activate substrates by forming complexes with lone pairs of C=Y (Y = O, N) and facilitate nucleophilic attack to electronically positive carbons.

As an example, formation of cyclic alkenyl ethers **2** and **3** from acetylenic aldehyde **1** is catalyzed by $Pd(OAc)_2$. Also, 2-alkynylbenzaldehyde **7** was converted to the cyclic alkenyl ether **8** in high yield in the presence of $Pd(OAc)_2$ (5 mol%) in MeOH. In these reactions, $Pd(OAc)_2$ as a Lewis acid, coordinates to the carbonyl group to facilitate the formation of the hemiacetals as shown by **5**. Then either 5-*exo* or 6-*endo* cyclization (oxypalladation of triple bond) occurs to give **6** or **6a**. Finally, protonolysis of **6** and **6a** affords the cyclized products **2** and **3** with regeneration of $Pd(OAc)_2$. In this reaction, $Pd(OAc)_2$ exhibits dual roles [1].



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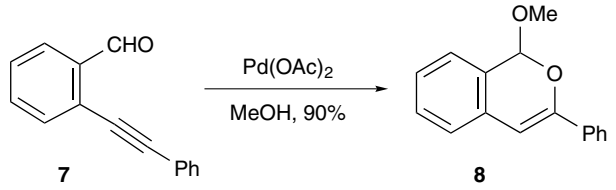
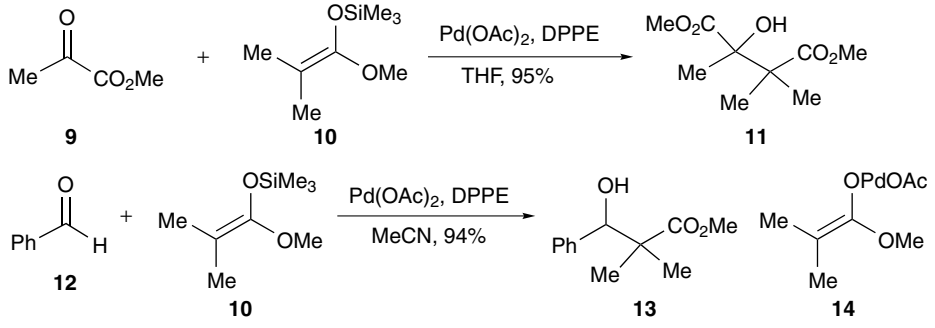
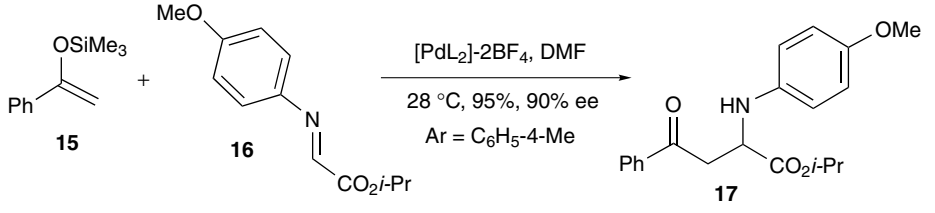
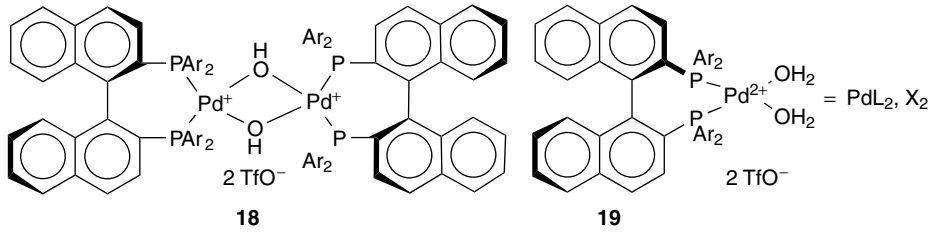


$Pd(OAc)_2$, combined with DPPE, catalyzes aldol condensation of aldehydes or ketones with ketene silyl acetal (Mukaiyama reaction) under neutral conditions. The ketene silyl acetal of methyl isobutyrate (**10**) reacted smoothly with methyl pyruvate (**9**) or benzaldehyde (**12**) in THF or MeCN using 0.1 % of the catalyst. In this reaction the Pd enolate **14** is generated by transmetallation of the ketene silyl acetal with $Pd(OAc)_2$, and the Pd moiety as a Lewis acid activates the carbonyl group to facilitate the attack by the enolate to provide **11** and **13** [2].

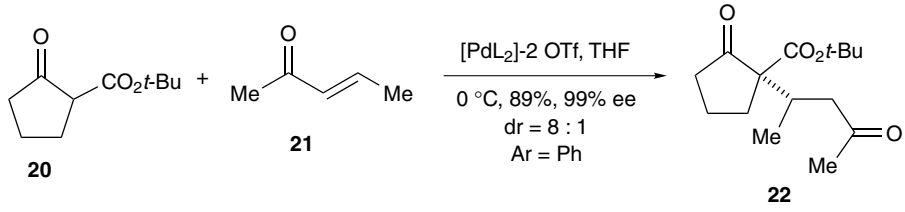


Sodeoka found that Pd(II) hydroxide complexes of BINAP derivatives **18** are excellent catalysts for asymmetric synthesis. Pd enolates are generated from silyl enol ethers by transmetallation. The asymmetric Mannich-type reaction of silyl enol ether of acetophenone (**15**) with the imine **16** proceeded smoothly using Pd complex of Tol-BINAP, and the ester of amino acid **17** with 90 % ee was obtained in 95 % yield [3].



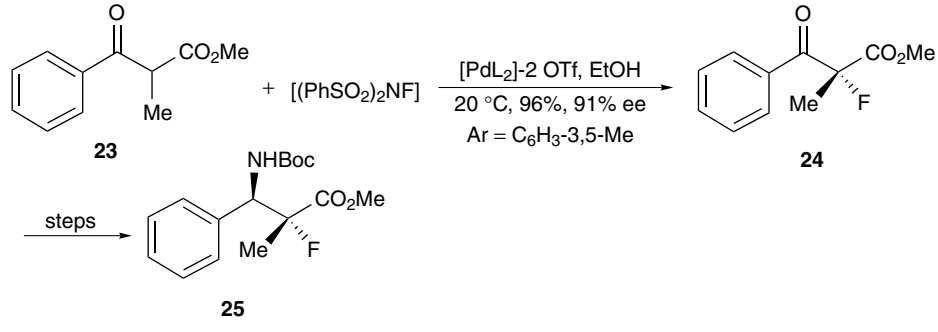


The Pd diaquo complex of BINAP **19** efficiently catalyzed the diastereoselective and enantioselective Michael addition of the β-keto ester **20** to 3-penten-2-one (**21**), and the Michael adduct **22** was obtained in 89 % yield (diastereomeric ratio = 8/1) and the ee of the major isomer was 99 %. Thus, congested vicinal tertiary and quaternary carbon centers were constructed. It is interesting to know that the Pd aquo complex **19** allows the successive supply of a Brönsted base and a Brönsted acid. The former activates the carbonyl compound to give the chiral palladium enolate and the latter cooperatively activates the enone [4].

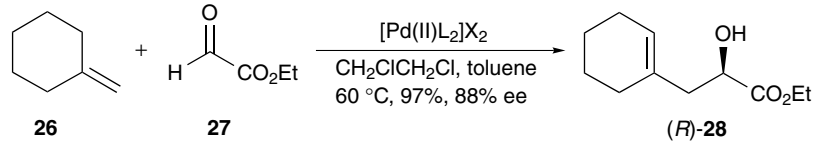


Lectka has shown that (*R*)-BINAP-Pd$(ClO_4)_2$, is effective for enantioselective reaction of imines with silyl enol ethers such as **15**. While Sodeoka used the aquo complexes, Lectka carried out the reaction under anhydrous conditions [5].

Efficient enantioselective fluorination of the β-keto ester **23** with $(PhSO_2)_2NF$ was achieved by using the (*R*)-DM-BINAP-Pd(II) complex in EtOH to give **24** with 91 % ee in 96 % yield, which was converted to a pharmaceutically important α-fluoro-β-amino acid ester **25** [6].

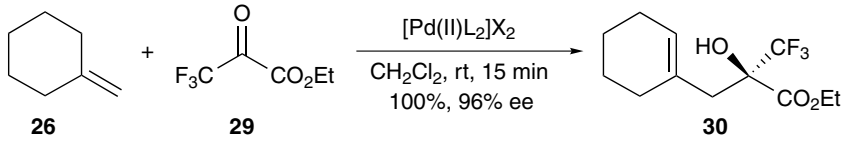


Furthermore, Pd(II) complexes catalyze asymmetric ene and Diels-Alder reactions. Mikami and co-workers reported enantioselective synthesis of α-hydroxy esters by the ene reaction of glyoxylate **27** using a chiral Pd catalyst. They obtained the (*R*)-hydroxy ester **28** with 88 % ee in 97 % yield by the reaction of methylenecyclohexane (**26**) with ethyl glyoxylate (**27**) at 60 °C using the cationic Pd(II) complex of (*S*)-Tol-BINAP [7].



$[Pd(II)L_2]X_2$ = $[Pd(MeCN)_2(S)$-Tol-BINAP$](SbF_6)_2$

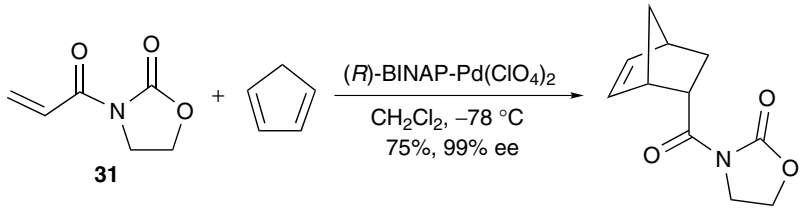
Ene reaction of **26** with ethyl trifluoropyruvate (**29**) proceeded with high enantioselectivity using the dicationic Pd catalyst prepared by the reaction of SEGPHOS (**XIV-3**)-$PdCl_2$ with $AgSbF_6$ to give **30** with 96 % ee quantitatively [8].



26 **29** **30**

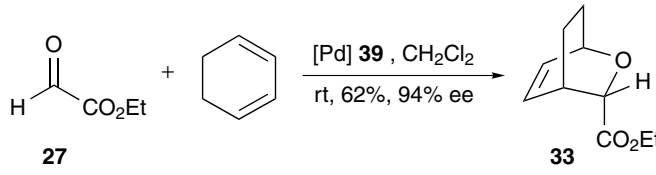
$[Pd(II)L_2]X_2$ = (*S*)-SEGPHOS-$PdCl_2$ + $AgSbF_6$

Ghosh found that the cationic (*R*)-BINAP-Pd(II) complex efficiently catalyzed the asymmetric Diels-Alder reaction of cyclopentadiene with acryloyl-*N*-oxazolidinone (**31**) at −78 °C, and obtained the *endo*-(2*S*)-cycloadduct **32** with 99 % ee in 75 % yield [9].



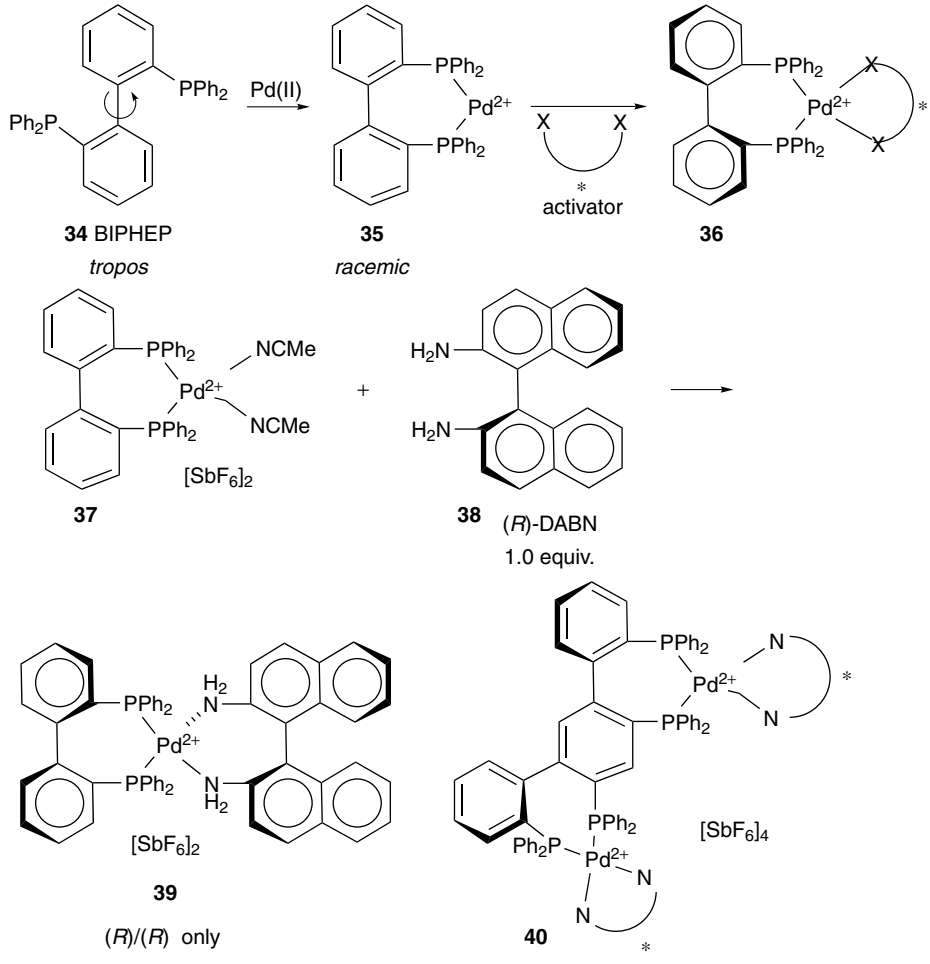
31 (2S)-**32**

Mikami carried out the asymmetric hetero Diels-Alder reaction of ethyl glyoxylate (**27**) with 1,3-cyclohexadiene and obtained the cycloadduct **33** with 94 % ee in 62 % yield [10].

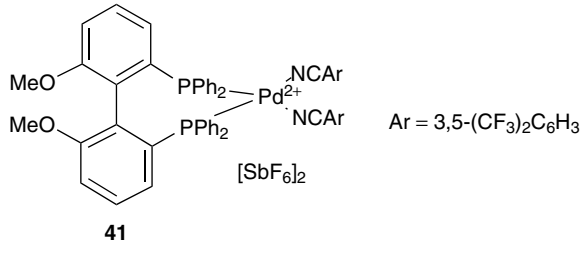


27 **33**

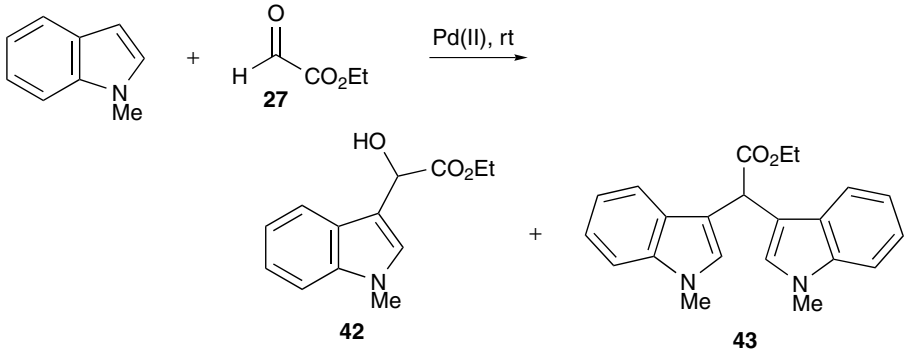
For this efficient asymmetric reaction, Mikami developed a very interesting chiral catalyst. He reasoned that the reaction of Pd(II) complex **35**, formed from BIPHEP **34**, which is *tropos* [11], with a chiral activator should give one of the diastereomers **36** selectively. Actually his group carried out the reaction of BIPHEP complex **37** with 1.0 equivalent of (*R*)-diaminobinaphthyl (DABN) **38**, and obtained (*R*)-BIPHEP-Pd/(*R*)-DABN **39** as a single diastereomer as expected, and this complex was used as the efficient chiral catalyst. By this unique strategy, 'asymmetric activation' of a racemic Pd catalyst bearing the *tropos* BIPHEP ligand was achieved without enantiomeric resolution or asymmetric synthesis. As further elaboration, Mikami has shown that TETRAPHOS-Pd/DABN **40** gives better results than **39** in the ene reaction of **26** with **27** [12].



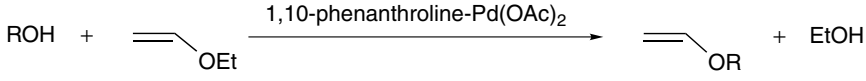
Gagne *et al*. group obtained high enantiomeric excesses (99 % ee) in the Diels-Alder reactions of **31** with cyclopentadiene, and the ene reaction of **26** with **27** using Pd complex of (*S*)-MeO-BIPHEP, coordinated by 3,5-di(trifluoromethyl)benzonitrile **41** [13].



A Friedel-Craft type reaction of *N*-methylindole with glyoxylate **27** is catalyzed by the Lewis acidity of Pd(II) complexes [14]. While the α-hydroxyindolylacetate **42** was obtained in 96 % yield when $PdCl_2(MeCN)_2$ was used, the diindolylacetate **43** was the main product when BIPHEP complex was used.

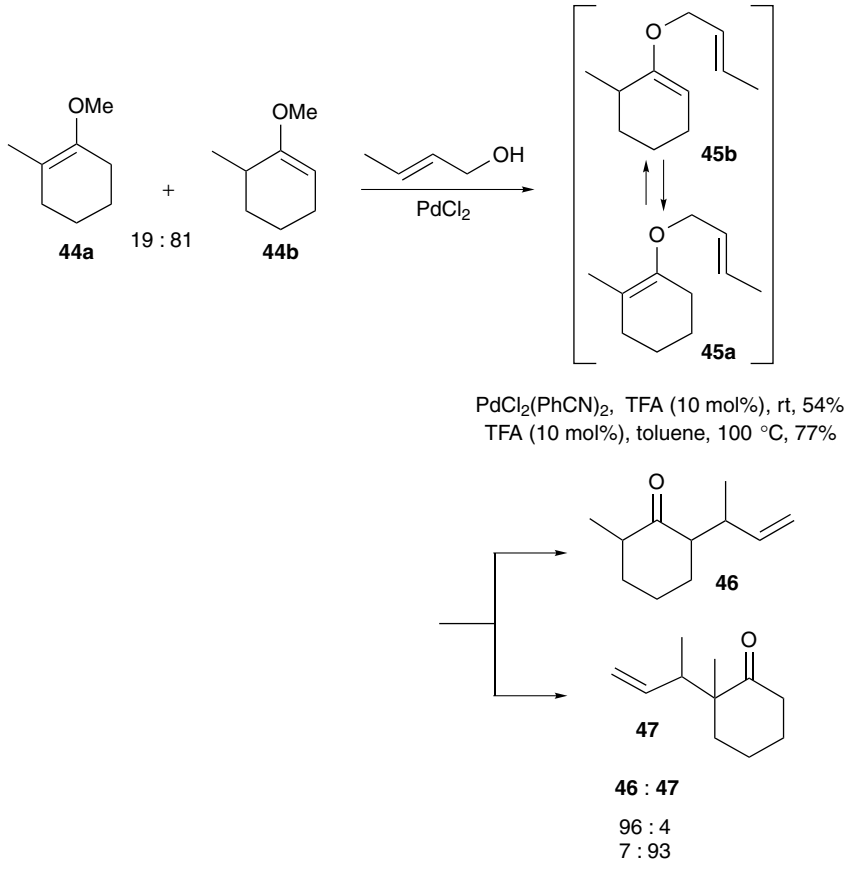


It is known that Claisen rearrangement of allyl vinyl ethers is catalyzed by Pd(II), and the reaction proceeds at room temperature [15]. Various vinyl ethers are prepared by the Pd(II)-catalyzed exchange reaction of easily available ethyl vinyl ether with alcohols. The phenanthroline–$Pd(OAc)_2$ complex is an active catalyst [16].



Sugiura and Nakai carried out Pd(II)-catalyzed regiocontrolled Claisen rearrangement of allyl vinyl ethers prepared by *in situ* enol ether exchange [17]. Treatment of a mixture of the regioisomers of 1-cyclohexenyl methyl ether **44a** and **44b** and 2-buten-1-ol in the presence of $PdCl_2(PhCN)_2$ and TFA (trifluoroacetic acid, 10 mol%) at room temperature afforded the cyclohexanones **46** and **47** in a ratio of 96 : 4 via *in situ* formation of the allyl enol ethers **45a** and **45b**. On the other hand, thermal rearrangement at 100 °C exhibited opposite regioselectivity, producing a mixture of **46** and **47** in a ratio of 7 : 93. Clearly Pd-catalyzed reaction provides the cyclohexanone **46** arising from the less-substituted enol ether **45b**. The enol ethers **45a** and **45b** are interconvertible under the conditions, and the regioselectivity seems to be determined by the difference in rate of rearrangement between the regioisomeric enol ethers **45a** and **45b**.

Miyaura and co-workers found that conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds can be carried out by using cationic Pd(II) complexes such as $[Pd(dppe)(PhCN)_2]X_2$ as catalysts. Neutral Pd complexes such as $PdCl_2(dppe)$ are not active. As anions, $X^- = ClO_4^-$, OTf^-, BF_4^-, PF_6^-, and SbF_6^- are effective. Coordination of DPPE and PhCN is important. The reaction proceeds at room temperature in THF or dioxane, and requires the presence of water. The addition of boronic acid **48** to cyclohexenone took place to give **49** in 95 % yield [18]. Also 3-phenylcyclohexanone (**50**) is prepared by the conjugate addition of $PhSi(OEt)_3$ to cyclohexenone [19].



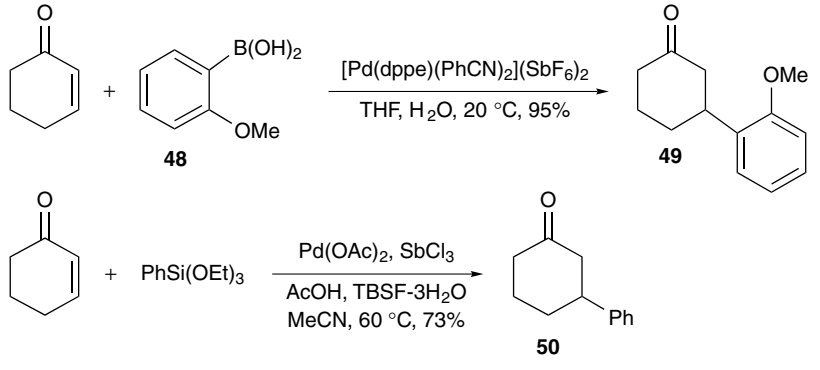


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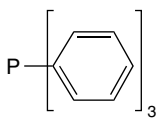
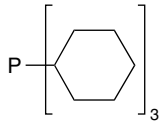
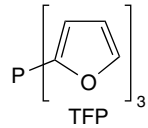
Table 1.1 Monophosphines.



I-1

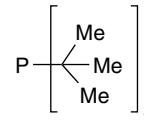


I-2

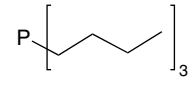


TFP

I-3



I-4



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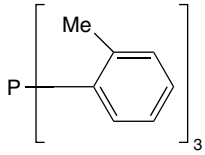

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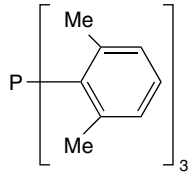

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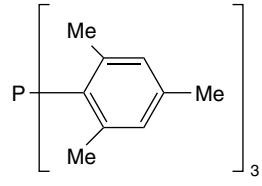

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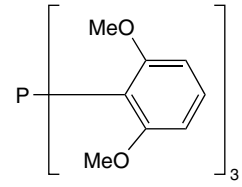
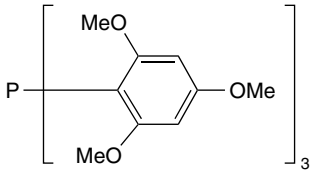


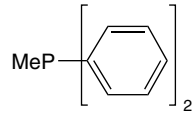
TDMPP

I-9



TTMPP

I-10



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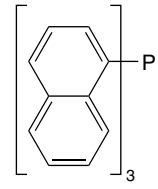

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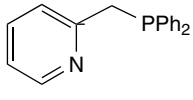

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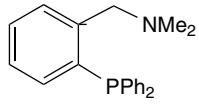

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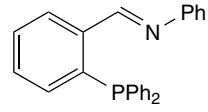

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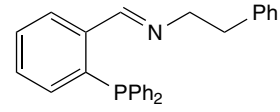
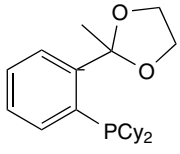
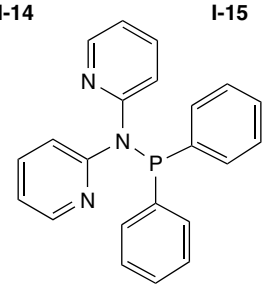


I-16



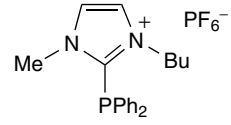
I-17

Tetrahedron Lett., **40**, 1237 (1999)



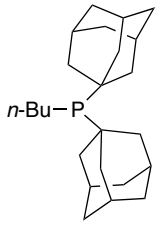
I-18

Angew. Chem. Int. Ed., **41**, 1521 (2002)

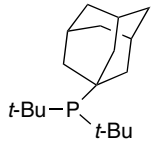


I-19

Synlett, 1613 (2000)



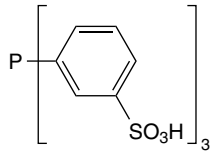
I-20



I-21

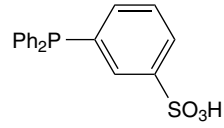
Palladium Reagents and Catalysts—New Perspectives for the 21st Century J. Tsuji
 ISBNs: 0-470-85032-9 (HB); 0-470-85033-7 (PB)

Table 1.2 Water-soluble phosphines.



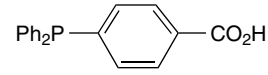
TSPP or TPPTS

II-1



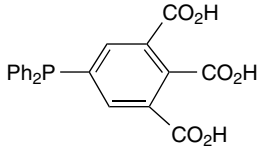
DPSPP or TPPMS

II-2

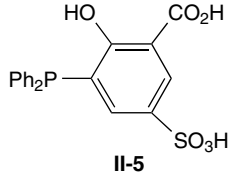


4-DPPBA

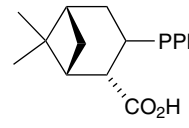
II-3



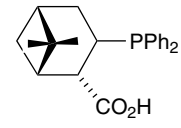
II-4



II-5

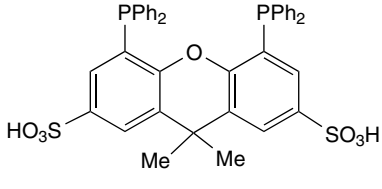


II-6



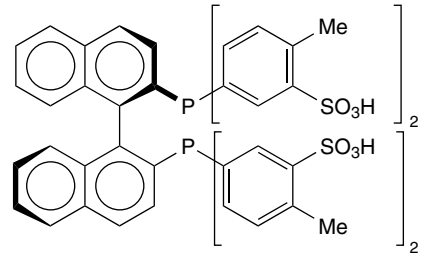
II-7

J. Organomet. Chem., **645**, 14 (2002)



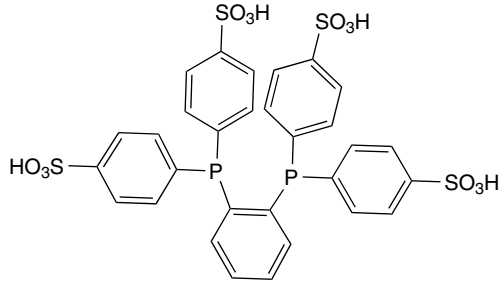
sulfoxantphos

II-8



(*R*)-TolBINAP, sulfonated

II-9



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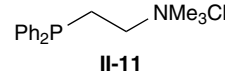

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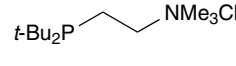

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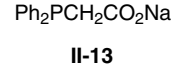

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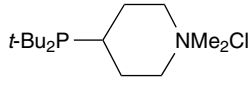

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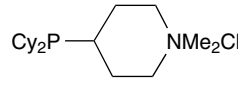
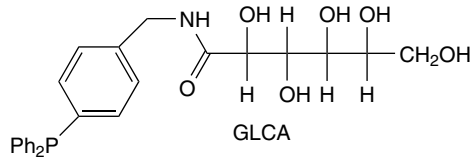


II-15

Org. Lett., **3**, 2757 (2001)

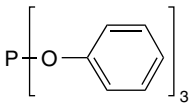


GLCA

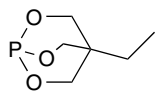
II-16

Synlett, 856 (2000)

Table 1.3 Phosphites.

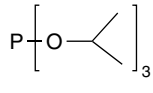


III-1

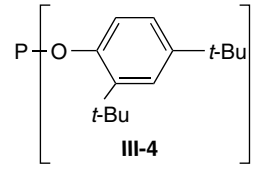


TMPP

III-2



III-3



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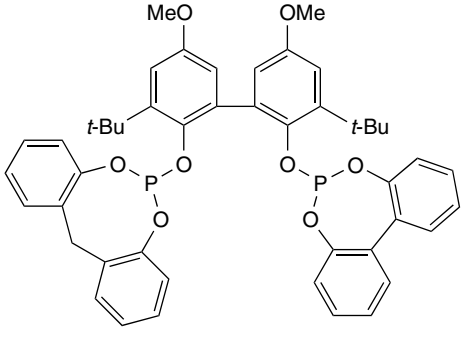
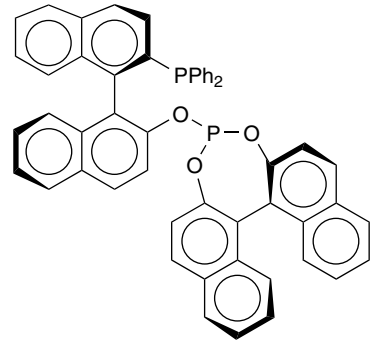


BIPHEPHOS

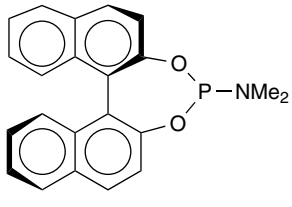
III-5



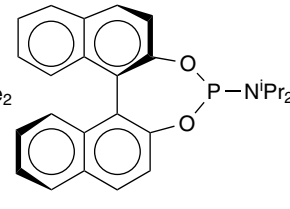
(*R,S*)-BINAPHOS

III-6

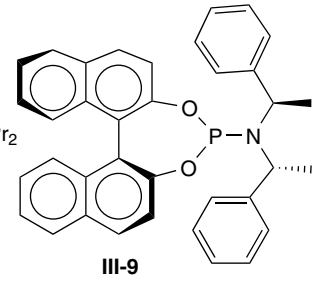
(*R*)-phosphoramidites



III-7

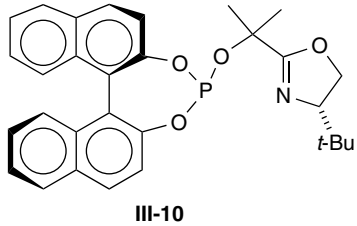


III-8

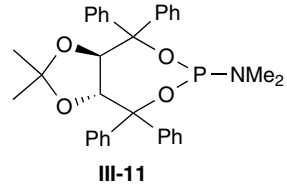


III-9

J. Am. Chem. Soc., **124**, 4558 (2002)



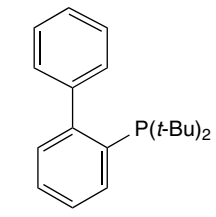
III-10



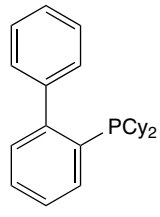
III-11

J. Am. Chem. Soc., **124**, 184 (2002)

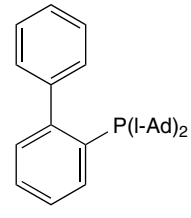
Table 1.4 Biphenyl-based monophosphines.



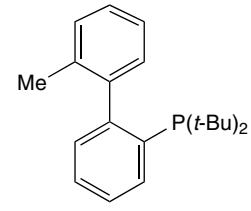
IV-1



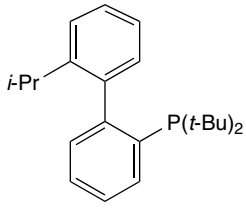
IV-2



IV-3



IV-4



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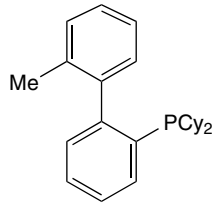

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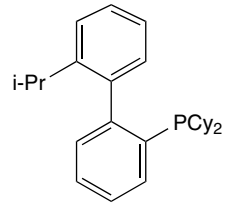

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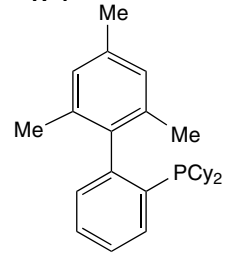

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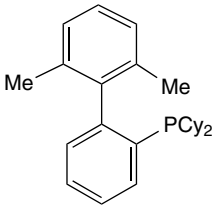
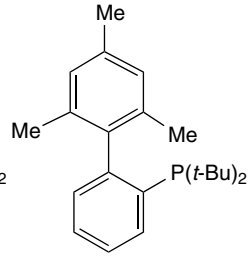
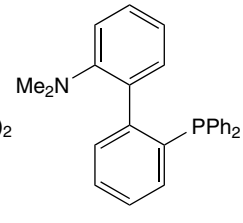


IV-9



IV-10



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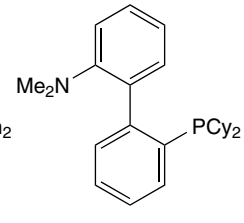

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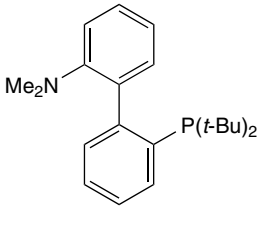
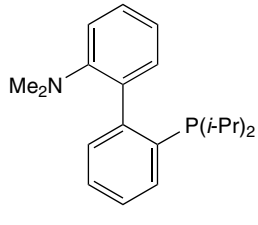
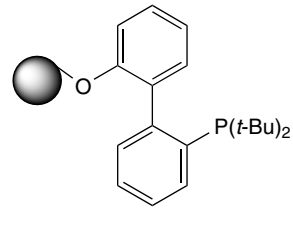


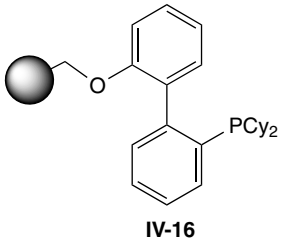
IV-13



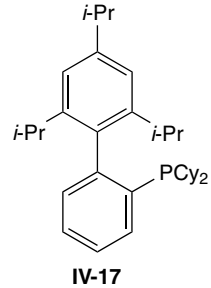
IV-14



IV-15

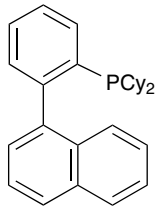


IV-16

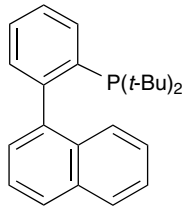


IV-17

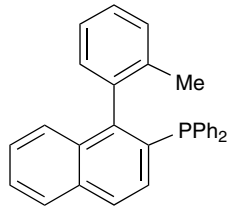
Table 1.5 Polyphenyl-based monophosphines.



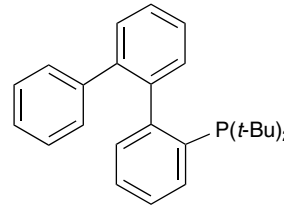
V-1



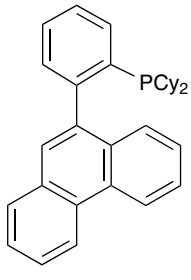
V-2



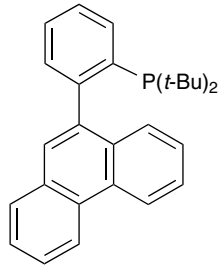
V-3



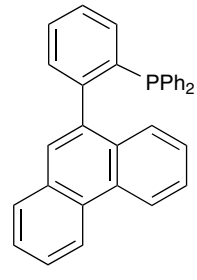
V-4



V-5

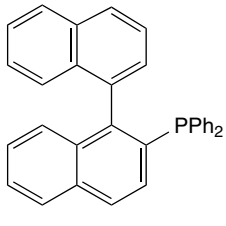


V-6

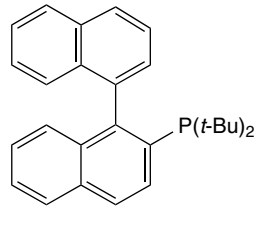


V-7

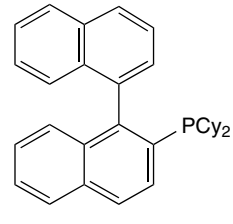
Table 1.6 Binaphthyl-based monophosphines (chiral and racemic).



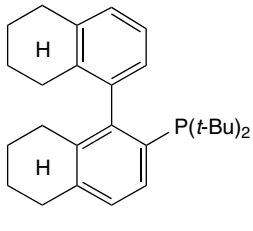
H-MOP
VI-1



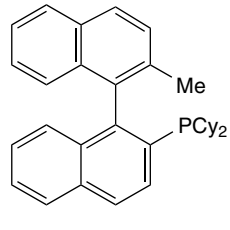
VI-2



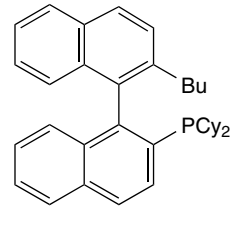
VI-3



VI-4



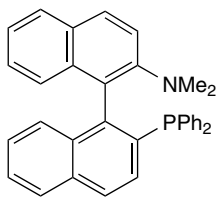
VI-5



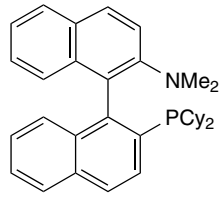
VI-6

(*continued overleaf*)

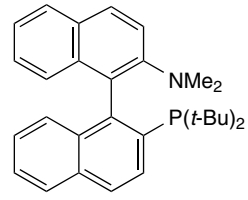
Table 1.6 (*continued*)



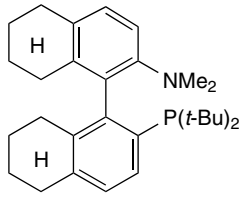
(MAP)
VI-7



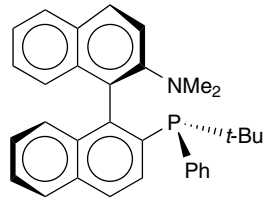
VI-8



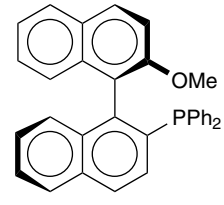
VI-9



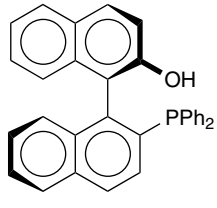
VI-10



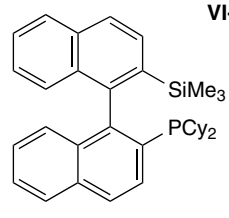
VI-11



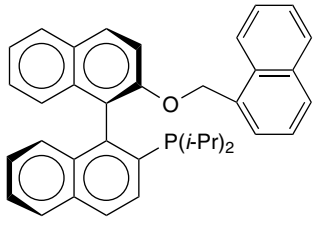
(*R*)-MeO-MOP
VI-12



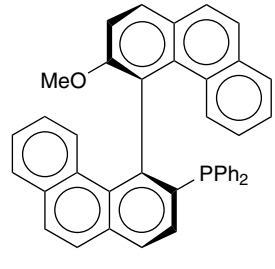
(*R*)-**VI-13**



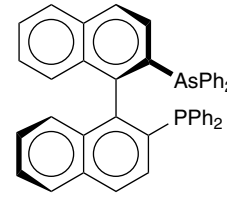
VI-14



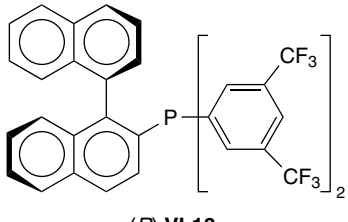
VI-15



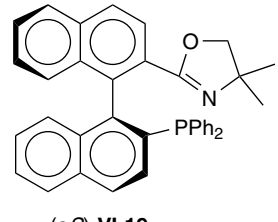
(*R*)-MOP-Phen
VI-16



(*R*)-**VI-17**



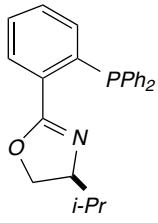
(*R*) **VI-18**



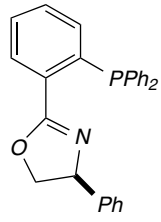
(a*S*)-**VI-19**

Table 1.7 Chiral monophosphines.

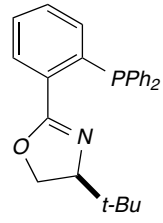
PHOX (Phosphinooxazoline) ligands



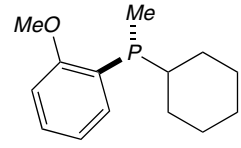
VII-1



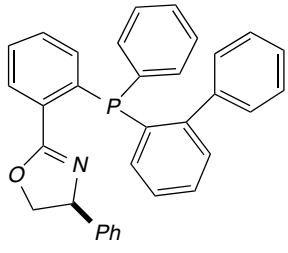
VII-2



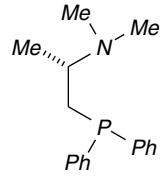
VII-3



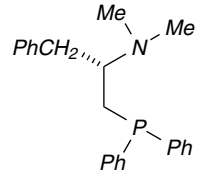
VII-4



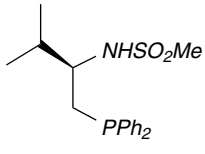
VII-5



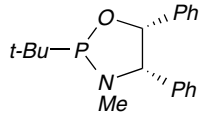
(S)-ALAPHOS
VII-6



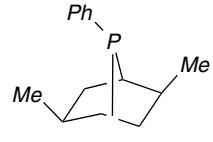
(S)-PHEPHOS
VII-7



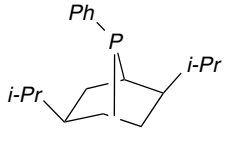
Ms-VALPHOS
VII-8



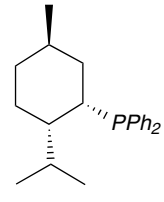
VII-9



VII-10

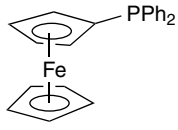


VII-11



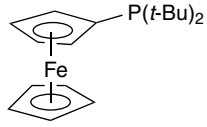
NMDPP
VII-12

Table 1.8 Ferrocenyl monophosphines (chiral and racemic).



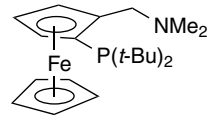
$FcPPh_2$

VIII-1

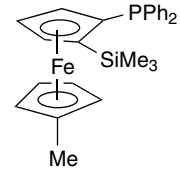


$FcP(t\text{-}Bu)_2$

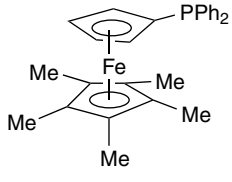
VIII-2



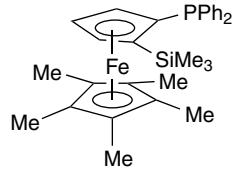
VIII-3



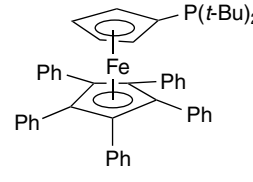
VIII-4



VIII-5



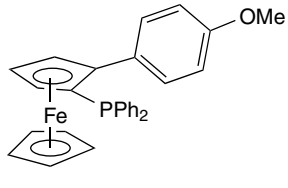
VIII-6



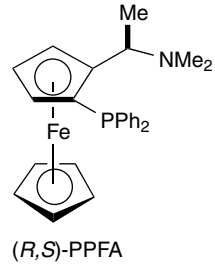
$Ph_5FcP(t\text{-}Bu)_2$

VIII-7

J. Org. Chem., **67**, 5553 (2002)

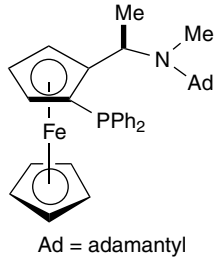


(S)-**VIII-8**



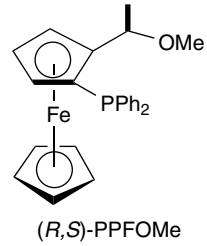
(*R,S*)-PPFA

VIII-9



Ad = adamantyl

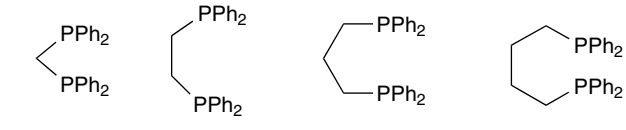
VIII-10



(*R,S*)-PPFOMe

VIII-11

Table 1.9 Diphosphines.



IX-1

DPPE

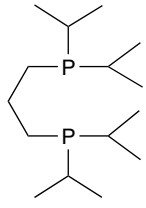
IX-2

DPPP

IX-3

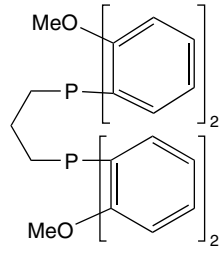
DPPB

IX-4



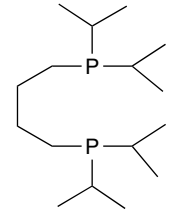
DiPPP

IX-5



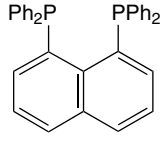
DMPPP

IX-6

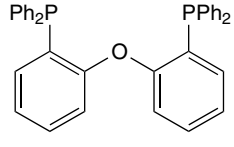


DiPPB

IX-7

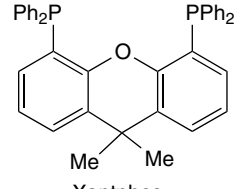


IX-8



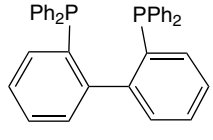
DPEphos

IX-9



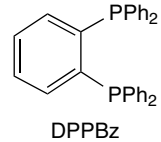
Xantphos

IX-10



DPBP

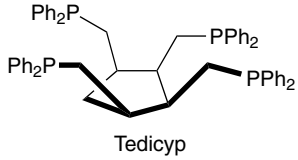
IX-11



DPPBz

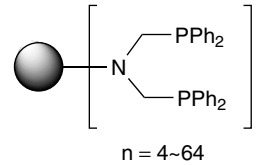
IX-12

Table 1.10 Polydentate phosphines.



Tedicyp

X-1

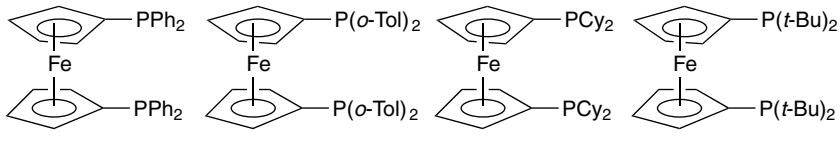


n = 4~64

= dendrimers

X-2

Table 1.11 Ferrocenyl diphosphines (chiral and achiral).

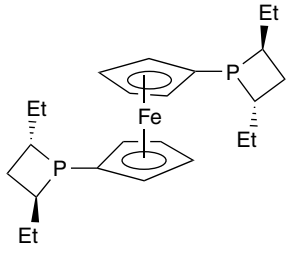


DPPF
XI-1

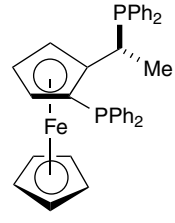
XI-2

XI-3

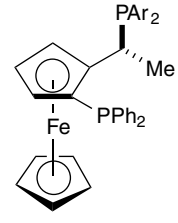
DtBPF
XI-4



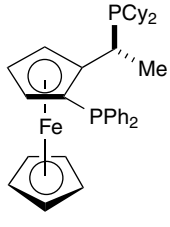
(*S*,*S*)-Et-FerroTANE
XI-5



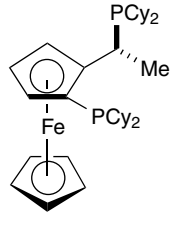
XI-6



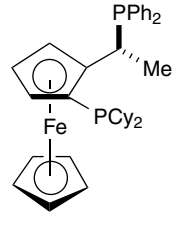
Ar = 3,5-Xyl
(*R*,*S*)-Josiphos
XI-7



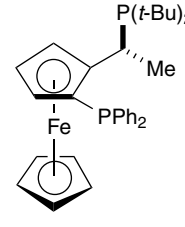
(*R*,*S*)-Cy-Josiphos
XI-8



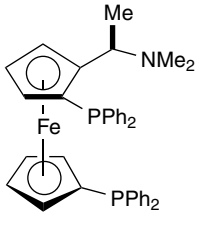
XI-9



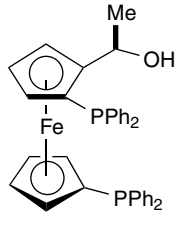
XI-10



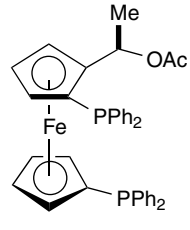
XI-11



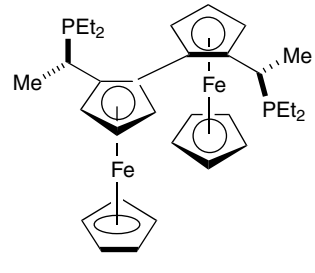
(*rac*)-BPPFA
XI-12



(*R*,*S*)-BPPFOH
XI-13

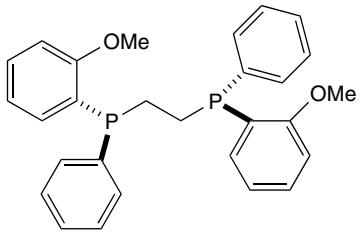


(*R*,*S*)-BPPFOAc
XI-14



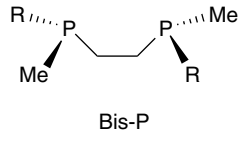
(*R*,*R*)(*S*,*S*)-EtTRAP
XI-15

Table 1.12 Chiral diphosphines.



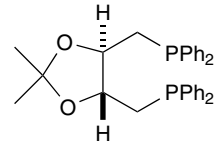
(*R,R*)-DIPAMP

XII-1



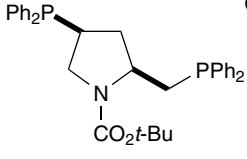
Bis-P

R = t-Bu **XII-2**
R = adamantyl **XII-3**



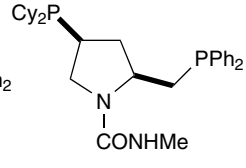
(*R,R*)-DIOP

XII-4



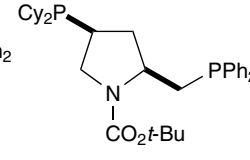
(*S,S*)-BPPM

XII-5



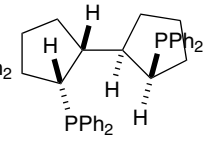
(2*S*,4*S*)-MCCPM

XII-6



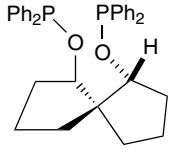
(*S,S*)-BCPM

XII-7



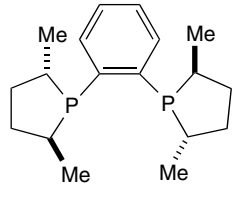
BICP

XII-8



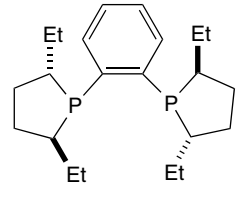
(*R*)-spirOP

XII-9



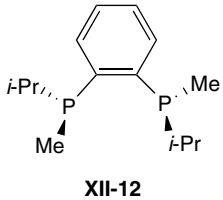
R = Me; (*S,S*)-Me-DuPHOS

XII-10

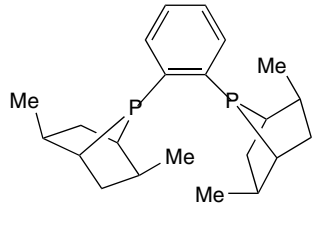


(*S,S*)-Et-DuPHOS

XII-11

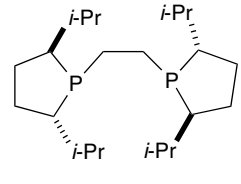


XII-12



(*R,S,R,S*)-Me-PennPHOS

XII-13

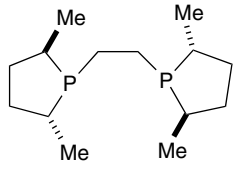


(*R,R*)-i-Pr-BPE

XII-14

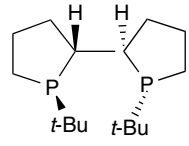
(*continued overleaf*)

Table 1.12 (*continued*)



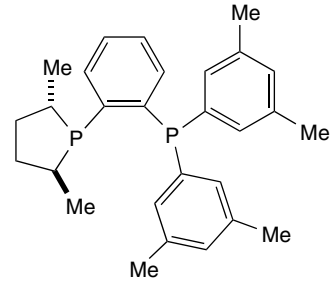
(*R,R*)-Me-BPE

XII-15



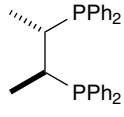
TangPhos

XII-16



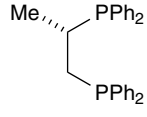
Me-UCAP-DM

XII-17



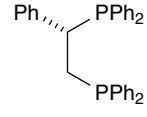
(*S,S*)-CHIRAPHOS

XII-18



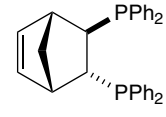
(*S*)-PROPHOS

XII-19



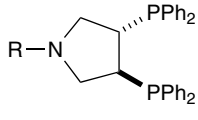
(*S*)-PHENPHOS

XII-20



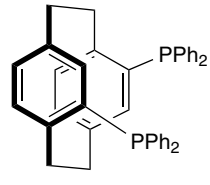
(*R,R*)-NORPHOS

XII-21



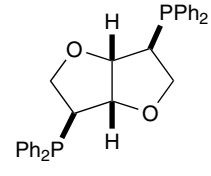
(*S,S*)-PYRPHOS
(Degphos)

XII-22



(*S*)-(2,2)-PHANEPHOS

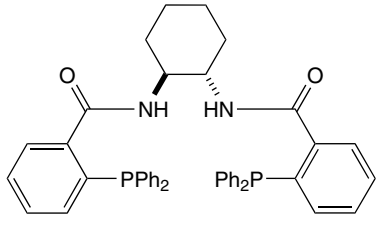
XII-23



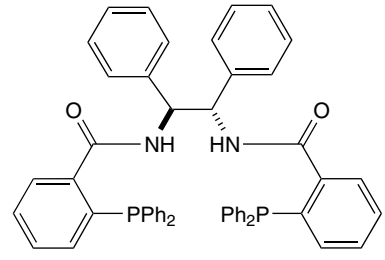
DDPPI

XII-24

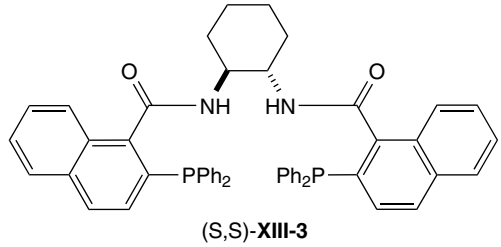
Table 1.13 DPPBA and DPPA-based diphosphine derivatives.



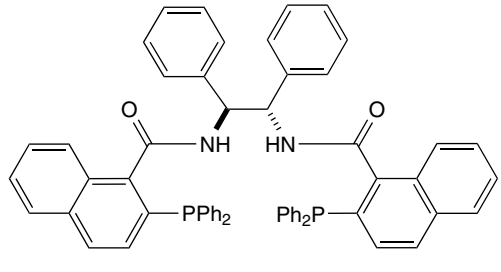
(*S,S*)-**XIII-1**



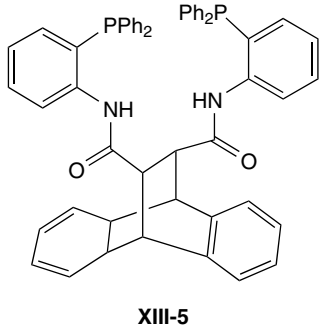
(*S,S*)-**XIII-2**



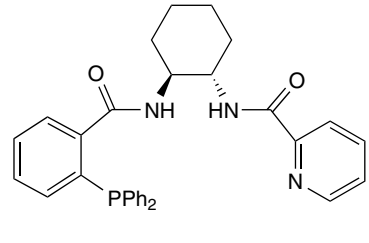
(S,S)-**XIII-3**



(*S,S*)-**XIII-4**

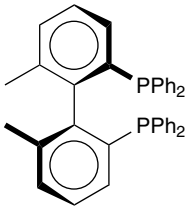


XIII-5



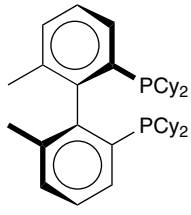
(*S,S*)-**XIII-6**

Table 1.14 Chiral biphenyl-based diphosphines.



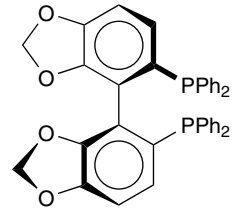
(*R*)-BIPHEMP

XIV-1



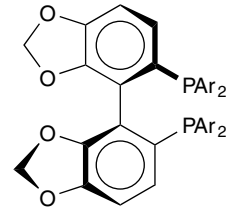
(*R*)-BICHEP

XIV-2



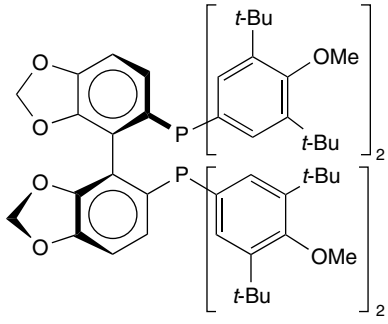
(*R*)-SEGPHOS,

XIV-3



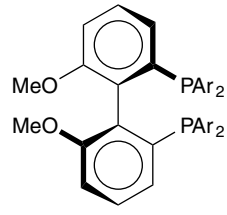
(*R*)-SEGPHOS,
Ar = 3,5-xyl

XIV-4



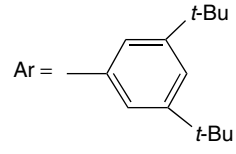
(*R*)-DTBM-SEGPHOS,

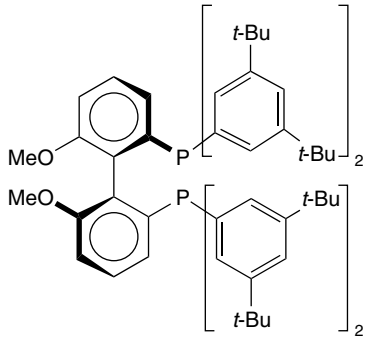
XIV-5



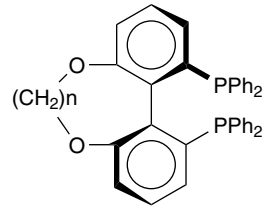
(*R*)-MeO-BIPHEP

XIV-6





XIV-7

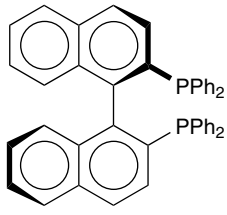


C_n TunaPhos

XIV-8

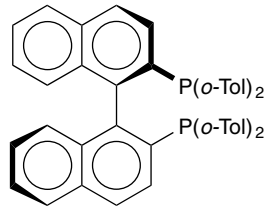
J. Org. Chem.,
65, 6223 (2000)

Table 1.15 Chiral binaphthyl-based diphosphines and diphosphites.



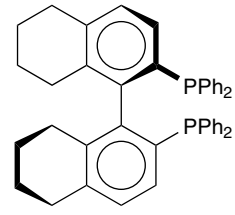
(*R*)-BINAP

XV-1



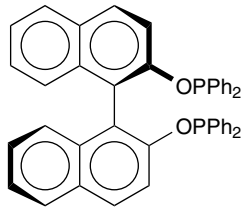
(*R*)-TolBINAP

XV-2



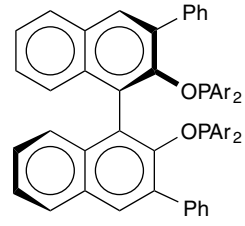
(*R*)-H_8-BINAP

XV-3



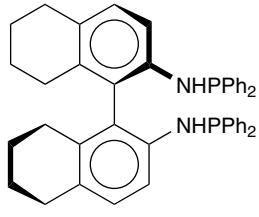
(*R*)-BINAPO

XV-4



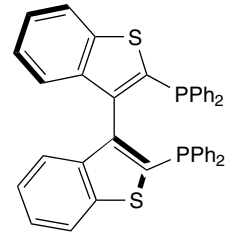
(*R*)-o-substituted BINAPO

XV-5



H_8-BDPAB

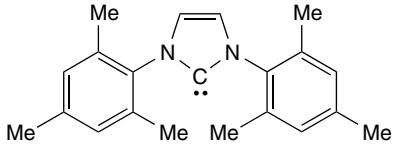
XV-6



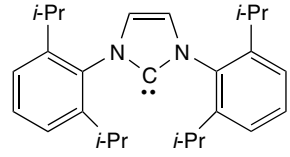
(*R*)-BITIANP

XV-7

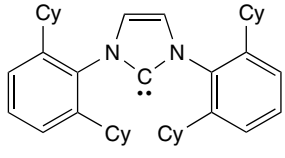
Table 1.16 Heterocyclic carbene ligands.



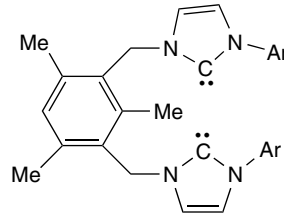
XVI-1



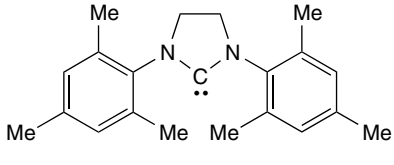
XVI-2



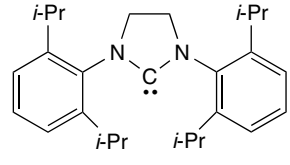
XVI-3



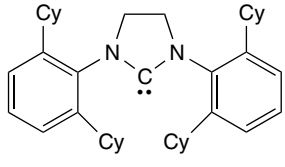
XVI-4



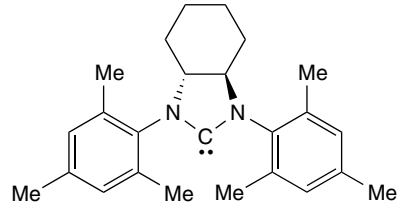
XVI-5



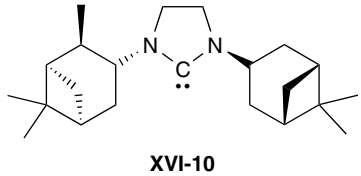
XVI-6



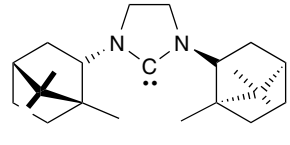
XVI-8



XVI-9

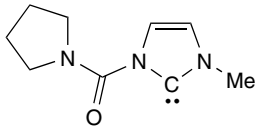


XVI-10

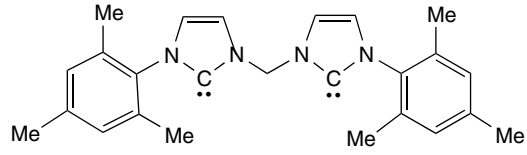


XVI-11

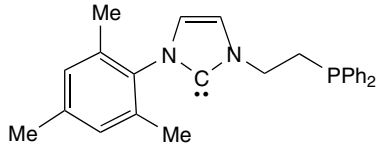
Table 1.16 (*continued*)



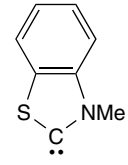
XVI-12



XVI-13

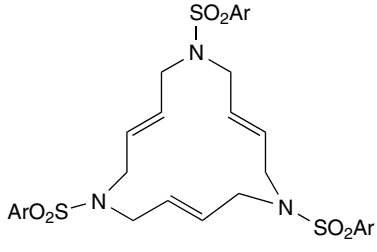


XVI-14



XVI-15
Tet.Lett.,
42, 4701 (2001)

Table 1.17 Miscellaneous ligands.



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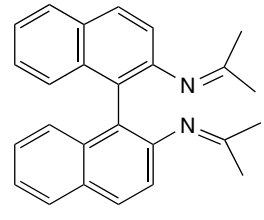

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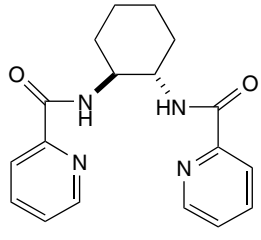

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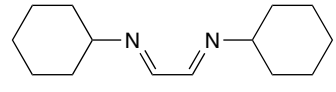

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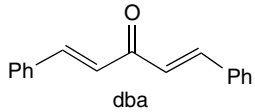

dba

XVII-5

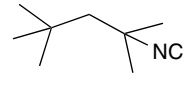

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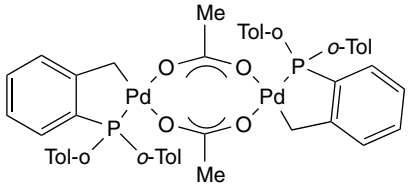
Table 1.18 Stable palladacycles and Pd complexes used as catalyst precursors.



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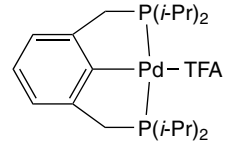

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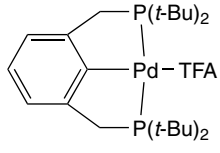
JACS, **119**, 11687 (1997)



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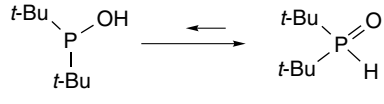
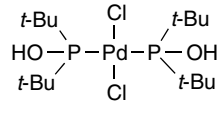
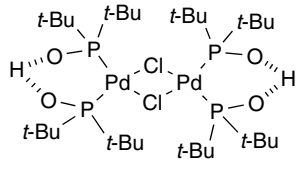
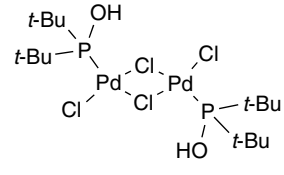




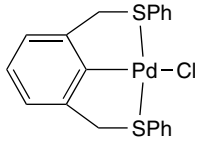
POPd **XVIII-4**



POPd 1 **XVIII-5**



POPd 2 **XVIII-6**



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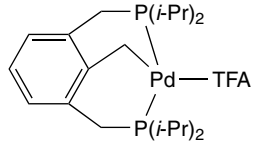

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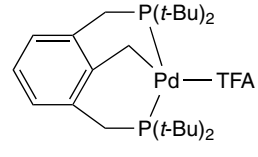

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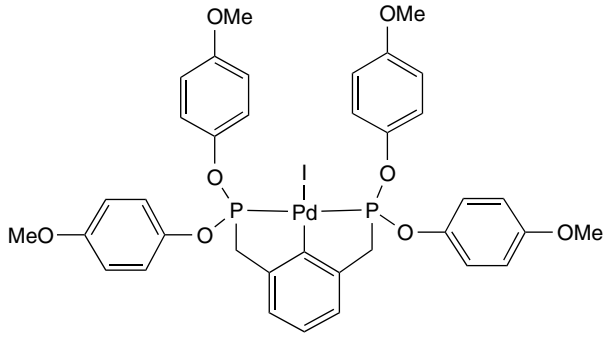
Table 1.18 (*continued*)



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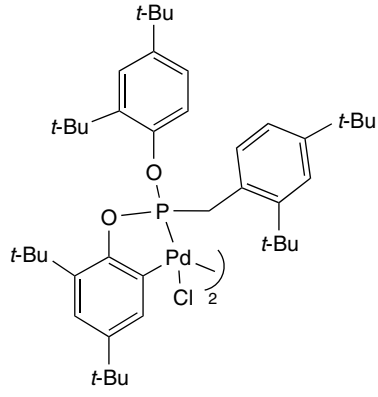
Tetrahedron Lett., **40**, 7379 (1999)



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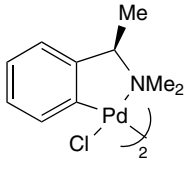

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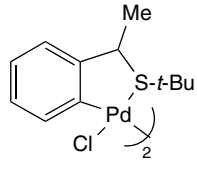

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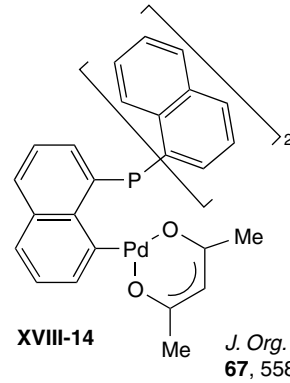

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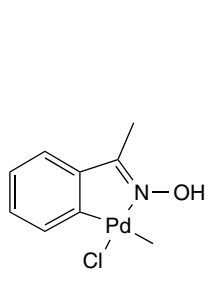
J. Org. Chem., **67**, 5588 (2002)

(*continued overleaf*)

Table 1.18 (*continued*)



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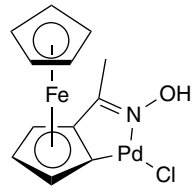

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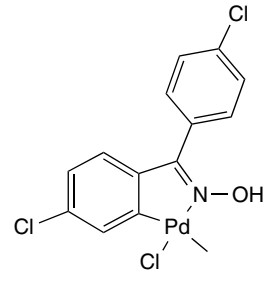

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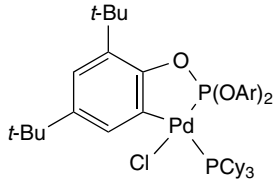

Ar = C_6H_3-2,4-*t*-Bu_2

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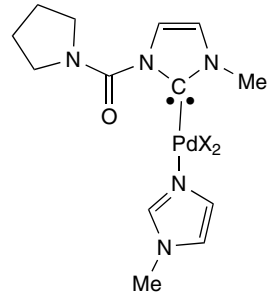
Angew. Chem. Int. Ed **41**, 4120 (2002)



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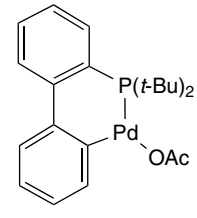
Org. Lett., **4**, 1411 (2002)



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Org. Lett., **5**, 2413 (2003)

Index

Palladium Reagents and Catalysts—New Perspectives for the 21st Century J. Tsuji

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