33
Addition to α,β-Unsaturated Aldehydes and Ketones

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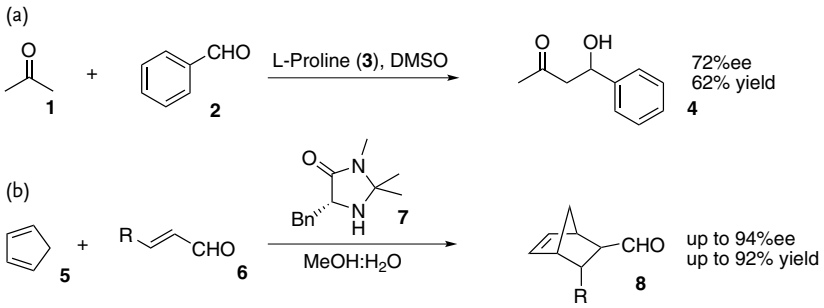
33.1
Introduction

In the last decade, organocatalysis has been developed as a powerful tool for the synthesis of complex molecules [1]. For example, amine catalysis allows the development of new and highly enantioselective methodologies for the asymmetric synthesis of new C-atom bonds.

The beginning of this new era can be traced to the pioneering works of List, Barbas, and Lerner in enamine chemistry [2] and MacMillan and coworkers in iminium chemistry (Scheme 33.1) [3].



Scheme 33.1 Earlier examples from (a) List and (b) MacMillan.

These two methodologies are complementary. While List, Lerner, and Barbas' methodology allows the electrophilic attack of the "*in situ*" enamine formed, MacMillan's methodology consists of the activation of α,β-unsaturated aldehydes to undergoes nucleophilic addition.

In this chapter cover the most important processes for nucleophilic addition to α,β-unsaturated aldehydes and ketones based on organocatalysis.

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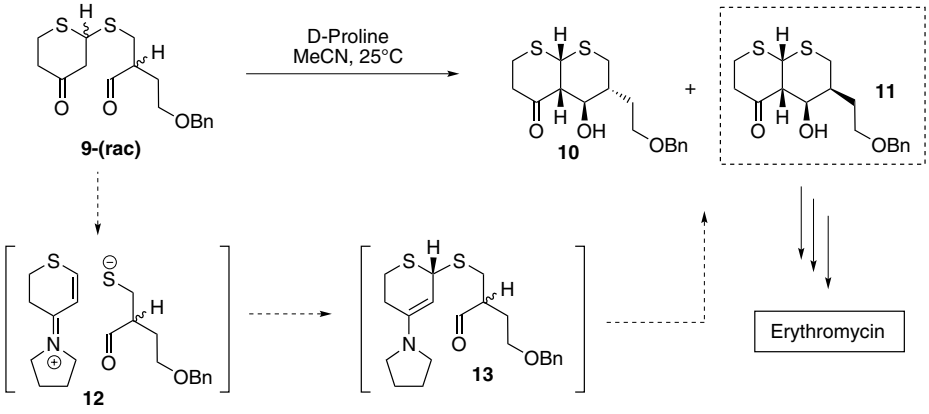
33.1.1 Iminium Activation

33.1.1.1 Historical Overview

The roots of iminium activation can be traced back to the pioneering works of Knoevenagel [4]. The Knoevenagel condensation became the first reaction that might proceed via iminium catalysis. Next, Pollack reported that several proteins and amino acids catalyzed the decarboxylation of acetoacetic acid. The mechanism suggested by Petersen involves an imine intermediate [5].

In 1937, Langenbeck reported the first iminium catalyzed conjugated addition. *N*-Methylglycine and piperidinium acetate were found to be good catalysts for the conjugate addition of water to crotonaldehyde [6].

Probably the most outstanding work in iminium catalysis before its rebirth in 2000 was the synthesis of erythromycin reported by Woodward *et al.* [7]. In this work, Woodward applied proline catalysis in a triple organocascade reaction consisting of a deracemization (via a retro-Michael, Michael addition) and an intramolecular aldol reaction that determines the stereochemical output of the reaction (Scheme 33.2).



Scheme 33.2 Triple organocascade reaction reported by Woodward.

Yamaguchi and coworkers reported in the early 1990s the use of alkali metal salts of proline (e.g., rubidium prolinate) for the conjugate addition of malonates to enals with promising results [8]. Soon after, Taguchi and coworker developed a similar reaction using (2-pyrrolidyl)(alkyl)ammonium hydroxide as catalyst [9].

33.2
Nucleophilic Addition to Enals and Ketones

33.2.1
Iminium Activation

Since its rediscovery by MacMillan in 2000, iminium activation catalysis has become a key catalytic concept in organocatalysis. After initial work centered on cycloadditions, Michael additions became the main area of interest and it is now established as a general strategy for the asymmetric conjugate addition of nucleophiles to α,β-unsaturated compounds.

The concept of this strategy was founded on the mechanistic hypothesis that the reversible formation of iminium ions from α,β-unsaturated aldehydes and chiral amines might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis [i.e., lowest-unoccupied molecular orbital (LUMO)–lowering activation] as shown in Figure 33.1.

The generally accepted mechanism for these reactions begins with the acid-promoted condensation of the carbonyl moiety with the amine to form an unsaturated iminium ion. This reactive intermediate then suffers the addition of the nucleophile at the β-position, leading to a β-functionalized enamine that could render, after protonation, a saturated iminium ion, or could undergo a cascade reaction with a suitable electrophile. Hydrolysis of these saturated iminium ions releases both the product and the catalyst (Figure 33.2).

In the case of enals, the most common catalysts are secondary chiral amines, which can be divided into two large groups: (i) amines substituted with a bulky group and (ii) amines with hydrogen-bond-directing groups. Another possible type of catalyst for this activation mode arises from ACDC (asymmetric counterion direct catalysis) developed by List. In these catalysts either a chiral or non-chiral amine forms a chiral ionic pair with a chiral phosphoric acid. A different possibility is the use of a primary chiral amine and a strong acid. These latter methods have

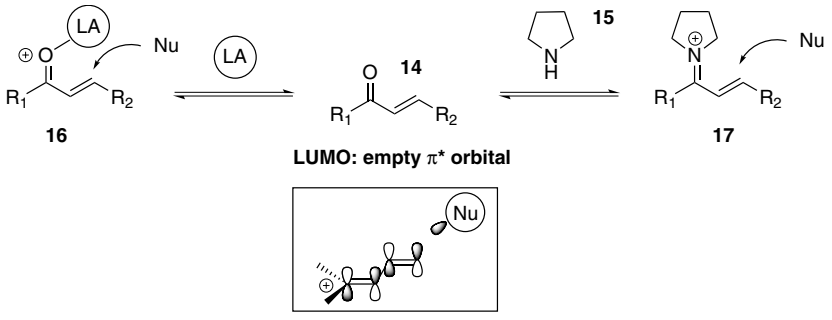


Figure 33.1 Iminium activation.

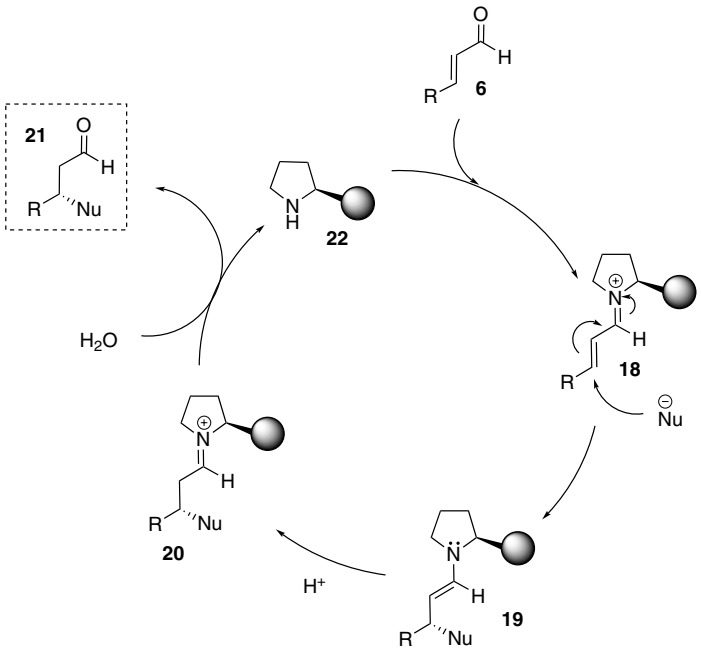


Figure 33.2 Mechanism of iminium activation with secondary amines.

shown excellent efficiency in the nucleophilic addition to enones and α-substituted enals.

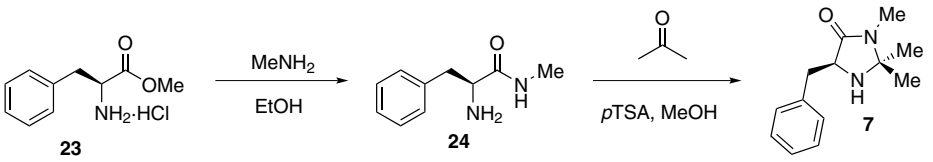
33.2.1.1 Catalyzed by Secondary Amines

33.2.1.1.1 Catalyzed by Secondary Amines Substituted with Bulky Groups

Mechanism After the first report of iminium activation by MacMillan *et al.* in 2000, many studies have been made in this area. Two of the most important families of catalysts are MacMillan's catalysts and the TMS *O*-protected diaryl substituted prolinols developed independently by Jørgensen and Hayashi in 2005.

The commonly accepted stereochemical outcome for such catalysts is depicted in Figure 33.2. This mechanism implies attack of the electrophile by the face opposite the bulky amine substituent, in the energetically favored *s*-trans conformer of the (*E*)-configured unsaturated iminium ion.

Catalysts In the last decade, several catalysts have been developed based on the concept of chiral secondary amines bearing a bulky substituent. MacMillan and coworkers have developed a family of chiral imidazolines derived from α-amino acids (Scheme 33.3).



Scheme 33.3 General synthesis for MacMillan's imidazoline catalyst.

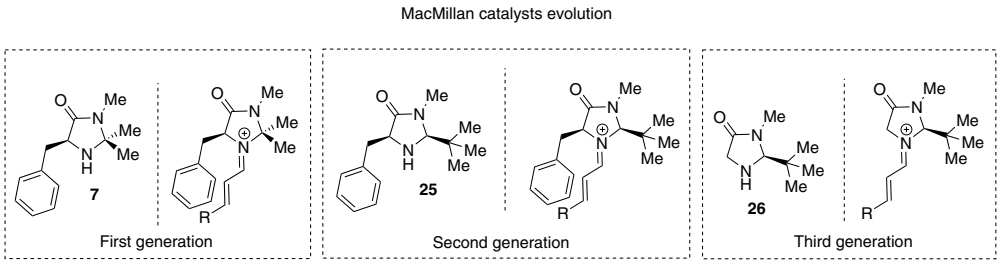


Figure 33.3 Evolution of MacMillan catalysts and the corresponding iminium catalysts.

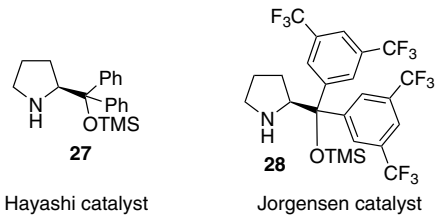


Figure 33.4 Hayashi and Jørgensen catalysts.

Since the first catalyst (**7**) used in the organocatalytic Diels–Alder reaction, several modifications have been made to improve its catalytic properties. In 2002 the commonly called MacMillan second-generation catalyst (**25**) was used in the addition of indoles to enals [10]. A few years later, MacMillan's third-generation catalyst (**26**) was used for the enantioselective transfer hydrogenation of enals (Figure 33.3) [11].

In 2005 Jørgensen [12] and Hayashi [13] developed almost at the same time diarylprolinol derivatives protected as silyl ethers (Figure 33.4) as a suitable catalysts for imine and enamine activation.

33.2.1.1.2 Catalyzed by Secondary Amines Substituted with Hydrogen-Bond-Directing Groups

Mechanism Secondary amines bearing hydrogen-bond directing groups have often been used in the activation of cyclic enones. The commonly accepted

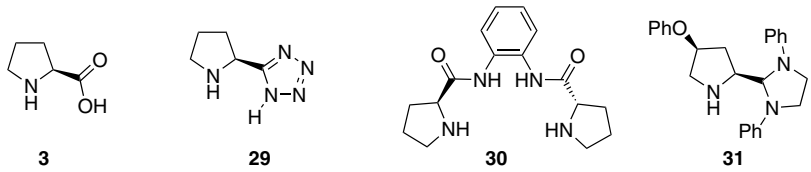


Figure 33.5 Example of secondary amine catalysts bearing a hydrogen donor group.

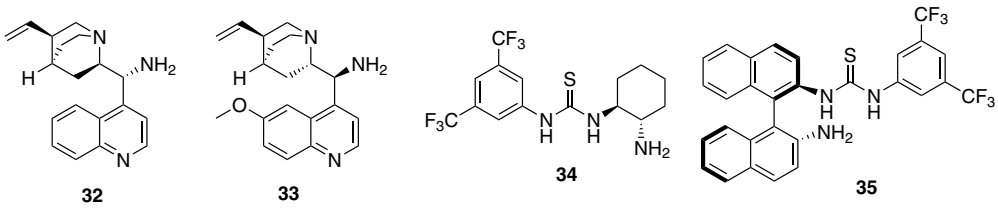


Figure 33.6 Primary amine catalysts.

mechanism for such catalysts implies that the attack of the electrophile takes place in an intramolecular fashion, via a cyclic transition state, by the same face to the hydrogen bond group substituent, in the energetically favored *s*-trans conformer of the (*E*)-configured unsaturated iminium ion.

Catalysts Most catalysts of this type are proline derivatives, bearing different groups such as thioureas, amides, and so on (Figure 33.5).

33.2.1.2 **Primary Amine Catalysis**

Primary amine catalysts have been used almost exclusively for the activation of enones or α-substituted enals due to the low reactivity of the secondary amine catalysts described below with these substrates. The stereochemical course of the reaction is highly dependent on the nature of the primary amine and in most cases is difficult to rationalize. The most common primary amines used as catalysts are cinchona alkaloid derivatives, chiral diamines, or BINAM derivatives (Figure 33.6).

33.2.1.3 **ACDC Catalysts**

Asymmetric counterion direct catalysis (ACDC) was first reported by List in 2006 [14]. List was intrigued by the observation of a strong counterion effect on the yield and enantioselectivity in iminium catalyzed reactions, hypothesizing that catalytic salts of achiral amines (primary or secondary) and chiral phosphoric acids could induce asymmetry in the process. Later on, this powerful methodology was extended to other chiral acids or even to the combination of chiral amines and chiral acids. Rationalization of the stereochemical course of the reaction is almost impossible due the nature of the ion pair (Figure 33.7).

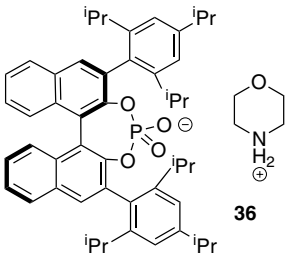


Figure 33.7 Example of an asymmetric counterion direct catalysis (ACDC) catalyst.

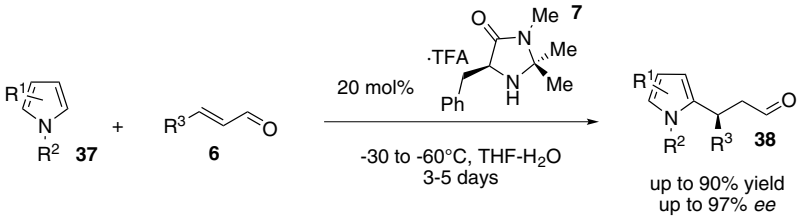
33.2.2
Scope of the Nucleophilic Addition to Enals

Since the first report from MacMillan in 2000 [3], the research community has devoted many efforts to the development of new methodologies based on the iminium activation of enals for the enantioselective construction of C–X bonds. Activation of the β position of the enal allows the attack of different nucleophiles. During the last decade carbon, nitrogen, oxygen, sulfur, or phosphorus nucleophiles have been used to form new stereogenic bonds with high levels of rate and stereoselectivity. In this chapter we describe the most important procedures developed in the field, taking into account the nature of the bond formed and avoiding as much as possible electrocyclic or tandem reactions that would be described in other chapters.

33.2.2.1 C–C Bond Formation

33.2.2.1.1 Conjugate Friedel–Craft Alkylation

The first organocatalytic asymmetric carbon nucleophilic addition to enals was reported by MacMillan in 2001 [15]. MacMillan reported the first Friedel–Craft alkylation between N-substituted pyrroles and enals promoted by catalyst **7**. The reaction renders the final compounds in good yields and enantioselectivities (Scheme 33.4).

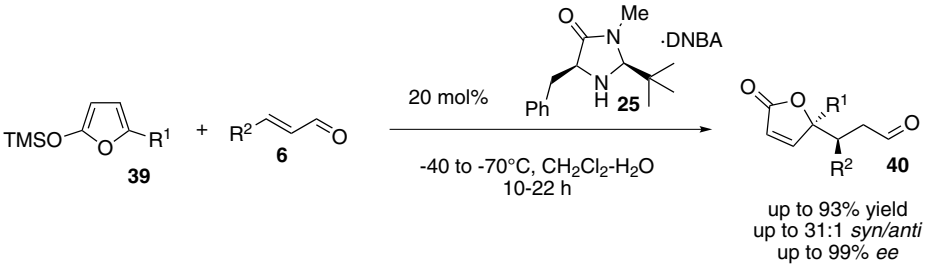


Scheme 33.4 Friedel–Craft reaction of enals.

In 2002 the same research group extended this methodology to electron-rich benzenes with excellent results [16].

33.2.2.1.2 Mukaiyama–Michael Reaction

In 2003, MacMillan and coworkers developed the first enantioselective organocatalytic Mukaiyama–Michael reaction that give access to a enantioenriched γ-butenolide architectures [17]. The reaction was efficiently catalyzed by MacMillan second-generation catalyst **25**, and renders the final compounds with excellent yields and enantioselectivities; the scope of the reaction is wide, allowing the use of almost any substituent in the β position of the enal without a substantial change in yield or diastereo- or enantioselectivities (Scheme 33.5). MacMillan and coworkers applied this methodology for the synthesis of spiculisporic acid and 5-epi-spiculisporic acid with excellent results. In 2005, Wei Wang and coworkers expanded the scope of this reaction by using different silyl enol ethers as suitable nucleophiles [18]. In 2009, MacMillan and coworkers reported an improved methodology for a general Mukaiyama–aldol reaction with enals [19].

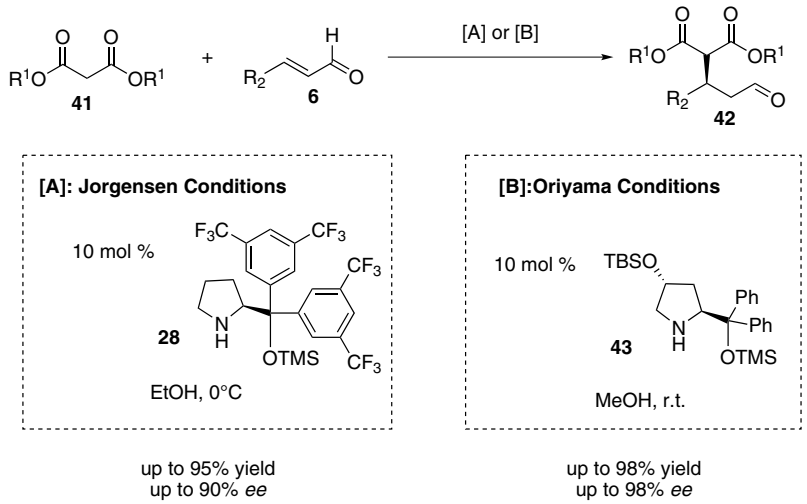


Scheme 33.5 Mukaiyama reaction reported by MacMillan.

33.2.2.1.3 Michael Reaction of Acidic C–H Bonds

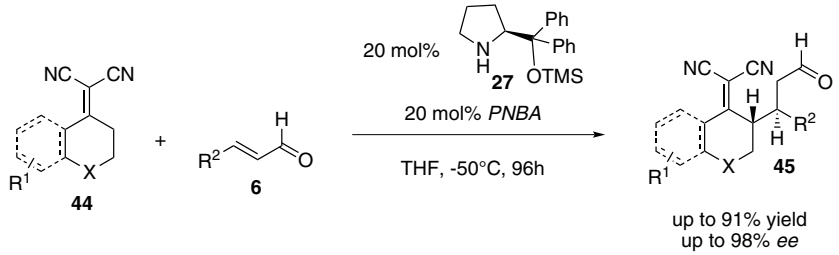
One of the first 1,3-dicarbonylic carbon nucleophiles added in asymmetric fashion to iminium activated enals was malonates. In 2006, Jørgensen *et al.* reported the reaction between malonates and enals catalyzed by catalyst **28** [20]. The final products **42** were obtained in good yields and excellent enantioselectivities. The only limitation of this methodology is that only aromatic enals could be used. To overcome this limitation, Oriyama and coworkers employed catalyst **43** to promote the reaction between crotonaldehyde and malonates in moderate yields and enantioselectivities (Scheme 33.6) [21].

Based on the pioneering report of Jørgensen, his research group and some other groups have developed several analogues with diphenylprolinol derivatives bearing an ionic liquid fragment as catalysts [22], using fluoromalonates [23], cyanoesters [24], or 4-hydroxycoumarins [25] instead of malonates or developing powerful cascade reactions with malonate derivatives [26]. In 2006, Deng and coworkers



Scheme 33.6 Addition of malonates to enals.

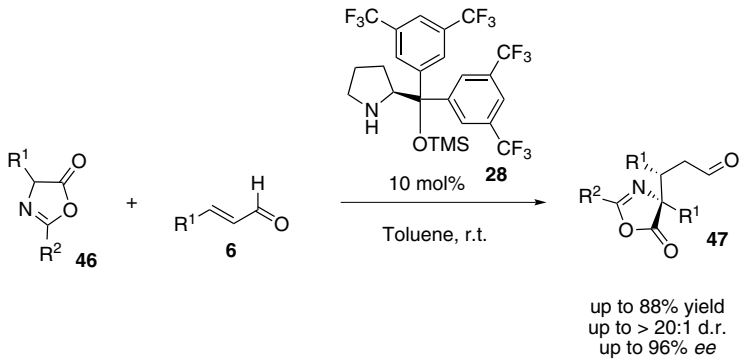
developed the first vinylogous Michael addition of α,α-dicyanoolefins to enals [27]. The reaction was efficiently catalyzed by **27**, achieving the final products, which have two vicinal chiral tertiary and carbon centers, in high regio-, chemo-, diastereo-, and enantioselectivities (Scheme 33.7).



Scheme 33.7 Deng reaction.

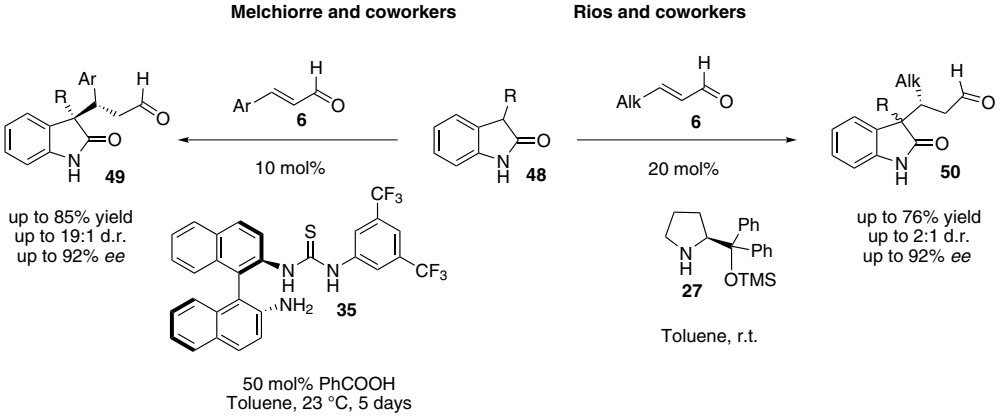
In 2008, Jørgensen and coworkers developed an extremely powerful methodology for the synthesis of α,α-disubstituted amino acids via a Michael addition of oxazolones to enals [28]. The reaction was catalyzed by catalyst **28** and renders the final amino acid precursors in good yields and excellent diastereo- and enantioselectivities when a bulky benzhydryl substituent was present at C2 of the oxazolone (Scheme 33.8).

Several research groups have developed Michael reactions with different heterocycles that contains an easily enolizable position. For example, Melchiorre



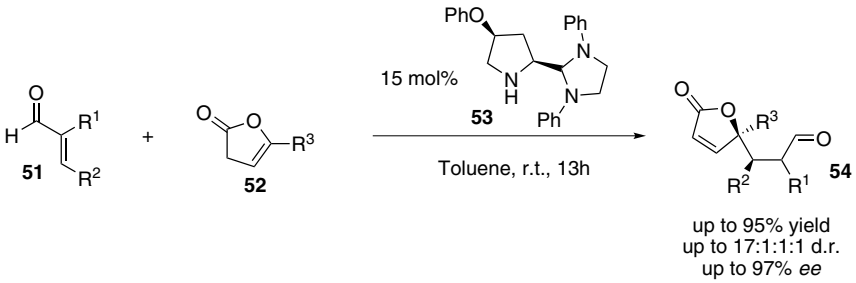
Scheme 33.8 Oxazolone addition to enals.

developed a highly enantio- and diastereoselective oxindoles addition to enals, using a primary amine bearing a thiourea moiety as catalyst (**35**) [29]. One limitation of this reaction was the need to use aromatic enals; when aliphatic enals were used the products were obtained in low stereoselectivities. To overcome this limitation, Rios and coworkers developed a similar reaction by using diphenylprolinol TMS ether (**27**) as catalyst [30]. The reaction with aliphatic aldehydes renders the final products in good yields and enantioselectivities, albeit with low diastereoselectivities (Scheme 33.9). Both groups, based on this approach, developed several cascade reactions leading to spiro-compounds [31].



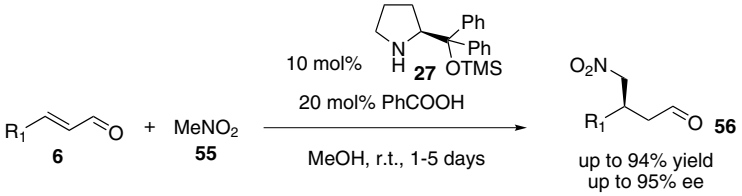
Scheme 33.9 Oxindole addition to enals.

Similar reactions were later reported by Alexakis [32] and Xue [33]. Alexakis reported the addition of γ-butenolides to enals catalyzed by proline derived catalyst **53.** In both cases, the results were excellent. The only limitation of Xue's methodology was the low enantioselectivity observed when aliphatic enals were used (Scheme 33.10).



Scheme 33.10 Addition of butenolides to enals.

Another key reaction for the addition of carbon nucleophiles to enals was reported by Wei Wang [34] and Hayashi in 2007 [35]. Hayashi developed the addition of nitromethane to enals catalyzed by **27**. The reaction renders the final γ-nitro-aldehydes in excellent yields and enantioselectivities with aromatic and aliphatic enals. At almost the same time Ye and coworkers reported the same reaction with slightly different reaction conditions (Scheme 33.11) [36]. The only limitation of the cited methodologies was the poor diastereoselectivities obtained when nitroalkanes other than nitromethane were reacted. Remarkably, these methodologies allow the synthesis of baclofen (a potent GABAβ receptor agonist) or pregabalin in enantiopure form in a few chemical steps.

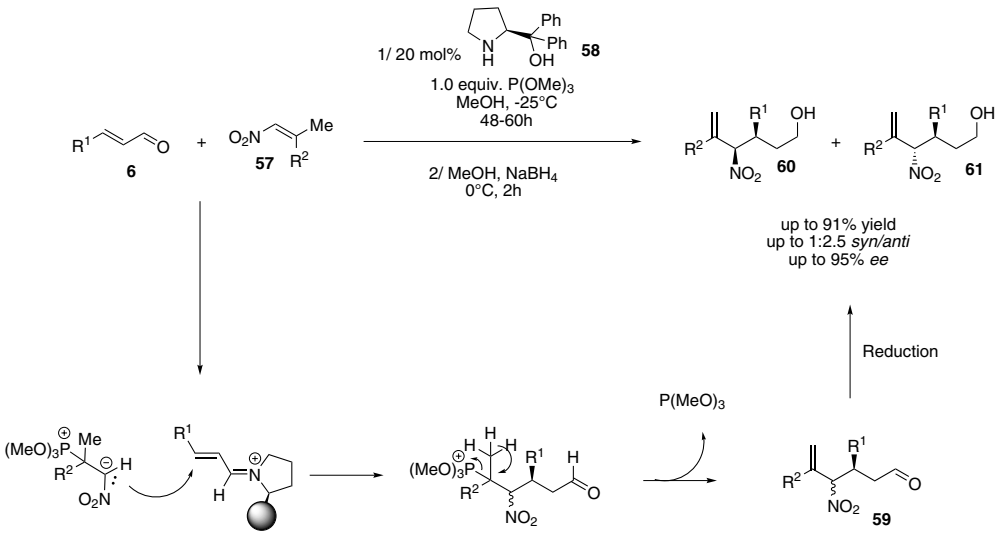


Scheme 33.11 Nitromethane addition to enals reported by Hayashi.

Based on these pioneering reports, several groups have developed cascade reactions using as a key step the addition of nitroalkane derivatives to enals [37].

Shi *et al.* developed an efficient cross double Michael addition between nitroalkenes and enals catalyzed by **58** and trimethyl phosphite via a dual activation pathway as shown in Scheme 33.12 [38]. The corresponding products were obtained in good yields and enantioselectivities, albeit with low diastereoselectivities.

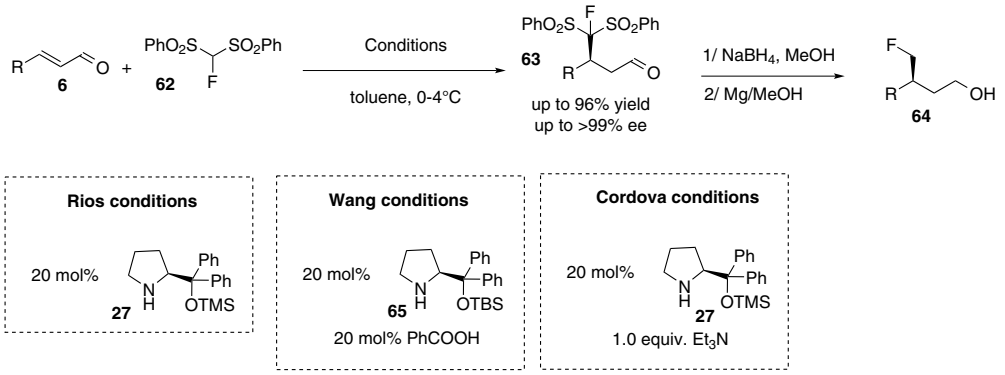
Later, Cid and Ruano reported that aryl-acetonitriles bearing an electron-withdrawing group at the *ortho*- or *para*-position could serve as suitable nucleophiles in organocatalytic Michael reactions with enals [39]. The reaction proceeded with good yields and good enantioselectivities, albeit with low



Scheme 33.12 Shi's cross double Michael addition.

diastereoselectivities. Remarkably, these adducts were transformed into diastereomerically pure lactones by a sequential procedure consisting of Michael addition, $NaBH_4$ reduction, and lactonization. A similar approach was reported by Melchiorre using nitrobenzylpyridines, obtaining similar results [40].

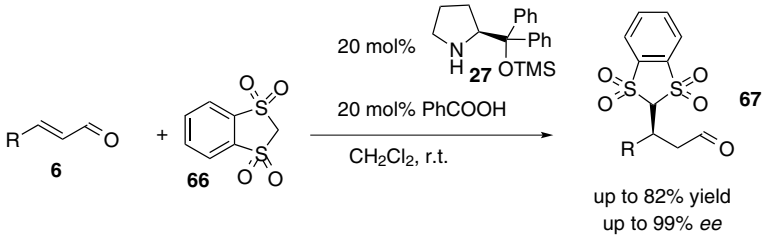
Rios [41], Wang [42], and Cordova [43] developed independently, almost at the same time, the formal fluoromethyl addition to enals. The authors took advantage of the easy removal of the bis-sulfonyl moiety. As shown in Scheme 33.13, the reaction between fluoro-bis(phenylsulfonyl)methane (FBSM, **62**) and enals (**6**) was efficiently catalyzed by **27** and the results in terms of yield and enantioselectivities



Scheme 33.13 Formal fluoromethylation of enals.

were excellent. In addition, the removal of the bis-sulfonyl moiety was performed with Mg/MeOH, furnishing the fluoromethylated products **64** in excellent yields and without any loss of enantioselectivity.

Soon after this, the research groups of Alemán [44], Rios [45], and Palomo [46] reported, almost at the same time, the first formal methyl addition to enals. Alemán and Rios used bis(phenylsulfonyl)methane as nucleophile while Palomo used a more active cyclic *gem*-bis(sulfone) (**66**). In the first two works, the reaction was limited to aliphatic enals, while the methodology reported by Palomo allows the use of both aliphatic or aromatic enals. In all the cases, the results in terms of yield and enantioselectivity were excellent (Scheme 33.14).



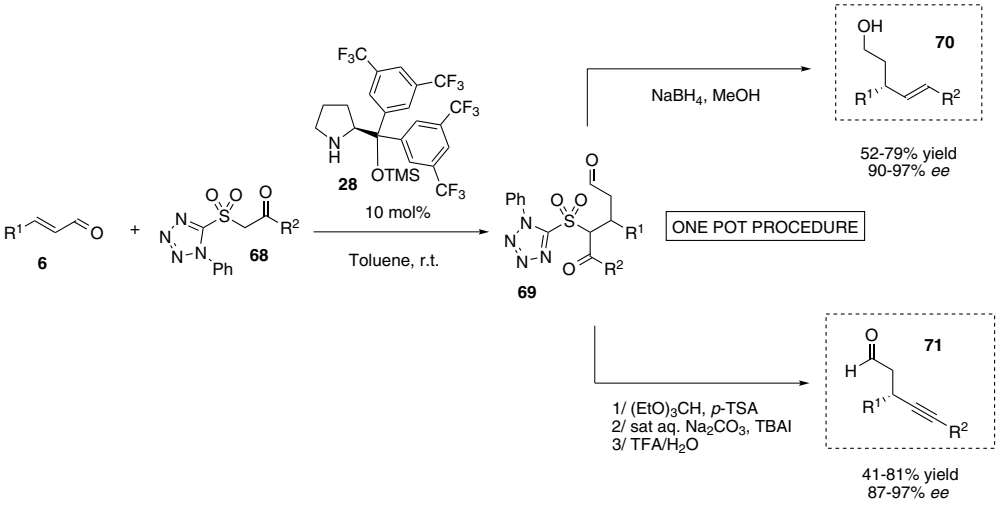
Scheme 33.14 Formal methylation of enals reported by Palomo.

Several other groups have used similar reactions, employing different sulfone derivatives. For example, Rios and Vesely developed the 1-fluoro-1-nitrophenylsulfonylmethane addition to enals [47], promoted by catalyst **27.** The final adducts were obtained in good yields and enantioselectivities but low diastereoselectivities.

Jørgensen and coworkers published an unprecedented organocatalytic protocol for the formal alkynylation and alkenylation of enals using β-keto heterocyclic sulfones [48]. The first step is, in both reactions, the Michael addition of β-keto heterocyclic sulfones to enals. The best results were obtained employing β-keto phenyltetrazole sulfones **68** as the Michael donor with diarylprolinol TMS ether (**28**) as catalyst in toluene at room temperature. Next, the Michael intermediate can be transformed into either alkynylated or alkenylated products by means of Smiles rearrangement in a simple one-pot protocol. This protocol gives access to highly enantioenriched compounds maintaining untouched the highly valuable carbonyl moiety, in contrast to the classical Julia–Kocienski transformation (Scheme 33.15).

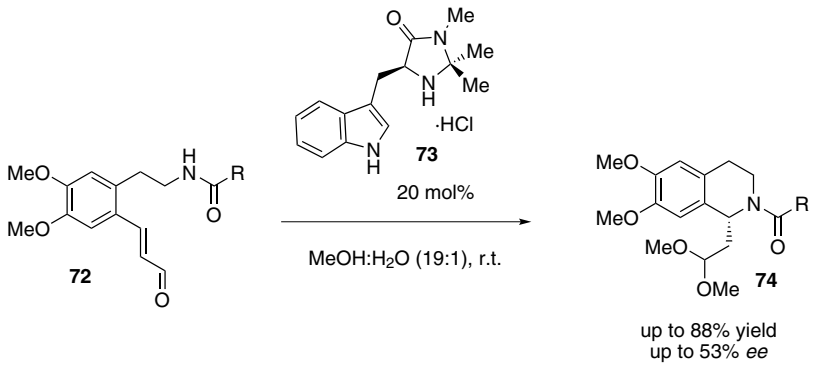
33.2.2.2 **C–N Bond Formation**

The enantioselective aza-Michael [49] reaction of enals has been emerged as one of the most important methodologies for the synthesis of enantiomerically pure C–N bonds. These methodologies led to the enantioselective synthesis of N-heterocyclic compounds such as pyrrolidines and piperidines.



Scheme 33.15 Michael reaction reported by Jørgensen.

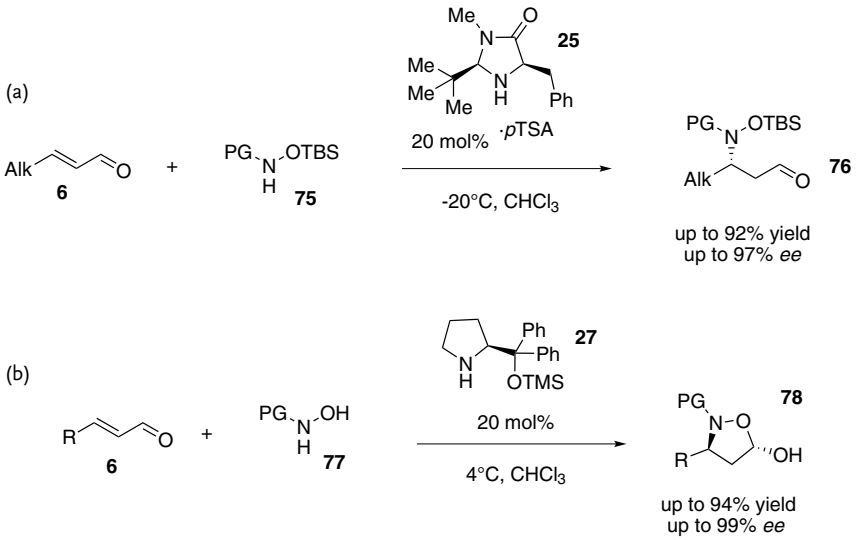
The first example of the aza-Michael reaction with enals was reported by Takasu and Ihara in 2003 [50]. They described the intramolecular aza-Michael reaction of dopamine derivatives bearing an enal and amide moiety catalyzed by imidazoline **73.** The reaction gives access to various 1,2,3,4-tetrahydroisoquinolines in good yields but with low enantioselectivities (Scheme 33.16).



Scheme 33.16 First organocatalytic aza-Michael reaction reported by Ihara.

Despite this early success, it was not until 2006 that MacMillan reported the first highly enantioselective intermolecular aza-Michael addition to enals [51]. In this work, MacMillan reported the use of *N*-silyloxycarbamates as nucleophiles. The N–O functionality would increase the nucleophilicity at the nitrogen center via the α-effect, while the carbamate functionality would decrease the basicity of the

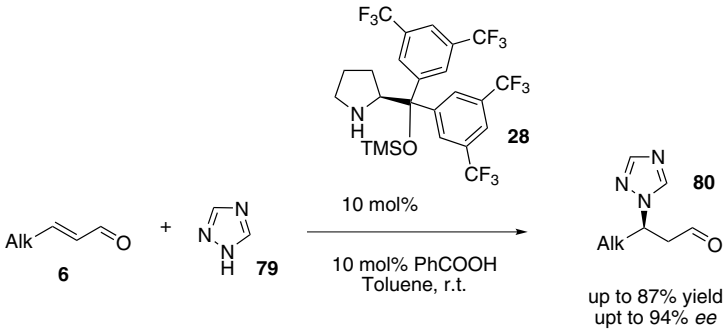
nitrogen in the final product, avoiding the reverse Michael reaction. The reaction was efficiently catalyzed by imidazoline catalyst **25,** affording the final compounds in good yields and excellent enantioselectivities. However, one limitation remains unsolved: aromatic enals are not reactive under these reaction conditions. To overcome this limitation, Cordova and coworkers proposed the use of OH free *N*-hydroxycarbamates [52]. In this case, subsequent cyclization of the Michael adduct forming the cyclic hemiacetal is the driving force that pushes the reaction to the final products. Thus, this enhancement of reactivity allows the use of aromatic enals, rendering the cyclic products in excellent yields and enantioselectivities (Scheme 33.17).



Scheme 33.17 Aza-Michael reaction reported by (a) MacMillan and (b) Cordova.

In 2007, the research groups of Cordova [53] and Jørgensen [54] reported almost simultaneously the addition of different nitrogen nucleophiles such as carbamate protected methoxyamines, phthalimides, or succinimides to enals catalyzed by diaryl prolinol derivatives. In both cases, excellent yields and enantioselectivities were obtained, but again the reaction was limited to aliphatic enals. Only phthalimide reacted with cinnamaldehyde derivatives, affording the final product in moderate yields but low enantioselectivities. Interestingly, in 2009, Lee and coworkers reported the same reactions, catalyzed this time by a chiral sulfonyl hydrazine (camphor derived), leading to the aminated compounds in similar yields and enantioselectivities [55]. Remarkably, several research groups have also developed cascade reactions based on the aza-Michael reaction. For example, Cordova developed an aza-Michael–aldol cascade reaction to afford dihydroquinolines [56] and Jørgensen developed a *syn*-diamination of enals [54]. In both cases the results were excellent.

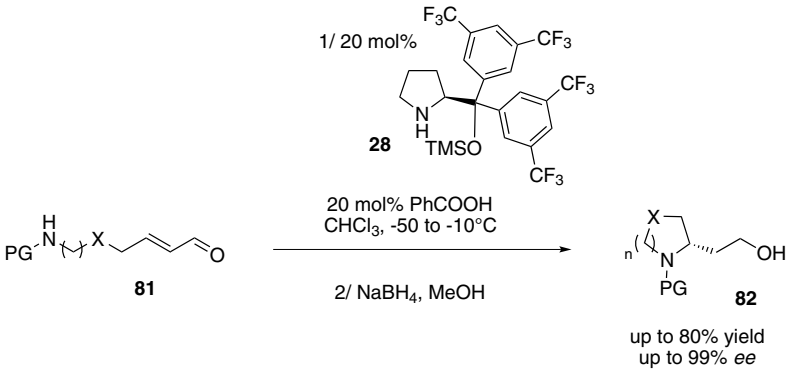
In 2007, Jørgensen and Vicario reported independently the addition of nitrogen heterocycles to enals. Jørgensen [57] reported the addition of 1,2,4-triazoles and 5-phenyltriazoles to enals catalyzed by diarylprolinol derivative **28** in excellent yields and enantioselectivities. However, in the case of 5-phenyltriazole the final adducts underwent racemization at room temperature and had to be subsequently reduced and esterified *in situ* to achieve high to excellent enantioselectivities. When benzotriazoles or 1,2,3-triazoles were added to enals a mixture of two regioisomers were obtained in acceptable yields and high enantioselectivities (Scheme 33.18). Vicario [58] reported the addition of phenyltetrazoles to aliphatic enals promoted by imidazoline catalysts. The reaction required low temperatures and renders the final compounds in good yields and enantioselectivities.



Scheme 33.18 Triazole addition of enals reported by Jørgensen.

Probably inspired by those two reports, Lin reported in 2009 a synthesis of INCB018424 (Janus kinase's inhibitor) based on an enantioselective aza-Michael reaction with an enal [59].

Based on the previous reports of Ihara, Fustero reported the synthesis of (+)-sedamine, (+)-allosedamine, and (+)-coniine via an intramolecular aza-Michael reaction using diarylprolinol derivative **28** as catalyst [60]. This methodology could be applied to the synthesis of pyrrolidine or piperidine derivatives with excellent yields and enantioselectivities. The same group studied the scope of the reaction by synthesizing (+)-myrtine, (–)-lupinine, and (+)-epiquinamide [61]. At almost the same time, Carter and coworkers independently reported a similar methodology using slightly different reaction conditions for the synthesis of enantioenriched pyrrolidine, piperidine, and indoline derivatives [62]. In contrast to Fustero's conditions, no acid additive was required. Later, Fustero expanded the scope of his reaction to the synthesis of indolines, isoindolines, tetrahydroisoquinolines, and tetrahydroquinolines using the same protocol. Moreover, he applied this methodology to the total synthesis of the alkaloid (+)-angusterine (Scheme 33.19) [63].



Scheme 33.19 Intramolecular aza-Michael reaction reported by Fustero.

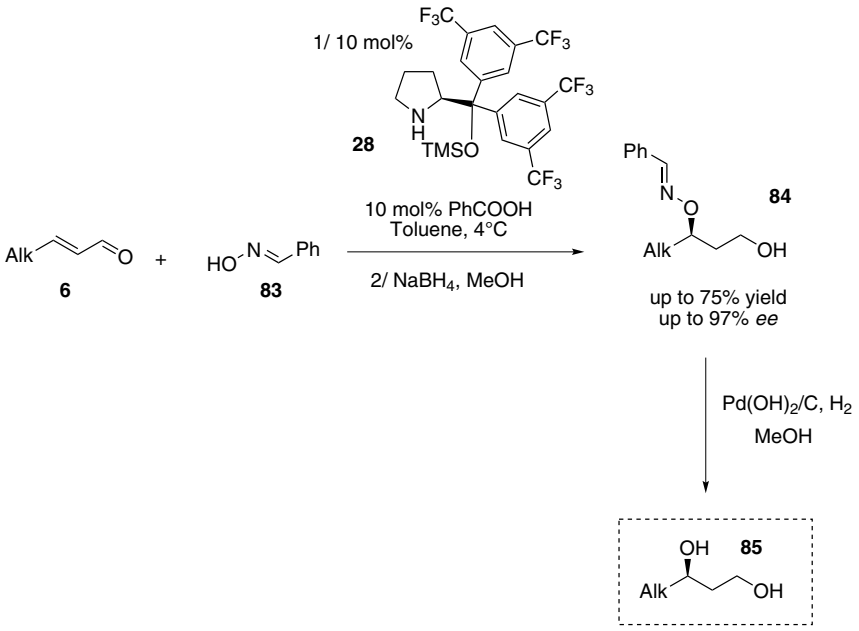
33.2.2.3 **C–O Bond Formation**

In contrast to the C–C Michael reactions or aza-Michael reaction the oxa-Michael reaction [64] has received considerably less attention from the synthetic community. The major drawbacks of the oxa-Michael reaction are the reversibility of the alcohol addition step as well as the poor nucleophilicity of the alcohols. Despite this fact, the oxa-Michael reaction is a very attractive methodology for the synthesis of valuable intermediates in organic synthesis like β-oxoacids, β-hydroxyketones, or β-aminoalcohols that can be found in a plethora of natural products. The organocatalytic oxa-Michael reaction with enals has been an elusive goal for organic chemists, despite the early success of Lloyd as early as 1878 in the addition of an alcohol to a conjugate acceptor. There are only few simple oxa-Michael additions of enals reported in the literature. Most of the research effort of the chemical community has gone into the development of tandem reactions that avoid the reversibility of the oxygen addition, and offer an efficient access to oxygen-containing heterocycles such as tetrahydropyrans and chromenes.

However, despite success in several tandem reactions, or in epoxidation reactions, there are only a few examples in the literature of simple oxo-Michael reactions with enals.

The first organocatalytic oxo-Michael addition to enals was reported by Jørgensen in 2007 [65]. Jørgensen used as a suitable nucleophile benzaldehyde oxime, which reacts with enals with catalysis by **28.** The resulting product, reduced directly to the alcohol due its liability, was obtained in excellent yields and enantioselectivities (Scheme 33.20). The oxime moiety can easily be cleaved to afford the 1,3-diols without loss of enantiomeric purity. However, aromatic enals turned out to be unreactive in this transformation.

In the same year, Maruoka and coworkers developed an alternative for the Michael addition of alcohols [66]. Using a biphenyl catalyst derivative, methanol, ethanol, and allylic alcohol react with aliphatic enals, albeit with moderate yields and enantioselectivities.



Scheme 33.20 Oxa-Michael reaction reported by Jørgensen.

33.2.2.4 **C–S Bond Formation**

One of the first reported C–S organocatalytic bond formations was reported by Pracejus in 1977. In this pioneering work benzylthiol, α-phthalimidomethacrylate, and catalytic amounts of chiral amines reacted to form several cysteine derivatives. With the advent of organocatalysis and iminium catalysis, several sulfa-Michael reactions have been developed.

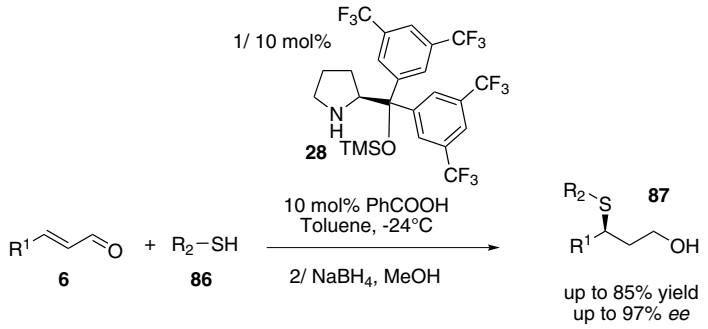
The first organocatalytic sulfa-Michael reaction of enals was reported by Jørgensen in 2005 [68]. In this report aliphatic and aromatic aldehydes reacted with several thiols in good yields and enantioselectivities under catalysis of **28.** The products must be reduced immediately due to their fast epimerization at room temperature (Scheme 33.21). In this work, Jørgensen and coworkers also developed several multicomponent cascade reactions with good to excellent results.

Since then, and inspired by this pioneering report, several groups have developed organocatalytic cascade reactions starting with a sulfa-Michael addition [68, 69].

33.2.2.5 **C–P Bond Formation**

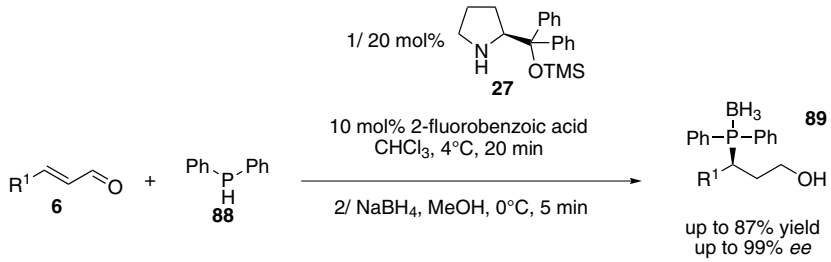
The phospha-Michael [70] additions are one of the most important methods for the enantioselective construction of C–P bonds.

The first report regarding phospha-Michael additions to enals was made independently and at the same time by the research groups of Melchiorre [71] and



Scheme 33.21 Sulfa-Michael reaction reported by Jørgensen.

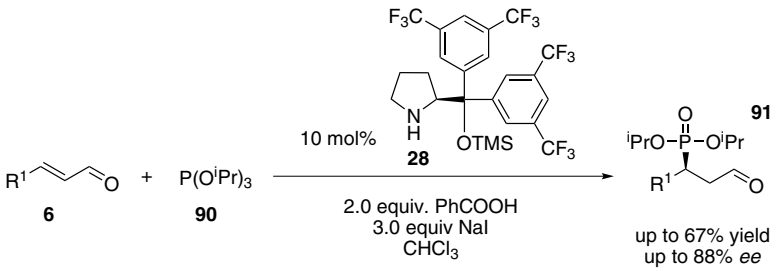
Cordova [72] in 2007. Both groups reported a hydrophosphination of enals with diphenylphosphine (**88**) catalyzed by diarylprolinol derivatives **27** (Scheme 33.22). The reactions were performed in the presence of benzoic acid derivatives as co-catalyst, and the originally formed adducts were either reduced to alcohols, which are stable and easier to handle, or oxidized to obtain the phosphine oxide derivatives. In both cases the reaction afforded the phosphine derivatives in good yields and enantioselectivities.



Scheme 33.22 Phosphination reported Cordova.

Jørgensen and coworkers reported in the same year a β-phosphonylation of enals by trialkyl phosphites [73]. The key to this reaction was the right choice of nucleophilic additive enabling the P^{III} to P^{V} oxidation by means of a S_N2-type dealkylation reaction. The optimum reaction conditions employed an excess of benzoic acid and NaI and triisopropyl phosphite (**90**) as a phosphonylation reagent under diphenylprolinol catalysis. Under these conditions the reaction afforded the final products **91** in good yields and excellent enantioselectivities (Scheme 33.23).

In 2008, Cordova expanded the scope of the previous reported reaction using different tri- or pentavalent phosphorous nucleophiles [72b]. However, the Michael adducts were formed in low yields and enantioselectivities in the best of the cases.



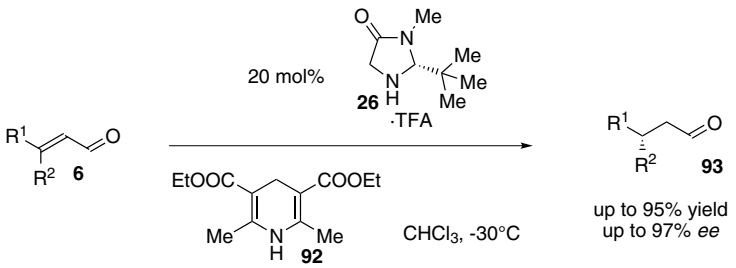
Scheme 33.23 Addition of phosphites to enals.

33.2.2.6 **C–H Bond Formation**

The asymmetric organocatalytic enantioselective conjugate hydrogen transfer reaction is clearly inspired by the mode of action in biological processes, in which reductions are accomplished by enzymes using hydride reduction cofactors like NADH.

Based on this biological approach, the research group of MacMillan [11] and List [74] reported at the same time the reduction of enals catalyzed by chiral imidazolines **26.** In both cases the key to success is the use of Hantzsch ester (**92**) as reducing agent. The Hantzsch ester can transfer simultaneously a hydride and a proton to the enal in a 1,4-addition process.

The reaction was performed with a wide range of enals, achieving in almost all the examples excellent yields and enantioselectivities (Scheme 33.24).



Scheme 33.24 Transfer hydrogenation of enals reported by MacMillan.

One important feature of this reaction is the enantioconvergence of the reaction. The reaction allowed the use of (*E*/*Z*) mixtures of the starting enal to furnish equally high enantioselectivities.

However, these two procedures have an important limitation, the low enantioselectivities obtained when β,β-dialiphatic enals were used. To overcome this limitation, List and coworkers applied the ACDC (asymmetric counterion direct catalysis) concept to this reaction [14]. When an achiral amine and a chiral phosphoric acid were used together as a catalytic system for this reaction, β,β-dialiphatic enals were reduced with good yields and exceptional levels of enantiocontrol.

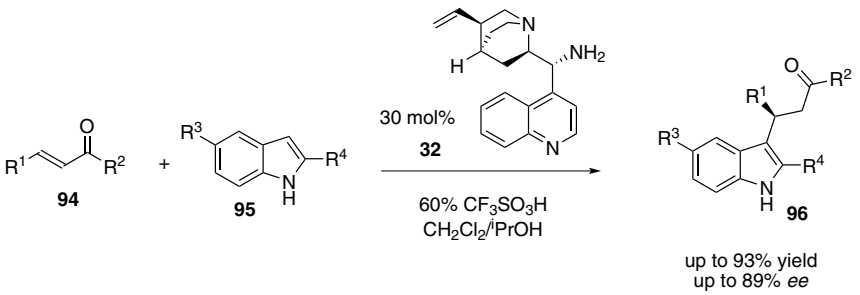
Since then, several research groups have developed several cascade and tandem reactions based on this concept [75].

33.2.3 Scope of the Nucleophilic Addition to α,β-Unsaturated Ketones

33.2.3.1 C–C Bond Formation

33.2.3.1.1 Conjugate Friedel–Craft Alkylation

Chen and coworkers in 2007 reported the first conjugate addition of indoles to enones catalyzed by 9-amino-9-deoxy-epi-cinchonine (**32**) CF_3SO_2H salts (a primary amine derived from cinchona alkaloids) [76]. The reaction proceeds with aliphatic and aromatic ketones with moderate to excellent yields and moderate to good enantioselectivities (Scheme 33.25). Soon after this, Melchiorre and coworkers reported a similar system using a hydroquinine derivative [77].



Scheme 33.25 Conjugate Friedel–Craft reaction.

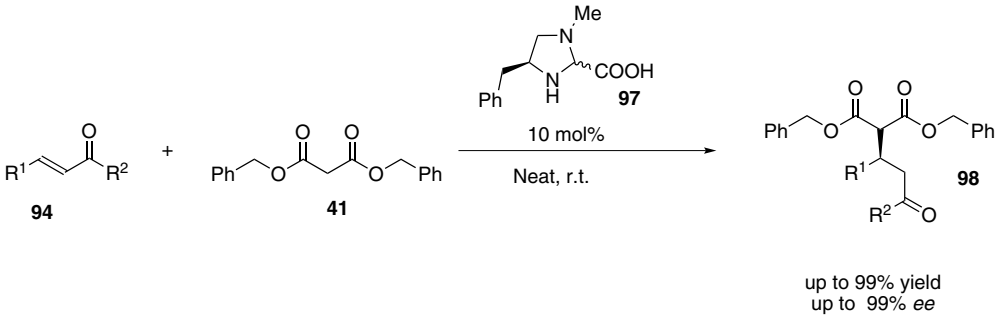
33.2.3.1.2 Michael Reaction of Compounds with Acidic C–H Bond

Probably the most important organocatalytic addition to α,β-unsaturated ketones is the synthesis of the Wieland–Miescher ketone. This bicyclic diketone is obtained by a Robinson annulation consisting of a first Michael addition to vinyl methyl ketone followed by an intramolecular aldol reaction.

The first organocatalytic enantioselective nucleophilic addition to α,β-unsaturated ketones was reported by Kawara and Taguchi in 1994 [9]. In this report they stated that chiral proline-derived ammonium hydroxides catalyzed the reaction between malonates and α,β-unsaturated ketones in good yields and moderate enantioselectivities (up to 71%).

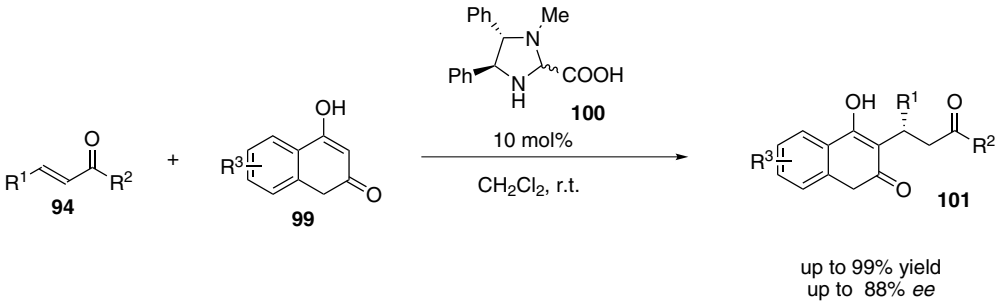
The next step in the organocatalytic nucleophilic addition to α,β-unsaturated ketones was made by Jørgensen and coworkers in 2003 [78]. In this report, Jørgensen reported that phenyl alanine derived catalysts (**97**) promote the addition of malonates to acyclic enones. The products (**98**) were obtained in good yields and selectivities when dibenzyl malonate (**41**) was used. However, with aliphatic

or more sterically demanding enones the yields dropped significantly (Scheme 33.26).



Scheme 33.26 Malonate addition to enones reported by Jørgensen.

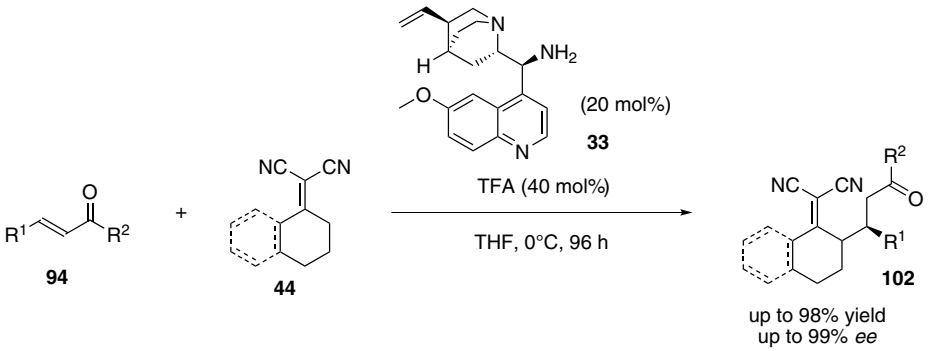
Next, the same research group expanded the scope of the reaction using cyclic 1,3-dicarbonyl compounds (4-hydroxycoumarin, **99**) [79]. This time the authors used catalyst **100**, which renders the final compounds **101** in good yields and good enantioselectivities (Scheme 33.27). However, the catalytic intermediate was not clear due to the stereochemical outcome of the reaction. Later, Chin and coworkers suggested that the catalyst decomposes under the reaction conditions to form the diamine, which could explain the facial selectivity observed.



Scheme 33.27 Jørgensen's addition of 4-hydroxycoumarin to enones.

Ley and coworkers reported in 2006 the use of the tetrazole analog of proline (**29**) in the conjugate addition of methyl or ethyl malonates to enones [80]. The reaction only needs a slight excess of the nucleophile and furnishes the final products in good yields and enantioselectivities.

In 2007, the research groups of Chen and Deng [81] applied the primary amine derived from quinine as an outstanding catalyst for the addition of different nucleophiles to enones. Chen and Deng tested this catalyst in the conjugate addition of dicyanoolefins (**44**) to enones with excellent results (Scheme 33.28). Chen [82] then

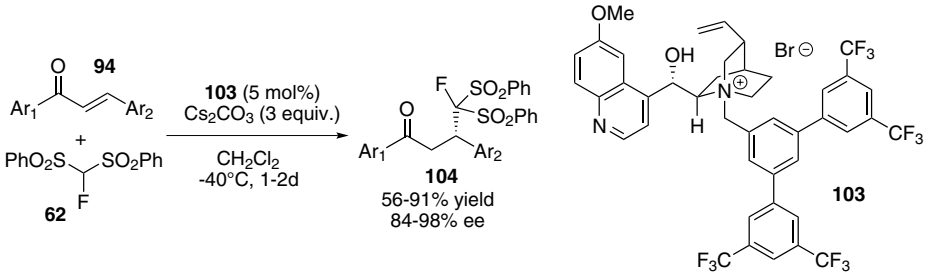


Scheme 33.28 Conjugate addition of dicyanoolefins to enones.

showed the high performance of this catalyst in the addition of 4-hydroxycoumarin to β-substituted enones with excellent results. In all these examples, the use of a strong acid as co-catalyst (usually TFA) is required. A similar reaction was reported by Feng in 2009, leading to the synthesis of warfarin using *C*2 symmetry diamines [83].

Recently, other research groups have developed the addition of 1,3 dicarbonyl or related compounds to enones. For example, Lattanzi reported the addition of malononitriles to enones catalyzed by cinchona alkaloids with good yields and enantioselectivities [84], Jaszay reported the addition of diethylcyanomethyl phosphonate to enones using thiourea catalysts with moderate yields and enantioselectivities [85], and Wang reported the Michael addition of ketones to chalcones using pyrrolidine-derived catalysts with good yields and excellent enantioselectivities [86].

To obtain a formal β-fluoromethylation of ketones, Shibata, Toru, and coworkers employed FBSM (**62**) as Michael donor in the enantioselective conjugated addition to α,β-unsaturated ketones [87]. The reaction was catalyzed by a quaternary salt derived from cinchona alkaloid (**103**), affording the final products **104** in high yields (up to 91%) and excellent enantioselectivities (Scheme 33.29).



Scheme 33.29 Enantioselective Michael addition of **62** to enones.

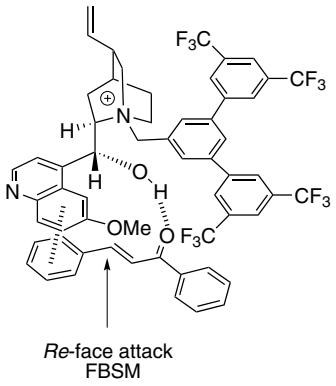


Figure 33.8 A proposed transition state assembly.

Several ammonium salts derived from cinchona alkaloids were screened as possible catalysts. Catalyst bearing the hydroxyl group methylated failed, revealing the importance of the free hydroxyl moiety in the catalyst, as well as sterically demanding benzyl substituents in the quaternary nitrogen. Thus, the quinidinium bromide catalyst (**103**) in combination with Cs_2CO_3, rendered the best results. Although only 5 mol% of catalyst was necessary, 3 equivalents of the inorganic base were necessary to achieve high enantiocontrol.

A series of chalcone derivatives and enolizable enones were reacted, affording the Michael adducts with excellent results. Finally, to obtain the fluoromethylated compound, the authors proposed a short sequence of three steps, consisting of reduction of the carbonyl moiety, reductive desulfonylation using Mg/MeOH, and oxidation with PCC. Desulfonylated products were obtained without racemization.

To justify the high enantiocontrol observed in this conjugated addition, the authors postulated a transition-state structure in which the free hydroxyl group captures the enone, presumably by hydrogen bond formation with the carbonyl oxygen atom (Figure 33.8). Aromatic π–π interaction between the enone's arylic rings and the aromatic "wings" of the catalyst additionally stabilize the transition-state structure, in which the catalyst blocks the *Si* face of the enone. Then, nucleophilic FBSM (**62**) conjugated attack through the *Re* face renders the desired product in high enantioselectivity.

In 2010, Xie reported a vinylogous Michael addition of 3-cyano-4-methylcoumarins to α,β-unsaturated ketones using primary amine catalysts derived from cinchona alkaloids to promote the reaction. The final compounds were afforded in good yields and good enantioselectivities [88].

2-Oxindoles and benzofuranones have been used as nucleophiles in the Michael addition to cyclic enones using as a catalyst primary amines derived from cinchona

alkaloids [89]. The reaction afforded the final compounds in good yields and enantioselectivities but with moderate diastereoselectivities.

Another important reaction by which to form C–C bonds is the nitroalkane Michael addition. The first attempt to obtain a nitroalkane enantioselective addition to enones was reported by Yamaguchi in 1994, using as a catalyst rubinate salts of proline. The first truly enantioselective organocatalytic addition of nitroalkanes to enones was developed by Hanessian using proline as catalyst in the presence of an amine additive. The reaction affords good yields and enantioselectivities when cyclic enones were used (up to 93% ee); however, the addition to chalcones renders the products in lower enantioselectivities (up to 68% ee) [90].

Jørgensen and coworkers reported in 2002 an organocatalytic addition of nitroalkanes to acyclic β-substituted enones catalyzed by a chiral diamine [91]. The products were obtained in good yields and enantioselectivities, with the limitation that heteroaromatic, aliphatic, or bulky substituted ketones render only moderate yields. When prochiral nitroalkanes were used the diastereoselectivity was very low in all the examples. Three years later the same research group reported the use of a tetrazole derivative for the same reaction [92]. The yields and enantioselectivities were similar but the reaction times were halved. However, the limitation regarding the low diastereoselectivity obtained when prochiral nitroalkanes were used remained unsolved.

At almost the same time, Ley and coworkers reported the use of tetrazole proline catalyst for the addition of nitroalkanes to enones [93]. As in Hanessian's example, this protocol requires the use of an amine additive. In this case, the enantioselectivities obtained were excellent, albeit with moderate yields.

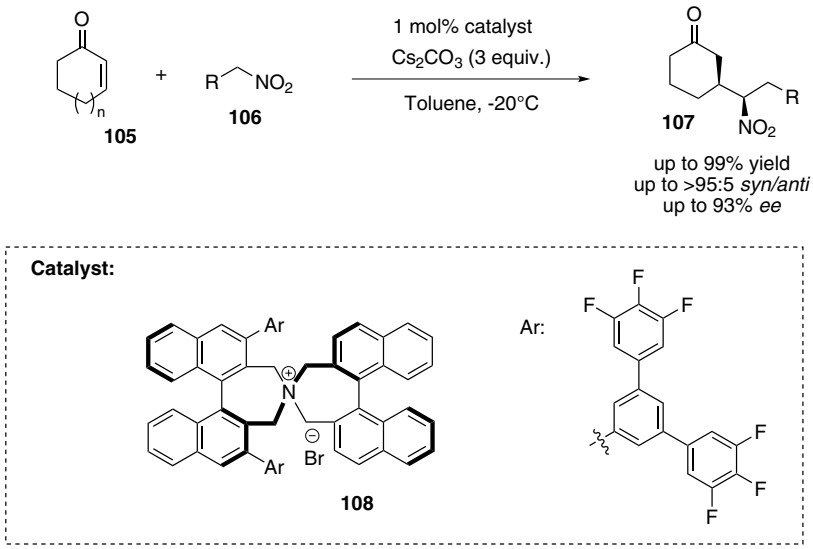
Other catalysts used in this reaction were published by Tsogoeva [94] (small peptides), Hanessian (4,5-methano-L-proline) [95], Zhao (primary–secondary amine catalysts) [96] with similar results.

In 2010, Du reported the use of chiral squaramides as catalyst for the Michel addition of nitroalkanes to chalcones with excellent results in terms of yields and enantioselectivities [97]. However, when cyclic enones were used the enantioselectivity dropped dramatically and when prochiral nitroalkanes were used the diastereoselectivity was very low.

To overcome the low diastereoselectivities reported in the Michael addition of prochiral nitroalkanes to enones, Maruoka and coworkers reported the use *N*-spiro quaternary ammonium salt (**108**) as phase-transfer catalysts [98a]. As shown in Scheme 33.30, the results in terms of yields and diastereo- and enantioselectivities were excellent. A year later, the same research group expanded the scope of the reaction with the use of silylnitronates instead of nitroalkanes [98b].

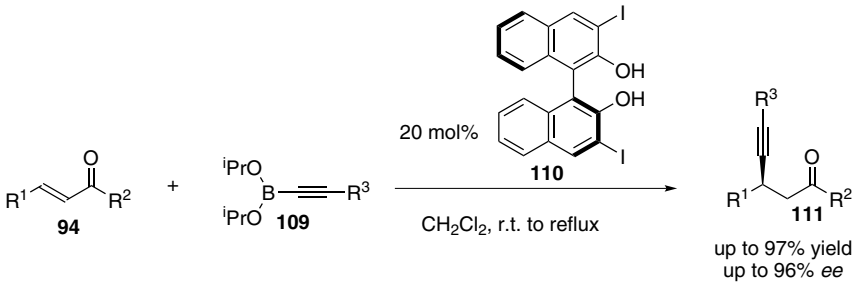
33.2.3.1.3 Other Michael Reactions Leading to C–C Bonds

An intriguing methodology for the organocatalytic asymmetric Michael addition of alkynyl borates to enones was reported by Chong in 2005 [99]. In this methodology BINOL derivatives are used as a catalyst and constitutes an example of a



Scheme 33.30 Addition of nitroalkanes to enones reported by Maruoka.

ligand-accelerated asymmetric process. The achiral starting boronate has a much slower rate than the BINOL-boronate. The proposed reaction is illustrated in Scheme 33.31. Achiral boronate **109** could undergo transesterification with a chiral BINOL (**110**) to form a chiral boronate, which might undergo reaction with enone and then transesterification occurred again to free the chiral BINOL. The reaction afforded the final alkynylated compounds in good yields and good enantioselectivities.



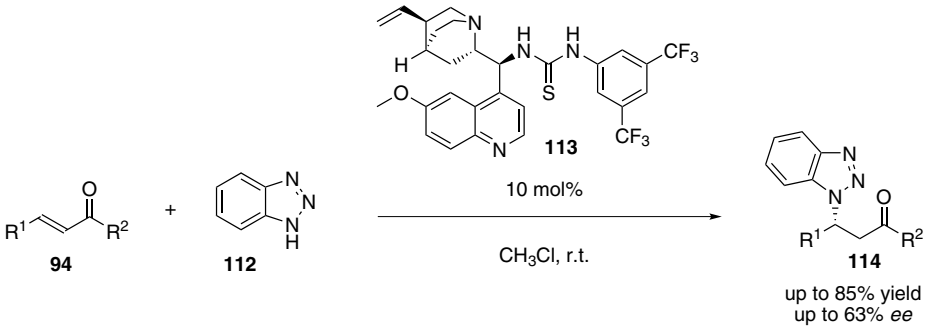
Scheme 33.31 Michael addition of alkynyl borates.

In 2009, Takemoto and coworkers reported an expansion of the scope of the above reaction, using alkenylboronic acids as nucleophiles and chiral thioureas as catalysts [100]. To activate the alkenylboronic acid a hydroxyl group at the β position was added to the enone. The thiourea activated the enone while the β-hydroxyl of the enone and the hydroxyl of the catalyst activate and direct the intramolecular

attack of the alkenylboronic ester, leading to the β-alkenylated enones in excellent yields and enantioselectivities.

33.2.3.2 C–N Bond Formation

In 2007, Wang and coworkers reported the 1*H*-benzotriazole (**112**) addition to enones catalyzed by a chiral thiourea derived from cinchona alkaloids (**113**). The final products **114** were obtained in good yields but modest enantioselectivities (up to 64% ee) (Scheme 33.32) [101]. Two years later the same research group improved these results by using as catalyst a primary amine derived from cinchona alkaloids and L-*N*-Boc-phenylglycine as an additive [102]. The enantioselectivities increased up to 88% enantioselective excess. Remarkably, the authors observed the formation of the isomeric N2-addition products with high enantioselectivities but low yields.



Scheme 33.32 Amination of enones reported by Wang.

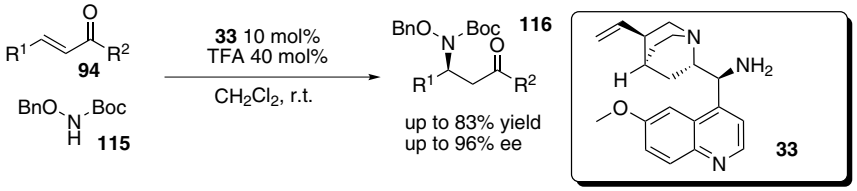
At almost the same time, Ricci and coworkers reported an asymmetric aza-Michael addition of *O*-benzylhydroxyamines to chalcones catalyzed by a thiourea derived from cinchona alkaloids. The amine derivatives were obtained in good yields but low enantioselectivities (up to 60% ee) [103]. Interestingly, the thiourea moiety has a major role in the catalyst activity. When alkaloids lacking the thiourea moiety were used the reaction resulted in very poor conversions.

The same year, Jørgensen and coworkers reported an enantioselective aza-Michael addition to enones using hydrazones as nucleophiles and cinchona alkaloids as catalyst [104]. This base-catalyzed reaction renders the final aminated products in good yields but only moderate enantioselectivities (up to 77% ee).

Scettri and Acocella have reported a similar base-catalyzed reaction under solvent-free conditions using simple anilines as nitrogen source [105]. The products were obtained in excellent yields albeit with poor enantioselectivities (up to 56% ee).

In 2008, Deng and coworker developed the first highly enantioselective aza-Michael reaction to enones [106]. In this work they used 9-amino cinchona alkaloid **33** as catalyst and TFA as additive. The reaction between Boc-protected *N*-benzylhydroxylamine (**115**) and enones under these conditions renders the final

products in moderate to good yields and excellent enantioselectivities. Remarkably, as was already stated by MacMillan in his aza-Michael reaction with enals, the α-effect on the oxygen linked to the nitrogen is crucial in enhancing the nucleophilicity of the nitrogen (Scheme 33.33).



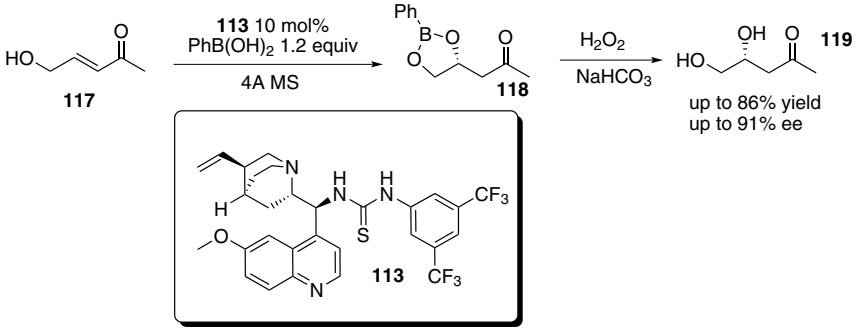
Scheme 33.33 Aza-Michael reaction developed by Deng.

A similar reaction was reported by Melchiorre [107]. Inspired by the hydroxylamine addition to enals developed by Cordova, Melchiorre reported the use of the same nucleophiles with enones catalyzed by primary amine catalysts. The results in terms of yield and enantioselectivities were excellent in almost all the examples.

Zhao and coworkers reported the use of 2-pyrazolin-5-ones as suitable nitrogen nucleophiles for the Michael reaction with enones [108]. In this report the use of 32 mol% of 9-epi-9-amino-9-deoxyquinine and 40 mol% of benzoic acid was necessary to obtain high yields and enantioselectivities.

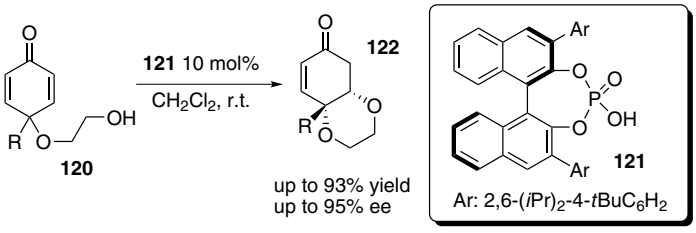
33.2.3.3 C–O Bond Formation

The first enantioselective organocatalytic oxo-Michael reaction to enones was reported by Falck [109]. Falck developed the intramolecular addition of boronic acids hemiesters to enones catalyzed by thiourea catalysts. Alkyl, aryl, and heteroaryl γ-hydroxy enones react with phenylboronic acid to furnish the corresponding boronic hemiesters **118**, which after oxidative cleavage of the resulting dioxaborolane renders the chiral 1,2 diols **119** in excellent yields and enantioselectivities (Scheme 33.34).



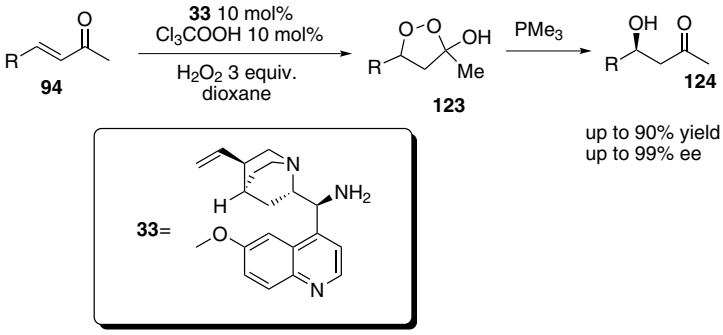
Scheme 33.34 Intramolecular addition of boronic acid hemiesters to enones.

You and coworkers developed a desymmetrization protocol based on an intramolecular oxo-Michael reaction, using as catalyst the phosphoric acid derivative **121** [110]. Cyclohexadienones **120** were transformed into the corresponding bicyclic systems **122** with high yields and enantioselectivities. Remarkably, the 4-substituent in the cyclohexadienone has a great influence on the enantioselective outcome of the reaction. Bulkier substituents at the 4-position lead to lower reaction rates and enantioselectivities (Scheme 33.35). This desymmetrization reaction was used as a key reaction for the efficient synthesis of the natural products cleroindicins C, D, and F, thereby showing the synthetic utility of this reaction.



Scheme 33.35 Desymmetrization reported by You.

List and coworkers reported an oxa-Michael reaction with aliphatic acyclic enones **94** using hydrogen peroxide as oxygen source [111]. Treatment of enones with catalytic amounts of cinchona alkaloid derived primary amine **33** (as its salt), followed by excess hydrogen peroxide furnished the intermediate peroxyhemiketals with high yields and stereoselectivities. Subsequent reduction of these compounds led to the corresponding β-hydroxyketones **124** without loss of enantioselectivity (Scheme 33.36). The same research group developed the asymmetric epoxidation of enones with excellent results [112].



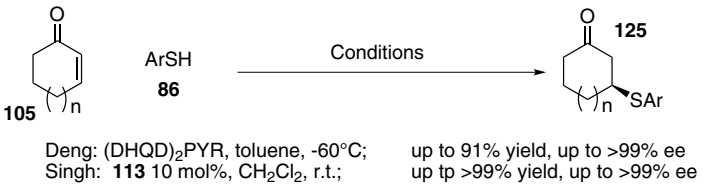
Scheme 33.36 Oxo-Michael reaction of enones reported by List.

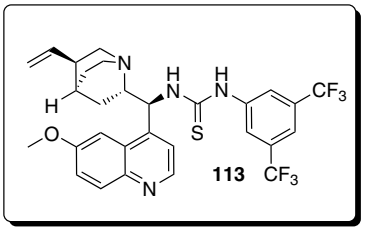
33.2.3.4 **C–S Bond Formation**

The first asymmetric organocatalytic sulfa-Michael reaction of enones was reported by Wynberg in 1977 [113]. In this report cyclohexenone reacts with thiophenyl

derivatives promoted by quinine, affording the addition products in good yields and moderate enantioselectivities. In 1981, the same research group reported the addition of thiocarboxylic acids to cyclic enones catalyzed by cinchona alkaloids, affording the thio adducts in good yields but moderate enantioselectivities.

Skarżewski reacted acyclic enones with thiols catalyzed by cinchona alkaloids [114]. Cinchonine was the best catalyst evaluated and the Michael adducts were obtained in excellent yields albeit with moderate enantioselectivities. Similar approximations were made by Mukaiyama and coworkers using hydroxyl-proline derivatives, affording the thio adducts in good yields and good enantioselectivities (up to 88% ee) [115]. However, the most effective thiol addition to enones was reported by Deng [116]. In this report $(DHQD)_2PYR$ (hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether) was used as catalysts, affording the final compounds in excellent yields and enantioselectivities (Scheme 33.37).





Scheme 33.37 Thio-Michael reaction reported by Singh and Deng.

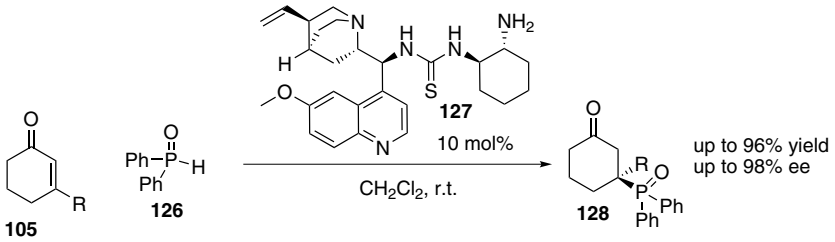
In 2006, Wang and coworkers reported the use of chiral bifunctional amine thiourea catalysts for the Michael reaction between thioacetic acid and different enones, affording products in excellent yields but moderate enantioselectivities (up to 63% ee) [117].

In 2010, Singh and coworkers reported the use of cinchona alkaloid derived urea **113** as catalyst for the Michael addition of aromatic thiols to enones [118]. The reaction renders excellent yields and enantioselectivities with aliphatic or cyclic enones, while aromatic enones afford slightly worst enantioselectivities (Scheme 33.37).

33.2.3.5 **Other Michael Reactions**

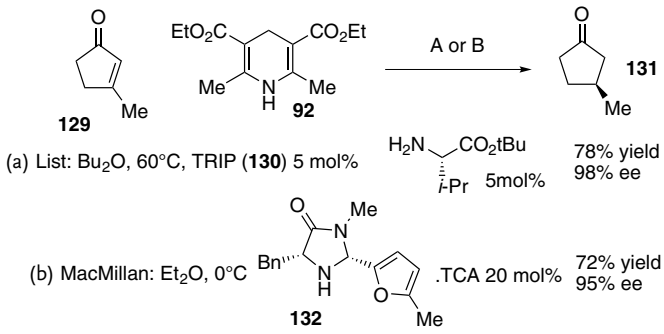
Despite the great interest in chiral phosphines and the success in the phospha-Michael addition to enals, only one example of an organocatalytic phospha-Michael reaction to enones can be found in the literature.

Ye, Liang, and coworkers reported the addition of diphenylphosphine oxide to enones catalyzed by a bifunctional primary amine thiourea catalyst (**127**) derived from cinchona alkaloid (Scheme 33.38) [119]. Cyclic and acyclic enones react with phosphine oxides under the optimized conditions to furnish the phosphine derivatives **128** in excellent yields and enantioselectivities. The primary amine of the catalyst activates the enone via an iminium, while the thiourea moiety activates and directs the phosphine group.



Scheme 33.38 Phosphination of enones reported by Ye.

In 2006, the research groups of List [120] and MacMillan [121] independently reported the organocatalytic, highly enantioselective transfer hydrogenation of enones using Hantzsch esters (**130**) as the hydrogen source. List used as catalysts primary amino esters derived from amino acids plus a chiral phosphoric acid. This combination results very effectively in the hydrogenation of cyclic enones or acyclic enones, affording the final products **131** in excellent yields and enantioselectivities. On the other hand, MacMillan used as catalyst a furyl imidazoline TCA salt (**132**). Under the optimized conditions the reaction furnishes the reduced products **131** in good yields and excellent enantioselectivities. The only limitation of MacMillan's methodology is that only cyclic enones could be used (Scheme 33.39).



Scheme 33.39 Transfer hydrogenation of enones.

33.3 Conclusion

Organocatalysis have emerged recently as one of the cornerstones for the enantioselective synthesis of C–C or C–heteroatom bonds. Owing to the easy prediction of the stereochemical outcome of the reactions, iminium activation and specific Michael reactions is one of the most studied reaction types in organocatalysis. In the literature, we can find multiple approaches to the organocatalytic Michael reaction using different catalysts or nucleophiles, most of them with exceptional levels of stereoselectivity. Moreover, these simple additions to enals or enones have inspired multiple organocatalytic tandem and cascade reactions and, in our view, open up a new pathway for the enantioselective construction of complex scaffolds in one-pot procedures.

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