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Edited by Jieping Zhu, Hugues Bienaymé

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Preface

The length of a synthesis is dependent upon the average molecular complexity produced per operation, which depends in turn on the number of chemical bonds being created. Therefore, devising reactions that achieve multi-bond formation in one operation is becoming one of the major challenges in searching for step-economic syntheses. By today's standards, besides being regio-, chemo- and stereoselective, an ideal multi-bond-forming process should satisfy the following additional criteria: (a) readily available starting materials; (b) operationally simple; (c) easily automatable; (d) resource effective (personnel, time, cost etc); (e) atom economical; and (f) ecologically benign. Multicomponent reaction (MCR) processes, in which three or more reactants are combined in a single chemical step to produce products that incorporate substantial portions of all the components, naturally comply with many of these stringent requirements for ideal organic syntheses.

Multicomponent reactions, though fashionable these days, have in fact a long history. Indeed, many important reactions such as the Strecker amino acid synthesis (1850), the Hantsch dihydropyridine synthesis (1882), the Biginelli dihydropyrimidine synthesis (1891), the Mannich reaction (1912), and the isocyanide-based Passerini reactions (1921) and Ugi four-component reactions (Ugi-4CRs) (1959), among others, are all multicomponent in nature. In spite of the significant contribution of MCRs to the state of the art of modern organic chemistry and their potential use in complex organic syntheses, little attention was paid to the development of novel MCRs in the second half of the twentieth century. However, with the introduction of molecular biology and high-throughput biological screening, the demand on the *number* and the *quality* of compounds for drug discovery has increased enormously. By virtue of their inherent convergence and high productivity, together with their exploratory and complexity-generating power, MCRs have naturally become a rapidly evolving field of research and have attracted the attention of both academic and industrial scientists.

The development of novel MCRs is an intellectually challenging task since one has to consider not only the reactivity match of the starting materials but also the reactivities of the intermediate molecules generated *in situ*, their compatibility, and their compartmentalization. With advances in both theory and mechanistic insights into various classic bimolecular reactions that allow for predictive analysis of reaction sequences, the development and control of new reactive chemical

entities, and the availability of new technologies that activate otherwise "inactive" functional groups, we are optimistic that many new and synthetically useful MCRs will be developed in the coming years.

As enabling technology, the development and application of MCRs are now an integral part of the work of any major medical research unit. It is nevertheless important to point out that MCRs have contributed to drug development, from lead discovery and lead optimization to production, long before the advent of combinatorial technologies. The one-step synthesis of *nifedipine* (Adalat®), a highly active calcium antagonist, by a Hantsch reaction is a classic demonstration. A more recent example is the synthesis of piperazine-2-carboxamide, the core structure of the HIV protease inhibitor Crixivan®, by a Ugi-4CR. We believe that the impact of MCRs on both target-oriented and diversity-oriented syntheses will become stronger and stronger as we enter the post-genomic era in this new millennium.

In editing this book, we were fortunate to be associated with more than a dozen experts who were willing to devote the time and effort required to write their contributions. These distinguished chemists are highly knowledgeable in the area reviewed, have contributed to its development, and are uniquely able to provide valuable perspectives. We are truly indebted to all the authors for their professionalism, their adherence to schedules, their enthusiasm, and most of all, their high-quality contributions. We thank all of our collaborators at Wiley-VCH, especially Dr. Elke Maase for her invaluable help from the conception to the realization of this project.

We hope that this monograph will be of value to both expert and novice practitioners in this area, further stimulating the development and application of novel MCRs and providing an appropriate perspective with which to evaluate the significance of new results.

Gif-sur-Yvette and Lyon, France
September 2004

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1
Asymmetric Isocyanide-based MCRs

Luca Banfi, Andrea Basso, Giuseppe Guanti, and Renata Riva

1.1
Introduction

Although the great utility of isonitrile-based multicomponent reactions in assembling complex pharmacologically important structures in a small number of steps and with the possibility of several diverse inputs is widely recognized [1, 2], the stereochemical issues still represent a challenge. Usually in Passerini and Ugi reactions (P-3CRs and U-4CRs) a new stereogenic center is generated, but most reactions reported so far suffer from low or absent stereoselectivity. It seems that MCRs are following the evolutionary trend experienced in the past by conventional organic syntheses. While in the 1960s and 1970s the main efforts were directed toward the discovery of new reactions, in the 1980s and 1990s the focus moved towards selectivity, in particular stereoselectivity, leading to highly efficient methodologies. For MCRs it is probable that the same thing will happen. Promising results are already appearing in the literature. We can foresee that in the next 20 years more and more researchers will dedicate their skills and ingenuity to devise methods to control the stereoselectivity in P-3CR and U-4CR, as well as in other less well-known isonitrile-based MCRs. We hope that this chapter may help to stimulate these efforts by describing the present state of the art.

1.2
Racemization Issues

Since asymmetric induction in P-3CRs or U-4CRs is achieved in most cases by using one or more chiral components in enantiomerically pure form, it is important to assess the possibility of racemization under the reaction conditions. While this does not seem to be a problem for carboxylic acid and amine components, there are some reports of racemization of chiral aldehydes or isocyanides.

For example, aldehydes having an α-alkyl substituent have been reported to be stereochemically unstable during Ugi condensation [3]. On the contrary, α-alkoxy substituted aldehydes do not racemize.

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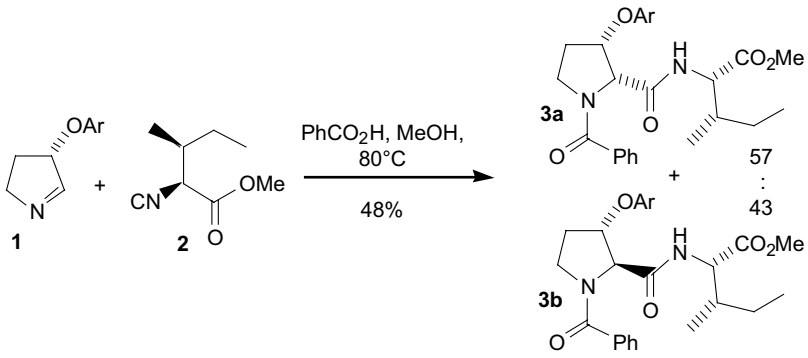


Scheme 1.1

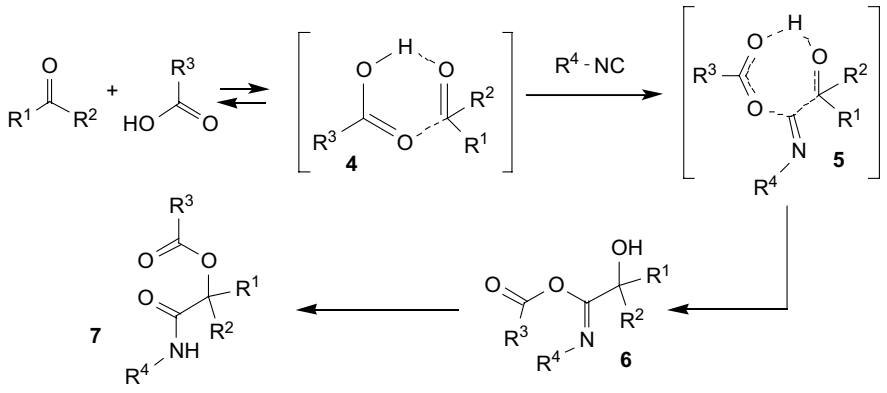
While enantiomerically pure α-substituted isocyanoacetates have been used in Passerini condensation without significant racemization [4–6], the same class of compounds is believed to be configurationally unstable under the conditions of U-4CRs [7]. However, one notable exception is the reaction shown in Scheme 1.1, where L-isoleucine-derived isocyanide **2** has been condensed without such problems with pyrroline **1** [8]. The bulkiness of this isocyanide or the use of a preformed cyclic imine, thus avoiding the presence of free amine in solution, may be the reasons for the absence of racemization.

Care should be taken during the preparation of chiral α-isocyanoesters from the corresponding formamides: while the use of diphosgene or triphosgene under controlled temperatures (especially with *N*-methylmorpholine as the base) seems to afford products endowed with high optical purity [5, 6, 8, 9], the combination of other dehydrating agents and bases, such as phosphorus oxychloride and diisopropylamine, leads to various degrees of racemization [10].

1.3 Asymmetric Passerini Reactions

1.3.1 Classical Passerini Reactions

In the classical Passerini reaction [11], an isocyanide is condensed with a carbonyl compound and a carboxylic acid to afford α-acyloxyamides **7** (Scheme 1.2). When the carbonyl compound is prochiral, a new stereogenic center is generated. It is generally accepted that the reaction proceeds through intermediate **6**, which rearranges to the product. The way this intermediate is formed is more debated. A possibility is a concerted non-ionic mechanism involving transition state **5**. Since the simultaneous union of three molecules is not a very likely process, another possibility is a stepwise mechanism, with the intermediacy of a loosely bonded adduct **4** between the carbonyl compound and the carboxylic acid [2]. Since all three

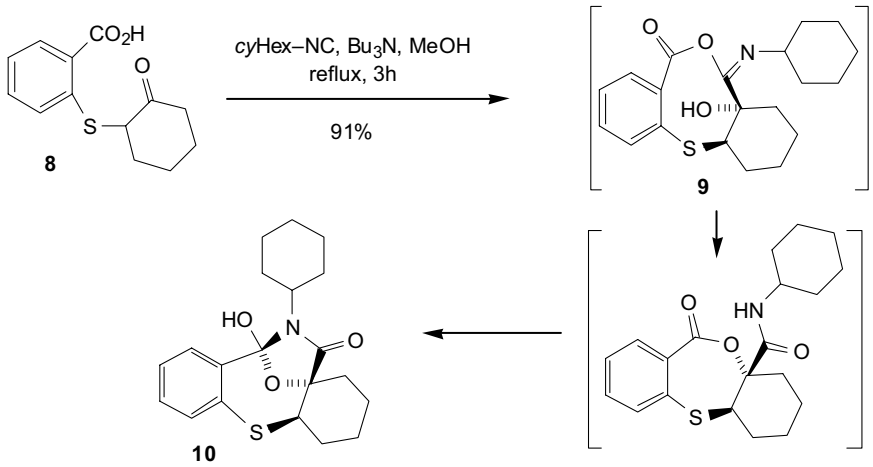


Scheme 1.2

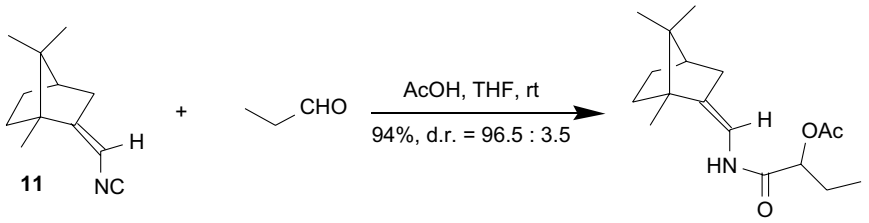
components are involved in rate-determining steps [12], in principle asymmetric induction may be achieved when at least one of them is chiral.

In nearly all the reported cases involving chiral carbonyl compounds, however, the diastereoselectivity is moderate, ranging from 1:1 to 4:1. This is somewhat surprising for the reactions of aldehydes with an α stereogenic center, which often afford high stereoselectivity in other types of nucleophilic additions. The low steric requirement of the isocyano group may account for this generally low stereoselectivity. A notable exception is the intramolecular reaction of chiral racemic keto-acid **8** to give **10** (Scheme 1.3) [13]. Only one of the two possible diastereoisomeric products is formed. The tricyclic nature of intermediate **9** makes the alternative diastereoisomer more sterically strained.

While chiral isocyanides such as α-substituted isocyanoacetates also usually react with low stereoselectivity, the specially designed, camphor-derived, isonitrile **11**



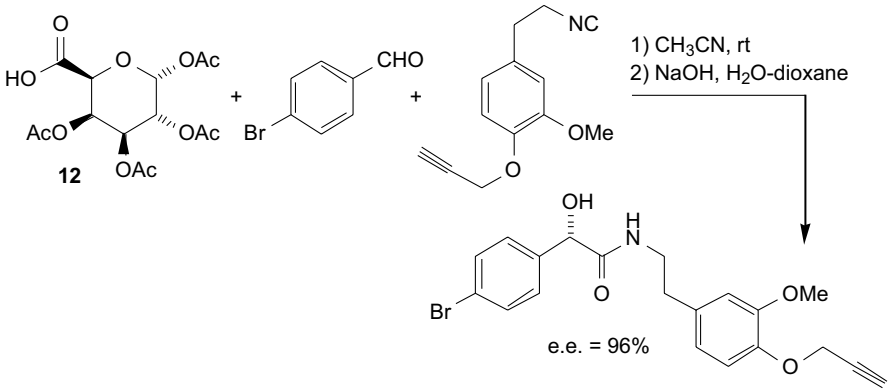
Scheme 1.3



Scheme 1.4

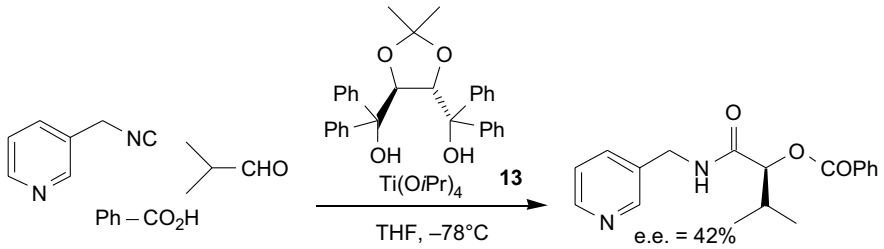
gives high asymmetric induction in the reaction with some aliphatic aldehydes [14] (Scheme 1.4). The chiral auxiliary may be removed after the condensation reaction to give a carboxylic acid or ester [15].

A recent screening of various chiral carboxylic acids has allowed the selection of galacturonic derivative **12** as a very efficient control in the stereochemical course of some Passerini reactions (Scheme 1.5). Although the *de* seems to be strongly dependent on the isocyanide employed, this result suggests the possibility of employing carboxylic acids as easily removable chiral auxiliaries in the asymmetric synthesis of biologically important mandelamides [16].



Scheme 1.5

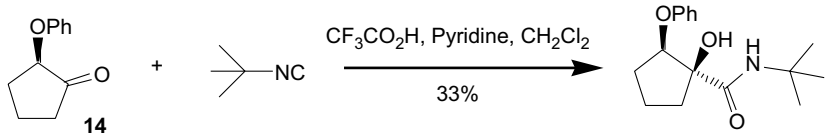
Finally a fourth way to achieve asymmetric induction in the Passerini reaction is by way of a chiral catalyst, such as a Lewis acid. This approach is not trivial since in most cases the Lewis acid replaces the carboxylic acid as third component, leading to α-hydroxyamides or to other kinds of products instead of the "classical" adducts **7** (*vide infra*). After a thorough screening of combinations of Lewis acids/chiral ligands, it was possible to select the couple **13** (Scheme 1.6), which affords clean reaction and a moderate *ee* with a model set of substrates [17]. Although improvements are needed in order to gain higher *ee*s and to use efficiently substoichiometric quantities of the chiral inducer, this represents the first example of an asymmetric classical Passerini reaction between three achiral components.



Scheme 1.6

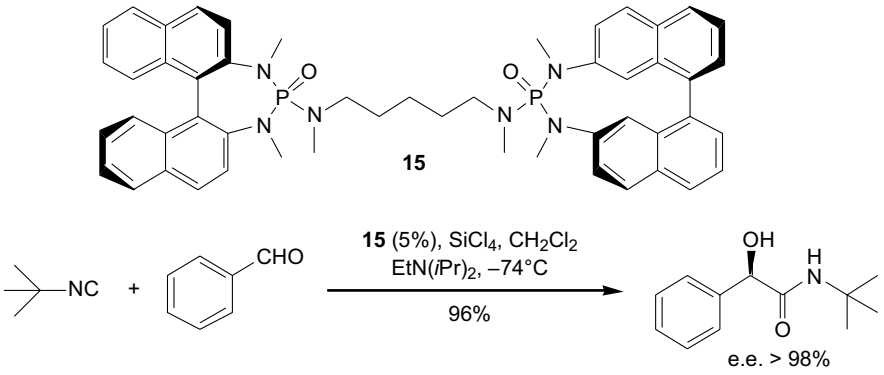
1.3.2
Passerini-type Reactions

When a mineral or Lewis acid replaces the carboxylic component in the Passerini reaction, the final products are usually α-hydroxyamides. Also in this case, when chiral carbonyl compounds or isocyanides are employed, the asymmetric induction is, with very few exceptions, scarce [18, 19]. For example, the pyridinium trifluoroacetate-mediated reaction of racemic cyclic ketone **14** with *t*-butyl isocyanide is reported to afford a single isomer [19] (Scheme 1.7). This example, together with those reported in Schemes 1.3 and 1.4, suggests that high induction may be obtained only by using rigid cyclic or polycyclic substrates.



Scheme 1.7

The Lewis acid-mediated Passerini reaction is particularly well suited for the exploitation of chiral mediators. However, after the pioneering unsuccessful attempts by Seebach et al. [6], this strategy has only recently been reinvestigated by Denmark and Fan [20]. They not only succeeded in obtaining excellent *ee*s, but also solved the problem of efficient catalyst turnover, by taking advantage of the concept of "Lewis base activation of Lewis acids". The weak Lewis acid $SiCl_4$ can be activated by catalytic quantities of chiral phosphoramides such as **15** (Scheme 1.8). Best results are achieved at low temperature, by slow addition of the isocyanide, since its low concentration favors the catalyzed pathway versus the uncatalyzed one. The *ee*s are excellent with aromatic or α,β-unsaturated aldehydes. On the other hand with aliphatic aldehydes they range from 35% to 74%. Also replacing *tert*-butyl isocyanide with other isonitriles brings about a slight decrease of the *ee*s.



Scheme 1.8

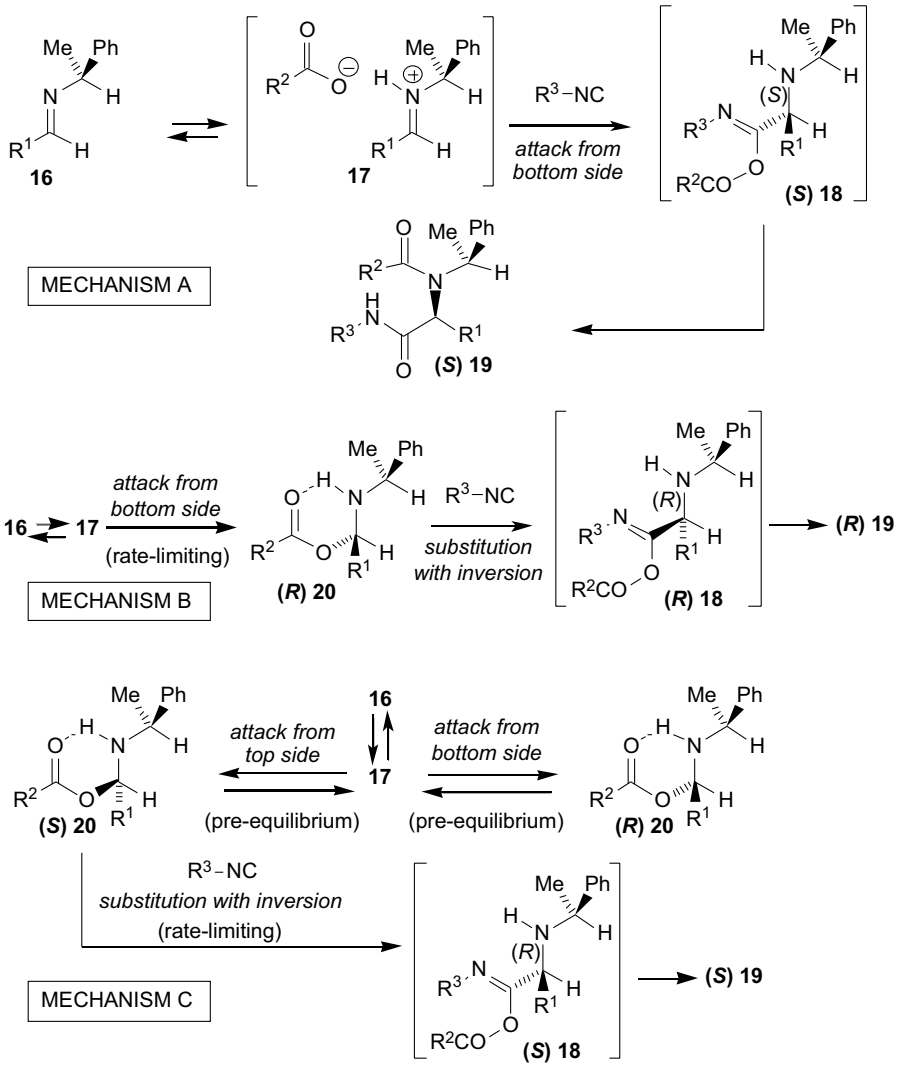
1.4 Asymmetric Intermolecular Ugi Reactions

1.4.1 General Remarks

The classical Ugi reaction [2] involves interaction of a carbonyl compound, an isonitrile, an amine and a carboxylic acid to obtain an α-acylaminoamide. The first step is the condensation of the carbonyl compound with the amine to give an imine. Preformed imines can be employed as well, in some cases with certain advantages in terms of reaction time and yields. The reaction of such imines with isonitriles and carboxylic acids can be considered as an aza analogue of the Passerini reaction and therefore, at first sight, one might assume that the two mechanisms are similar. However some experimental evidence suggests that the mechanistic scenario for the U-4CR may be different and more complex than that shown in Scheme 1.2 for the P-3CR. First of all it is well known that a U-4CR is favored in a polar solvent (MeOH being the most common) while a P-3CR is faster in relatively unpolar media such as CH_2Cl_2 and Et_2O. Secondly, the chiral isocyanide **11** (Scheme 1.4), that leads to excellent *dr* in the P-3CR, affords no stereoselectivity at all in the related U-4CR [21]. Finally it has been demonstrated by a thorough study [21, 22] that in a model asymmetric Ugi reaction involving (*S*)-α-methylbenzylamine as chiral auxiliary, at least two competing mechanisms, leading to opposite stereoselectivity, are operating.

In Scheme 1.9 this model reaction will be used as an example to show three possible competing mechanisms (A, B and C) that may be working. The first is similar to the one proposed in Scheme 1.2 for a P-3CR. Assuming that the imine has an (*E*) configuration and that the preferred conformation of the chiral auxiliary is the one shown (on the basis of allylic strain arguments) [23], the isocyanide should attack from the less encumbered bottom face, leading to (*S*)-**19** as the final product.

In mechanisms B and C, on the contrary, the iminium ion is first attacked by the carboxylate, which forms the hydrogen-bonded intermediate **20**. Then substitu-



Scheme 1.9

tion by the isonitrile proceeds with inversion of configuration [21]. The difference between B and C is the rate-limiting step. In B, addition of the carboxylate is rate-limiting and the stereochemical course is kinetically controlled to give intermediate (*R*)-**20** and hence (*R*)-**19** as major diastereoisomers [21].

Mechanism B may explain why in many cases chiral isocyanides (e.g. **11**) give no asymmetric induction at all [21]. Indeed, the isocyanide is not involved in the transition state. In mechanism C the substitution by the isocyanide is rate-limiting and reversible formation of **20** originates a pre-equilibrium. Although (*R*)-**20** should be kinetically favored, (*S*)-**20** may be more stable because of the destabilizing interac-

tion between Ph and R^1 in the (*R*) isomer [21]. After substitution and rearrangement, (*S*)-**20** again affords (*S*)-**19** as the major adduct, as for mechanism A.

The competition between mechanisms B and C has been invoked in order to explain the surprising inversion of diastereoselectivity achieved by a simple variation of the overall reactant concentration: at low concentration (*S*)-**19** prevails, while at high concentration (*R*)-**19** is formed in greater amounts [22, 23]. An increase in concentration of the isocyanide is indeed expected to favor mechanism B over C, because it accelerates the isonitrile attack, making it non-rate-limiting. The concentration of the other components has the same effect for all mechanisms.

Also the reaction temperature has been shown to have a remarkable effect on the extent of diastereoselectivity. Low temperatures seem to favor the formation of (*S*) diastereoisomers. This may be explained supposing that mechanisms A and C are more entropically disfavored than mechanism B. Therefore the entropy component in $\Delta G^{\neq}$ is higher and the decrease of rate on lowering the temperature is less pronounced.

In conclusion, the hypothesis that the Ugi reaction proceeds, at least in polar solvents, through the competing mechanisms B and C seems reasonable, and may explain some unexpected experimental results. The intervention of mechanism A, especially in non-polar solvent, may not, however, be definitely ruled out.

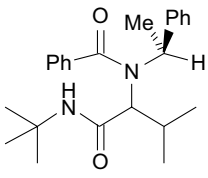
In any case, we must stress that these are at present only working hypotheses, not supported by unambiguous proofs. A better comprehension of the mechanism of U-4CRs, based on more solid grounds, is highly desirable for the development of efficient asymmetric modifications.

As in the case of P-3CRs, any of the four components can in principle, if chiral, control the generation of the new stereogenic center (with the exception of the isonitrile if mechanism B is operating). To date most efforts have been carried out with chiral amines, partly because removal of the chiral auxiliary is in this case easier and leads to synthetically useful secondary amides (instead of the tertiary amides usually obtained by the classical U-4CR).

1.4.2 Chiral Amines

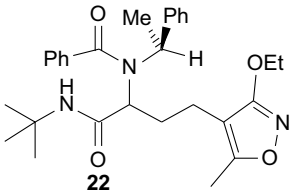
1.4.2.1 α-Methylbenzylamines

α-Methyl benzylamines have been used several times in order to control the new stereogenic center in U-4CR [3, 21–28]. The chiral auxiliary can be easily removed by hydrogenolysis. Scheme 1.10 shows selected literature examples regarding the synthesis of compounds **21** [3, 22], **22** [24], **23** [25] and **24** [26]. As already mentioned, either the (*R*) or (*S*) (at the new stereocenter) adducts are formed preferentially, depending on the reaction conditions, especially the concentration of reactants, the solvent and the temperature, but also on the structure of reactants. The asymmetric induction is usually only moderate, with the notable exception of **24**. In this case, the stereoselectivity strongly depends on the temperature. At 0 °C the *dr* was only 75:25! Although in the case of **24** the carboxylic acid is also chiral, its influence on the stereoselectivity is expected to be scarce.



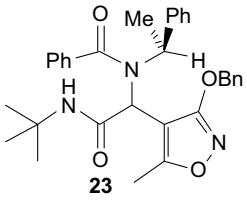
21

MeOH, –40°C, 0.10 M: (*S*) : (*R*) = 75 : 25
MeOH, –40°C, 2.0 M: (*S*) : (*R*) = 33 : 77



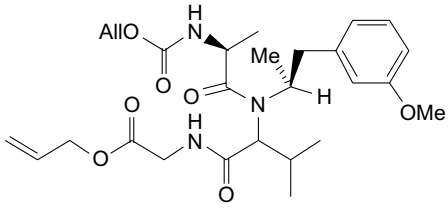
22

MeOH, 25°C, 0.58 M
(*S*) : (*R*) = 40 : 60



23

MeOH, 25°C, 0.40 M
(*S*) : (*R*) = 35 : 65



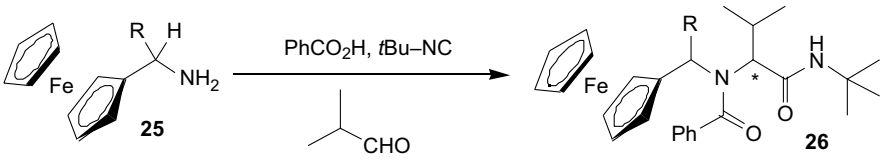
24

CF_3CH_2OH, –30°C, 0.50 M
(*S*) : (*R*) = 95 : 5

Scheme 1.10

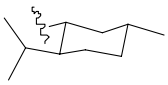
1.4.2.2 **Ferrocenylamines**

At the beginning of the 1970s Ugi et al. [29] reported the use of (+)-α-ferrocenylethylamine **25a** in the condensation with *iso*-butyraldehyde, benzoic acid and *tert*-butylisocyanide (Scheme 1.11). The Ugi adduct **26** could be obtained with different diastereomeric excesses, varying solvent, concentration and temperature in analogy [29] with the above described α-methylbenzylamine. Following this first study, different α-ferrocenylalkylamines have been employed [30, 31] and improvements in



25 **26**

Chiral aux.	Amine config.	R	Temp.	Conc. [M]	Solvent	Yield [%]	(*S*) : (*R*) (*)
25a	(*S*)	Me	–60°C	1.0	MeOH	n.r.	38 : 62
25a	(*S*)	Me	0°C	0.0375	MeOH	90	79 : 21
25b	(*R*)	*i*-Pr	–78°C	0.05	MeOH	97	99 : 1
25c	(*R*)	Menthyl	25°C	1.0	CF_3CH_2OH	46	82 : 18

Menthyl = 

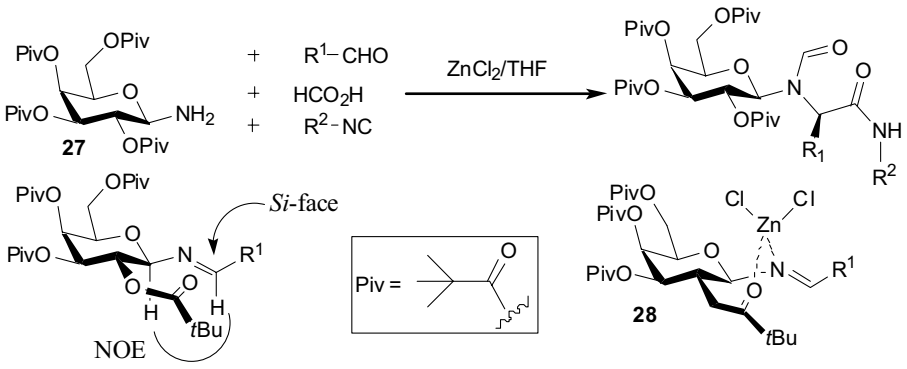
Scheme 1.11

diastereomeric excesses have been realized by substituting the methyl group with bulkier substituents, as in **25b** and **25c**. In particular, for R = *i*Pr, diastereomeric excesses up to 99% could be obtained working at −78 °C [31]. It is interesting to note that an overall reversal of stereoselectivity was obtained on passing from **25a** (R = Me) to **25b** and **25c**. Under the conditions used for entry 3 (low concentration and temperature), one would indeed have expected a preponderance of the (*R*) diastereoisomer, starting from the (*R*) chiral auxiliary. It is possible that in this case the isopropyl group plays the role of a "large" group.

Despite some interesting results, these chiral auxiliaries have not been investigated further, probably because of their structural complexity and chemical instability. In addition to these problems, the Ugi products are not always isolated in high yields and the removal of the chiral auxiliary requires an acid treatment not always compatible with the other parts of the molecule.

1.4.2.3 Glycosylamines

In 1987 Kunz [32] reported the use of 2,3,4,6-tetra-*O*-pivaloyl-*β*-D-galactopyranosylamine **27** as chiral auxiliary in the preparation of α-aminoacid derivatives *via* the Strecker reaction with aldehydes and trimethylsilyl cyanide. One year later he reported [33, 34] the use of the same chiral auxiliary in the Ugi reaction, where trimethylsilyl cyanide was replaced by an isocyanide and a carboxylic acid (Scheme 1.12).



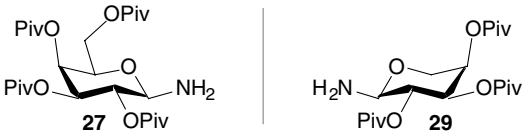
Scheme 1.12

Diastereomeric excesses were usually higher than 90% working between −25 °C and −78 °C in the presence of a Lewis acid such as zinc chloride; reaction times ranged from 24 h to 72 h and yields were generally high. Interestingly no reaction occurred in the absence of the Lewis acid. The observed stereoselectivity was attributed to the preferential geometry of the imine generated by reaction of **27** with an aldehyde [34]. NMR analysis showed a strong NOE between the anomeric and the aldiminic hydrogen, explainable *via* the conformation reported in Scheme 1.12,

where the *Re*-face of the imine is shielded by the 2-*O*-acyl substituent; therefore the attack by the isocyanide can take place only from the *Si*-face and an (*R*)-configured amino acid is generated. The presence of a Lewis acid like zinc chloride reinforces this geometry, presumably by its coordination to the iminic nitrogen and the carboxyl oxygen, as shown in formula **28**. Moreover, probably, the Lewis acid favors direct attack of the isonitrile (mechanism A of Scheme 1.9).

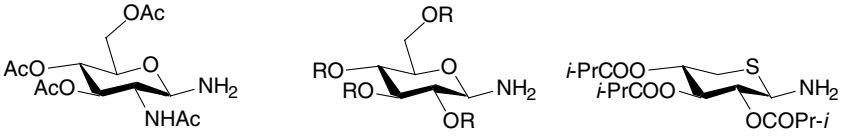
The substantial independence of the stereoselectivity from the structure of the aldehyde makes this methodology extremely convenient to prepare D-amino acid derivatives [35]. It has also been used for solid-phase syntheses [36]. However, some drawbacks can be envisaged, including the harsh conditions required for the removal of the chiral auxiliary (the acyl group of the Ugi product does not survive such conditions) and the difficulty in preparing L-amino acids following the same methodology, since L-galactose is not easily obtainable.

Therefore further modifications of this methodology have been mainly directed to overcome the above drawbacks. In order to obtain L-amino acids, Kunz [37] reported the use of 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine **29**, which can be considered with good approximation the enantiomer of **27**, but it is more easily synthesized (Scheme 1.13).



Scheme 1.13

In order to have a milder cleavage of the chiral auxiliary, various other glycosylamines have been introduced, such as 2-acetamido-3,4,6-tri-*O*-acetyl-1-amino-2-deoxy-β-D-glucopyranose **30** [38], 2,3,4,6-tetra-*O*-alkyl-β-D-glucopyranosylamines **31** [39] and 1-amino-5-desoxy-5-thio-2,3,4-tri-*O*-isobutanoyl-β-D-xylopyranose **32** [40] (Scheme 1.14).



Scheme 1.14

There are some interesting features related to these aminosugars; compound **30** possesses very high stereochemical inductivity, but cleavage conditions are still too

harsh. Interestingly the authors report that no stereoselectivity is observed when the Ugi reaction is performed without the Lewis acid; this is in contrast with what was reported earlier by Kunz, that no reaction occurred without the Lewis acid. The loss of stereoselectivity may be due to the intervention of alternative mechanisms B and C.

Cleavage conditions for aminosugars **31** are sufficiently mild; however, yields are usually not higher than 50% and stereoselectivities are lower and depend on the size of the R groups; interestingly in this case no influence of the temperature on the stereoselectivity is observed.

Compound **32** may be removed, after the Ugi reaction, under particularly mild conditions, thanks to sulfur activation by soft electrophiles, such as mercury salts. The yields obtained in zinc-mediated Ugi reactions are excellent and the diastereomeric ratios are in line with those obtained with **27**. Cleavage of the chiral auxiliary can be performed, after methylamine-promoted deacylation of the sugar hydroxy groups, by a diluted solution of CF_3CO_2H in the presence of $Hg(OAc)_2$. Under these conditions the acyl group on nitrogen is retained. However, the enantiomer of **32** is not easily accessible.

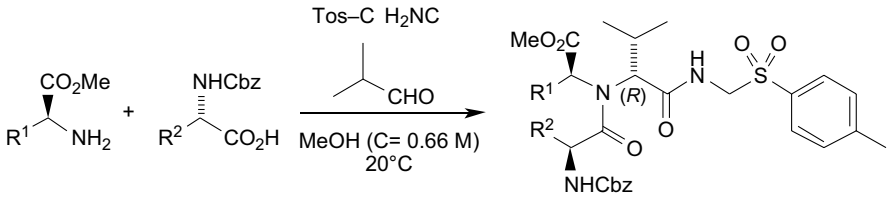
1.4.2.4 Esters of α-amino Acids

Esters of α-aminoacids can be conveniently used as amine components in the Ugi reaction. In principle they could be used in the Ugi reaction as chiral auxiliaries since they are readily available in both enantiomeric forms and there is a number of literature procedures for their removal at the end of the synthesis. Moreover in several synthetic applications in the field of peptidomimetics their structure may also be retained.

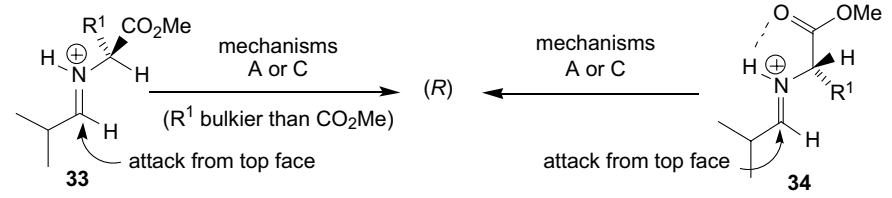
However, they have not yet found many applications in asymmetric Ugi reactions [41–43], and this is probably due to the fact that diastereomeric excesses are often only moderate and strongly influenced by the structure of the side chain of the α-amino acid. A thorough study was carried out by Yamada et al. [42], who observed that the configuration of the newly generated stereocenter of the major diastereoisomer is always opposite to that of the amino ester. Representative examples are shown in Scheme 1.15. Although Yamada often also used chiral protected aminoacids as the carboxylic component, they were proved to have a negligible influence on the stereoselectivity.

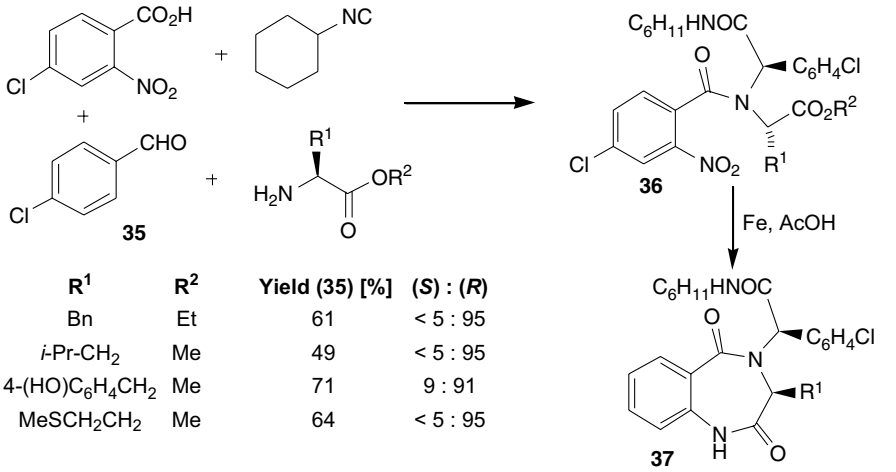
The preferential formation of (*R*) adducts may be explained by the arguments already outlined for α-methylbenzylamine. In this case, R^1 should play the role of "large" group. Alternatively, a different starting conformation of the protonated imine, namely **34**, involving a hydrogen bond between the carboxylic oxygen and the iminic proton, has been suggested [43].

The most selective example is represented by the synthesis of 1,4-benzodiazepin-2,5-diones **37** *via* Ugi reaction with different α-aminoesters. The use of aromatic aldehyde **35** leads in some cases to very high stereoselectivity in the preparation of intermediate **36**, and a single diastereoisomer is isolated after crystallization (Scheme 1.15) [43].



R^1	R^2	Yield [%]	(*S*) : (*R*)
Me	H	72	42 : 58
i-Pr	H	84	19 : 81
i-Pr	*i*-Pr	76	19 : 81
Bn	H	78	23 : 77
t-Bu	H	59	30 : 70





R^1	R^2	Yield (35) [%]	(*S*) : (*R*)
Bn	Et	61	< 5 : 95
i-Pr-CH_2	Me	49	< 5 : 95
4-(HO)$C_6H_4CH_2$	Me	71	9 : 91
$MeSCH_2CH_2$	Me	64	< 5 : 95

Scheme 1.15

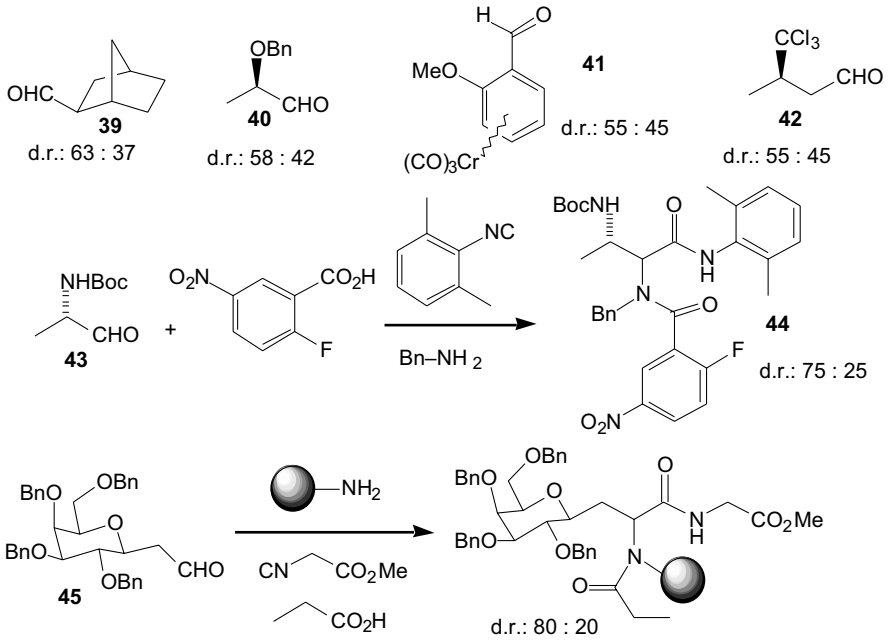
1.4.3
Chiral Isocyanides, Carboxylic Acids and Carbonyl Compounds

As already mentioned in Section 1.4.1, chiral isocyanides usually give no induction at all in Ugi reactions. For example, when using chiral α-substituted or α,α-disubstituted isocyanoacetates [7, 27, 44], the two resulting diastereoisomers are

typically obtained in a 1:1 ratio. Even isonitrile **11** (Scheme 1.4), which affords excellent stereoselectivity in the Passerini reaction, is totally inefficient in asymmetric Ugi reaction and this fact has led the authors of that paper to suggest that the isocyanide may not be involved in the step that determines the configuration of the new stereocenter [14]. Finally, even isocyanoglucoses, despite their steric biases, only afforded stereoselectivity of between 50:50 and 57:43 in Ugi condensations with achiral aldehydes, amines and carboxylic acids [45].

At present no chiral carboxylic acid capable of significantly controlling the stereochemistry of the new stereogenic center has been reported [42, 46].

In most cases chiral carbonyl compounds also afford low stereoselectivity. As for the related Passerini reaction, even the use of aldehydes that are known to give excellent asymmetric induction in the reaction with other kinds of C-nucleophiles, results in low or moderate diastereoisomeric ratios. For example, both norbornyl aldehyde **39** [47] and α-alkoxyaldehyde **40** [3, 48] gave *dr*s lower than 2:1 (Scheme 1.16). The same happens with ortho-substituted chromium complex **41** [49], which usually leads to very high asymmetric induction in other nucleophilic additions. Finally, β-substituted aldehyde **42** [50] gave poor results as well.



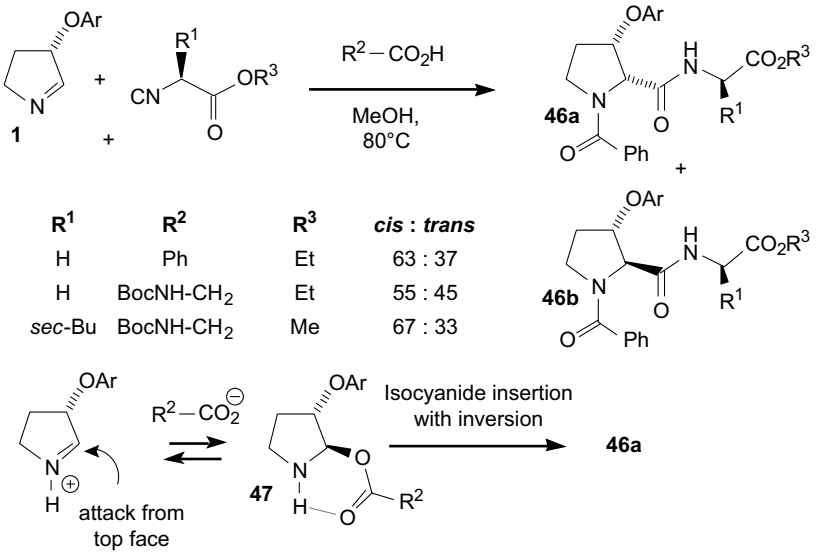
Scheme 1.16

Protected α-aminoaldehydes follow the same trend, although a notable exception is represented by the reaction of compound **43** with a bulky isonitrile, affording **44** in a 3:1 ratio (the relative configuration of the major product was not determined) [51].

Although various chiral glycosyl aldehydes with a direct attachment of the carbonyl group to the anomeric center showed low diastereoselectivity [52], a moderate stereoselectivity was observed in the condensation of **45** with methyl isocyanoacetate, propionic acid and a solid-supported amine [53].

1.4.4
Chiral Cyclic Imines

Only a few examples of U-3CRs involving chiral cyclic imines have been reported to date.

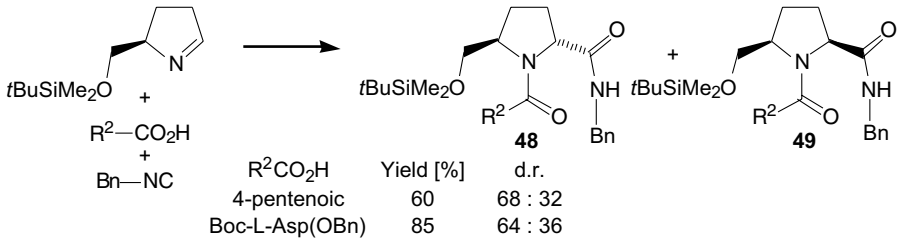


Scheme 1.17

Condensations employing 2-pyrrolines with the chirality on C-3 [8, 54] or C-5 [55] showed only moderate stereoselectivity.

In the first case the best combination of reagents gave a 2:1 cis:trans mixture (60% yield, Ar = *p*-cyanophenyl) [54]. To the best of our knowledge this represents the only example involving cyclic imines, in which the prevailing stereoisomer is the cis one. The observed stereoselectivity can be explained, according to the authors of that work if the reaction follows mechanism B or C to give preferentially the bicyclic hydrogen-bonded intermediate **47** after attack of the carboxylate from the side opposite to the OAr group. This intermediate, both kinetically and thermodynamically favored, finally undergoes insertion of the isocyanide with inversion to give the cis isomer.

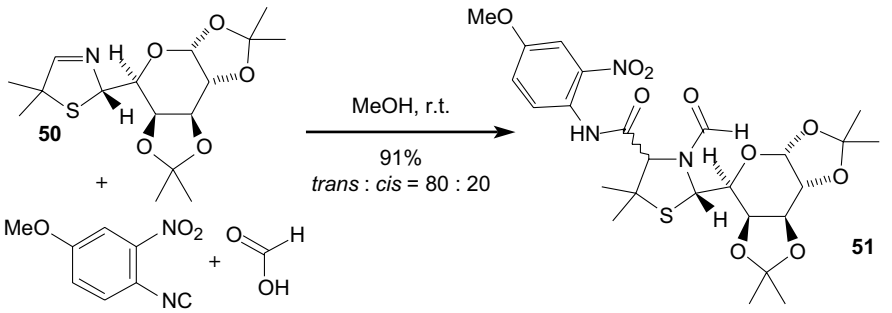
A reversal of stereoselectivity, with a ratio usually in the range 2:1, was observed when 5-substituted-2-pyrrolines were used [55]. 2,5-Pyrrolidines **48** and **49** (Scheme



Scheme 1.18

1.18) were therefore obtained, with the trans stereoisomer prevailing, employing a series of simple isocyanides and several acids or protected amino acids. However, when the bulky trityl group was present as protecting group on the pyrroline alcohol (instead of $SiMe_2tBu$) the reaction was almost completely non-stereoselective.

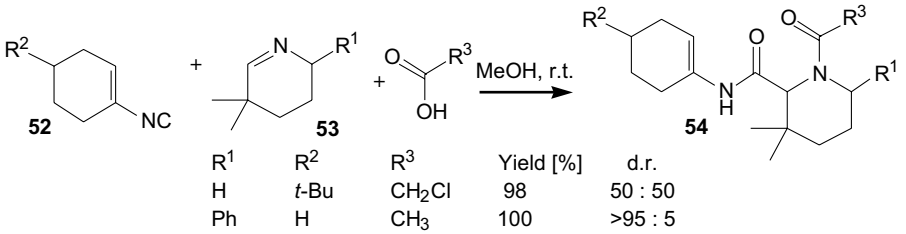
The enantiomerically pure 3-thiazoline **50**, obtained *via* Asinger reaction using a galactose-derived chiral auxiliary, was successfully submitted to an Ugi condensation affording the trans adduct **51** with good stereoselectivity, as reported in Scheme 1.19 [56].



Scheme 1.19

The synthesis of 6-substituted pipecolic acid derivatives has been carried out, in most cases with excellent stereoselectivities (> 95:5 *trans*:*cis*) and yields, by U-3CR between six-membered cyclic imines **53**, carboxylic acids and the convertible isonitriles **52**. Representative examples are reported in Scheme 1.20. On the other hand, when the chirality was present only on the isocyanide no stereoselectivity was observed, as expected [57]. *In situ* treatment of enamides **54** with an appropriate nucleophile allowed the conversion into the final products. The same trend in stereoselectivity was observed when similar imines were condensed with isocyanoacetic acid methyl ester and Boc-glycine to give a series of tripeptides [58].

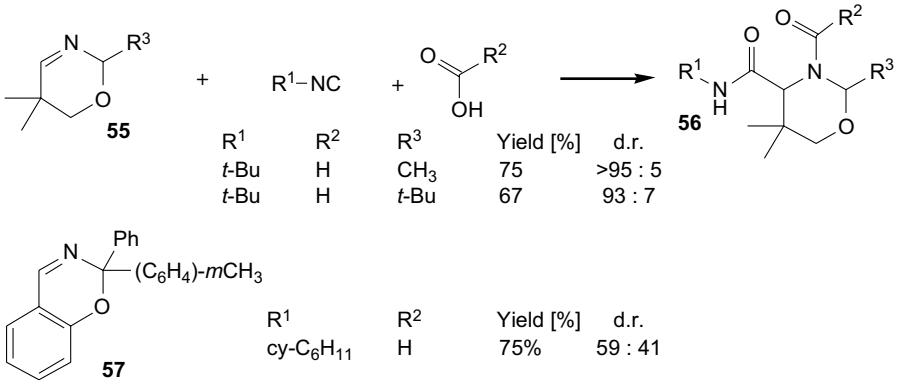
Other cyclic imines involved in U-3CRs are represented by 2-substituted 2*H*-1,3-oxazines **55** [59]. In this case also, the reaction was found to be very stereoselective and gave protected homoserine derivatives **56** (Scheme 1.21). No information is



52 53 54

R^1	R^2	R^3	Yield [%]	d.r.
H	*t*-Bu	CH_2Cl	98	50 : 50
Ph	H	CH_3	100	>95 : 5

Scheme 1.20



55 56 57

R^1	R^2	R^3	Yield [%]	d.r.
t-Bu	H	CH_3	75	>95 : 5
t-Bu	H	*t*-Bu	67	93 : 7
cy-C_6H_{11}	H		75%	59 : 41

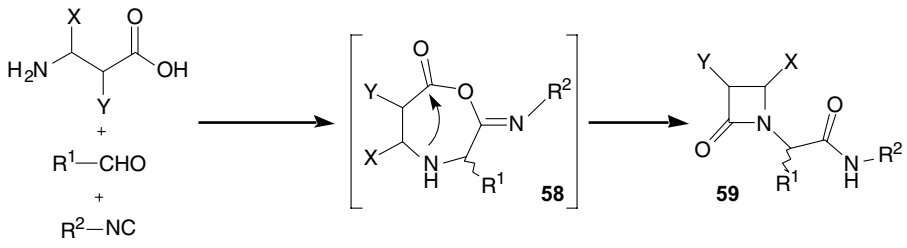
Scheme 1.21

given about the relative configuration of the products. Interestingly, when 2*H*-1,3-benzooxazine **57** was employed, the stereoselectivity dropped to a 59:41 ratio.

In some cases, therefore, 1,3-induction in the Ugi reaction using cyclic imines seems to be excellent. However, further investigations should be performed in order to rationalize the results, although it is clear that the position of the chirality on the imine, together with the hybridization of the carbon atoms in the ring, seems to play an important role both with regard to the diastereoselectivity and in determining the preferred face during isonitrile attack.

1.5
Asymmetric Intramolecular Ugi Reactions

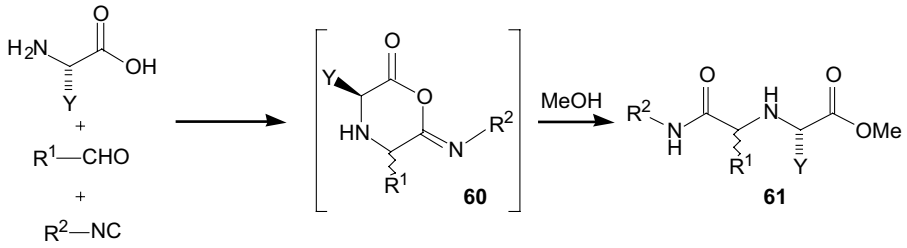
Intramolecular versions of the Ugi reaction, where two of the four functional groups involved belong to the same molecule, have attracted many scientists for their ability to generate various heterocycles relevant from a pharmacological point of view. Among others, reactions with α- and β-aminoacids have been reported to generate interesting stereochemical outcomes. The possibility of generating β-lactam rings using β-aminoacids has been known since 1961 as the Ugi four-center-three-component reaction (U-4C-3CR) [60]; the postulated mechanism



Scheme 1.22

evolves through a seven-membered intermediate **58** to give the final compound **59** *via* a ring contraction step (Scheme 1.22) [61].

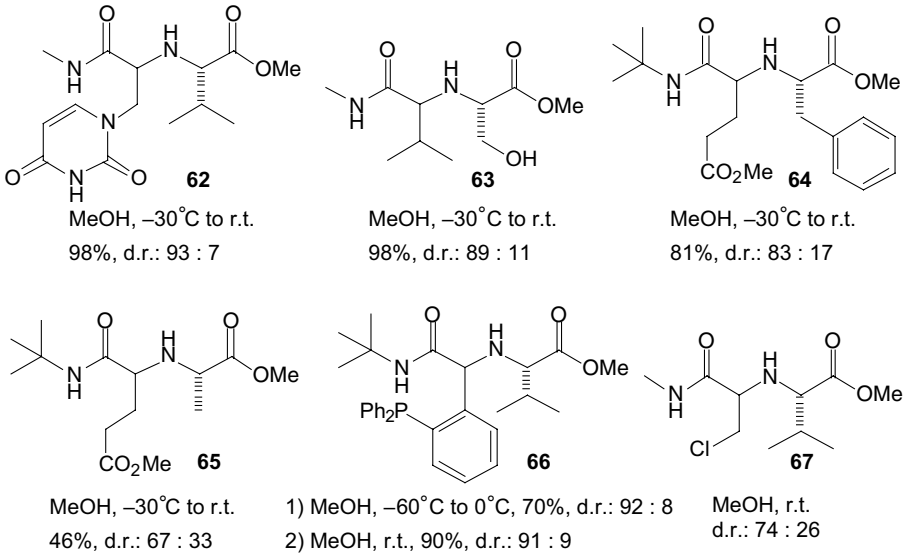
α-Aminoacids can react following a similar path [62]; however, the six-membered ring intermediate **60** cannot evolve *via* a ring contraction, owing to higher steric tensions, but reacts with an external nucleophile (e.g. methanol used as the solvent), giving rise to an Ugi five-center-four-component reaction (U-5C-4CR) that generates an α,α′-iminodicarboxylic acid derivative **61** (Scheme 1.23).



Scheme 1.23

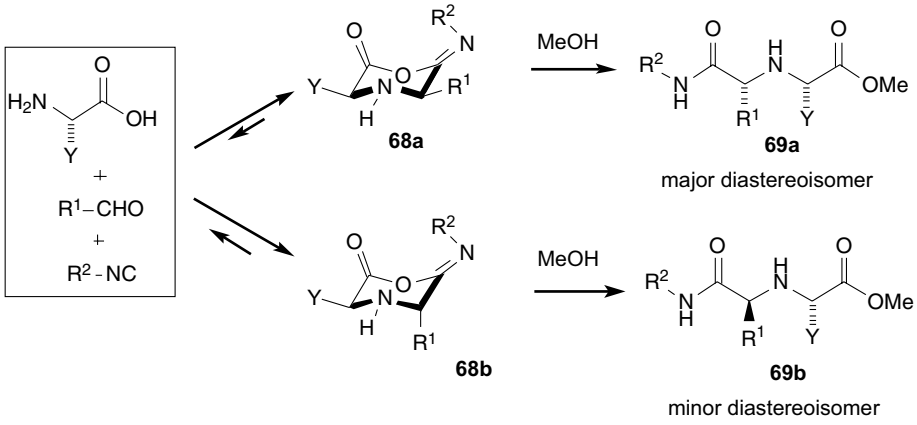
1.5.1
With α-Amino Acids

The U-5C-4CR with α-aminoacids typically leads to diastereoselectivities ranging from good to very good, as illustrated by the examples reported in Scheme 1.24, and has been exploited by different research groups [62–71]. Reactions are usually carried out at −30 °C and the temperature is then left to rise to 0 °C or room temperature; however, it is worth noting that, by performing the same reactions at room temperature, the diastereoselectivity seems not to be affected (see for example compound **66** [64]). It is also interesting to note that diastereoselectivity usually increases when bulky aminoacids (see for example compound **62** [62] using valine) and aldehydes (see for example compound **63** [67] using isobutyraldehyde) are used; similar considerations apply when comparing, for example, compounds **64** and **65** [69] or compounds **66** and **67** [70]).



Scheme 1.24

Sung et al. [71] attempted to explain the reasons for the observed stereoselectivities on the basis of the mechanism outlined in Scheme 1.25: it is assumed that the cyclic intermediate **68** is formed under thermodynamic control and can equilibrate to the more stable isomer before being attacked by the external nucleophile. When the aminoacid has a bulky side chain (for example Y = *i*-Pr), the cyclohexyl intermediate **68** will preferentially dispose this chain in the equatorial position. Between the two possible diastereoisomers, the most favored one will be that with R^1 in the equatorial position **68a** and therefore this will be formed preferen-



Scheme 1.25

tially and will generate the major diastereoisomer **69a** after reaction with methanol. The size of Y and R^1 is important: in fact less bulky groups furnish a lower *de* [71].

Although it is reported that the U-5C-4CR can work well with nucleophiles other than methanol, such as primary or secondary amines, the only examples reported in the literature are those where trifunctional α-aminoacids such as lysine [67] or homoserine [66] or bifunctional aldehydes such as glycolaldehyde [65] are employed. In these cases, the side-chain amino or hydroxy group acts as the nucleophile and opens the cyclic intermediate generating the corresponding lactams or lactones. A less nucleophilic solvent such as trifluoroethanol is usually employed, in order to maximize the intramolecular attack. The observed stereoselectivities are, apart from a few examples [66], usually not very high; this could be due to different factors: (a) the side chains of the α-amino acids are not very bulky; (b) the intramolecular nucleophilic attack could be faster than the methanol attack and the cyclic intermediate could not equilibrate to the thermodynamically favored isomer; (c) the intramolecular nucleophilic attack on the more stable diastereoisomeric cyclic intermediate could be kinetically less favored.

Ketones react with α-aminoacids in the same way [68], although reactions are reported to be slower; there is only one example with an unsymmetrical ketone (acetophenone) and the diastereomeric excess is not reported.

Finally, also N-alkylated α-aminoacids such as proline, azetidinecarboxylic acid or piperidinecarboxylic acid give the U-5C-4CR but, apart from one example [62], diastereoselectivities are very poor [65].

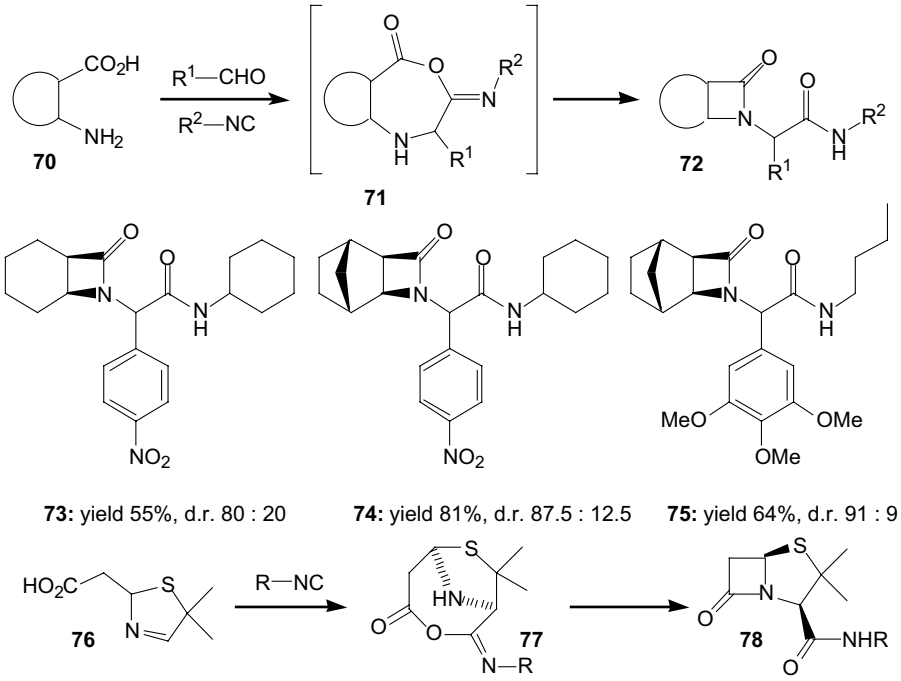
1.5.2 With Other Amino Acids

β-Amino acids can react with aldehydes and isocyanides in a similar way; however, the seven-membered cyclic intermediate is sufficiently flexible to evolve to β-lactam *via* a ring contraction [60, 72]. When the stereogenic center is at the α position, generally the diastereomeric excesses are low, owing to the greater distance between the pre-existing and the new stereocenters in the intermediate seven-membered ring. In these cases the two diastereoisomers are often obtained in a 1:1 ratio [61, 73]. Stereoselectivities are usually higher when the β-amino acids have a chiral carbon in the β position, in fact the final products are generated with diastereomeric excesses up to 70% [61, 74].

When the β-amino acid moiety is inserted into a monocyclic or bicyclic structure such as **70** and therefore possesses chiral centers at both the α and β positions, high diastereoisomeric excesses are sometimes observed, as reported in Scheme 1.26 [75].

The higher rigidity of the bicyclic scaffolds could favor the preferential formation of one of the two diastereoisomeric intermediates **71** and therefore explain the observed selectivity for compounds **73**–**75**.

Also in the case of the cyclic Schiff base **76**, the bridged bicyclic nature of inter-

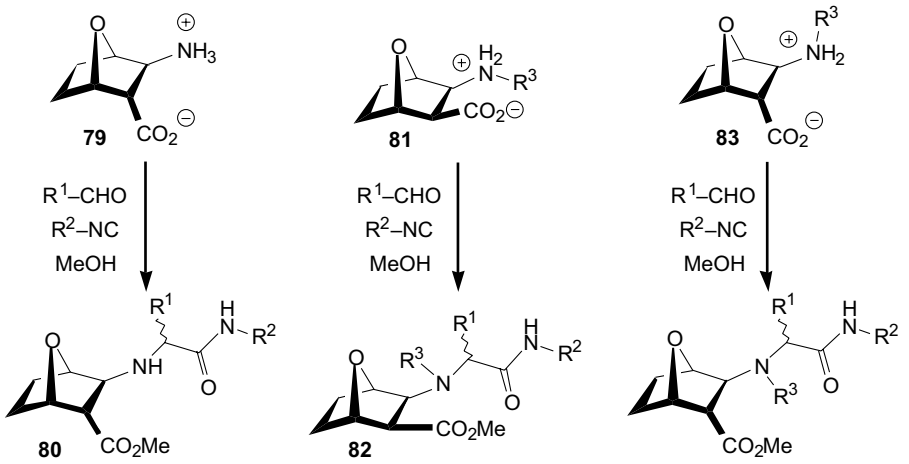


Scheme 1.26

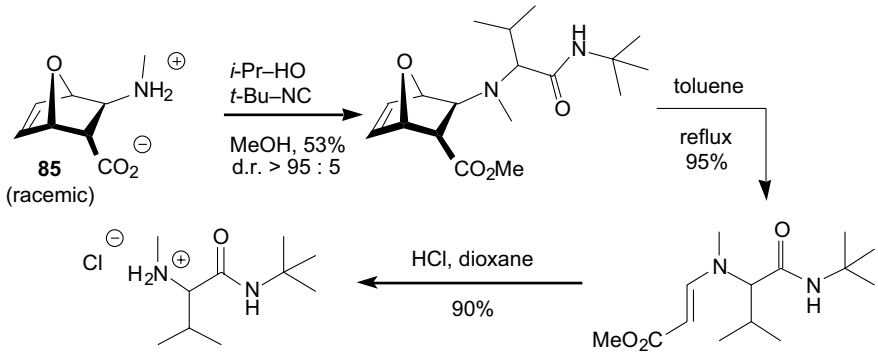
mediate **77** imposes a severe steric bias: as a result penicillanic derivative **78**, having the same relative configuration as natural penicillins, is exclusively formed with complete stereoselectivity [76].

Bicyclic β-aminoacids have also been used to study the chemical reactivity and stereochemical outcomes when the configuration of the carboxylic group is changed from exo to endo and when the nitrogen is alkylated [77]. The trans bicyclic β-amino acid **79** cannot evolve to the corresponding β-lactam *via* the U-4C-3CR, but generates the corresponding methyl ester **80** *via* the U-5C-4CR, in analogy with α-aminoacids. Similarly, N-alkylated cis and trans bicyclic β-amino acids **81** and **83** cannot undergo ring contraction and follow the U-5C-4CR path to give respectively **82** and **84** (Scheme 1.27). From the stereochemical point of view compound **83** is the most interesting: in fact only one diastereoisomer is observed with a wide variety of aldehydes and isocyanides. On the contrary, compounds **79** and **81** give high induction ($dr > 95{:}5$) only in particular cases, the degree of stereoselectivity being strongly dependent on the structure of the isonitrile and aldehyde employed.

In order to develop a removable analogue of **83**, unsaturated compound **85** was devised as a new chiral auxiliary that can be displaced at the end of the synthesis via a retro Diels–Alder reaction and subsequent acid treatment of the resulting enamine (Scheme 1.28).



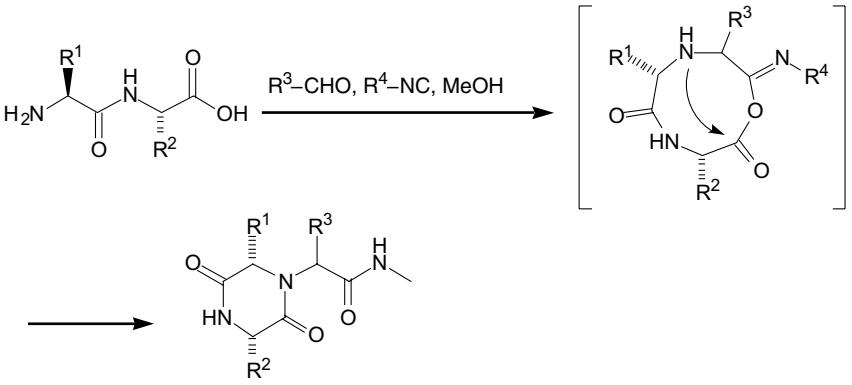
Scheme 1.27



Scheme 1.28

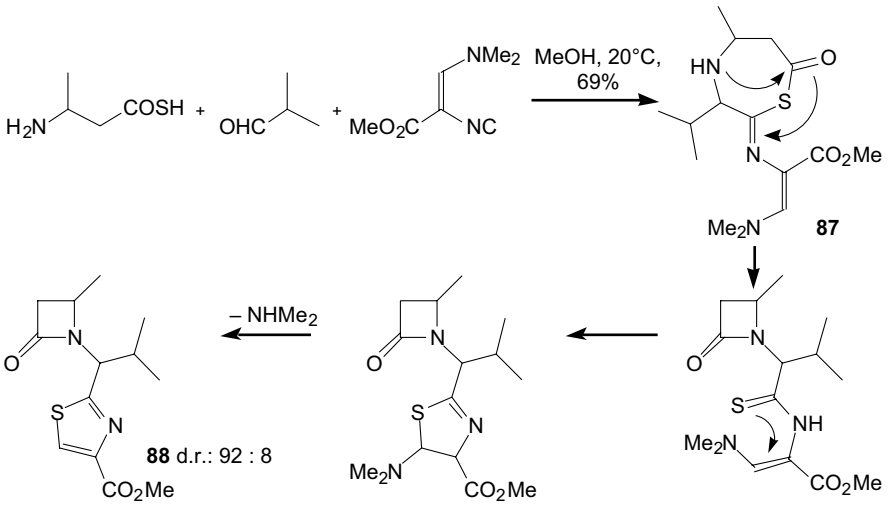
In the literature there is also an example of an intramolecular Ugi reaction with dipeptides used as bifunctional components, via their amino and carboxy groups [78] (Scheme 1.29). The postulated mechanism for this reaction, leading to N-substituted 2,5-diketopiperazines, is a U-4C-3CR characterized by the formation of a nine-membered cyclic intermediate that evolves to diketopiperazines **86** via ring contraction. Despite the ring size, the configurations of the two C_α of the dipeptide have some influence on the newly generated stereocenter, and diastereomeric ratios up to 6:1 can be obtained.

β-Aminothiocarboxylic acids react with aldehydes and 3-dimethylamino-2-isocyanoacrylic acid methyl ester following the pathway described for *β*-amino-acids, affording, after ring contraction of the seven-membered intermediate **87**, Michael-type cyclization and *β*-elimination, *β*-lactam **88** equipped with a thiazole



86: yield 21-87%, d.r. 60 : 40 to 86 : 14

Scheme 1.29

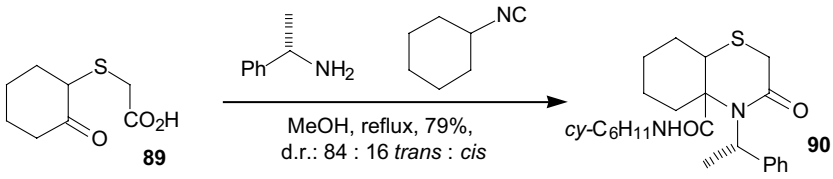


Scheme 1.30

ring in good yield (Scheme 1.30). The diastereoselectivity is excellent in contrast with the typical behavior of *β*-aminoacids [79].

1.5.3
With Keto Acids

To the best of our knowledge only one example of diastereoselective intramolecular Ugi reaction employing a ketoacid is known [80]. The condensation of acid **89** with (*S*)-1-phenylethylamine proved to be stereoselective, giving a mixture of the four possible diastereoisomers **90** in a 42:42:8:8 ratio, with the trans stereoisomers pre-



Scheme 1.31

vailing (Scheme 1.31). Other substrate combinations gave lower degrees of stereoselectivity.

1.6
Other Asymmetric Isonitrile-based Multicomponent Reactions

1.6.1
Tandem Ugi or Passerini Reaction/Intramolecular Diels–Alder (IMDA) Cyclizations

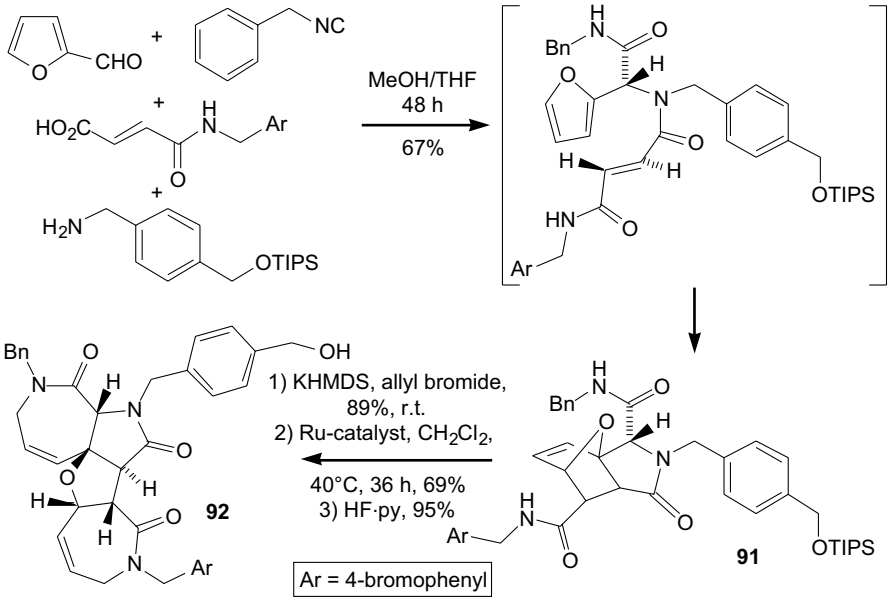
The possibility of coupling an Ugi-4CR or a Passerini-3CR with an *in situ* spontaneous, thermal or Lewis acid-catalyzed IMDA cyclization has been realized in a highly stereoselective manner by some research groups [81–83], allowing highly convergent syntheses of structurally complex compounds endowed with several heterocyclic rings. The stereoselectivity was, however, not displayed during the multicomponent reaction, but during the following IMDA cycloaddition of the intermediate α-acylaminoamide or α-acyloxyamide.

Toward this goal, a furane ring was included in the carbonyl or amine component, since this moiety will furnish a highly reactive diene for the following IMDA. In most cases 2-furaldehyde (or the corresponding 5-methyl derivative) was employed. The acid component was chosen in order to introduce an activated dienophile suited for the IMDA and was in turn a fumaric acid monocarboxyamide [82, 84], a maleic or fumaric acid monoester [84] or a 3-substituted propynoic acid [83]. Benzylamine (or a *para*-substituted derivative) [81–83] or *t*-butylamine [83] have been chosen as amine component for the Ugi reactions.

An example of this strategy is shown in Scheme 1.32 [82, 84]. On varying the isocyanide, the dienophile, the amine and the furaldehyde, analogues of **91** could be obtained in 70–89% yields and with *dr*s between 83:17 and 92:8. This Ugi/IMDA tandem methodology has been employed also in the solid phase, by anchoring the amine component to a suitable resin [82, 84].

In addition, the bisallylation of the two secondary amides of compound **91**, followed by treatment with an appropriate ruthenium catalyst, allowed a tandem ring-opening metathesis/ring-closing metathesis to give, after alcohol deprotection, the quite complex structure **92** [82].

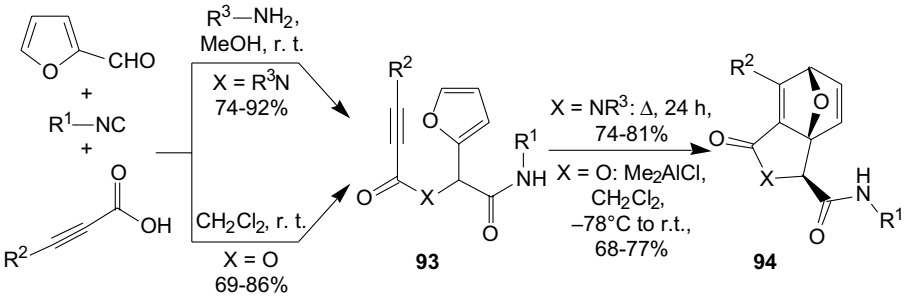
Interestingly, when the furane ring was present in the amine component, and



Scheme 1.32

benzaldehyde was used as the carbonyl partner, the tandem process was poorly stereoselective [84].

Both Ugi and Passerini reactions have been explored, using 3-substituted propynoic acids as dienophiles. The multicomponent adducts **93** have been submitted to IMDA under different conditions, depending upon the heteroatom X in the tether: Ugi adducts could be converted smoothly, usually under thermal conditions, to give **94** as the major stereoisomer (less than 10% of any other stereoisomer detected). On the contrary, Passerini adducts proved to be unreactive under thermal conditions, but reacted cleanly under Me_2AlCl catalysis to give bicyclic lactones in a highly stereoselective way (Scheme 1.33) [83].

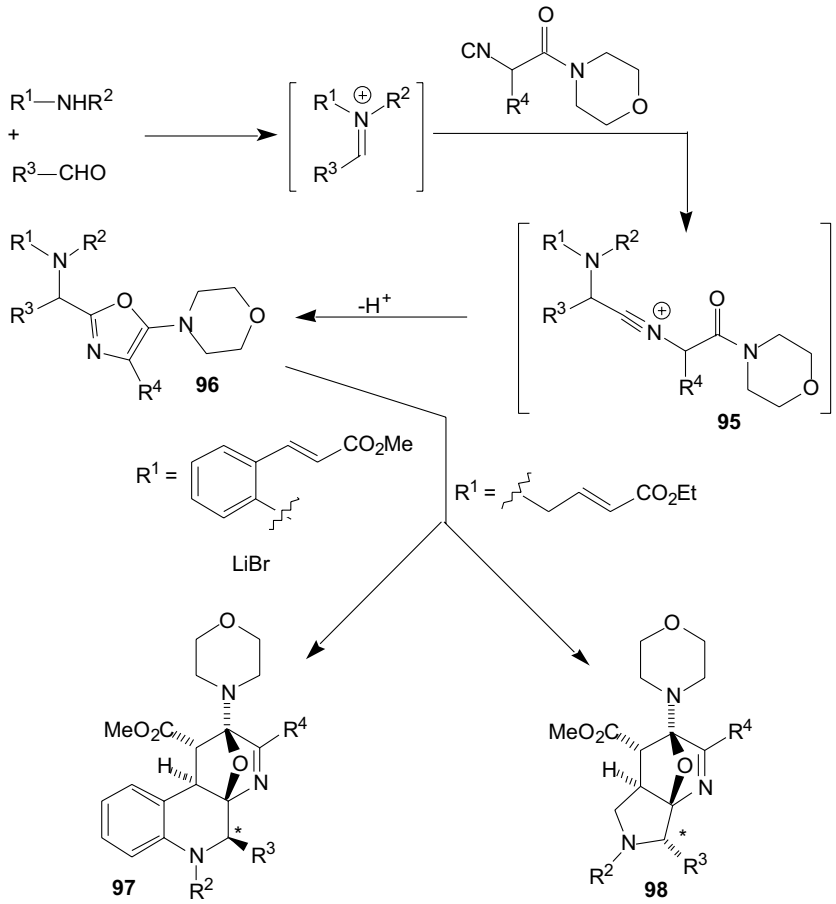


Scheme 1.33

1.6.2
Other Asymmetric Isonitrile-based Multicomponent Reactions

The 3C-reaction between a primary or a secondary amine, an aldehyde and an isocyanoacetamide affords 2,4-substituted-5-aminoxazoles (Scheme 1.34) [85]. Most probably, after formation of the initial imine or iminium species, the isonitrile reacts as a C-nucleophile to give intermediate **95** (Scheme 1.34), which undergoes an intramolecular nucleophilic attack by the amide oxygen to give the oxazole ring. During this reaction a new stereogenic center is created. In all cases, when enantiomerically pure isocyanides were employed, the corresponding oxazoles were obtained in racemic form. On the other hand a single example with a chiral amine component, namely proline methyl ester, was reported. In that case the *dr* was only 2.5:1.

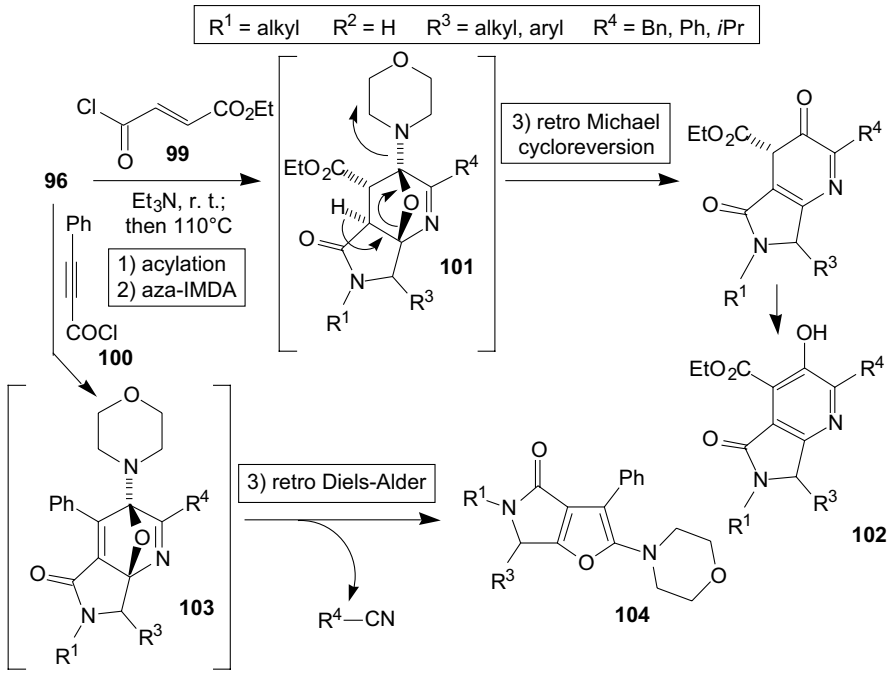
This new multicomponent reaction was coupled to IMDA, exploiting a strategy



Scheme 1.34

similar to that described in the previous paragraph [86–90]. When primary or secondary amines having a tethered electron-poor double bond were employed, oxazoles **96** cannot be isolated since they were directly converted into oxabridged derivatives **97** [86] or **98** [87] with the simultaneous creation of five stereogenic centers (Scheme 1.34). This is a consequence of a spontaneous aza-IMDA promoted by the presence of the electron-rich azadiene of the oxazole. In the case of compounds **97**, best results are obtained in the presence of LiBr as additive. The overall yields are good (42–78%) and the stereoselectivity is typically excellent. Only one relative configuration of the four stereogenic centers of the oxabridged ring is obtained. Thus only the aldehyde-derived stereogenic center (indicated with * in the Scheme) gives rise to two epimers, with *dr*s ranging from 3:1 to >95:5. Interestingly, the configuration of this center in the major stereoisomer is opposite for **97** and **98**.

Alternatively a two-step sequence was employed instead of a domino MCR-IMDA. Oxazoles **96** ($R^2 = H$) were isolated and acylated with unsaturated acyl chlorides **99** and **100**, equipped with an electron-withdrawing substituent, in the presence of triethylamine. By heating to 110 °C, an aza-IMDA occurred (Scheme 1.35). However, in this case the oxa-bridged compounds **101** and **103** can not be isolated. Owing to the presence of Et_3N, further transformations occur, depending upon the type of unsaturation of the dienophile, leading to: (a) pyrrolo[3,4*b*]-pyridin-5-ones **102**, arising from a retro Michael cycloreversion promoted by the base [88]; (b) 5,6-dihydrofuro[2,3-*c*]pyrrol-4-ones **104**, arising from a retro Diels–

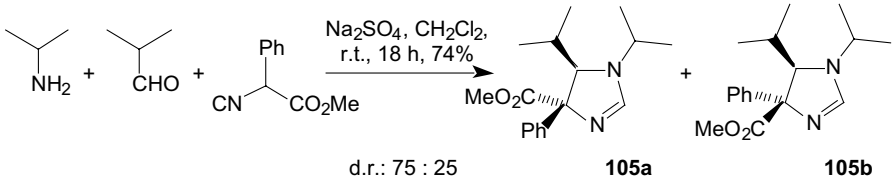


Scheme 1.35

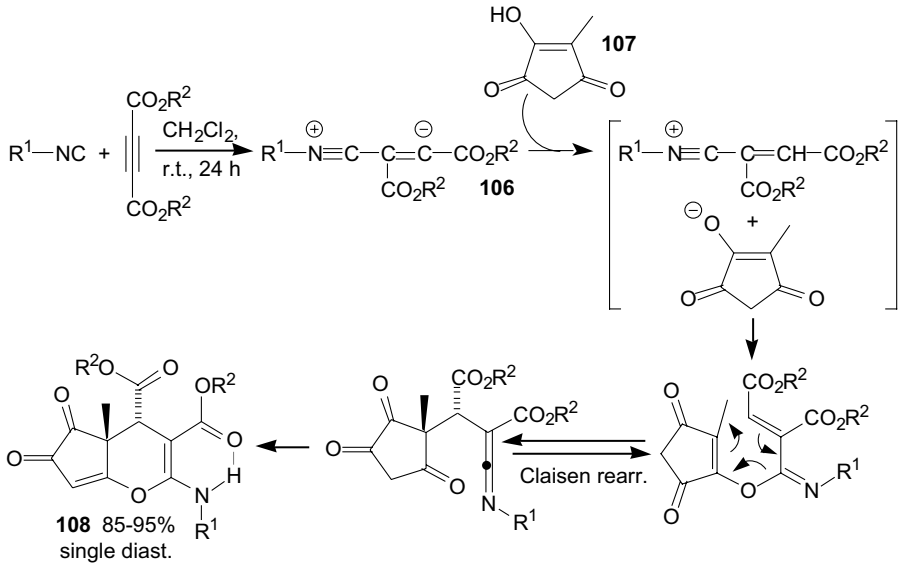
Alder reaction [89]. The latter compounds can be submitted again to a Diels–Alder reaction by treatment with maleimide and the resulting oxa-bridged intermediates, obtained as a mixture of diastereoisomers, can be transformed into hexasubstituted benzenes by thermal treatment. In these cases however, the possible asymmetric induction obtained during the cycloaddition is lost in the final part of the domino sequence.

The use of an α-isocyanoacetamide instead of an α-isocyanoacetate is essential in order to obtain oxazoles; when the latter compounds are employed, other condensations (Knoevenagel, Mannich), affording imidazolines or amidines, will take place [88]. This reaction has been explored for the preparation of a series of 2-imidazolines employing isocyanoacetates [91]. The reaction worked smoothly to give compounds **105a**,**b** (Scheme 1.36) with the trans isomer prevailing, provided that a racemic isocyanide with an acidic α-proton and a sterically undemanding amine are used.

Pyrane derivatives were obtained through a stereoselective isocyanide-based multicomponent reaction. The reaction between an isocyanide, a dialkyl acetylene-



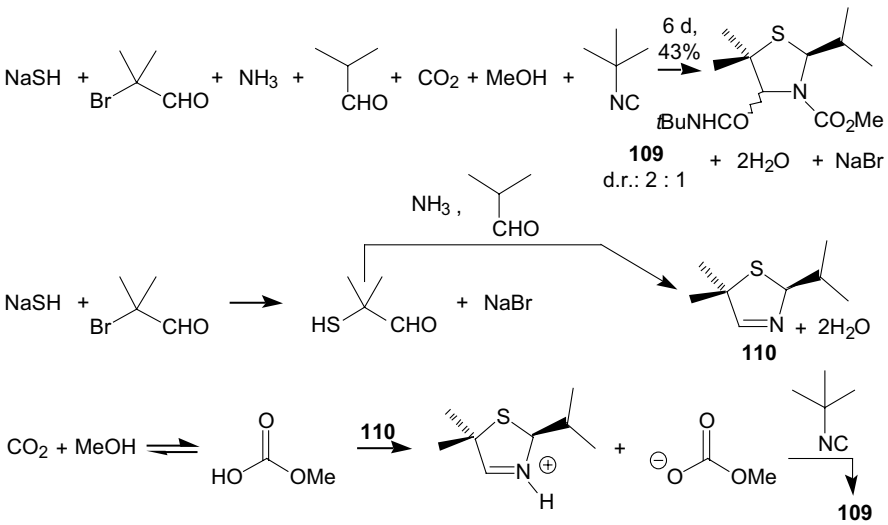
Scheme 1.36



Scheme 1.37

dicarboxylate and cyclopentanetrione **107**, allowed the preparation in excellent yields of a series of enaminoesters of general formula **108**, as single diastereoisomers [92]. The reaction most likely proceeds through the formation of zwitterionic intermediate **106**, followed by the nucleophilic attack of the enolate of **107** and a final Claisen rearrangement and cyclization, as depicted in Scheme 1.37. The relative stereoselectivity is controlled by the Claisen rearrangement step.

Finally, in the most complex multicomponent reaction involving isocyanides, the 7-CC proposed by Ugi in 1993 [93], a moderate diastereoselectivity, leading to a 2:1 mixture of epimeric thiazolidines **109** was observed. The reaction is a combination between an Asinger condensation, involving an α-mercaptoaldehyde (generated from the α-bromoaldehyde and SH^-) and an Ugi-type 4-CC with a monoalkyl carboxylate as acid component (Scheme 1.38). Although the relative configuration of the major stereoisomer was not demonstrated, it is probably trans, in line with the results of Ugi condensation with chiral thiazolines, reported above in Scheme 1.19.



Scheme 1.38

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2
Post-condensation Modifications of the Passerini and Ugi Reactions

Stefano Marcaccini and Tomás Torroba

Multicomponent reactions of isocyanides (I-MCRs) are extremely powerful synthetic tools for the preparation of structurally diverse complex molecules [1] as well as combinatorial libraries of compounds [2]. The enormous synthetic possibilities of I-MCRs can be further increased by post-condensation transformations. These modifications are usually accomplished by employing suitable functionalized and/or protected reagents and take place spontaneously or upon treatment with additional reagents. The design of cleavable reagents is therefore an important goal for I-MCR post-condensation reactions. The use of protected reagents such as acetals, *N*-Boc, *N*-Fmoc amino derivatives, etc. is well known [3]. A survey of cleavable reagents in I-MCRs has been published [4]. In this chapter the use of cleavable reagents will be discussed, convertible isocyanides will be introduced in a special section and a general approach to post-condensation reactions of the classical Passerini and Ugi reactions in syntheses of open-chain and heterocyclic products will be summarized.

2.1
Convertible Isocyanides

1-Cyclohexen-1-yl isocyanide **1** known as ''Armstrong convertible isocyanide'' has also been called ''universal isocyanide''. It was prepared in 1963 by Ugi and Rosendahl [5] to be used as a synthetic equivalent of the unknown ''hydrogen isocyanide''. The Ugi-4CR between **1**, cyclohexanone *N*-benzylimine **2**, and formic acid afforded *N*-cyclohexen-1-yl amide **3**, which was cleaved in acidic medium to afford the primary α-acylamino amide **4** rather than the *N*-substituted amides usually obtained by the Ugi-4CR (Scheme 2.1).

After the first report this isocyanide was not followed up until the studies of Armstrong and co-workers, which signaled the renaissance of 1-cyclohexen-1-yl isocyanide for synthetic purposes. Effectively, the Ugi-4CR adducts **5** obtained from **1** can be cleaved into the corresponding acids, esters, and thioesters **6** upon treatment with acids, alcoholic HCl, and thiols, respectively (Scheme 2.2) [6].

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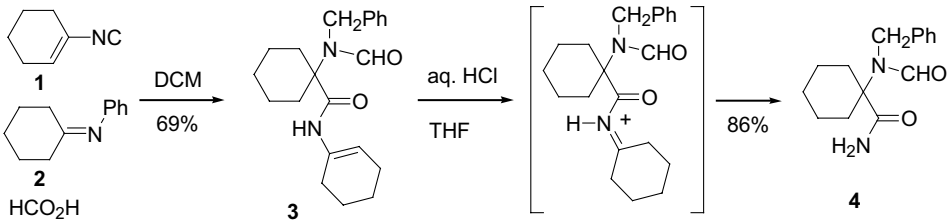
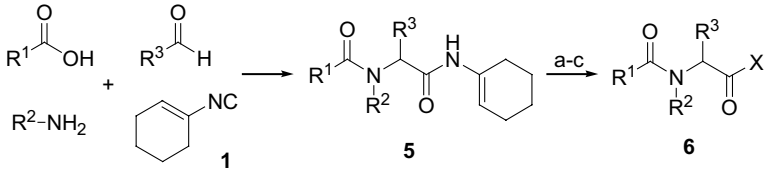


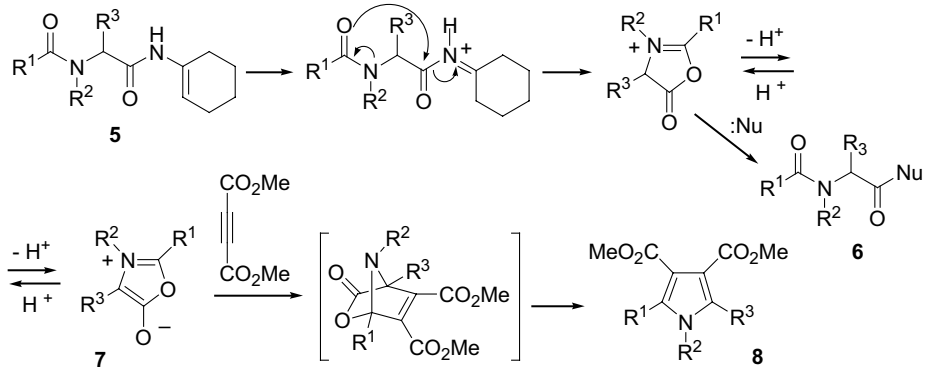
Scheme 2.1. 1-Cyclohexen-1-yl isocyanide as a synthetic equivalent of hydrogen isocyanide.



a) HCl, H_2O, X = OH; b) ROH, AcCl, X = OR; c) RSH, AcCl, X = SR

Scheme 2.2. Conversion of the Ugi-4CR adducts arising from isocyanide **1**.

The reaction mechanism involved the formation of highly reactive münchnones **7** (Scheme 2.3) as intermediates. Evidence for the assigned mechanism was provided by trapping the münchnones with dimethyl acetylenedicarboxylate. The initial 1,3-dipolar cycloaddition product eliminated CO_2 to give pyrroles **8** (Scheme 2.3) [6b].



Scheme 2.3. Mechanism and trapping of the intermediate münchnones.

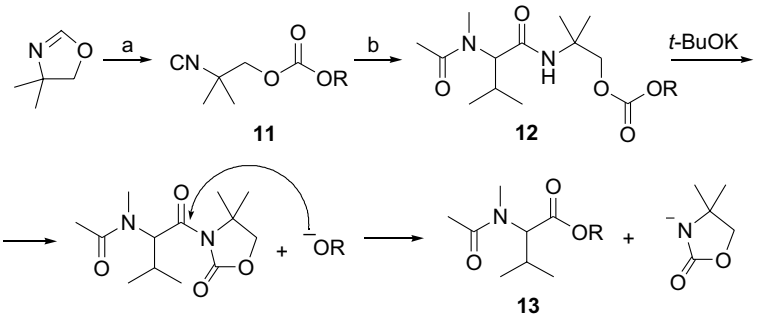
The discovery of this behavior was of great importance because a single product was converted into a variety of products. The conversion into primary amides or other carboxylic acid derivatives depended upon the structure of the Ugi adducts. An electron-rich *N*-acyl moiety was required for the formation of münchnones, otherwise the primary amide was obtained [7]. The conversion of cyclo-

hexenamides into primary amides [8] and acids [9] has been reported. The use of 1-cyclohexenyl isocyanide was, however, limited by its low stability, which prevented large-scale preparations and shelf-storage. Furthermore, the preparation of its stable precursors such as 1-formylamino-1-cyclohexanecarbonitrile and 1-formylamino-1-cyclohexene required tedious multi-step procedures [6b]. A convenient preparation of 1-formylamino-1-cyclohexene, starting from inexpensive cyclohexanone and formamide, has been reported by Martens and co-workers [8a]. The same group reported the synthesis of its more stable derivatives **9** and **10** (Scheme 2.4) [8a].

9 **10**

Scheme 2.4. Derivatives of 1-cyclohexen-1-yl isocyanide.

The Ugi group has designed a new class of convertible isocyanides, namely alkyl 2-isocyano-2-methylpropyl carbonates [7], prepared from commercially available 4,4-dimethyl-2-oxazoline. The Ugi-4CR of **11** afforded the expected products **12**, which were converted into *N*-acyl α-amino acid esters **13** and *N*-acyl α-amino acids by *in situ* hydrolysis (Scheme 2.5) [7].

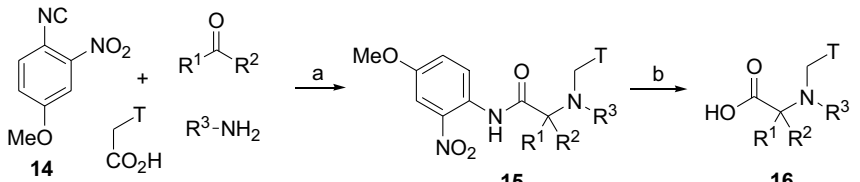


a) BuLi, THF, -78 °C,1 h, then $ClCO_2R$, -78 °C to rt, 80%.
b) Isobutyraldehyde, methylamine, acetic acid, MeOH, rt, 24 h, 80-90%

Scheme 2.5. The use of alkyl 2-isocyano-2-methylpropyl carbonates.

In general, the hydrolysis of amides requires conditions that are not compatible with the survival of several functional groups [10]. If the amide nitrogen is linked to an electron-withdrawing moiety, alkaline hydrolysis of the amide group is easier. Following this observation Martens and co-workers used 4-methoxy-2-nitrophenyl isocyanide **14** (or 2-methoxy-4-nitrophenyl isocyanide) as a convertible isocyanide for the preparation of Peptide Nucleic Acid (PNA) monomers [8a] (for another example, see Ref. [11]). The Ugi-4CR between isocyanide **14**, carboxymethyl nucleo-

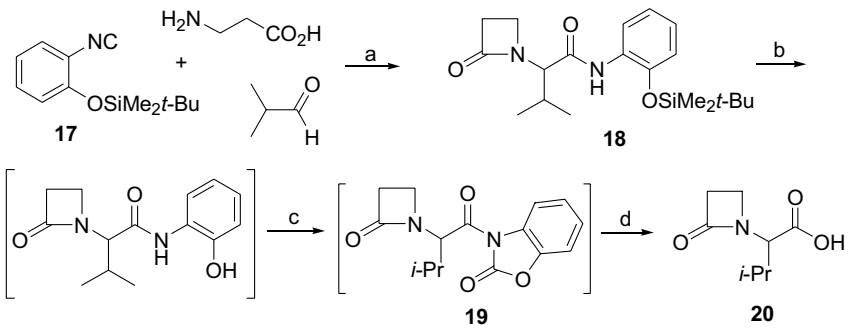
bases, carbonyl compounds, and amines containing an additional protected group afforded the totally protected Peptide Nucleic Acid (PNA) monomers **15** which were exposed to alkaline hydrolysis with methanolic potassium hydroxide to afford the partially protected PNA monomers **16** (Scheme 2.6) [8a].



a) MeOH, rt, 48 h, 20-85%; b) KOH (6 eq), MeOH, rt, then aq. HCl, extractive work-up, 71-83%

Scheme 2.6. 4-Methoxy-2-nitrophenyl isocyanide as a convertible isocyanide.

β-Lactams and β-lactam antibiotics are commonly synthesized by intramolecular Ugi reactions between β-amino acids, aldehydes, and isocyanides [12, 4]. Ugi and co-workers recognized that certain isocyanides such as 2-(*t*-butyldimethylsilyloxy)-phenyl isocyanide **17** were selectively cleaved in the presence of the β-lactam ring [13]. The Ugi reaction between **17**, 3-aminopropionic acid and isobutyraldehyde afforded the β-lactam **18**. Desilylation of **18** followed by treatment with carbonyldiimidazole gave the *N*-acyl-1,2-dihydro-2-oxobenzoxazole **19** which was easily hydrolyzed during work-up to give the desired acid **20** in a one-pot procedure (Scheme 2.7).



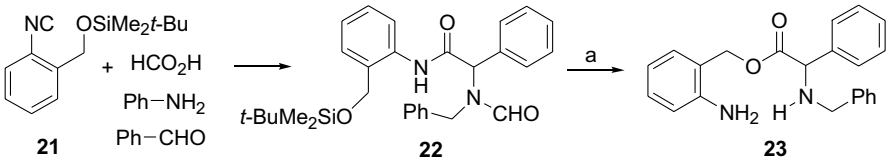
a) MeOH, N_2, 50 °C, 1 h, 55%; b) Bu_4NCl (2 equiv.), THF, 3 h; c) carbonyldiimidazole; d) evaporation, DCM/water, 90% overall.

Scheme 2.7. The use of isocyanide **17** as a cleavable reagent.

The transformation of secondary amides in the presence of the β-lactam ring has also been achieved by N-nitrosation of amides followed by thermal decomposition to esters, which were in turn hydrolyzed to the corresponding acids. Diphenylmethyl isocyanide [14] and 4-nitrobenzyl isocyanide (PNBNC) [15] have been suc-

cessfully employed to achieve this goal. The method was employed by Kehagia and Ugi [16] in the synthesis of 4-acetoxyazetidin-2-ones and by Isenring and Hofheinz in the synthesis of nocardicins [14b]. Subramanyam et al. [17] described the transformation of an *n*-methyl-α-acetoxy amide, arising from a Passerini reaction, into the corresponding methyl ester, *via* *N*-nitrosation, as a step in the approach to the marine alkaloid amphimedine.

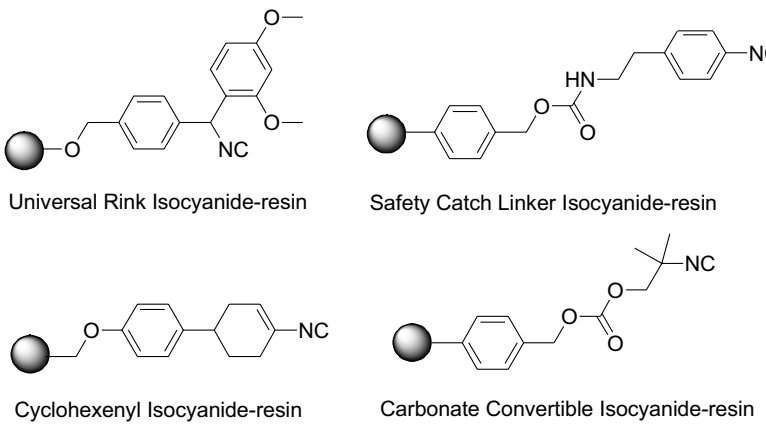
Another interesting convertible isocyanide, 2-(*t*-butyldimethylsilyloxymethyl)-phenyl isocyanide **21** was used by Linderman and co-workers [10] in a reaction with formic acid, benzylamine, and benzaldehyde to afford the Ugi adduct **22**, which, upon acid treatment followed by basification, underwent O-desilylation and amide/ester exchange to afford the ester **23** (Scheme 2.8). A remarkable feature of **21** is the high diastereoselectivity observed when it is employed in combination with chiral aminosugar derivatives in Ugi-4CR [10].



a) HCl, MeOH, 0 °C to rt, 5 h, then $NaHCO_3$, ca 100%

Scheme 2.8. Reactivity of isocyanide **21**.

The use of resin-bound convertible isocyanides such as the universal Rink isocyanide-resin [18], the safety-catch linker isocyanide-resin [8b, 19] the cyclohexenyl isocyanide-resin [8b], and the carbonate convertible isocyanide-resin [20] has found interesting applications in solid-phase Ugi-4CR and post-condensation transformations [21] (Scheme 2.9).



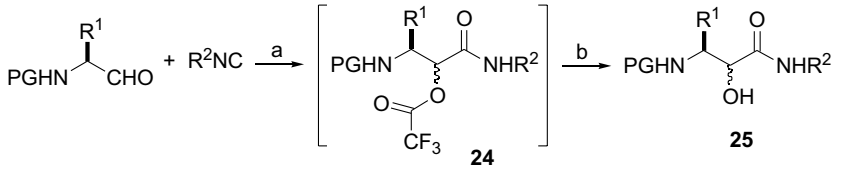
Scheme 2.9. Resin-bound convertible isocyanides.

2.2
I-MCR Post-condensation Reactions in Synthesis of Open-chain Products

The power of the Passerini and Ugi reactions in constructing polyfunctional molecules has been well appreciated since the early studies. The classical Passerini and Ugi reactions afford α-acyloxy carboxamides and α-acylamino amides respectively, that can be easily manipulated by post-condensation reactions, generating molecular diversity for drug discovery and natural product synthesis [22]. This strategy has been widely applied to the synthesis of natural peptides and open-chain peptide mimetics covered in this section.

2.2.1
Passerini 3CR + O-Deacylation

α-Acyloxyamides arising from the Passerini reaction can be selectively O-deacylated in acidic medium or in alkaline medium in mild conditions to afford the α-hydroxyamides. The O-deacylation processes of the Passerini-3CR adducts are of great importance when the carbonyl component is an α-protected amino aldehyde because it provides facile access to α-hydroxy-β-amino amide derivatives that are found in natural products that display important biological activities. Schmidt and Weinbrenner reported the first Passerini reaction performed with N-protected aldehydes [23]. In that case, the O-deacylation took place during the synthesis delivering α-hydroxy derivatives. An efficient route to α-hydroxy-β-amino amide derivatives was recently reported by Semple et al. [24] who used the Passerini reaction between N-protected α-aminoaldehydes, isocyanides, and trifluoroacetic acid in the presence of pyridine or alkylated pyridines to get the N-protected α-hydroxy-β-amino amides **25** in fair to good yields. Compounds **25** were presumably obtained by smooth hydrolysis of α-trifluoroacetoxy derivatives **24** during the work-up (Scheme 2.10).

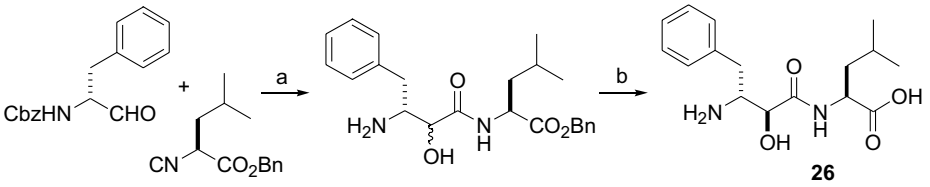


PG = Boc, Fmoc, Cbz; R^1 = H, Alkyl, Aryl; R^2 = t-Bu, CH_2CO_2Alkyl, (*S*)-CH(*i*-Bu)CO_2Bn
a) TFA (2 eq), pyridine (4 eq) DCM, 0 °C to rt; b) extraction or silica gel chromatography

Scheme 2.10. Preparation of N-protected α-hydroxy-β-amino amides *via* Passerini-3CRs.

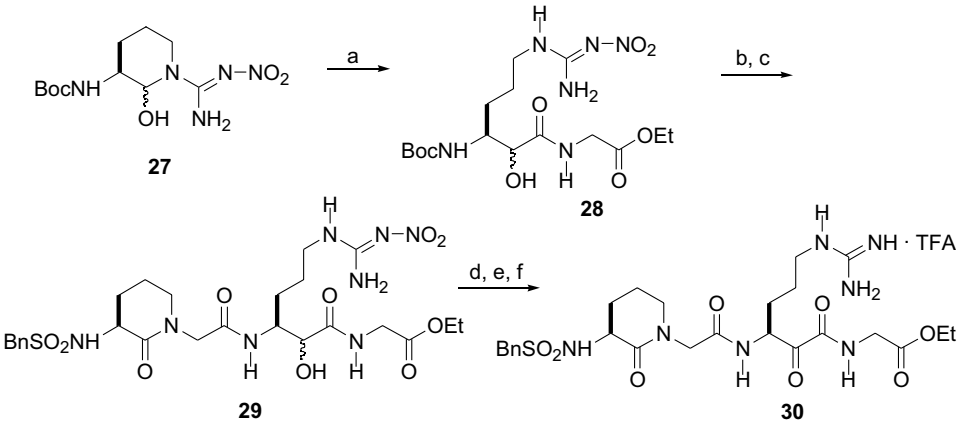
This methodology was employed in a short synthesis of bestatin **26** (Scheme 2.11) [24] which acts as a potent inhibitor of aminopeptidase and prolyl endopeptidase.

Oligopeptides containing the α-oxo-β-amino amide moiety are useful transition-state analogue inhibitors of serine [25] and cysteine proteases [26]. The α-hydroxy-



a) TFA, pyridine, DCM, 0°C to rt, 65%; b) H_2, Pd/C; c) HPLC separation, 29% (b+c)

Scheme 2.11. Synthesis of bestatin **26** *via* a Passerini-3CR.



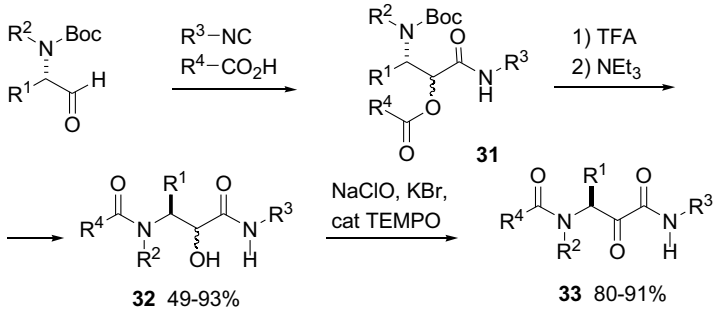
a) $CNCH_2CO_2Et$, TFA, pyridine, DCM, 0 °C to r. t., 38%; b) HCl, EtOH, 0 °C, 10 min, ca. 100%; c) (*S*)-2-oxo-3-($BnSO_2$-amino)piperidine-1-acetic acid, EDC, HOBt, DIEA, MeCN, r. t., 68%; d) H_2, Pd/C, AcOH, EtOH, H_2O, ca. 40 psi, ca. 100%; e) DMSO, EDC, Cl_2CHCO_2H, PhMe, 0 °C to r. t.; f) RP-HPLC, 61%.

Scheme 2.12. Synthesis of the thrombin inhibitor **30**.

β-amino amide derivatives are ideally suited for the preparation of *α*-oxo-*β*-amino amides. Semple et al. employed this methodology for the synthesis of the *α*-keto-argininamide thrombin inhibitor **30** (Scheme 2.12) [24].

2.2.2
Passerini-3CR + N-Deprotection + O → N Acyl Migration

This elegant methodology, first reported by the Banfi group [27], has greatly increased the potentiality of the Passerini reaction, allowing facile access to peptide mimetics and enzyme inhibitors. The strategy is based upon the use of *N*-Boc-protected *α*-aminoaldehydes as the carbonyl inputs in the Passerini reaction. The expected adducts **31** are subjected to the one-pot N-deprotection and acyl migration achieved upon treatment with trifluoroacetic acid followed by triethylamine, to afford *α*-hydroxy-*β*-acylamino amides **32** in good to excellent overall yields (Scheme 2.13). Furthermore *α*-hydroxy-*β*-acylamino amides are very useful precursors of



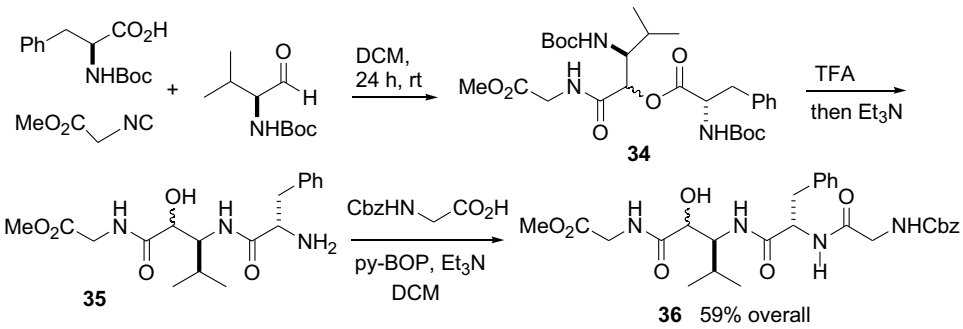
R^1 = Me, Et, *i*-Pr, $PhCH_2$, $MeOCH_2$; R^2 = H; R–R^2 = $(CH_2)_3$;
R^3 = Bn, *t*-Bu, *n*-Bu, CH_2CO_2Me, *c*-C_6H_{11}, $CH_2CH_2CO_2Bn$;
R^4 = Alkyl, Aryl, L-(Z)-Leu, L-(Boc)-Leu, (Z)-Gly, L-(Boc)-Phe, D-(Boc)-Phe.

Scheme 2.13. Synthesis of α-hydroxy-β-acylamino amides.

the corresponding α-oxo derivatives **33**. By employing enantiomerically pure acids only two diastereoisomers are detected, indicating that racemization of the α-aminoaldehyde in the course of the synthesis is negligible.

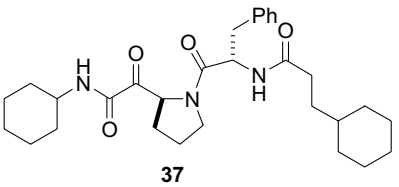
This methodology has been extended by employing functionalized carboxylic acids and/or isocyanides in order to increase the diversity of the reaction products and to achieve an easy access to four- or five-unit peptide mimetics [28]. For example, tetrapeptide **36** was obtained in 59% overall yield (Scheme 2.14).

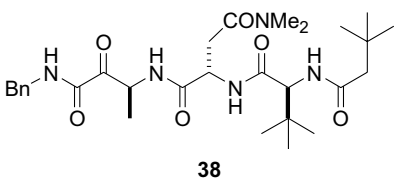
This strategy was employed by Semple and co-workers [29] in the synthesis of the N(10)–C(17) fragment of cyclotheonamides, a family of 19-membered cyclic pentapeptides isolated from the sponge *Theonella swinhoei*, which are serine protease inhibitors.



Scheme 2.14. Synthesis of tetrapeptide **36** *via* Passerini-3CR.

Oxidation of the α-hydroxy-β-acylamino amides obtained by this strategy constitutes an easy access to α-ketoamides. The Banfi group [28] reported the synthesis of α-ketoamides such as **37** and **38** starting from isocyanides and acid components

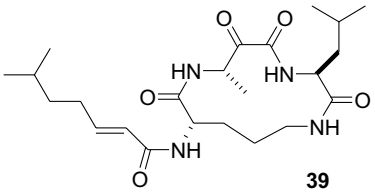




Scheme 2.15. α-Ketoamides obtained by oxidation of α-hydroxy-β-acylamino amides.

arising from α-amino acids (Scheme 2.15). This methodology was extended to the solid phase by employing a resin-immobilized isocyanide and Fmoc-protected α-aminoaldehydes [30].

A remarkable example of this approach is the synthesis of the prolyl endopeptidase inhibitor eurystatin A **39** reported by Semple et al. (Scheme 2.16) [31]. Another application of this methodology to the synthesis of a family of potent Factor Xa inhibitors was recently reported by the same group [25b].

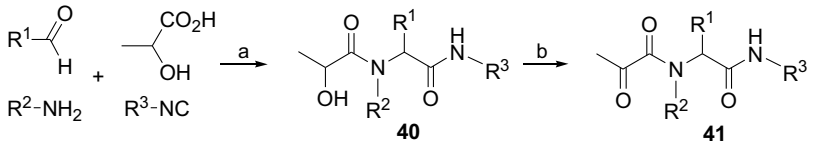


Scheme 2.16. Euristatin A.

2.2.3
Ugi-4CR + Oxidation

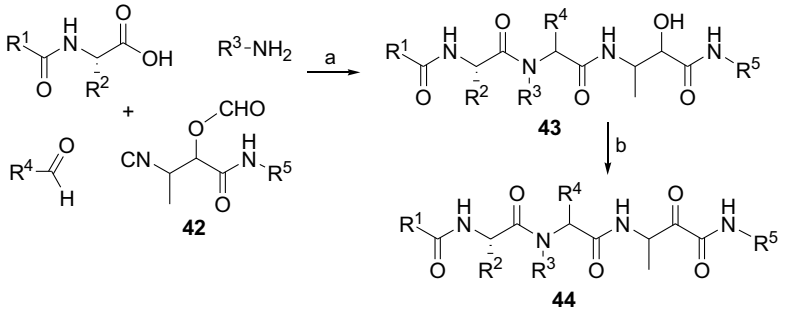
Peptide mimetics containing the α-ketoamide moiety are very important because they act as cysteine protease inhibitors. In fact, the α-ketoamide residue forms hemithioacetals with the –SH group of the cysteine residue of the enzyme [32]. Nakamura et al. [26b] reported the preparation of a 100-member combinatorial library of α-ketoamides by means of a two-step one-pot synthesis. The first step consisted of the Ugi-4CR between (+/−)lactic acid, amines, isocyanides, and aldehydes leading to the formation of the lactamides **40** which were oxidized to the corresponding pyruvamides **41**. This one-pot procedure was performed in THF since the PDC oxidation was incompatible with the presence of methanol. Five α-ketoamides showed an 80% average purity (Scheme 2.17).

Another approach to α-ketoamide peptide mimetics was employed by Xu et al. [33] for the preparation of a human cytomegalovirus protease inhibitor library. In this case the oxidizable –OH group, protected as formate, belonged to the starting isocyanides. Thus, the reaction between *N*-acylated α-amino acids, amines, aldehydes, and isocyanides **42** afforded the α-hydroxyamides **43** in modest yields. Cleavage of the *O*-formyl bond was accomplished during the reaction by employing two



a) THF, rt, 24 h; b) PDC, THF, 3 h, rt, chromatography, 23-77% overall

Scheme 2.17. Synthesis of α-ketoamides *via* U-4CR and oxidation.



a) MeOH/DCM, rt, 48 h, chromatography, 20-45%; b) Dess-Martin-Periodinane, TFA, DCM, 30 min, rt, then $Na_2S_2O_3$, $NaHCO_3$, water, chromatography, 68-90%

Scheme 2.18. Synthesis of peptide mimetics containing the α-ketoamide residue.

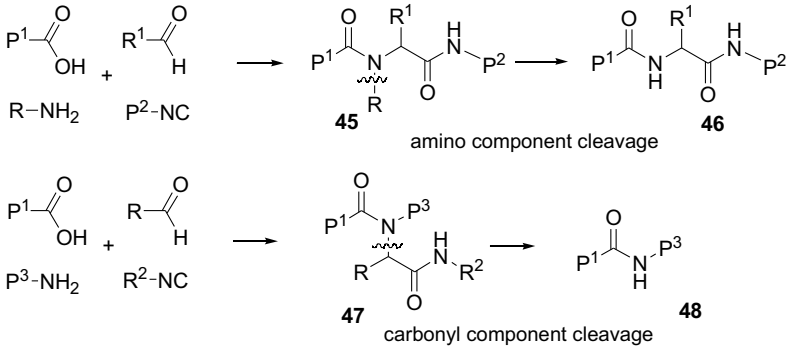
equivalents of the starting amine. Oxidation of **43** was performed with the Dess-Martin-Periodinane to give α-ketoamides **44** in good yields (Scheme 2.18).

2.2.4
Ugi-4CR + Hydrolysis

The sequence of Ugi-4CR + hydrolysis of the amino substituent has been employed in the stereoselective synthesis of chiral α-amino acid derivatives, by using a chiral amine component. Then the chiral template was covalently bound in close proximity to the newly synthesized chiral center. The amine residue of the product must be removable under mild conditions to avoid decomposition of the desired product. Chiral α-ferrocenylamines have been employed with some success [34], but the most useful auxiliaries were carbohydrate amines [35].

2.2.5
Ugi-4CR in Peptide Synthesis

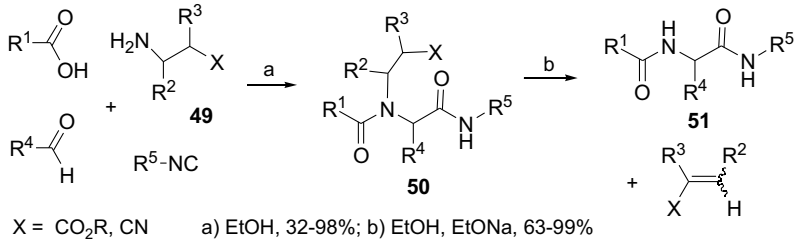
The Ugi reaction can be used in peptide synthesis following two different routes: (1) formation of an α-amino acid bridge and (2) promotion of peptide fragment coupling. Route (1) requires the use of a cleavable amine whereas route (2) requires the use of a cleavable aldehyde (Scheme 2.19).



P^1 = NH_2 protected amino acid or peptide, P^2-NC = isocyanide derived from CO_2H protected amino acid or peptide, P^3-NH_2 = CO_2H protected amino acid or peptide

Scheme 2.19. The use of Ugi-4CRs in peptide synthesis.

The cleavage of the amino component was first proposed by Ugi and Offermann [36] who used stabilized enamines (such as enaminoesters, -ketones, and -nitriles) as cleavable amino components, but the results were unsatisfactory. A great improvement was accomplished by using *β*-aminoesters or -nitriles **49** as the amino input. The resulting Ugi adducts **50**, generally obtained in high yields, were easily cleaved with sodium ethoxide in ethanol to give the final products **51** in high yields. Thus, *β*-aminoesters or -nitriles can be considered as synthetic equivalents of ammonia. Moderate diastereoselectivity was observed by employing diethyl L-aspartate as the amino component (Scheme 2.20).



X = CO_2R, CN a) EtOH, 32-98%; b) EtOH, EtONa, 63-99%

Scheme 2.20. Ugi-4CR with cleavable amino components.

Waki and Meienhofer [37] performed a detailed study of the use of Ugi-4CRs in peptide syntheses. 2-Aminomethylfluorene has been successfully employed as a cleavable amine [38]. Cleavage was achieved in excellent yields with DBU in pyridine. Much more recently, Sheehan et al. reported the use of 2,4-dimethoxybenzylamine as a cleavable amine input in Ugi-4CRs used to synthesize D-phenyl glycinamide inhibitors of the coagulation cascade serine protease factor Xa. Removal of the protecting group was performed with trifluoroacetic acid [39]. Cleavage of

the carbonyl component was achieved by utilizing some aldehydes under various cleavage conditions. Adducts obtained from 2-nitrobenzaldehyde were cleaved by photolysis [37]. Pyridine-4-carboxaldehyde was found to be suitable for cleavage by means of electroreduction [37], photolysis [40], and *via* autooxidation in the presence of Ni(II) phthalocyanine [41]. Good results in peptide fragment coupling were obtained by employing 9-formylfluorene as the carbonyl input in the Ugi-4CR [42] followed by cleavage with methanolic ammonia. The Ugi-4CR reaction of *N*-*tert*-butylglyoxylicamide, *tert*-butyl isocyanide and both *N*-protected and *O*-protected aminoacids, followed by oxidation with copper chloride–NEt_3–air, has been used for effective peptide segment coupling [43].

2.3 I-MCR Post-condensation Reactions in the Synthesis of Heterocycles

Among the I-MCR post-condensation transformations, those leading to the formation of heterocyclic cores are very important since they permit the preparation, often in a very simple manner, of heterocyclic compounds with substitution patterns that are not easily obtainable by other synthetic routes [44]. Furthermore, these transformations permit ready access to constrained peptides and peptide mimetics, which are of great interest in drug discovery programs [4]. From this point of view post-condensation transformations (PCTs) are more versatile than the bifunctional approaches (BIFAs) [45]. In this section, the I-MCR/PCTs leading to heterocyclic systems are classified according to the ring size and the number of heteroatoms in the cycle.

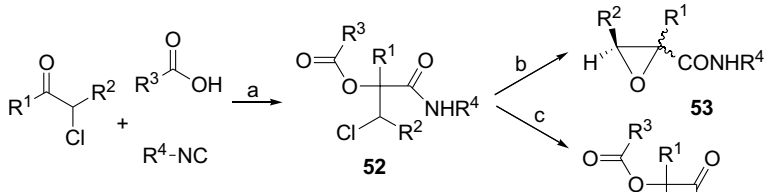
2.3.1 Three-, Four-, and Five-membered Rings and their Benzo-fused Derivatives

2.3.1.1 Oxiranes and β-Lactams by Passerini-3CR + O- or N-alkylation

The Passerini reaction between α-chloroketones, isocyanides, and carboxylic acids afforded α-acyloxy-β-chlorocarboxamides **52**, which, on treatment with an excess of powdered KOH in tetrahydrofuran, underwent *O*-deacylation followed by a Darzens-type *O*-alkylation to give the functionalized oxiranes **53**. When carboxamides **52** were treated with an excess of CsF, with or without a phase-transfer catalyst, a different ring closure took place to afford 3-acyloxy-2-azetidinones **54** in high yields (Scheme 2.21) [46].

2.3.1.2 β-Lactams and Succinimides by Ugi-4CR + C-Alkylation

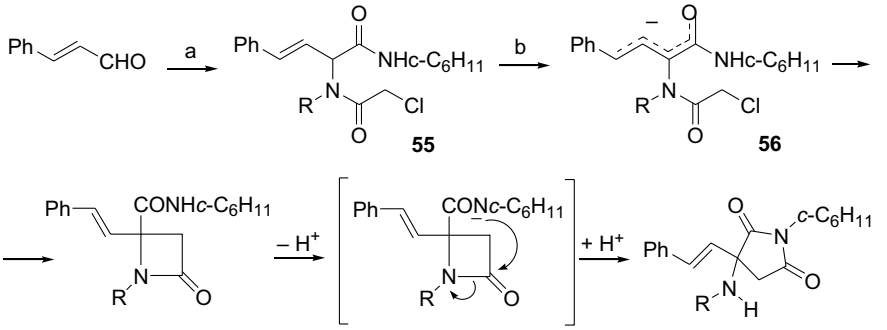
The Ugi-4CR between (*E*)-cinnamaldehyde, amines, cyclohexyl isocyanide, and chloroacetic acid afforded *N*-substituted 2-amino-4-phenylbutenoic amides **55** which were cyclized in basic medium to N-substituted 2-(phenylethenyl)-4-oxoazetidine-2-carboxamides **57** *via* the highly delocalized intermediate anion **56** [47]. When R was an electron-poor aryl group, the β-lactam ring underwent a rearrangement to give succinimides **58** (Scheme 2.22) [48].



R^1 = Me; R^2 = H, Me; R^3 = Me, Ph; R^4 = *t*-Bu, *i*-Pr

a) 0 °C to rt, stirring, 15 h, 53-98%
b) KOH, THF, rt, stirring, 40 - 90 min, 91-98%
c) CsF, TEBA (cat.), THF, reflux, stirring, 1-12 h, 81-98%

Scheme 2.21. Oxiranes and *β*-lactams from *α*-acyloxy-*β*-chlorocarboxamides.



R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$ **57** 63-83%

R = 4-$NO_2C_6H_4$, 4-$CH_3COC_6H_4$ **58** 49-77%

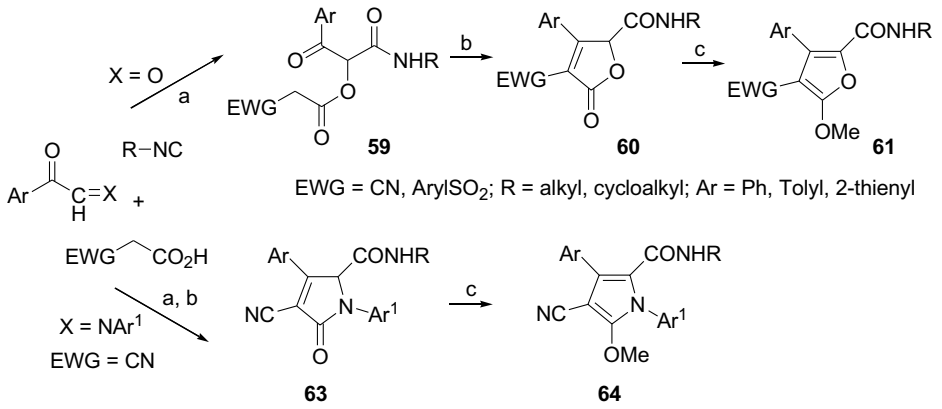
a) $ClCH_2CO_2H$, *c*-$C_6H_{11}NC$, RNH_2, MeOH, rt, 24 h, 80-89%; b) KOH, MeOH, rt, 30 min

Scheme 2.22. Synthesis of *β*-lactams and succinimides *via* an Ugi reaction.

2.3.1.3 Furans, Pyrroles, and Indoles by Passerini-3CR or Ugi-4CR and Knoevenagel Condensation

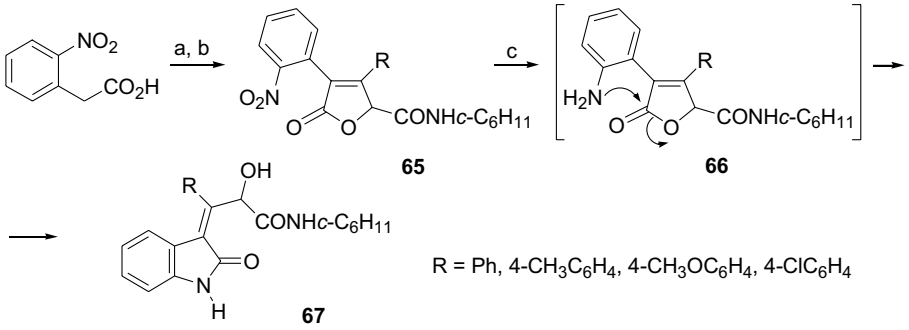
A two-step facile synthesis of functionalized furan derivatives was achieved by means of the tandem Passerini reaction/Knoevenagel condensation [49]. The reaction between arylglyoxals, isocyanides, and cyanoacetic acid afforded *N*-substituted 3-aryl-2-cyanoacetoxy-3-oxopropionamides **59**, which underwent intramolecular Knoevenagel condensation to give butenolides **60** that were treated with diazomethane to give the 5-methoxy derivatives **61**. Analogously, furan derivatives bearing an arylsulfonyl group in the 4-position were obtained [50]. The same procedure gave pyrroles **64** by performing the first step in the conditions of an Ugi-4CR [51] (Scheme 2.23).

Tandem Passerini/Knoevenagel reactions were also performed by employing 2-nitrophenylacetic acid as the acid component to give the butenolides **65** that were reduced to the intermediate amines **66**, which immediately cyclized to give indoles **67** in very high yields *via* a ring-switching process (Scheme 2.24) [52].



a) toluene/Et_2O, rt, 1-6 d, 65-82%; b) NEt_3, MeOH or EtOH, rt, then HCl, 40-85%;
c) CH_2N_2, $CHCl_3/Et_2O$, rt, 6-10 h, 73-92%.

Scheme 2.23. Furans and pyrroles *via* Passerini or Ugi/Knoevenagel reactions.



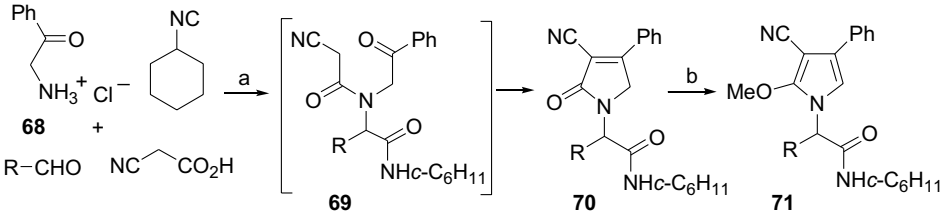
a) RCOCHO, c-C_6H_{11}NC, Et_2O, rt, 24 h, 77-90%; b) piperidine, EtOH, rt to 40 °C, then aq HCl, 69-76%;
c) Fe, AcOH, 35-40 °C to 60-65 °C, 15 min, 82-91%.

Scheme 2.24. Synthesis of indoles *via* Passerini/Knoevenagel/reduction reactions.

Another pyrrole synthesis [53] was based on the Ugi-4CR/Knoevenagel condensation between aldehydes, cyclohexyl isocyanide, cyanoacetic acid, and phenacylamine **68** as the carbonyl input. Also in this case the Ugi products **69** spontaneously cyclized to the pyrroles **70** which were methylated with diazomethane to give the 2-methoxy derivatives **71** (Scheme 2.25).

2.3.1.4 **Butenolides by Passerini-3CR and the Horner–Emmons–Wadsworth Reaction**

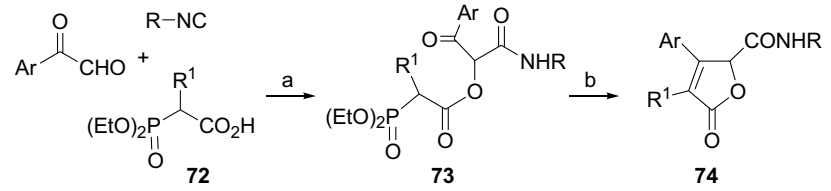
Another synthesis of the butenolide core was reported by the Dömling group [54]. The reaction between arylglyoxals, isocyanides, and α-diethylphosphonoalkanoic



R = 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeC$_6$H$_4$, 3,4-OCH$_2$OC$_6$H$_3$

a) MeOH/H$_2$O, K$_2$CO$_3$, rt, 2 d, 38-48%; b) CH$_2$N$_2$, CHCl$_3$/Et$_2$O, 69-82%.

Scheme 2.25. Synthesis of pyrroles by tandem Ugi-4CR/Knoevenagel condensation.



Ar = Ph, 2-thienyl, 4-HOC$_6$H$_4$, 2-naphthyl, 4-PhC$_6$H$_4$; R^1 = H, Ph, 4-FC$_6$H$_4$, 3-MeOC$_6$H$_4$

R = *n*-Bu, *t*-Bu, allyl, cyclohexyl, *t*-BuO$_2$C(Me)CH, *t*-BuO$_2$C(CH$_2$)$_2$, MeO$_2$C(*i*-Bu)CH

a) DEE or THF; b) LiBr, NEt$_3$, THF, 13-87%.

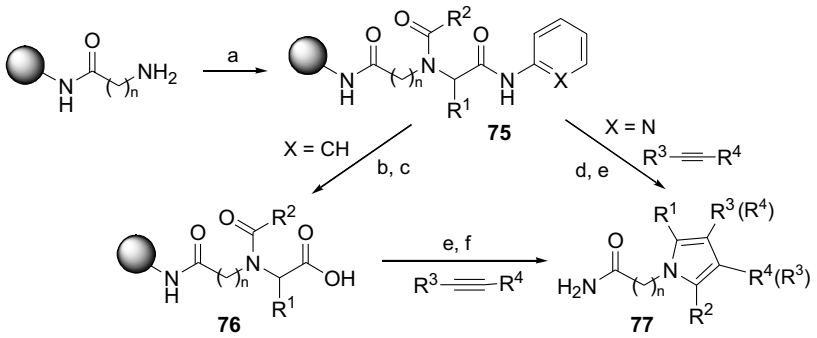
Scheme 2.26. Butenolides *via* Passerini/Horner–Emmons–Wadsworth reactions.

acids **72** afforded the expected Passerini adducts **73**, which were cyclized to the desired butenolides **74** according to the Horner–Emmons–Wadsworth procedure (Scheme 2.26).

2.3.1.5 Pyrroles and γ-Lactams by Ugi-4CR and Hydrolysis

The formation of münchnones upon acid treatment of Ugi products arising from 1-isocyano-1-cyclohexene **1** was demonstrated by Keating and Armstrong [6b] (see Scheme 2.3). The 1,3-cycloaddition of münchnones onto dipolarophiles, followed by spontaneous elimination of carbon dioxide, afforded pyrroles. The method has been extended to solid-phase synthesis [55]. Mjalli et al. [56] synthesized *N*-acyl-*N*-alkyl-α-amino amides by Ugi-4CR and cleaved them into the corresponding acids upon treatment with *t*-Boc$_2$O-DMAP followed by hydrolysis with LiOH, as an extension of a method by Flynn et al. [57]. This procedure has been adapted to solid-phase synthesis. Cyclodehydration of the α-acylamino acids **76** afforded the resin-bound münchnones, which reacted *in situ* with acetylene dipolarophiles to give pyrroles **77**, after resin cleavage. The resin-bound products **75**, arising from 2-isocyanopyridine, were directly transformed into the münchnones upon treatment with Ac$_2$O (Scheme 2.27).

Hulme and co-workers [8b] reported an interesting route to γ-lactams based on the UDC (Ugi/de-Boc/Cyclization) strategy. The reaction between *N*-Boc β-

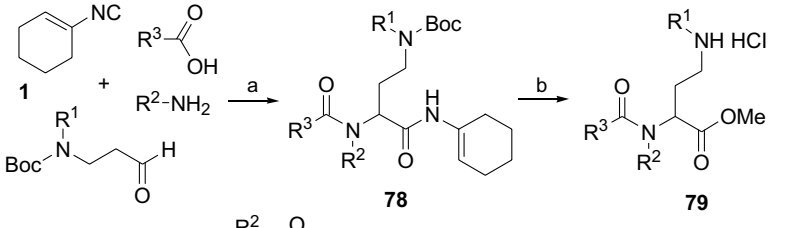


R^1 = Et, *n*-Pr, *n*-Bu; R^2 = Ph, Aryl, $PhCH_2$; R^3 = H, Et, CO_2Me; R^4 = CO_2H, CO_2Me

a) R^1CHO (1 eq), PhNC or 2-PyNC (1 eq), R^2CO_2H (1 eq), $CHCl_3$/Pyridine/MeOH, 65°C, 2d; b) TEA, DMAP, Boc_2O, DCM, 23 °C, 18 h; c) 1N LiOH (H_2O/THF 5%), 4:1, 23 °C, 6 h; d) acetylene, Ac_2O, 65-100 °C, 1-2 d; e) acetylene, isobutyl chloroformate, TEA, toluene, 100°C, 1-2 d; f) 20% TFA/DCM, 23 °C, 20 min, toluene azeotrope.

Scheme 2.27. Pyrrole derivatives from phenyl isocyanide and 2-isocyanopyridine.

amino aldehydes, amines, carboxylic acids, and **1** resulted in the formation of the Ugi products **78** which, upon exposure to methanolic hydrogen chloride, underwent N-deprotection and cyclohexenamide cleavage to give esters **79**. Treatment of **79** with a proton scavenger promoted the cyclization to γ-lactams **80** (Scheme 2.28). This procedure was adapted to solid-phase synthesis by employing the safety-catch linker and the immobilized cyclohexenyl isocyanide. The same procedure gave bicyclic γ-lactams in which the γ-lactam ring was fused with a piperazinone ring [8b] by employing levulinic acid as a bifunctional starting material.



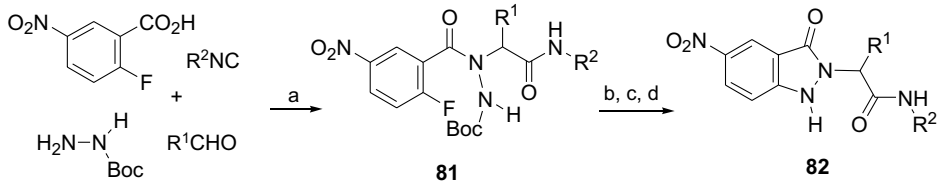
R^1 = H, $PhCH_2$; R^2 = $PhCH_2$, $Ph(CH_2)_3$
R^3 = *c*-$C_6H_{11}CH_2$; 4-PhC_6H_4, Ph_2CH

a) MeOH, rt, 24 h;
b) 10% AcCl in MeOH, rt, 24 h;
c) MP-carbonate (5 equiv), DCE.

Scheme 2.28. Synthesis of γ-lactams by the UDC strategy.

2.3.1.6 **Indazolinones by Ugi-4CR with N-deprotection and Aromatic Nucleophilic Substitution**

An interesting route to indazolinones was reported by Tempest and co-workers [58]. The reaction between 2-fluoro-5-nitrobenzoic acid, aldehydes, isocyanides,



R^1 = $Ph(CH_2)_2$, Ph, *i*-Bu; R^2 = *t*-Bu; *i*-Pr, *c*-C_6H_{11}

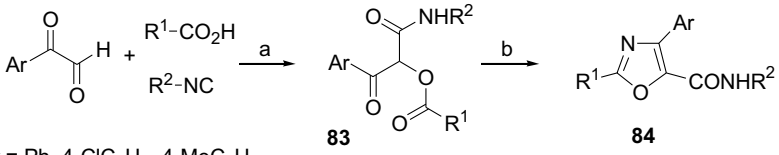
a) 2 equiv. aldehyde, MeOH, rt, 48 h; b) PS-tosylhydrazine (3 equiv), PS-diisopropylethylamine (3 equiv), THF/DCM, 24 h; c) PS-morpholine (3 equiv.), DMF, 36 h.

Scheme 2.29. Preparation of indazolinones *via* Ugi-4CRs.

and *N*-Boc-hydrazine afforded the expected *N*-Boc-protected Ugi-4CR products **81**. Deprotection of **81** with TFA in DCM followed by proton scavenging with resin-immobilized morpholine afforded the indazolinones **82** (Scheme 2.29).

2.3.1.7 Oxazole Derivatives and Imidazoles by Passerini-3CR or Ugi-4CR and Davidson Cyclization

Davidson's synthesis consists of the cyclization of α-acyloxyketones with ammonia or ammonium acetate to give 2,4,5-trisubstituted oxazoles. The Passerini reaction between arylglyoxals, carboxylic acids, and isocyanides afforded *N*-substituted 2-acyloxy-3-aryl-3-oxopropionamides **83** in high yields. Upon heating with an excess of ammonium acetate in acetic acid, compounds **83** were cyclized to *N*,2,4-trisubstituted oxazole-5-carboxamides **84** in fair yields [59]. A large number of α-acyloxy-β-ketoamides can be prepared by changing the reaction components, so the method provides straightforward access to a variety of oxazole-5-carboxamides (Scheme 2.30).



Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4

R^1 = Ph, 2-ClC_6H_4, 2-HOC_6H_4, $PhSCH_2$, 4-$MeC_6H_4SCH_2$, 4-$ClC_6H_4SCH_2$, Me, $ArylCH_2$

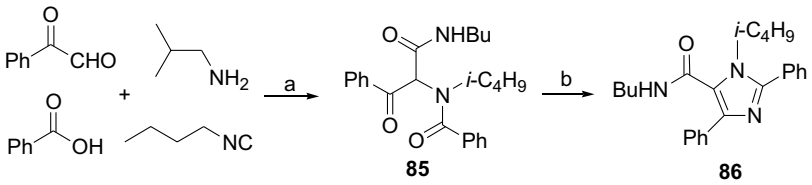
R^2 = *c*-C_6H_{11}, *c*-C_7H_{13}

a) Et_2O, rt, 6 h, 68-86%; b) NH_4OAc (19 equiv.), 45 min reflux or 100 °C, 3 h, 37-57%

Scheme 2.30. Oxazole-5-carboxamides *via* tandem Passerini-3CR/Davidson cycization.

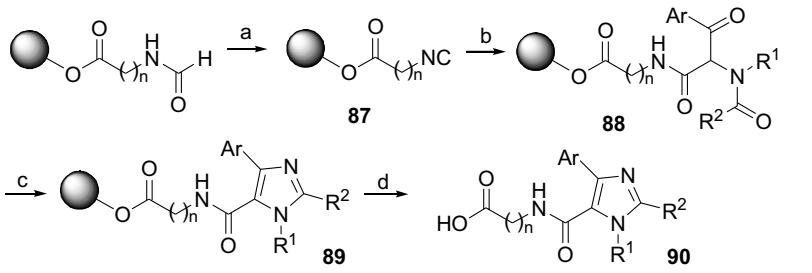
Analogously, the reaction between phenylglyoxal, isobutylamine, *n*-butyl isocyanide, and benzoic acid afforded 3-oxo-3-phenylpropanoic amide **85** which was cyclized to diphenylimidazol-5-carboxamide **86** in very high yield (Scheme 2.31) [60].

The procedure was extended to solid-phase synthesis by employing resin-bound isocyanides. Wang resin was preferred to Rink resin because of its stability. The reaction of the resin-bound isocyanides **87** with supporting Ugi reagents afforded the



a) MeOH, 23 °C, 2 d, 50%; b) NH_4OAc, AcOH, 100 °C, 16 h, 95%

Scheme 2.31. Synthesis of imidazole *via* tandem Ugi-4CR/Davidson reactions.



R^1 = *i*-C_4H_9, Ph, $PhCH_2$, 4-$MeOC_6H_4$; R^2 = Ph, *n*-C_4H_9, $PhCH_2$, 4-FC_6H_4
n = 2, 10; Ar = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4

a) PPh_3, CCl_4, NEt_3, DCM, >99%; b) ArCOCHO, R^1NH_2, R^2CO_2H, $CHCl_3$, MeOH, pyridine, 1:1:1, 65 °C, 3 d; c) NH_4OAc (60 equiv), AcOH, 100 °C, 20 h; d) 10% TFA, DCM, 23 °C, 20 min, 16-56%

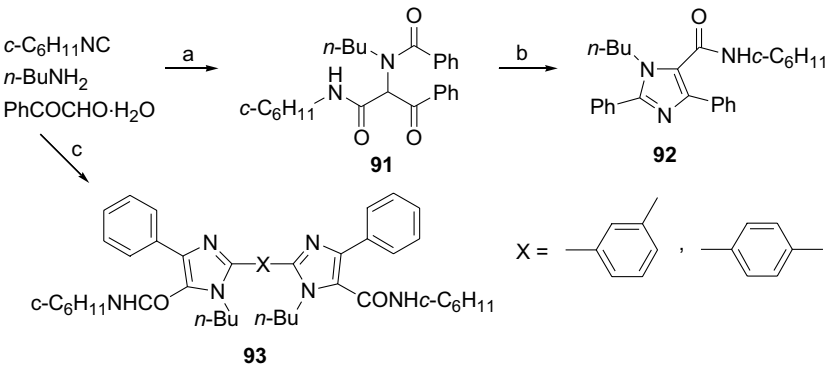
Scheme 2.32. Solid-phase synthesis of tetrasubstituted imidazoles.

resin-bound α-(*N*-acyl-*N*-alkylamino)-β-oxoamides **88** which were cyclized to resin imidazoles **89**. Final cleavage of **89** with 10% TFA in DCM gave the imidazoles **90** (Scheme 2.32).

An analogous synthesis was reported by Sung et al. [61]. Benzoic acid or bifunctional isophthalic or terephthalic acids were employed as the acid components in the Ugi condensation. The final products **93** possessed alternating benzene/imidazole systems and were potentially interesting for their optoelectronic properties (Scheme 2.33).

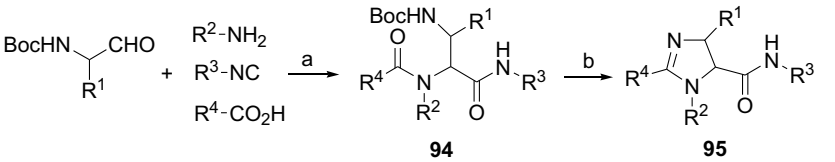
2.3.1.8 2-Imidazolines, Imidazolidin-2-ones and Benzimidazoles by Ugi-4CR with N-Deprotection and Cyclization

The Hulme group reported an efficient three-step, one-pot solution-phase synthesis of 2-imidazolines employing the UDC strategy [62]. The reaction between *N*-Boc-protected α-aminoaldehydes, amines, acids, and isocyanides afforded the *N*-Boc-protected α-acylamino amides **94** which, upon heating in acidic medium, underwent N-deprotection and cyclization to 2-imidazolines **95** (Scheme 2.34). This procedure was adapted to combinatorial synthesis in a rack of 96 reaction vials.



a) $PhCO_2H$, rt, filtration; b) $(NH_4)_2CO_3$ (100 equiv), AcOH, reflux, N_2, 2h, 55% overall;
c) (1,3) and (1,4) $C_6H_4(CO_2H)_2$, condition a) then b) 40% (1,3), 43% (1,4).

Scheme 2.33. Alternating benzene/imidazole systems *via* Ugi-4CR and Davidson cyclization.



R^1 = *i*-Pr, $ArCH_2$; R^2 = $PhCH_2$, $Ph(CH_2)_3$; R^3 = *c*-C_6H_{11}, $PhCH_2$; R^4 = $MeSO_2CH_2$, Ph_2CH
a) MeOH, rt, evaporation, 65 °C; b) 10%TFA/ DCE, rt, evaporation, 65 °C

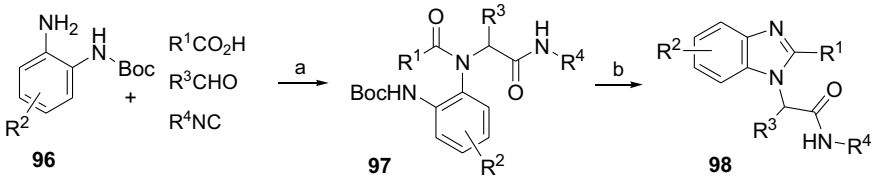
Scheme 2.34. Synthesis of 2-imidazolines by the UDC strategy.

An extension of the above method for the preparation of cyclic ureas (imidazolidin-2-ones) was developed by the same group [63], by employing carbon dioxide/methanol in place of a carboxylic acid, and the UDC strategy. Additionally, treatment of the Ugi-5CR products with base afforded hydantoins in good yield.

Tempest et al. [64] reported an interesting two-step solution-phase benzimidazole synthesis based on the UDC strategy. The key feature of this route was the use of *N*-Boc-protected 1,2-phenylenediamines **96**, which gave the *N*-Boc-protected adducts **97** in excellent yields. N-Deprotection with TFA led to formation of the internal nucleophile, which attacked the nearest amide carbonyl group to give benzi imidazole derivatives **98** in good yields (Scheme 2.35). A different ring-closure reaction took place when a sterically hindered acid was employed in combination with a non-hindered isocyanide, leading to dihydroquinoxalinones.

2.3.1.9 Spiroimidazolones and Spirothioimidohydantoins by Ugi-4CR and Further Transformations

A limitation of isocyanide-based multicomponent reactions lies in the small number of available isocyanides. The problem can be solved by transformation of a single isocyanide into many other isocyanides, as reported by Bossio et al. [65].

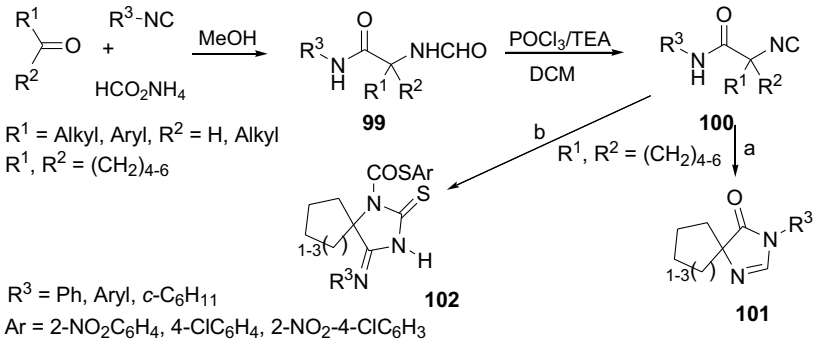


R^1 = Ph, *n*-C_5H_9, Ph_2CH, Et, 3-$HOC_6H_4CH_2$, PhCH(OH); R^2 = H, 3,4-Me_2
R^3 = *n*-Pr, *c*-C_6H_{11}, $Ph(CH_2)_2$, Ph, Aryl; R^4 = *n*-Bu, *n*-Pr, *c*-C_6H_{11}, $PhCH_2$, 2,6-xylyl

a) MeOH, rt, 48 h; b) PS-tosylhydrazine (3 equiv), PS-*N*-methylmorpholine (3 equiv), THF/DCM 1:1, 24 h, then TFA/DCM, 12 h

Scheme 2.35. Benzimidazoles from *N*-Boc-1,2-phenylenediamines *via* the UDC strategy.

The Ugi-4CR between isocyanides, aldehydes or ketones, and ammonium formate led to the formation of *N*-substituted 2-formylaminocarboxamides **99** which were subsequently dehydrated with $POCl_3$/TEA to the corresponding *N*-substituted 2-isocyanocarboxamides **100** in good yields (Scheme 2.36). Isocyanocarboxamides **100** were the starting materials for the preparation of spiroimidazolones **101** [66]. The same isocyanoamides **100** gave an interesting ring-closure reaction with arenesulfonyl thiocyanates to afford spirothioimidohydantoins **102** (Scheme 2.36) [67].



R^1 = Alkyl, Aryl, R^2 = H, Alkyl
R^1, R^2 = $(CH_2)_{4-6}$

R^3 = Ph, Aryl, *c*-C_6H_{11}
Ar = 2-$NO_2C_6H_4$, 4-ClC_6H_4, 2-NO_2-4-ClC_6H_3

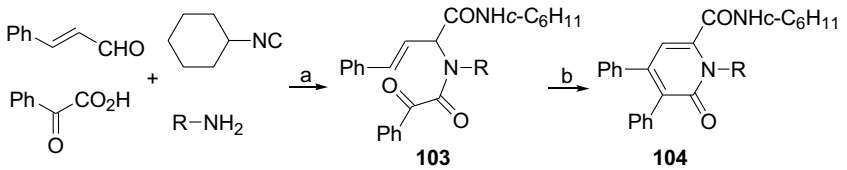
a) BuLi, THF, -60 °C to 0 °C, then aq. NH_4Cl or dil. AcOH, 0 °C, 65-93%
b) ArSSCN, DCM, -30 °C to rt, 65-84%

Scheme 2.36. Spiroimidazolones and spirothioimidohydantoins from Ugi-4CR adducts.

2.3.2 Six-membered Rings and Their Benzo-fused Systems

2.3.2.1 Pyridine Derivatives by Ugi-4CR and Aldol-type Condensation

The Ugi-4CR between cinnamaldehyde, benzoylformic acid, amines, and cyclohexyl isocyanide afforded the condensation products **103**, which, under basic conditions, cyclized to the 1,6-dihydro-6-oxopyridine-2-carboxamides **104** in high yields (Scheme 2.37) [68].



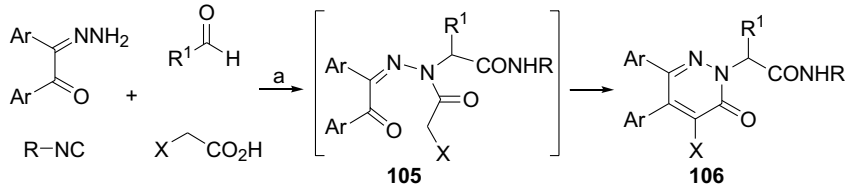
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3,4-$Cl_2C_6H_4$, 4-$ClC_6H_4CH_2$

a) MeOH, rt, 24 h, 75-86%; b) KOH, MeOH, rt, 1-2 h, 80-93%

Scheme 2.37. 6-Oxopyridine-2-carboxamides *via* Ugi-4CR/aldol condensation.

2.3.2.2 Pyridazine Derivatives by Ugi-4CR and Knoevenagel Condensation

The Ugi four-component condensation allowed straightforward access to pyridazine derivatives when benzil monohydrazones and active methylene acids were employed as the amino and the acid component, respectively. The Ugi products **105** spontaneously cyclized to 2,3-dihydro-3-oxopyridazines **106** in fair to good yields (Scheme 2.38) [69].



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; X = CN, 4-$MeC_6H_4SO_2$, CO_2Et; R = *c*-C_6H_{11}, 4-MeC_6H_4
R^1 =Me, Et, $PhCH_2$

a) MeOH, rt, 24 h, 41-74%; b) MeOH, rt, 24 h, 60-62%

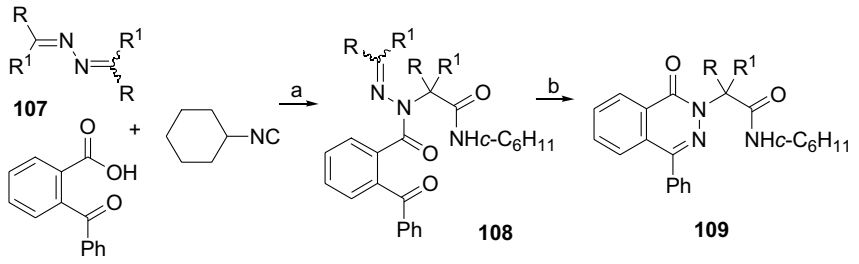
Scheme 2.38. 2,3-Dihydro-3-oxopyridazines *via* Ugi-4CR/Knoevenagel condensation.

2.3.2.3 Phthalazine Derivatives by Ugi-4CR with N-Deprotection and Cyclization

The reaction of azines **107**, prepared *in situ* from aldehydes or ketones and hydrazine, afforded the Ugi adducts **108**. The acid treatment of **108** resulted in the hydrolytic cleavage of the imino group with formation of the hydrazides, which immediately cyclized to phthalazinone amides **109** (Scheme 2.39) [70].

2.3.2.4 Piperazines and Pyrazin-2-ones by Ugi-4CR and Cyclization

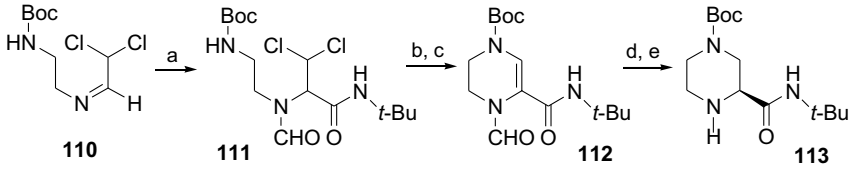
Rossen et al. [71a] has reported a synthesis of piperazine **113**, a key intermediate in the synthesis of the HIV protease inhibitor Crixivan®. The reaction between a preformed imine **110**, *t*-butyl isocyanide, and formic acid afforded the Ugi product **111**, which was dehydrohalogenated with triethylamine and cyclized with KO^tBu to the tetrahydropyrazine **112**. Catalytic hydrogenation in the presence of Rh-BINAP (97% ee) and deformylation with aqueous hydrazine gave the target piperazine **113** (Scheme 2.40).



R = Me, $PhCH_2$; R^1 = H; R-R^1 = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2N(COMe)(CH_2)_2$

a) MeOH or EtOH, rt, 8-48 h; b) aq. HCl, EtOH, rt or reflux, 5 min - 15 h; 59-81% overall.

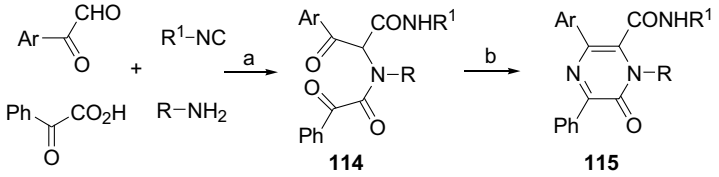
Scheme 2.39. Synthesis of 1-(2*H*)-phthalazinone-2-alkanoic acid amides.



a) *t*-BuNC, HCO_2H, MeOH, 0 ° to 23 °C, 2 d; b) TEA, 3 h, 23 °C, 100%, 2 steps;
c) KO*t*-Bu, *t*-BuOH/THF, 3 h, 23 °C, extractive work-up and chromatography, 60%;
d) MeOH, H_2, 100 atm, [(*R*)-BINAP(COD)Rh] OTf, 7 mol %, 40 °C, 24 h, 100%;
e) 35% aq hydrazine, 100 °C, 9 h, 91%

Scheme 2.40. Synthesis of the piperidine moiety of Crixivan® *via* Ugi-4CR.

The Ugi-4CR provides straightforward access to precursors of the pyrazine ring that are suitable for a Davidson cyclization [72]. The reaction between arylglyoxals, amines, isocyanides, and benzoylformic acid in ether afforded adducts **114**, which cyclized on treatment with an excess of ammonium acetate in acetic acid to give pyrazine carboxamides **115** (Scheme 2.41).

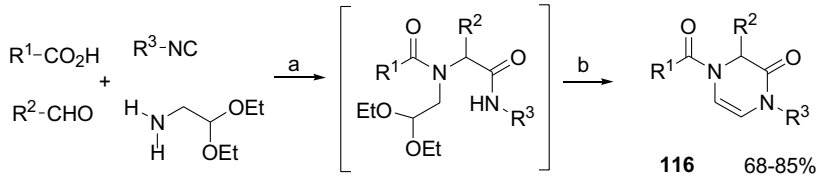


Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4
R = 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-ClC_6H_4, 4-$ClC_6H_4CH_2$, *i*-Bu
R^1 = *c*-C_6H_{11}, *n*-C_6H_{13}, 4-MeC_6H_4

a) Et_2O, rt, 3 d, 42-77%; b) NH_4AcO (25 equiv.), AcOH, 3 h reflux, 67-85%.

Scheme 2.41. 1*H*-Pyrazin-2-ones *via* Ugi-4CR/Davidson cyclization.

The Cheng group at Chugai Pharma reported a very efficient synthesis of Δ^5-2-oxopiperazines **116** as constrained dipeptidomimetics either in solution or in the solid phase by an Ugi-4CR reaction starting from aminoacetaldeyde diethyl acetal, followed by carbonyl deprotection and cyclization to give **116** (Scheme 2.42) [73].



R^1 = Ph, *n*-Bu, 4-$MeOC_6H_4$; R^2 = *n*-Pr, *i*-Pr, Ph; R^3 = CH_2CO_2Me, 1,1,3,3-tetramethybutyl
a) chloroform/methanol 1:1, rt, 48 h; b) TFA 50% in DCM, rt, 4 h

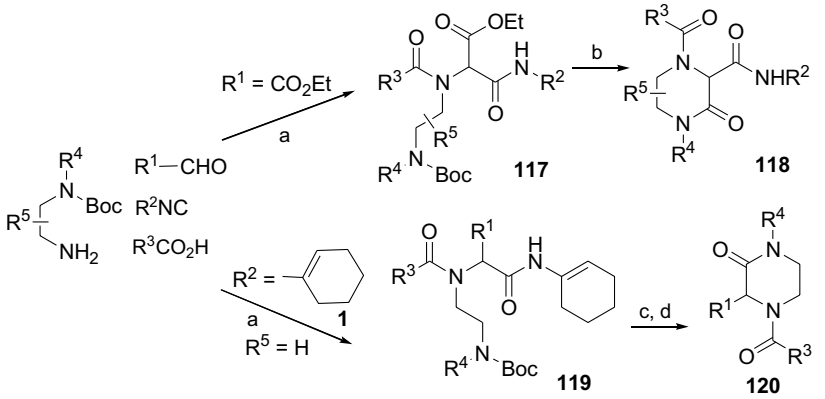
Scheme 2.42. One-pot synthesis of Δ^5-2-oxopiperazines.

2.3.2.5 Ketopiperazines, 2,5-Diketopiperazines and Quinoxalines by Ugi-4CR with N-Deprotection and Intramolecular Amide Bond Formation

The UDC strategy has been the most fruitful method for the synthesis of six- and seven-membered heterocycles. Two different approaches to ketopiperazines, both based on UDC methodology, have been reported by Hulme and co-workers [74]. The first method consisted of an Ugi-4CR between ethyl glyoxylate as bifunctional carbonyl input, *N*-Boc-protected ethylenediamines, isocyanides, and carboxylic acids. The crude Ugi products **117**, upon treatment with TFA, underwent *N*-Boc deprotection. Acid scavenging with MP carbonate completed the cyclization to the desired ketopiperazines **118**. The same method has been adapted to the synthesis of dihydroquinoxalinones, starting from *N*-Boc-protected 1,2-phenylenediamines (R^5 = 1,2-benzo in Scheme 2.43). The second approach combined the use of an N-protected reagent together with the convertible isocyanide **1**. The Ugi reaction between **1**, *N*-Boc-protected ethylenediamine, aldehydes, and carboxylic acids gave the Ugi products **119**, which were treated with methanolic hydrogen chloride, which removed the Boc protecting group and transformed the cyclohexenamide into an ester group. Finally, basic treatment promoted cyclization to the target ketopiperazines **120** (Scheme 2.43).

The Hulme group has reported two three-step, one-pot solution-phase procedures for the preparation of 2,5-diketopiperazines, based on the UDC strategy. The first method [74a] used ethyl glyoxylate as a bifunctional carbonyl input in an Ugi-4CR with amines, isocyanides, and *N*-Boc α-amino acids that afforded adducts **121**, which were N-deprotected and cyclized to the desired products **122** (Scheme 2.44). The second method [8c] used Armstrong's convertible isocyanide **1** in a reaction with *N*-Boc α-amino acids, aldehydes, and amines that afforded products **123**, which were deprotected and cyclized to diketopiperazines **124** (Scheme 2.44).

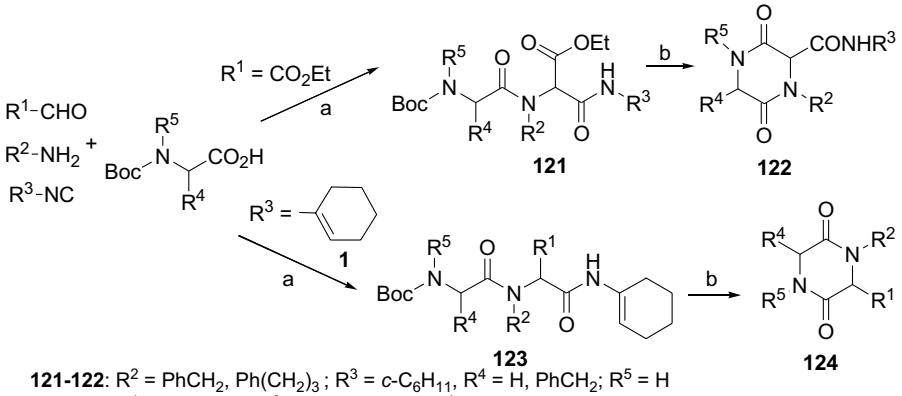
The UDC strategy is suitable for solid-phase synthesis and many methods that use this strategy have been reported. The Hulme group [75] described a



117-118: R^2 = *c*-C_6H_{11}, $PhCH_2$; R^3 = $PhCH_2$, $Ph(CH_2)_2$; R^4 = Me, $PhCH_2$; R^5 = H, 1,2-benzo
119-120: R^1 = Et, $Ph(CH_2)_2$; R^3 = 2-naphthyl, Ph_2CH_2; R^4 = H, Me, Ph, $PhCH_2$

a) MeOH, rt, 24 h; b) 10% TFA, DCE, 24 h, then evaporation, MP carbonate (3 equiv), DCE
c) HCl/MeOH; d) Et_2NH, DCE, rt, overnight

Scheme 2.43. Two different routes to ketopiperazines based on the UDC strategy.



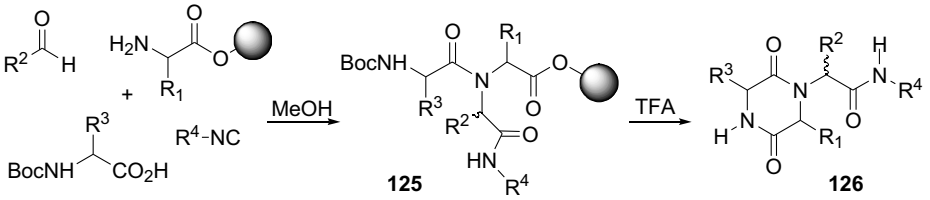
121-122: R^2 = $PhCH_2$, $Ph(CH_2)_3$; R^3 = *c*-C_6H_{11}, R^4 = H, $PhCH_2$; R^5 = H
123-124: R^1 = alkyl, aryl; R^2 = H, alkyl, aryl; R^4 = H, Me, $PhCH_2$

a) MeOH, rt, 24 h; b) 10% TFA in DCE, 24 h, evaporation at 65 °C, 3h

Scheme 2.44. Two different routes to diketopiperazines based on the UDC strategy.

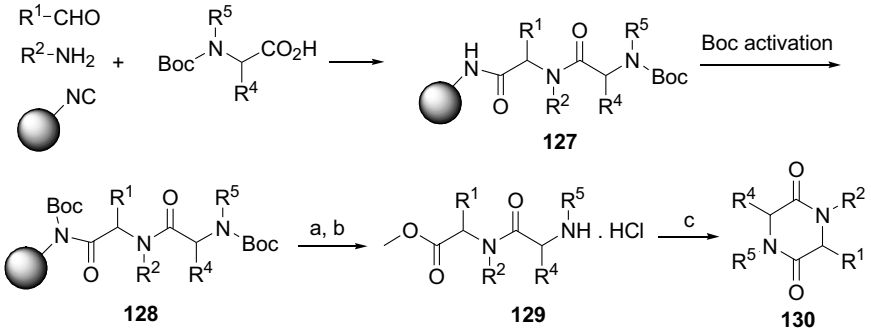
solid-phase synthesis of ketopiperazines by employing *N*-Boc α-aminoaldehydes as protected reagents and the UDC strategy. A straightforward approach to 2,5-diketopiperazines was reported by Szardenings et al. [76] from an Ugi-4CR between resin–bound α-amino acids as the amino components, aldehydes, isocyanides, and *N*-Boc protected α-amino acids. The *N*-Boc protected resin-bound products **125** were cleaved, deprotected, and cyclized to diketopiperazines **126** in a single step (Scheme 2.45). The method was extended to the synthesis of 2,5-diketomorpholines by employing α-hydroxy acids in place of *N*-Boc α-amino acids.

The Hulme group also developed an interesting resin-bound isocyanide, the ''safety-catch linker'' (Scheme 2.9), which was employed in the synthesis of sev-



R^1 = *i*-Pr, $PhCH_2$; R^2 = *c*-C_6H_{11}, $PhCH_2$, 4-$MeOCH_6H_4$; R^3 = *i*-Pr, $PhCH_2$; R^4 = *c*-C_6H_{11}, Me_3SiCH_2

Scheme 2.45. Synthesis of diketopiperazines with resin-bound α-amino acids.



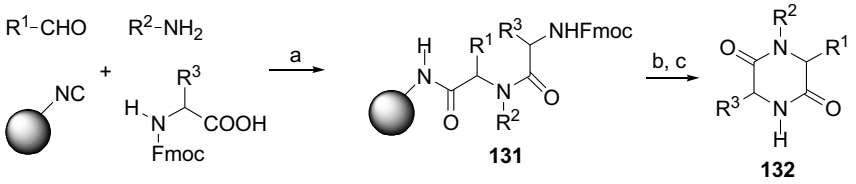
R^1 = $Ph(CH_2)_2$, 2-pyridyl, Me_3CCH_2; R^2 = *i*-Bu, $ArylCH_2$; R^4 = Me, $PhCH_2$; R^5 = H, Me

a) NaOMe, MeOH/THF 1:1; b) 10% AcCl/MeOH; c) Et_2NH, 5% in DCE or basic Dowex

Scheme 2.46. Use of the safety-catch linker in the synthesis of diketopiperazines.

eral products. The reaction of the resin-bound isocyanide with aldehydes, amines, and *N*-Boc α-amino acids gave the resin-bound products **127** which, upon Boc-activation to give **128**, underwent a facile cleavage to dipeptide derivatives **129**, which were cyclized to diketopiperazines **130** [19] (Scheme 2.46).

Chen and co-workers at Procter and Gamble developed a traceless synthesis of 2,5-diketopiperazines [18b] by employing the "universal Rink-isocyanide" resin. The Ugi-4CR between the resin, aldehydes, amines, and *N*-Fmoc-protected α-amino acids afforded the resin-bound dipeptide derivatives **131** which were N-deprotected on treatment with piperidine in DMF. Cyclization by heating with 10% AcOH in DCE smoothly provided the desired diketopiperazines **132** in good yields (Scheme 2.47).

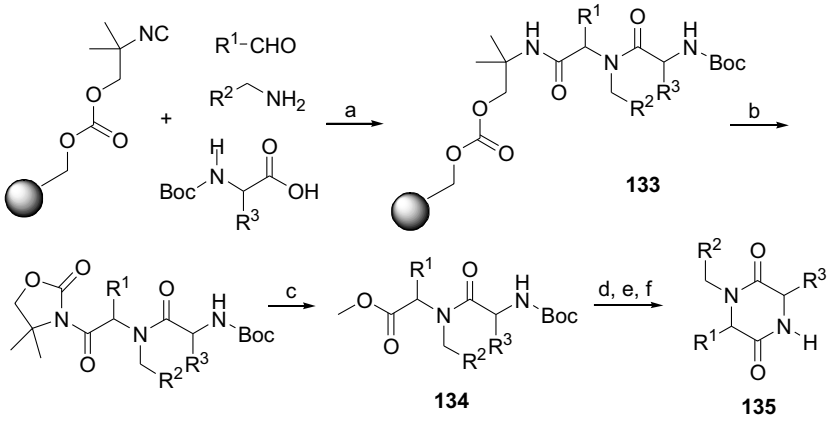


R^1 = *t*-Bu; R^2 = Bn, 3-$CH_3OC_6H_4CH_2$; R^3(aminoacid) = Gly, Aib, Pro.

a) MeOH/THF 1:1, 16 h; b) 20% piperidine/DMF; c) 10% AcOH/DCE 60 °C, 16 h.

Scheme 2.47. Solid-phase synthesis of diketopiperazines *via* Rink-isocyanide resin.

The Kennedy group at Array BioPharma described an elegant synthesis of 2,5-diketopiperazines employing the resin-bound carbonate convertible isocyanide (CCI resin; see Scheme 2.9) [20]. Ugi products **133** were converted into esters **134** and then deprotected and transformed into diketopiperazines **135** (Scheme 2.48).



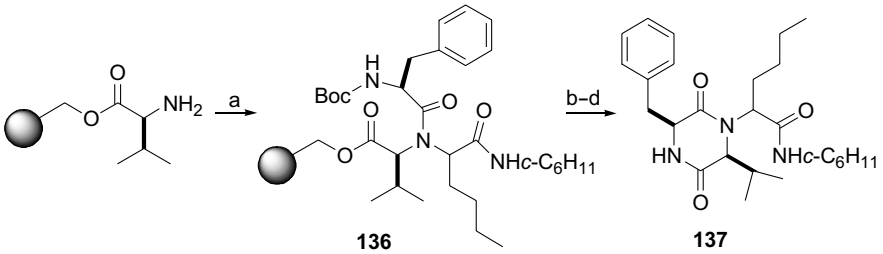
R^1 = 4-$MeOCH_6H_4$; R^2 = 4-morpholinomethyl, vinyl; R^3 = $PhCH_2$

a) Isocyanide (110 mmol), amine (10 equiv), aldehyde (10 equiv), Boc-D,L-amino acids, trifluoroethanol, 4 Å mol sieves, DCM, rt, 3 d; b) *t*-BuOK (2 equiv), THF, rt, 16 h; c) MeONa, MeOH, THF, rt, 48 h; d) hexafluoroisopropanol/TFA, 70:30, rt, 48 h; e) Silicycle TMA-Carbonate, THF, 6 h; f) Silicycle Isocyanate-3, THF, 16 h.

Scheme 2.48. Diketopiperazines from carbonate convertible isocyanide resin.

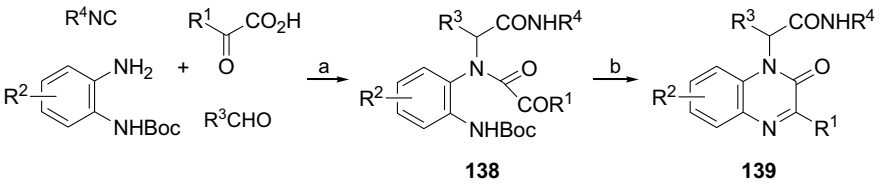
The Raillard group at Affymax developed a multigram synthesis of a 2,5-diketopiperazine and other heterocyclic systems by employing a high-load Merrifield resin transformed into polymer-supported valine, which was used as the amino component in an Ugi-4CR to gave the target diketopiperazine **137** after cleavage of **136** from the resin [77] (Scheme 2.49).

The synthesis of biologically significant quinoxalinones utilizing the UDC methodology was recently reported by Hulme et al. [78] who used the reaction between *N*-Boc-protected 1,2-phenylenediamines, glyoxylic acids, aldehydes, and iso-



a) *n*-BuCHO; *c*-$C_6H_{11}NC$, Boc-Phe; b) TFA/DCM 1:1; c) 1% AcOH/MeOH; d) Et_3N/MeCN.

Scheme 2.49. Solid-phase synthesis of a 3,5-diketopiperazine.



R^1 = Ph, 4-$HOC_6H_4CH_2$; R^2 = H; R^3 = *i*-Pr, $Ph(Ch_2)_2$, Aryl; R^4 = *c*-C_6H_{11}, $PhCH_2$, Aryl

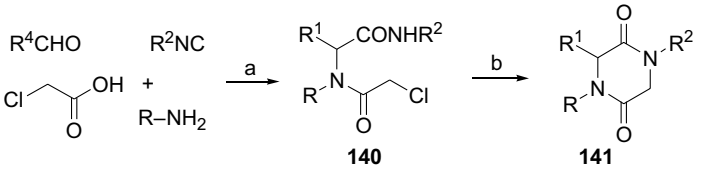
a) MeOH, rt, 36 h; b) PS-tosylhydrazine (3 equiv), THF/DCM, 24 h, then 10% TFA/DCM, 18 h

Scheme 2.50. Synthesis of quinoxalinones by the UDC strategy.

cyanides to obtain *N*-Boc-protected Ugi adducts **138**. These adducts were cyclized with TFA to give quinoxalinones **139** in good to excellent yields (Scheme 2.50).

2.3.2.6 2,5-Diketopiperazines and Morpholines from Bifunctional Ugi-4CR Reagents

A less common approach to 2,5-diketopiperazine was reported by Marcaccini et al. [79] who used a Ugi-4CR between amines, aldehydes, isocyanides, and chloroacetic acid to get adducts **140**. Treatment of **140** with ethanolic potassium hydroxide led to an intramolecular amide N-alkylation reaction, giving 2,5-diketopiperazines **141** (Scheme 2.51).



R = 4-$ClC_6H_4CH_2$, $PhCH_2$, *c*-C_6H_{11}; R^1 = 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 2-naphthyl, 4-BrC_6H_4, CH_3; R^2 = *c*-C_6H_{11}, $PhCH_2$

a) MeOH, rt, 68-86%: b) KOH, EtOH, rt, ultrasonication, 30 min, 71-86%

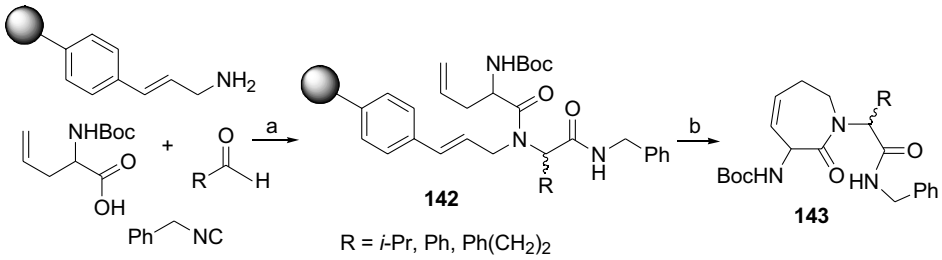
Scheme 2.51. Synthesis of 2,5-diketopiperazine *via* Ugi-4CR/intramolecular N-alkylation.

3-Substituted morpholin-2-one-5-carboxamide derivatives have been efficiently synthesized from commercially available glycolaldehyde dimer as the bifunctional component with various α-amino acids and isocyanides [80].

2.3.3 Seven-membered Rings and Their Benzo-fused Systems

2.3.3.1 Azepines by Ugi-4CR and Ring-closing Metathesis

A very interesting approach to the Freidinger lactam class of *β*-turn mimetics has been reported by Piscopio et al. [81], employing an Ugi-4CR between immobilized cinnamyl amine, *N*-Boc-protected allylglycine, benzyl isocyanide, and aldehydes to get the resin-bound adducts **142** which, under ring-closing metathesis conditions, gave the target lactams **143** (Scheme 2.52). Another efficient synthesis of seven-



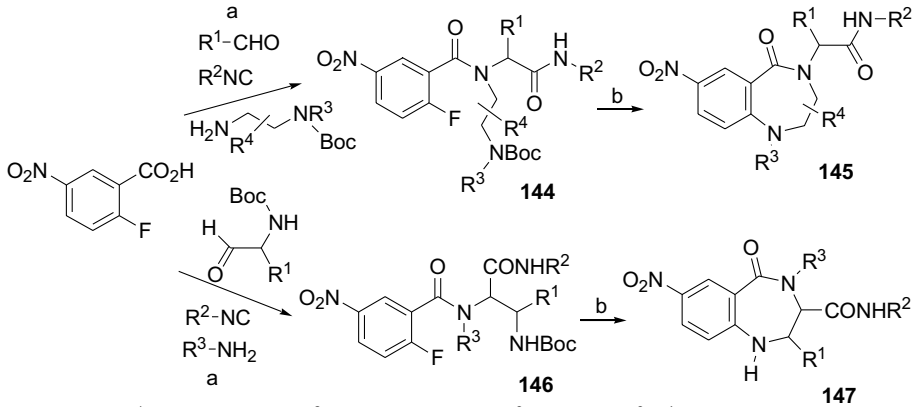
a) DCM/MeOH, rt, 48 h; b) $(Cy_3P)_2Cl_2Ru$=CHPh (5 mol %), DCE, 80 °C, 16 h, 21-62% overall.

Scheme 2.52. Synthesis of *β*-turn mimetics *via* tandem Ugi-4CR/Ring-closing metathesis.

membered unsaturated lactams based on the combination of the Ugi-4CR and ring-closing metathesis has been reported [82].

2.3.3.2 1,4-Benzodiazepine-5-ones by Ugi-4CR with N-Deprotection and Aromatic Nucleophilic Substitution

This strategy, developed by Tempest et al., allowed the solution-phase synthesis of arrays of biologically important heterocyclic systems. A simple access to 1,4-benzodiazepine-5-ones **145** [58] was achieved by reacting 2-fluoro-5-nitrobenzoic acid with *N*-Boc-protected 1,2-diaminoethanes, isocyanides, and aldehydes. The deprotection of adducts **144** followed by proton scavenging gave products **145** (Scheme 2.53). The method has been used for the synthesis of 1,4-benzoxazepine-4-ones by reacting 2-fluoro-5-nitrobenzoic acid with isocyanides, aldehydes, and *β*-hydroxyamines, and then by cyclizing the Ugi adducts to benzoxazepinones with resin-bound guanidine. The same group reported another application of this strategy for the solution-phase synthesis of 1,4-benzodiazepine-5-ones **147**



144-145: R^1 = Ph, $Ph(CH_2)_2$; R^2 = *c*-C_6H_{11}, $PhCH_2$; R^3 = H, CH_2; R^3-R^4 = $(CH_2)_3$
146-147: R^1 = CH_3, $PhCH_2$; R^2 = $PhCH_2$, *i*-Bu; R^3 = 2,6-xylyl, *t*-Bu, *i*-Pr

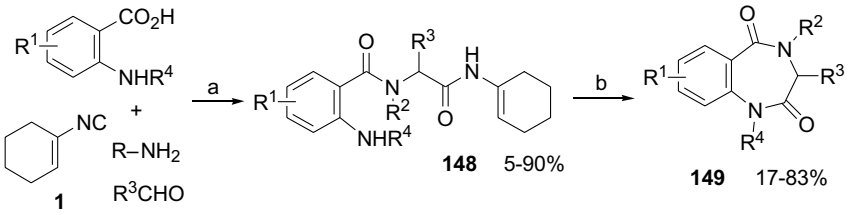
a) MeOH, rt, 48 h, then acid and aldehyde scavengers; b) 20% TFA/DCM , 4 h, then resin bound morpholine, DMF, rt, 36 h; **145**, 25-76%; **147**, 44-72%.

Scheme 2.53. Synthesis of 1,4-benzodiazepine-5-ones by Ugi-4CR/N-deprotection/S_NAr.

[83]. In this three-step procedure the key feature is the use of *N*-Boc-protected α-aminoaldehydes as the carbonyl input in an Ugi-4CR (Scheme 2.53).

2.3.3.3 1,4-Benzodiazepine-2,5-diones by Ugi-4CR with Convertible Isocyanides and UDC

An elegant two-step synthesis of 1,4-benzodiazepine-2,5-diones was reported by Keating and Armstrong [84]. Products **148** arising from the Ugi-4CR reaction between anthranilic acids, 1-isocyano-1-cyclohexene **1**, aldehydes, and amines were converted into 1,4-benzodiazepine-2,5-diones **149** on treatment with methanolic HCl (Scheme 2.54).



R^1 = I, OMe, NO_2; R^2 = Alkyl, Benzyl, 4-$MeOC_6H_4$; R^3 = Alkyl, Aryl; R^4 = H, Me

a) amine (1.25 equiv), aldehyde (1 equiv), MeOH, 1 h then acid (1 equiv) and **1** (1 equiv), 12-36 h; b) azeot. drying, methanol, AcCl (10 equiv), 55 °C, 6 h or toluene, MeOH cat., HCl/Et_2O (10 equiv), 100 °C, 6 h

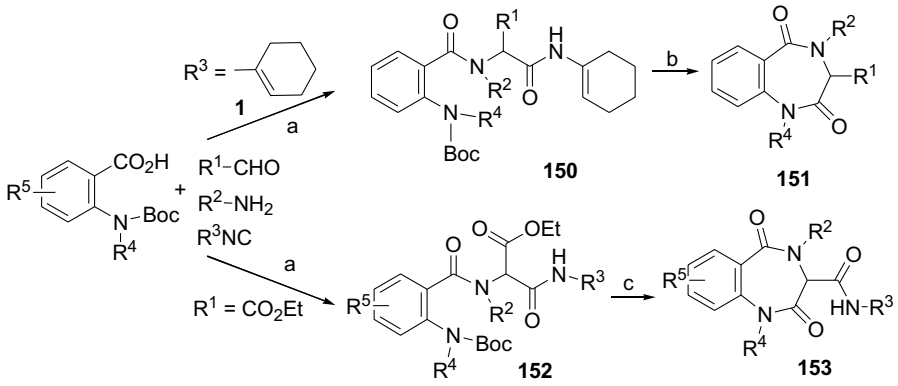
Scheme 2.54. Formation of 1,4-benzodiazepine-2,5-diones.

Another example was reported by Ugi and co-workers in a study concerning the synthetic applications of convertible (β-isocyanoethyl)alkyl carbonates [7a]. A solid-phase extension of the same procedure has been reported by the Kennedy group [20] at Array BioPharma who employed the resin-bound carbonate convertible isocyanide.

An alternative procedure for the solution-phase preparation of 1,4-benzodiazepine-2,5-diones was reported by Hulme et al. [85]. This method combines the UDC strategy and the use of the convertible 1-isocyano-1-cyclohexene **1**. The Ugi-4CR between **1**, *N*-Boc-protected anthranilic acids, amines, and aldehydes afforded the *N*-Boc-protected Ugi adducts **150** which, on treatment with HCl/MeOH or 10% TFA in DCE underwent N-deprotection, cyclohexenamide cleavage, and cyclization to the desired 1,4-benzodiazepine-2,5-diones **151** (Scheme 2.55). Hulme and Cherrier [74a] reported another high-yield one-pot solution-phase synthesis of 1,4-benzodiazepine-2,5-diones that used ethyl glyoxylate in a Ugi-4CR to give **152** and then **153** (Scheme 2.55).

A solid-phase extension of the UDC strategy for the preparation of highly pure and diverse arrays of 1,4-benzodiazepine-2,5-diones has been reported. The method employed Wang resin-bound α-amino acids [75]. Another interesting solid-phase synthesis of 1,4-benzodiazepine-2,5-diones was reported by Chen et al. [18b] that employed the Rink-isocyanide resin as the convertible isocyanide.

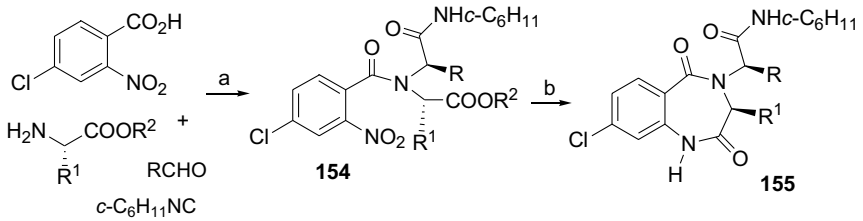
Faggi et al. [86] reported a different approach. The Ugi-4CR between 4-chloro-2-



R^1 = Alkyl, CO_2Me; R^2 = Alkyl, Aryl; R^3 = Alkyl, Cycloalkyl, Aryl; R^4 = H, Me; R^5 = H, Cl
a) methanol, rt, 24 h; b) evaporation in vacuo, 65 °C, 2 h, then AcCl/MeOH, rt, overnight
c) 10% TFA in DCE; rt, 24 h, evaporation in vacuo, 65 °C, 3 h, 75%

Scheme 2.55. 1,4-Benzodiazepine-2,5-diones synthesis *via* the UDC strategy.

nitrobenzoic acid, α-amino acid esters, aldehydes, and isocyanides gave the Ugi adducts **154** which were reduced, without isolation, with iron in acetic acid to the intermediate amines that spontaneously cyclized to the 1,4-benzodiazepine-2,5-diones **155** with good diastereoselectivity (Scheme 2.56).



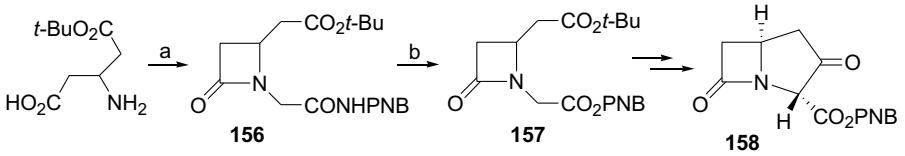
R^1 = $PhCH_2$, *i*-Bu, H, 4-$HOC_6H_4CH_2$; R = Me, 4-ClC_6H_4
a) MeOH, rt, 48 h; b) Fe, AcOH, 45 °C to 65-70 °C, 49-65% overall.

Scheme 2.56. 1,4-Benzodiazepine-2,5-diones *via* Ugi-4CR/reduction/cyclization.

2.3.4 Bicyclic Systems

2.3.4.1 Carbapenems and Carbacephems by Ugi-4CR and Dieckmann Condensation

Hatanaka and co-workers found that carbapenem derivatives were readily available by means of an Ugi-4CR between 3-aminoglutaric acid mono-*t*-butyl ester, formaldehyde, and 4-nitrobenzyl isocyanide that gave the β-lactam **156**, which was converted into the 4-nitrobenzyl ester **157**. The subsequent stereoselective Dieckmann condensation allowed the preparation of the 2-oxocarbapenem derivative **158** (Scheme 2.57) [87].

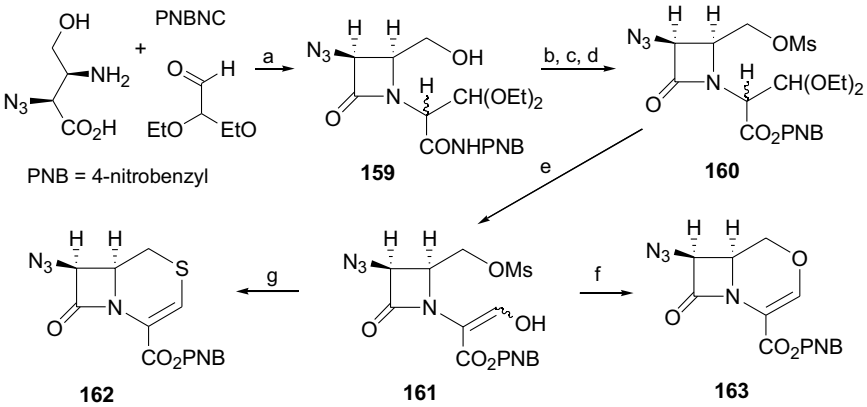


a) HCHO, PNBNC, 88%; b) N_2O_4, then CCl_4, reflux, 85%

PNB = p-$NO_2C_6H_4CH_2$

Scheme 2.57. Carbapenems *via* intramolecular Ugi-4CR.

An interesting approach to carbacephem derivatives was described by the Ugi group [88] by combining the intramolecular Ugi-4CR together with the chemistry of the oxazole ring and *N*-Boc-carbonamides. Hatanaka et al. [15] reported an interesting enantioselective synthesis of 2-isocephem and 2-isooxacephem nuclei starting from an Ugi-4CR between a functionalized β-amino acid, 2,2-diethoxyacetaldehyde and 4-nitrobenzyl isocyanide, leading to the β-lactam **159**. Subsequent methanesulfonylation and N-nitrosation afforded the 4-nitrobenzyl ester **160**, which was converted into the 2-isooxacephem derivative **162** by acidic hydrolysis affording **161**, followed by cyclodemesylation with triethylamine. The analogous 2-isocephem derivative **163** was obtained from **161** after methanesulfonylation and subsequent treatment with hydrogen sulfide (Scheme 2.58).



PNB = 4-nitrobenzyl

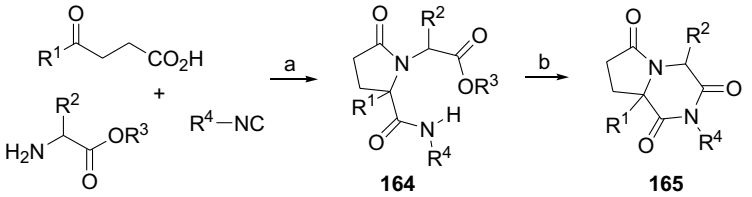
a) MeOH, rt, overnight, 93%; b) $MeSO_2Cl$, TEA, THF, 0 °C; c) N_2O_4/NaOAc, $CHCl_3$, 0 °C,1 h; d) CCl_4, reflux, 57% over 3 steps; e) 95% aq TFA, 50 °C, 1 h, 81%; f) TEA, DCM, reflux, 3 h, 94%; g) $MeSO_2Cl$, TEA, THF, then H_2S, DCM, 50%

Scheme 2.58. 2-Isocephem and 2-isooxacephem derivatives *via* Ugi-4CR.

2.3.4.2 Bycyclic Systems by Ugi-4CR and Cyclization

The synthesis of bicyclic γ-lactam-piperazinone derivatives has been reported by Hulme et al. [8b] as an extension of the UDC strategy. Alternatively, the formation of γ-lactams by reacting γ-keto acids, amines, and isocyanides [89] has been ex-

tended to the preparation of bicyclic or tricyclic systems containing the γ-lactam moiety [90]. Thus, the reaction between levulinic acid, α-amino esters, and isocyanides led to the formation of the functionalized pyrrolidin-2-ones **164**, which were treated with KO^{t}Bu to promote the formation of **165** (Scheme 2.59). Starting from 2-formylbenzoic acid, the same procedure gave the corresponding benzoderivative.

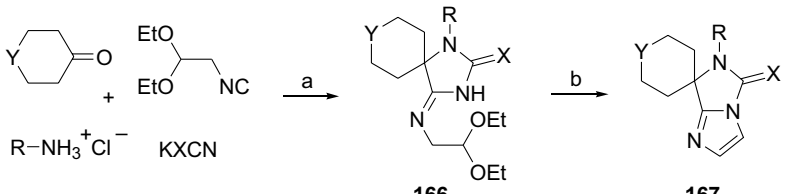


R^1 = Me, Ph; R^2 = H, *t*-Bu, *i*-Bu; R^3 = Me, Et; R^4 = CH_2CO_2Me(or Et), Me, *t*-Bu

a) MeOH, rt, 24h or reflux, 48 h, 58-100%; b) KO^{t}Bu, THF, reflux, 48 h, 5-33%

Scheme 2.59. Bicyclic γ-lactams *via* Ugi-4CR/intramolecular imide bond formation.

The Ugi-4CR between cyclic ketones, primary amine hydrochlorides, potassium thiocyanate (or selenocyanate), and 2,2-diethoxyethyl isocyanide [91] afforded the spiro 2-thio-(or seleno)hydantoin-4-imines **166.** On heating in acetic acid, compounds **166** underwent carbonyl deprotection and cyclization to spiro imidazo[1,5-*a*]imidazoles **167** (Scheme 2.60).



Y = CH_2, S X = S, Se

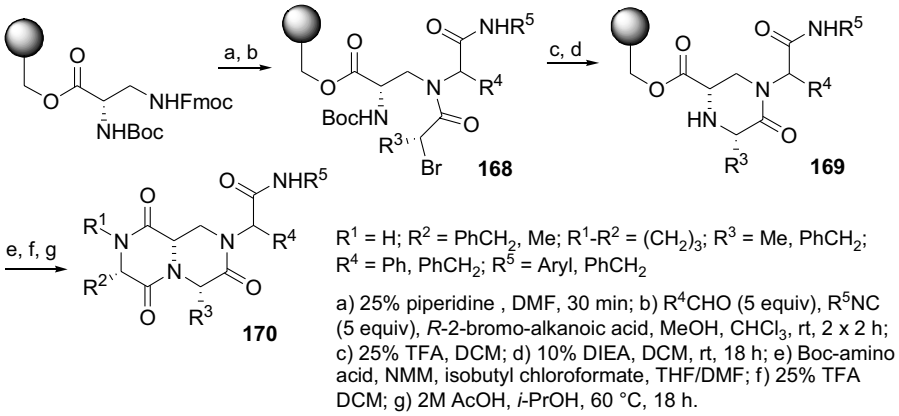
R = 4-FC_6H_4, 4-$EtOC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, Ph, 4-$NO_2C_6H_4CH_2$

a) MeOH, rt, 1-2 h, 10-71%; b) AcOH, reflux, 3 h, 9-52%

Scheme 2.60. Imidazo[1,5-*a*]imidazoles *via* Ugi-4CR/carbonyl deprotection/cyclization.

Golebiowski et al. reported the solid-phase [92] and the solution-phase [93] syntheses of bycyclic diketopiperazines which were of great interest because their conformation was similar to the type-1 β-turn motif. A Merrifield hydroxymethyl resin was esterified with α-*N*-Boc-β-*N*-Fmoc-L-diaminopropionic acid and then monodeprotected at the β-N with piperidine. Ugi-4CR of the resulting resin-bound amine gave the resin-bound adducts **168**. Subsequent *N*-Boc deprotection and intramolecular N-alkylation afforded the ketopiperazines **169**. The diketopiperazines **170** were formed *via* *N*-Boc amino acid coupling followed by *N*-Boc deprotection

and cyclization *via* intramolecular amide bond formation. The final products were obtained in fair yields and their purity was satisfactory since the resin cleavage was a consequence of the cyclization (Scheme 2.61).

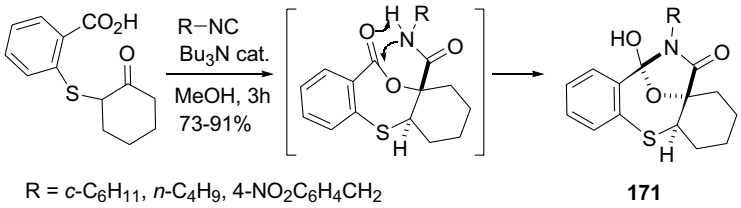


Scheme 2.61. Bicyclic diketopiperazines *via* Ugi-4CR/intramolecular N-alkylation.

2.3.5
Polycyclic and Macrocyclic Systems

2.3.5.1 Polycyclic Orthoamides by Passerini-3CR

The Passerini-3CR between bifunctional 6-oxo-4-thiacarboxylic acids and alkyl-isocyanides, in the presence of a catalytic amount of tributylamine, afforded the tetracyclic structure **171**, which included the 1,4-benzothioxepin group and an unexpected oxazolidinone ring, with formation of a rare orthoamide group (Scheme 2.62) [94].

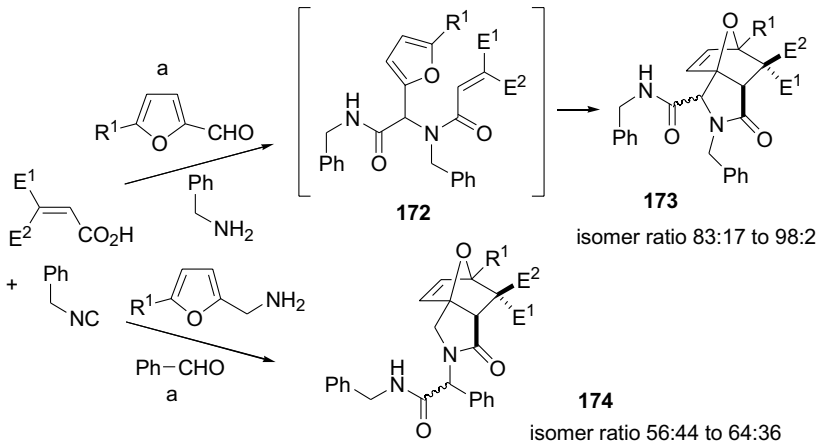


Scheme 2.62. Synthesis of polycyclic orthoamides by Passerini-3CR.

2.3.5.2 Polycyclic Systems *via* I-MCR and Intramolecular Diels–Alder Cycloaddition

The first example of a tandem Ugi-4CR/intramolecular Diels–Alder reaction was reported by Paulvannan at Affimax [95], who obtained precursors for intramolecular Diels–Alder cycloadditions by an Ugi-4CR between furan-2-carboxaldehydes, monoamides or monoesters of fumaric or maleic acids, benzylamine, and benzyl isocyanide. The Ugi-4CR adducts **172** were never isolated since they underwent

spontaneous intramolecular cycloaddition to give the tricyclic lactams **173**. An alternative approach consisted of the Ugi-4CR between furfurylamine, benzaldehyde, benzyl isocyanide, and dienophilic acids. Also the Ugi adducts spontaneously cyclized to the tricyclic lactams **174** (Scheme 2.63). The synthetic sequence was adapted to a solid-phase synthesis with similar good results.



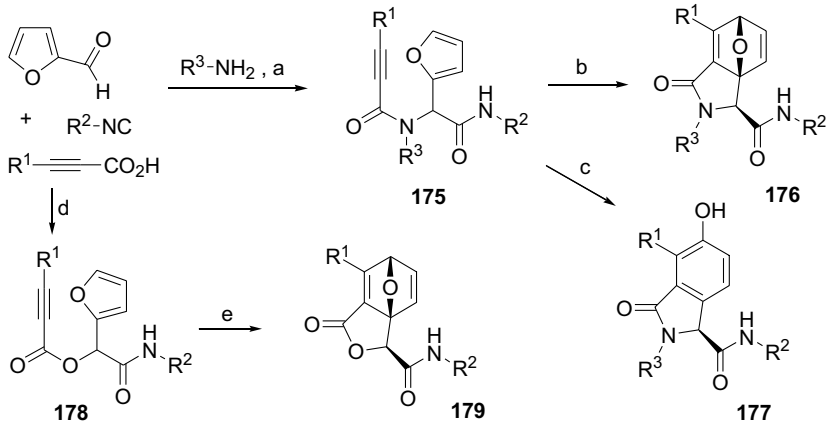
R^1 = H, Me; E^1 = CO_2Et, E^2 = H; E^1 = H, E^2 = CO_2Et; E^1 = H, E^2 = CO_2NHCH_2Ph
a) MeOH, rt, 36 h, 72-89%

Scheme 2.63. Tricyclic lactams *via* Ugi 4-CC/intramolecular Diels–Alder cycloaddition.

Wright and co-workers synthesized simplified analogues of wortmannin and viridin, two furanosteroids isolated from fungi, by means of I-MCR and intramolecular Diels–Alder cycloadditions [96]. The Ugi-4CR between 2-furancarboxaldehyde, acetylenic acids, isocyanides, and amines afforded adducts **175** which were converted into oxabicyclo[2.2.1]heptadiene derivatives **176** on heating. The cycloadditions were highly stereoselective and the major diastereoisomers showed an exo structure. The Ugi adducts **175** were converted into the isoindolines **177** in high yields on treatment with $Yb(OTf)_3$. The related Passerini-3CR adducts **178** underwent intramolecular cycloaddition on treatment with Me_2AlCl to give **179** (Scheme 2.64).

An interesting and elegant example of pairwise use of complexity-generating reactions was reported by Schreiber and co-workers [97]. The Ugi-4CR between furan-2-carboxaldehyde, benzyl isocyanide, *N*-(3-bromomethyl)fumaric acid monoamide, and 4-(triisopropylsilyloxy)methylbenzylamine afforded the adduct **180** which spontaneously underwent an intramolecular Diels–Alder cycloaddition to give the oxabicyclo[2.2.1]heptene **181** which in turn was diallylated at the two secondary amide nitrogens to give **182**, a structure suitable for a ring-opening-closing metathesis reaction. Treatment of **182** with the Grubbs second-generation catalyst afforded the tetracyclic product **183** (Scheme 2.65). This procedure was adapted to a solid-phase synthetic procedure.

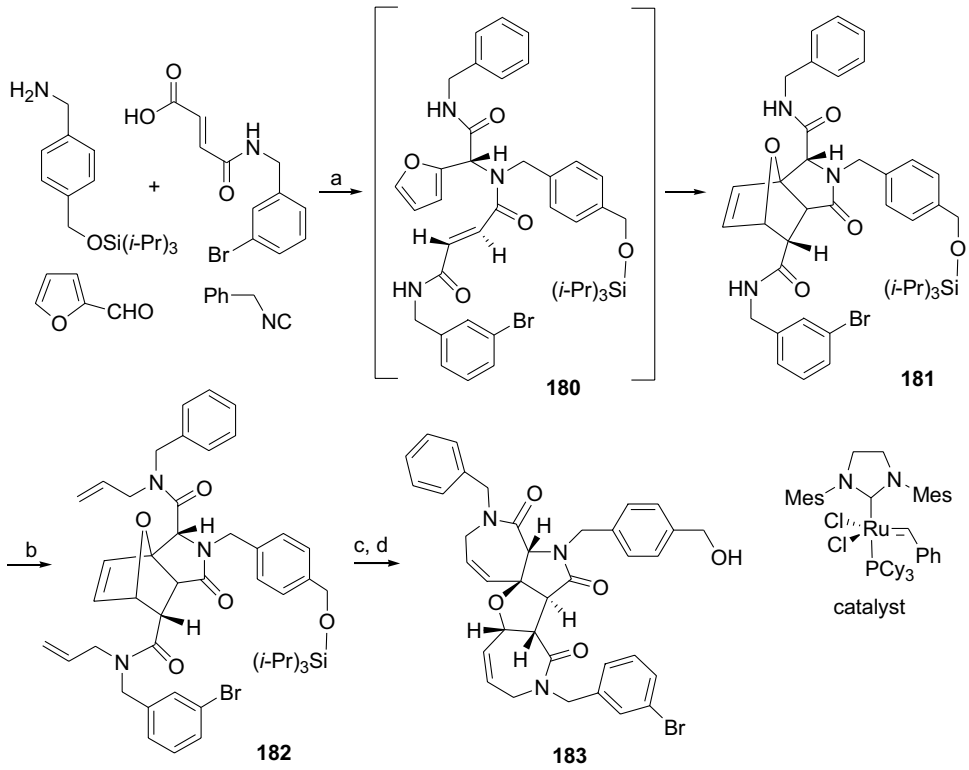
The same group reported that substrates having appendages that pre-encode



R^1 = Me, Ph, H; R^2 = $PhCH_2$, *t*-Bu; R^3 = $PhCH_2$, *t*-Bu

a) MeOH, 74-92%; b) toluene, 200 °C, sealed tube, < 24 h, 74-81%; c) $Yb(OTf)_3$, dioxane, 100 °C, sealed tube, 77-91%; d) DCM, 69-86%; e) Me_2AlCl, DCM, -78 °C to rt, 68-77%

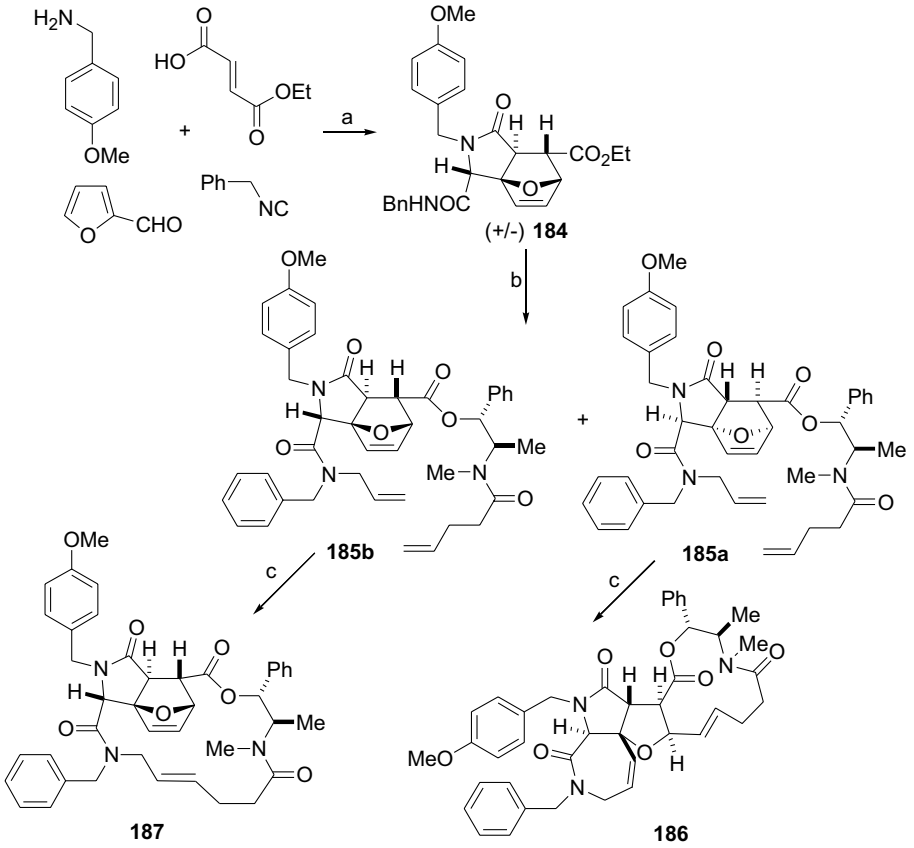
Scheme 2.64. Tandem Passerini-3CR or Ugi-4CR/intramolecular Diels–Alder-CA.



a) MeOH, THF, 48 h, 67%; b) KHMDS, allylBr, rt, 89%; c) catalyst, DCM, 40 °C, 36 h, 69%; d) HF, pyridine, 95%

Scheme 2.65. Tetracyclic system *via* tandem Ugi-4CR/Diels–Alder-CA/ring-closing metathesis.

skeletal information can be converted into products having distinct skeletons using a common set of reaction conditions. By the sequential use of the Ugi-4CR/intramolecular Diels–Alder cycloaddition that gave **184**, followed by allylation, hydrolysis, and acylation of a chiral amino alcohol appendage, substrates **185a**,**b** suitable for ring opening/ring closing or ring-closing metathesis reactions were obtained. The stereochemistry of the appendage and not its constitution controlled the outcome of the pathway selected, giving products **186** and **187** [98] (Scheme 2.66).

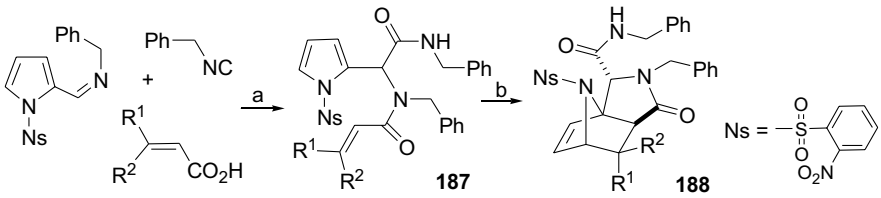


a) MeOH, THF, 48 h, 67%; b) CsOH, allylBr, THF; then $Ba(OH)_2 \cdot 8H_2O$, MeOH, 98%; diastereomeric separation c) 10% Grubbs catalyst 2nd generation, 65-87%

Scheme 2.66. Complex systems *via* tandem Ugi-4CR/Diels–Alder-CA/ring-closing metathesis.

Paulvannan has reported an efficient approach to rigid tricyclic nitrogen heterocycles *via* sequential and tandem Ugi-4CR/intramolecular Diels–Alder cycloaddition of pyrrole derivatives. The Ugi-4CR was used to prepare trienes **187** from maleic and benzylmaleamic acids, which on heating at 60–120 °C for 12 h yielded

the corresponding cycloaddition products **188**. In contrast, fumaric acid monoester and 3-acetylacrylic acid directly yielded the corresponding Ugi-4CR/intramolecular Diels–Alder cycloaddition products **188** in high yields at room temperature [99] (Scheme 2.67). As in previous examples, the intramolecular cycloaddition reactions proceed with excellent stereoselectivity with the formation of five stereogenic centers and three rings.



R^1 = H, R^2 = CO_2Et, CONHBn, a) MeOH, 36 h, rt, 70-80%; b) 60-120°C, 6-12h, 78-100%;
R^1 = CO_2Et, CH_3CO, R^2 = H, a) MeOH, 36 h, rt, not isolated; b) rt, 72-75%;

Scheme 2.67. Tandem or sequential Ugi-4CR/intramolecular Diels–Alder-CA.

2.3.5.3 **Macrocycles by Passerini-3CR, Ugi-4CR and Ring-closing Metathesis**

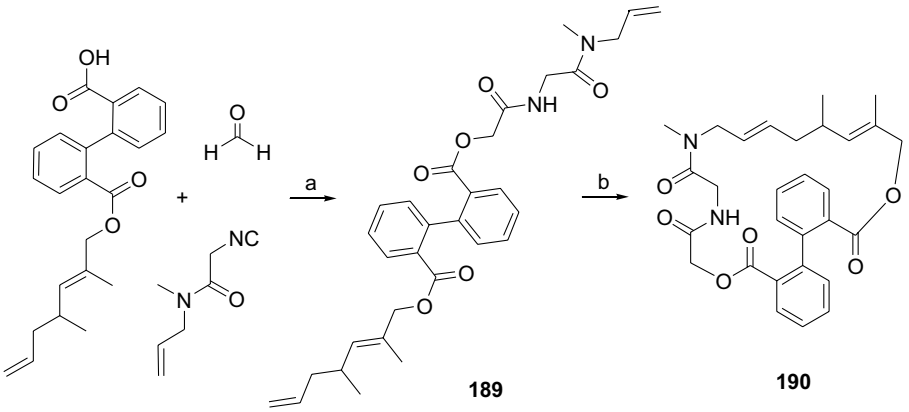
The ring-closing metathesis of bis-olefins arising from isocyanide-based MCR has been employed by Dömling and co-workers to achieve ready access to macrocyclic lactones [100], which are interesting for their similarity to natural products. Thus, the reaction of ω-olefinic carboxylic acids, double-bond-containing isocyanides, and carbonyl compounds afforded the expected Passerini adducts **189** and **191**, which were ideally suited for a ring-closing metathesis reaction to give macrocyclic lactones **190** and **192** (Scheme 2.68).

Hebach and Kazmaier reported the synthesis of cyclic peptidomimetics containing an alkylated amino acid *via* Ugi-4CR of N-terminal-protected aloc-amino acids, allyl isocyanoacetate, and chiral amines in trifluoroethanol. Allylic esters of tripeptides **193** were obtained in high yields and good stereoselectivity. Metathesis with 5% of Grubbs first-generation catalyst gave 16-membered cyclic peptides **194** in 30–50% yield (Scheme 2.69) [101].

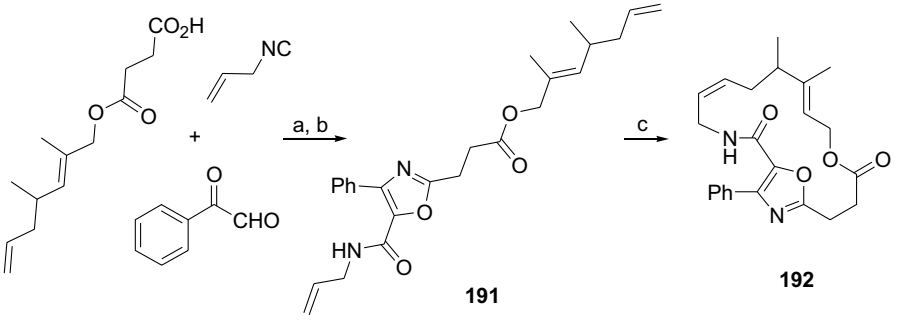
Banfi and co-workers applied the tandem Ugi reaction/ring-closing metathesis to the synthesis of unsaturated nine-membered lactams as potential reverse-turn inducers. Reaction of allyl-substituted racemic isocyanoacetates with preformed imines and carboxylic acids gave adducts **195** that were treated with Grubbs first-generation catalyst to give nine-membered lactams **196** (Scheme 2.70) [102].

2.3.5.4 **Macrocycles by Ugi-4CR and Nucleophilic Aromatic Substitution**

Zhu et al. [103] reported a facile access to biologically relevant macrocycles bearing an endo diaryl ether bond by means of a tandem Ugi-4CR/S_NAr. The reaction between 3-hydroxyphenylacetic [or 3-(3-hydroxyphenyl)propionic] acid, aldehydes, amines, and isocyanide **197** gave the expected dipeptide derivatives **198** as a 1:1 mixture of diastereoisomers. The reaction gave high yields when performed in tri-

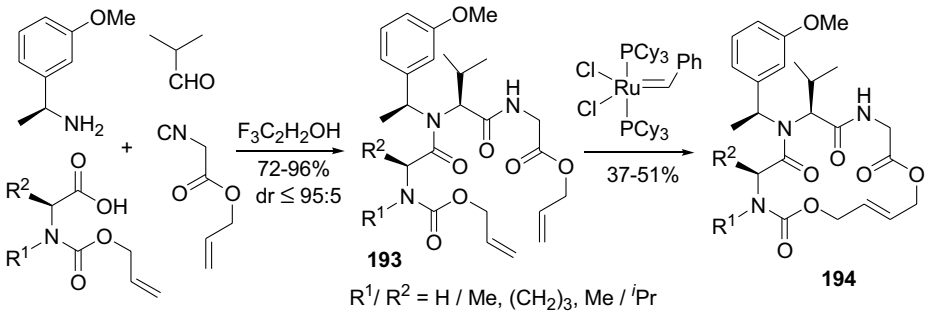


a) Et_2O, 20 °C, 3 d, 67%; b) Grubbs catalyst, Ti^iOPr_4, DCM, reflux, 2 d, 26%



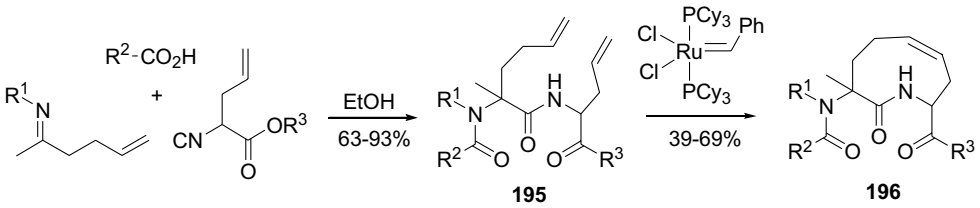
a) Et_20, 88%; b) $CF_3CO_2NH_4$, 4 h, 150 °C, 33%; c) Grubbs catalyst, Ti $(O^iPr)_4$, DCM, reflux, 25%

Scheme 2.68. Macrocyclic lactones *via* tandem Passerini-3CR/ring-closing metathesis.



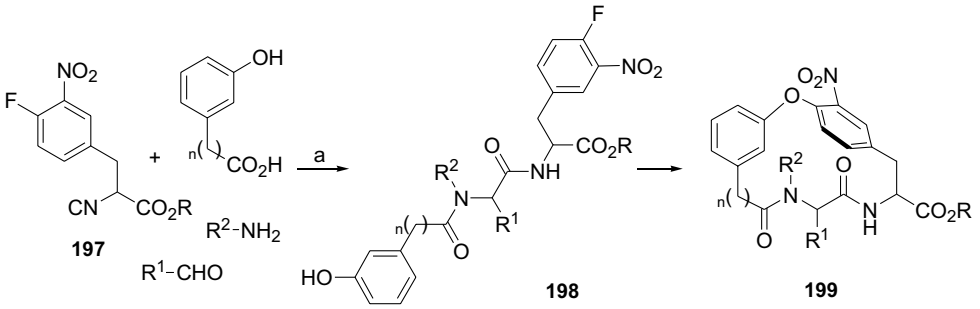
R^1/ R^2 = H / Me, $(CH_2)_3$, Me / ^{i}Pr

Scheme 2.69. Synthesis of cyclic peptidomimetics *via* Ugi-4CR/ring-closing metathesis.



R^1 = *n*-Bu, $PhCH_2$; R^2 = Me, $PhCH_2$, $PhCONHCH_2$, $BocNHCH_2$, $FmocNHCH_2$; R^3 = *t*-Bu, Et

Scheme 2.70. Nine-membered lactams by Ugi-4CR/ring-closing metathesis.



R = Me, Et

n = 0, 1; R^1 = *n*-C_6H_{13}, Ph, C_2H_4NHBoc, $PhCH_2CH_2$, *i*-Pr; R^2 = *n*-C_4H_9, 4-$MeOC_6H_4$, $PhCH_2$, *i*-Pr

a) toluene, 60 °C, 20 h, 43-73%; b) DMF, K_2CO_3, 60-97%

Scheme 2.71. Formation of macrocyclic ethers *via* coupling Ugi-4CR/S_NAr.

fluoroethanol (benzene or toluene in the presence of ammonium chloride were also employed). The cycloetherification of **198** took place easily in DMF in the presence of potassium carbonate, to give the macrocyclic diaryl ethers **199** in very good yields (Scheme 2.71). The presence of the nitro group in **199** allowed further transformations such as the reduction to amines and their transformations into amides, ureas, and sulfonylamides, and deamination *via* diazonium salts.

The possibilities for I-MCR in syntheses of complex molecules have not yet fully developed, although many pathways have been explored. For example, the sequence of an Ugi-4CR, followed by an intramolecular Heck reaction, has been employed as the key step [104] in a total synthesis of ecteinastidin 743, a potent antitumor alkaloid isolated from a marine tunicate, *Eteinascidia turbinata*, having a polyheterocyclic-macrocyclic structure [105]. More recently, the Gracias group at Abbott Laboratories developed a sequential Ugi-4CR/microwave-assisted intramolecular Heck cyclization for the synthesis of isoquinoline and benzazepine derivatives, both in solution and in solid-phase fashion [106]. The same group recently reported a two-step unprecedented Ugi-4CR/intramolecular *N*-oxide cyclization for the synthesis of fused isoxazoles and isoxazolines in moderate to good yields [107], showing that post-condensation reactions are almost endless. Several new sequences of compatible reactions are still waiting for exploration to contribute to this rich and useful chemistry.

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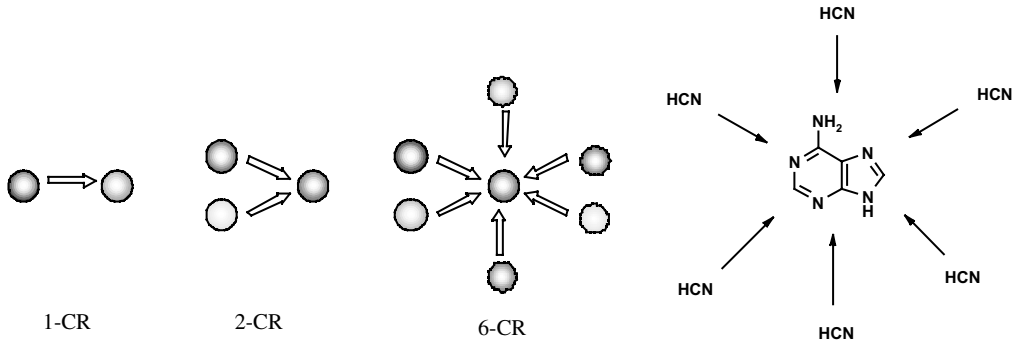
3
The Discovery of New Isocyanide-based Multicomponent Reactions

Alexander Dömling

3.1
Introduction

According to our definition a multicomponent reaction (MCR) comprises reactions with more than two starting materials participating in the reaction and, at the same time, the atoms of these educts contribute the majority of the novel skeleton of the product (Scheme 3.1) [1]. For example, adenine may be formed by the addition of five molecules of isocyanic acid, a reaction of possible high prebiotic relevance [2].



Scheme 3.1. Left: Schematic representation of a divergent 1-CR and 2-CR and a convergent 2-CR and a highly convergent MCR. Right: A prototype MCR is the formation of adenosine from 6 molecules of hydrocyanic acid, probably of major importance in the beginning of life.

MCRs of up to seven different starting materials have been described in the past [3]. MCRs have numerous advantages over classical approaches (linear, iterative or divergent synthesis) in assembling useful chemical products. The advantage of convergence over a divergent synthetic approach is well appreciated in the syn-

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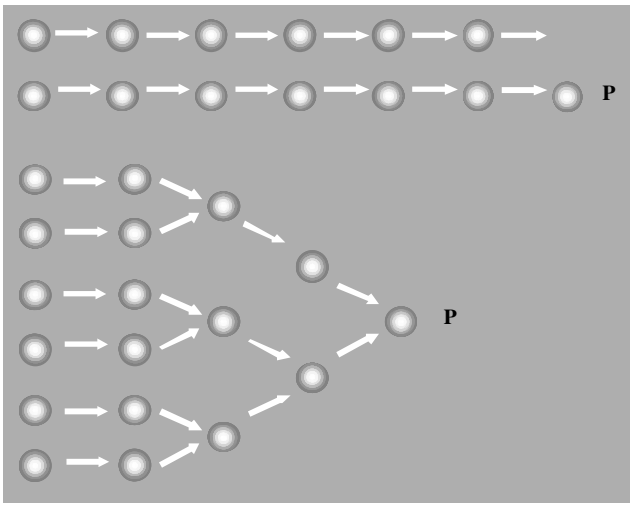


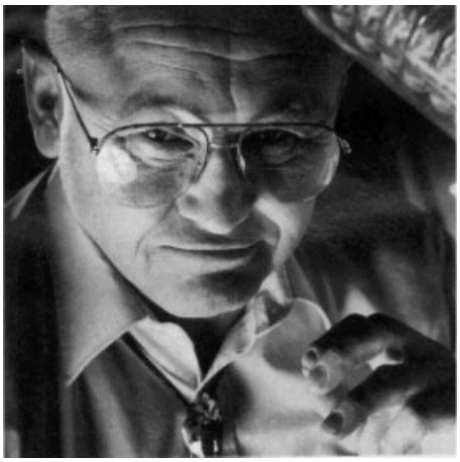
Scheme 3.2. A linear divergent 12-step synthesis and a convergent 12-step synthesis.

thetic community since assuming the same yields per step, the total yield of the convergent synthesis is considerable higher than the corresponding divergent synthesis (Scheme 3.2).

Convergence offers considerable process time reduction and better yields. Because several steps can be performed in parallel, these can be performed in different locations, thus leading to considerable time reduction. In analogy to the convergent multi-step synthesis approach, MCRs have been termed convergent reactions, because in one reaction step several molecules are convergently assembling the product molecule [3]. Moreover MCRs have the advantages of one-pot procedures.

Typically MCRs allow the synthesis of very many derivatives of a special scaffold. Since the number of possible products increases exponentially with the multiplicity of the MCR, very large chemical spaces can be inspected. These very large chemical spaces are not realistically accessible by classical sequential syntheses. As realized by Ugi in 1961 "starting with 1000 each of the educts carboxylic acid, amines, aldehydes and isocyanides 1000^4 products are accessible" [4]. In this seminal paper the roots of combinatorial chemistry are described. The authors noted that MCRs have huge variability. Although the paper describes the essentials of combinatorial chemistry, the time was not right for the great advances that only started 30 years later.

MCRs are now no longer confined to a few backbones, but hundreds of easily accessible chemical scaffolds have been described and the description of novel scaffolds available through MCRs is a very active area in the organic-chemical literature. Thus MCRs have become very popular in all areas of organic chemistry and especially in applied chemistry, such as the discovery of novel biologically active compounds as drugs or agricultural chemicals, and material sciences.



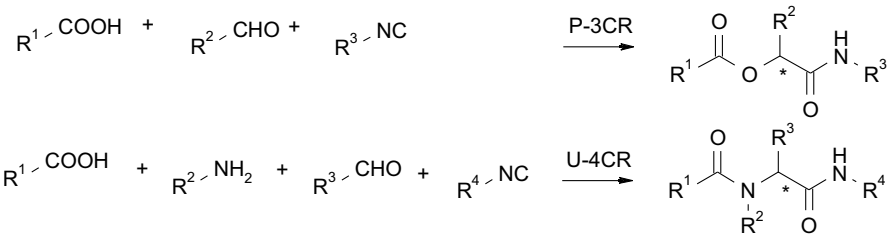
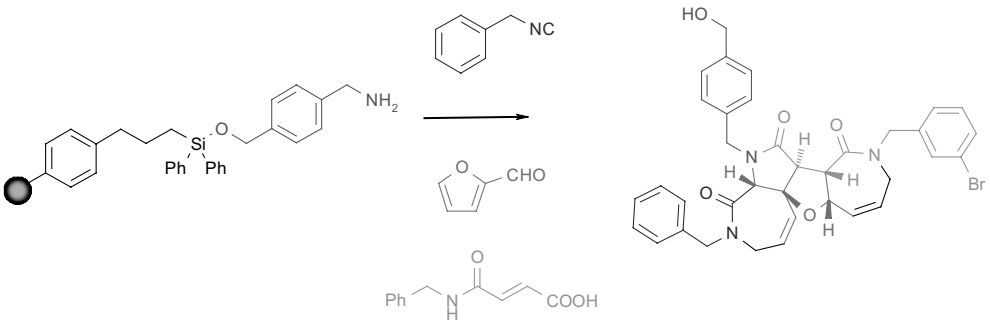


Fig. 3.1. The most important isocyanide-based MCRs are the archetypical Passerini and Ugi reactions (bottom). Top left: Mario Passerini; right: Ivar Ugi

An especially effective and fruitful way to synthesize novel scaffolds is by isocyanide-based MCRs (IMCRs). They mostly rely on the classical reactions of the pioneers of this chemistry, Passerini and Ugi (Figure 3.1). Passerini was born in 1891 in Scandicci and was a Professor of Chemistry in Italy, from 1930 to 1932 at the University of Siena and from 1932 at the University of Florence. He died in 1962. Ivar Ugi was born in 1930 in Estonia. After being ''Forschungsdirektor of the Zentrallabor in Leverkusen at BAYER'', he accepted a chair as full professor at the USC in Los Angeles from 1967 to 1970. From there he moved to the Technische Universität München in 1970, where he held the prestigious Emil Fischer chair until 2001.

In the classical Passerini 3-component reaction (P-3CR) electrophilic ketones or aldehydes react with carboxylic acids and isocyanides to form α-hydroxyacyl amides [5], whereas the Ugi reaction was first defined as the reaction of isocyanides with electrophilic imines or enamines and a nucleophile and an appropriate rearrangement [6]. Thus the Ugi reaction is much more versatile in term of accessible scaffolds, emerging from the multiplicity of reacting nucleophiles and the possibility of different rearrangement reactions. Advantageously all isocyanide-based MCRs are highly compatible with a range of functional groups not involved in the initial MCR. Moreover these can be used in a secondary reaction in order to perform, for example, a variety of ring-closure reactions. Thus IMCRs are perfectly suited for the diversity and complexity oriented synthesis of large arrays of compounds. Scheme 3.3 illustrates a short complexity-generating sequence involving a U-MCR, described by Schreiber et al. The sequence consists of four reactions, a first Ugi reaction that uses four simple, available starting materials, a Diels–Alder reaction, a double allylation of two secondary amide nitrogens, and finally a ring-opening/closing metathesis. During this short sequence as many as four new rings and fifteen new bonds are formed. This is noteworthy since in a typical sequential synthesis using two-component reactions, typically only one bond or ring is formed per step. Obviously, not all four reactions contribute similarly to the diversity and the complexity of the backbone structure and final product library. The diversity of the resulting compounds arises from the starting materials of the first Ugi reaction and to a much smaller degree from subsequent steps such as the allylation. The Ugi reaction determines most of the diversity *via* four independently introduced substituents. It also greatly contributes to complexity, since during the reaction five new bonds are formed. The Diels–Alder reaction contributes to complexity through the formation of two C–C bonds and the concomitant formation of three ring systems, but only one of them is retained in the final product. The allylation introduces new fragments (two new N–C bonds) and paves the way for the most dramatic molecular change in the overall sequence by the last reaction, the ring-opening/closing metathesis. During this reaction a five-membered ring is opened and two seven-membered rings are formed through four new C–C bonds. Overall the Ugi, and to a much lesser extent the allylation, reactions con-



Scheme 3.3

tribute to the diversity in this scaffold. The Ugi, Diels–Alder and metathesis reactions are responsible for the augmentation of complexity in this sequence as counted by bond formation and newly formed rings. Therefore, combining complexity- and diversity-generating MCRs together with other complexity-generating reactions provides a powerful tool towards the parallel synthesis of molecular libraries with impressive chemical structures. A detailed analysis of this reaction is given in ref [7].

Overall MCRs are a big step towards the ideal synthesis, which, according to Wender et al. "can be measured by parameters such as the step count, overall yield, selectivity, cost, scale, resource requirements, waste stream, development time, execution time and personnel" [8]. The discovery of novel IMCRs are explained and several conceptually different approaches towards this goal, with an emphasis on our recent contributions in this area are shown.

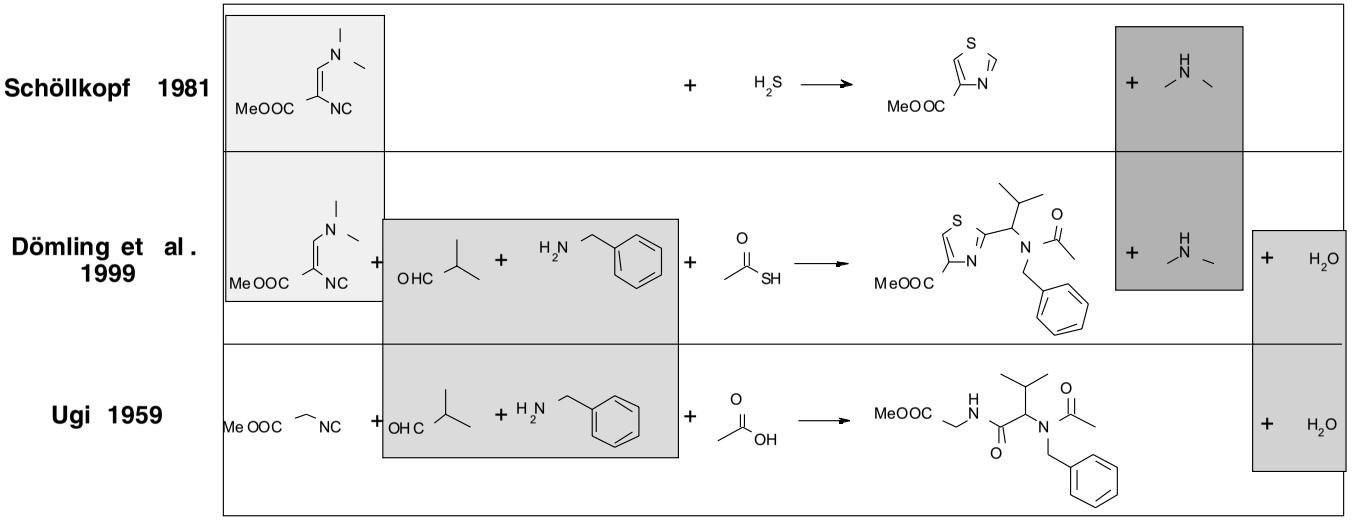
3.2 New MCRs*

A chemical reaction is the transformation of an ensemble of educts into an ensemble of products, whereupon the connectivity of the molecules in both ensembles is changed. Moreover a chemical reaction is composed of several elementary reactions, which constitute the mechanism of the corresponding reaction. These elementary reactions are performed in a highly ordered and consecutive fashion. The number of these elementary steps is limited, whereas thousands of organic reactions consisting of these elementary steps exist in the arsenal of synthetic reactions of organic chemists. Since the beginnings of organic chemistry in the early nineteenth century with Novalis, Berzelius, Döbereiner, Wöhler, Liebig and others, chemists have been looking for reactivity, the discovery of new reactions, their mechanism and their classification.

3.2.1 What are New Reactions?

Qualitatively the novelty of reactions is difficult to assess. One can for example compare a novel reaction with different similar reactions known from literature in terms of mechanism, educts and products and scope and limitation. Scheme 3.4 compares three reactions: Schöllkopf's thiazole synthesis, the thiazole 4-CR described by us in 1999 and the classical U-4CR. The shaded areas show the common educts and products of these reactions. Obviously reaction 2 has common educts and products with reactions 1 and 3. Each reaction also has at least two unique components. The products of all the reactions are not identical. Thus reactions 1

*) Nothing comes from nothing or everything has predecessors.



Scheme 3.4. The quality of new reactions.

and 2 result in thiazole products with non-identical substitution patterns. With reaction 1 only a single thiazole is accessible. However the thiazole of reaction 2 is highly variable. The product of reaction 3 is the most variable, but is not a thiazole. Qualitatively one can state that the "new thiazole synthesis" has several features in common with reactions 1 and 3 but is also different from them.

We recently developed a quantitative method of assessing the novelty of a reaction [9]. A molecule can be represented in different formats, e.g. as a formula or as a picture of an X-ray structure analysis. Another more "computer-friendly" way to depict chemical formulas is by the use of SMILES [10]. Moreover, reactions can be depicted using interconnected ensembles of SMILES, which are then called SMIRKES. An established way to compare the 2-D similarity of two molecules is to compare their SMILES and their sub-strings. We extended this comparison of molecules via their SMILES and sub-strings towards the comparison of reactions via their SMIRKES and their corresponding sub-strings. The advantage of this method is its quantitative nature. Scheme 3.5 illustrates how this method is applied by depicting Schöllkopf's thiazole synthesis, our thiazole MCR and the classical U-4CR as SMIRKES. The lower part of the scheme shows the similarity matrix constructed by comparison of all connected atom tupels over 0–7 bonds of the three reactions. A result of 1 means identity of two reactions and 0 means no similarity. The U-4CR shows only a low similarity with Schöllkopf's thiazole synthesis (0.10) and interestingly also low similarity with the thiazole-4CR (0.13). However Schöllkopf's thiazole synthesis is more similar to the thiazole-4CR (0.54).

In practice there are different approaches to the development of new MCRs. These are random discovery or chance, combinatorial chemistry, rational and computer-assisted design and the concept of unions of MCRs, and these will be described in the following sections.

3.3 Random Discovery

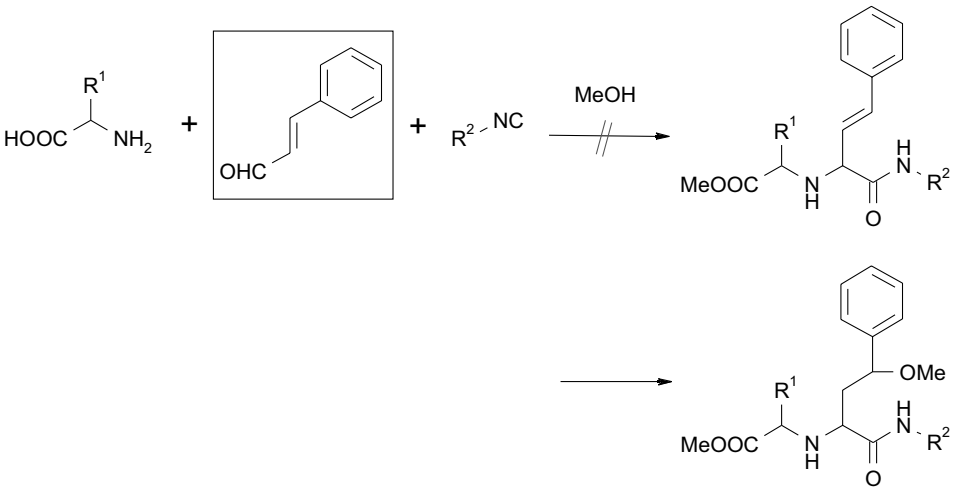
During random discovery or discovery by chance one performs a reaction, but the outcome is different from the expected one. During the investigation of the reactions and elucidation of the mechanism one may eventually discover a reaction with a defined and broad scope and limitations and thus a synthetically useful reaction. Thus, after being confronted with the experimental facts, for example the quantitative failure of whole rows or columns of synthesis in an array, one has to elucidate the novel structure and mechanism. The challenge during this approach is not to discard the unusual and unexpected experimental results, and thus to miss the new MCR, but rather to investigate the origin of this chemical discrepancy. The inspection of chemical arrays by the analytical method of mass spectroscopy is helpful in discovering such unexpected reactions. For example, during a recent synthesis of arrays of products by an Ugi variation (5C-4CR) of α-amino acids, aldehydes and isocyanides in methanol [11], we noticed a congruent discrepancy in

```
Schöllkopf:
COC(=O)c([N+]#[C-])cn(C)C.S>>COC(=O)c1cScn1.CNC

Dšmling:
COC(=O)c([N+]#[C-
])cn(C)C.O=CC(C)C.NCc1ccccc1.CC(=O)S>>COC(=O)c1cSc(C(C(C)C)N(Cc2ccccc2)C(=O)C)n1.CNC.O

Ugi:
COC(=O)C[N+]#[C-].O=CC(C)C.NCc1ccccc1.CC(=O)O>>COC(=O)CNC(=O)C(C(C)C)N(Cc1ccccc1)C(=O)C



>>>>> SIM Report <<<<<

Similarity matrix for 3 REACTION-SMILES:

 1: COC(=O)c([N+]#[C-])cn(C)C.S>>COC(=O)c1cScn1.CNC
 2: COC(=O)c([N+]#[C-
])cn(C)C.O=CC(C)C.NCc1ccccc1.CC(=O)S>>COC(=O)c1cSc(C(C(C)C)N(Cc2ccccc2)C(=O)C)n1.CNC.O
 3: COC(=O)C[N+]#[C-].O=CC(C)C.NCc1ccccc1.CC(=O)O>>COC(=O)CNC(=O)C(C(C)C)N(Cc1ccccc1)C(=O)C

   1   2   3
---------------
 1:  1.00 0.54 0.10
 2:  0.54 1.00 0.13
 3:  0.10 0.13 1.00


fingerprint generated: 0-7 bonds, 2048bits
```

Scheme 3.5. Quantification of the novelty of reaction by comparing their SMIRKES.

molecular mass in all wells containing cinnamic aldehyde. Thus instead of obtaining the anticipated molecular mass of the products we always saw $M+32$, which corresponds to the formal addition of methanol to the product. Obviously the reaction conditions strongly favor the addition of 1 equivalent of methanol to the double bond of cinnamic aldehyde (Scheme 3.6).

Another useful scaffold, discovered recently by chance in our laboratories during an array synthesis, is now available for combinatorial chemistry [12]. All wells containing 2-picolinic amine reacted in an unexpected way. Detailed inspection of these reactions provided a novel MCR towards 1,2,4-trisubstituted 1*H*-imidazol-4-yl-pyridines. Typical examples and their yields are given in Scheme 3.7. During



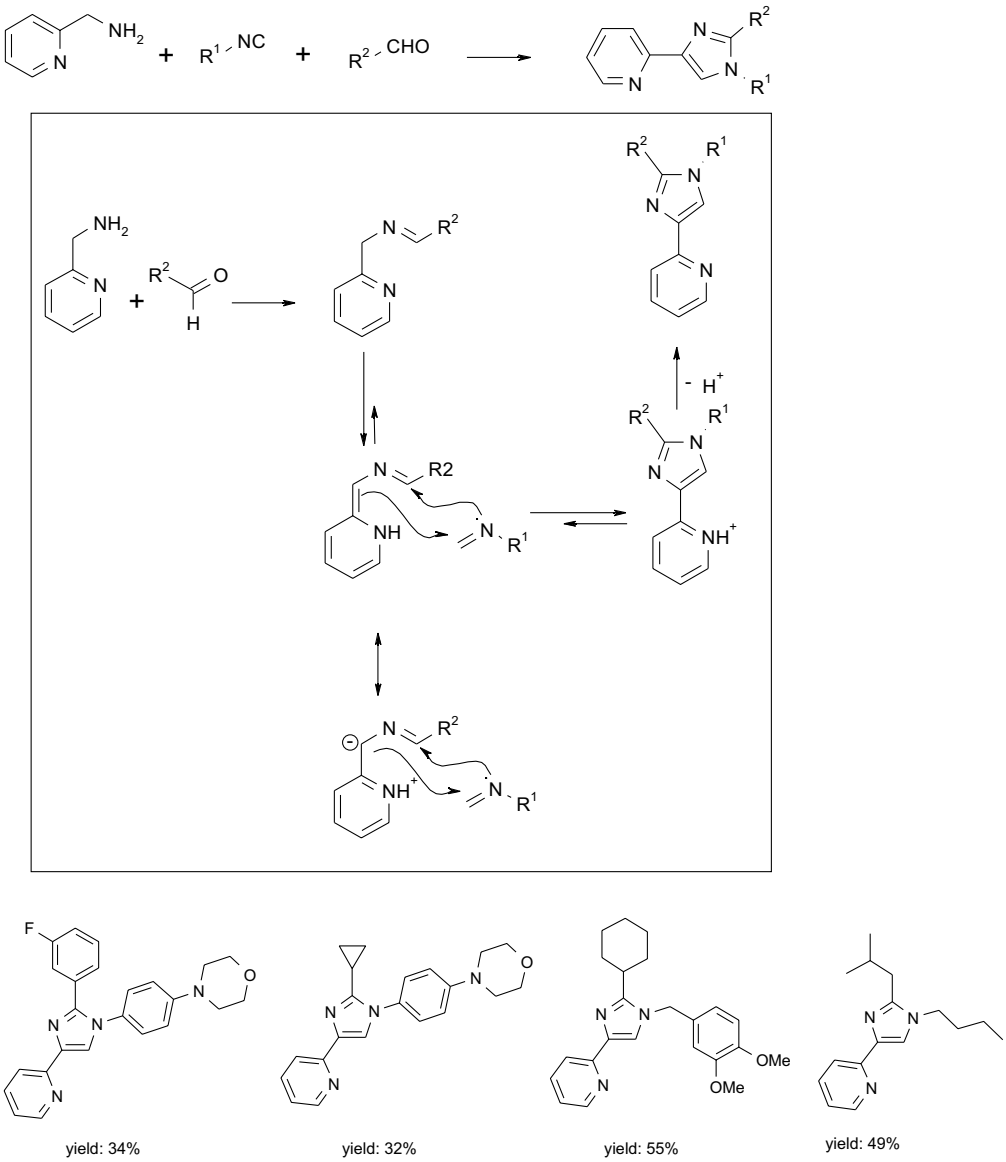
Scheme 3.6. The array synthesis of α-amino acids with aldehydes and isocyanides in the case of cinnamic aldehydes did not afford the expected products but rather the methanol adducts.

optimization of the reaction it turned out that addition of 50 mol% $InCl_3$ gave best results.

To rationalize the reaction the following mechanism is proposed. After forming the Schiff base, the 2-picolinic amine tautomerizes to the corresponding conjugated diene. A [3+2]-cyclo addition leads to the observed imidazole product. The fact that only 2-picolinic amine and not other isomeric picolyl amines reacts in the described manner points to the importance of the protonated pyridine nitrogen in the 2-position. The reaction turned out to be quite general in the selection of the aldehyde and isocyanide components. Several hundred combinations worked without problems in good yields and purities. More mechanistic studies are ongoing.

In another example the MCR of α-aminoacid amides with aldehydes and isocyanides in the presence of a base and subsequent acetic acid treatment was investigated [13]. Based upon a general understanding of the mechanism of the Ugi reaction it was proposed that the Schiff base is formed, followed by the formation of the α-adduct with the isocyanide (Scheme 3.8). This compound was assumed to be the end point of the reaction, and unable to rearrange.

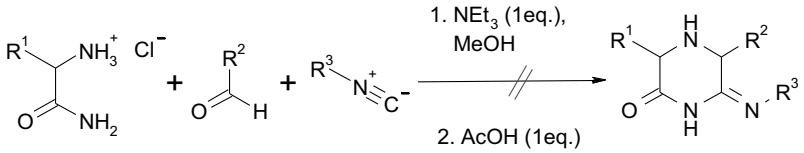
Surprisingly, detailed analysis of several NMR spectra of isolated and purified compounds and a crystal structure analysis revealed the formation of 2-amino-4-cyano-amides. This reaction is the first case in which the oxygen for the newly formed amide bond emerges not from the solvent (H_2O) but rather from the amide bond of a reactant. Also noteworthy is the concomitant nitrile formation from the primary amide, which does not normally occur under such mild conditions. Typical examples and their yields are given in Scheme 3.9.



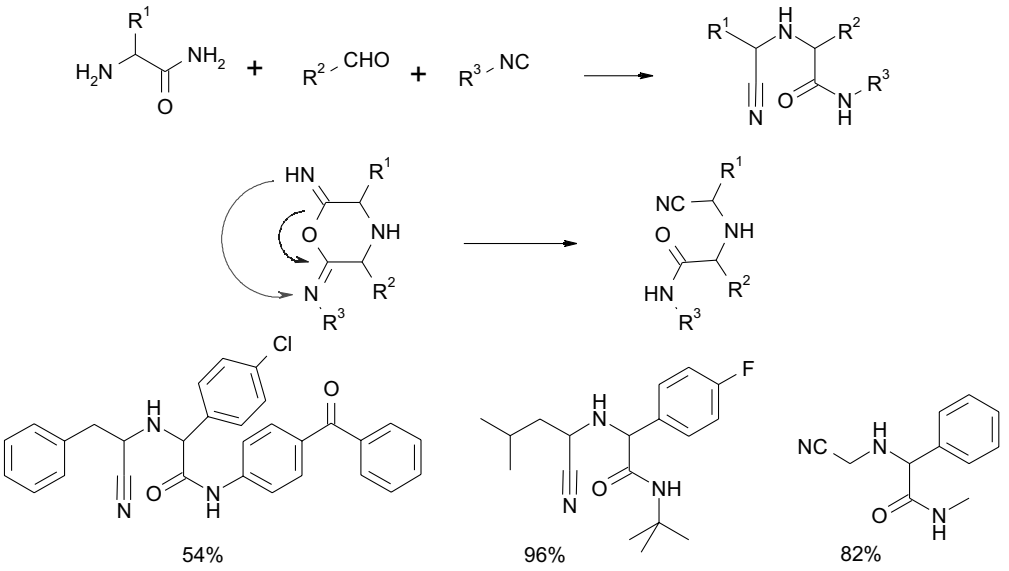
Scheme 3.7. A novel general MCR yielding 1,2,4-trisubsituted imidazoles was found by chance.

3.4
Combinatorial MCR Discovery

An extension of and systematic approach towards discovery by chance is the use of combinatorial chemistry. In a seminal paper [14], Weber and Lacke described a systematic approach involving array synthesis in order to discover novel MCRs. In this



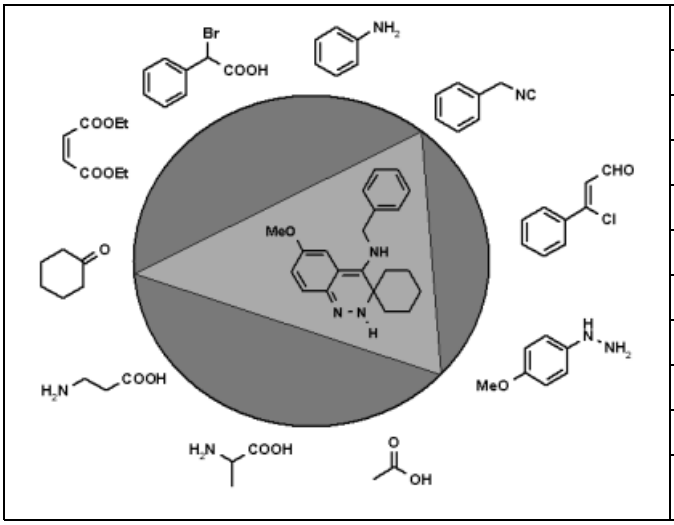
Scheme 3.8. The expected reaction of α-aminoacid amides, aldehydes and isocyanides to form ketopiperazines did not happen.



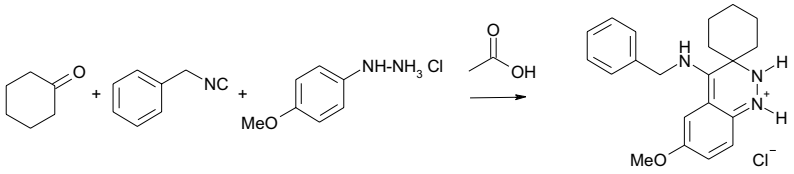
Scheme 3.9. The formation of 2-amino-4-cyano-amides.

approach 10 molecules with different functional groups were allowed to react together in all possible multicomponent fashions. Thus potentially one 10-CR, ten 9-CRs, and so forth are possible. Overall the 1013 combinations of the 10 starting materials are possible according to formula I. With an automatic liquid handling system, 0.1 M solutions of all starting materials were dispensed in all 1013 combinations and reacted at 20 °C for 24 h. All starting materials were chosen for their ready availability with one or more functional groups known to undergo several chemical transformations. The reactions were analyzed by HPLC-MS. Signals above a certain defined intensity threshold, not arising from starting materials or two-component reaction products, were intensively analyzed. The remaining interesting reactions were repeated on a preparative scale and the products isolated. Thus a novel MCR of benzylisocyanide, cyclohexanone and 4-methoxyphenyl hydrazine in the presence of acetic acid as a Brønstedt acid resulting in 2,3-dihydrocinnolines was discovered (Scheme 3.10). Later optimization of the reaction led to a 63% overall yield of the corresponding product.

Similarly Mironov et al. described a novel method of combinatorial searching for



z	n-CR
1	10
10	9
45	8
120	7
210	6
252	5
210	4
120	3
45	2
Σ = **1013**	



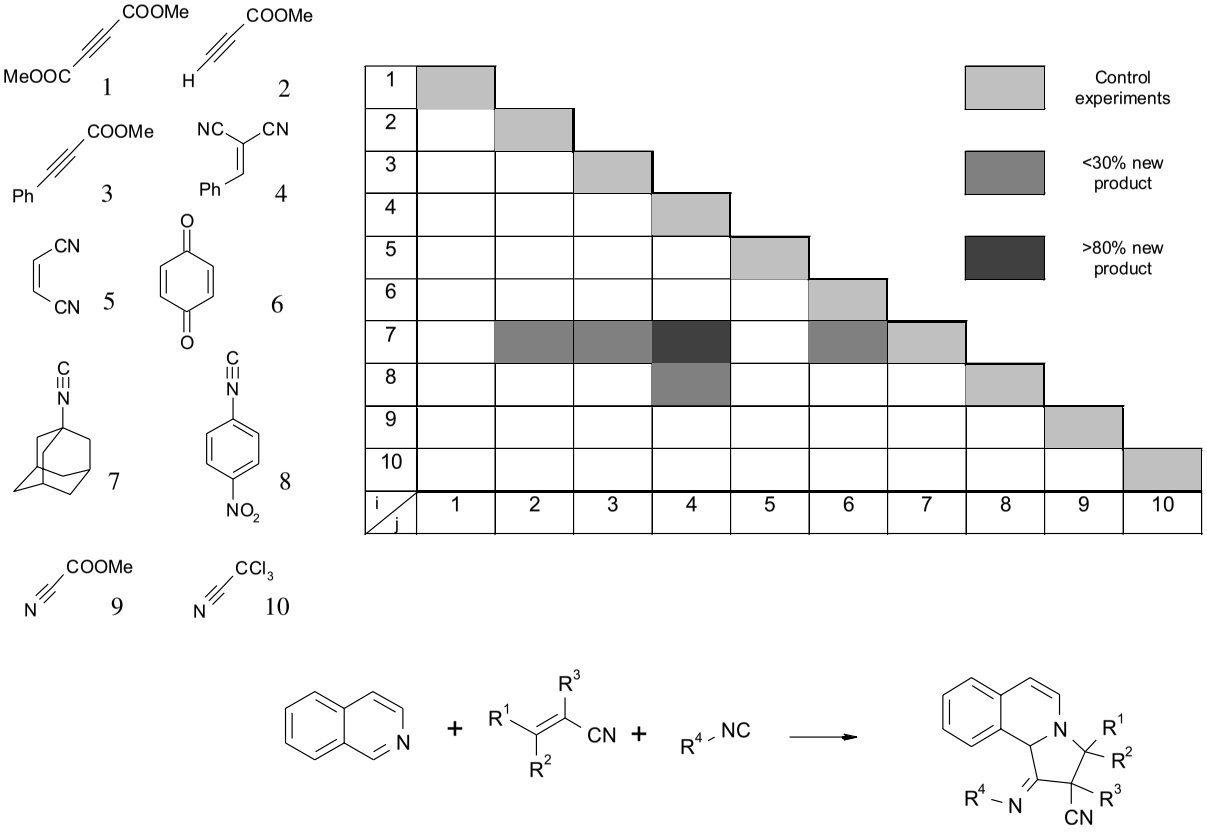
Scheme 3.10. Combinatorial MCRs by Weber et al. The formation of 2,3-dihydrocinnolines from ketones, isocyanides and electron-rich hydrazines was discovered in this way.

MCRs [15]. He found novel MCRs by replacing oligomerization participants by other reactants and could thus transform a poly- or oligomerization into an MCR leading to small molecules. Thus this group described for the first time a novel MCR of gem-diactivated olefins, isocyanides and isoquinolines yielding substituted 2,3-dihydro-10*H*-pyrrolo[2,1-*a*]isoquinoline-1-ones (Scheme 3.11). The reaction was described as having quite wide synthetic usefulness, giving yields between 42 and 90% after crystallization.

Thus the completely random approach to the discovery of new MCRs was transformed in a systematic, semi-rational and powerful way. Future research using this elegant approach will certainly reveal many more novel MCRs.

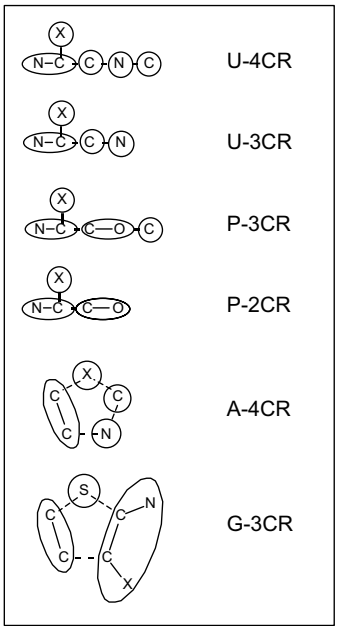
3.5 Discovery by Design

In addition to chance-based discovery, novel IMCRs can also be deliberately designed. For the design process it is important to consider the basic requirements



Scheme 3.11. Combinatorial MCR searching according to Mironov et al. A combinatorial set of different starting materials displaying multiple functional groups (left panel) was subject to HPLC-MS analysis (right panel).

for an MCR. Thus two components react to form a reactive intermediate (e.g. an imine) which combines with a third component. In order to react selectively, the starting material must not incorporate the functional group, e.g. a Schiff's base, that is formed in the intermediate, otherwise random reaction and polymerization takes place. Ideally reaction paths leading to a side product are reversible. Finally an irreversible step is needed to drive the reaction along the desired MCR path. Isocyanide-based MCRs are very helpful in reaction design, since generally many functional groups are compatible with these reactions without being involved in the first MCR, thus allowing for further reaction exploitation. Often these functional groups can be present without any protecting group. Moreover the isocyanide functionality is exothermically and thus irreversible transformed into another functional group, e.g. amide. A topological guide is given in Scheme 3.12 [16]. With the help of this connectivity table of Ugi, Passerini and related products an MCR can be recognized in a molecule and new MCRs discovered. It is important to note that no formal oxidation state is assigned to the atoms; only their connectivity is given.



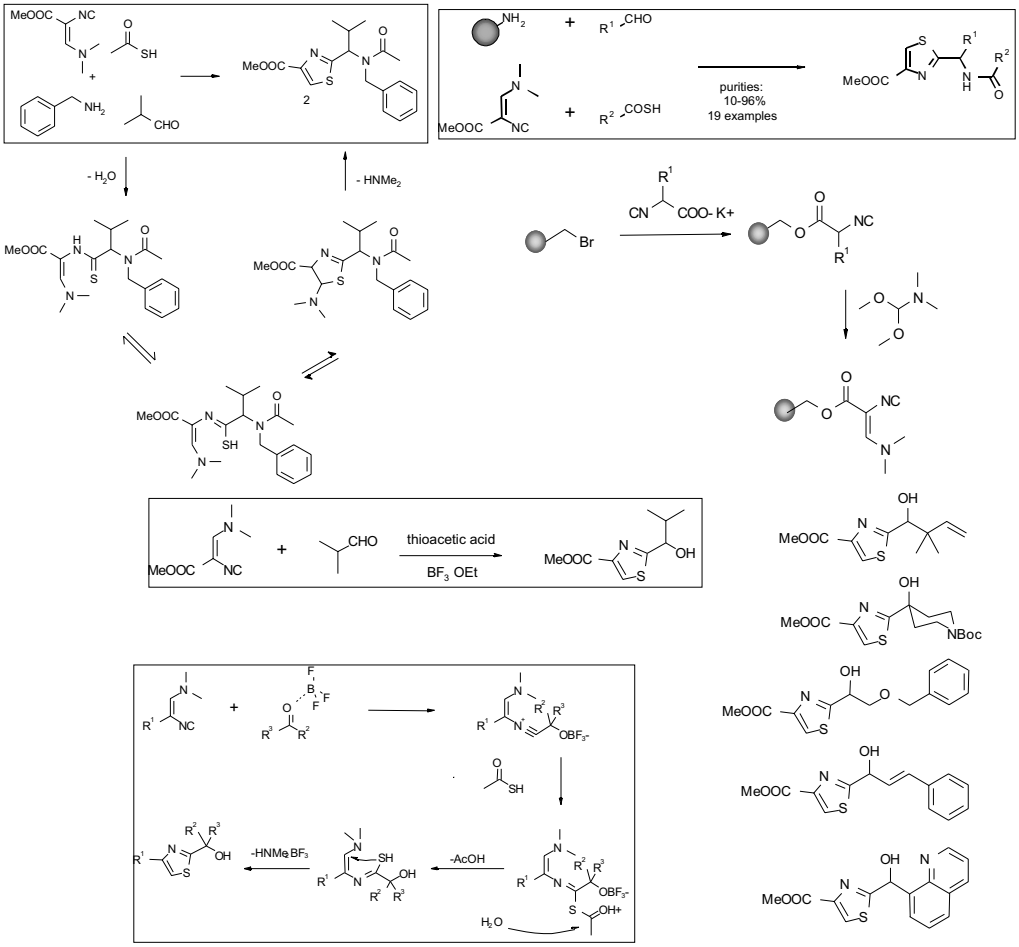
Scheme 3.12. The topological atom connectivity of several MCRs: Ugi-, Passerini-, Asinger- and Gewald variants.

In 1996 we performed a classical U-4CR of primary amines, aldehydes and isocyanides, but instead of using carboxylic acids we employed thiocarboxylic acids [17]. The reaction leads highly chemoselectively to α-aminoacyl thioamides and no trace of α-aminothioacyl amides is found. This finding is not noteworthy *per se* and

could be expected. We were aware that thioamides are the most common precursors for the assembly of thiazoles by the famous Hantzsch synthesis of thioamides and α-bromo ketones. Unfortunately during this reaction only primary thioamides can be used as starting materials. Thus we asked, is there nevertheless a way to use this interesting highly chemoselective Ugi reaction for a multicomponent thiazole synthesis?

Several variants of this useful and novel MCR thiazole synthesis have since been reported, including complexity-oriented syntheses of thiazolo-β-lactams [18], in which two ring systems and five heavy atom bonds are newly formed (2 C–N, 2 C–S, 1 C–C), solid phase synthesis [19], and a Passerini variant of this reaction leading to 2-hydroxymethyl thiazoles [20]. Scheme 3.13 illustrates some of the possibilities [21].

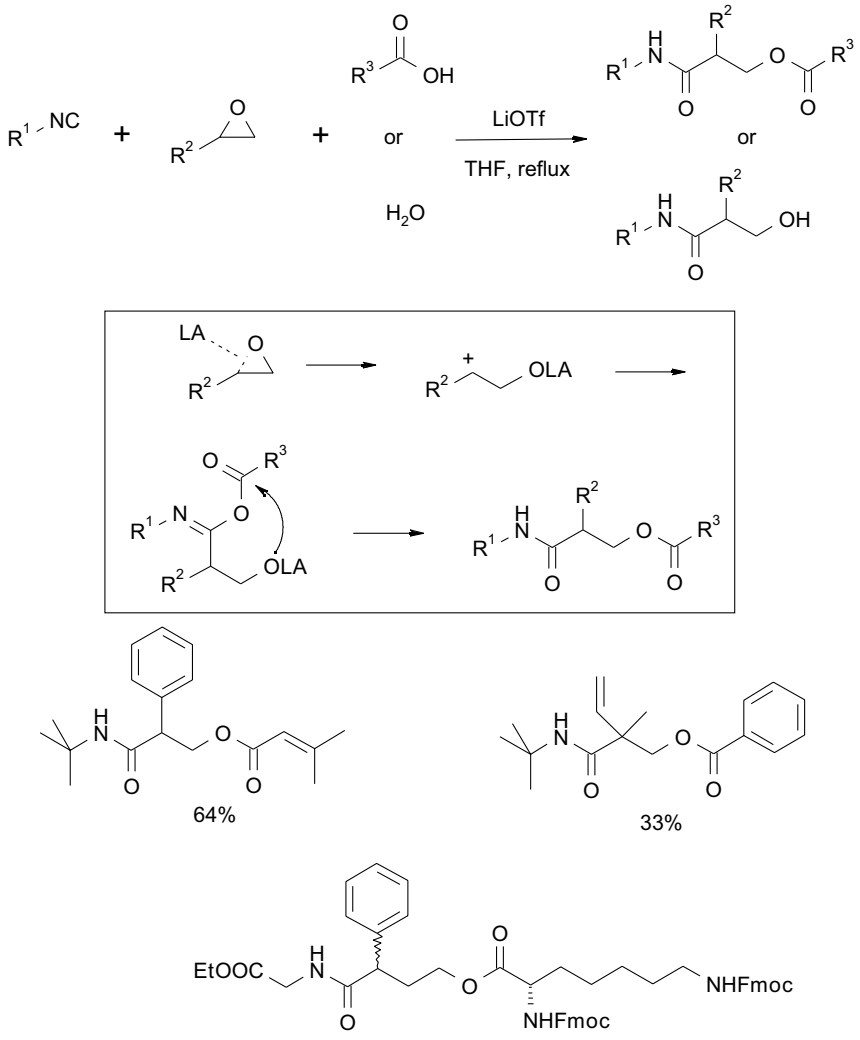
Kern et al. recently designed a novel isocyanide based MCR taking into account



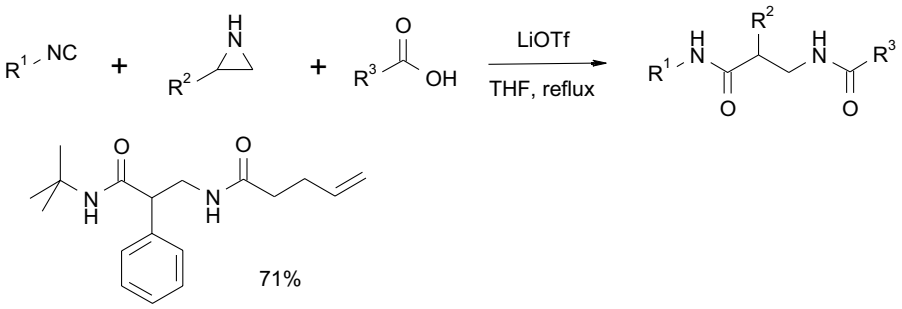
Scheme 3.13. Diverse novel MCR thiazole syntheses.

that epoxides in the presents of Lewis acids can exist as ring-opened carbocations [22]. This carbocation reacts with a carboxylic acid or water and the isocyanide carbon to form an α-adduct, which in analogy to the Passerini reaction mechanism rearranges to the β-hydroxyacyl amide derivative. Thus the outcome of this reaction is a homo-Passerini product. A remarkable variety of epoxides, carboxylic acids and isocyanides react well in this novel MCR. The mechanism and typical examples with their yields are given in Scheme 3.14.

Using the three-membered aziridines instead of epoxides under the same reaction conditions similarly resulted in β-aminoacyl amides, the homo-Ugi products.



Scheme 3.14. A homo-Passerini reaction with epoxides instead of aldehydes.



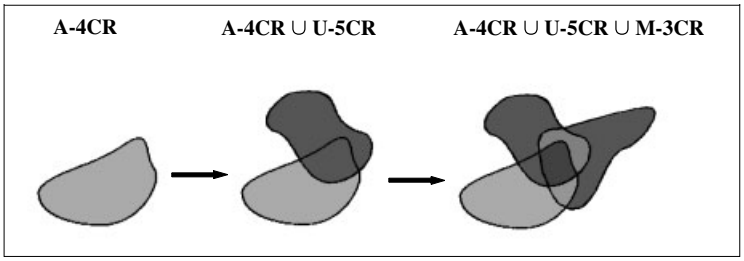
Scheme 3.15. A homo-Ugi reaction with aziridines instead of Schiff bases.

Typical examples with their yields are given in Scheme 3.15. It can be anticipated that this reaction will have much utility in combinatorial chemistry as well as in the total synthesis of natural products, especially if a stereo-selective variation can be established.

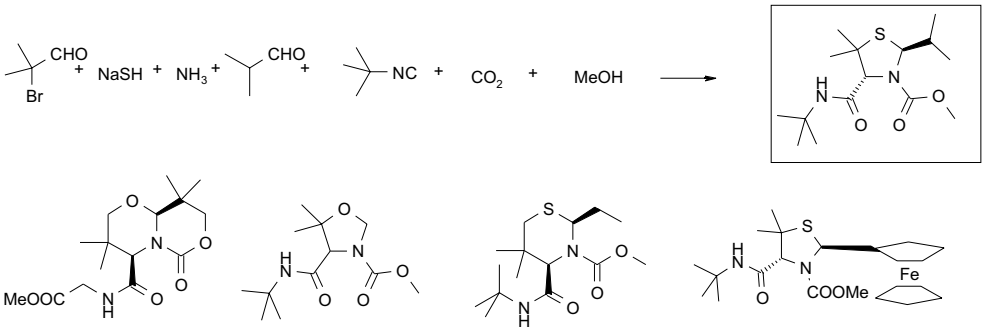
Many more designed MCRs have been published and will be mentioned in different chapters of this book, e.g. Hulme's UDC (Ugi–deboc–cyclization) approach and Zhu's interesting work.

3.6 The Union of MCRs

Another concept towards novel MCRs was established in 1993 by us: the union of MCRs [23]. Our objective was to find reactions with maximal numbers of participating starting materials. Thus we considered combining several MCRs, since a single MCR already contains a high number of educts. Two MCRs can be combined if the product or an advanced intermediate of the first MCR is a intermediate or starting material of the second MCR. The starting materials should ideally not have the possibility for irreversible side reactions under the reaction conditions used. Scheme 3.16 illustrates this approach.



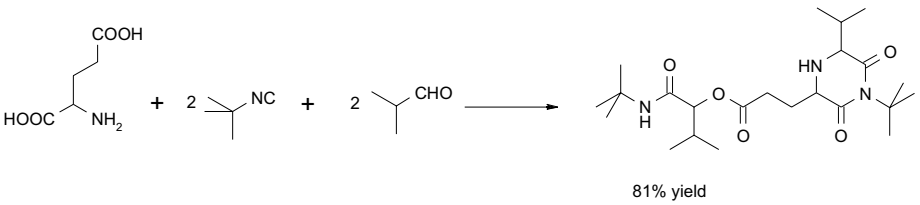
Scheme 3.16. Schematic representation of the union of MCRs. An Asinger 4CR (A-4CR) is combined with an Ugi 5CR (U-5CR) and a Mannich 3CR (M-3CR) resulting in the union of these three MCRs.



Scheme 3.17. The union of an A-4CR with a U-5CR, the first 7-CR.

The first such reaction we performed was between the seven components α-bromo isobutyric aldehyde, isobutyric aldehyde, ammonia, sodium hydrogen sulfide, *tert*-butyl isocyanide, carbon dioxide and methanol (Scheme 3.17). It comprises the union of the Asinger reaction with a variation of the Ugi reaction. During the A-4CR of α-bromo aldehydes, aldehydes, ammonia and sodium hydrogen sulfide a thiazoline is formed, which is a heterocyclic Schiff base. The Schiff base is a crucial intermediate in Ugi-type reactions. In order to augment the number of starting materials we did not choose a simple carboxylic acid, but rather an acid composed of carbon dioxide and alcohol, a carbonic acid monoester. The reaction is thus performed under a carbon dioxide pressure of 40–50 bar. The yield of the 7-CR is a synthetically useful 45%, which is quite remarkable taking into account the possible side reactions. Several more AU-7CRs could be performed leading to five- and six-membered thiazolidines, oxazolidines, thiazines and oxazines [24]. To date this still constitutes the reaction involving the greatest number of starting materials.

Another example of the strategy of union of MCRs was performed by Ugi et al. This involved the union of a U-5C-4CR with a P-3CR (Scheme 3.18). Glutaric acid or aspartic acid reacts in methanol with one equivalent of aldehyde and isocyanide to form the corresponding Ugi product, which in a second step without isolation of the intermediate reacts with the remaining carboxylic acid functionality and one equivalent of isocyanide and aldehyde to yield the Passerini product [25].



Scheme 3.18. The union of a U-5C-4CR with a P-3CR.

3.7 Outlook

Novel access to diverse backbones is of crucial interest for several areas of organic chemistry. For example, a novel, previously undescribed scaffold with biological activity provides a patent-free chemical space. Moreover, if this scaffold is accessible by MCR chemistry this has several advantages of resource and time saving. Often more variations around the principal scheme are possible.

Finally the discovery of novel MCRs touches a very basic task of chemists and poses an intellectually challenging task.

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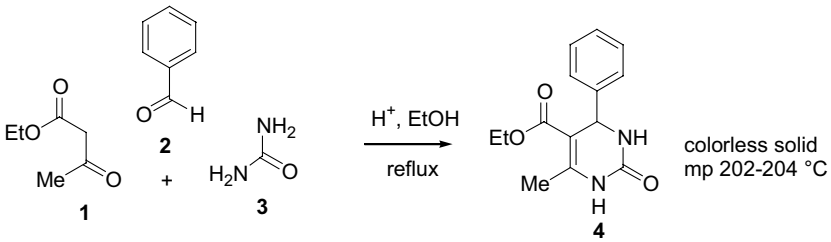
4
The Biginelli Reaction

C. Oliver Kappe

4.1
Introduction

In 1893, the Italian chemist Pietro Biginelli (University of Florence) for the first time reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate **1**, benzaldehyde **2**, and urea **3** [1]. The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling the reaction mixture was identified as 3,4-dihydropyrimidin-2(1*H*)-one **4** (Scheme 4.1) [2]. This reaction is nowadays referred to as the ''Biginelli reaction'', ''Biginelli condensation'' or as the ''Biginelli dihydropyrimidine synthesis''.



Scheme 4.1. The original Biginelli dihydropyrimidine condensation (1893).

While the early examples of this cyclocondensation process typically involved a β-ketoester, aromatic aldehyde and urea, the scope of this heterocycle synthesis has now been extended considerably by variation of all three building blocks, allowing access to a large number of multifunctionalized pyrimidine derivatives. For this particular heterocyclic scaffold the acronym DHPM has been adopted in the literature and is also used throughout this chapter. Owing to the importance of multicomponent reactions in combinatorial chemistry there has been renewed interest in the Biginelli reaction, and the number of publications and patents describing

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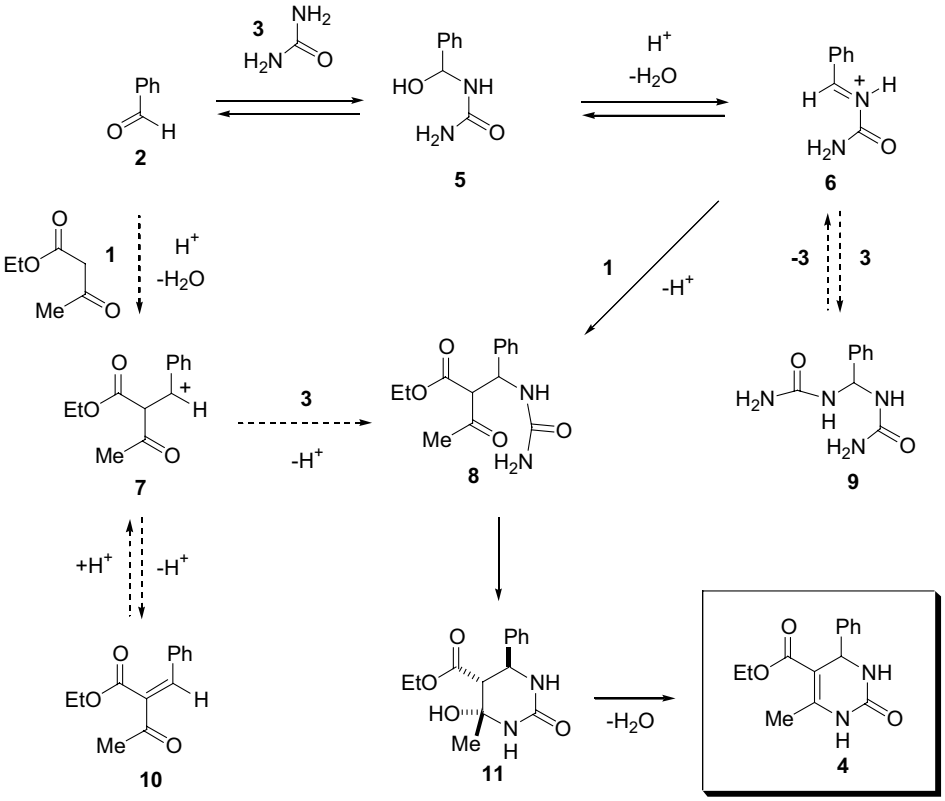
the synthesis of novel DHPM analogues is constantly growing. In this chapter, all three-component condensations involving suitable CH-acidic carbonyl compounds, aldehydes, and urea-type building blocks following the Biginelli concept are covered. Since a number of review articles and monographs on various aspects of the Biginelli reaction have appeared [3–7], the present work will emphasize advances made in the field in the last few years.

4.2 Mechanistic Studies

The mechanism of the Biginelli reaction has been the subject of some debate over the past decades. Early work by Folkers and Johnson suggested that bisureide **9**, the primary bimolecular condensation product of benzaldehyde **2** and urea **3**, is the first intermediate in this reaction [8]. In 1973 Sweet and Fissekis proposed a different pathway and suggested that carbenium ion **7**, produced by an acid-catalyzed aldol reaction of benzaldehyde **2** with ethyl acetoacetate **1** is formed in the first and rate-limiting step of the Biginelli condensation (**2** → **7** → **8**) [9]. The mechanism was reinvestigated in 1997 using $^{1}H/^{13}C$ NMR spectroscopy and trapping experiments, and it has been established that the key step in this sequence involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate of type **6** from the aldehyde **2** and urea **3** precursors (Scheme 4.2) [10]. Interception of the iminium ion **6** by ethyl acetoacetate **1**, presumably through its enol tautomer, produces open-chain ureide **8**, which subsequently cyclizes to the hexahydropyrimidine **11**. Acid-catalyzed elimination of water from **11** ultimately leads to the final DHPM product **4**. The reaction mechanism can therefore be classified as an α-amidoalkylation, or more specifically as an α-ureidoalkylation [11]. The alternative "carbenium ion mechanism" **2** → **7** → **8** [9] does not constitute a major pathway; however, small amounts of enone **10** are sometimes observed as a by-product [10].

Consistent with this mechanistic formulation, monosubstituted (thio)ureas furnish exclusively the N1-alkylated DHPMs, whereas N,N′-disubstituted ureas do not react under the reaction conditions [3]. Although the highly reactive *N*-acyliminium ion species **6** could not be isolated or directly observed, further evidence for the proposed mechanism was obtained by isolation of intermediates **12** and **13** (Figure 4.1), employing sterically bulky [12] or electron-deficient acetoacetates [13] respectively. The relative stereochemistry in hexahydropyrimidine **13** was established by an X-ray analysis [14]. In fact, a number of hexahydropyrimidines closely related to **13** have been synthesized using perfluorinated 1,3-dicarbonyl compounds or β-keto esters as building blocks in the Biginelli condensation [15, 16]. Elucidation of the mechanism of the Biginelli multicomponent reaction has prompted renewed interest in improving the efficiency of this process. Novel catalysts, in particular Lewis acids, are nowadays used to favor the formation and interception of the key *N*-acyliminium ion intermediates (see Section 4.4). It is proposed that these Lewis acids stabilize *N*-acyliminium ions of type **6** by coordina-



Scheme 4.2. The mechanism of the Biginelli reaction.

tion to the urea oxygen [12]. In some cases, a chelation of the 1,3-dicarbonyl component **1** by suitable Lewis acids – stabilizing the enol tautomer – has also been inferred [12].

4.3 Reaction Conditions

Today there is a great variety of suitable reaction conditions for Biginelli condensations. For the condensation of ethyl acetoacetate with benzaldehyde and urea, at

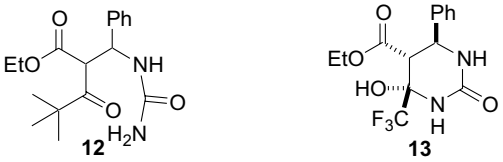


Fig. 4.1. Intermediates isolated in the Biginelli reaction.

least 100 different experimental conditions are now known [7]. Traditionally, Biginelli condensations are carried out in a solvent such as ethanol or methanol, but more recently aprotic solvents such as tetrahydrofuran [12, 13, 17, 18], dioxane [19] or acetonitrile [20–24] have also been used successfully. In some cases, it is necessary to use acetic acid as a solvent [25–27]. This is particularly important in cases where condensation of an aromatic aldehyde and urea will lead to precipitation of an insoluble bisureide derivative of type **9** [10], which might not react further along the desired pathway outlined in Scheme 4.2 when ethanol is used as a solvent. Biginelli reactions in water [28, 29] and ionic liquids [30, 31] are also known. A recent trend is to perform the condensation without any solvent [32, 33], with the components either adsorbed on an inorganic support [34] or in the presence of a suitable catalyst [35].

The Biginelli condensation is strongly dependent on the amount of acidic catalyst present in the reaction medium [8]. Traditionally, strong Brønsted acids such as hydrochloric or sulfuric acid have been employed [3], but nowadays the use of Lewis acids such as BF_3OEt_2 and CuCl [12], $LaCl_3$ [36, 37], $FeCl_3$ [38–44], $NiCl_2$ [41, 45], $Yb(OTf)_3$ [35, 46, 47], $La(OTf)_3$ [48], $InCl_3$ [49], $InBr_3$ [50], $In(OTf)_3$ [197], LiBr [18, 22], $CoCl_2$ [37], $BiCl_3$ [20], $LiClO_4$ [51], $Mn(OAc)_3$ [52], $ZrCl_4$ [53], $Cu(OTf)_2$ [21], $CuCl_2$ [198], $Bi(OTf)_3$ [54], $CeCl_3$ [29], VCl_3 [55], $Zn(OTf)_2$ [56, 57], $Sm(NO_3)_3$ [58], $SmCl_3$ [59] is prevalent. It is also possible to use a solid acid catalyst, such as an acidic clay [34, 60–65], a zeolite [66], an ion-exchange material such as Amberlyst [25], or a heteropolyacid such as $Ag_3PW_{12}O_{40}$ [199]. In addition, materials such as silica/H_2SO_4 [67] or silica aerogel–iron oxide nanocomposites [68] have been reported as efficient supported catalysts for the Biginelli reaction. Other reported reaction mediators include amidosulfonic acid [69–71], CBr_4 [72], NH_4Cl [73], *N*-butyl-*N*,*N*-dimethyl-α-phenylethylammonium bromide [74], *p*-toluenesulfonic acid [75–77], tartaric acid [3], polyphosphate ester [13, 78, 79], TMSCl/NaI [23], TMSCl/DMF [24], TMSOTf [200], boric acid [80], KH_2PO_4 [81], $KHSO_4$ [201], $CdSO_4$ [202], triphenylphosphonium perchlorate [203], and iodine [8]. It should be emphasized, however, that despite the plethora of catalysts and mediators that have been reported to be effective in facilitating the Biginelli condensation, some reports also comment on the fact that the reactions also proceed without any catalyst by just mixing and heating the neat reagents [32].

Biginelli condensations are generally fairly slow at room temperature [10], so activation by heating is necessary. Apart from traditional heating methods, microwave dielectric heating employing some of the solvent/catalyst systems mentioned above has been used to shorten reaction times significantly [25, 33, 40, 42, 43, 60–62, 76–79, 82–93, 197]. It is also feasible to carry out Biginelli reactions using ultrasound activation [71, 94], by IR irradiation [63] or by photochemical methods [95].

As far as the molar ratio of building blocks is concerned, Biginelli reactions generally employ an excess of the CH-acidic carbonyl or urea components, rather than an excess of the aldehyde. As DHPM products are usually only sparingly soluble in solvents such as methanol or ethanol at room temperature, work-up in many cases

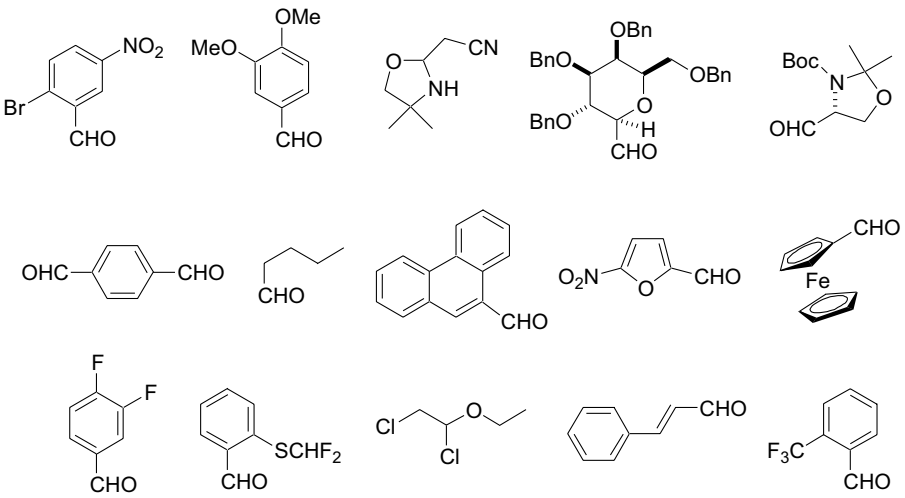


Fig. 4.2. Aldehyde building blocks used in the Biginelli reaction.

simply involves isolation of the product by filtration. It is also possible to precipitate the product by addition of water.

4.4 Building Blocks

Out of the three building blocks in the Biginelli reaction it is the aldehyde component that can be varied to the largest extent (Figure 4.2). In general, the reaction works best with aromatic aldehydes. These can be substituted in the *o*-, *m*- or *p*-position with either electron-withdrawing or electron-donating groups. Good yields are usually obtained with *m*- or *p*-substituted aromatic aldehydes carrying electron-withdrawing substituents. For *o*-substituted benzaldehydes having bulky substituents, yields can be significantly lower. Heterocyclic aldehydes derived from furan, thiophene, and pyridine rings also generally furnish acceptable yields of the corresponding DHPM products.

Aliphatic aldehydes typically provide only moderate yields in the Biginelli reaction unless special reaction conditions are employed, such as Lewis-acid catalysts or solvent-free methods, or the aldehydes are used in protected form [96]. The C4-unsubstituted DHPM can be prepared in a similar manner employing suitable formaldehyde synthons [96]. Of particular interest are reactions where the aldehyde component is derived from a carbohydrate. In such transformations, DHPMs having a sugar-like moiety in position 4 (*C*-nucleoside analogues) are obtained (see Section 4.7) [97–106]. Also of interest is the use of masked amino acids as building blocks [107, 108]. In a few cases, bisaldehydes have been used as synthons in Biginelli reactions [89, 109, 110].

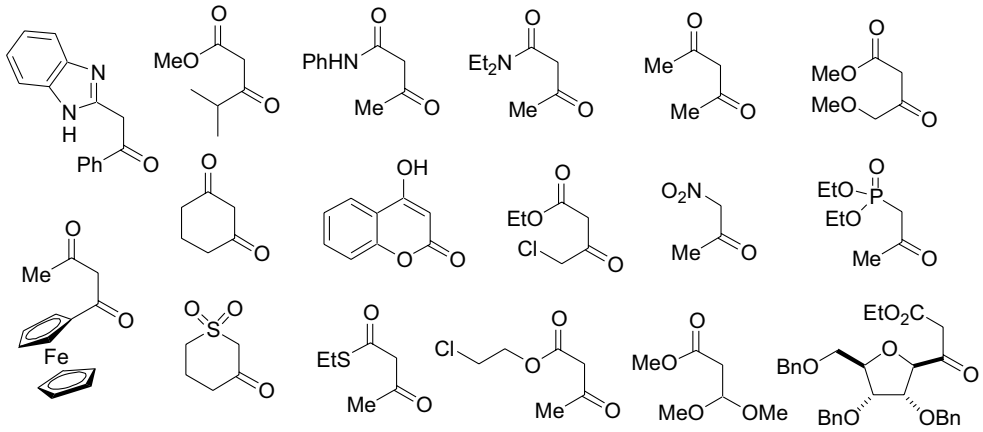


Fig. 4.3. CH-Acidic carbonyl building blocks used in the Biginelli reaction.

Traditionally, simple alkyl acetoacetates are employed as CH-acidic carbonyl building blocks, but other types of 3-oxoalkanoic esters or thioesters can also be used successfully. With methyl 4-chloroacetoacetate, for example, the corresponding 6-chloromethyl-substituted DHPMs, which can serve as valuable templates for further synthetic transformations, are obtained [111]. Benzoylacetic esters react analogously, but yields are usually significantly lower and the overall condensation process is more sluggish. Primary, secondary, and tertiary acetoacetamides can be used in place of esters to produce pyrimidine-5-carboxamides. In addition, β-diketones serve as viable substrates in Biginelli reactions. Condensations can also be achieved employing cyclic β-diketones such as cyclohexane-1,3-dione [112, 113] and other cyclic β-dicarbonyl compounds (Figure 4.3) [114, 115].

If a C6-unsubstituted DHPM derivative needs to be synthesized, the corresponding 3-oxopropanoic ester derivative in which the aldehyde function is masked as an acetal can be employed [116]. Apart from ester-derived CH-acidic carbonyl compounds, nitroacetone also serves as a good building block, leading to 5-nitro-substituted DHPM derivatives in generally high yields [117].

The urea is the component in the Biginelli reaction that faces the most restrictions in terms of allowed structural diversity (Figure 4.4). Therefore, most of the published examples involve urea itself as a building block. However, simple monosubstituted alkyl ureas generally react equally well, in a regiospecific manner (see above), to provide good yields of N1-substituted DHPMs. Thiourea and substituted

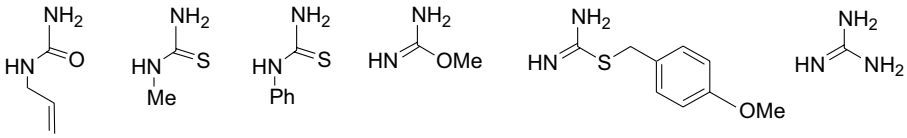


Fig. 4.4. Urea-type building blocks used in the Biginelli reaction.

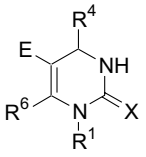
thioureas follow the same general rules as ureas, although longer reaction times are required to achieve good conversions. Yields are typically lower when compared to the corresponding urea derivatives. In some instances it is also possible to react protected urea or thioureas (isoureas), or guanidines under weak basic conditions with the aldehyde and CH-acidic carbonyl component (or with a precondensed Knoevenagel-type enone) to yield the corresponding protected DHPMs [118, 119]. This latter method, using precondensed enones **10** as building blocks has been frequently referred to as the "Atwal modification" of the Biginelli reaction (see Scheme 4.5) [120–122].

A tabular literature survey with about 650 entries listing all dihydropyrimidine derivatives of type **14** prepared *via* three-component Biginelli reactions up to the year 2001 has been published [7].

4.5 Synthesis of Combinatorial Libraries

Given the diversity in building-block selection that is tolerated in the Biginelli reaction it is evident that a large number of DHPM derivatives of general formula **14** can be synthesized by combination of a relatively small number of individual building blocks. Employing 20 aldehydes (point of diversity R^4), 10 CH-acidic carbonyl derivatives (points of diversity E and R^6) and 5 (thio)urea analogues (points of diversity X and R^1) in a Biginelli-type condensation would lead to a library of 1000 DHPM compounds, with a total of five diversity points around the dihydropyrimidine core. It is therefore not surprising that a literature search for the general DHPM structure **14** in the Chemical Abstracts Registry database leads to well over 10 000 hits.

Since the experimental conditions for the traditional Biginelli reaction are quite straightforward, small libraries of DHPMs are readily accessible by parallel synthesis. Along these lines the generation of a 140-member single compound DHPM library by combination of 25 aldehydes, 6 ureas/thioureas, and 7 acetoacetates or acetoamides under standard reaction conditions has been reported [123, 124]. More rapid approaches make use of microwave-enhanced solution-phase protocols [88, 89, 125]. Apart from these conventional solution-phase methods, it is also possible to employ polymer-supported reagents to aid in the purification and work-up protocol. Polymer-assisted solution-phase chemistry using polymer-supported



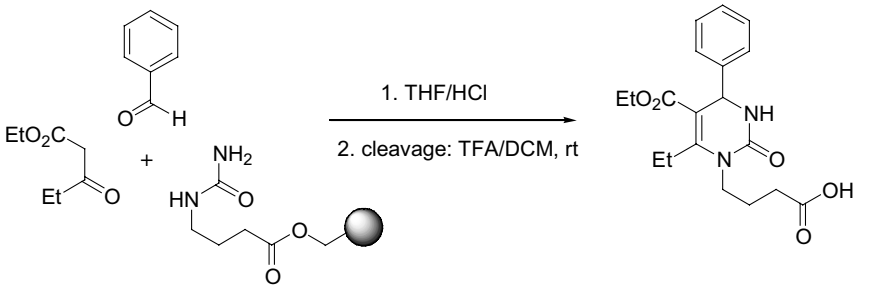
14

R^1 = H, alkyl
R^4 = H, alkyl, (het)aryl, carbohydrate
R^6 = H, alkyl, aryl
E = ester, acyl, amide, nitro, nitrile, phosphono
X = O, S, NR

Fig. 4.5. Combinatorial diversity in dihydropyrimidines synthesized via Biginelli condensation.

Lewis acid (Yb-(III)-reagent supported on Amberlyst 15) in combination with polymer-supported urea scavenging resins (Amberlyst 15 and Ambersep 900 OH) permits a rapid parallel Biginelli synthesis with a simple and efficient purification strategy [126].

Solid-phase protocols allow an even higher degree of throughput and automation as shown in the example in Scheme 4.3. In this example, a γ-aminobutyric acid-derived urea was attached to Wang resin using standard procedures. The resulting polymer-bound urea was then condensed with excess of a β-ketoester and aromatic aldehydes in the presence of a catalytic amount of hydrochloric acid to afford the corresponding immobilized DHPMs. Subsequent cleavage of the product from the polystyrene resin with trifluoroacetic acid provided DHPMs in high yields and excellent purities [17].

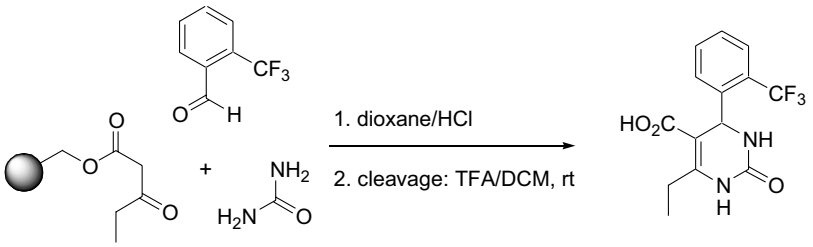


Scheme 4.3. Solid-phase Biginelli condensation using γ-aminobutyric acid-derived urea on Wang resin.

In a variation of the above protocol, the Biginelli synthesis was easily adapted to fluorous-phase conditions [127, 128]. Here a fluorous urea derivative was prepared by attaching a suitable fluorous tag to hydroxyethylurea. The fluorous urea was then condensed with excess of acetoacetates and aldehydes in a suitable solvent containing hydrochloric acid. After extraction of the fluorous DHPMs with fluorous solvent, desilylation with tetrabutylammonium fluoride followed by extractive purification provided the "organic" Biginelli products in good overall yields. Considering the simple experimental techniques used in this fluorous chemistry, automation should be feasible, thus allowing the preparation of DHPM libraries.

In addition to the methods described above where the urea component is linked to a solid (or fluorous) support, it is also possible to link the acetoacetate building block to the solid support, as shown in the example in Scheme 4.4. Thus, Biginelli condensation of Wang-bound acetoacetates with excess aldehydes and urea/thiourea provides the desired DHPMs on the solid support. Subsequent cleavage with trifluoroacetic acid furnishes the free carboxylic acids in high overall yields [19].

There are alternative solid-phase protocols described in the literature for the generation of DHPMs, not *via* the classical three-component Biginelli approach but through related modifications [129–131]. Furthermore, there have been reports de-

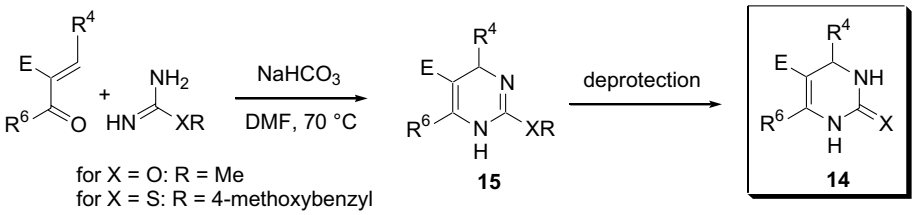


Scheme 4.4. Solid-phase Biginelli condensation using Wang resin-bound acetoacetates.

scribing the synthesis of Biginelli libraries using soluble polymer and dendrimer-supported syntheses [132–134]. By employing any of the solid-phase synthesis methods described above, large libraries of DHPMs can potentially be generated in a relatively straightforward fashion. A review has detailed the preparation of DHPM libraries via Biginelli and related types of cyclization [6].

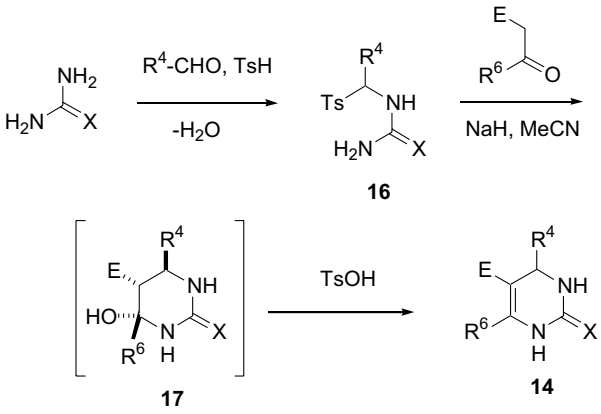
4.6
Alternative Synthetic Strategies

Apart from the traditional Biginelli condensation, only a few synthetic methods lead to DHPMs. Since most of these protocols lack the experimental and conceptual simplicity of the Biginelli one-pot, one-step procedure none of these have real significance today or can compete with the original Biginelli MCR approach . One noticeable exception is the so-called ''Atwal modification'' of the Biginelli reaction [120–122]. Here, an enone is first condensed with a suitable protected urea or thiourea derivative under almost neutral conditions. Deprotection of the resulting 1,4-dihydropyrimidine **15** with HCl (for X = O) or TFA/EtSH (for X = S, TFA = trifluoroacetic acid) leads to the desired DHPMs **14** (Scheme 4.5). Although this method requires prior synthesis of enones via Knoevenagel condensation, its reliability and broad applicability makes it an attractive alternative to the traditional one-step Biginelli condensation. In addition, 1,4-dihydropyrimidines **15** can be acylated regiospecifically at N3, thereby making pharmacologically important DHPM analogues readily accessible [120].



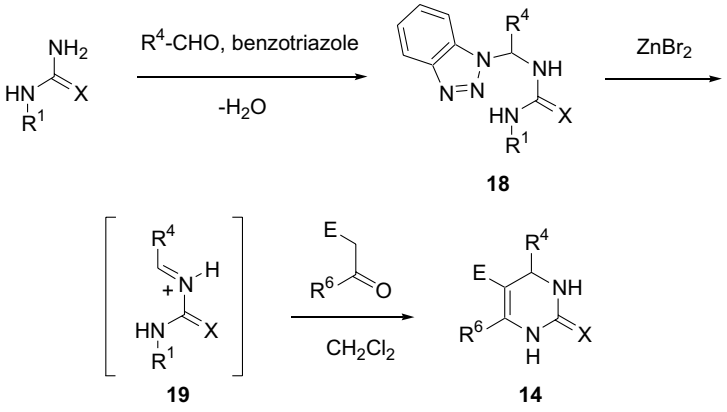
Scheme 4.5. The Atwal modification of the Biginelli reaction.

One other novel approach to DHPMs has been described by Shutalev et al. and is outlined in Scheme 4.6 [135]. This synthesis is based on the condensation of readily available α-tosyl-substituted (thio)ureas **16** with the (*in situ* prepared) enolates of acetoacetates or 1,3-dicarbonyl compounds. The resulting hexahydropyrimidines **17** need not be isolated and can be converted directly into DHPMs **14**. This method works particularly well for aliphatic aldehydes and thioureas and produces high overall yields of the desired target compounds.



Scheme 4.6. The Shutalev approach to dihydropyrimidines.

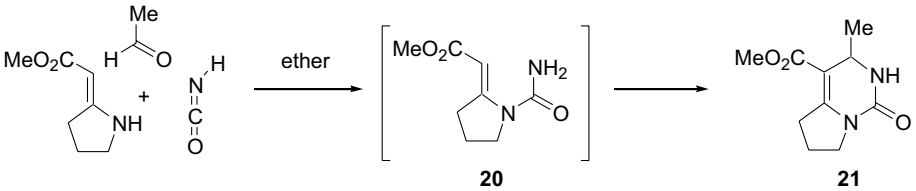
A somewhat related approach that makes use of benzotriazole as synthetic auxiliary has been reported (Scheme 4.7). Here, the aldehyde and urea components are first condensed in the presence of benzotriazole to form aminal **18**, which is more reactive than the bisureide **9** (see Scheme 4.2) in terms of the subsequent forma-



Scheme 4.7. Benzotriazole-mediated Biginelli condensations.

tion of the key *N*-acyliminium ion intermediate **19**. Treatment of aminal **18** with the Lewis acid $ZnBr_2$ in refluxing 1,2-dichloroethane in the presence of the CH-acidic carbonyl compound provides the desired DHPMs **14** in high yield [136].

A conceptually different approach to dihydropyrimidine analogues was developed by Kishi and co-workers (Scheme 4.8) [137, 138]. The trimolecular room-temperature condensation of an enamine, acetaldehyde, and isocyanic acid provides the bicyclic dihydropyrimidine derivative **21**. With some modification, this strategy was initially employed toward a stereospecific [138, 139] and later an enantioselective [140] synthesis of the natural product saxitoxin. Recent investigations by Elliott and coworkers have shown that substituted isocyanates can also be employed in this method [141–146], but a more general modification of this trimolecular condensation towards monocyclic dihydropyrimidine derivatives of the Biginelli type has not yet been reported.



Scheme 4.8. Three-component coupling of enamines, aldehydes, and isocyanates developed by Kishi.

4.7 Related Multicomponent Reactions

Apart from the traditional Biginelli three-component condensation, there are a number of related processes in which similar building blocks are employed, but the structure of the final product differs from a Biginelli DHPM. Alternatively, uncommon building blocks have been used by some authors, and these will also be covered in this section. One example of the latter category is the use of C-glycosylated substrates in the Biginelli condensation. Dondoni and coworkers have prepared a number of dihydropyrimidone glycoconjugates where the sugar residue was installed at the N1, C4, or C6 position in the monoglycosylated derivatives and at both the C4 and C6 positions in the bisglycosylated products (Figure 4.6) [105, 106]. The mono- and bisglycosylated products were obtained as mixtures of diastereomers with good to excellent selectivities due to asymmetric induction by the sugar residue in the formation of the C4 stereocenter of the dihydropyrimidine ring. Given the availability of various glycosylated aldehydes, ureas, and ketoesters, this methodology should permit access to combinatorial libraries of glycosylated DHPM derivatives with a wide range of structural and stereochemical elements of diversity.

The same group of authors has also utilized the Garner aldehyde in Biginelli reactions (Scheme 4.9), and obtained 4-oxazolidinyl-dihydropyrimidine **22** in fair

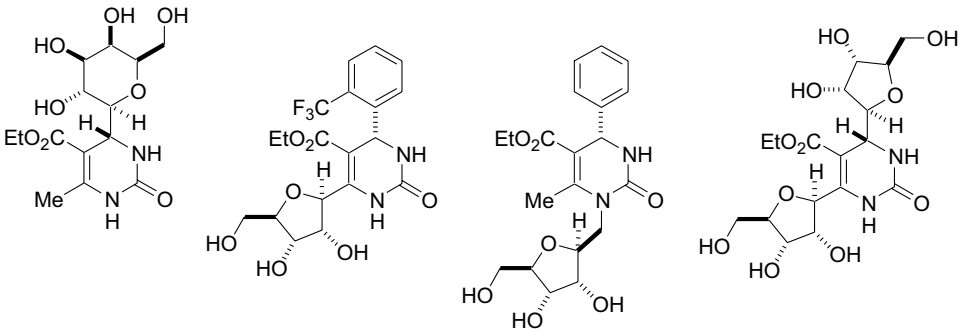
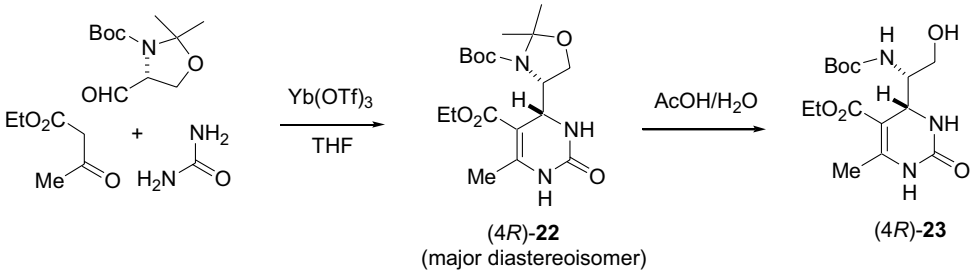


Fig. 4.6. Mono-and bisglycosylated DHPM derivatives.

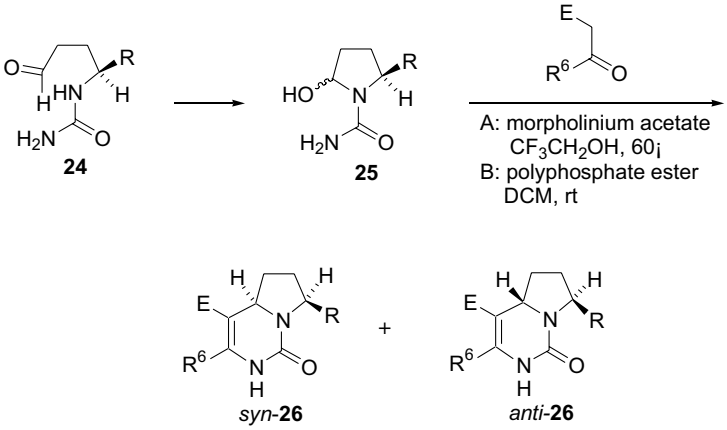


Scheme 4.9. Biginelli condensations with the Garner aldehyde.

yield as a 5:1 mixture of diastereomers owing to the formation of the stereocenter at C4 of the dihydropyrimidine ring [107]. Removal of the acetonide protective group under standard conditions transformed **22** into the *N*-Boc amino alcohol **23**.

Special variants of the Biginelli reaction are intramolecular or so-called tethered Biginelli condensations developed by Overman and co-workers, in which the aldehyde and urea components are linked together in one building block (Scheme 4.10) [147–156, 204]. The "tethered Biginelli strategy" has been used in the synthesis of various polycyclic guanidinium marine natural products such as the batzelladine alkaloids, which all have the hexahydropyrrolo[1,2-*c*]pyrimidine fragment **26** in common and display a range of interesting biological activities (Figure 4.7) [157]. For example, condensation of the chiral hemiaminal precursor **25** with a suitable β-ketoester leads to the desired hexahydropyrrolo[1,2-*c*]pyrimidine scaffold [147]. Importantly, depending on the reaction conditions (A or B), both the syn and anti stereoisomers of **26** can be obtained with high selectivities.

As mentioned above, cyclic β-diketones such as cyclohexane-1,3-dione and other cyclic β-dicarbonyl compounds are known to function well in Biginelli condensations (see Figure 4.3). However, for tetronic acid the reaction takes an entirely different course, following a pseudo-four-component pathway to furnish spiro heterobicyclic products in good yields (Scheme 4.11) [158]. The reaction proceeds by a regiospecific condensation of two molecules of aldehyde with the other reagents



Scheme 4.10. Diastereoselective intramolecular ("tethered") Biginelli condensations for the synthesis of hexahydropyrrolo[1,2-*c*]pyrimidines.

to afford products **27a** and **27b** having the C4 and C6 substituents exclusively in cis configuration. The classical Biginelli product was not detected. The same type of pseudo-four-component condensation was observed with cyclopentane-1,3-dione and 1,3-dimethylbarbituric acid, leading to spiroheterobicycles **28** and **29**, respectively [159].

A number of other "unusual" Biginelli-type structures are presented in Figure 4.8. For 1,3-dicarbonyl building blocks having a strong electron-withdrawing substituent (R^6) such as a trifluoromethyl group, the Biginelli sequence generally provides a hexahydropyrimidine derivative of type **30** [13, 14]. In fact, a variety of hexahydropyrimidines can be synthesized in this way using perfluorinated 1,3-

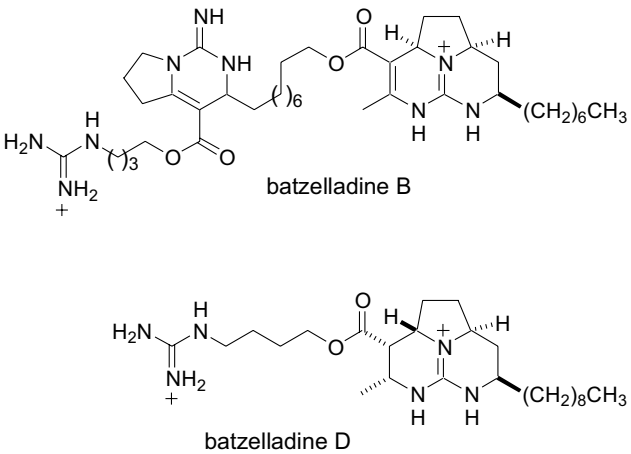
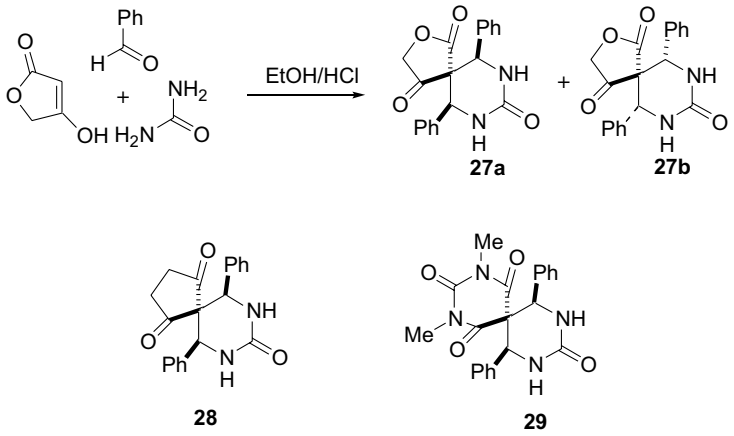


Fig. 4.7. Marine natural products with a Biginelli DHPM core structure.



Scheme 4.11. Pseudo-four-component cyclocondensation leading to spiroheterobicycles.

dicarbonyl compounds or β-ketoesters as building blocks [13–16, 35]. The steric proximity of an OH substituent in the ortho position of the aromatic ring and the C6 carbon of the pyrimidine ring in DHPMs enables the formation of a six-membered ring via intramolecular Michael addition [50, 123, 124, 160–162]. For example, with aromatic aldehydes such as salicylaldehyde, the expected product of a Biginelli condensation is not a simple DHPM but rather the 8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]tridecatriene derivative **31** (Figure 4.8) [50, 123, 124, 160–162]. Several examples of these unusual domino Biginelli condensation/Michael addition sequences have been reported. Another interesting variation of the standard Biginelli reaction involves the use of β-ketocarboxylic acids as CH-acidic carbonyl compounds. Under suitable reaction conditions, oxalacetic acid [163] and

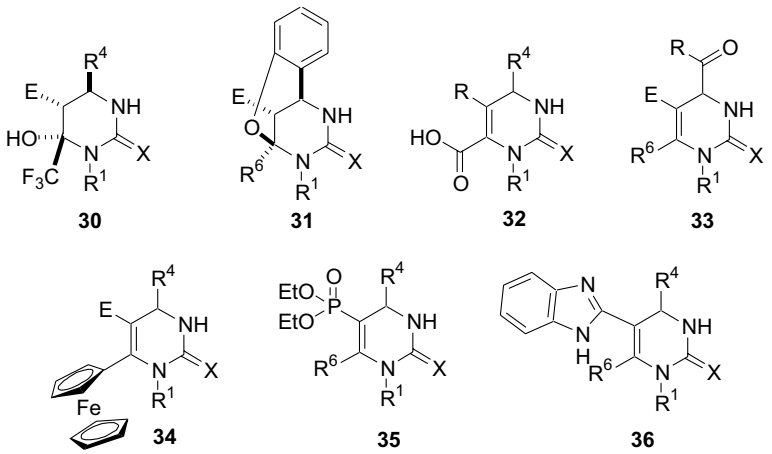
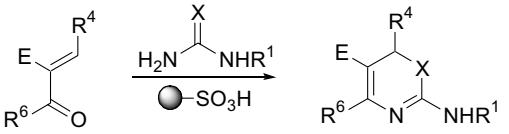


Fig. 4.8. Uncommon pyrimidine scaffolds derived from Biginelli-type condensations.

other α-keto acids [159] have proven excellent substrates in such condensations. Cyclization and *in situ* decarboxylation cleanly yields 5-(un)substituted 3,4-dihydropyrimidin-2(1*H*)-ones **32** (R = H) [159, 163]. By using TFA as the acidic catalyst and 1,2-dichloroethane (DCE) as the solvent, excellent yields of products can be obtained. The use of α-ketoaldehydes in the Biginelli condensation was reported to yield dihydropyrimidines such as **33** with an additional carbonyl group that provides an additional site for further derivatization [164]. Condensation of the appropriate CH-acidic carbonyl component (see Figure 4.3) with the corresponding aldehyde and urea building blocks furnishes the DHPM derivatives **34** [165], **35** [166], and **36** [167].

As a final example it should be mentioned that precondensed enones, prepared by standard Knoevenagel condensation of the aldehyde with the CH-acidic carbonyl component, when reacted with thioureas provided 1,3-thiazines **37**, which are isomeric to "thio-Biginelli compounds" of the general formula **14** (see Figure 4.5). A published report describes the combinatorial synthesis of a library of 29 derivatives of thiazines **37** utilizing polymer-supported reagents and catalysts [168].



37, X = S, Se

Scheme 4.12. Iso-Biginelli compounds (1,3-thiazines) via condensation of thioureas with enones.

4.8 Asymmetric Biginelli Reactions

DHPMs of the Biginelli type are inherently asymmetric molecules and the influence of the absolute configuration at the stereogenic center at C4 on biological activity is well documented [4]. In the calcium channel blocker SQ 32926, for example, it is exclusively the (*R*)-enantiomer that carries the therapeutically desired antihypertensive effect (Figure 4.9) [169]. In some related DHPM analogues, the individual enantiomers have in fact been demonstrated to have opposing antagonist/agonist pharmacological activity [170]. For the α_{1A}-selective adrenoceptor antagonist L-771,688 the (*S*)-enantiomer is significantly more active than the (*R*)-enantiomer [171], and recent work on the mitotic kinesin Eg5 inhibitor monastrol [172, 173] has shown that the (*S*)-enantiomer is the more potent inhibitor of Eg5 activity [174, 175]. A similar effect was also observed for Bay 41–4109, a non nucleosidic inhibitor of hepatitis B virus replication, where the (*S*)-enantiomer was found to be more active than the (*R*)-enantiomer (Figure 4.9) [176]. Access to enantiomerically pure DHPMs is therefore of considerable interest and a prerequisite for the development of any drugs in this field.

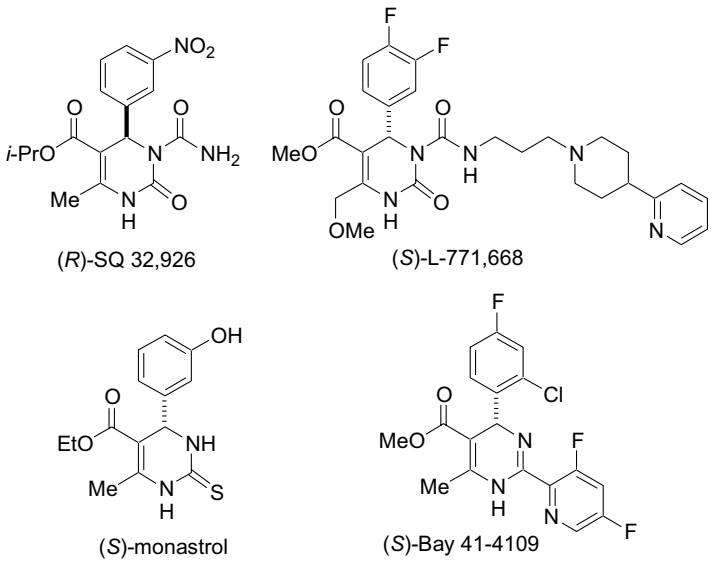
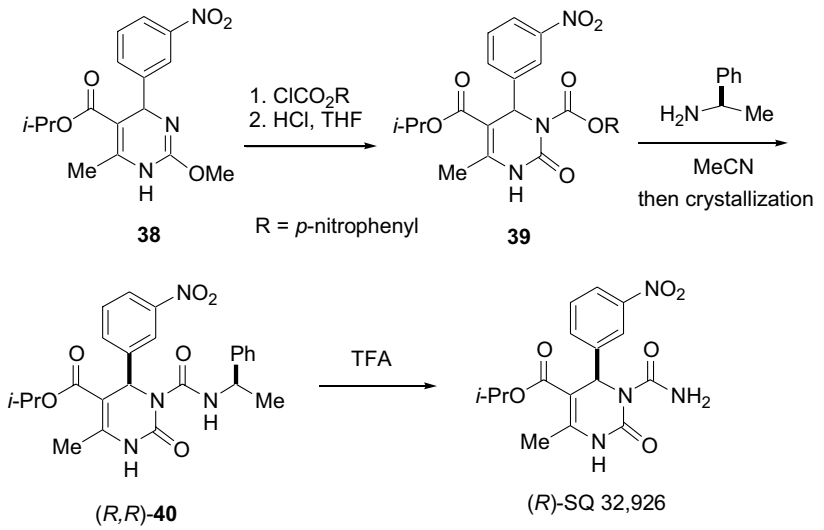


Fig. 4.9. Influence on the stereogenic center at C4 on biological activity.

In the absence of any known general asymmetric synthesis for this heterocyclic target system, resolution strategies have so far been the method of choice to obtain enantiomerically pure DHPMs. Optically pure DHPMs were obtained by resolution of the corresponding racemic 5-carboxylic acids via fractional crystallization of the corresponding diastereomeric α-methylbenzylammonium salts [177]. The absolute configuration of those acids was proven by single-crystal X-ray analysis of a suitable diastereomeric salt. Analytically, separation of DHPM derivatives can be readily achieved by enantioselective HPLC using a variety of different chiral stationary phases (CSPs) [178–183], including "designer-made" CSPs that are based on the principle of "reciprocal" recognition of chirality using the immobilized DHPM derivatives [123–124]. Such "designer-CSPs" could prove extremely useful for the efficient separation of not only DHPMs but other structurally related compounds as well.

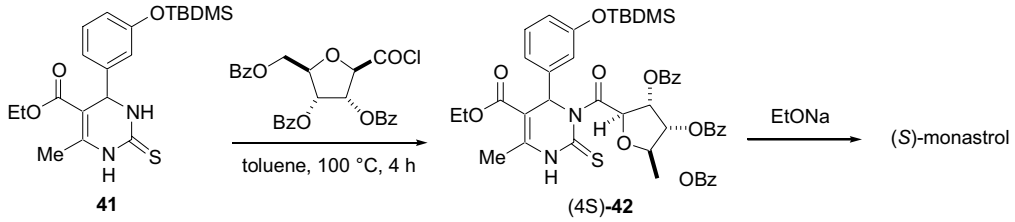
Alternatively, chiral separation can be performed by capillary electrophoresis (CE) with, for example, quaternary ammonium-β-cyclodextrin as chiral buffer additive [184, 185].

A preparatively useful approach to the enantiomerically pure antihypertensive agent (*R*)-SQ 32,926 was disclosed by Atwal et al. (Scheme 4.13) [169]. In the first step, the 1,4-dihydropyrimidine intermediate **38** is acylated at N3 with 4-nitrophenyl chloroformate followed by hydrolysis with HCl in THF to give DHPM **39**. Treatment with (*R*)-α-methylbenzylamine provided a mixture of diastereomeric ureas from which the (*R*,*R*) isomer **40** was separated by crystallization. Cleavage with TFA provided (*R*)-SQ 32,926 in high enantiomeric purity. Similar strategies have been used to obtain a number of pharmacologically important DHPM derivatives in enantiomerically pure form [169, 186, 187].



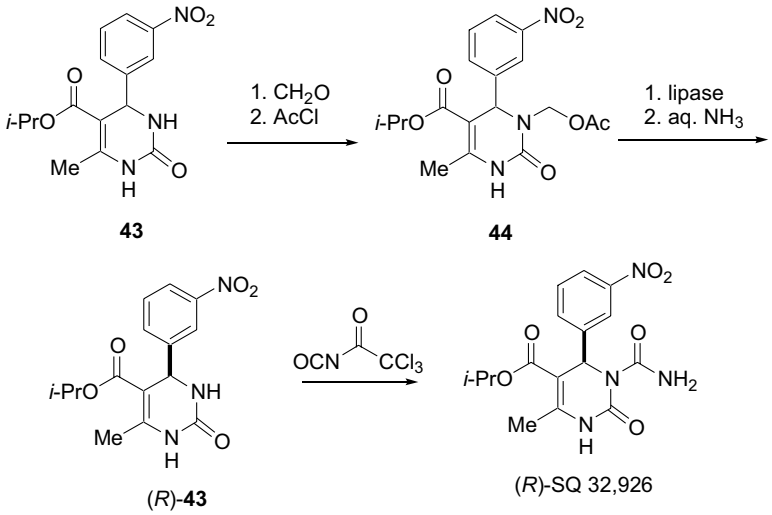
Scheme 4.13. Chemical resolution of dihydropyrimidines.

A different chemical resolution strategy was employed to gain access to enantiopure monastrol [188]. Here, the O-protected monastrol derivative **41** was acetylated regioselectively at the N3 position with a chiral, carbohydrate-derived β-linked *C*-glycosyl carboxylic acid chloride. The resulting diastereomeric amides **42** were separated by chromatography, and simultaneous removal of the TBDMS and the chiral sugar moiety by treatment with EtONa provided the desired enantiopure (*S*)-monastrol in good overall yield.



Scheme 4.14. Chemical resolution of monastrol.

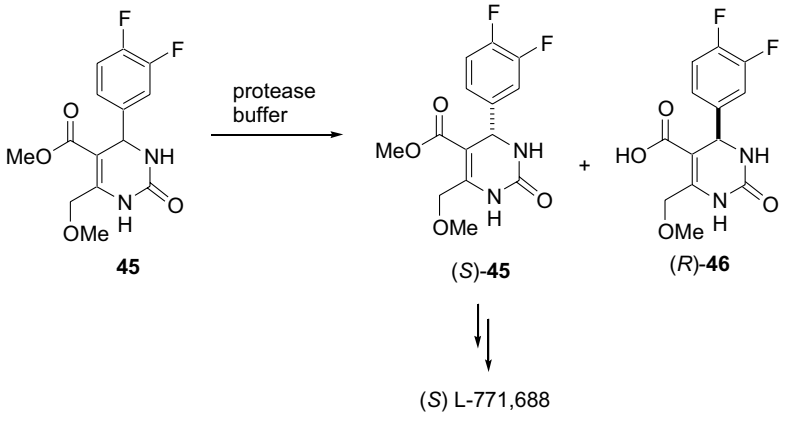
As an alternative to the chemical resolution methods described by Atwal et al. (Scheme 4.13), a biocatalytic strategy towards the preparation of enantiopure (*R*) and (*S*)-SQ 32,926 was developed (Scheme 4.15). The key step in the synthesis is the enzymatic resolution of an N3-acetoxymethyl-activated dihydropyrimidone precursor by *Thermomyces lanuginosus* lipase [189]. The readily available racemic DHPM **43** was hydroxymethylated at N3 with formaldehyde, followed by standard acetylation with acetyl chloride. The resulting N3-acetoxymethyl-activated DHPM



Scheme 4.15. Biocatalytic strategy toward (*R*)-SQ 32,926.

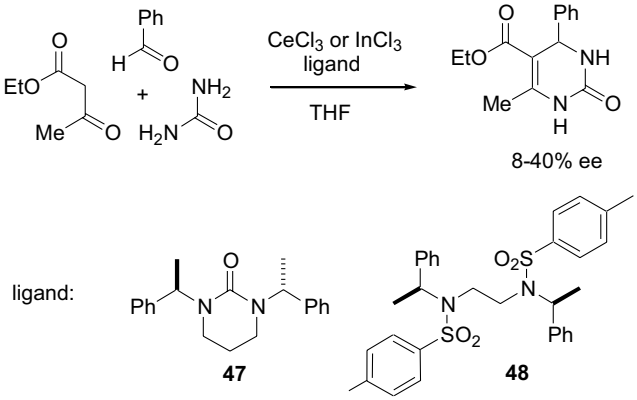
44 was then cleaved enantioselectively by *Thermomyces lanuginosus* with excellent selectivity ($E > 200$). Degradation of unreacted (*R*)-**44** with aqueous ammonia produced (*R*)-**43** which was converted into the desired target structure (*R*)-SQ 32926 in one step by N3-carbamoylation with trichloroacetyl isocyanate [190].

A considerably simpler approach in the context of a biocatalytic pathway was reported by Sidler et al. (Scheme 4.16). Here, the methyl ester **45** could be hydrolyzed selectively by the protease subtilisin (lipases and esterases were unreactive), allowing hydrolysis of the unwanted (*R*)-enantiomer. The desired (*S*)-**45** was recovered from the solution in 80–90% chemical yield (98% *ee*) and was further manipulated into (*S*) L-771,668 [191].



Scheme 4.16. Biocatalytic strategy toward (*S*) L-771,688.

Efforts to develop a practical asymmetric version of the Biginelli reaction itself have failed so far. While chiral acetoacetates, such as (−)-menthyl acetoacetate, show no diastereoselectivity at all [177], chiral aldehydes derived from carbohydrates (see Figure 4.6) or amino acids (Garner aldehyde, see Scheme 4.9) can induce chirality at C4 of the pyrimidine ring. The latter approach, however, is of little general use since the substituent at the C4 position of the DHPM scaffold will invariably be derived from the building blocks employed. The same is true for intramolecular asymmetric variations of the Biginelli reaction that have been developed for natural product synthesis (see Scheme 4.10 and Figure 4.7). A recent first step in the development of a truly catalytic enantioselective variation of the Biginelli reaction was reported by Juaristi and co-workers in 2003 [192]. These authors have employed $CeCl_3$ and $InCl_3$ as Lewis acids in the presence of chiral ligands such as amide **47** and sulfonamide **48** (Scheme 4.17). Moderate enantioselectivities (up to 40% *ee*) of enriched DHPMs were obtained performing the reaction at low temperatures under kinetic control. This modification of the Biginelli condensation may offer an encouraging alternative to resolution strategies in the future.



Scheme 4.17. Enantioselective variation of the Biginelli three-component condensation.

A critical point in every preparation of enantiomerically pure materials, regardless of the method, is the assignment of absolute configuration. For the DHPM series a simple protocol for absolute configuration assignment based on the combination of enantioselective HPLC and circular dichroism (CD) spectroscopy has been developed [179, 193]. By comparison of the characteristic CD spectra of individual DHPM enantiomers with reference samples of known absolute configuration, the absolute configuration of 4-aryl-DHPMs, such as monastrol [188, 194], SQ 32,926 [189], and of carbohydrate- [106] and Garner-aldehyde- [107] derived DHPMs (see Figure 4.6 and Scheme 4.9) could be established. The characteristic CD activity of the enamide chromophore around 300 nm allows the assignment of absolute configuration in this series of dihydropyrimidine derivatives.

4.9 Conclusion

The Biginelli dihydropyrimidine MCR, one of the oldest multicomponent reactions, has come a long way since its discovery in 1893 by Pietro Biginelli, an assistant working under the supervision of Professor Ugo Schiff at the University of Florence. From the preparation of simple pyrimidine heterocycles in the late nineteenth century, to the generation of targeted compound libraries of biofunctional DHPMs and the enantioselective total synthesis of complex natural products, the Biginelli MCR has been adopted successfully to the needs and expectations of modern organic chemistry. Today, the Biginelli dihydropyrimidine synthesis is one of the most well-known multicomponent reactions that has entered many undergraduate laboratories [195] since it exemplifies the beauty and power of multicomponent chemistry. Because of the pharmacological potency of the privileged DHPM scaffold [196], novel dihydropyrimidines with important biological properties will undoubtedly be discovered by combining combinatorial synthesis and high-throughput screening (HTS) techniques. A continuing exciting future for the Biginelli reaction in the 21st century is therefore secure.

References

1 P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360–413. In this 54-page article (!), Biginelli comments that his research was inspired by earlier work on *bimolecular* urea–aldehyde and urea–*β*-ketoester condensations, respectively.

2 In earlier publications, Biginelli originally proposed a linear-type structure instead of the correct DHPM structure **4**: (a) P. Biginelli, *Gazz. Chim. Ital.* **1891**, *21*, 497–500; (b) P. Biginelli, *Chem. Ber.* **1891**, *24*, 1317–1319.

3 C. O. Kappe, *Tetrahedron* **1993**, *49*, 6937–6963.

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5
The Domino-Knoevenagel-hetero-Diels–Alder Reaction and Related Transformations

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5.1
Introduction

The development of novel materials and the search for new bioactive compounds, such as natural products and analogues, drugs, diagnostics and agrochemicals, in academic and industrial chemistry is closely connected to the efficient preparation of such compounds. Thus, the view of synthesis has altered in recent years; the development of new, highly selective methods will still be an important task, but the main focus of today's chemists is on efficiency [1]. Multi-step syntheses with more than 20 steps have to be avoided since they are neither economically nor ecologically justifiable. Thus, modern syntheses must deal carefully with our resources and our time, must reduce the amount of waste formed, should use catalytic transformations and finally must avoid all toxic reagents and solvents.

In addition, synthetic methodology must be designed in a way that allows access to diversified substance libraries in an automated way [2]. Though solid-phase chemistry is now of a high standard for use in combinatorial chemistry, solution chemistry retains several advantages.

A general way to improve synthetic efficiency, which in addition also gives access to a multitude of diversified molecules in solution, is the development of multicomponent domino reactions which allow the formation of complex compounds starting from simple substrates. Domino reactions are defined as processes of two or more bond-forming reactions under identical conditions, in which the subsequent transformation takes place at the functionalities obtained in the former transformation; thus, it is a time-resolved process [1a,c,f,3]. The quality and importance of a domino reaction can be correlated to the number of bonds formed in such a process and the increase of complexity. Such reactions can be carried out as a single-, two- or multicomponent transformation. Thus, most of the known multicomponent transformations [4], but not all, can be defined as a subgroup of domino transformations.

Domino reactions can be classified according to the mechanism of the single steps, which may be of the same type or of different types. The majority of the domino reactions so far developed belong to the first category and consist of two

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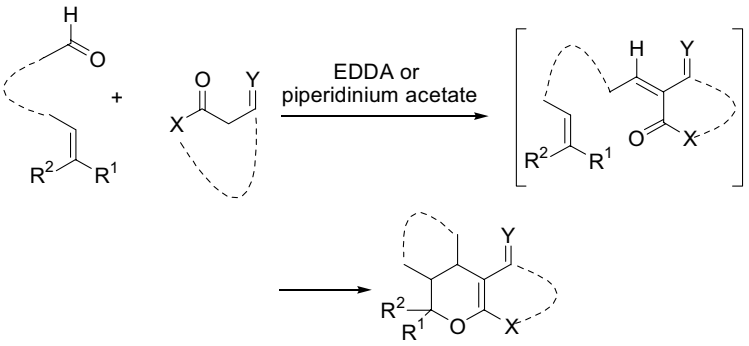
or more cationic, anionic, radical, pericyclic or transition metal-catalyzed transformations. Examples for the combination of mechanistically different reactions are anionic-pericyclic processes such as the domino-Knoevenagel-hetero-Diels–Alder reaction, the domino-Knoevenagel-ene reaction and the domino-Sakurai-ene reaction.

In recent years the domino-Knoevenagel-hetero-Diels–Alder reaction, developed in our group, has emerged as a powerful process that not only allows the efficient synthesis of complex compounds such as natural products starting from simple substrates but also permits the preparation of highly diverse molecules.

It consists of a Knoevenagel condensation [5] of an aldehyde with a 1,3-dicarbonyl compound in the presence of catalytic amounts of a weak base such as ethylene diammonium diacetate (EDDA) or piperidinium acetate (freshly prepared). In the reaction, a 1,3-oxabutadiene is formed as an intermediate, and this can undergo a hetero-Diels–Alder reaction [6] with either an enol ether or an alkene.



In this Diels–Alder reaction with inverse electron demand the overlap of the LUMO of the 1-oxa-1,3-butadiene with the HOMO of the dienophile is dominant. Since the electron-withdrawing group of the oxabutadiene at the 3-position lowers its LUMO dramatically, both the cycloaddition and the condensation usually take place at room temperature. The reaction can be performed as a two-, three- or four-component transformation. There is actually no restriction on the aldehydes; thus, aromatic, hetero-aromatic, saturated aliphatic and unsaturated aliphatic aldehydes may be used. In addition, ketones such as α-oxocarbocylic esters can also be employed. As 1,3-dicarbonyl compounds cyclic substances such as Meldrum's acid, barbituric acid and derivates, coumarines, any type of cycloalkane-1,3-dione and β-ketoesters, as well as their phosphorus, nitrogen or sulfur analogues and acyclic 1,3-diones may be utilized. In all cases, but especially using acyclic β-ketoesters as 1,3-dicarbonyl compounds, a domino-Knoevenagel-ene reaction might occur as a side reaction [7]. Depending on the substrates the domino-Knoevenagel-ene transformation may also be the main process. In addition, hetero-analogues of 1,3-dicarbonyl compounds, such as the aromatic pyrazolones and isoxazolones, can take part in the reaction. The most appropriate dienophiles are enolethers while enamines are more difficult to handle. Simple alkenes are also suitable as dieno-

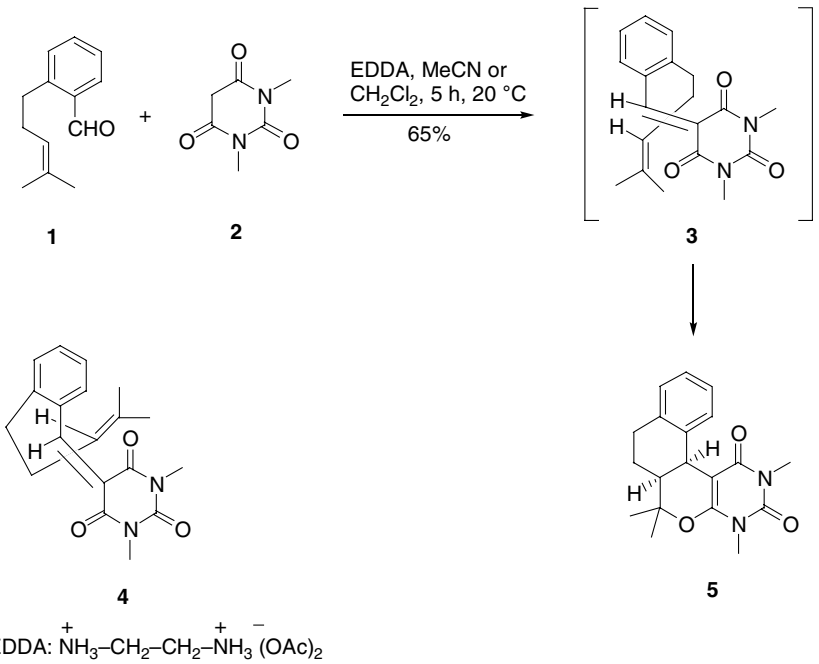
philes, but good yields are only obtained if the Diels–Alder reaction takes place in an intramolecular mode. In these cases an excellent control of the stereochemistry is possible. Using aromatic or aliphatic α,β-unsaturated aldehydes, usually only the cis-fused products are observed, whereas in the cases of simple aliphatic aldehydes the trans-annulated product is formed predominantly. For the synthesis of enantiopure compounds, chiral aldehydes and 1,3-dicarbonyl compounds may be employed. In addition, chiral catalysts or mediators can be used, which not only catalyze the Diels–Alder reaction but also the Knoevenagel condensation. However, a general enantioselective approach for the domino-Knoevenagel-hetero-Diels–Alder reaction is still awaited.

A wide range of solvents can be used. Most appropriate are acetonitrile, dichloromethane and toluene, but alcohols and water may also be employed. In those cases, depending on the substrates, an additional reaction such as cleavage of formed lactones or acetals might occur.

Several reviews have already been written about this topic, therefore here only a general overview and the newest developments are presented [1a,b,d,g,3].

5.2
Two-component Reactions with an Intramolecular Cycloaddition

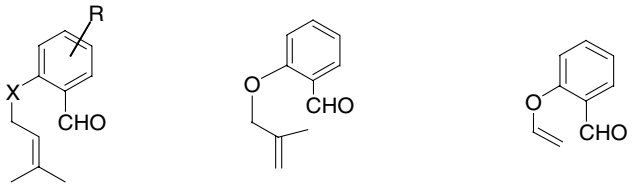
The reaction of aromatic aldehydes such as **1**, which contain a dienophile moiety, with *N*,*N*-dimethylbarbituric acid **2** in the presence of ethylene diammonium diacetate at 20 °C led to the cis-fused product **5** in 95% yield (Scheme 5.1) [8]. As an



Scheme 5.1. Domino-Knoevenagel-hetero-Diels–Alder reaction with aromatic aldehydes.

intermediate the benzyliden-1,3-dicarbonyl-compound **3** is formed, which can be identified by on-line NMR-spectroscopy. As transition-structure an endo-(*E*)-syn-orientation can be assumed, although an exo-(*Z*)-syn-transition structure **4** would lead to the same product, but seems less likely owing to steric interference.

There is actually no limitation regarding the aldehyde. Thus, any substituted aromatic and hetero-aromatic aldehyde can be employed and also aldehydes in which the dienophile moiety is connected to the phenyl group *via* a sulfur, a nitrogen or an oxygen such as **6**–**8** (Scheme 5.2).

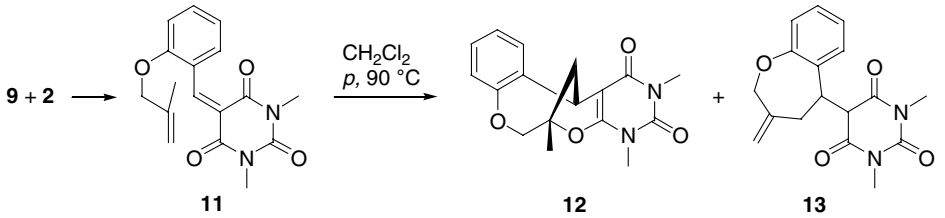


6 : X = O
7 : X = S
8 : X = N

9 **10**

Scheme 5.2. Aldehydes for the domino-Knoevenagel-hetero-Diels–Alder reaction.

The regioselectivity is controlled by the coefficients at the dienophile moiety. Thus, using aldehydes of type **9** or **10** favors the formation of bridged instead of fused compounds (Scheme 5.2). As an example, the reaction of **9** with **2** gave the 1-oxa-1,3-butadiene **11**, which underwent a cycloaddition to afford the cycloadduct **12** and in addition, a small amount of the ene product **13**. Interestingly, the ratio of **12** and **13** can be altered by applying high pressure (Scheme 5.3) [9].



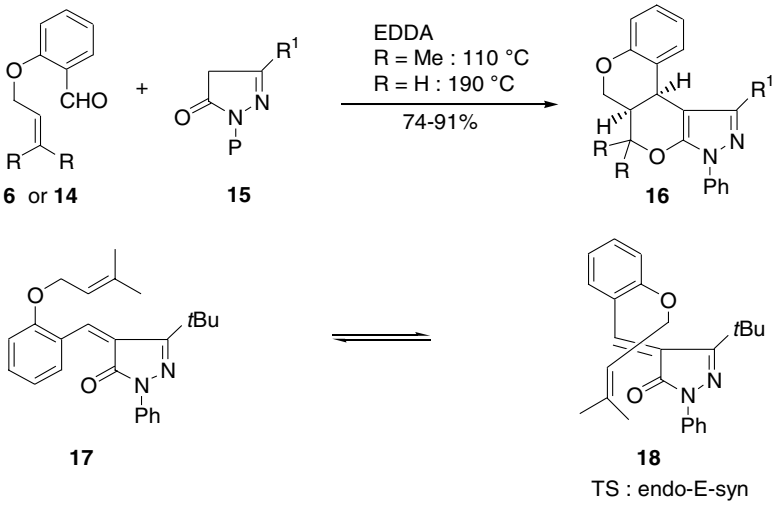
11 **12** **13**

Pressure [MPa]	Selectivity (**12** : **13**)
75	19.5 : 1
100	23.5 : 1
320	40.7 : 1
550	76.3 : 1

$\Delta\Delta V^{\neq} = -(10.7 \pm 1.9)\ cm^3\ mol^{-1}$
$\Delta\Delta H^{\neq} = -(32.4 \pm 7.2)\ kJ\ mol^{-1}$

Scheme 5.3. Influence of pressure on the chemoselectivity of the reaction of **11** in dichloromethane at 90 °C.

A higher reaction temperature is necessary when pyrazolones such as **15** and isoxazolones are used. The selectivity in these reactions depends on the substituent at the hetero-aromatic compound and the substituents at the dienophile moiety (Scheme 5.4) [10].

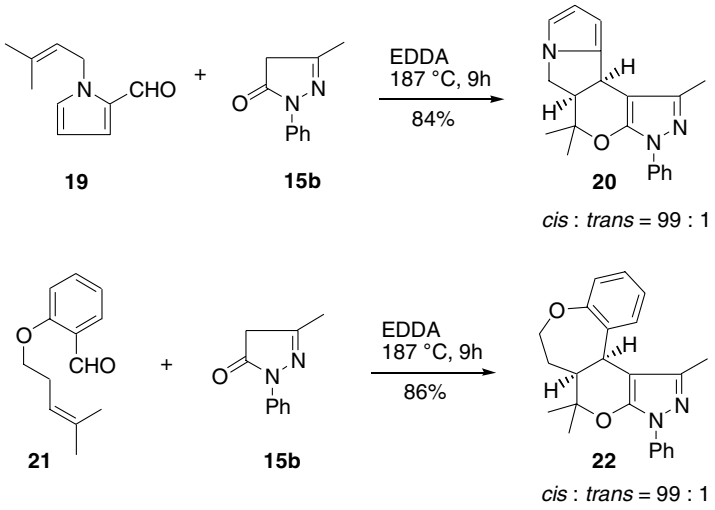


6 + **15**	R = Me : R^1	**16**: R= Me *cis* : *trans*	**14** + **15**	R = H : R^1	**16**: R= H *cis* : *trans*
a	H	4.62 : 1	**a**	H	3.16 : 1
b	Me	16.75 : 1	**b**	Me	23.2 : 1
c	Ph	4.49 : 1	**c**	Ph	10.2 : 1
d	*t*Bu	44.5 : 1	**d**	*t*Bu	10.3 : 1

Scheme 5.4. Domino-Knoevenagel-hetero-Diels–Alder reaction of pyrazolones.

In the Knoevenagel reaction using a pyrazolone with a bulky substituent at C3 a (*Z*)-benzylidene-moiety is obtained first owing to a steric interaction between the substituent at the formed double bond and the substituent at C3 of the pyrazolone. It could be proposed that the (*Z*)-1-oxa-1,3-butadiene undergoes a cycloaddition *via* an exo-(*Z*)-syn transition structure. However, it seems that this is less appropriate than the endo-(*E*)-syn transition structure. Thus, the Knoevenagel product first undergoes a (*Z*/*E*)-isomerization before the cycloaddition to allow the formation of a cis-fused cycloadduct **16** *via* the endo-(*E*)-syn transition structure **18**. Thus, the reaction of **6** and **15d** led to the isolable 1-oxa-1,3-butadiene **17** with a (*Z*)-configuration, which after isomerization at higher temperature yielded **16d** (R = Me) *via* **18** with an (*E*)-configuration. The transformation could be performed as a domino process at 110 °C; however, under irradiation with UV-light, which facilitates the double bond isomerization, the cycloadduct **16d** (R = Me) was formed at 40 °C.

By using a different length of tether between the aldehyde and the dienophile moiety in the aromatic or hetero-aromatic substrates various different highly diversified heterocyclic compounds can be prepared. Thus, reaction of **19** and **15b** led to **20** containing a new 5,6-ring system, whereas reaction of **21** and **15b** gave **22** with a 7,6-ring system (Scheme 5.5) [11].



Scheme 5.5. Synthesis of diversified heterocycles by domino-Knoevenagel-hetero-Diels–Alder reaction.

For the preparation of enantiopure products chiral 1,3-dicarbonyl compounds such as **23** and **24** have been used [12, 13]. In addition, chiral mediators such as **25** have been employed with great success (Figure 5.1) [14].

Using aliphatic aldehydes such as **26** the trans-annulated products are formed almost exclusively [15]. Moreover, a stereogenic center at the aldehyde has a strong influence on the facial selectivity. Thus, reaction of **27** led to **28** nearly exclusively.

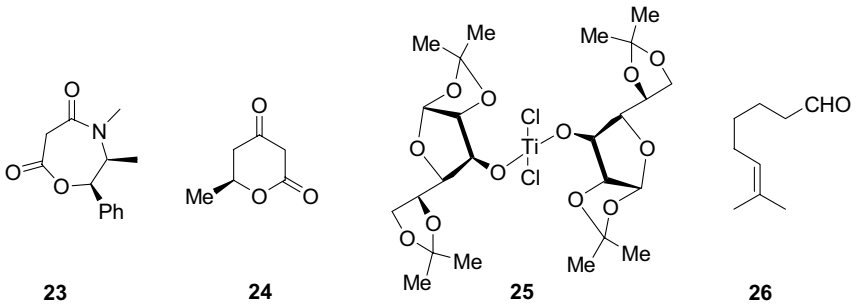
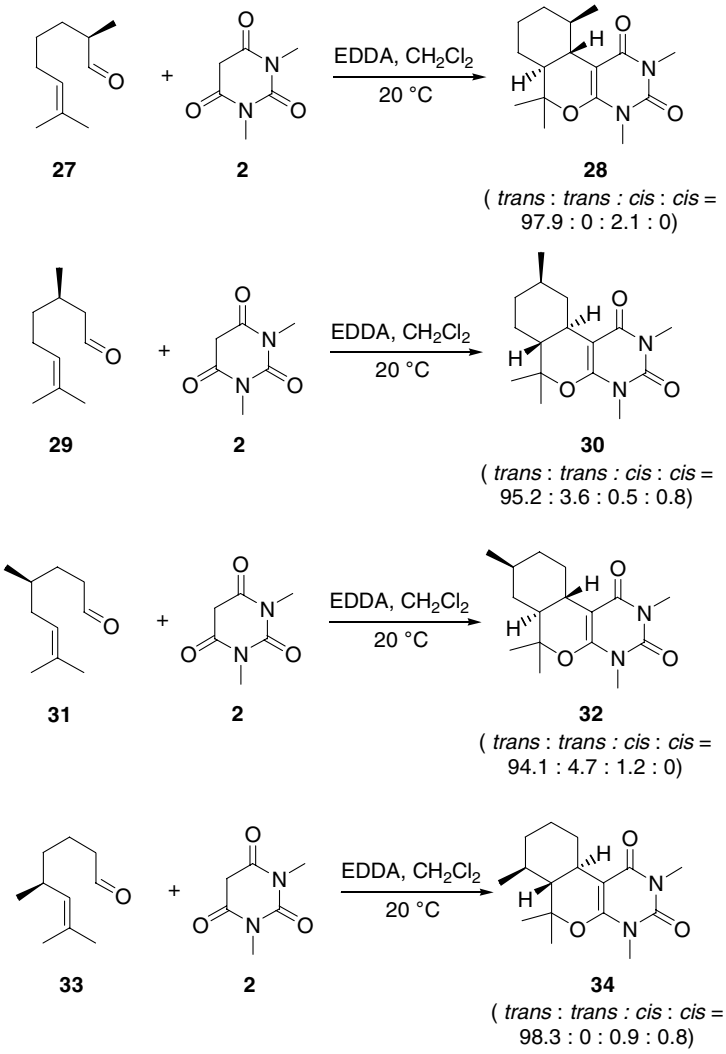


Fig. 5.1. Chiral 1,3-dicarbonyl compounds and chiral Lewis acids.



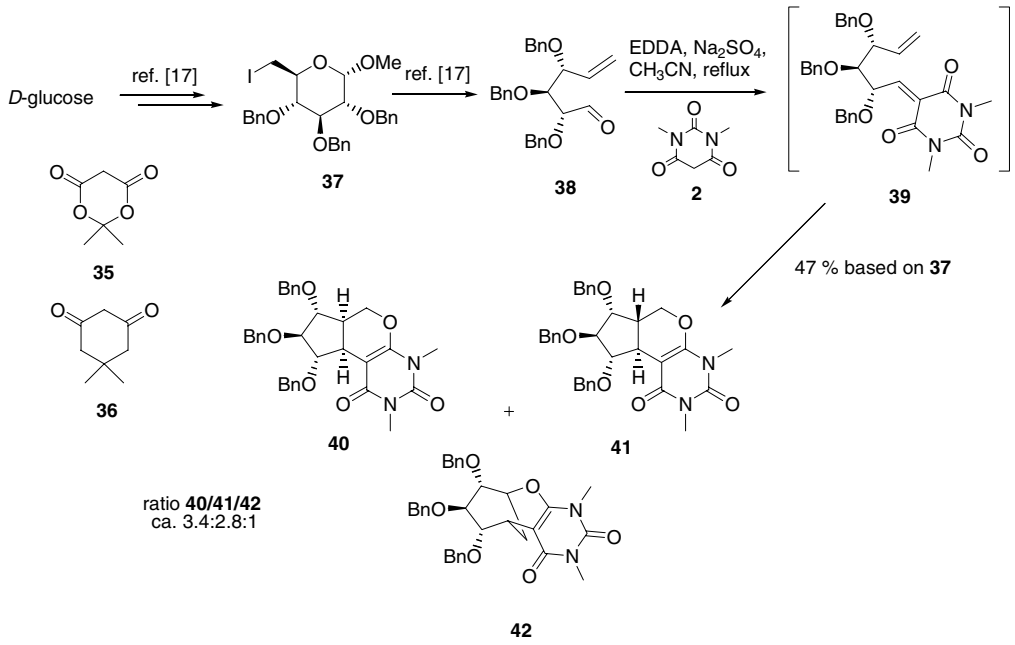
Scheme 5.6. Diastereoselective domino-Knoevenagel-hetero-Diels–Alder reaction with chiral aliphatic aldehydes.

In a similar way the aldehydes **29**, **31** and **33** yielded the products **30**, **32** and **34**, respectively, with excellent simple and induced diastereoselectivity (Scheme 5.6) [16]. This procedure has been used for the synthesis of deoxyloganin, an important intermediate in the biogenesis of indole alkaloids [17].

A nice extension of this protocol is the use of *δ*,*ε*-unsaturated aldehydes derived from sugars such as D-glucose and D-ribose to yield polyhydroxylated condensed dihydropyrans [18]. Good results were obtained using *N*,*N*-dimethylbarbituric acid

2 as the 1,3-dicarbonyl component whereas Meldrum's acid **35** and dimedone **36** gave less satisfying results.

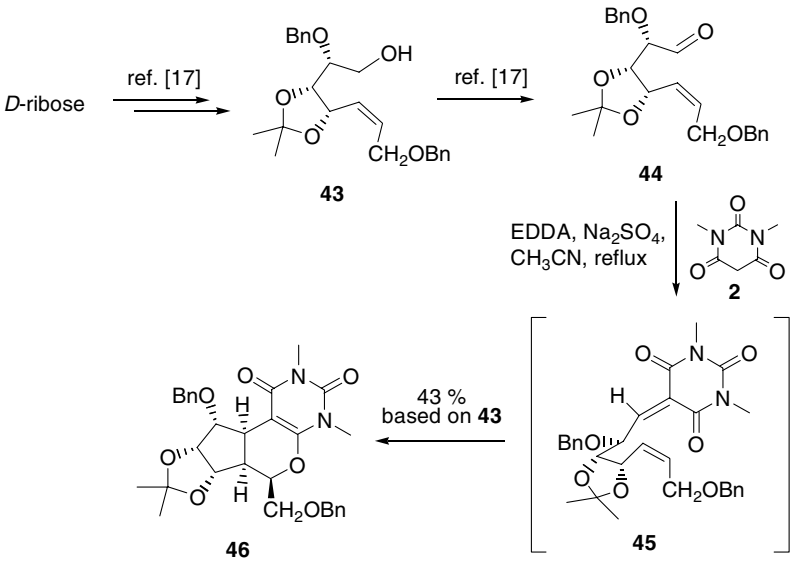
The required δ,ε-unsaturated aldehydes **38** and **44** were synthesized from iodide **37** (Scheme 5.7) and alcohol **43** (Scheme 5.8) and were used in the domino process without isolation. **37** and **43** were easily accessible from D-glucose and D-ribose, respectively [19].



Scheme 5.7. Domino-Knoevenagel-hetero-Diels–Alder reaction of aldehyde **38** derived from

The domino-Koevenagel-hetero-Diels–Alder reaction of **38** and **2** led to both the trans- and the cis-fused and the bridged cycloadducts **41**, **40** and **42** in 47% yield in a ratio of 3.4:2.8:1. Interestingly, the reaction of **44** and **2** afforded nearly exclusively the cis-fused product **46** in a good overall yield of 43%.

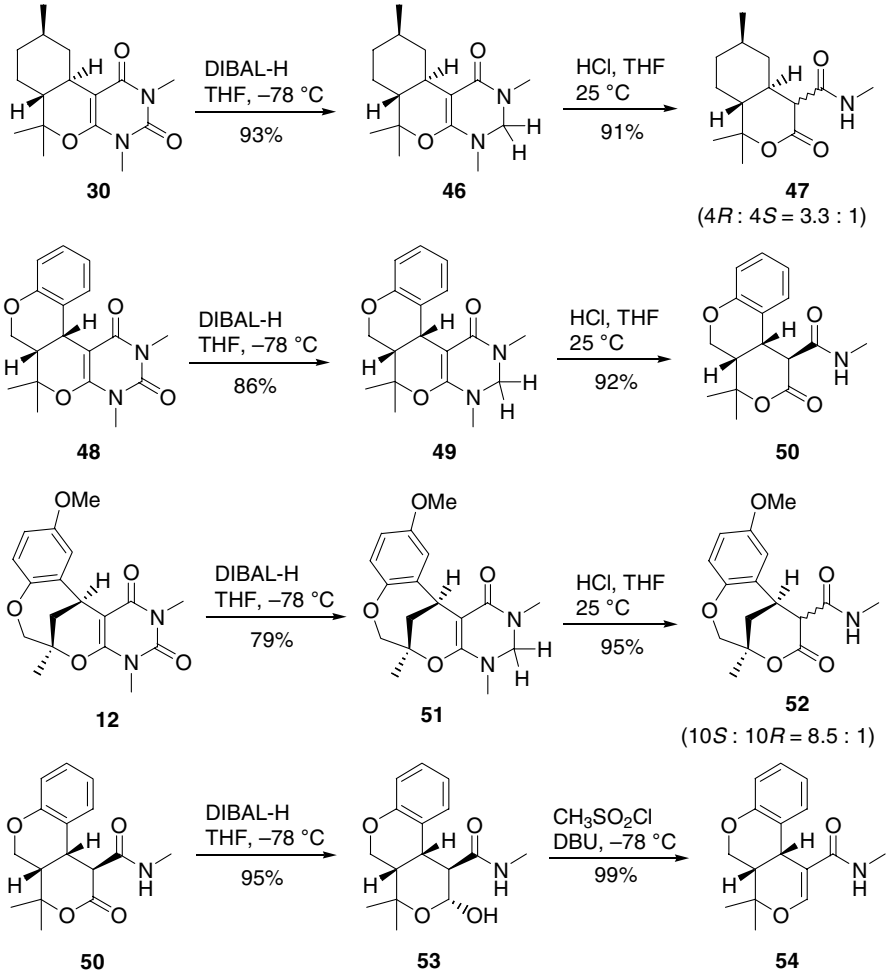
It has been assumed that the formation of the cis-fused product **46** in the domino reaction of aldehyde **44** is due to a strongly favored exo-(*Z*)-syn transition state. The endo-(*E*)-syn structure is prohibited by the rigidity of the acetonide existing in **45**, whereas the proximity of the same moiety to the benzyloxymethyl substituent at the double bond disfavors the exo-(*E*)-anti transition state, which would be responsible for the formation of the trans-fused diastereomer. The flexibility and the lack of steric interaction in intermediate **39** led to a mixture of several isomers.



Scheme 5.8. Domino-Knoevenagel-hetero-Diels–Alder reaction of aldehyde **44** derived from D-ribose.

One of the most reactive 1,3-dicarbonyl compounds used in the domino-Knoevenagel-hetero-Diels–Alder reaction is *N*,*N*-dimethyl barbituric acid **2**. It has been shown that the fairly stable products can easily been transformed into other compounds *via* a reduction of the urea moiety with DIBAL-H [20]. Thus, reaction of **30** with DIBAL-H at −78 °C led to **46**, which can be hydrolyzed to give **47** (Scheme 5.9). In a similar way, **48** was transformed into **50** *via* **49** and **12** to **52** *via* **51**. The obtained compounds containing a lactone and an amide moiety can again be further transformed using DIBAL-H followed by an elimination. In this way, dihydropyran **54** is obtained from **50** *via* **53** as one example.

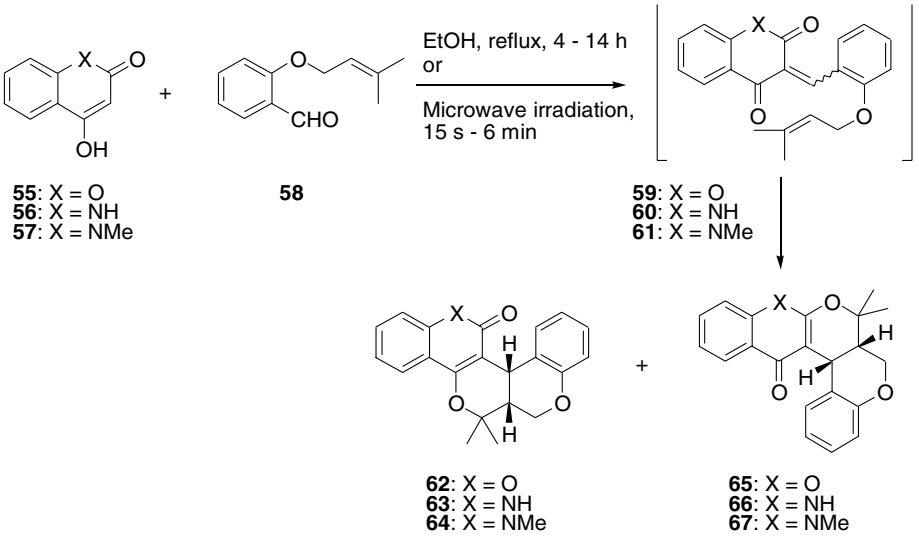
Besides *N*,*N*-dimethyl barbituric acid **2** and Meldrum's acid **35**, other useful 1,3-dicarbonyl compounds for the domino-Knoevenagel-hetero-Diels–Alder reaction are 4-hydroxycoumarins **55** and 4-hydroxyquinolinones **56** and **57** [21]. Here an additional problem arises from the coexistence of two different 1-oxa-1,3-butadienes formed in the Knoevenagel condensation. Interestingly, the degree of regioselectivity can be improved by performing the reaction under microwave irradiation [22]. Thus, reaction of 4-hydroxycoumarin **55** with the benzaldehyde derivative **58** in the presence of catalytic amounts of EDDA under normal heating led to the two cis-fused cycloadducts **62** and **65** in a ratio of 68:32 in 57% yield, whereas under microwave irradiation a ratio of 93:7 and 82% yield were observed. The remarkable improvement of the selectivity and the yield by the use of microwave irradiation was a general observation the authors made.



Scheme 5.9. Transformation of cycloadducts with *N*,*N*-dimethyl barbituric acid.

Similar results could be found for the reactions with **56** and **57** to give the cycloadducts **63** as well as **66** and **64** as well as **67**, respectively (Scheme 5.10, Table 5.1).

The domino process also proceeds nicely using benzocoumarins and naphthaldehydes. In the reaction of 4-hydroxycoumarin **55** as well as of the 4-hydroxyquinolinones **56** and **57** with citronellal **68** only the trans-fused cycloadducts **75–77** were observed. These are formed by a hetero Diels–Alder reaction of the more reactive unsaturated keto moiety in **69–71** [23]. However, compounds **72–74**, which are formed by an ene reaction, were also observed. As already mentioned, the ene reaction is a general side reaction that has been observed especially in the transformation of different aliphatic aldehydes [7]. In the domino process of **55–57** with **68**



Scheme 5.10. Domino-Knoevenagel-hetero-Diels–Alder reaction of substrates **55**–**57** with benzaldehyde **58**.

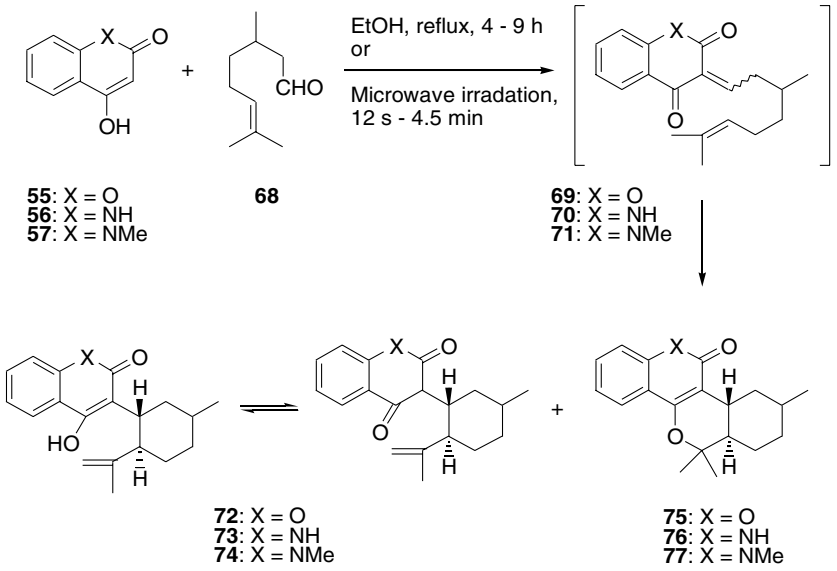
the amount of the ene product could readily be decreased using microwave irradiation (Scheme 5.11, Table 5.2).

Another useful unsymmetrical 1,3-dicarbonyl compound is hydroxypyridone **80** which has served as a substrate for the synthesis of *rac*-leporin A **78a** according to the retrosynthetic analysis shown in Scheme 5.12 [24].

The intermediate **79** obtained by the Knoevenagel condensation of **80** and **81** contains a 1-oxa-1,3-butadiene as well as a normal 1,3-butadiene moiety; thus both a hetero-Diels–Alder and a normal Diels–Alder reaction is possible. The dom-

Tab. 5.1. Reaction of **55**–**57** with benzaldehyde **58** under different conditions.

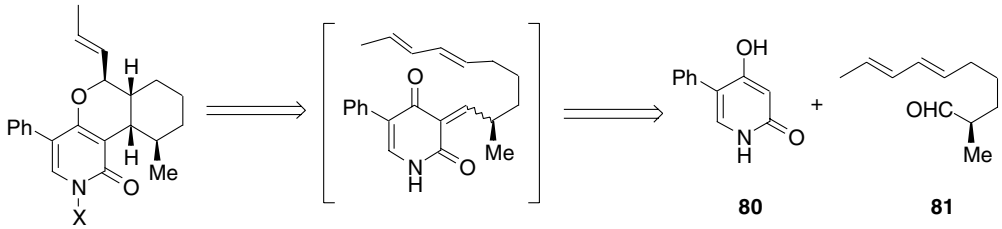
Entry	*Substrates 58 and*	*Reaction conditions*	*Reaction time*	*Base*	*Product ratio 62:65 or 63:66 or 64:67*	*Overall yield [%]*
1	**55**	Reflux	4 h	–	68:32	57
2	**55**	MW	15 s	–	93:7	82
3	**56**	Reflux	10 h	EDDA	53:47	60
4	**56**	Reflux	14 h	Piperidine	55:45	67
5	**56**	MW	3 min	EDDA	79:21	78
6	**56**	MW	3 min	Piperidine	88:12	79
7	**57**	Reflux	10 h	EDDA	55:45	42
8	**57**	Reflux	9.5 h	Piperidine	58:42	50
9	**57**	MW	6 min	EDDA	84:16	65
10	**57**	MW	3.5 min	Piperidine	86:14	66



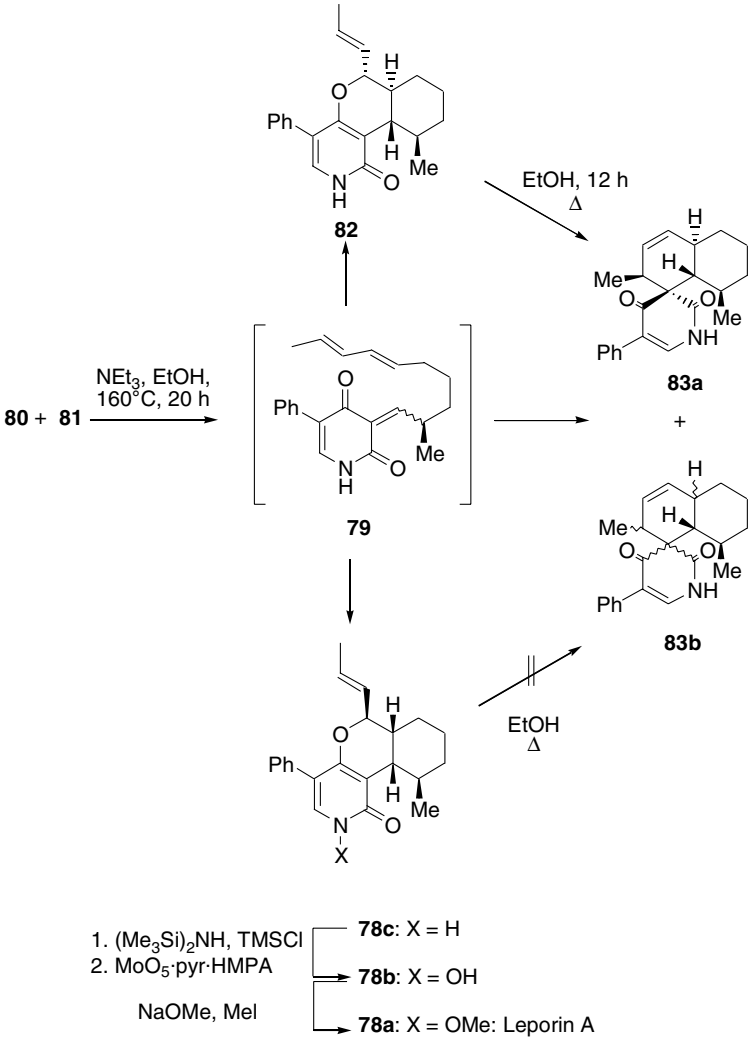
Scheme 5.11. Domino-Knoevenagel-hetero-Diels–Alder reaction of **55**–**57** with citronellal **68**.

Tab. 5.2. Some representative reactions of **55**–**57** with citronellal **68**.

Entry	*Substrates 68 and*	*Reaction conditions*	*Reaction time*	*Base*	*Ratio Diels–Alder/En product*	*Overall yield [%]*
1	**55**	Reflux	4 h	–	58:42	55
2	**55**	MW	12 s	–	88:12	81
3	**56**	Reflux	4.5 h	NEt_3	58:42	51
4	**56**	MW	3 min	NEt_3	84:16	68
5	**57**	Reflux	8.5 h	NEt_3	57:43	49
6	**57**	MW	4.5 min	NEt_3	83:17	80



Scheme 5.12. Retrosynthesis of leporin A **78a**.



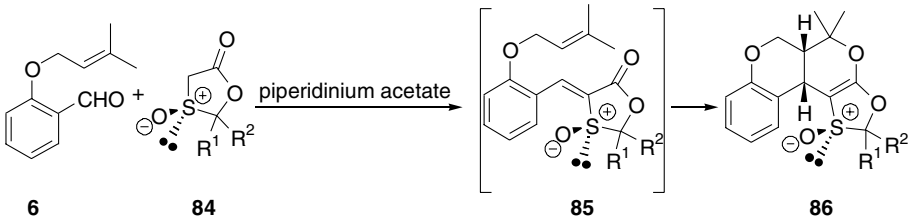
Scheme 5.13. Synthesis of leporin A **78a**.

ino process of **80** and **81** (Scheme 5.13) furnished the desired cycloadduct **78c** and also the spiro compound **83a** together with a diastereomer **83b** of undefined stereochemistry in 35% and 32% yield, respectively. In addition, around 4% of the trans-fused ring system **82** was also found.

It is not quite clear whether the spiro compounds **83** are obtained by a normal Diels–Alder reaction, since it could also be formed by a Claisen rearrangement occurring on adduct **82**. Actually, heating of the trans-fused adduct **82** in EtOH at reflux for 12 h led to **83a** with 65% conversion. On the other hand, the cis-fused adduct **78c** was completely stable under these conditions. Therefore, the 5:1 ratio

of **78c** and **82** isolated from the reaction mixture seems not to reflect the kinetic preference of the hetero- over the normal-Diels–Alder reaction, but it could be correlated to the instability of **82** under the reaction conditions. The first total synthesis of *rac*-leporin **78a** was completed by silylation of **78c** with TMSCl and subsequently oxidation with MoO_5·pyr·HMPA in CH_2Cl_2 with 57% yield. The resulting hydroxy pyridinone **78b** was then methylated with MeI to afford **78a** in 77% yield.

Another valuable system for the domino-Knoevenagel-hetero-Diels–Alder reaction is the chiral oxathiolane **84** which is easily accessible by condensation of 2-thioacetic acid and a ketone in the presence of *p*-TsOH followed by oxidation with hydrogen peroxide [25]. The Knoevenagel condensation of **84** with aldehydes such as **6** can be performed in dichloromethane in the presence of catalytic amounts of piperidinium acetate with azeotropic removal of water to give the benzylidene compound **85** in good yields and high (*Z*)-selectivity (Scheme 5.14). The cycloaddition takes place at 82 °C or with even better selectivity at room temperature by addition of $ZnBr_2$. In the latter case a single compound, **86**, with cis-annulation of the ring systems and anti-orientation of the aryl moiety to the oxygen of the sulfoxide, was obtained in 78% yield starting from acetone for the preparation of **84** ($R^1 = R^2 =$ Me). Thus, only one out of four possible diastereomers was formed. The transition structures have been calculated [25, 26]. Several other oxathiolanes and aldehydes for the domino-Knoevenagel-hetero-Diels–Alder reaction have also been used [25].



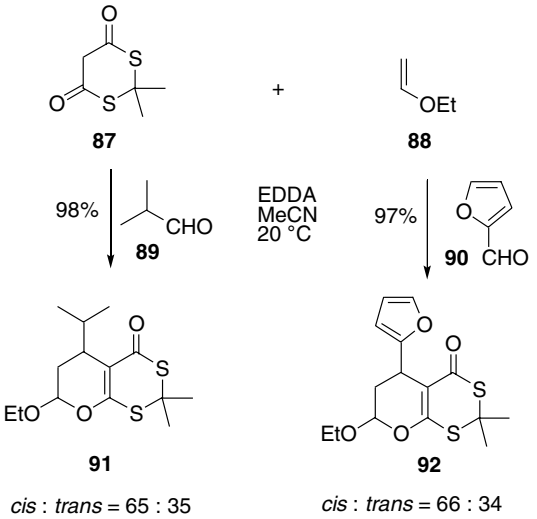
Scheme 5.14. Domino-Knoevenagel-hetero-Diels–Alder reaction of oxathiolanes.

5.3 Three- and Four-component-domino-Knoevenagel-hetero-Diels–Alder Reaction

The domino-Knoevenagel-hetero-Diels–Alder reaction can also be performed as three- and four-component transformations. In these processes the first step is again a Knoevenagel reaction of an aromatic, hetero-aromatic or aliphatic aldehyde with a 1,3-dicarbonyl compound; then the second step is an intermolecular hetero-Diels–Alder reaction of the formed 1-oxa-1,3-butadiene with a dienophile in the reaction mixture. The scope of this type of reaction and especially the possibility of obtaining highly diversified molecules is even higher than in the case of the two-component transformation; however, the stereoselectivity is less pronounced and so far only enol ethers as dienophiles give good results.

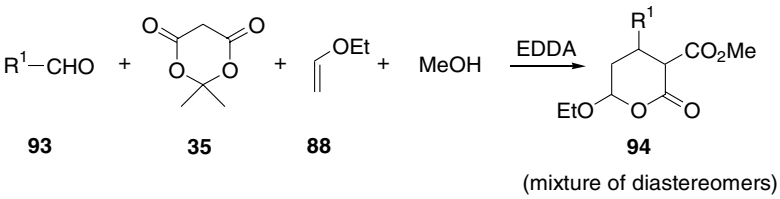
Thus, reaction of thia Meldrum's acid **87** with ethyl vinyl ether **88** with different

aldehydes such as **89** or **90** in the presence of EDDA in acetonitrile at room temperature gave the desired products **91** and **92**, respectively, in excellent yield but low diastereoselectivity (Scheme 5.15) [27].



Scheme 5.15. Three-component domino-Knoevenagel-hetero-Diels–Alder reaction.

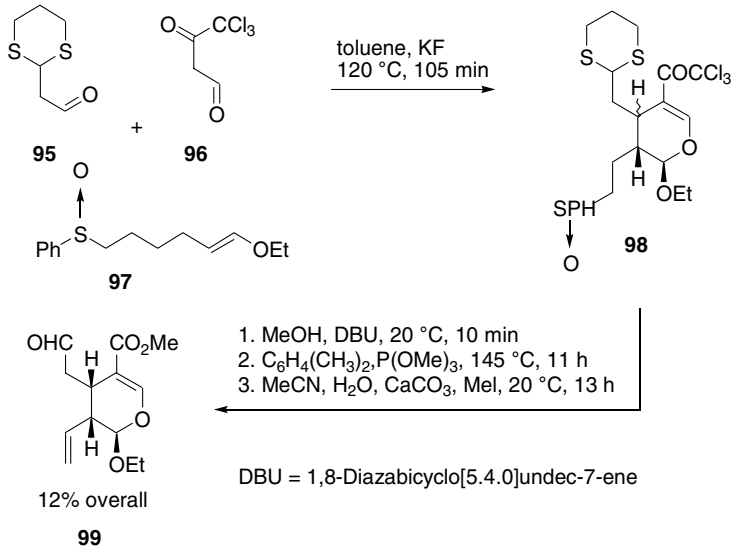
If one performs the transformation in an alcohol such as methanol with Meldrum's acid **35** as the 1,3-dicarbonyl compound, an opening of the Meldrum's acid moiety after the cycloaddition to give a lactone ester is observed. Thus, reaction of aldehyde **93** with Meldrum's acid **35** and ethyl vinyl ether **88** in methanol gave **94** (Scheme 5.16) [1a].



Scheme 5.16. Four-component domino-Knoevenagel-hetero-Diels–Alder reaction.

Generally, there is no limitation in the 1,3-dicarbonyl compound used. However, several types of these substances are not stable, such as malone dialdehydes or formyl acetic acid. In such cases, 1,1,1-trichloro-4-oxo-butanone **96** is an appropriate substitute, since the trichloromethylcarbonyl moiety can easily be transformed into a carboxylic acid ester after the reaction by treatment with an alcohol and a

base [28]. Thus, the secologanin aglucon ethyl ether **99** was obtained *via* a three-component domino Knoevenagel-hetero-Diels–Alder reaction of aldehyde **95** with enol ether **97** and the 1,3-dicarbonyl compound **96** to give the dihydropyran **98**, which already contains the complete carbon skeleton of **99** (Scheme 5.17). Solvolysis, elimination and cleavage of the thioacetal led to the desired secologanin derivative **99** [29].

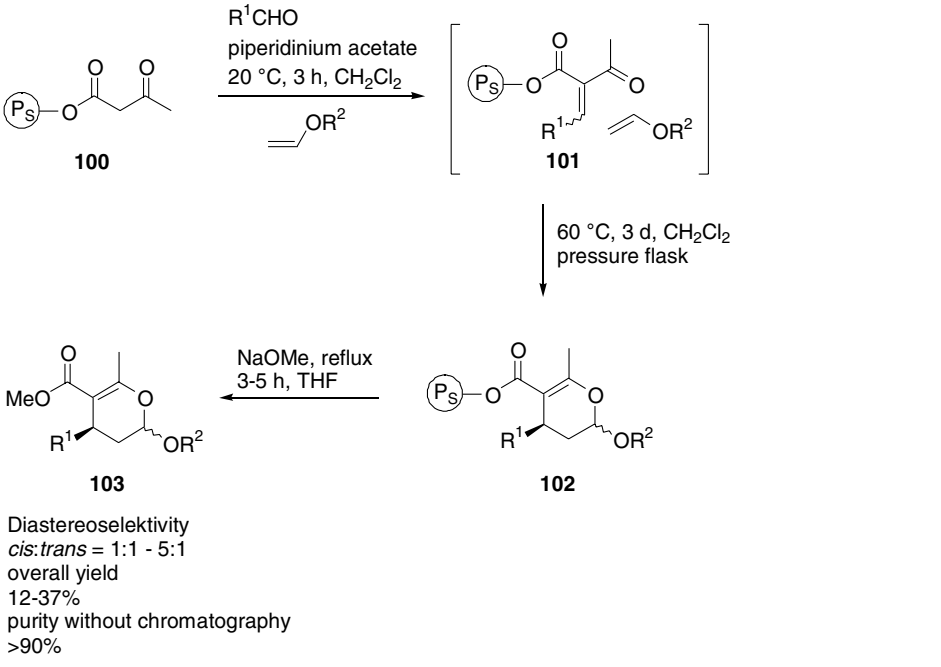


Scheme 5.17. Synthesis of secologanin aglucon ethyl ether **99**.

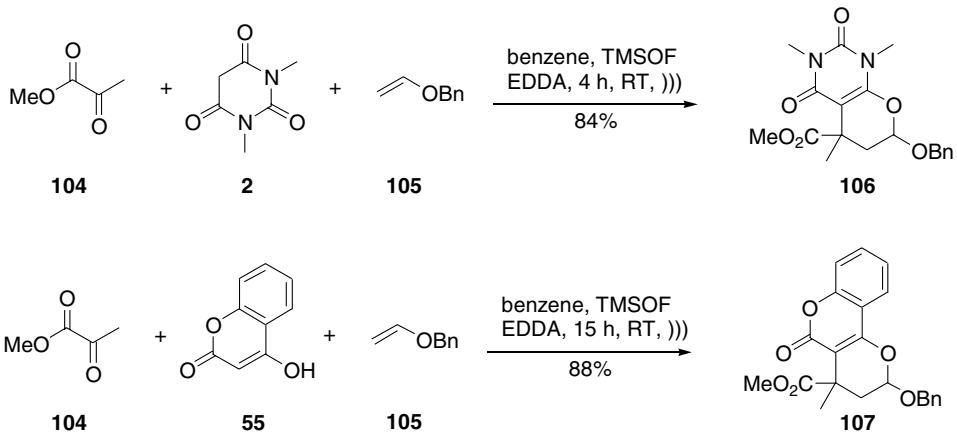
Solid-phase three-component domino-Knoevenagel-hetero-Diels–Alder reaction can also be performed using a resin-linked 1,3-dicarbonyl compound such as **100** with aldehydes and an enol ether to give dihydropyrans **102** *via* the intermediately formed 1-oxa-1,3-butadiene **101** (Scheme 5.18) [30]. The resin can be cleaved off after the reaction by solvolysis, for instance using sodium methanolate to give the corresponding methyl ester **103** as a mixture of diastereomers. The overall yield varies from 12 to 37% and the selectivity from 1:1 to 1:5 in favor of the cis-product depending on the applied aldehyde. The crude dihydropyrans thus obtained are reasonably pure (> 90% HPLC).

Besides aldehydes, α-ketoesters can also be used in the domino process [31]. Reaction of methyl pyruvate **104** with dimethylbarbituric acid **2** and enol ether **105** in the presence of trimethyl orthoformate (TMSOF) and a catalytic amount of EDDA gave the cycloadduct **106** (Scheme 5.19).

In a similar transformation using 4-hydroxycoumarin **55** as the 1,3-dicarbonyl compound the cycloadduct **107** was obtained also in good yield. To show the general applicability of this process a small library also using substituted pyruvate was prepared without optimizing the reaction conditions for the single transformations (Figure 5.2); α-ketonitriles can also be used, but with much lower yield.



Scheme 5.18. Solid-phase three-component domino-Knoevenagel-hetero-Diels–Alder reaction.



Scheme 5.19. Domino-Knoevenagel-hetero-Diels–Alder reaction with pyruvate.

The three-component domino-Knoevenagel-hetero-Diels–Alder reaction is especially fruitful if one uses aldehydes containing a protected amino function. In such cases the formed dihydropyranyl ether moiety can be used as a source of an aldehyde moiety that can undergo a condensation with the amino group after deprotection. Thus, several alkaloids such as hirsutine **108**, dihydrocorynantheine

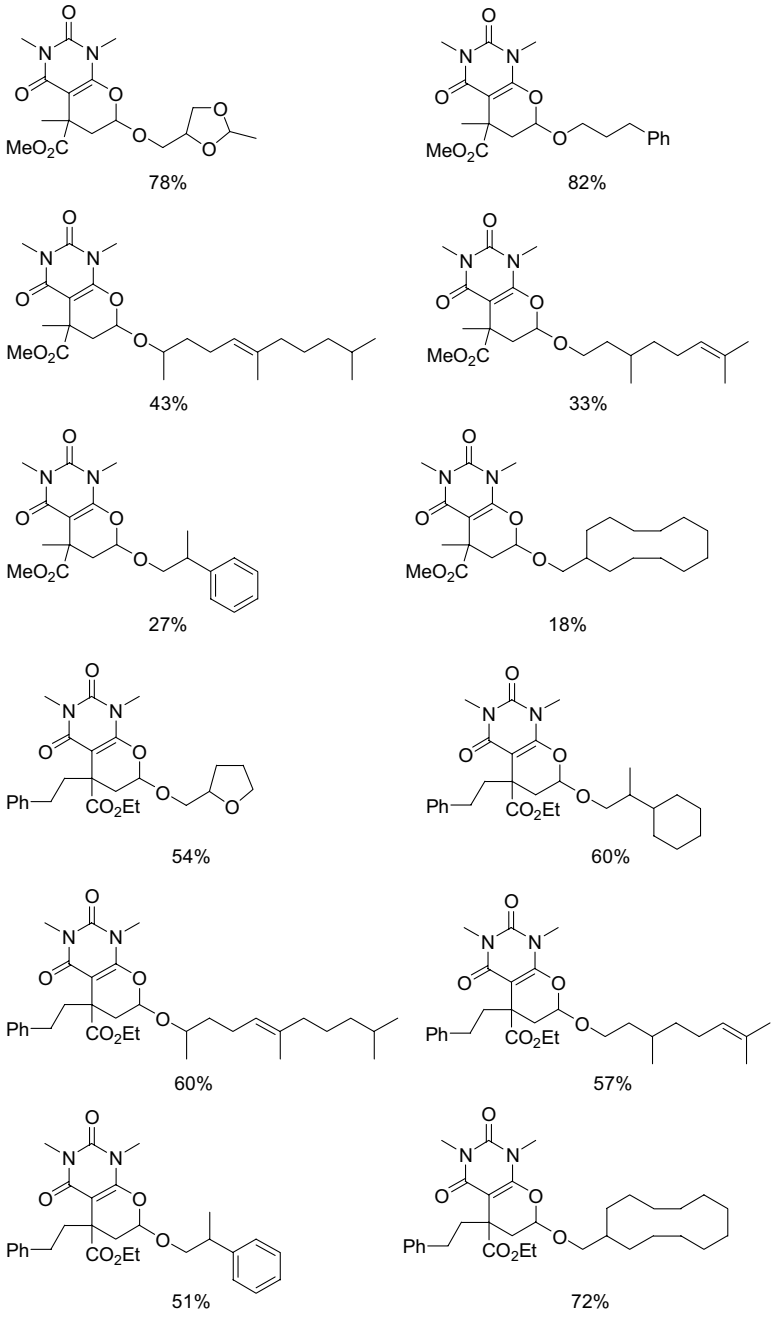


Fig. 5.2. Library of dihydropyrans obtained from α-ketoacid esters.

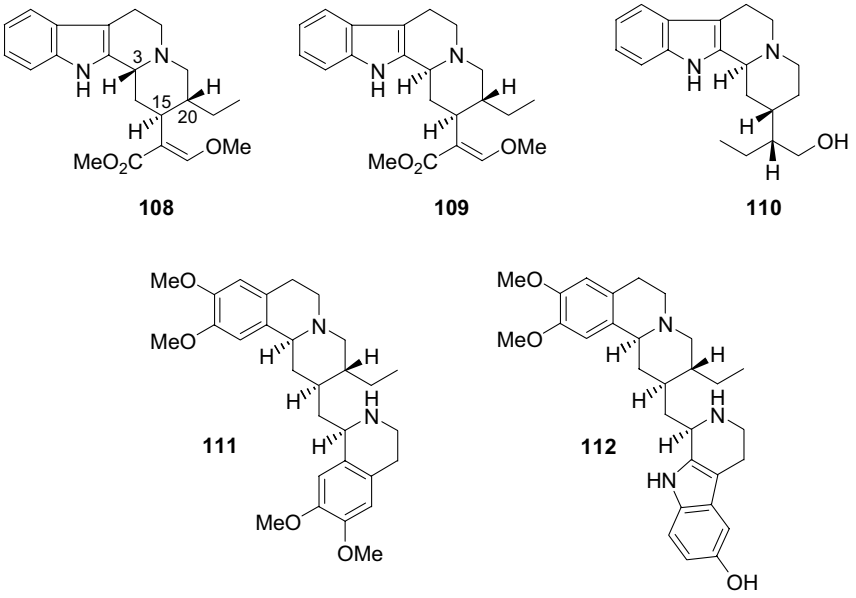


Fig. 5.3. Alkaloids synthesized by a three-component domino-Knoevenagel-hetero-Diels–Alder reaction.

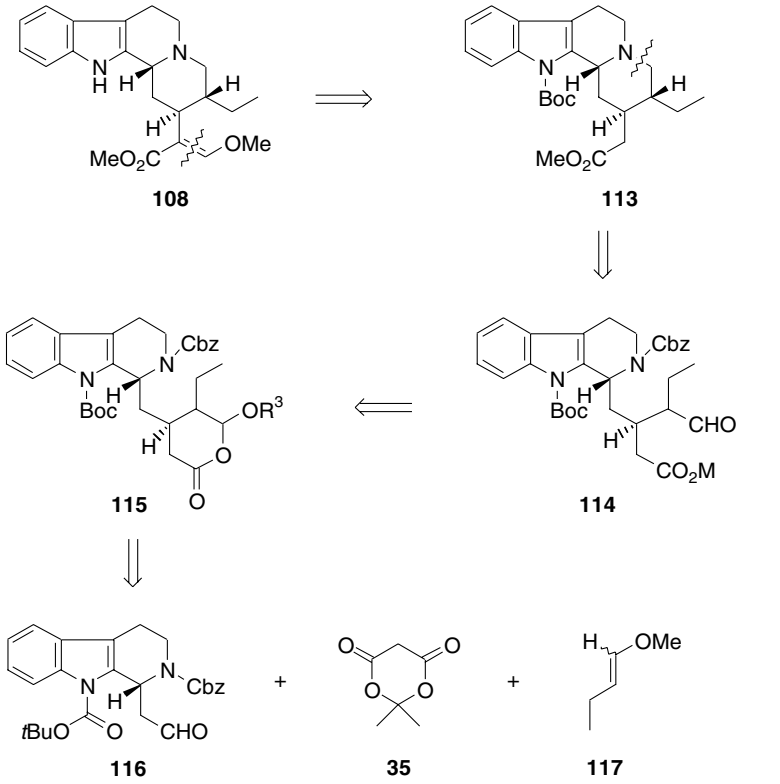
109, dihydroantirhin **110**, emetine **111** and tubulosine **112** (Figure 5.3) have been synthesized using this approach. In addition, two new concepts in combinatorial chemistry were developed based on this type of domino-Knoevenagel-hetero-Diels–Alder reaction.

Hirsutin **108**, which belongs to the corynanthe subgroup of the indole alkaloids, was isolated from the plant *Uncaria rhynchophylla* MIQ and used for the preparation of the old chinese folk medicine "Kampo" [32]. It is of pharmacological interest since it shows a strong inhibitory effect on the influenza A virus (subtype H3N2) with an EC_{50} of 0.40–0.57 μg ml^{-1}, which corresponds to a 11–20 higher bioactivity of hirsutin **108** compared to clinically used Ribavirin [33].

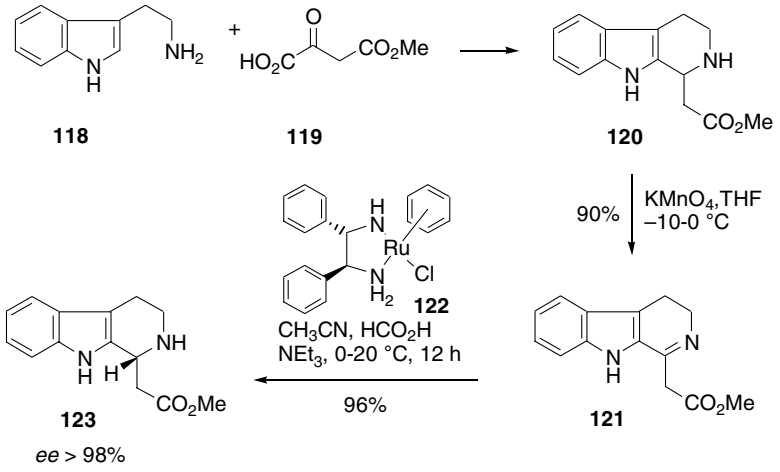
Retrosynthetic analysis of hirsutin **108** led to the tetrahydro-*β*-carboline (3*R*)-aldehyde **116**, Meldrum's acid **35** and the enol ether **117** *via* the retrosynthetic intermediates **113–115** (Scheme 5.20) [34].

The enantiopure aldehyde **116** could easily be obtained from ester **123** *via* an enantioselective transfer hydrogenation of the dihydrocarboline **121** with triethyl ammonium formate in the presence of the chiral Ru-catalyst (*S*,*S*)-122 developed by Noyori [35]; imine **121** is accessible by oxidation of *rac*-120 (Scheme 5.21) [36].

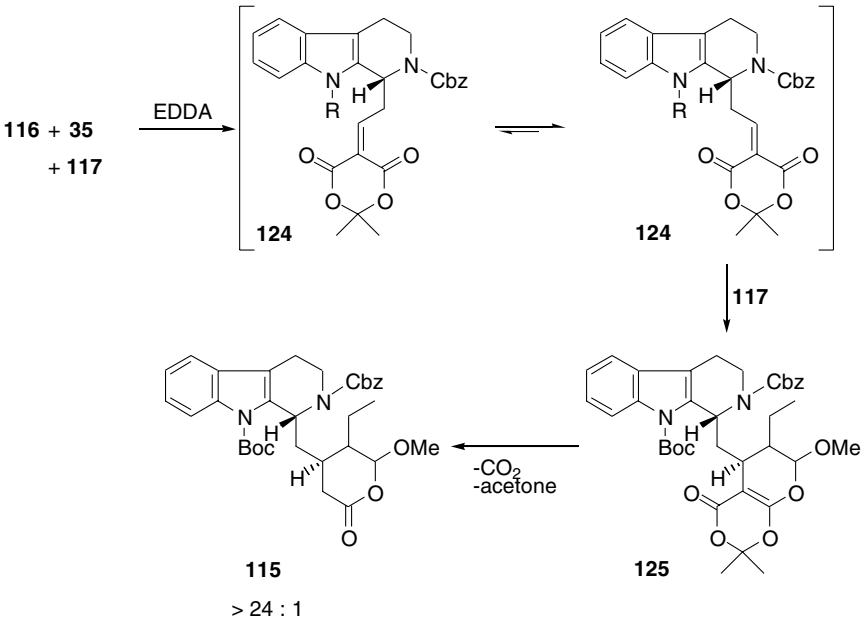
Reaction of aldehyde **116** with Meldrum's acid **35** and enol ether **117** ($E/Z = 1{:}1$) in the presence of a catalytic amount of EDDA for 4 h gave **115** in 90% yield with a 1,3 induction of >24:1; the Knoevenagel product **124** and the primarily produced cycloadduct **125** can be proposed as intermediates, the latter losing CO_2 and acetone by reaction with water formed in the condensation step (Scheme 5.22).



Scheme 5.20. Retrosynthesis of hirsutin **108**.

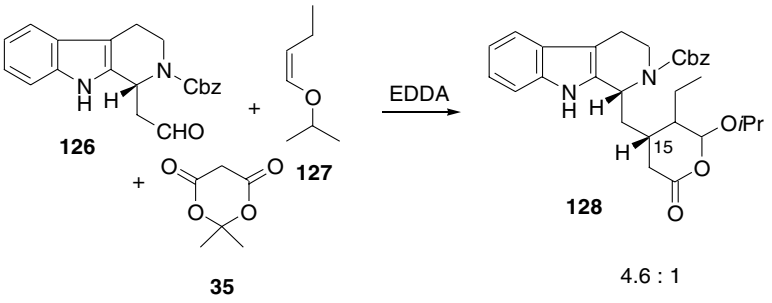


Scheme 5.21. Enantioselective hydrogenation of imines.



Scheme 5.22. Domino-Knoevenagel-hetero-Diels–Alder reaction of **116**, **35** and **117**.

Surprisingly, reaction of (3*R*)-aldehyde **126** containing an indole-*NH* group with **35** and **127** led to the epimer **128** with the opposite configuration at C15 as the main product although with a lower 1,3 induction of 4.6:1 (Scheme 5.23).

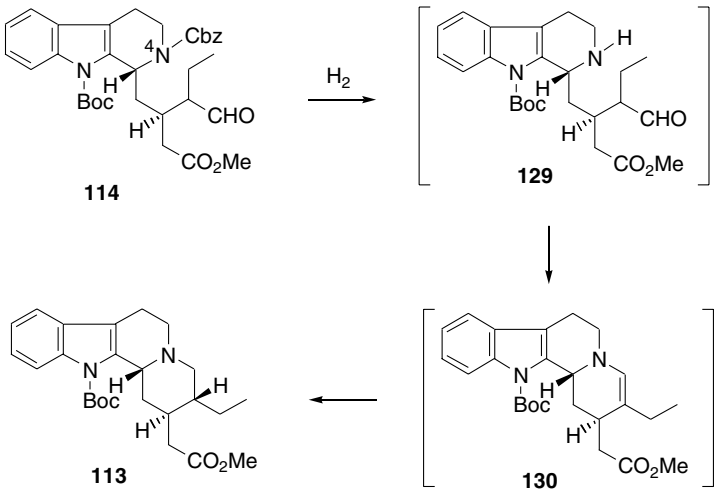


Scheme 5.23. Domino-Knoevenagel-hetero-Diels–Alder reaction of **126**, **35** and **127**.

The different facial selectivity can be explained by assuming a different conformation of the intermediately formed 1-oxa-1,3-butadiene moiety **124** as **124a** or **124b** in the transition state (Scheme 5.23). In the case of aldehyde **126** with the indole-NH group an interaction of the non-bonding electrons at the indole nitrogen with the π^*-orbital of the alkylidene-1,3-dicarbonyl group or the formation of a hydrogen bond between the NH and one of the carbonyl groups may stabilize the conformation **124a** (R = H) in the transition state, whereas using aldehyde

116 with an indole *N-tert*-butoxycarbonyl group the opposite conformation of the 1-oxa-1,3-butadiene as in **124b** (R = Boc) would be more populated since **124a** (R = Boc) is expected to be destabilized by steric interactions. The discussion is complicated by the fact that in **124** two 1-oxa-1,3-butadiene moieties, namely (*E*) and (*Z*), exist; however, as already discussed, it can be assumed that the (*E*)-1-oxa-1,3-butadiene is more reactive. The attack of the dienophile at the (*E*)-1-oxa-1,3-butadiene moiety in both **124a** and **124b** (R = H and R = Boc) should take place syn to the hydrogen at the stereogenic center C3 as the less hindered side, which in the case of **124b** would yield **125** and for **124a** a diastereomer with opposite configuration at C15 owing to different facial selectivity (Scheme 5.23).

Solvolysis of crude **115** with methanol in the presence of K_2CO_3 led to an opening of the lactone moiety with the formation of a methyl ester and a hemiacetal, which loses methanol to give the corresponding methyl ester with an aldehyde moiety. Under the following hydrogenolytic conditions the carbobenzoxy group at nitrogen N4 is removed to form the secondary amine **129**, which reacts with the aldehyde moiety to give enamine **130**. Under the reaction conditions the enamine is hydrogenated to produce indoloquinolizidine **113** as a single diastereomer in enantiopure form in a stereo-electronically controlled reaction *via* a chair-like transition state (Scheme 5.24).

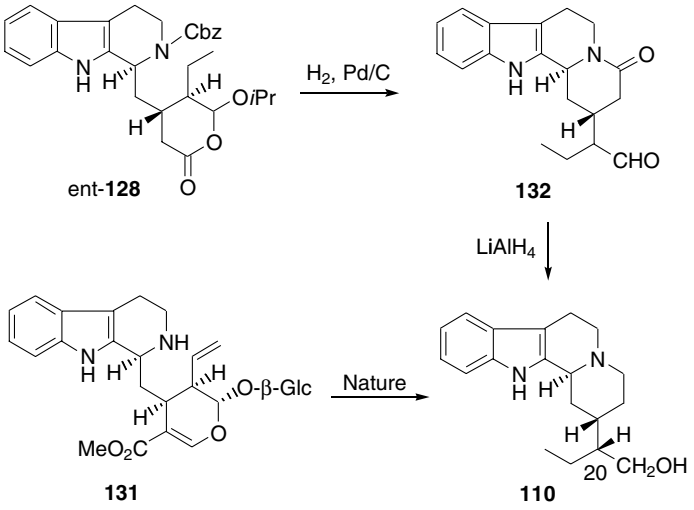


Scheme 5.24. Synthesis of quinolizidine **113**.

The synthesis of (−)-hirsutine **108** from **113** was concluded by removal of the Boc-group, condensation with methyl formate and methylation of the formed enol moiety. In a similar way to that described for **108**, (+)-dihydrocorynantheine **109** [37] with the (3*S*)- and (15*R*)-configuration was synthesized from *ent*-128.

The described approach also allows simple access to indole alkaloids of the vallesiachotamine type which in nature are formed by condensation of N4 with C17 in

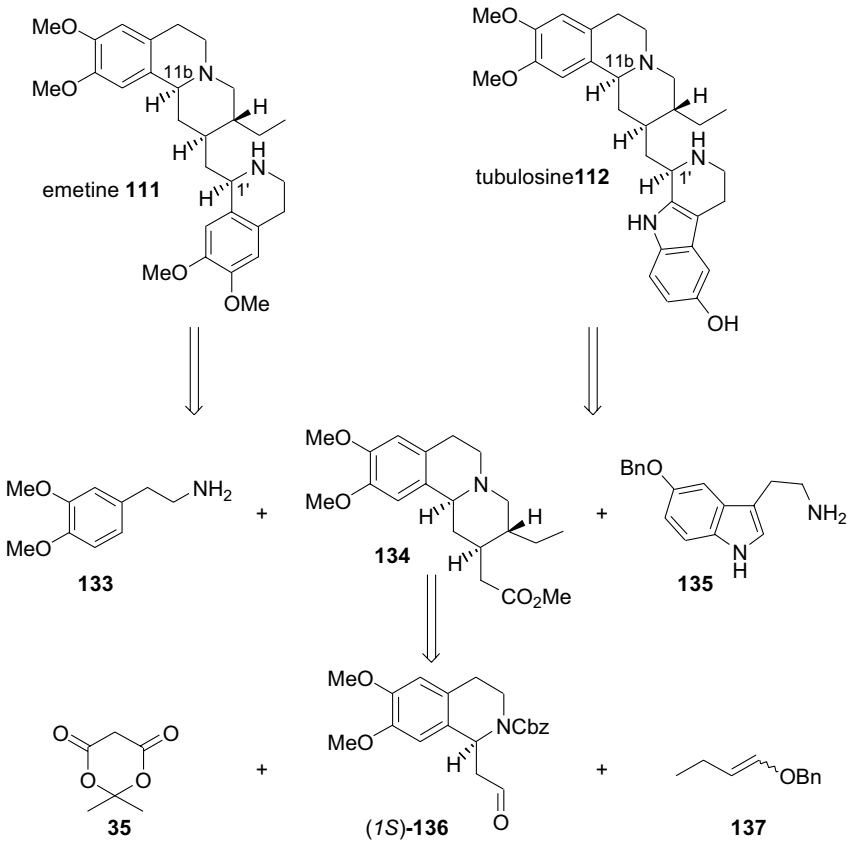
the intermediate strictosidine **131**. In this process the secondary amine in *ent*-128 is deprotected by hydrogenolysis, which then attacks the lactone moiety to form **132** containing a lactam and an aldehyde moiety. Reduction of **132** with lithium aluminum hydride group led to the indole alkaloid (−)-dihydroantirhin **110** [38]; the obtained product contains about 10% of the 20-epimer (Scheme 5.25) [39].



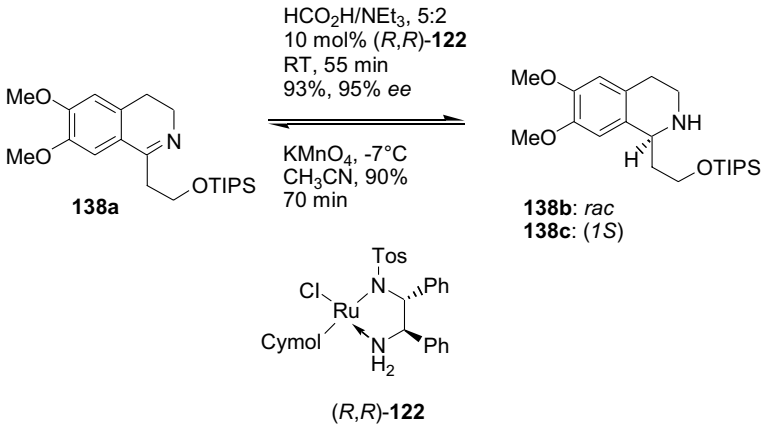
Scheme 5.25. Synthesis of dihydroantirhin.

Another class of alkaloids that has recently be synthesized using a three component domino-Knoevenagel-hetero-Diels–Alder reaction (Scheme 5.26) are the ipecacuanha alkaloids such as emetine **111** [40] and the alangium alkaloids such as tubulosine **112** [41], which both belong to the group of tetrahydroisoquinoline alkaloids and are formed in nature from dopamine and the monoterpene secologanin. Emetine **111** was isolated from *Radix ipecacuanha* and the roots of *Psychotria ipecacuanha* and *Cephalis acuminata* and possesses manifold interesting biological activities [42]. It shows antiprotozoic properties and activity in the treatment of lymphatic leukemia; formerly it was applied as emetic. Emetine is no longer used as a drug because of its considerable toxicity. Tubulosine **112** was isolated from the dried fruits of *Alangium lamarckii* and the sap of *Pogonopus speciosus*. It is remarkably active against several cancer cell lines and has been studied for various other biological activities, such as inhibition of protein biosynthesis and HIV reverse transcriptase inhibitory activities [43].

The retrosynthesis of **111** and **112** led to the amines **133** and **135**, respectively and the benzoquinolizidine **134**, which can be obtained by a domino-Knoevenagel-hetero-Diels–Alder reaction of the tetrahydroisoquinolinacetaldehyde (*S*)-**136**, Meldrum's acid **35** and the enol ether **137** (Scheme 5.26) [44]. The stereogenic centre in (*S*)-**136** was introduced *via* a transfer hydrogenation of dihydrohy-



Scheme 5.26. Retrosynthesis of emetine **111** and tubulosine **112**.

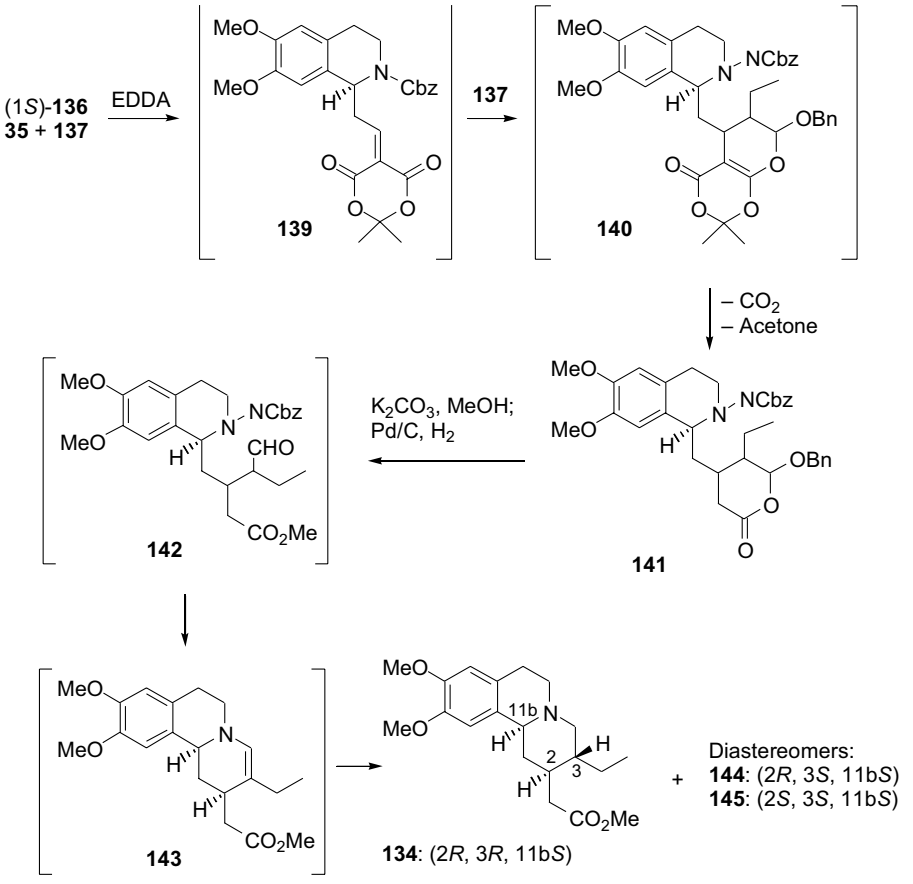


Scheme 5.27. Enantioselective hydrogenation of dihydroisoquinoline **138a**.

droisoquinoline **138a** with the chiral Ru-catalyst (*R*,*R*)-**122** [35] in 93% yield and 95% *ee* (Scheme 5.27). **138a** was prepared from the corresponding racemic tetrahydroisoquinoline **138b** by oxidation with $KMnO_4$ at −7 °C.

The domino reaction of (1*S*)-**136**, Meldrum's acid **35** and enol ether **137** in the presence of a catalytic amount of EDDA led to **141** *via* intermediates **139** and **140**. The cycloadduct **141** was not isolated, but treated with K_2CO_3/MeOH and a catalytic amount of Pd/C in methanol under a nitrogen atmosphere for 50 min and afterwards under a H_2 atmosphere for 2 h at room temperature to give benzoquinolizidine **134** with the correct stereochemistry at all stereogenic centres as in emetine **111** together with the two diastereomers **144** and **145** in a ratio of (1.5:1.0:1.8) (**134**:**144**:**145**) and an overall yield of 66% based on (1*S*)-**136** (Scheme 5.28).

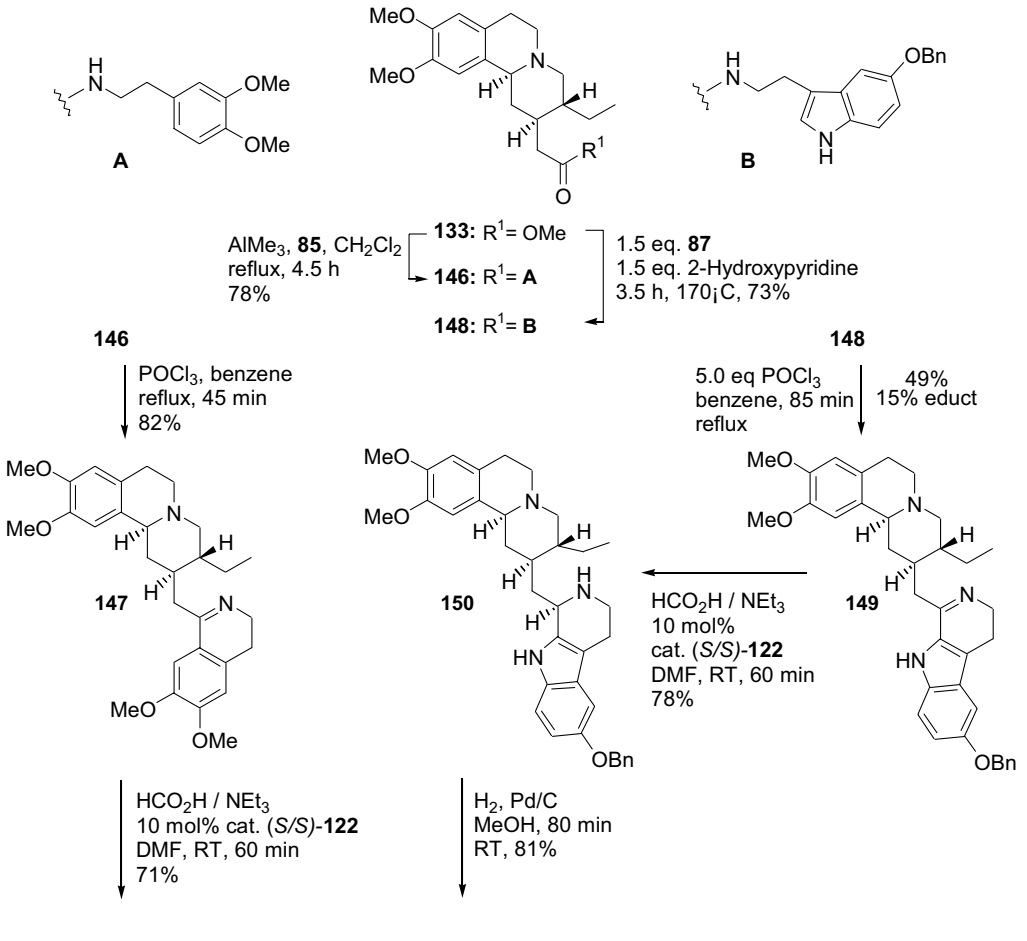
The diastereomers were separated by column chromatography and pure **134** was used for the synthesis of emetine **111** and tubulosine **112**. As intermediates in the



Scheme 5.28. Domino process for the synthesis of benzoquinolizidine **134**.

second domino process amino aldehyde **142** and enamine **143** can be assumed. Thus, in the first step the lactone moiety in **141** is attacked by methoxide to give a methyl ester and a hemiacetal which loses benzyl alcohol providing the corresponding aldehyde **142**. Hydrogenolytic removal of the Cbz protecting group leads to the corresponding secondary amine, which reacts with the aldehyde moiety to afford either an iminium ion or enamine **143**; both moieties would be hydrogenated under the reaction conditions.

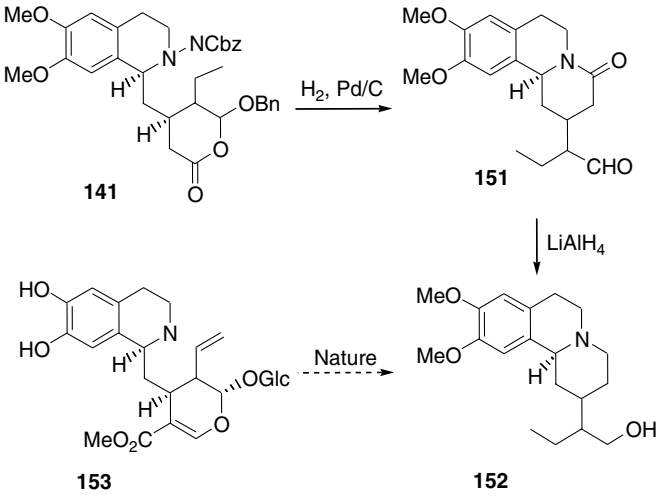
For the synthesis of emetine **111**, benzoquinolizidine **134** was treated with phenylethylamine **133** and trimethyl aluminum to give amide **146** which could then directly be transformed into the desired imine **147** using $POCl_3$. The final step towards emetine **111** was transfer hydrogenation using (*S*,*S*)-**122**, which allowed the introduction of the fourth stereogenic centre with a d.s. > 98:1 (Scheme 5.29).



Scheme 5.29. Synthesis of emetine **111** and tubulosine **112**.

In a similar approach, the alkaloid tubulosine **112** was synthesized by reaction of the benzoquinolizidine **135** with *O*-benzylseretonine **135**. Reaction of **133** and **135** in the presence of 2-hydroxypyridine allowed the formation of amide **148** in 73% yield, which is followed by a Bischler–Napieralski reaction to give the desired imine **149** in 49% yield. Transfer hydrogenation of **149** again using the catalyst (*S*,*S*)-**122** in the presence of triethyl ammonium formate gave tetrahydro-*β*-carboline **150** in 78% yield and a d.s. of >98:1. Cleavage of the benzyl ether by hydrogenolysis using Pd/C as a catalyst provided tubulosine **122** in high purity (Scheme 5.29).

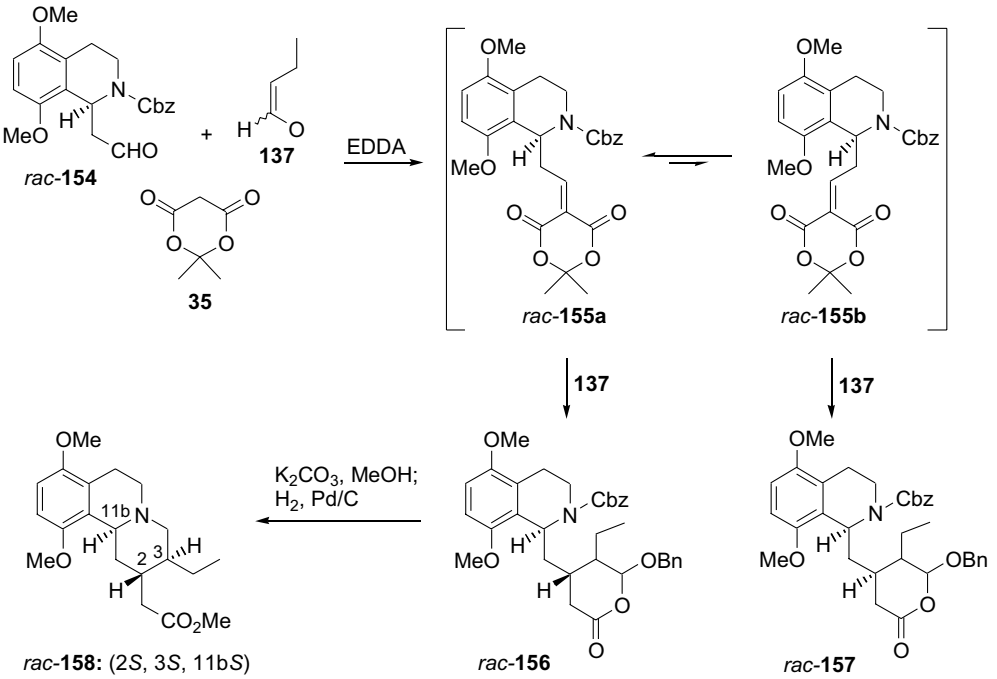
The diversity of the products obtained by the three-component domino-Knoevenagel-hetero-Diels–Alder reaction can be further increased by a different work-up of the formed cycloadduct **141**. Thus, hydrogenolytic removal of the Cbz-group in **141** led to **151** with a lactam and an aldehyde moiety by reaction of the formed secondary amine with the lactone moiety followed by elimination of benzyl alcohol. Reduction of **151** with lithium aluminum hydride gave benzoquinolizidine **152** (Scheme 5.30). Alkaloids of this type have so far not been found in nature, but it can be assumed that they might exist, since they could easily be formed from deacetylisopecoside **153**, which is an intermediate in the biosynthesis of emetine **111**.



Scheme 5.30. Synthesis of novel benzoquinolizidine alkaloids.

The formation of the three diastereomers **134**, **144** and **145** in the twofold-domino processes of (*S*)-**136**, **35** and **137** is primarily due to the flexibility of the 1-oxa-1,3-butadiene moiety in **139**, which can exist in the two different conformations. To improve the induced diastereoselectivity in the cycloaddition, benzyltetrahydoisoquinolineacetaldehyde **154** was synthesized, which contains a methoxy group at the 8-position [45]. The Knoevenagel condensation of **154** and Meldrum's

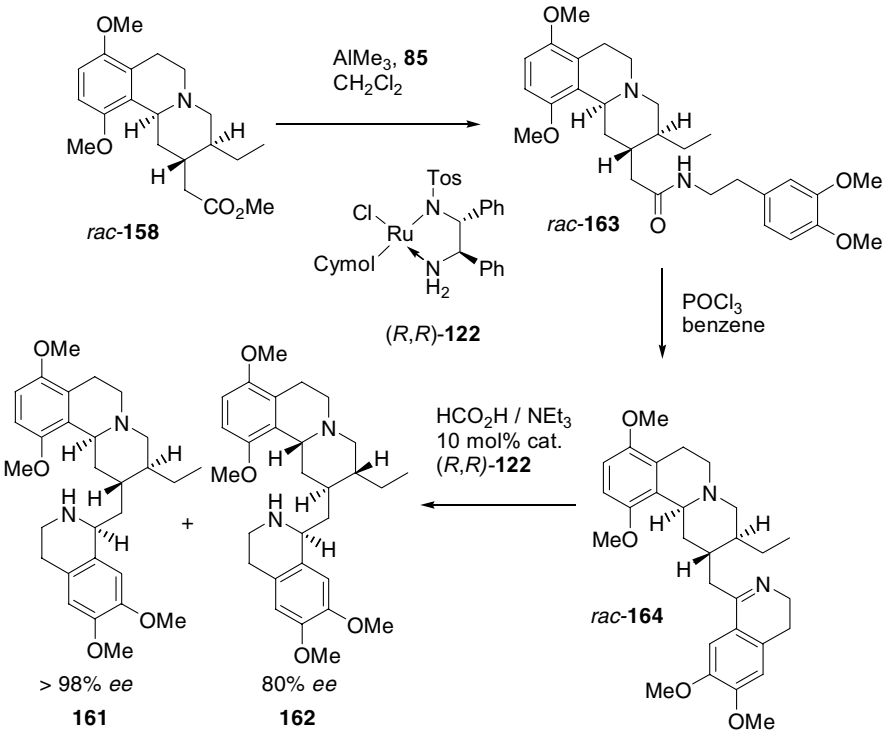
acid **35** leads to 1-oxa-1,3-butadiene **155**, which could exist in the two conformations **155a** and **155b**. Steric hindrance is probably unfavorable to conformer **155b**, which should be less populated in the transition state. Thus cycloaddition with enol ether **137** should take place preferentially at **155a** from below as the less hindered side to give **156** as the main product together with the diastereomer **157**. Indeed, the domino-Knoevenagel-hetero-Diels–Alder reaction of **154**, Meldrum's acid **35** and the enol ether **137**, followed by solvolysis with potassium carbonate and methanol as well as hydrogenation using Pd/C as catalyst afforded benzoquinolizidine **158** together with the two diastereomeric benzoquinolizidines **159** and **160** in a 7:1:1 ratio (Scheme 5.31).



Scheme 5.31. Synthesis of benzoquinolizidine **158**.

Formation of amide **163** from **158** and 3,4-dimethoxyphenylethylamine **133**, followed by a Bischler–Napieralski reaction and transfer-hydrogenation of the formed imine **164** with the ruthenium catalyst (*S*,*S*)-**122** (Scheme 5.32) gave the enantionpure epi-emetine analogue **161** (> 98% *ee*) and the enantioenriched diastereomer **162** (80% *ee*).

Another three-component domino-Knoevenagel-hetero-Diels–Alder reaction has

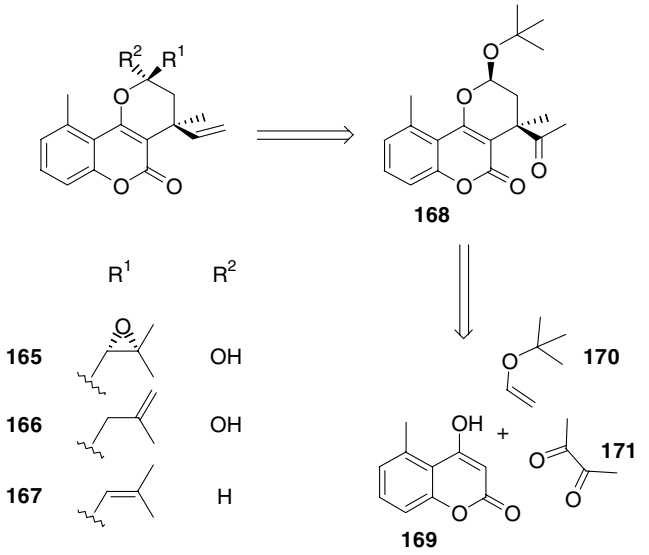


Scheme 5.32. Synthesis of the isoemetine analogues **161** and **162**.

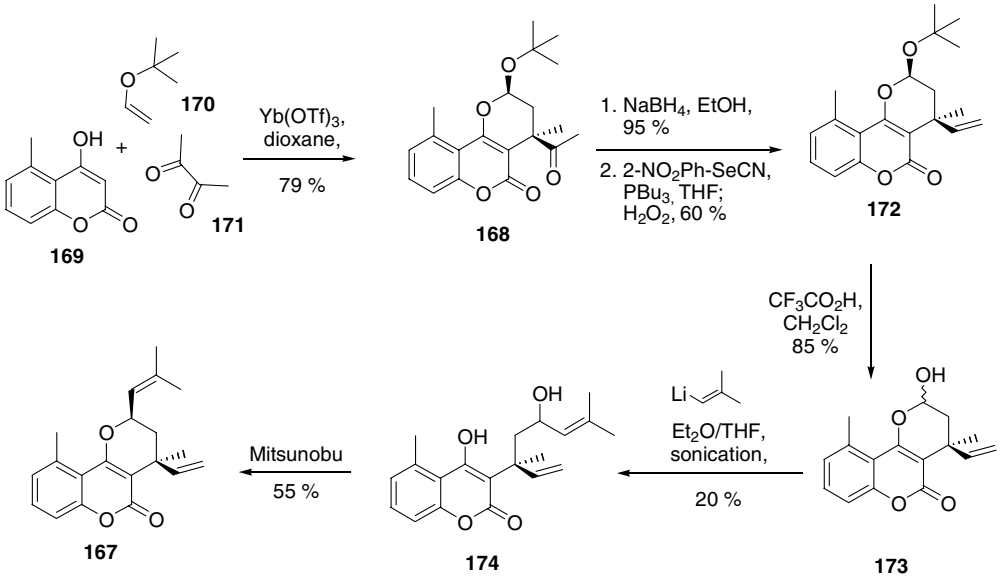
been used for the total synthesis of *rac*-preethulia coumarin **167** and analogues, employing previously unused α-diketones as the electrophilic carbonyl compound in the Knoevenagel condensation [46].

The class of shikimate-derived coumarins has been extensively investigated for their anticoagulant and phototoxic properties. In particular, the anthelmintic and molluscicidal properties of ethulia coumarin A **165** and the related analogues **166** and **167** were the reason for further synthetic investigations. **167** is accessible in sizeable amounts by isolation, but their plant source is not readily available. The retrosynthetic analysis of **167** (Scheme 5.33) led to acetal **168**, which is easily accessible by a domino-Knoevenagel-hetero-Diels–Alder reaction of 4-hydroxycoumarin **169**, *t*-butyl vinyl ether **170** and α-diketone **171** in the presence of $Yb(OTf)_3$ in 79% yield (Scheme 5.34). Transformation of **168** in a reduction–elimination sequence afforded **172**, which was followed by cleavage of the acetal to give **173** and addition of a vinyl lithium species to the formed aldehyde. Unfortunately, the latter reaction gave **174** in only 20% yield, and this was transformed into the preethulia coumarin **167** using a Mitsunobo reaction.

Another useful application of the domino-Knoevenagel-hetero-Diels–Alder reaction is a two-step synthesis of chiral non-racemic anticoagulants such as warfarin **175**, coumachlor **176** and acenocoumarol **177** (Scheme 5.35) [47]. Warfarin **175**

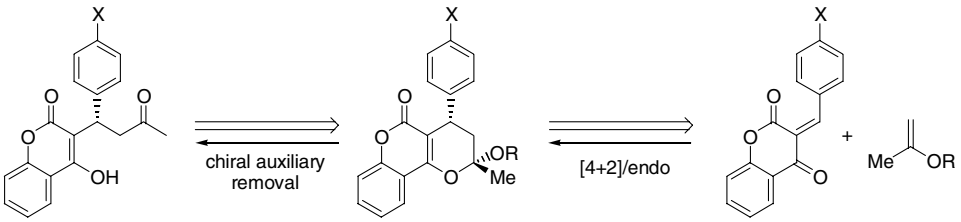


Scheme 5.33. Retrosynthetic analysis of preethulia coumarin **167**.



Scheme 5.34. Synthesis of preethulia coumarin **167**.

is the dominant coumarin anticoagulant and it is sold as the racemic sodium salt (Coumadin®). Since it is known that the (*S*)-(−)-enantiomer is six times more active than the (+)-enantiomer, an efficient synthesis of enantiopure (*S*)-(−)-warfarin would be beneficial.



175: X = H, warfarin
176: X = Cl, coumachlor
177: X = NO_2, acenocoumarol

178: X = H
179: X = Cl
180: X = NO_2

a: R = Me
b: R = (–)-menthyl

181 **182**

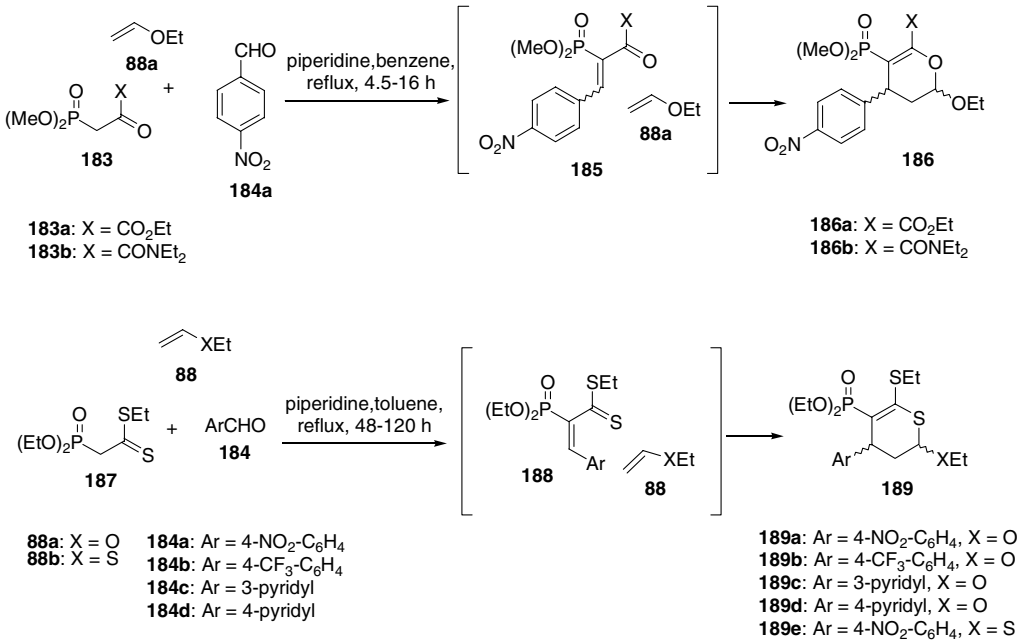
Scheme 5.35. Asymmetric synthesis of chiral non-racemic coumarin anticoagulants **175**–**177**.

In a first approach racemic **175**–**177** were synthesized by reaction of 4-hydroxycoumarin **55**, the corresponding aromatic aldehydes and 2-methoxypropen **182a** in dioxane at 90 °C in the presence of oven-dried 5-Å molecular sieves and a catalytic amount of EDDA. The products were isolated as a mixture of endo- and exo-cycloadducts with a ratio of 3:1 for **178a** and 1.3:1 to 2.1:1 for **179a** and **180a**. The isomers correspond to the cis- and trans-products regarding the 2-OMe and 4-Ph groups. Cleavage of the acetal moiety with a mixture of trifluoroacetic acid and water 19:1 furnished the coumarin anticoagulants in nearly quantitative yields.

The transformation could also be performed using a chiral enantiopure enol ether as dienophile. The best results were achieved with the isopropenyl ether **182b** derived from cheap and commercially available (−)-(1*R*,2*S*,5*R*)-menthol. The cycloadduct was obtained with an endo/exo-selectivity of 4.1:1 and an induced diastereoselectivity of 88:12. Treatment of **178b** with trifluoroacetic acid/water 19:1 provided (*S*)-warfarin **175** in an overall yield of 61% referred to 4-hydroxy coumarin **55** and an enantiomeric excess of 76% (HPLC), which could be increased to 95% *ee* by recrystallization using the purified endo-product **178b** as substrate for the hydrolysis. In the same manner (*S*)-coumachlor **176** and (S)-acenocoumarol **177** were obtained with 56% overall yield and 93% *ee* and 59% overall yield and 95% *ee*, respectively.

Instead of the usual 1,3-dicarbonyl compounds, hetero analogues such as the corresponding α-carbonylated phosphonates **183** can also be used in the domino-Knoevenagel-hetero-Diels–Alder process (Scheme 5.36) [48]. Reaction of **183** with aromatic aldehydes **184** and ethyl vinyl ether led to the expected 3,4-dihydro-2*H*-pyrans **186** *via* the intermediately formed 1-oxa-1,3-butadiene **185**. In a similar way an α-phosphono-dithioester **187** was also used, which gave the corresponding 3,4-dihydro-2*H*-thiopyrans **189** *via* **188** [49]. The transformations have been investigated under high pressure. The results were in accordance with the well established rule that under high pressure the more compact transition state is favored (Scheme 5.37) [50].

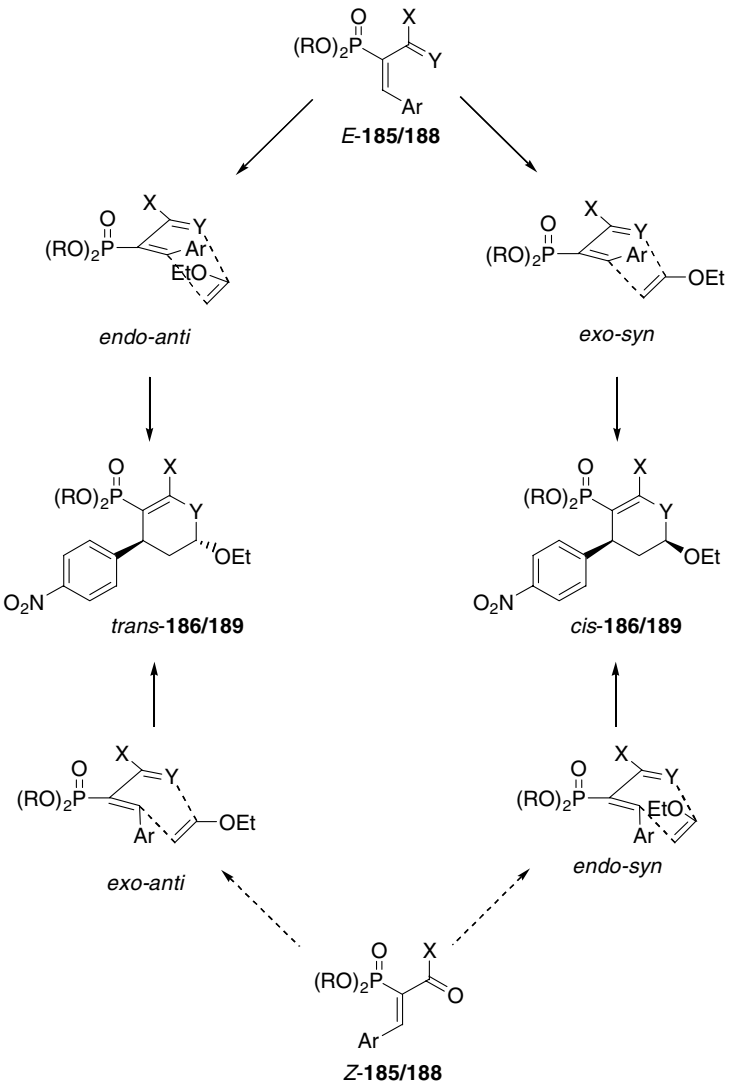
In the transformation of α-carbonylated phosphonate **183a** and benzaldehyde **184a** using a catalytic amount of piperidine as base, enol ether **88a** had to be added after complete formation of the Knoevenagel product (NMR-monitoring); other-



Scheme 5.36. Domino-Knoevenagel-hetero-Diels–Alder reaction of α-carbonylated phosphonates **183** and α-phosphonodithioesters **187** with aromatic aldehydes **184** and enol ethers **88**.

wise a so far unidentified unwanted product is formed. The dramatic difference in the diastereoselectivity of the domino reaction of **183a** with **184a** and **88a** in the presence of piperidine compared to the reaction of isolated (*E*)-**185a** with **88a** is worthy of note (table 5.3, entry 2 and 3). It was assumed that the piperidine plays a crucial role leading to a dominating dipolar cycloaddition mechanism, which was responsible for the change of selectivity. In the domino process of **183a** the cis-cycloadduct **186a** is the main product, whereas in the reaction of pure (*E*)-**185a** the trans-cycloadduct **186a** predominates. The role of piperidine is confirmed by the observation that pure (*E*)-**185a** also mainly reacts to the cis-product in the presence of this base. In contrast to the transformation of ester **185a** the (*E*)-configured α-carbonylated phosphonate **185b** reacted preferentially to the cis-substituted dihydropyran *cis*-**186** (*cis*:*trans* = 80:20) (table 5.3, entry 1 and 4), owing to a steric interaction of the bulky NEt_2 substituent at the diene with the dienophile, which makes the *exo–syn* transition state more likely (entry 4). In all cases the domino-process gave higher yields in comparison to the stepwise procedure.

Combinatorial chemistry is an important method for the development of pharmaceuticals [51], agrochemicals [52], catalysts [53] and materials [54]. It can be performed either on a solid phase or in solution, both processes having advantages and disadvantages. A procedure that combines the advantages of both is based on



Scheme 5.37. Transition structures for the formation of *trans*-**186**/**189** and *cis*-**186**/**189**.

a domino-Knoevenagel-hetero-Diels–Alder reaction of an N-protected amino aldehyde **190** with 1,3-dicarbonyl compound **191** and benzyl enol ether **192** [55]. After formation of the Diels–Alder adduct **194** *via* **193**, the carbobenzoxybenzyl group is taken off by hydrogenolysis using Pd/C as catalyst to give a free amino function; simultaneously also the benzyl moiety is also removed from the acetal to give an aldehyde which reacts with the amino function forming an enamine, being reduced under the reaction conditions (Scheme 5.38). The final products **195** contain a basic amino function and a C–H-acidic 1,3-dicarbonyl moiety which can form a

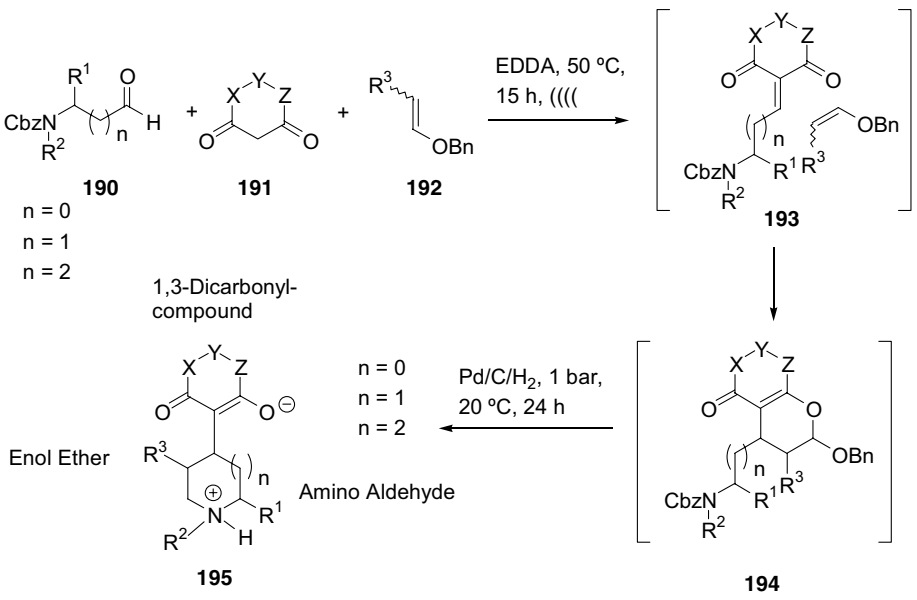
Tab. 5.3. Comparison of the domino-Knoevenagel-hetero-Diels–Alder reaction with the stepwise process.

Entry	*4-Nitro-benzaldehyde + substrate*	*Method*[a]	*Selectivity trans-186/189: cis-186/189*	*Yield [%]*
1	(*E*)-**185a**	A	70:30	58[b]
2	(*E*)-**185a**	B	72:28	58[b]
3	**183a**	C	24:76	87
4	(*E*)-**185b**	A	20:80	64[b]
5	(*E*)-**185b**	B	33:67	64[b]
6	**183b**	C	22:78	91

[a] A: Diels–Alder reaction in a sealed tube; B: Diels–Alder reaction under 10^9 Pa; C. Domino process using piperidine as a catalyst.
[b] Calculated yield of the stepwise process over two steps.

betaine and which can be precipitated in high purity from the reaction mixture by the addition of diethyl ether.

Thus, reaction of *N*-Cbz-protected α-, β- or γ-amino aldehydes **190** with 1,3-dicarbonyl compound **191** in the presence of benzyl enol ether **192** followed by hydrogenation led to substituted pyrrolidines, piperidines and azepanes as a mixture of diastereomers in >95% chemical purity in most cases.



Scheme 5.38. General scheme for a multicomponent domino-Knoevenagel-hetero-Diels–Alder-hydrogenation-sequence.

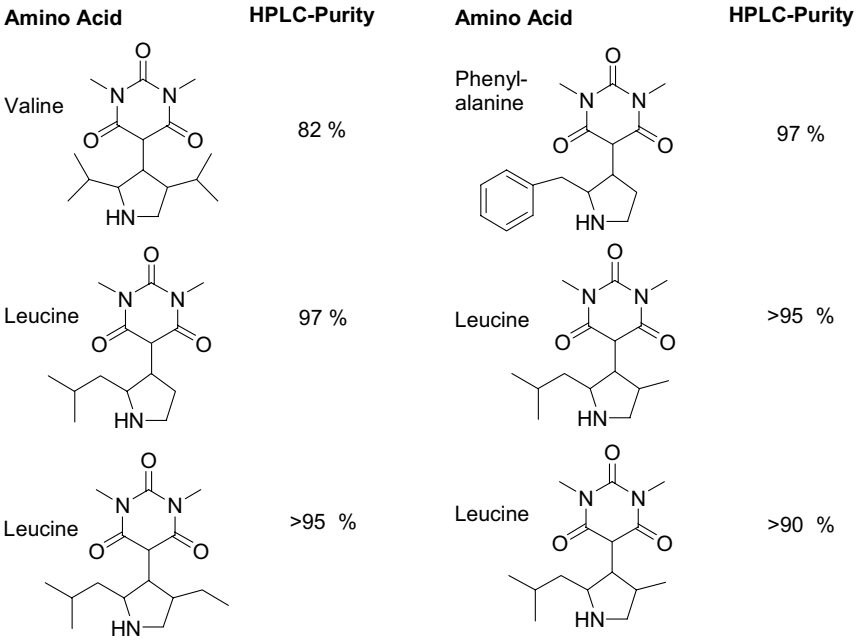


Fig. 5.4. Products of the domino-Knoevenagel-hetero-Diels–Alder-hydrogenation sequence of α-amino acids with *N*,*N*-dimethyl barbituric acid.

A small selection of pyrrolidines is given in Figure 5.4, which show scope and limitation of this procedure. Only in one case, where two isopropyl groups exist at the pyrrolidine molecule, a reduced purity of 82% of the precipitate was observed.

The necessary amino aldehydes are accessible from widely available amino acids and amino alcohols. In addition to *N*,*N*-dimethyl barbituric acid shown in Figure 5.3, other 1,3-dicarbonyl compounds can be employed, such as cyclohexane-1,3-diones or coumarines (Figure 5.5).

A disadvantage of the described method is the necessity of using preformed benzyl enol ethers, which are usually not available from stock and whose synthesis is not always a simple task. In addition, benzyl enol ethers of ketones are not available.

Therefore the value of the procedure is greatly improved by using trimethylsilyl (TMS) enol ethers **200**, which are easily accessible *in situ* from aldehydes and ketones in an (*E*)- or (*Z*)-selective way [56]. Here the liberation of the aldehyde moiety from the initially formed dihydropyran takes place under the reaction conditions after the cycloaddition. TBDMS ethers **197** are too stable and can not be used in the domino process (Scheme 5.39).

The reaction of TMS enol ether **200** with *N*,*N*-dimethylbarbituric acid **2** and the protected amino aldehyde **199** in the presence of TMOF and catalytic amounts of EDDA in an ultrasonic bath at 50–60 °C for 15 h followed by hydrogenation using

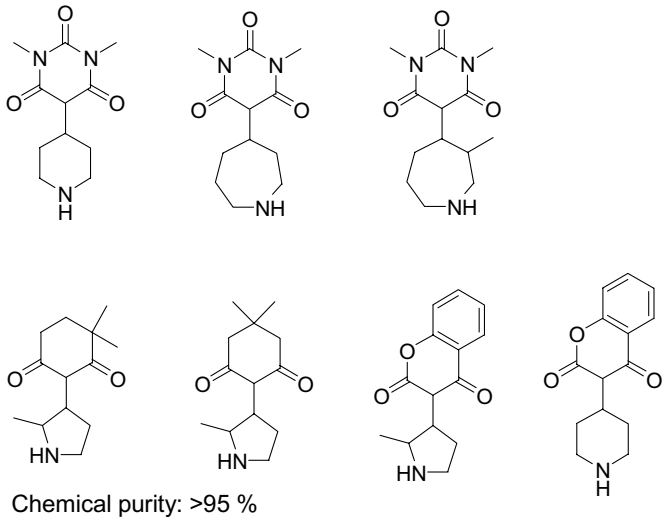
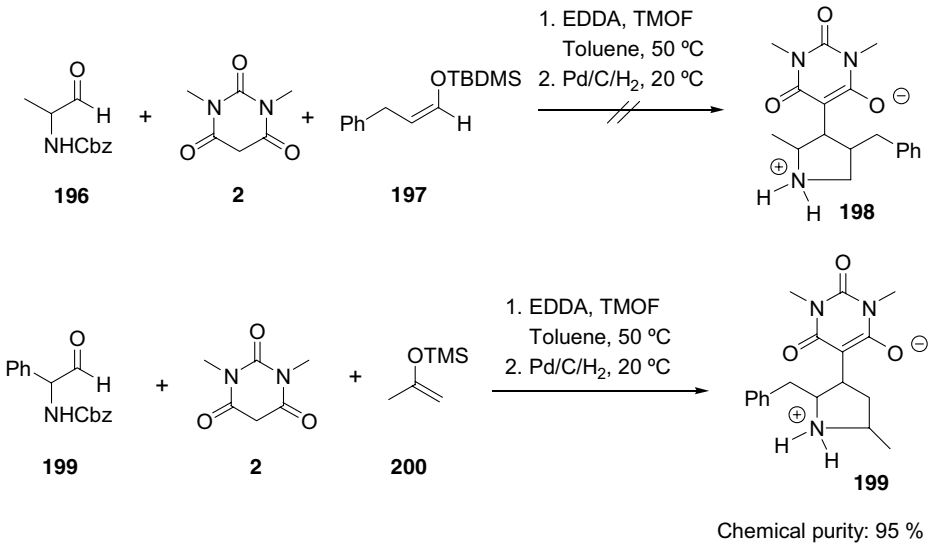
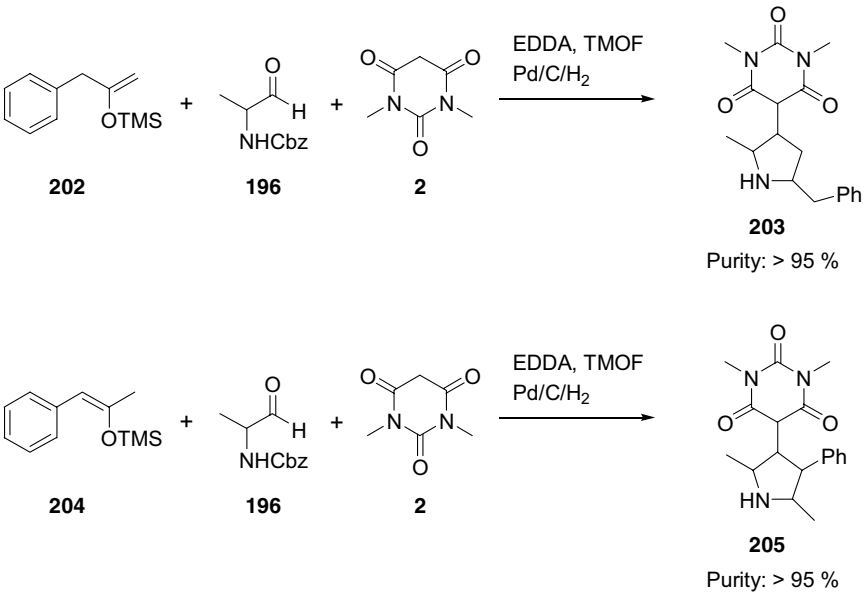


Fig. 5.5. Products of the multicomponent domino-Knoevenagel-hetero-Diels–Alder-hydrogenation sequence with α, β- and γ-amino aldehydes with different 1,3-dicarbonyl compounds.



Scheme 5.39. Domino-Knoevenagel-hetero-Diels–Alder-hydrogenation sequence with TMS enol ethers.

palladium on charcoal at 25 °C led to pyrrolidine **199**, which could be precipitated from methanol by adding diethyl ether, owing to its zwitterionic structure, in a purity of 98% according to HPLC (Scheme 5.39). TMS enol ethers of cyclic ketones are also suitable and diversity can be improved by making either the kinetic or

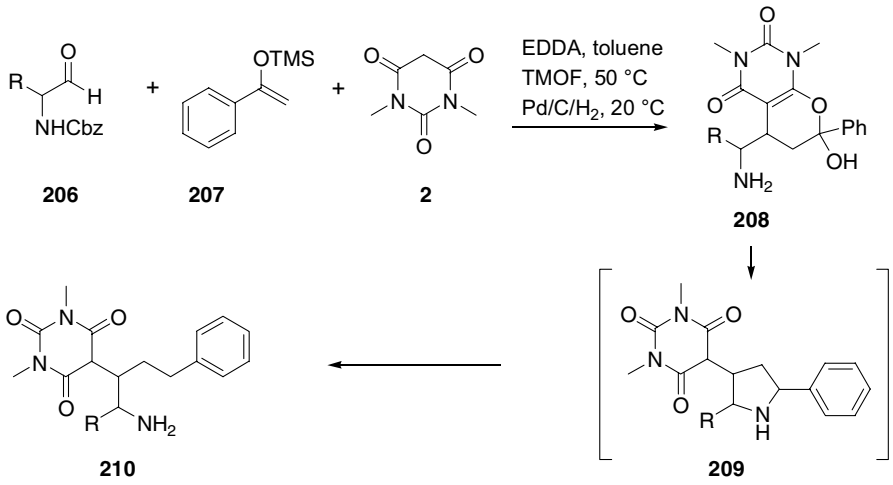


Scheme 5.40. Domino-Knoevenagel-hetero-Diels–Alder-hydrogenation sequence.

the thermodynamic enol ether employing methyl ketones (Scheme 5.40). Thus, reaction of TMS enol ether **202** formed from benzyl methyl ketone under kinetic control with **196** and **2** led to **203**, whereas with TMS enol ether **204**, formed under thermodynamic control, pyrrolidine **205** is obtained.

Using enol ethers of acetophenone **207** or similar compounds in a reaction with **206** and **2** one primarily obtains 2-phenyl-substituted N-heterocycles **209**, which can undergo hydrogenolysis under the reaction conditions to afford the corresponding open-chain compounds **210** as mixtures of several diastereomers (Scheme 5.41).

The main aim of combinatorial chemistry so far is the preparation of a multitude of organic compounds with high constitutional diversity. Until now stereochemical aspects have played only a minor role, although it is well known that the configuration of a molecule can have a dramatic affect on its biological activity. To address this problem, a new combinatorial strategy has been developed, in which stereogenic centers in a molecule are introduced by a catalyst-controlled transformation of a prostereogenic center. Using this approach in combination with a domino-Knoevenagel-hetero-Diels–Alder reaction, 12 out of the 16 possible stereoisomers of emetine **111** containing four stereogenic centers were synthesized [57]. For this purpose the two enantiomeric aldehydes **138d** and **212b**, obtained from imine **211** by transfer hydrogenation with the (*R*,*R*)- and the (*S*,*S*)-ruthenium complex **122** were used in the domino-Knoevenagel hetero-Diels–Alder reaction with Meldrum's acid **35** and enol ether **137** followed by sovolysis with methanol in the presence of potassium carbonate and hydrogenation (Scheme 5.42).



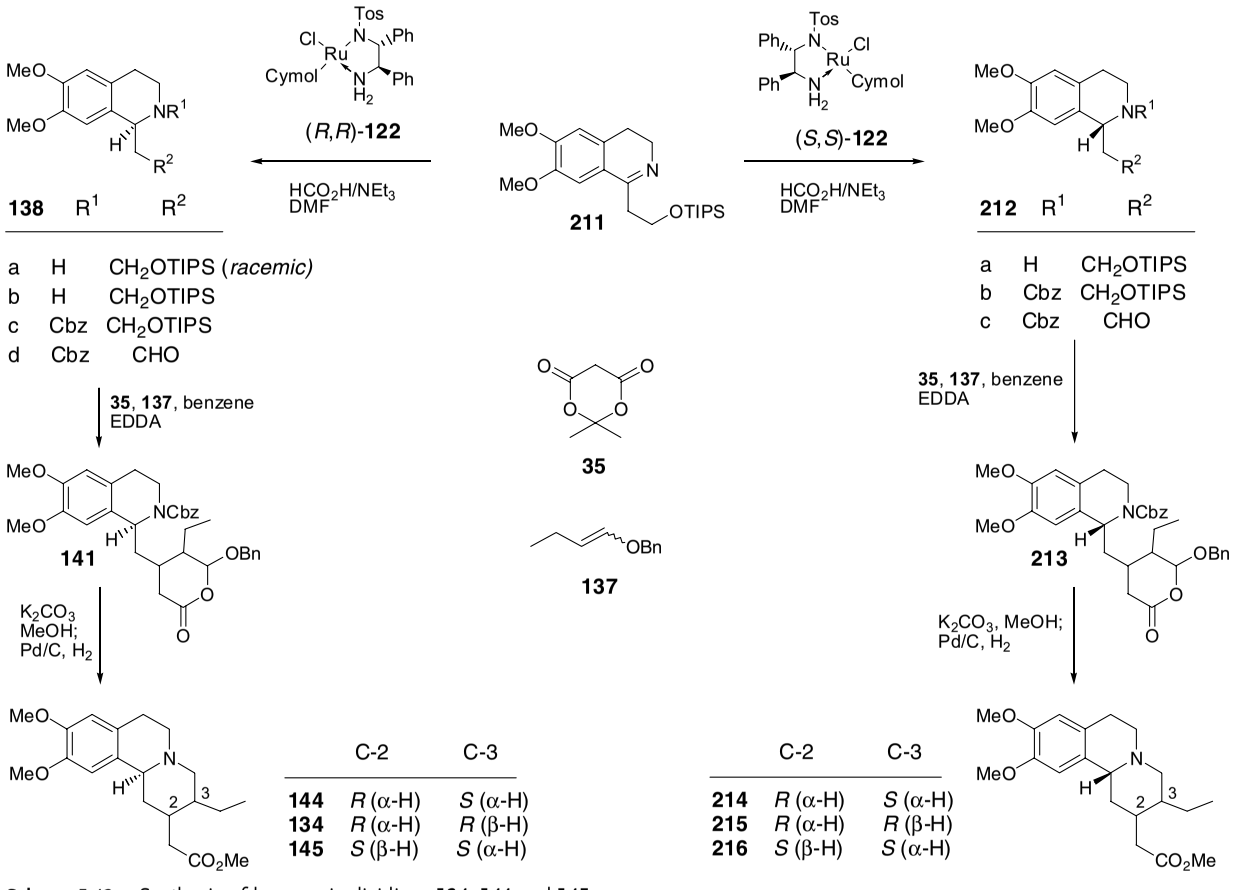
Scheme 5.41. Domino-Knoevenagel-hetero-Diels–Alder-hydrogenation sequence.

Using aldehyde **138d** as substrate the three diastereomers **134**, **144** and **145** were obtained and using aldehyde **212c** the three diastereomers **214**–**216**. The mixtures were separated and independently transformed into the imines **217a**–**c** and **218a**–**c**. The six compounds were reduced independently again using the (*R*,*R*)- and the (*S*,*S*)-ruthenium complex **122** as catalyst (Scheme 5.43). The hydrogenation proceeded in all cases with yields over 71%; the diastereoselectivity, however, was slightly different because of the formation of matched and mismatched combinations. Thus, in the transfer hydrogenation of **217a** with (*S*,*S*)-**122**, a selectivity > 98:2 was found, whereas in the worst case, namely the reaction of **217a** with (*R*,*R*)-**122**, a ratio of 91:9 was observed.

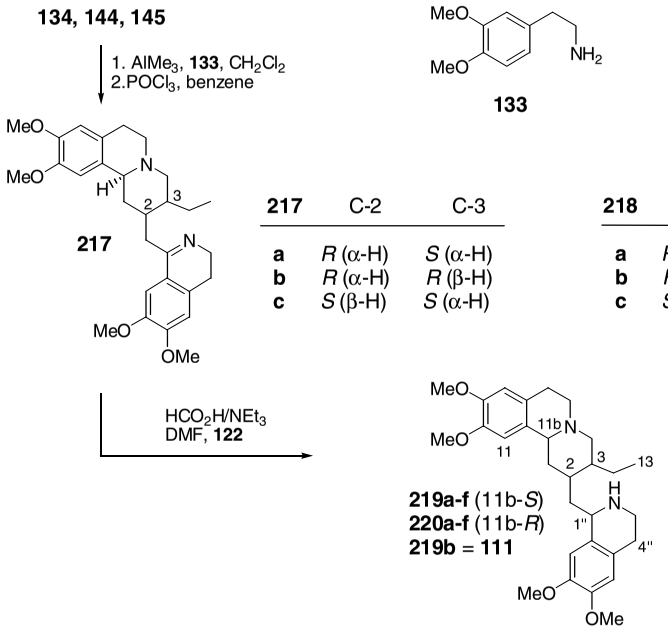
Closely related to the domino-Knoevenagel-hetero-Diels–Alder reaction are the domino-Knoevenagel ene and domino-Knoevenagel–Sakurai reactions [58] using aldehydes containing either an ene or an allylsilane moiety. The second reaction was extended to a combination of a photochemical Norrish I reaction of a silylmethyl-substituted ketone to give the corresponding aldehyde containing an allylsilane moiety [59]. Thus, reaction of ketone **221**, diethyl malonate **222** in the presence of BF_3-etherate under irradiation with a high-pressure mercury lamp gave the 1,2-trans-substituted cyclopentane derivative **223** with excellent selectivity (Scheme 5.44).

5.4 Synthesis of Azasteroids and Steroid Alkaloids

In a similar way to 1-oxa-1,3-butadienes, 2-aza-1,3-butadienes can also be prepared by condensation of an aldehyde such as **224** with anilines **225** to give, for example, novel azasteroids in a following cycloaddition reaction [60]. Thus, by condensa-



Scheme 5.42. Synthesis of benzoquinolizidines **134**, **144** and **145**.



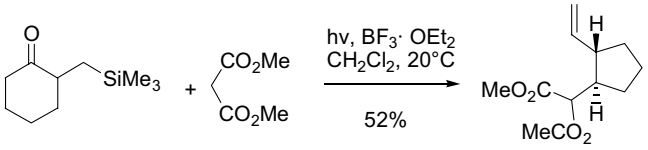
217	C-2	C-3
a	*R* (α-H)	*S* (α-H)
b	*R* (α-H)	*R* (β-H)
c	*S* (β-H)	*S* (α-H)

218	C-2	C-3
a	*R* (α-H)	*S* (α-H)
b	*R* (α-H)	*R* (β-H)
c	*S* (β-H)	*S* (α-H)

219	C-2	C-3	C-1"	Catalyst
a	*R* (α-H)	*S* (α-H)	*R*	(*S*,*S*)-**122**
b	*R* (α-H)	*R* (β-H)	*R*	(*S*,*S*)-**122**
c	*S* (β-H)	*S* (α-H)	*R*	(*S*,*S*)-**122**
d	*R* (α-H)	*S* (α-H)	*S*	(*R*,*R*)-**122**
e	*R* (α-H)	*R* (β-H)	*S*	(*R*,*R*)-**122**
f	*S* (β-H)	*S* (α-H)	*S*	(*R*,*R*)-**122**

220	C-2	C-3	C-1"	Catalyst
a	*R* (α-H)	*S* (α-H)	*R*	(*S*,*S*)-**122**
b	*R* (α-H)	*R* (β-H)	*R*	(*S*,*S*)-**122**
c	*S* (β-H)	*S* (α-H)	*R*	(*S*,*S*)-**122**
d	*R* (α-H)	*S* (α-H)	*S*	(*R*,*R*)-**122**
e	*R* (α-H)	*R* (β-H)	*S*	(*R*,*R*)-**122**
f	*S* (β-H)	*S* (α-H)	*S*	(*R*,*R*)-**122**

Scheme 5.43. Stereoselective synthesis of 12 stereoisomers of **111**.



221 **222** **223**

Scheme 5.44. Domino-Norrish I-Knoevenagel–Sakurai reaction.

tion of **224** with anilines **225** containing electron-donating substituents the iminium ion **227** is formed first, and this is attacked by the alkene moiety to give the primary carbocation **228**; electrophilic aromatic substitution then leads to the azasteroids **229** (Scheme 5.46, 1. pathway). However, it seems that the primary carbocation stays in an equilibrium with secondary carbocation **231** presumably *via* **227**, which is then stabilized by the addition of a nucleophile such as F^- using $BF_3{\cdot}OEt_2$ as a Lewis acid to give the novel substituted D-homosteroids **232** (Scheme 5.46, 2. pathway). This transformation dominates when anilines with electron-withdrawing groups are used which hamper the electrophilic aromatic substitution. Reaction of aniline itself gave a 1:1-mixture of azasteroid **229** and D-homosteroid **232** (Scheme 5.45).

As a side product in these reactions a novel bridged steroid alkaloid **230** is formed, presumable by an intermediate hydride shift in **227** from the benzylic position to the iminium ion to give a secondary amine, which then attacks the formed cationic benzylic position. This reaction becomes the main reaction with aniline, *p*-bromoaniline or nitroaniline in the presence of $BF_3{\cdot}OEt_2$ if a derivative of **224** is used containing a propyl instead of a propenyl side chain [61].

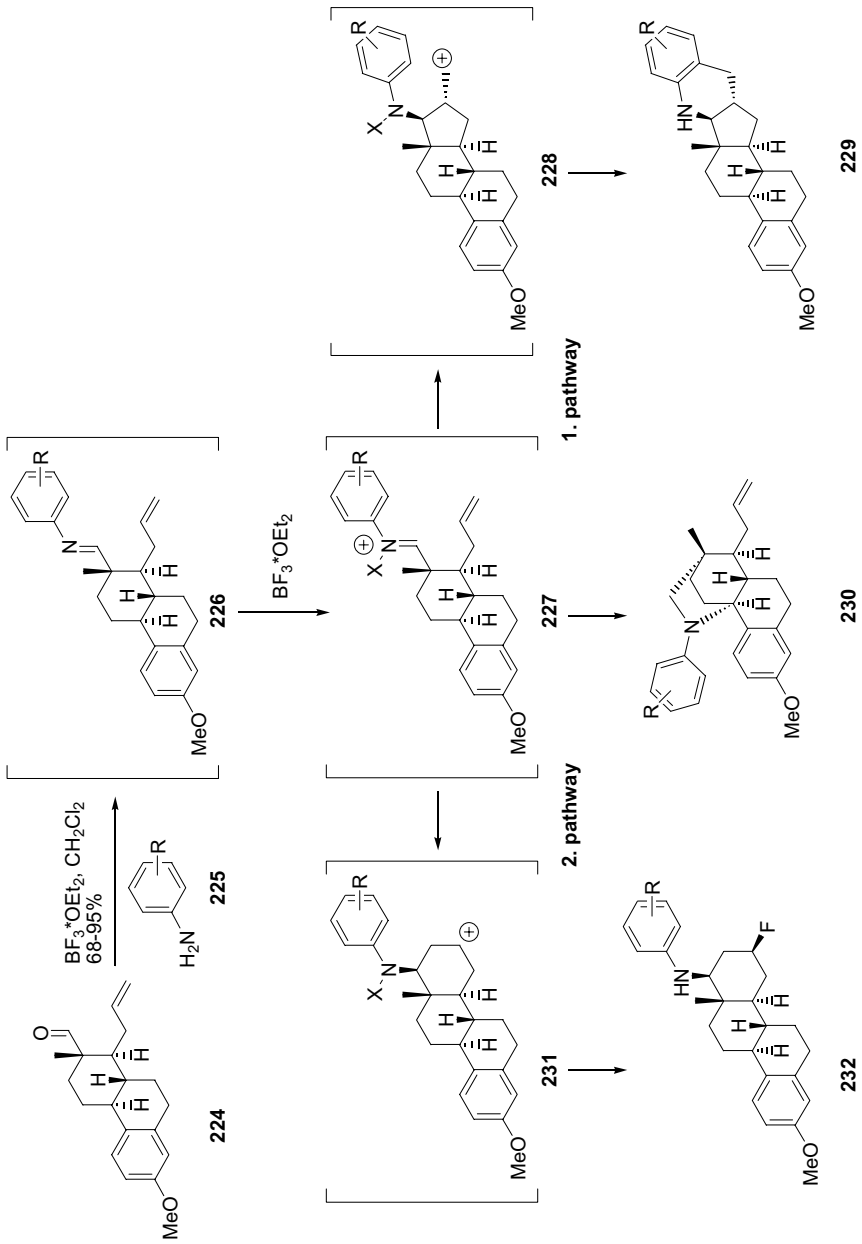
In a similar approach the condensation of aniline **234** with simple aliphatic aldehydes **233** containing a dienophile moiety in the presence of the Lewis acid $SnCl_4$ led to octahydroacridine **236** in high trans-selectivity, if R^1 and R^2 are methyl groups (Scheme 5.46) [62].

If R^1 and/or R^2 are hydrogen the selectivity drops nearly to zero. The transformation can also be performed in a two-step mode. Thus, imine **235** could be prepared by simple condensation of **233** and **234** in the presence of molecular sieves, and this then cyclized in the presence of $SnCl_4$.

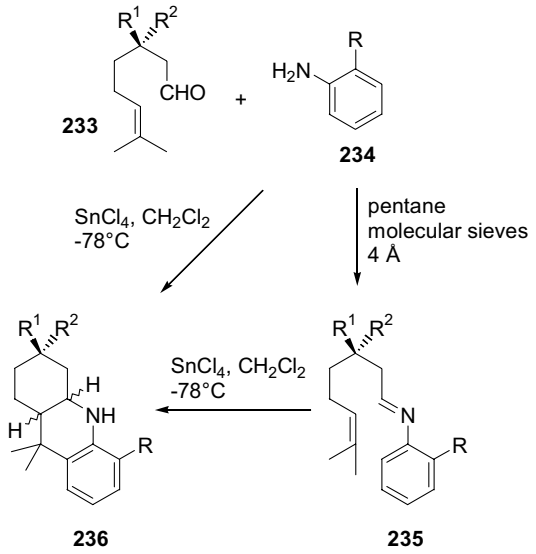
Several other options arise from this approach. Thus, amino-*N*-heterocycles such as **238** can also be used to form 1,3-diaza-1,3-butadiens such as **239** as intermediates which undergo the appropriate hetero-Diels–Alder reaction to give **240** and **241** in a ratio of 11:1 [63]. This approach has so far only been used in a two-component domino reaction (Scheme 5.47).

5.5
Domino-Knoevenagel-carbon-Diels–Alder Reactions

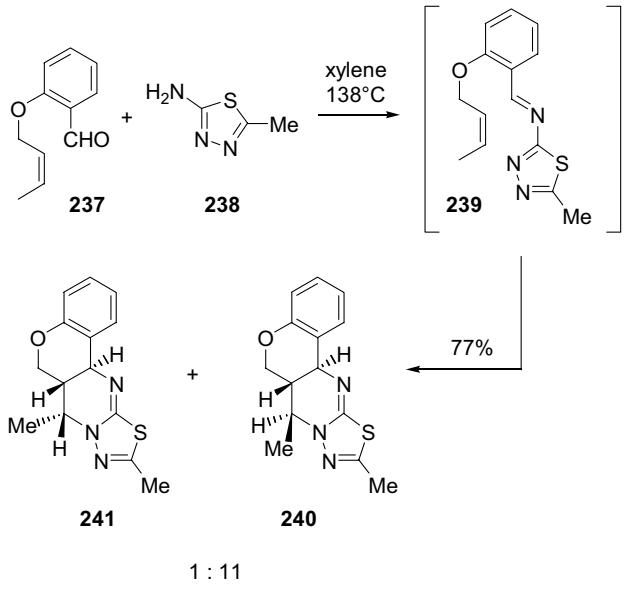
The alkylidene- or benzylidene-1,3-dicarbonyl compounds formed in the Knoevenagel condensation of aldehydes or ketones with 1,3-dicarbonyls, can act not only as a



Scheme 5.45. Synthesis of azasteroids.

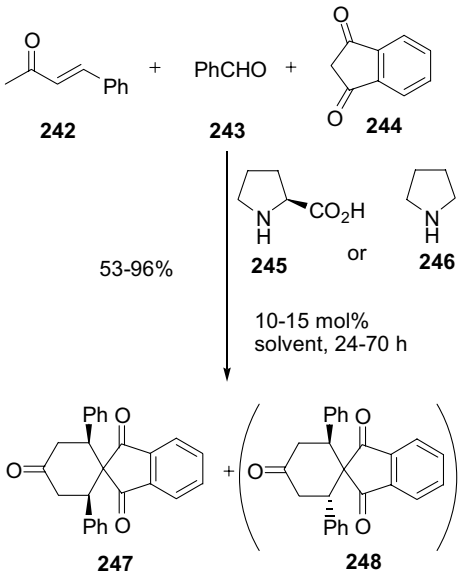


Scheme 5.46. Domino reaction of aniline **234** with aldehyde **233**.



Scheme 5.47. Domino-reaction of aminothiadiazole **238** with aldehyde **237**.

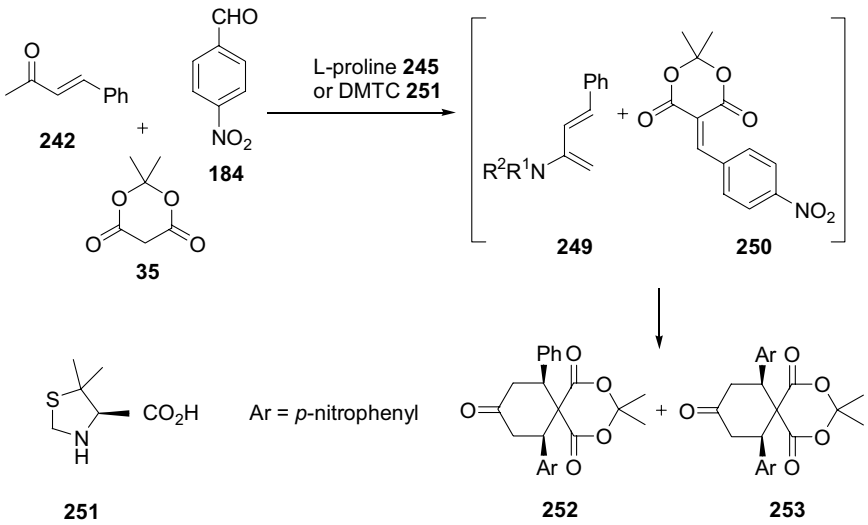
1-oxa-1,3-butadiene but also as powerful dienophiles. This behavior has recently been exploited by designing an efficient three-component domino-Knoevenagel-Diels–Alder reaction using pyrrolidine **246** or the amino acid proline **245** as catalysts (Scheme 5.48). Though this reaction does not fit exactly into the selected



Scheme 5.48. Domino-Knoevenagel-Diels–Alder process catalyzed by proline **245** or pyrrolidine **246**.

topic, it is a powerful domino process and is therefore also discussed here. Reaction of the readily available enone **242**, benzaldehyde **243** and indandione **244** furnished the substituted spirane **247** in up to 96% yield, which can be used as substrate for the synthesis of benzoannulated centropolyquinanes [64]. In addition to **247**, the thermodynamically unfavored *trans*-spirane **248** is also formed, which, however, is epimerized by prolonged reaction time or higher reaction temperature in a protic solvent such as methanol to give the *cis*-spirane **247**.

As well as indandione **244**, other 1,3-dicarbonyl compounds such as Meldrum's acid **35** can also be used. For this transformation the enantioselectivity when enantiopure amino acids are employed, and its dependence on the dielectric constant of the solvent, have been investigated [65]. Reaction of **242**, **184** and **36** in $CHCl_3$ in the presence of catalytic amounts of L-proline **245** gave exclusively the spiro compound **252** in a low yield of 24% but with a reasonably high enantioselectivity of 71%, whereas in methanol the yield was higher (92%) but the selectivity was decreased (*ee* = 60%; Scheme 5.49). In addition, small amounts of spiro compound **253** were found (**252**:**253** = 12:1) using methanol as solvent. Employing the liquid salt [bmim]BF_4 the selectivity dropped to 6% *ee* whereas the yield was highest (95%). The best results so far were obtained with 5,5-dimethylthiazolidine-4-carboxylic acid (DMTC) **251** to provide **252** in 95% yield and 88% *ee*. It can be assumed that in the described reactions the amino acid not only catalyzes the Knoevenagel condensation to provide the corresponding alkylidene Meldrum's acid **250** but also forms a 2-amino-butadiene **249** from **242** *in situ*, which then undergoes a concerted [4+2] cycloaddition with **250** to give **252**.



Scheme 5.49. Enantioselective Domino-Knoevenagel-Diels–Alder-sequence catalyzed by proline **245** or DMTC **251**.

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6
Free-radical-mediated Multicomponent Coupling Reactions

Mami Tojino and Ilhyong Ryu

6.1
Introduction

Radicals add to unsaturated bonds to form new radicals, which then undergo addition to other unsaturated bonds to generate further radicals. This reaction sequence, when it occurs iteratively, ultimately leads to the production of polymers. Yet the typical radical polymerization sequence also features the essence of radical-induced multicomponent assembling reactions, assuming, of course, that the individual steps occur in a controlled manner with respect to the sequence and the number of components. The key question then becomes how does one control radical addition reactions such that they can be useful multicomponent reactions? Among the possibilities are: kinetics, radical polar effects, quenching of the radicals by a one-electron transfer and an efficient radical chain system based on the judicious choice of a radical mediator. This chapter presents a variety of different answers to the question. Each example supports the view that a multicomponent coupling reaction is preferable to *uncontrolled* radical polymerization reactions, which can decrease the overall efficiency of the process.

Radical chemistry has witnessed remarkable progress since the mid 1980s [1]. In addition to common radical C2 synthons such as alkenes and alkynes [2], several radical C1 synthons are also available, including carbon monoxide, isonitriles, and sulfonyl oxime ethers [3, 4]. As featured in Scheme 6.1, a variety of combinations of radical C1 and C2 synthons are now possible, which makes radical methodologies more attractive and permits the design and implementation of a wide range of multicomponent processes.

In designing multicomponent coupling reactions, the nature of the individual components is obviously a key factor. Generally speaking, carbon radical species, such as alkyl radicals, aryl radicals, vinyl radicals, and acyl radicals are all classified as *nucleophilic* radicals, which exhibit high reactivity toward electron-deficient alkenes [2]. To give readers some ideas about this, kinetic results on the addition of *tert*-butyl and pivaloyl radicals are shown in Scheme 6.2. These radicals add to acrylonitrile with rate constants of 2.4×10^6 M^{-1} s^{-1} and 5×10^5 M^{-1} s^{-1} at

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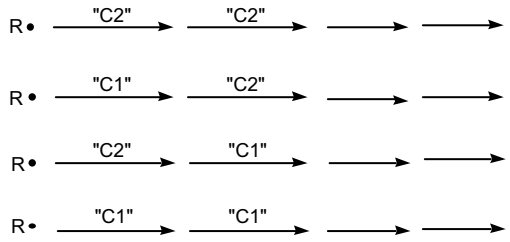
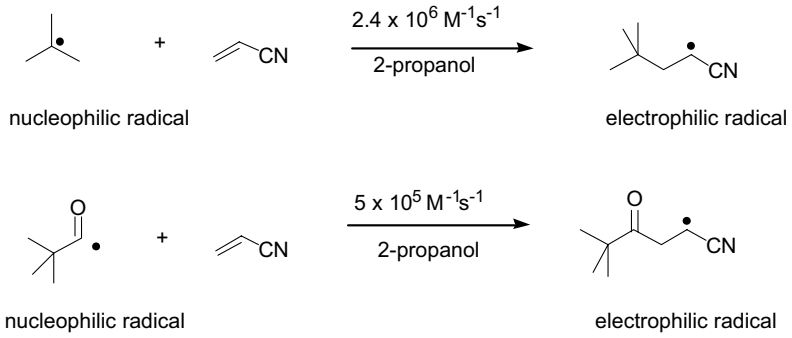


Radical C2 synthons: alkene, alkyne, etc.
Radical C1 synthons: CO, isonitrile, sulfonyl oxime ether, etc.

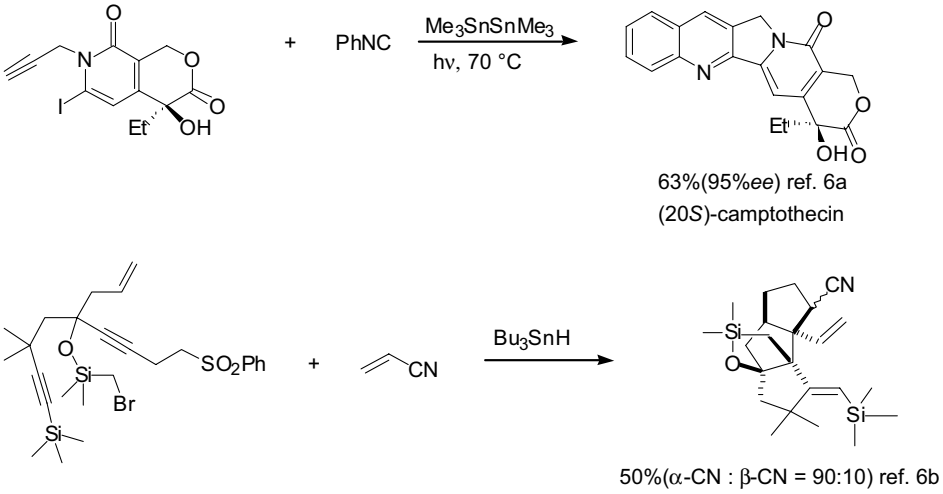
Scheme 6.1



Scheme 6.2

300 K, respectively [5]. These values are three orders of magnitude larger than that for addition to terminal alkenes such as 1-hexene. For this reason, electron-deficient alkenes are frequently employed for multicomponent reactions. However, as the resulting radicals have an electron-withdrawing group they are now *electrophilic*, and are likely to add to electron-rich alkenes with reasonable rate constants.

This chapter contains a survey of free-radical-mediated multicomponent reactions (MCRs), which permit the coupling of *three or more* components. Even though they are not technically classified as MCRs, remarkable *intramolecular* radical cascade processes have been developed. Some examples, such as those shown in Scheme 6.3, use an isonitrile or acrylonitrile as the intermolecular component for each reaction [6]. These examples demonstrate the tremendous power of the combination of inter- and intramolecular radical cascade processes in organic synthesis. Readers are advised to be aware of remarkable intramolecular aspects of modern radical chemistry through excellent review articles published elsewhere [1, 7]. It should also be noted that there has also been remarkable progress in the area of living radical polymerizations, but this will not be covered here.



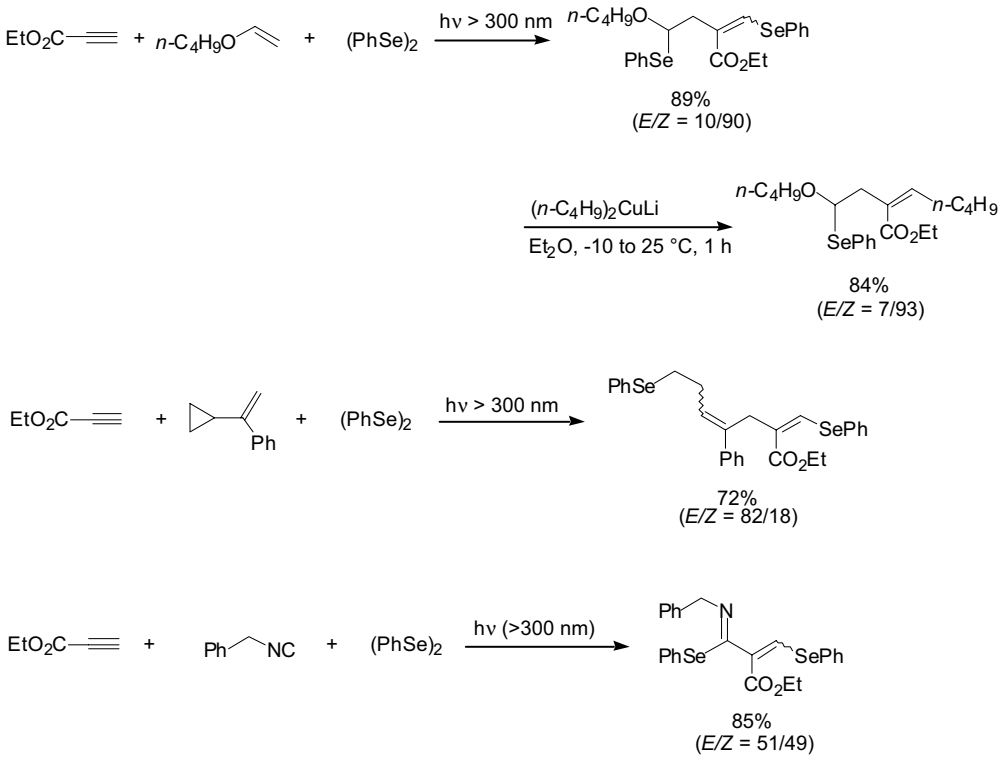
Scheme 6.3

6.2
Hetero-multicomponent Coupling Reactions

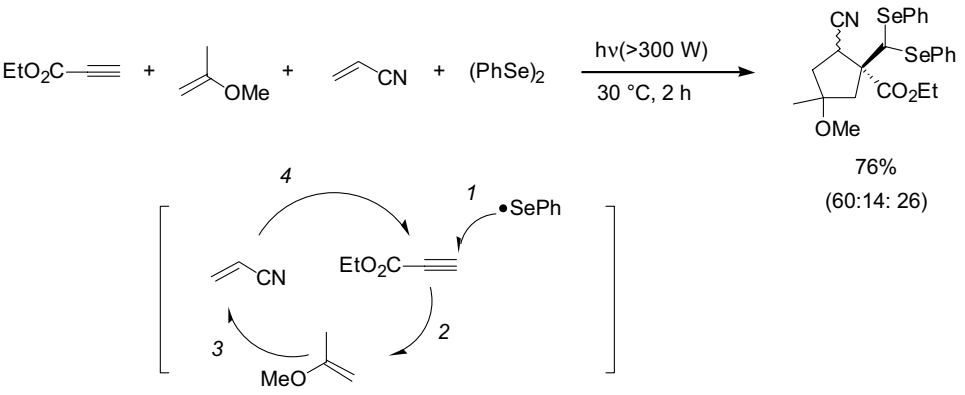
Three-component coupling reactions, which couple alkenes, alkynes, and compounds containing heteroatoms, have been extensively investigated. The first equation of Scheme 6.4 illustrates an example of a three-component reaction involving diphenyl diselenide, ethyl propiolate, and butyl vinyl ether, which utilizes the excellent group transfer ability of diphenyl diselenide [8]. Irradiation causes homolysis of the diselenide to give a phenylselenenyl radical, which undergoes addition to a carbon–carbon triple bond. The resulting vinyl radical then adds to the carbon–carbon double bond to form an alkyl radical, which then abstracts a phenylselenenyl group from the diselenide to give a phenylselenenyl radical, thus creating a radical chain. Coupled with the subsequent Michael addition/β-elimination sequence using lithium dibutylcuprate, a formal three-carbon-component reaction is achieved. The second example in Scheme 6.4 includes a cyclopropylcarbinyl to homoallyl radical rearrangement, which is one of the most rapid of the class of radical fragmentation reactions [9]. The third example employs an isonitrile instead of an alkene [10].

The diselenides-mediated reaction can be extended to a mixed alkene system comprising 2-methoxypropene and acrylonitrile (Scheme 6.5). The intermolecular C–C bond-forming processes (arrow *2* and *3*) are sequenced by 5-exo cyclization (arrow *4*) onto the newly formed C–C double bond [11].

Scheme 6.6 illustrates a coupling reaction related to the third example of Scheme 6.4, but with diphenyl disulfide and *m*-dinitrobenzene [12]. The resulting imidoyl radical is trapped by *m*-dinitrobenzene to give the corresponding amide,



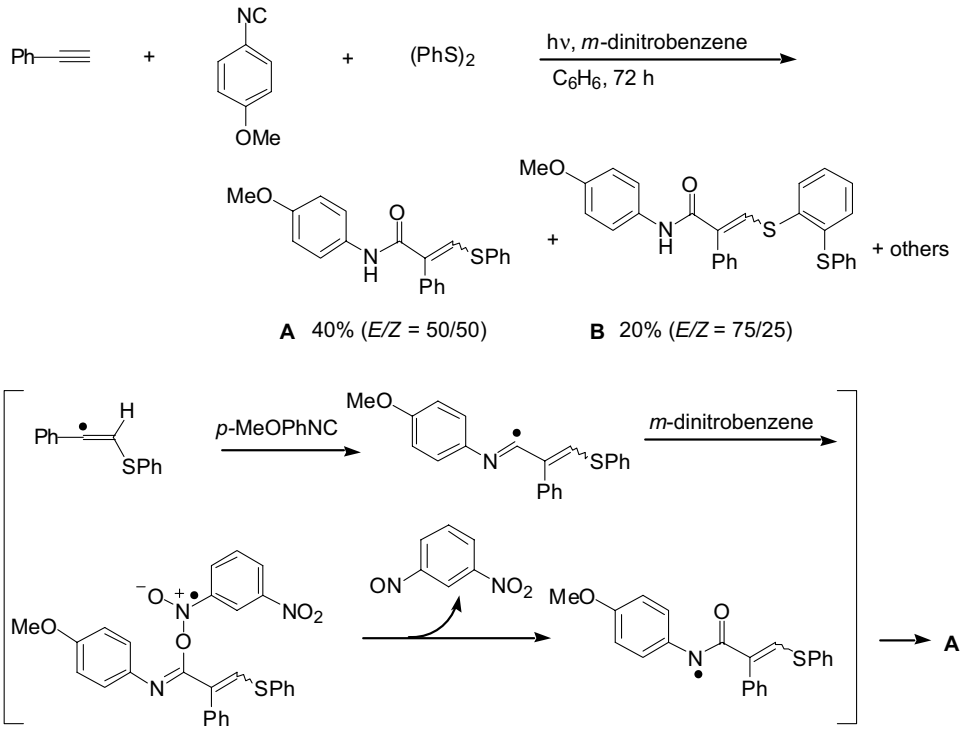
Scheme 6.4



Scheme 6.5

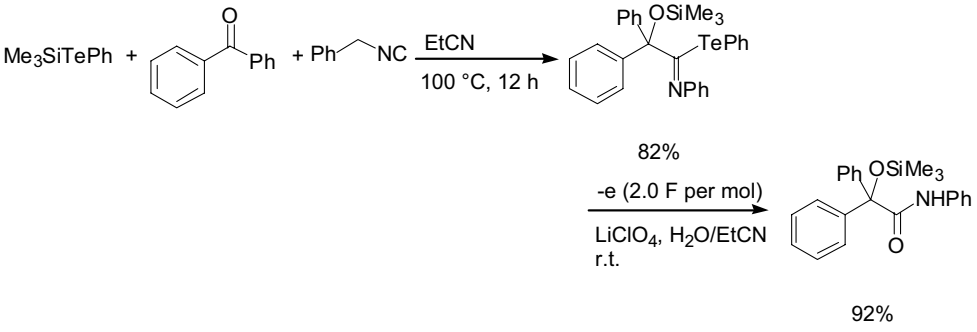
such as **A**, *via* elimination of nitroxide and subsequent H-abstraction. The reaction suffers in that side reaction products are formed.

Because of the weak C–Te bond, organotellurides can serve as efficient carbon radical precursors [13]. However, they are generally unstable to handle, unlike the

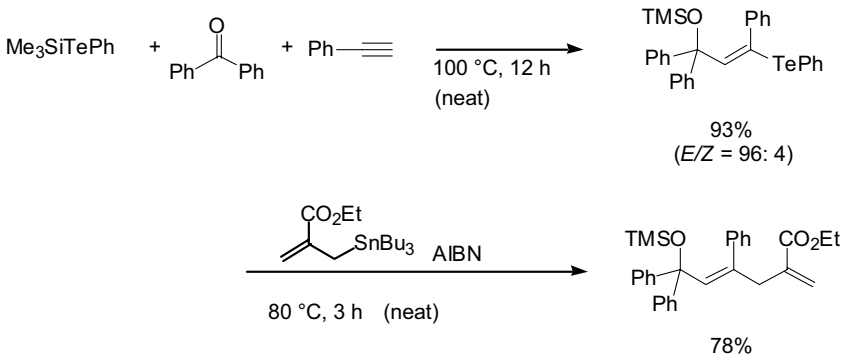


Scheme 6.6

corresponding selenium counterparts. The use of *in situ* generated organotellurium compounds provides a practical solution to this problem. The reaction illustrated in Scheme 6.7 demonstrates such a method. The first step is probably the spontaneous silyltelluration of benzophenone to give 1-siloxy-1-phenylbenzyl phenyl telluride. The second step is radical addition of the resulting telluride to phenyl isonitrile [14]. Subsequent electrolysis of the product gives the corresponding amide in high yield.



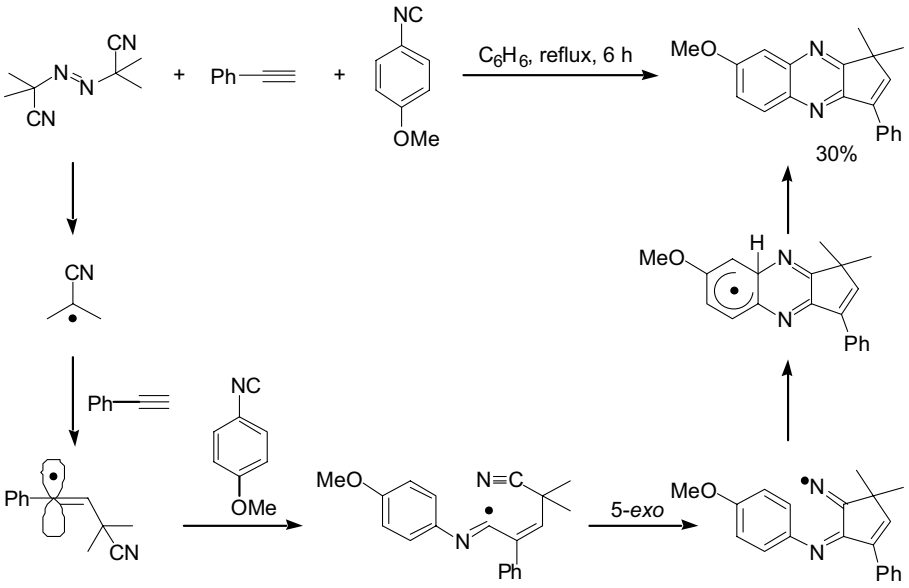
Scheme 6.7



Scheme 6.8

Using a similar protocol but with phenylacetylene instead of isonitrile, a carbotelluration product is formed in high yield (Scheme 6.8) [15]. The product, containing a vinyltellurium moiety is subjected to a second radical reaction with 2-(ethoxycarbonyl)allyltin, and the corresponding 1,4-diene is formed in good yield.

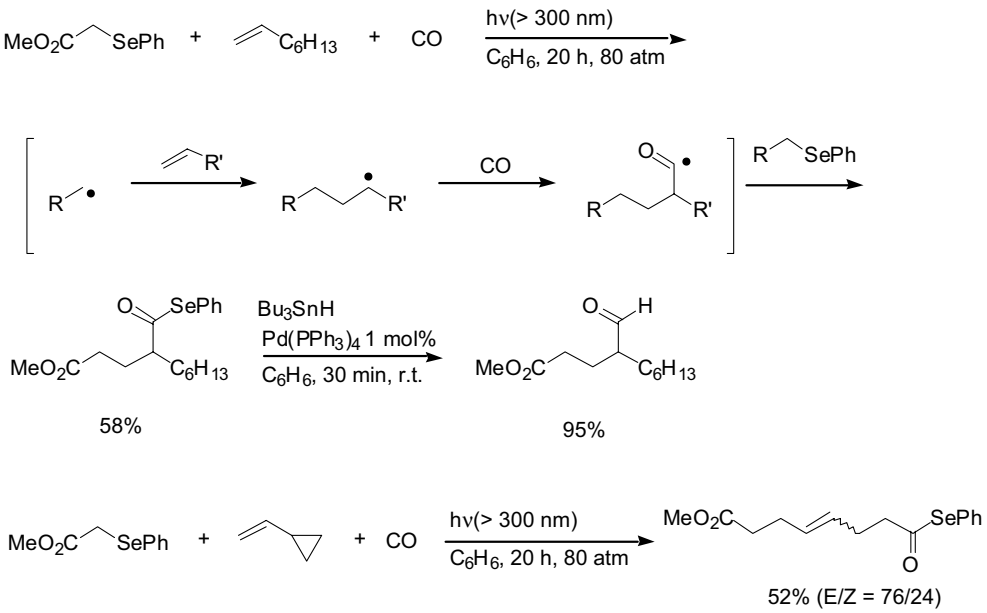
Although the yield and product selectivity require further improvement, the three-component coupling reaction of azo-bis-isobutyronitrile (AIBN), phenylacetylene, and *p*-methoxyphenyl isonitrile proceeds to give a quinoxaline derivative (Scheme 6.9) [16]. Decomposition of AIBN gives a cyanopropyl radical, which adds to phenylacetylene to form a vinyl radical. Addition of the vinyl radical to the isoni-



Scheme 6.9

trile gives an imidoyl radical, which cyclizes onto a cyano group to form a nitrogen radical. The final ring closure with the aromatic ring then leads to the quinoxaline derivative. This is an interesting strategy that is closely related to the Curran annulation (Scheme 6.3), which uses 5-exo cyclization onto carbon–carbon triple bonds rather than onto carbon–nitrogen triple bonds [6a].

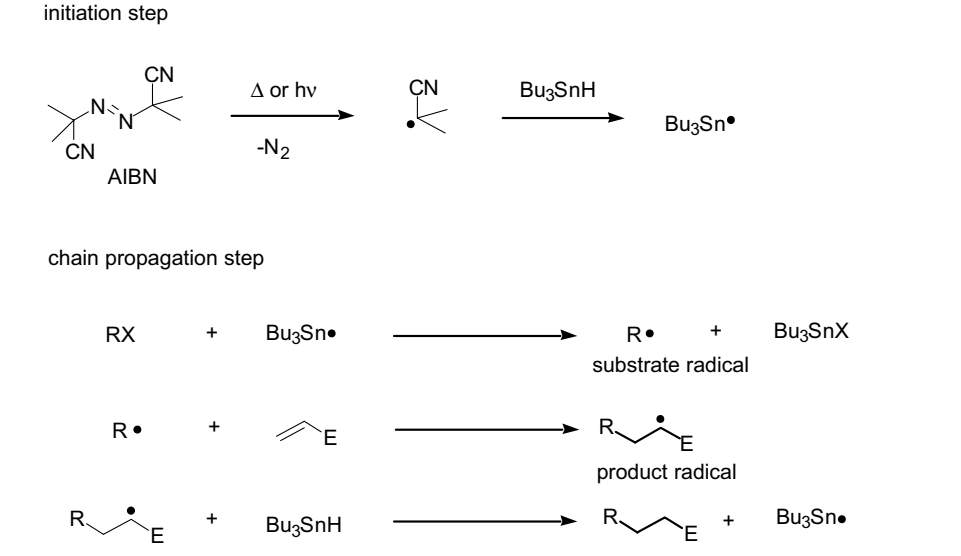
The group transfer ability of organoselenium compounds [17] has been applied to a three-component coupling reaction involving carbon monoxide (Scheme 6.10) [18]. The products here are acyl selenides, which can be reduced to the corresponding aldehydes in high yields by a Pd-catalyzed reduction with tributyltin hydride [19].



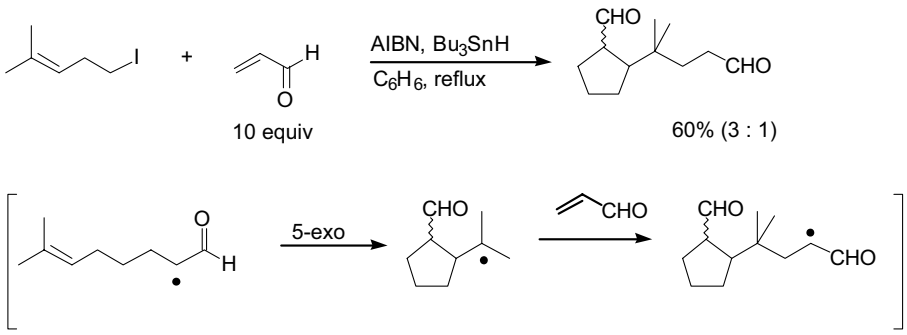
Scheme 6.10

6.3
Multicomponent Coupling Reactions Mediated by Group 14 Radicals

Many synthetic radical reactions have employed tributyltin hydride or related group 14 reagents as a radical mediator. The tributyltin radical is able to abstract halogen efficiently from organic halides to create a radical and after the reaction the tributyltin hydride delivers hydrogen to the product radical to regenerate the tributyltin radical. This is depicted in Scheme 6.11, where a Giese-type radical addition is shown as a model [2]. Hence, in the multicomponent reaction, the lifetimes of radical species are limited by the rate of abstraction of hydrogen from the tin hydride.



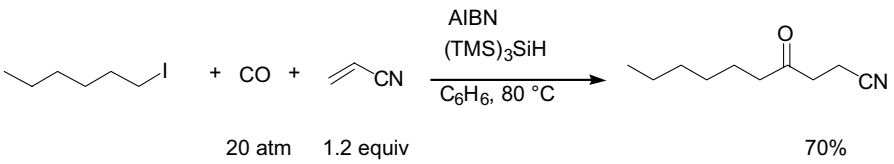
Scheme 6.11



Scheme 6.12

In the example shown in Scheme 6.12, one molecule of organic halide and two molecules of acrolein are coupled under tin hydride-mediated conditions [20]. As the first intermolecular C–C bond-forming process, the homoallyl radical adds to acrolein to form a radical α to a carbonyl group. The subsequent 5-exo cyclization produces a nucleophilic alkyl radical, which undergoes addition to the second molecule of acrolein.

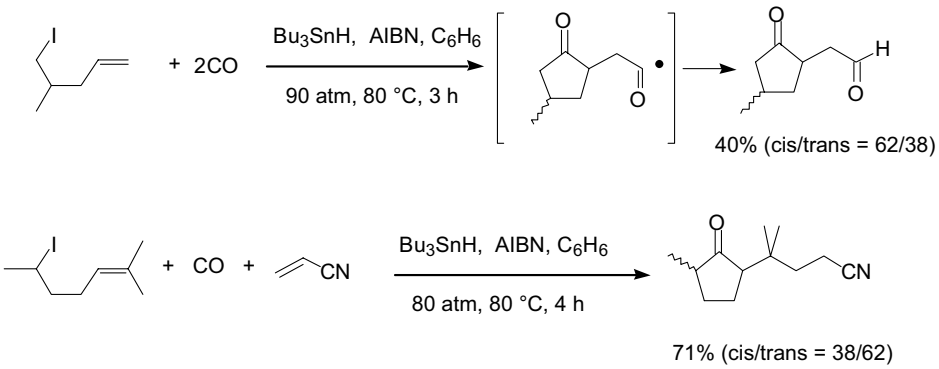
Unsymmetrical ketones can be synthesized by the formal double alkylation of carbon monoxide [21] in which the three-component coupling of alkyl halides, carbon monoxide, and electron-deficient alkenes is carried out using tributyltin hydride as a radical chain mediator (Scheme 6.13) [22]. The use of a slower radical mediator such as $(TMS)_3SiH$ [23] has subsequently proven to be superior to tribu-



Scheme 6.13

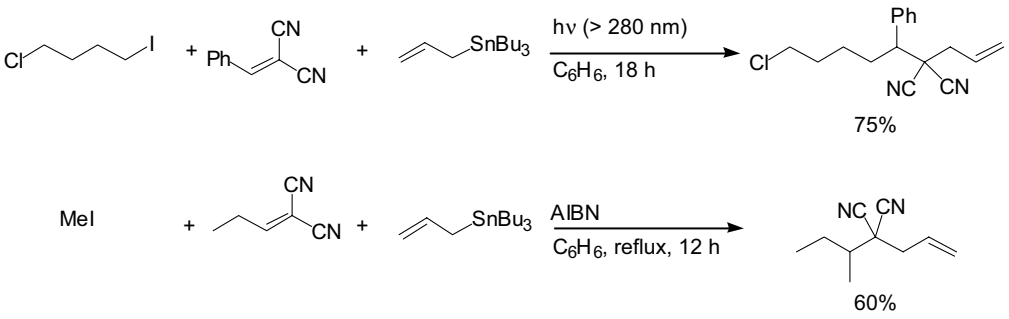
tyltin hydride for this type of reaction, since the reaction can be conducted using smaller amounts of alkenes along with lower CO pressures. This clearly demonstrates that the use of a slow mediator ensures that the lifetimes of each intermediate radical are sufficient to permit their participation in consecutive C–C bond-forming reactions. A highly sophisticated system for the quantitative synthesis of ketones has also been created using supercritical CO_2 as a reaction medium [24].

The following two examples demonstrate some interesting features of radical carbonylation reactions of 5-alkenyl iodides using tributyltin hydride (Scheme 6.14). The first example leads to a cyclic keto aldehyde *via* the incorporation of two molecules of carbon monoxide [25]. In the second example in Scheme 6.14, the cyclized radical is trapped by acrylonitrile rather than by the second molecule of CO [26]. This example involves the formation of a stable tertiary radical, the carbonylation of which is not smooth due to the backward decarbonylation. It should be noted that, in the former case, the use of a slower radical mediator, such as tributylgermane, does not improve the yield of keto aldehyde, since an iodine atom transfer to the acyl radical from the substrate is possible [25].



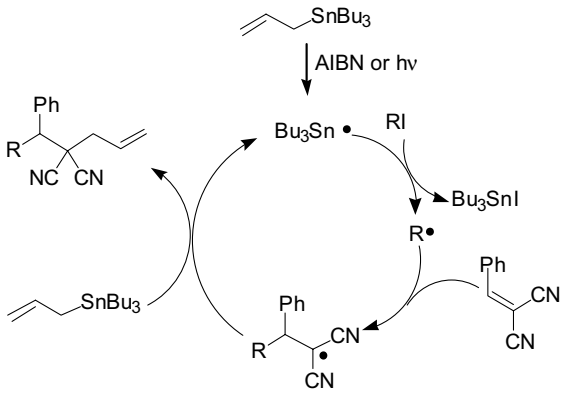
Scheme 6.14

Allyltin compounds are unique players in radical chemistry, since they are able to serve both as radical acceptors and at the same time as radical chain mediators to provide tin radicals [27]. Because of the nucleophilic nature of ordinary alkyl radicals, the addition of an alkyl radical to tributylallyltin is not very fast, yet fast enough to transfer the radical chain [28]. This is an advantage for the controlled



Scheme 6.15

sequential alkene addition reactions shown in Scheme 6.15, which shows two examples of tin radical three-component coupling reactions using a mixture of alkyl halides, electron-deficient alkenes and allyltin [29]. The reactions are conducted with a mixture of two alkenes. However, a *nucleophilic* alkyl radical prefers an electron-deficient alkene to allyltin. The resulting radical having two α-cyano groups is a highly electrophilic radical, which prefers addition to the allyltin. This chain-propagation mechanism is outlined in Scheme 6.16.

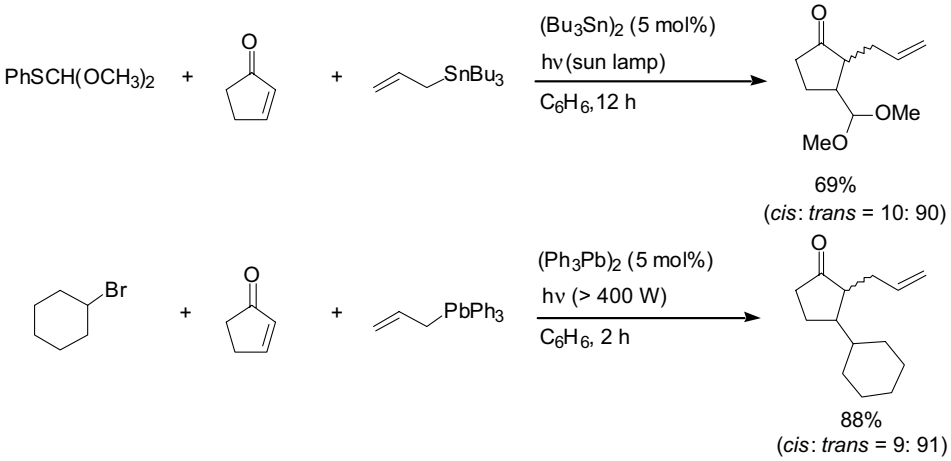


Scheme 6.16

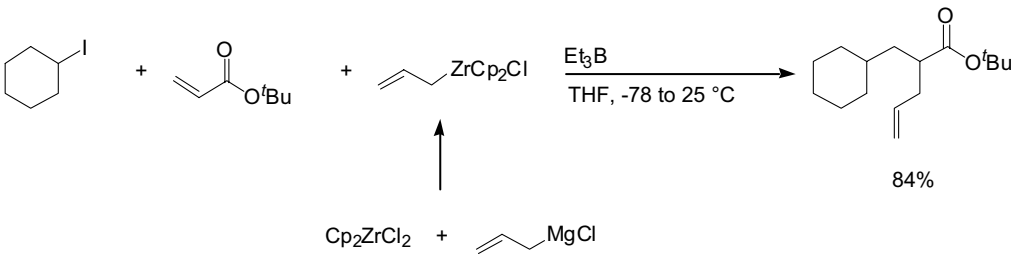
In Scheme 6.17, two examples of the *β*-, α-double alkylation of cyclopentenone are shown. In the first reaction an organosulfur compound is used as the radical precursor [30] and in the second allyltriphenyllead is used instead of allyltributyltin [31].

A recent variant of the three-component coupling reaction employs an allylzirconium reagent, obtained from zirconocene dichloride and allylmagnesium chloride (Scheme 6.18) [32].

Carbon monoxide is able to participate in allyltin-mediated multicomponent reactions. In Scheme 6.19, two examples of three-component coupling reactions giving unsaturated ketones are shown [33]. Because of the slow reaction of acyl



Scheme 6.17

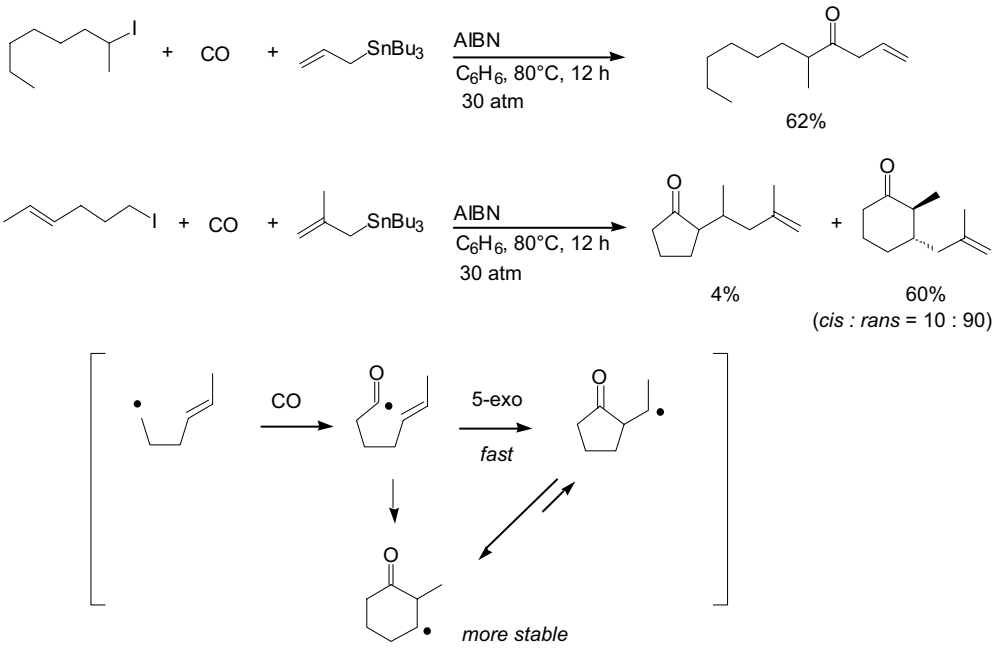


Scheme 6.18

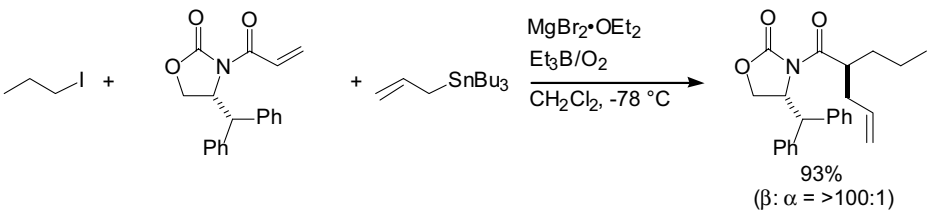
radicals with allyltin, the reaction can be conducted using high concentrations of reagents, such as 0.1 M (RX), whereas relatively low CO pressures (5–30 atm) can be used because the parent alkyl radicals react with allyltin only sluggishly. In the second example, six-membered ring formation predominates over five-membered ring formation. The slow reaction of the kinetically favored 5-exo radical with metallyltin permits its isomerization to the thermodynamically more stable six-endo radical [34].

In three-component allyltin-mediated processes, if the alkenes contain a chiral auxiliary, the allylation step proceeds with a high degree of stereocontrol [35]. In an example in Scheme 6.20, an acrylated oxazolidinone having a chiral substituent in the ring is employed as the alkene portion. Magnesium bromide is used as a Lewis acid to fix the acrylate moiety [36]. Allylation takes place diastereoselectively so as to avoid the face in which the bulky diphenylmethyl group is located.

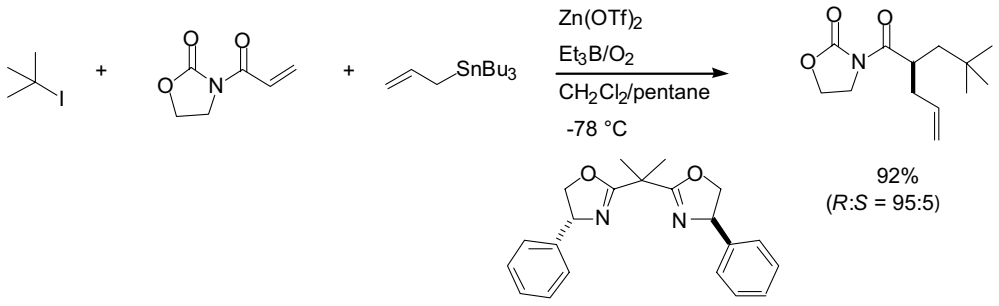
An enantioselective reaction also occurs in a system in which the alkene itself does not contain any chiral auxiliary, but a chiral ligand is used in combination with a Lewis acid. In the following example, a chiral bisoxazoline (BOX) ligand is successfully employed together with zinc triflate as a Lewis acid to achieve an enantiomeric excess as high as 90% (Scheme 6.21) [37].



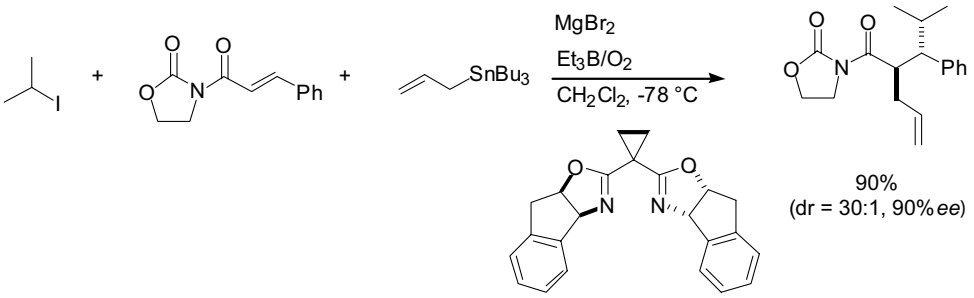
Scheme 6.19



Scheme 6.20



Scheme 6.21



Scheme 6.22

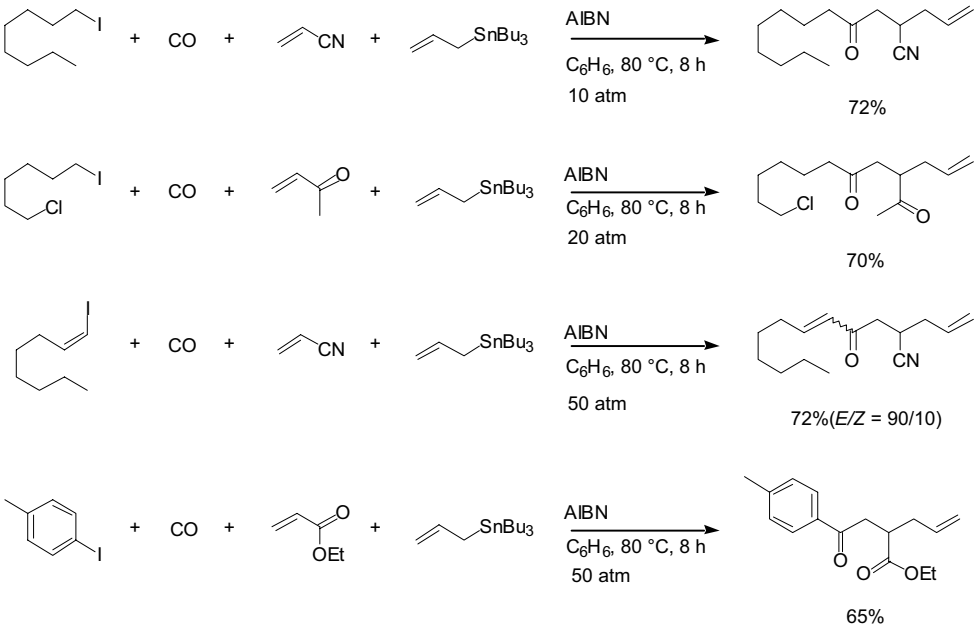
The following example shown in Scheme 6.22 is remarkable, since both β- and α-stereogenic centers are created with a high degree of enantio- and diastereoselective control [38, 39].

Free-radical-mediated four-component coupling reactions are rare. However, when an allyltin-mediated radical carbonylation is conducted in the presence of electron-deficient alkenes, four-component coupling reactions take place efficiently to give good yields of β-functionalized δ,ε-unsaturated ketones [40]. The wide scope of this four-component coupling reaction is noteworthy: Primary, secondary, and tertiary alkyl bromides and iodides can be used as well as aromatic and vinylic halides. A variety of electron-deficient alkenes, such as methyl vinyl ketone, ethyl acrylate, acrolein, acrylonitrile, and vinyl sulfone, can be used as the acyl radical trap (Scheme 6.23). Fluorous allyltin compounds can also be used in four-component coupling reactions [41].

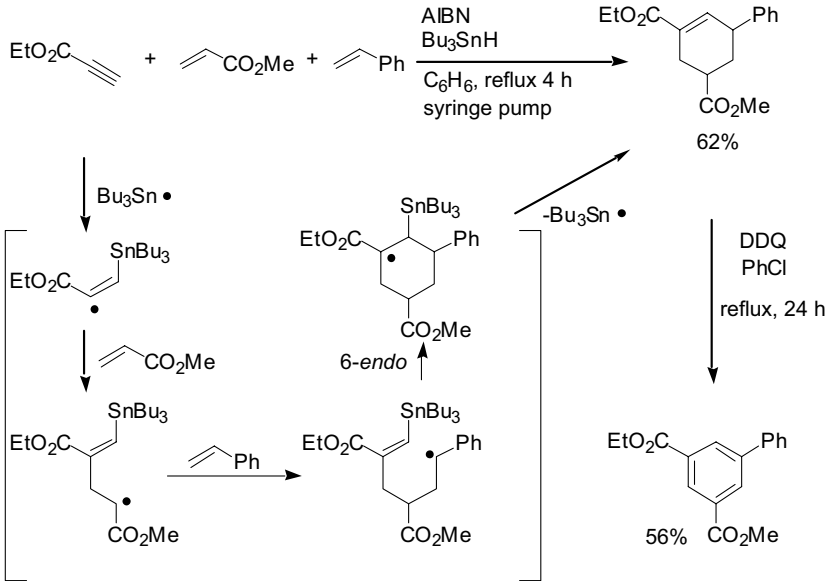
Three-component coupling reactions involving alkynes, electron-deficient alkenes, and electron-rich alkenes, and which give rise to six-membered ring compounds as the products, have been reported [42]. Scheme 6.24 shows an example of the coupling of ethyl propiolate, methyl acrylate, and styrene. A vinyl radical is formed by the addition of the tributyltin radical to ethyl propiolate, which then undergoes consecutive radical additions to methyl acrylate and styrene. Subsequently, 6-endo cyclization takes place to give the desired six-membered ring with the elimination of a tributyltin radical, which participates in the next reaction. Indeed, the procedure uses 0.5 mol equivalent of tin hydride. Oxidative aromatization by DDQ can be used to convert the product to the corresponding trisubstituted benzene.

Acyl selenides serve as acyl radical precursors when treated with tin radicals [43]. In the following reaction (Scheme 6.25), a cycloheptanone fused to an indanol skeleton is prepared *via* a three-component reaction [44]. The sequential addition of an acyl radical to two molecules of methyl acrylate followed by a 7-endo-type radical addition account for the annulation.

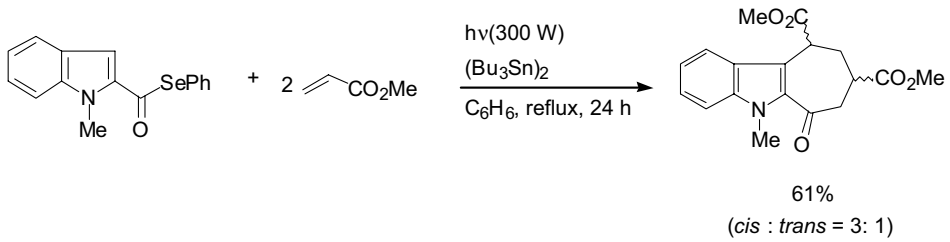
Sulfonyl oxime ethers function as efficient radical C1 acceptors [45]. The instance in Scheme 6.26, in which a bissulfonyl oxime ether is used as a radical C1 acceptor, showcases the strategic aspect of this unique method for the synthesis of



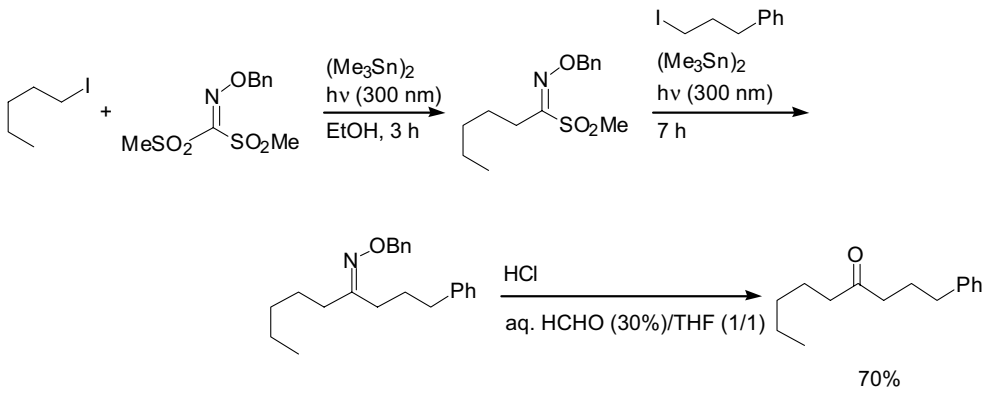
Scheme 6.23



Scheme 6.24



Scheme 6.25



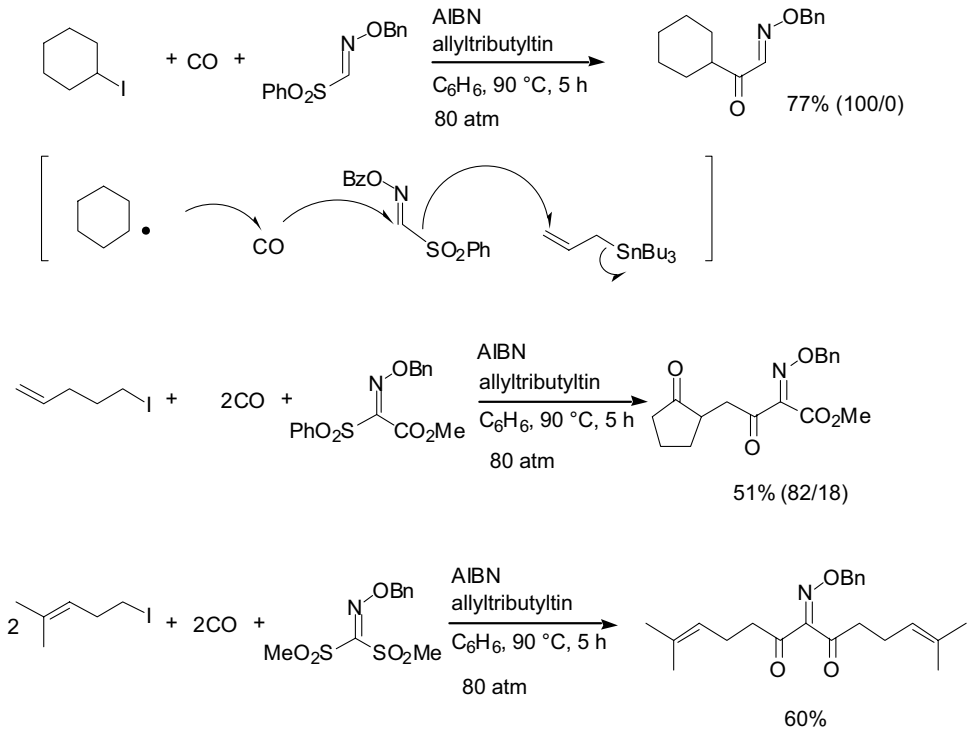
Scheme 6.26

unsymmetrical ketones. After the consecutive alkylation reactions using different alkyl halides, acidic treatment leads to deoximation to give the envisaged ketone.

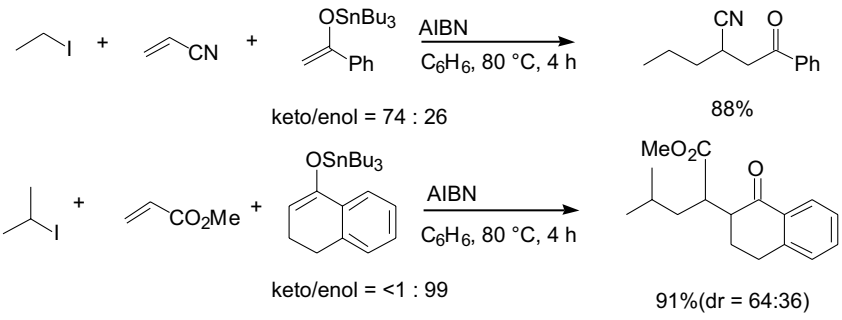
The combination of carbon monoxide with sulfonyl oxime ethers allow for a set of multicomponent coupling reactions involving consecutive C1/C1-type coupling, a rare class of radical multicomponent reactions. In Scheme 6.27, examples of three-, four-, and five-component coupling reactions are shown [46]. In these reactions, allyltin is not incorporated into the product, but serves as an acceptor of the phenylsulfonyl radical and a source of the tributyltin radical, which delivers the radical chain.

Tributyltin enolates are useful radical mediators [47], although they generally exist in equilibrium with α-tributyltin ketones [48]. Three-component coupling reactions proceed readily to give functionalized ketones in good to excellent yields, where an equilibrium shift to provide tin enolates operates efficiently (Scheme 6.28) [49]. Unlike the aforementioned case of allyltin-mediated reactions, acrolein is difficult to use in this reaction, since the Aldol reaction of the tin enolate with acrolein precedes the radical reaction.

The combination of tin enolate-mediated radical reactions with carbonylation is highly successful. Three-component coupling reactions involving an alkyl

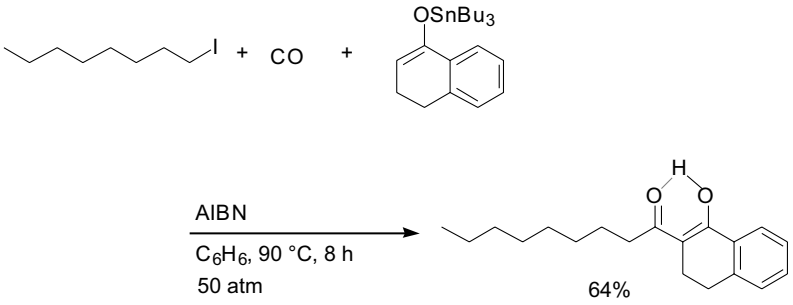


Scheme 6.27

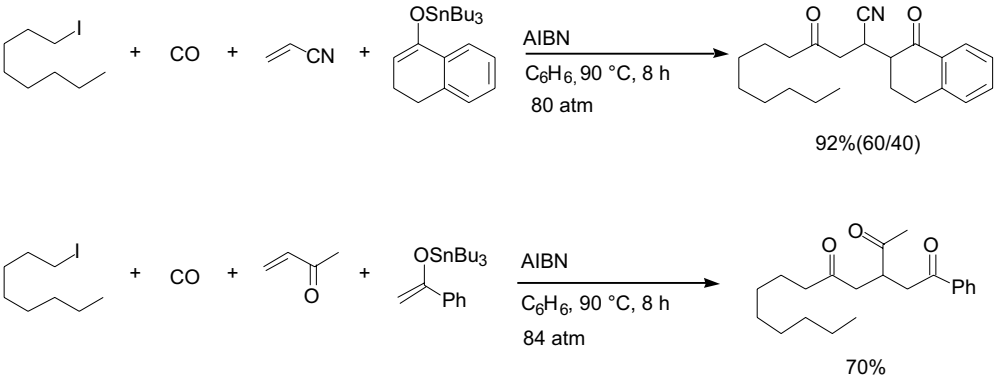


Scheme 6.28

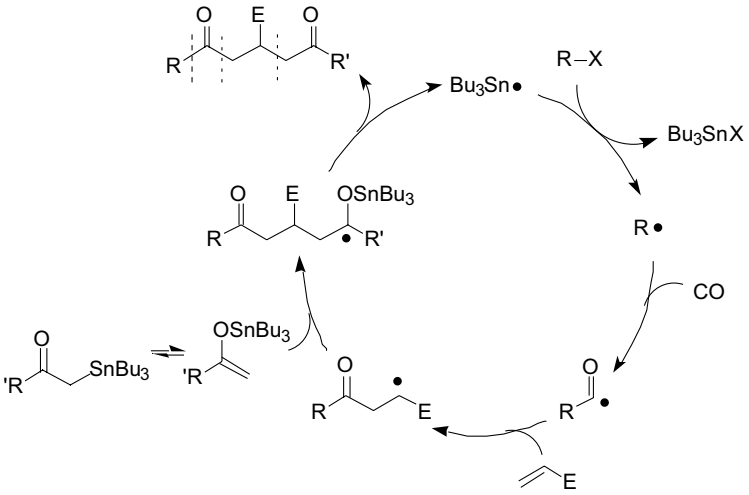
iodide, CO, and tin enolate proceed to give β-diketones (Scheme 6.29) [50]. Four-component reactions that combine alkyl halides, carbon monoxide, electron-deficient alkenes, and stannyl enolates also proceed smoothly in the given sequence (Scheme 6.30) [50]. A series of 1,5-diketones having a functionality at the 3-position have been prepared by this method using a variety of electron-deficient alkenes. The radical chain mechanism is illustrated in Scheme 6.31.



Scheme 6.29



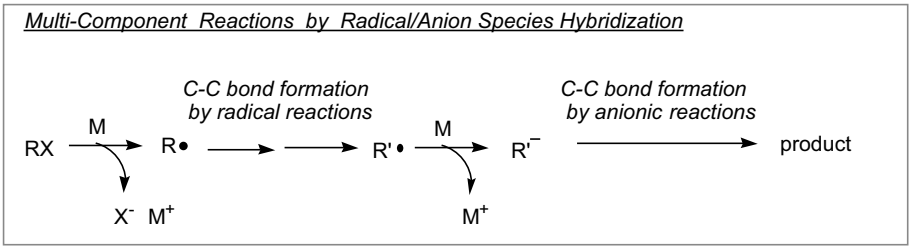
Scheme 6.30



Scheme 6.31

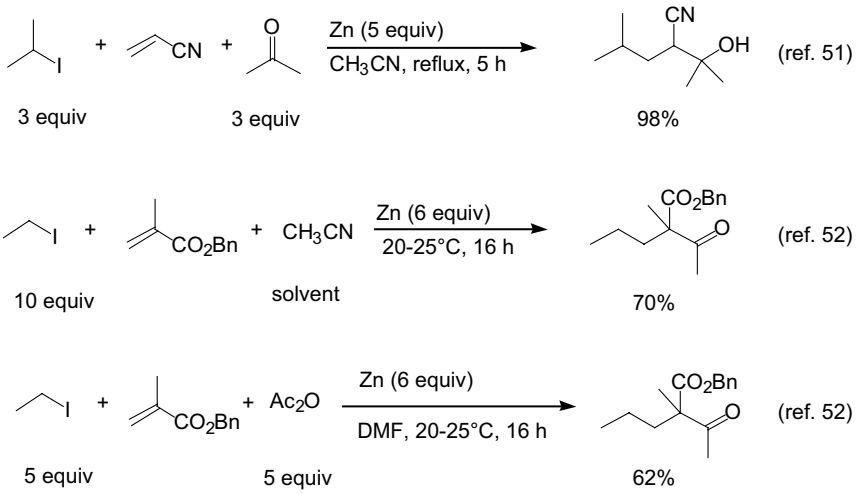
6.4
Multicomponent Coupling Reactions Involving Electron-transfer Processes

A metal-induced one-electron reduction is frequently used to generate radical species. Termination of the radical reactions is due to a one-electron reduction process to give anions and therefore constitutes a non-chain process. As featured in Scheme 6.32, in many cases the multicomponent processes described here are a combination of radical and anionic bond-forming reactions.



Scheme 6.32

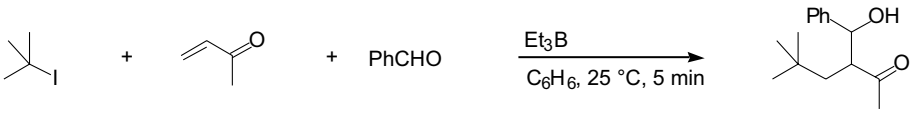
Scheme 6.33 illustrates an example of some zinc-induced three-component coupling reactions of alkyl iodides, electron-deficient alkenes, and carbonyl compounds [51]. In this instance, the isopropyl radical is generated by a one-electron reduction of isopropyl iodide followed by elimination of iodide ion. The resulting radical then adds to acrylonitrile to form an α-cyano alkyl radical, which is con-



Scheme 6.33

verted to an α-cyano carbanion by a second one-electron reduction by zinc. Finally, the carbanion is trapped by acetone and water, leading to product formation. In this three-component transformation, the first C–C bond-forming process is a radical process and the second C–C bond-forming process is an anionic process. Useful extensions of this zinc-induced three-component chemistry have appeared, which employ primary and secondary alkyl iodides, α,β-unsaturated esters, and nitriles [52]. Two examples are also given in Scheme 6.33. The second example uses acetic anhydride as an anion trap.

A similar three-component transformation can be achieved using triethylborane-induced radical reactions (Scheme 6.34) [53]. On exposure to air, triethylborane generates the ethyl radical, which abstracts iodine from alkyl iodides to generate the *t*-butyl radical. Addition of the resulting *t*-butyl radical to methyl vinyl ketone produces a radical α to the carbonyl group, which is trapped by triethylborane to form a boron enolate with the liberation of ethyl radical, thus creating a chain. The final step is a non-radical Aldol condensation.



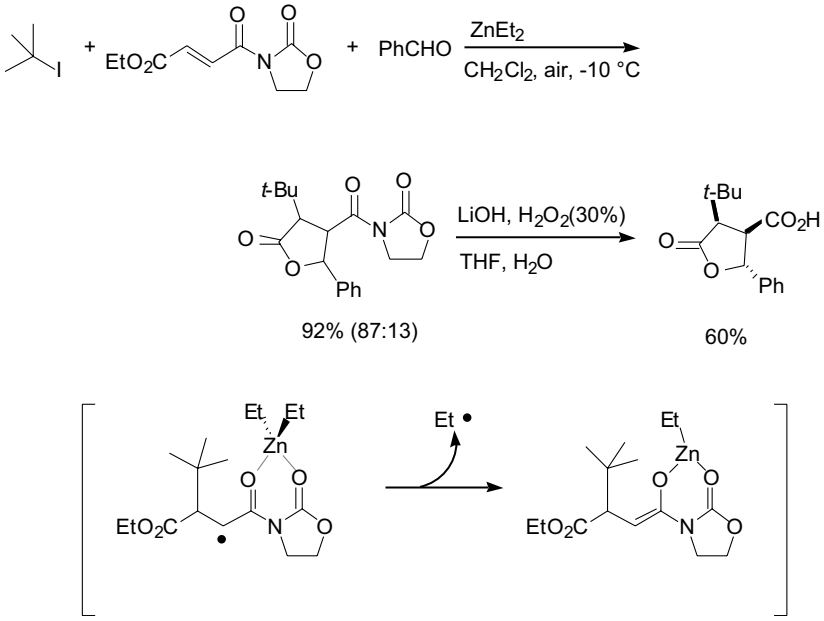
63%

Scheme 6.34

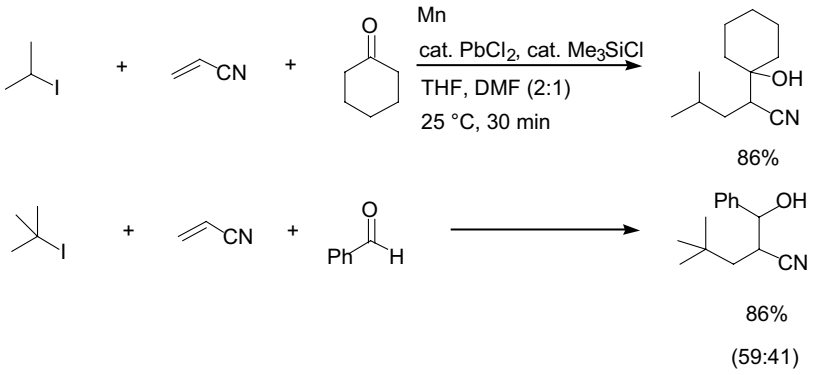
A combination of diethylzinc and oxygen generates ethyl radicals [54] in the same way as the triethylborane/air system [55]. This diethylzinc/air system can be utilized in a similar hybrid-type three-component reaction, where an *N*-enoyloxazolidinone is used as an electron-deficient alkene together with a ligand of diethylzinc [56]. One typical example is shown in Scheme 6.35. Analogous to the above case, an atom-transfer reaction, which is induced by ethyl radical, is the first key step. The resulting alkyl radical then adds to a C–C double bond to form a zinc enolate with the concomitant elimination of ethyl radical. Aldol condensation of the resulting zinc enolate with benzaldehyde takes place accompanied by dehydration to give a stereoisomeric mixture of γ-lactones. Epimerization and oxidative removal of oxazolidinone gives a stereo-defined lactone containing a carboxylic acid moiety.

A similar hybrid type of radical/anionic reactions can be effected, when manganese metal, activated by catalytic amounts of lead dichloride and trimethylchlorosilane, is employed instead of zinc, which makes the original process synthetically more reliable and attractive by reducing the amounts of reagents (RX and ketone) needed to a 1.5 molar excess over the alkenes (Scheme 6.36) [57].

An efficient addition reaction of THF to aldimines is possible when the dimethylzinc/air system is employed [58]. The reaction can be conducted in an



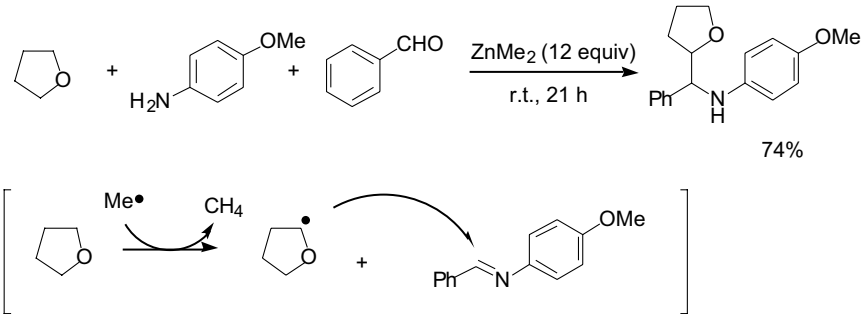
Scheme 6.35



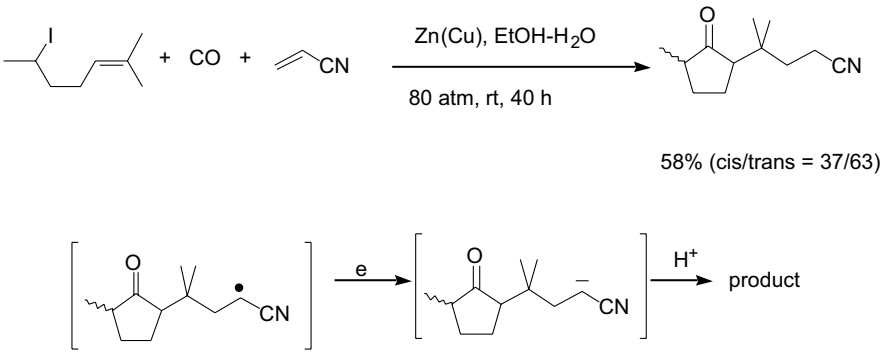
Scheme 6.36

equilibrium mixture of aldehydes and aryl amines without suffering the addition to aldehydes (Scheme 6.37).

Radical carbonylation can also be conducted in a zinc-induced reduction system. A similar three-component transformation reaction to that illustrated in the second equation of Scheme 6.14 can be attained using zinc and protic solvents (Scheme 6.38) [59]. The observed stereochemical outcome is identical to that for the tin hydride-mediated reaction, providing a additional evidence for free-radical generation, radical carbonylation, and acyl radical cyclization taking place simultaneously, even in the zinc-induced system. In this system, however, the final step is reduction to form a carbanion and protonation.

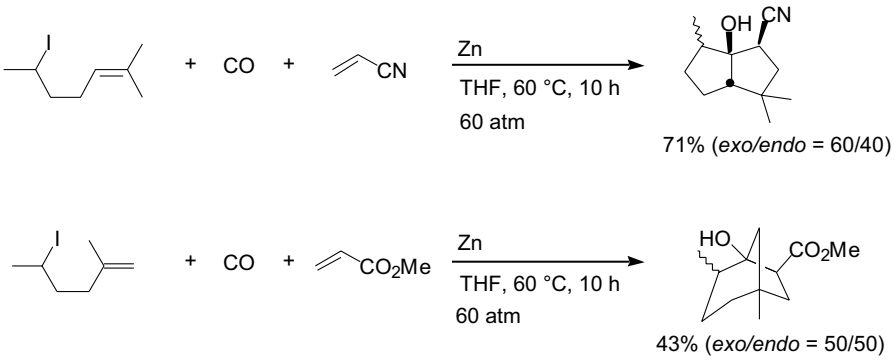


Scheme 6.37



Scheme 6.38

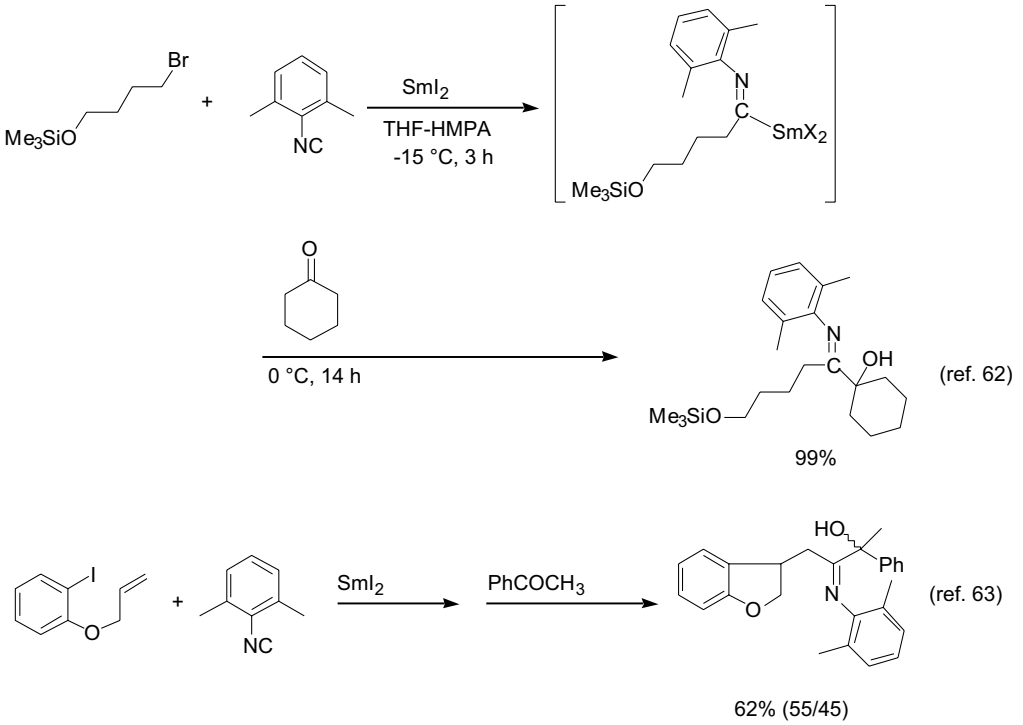
If an aprotic solvent is used in the reaction, the resulting carbanion would undergo nucleophilic attack at the internal carbonyl group [60]. The first equation in Scheme 6.39 represents such a dual annulation reaction leading to a bicyclo[3.3.0]octan-1-ol. In the second example, which starts with 5-iodo-2-methyl-



Scheme 6.39

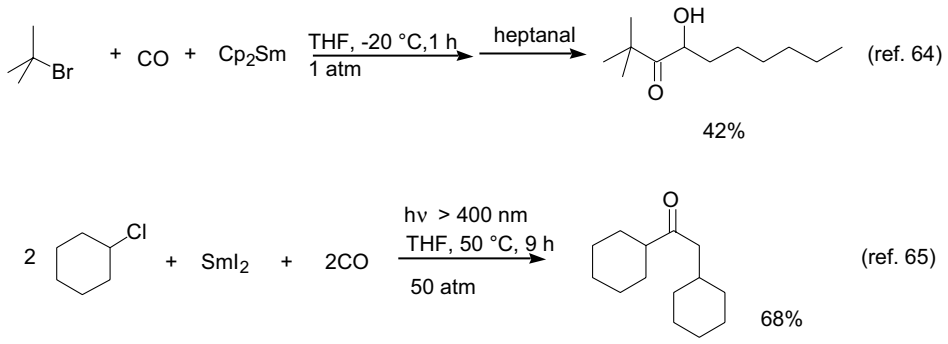
hex-1-ene, the acyl radical cyclization step favors the 6-endo mode because a stable tertiary radical is formed. The overall reaction in this case represents a dual annulation sequence leading to a bicyclo[3.2.1]octan-1-ol.

SmI_2 is a versatile one-electron reducing reagent that is soluble in polar solvents such as THF [61]. In many instances, in the final step, organosamarium compounds are formed, which can then be trapped by electrophilic carbons such as a carbonyl group. The two examples shown in Scheme 6.40 demonstrate three-component coupling involving xylyl isocyanide as one of the key components. In the first example an alkyl radical is formed by a one-electron reduction of alkyl bromide [62], while in the second example an aryl radical is formed and then isomerized to an alkyl radical [63]. In these two examples, imidoyl anions are formed, which are condensed with acetophenone and cyclohexanone, respectively. Two mechanistic possibilities exist for the first C–C bond-forming step, since it is known that radicals and carbanions can both add to isonitriles.



Scheme 6.40

The reaction of *t*-BuBr with CO in the presence of $SmCp_2$ leads to the formation of acylsamarium species presumably *via* a radical formation/carbonylation/reduction sequence, When heptanal is added to the reaction mixture, a ketol is

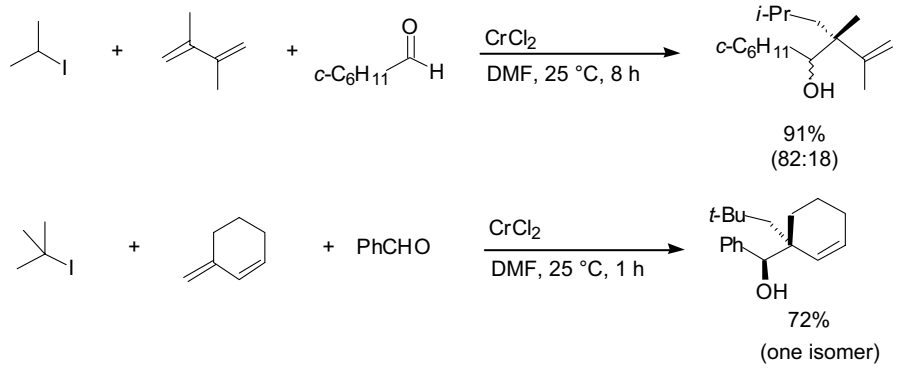


Scheme 6.41

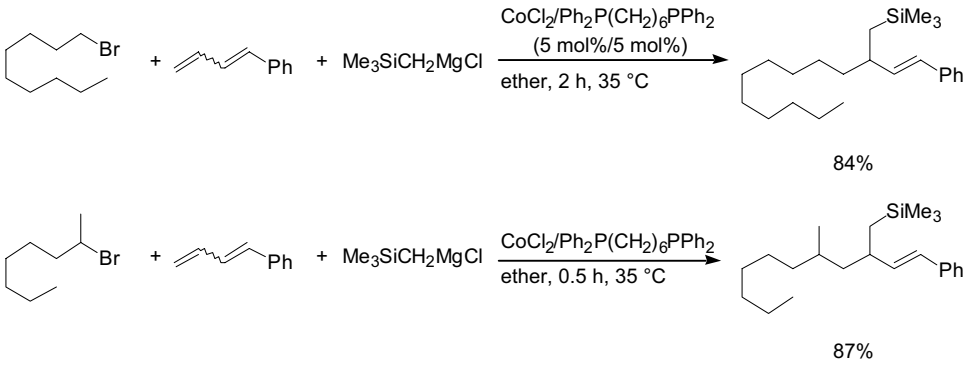
formed in 42% yield (the first equation in Scheme 6.41) [64]. Interestingly, samarium diiodide reduction when coupled with irradiation can boost the reduction of alkyl chlorides, whose oxidation potential is higher than those of the corresponding bromides and iodides [65]. When such a reduction of an alkyl chloride was attempted under CO pressure, an unsymmetrical ketone was obtained, composed of two molecules of alkyl chloride and two molecules of carbon monoxide (the second equation in Scheme 6.41). An α-hydroxy ketone, obtained *via* the dimerization of acylsamarium, is the likely precursor of the final product.

The mild reducing agent $CrCl_2$ allows useful three-component coupling reactions that can incorporate alkyl halides, 1,3-dienes, and aldehydes in one-pot (Scheme 6.42) [66]. In the following instance, alkyl radicals, generated by the one-electron reduction of iodoalkanes, add to 1,3-dienes. The resulting allylic radicals are reduced to give allylic anions, which then add to aldehydes to give the final products.

A related three-component reaction involving dienes employs a cobalt catalyst [67]. Unlike the above case, the third component here is a carbanion species, such

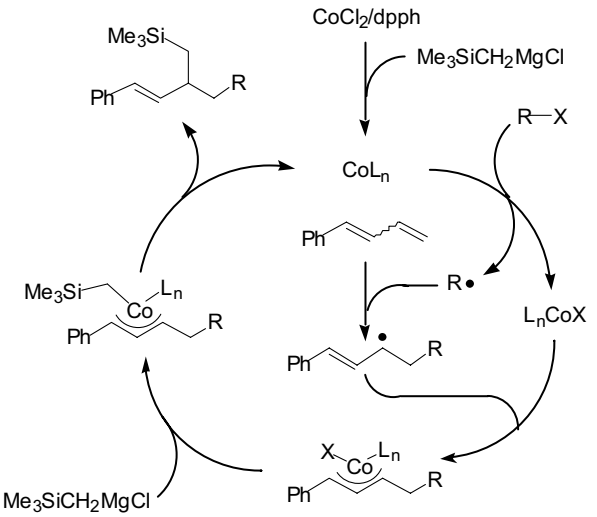


Scheme 6.42



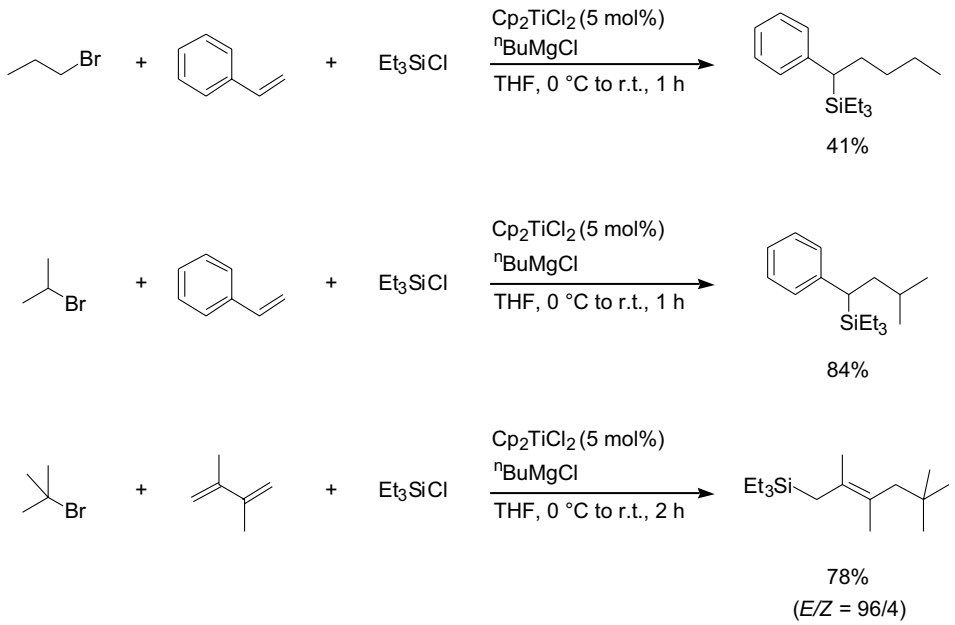
Scheme 6.43

as silylmethylmagnesium bromide (Scheme 6.43). Similar to the above case, the first key step is the addition of an alkyl radical to a diene to form an allylic radical. However, in this case the allylic radical couples with Co(I)Br to form an allylcobalt complex, which is the likely intermediate in the silylmethylation step as illustrated in Scheme 6.44.



Scheme 6.44

It should be noted that titanocene-catalyzed carbosilylation of alkenes and dienes, which uses alkyl halides and chlorosilanes, involves alkyl radical addition to styrenes and dienes [68]. The reaction uses butylmagnesiumchloride and a catalytic amount of titanocene dichloride, which would form the complex

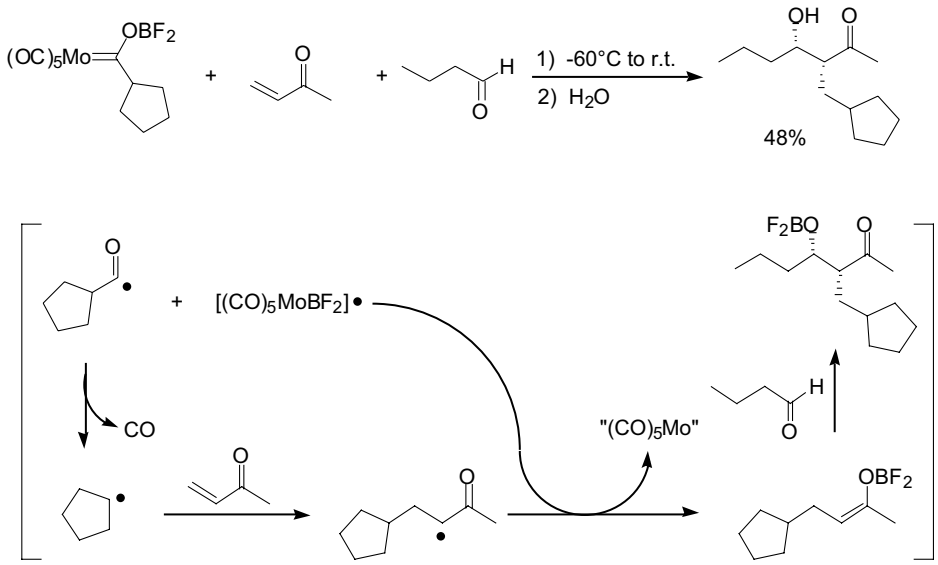


Scheme 6.45

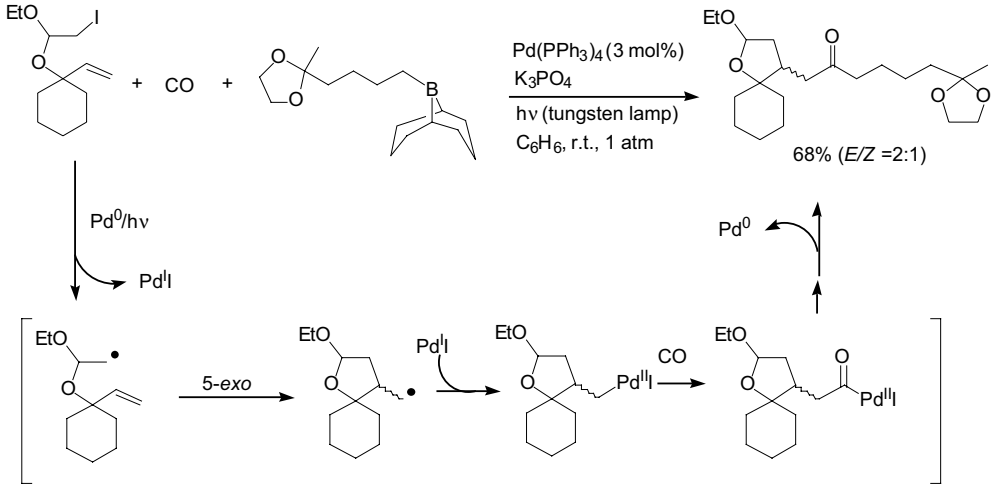
$Bu_2Cp_2TiMgCl$, capable of one-electron transfer to alkyl hakides. Three examples are shown in Scheme 6.45.

Fischer carbene complexes can serve as a source of acyl radicals [69]. The decarbonylative three-component coupling reaction of *in situ* generated Fischer carbene molybdenum complex, methyl vinyl ketone, and an aldehyde has been reported (Scheme 6.46) [70]. The Fischer carbene molybdenum complex is generated at −60 °C, and is then treated with methyl vinyl ketone and isobutanal. At room temperature, the reaction mixture is hydrolyzed by water to give the corresponding aldol product in 48% yield. In this reaction the cyclopentylcarbonyl radical is formed by decomposition of the carbene complex, which undergoes decarbonylation to give the cyclopentyl radical. The radical is trapped by the methyl vinyl ketone and the resulting radical is coupled with $\cdot BF_2 \cdot Mo(CO)_5$ to give a boron enolate. Aldol condensation with an aldehyde then takes place to give the product.

Palladium-catalyzed carbonylative cross-coupling reactions using 9-alkyl-9-borabicyclo[3.3.1]nonanes and aliphatic halides involve a radical mechanism [71]. Unsymmetrical ketones are synthesized in good yields when the reaction is conducted at an atmospheric pressure of carbon monoxide under irradiation from a tungsten lamp. As illustrated in Scheme 6.47, a likely mechanism involves five-membered radical cyclization followed by coupling with PdI to form an alkylpalladium complex, which would then undergo CO insertion and coupling with 9-octyl-9-borabicyclo[3.3.1]nonane, leading to the product.

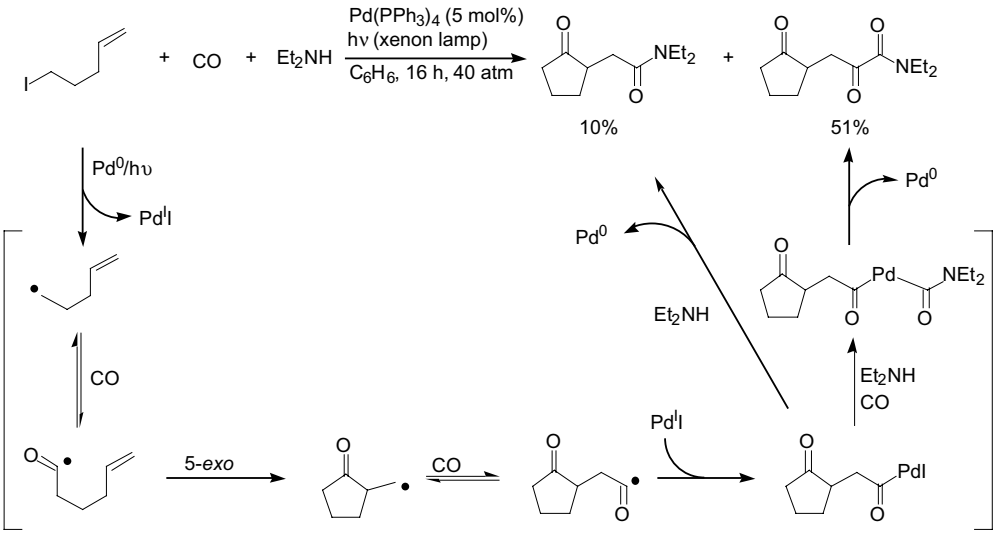


Scheme 6.46



Scheme 6.47

Similarly, cyclizative tandem double-carbonylation reactions of 4-pentenyl iodide under irradiation conditions, is boosted by the addition of a catalytic amount of palladium complexes [72]. When performed in the presence of diethylamine, the carbonylation provided a triply carbonylated α,δ-diketo amide as the major product along with the doubly carbonylated γ-keto amide (Scheme 6.48). Experimental evidence supports the interplay of two reactive species, radicals and organopalladium



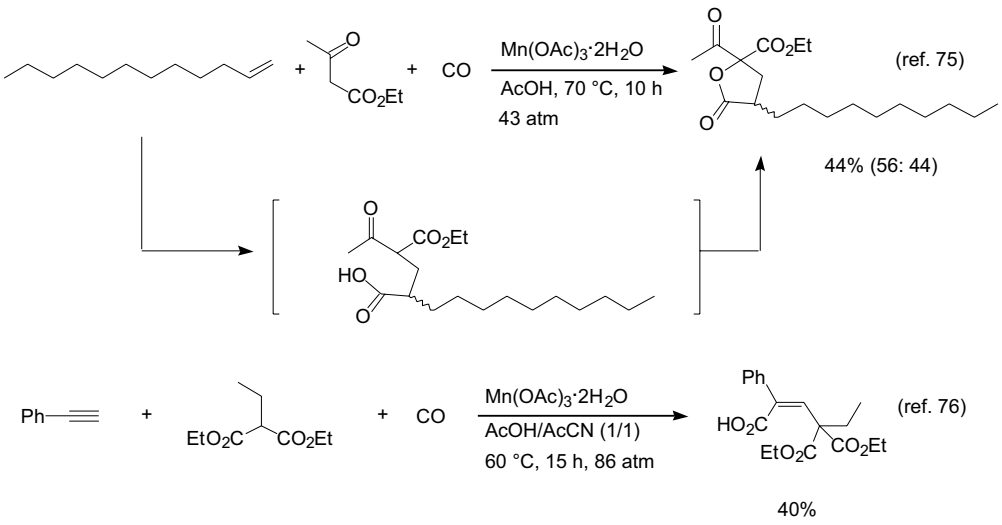
Scheme 6.48

species, in the transformation. Whereas five-membered ring formation is consistent with a radical pathway involving 5-exo acyl radical cyclization, the formation of keto amides would be predicted to be the product of acylpalladium intermediates [73]. Thus, (4-oxo-acyl)(carbamoyl)palladium complexes would be formed in the system, serving as key precursors of α-keto amides.

One-electron oxidation systems can also generate radical species in non-chain processes. The manganese(III)-induced oxidation of C–H bonds of enolizable carbonyl compounds [74], which leads to the generation of electrophilic radicals, has found some applications in multicomponent reactions involving carbon monoxide. In the first transformation given in Scheme 6.49, a one-electron oxidation of ethyl acetoacetate by manganese triacetate, yields a radical, which then consecutively adds to 1-decene and CO to form an acyl radical [75]. The subsequent one-electron oxidation of an acyl radical to an acyl cation leads to a carboxylic acid. The formation of a γ-lactone is due to the further oxidation of a carboxylic acid having an active C–H bond. As shown in the second equation, alkynes can also be used as substrates for similar three-component reactions, in which further oxidation is not observed [76].

6.5 Conclusions

Free-radical-mediated reactions have clearly been shown to be a powerful means of connecting three and more components into one molecule. The diversity of examples presented in this chapter provides ample proof for the utility of radical-



Scheme 6.49

based multicomponent methods as well as combined radical-ion and radical-metal methods.

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7
Multicomponent Reactions with Organoboron Compounds

Nicos A. Petasis

7.1
Introduction

Multicomponent reactions (MCRs) are processes that involve sequential reactions among three or more reactant components that co-exist in the same reaction mixture. In order to be efficient, MCRs rely on components that are compatible with each other and do not undergo alternative irreversible reactions to form other products or by-products.

In recent years there has been a renewed and growing interest in MCRs because they offer several attractive features to the chemical and pharmaceutical industries, including access to a large number of novel and diverse structures and lower production and environmental costs due to high convergence and a greater degree of atom economy.

Although several well-known MCRs have been used for over a century, some of the underlying conceptual principles and the enormous potential of MCRs have only become broadly appreciated in the most recent decade along with the emergence of combinatorial chemistry [1–4]. As a result, MCRs continue to attract growing attention resulting in many new variations of old MCRs, along with the discovery of new MCRs, as well as many applications in organic synthesis, combinatorial chemistry, medicinal chemistry and process chemistry [5–9].

According to Ivar Ugi [5], the leading pioneer of modern MCR chemistry, MCRs can be classified in three major types, according to the number of irreversible steps. MCRs of Type I are characterized by multiple reaction equilibria among all reactants and intermediates, while MCRs of Type II have one irreversible step leading to the product. Type-III MCRs consist of sequential irreversible steps and are related to cascade or domino reactions having the various reaction components embedded in the structure of the starting materials.

Among the various types of MCRs, the most synthetically attractive are those of Type II, which can produce high yields of pure products. Although such processes involve complex equilibria with many intermediates, these eventually lead to the irreversible formation of the final product only when all components have participated in the reaction.

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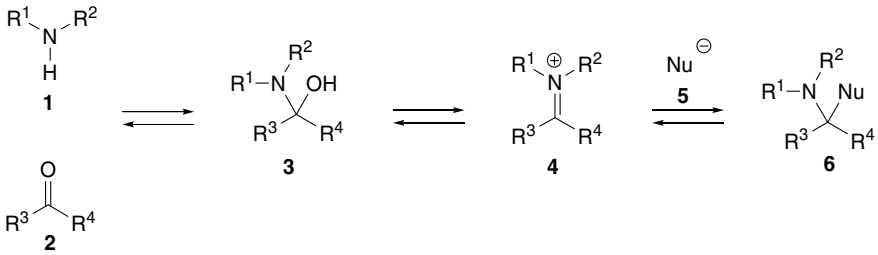
This chapter describes the discovery and development of a new category of Type II MCRs involving organoboron compounds, as well as several synthetic applications of these processes.

7.2
MCRs Involving Amines and Aldehydes or Ketones

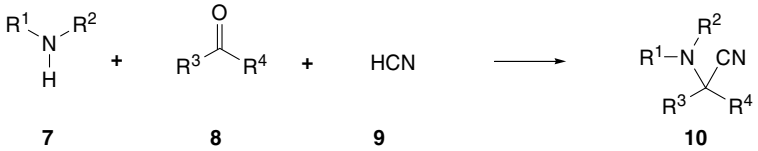
The longest known and most widely used MCRs involve amines and carbonyls as two of the key components (Scheme 7.1). These processes benefit from the ability of amines **1** to react with aldehydes and ketones **2** in a reversible manner initially to form aminols, which can lead to various condensation adducts including iminium salts **4**, depending on the substrates and reaction conditions. Reaction of **4** with a nucleophile **5** can lead to a new product **6**, while if **5** can co-exist or be generated in the presence of **1** and **2**, it would be possible to have an MCR process among **1**, **2** and **5**. If the reaction between **5** and **4** is reversible such an MCR would be of Type I, while an irreversible reaction will constitute a Type II MCR. Indeed, several well-established MCRs are based on the combination of an amine, a carbonyl and a third nucleophilic component.



Scheme 7.1

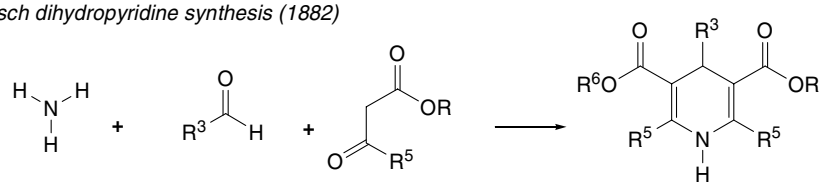
The first such process was realized over one and a half centuries ago with the discovery of the Strecker reaction [10] which has a cyanide ion as the nucleophile, leading to the formation of α-amino nitriles **10** (Scheme 7.2). These highly versatile synthetic intermediates can be hydrolyzed to α-amino acids or can be converted to other molecules [11, 12].

Strecker reaction (1850)



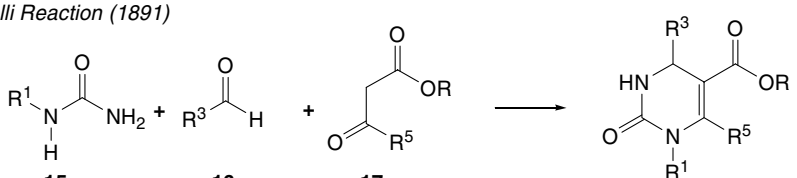
Scheme 7.2

Hantzsch dihydropyridine synthesis (1882)



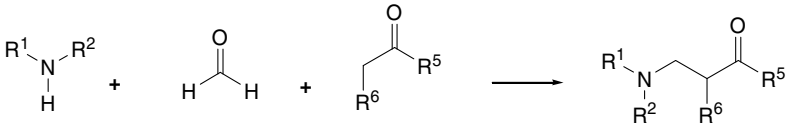
11 **12** **13** **14**

Biginelli Reaction (1891)



15 **16** **17** **18**

Mannich reaction (1912)



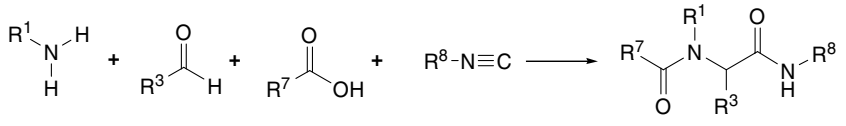
19 **20** **21** **22**

Scheme 7.3

A number of MCRs having enolate-derived nucleophilic components were subsequently discovered (Scheme 7.3), including the Hantzsch dihydropyridine synthesis [13], the Biginelli reaction [14, 15] and the Mannich reaction [16–20]. An added complication in many of these MCRs is the potential irreversible addition of the nucleophile to the carbonyl component, leading to carbonyl addition products. Such MCRs, however, become feasible by the appropriate selection of components that do not favor such alternative transformations. For example, the use of formaldehyde is more effective in the Mannich reaction, because its greater reactivity towards the amine prevents its undesired reaction with the enolate component.

Among the most widely used components for MCRs involving amines and carbonyls are the isocyanides (isonitriles) **26**, which were initially used in the Passerini reaction [21] and more extensively in a series of MCRs introduced by Ugi (Scheme 7.4) [1, 5, 22]. The great effectiveness of isocyanides in MCRs is apparently a result of their remarkable balance between nucleophilic and electrophilic reactivity that enables them to be relatively unreactive towards carbonyl compounds but quite reactive with activated derivatives such as the corresponding iminium species. Numerous applications of isocyanides in MCRs leading to a variety of novel multifunctional derivatives and heterocyclic systems have appeared in recent years [5–9].

Ugi reaction (1959)



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

Scheme 7.4

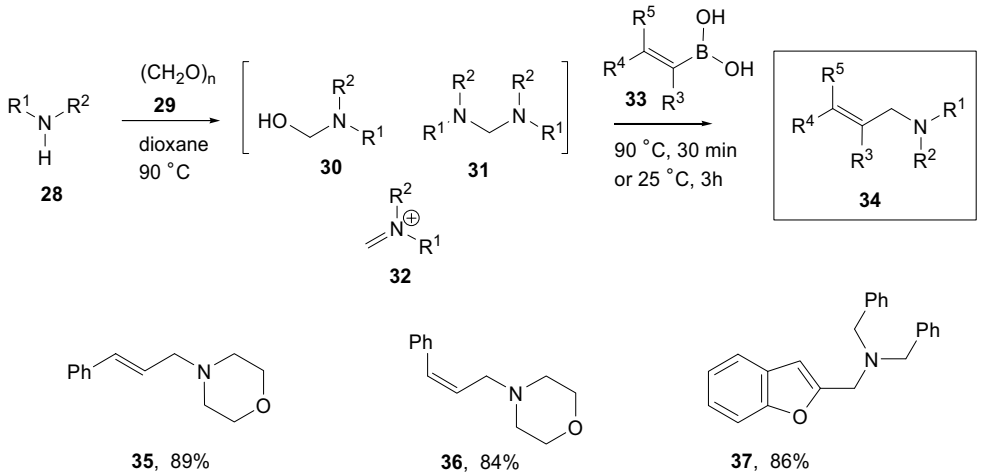
The challenge in developing new MCRs involving amines and carbonyls is to identify additional components that do not undergo irreversible nucleophilic addition to the carbonyl component, leading to carbonyl addition products.

7.3 MCRs Involving Organoboron Compounds

Prompted by the broad range of reactivity of organoboron compounds, which range from highly electrophilic to nucleophilic derivatives, some time ago we decided to explore the possibility of employing boronic acids or borates as reactants in processes involving the adducts of amines with aldehydes and ketones. These efforts led to the discovery and development of several novel MCRs involving organoboronic acid derivatives.

7.3.1 Synthesis of Allylamines and Benzylamines

In our initial study [23], we investigated the *stepwise* reaction of organoboronic acids with the preformed adducts of amines **28** and paraformaldehyde **29**, leading to the convenient synthesis of substituted allylic amines **30** (Scheme 7.5). Since the products of this process were similar to analogous products obtained from the Mannich reaction among amines, formaldehyde and enolates or electron-rich aromatic rings [17–20], we have initially termed this process the ''Boronic Acid Mannich (BAM) reaction''. Although initially we considered this process to be a rare example of using alkenyl nucleophiles in a Mannich-like process, the BAM name (which we subsequently stopped using) [24] incorrectly implied a reaction of the alkene moiety of the boronic acid with an intermediate iminium salt **32**, similar to bimolecular reactions with enolate equivalents as well as Friedel–Crafts-type reactions of **32** with activated aromatic rings [17]. Thus, additional evidence and further considerations suggested that this transformation apparently proceeds *via* a novel mechanism. Indeed, the boronic acids, being electrophilic in nature, presumably react with the aminols **30** or aminals **31**, and do not react directly with preformed iminium salts **32**. Further studies indicated that the geometry of the boronic acid is completely retained during the reaction to give geometrically pure

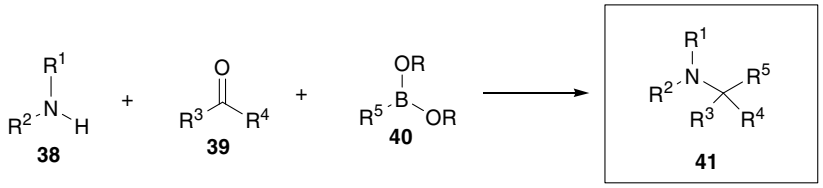


Scheme 7.5

(*E*)- or (*Z*)-allylamines (e.g. **35**, **36**. Analogous results under modified (one-step) conditions were also obtained with aryl and heteroaryl boronic acids which gave the corresponding benzylamines e.g. **37** [25].

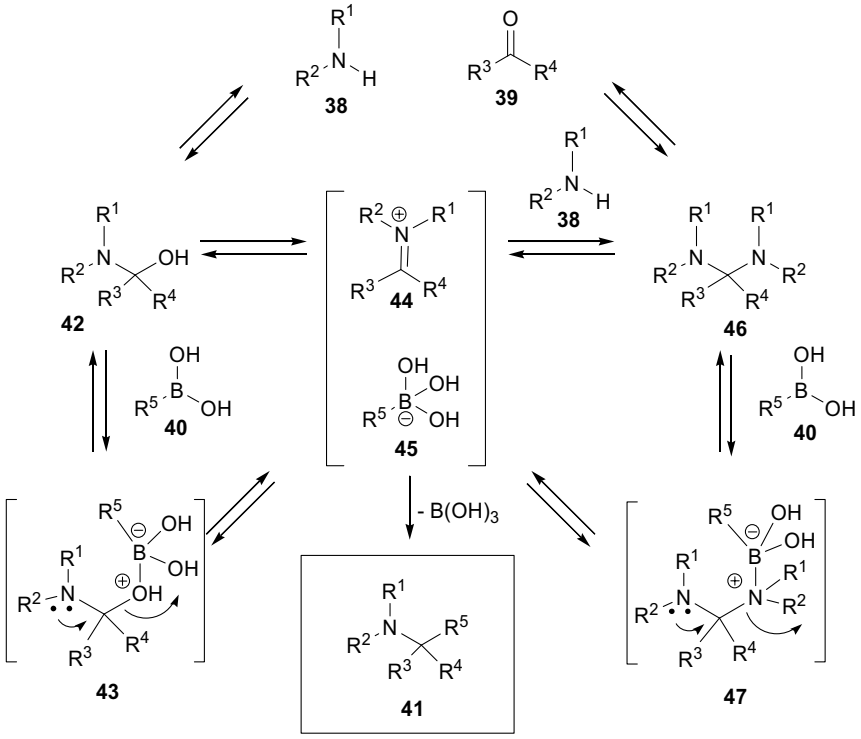
7.3.2
A New Three-component Process

While the above stepwise bimolecular process was well suited for reactions with paraformaldehyde, other aldehydes and ketones did not behave similarly, presumably because of incomplete reactions between the amine and the carbonyl components. To overcome these difficulties, we invented a *three-component process* (Scheme 7.6) based on the one-step reaction between various amines **38**, carbonyls **39**, and boronic acids or boronates **40** to give the corresponding amine derivatives **41** [26].



Scheme 7.6

Mechanistically, this novel process is apparently a Type II MCR, characterized by complex equilibria among the three components and various intermediates, which give the amine condensation products **41** *via* an irreversible C–C bond-forming step (Scheme 7.7). Thus, condensation between the amine **38** and carbonyl **39**



Scheme 7.7

forms the aminol **42**, which can be converted to the aminal **46** *via* the iminium salt **44**. The boronic acid **40**, while it can co-exist with the amine and carbonyl components, can react irreversibly with **42** or **46** as shown in **43** and **47** respectively, to simultaneously generate an electrophilic iminium species **44** and a nucleophilic borate species **45**. The irreversible C–C bond-forming reaction between **44** and **45** leads to the product **41** with the elimination of boric acid as a by-product. Since the reaction between **44** and **45** is the only irreversible step in this process, all intermediates can ultimately lead to the final product. Also, in cases where the amine or carbonyl components contain hydroxyl groups or other functionalities that can bind the boronic acid, the two reactive intermediates **44** and **45** can be linked together and the reaction would take place intramolecularly.

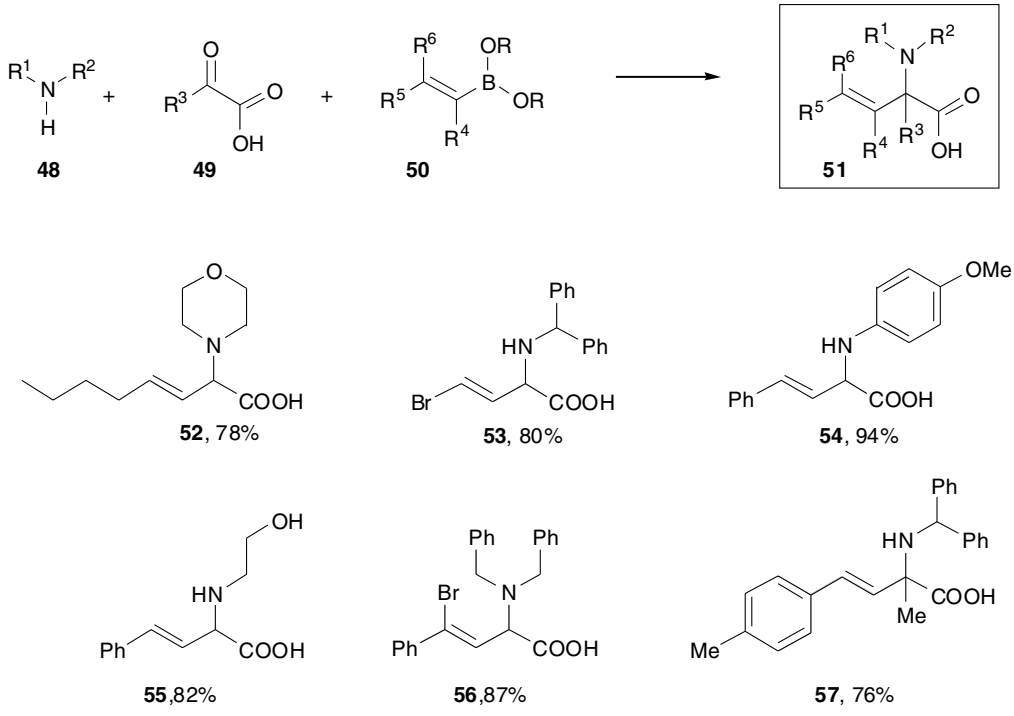
A major advantage of this MCR is that organoboronic acids are readily available in a large variety of structural configurations and they can be formed in isomerically pure forms. As a result of their widespread utility in Suzuki–Miyaura coupling [27, 28] and other reactions [29, 30], a variety of aryl and heteroaryl [31] boronic acids are now commercially available and can be employed in this MCR process. Most of these compounds are also air and water stable as well as non-toxic and environmentally friendly. They also tolerate many functional groups, thereby

allowing the facile synthesis of multifunctional molecules without the excessive use of protective groups.

As summarized below, this method can be used for the facile synthesis of a variety of amine derivatives, including many potentially bioactive and drug-like molecules. Also, the multicomponent nature of this process and the availability of a wide range of components allows the facile synthesis of large combinatorial libraries of diverse molecules [32, 33].

7.3.3 Synthesis of α-Amino Acids

The one-step three-component reaction among amines **48**, α-keto acids **49** and organoboronic acids or boronates **50** leads directly to α-amino acids **51** (Scheme 7.8) [26, 34]. While most other methods for amino acid synthesis [35–39] initially generate derivatives of the amino acid moiety, having the amino and or carboxylic acid units protected as amides, esters or other functional groups, this three-component process directly generates the amino acid unit with both a basic and an acidic group. As a result, the amino acid product **51** is typically insoluble in the reaction medium and precipitates out, allowing a simple isolation and purification procedure through filtration and washing. This reaction is practical and experimentally

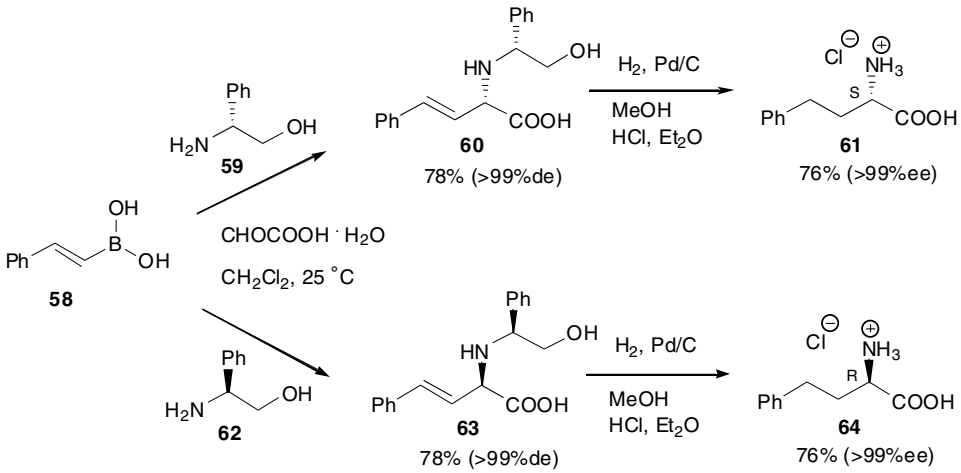


Scheme 7.8

convenient and proceeds by stirring the three components at room or higher temperature in a variety of solvents, including ethanol, toluene or dichloromethane, as well as water or aqueous mixtures.

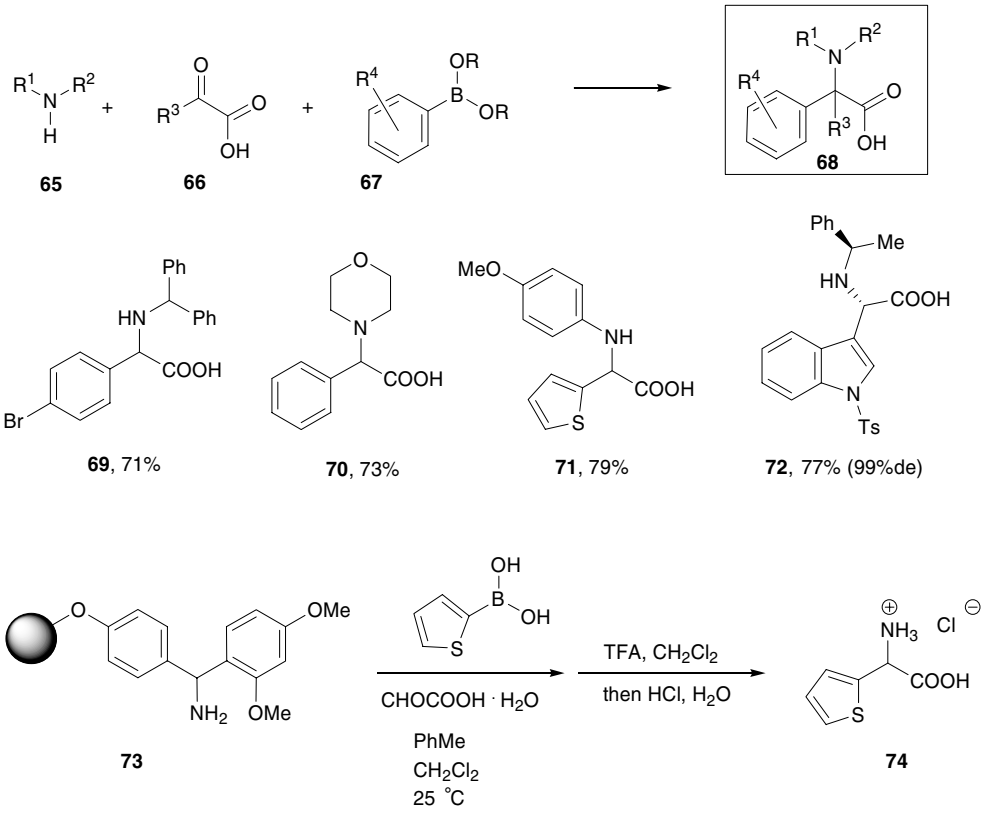
The use of alkenyl boronic acid derivatives **50**, which are readily prepared *via* hydroboration or bromoboration of alkynes, affords the corresponding *β*,*γ*-unsaturated amino acids (e.g. **52–57**) in a geometrically pure form [34]. A variety of amines **48**, including primary and secondary amines, anilines, amino alcohols and hydroxylamines can effectively participate in this process, while the alkenyl boronic acid can contain alkyl, aryl or bromo-substituents. Although the alkenyl amino acid side chain is introduced through the boronic acid component, the use of more substituted *α*-keto acids **49** allows the simultaneous incorporation of an additional *α*-substituent (e.g. **57**).

A very high degree of stereoselectivity was observed when certain chiral amino alcohols were used as the amine component (Scheme 7.9) [34]. For example, either enantiomer of homo-phenylalanine (**61** and **64**) could be efficiently prepared beginning with one of the two enantiomers of 2-phenylglycinol (**59** and **62**), followed by hydrogenolysis of the corresponding intermediate (**60** and **63**).



Scheme 7.9

The use of aryl or heteroaryl boronic acids **67** in this process affords the corresponding aryl glycines **68** (Scheme 7.10) [26, 40]. Amino acids of this type have attracted considerable attention [41] as a result of their presence in glycopeptide antibiotics [42] and other bioactive molecules. The wide availability of aryl and heteroaryl boronic acids makes our method highly versatile and convenient, affording a large variety of amino acid derivatives (e.g. **69–72**). This process was employed by Jiang [43] for the asymmetric synthesis of indolyl glycine derivatives **72**, and was also employed in the solid phase [26, 44–47] by utilizing an amine component attached to a solid support (e.g. **73**) [26].



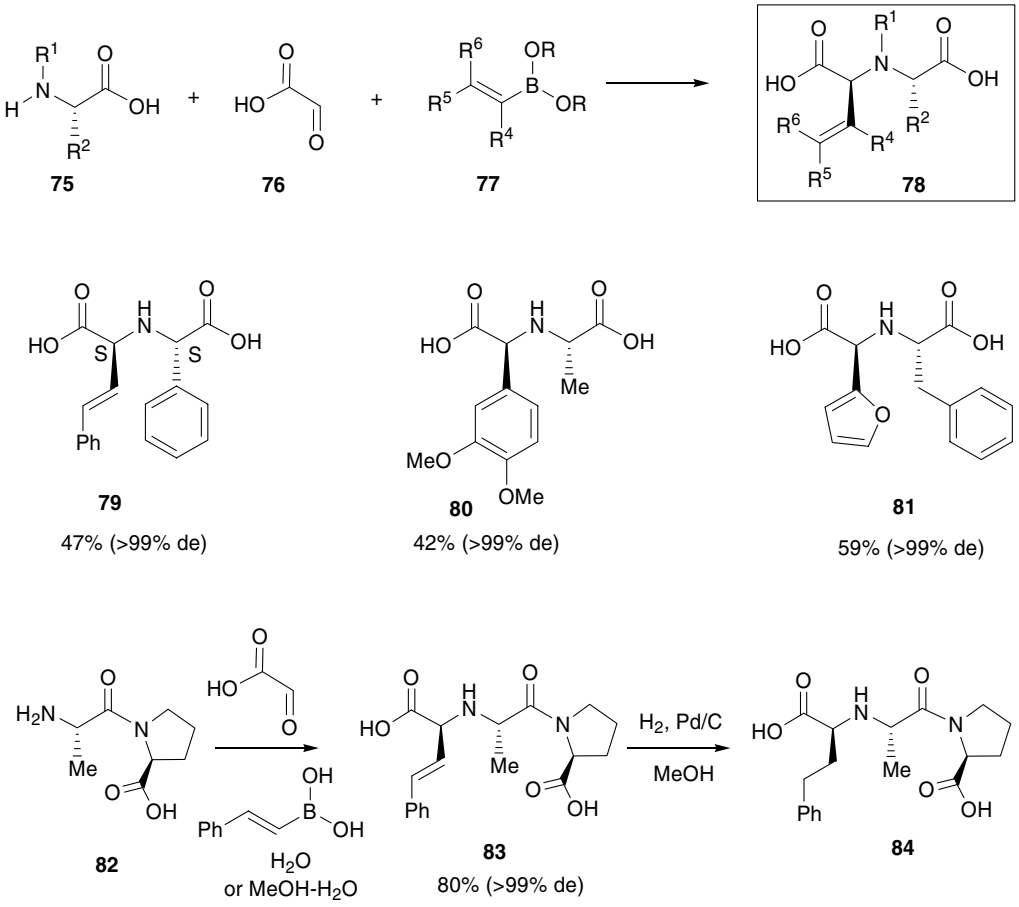
Scheme 7.10

Additional aspects of this method have been under investigation by us and others. While the reaction works well with a variety of boronic acids, the corresponding boronates also work, especially at higher temperatures or under microwave irradiation and preferably with secondary amines as the amine components [48]. While the use of typical chiral boronates in this process gave only low enantioselectivities [49], in some cases we have found that a much higher percentage *ee* is achievable [50], although a universally effective chiral boronate is still being investigated. The use of hydroxylamines and sulfinamides [51] as well as substituted hydrazines [52, 53] as the amine components in this process has also been reported, while it has been shown that highly electron-rich aromatic rings can replace the amine component to give carboxylic acid derivatives [54, 55].

An alternative multistep approach to the synthesis of α-amino acids, using the boronic acid as the precursor of the carboxylic acid group, was reported by Harwood et al. [56]. Thus, reaction of a chiral morpholinone derivative with furyl boronic acid and various aldehydes gave, in a diastereocontrolled manner, the corresponding adducts which were converted in several steps to the α-amino acids [56].

7.3.4
Synthesis of Iminodicarboxylic Acid Derivatives

Amino acids can also be used as the amine components in this process leading to iminodicarboxylic acid derivatives (Scheme 7.11) [26, 57]. This process typically proceeds with a very high degree of diastereocontrol, with the newly generated stereogenic center having the same configuration as that of the amino acid used. As a result of the notable ability of this reaction to operate in highly polar solvents, such as alcohols, water or aqueous mixtures, it is also possible to use peptides as the amine components, resulting in the direct synthesis of peptidomimetic systems. This was demonstrated in an efficient, highly stereocontrolled and environmentally friendly synthesis of the ACE inhibitor enalaprilat **84** (Scheme 7.11) [26, 57].

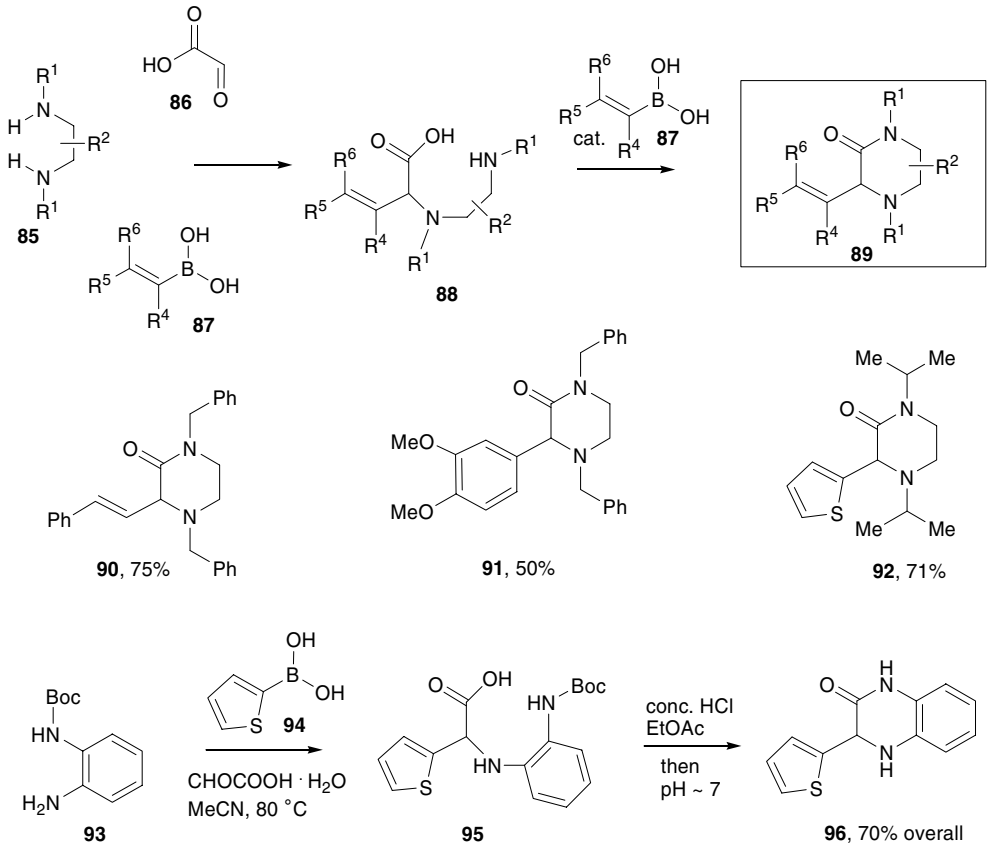


Scheme 7.11

7.3.5

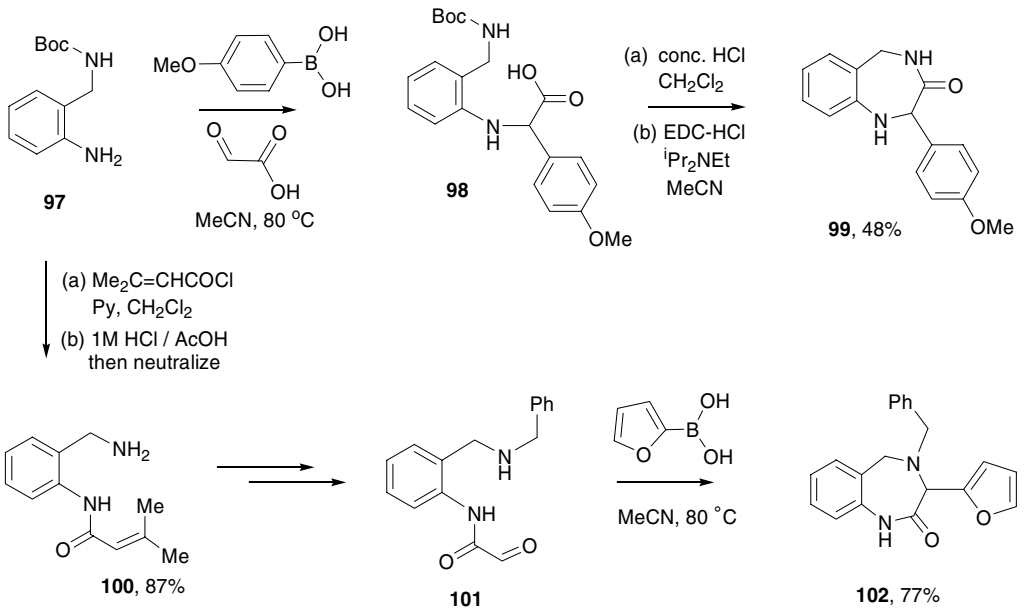
Synthesis of Peptidomimetic Heterocycles

The use of diamine derivatives in the three-component process leads to peptidomimetic heterocycles, such as 2-oxopiperazines (piperazinones) [58], benzopiperazinones [58] and benzodiazepines. In fact, the 2-oxopiperazines **89** can be obtained directly in one step *via* the reaction of a diamine **85** with glyoxylic acid **86** and a boronic acid **87** (Scheme 7.12) [58]. Presumably, the intermediate amino acids **88** can undergo a subsequent boronic acid-catalyzed lactamization [29] to afford **89**. A two-step approach was used for the synthesis of benzopiperazinones (e.g. **96**) [58].



Scheme 7.12

As shown in Scheme 7.13, a similar strategy can be used for the synthesis of 1,4-benzodiazepin-3-ones [59] (e.g. **99**), beginning with a three-component reaction of the monoprotected diamine **97**, followed by deprotection and cyclization. For the



Scheme 7.13

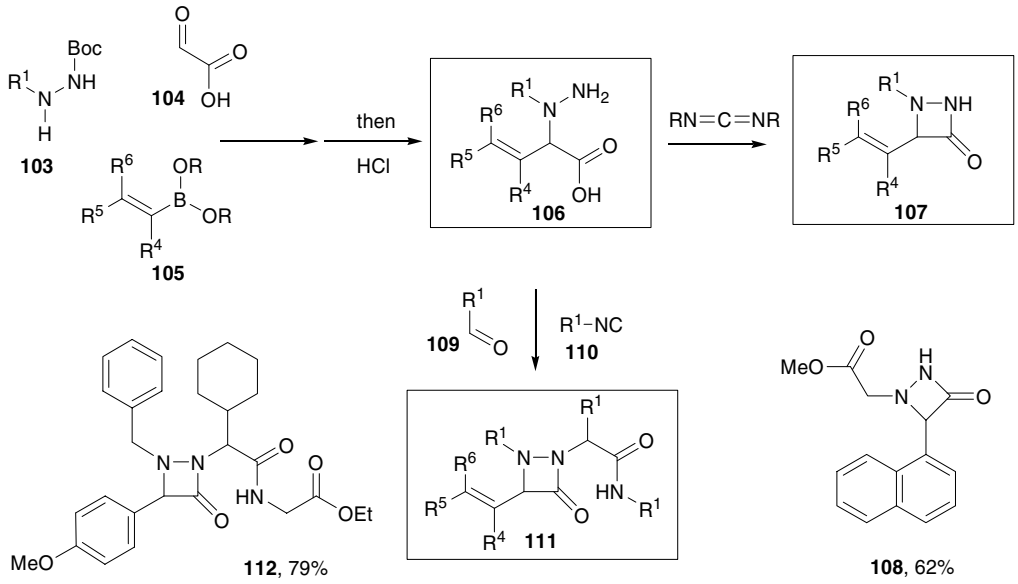
synthesis of 1,4-benzodiazepin-2-ones (e.g. **102**), an intramolecular variant of the three-component process has been developed [60]. Thus, compound **97** can be converted to **101**, which has the amino and carbonyl components connected, followed by a two-component reaction with the boronic acid to afford **102**.

A novel synthesis of aza-β-lactams (Scheme 7.14) from the adducts of the reactions with N-Boc hydrazines **103** was recently reported by Naskar [53]. Thus, direct cyclization of **106** [52] with DIC gave **107**, while participation in the Ugi reaction upon the addition of an aldehyde **109** and an isocyanide **110** gave more substituted derivatives **111** [53].

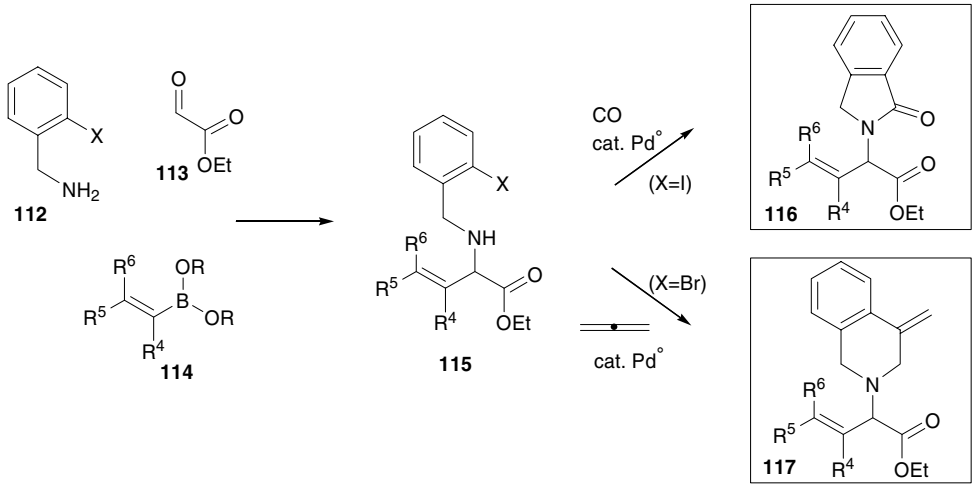
Grigg et al. [61] have recently reported a one-pot reaction involving the initial three-component condensation with a 2-halo-benzylamine **112**, ethyl glyoxylate **113** and an aryl boronic acid **114**, followed by Pd cyclization in the presence of carbon monoxide to give **116**, or in the presence of allene to form dihydroisoquinoline amino acid derivatives **117** (Scheme 7.15).

7.3.6
Reactions with Other Carbonyl Components

Several other carbonyl components have also been employed in this process, including α-keto-aldehydes which form directly the corresponding amino ketones **121** (Scheme 7.16) [62].

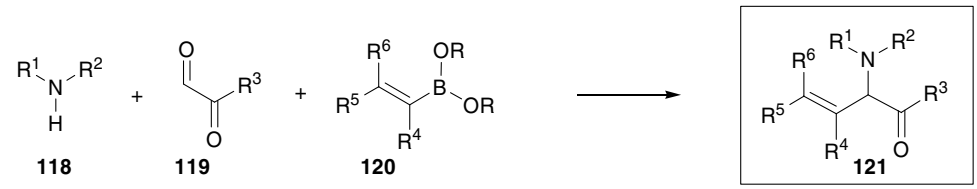


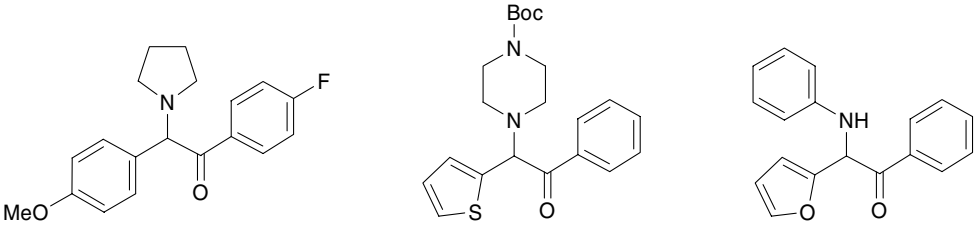
Scheme 7.14



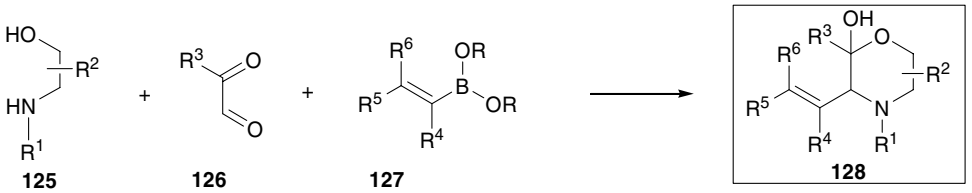
Scheme 7.15

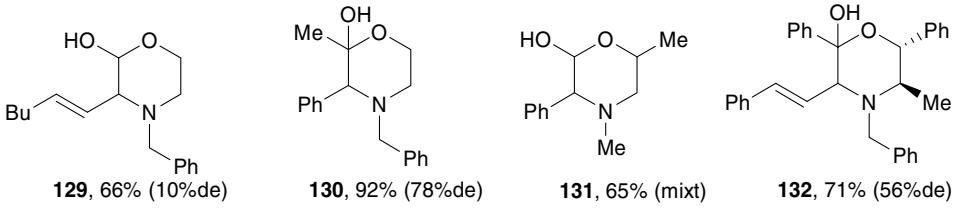
When amino alcohols are used as the amine components along with glyoxal or α-keto-aldehydes, this process generates 2-hydroxy-morpholines **128** (Scheme 7.17) [62, 63]. According to Carboni [63], this reaction proceeds with variable diastereoselectivities (e.g. **129–131**), and we have found that certain chiral amino alcohols give modest asymmetric induction (e.g. **132**) [62].





Scheme 7.16

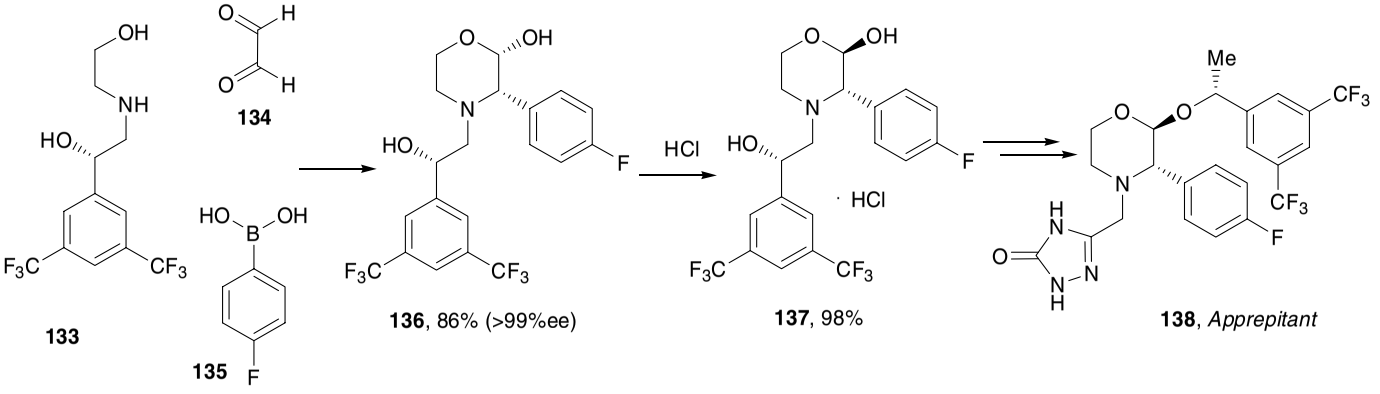




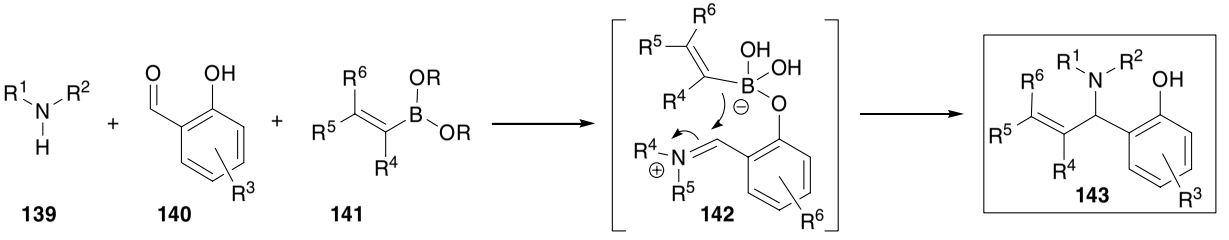
Scheme 7.17

A novel application of this chemistry to a short synthesis of enantiomerically pure 2-hydroxymorpholine **136**, an intermediate in the synthesis of the substance P antagonist Apprepitant **138** (Scheme 7.18), was reported by a group from Merck [64]. Interestingly, despite the initial formation of a complex diastereomeric mixture, compound **136** was isolated in high yield and enantioselectivity *via* a crystallization-induced diastereoselection and could be completely isomerized to **137**, a precursor to **138**.

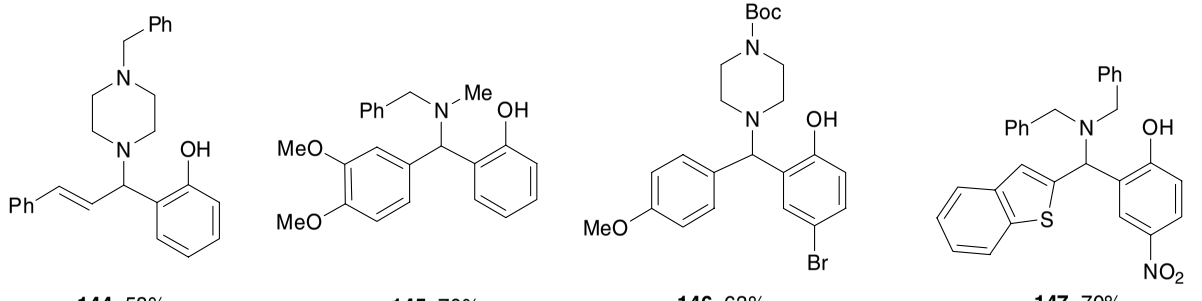
The one-step three-component process among amines, boronic acids and salicylaldehydes **140** gives the corresponding aminomethylphenol derivatives **143** (Scheme 7.19) [65], presumably *via* the intramolecular reaction among the iminium borate species, as illustrated in **142**.



Scheme 7.18

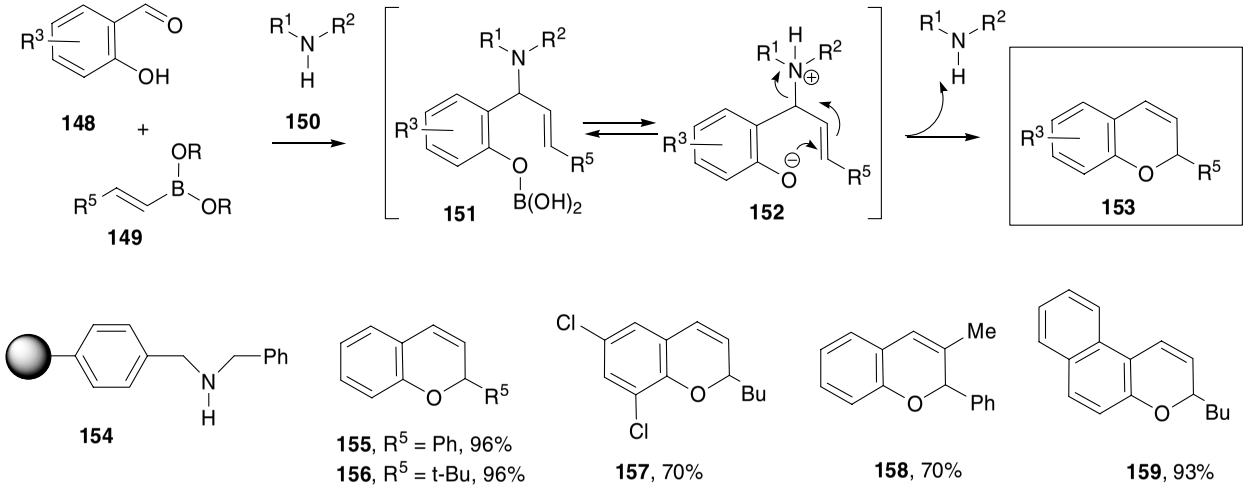


139 **140** **141** **142** **143**



144, 58% **145**, 70% **146**, 63% **147**, 70%

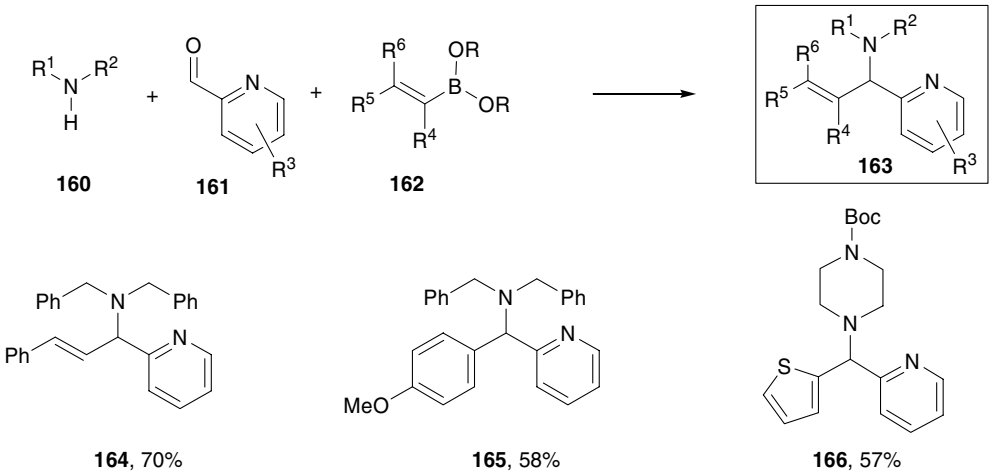
Scheme 7.19


148
149
150
151
152
153
154
155, R5 = Ph, 96%
156, R5 = t-Bu, 96%
157, 70%
158, 70%
159, 93%

Scheme 7.20

Finn [66] has reported that when alkenyl boronic acids are used in this process, the aminomethylphenol intermediates can undergo a further transformation to generate 2*H*-chromenes **153** (Scheme 7.20). This process can be done efficiently with catalytic amounts of dibenzylamine or the corresponding polymer-supported amine **154** to afford a variety of substituted 2*H*-chromenes **155–159** in one step.

2-Pyridylaldehydes **161** [67] and other similar heterocyclic aldehydes [68] also participate in the three-component process affording aminomethylpyridine derivatives **163** (Scheme 7.21). This process can be used to generate novel molecules, such as **166**, that contain three different heterocycles, each of which is introduced *via* one of the three components.



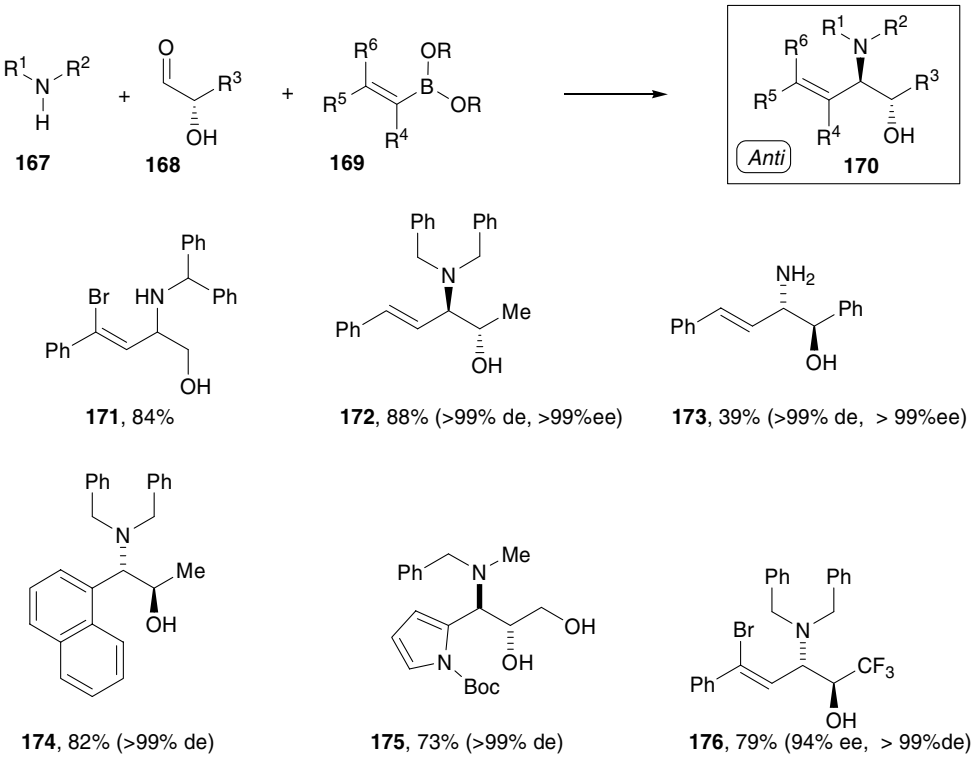
164, 70% **165**, 58% **166**, 57%

Scheme 7.21

7.3.7 Synthesis of Amino Alcohols

Among the most important variations of this multicomponent process are the reactions involving α-hydroxy-aldehydes **168** as the carbonyl components, to afford directly substituted vicinal amino alcohols **170** (Scheme 7.22) [26, 69]. These important molecules [70] are common targets in natural product synthesis, drug design and asymmetric synthesis. When chiral α-hydroxy-aldehydes **168** are used in the reaction, it generally proceeds with a very high degree of stereocontrol, often forming the product as a single enantiomer and a single diastereomer having the anti-configuration [69]. A variety of amines, boronic acids and aldehyde components work well in this process (e.g. **171–176**). Even ammonia can be used as the amine component forming primary amino alcohols (e.g. **173**) in good purity as long as the reaction is stopped early. Given the presence of the amine component, it is noteworthy that the enantiomeric purity of the aldehyde is generally retained during the reaction, allowing the stereoselective synthesis of highly functionalized amino alcohols, including derivatives having the trifluoromethyl group (e.g. **176**) [71].

The use of glyceraldehyde as the carbonyl component is also highly effective,



Scheme 7.22

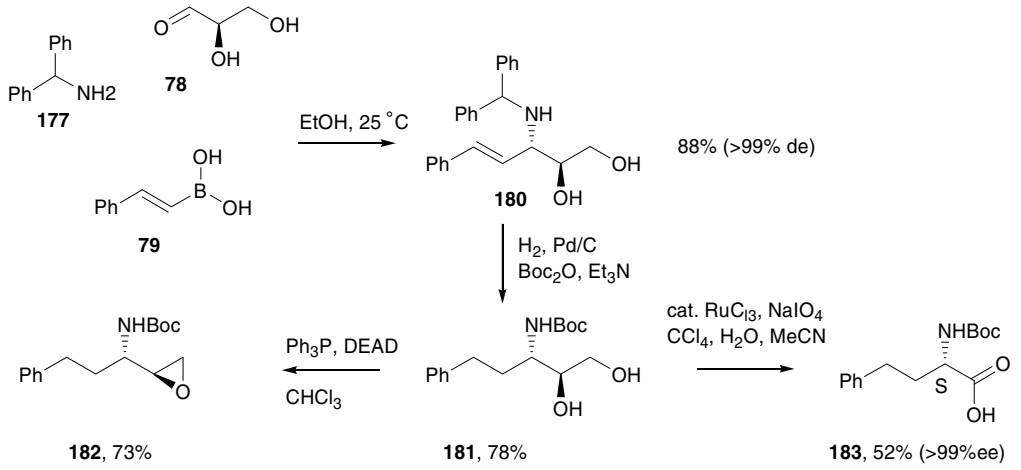
forming amino diol derivatives (e.g. **175**, **180**) with excellent stereochemical purity. Further manipulation of this versatile functionality can produce a range of useful products, such as amino epoxides **182** and amino acids **183** (Scheme 7.23) [69] in enantiomerically pure form.

By retaining the *anti*-amino alcohol unit and generating the carboxylic acid group, it is possible to use this methodology for the synthesis of stereochemically pure β-hydroxy-α-amino acids, as illustrated in Scheme 7.24 [72] for the synthesis of (2*S*,3*R*)-difluorothreonine **191** from difluoro-hydroxy aldehyde **185**.

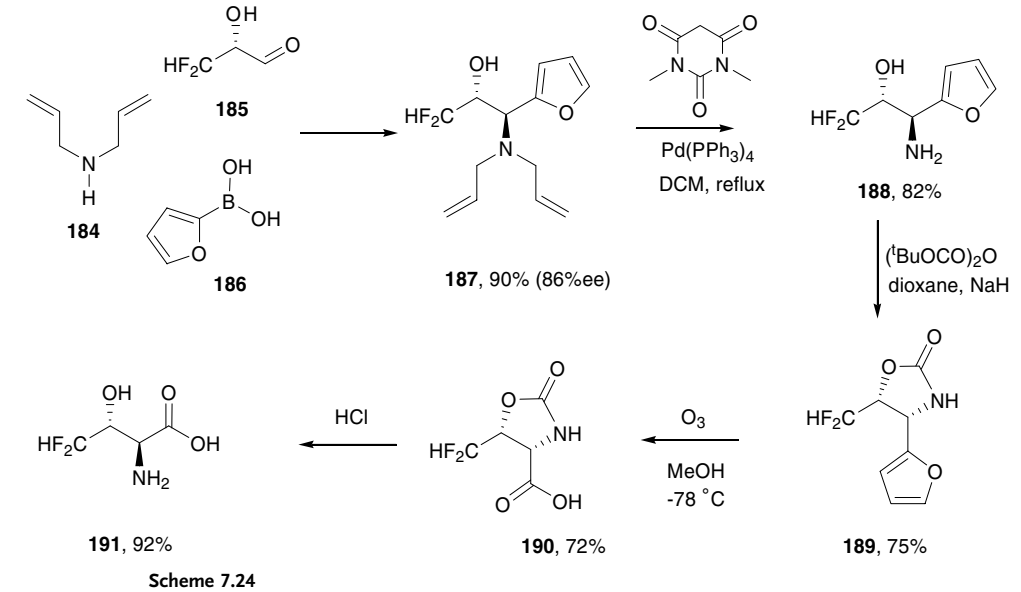
Although ketones are generally less reactive as the carbonyl components in this process, we have found that dihydroxy acetone **193** can participate quite effectively to afford the corresponding 2-aminopropane-1,3-diol derivatives **195** (Scheme 7.25) [26, 73]. We have also demonstrated the use of this chemistry in the synthesis of the immunosuppressant agent FTY720 **199** [73].

7.3.8
Synthesis of Amino Polyols and Amino Sugars

An unusual variation of the three-component process involves the use of *unprotected* carbohydrates **201**, nature's chiral α-hydroxy aldehydes, as the carbonyl com-

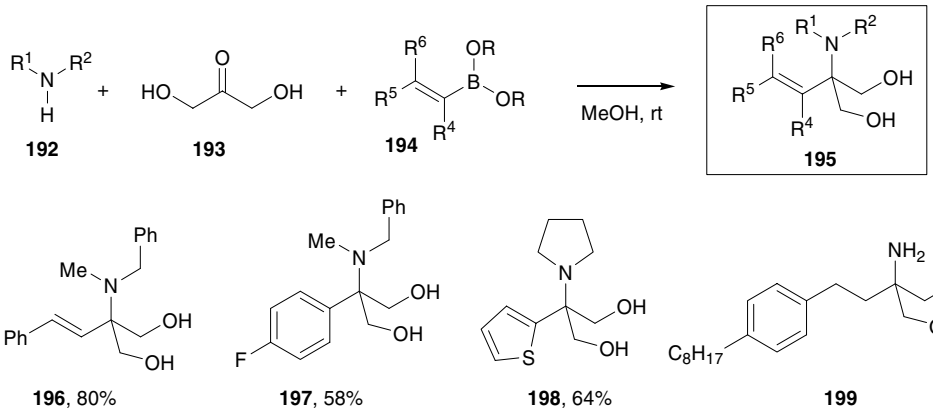


Scheme 7.23

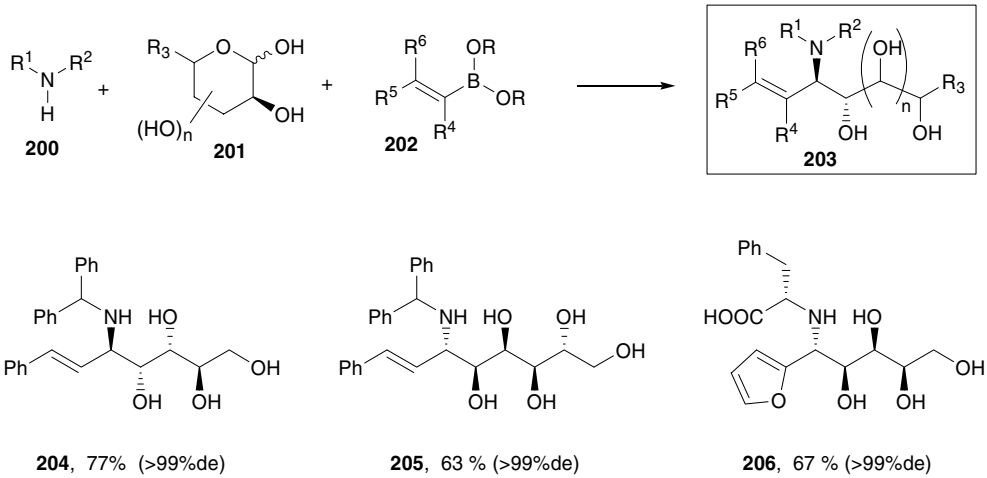


Scheme 7.24

ponents to give aminopolyols **203** with excellent diastereoselectivity (Scheme 7.26) [26, 74]. A variety of carbohydrates as well as amine components, including amino acids, can be employed in this reaction forming complex aminopolyols in stereochemically pure form (e.g. **204**–**206**). It is noteworthy that the three-component process is able to overcome the well-known reactions of carbohydrates with boronic acids to form cyclic boronates, presumably because such processes are reversible, while the carbon–carbon bond-forming step is irreversible.



Scheme 7.25

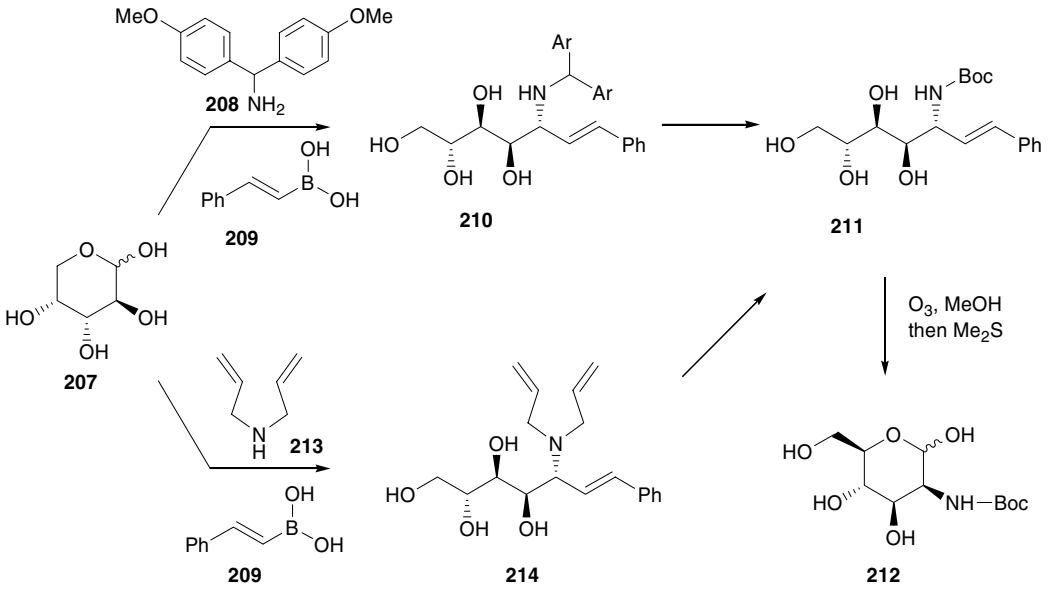


Scheme 7.26

The aminopolyol adducts obtained with carbohydrates can be manipulate further to produce aminosugars (Scheme 7.27) [26, 75]. For example, starting with D-arabinose **207** and a cleavable amine, such as **208** or **213**, followed by conversion to a protected aminopolyol **211** and ozonolysis of the alkene forms the protected mannosamine **212** in good overall yield and purity.

7.4 Summary and Conclusion

The one-step reaction among an amine, a carbonyl and a boronic acid derivative is a highly versatile multicomponent reaction that utilizes readily available compo-



Scheme 7.27

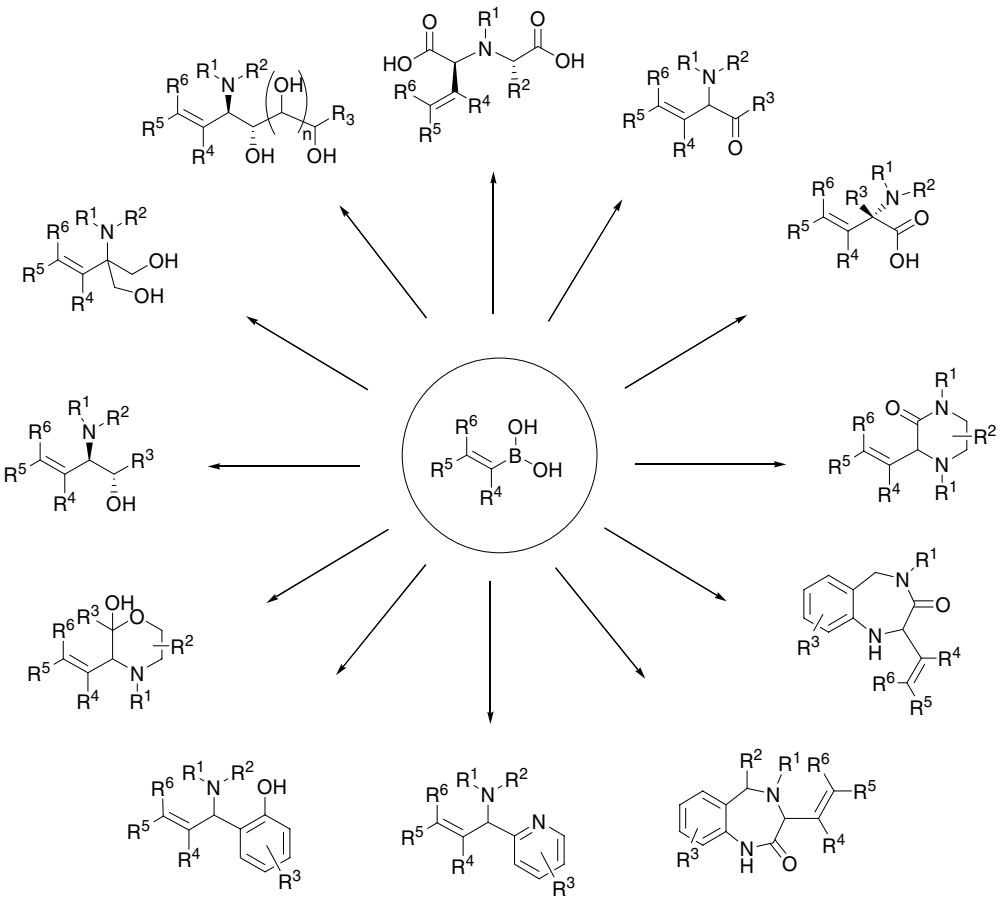
nents that are capable of incorporating a wide range of functional groups into the product. Apparently, the reaction proceeds *via* a novel mechanism that relies on the activation of the boronic acid moiety during the formation of an electrophilic iminium species.

This process is generally practical and experimentally convenient, and can be performed in a variety of solvents, including water. The reaction is also environmentally friendly or ''green'' since it does not require hazardous or toxic chemicals, while the boric acid byproduct of the reaction has a relatively small molecular weight and can be readily removed.

With certain chiral components the reaction proceeds with a very high degree of stereocontrol, allowing the synthesis of enantiomerically pure chiral molecules. Also, many functional groups can be tolerated during the reaction, and as result the need for using protecting groups is minimized.

In addition to forming known types of molecules in only a few steps, this process also enables the synthesis of a variety of novel structures and heterocycles with a high degree of molecular diversity. The commercial availability of an increasing number of structurally novel boronic acids and amine derivatives facilitates their further incorporation into the many types of products that can be synthesized.

As summarized in Scheme 7.28, this methodology allows the synthesis of a large variety of interesting molecules, including amino acids, amino ketones, amino alcohols, amino sugars and several types of heterocycles. Since many of these mol-



Scheme 7.28

ecules have desirable drug-like features, they are of potential interest to drug discovery and development. We are currently continuing to explore a number of additional variations and applications of this chemistry [76].

Acknowledgments

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8
Metal-catalyzed Multicomponent Reactions

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8.1
Introduction

In line with the tremendous renewed activity witnessed in recent years in the field of multicomponent reactions, remarkable new strategies have been developed based on metal-catalyzed coupling processes. Advances in this area take advantage of the myriad of bond-forming processes that can be achieved with metal catalysts.

Metal-mediated intermolecular reaction cascades proceeding *via* non-isolable intermediates such as catalytic organometallic species, are well suited for the design of ''ideal'' multicomponent reactions, those allowing the simultaneous addition of all reactants, reagents, and catalysts at the onset of the reaction with all reactants combining in a unique ordered manner under the same reaction conditions. Amongst transition metals, palladium, and to a lesser extent nickel and ruthenium, have become very popular for their ability to catalyze many cascade processes under mild conditions and, often, with high levels of chemo-, regio-, and stereoselectivities. Several books and reviews have appeared which cover many aspects of this chemistry [1–3]. Therefore, a number of metal-mediated multicomponent reactions have been based on well-planned applications of cascade processes to the assembling of properly designed building blocks. Nevertheless, serendipity still plays an important role in the discovery of such processes.

Besides the ''cascade strategy'' other strategies have gained in popularity based on sequences of individual transformations combined into a one-pot process designed to avoid isolation of intermediates. In these ''formal'' multicomponent reactions, addition of reactants, reagents, or catalysts may be delayed in time so as to increase efficiency and avoid side reactions. Adjustment of the reaction parameters may also be made during the course of these multireaction chemical processes. This strategy may apply to sequences of independent, consecutive metal-catalyzed processes involving either the same catalyst for all steps, or a different catalyst for each step. Combinations of metal-catalyzed reactions with other common organic transformations are also conceivable.

Another important advantage of transition metals is that they allow incorporation of carbon monoxide into a number of different sites in the final molecule,

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and this contributes to expanding the scope of the reactions. The vast number of three-component reactions based on carbonylative processes, which include alkoxy-, amino-, and hydroxycarbonylations as well as formylations, have been extensively reviewed [4]. Therefore the present work will only report those reactions involving insertion of carbon monoxide as a fourth partner in coupling processes. This work is not meant to be an exhaustive review of the literature but rather illustrates innovative strategies that give priority to diversity (maximum amount of variation). The less common multicomponent reactions directed toward target synthesis will also be discussed.

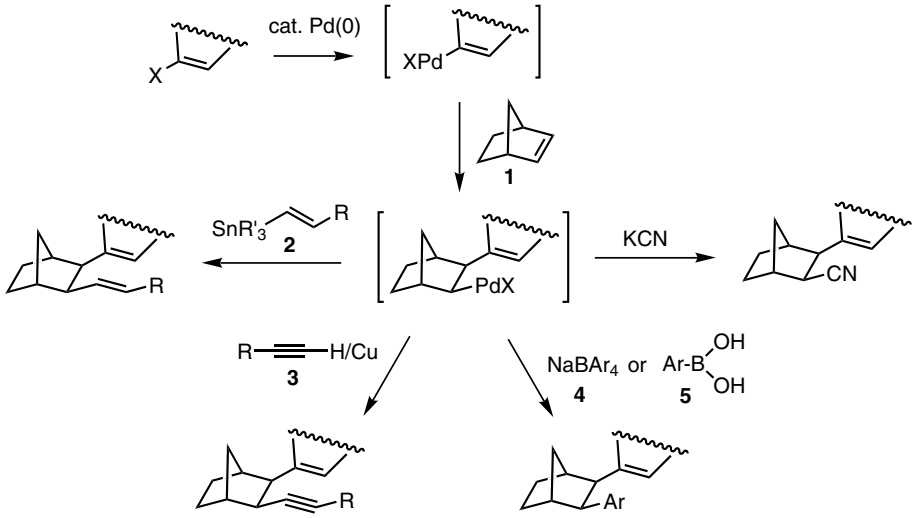
8.2 Vicinal Difunctionalization of Alkenes and Acetylenes *via* Intermolecular Carbometallation

8.2.1 Difunctionalization of Unactivated Alkenes and Acetylenes

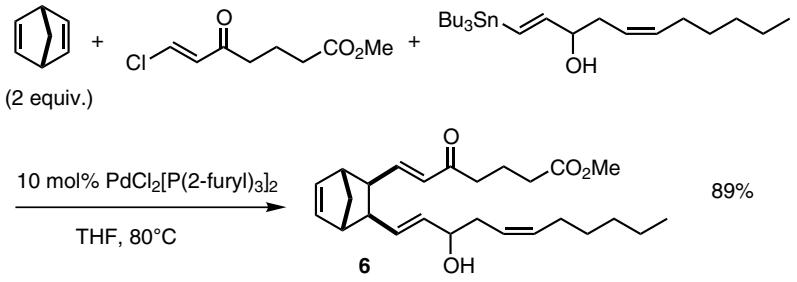
8.2.1.1 Carbopalladation of Norbornene and its Analogues

Three-component coupling reactions based on all-intermolecular cascade carbopalladation reactions have been developed using alkenes as relay. These tandem processes are essentially limited to substrates that lead to σ-alkyl palladium intermediates that do not readily undergo syn β-H-elimination [5]. In line with this, a great deal of interest has been devoted to norbornene **1** and its analogues [6–7]. Syn-carbopalladation of these alkenes with aryl or vinyl halides may be terminated by stereoselective trapping with nucleophiles such as alkenyl stannanes **2** (Stille coupling) [7], terminal acetylenes **3** (Cassar/Sonogashira coupling) [8, 9], tetraaryl borates **4** [10] and boronic acids **5** (Suzuki coupling) [11, 12], or cyanide ion [13] (Scheme 8.1). Scheme 8.2 illustrates the potential applications of such vicinal difunctionalization reactions to the construction of leucotriene model compounds **6** [14]. 1,3-Dioxolenes have also been successively used as olefinic relays in these processes [15].

More recently, Catellani and co-workers brought this chemistry to a new dimension when they discovered that palladacycles of type **7** may be generated from carbopalladation of norbornene with aryl halides. A new series of multicomponent coupling reactions emerged from this observation. Indeed, the process allows ortho alkylations [6, 16] or arylations [17] of the arene moiety, which upon elimination of norbornene can then be further functionalized by Heck [18] or Suzuki [19] coupling reactions of intermediate **9** (Scheme 8.3) to give vinyl arenes **10** and diaryls **11**, respectively. However, a fine tuning of the reaction parameters is necessary to minimize side reactions. Slow addition techniques and excesses of reagents are often required as well. Although norbornene is continuously recycled in these processes, stoichiometric amounts of this reagent are generally required for better efficiency. Based on this methodology, Lautens has recently developed a three-component assembling of various oxacycles **13** by successive inter- and intramolec-



Scheme 8.1

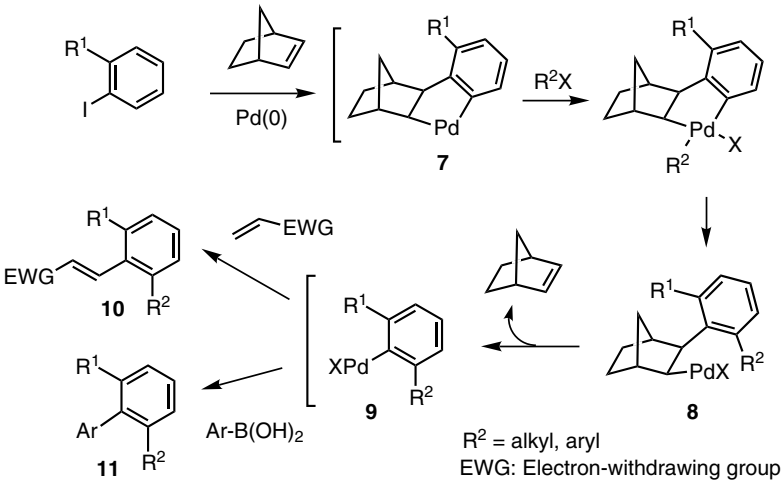


Scheme 8.2

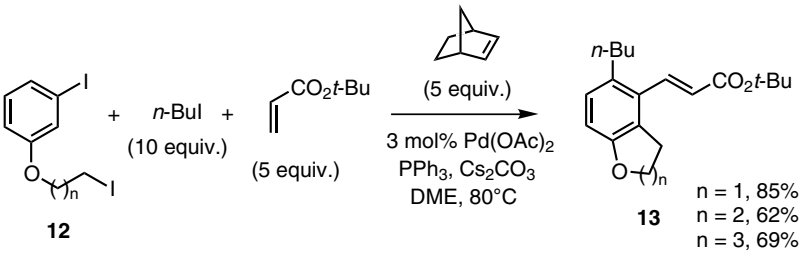
ular ortho bisalkylations of iodoarenes **12**, and subsequent trapping with an activated alkene [20] (Scheme 8.4).

8.2.1.2 **Carbometallation of Alkynes**

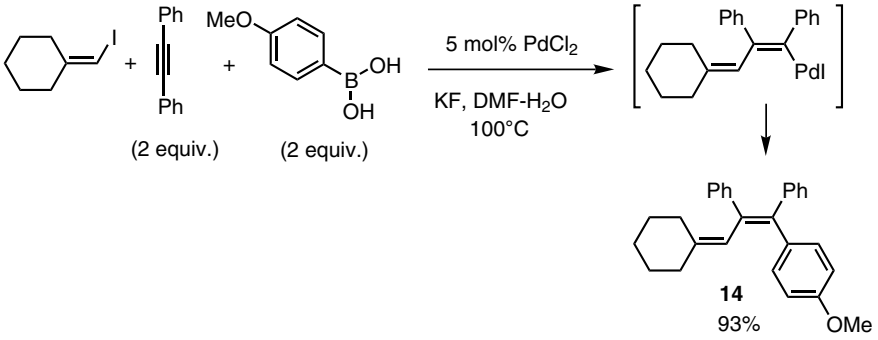
Three-component condensations based on carbometallation reactions of alkynes have also emerged as interesting strategies for regio- and stereoselective syntheses of multisubstituted olefins. Pertinent analyses of conceivable strategies and representative illustrations involving Pd (and Pt) [5, 21], Ni [22, 23], and other metals [24] can be found in recent reviews. Again, palladium reagents are particularly well suited for such tranformations. As illustrated in Scheme 8.5, Larock and coworkers have recently reported the synthesis of 1,3-dienes of type **14** based on the Pd-catalyzed coupling of vinylic halides, symmetrical internal alkynes, and organoboranes [25]. The geometry of the double bond is totally controlled by syn carbopalladation of the alkyne. However, regioselectivity may be a matter of concern



Scheme 8.3

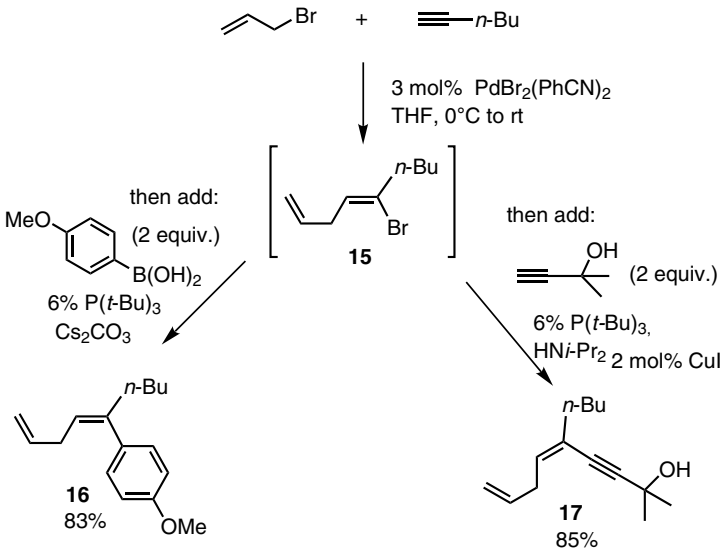


Scheme 8.4



Scheme 8.5

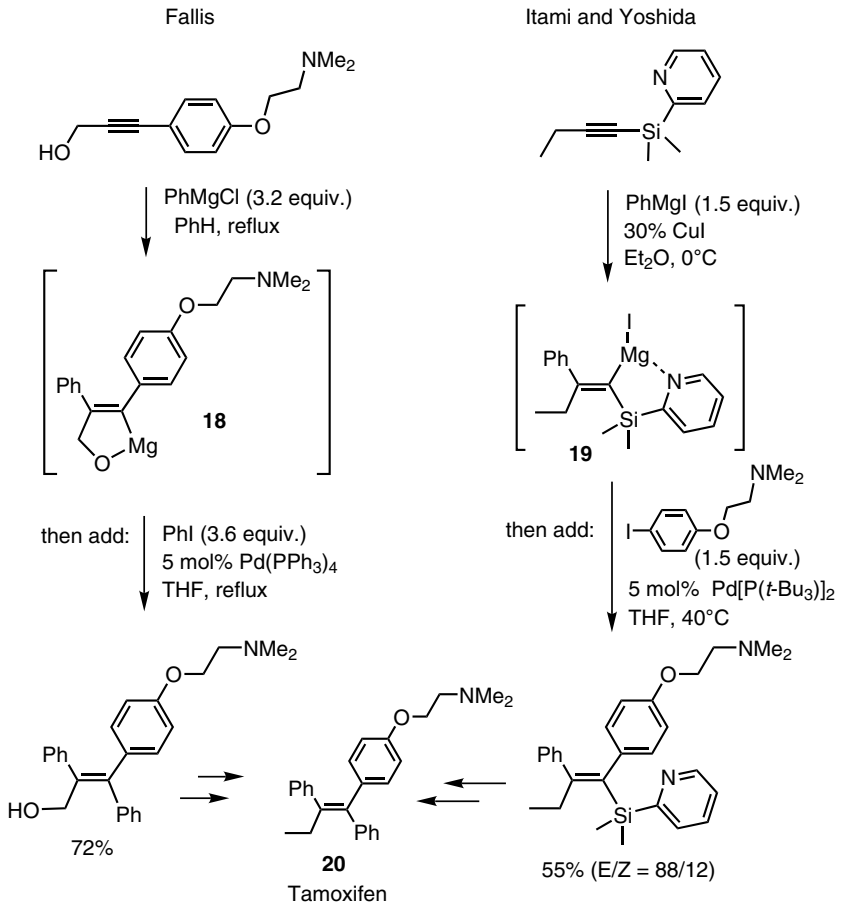
when unsymmetrical internal alkynes are involved [26]. A different approach to the regio- and stereoselective synthesis of dienes and enynes had been previously reported by Rawal. The strategy relied on the sequential one-pot realization of two mechanistically distinct Pd-catalyzed transformations using the same Pd



Scheme 8.6

catalyst. First, bromoallylation of an alkyne, following the procedure developed previously by Kaneda [27], was conducted in the presence of a catalytic amount of $PdBr_2(PhCN)_2$ (Scheme 8.6). Slow addition of the alkyne circumvented any Pd-catalyzed side reaction. Upon addition of a phosphine, $P(t\text{-}Bu)_3$, the same palladium was found to promote *in situ* the Suzuki cross-coupling of the resulting bromoallyl **15** with a boronic acid to yield the corresponding 1,4-diene (e.g. **16**) [28]. Alternatively, Sonogashira cross-couplings may be conducted by adding a terminal alkyne and catalytic amounts of copper iodide to access stereodefined enynes (e.g. **17**) [29, 30]. Interestingly, enynes of the same type can also be obtained *via* Ni-catalyzed cascade couplings of allyl chloride with terminal alkynes and alkynyltins [31]. Three-component carbosilylations [32] and carbothiolations [21] of alkynes have also been developed, which involve palladium and platinium catalysis, respectively. Carbopalladation reactions of electron-deficient alkynes, such as dimethylacetylene dicarboxylate (DMAD), have been reported to generate functionalized, conjugated (*Z*,*Z*)-dienes *via* dimerization/addition reactions [33].

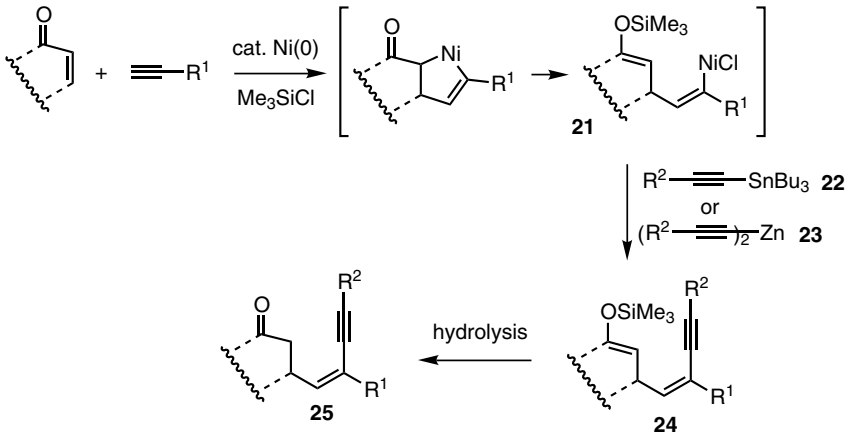
Another strategy toward stereodefined tetrasubstituted olefins based on syn-carbomagnesation/Pd-catalyzed cross-coupling (Kumada–Tamao–Corriu-type) sequences was recently reported by Fallis et al. [34] and by Itami and Yoshida [35]. These studies were particularly focussed on the synthesis of tamoxifen-like olefins **20** as potential anti-breast-cancer drugs. The regioselectivity of the carbomagnesation has been controlled either *via* formation of a magnesium chelate intermediate **18** (Fallis' approach) or by taking advantage of the strong directing effect of a 2-pyridyl group as shown for intermediate **19** (Itami and Yoshida's approach) (Scheme 8.7).



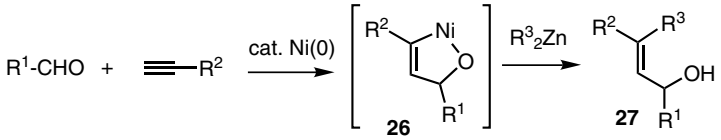
Scheme 8.7

Nickel-catalyzed intermolecular cascade reactions based notably on coupling reactions of carbonyl compounds with alkynes [22, 23, 36] or 1,3-dienes [37, 38] have also been investigated in the search for new multicomponent coupling processes. Ikeda and Sato have discovered that enones couple with alkynes in the presence of TMSCl and catalytic amounts of Ni(0) to form an alkenylnickel intermediate **21**. This reacts either with alkynyltins **22** [39] or alkynylzincs **23** [40] to produce the silyl enol ether **24** which upon hydrolysis gives the corresponding enyne **25** (Scheme 8.8). It is worth noting that difunctionalization of norbornene may also be achieved using this process [41].

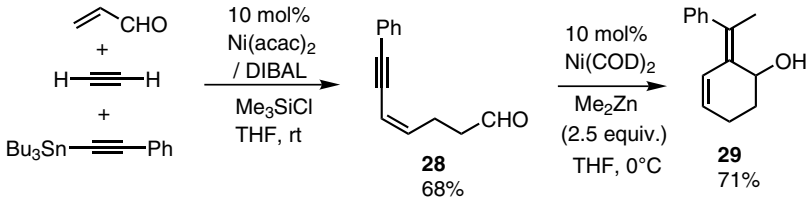
Montgomery and co-workers [36, 42] have shown that organozincs can also couple with alkynes and aldehydes *via* organonickel intermediates **26** with high degrees of chemo- and stereoselectivities to afford allylic alcohols **27** (Scheme 8.9). Recently, they reported a two-step, four-component synthesis of cyclohexenol de-



Scheme 8.8



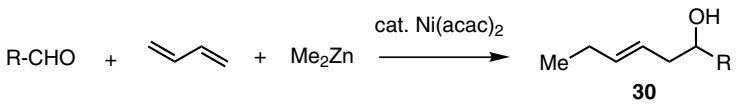
Scheme 8.9



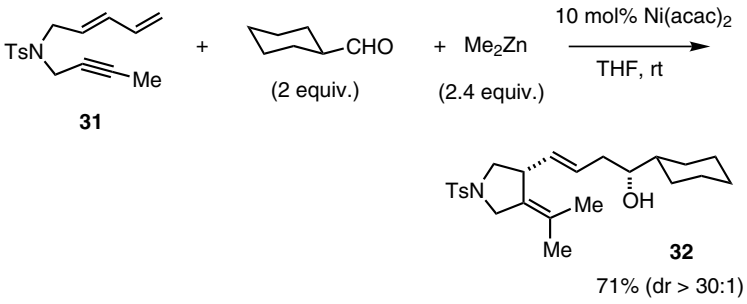
Scheme 8.10

rivatives (e.g. **29**) which combines an intramolecular version of this process, and Ikeda's three-component reaction involving enals (Scheme 8.10) [43].

Tamaru and Kimura have recently developed a three-component coupling reaction of carbonyl compounds, 1,3-dienes, and dimethylzinc leading to homoallylic alcohols **30** *via* Ni-catalyzed conjugate addition of the carbonyl compound to the 1,3-diene in a 1,4-fashion (Scheme 8.11) [44]. They later showed that 1,3-dienes



Scheme 8.11

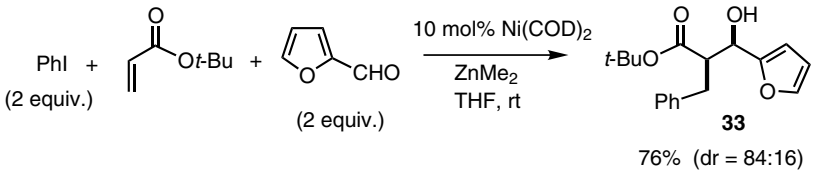


Scheme 8.12

bearing a pendent acetylene (e.g. **31**) may participate in this type of reaction which results in the formation of various carbo- and heterocycles (e.g. **32**) with excellent levels of 1,5-diastereoselectivity (Scheme 8.12) [45].

8.2.2
Difunctionalization of Activated Alkenes

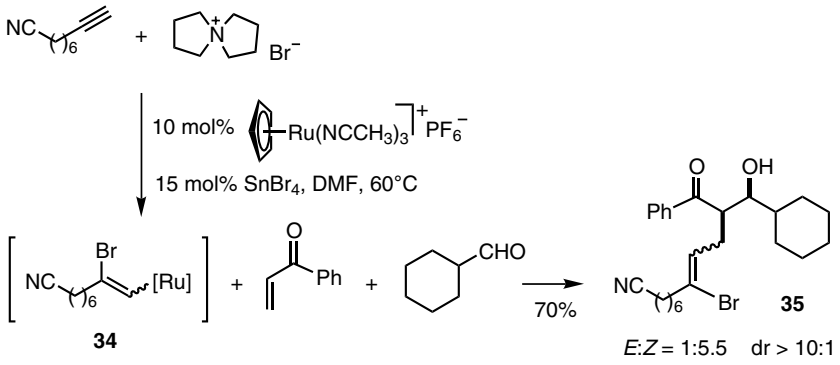
Multiple-component difunctionalization reactions of α,β-unsaturated carbonyl systems have been achieved by catalytic conjugate addition/aldol sequences. As Scheme 8.13 illustrates, an efficient method reported by Montgomery [46] allows regioselective addition of an aryl iodide to the β-position of an unsaturated ester under nickel catalysis and subsequent trapping with an aldehyde to give β-hydroxyesters (e.g. **33**). Significantly, premature termination of the sequence by the β-hydride elimination process that is usually observed in Pd-catalyzed Heck reactions does not occur here.



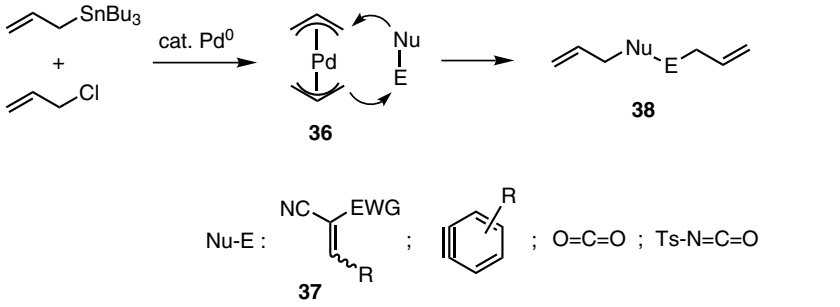
Scheme 8.13

Another method reported by Trost [47] is based on the addition of alkenylruthenium intermediates such as **34** generated by cis-bromoruthenation of alkynes (Scheme 8.14). Overall, the method allows coupling of four components with excellent levels of diastereoselectivity for the aldol step.

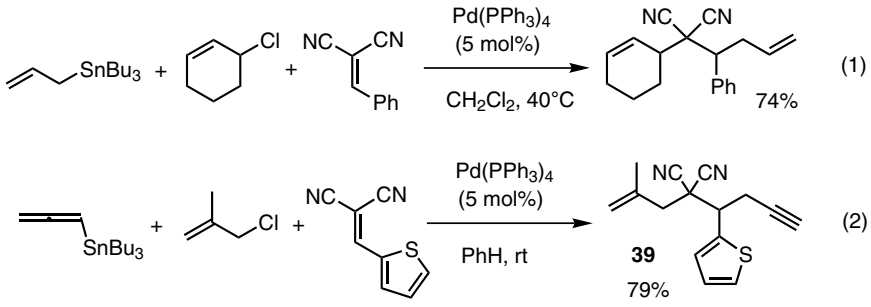
Bis-allylation of unsaturated compounds can be achieved by using amphiphilic bis-π-allylpalladium complexes **36** generated from allylstannanes and allyl chlor-



Scheme 8.14



Scheme 8.15



Scheme 8.16

ides, catalytically (Scheme 8.15). Yamamoto [48] and Szabó [49] have particularly well studied the reactivity of gem-diactivated olefins, essentially acrylonitriles **37**, to synthesize 1,7-dienes **38**. As demonstrated in Scheme 8.16 [Eq. (1)], high levels of regioselectivity can be achieved when unsymmetrical bis-π-allylpalladium intermediates are involved, which have been explained by electronic effects of the sub-

stituents on the allyl moieties. Interestingly, besides activated olefins, arynes [50], carbon dioxide [51], and isocyanates [52] have also been reported as excellent partners in this reaction. Recently, Cheng [53] has developed a similar process involving allenylstannanes, which opens access to 1,7-enynes of type **39** [Scheme 8.16, Eq. (2)].

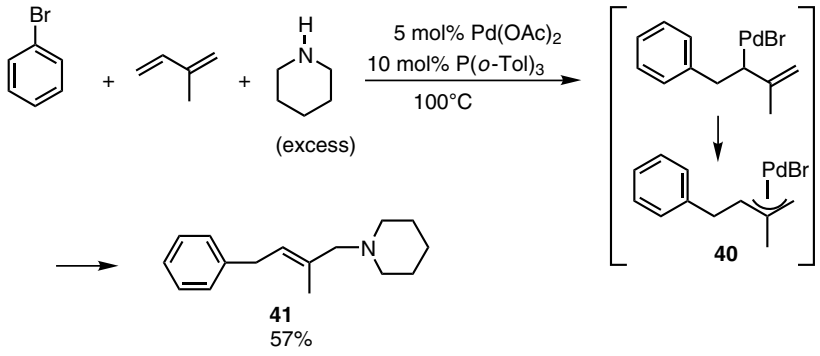
8.3 Reactions Involving π-Allyl Palladium Species as Intermediates

8.3.1 π-Allyl Palladium Species from Carbopalladation of Unsaturated Substrates

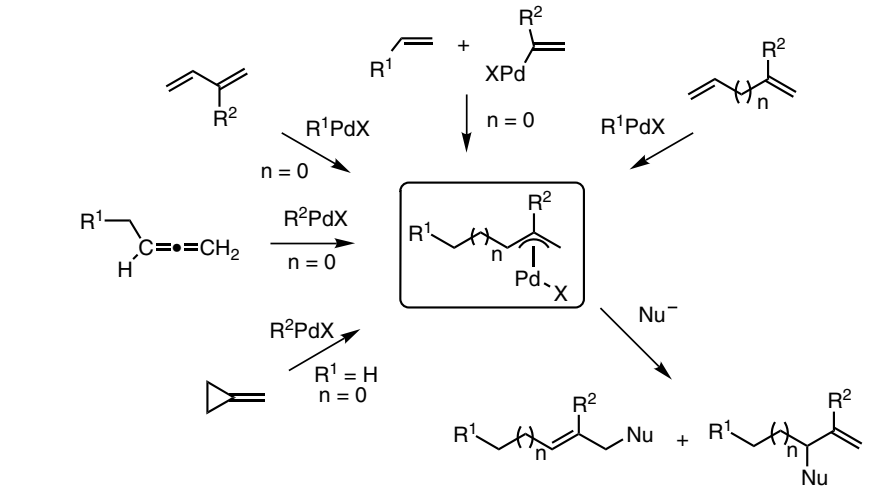
8.3.1.1 Carbopalladation of Conjugated Dienes

The carbopalladation of unsaturated substrates with organic halides or pseudo halides has been used for many years as a way of generating π-allyl palladium species [2]. Nucleophiles such as stabilized-carbon nucleophiles, amines, and alkoxides, attack the π-allyl palladium intermediate to form the three-component assembling products. The Pd(0)-catalyzed reaction of an aryl halide with a conjugated diene in the presence of an amine constitutes one of the first examples of these palladium-mediated three-component assembly reactions [54]. A representative example is the reaction of bromobenzene, isoprene, and piperidine that affords the corresponding arylated allylic amine **41** in 57% yield (Scheme 8.17). This three-component synthesis presumably proceeds by oxidative addition of the unsaturated halide to the active Pd(0) species and subsequent addition of the resulting organopalladium species to the least substituted double bond of isoprene to afford the π-allyl palladium intermediate **40**. Nucleophilic attack of this intermediate by a heteronucleophile such as piperidine gives arylated allylic amine **41** and regenerates the active palladium species.

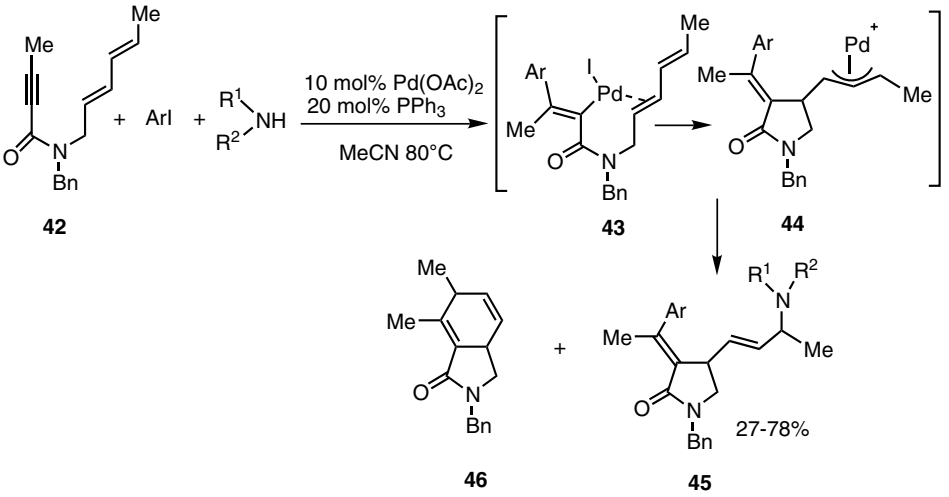
Analogous intermolecular processes involving various unsaturated substrates such as non-conjugated dienes, allenes, methylenecyclopropanes as well as addi-



Scheme 8.17



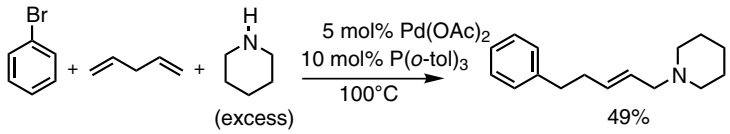
Scheme 8.18



Scheme 8.19

tion of vinylic palladium complexes to alkenes, were further developed (Scheme 8.18).

On the basis of the reaction of conjugated dienes with unsaturated halides in the presence of external nucleophiles, an elegant intramolecular version leading to α-alkylidene-γ-lactams, has been developed (Scheme 8.19). Starting with an aryl halide, the regioselective insertion of an arylpalladium halide to the triple bond of acyclic compound **42** gives the σ-vinylpalladium intermediate **43**. Subsequent intramolecular carbopalladation of the diene affords a π-allyl palladium intermediate



Scheme 8.20

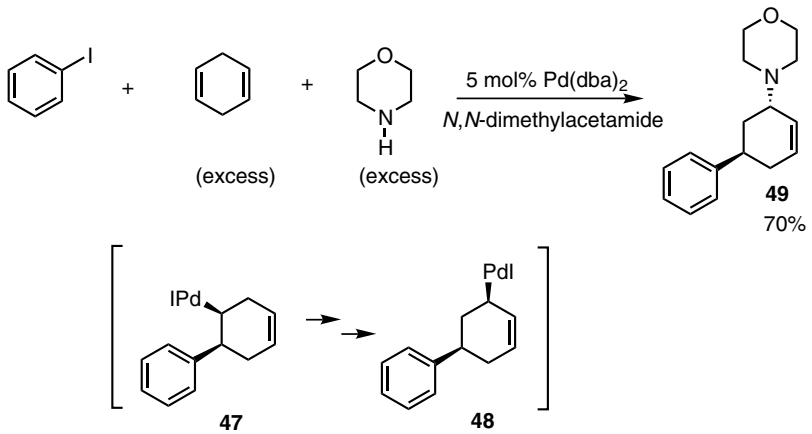
44 which leads to the cyclization product **45** after nucleophilic attack by a primary (benzylamine, isobutylamine, aniline) or a secondary (piperidine, morpholine, pyrrolidine) amine at the less hindered terminus. The by-product **46** produced by intramolecular Diels–Alder reaction of the starting compound is observed when aromatic amines are involved in this three-component reaction [55].

8.3.1.2 **Carbopalladation of Non-conjugated Dienes**

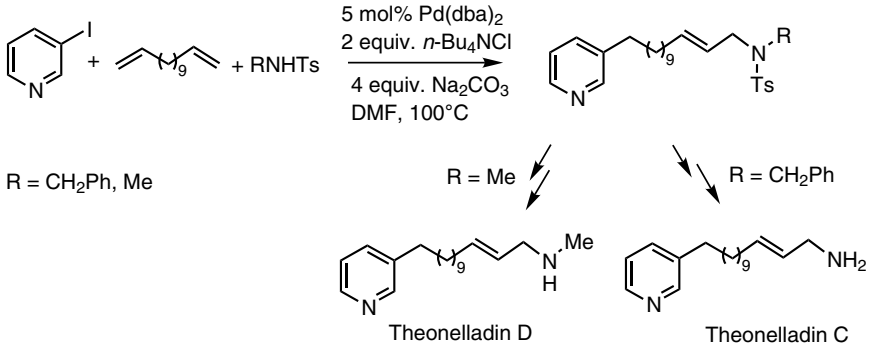
Early findings by Heck and co-workers [56] have shown that the palladium-catalyzed coupling of aromatic halides, non-conjugated 1,3 dienes and secondary amines gives the corresponding arylallylated amines. A representative example is given in Scheme 8.20.

On the basis of this concept, palladium three-component reactions with non-conjugated dienes, organic halides, and external nucleophiles such as amines [57] or soft nucleophiles [58] were further developed. An example where the single allyl amine **49** was obtained from the reaction of iodobenzene, 1,4-cyclohexadiene, and morpholine is given in Scheme 8.21. The formation of the three-component coupling product was explained by the rearrangement of the initial organopalladium species **47** to the π-allylpalladium intermediate **48** *via* successive palladium hydride syn eliminations and readditions. Due to the high stereospecificity of the migration process, the product is formed with a high degree of stereoselectivity by backside displacement of the palladium by the external amine.

This methodology was recently used by Larock and co-workers [59] for the prep-



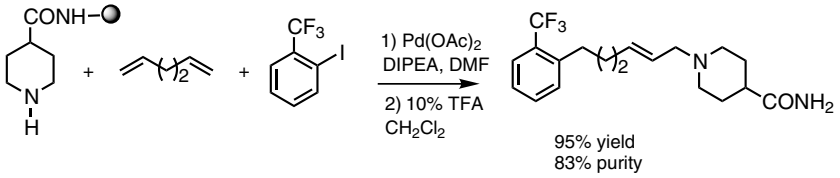
Scheme 8.21



Scheme 8.22

aration of natural pyridine alkaloids such as the antileukemic and antineoplastic theonelladins C and D (Scheme 8.22).

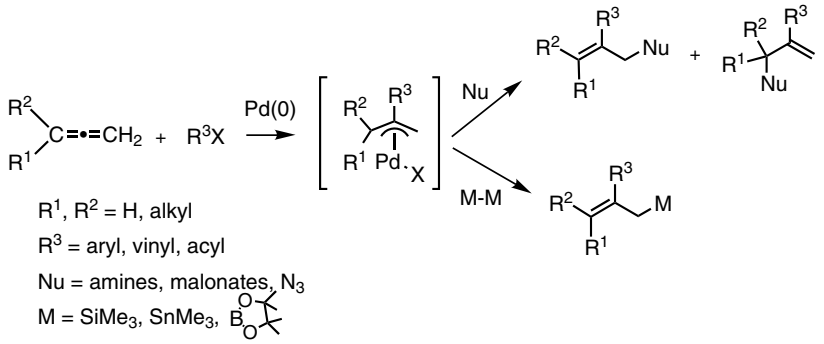
This palladium-catalyzed three-component coupling reaction leading to the formation of aryl-substituted allylic amines was recently adapted to solid-phase synthesis (Scheme 8.23). Amines were chosen to attach to a solid support (Rink resin) in this three-component coupling process and were reacted with a variety of aryl halides and linear or cyclic non-conjugated dienes, the reaction being carried out at 100 °C for two days in the presence of palladium acetate and diisopropylethylamine. A wide variety of aryl-substituted allylic amines were then obtained after cleavage from the solid support by trifluoroacetic acid [60].



Scheme 8.23

8.3.1.3 **Carbopalladation of Allenes**

The carbopalladation reaction of allenes with organic halides gives π-allylpalladium species. In this process, the addition of the organopalladium species occurs at the central carbon atom. The first palladium-catalyzed three-component coupling reactions based on this strategy were developed in 1984. Shimizu and Tsuji reported a palladium-catalyzed coupling of allenes, unsaturated halides, and amines [61] while Gore, Cazes, and co-workers developed this palladium-catalyzed three-component coupling reaction with carbon nucleophiles such as malonates [62]. In recent years, similar strategies were developed by Cheng and co-workers to prepare allyl azides [63] and allylic silanes [64]. The same group developed efficient palladium-mediated methods [65] for the assembling of acyl chlorides, allenes,

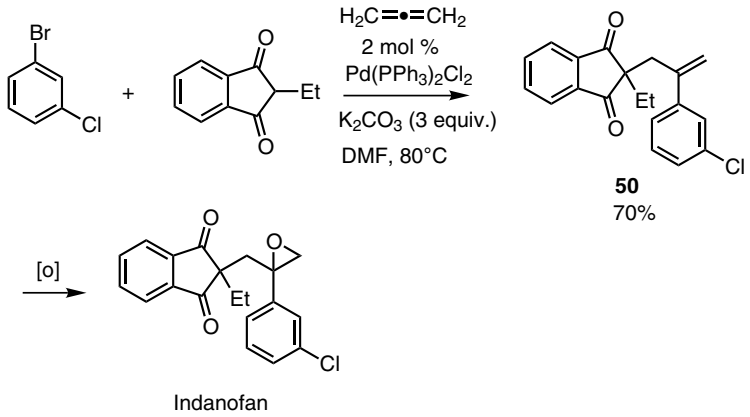


Scheme 8.24

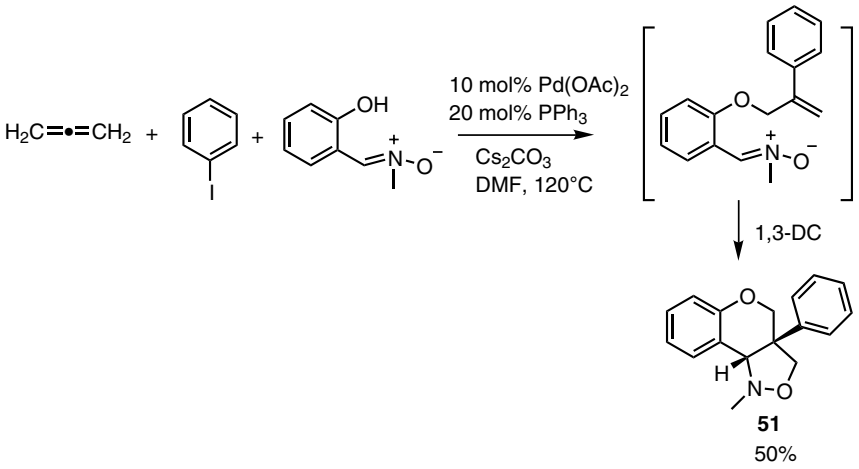
and bimetallic reagents such as bis(pinacolato)diboron, hexamethyldisilane, and hexabutylditin to form the corresponding 2-acylallylmetal reagents (Scheme 8.24). Related acylation of allenes using acyltetracarbonylcobalt complexes and subsequent intermolecular nucleophilic attack of the resulting π-allyl complexes by alkylnitronates had been developed previously by Hegedus [66].

This palladium-catalyzed three-component coupling reaction was recently applied to the synthesis of the key intermediate **50** of indafonan, a novel herbicide (Scheme 8.25). However, in this reaction, allene cannot be introduced to the vessel at the beginning of the reaction since a competitive reaction occurs. Therefore, the third component was bubbled into the mixture of the two other components in the presence of the palladium catalyst [67].

Quite recently, Grigg and co-workers have based several of their ingenious multicomponent reactions on the combination of the above-mentioned palladium-catalyzed coupling reactions of allenes with a subsequent reaction in a one-pot operation. For example, the catalytic π-allylpalladium species generated from the carbopalladation of the allene with iodobenzene was captured by a phenolic nucle-



Scheme 8.25

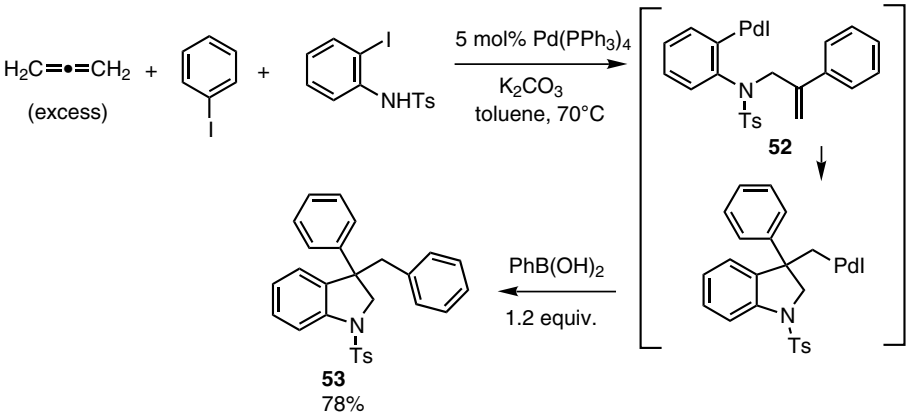


Scheme 8.26

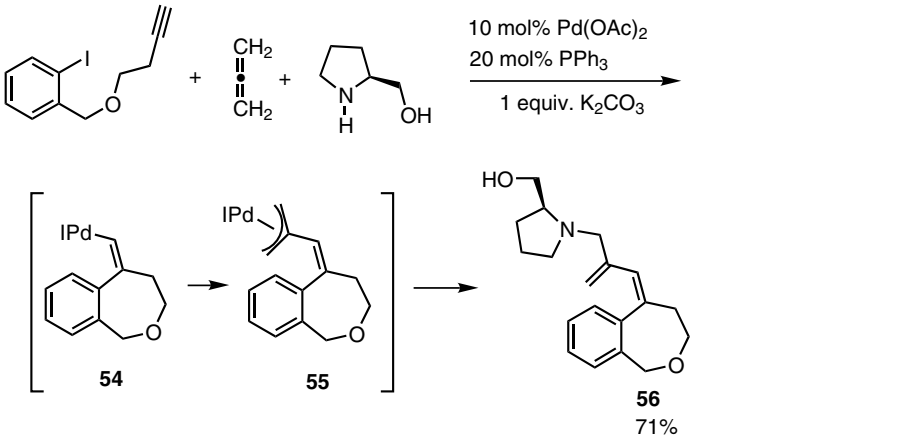
ophile bearing a nitrone moiety. This is followed by a 1,3-dipolar cycloaddition on the newly formed alkene to form the fused isoxazolidine **51** (Scheme 8.26) [68].

The same group developed an interesting intermolecular palladium-catalyzed allenation of aryliodide with *N*-tosyl *o*-iodoanilines with nucleophiles in combination with two palladium-coupling reactions [69]. In this reaction, the *N*-allyl(2-iodopalladium)aniline intermediate **52** underwent an intramolecular Heck reaction followed by a cross-coupling reaction with phenyl boronic acid to give the 3,3-disubstituted indoline **53** in 78% yield (Scheme 8.27).

A similar palladium-catalyzed process involving an intramolecular Heck-type reaction in the first step was developed by Grigg and co-workers [70]. The resulting seven-membered ring vinylpalladium(II) intermediate **54** reacts with the allene to



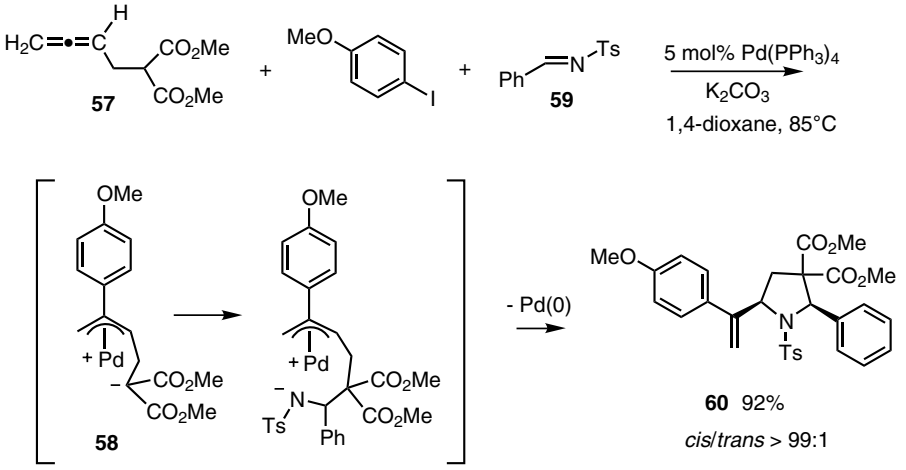
Scheme 8.27



Scheme 8.28

form the π-allylpalladium intermediate **55** which is trapped with (*S*)-(+)-2-prolinol to afford heterocycle **56** in 71% yield (Scheme 8.28). Additional examples on the use of a palladium-catalyzed three-component reaction in combination with other reactions, developed by the same group, can be found in several reviews [71].

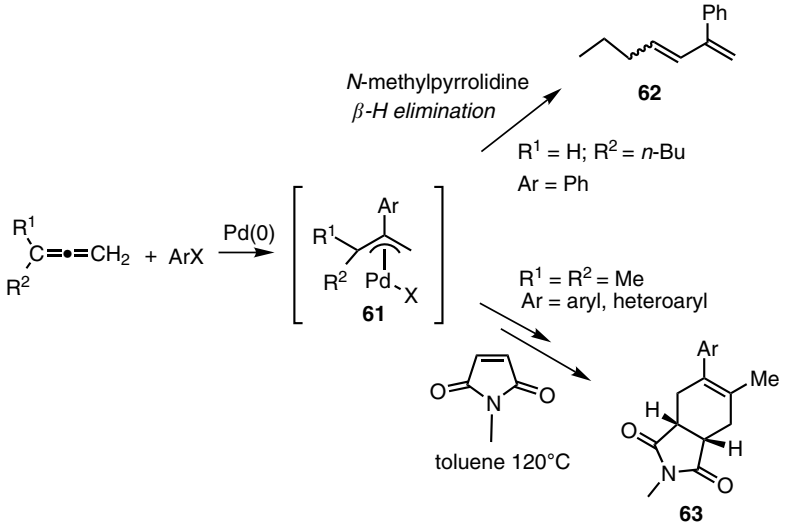
Ma and co-workers have reported the selective synthesis of pyrrolidine derivatives through a three-component reaction based on a conceptually related strategy (Scheme 8.29) [72]. Beginning with the catalytic intermolecular carbopalladation of γ-allenic malonate **57** in the presence of a base, they succeeded in intercepting the internal carbonucleophile **58** with an imine such as the *N*-benzylidene *p*-toluenesulfonamide **59**. The attack of the newly formed heteronucleophile on the π-allyl palladium intermediate affords the functionalized pyrrolidine **60** with high



Scheme 8.29

yield, and excellent regio- and stereoselectivity. In a similar way, several polysubstituted cis-pyrrolidine derivatives were obtained by varying the nature of the organohalides as well as that of the imine.

In their pioneering work on the catalytic carbopalladation reaction of 1,2-heptadiene with phenyl iodide in the presence of a suitable base, Shimizu and Tsuji observed the formation of the corresponding substituted 1,3-dienes **62** *via* a β-hydride elimination from the π-allyl intermediate **61** [61]. Based on these observations, a three-component Heck-Diels–Alder cascade process has been developed by Grigg and co-workers [73]. A wide variety of aryl and heteroaryl iodides were used for the intermolecular reaction with dimethylallene to afford the corresponding 1,3-dienes. These subsequently react *in situ* with *N*-methylmaleimide to give the bicyclic adducts **63** (Scheme 8.30).

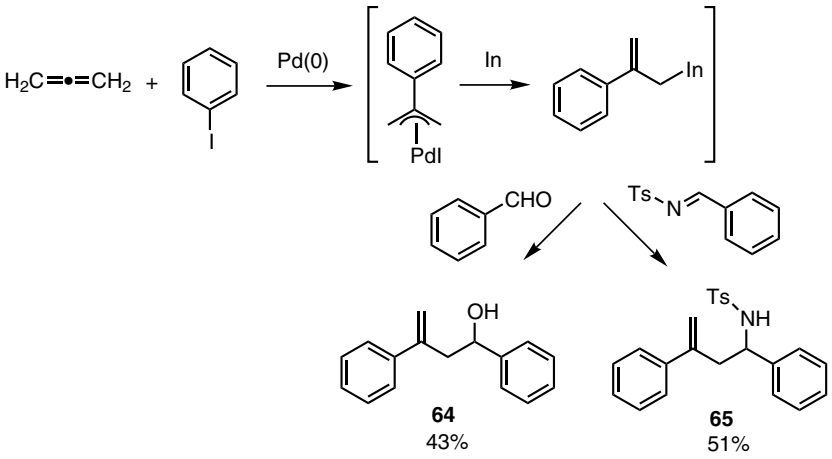


Scheme 8.30

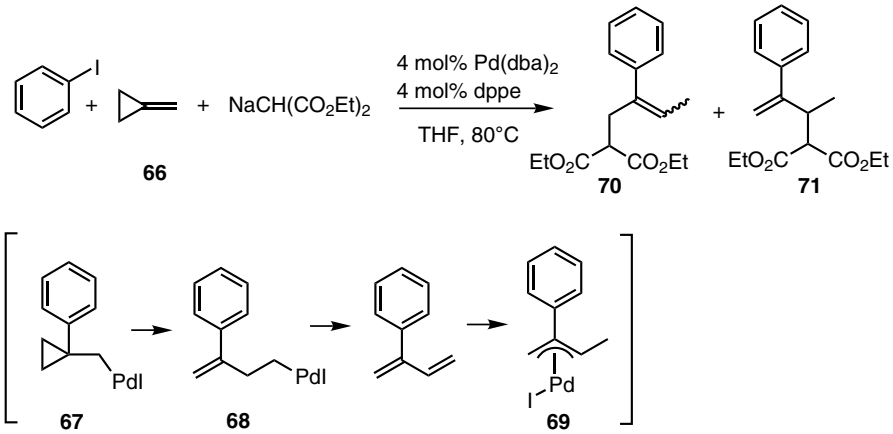
A three-component reaction based on the "umpolung" of π-allylpalladium (II) complexes indium metal was reported by Grigg and co-workers (Scheme 8.31) [74]. In this reaction, the electrophilic nature of the π-allyl palladium species generated from aryl halides and allenes is reversed by transmetallation with indium metal. The resultant nucleophilic allylindium reagent subsequently adds to the third component – aldehyde [75] or imine [76] – to give the corresponding homoallylic alcohol **64** or amine **65** respectively.

8.3.1.4 Carbopalladation of Methylenecyclopropane and Bicyclopropylidene

The palladium-catalyzed Heck-type reaction of methylenecyclopropane **66** in the presence of soft nucleophiles such as sodium diethylmalonate gives a mixture of isomeric alkenes **70** and **71** (Scheme 8.32) [77]. In this process, there is first a carbopalladation of the double bond of **66** giving the cyclopropylcarbinylpalladium in-



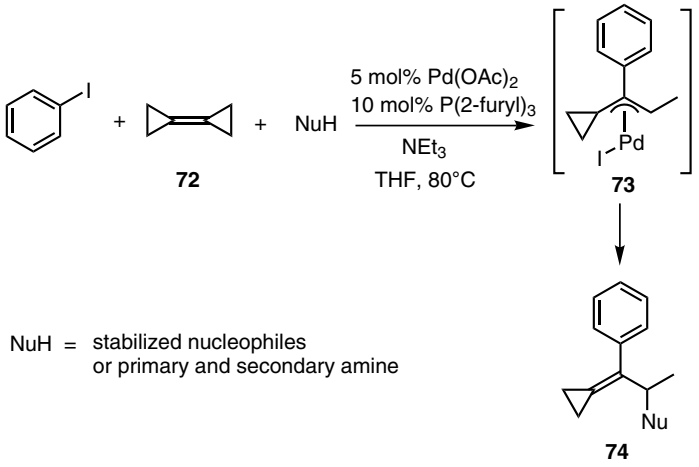
Scheme 8.31



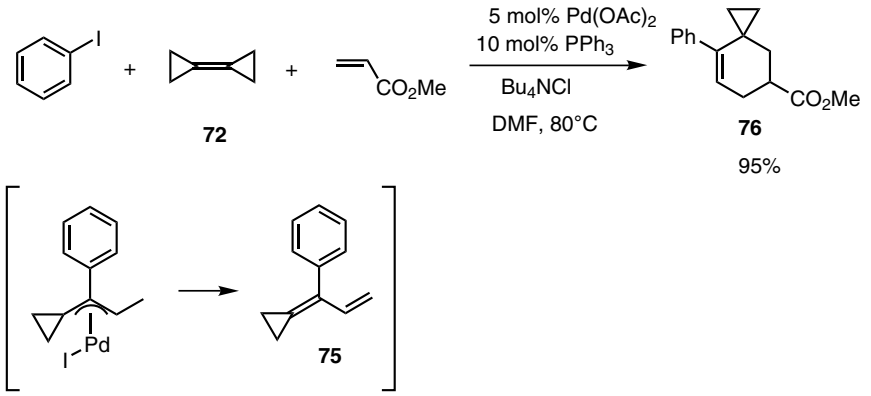
Scheme 8.32

termediate **67**. The selective ring opening of the cyclopropyl ring in **67** affords the homoallylpalladium intermediate **68** which is converted to the π-allylpalladium intermediate **69** after β-hydride elimination followed by readdition of palladium hydride. This is followed by a preferential attack of the carbonucleophile on the less substituted carbon of the allylic system giving predominantly the linear product **70** along with the branched product **71**.

De Meijere and co-workers have extended the scope of this process by applying this palladium-mediated multicomponent reaction to the bicyclopropylidene **72** as the alkene partner (Scheme 8.33). In this case, the intermolecular trapping of π-allyl palladium intermediate **73** with a soft carbonucleophile or with primary or secondary amines affords only products **74** having a methylenecyclopropane end group [78].



Scheme 8.33

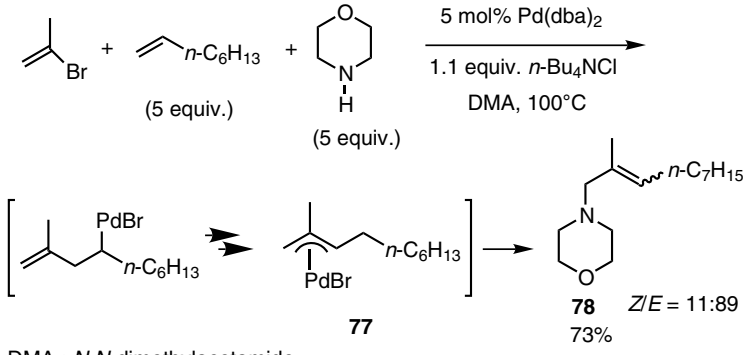


Scheme 8.34

When the carbopalladation of the bicyclopropylidene is performed in the presence of methyl acrylate, the reaction takes a different course (Scheme 8.34) [79]. The 1,3-diene intermediate **75** reacts *in situ* with the dienophile to give the spiro[2.5]octane derivative **76**. An extension of this cascade Heck-Diels–Alder reaction involving 1,3-dicyclopropyl-1,2-propadiene as the alkene partner, an alkenyl or aryl halide and a dienophile has been reported [80].

8.3.1.5 Palladium-mediated Reaction of Vinylic Halides with Alkenes

The Heck-type reaction of vinylic bromides with alkenes in the presence of nucleophiles such as stabilized enolates or secondary amines (morpholine or piperidine) are efficient three-component reactions that were developed in the late 1970s



DMA : *N,N*-dimethylacetamide

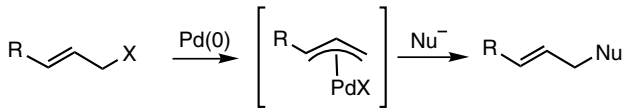
Scheme 8.35

by Heck and co-workers [81]. The reaction proceeds *via* the π-allylic complex formed after rearrangement of the initially formed σ-homoallylpalladium intermediate, as mentioned above. These three-component reactions were further revisited by Larock [82] and Weinreb [83]. As shown in Scheme 8.35, the reaction of 2-bromopropene with excess of hexene and morpholine gave the corresponding allylic amine **78** as a mixture of stereoisomers which results from an exclusive addition of the vinylic group to the terminal carbon of the alkene followed by a regioselective attack of the nitrogen nucleophile at the less substituted end of the π-allyl palladium intermediate **77**.

8.3.2
π-Allyl Palladium Species from Allylic Compounds

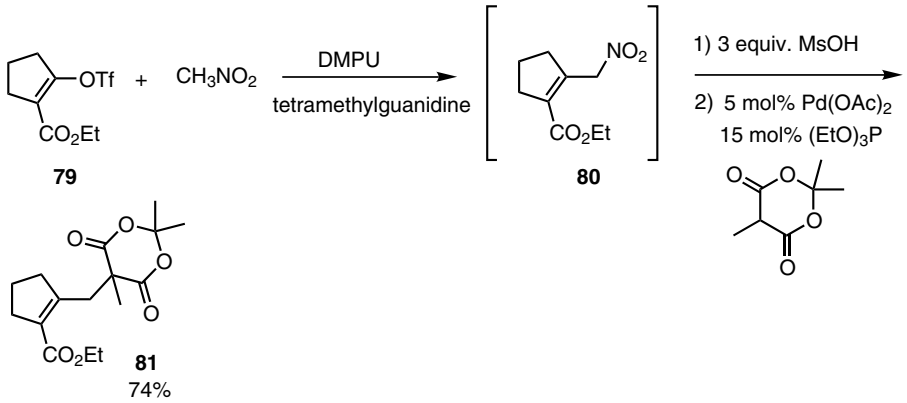
Oxidative addition of allylic substrates to palladium(0) is also a well-established reaction for generating π-allyl palladium species (Scheme 8.36). A wide range of allylic substrates have been used as precursors of these intermediates, and nucleophilic attack generally occurs at the less hindered terminus of the π-allylpalladium species [84].

An interesting one-pot sequential three-component reaction involving the nucle-



X = OAc, OCO_2R', OCONHR', OAr, OH, $OP(O)(OR')_2$,
NO_2, NR'_2,
SO_2R',
Cl...

Scheme 8.36



Scheme 8.37

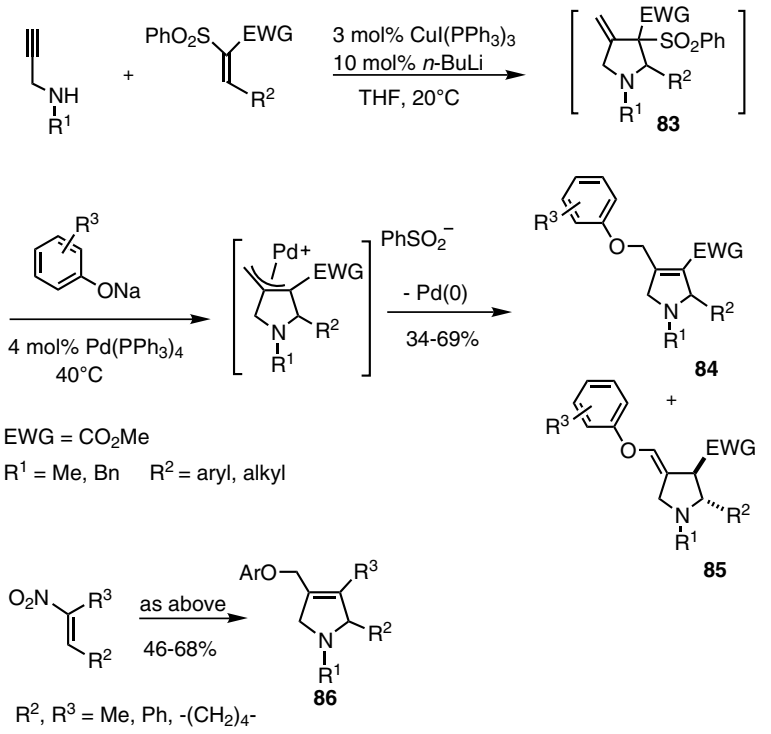
ophilic displacement of an allylic compound *via* a π-allylpalladium complex was developed by Chung and co-workers [85]. As shown in Scheme 8.37, the conjugate addition–elimination of nitromethane to the β-trifloxy acrylate **79** gave the allyl nitro product **80**. The crude mixture was then taken into the palladium-catalyzed allylation step after neutralization to give the three-component assembling product **81**.

In analogy to the process discussed above for allylic substrates, a one-pot procedure for the preparation of substituted five-membered nitrogen heterocycles, based on a sequence of two metal-catalyzed reactions has been developed [86]. The first step involves a Cu-catalyzed cycloaddition between propargyl amines and ethyl 2-aryl- or alkylsulfonyl cinnamates which gives access to heterocyclic allyl sulfones **83**. Subsequent *in situ* palladium-catalyzed sulfinate displacement by various phenolic derivatives afforded 3(4)-phenoxy-methyl pyrrolines **84** and their isomeric pyrrolidines **85**. This sequence exploits the dual reactivity of the sulfone moiety which can be used as a stabilizing carbanion in the cyclization step and as a leaving group in the nucleophilic displacement. The scope of this methodology has been extended to nitroolefins so as to permit the synthesis of the highly substituted pyrrolines **86** (Scheme 8.38).

8.4
Cross-coupling Reactions of Terminal Alkynes with Organic Halides

8.4.1
Reactions Based on a Pd/Cu-catalyzed Coupling–Isomerization Process

Since the late 1990s, new multicomponent reactions based on a palladium/copper-catalyzed coupling-isomerization sequence of 1-aryl prop-2-yn-1-ols and electron-deficient sp^2-hybridized halogen compounds leading to the correspond-

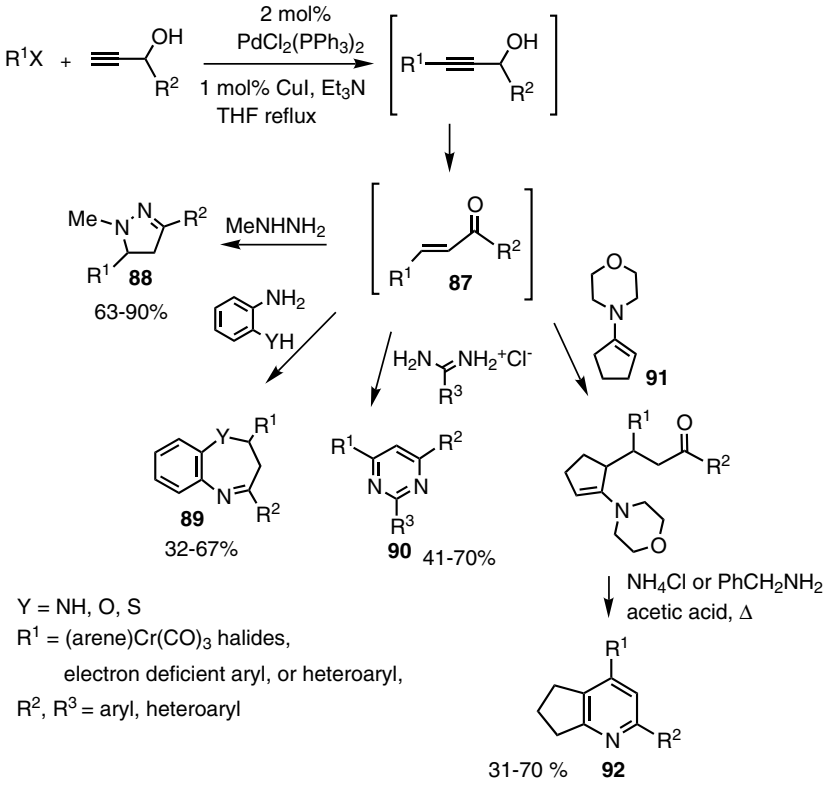


Scheme 8.38

ing enones have been developed by Müller and co-workers (Scheme 8.39). To do this, the newly formed enones were *in situ* engaged in several Michael addition–cyclocondensation sequences. Thus, various electron-poor (hetero)aryl halide, terminal propargyl alcohols were heated in THF in the presence of Et_3N and catalytic amounts of $[PdCl_2(PPh_3)_2]$ and CuI. The resulting chalcones **87** were then alternatively treated *in situ* with *N*-methylhydrazine [87], 2-amino- (or hydroxy-, or mercapto-) anilines [88] or amidinium salts [89a] to afford pyrazolines **88**, 1,5-benzoheteroazepines **89**, or pyrimidines **90** respectively upon heating. A four-component one-pot access to tetrahydroquinoline **92** based on the same concept was also reported, the coupling–isomerization process being here combined with the conjugate addition of cyclic enamine **91**. Finally the addition of ammonium chloride or benzyl amine and acetic acid to the reaction mixture afforded tetrahydroquinoline **92** in moderate to good yields [90].

8.4.2
Reactions Based on the *In Situ* Activation of Alkynes by a Sonogashira Coupling Reaction

Similar three-component reactions based on *in situ* activation of alkynes by a Sonogashira coupling reaction have also been developed by Müller and co-workers



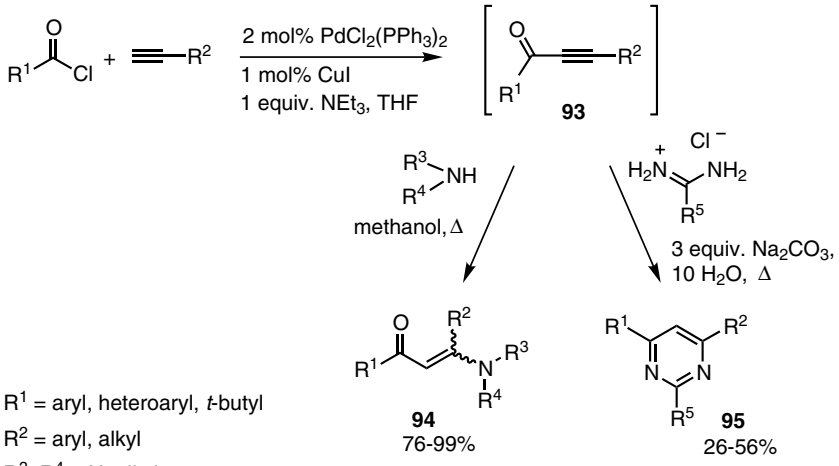
Scheme 8.39

[89b]. Thus, the coupling of acid chlorides with terminal alkynes under Sonogashira conditions gave alkynone **93**. This was followed by an *in situ* addition of amines or amidinium salts that affords the corresponding enaminones **94** or substituted pyrimidines **95** (Scheme 8.40).

Early studies from Torii reported a three-component reaction based, as mentioned above, on the conjugate addition of dialkylamines to alkynones [91]. Here the highly reactive Michael acceptor **96** is generated *in situ* from a carbonylative coupling between 2-aminophenylacetylenes and aryliodides. Addition of dialkylamines to **96** produces enaminoketones **97**, which then undergo a cyclocondensation between the carbonyl group and the internal arylamine, affording substituted quinolines **98** (Scheme 8.41).

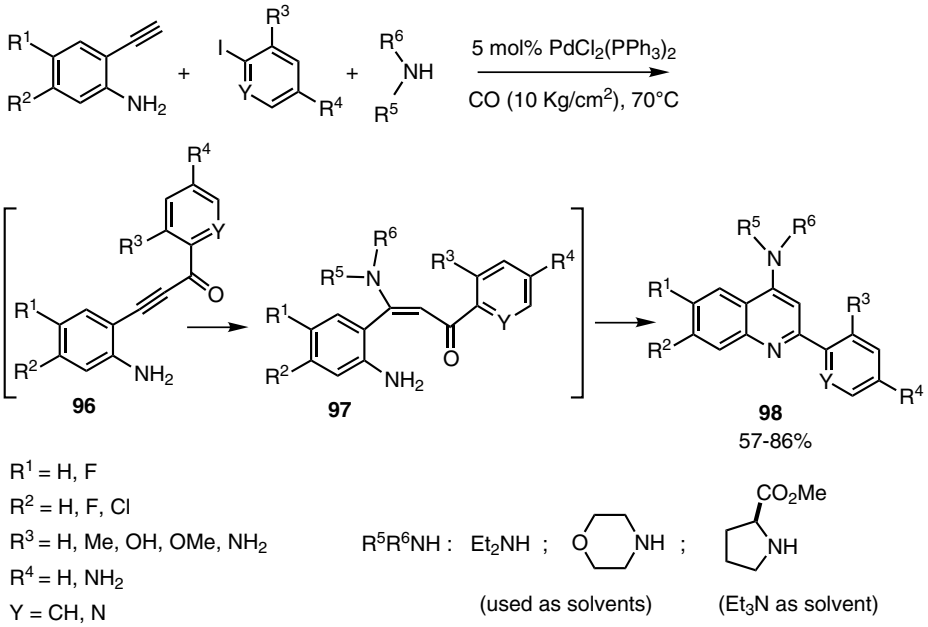
8.5
Cyclofunctionalization of Alkynes and Alkenes Bearing Pendant Nucleophiles

The cyclization of unsaturated substrates bearing a carbo- or heteronucleophile promoted by an organopalladium complex has recently emerged as a powerful



R^1 = aryl, heteroaryl, *t*-butyl
R^2 = aryl, alkyl
R^3, R^4 = H, alkyl
R^5 = CH_3, SMe, NO_2, NH_2, heteroaryl

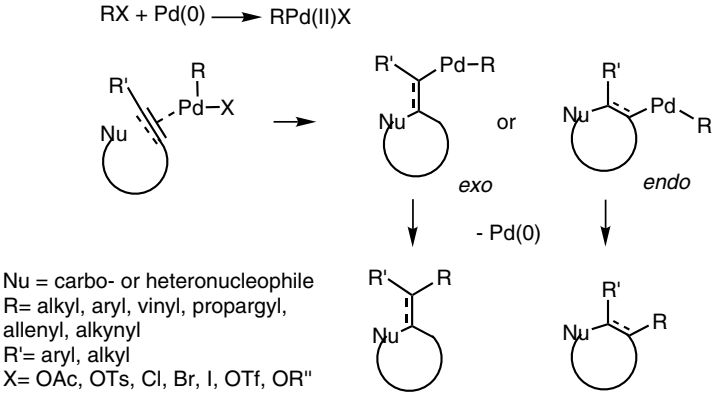
Scheme 8.40



R^1 = H, F
R^2 = H, F, Cl
R^3 = H, Me, OH, OMe, NH_2
R^4 = H, NH_2
Y = CH, N

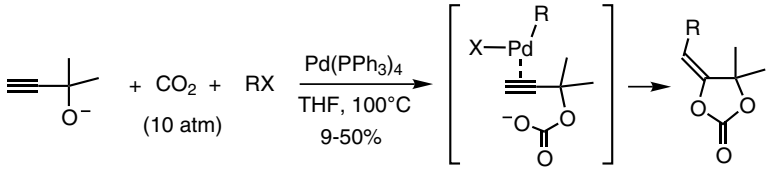
Scheme 8.41

method for the synthesis of complex molecules in one reaction [92]. This cyclization, which involves an attack by the nucleophile onto an unsaturation activated by an organopalladium(II) species, provides a new route to functionalized five- or six-membered rings with the advantage that it proceeds in a completely stereoselective trans manner (Scheme 8.42).



Nu = carbo- or heteronucleophile
R= alkyl, aryl, vinyl, propargyl, allenyl, alkynyl
R'= aryl, alkyl
X= OAc, OTs, Cl, Br, I, OTf, OR''

Scheme 8.42



RX = aryl iodide (or bromide), vinyl bromide allyl acetate (or chloride)

99 **100**

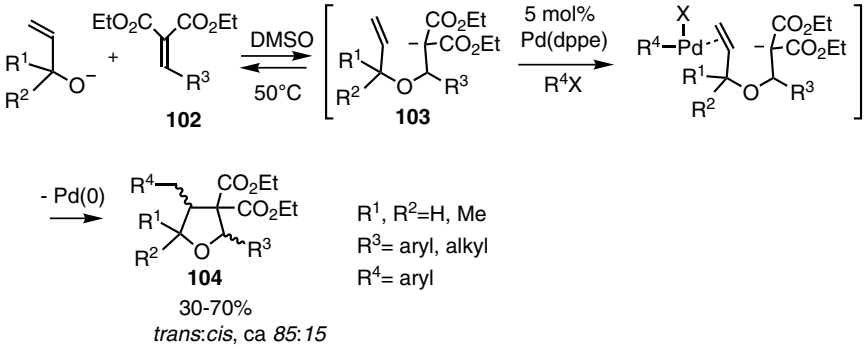
Scheme 8.43

The wide range of available organopalladium reagents and the simplicity of the procedures make this process highly attractive for the design of multicomponent reactions. To do this, the strategy has consisted of finding ways of generating *in situ* alkynes or alkenes possessing a carbo- or heteronucleophile in proximity to the unsaturation. The first report of such a reaction was by Inoue and co-workers in 1990 to access cyclic vinylidene carbonates **100** (Scheme 8.43) [93]. The reaction involves a palladium-catalyzed cyclization of a monoalkylcarbonate **99** generated *in situ* from the reaction of a propargyl alkoxide with carbon dioxide (10 atm). However, the process proved rather limited as the organic halide was found to be the sole flexible reactant.

8.5.1 Carbonucleophiles

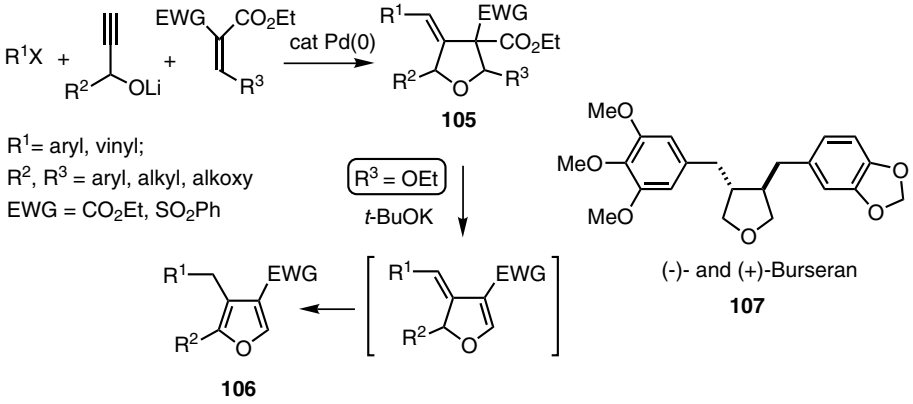
The synthesis of highly substituted tetrahydrofurans by means of a multicomponent reaction based on this palladium-mediated cyclization process was reported by Balme and co-workers [94]. In this reaction, formation of enolate **103** by the initial 1,4-addition of an allylic alcohol to the conjugate acceptor **102** is followed by a

palladium-mediated cyclization reaction involving the unsaturated halide. The use of slow addition techniques for the introduction of the allylic alkoxide component proved necessary in order to avoid side reactions. This method was successfully applied to the simple allylic alcohol leading to the substituted tetrahydrofurans **104** in a range of 60–70% yields, whereas secondary or tertiary allylic alcohols gave lower yields (Scheme 8.44).



Scheme 8.44

Interestingly, this strategy was applied to the more reactive propargyl alkoxides allowing for the simultaneously introduction of the three partners at the start of the reaction. In fact, in this case, no side reactions occurred [95]. This process is remarkably versatile, giving good yields of stereodefined 3-arylidene (and alkenylidene) tetrahydrofurans **105** with a variety of propargyl alcohols (primary, secondary, and tertiary) and unsaturated halides (aryl iodides, vinyl bromides, and triflates) (Scheme 8.45).



Scheme 8.45

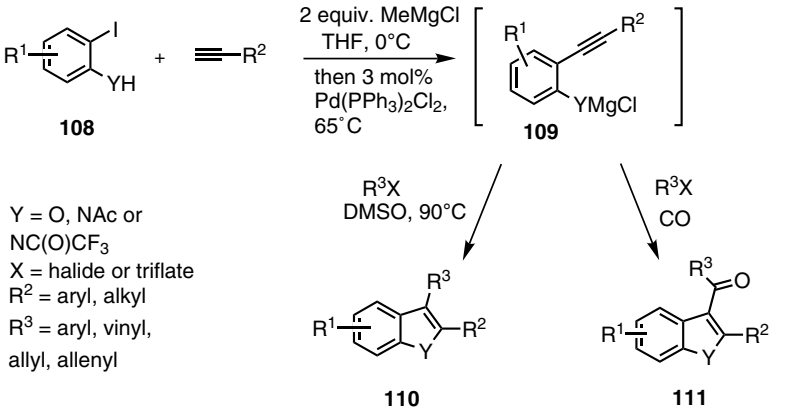
An interesting extension of this methodology to the one-pot preparation of furan derivatives **106** has been achieved using the commercially available diethyl ethoxymethylenemalonate as a Michael acceptor. In this case, the resulting tetrahydrofuran was converted to the expected furan **106** by *in situ* addition of a slight excess of potassium *t*-butoxide [96]. The entire process involved a sequence of a conjugate addition, a palladium-catalyzed cyclization–coupling reaction, an alkoxide-induced eliminative decarboxylation and, finally, a double bond isomerization. The potential utility of this process was illustrated by the formal synthesis of the lignan antitumor Burseran **107** (Scheme 8.45). An interesting extension of this strategy to the one-pot synthesis of various substituted pyrrolidines has been reported by the same group [97].

In a similar manner, Lu and Liu have more recently utilized the hetero-Michael addition of lithium propargylic alkoxides to alkylidene malonates in a synthesis of stereodefined allylidene tetrahydrofurans, based on the use of allylic chloride as coupling partner [98]. In this case, the cyclization reaction is initiated by a catalytic amount of palladium salt [$Pd(OAc)_2$] rather than by an organopalladium species as mentioned above.

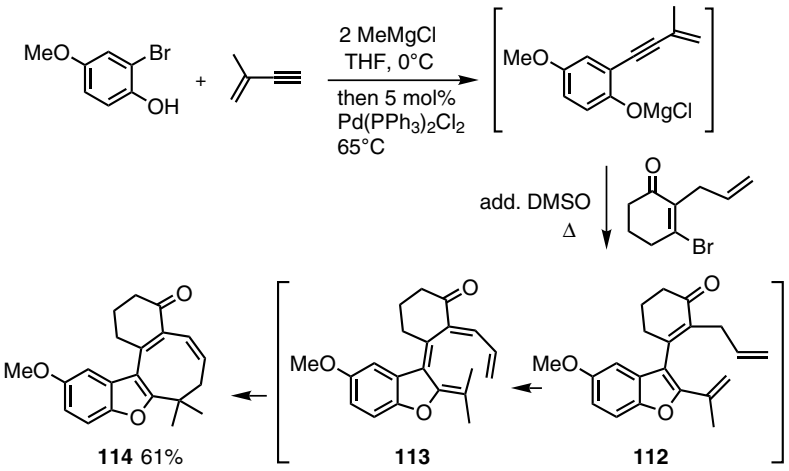
8.5.2 Heteronucleophiles

These palladium-mediated cyclization processes have also been used for the one-pot synthesis of various bicyclic heterocyclic systems starting from ortho-functionalized aryl or heteroaryl iodides, terminal alkynes, and organic halides. These new multicomponent approaches are based on the sequential one-pot combination of a Sonogashira coupling reaction with the palladium-mediated cyclization–coupling process, the organic halide entering the sequence once the first reaction has gone to completion, since competitive coupling reaction may occur. In this context, Flynn reported a practical procedure for the preparation of benzofurans from iodophenols, terminal alkynes, and organic halides (or triflates) [99, 100]. This process involved initial deprotonation of a mixture of **108** and terminal alkyne with two equivalents of methylmagnesium chloride to give the corresponding magnesium phenolate and acetylide. This was followed by a Sonogashira coupling reaction giving *o*-alkynylphenoxide intermediates **109**. *In situ* addition of a DMSO solution of the unsaturated halide afforded the corresponding benzo[*b*]-furans **110** in good yields. This methodology has also been applied to the synthesis of indole derivatives. In addition, this sequential three-component reaction may be performed under an atmosphere of carbon monoxide leading to **111** and this last sequence was applied to the one-step synthesis of some potent analogues of the anticancer agent combretastatin A-4 (Scheme 8.46) [101].

This multicomponent reaction was used by the same group to prepare a ring-expanded analogue **114** of the marine sesquiterpenoid frondosin B through a remarkable reaction cascade [102]. An unprecedented tandem 1,7-hydrogen shift, 8 π-electrocyclization converting **112** to **113** was proposed to explain the formation of this ring-expanded species (Scheme 8.47).

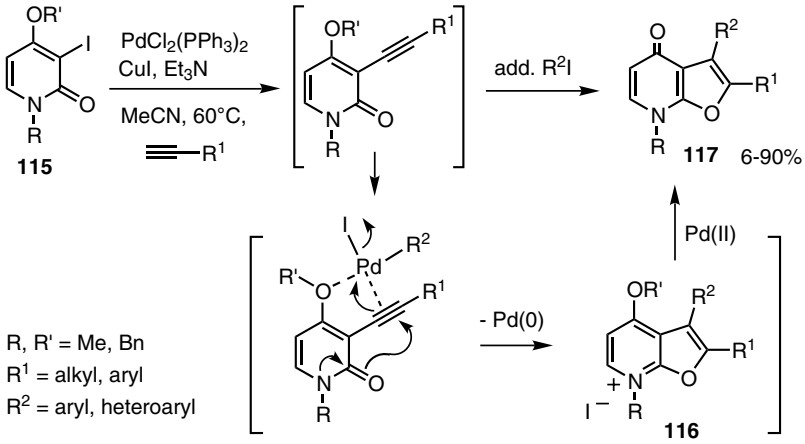


Scheme 8.46



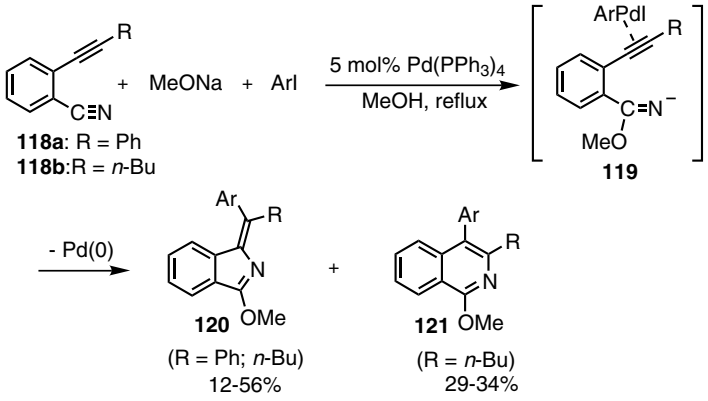
Scheme 8.47

Another illustration of this strategy is found in the three-component reaction that gives direct access to diversely substituted furo[2,3-*b*]pyridones (Scheme 8.48) [103]. In this process, a Sonogashira coupling between 3-iodo-pyridones **115** and terminal alkynes using palladium and copper was followed by the addition of aryl halides. The heteroannulative coupling produced furopyridinium salts **116** which collapse to form the desired pyridones **117** through subsequent cleavage of the oxygen protecting group, apparently by a palladium(II) species. Remarkably, in this three-component reaction, a single palladium catalyst intervenes in three different transformations acting alternatively as an organometallic reagent and as a Lewis acid.



Scheme 8.48

Wu and co-workers developed a synthesis of benzannulated nitrogen heterocycles **120** and **121** based on the addition of sodium methoxide to 2-alkynylbenzonitriles **118** in methanol, followed by the $Pd(PPh_3)_4$-catalyzed heteroannulation of ketimine intermediate **119** with aryl iodides [104]. The 5-exo versus 6-endo mode of cyclization leading to isoindoles **120** or isoquinolines **121**, respectively, proved to be dependent on the nature of the substituent on the terminal alkyne carbon. 2-(2-Phenylethynyl) benzonitrile **118a** underwent exclusive 5-exo cyclization whereas 2-(1-hexynyl)benzonitrile **118b** led to mixtures of isomers with a marked preference for the 6-endo mode of cyclization. This endo/exo balance was attributed to steric interactions between the entering group and the substituent on the terminal alkyne carbon (Scheme 8.49).

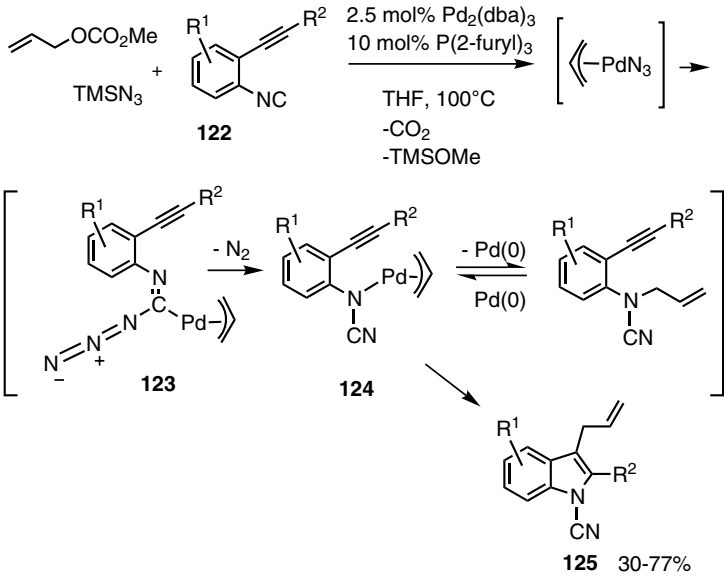


Scheme 8.49

8.6
Transition-metal-catalyzed Reactions Based on the Reactivity of Isonitriles

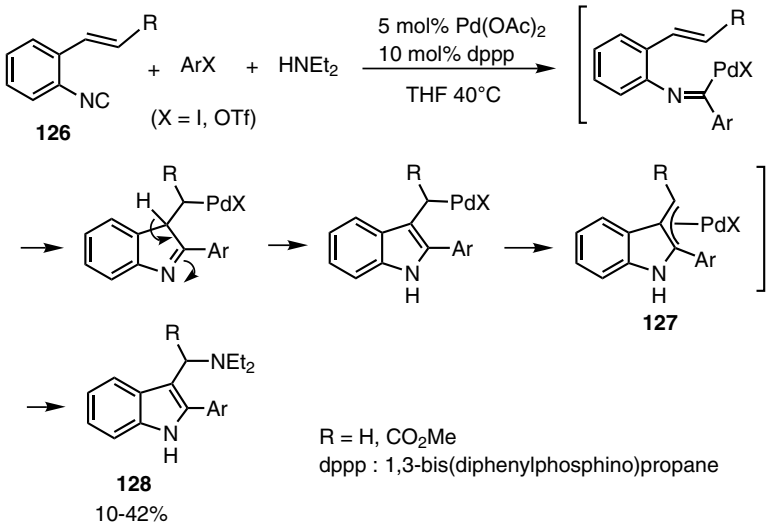
8.6.1
Three-component Synthesis of Indoles

Palladium-mediated cyclization based on the reactivity of *o*-alkynyl or alkenylphenyl isonitriles have been developed [105]. On the basis of their earlier studies on the three-component synthesis of allyl aryl cyanamides [106], Yamamoto and co-workers reported a palladium-catalyzed three-component coupling reaction of 2-alkynylisocyanobenzenes **122** with allyl methyl carbonate and trimethylsilylazide leading to *N*-cyanoindoles **125** [107]. One of the key steps of the proposed mechanism is the formation of π-allylpalladium carbodiimide **123** and its isomerization to π-allylpalladium cyanamide complex **124** (Scheme 8.50).



Scheme 8.50

Takahashi and co-workers reported a three-component synthesis of indoles starting from *o*-alkenylphenyl isonitriles, aryl iodides, and secondary amines [108]. The reaction proceeds in the presence of catalytic amounts of palladium acetate and of chelating ligands such as dppp. As shown in Scheme 8.51, the coupling reaction of *o*-alkenylphenyl isocyanides **126** with aryl iodides follows an unusual pathway. Thus, oxidative addition of the aryl iodide to Pd(0) and successive insertions of the isocyano and alkene groups is followed by 1,3-migration of hydrogen to form π-allylpalladium complex **127**. Intermolecular trapping of the latter with diethyl-



Scheme 8.51

amine allows production of 2,3-disubstituted indoles **128** in poor to moderate yields.

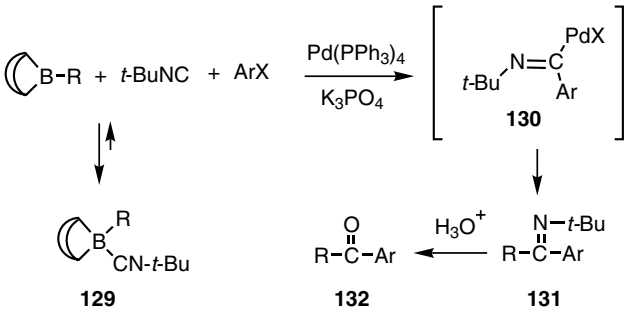
8.6.2
Iminocarbonylative Cross-coupling Reactions

Early findings by Suzuki and co-workers [109] showed that the palladium-catalyzed iminocarbonylative cross-coupling reaction between 9-alkyl-9-BBN derivatives, *t*-butylisocyanide, and arylhalides gives access to alkyl aryl ketones **132** after hydrolysis of the corresponding ketimine intermediates **131**. Presumably, the concentration of free isocyanide is kept to a minimum by its coordination with the borane. Formation of an iminoacylpalladium(II) halide **130** by insertion of isocyanide to the newly formed arylpalladium complex followed by a transmetallation step afford the ketimine intermediates **131** (Scheme 8.52).

Based on this concept, Whitby and co-workers [110] reported an interesting palladium-catalyzed three-component synthesis of aromatic and heteroaromatic amidines **133** starting from unsaturated halides, amines, and *t*-butylisocyanide (Scheme 8.53). The catalytic cycle for this iminocarbonylative coupling reaction is analogous to the reactions incorporating carbon monoxide–isoelectronic with isocyanides–as the third partner [111].

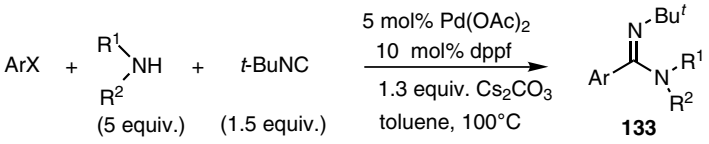
8.6.3
Titanium-catalyzed Three-component Synthesis of α,β-Unsaturated β-Iminoamines

α,β-Unsaturated β-iminoamines have been synthesized through a titanium-catalyzed coupling of an amine, an alkyne, and an isonitrile with a titanium cata-



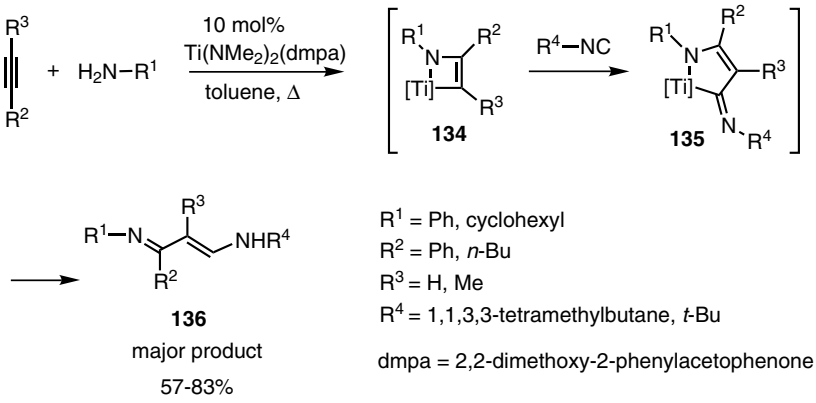
Ar = aryl, heteroaryl
R = alkyl

Scheme 8.52



Scheme 8.53

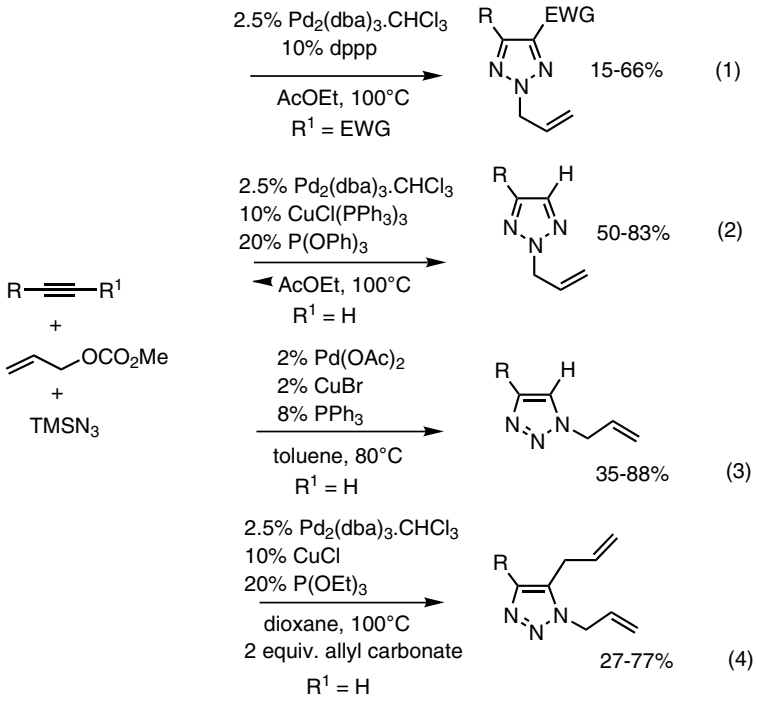
lyst [112]. The proposed mechanism involves the formation of metalloazacyclobutene **134** followed by isonitrile insertion into the Ti–C bond to generate iminoacyl complex **135**. Protonolysis of this complex by the amine generates the three-component coupling product **136**. In each case, smaller quantities of by-products are isolated resulting from two-component reactions (Scheme 8.54).



R^1 = Ph, cyclohexyl
R^2 = Ph, *n*-Bu
R^3 = H, Me
R^4 = 1,1,3,3-tetramethylbutane, *t*-Bu

dmpa = 2,2-dimethoxy-2-phenylacetophenone

Scheme 8.54



Scheme 8.55

8.7
Pd/Cu-catalyzed Synthesis of Triazoles

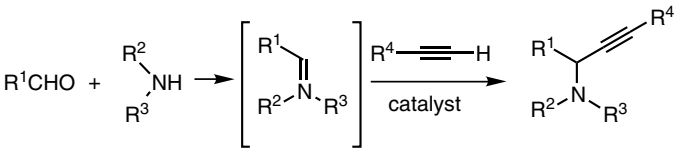
In a series of papers, Yamamoto has reported original syntheses of diversely substituted allyl triazoles based on the coupling of alkynes, allylic acetate, and $TMSN_3$. As illustrated in Scheme 8.55, the catalyst system had a dramatic effect on the course of the reactions. When palladium was used as sole catalyst, the reaction works only on alkynes activated by an electron-withdrawing group and leads to 2-allyltriazoles [Eq. (1)] [113]. However, unactivated alkynes have been found to participate in this reaction upon addition of a copper complex as cocatalyst [114] [Eq. (2)]. A selective synthesis of 1-allyltriazole was also accomplished by modifying the catalyst system [115] [Eq. (3)]. A four-component coupling reaction was developed based on the use of two equivalents of allyl carbonate and giving access to fully substituted triazoles [(Eq. 4)] [116]. A useful access to tetrazoles has also been realized by using a nitrile derivative in place of the alkyne partner [117].

8.8
Reactions Involving Imines as Intermediates

8.8.1
Grignard-type Addition of Acetylenic Compounds to Imines

8.8.1.1 Synthesis of Propargyl Amines

Addition of alkynes to imines to generate propargyl amines is an important reaction, allowing the synthesis of useful building blocks for the preparation of complex amino derivatives and bioactive compounds. Classical addition reactions require the use of stoichiometric amounts of organometallic reagents such as organolithium or Grignard reagents. Moreover, activation of the imine moiety by a Lewis acid is sometimes necessary, which in terms of atom economy and ecological considerations is not satisfactory [118]. Furthermore, isolation of the synthesized imines is a problem inherent to such a chemistry. The development of multicomponent metal-catalyzed processes was a major advance in this area, limiting metallic wastes and avoiding the isolation of imines. Several groups have developed methodologies based on the *in situ* generation of an imine from an aldehyde and an amine, and subsequent addition of alkynes (Scheme 8.56). The mechanism involves the formation of an alkynylmetal as intermediate which adds to the imine moiety.



Scheme 8.56

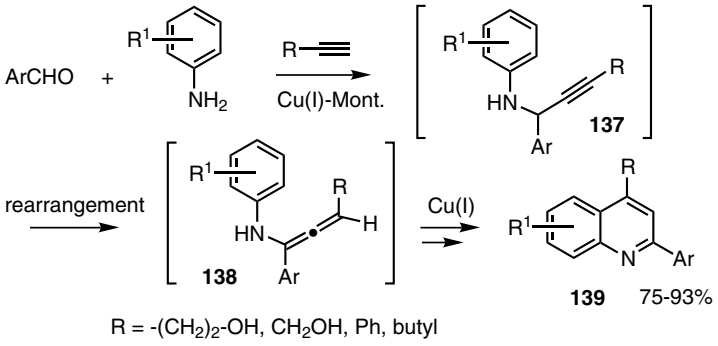
Diverse metal catalysts can be used as demonstrated by Li and co-workers who have developed gold- [119], silver- [120] and ruthenium/copper-catalyzed [121] routes to propargyl amines (Table 8.1). There has also been one report that an iridium derivative can be used in such a reaction [122]. Knochel and co-workers have published a very useful copper-catalyzed enantioselective synthesis of alkynyl amines using (*R*)-quinap as ligand. High yields and good enantioselectivities (up to 96% *ee*) have been achieved [123]. Paraformaldehyde has also been used for the synthesis of unsubstituted propargyl amines [124]. Solid-phase syntheses have also been performed using such methodologies [125].

8.8.1.2 Synthesis of Quinolines and Isoquinolines

Addition of alkynes to imines generated *in situ* can lead to quinolines when the reaction is conducted in the presence of copper chloride [126] or montmorillonite clay doped with copper bromide [127]. In the latter case, the reaction was performed under solvent-free conditions and was microwave assisted (Scheme 8.57).

Tab. 8.1. Addition of alkynes to imine generated *in situ*.

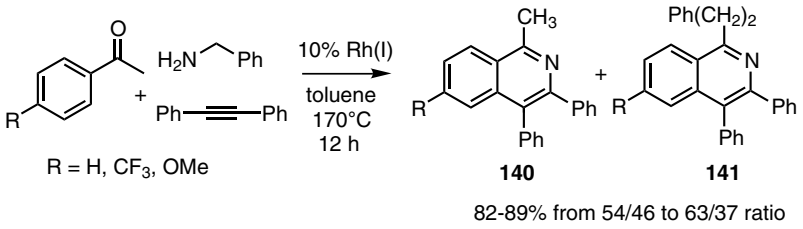
R^1CHO	R^2R^3NH	R^4—≡—H	Catalyst	Yield [%]	References
R^1 = aryl, alkyl	piperidine $R^2 = R^3$ = allyl, benzyl	R^4 = aryl, alkyl	$AuBr_3$	53–99	119
R^1 = aryl, alkyl	cyclic amine	R^4 = phenyl, naphthyl, silyl	AgI_2	47–99	120
R^1 = aryl, *t*-Bu	aryl amine	R^4 = phenyl	$RuCl_3$ CuBr	64–96	121
R^1 = aryl, alkyl, heteroaryl	$R^2 = R^3$ = allyl, benzyl	R^4 = aryl, alkyl, silyl	CuBr (*R*)-quinap	64–95 *ee* = 32–96	123
R^1 = *n*-propyl	R^2 = *n*-propyl, R^3 = H	R^4 = silyl	$Ir(COD)Cl_2$	–	122



Scheme 8.57

The proposed mechanism involves the initial rearrangement of alkynyl imine **137** into allenyl imine **138**. Subsequent coordination of copper(I) to the terminal bond of the allene triggers intramolecular attack of the aromatic ring, a process that finally leads to quinolines **139** *via* several intermediates.

Similarly, isoquinoline derivatives can be obtained by rhodium-catalyzed reaction of aromatic ketimines and alkynes [128] (Scheme 8.58). The authors suggested a



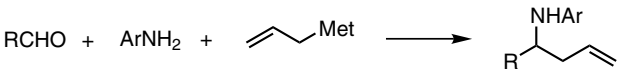
Scheme 8.58

first ortho-alkenylation of ketimine followed by an electrocyclic reaction leading to quinolines **140** and **141**.

8.8.2 Addition of Organometallic Reagents to Imines

8.8.2.1 Allylmetal Reagents

The stereoselective addition of allylmetal reagents to imines is one of the most important reactions in organic synthesis for carbon–carbon bond formation [118, 129] (Scheme 8.59).



Scheme 8.59

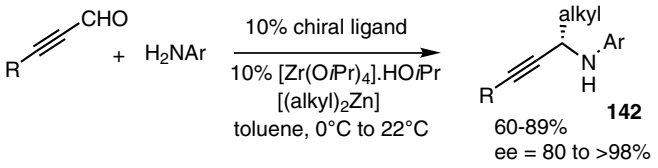
This useful reaction has been applied with success to multicomponent reactions using aldimines generated *in situ* and an allylmetal reagent (Table 8.2). First described by Kobayashi with allyltributylstannane and a Lewis acid such as $Zr(OTf)_4$ or $Hf(OTf)_4$ [130], this reaction was later reported to proceed in water as solvent in the presence of SDS (sodium dodecyl sulfate) as surfactant and $SnCl_2$ as catalyst [131]. The reaction was also developed using $Bi(OTf)_3$ as catalyst [132] or in ionic liquids [133]. Allylgermanes can efficiently replace allyltin reagents as demonstrated by Akiyama [134]. Allylzinc reagents in combination with lithium perchlorate have also been used in the synthesis of highly diastereomerically enriched secondary amines [135].

Tab. 8.2. Additions of allylmetal to imine generated *in situ*.

R^1CHO	R^2NH_2	*Allylmetal*	*Catalyst*	*Yield [%]*	*Reference*
R^1 = phenyl cyclohexyl	R^2 = aryl	allyltributyltin	$Zr(OTf)_4$ or $Hf(OTf)_4$	81–92	130
R^1 = aryl, heteroaryl, alkyl	R^2 = aryl	allyltributyltin	$SnCl_2 \cdot 2H_2O$	69–87	131
R^1 = aryl	R^2 = aryl	allyltributyltin	$Bi(OTf)_3$	60–90	132
R^1 = aryl, heteroaryl	R^2 = aryl	allyltributyltin	no catalyst ionic liquid	80–93	133
R^1 = aryl, *t*Bu	R^2 = aryl	allyltriethylgermane	$Sc(OTf)_3$	75–87	134a
R^1 = aryl, *t*Bu	R^2 = phenyl	allyltriethylgermane	$BF_3 \cdot Et_2O$	80–88	134b
R^1 = aryl	(*R*)-(+)-1-phenylethyl amine	allylzinc bromide	$LiClO_4$	76–78	135

8.8.2.2 Alkylmetal Reagents

Addition of organometallic reagents to imines is not limited to allylmetal derivatives. Hoveyda and Snapper have demonstrated that dialkylzinc reagents can add to imines in a one-pot procedure. Using a zirconium complex as metal catalyst and a chiral peptide, diverse enantioenriched aryl, aliphatic and alkynyl amines **142** have been obtained with high levels of enantioselectivity (Scheme 8.60) [136].

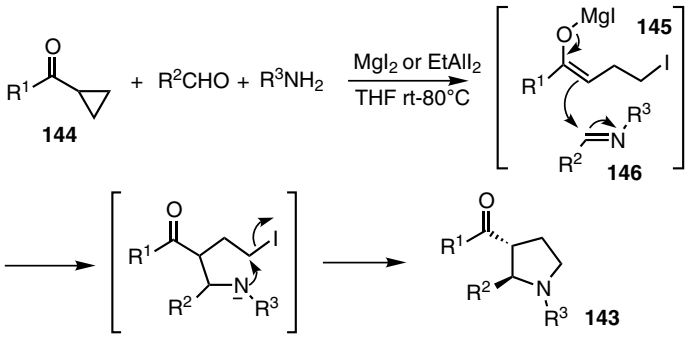


Scheme 8.60

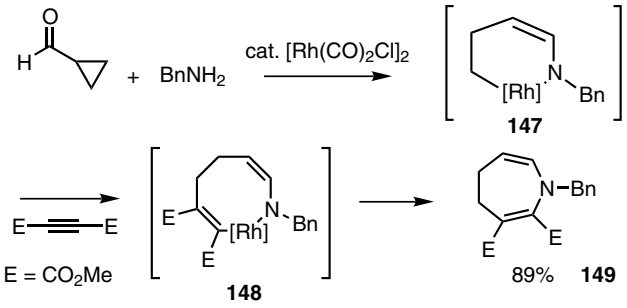
8.8.3 Miscellaneous Reactions Involving Imines

Three-component reactions involving imines as intermediates have also been applied to the synthesis of various nitrogen heterocycles. Thus, substituted pyrrolidines **143** can be obtained by MgI_2- (or $EtAlI_2$-)promoted ring-opening of cyclopropyl ketones **144** followed by attack of the resulting enolate **145** onto the imine **146** and subsequent cyclization to form **143** [137] (Scheme 8.61). It should be noted that $EtAlI_2$ also promotes the reaction of aliphatic aldehydes.

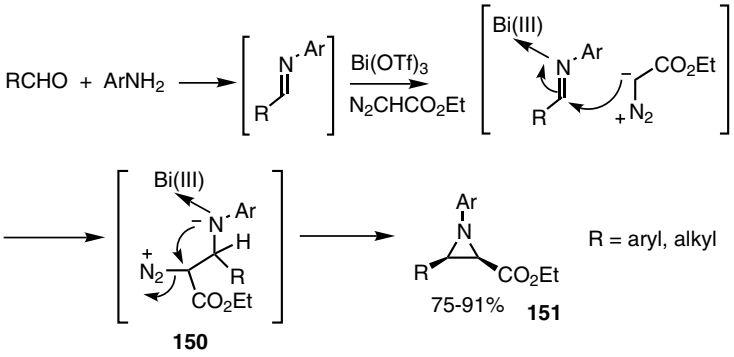
Dihydroazepines have been synthesized by the first rhodium-catalyzed hetero-[5+2] cycloaddition of cyclopropylimines and alkynes (Scheme 8.62) [138]. The reaction proceeds *via* formation of metallacycle **147** which undergoes migratory insertion of dimethyl acetylenedicarboxylate (DMAD) to form **148**. Finally, dihydroazepine **149** is obtained *via* reductive elimination.



Scheme 8.61



Scheme 8.62



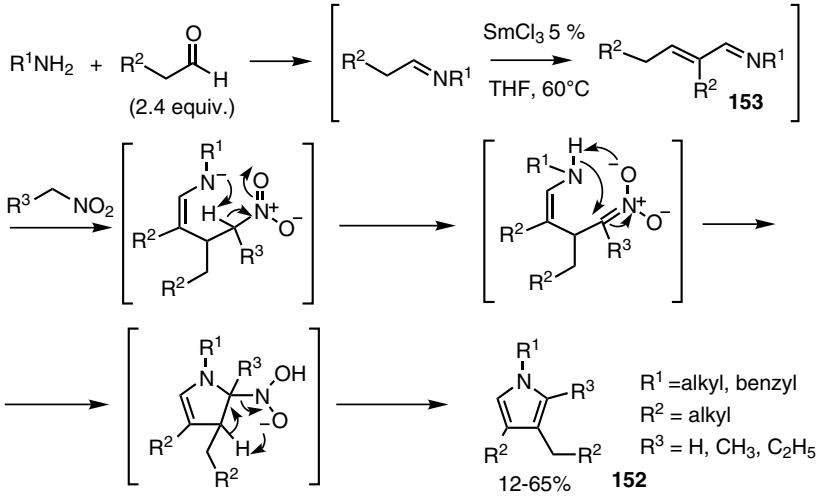
Scheme 8.63

Aziridines can be obtained by $Bi(OTf)_3$- or $Sc(OTf)_3$-catalyzed reaction of aldimines with ethyl diazoacetate in ionic liquid [139]. Ethyl diazoacetate adds to the imine leading to intermediate **150** which cyclizes to give the aziridine **151**. In most cases the reaction is highly stereoselective affording *cis*-aziridines predominantly (Scheme 8.63).

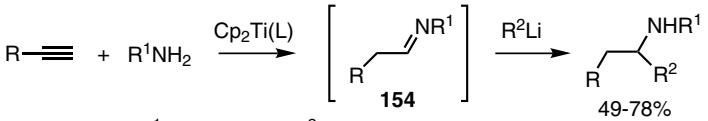
Ishii has shown that diversely substituted pyrroles **152** can be prepared by a one-pot operation involving formation of intermediate α,β-unsaturated imines **153** *via* a $SmCl_3$-catalyzed self-aldol-type condensation. The targeted heterocycles are formed upon addition of a nitroalkane and subsequent cyclization according to the mechanism depicted in Scheme 8.64 [140]. Interestingly, α,β-unsaturated ketones also participate in this process.

The hydroamination of alkynes is an efficient way to obtain aldimines with the advantage of avoiding formation of by-products. As shown in Scheme 8.65, the method has been developed into a multicomponent synthesis of α-branched amines. Aldimines **154** are formed using a titanium derivative as catalyst and reacted *in situ* with an organolithium reagent [141].

The Reformatsky-type addition of organozinc reagents to imines is a well-known process for β-aminoester synthesis. However, this transformation often affords



Scheme 8.64

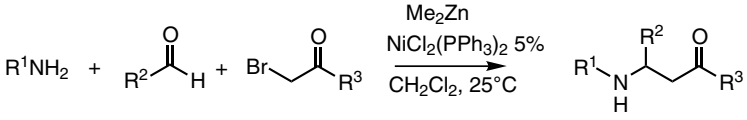


R = Ph, alkyl; R^1 = *t*-Bu, *s*-Bu; R^2 = *n*-Bu, Ph, Me

L = η^2-Me_3Si—≡—$SiMe_3$

Scheme 8.65

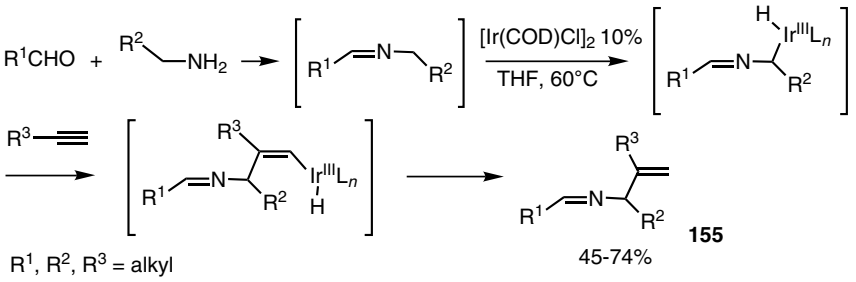
mixtures of *β*-aminoesters and *β*-lactams. The problem was overcome by involving imines generated from 2-methoxyaniline, which afforded *β*-aminoesters selectively [142]. This useful transformation was further extended to a multicomponent condensation that combines an aldehyde, an aniline, and an *α*-bromocarbonyl compound. A nickel catalyst and diethylzinc were used to generate the Reformatsky reactive species (Scheme 8.66). Furthermore, a small library of 64 members was prepared, thus demonstrating the great potential of this reaction [143]. A similar rhodium-catalyzed reaction has also been developed for the one-pot preparation of chiral *β*-aminoesters [144].



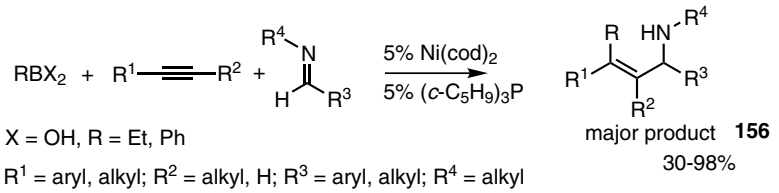
R^1 = aryl, R^2 = aryl, alkyl,

R^3 = OMe, *t*-Bu, $NCH_3(OCH_3)$, $N(CH_3)_2$

Scheme 8.66



Scheme 8.67



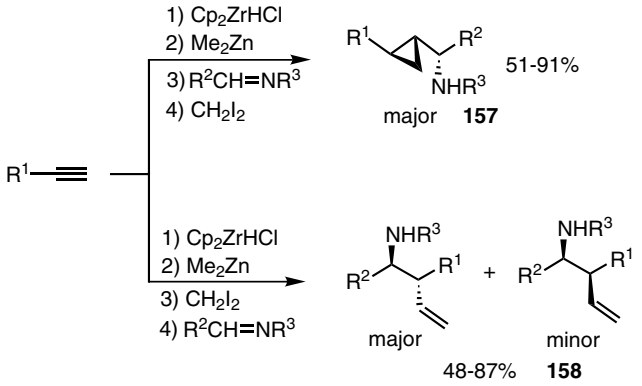
Scheme 8.68

Another unusual three-component coupling reaction involving an imine as intermediate has been developed by Ishii who has shown that a C–H bond adjacent to the nitrogen atom of an imine can be activated by an iridium complex. Carbometallation reactions of acetylenic compounds may then be achieved, which lead to unsaturated imines **155** (Scheme 8.67) [122].

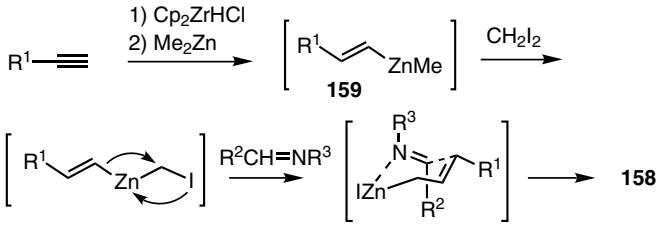
Jamison has reported the unprecedented nickel-catalyzed assembly of allylic amines **156** from three simple starting materials: alkynes, imines, and trialkylboranes or boronic acids. The participation of boronic acids in this methodology greatly enhances its synthetic potential, owing to their greater availability (Scheme 8.68) [145]. An asymmetric version of the reaction has also been developed but gave only moderate enantiomeric excesses (33 to 42%).

An original development of zirconocene chemistry to the synthesis of amino cyclopropanes and allylic amines has been reported by Wipf and co-workers [146]. The method involves hydrozirconation of an alkyne followed by transmetallation with dimethyl zinc to form an alkenyl zinc species (Scheme 8.69). The latter adds readily to a phosphinoylimine to give an allylic Zn-amide, which reacts *in situ* with CH_2I_2 to form amino cyclopropanes **157**. Interestingly, when the addition of reagents was reversed (i.e. addition of CH_2I_2 before the imine), homoallylic amine **158** was isolated as a mixture of diastereomers. The authors suggested that homologation of the allylic zinc intermediate **159** *via* a [1,2]-shift occurs prior to addition to the imine moiety (Scheme 8.70) [147].

The scope of the reaction was then extended to the preparation of *C,C*-dicyclopropylmethylamines starting from alkynylimines, which represents the first example of a double C,C-σ-bond insertion [148].

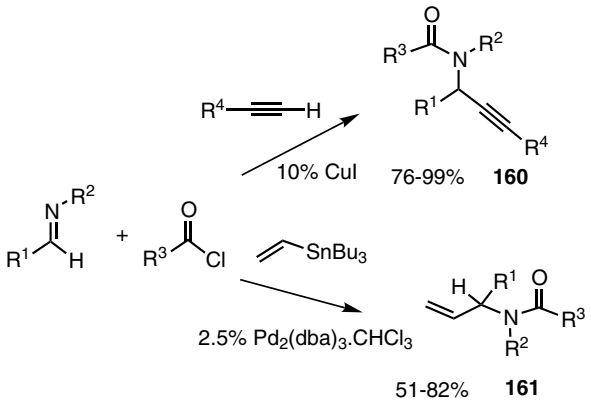


Scheme 8.69

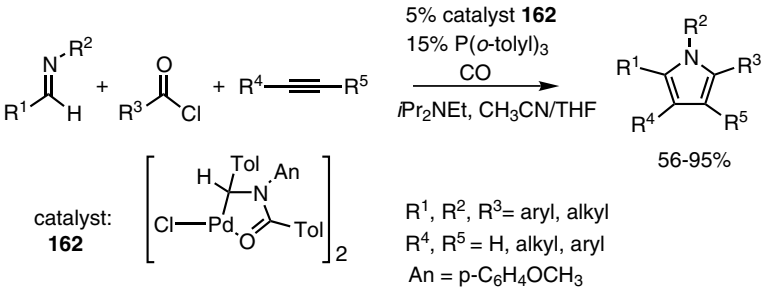


Scheme 8.70

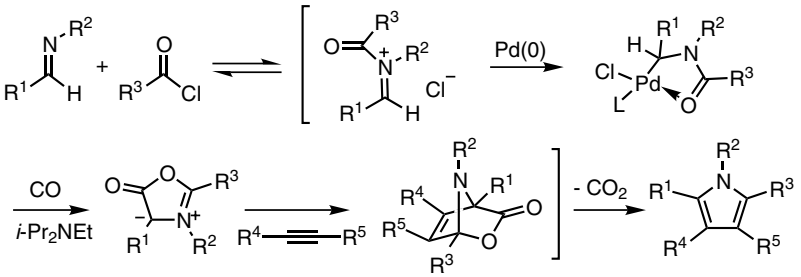
A new copper-catalyzed reaction involving imines, acid chlorides, and alkynes has been applied to the synthesis of propargyl amides **160** in a single operation by Arndtsen and co-workers. The same method allows the synthesis of *N*-carbamate-protected propargylamines [149]. α-Substituted amides **161** may also be prepared under palladium catalysis by substituting alkynes for vinyltin (Scheme 8.71) [150].



Scheme 8.71



Scheme 8.72



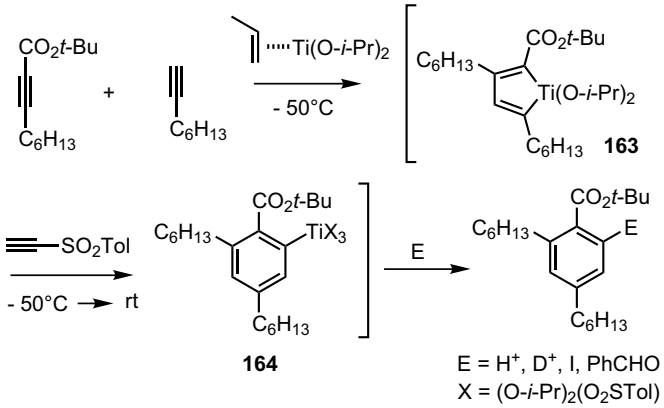
Scheme 8.73

A remarkable modular approach to polyfunctionalized pyrroles has also been developed by Arndtsen. A new palladium complex **162** was designed to catalyze this useful reaction, which combines four components: an imine, an acid chloride, an alkyne, and carbon monoxide (Scheme 8.72) [151]. A working mechanism proposed by the authors is presented in Scheme 8.73.

8.9
Cycloadditions and Related Reactions

8.9.1
Synthesis of Substituted Arenes

The trimerization of alkynes is a general and useful method for the preparation of aromatic compounds [152]. However, this method has serious limitations when three different alkynes are used, as numerous regioisomers may be formed. Takahashi and co-workers have reported the beginnings of a solution using zirconocyclopentadienes prepared *in situ* from two different alkynes. Substituted arenes were obtained upon addition of a third alkyne to the organometallic complex in the presence of copper chloride [153] or a nickel complex [154]. This approach is nevertheless limited by the fact that at least one of the alkynes must be symmetrical, and by

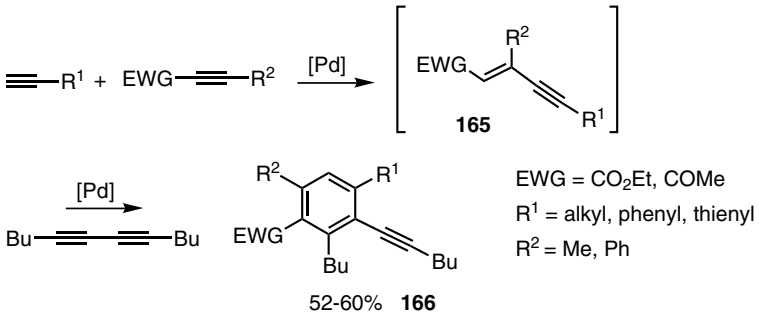


Scheme 8.74

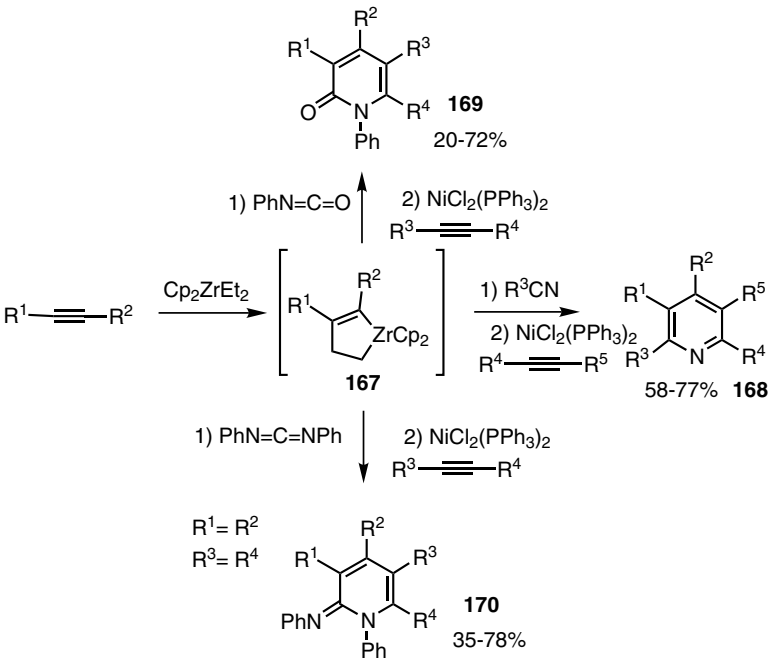
the necessity of using stoichiometric amounts of metal. A major improvement was introduced by Sato and co-workers, who have developed a titanium route to polysubstituted benzene rings [155]. Dialkoxytitanacyclopentadiene **163** was first prepared from two different and unsymmetrical alkynes. The third alkyne was then added to the reaction medium to give a single aryl titanium compound **164** which can be trapped by diverse electrophiles (Scheme 8.74). Another approach has been reported by Yamamoto and co-workers to avoid the use of stoichiometric amounts of transition metal derivatives. These authors have prepared enynes **165** using the palladium-catalyzed donor/acceptor alkyne coupling concept developed previously by Trost for the synthesis of 1,2,4-trisubstituted enynes [156]. *In situ* addition of the third alkyne component resulted in a benzannulation reaction that afforded pentasubstituted arenes **166** (Scheme 8.75).

8.9.2
Synthesis of Pyridines and Analogous Heterocycles

As an extension of the nickel-based approach to substituted arenes discussed above, Takahashi has reacted zirconocyclopentadienes **167** with either nitriles, iso-



Scheme 8.75



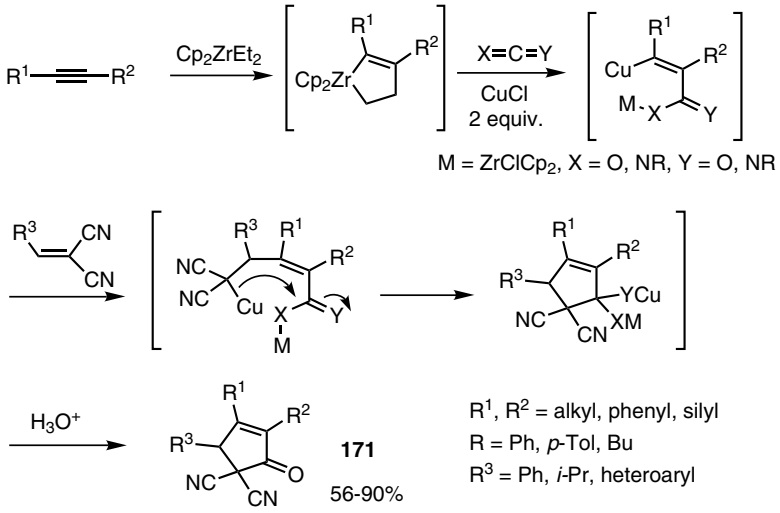
Scheme 8.76

cyanates, or carbodiimides to produce pyridines **168**, pyridones **169**, or iminopyridines **170**, respectively (Scheme 8.76). Symmetrical alkynes have been essentially used in these procedures; however, unsymmetrical systems have been involved in the synthesis of pentasubstituted pyridines [157]. Dialkoxytitanacyclopentadiene complexes developed by Sato (see Scheme 8.74) have also been used in the synthesis of pyridines [158]. Nevertheless, these methods require stoichiometric amounts of metallic salts, which can be a serious limitation. Developments toward the construction of pyridine rings by metal-mediated [2+2+2] cycloaddition have been reviewed [159].

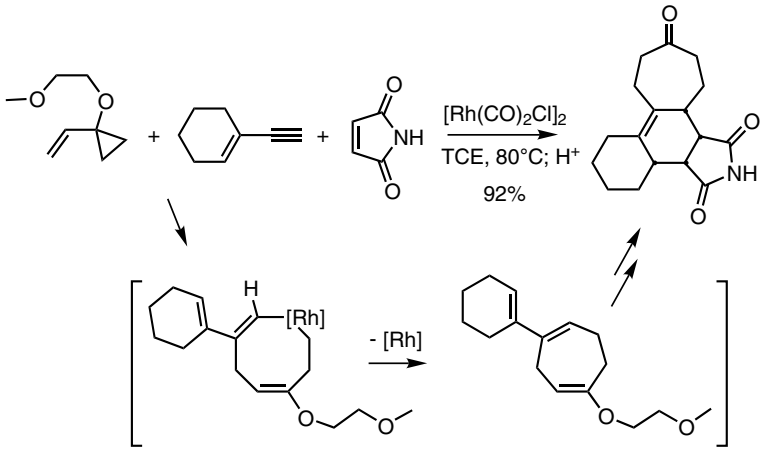
8.9.3 Related Reactions

Three-component reactions involving zirconocyclopentadienes have been also employed in cyclopentenone synthesis. The method combines disubstituted alkynes, isocyanates, and arylidene or alkylidene malononitriles to assemble polysubstituted cyclopentenones **171** (Scheme 8.77) [160].

In 1995, Wender described the first examples of rhodium-catalyzed [5+2] cycloadditions of vinylcyclopropanes and alkynes leading to cycloheptadienes [161]. This new reaction was further extended to a three-component reaction in an original sequence using serial [5+2]/[4+2] cycloadditions (Scheme 8.78) [162]. Carbon mon-



Scheme 8.77

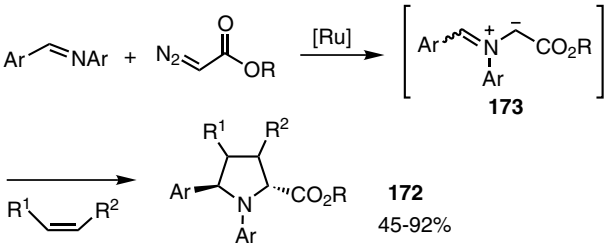


Scheme 8.78

oxide can also replace the dienophile as one of the three components allowing the synthesis of bicyclo[3.3.0]octenones [163].

8.10
Three-component Reactions Involving Metallocarbenes

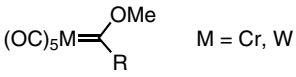
The decomposition of α-diazo esters by a ruthenium porphyrin catalyst has been used by Che and co-workers in a multicomponent strategy directed toward functionalized pyrrolidines **172**. The first step involves the formation of a ruthenium



Scheme 8.79

carbene, which after addition to an imine gives an azomethine ylide **173**. This can then react with various dipolarophiles (Scheme 8.79) [164]. The same strategy was reported by Scheidt and co-workers using a copper catalyst [165]. Another methodology involving rhodium carbenes has been developed by Jamison and co-workers who synthesized oxygen heterocycles using a dicobalt cluster [166]. Oxazole and pyrrole derivatives have been obtained by 1,3-dipolar cycloaddition of an acyl-substituted nitrile ylide resulting from decomposition of α-diazo esters by rhodium acetate [167].

It is worth noting that several multicomponent methodologies involving Fischer carbenes **173** have emerged, in particular those developed by Barluenga [168] and by Aumann [169], which give access to a wide range of complex structures.

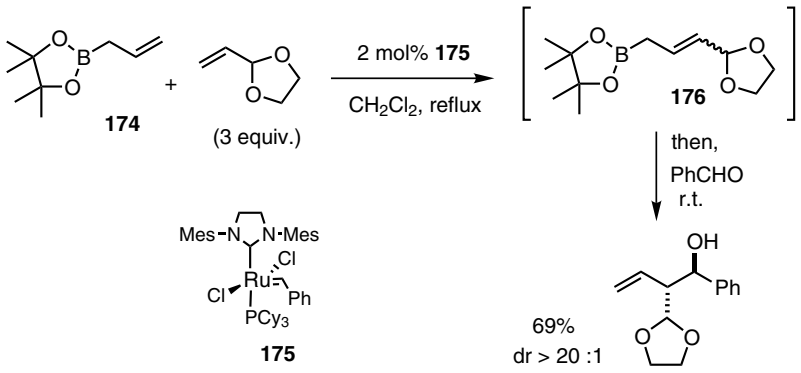


173 Fischer carbene

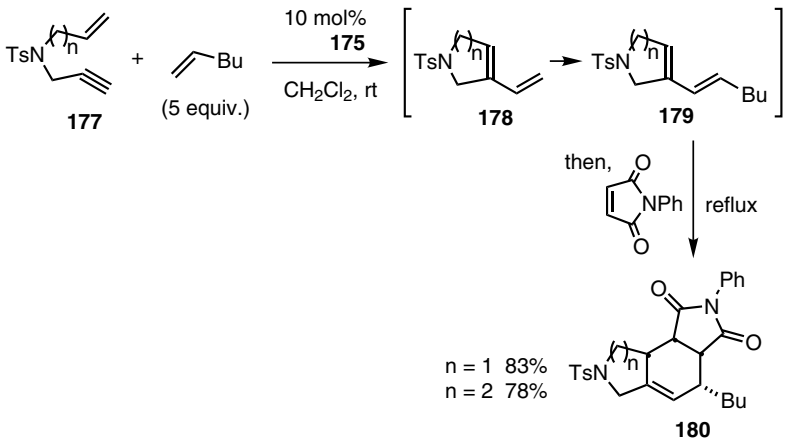
8.11 Metathesis

The utility of Ru-catalyzed cross-metathesis in multicomponent coupling strategies has also been demonstrated. For instance, one-pot cross-metathesis/allylboration sequences have been reported by Miyaura [170] and by Goldberg and Grubbs [171]. Pinacol allyl boronate **174** was reacted with a series of functionalized olefins, which include symmetrically 1,2-disubstituted olefins as well as hindered olefins and styrenes, in the presence of catalyst **175** to produce intermediate allyl boronates (e.g. **176**). The latter may then be reacted *in situ* with aldehydes to produce functionalized homoallylic alcohols with high levels of anti-selectivity (Scheme 8.80).

As seen in the preceding sections, many multicomponent procedures are based on the production of conjugated dienes that are *in situ* involved in Diels–Alder reactions to obtain polycyclic compounds. In recent years, intramolecular enyne metathesis has become a very popular method by which to access cyclic conjugated dienes [172]. In line with this, Lee [173] has developed a new three-component re-



Scheme 8.80



Scheme 8.81

action based on a tandem intramolecular/intermolecular metathesis coupled with a Diels–Alder reaction that assembles heterocyclic compounds **180** in a stereoselective manner from enynes of type **177**, monosubstituted olefins, and a dienophile, *N*-phenylmaleimide (Scheme 8.81). The dienophile was added once the tandem metathesis became complete in order to avoid premature reaction with dienic intermediate **178**.

8.12 Concluding Remarks

The chemistry illustrated above demonstrates the outstanding potential of metal-catalyzed processes for the discovery of new multicomponent one-pot reactions.

This research area has progressed at an exponential rate in recent years and attractive new developments have emerged that exploit an interesting feature of transition metal reactivity, that is their ability to catalyze multistep processes. Hence, tandem one-pot reactions in which the same metal catalyst performs several mechanistically distinct transformations are now well recognized as powerful tools for the design of multicomponent reactions. It is to be expected that future conceptual advances in this field will exploit the tandem action of two different, cooperative, metal catalysts. An additional and central challenging requirement for the development of the desired processes will be to find combinations of catalysts that are compatible. No doubt, many innovative methodologies will continue to emerge from this very stimulating research area.

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9
Catalytic Asymmetric Multicomponent Reactions

Jayasree Seayad and Benjamin List

9.1
Introduction

Multicomponent reactions (MCRs) are one-pot processes combining three or more substrates simultaneously [1]. MCR processes are of great interest, not only because of their atom economy but also for their application in diversity-oriented synthesis and in preparing libraries for the screening of functional molecules. Catalytic asymmetric multicomponent processes are particularly valuable but demanding and only a few examples have been realized so far. Here we provide an overview of this exciting and rapidly growing area.

A large number of catalytic asymmetric MCR are based on deoxo-bisubstitution reactions of carbonyl compounds such as the Mannich and Strecker reactions in which an oxo-group is displaced by two new σ-bonds, one to a nitrogen atom and one to a carbon atom. Other examples of deoxo-bisubstitutions include tandem processes that involve an initial Knoevenagel condensation followed by either a nucleophilic or a cycloaddition. These processes are characterized by the conversion of a C=O-π-bond into two new C–C-σ-bonds and have been termed carba-acetalizations.

9.2
Mannich Reactions

In origin, the Mannich reaction is a three-component reaction between an enolizable CH-acidic carbonyl compound, an amine, and an aldehyde producing β-aminocarbonyl compounds. Such *direct* Mannich reactions can encompass severe selectivity problems since both the aldehyde and the CH-acidic substrate can often act as either nucleophile or electrophile. Aldol addition and condensation reactions can be additional competing processes. Therefore preformed electrophiles (imines, iminium salts, hydrazones) or nucleophiles (enolates, enamines, enol ethers), or both, are often used, which allows the assignment of a specific role to each car-

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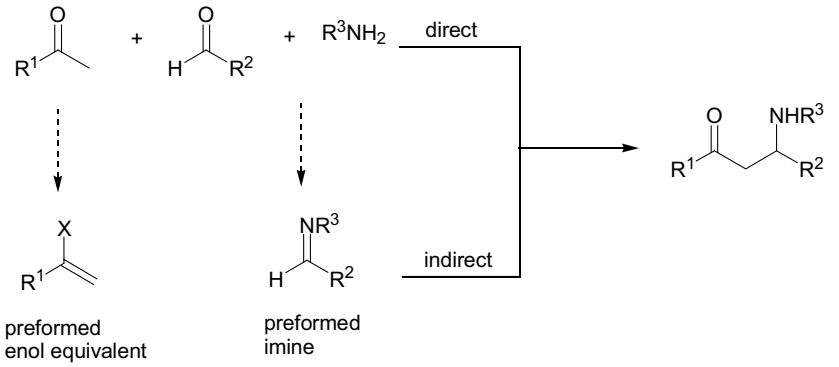
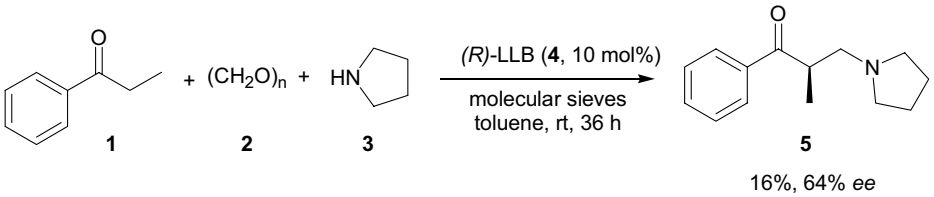


Scheme 9.1. Direct and indirect Mannich reactions.

bonyl component (Scheme 9.1). As a consequence, the first catalytic enantioselective Mannich reactions developed, although elegant and useful, were all indirect [2].

Shibasaki et al. described the first direct three-component catalytic enantioselective Mannich reaction [3], wherein propiophenone **1**, paraformaldehyde **2** and pyrrolidine **3** were reacted using (*R*)-LaLi$_3$tris(binaphthoxide) [(*R*)-LLB, **4**] as catalyst to form Mannich product **5** with 64% *ee* and in 16% yield (Scheme 9.2).

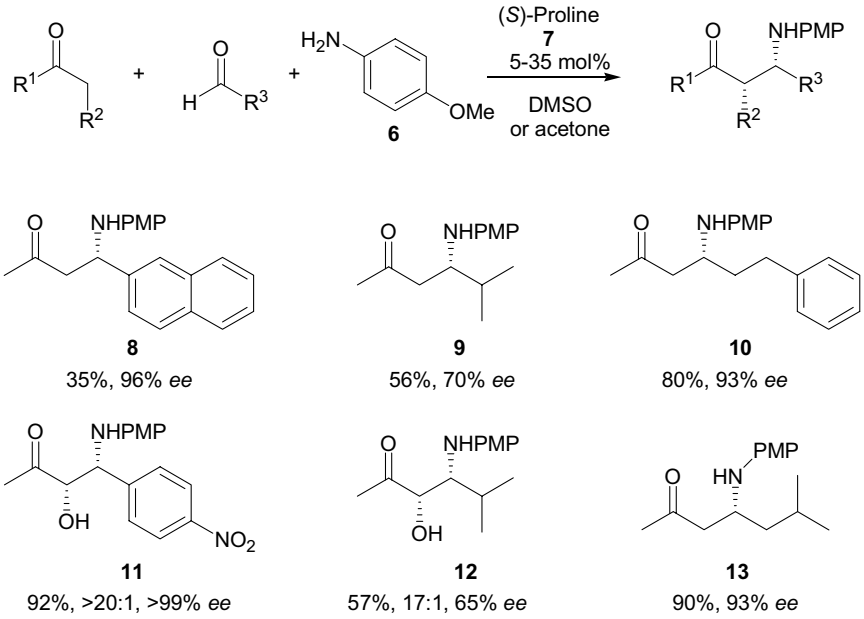


Scheme 9.2. (*R*)-LaLi$_3$tris(binaphthoxide)-catalyzed enantioselective three-component Mannich reaction.

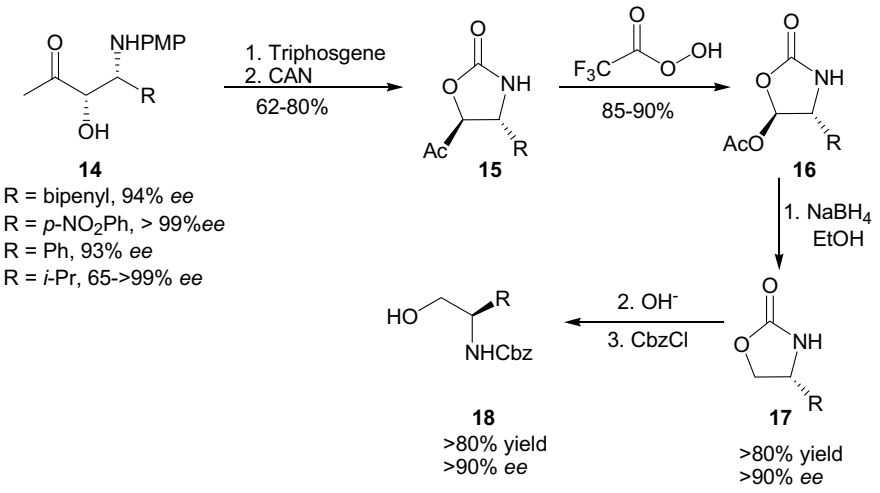
List and coworkers discovered the first efficient catalytic asymmetric three-component Mannich reaction. In this proline-catalyzed Mannich reaction between ketones, aldehydes, and amines (typically *p*-anisidine, **6**), Mannich products are formed in up to >99% *ee* and up to 96% yield (Scheme 9.3) [4].

An important feature of this reaction is that in contrast to most other catalytic asymmetric Mannich reactions, α-unbranched aldehydes are efficient electrophiles in the proline-catalyzed reaction. In addition, with hydroxy acetone as a donor, the corresponding *syn*-1,2-aminoalcohols are furnished with high chemo-, regio-, diastereo-, and enantioselectivities. The produced ketones **14** can be further converted to 4-substituted 2-oxazolidinones **17** and β-aminoalcohol derivatives **18** in a straightforward manner *via* Baeyer-Villiger oxidation (Scheme 9.4) [5].

The proline-catalyzed three-component Mannich reaction is proposed to proceed through the reaction of enamine **a**, formed by the reaction of the ketone with pro-



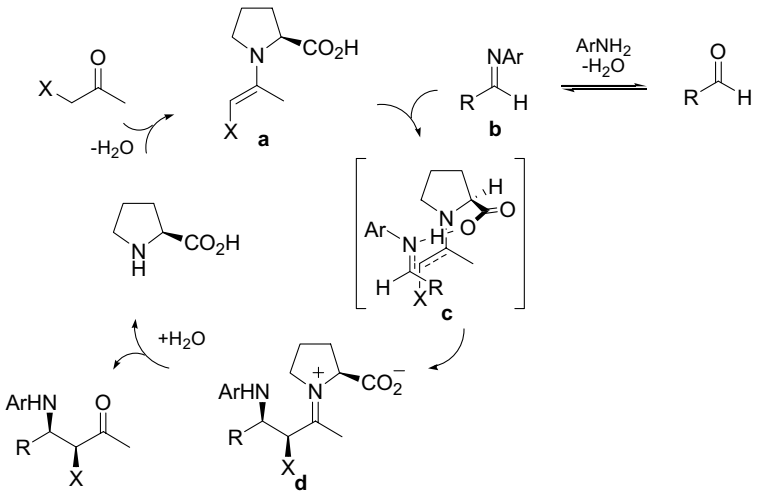
Scheme 9.3. The first proline-catalyzed Mannich reaction.



Scheme 9.4. Conversion of Mannich products **14** into aminoalcohols **18** and oxazolidinones **17**.

line, and an imine **b**, formed in a pre-equilibrium between the aldehyde and the amine. The observed stereochemistry is consistent with transition state **c** (Scheme 9.5). This model has been confirmed theoretically by the Houk group [6].

After publication of these results, Barbas and co-workers submitted and pub-



Scheme 9.5. Plausible mechanism of the proline-catalyzed Mannich reaction.

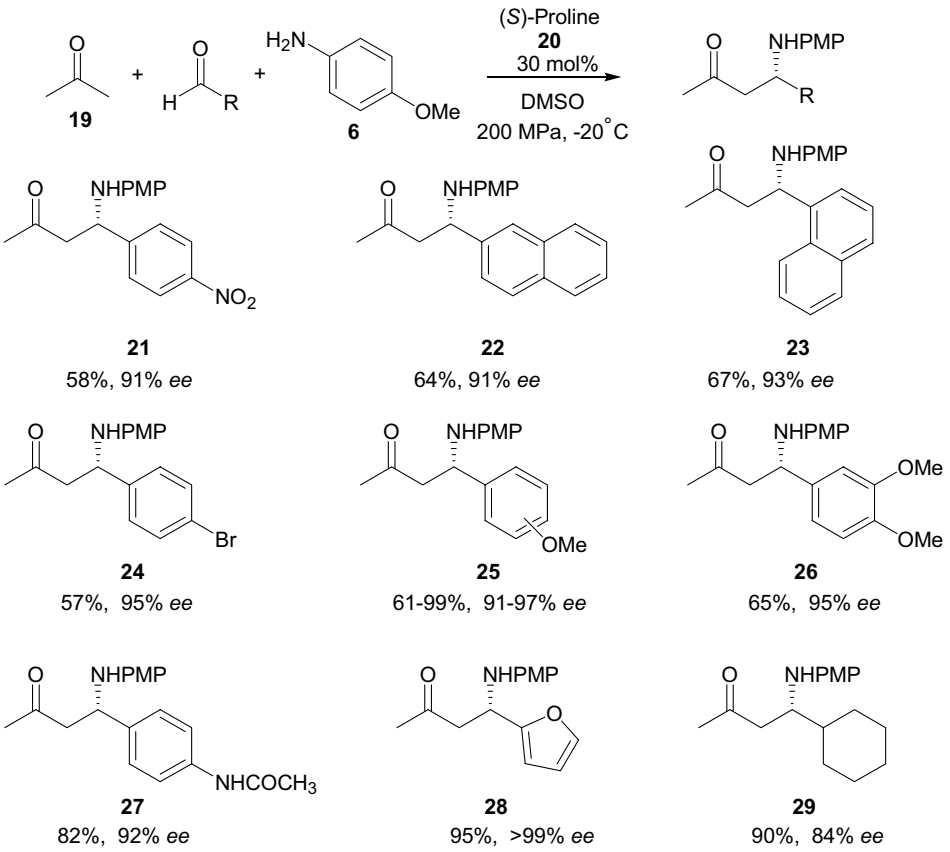
lished modestly enantioselective direct asymmetric Mannich reactions of acetone with *o*-anisidine imines using proline and related catalysts and also confirmed some of the previously reported three-component Mannich reactions [7].

A study by Hayashi et al. demonstrates that less reactive electron-rich aromatic aldehydes efficiently undergo Mannich reactions under high pressure induced by water freezing [8]. For instance, in the Mannich reaction of *p*-anisaldehyde, 3,4-dimethoxybenzaldehyde or *N*-acetyl-(4-formyl)aniline, with acetone and *p*-anisidine, good yields (61–99%) and excellent enantioselectivities (92–97%) have been obtained under water-freezing high-pressure conditions while there is no reaction at room temperature at 0.1 MPa (Scheme 9.6).

The Hayashi group [9], Córdova [10], and the Barbas group [11] have reported a one-pot protocol for the direct, enantioselective three-component cross-Mannich reaction of two different aldehydes to give *syn*-*β*-amino-*α*-alkyl aldehydes (Scheme 9.7). A single crystal of the Mannich product, 3-amino-2-methylpropan-1-ol, showed 2*S*, 3*S* configuration indicating that (*S*)-proline catalyzes si-facial attack on the aldimine generated *in situ* which is in agreement with the transition-state model proposed by List et al. and Houk et al.

Other direct asymmetric Mannich reactions that use preformed imines and unmodified ketones, aldehydes, malonates, and *β*-ketoesters have been described by the groups of Shibasaki [12], Trost [13], Barbas [11, 14], and Jørgensen [15]. As two-component reactions, these processes are not included here but have been reviewed elsewhere [16].

In another study by Dondoni et al. [17] the synthesis of *C*-glycosyl-*β*-aminoesters as single diastereomers is achieved *via* a Mannich-type three-component reaction of *β*-linked *C*-galactosyl or *C*-ribosyl formaldehyde, *p*-methoxybenzyl amine and ketene silyl acetals using catalytic amounts of $InCl_3$ (Scheme 9.8).



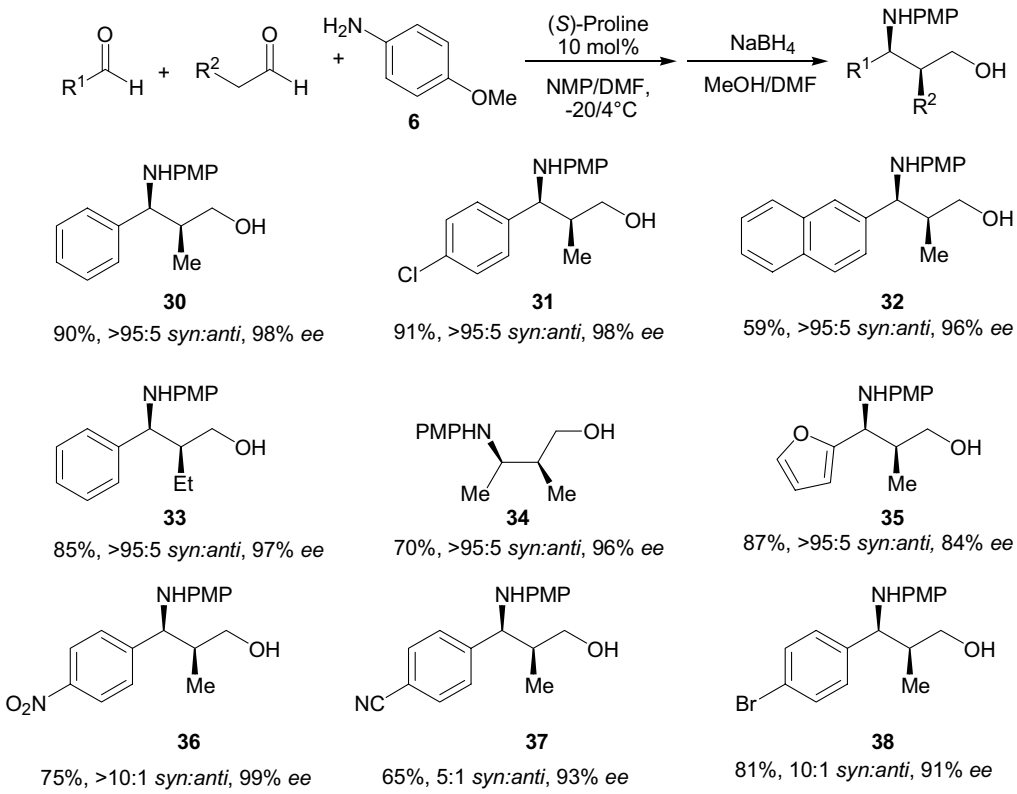
Scheme 9.6. Proline-catalyzed Mannich reaction under high pressure induced by water freezing.

9.3
Three-component Aldolizations

An interesting enzyme-catalyzed three-component aldolization reaction has been described by Gijsen and Wong [18]. Here, acetaldeyde, 2-substituted acetaldehydes, and dihydroxyacetone phosphate react in the presence of the aldolases 2-deoxyribose-5-phosphate aldolase (DERA) and fructose 1,6-diphosphate aldolase (RAMA) forming the corresponding 5-deoxyketose derivatives (Scheme 9.9).

9.4
Three-component Tandem Michael–Aldol Reaction

Shibasaki and co-workers [19] reported a catalytic asymmetric tandem Michael–aldol reaction wherein cylopentenone **50**, diethylmalonate, and 3-phenylpropanal react in the presence of Al-Li-(*R*)-BINOL complex catalyst **57** forming the corre-



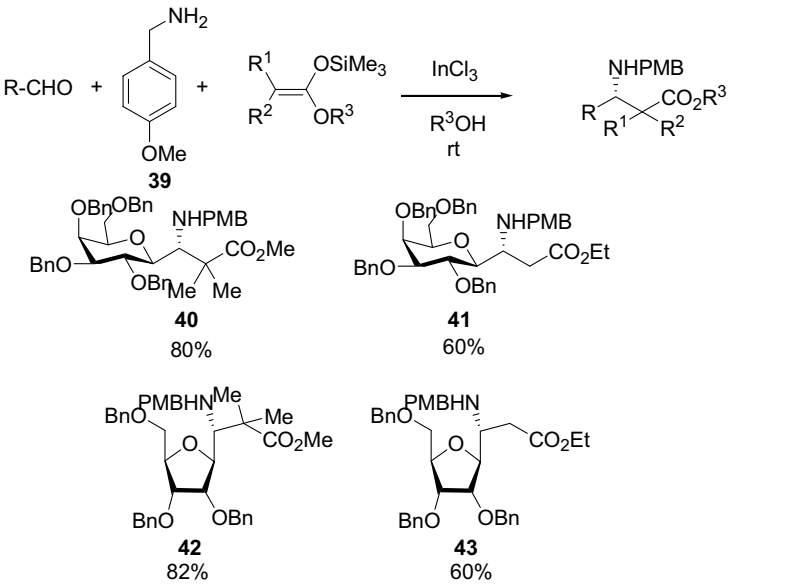
Scheme 9.7. Enantioselective three-component cross-Mannich reaction of two different aldehydes.

sponding three-component coupling product **53** in 64% yield and 91% *ee*. With benzaldehyde, coupling product **55** was formed diastereoselectively in 82% yield. Its oxidation gave diketone **56** in 100% yield and 89% *ee* (Scheme 9.10).

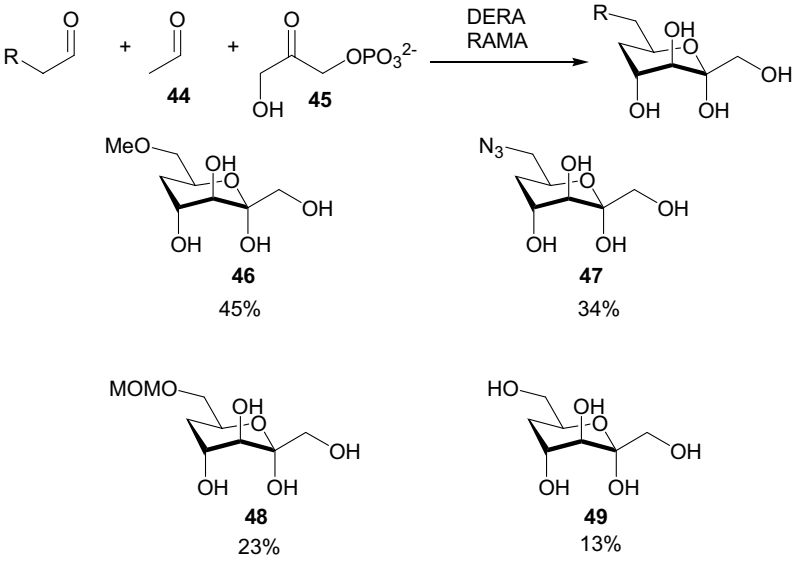
In another study Feringa et al. [20] reported a catalytic enantioselective three-component tandem conjugate addition–aldol reaction of dialkyl zincs. Here, zinc enolates were generated *in situ via* catalytic enantioselective Michael addition of dialkylzinc compounds to cyclohexenone in the presence of a chiral Cu catalyst. Their diastereoselective reaction with an aldehyde then gave trans-2,3-disubstituted cyclohexanones in up to 92% yields and up to >99% *ee*s (Scheme 9.11).

9.5 Passerini Reaction

In the classic Passerini reaction (P-3CR), an α-acyloxy carboxamide is formed from the reaction of an isocyanide, an aldehyde (or ketone), and a carboxylic acid. The



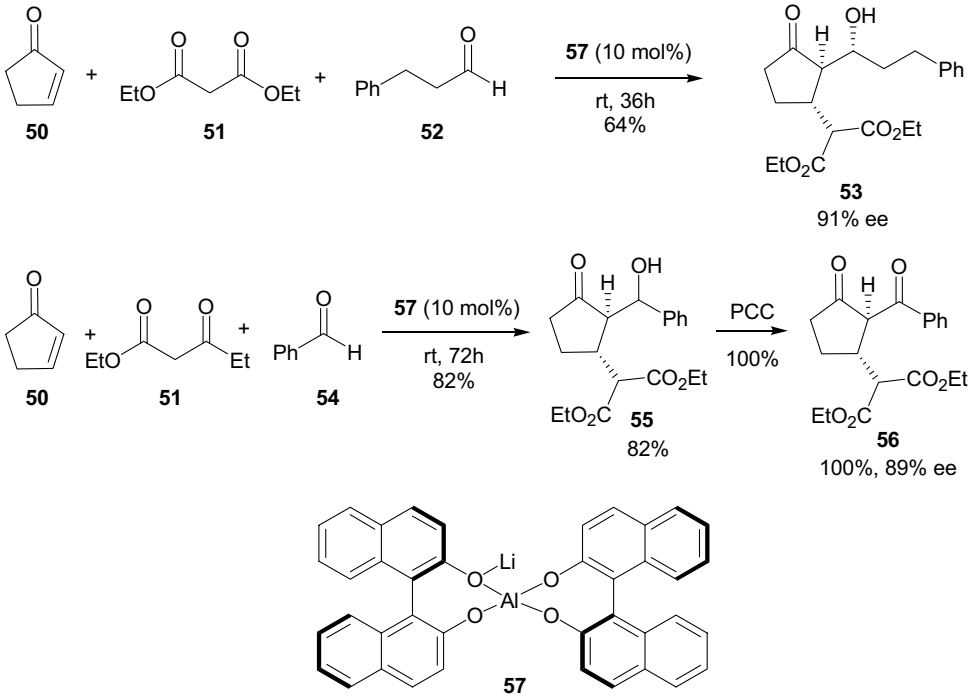
Scheme 9.8. Catalytic diastereoselective synthesis of *C*-glycosyl-β-aminoesters.



Scheme 9.9. Enzyme-catalyzed three-component aldolization.

mechanism involves an initial nucleophilic addition of the isocyanide on the aldehyde followed by an acyl rearrangement (Scheme 9.12).

Although this reaction has been known since 1921 and is widely applied in natural product synthesis and drug discovery, catalytic asymmetric variants are rare.



Scheme 9.10. Catalytic enantioselective tandem Michael–aldol reaction.

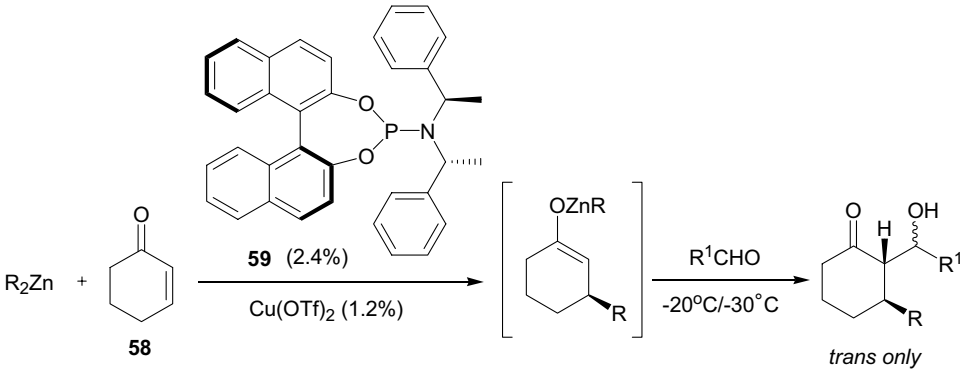
Dömling et al. [21] identified the first enantioselective Passerini MCR using a Lewis acid catalyst Ti(*i*-OPr)$_4$ in combination with (4*S*,5*S*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane as a chiral ligand by a massive parallel catalyst screening (Scheme 9.13).

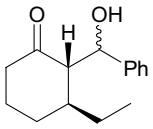
In a related study, Denmark and Fan [22] investigated chiral Lewis base-catalyzed enantioselective α-additions of isocyanides to aldehydes in a Passerini-type reaction (Scheme 9.14). The development of the reaction was based on the concept of Lewis base activation of a weak Lewis acid such as $SiCl_4$ forming a trichlorosilyl–Lewis base adduct which is capable of activating aldehydes towards nucleophilic attack.

Lamberth and co-workers [23] synthesized several chiral mandelamides in a Passerini reaction of 1,2,3,4-tetra-*O*-acetyl-α-D-galacturonic acid with achiral benzaldehydes and isocyanides (Scheme 9.15).

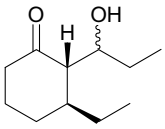
9.6 Strecker Reaction

The Strecker reaction is a three-component reaction of an aldehyde (or ketone), ammonia (**86**, or another amine) and hydrogen cyanide (**87**, or equivalents) to give α-amino nitriles and, after hydrolysis, α-amino acids (Scheme 9.16).

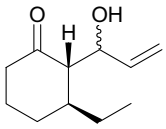




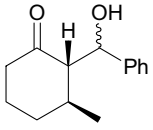
60
88%, 95% *ee*
31:69 (erythro:threo)



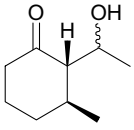
61
88%, 91% *ee*
32:68



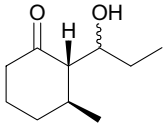
62
92%, 95% *ee*
44:56



63
67%, 91% *ee*
38:62

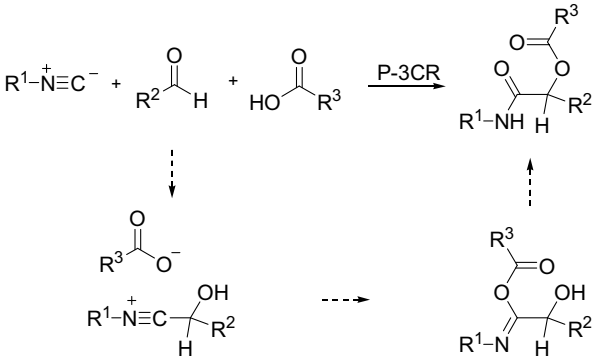


64
81%, 97% *ee*
65:35

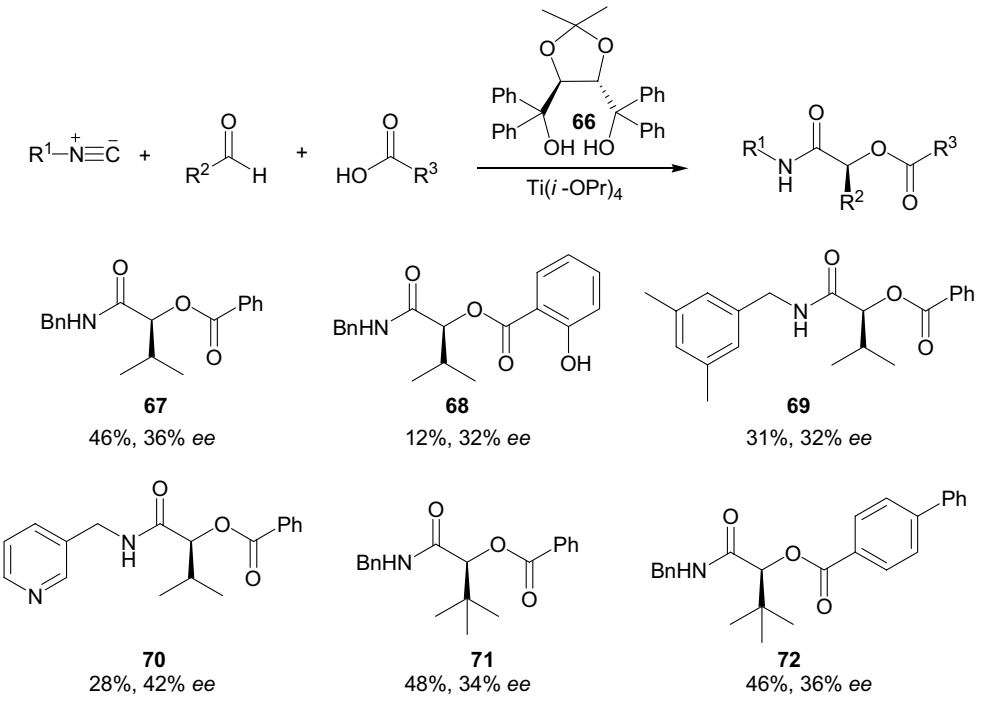


65
75%, 97% *ee*
48:52

Scheme 9.11. Catalytic enantioselective tandem conjugate addition–aldol reaction of dialkylzincs.



Scheme 9.12. Three-component Passerini reaction.

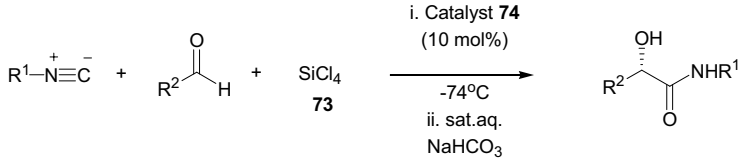


Scheme 9.13. Catalytic enantioselective Passerini reaction.

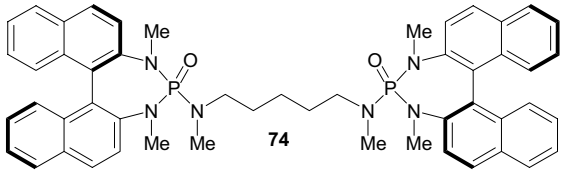
The Strecker reaction has been employed on an industrial scale for the synthesis of racemic α-amino acids, and asymmetric variants are known. However, most of the reported catalytic asymmetric Strecker-type reactions are indirect and utilize preformed imines, usually prepared from aromatic aldehydes [24]. A review highlights the most important developments in this area [25]. Kobayashi and coworkers [26] discovered an efficient and highly enantioselective direct catalytic asymmetric Strecker reaction of aldehydes, amines, and hydrogen cyanide using a chiral zirconium catalyst prepared from 2 equivalents of $Zr(Ot\text{-}Bu)_4$, 2 equivalents of (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol, [(*R*)-6-Br-BINOL], 1 equivalent of (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol, [(*R*)-3-Br-BINOL], and 3 equivalents of *N*-methylimidazole (Scheme 9.17). This protocol is effective for aromatic aldehydes as well as branched and unbranched aliphatic aldehydes.

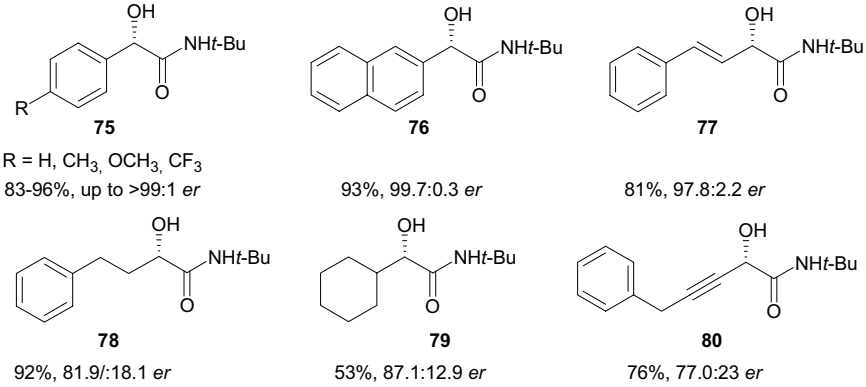
9.7 Aza Morita–Baylis–Hillman Reactions

Asymmetric aza Morita–Baylis–Hillman reactions of *N*-sulfonylimines or *N*-sulfinimines with Michael accepters in the presence a Lewis base catalyst to give the corresponding chiral α-methylene-β-amino compounds have been described [27].

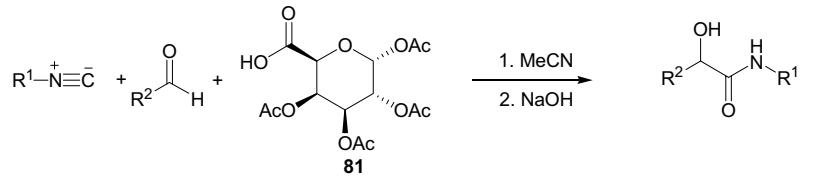


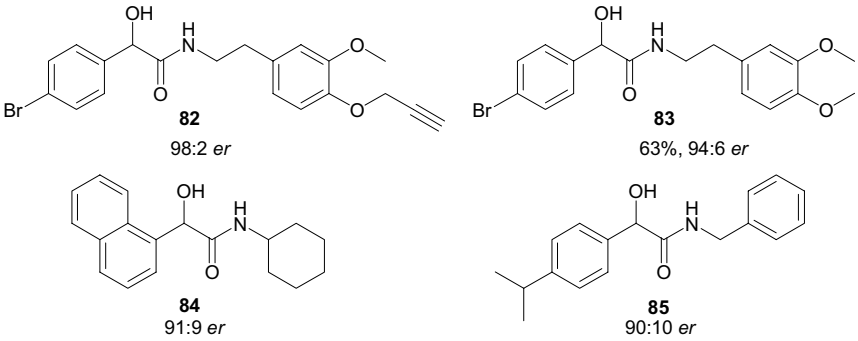
Catalyst



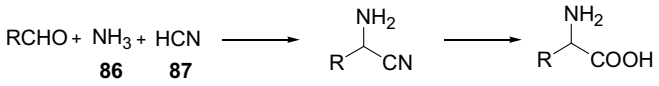


Scheme 9.14. Lewis base-catalyzed enantioselective Passerini-type reactions.

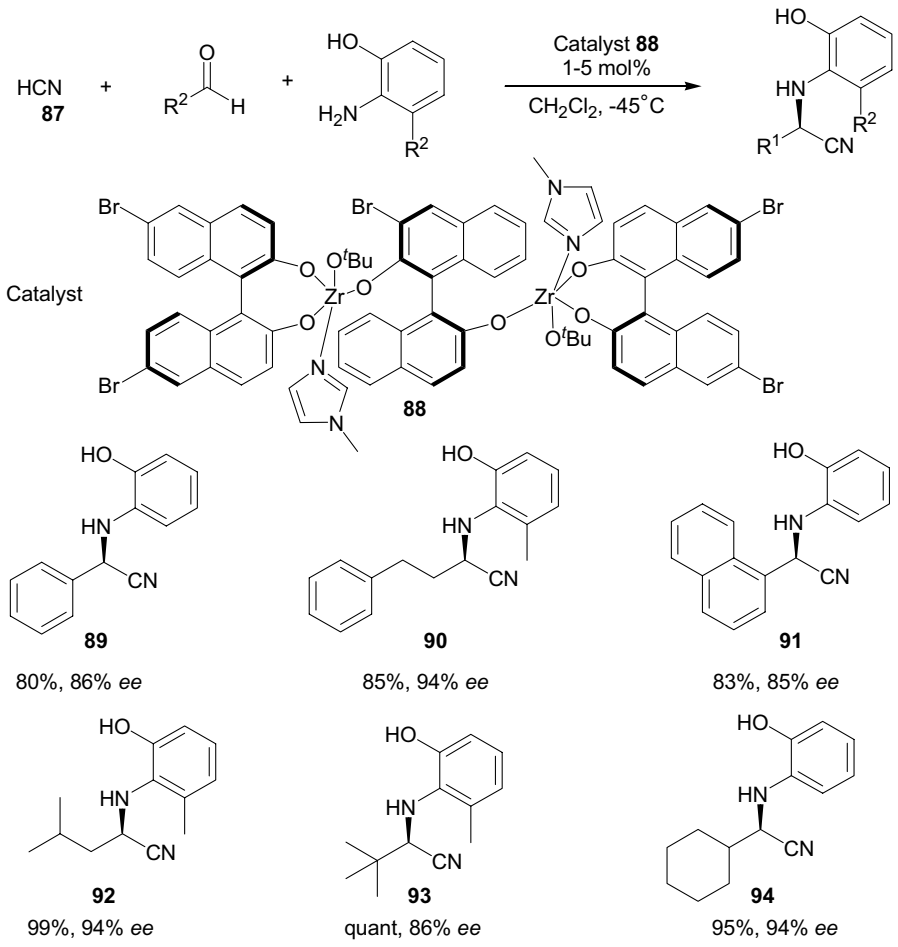




Scheme 9.15. Diastereoselective synthesis of mandelamides by a Passerini reaction.

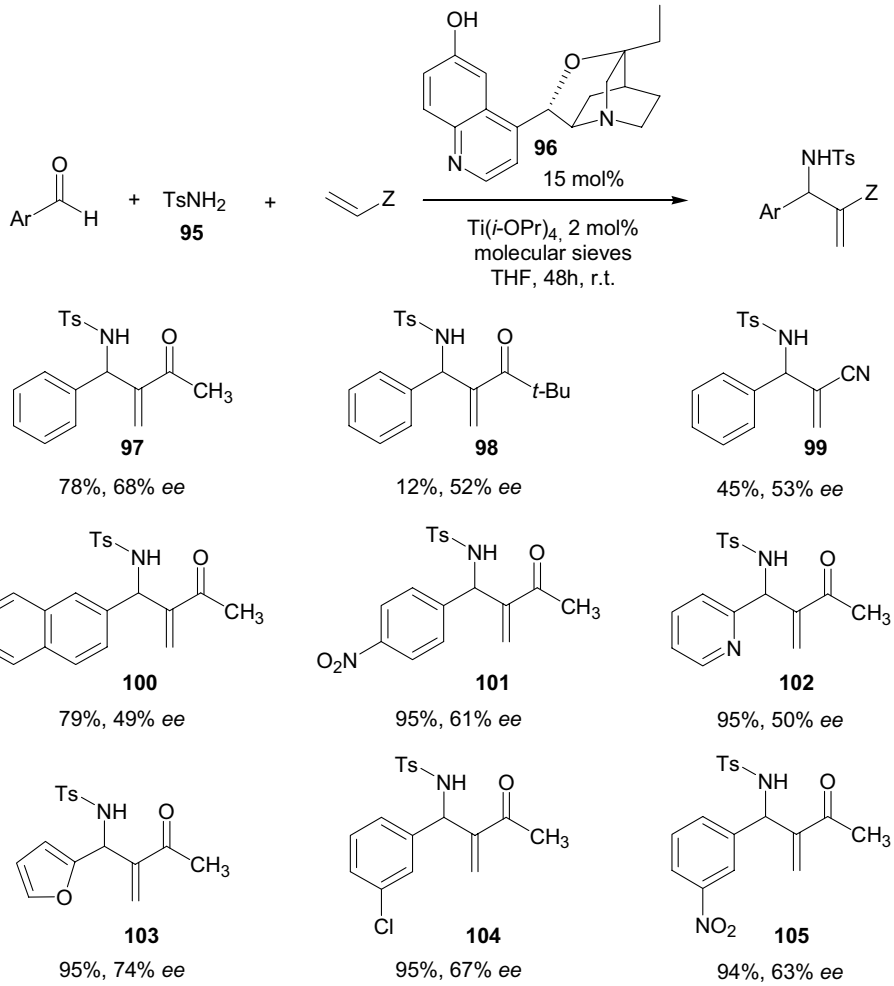


Scheme 9.16. Synthesis of α-amino acids *via* a Strecker reaction.



Scheme 9.17. Catalytic enantioselective Strecker reaction.

Balan and Adolfsson [28] reported a direct catalytic enantioselective three-component aza Baylis–Hillman reaction between arylaldehydes, tosylamides, and Michael acceptors using the quinidine-based Hatekayama catalyst **96** [29] together with titanium isopropoxide as a Lewis acid cocatalyst (Scheme 9.18). High chemical yields and stereoselectivity ranging between 49 and 74% *ee* were obtained using various substituted arylaldehydes.

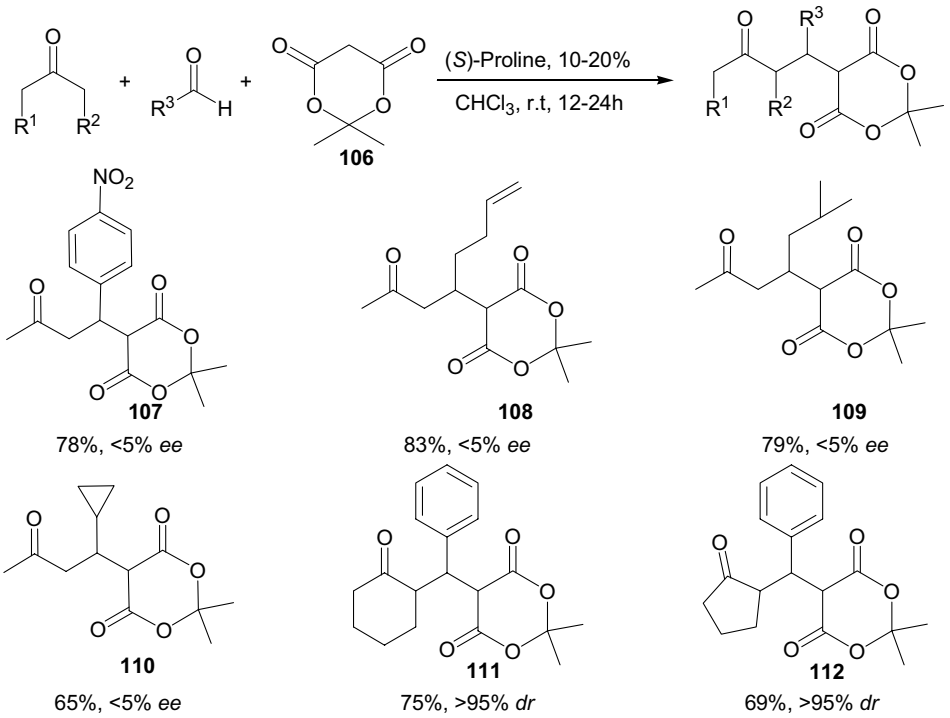


Scheme 9.18. Catalytic enantioselective three-component aza Baylis–Hillman reaction.

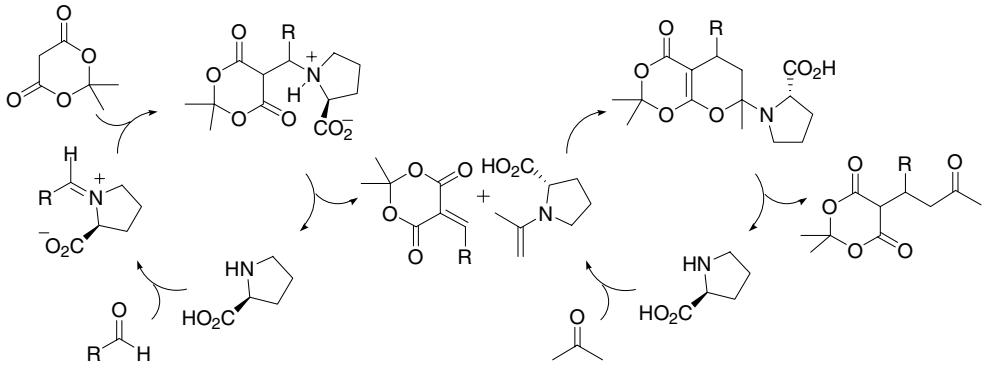
9.8
Domino-Knoevenagel-hetero-Diels–Alder-type Reactions

List and Castello discovered a proline-catalyzed three-component domino reaction between ketones, aldehydes, and Meldrum's acid forming corresponding ketoesters (Scheme 9.19) [30].

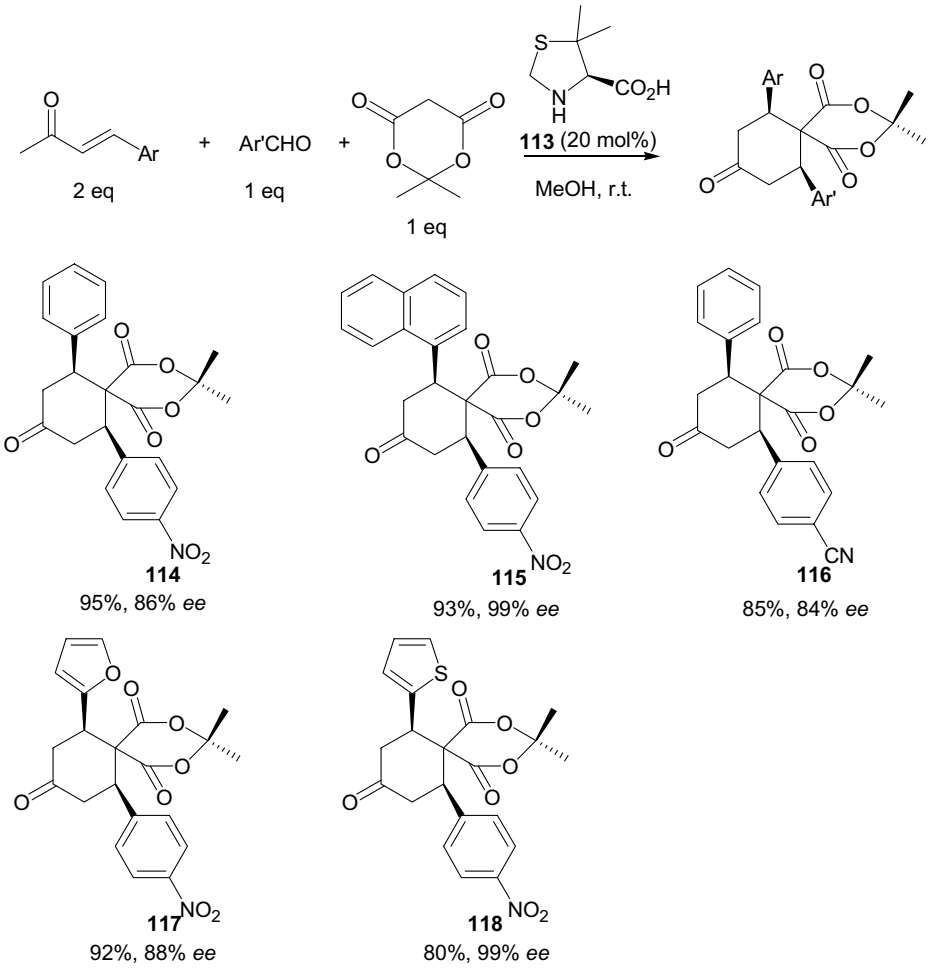
In this transformation two new C–C-σ-bonds are formed from three different components. The enantioselectivity of this reaction is generally low (< 5%). With cyclic ketones the corresponding products were obtained as single diastereomers. It is proposed that this reaction involves a Knoevenagel-hetero-Diels–Alder sequence where proline utilizes both iminium and enamine catalysis (Scheme 9.20).



Scheme 9.19. Proline-catalyzed three-component reaction of aldehydes with ketones and Meldrum's acid.



Scheme 9.20. Proposed mechanism for the proline-catalyzed three-component reaction of aldehydes with ketones and Meldrum's acid.



Scheme 9.21. DMTC-catalyzed asymmetric three-component domino-Knoevenagel-Diels–Alder reaction.

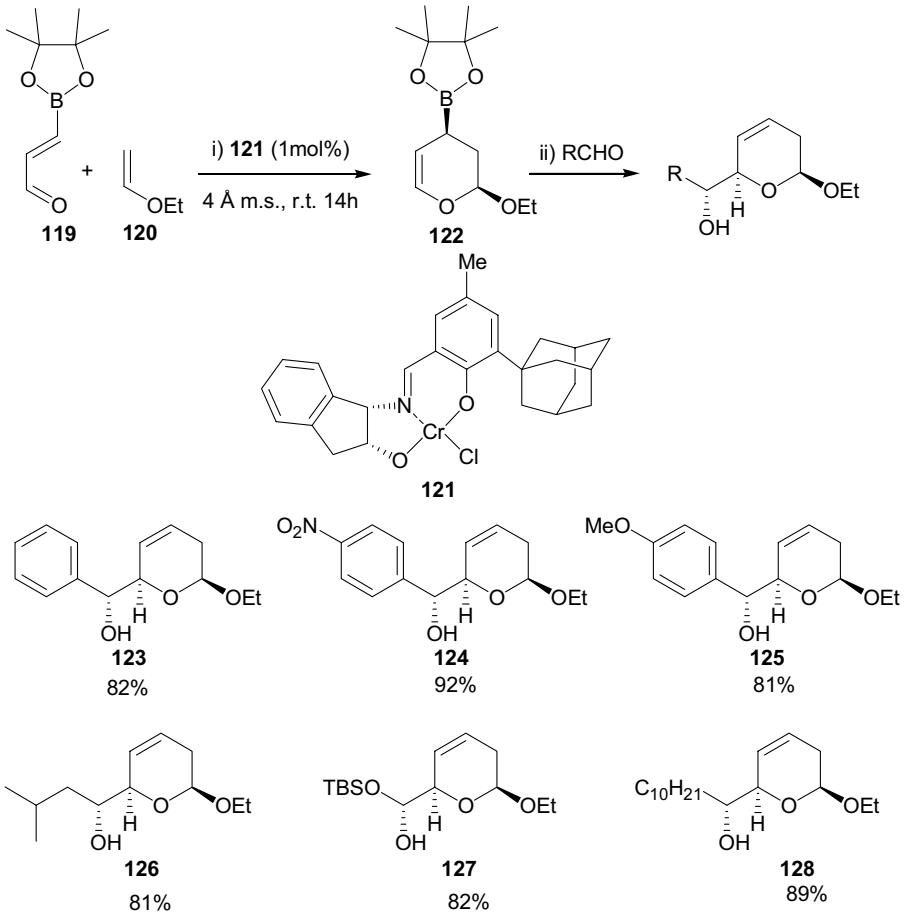
Barbas and co-workers [31] have reported a related reaction of a *trans*-4-aryl-3-buten-2-one, an arylaldehyde, and Meldrum's acid in the presence of catalytic amounts of an amino acid forming spirotriones in good yields and *ee*s (Scheme 9.21). Among a family of 19 pyrrolidine-based catalysts, 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) **113** was found to be the most efficient catalyst for this reaction.

Mechanistically it is proposed that the reaction proceeds *via* an initial Knoevenagel condensation of the aldehyde with Meldrum's acid followed by a Diels–Alder reaction of the resulting arylidene Meldrum's acid with an *in situ* generated chiral dienamine, which is formed in the reaction of the enone with the aminocatalyst.

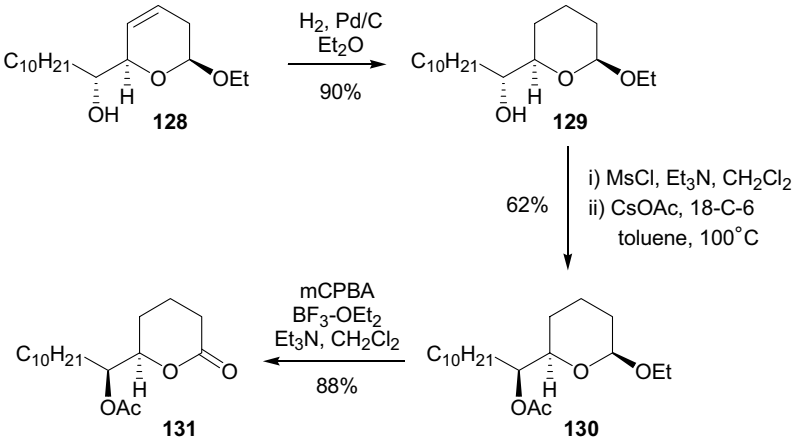
9.9
Three-component Hetero-[4+2]-cycloaddition–Allylboration Tandem Reaction

Gao and Hall [32] reported a three-component hetero [4+2]-cycloaddition–allylboration sequence of boronoacrolein pinacolate **119**, ethyl vinyl ether **120** and different aldehydes using Jacobsen's chromium(III) catalyst **121** [33]. Several aromatic and aliphatic aldehydes, including functionalized aldehydes, were converted to the corresponding dihydropyran products as single diastereomers in high yields (Scheme 9.22).

This one-pot, three-component reaction has been successfully applied to the total synthesis of (5*R*,6*S*)-6-acetoxy-5-hexadecanolide **131** (Scheme 9.23).



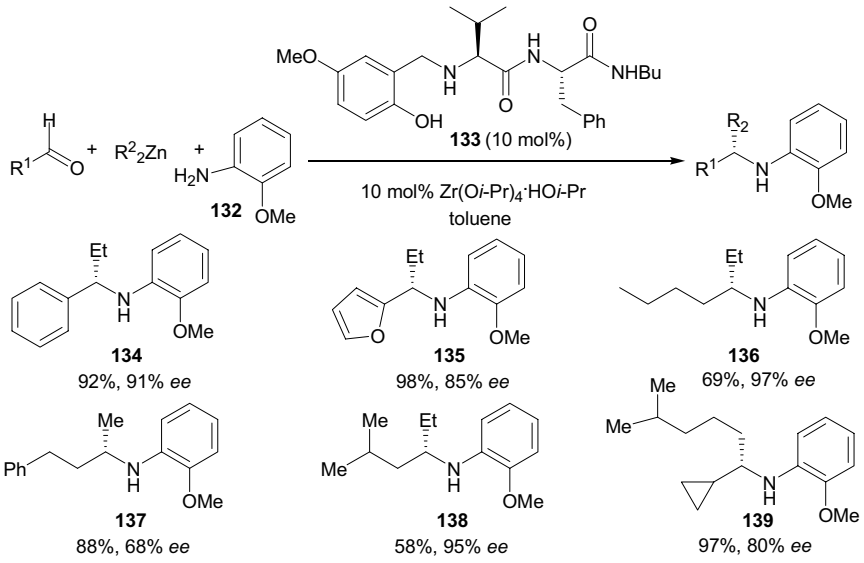
Scheme 9.22. Asymmetric three-component hetero [4+2]-cycloaddition–allylboration.



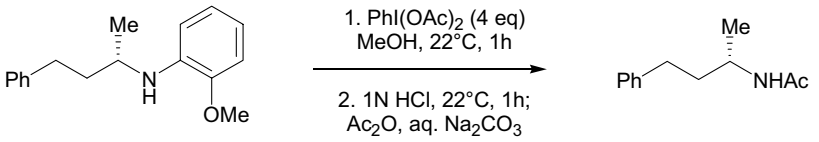
Scheme 9.23. Total synthesis of (5*R*,6*S*)-6-acetoxy-5-hexadecanolide.

9.10
Addition of Alkylzincs

Catalytic enantioselective addition reactions of alkyllithium or -zinc reagents to preformed imines have been described [34, 35]. Hoveyda, Snapper, and co-workers have described a direct three-component variant of this reaction [36]. Accordingly, several chiral, non-racemic aromatic as well as aliphatic amines were synthesized by the reaction of the corresponding aldehydes, *o*-anisidine **132**, and alkylzincs using a Zr catalyst with a chiral peptide ligand **133** (Scheme 9.24).



Scheme 9.24. Zr-catalyzed asymmetric three-component addition of alkylzincs to imines.



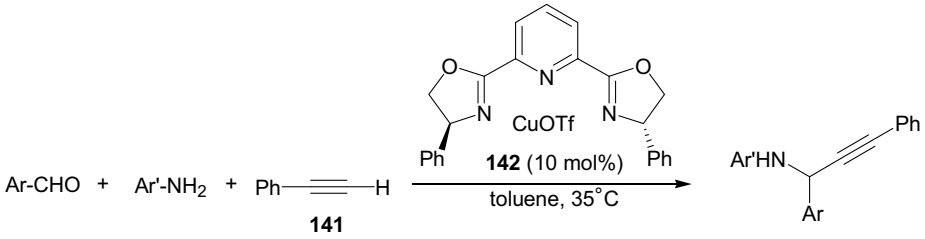
137 **140**

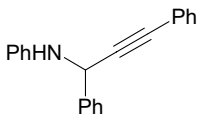
Scheme 9.25. Conversion of anisidines to optically enriched acylated amines.

This method is effective for aldehydes bearing α or β-alkyl substituents and alkyl zincs other than Et_2Zn. It is noteworthy that only negligible alkylation of aldehyde ($< 2\%$) is observed under these conditions. The produced amines can be further elaborated to optically enriched acylated amines with high efficiency and without any detectable loss of enantiopurity (Scheme 9.25).

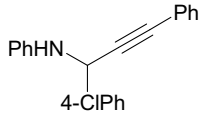
9.11 Alkyne Nucleophiles

Li and Wei [37] have developed additions of alkynes to imines generating propargyl amines in water or under solvent-free conditions. Recently, they established a highly enantioselective direct variant, in which phenylacetylene adds to *in situ* generated imines in the presence of Cu-bisoxazoline catalyst **145** forming the corresponding (+)-propargylamines in high yields (Scheme 9.26) [38].

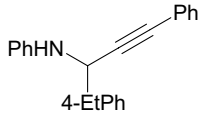




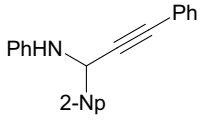
143
78%, 96% *ee*



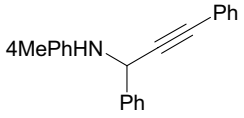
144
85%, 94% *ee*



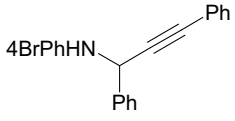
145
73%, 95% *ee*



146
67%, 82% *ee*

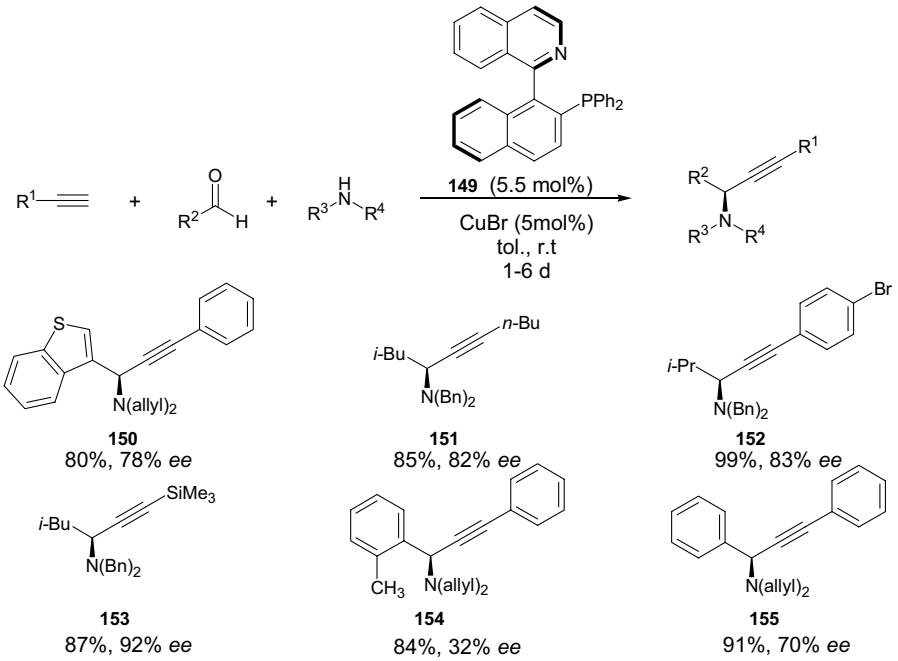


147
93%, 94% *ee*



148
93%, 91% *ee*

Scheme 9.26. Enantioselective addition of phenyacetylene to imines.



Scheme 9.27. Enantioselective three-component reaction for the synthesis of propargylamines.

Knochel and co-workers [39] reported a related three-component reaction between various alkynes, aldehydes, and secondary amines in the presence of CuBr and (*R*)-quinap **149** to give the corresponding propargylamines in excellent yields and good enantioselectivities (Scheme 9.27).

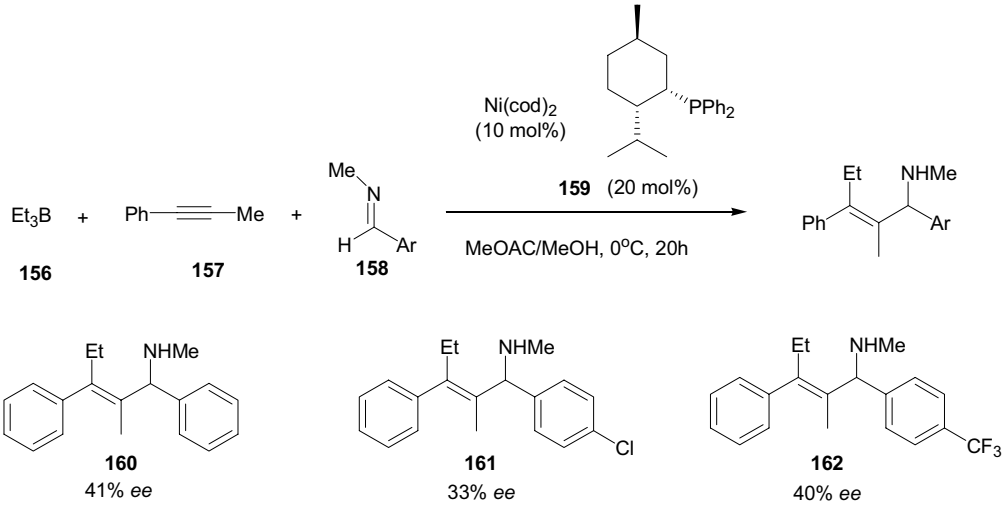
This reaction is believed to proceed *via* nucleophilic combination of *in situ* generated Cu-acetylide and iminium ion. Mechanistic studies indicate a strong positive non-linear effect based on which a catalytic cycle is proposed that involves a dimeric Cu/quinap complex as the active catalytic species.

9.12
Coupling of Alkynes, Imines and Organoboranes

Patel and Jamison [40] reported a catalytic three-component coupling of alkynes, imines, and triethylborane using a Ni complex and (*S*)-(+)-(neomenthyl)diphenylphosphane [(*S*)-NMDPP] **159** forming the alkylative coupling product (Scheme 9.28). No yields were reported.

9.13
Free-radical Reactions

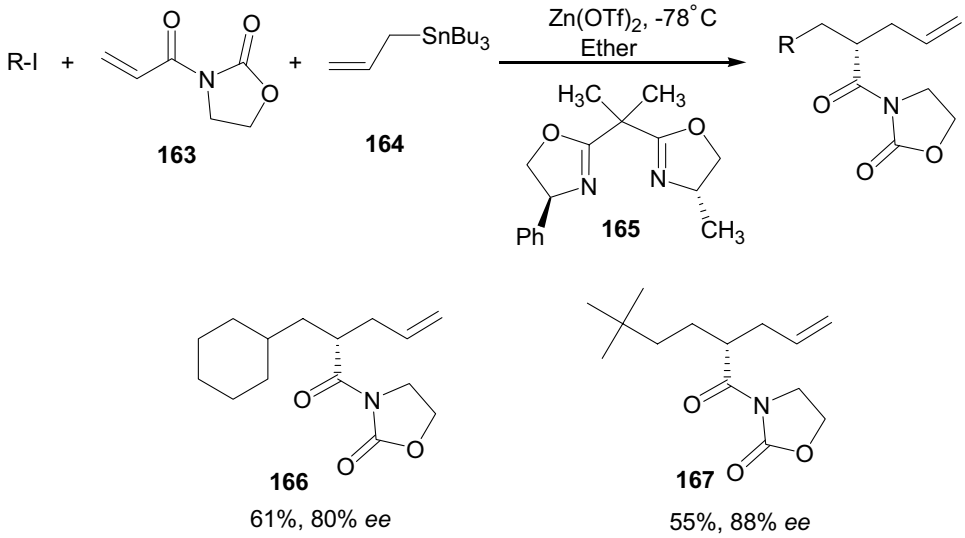
An interesting enantioselective addition–allyl-transfer sequence of an electron-deficient alkene **163** with alkyliodides and allyltributylstannane **164** was described



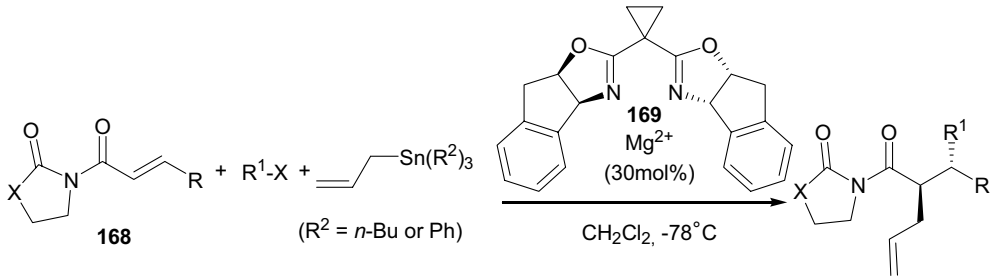
Scheme 9.28. Ni-catalyzed enantioselective coupling of alkynes, imines, and triethylborane.

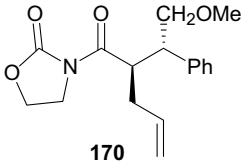
by Porter and co-workers [41]. The reaction proceeds with good yields and enantioselectivity using $Zn(OTf)_2$ as a Lewis acid catalyst and a chiral bidentate ligand **165** in the presence of triethylborane as a low-temperature initiator (Scheme 9.29).

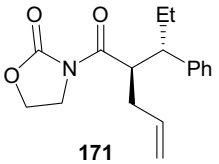
Sibi and Chen [42] reported a related tandem intermolecular nucleophilic free-radical addition–trapping reaction of enoate **168** establishing chirality at both α and β-centers with control over both absolute and relative stereochemistry (Scheme 9.30) using a Lewis acid catalyst and the bisoxazoline ligand **169**. They observed

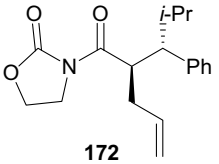


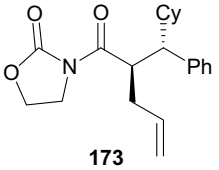
Scheme 9.29. Enantioselective three-component free-radical addition–allyl-transfer reaction.

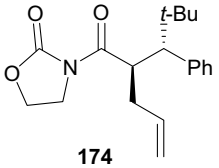


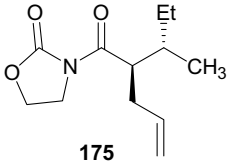

170
80%, 20:1 dr, 72% *ee*

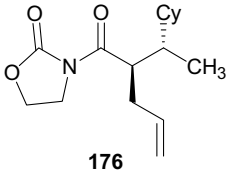

171
79%, 32:1 dr, 77% *ee*

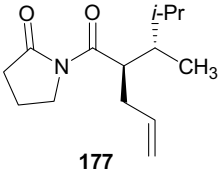

172
93%, 37:1 dr, 93% *ee*

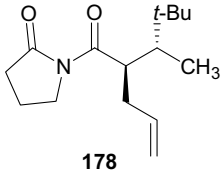

173
80%, 60:1 dr, 92% *ee*


174
84%, 99:1 dr, 97% *ee*


175
83%, 4:1 dr, 61% *ee*


176
83%, 4:1 dr, 62% *ee*


177
84%, 7:1 dr, 76% *ee*


178
85%, 19:1 dr, 92% *ee*

Scheme 9.30. Enantioselective tandem intermolecular free-radical addition–trapping reaction of enoates.

that Mg and Cu Lewis acids gave enantiomeric products using the same chiral source, and the stereoselectivity increases with the effective size of the nucleophilic radical, the addition of *t*-BuI giving the highest diastereoselectivity of 99:1.

9.14 Summary and Outlook

Catalytic asymmetric multicomponent reactions have only been available for a few years but have already demonstrated great potential for the efficient synthesis of diverse chiral non-racemic compounds. However, a number of important chal-

lenges remain to be solved. Catalytic asymmetric variants of classic multicomponent reactions such as the Ugi, Biginelli, or Petasis reactions, to name just a few, have still not been developed. Therefore nothing less but exciting discoveries are bound to be made in the very near future.

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10
Algorithm-based Methods for the Discovery of Novel Multicomponent Reactions

Lutz Weber

10.1
Introduction

Combinatorial chemistry has become a tool of organic chemists to speed up the search for biologically active molecules in the pharmaceutical industry, to find new agrochemicals, catalysts, polymers and other new materials with desired properties. Basically, combinatorial chemistry is an experimental design to find the combination of possible substituents of a given chemical backbone type that will exhibit the desired properties. Combinatorial synthesis has therefore induced a demand for novel synthetic methods that yield novel chemical skeletons. Multicomponent reactions (MCRs), in which more than two starting materials participate in the reaction and contribute the majority of the skeleton of the product, are regarded as especially interesting in meeting these demands. MCRs bear with the promise of novelty in terms of process and compound-related intellectual property. They also enable automation in synthesis, analytics and evaluation of the physicochemical or biological properties of resulting reaction products. Therefore, the discovery of new MCRs extends the power of combinatorial chemistry and is an interesting challenge for research in organic chemistry. Taking these considerations together, the discovery of novel multicomponent reactions can be considered as an interesting topic for academic research that also satisfies a practical interest of applied sciences.

Despite this interest, new reaction types in organic chemistry have been more usually found by chance than by rational design or logical consideration. In this chapter we emphasize that, although they are rarely used, there are both rational and, in particular, algorithm-based methods to discover novel multicomponent reactions.

10.2
A Definition – What Are Novel MCRs

To begin with, it might be useful to define in general what a ''new'' reaction is. There are several methods available that are used to classify chemical reactions.

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The most ancient classification considers whether a certain compound class or chemical scaffold is being formed with success under given reaction conditions – often described by the name of the chemist who discovered or made major contributions to this reactions. Between 700 and 900 such named reactions are known [1]. This classification is mostly product based, but can be connected in certain cases to specific starting materials, e.g. the nitrosamine rearrangement.

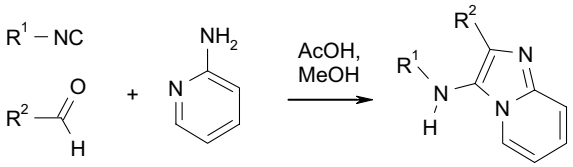
Mechanism-based classifications became popular with the advent of an understanding of the principles and mechanisms of organic reactions in the first half of the twentieth century. Subsequently, and especially in the years 1960–1980, reactions were classified according to the topology of atoms, electrons and bonds in the starting materials and products. This provided the basis for the introduction of computer-based methods that allowed the building and searching of databases of chemical reactions [2]. The ''computerization'' of reaction mechanisms is connected, to the names of Wipke [3–5], Hendrickson [6–9], Ugi [10–13] and others [14–20]. Using the concepts of chemical similarity, one easily can use these computer-based reaction descriptions to quantify the similarity between different reactions, resulting in a quantitative measure for the novelty of any given reaction. Daylight [21] and InfoChem [22] have developed widely applied computer-based descriptions of organic reactions that allow quantification of the similarity of chemical reactions.

In the context of MCRs the novelty of a reaction and the chemical backbone structures accessible from it can also be understood in terms of combining otherwise known reactions into a multicomponent assembly of starting materials that, via a domino process [23], yield a product. Although neither the individual reactions forming the MCR nor the product might be novel, in terms of creating a synthetically useful process we suggest that such MCRs should also be considered novel reactions as they create chemical innovation.

10.3 Unexpected Products Yield Novel MCRs

The number of individual reactions of a given reaction type that are currently performed and analyzed in parallel combinatorial chemistry approaches is much higher than in the past. Not surprisingly we often observe that some of the expected reaction products in a compound library are not formed since, for various reasons, the corresponding starting materials may not yield the desired product under the chosen reactions conditions. In other cases unexpected reaction products may be formed.

In one prominent example such an unexpected reaction product was observed in three research laboratories independently. During attempts to synthesize a library of Ugi-type four-component products using various isonitriles, aldehydes, acids and amines the reaction did not gave the desired Ugi-type four-component reaction product when amino pyridine-like starting materials were used as the amine component. In the case of such 2-amino pyridine-type amines the clean formation of

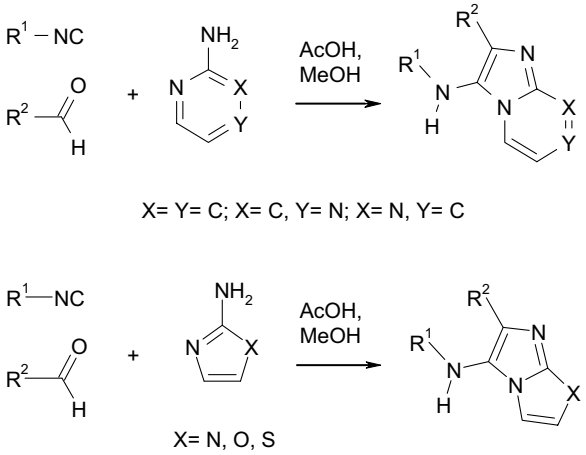


Scheme 10.1. A novel imidazo[1,2-*a*]pyridine synthesis found by chance.

imidazo[1,2-*a*]pyridines was found by a novel three-component reaction instead of the anticipated 4-CR product (Scheme 10.1) [24–27].

Compounds of this type were considered to be interesting for pharmaceutical research and previously could only be obtained over four sequential reaction steps.

After this primary observation the scope of this novel reaction was studied more extensively and found to give a range of similar hetero bicyclic products (Scheme 10.2).



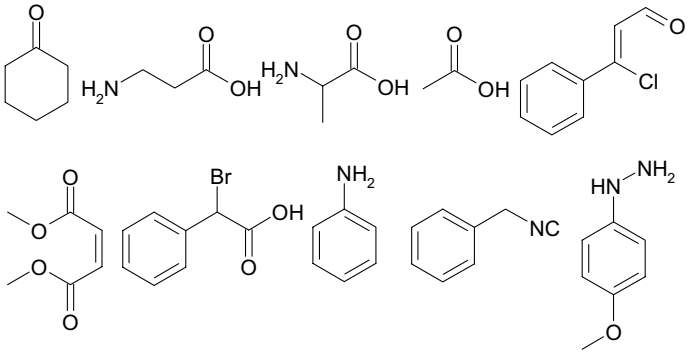
Scheme 10.2. The generalization of a novel imidazo[1,2-*a*]pyridine synthesis.

Acetic acid, the fourth component of the Ugi 4CR, is required as a catalyst. The in-depth evaluation of this new finding resulted in the extension of the [4+1] insertion reaction of isonitriles for a broad variety of aldehydes and five- and six-membered amines that contain an imino-amine substructure.

For example, amino-imidazoles and amino-thiazoles were also found to give a similar 3-CR product (Scheme 10.2). This experience inspired the idea of using combinatorial chemistry methods to find novel and unexpected reaction products and novel MCRs.

10.4
Experimental Designs to Search for New MCRs

The availability of high-performance and rapid analytical tools together with novel computational techniques that are able to analyze and abstract large volume of raw



Scheme 10.3. Ten starting materials used for a systematic search for novel reactions.

data has an impact on the way of how we can deal with reaction data. Thus, an alternative way to find new MCRs was introduced through the concept of combinatorial reaction finding [28].

Ten different starting materials were selected for this experiment as shown (Scheme 10.3).

All possible multicomponent reactions were carried out by the combinatorial variation of between two and ten starting materials (2-CR to 10-CR) in parallel in methanol at room temperature and using a robotic dispensing system. With the aid of automated liquid chromatography and data evaluation, products were searched that are unique to a specific mixtures by comparing the retention times with the starting materials and over all other mixtures that contain the respective sub-combinations. Thus, for example, a novel product of a four-component reaction should not be contained in all three possible 3-CR mixtures.

Overall there are $2^n - n - 1 = 1013$ variations of different two-, three-, four- up to the only one possible ten-component reaction mixture. From these 1013 different combinations of starting materials, several gave the expected and known MCR products. Using a minimum peak height requirement of 30% (compared to the sum of all peaks in the respective LC chromatogram) for a novel and unknown reaction product, unique MCR products were found. For example, the expected Ugi 4-CR product was "re-found" by this systematic search method (Figure 10.1).

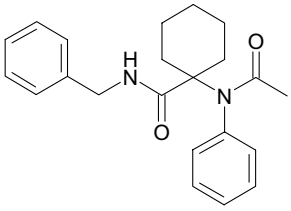
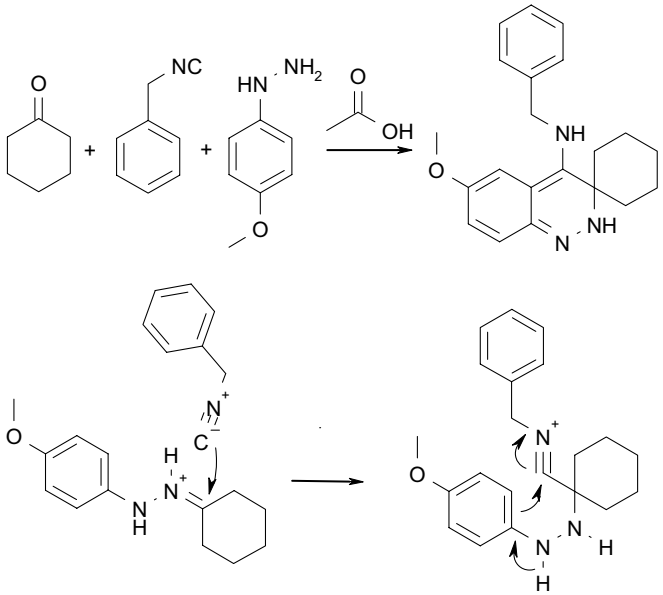


Fig. 10.1. Using the systematic variation of 10 starting materials, the Ugi four-component reaction product was "re-discovered".



Scheme 10.4. A novel three-component reaction found by the systematic variation of 10 starting materials.

However, in the reaction of cyclohexanone, benzylisonitrile, 4-methoxy-phenylhydrazine and acetic acid a dihydro-cinnoline was formed by a novel MCR (Scheme 10.4).

This reaction appears to be similar to the imidazo-pyridine formation mentioned above, most likely via a [5+1] insertion reaction of the isocyanide into the corresponding hydrazone. This reaction mechanism seems likely since only electron-rich aromatic hydrazines yielded cinnolines. The Ugi 4-CR reaction with phenylhydrazine is known and has been reported to give the expected Ugi-type 4-CR product.

Combinatorial chemistry is aiming at the generation of diverse compounds, which is achieved normally by using starting materials that cover a broad range of structural patterns and stereoelectronic properties, e.g. aromatic and aliphatic, electron-rich and -deficient amines. From the viewpoint of organic chemistry this combinatorial variation of starting materials is nothing other than the systematic investigation of the breadth and scope of the used reaction. The collected data can therefore provide a valuable tool to investigate the structure–reactivity relationship for that particular reaction and yield additional insights into the electronic and steric requirements of the underlying reaction mechanism – and in addition might yield new MCRs.

Thus, in a second example [29], we investigated the known Doebner three-component reaction using various aromatic amines, aldehydes and α-keto acids. While the reaction is known in textbooks to give quinolines, we found a rather

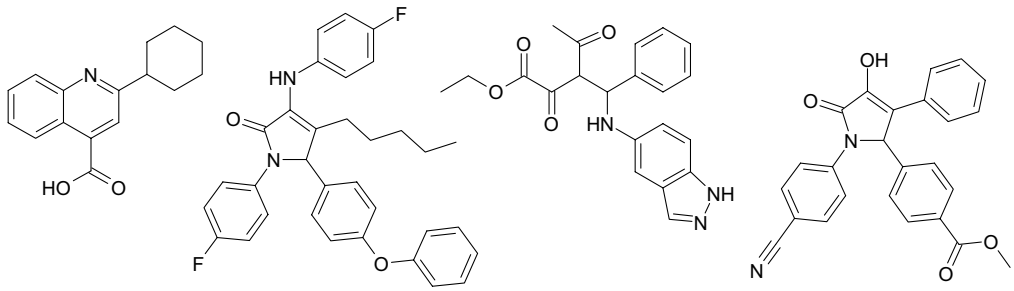


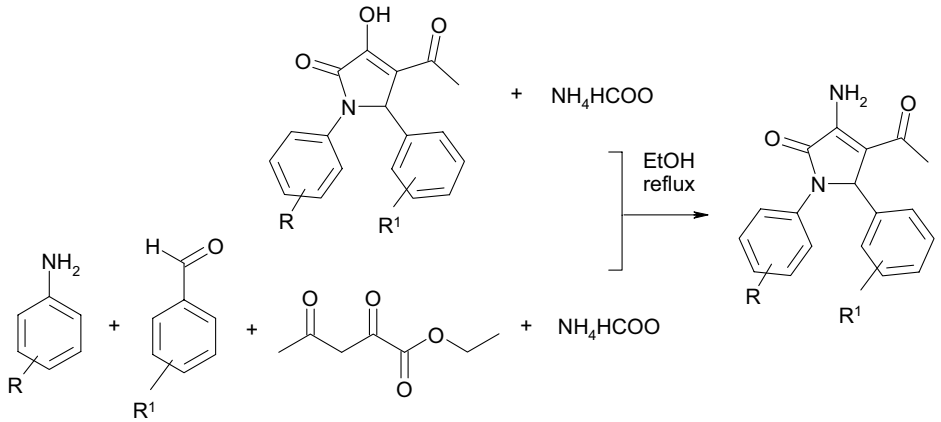
Fig. 10.2. Four different chemical scaffolds available through the Doebner MCR reaction.

broad spectrum of different reaction products depending on the nature of the corresponding starting materials. For the combinatorial reaction matrix, four aldehydes, four amines and four α-keto-carboxylic acids were used. From the $4 \times 4 \times 4 = 64$ different possible combinations of the respective starting materials, four different chemical scaffolds can be obtained by the Doebner MCR, depending on the starting materials used (Figure 10.2).

In some cases the formation of a four-component reaction product was observed where the amine was involved twice. By using ammonium acetate and an amine, a novel four-component reaction could be developed based on this finding (Scheme 10.5).

While the individual scaffolds are not new, this combinatorial evaluation of the Doebner reaction yielded a deeper and more complete understanding of this MCR and the dependence of the expected products on the structure of the used starting materials was evaluated in a very short time.

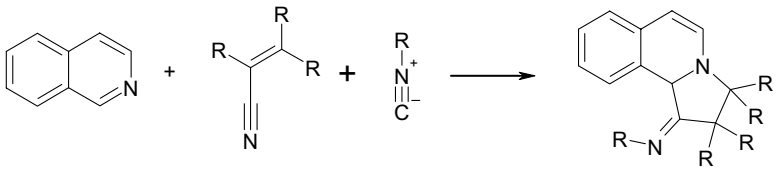
To carry out this parallel combinatorial approach towards the evaluation of organic reactions the automated analysis and structure elucidation of a large number



Scheme 10.5. Rational modification of the classical Doebner reaction yielded a novel four-component reaction.

of reaction products is necessary. The application of high-throughput MS and LC-MS-NMR allows generation of the necessary input data. Novel expert tools, used for the automatic evaluation, structure assignment and interpretation of these analytical data have been developed. Thus, the starting materials and the analytical data of the corresponding product are submitted to an ''artificial chemist'' – a suite of software tools based on the Daylight toolkit. Using a database of possible generic reactions a series of possible products is generated and looked up in the analytical data set [30].

In a recent example, Mironov used the rational replacement of starting materials for oligomerization reactions to discover new MCRs in a systematic way [31]. A reaction library of six alkenes/alkynes, two isonitriles, two nitriles and isoquinoline was set up, giving $(n^2 - n)/2$ different reactions products. A minimum peak height of 30% of the total reaction product was used as a criterion for identifying an efficient MCR. In this way, a novel MCR that yields pyrrolo[2,1-*a*]isoquinolin-1-ones from electron-deficient olefins, isonitriles and isoquinoline was found (Scheme 10.6).



Scheme 10.6. Systematic search for novel MCRs using the concept of replacing starting materials for oligomerization reactions.

This example clearly shows that introducing the concept of ''down-sizing'' polymerization reactions sequences can give useful novel MCRs.

10.5 Computational Methods of Finding Novel MCRs

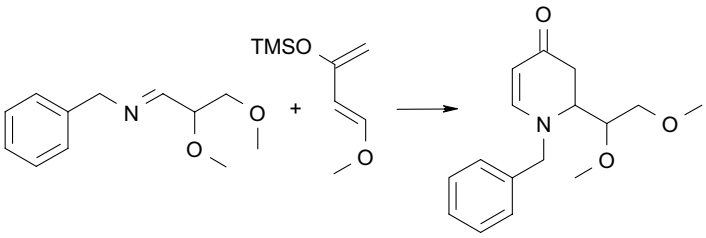
MCR construction guidelines can in principle be automated by using suitable computational reaction database-searching techniques. The first step in such an implementation is to derive from the pool of available reaction data ''reaction prototypes'' that describe both the reacting centers (atoms) as well as those neighbor atoms that have a marked influence on the reactivity of the reacting centers.For example, an azomethine formation using a primary amine and an aldehyde can be described as follows in the Daylight SMIRKS-notation [21]:

[C,c,#1:60][C:1](=[O:2])[C,c,#1:61].[C,c,#1:62][N:3]([#1:11])[#1:12]

$\gg$ [C,c,#1:60][C:1](=[N:3][C,c,#1:62])[C,c,#1:61].[O:2]([#1:11])[#1:12]

In the second step, the right part (the reaction product [C,c,#1:60][C:1](= [N:3] · [C,c,#1:62])[C,c,#1:61]) of this first equation may be used as a starting material in a second, subsequent reaction substructure search over a reaction database. Any reaction found should involve an additional starting material that is then checked to see whether it also undergoes an irreversible reaction with one of the original starting materials. If not, we may have found a candidate for a new MCR. This method may be viewed as a knowledge-based combinatorial search to find MCRs using known chemical reactions described in a reaction database – a task that is best accomplished by a computer.

For the described strategy, and using a program based on the Daylight reaction toolkit program suite, such a newly proposed reaction is given below. Initially starting from an aldehyde and an amine a Schiff base is formed, for which an ''orthogonal'' reaction with a 1,3-diene is described (Scheme 10.7).



Scheme 10.7. Systematic search for novel MCRs by using the Daylight reaction toolkit on a reaction database.

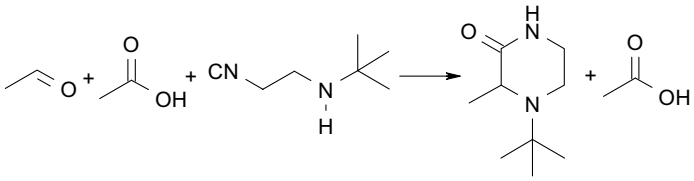
This reported hetero Diels–Alder reaction [32] is catalyzed by Lewis acids and is likely to work also when performed as a 3CR instead of isolating the azomethine and reacting it in a sequential way.

Similarly, the reaction of alkenyl boronic acids with azomethines can be found. Indeed, the corresponding 3-CR was used by Petasis [33] for the enantioselective synthesis of α-amino acids starting from amines, α-keto acids and alkenyl boronic acids.

In a different implementation, one may enter a set of starting materials into the program that has a list of known ''prototypic'' reactions as a knowledge base. The program then constructs all possible products by applying the prototypes in iterative cycles. Sometimes the results are surprising or unexpected as shown for a novel synthesis of a piperazinone that was proposed by the Daylight reaction toolkit using a knowledge base of simple organic transformations (Scheme 10.8).

The formation of this novel reaction product could be shown by the experiment *a posteriori*, thus representing an example of a computationally described novel MCR that has subsequently been validated in the laboratory.

However, the validity of such computer-proposed MCR reactions has always to be verified by experiment. Since such examples are scarce it cannot be judged how efficient this approach will be in suggesting useful MCRs.



Scheme 10.8. The application of a chemistry reaction knowledge base, using the Daylight reaction toolkit, provides new proposals for novel scaffolds.

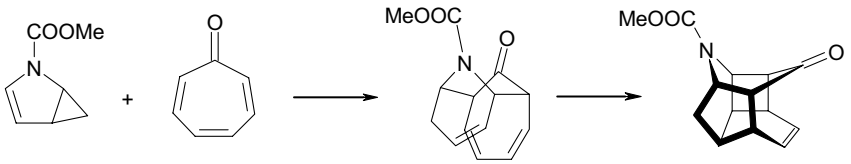
The outcome and use of this computational approach also depends on how many reactions are used and how exact the underlying reaction "prototypes" are. The conversion of the abundant knowledge on reaction data into such more abstract prototype reactions requires immense work and can only be automated to a limited degree.

The computational discovery of novel MCRs that are novel both from the product as well as from the mechanistic point of view is still an area in its infancy. The first, and to our knowledge only, example of such an approach was delivered by Ugi's group in 1988. Here [34], the computer program IGOR 2 (Interactive Generation of Organic Reactions) was used to propose a unique chemical transformation using a tropantrienone and a pyrrolin derivative to yield a tricyclic product. When the reaction was subsequently performed in the laboratory, a cage-like molecule was obtained, which can be considered a follow-up product of the "computer-planned" tricyclic compound (Scheme 10.9).

Thus, although not leading to the desired product and not being an MCR, the reaction suggested by the computational approach has certainly delivered novelty. It remains to be seen whether computer-based reaction design will become more widely used when the understanding of chemical reactions can be more tightly connected with knowledge databases and appropriate reaction descriptions.

10.6 Combinatorial Optimization of Reaction Conditions

Since a given MCR comprises a set of different reactions requiring different reaction conditions, finding optimal conditions for MCRs poses a more demanding problem than do single-step reactions. The problem of finding optimal catalysts, solvent or solvent mixtures, temperatures, concentrations of the starting materials



Scheme 10.9. IGOR 2 proposes a novel reaction that is distinct from all other known reactions.

and reaction time is a combinatorial problem by itself. Combinatorial methods in combination with experimental design methods such as genetic algorithms can be used to find optimal reaction conditions for these MCRs. Thus, a set of different parallel reaction conditions can be used to carry out one particular MCR.

The yield of the expected reaction product was used in an example as the feedback to a genetic algorithm (GA) driven method that proposes a new set of reaction conditions. After some cycles of synthesis and analysis the yield of this reaction was significantly improved by using better reaction conditions. In a second step, a set of different MCRs using a set of different conditions for each of them was carried out in parallel and optimized with a GA to find common optimal conditions [29].

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10
Algorithm-based Methods for the Discovery of Novel Multicomponent Reactions

Lutz Weber

10.1
Introduction

Combinatorial chemistry has become a tool of organic chemists to speed up the search for biologically active molecules in the pharmaceutical industry, to find new agrochemicals, catalysts, polymers and other new materials with desired properties. Basically, combinatorial chemistry is an experimental design to find the combination of possible substituents of a given chemical backbone type that will exhibit the desired properties. Combinatorial synthesis has therefore induced a demand for novel synthetic methods that yield novel chemical skeletons. Multicomponent reactions (MCRs), in which more than two starting materials participate in the reaction and contribute the majority of the skeleton of the product, are regarded as especially interesting in meeting these demands. MCRs bear with the promise of novelty in terms of process and compound-related intellectual property. They also enable automation in synthesis, analytics and evaluation of the physicochemical or biological properties of resulting reaction products. Therefore, the discovery of new MCRs extends the power of combinatorial chemistry and is an interesting challenge for research in organic chemistry. Taking these considerations together, the discovery of novel multicomponent reactions can be considered as an interesting topic for academic research that also satisfies a practical interest of applied sciences.

Despite this interest, new reaction types in organic chemistry have been more usually found by chance than by rational design or logical consideration. In this chapter we emphasize that, although they are rarely used, there are both rational and, in particular, algorithm-based methods to discover novel multicomponent reactions.

10.2
A Definition – What Are Novel MCRs

To begin with, it might be useful to define in general what a ''new'' reaction is. There are several methods available that are used to classify chemical reactions.

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The most ancient classification considers whether a certain compound class or chemical scaffold is being formed with success under given reaction conditions – often described by the name of the chemist who discovered or made major contributions to this reactions. Between 700 and 900 such named reactions are known [1]. This classification is mostly product based, but can be connected in certain cases to specific starting materials, e.g. the nitrosamine rearrangement.

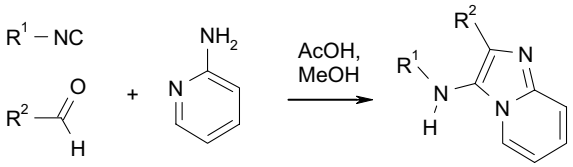
Mechanism-based classifications became popular with the advent of an understanding of the principles and mechanisms of organic reactions in the first half of the twentieth century. Subsequently, and especially in the years 1960–1980, reactions were classified according to the topology of atoms, electrons and bonds in the starting materials and products. This provided the basis for the introduction of computer-based methods that allowed the building and searching of databases of chemical reactions [2]. The ''computerization'' of reaction mechanisms is connected, to the names of Wipke [3–5], Hendrickson [6–9], Ugi [10–13] and others [14–20]. Using the concepts of chemical similarity, one easily can use these computer-based reaction descriptions to quantify the similarity between different reactions, resulting in a quantitative measure for the novelty of any given reaction. Daylight [21] and InfoChem [22] have developed widely applied computer-based descriptions of organic reactions that allow quantification of the similarity of chemical reactions.

In the context of MCRs the novelty of a reaction and the chemical backbone structures accessible from it can also be understood in terms of combining otherwise known reactions into a multicomponent assembly of starting materials that, via a domino process [23], yield a product. Although neither the individual reactions forming the MCR nor the product might be novel, in terms of creating a synthetically useful process we suggest that such MCRs should also be considered novel reactions as they create chemical innovation.

10.3 Unexpected Products Yield Novel MCRs

The number of individual reactions of a given reaction type that are currently performed and analyzed in parallel combinatorial chemistry approaches is much higher than in the past. Not surprisingly we often observe that some of the expected reaction products in a compound library are not formed since, for various reasons, the corresponding starting materials may not yield the desired product under the chosen reactions conditions. In other cases unexpected reaction products may be formed.

In one prominent example such an unexpected reaction product was observed in three research laboratories independently. During attempts to synthesize a library of Ugi-type four-component products using various isonitriles, aldehydes, acids and amines the reaction did not gave the desired Ugi-type four-component reaction product when amino pyridine-like starting materials were used as the amine component. In the case of such 2-amino pyridine-type amines the clean formation of

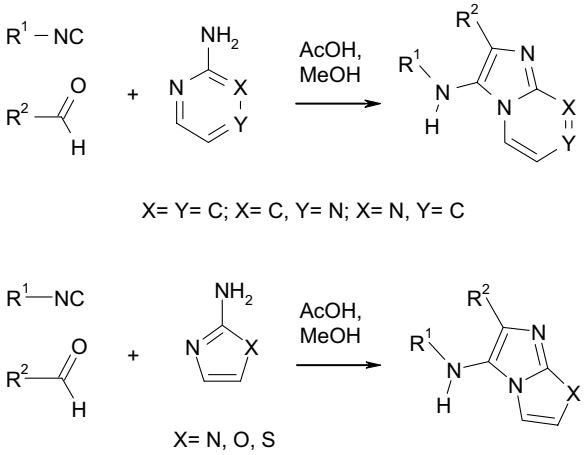


Scheme 10.1. A novel imidazo[1,2-*a*]pyridine synthesis found by chance.

imidazo[1,2-*a*]pyridines was found by a novel three-component reaction instead of the anticipated 4-CR product (Scheme 10.1) [24–27].

Compounds of this type were considered to be interesting for pharmaceutical research and previously could only be obtained over four sequential reaction steps.

After this primary observation the scope of this novel reaction was studied more extensively and found to give a range of similar hetero bicyclic products (Scheme 10.2).



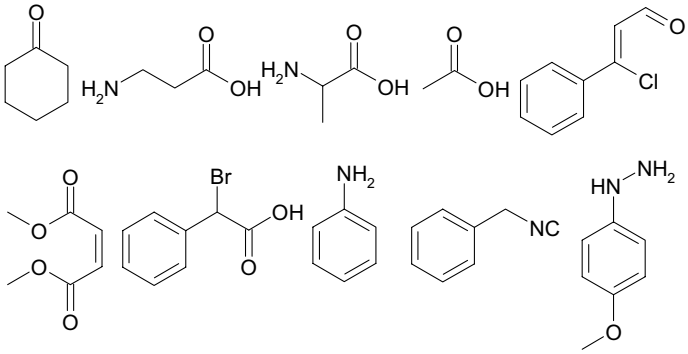
Scheme 10.2. The generalization of a novel imidazo[1,2-*a*]pyridine synthesis.

Acetic acid, the fourth component of the Ugi 4CR, is required as a catalyst. The in-depth evaluation of this new finding resulted in the extension of the [4+1] insertion reaction of isonitriles for a broad variety of aldehydes and five- and six-membered amines that contain an imino-amine substructure.

For example, amino-imidazoles and amino-thiazoles were also found to give a similar 3-CR product (Scheme 10.2). This experience inspired the idea of using combinatorial chemistry methods to find novel and unexpected reaction products and novel MCRs.

10.4
Experimental Designs to Search for New MCRs

The availability of high-performance and rapid analytical tools together with novel computational techniques that are able to analyze and abstract large volume of raw



Scheme 10.3. Ten starting materials used for a systematic search for novel reactions.

data has an impact on the way of how we can deal with reaction data. Thus, an alternative way to find new MCRs was introduced through the concept of combinatorial reaction finding [28].

Ten different starting materials were selected for this experiment as shown (Scheme 10.3).

All possible multicomponent reactions were carried out by the combinatorial variation of between two and ten starting materials (2-CR to 10-CR) in parallel in methanol at room temperature and using a robotic dispensing system. With the aid of automated liquid chromatography and data evaluation, products were searched that are unique to a specific mixtures by comparing the retention times with the starting materials and over all other mixtures that contain the respective sub-combinations. Thus, for example, a novel product of a four-component reaction should not be contained in all three possible 3-CR mixtures.

Overall there are $2^n - n - 1 = 1013$ variations of different two-, three-, four- up to the only one possible ten-component reaction mixture. From these 1013 different combinations of starting materials, several gave the expected and known MCR products. Using a minimum peak height requirement of 30% (compared to the sum of all peaks in the respective LC chromatogram) for a novel and unknown reaction product, unique MCR products were found. For example, the expected Ugi 4-CR product was "re-found" by this systematic search method (Figure 10.1).

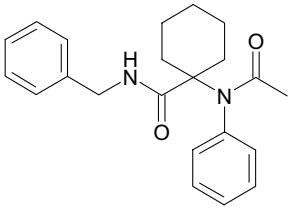
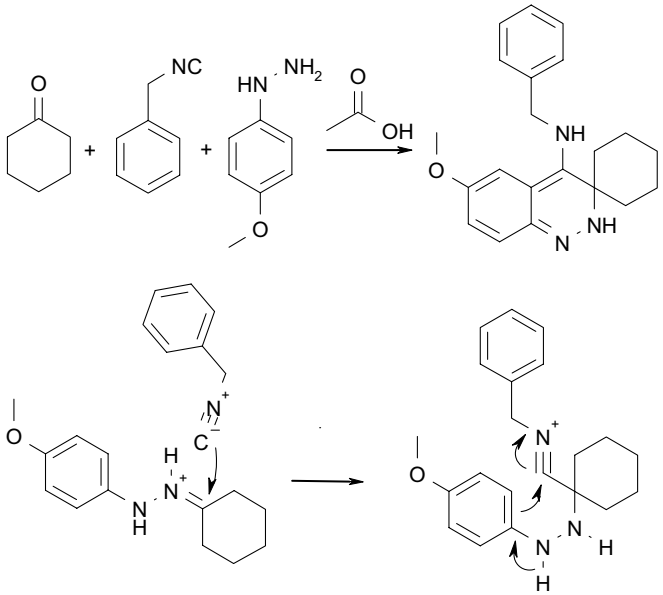


Fig. 10.1. Using the systematic variation of 10 starting materials, the Ugi four-component reaction product was "re-discovered".



Scheme 10.4. A novel three-component reaction found by the systematic variation of 10 starting materials.

However, in the reaction of cyclohexanone, benzylisonitrile, 4-methoxy-phenylhydrazine and acetic acid a dihydro-cinnoline was formed by a novel MCR (Scheme 10.4).

This reaction appears to be similar to the imidazo-pyridine formation mentioned above, most likely via a [5+1] insertion reaction of the isocyanide into the corresponding hydrazone. This reaction mechanism seems likely since only electron-rich aromatic hydrazines yielded cinnolines. The Ugi 4-CR reaction with phenylhydrazine is known and has been reported to give the expected Ugi-type 4-CR product.

Combinatorial chemistry is aiming at the generation of diverse compounds, which is achieved normally by using starting materials that cover a broad range of structural patterns and stereoelectronic properties, e.g. aromatic and aliphatic, electron-rich and -deficient amines. From the viewpoint of organic chemistry this combinatorial variation of starting materials is nothing other than the systematic investigation of the breadth and scope of the used reaction. The collected data can therefore provide a valuable tool to investigate the structure–reactivity relationship for that particular reaction and yield additional insights into the electronic and steric requirements of the underlying reaction mechanism – and in addition might yield new MCRs.

Thus, in a second example [29], we investigated the known Doebner three-component reaction using various aromatic amines, aldehydes and α-keto acids. While the reaction is known in textbooks to give quinolines, we found a rather

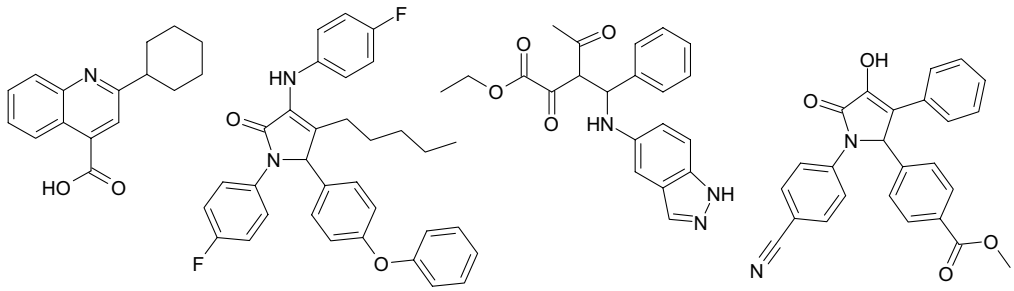


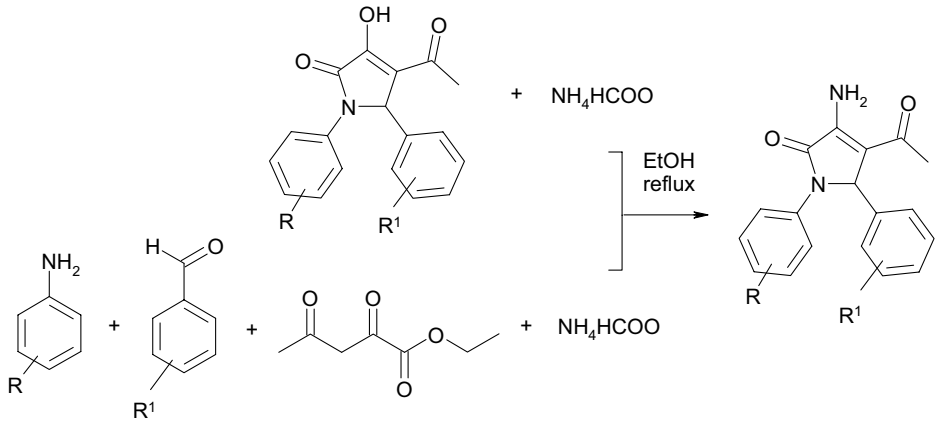
Fig. 10.2. Four different chemical scaffolds available through the Doebner MCR reaction.

broad spectrum of different reaction products depending on the nature of the corresponding starting materials. For the combinatorial reaction matrix, four aldehydes, four amines and four α-keto-carboxylic acids were used. From the $4 \times 4 \times 4 = 64$ different possible combinations of the respective starting materials, four different chemical scaffolds can be obtained by the Doebner MCR, depending on the starting materials used (Figure 10.2).

In some cases the formation of a four-component reaction product was observed where the amine was involved twice. By using ammonium acetate and an amine, a novel four-component reaction could be developed based on this finding (Scheme 10.5).

While the individual scaffolds are not new, this combinatorial evaluation of the Doebner reaction yielded a deeper and more complete understanding of this MCR and the dependence of the expected products on the structure of the used starting materials was evaluated in a very short time.

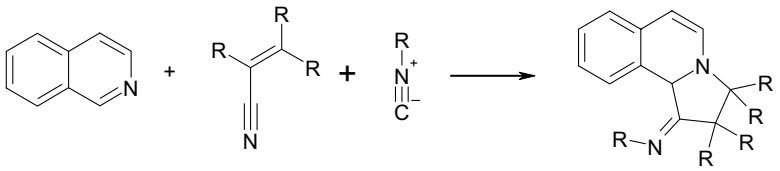
To carry out this parallel combinatorial approach towards the evaluation of organic reactions the automated analysis and structure elucidation of a large number



Scheme 10.5. Rational modification of the classical Doebner reaction yielded a novel four-component reaction.

of reaction products is necessary. The application of high-throughput MS and LC-MS-NMR allows generation of the necessary input data. Novel expert tools, used for the automatic evaluation, structure assignment and interpretation of these analytical data have been developed. Thus, the starting materials and the analytical data of the corresponding product are submitted to an ''artificial chemist'' – a suite of software tools based on the Daylight toolkit. Using a database of possible generic reactions a series of possible products is generated and looked up in the analytical data set [30].

In a recent example, Mironov used the rational replacement of starting materials for oligomerization reactions to discover new MCRs in a systematic way [31]. A reaction library of six alkenes/alkynes, two isonitriles, two nitriles and isoquinoline was set up, giving $(n^2 - n)/2$ different reactions products. A minimum peak height of 30% of the total reaction product was used as a criterion for identifying an efficient MCR. In this way, a novel MCR that yields pyrrolo[2,1-*a*]isoquinolin-1-ones from electron-deficient olefins, isonitriles and isoquinoline was found (Scheme 10.6).



Scheme 10.6. Systematic search for novel MCRs using the concept of replacing starting materials for oligomerization reactions.

This example clearly shows that introducing the concept of ''down-sizing'' polymerization reactions sequences can give useful novel MCRs.

10.5 Computational Methods of Finding Novel MCRs

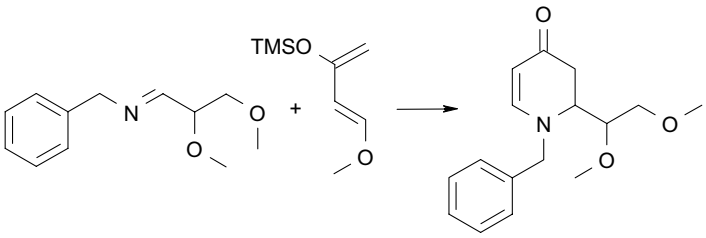
MCR construction guidelines can in principle be automated by using suitable computational reaction database-searching techniques. The first step in such an implementation is to derive from the pool of available reaction data ''reaction prototypes'' that describe both the reacting centers (atoms) as well as those neighbor atoms that have a marked influence on the reactivity of the reacting centers.For example, an azomethine formation using a primary amine and an aldehyde can be described as follows in the Daylight SMIRKS-notation [21]:

[C,c,#1:60][C:1](=[O:2])[C,c,#1:61].[C,c,#1:62][N:3]([#1:11])[#1:12]

$\gg$ [C,c,#1:60][C:1](=[N:3][C,c,#1:62])[C,c,#1:61].[O:2]([#1:11])[#1:12]

In the second step, the right part (the reaction product [C,c,#1:60][C:1](= [N:3] · [C,c,#1:62])[C,c,#1:61]) of this first equation may be used as a starting material in a second, subsequent reaction substructure search over a reaction database. Any reaction found should involve an additional starting material that is then checked to see whether it also undergoes an irreversible reaction with one of the original starting materials. If not, we may have found a candidate for a new MCR. This method may be viewed as a knowledge-based combinatorial search to find MCRs using known chemical reactions described in a reaction database – a task that is best accomplished by a computer.

For the described strategy, and using a program based on the Daylight reaction toolkit program suite, such a newly proposed reaction is given below. Initially starting from an aldehyde and an amine a Schiff base is formed, for which an ''orthogonal'' reaction with a 1,3-diene is described (Scheme 10.7).



Scheme 10.7. Systematic search for novel MCRs by using the Daylight reaction toolkit on a reaction database.

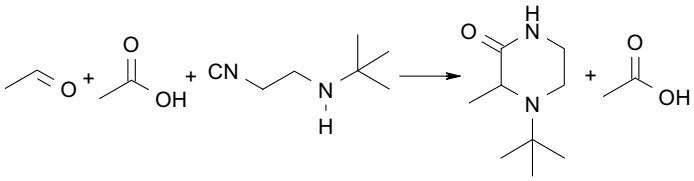
This reported hetero Diels–Alder reaction [32] is catalyzed by Lewis acids and is likely to work also when performed as a 3CR instead of isolating the azomethine and reacting it in a sequential way.

Similarly, the reaction of alkenyl boronic acids with azomethines can be found. Indeed, the corresponding 3-CR was used by Petasis [33] for the enantioselective synthesis of α-amino acids starting from amines, α-keto acids and alkenyl boronic acids.

In a different implementation, one may enter a set of starting materials into the program that has a list of known ''prototypic'' reactions as a knowledge base. The program then constructs all possible products by applying the prototypes in iterative cycles. Sometimes the results are surprising or unexpected as shown for a novel synthesis of a piperazinone that was proposed by the Daylight reaction toolkit using a knowledge base of simple organic transformations (Scheme 10.8).

The formation of this novel reaction product could be shown by the experiment *a posteriori*, thus representing an example of a computationally described novel MCR that has subsequently been validated in the laboratory.

However, the validity of such computer-proposed MCR reactions has always to be verified by experiment. Since such examples are scarce it cannot be judged how efficient this approach will be in suggesting useful MCRs.



Scheme 10.8. The application of a chemistry reaction knowledge base, using the Daylight reaction toolkit, provides new proposals for novel scaffolds.

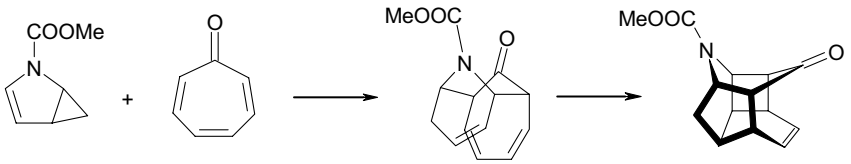
The outcome and use of this computational approach also depends on how many reactions are used and how exact the underlying reaction "prototypes" are. The conversion of the abundant knowledge on reaction data into such more abstract prototype reactions requires immense work and can only be automated to a limited degree.

The computational discovery of novel MCRs that are novel both from the product as well as from the mechanistic point of view is still an area in its infancy. The first, and to our knowledge only, example of such an approach was delivered by Ugi's group in 1988. Here [34], the computer program IGOR 2 (Interactive Generation of Organic Reactions) was used to propose a unique chemical transformation using a tropantrienone and a pyrrolin derivative to yield a tricyclic product. When the reaction was subsequently performed in the laboratory, a cage-like molecule was obtained, which can be considered a follow-up product of the "computer-planned" tricyclic compound (Scheme 10.9).

Thus, although not leading to the desired product and not being an MCR, the reaction suggested by the computational approach has certainly delivered novelty. It remains to be seen whether computer-based reaction design will become more widely used when the understanding of chemical reactions can be more tightly connected with knowledge databases and appropriate reaction descriptions.

10.6 Combinatorial Optimization of Reaction Conditions

Since a given MCR comprises a set of different reactions requiring different reaction conditions, finding optimal conditions for MCRs poses a more demanding problem than do single-step reactions. The problem of finding optimal catalysts, solvent or solvent mixtures, temperatures, concentrations of the starting materials



Scheme 10.9. IGOR 2 proposes a novel reaction that is distinct from all other known reactions.

and reaction time is a combinatorial problem by itself. Combinatorial methods in combination with experimental design methods such as genetic algorithms can be used to find optimal reaction conditions for these MCRs. Thus, a set of different parallel reaction conditions can be used to carry out one particular MCR.

The yield of the expected reaction product was used in an example as the feedback to a genetic algorithm (GA) driven method that proposes a new set of reaction conditions. After some cycles of synthesis and analysis the yield of this reaction was significantly improved by using better reaction conditions. In a second step, a set of different MCRs using a set of different conditions for each of them was carried out in parallel and optimized with a GA to find common optimal conditions [29].

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12
Multicomponent Reactions in the Total Synthesis of Natural Products

Barry B. Touré and Dennis G. Hall

12.1
Introduction

The synthesis of urea by Wöhler laid the foundation of the field of target-oriented organic synthesis [1]. Since then, significant progress has been achieved in this discipline; many powerful individual bond-forming reactions and asymmetric variants thereof have been developed. These discoveries have paved the way to the stereoselective assembly of complex organic molecules, a task deemed inconceivable by early practitioners. These successes, however, pale in comparison to the efficiency of nature, which, served by million of years of evolution, continues to inspire and challenge the synthetic community in their quest for better medicines and improved materials. A great many strategies were invented by chemists in order to facilitate the synthesis of complex natural products [2]. One avenue in emulating nature's efficiency would consist in merging compatible single bond-forming processes so as to allow multiple bond-formation processes between several substrates, a concept named multicomponent reactions (MCRs).

In the context of this chapter, MCRs are broadly defined, regardless of their mechanistic nature, as ''one-pot'' processes that combine three or more substrates either simultaneously (so called ''tandem'' or ''domino'' reactions [3]), or through a sequential addition procedure that does not require any change of solvent. By saving synthetic operations while maximizing the build-up of structural and functional complexity, these highly step-economical reactions are particularly appealing in the context of target-oriented synthesis. Although these advantages were demonstrated by Robinson as early as 1917, with the efficient one-step synthesis of the bridged bicyclic alkaloid tropinone **1** (Scheme 12.1) [4], multicomponent reaction strategies have remained under exploited for many decades. This chapter provides a review of the applications of MCRs in the total synthesis of natural products reported since the early 1970s. We have attempted to cover the literature in a comprehensive fashion, and to include all studies that featured an MCR as a key step in the synthesis of a natural product, or a very advanced intermediate. Owing to the limitations of literature database searches based on keywords, we may have overlooked reports that did not disclose such reactions as being ''three-component''

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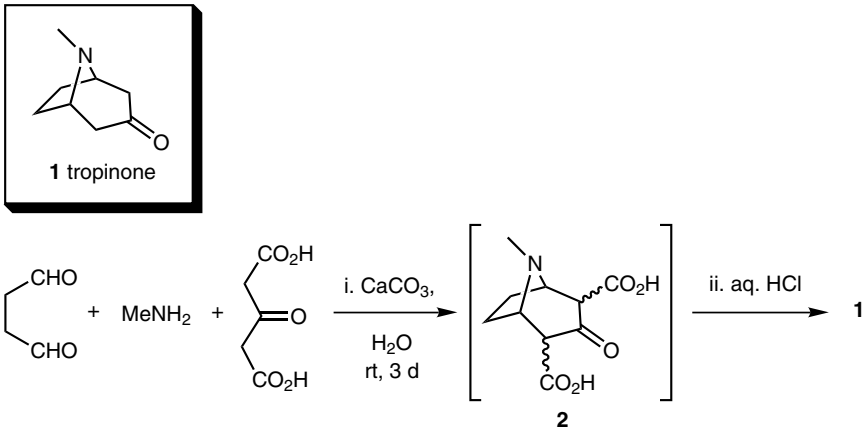


Scheme 12.1. Racemic synthesis of tropinone using a double Mannich 3CR, by Robinson [4].

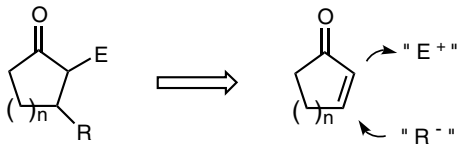
or "multicomponent". Similarly, we have not included most three-component reactions where one of the components is carbon monoxide (e.g. intermolecular Pauson–Khand reactions, or carbonylative cross-couplings). The contents are divided into classes of natural products targeted, and the legend at the bottom of each Scheme describes the key multicomponent reaction employed in reaching the target.

12.2
Cyclopentane-containing Natural Products

12.2.1
Prostanoids

Prostanoids have long captivated scientists for their complex structure and their crucial roles as local hormones in several physiological processes in mammals and other animals [5]. These powerful signaling molecules have significant potential therapeutic value. Thus, because they are produced in nature only in minute amounts, synthetic chemists have devised several strategies with a view to providing practical, large-scale access to the prostaglandins and unnatural analogues thereof [6]. For more than two decades, the Noyori three-component strategy has been one of the most popular synthetic strategies to access *trans*-1-2-substituted cyclopentane systems related to prostaglandins and other cyclopentane-containing natural products. This direct, highly convergent three-component reaction strategy, shown in a conceptual way in Scheme 12.2, is based on tandem conjugate addition on a cyclic enone followed by electrophilic trapping of the resulting enolate [7].

Early efforts to turn this process into a practically feasible general strategy were moderately successful [8]. Although the conjugate addition of organocopper

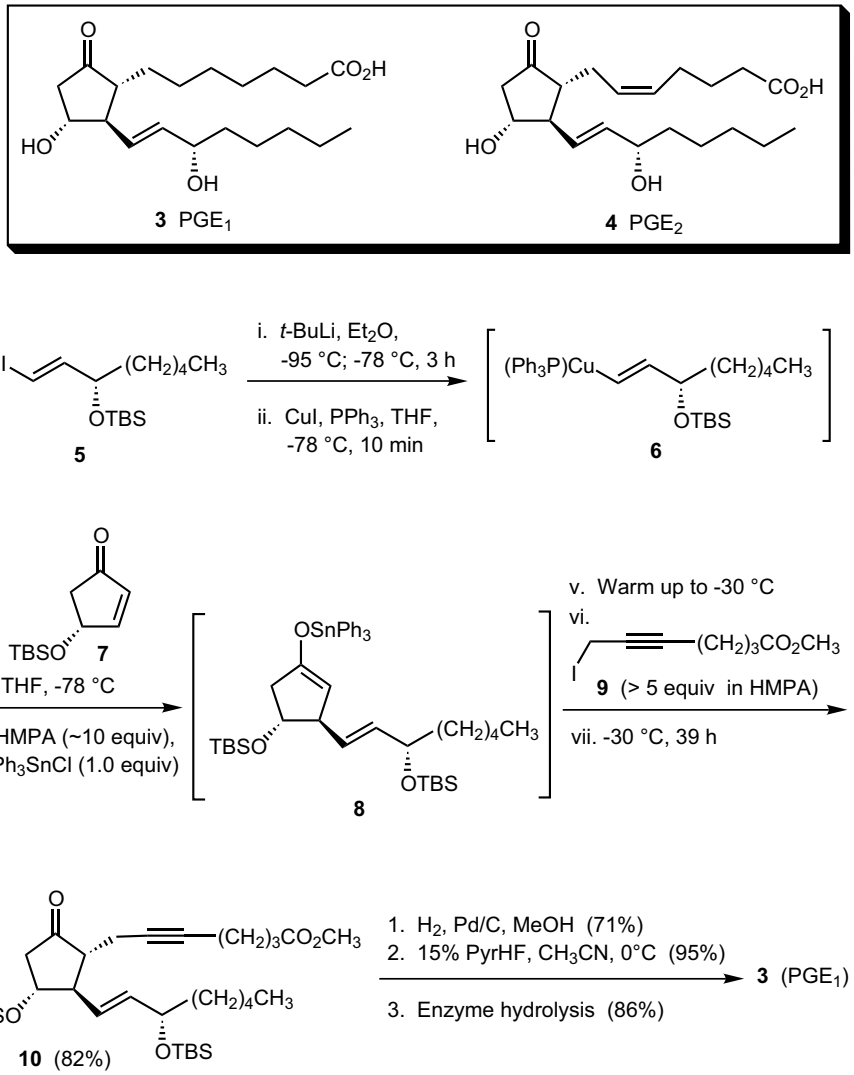


Scheme 12.2. Tandem conjugate addition/electrophilic trapping for the three-component synthesis of 1,2-disubstituted cycloalkanones.

reagents was found to proceed efficiently onto cyclopentenone derivatives, one-pot sequential trapping of the transient lithium enolate proved low-yielding, probably due in large part to enolate equilibration [9]. A method was sought by Noyori and co-workers that would allow *in situ* transmetallation of the Li/Cu enolate into a new, highly nucleophilic metal enolate with a weaker basic character. From this perspective, the use of tin enolates proved highly successful [10]. Thus, as exemplified for the synthesis of PGE_1 **3** (Scheme 12.3), slow and constant addition of enone **7** onto a solution containing the alkenylcopper(I)-triphenylphosphine complex **6** was followed by transmetallation with triphenyltin chloride to give tin enolate intermediate **8**. The reaction vessel was warmed to $-30\ ^{\circ}C$, and following the addition of propargyl iodide **9**, required in a large excess, compound **10** was isolated in 82% yield.

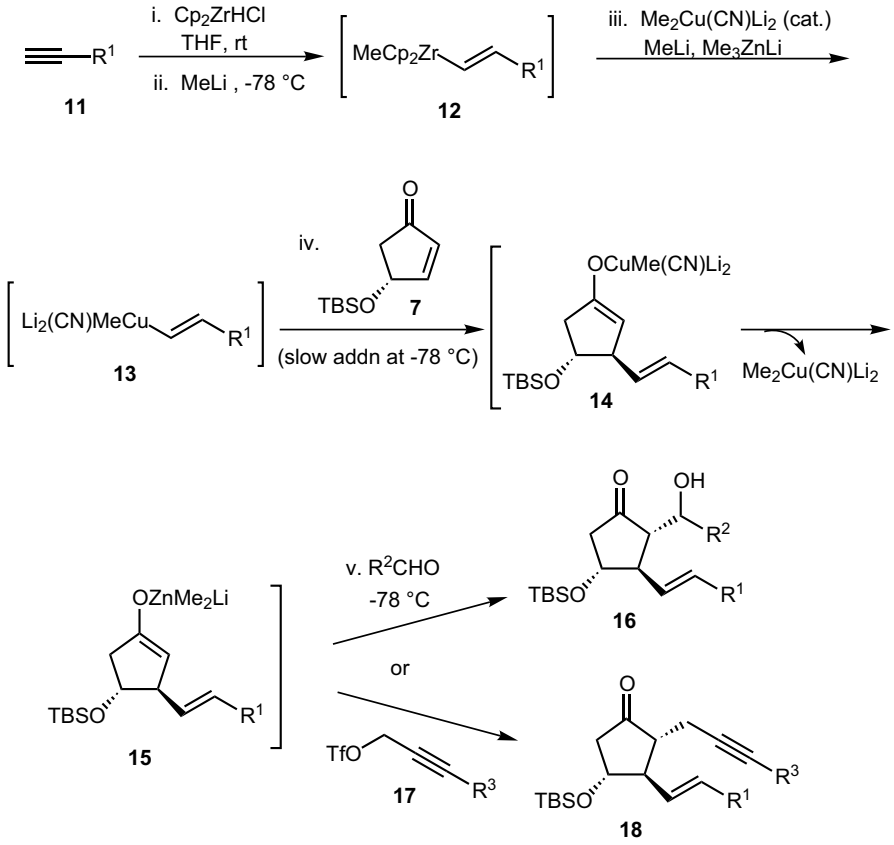
The efficiency of this process was even proven on a multigram scale, and the synthesis of PGE_1 was pursued first through a careful hydrogenation of **10** to leave the C13–C14 double bond intact. Desilylation and enzymatic hydrolysis [11] afforded PGE_1 **3** in only four steps from **7**. Partial hydrogenation of the alkyne, or alternatively the use of the corresponding (*Z*)-alkenyl iodide in the trapping operation, both afforded PGE_2 in high yield. The synthesis of prostacyclin PGI_2, a potent inhibitor of blood platelet aggregation, however, further demonstrated that the use of propargylic halides as electrophiles provides optimal flexibility for a general access to naturally occurring prostaglandins. Additionally, stereoselective reduction of the cyclopentanone also opened the doors to the synthesis of several other analogues of the D and F series. Noyori and co-workers subsequently developed and optimized a more environmentally benign (phosphine and HMPA-free) variant using triorganozinc reagents that allowed the process to occur through a highly reactive zinc enolate intermediate [12]. Yet, although these improvements expanded the range of compatible components, in practice only highly reactive electrophiles can be employed to assemble the α-side chain while minimizing undesirable enolate equilibration and competitive formation of side products. Although there was room for further improvements, these early reports of one-pot three-component reaction procedures to prostaglandin derivatives epitomized the enormous potential of multicomponent reactions as strategies in the synthesis of natural products.

Concerned with the need for an exhaustive multistep preparation of the required alkenylcopper or alkenylzinc intermediates, which are traditionally accessed from alkenyllithum precursors derived from alkynes, Lipshutz and Wood developed a



Scheme 12.3. Synthesis of prostaglandin E_1 using a three-component conjugate addition/enolate trapping on cyclopentenones, by Noyori and co-workers [10]. TBS = *t*-butyldimethylsilyl, THF = tetrahydrofuran, HMPA = hexamethylphosphoramide, Pyr = pyridine.

highly practical "single-flask" variant that bypassed the need for the intermediacy of an alkenyllithium intermediate and rather allowed the use of simple alkynes as precursors [13]. Previous work from this group showed that alkyne hydrozirconation can be followed by *in situ* transmetallation with a higher order cyanocuprate [14]. Based on this premise, Lipshutz and Wood rationalized that following the se-



Scheme 12.4. Multiple metal variant of the conjugate addition/enolate trapping 3CR on cyclopentenones, by Lipshutz and Wood [13]. THF = tetrahydrofuran, TBS = *t*-butyldimethylsilyl.

quential Zr-to-Cu transmetallation and the ensuing 1,4 addition onto the enone, the entire process could be made catalytic in copper by transmetallation of the resulting enolate with a suitable zincate reagent. In the event, the zincate reagent Me_3ZnLi was found to function extremely well in this multimetal transmetallation, as it does not compete for 1,4-addition with the higher order alkenylcuprate and it provides a putative zinc enolate of high reactivity towards carbon-based electrophiles. Thus, as shown in a general fashion in Scheme 12.4, room temperature hydrozirconation of alkyne **11** is followed by substitution of the Zr–Cl bond with methyllithium at −78 °C to give alkenylzirconocene **12**.

Transmetallation of **12** with a catalytic amount of the higher order cyanocuprate $Me_2Cu(CN)Li_2$, in the presence of Me_3ZnLi and with slow addition of enone **7** led first to the initial conjugate addition product **14**, then to zinc enolate **15** after Cu-to-Zn transmetallation. The third component, the electrophile, either an alde-

hyde or a propargyl triflate **17**, is then added at −78 °C to provide compounds **16** or **18**, respectively. Although no naturally occurring prostaglandins were formally synthesized using this impressive multimetal variant, **16** and **18** are a proven class of intermediates towards prostanoids.

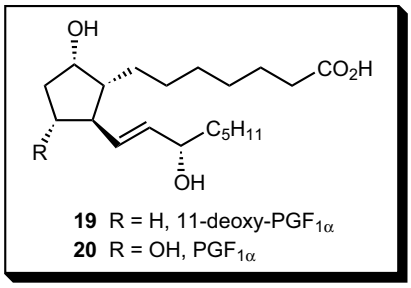
Several interesting variants of the Noyori three-component reaction strategy to prostaglandin natural products have been reported in the past five years. Only a representative selection of the most recent ones will be described.

Shibasaki and co-workers reported an elegant asymmetric total synthesis of 11-deoxy-$PGF_{1\alpha}$ **19** using the Al-Li bis(binaphthoxide) complex (ALB) **21** [15], a member of a novel class of heterobimetallic chiral catalysts showing dual behavior as both a Brønsted base and a Lewis acid (Scheme 12.5) [16].

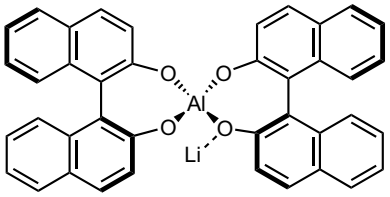
Thus, in a rare example of a catalytic enantioselective multicomponent reaction [17], a mixture of cyclopentanone, dibenzylmethylmalonate **23**, and aldehyde **22** were reacted in the presence of catalyst system (*S*)-ALB **21**/NaO-*t*-Bu (Eq. 1, Scheme 12.4). The tandem Michael/aldol addition product **24** was obtained exclusively as the trans disubstituted isomer, although as a mixture of diastereomeric secondary alcohols in 84% yield. The presence of a mixture is inconsequential as **24** was dehydrated to form alkene **25**. The enantioselectivity of the three-component reaction was assessed at this stage to be 92% *ee*. Following the enantioselective Michael addition step, this remarkable three-component reaction is thought to involve an aluminum enolate intermediate, and the latter was found to be sufficiently reactive to trap the aldehyde prior to protonation by the malonate. From the key intermediate **25**, the synthesis of 11-deoxy-$PGF_{1\alpha}$ **19** was completed in about eight steps. The same catalyst system was employed to operate a kinetic resolution on racemic cyclopentenone **7**, providing compound **26** in 97% *ee* [Eq. (2), Scheme 12.5]. The latter could serve as a useful intermediate to reach a variety of prostaglandin analogues including $PGF_{1\alpha}$.

Feringa and co-workers developed an efficient methodology for conjugate addition of dialkylzinc reagents to enones catalyzed by copper(II) and the remarkably versatile chiral monophosphoramidite ligand **27** (Scheme 12.6) [18].

Of all the different cycloalkenone ring sizes, cyclopentenones tend to give lower yields of the desired 1,4-addition products. When performed in the presence of an aldehyde to trap the zinc enolate and prevent side reactions, however, the yields increase. Hence, this methodology was extended to a one-pot tandem conjugate addition/aldol reaction, and it was successfully applied to a catalytic enantioselective total synthesis of PGE_1 methyl ester using a Noyori-type three-component reaction strategy [19]. The use of dialkenylzinc reagents and aliphatic aldehydes failed under these reaction conditions, thus the conceptually opposite stratagem was devised whereby the saturated side chain is introduced by conjugate addition and an unsaturated aldehyde is employed to trap the transient enolate. To avoid competitive conjugate addition on the enal, a temporary silicon group was used to hinder the 3-position on the aldehyde. Thus, by reacting cyclopenten-3,5-dione monoacetal **28** [20] with aldehyde **29** and reagent **30** under 3 mol% of the chiral copper catalyst made with ligand **27**, three-component coupling product **31** was obtained in 60% yield (in an 83:17 diastereomeric mixture at the exocyclic secondary alcohol,

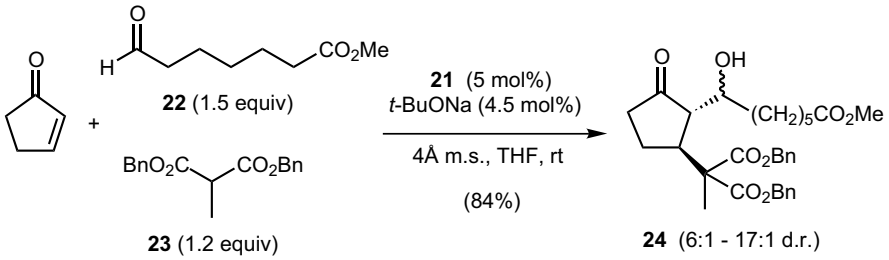


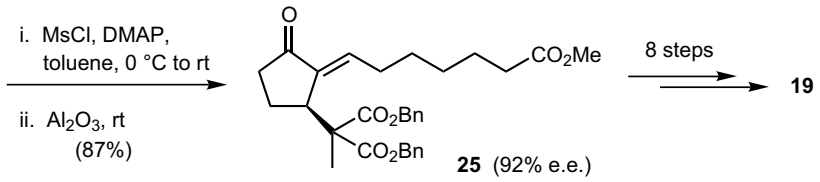
19 R = H, 11-deoxy-PGF$_{1\alpha}$
20 R = OH, PGF$_{1\alpha}$



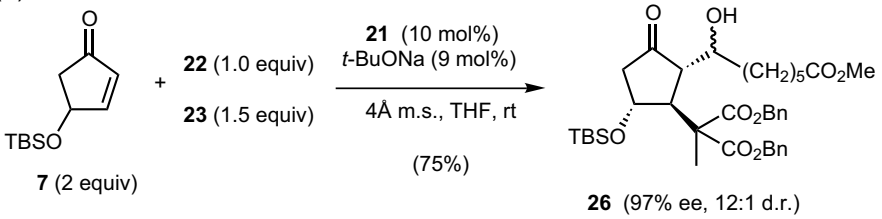
21 (*S*)-ALB

(1)



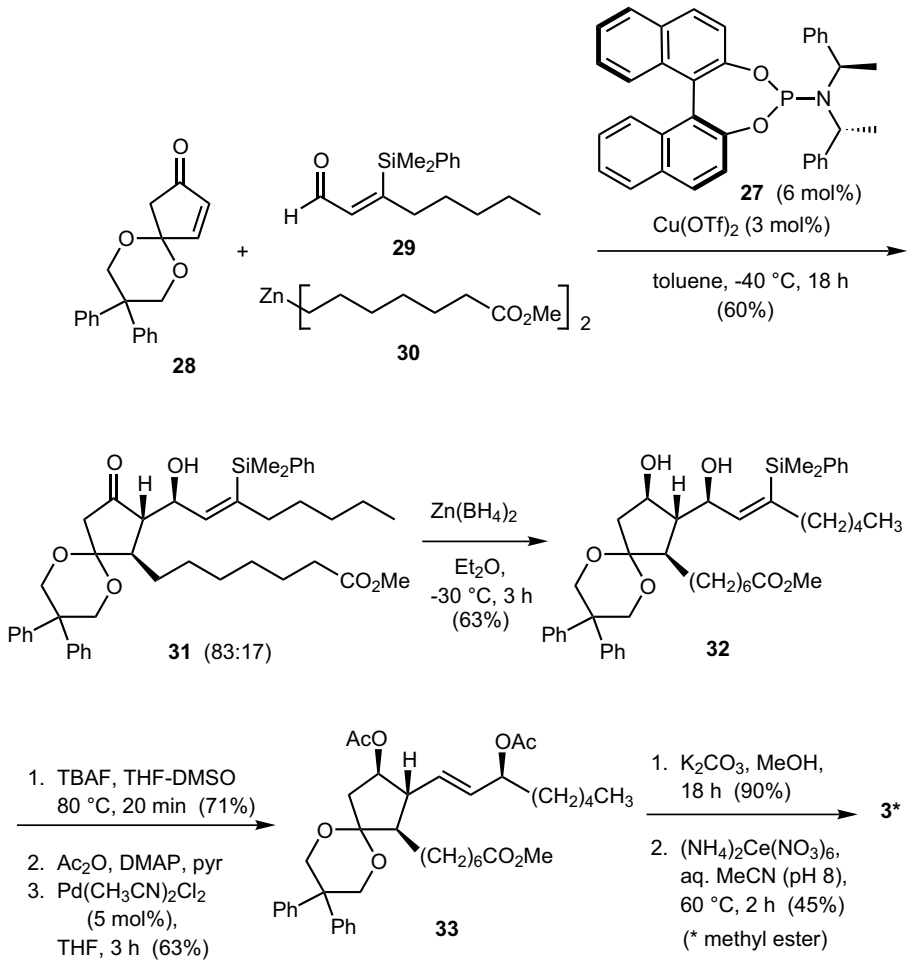


(2)



Scheme 12.5. Catalytic asymmetric synthesis of 11-deoxy-PGF$_{1\alpha}$ using a Noyori-type 3CR, by Shibasaki and co-workers [15]. ALB = aluminum lithium bis(binaphthoxide), Bn = benzyl, THF = tetrahydrofuran, Ms = methanesulfonyl, DMAP = 4-dimethylaminopyridine, TBS = *t*-butyldimethylsilyl.

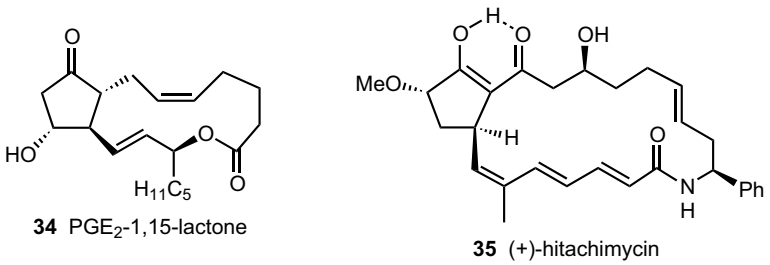
Scheme 12.6). Stereoselective reduction and chromatographic separation afforded diastereomerically pure derivative **32** in 94% *ee*. Removal of the silicon protecting group, followed by acetylation of the two secondary alcohols, set the stage for an elegant palladium-catalyzed allylic transposition that provided compound **33** with



Scheme 12.6. Catalytic asymmetric synthesis of PGE_1 using a Noyori-type 3CR, by Feringa and co-workers [19]. TBAF = *n*-tetrabutylammonium fluoride, THF = tetrahydrofuran, DMSO = dimethylsulfoxide, Ac = acetyl, DMAP = 4-dimethylaminopyridine, pyr = pyridine.

the required alkenyl side chain. A few more steps completed this new enantioselective route to PGE_1 methyl ester in 7% overall yield and only seven steps from acetal **28**.

In yet another successful application of the traditional Noyori three-component reaction, Fürstner and co-workers took advantage of their remarkable alkyne metathesis reaction [21] to synthesize therapeutically promising cyclic analogues of prostaglandins [22] such as PGE_2-1-15-lactone **34** (Figure 12.1) [23].



34 PGE_2-1,15-lactone

35 (+)-hitachimycin

Fig. 12.1. Chemical structures of PGE_2_1,15-lactone and (+)-hitachimycin.

12.2.2
Others

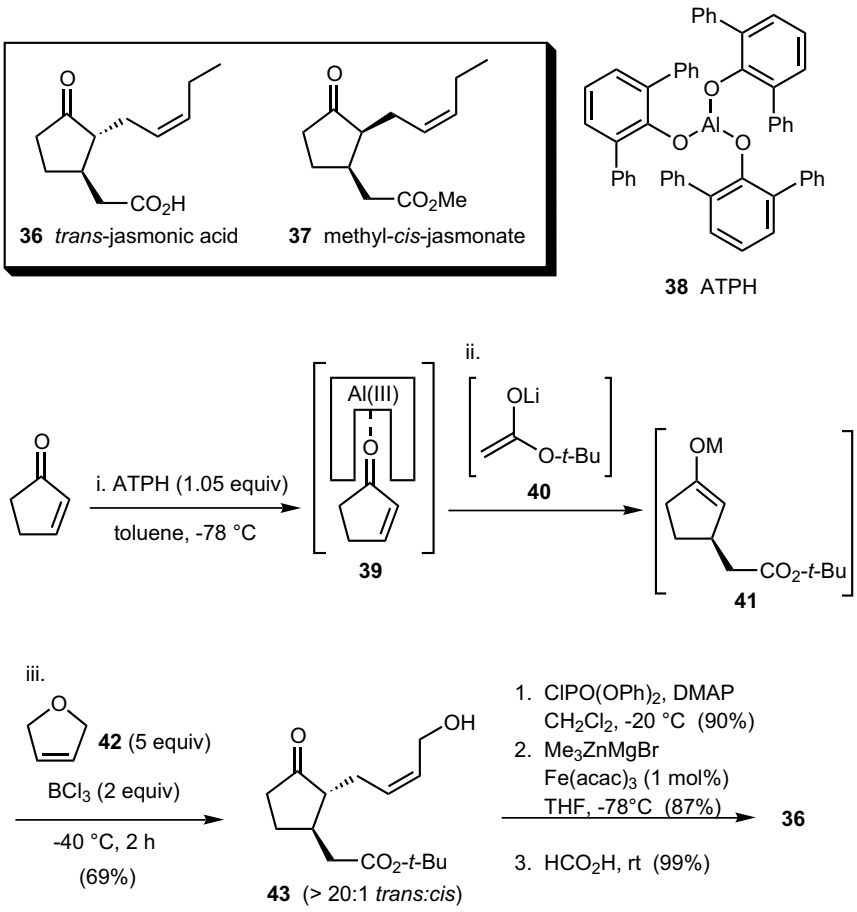
In the early 1990s, Smith and co-workers reported on the total synthesis of the antitumor antibiotic macrolactam (+)-hitachimycin **35** (Figure 12.1) using a Noyori three-component coupling to assemble the polysubstituted cyclopentane unit [24].

The jasmonates are another class of disubstituted cyclopentanoid natural products very reminiscent of the prostaglandins. To efficiently assemble their main skeleton, Yamamoto and co-workers developed a clever three-component reaction methodology that was demonstrated by the total synthesis of both *trans*- and *cis*-methyl jasmonates **36** and **37** (Scheme 12.7) [25].

Highly reactive organolithium reagents, even lithium enolates, tend to have an intrinsic preference for 1,2-addition on cyclopentenone derivatives. By using the very bulky Lewis acid aluminum tris(2,6-diphenylphenoxide) (ATPH, **38**) to pre-complex the carbonyl of enones [26], however, Yamamoto and co-workers demonstrated that strong organolithium reagents can be forced to undergo conjugate addition. The transient enolate can be trapped *in situ* with BCl_3-activated THF or DHF. Thus, pre-complexation of cyclopentenone at −78 °C with a stoichiometric amount of **38** provided the sterically hindered ketone complex **39**. The lithium enolate of butyl acetate was added, and after several hours, DHF **42** and BCl_3 were added sequentially to the mixture containing enolate **41** at −40 °C. This three-component reaction provided the *trans*-disubstituted cyclopentanone product **43**, which was isolated in good yield and high selectivity. From **43**, the synthesis of methyl *trans*-jasmonate was completed in just a few steps. Methyl *cis*-jasmonate **37** was synthesized using the same methodology, but starting with an alkynyl lithium reagent that for unknown reasons provides *cis*-selectivity in this particular tandem process.

12.3
Terpenoids

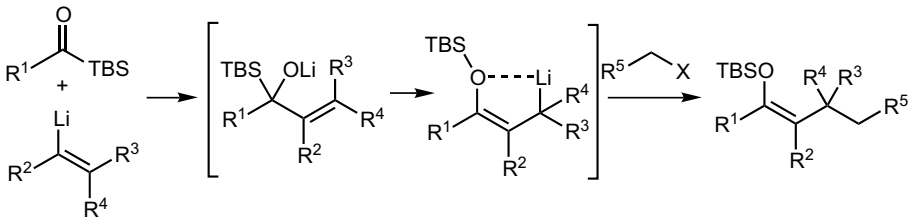
Terpenoids represent a large and structurally diverse class of natural products. Research efforts directed towards their synthesis was fueled by hypotheses on their



Scheme 12.7. Synthesis of jasmonates using a Noyori-type 3CR, by Yamamoto and co-workers [25]. ATPH = aluminum tris(2,6-diphenylphenoxide), DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran.

biosynthetic origin, and by the sheer challenge that represents the stereocontrolled construction of the unique array of ring systems, and the presence of interesting structural elements such as ring size and quaternary centers. Despite the numerous reports on their stereoselective synthesis, these compounds still continue to inspire the synthetic community as they seek for efficient and expedient approaches for their assembly. One emerging new concept in this area is the development and application of MCRs, which is exemplified here by a number of recent contributions from several research groups.

The domino π-cationic cyclization popularized by Johnson and co-workers has provided a powerful stereoselective approach to the steroid subfamily of terpenoids [27]. This pioneering biomimetic work established that the entire carbocyclic



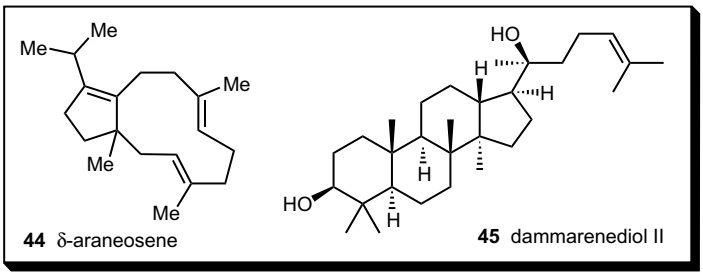
Scheme 12.8. Mechanistic sequence for the tandem three-component nucleophilic addition/Brook rearrangement/alkylation on acylsilanes TBS = *t*-butyldimethylsilyl.

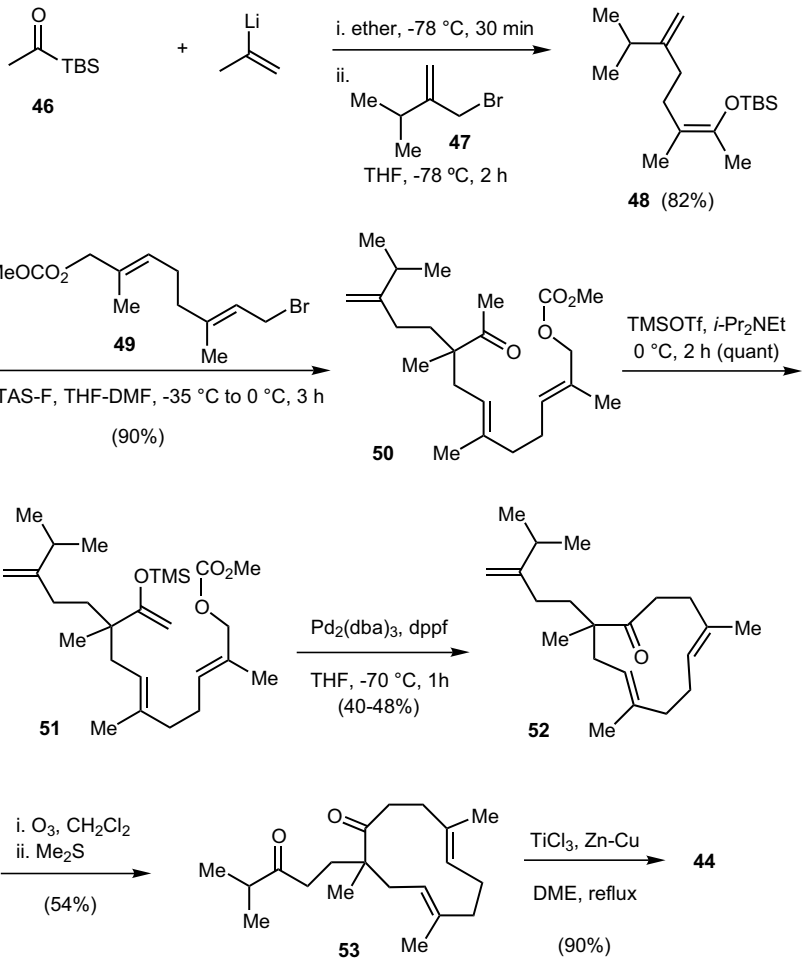
framework of these complex molecules could be accessed from simple acyclic polyene precursors. Although many approaches to the stereocontrolled synthesis of di- and trisubstituted olefins exist, the efficient elaboration of their tetrasubstituted counterparts still remains a synthetic challenge. An efficient route to the latter class of alkenes was devised by Corey and co-workers based on a three-component carbonyl addition/alkylation reaction sequence [28]. Crucial to this chemistry is the Brook rearrangement [29], a process involving the migration of a silane group from carbon to oxygen. As depicted in Scheme 12.8, the addition of alkenyllithium intermediates to acylsilanes triggers a tandem Brook rearrangement/double-bond isomerization to afford a putative five-membered chelated silylated enol ether, thereby setting the geometry of the olefin. The desired tetrasubstituted olefin can then be isolated following the introduction of an alkyl halide to the reaction mixture. This multicomponent coupling was key to the racemic total synthesis of δ-araneosene **44** by Hu and Corey (Scheme 12.9) [30].

This efficient synthesis was initiated by the treatment of methyl *tert*-butyldimethylsilyl ketone **46** with 2-propenyllithium in ether, followed by the introduction of a THF solution of 2-propylallylbromide **47**, affording (*Z*)-silyl enol ether **48** in 82% yield. The silyl enol ether functionality was first activated with a fluoride source, then the molecule was alkylated with allylic bromide **49** to afford methyl ketone **50**. The latter functional group was converted to its TMS-enol-ether equivalent **51**, followed by ring closure using palladium as catalyst. From cyclic ketone **52**, selective ozonolysis of the exocyclic alkene and McMurry cyclization completed this short synthetic sequence to afford target **44**. A similar synthetic strategy was also used for the synthesis of dammarenediol II **45** [31].

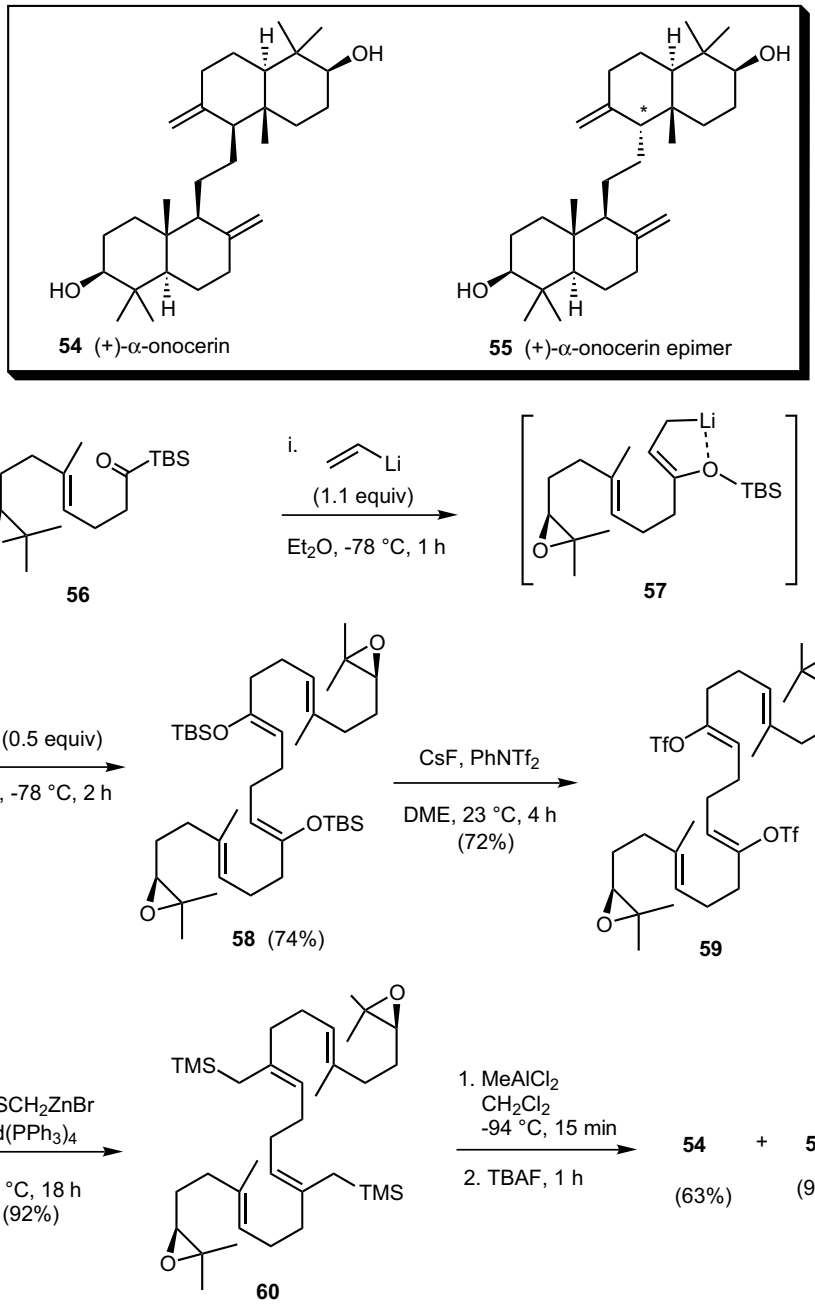
Using a similar process, (+)-α-onocerin **54**, a known acetylcholinesterase inhibitor [32], was assembled by Corey and co-workers in only four steps starting from advanced acyclic intermediate **56** (Scheme 12.10) [33].

This synthesis featured a four-component coupling involving an oxidative dimerization process. Treatment of homochiral acyl silane **56** with vinyl lithium at low temperature, followed by the addition of half an equivalent of iodine to the reaction mixture, furnished tetraene **58** in high yield and with a very high level of stereoselectivity. The TBS ether was then converted to its triflate equivalent **59** in a

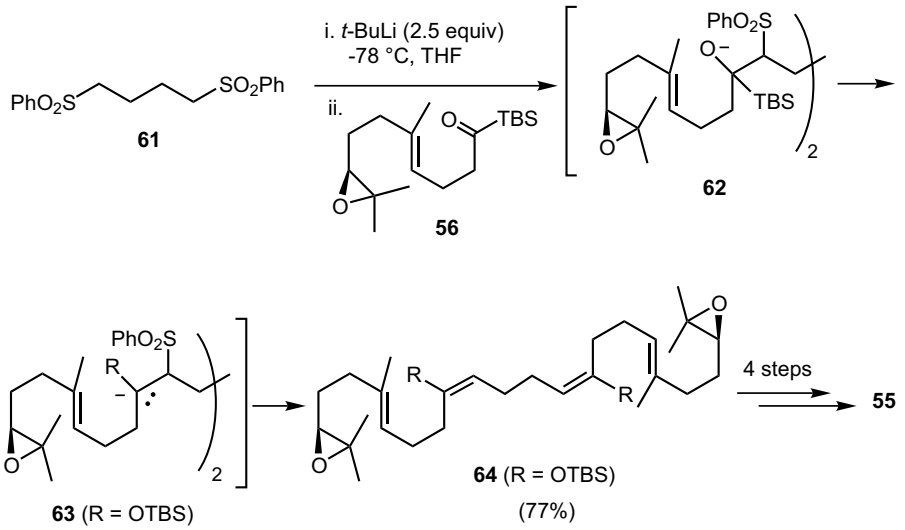




Scheme 12.9. Synthesis of δ-araneosene using a three-component nucleophilic addition/Brook rearrangement/alkylation on acylsilanes, by Hu and Corey [30]. TBS = *t*-butyldimethylsilyl, TAS-F = tris(dimethylamino)sulfur (trimethylsilyl)-difluoride, THF = tetrahydrofuran, DMF = dimethylformamide, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, dba = dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DME = 1,2-dimethoxyethane.



Scheme 12.10. Synthesis of α-onocerin using a three-component nucleophilic addition/Brook rearrangement/alkylation on acylsilanes, by Corey and co-workers [33]. TBS = *t*-butyldimethylsilyl, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl, DME = 1,2-dimethoxyethane, TMS = trimethylsilyl, TBAF = *n*-tetrabutylammonium fluoride.



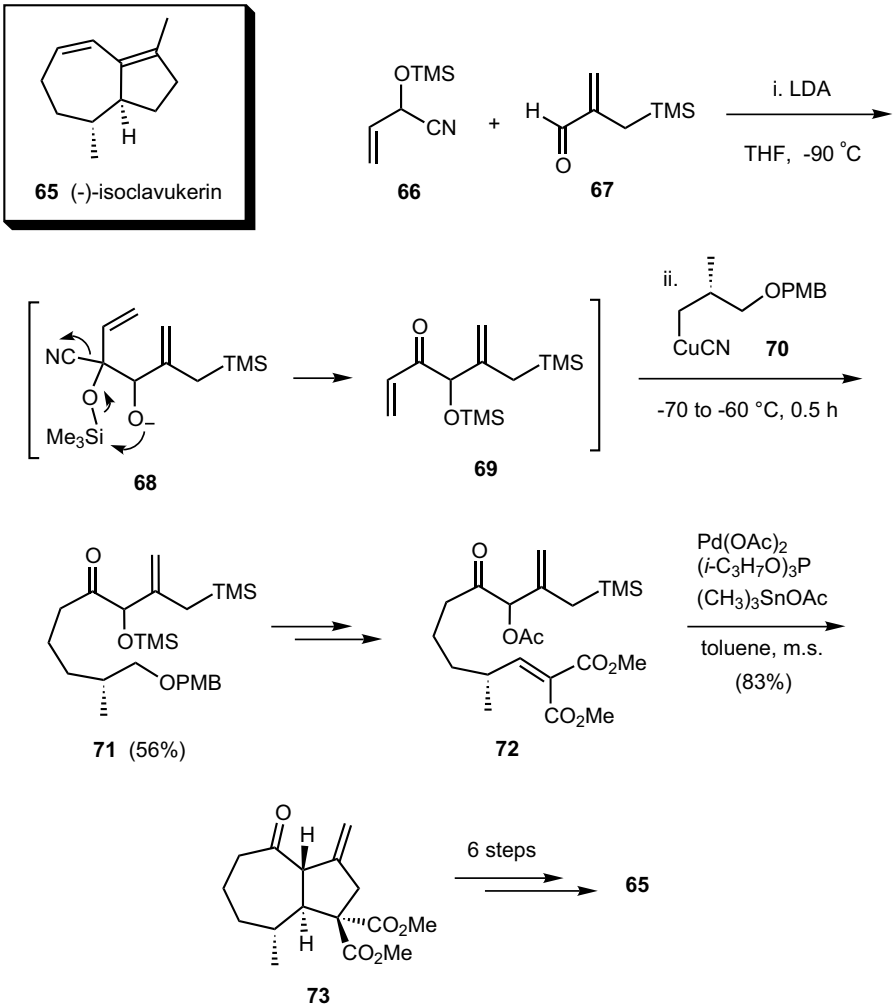
Scheme 12.11. Synthesis of epi-α-onocerin using a three-component nucleophilic addition/Brook rearrangement/elimination on acylsilanes, by Corey and co-workers [33]. TBS = *t*-butyldimethylsilyl.

stereospecific manner, thereby setting the stage for a one-carbon homologation using a Negishi-type coupling that provided the key precursor **60** containing all carbon atoms of the natural product skeleton. The Lewis acid-catalyzed cationic π-tetracylization of **60** and treatment with TBAF delivered the desired compound **54** in 31% overall yield and a small amount of its epimeric analogue **55**. The latter compound can also be efficiently assembled using a three-component reaction as outlined in Scheme 12.11 [33].

The dilithio derivative of 1,4-bisphenylsufonylbutane **61** was formed prior to the introduction of homochiral acylsilane **56** into the reaction mixture. The nucleophilic carbonyl addition/Brook rearrangement/elimination sequence delivered bis (*E*)-vinyl silyl ether **64** in high yield and with very high selectivity through the putative intermediates **62** and **63**. This short and effective synthesis of **55**, this time made as the major isomer, was then completed as described above for **54**.

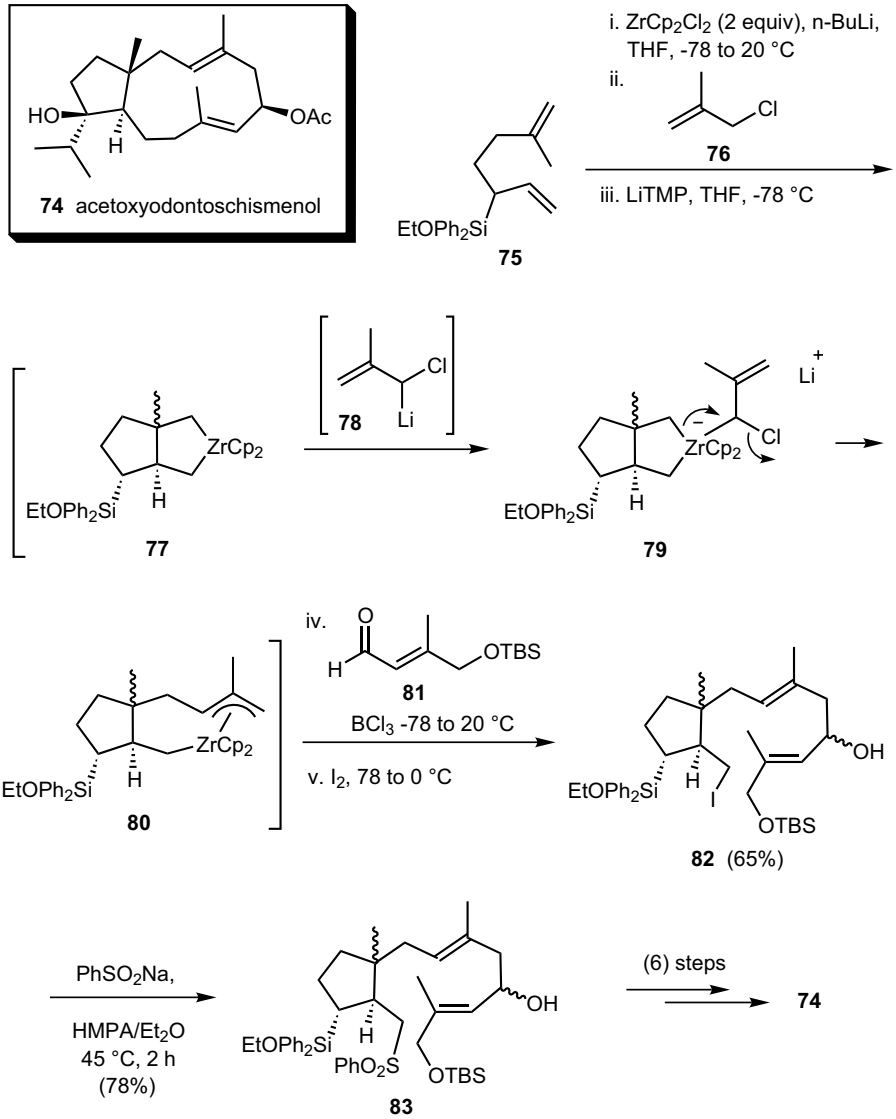
The biological activity displayed by the perhydroazulenes, ranging from diuretic and anti-inflammatory to antitumor, combined with the unique bicyclo [6-3-0] system make them very attractive synthetic targets. The approach of Trost and Higushi to this class of compounds, exemplified by the total synthesis of isoclavukerin **65** (Scheme 12.12) [34], has the distinctive feature that it allows the simultaneous formation of both the five- and seven-membered rings through a palladium-catalyzed formal [3+2] cyclization as its key step [35].

The crucial substrate for this reaction, malonate **72**, was derived from precursor **71**, which in turn was rapidly assembled through an elegant MCR between silylated cyanohydrin **66**, aldehyde **67** and the *in situ* generated organocuprate **70**. In



Scheme 12.12. Synthesis of isoclavukerin using a three-component nucleophilic addition/cyanohydrin breakdown/conjugate addition, by Trost and Higushi [34]. TMS = trimethylsilyl, LDA = lithium diisopropylamide, THF = tetrahydrofuran, PMB = *p*-methoxybenzyl, Ac = acetyl.

this reaction, initiated by a cyanohydrin anion condensation to give intermediate **68**, the ketone functionality is liberated through a 1,2-silyl transfer/cyanide expulsion sequence. The resulting intermediate, enone **69**, then underwent an *in situ* 1,4-addition with cyanocuprate **70**, affording the α-siloxy-ketone **71**. The latter intermediate was further elaborated into **72**, the required substrate for the palladium-catalyzed cyclization. Bicyclic product **73** was then converted in six steps into (−)-isoclavukerin A **65**, a perhydroazulene isolated from *Clavularia koellikeri* [36].



Scheme 12.13. Synthesis of acetoxyodontoschismenol using a three-component zirconocene induced co-cyclization/carbenoid insertion/electrophilic trapping, by Whitby and co-workers [38].

Ac = acetyl, Cp = cyclopentadienyl, THF = tetrahydrofuran, TMP = 2,2,6,6-tetramethylpiperidine, TBS = *t*-butyldimethylsilyl, HMPA = hexamethylphosphoramide.

Acetoxyodontoschismenol **74** (Scheme 12.13), a dolabellane diterpenoid, was isolated from the liverwort *Odontoschisma denudatum* and displayed moderate growth-inhibitory activity on a series of plant pathogenic fungi [37].

The challenging construction of the trans bicyclic [9.3.0] system, a common

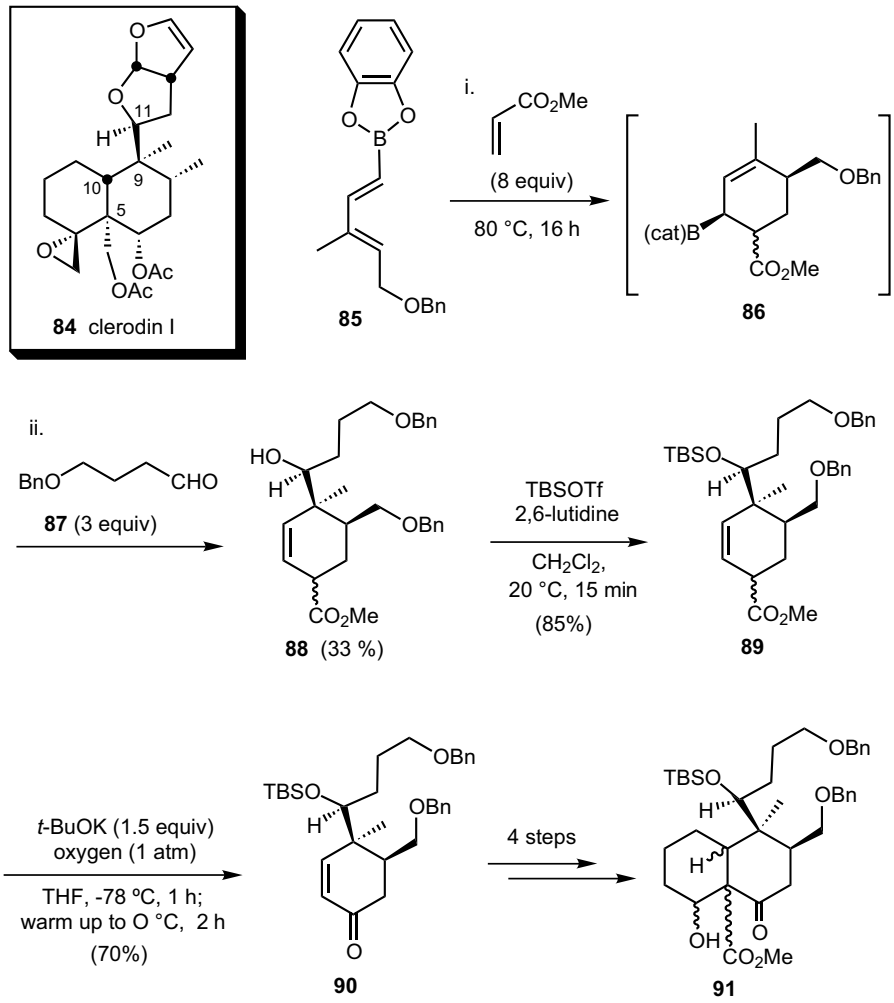
feature of this class of terpenes, was addressed by Whitby and co-workers [38]. The authors' approach hinged on a three-component zirconocene-induced co-cyclization [39], carbenoid insertion and electrophilic addition, and culminated in the total synthesis of racemic acetoxyodontoschismenol **74** as illustrated in Scheme 12.13. The dibutylzirconocene, generated *in situ* from zirconocene dichloride, was reacted with diene **75** at room temperature to furnish a transient zirconacyclopentane **77**, which was trapped with the carbenoid **78** resulting from the treatment of methallyl chloride **76** and lithium 2,2,4,4-tetramethylpiperidine, to afford the putative allylzirconium species **80**. The latter was further elaborated by the addition of aldehyde **81** in the presence of boron trichloride. Cleavage of the carbon–zirconium bond with iodine then furnished the final MCR-adduct **82** as a mixture of all four diastereomers in moderate yield. The unstable iodide **82** was then rapidly converted to sulfone **83** by reaction with sodium benzenesulfinate. The concise total synthesis of **74** was completed in six additional steps from **83** using a sequence of routine transformation.

By virtue of its seven contiguous stereogenic centers, including two quaternary centers, and the presence of very sensitive functionalities such as the exocyclic epoxide and the acetal unit, clerodin 1 **84** (Scheme 12.14) represents perhaps one of the most complex diterpenoids isolated.

It constitutes a very appealing and challenging synthetic target, which indeed has so far eluded total synthesis despite the fact that its structure has been known for more than 70 years. One promising synthetic approach to this interesting target was recently disclosed by Lallemand and co-workers [40]. Although a completion of the synthesis of clerodin **84** has not yet been reported, this elegant MCR approach to the construction of the decalin core warrants discussion. Previous work from this group had established that the furo[2,3-*b*]furan bicyclic system could be constructed from a simple 1,4-diol-containing substrate [41]. A simplified and attractive solution to the challenging construction of the C9 and C11 stereogenic centers was then devised based on the group's improved variant of a three-component reaction initially designed by Vaultier and co-workers (Scheme 12.14) [42].

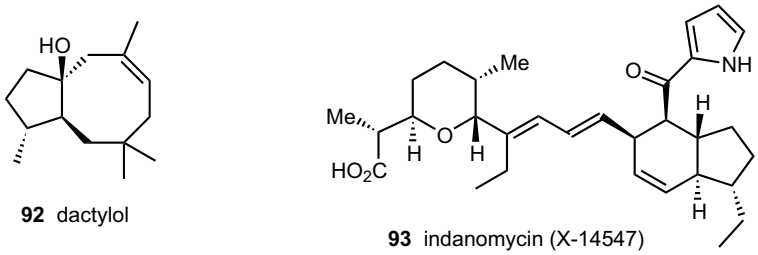
This multicomponent reaction merges two extremely powerful synthetic transformations, namely the Diels–Alder and the allylboration reactions, and delivers α-hydroxyalkyl cyclohexyl units as shown in Scheme 12.14. Upon heating, 4-borono-1,3-butadiene **85** underwent a stereoselective Diels–Alder reaction with methyl acrylate, thereby unmasking the cyclic allylboronate intermediate **86**, which condensed with γ-benzyloxy butanal **87** to afford the highly functionalized α-hydroxyalkyl cyclohexene **88**, as a single diastereomer, albeit in low yield. This advanced intermediate bears all the necessary functionalities for the rapid elaboration of both ring systems of clerodin 1. Protection of the secondary alcohol of **88** as its silyl ether followed by treatment of the resulting product **89** with potassium *t*-butoxide base in the presence of oxygen provided enone **90**. From the latter, several transformations led to an intermediate **91** featuring the decalin core of the clerodanes.

Cyclooctanoid terpenes represent a rapidly growing subfamily of natural prod-



Scheme 12.14. Synthetic approach to clerodin 1 using a three-component Diels–Alder cycloaddition/allylboration, by Lallemand and co-workers [40]. Bn = benzyl, TBS = *t*-butyldimethylsilyl, THF = tetrahydrofuran.

ucts. A total synthesis of one member of this family, (±)-dactylol **92** (Figure 12.2), was disclosed by Fürstner and co-workers in 1996 [43]. This synthesis featured a Noyori three-component reaction. Likewise, a Noyori three-component reaction was employed by Burke and co-workers to access a highly decorated *trans*-hydrindane intermediate in the total synthesis of the ionophore antibiotic X-14547A (indanomycin, **93**, Figure 12.2) [44].



92 dactylol

93 indanomycin (X-14547)

Fig. 12.2. Chemical structures of dactylol and indanomycin.

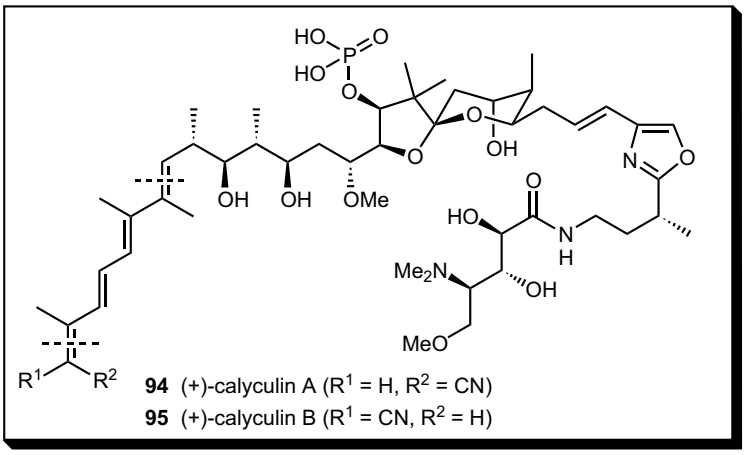
12.4 Polyenes and Polyynes

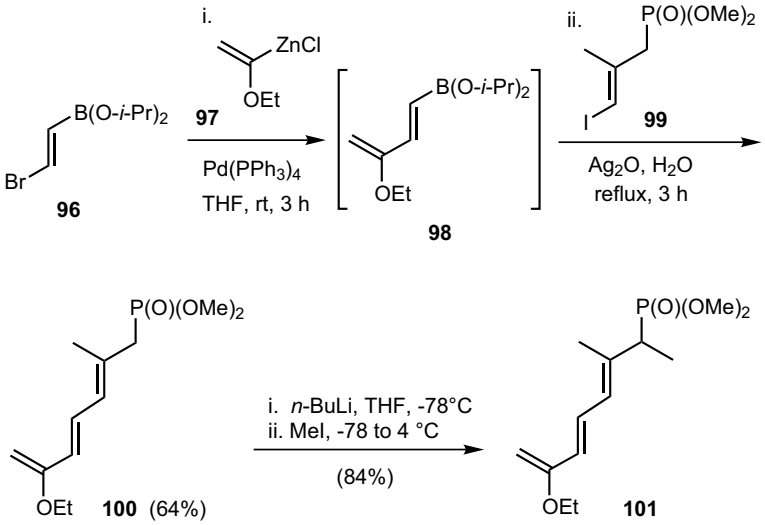
Polyene units are a common structural feature of several classes of natural products. Any effective multicomponent reaction strategy has to provide effective control of the geometry of individual double bonds. The calyculins, a class of potent and highly selective serine-threonine phosphatase inhibitors [45], present a conjugated tetraene unit as part of their structure characterized by a complex array of rings and functional groups. To elaborate the tetraene unit in their total synthesis of (+)-calyculin A **94** and (−)-calyculin B **95** [46], Smith and co-workers have applied an elegant one-pot three-component Suzuki cross-coupling [47] reaction between fragments **96**, **97** and **99** in order to reach desired intermediate **101** (Scheme 12.15).

The use of such a cross-coupling strategy does not entail issues of control of *E*/*Z* stereoselectivity, and to avoid any tedious separation later on, the three alkenyl components were prepared in advance with the requisite double-bond geometry. Thus, Negishi coupling between **96** and **97** affords dienylboronate **98**, which is then treated *in situ* with alkenyl iodide **99** under Kishi's mild conditions using silver oxide as promoter [48]. The sensitive trienyl phosphonate **100** thus isolated was methylated to afford desired fragment **101**. The latter was eventually coupled to an advanced aldehyde fragment by the retrosynthetic cuts shown in Scheme 12.15. Fragment **101** also features an enol ether as a masked ketone, which was eventually elaborated onto the required unsaturated nitrile to complete the total syntheses of calyculins A and B.

White and Kawasaki have employed a three-component strategy to access an advanced dienyl fragment in their total synthesis of (+)-latrunculin A **102** (Scheme 12.16) [49], an ichthyotoxic metabolite of the sponge *Latruncula magnifica* [50].

In contrast with the previous approach of Smith and co-workers, their strategy hinges on the stereoselective attack of nucleophiles onto butadienyltriphenylphosphonium halide salts to generate (*E*)-ylides [51]. The latter can be treated *in situ* with aldehydes to provide acyclic (*E*,*Z*)-dienes in a highly stereoselective Wittig reaction. Remarkably, *β*-dicarbonyl dianions and *α*-branched aldehydes are effective partners in this highly convergent three-component coupling approach. Thus, to synthesize (+)-latrunculin A, butadienyltriphenylphosphonium bromide **104** was

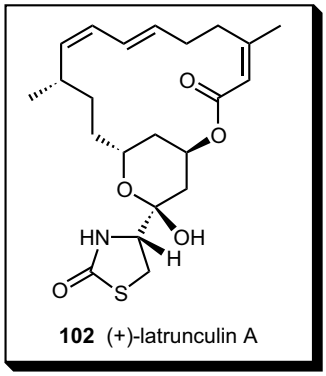




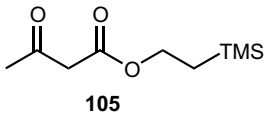
Scheme 12.15. Synthesis of a calyculin fragment using a three-component Negishi/Suzuki cross-coupling, by Smith and co-workers [46]. THF = tetrahydrofuran.

generated from phosphonium salt **103** and reacted *in situ* with Weiler dianion [52] **106** to give putative intermediate **107**. The ensuing addition of functionalized α-branched aldehyde **108** to the reaction mixture led to the isolation of (*E*,*Z*)-diene product **109** accompanied with traces of the (*E*,*E*)-isomer. Following this impressive three-component reaction, both ends of **109** were successfully elaborated into **102** after several additional steps.

Minquartynoic acid **110** (Scheme 12.17) was isolated from the bark of *Minquartia guianensis* and represents a very promising lead compound for cancer and AIDS therapy [53].

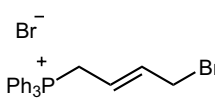


102 (+)-latrunculin A



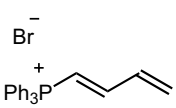
105

LDA (2 equiv)
THF, -78 °C



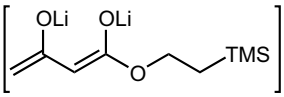
103

i.
LDA (1 equiv)
THF
- 78 to -50 °C,
30 min



104

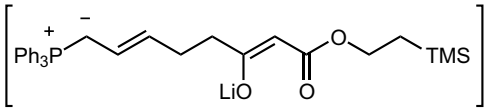
ii.



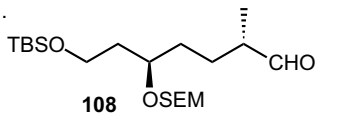
106

-50 °C; then 0 °C, 30 min

iii.

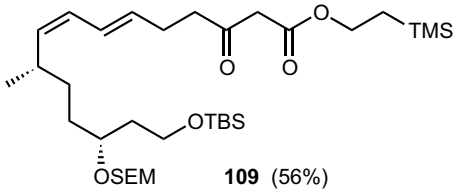


107



108

THF, 0 °C



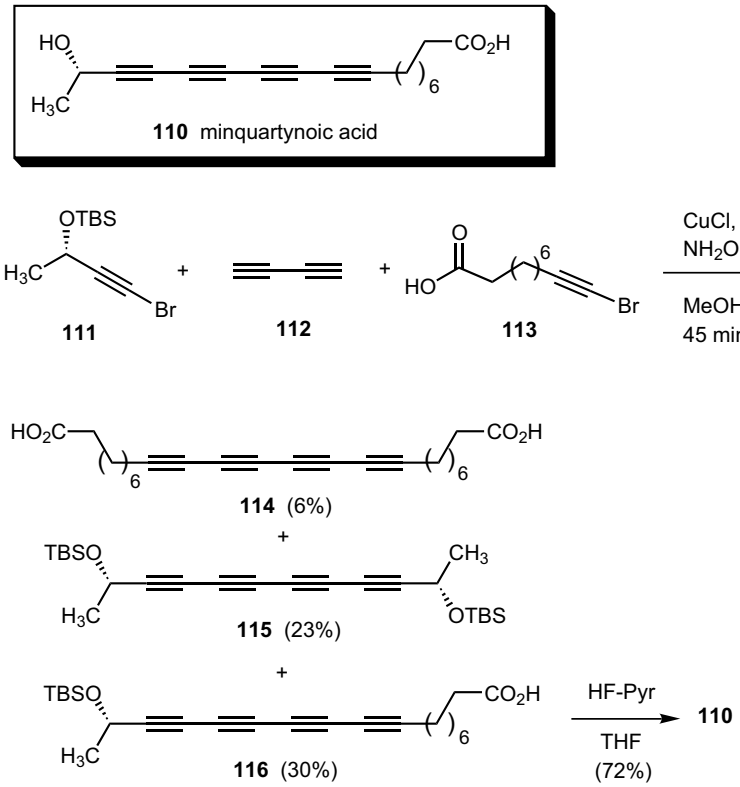
109 (56%)

11 steps

102

Scheme 12.16. Synthesis of latrunculin A using a three-component nucleophilic addition/Wittig olefination on dienyl phosphonium salt, by White and Kawasaki [49]. TMS = trimethylsilyl, LDA = lithium diisopropylamide, TBS = *t*-butyldimethylsilyl, SEM = trimethylsilylethoxymethyl.

Gung and Dickson reported the synthesis of this molecule [54] using a three-component Cadiot–Chodkiewicz coupling reaction [55] as the pivotal step (Scheme 12.17). In this three-component reaction, diyne **112** was utilized as a bidirectional synthon and was coupled successively with bromo alkynes **111** and **113** under



Scheme 12.17. Synthesis of minquartynoic acid using a three-component Cadiot–Chodkiewicz double cross-coupling, by Gung and Dickson [54]. TBS = *t*-butyldimethylsilyl, Pyr = pyridine, THF = tetrahydrofuran.

Cu(I) catalysis to afford a separable mixture of all possible cross-coupling products including the symmetrical tetracetylenes **114** and **115**, along with the desired unsymmetrical one, **116**, albeit in low yield. Despite this shortcoming, this synthesis highlighted the practical appeal of MCRs, as all attempts to assemble the target molecule using linear two-component couplings delivered unstable intermediates. The desired molecule **110** was obtained following removal of the silyl ether protecting group of **116**.

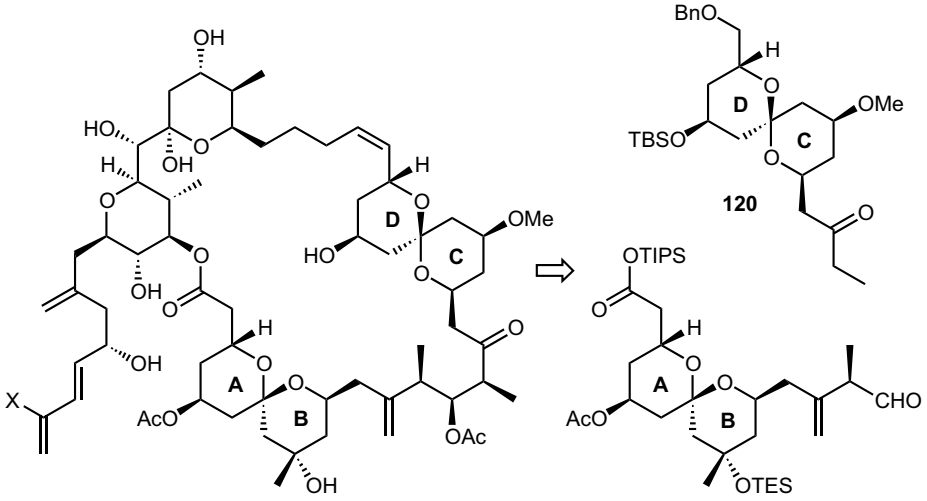
12.5
Oxacyclic Natural Products

Myriad natural products such as carbohydrates, ionophore antibiotics and many others possess polysubstituted oxygenated rings, such as furans, pyrans and lactone units, within their complex structure. Pyran and dihydropyran units are par-

ticularly common, and the biological importance of these classes of compounds has prompted several laboratories to develop new synthetic methodologies to access polysubstituted pyran derivatives in optically pure form [56]. Despite their appeal as operationally simple and highly convergent reaction processes, multicomponent reaction strategies have rarely been employed in the total synthesis of naturally occurring cyclic ethers and lactones. A number of recent examples, however, clearly demonstrate the appeal of these strategies.

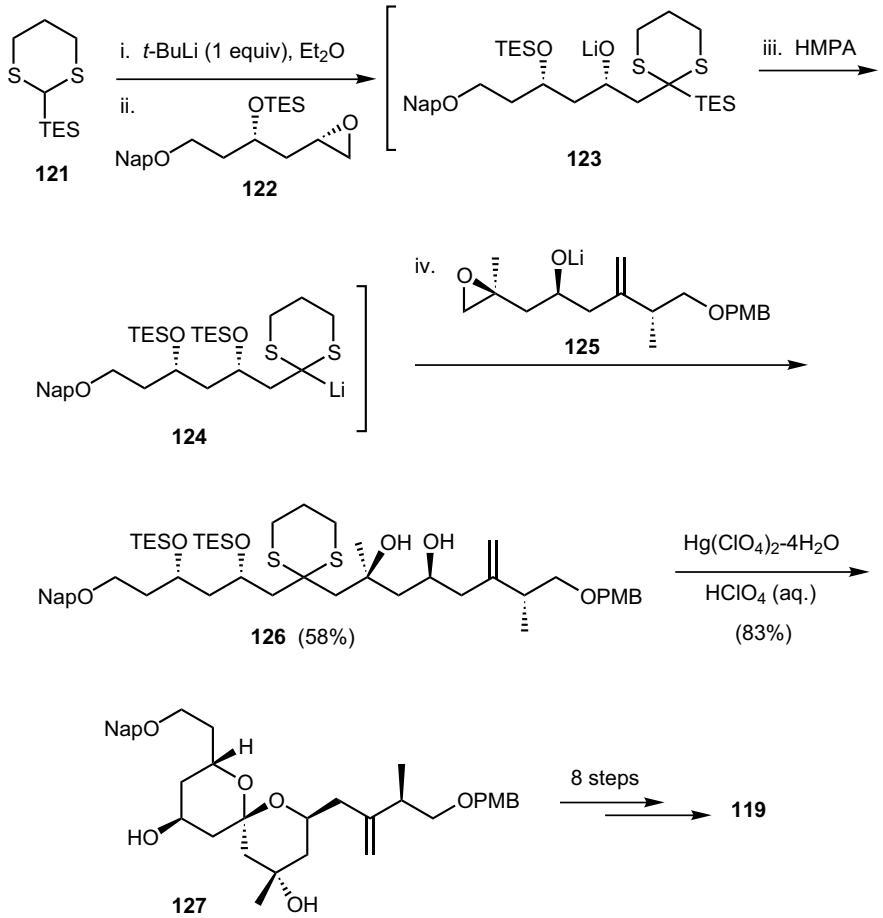
12.5.1 Cyclic Ethers

One of the most popular synthetic route to cyclic ethers and ketal derivatives is based on the cyclization of a linear ketodiol precursor. Smith and Boldi developed an elegant ''linchpin'' three-component reaction for the synthesis of polyol chains featuring the union of a silyl dithiane with two different terminal epoxides [57]. This reaction is based on two consecutive one-pot dithiane anion alkylations *via* the intermediacy of a Brook rearrangement [29] for generating the second anion *in situ* [58]. Recently, Smith and co-workers further demonstrated the power of this three-component reaction through the efficient syntheses of the A/B and C/D bisspiroketal units of the spongistatins **117** and **118** (Scheme 12.18) [59], which are members of a family of highly cytotoxic marine natural products. As demonstrated in the synthesis of A/B fragment **119** (Scheme 12.19), treatment of lithiated 2-triethylsilyl dithiane **121** with epoxide fragment **122** led to alkoxide intermediate **123**.



117 X = Cl spongistatin 1
118 X = H spongistatin 2

Scheme 12.18. Retrosynthesis of the spongistatins **117** and **118**. TBS = *t*-butyldimethylsilyl, Bn = benzyl, TIPS = triisopropylsilyl, TES = triethylsilyl, Ac = acetyl.



Scheme 12.19. Synthesis of a spongistatin spiroketal A/B fragment using a three-component dithianyl alkylation/Brook rearrangement/dithianyl alkylation, by Smith and co-workers [59]. Nap = 2-naphthylmethyl, TES = triethylsilyl, HMPA = hexamethyl-phosphoramide, PMB = p-methoxybenzyl.

The addition of HMPA to the flask, a procedure known to accelerate similar types of 1,4-Brook rearrangements [60], triggers the transfer of the TES group of **123** from carbon to oxygen, thereby generating the second dithianyl anion **124**. Addition of epoxide fragment **125** to the latter ultimately afforded polyol derivative **126** after work-up. In this solvent-controlled reaction, the sequential addition of HMPA followed by the second epoxide is crucial to insure that no bisalkylation of the first epoxide is observed, thereby allowing the desired reaction sequence to proceed in a one-pot procedure. Deprotection of the ketone through mercury(II)-promoted dithiane hydrolysis on **126**, concomitant with *in situ* spiroketalization, provided product **127** as a single isomer. From **127**, a number of standard functional-group transformations led to advanced A/B fragment **119**. The C/D frag-

ment **120** (Scheme 12.18) was elaborated using a similar linchpin three-component strategy. The union of the two fragments *via* a stereoselective aldol reaction led to an advanced intermediate described by Paterson and co-workers [61], thereby providing a formal total synthesis of spongistatin 1 **117**.

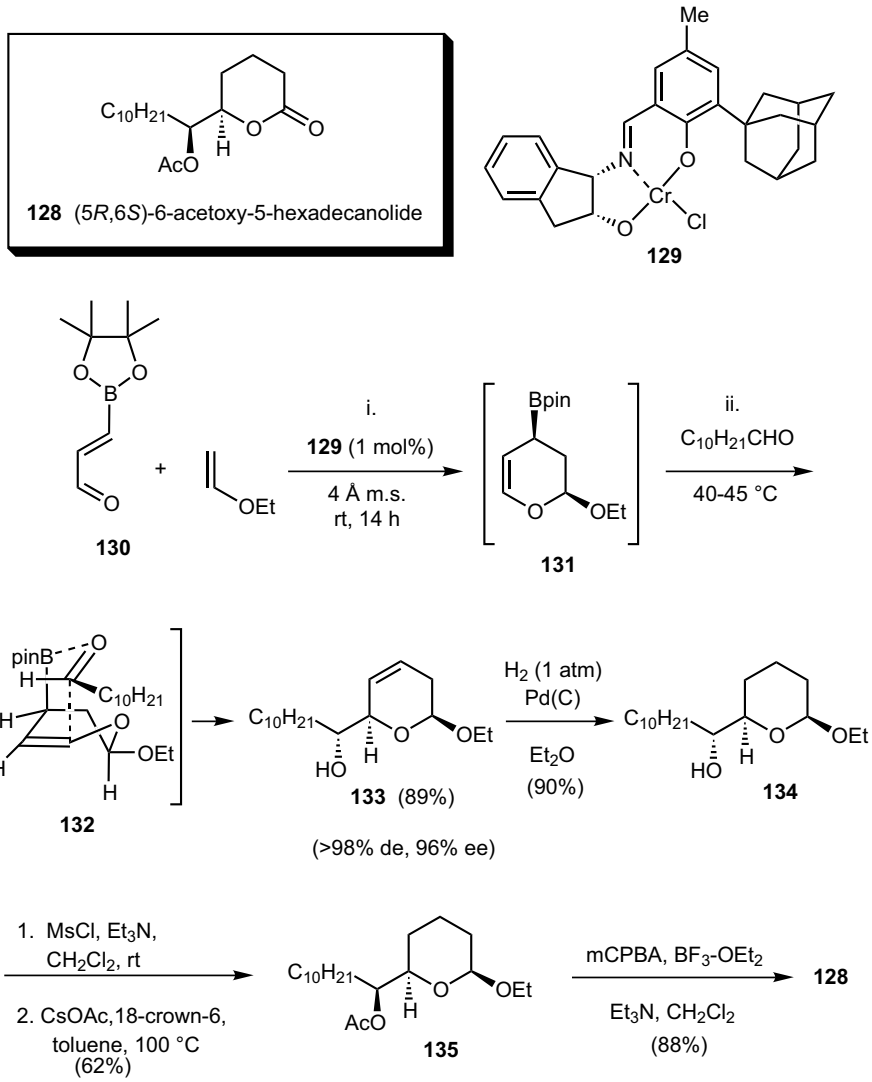
12.5.2 Lactones

Based on the previous work of this group on the three-component aza[4+2]/allylboration strategy to construct polysubstituted piperidines [62], Gao and Hall developed a catalytic enantioselective version [63] of the corresponding oxygeneous process to construct α-hydroxyalkylated pyrans from 3-boronoacrolein [64]. This recent variant of a Vaultier–Lallemand one-pot three-component reaction (see Scheme 12.14) was successfully applied to a concise total synthesis of (5*R*,6*S*)-6-acetoxy-5-hexadecanolide **128** (Scheme 12.20), the oviposition attractant pheromone of the female *Culex* mosquito [65] capable of transmitting the West Nile virus.

In this work, 3-boronoacrolein pinacolate **130** was found to be a very effective and versatile heterodiene in Jacobsen's enantioselective reverse electron demand hetero[4+2] reaction with enol ethers, catalyzed by the tridentate (Schiff-base) chromium complex **129** [66]. The reaction between **130** and ethyl vinyl ether, used as solvent, unmasked the cyclic allylboronate **131** in high enantioselectiviy (96% *ee*) using an exceptionally low loading of catalyst **129** (1 mol%). Following the cycloaddition step, intermediate **131** could be further transformed by simple addition of undecanal and gentle heating to provide α-hydroxyalkyl dehydropyran **133** as the final product of this one-pot sequential MCR. The allylboration occurred at a slightly elevated temperature (40–50 °C) in ethyl vinyl ether, and afforded **133** as a single diastereomer consistent with the expected chair-like Zimmerman–Traxler transition structure **132**. The facility of the hetero[4+2] cycloaddition step relative to the allylboration was crucial in suppressing the potential ''self-allylboration'' between **131** and aldehyde **130**, and thus ensured the feasibility of this MCR. To complete the synthesis of lactone **128**, the pyran intermediate **134** was obtained from the hydrogenation of **133**, and acetylation of the secondary alcohol by inversion of configuration afforded **135**. Oxidation of the acetal led to the desired mosquito pheromone **128** after only seven steps from commercial 3,3-diethoxy-1-propyne. The presence of the C4–C5 unsaturation in the 3CR adducts (e.g. **133**) confers remarkable synthetic versatility to this powerful catalytic enantioselective hetero[4+2]/allylboration three-component reaction. For example, appropriate oxidation of the double bond would lead to carbohydrate derivatives and other highly oxygenated pyran-containing natural products.

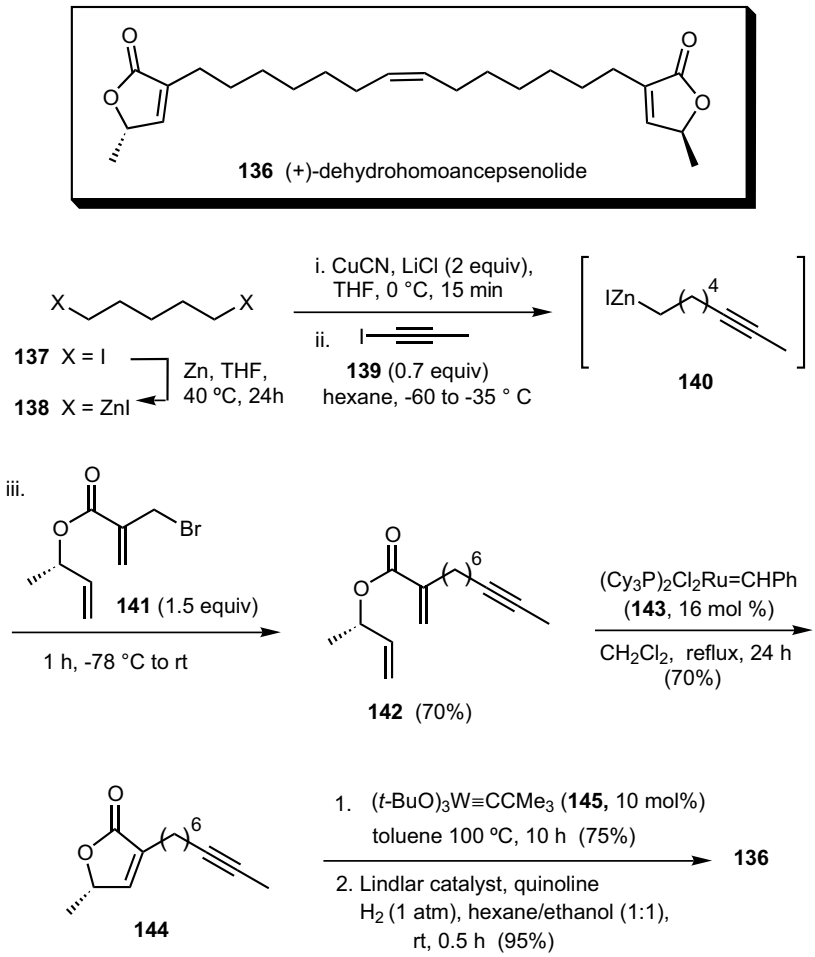
Fürstner and co-workers relied on a three-component Knochel-type [67] coupling to achieve the synthesis of (+)-dehydrohomoancepsenolide **136** (Scheme 12.21) [68], a secondary metabolite isolated from the gorgonian octocoral *Pterogorgia citrina* collected off the west coast of Puerto Rico [69].

The key heterobimetallic intermediate **138** was generated *in situ* by insertion of



Scheme 12.20. Synthesis of (5*R*,6*S*)-6-acetoxy-5-hexadecanolide using a three-component hetero[4+2] cycloaddition/allylboration, by Gao and Hall [63]. Ac = acetyl, pin = pinacolato, Ms = methanesulfonyl, mCPBA = *m*-chloroperoxybenzoic acid.

activated zinc into both C–I bonds of 1,5-diodopentane **137** followed by transmetallation with one equivalent of Cu(I). Consecutive addition of 1-iodo-1-propyne **139** and unsaturated ester **141** resulted in a double nucleophilic displacement to afford the crucial three-component adduct **142** in good yield. With this key intermediate in hand, metathesis methodologies were called upon for the completion of the syn-

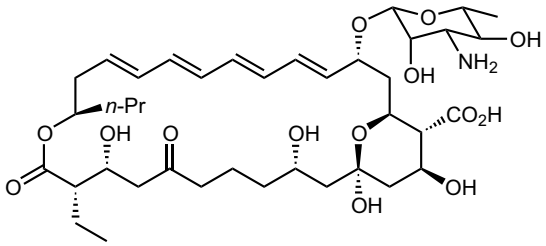


Scheme 12.21. Synthesis of dehydrohomoancepsenolide using a three-component cross-coupling/alkylation, by Fürstner and Dierkes [68]. THF = tetrahydrofuran, Cy = cyclohexyl.

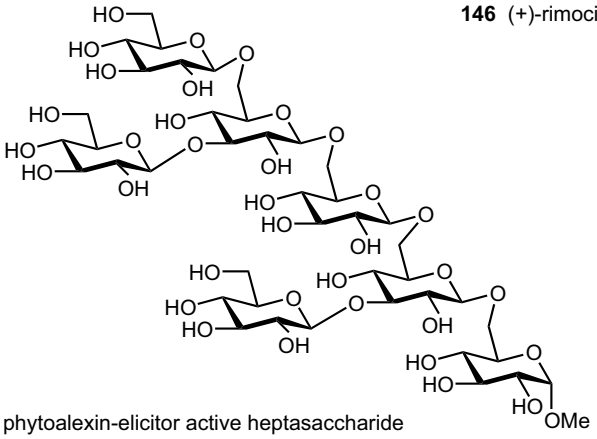
thesis; a rather bold strategy as it required two selective catalysts to differentiate between π-systems. These chemoselective transformations were carried out using the first-generation Grubb's catalyst **143** [70], providing butenolide **144**, followed by use of the Schrock alkylidyne complex **145** [71], affording **136** in very good yield after hydrogenation using Lindlar's catalyst.

12.6
Polyols and Polysaccharides

A large number of macrolide natural products contain long, stereodefined polyol fragments. In their original report on the ''linchpin'' three-component coupling



146 (+)-rimocidin



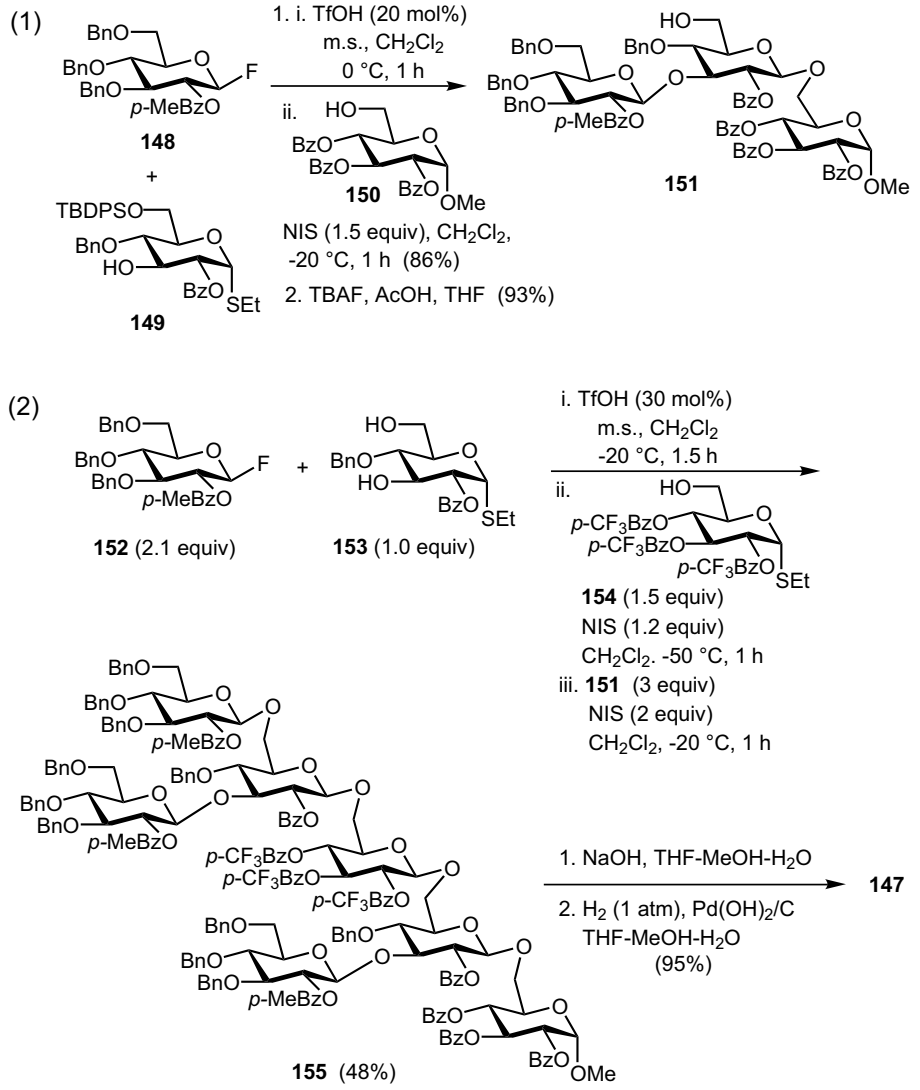
147 phytoalexin-elicitor active heptasaccharide

Fig. 12.3. Chemical structures of polyol (+)-rimocidin and heptasaccharide **147**.

of silyl dithianes with epoxides [57], Smith and Boldi prepared a protected 11-carbon fragment related to the 1,3-polyol half of the macrolide roflamycoin. Recently, using a powerful strategy similar to that of the synthesis of the calyculins described above (Scheme 12.19), Smith and co-workers reported the preparation of an advanced 18-carbon polyol fragment of the antifungal glycosylated macrolide (+)-rimocidin **146** (Figure 12.3) [72].

Polysaccharides are amongst the most ubiquitously distributed natural products. For instance, they are attached to newly synthesized mammalian proteins where they play key role in the intracellular trafficking process; they are also encountered as protein complexes at the surface of virtually all mammalian cells [73]. Many biologically important small organic molecules have also been isolated as sugar complexes. The synthesis of these natural biopolymers therefore represents an important step towards a better understanding of their roles. The current section is aimed at illustrating the application of MCRs to the synthesis of polysaccharides and small-molecule–sugar complexes.

The synthesis of the antibiotic phytoalexins in plants is triggered by molecules known as elicitors [74]. These complex oligosaccharides constitute key elements of the defense mechanism of plants as they proved to be toxic to a wide variety of microorganisms. One such phytoalexin-elicitor active is heptasaccharide **147** (Figure 12.3), which was synthesized by Jona and co-workers [75] using a one-pot multicomponent glycosylation reactions inspired by orthogonal and armed–disarmed concepts in sugar chemistry (Scheme 12.22) [76].



Scheme 12.22. Synthesis of heptasaccharide **147** using the armed–disarmed glycosylation approach, by Jona and co-workers [75]. Bn = benzyl, Bz = benzoyl, Tf = trifluoromethanesulfonyl, NIS = *N*-iodosuccinimide, TBAF = *n*-tetrabutylammonium fluoride, THF = tetrahydrofuran.

Several other examples of selective multicomponent glycosylation protocols have been designed based on steric and/or electronic control of reactivity between glycosyl donors and acceptors [77]. In the context of this chapter, these MCR strategies will be exemplified with the synthesis of **147**, which was initiated with the triflic

acid-catalyzed glycosylation of thioglycoside **149** with glycosyl fluoride **148**. The corresponding thiodisaccharide was further reacted *in situ* through the NIS-TfOH-mediated glycosylation of methyl glycoside **150** to afford trisaccharide **151**. Similarly, double glycosylation of diol **153** with glycosyl fluoride **152** generated a trisaccharide intermediate, which was directly engaged in the armed–disarmed glycosylation reaction using reactivity-tuned thioglycoside **154**. The coupling between trisaccharide **151** and the newly generated tetrasaccharide intermediate then furnished heptasaccharide molecule **155**. The latter was transformed to the targeted elicitor **147** through a short sequence of protecting-group removal manipulations.

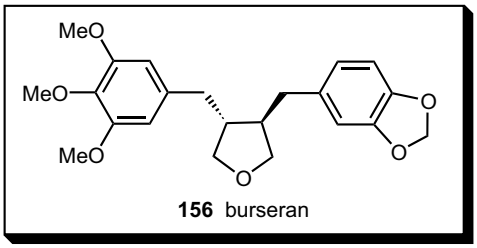
12.7 Lignans

Lignans are aromatic polyols that may comprise one or more distinct structural elements such as cycloalkanes or heterocycles. A palladium-catalyzed three-component reaction approach to furan derivatives was reported by Balme and co-workers [78]. From this reaction, initiated by a conjugate addition of alkoxides to electron-deficient alkenes, the desired functionalized furans are isolated in good yield following coupling and a Wacker-type cyclization process. This interesting MCR was applied to the formal synthesis of the antitumor lignan bursuran **156** (Scheme 12.23) [79].

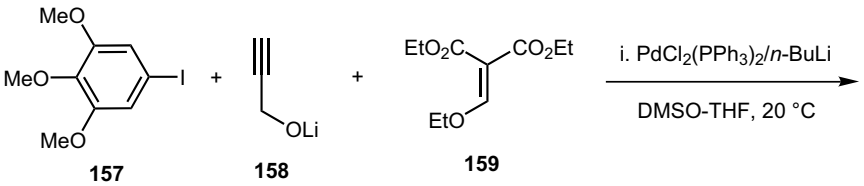
An equimolar mixture of 3,4,5-trimethoxy phenyl iodide **157**, lithium propargyl alkoxide **158**, and diethyl ethoxymethylene malonate **159** was stirred at room temperature in the presence of a palladium catalyst. Then, to the resulting intermediate **161** potassium *t*-butoxide was added, and the ensuing base-promoted decarboxylative aromatization afforded tetrahydrofuran MCR adduct **162** in good yield. The ester was first reduced and the furan ring was hydrogenated with Raney nickel to furnish a diastereomeric mixture of products **163** in high yield. Further synthetic manipulations then provided a known precursor to the natural product.

The traditional Chinese herbal medicine Shin-i is highly praised for its anti-inflammatory effect [80]. Magnoshinin **164** (Scheme 12.24), isolated from the dry flower buds of *Magnolia ulicifolia*, has been shown to be the lignan responsible for this interesting biological property [81].

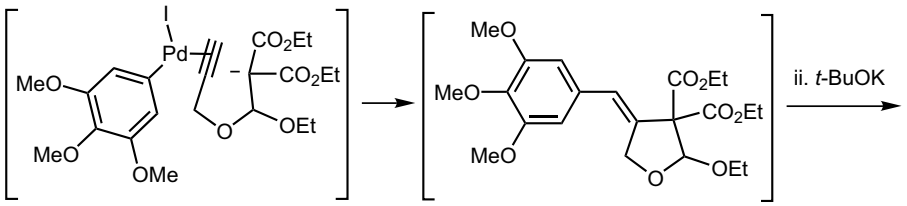
A synthesis of this compound was devised by Ohmizu, Iwasaki and co-workers and featured a three-component tandem conjugate addition/enolate trapping as key step (Scheme 12.24) [82]. In this synthesis, the acyl anion equivalent cyanohydrin **165** was first treated with LDA and allowed to react with methyl crotonate **166**. The resulting enolate was trapped with 2,3,5-trimethoxy benzylbromide **168** to afford crude intermediate **169**, which was immediately deprotected *in situ* to afford ketone product **170**. Both the ester and the ketone functionalities were then reduced at low temperature to afford the corresponding diol **171**. Upon treatment with trifluoroacetic acid, the desired Friedel–Craft cyclization adduct **172** was obtained. The latter tricyclic compound was then further elaborated to the final target **164** through a short sequence of standard transformations.



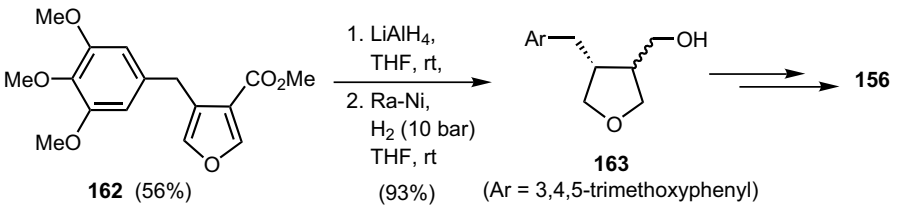
156 burseran



157 **158** **159**



160 **161**

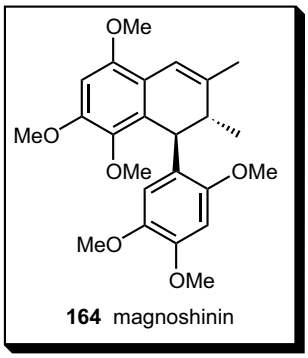


162 (56%) (93%) **163** (Ar = 3,4,5-trimethoxyphenyl)

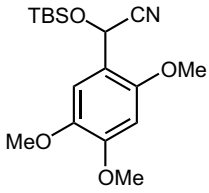
Scheme 12.23. Synthesis of burseran using a three-component conjugate addition/Wacker-type cyclization, by Balme and co-workers [79]. DMSO = dimethylsulfoxide, THF = tetrahydrofuran, Ra-Ni = Raney nickel.

12.8 Alkaloids

Alkaloids represent one of the largest classes of natural products so far isolated. They originate from amino acids and are often isolated from plants although a few are derived from animals. They display a wide range of biological activity. Their biological properties, along with the enormous breath of structural variation, make them prime synthetic targets [83]. The following section described the synthesis of some alkaloids through the application of MCRs.



164 magnoshinin

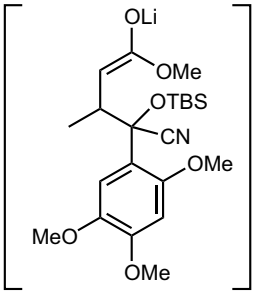


165

i. LDA, THF, -78 °C

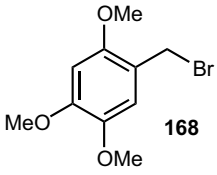
ii. CO_2Me

166

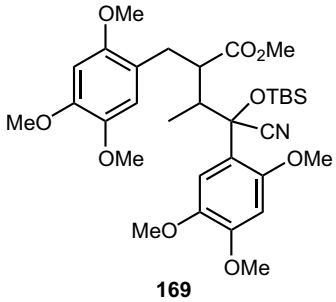


167

iii. HMPA, -78 °C



168

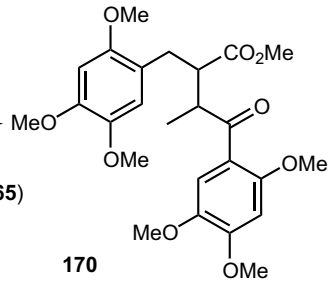


169

Bu_4NF

CH_2Cl_2, rt

(65% from **165**)

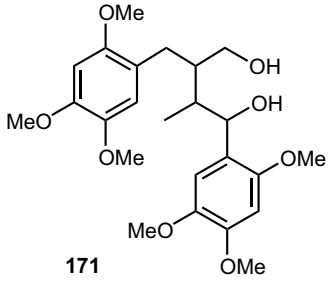


170

$LiAlH_4$

THF, O °C

(90%)

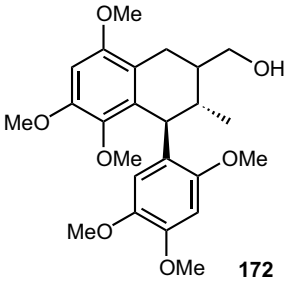


171

i. CF_3COOH, rt

ii. K_2CO_3, MeOH, rt

(86%)



172

1. i. TsCl, Et_3N, CH_2Cl_2, rt
   ii. NaI, acetone, reflux
2. KO-*t*-Bu, DMF, rt

(73%, 2 steps)

164

Scheme 12.24. Synthesis of magnoshinin using a three-component conjugate addition/alkylation, by Ohmizu, Iwadaki and co-workers [82]. TBS = *t*-butyldimethylsilyl, LDA = lithium diisopropylamide, THF = tetrahydrofuran, HMPA = hexamethylphosphoramide, Ts = toluenesulfonyl, DMF = dimethylformamide.

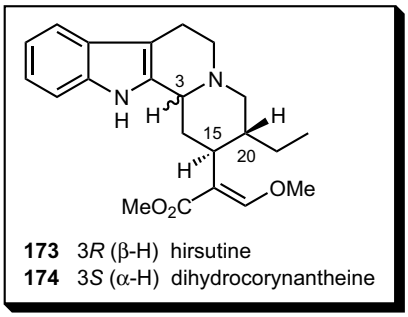
12.8.1 Indoles

Indole alkaloids are a prominent class of bioactive natural products [84]. In addition to the indole nucleus, they present a wide variety of additional functionalities and structural elements. Thus, it is not surprising that several members of this class may be accessed using multicomponent reactions as key synthetic strategies. Although a number of multicomponent reactions to construct polysubstituted indoles have been reported [85], as yet none of these have been employed in the total synthesis of indole alkaloids. The application of multicomponent reaction strategies in target-oriented syntheses of indole alkaloids, however, may not necessarily serve to establish the indole unit. For example, to construct the second piperidine unit and generate two new stereocenters *en route* to the total biomimetic syntheses of hirsutine and dihydrocorynantheine **173** and **174** (Scheme 12.25) [86], Tietze and Zhou applied a very elegant three-component Knoevenagel/hetero-Diels–Alder reaction previously optimized by the same group and used in the synthesis of a number of other indole alkaloids [87].

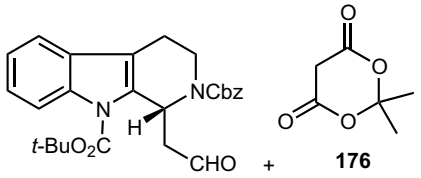
In this latest example, optically pure tetrahydro-β-carboline carbaldehyde **175** was employed as an advanced precursor. Thus, as exemplified in the total synthesis of hirsutine **173**, (Scheme 12.25), a potent inhibitor of the influenza A virus, a one-pot domino-Knoevenagel/hetero-Diels–Alder reaction between **175**, Meldrum's acid **176** and enol ether **177** afforded lactone **181** with a high degree of stereoselectivity ($>$ 20:1 at C15). This three-component process is carried out under sonication and mild acid catalysis, and is initiated by a Knoevenagel condensation between **176** and the aldehyde group of **175**, leading to the formation of intermediate **178**. The latter plays the role of 1-oxabutadiene and is trapped with enol ether **177** in a highly face-selective hetero-Diels–Alder reaction to generate intermediate **179**. Under the reaction conditions, the latter rapidly decomposes to lose acetone, presumably giving ketene **180** from a formal retro-[4+2] process. This event, followed by a decarboxylation induced by the reaction of **180** with the water generated in the Knoevenagel condensation, afforded lactone **181** in good yield. The synthesis was completed by another one-pot domino process consisting of methanolysis, cyclic enamine formation, and *in situ* stereoselective hydrogenation to give fused bipiperidine **183**. From **183**, cleavage of the *t*-Boc group followed by condensation with methyl formate and treatment with diazomethane provided the desired indole alkaloid hirsutine **173**. A similar synthetic approach led to C3-epimer **174**, albeit with a lower diastereoselectivity. This impressive sequence of chemical reactions provides a striking demonstration of the use of multicomponent reactions to rapidly generate complex polycyclic structures in a highly stereoselective fashion.

12.8.2 Piperidines

The intermolecular Mannich reaction combines an aldehyde, an amine and an enolizable carbonyl compound for the one-pot synthesis of β-amino ketones or

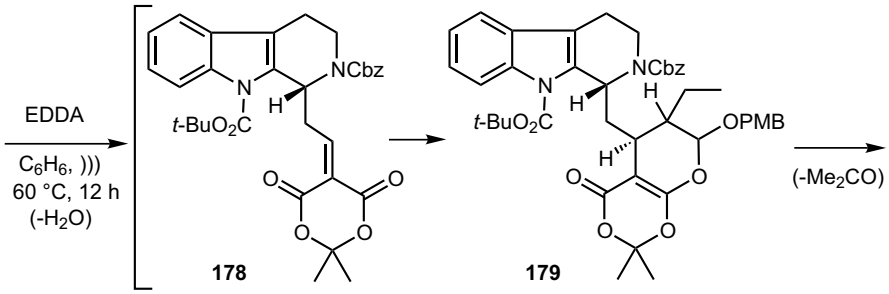


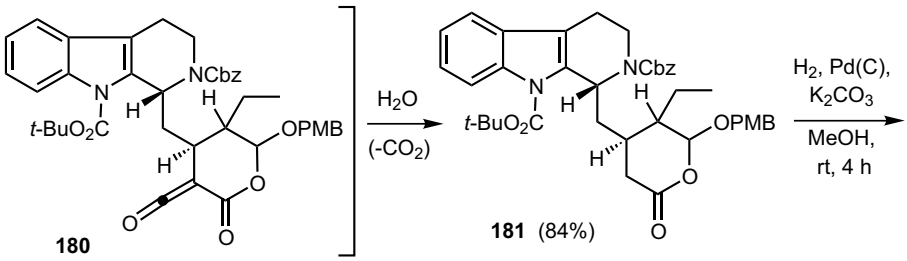
173 3*R* (β-H) hirsutine
174 3*S* (α-H) dihydrocorynantheine

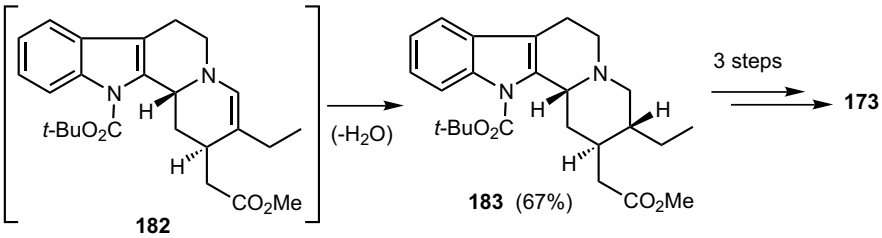


175 + **176**

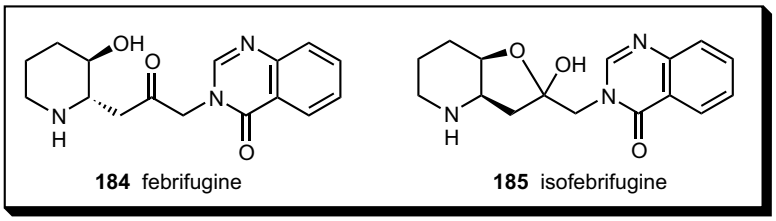
177

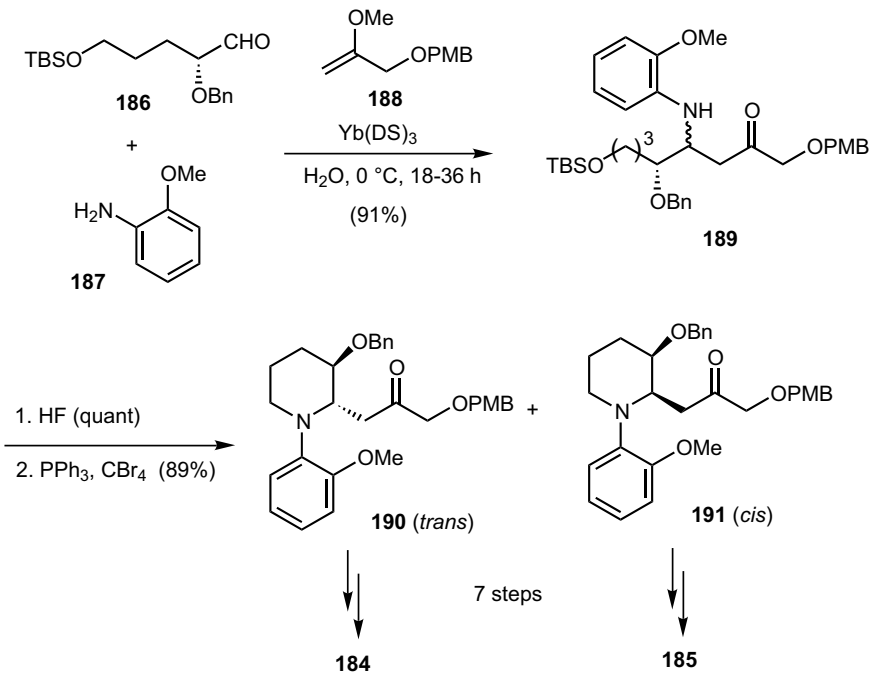






Scheme 12.25. Syntheses of hirsutine and dihydrocorynantheine using a three-component Knoevenagel/hetero[4+2] cycloaddition/retro[4+2] fragmentation, by Tietze and Zhou [86]. Cbz = benzyloxycarbonyl, PMB = *p*-methoxybenzyl, EDDA = ethylenediammonium diacetate [$(H_3NCH_2CH_2NH_3)(OAc)_2$].





Scheme 12.26. Syntheses of febrifugine and isofebrifugine using a three-component Mannich-type reaction, by Kobayashi and co-workers [89] TBS = *t*-butyldimethylsilyl, Bn = benzyl, PMB = p-methoxybenzyl, DS = dodecyl sulfate.

esters [88]. It is among the most useful synthetic transformations and has found widespread applications. This process was recently used as a key step for the asymmetric synthesis of the anti-malarial alkaloids febrifugine **184** and isofebrifugine **185** by Kobayashi and co-workers (Scheme 12.26) [89].

The required aldehyde precursor **186** was obtained by a Sn(II)-catalyzed asymmetric aldol reaction [90]. It was then mixed in one pot with *o*-methoxy aniline **187** and enol ether **188** to afford the key *β*-amino ketone **189** in a 2:1 diastereomeric ratio through a Mannich-type three-component reaction. This reaction was performed in an aqueous medium and the use of a surfactant such as dodecyl sulfate (DS) was essential. The diastereomeric mixture **189** was treated with HF and the

resulting primary alcohol was converted to a bromide, which underwent nucleophilic cyclization to afford piperidines **190** and **191**, which were then separated and independently elaborated in seven steps into **184** and **185**. The measured optical rotation of these compounds led to the conclusion that they were antipodes of the natural products. A similar synthetic sequence led to the synthesis of the corresponding enantiomers, which were shown to have optical rotations identical to the respective natural products.

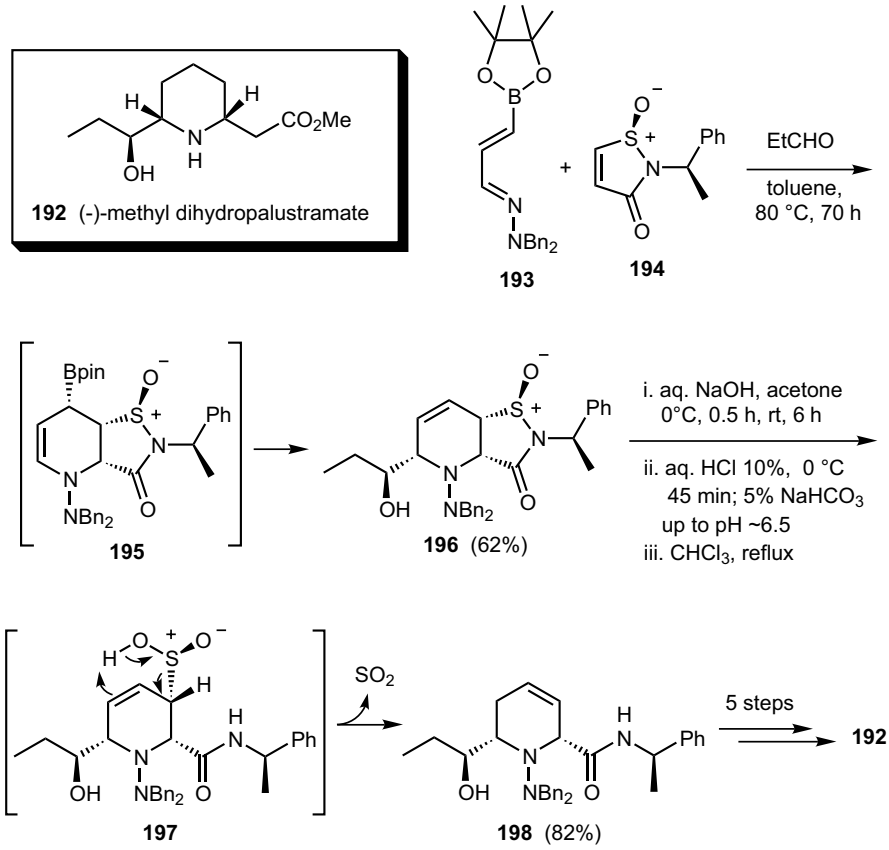
The stereocontrolled synthesis of α-hydroxyakylated piperidines, a motif frequently encountered in natural products, represents a difficult synthetic challenge that was recently tackled by Hall and co-workers using the aza-variant of the Vaultier–Lallemand three-component reaction described in Scheme 12.14 [62]. One interesting feature of this reaction is the use of hydrazines, as masked amines, which allows the hetero-Diels–Alder reaction to operate on a normal electron demand manifold. Touré and Hall recently applied this powerful MCR to the asymmetric synthesis of (−)-methyl dihydropalustramate **192** [91], a degradation product and postulated biosynthetic precursor of (+)-palustrine (Scheme 12.27) [92].

This synthesis featured the thermal reaction of a mixture of 1-dibenzylamino-1-aza-4-boronodiene **193**, Waldner's chiral dienophile **194** [93] and propionaldehyde in toluene for three days. The tandem [4+2]/allyboration adduct **196** was isolated as a single regio- and diastereomer in good yield. The latter compound was then treated with sodium hydroxide followed by acidification to afford the corresponding sulfinic acid intermediate **197**, which fragmented in refluxing chloroform to give amide **198** in good yield through a retro-sulfinyl-ene rearrangement [94]. The completion of the synthesis of **192** included a one-carbon homologation and the cleavage of the N–N bond to reveal the piperidine moiety.

The antibiotic and G-protein coupled receptor ligand martinelline **199** (Scheme 12.28) is a quinoline alkaloid that was isolated from root extracts of *Martinella iquitosensis* [95].

The retrosynthesis of this compound by Batey and co-workers [96] recognized that the unprecedented hexahydropyrrolo[3,2-*c*]quinoline core could be synthesized using a three-component Pavarov hetero-Diels–Alder reaction [97]. For this synthetic strategy to be successful, however, reaction conditions that favor the exo approach of the dienophile over the endo approach had to be found. For this purpose, a variety of protic acids were tested, and it was found that the reaction was best carried out in the presence of camphorsulfonic acid (CSA). Indeed, a mixture of 4-aminobenzoate **200** and *N*-Cbz 2-pyrroline **201** were stirred at room temperature in the presence of catalytic CSA to afford exo cyclo-adduct **203** as the major product (Scheme 12.28). The *N*-Cbz 2-pyrroline served as both an aldehyde equivalent and a dienophile in this context. The Diels–Alder adduct **203** already bore all the requisite functionalities for the successful completion of the synthesis, which was achieved in six additional steps.

Symmetrically substituted cyclopentanones have proven to be very good substrates in allylic substitution chemistry [98]. This chemistry is elegantly exploited by Blechert and co-workers for the synthesis of the nerve poisoning tetraponerine

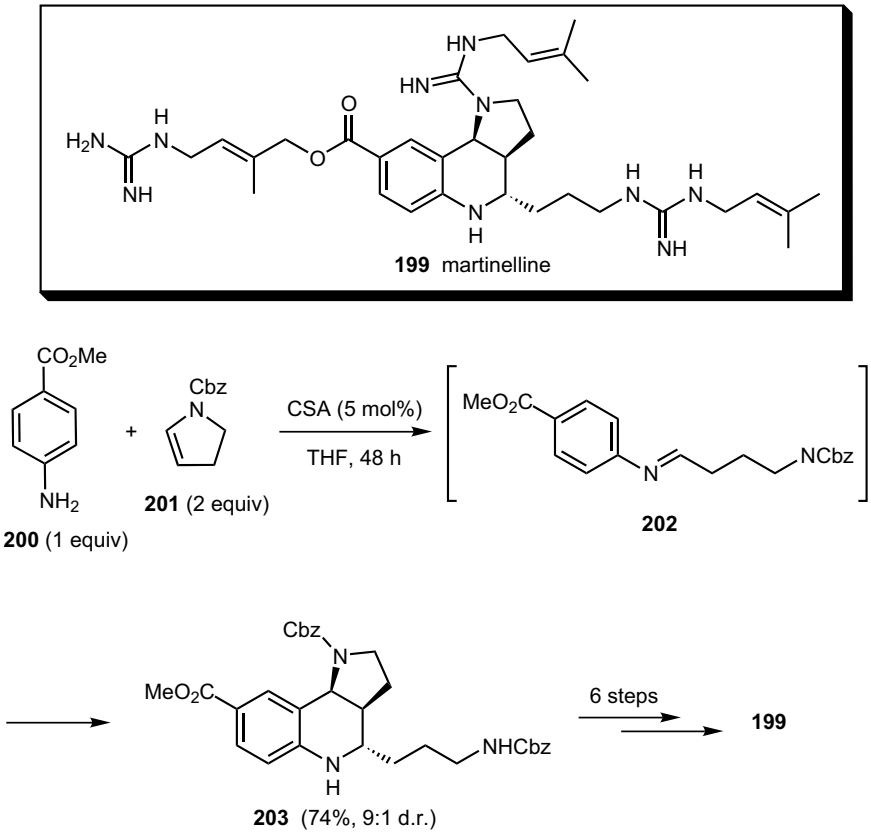


Scheme 12.27. Synthesis of methyl dihydropalustramate using a three-component aza[4+2] cycloaddition/allylboration, by Touré and Hall [91] Bn = benzyl, pin = pinacolato.

natural products, exemplified by **204** (Scheme 12.29) [99], isolated from the New Guinean ant *Tetraponera* sp. [100].

The desymmetrization of dicarbonate **206** was initiated by the addition of one equivalent of *N*-(3-butenyl) nosylamide **207** under palladium catalysis in the presence of Trost's chiral diphosphine ligand **205**. When the first allylic substitution was completed, the reaction was warmed and the resulting intermediate **208** was treated *in situ* with one equivalent of a second nosylamide **209**. Product **210** resulting from this double substitution reaction was submitted to a tandem intramolecular ROM/RCM to furnish key precursor **211**, which was engaged in the final cyclization step by the reduction of the double bonds, followed by the HCl-promoted domino deprotection of the acetal and aminal formation.

Two other piperidine-containing natural products were synthesized using MCRs already discussed in this chapter. Tietze and co-workers used asymmetric transfer

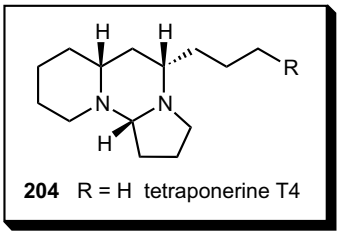


Scheme 12.28. Synthesis of martinelline using a Pavarov 3CR, by Powell and Batey [96] Cbz = benzyloxycarbonyl, CSA = camphorsulfonic acid, THF = tetrahydrofuran.

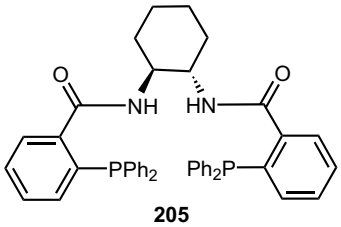
hydrogenation of imines [101] as a tool for the elaboration of optically active isoquinolines, a class of alkaloids exemplified by emetine **212** (Figure 12.4).

Emetine is the main alkaloid found in the root of *Cephaelis ipecacuanha* [102], which has been used for centuries as an emetic and was subsequently shown to be a potent antiamebic [103]. A concise synthesis of this compound as well as a small library of analogues was recently reported by Tietze and co-workers [104], who made use of their powerful three-component domino-Knoevenagel-condensation/hetero-[4+2] reaction sequence previously described in Section 8.1.

The dendrobatid alkaloid 251F **213** (Figure 12.4) was isolated from the skin exudates of a Columbian dendrobatid poison frog, *Minyobates bombetes* [105]. The asymmetric total synthesis of this molecule has been reported by Aubé and co-workers [106]. The synthesis featured a Noyori-type three-component reaction to access an advanced bicyclopentenone intermediate, and also included a tandem ROM/RCM reaction sequence and a Schmidt rearrangement as key steps.



204 R = H tetraponerine T4



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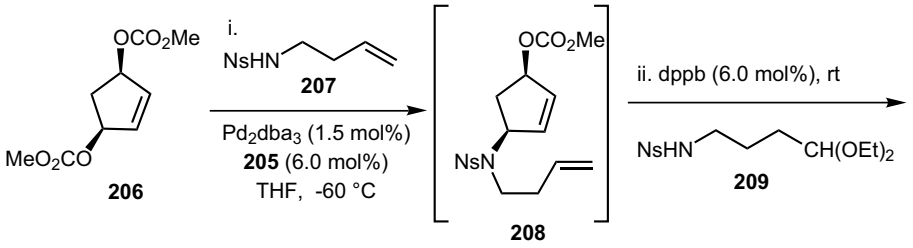
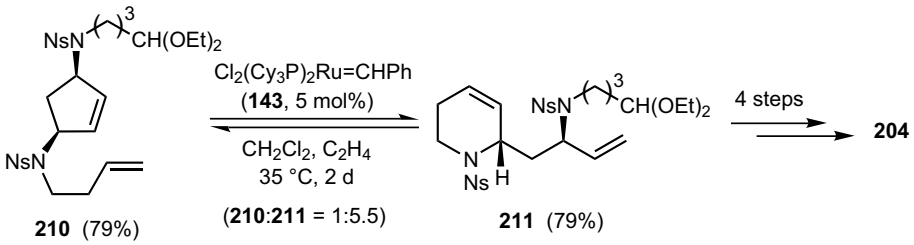
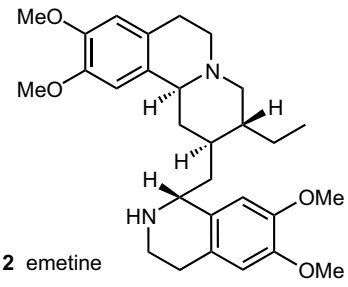


206 **208** **209**

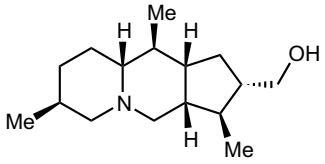


210 (79%) **211** (79%)

Scheme 12.29. Synthesis of tetraponerines using a three-component double allylic amination, by Stragies and Blechert [99] Ns = nosyl, dba = dibenzylideneacetone, dppb = 3,4-di(bisphenylphosphino)butane, Cy = cyclohexyl.

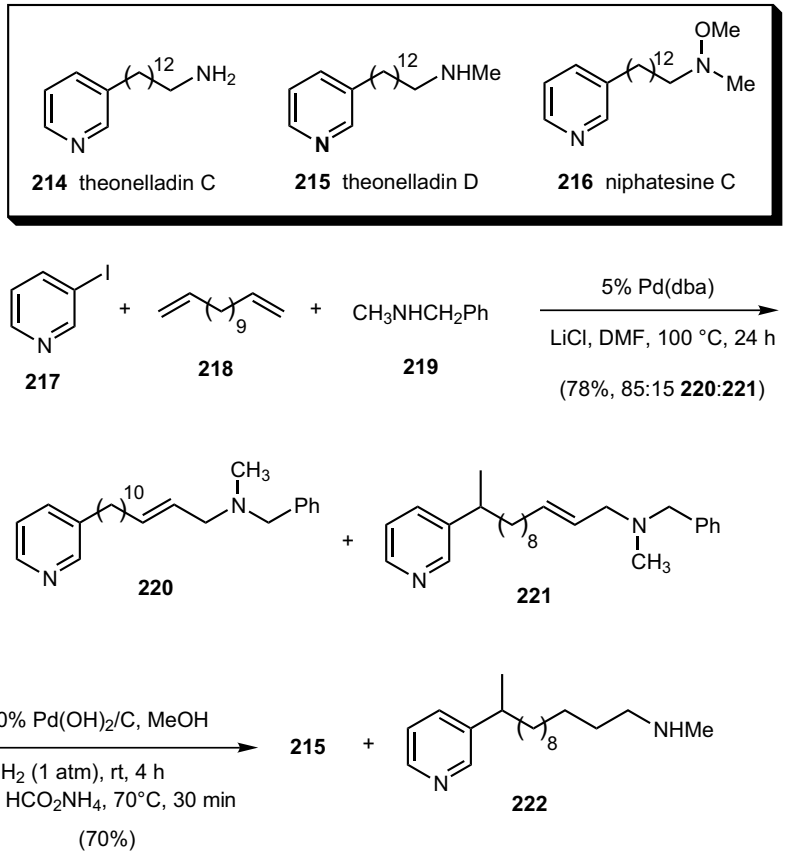


212 emetine



213 dendrobatid 251F

Fig. 12.4. Chemical structures of emetine and dendrobatid 251F.



Scheme 12.30. Synthesis of theonelladin D using a three-component hetero-cross-coupling reaction, by Larock and co-workers [108] dba = dibenzylideneacetone, DMF = dimethylformamide.

12.8.3 Pyridines

Theonelladins C **214** and D **215** and niphatesine C **216** are members of a rapidly growing class of 3-substituted pyridine alkaloids that are known to display important biological activities (Scheme 12.30) [107]. For instance, theonelladins C and D have shown antileukemic and antineoplastic properties while niphatesine C is a known antileukemic agent.

These interesting biological properties have fueled the development of new synthetic methods aimed at rapidly assembling these simple compounds and analogues thereof. Within this context, Larock's three-component cross-coupling reaction involving halo-pyridines, dienes and amines stands as a powerful method as it

tolerates a wide variety of aryl halides, dienes and nucleophiles [108]. For the synthesis of **215**, 3-iodo pyridine **217** was mixed in one pot with 1,12-tridecadiene **218** and *N*-benzyl methylamine **219** under palladium catalysis to afford key intermediate **220** and a small amount of an inseparable impurity **221** (Scheme 12.30). A one-pot, stepwise hydrogenation of the double bond followed by debenzylation then afforded the natural product **215** and its analogue **222** as an inseparable mixture. One minor limitation of this multicomponent chemistry lies in the fact that it is mainly compatible with secondary amines. Thus, for the synthesis of **214**, a protected amine, *N*-benzyl tosylamide, was employed. The synthesis of **215** was also revisited using *N*-methyl tosylamide, which allowed the preparation of **215** as a single isomer. A similar synthetic strategy also led to the synthesis of niphatesine C **216**.

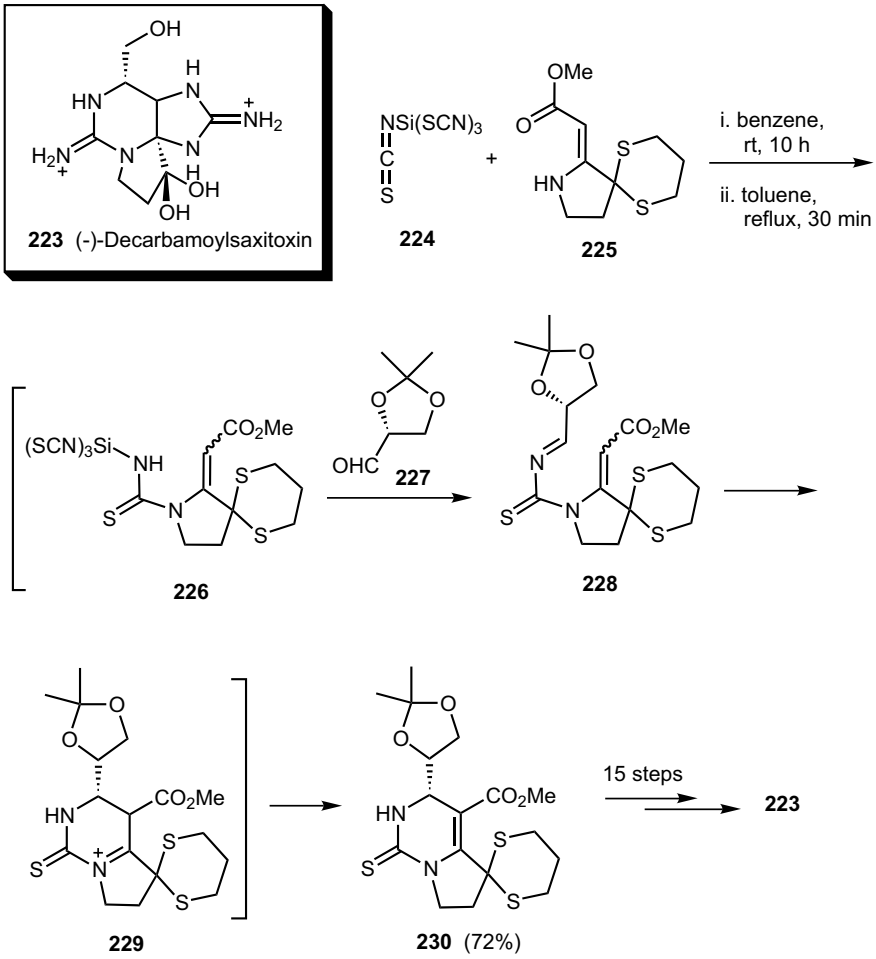
12.8.4
Guanidiniums

(−)-Decarbamoylsaxitoxin **223** (Scheme 12.31) was first obtained from saxitoxin by acid hydrolysis and was latter isolated as the minor toxic principle of the bivalve *Spondylus butleri* collected at Arumizu Bay in Palau [109].

The toxicity of these compounds stems from their ability to block sodium channels. The unique heterocyclic backbone, together with the sensitive functionalities embedded within this molecule, make it a daring synthetic target. The enantioselective synthesis of the unnatural antipode by Kishi and co-workers was motivated by the controversy surrounding its biological activity (Scheme 12.31) [110]. The key sequence started with a trimolecular cyclization of vinylogous urethane **225**, silicon tetraisothiocyanate **224**, and (*R*)-glyceraldehyde 2,3-acetonide **227**. The proposed stepwise mechanism of this elegant MCR features the Mannich-type cyclization of **228**, which stereochemical outcome can be explained using a simple Felkin–Ahn model. The resulting product **230** was transformed into synthetic **223** using a relatively standard sequence. Coincidentally, it did not display any of the sodium channel blocking activity of its natural counterpart.

12.9
Peptides

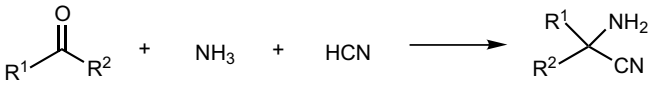
Protein–protein and protein–peptide interactions are of fundamental importance as they regulate a host of biological processes. The understanding of these phenomena therefore represents a prerequisite to the rational design of new medicines [111]. Synthetic peptides and their analogues have so far played major roles in this context, due in large part to the development of powerful methods and reagents for direct amide coupling [112], and the invention of solid-supported synthesis [113]. Despite these advances, new avenues for the rapid elaboration of these biopolymers are still being explored. One emerging concept in this area is the development of MCRs. While the application of MCRs is still in its infancy, it has



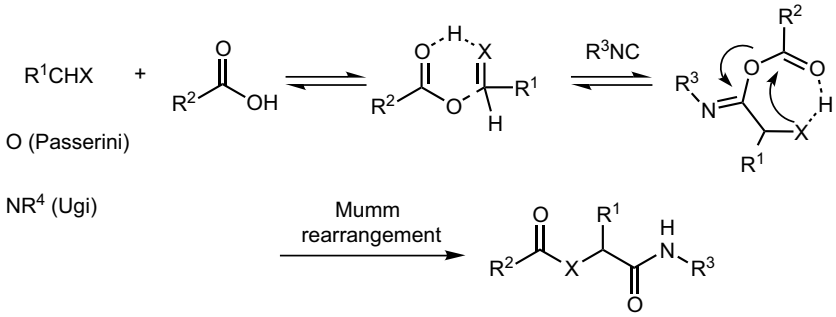
Scheme 12.31. Synthesis of decarbamoylsaxitoxin using a three-component thiourea formation/imine addition, by Hong and Kishi [110].

already delivered three of the most powerful and common tools for the synthesis of amino acids, peptides and peptoids, be it cyclic or linear. The Strecker amino acid synthesis is of historical importance in chemistry as it represents one of the early examples of MCRs [114]. Coincidentally, this reaction addressed the formation of some of nature's fundamental building blocks: amino acids. Indeed, in 1850, Strecker demonstrated that α-amino cyanides could be obtained from simple and easily accessible materials such as ammonia, carbonyl compounds and hydrogen cyanide (Scheme 12.32). This reaction process has been utilized for the synthesis of natural and synthetic amino acids and many asymmetric variants are now available [115].

A. The Strecker reaction



B. Proposed mechanism for the isocyanide MCRs

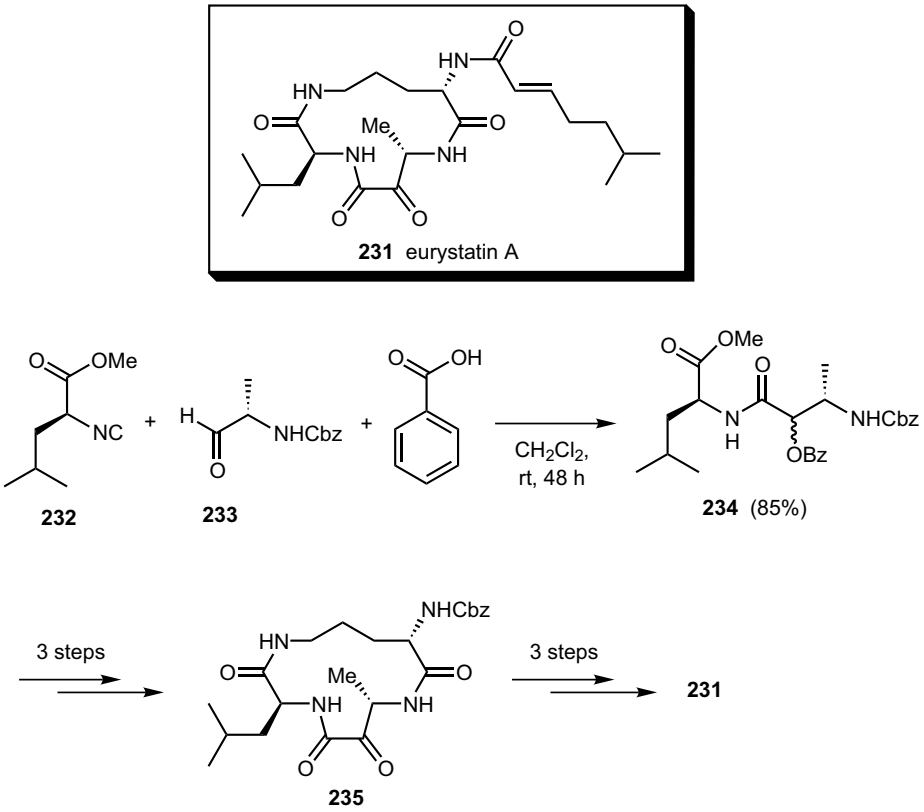


Scheme 12.32. Multicomponent reactions for amino acid and peptide synthesis.

Isocyanides, formal divalent carbon functionalities, are ideal candidates for the development of MCRs. Their reaction with carbonyls and imines, through an α-addition process, generates a zwitterionic intermediate, which is then trapped by a nucleophile. The resulting double α-addition adduct is unstable and rapidly undergoes the Mumm rearrangement to afford the final product (Scheme 12.32). The venerable three-component Passerini reaction is the first MCR based on this type of reaction process [116]. It addresses the formation of α-acyloxycarboxamides, which constitute a class of very versatile synthons in organic chemistry. In the present context, this reaction was utilized by Schmidt and collaborators for the elaboration of intermediate **234** [117], a key fragment for the synthesis of the prolyl endopeptidase inhibitor Eurystatin A **231** (Scheme 12.33) [118].

The initial α-addition adduct from the reaction of methyl (*S*)-2-isocyano-4-methylpentanoate **232** and protected (*S*)-alaninal **233** further reacted with benzoic acid to furnish **234** as a diastereomeric mixture. The stereochemistry of the resulting benzoyl-protected alcohol was inconsequent since the latter functionality is oxidized during the course of the synthesis using pyridinium dichromate to afford the α-oxoamide in the final target. In general, however, in isocyanide MCRs the control of the newly created stereogenic center is problematic and separation of diastereomeric mixtures cannot be avoided. A recent report by Denmark and Fan on a catalytic asymmetric variant of this reaction therefore represents an interesting development [119].

The Ugi four-component reaction (4CR) stands as a powerful method for the

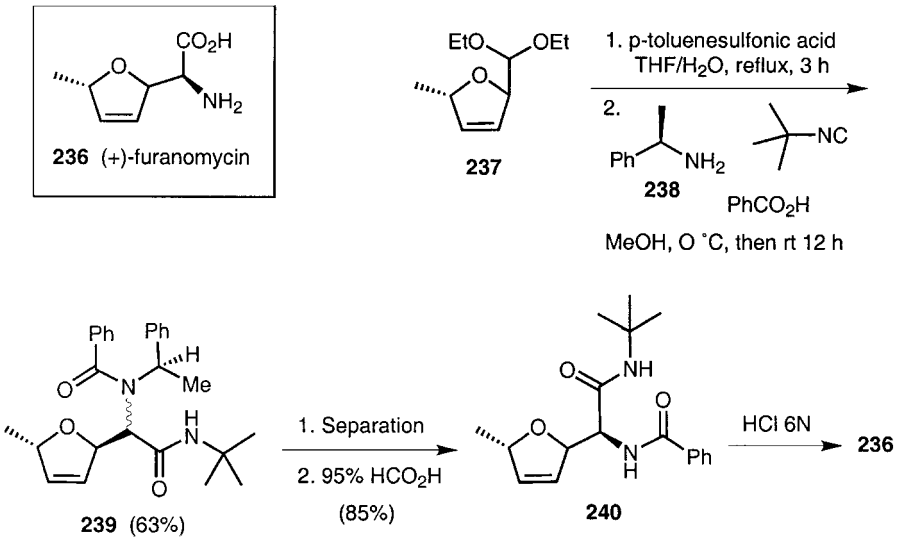


Scheme 12.33. Synthesis of eurystatin using a Passerini 3CR, by Schmidt and Weinbrenner [117] Cbz = benzyloxycarbonyl, Bz = benzoyl.

synthesis of peptide fragments although the development of an efficient asymmetric variant still remains an active area of research. Despite this apparent limitation, the Ugi reaction has found widespread applications in combinatorial synthesis [120]. The reaction combines an amine, aldehyde, carboxylic acid and isocyanide in one pot to afford α-acylamino-amide-containing compounds through a mechanism similar to the Passerini reaction (Scheme 12.32). The applications of this powerful four-component reaction in target-oriented synthesis are discussed next.

The potent amino acid antibiotic furanomycin **236** (Scheme 12.34), isolated from *Streptomyces threomyceticus* [121], was synthesized by Joullié and co-workers using an Ugi four-component reaction as key step [122].

Enantiopure acetal **237** and α-methyl benzylamine **238** were mixed in methanol in the presence of *tert*-butyl isocyanide and benzoic acid to afford a separable diastereomeric mixture of the Ugi reaction 4CR product **239**. Debenzylation using



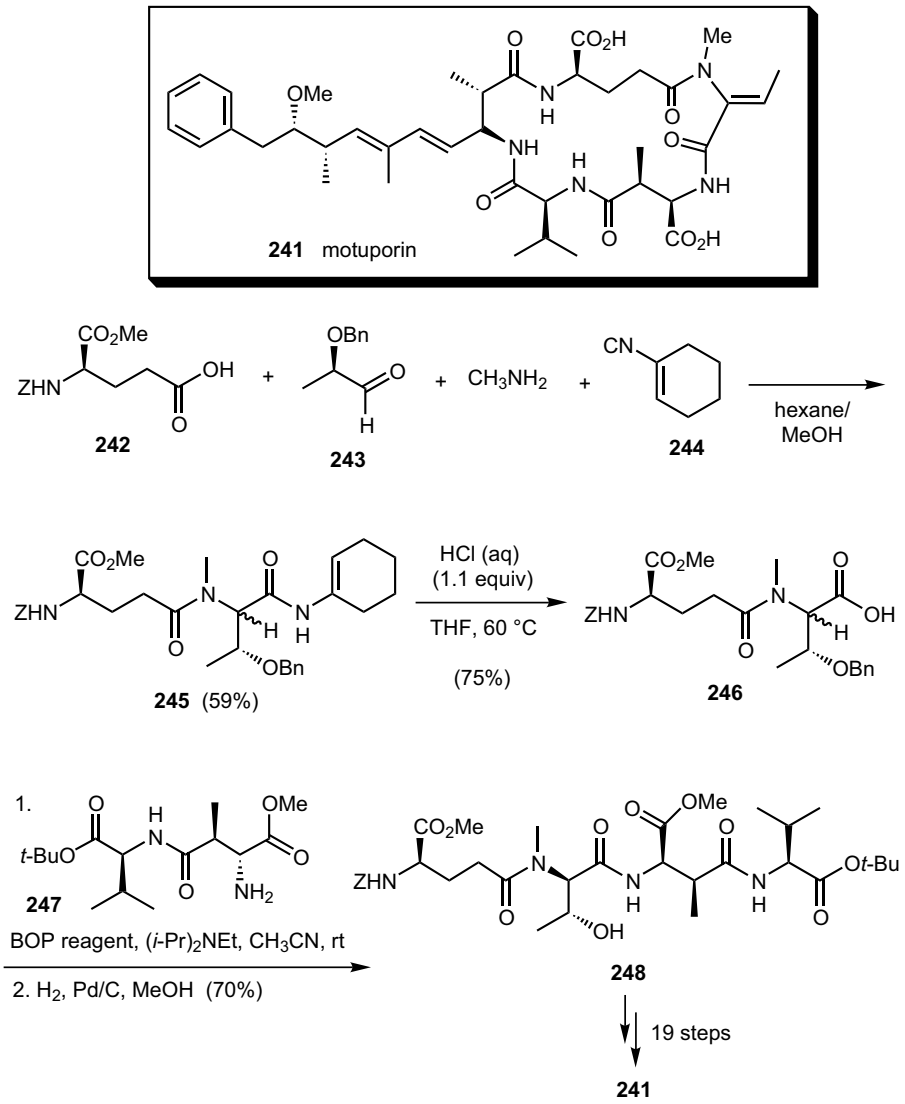
Scheme 12.34. Synthesis of furanomycin using a Ugi 4CR, by Joullié and co-workers [122] THF = tetrahydrofuran.

formic acid, aimed at preserving the double bond, followed by acid hydrolysis of the secondary amides of **240**, afforded the target molecule. The same group also devised a potential route to the 14-membered cyclopeptide alkaloid Nummularine-F based on an Ugi three-component reaction for which the imine component was preformed [123].

The Ugi four-component reaction can frequently offer an interesting alternative to the difficult coupling between secondary amines and carboxylic acids when using traditional methods for amide bond formation. Guided by this premise, Armstrong and co-workers efficiently synthesized the *N*-methylated dipeptide **245** *en route* to motuporin **241** (Scheme 12.35) [124], an inhibitor of protein phosphatases [125].

The synthesis started with an Ugi four-component condensation involving protected glutamic acid **242**, aldehyde **243**, methylamine and cyclohexenyl isocyanide **244**. The resulting dipeptide product **245** was first hydrolyzed to acid **246**, which was then coupled with amine **247**. Further derivatizations of the resulting tripeptide **248** afforded the desired natural product.

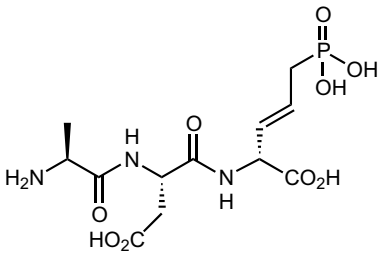
A few other biologically interesting and naturally occurring peptides and amino acids of rather simple structure were synthesized using the Ugi four-component reaction (Figure 12.5): the phosphonic acid antibiotics plumbemycin A **249** and B **250** [126], both epimers of the polychlorinated antihypertensive peptide (+)-demethyldysidenin **251** [127], and the nucleoside antibiotic nikkomycin **252** [128].



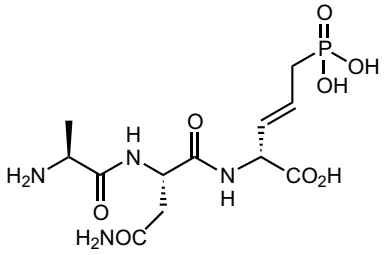
Scheme 12.35. Synthesis of motuporin using a Ugi 4CR, by Bauer and Armstrong [124] Z (Cbz) = benzylozycarbonyl, Bn = benzyl, THF = tetrahydrofuran, BOP = benzotriazolyl-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate.

12.10 Other Natural Products

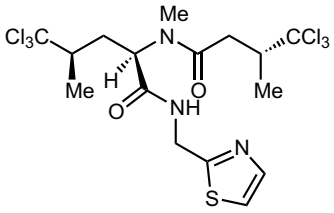
Preethulia coumarin **253** (Scheme 12.36) represents a naturally occurring analogue of ethuliacoumarin, a prenylated polyketide.



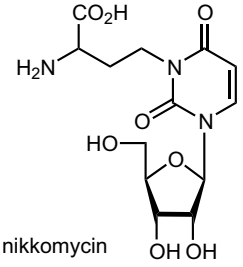
249 plumbemycin A



250 plumbemycin B



251 demethyldysidenin

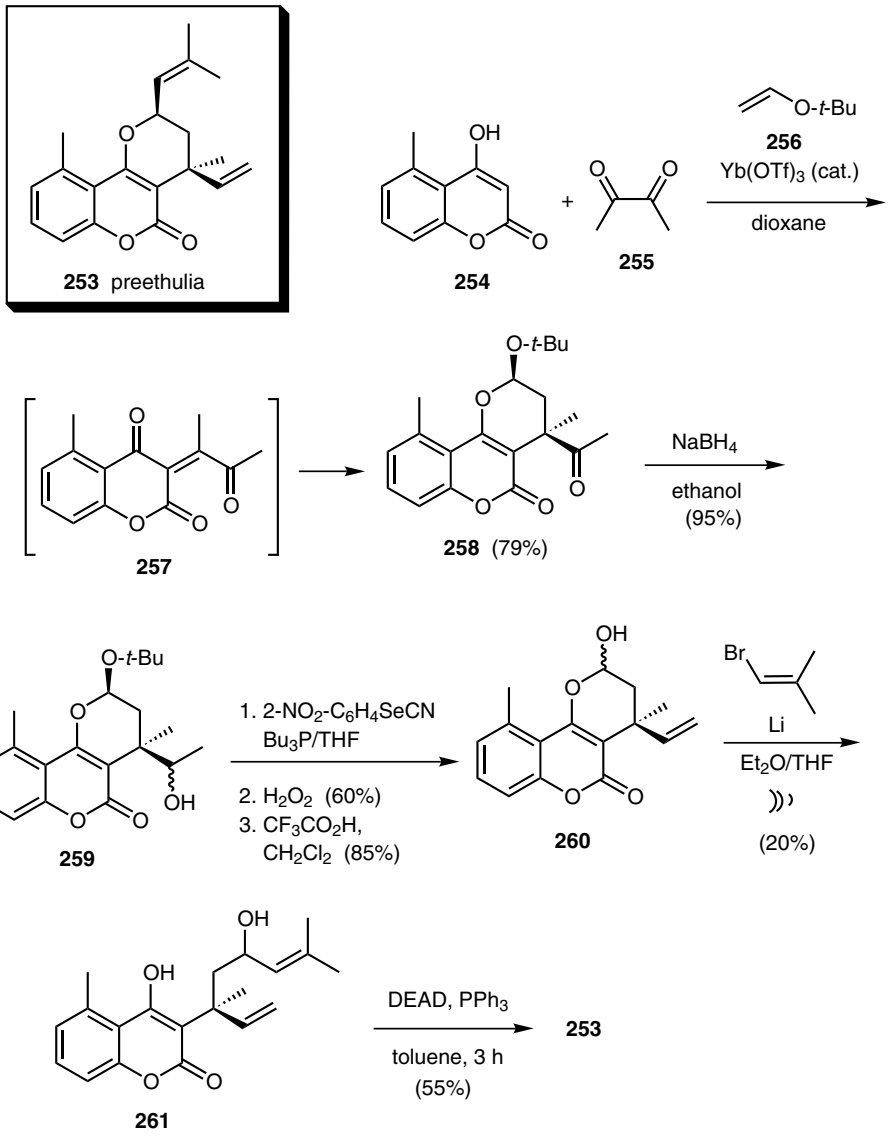


252 nikkomycin

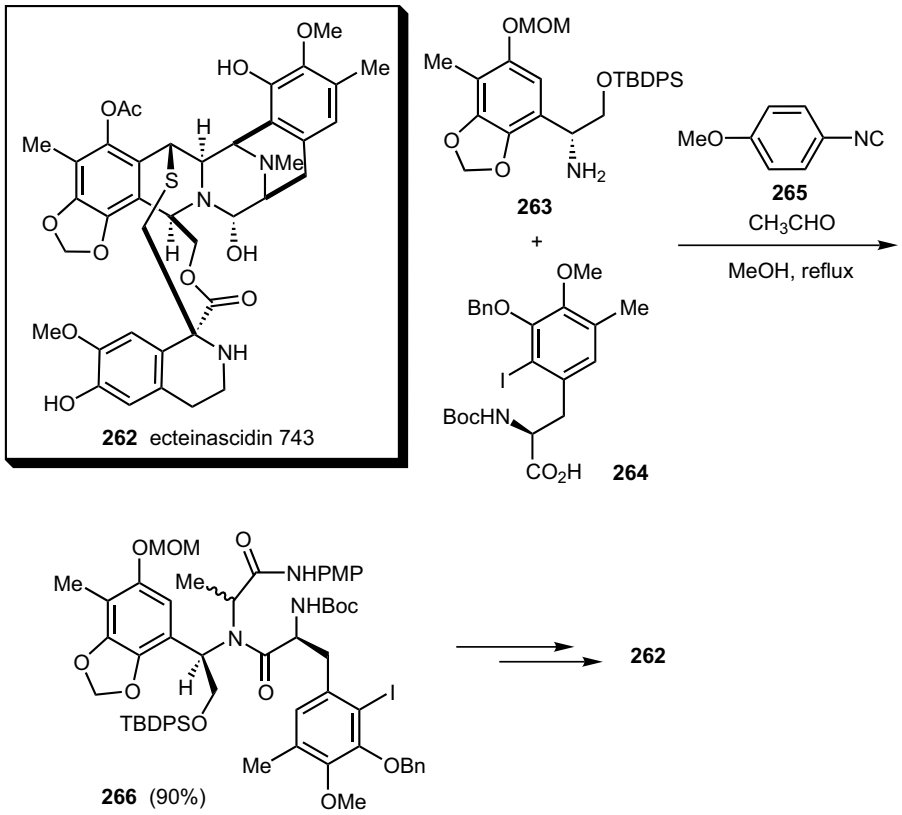
Fig. 12.5. Chemical structures of plumbemycin A and B, demethyldysidenin, and nikkomycin.

The latter compound possesses powerful anthelmintic and molluscicidal activities [129]. Some analogues have also shown a similar activity profile which rendered their syntheses rather rewarding. The synthesis of (±)-preethulia coumarin by the groups of Appendino, Cravotto and co-workers [130] started with a variant of the three-component Knoevenagel/hetero Diels–Alder reaction developed by Tietze and collaborators [86, 87]. Thus, 4-hydroxycoumarin **254**, 2,3-butadione **255** and vinyl *t*-butyl ether **256** were combined under established reaction conditions to afford the desired adduct **258** in satisfactory yield (Scheme 12.36). The ketone was then reduced with $NaBH_4$ and the alcohol was eliminated to install the required terminal olefin of intermediate **260**. The latter was obtained as an unstable mixture of hemiacetals following cleavage of the *t*-butyl ether with trifluoroacetic acid, and it was immediately submitted to norprenylation to furnish diol **261**. An intramolecular Mitsunobu etherification afforded the target molecule **253**.

Ecteinascidin 743 **262** (Scheme 12.37) represents a powerful antitumor agent, which has been submitted to clinical trial. This complex polyazacyclic, polyaromatic compound was isolated from the marine tunicate, *Ecteinascidia turbinate* [131]. A total synthesis of this natural product, which featured an Ugi four-component reaction as pivotal step, was recently reported by Fukuyama and co-workers [132]. The highly decorated phenylglycinol **263** was obtained *via* an asymmetric Mannich-type reaction [133], and was engaged in a multicomponent condensation process involving the protected amino acid **264**, *p*-methoxyphenyl isocyanide **265** and acetaldehyde to afford dipeptide **266** in high yield. This com-



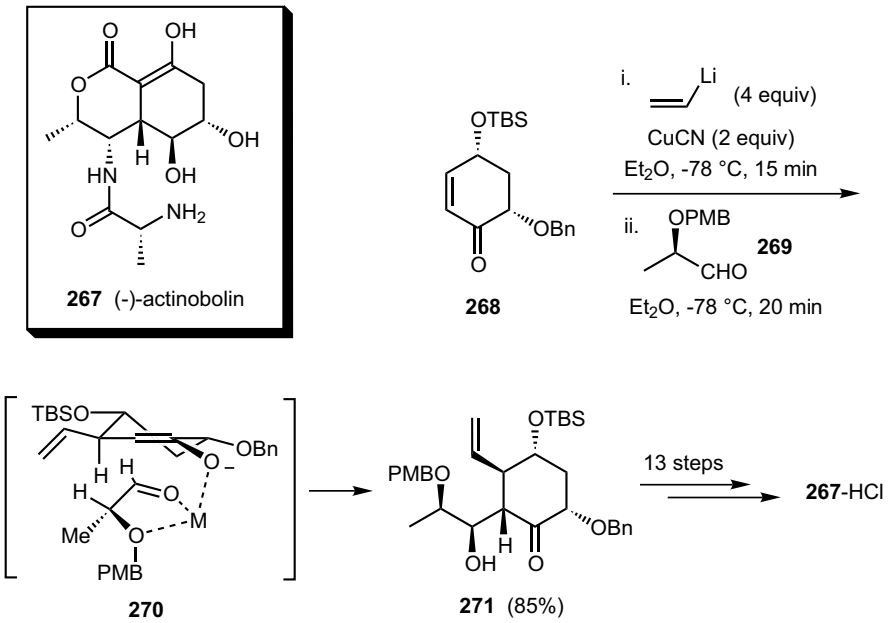
Scheme 12.36. Synthesis of preethulia using a three-component Knoevenagel/hetero[4+2] cycloaddition, by Appendino, Cravotto, and co-workers [130] Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, DEAD = diethylazodicarboxylate.



Scheme 12.37. Synthesis of ecteinascidin 743 using a Ugi 4CR, by Fukuyama and co-workers [132] MOM = methoxymethyl, TBDPS = *t*-butyldiphenylsilyl, Boc = *t*-butoxycarbonyl, Bn = benzyl, PMP = p-methoxyphenyl.

pound included all the necessary carbon atoms for the elaboration of the upper fragment. The synthesis of **262** was eventually completed in about 36 steps.

The antibacterial and antitumor agent actinobolin **267** (Scheme 12.38) was isolated from culture broths of *Streptomyces* [134]. A formal total synthesis of both antipodes of this molecule was recently reported by Chiba and co-workers using a Noyori-type three-component reaction as a key step [135]. Using a sequence of standard synthetic transformations D-glucose was first transformed in seven steps to the key intermediate, cyclohexenone **268**, which was then engaged in the crucial three-component reaction. Conjugate addition using a higher order vinylcuprate proceeded anti to the bulky siloxy group, and the ensuing enolate was trapped with aldehyde **269** to afford the tandem conjugate addition/aldol adduct **271** in 85% yield. The aldol step occurred in a highly stereoselective manner as illustrated in the proposed transition structure **270** (Scheme 12.34). From key intermediate **271**, the synthesis of the antipode of the natural product, (−)-actinobolin **267** was



Scheme 12.38. Synthesis of actinobolin using a three-component conjugate addition/aldol condensation, by Chida and co-workers [135] TBS = *t*-butyldimethylsilyl, Bn = benzyl, PMB = p-methoxybenzyl.

then completed in 13 steps. The synthesis of the naturally occurring enantiomer was completed using a similar strategy.

Although this chapter focused mainly on MCRs that led to the accomplishment of the total synthesis of a natural product, it is worth mentioning that a number of multicomponent reaction strategies have been reported as efficient approaches towards natural-product-like molecules. For example, using isocyanide-based MCRs, Zhu and co-workers have reported the synthesis of natural-product-like biaryl ether macrocycles [136], as well as an approach to the lennoxamine family [137]. A similar concept was also exploited by Dömling and co-workers in their design of natural-product macrocycles [138]. Posner and co-workers have reported a three-component Michael–Michael–Dieckman approach to *β*-vetivone [139]. Márko and co-workers also described an interesting three-component reaction that operated on a silyl-modified Sakurai reaction-type manifold, affording subunits present in many natural products [140]. Recently, Lindsley and co-workers reported a three-component condensation to polysubstituted triazines, which were used as precursors to the skeleton of canthine alkaloids [141]. As exemplified by recent reports from the research groups of Wender [142], Montgomery [143], Ikeda [144] and Murakai [145] several transition metal-promoted MCRs have also demonstrated undeniable potential towards the formation of medium and strained bicyclic ring

structures reminiscent of specific families of natural products. It seems only a matter of time before these powerful processes become commonly used in the total synthesis of complex natural products.

12.11 Conclusion

It is clear from the variety of natural products described in this chapter that multicomponent reaction strategies encompass a very broad scope of synthetic transformations. The development of new MCRs constantly generates new opportunities, and it is likely that the application of these powerful processes in natural product synthesis is still in its infancy. Appealing characteristics of MCR strategies such as convergence and step-economy are expected to draw more and more synthetic chemists to design and implement MCRs in the total synthesis of complex natural products.

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13
The Modified Sakurai and Related Reactions

Thomas Jacques, István E. Markó, and Jiří Pospíšil

13.1
Introduction

Chemists are continuously searching for new, even more efficient methodologies that are also highly convergent, atom economical and, nowadays, environmentally friendly. From this perspective, novel synthetic processes that construct several C–C bonds or ring systems in a single operation are particularly worthwhile. Such is the case for multicomponent condensations in which fine tuning the reactivity of the various substrates leads to remarkable control in the subsequent cascade of sequential elementary transformations. This chapter is dedicated to a silicon-based multicomponent methodology, the silyl-modified Sakurai reaction, and some of its most useful variations.

Silicon is a widespread element on Earth, easy to purify and employed in a large variety of applications, from glass to drugs *via* computer components. Silicon is σ-donor (Pauling electronegativity = 1.8) compared to carbon (2.5) and its low-lying empty d-orbitals make it a good π-acceptor (Figure 13.1). This last concept explains why the Si–Cl and Si–O bonds are shorter than expected.

Silicon also stabilizes an anion at the α position and a cation at the β position. The α effect is explained by the dilution of the negative charge into the σ^*(Si–C) bond and the β effect is due to the interaction between the carbon–silicon σ-bond and the empty p orbital (Figure 13.2) [1, 2].

Most organosilicon compounds (silyl ethers, silylenolethers, allyl- and vinylsilanes) are stable enough to be easily prepared, handled and stored with a minimum of precautions. Whilst silyl ethers are mainly considered as protected alcohol

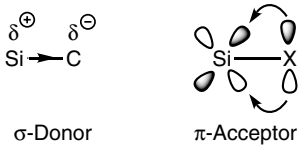

Fig. 13.1. Silicon can act as both a σ-donor and a π-acceptor.

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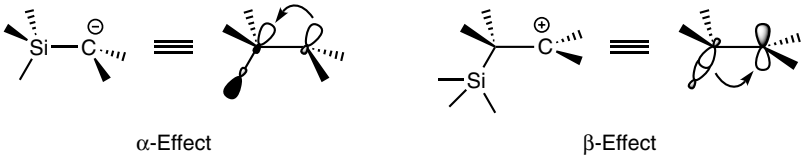
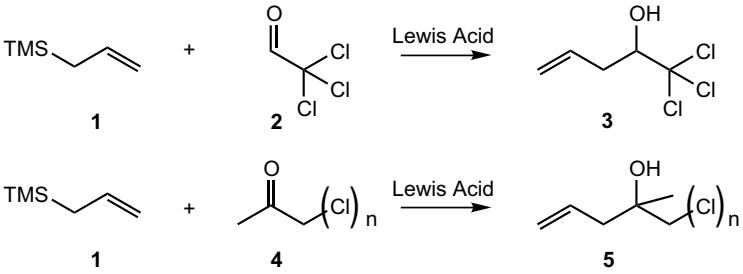


Fig. 13.2. The influence of silicon on adjacent α- and β-positions.

functions, silylenolethers, allyl- and vinylsilanes are important intermediates in many total syntheses. Excellent reviews have appeared on the chemistry of silylenolethers. In this chapter, we focus on multicomponent condensations involving allyl- and vinylsilanes. We discuss both inter- and intramolecular coupling reactions, placing special emphasis on their synthetic utility.

13.2 The Sakurai–Hosomi Reaction

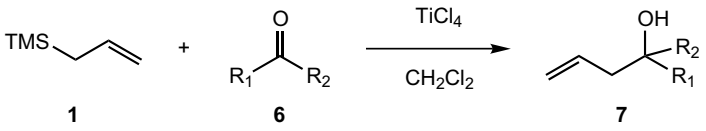
The first addition of allylsilane **1** to activated carbonyl compounds, such as chloral **2** or α-chloroacetone **4**, leading to γ-δ-unsaturated alcohols **3** or **5**, was reported by Calas *et al.* [3, 4] in 1974 and Abel and Rowley [5] in 1975. A Lewis acid, such as $AlCl_3$, $GaCl_3$ or $InCl_3$ is required to promote this condensation (Scheme 13.1).



Scheme 13.1

At the same time, Sakurai and Hosomi [6] extended this reaction to a wide range of non-activated carbonyl compounds **6**, using $TiCl_4$ as Lewis acid (Scheme 13.2). The allylation occurred rapidly at room temperature and is applicable to both aldehydes and ketones.

Benzaldehyde (entry 3) and the hindered *iso*-butyraldehyde (entry 2) give the lowest yields. Sakurai and Hosomi next extended the addition of allylsilane **1** to enones **8** [7]. In the presence of $TiCl_4$, the 1,4-adduct **9** is obtained in good yields (Scheme 13.3). It is interesting to note that allylcuprates are less selective than allylsilanes and that β,β-disubstituted enones react efficiently, leading to ketones bearing a quaternary carbon center at the β position (entry 3).

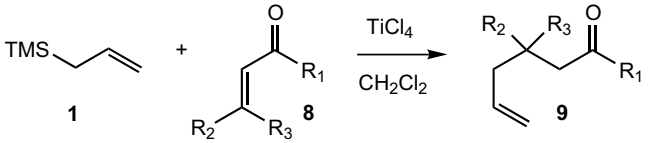


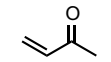
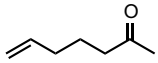
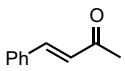
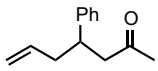
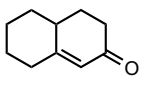
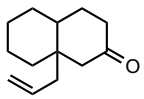
1 6 7

Entry	R^1	R^2	Time (min)	Yield (%)[a]
1	Pr	H	0.5	87
2	*i*-Pr	H	10	54
3	Ph	H	1	58
4	Me	Me	1	83
5	$-CH_2-(CH_2)_3-CH_2-$		3	70

[a] All yields refer to pure, isolated products

Scheme 13.2



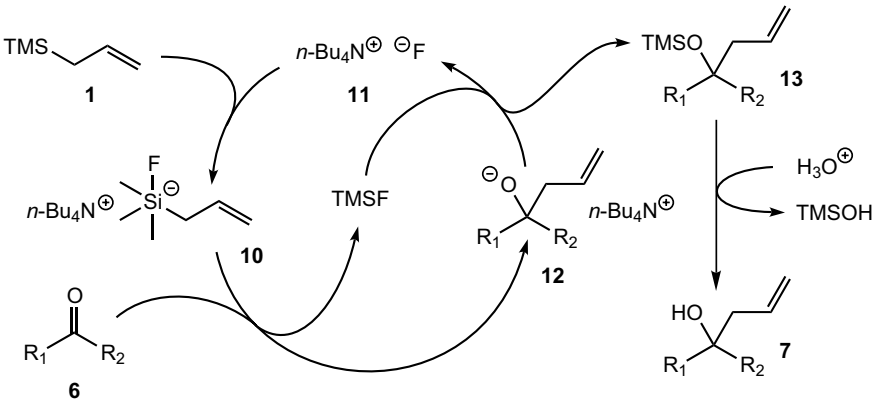
Entry	Enone	Yield (%)[a]	Product
1		59	
2		69	
3		88	

[a] All yields refer to pure, isolated products

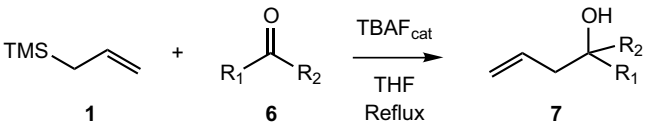
Scheme 13.3

In 1982, Sakurai [7] described a catalytic version of this reaction (Scheme 13.4). The addition of small quantities of fluoride anions to the allylsilane **1** generates the pentacoordinated silicon species **10**, probably in equilibrium with the starting materials **1** and **11**. This activated species can react with the carbonyl derivative **6** to yield the alkoxide **12** which is trapped by fluorotrimethylsilane. This last step not only furnishes the silylated compounds **13** but also regenerates the fluoride catalyst **11**. Acidic work-up then leads to the desired homoallylic alcohol **7**.

This addition occurs on aldehydes and ketones and is favored by the strong affinity of the fluoride anion for silicon (Si–F dissociation energy = 140 kcal mol^{-1})



Scheme 13.4



Entry	R^1	R^2	Yield (%)[a]
1	Pr	H	83
2	Ph	H	93
3	$-CH_2-(CH_2)_3-CH_2-$		60

[a] All yields refer to pure, isolated products

Scheme 13.5

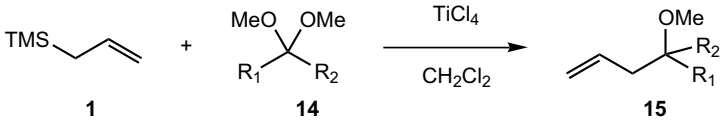
(Scheme 13.5). The reaction takes place in refluxing THF and typically employs tetrabutylammonium fluoride (TBAF) as the fluoride source.

These two methods of activation are complementary. The Lewis-acid (pull) procedure is most efficient for aliphatic carbonyls and the Lewis-base (push) protocol for the aromatic ones. It is noteworthy that TBAF, which often contains residual water, does not inhibit the reaction.

Sakurai *et al.* reported the condensation of allylsilane **1** with acetals [8], leading to the preparation of homoallylic ethers **15** (Scheme 13.6). The reaction occurs at −78 °C, in dichloromethane. The yields are usually excellent, even though the condensation is slower than with aldehydes and ketones.

In all these reactions, an equimolar amount of Lewis acid [8–10] was used. In 1981 [11], a catalytic version was developed, using 10 mol% of iodotrimethylsilane **17** (TMSI) as the Lewis acid. A few examples are shown in Scheme 13.7. The postulated mechanism is depicted in Scheme 13.8.

The acetal **14**, activated by the iodotrimethylsilane **17**, produces the oxonium cation **16** which can be intercepted by allylsilane **1** yielding homoallylic ether **15**, one equivalent of methoxytrimethylsilane **18** and the catalyst **17**.



1 14 15

Entry	R^1	R^2	Time (hrs)	Yield (%)[a]
1	*i*-Bu	H	3	90
2	Ph	H	1	74
3	Me	Me	3	98
4	$PhCH_2CH_2$	Me	3	71

[a] All yields refer to pure, isolated products

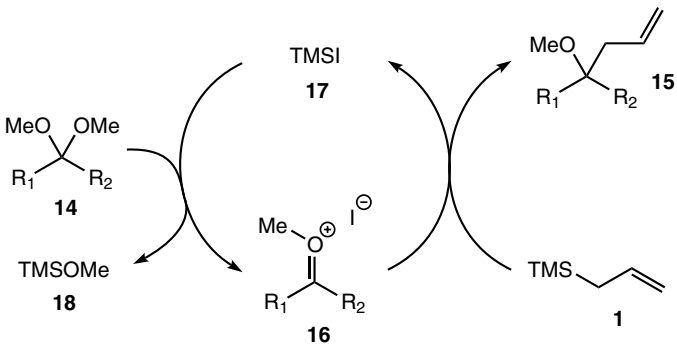
Scheme 13.6

1 14 15

Entry	R^1	R^2	Time (hrs)	Yield (%)[a]
1	*i*-Bu	H	2.5	70
2	Ph	H	8	81
3	Me	Me	3.5	83
4	$PhCH_2CH_2$	Me	6	95

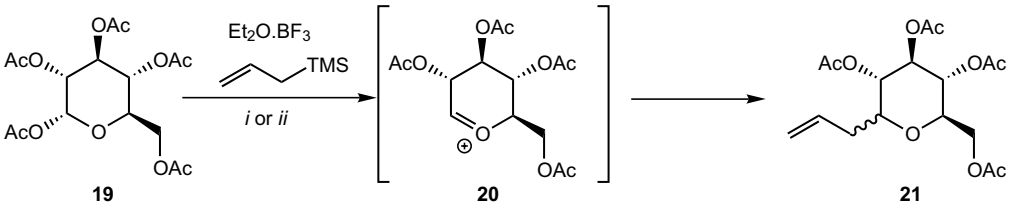
[a] All yields refer to pure, isolated products

Scheme 13.7

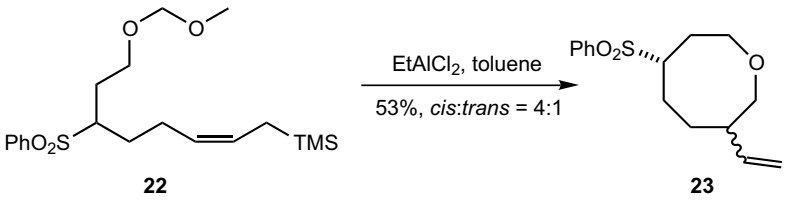


Scheme 13.8

Sakurai *et al.* as well as Sandhoff *et al.* used this approach for the synthesis of allyl-*C*-glycopyranosides **21** from readily accessible peracetylated or perbenzylated glycopyranoses **19** [12, 13]. Addition of allylsilane to oxonium **20** proceeds with an axial/equatorial selectivity that is considerably affected by the polarity of the solvent (Scheme 13.9).



Scheme 13.9

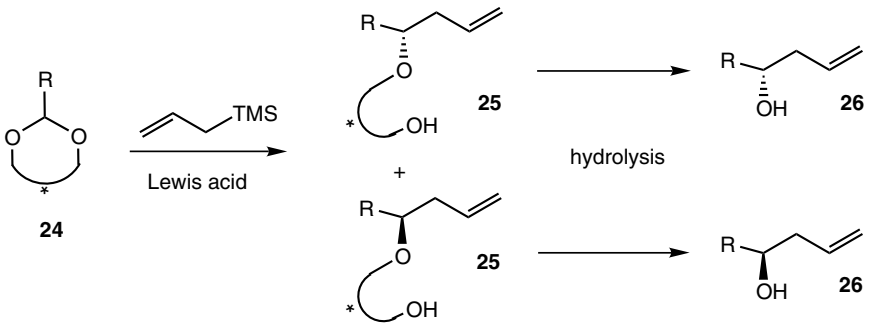


Scheme 13.10

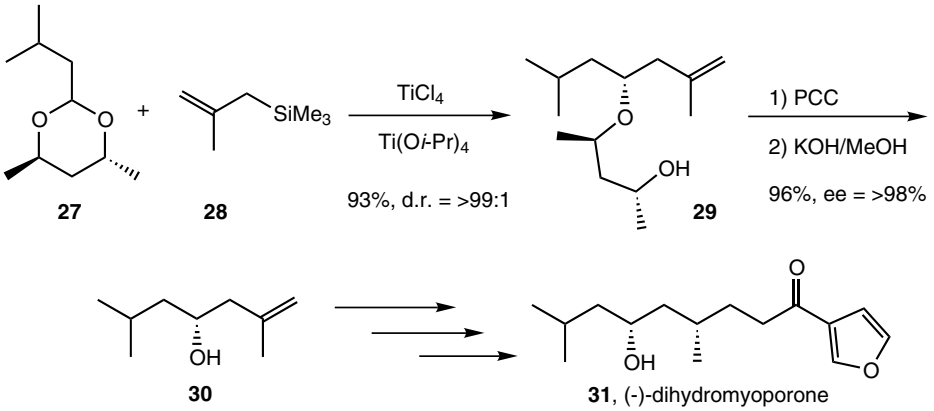
Simpkins *et al.* used an intramolecular variation of this allylsilane addition to oxonium cations for the synthesis of eight-membered rings [14]. Allylsilane **22**, containing the oxonium ion precursor (acetal function) is transformed upon treatment with $EtAlCl_2$ into the medium-sized ring **23** in moderate yield and stereoselectivity (Scheme 13.10).

Acetals and ketals **14** are the most often used precursors for the generation of oxonium species **16**. Their main advantages lie in their resistance towards various basic reagents, their easy conversion into the desired oxonium intermediates in the presence of a suitable Lewis acid and in their ability to produce, by reaction with allylsilanes, enantiomerically pure homoallylic alcohols **26**. For example, both enantiomers of **26** can be obtained starting from the enantiopure acetals **24** (Scheme 13.11).

Such a function is easily prepared by the condensation of homochiral diols such



Scheme 13.11



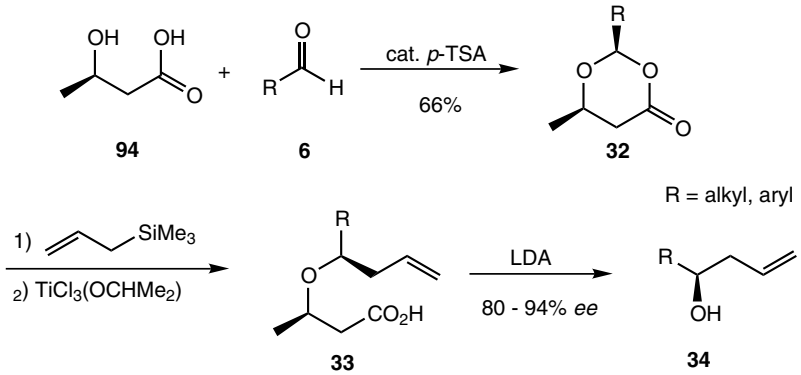
Scheme 13.12

as (*R*,*R*)-2,3-butanediol, with the corresponding aldehyde or ketone [15]. Johnson *et al.* utilized this method during the synthesis of (−)-dihydromyoporone **31** [16].

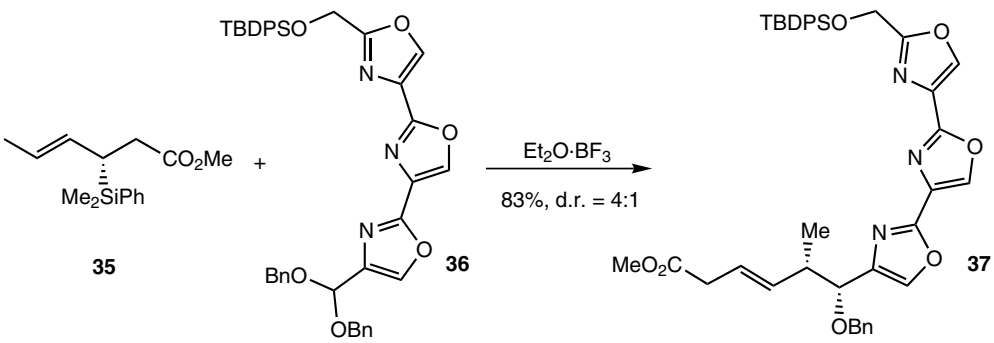
The addition of trimethyl (2-methylallyl)silane **28** to acetal **27** was chosen as the key step. The reaction proceeded smoothly and generated homoallylic ether **29** with high diastereoselectivity. The desired homoallylic alcohol **30** could subsequently be obtained, in high enantiomeric purity, by oxidative deprotection of the chiral template (Scheme 13.12).

An alternative way leading to optically active homoallylic alcohols involves the use of 1,3-dioxan-4-ones **32**. These heterocycles can be easily prepared, in good yield, from an aldehyde or ketone **6** and enantiomerically pure 3-hydroxybutanoic acid **94** (Scheme 13.13) [17].

Upon treatment with $TiCl_3(OCHMe_2)$, compound **32** reacts with allyltrimethylsilane to form ether **33** in good yield and selectivity. The chiral template is then removed by treatment with an excess of LDA affording the desired homoallylic alcohol **34** in 80–94% *ee*.



Scheme 13.13



Scheme 13.14

Another approach towards diastereo- and enantio-enriched homoalyllic ethers was used by Panek *et al.* during their synthesis of kabiramide C [18]. In this case, optically pure allylsilane **35** was allowed to react with acetal **36**, forming the expected syn ether **37** with moderate diastereocontrol (Scheme 13.14).

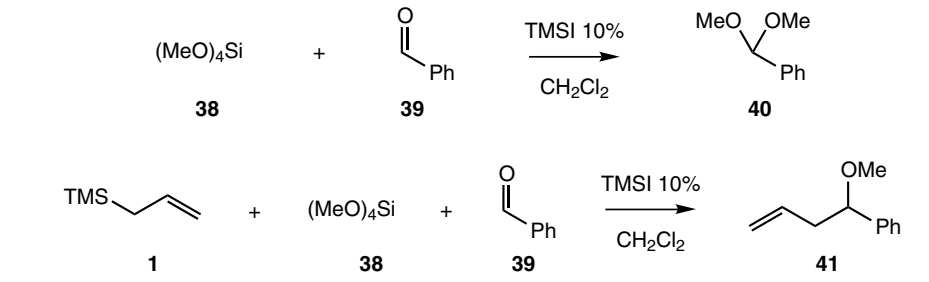
Since the 1980s, chemists have attempted to develop novel Lewis acids and Lewis bases able to catalyze the Sakurai reaction with full diastereo- and enantiocontrol. A review by Denmark and Fu [19] summarizes the most recent advances in this area. Thus, we will not discuss these aspects of the Sakurai reaction but shall focus our attention on the one-pot three-component synthesis of homoallylic alcohols and ethers.

13.3
The Silyl-modified Sakurai Reaction

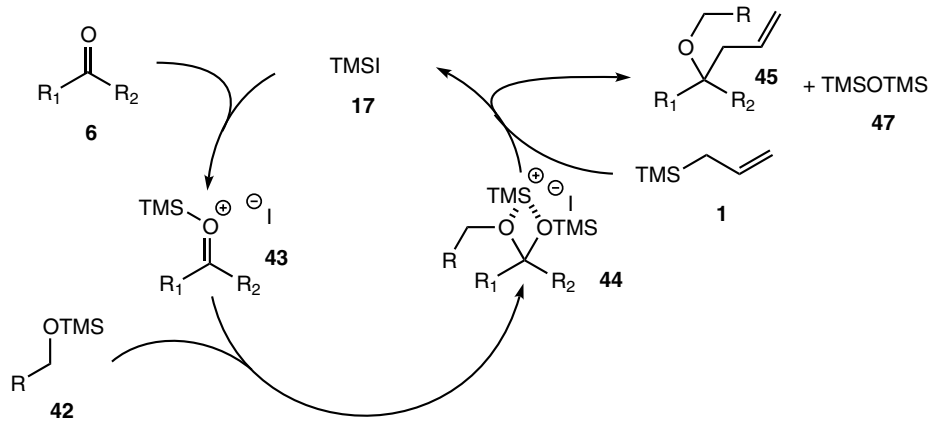
13.3.1
History and Asymmetric Versions

At the end of his review [7] dealing with the acetalization of carbonyl compounds, Sakurai reported a previously unpublished observation. In the presence of catalytic amounts of iodotrimethylsilane and one equivalent of tetramethoxysilane **38**, allyltrimethylsilane **1** underwent smooth condensation with benzaldehyde **39**, leading to adduct **41** in good yield. The silyl-modified Sakurai reaction was born (Scheme 13.15).

Employing a silyl ether instead of **38** provided a connective assembly of homoallylic ethers. This three-component reaction leads to the formation of homoallylic ethers **45** *via* activation of carbonyl **6** by Lewis acid **17**. The *in situ* generated oxonium cation **43** can then be trapped by the nucleophilic silyl ether **42** affording **44**. The new species can then react with allyltrimethylsilane **1**, to form the desired ether **45** with subsequent regeneration of the catalyst and loss of TMSOTMS **47** (Scheme 13.16).



Scheme 13.15

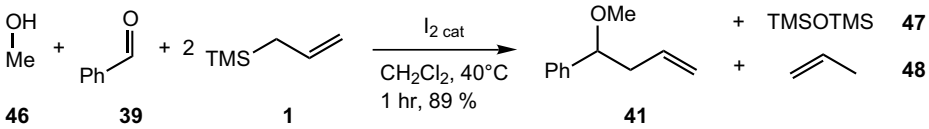


Scheme 13.16

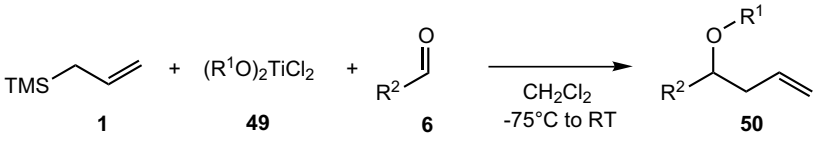
A wide variety of silyl ethers can be employed, leading to functionalized homoallylic alcohols or ethers. This three-component coupling reaction, which generates in a single operation a range of homoallylic ethers, does not require the initial and independent synthesis of the acetal (or ketal) derived from **6**.

Sakurai *et al.* [20] subsequently described a variant of this process in which the catalyst was generated *in situ*. Thus, mixing a catalytic amount of iodine with a free alcohol **46**, a carbonyl derivative **39** and two equivalents of allylsilane **1**, in dichloromethane, provided in 89% yield homoallylic adduct **41** (Scheme 13.17).

The use of alcohol **46** is attractive as it avoids a preliminary silylation step. The second equivalent of allylsilane **1** is consumed whilst generating the catalyst (iodotrimethylsilane) and is liberated in the form of propene **48**. A year later, Seebach and Imwinkelried [21] employed dialkoxydichlorotitanium complex **49** instead of



Scheme 13.17



1 49 6 50

Entry	R	R^1	Yield (%)[a]
1	Ph	*i*-Pr	90
2	Ph	Et	95
3	Ph	Allyl	50
4	$PhCH_2CH_2$	*i*-Pr	95

[a] All yields refer to pure, isolated products

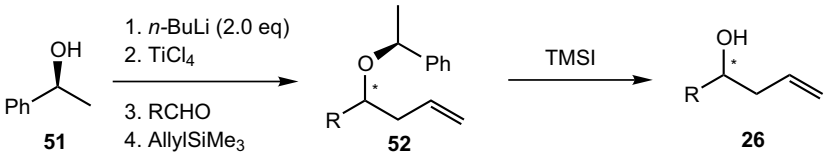
Scheme 13.18

the free alcohol in the same condensation. Using this procedure, homoallylic ether **50** can be obtained in good yield (Scheme 13.18).

Interestingly, the use of optically active alcohol **51** in this protocol leads, after cleavage of the benzylic ether in the initial adduct **52**, to the enantiomerically enriched homoallylic alcohol **26**. This approach appears to be the first asymmetric preparation of homoallylic alcohols *via* open-chain acetal derivatives (Scheme 13.19).

Inspired by this work, Mukaiyama *et al.* [22] used the silylated chiral alcohol **53** and performed the same reaction using diphenylboryltriflate as the catalyst. In all cases, the yields were good and the diastereoisomeric excesses excellent, except for benzaldehyde (Scheme 13.20, entry 5).

Mukaiyama rationalized this low selectivity by invoking the facile formation of benzylic oxonium cations which prefer to react *via* S_N1-type transition states with reduced chiral induction. His catalyst was prepared *in situ* by the addition of silver triflate to chlorodiphenylborane in a 1:1 ratio.

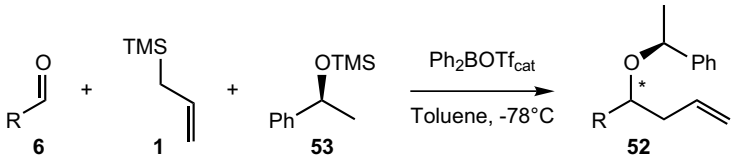


51 96% *ee* **52** **26**

Entry	R	Yield, *de* (%)[a,b]	Yield, *ee* (%)[a,c]
1	$PhCH_2CH_2$	42, 91.5	75, 80 (*R*)
2	*i*-Pr	50, 90	75, 78 (*S*)

[a] All yields refer to pure, isolated products
[b] Yields and *de* refer to the allylation step
[c] Yields and *ee* refer to the deprotection step

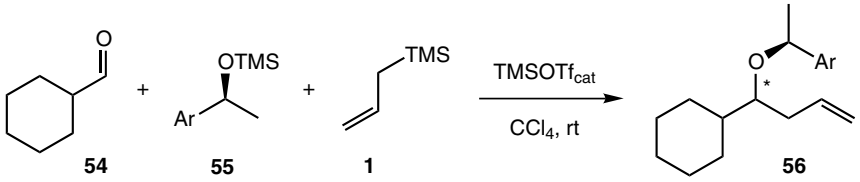
Scheme 13.19



Entry	R	Yield (%)[a]	*de* (%)
1	$PhCH_2CH_2$	71	93 (*R*)
2	*cyc*-C_6H_{11}	74	85 (*S*)
3	*i*-Pr	66	99 (*S*)
4	$PhCH_2O(CH_2)_2$	81	90 (*S*)
5	Ph	77	48 (*S*)

[a] All yields refer to pure, isolated products

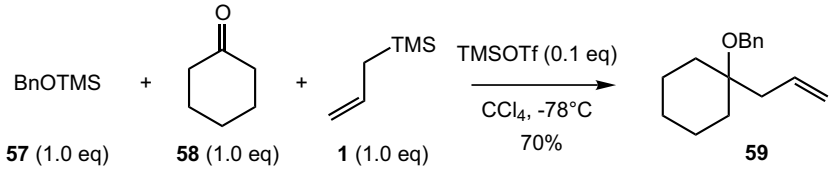
Scheme 13.20



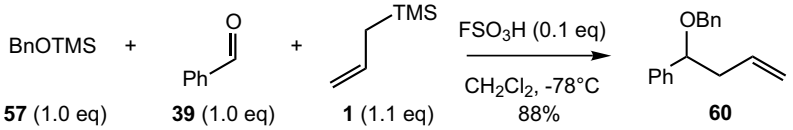
Scheme 13.21

In 1991, Markó and Mekhalfia [23] employed the readily available trimethylsilyltriflate (TMSOTf) as the catalyst and decided to call this reaction SMS for ''silyl-modified Sakurai'' condensation. Carbon tetrachloride appeared to be the best solvent and the presence of two chlorine atoms at the *ortho,ortho'* positions of the aromatic ring provided good selectivity (Scheme 13.21).

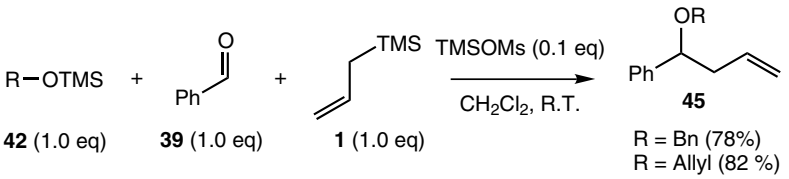
Ketones were also reacted under these conditions, leading to tertiary ethers. Thus, by mixing equimolar quantities of a carbonyl (aldehyde or ketone), allylsilane and a silylated alcohol, followed by the addition of a catalytic amount of TMSOTf, homoallylic ethers can be obtain in good yields *via* a three-component coupling reaction (Scheme 13.22).



Scheme 13.22



Scheme 13.23



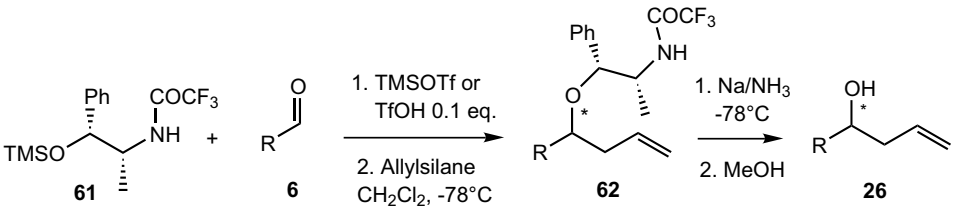
Scheme 13.24

The generation of trimethylsilylfluorosulfonate (TMSOFs) *in situ* by Lipshutz *et al.* [24]. provided another alternative for this methodology (Scheme 13.23).

Wang *et al.* [25] used trimethylsilylmethanesulfonate (TMSOMs) prepared from methanesulfonic acid and allyltrimethylsilane, as the catalyst. This catalyst is cheaper and easier to handle than TMSOTf and gives similar yields of condensation products (Scheme 13.24).

Since 1995, Tietze *et al.* [26–32] have studied the use of norpseudoephedrin derivative **61** as a chiral auxiliary in order to perform a diastereocontrolled SMS reaction. Further cleavage of the benzylic ether bond of **62** by Na/NH_3 led to optically active homoallylic alcohol **26** with good yields and selectivity (Scheme 13.25).

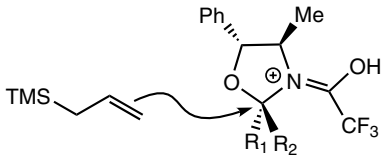
This method is remarkable in that ketones can also be allylated with high levels of enantiocontrol, a transformation that is rarely encountered in the literature. Tietze postulated that the cyclic oxazolidinium cation **63** acted as the key intermediate in the asymmetry-inducing allylation step (Scheme 13.26).



Entry	R	Yield (%)[a,b]	*dr*	Yield (%)[a,c]
1	Et	82	89:11	76
2	$PhCH_2CH_2$	63	91:9	92
3	*i*-Pr	53	>95:5	85

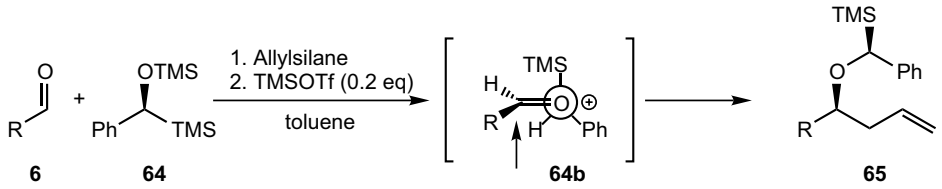
[a] All yields refer to pure, isolated products
[b] Yields refers to the allylating step
[c] Yields refers to the cleavage step

Scheme 13.25



63

Scheme 13.26



6 **64** **64b** **65**

Entry	R	Yield (%)[a]	*dr*
1	*cyc*-C_6H_{11}	7	97:3
2	*n*-C_5H_{11}	86	97:3
3	Ph	96	91:9
4	$TBDPSOCH_2CH_2$	69	95:5

[a] All yields refer to pure, isolated products

Scheme 13.27

Finally, Rychnovsky and Cossrow [33] preferred to use optically pure α-trimethylsilylbenzylether **64** as the chiral auxiliary. In this case, the oxocarbenium intermediate **64b** adopts a well-defined conformation, proposed initially by Linderman [34], which provides the maximum β-silyl-effect. The nucleophile then approaches from the opposite side of the TMS group (Scheme 13.27).

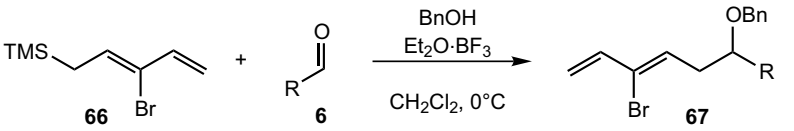
The yields are good and the selectivity is excellent. The chiral auxiliary is prepared from the corresponding ketone by Noyori's hydrogenation (both enantiomers are accessible) and can be removed, in high yield after SMS condensation, by a two-step sequence involving a desilylation–debenzylation.

Substituted allylsilanes such as bromopentadienylsilane **66** of Parrain, Santelli and Roux [35] can be employed in this condensation. Generated with high yields from cheap 1,4-bis(trimethylsilyl)-but-2-ene and bromoform, silane **66** reacts under SMS conditions (the use of $BF_3{\cdot}OEt_2$ as the Lewis acid in conjunction with the free alcohol is described in Section 13.4) to yield a new diene **67** (Scheme 13.28).

Only one stereoisomer is generated in each case and further functionalization of this useful product can be performed easily.

The reactivity of 1-silyl-1-boryl-2-alkenes **68** obtained by *gem*-silylboration of allylchloride were studied by Hiyama *et al.* [36]. Allylsilanes **68**, engaged in SMS reactions, afford the desired *trans*-vinylboranes **69** with good yields (Scheme 13.29).

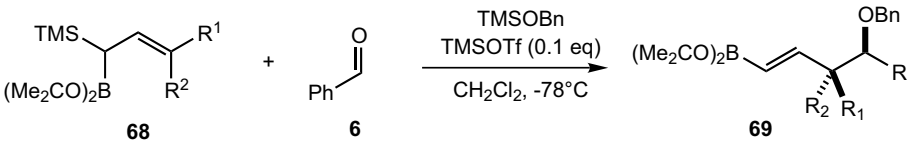
The selectivity is excellent and the geometry of the double bond of substrate **68** induces the spatial relationship between the ether substituent and the R group of



Entry	R	Yield (%)[a]
1	n-C_5H_{11}	87
2	Ph	86
3	p-CF_3Ph	96

[a] All yields refer to pure, isolated products

Scheme 13.28



Entry	R^1	R^2	Yield (%)[a]	*dr*
1	H	H	88	>95:5
2	Pr	H	75	84:16
3	H	Pr	94	9:91

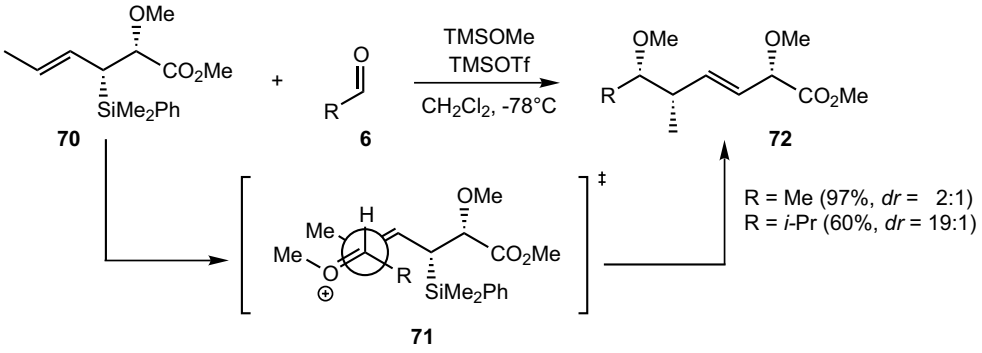
[a] All yields refer to pure, isolated products

Scheme 13.29

69. Moreover, the subsequent vinyl borane **69** can undergo further transformations such as cyclopropanation, Suzuki coupling and so on.

Optically pure crotylsilanes **70** were used by Panek *et al.* [37, 38] who prepared functionalized homoallylic ethers **72**, Scheme 13.30.

The *syn* relationship between the methyl and the ether function is usually



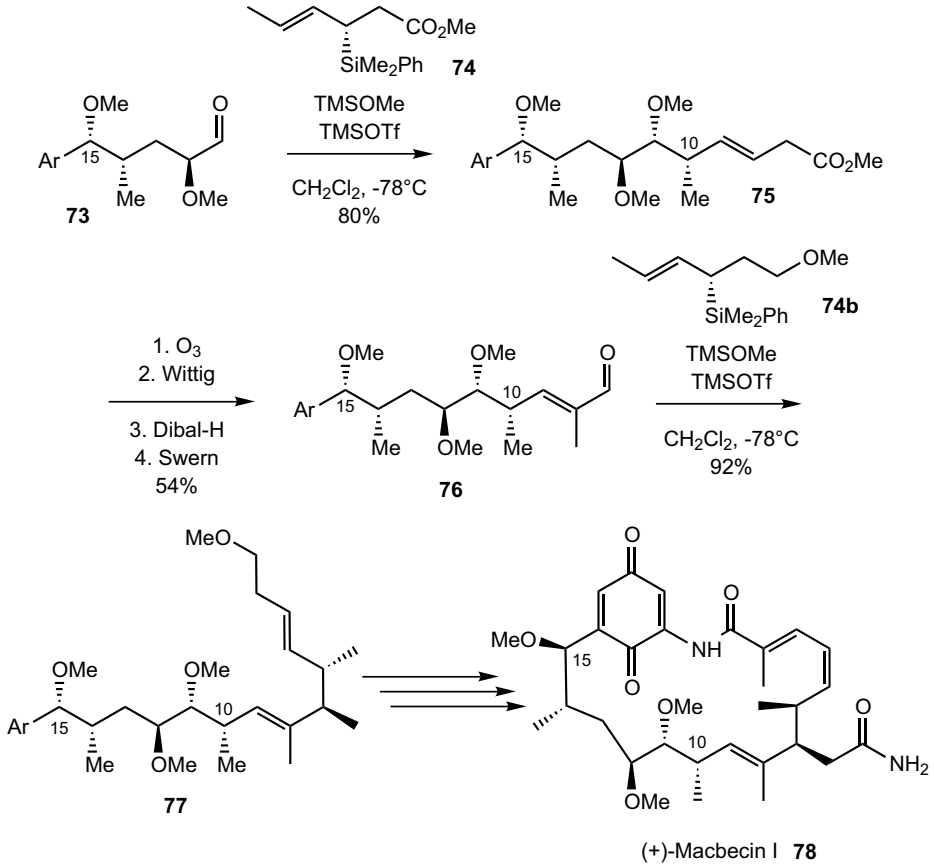
Scheme 13.30

favored (up to 30:1) in agreement with an open transition state. This reaction allows the creation of a new chiral center and the transfer of another one.

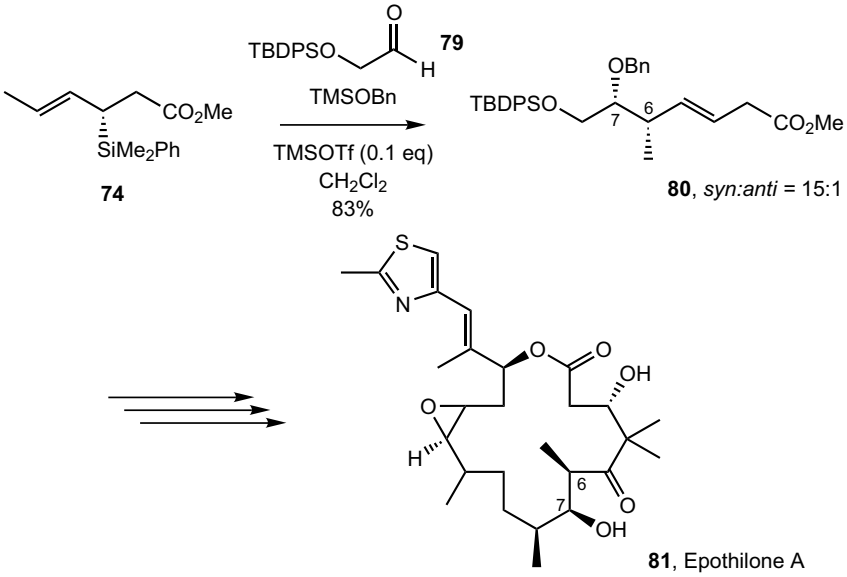
13.3.2 Use in Total Synthesis

Panek *et al.* based their total synthesis of (+)-Macbecin I **78** [39], Epothilone A **81** [40, 41] and Rutamycin B **84** [42] on a sequence of SMS reactions using the optically pure crotyl silane **74**. This allylsilane is readily obtained by kinetic resolution using a PAK lipase.

The total synthesis of (+)-Macbecin I **78** [39] began with aldehyde **73**, prepared *via* the addition of optically pure crotylsilane onto a benzylic acetal, which underwent an SMS reaction to give ester **75** in a 12:1 *syn*/*anti* ratio. Oxidative cleavage of the double bond, Wittig olefination of the resulting aldehyde and a reduction-oxidation sequence yielded α,β-unsaturated aldehyde **76**. A second SMS reaction was then performed leading to polyether **77** ($dr \geqslant 20{:}1$) that contains all the chiral centers of (+)-Macbecin I **78**, Scheme 13.31.



Scheme 13.31



Scheme 13.32

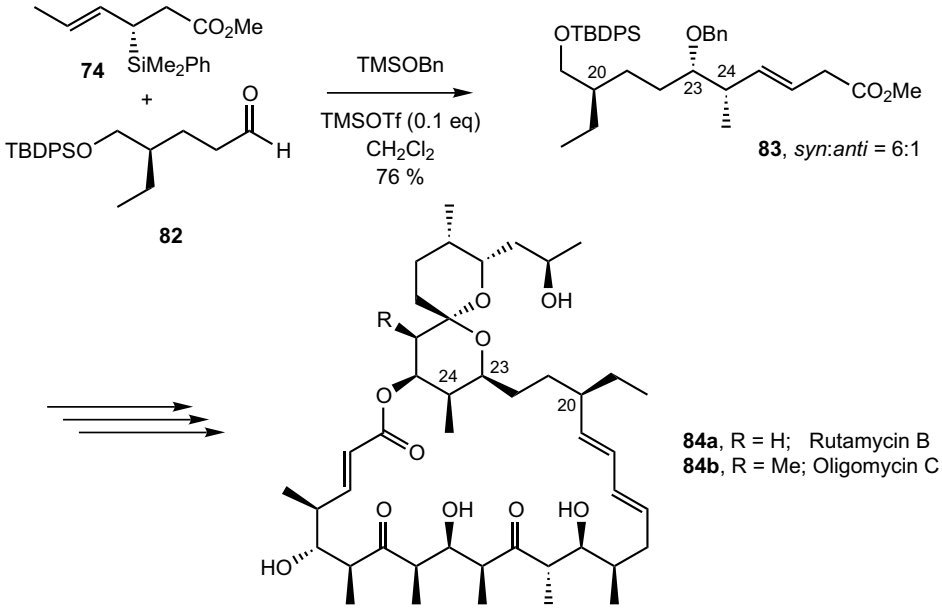
Panek applied the same strategy and used the same optically pure crotylsilane **74** to prepare Epothilone A **81** [40, 41]. The SMS condensation between **74** and **79** afforded ester **80** in 83% yield and with a *syn*/*anti* ratio of 15:1. This fragment contains the two chiral centers present at C6 and C7 of Epothilone A **81** (Scheme 13.32).

In 2001, the total synthesis of Rutamycin B **84a** and Oligomycin C **84b** was achieved by Panek's group using the same methodology. In this case, the SMS reaction gave less satisfactory selectivities, presumably owing to a mismatch effect with the ethyl substituent of **82** (Scheme 13.33).

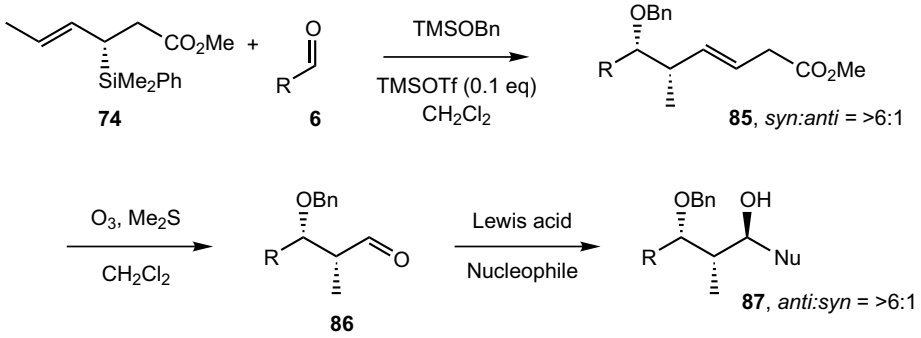
In these two syntheses, the SMS reaction afforded a β,γ-unsaturated ester **85**. This olefin was cleaved by ozonolysis, and the subsequent aldehyde **86** thus generated reacted with another nucleophile to form a new stereogenic center with a diastereoselectivity greater than 6:1. This sequence allows the construction of at least three stereogenic centers starting from a single one with a *syn-anti* stereoselectivity (Scheme 13.34).

13.3.3 Deviance

Even if the SMS reaction typically involves allylsilanes, carbonyls and alcohols (or silyl ethers), some transformations can be considered as belonging to the same family. For example, in 2001, Yokozawa *et al.* described [43] a three-component reaction between aldehydes **6**, alkoxysilanes **38** and propargylsilane **88** (instead of allylsilane). Tritylperchlorate was used as the catalyst and α-allenyl ethers **89** were



Scheme 13.33

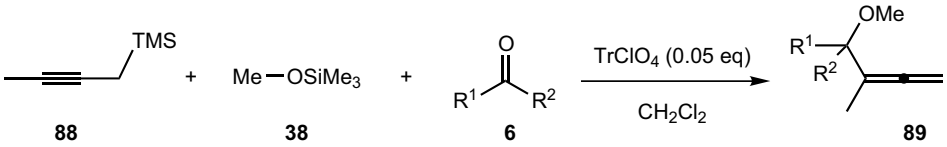


Scheme 13.34

obtained, usually in good yields (Scheme 13.35). This process appears, however, to be limited to aromatic aldehydes.

Yokozawa [44] also inverted the methodology and generated α-propargyl ethers **91** from carbonyls **6**, alkoxysilanes **38** and allenylsilanes **90**. Aromatic aldehydes remained the best substrates but aliphatic aldehydes or ketones could be induced to react, though the yields remained modest (Scheme 13.36).

The aza-analogue of the SMS condensation has been reported [35, 45–47]. Veenstra and Schmid in 1997 [46] were the first to perform the three-component condensation between an aldehyde **6**, an amine **92** and an allylsilane **1**. A stoichiometric amount of $Et_2O{\cdot}BF_3$ was generally used and the yields were good (Scheme 13.37).

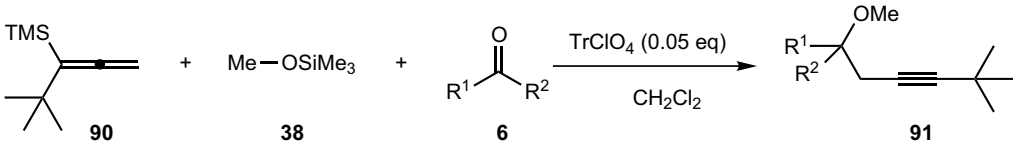


88 38 6 89

Entry	R^1	R^2	Yield (%)[a]
1	H	Ph	95
2	H	*p*-Cl-Ph	72
3	Me	Ph	-

[a] All yields refer to pure, isolated products

Scheme 13.35

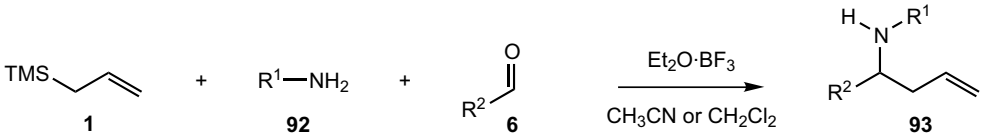


90 38 6 91

Entry	R^1	R^2	Yield (%)[a]
1	H	Ph	93
2	H	*p*-Cl-Ph	89
3	H	*p*-MeO-Ph	64
4	H	Et	38
5	$-CH_2(CH_2)_2CH_2-$		12

[a] All yields refer to pure, isolated products

Scheme 13.36



1 92 6 93

Entry	R^1	R^2	Yield (%)[a]
1	Pr	BnOCO	80
2	*i*-Pr	MeOCO	79
3	Pr	Boc	74
4	Ph	*n*-PrCO	41
5	Ph	BnOCO	95

[a] All yields refer to pure, isolated products

Scheme 13.37

13.3.4
Conclusions

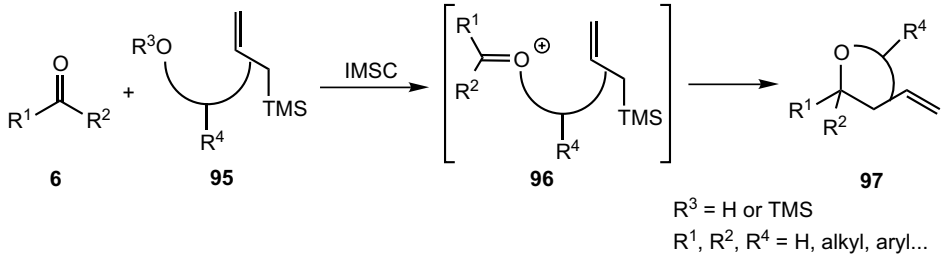
In summary, the SMS reaction is a truly efficient process, possessing a broad scope and applicable to a number of carbonyls, allylsilanes, alcohols (silyl ethers) or amines. Its usefulness has been validated in several total syntheses and demonstrated by the preparation of chiral homoallylic alcohols. During the development of the SMS reaction, Melkafia and Markó [48] realized that the homoallylic alcohol (ether), if connected to an allylsilane, would form novel annelating agents that would lead to tetrahydropyran derivatives *via* condensation with carbonyl compounds. This reaction was called IMSC for "intramolecular Sakurai cyclization" and will be discussed in the next section.

13.4
Intramolecular Sakurai Condensation

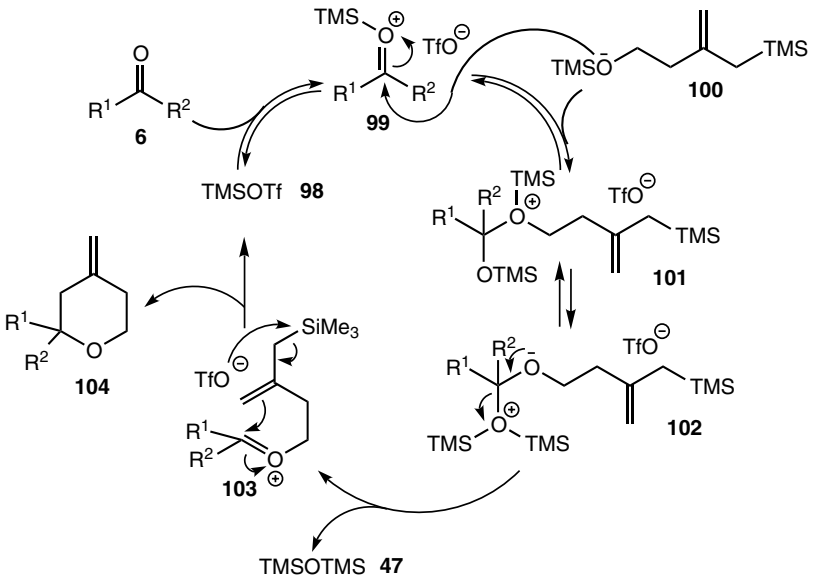
The intramolecular Sakurai condensation (IMSC) can be considered as one of the most powerful synthetic tools for the stereocontrolled construction of polysubstituted tetrahydropyran rings [48–50]. Using this methodology, the synthesis of five- [51–54] or seven-membered [55, 56] rings, their nitro analogues [57, 58] and spiro [59] compounds is possible.

The reaction is based upon the two components condensation between an aldehyde or ketone **6** (or their synthetic equivalents) and alcohol **95**, which contains an allylsilane (or vinylsilane) moiety. The IMSC reaction is mediated by Lewis or Brønsted acids, which activate the carbonyl group of **6** towards nucleophilic attack. After addition of alcohol **95** on the activated carbonyl, the oxonium cation **96** is formed, which is intramolecularly captured by the pendant allylsilane function, leading to oxygen-containing rings **97** (Scheme 13.38). This process typically requires a stoichiometric (or more) amount of Lewis acid.

If the alcohol **95** is protected as a trimethylsilyl ether and TMSOTf is employed as the Lewis acid, only catalytic amounts of Lewis acid have to be used (Scheme 13.39) [60]. Such a process is known in the literature under the name "intramolecular silyl-modified Sakurai reaction" (ISMS) [48].



Scheme 13.38

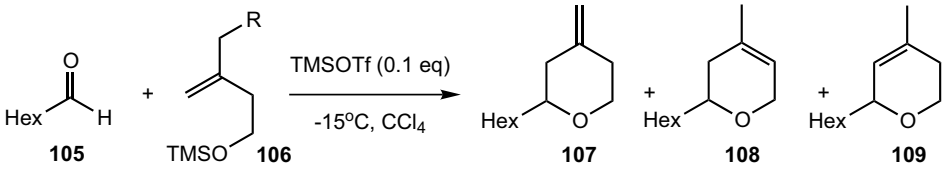


Scheme 13.39

13.4.1
Tetrahydropyran Rings

Numerous natural products contain in their structure one or more tetrahydropyran subunits and therefore versatile and rapid syntheses of such ring systems are valuable tools for synthetic chemists [61].

Nowadays, the intramolecular Sakurai cyclization stands as one of the most suitable methodologies for the assembly of such subunits [62–64]. However, in 1991, when Markó *et al.* [48] initially published the TMSOTf-catalyzed condensation (ISMS) of aldehyde **105** with TMS-ether **106a**, the results of this reaction were far from perfect (Scheme 13.40). Indeed, this condensation resulted in the formation of three products. Surprisingly, not only the expected product **107** was formed, but the isomerized adducts **108** and **109** were also present in the reaction mixture.



106a, R = TMS
106b, R = H

107 : **108** : **109** = 16 : 3 : 2, overall yield = 88%
107 : **108** : **109** = 7 : 10 : 4, overall yield = 91%

Scheme 13.40

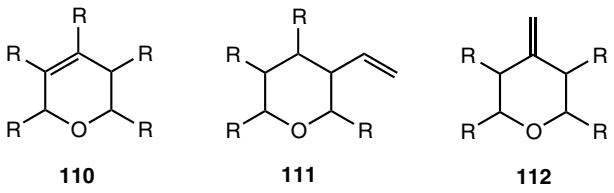


Fig. 13.3. Ring structures formed by the ISMS.

The condensation utilizing aldehyde **105** and alcohol **106b** gave even more unsatisfactory results.

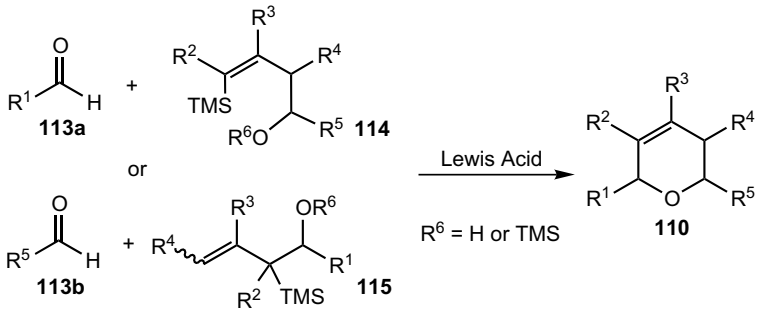
Those early problems, mostly related to the adventitious presence of triflic acid, were readily solved [65] and the scope and limitations of the methodology rapidly uncovered. The advantage of the IMSC reaction lies in the highly stereoselective formation of dihydropyran rings **110** and tetrahydropyran rings **111** and **112** (Figure 13.3). In most cases, only one of all the possible diastereoisomers is formed, with a high degree of diastereoselectivity.

13.4.1.1 Dihydropyrans

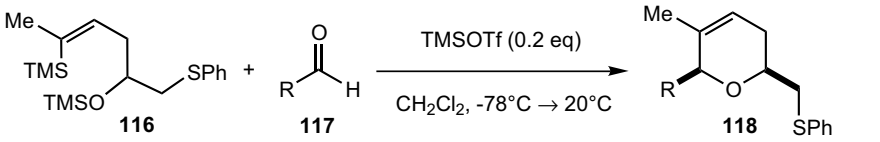
Dihydropyrans of general structure **110** can be prepared by two complementary strategies starting from aldehyde **113** (or its synthetic equivalent). Condensation with vinylsilane **114** or allylsilane **115** affords in each case the adduct **110** (Scheme 13.41).

Markó *et al.* used the vinylsilane annulating agent **116** and aldehyde **117a** as key fragments for the synthesis of the right-hand subunit of ambruticin **118a** (Scheme 13.42) [62, 66]. The ISMS cyclization afforded the desired product **118a** in 83% yield. Interestingly, the reaction is highly stereoselective and only the *cis*-2,6-disubstituted dihydropyrans **118** are produced (for other examples see refs [66–70]).

The same observation was made by Dobbs *et al.*, who used a similar annulating agent **119** and reacted it with various aldehydes in the presence of indium trichlor-



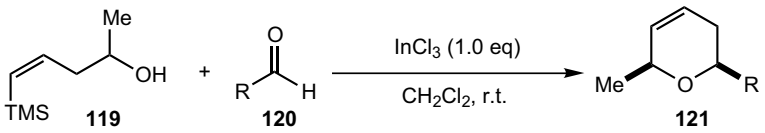
Scheme 13.41



117a, R = CH_2CH_3
117b, R = CH_2CH_2Ph

118a, R = CH_2CH_3, 83%
118b, R = CH_2CH_2Ph, 80%

Scheme 13.42



Entry	R	Yield (%)[a]
1	*n*-C_5H_{11}	65
2	Ph_2CH	78
3	*p*-$NO_2C_6H_4$	60

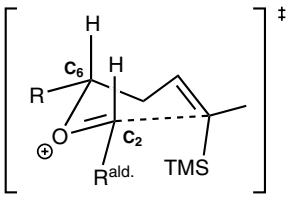
[a] All yields are for pure, fully characterized, products

Scheme 13.43

ide [67]. The reactions proceeded smoothly at room temperature and gave the desired dihydropyrans **121** in good yields (Scheme 13.43). It is worth mentioning that these condensations also proceed efficiently when $Et_2O{\cdot}BF_3$ or TMSOTf are used as Lewis acids. The dihydropyrans are obtained in comparable yields [67]. However, in those cases, the reactions have to be carried out at −78 °C.

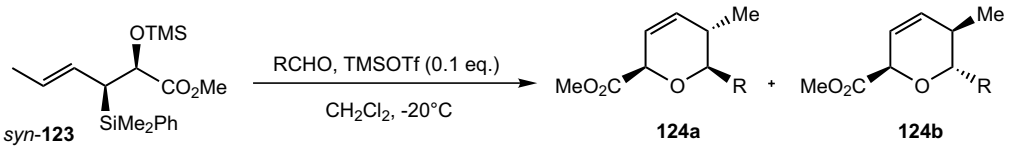
The *cis*-stereochemical relationship between the substituents at carbon centers C2 and C6 is explained by invoking a mechanism proceeding through the cyclic transition state **122**. In this six-membered transition state, both substituents at carbon centers C2 and C6, occupy equatorial positions. The trimethylsilyl moiety is locked in the axial position by the olefin geometry (Figure 13.4) [62].

Another approach towards dihydropyrans **124** and **125** was developed by Panek *et al.* [64] In this methodology, two enantiomerically enriched diastereoisomers,



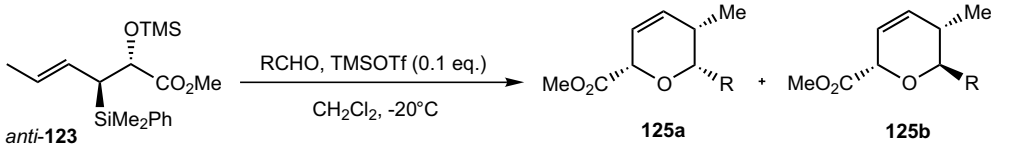
122

Fig. 13.4. Structure of the cyclic transition state **122**.



Entry	R	Yield (%)[a]	dr; C_2:C_6-*cis*:*trans*
1	*n*-Bu	88	15:1
2	*cyc*-C_6H_{11}	85	15:1
3	Ph	85	25:1

[a] All yields are for pure, fully characterized, products



Entry	R	Yield (%)[a]	dr; C_2:C_6-*cis*:*trans*
1	*n*-Bu	88	1:11
2	*cyc*-C_6H_{11}	85	1:10
3	Ph	87	<1:30

[a] All yields are for pure, fully characterized, products

Scheme 13.44

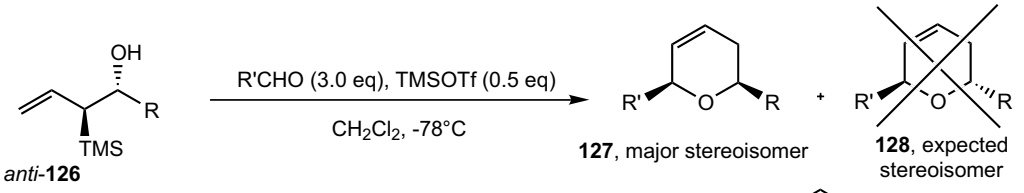
syn or *anti*-allylsilanes **123**, were allowed to react with a range of aldehydes in the presence of catalytic amounts of TMSOTf (0.1 equivalent) (Scheme 13.44).

It was observed that the cyclization of *syn*-**123** produced mainly the dihydropyran **124a** accompanied by dihydropyran **124b** as a minor diastereoisomer. In contrast, the cyclization of *anti*-**123** provided dihydropyran **125b** as the major isomer and the all-*cis*-substituted dihydropyran **125a** as the minor product. In all cases, the diastereoselectivity ranged from good to excellent.

The same reaction was studied by Roush *et al.* [50]. However, in this case, the cyclization of *anti*-allylsilane **126** resulted in the production of only *cis*-2,6-disubstituted dihydropyrans **127**. No *trans*-2,6-disubstituted dihydropyrans **128** were formed. Moreover, significant amounts of adducts **129** and **130** were observed (Scheme 13.45). These products probably originate from a side-chain exchange process (*vide infra*).

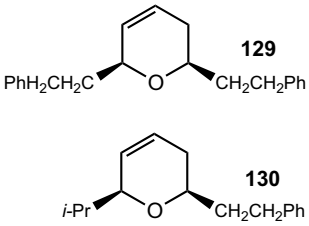
This side reaction, which complicates the condensation of allylsilanes *anti*-**126**, was suppressed by using α-acetoxy acetals such as *anti*-**131** as the oxonium cation precursor. Under these conditions, the desired *cis*-2,6-disubstituted dihydropyran **132** was isolated in moderate yields but high diastereoselectivity ($dr = 94{:}6$; Scheme 13.46).

Roush and Dilley suggested [50] that the preferential formation of *cis*-2,6-disubstituted dihydropyrans **127** and **132** instead of the expected *trans*-2,6-disubstituted

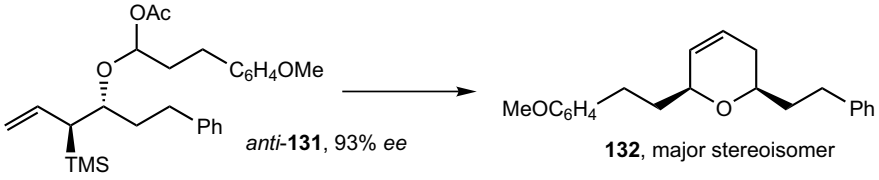


Entry	R	R'	Yield (%)[a]	dr; C_2:C_6-*syn:ant*
1	$PhCH_2CH_2$	$PhCH_2CH_2$	82	94:6
2	*i*-Pr	$PhCH_2CH_2$	17[b]	94:6

[a] All yields are for pure, fully characterized, products
[b] Products **129** (50%) and **130** (3%) are also formed

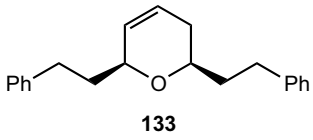


Scheme 13.45



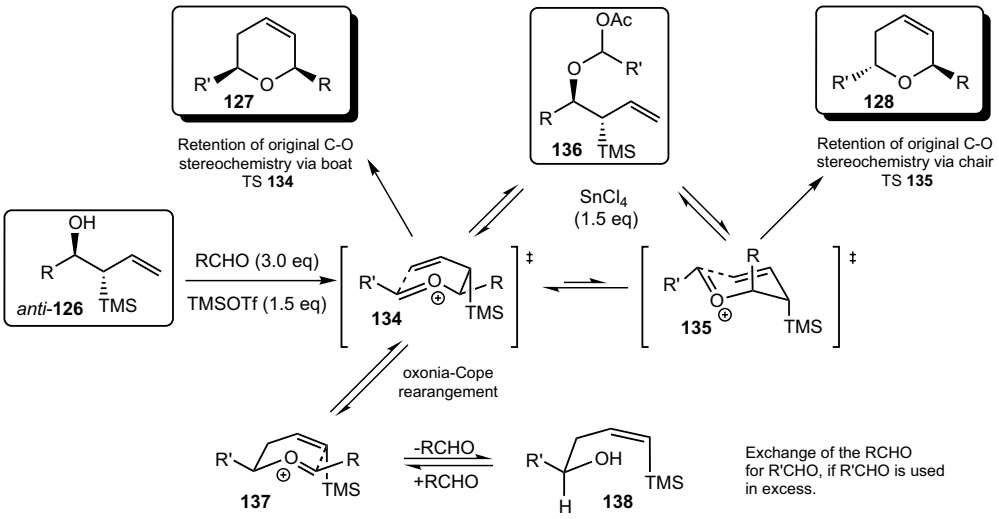
Entry	Conditions	Yield (%)[a]	dr; C_2:C_6-*cis:trans*
1	TMSOTf (1.5 eq) CH_2Cl_2, -78°C	50[b]	94:6
2	$SnCl_4$ (1.5 eq) toluene, -78°C → -15°C	60[c,d]	94:6

[a] All yields are for pure, fully characterized, products
[b] Product **133** was formed in 3%
[c] Product **133** was formed in 4%
[d] Product **132** was formed with 94% *ee* purity



Scheme 13.46

dihydropyrans **128**, as well as the unanticipated exchange of allylsilane side chains (leading to products **129** and **133**, respectively), can be explained by invoking competitive and extremely facile oxonia-Cope rearrangements during the intramolecular allylation process (Scheme 13.47) [71]. Based upon the retention of stereochemistry observed during the course of the reaction (Scheme 13.46, entry 2), they proposed that the reaction proceeded *via* a boat-like transition state **134**. Such a transition state rationalizes the formation of the *cis*-2,6-disubstituted dihydropyran **127**, with retention of stereochemistry, whilst the oxonia-Cope rearrangement explains the formation of product **133**. This compound originates from the exchange process **137** → **138**.



Scheme 13.47

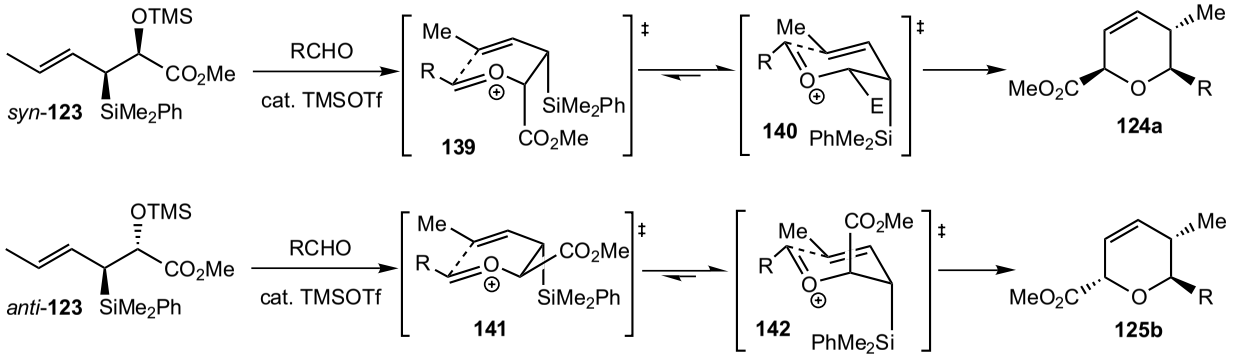
Based upon this postulated mechanism, the formation of *cis*-2,6-disubstituted dihydropyran **124a** and *trans*-2,6-disubstituted dihydropyran **125b** (Scheme 13.44) can also be rationalized. It appears that the formation of **124a** and **125b** proceeds preferentially through the chair-like transition states **140** (leading to **124a**) and **142** (leading to **125b**). Indeed, the boat-like transition states **139** and **141**, in which the oxonium ions adopt the more stable *E*-geometry, suffer from eclipsing interactions involving the aldehyde R group and the Me substituent present in the crotylsilanes **123**. The transition state **139** also suffers from repulsive interaction between the axial CO_2Me group and the pseudoaxial $-SiMe_2Ph$ (Scheme 13.48).

The absence of products derived from the oxonia-Cope rearrangement in the Panek study [64] can be explained by the presence of the CO_2Me group, which would destabilize the oxonia-Cope product **137** (R = CO_2Me) because the electron-withdrawing group is directly attached to the oxonium ion carbon.

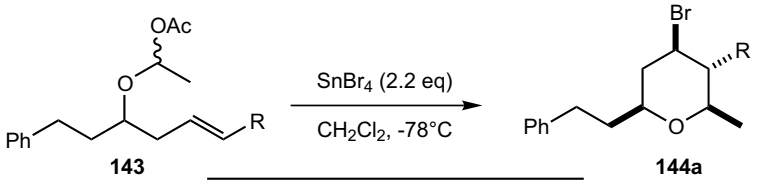
Rychnovsky *et al.* have postulated the same mechanism during their study of the α-acetoxy acetal **143** cyclization and of the condensation of alcohol **145** with cinnamyl aldehyde (Scheme 13.49) [72–74]. In both cases, the desired adducts **144a**,**b** were obtained in good yields and excellent diastereoselectivity.

As early as 1997, Hiemstra and Speckamp postulated the participation of an oxonia-Cope rearrangement as a crucial step during the cyclization of vinyl silane **146** (Scheme 13.50) [75]. Both (*E*)- and (*Z*)-vinylsilanes, (*E*)-**146** and (*Z*)-**146** respectively, were used in this study. The cyclization proceeded in both cases in good to excellent yields, furnishing the 2,6-disubstituted dihydropyrans **147**. Surprisingly, the cyclization of (*E*)-vinylsilanes (*E*)-**146** gave *anti*-2,6-dihydropyran *anti*-**147** as the major stereoisomer, whilst in the case of (*Z*)-vinylsilane (*Z*)-**146**, the *syn*-dihydropyran *syn*-**147** was formed as the major product.

The preferred formation of the anti-product from the (*E*)-vinylsilane can be explained by the mechanism shown in Scheme 13.51. The initially generated carbo-


OTMS
CO2Me
syn-123 SiMe2Ph
RCHO
cat. TMSOTf
Me
R
O
SiMe2Ph
CO2Me
139
‡
Me
R
O
E
140 PhMe2Si
‡
Me
MeO2C
O
R
124a
OTMS
CO2Me
anti-123 SiMe2Ph
RCHO
cat. TMSOTf
Me
R
O
CO2Me
SiMe2Ph
141
‡
Me
CO2Me
R
O
142 PhMe2Si
‡
Me
MeO2C
O
R
125b

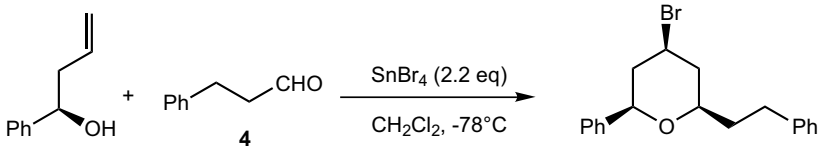
Scheme 13.48



143 **144a**

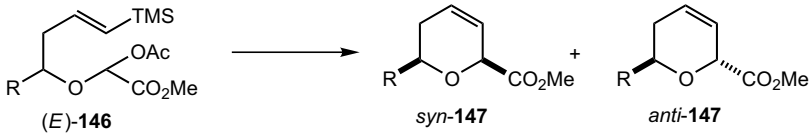
Entry	R	Yield (%)[a]
1	H	73
2	Me	68

[a] All yields are for pure, fully characterized, products



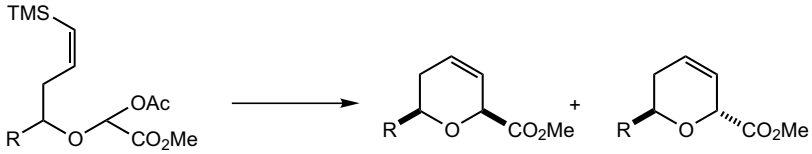
(*R*)-**145**, 87% *ee* **144b**, 77%, 85% *ee*

Scheme 13.49



Entry	Conditions	R	Yield (%)[a]	**147** (*syn:anti*)
1	$BF_3.Et_2O$ CH_2Cl_2, -78°C	Me	73	30:70
2	$BF_3.Et_2O$ CH_2Cl_2, -78°C	*cyc*-C_6H_{11}	94	11:89
3	$SnCl_4$ CH_2Cl_2, -78°C	*tert*-Bu	87	17:83

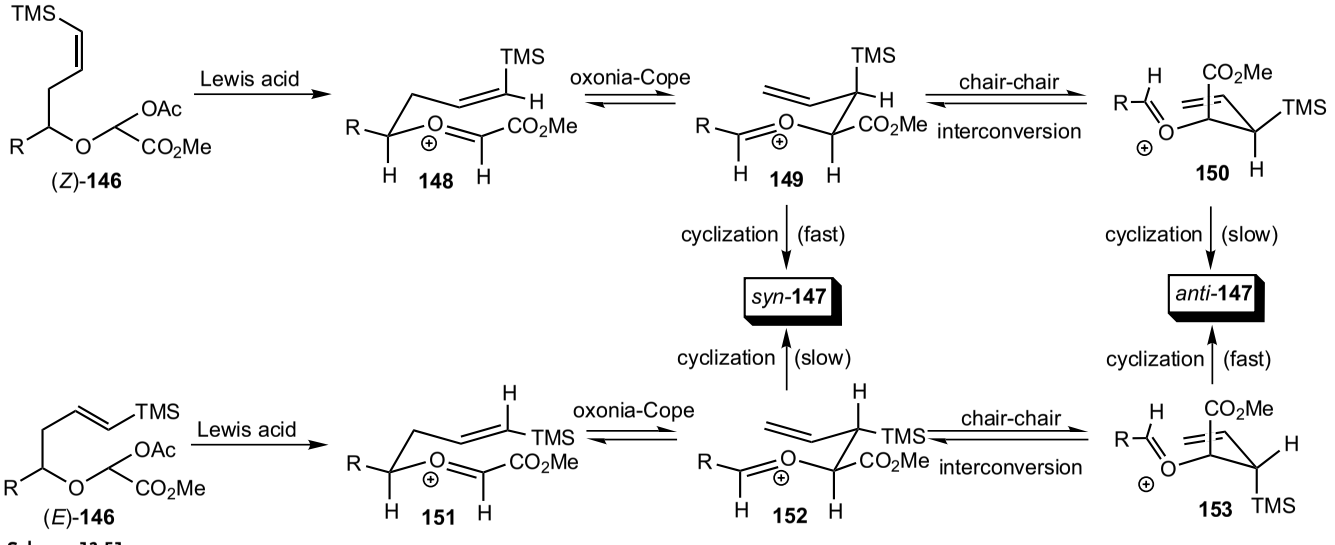
[a] All yields are for pure, fully characterized, products



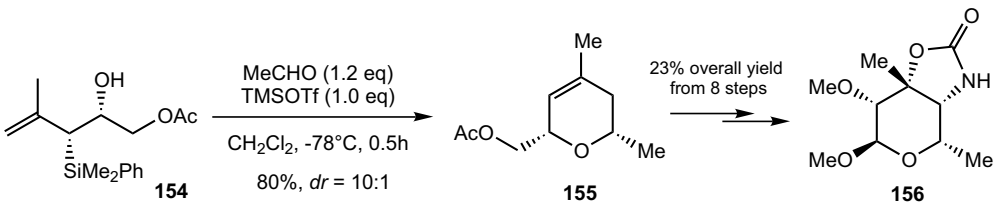
Entry	Conditions	R	Yield (%)[a]	**147** (*syn:anti*)
1	$BF_3.Et_2O$ CH_2Cl_2, -78°C	Et	69	93:7
2	$BF_3.Et_2O$ CH_2Cl_2, -78°C	*cyc*-C_6H_{11}	86	92:8
3	$SnCl_4$ CH_2Cl_2, -78°C	CH_2OBn	76	>98:2

[a] All yields are for pure, fully characterized, products

Scheme 13.50


TMS
OAc
R
O
CO2Me
(Z)-146
Lewis acid
TMS
H
R
O
CO2Me
H
148
H
oxonia-Cope
TMS
H
R
O
CO2Me
H
149
H
chair-chair
interconversion
H
CO2Me
R
O
TMS
150
H
cyclization
(fast)
cyclization
(slow)
syn-147
anti-147
cyclization
(slow)
cyclization
(fast)
TMS
OAc
R
O
CO2Me
(E)-146
Lewis acid
H
TMS
R
O
CO2Me
H
151
H
oxonia-Cope
H
TMS
R
O
CO2Me
H
152
H
chair-chair
interconversion
H
CO2Me
R
O
H
153
TMS

Scheme 13.51



Scheme 13.52

cation **151** (drawn in its most stable chair-like conformation) is in equilibrium with **152** *via* a cationic oxonia-Cope equilibrium. Intermediate **152** is probably more stable than **151** owing to the destabilizing effect of the electron-withdrawing group on the oxonium. However, the cyclization of **152**, which would lead to the *syn* product, appears to be slow because the silyl group is not well orientated to assist the ring closure. Chair–chair interconversion of **152** generates the oxycarbenium ion intermediate **153**, which features an allylsilane with an axial silyl function. Cyclization of **153** now becomes a fast process and leads to the product *anti*-**147**.

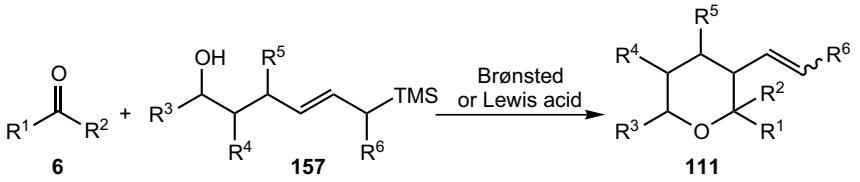
In the case of the (*Z*)-vinylsilane (*Z*)-**146**, the observed syn selectivity results from the cyclization of intermediate **149** in which the TMS group is already axially orientated due to the *Z*-double bond geometry of the precursor.

This approach was used by Panek *et al.* [76] as a key step in the enantioselective synthesis of methyl-ι-callipeltose **156** (Northern-part of Callipeltoside A [77]). Starting from enantioenriched allylsilane **154**, acetal **156** was prepared in eight steps and 23% overall yield (Scheme 13.52).

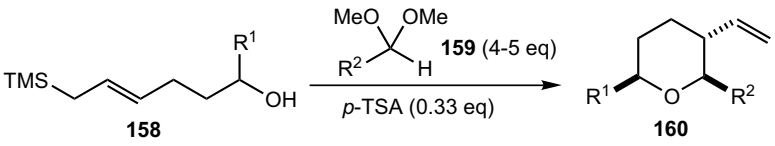
13.4.1.2 **Vinyl Tetrahydropyrans**

Tetrahydropyrans of general formula **111** can be prepared from aldehydes or ketones **6** (or acetals and ketals) and allylsilanes **157** (Scheme 13.53).

When Mohr [69] initially published the synthesis of vinyltetrahydropyrans **160** in 1995, the reaction conditions required four to five equivalents of starting acetal **159** per equivalent of allylsilane **158**. The condensation was catalyzed by the Brønsted acid: *p*-TSA (Scheme 13.54). The reaction proceeded with excellent stereoselectivity and generally the *syn-anti*-trisubstituted tetrahydropyran **160** was formed with overwhelming preference. However, **160** proved to be very difficult to purify and was always contaminated by 5% or less of the other three stereoisomers. The yields of the reaction varied from moderate to good.



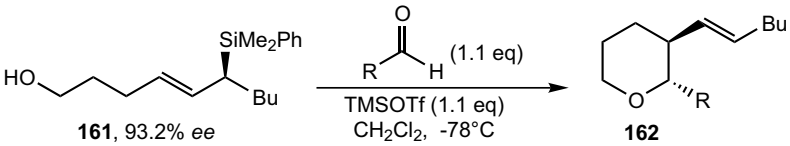
Scheme 13.53



Entry	R^1	R^2	Yield (%)[a]
1	CH_3	Ph	69
2	CH_3CH_2	$PhCH_2$	67
3	Ph	CH_3	86

[a] All yields refer to compounds contaminated with 5% or less of the other three isomers

Scheme 13.54



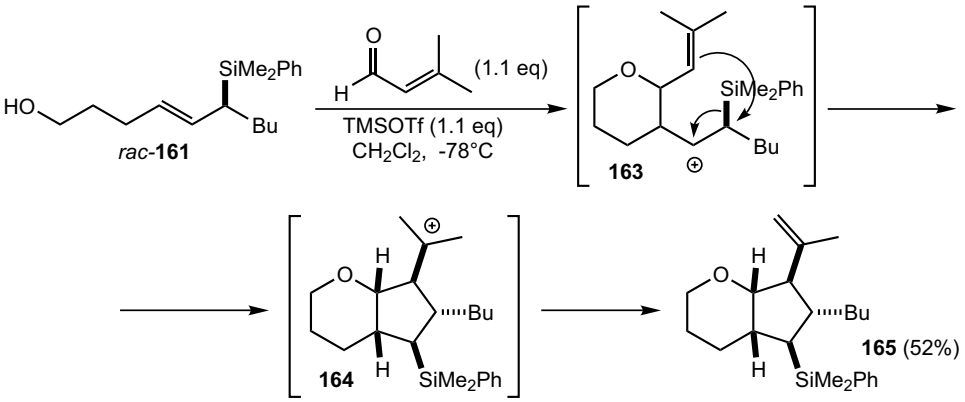
Entry	R	Yield (%)[a]	*trans*/*cis*[b]	*ee*(%)[c]
1	*n*-Hex	92	>10:1	92.1
2	*i*-Pr	98	99:1	92.8
3	*tert*-Bu	88	9:1	93.6
4[d]	$Me_2C{=}CH$	72	9:1	92.0

[a] All yields refer to pure, isolated products
[b] Refers to stereochemistry of six-member ring
[c] The values (+/-0.2) were determined by HPLC
[d] Reaction in MeCN at -30°C in the presence of TMSOTf (0.1 eq)

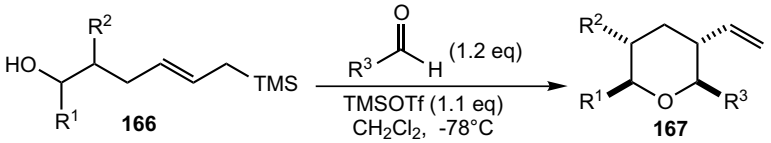
Scheme 13.55

Three years later, in 1998, Ito *et al.* published [78] a similar reaction using the enantio-enriched allylsilane **161** (Scheme 13.55). This condensation reaction furnished the *trans*-2,3-disubstituted tetrahydropyranes **162** with 92.1 to 93.4% *ee* (indicating that the reaction proceeded with nearly complete chirality transfer), high diastereoselectivity and very good yields. In this case, the reaction was mediated by TMSOTf (1.1 equivalents) and the first steps presumably involved the silylation of the free alcohol function. It is noteworthy that the double bond in **162** possesses exclusively the *E*-geometry.

Unexpectedly, the intramolecular allylation of α,β-unsaturated aldehydes, under identical reaction conditions, gave bicyclic product **165** as a single diastereoisomer (Scheme 13.56). This cyclization probably proceeded through a [1,2]-migration of the silyl group in the β-silyl cationic species **163**, followed by a subsequent intra-



Scheme 13.56



Entry	R^1	R^2	R^3	Yield (%)[a]
1	Me	H	*i*-Pr	70
2	Ph	H	*i*-Pr	70
3	H	$HOCH_2$	*i*-Pr	64[b]
4	H	$HOCH_2$	Ph	62[b]

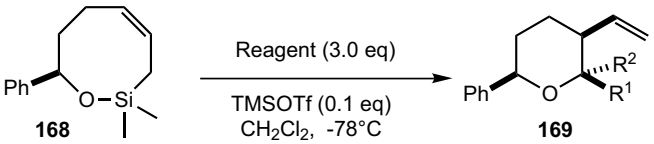
[a] All yields refer to pure, isolated products
[b] 2.4 eq. of TMSOTf was used

Scheme 13.57

molecular capture of the resulting cation by the pendant alkene. If MeCN is used as a solvent instead of CH_2Cl_2 and if the amount of TMSOTf is decreased to 0.1 equivalent, tetrahydropyran **162** (Scheme 13.55, entry 3) is formed in 72% yield along with traces of bicycle **165** (less than 5% yield) [78].

Finally, Szabó *et al.* examined the reactions of disubstituted allylsilanes **166** with aldehydes. In the presence of TMSOTf, the 2,3,5,6-tetrasubstituted tetrahydropyrans **167** are formed in good yields (Scheme 13.57). In complete analogy with the results of Ito [78] and Mohr [69], a remarkably high stereoselectivity was also observed.

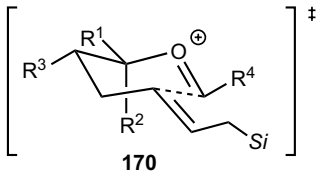
Cossy and Meyer [68] published an elegant route towards tetrahydropyrans of general structure **111**. Thus, tetrahydropyrans **169** were obtained by the reaction of cyclic siloxanes **168** with aldehydes or ketals (Scheme 13.58). The reactions are carried out in the presence of catalytic amounts of TMSOTf (0.1 equivalent) and the desired adducts **169** are produced in excellent yields.



Entry	Reagent	R^1	R^2	Yield (%)[a]
1	MeCHO	Me	H	84
2	$Me_2CH(OMe)_2$	Me	Me	85

[a] All yields refer to pure, isolated products

Scheme 13.58



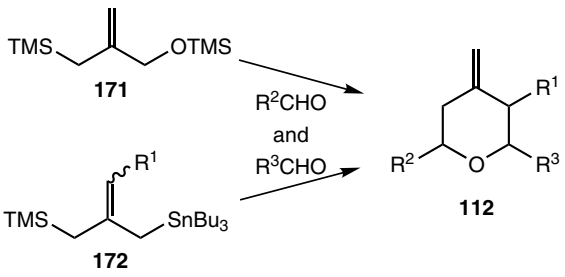
Si = $SiMe_3$, $SiMe_2Ph$, $SiMe_2OMe$,...

Fig. 13.5. Postulated structure of transition state **170**.

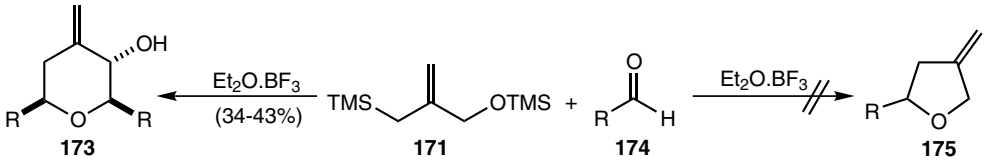
Based upon the previously described cyclization reactions, a possible transition state for the ISMS condensations leading to product **111** can be postulated (Figure 13.5) [68–70, 78]. It appears that the reaction proceeds through the chair-like transition state **170**, in which all the bulky substituents adopt the thermodynamically preferred equatorial positions.

13.4.1.3 *exo*-Methylene Tetrahydropyrans

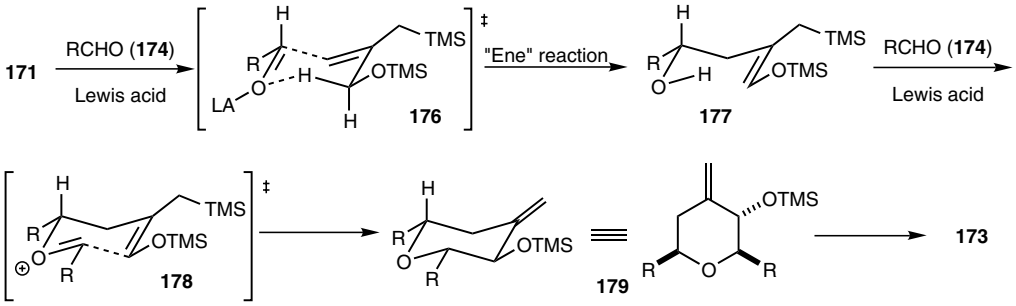
Finally, the IMSC methodology can be employed successfully for the preparation of 4-*exo*-methylene tetrahydropyrans of general structure **112**. These can be obtained in two steps starting from allylsilane **171** or allylstannanes **172** (Scheme 13.59).



Scheme 13.59



Scheme 13.60

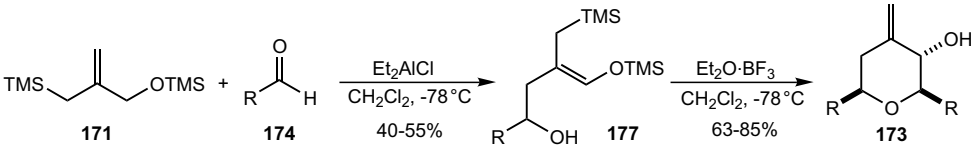


Scheme 13.61

Markó *et al.* initially employed allylsilane **171** during their study on the scope and limitations of the IMSC methodology in 1993 [65] and expected to obtain the *exo*-methylene tetrahydrofurans **175** (Scheme 13.60). However, none of the desired furan derivatives **175** was obtained when a mixture of **171** and aldehydes **174** was treated with a range of Lewis acids. Rather, the diastereomerically pure *exo*-methylene tetrahydropyrans **173** were isolated, albeit in modest yields (Scheme 13.61). In 1995, Oriyama *et al.* [79] published the IMSC reaction of acetals with allylsilane **171**, yielding the desired tetrahydrofurans **175** in the presence of the $SnCl_2$/AcCl system (See Chapter 13.4.2). Interestingly, product **173** was not formed when the corresponding acetals were used instead of the aldehydes in this coupling reaction and *vice-versa* [49, 65].

Closer examination of tetrahydropyrans **173** clearly reveals that two molecules of aldehyde **174** have been appended onto allylsilane **171** *via* a novel three-component coupling reaction. Markó *et al.* proposed the mechanism depicted in Scheme 13.61 [65]. Formation of heterocycles **173** is described as a sequence of two processes: an initial ene-type reaction [80] which leads to alcohol **177** *via* the chair-like transition state **176**, in which both the aldehydic R-group and the OTMS substituent assume an equatorial position. The high regio- and stereoselectivity observed in this ene-reaction can be nicely explained by considering the stabilizing β-silicon effect and the repulsive 1,3-diaxial interactions. Transition state **176** contains no 1,3-diaxial interactions and benefits fully from the stabilizing β-silicon effect [81, 82] (for more detailed transition-state discussion see ref. [63]).

Further condensation of the free hydroxyl group of **177** with another molecule of



R = *n*-Pr-, *cyc*-Hex- or $PhCH_2CH_2$-

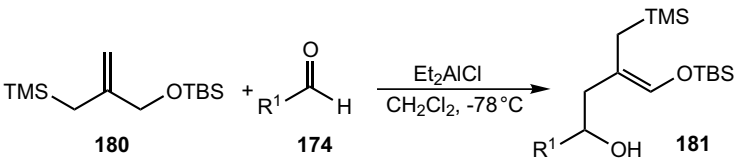
Scheme 13.62

aldehyde **174** generates the oxonium cation **178**, which undergoes an IMSC reaction, producing the *exo*-methylene tetrahydropyran **179** in which all the substituents occupy an equatorial position. Desilylation during the work-up finally gives the observed product **173**.

An interesting observation that lends some credit to the above-proposed mechanism comes from the reaction of allylsilane **171** with various aldehydes **174** in the presence of Et_2AlCl. This reaction afforded for the first time, the silylenol ether **177** as a single double-bond isomer. When **177** was further treated with $Et_2O{\cdot}BF_3$ in the presence of a second equivalent of aldehyde **174**, smooth formation of **173** ensued, indicating that **177** is a plausible intermediate in the transformation of **171** to **173** (Scheme 13.62).

The problem of the rather moderate yields of ene-adducts **177** was solved when the more robust TBDMS protecting group was employed. Using reagent **180** instead of **171**, a smooth ene-reaction occurred, affording the silyl enol ethers **181** in improved yields (Scheme 13.63).

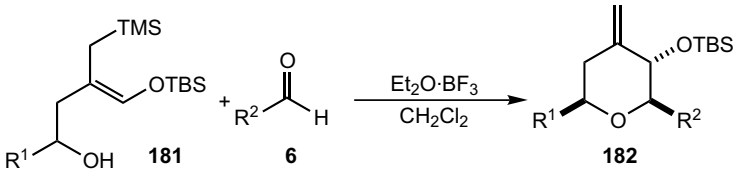
The substituted homoallylic alcohols **181** were then transformed into the desired *exo*-methylene derivatives **182** by the addition of an aldehyde **6** in the presence of $Et_2O{\cdot}BF_3$ (Scheme 13.64). In general, good to excellent yields of heterocycles **182**, in which the robust TBDMS group has been retained, were obtained. In all cases, the substituents around the ring occupy equatorial positions, according to the suggested chair-like transition state **178**. It is noteworthy that the reaction conditions



Entry	R^1	Yield (%)[a]
1	*n*-Pr	73
2	*cyc*-C_6H_{11}	52
3	H	65

[a] All yields refer to pure, isolated products

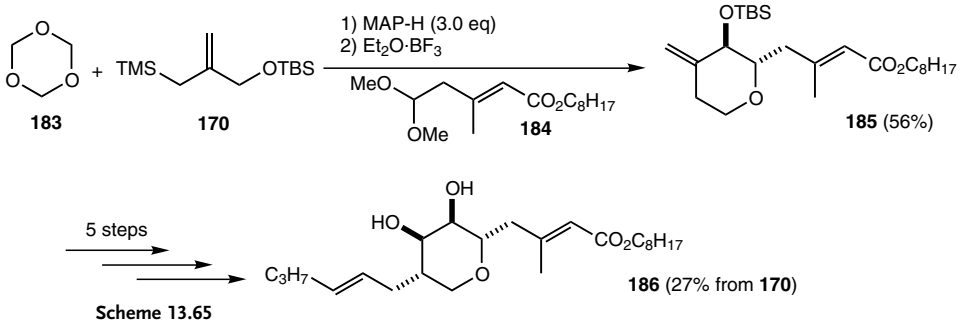
Scheme 13.63



Entry	R^1	R^2	Yield (%)[a]
1	*n*-Pr	*cyc*-C_6H_{11}	63
2	*n*-Pr	$CH_2CH(OTBS)CH_2$	72
3	$CH_3CH{=}CH$	$CH_3CH{=}CH$	85

[a] All yields refer to pure, isolated products

Scheme 13.64



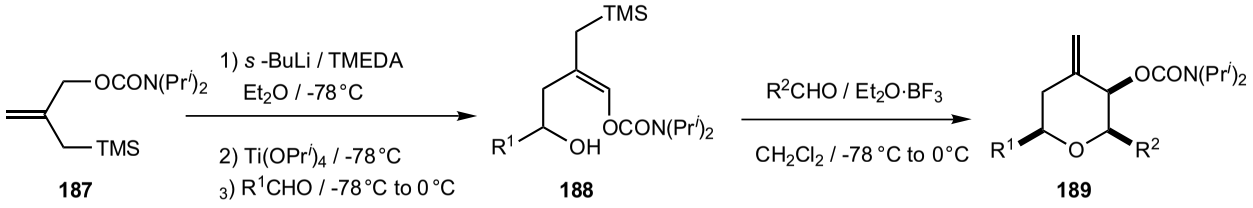
Scheme 13.65

tolerate a wide range of functionalities, both in the aldehyde **6** and the silyl enol ether **181**.

Tetrahydropyrans **182**, formed by this process, proved to be highly valuable intermediates for the synthesis of 2,3,4,6-tetrasubstituted tetrahydropyrans. Indeed, the *exo*-methylene double bond can be easily transformed, with high stereocontrol, into a variety of useful functionalities. For example, Markó *et al.* used this approach during the total synthesis of pseudomonic acid analogue (Scheme 13.65) [49].

Similarly, tetrahydropyrans **189**, containing the all-*cis* substitution pattern could be easily synthesized by using the *Z*-enol carbamate **188**, the geometric isomer of **181**. Such a compound was readily prepared by applying the modified allylmetallation protocol reported by Hoppe to the carbamate derivative **187** (Scheme 13.66) [83–85].

IMSC reactions of **188** proceeded smoothly and afforded the expected tetrahydropyran **189** with exquisite diastereocontrol. In every case, the carbamate substituent adopts an axial position, in agreement with the geometry of the starting olefin **188** and the proposed chair-like transition state **190** (Figure 13.6).



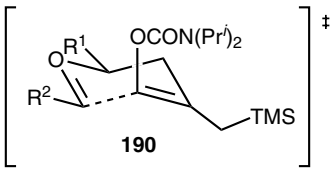
Entry	R^1	Yield (%)[a]
1	*n*-Pr	71
2	*cyc*-C_6H_{11}	70
3	$CH_3CH{=}CH$	56

[a] All yields refer to pure, isolated products

Entry	R^1	R^2	Yield (%)[a]
1	*n*-Pr	$PhCH_2CH_2$	91
2	*cyc*-C_6H_{11}	*tert*-Bu	78
3	$CH_3CH{=}CH$	$CH_3CH{=}CH$	88

[a] All yields refer to pure, isolated products

Scheme 13.66



190

Fig. 13.6. Proposed structure of transition state **190**.

The same allyl-metallation protocol can be used for the preparation of allylstannane **191**. Taking advantage of the greater nucleophilic propensity of the allylstannane function over the allylsilane one, **191** was treated with various aldehydes in the presence of $Et_2O{\cdot}BF_3$, affording the homoallylic alcohols **192** in excellent yields (Scheme 13.67) [86]. It is noteworthy that complete *syn*-stereocontrol is observed in all these transformations.

More interestingly, it was found that in the condensation of allylstannane **191** with α-alkoxyaldehyde **193**, the stereochemistry of the final adduct could be controlled by the amount of Lewis acid employed. Remarkably, if one equivalent of $SnCl_4$ is used, the *anti*-homoallylic alcohol **194** is produced exclusively (Scheme 13.68) [87]. In stark contrast, if two equivalents of $SnCl_4$ are employed, the reaction produces only the *syn*-homoallylic alcohol **195**.

The homoallylic alcohols **192**, **194** and **195** can be easily transformed into the corresponding *exo*-methylene tetrahydropyrans **189** and **196** by a Bi(III)-promoted IMSC condensation (Scheme 13.69). Tetrahydropyrans **189** and **196** are obtained in excellent yields and with complete stereocontrol.

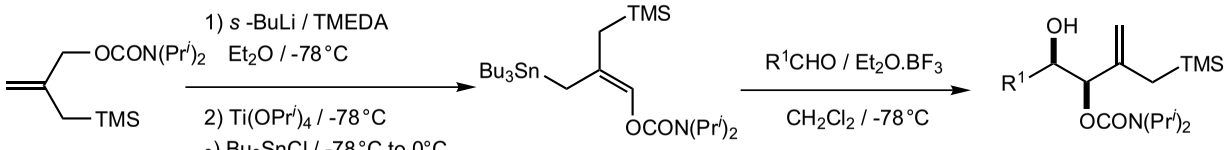
Recently, Yu *et al.* [88] and Keck *et al.* [89] reported the synthesis of enantio-enriched homoallyl alcohols **198**. Alcohols **198** are prepared from allylstannane **197**, by using chiral Ti(IV)-based catalysts [88, 89], with *ee*s ranging from 90 to 96% (Scheme 13.70).

The optically active homoallylic alcohols **198** were then used in subsequent TMSOTf- or $TMSNTf_2$-promoted IMSC condensations providing enantio-enriched tetrahydropyrans **199** in excellent yields and diastereoselectivity (Scheme 13.71).

Rychnovsky *et al.* used another approach to *exo*-methylene tetrahydropyrans of the general structure **112**. In this case, enols **200** and **201** were reacted with various aldehydes **6** in the presence of a Lewis acid to furnish tetrahydropyrans **202** and **203** respectively (Scheme 13.72) [90–92].

The yields ranged from good to excellent, and the *syn*-2,6-disubstituted tetrahydropyran products **203** were formed stereoselectively. The facial selectivity in the addition to the aldehyde, however, was minimal, as might be expected considering the distance between the reactive end of the enol function and the stereogenic center in enols **200** and **201**.

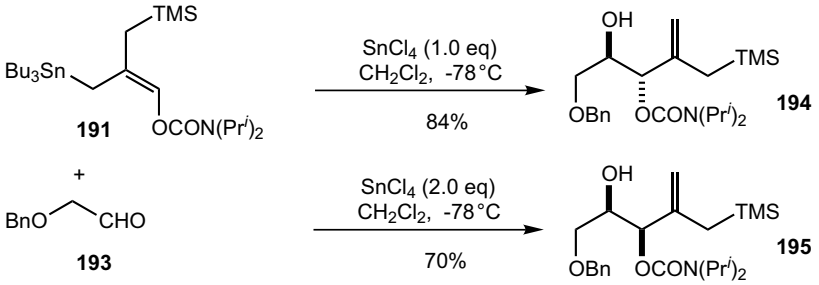
A plausible mechanism for the reaction is depicted in Scheme 13.73. Enol ether **200** reacts with the activated aldehyde to give the oxonium cation **204**. This species is trapped intramolecularly by the allylsilane nucleophile and a new tetrahydropyran ring **202** is formed.



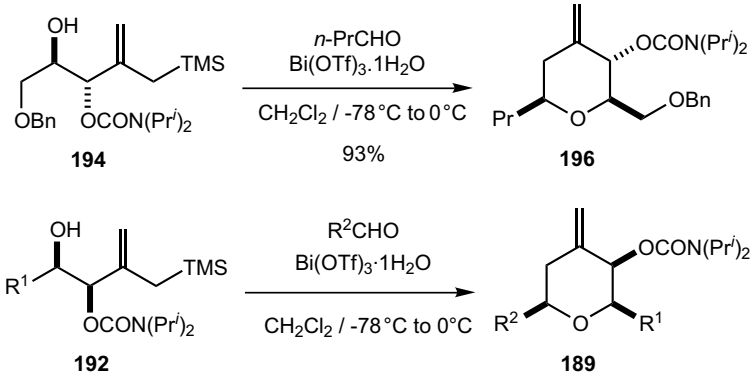
Entry	R^1	Yield (%)[a]
1	*n*-Pr	94
2	*cyc*-C_6H_{11}	94
3	$CH_3CH{=}CH$	98

[a] All yields refer to pure, isolated products

Scheme 13.67



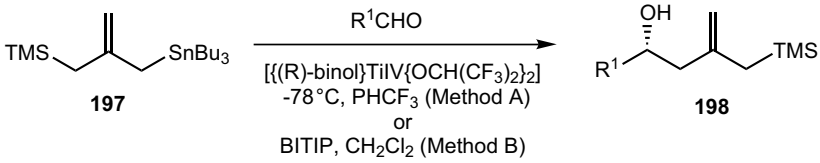
Scheme 13.68



Entry	R^1	R^2	Yield (%)[a]
1	$PhCH_2CH_2$	*n*-Pr	91
2	*n*-Pr	*cyc*-C_6H_{11}	91
3	$BnOCH_2$	*n*-Pr	98

[a] All yields refer to pure, isolated products

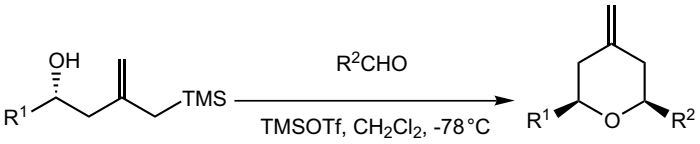
Scheme 13.69



Entry	R^1	Yield (%)[a]	*ee*(%)
1	$PhCH_2CH_2$	A: 74 B: 92	91 96
2	*n*-C_6H_{11}	A: 69	97
3	$TBDPSOCH_2CH_2$	B: 74	92

[a] All yields refer to pure, isolated products

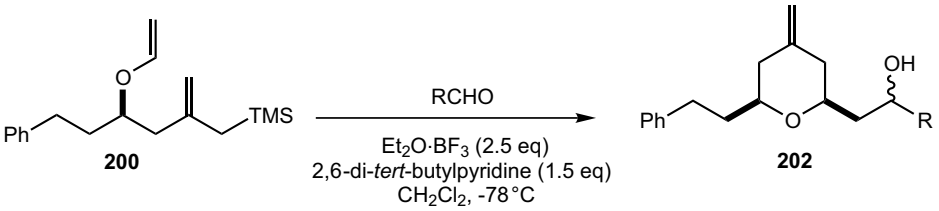
Scheme 13.70



Entry	R^1	R^2	Yield (%)[a]
1	Ph	$PhCH_2CH_2$	91
2	$PhCH_2CH_2$	$PhCH_2CH_2$	95
3	$BnOCH_2$	Et	96

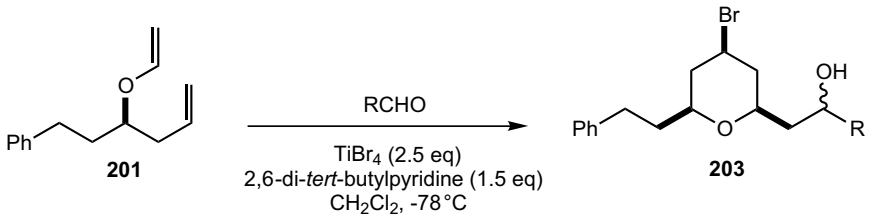
[a] All yields refer to pure, isolated products

Scheme 13.71



Entry	R	Epimer ratio	Yield (%)[a]
1	Ph	1.2:1	84
2	*i*-Pr	1:1	98
3	$TBSOCH_2CH_2$	1.8:1	87

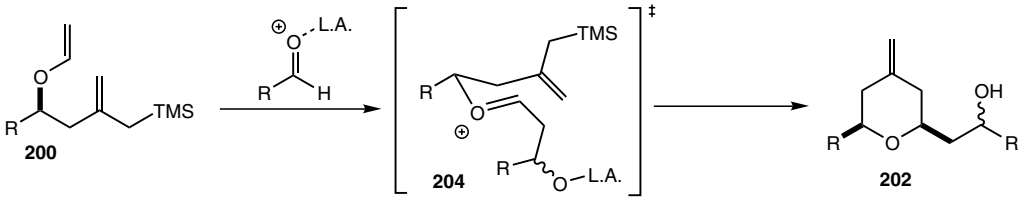
[a] All yields refer to pure, isolated products



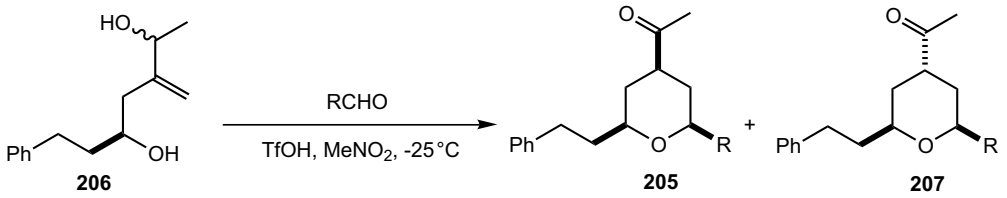
Entry	R	Epimer ratio	Yield (%)[a]
1	Ph	1.3:1	53
2	*i*-Pr	1.1:1	78
3	$TBSOCH_2CH_2$	1.2:1	70

[a] All yields refer to pure, isolated products

Scheme 13.72



Scheme 13.73



Entry	R	**205**: **207**	Yield (%)[a]
1	Ph	8:1	61
2	$PhCH_2CH_2$	18:1	81
3	*i*-Pr	14:1	65

[a] All yields refer to pure, isolated products

Scheme 13.74

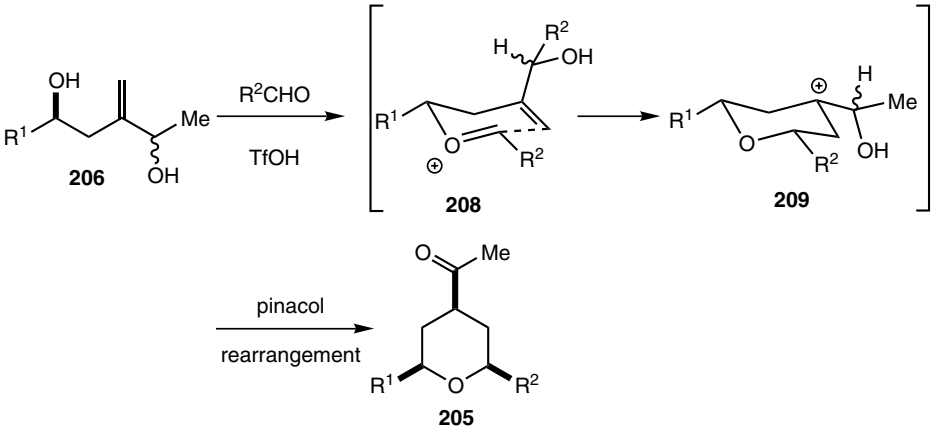
Another elegant way leading to tetrahydropyrans **205** was described by Overman *et al.* [93] In this case, homoallylic alcohol **206** was reacted with various aldehydes in the presence of TfOH to furnish the carbonyl-substituted tetrahydropyrans **205** along with its C4 stereoisomer **207** (Scheme 13.74). The reaction is highly stereoselective and the *syn*-2,4,6-trisubstituted tetrahydropyrans **205** were obtained as the major products in good yields.

The proposed mechanism for the reaction is shown in Scheme 13.75. In the first step, the oxonium cation **208**, formed by TfOH-catalyzed condensation of an aldehyde with alcohol **206**, undergoes an intramolecular cyclization to form the tertiary carbocation **209**. In a subsequent step, cation **209** undergoes a pinacol rearrangement, leading to the observed tetrahydropyran **205**.

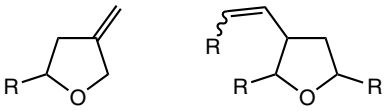
13.4.2 Tetrahydrofuran Rings

The synthesis of tetrahydrofurans of general structures **175** and **210** *via* the ISMC condensation is also possible. However, this methodology is not as developed as the tetrahydropyran synthesis (Scheme 13.76).

As mentioned previously, when Markó *et al.* [63] attempted to prepare the *exo*-methylene tetrahydrofurans **175** by coupling allylsilane **171** with aldehyde **174**,

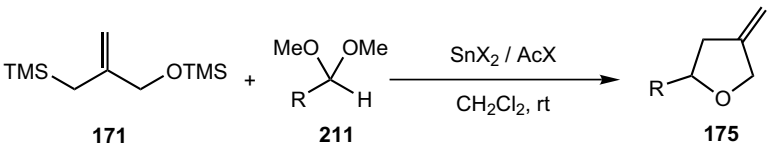


Scheme 13.75



R = H, alkyl, aryl

Scheme 13.76

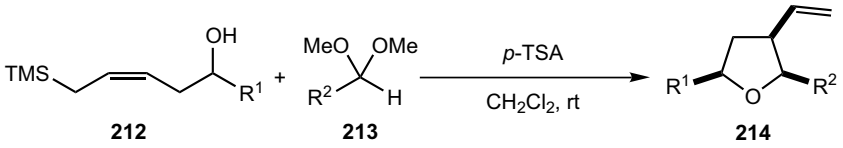


Entry	R	X	Yield (%)[a]
1	2-MeOC$_6$H$_4$	Cl	97
2	2-Furyl	Br	91
3	(*E*)-PhCH=CH	Br	64

[a] All yields refer to pure, isolated products

Scheme 13.77

only the *exo*-methylene tetrahydropyrans **173** were obtained (Scheme 13.63). Remarkably, Oriyama *et al.* found that by replacing the aldehyde **174** by the acetal **211** and using SnX_2 (0.1 equivalent)/AcX (0.1 equivalent) system as the Lewis acid, the formation of *exo*-methylene tetrahydrofurans **175** could be accomplished (Scheme 13.77). The desired tetrahydrofurans **175** were formed in good to excellent yields. Unfortunately, this method is limited to aryl acetals.

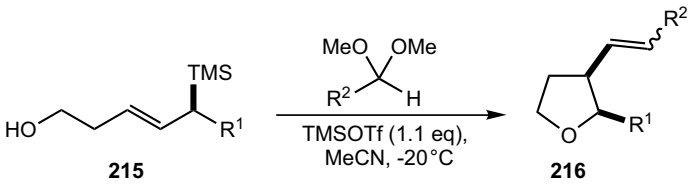


212 213 214

Entry	R^1	R^2	Yield (%)[a]
1	$PhCH_2$	Ph	95
2	$PhCH_2$	Et	83
3	CH_2Cl	Et	66

[a] All yields refer to pure, isolated products

Scheme 13.78



215 216

Entry	R^1	R^2	Yield (%)[a]	*cis*/*trans*[b]	*E*/*Z*
1	Ph	H	99	>10:1	-
2	$PhCH_2CH_2$	H	90	>10:1	-
3	*i*-Pr	*n*-C_4H_9	99	>10:1	1:1

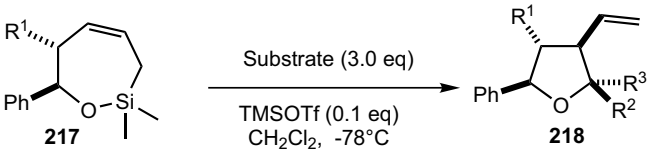
[a] All yields refer to pure, isolated products
[b] Refers to stereochemistry in five-membered ring

Scheme 13.79

Vinyl tetrahydrofurans **214** were initially synthesized by the IMSC-methodology in 1993 by Mohr [51]. The reaction was catalyzed by *p*-toluenesulfonic acid (0.3 equivalent), and five equivalents of acetals **213** were required (Scheme 13.78).

Oriyama *et al.* [52] and Ito *et al.* [78] published independently the preparation of similar tetrahydrofurans **216**. In these cases, TMSOTf is used as the promoter and the desired tetrahydrofurans **216** are produced in excellent yields and stereoselectivity. In all cases, the *cis*-2,3-disubstituted vinyl tetrahydrofuran **216** is formed as the major adduct. In contrast, the selectivity in the formation of the new carbon–carbon double bond remains unsatisfactory (Scheme 13.79).

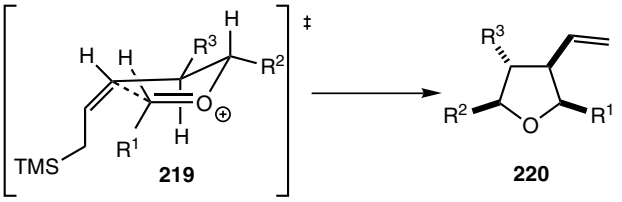
Based upon their previously reported methodology, Cossy and Meyer [68] obtained tetrahydrofurans **218** by reacting cyclic allylsiloxanes **217** with aldehydes or ketones in the presence of TMSOTf (0.1 equivalent). The resulting tetrahydrofurans **218** are formed in remarkably high stereoselectivity; a single diastereoisomer being produced in all cases (Scheme 13.80).



Entry	Substrate	R^1	R^2	R^3	Yield (%)[a]
1	MeCHO	H	Me	H	83
2	$Me_2CH(OMe)_2$	H	Me	Me	82
3	MeCHO	Me	Me	H	78
4	$Me_2CH(OMe)_2$	Me	Me	Me	72

[a] All yields refer to pure, isolated products

Scheme 13.80



Scheme 13.81

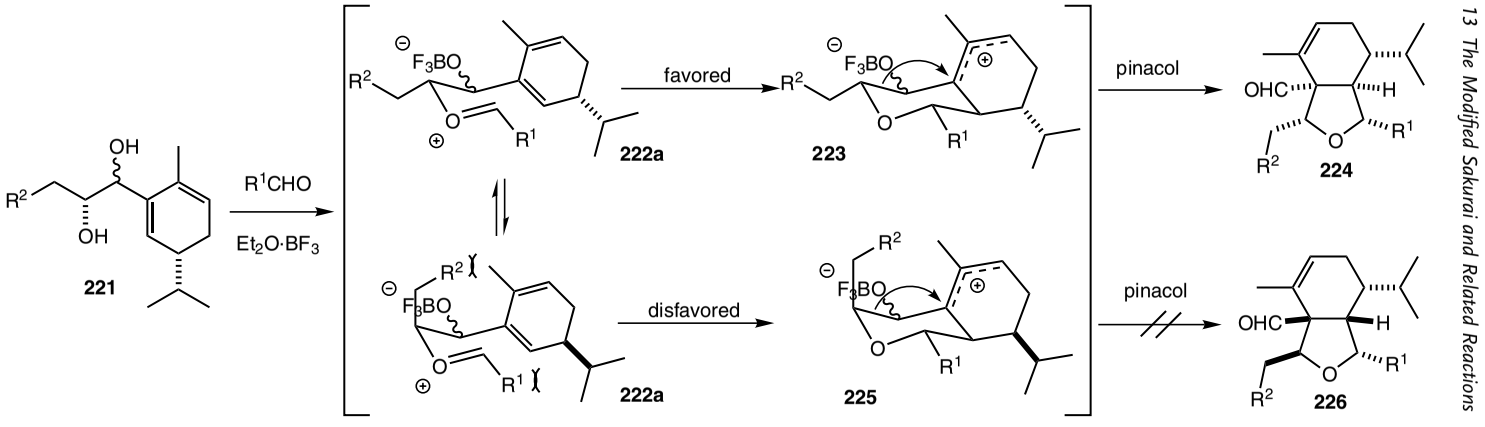
The proposed transition state for the IMSC condensation leading to these five-membered ring heterocycles is depicted in Scheme 13.81. In this envelope-like conformation **219** the substituents preferentially occupy pseudo-equatorial positions.

The most general method for the synthesis of tetrahydrofurans based upon the IMSC methodology was developed by Overman *et al.* [53, 54, 94–96] For example, condensation of alcohol **221** with an aldehyde or a ketone in the presence of a Lewis acid leads to the formation of the carbocations **222a**,**b**. The tertiary carbocation **222a** undergoes a pinacol rearrangement and forms the desired heterocycle **224** (Scheme 13.82). Overman *et al.* used this approach during the synthesis of the various cladiellin diterpenes, which possess the core skeleton **224** [53].

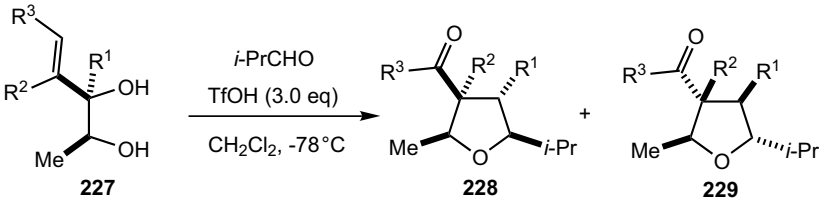
This methodology provides a general access to the desired tetrahydrofuran rings in high yields and selectivity. Several representative examples of tetrahydrofurans formed under these conditions are presented in Scheme 13.83.

13.4.3
Seven-, Eight- and Nine-membered Rings

The synthesis of oxygen-containing seven- or eight-membered rings by IMSC reaction has been little studied as compared to their five- and six-membered analogues.

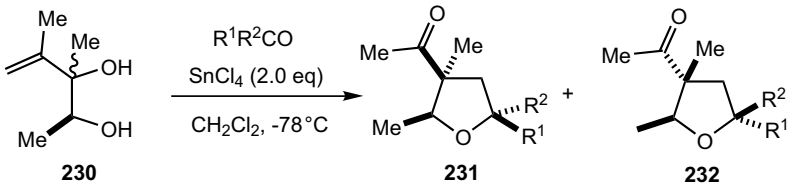

OH
R2
OH
221
R1CHO
Et2O·BF3
F3BO
R2
O
R1
222a
favored
223
pinacol
OHC
H
224
disfavored
225
226

Scheme 13.82



Entry	R^1	R^2	R^3	Yield (%)[a]	**228**: **229**
1	H	H	Me	90	>99:1
2	H	Me	Me	88	97:3
3	H	H	*i*-Pr	98	96:4

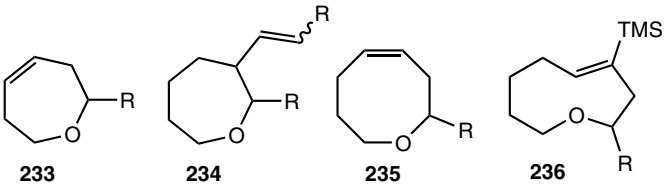
[a] All yields refer to pure, isolated products



Entry	R^1	R^2	Yield (%)[a]	**231**: **232**
1	Et	Me	89	81:19
2	CH_2Br	Me	67	68:32
3	Ph	Me	98	62:38

[a] All yields refer to pure, isolated products

Scheme 13.83

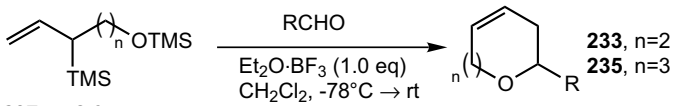


Scheme 13.84

This approach should, however, receive more attention since the IMSC reaction is usually highly stereoselective.

To the best of our knowledge, only a few publications describe IMSC condensations leading to seven- (**233** and **234**), eight- (**235**) and nine-membered heterocycles (**236**) (Scheme 13.84).

Miginiac *et al.* [97] synthesized oxepin **233** and oxocin **234** starting from allylsilane silyl ether **237**, which was condensed with various aldehydes in the presence of $Et_2O{\cdot}BF_3$ (1.0 equivalent) (Scheme 13.85). The resulting seven- and eight-membered rings were obtained in moderate to excellent yields.

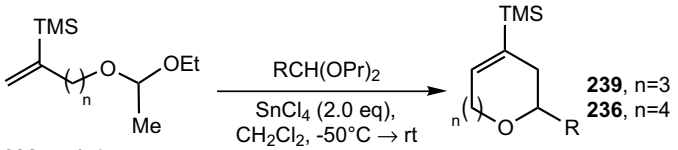


237, n=2,3

Entry	R	Yield (%)[a]	
1	Et	87 (n=2)	55 (n=3)
2	*i*-Pr	87 (n=2)	56 (n=3)
3	Ph	90 (n=2)	77 (n=3)

[a] All yields refer to pure, isolated products

Scheme 13.85



238, n=3,4

Entry	R	Yield (%)[a]	
1	Pr	67 (n=3)	45 (n=4)
2	H	40 (n=3)	20 (n=4)

[a] All yields refer to pure, isolated products

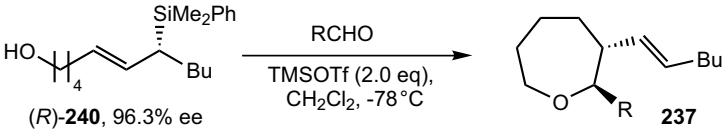
Scheme 13.86

Overman and Blumenkopf prepared various seven- to nine-membered rings starting from vinylsilane **238** which was condensed with various acetals (Scheme 13.86) [56, 98, 99]. The desired medium-sized rings were obtained in moderate to good yields.

The synthesis of optically active vinyl oxepans **234** [55], was reported by Ito *et al.* starting from the enantioenriched allylsilanes **240**. This annelating agent reacted with various aldehydes in the presence of TMSOTf (2.0 equivalents), leading to the oxepans **234** in good yields and excellent stereoselectivity (Scheme 13.89). The condensation of benzaldehyde with **237** is the only case in which an erosion of the *trans*/*cis* stereoselectivity is observed, though this ratio still remains an impressive 50:1 (Scheme 13.87, entry 3).

13.4.4 Spiro Compounds

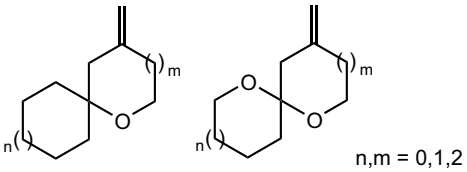
The synthesis of spirobicyclic compounds of general structure **241** and **242** (Figure 13.7) is another area in which the utility of the IMSC methodology has been amply demonstrated, this condensation leading to the desired spiro-compounds efficiently and in a few steps [59, 60, 100, 101]. The ketal subunit **242** is often present



Entry	R^1	Yield (%)[a]	*trans*/*cis*[b]	*E*:*Z*	*ee* (%)
1	*n*-Hex	71	>99:1	>99:1	93.6
2	*tert*-Bu	71	>99:1	>99:1	93.9
3	Ph	82	50:1	>99:1	95.6

[a] All yields refer to pure, isolated products
[b] Refers to stereochemistry of the five-membered ring

Scheme 13.87



241 **242**

Fig. 13.7. Spiro-compounds formed by IMSC.

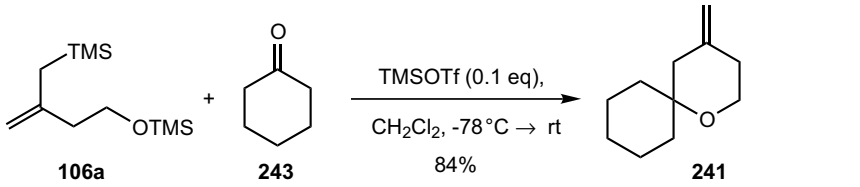
in a wide range of natural products, such as Okadaic acid [102], Milbemycin β [103] and insect pheromones [104].

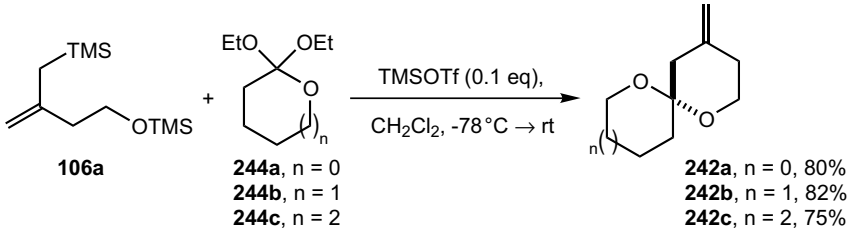
Spiroethers **241** and spiroketals **242** can be easily prepared by condensation of readily available annelating agents such as **106a** with cyclic ketones, for example **243** and ortholactones **244**, respectively. Both spiro-derivatives **241** and **242** are obtained in excellent yields (Scheme 13.88).

The stereoselective formation of spiroketals **242** can be explained in terms of the thermodynamic stability of the three possible products. Oxonium cation **245**, formed by the condensation of ortholactone **244b** and allylsilyl ether **106a**, is in equilibrium with the starting materials. Spiroketal **242** also equilibrates under the reaction conditions with the other anomers. The thermodynamically more stable product **242b**, stabilized by a double anomeric effect, is obtained as the only product of the reaction (Scheme 13.89) as the substituents attempt to occupy equatorial positions in the newly generated tetrahydropyran ring.

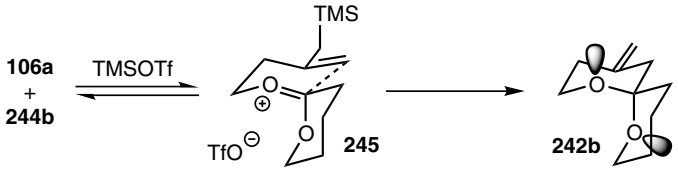
Markó *et al.* used this approach during the total synthesis of one of the major components of the *Dacus oleae* sex pheromone mixture (Scheme 13.90) [59, 60]. The desired spiro-ketal **246** was obtained in three steps and 51% overall yield starting from allylsilyl ether **106a**.

Similarly, the spiroketal subunit of milbemycin β_3 **249** [60, 100] was prepared in four steps and 36% yield starting from orthoester **244b** (Scheme 13.91).

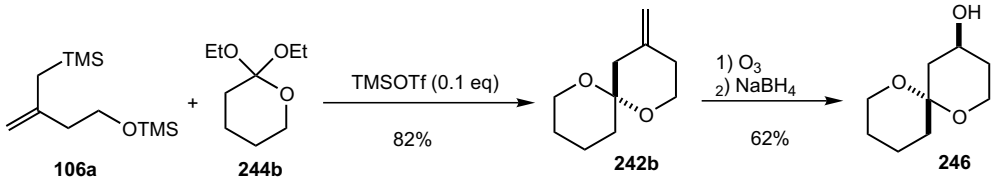




Scheme 13.88



Scheme 13.89



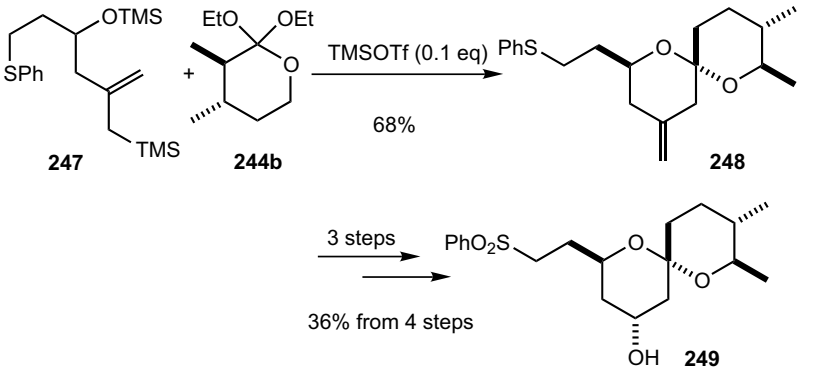
Scheme 13.90

13.4.5
Nitrogen Atom-containing Analogues

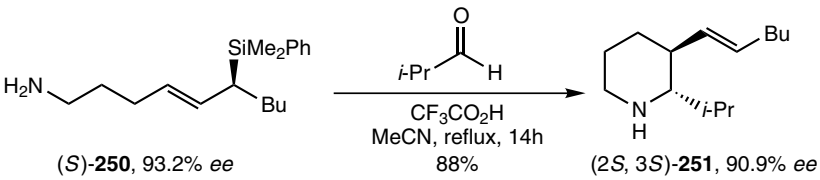
Piperidines [57, 58, 78] and oxazolines [105] can also be synthesized *via* a slightly modified IMSC protocol.

Generally, allylsilylamines are used instead of allylsilylalcohols. Two examples of such a reaction, employing optically active allylsilylamines, are described below.

In the first example, Ito *et al.* used the optically active amine **250** and coupled it with isobutyraldehyde [78]. Surprisingly, harsh conditions were required for cyclization and the reaction mixture had to be refluxed in acetonitrile for 14 h in the



Scheme 13.91



Scheme 13.92

presence of 3.0 equivalents of trifluoroacetic acid. Despite this severe treatment, piperidine **251** could be isolated in 88% yield and 90.9% *ee* (Scheme 13.92).

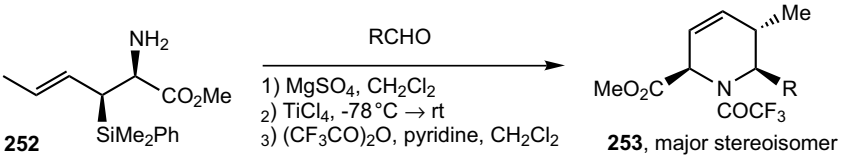
Panek et al. employed the optically active amines **252** and **254** [57]. Their condensation with various aldehydes in the presence of $MgSO_4$ probably afforded the corresponding imines, which were treated with $TiCl_4$. The resulting substituted 1,2,5,6-tetrahydro pyridines were finally protected, affording the corresponding trifluoroacetamides **253** and **255**. In all cases, the desired tetrahydropyridines **253** and **255** could be isolated in excellent yields. The IMSC condensation also displays a high diastereoselectivity (Scheme 13.93).

Panek *et al.* [57] used this methodology as a key step in their synthesis of the quinolizidine alkaloid (−)-**217**(A) which was obtained in 11 steps and 19% overall yields starting from amine **256** (Scheme 13.94).

Aubé *et al.* [105] employed an interesting variant during their preparation of the oxazolines **259** and the dihydro oxazines **261** based upon the use of an azide function as the nucleophile instead of an allylsilane.

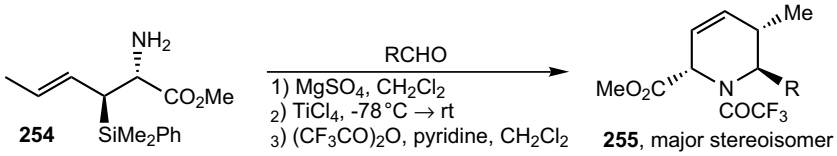
Thus, reaction of 1,2- and 1,3-azido alcohols **258** and **260** with aldehydes, in the presence of $Et_2O{\cdot}BF_3$, gave the desired products **259** and **261** in good to excellent yields (Scheme 13.95).

The proposed mechanism for these reactions is shown in Scheme 13.96 [106]. The initial formation of hemiketal **262** is followed by loss of water and generation of oxonium cation **263**. Subsequent intramolecular addition of the azide function onto the cation produces intermediate **264**. Elimination of a proton and of N_2 directly affords the heterocyclic products. An alternative mechanism involving a



Entry	R	Yield (%)[a]	dr; C_2:C_6-*cis*:*trans*
1	*cyc*-C_6H_{12}	78	10:1
2	*p*-BrPh	82	>30:1
3	2-furyl	75	8:1

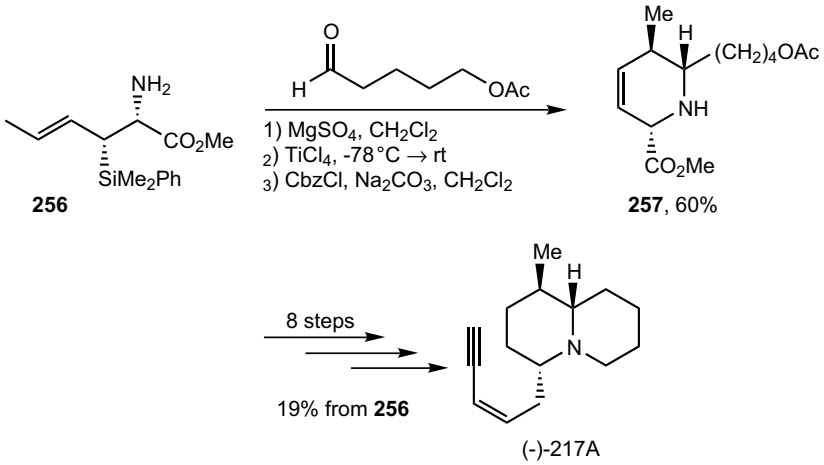
[a] All yields are for pure, fully characterized, products



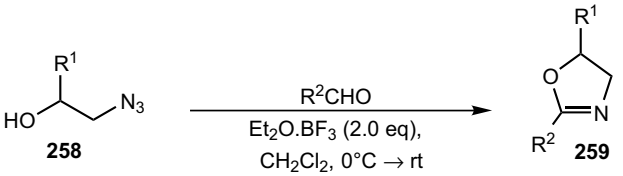
Entry	R	Yield (%)[a]	dr; C_2:C_6-*cis*:*trans*
1	*i*-Pr	73	1:13
2	2-furyl	89	1:10
3	*m*-NO_2Ph	90	<1:30

[a] All yields are for pure, fully characterized, products

Scheme 13.93

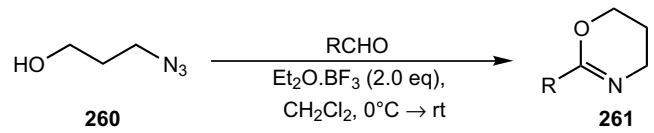


Scheme 13.94



Entry	R^1	R^2	Yield (%)[a]
1	H	*n*-C_5H_{11}	67
2	Ph	*n*-C_5H_{11}	79
3	Ph	Ph	96

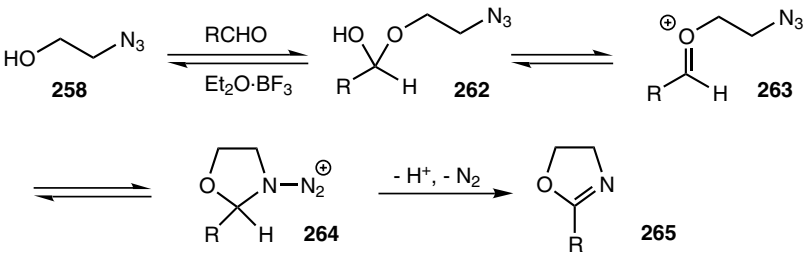
[a] All yields refer to pure, fully characterized, products



Entry	R	Yield (%)[a]
1	$PhCH_2$	70
2	*tert*-Bu	70
3	*p*-NO_2Ph	76

[a] All yields refer to pure, fully characterized, products

Scheme 13.95



Scheme 13.96

1,2-hydride shift coupled with the loss of N_2 is also possible, but seems less likely in light of the poor migratory aptitude of a hydride in similar processes [107].

13.4.6 Conclusions

The IMSC methodology is a highly efficient and versatile process, possessing a broad scope, encompassing a broad range of carbonyls, allylsilanes, alcohols and

amines. A large number of oxygen- and nitrogen-containing heterocycles can be rapidly prepared by this connective method. Additionally, various spiro-compounds can be constructed using this multicomponent methodology.

The power of the IMSC methodology has been demonstrated in numerous total syntheses in which a highly stereoselective heterocycle-ring formation by IMSC is generally one of the key steps.

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