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Tetrahedron: *Asymmetry* 18 (2007) 299–365
Tetrahedron: *Asymmetry*

Tetrahedron: *Asymmetry* report number 92

Organocatalytic asymmetric conjugate additions

Diana Almaşi, Diego A. Alonso* and Carmen Nájera*

Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO), Facultad de Ciencias, Universidad de Alicante, Apartado 99, E-03080 Alicante, Spain

Received 4 December 2006; accepted 13 January 2007

Abstract—The asymmetric organocatalytic conjugate addition of nucleophiles to Michael acceptors is reviewed. Herein an overview of the most important developments and concepts of this flourishing area of catalysis organized by the type of nucleophile involved in the process is reported.

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* Corresponding authors. Tel./fax: +34 96 5903549; e-mail addresses: diego.alonso@ua.es; cnajera@ua.es

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doi:10.1016/j.tetasy.2007.01.023

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1. Introduction

Asymmetric organocatalysis employs small chiral organic molecules to accelerate asymmetric reactions.[1] This type of processes has become very attractive in recent years since environmentally friendly and metal-free transformations are desired. The conjugate addition of nucleophiles to electron-poor alkenes is one of the most frequently used C–C and C–heteroatom bond forming reactions in organic synthesis.[2] The catalytic asymmetric version of this reaction[3] employing chiral catalysts has developed significantly as evidenced by the large number of publications to appear in this field over the last few years (Fig. 1). This tendency is even more spectacular when we take a look at the number of studies that have been recently carried out regarding asymmetric conjugate additions promoted by chiral organocatalysts (Fig. 1).

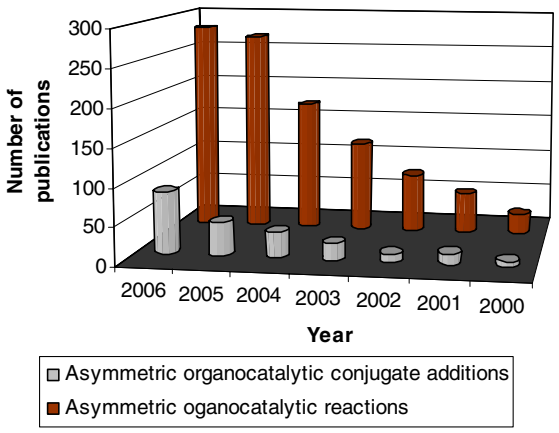


Figure 1. Publications for asymmetric organocatalytic conjugate additions and organocatalytic reactions during 2000–2006. Source: Scifinder.

From a mechanistic point of view, interactions between the catalyst and the substrates in an asymmetric organocatalytic conjugate addition are rather different to those implicated in a metal-catalyzed process. Organocatalysts provide a chiral environment to the process activating the nucleophile, the electrophile or both reagents through weak interactions, such as hydrogen bonding or ion pairing[4] or much stronger interactions such as covalent bonding. Enantioselective phase-transfer catalysis (PTC)[5] illustrates how weak interactions, such as ion pairing, can be used to carry out enantioface discrimination in conjugate addition reactions (**A**, Fig. 2). Chiral ion pairs can be formed either by deprotonation with a chiral base or by employing a chiral phase-transfer catalyst and are responsible for asymmetric induction in the process. The reactions are usually carried out in two- or three-phase systems, in vigorously stirred aqueous-apolar solvent mixtures. Reactions under PTC were initially carried out with ammonium salts derived from *Cinchona* alkaloids although recently better enantioselectivities have been obtained in conjugate addition processes by optimizing the catalyst structures, the reagents used, and the reaction conditions.

On the other hand, electrophile activation by chiral small-molecules bearing hydrogen-bond donors has emerged as an important tool in enantioselective catalysis.[6] Hydrogen bonding to the conjugate acceptor decreases its electron density thus activating it toward nucleophilic attack (**B**, Fig. 2). Chiral ureas, thioureas, guanidinium, and amidinium ions, diols, biphenols, hydroxy acids, and amides are amongst the most successfully used chiral hydrogen-bond donors in conjugate additions.

With respect to covalent activation, the catalyst can either reversibly form a chiral enamine to activate the nucleophile (**C**, Fig. 2), or a chiral iminium ion to activate the acceptor (**D**, Fig. 2). Finally, the ability of certain bifunctional organocatalysts to perform simultaneous activation of the nucleophile and the electrophile is worth noting. This concept was established by Shibasaki in his pioneering work with organometallic chiral Lewis acids equipped with additional Bronsted or Lewis basic functionalities.[7] The use of bifunctional organocatalysis has been shown to be very successful in conjugate additions and as a result is becoming a more and more common place.

Over the last few years, interest in the field of asymmetric organocatalytic conjugate additions has increased spectacularly with many new different catalysts showing impressive results in terms of efficiency and selectivity. This review intends to provide an overview of this exciting and

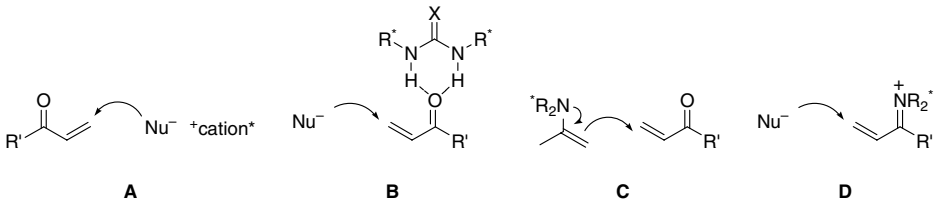


Figure 2. Organocatalytic activations in conjugate addition reactions.

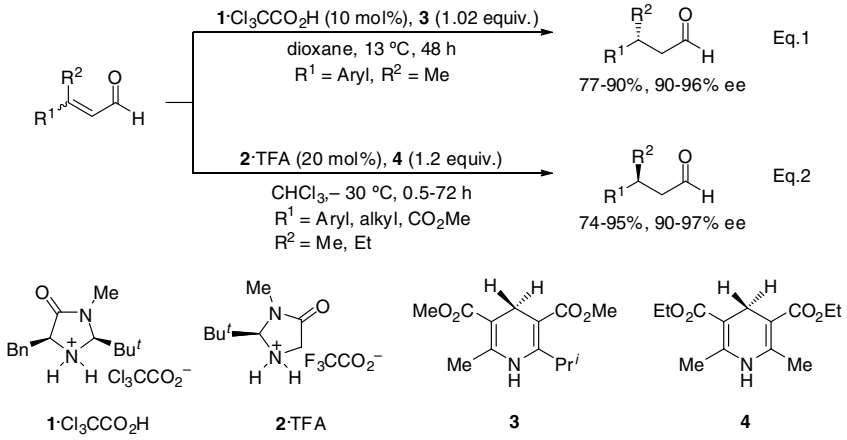
rapidly growing field emphasizing the structural and mechanistic features that contribute to such results.

2. Organocatalytic asymmetric transfer hydrogenation

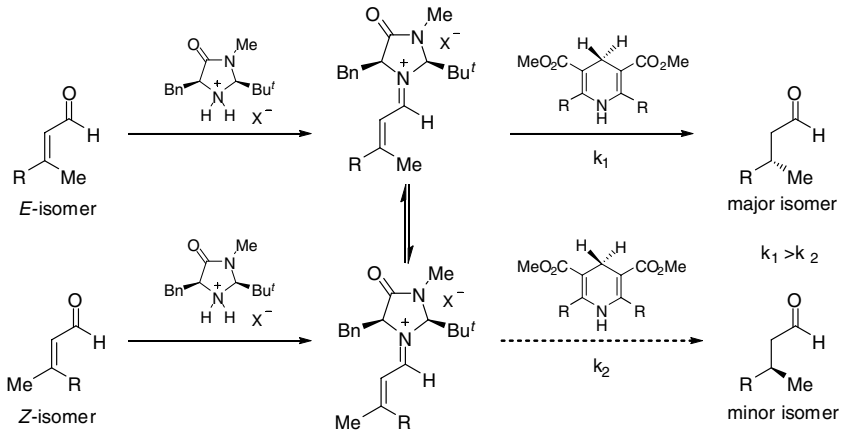
Recently, all methods developed for the enantio- and chemoselective conjugate reduction of α,β-unsaturated carbonyl compounds were based on the use of chiral metal catalysts. However, very recent studies have demonstrated that organocatalytic transfer hydrogenation of carbonyl compounds can be accomplished with small molecules as catalysts, such as chiral amines and Hantzsch ester pyridines mimicking the conceptual blueprints of biochemical reductions: enzymes and NADH cofactors.[8] List et al.[9] and MacMillan et al.[10] reported a highly enantioselective conjugate reduction of β,β-disubstituted α,β-unsaturated aldehydes by employing imidazolidinone derivatives **1** and **2**, respectively (Scheme 1). With respect to the substrate, MacMillan's catalyst **2** seemed to be more general than List's one **1** since under optimized conditions, a wide variety of trisubstituted α,β-unsaturated aldehydes were reduced in high yields (74–95%) and enantioselectivities (up to 97% ee),[10] though using higher catalyst loadings (Scheme 1, Eq. 2). Interestingly, the reaction conditions were compatible with functional groups that are often susceptible to reduction such as aldehydes and aromatic halogens.[10] Furthermore, a strong solvent and counteranion effect on the yield and enantioselectivity of the reaction was observed, the trichloroacetic and trifluoroacetic salts of the oxazolidinone derivatives being the most active catalysts (Scheme 1).

Another interesting feature was the enantioconvergent character of the reduction, which made it unnecessary to work with geometrically pure enals (Scheme 1). This was due to rapid interconversion of the two initially formed iminium ions prior to the rate determining hydride attack from the dihydropyridine (Scheme 2). The hydride ion was then selectively transferred to the *E*-olefin from the least sterically hindered face to produce the corresponding isomer of the product.

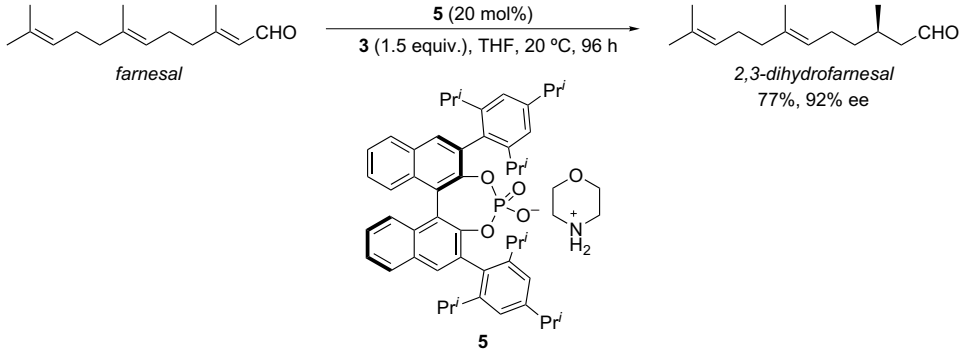
Based on the observed strong counteranion effect over the yield and selectivity in the conjugate reduction of enals,[9,10] List et al. recently developed a highly stereoselective reduction of enals employing catalytic amounts of the achiral ammonium ion of morpholine and the chiral sterically hindered phosphoric acid 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **5**.[11] This new catalytic system was shown to be very effective with sterically unhindered α,β-unsaturated aldehydes, such as



Scheme 1. Enantioselective organocatalytic hydride conjugate reduction.



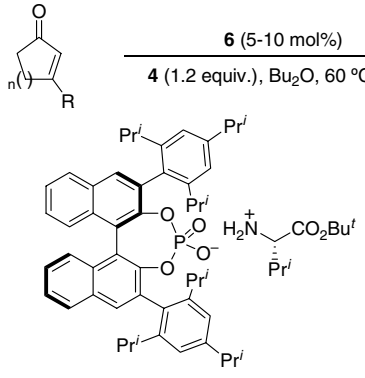
Scheme 2. Proposed mechanism for the enantioselective organocatalytic hydride conjugate reduction of enals.



Scheme 3. Asymmetric counteranion directed conjugate reduction of enals.

farnesal (Scheme 3), which extended the substrate scope of the iminium catalytic transfer hydrogenation.

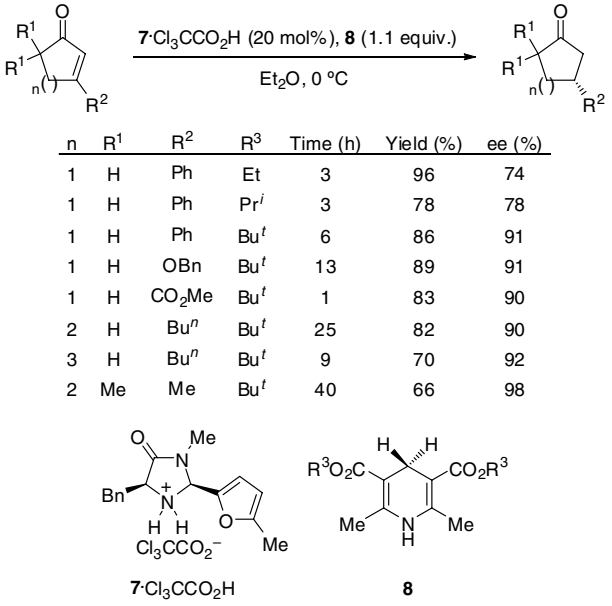
Asymmetric counteranion directed organocatalysis was also applied to the enantioselective transfer hydrogenation of α,β-unsaturated ketones employing catalyst **6**, which involved a chiral cation such as a valine ester phosphate salt and a chiral binaphthol derived phosphate.[12] This combination, in the presence of Hantzsch ester **4**, proved to be a very active and enantioselective system for the transfer hydrogenation of a variety of cyclic α,β-unsaturated ketones (Scheme 4). Acyclic ketones were also reduced but with slightly lower enantioselectivities.



n	R	Yield (%)	ee (%)
1	Me	78	98
1	Et	71	96
2	Me	99	94
2	Et	98	96
2	Pr^i	94	98
2	Ph	99	86
3	Me	>99	96

Scheme 4. Enantioselective transfer hydrogenation of cyclic enones catalyzed by **6**.

Very recently, the organocatalytic transfer hydrogenation of cyclic enones was also studied when employing the imidazolidinone derivative **7**.[13] In this particular case, the structure of the dihydropyridine reagent seemed to have an important effect on the selectivity of the process, since improved enantiocontrol of the reaction was observed as the steric demand of the ester moiety increased (Scheme 5). The reaction, which was performed with substoichiometric amounts of imidazolidinone **7** in ether at 0 °C, allowed a rapid access to a wide variety of enantioenriched cycloalkanones in high yields (66–85%) and enantioselectivities up to 98% ee (Scheme 5). The sense of asymmetric induction observed in all cases was consistent with a selective hydride attack to the *Si*-face of the corresponding *Z* iminium isomer.

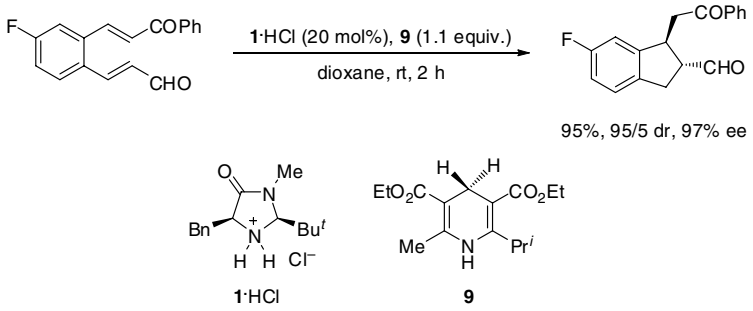


n	R^1	R^2	R^3	Time (h)	Yield (%)	ee (%)
1	H	Ph	Et	3	96	74
1	H	Ph	Pr^i	3	78	78
1	H	Ph	Bu^t	6	86	91
1	H	OBn	Bu^t	13	89	91
1	H	CO_2Me	Bu^t	1	83	90
2	H	Bu^n	Bu^t	25	82	90
3	H	Bu^n	Bu^t	9	70	92
2	Me	Me	Bu^t	40	66	98

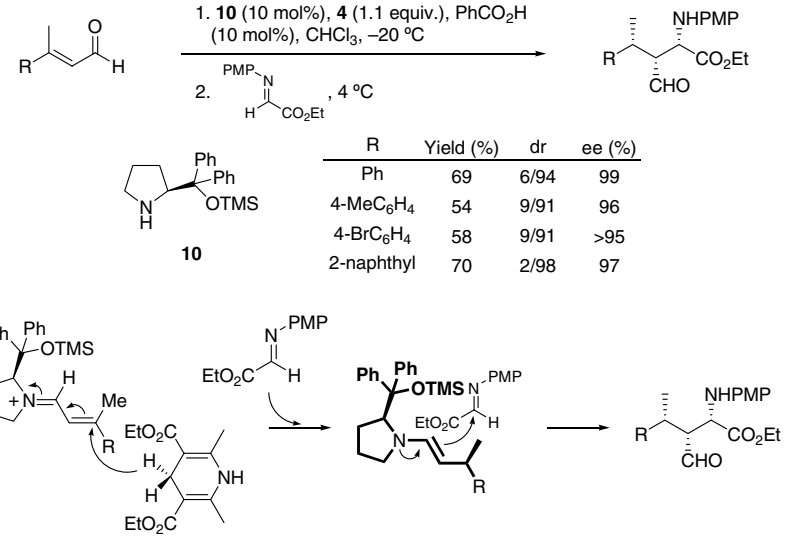
Scheme 5. Transfer hydrogenation of cyclic enones catalyzed by **7**.

The hydrochloride salt of chiral imidazolidinone **1** (20 mol %) was reported as a highly chemo-, regio-, diastereo-, and enantioselective organocatalyst for the reductive Michael cyclization of formyl enones.[14] This tandem reaction, which combined for the first time iminium and enamine catalysis, proceeded via an iminium catalytic conjugate reduction of the enal moiety followed by an in situ enamine-catalyzed asymmetric Michael cyclization (Scheme 6).

Córdova applied the List–MacMillan transfer hydrogenation reaction of aromatic enals in a novel highly enantioselective direct organocatalytic asymmetric domino reductive Mannich-type reaction to generate polyfunctionalized α-amino acid derivatives, with up to three stereogenic centers.[15] In the presence of 10 mol % of chiral pyrrolidine **10** and Hantzsch ester **4**, the reaction proceeded with high chemo-, diastereo-, and enantioselectivity giving the corresponding α-amino acid derivatives in good yields and up to 99% ee (Scheme 7). The stereochemical outcome of the process was explained according to the reaction pathway shown in Scheme 7, where efficient shielding of the *Re*-face of the iminium ion with a *trans*-configuration



Scheme 6. Organocatalytic asymmetric reductive Michael cyclization.



Scheme 7. Direct organocatalytic asymmetric reductive Mannich-type reductions.

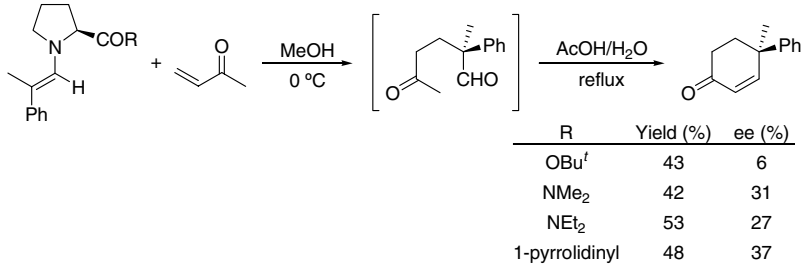
led to *Si*-facial attack by the hydride, which gave the corresponding chiral enamine. This intermediate attacked then the *Si*-face of the imine with a *trans*-configuration to afford the corresponding amino acid derivative with high diastereoselectivity.

3. Organocatalytic asymmetric conjugate addition of carbon nucleophiles

3.1. Conjugate addition of aldehydes

A wide variety of carbon nucleophiles have been successfully used in the organocatalytic asymmetric inter- and intramolecular Michael addition to different α,β-unsaturated systems. Among them, the addition of aldehydes to diverse Michael acceptors, such as α,β-unsaturated ketones, alkylidene malonates, β-nitrostyrenes, and vinyl sulfones, was one of the most studied reactions.

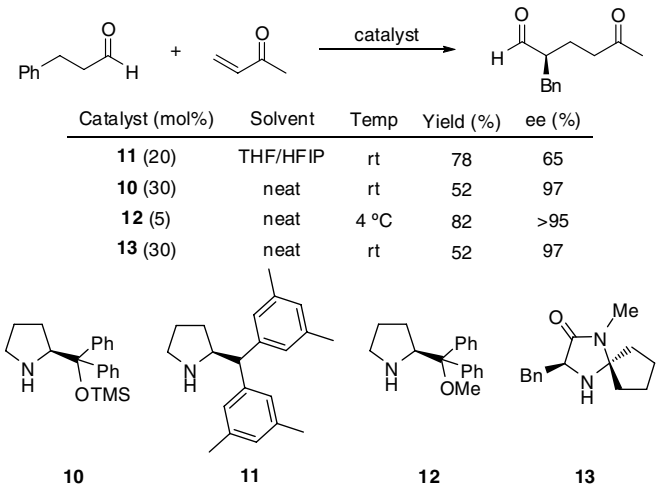
3.1.1. Conjugate addition of aldehydes to α,β-unsaturated carbonyl compounds. In 1969, Yamada and Otani reported the stereoselective stoichiometric synthesis of 4,4-disubstituted 2-cyclohexenones through an asymmetric Robinson annulation between preformed chiral aldehyde L-proline-derived enamines and methyl vinyl ketone (Scheme 8).[16] Surprisingly, relatively few examples of the organocatalyzed Michael additions have been reported



Scheme 8. Yamada's asymmetric Robinson annulation.

since which involve simple aldehyde donors with enones as acceptors.

It was not until 2003 when Jørgensen et al. found modest enantioselectivities in the first catalytic version of the direct enantioselective Michael addition of aldehydes to vinyl ketones catalyzed by the chiral amine (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine **11** (Scheme 9).[17] Further studies on the reaction were carried out by different groups drove to more efficient catalysts such as diphenylprolinol ethers **10**[18] and **12**[19] and imidazolidinone **13**[20] (Scheme 9). An especially interesting result was obtained with the diphenylprolinol derivative **12**, which catalyzed the intermolecular Michael addition of a wide variety of aldehydes with different vinyl ketones with the highest enantioselectivities reported to date (95–99% ee) employing significantly lower catalyst loadings (1–5 mol %) than those reported with other organocatalysts (20–30 mol %).[18]



Catalyst (mol%)	Solvent	Temp	Yield (%)	ee (%)
11 (20)	THF/HFIP	rt	78	65
10 (30)	neat	rt	52	97
12 (5)	neat	4 °C	82	>95
13 (30)	neat	rt	52	97

Scheme 9. Enantioselective Michael addition of aldehydes to vinyl ketones.

On the basis of different theoretical and experimental studies,[17,20] it was demonstrated that this type of catalysts acted as nucleophile activators rather than electrophile activators reacting with the aldehyde to form the corresponding enamine intermediate, which suffered conjugate addition to the vinyl ketone. In the case of catalyst **11**,[17] the most stable *anti*-enamine **A** [*E* configuration about the N–C(sp^2) bond, Fig. 3] was formed, shielding the bulky groups present at the 2-substituent of the catalysts their *Re*-face, leaving the *Si*-face available for electrophile approach. The observed non-linear effect for this particular case could not exclude that an iminium intermediate, probably present in a very small amount and more reactive compared to the vinyl ketone, could also contribute to the reaction. The same configuration for enamine **C** was observed for imidazolidinone **13** (Fig. 3).[20]

List et al. successfully employed MacMillan's imidazolidinone **14** in the intramolecular Michael addition of aldehydes to aliphatic and aromatic enones (Scheme 10, Eq. 1).[21] The Michael addition, which also worked in lower enantioselectivity, for the intramolecular addition of aldehydes to enals (Scheme 10), was assumed to follow an enamine mechanism. However, the fact that only enones and not other Michael acceptors such as α,β-unsaturated esters, thioesters, and nitroalkenes reacted to give the corresponding functionalized cyclopentanes with very high enantioselectivity could be regarded as confirmation for a dual-activation mechanism involving the formation of both enamine and iminium intermediates.[21] Cysteine-derived organocatalyst **15** was also successfully used in the intramolecular Michael addition of aldehydes to enones.[22] Noteworthy was the diastereo- and enantioselective formation of the kinetic *cis*-isomer, a result, which was opposite to the result obtained with MacMillan's catalyst **14** (Scheme 10, Eq. 1). Catalyst **15** seemed then to be more general than **14**, since *trans*-disubstituted cyclopentanes are easily obtained via isomerization of the *cis*-isomer under basic conditions.

Very recently Watanabe et al. carried out a detailed investigation of the scope and mechanism of the organocatalyzed self-condensation of α,β-unsaturated aldehydes.[23] 1,2,4-Trisubstituted cyclohexadienecarboxaldehydes were prepared under mild reaction conditions (EtOH, rt) in high yields and moderate enantioselectivities by self-condensation of different β-methyl substituted α,β-unsaturated aldehydes employing L-proline **16** (Scheme 11).

With respect to the reaction mechanism, L-proline promoted the Michael addition via dual activation of the enal through iminium ion and enamine formation, as shown in Scheme 12. Reaction between the organocatalyst and the enal resulted in the formation of iminium ion **I**, which tautomerized to afford the corresponding enamine **II**. The conjugate addition between **I** and **II** started the dimerization process (Scheme 12). NMR and MS time course analysis of the process provided evidence for the intermediacy of iminium ions **I** and **V**. Furthermore, the moderate enantioselectivities observed in the reaction (Scheme 11) supported

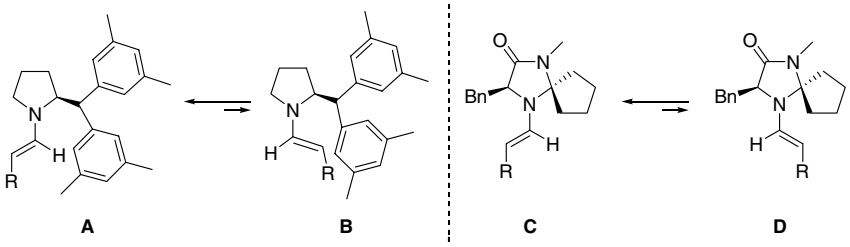
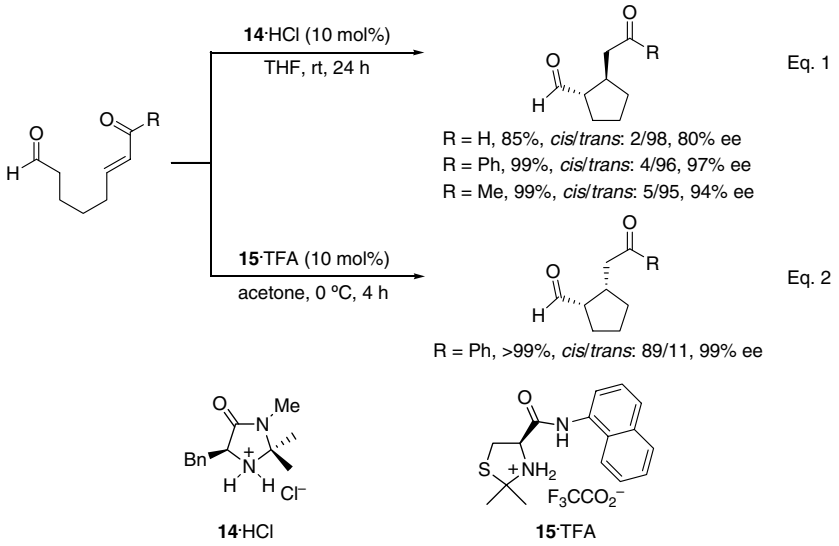
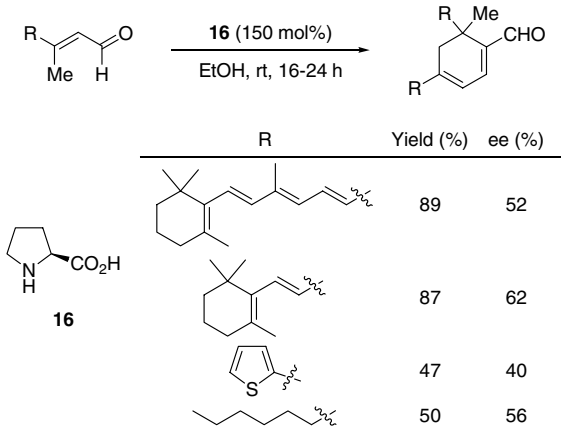


Figure 3. Enamine intermediates for the Michael addition of aldehydes to vinyl ketones.



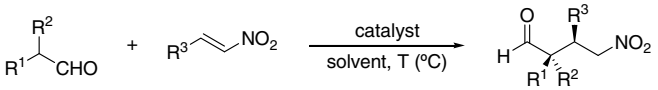
Scheme 10. Catalytic asymmetric intramolecular Michael addition of aldehydes to enones and enals.



Scheme 11. L-Proline promoted self-condensation of α,β-unsaturated aldehydes.

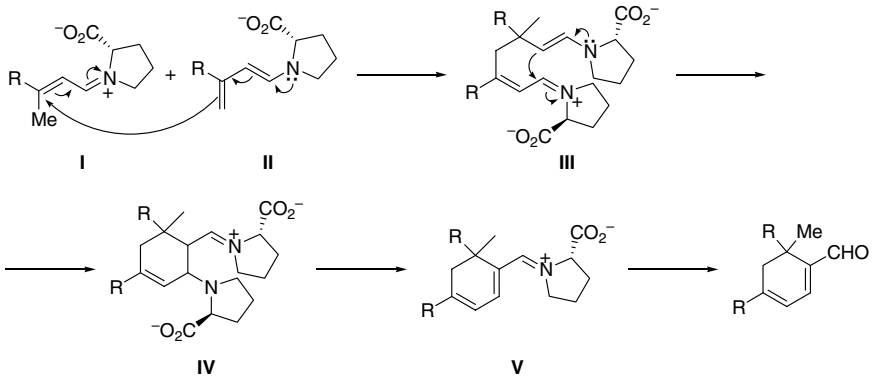
a conjugate mechanism versus a Diels–Alder-based mechanism between **I** and **II**. In a Diels–Alder mechanism, the effect of the chiral auxiliary should be quite pronounced since it involves two reaction centers, while the conjugate addition involves only the γ-position, a remote carbon center, of the *s-cis*-diene, thus supporting the low enantioselectivities observed.

3.1.2. Conjugate addition of aldehydes to nitroolefins. The Michael reaction of an aldehyde with a nitroalkene is, by far, the most studied reaction when using aldehydes as nucleophiles (Scheme 13). This is due to the generation of up to three stereogenic centers in the process and also because chiral nitroalkanes are highly versatile synthetic intermediates, due to the ability to transform the nitro group into other useful functionalities.[24]



Scheme 13. Asymmetric Michael addition of aldehydes to nitroalkenes.

For this reason, since the first study by Barbas et al. on the catalytic asymmetric Michael reaction of aldehydes with β-nitrostyrenes (Scheme 13, $R^3 = Ar$) employing chiral diamine **17**[25] as a catalyst, a wide variety of efficient organocatalysts **10** and **18**–**29** have appeared in the



Scheme 12. Proposed mechanism for the L-proline promoted self-condensation of α,β-unsaturated aldehydes.

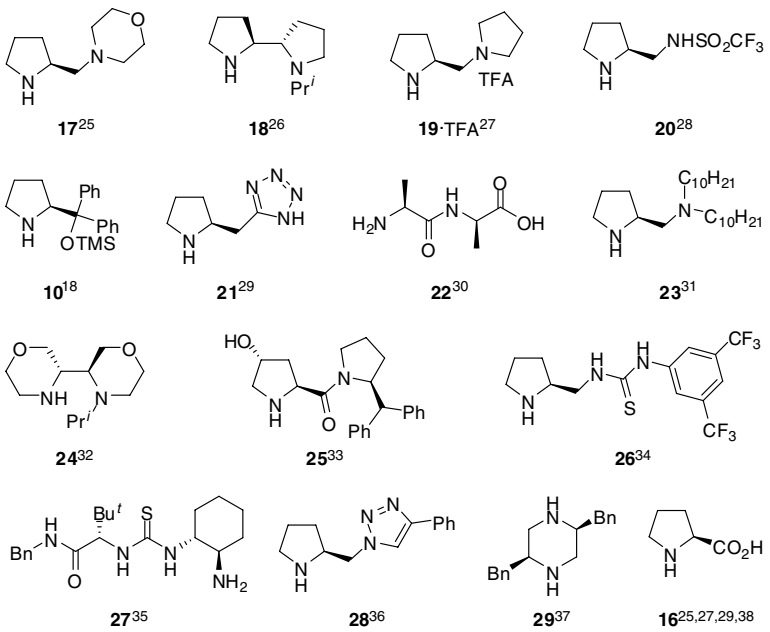


Figure 4. Organocatalysts for the direct asymmetric Michael addition of aldehydes to β-nitrostyrenes.[18,25–38]

literature to efficiently promote this process (Fig. 4). These systems, which are commercially available and/or easily prepared from the chiral pool through very simple chemical transformations, usually consist of chiral secondary amines, probably due to the favorable imine-secondary enamine equilibrium, although primary amine catalysts have also been developed such as **22**[30] and **27**.[35] Both primary and secondary chiral amines fill the gap left by L-proline **16** catalyst that, while still playing a central role in aminocatalysis, provided modest enantioselectivities (23–51% ee) in this process under different reaction conditions.[25,27,29,38]

Concerning the Michael addition of *linear aldehydes* to β-nitrostyrene (Scheme 13, $R^2 = H$, $R^3 = Ph$, Table 1), Barbas et al. obtained higher enantioselectivities than those achieved with L-proline for the *syn*-selective addition (56–69% ee) employing substoichiometric amounts (20 mol %) of (*S*)-2-(morpholinomethyl)pyrrolidine **17** (Table 1, entry 1).[25] Better diastereo- and enantioselectivities were obtained later with *N*-isopropyl-2,2′-bipyrrolidine **18** for the addition of linear aldehydes.[26] However, neither of these two catalysts reached the levels of stereocontrol shown by catalysts **10**,[18] **20**,[28] and **25**[33] with diastereoselectivities and enantioselectivities at the limits of perfect enantiocontrol (Table 1, entries 7, 10, and 19, respectively). Furthermore, **10** and **25** were able to reach those levels of stereocontrol using the lowest catalyst loading reported to date for this reaction (5 mol %), and employing a slight excess of aldehyde (1.2 equiv relative to β-nitrostyrene, only in the case of **25**). Under these conditions, catalysts **10** and **25** also efficiently promoted the addition of β-*branched aldehydes* such as isovaleraldehyde to different nitrostyrenes with very high levels of diastereo- and enantioselectivity (Table 1, entries 11 and 20), respectively.

Few methods were reported for the catalytic enantioselective construction of quaternary stereocenters.[39] The first studies in the direct asymmetric organocatalytic Michael reactions of α,α-*disubstituted aldehydes* with nitrostyrenes were carried out by Barbas et al.[27] by employing 30 mol % of diamine/TFA bifunctional catalyst **19**, which afforded in high yields (up to 96%) chiral α,α-disubstituted γ-nitroaldehydes with modest diastereomeric ratios (*syn*/*anti* from 54/46 to 89/11) and up to 91% ee (Table 1, entries 5 and 6). Although this reaction provided direct access to chiral building blocks with contiguous quaternary and tertiary stereogenic centers, very few examples have been reported with α,α-unsymmetrically disubstituted aldehydes; in all cases low diastereo- and enantioselectivities were obtained (Table 1, entries 8 and 15). However, high enantioselectivities were obtained for the addition of α,α-symmetrically disubstituted aldehydes to nitrostyrenes with different catalysts such as **20**,[28] **24**,[32] and **26**[34] as depicted in Table 1, entries 9, 18, and 21.

Very recently Jacobsen et al. employed the chiral primary amine-thiourea catalyst **27** for a highly enantioselective direct conjugate addition of a wide range of α,α-unsymmetrically disubstituted aldehydes (only a twofold excess of aldehyde relative to nitroalkene) to nitrostyrenes (see Table 1, entry 22, for the addition to β-nitrostyrene).[35] In general, for all the catalysts studied, the electronic and steric nature of the β-nitrostyrene derivatives had no influence on the diastereo- or enantioselectivity of the reaction.

From a practical point of view, the Michael addition of aldehydes to β-nitrostyrene typically required large (tenfold) excess of the nucleophile, due to competing aldol pathways. With respect to the mechanism, the asymmetric Michael reaction employing catalysts **10** and **16**–**29** proceeds via a plausible catalytic enamine mechanism (Fig. 5). In the case of pyrrolidine-derived catalysts, the high *syn*-diastereoselectivities, as well as the enantioselectivities, can be explained by the preferential formation of

Table 1. Asymmetric Michael addition of aldehydes to β-nitrostyrene

Entry	Catalyst (mol %)	R^1	R^2	Time	Solvent	Temp	Yield (%)	*syn*/*anti*	ee[a] (%)
1	**17** (20)	Bu^n	H	27 h	THF	rt	87	85/15	69
2	**17** (20)	Pr^i	H	3 d	THF	rt	78	92/8	72
3	**18** (15)	Pr^n	H	4 d	$CHCl_3$	−25 °C	98	94/6	87
4	**18** (15)	Pr^i	H	2 d	$CHCl_3$	rt	99	87/13	73
5	**19** (30)	Pr^n	Me	4 d	Pr^iOH	4 °C	95	74/26	86[b]
6	**19** (30)	$-(CH_2)_4-$		1 d	Pr^iOH	4 °C	93	—	91
7	**20** (20)	Pr^n	H	20 h	Pr^iOH	0 °C	99	98/2	96
8	**20** (20)	Pr^n	Me	3 d	Pr^iOH	0 °C	72	57/43	60[c]
9	**20** (20)	Me	Me	4.5 h	Pr^iOH	0 °C	85	—	90
10	**10** (10)	Pr^n	H	2 d	Hexane	0 °C	74	95/5	99
11	**10** (20)	Pr^i	H	1 d	Hexane	23 °C	77	94/6	99
12	**10** (20)	Me	Me	4 d	Hexane	23 °C	85	—	68
13	**21** (15)	Pr^i	H	1 d	IPA/EtOH	20 °C	39	>95/5	37[d]
14	**22** (15)	Me	Me	3 d	DMSO/NMP[e]	−20 °C	57	—	58
15	**23** (10)	Pr^n	Me	4 d	Brine	25 °C	97	61/39	64
15	**23** (10)	Me	Me	30 h	Brine	25 °C	76	—	76
16	**24** (15)	Pr^n	H	3 d	$CHCl_3$	rt	88	87/13	89
17	**24** (15)	Pr^i	H	3 d	$CHCl_3$	rt	85	94/6	88
18	**24** (15)	$-(CH_2)_5-$		13 d	$CHCl_3$	rt	88	95/5	90
19	**25** (5)	Pr^n	H	20 h	CH_2Cl_2	0 °C	90	99/1	>99
20	**25** (10)	Pr^i	H	20 h	CH_2Cl_2	rt	75	95/5	91
21	**26** (20)	Me	Me	2 d	CH_2Cl_2	rt	61	—	82[f]
22	**27** (20)	PhO	Me	1 d	CH_2Cl_2	23 °C	78	91/9	94[g]
23	**28** (20)	Pr^i	H	1.5 d	—	rt	80	97/3	40[h]
24	**29** (10)	Et	H	2 d	CH_2Cl_2/hexane	0 °C	63	97/3	84

[a] Enantiomeric excess for the *syn* diastereomer.
[b] 67% ee for the *anti* isomer.
[c] 65% ee for the *anti* isomer.
[d] The (2*S*,3*R*) enantiomer was obtained.
[e] The reaction was performed in the presence of 10 equiv of H_2O as an additive.
[f] The reaction was performed in the presence of 10 mol % of *n*-butyric acid as an additive.
[g] 92% ee for the *anti* isomer.
[h] The reaction was performed in the presence of 2.5 mol % of TFA as an additive.

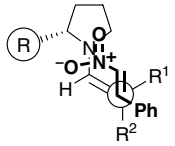
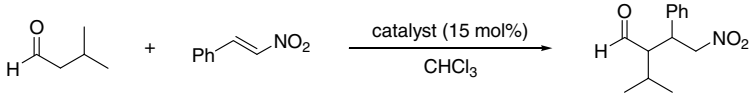


Figure 5. Proposed transition state model for the Michael addition of aldehydes to nitroolefins catalyzed by pyrrolidine-derived organocatalysts.

the *anti*-enamine with the double bond oriented away from the bulky substituent at the 2-position of the pyrrolidine ring. The enamine then reacts with the nitro olefin via an acyclic synclinal transition state as proposed by Seebach and Golinski.[40] In this model, there are favorable electrostatic interactions between the partially positive nitrogen of the enamine and the partially negative nitro group (Fig. 5). A bulky substituent at the 2-position of the pyrrolidine ring plays two important roles: it favors the selective formation of the *anti* enamine and also shields its *Re*-face.

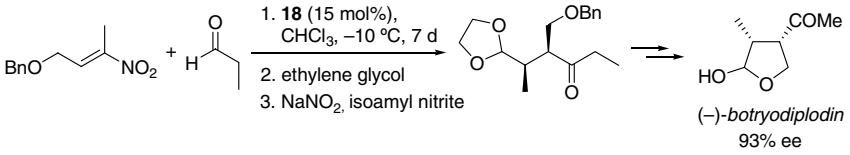
Catalyst *ent*-**18** was employed by Alexakis et al. to show that significant rate enhancements, without erasing the selectivity of the process, could be achieved in the organocatalytic Michael addition of aldehydes to *trans*-β-nitrostyrene via microwave irradiation (Scheme 14).[41]

With respect to the Michael addition to β-alkyl substituted nitro olefins, very high yields and selectivities were obtained with catalysts **10**,[18] **18**,[26] **25**,[33] and **27**[35] (Fig. 4). Taking advantage of the good results obtained with catalyst **18**, Alexakis et al. performed the total synthesis of the mycotoxin (−)-botryodiplodin,[42] which constituted as the first and only example of Michael addition of aldehydes to an α-substituted nitroolefin (Scheme 15).



Organocatalyst	Temp	Time (h)	Yield (%)	*syn*/*anti*	ee (%)
18	rt	48	99	87/13	73 (*R*,*S*)
ent-**18**	27 °C (μW)	1	97	90/10	78 (*S*,*R*)

Scheme 14. Organocatalyzed Michael addition of aldehydes to β-nitrostyrene under microwave irradiation.



Scheme 15. Total synthesis of (−)-botryodiplodin.

In a very recent study, L-prolinol **30** was successfully used as an organocatalyst in the enantioselective Michael addition of aldehydes to β-nitroacrolein dimethyl acetal.[43] The reaction, which represented a straightforward synthesis of highly functionalized enantioenriched nitro compounds, was performed using a 1/1 aldehyde/nitroalkene ratio in Pr^{i}OH at rt (Scheme 16). Disappointingly, for the most part of the examples studied, the diastereomeric ratio of the reaction was very low.

One of the main problems associated with organocatalysis is the high catalyst loading, usually in the range of 10–30 mol %, required to perform the desired transformation. This is a problem when expensive chiral materials are used to prepare the organocatalysts, especially when they are employed in large scale syntheses. Among the advantages that organic catalysts present over enzymes and metal-based catalysts should be emphasized the possibility of ready immobilization on a solid support with the aim of facilitating catalyst recovery and recycling.[44] Catalysts **31**,[45] **32**,[46] and **33**[47] were recently demonstrated to efficiently promote the asymmetric Michael addition of a wide range of aldehydes to nitroolefins at rt with excellent levels of enantio- and diastereoselectivity (Fig. 6). Catalysts **31** and **32** could be easily recovered by fluorous solid-phase extraction and precipitation in MeOH, respectively, and reused several times, while still retaining a high catalytic activity. On the other hand, fluorous (*S*)-pyrrolidine sulfonamide **33** (Fig. 6) promoted the Michael addition of aldehydes to nitrostyrene in water, and could be easily recovered by fluorous solid-phase extraction and reused. A preliminary study regarding the use of chiral ionic liquids as asymmetric organocatalysts in the Michael addition of aldehydes to nitrostyrene was presented very recently.[48] Catalyst **34** (Fig. 6), which consisted of a chiral pyrrolidine covalently tethered to an imidazolium cation, was demonstrated to be an efficient organocatalyst for the reaction of α- and β-substituted aldehydes to nitrostyrene under neat conditions in the presence of TFA as a cocatalyst. This result was very interesting since Michael additions of aldehydes to β-nitrostyrenes in ionic liquids

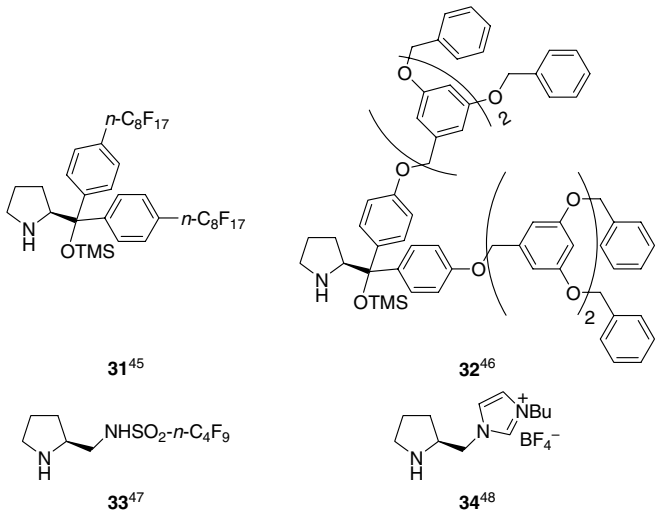
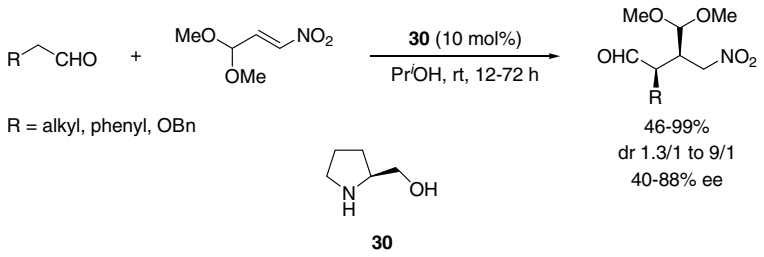


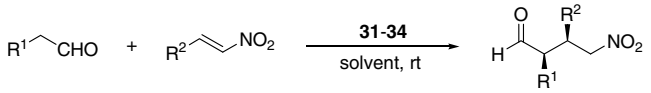
Figure 6. Recyclable organocatalysts for the conjugate addition of aldehydes to nitroolefins.

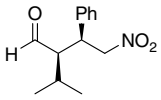
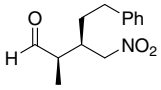
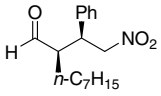
such as (bmim)PF_6 employing different organocatalysts afforded very low diastereo- and enantioselectivities (Scheme 17).[38]

Asymmetric catalyzed domino reactions produce chiral structures elaborate in a rapid, atom-economic, and competent manner.[49] An efficient and elegant chemo-, diastereo-, and enantioselective three component domino synthesis of tetrasubstituted cyclohexenecarboxaldehydes was accomplished by Enders et al. employing prolinol-derived catalyst **10**.[50] The catalytic cascade consisted of a three component reaction, comprising of linear aldehyde, a nitroalkene, an α,β-unsaturated aldehyde, and catalyst **10**, which was capable of catalyzing each step of the process (Scheme 18). The four stereogenic centers were generated in three consecutive C–C bond formations with good diastereocontrol and complete enantiocontrol. The first step of the catalytic cycle consisted of a stereoselective Michael addition of the linear aldehyde to the nitroalkene

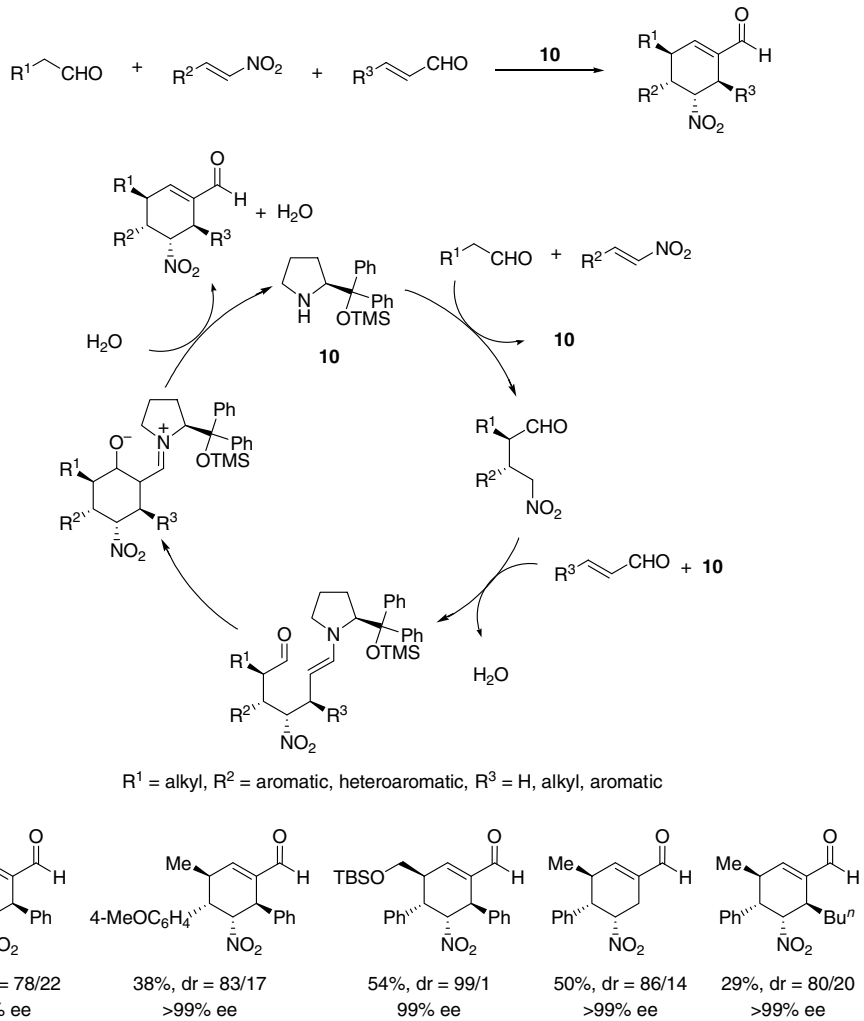


Scheme 16. Asymmetric Michael addition of aldehydes to β-nitroacrolein dimethyl acetal.



Catalyst (mol%)	Additive	Solvent	Time	Yield (%)	*syn/anti*	ee (%)	Adduct
31 (20)	–	$PhCF_3$	1.5 d	86	94/6	>99	
32 (10)	–	CCl_4	3 d	81	81/19	99	
34 (15)	THF (5 mol%)	–	60 h	100	90/10	72	
31 (20)	–	$PhCF_3$	13 h	82	95/5	>99	
33 (10)	–	H_2O	12 h	98	80/20	81	

Scheme 17. Conjugate addition of aldehydes to nitroolefins catalyzed by **31**–**34**.



R^1 = alkyl, R^2 = aromatic, heteroaromatic, R^3 = H, alkyl, aromatic

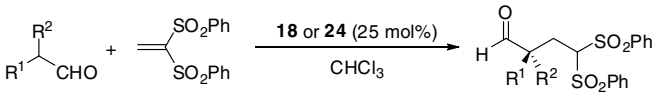
40%, dr = 78/22	38%, dr = 83/17	54%, dr = 99/1	50%, dr = 86/14	29%, dr = 80/20
>99% ee	>99% ee	99% ee	>99% ee	>99% ee

Scheme 18. Three component double Michael addition organocatalytic sequence.

via enamine formation. This step was responsible for the high stereoselectivity of the process, the selectivity being kept or enhanced in the second step, the conjugate addition of the nitroalkane formed to the activated chiral iminium of the α,β-unsaturated aldehyde. A final intramolecular aldol condensation via enamine activation with subsequent

hydrolysis released the desired tetrasubstituted cyclohexene carboxaldehyde (Scheme 18). This protocol allowed the synthesis of a wide variety of polyfunctionalized cyclohexene building blocks, since different substituents were tolerated in the starting materials.

3.1.3. Conjugate addition of aldehydes to vinyl sulfones. *N*-Isopropyl-2,2′-bipyrrolidine **18** and *N*-isopropyl-2,3′-bimorpholine **24** (Fig. 4) promoted the Michael addition, by enamine formation, of aldehydes to 1,1-bis(benzenesulfonyl)ethylene (Scheme 19).[32,51] Better results were observed with catalyst **18**, the best enantioselectivities being obtained with hindered aldehydes in $CHCl_3$ as the solvent at low temperatures. On the other hand, α,α-disubstituted and β-branched aldehydes required higher temperatures for good conversions, although very low enantioselectivities were observed. With respect to the mechanism, the acyclic synclinal model proposed by Seebach and Golinski[40] involving a *trans* enamine intermediate could also be postulated for the addition of aldehydes to vinyl sulfones. The less hindered *Si*,*Si* transition state is more favored than the *Re*,*Re* one leading to the *R* adducts (Fig. 7).



Catalyst	R^1	R^2	Temp	Time	Yield (%)	ee (%)
18	Pr^i	H	–60 °C	2 h	71	75
24	Pr^i	H	–60 °C	2 h	79	55
18	Me	H	–60 °C	2 h	72	0
18	Pr^n	H	–60 °C	2 h	76	53
18	Bu^t	H	–60 °C	2 h	78	80
18	Et	Me	rt	4 h	59	12
18	Pr^i	H	rt	4 d	0	–

Scheme 19. Michael addition of aldehydes to vinyl sulfones.

3.2. Conjugate addition of ketones

The asymmetric organocatalytic conjugate addition of ketones has been performed employing, as Michael acceptors, α,β-unsaturated carbonyl compounds, alkylidene malonates, and nitroolefins. The process has been studied under homogeneous and PTC conditions using a wide variety of chiral organocatalysts such as *Cinchona* alkaloid derivatives as well as small peptides and chiral primary and secondary amines derived from the chiral pool or obtained synthetically. This methodology has led to the preparation of different enantiomerically enriched compounds, such as 1,5-dicarbonyl compounds, functionalized cyclopropanes, and γ-nitroketones.

3.2.1. Conjugate addition of ketones to α,β-unsaturated ketones. L-Proline derivatives, as well as chiral quaternary ammonium salts, have been shown to mediate the enantioselective addition of ketones to enones under either homogeneous or biphasic PTC conditions. The stoichiometric asymmetric addition of ketones to α,β-unsaturated compounds is a well-known reaction since 1969 when Yamada et al. reported an asymmetric synthesis of optically active 2-alkylcyclohexanone derivatives employing various L-proline ester derivatives to form the corresponding chiral enamines.[52] The intramolecular proline-catalyzed version of the reaction was later described by other authors[53] although in modest enantioselectivities and employing stoichiometric amounts of the catalyst and long reaction times. Catalyst **20** (Fig. 4) was very recently used for the highly enantioselective organocatalytic Michael addition of ketones to chalcones.[54] The reaction was carried out under mild conditions to afford synthetically useful 1,5-dicarbonyl compounds in high yields and with high to excellent levels of enantio- and diastereoselectivity in the case of using six-membered ring ketones as nucleophiles (Scheme 20). Unfortunately, low diastereoselectivities and no enantioselectivity were observed when using cyclopenta-

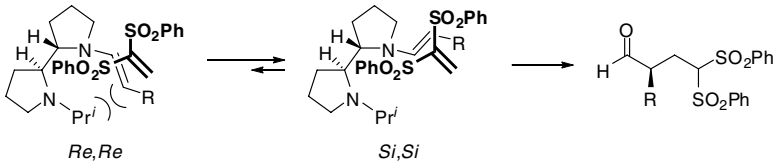
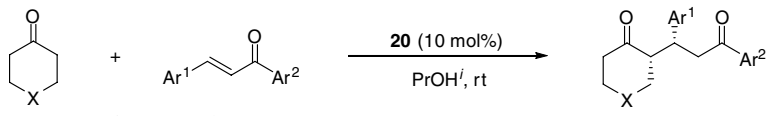
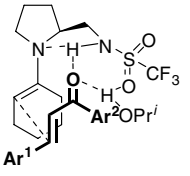


Figure 7. Proposed transition state model for the Michael addition of aldehydes to vinyl sulfones catalyzed by diamine **18**.



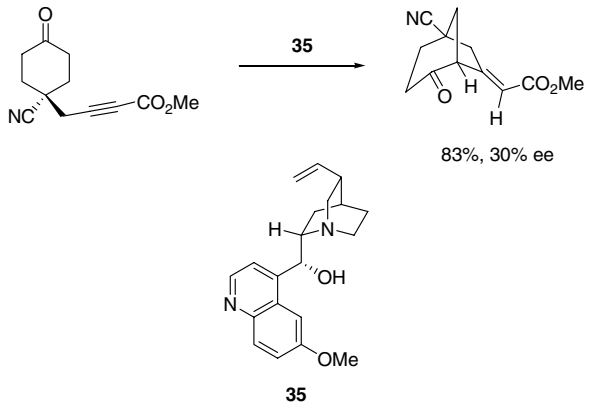
X	Ar^1	Ar^2	Yield (%)	Time(d)	*syn/anti*	ee (%)
CH_2	4-ClC_6H_4	Ph	80	4	>98/2	90
CH_2	4-$NO_2C_6H_4$	Ph	87	4	>98/2	92
CH_2	2-thienyl	2-thienyl	65	6	>98/2	90
NMe	4-ClC_6H_4	Ph	89	4	96/4	97
O	4-ClC_6H_4	Ph	73	5	98/2	87



Scheme 20. Enantioselective organocatalytic Michael addition of ketones to chalcones.

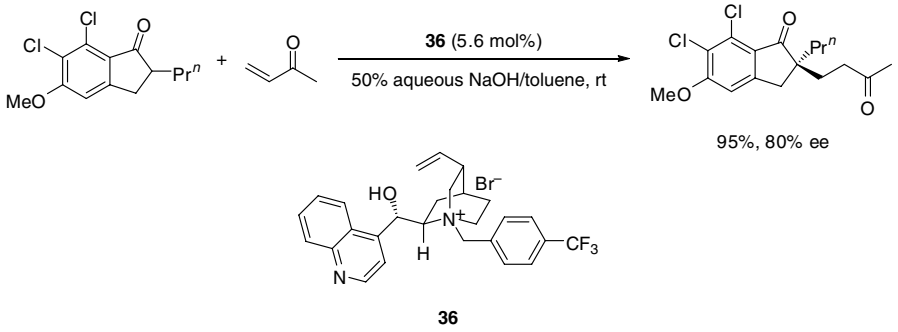
none and cycloheptanone, respectively.[54] The high levels of enantio- and diastereoselectivity for cyclohexanones could be rationalized with the proposed transition state model shown in Scheme 20. The NH proton of the triflamide group provides stabilization through a hydrogen-bonding interaction with the chalcone carbonyl group. In addition, the triflamide group might participate in an additional H-bonding interaction with the carbonyl group through the solvent, synergistically bringing about a tighter transition state. As earlier stated for other related catalysts, the triflamide moiety also produced a high facial preference for the approaching enone (Scheme 20).

With respect to the use of *Cinchona* alkaloid-derived catalysts, the first example of asymmetric Michel addition of ketones to α,β-unsaturated ketones appeared in 1979 when Trost illustrated, during the total synthesis of the sesquiterpene (±)-hirsutic acid C,[55] a stereoselective quinine-catalyzed intramolecular conjugate addition of an intermediate functionalized cyclohexanone (Scheme 21). After this low enantioselective process, the employment of ammonium salts derived from *Cinchona* alkaloid catalysts, such as [4-(trifluoromethyl)benzyl]cinchoninium bromide **36**, for the PTC conjugate addition of 2-alkylindanones to methyl vinyl ketone was carried out in a two phase toluene/50% aqueous NaOH system, yielding higher enantioselectivities (up to 80% ee) of the corresponding Michael adduct, which is a key intermediate in drug synthesis (Scheme 22).[56]

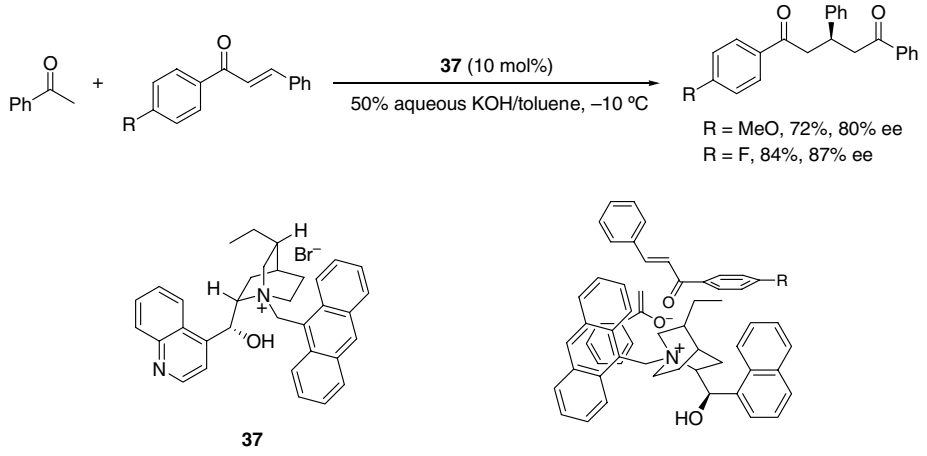


Scheme 21. Quinine-catalyzed intramolecular Michael addition.

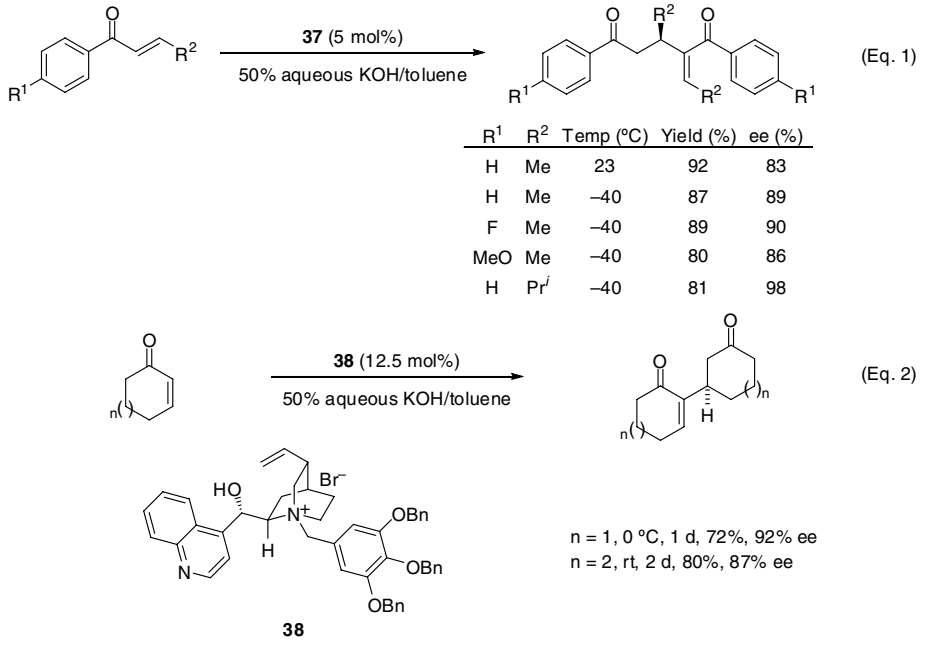
N-Alkylated cinchonidinium cation **37** mediated the enantioselective conjugate addition of acetophenone to chalcones under PTC conditions (Scheme 23).[57] In the proposed transition state of the reaction, the acetophenone enolate and the α,β-enone are contact ion paired with the ammonium nitrogen of the catalyst (Scheme 23). Moreover, the phenyl group of the nucleophile is positioned to π-stack with the 9-anthracenyl subunit of the catalyst,



Scheme 22. Asymmetric Michael addition to methyl vinyl ketone catalyzed by **36**.



Scheme 23. Cinchonidinium-catalyzed Michael addition of ketones to chalcones.

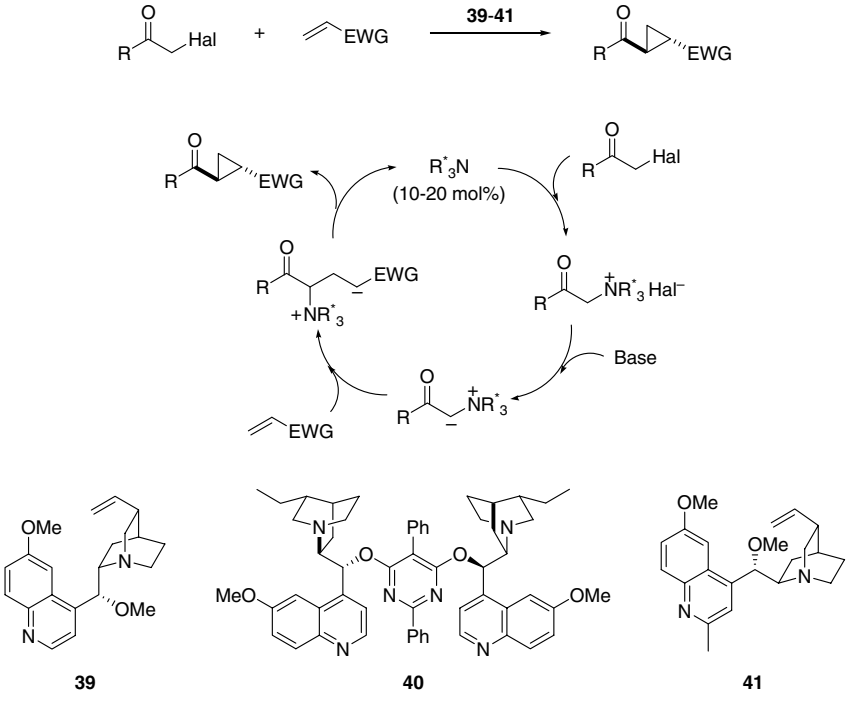


R^1	R^2	Temp (°C)	Yield (%)	ee (%)
H	Me	23	92	83
H	Me	–40	87	89
F	Me	–40	89	90
MeO	Me	–40	80	86
H	Pr^i	–40	81	98

Scheme 24. Cinchonidinium-catalyzed dimerization of α,β-unsaturated ketones.

which definitely confers rigidity and a proper chiral atmosphere onto the system.

Catalyst **37** also promoted the enantioselective dimerization, under the same chiral phase-transfer catalysis conditions, of α,β-enones able to generate dienolates by deprotonation of a γ-hydrogen to yield chiral 1,5-dicarbonyl compounds through an enantioselective Michael addition-double bond isomerization sequence.[58] At low temperatures, this dimerization reaction generally afforded good yields (80–90%) and high enantioselectivities (86–98%), the best results being for π-electron-deficient enones and those having a bulkier substituent at the β-position (Scheme 24, Eq. 1). The products of the dimerization were useful intermediates for the synthesis of chiral γ-keto acids, important chiral building blocks for peptide isosteres. A



Scheme 25. Enantioselective organocatalytic cyclopropanation.

similar mechanistic model, as previously described for the addition of ketones to chalcones (Scheme 23), is operative in this transformation.

The cinchonidiunium-catalyzed dimerization reaction was recently extended to cyclic enones, such as cyclohex-2-enone and cyclohept-2-enone, employing ammonium catalyst **38**, in high yields and up to 92% and 87% ee, respectively (Scheme 24, Eq. 2).[59]

A further application of the asymmetric conjugate addition of ketones to enones mediated by chiral tertiary bases was asymmetric cyclopropanation via ammonium ylides.[60] This recently developed approach to chiral functionalized cyclopropanes engages the intra- or intermolecular reaction between α-halogeno carbonyl compounds with electron-deficient alkenes through a catalytically generated ammonium ylide (Scheme 25). The initial non-enantioselective DABCO-catalyzed reaction by Gaunt et al.[60a] led to the authors employing natural or modified *Cinchona* alkaloids, such as **39**–**41**, as chiral organocatalysts (Scheme 25). This process took place with extremely good results in terms of yield, diastereo- and enantioselectivity for the inter-[60c] and intramolecular[60d] version of the reaction. Notably, both enantiomers of the cyclopropane derivatives could be accessed in excellent yields and enantioselectivities by using the corresponding pseudoenantiomeric *Cinchona* alkaloid catalyst. Inorganic bases such as Na_2CO_3 or Cs_2CO_3, in MeCN at 80 °C and catalyst loadings typically in the range 10–20 mol % were standard reaction conditions.

With respect to the substrate scope, ketones were the best carbon nucleophiles to be employed although the intermolecular version of the reaction also worked well for esters, amides and Weinreb amides (Fig. 8). Regarding the Michael acceptor, enones were the best substrates for this reaction with a wide range of substituents tolerated (alkyl, aryl, and heteroaryl ketones). α,β-Unsaturated esters, in the case of intermolecular cyclopropanation, and α,β-unsaturated diimides for the intramolecular version of the reaction, extended the substrate scope of the process (Fig. 8). A transition state model for the intramolecular cyclopropanation reaction was proposed as depicted in Scheme 26 for catalyst **41**.[60d] In this model, the ammonium salt adopts a conformation that gives the *Z*-enolate of the nucleophile upon deprotonation with the base. The intramolecular conjugate addition of the enolate then takes place through a boat-type transition state.

3.2.2. Conjugate addition of ketones to alkylidene malonates and malononitriles. Alkylidene malonates were also used as Michael acceptors of ketones employing L-proline **16**[61] and proline-derived diamines, such as **19**[25b,62] (Fig. 4), as organocatalysts. Better results were obtained with chiral diamine **19**, although with moderate yields and enantioselectivities, under the reaction conditions studied (Scheme 27).[62] Lowering the temperatures enhanced the enantioselectivities but also dramatically reduced the chemical yields (Scheme 27).

Very recently, cinchonidine **42** extended the substrate scope of the reaction to β-substituted methylidenemalononitriles, which, after reaction with α-chloromethyl ketones, afforded tetrasubstituted cyclopropanes in up to 82% ee (Scheme 28).[63]

3.2.3. Conjugate addition of ketones to nitroolefins. Barbas[61] and List[64] independently reported the first organocatalytic addition of ketones to *trans*-β-nitrostyrene using L-proline as a catalyst and with good yields but very disappointing enantioselectivities (0–23% ee). A related study by Enders et al. showed a profound solvent effect on the reaction since in MeOH, the enantioselectivity could be increased to 76% for the major *syn* diastereomer in the

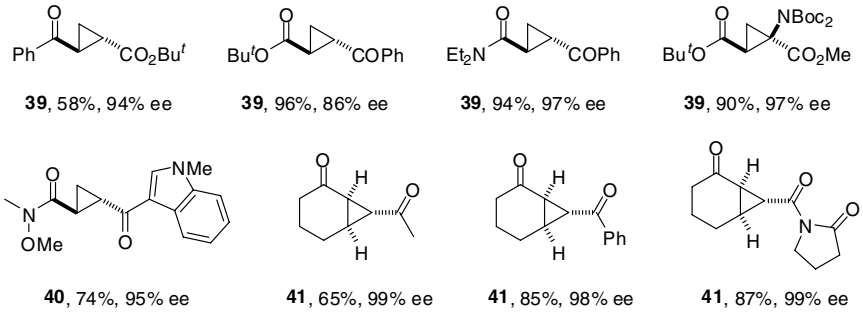
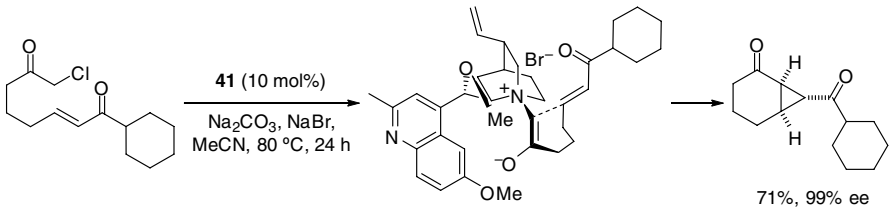
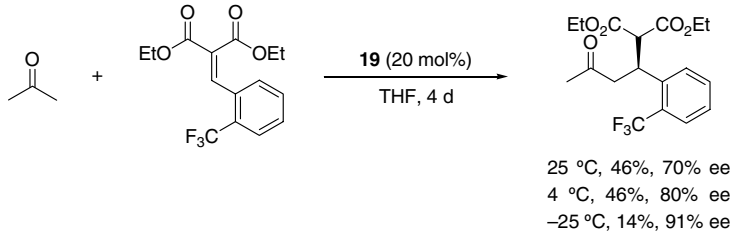


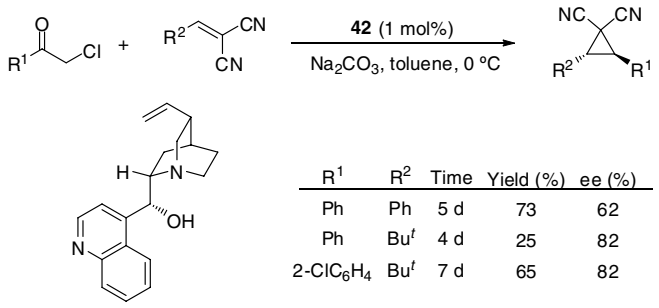
Figure 8. Substrate scope for organocatalytic cyclopropanation using catalysts **39**, **40**, and **41**.



Scheme 26. Proposed origin of the enantioselectivity for the organocatalytic cyclopropanation.



Scheme 27. Conjugate addition of ketones to alkylidene malonates.



R^1	R^2	Time	Yield (%)	ee (%)
Ph	Ph	5 d	73	62
Ph	Bu^t	4 d	25	82
2-ClC_6H_4	Bu^t	7 d	65	82

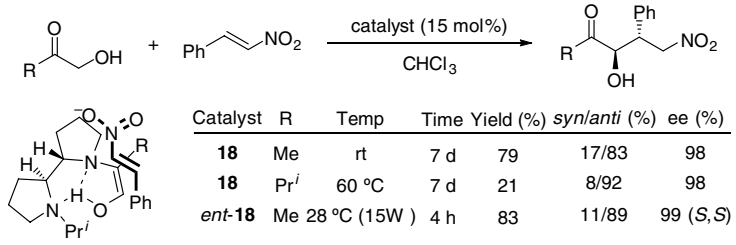
42

Scheme 28. The enantioselective synthesis of activated cyclopropanes catalyzed by cinchonidine **42**.

reaction between 3-pentanone and *trans*-β-nitrostyrene employing 20 mol % of L-proline as a catalyst.[65] Later work by Alexakis et al. dealt with the use of the hydrochloride salt of *N*-isopropyl-2,2′-bipyrrolidine **18** (Fig. 4) as a catalyst in $CHCl_3$ as the solvent. In this study the highest obtained enantioselectivity was 81% for the addition of cyclohexanone to nitrostyrene with a very high diastereoselectivity (*syn*/*anti*: 94/6).[26] As in the case of the conjugate addition of aldehydes (Fig. 5), the observed *syn*-selectivity was in accordance with the Seebach–Golinski model.[40] Interestingly, **18** mediated an *anti*-selective Michael addition when α-hydroxyketones were employed as nucleophiles (Scheme 29).[26b,66] Although long reaction times were necessary for completion (7 days), rate enhancement without loss of selectivity was achieved performing the reaction under microwave irradiation (15 W).[41] The reversal of the diastereoselectivity was ascribed to the putative formation of the *Z*-enamine intermediate, which was favored through formation of hydrogen bonds between the OH group of the nucleophile and the tertiary nitrogen atom of the catalyst.

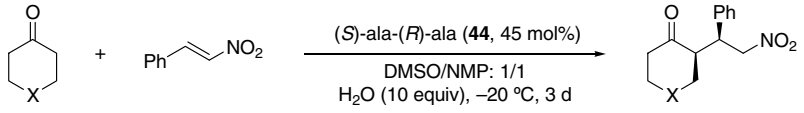
Later, List et al. showed that N-terminal prolylpeptides efficiently catalyzed the enantioselective Michael reaction of acetone to β-*trans*-nitrostyrene in DMSO, although with very low enantioselectivities (31% ee for Pro-Val).[67] On the other hand, much better results were obtained for the addition of cyclohexanone derivatives by Córdova et al. employing substoichiometric amounts (30–45 mol %) of alanine-derived small peptides, such as (*S*)-ala-(*S*)-ala **43** or (*S*)-ala-(*R*)-ala **44** in DMSO/NMP mixtures and in the presence of H_2O as an additive (Scheme 30).[30] Unfortunately, other ketones, such as hydroxyacetone and cyclopentanone, afforded low diastereo- and enantioselectivities.[30]

The dependence of the organocatalyst on the nucleophilic substrate is a general phenomenon in organocatalysis.



Catalyst	R	Temp	Time	Yield (%)	*syn*/*anti* (%)	ee (%)
18	Me	rt	7 d	79	17/83	98
18	Pr^i	60 °C	7 d	21	8/92	98
ent-**18**	Me	28 °C (15W)	4 h	83	11/89	99 (*S*,*S*)

Scheme 29. Conjugate addition of α-hydroxyketones to β-nitrostyrene catalyzed by **18**.

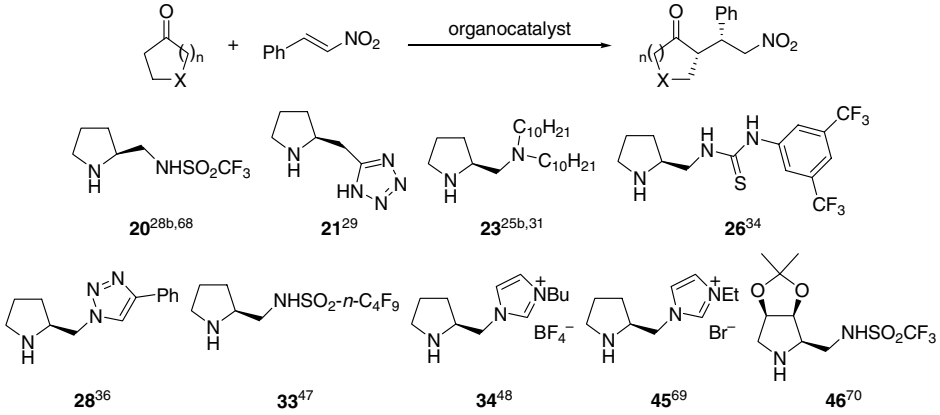


X	Yield (%)	*syn*/*anti*	ee (%)
CH_2	62	94/6	97
O	95	94/6	90
S	66	96/4	98

Scheme 30. Small peptide-catalyzed enantioselective addition of cyclohexanones to β-nitrostyrene.

Some of the catalysts developed for the asymmetric addition of aldehydes to nitroolefins, such as **20**,[28b,68] **21**,[29] **23**,[25b,31] **26**,[34] **28**,[36] **33**,[47] **34**,[48] and others recently developed such as **45**[69] and **46**[70] were also very efficient for the addition of six-membered ring ketones to β-nitrostyrene and derivatives (Scheme 31, Table 2). However, acyclic ketones or different cyclic nucleophiles, such as cyclopentanone always showed lower levels of diastereo- and enantioselectivity (Scheme 31, Table 2). Catalysts **23**[31] and **33**[47] were of special interest since they were able to work in brine and water as solvent, respectively. On the other hand, catalysts **26**[34] and **34**[48] promoted the conjugate addition under neat conditions employing acidic additives as cocatalysts. The chiral ionic liquids **34**[48] and **45**[69] performed much better than other chiral pyrrolidine-derived catalysts in ionic liquids as the reaction media.[38,71] Interestingly, while catalyst **34** showed the best activity and selectivity under neat conditions, imidazolium-supported organocatalyst **45** showed a better catalytic performance in [bmim]PF_6 in terms of productivity and enantioselectivity. Moreover, these catalysts and fluorous sulfonamide **33** could be easily recycled and reused without any significant loss of activity and stereoselectivity.

The fact that mostly cyclic six-membered ring ketones were suitable nucleophiles for the enantioselective conjugate addition to nitrostyrenes was also usually found in the other recently developed organocatalysts **47**–**52** (Fig. 9).[72–77] For this reason, special efforts were made to develop highly selective organocatalytic systems for the conjugate addition of aliphatic ketones to nitroolefins. Among the most active catalysts **53**–**58**,[78–83] Jacobsen's thiourea **58**[83] resulted in the most efficient organocatalyst reported so far for this process (Figs. 10 and 11). Under very mild reaction conditions (10 mol % of **58**, toluene, rt), this catalyst was able to efficiently catalyze the conjugate addition of different



Scheme 31. Enantioselective addition of cyclic ketones to β-nitrostyrene.

Table 2. Enantioselective addition of cyclic ketones to β-nitrostyrene

n	X	Catalyst (mol %)	Solvent	Temp	Time (h)	Yield (%)	*syn*/*anti*	ee[a] (%)
2	CH_2	**20** (20)	Pr^{i}OH	0 °C	10	96	98/2	97
2	O	**20** (20)	Pr^{i}OH	0 °C	24	87	98/2	98
2	NMe	**20** (20)	Pr^{i}OH	0 °C	24	83	98/2	96
2	S	**21** (15)	Pr^{i}OH/EtOH	20 °C	24	61	>95/5	90
2	CH_2	**23** (20)	THF	rt	22	92	98/2	90
2	CH_2	**23** (5)[b]	Brine	25 °C	12	93	95/5	89
2	CH_2	**26** (20)[c]	Neat	0 °C	38	93	96/4	90
2	O	**32** (10)	H_2O	rt	24	56	98/2	95
2	CH_2	**33** (15)[d]	Neat	rt	8	100	99/1	99
1	CH_2	**20** (20)	Pr^{i}OH	0 °C	72	11	—	—
1	CH_2	**23** (20)	THF	rt	72	46	86/14	74
1	CH_2	**26** (20)[c]	Neat	rt	144	27	75/25	71
1	CH_2	**33** (15)[d]	Neat	rt	80	61	75/25	83
2	CH_2	**28** (10)[e]	Neat	rt	18	99	98/2	92
1	CH_2	**28** (10)[e]	Neat	rt	23	72	60/40	80
2	CH_2	**45** (20)	[bmim]PF_6	rt	24	98	92/8	97
2	S	**46** (15)	$CHCl_3$	rt	16	45	>97.5/2.5	94

[a] Ee for the *syn* diastereomer.
[b] TFA (10 mol %) was used as cocatalyst.
[c] *n*-Butyric acid (10 mol %) was used as a cocatalyst.
[d] TFA (5 mol %) was used as a cocatalyst.
[e] TFA (2.5 mol %) was used as a cocatalyst.

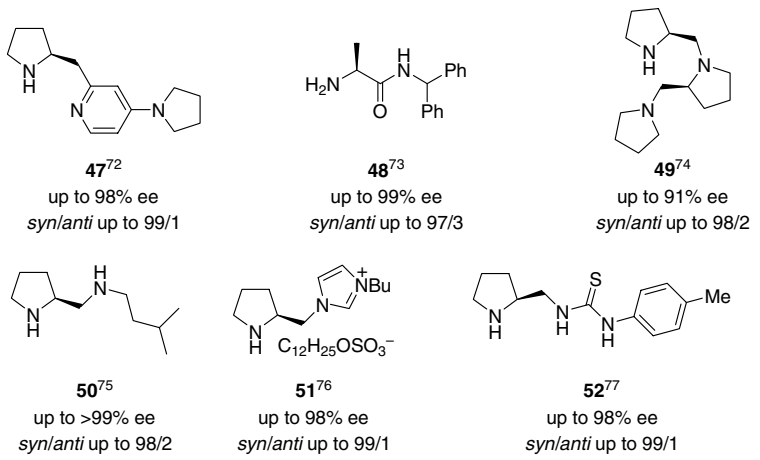


Figure 9. Enantioselective conjugate addition of six-membered ring ketones to β-nitrostyrenes.

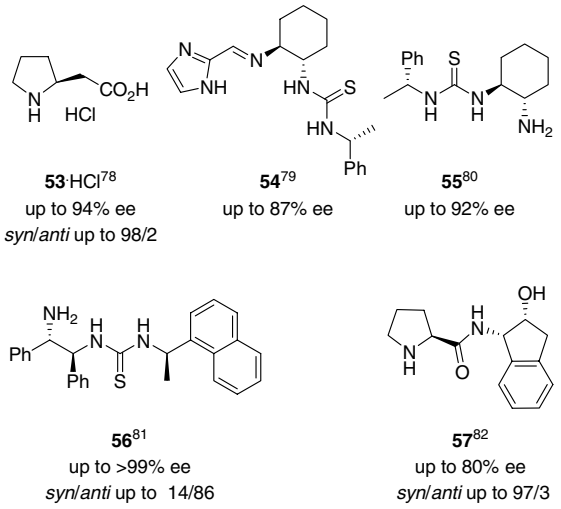


Figure 10. Enantioselective conjugate addition of acyclic ketones to β-nitrostyrenes.

aliphatic ketones with not only nitrostyrenes, but also nitroalkenes bearing aliphatic β-substituents with very high regio-, *anti*-diastereo-, and enantioselectivities (Fig. 11).

Very small changes in an organocatalyst structure may often alter its catalytic activity especially in terms of enantioselectivity. These modifications of the catalyst structure are mostly performed through organic transformations leading to new chiral organocatalysts. However, very recently, Clarke and Fuentes demonstrated that the catalytic activity of prolinamide-derived organocatalyst **59** could be modulated in the presence of achiral additives, such as pyridinone **60**.[84] This methodology, which was based on self-assembling of the components through complementary hydrogen bonding (Scheme 32), allowed the authors to prepare a small catalyst library using a single chiral catalyst and different achiral additives. By employing different pyridinones, Clarke and Fuentes fine-tuned the catalytic activity of the prolinamide-derived organocatalyst **59** for the conjugate addition of cyclohexanones to β-nitrostyrenes without needing to prepare new chiral catalysts (Scheme 32). In fact, the presence of the achiral hydrogen-bonding additive did not just fine-tune the enantioselectivity of the catalyst, but also transformed it into a highly effective promoter for the reaction.

Few experimental and theoretical studies have been carried out in order to try to explain the mechanism and observed stereochemical outcomes of the Michael addition of ke-

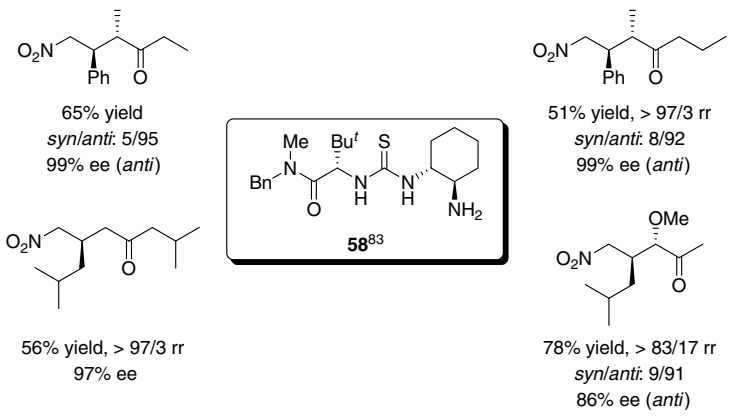
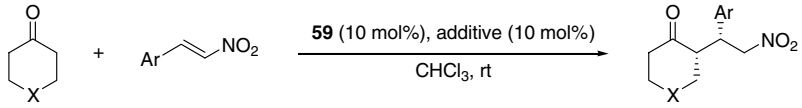
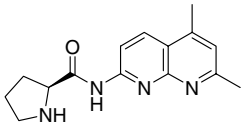


Figure 11. Jacobsen's chiral primary amine-thiourea addition of ketones to nitroalkanes.

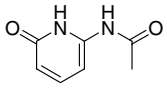


X	Ar	Additive	Time (h)	Conv. (%)	*syn*/*anti*	ee (%)
CH_2	Ph	–	42	63	91/9	16
CH_2	Ph	**60**	22	94 (71)[a]	95/5	75
CH_2	4-$MeOC_6H_4$	–	65	36	92/8	13
CH_2	4-$MeOC_6H_4$	**60**	65	81 (70)[a]	96/4	61
S	3-$NO_2C_6H_4$	–	42	7	–	–
S	3-$NO_2C_6H_4$	**60**	65	70 (60)[a]	97/3	94

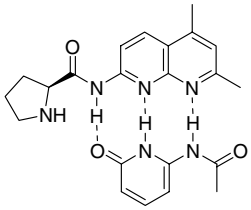
[a] Isolated yield.



59



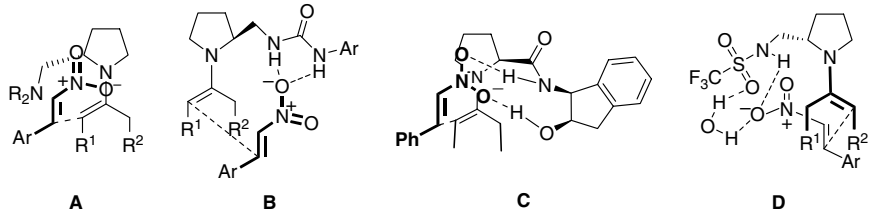
60



Scheme 32. Asymmetric Michael addition of cyclohexanone to β-nitrostyrene catalyzed by self-assembled organocatalysts.

tones to nitroolefins. When primary or secondary chiral amines are used as catalysts, the reaction clearly involves a catalytic, energetically favored, enamine mechanism. The existence of the enamine intermediate in the Michael addition has been confirmed by employing techniques such as the ESI-MS method on different catalysts, such as **51**,[76] **55**,[80] **56**,[81] **57**,[85] and **58**.[83] In the case of the proline-derived organocatalyst, an acyclic synclinal transition state assembly[40] explains the usually obtained *syn*-diastereoselectivity and absolute configuration. Depending on the catalyst employed, two potential models for the stereochemical outcome of the reaction have been postulated. Both models propose an electrostatic interaction between the nitro group and the nitrogen of the pyrrolidine ring. However, depending on the functionality present at the 2-position of the pyrrolidine ring, it has been suggested that facial bias is induced by steric factors (**A**,[26] Fig. 12) or through hydrogen-bonding interactions (**B**[34] and **C**,[85] Fig. 12). The first possibility involves the generation of a *syn*-enamine, while hydrogen-bonding transition states engage the generation of an *anti*-enamine. The different solvents, additives, and cosolvents present in the reaction media can assist in the stabilization of the transition state and favor one facial preference for the approach of the substrates as depicted in proposed transition state **D**[28b] (Fig. 12) for the **20**-catalyzed Michael addition of ketones to nitrostyrene. In this case, a cooperative hydrogen-bond solvent participation (represented by H_2O) takes place resembling the oxyanion hole commonly found in enzymes for stabilizing transition states. It seems then very clear that intra- and intermolecular hydrogen-bonding interactions play a key role in the organocatalytic cycle.

Chiral primary amine-thiourea catalysts **56** and **58** developed by Tsogoeva[81] and Jacobsen,[83] respectively, showed an opposite sense of relative stereoinduction in the conjugate addition of acyclic ketones to nitroolefins (see Fig. 11 for **58**). These *anti* selective catalysts stand in contrast to the usually obtained results, which lead to selective formation of the *syn*-diastereomers. This unexpected situation suggested the participation of a *Z*-enamine intermediate. Moreover, with respect to the electrophile activation



A *syn*-enamine *Re,Re* | **B** *anti*-enamine *Re,Re* | **C** *anti*-enamine *Re,Re* | **D** *anti*-enamine *Re,Re*

Figure 12. Proposed transition state models for the conjugate addition of ketones to β-nitrostyrenes.

by the urea-type catalysts, it was also demonstrated that only one oxygen of the nitro group is bound to the thiourea moiety in an out-of-plane arrangement.[80,83]

3.3. Conjugate addition of silyl enol ethers

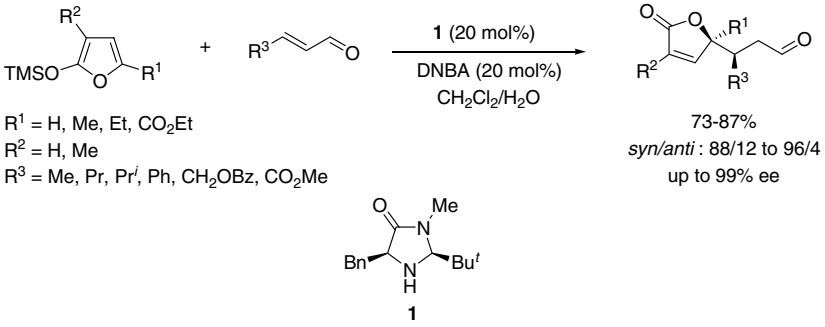
The Mukaiyama–Michael conjugate addition reaction is a powerful tool for the preparation of synthetically useful 1,5-dicarbonyl compounds. The Michael addition to α,β-unsaturated aldehydes has proven to be very challenging due to the greater susceptibility of these compounds to 1,2-addition when using metal-containing Lewis acid catalysts. MacMillan et al. demonstrated that organocatalysis by means of iminium intermediates, using chiral imidazolidinones, overcame such limitations providing the enantioselective Mukaiyama–Michael reaction of 2-(silyloxy)furans to simple unsaturated aldehydes.[86] On the basis of molecular modeling studies, MacMillan et al. anticipated that α,β-unsaturated iminium ions arising from chiral amine **1** might be inert to the 2-(silyloxy)furan 1,2-addition on the basis of steric constraints imposed by the catalyst framework. The reaction was used to prepare chiral γ-butenolides with good *syn* selectivity (up to 92% de) and high ee's (84–99%) (Scheme 33). An optimum catalytic performance was achieved using the 2,4-dinitrobenzoic acid (DNBA) ammonium salt of the catalyst employing protic cosolvents such as water or alcohols due to their ability to quench the putative silyl cation formed, which was shown to inhibit the catalytic cycle through the formation of $(TMS)_2O$.

A delicate balance between the *syn*- and *anti*-addition seemed to exist in the process, which could be shifted deliberately by appropriate choice of the acid cocatalyst, the solvent, the temperature and the steric demand of the ester group present in the enal.[86] In Scheme 34 it is shown how just the solvent and the catalyst were able to control the diastereoselectivity of the reaction.

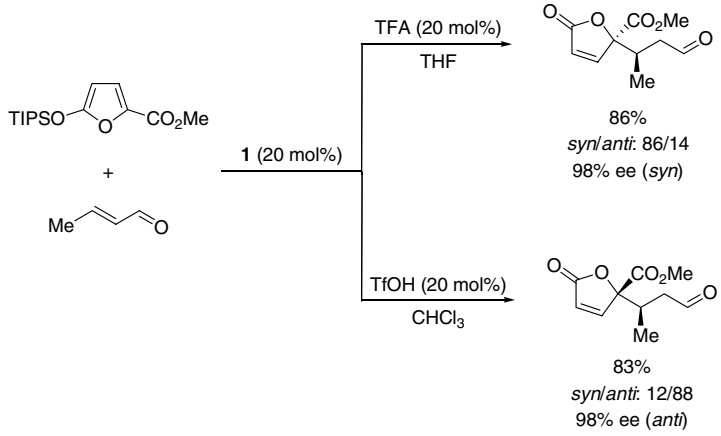
The organocatalytic Mukaiyama–Michael reaction was used in the synthesis of different natural products such as spiculisporic acid[86] and the inhibitor of the hydroxymethylglutaryl coenzyme A reductase (+)-compactin (Scheme 35).[87]

MacMillan's chiral imidazolidinone **1** was also employed by Wang et al. to promote the Mukaiyama–Michael reaction between silyl enol ethers and α,β-unsaturated aldehydes in the presence of 2,4-dinitrobenzoic acid (DNBA) as an additive.[88] High yields (56–87%) and high enantioselectivities (85–97% ee) were obtained for a wide range of important chiral synthetic building blocks following this methodology (Scheme 36).

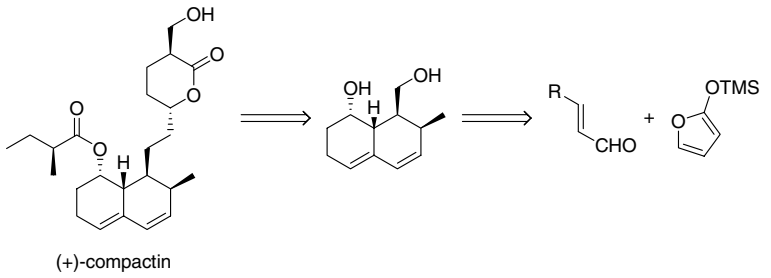
Aqueous-organic biphasic PTC conditions (toluene/50% aqueous KOH) were used by Zhang and Corey for the



Scheme 33. Organocatalyzed Mukaiyama–Michael addition of 2-(silyloxy)furans to α,β-unsaturated aldehydes.

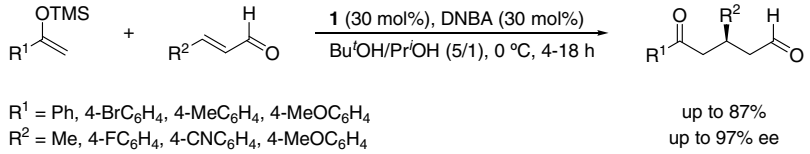


Scheme 34. Control of diastereoselectivity in the Mukaiyama–Michael addition.



(+)-compactin

Scheme 35. Enantioselective synthesis of (+)-compactin.



Scheme 36. Organocatalyzed Mukaiyama–Michael addition of silyl enol ethers to α,β-unsaturated aldehydes.

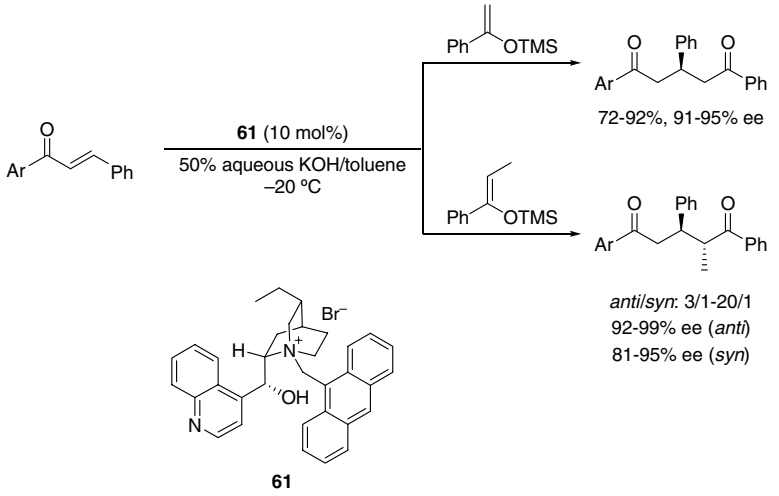
Mukaiyama–Michael addition of different silyl enol ethers to chalcones promoted by the quaternary ammonium salt *N*-(9-anthracenylmethyl)dihydrocinchonidinium bromide **61** at −20 °C (Scheme 37).[89] The addition products were obtained in good yields, very high enantioselectivities and *anti*-diastereoselectivities in the case of using preformed *Z*-silyl enol ethers.

Chiral quaternary ammonium phenoxides derived from *Cinchona* alkaloids were used by Mukaiyama et al. as catalysts in a new and efficient method for the preparation of optically active 3,4-dihydropyran-2-one derivates via tandem Mukaiyama–Michael addition/lactonization between α,β-unsaturated ketones and the silyl enolate derived from phenyl isobutyrate (Scheme 38).[90] In this reaction, the phenoxy group contained in the silyl enolate behaved as an effective leaving group to facilitate the intramolecular cyclization of in situ formed Michael adduct, and the liberated phenoxide ion also worked as a Lewis base catalyst to activate the silyl enolate. A variety of chiral quaternary ammonium phenoxides were screened with catalyst **62** showing the best catalytic activity (Scheme 38).

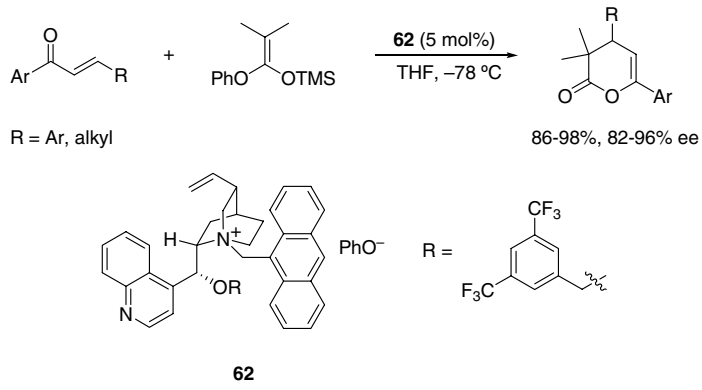
Maruoka et al. have developed and used *N*-spiro C_2-symmetric chiral quaternary ammonium bifluorides[91] **63** and **64**, and more recently **65** to promote the *regio*- and *anti*-selective Mukaiyama–Michael addition of silyl nitronates to α,β-unsaturated aldehydes,[92] cyclic α,β-unsaturated ketones,[93] and nitroalkenes[94] with good yields and enantioselectivities (Scheme 39). The final chiral silyl enol ethers could be easily hydrolyzed to the corresponding carbonyl compounds or functionalized at the α-position by reaction with electrophiles.

3.4. Conjugate addition of nitroalkanes

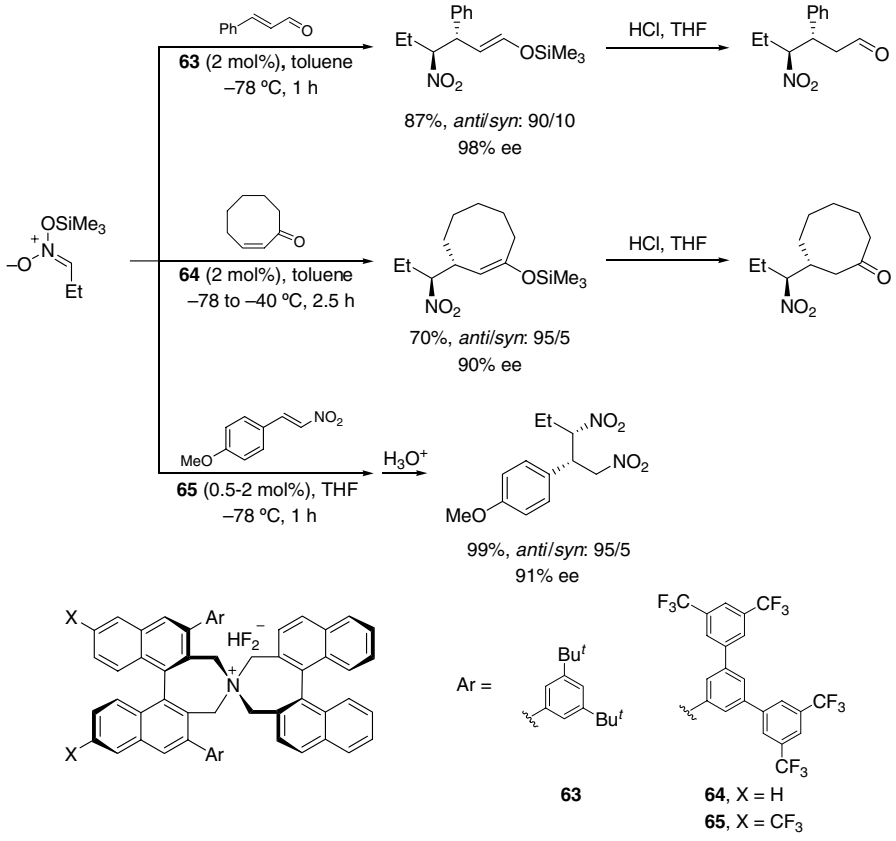
The conjugate addition of nitroalkanes to electron-poor alkenes has been recently reviewed.[95] In 1994, Yamaguchi et al. reported an organocatalytic iminium-type enantioselective Michael addition of primary and secondary



Scheme 37. PTC Mukaiyama–Michael addition of silyl enol ethers to chalcones.



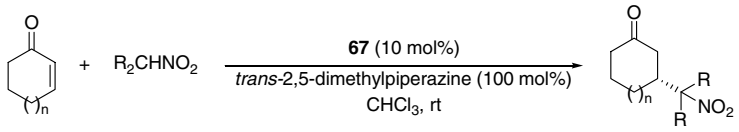
Scheme 38. Enantioselective synthesis of 3,4-dihydropyran-2-ones.

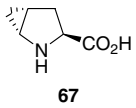


Scheme 39. Asymmetric Michael addition of silyl nitronates to α,β-unsaturated aldehydes, ketones, and nitroalkenes.

nitroalkanes to cyclic and acyclic enones and enals catalyzed by L-proline rubidium salt **66** in moderate to good enantioselectivities (29–86% ee).[96] Later, higher enantioselectivities (up to 93% ee) were obtained in the Michael addition of secondary nitroalkanes to cyclic enones catalyzed by a combination of L-proline (3–7 mol %) and *trans*-2,5-dimethylpiperazine (100 mol %).[97] Less selective results were observed when primary nitroalkanes such as nitromethane and nitroethane were tested (up to 87% ee). The same group notably improved those selectivities employing *trans*-4,5-methano-L-proline **67** as an organocatalyst under similar reaction conditions.[98] As depicted in Scheme 40, very high enantioselectivities were obtained when employing catalyst **67** for the addition of symmetrical 2-nitroalkanes to cyclic enones. In the case of the addition of 1-nitroalkanes to cyclic enones, very low diastereoselectivities were observed although with good enantioselectivities for both diastereomers (60–91% ee). A complex multicomponent chiral catalytic system was assumed to operate on the basis of a pronounced non-linear effect detected in the reaction. The piperazine cocatalyst seemed to act as a counter cation to the iminium carboxylate in the transition state, thus leading to higher enantioselectivities.[97b,98]

Jørgensen et al. developed a new organocatalytic system for the enantioselective Michael addition of nitroalkanes





67

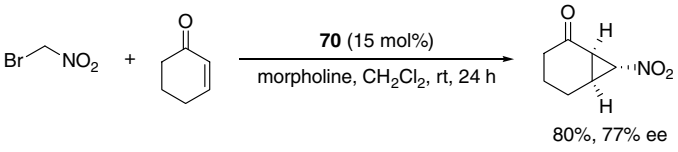
n	R	Time	Yield (%)	ee (%)
0	Me	96 h	87	80
0	$(CH_2)_4$	98 h	90	87
1	Me	140 h	92	99
1	$(CH_2)_4$	141 h	93	99
2	Me	144 h	57	99
2	$(CH_2)_4$	144 h	56	99

Scheme 40. Asymmetric addition of nitroalkanes to cyclic enones catalyzed by **67**.

to α,β-unsaturated enones, employing the new imidazolidine catalyst **68** (Fig. 13), easily prepared from phenylalanine.[99] Although employing very long reaction times (4.5–12.5 d), due to the low solubility of the catalyst, both acyclic and cyclic nitroalkanes reacted with a wide variety of acyclic α,β-unsaturated enones in high yields and similar levels of enantioselection than those obtained with proline derivatives (up to 86% ee). However, only moderate enantioselectivity was obtained using cyclohexanone as the acceptor (49% ee). A new more soluble chiral imidazolidine-2-yltetrazole organocatalyst **69** was then developed by the same group, which not only decreased the reaction times (3–8 d) but also notably improved the enantioselectivities especially for acyclic enones (up to 92% ee) (Fig. 13).[100] A possible explanation for the enantiofacial preference observed in the reaction would involve the formation of an iminium ion intermediate between the enone and the imidazolidine catalysts. In the most stable conformation of this intermediate, the benzyl group would shield the *Re*-face of the electrophile leaving the *Si*-face available for the approach of the nucleophile (Fig. 13).

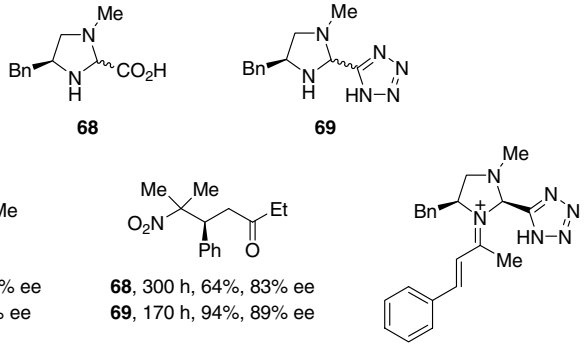
Pyrrolidine-tetrazole **70** was also a very useful organocatalyst for the conjugate addition of a wide variety of nitroalkanes to cyclic and acyclic enones using *trans*-2,5-dimethylpiperazine as a stoichiometric base additive (Scheme 41).[101] Excellent enantioselectivities (94–97% ee) were obtained for the addition of primary and secondary nitroalkanes to cyclohexenone, although low diastereoselectivities were always detected. The level of enantioselection displayed by catalyst **70** in the case of the conjugate addition to acyclic enones was similar to that obtained with catalyst **69** (Scheme 41). On the other hand, catalyst **70** was employed with little success in the Michael addition of 2-nitropropane to α,β-unsaturated aldehydes, such as (*E*)-but-2-enal (40%, 46% ee) and cinnamaldehyde (67%, 0% ee).

A new asymmetric organocatalytic nitrocyclopropanation of cyclohex-2-enone has been recently reported by Ley et al.[102] The conjugate addition of bromonitromethane to cyclohex-2-enone with subsequent cyclopropanation was performed in CH_2Cl_2 at rt and in the presence of catalytic amounts of tetrazole catalyst **70** (15 mol %) and substoichiometric amounts of morpholine as a base providing the product in 80% yield and 77% ee (Scheme 42).



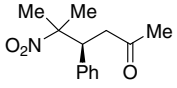
Scheme 42. Organocatalytic cyclopropanation of cyclohex-2-enone.

Tsogoeva et al. studied the Michael addition of nitroalkanes to cyclic enones employing di- and tetrapeptides as organocatalysts.[103] Proline-based dipeptide **71** (Fig. 14) was shown to catalyze under very low loading conditions (2 mol %) the conjugate addition with up to 88% ee and up to 100% yield. Interestingly, the presence of



68

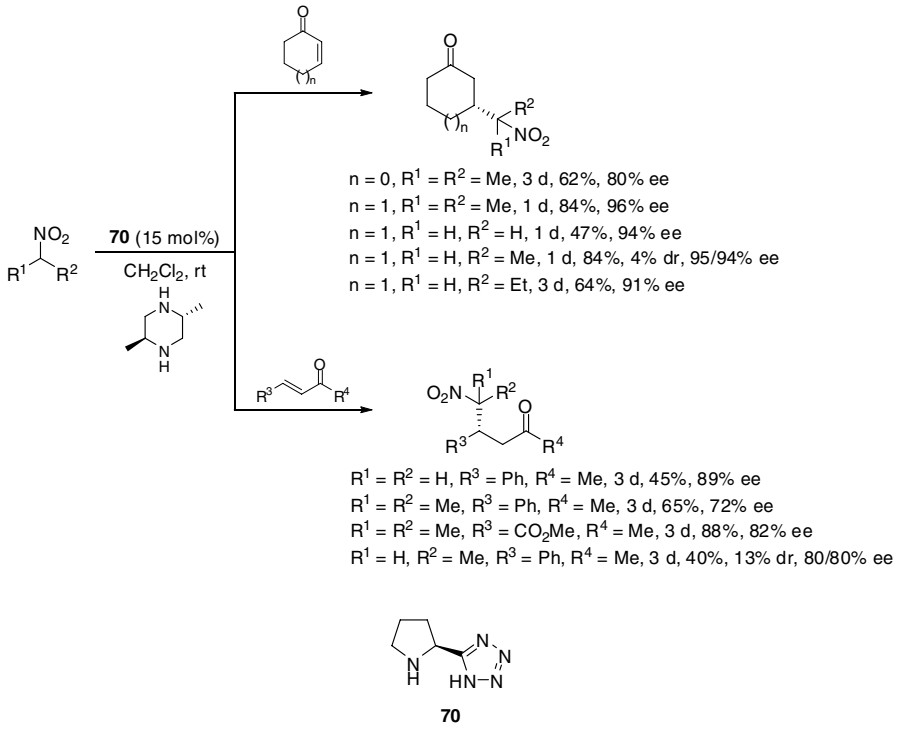
69



68, 240 h, 95%, 79% ee
69, 78 h, 97%, 87% ee

68, 300 h, 64%, 83% ee
69, 170 h, 94%, 89% ee

Figure 13. Imidazolidine-catalyzed asymmetric Michael addition of 2-nitropropane to enones.



Scheme 41. Asymmetric addition of nitroalkanes to cyclic enones catalyzed by pyrrolidine-tetrazole **70**.

trans-2,5-dimethylpiperazine as a cocatalyst was again essential for good catalytic performance.[103b]

In 1975, Wynberg and Helder reported the first asymmetric Michael addition of the doubly activated α-tosylnitroalkanes to methyl vinyl ketone catalyzed by quinine **35** (1.2 mol %) in toluene at rt.[104] The enantiomeric excess was determined just for the addition of α-tosylnitroethane to methyl vinyl ketone (56% ee). Later, in 1981, Matsumoto demonstrated that, in the presence of catalytic amounts of quinine or quinidine, it was possible to perform an enantioselective conjugate addition of nitromethane to *trans*-chalcone in apolar solvents, such as toluene, under high pressure conditions (400 MPa) but with moderate selectivities (up to 60% ee).[105] More recently, *Cinchona* alkaloid-derived bases such as **72**[106] and **73**[107] were employed as catalysts for the conjugate addition of nitrocycloalkanones to methyl vinyl ketone and nitromethane to chalcones, respectively (Fig. 14). Interestingly, in the case of cinchonine **72** (employed in stoichiometric amounts), the absolute configuration of the major enantiomer obtained was nitrocycloalkanone ring-sized dependant. The (*R*)-configuration was usually obtained for large rings (9–16-membered rings), while the stereochemistry of medium rings did not follow a clear trend (Fig. 14).[106] On the other hand, *Cinchona* alkaloid-derived chiral bifunctional thiourea organocatalyst **73** afforded very high enantioselectivities (89–98% ee) in the nitromethane addition to chalcones in toluene at rt (Fig. 14).[107]

The first organocatalytic enantioselective conjugate addition of nitroalkanes to nitrostyrenes has very recently been reported by employing the modified *Cinchona* alkaloid **74**.[108] Under neat conditions and employing long reaction times (6–12 d), this process afforded enantiomerically enriched 1,3-dinitro compounds in good yields (70–82%) and good enantioselectivities (67–88% ee) for both linear and more sterically hindered branched nitroalkanes (Scheme 43). Unfortunately, no reaction occurred for less reactive aliphatic nitroolefins. Surprisingly, a large scale reaction demonstrated that better yields and reaction rates could be achieved by employing just a small excess of the nitrostyrene (1.44 equiv) with a slight drop in enantioselectivity (75% vs 78% ee for neat conditions).

Chiral quaternary ammonium salts were also employed as phase-transfer catalysts for the conjugate addition of nitroalkanes to α,β-unsaturated systems such as α,β-unsaturated ketones and alkylidene malonates. Pioneering work by Wynberg and Helder and Colonna et al. with regards to the enantioselective Michael addition of nitroalkanes to chalcones employing chiral phase-transfer catalysts derived from *Cinchona* and *Ephedra* alkaloids[104,109] was significantly improved by Corey and Zhang[110] in 2000 with the *N*-(9-anthracenylmethyl)cinchonine derivative **75**, and applied to the synthesis of (*R*)-baclofen hydrochloride, a γ-amino acid that acts as a $GABA_B$ receptor agonist (Scheme 44). Although the enantioselectivity of the process was modest (70% ee), the ee of the product could be improved to 95% after a single recrystallization. Other cinchonidine-derived catalysts were later employed in the same reaction with similar results in terms of yield (61–94%) and selectivity (up to 69% ee).[111]

Catalyst **76** afforded the best enantioselectivity in the conjugate addition of chiral nitroacetyl derivatives to methyl vinyl ketone.[112] In the presence of KF as a catalyst this reaction took place with modest diastereoselectivities.

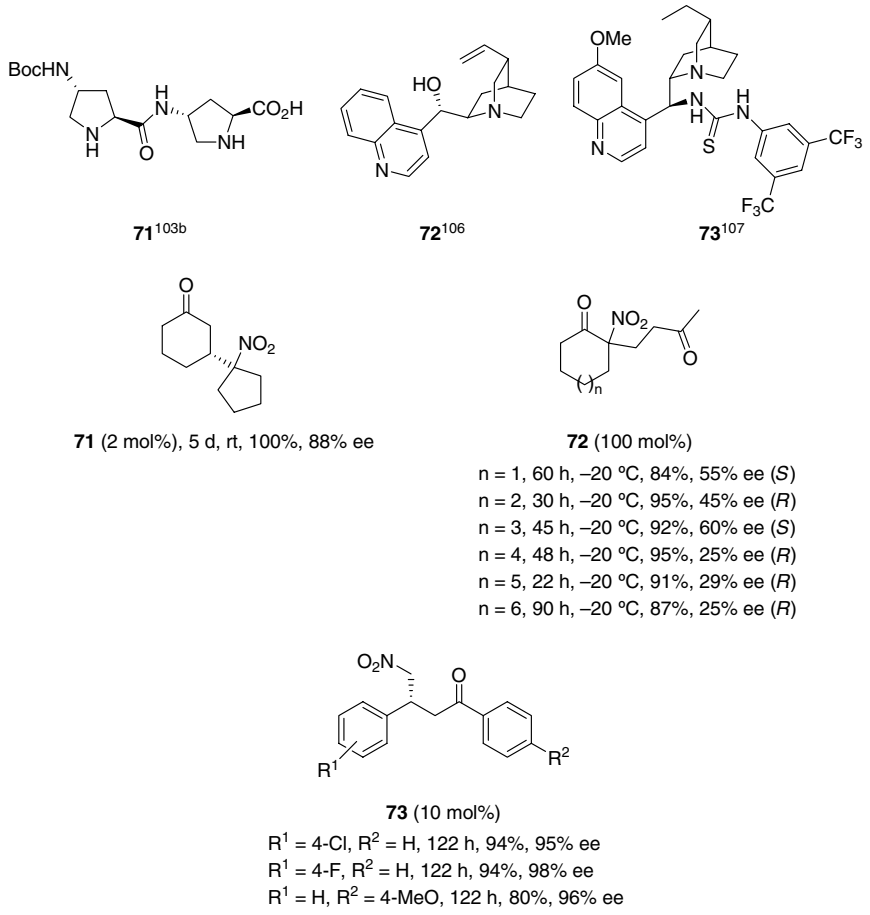
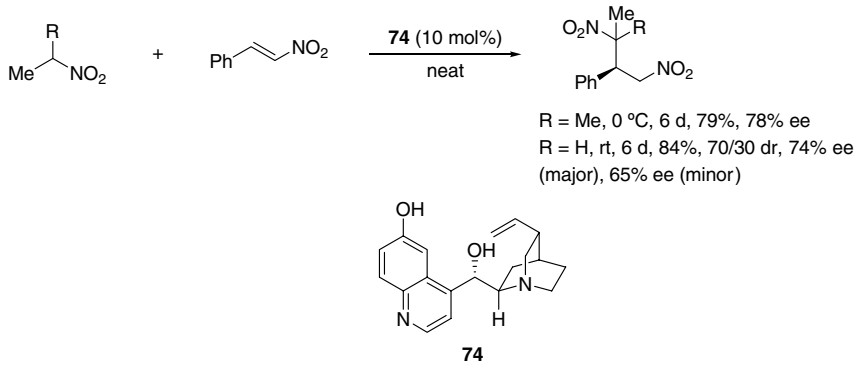


Figure 14. Michael addition of nitroalkanes to enones catalyzed by **71**–**73**.



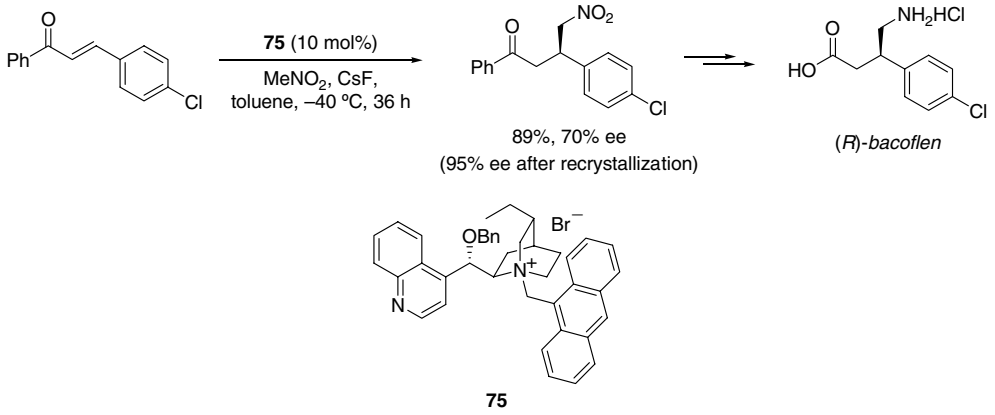
Scheme 43. Asymmetric addition of nitroalkanes to nitrostyrene.

However, the addition of 1 mol % of **76** improved the diastereoselectivity of the process (Scheme 45).

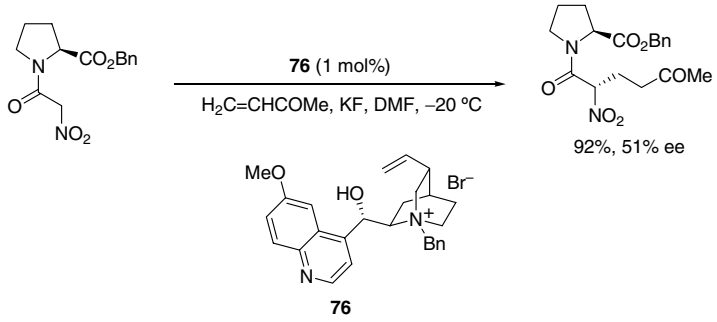
Catalyst **77** was employed in the asymmetric tandem conjugate addition-nucleophilic substitution between nitromethane and 2-bromocyclopent-2-enone to afford the corresponding chiral cyclopropane in modest yields and moderate enantioselectivity (Scheme 46).[113]

Carbohydrate-derived azacrown ethers were studied intensively as phase-transfer catalytic systems for the conjugate addition of 2-nitropropane to chalcones.[114] A wide variety of structural modifications were introduced both in the azacrown core and in the carbohydrate (D-glucose, D-mannitol, and D-mannose) unit in order to obtain good enantioselectivities; the best results were obtained with the D-glucose and D-mannose derivatives **78**–**82** (Scheme 47).

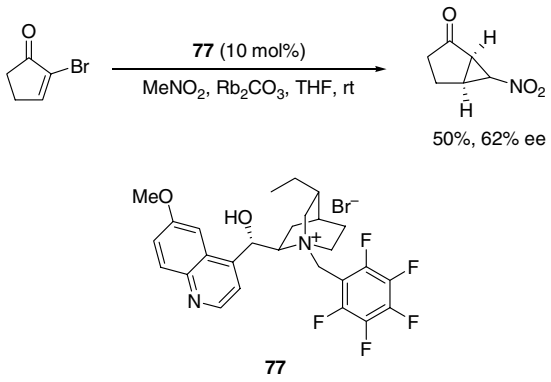
A considerable amount of work was devoted to the development of C_2-symmetric ammonium catalysts from either natural products or synthetic compounds, for use in the asymmetric conjugate addition of nitroalkanes. Among



Scheme 44. Asymmetric PTC addition of nitroalkanes to enones.



Scheme 45. PTC-conjugate addition of chiral nitroacetyl derivatives to methyl vinyl ketone.



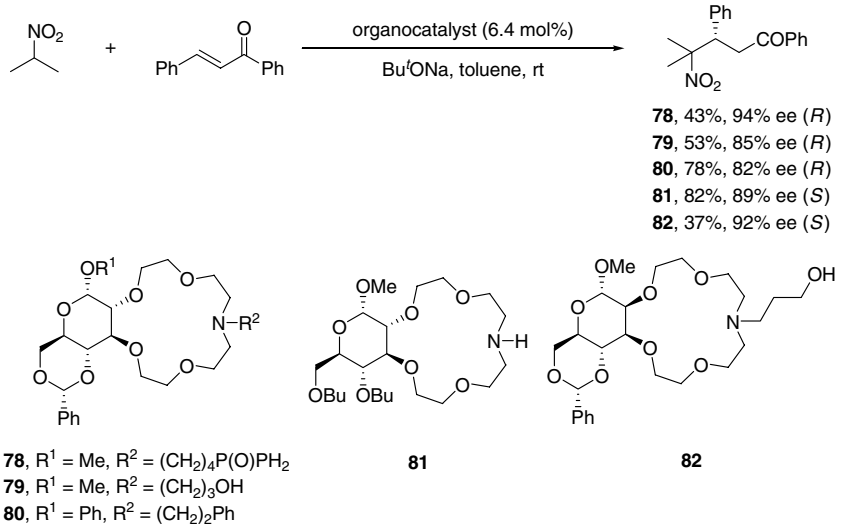
Scheme 46. Asymmetric cyclopropanation under PTC conditions.

these catalysts, C_2-symmetric guanidines and guanidinium salts were tested as chiral phase-transfer catalysts in the conjugate addition of nitroalkanes with enones.[115] The best results so far were obtained with spirocyclic guanidine **83**, which catalyzed the addition of 2-nitropropane to chalcone in high yield and good enantioselectivity (Scheme 48).[115b]

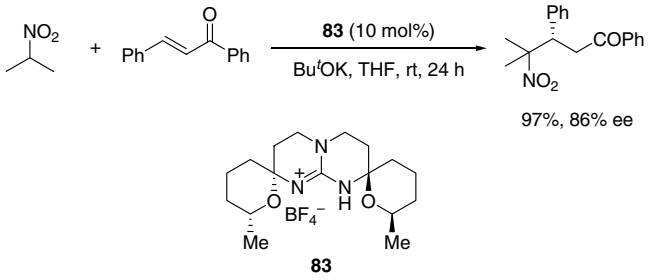
N-Spiro C_2-symmetric chiral biaryls derivatives **84** and **85** led to remarkable reactivity and selectivity in the conjugate addition of nitroalkanes to alkylidene malonates[116] and cyclic enones[117] under mild solid–liquid PTC (Scheme 49). This class of catalysts has the advantage over other synthetic phase-transfer catalysts in that their structure can be modified allowing rapid access to a variety of analogues. In the case of employing alkylidene malonates as Michael acceptors, the reaction, which was *anti*-selective, provided facile access to chiral γ-amino acid derivatives in good yields and high enantioselectivities (Scheme 49). On the other hand, the conjugate addition with cyclic α,β-unsaturated ketones afforded the corresponding γ-nitro ketones in excellent chemical yields with unprecedented levels of *syn*-diastereo and enantiocontrol (Scheme 49). Assuming the predominant generation of the *E*-nitronate, the observed *syn* selectivity could be rationalized by the severe steric congestion caused by the chiral quaternary ammonium cation overwhelming the repulsion between the cyclic ketone and the nitroalkane side chain (Scheme 49). The chiral ammonium cation shielded the *Re*-face of the nitronate, which produced a selective approach of the cyclic enone from the *Si*-face.

3.5. Conjugate addition of activated methylenes

The asymmetric conjugate addition of activated methylenes is one of the most studied organocatalytic reactions. A wide variety of Michael acceptors, such as enals, enones, α,β-unsaturated nitriles, nitroolefins, α,β-unsaturated imides, and vinyl sulfones, have been successfully employed as electrophiles with a high degree of stereocontrol.



Scheme 47. Enantioselective Michael addition of 2-nitropropane to chalcone catalyzed by chiral azacrown ethers.



Scheme 48. Asymmetric conjugate addition of 2-nitromethane to chalcone catalyzed by C_2-symmetric guanidinium salts.

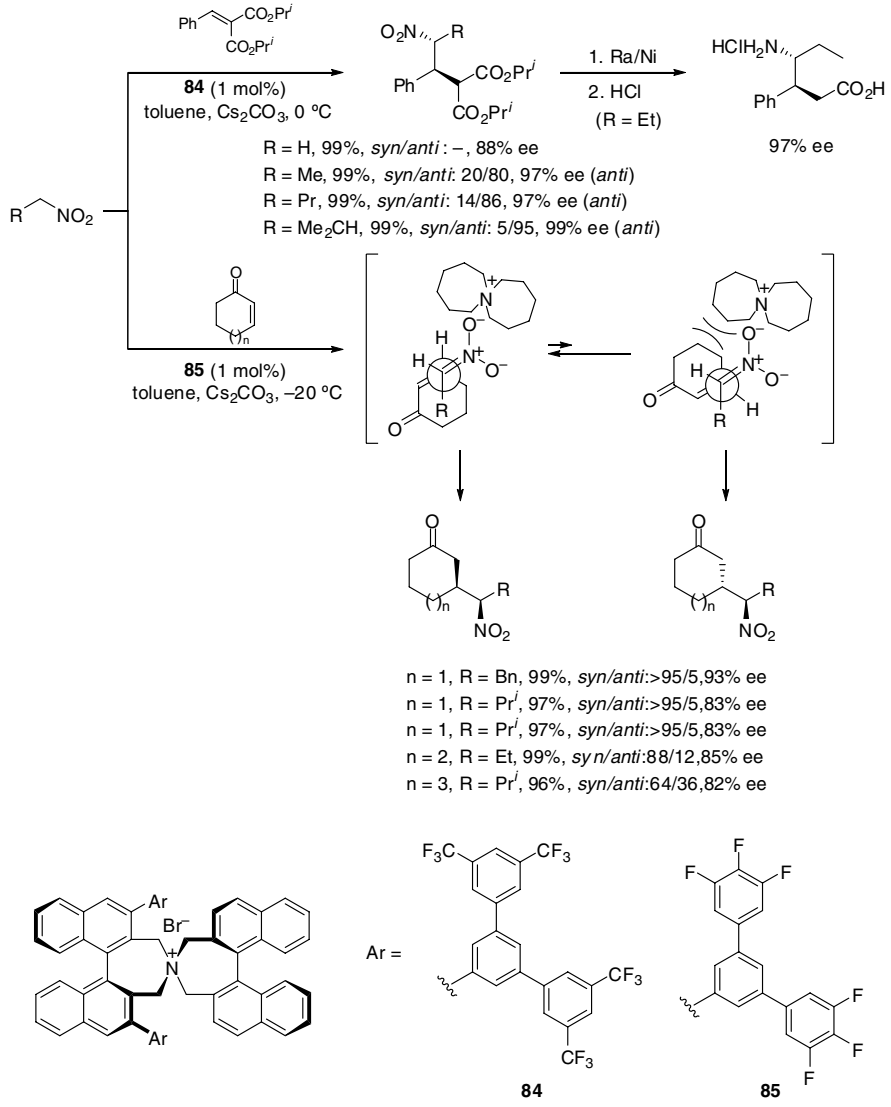
3.5.1. Conjugate addition of activated methylenes to α,β-unsaturated aldehydes. The asymmetric conjugate addition of activated methylenes to α,β-unsaturated aldehydes has been studied with a wide variety of nucleophiles such as 1,3-diketones, malonates, and malononitriles (Scheme 50).

Långström and Bergson carried out the first studies on the catalytic asymmetric Michael addition of 2-methoxycarbonyl-1-indanone to acrolein with partially resolved (5.57% ee) (*R*)-2-(hydroxymethyl)quinuclidine **86** as a catalyst, obtaining certain asymmetric induction in the process $\{[\alpha]_{546}^{21} = +8.8\}$.[118] Twenty years later, Yamaguchi et al. reported an asymmetric organocatalyzed Michael addition of malonates to α,β-unsaturated aldehydes employing L-proline rubidium salt **66** with poor enantioselectivities (up to 41% ee).[96b,119] Despite the significant importance of this asymmetric process, no more examples were described until 2003 when Maruoka et al. reported two examples of a highly enantioselective (up to 90% ee) Michael addition of 2-carboxycyclopentanones to acrolein where a significant improvement in the selectivity of the reaction was achieved by employing just a 2 mol % of chiral quaternary ammonium salt **87** under PTC conditions (K_2CO_3, toluene) (Fig. 15).[120] Three years later, Deng et al. developed the first highly efficient and general asymmetric conjugate addition of carbonyl donors to α,β-unsaturated aldehydes employing bifunctional *Cinchona* alkaloids **88**–**91**.[121] The catalytic system developed, which was also applied to the synthesis of the marine toxin (+)-tanikolide, was applicable not only to a wide variety of α-substituted-β-dicarbonyl donors, but also to α-aryl-α-cyanoacetates as nucleophiles by employing in the latter case catalyst **91** (Fig. 15).

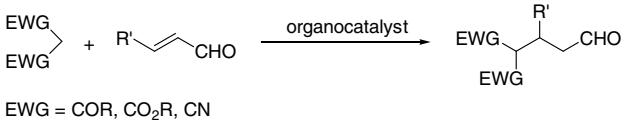
In 2006, Jørgensen et al. developed the first organocatalytic enantioselective addition of malonates to aromatic α,β-unsaturated aldehydes employing iminium ion activation with prolinol-derived catalyst **92**.[122] The reaction, which was solvent dependent was applied to the enantioselective synthesis of (+)- and (−)-paroxetine as well as (+)-femoxetine, proceeded especially well for benzyl and methyl malonates, being non-diastereoselective for unsymmetrical malonates (Scheme 51). With regards to the α,β-unsaturated aldehyde partner, the process was quite general tolerating many functional groups with excellent enantioselectivities observed for all the substrates studied (86–95% ee). Owing to steric interactions, *ortho*-substituents in the aromatic ring of the electrophile led to very low yields (Scheme 51).

Prolinol-derived catalyst **92** was also employed by these authors in an organocatalytic asymmetric one-pot Michael–Darzens condensation to prepare highly functionalized epoxycyclohexanone derivatives, with up to four stereogenic centers.[123] The reaction between γ-chloro-β-ketoesters and α,β-unsaturated aldehydes took place in the presence of **92** and NaOAc as an additive in CH_2Cl_2, to afford cyclohexanone-derived chlorohydrins, which were then converted in the optically active epoxy cyclohexanone derivatives in the presence of K_2CO_3 and DMF as cosolvent. These derivatives were then transformed via simple procedures in different optically active substrates as depicted in Scheme 52.

Very recently, Jørgensen et al. presented a one-pot approach to optically active 2,5-disubstituted cyclohex-2-en-



Scheme 49. Conjugate addition of nitroalkanes catalyzed by *N*-spiro chiral ammonium bromides.



Scheme 50. Asymmetric conjugate addition of activated methylenes to α,β-unsaturated aldehydes.

ones, a process, which involves the first organocatalytic asymmetric conjugate addition of β-ketoesters to α,β-unsaturated aldehydes in aqueous solutions or under solvent-free conditions.[124] In the presence of catalyst **92** (10 mol %), β-ketoesters could be added asymmetrically to a variety of enals affording the corresponding Michael-adduct intermediates, which suffered an additional decarboxylation/cyclization/dehydratation sequence to yield enantiomerically enriched 2,5-disubstituted cyclohex-2-enones in high yields and excellent enantioselectivities (Scheme 53). Under the optimized reaction conditions, *p*-TSA worked as a second organocatalyst leading directly to the chiral cyclohexenones. The *tert*-butyl ester group was essential for the success of the one-pot reaction since the acid was capable of catalyzing hydrolysis of the ester, the decarboxylation of the newly formed β-ketoacid, the intramolecular aldol reactions and the final elimination reaction.

3.5.2. Conjugate addition of activated methylenes to α,β-unsaturated ketones. The earliest studies on the catalytic asymmetric Michael addition of activated methylenes were conducted with readily available natural amines. Firstly, Wynberg demonstrated that *Cinchona* alkaloids could be employed for the Michael addition of cyclopentanone and cyclohexanone-derived 1,3-dicarbonyl compounds, such as 2-methoxycarbonylindan-1-one, to α,β-unsaturated enones with excellent yields and enantioselectivities of up to 76%.[104,125] Lower rates and enantioselectivities were obtained with a polymer-supported version of this type of catalyst. For instance, succinated polystyrene-divinylbenzene attached to *Cinchona* alkaloids, such as **93** (Scheme 54),

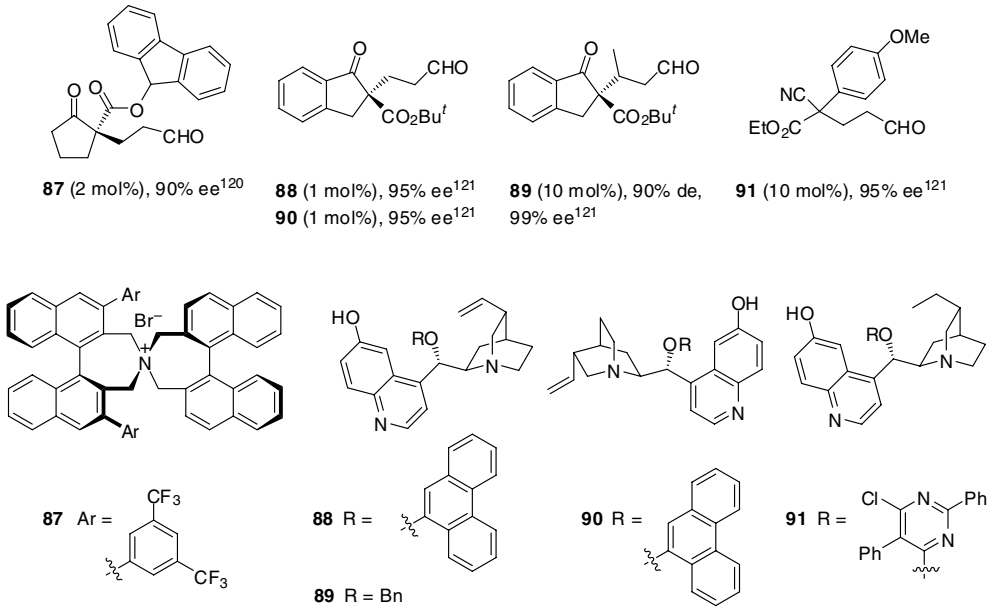
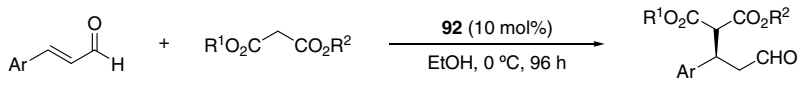
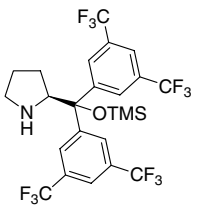


Figure 15. Conjugate addition of activated methylenes to α,β-unsaturated aldehydes.

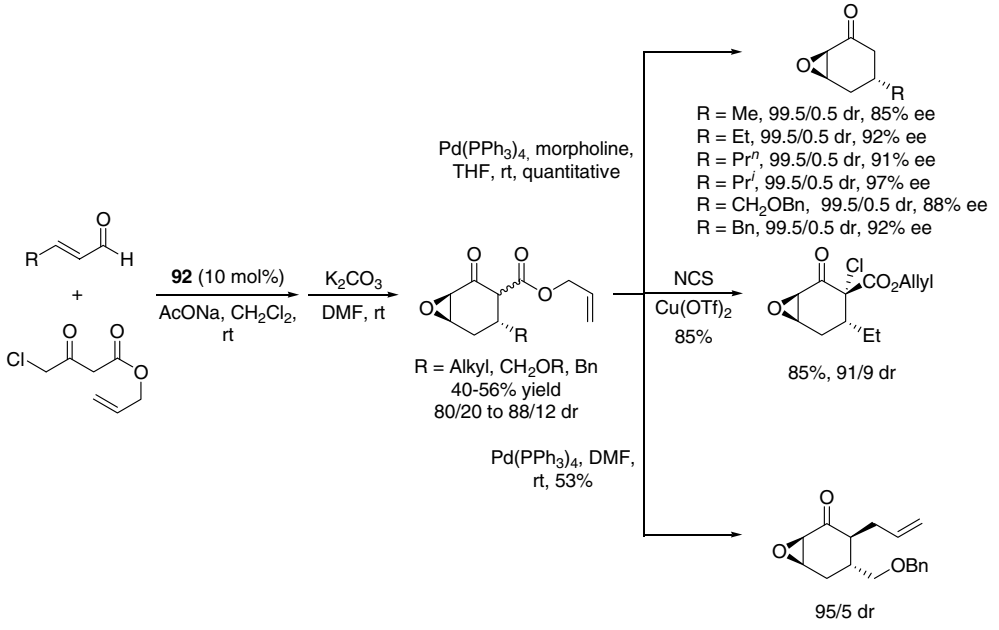




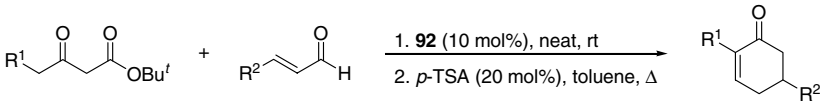
92

Ar	R^1	R^2	Yield (%)	dr	ee (%)
Ph	Bn	Bn	80	–	91
Ph	Me	Me	85	–	94
Ph	Et	Et	42	–	89
Ph	Pr^i	Pr^i	0	–	–
Ph	Bn	Me	nd	1/1	nd
2-BrC_6H_4	Bn	Bn	34	–	88
2-naphthyl	Bn	Bn	69	–	88
2-thienyl	Bn	Bn	83	–	92

Scheme 51. Conjugate addition of malonates to aromatic α,β-unsaturated aldehydes catalyzed by **92**.

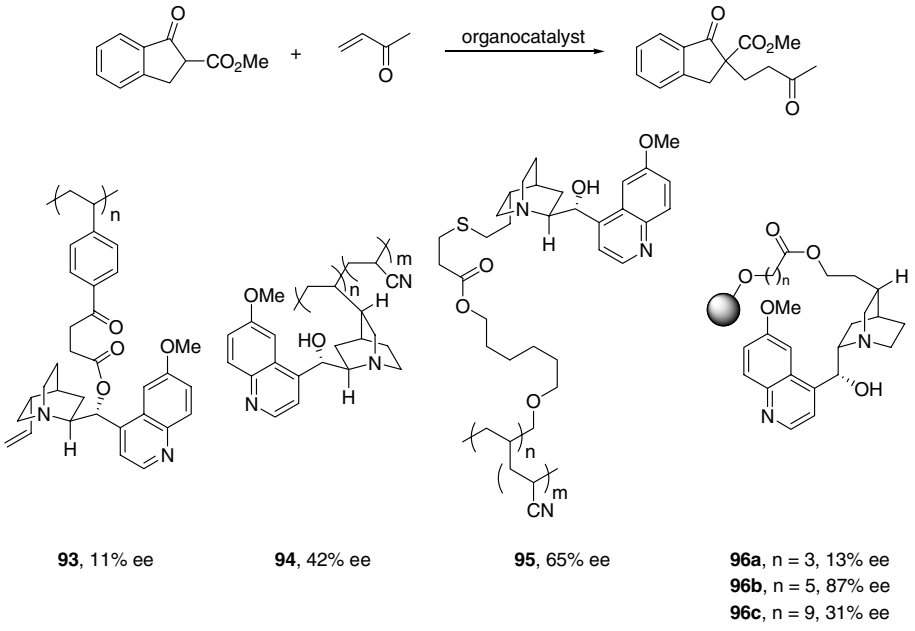


Scheme 52. One-pot organocatalytic domino Michael-aldol and intramolecular S_N2 reaction.



R^1	R^2	Yield (%)	ee (%)
H	Me	93	80
H	Et	98	94
H	Pr^i	56	96
H	Bu	69	92
H	Ph	63	94
H	4-FC_6H_4	65	95
H	3-MeC_6H_4	72	94
Me	Et	82	91
Et	Et	74	89

Scheme 53. One-pot organocatalytic synthesis of chiral 2,5-disubstituted cyclohex-2-enones catalyzed by **92**.



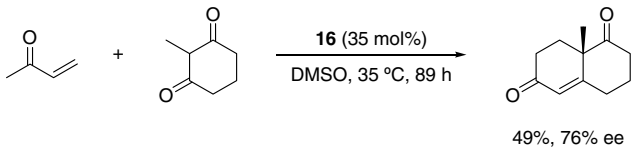
Scheme 54. Polymer-supported organocatalysts for the Michael addition of 2-methoxycarbonylindan-1-one to methyl vinyl ketone.

promoted the addition of 2-methoxycarbonyl-1-indanone to methyl vinyl ketone with 11% ee.[126] A higher 42% ee was obtained in the same process in the presence of quinidine-acrylonitrile copolymer **94**.[105b,127] The introduction of spacers between the polymer backbone and the chiral amine as in **95** (Scheme 54) brought the enantioselectivity of the process nearer to the homogeneous reaction levels (up to 65% ee).[128] The best result obtained so far in the reaction (87% ee for **96b**) also demonstrated that the length of the spacer arm inserted between the polymer matrix and the alkaloid was critical in order to obtain a good enantioselectivity.[129]

Generally, 2-methoxycarbonyl-1-indanone was the standard substrate to evaluate the efficiency of the newly developed organocatalysts. Yamaguchi et al. enlarged the scope of the reaction by employing the rubidium salt of L-proline **66** as the catalyst, which turned out to be an efficient promoter in chloroform for the asymmetric addition of diisopropyl malonate to a wide range of cyclic and acyclic enones with enantioselectivities of up to 59% and 77% ee, respectively.[119]

The malonate preferentially attacked cyclic *Z*-enones from the *Re*-face and acyclic *E*-enones from the *Si*-face, which meant that the nucleophile attacked from the same side of the enone plane, irrespective of its stereochemistry. Later studies increased the enantioselectivity of the rubidium salt of L-proline-catalyzed addition of di-*tert*-butyl malonate to *E*-pentenone to a maximum of 88% ee just using 20 mol % of CsF as cocatalyst.[96b] Kawara and Taguchi employed L-proline-derived ammonium salts as catalysts for the malonate addition to enones though lower yields (21–96%) and selectivities (up to 71% ee) were observed.[130] Even though

the chiral induction of the process was produced in the aldol condensation and the process then cannot be considered as an asymmetric conjugate addition, L-proline itself was demonstrated to promote the asymmetric Robinson annulation, resulting in an efficient catalyst for the single step enantioselective synthesis of the Wieland–Miescher ketone (Scheme 55).[131]



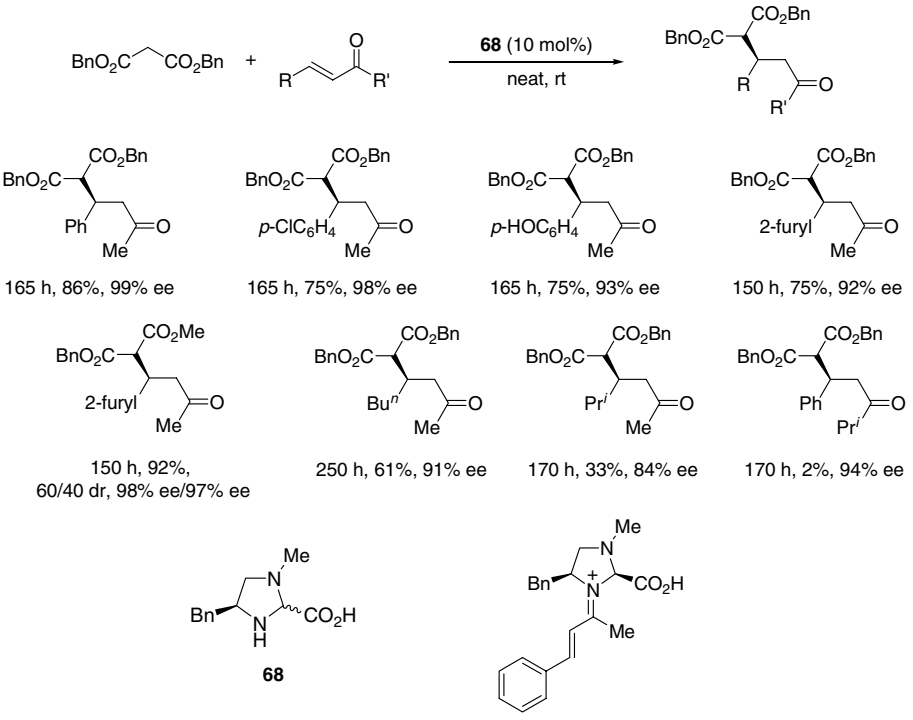
Scheme 55. Synthesis of the Wieland–Miescher ketone.

Jørgensen et al. showed that imidazolidine derivative **68** was a very effective organocatalyst for the enantioselective conjugate addition of malonates to α,β-unsaturated enones.[132] The ester functionality of the nucleophile had a large influence on the yield and enantioselectivity of the process. Benzyl malonates proved to be the best nucleophiles affording the corresponding Michael adducts in good to excellent yields and excellent enantioselectivities (Scheme 56).[132] In the case of non-symmetrical malonates, the diastereoselectivity and the rate of the process were low but not the asymmetric induction. However, the enantioselectivity diminished notably when using sterically hindered enones. In accordance with the observed absolute configuration of the products, an iminium ion intermediate was proposed with the *Re*-face of the enone shielded by the benzyl group of the chiral catalyst.[132]

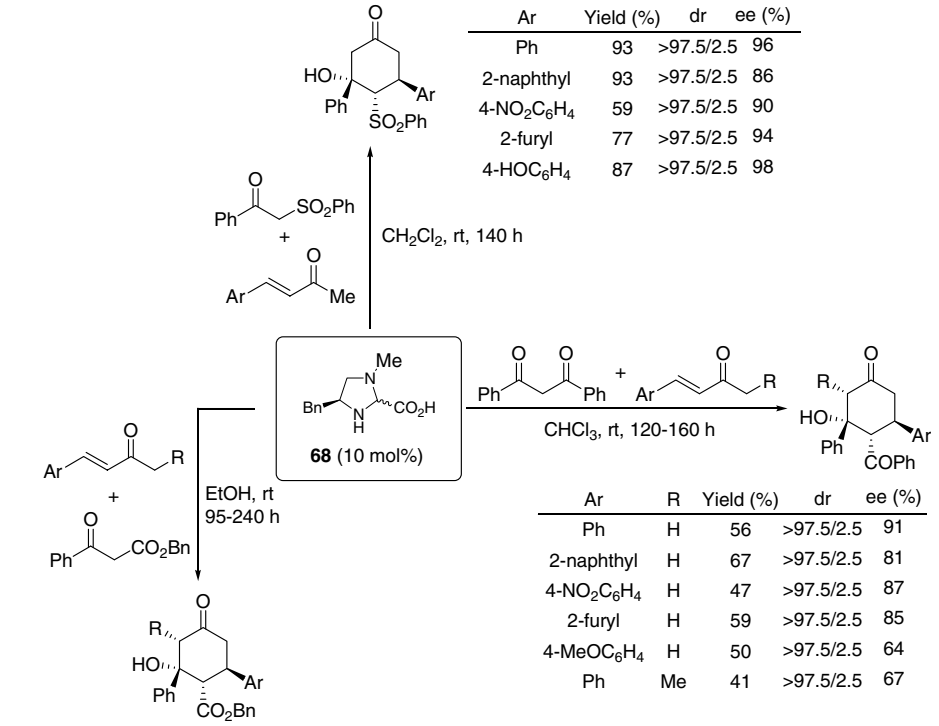
Chiral imidazolidine **68** was also reported by the same authors to be a very effective organocatalyst for the enantio- and diastereoselective domino Michael-aldol reaction of β-diketones,[133] β-ketosulfones,[133] and β-ketoesters[134] with α,β-unsaturated ketones to afford optically active cyclohexanones having three or four contiguous stereogenic centers (Scheme 57). Lower selectivities were obtained for the L-proline-catalyzed domino Michael-aldol reaction of 1,3-diketones with methyl vinyl ketone.[135]

A highly enantioselective organocatalytic Michael addition of hydroxycoumarines and related compounds to α,β-unsaturated ketones was performed employing imidazolidine catalyst **97**.[136] The reaction, which gave high yields and enantioselectivities for a wide range of cyclic 1,3-dicarbonyl compounds and enones, was employed for the asymmetric synthesis of the anticoagulant warfarin (Scheme 58).[136] Very recent studies have demonstrated that the truly active catalyst in the process is chiral diamine **98**, which is formed in catalytic amounts under the reaction conditions by reaction with the hydroxycoumarin (Scheme 59).[137] The intermediate in the reaction was then postulated to be a chiral diimine formed from the diamine and the enone. In this intermediate one of the faces of the electrophile was efficiently shielded from nucleophilic attack. This finding led the authors to explore the use of chiral C_2-symmetric diamines as organocatalysts in the conjugate addition giving higher yields (up to 98%) and enantioselectivities (up to 92% ee) for the synthesis of warfarin (Scheme 59).[137]

Proline-tetrazole catalyst **70** (Scheme 41) was also successfully employed in the conjugate addition of malonates to cyclic and acyclic enones.[138] This catalyst circumvented the use of a large excess of nucleophile and provided good



Scheme 56. Enantioselective organocatalytic conjugate addition of malonates to acyclic α,β-unsaturated enones catalyzed by **68**.

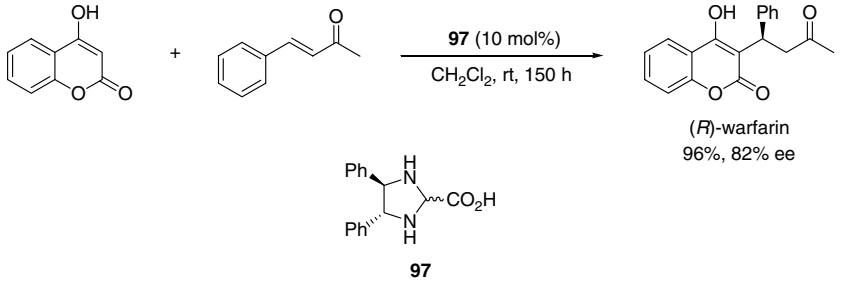


Ar	Yield (%)	dr	ee (%)
Ph	93	>97.5/2.5	96
2-naphthyl	93	>97.5/2.5	86
4-$NO_2C_6H_4$	59	>97.5/2.5	90
2-furyl	77	>97.5/2.5	94
4-HOC_6H_4	87	>97.5/2.5	98

Ar	R	Yield (%)	dr	ee (%)
Ph	H	56	>97.5/2.5	91
2-naphthyl	H	67	>97.5/2.5	81
4-$NO_2C_6H_4$	H	47	>97.5/2.5	87
2-furyl	H	59	>97.5/2.5	85
4-$MeOC_6H_4$	H	50	>97.5/2.5	64
Ph	Me	41	>97.5/2.5	67

Ar	R	Yield (%)	dr	ee (%)
Ph	H	80	>97/3	95
2-naphthyl	H	85	>97/3	91
4-$NO_2C_6H_4$	H	56	>97/3	96
2-furyl	H	40	>97/3	85
Ph	Me	50	>97/3	95

Scheme 57. Synthesis of chiral polyfunctionalized cyclohexanones catalyzed by imidazoline **68**.

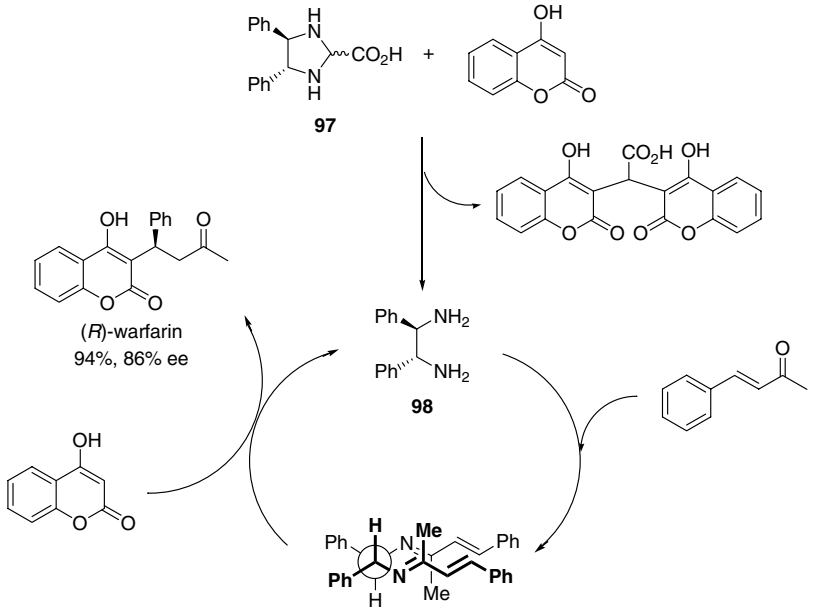


Scheme 58. Organocatalytic asymmetric synthesis of anticoagulant warfarin catalyzed by **97**.

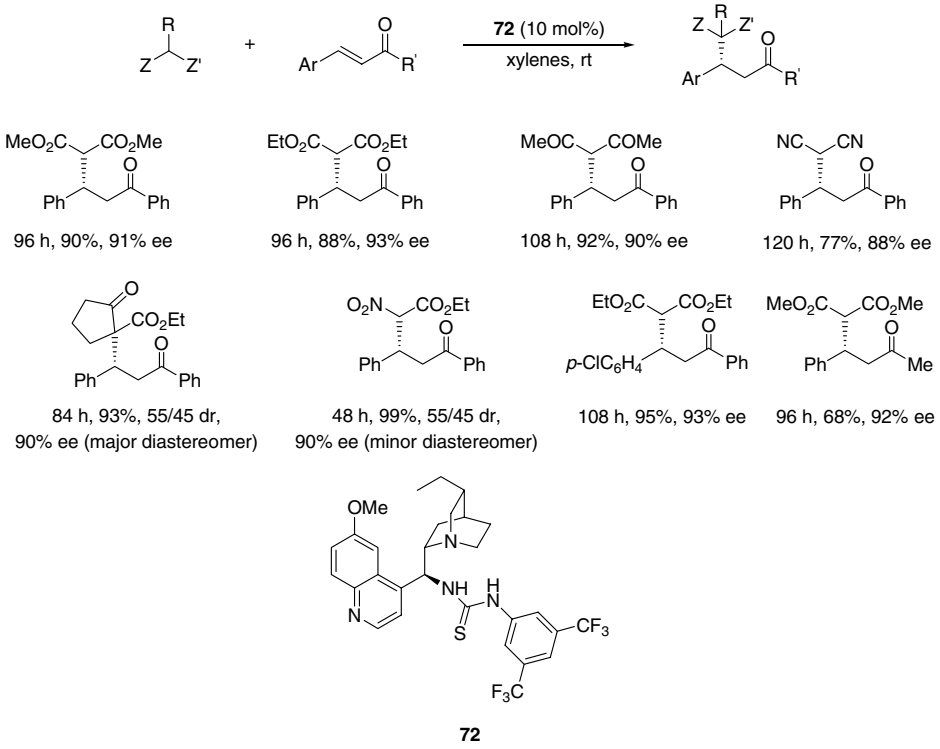
enantioselectivities when using dimethyl malonate, circumstances that were considered as advantages over the previously reported organocatalysts.

Cinchona alkaloid-derived chiral bifunctional thiourea derivative **72** represents one of the most versatile organocatalysts prepared so far for the addition of activated methylenes to enones since it afforded, although with poor diastereoselectivities, excellent enantioselectivities and high yields in the conjugate addition of a broad spectrum of nucleophilic enol species, such as malonate esters, β-keto-esters, 1,3-diketones, nitroesters, and 1,3-dinitriles to enones (Scheme 60).[139]

Bifunctional chiral thiourea **99** was used by Chen et al. as a very efficient organocatalyst for the enantioselective Michael addition of α-substituted cyanoacetates to vinyl ketones.[140] The reaction, which afforded multifunctional compounds with all-carbon-substituted quaternary stereocenters in excellent yields (61–99%) and enantioselectivities (82–97% ee), was employed for the asymmetric synthesis of biologically important $\beta^{2,2}$-amino acid esters, as depicted in Scheme 61 for a selected example. Based on the absolute configuration of the products and semi-empirical calculations, the authors proposed a transition state involving multiple hydrogen-bonding interactions: a strong hydrogen bond between the OH group of the enolate and the Me_2N



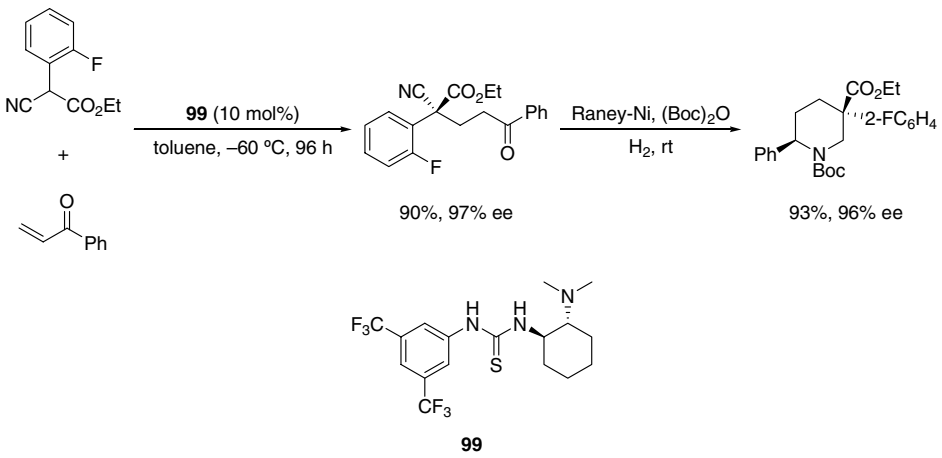
Scheme 59. Organocatalytic asymmetric synthesis of anticoagulant warfarin catalyzed by **98**.



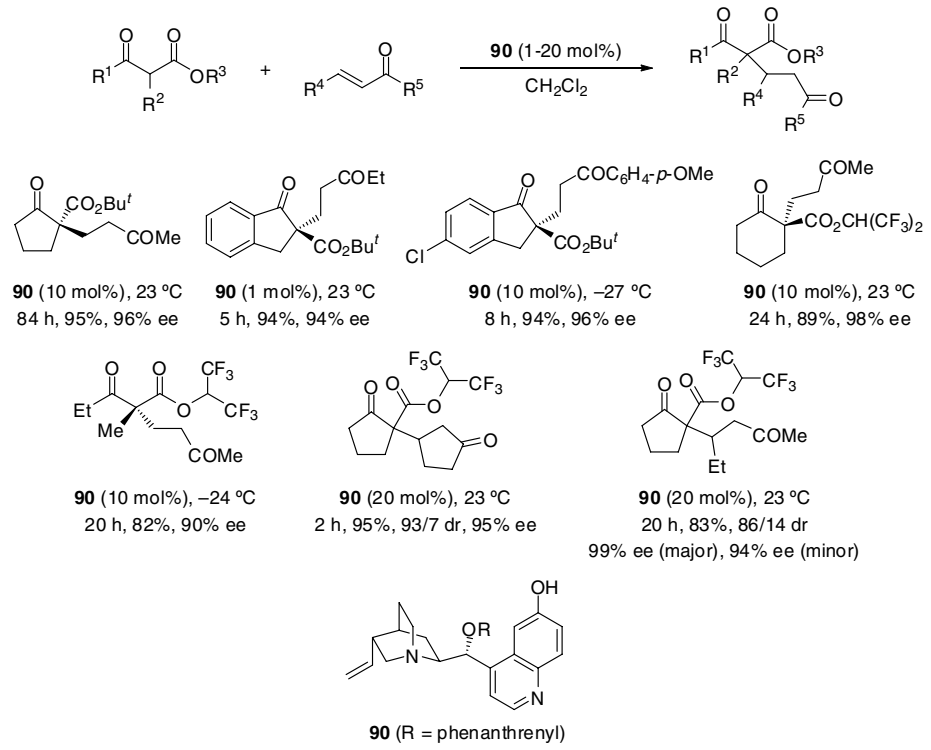
Scheme 60. Organocatalytic enantioselective conjugate additions to enones catalyzed by bifunctional thiourea **72**.

group of the catalyst and a weaker hydrogen bond concerning the OEt group of the enolate and the NH of the thiourea moiety.

Deng et al. reported the use of simple cupreines, such as **90**, as efficient organocatalysts for the construction of stereogenic quaternary centers through the conjugate addition of α-substituted β-ketoesters to α,β-unsaturated ketones.[141] The reaction afforded excellent yields as well as diastereo- and enantioselectivities for a wide variety of α-substituted β-ketoesters and a wide range of enones, usually working at room temperature and employing very low catalyst loadings (usually in the range 1–10 mol %) (Scheme 62). This study disclosed the first examples of a highly enantio- and diastereoselective catalytic conjugate addition of a trisubstituted carbon nucleophile to a cyclic enone.



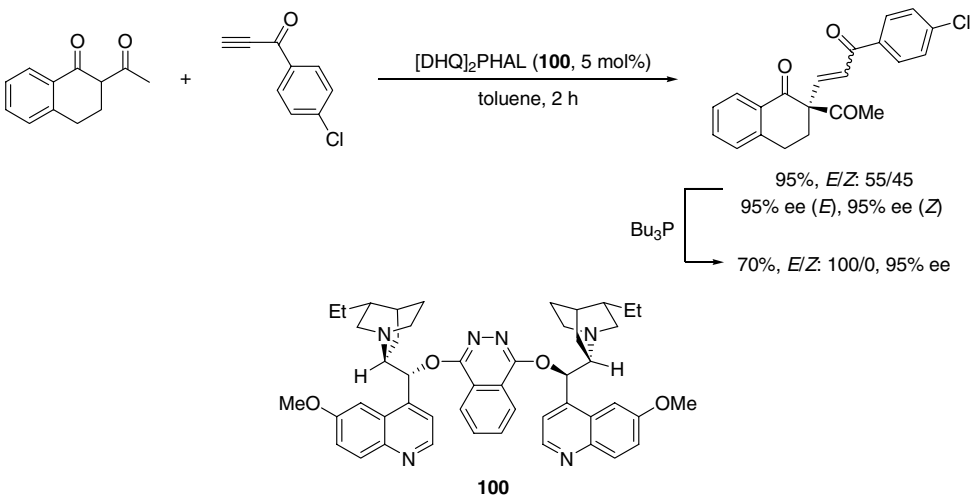
Scheme 61. Organocatalytic enantioselective synthesis of $\beta^{2,2}$-amino acid esters catalyzed by chiral thiourea **99**.



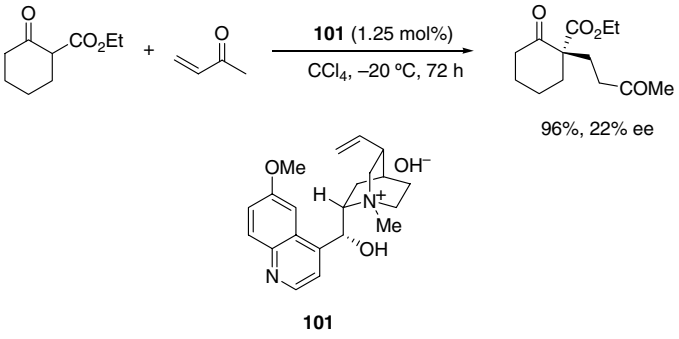
Scheme 62. Organocatalytic asymmetric conjugate addition of α-substituted β-ketoesters to α,β-unsaturated ketones catalyzed by **90**.

The first organocatalytic enantioselective conjugate addition of 1,3-dicarbonyl compounds to alkynones has recently been developed by Bella and Jørgensen.[142] The reaction, which was catalyzed by very low loadings (5 mol %) of the *Cinchona* alkaloid $[DHQ]_2PHAL$ **100**, was highly enantioselective for the addition of β-diketones to both aromatic and aliphatic alkynones giving a mixture of *E*- and *Z*-enones (Scheme 63). An additional advantage of the method was the possibility of performing a one-pot isomerization of the mixture of *E*/*Z*-enones to the *E*-isomer, without affecting the yield or the enantioselectivity (Scheme 63).

Chiral phase-transfer catalysts are also involved in the formation of chiral ion pairs between the enolate and the ammonium cation, so they have been often used as promoters in the conjugate addition of activated malonates to α,β-unsaturated ketones. Phase-transfer catalysts are stronger bases compared to the amine catalysts, so their use was initially focused on the conjugate addition of less-acidic nucleophiles, where chiral amines had not been successful. Thus, different chiral phase-transfer systems such as *N*-alkylated cinchonium derivatives (Scheme 64)[125b,143] and ephedrinium salts[143,144] were prepared and tested in the conjugate addition of 1,3-dicarbonyl



Scheme 63. Organocatalytic asymmetric conjugate addition of α-substituted-β-diketones to alkynones.



Scheme 64. Initial studies on the phase-transfer catalyzed addition of 1,3-dicarbonyl compounds to enones.

compounds to enones under phase-transfer conditions. Although the observed enantioselectivities ranged from low to moderate, these early experiments came up with some interesting conclusions, such as the influence that steric and electronic interactions (van der Waals, π-stacking and hydrogen bonding) between substrates and catalysts had on the selectivity of the process.

The preliminary studies led to the employment of the *Cinchona* alkaloid catalysts **102**,[145] **103**,[146] and **104**[147] in the enantioselective conjugate addition of malonates to enones in the presence of K_2CO_3 as a base (Fig. 16). Different fragrances, such as methyl dihydrojasmonate and *trans*-magnolione, were prepared following this methodology.[145]

The best selectivities in the phase-transfer catalyzed Michael addition of 1,3-dicarbonyl compounds to enones were recently achieved by Maruoka et al.[120,148] As shown in Scheme 65, just 2 mol % of the binaphthyl-derived phase-transfer catalyst **87** (Fig. 15) in the presence of 10 mol % of solid potassium carbonate, was able to achieve a highly efficient and enantioselective addition of 2-(9-fluorenoxycarbonyl)cyclopentanone to methyl vinyl ketone.[120]

The catalytic activity of chiral bifunctional ammonium bromide **105** was much more general. Under very low loading conditions, catalyst **105** was able to promote the Michael addition of malonates (especially ethyl malonates) and malononitrile to chalcone derivatives in a highly enantioselective manner, as depicted in Scheme 66.[148] The authors also showed the importance of the hydroxy functionality of the catalyst to afford adequate enantiofacial differentiation of the prochiral chalcone. Unfortunately, the methodology could not be extended to aliphatic enones (Scheme 66).

Following their studies about the organocatalytic conjugate addition of activated methylenes, Jørgensen and coworkers presented the first examples of an organocatalytic highly diastereo- and enantioselective vinylic substitution reaction in 2006.[149] This process, which consisted of a

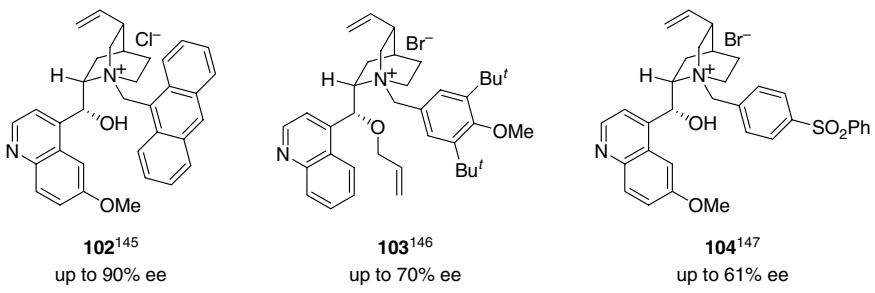
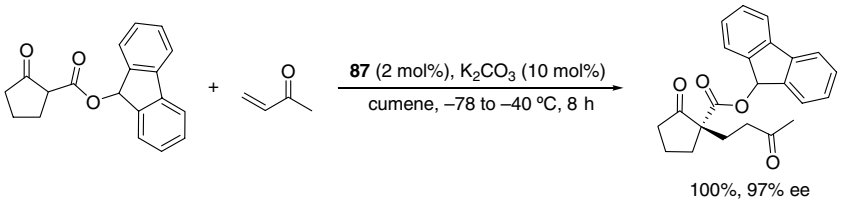
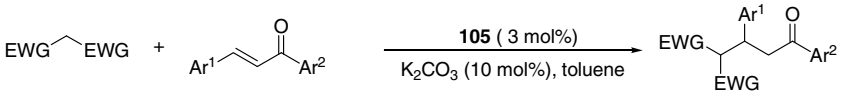


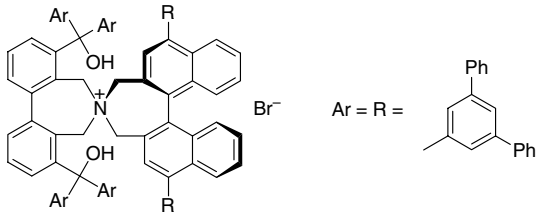
Figure 16. Cinchonium-derived catalysts for the enantioselective Michael reaction of malonates and α,β-unsaturated enones.



Scheme 65. Enantioselective phase-transfer catalytic Michael addition of β-ketoesters to enones catalyzed by **87**.



EWG	Ar^1	Ar^2	Temp (°C)	Time (h)	Yield (%)	ee (%)
CO_2Et	Ph	Ph	–20	24	99	90 (*R*)
CO_2Et	2-naphthyl	Ph	–20	48	94	91
CO_2Et	4-$MeOC_6H_4$	Ph	–20	24	99	87
CO_2Et	4-ClC_6H_4	Ph	–20	24	99	85
CO_2Et	2-pyridyl	Ph	–30	48	99	90
CO_2Et	2-furyl	Ph	–20	24	99	86
CO_2Et	2-thienyl	Ph	–20	24	99	94
CO_2Et	Ph	2-thienyl	–20	24	99	94
CO_2Et	Ph	Me	0	96	98	8
CN	Ph	Ph	–50	48	98	81



105

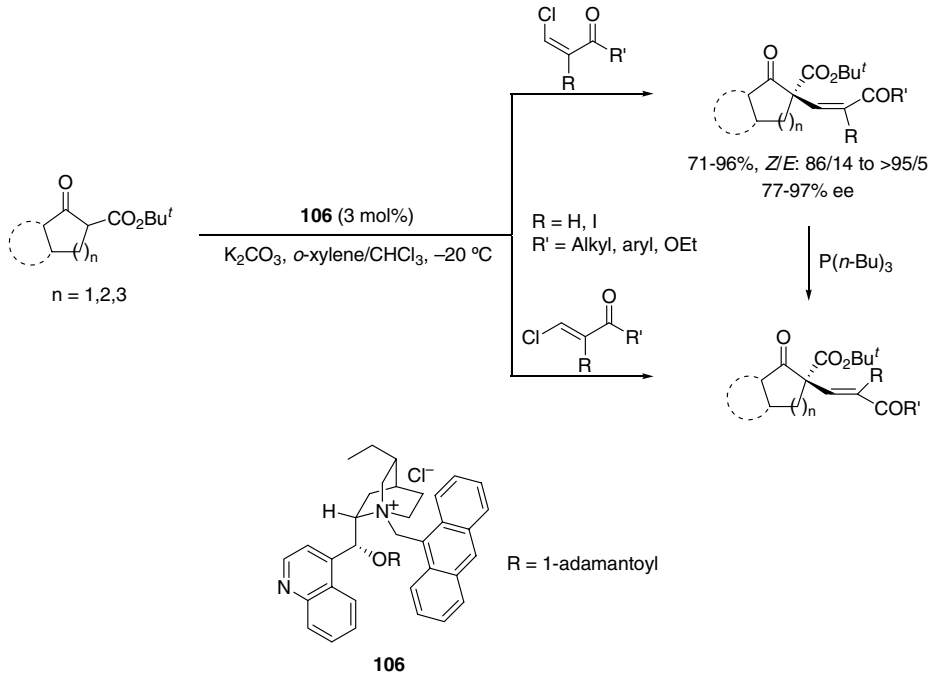
Scheme 66. Enantioselective phase-transfer catalytic Michael addition of malonates to chalcone derivatives.

Csp^3–Csp^2 coupling between β-ketoesters and electron-deficient *Z*- or *E*-vinylic chlorides (β-acylvinyl cation equivalents), was efficiently catalyzed by the new bulky phase-transfer catalyst **106** under very simple reaction conditions (Scheme 67). The reaction took place with retention of configuration of the double bond, which was rationalized by the authors through an Ad_N-E mechanism. Moreover, easy access to both double bond isomers could also be achieved through isomerization of the *Z*-double bond to the more stable *E*-configuration in the presence of catalytic amounts of phosphanes. A limitation of the catalytic system was the low enantioselectivities obtained with non-cyclic β-ketoesters (up to 40% ee).[149]

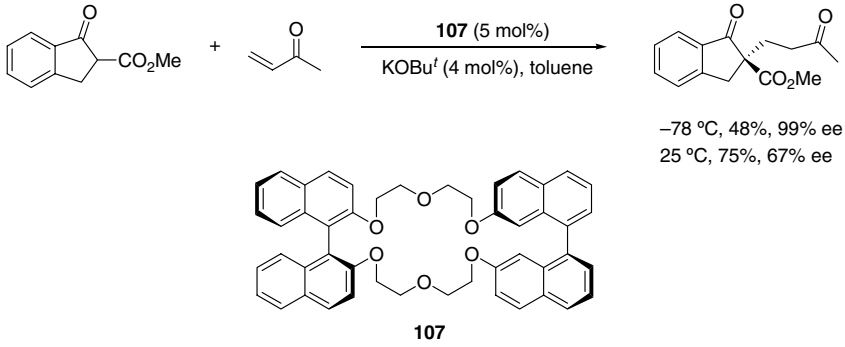
Chiral crown ether **107** was used as a phase-transfer catalyst for the Michael addition of 2-methoxycarbonylindanone to methyl vinyl ketone employing catalytic amounts of potassium *tert*-butoxide as base.[150] The reaction afforded the Michael adduct in very high enantioselectivity when working at −78 °C (Scheme 68).

The employment of chiral ionic liquids derived from *N*-methylimidazole as chiral solvents for the conjugate addition of diethyl malonate to chalcone has recently been studied.[151] Unfortunately, very poor enantioselectivities were obtained under optimized reaction conditions (up to 15% ee).

3.5.3. Conjugate addition of activated methylenes to α,β-unsaturated nitriles. Very recently, Deng et al. extended the scope of *Cinchona* alkaloid catalysis in the conjugate addition of activated methylenes to the catalytic asymmetric tandem conjugate addition–protonation between trisubstituted carbon donors such as β-ketonitriles or β-ketoesters and α-substituted Michael acceptors such as α-chloro acrylonitriles.[152] This reaction established a new and versatile catalytic and asymmetric approach to the one-step construction of non-adjacent 1,3-tertiary-quaternary stereocenters. Cupreine **87** catalyzed the tandem conjugate addition–protonation of cyclic β-ketonitriles or β-ketoesters to afford the corresponding adducts in high yields (71–95%), diastereoselectivities (7/1–25/1 dr) and enantioselectivities (91–99% ee) (Scheme 69). On the other hand, cupreidine **108** proved to be the most effective organocatalyst when acyclic trisubstituted carbon donors, such as α-cyanoacetates and α-cyanothioacetates, were used as



Scheme 67. Organocatalytic enantioselective nucleophilic vinylic substitution.



Scheme 68. Asymmetric Michael addition catalyzed by chiral crown ether **107**.

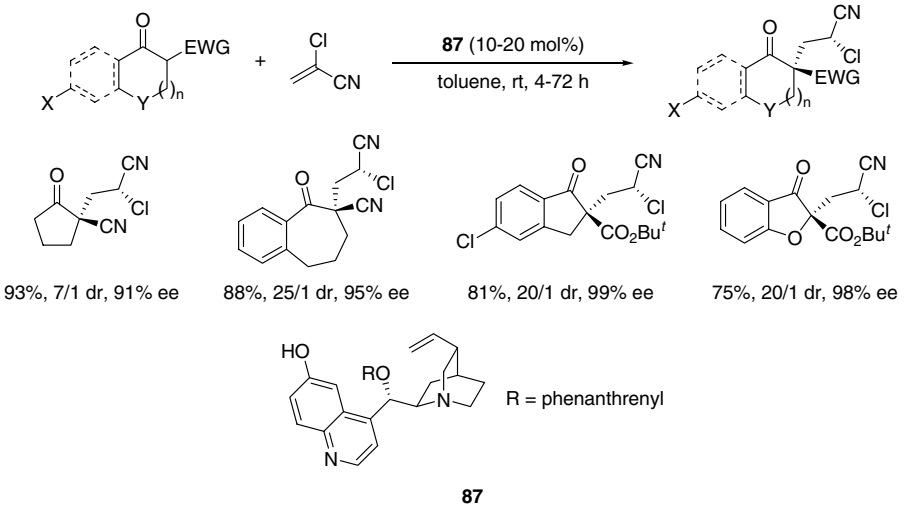
demonstrated in the synthesis of an intermediate of bromopyrrole alkaloid (−)-manzacidin A (Scheme 70).

With respect to the reaction mechanism, the authors postulated the dual role of the organocatalyst in the process of forming an asymmetric network of hydrogen bonds with the reactants: to promote the conjugate addition between the reactants and the subsequent protonation of the transient enol intermediate in a stereoselective manner (Scheme 71). The absolute stereochemistry of the products obtained was consistent with this mechanistic proposal.[152]

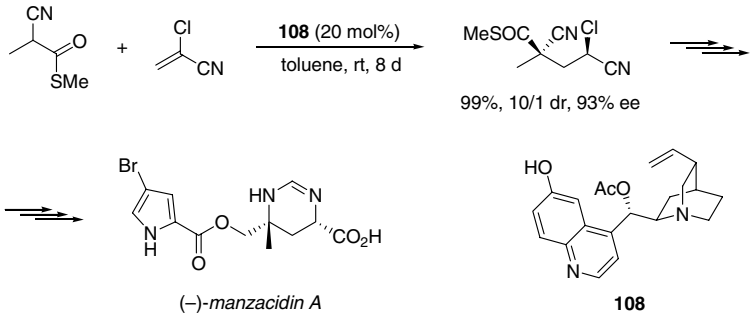
3.5.4. Conjugate addition of activated methylenes to nitroolefins. The first highly enantioselective organocatalytic conjugate addition of 1,3-dicarbonyl compounds to nitroolefins was reported by Takemoto et al. using bifunctional thiourea-amine catalyst **99**.[153] After Takemoto's report, a wide variety of bifunctional organocatalysts were developed and successfully applied to this reaction expanding the scope of the Takemoto catalyst (Fig. 17).

As shown in Scheme 72 for representative results, in the presence of catalytic amounts (2–10 mol %) of these bifunctional organocatalysts, the conjugate addition of a wide variety of malonate derivatives to β-nitrostyrenes and β-alkylnitroolefins could be achieved with high yield and levels of stereoinduction. The exceptionally wide scope for α-functionalized trisubstituted malonates shown by chiral thiourea **99**, which should be useful for the synthesis of many multifunctional chiral building blocks containing quaternary stereocenters (Scheme 72), was of particular interest.[153] A remarkable feature was also the highly enantioselective addition of malonate esters to sterically hindered γ-branched nitroalkenes such as *trans*-(2-nitrovinyl)cyclohexane reported for catalysts **109**[154] and **115**,[159] since such nitroalkenes have been shown to be relatively challenging substrates in metal-catalyzed processes.

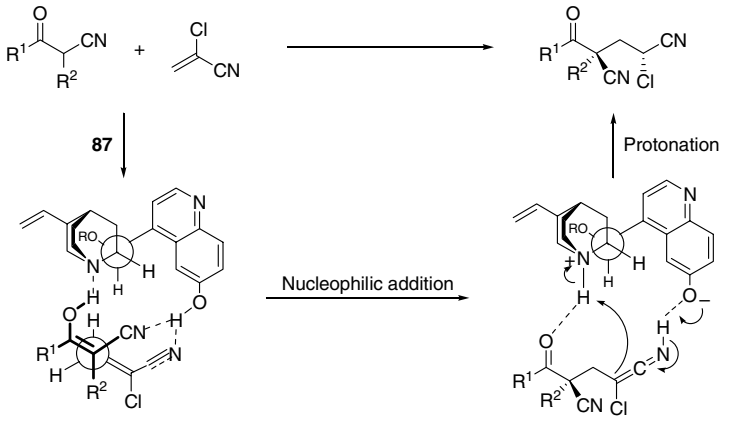
When using 1,3-diketones as nucleophiles, different organocatalysts such as **99**,[153] **110**,[155] **111**,[155] **114**,[158] and **115**[159] were able to promote the addition to aromatic nitroolefins



Scheme 69. Catalytic asymmetric tandem conjugate addition–protonation reaction.



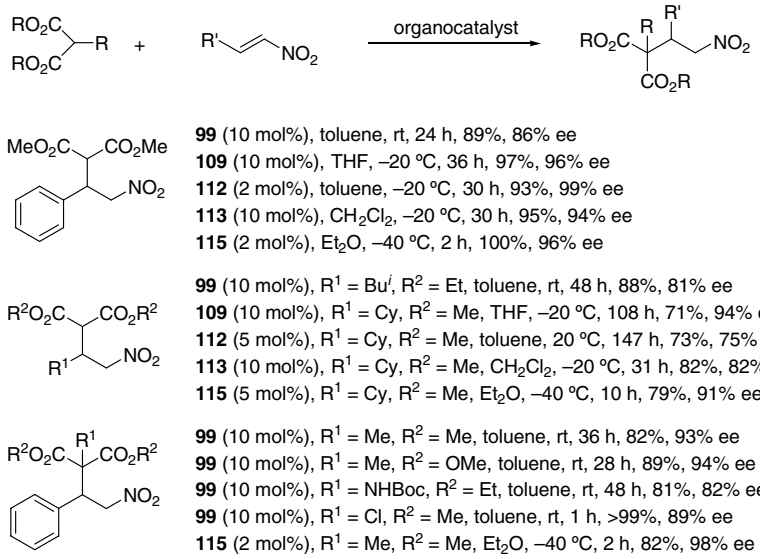
Scheme 70. Asymmetric formal synthesis of (−)-manzacidin A.



Scheme 71. Proposed mechanism for the catalytic asymmetric tandem conjugate addition–protonation reaction.

with high yields and enantioselectivities. For instance, *Cinchona* alkaloid-derived organocatalyst **110** afforded a very enantioselective conjugate addition of prochiral 2-acetylcyclopentanone to *trans*-β-nitrostyrene with moderate but still useful diastereoselectivity (Scheme 73).[155]

α-Unsubstituted and α-substituted β-ketoesters were also shown to be efficient nucleophiles for highly diastereo- and enantioselective conjugate addition to nitrostyrenes. This process was very interesting since it generated adjacent tertiary and quaternary stereocenters, which are common structural motifs in complex natural products. In the case of the conjugate addition of α-unsubstituted β-ketoesters, organocatalysts **99**,[153] **109**,[154] and **115**[159] afforded the corresponding Michael adducts with very high enantioselectivities (89–91% ee), but no diastereoselectivity as



Scheme 72. Enantioselective Michael reaction of malonates to nitroolefins catalyzed by bifunctional organocatalysts **99** and **109**–**115**.

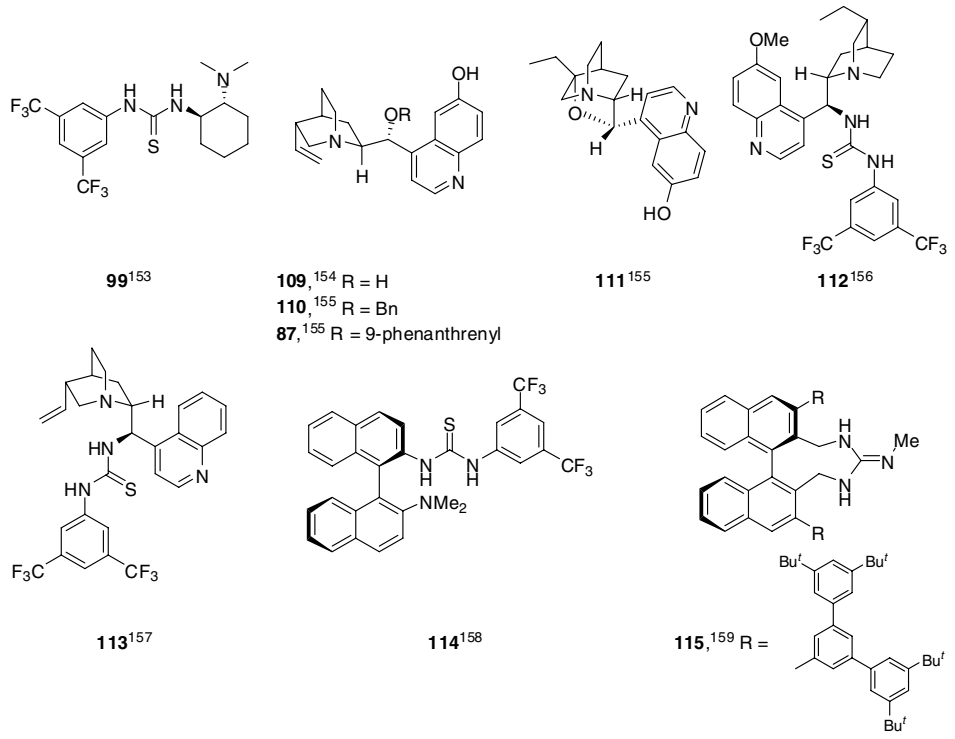
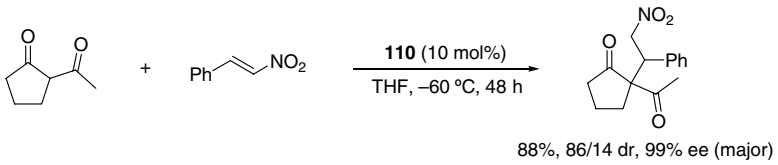


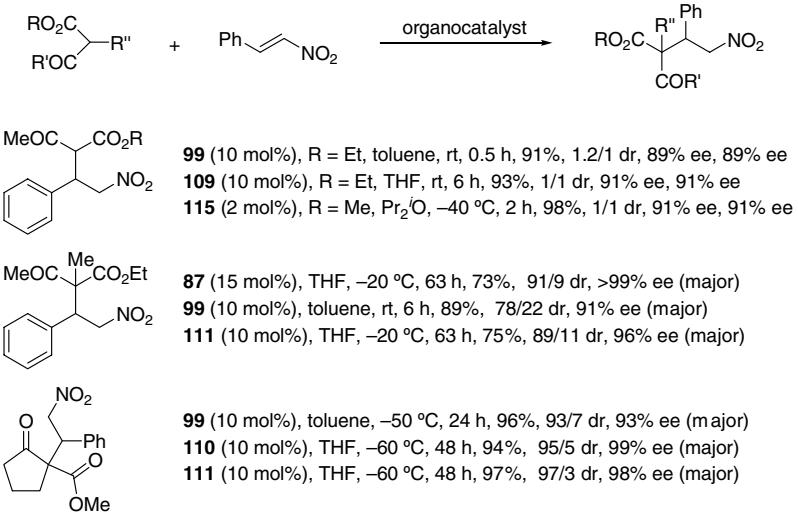
Figure 17. Chiral organocatalysts for the conjugate addition of activated methylenes to nitroolefins.[153–159]

depicted in Scheme 74 for the addition of ethyl(methyl) acetoacetate to *trans*-β-nitrostyrene. High levels of diastereoselection were observed in the case of α-substituted β-ketoesters where Takemoto's chiral thiourea **99**[153] and *Cinchona* alkaloid-derived catalysts **87**,[155] **110**,[155] and **111**[155] were the most efficient organocatalysts. Importantly, when using catalyst **110**, high diastereoselectivity and enantioselectivity could also be attained with trisubstituted activated methylenes other than 1,3-dicarbonyl compounds such as β-nitro- and β-cyanoesters (Scheme 74).[155]

Kinetic studies carried out with different organocatalysts, such as **99**, **109**, and **110**, established that the conjugate addition followed a first-order dependence on the catalyst, the nucleophile and the electrophile. The absence of nonlinear effects also suggested monomeric species as the truly active catalyst. These results and catalyst modification studies were consistent with the mechanistic proposals presented by Takemoto, who reported the activation of both the nucleophile and the electrophile by thiourea **99**. The nitroolefin was assumed to interact with the thiourea



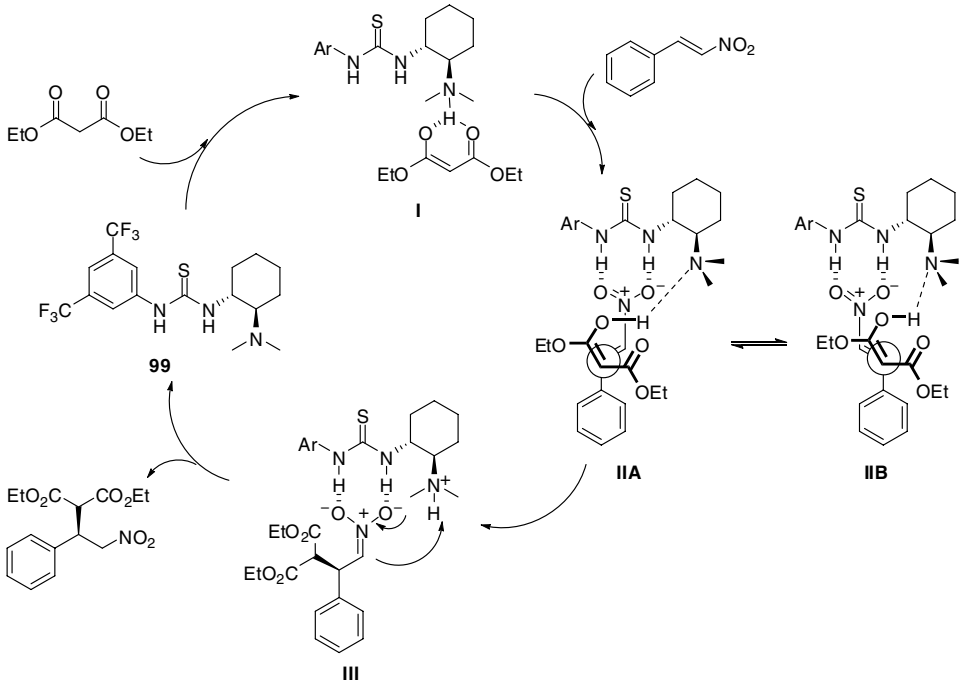
Scheme 73. Asymmetric conjugate addition of 2-acetylcyclopentanone to *trans*-β-nitrostyrene catalyzed by **110**.



Scheme 74. Asymmetric conjugate addition of β-ketoesters to nitroolefins catalyzed by bifunctional organocatalysts.

moiety of the catalyst via multiple hydrogen bonds, enhancing in this way its electrophilic character. On the other hand, the enolic forms of the 1,3-dicarbonyl nucleophile were assumed to interact with the tertiary amine group, and a subsequent deprotonation resulted in a highly nucleophilic enolate species (Scheme 75).

According to the final product configuration, Takemoto proposed that complex **IIA** should give nitronate complex **III** bearing an (*R*)-configuration, which takes the proton from the amino group to provide the chiral product along with the catalyst (Scheme 75). In this model, the C–C bond forming took place via the formation of a ternary H-



Scheme 75. Proposed mechanism for the conjugate addition of 1,3-dicarbonyl compounds to nitroolefins catalyzed by **99**.

bonded complex and the enantioselectivity of the reaction was related to the binding mode of the electrophile to the thiourea moiety.[153]

A very recent density functional theory study on a bifunctional urea-catalyzed Michael reaction between malonates and nitroolefins postulated, however, that the reaction should take place through complex **IIB** with the double bond of the nitroolefin pointing to the chiral scaffold. The origin of the enantioselectivity of the reaction was then attributed to the C–C bond forming step, while the rate determining step of the reaction was proton transfer from the amino group of the catalyst to the α-carbon of the nitronate.[160]

A detailed computational mechanistic study using DFT calculations of the conjugate addition of acetylacetone to a nitroolefin catalyzed by a thiourea-based chiral bifunctional organocatalyst has also been recently reported with some interesting results.[161] With respect to the reaction mechanism, the authors claimed that even the generally accepted mechanism (electrophile activation through substrate binding to thiourea and subsequent C–C bond formation between simultaneously activated components) was feasible kinetically and thermodynamically, an alternative reaction pathway, which involved activation of the electrophile by the protonated amino group, led to a ternary intermediate complex and a related transition state remarkably more stable and compatible with Takemoto's kinetic results (Fig. 18). This novel proposal also accounted for the observed enantioselectivity.

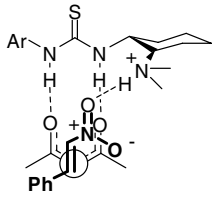


Figure 18. Proposed transition state for the conjugate addition of acetyl acetone to nitroolefins via electrophile activation by the protonated amine group.

In their attempt to rationalize the results obtained for the addition of α-ketolactones to nitroalkenes employing cupreine **110**, Deng et al. postulated an *anti*-open conformation for the catalyst in the transition state, the phenolic hydroxy group being responsible for control of the stereochemistry of the process through hydrogen bonding of both the nucleophile and the electrophile (Fig. 19).[155] A selectivity model for the unnatural 9-*epi*-C-9 thiourea-derived organocatalyst **112** based on experimental results and MM2 calculations was also proposed by McCooey and Connon to account for the catalyst activity and sense of stereoinduction observed in the addition of dimethylmalonate to *trans*-β-nitrostyrene.[156a]

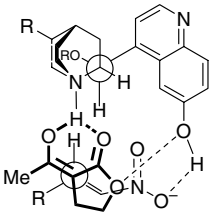
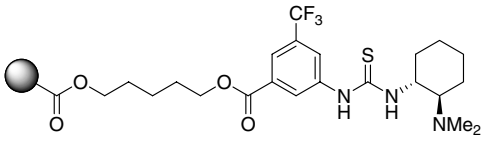
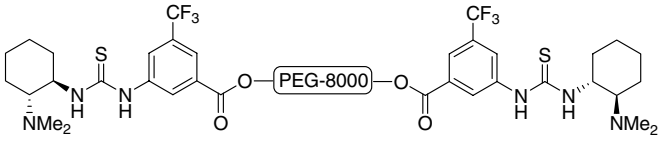


Figure 19. Stereochemical model for conjugate addition of cyclic β-ketoesters to nitroolefins catalyzed by **112**.

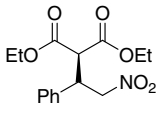
Catalyst **99** was also able to promote the diastereo- and enantioselective tandem Michael reaction between γ,δ-unsaturated β-ketoesters and nitroalkanes to afford highly functionalized cyclohexanones with three contiguous stereogenic centers (up to >99% de and 92% ee).[153c] The synthetic utility of this organocatalyzed reaction was demonstrated by its efficient use as a key step in the stereoselective total synthesis of (−)-epibatidine.[153c] The immobilization of **99** was also studied by the same authors.[153d]



Carboxypolystyrene HL and TentaGel carboxy resin-derived thioureas



PEG-bound thiourea



Carboxypolystyrene HL resin-bound thiourea, 37%, 87% ee
TentaGel carboxy resin-bound thiuorea, 4%, 88% ee
PEG-bound thiourea, 71%, 86% ee

Figure 20. Thiourea catalyst anchored to polymeric supports.

The soluble PEG-bound **99** showed better catalytic activity than crosslinked carboxypolystyrene HL resin-bound and TentaGel carboxy resin-bound organocatalyst (Fig. 20). In the presence of PEG-bound thiourea, Michael and tandem Michael reactions proceeded with a lower rate but similar yields and enantioselectivities if compared with the results obtained with monomeric **99** (Fig. 20).[153d]

3.5.5. Conjugate addition of activated methylenes to α,β-unsaturated imides. Takemoto reported the first highly enantioselective addition of several activated methylene compounds to α,β-unsaturated imides derived from 2-pyrrolidinone and 2-methoxybenzamide catalyzed by chiral thiourea **99**.[162] In terms of substrate scope, reaction rate and stereoselectivity, *N*-alkenoyl-2-methoxybenzamides were excellent Michael acceptors to afford the corresponding adducts in high yields and enantioselectivities (Scheme 76). The high reactivity shown by these electrophiles, with soft nucleophiles such as malononitrile and α-cyanoacetate, was attributed to intramolecular hydrogen bonding between the imide NH moiety and the methoxy group of the benzamide in the ternary transition state structured by the catalyst, the nucleophile and the imide.

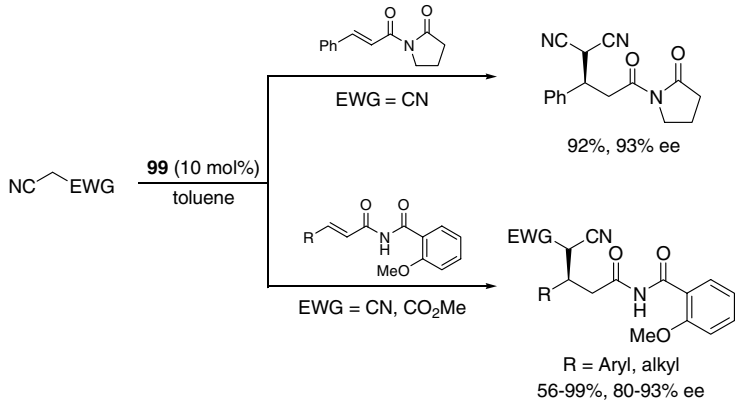
Bartoli and Melchiorre successfully extended the scope of nucleophile in the conjugate addition of *N*-benzyl maleimides to 1,3-dicarbonyl compounds employing natural *Cinchona* alkaloids such as quinine **35**.[163] The reaction afforded highly functionalized products with two adjacent stereogenic carbon atoms in high diastereo- (up to 92/2 dr) and enantioselectivity (up to 98% ee) with cyclic and acyclic β-ketoesters and cyclic β-diketones as depicted in Scheme 77 for a cyclic β-ketoester.

3.5.6. Conjugate addition of activated methylenes to vinyl sulfones. A further application of organocatalysis was the asymmetric conjugate addition of activated methylenes to vinyl sulfones. The asymmetric 1,4-addition of α-substituted cyanoacetates to vinyl sulfones was efficiently carried out by Deng et al.[164] and Chen et al.,[165] employing *Cinchona* alkaloid-derived catalysts and chiral bifunctional thioureas, respectively. As shown in Scheme 78, quinine-derived catalyst **90**[164] and chiral bifunctional thiourea **116**[165] were able to construct highly functionalized all-carbon-substituted quaternary stereocenters with high levels of asymmetric induction, adducts, which were used for the synthesis of optically active α,α-disubstituted amino acids.[164]

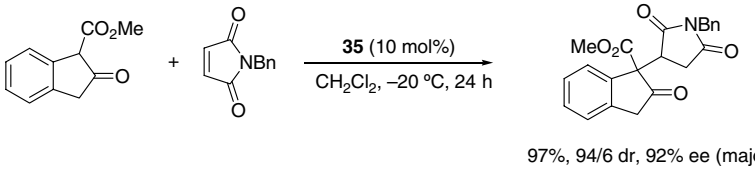
3.6. Conjugate addition of amino acid derivatives

In this section, the electrophilic addition of enolates derived from iminic α-amino acid esters to Michael acceptors employing chiral phase-transfer catalysts is discussed.[5] This route to α-functionalized α-amino acids has been much less studied than the alkylation via nucleophilic substitution with alkyl halides, but still offers a practical route to the most important, numerous, and diverse family of natural amino acids, mainly glutamic acid derivatives.

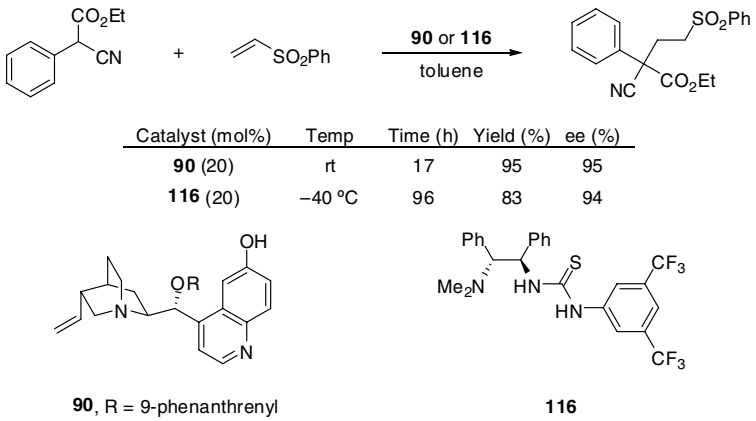
The enantioselective phase-transfer catalyzed Michael addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester to several Michael acceptors, such as methyl acrylate, cyclohex-2-enone and ethyl vinyl ketone, was initially studied by Corey et al. employing *O*(9)-allyl-*N*-9-anthracenylmethylcinchonidinium bromide **117** (Fig. 21) as a catalyst and cesium hydroxide as a base.[166] Different studies fol-



Scheme 76. Thiourea-catalyzed asymmetric Michael addition of activated methylenes to α,β-unsaturated imides.



Scheme 77. Quinine-catalyzed asymmetric Michael addition of 1,3-dicarbonyl compounds to *N*-benzyl α,β-unsaturated imides.



Scheme 78. Catalytic enantioselective conjugate addition to vinyl sulfones.

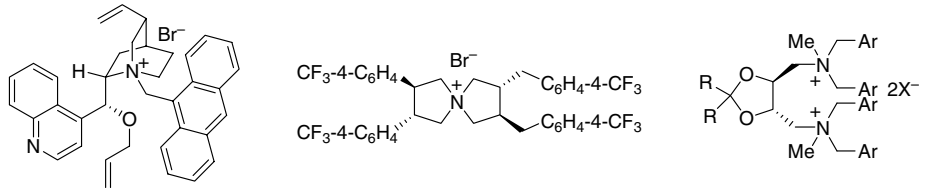
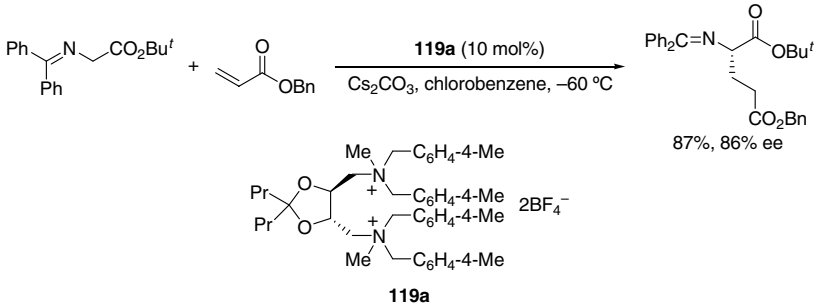


Figure 21. Chiral phase-transfer catalysts for the conjugate addition of glycine derivatives.

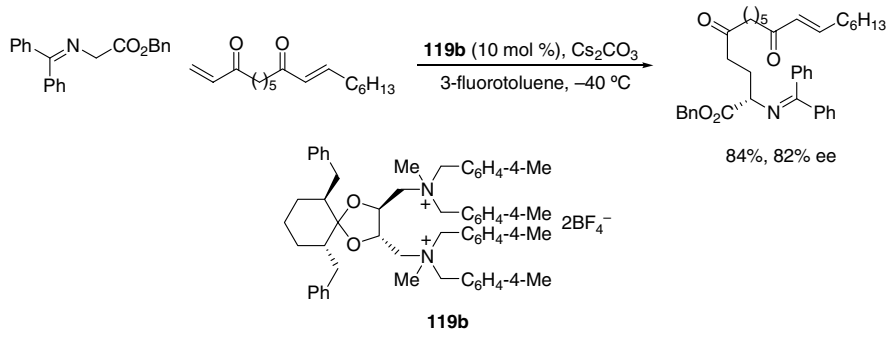
lowed this pioneering work, presenting diverse modifications over the standard procedure such as the employment of non-ionic bases,[167] variations of the nucleophile functionality,[168] and using new chiral phase-transfer catalysts, the most attention paid to this latter feature. For instance, catalyst **117** was successfully employed in the enantioselective synthesis of any of the $^{13}C/^{15}N$ isotopomers of different natural and unnatural amino acids such as L-glutamate, L-ornithine, L-proline, L-lysine, L-amino adipic acid, and L-citrulline using conjugate additions of *N*-(diphenylmethylene)glycine *tert*-butyl ester to methyl acrylate and acrylonitrile at rt.[169]

(*S*)-Glutamic acid is one of the most important excitatory neurotransmitters in the mammalian central nervous system, playing a crucial role in memory and learning. Considerable efforts have been devoted to the discovery of glutamic acid derivatives since this α-amino acid is implicated in the pathogenesis of neural damage that causes various neural diseases.[170] Cinchonidine-derived catalyst **117** was also efficiently employed in the asymmetric synthesis of 4-alkylidene glutamic acid derivatives through a tandem conjugate addition–elimination reaction between the Schiff base of glycine *tert*-butyl ester and activated allylic acetates under phase-transfer conditions.[171] The reaction, which was performed in the presence of a 10 mol % of **117** at low temperature (−78 °C) in CH_2Cl_2 and employing $CsOH{\cdot}H_2O$ as a base, allowed the preparation of 4-alkylidenyl glutamic acid derivatives with up to 97% ee.

On the other hand, alternative tartrate-derived chiral phase-transfer catalysts, such as **118**[172] and **119**,[173] were very recently synthesized and successfully employed in the conjugate addition of amino acid derivatives to different Michael acceptors, such as acrylates and vinyl ketones (Fig. 21). For instance, Shibasaki's tartrate-derived bis-ammonium salts **119a** and **119b** were productively used in the key steps of the enantioselective syntheses of the serine protease inhibitor aeruginosin 298-A (Scheme 79)[173b] and the marine alkaloid (+)-cylindricine C (Scheme 80).[173d]



Scheme 79. Phase-transfer catalyzed key step in the enantioselective synthesis of aeruginosin 298-A.



Scheme 80. Phase-transfer catalyzed key step in the enantioselective synthesis of (+)-cylindricine C.

During the studies leading to the synthesis of aeruginosin 298-A, the authors reported for the first time an exceptional counteranion effect in a PTC process.[173b]

A significant enantioselectivity counteranion dependence was observed in the conjugate addition of benzophenone imine-derived glycinate with electron-poor olefins such as acrylates, enones, and acrylonitriles catalyzed by the dimeric *Cinchona* alkaloid ammonium salts **120** (X = Br, BF_4, PF_6)[174] (Fig. 22). This type of system afforded high enantioselectivities (up to 97% ee) and could be recovered by precipitation with ether and then reused.

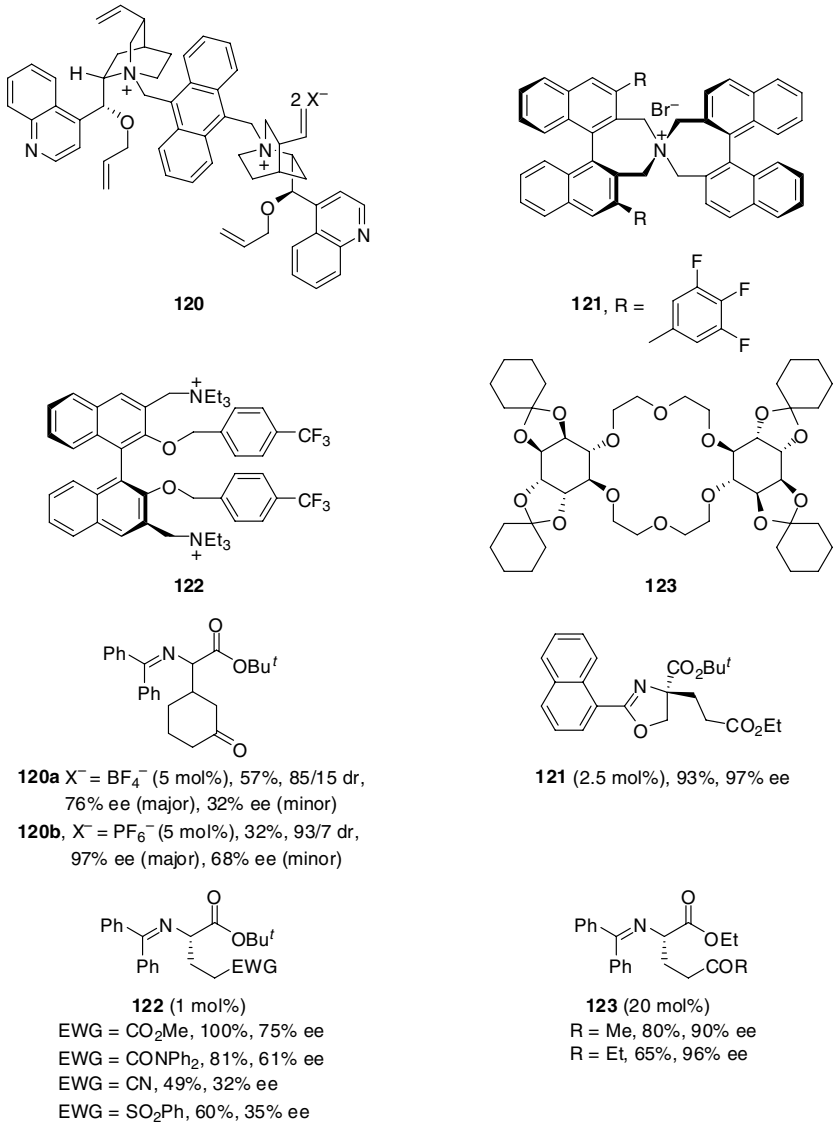
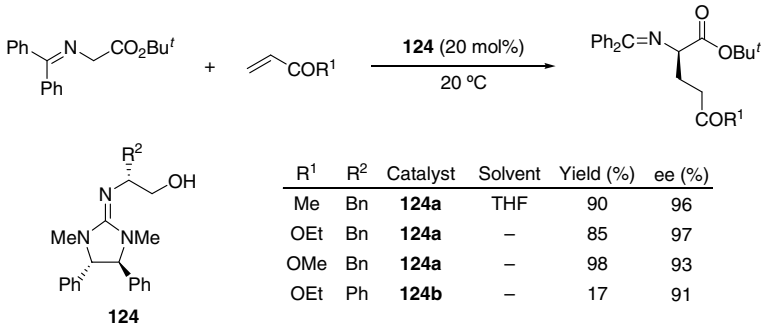


Figure 22. Chiral phase-transfer catalysts for the conjugate addition of amino acid derivatives.



R1	R2	Catalyst	Solvent	Yield (%)	ee (%)
Me	Bn	**124a**	THF	90	96
OEt	Bn	**124a**	–	85	97
OMe	Bn	**124a**	–	98	93
OEt	Ph	**124b**	–	17	91

Scheme 81. Asymmetric conjugate addition of glycine imine to electron-poor alkenes catalyzed by chiral guanidines.

On the other hand, α-(hydroxymethyl)glutamic acid, which has been recognized as a strong antagonist of the metabotropic membrane receptor (mGluR2), and a weak agonist of metabotropic membrane receptor (mGluR3), was easily synthesized in 97% ee from the Michael adduct obtained through the catalytic Michael addition of 2-naphthalen-1-yl-2-oxazoline-4-carboxylic acid *tert*-butyl ester to ethyl acrylate in the presence of chiral ammonium Binol-derived catalyst **121** (Fig. 22).[175] Interestingly, a non-ionic neutral phosphazene base, such as BEMP, gave the highest yield and enantioselectivity in the process (93%, 97% ee).

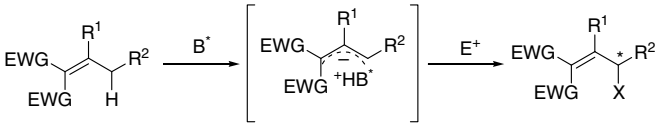
In order to extend the substrate scope of the process to electron-poor alkenes other than acrylates and α,β-unsaturated ketones, Arai et al. synthesized the new chiral quaternary ammonium salt derived from (*S*)-Binol **122** (Fig. 22).[176] This catalyst afforded low to moderate enantioselectivities (32–75% ee) in the conjugate addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester to acrylic esters, acrylonitriles, acrylamides and vinyl sulfones using Cs_2CO_3 as a base and chlorobenzene as a solvent at –30 °C.[176]

The chiral crown ether **123** was successfully employed as an organocatalyst under very low loading conditions (0.2 mol %) in the enantioselective 1,4-addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester to vinyl ketones, obtaining very good enantioselectivities (up to 96% ee) at −78 °C (Fig. 22).[177]

Even though the vast majority of asymmetric organocatalyzed conjugate additions of amino acid derivatives to electron-poor alkenes were performed employing chiral ammonium salts derived from *Cinchona* alkaloids and other ammonium salts such as spiro Binol systems, different neutral organocatalysts were also shown to promote the reaction with good levels of enantioselection. Among them, chiral guanidines[178] were shown to efficiently catalyze the enantioselective addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester to acrylic acid esters, vinyl ketones, and acrylonitriles. As depicted in Scheme 81, chiral guanidines **124** catalyzed the Michael addition with high enantioselectivities specially when using acrylic acid derivatives and vinyl ketones as Michael acceptors, even when working under solventless conditions.[178b]

3.7. Deconjugative Michael additions

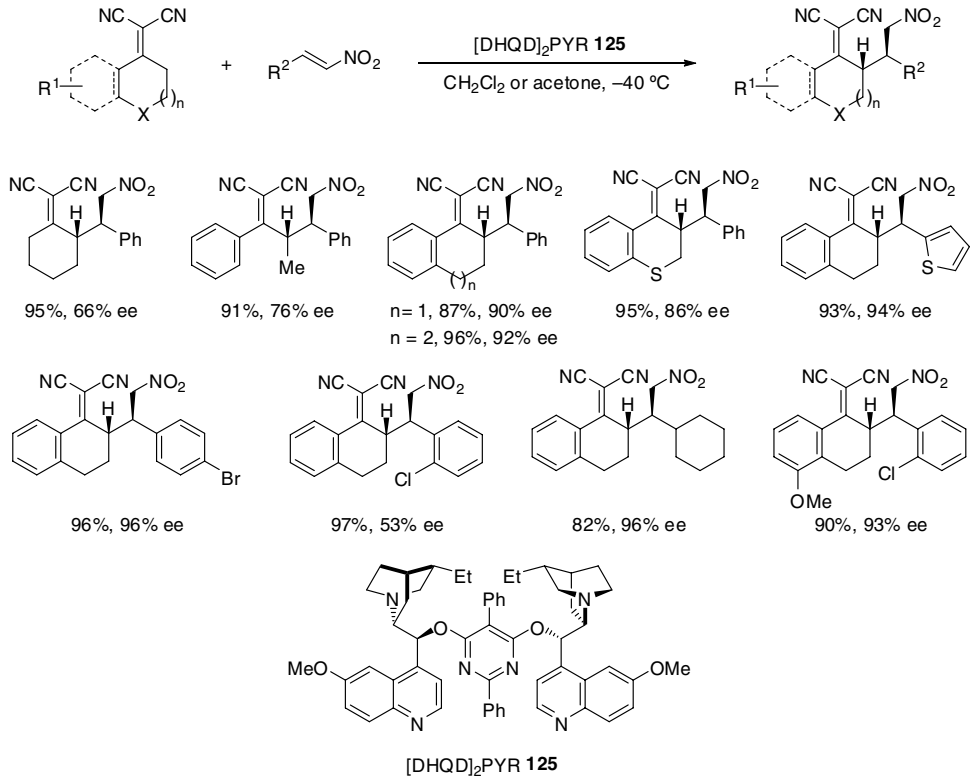
Activated alkylidene structures are common intermediates in complex molecule synthesis, where their electrophilic character has been especially exploited. However, this type of compounds also has a latent reactivity as a nucleophile when they are activated through allylic deprotonation with an appropriate chiral base (Scheme 82). The final result is an enantioselective C–C bond forming reaction in the allylic position of the activated systems.



Scheme 82. Deconjugative Michael additions.

Very recently, Deng et al.[179] and Jørgensen et al.[180] presented their pioneering results in the organocatalyzed asymmetric version of this process employing vinyl malononitriles or alkylidene cyanoacetates as nucleophiles and nitroolefins or α,β-unsaturated aldehydes as Michael acceptors. With respect to the addition to nitroolefins, both authors reported that *Cinchona*-derived chiral tertiary amine $[DHQD]_2PYR$ **125** was the best catalyst to perform the Michael addition with electron-deficient vinyl malononitriles as the nucleophilic species.[179a,180a] The reaction was completely γ-regioselective affording the corresponding adducts with very high diastereo- (usually only the *anti* diastereomer is observed, dr >99:1) and enantioselectivity working at low temperatures (−40 °C) in CH_2Cl_2 or acetone (Scheme 83). Only in the case of using nucleophiles derived from cyclohexanone and acyclic aromatic ketones, or in the case of sterically hindered nitroolefins such as *o*-chloro-*trans*-β-nitrostyrene, were the observed enantioselectivities lower (66%, 76%, and 53% ee, respectively).

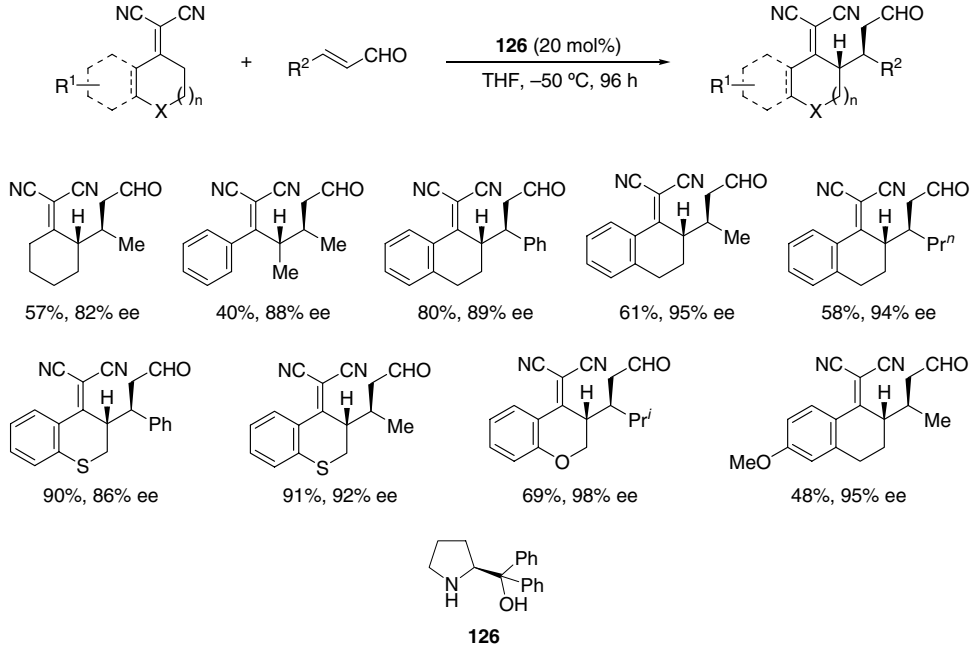
A very efficient method for the organocatalytic diastereo- and enantioselective vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes was developed by Deng et al.[179b] After a catalyst screening, chiral L-prolinol-derivatives such as **126** (20 mol %) were found to be very efficient organocatalysts affording the *anti*-Michael adducts in good yields and enantioselectivities working at low temperatures (−50 °C) in THF and in the presence of



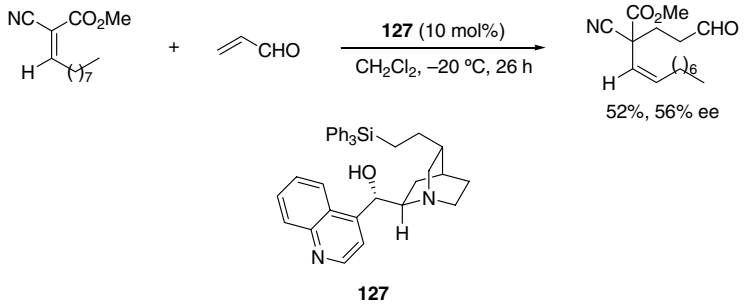
Scheme 83. Deconjugative Michael addition of malononitriles to nitroolefins catalyzed by **125**.

p-nitrobenzoic acid (20 mol %) as an additive (Scheme 84). The reaction scope proved to be quite broad with respect to the nucleophile and the β-substitution on the electrophile, with only the *anti* products for all the tested reactions observed. Only when using acyclic dicyanoolefins were very small amounts of the *syn* adduct observed (2%, 48% ee). With regards to the mechanism, the fact that the reaction could not be catalyzed by tertiary amines such as quinine pointed to enal activation by the chiral secondary amine.

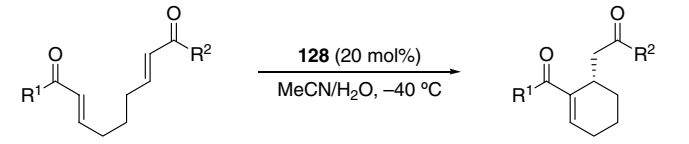
Very recently, after careful optimization of the reaction conditions and screening of different chiral tertiary amines,

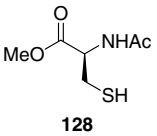


Scheme 84. Deconjugative Michael addition of malononitriles to nitroolefins catalyzed by **126**.



Scheme 85. Deconjugative Michael addition of alkylidene cyanoacetates to acrolein.





R^1	R^2	Time (h)	Yield (h)	ee (%)
Ph	Ph	24	75	92
4-$MeOC_6H_4$	4-$MeOC_6H_4$	24	73	90
4-BrC_6H_4	4-BrC_6H_4	24	70	93
4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	4	71	84
Me	Me	40	55	90
2-furyl	2-furyl	40	54	92
Ph	OEt	24	66	67

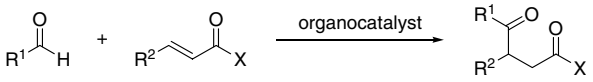
Scheme 86. Enantioselective organocatalyzed Rauhut–Currier reaction.

Jørgensen et al. widened the deconjugative Michael addition methodology to alkylidene cyanoacetates. Employing cinchonidine-derived catalyst **127**, these authors were able to perform an asymmetric deconjugative Michael addition of alkylidene cyanoacetates with acrolein, although in moderate yields and enantioselectivities (Scheme 85).[180b]

The enantioselective Rauhut–Currier reaction promoted by a cysteine derivative has recently been presented by Aroyan and Miller.[181] The process, which was catalyzed by cysteine derivative **128**, involved the intramolecular cyclization of bis α,β-unsaturated carbonyl compounds and was very sensitive to different reaction conditions such as solvent, temperature and the amount of water present in the reaction medium. Under optimized reaction conditions, MeCN as solvent at −40 °C, and in the presence of 20 equiv of water as an additive and 20 mol % of **128**, the reaction afforded in very high enantioselectivities functionalized cyclohexenes when working with symmetrical aliphatic and aromatic bis(enones) (Scheme 86). On the contrary, unsymmetrical ketoesters yielded the corresponding products in moderate yields and selectivities.

3.8. The Stetter reaction

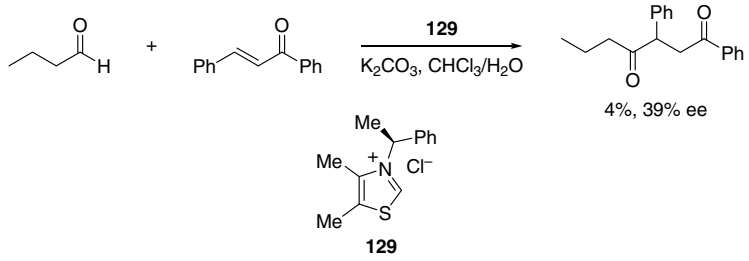
In comparison to asymmetric catalytic reactions involving enolate equivalents, the catalytic chemistry of acyl anion equivalents[182] has received considerably less attention. Reactivity umpolung reverses the normal mode of aldehyde polarity, thus rendering a nucleophilic aldehyde. The asymmetric Stetter,[183] as well as the asymmetric benzoin reactions,[184] takes advantage of the reverse carbonyl polarity usually mediated by chiral heterazolium carbenes.[185] The Stetter reaction consists of the reaction between an acyl anion equivalent and an electron-deficient olefin (Scheme 87).



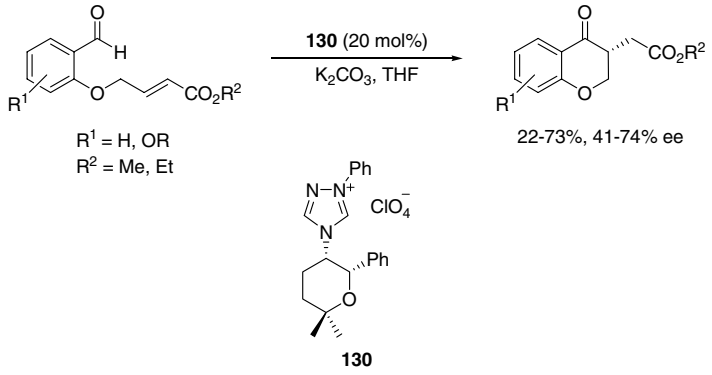
Scheme 87. The Stettter reaction.

The enantioselective organocatalytic Stetter reaction was originally achieved by Enders employing new chiral thiazolium salts such as **129**.[186] As depicted in Scheme 88 for the reaction between butanal and chalcone, the process was not efficient at all (4% yield) but it was quite enantioselective (39% ee).

Unfortunately, further studies on this intermolecular process were not successful enough to improve the selectivity by employing different organocatalysts, so the efforts were turned to the intramolecular version of the reaction where the reactivity of the substrate should be enhanced due to entropic factors. The first asymmetric intramolecular Stetter reaction was reported in 1996 by Enders et al.[187] using the chiral triazolium salt **130** as a catalyst (Scheme 89). This protocol opened up an enantioselective pathway to the synthesis of chiral chroman-4-one derivatives with



Scheme 88. The first asymmetric organocatalyzed intermolecular Stetter reaction.



Scheme 89. First asymmetric organocatalyzed intramolecular Stetter reaction.

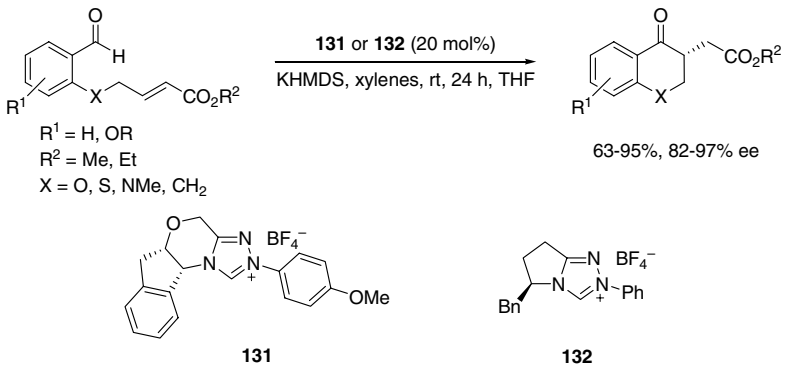
moderate to good yields (22–73%) and ee's of up to 74% (Scheme 89).

Recent studies by Rovis et al. led to a notable improvement of the enantioselectivity of the reaction and substrate scope using triazolium salts **131** and **132** as catalysts and KHMDS as base, obtaining good yields and enantioselectivities in the synthesis of a wide array of chromanones as well as aza, and thia analogues (Scheme 90).[188]

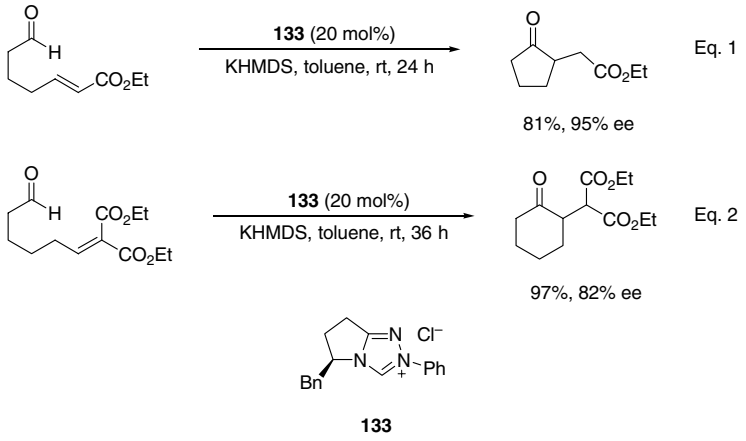
The reaction could also be performed with aliphatic substrates as depicted in Scheme 91.[189] In this case, catalyst **133** proved to be the most active affording chiral functionalized cyclic ketones in good yields and enantioselectivities. Further activation of the Michael acceptor was necessary when increasing the conformational freedom of the substrate, which critically diminished its reactivity (Scheme 91, Eq. 2).

The scope of organocatalytic intramolecular Stetter reaction was later expanded upon by the same authors to synthesize chiral compounds with quaternary stereocenters.[190] In this case, as shown for the selected example in Scheme 92, the electron-deficient triazolium salt **134** was essential to obtain good yields and enantioselectivities in the process.

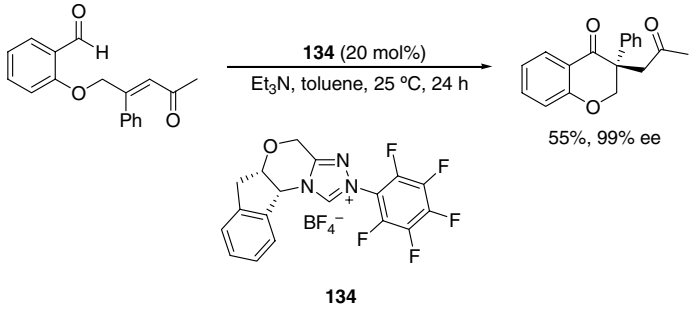
Miller et al. performed a peptide-catalyzed intramolecular Stetter cyclization employing a family of novel catalysts that incorporate a thiazolylalanine moiety into a peptide sequence such as **135**.[191] This new type of catalysts, however, did not improve the results obtained by Ravis et al.,



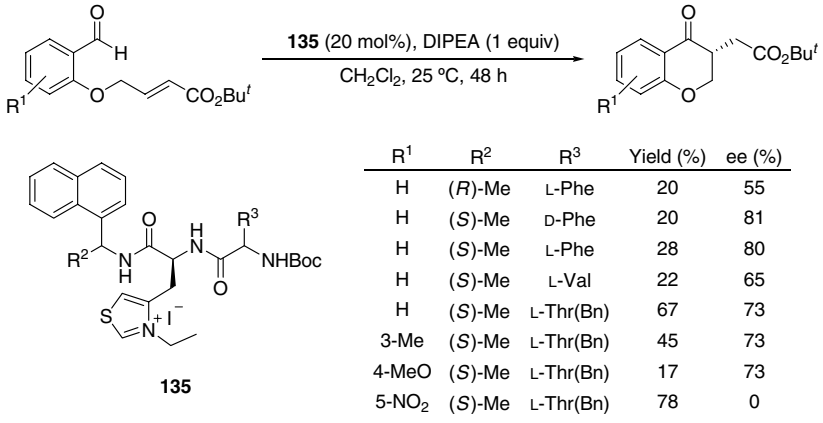
Scheme 90. Intramolecular Stetter reaction catalyzed by **131** and **132**.



Scheme 91. Intramolecular Stetter reaction with aliphatic substrates catalyzed by **133**.



Scheme 92. Intramolecular asymmetric Stetter reaction catalyzed by **134**.



R^1	R^2	R^3	Yield (%)	ee (%)
H	(*R*)-Me	L-Phe	20	55
H	(*S*)-Me	D-Phe	20	81
H	(*S*)-Me	L-Phe	28	80
H	(*S*)-Me	L-Val	22	65
H	(*S*)-Me	L-Thr(Bn)	67	73
3-Me	(*S*)-Me	L-Thr(Bn)	45	73
4-MeO	(*S*)-Me	L-Thr(Bn)	17	73
5-NO_2	(*S*)-Me	L-Thr(Bn)	78	0

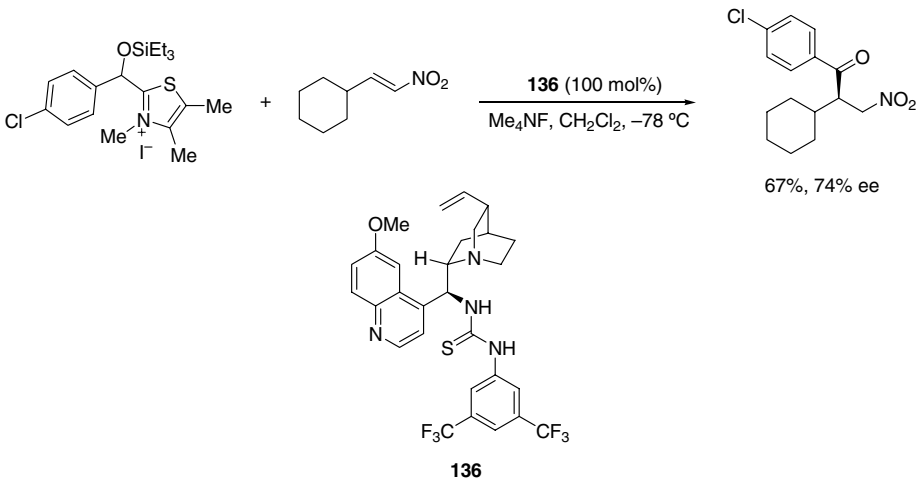
Scheme 93. Tripeptide-catalyzed intramolecular Stetter reaction.

affording low yields and moderate to good enantioselectivities as depicted in Scheme 93.

Finally, it is worthy mentioning a very recent and interesting work by Scheidt et al. where the first direct enantioselective intermolecular nucleophilic addition of a carbonyl unit to a nitroalkene was reported.[192] The strategy followed by these authors consisted of the use of a silyl-protected thiazolium carbinol as a storable and stoichiometric acyl anion when exposed to a fluoride source. This protocol avoided the employment of amines as bases, which are known to induce decomposition of the nitroolefins. As shown in Scheme 94, in the presence of stoichiometric amounts of chiral thiourea **136** gave a promising yield and enantioselectivity (74% ee).

3.9. Friedel–Crafts-type conjugate additions

The Friedel–Crafts reaction is one of the most powerful methods for the formation of a new C–C bond.



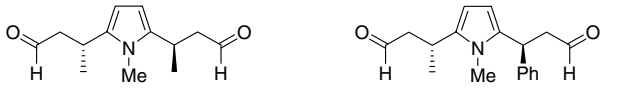
Scheme 94. Intermolecular Stetter reaction to nitroolefins.

π-Electron-rich aromatic and heteroaromatic compounds are able to behave as C-nucleophiles and have been used in the enantioselective Friedel–Crafts-type conjugate addition to different electrophiles, such as α,β-unsaturated aldehydes and nitroolefins.

MacMillan et al. successfully employed chiral imidazolidinone catalysts to perform a highly enantioselective 1,4-addition of different aromatic compounds, such as pyrroles, indoles, and benzene derivatives to α,β-unsaturated aldehydes.[193] Imidazolidinone catalysts diminish the energy of the LUMO of the electrophile through the formation of an iminium ion conjugate with a double bond, which facilitates the reaction with electron-rich aromatic and heteroaromatic compounds.

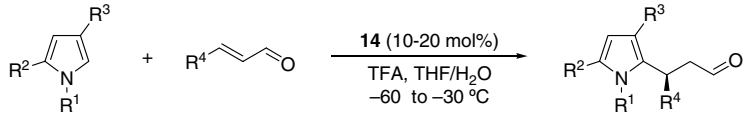
In the case of the enantioselective alkylation of pyrroles with enals[193a] (Scheme 95), the reaction was highly enantioselective (87–97% ee) in the presence of imidazolidinone **14** to afford the corresponding adducts in good to excellent yields (68–90%) working under aerobic conditions and using wet solvents. Furthermore, for the best catalytic efficiency and selectivity, trifluoroacetic acid was identified as the optimum cocatalyst for most of the substrates.

Double alkylation of *N*-methylpyrrole to generate C_2-symmetric dialkylation products could also be achieved in the presence of catalyst **14** with an excess of an enal electrophile, for example, crotonaldehyde, affording the 2,5-disubstituted product in 83% yield, a C_2/*meso* ratio of 90:10, and 98% ee (Fig. 23). Similar selectivities were obtained when the two alkylation steps were performed consecutively with

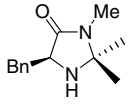


83%, C_2/*meso* = 90/10, 98% ee 72%, *syn*/*anti* = 10/90, 99% ee (*anti*)

Figure 23. Double alkylation of *N*-methyl pyrrole.



R^1	R^2	R^3	R^4	Yield (%)	ee (%)
Me	H	H	Me	83	91
Me	H	H	Pr^n	81	90
Me	H	H	Pr^i	80	91
Me	H	H	Ph	87	93
Bn	H	Ph	Ph	80	89
Allyl	H	H	Ph	83	91
Me	Bu^n	H	Ph	87	90
Me	H	Pr^n	Ph	68	97
Me	H	H	4-$MeOC_6H_4$	79	91
Me	H	H	CH_2OBn	90	87
Me	H	H	CO_2Me	72	90
H	H	H	CO_2Me	74	90



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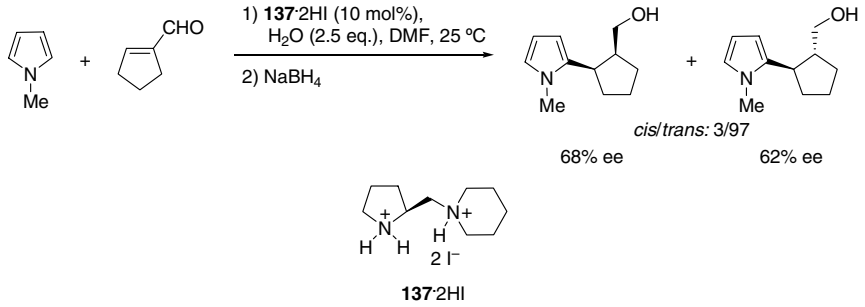
Scheme 95. Asymmetric conjugate Friedel–Crafts addition of pyrroles to enals catalyzed by **14**.



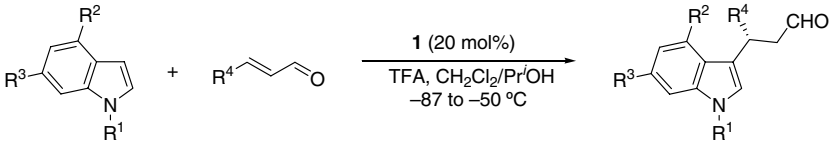
Scheme 96. Asymmetric Friedel–Crafts addition of *N*-methylpyrrole to cyclopent-1-enecarboxaldehyde.

two different electrophiles, for example, crotonaldehyde and cinnamaldehyde, affording the corresponding non-symmetrical bis-alkylated product (Fig. 23).

Although it gave moderate enantioselectivities, proline-derived hydroiodide **137** catalyzed the diastereoselective alkylation of *N*-methylpyrrole with cycloalkenylcarboxaldehydes such as cyclopent-1-enecarboxaldehyde (Scheme 96).[194]

Further studies carried out by Paras and MacMillan with chiral imidazolidinones as organocatalysts demonstrated that compound **1** was a very active system for the highly enantioselective 1,4-addition of indoles to enals.[193c] As summarized in Scheme 97, this catalyst also enabled further oxidation of the formyl moiety providing β-chiral β-indolebutyric acids that are of pharmaceutical interest as cyclooxygenase-2 inhibitors.

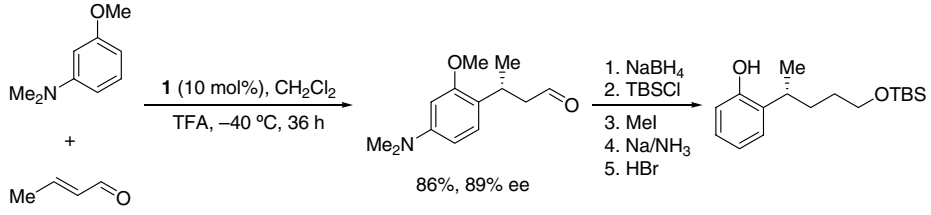
Iminium catalysis employing chiral imidazolidinone **1** was extended by MacMillan's group to the asymmetric Friedel–Crafts-type alkylation of electron-rich benzene derivatives, in particular N,N-dialkylated anilines, with enals as depicted in Scheme 98 for a selected example.[193b] One elegant application of this methodology was also presented by the same group consisting of a methylation/reductive



R^1	R^2	R^3	R^4	Yield (%)	ee (%)
Me	H	H	Me	82	92
Me	H	H	Pr^n	80	93
Me	H	H	Pr^i	74	93
Me	H	H	CH_2OBn	84	96
Me	H	H	Ph	84	90
Me	H	H	CO_2Me	89	91
H	H	H	Me	72	91
Allyl	H	H	Me	70	92
Bn	H	H	Me	80	89
H	Me	H	Me	94	94
Me	OMe	H	Me	90	96
H	H	Cl	Me	73	97

1

Scheme 97. Asymmetric Friedel–Crafts addition of indoles to enals catalyzed by **1**.



Scheme 98. Asymmetric Friedel–Crafts addition of *N*,*N*-dimethylaniline to enals and methylation/reductive deamination.

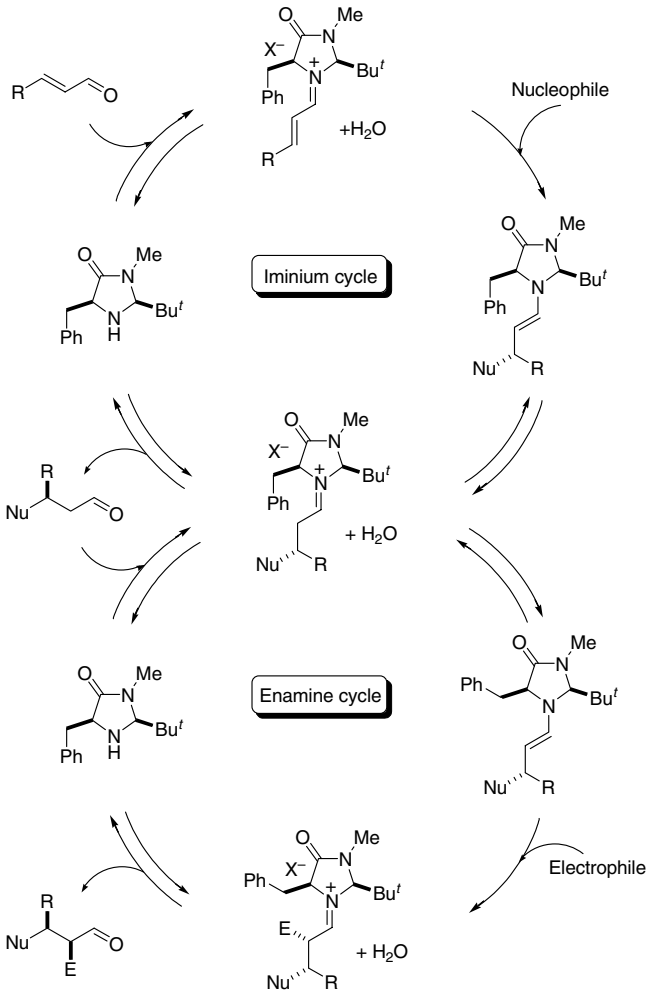
deamination protocol with the Michael adducts, which enabled them to use *N*,*N*-dialkylanilines as benzene surrogates.[193b]

MacMillan et al. also demonstrated that chiral imidazolidinone **138** could carry out simultaneous substrate activation in the form of iminium ions (LUMO-lowering) and enamine (HOMO-raising) and applied this finding to an interesting enantioselective organo-cascade catalytic sequence (Scheme 99).[195] A broad variety of α,β-unsaturated aldehydes and aromatic and heteroaromatic π-nucleophiles could be employed giving access to 3,3′-disubstituted 2-chloropropanals (*syn*/*anti*: 90/10 to >96:4, ⩾99% ee), with EtOAc being the best solvent studied under the reaction conditions (−40 °C).

With respect to the reaction mechanism, the authors proposed the catalytic cycles depicted in Scheme 100 where the imidazolidinone catalyst generates activated iminium and enamine species ensuring high levels of diastereo- and enantioselectivity for the overall process.[195]

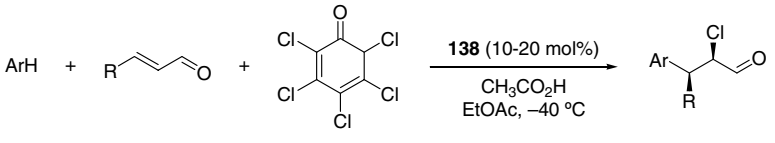
Indoles were submitted to alkylation with nitroolefins, employing different organocatalysts. For instance, chiral thiourea **139**[196] promoted the alkylation of indoles with various aromatic and aliphatic nitroalkenes providing optically active 2-indolyl-1-nitro derivatives in good yields (35–88%) and enantioselectivities (73–89% ee) (Scheme 101). The authors proposed a plausible bifunctional mode of action of the catalyst. Whereas the two thiourea hydrogen atoms activated the nitroalkene by a double hydrogen bond, the free hydroxy group would interact with the indolic proton through a weak hydrogen bond, directing the attack of the incoming nucleophile on the *Si*-face of the nitroolefin (Scheme 101).[196]

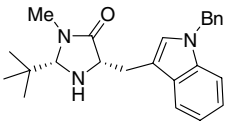
In the case of the addition of *N*-methylindole to nitrostyrenes, Connon et al. synthesized and evaluated a small library of thiourea-based axially chiral organocatalysts and found that catalyst **140** afforded the corresponding alkylated products in good yields (54–98%) although in low to moderate enantioselectivities (12–50% ee) (Scheme 102).[197]



Scheme 100. Proposed mechanism for the enantioselective organocatalyzed cascade synthesis of β-aryl-α-chloroaldehydes.

Jørgensen et al. showed that chiral bis-sulfonamides were effective catalysts for the enantioselective Friedel–Crafts addition of indoles and *N*-methylindoles to a wide range of nitroolefins.[198] The reaction proceeded with only





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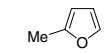
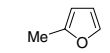
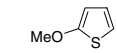
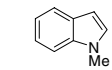
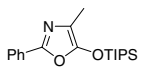
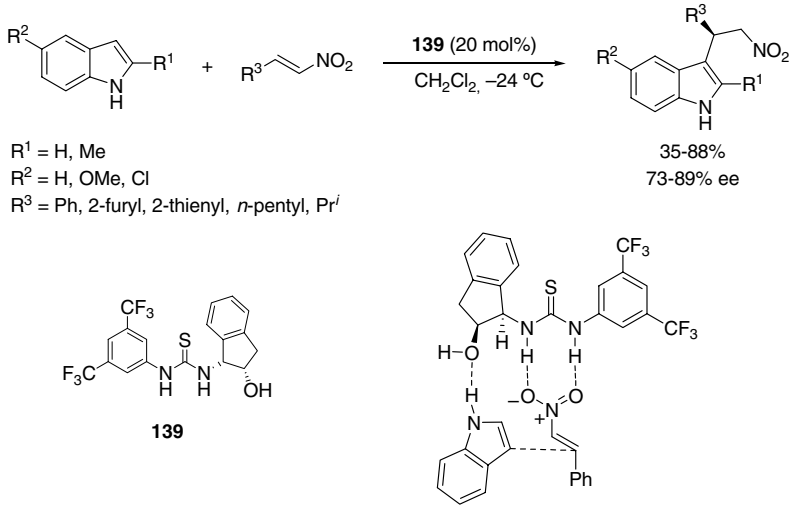
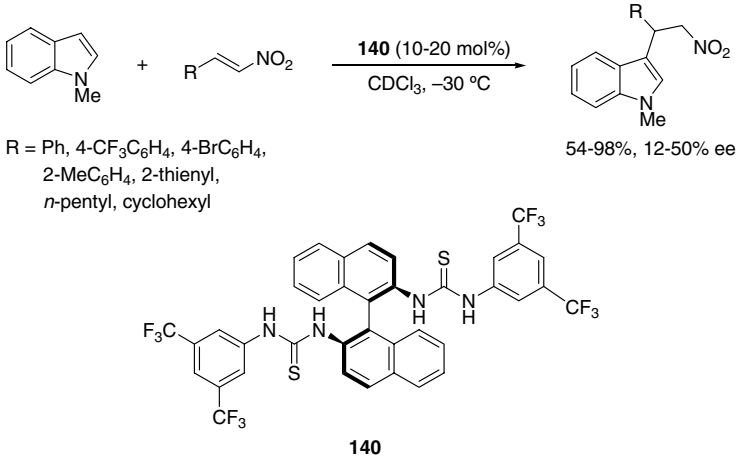
Nu	R	Yield (%)	*syn*/*anti*	ee (%)
	Me	86	14/1	99
	CO_2Et	80	22/1	99
	Me	77	14/1	99
	Pr^i	67	12/1	>99
	Me	97	9/1	>99

Scheme 99. Enantioselective organocatalyzed cascade synthesis of β-aryl-α-chloroaldehydes.

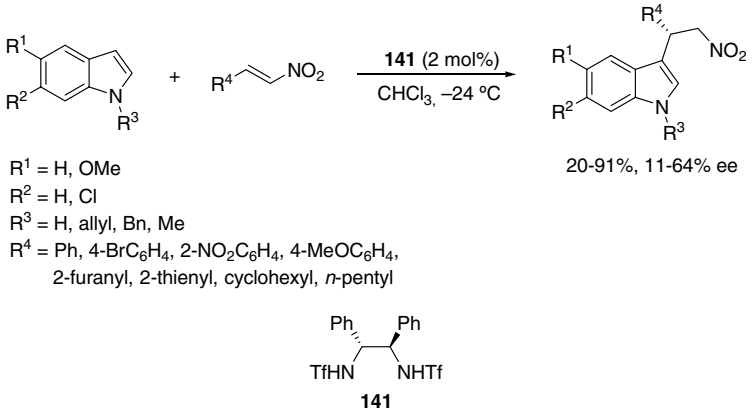


Scheme 101. Asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes catalyzed by thiourea **139**.

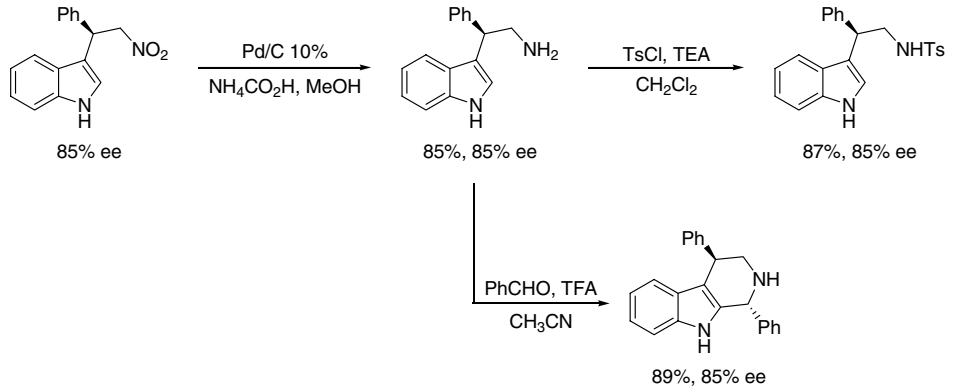


Scheme 102. Asymmetric Friedel–Crafts addition of *N*-methylindole to nitroolefins.

2 mol % of catalyst **141** and the optically active Friedel–Crafts adducts were obtained in moderate to high yields (20–91%) and with enantioselectivities of up to 64% ee (Scheme 103). By comparison of different bis-sulfonamide catalysts, the authors underlined the importance that the dihedral angle of the organocatalysts had over the selectivity of the process. An appropriate angle, the bigger the better, led to more efficient coordination of the electrophile, which produced better face discrimination by the nucleophile.



Scheme 103. Enantioselective Friedel–Crafts addition of indoles and *N*-methylindoles to nitroolefins catalyzed by **141**.

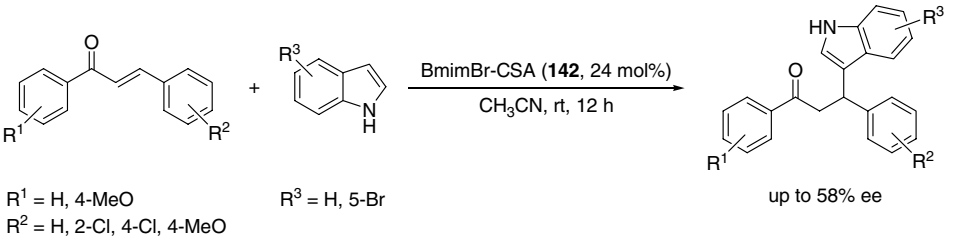


Scheme 104. Useful transformations of the optically active Friedel–Crafts adducts.

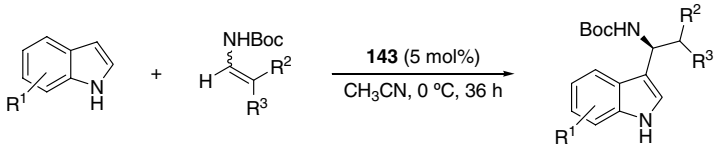
The synthetic applicability of the Friedel–Crafts alkylation of indole derivatives was also demonstrated by the same authors preparing chiral tetrahydro-β-carbolines through reduction of the nitro group to the amine and stereocontrolled acid-catalyzed Pictet–Spengler cyclization (Scheme 104). This process occurred without any loss in the enantiomeric excess of the product.[198]

Aromatic enones have been very recently used as electrophiles in the Michael-type Friedel–Crafts reaction with indoles.[199] Chiral Brønsted acid complex **142** comprised D-camphorsulfonic acid (CSA) and the ionic liquid 1-butyl-3-methyl-1*H*-imidazolium bromide (BmimBr) and was found to be an efficient organocatalyst in the process affording the corresponding β-indolyl ketones in excellent yields (74–96%) but low enantioselectivities (up to 58% ee) (Scheme 105).

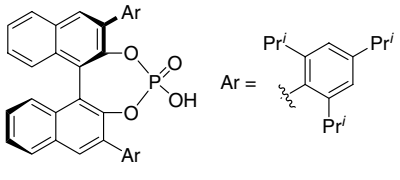
Terada and Sorimachi reported the first enantioselective Friedel–Crafts reaction employing electron-rich alkenes



Scheme 105. Enantioselective Friedel–Crafts reaction of indoles with aromatic enones catalyzed by the chiral Brønsted acid complex **142**.

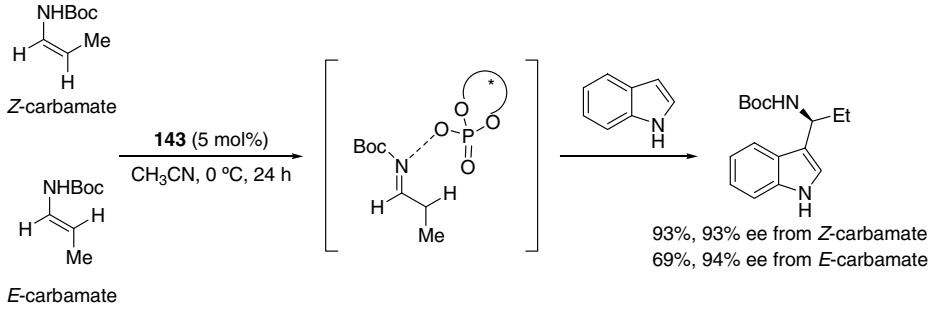


R^1	R^2	R^3	*Z*/*E*	Yield (%)	ee (%)
H	H	Me	<1/99	87	94
H	H	Bu^n	50/50	98	94
H	H	Bn	50/50	82	93
H	H	Pr^i	50/50	80	91
H	H	Ph	<1/99	63	90
H	Me	Me	–	69	94
5-MeO	H	Me	<1/99	90	90
5-Me	H	Me	<1/99	84	93
5-Br	H	Me	<1/99	91	93
6-Br	H	Me	<1/99	78	96
5-CO_2Me	H	Me	<1/99	86	93



143

Scheme 106. Enantioselective Friedel–Crafts reaction of indoles with enecarbamates catalyzed by chiral Brønsted acid **143**.



Scheme 107. Proposed intermediate for the Brønsted acid-catalyzed Friedel–Crafts reaction between enecarbamates and indoles.

such as enecarbamates as electrophilic counterparts catalyzed by the Binol-derived monophosphoric acid **143**.[200] The reaction provided a wide variety of chiral 1-indolyl-1-alkylamine derivatives in high yields (63–98%) and excellent enantioselectivities (90–96% ee) under low catalyst loadings (5 mol %) in CH_3CN as solvent and at 0 °C (Scheme 106). Isomeric enecarbamates gave the corresponding product with the same level of enantioselectivity (Scheme 107). This result suggested that a common intermediate composed of the chiral organocatalyst and the imine generated by protonation of the enecarbamate.

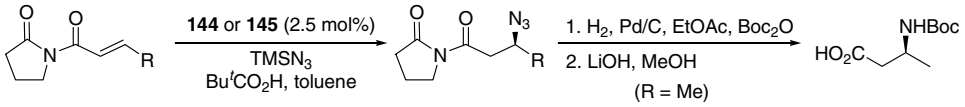
4. Conjugate addition of heteroatom nucleophiles

The organocatalytic asymmetric conjugate addition of heteroatom nucleophiles to different electrophilic olefins has become a very popular reaction over the last few years. Different nitrogen, oxygen, sulfur, and selenium nucleophilic species have been successfully used leading to enantiomerically enriched hetero functionalized derivatives.

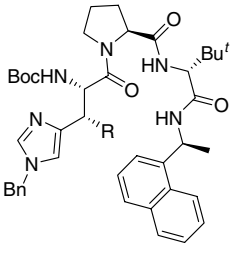
4.1. Conjugate addition of nitrogen nucleophiles

The asymmetric organocatalytic Michael addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds is a very important reaction since it allows the preparation of optically active β-amino acids.[201] In 2000 Miller et al. reported the employment of tripeptide **144** as an efficient and selective organocatalyst for the enantioselective conjugate addition of the azide ion to α,β-unsaturated carbonyl compounds (Scheme 108).[202] Conformational studies for catalyst optimization led to the conclusion that decreasing the conformational freedom of the N-terminal histidine of the peptide residue with a β-substituent should be beneficial for the catalyst activity.[202b] In fact, as summarized in Scheme 108, the β-methylated peptide **145** effected the addition of TMS–N_3 to several unsaturated imides with better enantioselectivities than **144**.[202b] Typically, 2.5 mol % peptide catalyst **144** or **145** was employed, and enantiomeric excesses up to 92% were achieved. The β-azido imides were readily converted to *N*-Boc protected β-amino acids by hydrogenation/Boc-protection and hydrolysis.[202a]

The same group, by taking advantage of the optimized enantioselective β-azidation of imides with tripeptide **145**, reported a highly enantioselective synthesis of triazolines and triazoles via an azidation-1,3-dipolar cycloaddition sequence increasing the potential utility of the reaction.[202b] As depicted in Scheme 109, this process led to a wide variety of heterocyclic derivatives obtained through either an efficient intramolecular or intermolecular 1,3-dipolar cycloaddition process without erosion of the substrate enantiomeric purity.

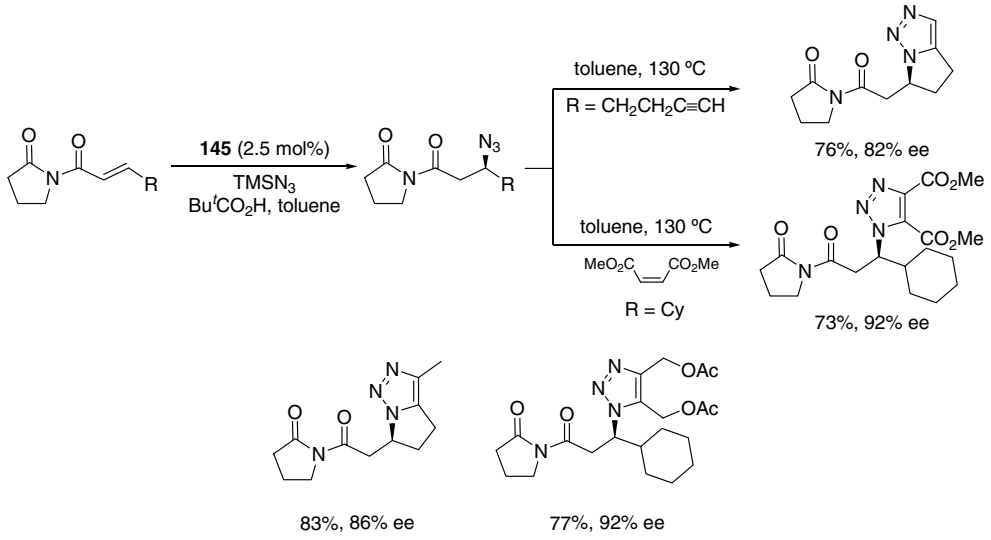


Catalyst	R	Temp (°C)	Yield (%)	ee (%)
145	Me	25	90	78
145	Me	–10	90	86
144	Cy	25	97	63
145	Cy	25	88	89
145	Cy	–10	65	92
144	Pr^i	25	79	85
145	Pr^i	25	89	84
145	Pr^i	–10	75	90
144	Et	25	85	71
145	Et	25	95	77
145	Et	–10	83	85



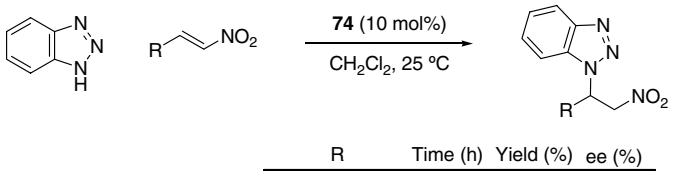
144, R = H
145, R = Me

Scheme 108. Addition of TMS–N_3 to several unsaturated imides catalyzed by tripeptides **144** and **145**.



Scheme 109. Enantioselective synthesis of triazoles catalyzed by **145**.

Nitrogen containing heterocycles have been the focus of numerous synthetic efforts due to their broad applications in organic and medicinal chemistry, as well as material science.[203] The asymmetric conjugate addition of nitrogen heterocycles to electron-deficient olefins is one of the most employed methods for preparing chiral heterocyclic compounds. An organocatalytic method for the enantioselective Michael addition of benzotriazoles, triazoles and tetrazoles to a wide range of nitroolefins was reported employing cupreidine **74**.[204] With benzotriazol as the nucleophile (Scheme 110), the process took place efficiently (64–90%) with moderate to excellent levels of enantioselectivity (57–94% ee) when applied to aromatic and heterocyclic substituted nitroolefins or aliphatic nitroalkenes as Michael acceptors. When using aromatic nitroolefins, the position of the substituent on the aromatic ring had a significant effect on the enantioselectivity. Reaction of nitroolefins with substituents at the *para*-position occurred with relatively low enantioselectivities (70–78% ee), but higher enantioselectivity (80–94% ee) accompanied the reactions of substrates with substituents at the *ortho*-position.[204]



R	Time (h)	Yield (%)	ee (%)
Ph	24	87	70
4-$BnOC_6H_4$	48	73	78
2-$BnOC_6H_4$	48	87	92
2-$PhCO_2C_6H_4$	36	75	94
2-thienyl	48	79	80
$PhCH_2CH_2$	48	83	57
n-C_6H_{13}	24	76	64

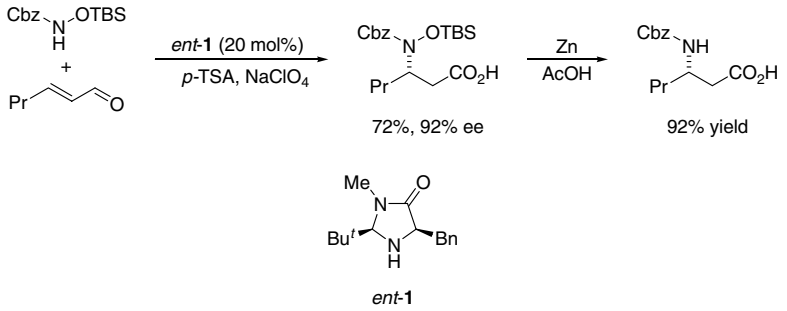
74

Scheme 110. Enantioselective Michael addition of benzotriazole to nitroolefins catalyzed by **74**.

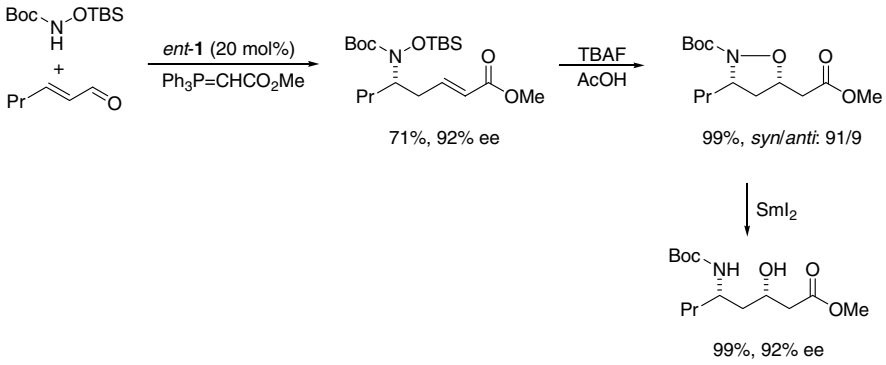
MacMillan et al. employed *N*-silyloxycarbamates as the nucleophilic component in the asymmetric organocatalyzed Michael addition to α,β-unsaturated aldehydes using imidazolidinone *ent*-**1** as a catalyst.[205] The choice of *N*-silyloxycarbamates as nucleophiles was due to several factors. First, the amine worked only as a 1,4-addition nucleophile and not as iminium activator. Second, and also very importantly, the process had to proceed under kinetic control, so that the stereodefining heteroatom addition step should be accompanied by irreversible loss of the nucleophile proton. These requirements were fulfilled by *N*-silyloxycarbamates since the N–O functionality enhanced the nucleophilicity of the nitrogen center via the α-effect. In addition, the estimated pK_a (~9.0) of the sililoxycarbamate N–H maintained the reaction under kinetic control rendering the amino aldehyde product. In this manner, the enantioselective organocatalytic conjugate addition of *N*-silyloxycarbamates to a wide range of α,β-unsaturated aldehydes provided the desired β-aminoaldehydes in good yields (69–92%) and good levels of enantiocontrol (87–97% ee). The utility of this organocatalytic amine addition was demonstrated with the conversion of simple aldehydes to enantioenriched β-amino acids or 1,3-amino alcohols as depicted for selected examples in Schemes 111 and 112, respectively.[205]

Highly enantioselective tandem *O*-nitroso aldol/Michael reactions were independently presented by Yamamoto[206] and Hayashi.[207] The process involved an initial synthesis of the nitroso Diels–Alder adduct, through an *O*-nitroso aldol reaction, followed by an intramolecular Michael addition reaction. The Diels–Alder adducts were obtained with moderate yields but with high levels of enantioselection (98–99% ee) using pyrrolidine based tetrazole **146**[206] or *trans*-4-*tert*-(butyldimethylsiloxy)-L-proline **147** as organocatalysts as shown in Scheme 113 for the reaction between 4,4-dimethylcyclohex-2-enone and nitrosobenzene.[206,207]

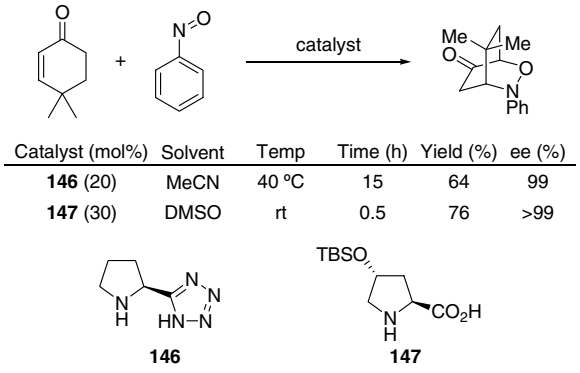
On the other hand, a highly diastereo- and enantioselective L-proline-catalyzed tandem Mannich–Michael reaction be-



Scheme 111. Conversion of simple aldehydes to enantioenriched β-amino acids.



Scheme 112. Conversion of enals to 1,3-amino alcohols.

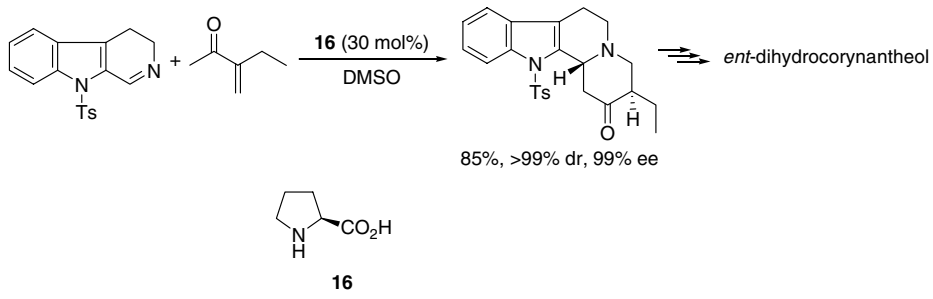


Scheme 113. Stepwise *O*-nitroso aldol/Michael reaction.

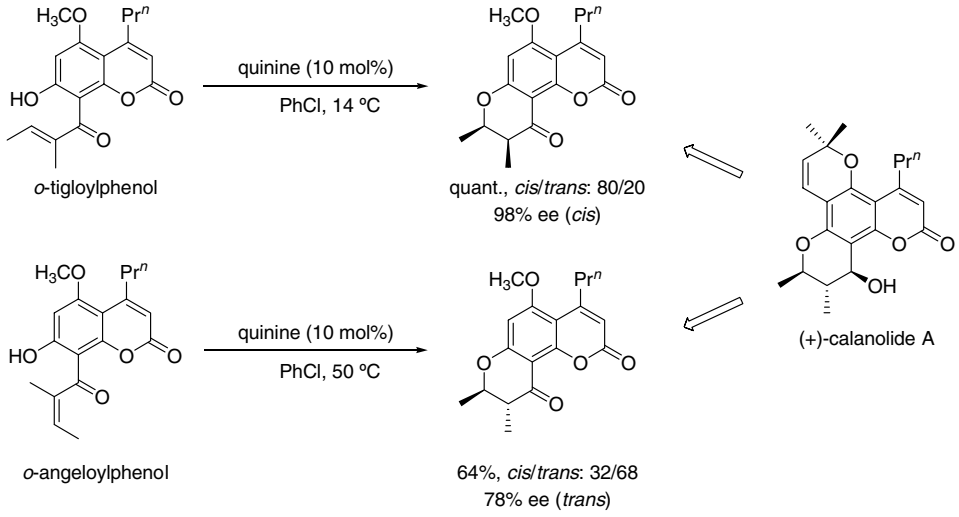
tween a dihydro-β-carboline and 3-ethyl-3-buten-2-one was recently used for the synthesis of tetracyclic indole alkaloid *ent*-dihydrocorynantheol (Scheme 114).[208]

4.2. Conjugate addition of oxygen nucleophiles

Pioneering studies on the title reaction were carried out quite recently by Ishikawa et al. who reported a quinine-catalyzed intramolecular phenol conjugate addition to enones over the course of the synthesis of the potential anti-HIV-active natural product (+)-calanolide A.[209] In an initial study, the authors showed that the *O*-tigloylphenol could be cyclized by quinine (19 mol %) to afford a 50/50 mixture of the *cis* (87% ee) and *trans* products (racemic).[209a] Subsequent optimization of the reaction conditions led to the identification of chlorobenzene as the optimum reaction solvent (Scheme 115). Then, cyclization of the *o*-tigloylphenol at 14 °C in chlorobenzene afforded an 80/20 mixture of the *cis*- and *trans*-precursors of (+)-calanolide A, in which the *cis*-product was formed with 98% ee.[209b] Employing the same solvent but at 50 °C, the *o*-angeloylphenol gave a 32/68 *cis*/*trans* relationship, with a 78% ee of the major *trans* product (Scheme 115).[209b]



Scheme 114. Synthesis of *ent*-dihydrocorynantheol employing L-proline as a catalyst.



Scheme 115. Enantioselective synthesis of (+)-calanolide A.

Cinchona alkaloid derivatives were also used by Merschaert et al. for the asymmetric synthesis of 2-substituted chiral chromanes via intramolecular Michael addition of phenolic nucleophiles with α,β-unsaturated esters with moderate enantioselectivities.[210]

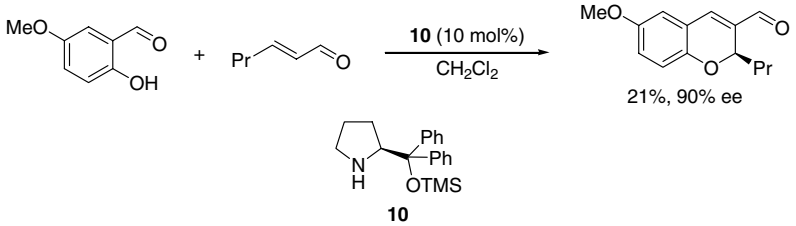
The asymmetric O-Michael addition was very recently employed in the synthesis of chiral benzopyranes by Arvidsson et al.[211] The benzopyran unit was constructed through a domino reaction involving the oxa-Michael attack of salicylic aldehyde derivatives onto the α,β-unsaturated aldehydes, activated through an iminium ion with catalyst **10**, followed by an intramolecular aldol reaction and subsequent elimination of water (Scheme 116). This overall reaction sequence provided benzopyranes with aromatic C-2 substituents in up to 60% yield and 60% ee, while C-2 aliphatic analogues were obtained in 90% ee, but in low yields (20%).

4.3. Conjugate addition of sulfur and selenium nucleophiles

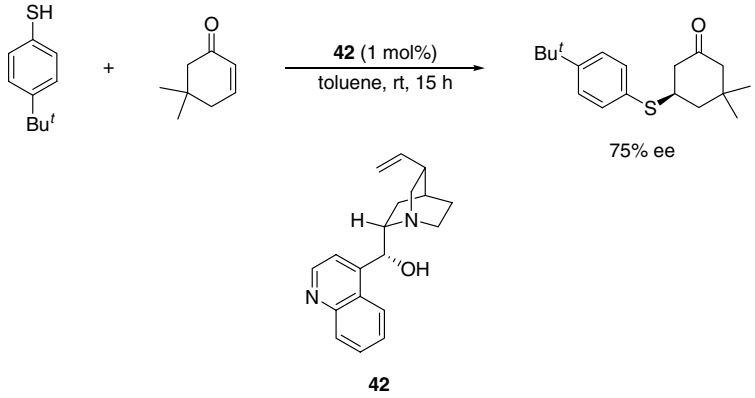
The first asymmetric organocatalyzed conjugate addition of a sulfur nucleophile to α,β-unsaturated ketones was reported by Wynberg et al. in 1977.[212] These authors obtained very good yields (82–95%) and enantiomeric excesses of up to 46% using quinine (0.8 mol %) as chiral base for the conjugate addition of thiophenol derivatives and benzyl mercaptan to cyclohexenone. Various studies followed these preliminary results in order to improve the reaction with respect to the mechanism and reaction scope. For instance, subsequent studies carried out by the same group resulted in a detailed mechanistic study of the chiral base-catalyzed addition of thiophenols to cyclic enones providing enantiomeric excesses of up to 75% ee using cinchonidine **42** as the catalytic base (Scheme 117).[213] The authors demonstrated that the addition of the thiophenolate anion to the β-carbon atom of the electrophile was indeed the rate and chirality determining step, with the transition state of the reaction a ternary complex formed by the protonated catalytic base, the thiophenolate anion, and the enone. A bifunctional activation mode of the catalyst was then proposed since the electrophile was supposed to suffer hydrogen bonding to the catalyst β-hydroxy group.

Pracejus et al. expanded upon the electrophile scope of the alkaloid-catalyzed thiol conjugate addition to α-phthalimido acrylates, methylene azalactones, and nitroolefins.[214] On the other hand, Yamashita and Mukaiyama performed the enantioselective addition of thiophenol to diisopropyl maleate in the presence of cinchonine **72** (1 mol %) with good yield and enantioselectivity (95%, 81% ee).[215]

Different studies regarding the employment of polymeric *Cinchona* alkaloids[216] or the corresponding supported ammonium salts[217] in the conjugate addition of sulfur nucleophiles to enones and nitroolefins under homogeneous or PTC conditions clearly demonstrated the poor

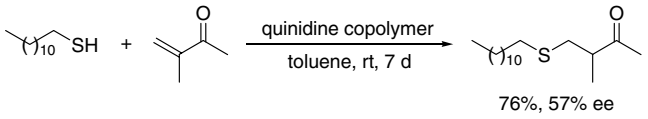


Scheme 116. Organocatalyzed asymmetric synthesis of chiral benzopyranes.



Scheme 117. Cinchonidine-catalyzed addition of thiophenols to enones.

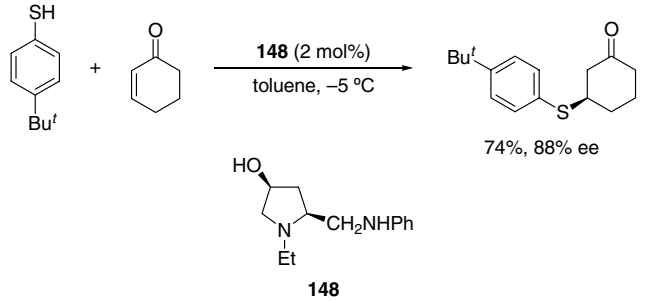
performance of these systems as catalyst as shown in Scheme 118 for one of the most selective examples, the addition of dodecanethiol to isopropenyl methyl ketone employing a quinidine-acrylonitrile copolymer (2.4 mol % quinidine).[216a]



Scheme 118. Thiol conjugate addition to enones catalyzed by polymeric quinidine.

Kobayashi and Iwai studied the alkaloid-catalyzed addition of thioglycolic acid to *trans*-β-nitrostyrenes and β-alkyl substituted nitroolefins.[218] Moderate enantioselectivities were observed in all cases (58% ee for the addition of thioglycolic acid to *trans*-β-nitrostyrene and 37% ee for the addition to non-aromatic nitroolefins) even when using stoichiometric amounts of the most active catalyst studied, quinine.

In 1981, Mukaiyama et al. presented 2-(anilinomethyl)-1-ethyl-4-hydroxypirrolidine **148** as an efficient organocatalyst for the addition of thiophenols to cycloalkenones.[219] This catalyst, easily prepared from 4-hydroxyproline, afforded high yields (74–84%) and up to 88% ee in the process under low catalyst loadings, as depicted in Scheme 119 for a selected example.

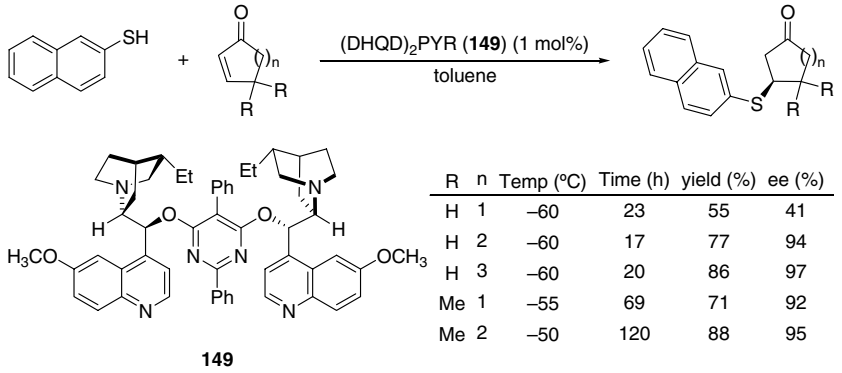


Scheme 119. Asymmetric addition of 4-*tert*-butylthiophenol to cyclohex-2-enone.

In 2002, Deng et al. presented a selectivity improvement in the field of the asymmetric conjugate addition of (*S*)-nucleophiles to cyclic enones employing a commercially available ether of *Cinchona* alkaloids.[220] After a systematic screening of monomeric and dimeric *Cinchona* alkaloid derivatives, these authors identified the dihydroquinidine-pyrimidine catalyst $(DHQD)_2PYR$ **149** (Scheme 120) as the most effective promoter for the reaction. Although moderate enantioselectivity was obtained with cyclopentenone (Scheme 120) addition of 2-thionaphthol to a wide variety of six- to nine-membered cyclic enones and substituted cyclopentenone as well as various cyclohexenones afforded the corresponding Michael adducts in high yields and enantioselectivities. Due to the absence of hydrogen donor functionalities in the structure of **149**, this catalyst was unable to promote the conjugate addition through a bifunctional catalysis mechanism similar to that proposed for **42**[213] and **148**.[219] Furthermore the sense of the asymmetric induction of the 1,4-addition of thiophenol to cyclohexenone catalyzed by the modified (absolute configuration of C9 and C10) *Cinchona* alkaloid $(DHQD)_2PYR$ was opposite to that obtained with natural *Cinchona* alkaloids, such as quinidine. This result definitively indicated different reaction mechanisms for the conjugate addition catalyzed by modified or natural *Cinchona* alkaloids.[220]

More recently, Takemoto's chiral thiourea **99** (see Fig. 17) was demonstrated to efficiently catalyze the asymmetric Michael addition of arylthiols to α,β-unsaturated imides and cyclic enones.[221] As depicted in Figure 24, the reaction, which was performed in CH_2Cl_2 at low temperatures, showed good substrate scope to give high yields for a wide variety of Michael adducts, although in moderate to good enantioselectivities (up to 77% ee for the benzenethiol addition to unsaturated imides and 85% ee for the addition to cyclic enones) in all the cases studied.

Very recently, α,β-unsaturated aldehydes were used as electrophilic counterparts in the 1,4-addition of sulfur nucleophiles by Jørgensen et al.[222] Employing L-proline-derived catalyst **150**, they reported very high enantioselectivities for the addition of a wide variety of aliphatic thiols to different aromatic and aliphatic enals (Scheme 121). Since the thiol addition to α,β-unsaturated aldehydes is a process in equilibrium and the products generally racemize under



R	n	Temp (°C)	Time (h)	yield (%)	ee (%)
H	1	–60	23	55	41
H	2	–60	17	77	94
H	3	–60	20	86	97
Me	1	–55	69	71	92
Me	2	–50	120	88	95

Scheme 120. Asymmetric 1,4-addition of 2-thionaphthol to cyclic enones catalyzed by $(DHQD)_2PYR$.

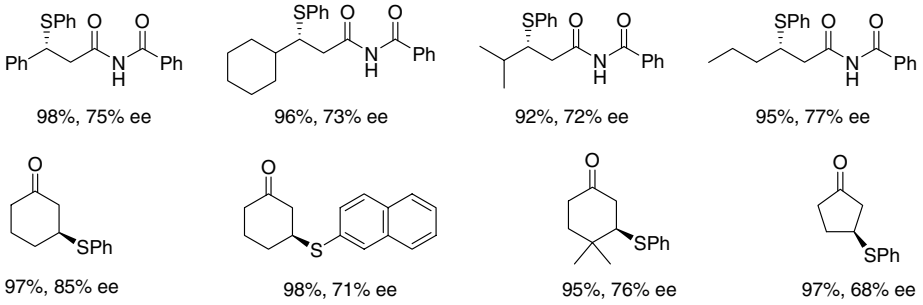
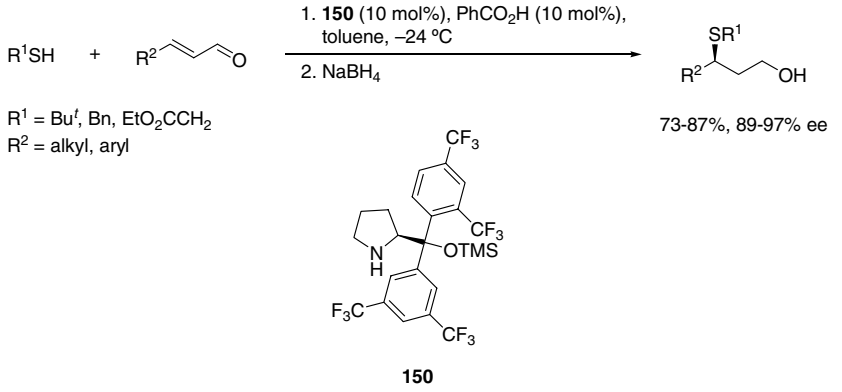


Figure 24. Enantioselective Michael addition of arylthiols to α,β-unsaturated imides and cyclic enones catalyzed by **99**.



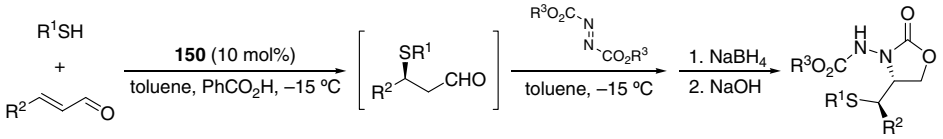
Scheme 121. Organocatalyzed conjugate addition of thiols to α,β-unsaturated aldehydes.

room temperature conditions, it was very important to perform the reaction at low temperatures (Scheme 121). Low temperatures diminished the reaction rate and so the conjugate addition had to be performed in the presence of catalytic amounts of benzoic acid as a cocatalyst in order to achieve good chemical yields in reasonable reaction times.

Taking advantage of the excellent results obtained in the conjugate addition of thiols to enals, Jørgensen et al. carried out a multicomponent domino organocatalyzed conjugate addition–amination reaction to prepare highly functionalized chiral oxazolidinones with excellent yields and enantiomeric excesses (Scheme 122).[222]

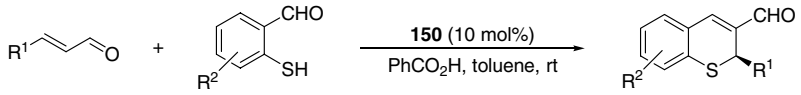
After Jørgensen's report, different studies carried out by the same group and others appeared in the literature showing the competence of prolinol-derived catalyst **150** in different organocatalytic tandem and domino reactions leading to chiral heterocyclic compounds. For instance, the organocatalytic Michael-aldol domino reaction between 2-mercaptobenzaldehydes and a wide variety of alkyl- or aryl-substituted α,β-unsaturated aldehydes led, in the presence of **150** (10 mol %) and benzoic acid as an additive, to the corresponding chiral thiochromenes in high yields (72–96%) and enantioselectivities (89–95% ee) as depicted in Scheme 123 for selected examples.[223]

The utility of catalyst **150** was further illustrated by the asymmetric synthesis of highly functionalized tetrahydrothiophenes through a new organocatalytic Michael-aldol reaction between 2-mercapto-1-phenylethanone and different α,β-unsaturated aldehydes.[224] As depicted in Scheme



R^1	R^2	R^3	Time (h)	Yield (%)	dr	ee (%)
Bn	Me	Et	3.5	57	95/5	>99
Bn	Et	Et	16	42	96/4	>99
Bn	Me	Bn	16	44	89/11	>99
Et	Me	Bn	16	51	88/12	>99
Et	Et	Bn	16	38	95/5	97

Scheme 122. Organocatalyzed asymmetric synthesis of oxazolidinones.

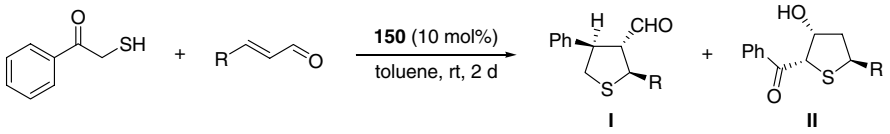


R^1	R^2	Time (h)	Yield (%)	ee (%)
Ph	H	16	85	94
4-$MeOC_6H_4$	H	12	82	85
2-$MeOC_6H_4$	H	12	96	94
4-$NO_2C_6H_4$	H	12	95	92
Et	H	12	81	95
Pr^n	H	12	96	94
Me	5-Cl	12	91	91
Me	5-MeO	12	80	93
Me	5-Me	12	97	90

Scheme 123. Organocatalyzed asymmetric synthesis of thiochromenes.

124, the reaction was very sensitive to the additive used. While the employment of benzoic acid yielded, in a very regio-, diastereo-, and enantioselective manner, the corresponding tetrahydrothiophene carbaldehydes (up to 96% ee), the use of a base such as $NaHCO_3$ led to the formation of (tetrahydrothiophen-2-yl)phenyl methanones in moderate yields (44–66%) and good selectivities (up to 82% ee).

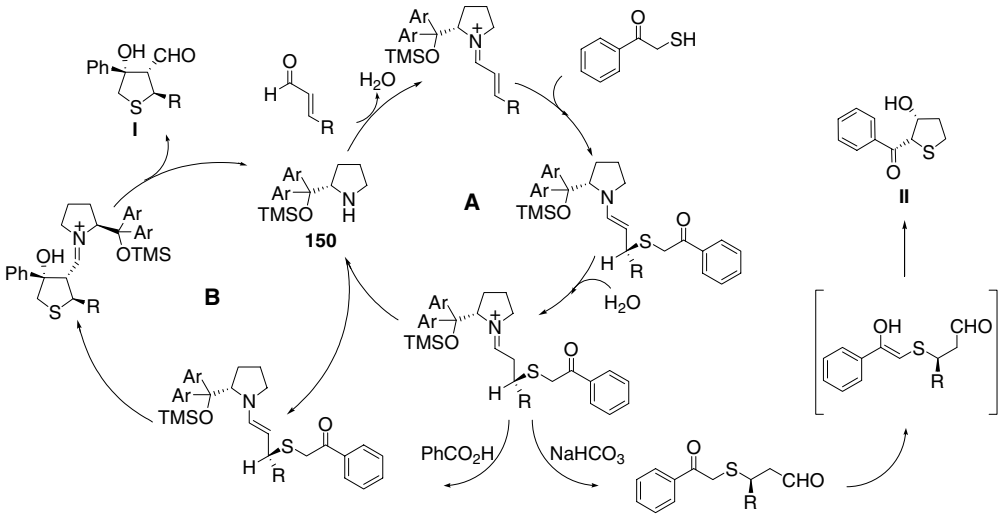
The mechanisms for the domino reaction proposed by the authors are summarized in Scheme 125. The TMS-protected proline derivative **150** generates, with the α,β-unsaturated aldehyde, the corresponding iminium ion whose *Si*-face is strongly shielded by the silylated arm of the catalyst (Scheme 125, cycle A). Nucleophilic attack from the *Re* side affords the corresponding (*R*)-configured enamine (dr ~ 86/14), which, depending upon the reaction conditions, leads to tetrahydrothiophene carbaldehydes or (tetrahydrothiophen-2-yl)phenyl methanones **II** (Scheme 125). In aqueous media or in the presence of $NaHCO_3$, the catalytic cycle ends up releasing **150** and the



R	Additive	I/II	Yield (%)	ee (%)
Me	$PhCO_2H$	100/0	59 (**I**)	90
Me	$NaHCO_3$	0/100	59 (**II**)	74
Pr^n	$PhCO_2H$	100/0	74 (**I**)	95
Pr^n	$NaHCO_3$	0/100	43 (**II**)	82
Pr^i	$PhCO_2H$[a]	100/0	51 (**I**)	89
Pr^i	$NaHCO_3$	2/98	61 (**II**)	80
$(CH_2)_2OTBDMS$	$PhCO_2H$	100/0	44 (**I**)	96
$(CH_2)_2OTBDMS$	$NaHCO_3$	0/100	61(**II**)	70

[a] Reaction performed with *ent*-**150**

Scheme 124. Organocatalyzed asymmetric synthesis of tetrahydrothiophenes.



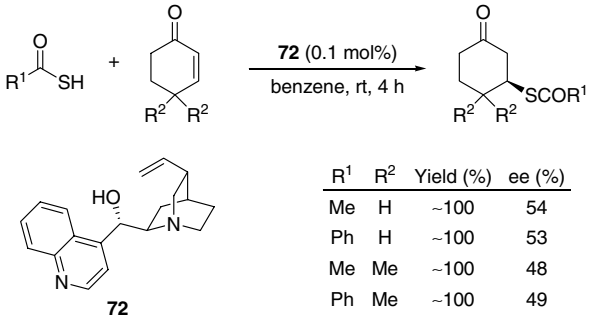
Scheme 125. Proposed mechanism for the domino Michael-aldol reaction catalyzed by **150**.

corresponding thioether, which suffers a diastereospecific intramolecular aldol reaction to yield **I** after a fast enolization process by the base without further asymmetric induction by the catalyst. On the other hand, in the presence of benzoic acid as an additive, no hydrolysis takes place, and the chiral enamine intermediate suffers the corresponding intramolecular aldol reaction. Due to the steric hindrance of the chiral substituent in the pyrrolidine ring, the *E*-enamine selectively attacks the carbonyl moiety from the *Re* side leading to the observed stereochemistry in the final product **I** (Scheme 125, cycle B). The higher enantioselectivities observed for compounds **I** were in accordance with the proposed mechanism since in this case the catalyst had a multiple asymmetric induction role.

In related studies, Córdova et al. identified chiral diamine **19** and L-prolinol **30** as very efficient catalysts for the enantioselective domino reaction between 2-mercaptobenzaldehyde and cyclic α,β-unsaturated ketones.[225] The reaction, which afforded chiral tetrahydrothioxanthenones, proceeded in high yields with excellent chemoselectivity although in moderate enantioselectivities as depicted in Scheme 126 for selected examples.

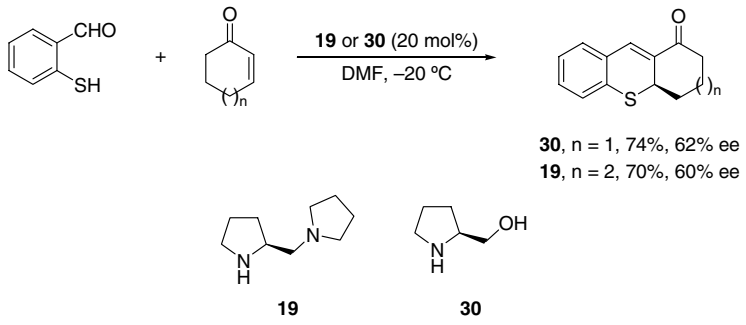
Few examples have been reported for the organocatalytic asymmetric conjugate addition of sulfur nucleophiles other than thiols. The conjugate addition of thiocarboxylic acids to cyclohex-2-enones[226] and α,β-unsaturated esters[227] was studied by Wynberg et al. as early as 1981 and 1983, respectively. Employing *Cinchona* alkaloid catalysts these authors reported the first enantioselectivities for these processes, as depicted in Scheme 127, for the addition of thiocarboxylic acids to cyclohex-2-enones catalyzed by cinchonine **72**.[226]

Very recently, similar levels of enantioselection (up to 63% ee) were obtained by Wang et al. in the addition of thioacetic acid to a range of *trans*-chalcones using the Takemoto's chiral thiourea **99** as a catalyst.[228] Relatively low enantioselectivities were observed for chalcone containing elec-



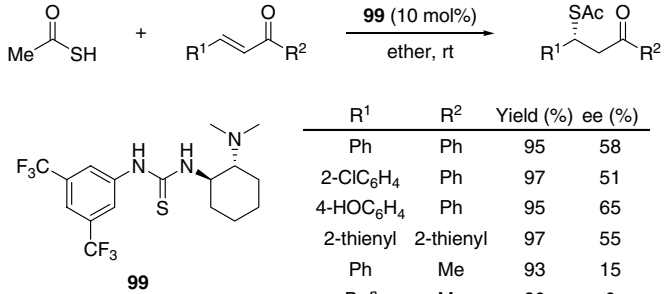
R^1	R^2	Yield (%)	ee (%)
Me	H	~100	54
Ph	H	~100	53
Me	Me	~100	48
Ph	Me	~100	49

Scheme 127. Cinchonine-catalyzed asymmetric addition of thiocarboxylic acids to cyclohex-2-enones.



Scheme 126. Organocatalytic asymmetric synthesis of tetrahydrothioxanthenones.

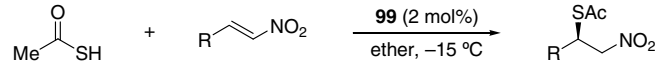
tron-withdrawing groups (33–51% ee), while electrophiles containing neutral or electron donating groups gave the corresponding adducts with higher enantioselectivities (50–65% ee) (Scheme 128). Very poor or no enantioselection was observed in the case of employing alkyl substituted enones as electrophiles.



R^1	R^2	Yield (%)	ee (%)
Ph	Ph	95	58
2-ClC_6H_4	Ph	97	51
4-HOC_6H_4	Ph	95	65
2-thienyl	2-thienyl	97	55
Ph	Me	93	15
Bu^n	Me	90	0

Scheme 128. Asymmetric addition of thioacetic acid to α,β-unsaturated enones.

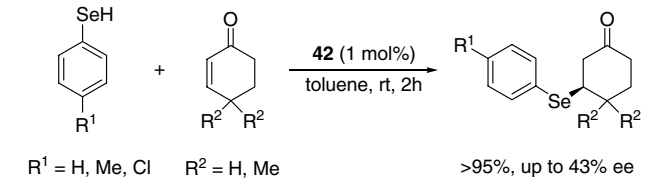
Slightly better enantiomeric excesses (up to 70% ee) were obtained by the same group in the addition of thioacetic acid to *trans*-β-nitrostyrenes and alkyl nitroalkenes under low loading conditions (**99**, 2 mol %) by employing ether as solvent and at lower temperatures (−15 °C) (Scheme 129).[229] The processes took place in excellent yield (91–98%) for all the nitroolefins tested. With respect to the enantioselectivity, similar trends as observed for the addition to chalcones were obtained; thus electron-rich aromatic nitrostyrenes provided Michael adducts with higher enantioselectivities (56–70% ee) than those possessing electron-withdrawing groups (20–27% ee).



R	Time (h)	Yield (%)	ee (%)
Ph	0.75	93	70
2-$MeOC_6H_4$	0.5	98	56
2-$CF_3C_6H_4$	0.5	92	24
$PhCH_2CH_2$	1	92	52

Scheme 129. Addition of thioacetic acid to *trans*-β-nitrostyrenes catalyzed by **99**.

Very few studies have been carried out on the organocatalytic asymmetric conjugate reaction of selenium nucleophiles. Furthermore, the study was restricted to the addition of selenophenols to enones catalyzed by cinchonidine **42** to afford very low enantioselectivities (up to 43% ee) as shown in Scheme 130.[230]



Scheme 130. Addition of selenophenols to enones catalyzed by cinchonidine.

5. Conclusions and perspectives

Even though the asymmetric conjugate addition reaction catalyzed by a chiral organic molecule is one of the earliest examples of a catalytic asymmetric transformation, it has suffered a spectacular advance during recent years. Conjugate additions of hydrogen, as well as carbon and heteroatom nucleophiles, to a wide variety of Michael acceptors such as α,β-unsaturated carbonyl compounds, nitroolefins, vinylic sulfones, and acrylonitriles can be efficiently performed at this time by employing readily available organocatalysts with excellent levels of asymmetric induction and in short reaction times. This has provided a wide range of Michael adducts in enantiomerically pure form, which have been employed as chiral building blocks in the total synthesis of different natural products. On the other hand, despite the considerable progress that has been made in the elucidation of transition states, there is still much room to fill with respect to new organocatalytic transformations and, especially, to the rational design of general catalysts based on all of the aspects that control the reactivity and selectivity of these reactions.

Acknowledgements

This work has been supported by the Dirección General de Investigación of the Ministerio de Educación y Ciencia (CTQ2004-00808/BQU), by the Generalitat Valenciana (CTIOIB/2002/320, GRUPOS03/134, GRUPOS05/11, and GV05/157) and the University of Alicante. D.A. thanks the Ministerio de Educación y Ciencia for a predoctoral fellowship.

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