Iminium Catalysis

Anniina Erkkilä, Inkeri Majander, and Petri M. Pihko*

Laboratory of Organic Chemistry, Department of Chemical Technology, Helsinki University of Technology, P.O. Box 6100, FI-02015 TKK, Finland

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* To whom correspondence should be addressed. Tel.: +358 9 451 2536, +358 50 528 9132. Fax: +358 9 451 2538. E-mail: Petri.Pihko@tkk.fi.

1. Introduction

This review covers reactions where iminium ions are likely to be active intermediates in the catalytic cycle. The focus of the review is on synthetically useful protocols and small-molecule catalysts. We will, thus, exclude enzymatic iminium catalysis unless it provides mechanistic or conceptual analogues to the small-molecule catalysts under discussion. The subset of reactions where the initially formed iminium ion loses a proton to form an active enamine intermediate are also excluded from this review, although we will briefly discuss these reactions in view of their historical importance to iminium catalysis. In addition, examples of reactions for which competing mechanistic scenarios have been established, such as the Mannich and Knoevenagel reactions, will be included only when there are good reasons to believe that these reactions take place via an iminium mechanism.

Several accounts and partial reviews of the subject have appeared recently.[1−16] The Knoevenagel[17] and Mannich[18] reactions have also been extensively reviewed. The coverage of this review extends until March 2007.

The review is organized as follows. We will first introduce the concept of iminium catalysis. To illustrate the evolution of iminium catalysis over the years, we will give an overview of the history, retracing the footsteps of the field that dates back more than a century. We will then conclude section 2 by a short discussion of the structural requirements of iminium catalysis. Subsequent section illustrate the individual reactions in the following order: cycloadditions, conjugate addition reactions, reactions involving both iminium and enamine intermediates, domino processes, and reactions with saturated compounds.

2. Iminium Catalysis

2.1. Iminium Ions

The condensation of aldehydes or ketones with primary amines typically results in equilibrium where a considerable amount of the imine is present (Scheme 1).[19] This reaction was discovered in 1864 by Schiff,[20] and the resulting imines are also called Schiff bases. These primary amine-derived imines are basic (pK_a ca. 7),[21] and they readily exist as iminium ions in acidic solution.

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Anniina Erkkilä was born in 1980 in Helsinki, Finland. She received her M.Sc. (Tech.) degree in Organic Chemistry from the Helsinki University of Technology in 2003. Subsequently, she joined the research group of Dr. Petri Pihko as a graduate student working on developing new methodologies for organocatalytic reactions. In 2005, she worked as a visiting researcher in the laboratory of Professor Benjamin List at Max-Planck-Institut für Kohlenforschung in Germany for 3 months. In May 2007, she was awarded the Publication Prize of the Division of Synthetic Chemistry, Association of the Finnish Chemical Societies. She has fulfilled the requirements for her thesis, earning her D.Sc. (Tech.) degree in 2007.

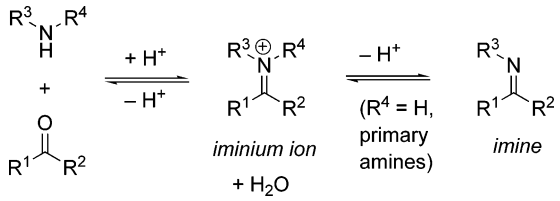
Inkeri Majander was born in 1982 in Kuusankoski, Finland. She received her M.Sc. (Tech.) degree in Organic Chemistry from the Helsinki University of Technology in early 2007. After graduation, she joined the research group of Dr. Petri Pihko as a Ph.D. student and continued working on the fields of catalyst design and organocatalysis.

With secondary amines, aldehydes and ketones may also condense to form iminium cations. In this case, deprotonation to form imines is impossible, and as such, these iminium cations can only be isolated as salts of strong acids. For iminium catalysis, both primary and secondary amines can be used, although the secondary amines tend to dominate the field. The primary amines always require an external acid cocatalyst, and the use of acid cocatalyst is also very common with secondary amines. The structural requirements of the amine catalysts are discussed in further detail in section 2.3.

Iminium salts are more electrophilic than the corresponding aldehydes or ketones (see below). For this reason, the reversible formation of the iminium salt activates the carbonyl component toward nucleophilic attack. This type of activation is similar to that induced by Lewis or Brønsted acids. It should be emphasized that the activation provided by iminium ion formation is very general, and many different types of nucleophile−electrophile interactions can be envisaged. This includes cycloadditions, nucleophilic additions, attacks by bases (resulting in deprotonation and enamine formation), and retroaldol type processes such as decarboxylation. Examples of possible modes of iminium activation are provided in Scheme 2.

Petri Pihko was born in 1971 in Oulu, Finland. He became interested in chemistry several years before entering the university. He studied chemistry at the University of Oulu and joined the research group of Professor Ari Koskinen, graduating with a Ph.D. in 1999. He then spent nearly 2 years as a postdoctoral associate with Professor K. C. Nicolaou at the Scripps Research Institute in La Jolla, California. In 2001, he joined the faculty of Helsinki University of Technology (TKK), where he currently holds the post of Senior Lecturer. For the years 2004–2005, his research group was awarded the title "Outstanding Junior Research Group" by Helsinki University of Technology. His research interests include organocatalysis, catalyst design, and total synthesis of natural products.

Scheme 1. Formation of Iminium Ions and Imines



The iminium-activated reaction will be catalytic only if the amine catalyst is released in the final hydrolysis or elimination step. As an example, nucleophilic addition of hydride ion to the C═N double bond is the basis of reductive amination processes. These reactions proceed via iminium intermediates and are properly called iminium-activated reactions. However, they are not iminium-catalyzed, since the amine becomes trapped in the reduction step.

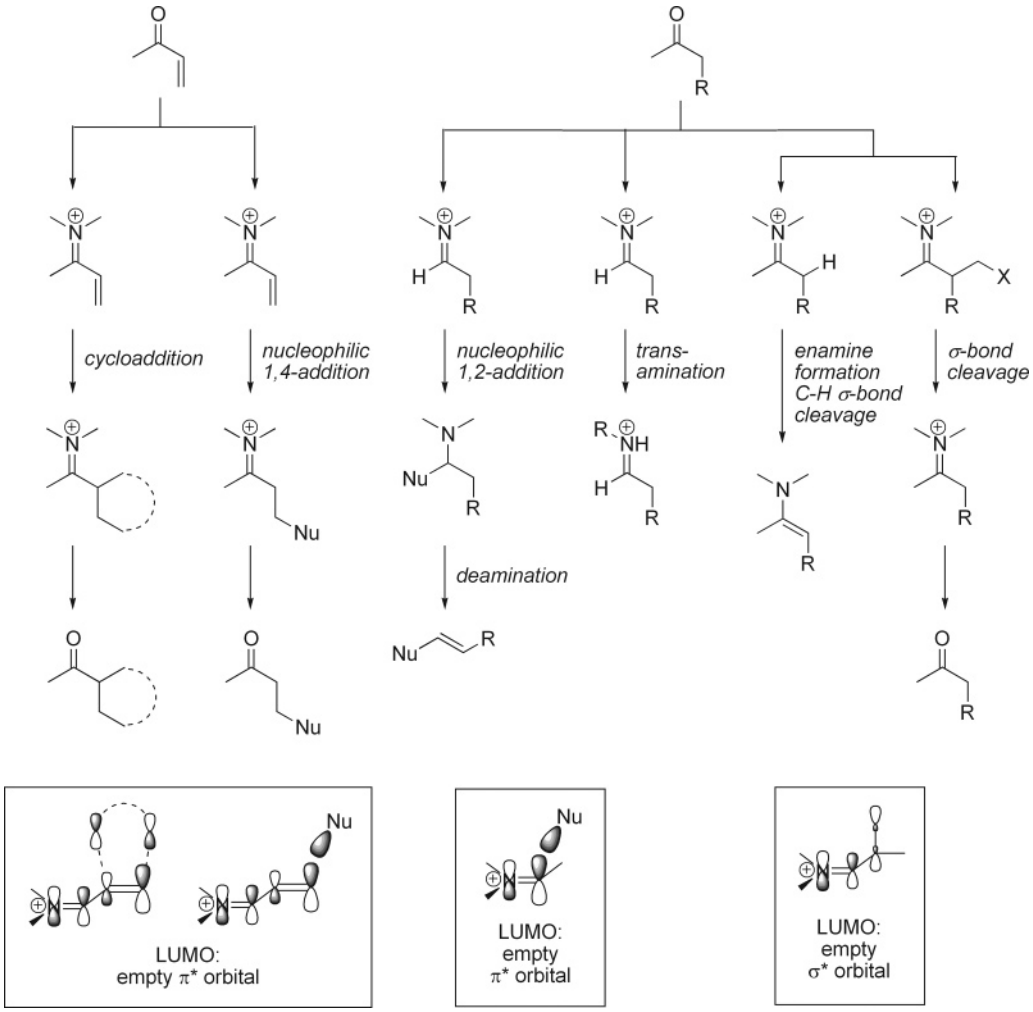
With the exception of the cycloaddition reaction, each of these iminium-catalyzed reaction types were discovered, at least in some form, prior to World War II. In the following discussion, we will briefly outline the history of the field.[22]

2.2. Historical Development of Iminium Catalysis

No specific date can be given for the introduction of the concept of iminium catalysis. Instead, the history of iminium catalysis is characterized by serendipitous discoveries and intervening theoretical advances. Scheme 3 illustrates the key developments of the field.

Perhaps the earliest recorded example of an iminium-catalyzed process is the Knoevenagel condensation[17,23] mediated by primary or secondary amines. The idea that the Knoevenagel reaction might proceed via iminium catalysis emerged slowly. Knoevenagel himself suggested a possible role for the aldehyde-derived imines or aminals in this reaction.[24] It is known, however, that the Knoevenagel-type reactions can also be catalyzed by tertiary amine bases.[17] The iminium mechanism is, thus, only one of the mechanistic

Scheme 2. Different Activation Modes of Iminium Catalysts



possibilities. In 1931, Blanchard et al. suggested that positive ions are involved in the catalysis of the Knoevenagel reaction with secondary amines.[25] Twenty years later, Crowell and Peck presented kinetic evidence for imine/iminium intermediates in the Knoevenagel-type condensations.[26] Today, the contribution of iminium catalysis to the Knoevenagel reaction is generally recognized.[17]

The first reaction where iminium ions were postulated as active intermediates is the decarboxylation of β-ketocarboxylic acids. In 1907, Pollak reported that different proteins and extracts such as albumin and casein as well as different amino acids and ammonium salts catalyzed the decarboxylation of acetoacetic acid.[27] Pollak also suggested that imines are likely intermediates in these reactions. In 1922, Widmark and Jeppsson studied the aniline-catalyzed version of this reaction.[28] They also identified that the reaction has a definite pH optimum between pH 3 and 4.

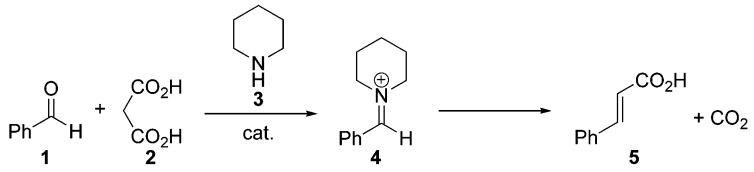
In 1934, Pedersen suggested that the amine-catalyzed decarboxylation of β-ketoacids takes place via a mechanism that involves iminium activation.[29,30] Four years later, Westheimer and Cohen proposed a mechanism similar to that of Pedersen to explain the catalysis of the retroaldol of diacetone alcohol with primary and secondary amines.[31] In 1959, Hamilton and Westheimer corroborated these findings with their studies on carboxylase enzyme.[32] Using ^{18}O-enriched acetoacetic acid as the substrate, they found that the product acetone had lost nearly all of its ^{18}O. These results were fully consistent with the imine/iminium mechanism proposed by Pedersen.

The first iminium-catalyzed conjugate addition reaction was reported in 1937 by Langenbeck and co-workers.[33,34] Piperidinium acetate and sarcosine (*N*-methylglycine) were found to be effective catalysts for the conjugate addition of water to crotonaldehyde. In the presence of glycine, only polymeric resins were obtained. Langenbeck noted that the aldol product is in equilibrium with the starting material. He also made a cautious suggestion that the reaction might proceed via enamine intermediates.

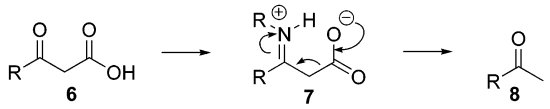
Other noteworthy milestones in the field of iminium-catalyzed conjugate additions include the proline-catalyzed partial deracemization of a thianone intermediate **20** in the Woodward synthesis of erythromycin[35] and the use of alkali metal salts of proline in the conjugate addition of malonates by Yamaguchi and co-workers.[36] The discovery of the iminium-catalyzed transimination reaction by Cordes and Jencks in 1962 also represents another landmark in the history of iminium catalysis.[37] These reactions are further discussed in section 7.1. In the 1960s and 1970s, the attention of the research community shifted to iminium catalysis of the deprotonation reaction, i.e., enamine formation. Thanks to the elaborate studies on iminium-catalyzed enamine formation reaction by the groups of Westheimer,[32,38] Hine,[39] Spencer,[40] Yasnikov,[41] and many others,[42] the role of iminium ions in enamine catalysis is now widely known.

Scheme 3. Historical Development of Iminium Catalysis

1894-1898 Knoevenagel discovers a family of iminium-catalyzed condensation reactions:

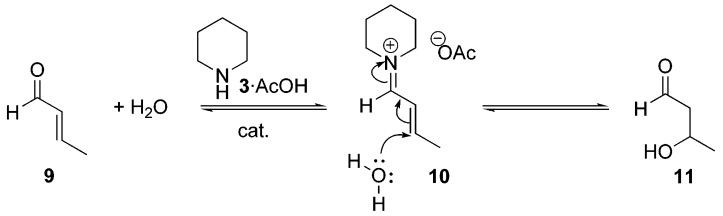


1907 Iminium-catalyzed β-decarboxylation reactions discovered by Pollak

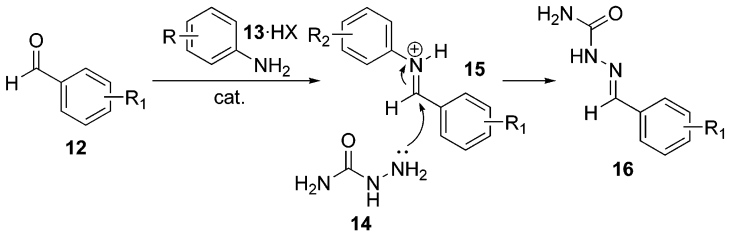


1934 Pedersen proposes the intermediacy of iminium ions as intermediates in the decarboxylation reaction

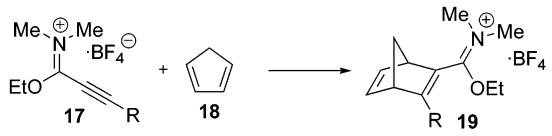
1937 Langenbeck discovers the first iminium-catalyzed conjugate addition



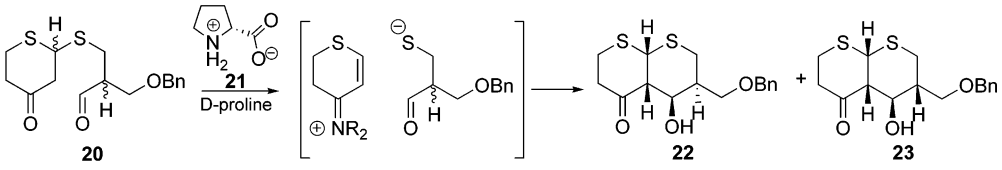
1962 Jencks discovers aniline catalysis of semicarbazone formation



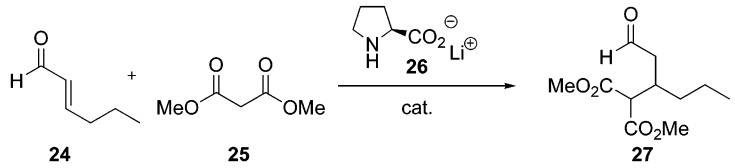
1976 The role of iminium activation in cycloadditions recognized by Viehe and Baum



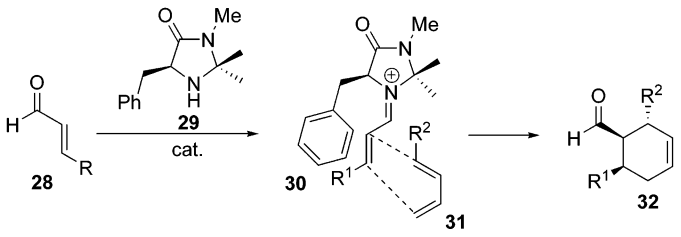
1981 Woodward and co-workers use asymmetric proline catalysis to effect an iminium-catalyzed deracemization and intramolecular aldol reaction in the total synthesis of erythromycin



1991 The first catalytic asymmetric iminium-catalyzed conjugate addition reactions discovered by Yamaguchi



2000 MacMillan reports the first asymmetric iminium-catalyzed cycloaddition reactions



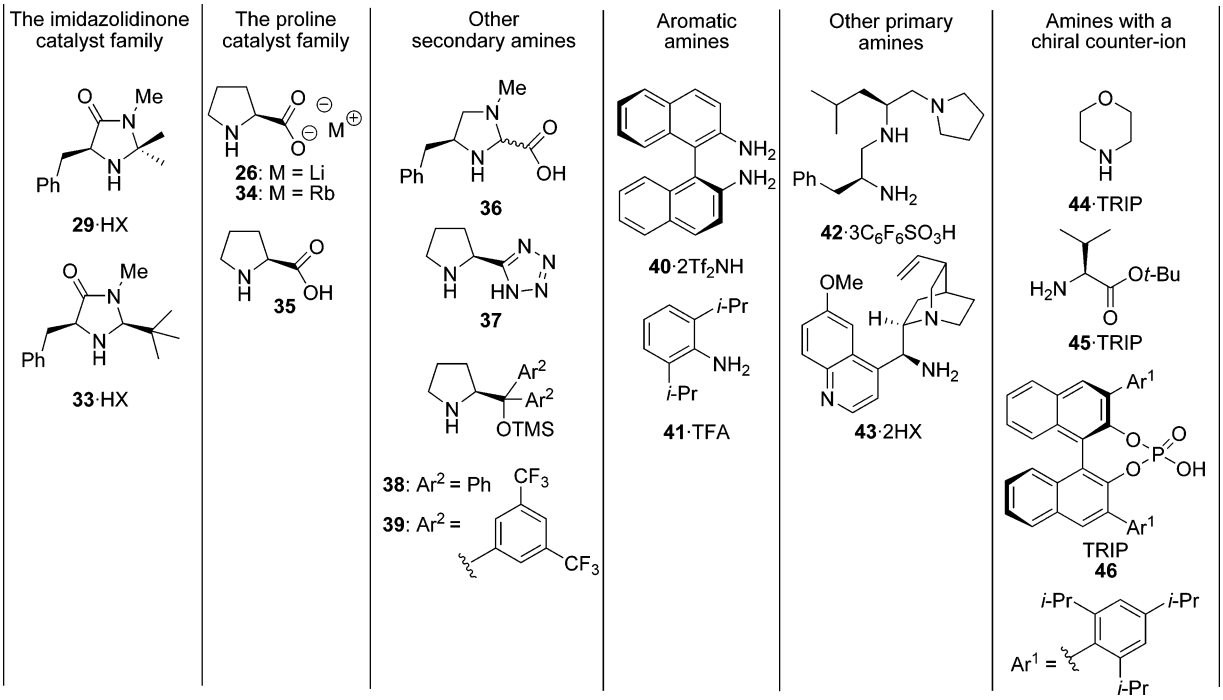


Figure 1. Collection of different amines and amine salts that have been successfully used as iminium catalysts.

Iminium-catalyzed cycloadditions were not discovered until the turn of the century. In 1976, Baum and Viehe reported that iminium salts provide significant acceleration in the Diels−Alder reaction.[43] However, it was not until 2000 that MacMillan and co-workers disclosed a more general catalysis strategy for the Diels−Alder reaction, using enantioselective iminium catalysis.[44] MacMillan and co-workers were also the first to describe the iminium catalysis concept in modern terms, using the term "LUMO-lowering catalysis" to describe the catalysis strategy common to both Lewis acids and chiral amine catalysts. The simplicity of MacMillan's imidazolidinone catalyst family[45] and the generality of the concept set in motion the discovery of a whole range of enantioselective iminium-catalyzed processes. These reactions are covered in more detail in subsequent sections.

2.3 Structure−Activity Relationships

Although full, systematic studies into structure−activity relationships in different types of iminium catalysts are not available, insights into the reactivity of different catalyst types might be gained by inspection of successful iminium catalyst structures (Figure 1). Perhaps the widest variety of amine catalysts has been employed in cycloaddition reactions. The first iminium-catalyzed cycloadditions were reported with imidazolidinone **29**,[44] and the imidazolidinone catalyst family has proved to be a very general and robust platform for a variety of different iminium-catalyzed reactions.[8] The cycloadditions require the use of a relatively strong acid cocatalyst. For imidazolidinones, the acid of choice is typically HCl, CF_3COOH (TFA), or $HClO_4$. In general, the strength and the nature of the acid cocatalyst appear to have a marked influence on the reactivity of the iminium catalyst. According to NMR studies, iminium ions exist as contact ion pairs in aprotic solvents.[46] The relative strengths of the iminium cation−counteranion interactions in different solvents are, however, very difficult to predict, and therefore, the effects of different acid cocatalysts on reactivity cannot be easily generalized.

In addition to the imidazolidinone catalyst family, other cyclic amines, mainly substituted pyrrolidines, have been employed as iminium catalysts. Proline and its derivatives have been very popular, especially for a variety of ring-forming and domino reactions. The diarylprolinol silyl ethers (e.g., **38** and **39**), discovered by the Jørgensen[47] and Hayashi[48] groups, have also enjoyed increasing popularity.

Primary amine catalysts have been less popular than secondary amines. They have, however, been advantageous in the reactions of α-substituted enals, which appear to be too hindered to give acceptable rates or selectivities with chiral secondary amine catalysts. Aromatic amines, such as the hindered aniline derivative **41**[49] as well as diamines such as BINAM **40**,[50,51] have been successfully employed. In addition, a highly interesting chiral triamine **42** has been introduced as a catalyst for the Diels−Alder reaction.[52]

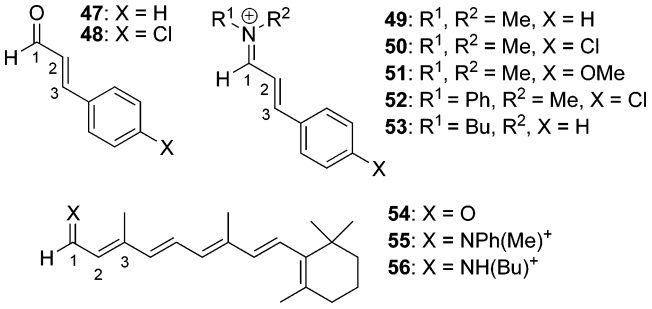
Because of the tight interaction between the iminium cation and the counteranion, chiral counteranions can also influence the enantioselectivity of iminium-catalyzed processes. In fact, it has been proven to be possible to use an *achiral* amine component such as morpholine together with a bulky, chiral phosphoric acid TRIP **46**.[53,54]

2.4. Structural Studies of Iminium Ions

Most structural studies on iminium systems have focused on retinal chemistry, especially the linkage between retinal **54** and a lysine residue in opsin proteins such as rhodopsin and bacteriorhodopsin.[55−58] In addition to retinal itself, cinnamaldehyde **47** has been commonly used as a model compound.[59−62] A number of these studies emanate from the group of Childs and co-workers.

A general feature that emerges from the ^{13}C NMR studies of unsaturated imines is the observed downfield shift (ca. 5−10 ppm) at C^3 in iminium salts compared to the parent unsaturated aldehydes. This feature might reflect the increased electrophilicity of the iminium cation at C^3 compared to the parent aldehyde. In these studies, secondary amines have effected somewhat larger chemical shift changes at the

Table 1. ^{13}C NMR Shifts of Some Cinnamaldehyde and Retinal Derivatives



entry	compound	δ_C at C^1 (ppm)	δ_C at C^2 (ppm)	δ_C at C^3 (ppm)
1[65]	aldehyde **47**	193.4	128.5	152.5
2[65]	aldehyde **48**	193.9	129.6	151.5
3[61]	**49**[a]	171.3	117.8	162.0
4[61]	**50**[a]	171.2	118.3	160.3
5[61]	**51**[a]	170.8	115.0	162.0
6[62]	**52**[b]	169.6	116.4	164.8
7[61]	**53**[b]	172.1	120.5	159.2
8[55]	**54**	190.7	129.0	154.5
9[57]	**55**[a]	160.6	118.1	171.3
10[55]	**56**[c]	163.6	120.1	162.3

[a] Counteranion ClO_4^-. [b] Counteranion $CF_3CO_2^-$. [c] Counteranion Cl^-, ^{13}C NMR data for **56** with TfO^- as the counteranion has also been reported.[57]

C^2 and C^3 positions than primary amines (Table 1, entries 1, 3, and 7). This small difference may be connected with the observed higher activity of secondary amine catalysts when compared to primary amines. A phenyl substituent on the nitrogen also increased the shift changes as compared to two alkyl substituents (entries 2, 4, and 6). Similar trends were also observed with retinal.[55,57] However, it should be kept in mind that the data available for the simpler systems is not very extensive, and these conclusions should be regarded with appropriate caution.

Unfortunately, a direct comparison of the iminium compounds with Lewis acid complexes was not feasible, as there were no reports where identical carbonyl substrates would have been used. Childs et al. have published an interesting NMR study of Lewis acid−crotonaldehyde complexes, however.[63]

X-ray crystal structures have been reported for only three simple iminium salts: **49**, its *p*-methoxy derivative (R^1, R^2 = Me, *X* = MeO), and **52**.[61,62] Recently, Ogilvie and co-workers also reported the crystal structure for the iminium ion of cinnamaldehyde and the hydrazide catalyst **81** (see section 3.1.2).[64] However, sufficient structural data is not available to allow a reliable and meaningful comparison between iminium salts and unactivated aldehydes.

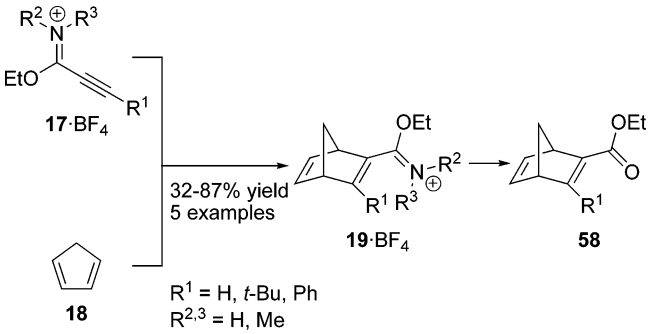
3. Cycloadditions

3.1. Diels−Alder Reactions

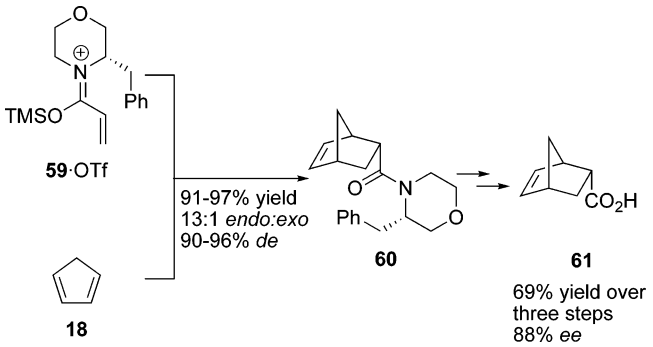
3.1.1. Historical Noncatalytic Precedents

As mentioned above (section 2.2), the concept of iminium activation of α,β-substituted carbonyl compounds in Diels−Alder reactions was introduced by Baum and Viehe in 1976.[43] Their method, however, was not catalytic, as the acetylenic iminium ethers **17** had been prepared beforehand. Reactions between **17** and cyclopentadiene afforded cyclo-

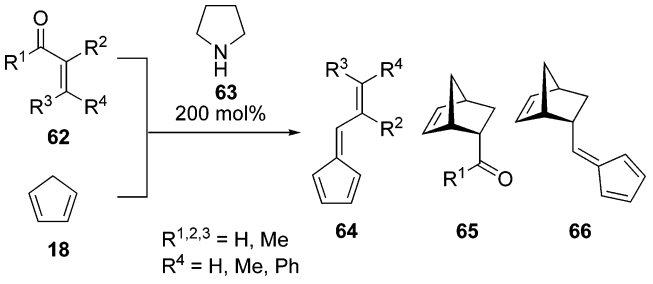
Scheme 4. Diels−Alder Reaction of Iminoacetylenes[43]



Scheme 5. Asymmetric Diels−Alder Reactions of Chiral Iminium Salts[66]



Scheme 6. Synthesis of Fulvenes Mediated by Amines[67]



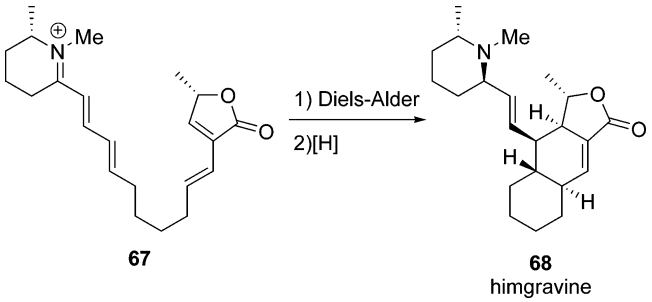
adducts **19** that could be further hydrolyzed to the bicyclic esters **58** (Scheme 4). The amidium moiety was found to be more activating than any carbonyl functionality when conjugated with the multiple bond. In addition to the Diels−Alder reactions, [3+2]-cycloadditions involving **17** and diethyl azoacetate or munchnone were also reported.

Jung and co-workers reported an enantioselective version of this reaction type in 1989.[66] Chiral 2-alkylpyrrolidines or 3-alkylmorpholines were condensed with acryloyl chloride to form an amide and converted in situ to the corresponding silyl triflates **59** (Scheme 5). Good yields and stereoselectivities were obtained with all the auxiliaries. However, hydrolysis of the auxiliaries proved difficult, requiring two separate steps and notably lowering the final yields.

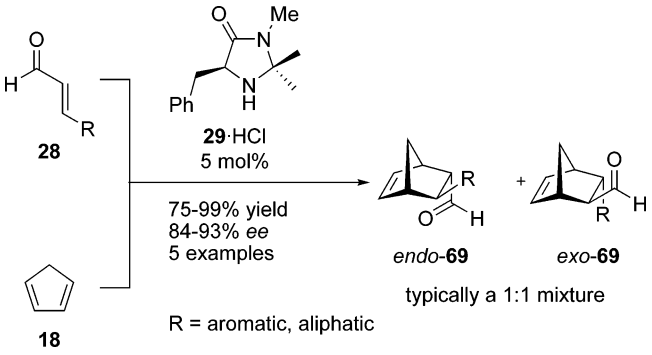
Griesbeck's synthesis of pentafulvenes **64** in the same year provides another early example of iminium-activated cycloadditions.[67] Two equivalents of pyrrolidine were used in the reaction. Depending on the substitution of the starting material **62**, the reaction yielded the desired pentafulvene **64** (62−71% yield), a Diels−Alder product **65** (89%), or a combination of these two **66** (58%) (Scheme 6). The author did not comment on the mechanism leading to the formation of the undesired Diels−Alder products.

In 1995, Baldwin and co-workers proposed an iminium-accelerated Diels−Alder reaction taking place in the bio-

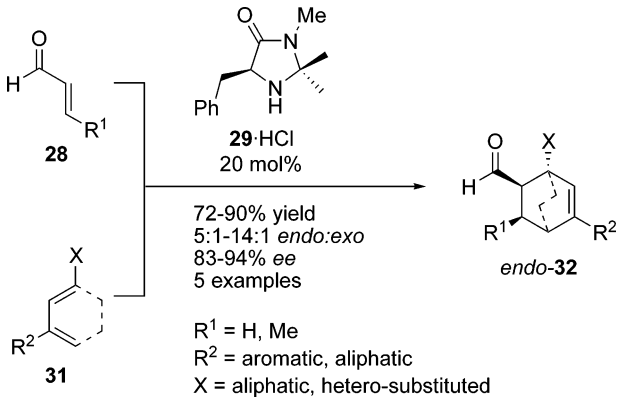
Scheme 7. Proposed Diels−Alder Key Step in the Biosynthesis of Himgravine[68]



Scheme 8. Enantioselective Diels−Alder Reaction between Aldehydes and Cyclopentadiene[44]



Scheme 9. Enantioselective Diels−Alder Reaction between Enals and Acyclic Dienes[44]



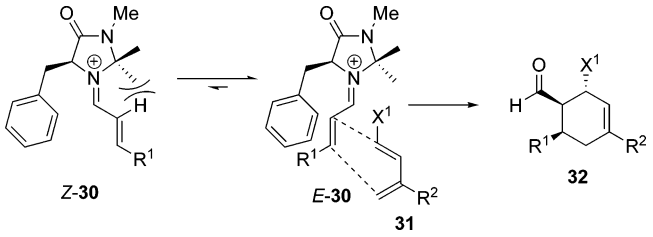
synthesis of himgravine **68**, one of the *Galbulimina* type I alkaloids (Scheme 7).[68] Later, this strategy was further exploited in the biomimetic syntheses of the related alkaloids himbacine, himbeline, and himandravine.[69]

3.1.2. Diels–Alder Reactions of Enals

The first organocatalytic Diels−Alder reaction reported by MacMillan and co-workers in 2000 set in motion the development of iminium-catalyzed cycloaddition and rekindled the interest in the field in general.[44] The chiral imidazolidinone catalyst **29** activated enals **28** to react with dienes by iminium ion formation (Scheme 8), affording cyclic products *exo*-**69** and *endo*-**69** with good enantioselectivity (83−96% enantiomeric excess (ee)). The diastereoselectivity was poor with cyclopentadiene, but acyclic dienes as well as cyclohexadiene afforded good selectivities (Scheme 9). These dienes required catalyst loadings up to 20 mol %, however.

MacMillan explained the selectivity trends of catalyst **29** with a MM3 force field simulation.[44] According to their

Scheme 10. Mechanistic Explanation for the Selectivity in the Organocatalytic Diels−Alder Reaction[44]



model, the catalyst and the aldehyde selectively form an *E*-iminium ion *E*-**30** where the hydrogen atom in the α-position is able to avoid the unfavorable interactions with the geminal methyl groups of the catalyst (Scheme 10). The diene approaches the iminium ion preferably from the *si* face. This allows the diene to avoid the large benzyl substituent stacked on top of the double bond. The position of the benzyl group is presumably favored by π-stacking between the electron-rich benzyl group and the electron-poor iminium cation.

The above model has been criticized in light of more powerful density functional theory (DFT) ab initio calculations (B3LYP/6-31G(d)). On the basis of their computational results, Houk and co-workers suggested that the most stable conformation of *E*-**30** is the compound where the benzyl group is not stacked on top of the double bond but is situated almost orthogonally against it (Figure 2).[70,71] According to

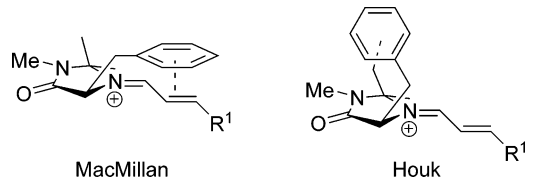


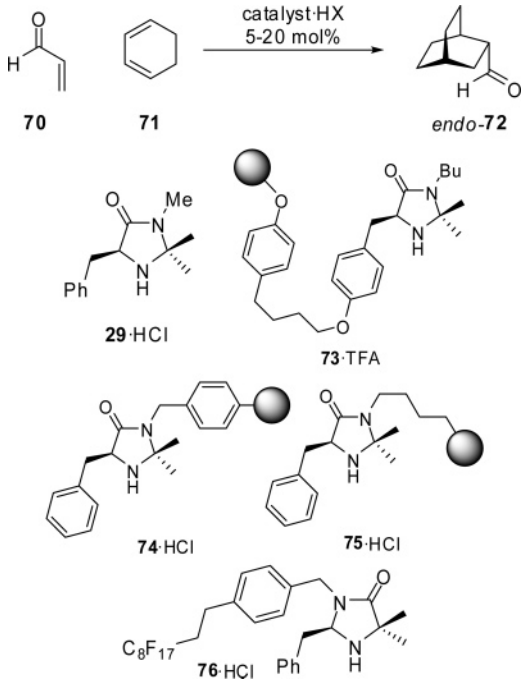
Figure 2. Suggestions for the most favored conformation of the iminium ion *E*-**30**.[44,71]

their model, this arrangement allows favorable C−H π-interactions between the aromatic ring and one of the geminal methyl groups. In other respects, the calculations supported MacMillan's conclusions.

The covalent nature of the iminium catalysts has promoted efforts toward the development of polymeric and solid supported versions of the catalysts.[11] Consequently, several research groups have prepared derivatives of the imidazolidinone catalyst **29** mounted on solid supports. The first of these was disclosed by Cozzi and co-workers in 2002.[72] They prepared an analog **73** of catalyst **29** starting from (*S*)-tyrosine, which allowed the catalyst to be linked to a poly(ethylene glycol) (PEG) polymer from the *p*-hydroxyl group in the benzylic moiety. PEG is soluble in water and in many organic solvents, but it precipitates from diethylether. This facilitates its isolation from the reaction mixtures and recycling of the catalyst.

Catalyst **73** was tested mostly in the Diels−Alder reaction between acrolein **70** and cyclohexadiene **71**, yielding the cycloadduct **72** (Table 2, entries 1 and 2). Enantioselectivities were comparable to those obtained with **29**, and diastereoselectivities were slightly better (entry 8). However, the yields remained lower, especially when using the recycled catalyst (entry 2). In a subsequent article, the authors explained this by the observation that the imidazolidinone moiety itself is being destroyed under the reaction conditions containing acid and an enal.[73] The more reactive the enal, the more extensive

Table 2. Comparison of Recyclable Iminium Catalysts for the Diels−Alder Reaction[44,72,74−76]



	catalyst	yield	endo/exo	% ee[a]
1	**73** (10 mol %)	67%	16:1	92
2	**73**[b] (10 mol %)	50%	16:1	87
3	**74** (20 mol %)	30%	13:1	98
4	**75** (20 mol %)	83%	14:1	90
5	**29**[c] (5 mol %)	76%	17:1	93
6	**29**[b,c] (5 mol %)	70%	17:1	87
7	**76** (10 mol %)	83%	12:1	92
8	**29** (5 mol %)	82%	14:1	94

[a] Endo ee. [b] The catalyst was reused from two previous reactions. [c] The catalyst was contained in [Bmim]PF_6.

was the degradation. Interestingly, the degradation products did not appear to interfere with the enantioselectivity of the remaining catalyst.

Pihko and co-workers had a different approach to this challenge, attaching the catalyst to the support through the nitrogen atom in the 3-position.[74] Two different versions of the catalyst were prepared. Catalyst **74** was attached to JandaJel polymer, and **75** was attached to silica gel. It was hoped that the more polar environment of **75** would stabilize the transition state of the reaction. JandaJel catalyst **74** yielded product **72** with good diastereoselectivities but only modest yields. The enantioselectivity clearly exceeded that obtained with amine **29** (Table 2, entry 3 vs entry 8). However, the yields were better in reactions with cyclopentadiene (58−73%). Recycling of **74** was also possible at least once without a notable decrease in yields and selectivities.

The silica-supported catalyst **75** was fairly active, and good yields were obtained with a variety of dienes (entry 4). The diastereoselectivity was comparable to that of catalyst **29**, and the enantioselectivity was slightly lower. Catalyst **75** was found to be active at as low as 3.3 mol % quantities under certain conditions. The spent catalyst could be readily recovered by filtration.

In 2004, Kim and co-workers reported studies on catalyst **29** in an ionic liquid.[75] The hydrophobic ionic liquids [Bmim]PF_6 and [Bmim]SbF_6 proved to be the most suitable liquids. The yields and enantioselectivities remained lower

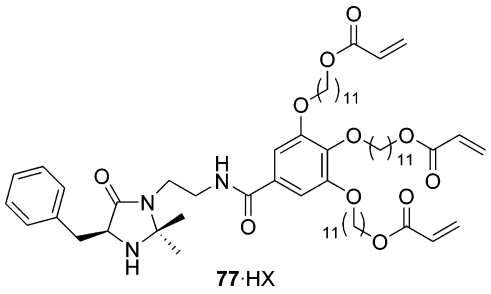


Figure 3. Starting material for a nanostructured organocatalyst.[77]

when hydrophilic liquids were used, although they could be improved by adding water to the mixture. Catalyst **29** afforded **72** with a slightly lower yield and better diastereoselectivity in the ionic liquid than in an ordinary solvent (Table 2, entry 5 vs entry 8). The diastereoselectivity in the reactions with cyclopentadiene was poor, as was the case with the free catalyst. The products could be isolated from the ionic liquid by a simple extraction with diethylether, after which the ionic liquid along with the catalyst could be recycled. The activity of the catalyst remained high until the second cycle, after which it started deteriorating notably (entry 6).

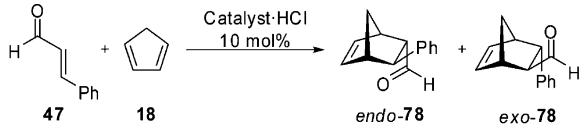
Most recently, in 2006, Zhang and co-workers reported a recyclable fluorous catalyst **76**.[76] Generally, the catalyst performed in the test reactions as well as the primary catalyst **29** (entry 7 vs entry 8). Both product **72** and catalyst **76** could be isolated after the reaction using a fluorous solid-phase extraction technique. The catalyst was recovered in 86% yield and 97% purity. The results were compared to the recovery of catalyst **29** by acid−base extraction (65% recovery yield, 74% purity).

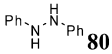
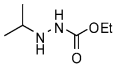
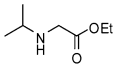
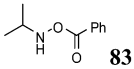
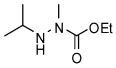
Gin and co-workers introduced a nanostructured solid organocatalyst for the Diels−Alder reaction in 2005.[77,78] Various salts of the imidazolidinone derivative **77** were found to display liquid crystal (LC) behavior in solution (Figure 3). Radical photo-cross-linking of the molecules in LC formations afforded nanostructures containing built-in imidazolidinone catalyst moieties. The catalyst was tested in the Diels−Alder reaction between crotonaldehyde and cyclopentadiene. However, there were no major differences instereoselectivities between the free catalyst **77** and catalysts cross-linked either isotropically or in LC formations. Catalyst **29** performed equally well under the reaction conditions.

Ying and co-workers reported a Diels−Alder reaction between cinnamaldehyde and cyclopentadiene using an imidazolidinone catalyst supported on solid mesocellular foam (MCF) in 2006.[79] The nature of the MCF surface was found to affect the reaction. Catalysts with tetramethylsilane (TMS)-capped or polymer-coated surfaces afforded better enantioselectivities (83−87% ee) than surfaces with free silanol groups (73−74% ee). The polymer-coated catalyst also was recyclable at least once without a decrease in the ee. In addition, Liang and Fréchet reported installing the imidazolidinone catalyst **29** on a polyaryl ether dendrimer and testing it in the Diels−Alder reaction between cinnamaldehyde and cyclopentadiene.[80]

In order to improve the efficiency of the iminium catalysts, Tomkinson, Platts, and co-workers have studied the influence of the so-called α-effect in iminium-catalyzed Diels−Alder reactions.[81−83] The α-effect is related to the increase in reactivity of a nucleophilic center due to an adjacent heteroatom at the α-position.[84] Usually, the nucleophilicity and the Brønsted basicity of a molecule correlate with each

Table 3. Comparison of Catalysts Having an α-Heteroatom in the Diels−Alder Reaction[82]



	Catalyst	Time (h)	Yield
1[a]	 **79**	48	22 %
2[a]	 **80**	48	33 %
3[b]	 **81**	6	90 %
4	 **82**	6	5 %
5	 **83**	6	28 %
6	 **84**	6	98 %

[a] 19:1 MeOH/H_2O as the solvent; in other entries, MeOH. [b] In 19:1 MeOH/H_2O, the yield was 74%.

other. The α-effect describes the anomalously high nucleophilicity observed with nucleophiles bearing an α-heteroatom. Since the formation of the iminium ion involves a nucleophilic attack of the amine catalyst to the aldehyde or ketone, increasing the nucleophilicity of the catalyst might increase the concentration of the active iminium species and improve the overall catalytic activity.

Tomkinson and Platts reported that hydrazines catalyze the Diels−Alder reaction between cinnamaldehyde **47** and cyclopentadiene **18** faster than simple amines (Table 3, entries 1 and 4 vs entries 2 and 3).[82] An electron-withdrawing group at the β-position made the hydrazine catalyst even more efficient (entry 3 vs entry 4). An α-nitrogen activated the catalyst more than an α-oxygen (entry 5). The optimal substituents on the nitrogen atoms were isopropyl and methyl, as in compound **84** (entry 6). The diastereoselectivities of the catalysts were at best modest (2.1:1−1:2.0 endo/exo). It should be noted, however, that comparable rates for the same test reaction have been obtained with catalysts lacking the α-nitrogen,[85] and as such, the α-effect is not the only possible explanation for these results.

Lemay and Ogilvie published a Diels−Alder reaction catalyzed by the camphor-derived hydrazine catalyst **85**.[86] The catalyst structure with its α-heteroatom and β-carbonyl groups corresponds to the optimal catalyst described by Tomkinson and Platts and co-workers.[81,82] Diastereoselectivities in the reactions between *p*-substituted cinnamaldehyde derivatives and cyclopentadiene remained poor, but the enantioselectivities were good (Table 4, entry 1). The acid cocatalyst had a great effect on the yield and the enantioselectivity, with stronger acids generally affording better results.[86]

The authors also carried out ^{1}H NMR studies to investigate the rates of the Diels−Alder reaction catalyzed by **85**.[87] The conversion of **85** and cinnamaldehyde to the iminium ion was complete in 6 min when the reaction mixture (CD_3NO_2) contained 5% water. Both the iminium formation and the hydrolysis were fast, leaving the actual Diels−Alder reaction to be the rate-determining step. For comparison, in the case of the imidazolidinone catalysts such as **29**, both the iminium ion and carbon bond formations were thought to affect the rate.[88]

Recently, Ogilvie and co-workers also disclosed an improved catalyst **86** with an extra methyl group in the *N*-benzylic side chain (Table 4, entry 2).[64] Compared to catalyst **85**, **86** afforded slightly better yields and enantioselectivities. A PM3 semiempirical analysis suggested that the methyl group makes the transition state leading to the minor endo-product more disfavored. In addition, an X-ray crystal structure of the iminium ion of **86** and cinnamaldehyde was reported, revealing full conjugation over the hydrazide−iminium system.

Maruoka and co-workers developed an exo-selective binaphtyl-derived diamine catalyst **87**.[89] Thus far, most of the organocatalysts have been endo-selective in the Diels−Alder reaction. **87** catalyzed the reaction between cyclopentadiene and cinnamaldehyde with good yields and stereoselectivities at −20 °C (Table 4, entry 3). Shorter reaction times were obtained by raising the temperature, but this also deteriorated the enantioselectivity. In addition, the reaction was successful with no other dienes but cyclopentadiene, and the use of other dienophiles instead of cinnamaldehyde lowered the yields.

Recently, Bonini and co-workers published a study that used an aziridine derivative **88** as an organocatalyst for the Diels−Alder reaction (Table 4, entry 4).[90] The yield and ee of the reaction were only moderate, and the reaction was tested with no more than one diene and two different aldehydes, crotonaldehyde and cinnamaldehyde. However, knowing the high reactivity of aziridines, it is interesting that these compounds could nevertheless be used as relatively efficient organocatalysts.

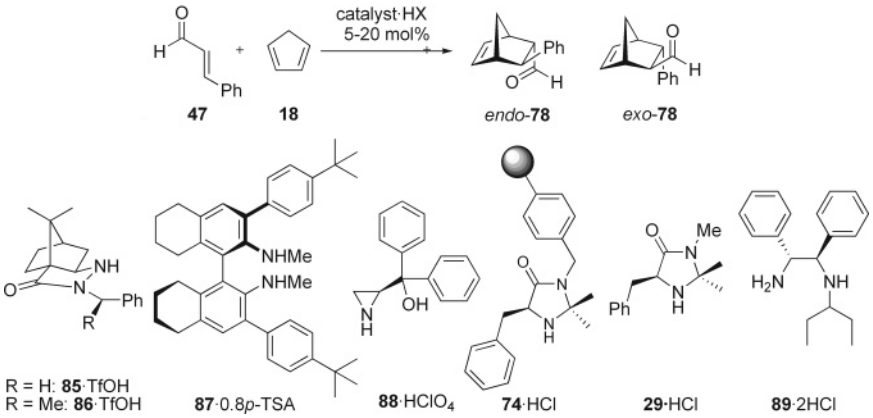
To improve the reaction rate, Mossé and Alexakis also performed the organocatalytic Diels−Alder reaction under microwave irradiation.[91] The reaction time was shortened to just 1 h. However, both the yield and the enantioselectivity were lowered by 17 and 15%, respectively (entry 5 vs entry 6). Similar results were also obtained by traditional heating.

Different iminium catalysts for the Diels−Alder reaction are compared in Table 4, using the reaction between cyclopentadiene and cinnamaldehyde as the standard. Compared to MacMillan's benchmark catalyst **29**−HCl, catalysts **85** and **86** also offer similar yields and selectivities (entries 1 and 2 vs entry 6). The polymer-supported catalyst **74** affords the lowest yield but the best enantioselectivity in the reaction (entry 7). Catalyst **29** immersed in the ionic liquid afforded good yields but only moderate selectivities as compared to the other catalysts in the table (entry 8).[44,74,75] The primary amine catalyst **89** affording moderate yield and selectivity (entry 9) will be discussed in further detail in a following section.[82]

The 3.1.3. Diels–Alder Reactions of Enones

Northrup and MacMillan reported an asymmetric Diels−Alder reaction for enones in 2002.[93] In the preliminary tests

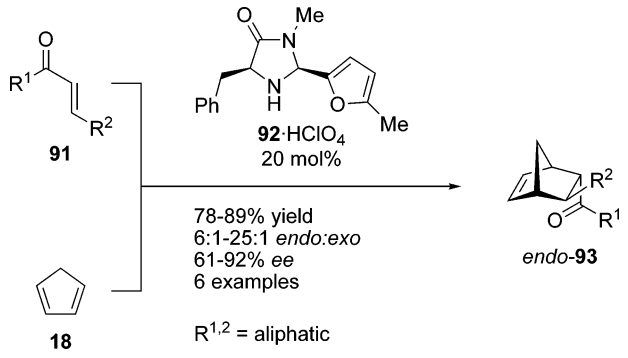
Table 4. Representative Catalysts and Conditions for the Diels−Alder Reaction[44,64,86,89−92,74,75]



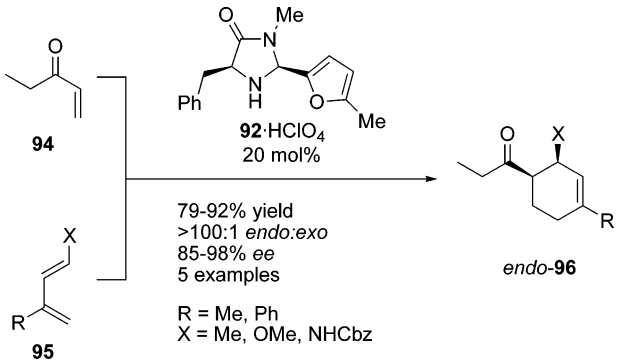
	catalyst	reaction time	solvent	yield	endo/exo	% ee[a]
1	**85** (20 mol %)	n/a at 20 °C[b]	H_2O	96%	1:2	88/90
2	**86** (20 mol %)	n/a at 23 °C[b]	H_2O	94%	1:2.8	93/95
3	**87** (12 mol %)	160 h at −20 °C	CF_3Ph	80%	1:13	91/92
4	**88** (10 mol %)	48 h at 18 °C	H_2O	74%	1.7:1	57/66
5	**29** (5 mol %)	1 h at 65 °C[c]	5% H_2O/MeOH	82%	1:1.2	78/78
6	**29** (5 mol %)	21 h at 23 °C	5% H_2O/MeOH	99%	1:1.3	93/93
7	**74** (20 mol %)	24 h at rt	CH_3CN	70%	1:1.2	99/99
8	**29** (5 mol %)	7h at rt	5% H_2O/[Bmim]PF_6	99%	1:1.1	82/76
9	**89** (5 mol %)	36 h at rt	5% H_2O/dioxane	75%	9:1	78/17

[a] ee of the endo/exo diastereomer. [b] Reaction times were not available. [c] The reaction was irradiated in a MW reactor at 50 W power.

Scheme 11. Enantioselective Diels−Alder Reaction between Enones and Cyclopentadiene[93]



Scheme 12. Enantioselective Diels−Alder Reaction between Dienes and Ethyl Vinyl Ketone[93]

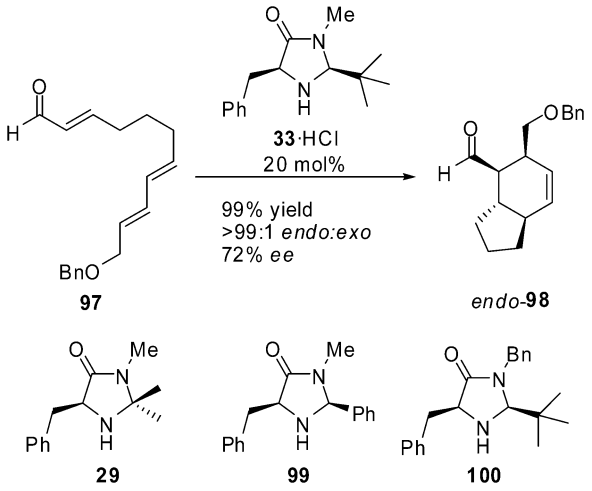


with catalyst **29**, no enantioselectivity was observed and the yield remained at 20%. A successful reaction required the introduction of a new catalyst **92** that had a (5-methyl)furyl group in the 2-position instead of the two methyl groups. In general, **92** catalyzed the reactions between cyclopentadiene and different ketones **91** with good yields and selectivities (Scheme 11). However, when the R^1-substituent was methyl, the ee of the product dropped to 61%. When R^1 was isopropyl, no enantioselectivity was observed, and the yield remained at 24%. A drop in ee was also observed with small cyclic ketones, such as cyclopentenone (48% ee) and cyclohexenone (63% ee). However, the enantioselectivity was good with larger rings. The diene part of the reaction had more freedom concerning its structure. A variety of simple dienes **95** reacted with ethyl vinyl ketone **94** with good yields and stereoselectivities (Scheme 12).

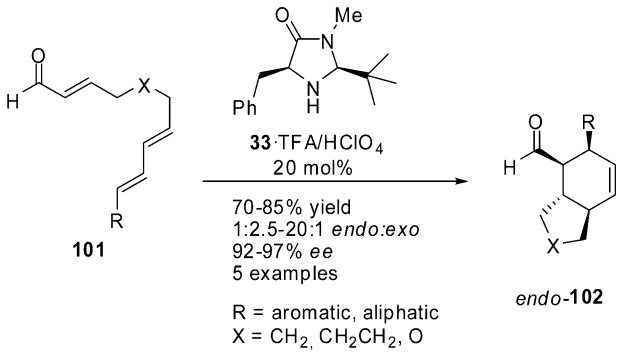
Northrup and MacMillan rationalized the selectivity trends of catalyst **92** with a MM3 force field simulation.[93] According to the model, the ketone preferentially forms a *cis*-iminium ion with the catalyst, because of the unfavorable interactions in the *trans*-isomer between the benzyl side chain of the catalyst and the R^1-substituent of the ketone. The poor selectivity observed with methyl-substituted and small cyclic ketones was attributed to the fact that there is not a large enough size difference between the substituents of the ketone. Consequently, neither the *cis*-isomer nor the *trans*-isomer was favored. On the other hand, the isopropyl substituent is presumably too large for the active site of the catalyst in either conformation. The exceptionally poor 24% yield in the reaction points to the possibility of a noncatalytic background reaction.

Gordillo and Houk determined activities of catalysts **29** and **92** in the reaction between cyclopentadiene and an enone.[71] These theoretical results affirmed the observations by MacMillan. It is possible to find several iminium conformers and transition states for the reaction, but in all cases, the diene approaching from the least-hindered direction is favored. A similar explanation was also invoked by MacMillan based on the MM3 models. Catalyst **29** forms an iminium ion with a ketone only with difficulty because of severe steric hindrances. The poor 20% yield obtained with catalyst **29** was possibly due to the slow background reaction with no iminium activation.

Scheme 13. First Asymmetric Intramolecular Organocatalytic Diels−Alder Reaction[94]



Scheme 14. Asymmetric Intramolecular Diels−Alder Reactions of Various Trienes[95]

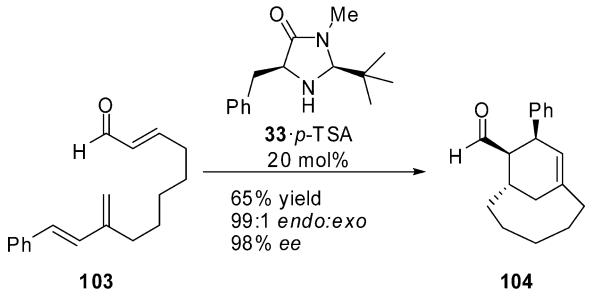


3.1.4. Intramolecular Diels–Alder Reactions

Selkälä and Koskinen succeeded in the first intramolecular organocatalytic Diels−Alder reaction in 2005, using the trienealdehyde **97** as the starting material.[94] The reaction was tested with four different imidazolidinone catalysts (Scheme 13). Austin and MacMillan had previously utilized **33** in enantioselective alkylations of indoles.[88] Catalysts **29** and **99** afforded the desired product only with poor enantioselectivity. Catalysts **33** and **100** had no major differences in the close proximity of the active center. In spite of this, catalyst **33** was significantly more active (99% vs 54% yield) and more selective (72% ee vs 47% ee) than **100** in identical reaction conditions.

MacMillan and co-workers also studied intramolecular Diels−Alder reactions using similar trienes **101** as starting materials (Scheme 14).[95] The bicyclic aldehydes **102** were obtained as products. MacMillan and co-workers reported better enantioselectivities than Selkälä and Koskinen. The differences in the results of the two groups despite the similar substrates could be attributed to the use of different acid cocatalysts. Selkälä and Koskinen had used HCl salts in the reaction, while MacMillan and co-workers used TFA or $HClO_4$ salts. The reaction was highly endo-selective with β-monosubstituted enals, while β-disubstitution afforded modest exo-selectivity. However, catalyst **29** (as an HCl salt) was highly exo-selective with a β-disubstituted enal (1:20 as compared to 1:2.5 endo/exo ratio obtained with catalyst **33**). In other aspects, catalyst **29** was inferior to **33**, although occasionally comparable results were obtained. A type II intramolecular Diels−Alder reaction with the dienophile tethered to the 3-position of the diene could also be performed (Scheme 15). Catalyst **33** (20 mol %) as a *p*-TSA salt afforded product **104** in excellent stereoselectivity.

Scheme 15. Type II Intramolecular Asymmetric Diels−Alder Reaction[95]



In 2006, Christmann and co-workers suggested the possibility of using the intramolecular Diels−Alder methodology in kinetic enrichment of the diene *E,Z*-**105** (Figure 4).[96] Only

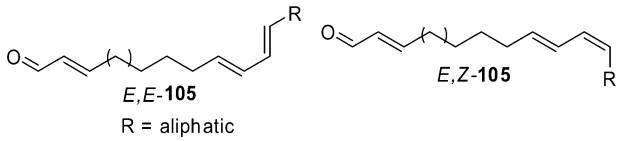


Figure 4. Diene isomers for purification by an intermolecular Diels−Alder reaction.[96]

the undesired side product *E,E*-**105** would react in the Diels−Alder reaction, leaving the *E,Z*-isomer unaffected. Using this strategy, a variety of pure *E,Z*-diene enals were synthesized and utilized in the synthesis of lepidopteran sex pheromones.

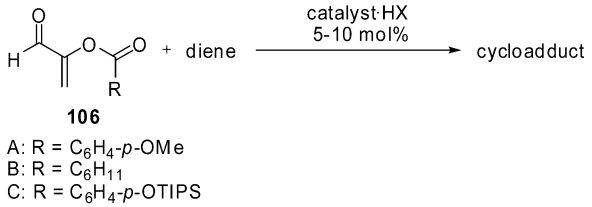
3.1.5. Diels–Alder Reactions Catalyzed by Primary Amines

All amine catalysts discussed so far have been secondary amines, and all of them have a common limitation. The catalytically active nitrogen atom is located in a sterically hindered environment, imposing strict demands on the structure of the substrate aldehyde or ketone. The activation of α-substituted enals is particularly difficult, probably because of the poor generation of the iminium ion.[50,52] This likely caused the 0% yield in the Diels−Alder reaction with an isopropyl-substituted ketone[93] (see section 3.1.3) as well as the poor conversion in the catalytic cyclopropanation of methacrolein[97] (see section 6.1.1) as reported by MacMillan and co-workers.

In 2005, Ishihara and Nakano were the first to succeed in the organocatalytic Diels−Alder reaction of α-acyloxyacroleins **106** by using sterically less-hindered primary amines as catalysts (Table 5).[52] The triamine catalyst **42** could be prepared from the dipeptide of phenylalanine and leucine. A year later, the group disclosed another primary amine catalyst for the Diels−Alder reaction, the aromatic diamine BINAM **40**.[50,51] A superacid Tf_2NH was used as the cocatalyst, as the stereoselectivities suffered from the use of a weaker acid.

Catalyst **42** (10 mol %) afforded Diels−Alder cycloadducts with good yields and enantioselectivities (typically 80−90% ee). Catalyst **40** afforded slightly lower yields, but only 5 mol % of the catalyst was required (Table 5). The Diels−Alder reactions were mostly exo-selective, but as an exception, cyclohexadiene afforded excellent endo-selectivities (13:1−99:1 endo/exo).

Table 5. Enantioselective Primary Amine Catalysts in the Diels−Alder Reaction[50,52]



	cat	R	diene[a]	yield	endo/exo	% ee[b]
1	**42**	A	CP	97%	1:6	80
2	**42**	A	DMB	92%		92
3	**40**	A	CP	48%	1:13	94
4	**40**	B	CP	88%	1:12	91
5	**40**	C	CP	76%	1:13	94
6	**40**	B	DMB	88%		70
7	**40**	C	DMB	85%		85

[a] CP = cyclopentadiene, DMB = 2,3-dimethylbutadiene. [b] ee of the main diastereomer.

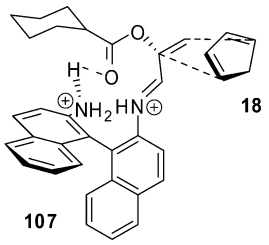


Figure 5. Possible transition state **107** for catalyst **40**.[50]

Ishihara and Nakano explained the selectivity trends of catalyst **40** with a model where one of the amino groups forms an iminium ion or a hydrogen bond-activated imine with the aldehyde and the other forms an ammonium salt with Tf_2NH. The authors presented two possible transition-state models, both having a hydrogen bond between the ammonium group of **40** and the acyloxy group of **106**. One of these models is presented in Figure 5. The necessity of the hydrogen bonding is supported by the fact that a Diels−Alder reaction with methacrolein, where a similar hydrogen bonding is not possible, resulted in only 62% ee.

Ha and co-workers described the use of 1,2-diamino-1,2-diphenylethane derivatives as catalysts in the Diels−Alder reaction soon after the study by Ishihara and Nakano.[92] These compounds also contained at least one primary amino group. Ha and co-workers suggested that the primary amine and the aldehyde form an imine **108** that is activated by the protonated secondary amino group through a hydrogen bond (Figure 6). The alkyl group R adopts a conformation that minimizes the unfavorable interactions with one of the phenyl rings. Together with the other phenyl group, it prevents the diene from approaching from the other face of the double bond. Although this mechanism formally demands only 1 equiv of acid, selectivities suffered when <2 equiv were used. However, the model by Ha and co-workers suggests that the diprotonated iminium in its most-stable conformation should lead to the formation of the opposite enantiomer.

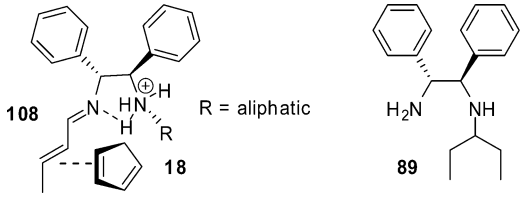
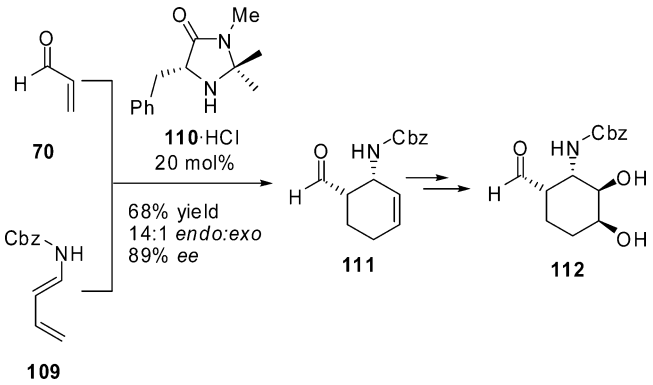


Figure 6. Mechanistic explanation for the selectivity exhibited by catalyst **89** in the Diels−Alder reaction.[92]

Scheme 16. Asymmetric Diels−Alder Reaction as a Part of β-Amino Acid Synthesis[98]



Increasing the size of the acid counteranion was observed to deteriorate the stereoselectivity. Monoalkylated catalysts such as **89** afforded the best results (Table 4, entry 9), but the nonalkylated catalyst was also active (96% yield, 4.8:1 endo/exo, 79% endo ee). On the other hand, *N*,*N*′-dialkylated catalysts were not very enantioselective (19−22% endo ee). The ee's of the endo products (19−91%) were generally better than those of the exo products (9−49%). **89** also catalyzed the Diels−Alder reaction between methacrolein and cyclopentadiene with a modest 34% ee. Surprisingly, the reaction was exo-selective, and the ee's of the diastereomers were of the same order of magnitude.

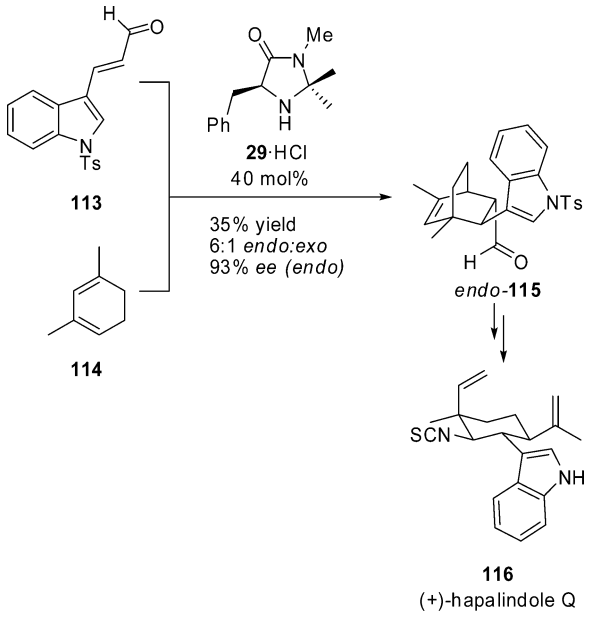
3.1.6. Applications in Natural-Product Synthesis

Wipf and Wang applied the organocatalytic Diels−Alder reaction for the synthesis of the β-amino acid **112**.[98] The asymmetric Diels−Alder reaction was the first step in the synthesis route (Scheme 16). The organocatalytic method was tested in parallel with a method utilizing the (*R*)-BINOL complex of the Lewis acid $Sc(OTf)_3$. The yield and the diastereoselectivity were slightly lower in the organocatalytic method, but the Lewis acid method required an oxazolidinone derivative of the aldehyde to be used as the starting material. The authors expressed satisfaction with both of the methods.

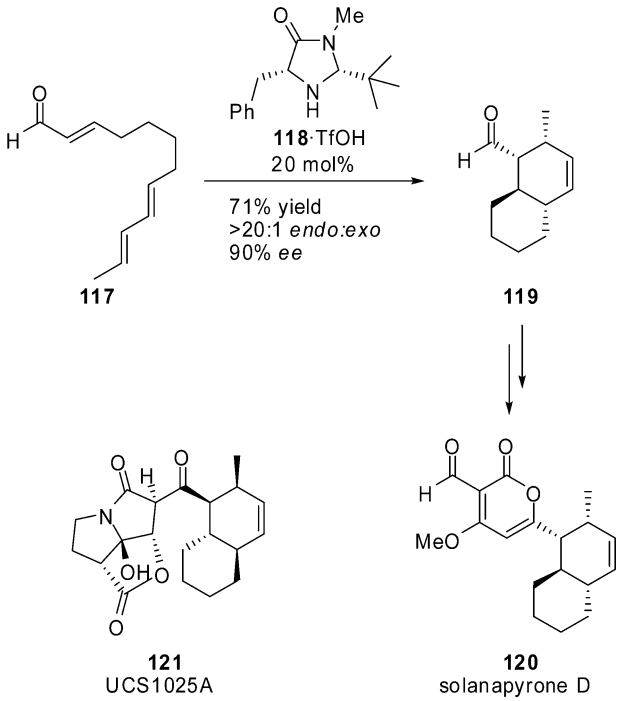
The organocatalytic asymmetric Diels−Alder reaction was first utilized in natural-product total synthesis by Kinsman and Kerr in 2003.[99] Their target molecule was (+)-hapalindole Q **116** (Scheme 17). Catalyst **29** transformed the achiral starting materials **113** and **114** into the chiral cycloadduct **115** with a 35% yield under optimized conditions. The poor yield was thought to result from the excess reactivity of diene **114**, leading to the formation of unwanted side products. This also excluded the use of the alternative Lewis acid catalysis. However, this synthetic route was still attractive, considering how rapidly and enantioselectively the simple starting materials were transformed into the highly complex cycloadduct **115**.

An intramolecular Diels−Alder reaction was applied to the synthesis of the natural product solanapyrone D **120**

Scheme 17. Asymmetric Diels−Alder Reaction in the Total Synthesis of (+)-Hapalindole Q[99]



Scheme 18. Intramolecular Enantioselective Diels−Alder Reaction in the Syntheses of Solanapyrone D and UCS1025A[95,100]



(Scheme 18).[95] The opposite enantiomer **118** of catalyst **33** was used as a triflate salt in this reaction. In addition, Lambert and Danishefsky prepared the opposite enantiomer of compound **119** under the same conditions.[100] The bicyclic compound was subsequently used as a building block in the total synthesis of the telomerase inhibitor UCS1025A **121**. Recently, Christmann and co-workers also used the same building block in the synthesis of a maleimide analogue of UCS1025A.[101] Enantiomeric **119** was prepared using only 10 mol % of the catalyst in an acceptable yield (74%) and ee (84%) that could be further increased by recrystallization.

Recently, Mulzer and co-workers tested the imidazolidinone catalyst **29** in the Diels−Alder key step in the synthesis of (−)-ovalicin.[102] However, the enantioselectivity obtained was poor (<10% ee), and a strategy based on the use of a chiral auxiliary was adopted instead.

Scheme 19. Enantioselective [3+2]-Cycloaddition Reaction[103]

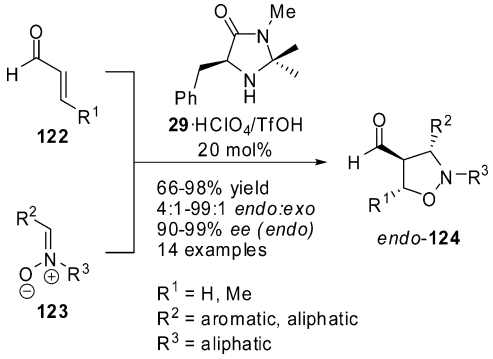
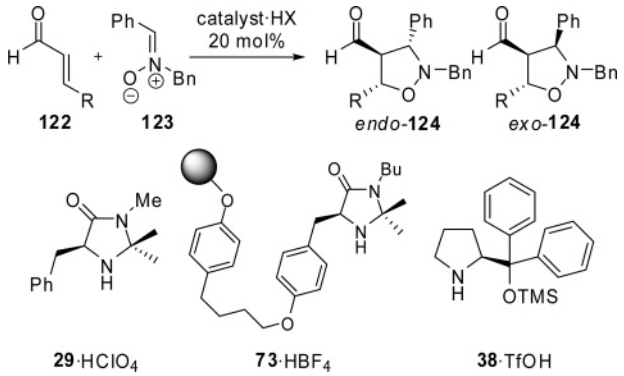


Table 6. Comparison of Catalysts in the Asymmetric [3+2]-Addition[73,103,104]



	cat.	R	yield	endo/exo	%ee[a]
1	**29**	H	80%	6:1	92
2	**73**	H	71%	6:1	87
3	**29**	Me	98%	16:1	94
4	**73**	Me	59%	13:1	87
5	**73**[b]	Me	26%	9:1	88
6	**38**[c]	Me	92%	24:1	95
7	**38**[d]	H	79%	13:1	86

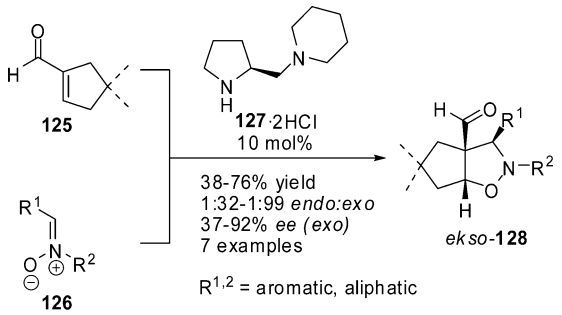
[a] Endo ee. [b] The catalyst was reused from two previous reactions. [c] 5 mol % of the catalyst was used. [d] 10 mol % of the catalyst was used.

3.2. [3+2]-Cycloadditions

The [3+2]-addition between enals and nitrones is another major class of organocatalytic cycloadditions. MacMillan and co-workers reported an organocatalytic [3+2]-addition soon after publishing the Diels−Alder reaction in 2000.[103] The imidazolidinone **29** catalyzed both of these reactions. The [3+2]-addition afforded isoxazolidines **124** with moderate-to-good yields and good selectivities (Scheme 19, Table 6).

Benaglia and co-workers applied the polymer-supported catalyst **73** to the [3+2]-addition in 2004.[73] Previously, the catalyst had been used successfully in the Diels−Alder reaction, in which it had proved to be slightly inferior to catalyst **29** in terms of yields and selectivity (Table 2).[44,72] The same tendency could be observed in the [3+2]-addition reactions (Table 6, entries 1−4). Catalyst **73** was recycled by precipitating from Et_2O and filtering. The diastereoselectivity and the yield in particular decreased after two cycles, likely due to the degradation of the catalytic imidazolidinone

Scheme 20. Enantioselective [3+2]-Additions of Cyclic Aldehydes[105,106]



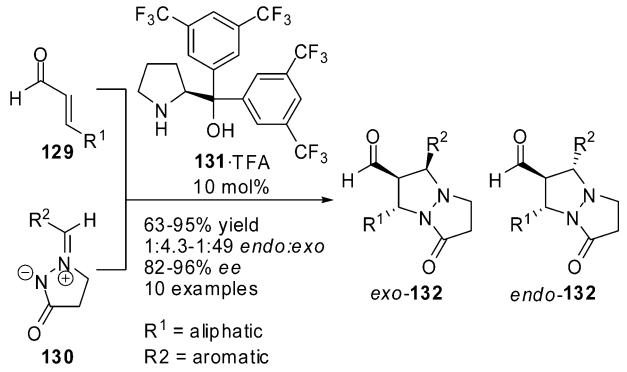
moiety under the reaction conditions. Nevertheless, the enantioselectivity remained constant (entry 5).

Most recently, Nevalainen and co-workers also published [3+3]-additions of nitrones using the triflate salt of the prolinol derivative **38** as the catalyst (Table 6, entries 6 and 7).[104] A smaller amount (5−10 mol %) of the catalyst was sufficient for catalyzing the cycloaddition, as compared to catalysts **29** and **73**. Interestingly, increasing the amount of the catalyst decreased the reaction rates and yields, possibly by promoting polymerization or decomposition of the starting materials. A short series of reactions using cyclic nitrones was also reported.

Karlsson and Högberg reported a [3+2]-addition between the cyclic aldehyde 1-formylcyclopentene **125** and a variety of nitrones **126** in 2002 (Scheme 20).[105,106] First, the imidazolidinone catalyst **29** was tested in the reaction, but the product was obtained in poor yields and as a racemate. This is not surprising considering that aldehyde **125** is α-substituted. However, diamine **127** was found to catalyze the reaction effectively and selectively. The yields and enantioselectivities varied notably between different nitrone starting materials, but the diastereoselectivities were generally good. Longer reaction times and higher temperatures decreased the ee of the product. The authors suspected that aldehyde **125** could form cyclopentenylnitrone in the reaction mixture. This nitrone could react further with nitrone **126** in a nonstereoselective fashion, and during workup, the product would hydrolyze into racemic **128**. The reaction was also tested with a sterically more demanding 4,4-dimethyl-1-formylcyclopentene. The desired product was formed, but only with modest yields and enantioselectivities (38% yield, 37% ee).

In 2006, Chen and co-workers reported a [3+2]-cycloaddition reaction between enals **129** and cyclic azomethine imines **130** (Scheme 21).[107] Catalyst **131** afforded the bicyclic products **132** with good yields and stereoselectivities. The acid cocatalyst was important regarding the enantioselectivity, although higher yields were obtained without the acid. The substituents on the enal (R^1) needed to be aliphatic. In the case of cinnamaldehyde, the decomposition of the azomethine imine **130** and the formation of a new one from cinnamaldehyde (R^2 = Ph) were observed. The substituents (R^2) of imine **130** in Scheme 21 were all aromatic. An aliphatic imine (R^2 = *n*-Pr) was also tested in the reaction, and in this case, the imidazolidinone catalyst **29** afforded the best results (40% yield, 1:19 endo:exo, 77% ee).

Scheme 21. Asymmetric [3+2]-Addition with Azomethine Imines[107]

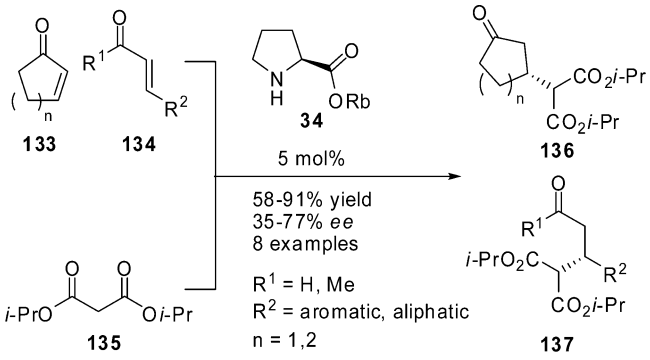


4. Conjugate Additions

4.1. Introduction

A number of nucleophiles can be added to enals and enones in 1,4-fashion. After the seminal Langenbeck 1937 study and studies on proline salt-catalyzed conjugate addition by Yamaguchi and co-workers in the 1990s, the field has grown extensively during the past 5 years with the introduction of new catalysts and substrate classes. The following discussion is divided into five sections according to the hardness of the nucleophile, starting with the soft nucleophiles (C-nucleophiles) and progressing toward harder nucleophiles that are more difficult to add in a 1,4-fashion.

Scheme 22. Enantioselective Conjugate Addition of Malonates to Enones and Enals[108]



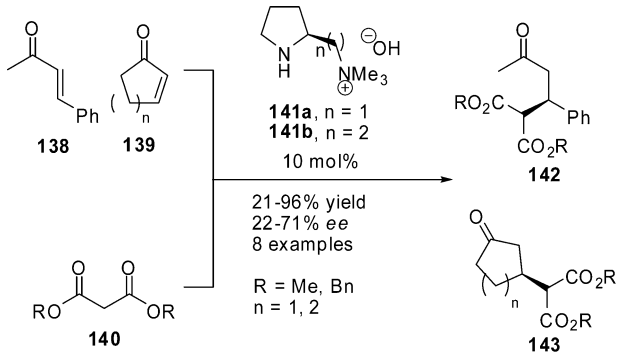
4.2. C-nucleophiles

4.2.1. 1,3-Dicarbonyl Compounds

The first iminium-catalyzed conjugate addition using malonate nucleophiles was reported by Yamaguchi and co-workers in 1991.[36] They described the addition of dimethyl malonate **25** to hexenal **24** being readily promoted by pyrrolidine derivatives as well as some amino acids, including proline. Their most active catalyst was the lithium salt of proline **26** that was used to catalyze the addition of dimethyl malonate to aliphatic β-substituted enals and cinnamaldehyde, as well as to α-substituted enals, methacrolein and 1-formylcyclopentene (see Scheme 3 on the historical development of iminium catalysis in section 2.2). The yields were good, but no enantioselectivities were reported. Later, the method was further optimized and a proline rubidium salt **34** was identified as a more-potent catalyst.[108] With the aid of this enhanced catalyst, diisopropyl malonate **135** was selectively added to both cyclic and acyclic β-substituted enones in good yields (Scheme 22). The enantioselectivities varied from 35% ee to 77% ee depending on the structure of the enone, with aliphatic enones providing the best selectivities.

In 1994, Kawara and Taguchi reported that chiral proline-derived ammonium hydroxides **141** catalyzed the formation

Scheme 23. Asymmetric Conjugate Addition of Malonates to Enones[109]



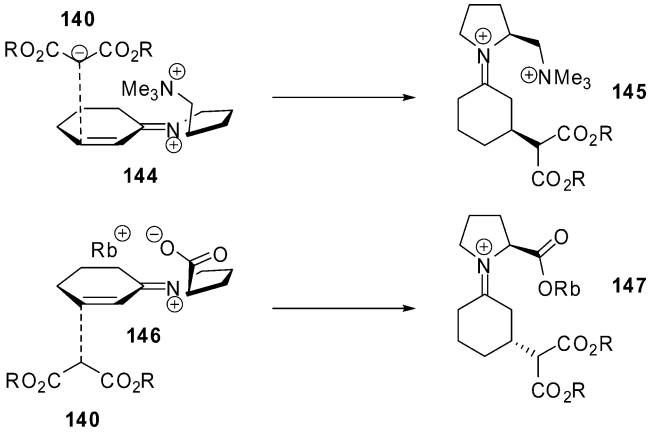
of Michael adducts **142** and **143** of cyclopentenone and cyclohexenone as well as 4-phenyl butanone from dibenzyl malonate (Scheme 23).[109] Moderate yields and enantioselectivities were obtained. Generally, catalyst **141a** ($n = 1$) provided better results. However, the acyclic enone behaved poorly with both of the catalysts, with catalyst **141a** ($n = 1$) affording better selectivity but a very low yield (21% yield, 68% ee vs 53% yield, 22% ee). The reactions typically took one week to complete. Using an excess of acidic additive (hexafluoropropanol) was found to be crucial for obtaining good enantioselectivity.

In 1996, Yamaguchi's group revisited their malonate conjugate addition methodology.[110] The group screened a number of L-proline metal and tetraalkylammonium salts as catalysts. The highest asymmetric inductions were afforded by rubidium prolinate, while the proline ammonium salts provided the fastest reaction rates. Interestingly, the group also observed that the size of the catalyst countercation governed the facial selectivity of the reaction. As already noted by Kawara and Taguchi,[109] opposite facial selectivities were induced by metal salts and alkyl ammonium salts of proline. The increase of the size of the cation from lithium to rubidium reversed the absolute configuration of the product from *S* to *R*. The ammonium salts displayed an enantiomeric trend: increasing the size of the alkyl chains reversed the configuration from *R* to *S*. Yamaguchi and co-workers explained the selectivity trends in a similar fashion as Kawara and Taguchi, suggesting a reaction mechanism involving an iminium salt. With optimized reaction conditions, Yamaguchi and co-workers extended the conjugate addition methodology to include di-*tert*-butyl malonates as nucleophilic reaction partners. The yields with the di-*tert*-butyl malonate were comparable to those obtained with the dimethyl malonate. However, the use of bulkier nucleophiles afforded better selectivities.

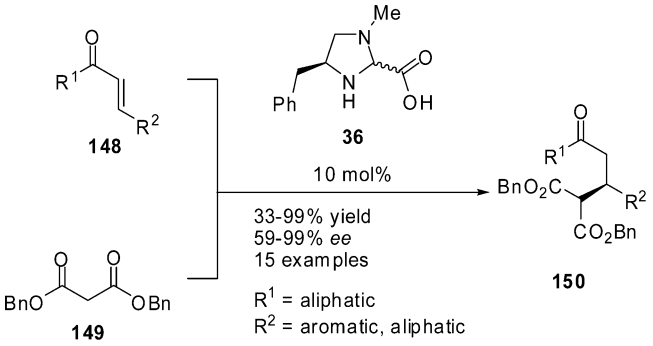
Although the same absolute configuration of the proline framework was used in this reaction and in the Yamaguchi and co-workers reactions, the opposite facial selectivity was obtained. This was explained by the face control of the approaching nucleophile (Scheme 24). In the case of the ammonium hydroxide catalyst, the malonate nucleophile favors the vicinity of the ammonium cation and, thus, approaches the iminium double bond from the *si* face. This type of electrostatic activation was later used by MacMillan and co-workers in the iminium-catalyzed cyclopropanation reaction (section 6.1.1.) On the other hand, with the rubidium salt, the malonate nucleophile approaches from the *re* face, avoiding the steric bulk of the side chain.

Jørgensen and co-workers reported in 2003 that a phenylalanine-derived catalyst **36** promotes the addition of malonates to acyclic enones, with the malonate as the solvent.[111] The ester functionality of the malonate nucleophile had a significant effect on both the efficiency and the selectivity of the reaction. While the reactions of sterically more-hindered malonates proceeded slowly and gave poor yields, the medium-sized malonates, such as dibenzyl malonate **149**, afforded excellent yields and enantioselectivities.

Scheme 24. Plausible Explanation for the Opposite Facial Selectivity Exhibited by Catalysts 34 and 141[108,109]



Scheme 25. Catalyst 36 Promotes Asymmetric Conjugate Addition of Dibenzylmalonate[111]

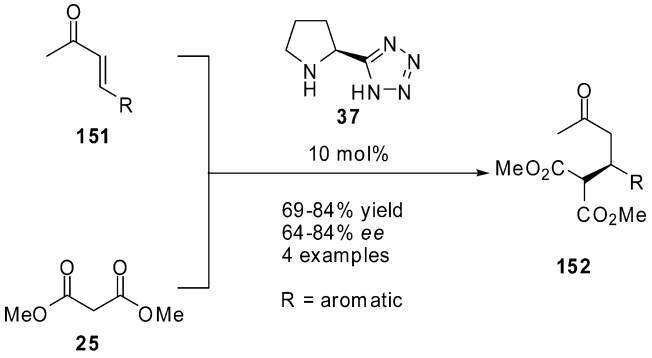


The products were obtained in generally good yields and selectivities with the optimal malonate nucleophile **149** (Scheme 25). However, with aliphatic and more sterically demanding enals, the yields dropped significantly. The reactions also failed to proceed if steric bulk was introduced next to the ketone functionality. However, the group managed to perform a reaction between malonate and cyclohexenone in 78% yield and 83% ee.

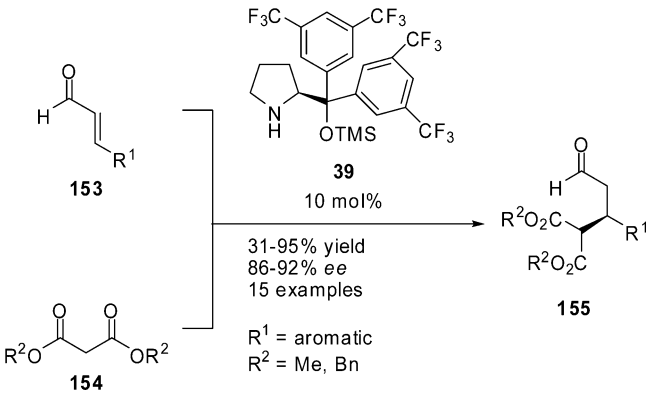
Ley and co-workers aspired to avoid the use of dibenzyl malonate in order to achieve good stereoselection and reaction rate.[112] In 2005, they published the application of the tetrazole analogue of proline **37** to the conjugate addition reactions of dimethyl and diethyl malonates. The catalyst had been previously successfully used in enamine-catalyzed transformations[113] as well as in the conjugate additions of nitroalkanes.[114] The catalyst was shown to promote the reaction efficiently and selectively, and only a slight excess of the nucleophile was required. Under these conditions, the homologated proline tetrazole catalyst analogue failed to provide any selectivity. The method was applied to four aromatic and heteroaromatic enones as well as to cyclohexenone in good yields and enantioselectivities (Scheme 26).

In 2006, Jørgensen and co-workers published studies on the malonate conjugate addition methodology with enals.[115] Prior to this, only scattered examples of malonate additions

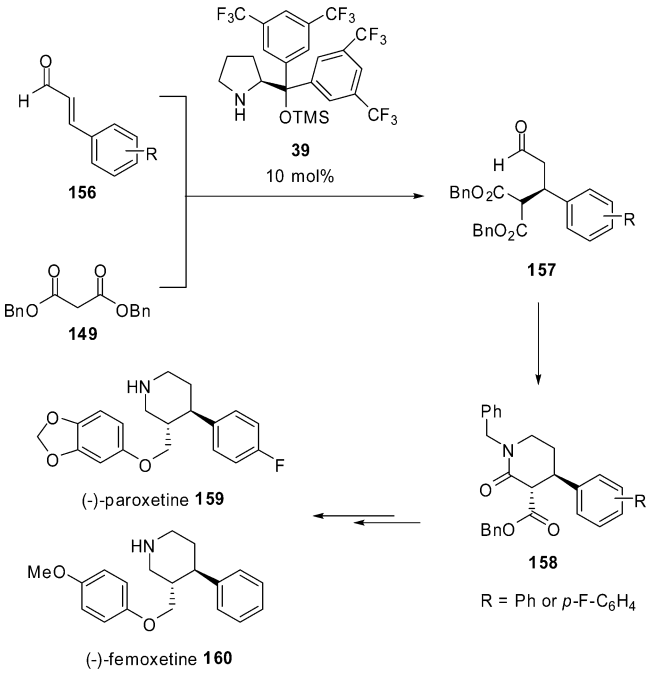
Scheme 26. Enantioselective Conjugate Addition of Dimethyl Malonate to Enals[112]



Scheme 27. Asymmetric Conjugate Addition of Malonates to Enals[115]



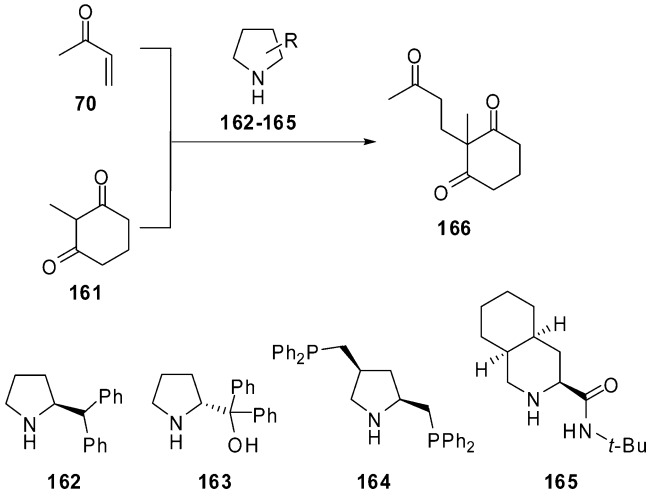
Scheme 28. Iminium-Catalyzed Asymmetric Synthesis of (−)-Paroxetine and (+)-Femexotine[115]



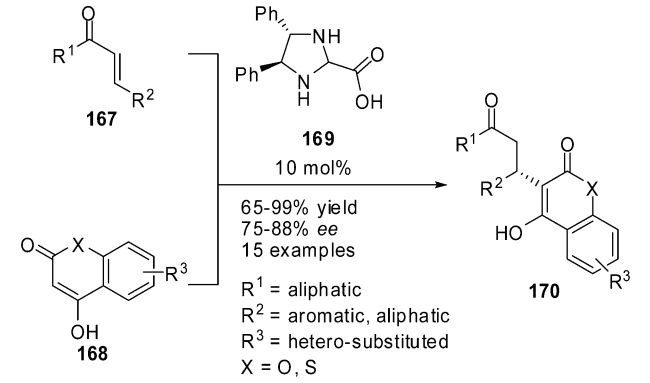
to enals had been reported. The group succeeded in transforming aromatic β-substituted enals **153** into the corresponding malonate derivatives **155** in uniformly good yields and enantioselectivities with catalyst **39** (Scheme 27). However, with halogen-substituted cinnamaldehyde derivatives, the yields were slightly lower.

The group applied their method in the enantioselective formal total syntheses of (−)-paroxetine **159** and (+)-femexotine **160**. Addition of dibenzyl malonate **149** to cinnamaldehyde or *p*-fluorocinnamaldehyde established one of the two required stereocenters in 80% or 72% yield and 91% or 86% ee, respectively (Scheme 28). Following the synthesis of these essential building blocks **157**, a reductive amination−cyclization sequence yielded the respective chiral lactams **158** that could be converted to the desired natural products by known transformations.

Scheme 29. Iminium-Catalyzed Conjugate Addition of Wielend−Miescher Ketone[116]



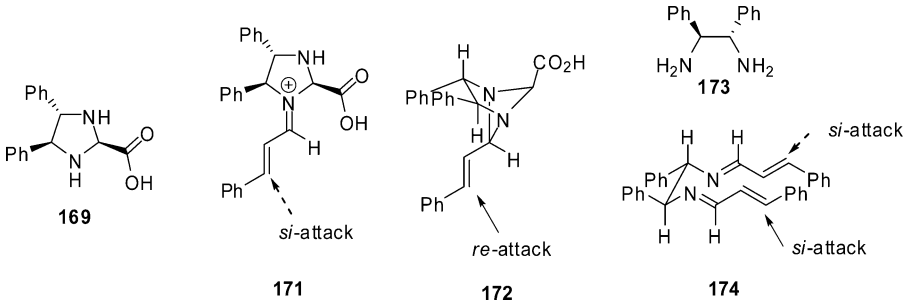
Scheme 30. Asymmetric Conjugate Addition of 4-Hydroxycoumarins to Enones[118]



In 2000, Bui and Barbas studied proline-catalyzed Robinson annulation reactions. In this context, they discovered that some of the catalysts **162**−**165** only catalyzed the conjugate addition of **161** to methyl vinyl ketone **70** to form **166** (Scheme 29) but failed to promote the formation of the bicyclic annulation product **423** (see section 6.1.3, Scheme 95).[116] The authors did not report the yields of these reactions, however.

In 2001, Cravotto and co-workers disclosed that piperidine **3** and acetic anhydride can promote the conjugate addition of the cyclic diketone, 4-hydroxycoumarin **168**, to enals such as carvone, 2-cyclohexanone, and ethyl vinyl ketone.[117] However, this method was not catalytic, leading to the intramolecular cyclization of the product. Two years later, in 2003, Jørgensen and co-workers discovered that the addition of 4-hydroxycoumarin to acyclic enones **167** could be catalyzed by the imidazolidine catalyst **169**.[118] 4-hydroxycoumarin **168** was reliably added to several benzylideneacetone derivatives as well as to four other heteroaromatic or aliphatic β-substituted enones (Scheme 30). Uniformly good yields and enantioselectivities were obtained. The

Scheme 31. Possible Origin of Stereoselectivity Exhibited by the Catalyst 169[118]



reaction times ranged from a couple of days up to 2 weeks. Several other 1,3-dicarbonyl compounds were applied to the reaction with benzylideneacetone without significant change in the efficiency or the selectivity of the reaction.

Jørgensen proposed that the catalytic activity and selectivity of the reaction might not result from the formation of an iminium ion and suggested that aminal species **172** is the actual catalytic intermediate (Scheme 31). However, this mechanism would lead to the formation of the enantiomer of the observed product. Later, Chin and co-workers suggested that the breakdown of the catalyst in the reaction conditions could better account for the selectivity.[119] This would lead to the formation of diamine **173** and a nucleophile−acid complex. DFT (B3LYP/6-31G*) calculations supported the authors' suggestion that the catalytically active species would, thus, be the diimine intermediate **174**. Nonetheless, the iminium intermediate **171** formed from the original catalyst complex could also explain the observed facial selectivity.

Chin and co-workers studied aryl diamines for the synthesis of warfarin **175** (Figure 7, Scheme 32).[119] The iminium-catalyzed addition of hydroxycoumarin to phenylbutenone leads to the formation of warfarin in one step. Chin's group based their studies on the proposal that the

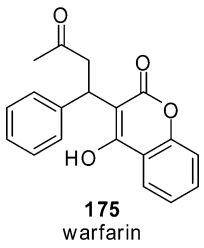
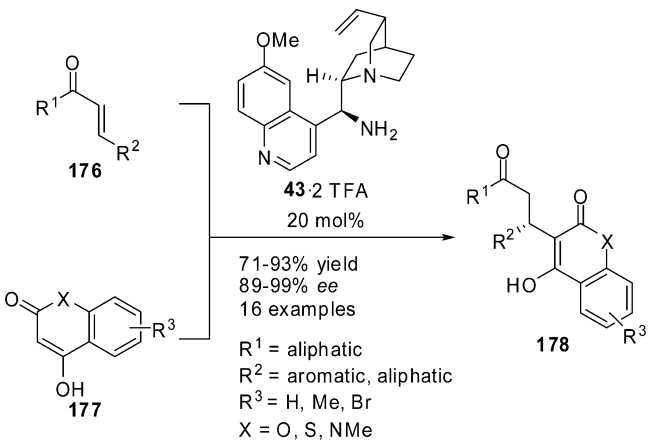
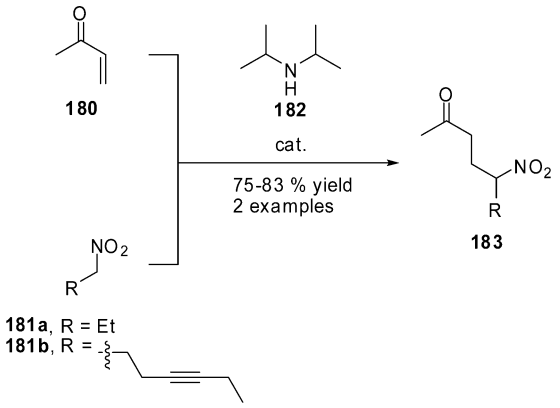


Figure 7. Structure of warfarin.

Scheme 32. Asymmetric Conjugate Addition of 4-Hydroxycoumarines to Enones[121]



Scheme 33. Conjugate Addition of Nitroalkanes to Methyl Vinyl Ketone[128]



chiral vicinal diimine **174** is the catalytically active species within the reaction. They found that, while the more-basic alkyl diamines were more active iminium catalysts than the less-basic aryl diamines, the best stereochemical induction was delivered by increasing the bulkiness of the aryl component. Jorgensen and co-workers have also utilized diphenyl diamine and cyclohexyldiamine in their synthesis of warfarin.[120]

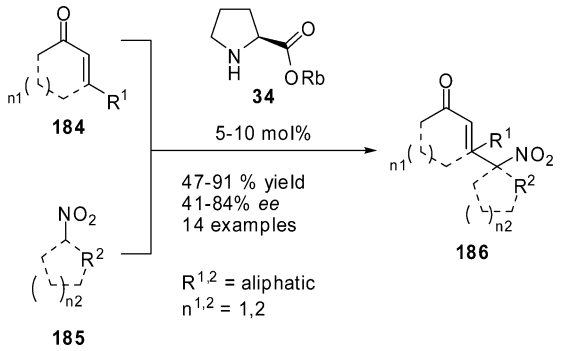
In 2007, Chen and co-workers applied catalyst **43** to the addition of 4-hydroxycoumarin **177** to β-substituted enones **176** (Scheme 32).[121] They had utilized the catalyst in the conjugate addition of dicyanoolefins to enones in their prior studies.[122] The products **178** were provided in high yields and excellent enantioselectivities by the catalyst combined with a TFA cocatalyst. In addition to 4-hydroxycoumarin (X = O) and its derivatives, hydroxythiocoumarin (X = S, R^3 = H) and methylhydroxycarbostyril (X = NMe, R^3 = H) were also tested as reaction partners. Both exhibited a slightly lower reactivity than 4-hydroxycoumarin. 4-Hydroxycoumarins have also been reported to add to enals in a 1,2-fashion, resulting in a Knoevenagel-type condensation when stoichiometric amounts of piperidine **3** are used to promote the reaction.[117]

Iminium activation has also been utilized in the additions of β-ketoesters to enones[123−125] and enals[126,127] in the context of domino reaction sequences. These reactions will be discussed in section 6.1.

4.2.2. Nitroalkanes

An early example of an iminium-catalyzed nitroalkane conjugate addition was published by McMurry and Melton in 1971.[128] They exploited the conjugate addition of a nitroalkanes **181** to an enone **180** while preparing starting materials **183** for the synthesis of 1,4-diketones (Scheme 33). The nitro group was later transformed into a carbonyl.

Scheme 34. Proline Rubidium Salt 34 Promotes Enantioselective Conjugate Addition of Nitroalkanes[130]



Diisopropylamine catalyzed the additions of 1-nitropropane **181a** and the more complex nitroalkane **181b** to methyl vinyl ketone. Later, Belokon and co-workers reported a prolinol-catalyzed enantioselective addition of β-nitro methyl ester to crotonaldehyde.[129]

Since the early examples, the development of conjugate additions of nitroalkanes has been parallel and alike to that of malonates. In 1994, Yamaguchi and co-workers reported the Michael addition of nitroalkanes **185** to both cyclic and acyclic β-substituted enones **184**.[130] The reaction was catalyzed by proline rubidium salt **34** and intermediated by an iminium ion (Scheme 34). The yields were generally good, while the enantioselectivities varied from moderate to good. Bulkier nitroalkanes afforded better results. In a more extensive study, Yamaguchi et al. also demonstrated that the proline framework tolerates substitution at both the 3- and 4-positions, with the carboxylate group in the 2-position governing the selectivity.[131]

Hanessian and Pham utilized proline as a catalyst in the conjugate addition of nitroalkanes to cyclic enones in the presence of an amine additive.[132] Instead of rubidium salt, they used proline **35** to provide Michael adducts with enhanced yields compared to the rubidium prolinate catalyst **34** (Table 7, entry 2). Use of an amine additive was required. The highest enantioselectivities were obtained with cyclohexenone (up to 93% ee). Addition of nitropropane to an acyclic enone, chalcone, was reported to afford 68% ee. Interestingly, the catalyst system was shown to exhibit a pronounced nonlinear effect in the presence of the *trans*-2,5-dimethylpiperazine additive **188** (Figure 8). In the absence of the additive, the relationship between the catalyst ee and the product was linear.

Attempts to further refine and extend the substrate scope of the nitroalkane addition reaction have led to the introduction of several new catalysts. In 2002, Jørgensen and co-workers reported a conjugate addition to acyclic β-substituted enones **189** catalyzed by the chiral amine **36** illustrated in Scheme 35.[133] Using 2-nitropropane as a solvent, a diastereomeric mixture of the catalysts **36** afforded the corresponding products in good yields and selectivities with aromatic enones (Table 7, entry 3). However, when the size of the R^1 substituent was increased to ethyl of isopropyl, the yields dropped dramatically. Heteroaromatic and aliphatic enones gave only moderate yields. Variation of the nitroalkane structure had little effect on the selectivity of the reactions, but conversions were slightly retarded, especially with nitromethane and nitrocyclopentane. Prochiral nitroalkanes showed none or only a very modest diastereoselectivity in the reaction.

Jørgensen proposed that the observed stereoselectivity could be explained by an iminium intermediate in which the benzyl group of the catalyst stacks on the side of the enone side chain and shields the *re* face on the enone from the attack. This model is in accordance with Northrup and MacMillan's model for the Diels−Alder reaction of enones[93] and similarly explains the diminished reactivity of the enones with large R^1 groups.

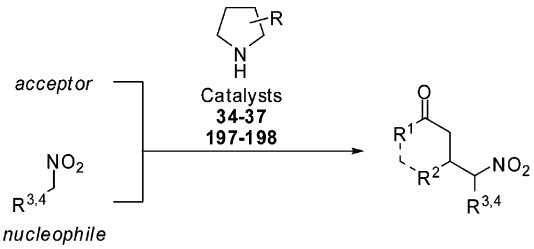
Three years later, the same group reported the tetrazole derivative **197** of the imidazolidinine catalyst **36** as an equally viable catalyst for the conjugate addition of nitroalkanes.[134] Compared to their original catalyst **36**, catalyst **197** afforded very similar results in terms of yields and selectivities (Table 7, entry 4). However, the reaction times were halved in most cases, and a broader scope of nitroalkanes exhibited good turnover in the reaction. Nonetheless, the diastereoselectivities with nonsymmetric nitroalkanes remained poor.

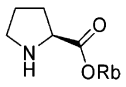
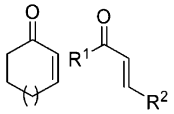
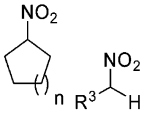
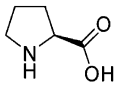
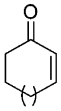
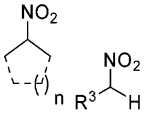
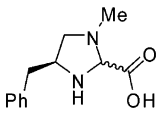
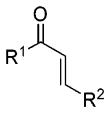
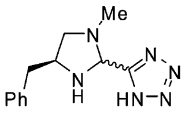
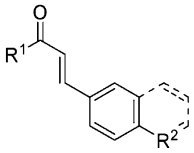
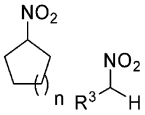
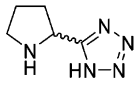
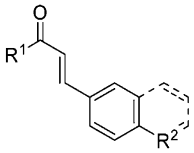
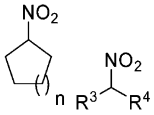
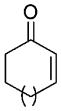
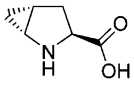
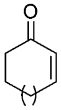
Around the same time, Ley and co-workers showed that the proline tetrazole derivative **37** also catalyzes the conjugate addition nitroalkanes to cyclohexenone, cyclopentenone, and various acyclic enones.[114] In accordance with the related proline-catalyzed conjugate addition developed by Hanessian and Pham,[132] the Ley method also required the use of an amine additive **188** (Figure 8). While the yields were moderate, enantioselectivities were excellent with the cyclohexenone adducts and good with phenylbutenone adducts (Table 7, Entry 5). Additionally, cyclopentenone, some electron-withdrawing and electron-donating phenylbutenone derivatives, and a couple of aliphatic acyclic enones were transformed to the corresponding Michael adducts in good yields and moderate-to-high stereoselectivities. On the basis of kinetic studies, the group proposed that the reaction proceeds via iminium species.[135]

Tsogoeva and co-workers studied small peptides (Figure 9) as catalysts for the addition of nitroalkanes to cyclopentanone and cyclohexanone. In 2004, they reported that, in the presence of amine additive **188**, the proline tripeptide **192** catalyzes the addition of 2-nitropropane to cyclohexenone in $CHCl_3$ in 77% ee and 80% yield.[136] Slightly higher ee was obtained in acetone, but the yield was somewhat lower. Similar results were obtained with four other cyclic and acyclic nitroalkanes. In the same year, Tsogoeva and Jagtap introduced two histidine-based dipeptides **195** and **196** as catalysts for the transformation.[137] These catalysts exhibited only moderate stereoselectivities (up to 60% ee) in cooperation with several chiral and achiral amine additives. In addition, proline-derived dipeptide **193** and tetrapeptide **194** were studied as catalysts.[138] However, neither of these catalysts could match the results obtained with the earlier reported proline tripeptide **192**. Nevertheless, both catalysts promoted additions of seven acyclic and cyclic nitroalkanes to cyclohexenone and cyclopentenone in good-to-excellent yields and up to 88% ee's.

In 2006, Hanessian and co-workers introduced a new catalyst, 4,5-methano-L-proline **198**. In the presence of the amine additive **188**, the catalyst promoted the reaction of cyclopentenone and cyclohexenone with nitroalkenes.[139] The reaction times were significantly longer than those with proline catalysts, but the enantioselectivities and yields were clearly superior (Table 7, entry 6). Reactions with prochiral nitroalkanes produced only exiguous diastereoselectivity, slightly favoring the syn diastereomer. However, enantioselectivities of the minor anti diastereomers were consistently higher than those of the syn diastereomers.

Table 7. Results Obtained with Different Catalysts in Conjugate Additions of Nitroalkanes



	Group	Catalyst	Acceptor	Nucleophile	No of examples	Yield *ee*
1	Yamaguchi[127,128]	 **34**			13	47-91 29-68% ee
2	Hanessian[129] 2000	 **35**			15	30-88% 62-93% *ee*
3	Jorgensen[130] 2002	 **36**			19	52-100% 34-99% *ee*
4	Jorgensen[131] 2005	 **197**			11	48-93% 71-92% *ee*
5	Ley 2005[111] 2006[132]	 **37**			10	47-84% 94-98% *ee*
					32	21-97% 0-91% *ee*
6	Hanessian[39] 2006	 **198**			10	50-94% 60-91% *ee*

As a summary of the developments in the additions of nitroalkanes to enones, the results obtained with several

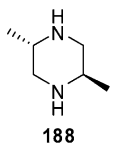
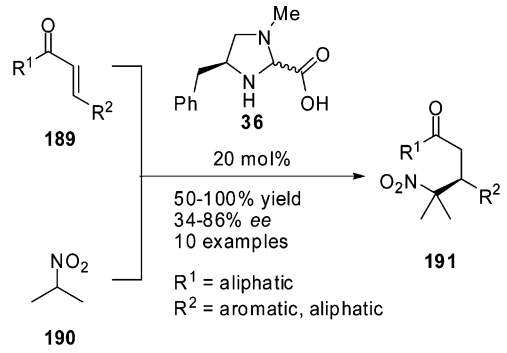

188

Figure 8. Amine additive *trans*-2,5-dimethylpiperazine.

different catalysts as well as their representative scopes have been collected in Table 7. Arvidsson and co-workers developed a histidine-based variant **201** of the imidazolidine catalyst **110** for the conjugate addition of nitroalkanes **200** to enals **199**.[140] Prior to this, only the groups of Yamaguchi and Ley had reported few examples of reaction with enals. Catalyst **201** promoted the addition of nitroethane to cinnamaldehyde in 93% conversion, 1:1 anti/syn selectivity, and 82% ee for both diastereomers. Additions with symmetric

Scheme 35. Asymmetric Conjugate Addition of Nitroalkanes[133]



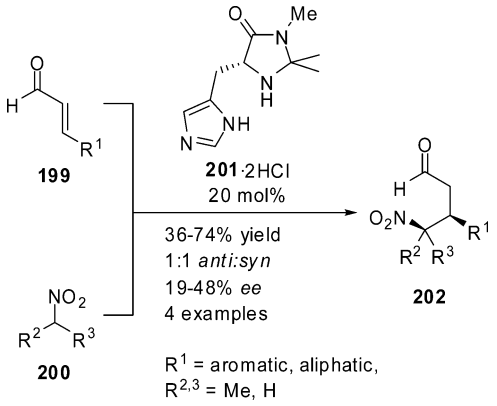
nitroalkanes, such as nitromethane and 2-nitropropane, afforded the corresponding products **202** in only moderate yields and selectivities, as illustrated in Scheme 36. Reactions were performed in the presence of 4-fold excess of nitroalkane under neat conditions. With electron-withdrawing substitutients on the phenyl ring of the substrate, a substantial amount of 1,2-addition was observed. In the case of α-methylcinnamaldehyde, only the product resulting from 1,2-addition was detected.

4.2.3. Aromatic Compounds

In contrast with the additions of malonates and nitroalkanes, the studies on conjugate additions of aromatic carbon nucleophiles have focused on additions to enals. Soon after introducing the chiral imidazolidinone **29** as a powerful Diels−Alder catalyst,[44] MacMillan and co-workers demonstrated that the same catalyst also is active in the Friedel−Crafts alkylation of pyrroles.[141] The reaction of *N*-methylpyrrole with several *β*-substituted enals **203** afforded the corresponding Friedel−Crafts adducts **205** in good yields and enantioseletivities (72−90% yield, 87−93% ee) in all cases (Scheme 37). The pyrrole core **204** was shown to tolerate substitution at the 2- and 3- positions as well as different *N*-protecting groups without a change of activity.

The same methodology was successfully used by Hedenström and co-workers in the conjugate addition of *N*-methylpyrrole to a cyclic α,*β*-disubstituted aldehyde 1-formylcyclopentene **206** (Scheme 38).[142] Although MacMillan and co-workers's catalyst **29** gave moderate diastereoselectivity (27:73) in the reaction, the product was more or less racemic. A successful reaction required the introduction of diamine catalyst **127**, which Karlsson and Högberg had earlier used in the [3+2]-addition of the pentacyclic enals **125** (see section 3.2, Scheme 20).[105,106] The acid cocatalyst had a strong influence on both the diastereo- and enantioselectivity of the reaction. Adding two equivalents of the strong acid HI to the free amine **127** afforded the best selectivity of 97:3 trans/cis and 62% ee, with a 55% yield after $NaBH_4$ reduction.

Scheme 36. Asymmetric Conjugate Addition of Nitroalkanes to Enals[140]



In 2006, Ying and co-workers reported studies on the catalyst **29** immobilized on the siliceous mesocellular foam (MCF) as well as on polymer-coated MCF to form catalyst **210**.[79] The yields obtained in the Friedel−Crafts reactions with the immobilized catalyst **210** were similar to those obtained with the corresponding unsupported catalyst **29** (Scheme 39). Depending on the nature of the surface, the stereoselectivities varied because of strong interactions between the silica surface and the catalyst. Alteration of the position of the linker group was shown to enhance enantioselectivity when the position was changed from the phenyl group to the amide group in the case of unsupported catalysts; however, with the polymer-supported catalysts, the selectivity dropped. The best recyclabilities were observed with the polymer-coated catalysts. The catalyst has also been applied to Diels−Alder reactions (discussed in section 3.1.1).

Banwell and co-workers used the imidazolidine catalyst **29** in intramolecular Michael addition of pyrroles in 2004. Instead of the usual enal substrate, they employed unsaturated acetals that readily liberated the iminium, forming aldehyde in situ. Six- and seven-membered rings were formed in good yields (75−83%) and high enantioselectivities (87−96% ee) with this method, although the five-membered ring failed to form.[143] Later in 2006, they utilized a related intramolecular pyrrole addition in the total synthesis of some alkaloid natural products including (−)-rhazinilam (Scheme 40).[144] When substrate **211** was subjected to catalyst **29**, it cyclized to form the bicyclic aldehyde **212** in 81% yield. After the setting up of the core structure, all of the desired natural products **213**−**216** could be obtained after a series of subsequent reactions.

In light of the promising results obtained with the pyrrole addition, MacMillan and co-workers explored the applicability of the methodology to the Friedel−Crafts alkylation of the significantly less activated indole framework.[88] Catalyst **29** exhibited poor rates and enantioselectivities in the reaction between crotonaldehyde and *N*-methylindole. However, with a new *tert*-butyl-substituted variant **33** of the imidazolidinone

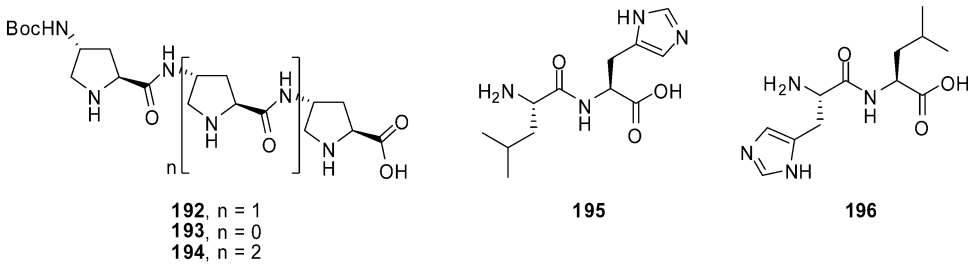
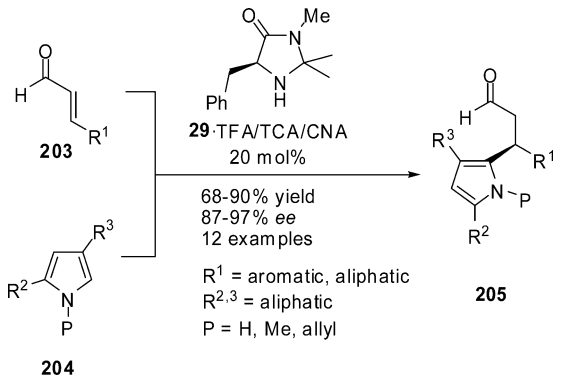
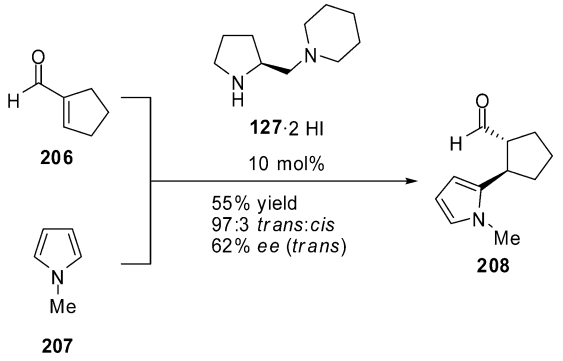


Figure 9. Peptide catalysts for conjugate additions of nitroalkanes to enones.[136−138]

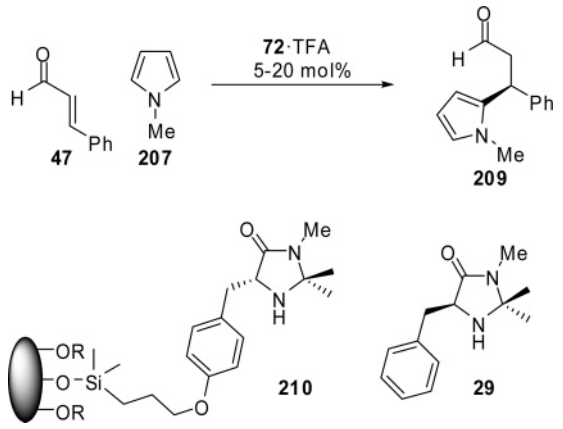
Scheme 37. Asymmetric Friedel−Crafts Alkylation of Pyrroles[141]



Scheme 38. Enantioselective Conjugate Addition of Pyrrole to a Cyclic Enal[142]



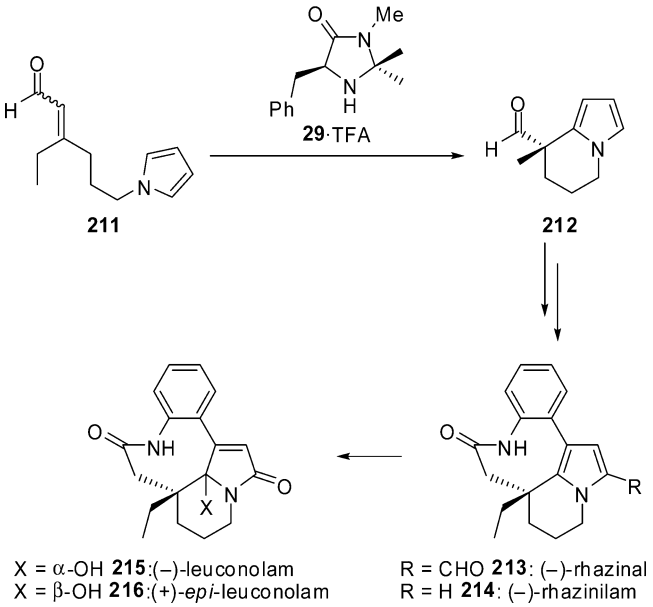
Scheme 39. Heterogenenous Catalyst for Conjugate Addition of Pyrroles to Enals[79]



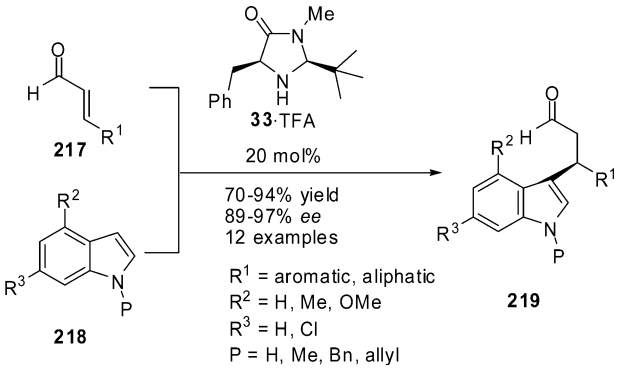
catalyst, the desired reaction could be conducted with high yield and excellent enantiocontrol (Scheme 41). The acid cocatalyst was shown to significantly affect the rate of the reaction. By far the fastest reaction times were observed with the TFA salt of the catalyst. The reaction performed equally well with both electron-deficient aliphatic enals and cinnamaldehyde. Variation of the indole substitution was also tolerated. MacMillan and co-workers capitalized their indole alkylation strategy in the total synthesis of flustramine B **406** (see section 6.1.2, Scheme 91),[145] where the conjugate addition of 3-alkylamino-substituted indole was followed by an immediate domino cyclization to establish the flustramine ring structure. This reaction will be discussed in more detail in the domino section of this review.

Houk and co-workers explained MacMillan and co-workers' observations of different activities of catalysts **29** and **33** with theoretical calculations on B3LYP/6-31G(d)

Scheme 40. Asymmetric Syntheses of (−)-Rhazinilam and Related Alkaloids[144]



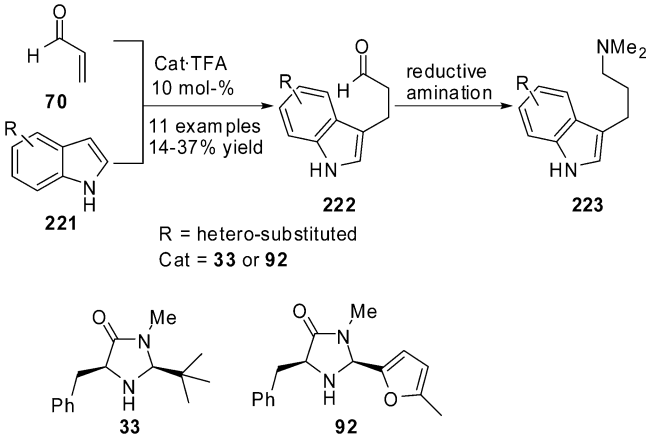
Scheme 41. Asymmetric Alkylation of Indoles[88]



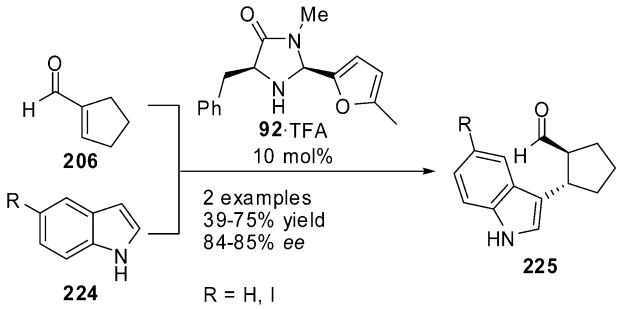
level based on transition-state conformers of the Friedel−Crafts addition to pyrrole.[146] In the case of catalyst **29**, the dimethyl substituents on the catalyst framework led to displacement of the benzyl side chain for the reactive site due to stabilizing C−H interaction between one of the methyl substituents and the phenyl ring of the benzyl group. In the case of Friedel−Crafts reactions, this leads to impaired facial selectivity. However, in Diels−Alder reactions, good selectivities were obtained even with catalyst **29**,[44] even though **33** was found to be more selective in intramolecular reactions.[94,95] In the case of catalyst **33**, the bulky *tert*-butyl substituent restricts the motion of the benzyl side chain, and thus, increased enantioselectivity is observed.

King and Denhart with their co-workers at BMS extended the choice of the enal partner in the indole alkylation to unsubstituted acrolein **70**[147] (Scheme 42) and to the cyclic enal 1-formylcyclopentene **206**[148] (Scheme 43). The reactions between acrolein and several substituted indoles **221**, followed by in situ reductive amination, provided homotryptamines **223** in rather low yields when catalyzed by either *tert*-butyl- or methylfurylimidazolidinone catalysts **33** and **92**. The methylfuryl catalyst **92** was found to be successful in the addition of indole or 5-iodoindole to the cyclic enal, whereas **33** failed to catalyze the reaction. The product **225** (R = I) could be prepared in a 21 g quantity. This is an interesting example of the use of secondary amine catalysts

Scheme 42. Synthesis of Homotryptamines from Acrolein and Various Indoles[147]



Scheme 43. Enantioselective Indole Additions to a Cyclic Enal[148]



with α-substituted enals. Typically, α-substituted enals display low reactivity with secondary amines.

In 2006, Bonini and co-workers utilized aziridine carbinol catalysts such as **88** (Figure 10) in the alkylation of *N*-methylpyrrole and *N*-methylindole with crotonaldehyde and cinnamaldehyde as well as in the Diels−Alder reaction of these aldehydes with cyclopentadiene.[90] Previously, this type of rigid iminium catalyst has been tested in the formal aza-[3+3]-cycloaddition.[149] Preformed TFA salts of the catalysts promoted the Friedel−Crafts alkylations in moderate yields and up to 75% ee.

Xiao and co-workers showed that some aliphatic β-substituted enones as well as an aromatic enone **226**, when reacted with indole **227**, afford the corresponding racemic Friedel−Crafts adducts **228**. They used a catalytic amount of the $HClO_4$ salt of pyrrolidine **63** (Scheme 44).[150] With aliphatic enones, the reaction times were usually between 10 and 15 h and the yields were uniformly good (83−92%). Reaction times were significantly longer with the aromatic enones, especially when *N*-methylindole was used as the nucleophile. Also the yields were slightly compromised. Utilizing the imidazolidinone catalyst **92**, Xiao and co-workers were able to reach very modest enantiocontrol (28% ee) over the reaction between indole and an acyclic aliphatic enone **226** (R^1 = *i*-Pr).

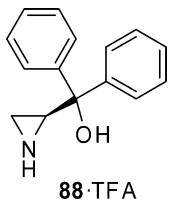
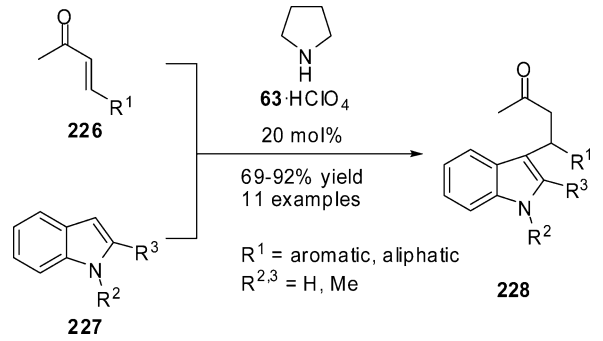
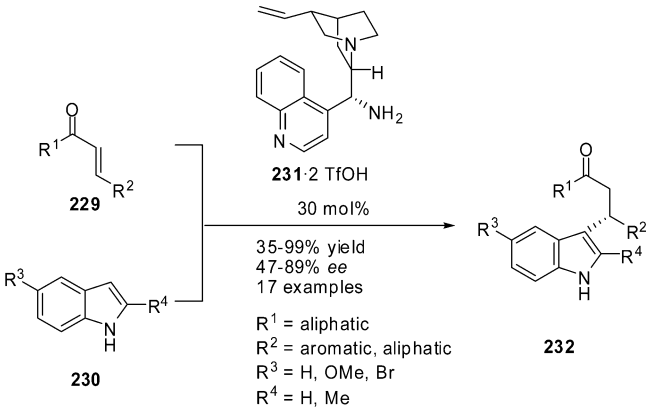


Figure 10. Aziridine carbinol catalyst used by Bonini and co-workers.[90]

Scheme 44. Pyrrolidine-Catalyzed Conjugate Addition of Indoles to Enones[150]



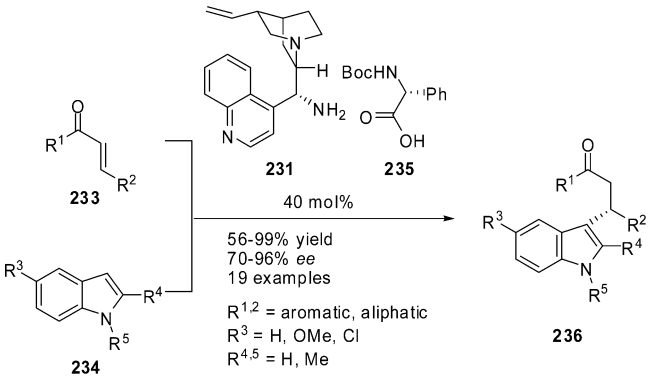
Scheme 45. Asymmetric Conjugate Addition of Indoles to Enones[151]



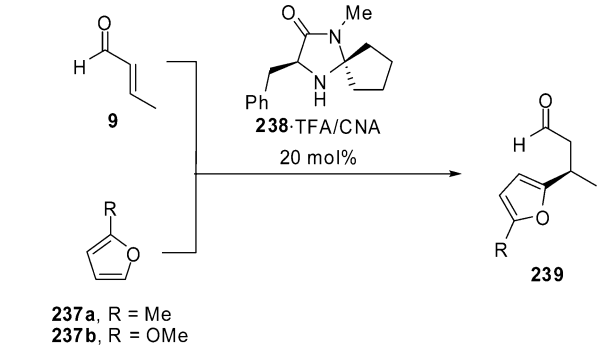
A major breakthrough in asymmetric conjugate addition of indole to enones was achieved by Chen and co-workers in 2007.[151] They postulated that formation of the iminium ion between an enone and a secondary amine would be unfavored because of steric hindrance. Thus, a number of primary amines were tested in the reaction between indole and an enone. 9-Amino-9-deoxy-*epi*-cinchonine **231** CF_3SO_3H salt was identified as the most active iminium catalyst for these types of reactions. The catalyst promoted reactions between indoles **230** and both aromatic and aliphatic enones **229** in varying yields and moderate-to-good enantioselectivities (Scheme 45). The reactions typically took 2−6 days to complete in subambient temperatures (0−20 °C). While the increment of the size of the R^1 group from methyl to ethyl or butyl retarded the reaction rate, it had a beneficial effect on the enantioselectivity, causing it to rise from 65% ee to 81% ee in the cases of indole addition to 4-phenylbuten-2-one and 5-phenylpenten-3-one, respectively.

Soon after the report from Chen and co-workers, a similar catalyst system was proposed by Melchiorre and co-workers.[152] They described that 9-amino-9-deoxy-*epi*-hydroquinine **231** coupled with chiral acid cocatalysts facilitates the addition of indole **234** to aromatic and aliphatic enones **233**. Similar counterion-directed catalysis had earlier been disclosed by List and co-workers for the transfer hydrogenation of enones.[54] *N*-Bocphenylglycine cocatalyst **235** exhibited the most beneficial effect in achieving high stereoselectivities (Scheme 46). With the new catalyst, Melchiorre could reduce the catalyst loadings while the reaction times remained comparable to Chen and co-workers' conditions. However, the yields and enantioselectivities were substantially better and more uniform.

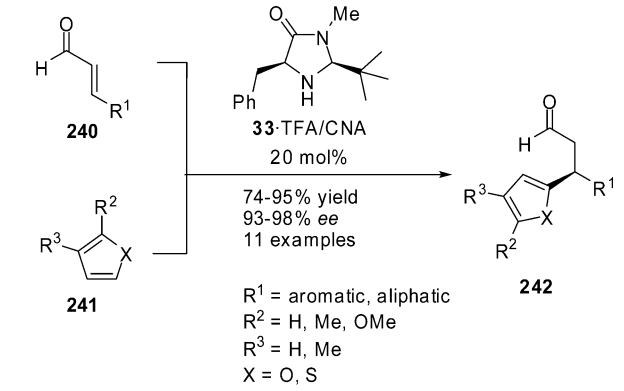
Scheme 46. Asymmetric Conjugate Addition of Indoles to Enones Utilizing an Amino Acid Cocatalyst[152]



Scheme 47. Asymmetric Conjugate Addition of Furans to Enals[153]



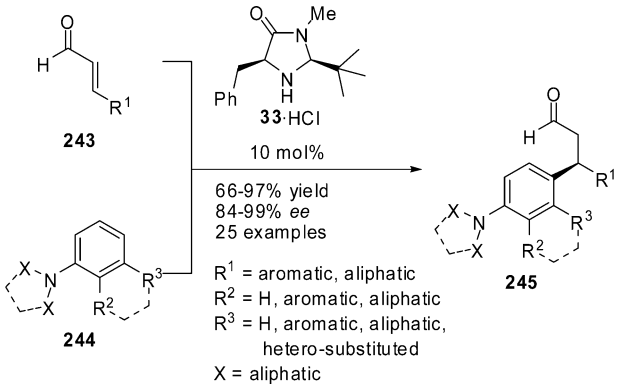
Scheme 48. Asymmetric Conjugate Addition of Thiophenes and Furanes[153]



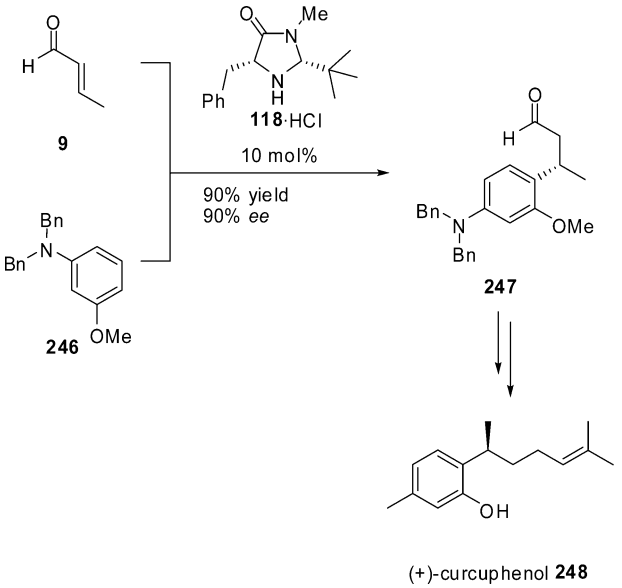
MacMillan and Brown have also reported the conjugate addition of furans **237a** and **237b** to crotonaldehyde with catalyst **238** (Scheme 47).[153] They also expanded the methodology to include thiophenes as nucleophiles. The use of **33** as the catalyst yielded several Michael adducts in high yields and enantioselectivities (Scheme 48). Additionally, the methodology was exploited in the domino reaction sequence, which will be discussed in section 6.1.3.[154]

Paras and MacMillan have extended the iminium-catalyzed Friedel−Crafts reactions to substrate systems with other electron-rich aromatic frameworks.[155] The catalyst **33** was used to promote the conjugate addition of electron-rich benzenes to linear aromatic and aliphatic enals. Dimethylanisidine **244** and *N*-phenylpyrrolidine **244** were transformed to the corresponding F−C adducts **245** in good yields (68−90%) and selectivities (87−92% ee) regardless of the nature of the enal **243** (Scheme 49). A more diverse set of *N*-diprotected substituted anilines were added to aldehyde

Scheme 49. Asymmetric Conjugate Addition of Electron-Rich Benzenes to Enals[155]



Scheme 50. Iminium-Catalyzed Asymmetric Synthesis of (+)-Curcuphenol[156]



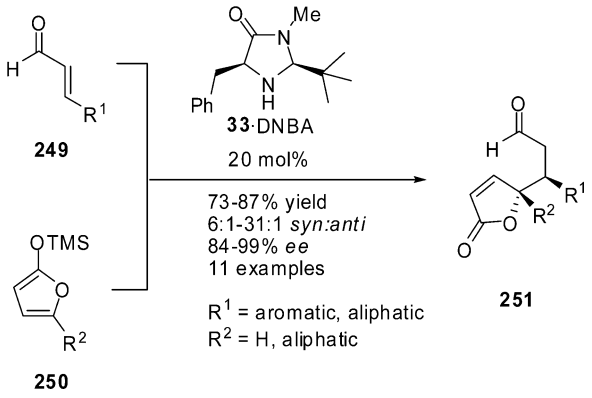
243 (R^1 = CO_2Me). Also in these cases, the yields and enantioselectivities were generally excellent when the reactions were conducted at −10 or −20 °C, although the reactions took up to 80 h to complete. However, at room temperature, the reaction rates were considerably higher and the selectivities were only slightly decreased.

In 2005, the iminium-catalyzed Friedel−Crafts reaction between crotonaldehyde **9** and dibenzyl-*o*-anisidine **246** was used in the total synthesis of (+)-curcuphenol **248** by Kim and co-workers as illustrated in Scheme 50.[156] The catalyst **118** established the required stereogenic center in their target molecule in 90% ee. The product was then reduced to the corresponding alcohol and deprotected. After following transformations including Sandmeyer-type bromination and a Negishi-type coupling as key steps, they were able to isolate the desired natural product in 22% overall yield.

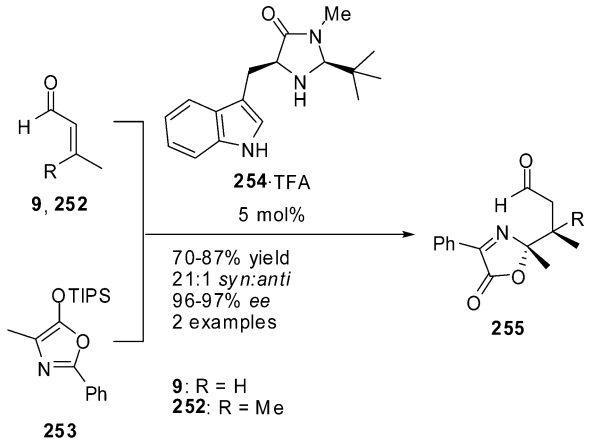
4.2.4. Silyl Enol Ethers

MacMillan and co-workers reported in 2003 that 5-silyloxyfurans **250** could be used as nucleophiles in Mukaiyama−Michael-type reactions to afford products with the butenolide architecture **251**.[157] The 2,4-dinitrobenzoic acid (DNBA) salt of catalyst **33** promoted reactions with aliphatic β-substituted enals and cinnamaldehyde in up to 99% ee at subambient

Scheme 51. Enantioselective Mukaiyama−Michael Reaction of Silyloxyfurans[157]



Scheme 52. Enanatioselective Mukaiyama−Michael Reaction of Silyloxyoxazoles[153]



temperatures (−20 to −70 °C) with good yields (Scheme 51). Alteration of the siloxyfuran substitution pattern was tolerated without change of selectivity or efficiency of the reaction. Also, siloxyoxazoles **253** could be utilized in the Mukaiyama−Michael reactions, as illustrated in Scheme 52.[153] These reactions are promoted by tryptophane-derived catalyst **254** in good yields and high enantioselectivities. This reaction has also been used in context of domino reaction sequences (section 6.2).[154]

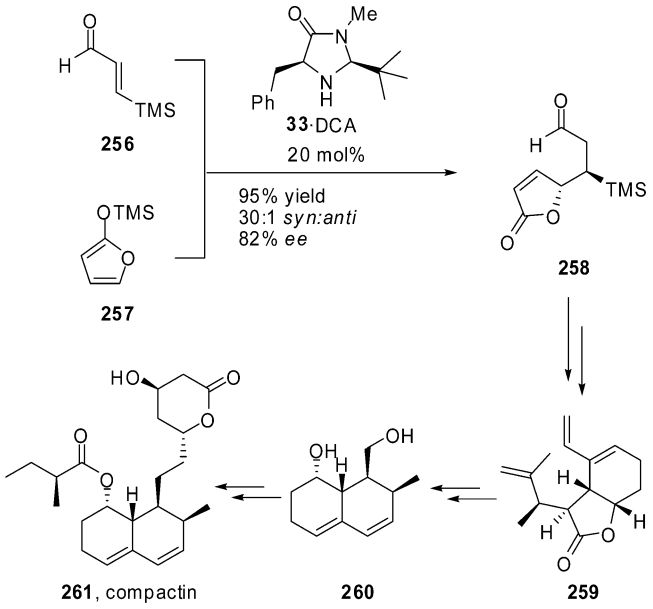
Robichaud and Tremblay utilized this methodology to develop a short, stereoselective synthesis of compactin **261** (Scheme 53).[158] The key step consists of an iminium-catalyzed Mukaiyama−Michael reaction of furan **257** to enal **256** to provide the α,β-unsaturated lactone **258** with 82% ee and 31:1 syn/anti selectivity. This adduct was then readily converted to the core ring system of compactin **260** via diastereoselective cyclization, conjugate addition, and a final ring-closing metathesis.

In 2005, Wang and co-workers also reported that silyl enol ethers **263** could also be used as nucleophiles in Mukaiyama−Michael-type reactions.[159] Several aromatic TMS enol ethers **263** were added to crotonaldehyde as well as to cinnamaldehyde and its derivatives **262** in moderate yields and high enantioselectivities (Scheme 54).

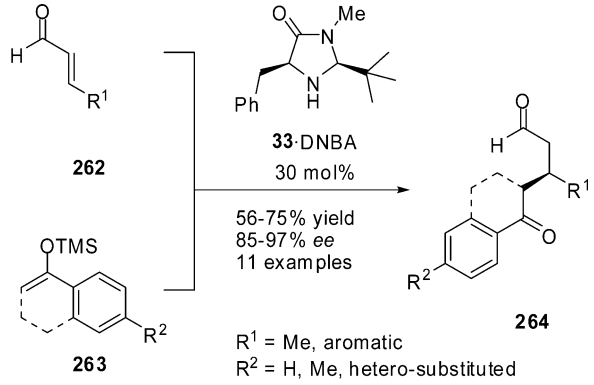
4.2.5. Other Nucleophiles

A vinylogous Michael addition was published by the groups of Chen and Deng in 2006.[160] Dicyanoolefins **266** add to aromatic and aliphatic β-substituted enals **265** in the

Scheme 53. Iminium-Catalyzed Asymmetric Synthesis of Compactin[158]



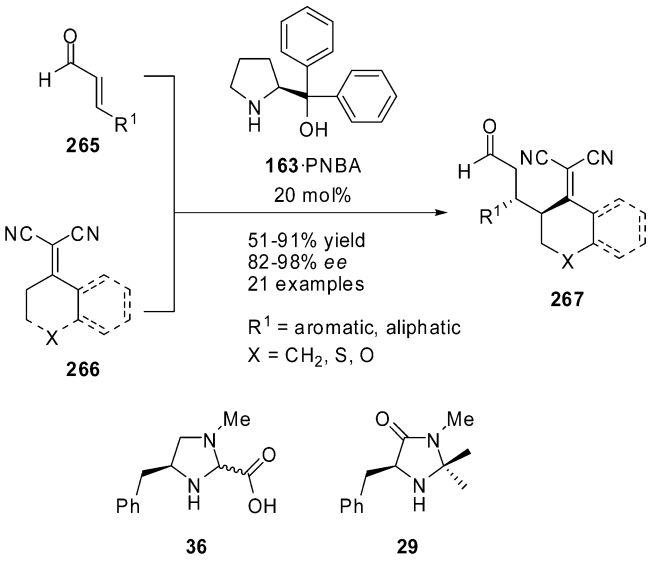
Scheme 54. Enantioselective Mukaiyama−Michael Reaction of Enals and Silyl Enol Ethers[159]



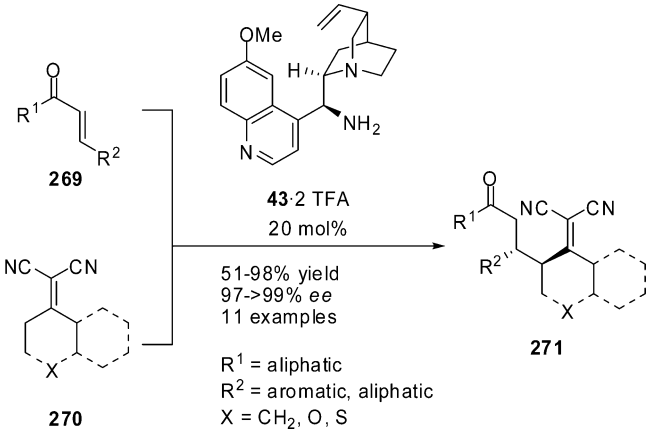
presence of a catalytic amount of the *para*-nitrobenzoic acid (PNBA) salt of **163**. Interestingly, catalyst **29** failed to promote this reaction, whereas catalyst **36** provided very fast reaction rates but led to racemic product. In general, **163** catalyzed the reactions with aromatic olefins in good yields and excellent enantioselectivities with only one detectable diastereomer (Scheme 55). Steric hindrance in aliphatic enals as well as substitution in the aromatic enals decreased their reactivity without affecting the enantioselectivity. Aliphatic olefins reacted with crotonaldehyde in slightly diminished yields and selectivities (49−57%, 68−82% ee). No catalytic activity of **163** was observed in additions to enones.

Later, in 2007, the Chen and Deng groups applied the quinine-derived catalyst **43** for the conjugate addition of dicyanoolefins to enones.[122] The catalyst had earlier been tested in the Friedel−Crafts reaction of indoles with enones, where it had performance inferior to catalyst **231** and had thus been discarded.[151] The reactions were performed in tetrahydrofuran (THF) at 0 °C with amine TFA salt **43** and afforded the vinylogous Michael products **271** in good yields and high enantioselectivities (Scheme 56). Two equivalents of the acid cocatalysts per free amine were required for the optimal performance of the catalyst. Not unlike the enone substrates, in this case, the products were also obtained as

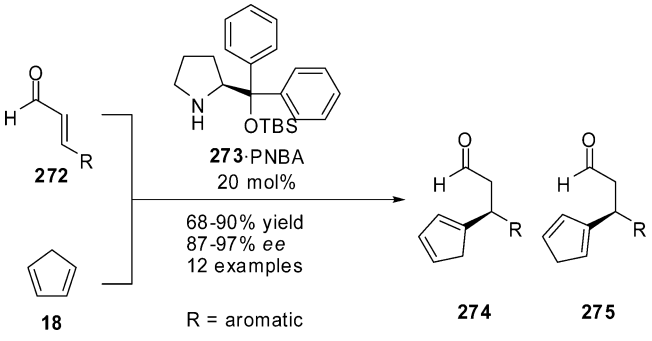
Scheme 55. Enantioselective Vinylogous Michael Addition of Dicyanoolefins[160]



Scheme 56. Asymmetric Conjugate Addition of Dicyanoolefins to Enones[122]



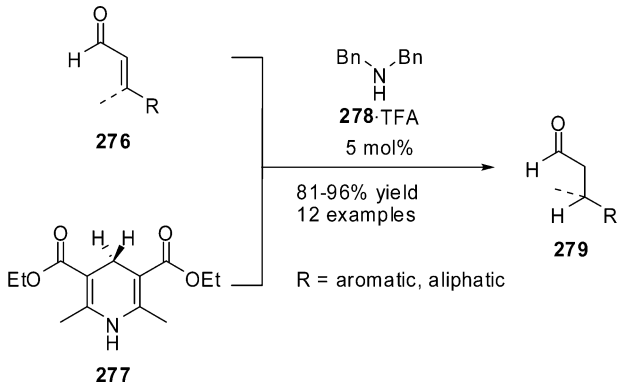
Scheme 57. Asymmetric Ene Conjugate Addition[161]



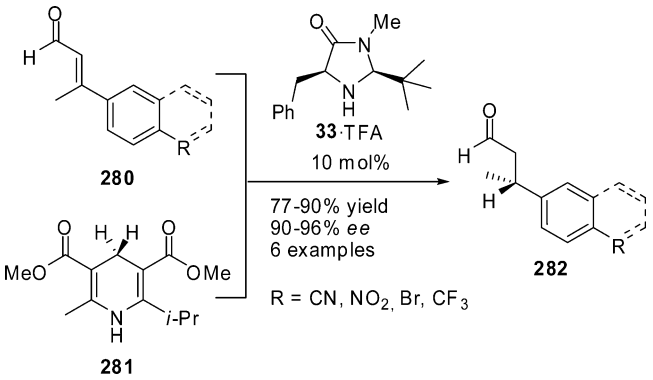
single diastereomers. This reaction was also applied to domino reactions. These are discussed in section 6.1.3.

An iminium-catalyzed ene reaction has been recently reported by Hayashi and co-workers.[161] They found that silylprolinol ethers promote the ene conjugate addition of cyclopentadiene to cinnamaldehyde instead of the expected Diels−Alder reaction. Thus, several aromatic β-substituted enals **272** were transformed to the corresponding Michael adducts **274** and **275** in high yields and enantioselectivities (Scheme 57). However, the products were always obtained as mixtures of two regioisomers **274** and **275**.

Scheme 58. Iminium-Catalyzed Transfer Hydrogenation of Enals[162]



Scheme 59. Asymmetric Transfer Hydrogenation of Enals[163]



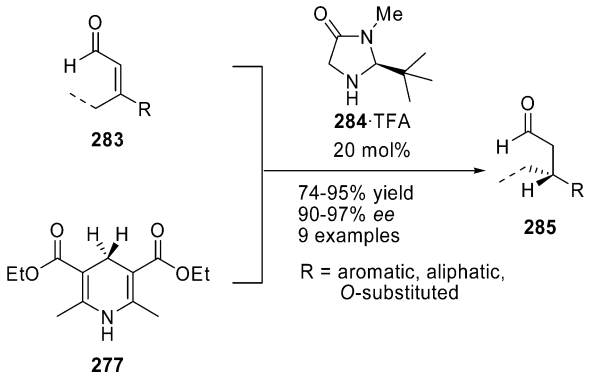
4.3. *H*-Nucleophiles

In 2004, List and co-workers reported a novel strategy to the transfer hydrogenation of enals.[162] They found that several secondary ammonium salts catalyze conjugate addition of a hydride to *o*-nitrocinnamaldehyde. The hydride was delivered by a commercially available Hantzsch ester **277**, mimicking the reductive cofactor NADH found in enzymatic processes. After identifying dibenzylammonium trifuoroacetate **278** as the most active iminium catalyst for this reaction type, they were able to reduce number of aromatic and aliphatic β-substituted enals in uniformly high yields (81−96% yield), as illustrated in Scheme 58.

Shortly after this, the same group demonstrated that the transfer hydrogenation of enals could also be facilitated in enantioselective fashion.[163] They employed an imidazolidinone trifluoroacetate salt **33** as a chiral catalyst for the addition of hydride, delivered now by the modified Hantzsch ester **281**, to β-disubstituted aromatic enals **282** under mild conditions to produce the corresponding saturated aldehydes (Scheme 59). The authors found the reaction to be enantioconvergent: the geometry of the double bond had no influence in the stereochemical outcome of the reaction. Both the *Z*- and *E*-isomers of the starting material delivered the same enantiomer of the product.

At the same time, a similar reduction protocol was independently reported by MacMillan and co-workers.[164] They found that the benzylic side chain of the imidazolidinone catalyst was not necessary for good stereocontrol in the reaction and, thus, presented a new alternative catalyst **284**. Treatment of a diverse set of β-disubstituted aliphatic and aromatic enals **283** with catalyst **284** and Hantzsch ester **277** in chloroform at −20 °C produced the corresponding saturated aldehydes in high ee's and yields (Scheme 60).

Scheme 60. Asymmetric Transfer Hydrogenation of Enals[164]



The hydride could be delivered even to an enal with a bulky R *tert*-butyl group without a loss of enantiocontrol (97% ee), and the reactions could be performed at room temperature. The starting enals could consist of a mixture of *E*- and *Z*-isomers since the catalyst rapidly isomerized the resulting iminium salts, resulting in similar enantioconvergence that was also reported by List and co-workers.

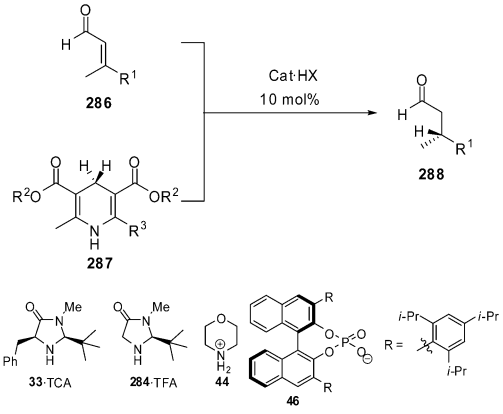
A conceptually new iminium catalyst was introduced when Mayer and List utilized a chiral phosphate salt (TRIP, **46**) of morpholine **44** as a catalyst in the transfer hydrogenation reaction of enals.[53] The *counterion* of the iminium ion was the source of all asymmetric induction. The catalyst transferred a number of aromatic β-disubstituted enals **286** as well as citral and farnesal to the corresponding saturated aldehydes **288** in moderate-to-good yields (63−90%) and high enantioselectivities (96−99% ee). In comparison, the imidazolidinone-type iminium catalysts have only produced modest enantioselectivites in conjugate reductions of sterically unhindered aliphatic substrates (Table 8). A drawback of this new catalyst was the long reaction time, even when the reactions were performed at slightly elevated reaction temperatures.

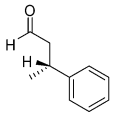
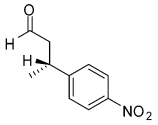
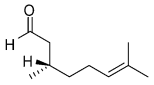
Following the studies of List and co-workers and MacMillan and co-workers, Zhao and Córdova utilized the Jørgensen diphenyl prolinol catalyst **38** in a similar transformation in the context of reductive Mannich-type condensations.[165] This reaction will be discussed in section 6.2. Additionally, Christmann and co-workers have disclosed a Wittig olefination−transfer hydrogenation sequence for the synthesis of lepidopteran sex pheromones.[96] They applied List and co-workers' achiral dibenzylamine catalyst **278** as a TfOH salt for the iminium-mediated reduction step.

Recent independent reports from the groups of MacMillan and List added enones to the substrate scope of the hydrogenation reaction. MacMillan and co-workers' approach[166] relies on a variant of their imidazolidinone catalyst **92**, which previously had been shown to catalyze Diels−Alder reactions of enones.[93] The imidazolidinone trichloroacetate **92** readily catalyzed the conjugate reduction of a variety of cyclic β-substituted enones **289** in good yields and enantioselectivities (Scheme 61).

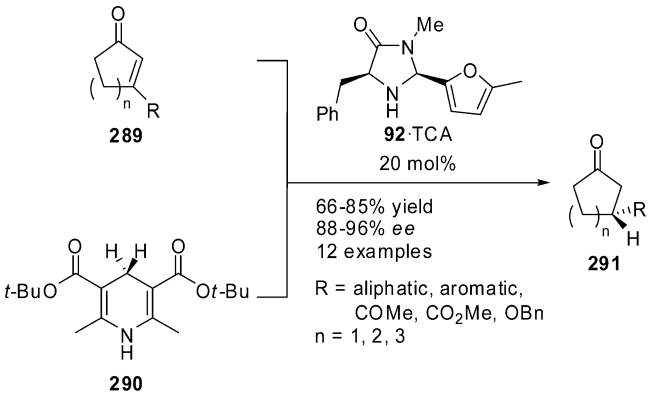
List and co-workers showed that the reduction of enones can also be conducted in the presence of a catalytic amount of L-valine *t*-butyl ester **45** with the help of a chiral counteranion (*R*)-TRIP **46**.[54] The optimized conditions were effective for both cyclic and acyclic β-substituted enones (Scheme 62). High enantioselectivities and yields were observed with all presented substrates, although in the case of cyclopentenones, the yields are slightly diminished (68−78%).

Table 8. Comparison of Catalysts for Transfer Hydrogenation of Enals[53,163,164]



Entry	Product	Catalyst	Yield	% *ee*
1		**33**·TCA	77%	90
		284·TFA	79%	93
		44 TRIP	n.d.	n.d.
2		**33**·TCA	83%	94
		284·TFA	n.d.	n.d.
		44 TRIP	90%	98
3		**33**·TCA	58%	40
		284·TFA	82%	40
		44 TRIP	71%	90

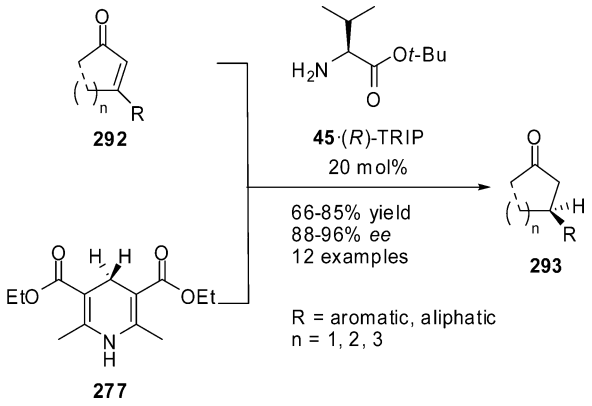
Scheme 61. Asymmetric Transfer Hydrogenation of Enones[166]



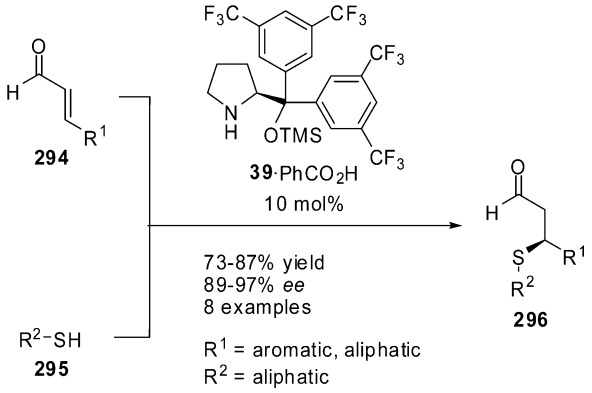
4.4. *S*-Nucleophiles

In 2005, an iminium-catalyzed thio-Michael addition was reported by Jørgensen and co-workers in the context of domino reaction sequences.[167] Aliphatic and aromatic β-substituted enals **294** gave the corresponding Michael adducts **296** when reacted with *tert*-butyl and benzyl mercaptan **295** (Scheme 63). After a $NaBH_4$ reduction, the corresponding

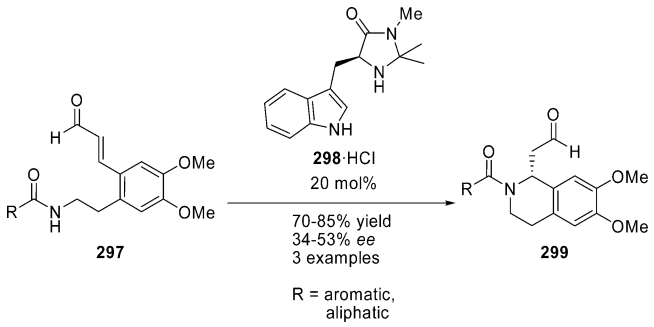
Scheme 62. Asymmetric Transfer Hydrogenation of Enones Using the Chiral Acid Cocatalyst Trip[54]



Scheme 63. Asymmetric Conjugate Addition of Thiols[167]



Scheme 64. Intramolecular Asymmetric Aza−Michael Reaction[172]



alcohols were obtained with good yields and excellent enantioselectivities (89−97% ee).

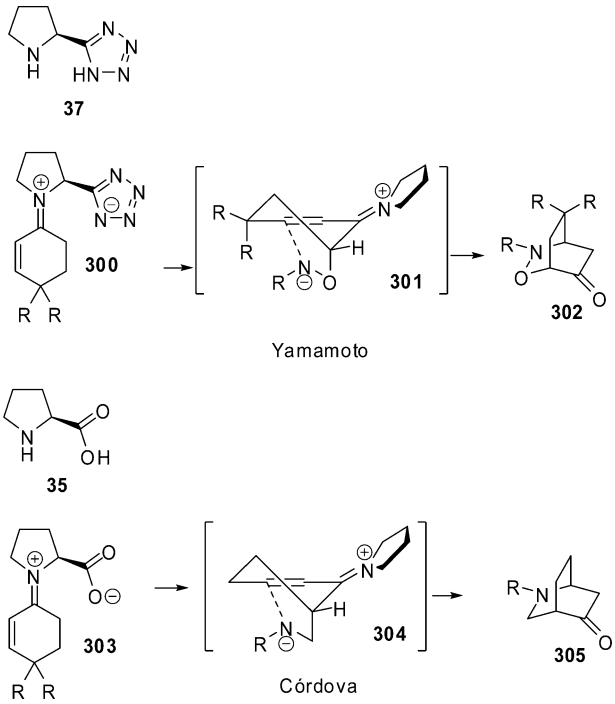
Later, more examples of thiol additions to enals[168,169] and enones[170] were reported in the context of domino reactions. These reactions will be discussed in detail in section 6.1.3.

4.5. *N*-Nucleophiles

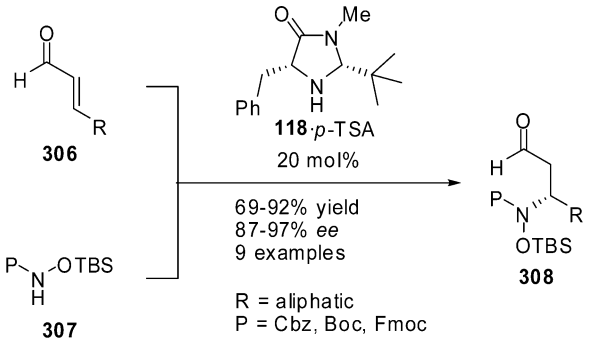
An intramolecular conjugate addition of nitrogen nucleophiles to enals via iminium ion intermediate was first published by Takasu and co-workers.[172] They applied the modified first-generation oxazolidinone catalyst **298** to the ring-closure of dopamine derivates **297**. The reactions proceeded very slowly and took up to 10 days to complete. The cyclized products **299** could then be isolated as acetals in high yields but modest enantioselectivities (Scheme 64).

In 2004, Yamamoto and co-workers investigated intramolecular additions to enones in the context of enamine−iminium reaction cascades.[173] Following a proline−tetrazole catalyzed *O*-nitrosoaldol reaction of a cyclic enone with nitrosobenzene, the resulting aminooxy anion cyclized to generate bicyclic products **302** in high (up to 99%) ee's. In the following year, Córdova and co-workers demonstrated that an analogous intramolecular conjugate addition can be facilitated after a proline-catalyzed Mannich reaction (Scheme 65).[174] Since these reactions are essentially domino reactions, they are discussed in detail in section 6.1.4.

Scheme 65. Transition States of Two Intramolecular Aza−Michael Reactions[173,174]



Scheme 66. Asymmetric Aza−Michael Reaction of Enals[175]

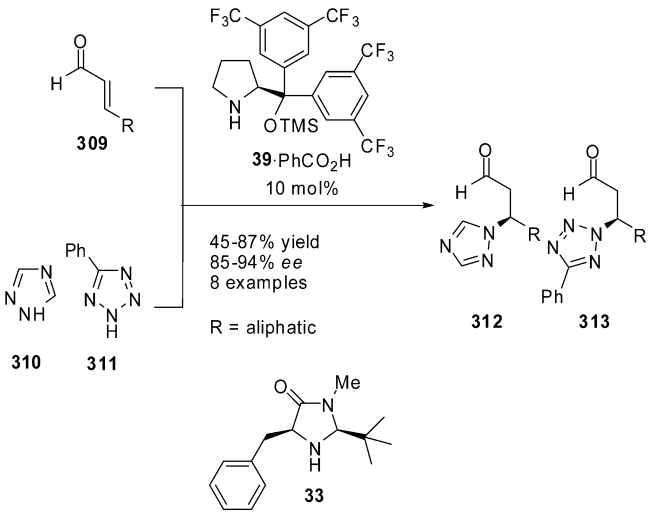


In 2006, MacMillan and co-workers demonstrated that the direct enantioselective conjugate addition of nitrogen is possible with *N*-silyloxy carbamate nucleophiles **307** (Scheme 66).[175] The best selectivities were obtained in $CHCl_3$ at −20 °C. The PTSA salt of their previously reported catalyst **118** promoted the reaction in uniformly high yields and enantioselectivities.

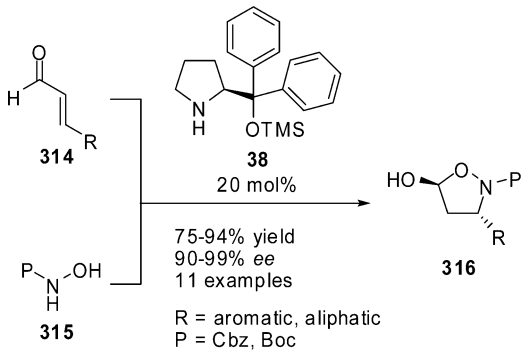
This concept was also utilized by Córdova and co-workers who described diphenylprolinol silyl ethers **38** as potential catalysts in the amine conjugate addition reaction.[176] Somewhat lower yields were obtained, while the enantioselectivities remained good.

In early 2007, Jørgensen and co-workers reported the addition of *N*-heterocyclic nucleophiles to aliphatic enals

Scheme 67. Asymmetric Conjugate Addition of Triazoles and Tetrazoles to Enals[177,178]



Scheme 68. Chiral Isoxazolidines by a Domino Reaction[179]

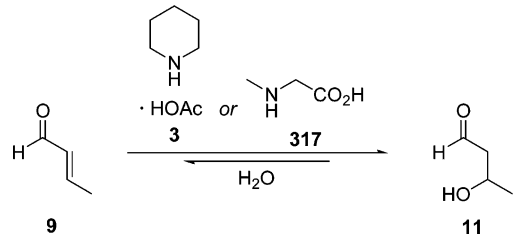


309.[177] Catalyst **39** in cooperation with a benzoic acid cocatalyst promoted the additions of triazole **310** and tetrazole **311** in good yields and high enantioselectivities (Scheme 67). The reaction rates were considerably slower and the yields were slightly lower in the case of tetrazole additions. These products were isolated after reduction with $NaBH_4$. Only aliphatic β-substituted enals could be used as acceptors; the reaction of triazole with cinnamaldehyde gave only low conversions (<20%). On the basis of B3LYP/6-311G(d,p) DFT calculations, they suggested that the reaction proceeds via an *E*-configured iminium species that is attacked by the *N*-heterocycle from the unshielded *re* face, while the phenyl rings of the side chain block the approach for the *si* face.

A similar reaction was later reported by Vicario and co-workers.[178] Unlike Jørgensen's group, they utilized the imidazolidinone catalyst **33** in additions of tetrazole **311** to aliphatic enals. After subsequent reduction with $NaBH_4$, the products were isolated in good yields and enantioselectivities (67−97% yield, 76−99% ee).

Cordóva and co-workers published an organocatalytic synthesis of 5-hydroxyisoxazolidines **316** from enals **314** and carbamate-protected hydroxylamines **315** (Scheme 68).[179] Prolinol **38** was used as the catalyst, and the yields and enantioselectivities of the reaction were excellent. The softer nitrogen atom of the hydroxylamine **315** attacks the C=C-bond of the iminium ion, and the harder oxygen atom traps the aldehyde as a hemiacetal. The hemiacetal formation seems to push the reaction forward. In contrast to the results obtained with the MacMillan catalyst, under these conditions,

Scheme 69. Langenbeck's Early Discovery: The Addition of Water to Crotonaldehyde Is Catalyzed by Secondary Amines[33]



O-protected hydroxylamines failed to form the conjugate-addition intermediate.

4.6. *O*-Nucleophiles

Perhaps the earliest example of an oxa-Michael addition to enals was reported by Langenbeck in 1937.[33] As illustrated in Scheme 69, treatment of crotonaldehyde **9** with water in the presence of a catalytic amount of piperidinium acetate **3** or sarcosine **317** provided the corresponding β-hydroxyaldehyde **11**. Although seemingly oblivious of the mechanism behind the transformation, Langenbeck was the first to demonstrate that a simple secondary amine can catalyze the addition of water to an enal. This process very likely involves the condensation of amine and enal to produce an iminium ion, which then goes to the observed aldol product by conjugate addition of water.

In 1997, Brossmer and Arntz of the DuPont Company patented the use of ion-exchange resins **322** incorporating secondary amine and carboxylic acid groups in the hydration of acrolein.[180] Simultaneously, the use of iminodiacids **318**−**321** was also patented for the same purpose.[181] The catalyst types are presented in Figure 11. According to the inventors,

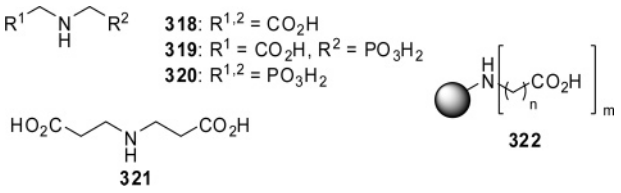


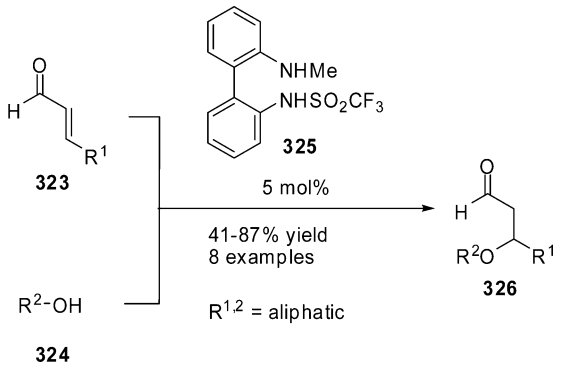
Figure 11. Amino acid catalysts for hydration of acrolein.[180,181]

the catalyst systems offered improved activity and selectivity over traditional acid catalysis, allowing higher conversions and, thus, better space-time yields. Consistent with an iminium-catalysis hypothesis, *N*-alkylated iminodiacids were found to be nonactive in the hydration reaction. Interestingly, these catalyst systems have a close resemblance to the sarcosine catalyst utilized by Langenbeck.

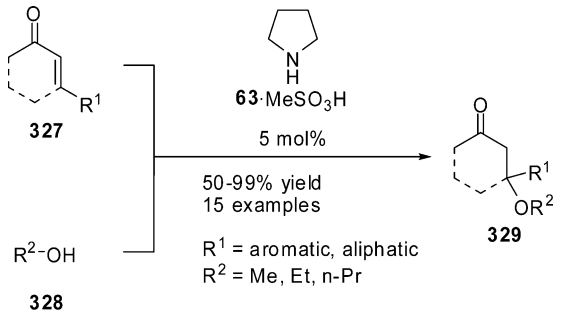
Almost a century after Langenbeck's seminal report, Maruoka and co-workers disclosed a related study of conjugate addition of alcohols to enals.[182] Only 5 mol % of a biphenyldiamine catalyst **325** was reported to catalyze the reaction with a variety of linear aliphatic enals **323** at 0 °C in good yields when the alcohol nucleophile **324** was used as the solvent (Scheme 70).

Ramachary and Mondal expanded the catalysis strategy to the hydroxyalkylation of enones.[183] In a manner similar to Maruoka and co-workers' approach, pyrrolidine methyl sulfonate **63** catalyzed the addition of methanol and ethanol

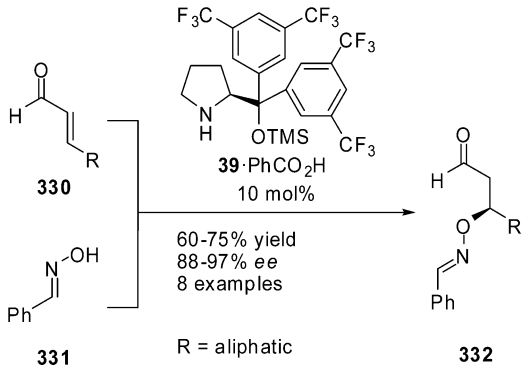
Scheme 70. Addition of Alcohols to Enals[182]



Scheme 71. Addition of Alcohols to Enones[183]



Scheme 72. Asymmetric Addition of Oximes to Enals[184]

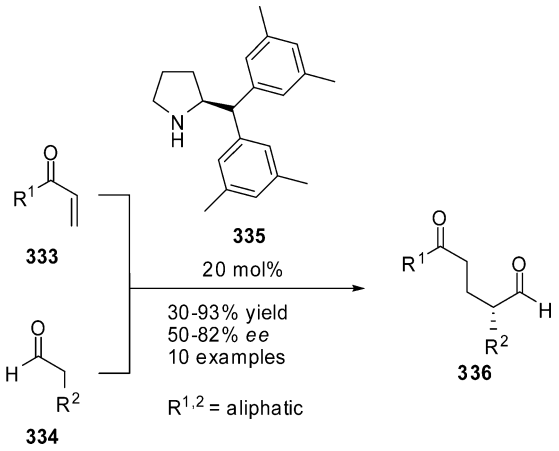


to several acyclic and cyclic enones **327** (Scheme 71). Additionally, a wider variety of alcohols **328** as well as benzyl thiol were shown to add to 3-nonen-2-one. As in the Maruoka study, alcohol nucleophiles **328** were used as the solvent. When pyrrolidine **63** was used without an acid in the conjugate addition reaction of 3-hexen-2-one, the reaction led to the formation of a dimerization product of the enone. The mechanism of the formation of this unexpected side product was speculated to be an amine-catalyzed Basavaiah−Baylis−Hillman reaction.

Finally, an enantioselective conjugate addition of *O*-nucleophiles, in the form of aromatic oximes, to enals was achieved by Jørgensen and co-workers in early 2007.[184] In the presence of catalyst **39**, several β-substituted enals **330** were transformed to the corresponding Michael adducts **332** in good yields and high enantioselectivities when 3 equiv of *E*-benzaldehyde oxime **331** was used as a nucleophile in a highly concentrated toluene solution (Scheme 72). Mesitylaldehyde oxime and salicylaldehyde oxime were also tested as nucleophiles, but their use led to longer reaction times and lower conversions.

It should be noted that the reaction equilibrium of the conjugate addition of oxygen nucleophiles in general is poor

Scheme 73. Enantioselective Conjugate Addition of Aldehydes to Enones[189]



and, thus, requires use of a high excess of the nucleophile (sometimes used as a solvent). Good conversions have been achieved also by subjecting the products to subsequent (domino) reaction sequences. For example, salicylaldehydes have been added to enals[185−187] and cyclic enones[188] utilizing this method. Applications of this latter method are discussed in section 6.1.3.

5. Iminium–Enamine Manifold

There are several amine-catalyzed reactions that do not easily fall into specific mechanism types, or it is conceivable that one or two mechanisms cooperate. The reactions most likely proceed via enamines, but the possibility that enone- or enal-derived iminium ions are active intermediates cannot be excluded. Reactions of this type are discussed below.

Melchiorre and Jørgensen reported that conjugate additions of aldehydes **334** to enones **333** are readily promoted by pyrrolidine derivative **335**.[189] In most cases, high yields and good enantioselectivities were obtained (Scheme 73). The presence of both aldehyde and enone functionalities allows speculation over the reaction mechanism. Poor conversion of an enone with a bulky R^1 group led authors to study linearity between the ee of the catalyst and the ee of the product in that particular reaction. They observed a negative nonlinear effect. However, with other enones, no deviation from linearity was observed. To account for the nonlinear effect, the authors stated that involvement of an iminium intermediate cannot be excluded.

Gellman and co-workers investigated the effect of imidazolidinone catalyst **29** on an intramolecular aldehyde−enone system similar to that of Melchiorre and Jørgensen's.[190] They used *para*-ethyl ester-substituted catechol **337** as the cocatalyst (Figure 12). The catalyst combination produced the

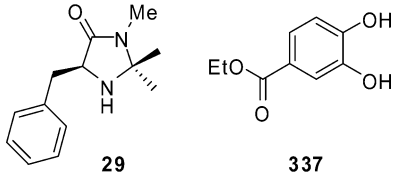
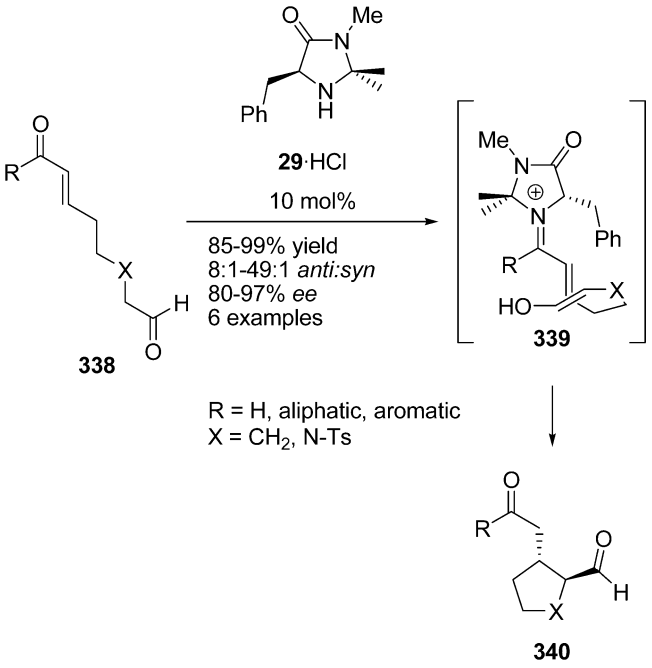


Figure 12. Imidazolidinone catalyst **29** and a catechol additive.[190]

desired Michael adducts in good-to-high yields and enantioselectivities that were consistently higher than Jørgensen's. The authors stressed the presence of an enamine in the

Scheme 74. Intramolecular Enantioselective Michael Addition[191]



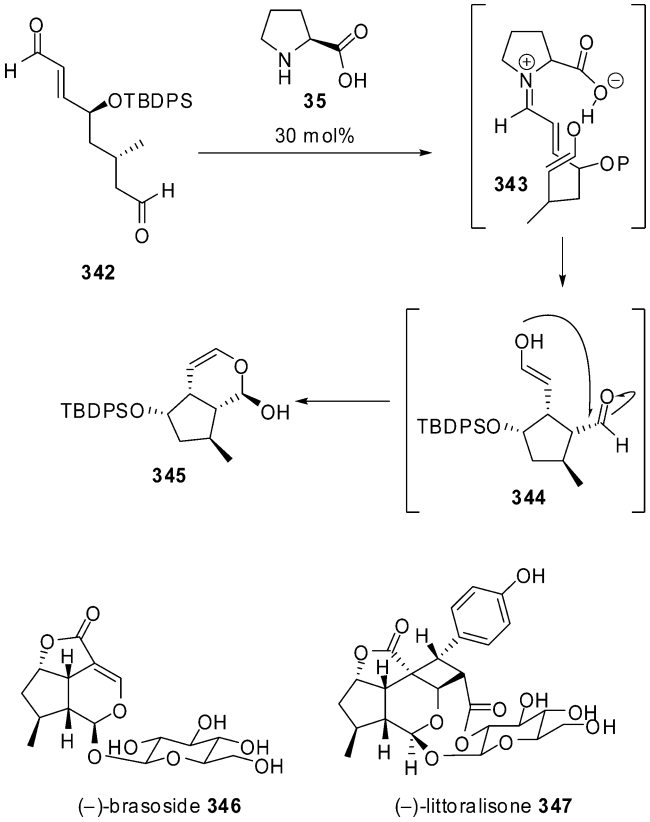
reaction mechanism but did not comment on the possible coexistence of iminium species. However, they were able to generate the catalyst aldehyde−enamine complex quantitatively by mixing the saturated aldehyde with the catalyst in the presence of 4 Å molecular sieves.

In 2004, Hechavarria Fonseca and List described the intramolecular Michael reaction (Scheme 74), where a C−C bond is formed between the α-carbon of saturated aldehyde and the carbon at the β-position of an enal or enone.[191] The authors suggested that the observed reaction may be result of either enamine catalysis or dual enamine−imine activation. They reported six examples of this reaction with excellent yields and high enantioselectivities. The observed absolute configurations of the products are in agreement with an iminium mechanism.

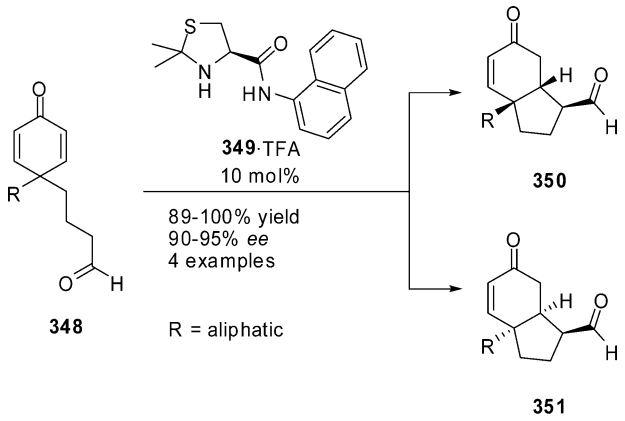
Mangion and MacMillan utilized the intramolecular Michael-addition strategy in the total syntheses of brasoside **346** and littoralisone **347**.[192] Exposure of **342** to L-proline **35** provided lactol **345** in 91% yield and 10:1 cis/trans selectivity. Extended reaction times led to complete conversion to the thermodynamically favored trans isomer. Interestingly, the observed diastereoselectivity was cis, whereas the analogous reaction published by Hechavarria and List provided the trans products. This difference can be attributed to the electrostatic interaction of the carboxylate side chain with the enolate. The authors did not comment on the reaction mechanism, but both iminium and enamine mechanisms are possible. The observed configuration of the product is consistent with an iminium mechanism, as illustrated in Scheme 75. The possibility of enamine activation, however, cannot be excluded.

Hayashi and co-workers have also studied amine-catalyzed intramolecular additions between aldehydes and cyclic and acyclic enones.[193] Catalyst **349** (10 mol %) yielded the bicyclic products **350** and **351** in uniformly high yields and selectivities regardless of the nature of the R-group (Scheme 76). With acyclic ketone substrates **352**, they obtained opposite diastereoselectivities (Scheme 77) to those reported by Hechavarria Fonseca and List with catalyst **29** (Scheme

Scheme 75. Intramolecular Asymmetric Michael Additions in Natural Product Synthesis[192]



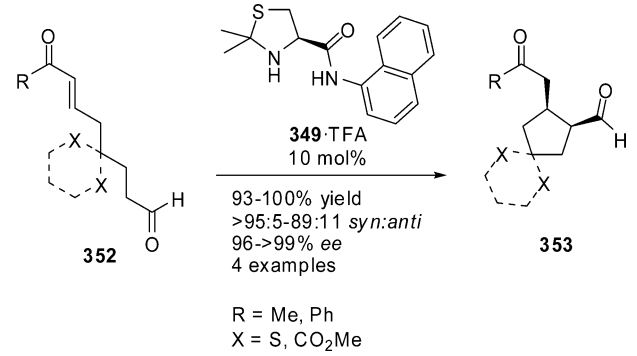
Scheme 76. Enantioselective Intramolecular Reaction of Cyclic Enones with Aldehydes[193]



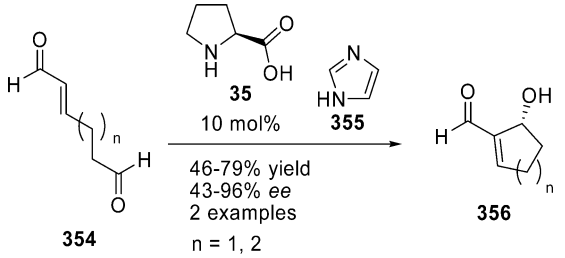
74). As discussed above, the diastereoselectivity of the reaction may be explained by electrostatic interactions.

An intramolecular amine-catalyzed reaction between an aldehyde and an enal has been described by Hong and co-workers.[194] Unlike the intramolecular reactions between these functionalities discussed above, this reaction resulted in a Baylis−Hillman-type adduct (Scheme 78). The optimized reaction was performed in the presence of imidazole **355**. Interestingly, the reaction did also proceed in the absence of imidazole, but with a reversed facial selectivity. The authors suggested two alternative reaction pathways to explain the observed results. They proposed that, in the absence of imidazole, the amine catalyst forms an iminium ion with the enal part of the molecule. This iminium ion then loses a proton to generate the corresponding γ-enamine compound.[195] This enamine would then react from its 2-position with the aldehyde. Alternatively, the imidazole

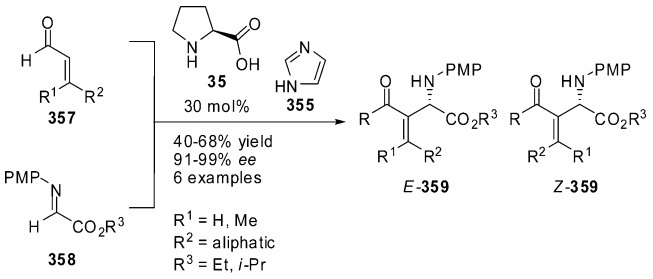
Scheme 77. Enantioselective Intramolecular Reaction of Acyclic Enones with Aldehydes[193]



Scheme 78. Proline-Catalyzed Intramolecular Baylis−Hillman Reaction[194]



Scheme 79. Intermolecular Asymmetric Baylis−Hillman Reaction[196]



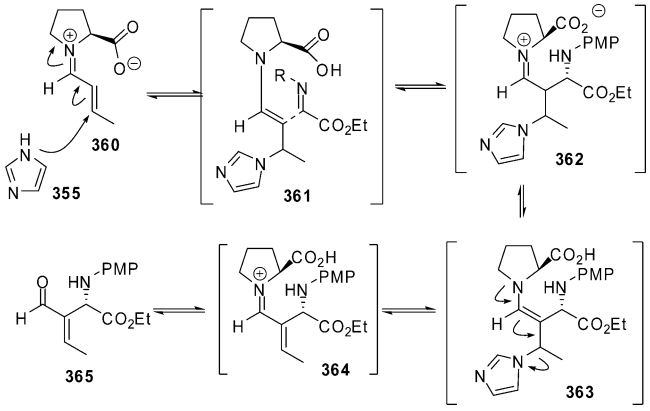
might act as a nucleophilic catalyst adding to the iminium ion, forming an enamine, which then reacts with the aldehyde.

Barbas and co-workers reported a proline-catalyzed Baylis−Hillman-type α-addition of PMP protected α-imino esters **358** to β-substituted enals **357** in 2007 (Scheme 79).[196] The reaction also required the presence of imidazole **355** as an additive. As illustrated in Scheme 80, the reaction presumably proceeds via iminium-catalyzed conjugate addition of imidazole to form enamine species, which then react with the imino ester. Elimination of the added imidazole then restored the enal double bond. In the presence of 30 mol % proline, reactions proceeded in moderate yields and high enantioselectivities that favor *E*-stereoisomer.

6. Domino Processes

In a domino process, the first reaction provides a starting material or an intermediate that is ready for the second reaction. Several consecutive reactions can be coupled in a domino fashion.[197] Since the nucleophilic addition to an α,β-unsaturated iminium ion generates a reactive enamine intermediate, domino reactions where both iminium and enamine intermediates are active can be envisaged. An excellent review on organocatalytic domino reactions has been recently published by Enders and co-workers.[9]

Scheme 80. Possible Iminium-Mediated Mechanism of Baylis−Hillman Reaction[196]



The domino reactions discussed here can be divided into two classes according to the type of the last reaction step. The most common case is one where the intermediate formed in the first reaction step reacts further in an intramolecular fashion, creating a ring. These reactions are categorized as intramolecular, even if some of the previous steps have been intermolecular.

These intramolecular domino reactions can be divided into several distinct reaction types according to their likely mechanisms (Scheme 81). For example, in an enamine−iminium-type I domino cyclization, the final cyclization step takes place via iminium activation. An alternative possibility is that these reactions proceed via an enamine−Diels−Alder mechanism. In contrast, in an iminium−enamine-type II cyclization, the final cyclization step is typically an enol−exo aldol-type step. The type III double iminium/enamine reactions can be seen as a subtype of the type I reactions. However, in this type, both reaction steps likely are iminium-activated, whereas in the type I, only the second step is iminium-activated. Furthermore, several of these reactions do not neatly fall into either of these categories. For this reason, the domino reactions of this section are discussed in the order of increasing ring size and complexity.

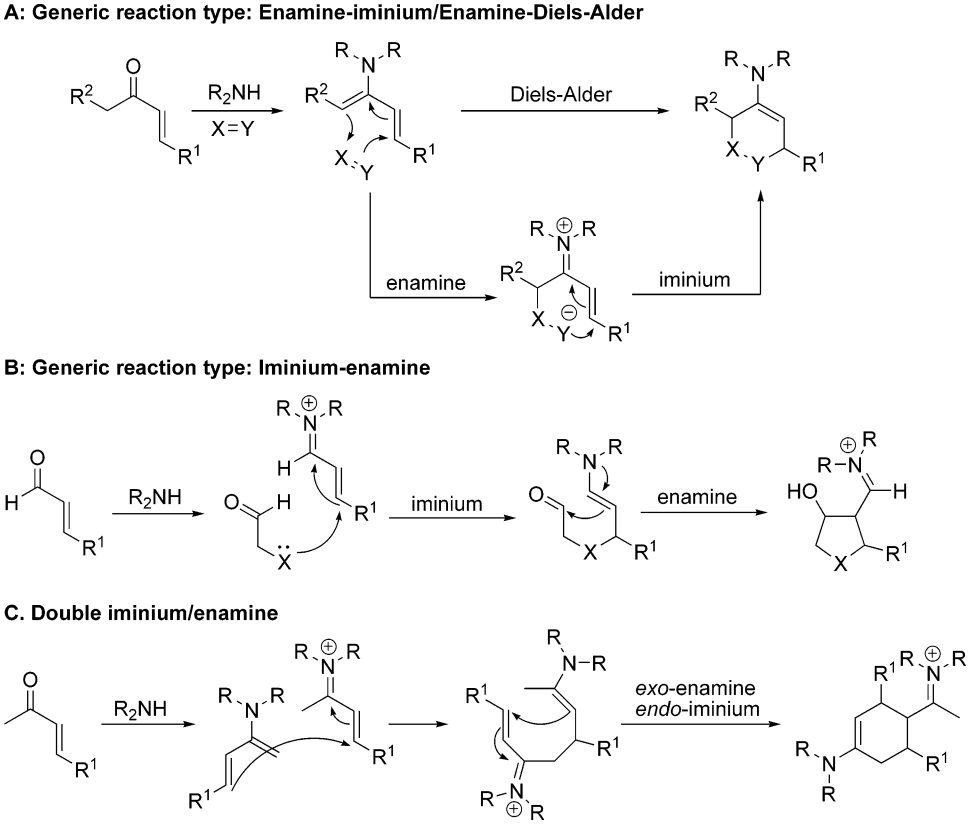
6.1. Intramolecular Domino Reactions

6.1.1. Three-Membered Rings

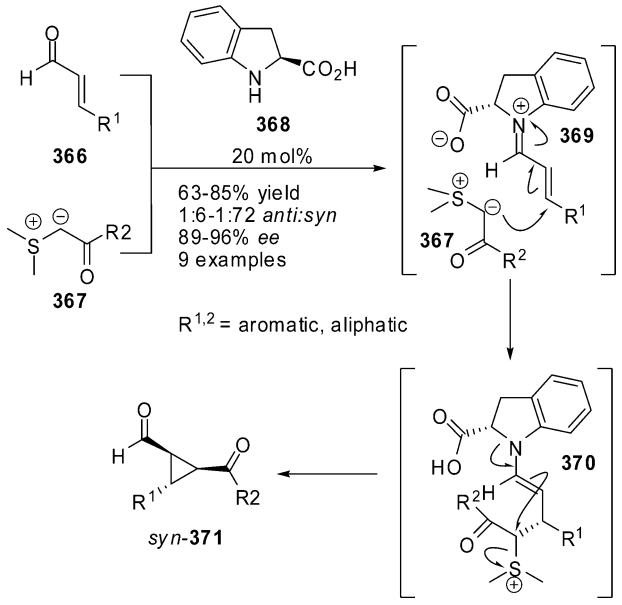
6.1.1.1. Cyclopropanation. In 2005, Kunz and MacMillan reported a cyclopropanation reaction based on iminium activation.[97] A nucleophilic ylide **367** reacts with an iminium ion **369** formed from the aldehyde **366** and the catalyst. Subsequently, the enamine addition closes the cyclopropane ring, eliminating dimethylsulfide in the process. Various cyclopropanes were prepared in good stereoselectivities and moderate yields. The stereocontrol of the reaction is based on electrostatic interactions, as illustrated in Scheme 82. The negatively charged acid functionality draws near the positively charged sulfur end of the ylide, directing the cyclopropanation to proceed from the side of the acid functionality.

Another example of an iminium-catalyzed cyclopropanation reaction is the nitrocyclopropanation of cyclohexenone **372** published by Ley and co-workers.[198] They utilized a proline tetrazole catalyst **374** that previously had been successful in the addition of nitroalkanes to enones.[114,135] After an extensive study on the catalyst system and the reaction conditions, they were able to produce compound

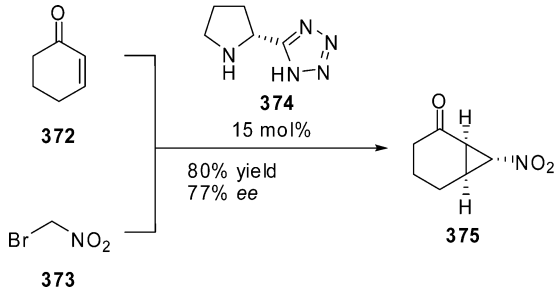
Scheme 81. Distinct Modes of Iminium-Mediated Domino Reactions



Scheme 82. Asymmetric Cyclopropanation Stereocontrolled by Electrostatic Interactions[97]



Scheme 83. Enantioselective Cyclopropanation Using Bromonitromethane[198]



375 in 80% yield and 77% ee with the aid of a morpholine additive with only a small excess of bromonitromethane **373** (Scheme 83).

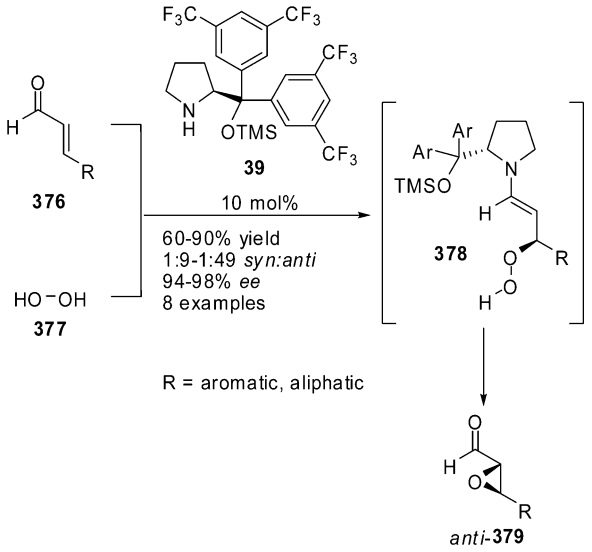
6.1.1.2. Epoxidation. The first iminium-catalyzed epoxidation reaction was reported by Jørgensen and co-workers in 2005 (Scheme 84).[199] A prolinol derivative **39** catalyzed the addition of hydrogen peroxide **377** to β-substituted enals **376** in excellent stereoselectivities and moderate yields. In addition to hydrogen peroxide, organic peroxides could also be used as oxidants, without impairing the enantiocontrol, although conversions were clearly diminished. Stereoselectivities in the reactions with β-disubstituted enals were lower than those with β-monosubstitution, especially with β-dimethyl substitution.

In their initial publication, Jørgensen and co-workers had performed the reactions in CH_2Cl_2. A follow-up study demonstrated that the same reaction could also be conducted in a mixture of water in ethanol.[200] The enantioselectivity of the reaction was slightly reduced but remained at good levels (85−96% ee). Also, diastereoselectivities were deteriorated (1:1−1.6 syn/anti). Significantly lower yields (34−56%) were explained by a partial acetalization of the product.

Subsequently in 2006, Córdova and co-workers reported that also the simpler prolinol catalyst **38** as well as the diamine **380** is a viable epoxidation catalyst (Figure 13).[201] In addition, the oxazolidinone catalyst **29** produced good diastereoselectivities, but enantioselectivities were very low with this catalyst. The same tendency was observed with diamine **381**.

An alternative epoxidation strategy was proposed by MacMillan and co-workers later that year.[202] Utilizing their well-established imidazolidinone catalyst **118** as a $HClO_4$

Scheme 84. Asymmetric Epoxidation of Enals[199]



salt, they used in situ produced iodosobenzene to attack enals **382** via a domino iminium−enamine cascade (Scheme 85). Slow release of iodosobenzene from NsNIPh **383** in the presence of acid was found to be optimal when compared to the use of pure iodosobenzene. Under the optimized conditions, both aromatic and aliphatic β-substituted enals **382** were converted to the corresponding epoxides **385** in high enantioselectivites (87−97% ee) and yields.

Pihko and co-workers developed an *o*-substituted aniline catalyst that readily transformed α- or α,β-substituted aliphatic enals **386** to the corresponding epoxides **388**.[49] 2,6-Diisopropylaniline **41** was found to be the most active aniline catalyst in this transformation. The activity of the catalysts was suggested to be enhanced by the large isopropyl

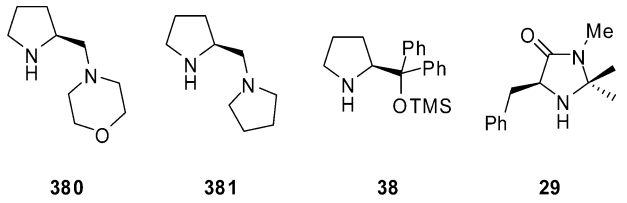
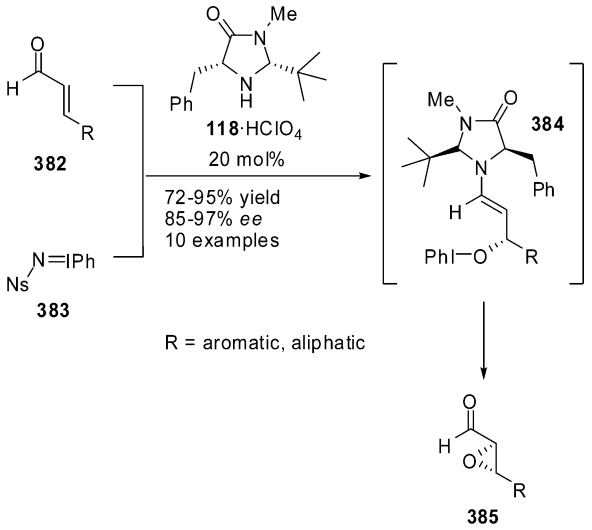
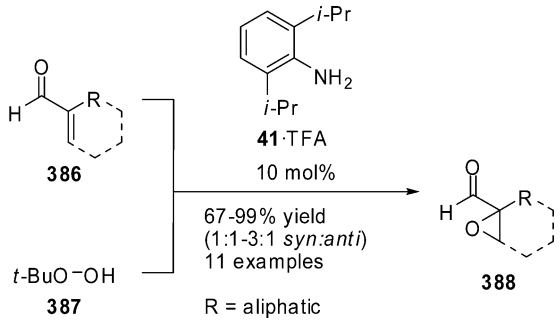


Figure 13. Amine catalysts used in epoxidation reactions.[201]

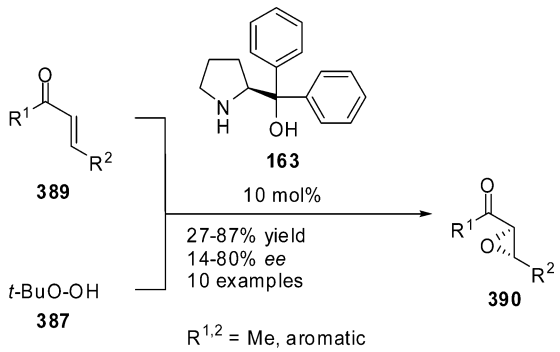
Scheme 85. Asymmetric Epoxidation of Enals Using Iodosobenzene[202]



Scheme 86. Aniline-Catalyzed Epoxidation of α-Acroleins[49]



Scheme 87. Diphenyl Prolinol 148 Promotes Enantioselective Epoxidation of Enones[203]



substituents that force the iminium π-system to twist out of conjugation. This would then destabilize the imine or iminium ion, allowing hydrolysis and regeneration of the catalyst. Optimized reaction conditions delivered a variety of racemic epoxides **388** in excellent conversion that could be isolated after an optional in situ $NaBH_4$ reduction in good yields (Scheme 86).

6.1.1.2.a. Epoxidation of Enones. Applications for diaryl proline-catalyzed enone epoxidation have been developed by Lattanzi and later by Zhao. Lattanzi reported in 2005 that chalcone derivatives as well as 4-aryl 2-butanone can be epoxidated in the presence of diphenylprolinol **163** and TBHP **387** in hexanes (Scheme 87).[203] The products were obtained in generally varying yields and stereoselectivites (16−98% yield, 6−92% ee). In following publications, Lattanzi reported that higher enantioselectivites can be realized by the use of variously substituted diphenyl prolinols. The best results were obtained with *meta*-dimethyl-substituted catalyst **391** (Figure 14).[204] Furthermore, addition of extra *para*-methoxy group **392** led to shortened reaction times while retaining the selectivity.[205]

Zhao and co-workers also studied the diarylprolinols in the epoxidation of chalcone derivatives. In accordance with the results reported by Lattanzi, they reported that *meta*-disubstitution is beneficial to the selectivity of the reaction.[206] On the basis of this observation, they introduced a recyclable dendritic proline-based catalyst **394**. Later, they studied the effect of 4-*cis*-subsitution of the pyrrolidine core structure and reported high yields and stereoselectivities for various chalcone epoxidation products with **393**.[207]

In both Lattanzi's and Zhao and co-workers' studies, the products were obtained in opposite facial selectivity compared to epoxidations of enals catalyzed by TMS−prolinol derivatives. On the basis of this observation, both authors suggest that the reaction mechanism does not involve iminium ions at all. They claim that opposite facial selectivity should be obtained if an iminium intermediate would be

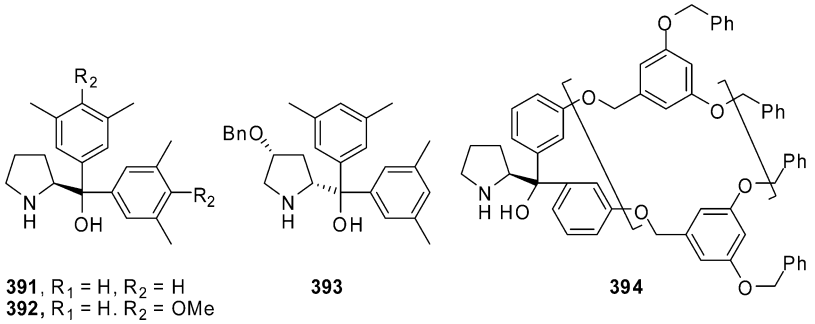
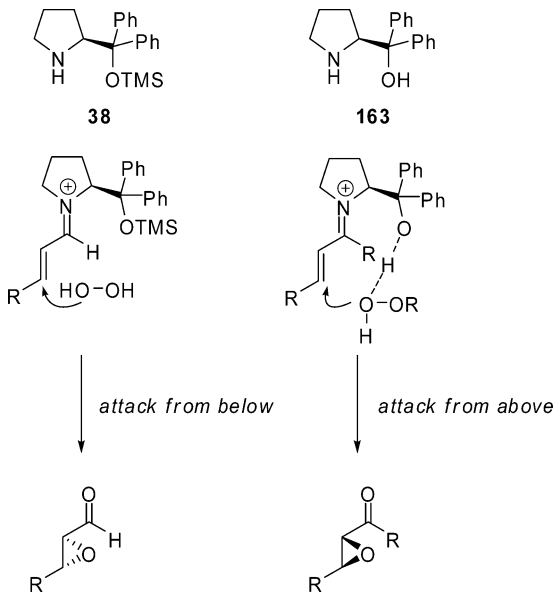


Figure 14. Prolinol-based epoxidation catalysts **391**−**394**.[204−207]

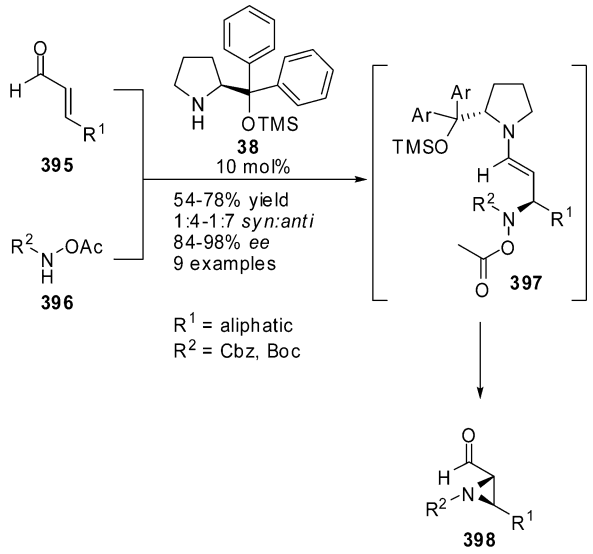
Scheme 88. Possible Origin of Opposite Stereoselectivity with Catalysts 38 and 163[201,203]



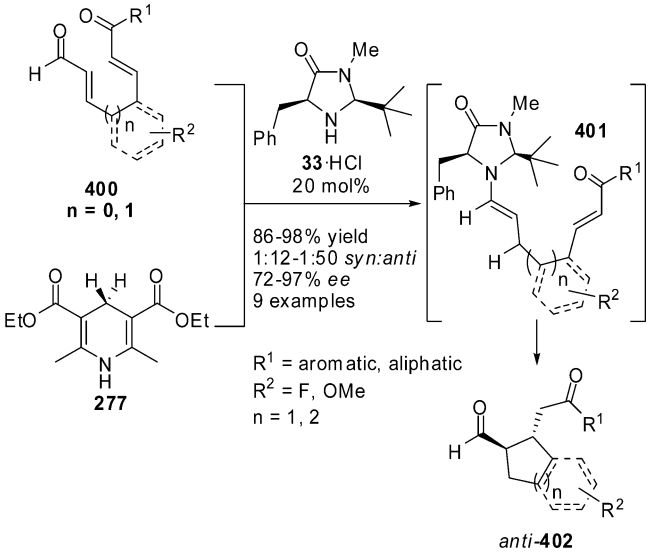
present. It should be noted, however, that opposite diastereomeric selectivities were similarly obtained with TMS diphenyl prolinol **38** and unprotected prolinol **163** in Córdova and co-workers' studies involving enals.[201] As such, the selectivity patterns with enones could also be explained by an iminium activation paradigm where the free alcohol of the prolinol acts as a directing unit, as has been observed with the proline acid side chain in the organocatalytic aldol reaction,[208] and, thus, invites the peroxide to attack on the same face (Scheme 88). Additionally, similar hydrogen bonding has been suggested by Sharpless and Verhoeven to explain the epoxide orientation in the Henbest epoxidation.[209] In the case of TMS-protected prolinol, the controlling hydrogen bond is missing and the side chain provides only steric bulk, thus directing the peroxide to approach from above. However, since no iminium ions have been detected in these studies, the ion-pair mechanism favored by Lattanzi and Zhao and co-workers remains a viable possibility.

6.1.1.3. Aziridination. In 2007, Córdova and co-workers disclosed an aziridination reaction of enals that is analogous to the epoxidation reaction.[210] They employed the prolinol derivative **38** as the catalyst in the reaction while the nitrogen in the aziridine ring was provided by an acylated hydroxycarbamate **396**. The reaction proceeds via conjugate addition of the hydroxycarbamate to the iminium intermediate to form the enamine **397**, as illustrated in Scheme 89. The aziridine ring is then closed analogously to the cyclopropanation and epoxidation paradigms, assisted by the departure of the

Scheme 89. Asymmetric Aziridination of Enals[210]



Scheme 90. Asymmetric Domino Reduction−Cyclization[211]

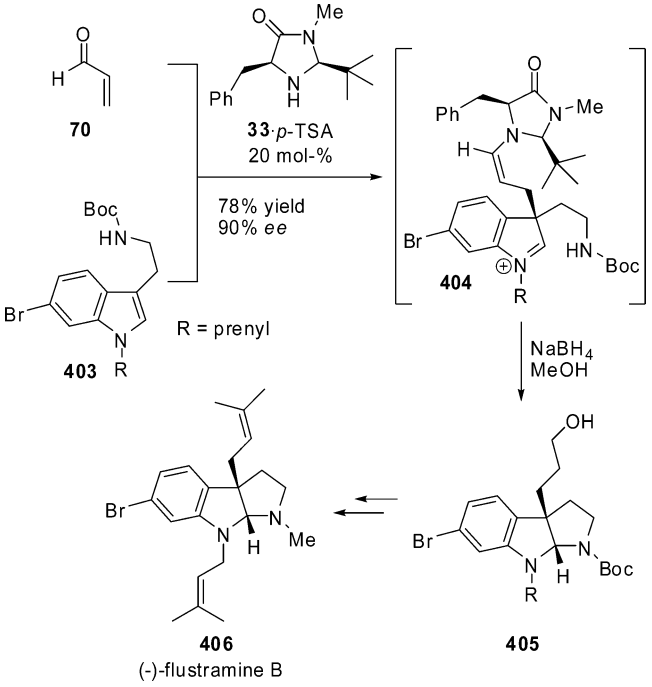


acetate group. The reaction produced aziridines **398** in reasonable yields and good stereoselectivities.

6.1.2 Five-Membered Rings

6.1.2.1. Carbocyclic. List and co-workers reported a domino conjugate reduction−addition reaction using enone enals **400** and the imidazolidinone catalyst **33** (Scheme 90).[211] The first step was an iminium-activated conjugate reduction in which the Hantzsch ester **277** served as the hydride donor. The sterically less-hindered aldehyde formed the iminium

Scheme 91. Asymmetric Synthesis of (−)-Flustramine B[145]

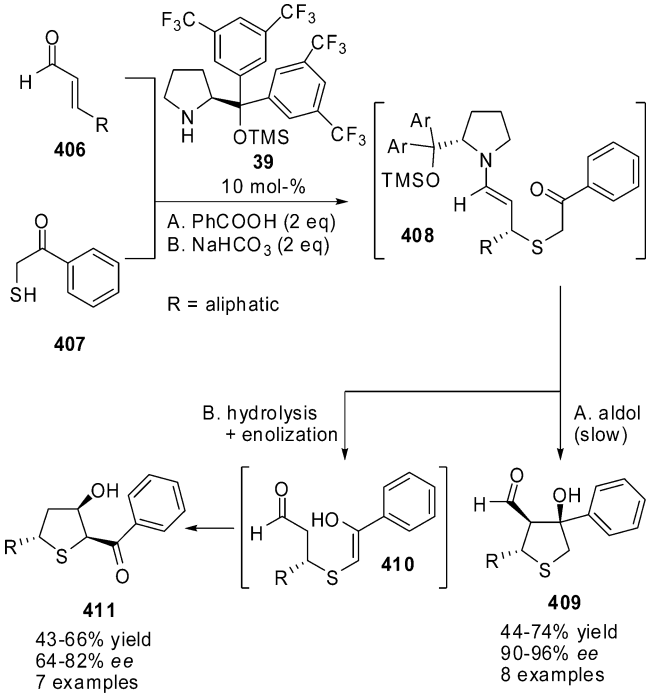


ion chemoselectively and was reduced, leading to enamine formation. The enamine then underwent a conjugate addition to the ketone moiety, affording the bicyclic product **402** in good yields. The reaction also was successful with starting materials that did not contain an aromatic. In the case of a formation of a six-membered ring, the yields and selectivities were hardly affected (85% yield, 1:12 syn/anti, 95% ee). However, in the case of a five-membered ring, the enantioselectivity suffered notably (95% yield, 1:24 syn/anti, 72% ee).

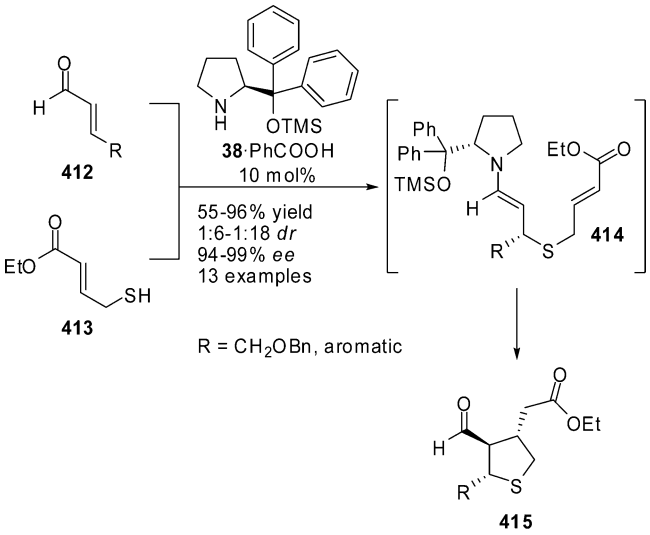
6.1.2.2. Heterocyclic. In 2004, MacMillan and co-workers published an interesting synthesis route to (−)-flustramine B **406** using a double iminium-activated domino reaction as the key step (Scheme 91).[145] The first step of the reaction was a standard iminium-activated enantioselective conjugate addition to the enal **70**. The intermediate **404** cannot rearomatize because of the newly formed quaternary carbon center. The formed cyclic iminium ion is instead quenched intramolecularly by the tethered amino group. In situ $NaBH_4$ reduction affords product **405** with a moderate yield and good enantioselectivity. Prior to this, several amine-protecting groups were screened, as well as different substituents at the 5−7-positions of the indole moiety. The yields and enantioselectivities were generally good (82−99% yield, 89−99% ee). Preparation of furanoindolines by the corresponding domino strategy was also reported (80−90% yield, 82−93% ee).

In 2006, Jørgensen and co-workers reported a domino Michael−aldol reaction using enals and a ketothiol **407** (Scheme 92).[168] The first step of the sequence was an iminium-activated enantioselective conjugate addition to the enal. However, the fate of the resulting enamine intermediate depended on whether the reaction was carried out under acidic or basic conditions. The authors suggest that basic conditions promote the hydrolysis of the enamine **408**, as well as the formation of the thermodynamically most stable enol **410**, leading to product **411**. On the other hand, with benzoic acid, the ketone reacts with the newly formed enamine, leading to the formation of product **409**. These

Scheme 92. Tetrahydrothiophenes by an Enantioselective Domino Reaction According to Jørgensen and Co-workers[168]



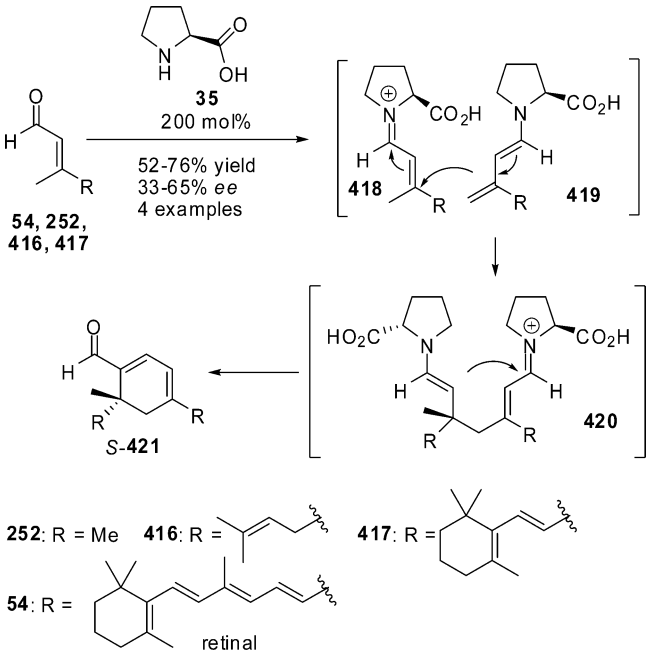
Scheme 93. Asymmetric Synthesis of Tetrahydrotiophenes According to Wang and Co-workers[212]



mechanistic considerations are supported by the fact that products **411** were obtained in notably lower ee's than products **409**. The aldol step with benzoic acid was promoted by chiral catalyst **39**, leading to enantioenrichment of the products. Under basic conditions, the asymmetric induction was solely derived from the primary conjugate addition step. The yields of both products were of the same order of magnitude, and only one diastereomer of each of the products was formed in the reaction.

Recently, Wang and co-workers also disclosed a method for preparing tetrahydrothiophenes **415** using a domino double Michael reaction between the enal **412** and *trans*-ethyl-4-mercapto-2-butenoate **413** (Scheme 93).[212] The products were obtained in good yields and excellent ee's. Enals **412** were mostly aromatic, but an alkyl-substituted (R = CH_2OBn) enal was reported to perform almost equally well in the reaction (62% yield, 1:7 dr, 94% ee).

Scheme 94. Proline-Catalyzed Dimerization of Aldehydes[213]



In addition, Córdova and co-workers reported an organocatalytic synthesis of 5-hydroxyisoxazolidines from enals and carbamate-protected hydroxylamines.[179] This reaction was already discussed in the section regarding conjugate additions of *N*-nucleophiles (see section 4.5, Scheme 68).

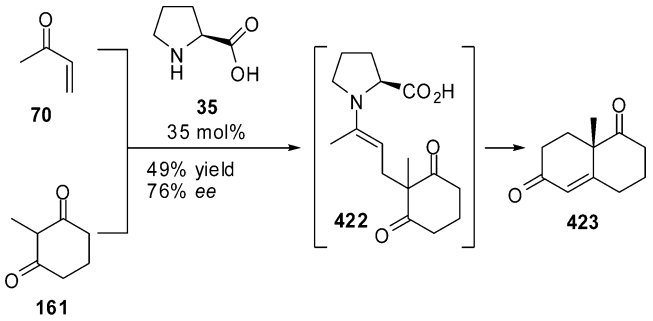
6.1.3. Six-Membered Rings

6.1.3.1. Carbocyclic. In 1992, Liu and co-workers published the dimerization of enals **54**, **252**, **416**, and **417** into cyclic products **421** (Scheme 94).[213] The group had previously observed the dimerization of aldehyde **417** in low yields in the presence of the milk whey protein β-lactoglobulin. Subsequently, they discovered that the simple amino acid proline **35** proved to be even better at activating the reaction. The reaction was also expanded to other aldehydes. The mechanism involves the formation of a γ-enamine **419** that supposedly reacts with the iminium ion **418** of the aldehyde and proline. Strictly speaking, the reaction is not catalytic, as an excess of proline was used at all times. However, it is an early and interesting example of a reaction type that will be encountered several times during this review.

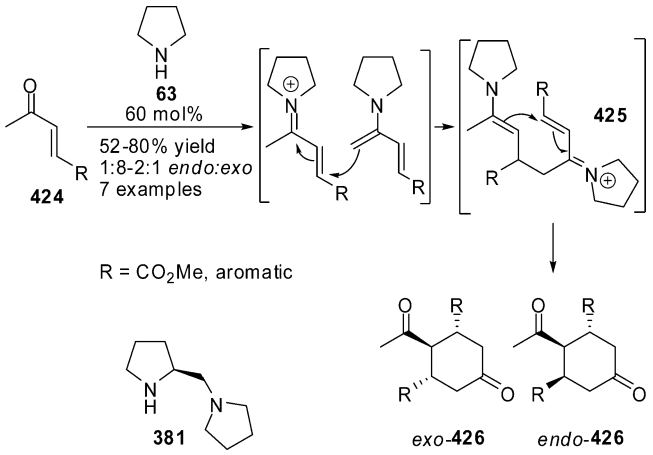
The reaction was moderately enantioselective, but the absolute configurations of the products were not reported. The group did not comment on the reaction mechanism. However, one of the authors suggested in a subsequent article that similar proline-catalyzed reactions proceed through a domino conjugate−aldol−addition route instead of a one-phase pericyclic one.[214] In the same article, the configuration of the major isomer was presented as *S*-**421**.

Watanabe had been a member of the group of Liu and Asato, who reported the aldehyde dimerizations in 1992 (Scheme 94).[213] 14 years later, in 2006, he and his co-workers revisited this proline-catalyzed reaction. The dimerizations were tested with several enals using 1.5 equiv of proline, but the results remained similar to those reported in the original article (42−89% yield, 26−62% ee). Using proline-derived alcohols or esters as catalysts further lowered the ee. The authors suggest that the modest enantioselectivity is an indicator of a domino reaction mechanism, where the stereochemistry is determined at the β- and γ-carbons far from the chiral amine auxiliary. In a Diels−Alder reaction mechanism, the auxiliary should have a stronger effect on the stereochemistry. However, swapping the amine from proline to diethylprolinol did have a relatively large effect, causing a drop of 35% in the ee.[214]

Scheme 95. All-Proline-Catalyzed Robinson Annulation[116]



Scheme 96. Dimerization of Ketones and a Possible Reaction Mechanism[216]

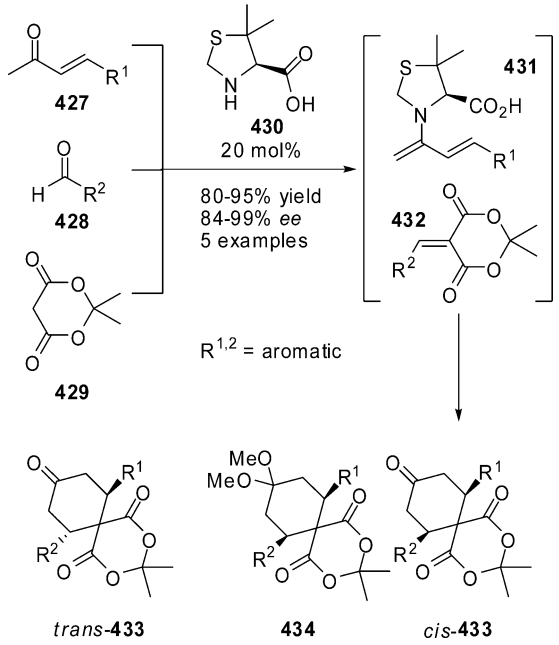


Bui and Barbas disclosed an all-proline-catalyzed Robinson annulation in 2000.[116] The conjugate addition step and the cyclization step were performed separately in the traditional method, with the first step being acid-catalyzed. The method by Bui and Barbas enabled the first step to be catalyzed by proline as well (Scheme 95). Swaminathan and co-workers used a similar approach in preparing spiroenediones from methyl vinyl ketone and cyclic ketoaldehydes.[215] In general, 1 equiv of proline was used, affording products in modest yields (43−49%) and enantioselectivities (0−34% ee).

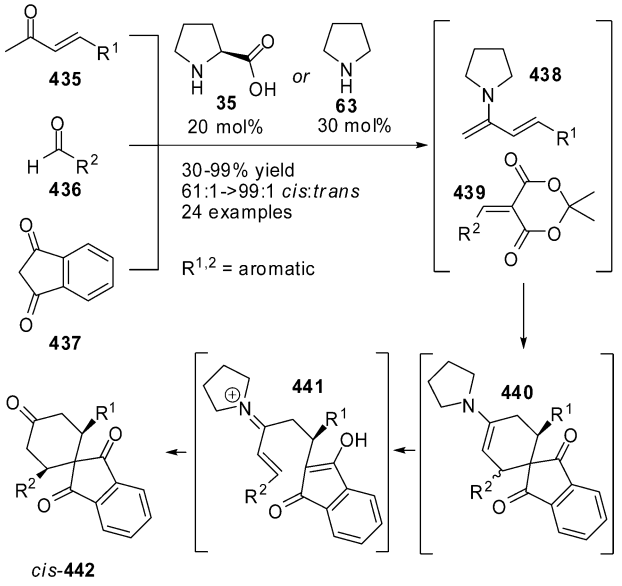
Barbas and co-workers also reported an amine-catalyzed dimerization of enones **424** in 2002 (Scheme 96).[216] Pyrrolidine **63** was found to be the best catalyst for this transformation. Proline **35** and (*S*)-1-(pyrrolidinylmethyl)-pyrrolidine **381** were also tested as catalysts for the dimerization. The formation of the prochiral *exo*-**426** was favored under most conditions. The best exo-selectivities were obtained when water was used as the solvent. The formation of the endo-product was modestly enantioselective. The cycloadduct *endo*-**426** (R = −SPh) was obtained in 23% ee using proline as the catalyst. The authors themselves did not comment on the reaction mechanism. Both stepwise as well as concerted mechanisms could be operating as depicted above in Scheme 81A.

A couple of months earlier, Tanaka and co-workers had also reported an amine-activated formal Diels−Alder reaction between nitroalkenes and enones.[217] Assuming that the

Scheme 97. Enantioselective Domino Knoevenagel−Formal Diels−Alder Reaction[218]



Scheme 98. Domino Knoevenagel−Formal Diels−Alder Reaction Using Indandiones as Starting Materials[219]



reaction mechanism is a double conjugate addition instead of a one-step Diels−Alder reaction, it is likely that the final cyclization step is iminium-activated. One equivalent of proline **35** or diamine **381** was used, but it was noted that the reaction also proceeded with only 30 or 50 mol % of the amine.

In 2003, Barbas and co-workers achieved an amino acid-catalyzed synthesis of spirotriones *cis*-**433** in one pot from three starting materials (Scheme 97).[218] A variety of amine catalysts were screened for the reaction. The thiaproline **430** was found to be the most active, and it also afforded good enantioselectivity. The first reaction step involves Meldrum's acid **429** that reacts with aldehyde **428**, forming the Knoevenagel adduct **432**. This step is likely to be iminium-catalyzed. Following this, the enone and the catalyst form an enamine **431** that reacts with **432** in a formal Diels−Alder reaction. This reaction may be an actual Diels−Alder reaction or, more likely, an enamine−iminium-activated double conjugate addition. Product **433** is obtained as a single *cis*-diastereomer with good yields and enantioselectivities. In addition to ketone product **433**, acetal **434** was also obtained in some of the reactions. Proline was an excellent catalyst for the preparation of prochiral ($R^1 = R^2$) products (85−99% yield, 2 examples). However, proline afforded chiral ($R^1 \neq R^2$) *trans*-**433** products in only 34% ee.

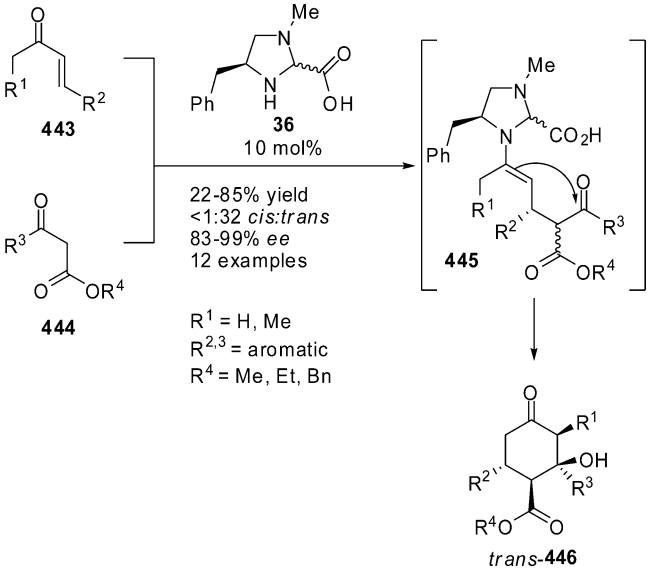
Barbas and co-workers also expanded the domino sequence to include 1,3-indanediones as starting materials.[219,220] Analogous to the previous domino sequence, indanedione **437** and aldehyde **436** form a Knoevenagel adduct **439** that reacts with enamine **438** in a formal Diels−Alder reaction. Various amine catalysts, including thiaproline **430**, were screened, but no satisfactory ee was obtained. For this reason, the studies were directed at the preparation of diastereopure products. After the formal Diels−Alder step, both cis- and trans-products **442** were observed, but the kinetic *trans*-**442** readily epimerized through an amine-catalyzed retroconjugate addition mechanism via intermediate **441** (Scheme 98). No epimerization occurred in the absence of the catalyst. Good yields and diastereoselectivities were obtained for both symmetric ($R^1 = R^2$) products (60−98% yield, 99:1 cis/trans, catalyzed by proline **35**) as well as for nonsymmetric ($R^1 \neq R^2$) ones (30−99% yield, 6:1−99:1 cis/trans, catalyzed by pyrrolidine **63**).

Ramachary and Barbas also described a proline-catalyzed domino synthesis of spirotriones that consisted of a Wittig−Knoevenagel−Diels−Alder sequence.[221] In this reaction sequence, the enone is formed in situ from an aromatic aldehyde and phosphorane. The reaction was fully diastereoselective if the cyclohexane ring of the spirolactone contained no substituents. An unsymmetrically substituted spirolactone afforded a 1:1 mixture of diastereomers. The authors had also tested an aldol reaction as one of the reaction steps before deciding in favor of the Wittig reaction. However, the aldol reaction was dismissed because of the formation of unwanted side products. Obtaining asymmetric products also was possible by using two different aromatic aldehydes in the Wittig−Knoevenagel−Diels−Alder sequence. The selectivity of the reaction was controlled simply by the order of addition of the reactants. The diastereoselectivity remained high (>100:1), but the enantioselectivity was only moderate (42−70% ee).

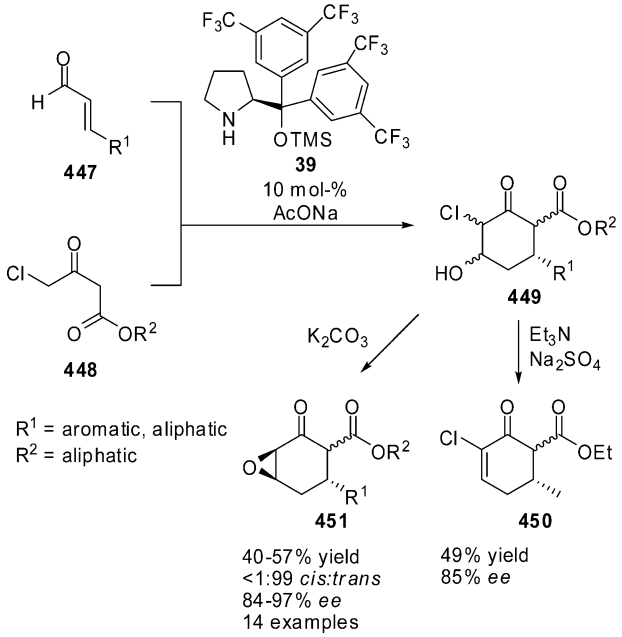
In 2004, Jørgensen and co-workers reported a domino cyclization between enone **443** and β-ketoester **444** (Scheme 99).[123] The first step is the enantioselective iminium-activated conjugate addition catalyzed by the imidazolidine **36**. Two stereogenic centers are formed in intermediate **445**, but the one positioned in the α-position of the β-ketoester moiety epimerizes readily. However, only one of these diastereomeric intermediates cyclizes, forming the stable six-membered ring *trans*-**446** with all the large substituents equatorial. The authors presumed this step to be base-catalyzed but did not completely exclude the possibility of enamine catalysis. The stereoselectivities of the reaction were good, but the yields varied depending on the starting materials. For instance, the yields remained poor (22−44%) when R^4 was not benzyl (R^4 = Me, Et).

Jørgensen and co-workers published an extension to this reaction that allowed β-diketones and β-ketosulfones to be used as Michael donors in addition to β-ketoesters.[124] However, aliphatic substituents on these compounds were not tolerated, affording only trace yields. Results were only reported with phenyl-substituted diketones and ketosulfones.

Scheme 99. Enantioselective Cyclization of Enones and β-Ketoesters[123]



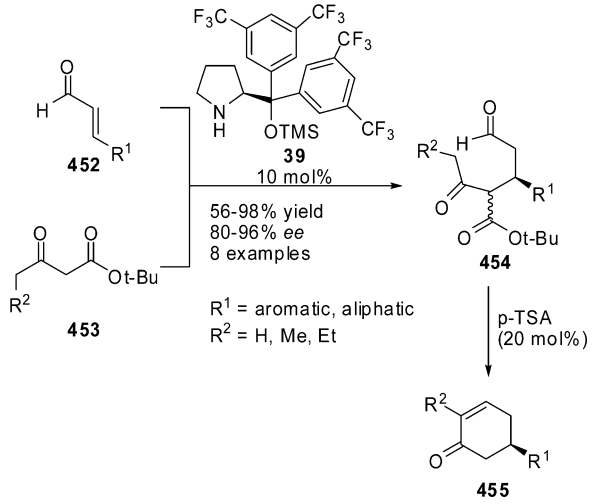
Scheme 100. Asymmetric Domino Michael−Aldol−Epoxidation/Elimination Reaction[126]



Diastereoselectivities were excellent with both compounds, but yields and enantioselectivities were better with the ketosulfones (48−95% yield, 90−99% ee) than with the diketones (41−87%, 64−91% ee). Gryko has reported a proline-catalyzed version of this reaction, using β-diketones and methyl vinyl ketone as starting materials.[125] In this approach, the stereochemistry is determined later, at the enamine-catalyzed aldol step. This seemed to result in somewhat lower enantioselectivities (43−80% ee), although the yields were generally acceptable (39−93%). In addition, diketones with different aromatic substituents afforded products with good regioselectivity (1:14 or higher).

Jørgensen and co-workers also reported a domino Michael−aldol−epoxidation/elimination reaction (Scheme 100).[126] The Michael and aldol steps proceeded in the usual iminium−enamine-activated manner, yielding the intermediate **449** with a single stable stereocenter. The authors presumed the aldol step to be base-catalyzed and reversible. After the completion

Scheme 101. Enanatioselective Domino Cyclization of Enals and β-Ketoesters[127]



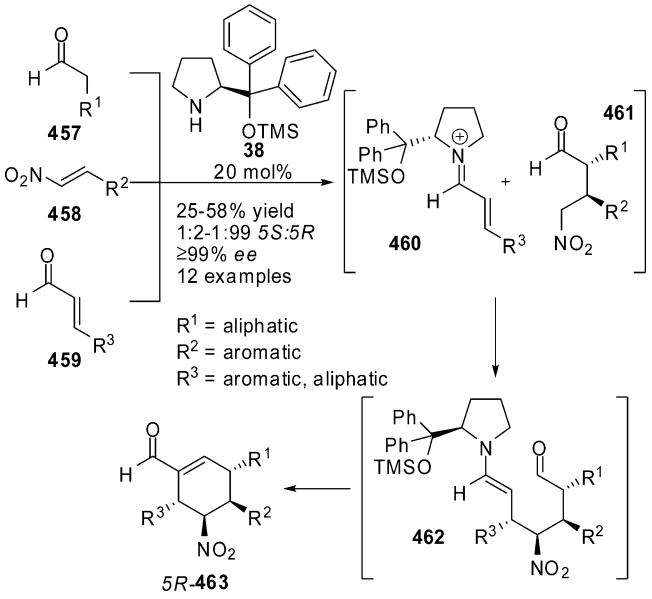
of the aldol step, deprotonation of the hydroxyl group by a stronger base K_2CO_3 triggered the epoxidation. The excellent diastereoselectivity observed in this reaction ensues from the fact that, for the epoxide formation to proceed, both the chloride and hydroxyl groups need to be in axial positions. In addition, the conformation having the R^1-substituent equatorial is strongly favored. The reaction affords epoxides **451** with moderate yields and good enantioselectivities. If intermediate **449** is treated with triethylamine and a drying agent instead of K_2CO_3, a molecule of water is eliminated by an E1cB mechanism, yielding the condensation product **450**.

In 2006, Jørgensen and co-workers reported an extension of their studies on domino cyclizations with β-ketoesters.[127] The recent studies focused on finding environmentally friendly reaction conditions. A conjugate addition catalyzed by **39** afforded the acyclic intermediate **454** in high ee, which upon addition of acid went through ester hydrolysis, decarboxylation, and aldol ring-closure. **455** was obtained in acceptable yields and generally good ee's (Scheme 101). The reactions were performed in neat conditions, without any additional solvent. Interestingly, performing the first part of the reaction in beer (sic!) instead of water afforded the conjugate addition intermediate in a slightly better yield and ee (90% vs 98% yield and 94% vs 96% ee).

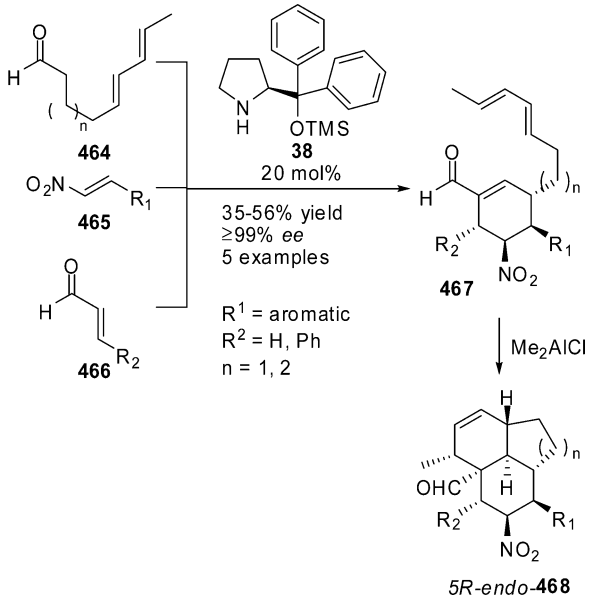
Enders and co-workers have published a method for preparing tetrasubstituted carbaldehydes **463** from three achiral starting materials (Scheme 102).[222] Catalyst **38** was able to catalyze every step of the reaction. First, the catalyst and aldehyde **457** form an enamine that adds to nitroalkene **458**. Then the catalyst forms an iminium ion with enal **459**, and the newly formed nitroalkane **461** adds to iminium **460** in a conjugate fashion. Finally, the resulting enamine **462** undergoes an intramolecular aldol addition with the aldehyde, forming the cyclic product **463**.

The chemoselectivity of the first step of the reaction was explained by nitroalkene **458** being a better Michael acceptor than enal **459**. The final product **463** also is a Michael acceptor, but the nitroalkane reacts preferentially with the sterically less-hindered iminium intermediate **460** in the second step. The enantioselectivities were excellent, and the diastereoselectivities were fairly good with an average of 1:5 5*S*/5*R*. Only two diastereomers were formed in the reaction, out of the numerous possibilities. These differ in

Scheme 102. Cyclic Carbaldehydes via an Asymmetric Triple Domino Reaction[222]



Scheme 103. Asymmetric Triple Domino Reaction Coupled with a Lewis Acid-Catalyzed Diels−Alder Reaction[223]

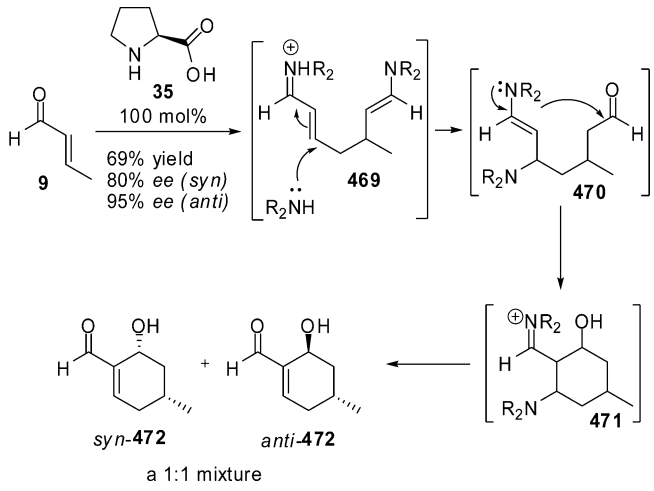


the configuration of the nitro group at the 5-position. The yields were generally modest, and lower yields were obtained if the R^3-substituent on the enal was aliphatic (25−29% yield). Besides aromatic aldehydes, acrolein also afforded good results (50% yield). The substituent on nitroalkene **458** was required to be aromatic.[222]

Recently, Enders and co-workers reported an extension to the three-step domino sequence that includes a Lewis acid-catalyzed Diels−Alder reaction performed in the same pot.[223] One of the starting materials possesses a diene moiety able to react in the Diels−Alder reaction. The first part of the sequence is identical to the previously reported carbaldehyde synthesis, yielding intermediate **467**. Catalyst **38** was not able to catalyze the Diels−Alder reaction, possibly because of the steric hindrance of the highly substituted aldehyde intermediate. However, the Diels−Alder reaction could be activated by adding an excess of the Lewis acid Me_2AlCl after completion of the organocatalytic part of the sequence. The reaction afforded the tricyclic product **468** with moderate yield and excellent stereoselectivity (Scheme 103). A total of eight stereocenters were formed in a single operation. The Diels−Alder reactions leading to the formation of three 6-membered rings ($n = 2$) were fully diastereoselective. On the other hand, the reactions leading to the formation of one 5-membered ring ($n = 1$) yielded two diastereomers. In addition, one diastereomer (5*S*/5*R*) originated from the earlier reaction steps.

Hong and co-workers have also published iminium-activated domino cyclizations of enals, using typically 1 equiv of amine, such as proline or pyrrolidine.[224,225] Among these were formal [2+4]-additions similar to those previously reported by Liu and Asato (see Schemes 81C and 90).[213] However, in these studies, two different enals were also coupled selectively, instead of performing only dimerizations. In addition, formal [3+3]-cycloadditions were disclosed.[226] The authors suggest that these reactions proceed through a Morita−Baylis−Hillman-type mechanism involving a total of three amine molecules in the second addition step (Scheme 104). This reaction type only prevails with relatively small enals, such as crotonaldehyde. Larger enal substrates favor the simpler [2+4]-addition pathway.

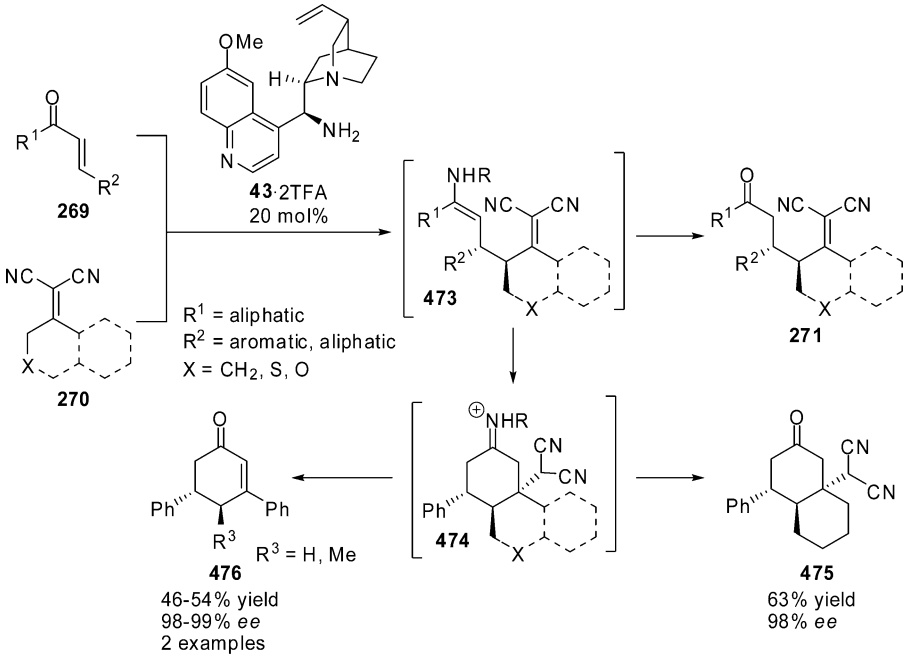
Scheme 104. Formal [3+3]-Dimerization of Crotonaldehyde[226]



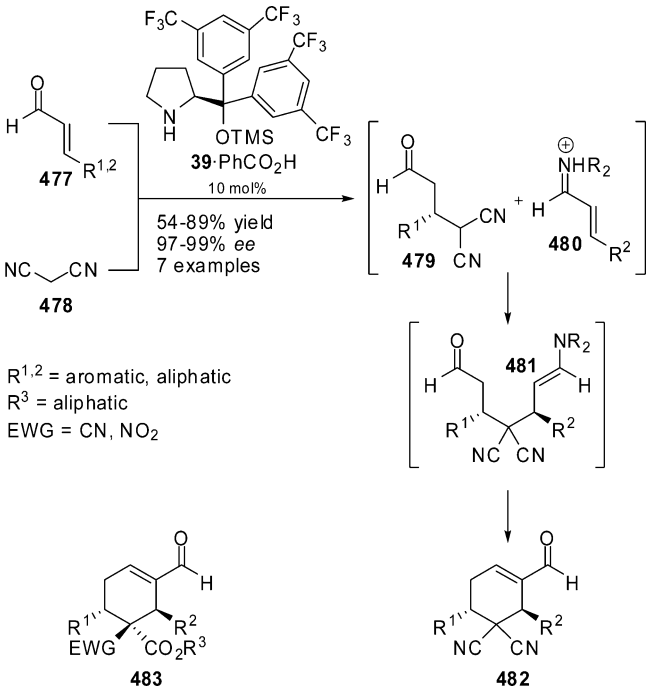
Chen and co-workers studied asymmetric conjugate additions of vinylogous enolates of α,α-dicyanoalkenes to enones.[122] The aim of the work was to perform double conjugate additions catalyzed by the primary amine **43**, affording cyclic dicyanoketones of the type **475** as products. However, most reactions stopped after the first step, likely because of steric reasons, affording conjugate addition products **271**. These reactions have been discussed in section 4.2.5. On the other hand, small dicyanoalkenes reacted with 4-phenylbutenone even further than expected, cleaving malononitrile in a final retro-Michael-type transformation, yielding cyclic enones **476** as products (Scheme 105). The reaction had excellent stereoselectivities but modest yields. The final reaction steps could also be promoted by smaller primary amines such as $BnNH_2$ in a separate step, which enabled the use of larger dicyanoalkenes as reaction substrates. In addition, with 2-cyclohexylidenemalononitrile, the reaction stopped after the two Michael steps, affording ketone **475** as the product (63% yield, 98% ee).

Jørgensen and co-workers published a domino double Michael reaction using activated methylene compounds as the nucleophiles (Scheme 106).[227] The methylene compound

Scheme 105. Primary Amine-Catalyzed Asymmetric Triple Domino Reaction Using Dicyanoalkenes[122]

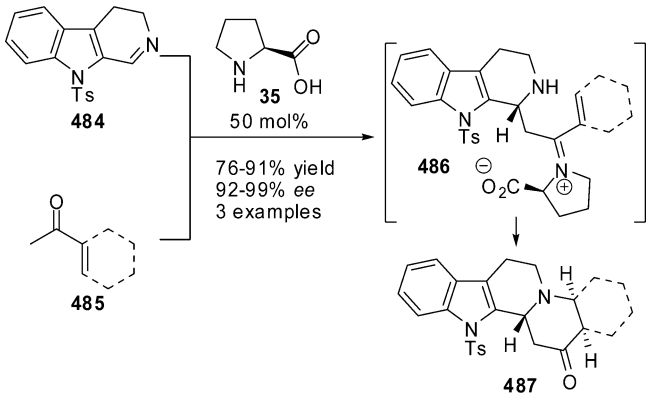


Scheme 106. Enantioselective Double Michael Reactions of Malononitriles[227]



first reacts with the iminium ion of the catalyst and enal **477**. The intermediate adduct **479** is able to add to yet another intermediate iminium ion **480**, forming a product that immediately cyclizes via an intramolecular aldol reaction. Product **482** was obtained with an excellent enantioselectivity and as a single diastereomer. Generating products with two different R-substituents regioselectively was also possible if R^1 was bulkier than R^2 and if the enal bearing the R^2-substituent was added to the reaction mixture after the first reaction had proceeded to completion (51−52% yield, 97−99% ee, 2 examples). The possibility of using methylene compounds with two different electron-withdrawing groups was also investigated. Cyano- and nitroesters afforded **483** as the main diastereomer with excellent enantioselectivity

Scheme 107. Proline-Catalyzed Reaction of 9-Tosyl-3,4-dihydro-β-carboline with Enones[229]

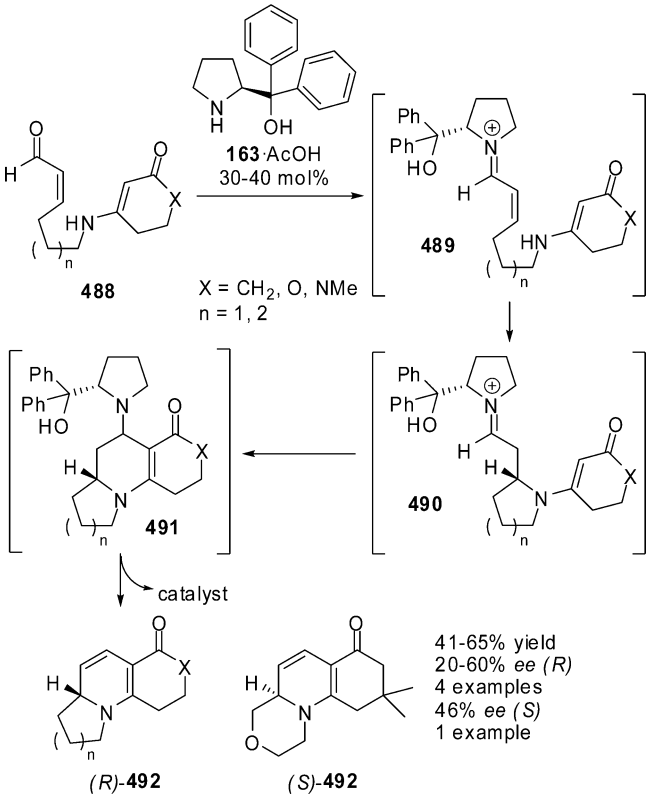


but modest yield and varying diastereoselectivity (40−53% yield, 1:1.5−1:49 dr, 98−99% ee, 4 examples). The best diastereoselectivities were obtained with bulky substituents.

6.1.3.2. Heterocyclic. Ohsawa and co-workers reported a proline-catalyzed asymmetric addition reaction between 9-tosyl-3,4-dihydro-β-carboline **484** and different ketones in 2003.[228] The proline reacts first with the ketone, forming an enamine that reacts with the imine moiety of the carboline. With enones such as **485**, the initial amine adduct **486** undergoes a conjugate addition to the simultaneously formed iminium ion (Scheme 107).[229]

In 2005, Hsung and co-workers disclosed a formal intramolecular aza-[3+3]-cycloaddition using vinylogous amides **488** (Scheme 108).[149] Several C_1- and C_2-symmetric catalysts were tested in the reaction, including catalyst **36** and imidazolidinones **29** and **33**. However, diphenylprolinol **163** proved to be the best catalyst with a 60% yield and a 62% ee (*R*) in the test reaction. The yields and enantioselectivities were of the same order of magnitude with all the tested amides **488**, except for the one having a shorter carbon tether of only three atoms ($n = 1$). This amide afforded only a 20% ee. The enantioselectivity was opposite, leading to the formation of (*S*)-**492** in one occasion. C_2-symmetric catalysts also favored the formation of the (*S*)-product.

Scheme 108. Formal Iminium-Catalyzed Intramolecular [3+3]-Cycloaddition[149]

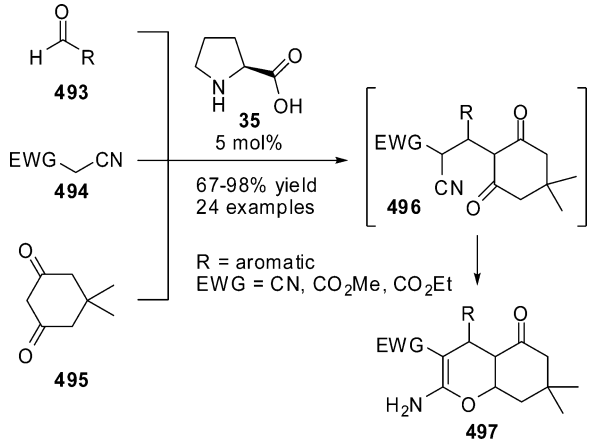


The authors observed that the *Z*/*E*-isomerism of amide **488** had no effect on the ee of product **492**. Possible racemization through electrocyclic ring opening and closure could also be excluded. The NMR spectra indicated that the intermediate **491** consisted of only two diastereomers. This led the authors to believe that the stereochemistry was determined in the earlier 1,4-addition step. The selectivity was also studied by computer simulations. In addition, a vinylogous amide containing a methyl group in the α-position of the aldehyde was synthesized. In this case, the reaction was slow and, although the diastereoselectivity was good, the product was racemic. This was probably due to the noncatalytic background reaction.

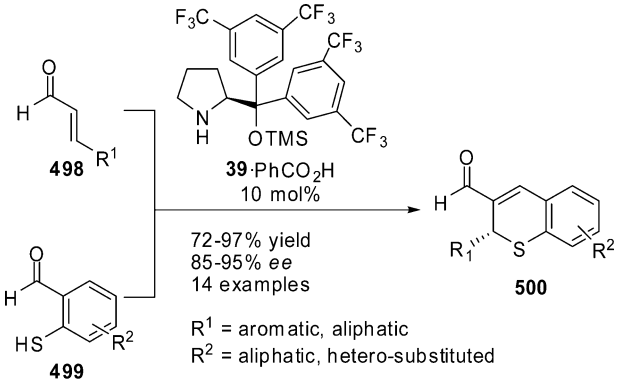
Balailae and co-workers reported a proline-catalyzed domino Knoevenagel−cyclization reaction in 2006. They used aromatic aldehydes **493**, activated methylene compounds **494**, and dimedone **495** as starting materials (Scheme 109).[230] The authors suggest that the first step is an iminium-activated Knoevenagel condensation between the aldehyde and the methylene compound, followed by a conjugate addition by dimedone. This intermediate would then undergo a cyclization, affording **497** as the product. The product is obtained as racemate, but the yields are good and only a small amount of catalyst is required for the reaction to proceed.

In 2006, Wang and co-workers disclosed a method for preparing thiochromenes **500** using a domino reaction catalyzed by **39**.[169] Thiol **499** reacts with the iminium ion of enal **498** in a conjugate fashion, after which the formed enamine adds to the benzaldehyde moiety (Scheme 110). An acid cocatalyst improved both yields and enantioselectivities. The optimized reaction conditions also included addition of 4 Å molecular sieves and using toluene as the solvent. The reaction afforded thiochromenes with good yields and

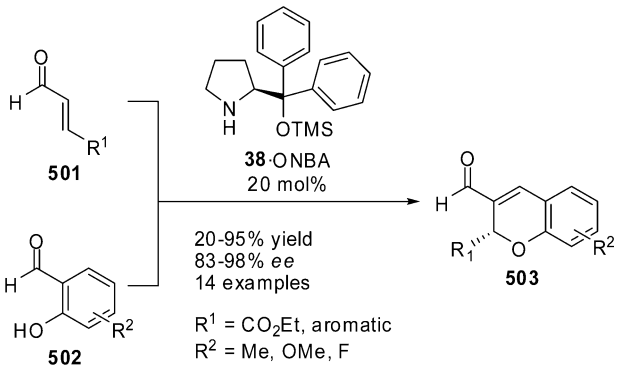
Scheme 109. Proline-Catalyzed Domino Knoevenagel−Cyclization[230]



Scheme 110. Thiochromenes by an Enantioselective Domino Reaction[169]



Scheme 111. Chromenes by an Enantioselective Domino Reaction[185]

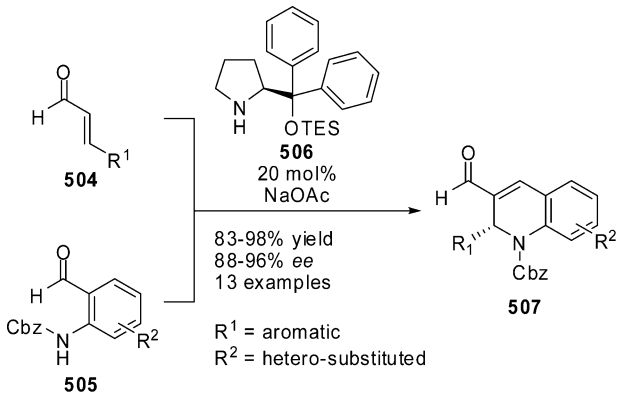


enantioselectivities. Córdova and co-workers have also obtained comparable results under similar reaction conditions.[170]

Simultaneously, Córdova and co-workers reported the preparation of chromenes **503** by a corresponding domino reaction starting from 2-hydroxybenzaldehydes **502** (Scheme 111).[185] The acid cocatalyst proved to be essential for a high enantioselectivity in this reaction as well. The ee of a test reaction was increased from 9% to 88% by the addition of 2-nitrobenzoic acid, and 4 Å molecular sieves improved the yields.

Also in 2006, Arvidsson and co-workers published a similar reaction sequence catalyzed by **38** (10 mol %).[186] The chromene products were obtained in modest yields (14−70%) and moderate enantioselectivities (27−90% ee). A variety of acids and bases were tested as additives, but

Scheme 112. Dihydroquinolines by an Enantioselective Domino Reaction[231]



the results were not satisfactory. 4-chlorobenzoic acid increased the ee 20% (to 72% ee) in the test reaction, but with concomitant reduction in the yield. Córdova and co-workers had encountered the same difficulty, but they compensated for it by applying molecular sieves and changing the solvent from chloroform to toluene. Most recently, Wei and co-workers also reported a domino synthesis of chromenes using TES-protected diphenylprolinol as the catalyst.[187] The reaction afforded chromenes with good yields and enantioselectivities (53−98% yield, 75−99% ee). Enals with electron-withdrawing substituents were found to give the best results.

Recently, Wang and co-workers also published a similar domino reaction sequence for preparing 1,2-dihydroquinolines **507** from enals **504** and *N*-protected 2-aminobenzaldehydes **505**.[231] The products were obtained in very good yields and ee's (Scheme 112). However, the enals **504** in Scheme 112 are all aromatic. Alkyl-substituted enals (R^1 = Me, CH_2OBn) reacted well with tosyl-protected 2-aminobenzaldehyde, affording 86% yield and 91−92% ee. The base additive was noted to be essential for obtaining good yields. In addition, 4 Å molecular sieves were found to facilitate the final dehydration step.

Córdova and co-workers also disclosed a version of this reaction using 2-mercaptobenzaldehydes and cyclic enones as starting materials instead of enals.[171] The reaction was catalyzed by prolinol **508** or diamine **346** (Figure 15),

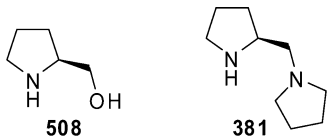
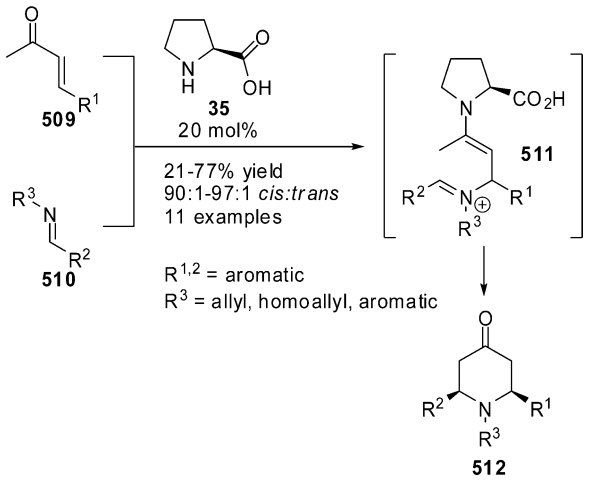


Figure 15. Catalysts for preparation of tetrahydrothioxanthenones.[171]

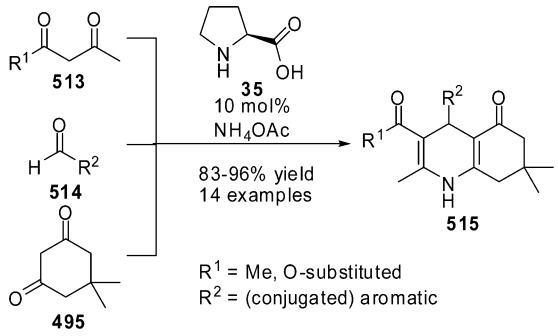
affording tricyclic tetrahydrothioxanthenones as the products. However, the enantioselectivity of this reaction was only moderate at best (38−67% ee). Recently, the same group also reported a corresponding route to tetrahydroxanthenones starting from 2-hydroxybenzaldehydes and enones.[188] The products were obtained in good ee's (85−91% ee) but modest yields (51−56%).

Aznar and co-workers reported a proline-catalyzed formal imino−Diels−Alder reaction.[232] The formation of the prochiral cis-product **512** was strongly favored under all conditions. Preparation of chiral products with different aryl groups was also attempted, but the products were obtained racemic. Nevertheless, the diastereoselectivity was excellent. As for

Scheme 113. Proline-Catalyzed Formal Imino−Diels−Alder Reaction[232]



Scheme 114. Organocatalytic Hantzsch Reaction[233]



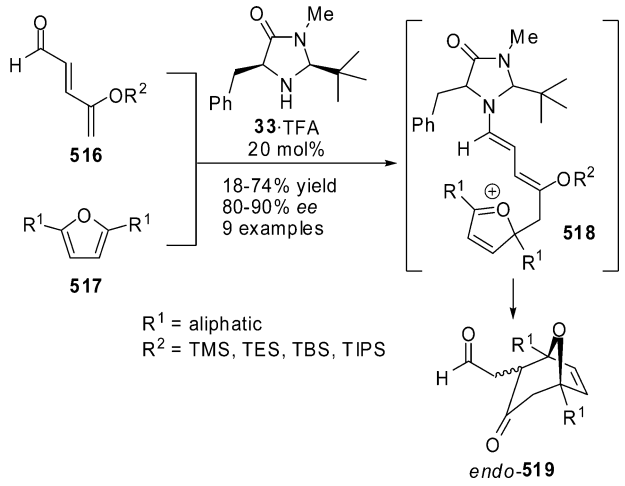
the reaction mechanism, the authors suggested that the enamine of the catalyst and the enone would undergo a Diels−Alder reaction with the imine. This is a valid suggestion, but we feel that there also is a possibility that this reaction might proceed in a stepwise manner, via an iminium-activated domino mechanism as depicted in Scheme 113.

Kumar and Maurya published a proline-catalyzed unsymmetric Hantzsch reaction (Scheme 114).[233] The reaction was tested in both ethanol and water, but the best results were obtained in neat conditions. The authors suggest that the reaction begins with a proline-catalyzed Knoevenagel condensation between the aldehyde **514** and either of the dicarbonyl compounds **513** or **495**. Simultaneously, the amine salt forms an enamine with the other dicarbonyl compound. Finally, the intermediates react with each other in a Michael-type reaction. Without any catalyst, polyhydroquinolines and adduct of the aldehyde and dimedone was obtained. The chemoselectivity of the reaction was excellent, but the product was formed as a racemate.

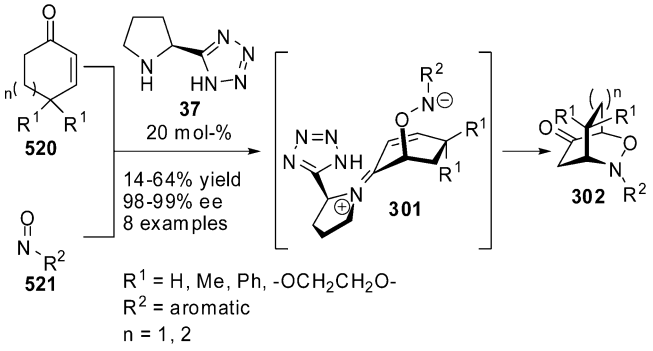
6.1.4. Other Ring Sizes

Harmata and co-workers disclosed a formal [3+4]-cycloaddition reaction between 2,5-disubstituted furans **517** and silyloxypentadienals **516**.[234] The bicyclic products **519** were obtained with good stereoselectivities and acceptable yields (Scheme 115). The reaction most likely proceeds via a stepwise domino mechanism. When a 2-monosubstituted furan was used as the starting material, the reaction stopped at the intermediate **518,** and an alkylation product was obtained. Unsubstituted furan afforded only trace yields of products. 3,4-fused 2,5-diphenylisobenzofuran afforded a

Scheme 115. Formal Asymmetric [3+4]-Cycloaddition[234]



Scheme 116. Asymmetric Domino *O*-Nitroso Aldol−Conjugate Addition[173]

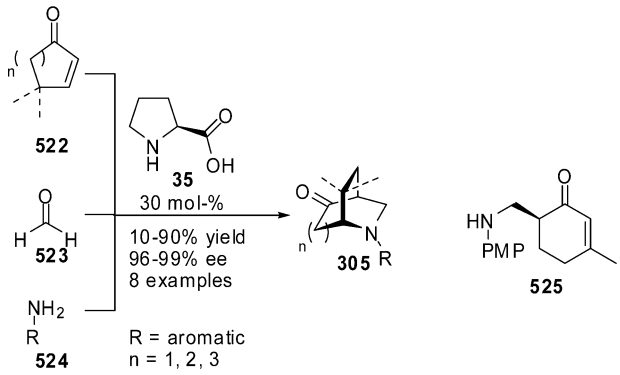


mixture of endo- and exo-products (56% yield, 3.7:1 endo/exo) with modest enantioselectivities (12% endo ee, 68% exo ee).

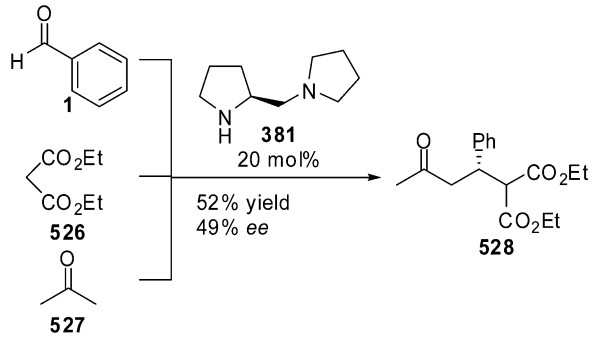
Yamamoto and co-workers reported a domino *O*-nitroso aldol−conjugate addition reaction using cyclic enones **520** and aromatic nitroso compounds **521** (Schemes 65 and 116).[173] The pyrrolidine-based tetrazole catalyst **37** forms an enamine that adds to the oxygen atom of **521**. The authors suggest that the resulting iminium ion **301** exists in a boat form, with the aminoxy group being in an axial position on the convex side of the boat. This places the nitrogen atom in an optimal position for a conjugate addition to the iminium moiety. The aldol part of this reaction could also be promoted by a silver catalyst. However, no metal, acid, or base catalyst seemed to be able to promote the subsequent cyclization. On the contrary, the organocatalytic reaction afforded bicyclic products with moderate yields and excellent enantioselectivities. In the case of heptenone ($R^1 = H$, $n = 2$), better yields were achieved with a proline catalyst **35** (51%) than with tetrazole **37** (14%). Shortly afterward, Hayashi and co-workers[235] as well as Adolfsson and Córdova and co-workers[236] also reported this reaction type in their articles discussing organocatalytic α-aminoxylations.

In the following year, Córdova and co-workers published an analogous formal aza-Diels−Alder addition, in which imines were used instead of nitroso compounds (Schemes 65 and 117).[174] The imines were formed in situ from formaldehyde **523** and anilines **524**. The reaction was proline-catalyzed, affording azabicycloketones **305** as products in varying yields and high enantioselectivities. Cyclopentenone as the enone and *p*-halogen-substituted anilines gave the

Scheme 117. Enantioselective Domino Imine Aldol−Conjugate Addition[174]



Scheme 118. Domino Knoevenagel−Conjugate Addition[237]



poorest yields (10−32%). A β-substituted enone did not react past the first step, affording the Mannich adduct **525** as the only product (40% yield, 94% ee).

6.2. Intermolecular Domino Reactions

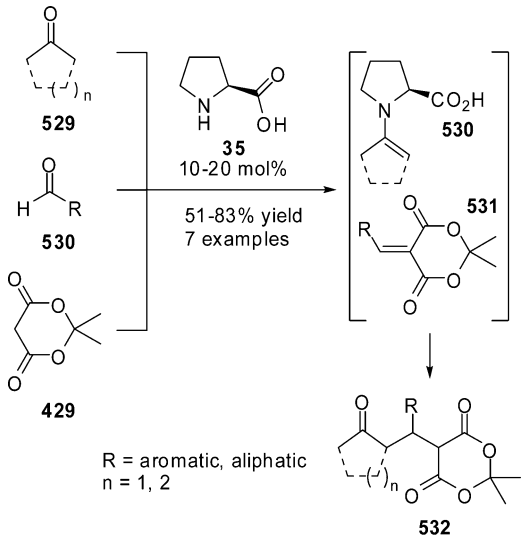
Barbas and co-workers reported a domino Knoevenagel−conjugate addition reaction in 2001.[237] The main subject of the article was amine-catalyzed conjugate additions of acetone **527** to alkylidene malonates. However, it was noted that the diamine **381** also catalyzed the formation of the alkylidene malonates from benzaldehyde **1** and diethyl malonate **526** in the same pot. The reaction sequence afforded **528** with a moderate yield and ee (Scheme 118).

Shortly after, List and co-workers expanded the Knoevenagel−conjugate addition methodology to various aldehydes **530** and Meldrum's acid **429**, using proline **35** as the catalyst (Scheme 119).[238] Products **532** were obtained racemic; ee's < 5% were reported. In addition to acetone, the reaction was also performed with cyclopentanone and cyclohexanone. These products were obtained in moderate yields (69−75%) and as single diastereomers.

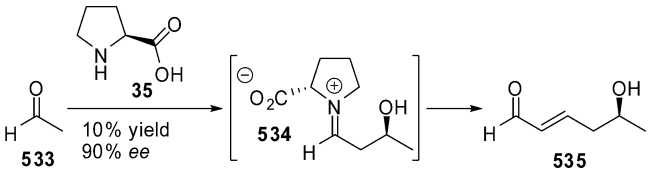
In 2002, Barbas and co-workers also disclosed a proline-catalyzed trimerization of acetaldehyde **533**.[239] The first step of the sequence is a standard enamine-activated asymmetric aldol reaction. However, the authors suggest that the intermediate iminium ion **534** would not be hydrolyzed after the first step but would instead react further in a Mannich-type condensation. Optimized reaction conditions afforded **535** with a poor yield but a good ee (Scheme 120).

Nakamura and Yamamoto reported a domino α-methylenation−Diels−Alder reaction between cyclic ketones **537** and dienes **541** in 2002 (Scheme 121).[240] The first reaction step consists of the diamine **536** forming an enamine **538** with the ketone and the MOM (methoxymethyl) chloride. The enamine attacks intramolecularly to the MOM chain.

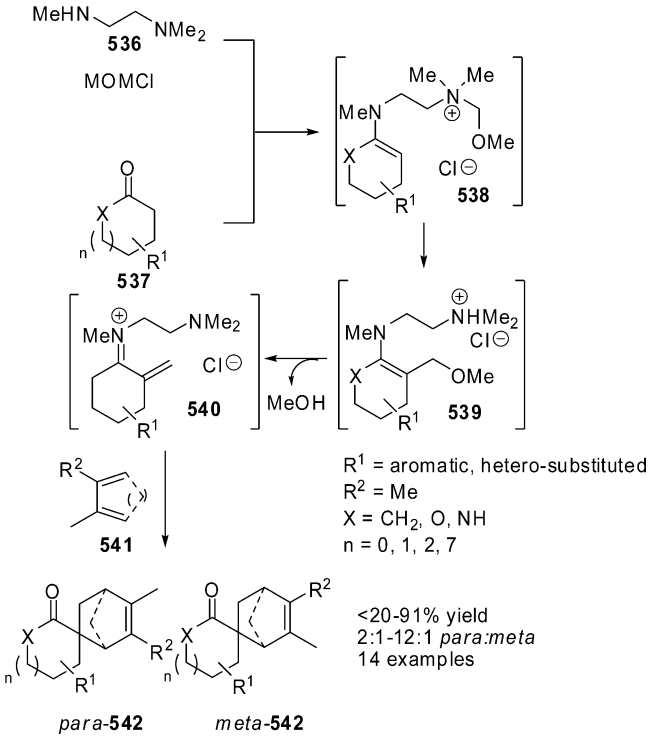
Scheme 119. Domino Knoevenagel−Aldol Reaction[238]



Scheme 120. Asymmetric Aldol−Mannich Sequence[239]

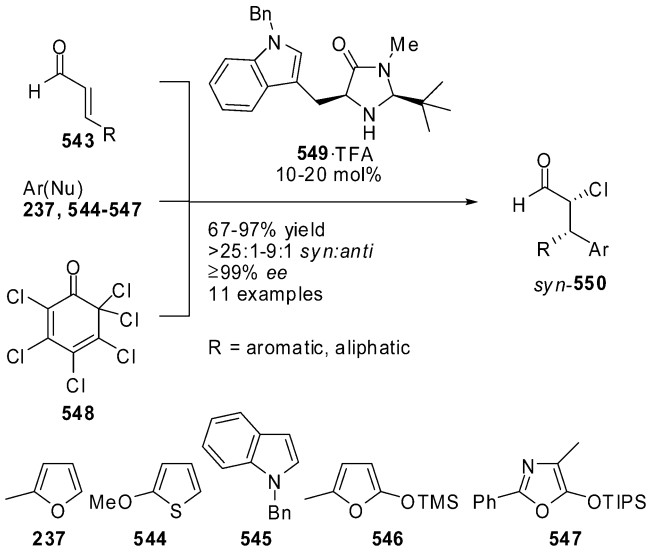


Scheme 121. Domino α-Methylenation Diels−Alder Reaction[240]



Subsequently, a molecule of methanol is cleaved when the enamine converts to the iminium ion **540**. The resulting 2-methylene iminium ion is able to react with the diene added to the reaction mixture, forming spiranones **542**. This reaction is not strictly catalytic, because a stoichiometric amount of the diamine is used. Nevertheless, the reaction is a good example of iminium activation, as the unactivated 2-methylenecyclohexanone was completely unreactive toward dienes in the reaction conditions.

Scheme 122. Enantioselective Domino Conjugate Addition−Halogenation[154]

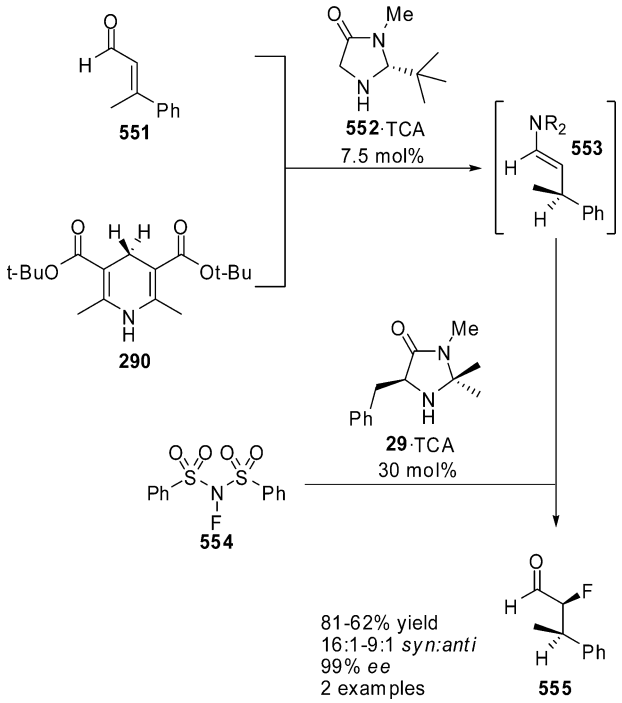


MacMillan and co-workers published a domino conjugate addition−halogenation reaction in 2005 (Scheme 122).[154] Heteroaromatic nucleophiles **237** and **544**−**547** add in a conjugate fashion to the iminium ion of enal **543** and amine catalyst **549**. Afterward, the same catalyst forms an enamine that will react with electrophiles, such as the chlorination reagent **548**. Product **550** is formed with high stereoselectivities and generally good yields.

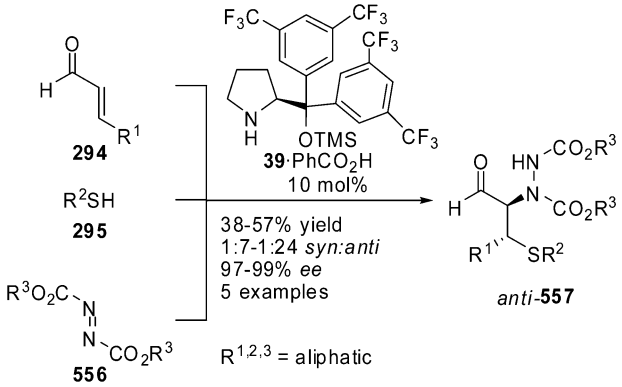
In the same article, MacMillan and co-workers also reported a domino reduction−halogenation reaction, in which a molecule of HF or HCl is formally added to enal **551**.[154] The first step of the sequence was an iminium-activated conjugate reduction, in which the Hantzsch ester **290** served as the hydride donor. The entire sequence could be catalyzed by imidazolidinone **552**. H and F were syn (3:1 syn/anti), and H and Cl were anti (1:8 syn/anti) in the major products. The stereocenters could also be controlled separately, if the second catalyst **29** was added along with the halogen transfer reagent **554** after the first reaction went to completion (Scheme 123). However, a fourfold amount of the catalyst was required as compared to the first catalyst. Therefore, the stereochemistry of the second addition was controlled by the catalyst instead of the substrate. The yields and enantioselectivities were of the same order of magnitude in both single- and double-catalyst methods. Slightly better diastereoselectivities were obtained if two different catalysts were used.

Simultaneously with the MacMillan study, Jørgensen and co-workers disclosed a domino reaction between an enal **294**, a thiol **295**, and an azodicarboxylate **556** (Scheme 124).[167] The reaction was catalyzed by the prolinol-derivative **39**. The authors had started their work by studying the iminium-activated enantioselective conjugate addition of the thiol to the enal. The next task was to subject the formed enamine intermediate for reaction with the azodicarboxylate electrophile. According to Jørgensen, hydrolysis of the iminium ion derived from the first step was slow, leading to a low concentration of the free catalyst. In fact, the rate of the first step was observed to accelerate when the addition reaction was included as a part of a domino sequence. The final product **557** was sterically very demanding, and the hydrolysis of the catalyst became more favored. The diastereose-

Scheme 123. Enantioselective Formal Addition of HF to an Enal[154]



Scheme 124. Asymmetric Domino Iminium/Enamine−Addition Reaction[167]



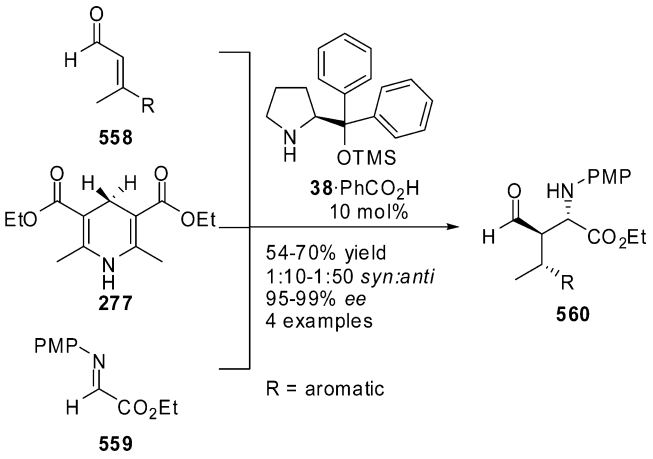
lectivity of the reaction was good, and the enantioselectivity was excellent. The reaction was tested with simple aliphatic starting materials (R^{1-3} = Me, Et or Bn).

In 2006, Córdova and co-workers published a domino reduction−α-addition of enals (Scheme 125).[165] The first step was a conjugate reduction using the Hantzsch ester **277**, and the second was a Mannich-type addition of the resulting enamine to electrophilic *N*-protected α-iminoglyoxylate **559**. The prolinol-derivative **38** was used as the catalyst in 10 mol % quantities. Moderate yields and good stereoselectivities were achieved in the reaction (54−70% yield, 1:10−1:50 syn/anti, 95−99% ee, 4 examples). The diastereoselectivity of the reaction could be reversed if (*R*)-proline was added along with the imine electrophile in the second reaction step (80% yield, 5:1 syn/anti, 96% ee).

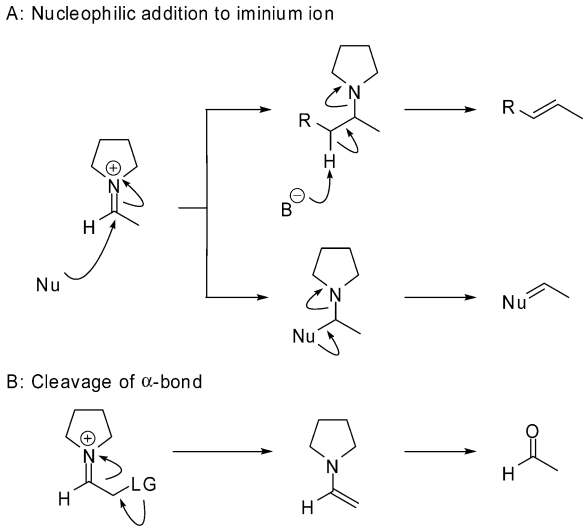
7. Iminium-Catalyzed Reactions of Saturated Carbonyl Compounds

In addition to the cyclo- and conjugate additions to enals and enones, there are several other reaction modes that fall

Scheme 125. Asymmetric Domino Conjugate Reduction−Mannich Reaction[165]



Scheme 126. Modes of Iminium Catalysis with Saturated Carbonyl Compounds



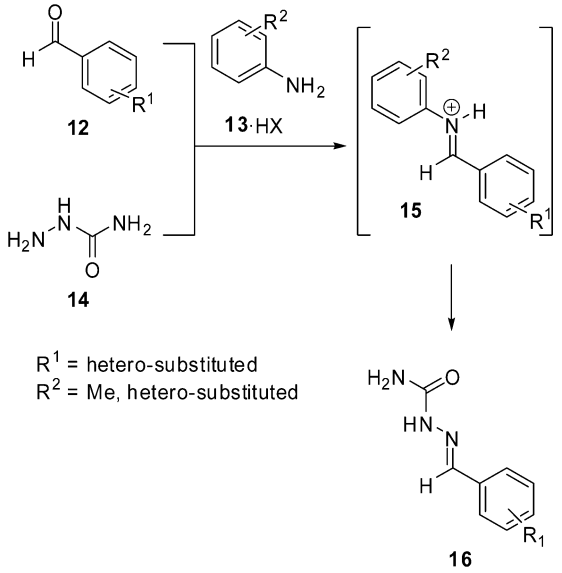
under the definition of iminium catalysis. In general, these reactions can be divided into three subgroups: (i) iminium-promoted 1,2-additions to carbonyl compounds that are followed by elimination of the formed Mannich base, (ii) iminium-promoted amination of carbonyl compounds that proceed via transimination of the iminium catalyst complex, and (iii) cleavage of the C−X α-bond of iminium, forming a carbonyl compound (a special case of this type of enamine formation is the cleavage of the C−H α-bond, often leading to enamine-promoted reactions). All these reactions lead to formation of a C=C or C=N double bond either in the product or at the intermediate state (Scheme 126).

7.1. Transamination

In 1962, Jencks and co-workers described an aniline-catalyzed semicarbazone (imine) formation from benzaldehydes **12** that proceeds via transamination of the iminium ion formed between the starting material and the aniline catalyst **13** illustrated in Scheme 127.[37] They performed exhaustive kinetic experiments to confirm the existence of the iminium intermediate.

More than 40 years later, Dawson and co-workers utilized anilines as iminium catalysis in oxime ligation.[241] They applied the aniline catalyst to the ligation of two unprotected peptides **561** and **562** at pH 4.5 (Scheme 128). The time

Scheme 127. Aniline-Catalyzed Imine Formation[37]



required to reach 50% conversion was only 25 min, whereas in the absence of the aniline catalyst, the same conversion was achieved in 310 min.

Subsequently, Dawson and co-workers investigated the use of aniline in hydrazone formation between two unprotected peptides **565** and **566** (Scheme 129).[242] The reaction rates were compared in the absence and in the presence of the aniline catalyst. On the basis of this and the interception of catalyst starting material iminium complex by reducing to the corresponding alkylated aniline, the authors proposed a similar transamination of an iminium intermediate as Jencks had suggested earlier.

7.2. Iminium Catalysis Followed by Elimination of the Amine

7.2.1. Knoevenagel Condensations

In 1894, Knoevenagel reported that condensation between formaldehyde and two molecules of diethyl malonate can be promoted by the presence of a catalytic amount of diethylamine or piperidine.[23] Two years later, he published an analogous reaction between benzaldehyde **1** and dimethyl malonate **25**.[243] In addition to condensation product **570** resulting from the reaction with two molecules of the malonate, the condensation between aldehyde and one malonate molecule to afford **569** was also promoted by piperidine at 0 °C (Scheme 130). Knoevenagel subsequently suggested a mechanism where the amine catalyst forms a covalent intermediate with the aldehyde. This intermediate would then react with malonate either once on twice.[244]

Since these early publications, this reaction type, generally known as the Knoevenagel reaction, has been under extensive investigation. Not all Knoevenagel condensations proceed via iminium intermediates since the reaction can also be catalyzed by tertiary amines and other bases that are incapable of iminium ion formation. The Knoevenagel reaction has been subject to extensive reviews, and a comprehensive review was published in 1992.[17,245] In the following discussion, amine-catalyzed Knoevenagel reactions where iminium intermediate is plausible are discussed. The coverage is limited to those reactions published in 1992−2007.

Lam and co-workers reported that the pyrrolidium acetate-catalyzed condensation of 2-hydroxybenzaldehydes with Meldrum's acid followed by subsequent lactonization can be used in the synthesis of coumarin−3-carboxylic acids (Scheme 131).[246] The reactions proceeded cleanly, providing product in good yields (61−98%). Similar solid-phase syntheses of coumarin−3-carboxylic acids have been disclosed by Watson and Christiansen.[247] They used an identical catalyst system, but the malonate was attached to the Wang resin. In a similar fashion, amine-catalyzed Knoevenagel condensation has been utilized in the proline-catalyzed synthesis of of alkylidene and arylidene malonates by Cardillo and co-workers.[248]

In 2002, Shevelev and co-workers published a synthesis of dinitrothiochromanes **575** from aromatic aldehydes **573** and the sulfonyl ester **574** derived from TNT (Scheme 132).[249] The Knoevenagel-type condensation was promoted by piperidine, affording products in varying yields.

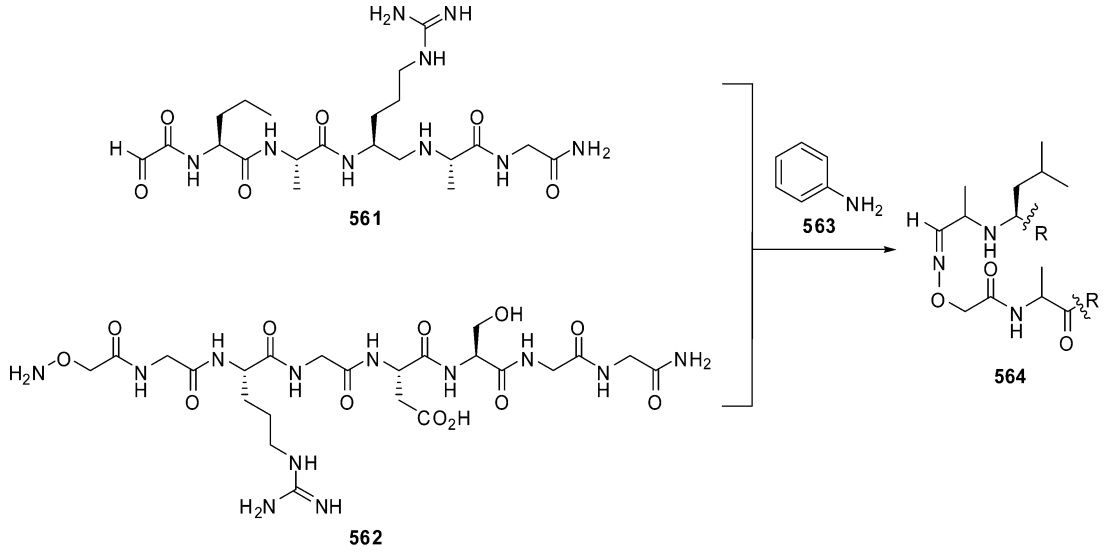
Inokuchi and Kawafuchi have reported an *E*-selective Knoevenagel condensation of aldehydes and acetoacetic derivatives (Scheme 133).[250] They investigated the effect of acylated substituents on the *E*/*Z* selectivity of Knoevenagel condensation in the presence of catalytic amounts of piperidine **3** and acetic acid cocatalyst. Bulky β-ketoamides derived from 2,2,6,6-tetramethylpiperidine (e.g., **577)** were identified to be highly favorable for obtaining the desired *E*-stereochemistry of the product. However, only cyclic aldehydes gave the desired selectivity. Interestingly, the Weinreb amide analogues of **577** favored the *Z*-isomers. Earlier, Tanikaga and co-workers had already reported *E*-selective condensations of activated methylene compounds with aldehydes.[251] The authors explained that the geometry of the condensation products is determined at the elimination step of the amine catalyst for the intermediate. They also were able to isolate the amine intermediates.

Shang and co-workers investigated proline-catalyzed Knoevenagel condensations in imidazolium-based ionic liquids. In these conditions, the presence of 10 mol % of proline promoted the reaction between diethyl malonate and several aromatic aldehydes in high yields. The use of [emim][BF_4] as the solvent produced higher yields with benzaldehydes with an electron-withdrawing group than the use of [bmim][BF_4]. However, reactions with furfural were completed faster in [bmim][BF_4].[252]

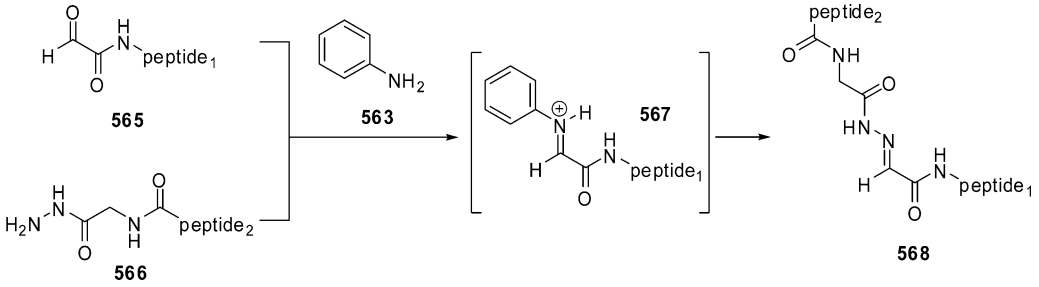
An interesting Knoevenagel-type condensation of benzaldehyde **1** with *N*-methylpyrrole **207** was published by Benaglia and co-workers in 2006.[253] Pyrrolidine HBF_4 salt promoted the formation of **579** in wet THF in 66% yield, while corresponding trimer **580** was isolated in 19% yield as a side product (Scheme 134). They also applied other aromatic aldehydes with similar results, whereas aliphatic aldehydes granted only small amounts of the product. Interestingly, when the reaction was performed with cinnamaldehyde, no evidence of formation of the conjugate addition product was observed, although MacMillan and co-workers had earlier reported that this reaction proceeds readily in the presence of a chiral oxazolidinone TFA salt **29**.[141] Instead, the condensation product corresponding to **579** was obtained in 30% yield.

Several heterogeneous amine catalysts have been developed for Knoevenagel reactions.[11] Sammelson and Kurth have covered these types of Knoevenagel reactions in their review in 2001. As such, the following discussion is limited to reactions published since 2001.[254] In a typical reaction,

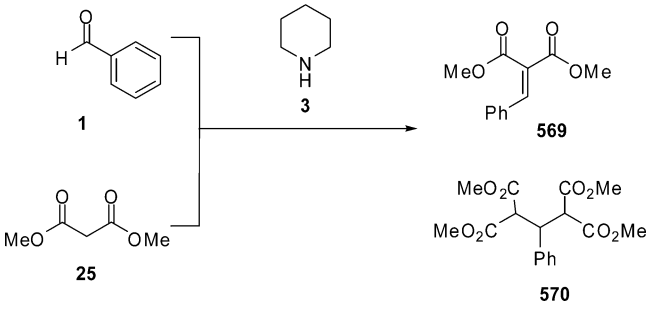
Scheme 128. Aniline-Catalyzed Oxime Ligation[241]



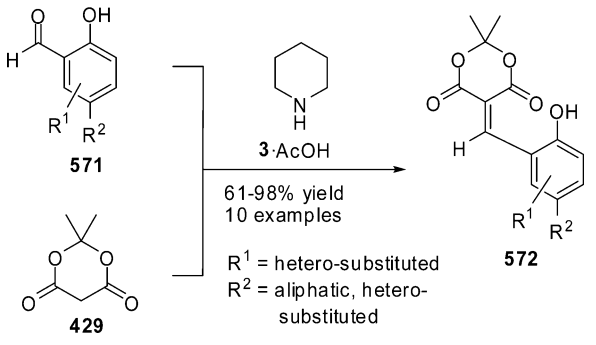
Scheme 129. Aniline-Catalyzed Hydrazone Formation[242]



Scheme 130. Piperidine-Promoted Knoevenagel Condensations[243]



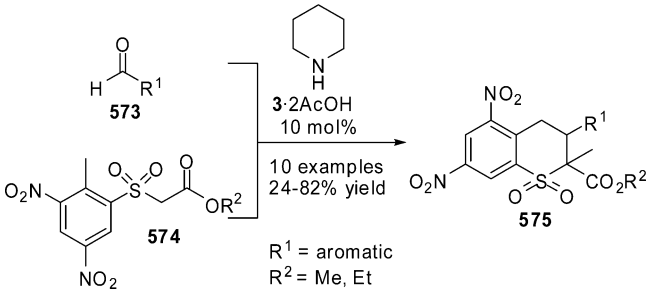
Scheme 131. Iminium-Catalyzed Condensation of Aldehydes with Meldrum's Acid[246]



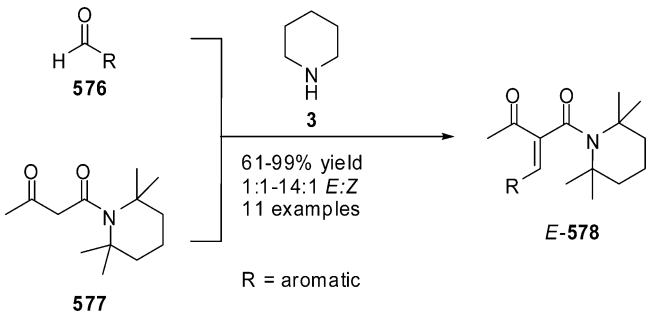
aldehydes condense with activated carbonyl compounds such as malonates, cyanoacetates, or β-ketoesters to produce the corresponding condensation products (Scheme 135).

A mesoporous silica-supported propylamine catalyst **581** (Figure 16) was utilized by Sartori's group in the condensa-

Scheme 132. Preparation of Dinitrothiochromanes from a TNT Derivative[249]



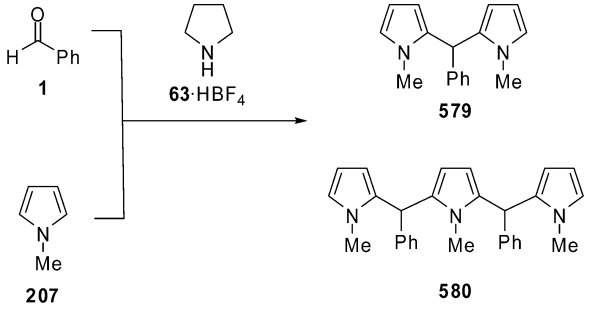
Scheme 133. *E*-Selective Knoevenagel Condensation[250]



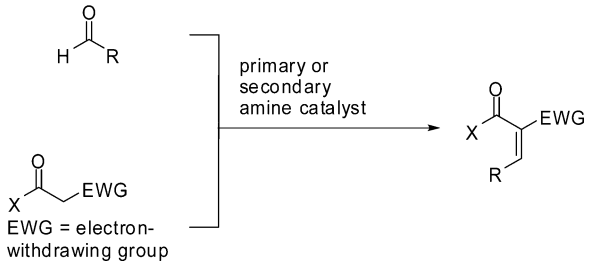
tion of aromatic aldehydes with nitroalkanes.[255] On the basis of their observation that imines are present on the silica after it has been treated with benzaldehyde, they proposed that the reaction proceeds via iminium intermediates.

Cheng and co-workers studied a mesoporous silica-supported propylamine catalyst in the reaction between ethyl cyanoacetate and ketones and benzaldehyde.[256] They reported

Scheme 134. Pyrrolidine-Catalyzed Condensation of Benzaldehyde with *N*-Methylpyrrole[253]



Scheme 135. Typical Knoevenagel Condensation



varying (50−99%) yields and clean reactions. Similar catalysts were described by Hagiwara and co-workers for the condensation of ethyl cyanoacetate with aldehydes in water.[257] In addition to primary and secondary amine catalysts capable of iminium catalysis, they also reported that tertiary amines work in this reaction. However, the reaction times were substantially longer, which may indicate a change in the reaction mechanism. The primary amines promoted condensation of ethyl cyanoacetate and malononitrile with 13 different aldehydes in good yields within 1−5 h. Much shorter reaction times were published by Rajender Reddy and co-workers, who investigated the use of chitosan hydrogel **582** as an iminium Knoevenagel catalyst (Figure 16).[258] High conversions in reactions between aromatic aldehydes and malononitrile, ethyl cyanoacetate, and diethyl malonate were obtained. The reactions took only minutes to complete. In addition, Tamami and Fadavi have investigated the use of polyacrylamine-based primary amine catalyst **583** in the Knoevenagel condensation of different aldehydes with malononitrile, cyanoacetamide, and cyanoethylacetate.[259] Simpson and co-workers used piperazine **584** on Merrifield's solid-phase resin to synthesize libraries of caffeic acid derivatives.[260] In turn, Bandgar and co-workers used morpholine absorbed on silica gel as a catalyst for the synthesis of various α,β-unsaturated nitroalkenes in good-to-excellent yields from benzaldehyde derivatives and nitroalkanes. Likewise, Macquarrie and co-workers have used amine-containing mesoporous silicas,[261] and Sullivan and co-workers have utilized modified polysilsesquioxanes[262] in Knoevenagel condensations. The groups of Ferri[263] and Katz[264] have also studied Knoevenagel reactions promoted by heterogeneous catalysts.

As an alternative to crafting the Knoevenagel amine catalyst onto a solid support, reactions with supported

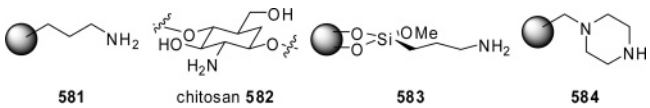
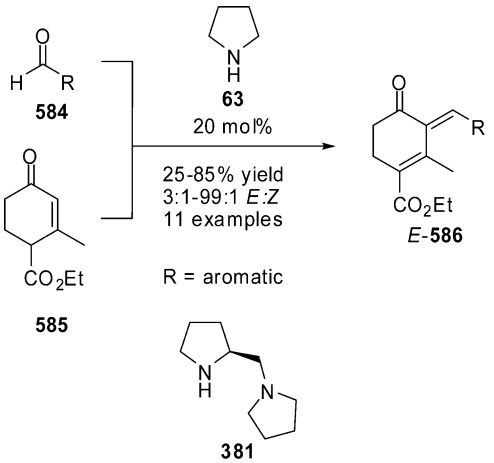


Figure 16. Heterogeneous amine catalysts capable of iminium catalysis for Knoevenagel condensations.[255,258−260]

Scheme 136. Knoevenagel Condensation of Hagemann's Esters[270]



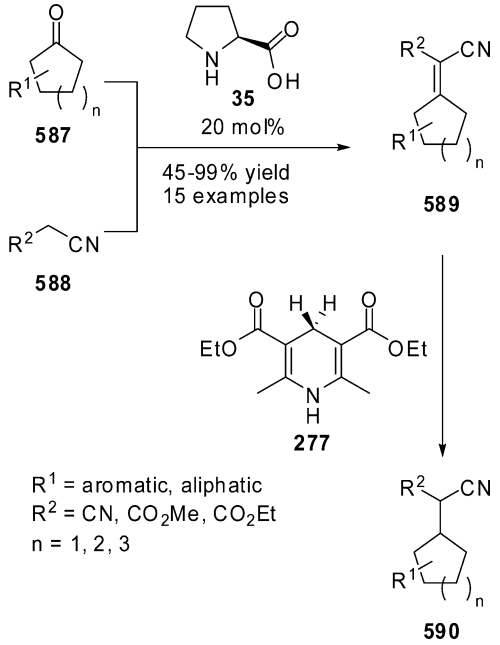
substrates have been performed as well. Ionic-liquid-supported benzaldehyde participates readily in the condensation with malonates and cyanoacetate esters with 2 mol % of piperidine.[265] Considerably higher amounts of the piperidine catalyst are required if the nucleophile is bound on solid support, as shown by Zhang and Rana. They reported the reaction between *para*-tolualdehyde and Wang resin-bound β-acetoacetamino acid to be promoted by 50 mol % of the amine catalyst and heated to 80 °C.[266] A similar reaction with polymer-bound cyanoacetatamide also required an equal amount of piperidine.[267]

Peng and Song have performed microwave- and ultrasound-accelerated Knoevenagel−Doebner reactions between malonic acid and aromatic aldehydes in aqueous media.[268] Scott and co-workers studied calorimetrically piperidine-catalyzed Knoevenagel condensations between aromatic aldehydes and activated methylene compounds.[269] The formation of the iminium intermediate was observed to be the major contribution to the exothermic nature of the condensation reaction.

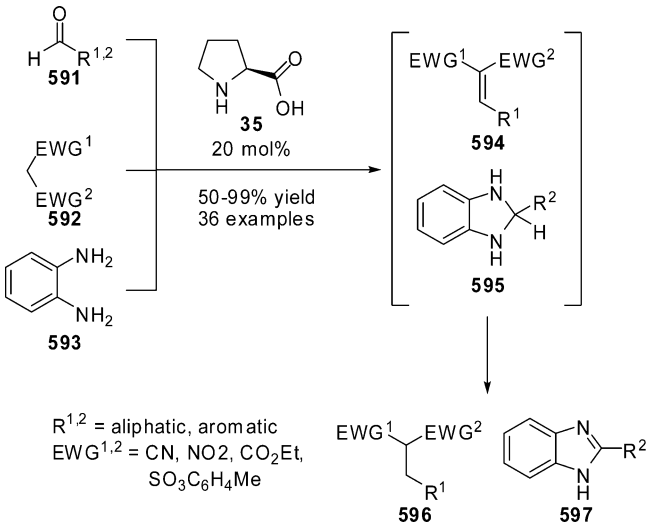
Knoevenagel condensation of Hagemann's esters with aromatic aldehydes can be catalyzed by pyrrolidine **63**.[270] Ramachary and co-workers applied this method to the synthesis of **586** (Scheme 136). The products were isolated in moderate yields. The authors suggested that the reaction proceeds either as a iminium-catalyzed Knoevenagel reaction where the ketoester reacts either as its enol form or as an enamine catalyst complex. Additionally, diamine **381** catalyzed the reactions, affording similar results. However, isomerization to the aromatic product was observed with *para*-cyano- or *para*-nitro-substituted benzaldehydes.

Sasson and co-workers reported a domino reaction composed of a catalytic Knoevenagel condensation and simultaneous hydrogenation.[271] They used ethylenediammonium diacetate as the catalyst for the condensation step. Several aromatic and aliphatic aldehydes and ketonones were condensed with a cyanoacetate ethyl ester to yield saturated substituted cyanoacetate esters in high yields (70−100%). Recently, Ramachary and co-workers disclosed similar proline-catalyzed Knoevenagel condensation cyanoacetates **588** with cyclic and acyclic ketones **587** where the formed olefin **589** is reduced in situ by the Hantzsch ester to the corresponding hydrogenated product **590** (Scheme 137).[272] A range of products could be isolated with high yields. Asymmetric and chiral ketones induced varying stereoselectivities (1.4:1−10:1) depending on the bulkiness of the

Scheme 137. Proline-Catalyzed Knoevenagel Condensation of Cyanoacetates[272]



Scheme 138. Knoevenagel Condensation Followed by a Domino Reduction[273]

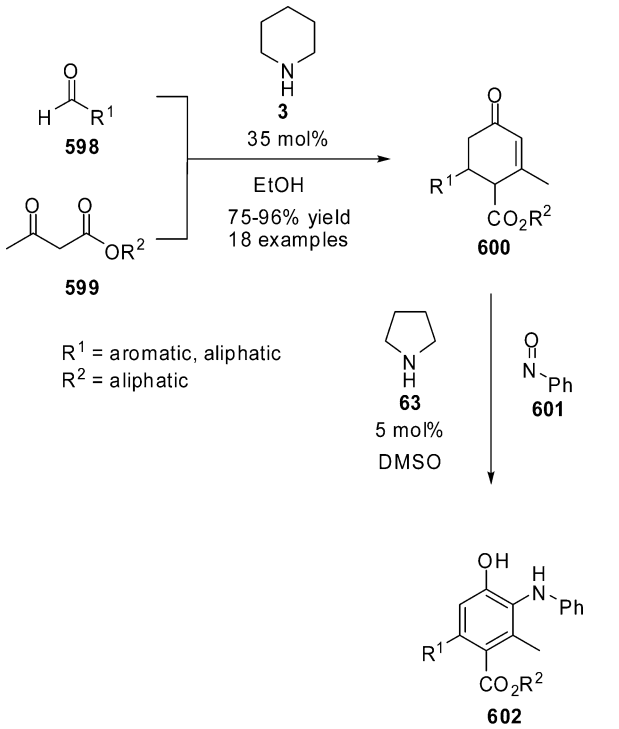


ketone. Interestingly, the authors also reported that Hantzsch ester, in the absence of iminium-forming amine catalyst, can promote the reaction in some cases.

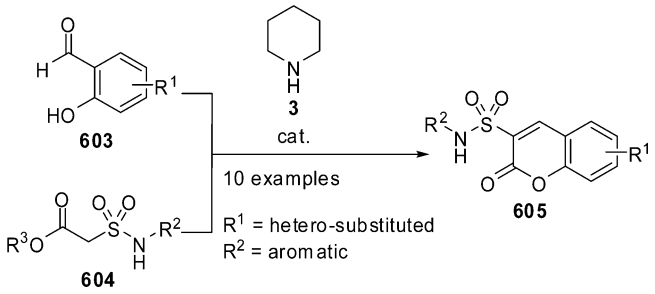
Ramachary and Reddy also reported a Knoevenagel condensation between aldehydes **591** and activated methylene compounds **592**, followed by an in situ domino reduction by the simultaneously formed side product **595** (Scheme 138).[273] The reaction also proceeded without any additional catalyst, as diamine **593** and side product **597** were sufficiently active to catalyze the Knoevenagel condensation. However, addition of proline catalyst increased the reaction rate.

Ramachary and co-workers have also disclosed an organocatalytic approach to substituted anilines that utilized Knoevenagel condensation in its first step (Scheme 139).[274] After condensation of two molecules of β-ketoester **599** with aldehyde **598**, a six-membered ring was formed after dehydration, eliminating one of the ester functionalities in the process. Subsequent reaction with nitrosobenzene **601**

Scheme 139. Knoevenagel-Mediated Synthesis of Substituted Anilines[274]



Scheme 140. Piperidine-Catalyzed Synthesis of Coumarin 3-(*N*-Aryl)Sulfonamides[276]

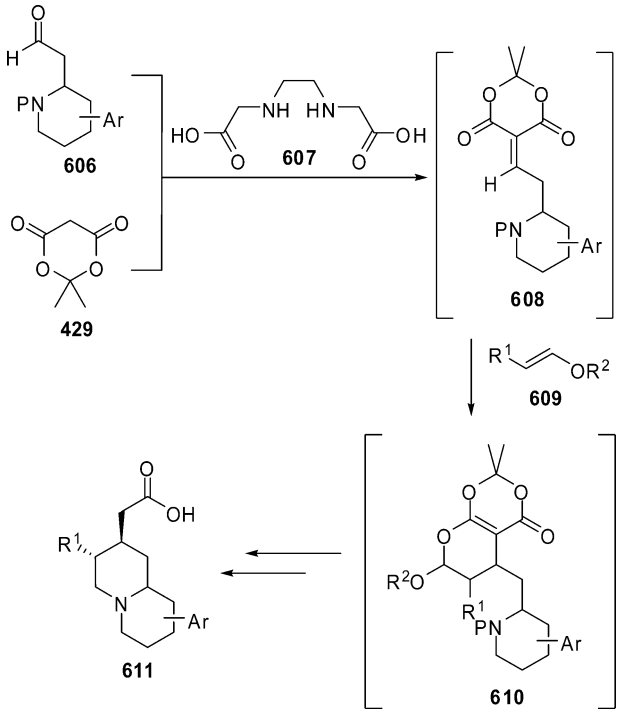


followed by isoaromatization led to formation of anilines **602**.

The classical Knoevenagel condensation has often been used in the synthesis of coumarin derivatives.[275] In 2004, Reddy and co-workers disclosed a novel catalytic route for the synthesis of coumarin 3-(*N*-aryl)sulfonamides (Scheme 140).[276] They employed either catalytic amounts of benzylamine and acetic acid to the condensation of substituted salicyl aldehydes with anilinosulfonyl acetic acids or catalytic amount of piperidine in ethanol to condense salicylaldehydes with methylaniline−sulfonyl acetates. Several coumarin derivatives were synthesized, but no yields were reported.

The classical Knoevenagel condensation is often used as a key C−C bond-forming reaction in the total synthesis of natural products and bioactive compounds. Recent examples include the syntheses of ptilomycalin A,[277] maculalactones A−C,[278] a precursor of leucettamine B,[279] dual 5-lipoxygenase and cycloozygenase inhibitors,[280] 3,4-methylenedioxymethamphetamine and its metabolites,[281] potential antimalarial agent PfA-M1,[282] protein tyrosine phosphatase 1B inhibitor,[283] *para*-aryl thiocinnamides,[284] HIV protease inhibitor PNU-140690,[285] and a potent selective glycine-site NMDA receptor antagonist.[286] Also, the Knoevenagel strat-

Scheme 141. Amine-Catalyzed Condensation as the First Step in Domino Knoevenagel−Hetero-Diels−Alder Reaction in Synthesis of Natural Products[289]



egy has been utilized in the synthesis of barbituric acid-terminated oligomer.[287]

Tietze and co-workers have employed iminium-mediated Knoevenagel reactions in several syntheses of active natural products and drugs.[288,289] The central benzoquinolizidine stucture of these compounds is typically formed by a Knoevenagel condensation catalyzed by the diamine EDDA **607**, followed by a reverse electron demand hetero-Diels−Alder reaction between the Knoevenagel adduct **608** and an enol ether **609** (Scheme 141). In 2004, the Tietze group also published the syntheses of ametine and tubulosine.[288]

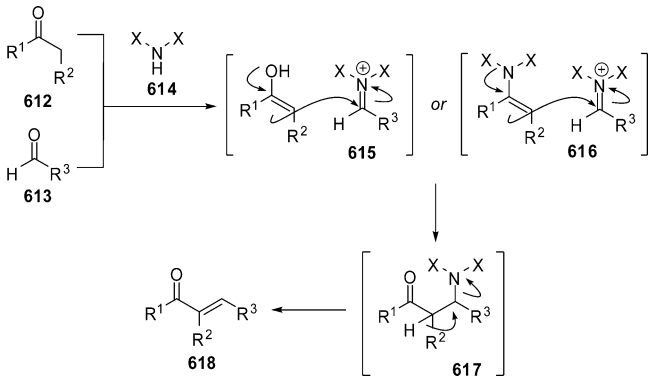
Iminium-promoted Knoevenagel reactions have also been utilized widely in the context of domino reaction protocols. These reactions were discussed above in section 6.

7.2.2. Knoevenagel–Mannich

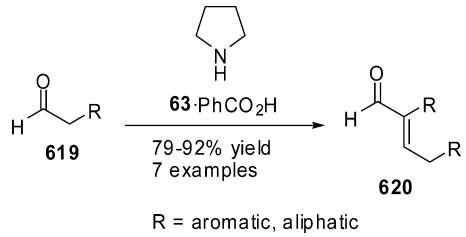
Knoevenagel-type (aldol) condensations of aldehydes with ketones or aldehydes have been investigated widely. This reaction type proceeds through a Mannich-type intermediate **617**[290] that loses the amine via elimination. The enolizable aldehyde can then react either as its enol **615** or its enamine adduct **616** (Scheme 142). This reaction has been reviewed thoroughly, typically focusing on the Mannich-base-forming step of the reaction.[291]

Condensation reactions between two aldehydes have been promoted by primary and secondary amine catalysis.[292] Cross-condensation reactions between simple alkyl aldehydes and formaldehyde, in turn, are typically performed using secondary amines and acid cocatalysts under relatively drastic conditions, including high temperature, high pressure, and rapid distillation of the product from the reaction mixture.[293] These α-methylenation reactions have only rarely been performed with more complex aldehydes.[294] In these cases, stoichiometric amounts of the amine and long reaction times have often been required. All these reactions likely proceed

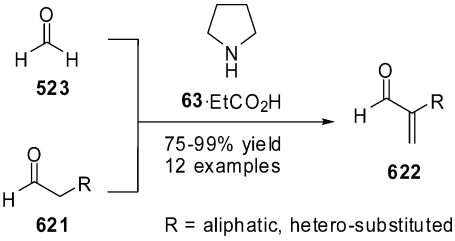
Scheme 142. Mechanistic Possibilities for the Knoevenagel−Mannich Reaction



Scheme 143. Pyrrolidine-Catalyzed Self-condensations of Aldehydes[295]



Scheme 144. Pyrrolidine-Catalyzed α-Methylenations of Aldehydes[296]



via a Knoevenagel−Mannich-type condensation involving an iminium ion.

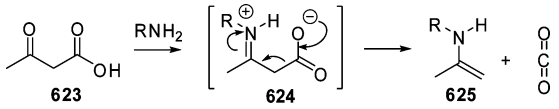
Ishikawa and co-workers have reported self-condensation of aldehydes catalyzed by pyrrolidine **63** (Scheme 143).[295] In the presence of 5 mol % of pyrrolidine **63** and 2 mol % of benzoic acid cocatalyst, they were able to transform several unbranched aliphatic aldehydes **619** to the corresponding enals **620** in good-to-high yields. The reactions took typically 12−48 h to complete. The authors suggested a mechanism where the enol form of the aldehyde attacks the iminium adduct of another aldehyde molecule.

Erkkilä and Pihko recently disclosed an amine−iminium-catalyzed method for α-methylenation of aldehydes (Scheme 144).[296] 10 mol % of propionic acid salt of pyrrolidine **63** promoted condensation of α-monosubstituted aldehydes **621** with formaldehyde **523**. The authors suggested that this reaction proceeds via a Mannich−Knoevenagel-type mechanism, where the formaldehyde forms an iminium ion with pyrrolidine salt.[297]

7.3. Cleavage of C–X α-Bond

Iminium ions with saturated α-carbons readily lose an electrophile at the α-carbon. The most common example of this reaction is the formation of enamines via loss of proton. These reactions have been studied extensively (cf. section 2.2), and they are reviewed elsewhere in this issue.

Scheme 145. Mechanism of Iminium-Catalyzed Decarboxylations



A common electrophile is carbon dioxide. The amine-catalyzed decarboxylation of β-ketoacids **623** proceeds by the following mechanism (Scheme 145). After formation of the iminium **624**, carbon dioxide cleaves to form enamine **625**, which is then hydrolyzed to the corresponding ketone.

As discussed in section 2.2, these reactions were probably the first reactions for which discrete iminium species were suggested as key intermediates. These reactions have been subject to intense studies. Guthrie and Jordan have compared different primary amines as catalysts and identified aminoacetonitrile as the most powerful catalyst in a series of primary amines (other amines studied included butylamine, trifluoroethylamine, aniline, and *p*-aminobenzoate).[298] Ogino and co-workers have demonstrated that cyclic and acyclic 1,3-diamines exhibit significant catalytic activity on the decarboxylation of oxaloacetate.[299] Surprisingly, the amine-catalyzed decarboxylation, although an extremely facile reaction, has found very little use in the synthetic community, although decarboxylation reactions of β-ketoacids derived from β-ketoesters are relatively common procedures in β-ketoester chemistry.

7.4. Other Iminium-Catalyzed Reactions

In addition to the reactions discussed above, an important iminium-catalyzed reaction in nature is the isomerization of retinals **54**, a key reaction in vision.[300] Recently, Janda and co-workers investigated the nornicotine-induced isomerization of enals and enones, including retinals.[301] They reported that the product of retinal isomerization is all-*E*-retinal, a process that is associated with age-related macular degeneration. The iminium-catalyzed isomerization has been exploited in synthesis in the transfer hydrogenation reactions by List and co-workers[163] and MacMillan and co-workers,[164] where enals with low isomeric purity could be isomerized to the *E*-isomers prior to the attack of the hydride source.

8. Conclusions

Iminium catalysis has now been established as one of the key catalytic concepts in organocatalysis. However, there are certainly several catalytic reactions still waiting to be discovered. Future efforts will likely focus the development of faster and more selective catalysts. Many iminium-catalyzed reactions still require relatively high catalyst loadings (up to 20−30 mol %), but we believe that these figures will improve with increased understanding of these catalysts. At present, the kinetic details of many iminium-catalyzed reactions remain obscure. Improvements in turnover numbers and frequencies are to be expected with the advent of more systematic studies into iminium activation and iminium catalysis.

However, at the same time, the element of serendipity should not be forgotten. Nearly all iminium-catalyzed processes are very user-friendly to operate: the reactions are not particularly sensitive to moisture or air, most reactions can be conducted at ambient temperatures, and the catalysts are often readily available or easy to prepare. For these reasons, we expect that the fast pace of discovery in iminium-catalyzed reactions will continue for some time.

9. Abbreviations

CNA	cyanoacetic acid
CSA	camphorsulfonic acid
DBA	dibromoacetic acid
DCA	dichloroacetic acid
DNBA	2,4-dinitrobenzoic acid
DPP	diphenyl phosphate
EDDA	ethylenediamineacetic acid
EWG	electron-withdrawing group
ONBA	*ortho*-nitrobenzoic acid
PEG	poly(ethylene glycol)
PMP	*p*-methoxyphenyl
PNBA	*para*-nitrobenzoic acid
TBHP	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid
TRIP	3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-dihydrogen phosphate
p-TSA	*para*-toluenesulfonic acid
TCA	trichloroacetic acid

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