Rainer Mahrwald *Editor*

Enantioselective Organocatalyzed Reactions II

Asymmetric C-C Bond Formation Processes

Foreword by Carlos F. Barbas, III

Springer

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Foreword

It is part of the human experience to wonder and marvel at the beauty of life in the world around us. An astronomer might look up in awe and question the size, shape and age of the universe. A biologist might pay keen attention to the anatomical features unique to a given organism and see the beauty in the organism's adaptability. The organic chemist, however, tends to look deeper and ponder the actual molecules, focusing on the unique mechanisms that create a wide array of complex molecules that in turn conspire to create life itself. This is as true today as it was more than a century ago when the great organic chemist Emil Fischer stated "If we wish to catch up with Nature, we shall need to use the same methods as she does, and I can foresee a time in which physiological chemistry will not only make greater use of natural enzymes, but will actually resort to creating synthetic ones."[1] Fischer foresaw that if we could understand how Nature's enzymes catalyze reactions, we could create our own synthetic catalysts. Indeed, it was in recreating Nature's aldolase enzymes that we were led to re-examine the chemistry of Hajos and Parrish in a new light. Through experimentation, we realized that the simple amino acid proline could recapitulate the 'complex' chemistry of an aldolase enzyme thereby providing a stunningly simple solution to the direct asymmetric aldol, Michael, Mannich and other reactions. Indeed, catalytic activity of amino acids, particularly in enamine and iminium chemistry, is not restricted to the amino acid proline but rather is a feature that most, if not all, amino acids have in common.

A decade has now passed since the studies of my laboratory and those of David MacMillan's refocused the considerable attention of the community on the profound potential of small organic molecules to catalyze asymmetric reactions. In this time, the scope of organocatalysis has enlarged considerably with respect both to the type of reactions catalyzed (aldol, cycloaddition, redox, asymmetric assembly and domino reactions, conjugate addition reactions, etc.) and the mechanisms used

[1] Fischer E: Synthesen in der Purin- und Zuckergruppe. In Les Prix Nobel en 1902. Edited by Cleve PT, Hasselberg C-B, Morner K-A-H: P-A Norstedt & Fils; 1905.

to affect catalysis (enamine, iminium, hydrogen bonding, Bronsted or Lewis acid/base chemistry, SOMO activation, etc.). With each new reaction and mechanistic lever applied, "the veil behind which Nature has so carefully concealed her secrets is being lifted."[1] Indeed, there is much to be gained in envisioning an enzyme as an organic flask that affects catalysis through the side chains of amino acids, their intervening amide linkages, organic cofactors, and the flask itself.

Although the notion of organocatalysis has been with us since the very beginnings of organic chemistry, in the last decade organocatalysis has created a sea change with respect to our abilities both to synthesize molecules asymmetrically and to understand how these molecules were synthesized in a prebiotic world before enzymes themselves existed. We speculate that the first carbohydrates might have been first synthesized via amino acid catalysis and can envision a route to homochirality that might have been exploited to create life. Thus organocatalysis might have been the key chemistry available in the prebiotic word and might have provided the homochiral building blocks that allowed life to form. Indeed, biosynthetic reactions occurring in organisms today that are catalyzed by small organic molecules might explain our inability to find protein enzymes for certain reactions. The secret of life now feels a bit closer. Organocatalysis has also changed our notions concerning what is possible in catalytic asymmetric synthesis. We are not so much concerned with creating a single stereogenic center now or a single bond connection, but with creating arrays of 2, 3, 4, 5, or more stereocenters and bond connections under organocatalysis in a single pot with excellent control of enantio- and diastereoselectivity. Such reports are now becoming commonplace whereas a decade ago they would have been greeted as major triumphs. This has led many to suggest that we are in the golden age of organocatalysis, that the creative stage of this endeavor has somehow now passed. I believe we are just at the beginning of this endeavor and that much fascinating and unexpected chemistry lies ahead of us.

The explosive growth of asymmetric organocatalysis has been driven by a newfound appreciation for reactivity among small organic molecules, but we have barely begun to explore this space. How big is this space and what might we find? It is easier to answer the first part of this question. It is vast indeed. If we consider calculations performed to define the space of small molecules of molecular weight of less than 500 Da that consist of only C, H, N, O, P, S, Cl, and Br and are stable at room temperature and to oxygen and water, the number is unimaginable – more than 10^{63} molecules.[2] With this in mind, I believe that the organocatalysts known today represent islands of reactivity or catalytic potential in a near infinite sea. The discovery of new islands of catalytic potential will rely on the scientific method, chemical intuition, and luck but they are out there to be discovered and they promise new and ever more stunning catalytic syntheses of complex molecules and ever greater understanding of how atoms born in stars eventually conspired to create life.

[2] W.C. Guida et al. (1996) Med. Res. Rev. 16, 3–50.

As Emil Fischer told us more than a century ago, progress towards this goal will "not so much be determined by brilliant achievements of individual workers, but rather by the planned collaboration of many observers."[1] And so, the future of organocatalysis is vast and bright and will continue to benefit from the community of chemists that join this endeavor. Stunning reactions and reactivities await us.

The Scripps Research Institute
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Carlos F. Barbas, III

Preface

Without any doubt organocatalysis belongs to the most exiting and innovative chapters of organic chemistry today.

Since this chapter was first opened systematically 10 years ago, a plethora of methods and catalysts have been developed to solve problems of organic chemistry. More and more these methodologies have been applied in total syntheses of natural products. This is what this two-volume book set wants to demonstrate - the full power of organocatalysis.

Asymmetric C-C bond formation processes form the subject of the second book while functionalization, catalysts and general aspects of organocatalysis are covered in the first one. Overlappings cannot be entirely avoided by such an approach. However, often these overlappings are desirable and valuable in order to illustrate a methodology by different views as this is true for asymmetric hydrogenation, enantioselective conjugate hydride addition, oxidation or transfer hydrogenation catalyzed by chiral primary amines.

It took great pleasure in working together with a team of leading experts in this field. I have to thank them for organizing these overviews.

Also, I thank the team at Springer UK to help us to publish these results.

Berlin
Spring 2011

Rainer Mahrwald

Contents

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Chapter 1
General Aspects of Organocatalytic Cyclizations

Alexander J. André Cobb

Abstract Ring-forming reactions are an essential part of synthetic chemistry and allow access to a range of useful natural products and biologically important molecules. The applications of *organocatalysis* to the synthesis of functionalised, enantiopure structures really begins where organocatalysis itself begins; with the Hajos-Parrish reaction in the 1970s for the synthesis of steroids using proline. This chapter then will review the uses of organocatalysts in cyclization methodology – from the initial Hajos-Parrish discovery to current advances in the field.

1.1 Background

The ability to generate functionalized ring systems is of fundamental importance to the natural product chemist. In particular the synthesis of *enantiopure* ring systems is essential, especially if there is a medicinal objective to the synthesis of the ring-containing natural product. Examples of such systems are, as you would expect, diverse and plentiful. One could select extreme biomolecules such as the highly toxic ciguatoxin **1**, with its multitude of fused ring systems snaking from a five-membered acetal, through rings of between 6 and 9 atoms in size, before ending at the fangs of a terminal diol. Or one could select simpler systems such as bromophycolide A **2**, a cytotoxic diterpene isolated from the Fijian red alga *Callophycus serratus*, or perhaps the more well-known thromboxane A2 **3**, an important vasoconstrictor. In each case, a chemical synthesis – whereby the ring system is formed by cyclization – would require conditions which are both favourable to ring formation and, at the same time, have the ability to exert a high degree of stereocontrol. Amongst the many

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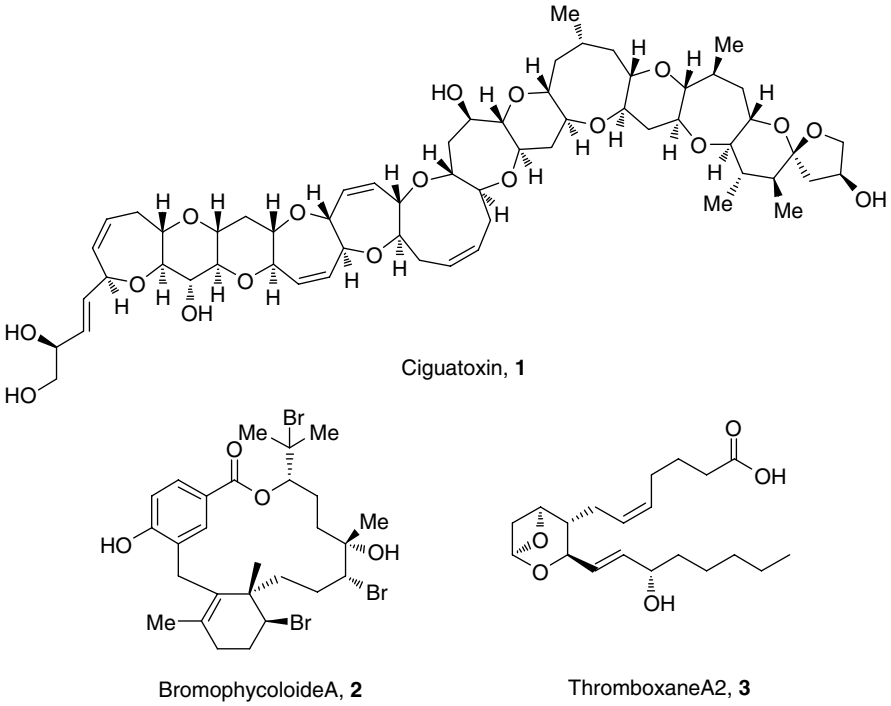


Fig. 1.1 Ring-containing natural products

methods to address this, asymmetric organocatalysis has emerged as an important and powerful way of constructing highly functionalized and enantiopure cyclic compounds (Fig. 1.1).

This chapter focuses on the organocatalytic methods that have been developed to facilitate asymmetric ring closure. As such, pericyclic processes are not covered and these are described elsewhere within these books (see Volume II, Chapter 3). Sections are divided up into the ring size being formed, starting with three-membered rings where only cyclopropanes are discussed (epoxidations and aziridinations are detailed in Volume I). The non-[2+2] organocatalysed synthesis of four-membered rings is then examined briefly. Ring formations of systems containing five and six atoms are then discussed together, as the methodologies developed are often applicable to both. Finally, domino processes to cyclic systems are reviewed. It is hoped that this chapter will clarify the conditions and rules involved in all of these processes.

1.2 General Modes of Cyclization

In general, organocatalytic cyclization processes conform to Baldwin's Rules of ring closure and all fall into one of the four following classes [1]. The most common modes of cyclization, are the enolexo-exo-trig (Fig. 1.2a) and the enolendo-exo-trig

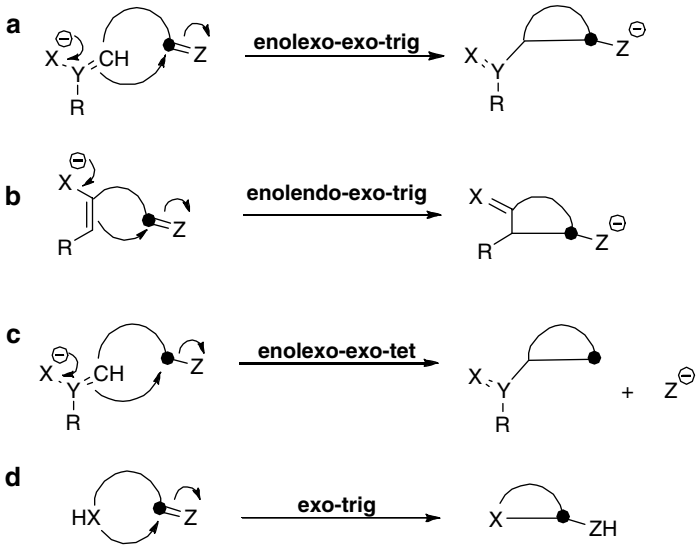


Fig. 1.2 Most common modes of cyclization in organocatalysis

(Fig. 1.2b) classes wherein an 'enolizable' nucleophile (commonly an enamine, nitronate or 1,3-dicarbonyl) cyclizes onto an sp^2 carbon. Enolexo-exo-tet cyclizations (Fig. 1.2c) are less common however, and tend to occur predominantly in cyclopropanation reactions. Indeed, alkylations using secondary amine catalysis are difficult under standard organocatalytic conditions owing to problems associated with the alkylation of the catalyst itself, although various methods have been adopted to address this. Finally, exo-trig cyclizations of heteroatoms onto sp^2 centres (Fig. 1.2d) are a useful way of constructing enantiopure heterocycles.

1.3 Cyclizations to Form Cyclopropanation Systems

Enantiopure cyclopropanes occur in both nature and medicinal chemistry. Callipeltoside A **4** [2], for example is a moderately cytotoxic macrolide, isolated from the marine sponge *Callipelta sp.* and contains a *trans*-chlorocyclopropane side chain. An interesting compound from Eli-Lilly aimed at schizophrenia, which unfortunately fell at Phase II trials is the cyclopropane glutamate analogue LY2140023 which contains four contiguous stereocentres (Fig. 1.3).

1.3.1 Access to Cyclopropanes via Ammonium Ylids

Some of the first reports of an organocatalytic cyclopropanation were made by Gaunt and co-workers who used ammonium ylids as nucleophiles and reacted them into

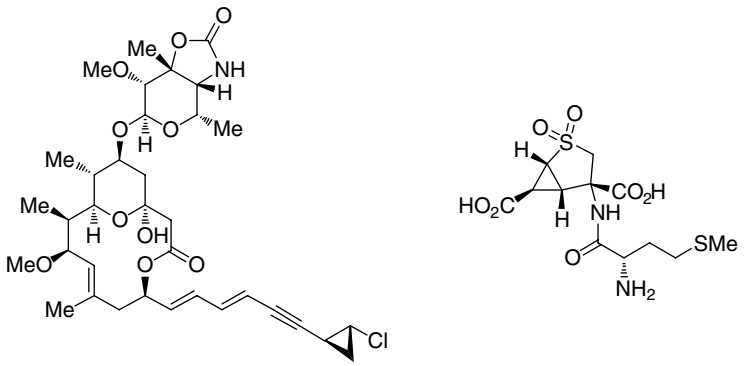
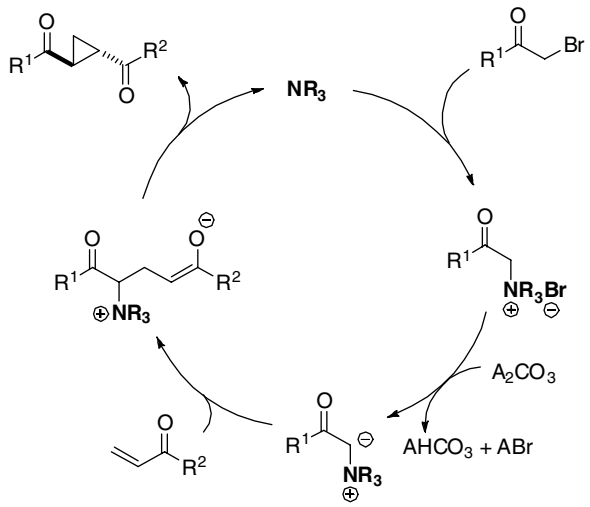


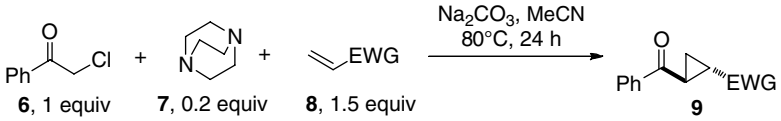
Fig. 1.3 Cyclopropane-containing structures

conjugated esters. The resulting enolate would then form the three-membered ring in a 3-enolexo-exo-tet process *via* displacement of the quaternary amine (Scheme 1.1) [3].

Scheme 1.1 Proposed catalytic cycle for tertiary amine organocatalyzed cyclopropanantion



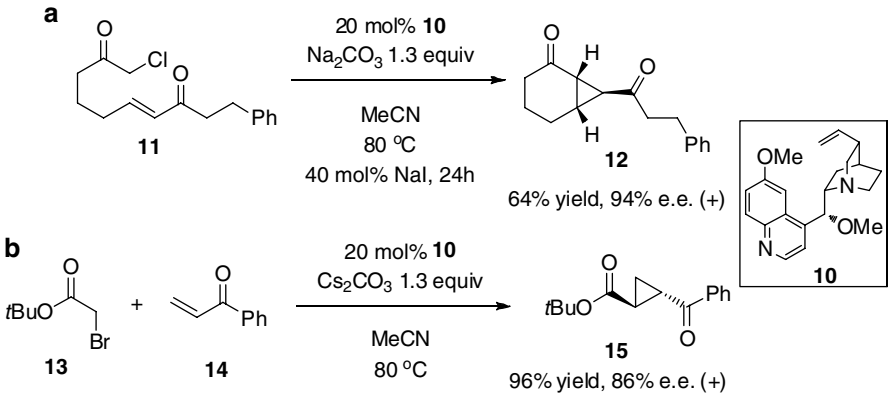
In the original sequence, the ylid was generated by addition of catalytic DABCO to phenacyl chloride and treatment with sodium carbonate in the presence of a Michael 1,4-addition acceptor (Scheme 1.2).



Scheme 1.2 Gaunt's original organocatalytic cyclopropanation conditions

Gaunt then extended this methodology to an enantioselective process in both intramolecular [4] and intermolecular systems [5] using cinchona alkaloid **10** as the tertiary amine. In the intramolecular reaction (Scheme 1.3a), a fused [4.1.0]-heptane

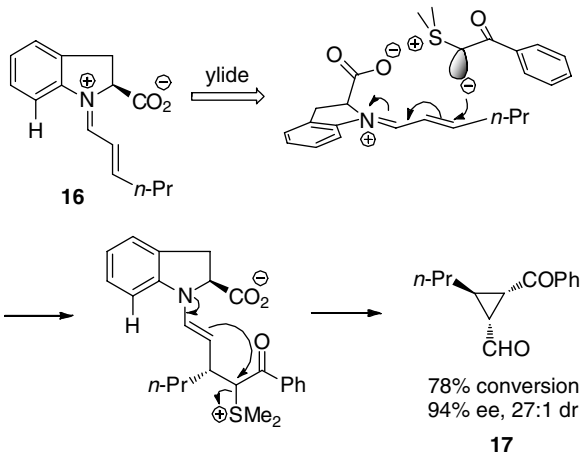
system formed, and it was found that the use of a sodium iodide or sodium bromide additive improved both the reaction times and enantioselectivities of the process. In the enantioselective intermolecular process, cesium carbonate was found to be the best base (Scheme 1.3b).



Scheme 1.3 Enantioselective (**a**) Intramolecular and (**b**) intermolecular tertiary amine catalyzed cyclopropanations

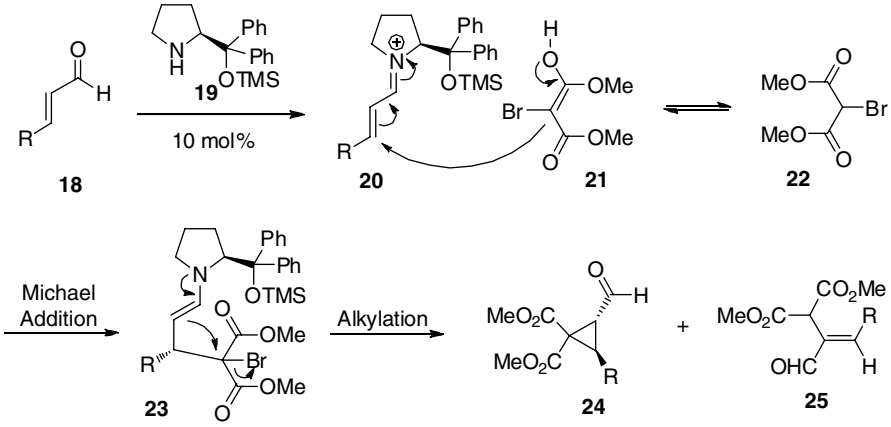
1.3.2 Access to Cyclopropanes via Secondary Amine Catalysis

Secondary amine catalysis was first used in organocatalytic cyclopropanations by MacMillan and co-workers whereby a carboxylic dihydroindole was used to effect the reaction between an α, β-unsaturated aldehyde and a stabilized ylide [6]. It was postulated that the secondary amine forms a conjugated iminium **16** with the aldehyde. The carboxylate of the resulting species then interacts with the positively charged sulfur atom of the ylide, thus directing the carbanion towards conjugate addition. The resulting enamine then cyclizes (again in a 3-enolexo-exo-tet process) to produce the cyclopropane **17**. (Scheme 1.4).



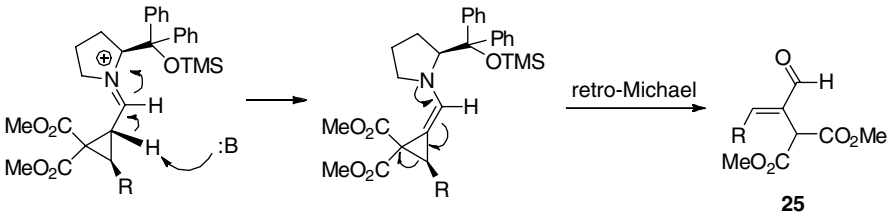
Scheme 1.4 MacMillan's directed electrostatic activation in the cyclopropanation of an α, β-unsaturated aldehyde

In the same way that MacMillan's sulfur ylide and Gaunt's ammonium ylide chemistries benefit this reaction by virtue of containing a carbon atom which starts off as a nucleophile and then becomes an electrophile (to enable cyclization), so too have bromomalonates been used in cyclopropanation processes. Wang and co-workers have developed a system whereby they utilize Jørgensen catalyst **19** in the addition of bromodimethylmalonate **21** to a conjugated aldehyde **18** [7]. The resulting enamine again undergoes a 3-enolexo-exo-tet cyclization to substitute the bromine atom (Scheme 1.5).



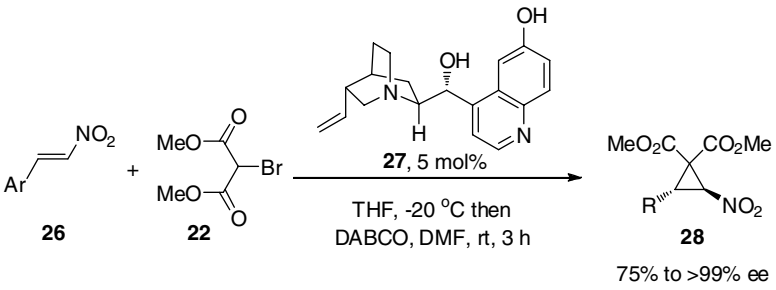
Scheme 1.5 Wang's organocatalytic cyclopropanation with unexpected ring-opened product

Interestingly, an unexpected ring-opened product **25** was also produced. Its formation is proposed to occur after cyclopropane formation but before hydrolysis of the iminium, whereby an enamine is formed a second time and undergoes a retro-Michael reaction to give the olefin (Scheme 1.6).



Scheme 1.6 Unexpected cyclopropane ring-opening mechanism

Yan and co-workers have also utilized bromomalonate **22**, but using a nitro-olefin as the electrophile and a β-aminoalcohol quinine derivative **27** as the organocatalyst (Scheme 1.7) [8]. No retro-Michael reaction appears to have been observed.



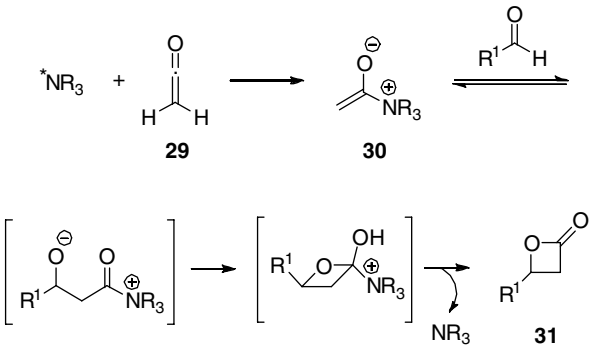
Scheme 1.7 Yan's cyclopropanation using hydrogen-bonding catalysis

1.4 Cyclization to Four Membered Rings

1.4.1 Access to Four-Membered Rings via Ammonium Enolates

1.4.1.1 β-Lactone Formation

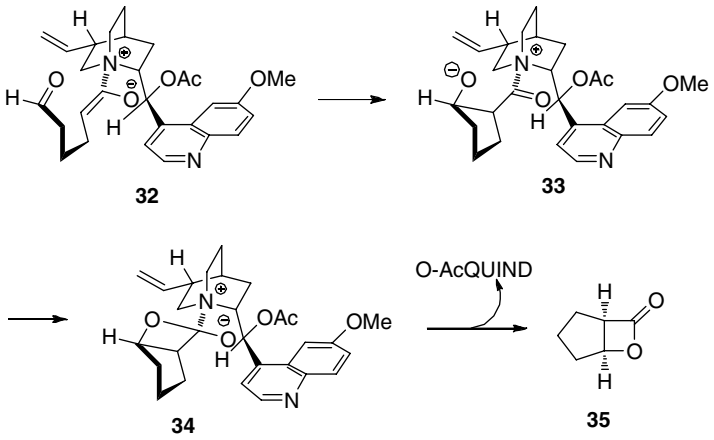
Four membered rings which are synthesized by an organocatalytic mechanism *not* involving a [2+2] cycloaddition are very uncommon. However, in the early to mid 1980s, Wynberg developed an organocatalytic system for the synthesis of 4-substituted 2-oxetanones using cinchona alkaloids [9]. As with the cyclopropanation described in the previous section, this is not a *direct* cyclization, but an *intermolecular* reaction followed by a subsequent ring forming process. In this case the intermolecular reaction is between an ammonium enolate **30** (generated from reaction of a tertiary amine with a ketene) and an aldehyde to generate a secondary oxyanion. This then undergoes a 4-exo-trig to generate the β-lactone **31** (Scheme 1.8).



Scheme 1.8 Mechanism for the Nucleophile-Catalyzed Aldol-Lactonization (NCAL)

A further development of this reaction should arguably appear in the section on the formation of five and six membered rings. However, it appears here as it is an extension of the methodology described above. It comes from the group of Romo, who described

an *intramolecular* aldolization of the ammonium enolate to generate a five-membered ring prior to β-lactonization (Scheme 1.9). It is suggested that this indicates that an ionic pathway is much more likely than a [2+2] cycloaddition mechanism, since in the latter there would be no opportunity for the catalyst to induce enantioselectivity [10].



Scheme 1.9 Organocatalytic synthesis of a bicyclic β-lactone

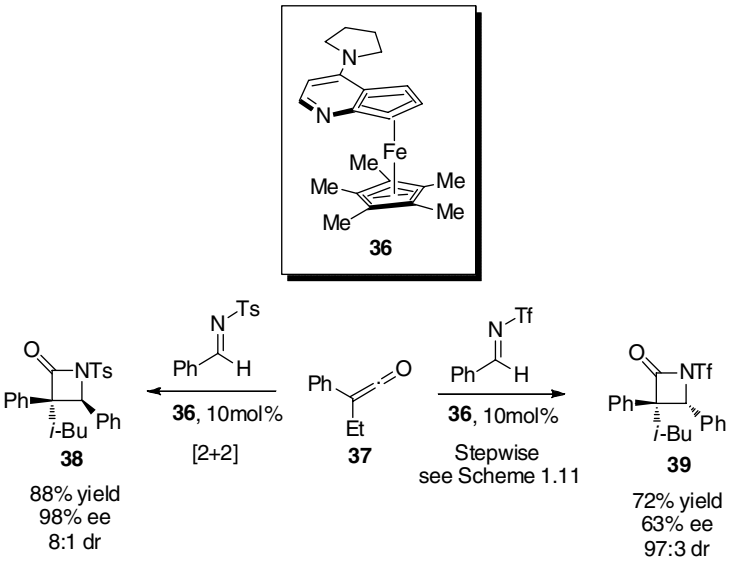
1.4.1.2 β-Lactam Formation

The Staudinger reaction is an overall [2+2]-cycloaddition process between ketenes and imines to form β-lactams, important antibiotic structures, and has been used to good effect in organocatalytic processes. However, Fu and co-workers have described a Staudinger process which is thought to happen in a *stepwise* fashion (Schemes 1.10 and 1.11), whereby the chiral amine **36** attacks the highly electrophilic triflate imine **40** to generate a triflimide anion **41**. This attacks the ketene **37** resulting in intermediate **42** which undergoes intramolecular cyclization to form the β-lactam and regenerate the tertiary amine catalyst **36** [11].

A large range of triflate imines and ketenes were employed, giving yields between 60% and 89%, diastereoselectivities up to 98:2 and enantioselectivities of between 63% and 99%.

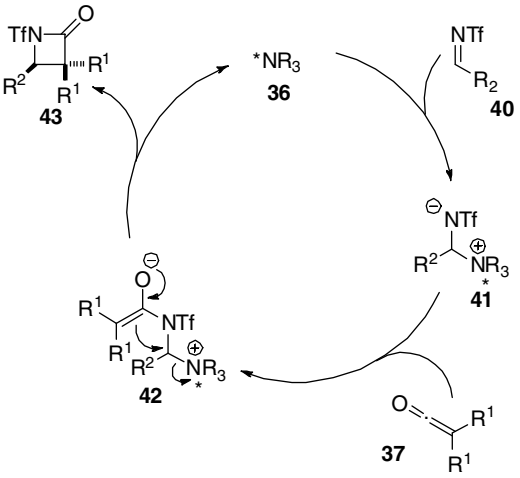
1.5 Direct Cyclizations to Five- and Six-Membered Rings

Enantiopure five and six-membered rings are amongst the most common structural motifs in biology and medicinal chemistry and as such their asymmetric synthesis has been the subject of intense investigation through the ages. Organocatalytic methods have also been scrutinized and a large variety of very useful protocols exist.



Scheme 1.10 Formation of β-lactams by Staudinger reaction is thought to occur through a stepwise mechanism when Tf-imines are used

Scheme 1.11 Proposed catalytic cycle for the stepwise Staudinger process



1.5.1 Access to Five and Six-Membered Rings via Secondary Amine Catalysis

Chiral secondary amines have proven to be amongst the most dynamic and efficient of asymmetric catalysts. There are essentially two modes of activation by secondary amines whereby a nucleophilic enamine or an electrophilic iminium ion is generated. Figure 1.4 shows a generic scheme of these two modes of activation and how they would be used in asymmetric organocatalytic cyclizations. A third mode of catalysis, named 'Organo-SOMO' catalysis is discussed in Sect. 1.5.1.5.

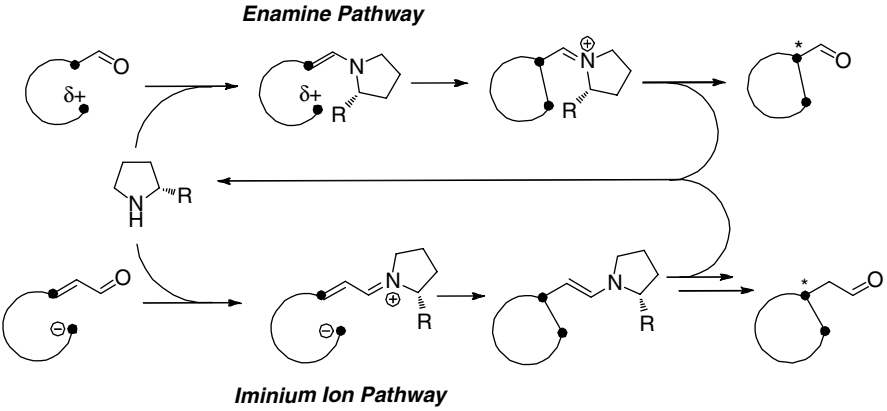
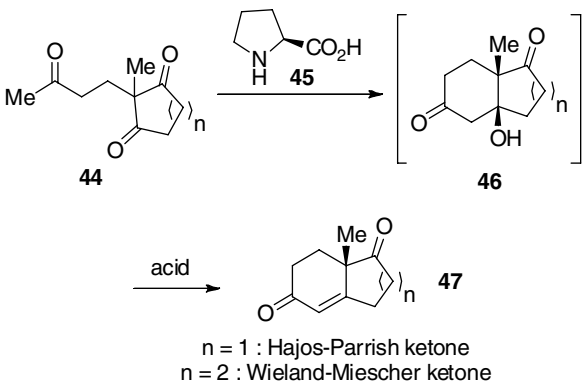


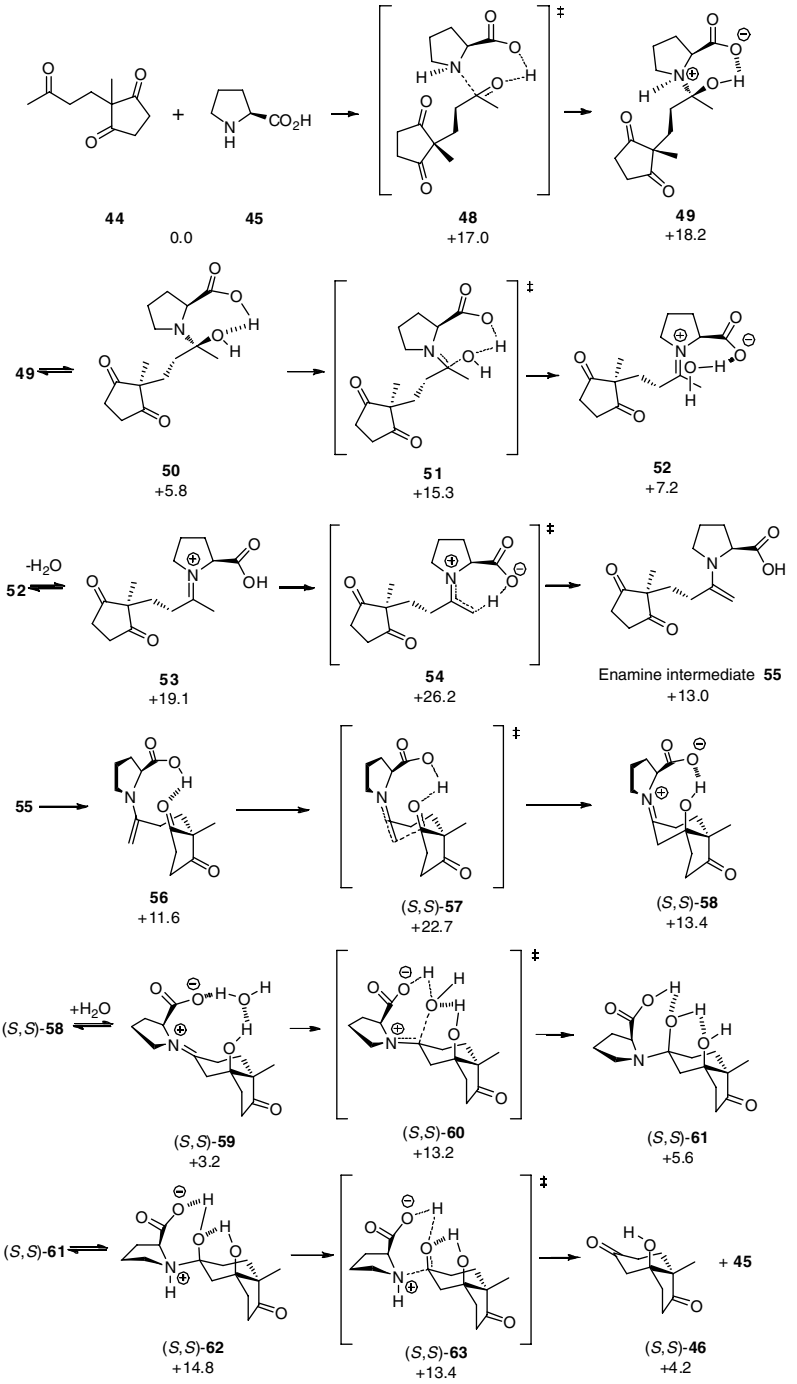
Fig. 1.4 Examples of the two main modes of secondary amine catalysis

1.5.1.1 Intramolecular Aldol Additions *via* Secondary Amine Catalysis

The aldol addition is probably one of the most well-investigated organocatalytic processes. The organocatalytic intramolecular version of this reaction was reported in the early 1970s when Hajos-Parrish-Eder-Sauer-Wiechert reaction used L-proline **45** to effect an asymmetric ring closure on prochiral 2-alkyl-2-(3-oxoalkyl)-cyclopentane-1,3-diones (Hajos-Parrish, Scheme 1.12, n = 1) or on 2-methyl-2-(3-oxobutyl)-cyclohexane-1,3-dione (Wieland-Miescher, Scheme 1.12, n = 2) [12, 13]. This enolendo-aldolization is the basis of computational evidence for the widely proposed enamine mechanism catalyzed by proline [14]. Clemente and Houk calculated not only the energy of the transition state, but also of all the possible intermediate steps of the process, and used this model to explain the stereochemical outcome of the process (Scheme 1.13).



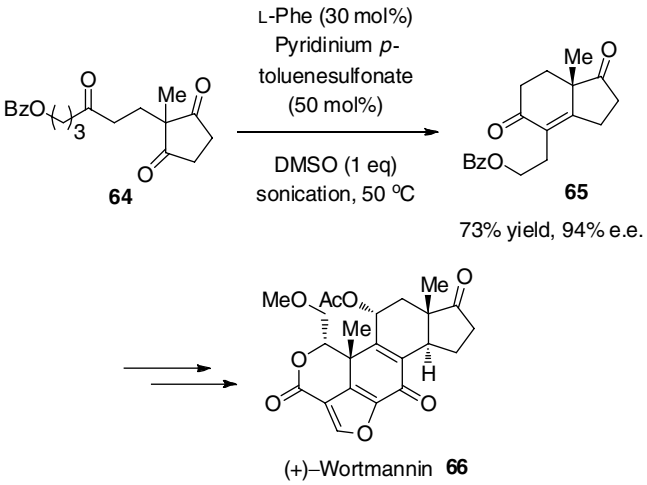
Scheme 1.12 One of the earliest organocatalytic reactions, the Hajos-Parrish-Eder-Sauer-Wiechert reaction



Scheme 1.13 Calculations for the formation of the Hajos-Wiechert ketone with relative gas-phase energies (kcal mol^{-1})[14]

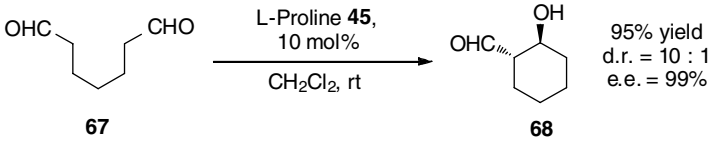
In this mechanistic pathway, Clemente and Houk showed that the most likely intermediate was the widely postulated enamine **55**, whereby the acid group of the proline co-ordinates to the electrophile to set up cyclization to iminium ion **58**. Hydrolysis of this returns the catalyst **45** and the aldol product **46**.

This reaction has been used to good effect over time. For example, Oshima, Shibasaki and co-workers synthesized (+)-wortmannin **66**, using L-phenylalanine instead of L-proline (Scheme 1.14) [15].



Scheme 1.14 Application of the Hajos-Parrish-Eder-Sauer-Wiechert reaction to natural product synthesis

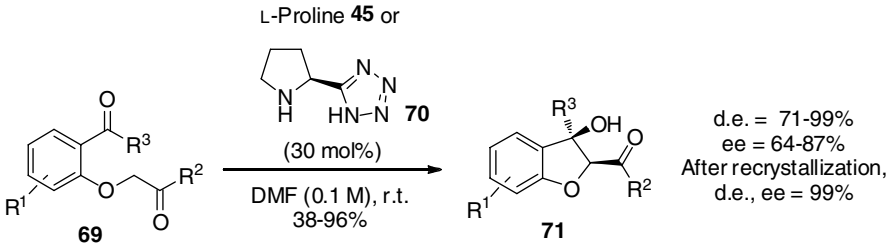
After development of the proline-catalyzed intermolecular aldol reaction by List, Lerner and Barbas in 2000 [16], which led to intense world-wide investigation, List himself developed a further intramolecular proline catalyzed cyclization which was enol-exo in nature as opposed to the enol-endo type cyclization of the Hajos-Parrish-Eder-Sauer-Wiechert process (Scheme 1.15). A range of substrates were applied using the methodology and excellent enantioselectivities were obtained [17].



Scheme 1.15 6-Enolexo-exo-trig aldolization

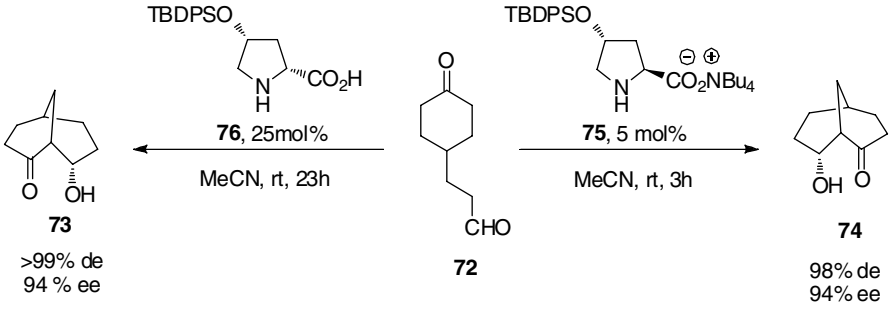
Another enol-exo cyclization was also described by Enders who employed similar methodologies to generate *cis*-substituted dihydrobenzofuranols using either

L-proline **45** or 5-pyrollidin-2-yl-tetrazole **70** [18] to effect cyclization (Scheme 1.16) [19]. Usefully, diastereoselectivities and enantioselectivities were greatly enhanced upon recrystallization.



Scheme 1.16 Enders' 5-enolexo-exo-trig aldolization

Iwabuchi and co-workers utilized 4-hydroxy proline derivatives **75** and **76** in their intramolecular aldol condensation of 3-(4-oxocyclohexyl)propionaldehyde **72**. Interestingly, obtaining the oppositely configured product did not rely on utilization of the oppositely configured organocatalyst. Indeed it was acquired by inversion of the α-stereocentre of the catalyst, but where the 4-hydroxy configuration remained the same (Scheme 1.17). The authors propose a transition state that again relies on hydrogen bond participation of the carboxylic acid [20].

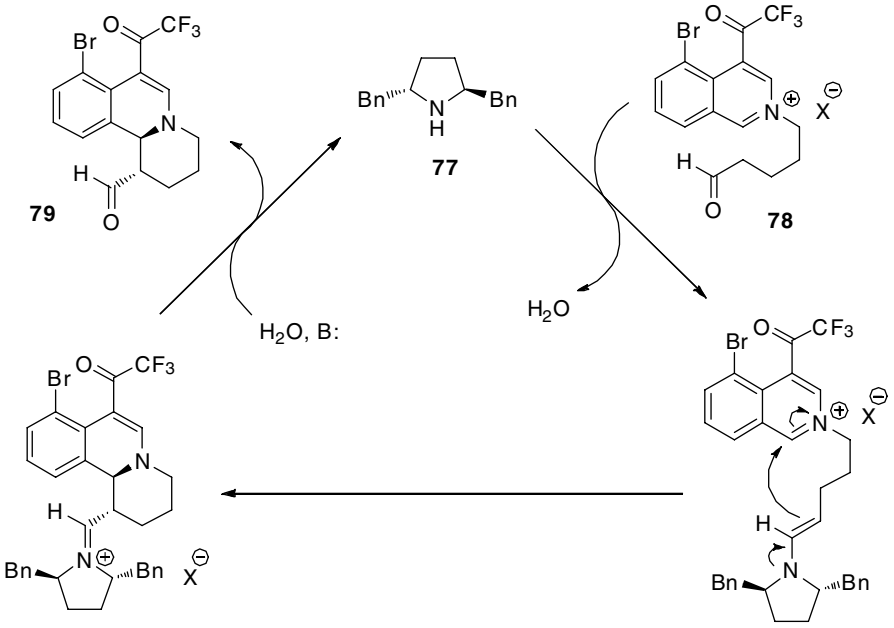


Scheme 1.17 Iwabuchi's intramolecular aldol reaction

1.5.1.2 Intramolecular Addition to C=N via Secondary Amine Catalysis

Far less common is the secondary amine catalyzed intramolecular Mannich-type reaction. This is mainly due to the difficulties associated with synthesizing substrates which contain both an aldehyde or ketone functionality *and* an imine functionality within the same molecule. However, Jørgensen and co-workers have described such a process in the construction of optically active 1,2-dihydroisoquinoline and

1,2-dihydrophthalazine derivatives *via* a 6-enolexo-exo-trig cyclization [21]. It was found that use of C_2-symmetric organocatalyst **77** gave the best results in terms of yield, diastereoselectivity and enantioselectivity. The mechanistic proposal again invokes the use of a chiral enamine (Scheme 1.18).

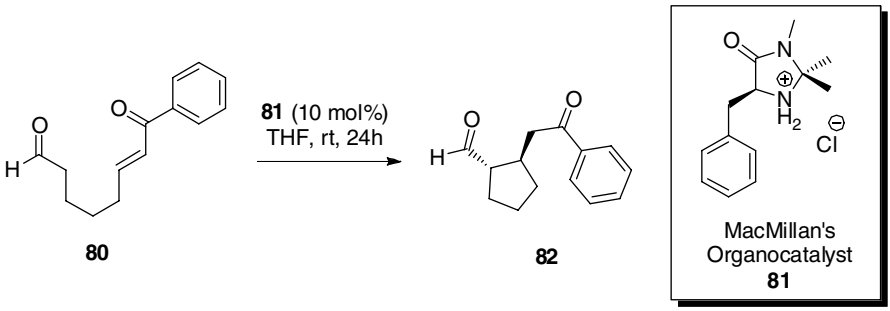


Scheme 1.18 Jørgensen's organocatalytic intramolecular addition to C=N

1.5.1.3 Intramolecular Conjugate Additions *via* Secondary Amine Catalysis

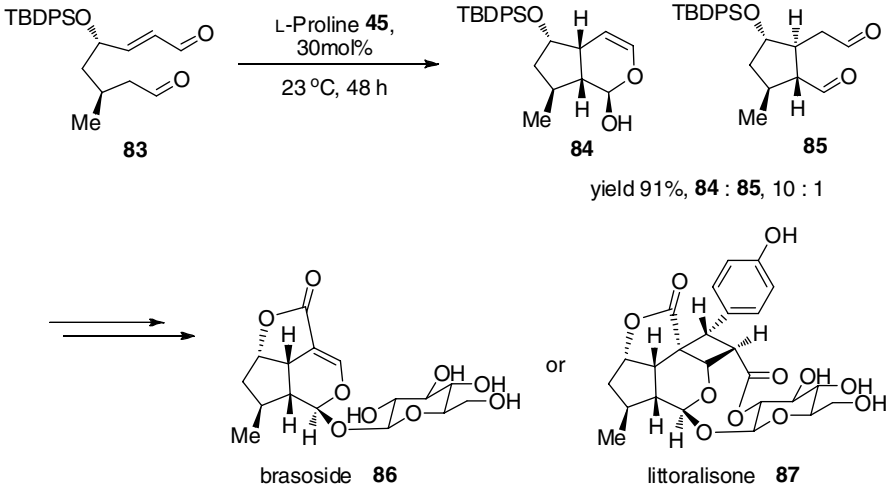
The conjugate addition is one of the most important carbon-carbon bond forming reactions available to the organic chemist. Again List led the way with the first report of an asymmetric organocatalytic intramolecular Michael 1,4-addition reaction of an aldehyde [22]. Using MacMillan's catalyst **81**, List and co-workers cyclized formylenones in tetrahydrofuran to give a range of ketoaldehydes in excellent yields and enantioselectivites (Scheme 1.19). Interestingly, this was one of the first reports to use an imidazolidinium salt – commonly used in iminium ion chemistry – in *enamine* catalysis, although there is the possibility in this case that there is a combination of the two at work.

MacMillan himself has utilized the same type of cyclization in the synthesis of the iridolactone core of (−)-brasoside **86** and (−)-littoralisone **87** [23]. Using enal **83** in the presence of L-proline **45** in DMSO, MacMillan and co-workers managed to synthesize *cis*-lactol **84**, importantly avoiding too much of the unwanted cyclopentyl



Scheme 1.19 Intramolecular Michael addition using secondary amine catalysis

product **85** (Scheme 1.20). This is of course in contrast to the work by List and co-workers who generated the *trans*-system.

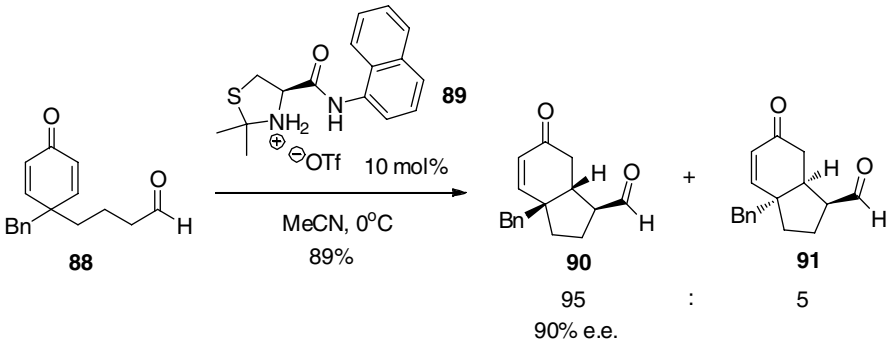


Scheme 1.20 MacMillan's synthesis of an iridolactone core using secondary amine catalysis

cis-Systems were also favoured under conditions developed by Hayashi and co-workers who used cysteine-derived organocatalyst **89** in a 5-enolexo-exo-trig Michael addition in a similar process. In this work, not only were simple 1,2-*cis*-substituted cyclopentanes made, but also a range of bicyclo[4.3.0]nonenes where the organocatalyst discriminates between two enantiotopic π-bonds (Scheme 1.21) [24].

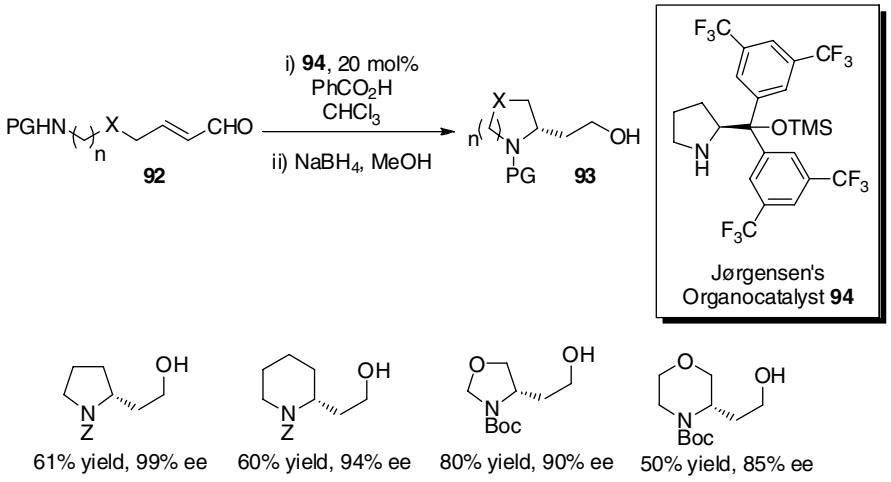
Although it can be argued that each of the conjugate addition processes described above might rely on both enamine and iminium ion chemistries, the intramolecular addition of heteroatoms onto conjugated systems is *totally* reliant on the latter.

Fustero and co-workers have utilized Jørgensen's catalyst **94** in organocatalyzed 5- and 6-exo-trig process *en route* to the synthesis of (+)-sedamine, (+)-allosedamine and (+)-coniine. In this reaction, carbamate protected amines **92** underwent



Scheme 1.21 Hayashi's access to bicyclo[4.3.0]nonenes by secondary amine catalysis

intramolecular conjugate addition to generate the heterocycles **93** in good yield and excellent enantioselectivities. A broad range of products were synthesized, including some with more than one heteroatom (Scheme 1.22) [25, 26].

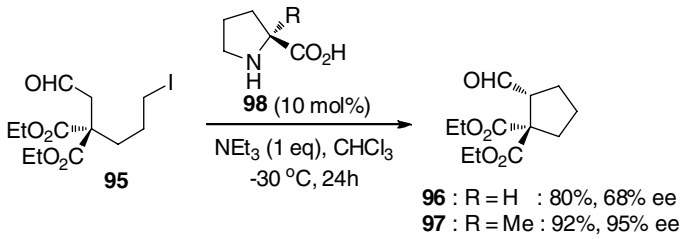


Scheme 1.22 Selected examples of Fustero's organocatalytic 5- and 6-exo-trig cyclizations

1.5.1.4 Intramolecular Alkylations *via* Secondary Amine Catalysis

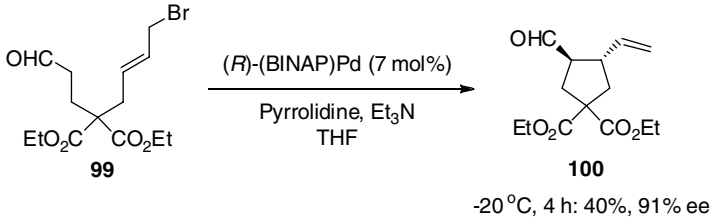
Enamines have again been used to good effect in the construction of enantiopure, functionalized five-membered rings. List and co-workers [27, 28] have produced one of the few examples of an intramolecular *alkylation* using a secondary amine. As mentioned, alkylations have often proven difficult with this mode of catalysis owing to problems associated with *N*-alkylation of the catalyst itself. Interestingly in this system, such a side-reaction does not seem to have been a problem, and indeed proline itself catalyzed the reaction to good yield and reasonable enantioselectivity.

More interesting, is that the use of (*S*)-α-methyl proline **98** significantly improved both the yield and importantly – the enantioselectivity. It is postulated that this improvement is due to the effect of the α-methyl substituent on the geometry of the resulting enamine (favouring the *anti*-conformation instead of the 1,3-allylically strained *syn*-conformation – Scheme 1.23).



Scheme 1.23 List's organocatalytic intramolecular alkylation

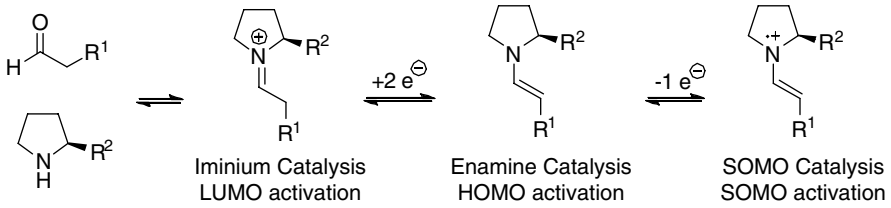
Saicic and co-workers [29] have also asymmetrically synthesized a five-membered ring using secondary amine catalysis. In this example, however, the alkylation was achieved *via* use of a π-allylpalladium complex as the electrophile (Scheme 1.24) [30]. However, it should be noted that the asymmetric induction comes from the palladium ligand as opposed to the use of a chiral secondary amine (which failed to give either any reaction or impart any enantioselectivity) [31].



Scheme 1.24 Dual catalysis using a secondary amine and a π-allylpalladium complex

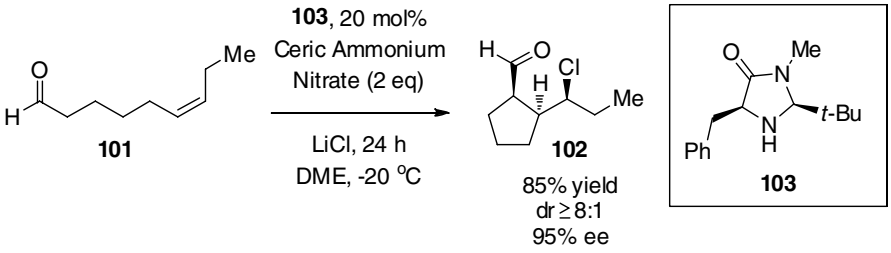
1.5.1.5 Intramolecular SOMO-catalysis

The use of secondary amine catalysis in combination with radical chemistry was first introduced by MacMillan in 2007 in a process he termed as 'organo-SOMO catalysis' [32]. In this system, the enamine that is generated in the condensation of a chiral secondary amine and a carbonyl, is oxidized *via* a single electron process. This generates a three-π-electron radical cation with a singly occupied molecular orbital (SOMO) which can react asymmetrically in a variety of different processes (Scheme 1.25).



Scheme 1.25 MacMillan's SOMO catalysis introduced a further dimension to secondary amine catalysis

An intramolecular application of this type of catalysis was included in his first publication on this process, whereby the SOMO activated enamine cyclized onto an unactivated alkene using catalyst **103** (Scheme 1.26).

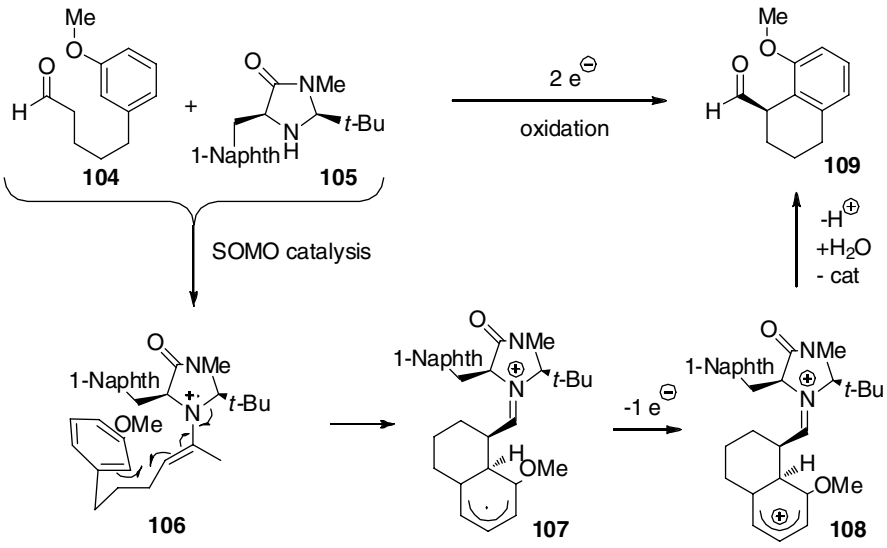


Scheme 1.26 First demonstration of an intramolecular SOMO-catalyzed process

MacMillan and co-workers then developed the α-arylation of aldehydes and showed it to be *ortho*-selective. The single electron oxidant in this case was $[Fe(phen)_3]\cdot(PF_6)_3$ in place of CAN, as it was shown to provide a superior catalyst/oxidant combination. The general applicability of this procedure was demonstrated with a wide variety of substrates [33, 34]. The mechanism proposed by MacMillan and co-workers is an overall two electron oxidation whereby the 3- π-radical cation reacts with the benzene ring to form a bicyclic radical cation **107** that upon further oxidation, generates a dienyl cation **108**. Rearomatisation and hydrolysis of the iminium species generates the product and regenerates the catalyst (Scheme 1.27).

1.5.2 Access to Five and Six-Membered Rings via Brønsted Acid Catalysis

The use of chiral Brønsted acid catalysis as a mode of asymmetric activation burgeoned dramatically in the early part of the twenty first century [35]. The role of hydrogen in this process is, in essence, similar to that of Lewis acid catalysts – *i.e.* activation of the C=X bond (X = O, NR, CR_2) by decreasing the LUMO energy and ultimately leading to promotion of nucleophilic addition to the C=X bond (Fig. 1.5).



Scheme 1.27 Ortho-selective α-arylation of aldehydes *via* Organo-SOMO catalysis

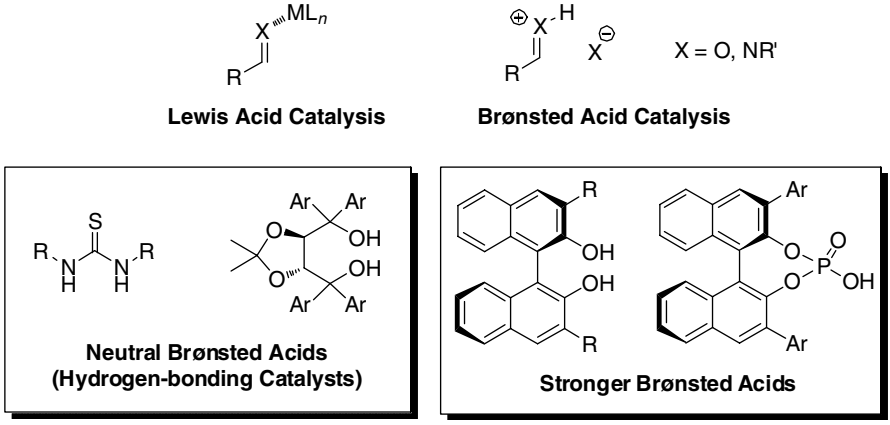
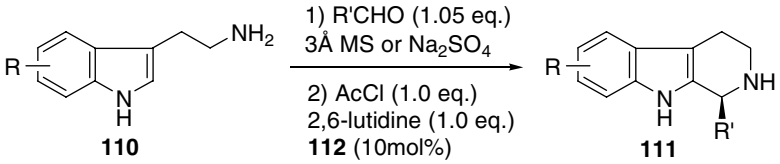


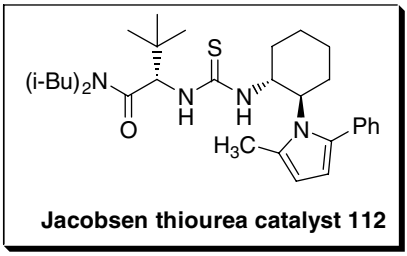
Fig. 1.5 Mode of action of Brønsted acid catalysis and some examples

The advantage that Brønsted acids have over Lewis acids is their relative stability, thus they are easier to handle and store for long periods of time. Scale up is therefore more achievable, and in keeping with the general advantages of organocatalysis over metal-based catalysis, are more environmentally compatible since precious mineral resources are not consumed.

Chiral Brønsted acids are divided into two categories. The first are neutral Brønsted acids such as thiourea [35b] and TADDOL derivatives, also known as hydrogen-bonding catalysts, and the second are stronger Brønsted acids such as BINOL derivatives or phosphoric acids.

Table 1.1 Asymmetric Acyl-Pictet-Spengler Thiourea catalyzed reaction





Entry	R	R′	T (°C)	yield (%)	ee (%)
1	H	$CH(CH_3)_2$	–40	67	85
2	H	n-C_5H_{11}	–60	65	95
3	H	$CH_2CH(CH_3)_2$	–60	75	93
4	H	$CH_2CH_2OTBDPS$	–60	77	90
5	6-MeO	$CH(CH_2CH_3)_2$	–50	76	86

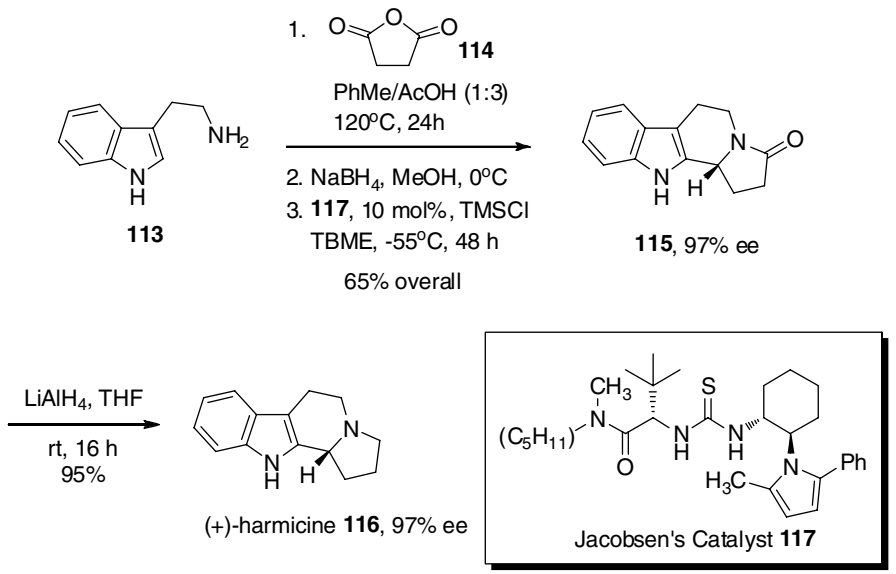
The contribution these catalysts have made to asymmetric synthesis has been remarkable, although their use in intermolecular reactions far outnumbers that of intramolecular reactivity.

1.5.2.1 Acyl-Pictet-Spengler Reaction

Amongst the first intramolecular processes developed using thiourea catalysis was that of the acyl-Pictet-Spengler reaction, devised by Jacobsen in 2004 [36, 37]. In the initial reaction, thiourea **112** was found to perform well in terms of both yield and enantioselectivity and a range of substrates were shown to undergo reaction (Table 1.1).

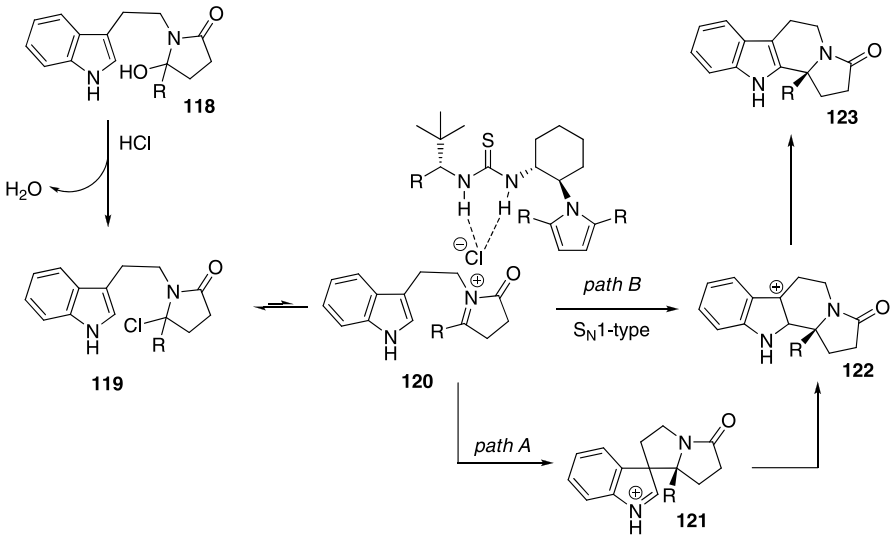
In a subsequent paper, Jacobsen and co-workers utilized hydroxylactams as precursors to a reactive *N*-acyliminium ion intermediate. Again, a wide variety of substrates were demonstrated using this methodology including the synthesis of (+)-harmicine **116** [36], an antiparasitic compound derived from the Malaysian plant *Kopsia griffithii* (Scheme 1.28) [38].

The mechanism was proposed to occur *via* a co-ordination of the chloride anion associated with the *N*-acyliminium cation, to the thiourea portion of the organocatalyst **117**. Thus the attack of the indole onto this electrophile is stereochemically controlled. There are two mechanistic possibilities in the ring forming stage of this process. Either a 5-enolexo-endo-trig cyclization occurs followed by Plancher



Scheme 1.28 Pictet-Spengler-type cyclization of a hydroxylactam in the synthesis of (+)-harmicine

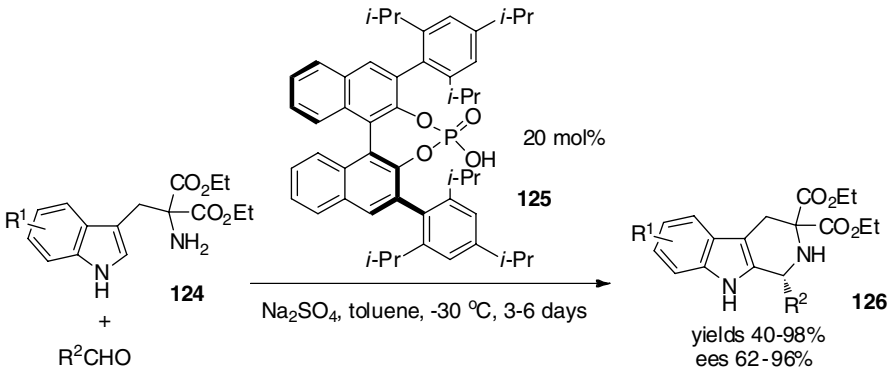
Rearrangement [39] of the more substituted carbon to form the indole (Path A), or there is a simple S_N1- type reaction (Path B, Scheme 1.29). Either way, Jacobsen and co-workers argue that there must be a dissociation of the chloride anion, as there would otherwise be no productive Lewis basic site for catalyst binding.



Scheme 1.29 Potential mechanism of the Pictet-Spengler-type cyclization of hydroxylactams

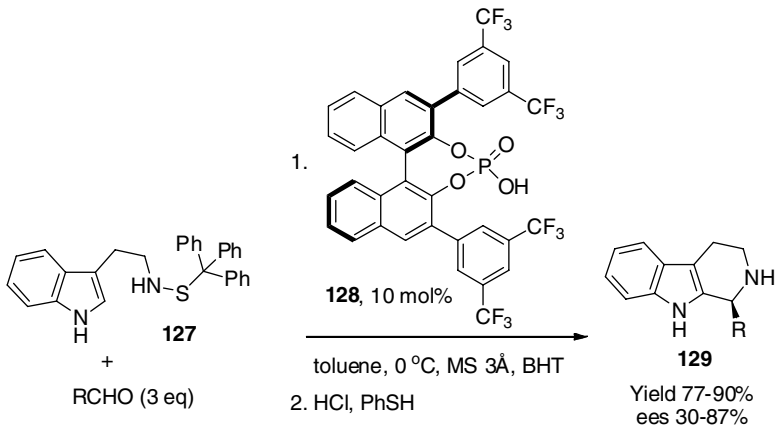
Furthermore, pronounced halide counterion effects and solvent effects on enantioselectivity were observed, thus supporting this hypothesized mechanism.

Stronger Brønsted acids have also been applied to this reaction. List and co-workers used the phosphoric acid **125** to fairly good effect in the asymmetric Pictet-Spengler reaction of indole **124** and a range of aldehydes (Scheme 1.30) [40]. However, the limitation of this approach was the requirement for a diester functionality to control the electronic properties of the primary amine.



Scheme 1.30 Pictet-Spengler reaction catalyzed by a chiral phosphoric acid

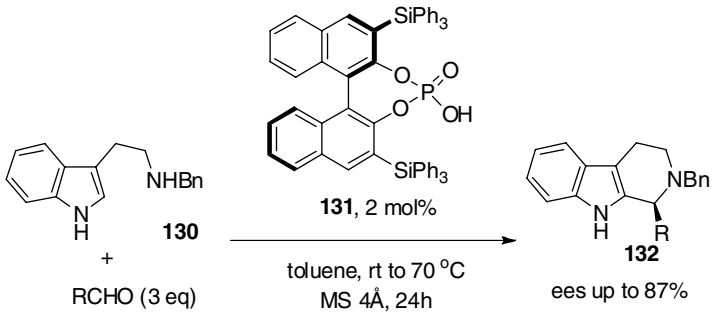
Hiemstra and co-workers described a similar process with the use of *N*-sulfenyl tryptamines, whereby it was theorized that the sulfenyl substituent would not only stabilize the intermediate iminium ion but also have the benefit of being removed easily [41]. Using another chiral phosphoric acid **128**, Hiemstra demonstrated the Pictet-Spengler reaction using (triphenyl)methylsulfenyl tryptamine **127** and a variety of aldehydes (Scheme 1.31).



Scheme 1.31 *N*-Sulfenyltryptamines in a chiral Brønsted acid catalyzed Pictet-Spengler process

BHT (3,5-di(*tert*-butyl)-4-hydroxytoluene) was added as a radical scavenger to the reaction mixture, as the sulfenyl products of the cyclization appeared to be unstable owing to possible homolytic cleavage of the trityl sulfur bond. Nevertheless, *in situ* conversion of the intermediate using thiophenol and then HCl, gave the hydrochloride salt of the tetrahydro-β-carboline which was collected by filtration and neutralized to give **129**.

The same group then went on to describe the use of catalyst **131** in the Pictet-Spengler reaction of *N*-benzyltryptamines with various aldehydes, and obtained cyclized products **132** in up to 87% ee (Scheme 1.32) [42].



Scheme 1.32 *N*-Benzyltryptamines in a chiral Brønsted acid catalyzed Pictet-Spengler process

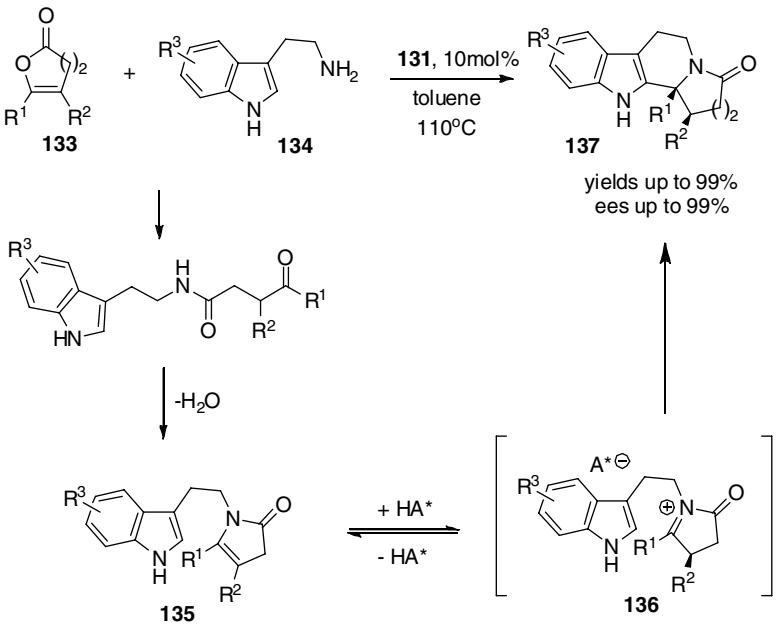
Fascinatingly using this system, a much lower catalyst loading is required, and the need for *in situ* deprotection of the nitrogen substituent is no longer required.

In a related process, Dixon and co-workers reported a cascade process with the same chiral phosphoric acid in the reaction between tryptamine **134** and enol lactone **133** (Scheme 1.33) [43]. In this reaction, it is postulated that the primary amine of the tryptamine ring-opens the lactone which is then followed by chiral Brønsted acid catalyzed dehydrative cyclization to give an *N*-acyliminium ion intermediate **136**. Presumably as with the other reactions of this class described above, there is an association between the conjugate base of the chiral acid and the acyl iminium species, allowing the subsequent cyclization onto the indole to be asymmetrically controlled and generate enantiopure product **137**.

Also of interest in this report was Dixon's use of a multicatalytic cascade process whereby the lactone was formed *in situ* via the gold(I)-catalyzed cycloisomerization of alkynoic acids in the presence of the same chiral phosphoric acid. In this system, ees of up to 95% were obtained.

1.5.2.2 Intramolecular Michael Addition of Nitronates onto Conjugated Esters

Although organocatalytic intramolecular conjugate additions have been reported (see Sect. 1.3.1.3), the Michael acceptor is almost always either a ketone or an aldehyde, since the common mode of activation for these systems is through iminium ion



Scheme 1.33 Dixon's cascade approach to tetracyclic product **137**. HA* – chiral Brønsted acid

catalysis. The use of conjugated esters, on the other hand, was not at all common, which was surprising given their synthetic utility. Cobb and co-workers addressed this through the use of bifunctional organocatalyst **140** in the intramolecular Michael addition of a nitronate onto a conjugated ester *via* a 6-enolexo-exo-trig process (Table 1.2) [44].

In this report, it was shown that only the (*E*)-conjugated ester worked appropriately. This was explained through the use of a computational model which suggested that for the reaction to work, the organocatalyst needed to be co-ordinated to both the nitronate and to the conjugated ester simultaneously – a transition state that could not be achieved with the (*Z*)-ester.

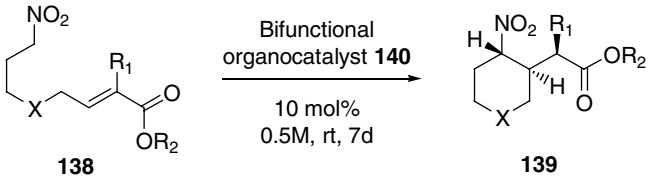
The resulting constructs are precursors to useful γ-amino acids which have wide application in both chemical biology [45] and medicinal chemistry [46].

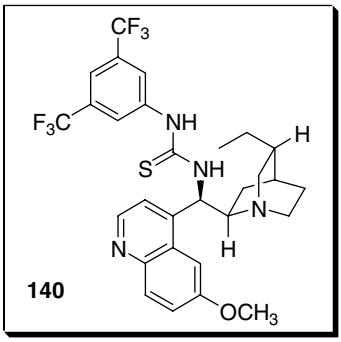
1.5.3 Access via Other Modes of Organocatalysis

1.5.3.1 The Intramolecular Stetter Reaction

The use of *N*-heterocyclic carbene (NHC) as organocatalysts is well-documented [47]. However, it is their ability to render aldehydes as nucleophilic, thus setting up an umpolung reactivity, which is their greatest asset to organocatalysis. This 'nuclephilic

Table 1.2 Organocatalytic intramolecular cyclization of nitronates





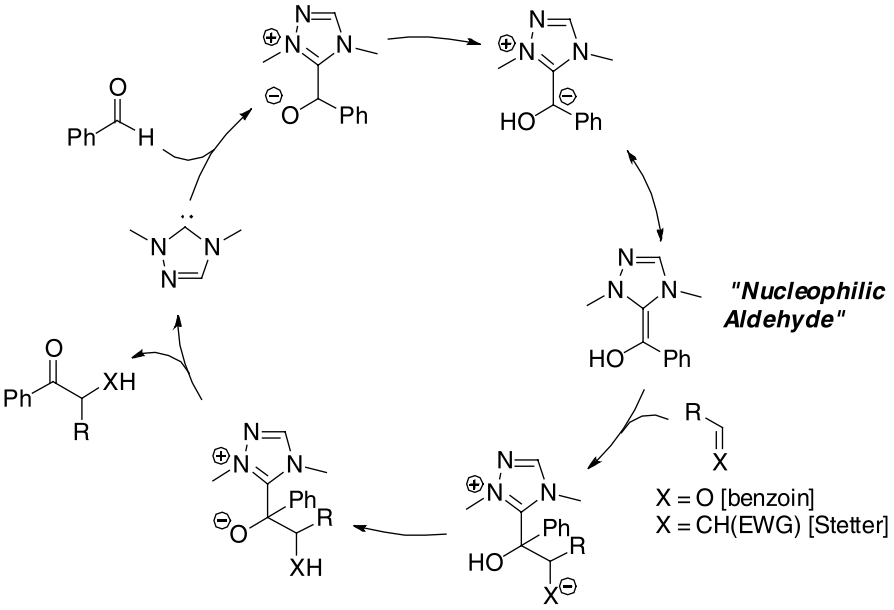
Entry	R_1	R_2	X	Yield(%)	dr	ee (%)
1	H	Me	CH_2	57	4:1	96
2	H	Bn	CH_2	66	4:1	98
3	H	Et	CH_2	87	>19:1	96
4	Me	Et	CH_2	50	>19:6:1	94
5	Bn	Et	CH_2	52	>19:4:1	>99
6	NHCBz	Me	CH_2	65	2:1:<1	95
7	H	Et	O	69	>19:1	92
8	H	Et	$C(CH_3)_2$	76	>19:1	96
9	NHBoc	Me	CH_2	11	3:1:<1	>99

aldehyde' can then be reacted with a further electrophile. If this electrophile is an aldehyde, it is a benzoin reaction. If it is a conjugated system, it is known as a Stetter reaction (Scheme 1.34).

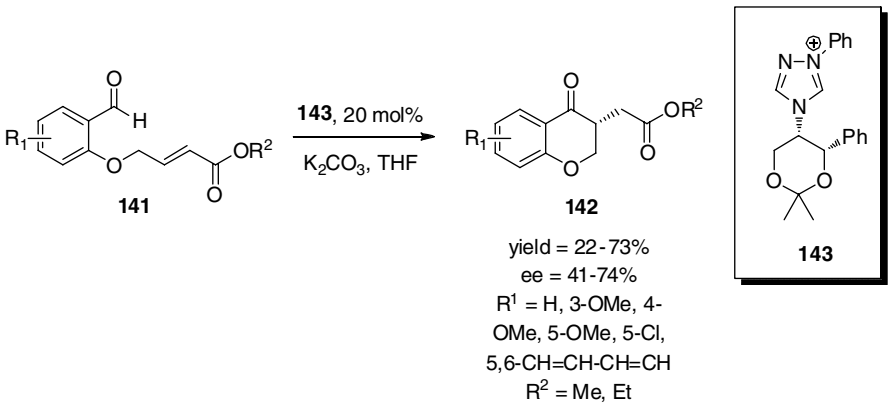
The first asymmetric intramolecular process was described by Enders in 1996, who used triazolium salt **143** in the synthesis of chiral chroman-4-one derivatives. Moderate yields (22–73%) and enantioselectivities of up to 74% were obtained (Scheme 1.35) [48].

A great deal of the development of this reaction came from the labs of Tomislav Rovis who developed a range of novel chiral triazolium salts (Fig. 1.6) for this process [49].

Using 20 mol% of the selected catalyst and 20 mol% of KHMDS (to generate the NHC) in xylene at room temperature, Rovis successfully synthesized a range of cyclic compounds in good yield and excellent enantioselectivity (Table 1.3) including a desymmetrisation step (Entry 4) and the formation of a five-membered ring (Entry 7).



Scheme 1.34 Proposed mechanism of the benzoin and Stetter reactions[49c]



Scheme 1.35 The first asymmetric intramolecular Stetter reaction

Fig. 1.6 Rovis' chiral triazolium salts for intramolecular Stetter reaction

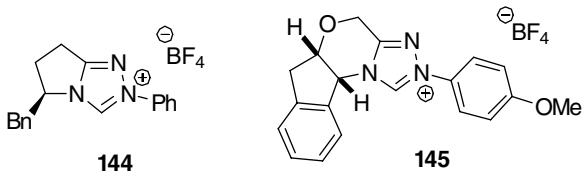
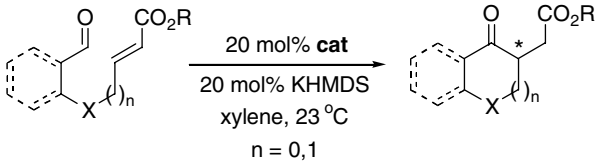
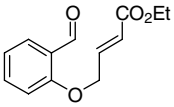
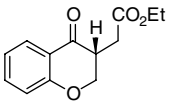
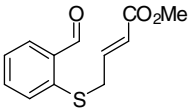
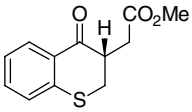
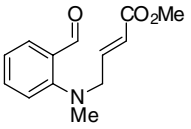
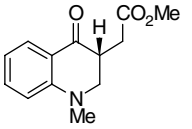
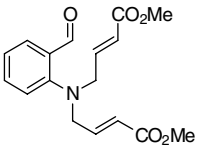
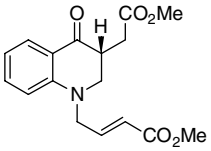
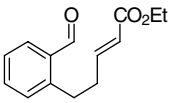
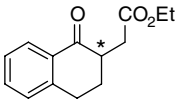
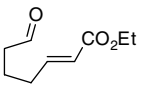
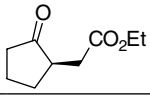


Table 1.3 Intramolecular Stetter reaction



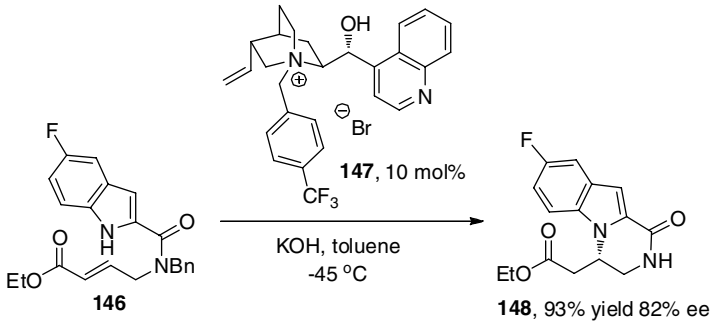
Entry	Substrate	Product	Catalyst	Yield (%)	ee (%)
1			**145**	94	94
2			**145**	63	96
3			**145**	64	82
4			**145**	72	84
5			**145**	35	94 (*S*)
6			**144**	90	92 (*R*)
7			**145**	81	95

Rovis and co-workers have explored this process in depth, varying either the aromatic backbone or the conjugated system, as well as examining the effect of aliphatic aldehydes [50] and even generating substrates with quaternary centres [51].

1.5.3.2 Phase Transfer Catalysts (PTCs)

The benefits of phase transfer catalysts (PTCs) within organic synthesis have been well-documented for some time and it is the mild reaction conditions required, along with their environmental compatibility, and the ability to scale up these processes, which has established PTCs as useful reagents. *Asymmetric* phase transfer catalysts have also found extensive utility, particularly in intermolecular alkylation

processes [52], although the use of phase transfer conditions for *intramolecular* reactions is much less well documented. However, Umani-Ronchi and co-workers utilized phase transfer catalyst **147** in the synthesis of 3,4-dihydropyrazino[1,2-*a*] indol-1-(2*H*)-ones (Scheme 1.36). It is suggested that the excellent chiral induction is due to the tight ion pair associated between the phase transfer cation and the nucleophilic indolate intermediate [53].



Scheme 1.36 Enantioselective phase-transfer-catalyzed intramolecular aza-Michael Reaction

1.6 Organocatalytic Ring Synthesis by Domino Reactions

Domino reactions are processes whereby an initial bond-forming reaction leads to a reactive intermediate which can then undergo a subsequent reaction under the same reaction conditions to form complex molecular architectures. It is therefore an extremely useful and atom-economic way of constructing highly functionalized and enantiomerically pure molecules. There are several ways in which this can be achieved, and for the purposes of this review, they are divided into different classes: Class I, Class II, Class III and Class IV (Figs. 1.7–1.9).

Class I domino reactions (Fig. 1.7) occur when a conjugated system undergoes 1,4-addition to generate an intermediate that has nucleophilic character. This can then undergo attack onto a subsequent electrophile. An application of this approach has already been described in Sect. 1.3 in the synthesis of cyclopropanes, but a large amount of work exists whereby larger ring sizes have been constructed. There are then two ways in which a ring-forming process can occur. Firstly, when the nucleophile that has been generated from the first conjugate addition reacts intramolecularly with an internal electrophile. This electrophile can either be attached to the initial nucleophile (we have deemed this a Class IA domino processes) or it can be attached to the initial Michael acceptor (deemed a Class IB domino processes). Secondly, ring synthesis can occur in a more elaborate cascade process involving a third molecule (Class IC domino processes) whereby the nucleophile generated from the first conjugate addition reacts with another conjugated system. This then unmasks a second nucleophile which can reacted intramolecularly with an internal electrophile to generate highly functionalized six-membered rings.

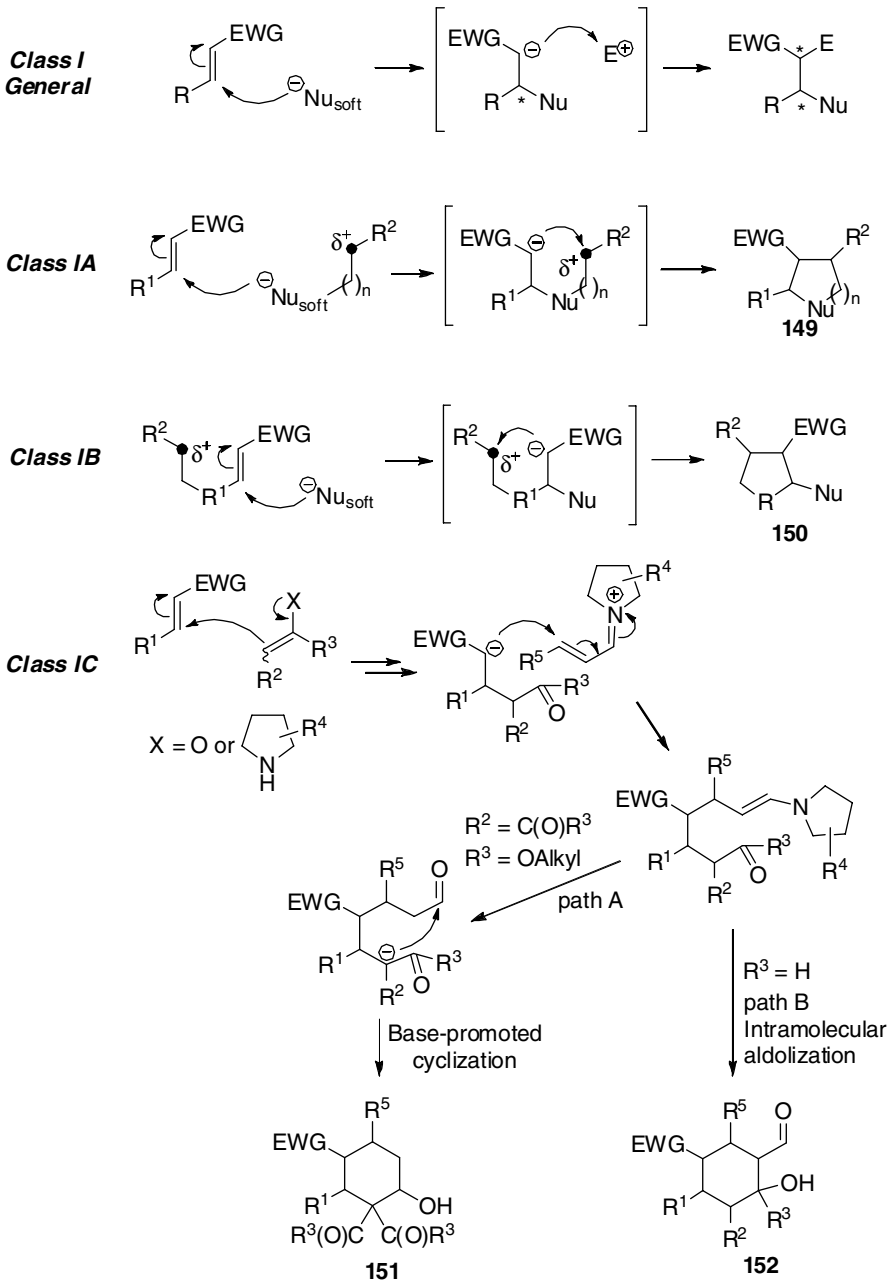


Fig. 1.7 Depiction of Class I organocatalytic domino processes. Cyclization events occur when the electrophile for the second step is attached to either the initial Michael acceptor (Class IA) or on the initial nucleophile (Class IB). It is also possible for a third component to be involved (Class IC)

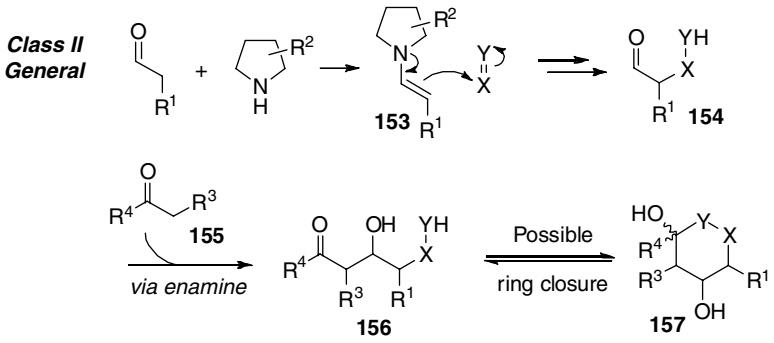


Fig. 1.8 Depiction of Class II organocatalytic domino processes. Cyclization events (Class IIA) occur when the intial heteroatom (Y) intramolecularly attacks the final aldehyde

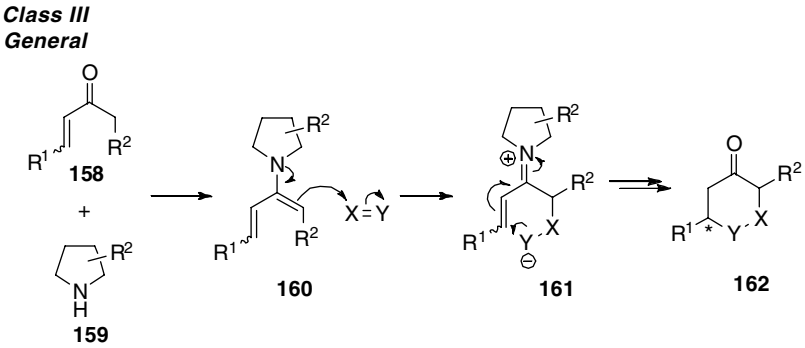


Fig. 1.9 Depiction of Class III organocatalytic domino processes. The cyclization event always occurs wherein the generated nucleophile Y⁻ attacks the initial conjugated system

Class II domino reactions (Fig. 1.8) can occur when an enolizable aldehyde forms an enamine **153** with a secondary amine and reacts with either itself or a second electrophile (X = Y) to generate an intermediate aldehyde **154**. This is also electrophilic in nature and can undergo reaction with a second enamine to generate a new aldehyde **156**. Cyclization occurs when the intial heteroatom (Y in Fig. 1.8) attacks the final aldehyde intramolecularly which is of course reversible.

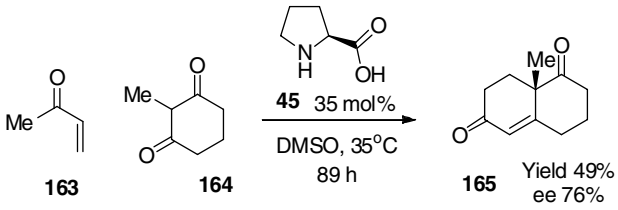
Class III domino reactions (Fig. 1.9) are always intramolecular in nature and occur when an enolizable, but conjugated system **158**, is converted to the corresponding enamine and undergoes nucleophilic attack into an X = Y type system. The resulting anion (Y⁻) in **161** then partakes in an intramolecular 1,4-addition onto the initial conjugated system. They are therefore closely related to Class IA processes, except that the initial nucleophile attacks a 1,2-species (**160**), as opposed to a 1,4-species.

Class IV domino reactions processes are reserved for reactions which do not fall clearly into any of these first three categories, although they are often a combination or an extension of one or more of these.

There are many reported organocatalytic domino processes and as such it is not the intention of this section to give a thorough review of the area, but rather to highlight examples of each of the above classes using selected examples.

1.6.1 Class I Processes

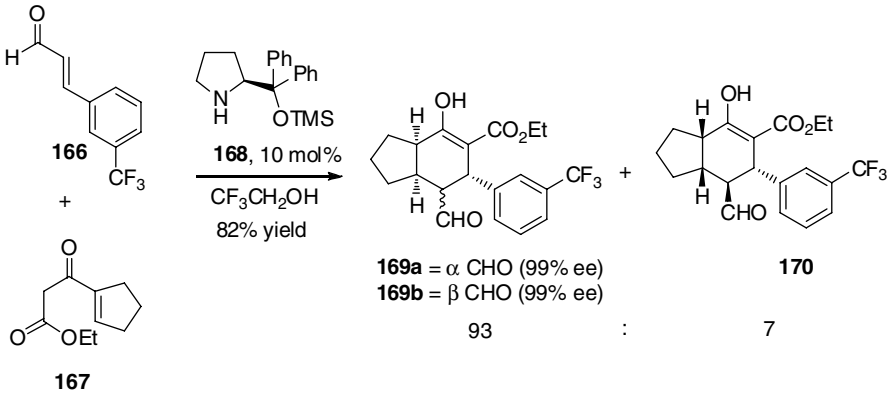
This is by far the largest class of organocatalytic domino processes and leads to a great diversity of highly functionalized and complex molecules. In terms of Class I processes that lead to cyclization, Class IA are the most populous. For example, Barbas and Bui described a Robinson annulation for the synthesis of the Wieland-Miescher ketone discussed in Sect. 1.5.1.1 using L-proline **45** (Scheme 1.37) [54].



Scheme 1.37 Barbas' Robinson Annulation

In this process, the 1,3-diketone acts as the initial nucleophile and then acts as an electrophile *via* one of its ketones in the final intramolecular aldol cyclization.

Brenner and McGarraugh designed a Class IA system whereby the nucleophile **167** is also a 1,3-dicarbonyl system, but is conjugated to a double bond through one of the carbonyls giving a 1,4-system. As with the List system, the 1,3-dicarbonyl adds in to a conjugated iminium species and the resulting enamine attacks the electrophilic system on the initial nucleophile – in the case of the List system the electrophile was a carbonyl leading to 1,2-reactivity; in this system it is a conjugated system leading to 1,4-reactivity (Scheme 1.38) [55].

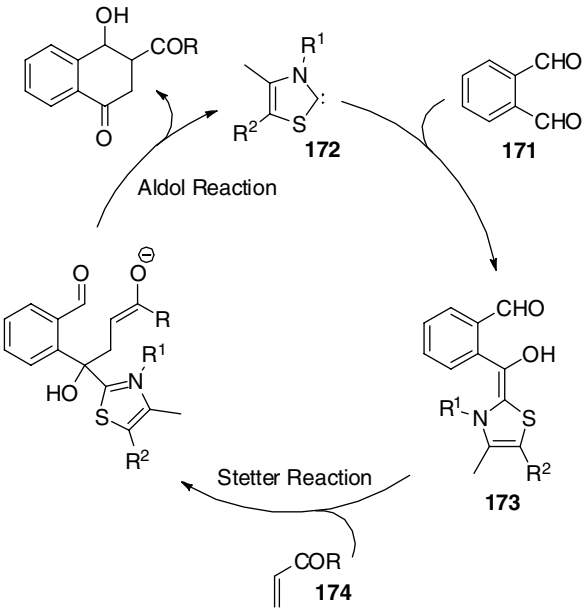


Scheme 1.38 Class IA Michael-Michael cyclization

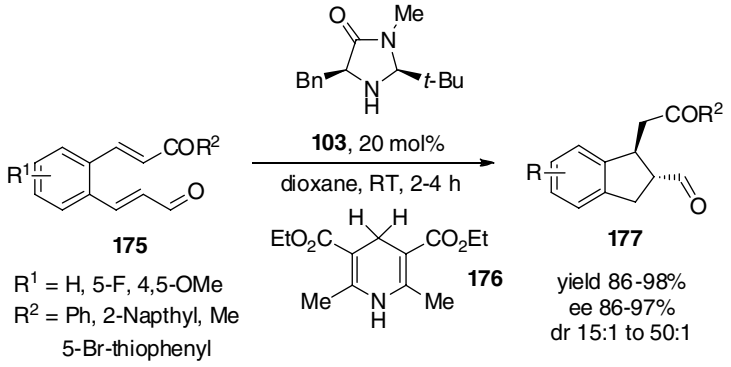
Another interesting process which falls within this category is a cascade Stetter-reaction Aldol process developed by Ye and co-workers [56]. In this reaction, phthalaldehyde **171** was reacted with an achiral *N*-heterocyclic carbene (NHC) **172**.

The resulting 'nucleophilic aldehyde' **173** then reacts with an enone **174** whereupon the resulting enolate participates in an intramolecular aldol reaction. Ye and co-workers propose a plausible catalytic cycle for this process (Scheme 1.39). Unfortunately, their attempts at utilizing chiral NHCs were not successful in this report.

Scheme 1.39 Domino Stetter-Aldol Reaction of Type IA reactivity



List and co-workers demonstrated a Class IB process using enal-enone systems with a hydrogen nucleophile (Hantzsch ester **176**) to give functionalized ring systems (Scheme 1.40) [57].

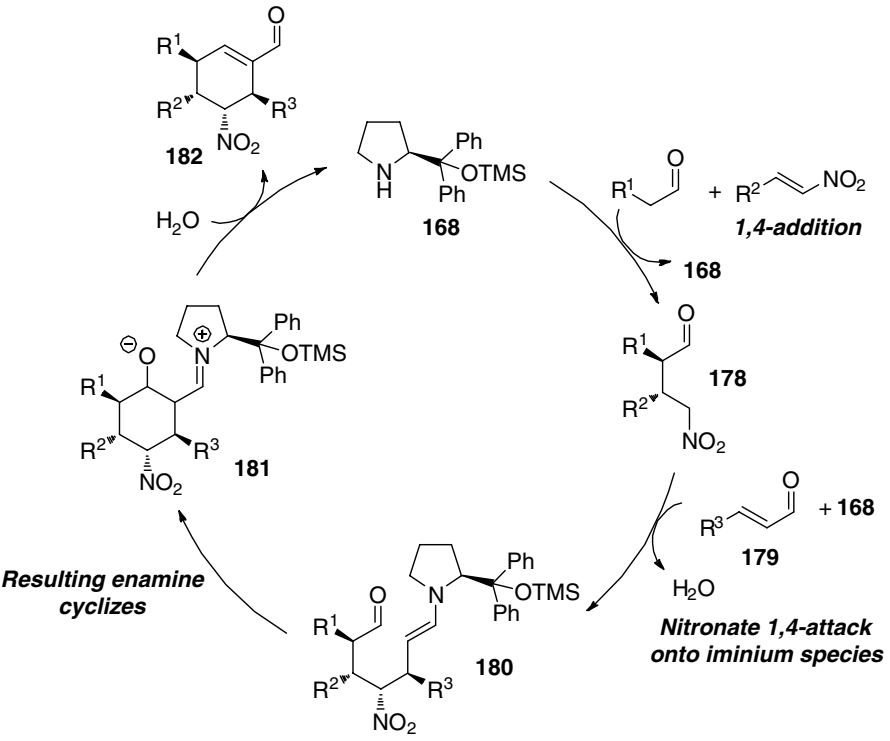


Scheme 1.40 Asymmetric organocatalytic reductive Michael cyclization

In this case the second electrophilic species is on the initial electrophile itself. This then required the two electrophiles within the same molecule **175** to have very

different reactivities, and this was achieved through the use of a conjugated ester vs a conjugated enal. Only the latter can form the conjugated iminium species with the secondary amine whereupon its LUMO is sufficiently lowered (beyond that of the conjugated ester and of course the enal itself) to react with the hydrogen nucleophile. This then generates the intermediate enamine required for the second cyclization onto the conjugated ester, thus generating the highly substituted cyclopentane system **177**.

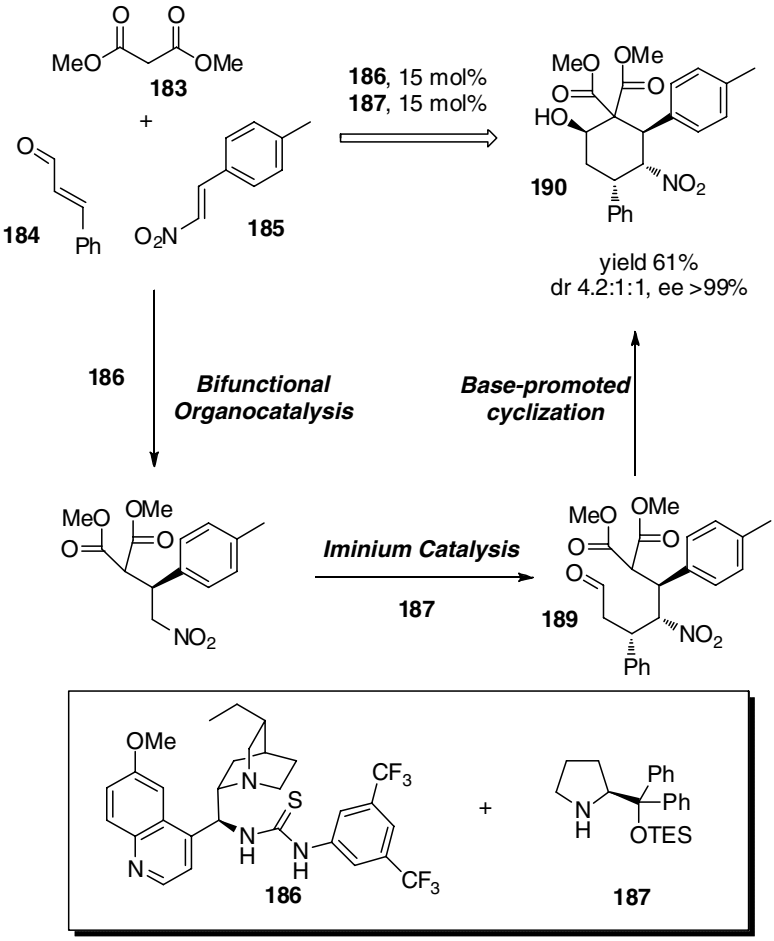
An excellent example of the more complex Class IC systems described, whereby a third molecule is involved in the cascade, came from the group of Enders. They described a secondary amine catalyzed system where initially an enamine attacks a nitroolefin *via* 1,4-conjugate addition. In the same way that iminium ions can undergo conjugate 1,4-addition and then act as a nucleophile *via* the resulting enamine, so too can the nitro-olefin form the equivalent nit**r**onate intermediate that has subsequent reactivity. In this example, it goes on to react in another 1,4-reaction with a third species which is an iminium ion, formed from the condensation of an enal **179** with the catalytic secondary amine **168**. As before this conjugate addition generates a further enamine **180** which can cyclize onto the original aldehyde (Scheme 1.41).



Scheme 1.41 Proposed catalytic cycle for Enders' Class IC process

By this method, a wide range of highly functionalized nitrocyclohexanes were reported in isolated yields of up to 58% and ees of up to >99% [58].

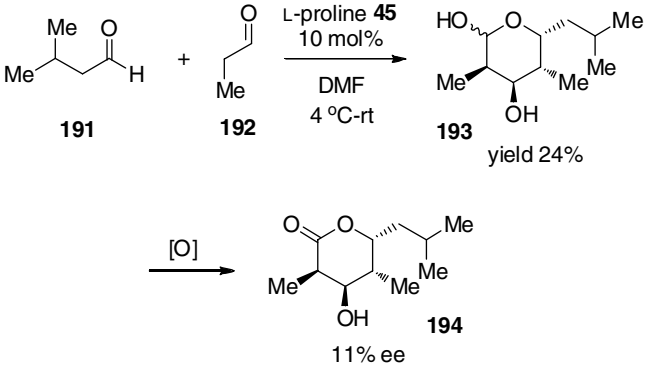
Xu and Dixon and co-workers also described a trimolecular cascade process, also involving a nitro-olefin. In this case, however, the nucleophile was a 1,3-dicarbonyl compound **183** whose 1,4-addition into the nitro-olefin **185** was facilitated by bifunctional thiourea catalyst **186**. However, a secondary amine **187** was still utilized to allow for the subsequent addition of the resulting nitronate **188** into the conjugated iminium as described for the Enders process above. The major difference however, is that instead of a final enamine promoted cyclization, the regenerated 1,3-dicarbonyl species acts as the nucleophile to promote ring closure (Scheme 1.42) [59].



Scheme 1.42 A bi-organocatalytic cascade reaction

1.6.2 Class II Processes

An example of a Type II process where a cyclic product is generated, came from the group of Barbas, who showed the self-aldolization of acetaldehyde to give (+)-5-hydroxy-(2*E*)-hexenal in 90% ee [60]. The trimerization of simple aldehydes **192** to carbohydrates and polyketides was then described (Scheme 1.43) [61]. Although the ees and yields were low, this was one of the first examples of carbohydrate synthesis using an organocatalytic cascade process.



Scheme 1.43 A first example of carbohydrate synthesis using cascade organocatalysis

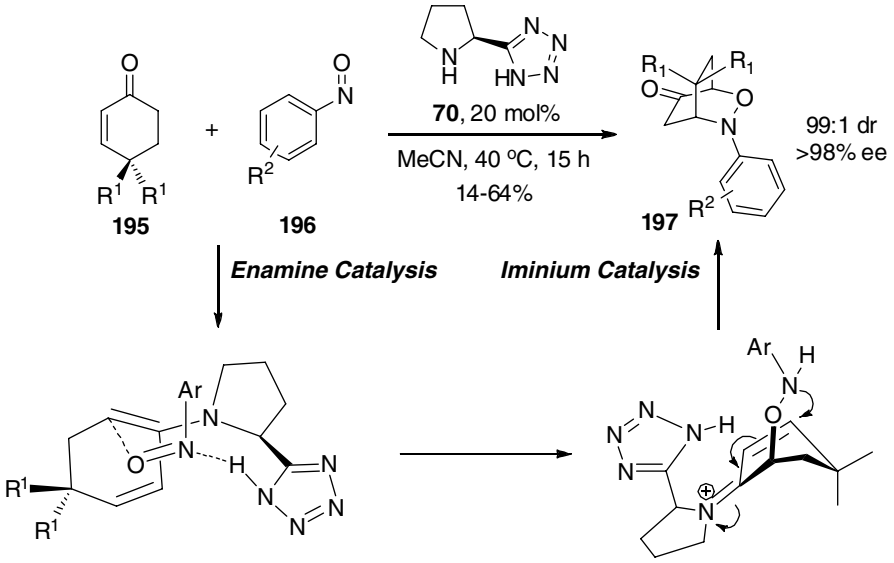
1.6.3 Class III Processes

Yamamoto and co-workers developed a Class III process, whereby tetrazole catalyst **70** was utilized in an α-amino-hydroxylation. The resulting nitrogen anion then undergoes 1,4-addition to generate bicyclic species **197** (Scheme 1.44) [62], which although formally a [4+2] product gives the opposite regiochemistry to normal nitroso-Diels-Alder reaction (Fig. 1.10).

1.6.4 Class IV Processes

Class IV processes are those which do not clearly fall into the first three categories. An example of this is the MacMillan synthesis of (−)-flustramine B **198** where an indole reacts asymmetrically with a conjugated iminium species and an appending and already present side chain cyclizes onto the resulting C=N bond (Scheme 1.45) [63].

Finally, Gong and co-workers developed a Brønsted acid **203** catalyzed Hantzsch reaction where by an enal forms an iminium ion with an aromatic amine. This enal



Scheme 1.44 A Type III domino process generating bicyclic adducts

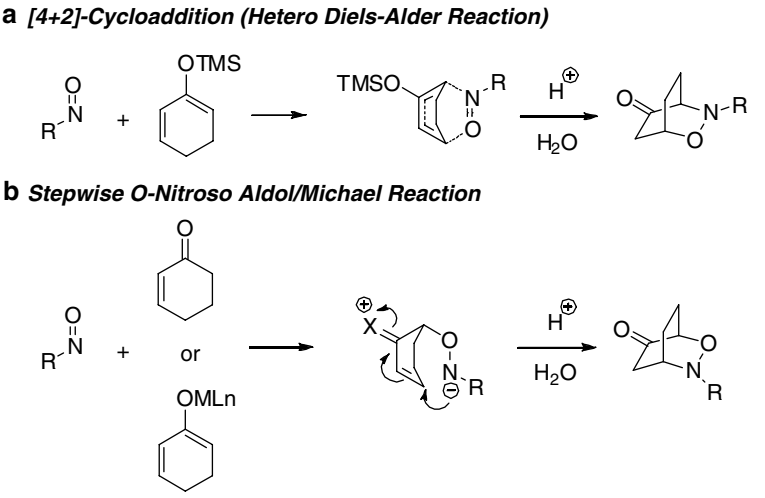
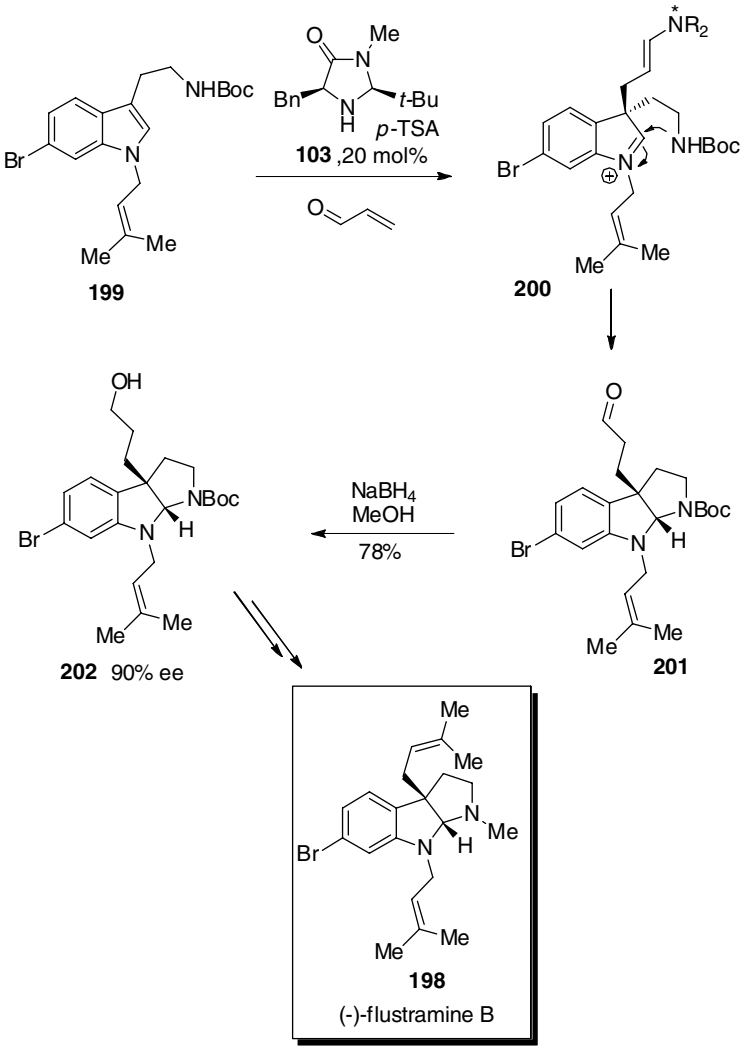
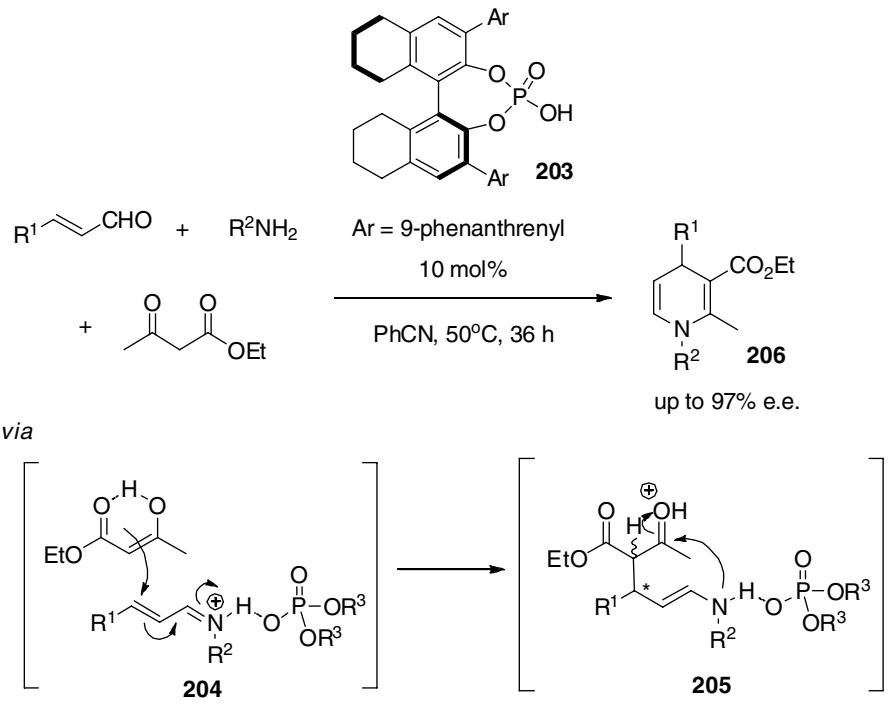


Fig. 1.10 Comparative regioselectivity of a cycloaddition and a stepwise organocatalytic Type III domino process



Scheme 1.45 An example of a Class IV process where an intermolecular organocatalytic reaction generates an intermediate allowing an already appended functionality to react intramolecularly

co-ordinates to the catalyst, thereby not only activating it to nucleophilic attack by a 1,3-dicarbonyl compound, but also setting up a chiral environment. Once this occurs the nitrogen of the enamine cyclizes onto the carbonyl of the original malonate and eliminates water to give the 1,4-dihydropyridine (Scheme 1.46). It is therefore very similar to the class IA process described herein, but instead of an enamine promoted cyclization, it is the nitrogen which forms the final ring [64].



Scheme 1.46 Organocatalytic synthesis of Hantzsch-esters. Similar to a Class IA process, but cyclization is *via* the nitrogen instead of the enamine

1.7 Conclusions

Organocatalysis has proven to be an extremely useful tool in the synthesis of enantiopure, highly functionalized cyclic compounds. Although secondary amine catalysis has laid the foundations of this field, other methods and approaches are coming to the fore and proving to be invaluable in ring synthesis. In particular Domino reactions will undoubtedly continue to be developed whereby increasing multi-componency will lead to evermore elaborate and useful constructs.

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Chapter 2
Organocatalyzed Conjugate Additions

Diego A. Alonso*

Abstract In this chapter, the asymmetric organocatalytic conjugate addition of nucleophiles to Michael acceptors is covered. This report presents an overview of the most important developments and concepts of this area of catalysis organized by the type of nucleophile involved in the process.

2.1 Introduction

Asymmetric organocatalysis has become a very attractive methodology in recent years since employs small chiral organic molecules, to catalyze asymmetric reactions with high enantioselectivity and broad substrate scope [1]. The conjugate addition of nucleophiles to electron-deficient alkenes is one of the most frequently used C-C and C-heteroatom bond forming reactions in organic synthesis [2]. Over the past few years, catalytic asymmetric conjugate additions [3] employing chiral catalysts have suffered a significant development as evident by the large number of publications appeared in the field (Fig. 2.1). This tendency is even more spectacular when we take a look at the large number of studies that have been carried out in a very short period of time, about asymmetric conjugate additions promoted by chiral organocatalysts (Fig. 2.1) [4]. The most studied organocatalyzed 1,4-additions have been those involving carbon nucleophiles, although hydride and various heteronucleophiles such as nitrogen-, oxygen-, phosphorous-, and sulfur containing species have been used with success. With respect to the solvent, polar non-protic solvents

* Dedicated to Professor Carmen Nájera on Occasion of her 60th Birthday

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R. Mahrwald (ed.), *Enantioselective Organocatalyzed Reactions II: Asymmetric C-C Bond Formation Processes*, DOI 10.1007/978-90-481-3867-8_2,

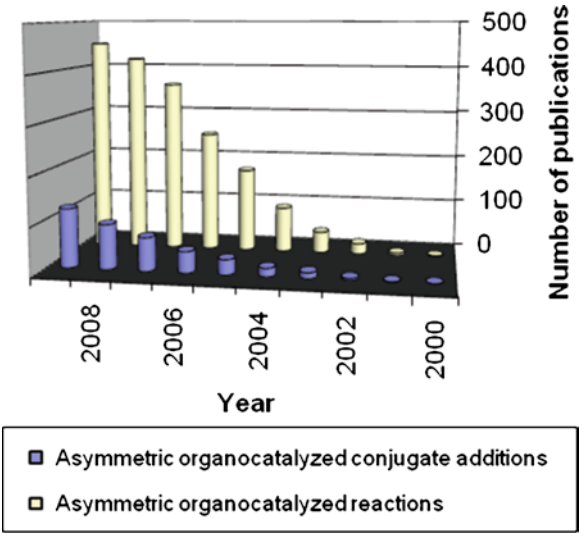


Fig. 2.1 Publications for asymmetric organocatalytic conjugate additions and organocatalytic reactions during the period 2000–2009. Source: Scifinder

are the most employed, though excellent results in terms of activity and selectivity have been also reported using water or under aqueous conditions [5]. The use of water constitutes an environmentally benign solvent and in some cases also helps to improve the reactivity and stereoselectivity of organocatalytic reactions.

With respect to the catalysts employed in conjugate additions, a big collection of efficient stable and environmentally friendly natural or newly designed chiral organocatalysts has already been developed. These catalysts are usually cheap to prepare and readily accessible in a range of quantities. They fall into four major classes: Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids [1f]. The identification of the generic modes of activation of these catalysts has been crucial to the success of organocatalysis.

Regarding conjugate additions, the organocatalysts provide chiral environment to the process activating the nucleophile, the electrophile or both reagents (bifunctional organocatalysts) through weak interactions such as ion pairing [6] or hydrogen bonding [7], or by stronger interactions such as covalent bonding. Electrophile activation by small-molecule chiral hydrogen bond donors has emerged as an important tool in enantioselective catalysis [7]. Hydrogen bonding to the conjugate acceptor decreases its electron density thus activating it towards nucleophilic attack (A, Fig. 2.2). Chiral ureas, thioureas [7e], guanidinines [7g, j], amidines, diols, hydroxy acids, phosphoric acids [7c], and amides [7h] are among the most successfully used chiral hydrogen bond donors in conjugate additions.

Chiral ion pairs (B, Fig. 2.2) can be formed by deprotonation of the pronucleophile with a chiral Brønsted base or employing an achiral base and a chiral phase-transfer catalyst. Chiral phase-transfer catalysis (PTC) [8] illustrates how ion pairing interactions can be used to carry out the enantioface discrimination in conjugate addition reactions. In both cases, the chiral cation is responsible for

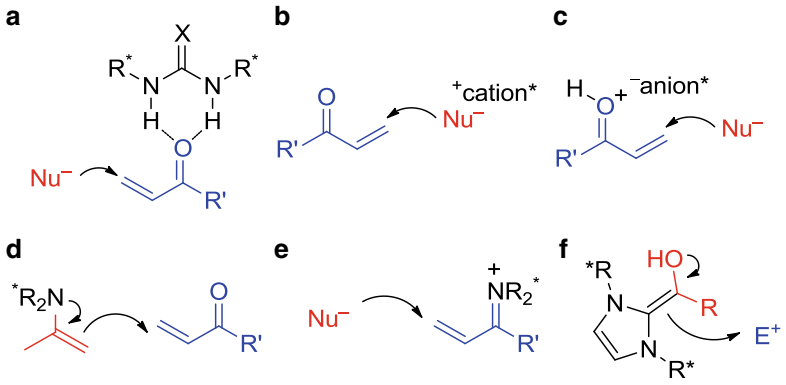


Fig. 2.2 Organocatalytic activations in conjugate addition reactions

the enantioselectivity of the addition and chiral *Cinchona* alkaloid derivatives have been widely used as Brønsted bases or phase transfer catalysts [9]. A chiral ion pair can be also formed as a result of a protonation of the electrophile, for instance, a carbonyl compound, by a chiral Brønsted acid catalyst (C, Fig. 2.2) [10]. In this approach, the chiral anion controls the selectivity of the process.

With respect to the covalent activation in conjugate additions, the catalyst, usually a primary or a secondary amine, can reversibly form a chiral enamine [11] to activate the nucleophile (D, Fig. 2.2) or a chiral iminium ion [12] to activate the acceptor (E, Fig. 2.2). The detection of enamine intermediates in asymmetric organocatalysis has been for a long time the missing piece of evidence for the commonly accepted mechanism of enamine catalysis. This gap has been recently solved with the first detection and structural characterization of enamine intermediates in proline-catalyzed aldol reactions by real-time NMR spectroscopy [13] and the direct observation of an enamine intermediate in the crystal structure of an aldolase antibody [14].

Another important class of covalent catalysis is carried out by chiral *N*-heterocyclic carbenes [15] that react with carbonyl compounds forming chiral acyl anion equivalents whose reaction with the corresponding electrophile complete the catalytic cycle (F, Fig. 2.2). Finally, it is worthy to mention the ability of certain bifunctional organocatalysts to perform simultaneous activation of the nucleophile and the electrophile. The use of bifunctional organocatalysis has been shown to be very successful in conjugate additions.

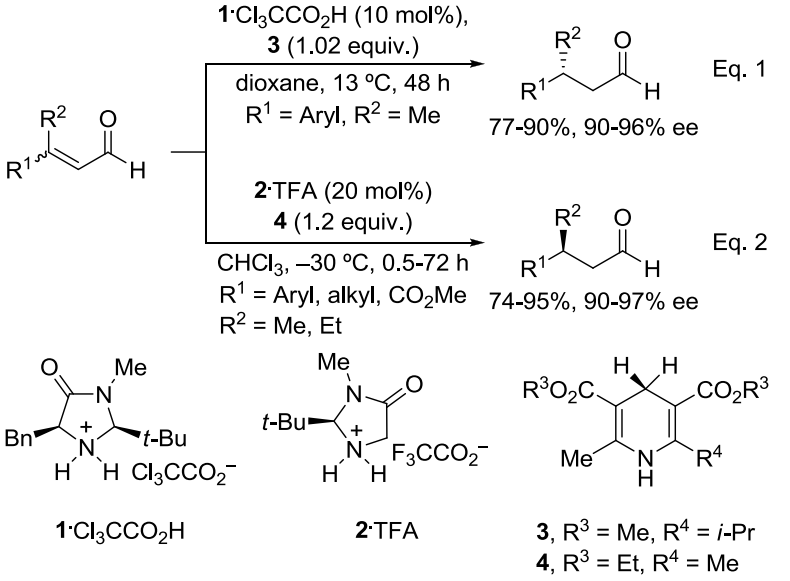
During the last few years, the interest in the field of asymmetric organocatalytic conjugate additions has increased spectacularly with many different new catalysts and reaction partners showing impressive results in terms of efficiency and selectivity. This chapter pretends to provide an overview of this exciting and rapidly growing field emphasizing the structural and mechanistic features that contribute to such results. The chapter is organized according to the type of nucleophile involved in the 1,4-addition providing special emphasis on the activation mode of the catalyst. Representative examples of recent applications of organocatalytic conjugate additions in the synthesis of natural products and biologically active compounds are also

provided when suitable. α-Heteroatom functionalization reactions triggered or involving conjugate addition-type processes such as, epoxidation and aziridination of electron-poor olefins, α-aminations with azodicarboxylates, and Morita-Baylis-Hillman reactions are not covered.

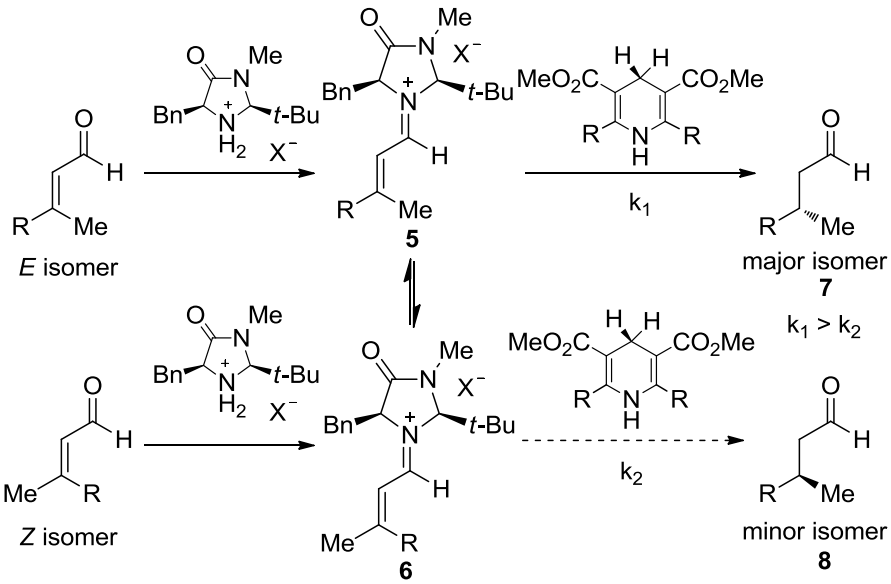
2.2 Organocatalytic Asymmetric Transfer Hydrogenation

Since a comprehensive discussion of the organocatalyzed asymmetric transfer hydrogenation reaction is presented in Chapter of Tommaso Marcelli, the asymmetric conjugate reduction will be discussed briefly here. The enantio- and chemoselective conjugate reduction of α,β-unsaturated carbonyl compounds has been usually linked to the use of chiral metal catalysts. However, recent studies have demonstrated that the organocatalytic transfer hydrogenation of carbonyl compounds and imine derivatives 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 [16]. This methodology has been successfully applied to the conjugate reduction of a wide variety of functionalized Michael acceptors such as enals, enones, nitroolefins, quinolines, and alkynyl imino esters. Regarding modes of activation, this conjugate reduction has been carried out using iminium catalysis with chiral imidazolidinone and prolinol derivatives as catalysts, as well as hydrogen-bonding catalysis using chiral BINOL-based phosphoric acids. Initial studies by the groups of List [17] and MacMillan [18] have shown a highly enantioselective conjugate reduction of α,β-disubstituted α,β-unsaturated aldehydes employing imidazolidinone derivatives 1 and 2, respectively (Scheme 2.1). Catalyst 2 seems to be more general than catalyst 1 in terms of substrate scope since under optimized conditions a wide variety of trisubstituted α,β-unsaturated aldehydes are reduced in high yields (74–95%) and enantioselectivities (up to 97% ee) [18], though using higher catalyst loadings (Scheme 2.1, Eq. 2). Interestingly, the reaction conditions are compatible with functional groups that are often susceptible to reduction such as aldehydes and aromatic halogens [18]. Furthermore, it has been observed a strong solvent and counteranion effect on the yield and enantioselectivity of the reaction, being the trichloroacetic and trifluoroacetic salts of the oxazolidinone derivatives the most active catalysts. This methodology has been very recently applied to the reduction of β-azole containing α,β-unsaturated aldehydes [19]. These derivatives have been hydrogenated in good yields and up to 94% optical purity employing catalysts **1**·TFA or **2**·TFA (20 mol%) in the presence of 1.2 equivalents of Hantzsch ester **4** (R3 = *t*–Bu) in $CHCl_3$ or toluene as solvent, a simple process which has allowed the asymmetric synthesis of the C7–C14 fragment of ulapualide A, a natural product which exhibits promising antitumor activity.

Concerning reaction mechanism, the enantioconvergent character of the reduction makes unnecessary to work with geometrically pure enals (Scheme 2.1). This is due to the rapid interconversion of the two initially formed iminium ions **5** and **6** prior to the rate determining hydride attack from the dihydropyridine (Scheme 2.2).



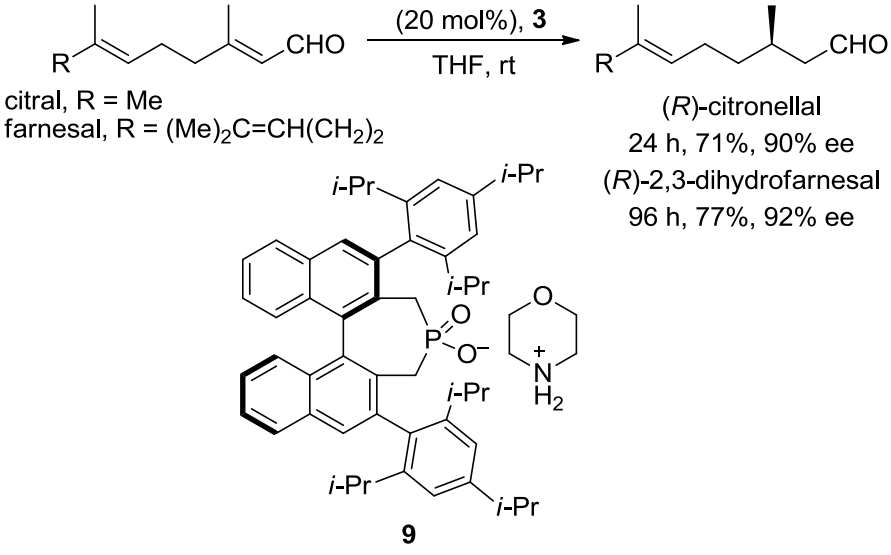
Scheme 2.1 Enantioselective organocatalytic hydride conjugate reduction



Scheme 2.2 Proposed mechanism for the enantioselective organocatalytic hydride conjugate reduction of enals

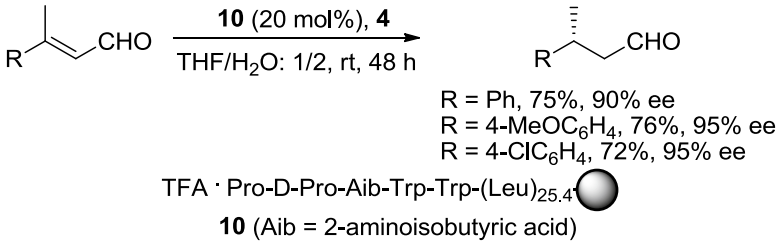
Then, the hydride ion is selectively transferred to the *E*-olefin from the least sterically hindered face to produce the corresponding isomer of the product. Furthermore, although a kinetic preference for the (*Z*)-iminium ion formation has been demonstrated, the (*E*)-iminium ion intermediates, which dominate the equilibrium ratio, react with nucleophiles faster than the (*Z*)-isomers when diarylprolinol and imidazolinone-based chiral catalysts are employed in conjugate additions to α,β-unsaturated aldehydes [20].

On the other hand, non-sterically hindered enals have been reduced with high stereoselectivities employing catalytic amounts (20 mol%) of the salt composed by the achiral ammonium ion of morpholine and the chiral sterically hindered phosphoric acid 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphtyl-2,2′-diyl hydrogen phosphate (**9**) [21]. This asymmetric counteranion–directed hydrogenation is also preceded by a rapid *E*/*Z* enal equilibration, and has shown good yields and high enantioselectivities in THF for the reduction of β-methyl substituted cinnamaldehydes (96–99% ee) and other interesting aliphatic substrates with industrial applications such as citral and farnesal (Scheme 2.3). The asymmetric induction of the process is presumed to occur in the cationic transition state of the process through hydrogen bonding interactions involving the chiral phosphate counteranion.



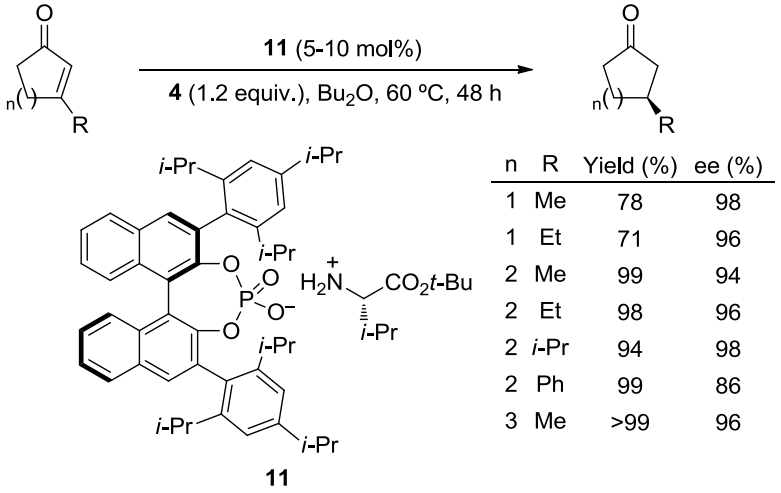
Scheme 2.3 Asymmetric counteranion directed conjugate reduction of enals citral and citronellal

β-Methyl substituted cinnamaldehydes have been reduced under aqueous media employing a resin-supported *N*-terminal prolyl peptide having a β-turn motif and a hydrophobic polyleucine chain [22]. The reaction, which is performed in a mixture of THF and water (1/2) at rt, allows the preparation of chiral aldehydes with high enantioselectivities (93–96%) employing a 20 mol% of catalyst **10** and 1.2 equivalents of ester **4** in aqueous media at rt (Scheme 2.4).



Scheme 2.4 Asymmetric transfer hydrogenation in aqueous media

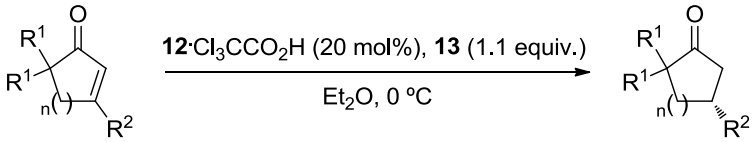
The asymmetric counteranion directed organocatalysis has been also applied to the enantioselective transfer hydrogenation of α,β-unsaturated ketones employing catalyst **11**, which involves a chiral cation such as a valine ester ammonium salt and a chiral binaphthol derived phosphate [23]. This combination, in the presence of the Hantzsch ester **4**, is a very active and enantioselective system for the transfer hydrogenation of a variety of cyclic α,β-unsaturated ketones (Scheme 2.5). Acyclic ketones are also reduced but with slightly lower enantioselectivities.



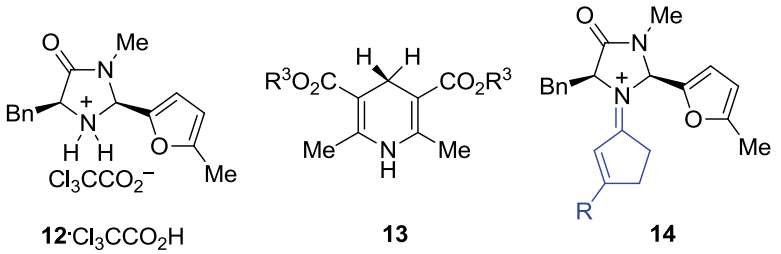
n	R	Yield (%)	ee (%)
1	Me	78	98
1	Et	71	96
2	Me	99	94
2	Et	98	96
2	*i*-Pr	94	98
2	Ph	99	86
3	Me	>99	96

Scheme 2.5 Enantioselective transfer hydrogenation of cyclic enones catalyzed by **11**

The organocatalytic transfer hydrogenation of cyclic enones has been also successfully achieved employing the imidazolidinone **12** [24], catalyst that also promotes enantioselective Diels-Alder reactions with cyclic enones [25]. The structure of the dihydropyridine reagent seems to have an important effect on the selectivity of the process since better enantioselectivities are observed when increasing the steric hindrance of the ester moiety **13** (Scheme 2.6). The reduction, which is performed with substoichiometric amounts of imidazolidinone **12** in ether at 0°C,



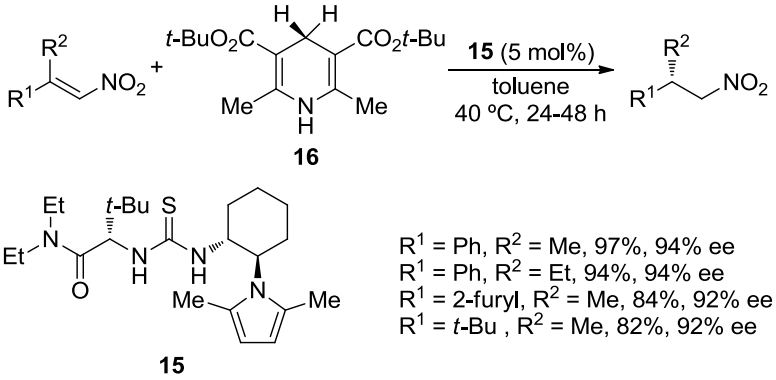
n	R^1	R^2	R^3	Time (h)	Yield (%)	ee (%)
1	H	Ph	Et	3	96	74
1	H	Ph	*i*-Pr	3	78	78
1	H	Ph	*t*-Bu	6	86	91
1	H	OBn	*t*-Bu	13	89	91
1	H	CO_2Me	*t*-Bu	1	83	90
2	H	*n*-Bu	*t*-Bu	25	82	90
3	H	*n*-Bu	*t*-Bu	9	70	92
2	Me	Me	*t*-Bu	40	66	98



Scheme 2.6 Transfer hydrogenation of cyclic enones catalyzed by **12**

allows a rapid access to a wide variety of enantioenriched cycloalkenones in high yields (66–85%) and enantioselectivities up to 98% ee. The sense of asymmetric induction observed in all cases has been initially explained by the condensation of the enone with catalyst **12** to predominantly form in the equilibrium the (*E*)-iminium ion intermediate **14** and a subsequent hydride attack by the Hantzsch ester from the less hindered *si* face. This assumption has been recently corroborated using DFT calculations which have determined the preference for the *E* iminium transition state, due to the inherently higher stability of the *E* iminium salt, and that the steric effects dominate the mode of hydride attack [20, 26].

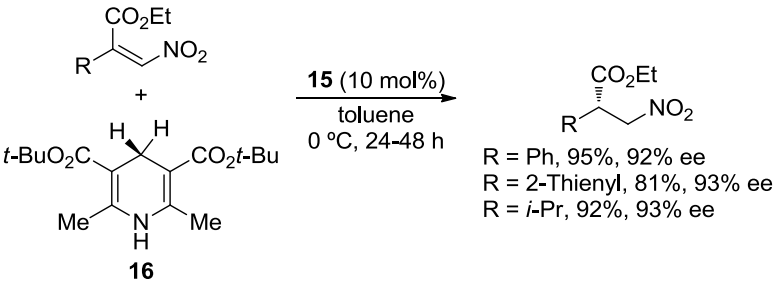
With respect to the conjugate reduction of other types of electrophiles, List et al. have reported a very efficient organocatalytic asymmetric transfer hydrogenation of nitroolefins [27] and β-nitroacrylates [28] employing Jacobsen-type thiourea **15**, which involves a hydrogen-bonding general acid type catalysis through interactions between the nitro group and the thiourea moiety. As depicted in Scheme 2.7 for the reduction of nitroolefins [27], the reaction has a broad substrate scope and gives products with high yields and enantioselectivities with a



Scheme 2.7 Transfer hydrogenation of nitroolefins catalyzed by **15**

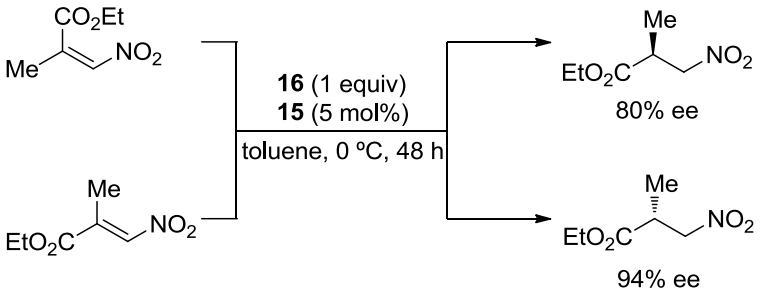
number of β-alkyl-substituted nitrostyrenes and aliphatic nitroalkenes. Remarkably, the enantioselectivity is strongly dependent on the olefin geometry.

The synthesis of β-amino acids has attracted considerable attention due to the potentially biological and medicinal applications of β-peptides. Catalyst **15** (10 mol%) allows the preparation of optically active β-nitroesters, which are easily transformed in β-amino acids by reduction with H_2, by asymmetric transfer hydrogenation of β-nitroacrylates under very similar reaction conditions to those employed for the reduction of trisubstituted nitroolefins [29]. The reaction is fairly general and works well with a wide variety of substrates as depicted in Scheme 2.8 for selected examples. Interestingly, the enantioselectivity of the reduction strongly depends on the olefin geometry, and both enantiomers of the β-nitro ester are accessible simply by reducing the corresponding (*E*) or (*Z*) nitroolefins (Scheme 2.9).



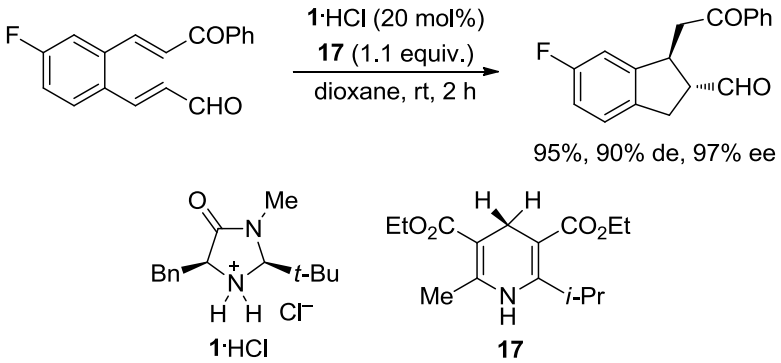
Scheme 2.8 Organocatalyzed synthesis of chiral β-amino acids

Some interesting organocatalyzed asymmetric double conjugate additions have been recently reported. For instance, the hydrochloride salt of chiral imidazolidinone



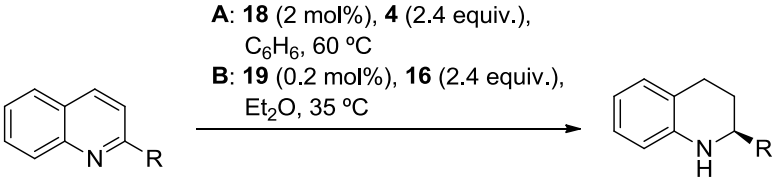
Scheme 2.9 Effect of olefin geometry on the organocatalyzed conjugate reduction of β-nitroacrylates

1 (20 mol%) has been shown to be a highly chemo-, regio-, diastereo-, and enantioselective organocatalyst for the reductive Michael cyclization of formyl enones [30]. This reaction, which has combined for the first time iminium and enamine catalysis, proceeds via an iminium catalytic conjugate reduction of the enal moiety, employing Hantzsch ester **17**, followed by an in situ enamine-catalyzed asymmetric Michael cyclization (Scheme 2.10).



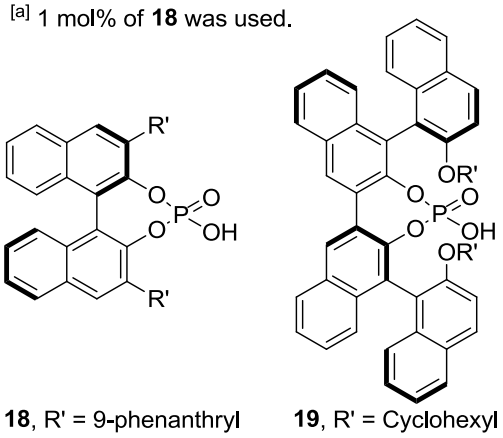
Scheme 2.10 Organocatalytic asymmetric reductive Michael cyclization

Chiral phosphoric acids are powerful organocatalysts successfully employed in a wide variety of asymmetric transformations [31]. Regarding the asymmetric conjugate reduction, a highly enantioselective Brønsted acid-catalyzed transfer hydrogenation of quinolines has been carried out using BINOL-derived chiral phosphoric acids as catalysts to afford chiral tetrahydroquinolines [32]. As depicted in Scheme 2.11, high yields and enantioselectivities are obtained employing catalysts **15** [32a] and **19** [32b] with different 2-substituted quinolines, though lower catalyst loadings and higher enantioselectivities are usually observed for 2-alkyl-substituted substrates when catalyst **19** is used (Scheme 2.11). Furthermore, catalyst **19** is also very effective for the reduction of 2,3-disubstituted quinolines with excellent diastereoselectivities and high enantioselectivities (up to 92% ee).



R	Conditions	Yield (%)	ee (%)
Ph	**A**	92	97
Ph	**B**	>99	96
2-naphthyl	**A**	93	>99
2-naphthyl	**B**	>99	97
n-Bu	**A**	91	87
n-Bu	**B**	>99[a]	94
2-phenylethyl	**A**	90	90
2-phenylethyl	**B**	>99[a]	93

[a] 1 mol% of **18** was used.



18, R' = 9-phenanthryl **19**, R' = Cyclohexyl

Scheme 2.11 Asymmetric transfer hydrogenation of quinolines

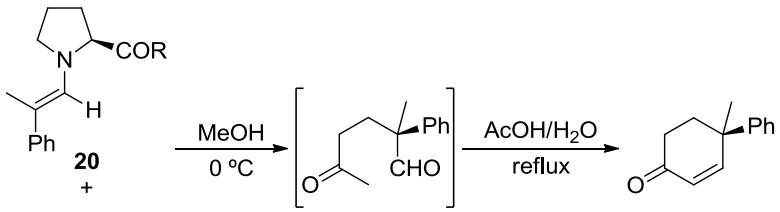
2.3 Organocatalytic Asymmetric Conjugate Addition of Carbon Nucleophiles

2.3.1 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, is one of the most studied reactions. Enamine catalysis is the most frequently employed chiral activation found in the literature.

2.3.1.1 Conjugate Addition of Aldehydes to α,β-Unsaturated Carbonyl Compounds

In 1969 Yamada and Otani reported an stereoselective stoichiometric synthesis of 4,4-disubstituted 2-cyclohexenones through an asymmetric Robinson annulation between preformed chiral aldehyde L-proline-derived enamines **20** and methyl vinyl ketone (Scheme 2.12) [33]. Surprisingly, only few examples of organocatalyzed Michael additions of aldehydes to enones have been reported since then.

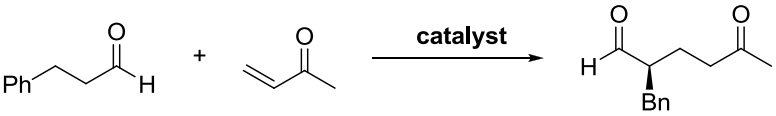


R	Yield (%)	ee (%)
O*t*-Bu	43	6
NMe_2	42	31
NEt_2	53	27
1-pyrrolidinyl	48	37

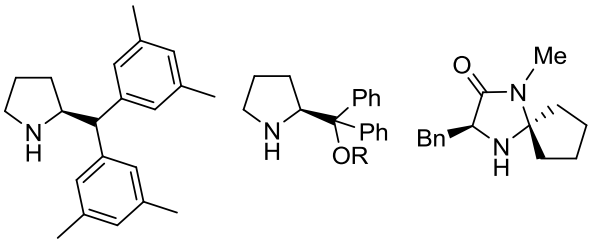
Scheme 2.12 Stoichiometric Robinson annulations

In 2003, Melchiorre and Jørgensen 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 (**21**) (Scheme 2.13) [34]. Further studies on the reaction carried out by different groups led to more efficient catalysts such as diphenylprolinol ethers **22a** [35] and **22b** [36] and imidazolidinone **23** [37] (Scheme 2.13). The highest enantioselectivities reported to date (95–99% ee) have been obtained with catalyst **22b** employing significantly lower catalyst loadings (1–5 mol%) than those reported with other organocatalysts (20–30 mol%)[36].

On the basis of different theoretical and experimental studies [34, 37] it has been demonstrated that this type of catalysts act as nucleophile activators rather than electrophile activators forming the enamine of the aldehyde which suffers conjugate addition to the vinyl ketone. In the case of catalyst **21** [34], the most stable *anti*-enamine A [*E* configuration about the N-C(sp^2) bond, Fig. 2.3] is formed shielding



Catalyst (mol%)	Solvent	Temp	Yield (%)	ee (%)
21 (20)	THF/HFIP	rt	78	65
22a (30)	neat	rt	52	97
22b (5)	neat	4 ºC	82	>95
23 (30)	neat	rt	52	97



21 **22a**, R = TMS **23**
22b, R = Me

Scheme 2.13 Enantioselective Michael addition of aldehydes to vinyl ketones

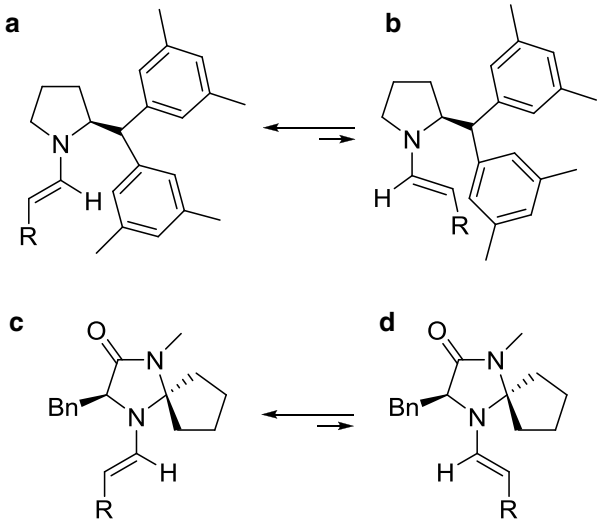
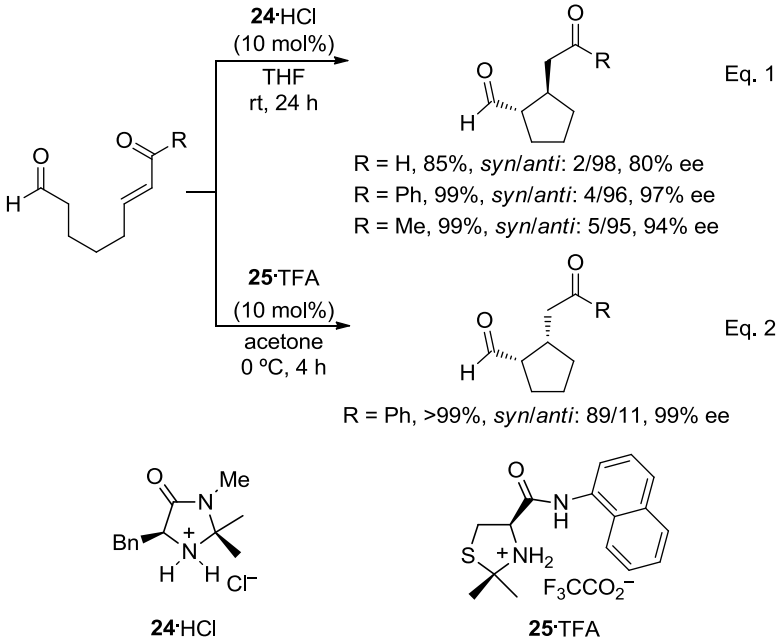


Fig. 2.3 Enamine intermediates for the Michael addition of aldehydes to vinyl ketones

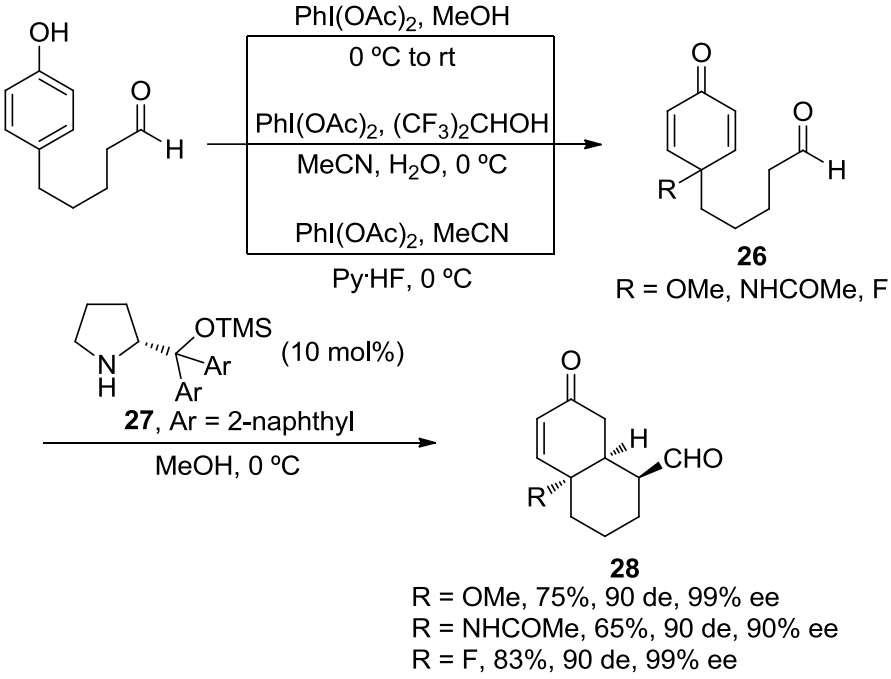
the bulky groups present in the 2-substituent of the catalysts its *Re*-face, leaving the *Si*-face available for the electrophile approach. The presence of an iminium intermediate, probably present in a very small amount and more reactive compared to the vinyl ketone cannot be excluded according to kinetic studies. The same configuration for the enamine C was observed for imidazolidinone **23** (Fig. 2.3) [37].

Enamine and/or iminium activation efficiently promotes asymmetric intramolecular conjugate additions of aldehydes to enones. For instance, List et al. have successfully employed MacMillan's imidazolidinone **24** in the intramolecular Michael addition of aldehydes to aliphatic and aromatic enones (Scheme 2.14, Eq. 1) [38]. The Michael addition, which shows lower enantioselectivity for the intramolecular addition of aldehydes to enals (Scheme 2.14), is assumed to follow an enamine mechanism. However, the fact that only enones and not other different Michael acceptors such as α,β-unsaturated esters, thioesters, and nitroalkenes react to give the corresponding functionalized cyclopentanes with very high enantioselectivity, could be regarded as a confirmation for a dual-activation mechanism involving the formation of both enamine and iminium intermediates [38]. On the other hand, cysteine-derived organocatalyst **25** catalyzes the intramolecular Michael addition of aldehydes to enones [39]. Noteworthy is the diastereo- and enantioselective formation of the kinetic *syn*-isomer, result which is opposite to the result obtained with MacMillan's catalyst **24** (Scheme 2.14, Eq. 1). Catalyst **25** seems then to be more general than **24** since the *trans* disubstituted cyclopentanes are easily obtained via isomerization of the *cis* isomer under basic conditions.



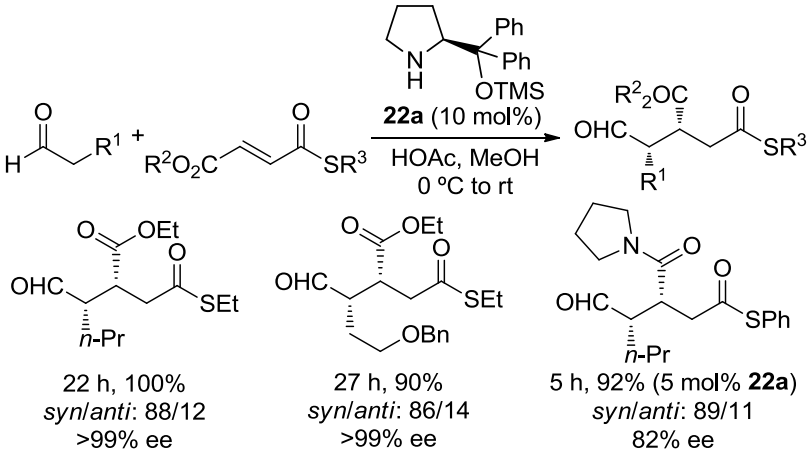
Scheme 2.14 Catalytic asymmetric intramolecular Michael addition of aldehydes to enones and enals

Recently, an oxidative dearomatization of substituted phenols followed by a desymmetrizing asymmetric intramolecular Michael addition catalyzed by the prolinol derivative **27** has been described towards the synthesis of highly functionalized polycyclic molecules with excellent enantioselectivities [40]. As shown in Scheme 2.15, the reaction starts with an oxidation of the phenol moiety to the corresponding *meso*-cyclohexadienones employing $PhI(OAc)_2$, mild oxidant that does not react with the aldehyde nor with the catalyst. In the presence of different nucleophiles such as, methanol, cyanide, or fluoride, intermediates **26** are formed, which suffer intramolecular Michael addition of the aldehyde moiety to afford the desired chiral products **28** with excellent diastereo- and enantioselectivities.



Scheme 2.15 Organocatalytic oxidative dearomatization

α,β-Unsaturated thiol esters [41] and γ-keto-α,β-unsaturated esters [42] have been recently employed as electrophiles for the conjugate addition of aldehydes employing prolinol derivative **22a** as catalyst. The reactions are carried out in MeOH at rt employing 5–10 mol% of catalyst, occur with good yields, high *syn*-diastereoselectivity, regioselectivity, and excellent enantioselectivities, as depicted in Scheme 2.16 for selected examples when using thiol esters. In this particular case, only activated substrates with ester or amide γ-substitution are reactive enough to suffer the conjugate addition, showing high regioselectivities due to the difference



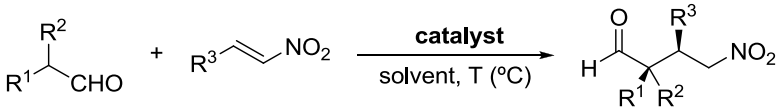
Scheme 2.16 Enantioselective conjugate addition of aldehydes to α,β-unsaturated thiol esters

in the electron-withdrawing nature between the thioester and ester or amide moieties [43]. Also, fumaric diesters are not reactive, which indicates the importance of the thioester group. With respect to the addition to γ-keto-α,β-unsaturated esters [42], the reaction is also highly regioselective to give the corresponding Michael adducts with excellent enantioselectivities (95–>99% ee).

Asymmetric organocatalyzed domino reactions [44] are covered in Chap. 1. With respect to the domino processes triggered by conjugate additions engaging aldehydes as nucleophiles, it is worthy to mention some recent examples where these interesting reactions have been employed as key steps in the synthesis of different biologically active natural products or precursors such as, the decahydroacenaphthylene and decahydrophenalene cores (characteristic structural units of diterpenoid natural products such as the hainanolides and amphilectanes) [45], the antibiotic Platensimycin [46], and the anti-HIV Biyouyanagin A [47].

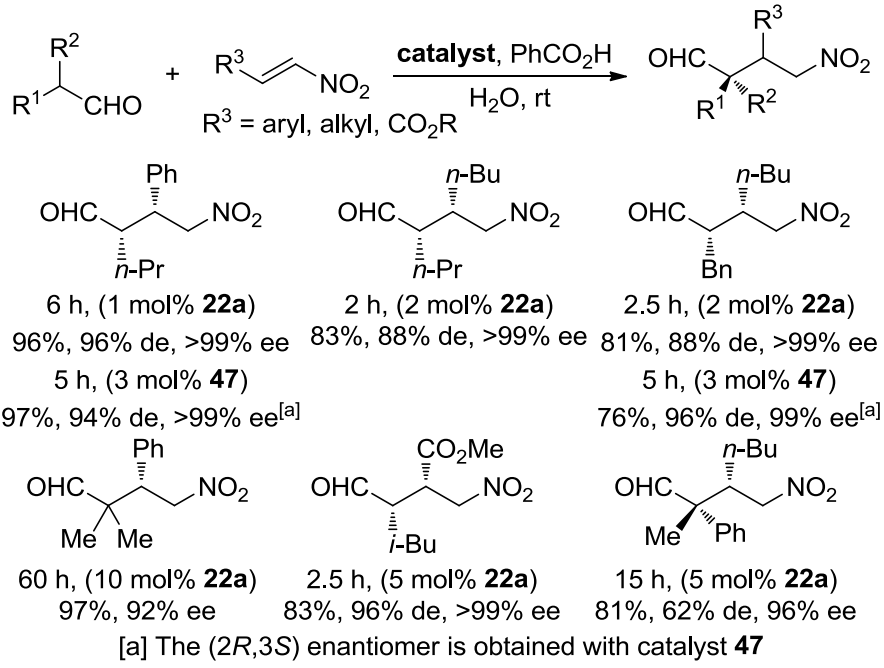
2.3.1.2 Conjugate Addition of Aldehydes to Nitroolefins

The Michael addition between aldehydes and nitroalkenes (Scheme 2.17) is, by far, the most studied reaction when using aldehydes as nucleophiles due to the importance of chiral nitroalkanes as highly versatile synthetic intermediates in organic synthesis [48].



Scheme 2.17 Asymmetric Michael addition of aldehydes to nitroalkenes

For this reason, since the first study by Barbas group on the catalytic asymmetric *syn*-selective Michael reaction of aldehydes with β-nitrostyrenes (Scheme 2.18, R^3 = Ar) employing chiral diamine **29** [49] as catalyst, a wide variety of efficient organocatalysts have appeared in the literature showing high efficiency in this reaction (Fig. 2.4, Table 2.1, R^3 = Ar). These systems, which are commercially available and/or easily prepared from the chiral pool, usually consist of chiral secondary amines, probably due to the favorable imine-secondary enamine equilibrium, although primary amine-derived catalysts have been also shown to be effective as in the case of catalysts **39** [59], **41** [61], **44** [64], and **45** [65]. All the catalysts shown in Fig. 2.4, which also include amino acid salts and small peptides, fulfill the gap left by L-proline, catalyst that still playing a central role in aminocatalysis, provides modest enantioselectivities (23–51% ee) in this reaction [49, 51, 53]. Concerning activity and selectivity, special mention deserves Wennemers tripeptide **43** [63] which has reached very high levels of stereocontrol under the lowest catalyst loadings reported to date (down to 0.1 mol% of **43**, Table 2.1, entry 17). Furthermore, kinetics studies have revealed that in the peptide-catalyzed conjugate addition of aldehydes to nitroolefins, not the enamine formation but both the reaction of the enamine with the electrophile and the hydrolysis of the resulting imine are rate limiting [63b].



Scheme 2.18 Michael addition of aldehydes to nitroalkenes on water

First studies in the direct asymmetric organocatalytic Michael reactions of α,α-disubstituted aldehydes with nitrostyrenes were carried out by Barbas et al. [51] employing 30 mol% of diamine/TFA bifunctional catalyst **31**, which afforded

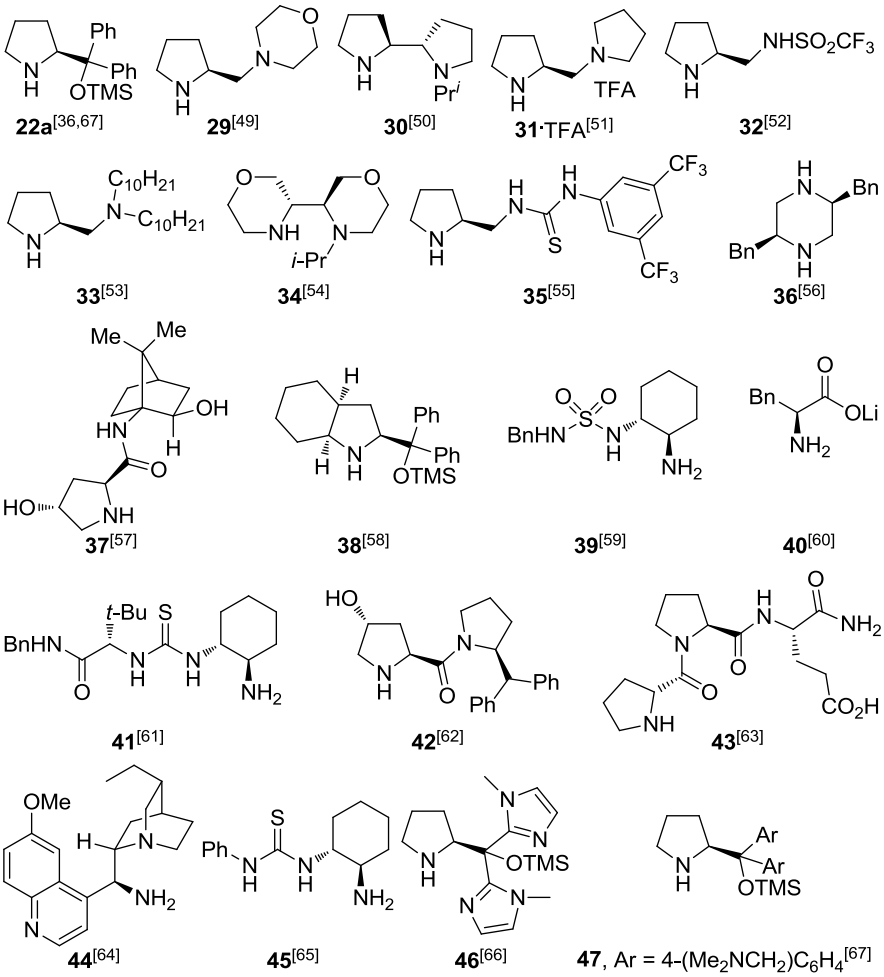


Fig. 2.4 Organocatalysts for the direct asymmetric Michael reaction of aldehydes and β-nitrostyrenes

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 (see, for instance, Table 2.1, entry 3). Since this reaction provides direct access to chiral building blocks with contiguous quaternary and tertiary stereogenic centers, strong efforts have been recently carried out to improve Barbas preliminary results. In this manner, high yields and enantioselectivities have been reported for the addition of α,α-symmetrically disubstituted aldehydes such as isobutyraldehyde to nitrostyrenes with sulfamide **39** [59], phenylalanine lithium salt **40** [60], quinine-derived catalyst **44** [64], and thiourea **45** [65].

Very recently Jacobsen et al. have expanded the reaction scope of the conjugate addition to nitrostyrenes to α,α-unsymmetrically disubstituted aldehydes [61].

Table 2.1 Asymmetric Michael addition of aldehydes to β-nitrostyrene

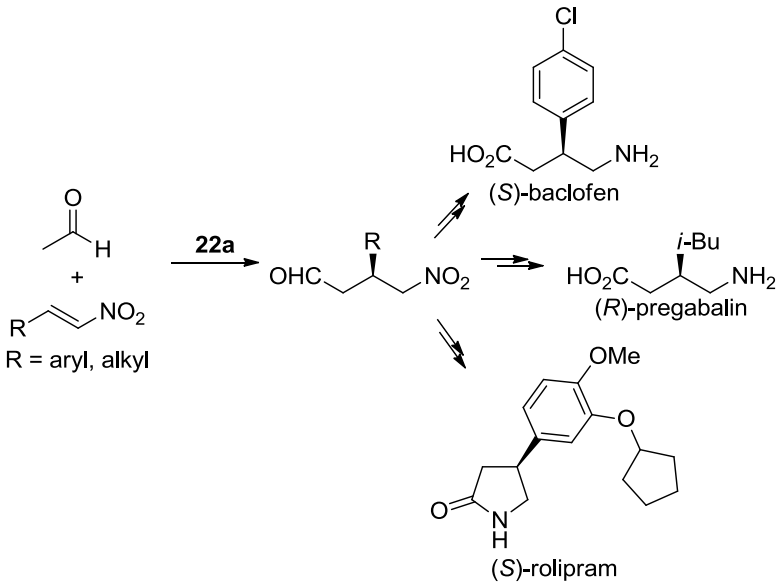
Entry	Catalyst (mol%)	R^1	R^2	Time (h)	Solvent	Temp	Yield (%)	*syn*/*anti*	ee (%)[a]
1	**29** (20)	*n*-Bu	H	27	THF	rt	87	85/15	69
2	**30** (20)	*n*-Pr	H	96	$CHCl_3$	−25°C	98	94/6	87
3	**31** (30)	*n*-Pr	Me	96	IPA	4°C	95	74/26	86
4	**32** (20)	*n*-Pr	H	20	IPA	0°C	99	98/2	96
5	**22a** (10)	*n*-Pr	H	48	hexane	0°C	74	95/5	99
7	**33** (10)	*n*-Pr	Me	96	brine	25°C	97	61/39	64
8	**34** (15)	*n*-Pr	H	72	$CHCl_3$	rt	88	87/13	89
9	**35** (20)	Me	Me	48	CH_2Cl_2	rt	61	–	82[b]
10	**36** (10)	Et	H	48	CH_2Cl_2/hexane	0°C	63	97/3	84
11	**37** (10)	Me	H	48	$CHCl_3$/MeOH	0°C	92	95/5	94
12	**38** (10)	Me	H	8	CH_2Cl_2	20°C	93	92/8	99
13	**39** (20)	Me	Me	3	$CHCl_3$	rt	83	–	99[c]
14	**40** (20)	Me	Me	72	CH_2Cl_2	0°C	82	–	98
15	**41** (20)	PhO	Me	24	CH_2Cl_2	23°C	78	91/9	94
16	**42** (5)	*n*-Pr	H	20	CH_2Cl_2	0°C	90	99/1	>99
17	**43** (0.1)	Et	H	48	$CHCl_3$/IPA	rt	87	94/6	97[d]
18	**44** (15)	*i*-Pr	H	96	neat	rt	76	87/13	95[e]
19	**45** (20)	Me	Me	2	$CHCl_3$	rt	92	–	98[f]
20	**46** (10)	*n*-Pr	H	48	brine	rt	90	91/9	99[g]

[a]Enantiomeric excess for the *syn* diastereomer
[b]The reaction is performed in the presence of 10 mol% of *n*-butyric acid as additive
[c]The reaction is performed in the presence of 20 mol% of DMAP as additive
[d]The reaction is performed in the presence of 0.1 mol% of NMM and TFA as additives
[e]The reaction is performed in the presence of 15 mol% of $PhCO_2H$ as additive
[f]The reaction is performed in the presence of 20 mol% of DMAP as additive
[g]The reaction is performed in the presence of 20 mol% of $NaHCO_3$ as additive

Using the bifunctional chiral primary amine thiourea catalyst **41** (20 mol%) in CH_2Cl_2 and in the presence of five equivalents of H_2O as additive, 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 nitroolefins is obtained (see Table 2.1, entry 15, for a representative example) [61]. The beneficial role of water is proposed to lie in increasing turnover by eliminating potential catalyst deactivation pathways, and accelerating the final imine hydrolysis.

From the experimental point of view, the Michael addition of aldehydes to nitroolefins typically requires large (tenfold) excess of the nucleophile due to competing aldol pathways. This disadvantage has been solved by catalysts with improved activity such as **37**–**41** and **43** that require lower nucleophile excess (1.5–3 equivalents). With respect to the solvent, the reactions are typically performed in highly polar and volatile organic solvents such as DMSO, DMF, CH_2Cl_2, and $CHCl_3$. From the green chemistry point of view, the employment of water as solvent is highly desirable [5]. First attempts performed by Barbas group in the conjugate addition of aldehydes to nitrostyrene employing catalyst **33** (10 mol%) in brine, brought promising results though still with moderate enantioselectivities (38–76% ee, see Table 2.1, entry 7 for a representative result) [53]. Further studies by the groups of Ma [67] and Ni [68] have shown prolinol-derived organocatalyst **22a** and **47** as very effective promoters in the presence of benzoic acid as cocatalyst for the conjugate addition between aldehydes and nitroolefins in water (**22a**: 0.5–10 mol%, **47**: 3 mol%) leading to the corresponding chiral derivatives in good yields (74–99%), very high *syn*-diastereoselectivities (*syn*/*anti* up to 98/2), and enantioselectivities (92–99% ee). The substrate scope is broad since excellent results are obtained with linear and α-substituted aldehydes as well as aryl- and alkyl substituted nitroolefins. Furthermore, catalyst **47** [68] is also very active for the conjugate addition to 3-nitroacrylates. Representative examples are depicted in Scheme 2.18. It is worthy to mention that catalyst **47** is easily recovered from the reaction mixture with a simple extraction and it can be reused for seven cycles with no loss in activity and selectivity [68].

The diphenylprolinol silyl ether **22a** has been also responsible for the very interesting and recent asymmetric organocatalyzed conjugate addition of acetaldehyde to nitroolefins [69]. Control the reactivity of acetaldehyde is tricky due to its high reactivity both as nucleophile and as electrophile, reactivity which is also present in the reaction product that also contains a reactive α-unsubstituted aldehyde moiety. List [69a] and Hayashi [69b] groups have independently reported that acetaldehyde reacts at rt or 0°C, with both aromatic and aliphatic nitroolefins in the presence of catalyst **22a** (10–20 mol%) to afford the corresponding α-substituted γ-nitro aldehydes in moderate to good yields (38–77%) and excellent enantioselectivities (90% to>99% ee). The homodimerization reaction of acetaldehyde is suppressed by slow addition of the nucleophile over the Michael acceptor, being the solvent of choice 1,4-dioxane where the catalyst loading is lower (20 mol%) [69b]. The utility of this process has been exemplified in the formal synthesis of the pharmaceuticals baclofen, pregabalin, and rolipram (Scheme 2.19) [69a].



Scheme 2.19 Michael reaction of acetaldehyde and synthetic applications

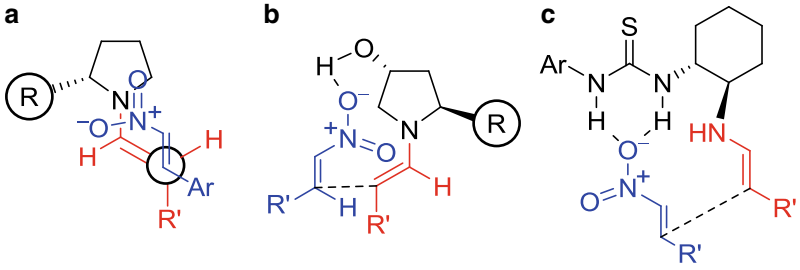
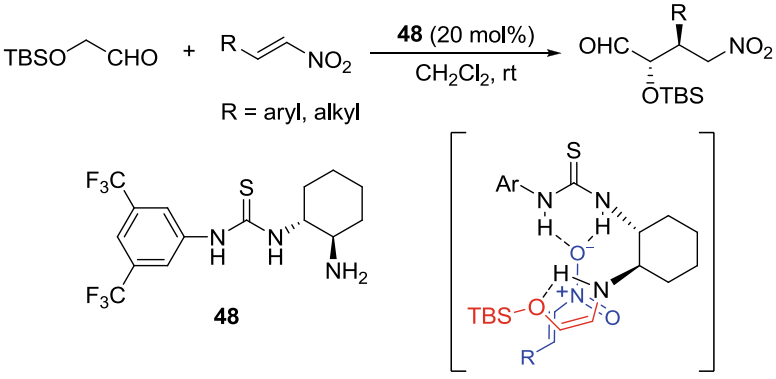


Fig. 2.5 Proposed transition state models for the Michael addition of aldehydes to nitroolefins

With respect to the mechanism, the asymmetric Michael reaction proceeds via a catalytic enamine mechanism. In the case of pyrrolidine-derived catalysts, the high *syn*-diastereoselectivities as well as the enantioselectivities can be explained by the preferential formation of the *anti*-enamine with the double bond oriented away from the bulky substituent in the 2-position of the pyrrolidine ring. The enamine then reacts with the nitroolefin via an acyclic synclinal transition state proposed by Seebach and Golinski (**A**, Fig. 2.5) [70]. In this model there are favorable electrostatic interactions between the partially positive nitrogen of the enamine and the partially negative nitro group. A bulky substituent on the 2 position of the pyrrolidine ring plays two important roles: it favors the selective formation of the *anti* enamine and shields its *re* face.

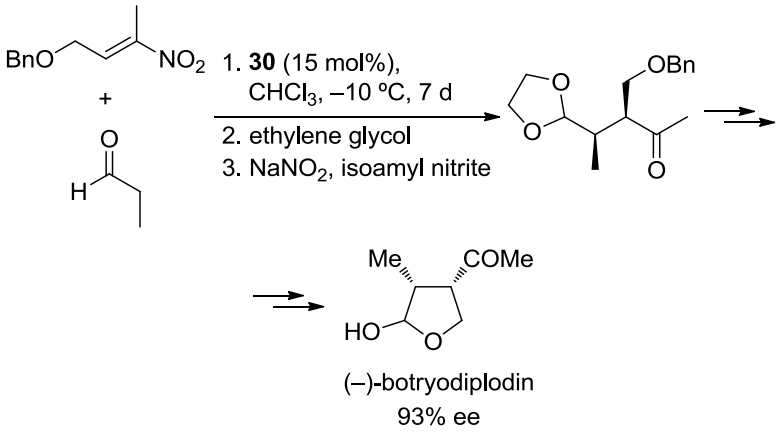
Depending of the catalyst structure, a dual catalyst activation mode may be involved in the process. For instance, in catalyst **42** (Fig. 2.4) [62] the presence of the *trans*-OH group in the 4-position of the pyrrolidine ring helps to activate the electrophile and also directs its approach from the less hindered face of the *E*-enamine (**B**, Fig. 2.5). The bifunctional catalyst activation behavior is also suggested for other catalysts such as Jacobsen's thiourea **41** (Fig. 2.4) [61], where binding of the nitroalkene by the thiourea moiety allows the thermodynamically favorable *E* enamine to attain in close proximity for a highly diastereo- and enantioselective C-C bond-formation (**C**, Fig. 2.5).

Very recently a very interesting highly *anti*-selective asymmetric Michael reaction of aldehydes to nitroolefins has been recently reported by Barbas et al. [71]. Thus, the conjugate addition of TBS-protected 2-hydroxyacetaldehyde to electron-deficient, electron-rich, and sterically hindered nitrostyrenes as well as alkyl-substituted nitroolefins catalyzed by the primary amine/thiourea **48** (20 mol%), affords the corresponding *anti* Michael adducts with good yields (57–83%) and excellent diastereo- (*anti*/*syn*: 92/8 to 98/2) and enantioselectivities (97–98% ee) (Scheme 2.20). The stereochemistry outcome of the reaction, strongly suggest preference for the formation of the aldehyde enamine with the *Z* configuration due to intramolecular hydrogen-bonding stabilization. This methodology has been recently applied to the stereoselective synthesis of carbohydrate derivatives [72].



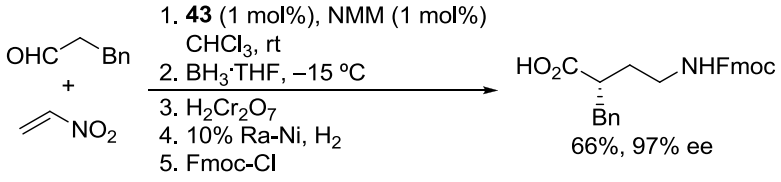
Scheme 2.20 *anti*-Selective asymmetric conjugate addition of aldehydes to nitroolefins

Regarding substrate scope, catalysts **22a**, **30**, **37**, and **40**–**44** (Fig. 2.4) are efficient promoters for the Michael addition of aldehydes to β-alkyl substituted nitroolefins. Taken advantage of the good activity exhibited by catalyst **30** in this process, Alexakis et al. have achieved the total synthesis of the mycotoxin (−)-botryodiplodin [73], process which involves an attractive Michael addition between an aldehyde and an α-substituted nitroolefin (Scheme 2.21).



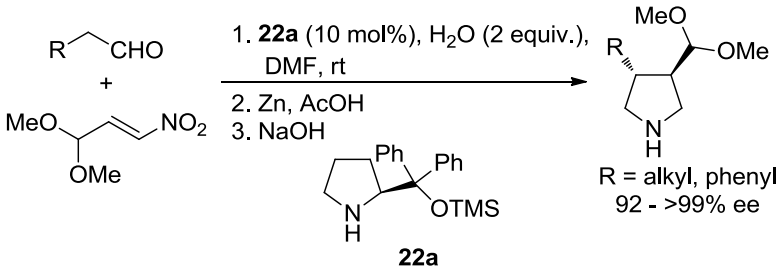
Scheme 2.21 Total synthesis of (–)-botryodiplodin

α-Monosubstituted γ^2-amino acids are important building blocks for the development of γ-peptides, therapeutics, as well as in foldamer research. The preparation of these derivatives is challenging which so far has limited the study of γ-peptide foldamers to date. In 2008, the groups of Gellman [74] and Wennemers [75] independently reported a highly efficient organocatalytic synthesis of chiral α-substituted γ-nitroaldehydes, derivatives which are easily converted in monosubstituted γ^2-amino acids. Thus, the conjugate addition of aldehydes to nitroethylene at rt, catalyzed by prolinol-derived catalyst **22a** (2 mol% with 20 mol% of 3-$NO_2C_6H_4CO_2H$ as cocatalyst) [74] or the tripeptide **43** (1 mol% with 1 mol% of NMM as cocatalyst) [75], affords monosubstituted γ-nitroaldehydes in high yields and enantioselectivities requiring in both cases only a small excess of the nucleophile (1.5–2 equivalents). As depicted in Scheme 2.22 for a representative example using catalyst **43** [75], this methodology, which is a formal aminoethylation of aldehydes, is a valid alternative to the already established methods for the synthesis of chiral γ^2-amino acids. Furthermore, constrained chiral γ^2-amino acids have been recently synthesized from the corresponding γ-nitroaldehydes obtained by **22a**-catalyzed conjugate addition of aldehydes to 1-nitrocyclohexene [76]. The Michael addition is carried out in CH_2Cl_2 as solvent at rt, and under high catalyst loadings (20 mol%) to obtain optimal results in terms of yield (70–87%), diastereoselectivity (76–88% de), and enantioselectivity (96% to >99%).



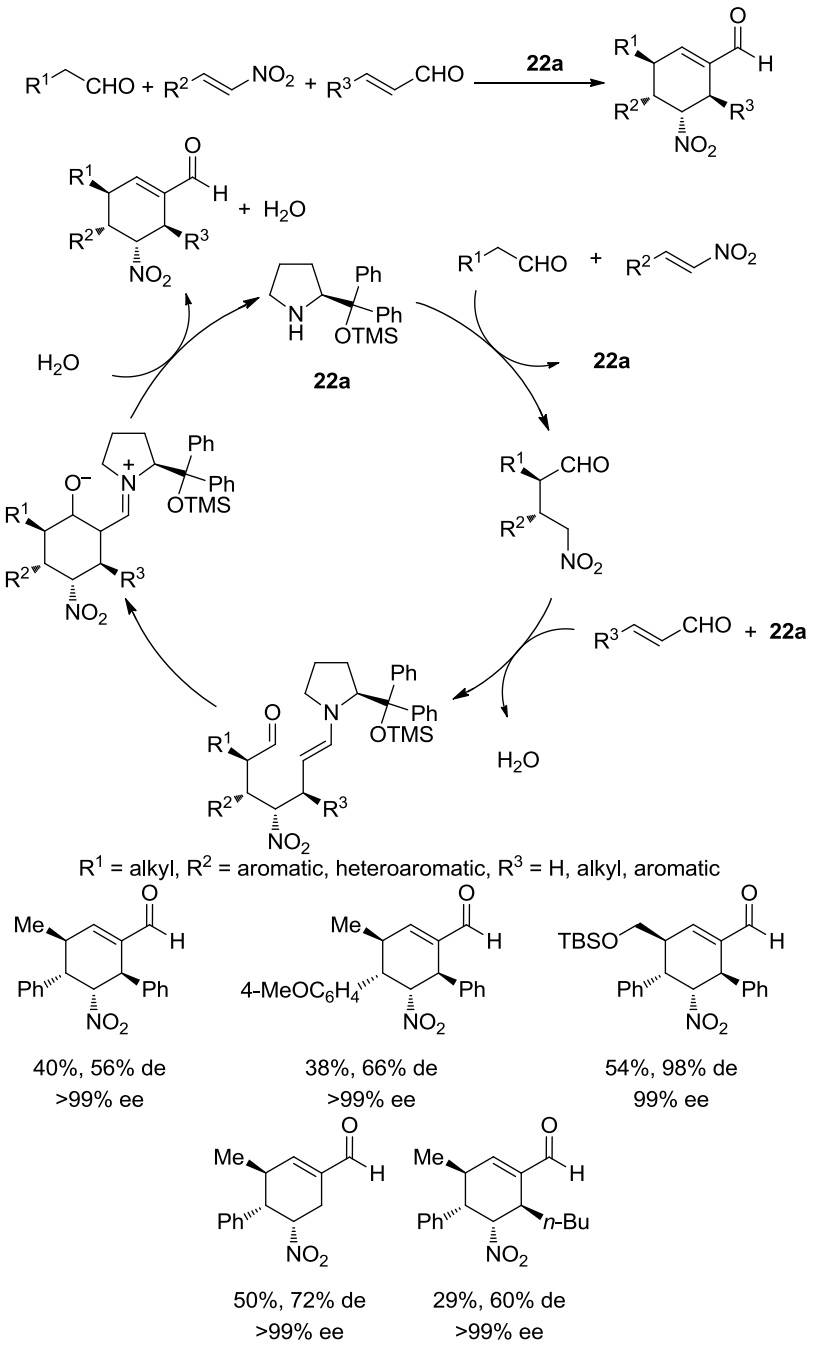
Scheme 2.22 Synthesis of chiral γ^2-amino acids

Some other interesting synthetic applications that have made use of the structural versatility and intrinsic reactivity offered by the Michael adducts have been recently reported. For instance, a sequential asymmetric organocatalyzed Michael addition/[3+2]-heterocyclization has been successfully used for the stereoselective synthesis of cyclopentanoids bearing up to four stereogenic centers [77], Also, a highly enantioselective synthesis of functionalized polysubstituted pyrrolidines has been accomplished via a *syn*-diastereoselective conjugate addition of linear aldehydes to β-nitroacroleine dimethyl acetal catalyzed by prolinol **22a** (10 mol%), followed by Zn reduction of the nitro group and subsequent reductive amination (Scheme 2.23) [78]



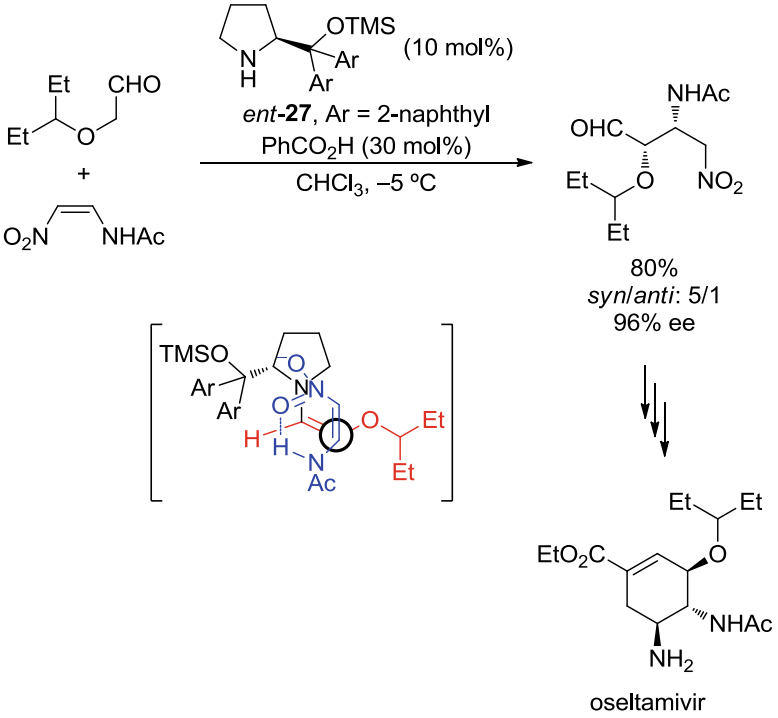
Scheme 2.23 Asymmetric synthesis of pyrrolidines

The conjugate addition of aldehydes to nitroolefins has been involved in a wide number of different asymmetric catalyzed domino reactions producing chiral elaborate structures in a rapid, atom-economic, and competent manner [44]. An efficient and elegant chemo-, diastereo-, and enantioselective three component domino synthesis of tetrasubstituted cyclohexene carboxaldehydes has been accomplished by Enders et al. employing catalyst **22a** [79]. The catalytic cascade consisted of a three component reaction comprising a linear aldehyde, a nitroalkene, an α,β-unsaturated aldehyde, and catalyst **22a**, which is capable of catalyzing each step of the process (Scheme 2.24). The four stereogenic centers are generated in three consecutive C-C bond formations with good diastereocontrol and complete enantiocontrol. The first step of the catalytic cycle consists of a stereoselective Michael addition of the linear aldehyde to the nitroalkene via enamine formation. This step is responsible for the high stereoselectivity of the process, the selectivity being kept or enhanced in the second step, the conjugate addition of the formed nitroalkane 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. This protocol allows the synthesis of a wide variety of polyfunctionalized cyclohexene building blocks since different substituents are tolerated in the starting materials. For instance, Hayashi et al. have developed an elegant high-yielding synthesis of the anti-Influenza neuramidasa inhibitor (−)-oseltamivir, where the key step involves a one-pot four components asymmetric organocatalyzed domino reaction which starts with a conjugate addition between a



Scheme 2.24 Three components double Michael addition organocatalytic sequence

α-alkoxy aldehyde and (*E*)-*tert*-butyl 3-nitroacrylate [80]. Very recently, (−)-oseltamivir has been also prepared using a *syn*-diastereo- and highly enantioselective conjugate addition of 2-(pentan-3-yloxy)acetaldehyde to (*Z*)-*N*-(2-nitrovinyl)acetamide catalyzed by *ent*-**27** (Scheme 2.25) [81]. The reaction has been proposed to occur through an acyclic synclinal transition-state model [70] involving the formation of the *Z*-enamine due to marked steric interactions between the aldehyde substitution and the acetamido group.



Scheme 2.25 Synthesis of (−)-oseltamivir

In some reactions, organocatalysis has been considered to be of low efficiency as a result of the high catalyst loadings, typically in the range 10–20 mol%, usually required to perform the desired transformation, and the difficulties in catalyst separation and recycling. The immobilization of organocatalysts may provide potential solutions to these challenges [82]. Regarding the conjugate addition of aldehydes to nitroolefins, immobilization of organocatalysts has been achieved by a covalent attachment as in catalysts **49** [83] and **50** [84], where polystyrene and a dendrimer have been used as a support, respectively (Fig. 2.6). On the other hand, non-covalent immobilization using ionic liquid supports, as in catalysts **51**–**53** [85], and fluorous technologies, as in pyrrolidines **54** and **55** [86] (Fig. 2.6), has also been successfully

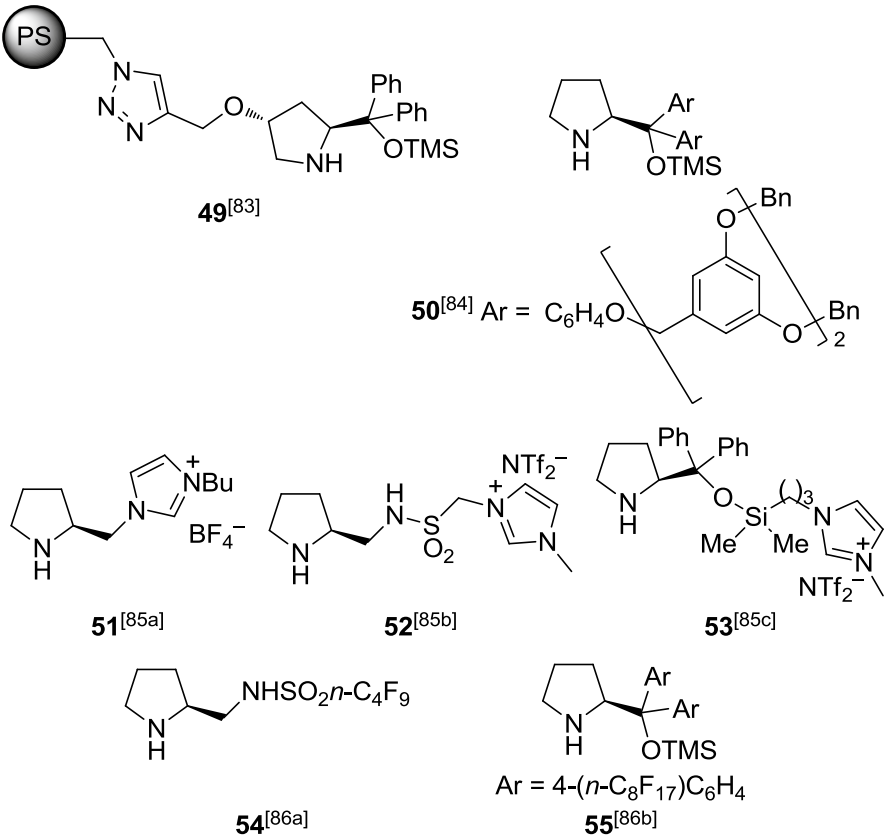


Fig. 2.6 Recyclable organocatalysts for the conjugate addition of aldehydes to nitroolefins

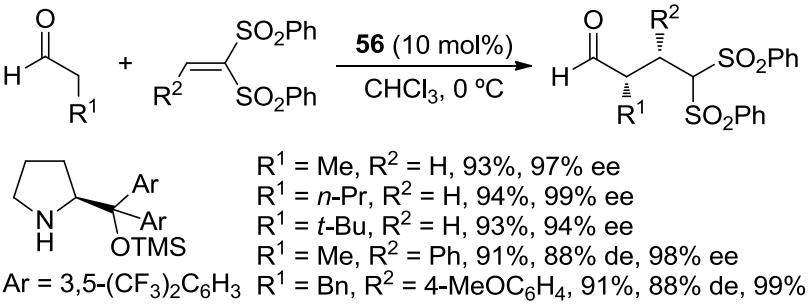
used in the conjugate addition of aldehydes to nitroolefins. All these systems catalyze the conjugate addition of linear aldehydes to nitrostyrenes in high yields, diastereo- and enantioselectivities with catalyst loadings in the range of 10–20 mol%. Of special interest results prolinol-derived catalyst **53** [85c] since it also promotes the conjugate addition of α-branched aldehydes as well as β-alkyl substituted nitroolefins under very low loading conditions (1–5 mol%) and using water as solvent. With respect to recyclability, catalysts **49**, which is selective for linear aldehydes showing no reactivity in competition experiments towards α-branched aldehydes and ketones, as well as pyrrolidines **50**, and **52** are easily recovered from the reaction mixture by filtration which has allowed them to be reused for 5–6 cycles without loss of activity and selectivity. Similarly, catalysts **54**, which is very active and selective using water as solvent at rt, and **55**, are easily recovered by fluorous solid-phase extraction and reused several times, still retaining high catalytic activity.

2.3.1.3 Conjugate Addition of Aldehydes to Vinyl Sulfones

Lately, sulfones have become especially important substrates in organocatalysis [87]. First studies on the asymmetric conjugate addition of aldehydes to vinyl sulfones were carried out by Alexakis and Mossé employing as catalyst bipyrrolidine **30** (25 mol%) for the addition of linear and α-branched aldehydes to 1,1-bis(benzenesulfonyl)ethylene [88]. Large excess of aldehyde (10 equivalents) was required and moderate levels of enantioselection were obtained for linear aldehydes (53–80% ee), while reactions with α-branched nucleophiles led to racemic or very low selectivities (0–12% ee). With respect to the mechanism, the acyclic synclinal model proposed by Seebach and Golinski [70] involving a *trans* enamine intermediate was postulated.

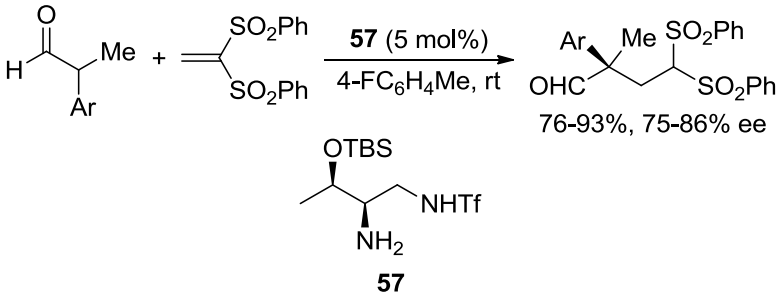
Some years later, further developments by Alexakis et al. have shown that prolinol derivative **22a** (10 mol%) is a better catalysts for the reaction [89]. The results vary from good, for conjugate addition of linear aldehydes to 1,1-bis(benzenesulfonyl) ethylene (77–90% yields; 76–93% ee), to moderate (12–91% ee) when using α-branched aldehydes as nucleophiles. Catalyst **22a** has been also used by Palomo et al. for the enantioselective conjugate addition of linear and β-branched aldehydes to *E*-α-ethoxycarbonyl vinyl sulfones and *E*-α-cyano vinyl sulfones [90], derivatives that after further transformations, which usually involve a reductive desulfonylation process [91], have made possible the synthesis of different interesting chiral building blocks.

On the other hand, Lu et al. have found that the trifluoromethyl substituted silylated diphenylprolinol catalyst **56** is more effective than **22a** in the process, leading to excellent yields and enantioselectivities for the conjugate addition of linear aldehydes to 1,1-bis(benzenesulfonyl)ethylene (93–97% yield, 94% to >99% ee) and 2-aryl-substituted 1,1-bis(benzenesulfonyl)ethylene (82–94% yield, 50–88% de, 95% to >99% ee) (Scheme 2.26) [92].



Scheme 2.26 Michael addition of aldehydes to vinyl sulfones

Very recently, the same group has also optimized a stereoselective conjugate addition of 2-aryl-substituted aldehydes to 1,1-bis(benzenesulfonyl)ethylene using the threonine-based *N*-sulfonamide organocatalyst **57** (Scheme 2.27) [93]. The reaction is performed in 4-fluorotoluene at rt and allows the synthesis of optically

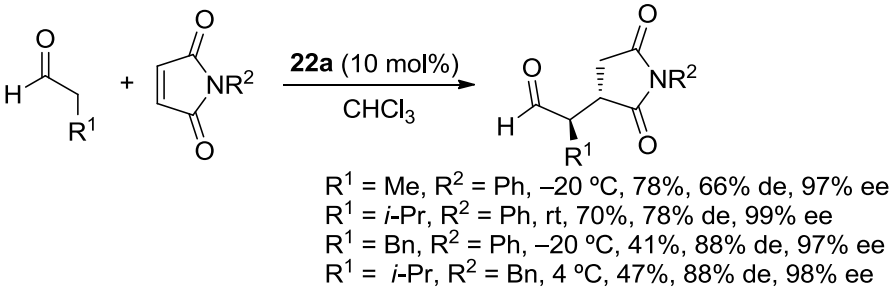


Scheme 2.27 Michael addition of 2-aryl-substituted aldehydes to vinyl sulfones

active aldehydes bearing an adjacent quaternary stereocenter with good enantioselectivities (up to 86% ee), which are useful building blocks for the synthesis of interesting chiral compounds.

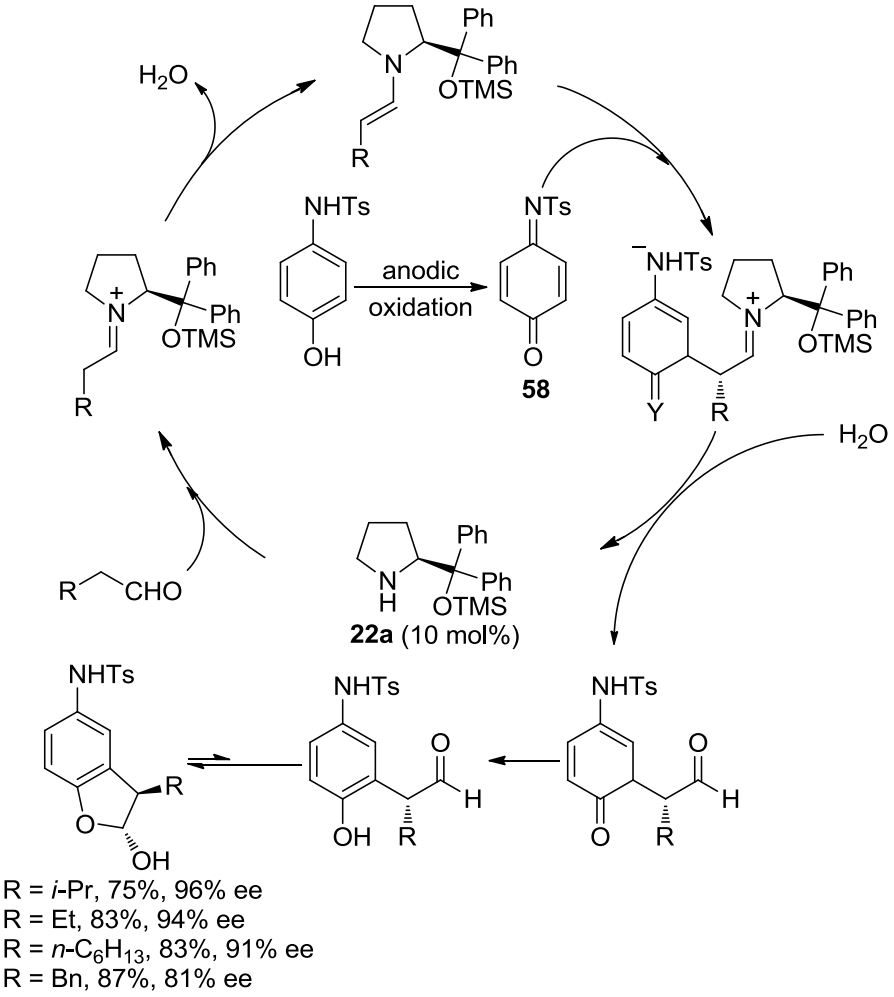
2.3.1.4 Conjugate Addition of Aldehydes to Other Electrophiles

Through enamine catalysis, silylated prolinols **22a** and **56** also catalyze the conjugate addition of α-unsubstituted aldehydes to other different electrophiles. For example, the addition of aldehydes to 1,1-bis(diethylphosphonate)ethylene in the presence of 20 mol% of **22a** in $CHCl_3$ at rt, affords the corresponding products in good yields (65–85%) and moderate to high enantioselectivities (46–97% ee) [89]. *N*-Substituted maleimides are also suitable electrophiles for the conjugate addition of aldehydes in $CHCl_3$, using **22a** as catalyst (10 mol%) [94]. In this case, the process is highly enantioselective and the corresponding α-substituted succinimides are obtained with high optical purity (97–99% ee) as depicted in Scheme 2.28 for representative examples.



Scheme 2.28 Michael addition of aldehydes to *N*-substituted maleimides

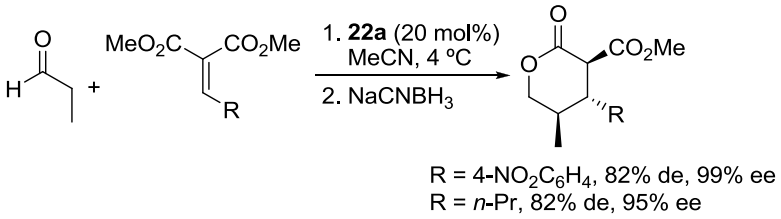
On the other hand, Jørgensen et al. have reported an interesting α-arylation of aldehydes with electron-rich aromatic compounds such as *N*-(4-hydroxyphenyl)-4-methylbenzenesulfonamide through a novel anodic oxidation/organocatalytic protocol [95]. As depicted in Scheme 2.29, the reaction firstly involves the



Scheme 2.29 Asymmetric organocatalyzed α-arylation of aldehydes

electrochemical activation of the aromatic compound leading to the formation of the Michael acceptor **58**, which suffers conjugate addition from the chiral enamine generated by condensation of the aldehyde and organocatalyst **22a**. Interestingly, the reaction can be also performed using chemical in situ oxidation with iodobenzene diacetate [$PhI(OAc)_2$], affording similar results to those obtained by the electrochemical approach.

Finally, an interesting conjugate addition of aldehydes to alkylidene malonates has been reported by Córdova employing catalyst **22a** (20 mol%) [96]. The reaction, which is usually carried out in $CHCl_3$ at ~20°C or CH_3CN at 4°C, is highly diastereo- and enantioselective (up to 87% de, 95% to >99% ee), and has been successfully employed in the synthesis of poly substituted lactones (Scheme 2.30).



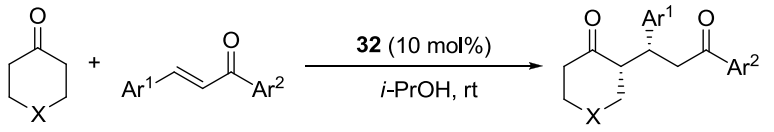
Scheme 2.30 Asymmetric organocatalyzed synthesis of chiral lactones

2.3.2 Conjugate Addition of Ketones

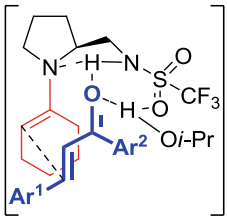
Different Michael acceptors such as, α,β-unsaturated carbonyl compounds, nitroolefins, and electron-poor alkylidene derivatives have been efficiently used in asymmetric organocatalytic conjugate additions when the nucleophile is a ketone. This conjugate addition has been studied under homogeneous and PTC conditions using a wide variety of chiral organocatalysts such as *Cinchona* alkaloid derivatives, small peptides, and chiral primary and secondary amines derived from the chiral pool or synthetically obtained. Thus, different modes of activation have been reported, such as enamine-, chiral ion pairing-, and hydrogen bonding catalysis, being the major mechanistic pathway mostly governed by the structure of the substrates and catalysts. Regarding synthetic applications, this reaction has been involved in the preparation different enantiomerically enriched compounds such as 1,5-dicarbonyl compounds, functionalized cyclopropanes, and γ-nitroketones.

2.3.2.1 Conjugate Addition of Ketones to α,β-Unsaturated Carbonyl Compounds

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 [97]. The intramolecular proline-catalyzed version of the reaction was later described by other authors [98] although in modest enantioselectivities and employing stoichiometric amounts of the catalyst and long reaction times. More recently, chiral pyrrolidine sulfonamide **32** has been shown as a very efficient catalyst for the conjugate addition of cyclohexanones to chalcones [99]. The reaction, which is carried out using 10 mol% of the catalyst in *i*-PrOH at rt, yields synthetically useful 1,5-dicarbonyl compounds in high yields and with high to excellent levels of enantio- and *syn*-diastereoselectivity (Scheme 2.31). The high levels of selectivity for cyclohexanones has been rationalized with the proposed transition state model shown in Scheme 2.31, where 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, then



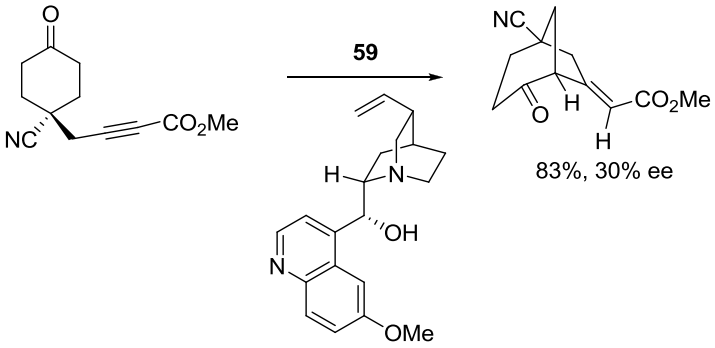
X	Ar^1	Ar^2	Yield (%)	Time (d)	*syn*/*anti*	ee (%)
CH_2	4-ClC_6H_4	Ph	80	4	>98/2	90
CH_2	4-$NO_2C_6H_4$	Ph	87	4	>98/2	92
CH_2	2-thienyl	2-thienyl	65	6	>98/2	90
NMe	4-ClC_6H_4	Ph	89	4	96/4	97
O	4-ClC_6H_4	Ph	73	5	98/2	87
–	4-ClC_6H_4	Ph	87	2	75/25	73



Scheme 2.31 Enantioselective organocatalytic Michael addition of cyclohexanones to chalcones

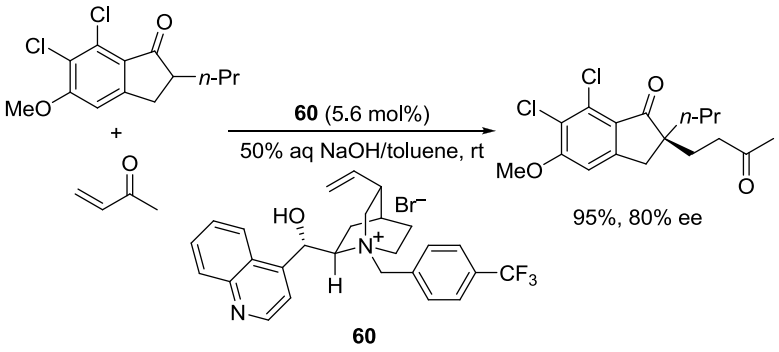
synergistically bringing about a tighter transition state. As earlier commented for other related catalysts, the triflamide moiety also produced a high facial preference for the approaching enone. Catalyst **32** is not so competent for the conjugate addition to chalcones of other cyclic ketones such as, cyclopentanone (Scheme 2.31) and cycloheptanone. The cyclopentanone issue has been recently solved employing as catalyst the chiral salt formed by (1*R*,2*R*)- or (1*S*,2*S*)-1,2-diaminocyclohexane and hexanedioic acid, which affords in a mixture MeOH/$CHCl_3$ at rt, the corresponding Michael adducts in good yields (43–92%), low to excellent diastereoselectivities, and very high enantioselectivities for both diastereoisomers (95–99.9% ee) [100].

With respect to the use of *Cinchona* alkaloid-derived organocatalysts, the first example of asymmetric Michel addition of ketones to enones appeared in 1979 when Trost illustrated, during the total synthesis of the sesquiterpene (±)-hirsutic acid C [101], a stereoselective (30% ee) quinine (**59**)-catalyzed intramolecular conjugate addition of an intermediate functionalized cyclohexanone (Scheme 2.32).



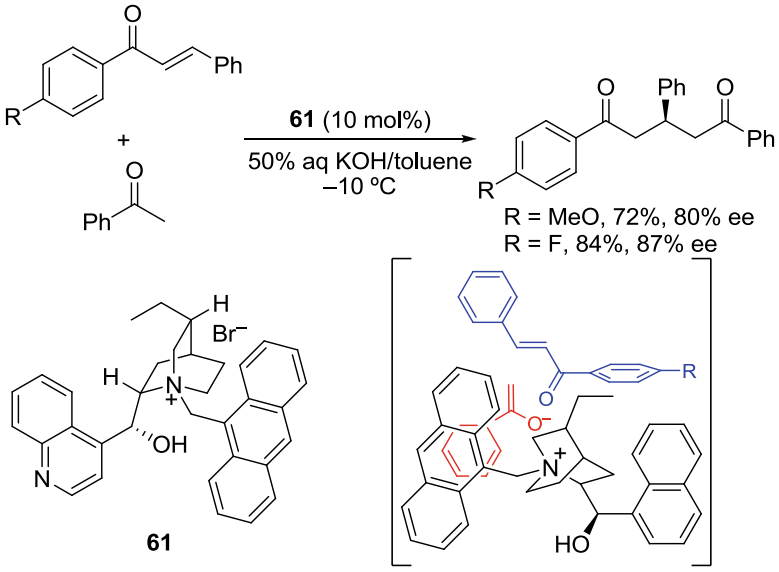
Scheme 2.32 Quinine-catalyzed intramolecular Michael addition

After this study, the employment of ammonium salts derived from *Cinchona* alkaloid catalysts, such as [4-(trifluoromethyl)benzyl]cinchoninium bromide (**60**), 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 2.33) [102].



Scheme 2.33 Asymmetric Michael addition to methyl vinyl ketone catalyzed by **60**

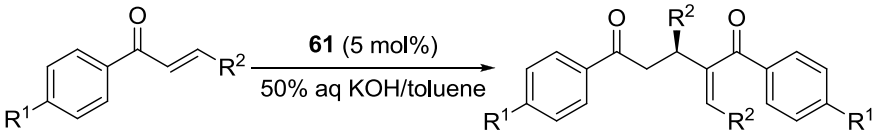
More recent studies on asymmetric PTC Michael reactions involving ketones, have sown that the *N*-alkylated cinchonidinium cation **61** mediates the enantioselective conjugate addition of acetophenone to chalcones (Scheme 2.34) [103]. In the proposed transition state of the reaction, the acetophenone enolate and the α,β-enone are contact



Scheme 2.34 Cinchonidinium-catalyzed Michael addition of ketones to chalcones

ion paired with the ammonium nitrogen of the catalyst. Moreover, the phenyl group of the nucleophile is positioned to π-stack with the 9-anthracenyl subunit of the catalyst which definitely confers rigidity and a proper chiral atmosphere to the system.

Catalyst **61** also promotes the enantioselective dimerization, under the same chiral PTC conditions, of α,β-enones capable of generating dienolates by deprotonation of a γ-hydrogen [104]. The reaction yields chiral 1,5-dicarbonyl compounds after an enantioselective Michael addition-double bond isomerization sequence. At low temperatures, this dimerization reaction generally affords good yields (80–90%) and high enantioselectivities (86–98% ee), the best results being for π-electron deficient enones and those having a bulkier substituent in the β position (Scheme 2.35). The products of the dimerization are very useful intermediates for the synthesis of chiral γ-keto acids, important chiral building blocks for peptide isosteres. A similar mechanistic model as previously described for the addition of ketones to chalcones (Scheme 2.34) is operative in this transformation.

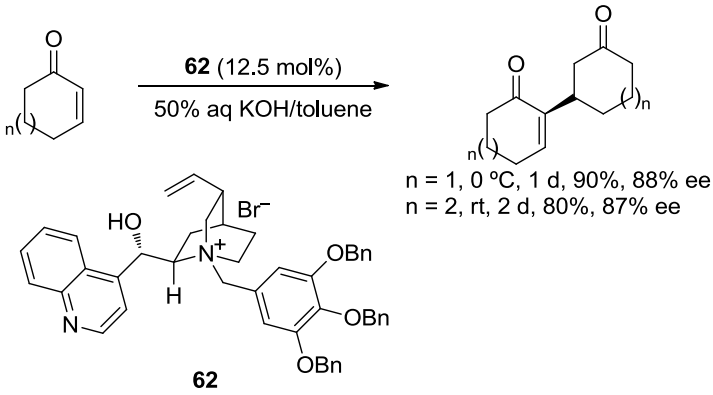


R^1	R^2	Temp (ºC)	Yield (%)	ee (%)
H	Me	23	92	83
H	Me	–40	87	89
F	Me	–40	89	90
MeO	Me	–40	80	86
H	*i*-Pr	–40	81	98

Scheme 2.35 Cinchonidinium-catalyzed dimerization of acyclic α,β-unsaturated ketones

On the other hand, the cinchoninium-catalyzed dimerization reaction has been recently applied to cyclic enones such as cyclohex-2-enone and cyclohept-2-enone, employing ammonium catalyst **62**, in high yields and up to 92% and 87% ee, respectively (Scheme 2.36) [105].

A further application of the asymmetric conjugate addition of ketones to enones mediated by chiral tertiary bases is the synthesis of chiral cyclopropanes via ammonium ylides [106]. 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 2.37). The initially discovered non-enantioselective DABCO-catalyze reaction by Gaunt et al. [106a,b], led to these authors to employ natural or modified *Cinchona* alkaloids such as **63**–**65** as chiral organocatalysts. This process takes place with extremely good



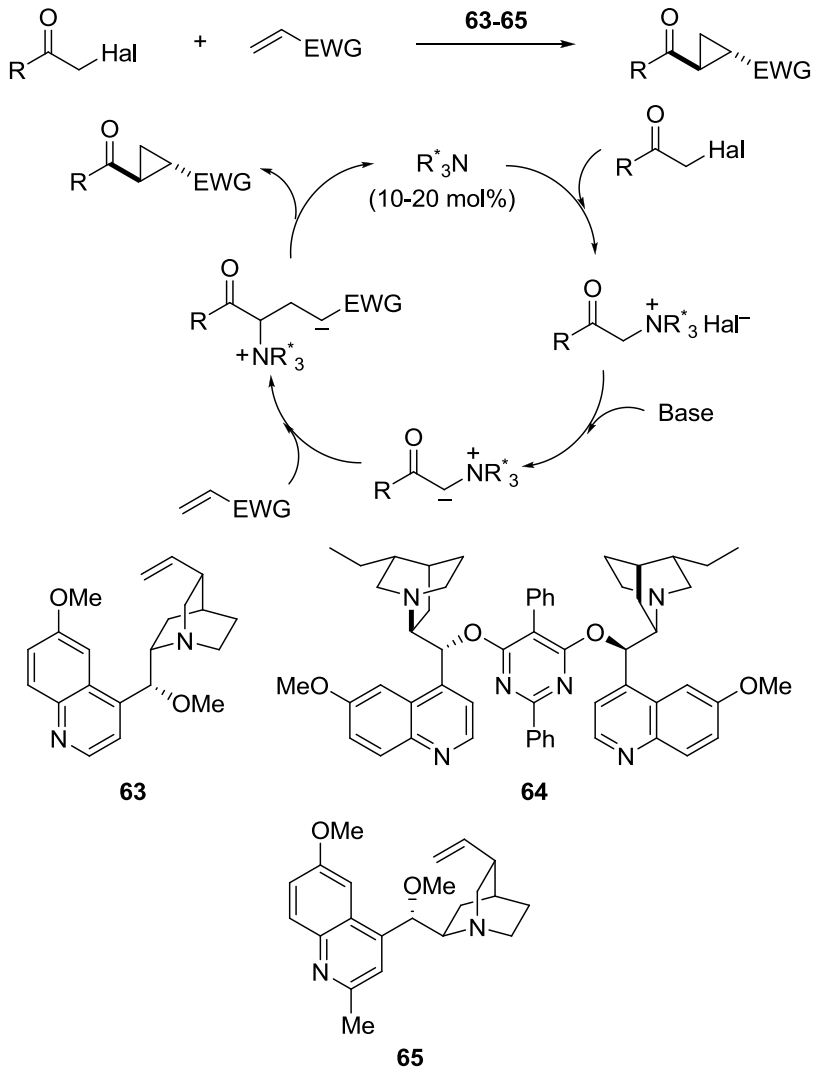
Scheme 2.36 Cinchoninium-catalyzed dimerization of cyclic α,β-unsaturated ketones

yields, diastereo- and enantioselectivities both for the inter- [106c] and intramolecular [106d] version of the reaction. Notably, both enantiomers of the cyclopropane derivatives can be accessed 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% are standard reaction conditions (Scheme 2.37). Recently, this methodology has been employed to synthesize oxylipin class of natural products using quinine and quinidine-based alkaloids [106e].

With respect to the substrate scope, ketones are the most efficient nucleophiles although the intermolecular reaction works also well for esters, amides and Weinreb amides (Fig. 2.7). Regarding the Michael acceptor, enones are the best electrophiles with a wide range of substituents tolerated (alkyl, aryl and heteroaryl ketones). α,β-Unsaturated esters, in the case of the intermolecular cyclopropanation, and α,β-unsaturated diimides for the intramolecular reaction, extends the substrate scope of the process (Fig. 2.7). A transition state model for the intramolecular cyclopropanation reaction has been proposed as depicted in Scheme 2.38 for catalyst **65** [106d]. In this model the ammonium salt adopts a conformation that gives the *Z*-enolate of the nucleophile on deprotonation with the base. The intramolecular conjugate addition of the enolate then takes place through a boat-type transition state.

2.3.2.2 Conjugate Addition of Ketones to Nitroolefins

The first organocatalytic conjugate addition of ketones to *trans*-β-nitrostyrene was independently reported by Barbas [107], and List [108] using L-proline as catalyst with good yields but very low enantioselectivities (0–23% ee). A subsequent study by Enders et al. showed a profound solvent effect in the reaction since in MeOH the enantioselectivity could be increased to 76% for the major *syn* diastereoisomer in the reaction between 3-pentanone and *trans*-β-nitrostyrene employing a 20 mol% of



Scheme 2.37 Enantioselective organocatalytic cyclopropanation

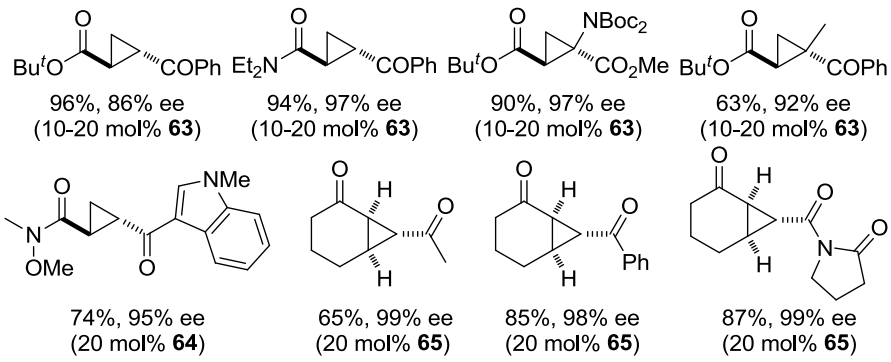
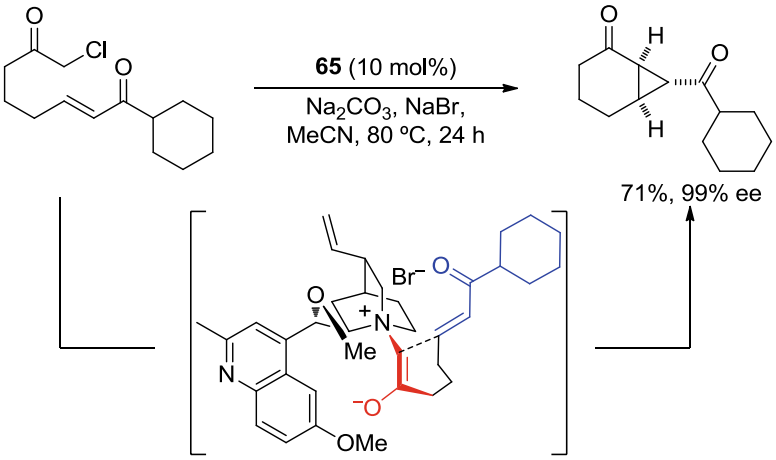


Fig. 2.7 Substrate scope for organocatalytic cyclopropanation



Scheme 2.38 Proposed origin of the enantioselectivity for the organocatalytic cyclopropanation

L-proline as catalyst [109]. Further studies on the reaction were carried out by Alexakis et al. using the hydrochloride salt of *N*-isopropyl-2,2′-bipyrrolidine (**30**, Fig. 2.4) as catalyst in $CHCl_3$ as solvent. In this study the highest enantioselectivity (81%) was obtained for the addition of cyclohexanone to nitrostyrene also with a very high diastereoselectivity (*syn*/*anti*: 94/6) [50]. As in the case of the conjugate addition of aldehydes, the observed *syn* selectivity was in accordance with the Seebach-Golinski model [70].

The above mentioned initial steps on the reaction have been followed by a wide number of studies performed by various groups where the activity of different organocatalysts in the conjugate addition of ketones to nitroolefins has been systematically studied. In general, very high activities and selectivities have been obtained when using cyclohexanones and derivatives as nucleophiles and nitrostyrenes as Michael acceptors using enamine and/or hydrogen-bonding activation modes. Thus, some of the catalysts developed for the asymmetric addition of aldehydes to nitroolefins such as **32** [52, 110], **66** [111], **33** [49, 53], **35** [55], and **67** [112], as well as others more recently developed such as **68** [113], **69** [114], **70** [115], **71** [116], **72** [117], **73** [118], and **74** [119], have also been demonstrated to be very efficient for the *syn*-selective addition of cyclohexanones to β-arylated nitroolefins with catalyst loadings usually in the range 10–20 mol%, ee values of up to 99%, and diastereomeric ratios of up to 99/1. The reaction is usually performed using a large excess of ketone (5–10 equiv), to guarantee convenient kinetics and conversion, at room temperature, in a wide variety of organic solvents. Organocatalysts **33**, **69**, **71**, and **74** are particularly interesting since they are very efficient using water as solvent (Fig. 2.8).

Very small changes in the organocatalyst structure may often alter its catalytic activity especially in terms of enantioselectivity. These modifications over the catalyst structure are mostly performed through organic transformations leading to new chiral organocatalysts. However, very recently, Clarke et al. have shown that the catalytic activity of prolinamide-derived organocatalyst **75** can be modulated in the presence of achiral additives such as pyridinone **76** [120]. The methodology, which is

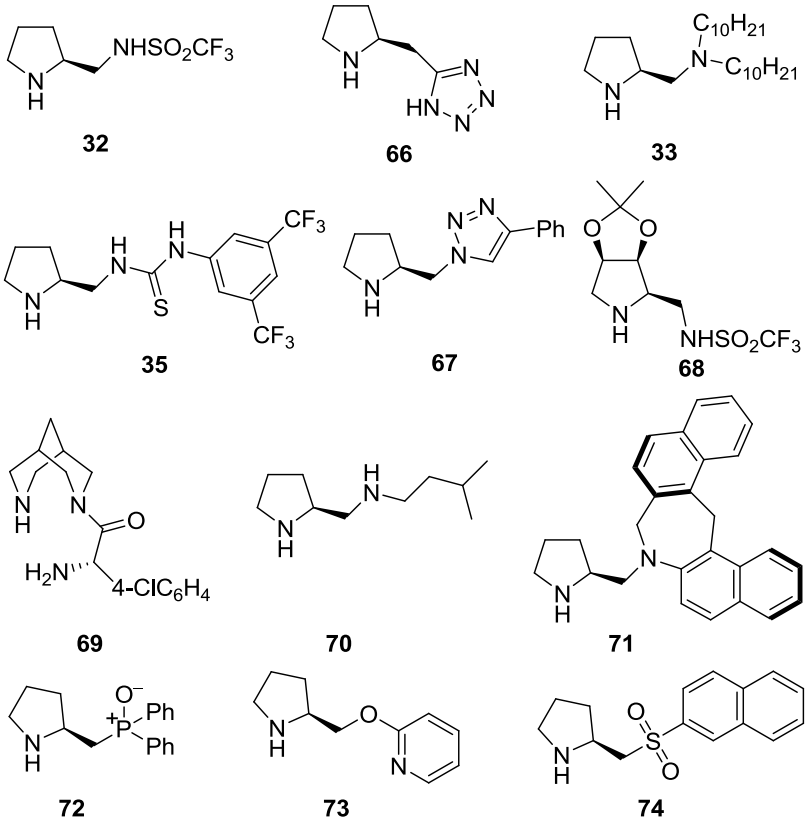
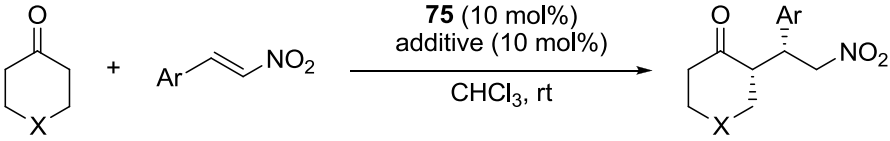


Fig. 2.8 Efficient organocatalysts for the conjugate addition of cyclohexanone derivatives to β-nitrostyrenes

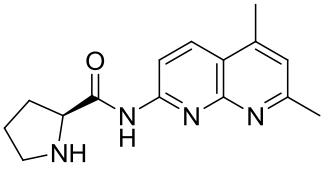
based on the self-assembling of the components through complementary hydrogen bonding (Scheme 2.39) allows the preparation of a small catalyst library using a single chiral catalyst and different achiral additives. Employing different pyridinones Clarke et al. have fine-tuned the catalytic activity of the prolinamide-derived organocatalyst **75** for the conjugate addition of cyclohexanones to β-nitrostyrenes without needing to prepare new chiral catalysts (Scheme 2.39). In fact, the presence of the achiral hydrogen-bonding additive does not just fine-tune the enantioselectivity of the catalyst, but transforms it into a highly effective promoter for the reaction.

The selectivity of the addition of ketones to nitroolefins remains highly substrate-dependent. Therefore, considerably lower diastereo- and enantioselectivities have been normally observed with the greater part of reported organocatalysts when using cyclopentanone or acyclic symmetrical and non-symmetrical ketones as nucleophiles. Regioselectivity problems contribute to convert with non-symmetrical derivatives in challenging substrates in asymmetric organocatalysis. Recently, ionic interactions between ammonium and carboxylate ions have been utilized for the formation of highly selective organocatalytic self-assemblies

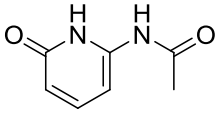


X	Ar	Additive	Time (h)	Conv. (%)	*syn*/*anti*	ee (%)
CH_2	Ph	–	42	63	91/9	16
CH_2	Ph	**76**	22	94 (71)[a]	95/5	75
CH_2	4-$MeOC_6H_4$	–	65	36	92/8	13
CH_2	4-$MeOC_6H_4$	**76**	65	81 (70)[a]	96/4	61
S	3-$NO_2C_6H_4$	–	42	7	–	–
S	3-$NO_2C_6H_4$	**76**	65	70 (60)[a]	97/3	94

[a] Isolated yield.



75



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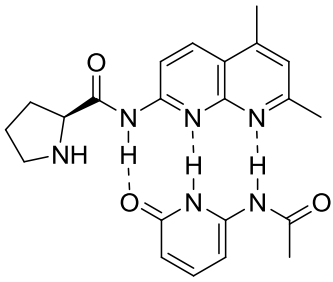
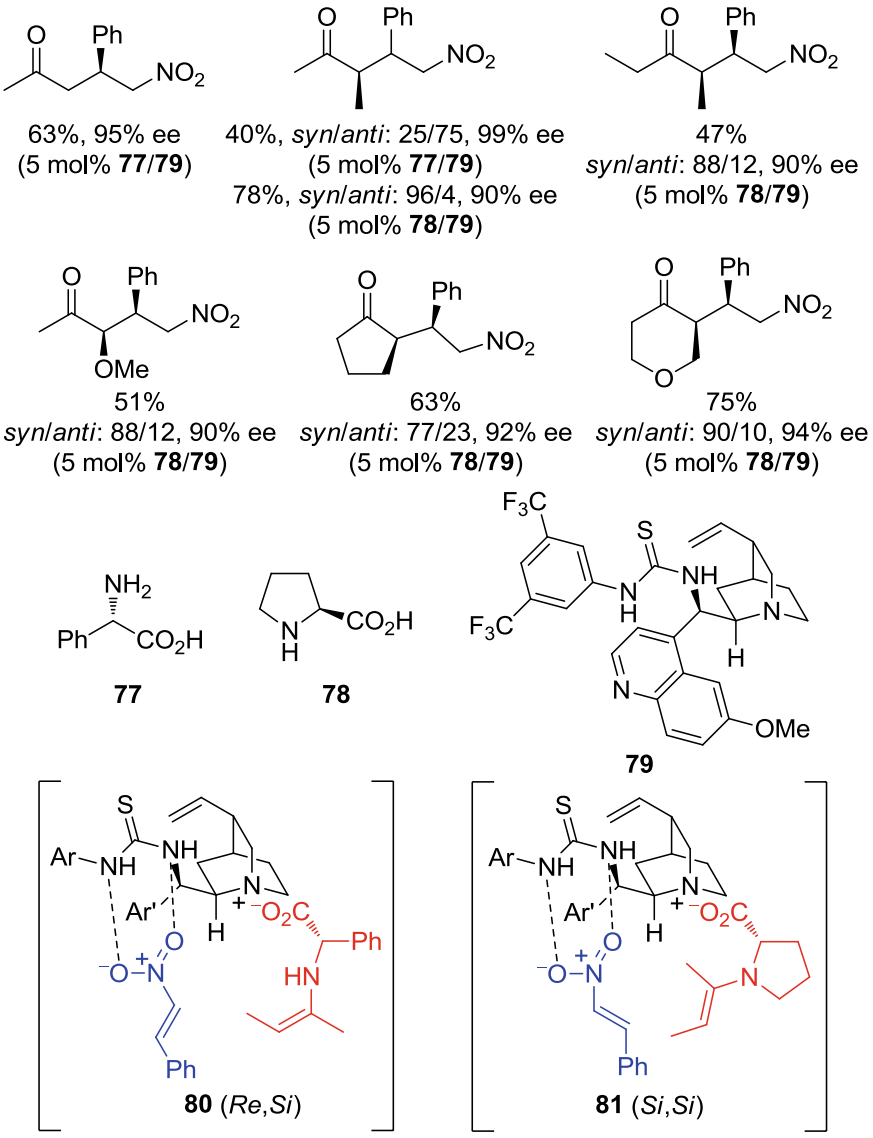


Scheme 2.39 Asymmetric Michael addition of cyclohexanone to β-nitrostyrenes catalyzed by hydrogen-bonding self-assembled organocatalysts

between readily available α-amino acids and alkaloid derivatives [121]. In particular, the self-assemblies formed by the amino acids L-phenylglycine (**77**) or L-proline (**78**) with quinidine thiourea **79** (5 mol%) are selective chiral organocatalysts for the conjugate addition of both cyclic and linear ketones with nitrostyrenes in benzene at rt. Although the reaction requires long reaction times (3–8 days) and moderate to good yields are generally observed, a wide variety of enantiomerically enriched γ-nitroketones are obtained with good diastereoselectivities and excellent enantioselectivities from both cyclic and linear ketones (Scheme 2.40). Generally, the self-assembly formed from L-phenylglycine and **79** is more active and selective when using acetone as nucleophile, while most other ketone substrates such as longer chain methyl ketones, 3-pentanone, and cyclic ketones require the formation of the L-Pro enamine. Interestingly, opposite senses of enantioselectivity and diastereoselectivity for the assemblies of L-phenylglycine and L-proline with **79** are obtained, which has been rationalized by the proposed transitions states showed



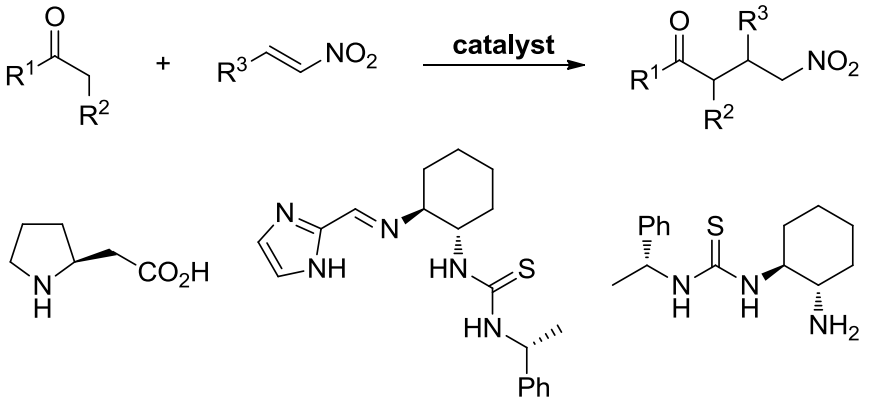
Scheme 2.40 Asymmetric Michael addition of ketones to β-nitrostyrenes catalyzed by ionic self-assembled organocatalysts

in Scheme 2.40. In the case of L-phenylglycine (transition state **80**), the *Re*,*Si* attack of the hydrogen-bonded nitrostyrene on the favored *Z*-enamine leads to the major (3*R*,4*R*)-configured *anti* product. On the other hand, in the case of L-proline, a *Si*,*Si* attack involving the *E*-enamine (transition state **81**) leads to the (3*R*,4*S*)-configured *syn* diastereoisomer.

Some other reports have also described efficient catalysts for the conjugate addition of acyclic aliphatic ketones with similar levels of enantioselection to those commented above for the organocatalytic chiral assemblies. Among representative examples (**82**–**89**, Fig. 2.9) [122–129], Jacobsen's thiourea **90** (Scheme 2.41) [130] is the most efficient organocatalyst reported so far for this process. Under mild reaction conditions (10 mol% of **90**, toluene, rt), this catalyst is able to efficiently catalyze the conjugate addition of different aliphatic ketones with not only nitrostyrenes, but also nitroalkenes bearing aliphatic β-substituents with very high regio-, *anti*-diastereo- and enantioselectivities. Representative examples are depicted in Scheme 2.41. It is also worthy to mention that thiourea **90** (10 mol%) catalyzes the conjugate addition of acetophenone to β-nitrostyrene in a high 86% yield and 99% ee, interesting result which has provided the starting point for the development of other very active and selective thiourea-based organocatalysts for the conjugate addition of aromatic ketones [131].

With respect to α-functionalized ketones, Alexakis et al. have studied the conjugate addition of α-alkoxyketones [50, 132] and α-aminoketones [50, 133] to nitrostyrenes. As shown in Scheme 2.42, nearly perfect control of regioselectivity are obtained for the conjugate addition of these substrates to nitroolefins due to the difference of acidity between the α- and α′-protons of the ketone. In the case of using α-dimethylamino acetone, the corresponding linear adduct is the only regioisomer observed because the balance between steric effects and acidity favors the formation of the terminal enamine. With respect to the diastereoselectivity, the expected *syn*-isomer is obtained for all the nucleophiles except for α-hydroxyacetone due to the formation of the *Z*-enamine intermediate, favored through the formation of hydrogen bonds between the OH group of the nucleophile and the tertiary nitrogen atom of the catalyst. Finally, it is worthy to mention that rate enhancement without loss of selectivity can be achieved, especially in the case of using α-hydroxyacetone as nucleophile, performing the reaction under microwave irradiation (15 W) [134].

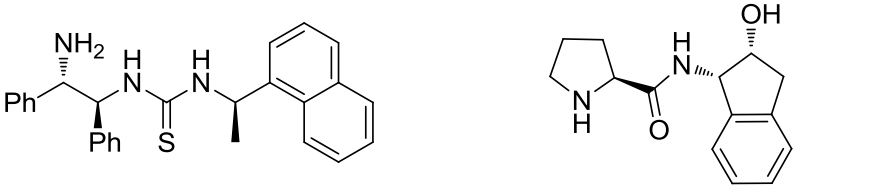
About the reaction mechanism of the Michael addition of ketones to nitroolefins, experimental and theoretical studies have been performed to try to explain it as well as the observed stereochemical outcomes under the influence of different organocatalysts. In general, when primary or secondary chiral 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 employing techniques such as the ESI-MS method over different catalysts such as **84**–**86** and **90**. In the case of proline-derived organocatalyst, an acyclic synclinal transition state assembly [70] explains the usually obtained *syn*-diastereoselectivity and the absolute configuration. Depending of the catalyst employed, two potential models for the stereochemical result 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 of the functionality present in the 2-position of the pyrrolidine ring, it has been suggested either facial bias induced by steric factors (**A**, Fig. 2.10) or through hydrogen bonding interactions (**B** [61] and **C** [126]). The first possibility involves the generation of a *syn*-(*E*)-enamine while hydrogen bonding transition states engage the generation of an *anti*-(*E*)-enamine.



t-BuOH, rt
up to 94% ee
syn/*anti* up to 98/2
(20 mol% **82**)[122]

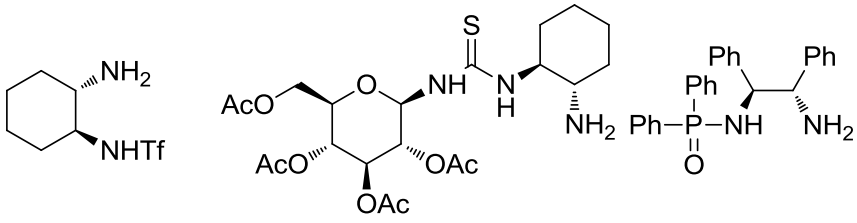
toluene, rt
up to 87% ee
(15 mol% **83**)[123]

AcOH (15 mol%)
toluene, rt
up to 92% ee
(15 mol% **84**)[124]



AcOH (15 mol%)
toluene, rt
up to >99% ee
syn/*anti* up to 14/86
(15 mol% **85**)[125]

4-$NO_2C_6H_4CO_2H$ (20 mol%)
NMP, rt
up to 81% ee
syn/*anti* up to 97/3
(20 mol% **86**)[126]

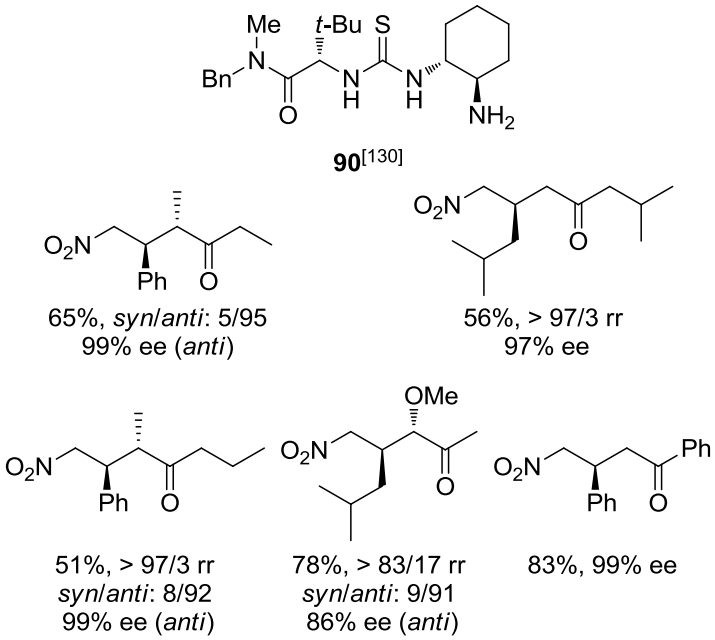


H_2O (15 mol%)
$CHCl_3$, H_2O, rt
syn/*anti* up to 75/25
up to 96% ee
(15 mol% **87**)[127]

AcOH (5 mol%), CH_2Cl_2, rt
up to 96% ee
(5 mol% **88**)[128]

toluene, rt
up to 96% ee
(10 mol% **89**)[129]

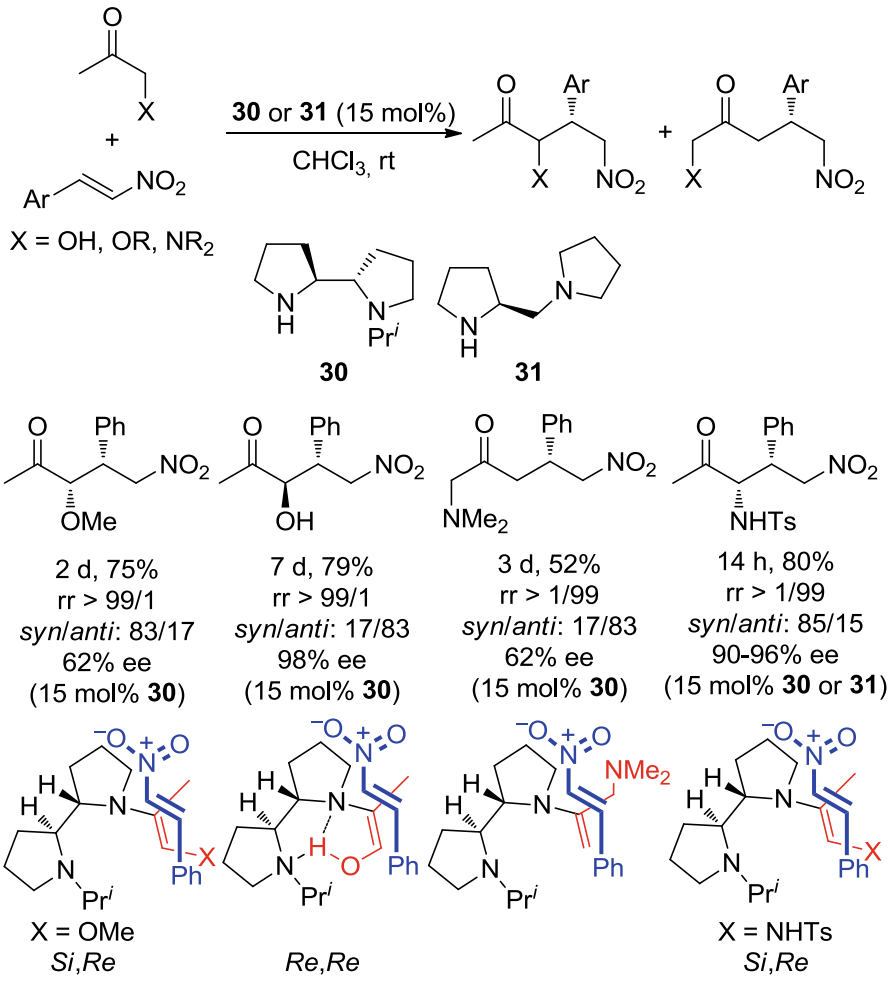
Fig. 2.9 Efficient organocatalysts for the enantioselective conjugate addition of acyclic ketones to β-nitrostyrenes



Scheme 2.41 Jacobsen's chiral primary amine-thiourea addition of ketones to nitroalkenes

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 approaching of the substrates as depicted in proposed transition state **D** [52b] (Fig. 2.10) for the **32**-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.

On the other hand, chiral primary amine-thiourea catalysts **85** and **90** developed by Tsogoeva [125] and Jacobsen [130], respectively, show an opposite sense of relative stereoinduction in the conjugate addition of acyclic ketones to nitroolefins (see Scheme 2.41 for **90**). These *anti* selective catalysts stand in contrast to the usually obtained results which lead to selective formation of the *syn*-configured diastereoisomers. The unexpected situation suggests participation of a *Z*-enamine intermediate. Moreover, with respect to the electrophile activation by the urea-type catalysts, it is also demonstrated that only one oxygen of the nitro group is bound to the thiourea moiety in an out-of-plane arrangement [125, 130].



Scheme 2.42 Asymmetric Michael addition of α-heterosubstituted ketones to nitroolefins

With regard to the employment of recyclable chiral organocatalysts in the conjugate addition of ketones to nitroolefins, various immobilization strategies, including attaching the catalysts to organic or inorganic supports, as well as to ionic liquids, and the so-called biphasic technology, have been extensively studied. Among them, the best results in terms of activity and selectivity have been obtained with polystyrene-supported catalysts, employing ionic liquid immobilizations, and by using the fluorous sulfonamide **54** [86a] (Fig. 2.6). Regarding the polymer-supported organocatalysts [135], with covalent attachment, high diastereo- (*syn*/*anti* up to >99/1) and enantioselectivities (up to >99% ee) have been reported for the conjugate addition of cyclohexanones to nitrostyrenes in water using the polystyrene-supported pyrrolidine **91** (10 mol%) [135a] or under neat conditions using the polystyrene-immobilized pyrrolidine-based chiral ionic liquid **92** (10 mol%) [135b] (Fig. 2.11). Very high selectivities have been also obtained for the **93**-catalyzed

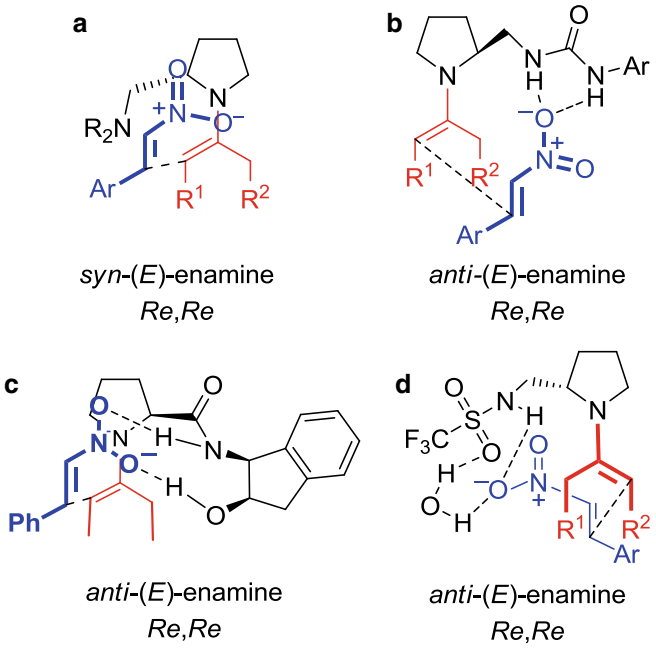


Fig. 2.10 Proposed transition state models for the conjugate addition of ketones to β-nitrostyrenes

(10 mol%) conjugate addition of cyclic and acyclic ketones with nitrostyrenes and β-alkyl substituted nitroolefins in water [135d]. On the other hand, catalyst **94**, where a non-covalent acid–base immobilization between the polystyrene support and the catalyst is involved, has been recently demonstrated to catalyze the Michael addition of cyclohexanone to nitrostyrenes (10 mol%, *syn*/*anti*: 94/6, 88% ee(*syn*)) [135e]. All the above mentioned catalysts are easily recovered from the reaction medium and reused without loss of activity for 6–8 cycles.

Regarding ionic liquid immobilization, different pyrrolidine-based organocatalysts have been synthesized and demonstrated excellent selectivities (*syn*/*anti*: >99/1, >99% ee) for the conjugate addition of cyclohexanone to nitrostyrenes [136]. These catalysts are easily recovered by precipitation, extraction, or filtration and reused for several cycles. Representative examples (**95**–**97**) of some of the most active systems are depicted in Fig. 2.11.

2.3.2.3 Conjugate Addition of Ketones to Alkylidene Malonates, Alkylidene Malononitriles, and Vinyl Sulfones

First studies in relation to the conjugate addition of ketones with alkylidene malonates were performed by Barbas group initially using L-proline [107] and proline-derived diamines such as **31** [49, 138] (Fig. 2.4) as organocatalysts, showing that acetone, cyclohexanones, and cyclopentanone could add to various aryl- and alkylidene malonates with moderate yields and enantioselectivities. Very recently,

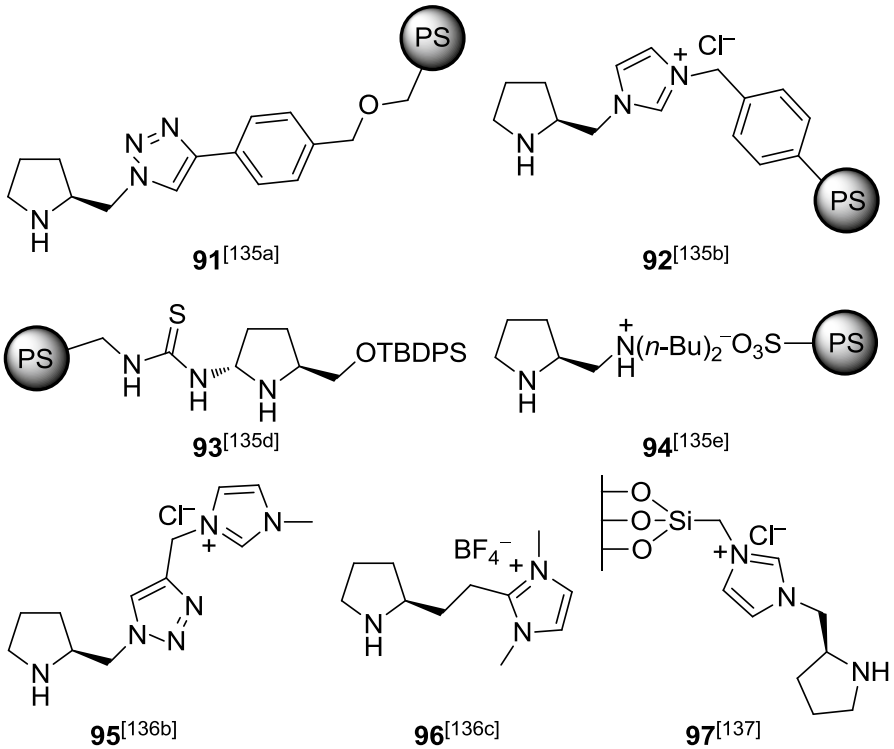
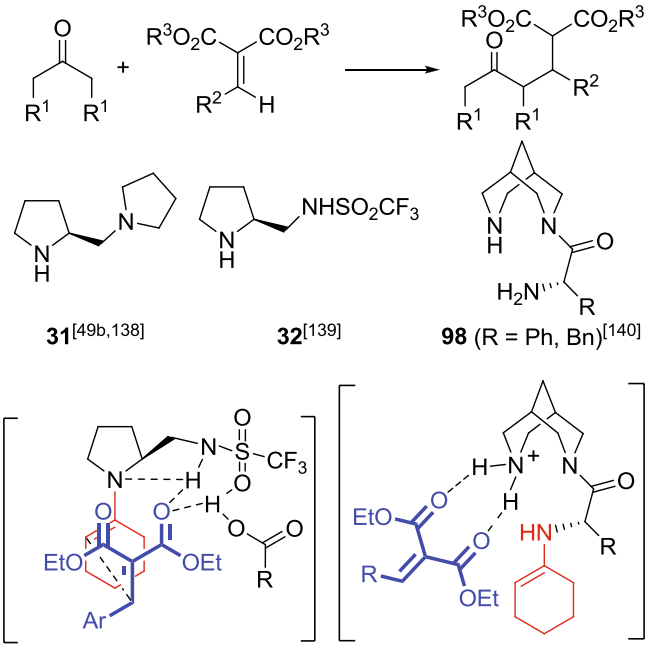


Fig. 2.11 Polymer-supported chiral organocatalysts for the conjugate addition of ketones to nitrostyrenes

Tang et al. have reported that catalyst **32** (20 mol%) yields Michael adducts in moderate to good yields, high *syn*-diastereoselectivities (*syn*/*anti* up to 95/5), and good to high enantioselectivities (up to 94% ee), depending upon the substituents present on the ketone nucleophile and the electrophilic malonate [139]. Generally, the reaction works well when using cyclic ketones and arylidene malonates. However, acyclic ketones, such as acetone or 3-pentanone, and alkylmethylene malonates are not suitable partners for pyrrolidine **32** (Scheme 2.43). Alternatively, bispidine-derived organocatalysts **98** (20 mol%, Scheme 2.43) have shown good stereocontrol (*syn*/*anti* up to 99/1, up to 97% ee) in the addition of cyclohexanone, cyclopentanone, acetone, and 3-pentanone to arylidene malonates in water at rt [140]. The reaction, which is carried out in the presence of 3,5-dinitrosalicylic acid (20 mol%) as cocatalyst, affords lower selectivities in the case of using acyclic ketones (81–87% ee), and very poor for alkylidene malonates (30% ee). Proposed transitions states for catalysts **32** and **98** involving activation through enamine and hydrogen-bonding networks, are illustrated in Scheme 2.43.

Substoichiometric amounts of diamine **31** (30 mol%) catalyze a highly regio- and enantioselective (85–99% ee) conjugate addition of alkyl methyl ketones to β-dimethyl(phenyl)silylmethylene malonate in the presence of TFA (10 mol%) as

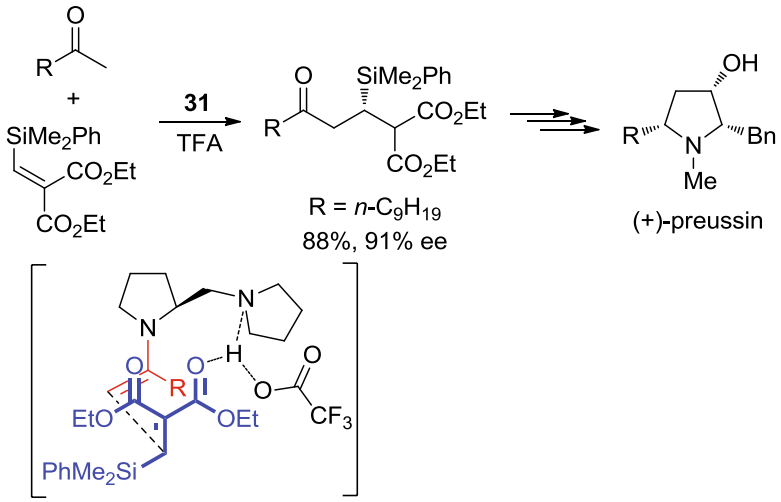


Scheme 2.43 Organocatalyzed stereoselective Michael addition of ketones to alkylidene malonates

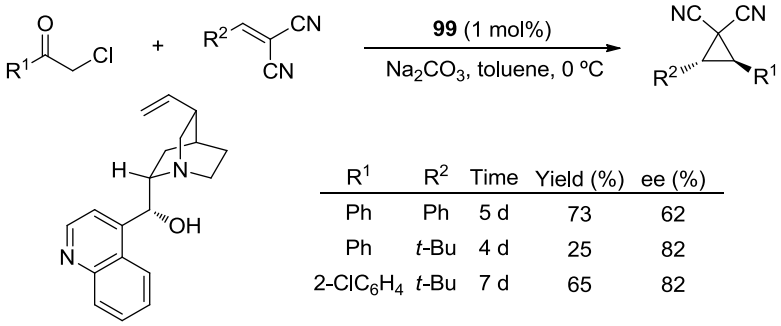
cocatalyst [141]. This conjugate reaction is carried out in NMP as solvent at −10°C, and it has allowed the synthesis of highly substituted pyrrolidines such as (+)-preussin (Scheme 2.44). The stereochemical outcome of the reaction has been explained with a transition state where the malonate approaches the enamine from the less hindered *si* face. The presence of hydrogen bonding interactions among the tertiary nitrogen, one of the carbonyl groups of the electrophile, and the cocatalyst would bring all the reactants to proximity.

Cinchonidine (**99**) has extended the substrate scope of the ketone conjugate additions to β-substituted methylidene malononitriles. In particular, the reaction of α-chloromethyl ketones, under very low loading conditions, affords tetrasubstituted cyclopropanes in moderate to good enantioselectivities after intramolecular cyclization (Scheme 2.45) [142]. A similar strategy has been followed to synthesize, with moderate to good enantioselectivities (56–90% ee) optically active naphthopyran derivatives by a conjugate addition/cyclization sequence between 2-naphthol and α,α-dicyanoolefins[143].

Finally, a primary amine directed enamine activation has been used for a highly enantioselective conjugate addition of cyclohexanones to 1,1-bis(benzenesulfonyl) ethylene [144]. The reaction, which is efficiently catalyzed by Cinchonidine-derived primary amine **100** (10–20 mol%) is carried out in $CHCl_3$ at 0°C in the presence of benzoic acid as cocatalyst. As depicted in Scheme 2.46, an enantioselective synthesis of (*S*,*S*)-sodium cyclamate has been achieved following this methodology.

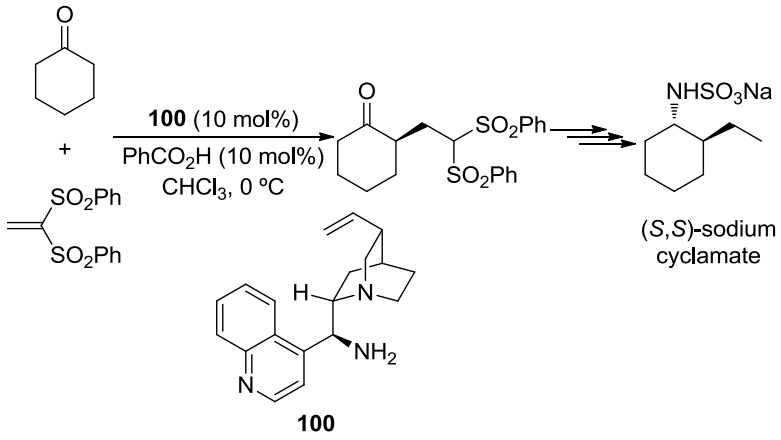


Scheme 2.44 Formal synthesis of (+)-preussin and proposed transition state for the conjugate addition



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

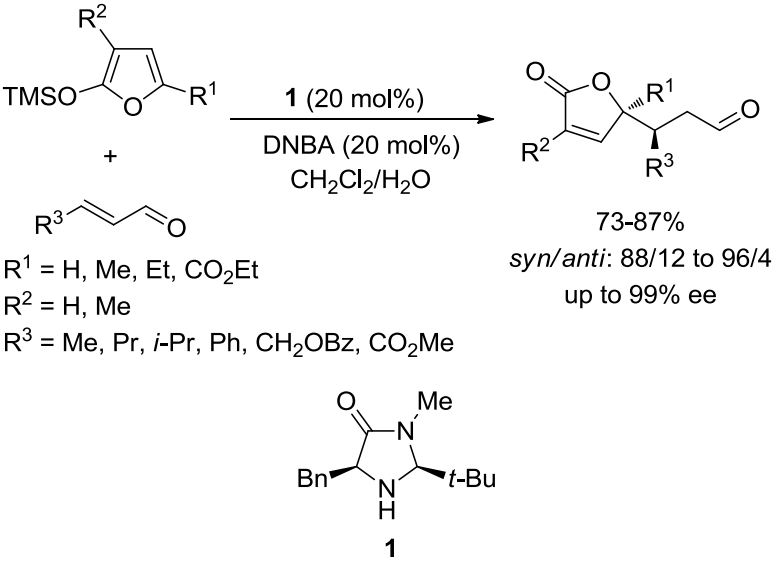
Scheme 2.45 Enantioselective synthesis of activated cyclopropanes catalyzed by Cinchonidine



Scheme 2.46 Enantioselective synthesis of (*S*,*S*)-sodium cyclamate

2.3.3 *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 this compounds to 1,2-addition when using metal-containing Lewis acid catalysts. With respect to organocatalyzed approaches, the enantioselective Mukaiyama-Michael reaction has been achieved by the use of iminium or ion-pairing activation approaches. Concerning the former activation mode, MacMillan et al. have demonstrated that chiral imidazolidinone **1** catalyzes the enantioselective Mukaiyama-Michael reaction of 2-(silyloxy)furans to simple unsaturated aldehydes (Scheme 2.47) [145]. On the basis of molecular modeling studies, MacMillan's group anticipated the inertness of α,β-unsaturated iminium ions arising from chiral amine **1** towards 1,2-addition to the 2-(silyloxy)furan 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 2.47). Optimum catalytic

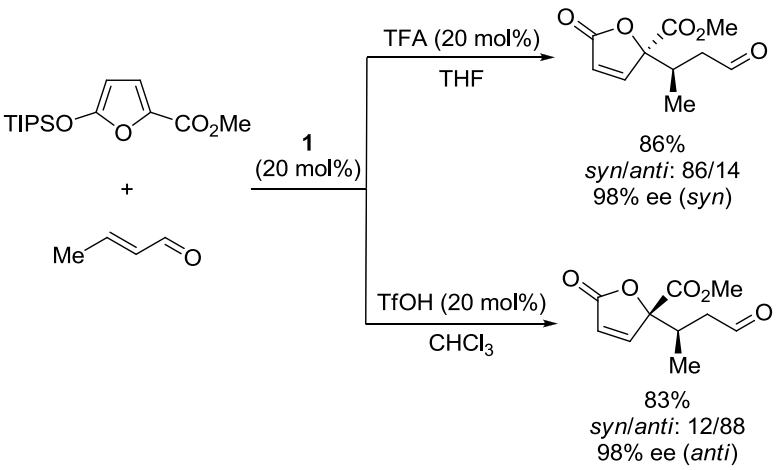


Scheme 2.47 Organocatalyzed vinylogous Mukaiyama-Michael addition of 2-(silyloxy)furans to α,β-unsaturated aldehydes

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 $(TMS)_2O$. This methodology, which has been recently broaden to S-alkyl and 1-pyrrolyl silylketene acetals [146], has been applied to the

synthesis of different natural products such as spiculisporic acid [145] and the inhibitor of the hydroxymethylglutaryl coenzyme A reductase (+)-compactin [147].

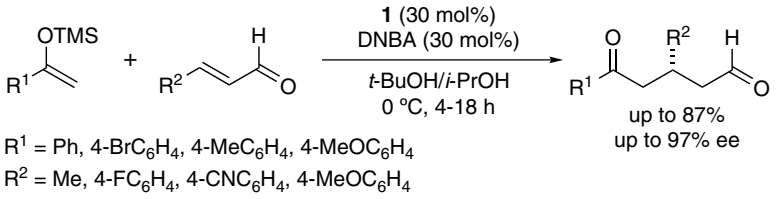
A delicate balance between *syn*- and *anti*- addition seems to exist in the process, which can be shifted deliberately by appropriate choice of the acid cocatalyst, the solvent, the temperature and the steric demand of the ester group present in the enal [145]. Scheme 2.48 shows how the solvent and the catalyst are able to control the diastereoselectivity of the reaction.



Scheme 2.48 Control of diastereoselectivity in the vinylogous Mukaiyama-Michael addition

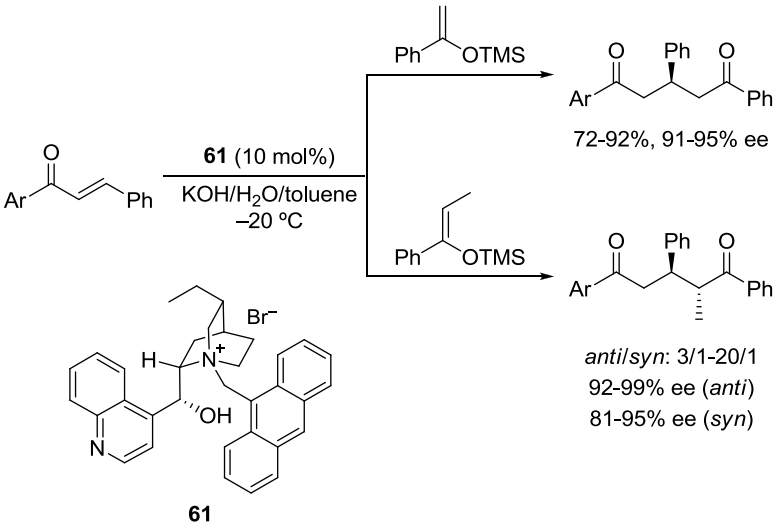
MacMillan's chiral imidazolidinone **1** has been also employed by Wang et al. to promote the Mukaiyama-Michael reaction between silyl enol ethers and α,β-unsaturated aldehydes in the presence of 2,4-dinitrobenzoic acid (DNBA) as additive [148]. High yields (56–87%) and high enantioselectivities (85–97% ee) have been obtained for a wide range of important chiral synthetic building blocks following this methodology (Scheme 2.49).

Aqueous-organic biphasic PTC conditions (toluene/50% aqueous KOH) have used by Corey and Zhang for the Mukaiyama-Michael addition of different silyl enol



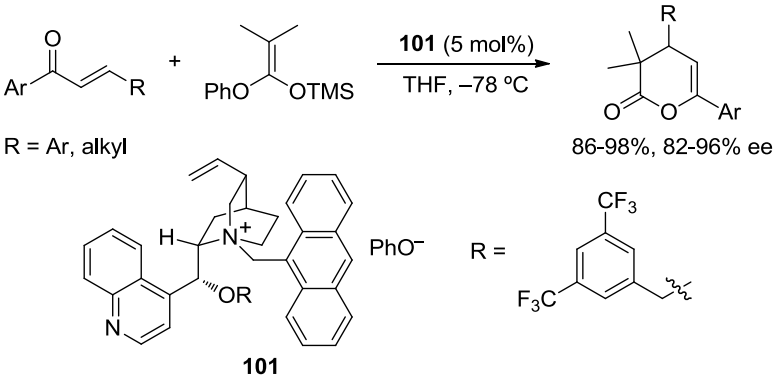
Scheme 2.49 Organocatalyzed Mukaiyama-Michael addition of silyl enol ethers to α,β-unsaturated aldehydes

ethers to chalcones promoted by the quaternary ammonium salt *N*-(9-anthracenyl methyl)dihydrocinchonidinium bromide (**61**) at 20°C (Scheme 2.50) [149]. The addition products are obtained in good yields, very high enantioselectivities and *anti*-diastereoselectivities in the case of using preformed *Z*-silyl enol ethers.



Scheme 2.50 PTC Mukaiyama-Michael addition of silyl enol ethers to chalcones

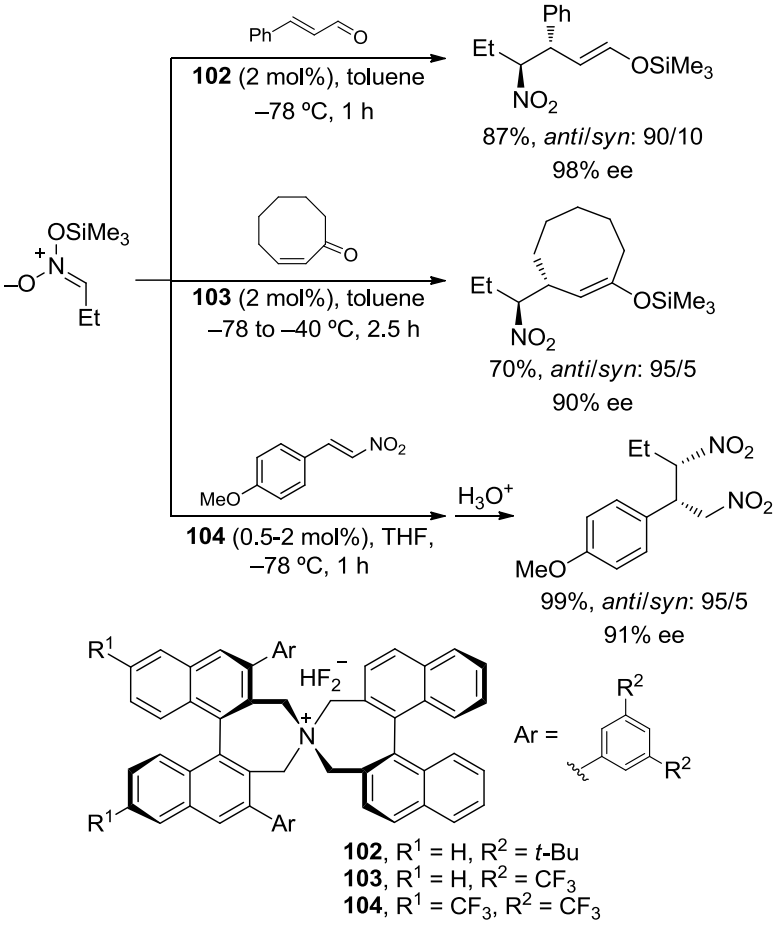
Mukaiyama et al. have productively employed chiral quaternary ammonium phenoxides derived from *Cinchona* alkaloids as catalysts in a new and efficient method for the preparation of optically active 3,4-dihydropyran-2-one derivates via tandem Mukaiyama-Michael addition/lactonization between α,β-unsaturated ketones and the silyl enolate derived from phenyl isobutyrate (Scheme 2.51) [150]. In this



Scheme 2.51 Enantioselective synthesis of 3,4-dihydropyran-2-ones

reaction, the phenoxy group contained in the silyl enolate behaves as an effective leaving group to facilitate intramolecular cyclization of in situ formed Michael-adduct, and the liberated phenoxide ion also works as a Lewis base catalyst to activate the silyl enolate. A variety of chiral quaternary ammonium phenoxides have been screened, catalyst **101** showing the best catalytic activity (Scheme 2.51).

Maruoka et al. have developed and used *N*-spiro C2-symmetric chiral quaternary ammonium bifluorides [151] **102**, **103**, and more recently **104**, to promote the regio- and *anti*-selective Mukaiyama-Michael addition of silyl nitronates to α,β-unsaturated aldehydes [152], cyclic α,β-unsaturated ketones [153], and nitroalkenes [154] with good yields and enantioselectivities (Scheme 2.52). Final chiral silyl enol ethers are easily hydrolyzed to the corresponding carbonyl compounds or functionalized at the α-position by reaction with electrophiles.



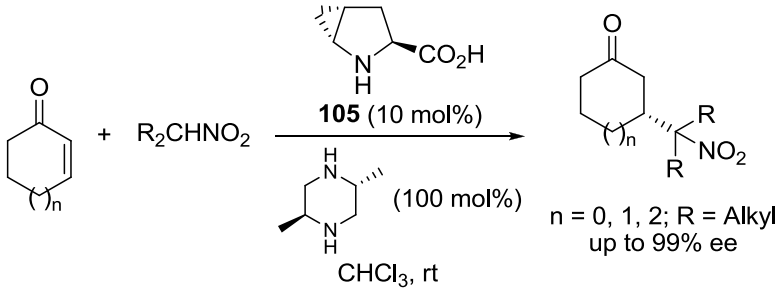
Scheme 2.52 Asymmetric Michael addition of silyl nitronates to α,β-unsaturated aldehydes, ketones, and nitroalkenes

2.3.4 *Conjugate Addition of Nitroalkanes*

The employment of nitroalkanes as nucleophiles in conjugate additions has recently drawn enormous attention in asymmetric organocatalysis [155]. Thus, highly enantioselective nitro-Michael additions to a wide variety of electrophiles such as, enones, enals, electron-poor allenes, α,β-unsaturated amides and esters, styrylisoxazoles, nitroalkenes, and vinyl sulfones have been already accomplished using small chiral molecules as catalysts. Regarding the activation mode, electrophile-iminium activation using chiral secondary amines, non-covalent hydrogen-bonding, and ion-pairing catalysis are the most frequently used catalysis.

2.3.4.1 Conjugate Addition of Nitroalkanes to α,β-Unsaturated Ketones

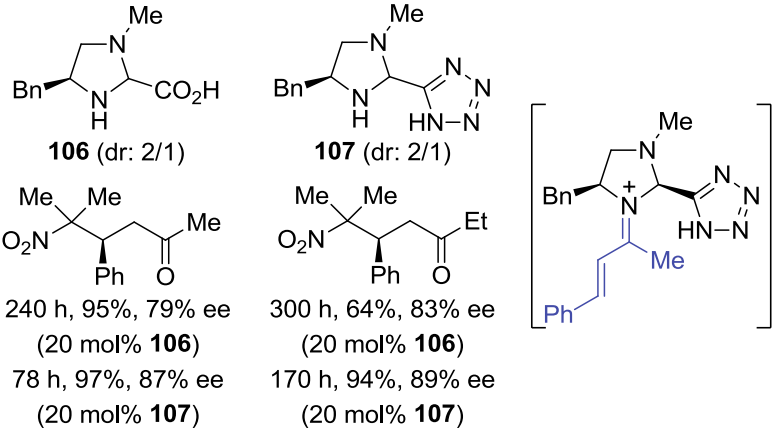
The conjugate addition of nitroalkanes to enones yields products that are useful and versatile precursors for a variety of structures such as aminocarbonyl compounds, aminoalkanes, and pyrrolidines. In 1994, Yamaguchi et al. reported an organocatalytic iminium-type enantioselective Michael addition of primary and secondary nitroalkanes to cyclic and acyclic enones and enals catalyzed by L-proline rubidium salt in moderate to good enantioselectivities (29–86% ee) [156]. 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%) [157]. 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 (**105**) as organocatalyst under similar reaction conditions [158]. As depicted in Scheme 2.53, very high enantioselectivities were obtained when employing catalyst **105** for the addition of symmetrical 2-nitroalkanes to cyclic enones. In the case of the addition of 1-nitroalkanes to cyclic enones, low diastereoselectivities were observed although with good enantioselectivities for both diastereoisomers (60–91% ee). A complex multicomponent chiral catalytic system was assumed to operate in the basis of the pronounced non-linear effect detected in the reaction.



Scheme 2.53 Asymmetric addition of nitroalkanes to cyclic enones catalyzed by **105**

The piperazine cocatalyst seemed to act as a counter cation to the iminium carboxylate in the transition state thus leading to higher enantioselectivities [157, 158].

After the preliminary studies on the reaction, a wide variety of efficient chiral organocatalysts has been developed by different groups for the Michael addition of nitroalkanes to enones. For instance, Jørgensen's group has reported that imidazolidine catalyst **106** (Scheme 2.54), easily prepared from phenylalanine, promotes the conjugate addition of acyclic- and cyclic nitroalkanes with a wide variety of acyclic

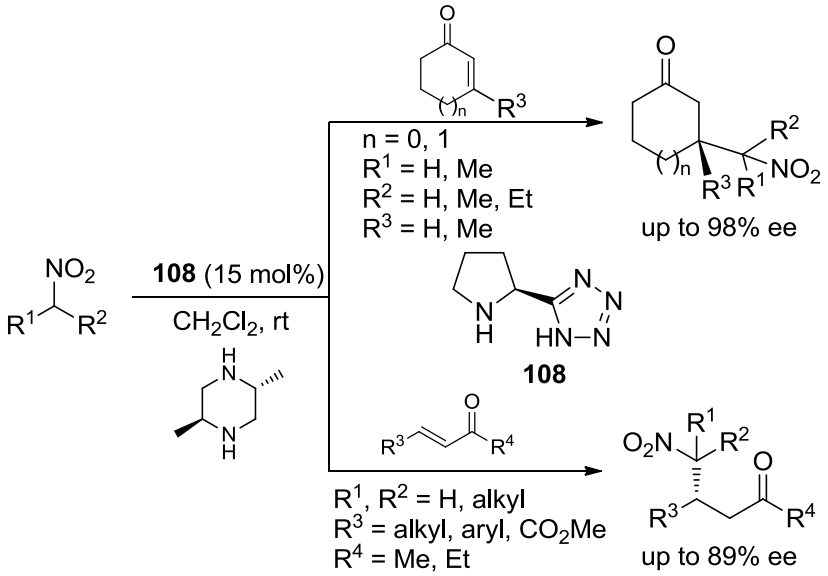


Scheme 2.54 Imidazolidine-catalyzed asymmetric Michael addition of 2-nitropropane to enones

α,β-unsaturated ketones in high yields and similar levels of enantioselection than those obtained with proline derivatives (up to 86% ee) [159]. However, due to solubility problems, **106** requires very long reaction (up to 12 days) and moderate enantioselectivity is obtained for cylohexenone (49% ee)(Scheme 2.54). The more soluble chiral imidazolidine-2-yltetrazole catalyst **107** has been shown by the same group to be more active, reducing the reaction times (3–8 days) and notably improving enantioselectivities for acyclic enones (up to 92% ee) [160]. Unfortunately, poor selectivities (61–77% ee) are obtained with cyclic enones. As depicted in Scheme 2.54, the formation of an iminium ion intermediate between the enone and the catalysts, with the benzyl group shielding the *Re*-face of the electrophile is responsible for the enantioselectivity observed.

Pyrrolidine-tetrazole **108** is also a very useful catalyst for the conjugate addition of a wide variety of nitroalkanes to cyclic and acyclic enones using *trans*-2,5-dimethylpiperazine as base (Scheme 2.55) [161]. Excellent enantioselectivities (94–97% ee) are obtained for the addition of primary and secondary nitroalkanes to cyclohexenone and 3-methyl-2-cyclohexenone. On the other hand, the level of enantioselection displayed by catalyst **108** in the case of the conjugate addition to acyclic enones is similar to that obtained with catalyst **107** (Scheme 2.55).

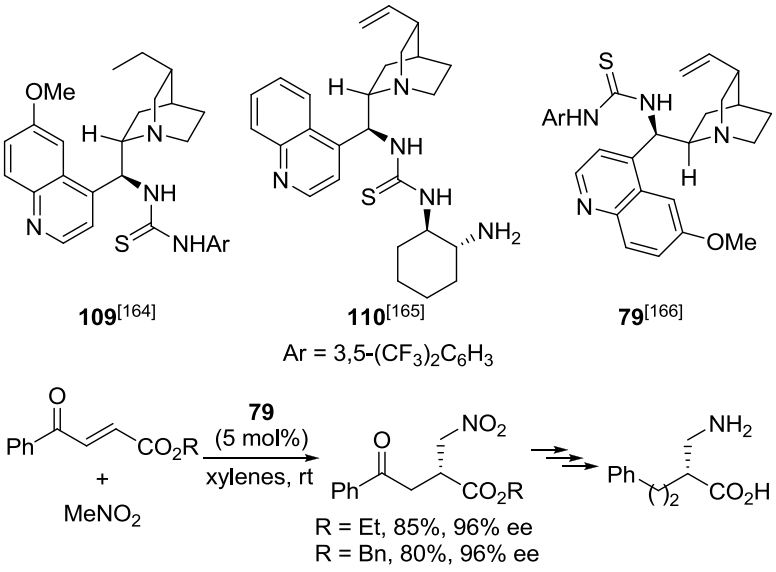
In 1975, Wynberg and Helder reported the first asymmetric Michael addition of the doubly activated α-tosylnitroalkanes to methyl vinyl ketone catalyzed by quinine



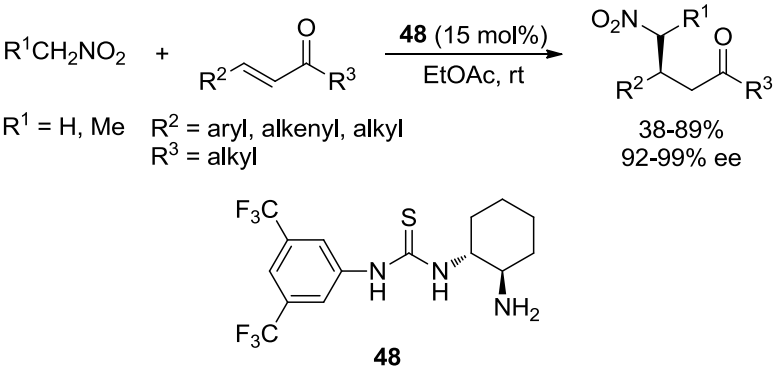
Scheme 2.55 Asymmetric addition of nitroalkanes to enones catalyzed by pyrrolidine-tetrazole **108**

(1.2 mol%) in toluene at rt [162]. The enantiomeric excess was determined just for the addition of α-tosylnitroethane to methyl vinyl ketone (56% ee). Six years later, 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) [163]. More recently, *Cinchona* alkaloids-derived thioureas such as **109**, **110** and **79** (Scheme 2.56), have been successfully employed as catalysts for the conjugate addition of nitroalkanes to acyclic and cyclic enones with very promising results. For instance, the quinine-derived bifunctional thiourea **109** affords very high enantioselectivities (89–98% ee) for the nitromethane addition to chalcones in toluene at rt [164].

On the other hand, chiral γ-keto esters have been synthesized with complete regioselectivity and high enantioselectivity (up to 98% ee) by a conjugate addition of nitroalkanes to 4-oxoenoates catalyzed by quinidine-derived thiourea **79** [166]. The reaction, which is performed in xylenes at rt using 5 mol% of **79**, affords good yields and selectivities for a wide variety of Michael acceptors, such as 4-aryl- and 4-alkyl substituted 4-oxoenoates, and nucleophiles, such as nitromethane, nitroethane, and ethyl 2-nitropropionate. As depicted in Scheme 2.57, this reaction has been successfully used for the synthesis of chiral β-amino acids. In relation with this conjugate addition, quinine has been very recently shown as an excellent promoter for a highly enantioselective (up to 98% ee) conjugate addition of linear nitroalkanes to cyclic α,β′-unsaturated β-ketoesters [167].



Scheme 2.56 Cinchona-derived organocatalysts for the addition of nitroalkanes to enones

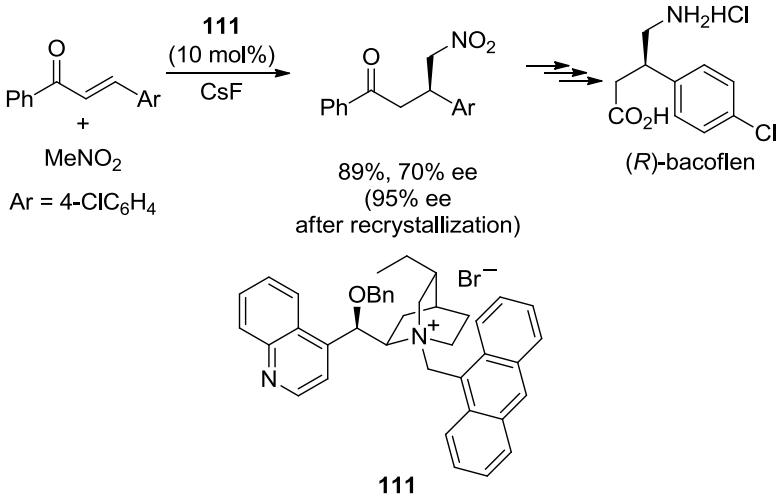


Scheme 2.57 Asymmetric conjugate addition of nitroalkanes to acyclic enones

A highly enantioselective conjugate addition of nitromethane and nitroethane to acyclic enones has been recently achieved using chiral cyclohexanediamine-derived primary amine thiourea **48** (Scheme 2.57) [168]. With respect to the electrophile, the reaction shows a broad substrate scope and not only 1-aryl- but also 1-alkyl enones afford the corresponding chiral γ-nitroketones with good yields and excellent enantioselectivities (92–99% ee).

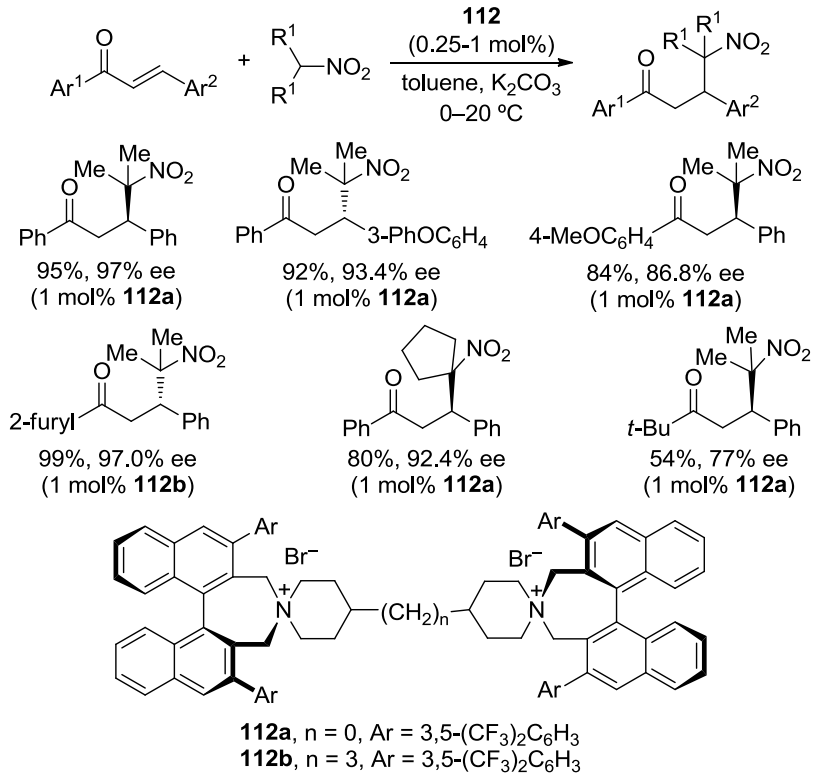
Chiral quaternary ammonium salts are competent phase-transfer catalysts for the conjugate addition of nitroalkanes to α,β-unsaturated ketones. Pioneering work by Wynberg and Colonna groups about the enantioselective Michael addition of nitroalkanes to chalcones employing chiral phase-transfer catalysts derived from *Cinchona*

and Ephedra alkaloids [162, 169], was significantly improved by Corey and Zhang [170] in 2000 using the *N*-(9-anthracenylmethyl)cinchonine derivative **111**, and applied to the synthesis of (*R*)-baclofen hydrochloride a γ-amino acid that acts as GABA receptor agonist (Scheme 2.58).



Scheme 2.58 Asymmetric PTC synthesis of (*R*)-bacoflen

New chiral quaternary ammonium salts **112** have been very recently developed to catalyze the conjugate addition of secondary nitroalkanes to chalcone and derivatives in high yields and enantioselectivities (Scheme 2.59) [171]. Bifunctional organocatalysts **112** are based on the concept of a linker-dictated structure that tunes rigidity and flexibility, giving access to both enantiomeric products of the conjugate addition reaction from the common BINOL chirality source. This outcome represents a rare example of accessing both enantiomers of an asymmetric transformation by using catalyst possessing a common chiral element. Thus, the positive synergy of the two chiral fragments of the catalyst is directly related to the nature of the linker, catalyst **112a** (n = 0, Scheme 2.59) giving mainly the *R* enantiomer, while catalyst **112b** (n = 3) affords the corresponding *S* adduct (Scheme 2.59). Also, the structural rigidity of the two chiral centers in both catalysts is well preserved, the two structures differing mainly in the size of the open cavity and the relative orientation of the chiral binaphthyl units. Furthermore, catalysts **112** can be recovered and reused without any loss of activity and selectivity. As depicted in Scheme 2.59, the scope of the reaction is not limited to chalcones with different electronic properties (86.8–99.8% ee), as also heterocyclic substitution in the electrophile affords the corresponding derivatives in high yields and enantioselectivities (84.8–98.6% ee), even when using nitrocyclopentane and nitrocyclohexane, derivatives which have rarely been used in conjugate additions due to their intrinsic low reactivity. Only enones derived from aliphatic ketones afforded the products in modest yields and enantioselectivities (66.6–77% ee).

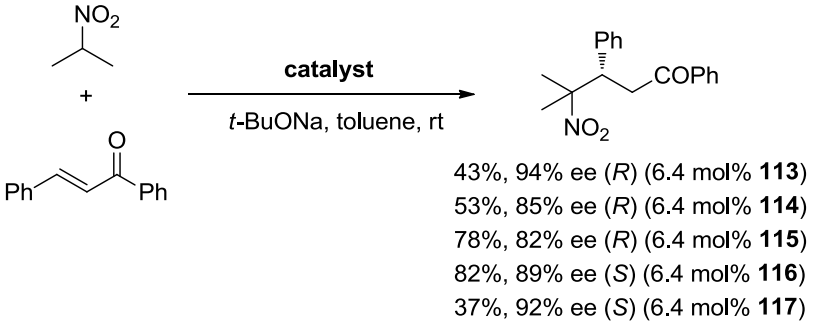


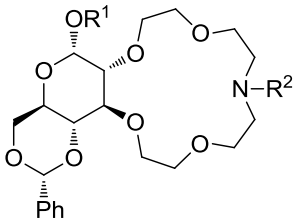
Scheme 2.59 Asymmetric conjugate addition of nitroalkanes to acyclic enones

Carbohydrate-derived azacrown ethers have been intensely studied as phase-transfer catalysts for the conjugate addition of 2-nitropropane to chalcones [172]. Various structural modifications have been 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 been obtained with D-glucose and D-mannose derivatives **113**–**117** (Scheme 2.60).

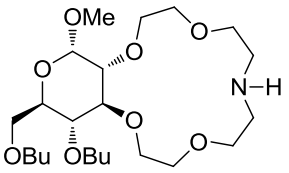
Considerable amount of work has been lately devoted to the development of C_2-symmetric ammonium catalysts from either natural products or synthetic compounds, for use in the asymmetric conjugate addition of nitroalkanes. Among these catalysts, C_2-symmetric guanidines and guanidinium salts have been tested as chiral phase-transfer catalysts in the conjugate addition of nitroalkanes with enones [173]. The best results so far, has been obtained with spirocyclic guanidine **118**, which catalyzes the addition of 2-nitropropane to chalcone in high yield and good enantioselectivity (Scheme 2.61) [173b].

On the other hand, *N*-spiro C_2-symmetric chiral biaryl derivative **119** shows remarkable reactivity and selectivity in the conjugate addition of nitroalkanes to cyclic enones under mild solid–liquid PTC (Scheme 2.62) [174]. This class of





113, R^1 = Me, R^2 = $(CH_2)_4P(O)Ph_2$
114, R^1 = Me, R^2 = $(CH_2)_3OH$
115, R^1 = Ph, R^2 = $(CH_2)_2Ph$



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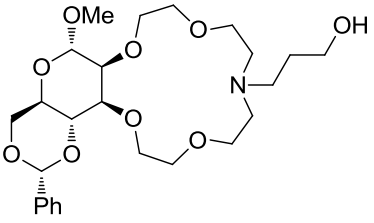

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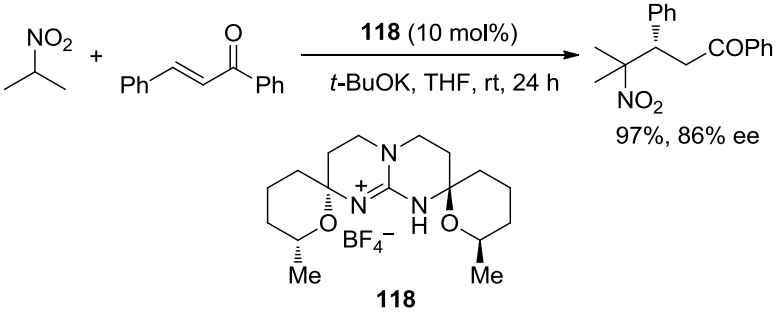
Scheme 2.60 Enantioselective Michael addition of 2-nitropropane to chalcone catalyzed by chiral azacrown ethers



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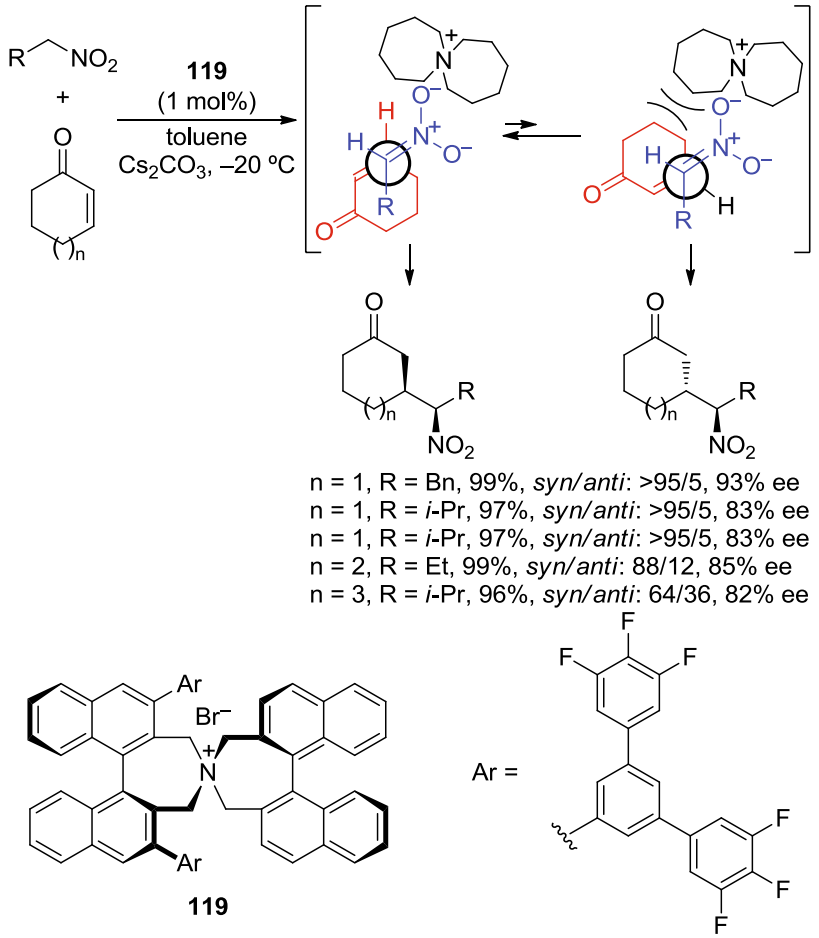
Scheme 2.61 Asymmetric conjugate addition of 2-nitropropane to chalcone catalyzed by C_2-symmetric guanidinium salt **118**

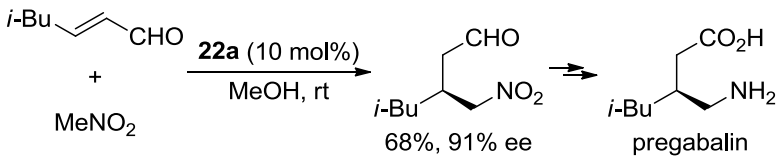


Scheme 2.62 Conjugate addition of nitroalkanes catalyzed by *N*-spiro chiral ammonium bromides

catalyst has the advantage over other synthetic phase-transfer catalysts that its structure can be modified allowing a rapid access to a variety of analogues. The **119-**catalyzed conjugate addition of nitroalkanes with cyclic enones affords the corresponding γ-nitro ketones in excellent chemical yields with unprecedented levels of *syn*-diastereo- and enantiocontrol (Scheme 2.62). Assuming the predominant generation of the *E*-nitronate, the observed *syn* selectivity has been 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. The chiral ammonium cation shields the *Re*-face of the nitronate, which produces a selective approach of the cyclic enone from the *Si*-face.

2.3.4.2 Conjugate Addition of Nitroalkanes to α,β-Unsaturated Aldehydes

The scope of the iminium activation has been further extended to the asymmetric conjugate addition of nitroalkanes to enals. Imidazolidinone-derived catalysts were initially employed by Arvidsson et al. for the reaction between nitroalkanes and cinnamaldehydes obtaining very low diastereoselectivities and moderate to good enantioselectivities (53–90% ee) [175]. Almost simultaneously, much higher selectivities have been obtained by three different groups for the conjugate addition of nitroalkanes and enals employing diphenylprolinol silyl ether **22a** as catalyst under pretty similar reaction conditions [176]. The addition of nitroalkanes to cinnamaldehyde derivatives gives full conversions and excellent enantioselectivities (90–97% ee). Also, very promising results are obtained when using β-alkyl substituted enals such as crotonaldehyde, 2-pentenal, 2-hexenal, and 2-decenal, where full conversions and good to excellent enantioselectivities (81–94% ee) are also obtained. This reaction has been applied to the synthesis of the GABA receptor agonist baclofen [176] and the anticonvulsant pregabalin (Scheme 2.63) [176b].

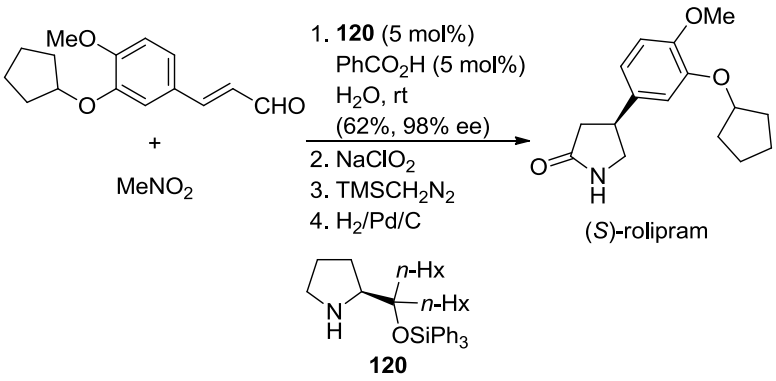


Scheme 2.63 Enantioselective synthesis of pregabalin

Interestingly, Palomo et al. have developed a new family of prolinol-based organocatalysts that enable iminium activation of enals using water as solvent [177]. In this manner, using only a 5 mol% of catalyst **120**, these authors have been able to carry out the conjugate addition of nitromethane to a wide variety of cinnamaldehydes and crotonaldehyde with enantioselectivities ≥90% in all cases. The asymmetric synthesis of (*S*)-rolipram is an interesting application of the methodology developed by this group (Scheme 2.64). Very high enantioselectivities in water have been also obtained with a PEG-supported diarylprolinol silyl ether catalyst, which avoids chromatographic purification of the sensitive aldehyde products [178].

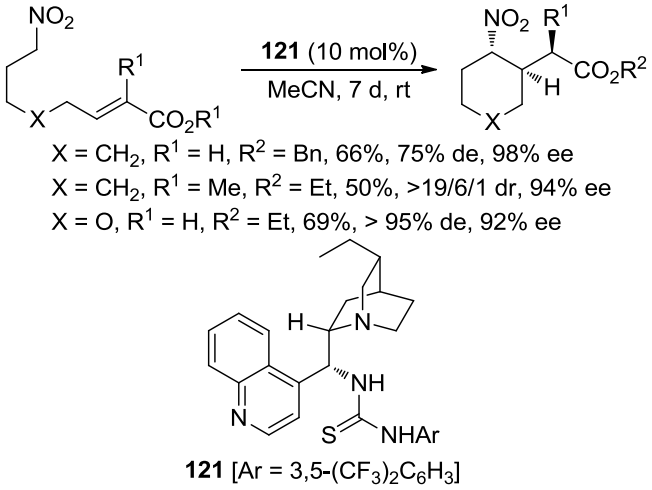
2.3.4.3 Conjugate Addition of Nitroalkanes to α,β-Unsaturated Carboxylic Acid Derivatives

α,β-Unsaturated carboxylic esters and acids are generally poor substrates in enantioselective organocatalyzed Michael reactions with nitroalkanes due to their low electrophilic quality and their usually not well-defined interactions with commonly used organocatalysts which avoids an efficient transfer of chirality from the catalyst to the substrate. However, efficient organocatalysts have been recently developed



Scheme 2.64 Organocatalyzed synthesis of rolipram

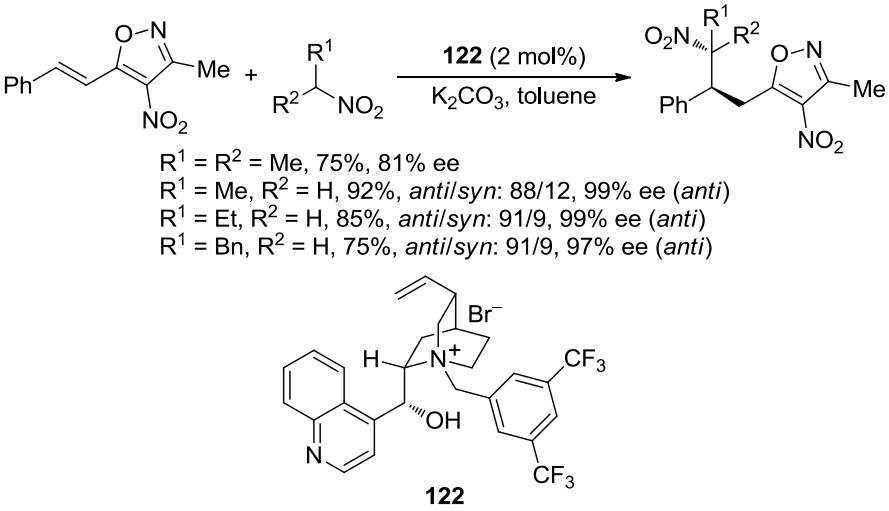
which overcome these problems at the same time that various α,β-unsaturated carbonyl compounds have been used as equivalents of the corresponding esters or carboxylic acids. Thus, different chiral organic molecules are able to catalyze the conjugate addition of nitroalkanes to other electron-deficient olefins, such as α,β-unsaturated esters [179], α,β-unsaturated acylpyrroles [180], styrylisoxazoles [181], and activated allenes [182] with high yields and selectivities. For instance, bifunctional hydrocinchonidine catalyst **121** efficiently catalyzes the intramolecular Michael addition of nitronates to *trans* α,β-unsaturated esters to afford with high diastereo- and enantioselectivity, precursors of cyclic γ-amino acids with up to three stereogenic centers (Scheme 2.65) [179]. The reaction is carried out in acetonitrile at rt and shows no reactivity towards α,β-unsaturated esters with *Z* configuration. The reason for this behavior is explained from the proposed transition



Scheme 2.65 Intramolecular Michael addition of nitronates with conjugated esters

state of the reaction, where the thiourea coordinates both the ester and the nitronate moieties to activate the system and allow the reaction to proceed, scenario that can only occur effectively with the *E* ester. Ab initio calculations support this assumption [179].

Chiral γ-amino acids and γ-nitroesters have been prepared, under PTC conditions, from 4-nitro-5-styrylisoxazoles, derivatives efficiently used as cinnamate equivalents in the asymmetric Michael reaction with nitroalkanes[181]. The reaction is catalyzed by Cinchonidine-derived catalyst **122** (2–5 mol%) at low temperatures (−30 to 0°C) affording high selectivities not only with nitromethane but also with secondary and tertiary nitroalkanes as nucleophiles. As seen in Scheme 2.66, the



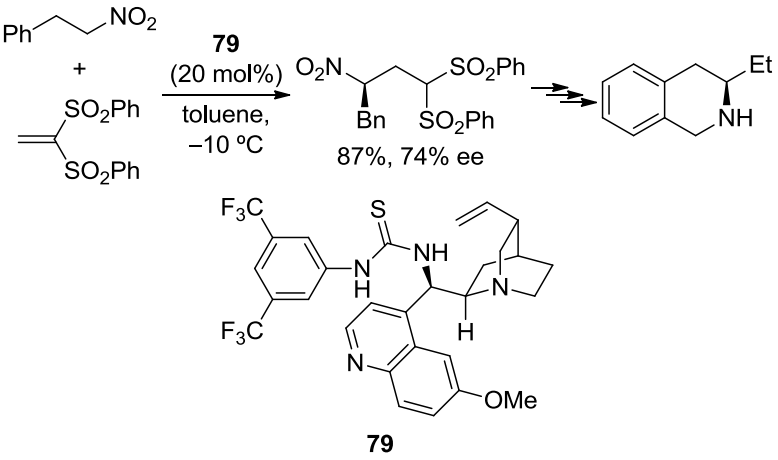
Scheme 2.66 Asymmetric Michael addition of nitroalkanes to 4-nitro-5-styrylisoxazoles

anti kinetic isomer prevailed when corresponding. This result has been rationalized on the basis on an acyclic, extended transition state. The more thermodynamically stable *syn* isomers can be obtained, with moderate diastereoselectivity, by simply stirring the reaction mixture at rt after the catalytic Michael addition is complete. A plausible coordination between the nitronate and the hydroxyl group of the catalyst has been suggested [182], since the *O*-benzylated catalyst related to **122**, affords very low enantioselectivities in the process.

2.3.4.4 Conjugate Addition of Nitroalkanes to Vinyl Sulfones, Nitroolefins, and Alkylidene Malonates

Bifunctional alkaloid-derived thiourea catalyst **79** promotes the conjugate addition of nitroalkanes to 1,1-bis(benzenesulfonyl)ethylene in toluene to afford the corresponding enantiomerically enriched γ-sulfonyl derivatives at −10°C [183]. Although

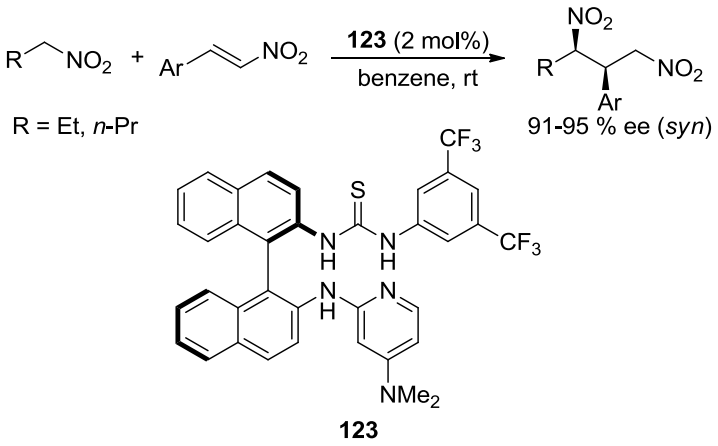
high catalyst loadings are required (20 mol%) and moderate to good enantioselectivities are obtained, this methodology is a good approach towards the synthesis of α-alkylated chiral amines as depicted in Scheme 2.67 [183]. With respect to the reaction mechanism, a bifunctional transition state model where activation of the nucleophile and the electrophile by the catalyst through hydrogen-bonding and ionic interactions has been proposed.



Scheme 2.67 Asymmetric conjugate addition of nitroalkanes to vinyl sulfones

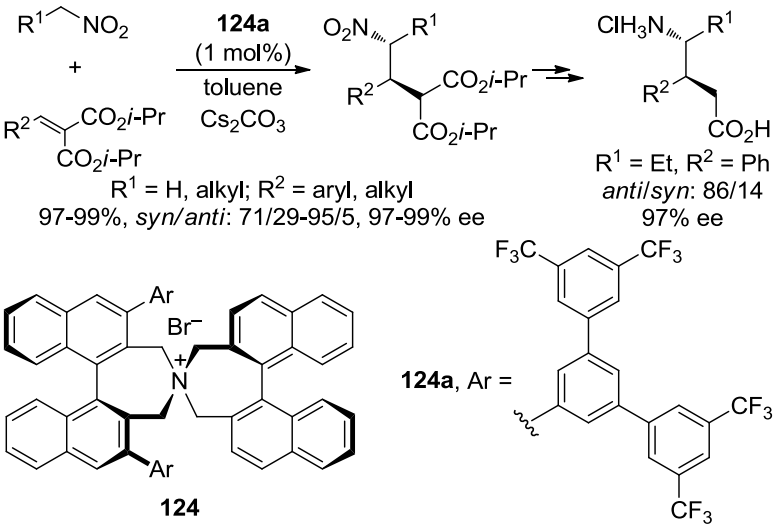
With respect to the conjugate addition to nitroolefins, the first organocatalytic enantioselective reaction with nitroalkanes was reported by Wang et al. in 2006 employing cupreidine as organocatalyst [184]. Under neat conditions and long reaction times (6–12 d), this process afforded enantiomerically 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. On the other hand, some progress has been recently reported by Wulff et al. in the reaction in terms of selectivity using catalyst **123** [185]. As seen in Scheme 2.68, chiral thiourea **123** is an effective catalyst for the addition of linear nitroalkanes to nitrostyrenes in benzene at rt under low catalyst loadings (2 mol%), affording the corresponding dinitro derivatives with good *syn* diastereoselectivities (*syn*/*anti* up to 90/10) and excellent enantioselectivities (up to 95% ee). Unfortunately, no reaction is reported with secondary nucleophiles and, as in the case of using cupreidine, a much less selective outcome (42% ee) is obtained when using β-alkyl substituted nitroolefins as Michael acceptors. Also, a large excess of nucleophile (30 equiv) is required.

N-Spiro C_2-symmetric chiral biaryl derivatives **124** present remarkable reactivity and selectivity in the conjugate addition of nitroalkanes to diisopropyl alkylidene- and



Scheme 2.68 Asymmetric Michael addition of nitroalkanes to nitrostyrenes

benzylidenemalonates under mild solid–liquid PTC (Scheme 2.69) [186]. In the presence of catalyst **124a**, the reaction, which is *anti*-selective and is usually performed at low temperatures (–40 to 0°C), provides a facile access to chiral γ-amino acid derivatives in good yields and high enantioselectivities under very low catalyst loading conditions (0.1–1 mol%).



Scheme 2.69 Asymmetric Michael addition of nitroalkanes to alkylidenemalonates

2.3.5 *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 high degree of stereocontrol.

2.3.5.1 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 malonates, 1,3-diketones, β-ketoesters, malononitriles, benzylic methylenes, and sulfonyl nucleophiles.

Långström and Bergson groups 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 as catalyst obtaining certain asymmetric induction in the process {$[\alpha]_{546}^{21}$ +8.83°} [187]. Twenty years later, Yamaguchi et al. reported an asymmetric organocatalyzed Michael addition of malonates to α,β-unsaturated aldehydes employing L-proline rubidium salt with poor enantioselectivities (up to 41% ee) [156, 188]. 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 with acrolein where the significant improvement on the selectivity of the reaction was achieved employing only a 2 mol% of chiral quaternary ammonium bromide **124b** [Fig. 2.12, **124**, Ar = 3,5-$(CF_3)_2C_6H_3$] under PTC conditions (K_2CO_3, toluene) [189]. Three years later, Deng et al. developed a highly efficient and general asymmetric conjugate addition of β-ketoesters to acrolein and β-alkyl substituted α,β-unsaturated aldehydes employing bifunctional *Cinchona* alkaloids **125**–**128** (Fig. 2.12) [190]. The reaction, which was used as key step in the synthesis of the marine toxin (+)-tanikolide, was also applicable not only to a wide variety of α-substituted-β-ketoester donors, but also to α-aryl substituted α-cyanoacetates as nucleophiles, being catalyst **128** the most efficient for the latter case (Fig. 2.12).

Jørgensen et al. have presented a one-pot approach to optically active 2,5-disubstituted cyclohex-2-enones, process which involves an iminium activation-based organocatalytic asymmetric conjugate addition of β-ketoesters to α,β-unsaturated aldehydes [191]. Under aqueous solution or solvent-free conditions, TMS-protected prolinol **56** (10 mol%) catalyzes the conjugate addition of β-ketoesters with a wide 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 2.70). Under the optimized reaction conditions *p*-TSA acts as a second organocatalyst leading directly to the chiral cyclohexenones. The *tert*-butyl ester group is essential for the success of the one-pot

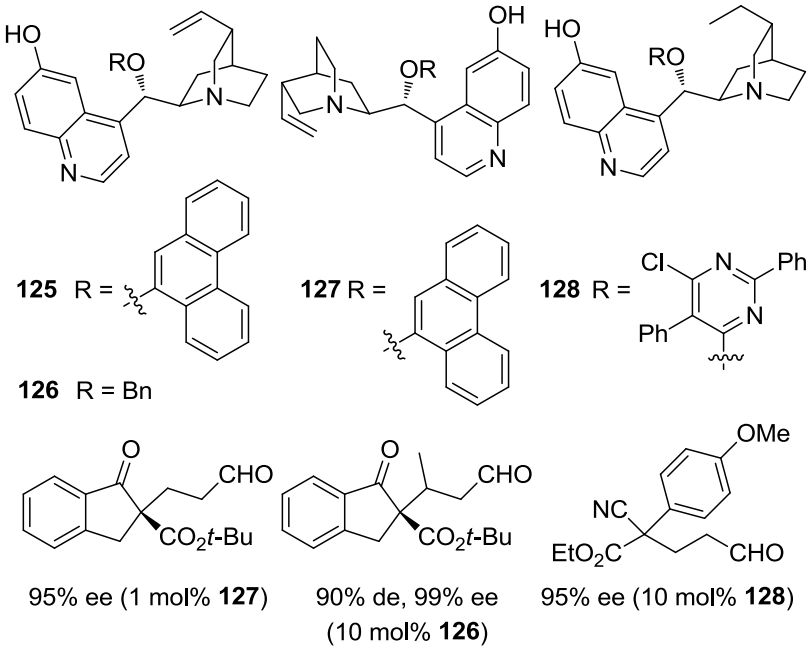
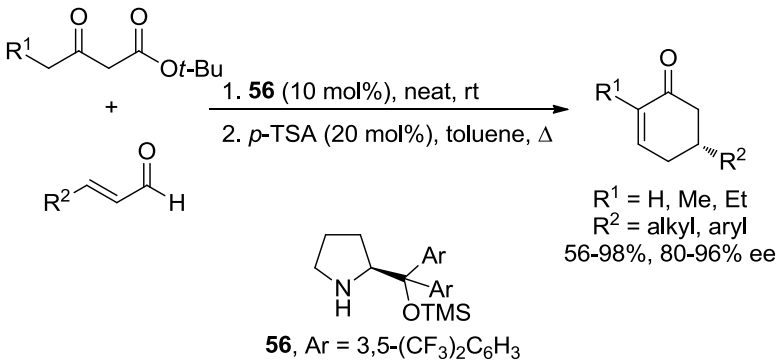


Fig. 2.12 Conjugate addition of activated methylenes to α,β-unsaturated aldehydes



Scheme 2.70 One-pot organocatalytic synthesis of chiral 2,5-disubstituted cyclohex-2-enones catalyzed by **56**

reaction since the acid is capable of promoting the hydrolysis of the ester, the decarboxylation of the newly formed β-ketoacid, the intramolecular aldol reaction and the final elimination.

Following similar iminium activation strategies using prolinol-derived organocatalysts, highly functionalized chiral cyclohexanone derivatives [192], dihydropyranone compounds [193], and polysubstituted cyclopentanones [194] have been also synthesized.

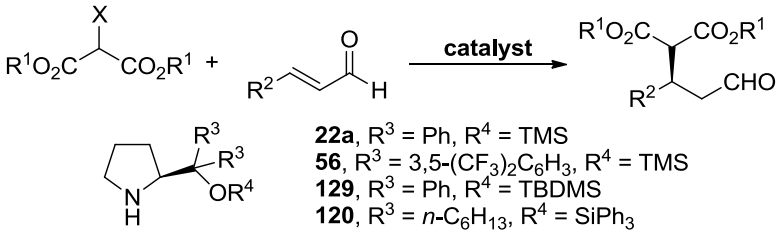
Table 2.2 Enantioselective Michael addition of malonates to enals

Entry	Catalyst (mol%)	R^1	R^2	X	Solvent	T (°C)	Yield (%)	ee (%)
1	**56** (10)	Bn	Ph	H	EtOH	0	80	91
2	**56** (10)	Me	Ph	H	EtOH	0	85	94
3	**56** (10)	Bn	2-BrC_6H_4	H	EtOH	0	34	88
4	**56** (10)	Bn	2-naphthyl	H	EtOH	0	69	88
5	**56** (10)	Bn	2-thienyl	H	EtOH	0	83	92
6	**22a** (20)	Et	Ph	F	CH_2Cl_2	rt	66	96
7	**22a** (1)	Et	Ph	H	CH_2Cl_2/MeOH	rt	81	96
8	**22a** (1)	Et	Me	H	CH_2Cl_2/MeOH	rt	71	80
9	**22a** (5)	Et	*n*-Pr	H	CH_2Cl_2/MeOH	rt	67	88
10	**22a** (5)	Me	Ph	H	H_2O	rt	90	96
11	**22a** (20)	Bn	Me	H	H_2O	rt	55	79
12	**129** (7)	Bn	Ph	H	EtOH/H_2O	0	97	99
13	**129** (7)	Bn	*n*-Bu	H	EtOH/H_2O	0	55	96
14	**120** (5)	Bn	Ph	H	H_2O	25	77	96

Concerning the use of malonates as nucleophiles, Jørgensen et al. have reported the first organocatalytic and enantioselective addition to aromatic α,β-unsaturated aldehydes employing iminium ion activation with catalyst **56** [195]. The reaction, which is solvent dependent and has been successfully applied to the enantioselective synthesis of (+)- and (−)-paroxetine as well as (+)-femoxetine, proceeds especially well for benzyl and methyl malonates, being non diastereoselective for unsymmetrical malonates (Table 2.2, entries 1–5). The process is general tolerating many functional groups and affording excellent enantioselectivities for all the studied substrates (86–95% ee). Owing to steric interactions, *ortho*-substituents in the aromatic ring of the electrophile lead to very low yields.

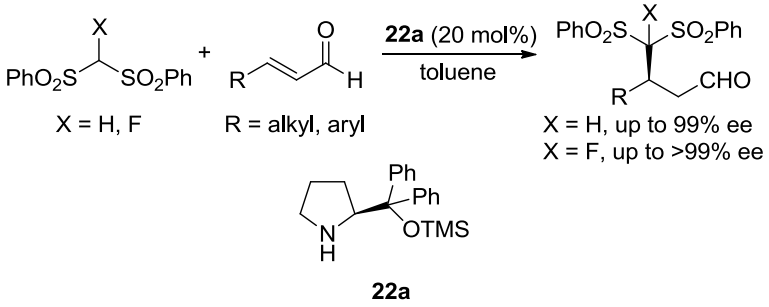
After Jørgensen's studies, the reaction scope has been improved by using other different silyl-protected prolinols such as **22a** [196–198], **129** [199], and **120** [177] (Table 2.2). For instance, prolinol **22a** has been shown as an excellent catalyst for the conjugate addition of diethyl 2-fluoromalonate to cinnamaldehydes in CH_2Cl_2 at rt and employing 1 equivalent of NaOAc as base [196]. Catalyst **22a** (5–20 mol%) is also an excellent promoter for the addition of dialkyl malonates to cinnamaldehyde derivatives in a mixture CH_2Cl_2/MeOH (Table 2.2, entries 7–9) using lithium 4-fluorobenzoate as base (65–85% yield, 84% to >99% ee)[197], and in water (74–93% yield, 88–97% ee) in the presence of AcOH as additive (Table 2.2, entries 10,11)[198]. In both cases, the yields and selectivities are lower if β-alkyl substituted α,β-unsaturated aldehydes are involved in the reaction (61–71% yield, 80–88% ee). In this case, better selectivities, although in moderate yields, are observed when TBDMS-protected prolinol **129** is used as catalyst (Table 2.2, entry 13). When using this catalyst, a strong accelerating effect is observed in the presence of benzoic acid and water as cocatalysts, allowing considerably shorter reaction times (5–24 h) and lower catalyst loadings. Also, the negative nonlinear effect observed in the process has been rationalized by a double nucleophilic-electrophilic activation mechanism

involving two catalyst molecules, one forming the chiral iminium electrophile, and the second forming a chiral nucleophile by hydrogen bonding to the enol form of the malonate (Scheme 2.71) [199].



Scheme 2.71 Organocatalyzed conjugate addition of malonates to enals

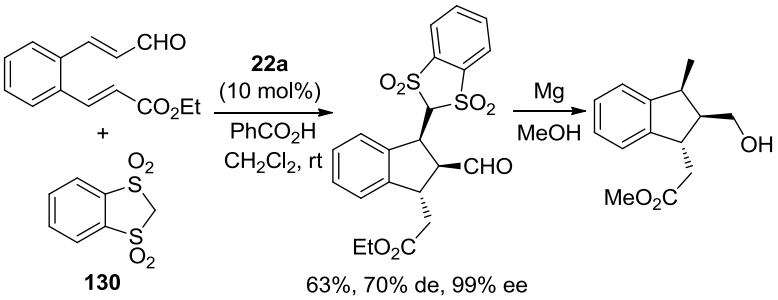
Iminium activation has been recently used to achieve the enantioselective conjugate addition of geminal bis(sulfone)s and β-keto sulfones to α,β-unsaturated aldehydes. Almost simultaneously, different groups have reported the efficient use of catalyst **22a** in the addition of bis(phenylsulfonyl)methane [200] and fluorobis(phenylsulfonyl) methane [201] to a wide variety of enals to yield the corresponding Michael adducts in excellent yields and enantioselectivities (Scheme 2.72). This reaction is particularly attractive since allows the preparation of interesting chiral building blocks by further synthetic transformations over the aldehyde moiety and reductive desulfonylation [91] of the bis(phenylsulfonyl) group.



Scheme 2.72 Enantioselective Michael addition of bis(phenylsulfonyl)methanes to enals

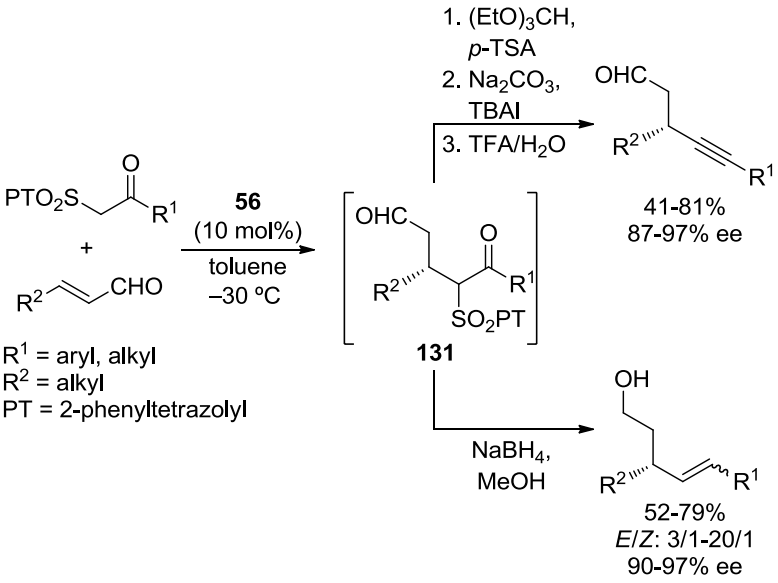
An interesting application of the conjugate addition of *gem*-bis(sulfone)s to enals has been reported by Palomo et al. [202] As depicted in Scheme 2.73, optically active trisubstituted indanes can be prepared in good yields by a tandem Michael-Michael process employing cyclic *gem*-bis(sulfone) **130**.

Jørgensen et al. have recently developed an interesting one-pot asymmetric organocatalytic formal alkynylation and alkenylation of α,β-unsaturated aldehydes using β-keto phenyltetrazolyl (PT) sulfones as nucleophiles [203]. The reaction is initiated



Scheme 2.73 Synthesis of trisubstituted indanes

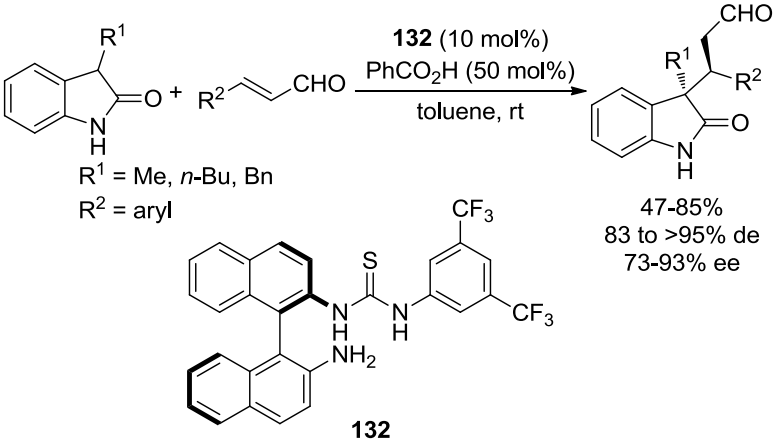
with an iminium-type activation highly enantioselective **56**-catalyzed conjugate addition of the corresponding sulfone to the α,β-unsaturated aldehyde, affording Michael intermediates **131** which can be transformed in situ to the final optically active products (Scheme 2.74). The one-pot formation of the chiral β-alkynylated aldehydes takes place after aldehyde protection with ethyl orthoformate, enolate-type Smiles rearrangement under mild basic conditions, and final deprotection with TFA (Scheme 2.74). The alkynylation reaction proceeds with good yields and excellent enantioselectivities for a variety of β-alkyl substituted enals using both aliphatic and aromatic ketones as nucleophiles. With respect to the alkenylation reaction, these products are formed after in situ reduction of intermediates **131** with $NaBH_4$ which



Scheme 2.74 Asymmetric organocatalyzed formal alkynylation and alkenylation of α,β-unsaturated aldehydes

affords, after Smiles rearrangement, the corresponding optically active olefins in good yields and diastereoselectivities and excellent enantioselectivities.

Anthrones [204] and 3-substituted oxindoles [205] possess activated methylenes which have been able to react under asymmetric iminium catalysis with α,β-unsaturated aldehydes. The reaction with 3-substituted oxindoles is especially attractive, since chiral quaternary stereocenters are generated. For this purpose, chiral primary amine thiourea catalyst **132** has been demonstrated as a very efficient promoter for the addition of 3-alkyl substituted oxindoles to β-aryl substituted enals in the presence of benzoic acid as cocatalyst in toluene at rt to afford the corresponding Michael adducts in good diastereoselectivities (dr up to >19/1) and good enantioselectivities (73–93% ee) (Scheme 2.75) [205a]. β-Alkyl substituted enals are not suitable partners for the reaction affording very low diastereo- and enanti-



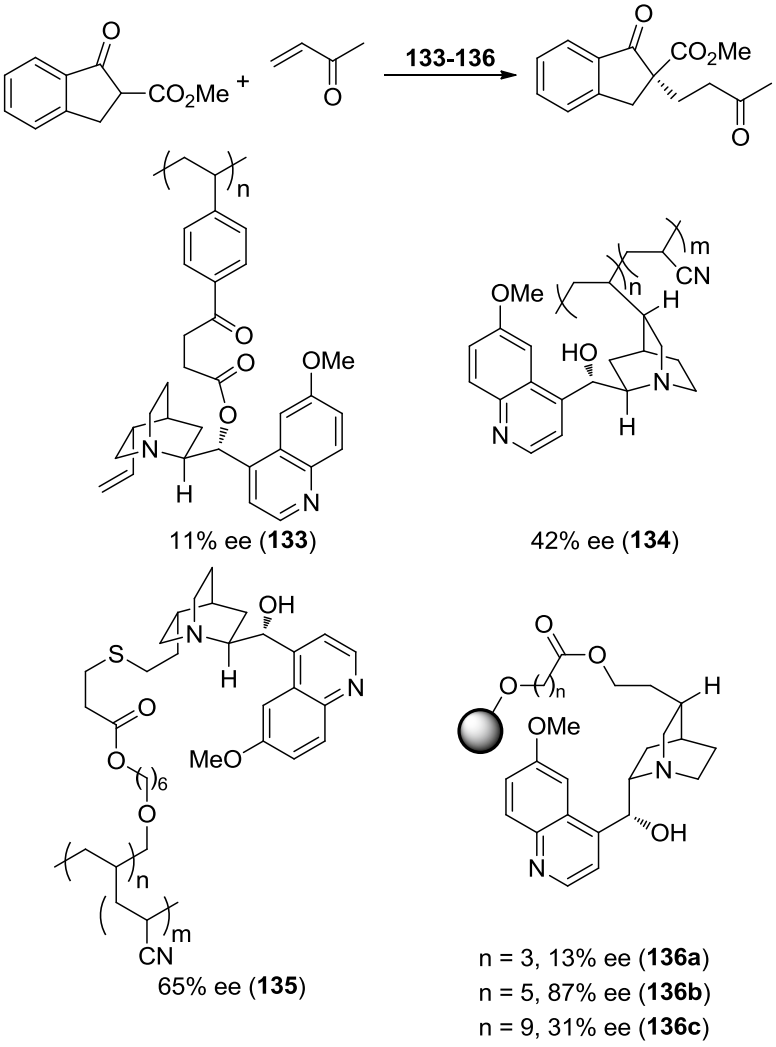
Scheme 2.75 Asymmetric organocatalyzed conjugate addition of 3-substituted oxindoles to α,β-unsaturated aldehydes

oselectivities (2.3/1 dr and 24% ee for crotonaldehyde). With respect to the reaction mechanism, the use of catalyst **132** is quite interesting since primary amine enal iminium activation is taken place, which is a not so frequent feature in organocatalyzed conjugate additions. Also, and due to the bifunctional character of the catalyst, a hydrogen bonding activation of the enol form of the nucleophile by the thiourea moiety is postulated [205a].

2.3.5.2 Conjugate Addition of Activated Methylenes to α,β-Unsaturated Ketones

The earliest examples of catalytic asymmetric Michael additions involving activated methylenes and enones were conducted with readily available natural amines as catalysts. Wynberg and Helder demonstrated that *Cinchona* alkaloids such as

quinine, cinchonidine, and cinchonine, were able to catalyze the Michael addition of cyclopentanone and cyclohexanone-derived 1,3-dicarbonyl compounds such as 2-methoxycarbonylindan-1-one to α,β-unsaturated ketones with excellent yields and enantioselectivities up to 76% [162, 206]. Subsequent studies with immobilized versions of this type of alkaloid catalysts afforded lower rates and enantioselectivities for the conjugate addition of β-ketoesters and enones. For instance, succinated polystyrene-divinylbenzene attached to *Cinchona* alkaloids such as **133** (Scheme 2.76) promoted the addition of 2-methoxycarbonyl-1-indanone to methyl vinyl ketone



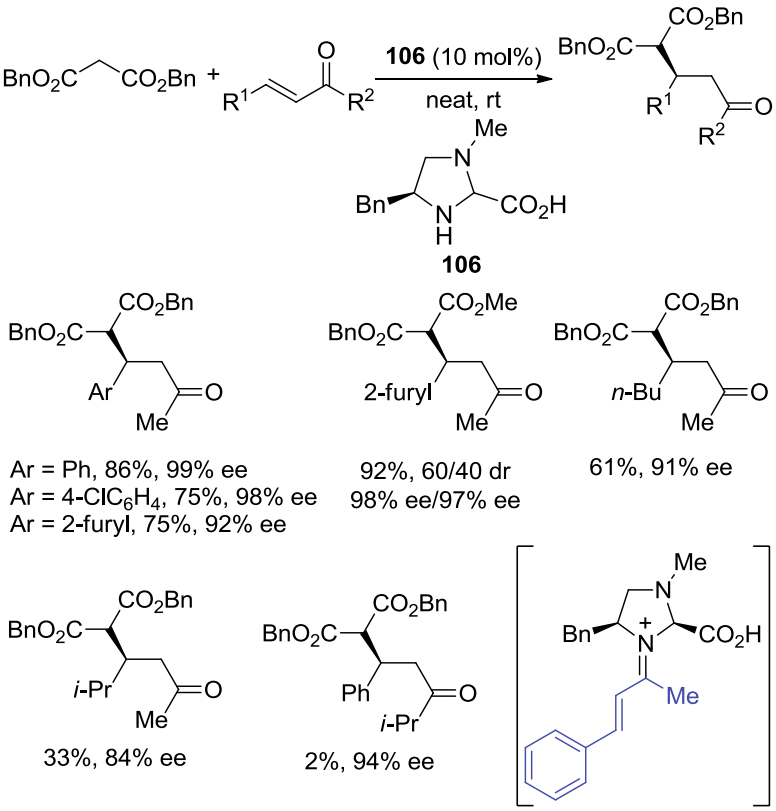
Scheme 2.76 Polymer-supported alkaloid-derived organocatalysts for the Michael addition of 2-methoxycarbonylindan-1-one to methyl vinyl ketone

with an 11% ee [207]. A higher 42% ee was obtained in the same process in the presence of quinidine-acrylonitrile copolymer **134** [163, 208]. Introduction of spacers between the polymer backbone and the chiral amine as in **135** (Scheme 2.76) brought the enantioselectivity of the process nearer to the homogeneous reaction levels (up to 65% ee) [209]. The best result obtained so far in the reaction (87% ee for **136b**) also demonstrated that the length of the spacer arm inserted between the polymer matrix and the alkaloid was critical to obtain a good enantioselectivity [210].

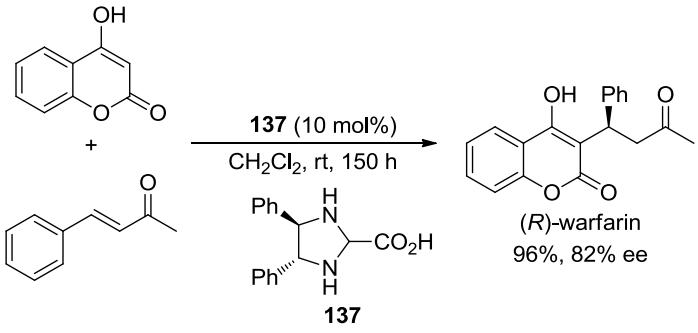
The scope of the reaction was later enlarged to malonates as nucleophiles employing L-proline rubidium salt [156, 188] and L-proline-derived ammonium salts [211], which turned to be efficient catalysts for the asymmetric addition of malonates to cyclic and acyclic enones with enantioselectivities of up to 88% ee.

After the above mentioned pioneering studies in the reaction, different groups have come into the field and have reported a number of different catalysts which are able to efficiently catalyze the conjugate addition of activated methylenes to α,β-unsaturated ketones under homogeneous and heterogeneous PTC conditions. Among them, Jørgensen's group has achieved significant progress in the reaction by careful investigation of the catalyst structure, developing very efficient organocatalyzed enantioselective conjugate addition reactions of different activated methylenes such as malonates [212], chromandiones [213], β-ketoesters [214], 1,3-diketones [215], and β-ketosulfones [216] to α,β-unsaturated ketones by using imidazolidine-derived organocatalysts. For instance, imidazolidine derivative **106** is a very effective organocatalyst under neat conditions for the enantioselective conjugate addition of benzyl malonates to α,β-unsaturated enones to afford the corresponding Michael adducts in good to excellent yields and excellent enantioselectivities (Scheme 2.77) [212]. In the case of non symmetrical malonates the diastereoselectivity and the rate of the process is low but not the asymmetric induction. However, the enantioselectivity is diminished notably when using sterically hindered enones. According with the observed absolute configuration of the products, an iminium ion intermediate is proposed being the *Re* face of the enone shielded by the benzyl group of the chiral catalyst [212].

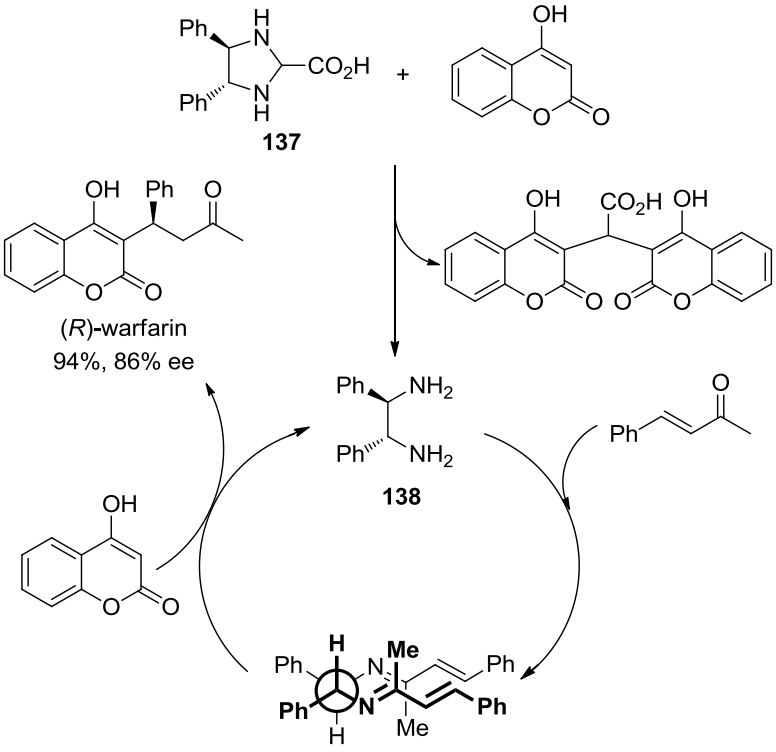
A highly enantioselective organocatalytic Michael addition of 4-hydroxycoumarines and related compounds to α,β-unsaturated ketones has been also achieved using imidazolidine catalyst **137** [213]. The reaction, which gives high yields and enantioselectivities for a wide range of cyclic 1,3-dicarbonyl compounds and enones, has been successfully employed for the asymmetric synthesis of the anticoagulant warfarin (Scheme 2.78) and derivatives [213]. With respect to the reaction mechanism, very recent studies have demonstrated that the truly active catalyst in the process was the chiral diamine **138**, which is formed in catalytic amounts under the reaction conditions by reaction with the hydroxycoumarine (Scheme 2.79) [216]. The intermediate of the reaction is then postulated to be a chiral diimine formed from the diamine and the enone. In this intermediate one of the faces of the electrophile is efficiently shielded from the nucleophilic attack. This finding led to 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 2.79) [216].



Scheme 2.77 Enantioselective organocatalytic conjugate addition of malonates to acyclic α,β-unsaturated enones catalyzed by **106**



Scheme 2.78 Organocatalytic asymmetric synthesis of anticoagulant warfarin catalyzed by **137**

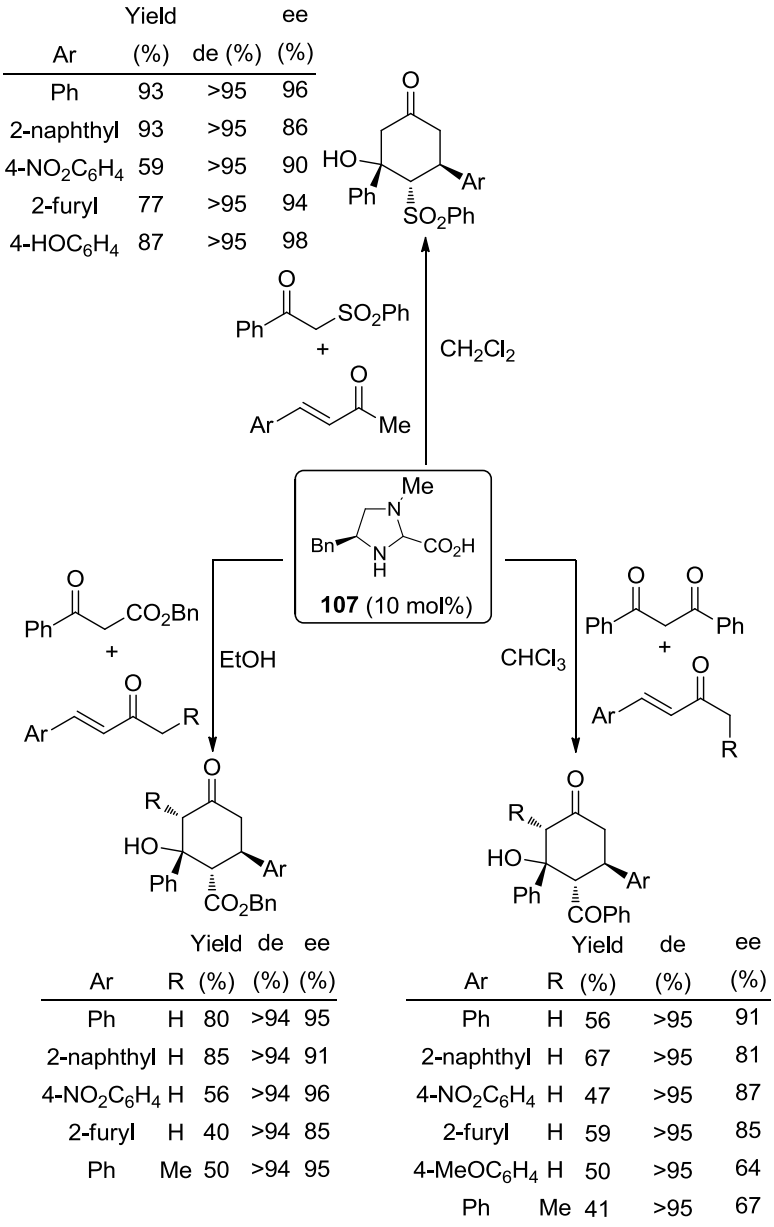


Scheme 2.79 Organocatalytic asymmetric synthesis of anticoagulant warfarin catalyzed by **137**

Chiral imidazolidine **106** is also a very effective organocatalyst for the enantio- and diastereoselective domino Michael-aldol reaction of β-diketones [215a], β-ketosulfones [215a], and β-ketoesters [214] with α,β-unsaturated ketones at rt to afford optically active cyclohexanones having three or four contiguous stereogenic centers (Scheme 2.80).

Cinchona alkaloid-derived organocatalysts are also considered as privileged systems for the conjugate addition of activated methylenes to enones. These bifunctional catalysts have been employed by different groups with great success in the conjugate addition of a variety of nucleophiles such as malonates, β-ketoesters, 1,3-dicarbonyl compounds, malononitriles, α-nitroesters, and fluoro bis (phenylsulfonyl) methane usually employing an excess of the nucleophile (3–6 equiv). In Fig. 2.13 are shown a collection of the most selective *Cinchona* alkaloid-derived organocatalysts.

Among them, chiral bifunctional thiourea derivative **109** represents one of the most versatile organocatalyst prepared so far for the addition of activated methylenes to enones since affords, 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-ketoesters, 1,3-diketones, nitroesters, and 1,3-dinitriles to enones in xylenes at rt (Scheme 2.81)[217].



Scheme 2.80 Synthesis of chiral polyfunctionalized cyclohexanones catalyzed by imidazolidine **106**

Deng et al. have reported the use of simple cupreines such as **127** as efficient organocatalysts for the construction of stereogenic quaternary centers through the conjugate addition of α-substituted β-ketoesters to α,β-unsaturated ketones [218]. The reaction affords excellent yields as well as diastereo-, and enantioselectivities

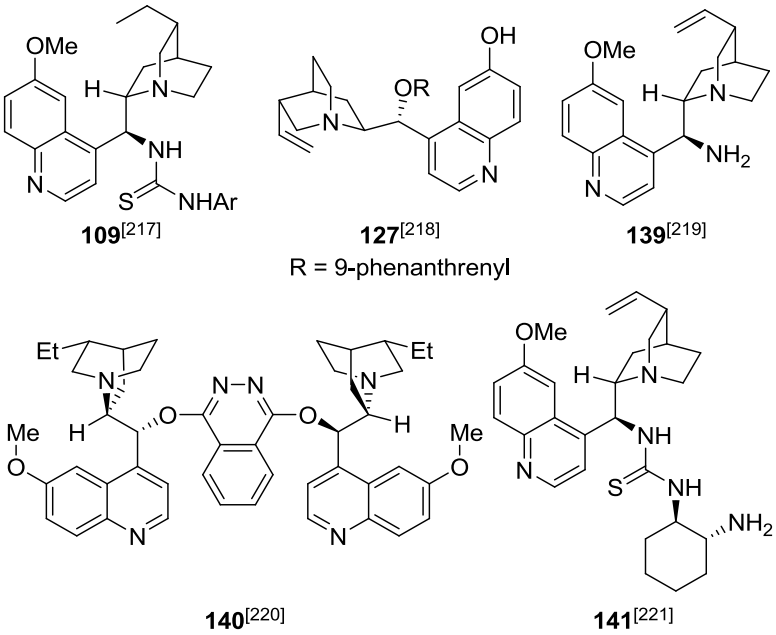
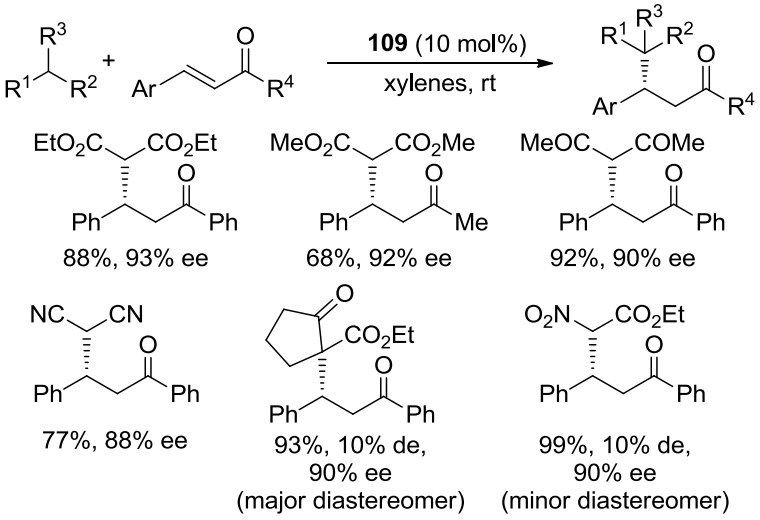
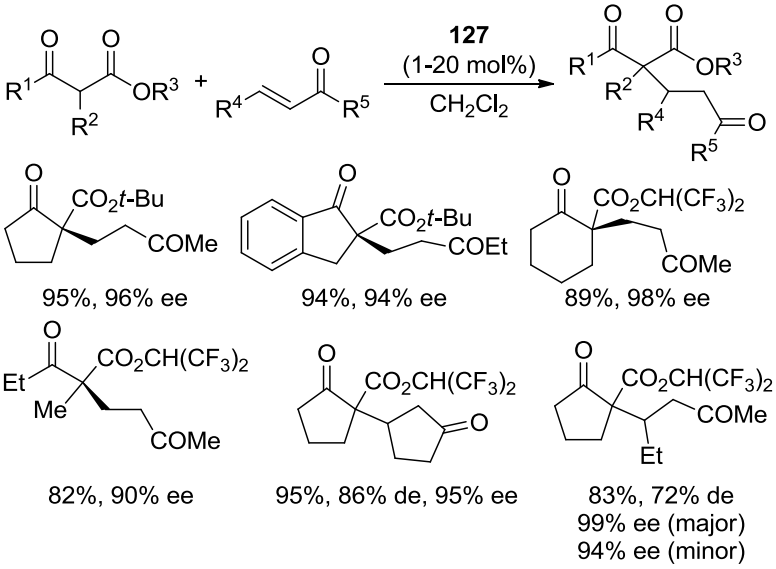


Fig. 2.13 *Cinchona*-derived organocatalysts for the conjugate addition of activated methylenes to enones



Scheme 2.81 Organocatalytic enantioselective conjugate additions to enones catalyzed by bifunctional thiourea **109**

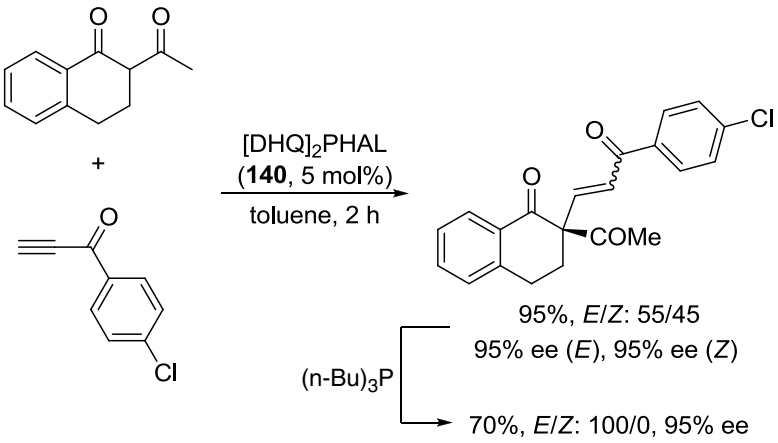
for a wide variety of α-substituted β-ketoesters and a wide range of enones, usually working under room temperature conditions and employing very (usually in the range 1–10 mol%) catalyst loadings (Scheme 2.82). This study encloses the first examples of a highly enantio- and diastereoselective catalytic conjugate addition of a trisubstituted carbon nucleophile to a cyclic enone.



Scheme 2.82 Organocatalytic asymmetric conjugate addition of α-substituted β-ketoesters to α,β-unsaturated ketones catalyzed by **127**

The first organocatalytic enantioselective conjugate addition of 1,3-dicarbonyl compounds to alkynones has been recently developed by Jørgensen et al. [220] The reaction, which is catalyzed using very low loadings (5 mol%) of the *Cinchona* alkaloid $[DHQ]_2PHAL$ (**140**, Fig. 2.13) is highly enantioselective for the addition of β-diketones to both aromatic and aliphatic alkynones giving a mixture of *E*- and *Z*-enones (Scheme 2.83). An additional advantage of the method is the possibility to perform a one-pot isomerization of the mixture of *E*/*Z*-enones to the *E*-isomer without affecting the yield or the enantioselectivity.

Further studies have been carried out by different groups on the asymmetric conjugate addition of activated-methylene containing compounds to electron-deficient alkynes and allenes usually employing *Cinchona*-based chiral ammonium salts. For instance, Maruoka's group has developed an enantioselective PTC conjugate addition (up to 97% ee) of α-alkyl-α-cyanoacetates to acetylenic esters employing BINOL-derived chiral ammonium salts [222]. On the other hand, Jørgensen's group has reported the first enantioselective conjugate addition of cyclic β-ketoesters to electron-deficient allenes affording the corresponding adducts in excellent diastereo- and enantioselectivities (90–96% ee) [223].

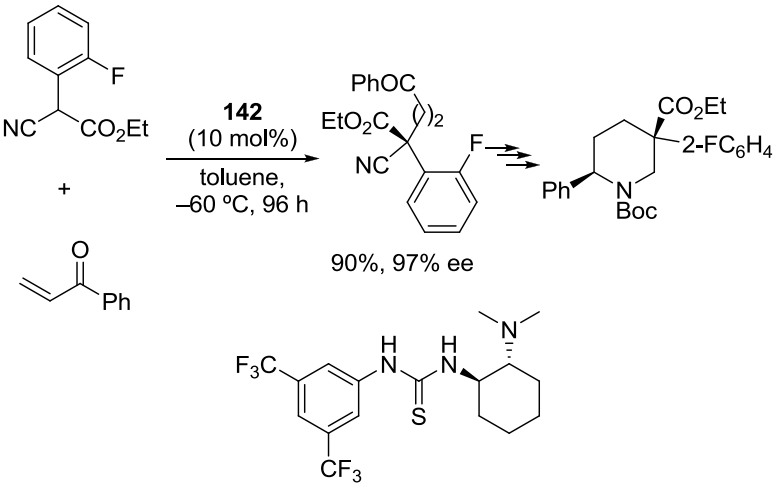


Scheme 2.83 Organocatalytic asymmetric conjugate addition of α-substituted-β-diketones to α-alkynones

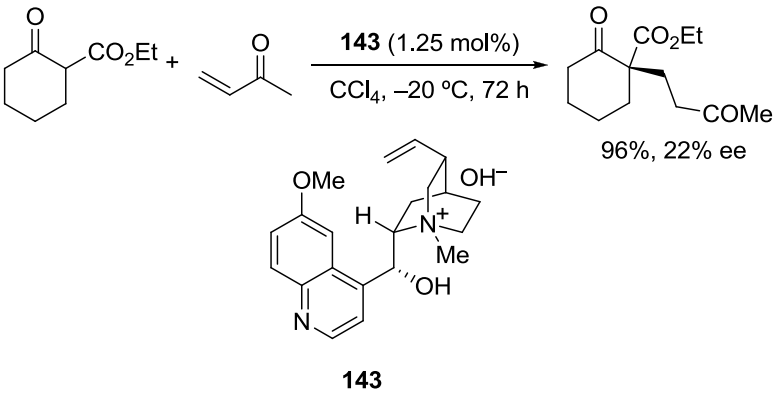
Other very effective *Cinchona*-based organocatalyst used in the conjugate addition of activated methylenes to enones worth mentioning is the quinine-derived primary amine **139**, that catalyzes conjugate additions of chroman-2,4-diones [219a], fluoro bis(phenylsulfonylmethane) [219b], and β-keto sulfones [219c], as well as quinine-derived primary amine thiourea **141** which promotes the addition of dialkyl malonates to cyclic and acyclic α,β-unsaturated ketones [221] (Fig. 2.13).

On the other hand, good results have been also reported for the addition of different nucleophiles to enones using other non alkaloid-type small chiral molecules, such as tertiary amine thioureas [224], guanidines [225], primary-secondary diamines [226], and small peptides [227]. For instance, bifunctional chiral thiourea **142** has been used by Chen et al. as a very efficient organocatalyst for the enantioselective Michael addition of α-substituted cyanoacetates to vinyl ketones [224a]. The reaction, which affords multifunctional compounds with an all-carbon-substituted quaternary stereocenters in excellent yields (61–99%) and enantioselectivities (82–97% ee), has been employed for the asymmetric synthesis of biologically important $\beta^{2,2}$-amino acid esters as depicted in Scheme 2.84 for a selected example. Based on the absolute configuration of the products and semi-empirical calculations, the authors have proposed a transition state involving multiple hydrogen bonding interactions: a strong hydrogen bond between the OH group of the enolate and the Me_2N group of the catalyst and a weaker hydrogen bond concerning the EtO-group of the enolate and the NH of the thiourea moiety.

Chiral phase-transfer catalysts 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 derivative **143** (Scheme 2.85) [206, 228] and ephedrinium



Scheme 2.84 Organocatalytic enantioselective synthesis of $\beta^{2,2}$-amino acid esters catalyzed by chiral thiourea **142**



Scheme 2.85 Initial studies on the phase-transfer catalyzed addition of 1,3-dicarbonyl compounds to enones

salts [228, 229] were at first prepared and tested in the conjugate addition of 1,3-dicarbonyl compounds to enones under phase-transfer conditions. Albeit the observed enantioselectivities were 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 over the selectivity of the process.

Preliminary studies led to the employment of the *Cinchona* alkaloid catalysts **144** [230], **145** [231], and **146** [232] in the enantioselective conjugate addition of malonates to enones in the presence of K_2CO_3 as base Fig. 2.14. Different fragances

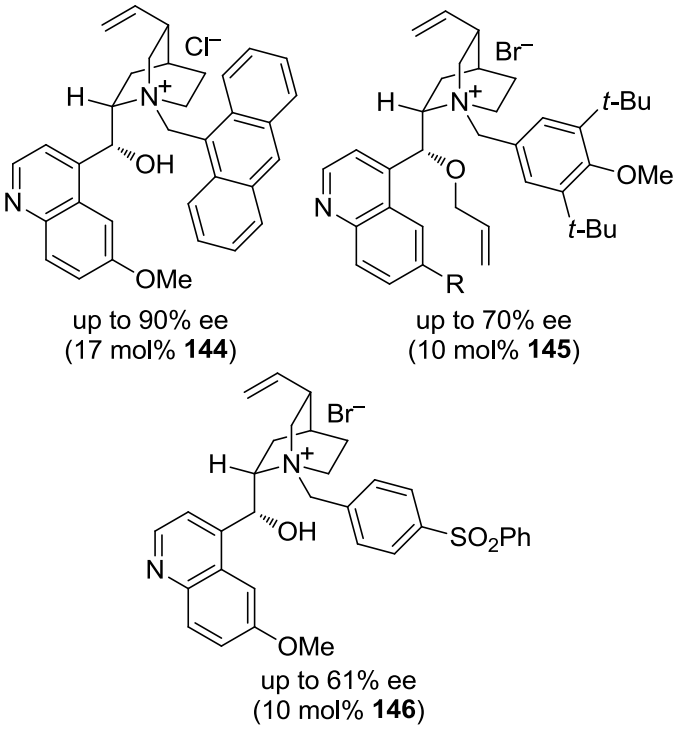
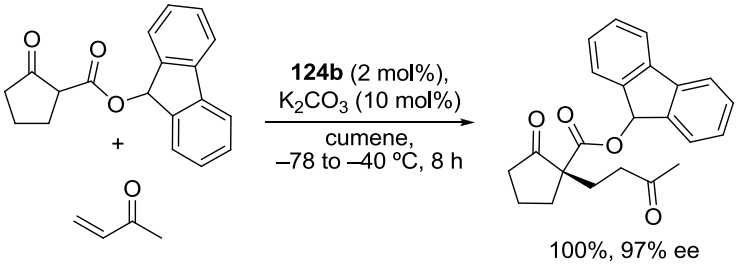


Fig. 2.14 Quininium-derived catalysts for the enantioselective Michael reaction of malonates and α,β-unsaturated enones

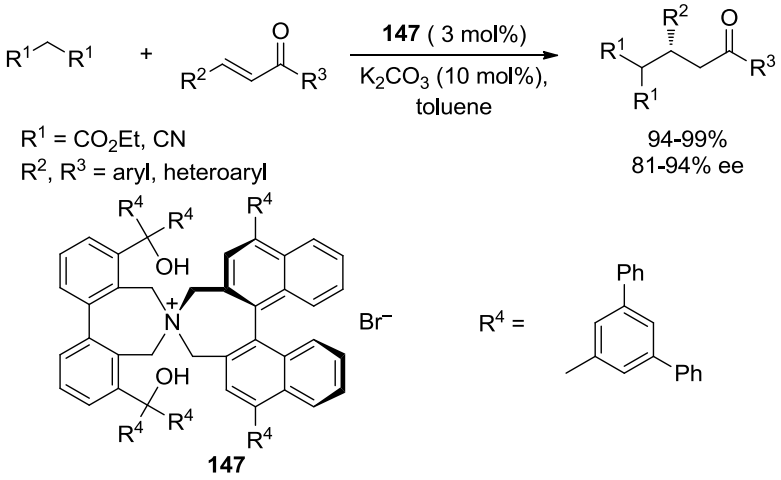


Scheme 2.86 Enantioselective phase-transfer catalytic Michael addition of β-ketoesters to enones

such as methyl dihydrojasmonate and *trans*-magnolione were prepared following this methodology [230].

Very high enantioselectivities in the PTC Michael addition of 1,3-dicarbonyl compounds to enones have been achieved by Maruoka et al. [189, 233] As shown in Scheme 2.86, just a 2 mol% of the binaphthyl-derived phase-transfer catalyst **124b** [Scheme 2.70, **124**, Ar = 3,5-$((CF_3)_2C_6H_3)$] in the presence of 10 mol% of solid K_2CO_3, is able to achieved a highly efficient and enantioselective addition of 2-(9-fluorenoxycarbonyl)cyclopentanone to methyl vinyl ketone [189].

Alternatively, the catalytic activity of chiral bifunctional ammonium bromide **147** has resulted more general than for catalyst **124b**. Under low loading conditions (3 mol%), catalyst **147** is 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 2.87 [233]. The authors have also shown

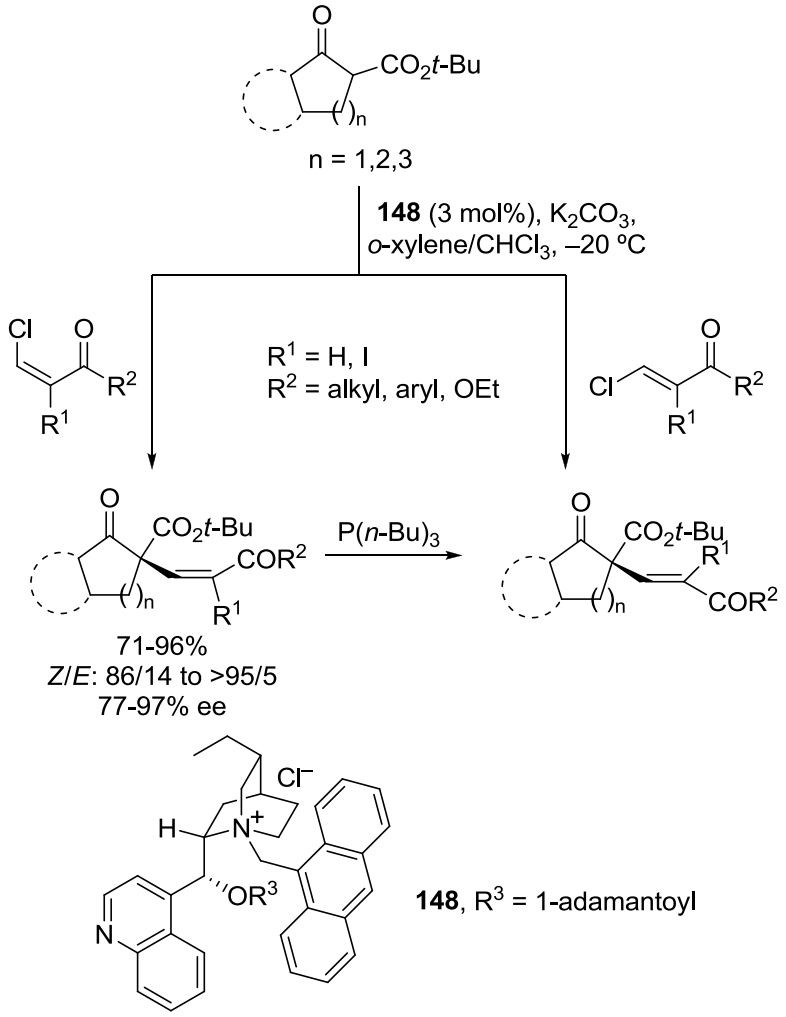


Scheme 2.87 Enantioselective phase-transfer catalytic Michael addition of malonates to chalcone derivatives

the importance of the hydroxyl functionality of the catalyst to afford an adequate enantiofacial differentiation of the prochiral chalcone. Unfortunately, the methodology could not be extended to aliphatic enones and very low enantioselectivities are obtained for this type of substrates.

In 2006, and following with their studies about the organocatalytic conjugate addition of activated methylenes, Jørgensen et al. reported the first examples of an organocatalytic highly diastereo- and enantioselective vinylic substitution reaction [234]. This process, which consists on a Csp^3-Csp^2 coupling between β-ketoesters and electron-deficient *Z*- or *E*-vinylic chlorides (β-acyl vinyl cation equivalents), is efficiently catalyzed by the new bulky phase-transfer catalyst **148** under very simple reaction conditions (Scheme 2.88). The reaction takes place with retention of the configuration of the double bond, which is rationalized by the authors through an Ad_N-E mechanism. Moreover, easy access to both double bond isomers is also 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 acyclic β-ketoesters (up to 40% ee) [234]. Jørgensen's group has also demonstrated the activity of catalyst **148** for a highly enantioselective α-alkynylation of cyclic β-ketoesters via a conjugate addition-elimination sequence with activated β-halo alkynes [235].

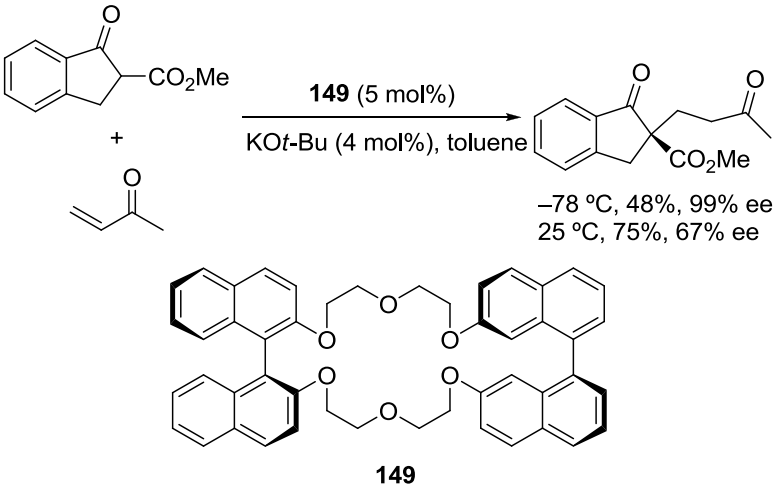
Chiral crown ether **149** is an efficient phase-transfer catalysts for the Michael addition of 2-methoxycarbonylindanone to methyl vinyl ketone employing catalytic



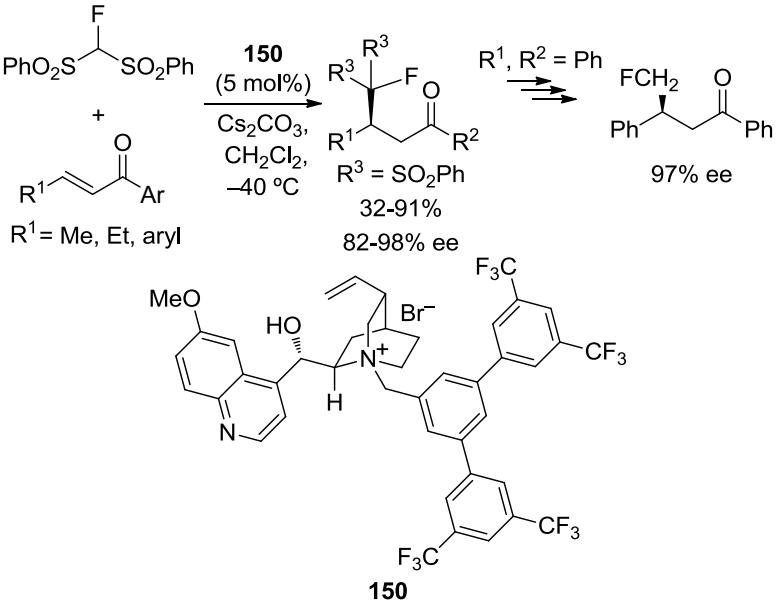
Scheme 2.88 Organocatalytic enantioselective nucleophilic vinylic substitution

amounts of potassium *tert*-butoxide as base [236]. The reaction affords the Michael adduct in very high enantioselectivity when working at −78°C (Scheme 2.89).

Flouro bis(phenylsulfonyl)methane has been employed as a monofluoromethylation reagent of chalcones via conjugate addition under PTC conditions using quinidine ammonium bromide **150** as catalyst (5 mol%) in CH_2Cl_2 as solvent at low temperatures (Scheme 2.90) [237]. Hydrogen bonding interactions between the free OH group of the catalyst and the electrophilic carbonyl moiety, as well as aromatic π–π interactions between **150** and the enone, have been claimed by the authors to play a key role in the enantioselectivity of the process. Also, steric hindrance by the bulky benzyl substituent of the catalyst seems to direct the nucleophile approach in the conjugate addition [237].



Scheme 2.89 Asymmetric Michael addition catalyzed by chiral crown ether **149**



Scheme 2.90 PTC asymmetric conjugate addition of fluoro bis(phenylsulfonyl)methane to enones

2.3.5.3 Conjugate Addition of Activated Methylenes to Nitroolefins

In 2003, Takemoto et al. reported the first highly enantioselective organocatalytic conjugate addition of 1,3-dicarbonyl compounds to nitroolefins catalyzed by bifunctional thiourea-amine catalyst **142** (Fig. 2.15)[238]. After Takemoto's report a wide

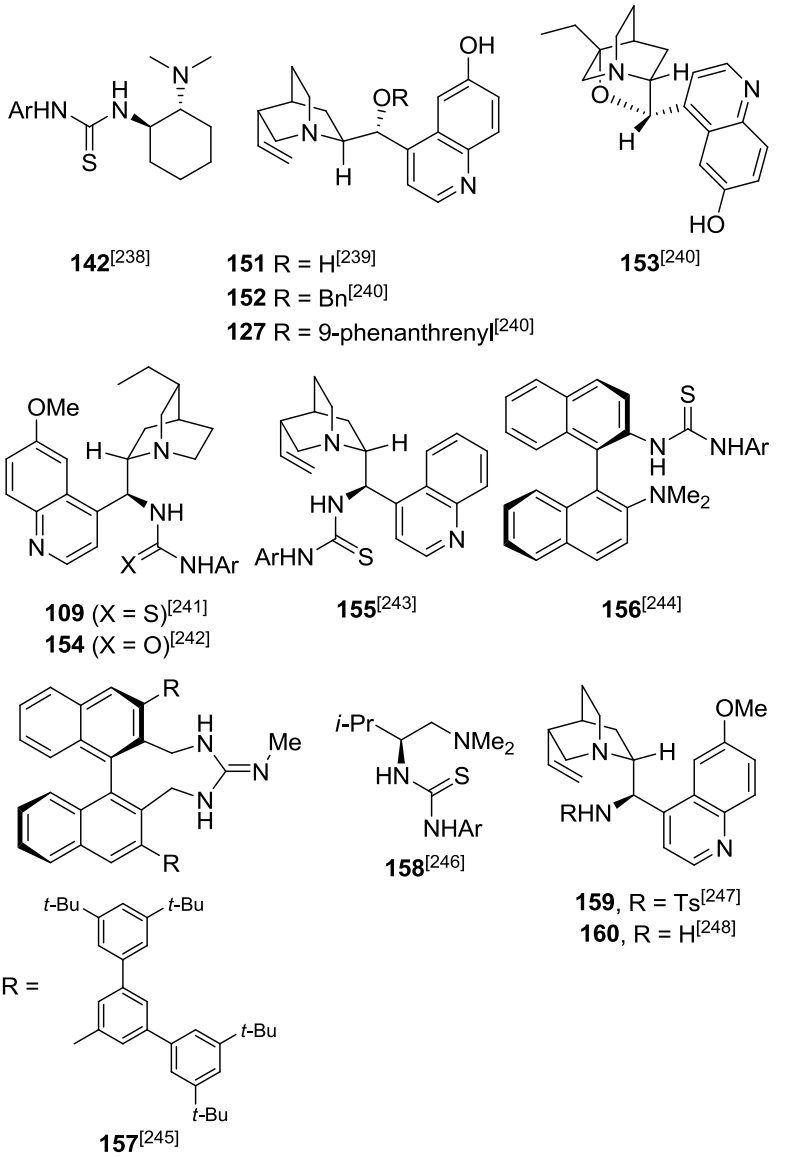


Fig. 2.15 Privileged chiral organocatalysts for the conjugate addition of activated methylenes to nitroolefins (Ar = 3,5-$(CF_3)_2C_6H_3$)

variety of highly active and selective bifunctional organocatalysts have been developed by different groups using diverse chiral scaffolds and hydrogen-bond forming functional groups. Some of the privileged and most representative systems are depicted in Figs. 2.15 and 2.16.

As shown in Fig. 2.17 for representative results, in the presence of catalytic amounts (2–20 mol%) of these bifunctional organocatalysts, the conjugate addition

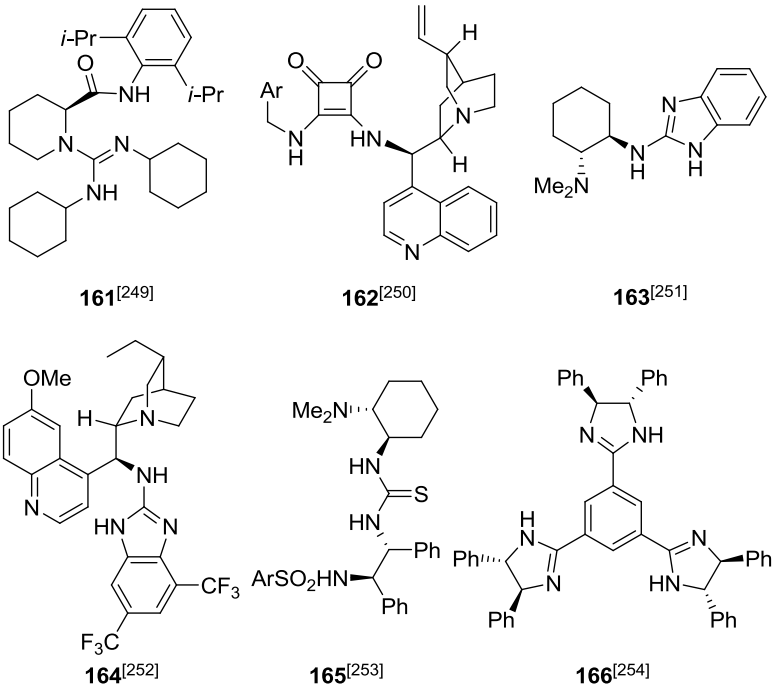
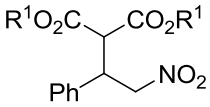


Fig. 2.16 Privileged chiral organocatalysts for the conjugate addition of activated methylenes to nitroolefins (Ar = 3,5-$(CF_3)_2C_6H_3$)

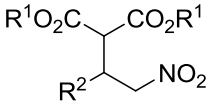
of a wide variety of malonate derivatives to β-nitrostyrenes and β-alkylnitroolefins can be achieved with high levels of yield and stereoinduction. Of special interest resulted the exceptionally high activity and selectivity for α-functionalized trisubstituted malonates shown by some of these catalysts, which should be useful for the synthesis of many multifunctional chiral building blocks containing quaternary stereocenters. A remarkable feature results also the highly enantioselective addition of malonate esters to sterically hindered γ-branched nitroalkenes such as *trans*-(2-nitrovinyl)cyclohexane reported for catalysts **157** [245] since such electrophiles are challenging substrates in metal-catalyzed processes.

Some interesting applications of the conjugate addition of malonates to nitroolefins are the stereoselective synthesis of the antispastic agent (*R*)-Baclofen [238b], and the antidepressant drug (*R*)-rolipram, the latter obtained via highly stereoselective conjugate addition of a malonic acid half-thioester to a nitrostyrene derivative catalyzed by urea **154** [242].

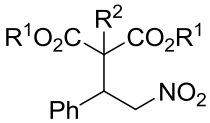
In the case of using 1,3-diketones as nucleophiles, catalysts **142** [238], **152** [240], **153** [240], **156** [244], **157** [245], **160** [248], **162** [250], **163** [251], and **165** [253] are able to promote the addition to aromatic nitroolefins with high yields and enantioselectivities. Among them, it is worthy to mention BINAM-derived catalyst **156** and squarimide-cupreidine catalyst **162**, that afford very good selectivities under very low catalyst loadings (1 and 0.5 mol%, respectively). As depicted in Fig. 2.18, squa-



142 (10 mol%), R^1 = Et, toluene, rt, 24 h, 86%, 93% ee
151 (10 mol%), R^1 = Me, THF, –20 ºC, 36 h, 97%, 96% ee
109 (2 mol%), R^1 = Me, toluene, –20 ºC, 30 h, 93%, 99% ee
155 (10 mol%), R^1 = Me, CH_2Cl_2, –20 ºC, 30 h, 95%, 94% ee
157 (2 mol%), R^1 = Me, Et_2O, –40 ºC, 2 h, 100%, 96% ee
158 (10 mol%), R^1 = Me, toluene, –18 ºC, 44 h, 90%, 95% ee
163 (10 mol%), R^1 = Et, toluene, rt, 48 h, 97%, 92% ee
164 (2 mol%), R^1 = Me, CH_2Cl_2, –20 ºC, 40 h, 98%, 95% ee



142 (10 mol%), R^1 = Et, R^2 = *i*-Bu, toluene, rt, 48 h, 88%, 81% ee
151 (10 mol%), R^1 = Me, R^2 = *i*-Bu, THF, –20 ºC, 72 h, 84%, 94% ee
109 (5 mol%), R^1 = Me, R^2 = Cy, toluene, 20 ºC, 147 h, 63%, 75% ee
155 (10 mol%), R^1 = Me, R^2 = Cy, CH_2Cl_2, –20 ºC, 31 h, 82%, 82% ee
157 (5 mol%), R^1 = Me, R^2 = Cy, Et_2O, –40 ºC, 10 h, 79%, 91% ee
158 (10 mol%), R^1 = Et, R^2 = $PhCH_2CH_2$, toluene, –18 ºC, 144 h, 69%, 81% ee
164 (2 mol%), R^1 = Me, R^2 = *n*-C_6H_{13}, CH_2Cl_2, –20 ºC, 96 h, 70%, 94% ee



142 (10 mol%), R^1 = Me, R^2 = Me, toluene, rt, 36 h, 82%, 93% ee
142 (10 mol%), R^1 = Me, R^2 = OMe, toluene, rt, 28 h, 89%, 94% ee
142 (10 mol%), R^1 = Et, R^2 = Cl, toluene, rt, 1 h, >99%, 89% ee
157 (20 mol%), R^1 = Me, R^2 = F, $CHCl_3$, rt, 24 h, 97%, 97% ee
157 (2 mol%), R^1 = Me, R^2 = Me, Et_2O, –40 ºC, 2 h, 82%, 98% ee
158 (10 mol%), R^1 = Me, R^2 = Me, toluene, –18 ºC, 72 h, 57%, 96% ee
158 (10 mol%), R^1 = Me, R^2 = Cl, toluene, –18 ºC, 1 h, 86%, 99% ee

Fig. 2.17 Enantioselective Michael reactions of malonates to nitroolefins

rimide **162** is especially interesting since catalyzes the conjugate addition of a wide variety of 1,3-diketones to β-aryl substituted nitroolefins in high yields, moderate diastereoselectivities and excellent enantioselectivities at rt [250].

With respect to aliphatic nitroolefins, 2-aminobenzimidazole-derived catalyst **163** [251] and thiourea **165** [253] have been demonstrated to catalyze the conjugate addition of 1,3-diketones to β-alkyl substituted nitroolefins, generally with slightly

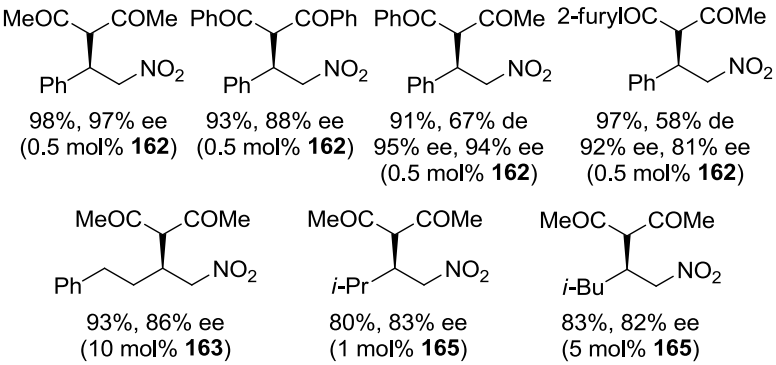


Fig. 2.18 Enantioselective Michael addition of 1,3-diketones to nitroolefins

lower enantioselectivities than those obtained with nitrostyrenes (Fig. 2.18). Furthermore, 2-aminobenzimidazole-derived catalyst **163**, which is active in the presence of TFA as cocatalyst, can be recovered from the reaction mixture by acid–base extraction with no loss of optical activity.

Regarding the reaction mechanism and the origin of the stereoinduction, kinetic studies carried out with catalysts **142** [238] and **152** [240] have established that the conjugate addition follows a first-order dependence on the catalyst, the nucleophile and the electrophile. The absence of non-linear effects also suggests monomeric species as the truly active catalyst. These results and catalyst modification studies are consistent with the mechanistic proposal presented by Takemoto, which consists on the activation of both the nucleophile and the electrophile by thiourea **142** [238]. Thus, in the transition state, the nitroolefin is assumed to interact with the thiourea moiety of the catalyst via multiple hydrogen bonds, enhancing in this way its electrophilic character. On the other hand, the enolic form of the 1,3-dicarbonyl nucleophile is assumed to interact with the tertiary amine group, and a subsequent deprotonation results in a highly nucleophilic enolate species (**A**, Fig. 2.19). Then, the C–C bond formation step takes place via the formation of a ternary H-bonded complex and the enantioselectivity of the reaction is related to the binding mode of the electrophile to the thiourea moiety [238].

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 been presented reporting some interesting results [255]. With respect to the reaction mechanism Pápai et al. have claimed that even the generally accepted mechanism (electrophile activation through substrate binding to thiourea and subsequent C–C bond formation between simultaneously activated components) is kinetically and thermodynamically feasible, an alternative reaction pathway is also possible. This new proposal involves activation of the electrophile by the protonated amino group, leading to a ternary intermediate complex whose related transition state is remarkably more stable and compatible with Takemoto's kinetic results (**B**, Fig. 2.19). This novel proposal also accounted for the observed enantioselectivity.

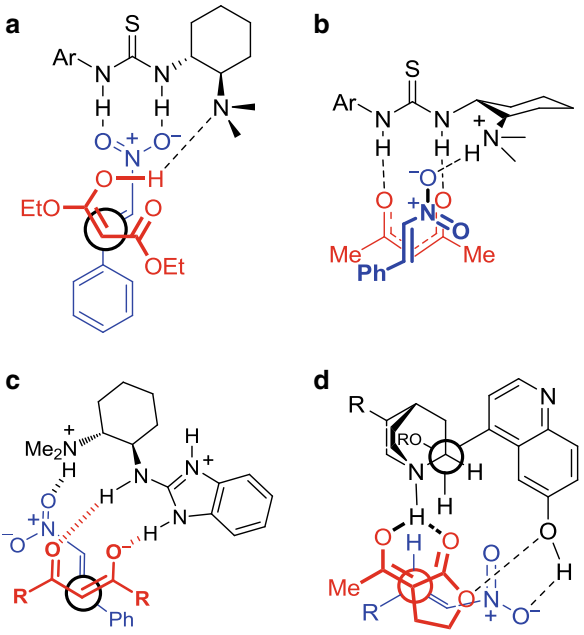


Fig. 2.19 Proposed transition states for the conjugate addition of 1,3-dicarbonyl compounds to nitroolefins

A similar scenario has been demonstrated by Nájera et al. to support the bifunctional Brønsted acid–base organocatalytic character and the origin of the observed enantioselectivity achieved by protonated 2-aminobenzimidazol-derived catalyst **163** in the conjugate addition of malonates and 1,3-diketones to nitroolefins [251]. DFT calculations have shown that the lowest energy transition state corresponds to the addition of the malonate or diketone to the electrophile with activation of the nucleophile by formation of two hydrogen bonds with the amino-benzimidazole moiety and activation of the nitroolefin better achieved by the protonated tertiary amine (**C**, Fig. 2.19).

β-Ketoesters have been also used as efficient nucleophiles in a diastereo- and enantioselective conjugate addition to nitrostyrenes. This reaction is very interesting since, depending of the structure of the nucleophile, generates adjacent tertiary/tertiary or tertiary/quaternary stereocenters, which are common structural motifs in complex natural products. Successful catalysts employed in this conjugate addition reaction are thiourea **142** [238], *Cinchona*-derived systems **152** [240], **151** [239], **159** [247], and **162** [250], chiral guanidines **157** [245] and **161** [249], chiral 2-aminobenzimidazol **163** [251], and C_3-symmteric chiral trisimidazoline **166** [254]. In general, all these catalysts afford the corresponding Michael adducts with very high enantioselectivities but low diastereoselectivity when using α-unsubstituted β-ketoesters (see Fig. 2.20 for selected examples). Higher levels of diastereoselection are observed in the case of α-substituted β-ketoesters (Fig. 2.20).

In their attempt to rationalize the results obtained for the addition of α-ketolactones to nitroalkenes employing cupreine **152** as catalyst, Deng et al.

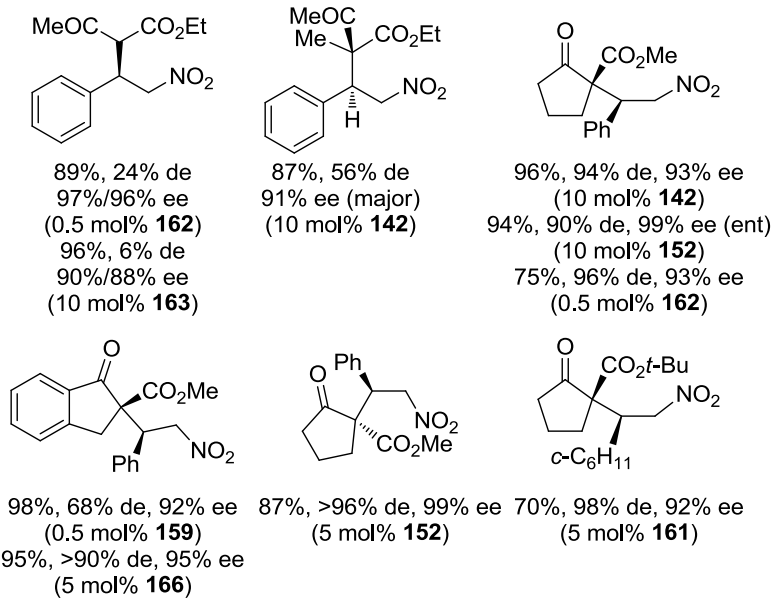


Fig. 2.20 Asymmetric conjugate additions of β-ketoesters to nitroolefins catalyzed by bifunctional organocatalysts

have postulated an *anti*-open conformation for the catalyst in the transition state being the phenolic hydroxyl group responsible for the control of the stereochemistry of the process through hydrogen bonding of both the nucleophile and the electrophile (**D**, Fig. 2.19) [240].

Recent further studies on the reaction scope have demonstrated the ability of certain bifunctional organocatalysts to achieve a highly enantioselective conjugate addition of α-fluoro-β-ketoesters to nitroolefins [256]. The best results have been obtained with quinidine- and cupreine-derived organocatalysts **79** [256a] and **127** [256b], that allow the preparation of fluorine-containing quaternary carbons adjacent to tertiary stereocenters from β-aryl- and β-alkyl substituted nitroolefins in high yields and excellent enantioselectivities. As depicted in Fig. 2.21 for selected examples, better diastereoselectivities are obtained with quinidine **79**, though much lower catalyst loadings are employed with cupreine **127**.

The usefulness of the asymmetric conjugate addition of β-ketoesters to nitroolefins has been demonstrated through to the synthesis of analogues of the antihypertensive ramipril [249], naturally occurring γ-butyrolactone autoregulators IM-2 and VB-D [257], and the marine alkaloid (−)-nakadomarin A (Scheme 2.91) [258].

Other activated methylene-containing nucleophiles that have been successfully used in the conjugate addition to nitroolefins are α-nitroesters [240], α-cyanoesters [240], α-isocyanoesters [259], 2-hydroxy-1,4-naphthoquinones [260], 3-substituted oxindoles [261], and anthrone [262]. For instance, cupreidine-derived catalysts **151** and **152** (see Fig. 2.15) afford very good yields, diastereo- and enantioselectivities

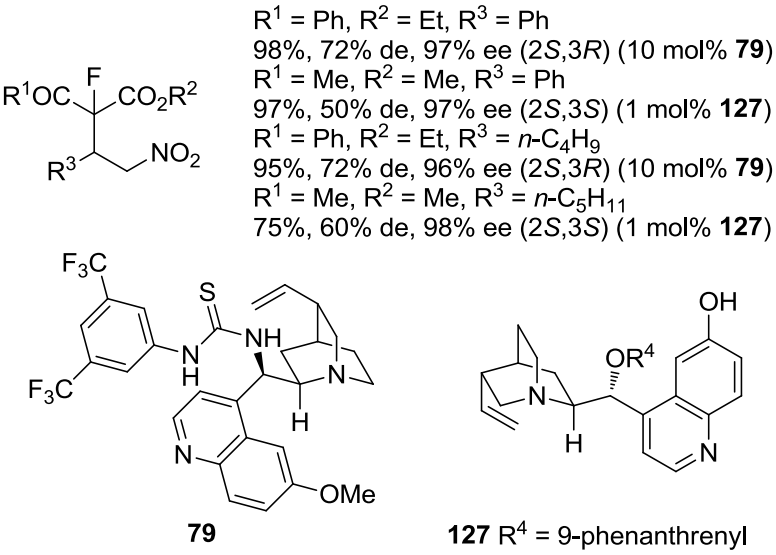
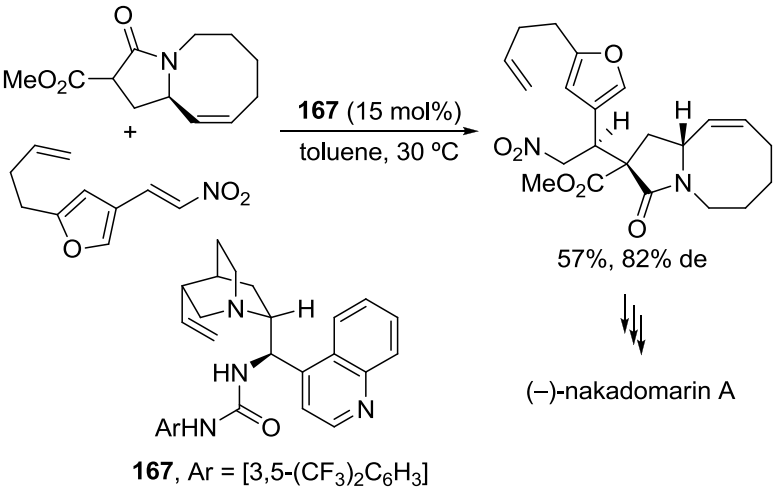


Fig. 2.21 Asymmetric conjugate additions of α-fluoro- β-ketoesters to nitroolefins



Scheme 2.91 Key step for the stereoselective synthesis of (−)-nakadomarin A

in the conjugate addition of α-substituted α-nitro- and α-cyanoesters to β-aryl and β-alkyl substituted nitroolefins (Fig. 2.22) [240].

The first organocatalyzed stereoselective conjugate addition of 3-substituted oxindoles to nitroolefins has been recently reported by Barbas et al. using thiourea **168** as catalyst [261a]. The reaction, which is performed in THF as solvent at −20°C, generates adjacent quaternary/tertiary stereocenters and affords the corresponding

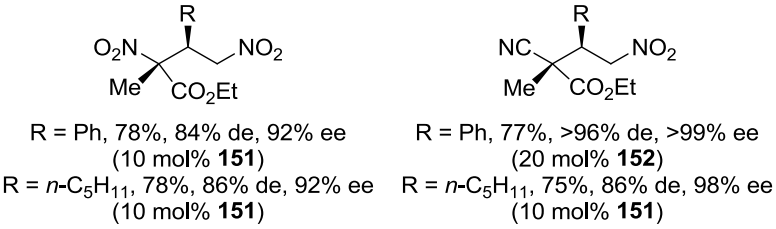
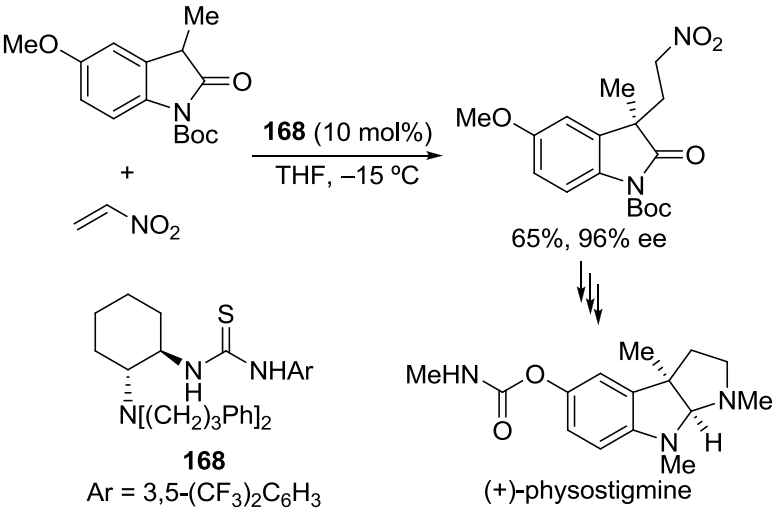


Fig. 2.22 Asymmetric conjugate additions of β-ketoesters to nitroolefins catalyzed by bifunctional organocatalysts

Michael adducts from β-aryl- and β-alkyl substituted nitroolefins in high yields (68–97%), good diastereoselectivities (dr: 3/1 to >20/1), and excellent enantioselectivities (88–99% ee). This novel organocatalytic approach has been used in the formal synthesis of the alkaloid (+)-physostigmine (Scheme 2.92). Catalyst **168** was

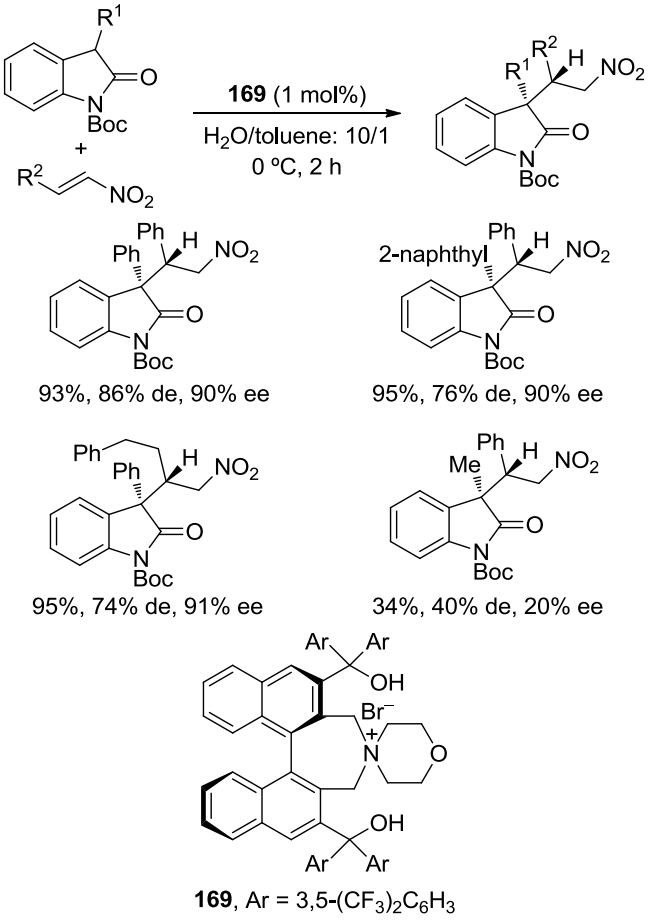


Scheme 2.92 Formal synthesis of (+)-physostigmine

selected by the authors among a collection of structurally and electronically different *N*-aryl substituted chiral thiourea derivatives. Remarkably, Luo, Cheng, et al. have very recently demonstrated that high yields and enantioselectivities can be also obtained in this conjugate addition by using alkyl-substituted thioureas bearing electron-withdrawing groups [261b].

A few months later, Maruoka et al. reported an interesting base-free enantioselective PTC version of the reaction [261c]. Using very low loadings (1 mol%) of the chiral ammonium bromide salt **169** in a 10/1 mixture of H_2O and toluene as solvent, these authors have achieved high enantioselectivities in the Michael addition of

3-aryl substituted oxindoles to nitroolefins (Scheme 2.93). In contrast, low yields and enantioselectivities are obtained for 3-alkyl substituted oxindoles. The reaction, which involves a chiral ion pair formed by the oxindole enolate and the catalyst, is regarded as a rare example of PTC reactions involving chiral ammonium salts as catalysts, since it does not require the presence of a base.



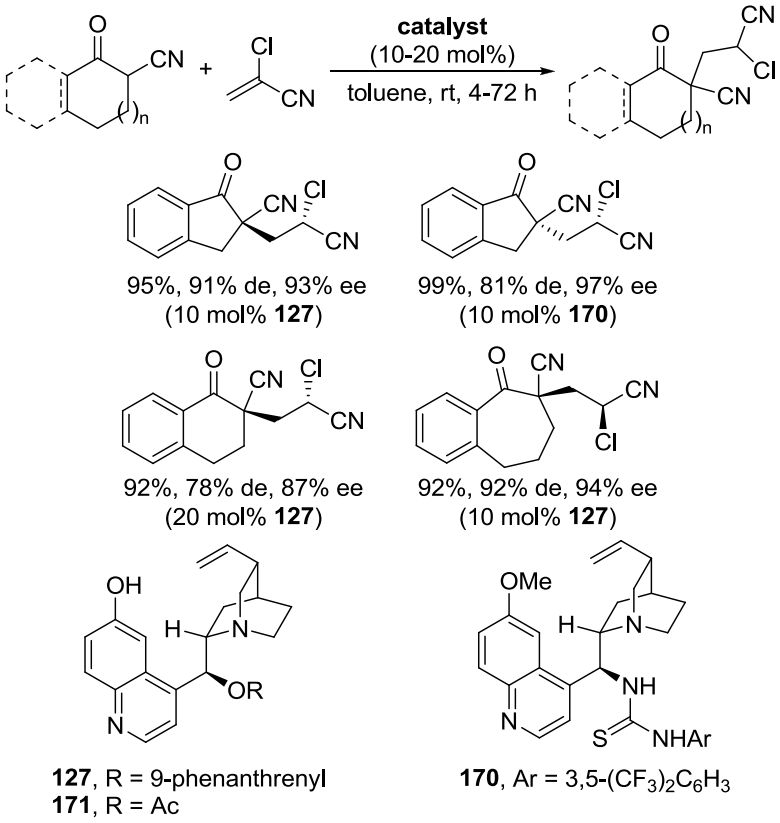
Scheme 2.93 PTC asymmetric conjugate additions of oxindoles to nitroolefins

2.3.5.4 Conjugate Addition of Activated Methylenes to Other Michael Acceptors

Acrylic acid derivatives as well as α,β-unsaturated nitriles, imides, phosphonates, and sulfones have been also studied as Michael acceptors for activated methylenes. Dixon et al. have demonstrated the efficacy of bifunctional cupreidine **125** (Fig. 2.12)

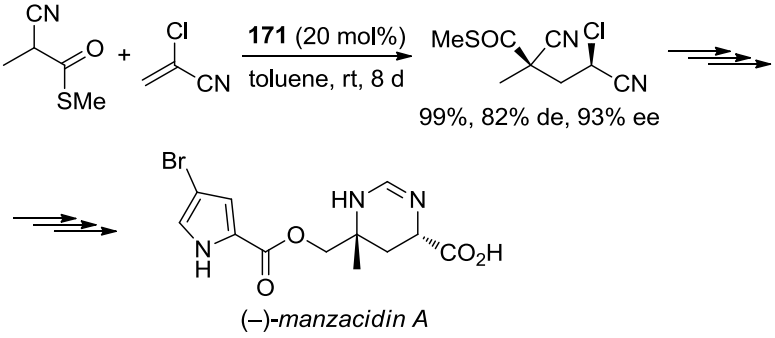
in the conjugate addition of β-ketoesters to acrylate and thioacrylate esters, as well as to *N*-acryloyl pyrroles, to yield in high yields and enantioselectivities (up to 98% ee) the corresponding Michael adducts [263].

Regarding α,β-unsaturated nitriles, Deng et al. have reported a highly diastereo- and enantioselective conjugate addition of cyclic and acyclic α-substituted cyanoacetates, cyanothioacetates, and cyanoketones to 2-chloroacrylonitrile to afford highly functionalized chiral compounds containing non adjacent stereocenters [264]. Using *Cinchona* alkaloid-derived organocatalysts these authors have been able to accomplish a one-step and stereoselective construction of 1,3-tertiary-quaternary stereocenters in any of the four possible absolute configurations with the proper catalyst selection. For instance, cupreine **127** catalyzes the tandem conjugate addition-protonation of cyclic β-ketonitriles to yield the corresponding Michael adducts in high yields, diastereoselectivities and enantioselectivities (Scheme 2.94) [264a]. Complementary sense of diastereoselectivity is obtained if quinine thiourea **170** is employed as catalyst [264b].



Scheme 2.94 Catalytic asymmetric tandem conjugate addition-protonation reaction

This methodology, which can also be applied to acyclic α-substituted cyanoacetates, cyanothioacetates, and cyanoketones as nucleophiles, as well as acrylonitrile as Michael acceptor by using cupreine **171**, quinine **170**, and their respective pseudoenantiomers as catalysts, has been successfully employed in the enenatioselective synthesis of an intermediate of the bromopyrrole alkaloid (−)-manzacidin A (Scheme 2.95) [264a].



Scheme 2.95 Asymmetric formal synthesis of (−)-manzacidin A

With respect to the reaction mechanism, a bifunctional role of the organocatalysts through an asymmetric network of hydrogen bonds with the reactants has been postulated [264]. As depicted in Fig. 2.23, for catalysts **170** and **171**, the absolute and relative stereochemistry of the products is consistent with the proposed transition state models **A** and **B**.

Takemoto's group 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 **142** (Scheme 2.96) [265]. In terms of substrate scope, reaction rate and stereoselectivity, *N*-alkenoyl-2-methoxybenzamides resulted excellent Michael acceptors affording the corresponding adducts in high yields and enantioselectivities. The better 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 proposed ternary transition state structured by the catalyst, the nucleophile and the imide, as depicted in Scheme 2.96 for the conjugate addition of malononitrile. Recent DFT calculation studies on the reaction have rationalized and confirmed the experimentally proposed transition state [266].

After Takemoto's studies, Bartoli and Melchiorre have successfully used β-ketoesters and 1,3-diketones in the conjugate addition to *N*-benzyl maleimides employing the natural cinchona alkaloids quinine or quinidine as catalysts [267]. The reaction, which is one of the few reported examples of a very stereoselective conjugate addition catalyzed by quinine (or quinidine), affords 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

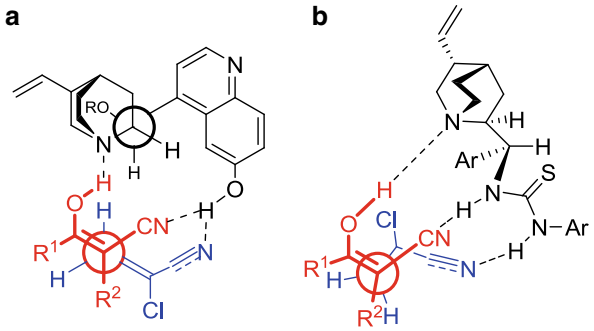
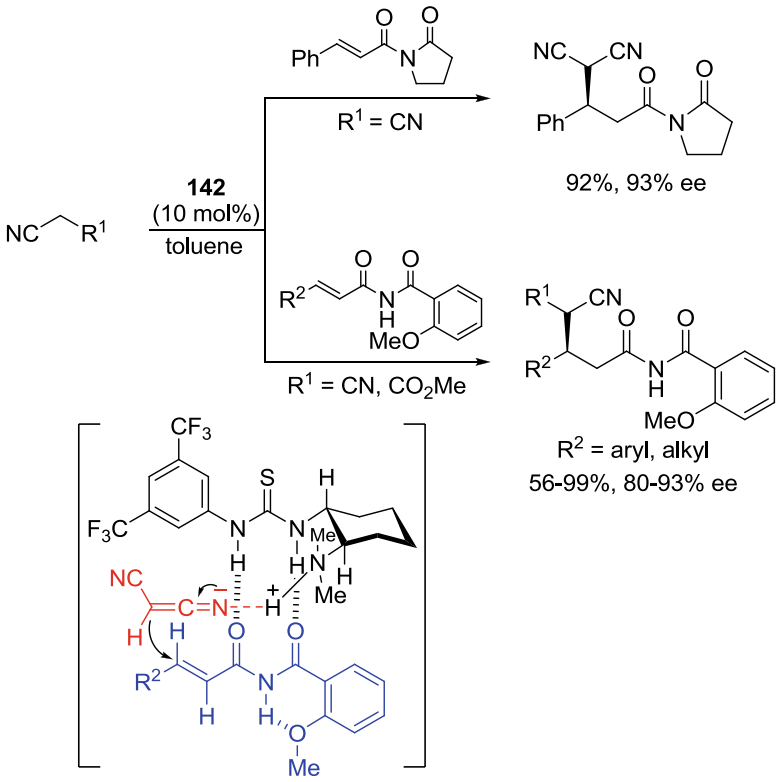
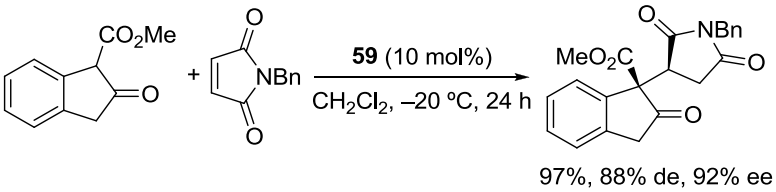


Fig. 2.23 Proposed transition state models for the catalytic asymmetric tandem conjugate addition-protonation reaction



Scheme 2.96 Thiourea-catalyzed asymmetric Michael addition of activated methylenes to α,β-unsaturated imides

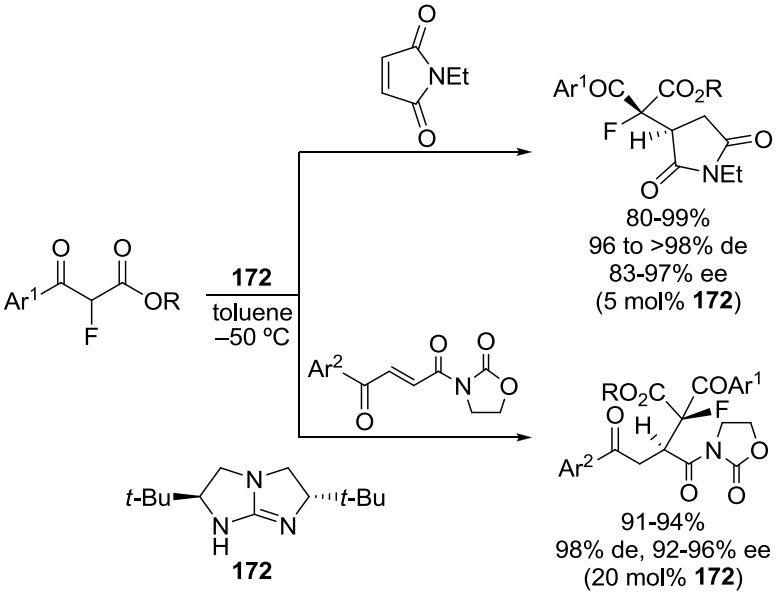
and cyclic β-diketones as depicted in Scheme 2.97 for the reaction of a cyclic β-ketoester catalyzed by quinine (**59**). With respect to the mechanism and activation mode of the catalyst, calculation studies have demonstrated the bifunctional character



Scheme 2.97 Quinine-catalyzed asymmetric Michael addition of 1,3-dicarbonyl compounds to *N*-benzyl maleimide

of the catalyst with its ammonium group binding the enolate and its hydroxyl group orienting and activating the maleimide via hydrogen bond [268].

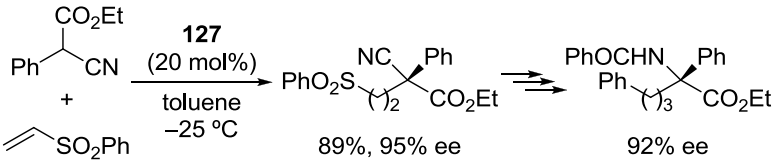
The Michael addition of α-fluoro- β-ketoesters to α,β-unsaturated imides has been recently reported using chiral guanidines as organocatalyst [269]. As shown in Scheme 2.98, chiral guanidine **172** (5–20 mol%) is an excellent bifunctional catalyst at low temperature for the addition of acyclic α-fluoro-β-ketoesters to *N*-ethyl maleimide and *trans*-4-oxo-4-arylbutenamides, affording the corresponding chiral derivatives bearing adjacent tertiary/fluorine-containing quaternary stereocenters in high yields, diastereo- and enantioselectivities.



Scheme 2.98 Guanidine-catalyzed asymmetric Michael addition of α-fluoro-β-ketoesters to imide derivatives

On the other hand, the enantioselective conjugate addition of α-substituted cyanoacetates and cyanoketones to α,β-unsaturated sulfones has been reported by Deng et al. using bifunctional cupreine **127** as catalyst [270]. Substoichiometric amounts of **127** (20 mol%) catalyze the synthesis of chiral sulfones containing all-carbon

substituted quaternary stereocenters in high yields and enantioselectivities, adducts which have been used as efficient precursors towards the synthesis of optically active α,α-disubstituted amino acids as shown in Scheme 2.99 for a selected example.



Scheme 2.99 Catalytic enantioselective conjugate addition to vinyl sulfones

2.3.6 Conjugate Addition of Amino Acid Derivatives

In this section, the Michael addition of amino acid derivatives to Michael acceptors employing chiral organocatalysts is discussed. The reaction is usually carried out using chiral, non-racemic quaternary ammonium salts, derivatives which have been successfully used as catalysts to achieve other highly selective conjugate addition reactions [8]. Furthermore, recent advances based on activation modes other than chiral ionic pair formation are also briefly commented. Although much less studied than the alkylation via nucleophilic substitution with alkyl halides, the addition of glycinate Schiff bases to Michael acceptors offers a practical route to a variety of α-amino acids having an additional carbonyl functionality [271].

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 (**173**) (Fig. 2.24) as catalyst and cesium hydroxide as base [272]. Different studies followed this pioneering work, presenting diverse modifications over the standard procedure such as the employment of non-ionic bases [273], variations of the nucleophile functionality [274], and using new chiral phase-transfer catalysts, the most attention paid to this latter feature. For instance, catalyst **173** 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 [275].

Cinchonidine-derived catalyst **173** (10 mol%) has been also employed in the asymmetric synthesis of 4-alkyliden glutamic acid derivatives through a tandem conjugate addition-elimination reaction between the Schiff base of glycine *tert*-butyl ester and activated allylic acetates under PTC conditions using $CsOH{\cdot}H_2O$ as base [276]. The reaction, which is performed at –78°C in CH_2Cl_2, allows the preparation of 4-alkylidenyl glutamic acid derivatives with up to 97% ee (Scheme 2.100). This is a quite interesting process since glutamic acid derivatives are known to be implicated in the pathogenesis of neural damage that causes various neural diseases [277].

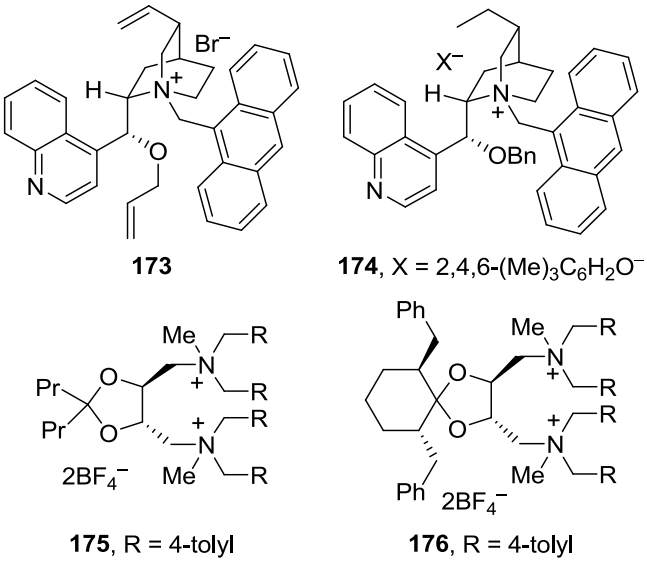
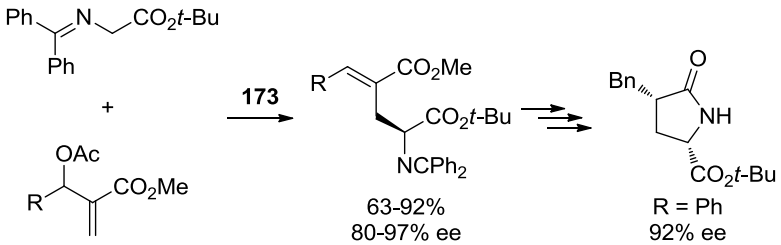


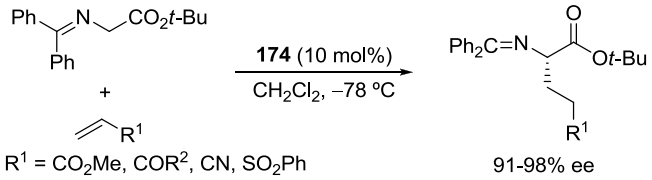
Fig. 2.24 Chiral phase-transfer catalysts for the conjugate addition of glycine derivatives



Scheme 2.100 PTC asymmetric synthesis of 4-substituted pyroglutamates

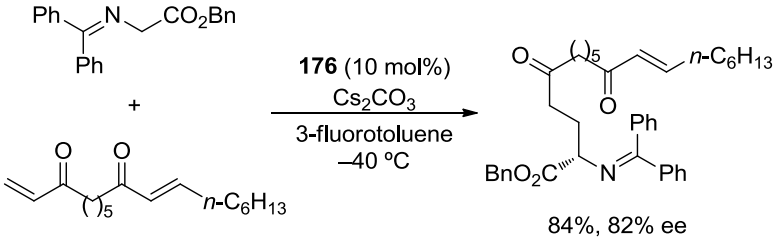
Phase transfer-catalyzed Michael additions usually suffer from non-selective base-catalyzed background reactions. An interesting study carried out by Lygo et al. has recently demonstrated that it is possible to generate in situ the otherwise challenging quaternary ammonium salts bearing basic counteranions, just by mixing an alkoxide with a suitable quaternary ammonium bromide [278]. In this manner, Cinchonidine-derived ammonium 2,4,6-trimethylphenolate **174** has been prepared and demonstrated to promote a highly enantioselective Michael addition of the Schiff base of glycine *tert*-butyl ester to diverse Michael acceptors, such as methyl acrylate, acrylonitrile, vinyl ketones, and phenyl vinyl sulfone (Scheme 2.101). These results represent a big improvement in the substrate scope of the reaction since much lower enantioselectivities have been usually obtained with other chiral ammonium catalysts [279].

Tartrate-derived chiral phase-transfer catalysts **175** and **176** (Fig. 2.24) have been synthesized and successfully employed in the conjugate addition of amino acid derivatives to different Michael acceptors such as acrylates and vinyl ketones [280].



Scheme 2.101 PTC asymmetric Michael additions catalyzed by **174**

The reactions, which are normally carried out at low temperatures and employing Cs_2CO_3 as base, show exceptional counteranion [280b] and additive effects [280d], and have been productively used in key steps of the enantioselective synthesis of the serine protease inhibitor aeruginosin 298-A [280b] and the marine alkaloid (+)-cylindricine C (Scheme 2.102) [280d]. Although there are several efficient PTC reactions promoted by *Cinchona*-based catalysts, these processes are good examples of the few synthetic applications for complex natural products reported so far.



Scheme 2.102 PTC Phase-transfer catalyzed key step in the enantioselective synthesis of (+)-cylindricine C

Other non alkaloid-derived organocatalysts have also shown high selectivities in the conjugate additions of amino acid derivatives. For instance, 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), has been easily synthesized in a 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 **177** (Fig. 2.25) [281]. Interestingly, a non-ionic neutral phosphazene base such as BEMP gave the highest yield and enantioselectivity in the process (93%, 97% ee).

Besides ionic par-based activations using phase transfer catalysts, the Michael addition of glycine imines has been studied using other different organocatalysts. For instance, Akiyama et al. have employed a chiral crown ether derived from L-quebracitol under very low loading conditions (0.2 mol%) as organocatalyst for the 1,4-addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester to vinyl ketones, obtaining very good enantioselectivities (up to 96% ee) using potassium *tert*-butoxide

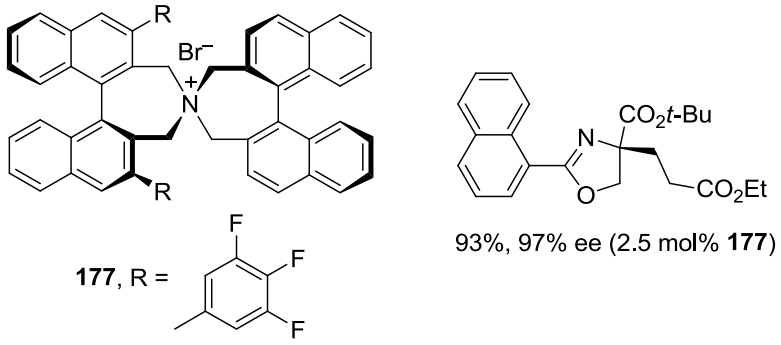
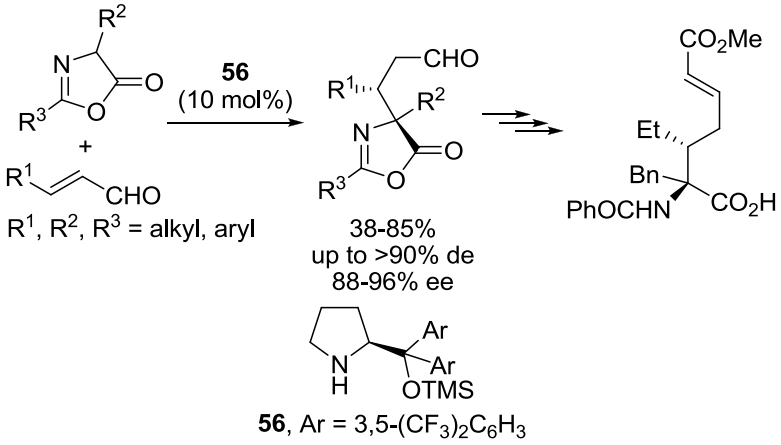


Fig. 2.25 Chiral phase-transfer catalysts for the conjugate addition of amino acid derivatives

as base at −78°C [282]. Lower selectivities have been observed with acrylates (up to 87% ee) and acrylonitrile (46% ee) as electrophiles. Similar selectivities have been reported by Ishikawa et al. using chiral guanidines synthesized from C_2-symmetric diamines [283].

Finally, Jørgensen et al. have developed a highly enantioselective synthesis of α,α-disubstituted α-amino acids through the organocatalyzed asymmetric conjugate addition of oxazolones to α,β-unsaturated aldehydes [284]. Using a 10 mol% of the diarylprolinol silyl ether **56** as catalyst in toluene at rt, a wide variety of oxazolones reacts with aromatic and aliphatic enals with moderate to good yields and diastereoselectivities and excellent enantioselectivities (88–96% ee). A wide variety of highly functionalized optically active compounds has been synthesized using this conjugate addition, such as α,α-disubstituted α-amino acids, α-quaternary proline derivatives, amino alcohols, lactams, and tetrahydropyranes, a representative example of the former being depicted in Scheme 2.103.



Scheme 2.103 Asymmetric synthesis α,α-disubstituted α-amino acids

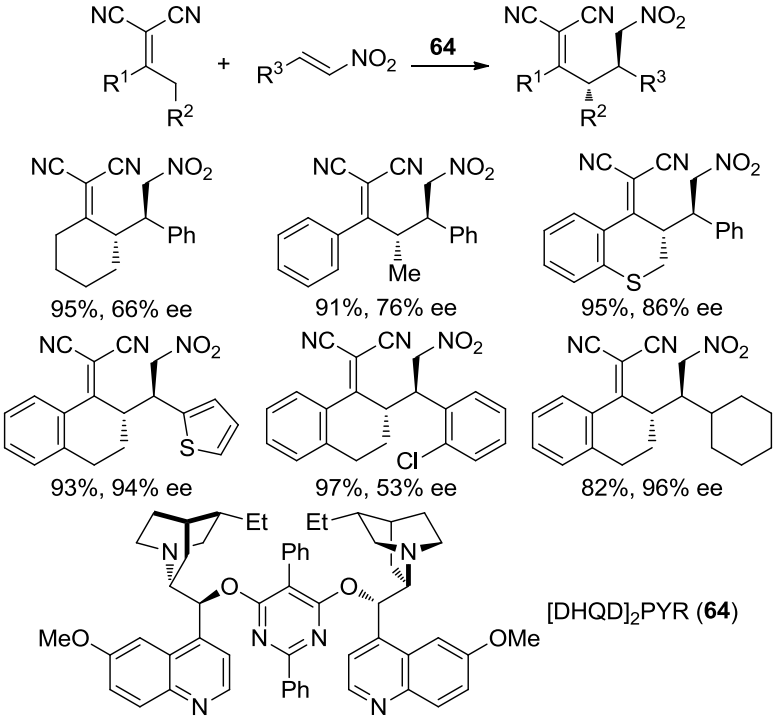
The conjugate addition of oxazolones to nitroalkenes has been also studied by Jørgensen's group using bifunctional *Cinchona*-derived thiourea organocatalysts, being the reaction less enantioselective than for enals, especially when using β-alkyl substituted nitroolefins as Michel acceptors [285].

2.3.7 Umpolung Conjugate Additions

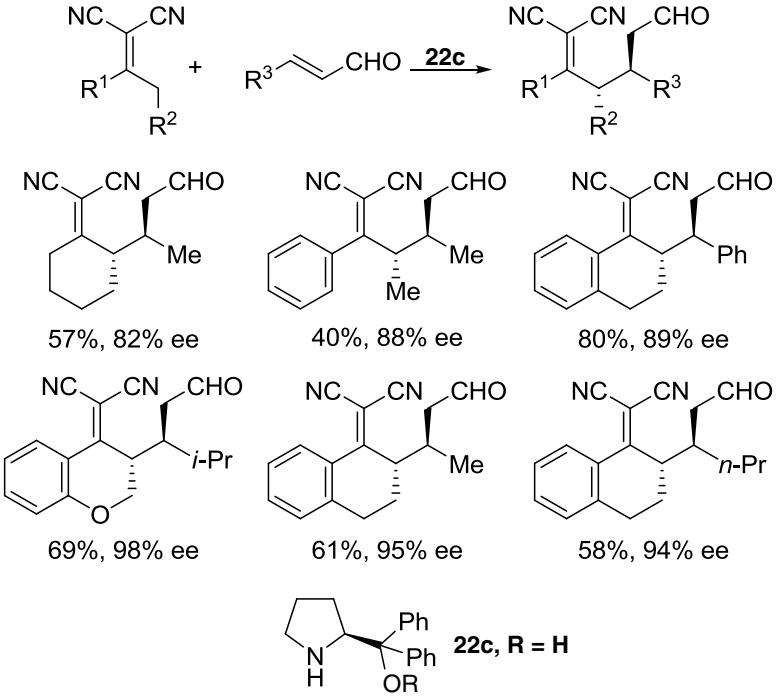
In this chapter, asymmetric organocatalyzed umpolung conjugate additions are considered. Particular emphasis on deconjugative Michael additions with α,α-dicyanoalkenes, the intramolecular Rauhut-Currier reaction, and the Stetter reaction is placed. These are very efficient transformations in the synthetic chemist's arsenal, but they are also challenging to control.

Activated alkylidene structures are common intermediates in complex molecule synthesis, where their electrophilic character has been especially exploited in asymmetric organocatalyzed conjugate additions. Interestingly, this type of compounds has also a dormant reactivity as nucleophiles either when they are activated through allylic deprotonation with an appropriate organic chiral base or they react with an activated electrophile. Among activated alkylidenes, α,α-dicyanoalkenes have been the most studied substrates showing excellent reactivity towards nitroolefins [286, 287], enals [288], enones [289], maleimides [290], Baylis-Hillman adducts [291], and quinones [292]. With respect to the addition to nitroolefins, Deng et al. firstly reported that *Cinchona*-derived chiral tertiary amine $[DHQD]_2PYR$ **64** (5 mol%) is a highly enantioselective catalyst for the conjugate addition to β-aryl substituted nitroolefins affording the corresponding adducts in high yields (85–95%) and enantioselectivities (up to 94% ee) at −40°C in CH_2Cl_2 as solvent [286]. The reaction exhibits exclusive γ-regio- and *anti*-selectivity, as depicted in Scheme 2.104 for selected examples. Almost simultaneously, Jørgensen et al. enlarged the substrate scope of the reaction to aliphatic nitroolefins also using **64** as catalyst under slightly modified reaction conditions (acetone as solvent and 10 mol% of **64**) [287]. As shown in Scheme 2.104, only in the case of using nucleophiles derived from cyclohexanone, acyclic aromatic ketones, or sterically hindered electrophiles such as *o*-chloro-*trans*-β-nitrostyrene, lower enantioselectivities are obtained.

The first organocatalytic conjugate addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes [289] and ketones [289] was reported by Deng et al. In the case of enals, chiral iminium activation using diphenyl prolinol **22c** (20 mol%) is responsible for a highly regio-, diastereo-, and enantioselective vinylogous Michael addition to β-aryl- and β-alkyl substituted electrophiles in THF at −50°C, and in the presence of *p*-nitrobenzoic acid (20 mol%) as additive. The reaction scope is fairly broad with respect to the nucleophile and the β-substitution on the electrophile, being exclusively observed the *anti*-configured adducts (Scheme 2.105) [288]. Recent attempts to use aqueous conditions (brine) in the process using long-chain dialkyl prolinols have led to lower enantioselectivities [293].

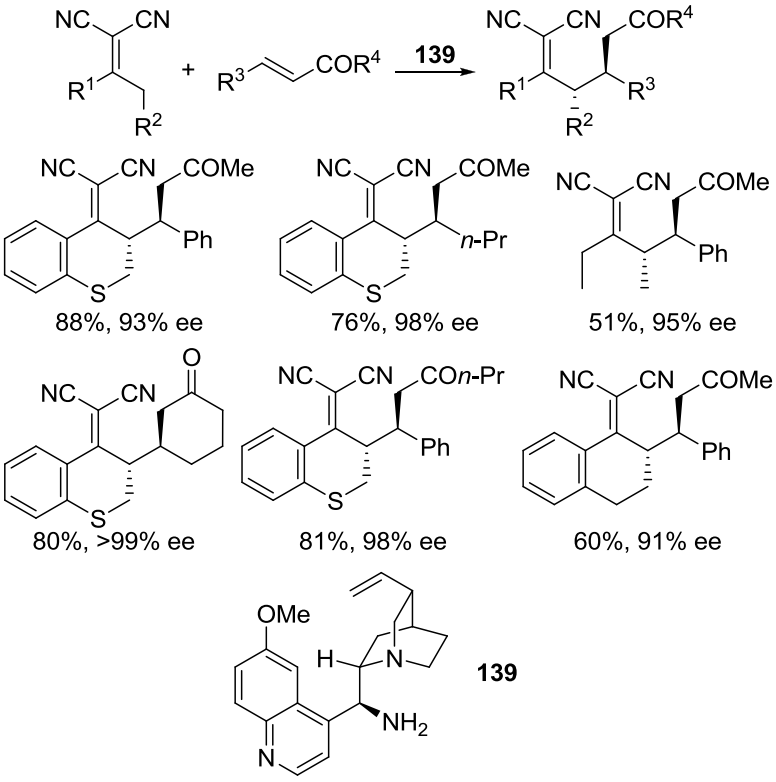


Scheme 2.104 Deconjugative Michael additions to nitroolefins



Scheme 2.105 Deconjugative Michael additions to enals

Concerning α,β-unsaturated ketones [289] the vinylogous Michael addition of α,α-dicyanoalkenes is catalyzed by the quinine-derived primary amine **139** which, under substoichiometric loadings (20 mol%) and in the presence of 40 mol% of TFA as cocatalyst, affords the corresponding highly functionalized adducts in good yields and high selectivities in THF at 0°C, as depicted in Scheme 2.106 for selected

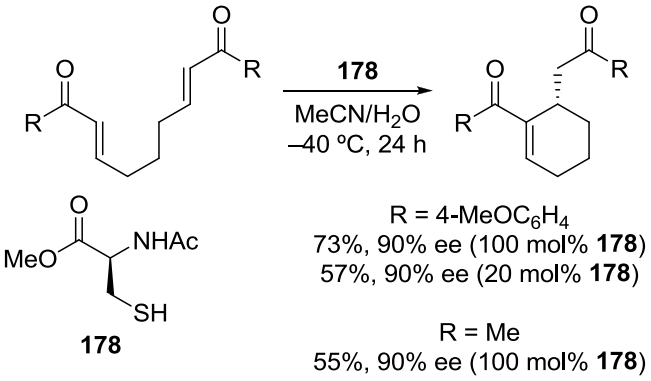


Scheme 2.106 Deconjugative Michael additions to enons

examples. Regarding substrate scope, excellent stereoselectivities are observed from cyclic and acyclic nucleophiles as well as for cyclic, acyclic, aromatic, and aliphatic enones. Interestingly, the authors postulate iminium activation, scenario which is not so common in organocatalysis since the application of primary amines as iminium catalysts in conjugate additions has hardly been explored. This type of iminium activation with primary amine-derived catalysts has been also recently proposed for the asymmetric vinylogous Michael addition of γ-butenolides to chalcones [294].

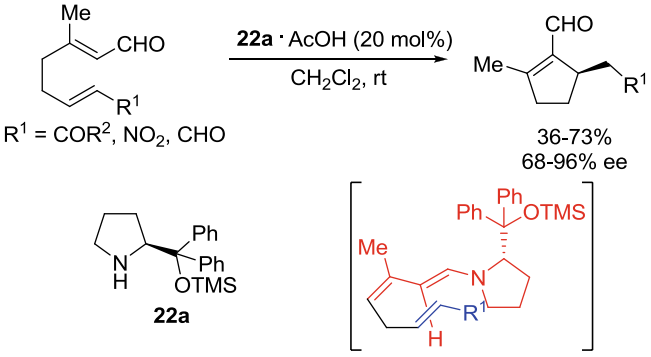
The intramolecular enantioselective Rauhut-Currier reaction [295] generates optically active cycloalkenes from acyclic precursors bearing two tethered Michael acceptors. In 2007, Miller et al. reported the first organocatalyzed intramolecular cyclization of symmetrical bis(α,β-unsaturated ketones) to afford in good yields

and high enantioselectivities (84–95% ee) functionalized cyclohexenes promoted by the chiral nucleophilic cysteine catalyst **178** (Scheme 2.107) [296]. The reaction was very sensitive to different reaction conditions such as solvent, temperature and water as cocatalyst, and required stoichiometric amounts of catalyst to obtain synthetically useful yields.



Scheme 2.107 Enantioselective organocatalyzed Rauhut-Currier reaction of bis(enones)

More recently, chiral cyclopentenes bearing a tetra-substituted olefin have been obtained in moderate to good yields and good enantioselectivities by an intramolecular Rauhut-Currier reaction catalyzed by the Jørgensen/Hayashi prolinol derivative **22a** [297]. A novel activation strategy involving the formation of electron-rich dienamines as key intermediates from enals has been used in this methodology, which has allowed the preparation of 1,2,5-trisubstituted cyclopentenecarbaldehydes, interesting precursors towards the synthesis of iriods (Scheme 2.108).



Scheme 2.108 Enantioselective organocatalyzed Rauhut-Currier reaction of enals

In comparison to asymmetric catalytic reactions involving enolate equivalents, the catalytic chemistry of acyl anion equivalents [298] has received considerable

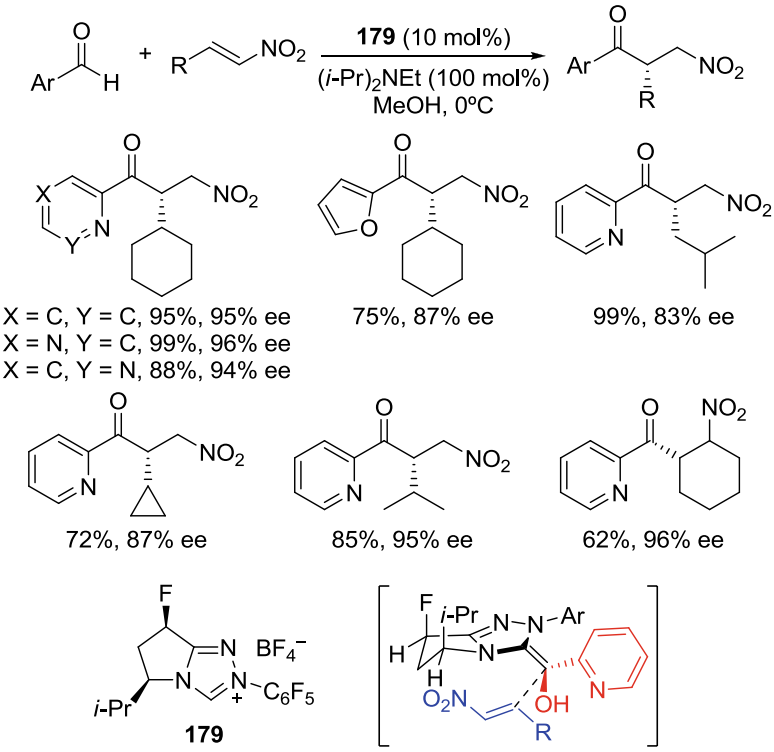
less attention. Umpolung reactivity reverses the normal mode of aldehyde polarity, thus rendering a nucleophilic aldehyde. The asymmetric Stetter reaction [299], takes advantage of the umpolung reactivity of aldehydes to give rise to acyl anion equivalents capable of participating in inter- and intramolecular conjugate additions with a variety of Michael acceptors usually employing a chiral *N*-heterocyclic carbene as catalyst [300]. *N*-heterocyclic carbenes and their unique and versatile reactivity have already proven wide applicability in the Stetter reaction.

The asymmetric intermolecular Stetter reaction has met with limited success so it has received much less attention than the intramolecular process. Enders et al. originally achieved the first enantioselective organocatalyzed intermolecular Stetter reaction using chiral thiazolium salts as catalysts obtaining the corresponding adducts in very low enantioselectivities and negligible yields [300a, b]. In 2006, Scheidt et al. reported a single example of the asymmetric conjugate addition of a stoichiometrically generated acyl anion equivalent (silyl-protected thiazolium carbinol) to nitroalkenes using stoichiometric amounts of the quinine-derived thiourea **170** as catalyst to afford the product in a modest 74% ee [301]. Moderate enantioselectivities have been also obtained by Enders et al. in the Stetter reaction between aromatic aldehydes and chalcones (56–78% ee) [302a] and aromatic heterocyclic aldehydes and arylidenemalonates (30–78% ee) [302b] catalyzed by a chiral triazolium carbene.

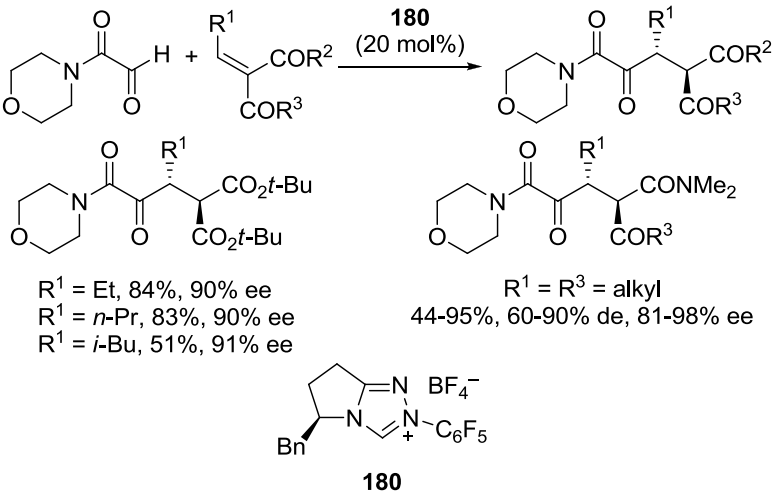
On the other hand, Rovis group has placed great effort to develop efficient chiral heterocyclic carbene catalysts for the intramolecular Stetter reaction. As a result, a highly enantioselective conjugate addition between a variety of heterocyclic aromatic aldehydes and β-alkyl substituted nitroolefins has been achieved in MeOH at 0°C using triazolium salt **179** (10 mol%) as catalyst precursor (Scheme 2.109) [303]. Five and six-membered heterocyclic aldehydes participate with good to excellent yield and enantioselectivity. Benzaldehyde fails to participate under the reaction conditions studied. However, the role of the heteroatom in the aldehyde is not clear at the moment and can not be ascribed only to a proximal Lewis base functionality. Secondary alkyl substitution of the nitroalkene provides high yield and excellent selectivity as well, while primary substitution results in somewhat reduced selectivities. In all the studied cases, fluorine-modified triazolium salt **179** outperforms the nonfluorinated analogue in terms of enantioselectivity. This has been explained by a stereoelectronic-directed (stabilizating gauche effects) conformational change in the bicyclic ring system of the catalyst to a Cγ-exo conformation in the presence of the fluorine atom which improves enantiofacial discrimination on the incoming nitroalkene.

Very recently, Rovis et al. have examined the intermolecular Stetter reaction of glyoxamide with alkylidenemalonates [304] and alkylideneketoamides [305]. In the presence of a suitable base, phenylalanine-derived triazolium salt **180** catalyzes the reactions in CCl_4 at low temperature to afford the corresponding adducts in good yields, good diastereoselectivities, and excellent enantioselectivities (Scheme 2.110).

Unlike the intermolecular Stetter reaction, significant progress has been made in the asymmetric intramolecular variant of the reaction since first examples reported by Enders et al. in 1996 towards the synthesis of optically active chroman-4-one derivatives using chiral triazolium salts as catalysts [306]. Recently, Rovis group

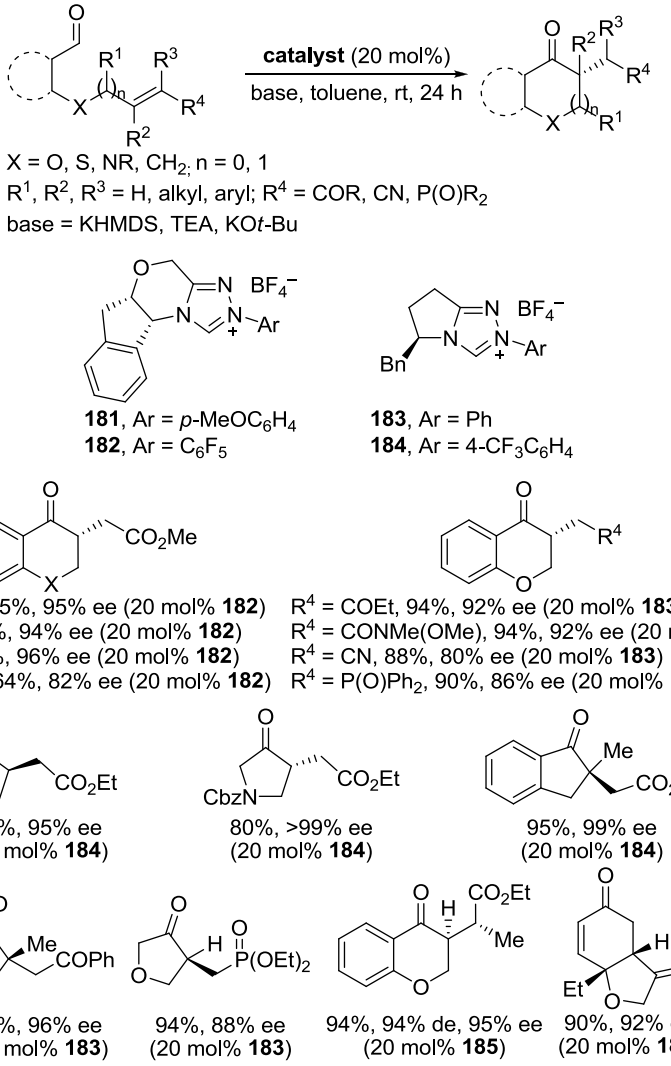


Scheme 2.109 Enantioselective organocatalyzed intermolecular Stetter reaction of heterocyclic aldehydes with nitroalkenes



Scheme 2.110 Enantioselective organocatalyzed intermolecular Stetter reaction of glyoxamides

has developed a family of triazolinylidene carbenes **181**–**184** and has shown their efficiency to catalyze the asymmetric intramolecular Stetter reaction [307]. Usually, the reactions are carried out in the presence of 20 mol% of the carbene precatalyst in toluene at rt, and using a strong base with non-coordinating counteranion such as KHMDS. With respect to the substrate scope, through an appropriate substrate/catalyst combination, the process has proven tolerant to aromatic and aliphatic aldehydes and to many tethered *trans*-Michael acceptors such as, unsaturated esters, ketones, thioesters, amides, nitriles, phosphane oxides, and phosphonates with different substitution patterns (Scheme 2.111). Low enantioselectivities are observed



Scheme 2.111 Organocatalyzed intramolecular Stetter reaction

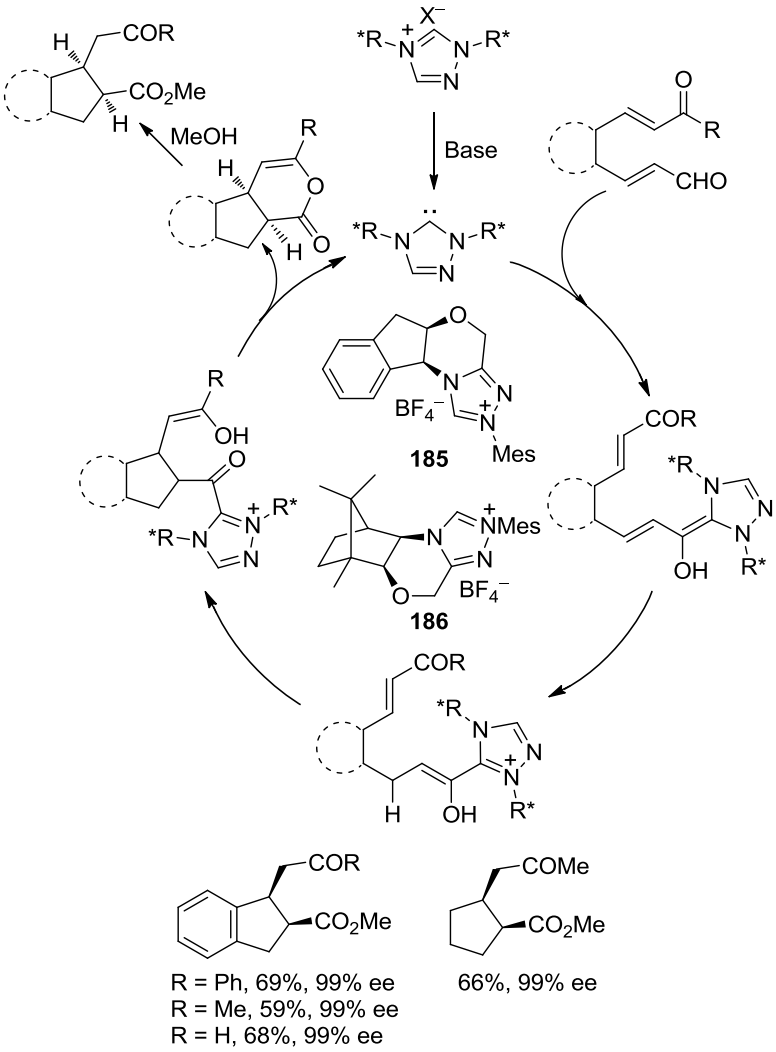
for α,β-unsaturated aldehydes and no reaction occurs if the tether length is increased by one methylene unit (Scheme 2.111, n = 2). Employing a suitable starting material, Rovis group has been able to prepare quaternary stereocenter- and adjacent quaternary/tertiary stereocenter-containing derivatives in a highly enantio- and diastereoselective fashion, as depicted in Scheme 2.111 for selected examples. The development of the new and efficient chiral triazolinylidene carbenes **181**–**184** has allowed the appearance of the first successful applications of the asymmetric Stetter reaction in total syntheses [308].

Finally, it is worthy to mention an interesting triazolium carbene-catalyzed enantioselective intramolecular Stetter-type Michael addition between enone- and enal-tethered enals developed by Scheidt et al. for the preparation of chiral cyclopentanes using aminoindanol-derived triazolium carbene precursor **185** (10 mol%) as catalyst [309]. As shown in Scheme 2.112, the reaction initially involves the addition of the chiral carbene to the α,β-unsaturated aldehyde, followed by subsequent β-protonation generating a reactive enol intermediate that undergoes conjugate addition to the enone. Final acylation and reaction with an external nucleophile such as MeOH yields the corresponding chiral *cis*-cyclopentenes in good yields and excellent diastereo- and enantioselectivities. On the other hand, the D-camphor-derived triazolium salt **186** (Scheme 2.112) has shown similar selectivity in the reaction than catalyst **185**, but higher activity allowing to reduce the catalyst loading down to 1 mol% [310].

2.3.8 Friedel-Crafts Type Conjugate Additions

The Friedel-Crafts alkylation is one of the oldest synthetic methodologies known. The catalytic asymmetric version of the reaction [311] enables the preparation of important chiral building blocks. Electron-rich aromatic and heteroaromatic compounds have been productively used in organocatalyzed enantioselective inter- and intramolecular Friedel-Craft-[312] type conjugate additions over different Michael acceptors such as, α,β-unsaturated aldehydes, α,β-unsaturated ketones, nitroolefins, and α,β-unsaturated acyl phosphonates.

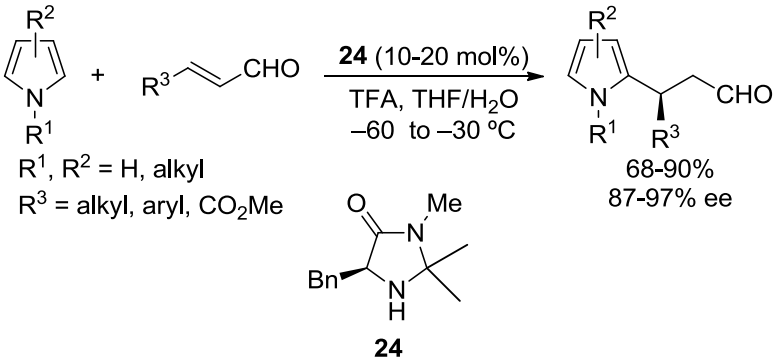
MacMillan's group has successfully employed phenylalanine-derived chiral imidazolidinones to carry out a highly enantioselective 1,4-addition of different aromatic compounds such as pyrroles, indoles, and anilines to α,β-unsaturated aldehydes [313]. MacMillan's LUMO-lowering activation of enals through the reversible formation of intermediate chiral iminium ions provides electrophile activation and efficient stereodifferentiation of the diastereotopic faces of the Michael acceptor. For instance, a highly enantioselective (87–97% ee) alkylation of pyrroles with aromatic and aliphatic enals has been reported by MacMillan's group using first generation imidazolidinone **24** in the presence of TFA as cocatalyst affording the corresponding Michael adducts in good to excellent yields (68–90%) under aerobic conditions and using wet solvents (Scheme 2.113) [313a].



Scheme 2.112 Asymmetric synthesis of cyclopentanes

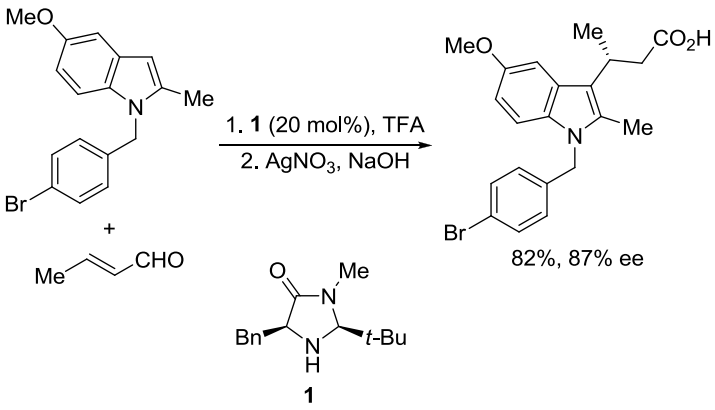
Double alkylation of *N*-methylpyrrole to generate C_2-symmetric dialkylation products can be also achieved in the presence of catalyst **24** with an excess of an enal electrophile, e.g. crotonaldehyde, affording the 2,5-disubstituted product in 83% yield, a C_2/meso ratio of 90:10, and a 98% ee. Similar selectivity is obtained when the two alkylation steps are performed consecutively with two different electrophiles, e.g. crotonaldehyde and cinnamaldehyde, affording the corresponding non-symmetrical bis-alkylated products [313a].

Functionalized indoles have become privileged structures in pharmaceuticals, fragances, agrochemicals, pigments, and materials science [314]. Further studies carried



Scheme 2.113 Asymmetric conjugate Friedel-Crafts addition of pyrrols to enals

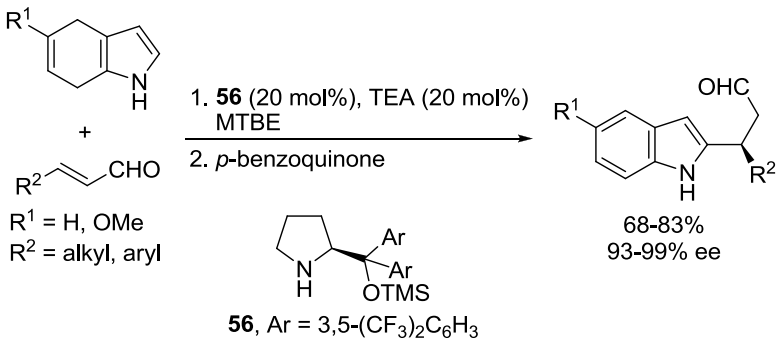
out by MacMillan's group on the activity of phenylalanine-derived chiral imidazolidinones as organocatalysts have demonstrated that second-generation chiral imidazolidinone **1** is a very active and selective catalyst for the highly enantioselective 1,4-addition of indoles to enals [313, 315]. This transformation is general with respect to substrate scope, occurs at low temperature (−40 to −87°C) with 20 mol% of catalyst loading, and it yields the desired alkylated indoles in very good yields (70–94%) and excellent enantioselectivities (89–97% ee). Similar levels of enantioselection have been very recently obtained by Wang et al. using TMS-protected prolinol catalyst **22b** [316]. An interesting and practical application of this reaction is the preparation of indolobutyric acid, a COX-2 inhibitor (Scheme 2.114) [313b].



Scheme 2.114 Asymmetric synthesis of indolobutyric acid

Less common 2-substituted indole derivatives can be prepared by Friedel-Crafts alkylation of 4,7-dihydroindoles with α,β-unsaturated aldehydes, followed by oxidation with *p*-benzoquinone [317]. 4,7-Dihydroindoles, which can be considered as 2,3-disubstituted pyrroles, react with a wide variety of aromatic and aliphatic enals

in the presence of 20 mol% of prolinol-derived catalyst **56** and 20 mol% of TEA as additive, in *tert*-butyl methyl ether (MTBE) as solvent at ambient temperature, to afford the corresponding adducts in good yields (61–93%) and excellent enantioselectivities (92–99% ee). Final oxidation occurs without erosion of the enantioselectivity, so this methodology complements previously described methods towards the synthesis of 3-substituted indoles (Scheme 2.115).



Scheme 2.115 Asymmetric synthesis of 2-substituted indoles

With respect to non-heterocyclic nucleophiles, iminium catalysis employing **1**·HCl (1–10 mol%) has been extended by MacMillan's group to the asymmetric Friedel-Crafts alkylation of *N*,*N*-dialkylated anilines with enals affording the corresponding adducts in very good yields (65–97%) and excellent enantioselectivities (up to 99% ee) [313c]. Subsequent methylation/reductive deamination of the Friedel-Crafts products converts *N*,*N*-dialkylanilines in competent benzene surrogates. In a similar manner, 1-naphthols have been used to prepare optically active chromanes and dihydrobenzopyranes via Michael-type Friedel-Crafts alkylation with enals catalyzed by protected prolinol **56** followed by cyclization [318].

On the other hand, catalysts **1** and **56** have been successfully used by Xiao's group in the enantioselective intramolecular ring-closing Friedel-Crafts-type alkylations of indole- [319] and anilino-tethered [320] α,β-unsaturated aldehydes, respectively. As depicted in Fig. 2.26, this reaction provides access to the synthesis of a wide variety of heterocyclic compounds in high yields and excellent enantioselectivities.

The employment of the enantioselective inter- and intramolecular Friedel-Crafts-type conjugate additions to enals as a key step in the synthesis of different natural and biologically active products, such as (−)-flustramine B [321], (+)-curcuphenol [322], the alkaloids (−)-rhazinal, (−)-rhazinilam, (−)-leuconolam, and (+)-*epi-le*uconolam [323], as well as the serotonin reuptake inhibitor BMS-594726 [324], is also worth mentioning. Also, highly selective organo-cascade iminium-enamine organocatalytic processes have been developed involving Friedel-Crafts-type alkylations [325].

Although the Friedel-Crafts alkylation using enals as electrophiles has been well studied so far, the reaction with enones is a real challenge in organocatalysis. In 2006, Xu et al. reported the first studies on the enantioselective Friedel-Crafts indole alkylation of α,β-unsaturated ketones using D-camphorsulfonic acid-derived organocatalysts, affording the corresponding adducts with low enantioselectivities (up to 58% ee) [326].

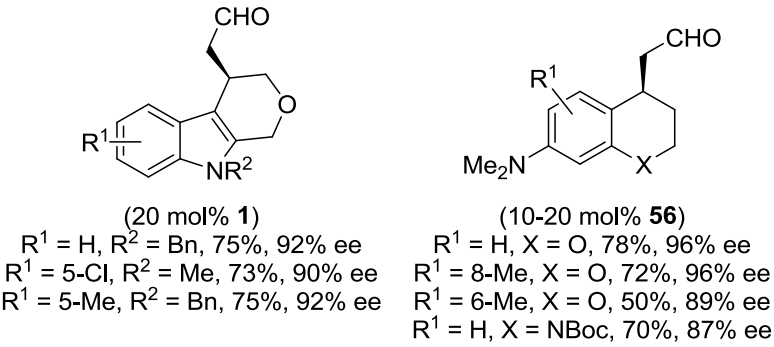
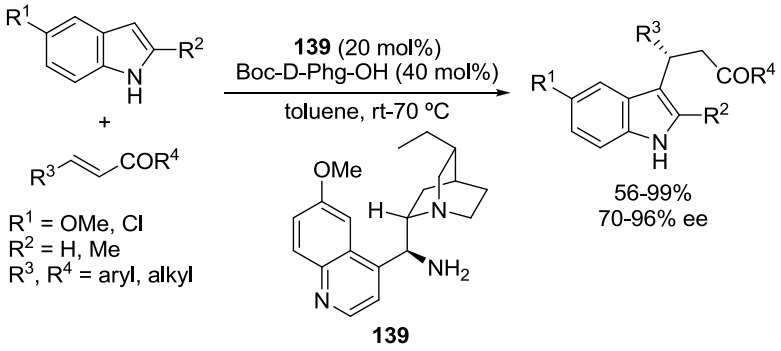


Fig. 2.26 Asymmetric synthesis of heterocyclic compounds by intramolecular Friedel-Crafts reaction

In 2007, Chen's group reported better enantioselectivities for the reaction (47–89% ee) employing substoichiometric amounts (30 mol%) of a cinchonidine-derived primary amine as organocatalyst in the presence of CF_3SO_3H as cocatalyst [327]. Almost simultaneously, the selectivity of the reaction was improved by Melchiorre's group using a counterion-directed organocatalytic system in which both the amino-*epi*-hydroquinine **139** (20 mol%) and the acid cocatalyst (D-*N*-Boc-phenylglycine, 40 mol%) were chiral (Scheme 2.116) [12, 328]. This iminium-catalyzed reaction was general with respect the nucleophile and the enone being the desired products isolated in good yields (56–99%) and enantioselectivities (70–96% ee). Interestingly, the catalytic system shows no matched/mismatched combination effect, and very similar selectivity is observed when employing the racemic or the opposite enantiomeric counterion.



Scheme 2.116 Asymmetric Friedel-Crafts alkylation of indoles with enones

The ability of the less sterically hindered primary amines to perform iminium activation with challenging substrates such α,β-unsaturated ketones has been also applied to the Friedel-Crafts alkylation of 4,7-dihydroindoles using simple 1,2-vicinal diamines derived from L-leucine [329].

Chiral phosphoric acids derived from binaphthol efficiently catalyze the inter- and intramolecular alkylation of indoles and 4,7-dehydroindoles with enones by

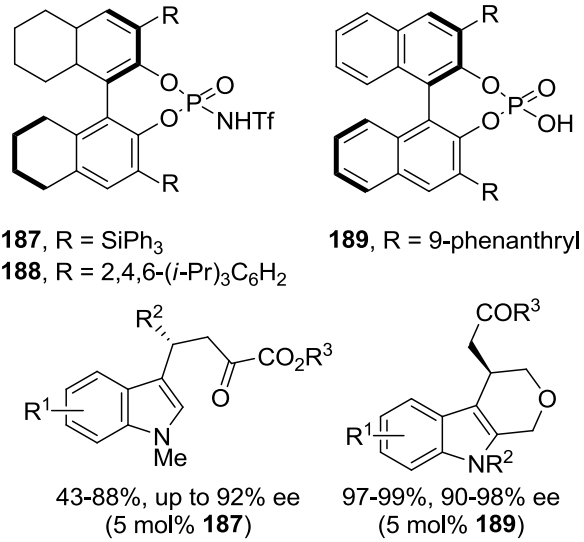
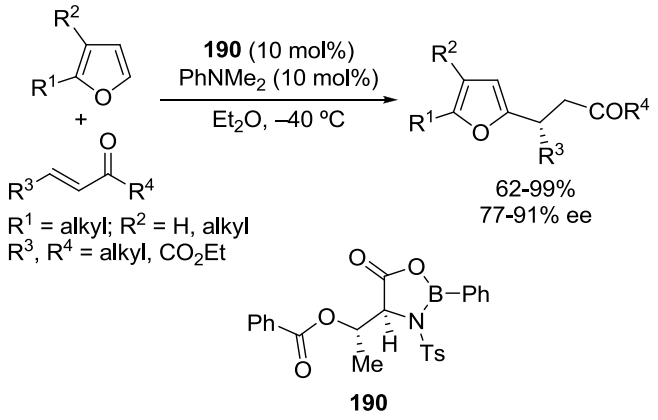


Fig. 2.27 Inter- and intramolecular asymmetric Friedel-Crafts alkylation of indoles with enones catalyzed by Brønsted acids

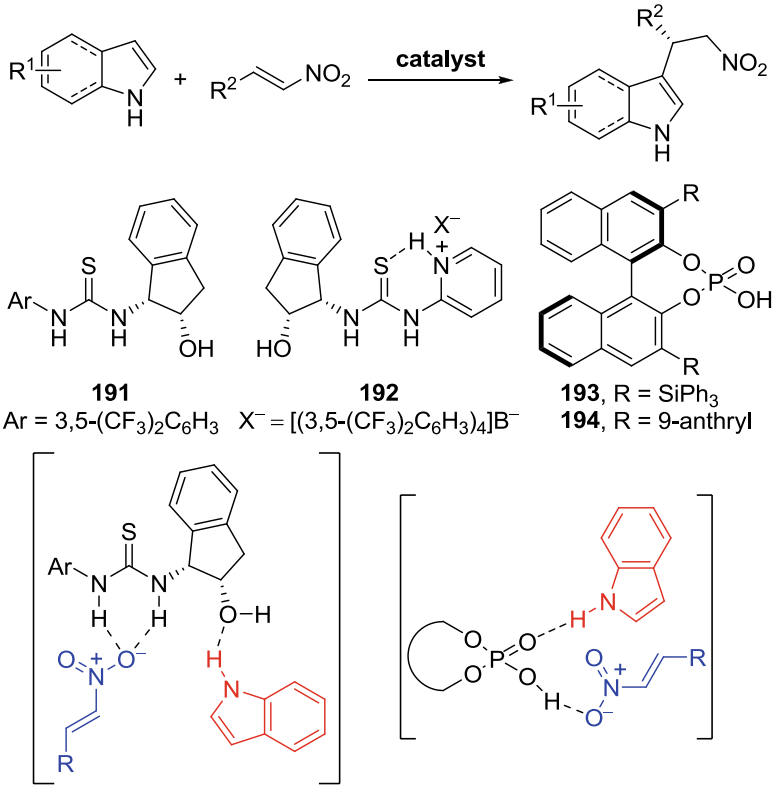
Brønsted acid activation of the electrophile. Figure 2.27 lists the most efficient phosphoric acids and derivatives used in this transformation which are usually based on a binaphthol or octahydrobinaphthol structure bearing bulky substituents at the C-3 and C-3′ positions. Catalyst **187** has been shown by Rueping et al. to promote the Friedel-Crafts alkylation of *N*-methyl indoles with β,γ-unsaturated α-keto esters in good yields (43–88%) and enantioselectivities (up to 92% ee) [330]. Worth mentioning, among all tested binaphthol-derived organocatalysts, only *N*-triflylphosphoramide **187** avoided the 1,2-addition to the ketone group. Alternatively, catalyst **188** has also shown high selectivities (87–98% ee) in the same process but using *N*-methyl 4,7-dihydroindoles as nucleophiles [331]. Finally, You et al. have achieved a highly enantioselective synthesis of polycyclic indoles by intramolecular Friedel-Crafts alkylation of indolyl enones using phosphoric acid **189** (5 mol%) [332]. Notably, the process can be also performed in a one pot sequential cross-metathesis/Friedel-Crafts cyclization with excellent results.

Furans represent an important class of electron-rich heterocycles which are useful intermediates in synthetic chemistry and are broadly found as structural motifs of many natural products and pharmaceutically important substances [333]. Since furans are generally less nucleophilic than indoles and pyrroles, their catalytic enantioselective Friedel-Crafts-type conjugate addition has been much less developed so far. Very recently Harada et al. have developed a catalytic system able to achieve good enantioselectivities in the Friedel-Crafts alkylation of electron-rich furans with acyclic α,β-unsaturated ketones [334]. As depicted in Scheme 2.117, *allo*-threonine-derived oxazaborolidinone **190** (10 mol%) in the presence of *N*,*N*-dimethyl benzylamine (10 mol%) as cocatalyst in ether at −40°C, is an efficient catalytic system for the reaction affording the corresponding functionalized furans with good yields and enantioselectivities.



Scheme 2.117 Asymmetric Friedel-Crafts alkylation of furans with enones

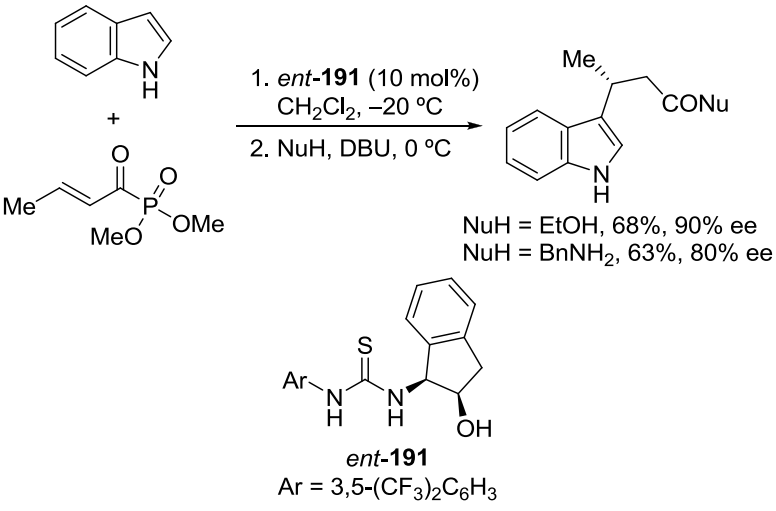
With respect to nitroolefins as electrophiles, indoles [335–337], 4,7-dihydroindoles [338], pyrroles [339], and naphthols [340] have been used with success in the reaction employing different chiral bifunctional organocatalysts. Scheme 2.118 shows



Scheme 2.118 Asymmetric Friedel-Crafts alkylation of indoles with nitroolefins

the most active catalysts to promote the Friedel-Crafts-type conjugate addition of indoles and pyrroles to nitroolefins. The early aminoindanol-derived thiourea **191** (20 mol%), developed by Ricci et al. [335] although exhibits moderate to good enantioselectivity towards β-aryl- (71–89% ee) and β-alkyl (81–83% ee) substituted nitroolefins, has played an important role in the development of other more efficient bifunctional catalysts. For instance, under much lower loadings (2–5 mol%), cationic thiourea **192**, where the acidity of the thiourea moiety is increased by intramolecular hydrogen bonding with the pyridinium subunit, promotes the Friedel-Crafts-type conjugate addition of a wide variety of substituted indoles to both aromatic- (90–97% ee) and aliphatic nitroolefins (90–95% ee) in $CHCl_3$ as solvent at low temperatures (0°C to −60°C) [336]. A bifunctional activation mode of the nucleophile and electrophile through hydrogen bonding interactions with the catalyst has been also proposed for BINOL-derived chiral phosphoric acids **193** and **194** (Scheme 2.118), molecules that promote the addition to nitroolefins of *N*-H indoles [337], 4,7-dihydroindoles [338], and pyrroles [339]. Especially interesting results phosphoric acid **193** (10 mol%) which catalyzes the addition to aromatic and aliphatic nitroolefins in good yields and high enantioselectivities (88–94% ee). Representative transition state models proposed for the bifunctional activation of hydroxyl thiourea- and phosphoric acid-derived catalysts are also depicted in Scheme 2.118.

Jørgensen's group has very recently demonstrated the usefulness of α,β-unsaturated acyl phosphonates as hydrogen-bond acceptors in the enantioselective Friedel-Crafts reaction with indoles [341]. Since the acyl phosphonate moiety is a powerful ester and amide surrogate, this reaction is an interesting approach towards the synthesis of optically active β-(3-indolyl)esters and amides as represented in Scheme 2.119 for selected examples. The reaction is catalyzed by chiral thiourea-based catalyst *ent*-**191** that activates the nucleophile and the electrophile through hydrogen-bond interactions.



Scheme 2.119 Asymmetric synthesis of optically active β-(3-indolyl)esters and amides

2.4 Organocatalytic Asymmetric Conjugate Addition of Heteroatom Nucleophiles

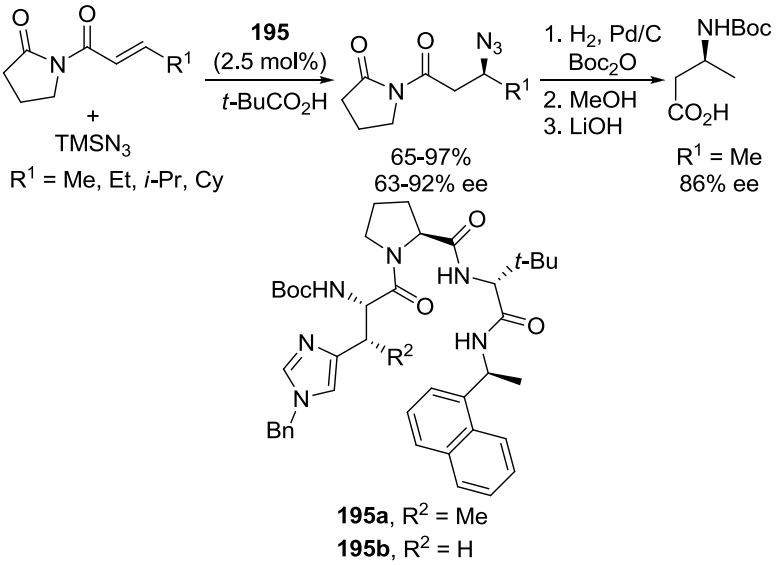
The organocatalytic asymmetric conjugate addition of heteroatom nucleophiles to different electrophilic olefins has become a very popular reaction during the last few years. Different nitrogen, oxygen, sulfur, and selenium nucleophilic species have been successfully used leading to enantiomerically enriched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

2.4.1 Conjugate Addition of Nitrogen Nucleophiles

During the past few years, tremendous progress has been achieved in the inter- and intramolecular organocatalyzed asymmetric conjugate addition of nitrogen nucleophiles, especially regarding substrate and catalyst scope [342]. Nowadays, high enantioselectivities can be obtained for the conjugate addition of a wide variety of nucleophiles, such as amines, azides, amides, carbamates, imides, hydroxylamines, hydrazones, and nitrogen heterocycles to enals, enones, and nitroolefins. This methodology is ideal for the synthesis of chiral nitrogen-containing compounds, and so, it has been applied in highly selective domino reactions as well as in the synthesis of biologically active natural products [342]. Iminium-ion activation with chiral primary and secondary amines is the most widely used protocol for the aza-Michael reaction, though Brønsted acid/base catalysis, ionic pair phase transfer catalysis, and hydrogen-bonding interactions have been also used with remarkable success.

The enantioselective conjugate addition of azide to Michael acceptors is a simple and easily approach to synthesize optically active β-amino functionalized derivatives. However, very few studies have been reported so far using chiral organocatalysts to perform this transformation. In 2002 Miller et al. reported the employment of the β-turn tripeptide armed with a τ-(benzyl)-His residue **195a** as efficient and selective organocatalyst for the enantioselective conjugate addition of trimethylsilyl azide to α,β-unsaturated imides (Scheme 2.120) [343]. In the same study, these authors have demonstrated the utility of the obtained β-azido Michael adducts towards the synthesis of chiral β-amino acids [343a], triazolines [343b], and triazoles [343b]. With respect to the catalyst, conformational studies led to the conclusion that the conformational rigidification through dihedral angle restriction of the *N*-terminal histidine of the peptide residue with a β-methyl substituent was beneficial for catalyst selectivity [343b]. In fact, the β-methylated peptide **195a** (2.5 mol%) catalyzed the addition of TMS-N_3 to several unsaturated imides with better enantioselectivities (up to 92% ee) than the corresponding non-methylated system **195b** (up to 85% ee).

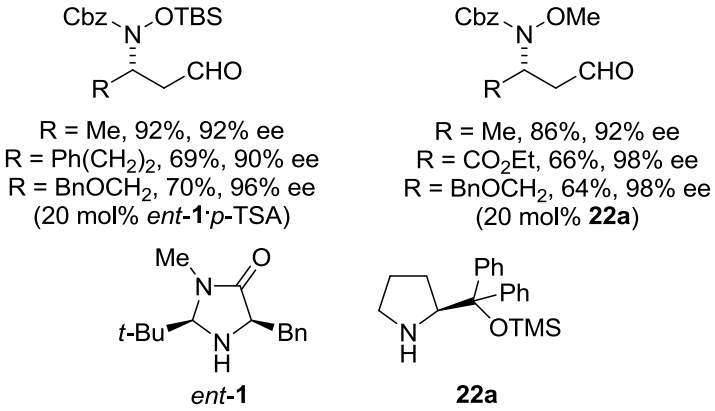
On the other hand, more recent studies on the conjugate addition of azide to nitroolefins catalyzed by *Cinchona* alkaloids have led to the synthesis of optically active β-azido nitro compounds in high yields but with low enantioselectivity [344].



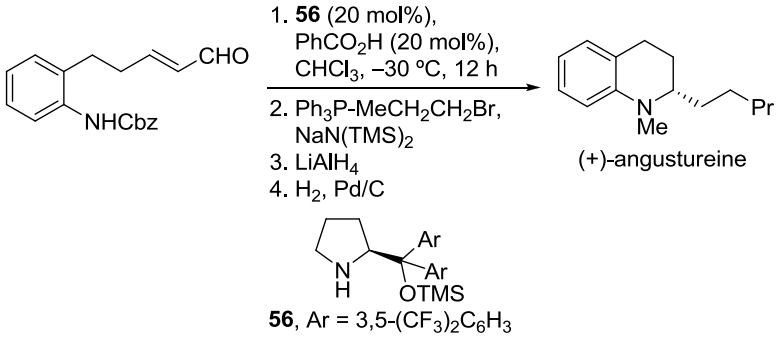
Scheme 2.120 Asymmetric conjugate addition of TMS-N_3 to α,β-unsaturated imides

Recently, MacMillan [345] and Córdova [346] have independently reported an interesting enantioselective synthesis of β-amino aldehydes and derivatives, through the conjugate addition of *N*-silyloxycarbamates and *N*-methoxycarbamates to α,β-unsaturated aldehydes using imidazolidinone *ent*-**1**·*p*-TSA and prolinol **22a** as iminium catalysts, respectively. Alkoxycarbamates are excellent nucleophiles since first, the amine moiety works only as a 1,4-addition nucleophile and not as iminium activator, and second, a kinetic control is secured, since the stereodefining heteroatom addition step is accompanied by irreversible loss of the nucleophile proton. In this manner, the enantioselective organocatalytic conjugate addition of *N*-silyloxy- and *N*-methoxycarbamates to a wide range of α,β-unsaturated aldehydes has been performed to afford the corresponding β-aminoaldehydes in good yields and very high enantioselectivities as depicted in Scheme 2.121 for selected examples. The low yields and moderate enantioselectivities obtained for cinnamic aldehyde derivatives (**22a**, 40–82% ee) in the main disadvantage of the methodology.

The utility of the organocatalytic hydroxylamine addition has been demonstrated with the preparation of a wide range of interesting enantioenriched compounds such as, β-amino acids [345, 346], β-amino alcohols [345, 346], 1,3-diamines [346], and different five- and six-membered nitrogen-containing heterocycles [347], as depicted in Scheme 2.122 for the enantioselective synthesis of the alkaloid (+)-Angustureine



Scheme 2.121 Asymmetric conjugate addition of carbamates to α,β-unsaturated aldehydes

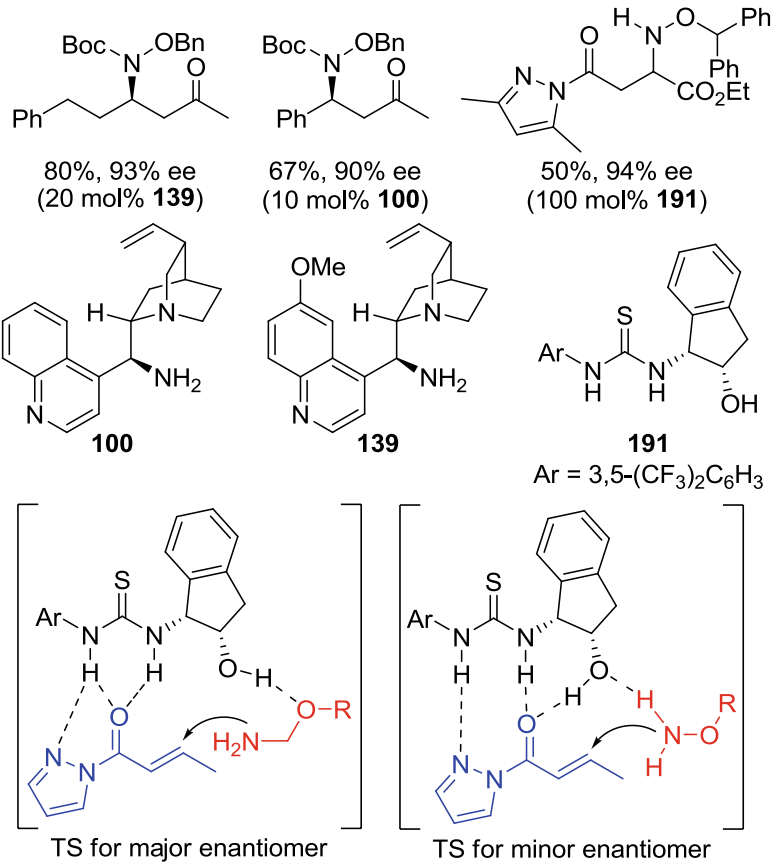


Scheme 2.122 Enantioselective synthesis of (+)-angustureine

employing catalyst **56** [347c]. Also, highly efficient and enantioselective syntheses of aziridines from enals [348] and enones [349] have been recently reported.

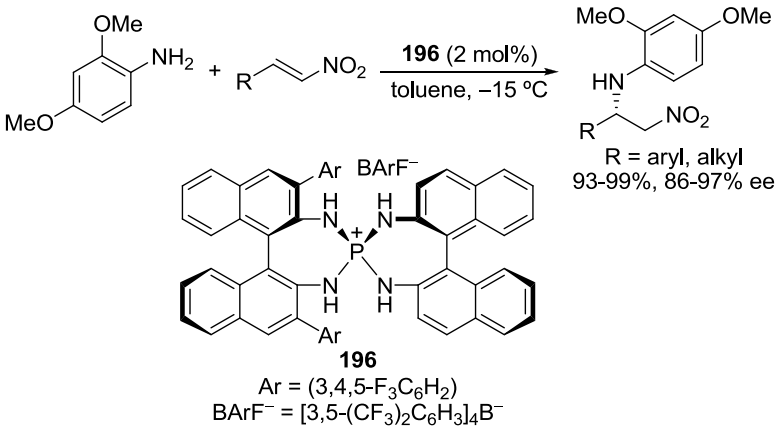
On the other hand, a bifunctional activation mode is necessary if enone derivatives are employed as electrophiles [350]. Thus, while cinchonidine and quinine primary amine derivatives **100** and **139** (10–20 mol%) have been successfully employed in the first highly enantioselective (86–96% ee) conjugate addition of benzyloxy carbamates to α,β-unsaturated ketones involving enamine and hydrogen bond activation modes [350b], the 2-aminoindanol-derived chiral thiourea **191** (30–100 mol%) catalyzes the addition of *O*-benzhydryl- and *O*-*tert*-butyldimethylsilyl hydroxylamines to 2-alkenoyl pyrazoles (67–98% ee) activating both reaction partners through hydrogen bond interactions [350a]. In Scheme 2.123 representative

results and the calculated transition state for catalyst **191** [350c], are shown. In the proposed transition state, an *s-trans* conformation for the pyrazole N–N–C=O bond and multiple hydrogen-bonding stabilizing interactions between the catalyst and the reactants account for the observed enantioselectivity [350c]. Interestingly, the thiourea hydrogen bonds play different roles in the preferred transition states for the major and the minor enantiomers as well as the conformation of the electrophile (Scheme 2.123).



Scheme 2.123 Enantioselective aza-Michael reaction to enones

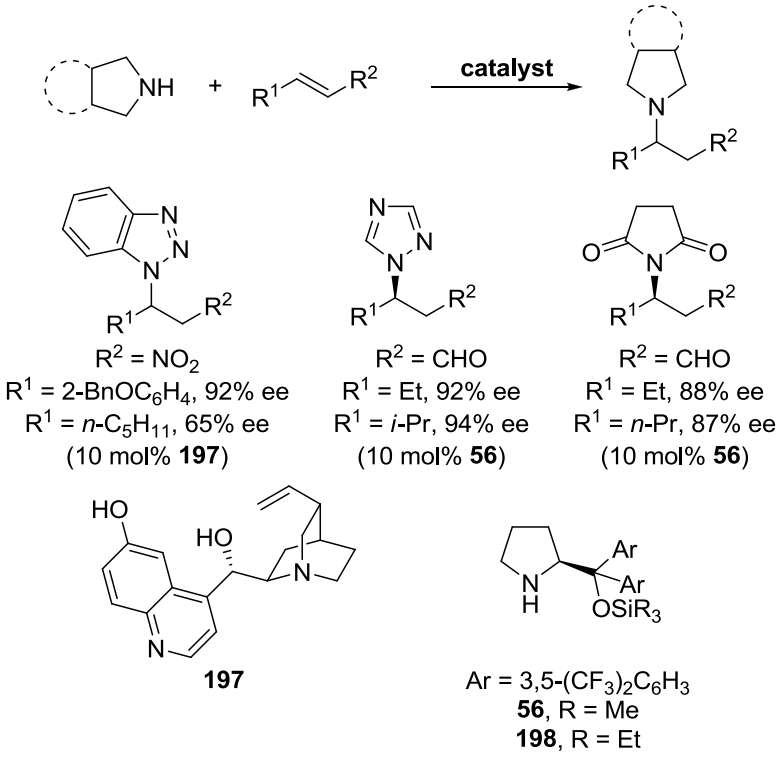
It is also worthy to mention that aniline derivatives have been used as nucleophiles in the Michael addition to chalcones [351] and nitroolefins [352]. Especially interesting has resulted the addition to nitroolefins, reaction which is catalyzed by the heterochiral [7.7]-*P*-spirocyclic arylaminophosphonium barfate **196**, a novel charged cationic Brønsted acid catalyst which efficiently promotes the addition of electron-rich anilines to nitrostyrenes and β-alkyl substituted nitroolefins in toluene at −15°C under very low loading conditions (Scheme 2.124).



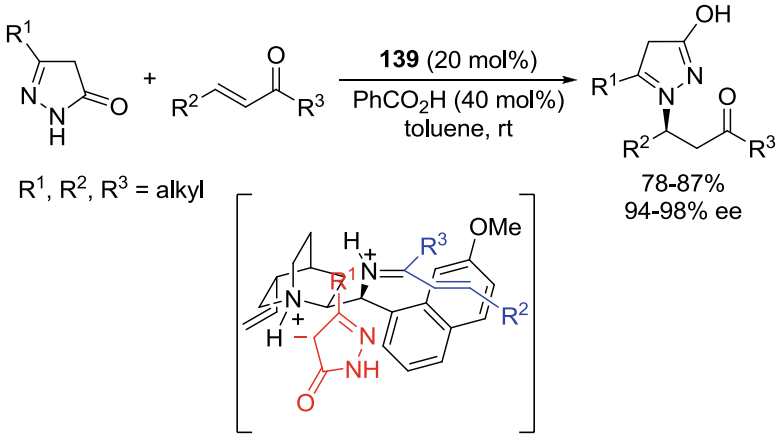
Scheme 2.124 Enantioselective conjugate addition of electron-rich anilines to nitroolefins

Nitrogen containing heterocycles have focused numerous synthetic efforts due to their broad applications in organic and medicinal chemistry as well as material science [353]. In 2006, Wang et al. reported the enantioselective conjugate addition of benzotriazole, 1*H*-1,2,3-triazole, and 5-phenyl-1*H*-tetrazole to nitroolefins employing a 10 mol% of bifunctional cupreidine **197** [354]. In general, the reaction afforded the corresponding Michael adducts in good yields (64–90%) and moderate to excellent enantioselectivities (67–94% ee) for aromatic nitroolefins (Scheme 2.125) and lower enantioselectivities for β-alkyl substituted electrophiles (57–68% ee). One year later, Jørgensen et al. developed the enantioselective aza-Michael addition of 1,2,4-triazole (92–94% ee) [355], 5-phenyltetrazole (85–92% ee) [332], and succinimide (78–90% ee) [356] to aliphatic α,β-unsaturated aldehydes through iminium-ion activation using catalyst **56** (10 mol%) (Scheme 2.125), methodology successfully applied to the synthesis of optically active homopropargylic *N*-heterocycles [357]. Vicario et al. have demonstrated the usefulness of imidazolidinone **1** in the reaction with 5-phenyltetrazole as nucleophile [358]. On the other hand, catalyst **198** has been used in the conjugate addition of pyrazole derivatives to 3-cyclopentylacrylaldehyde, reaction that has been applied to the synthesis of Janus Kinase Inhibitor INCB018424 [359].

Initial studies on the conjugate addition of nitrogen heterocycles such as benzotriazole and 5-phenyltetrazol to α,β-unsaturated ketones using *Cinchona* alkaloid-derived organocatalysts, have led to moderate chemo- and enantioselectivities [360]. On the other hand, β-(3-hydroxypyrazol-1-yl)ketones have been recently prepared in high yields and excellent enantioselectivities (94–98% ee) via conjugate addition of 2-pyrazolin-5-ones to aliphatic acyclic α,β-unsaturated ketones using bifunctional 9-*epi*-9-amino-9-deoxyquinine (**139**, 20 mol%) as catalyst and benzoic acid as cocatalyst (Scheme 2.125) [361]. The reaction is carried out in toluene at rt, and although it is known that this type of carbanions adds to enones as a carbon nucleophile under basic conditions, an aza-Michael addition takes place instead, due to the mild acidic reactions conditions, through the proposed tight transition state depicted in Schemes 2.125 and 2.126.

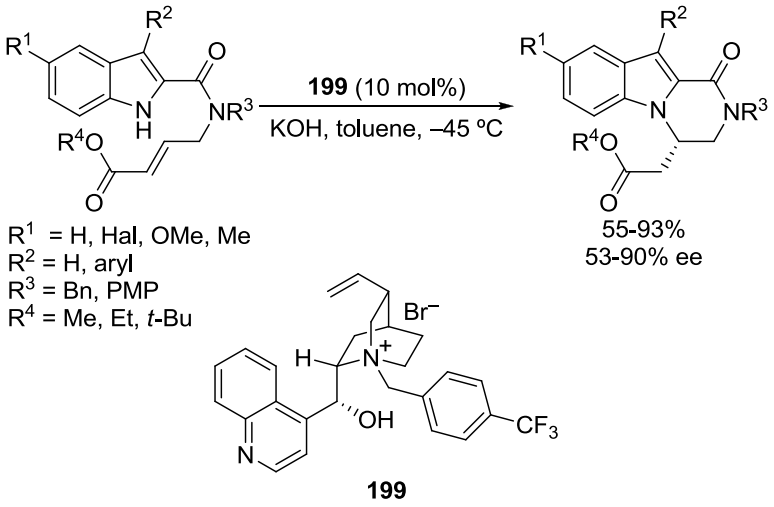


Scheme 2.125 Asymmetric conjugate addition of nitrogen heterocycles



Scheme 2.126 Asymmetric synthesis of β-(3-hydroxypyrazol-1-yl)ketones

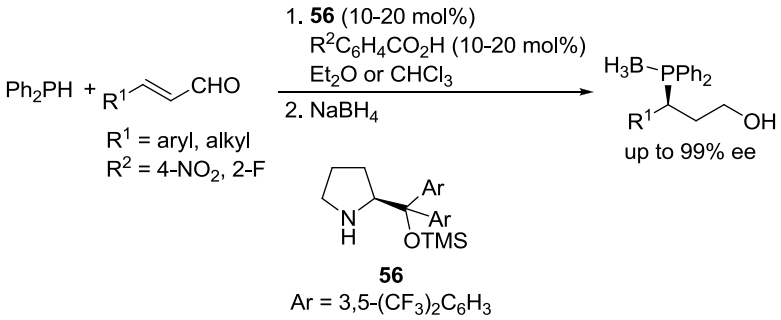
An interesting enantioselective phase-transfer catalyzed intramolecular aza-Michael reaction of indoles-tethered α,β-unsaturated esters has been recently reported by Bandini and Umani-Ronchi [362] which has allowed the synthesis of pyrazino [1, 2]indole derivatives, compounds with interesting biological activities. The reaction is catalyzed by cinchonidine-derived ammonium salt **199** which provides enough rigidity to the transition state to guarantee good enantioselection in the process (Scheme 2.127). Weaker ion-par interactions are postulated when chiral organic *Cinchona* alkaloid-derived bases are used since these catalysts lead to racemic compounds.



Scheme 2.127 Asymmetric PTC intramolecular conjugate addition of indoles

2.4.2 Conjugate Addition of Phosphorous Nucleophiles

The phospha-Michael reaction constitutes one of the most important methods for the construction of P–C bonds [363]. Albeit the significance of this reaction, only few reports towards the synthesis of stereogenic P–C bonds have recently appeared in the literature employing iminium and hydrogen-bonding catalysis and trivalent and pentavalent phosphorous nucleophiles [364]. With respect to the conjugate addition using chiral secondary amines as catalysts, in 2007 Melchiorre [365] and Córdova [366] independently reported the enantioselective hydrophosphination of enals with diphenylphosphane catalyzed by diarylprolinol trimethylsilyl ether **56** (10–20 mol%). As depicted in Scheme 2.128, both groups performed the reaction in the presence of a benzoic acid derivative as cocatalyst

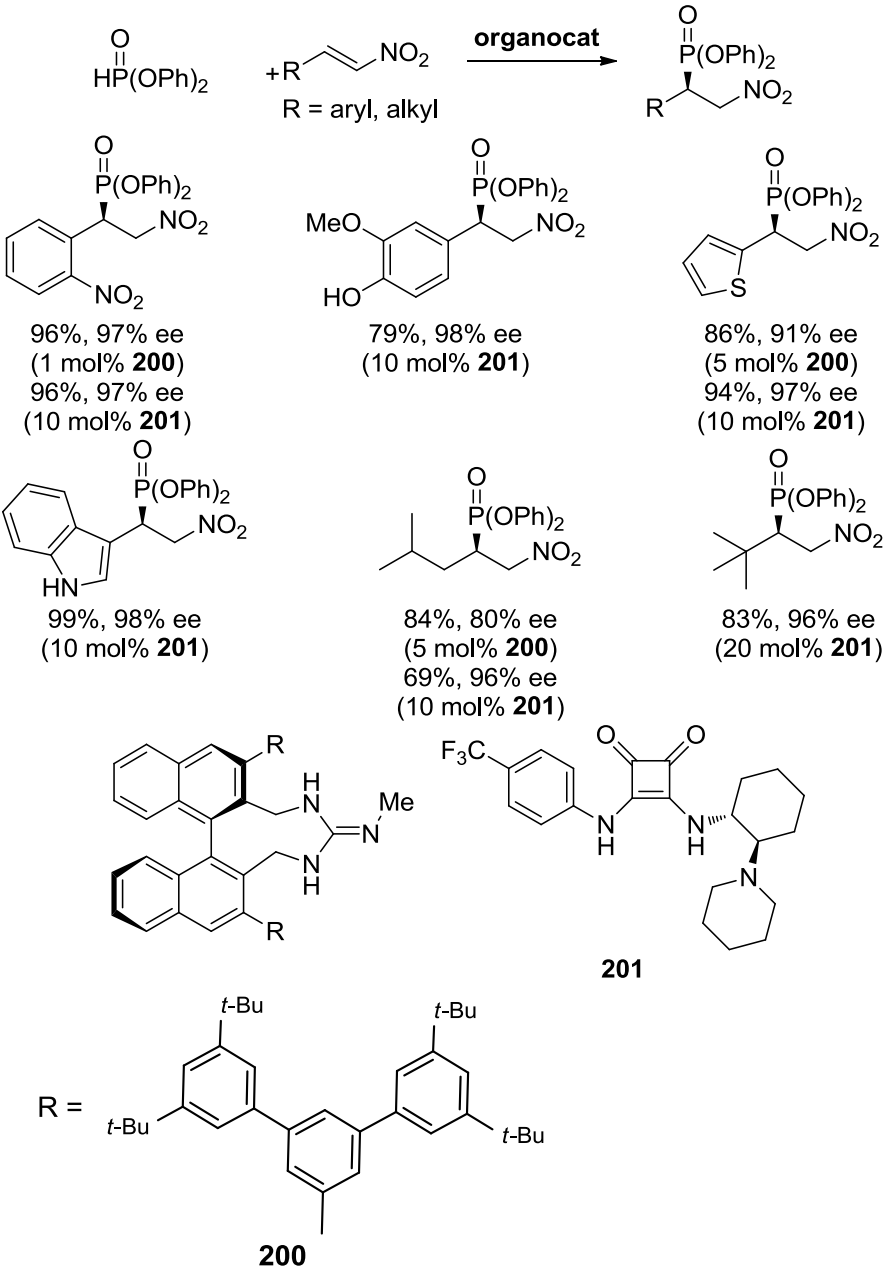


Scheme 2.128 Asymmetric conjugate addition of diphenylphosphane to enals

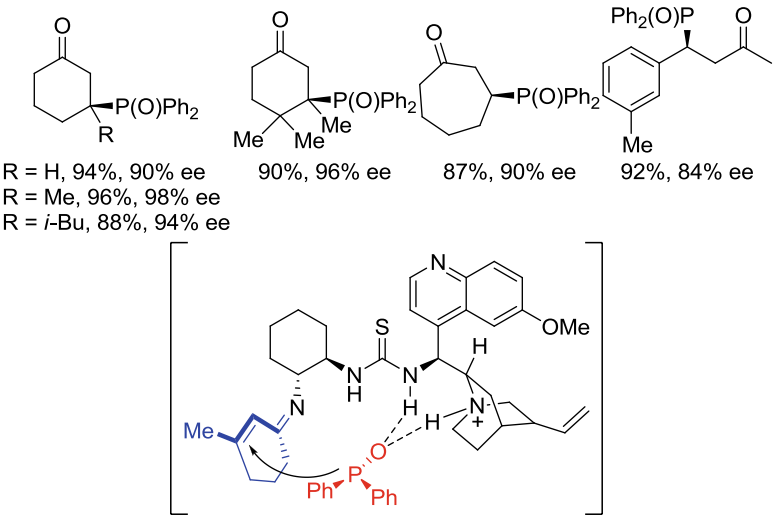
(10–20 mol%) at low temperatures affording, after in situ reduction with sodium borohydride, the corresponding Michael adducts with excellent enantioselectivities. These adducts have been proven to be useful precursors of various chiral P-containing products.

Nitroolefins have been the electrophiles most studied in the phospha-Michael addition when using hydrogen-bonding catalysis. Thus, *Cinchona*-derived organocatalysts [367] as well as chiral guanidines [368], and chiral squarimides [369] have been demonstrated to efficiently promote the conjugate addition of diphenylphosphane and diarylphosphites to nitroolefins. Among them, axially chiral guanidine **200** [368] and chiral squarimide **201** [369] are the most efficient organocatalysts with respect to substrate scope, reaction time and catalyst loading. They are able to catalyze the addition of diphenyl phosphite to a wide range of aromatic, heteroaromatic, and aliphatic nitroolefins (Scheme 2.129). In the case of guanidine **200**, Terada et al. have demonstrated the pronounced impact of the steric hindrance of the catalyst on the enantioselectivity of the reaction, obtaining the best results using methyl *tert*-butyl ether as the solvent at −40°C [368]. On the other hand, chiral squarimide **201** affords excellent yields and enantioselectivities using methylene chloride as solvent at 0°C. This catalyst is especially interesting since gives the best results reported so far for the 1,4-addition to aliphatic nitroolefins (95–97% ee) [369] This reaction facilitates the highly enantioenriched synthesis of β-amino phosphonate derivatives of biological and pharmaceutical importance.

A bifunctional iminium/hydrogen-bonding catalysis has been very recently employed for the first enantioselective organocatalytic conjugate addition of a phosphorous nucleophile (diarylphosphane oxides) to α,β-unsaturated ketones [370]. The process, which allows efficient additions to cyclic and linear enones as well as the generation of quaternary stereocenters, is catalyzed by quinine-derived thiourea



Scheme 2.129 Asymmetric conjugate addition of diphenylphosphite to nitroalkenes



Scheme 2.130 Asymmetric conjugate addition of diarylphosphane oxides to enones catalyzed by amine-thiourea **141**

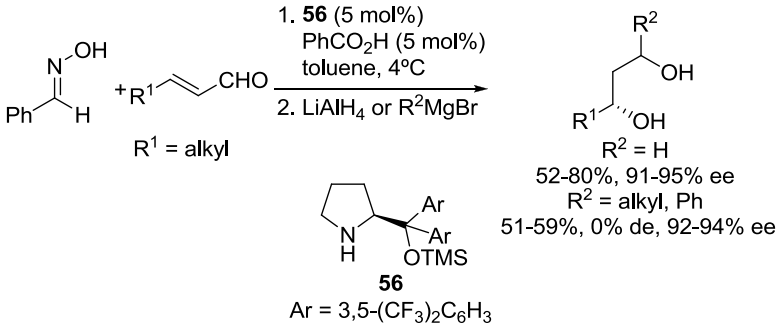
141 (10 mol%) in methylene chloride as solvent at rt, affording the corresponding Michael adducts in excellent yields (82-97%) and enantioselectivities (84–98% ee) (Scheme 2.130).

2.4.3 Conjugate Addition of Oxygen Nucleophiles

The 1,4-addition of oxygen nucleophiles to Michael acceptors (oxa-Michael reaction) [371] has gained considerably less attention than other conjugate additions in the past decades since it has suffered from major drawbacks such as low reactivity and selectivity, as well as reversibility problems. In particular, the asymmetric organocatalyzed oxa-Michael reaction has not been reported until quite recently when efficient chiral molecules have been shown to promote this reaction usually through iminium or hydrogen-bonding catalysis achieving high levels of asymmetric induction.

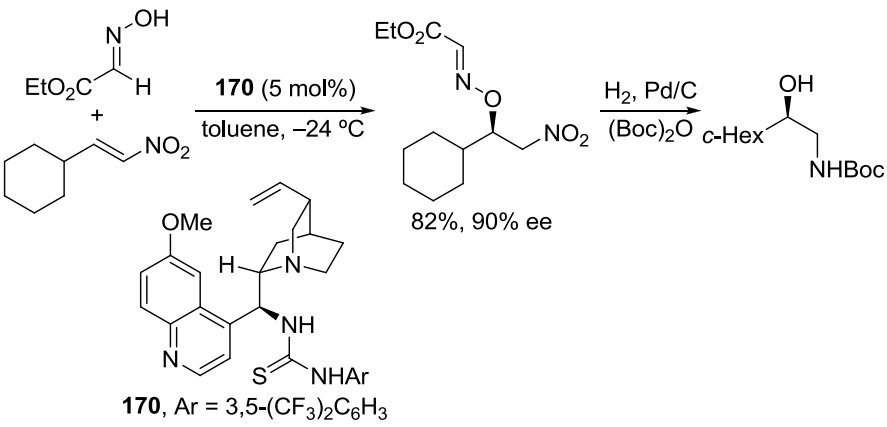
Attempts to carry out conjugate additions of aliphatic alcohols to α,β-unsaturated aldehydes have been performed by Maruoka et al. using axially chiral biphenyl diamine-based organocatalysts with limited success so far [372]. On the other hand, oxime adducts are less prone to undergo a retro-Michael process which reduces problems associated with purification and optical purity deterioration. Moreover, oxime ethers contain a labile N-O bond, enabling a reductive cleavage to afford formal hydration products. Also, in the case of adding to enals, oximes have reduced tendency towards hemiacetal or acetal formation. Thus, oxime derivatives have been successfully used in the 1,4-addition to enals [373], nitroolefins [374] and enones [375]. For instance, Jørgensen et al. have optimized the β-hydroxylation of α,β-unsaturated aldehydes [373] employing a highly enantioselective oxa-Michael

reaction of benzaldoximes to various aliphatic and ester β-substituted enals catalyzed by prolinol derivative **56**, to obtain the corresponding Michael adducts in good yields (60–75%) and selectivities (88–97% ee) after reduction of the aldehyde moiety with sodium borohydride [373]. Although cinnamic aldehydes turned out to be unreactive in this transformation, Jørgensen demonstrated the significance of this addition process by the preparation of optically active 1,3-diols after subsequent in situ reduction or Grignard addition as illustrated in Scheme 2.131 [373]



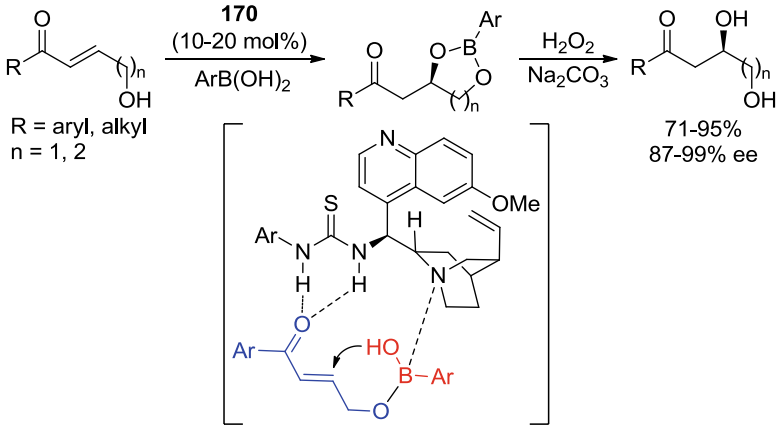
Scheme 2.131 One-pot stereoselective synthesis of biologically active 1,3-diols

Regarding the hydroxylation of nitroolefins, the reaction is performed under hydrogen-bonding catalysis using quinine-derived thiourea **170** (5 mol%), ethyl glyoxylate oxime as nucleophile in toluene at −24°C [374]. This process, which constitutes a valid alternative to the Henry reaction, yields the corresponding hydroxylated nitrocompounds in good yields (63–83%) and enantioselectivities (48–93% ee) from aliphatic electrophiles (styrene derivatives are prone to retro-Michael addition) and has been successfully employed in the synthesis of optically active β-amino alcohols (Scheme 2.132) [375].



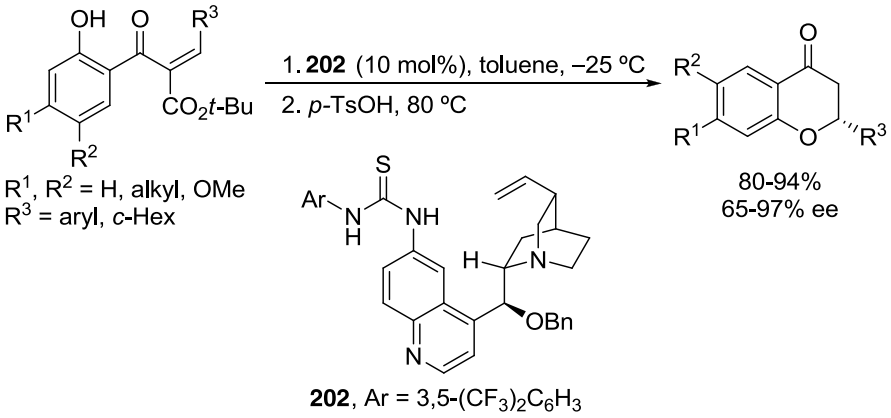
Scheme 2.132 Enantioselective hydroxylation of nitroolefins

A remarkable breakthrough in the oxa-Michael reaction has been recently achieved by Falck et al. who have developed an enantioselective intramolecular addition of boronic acid hemiesters to enones catalyzed by the bifunctional thiourea **170** [376]. As outlined in Scheme 2.133, aliphatic and aromatic γ- and δ-hydroxy enones react with arylboronic acids in methylene chloride to afford the corresponding boronic acid hemiesters, which undergo subsequent intramolecular oxa-Michael addition promoted by the chiral organocatalyst. Final oxidative cleavage of the resulting dioxaborolane affords the optically active 1,2- or 1,3-diols in high yields and enantioselectivities. With respect to the addition mechanism, the thiourea catalyst activates the enone via hydrogen bonding while the catalyst tertiary amine enhances the nucleophilicity of the boronic acid hemiester as shown in Scheme 2.133.



Scheme 2.133 Enantioselective hydroxylation of enones

The intramolecular organocatalyzed oxa-Michael reaction has been widely applied to the stereoselective synthesis of heterocycles such as benzopyrans, chromanes, chromanones, flavanones, etc., since early studies by Ishikawa et al. on the quinine-catalyzed intramolecular phenol conjugate addition to enones in the course of the synthesis of potential anti-HIV-active natural products such as (+)-calanolide A and (+)-inophyllum B [377]. For instance, a very interesting synthesis of optically active flavanones and chromanones has been recently reported by Scheidt et al. [378] Employing 2-(alkylidene β-ketoester) phenol derivatives as starting materials and the bifunctional chiral thiourea **202** as catalyst, Scheidt' group has synthesized various flavanones (R^3 = aryl) and chromamones (R^3 = alkyl) in high yields and enantioselectivities via oxa-Michael reaction and subsequent decarboxylation (Scheme 2.134). The enantioselective synthesis of this type of 2-substituted chiral heterocycles is a significant advantage of this synthetic approach, due to the



Scheme 2.134 Enantioselective synthesis of flavanones and chromanones

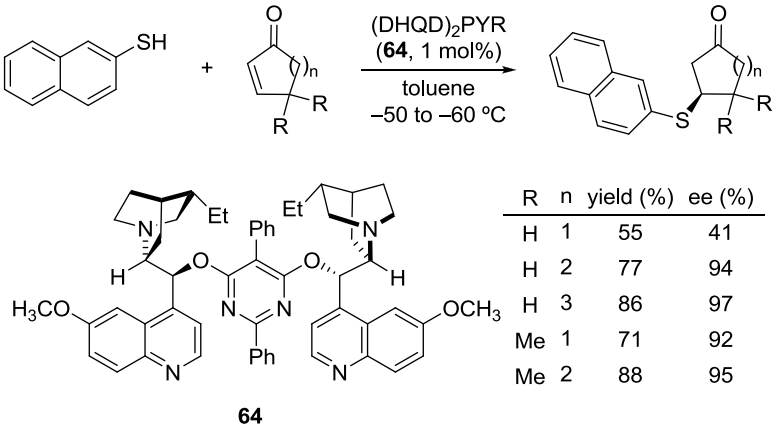
potential of these compounds for reversible phenoxide elimination. The bifunctional role of the catalyst activating the Michael acceptor by hydrogen-bonding and deprotonating the phenol with the tertiary amine has been proposed.

2.4.4 Conjugate Addition of Sulfur Nucleophiles

Optically active sulfur containing compounds play a very important role in biochemistry as well as synthetic chemistry. The asymmetric conjugate addition of sulphur nucleophiles, or sulfa-Michael addition [379], provides a direct and versatile approach toward optically active sulfur compounds. This strategy is particularly valuable, since enantioselective nucleophilic additions to a C–S double bond, unlike those to carbonyls and imines, are not synthetically feasible.

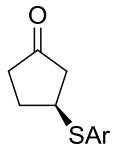
Since pioneering studies by Pracejus [380] and Wynberg [381] on the asymmetric organocatalyzed conjugate addition of sulphur nucleophiles to α-phthalimidomethacrylate, β-nitrostyrenes, and cyclic enones employing *Cinchona* alkaloids as catalysts, much effort has been focused on the design and synthesis of efficient organocatalysts for the sulfa-Michael reaction.

In 2002, Deng et al. reported a highly enantioselective conjugate addition of thiols to cyclic enones [382]. After a systematic screening of monomeric and dimeric *Cinchona* alkaloid derivatives, Deng's group identified the dihydroquinidine-pyrimidine catalyst $(DHQD)_2PYR$ (**64**, Scheme 2.135) as the most effective promoter for the reaction under low loading conditions (1 mol%). Although low enantioselectivity was obtained with cyclopentenone (41% ee), addition of 2-thionaphtol 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 (92–97% ee).

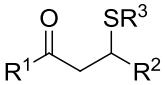


R	n	yield (%)	ee (%)
H	1	55	41
H	2	77	94
H	3	86	97
Me	1	71	92
Me	2	88	95

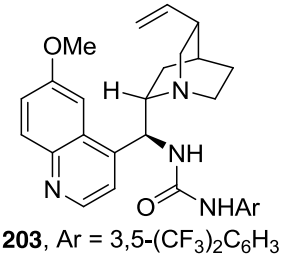
Scheme 2.135 Asymmetric 1,4-addition of 2-thionaphthol to cyclic enones catalyzed by $(DHQD)_2PYR$



catalyst (mol%)	Ar	yield (%)	ee (%)
203 (0.1 mol%)	Ph	>99	80
203 (0.1 mol%)	2-tolyl	98	90
203 (0.1 mol%)	2-$MeOC_6H_4$	93	91



catalyst (mol%)	R^1	R^2	R^3	yield (%)	ee (%)
203 (0.1 mol%)	Ph	*t*-Bu	2-tolyl	98	90
204 (15 mol%)	Ph	Me	Bn	81	85
204 (20 mol%)	Me	Et	Bn	55	94
204 (20 mol%)	Ph	Me	*t*-Bu	59	95



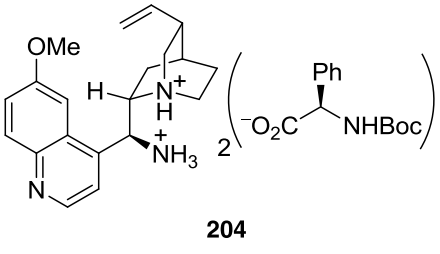


Fig. 2.28 Conjugate addition of thiols to cyclopentenone and acyclic enones

Cyclopentenone as well as acyclic enones have been productively used in the conjugate addition with aromatic and aliphatic thiols employing catalysts **203** [383] and **204** [384] (Fig. 2.28). Quinine-derived urea catalyst **203** is a very active organocatalyst for the addition of aromatic nucleophiles to cyclic and acyclic enones working at rt under very low loading conditions (0.1 mol%) [383].

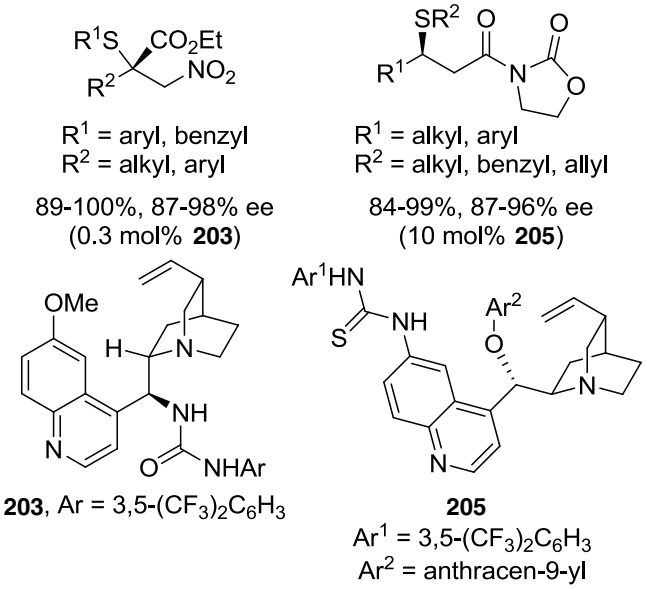


Fig. 2.29 Conjugate addition of thiols to nitroacrylates and α,β-unsaturated *N*-acylated oxazolidin-2-ones

A bifunctional catalysis involving urea/ketone hydrogen-bond interactions and ion-pair formation between the nucleophile and the quinuclidine nitrogen are postulate to explain the observed enantioselectivity. On the other hand, iminium catalysis is proposed for salt **204**, where both the cation and the anion are chiral, which exhibits high reactivity and selectivity for the addition of alkylic nucleophiles to linear enones (Fig. 2.28) [384].

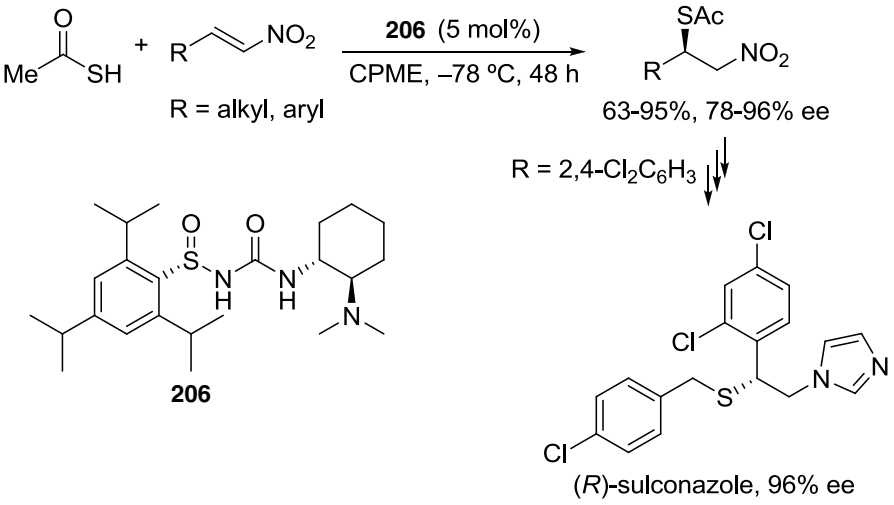
In 2005, Jørgensen et al. extended the conjugate addition of sulfur nucleophiles to α,β-unsaturated aldehydes under iminium catalysis with trimethylsilyl ether **56** (10 mol%) as catalyst [385]. Very high enantioselectivities (89–97% ee) were reported for the addition of aliphatic thiols to different aromatic and aliphatic enals at low temperatures (−24°C) where the employment of an acid cocatalyst ($PhCO_2H$, 10 mol%) was mandatory in order to improve the reaction rate. This methodology has been incorporated into domino reactions by the same group and others to successfully prepare optically active sulfur-containing heterocyclic compounds [385, 386].

Recently an expansion of the electrophile scope of the conjugate addition of sulfur nucleophiles has been reported by different groups. As depicted in Fig. 2.29 for selected examples, *Cinchona*-derived catalysts **203** and **205** promote highly enantioselective additions to nitroolefins [387] and α,β-unsaturated *N*-acylated oxazolidin-2-ones [388] through non-covalent catalysis. Especially interesting results the Michael reaction to β-substituted nitroacrylates catalyzed by chiral thio-

urea **203** which, under very low loading conditions (0.3 mol%), gives access to optically active to $\beta^{2,2}$-amino acids with hetero-quaternary stereocenters in high yields and enantioselectivities via synergistic cooperative activation of the nucleophilic thiol and the electrophilic nitroacrylate (Fig. 2.29) [387]. With respect to the addition to α,β-unsaturated *N*-acylated oxazolidin-2-ones [388], this reaction provides a facile access to the valuable β-mercapto acid derivatives, compounds only accessible by chiral auxiliary-directed conjugate additions so far [389].

Few examples have been reported for the organocatalytic asymmetric conjugate addition of sulfur nucleophiles other than thiols. The reaction of thiocarboxylic acids to cyclohex-2-enones [390] and α,β-unsaturated esters [391] was initially studied by Wynberg et al. employing *Cinchona* alkaloid catalysts with limited success in terms of selectivity (up to 54% ee). Slightly better enantioselectivities have been recently obtained by Wang et al. in the 1,4-addition of thioacetic acid to β-nitrostyrenes (up to 78% ee) [392] and *trans*-chalcones (up to 65% ee) [393], using Takemoto's thiourea **142** as catalyst (2–10 mol%).

The best results obtained so far for an organocatalyzed asymmetric conjugate addition of thioacetic acid have been reported by Ellman's group using nitroalkenes as electrophiles and the chiral sulfinyl urea catalyst **206** [394]. The reaction, which is performed in cyclopentyl methyl ether (CPME) as solvent at −78°C constitutes the first highly enantioselective 1,4-addition of thioacetic acid to aromatic and aliphatic nitroolefins and serves as a general method for preparing chiral 1,2-aminothiols, which are appropriate precursors of compounds of pharmaceutical interest such as the antifungal (*R*)-Sulconazole (Scheme 2.136).



Scheme 2.136 Asymmetric conjugate addition of thioacetic acid to nitroolefins

2.5 Summary and Outlook

This chapter reviews the intensive research toward asymmetric organocatalyzed conjugate additions, summarizes the development and synthetic applications of these interesting reactions, and presents mechanistic proposals to explain the observed stereochemical outcome of the catalytic procedures. Even being one the earliest examples of a catalytic asymmetric transformation, the asymmetric conjugate addition reaction catalyzed by a chiral organic molecule has suffered a spectacular advance during recent years. Nearly 400 journal articles (2000–2009, source: Scifinder) including interesting reviews and book chapters impressively confirm the successful recent story of this reaction. 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, acrylonitriles, etc. can be efficiently performed at this time 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 the aspects that control the reactivity and selectivity of these reactions.

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Chapter 3
Organocatalyzed Cycloadditions

Bor-Cherng Hong

Abstract Cycloadditions have been for a long time one of the most useful reactions in organic synthesis. Recently, the ability to promote the reactions by organocatalysts further expands the realm of its synthetic application. This review aims to highlight the recent advances in this area with particular emphasis on the asymmetric cycloaddition promoted by organocatalysts.

3.1 Introduction

Generating selectively the maximum number of bonds and stereogenic centers in a one-step (or one-pot) reaction constitute to be of key interest in synthetic chemistry. Among many methodologies for the objective, cycloaddition stand out. While searching for a better and tunable catalyst able to promote a wide spectrum of cycloaddition, organocatalysis was revealed as a powerful tool for efficient operations and many other merits, *e.g.*, high stereoselectivity, moisture and air resistant, environmental benign and user friendly. Surprisingly, organocatalytic synthesis was virtually dominant for few decades until just the turn of this century [1]; nevertheless, it soon become the focal point, and it has occupied an important chapter in the modern synthetic chemistry [2]. In a very short period of time, more than hundred review articles of organocatalytic reactions were reported, and the papers are continuing to appear for summarizing up the thriving and robust subject. Several theoretical studies, including the computational

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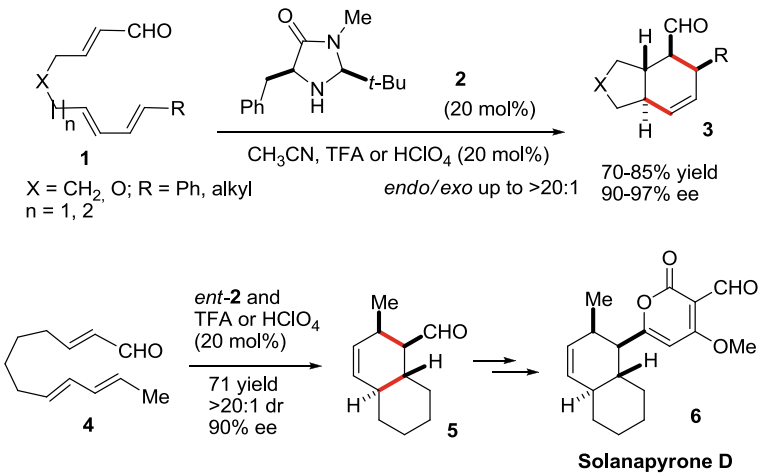
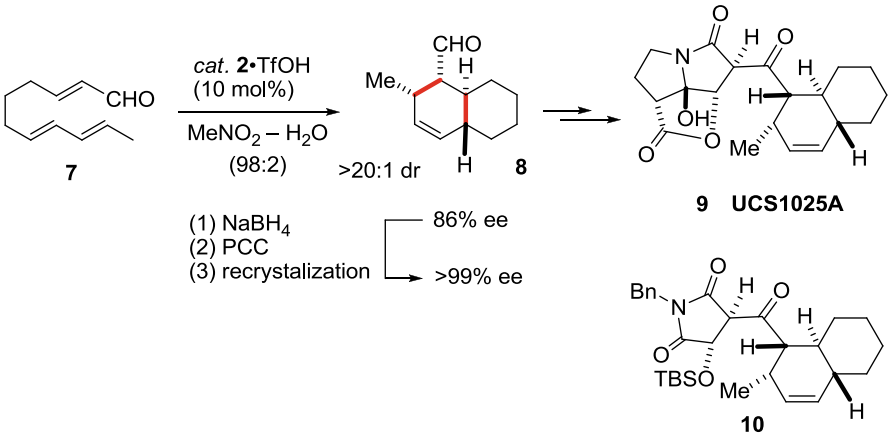
prediction of small-molecule catalysts [3] and conceptual, qualitative, and quantitative theories of additions to α,β-unsaturated aldehydes, 1,3-dipolar and Diels–Alder cycloadditions [4] were also reported. In order to gain deeper insights into the reported organcatalyzed cycloaddition for creating the more efficient methodologies, a throughout review in this subject is essential. This review covers the organocatalytic cycloaddition published after 2000, under the special focus of enantioselectivity. Organocatalytic formal cycloaddition, e.g. [4 + 2], [3 + 2], [3 + 3], etc., via stepwise addition and cyclization reactions are not included in this chapter.

3.2 Intramolecular Cycloadditions

In 2005, MacMillan reported an enantioselective organocatalytic intramolecular Diels-Alder reaction (IMDA) of α,β-unsaturated aldehyde and diene, as well as the application in the asymmetric synthesis of solanapyrone D (**6**), Scheme 3.1 [5]. Later, Danishefsky and Christmann individually reported the total synthesis of UCS1025A (**9**) by coupling reaction with MacMillan aldehyde (**8**) [6]. The malimide analogue **10** of the telomerase inhibitor UCS1025A (**9**) was also prepared by Christmann et al. by modified MacMillan's conditions (10 mol% catalyst loading in nitromethane, affording 74% yield and >99% ee after a sequence of recrystallization and oxidation), Scheme 3.2 [7].

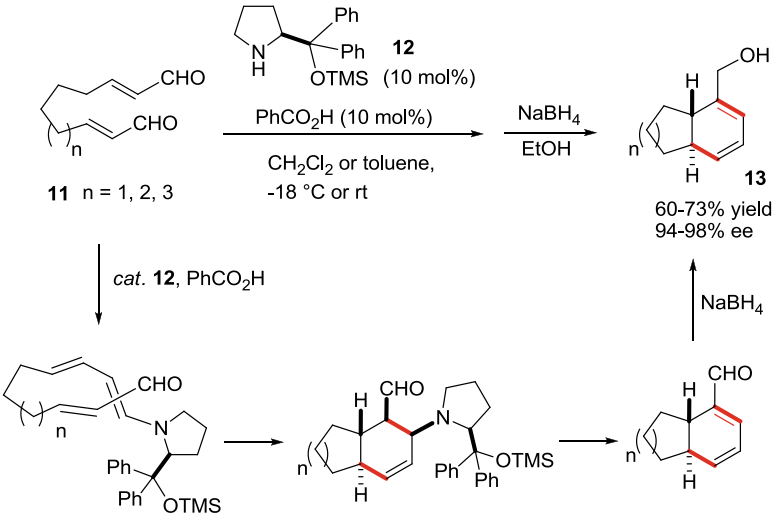


Scheme 3.1 Organocatalyzed intramolecular Diels-Alder reaction of trienes

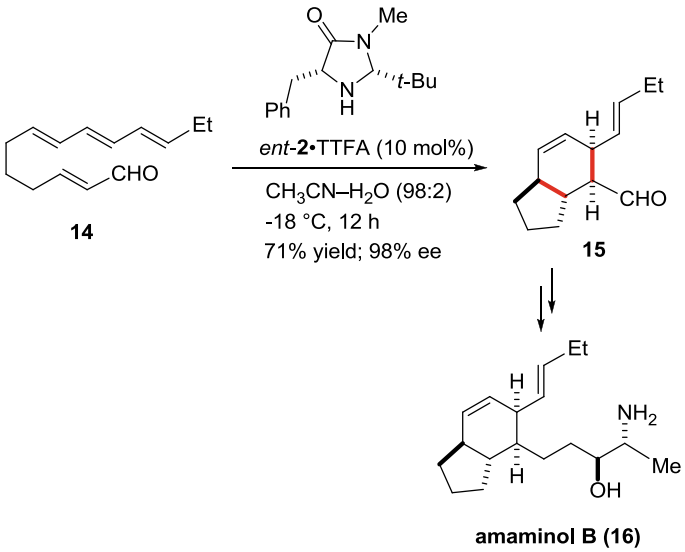


Scheme 3.2 Organocatalyzed intramolecular Diels-Alder reaction of trienes

Later on, Christmann, et al. developed an organocatalytic intramolecular Diels-Alder reaction of α,β-unsaturated dialdehydes, providing the bicyclic systems (such as decalins **13**), [8] (Scheme 3.3). The mechanism was assumed to undergo the vinylogous enamine activation [9], followed by a rapid IMDA reaction and subsequent ß-hydride elimination. On the other hand, the synthesis of the cytotoxic marine natural product amaminol B (**16**) was achieved by Christmann and his co-workers with the key step of the organocatalytic IMDA reaction of **14**, Scheme 3.4 [10].

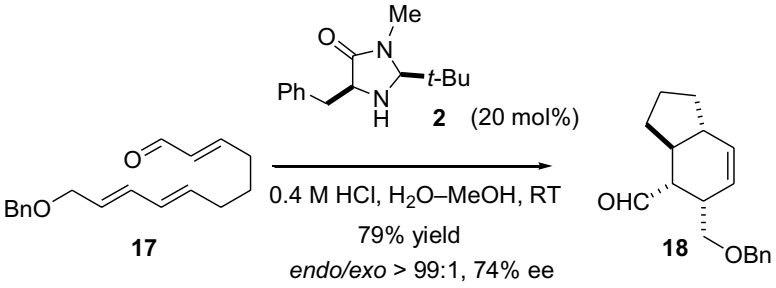


Scheme 3.3 Organocatalyzed intramolecular Diels-Alder reaction of dienals by diarylprolinol silyl ether **12**



Scheme 3.4 Organocatalyzed intramolecular Diels-Alder reaction of tetraenes by *ent*- **2**

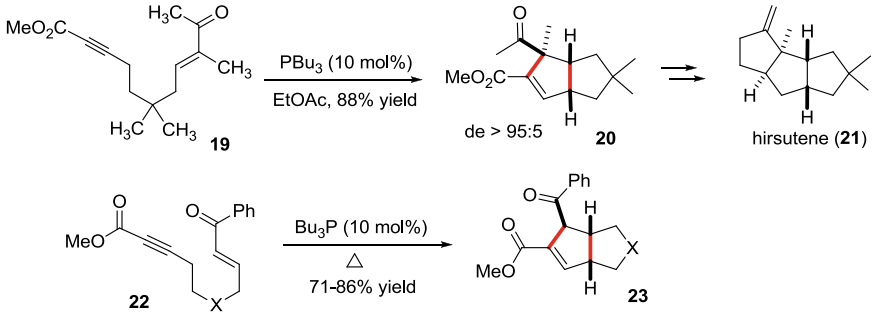
Alternatively, Koskinen and Selkälä reported an organocatalytic intramolecular Diels–Alder reaction of triene aldehyde **17** for the preparation of bicyclo[4.3.0] nonanes **18**, Scheme 3.5 [11].



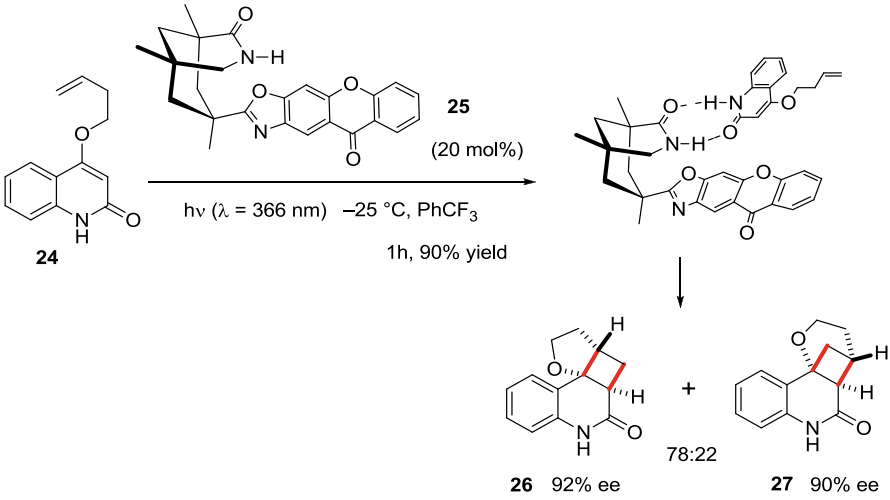
Scheme 3.5 Organocatalyzed intramolecular Diels-Alder reaction of trienes

In 2003, an interesting intramolecular organocatalytic [3 + 2] dipolar cycloaddition of an enynoate (**19**) catalyzed by PBu_3 was developed by Krische and his coworker in the total synthesis of (±)-hirsutene (**21**), Scheme 3.6 [12]. The intramolecular phosphane-catalyzed [3 + 2] dipolar cycloaddition provides a concise approach to the linear triquinane hirsutene, whereby three contiguous stereogenic centers are created and controlled in a single reaction step.

A light-driven enantioselective organocatalysis intramolecular [2 + 2] photocycloaddition of quinolone (**24**) was developed by Bach et al., Scheme 3.7 [13].



Scheme 3.6 Intramolecular phosphane-catalyzed [3+2] cycloaddition of electron-deficient 1,7-enynes

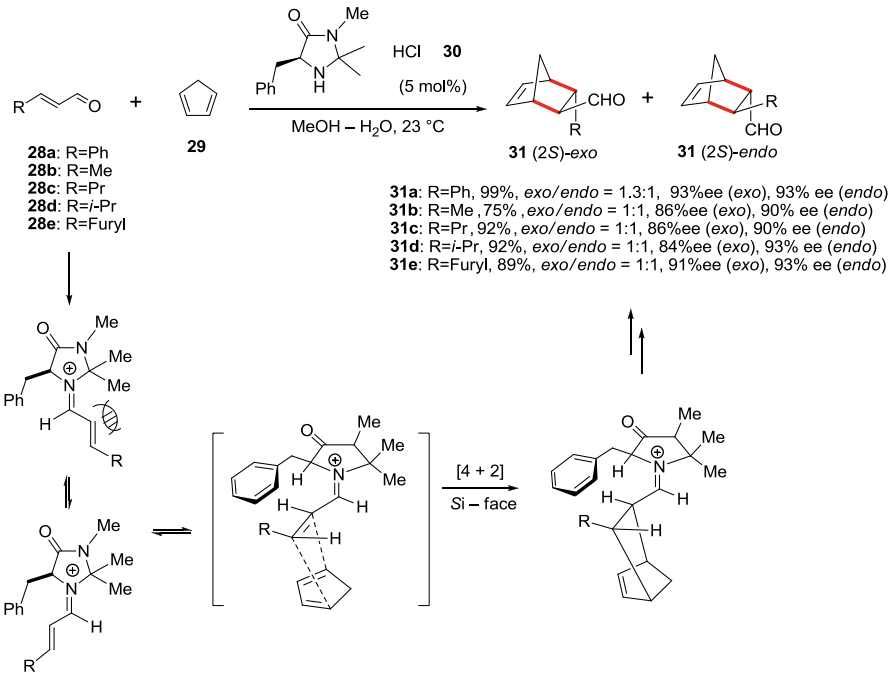


Scheme 3.7 Intramolecular organocatalytic [2+2] photocycloaddition of prochiral 4-(3′-buteny-loxy)quinolone

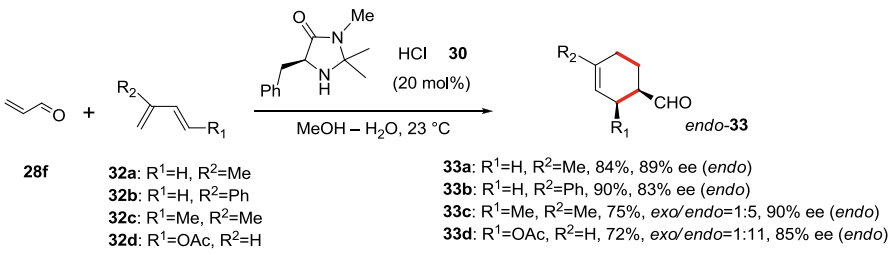
3.3 Two-Component Cycloadditions

3.3.1 [4+2] and Diels–Alder Reaction

Few reviews in organocatalytic [4+2] cycloadditions including iminium activation [14], Brønsted-acid and Brønsted-base catalysis [15], camphor derivatives catalysis [16] as well as bifunctional organic catalysis [17] have been reported [18]. The first highly enantioselective organocatalytic Diels–Alder reaction was reported by MacMillan and his co-workers in the reaction of α,β-unsaturated aldehydes **28** and dienes, *e.g.*, cyclopentadiene **29**, Schemes 3.8 and 3.9 [19]. The LUMO-lowering strategy was successively employed by catalytic quantities of catalyst **30** in the



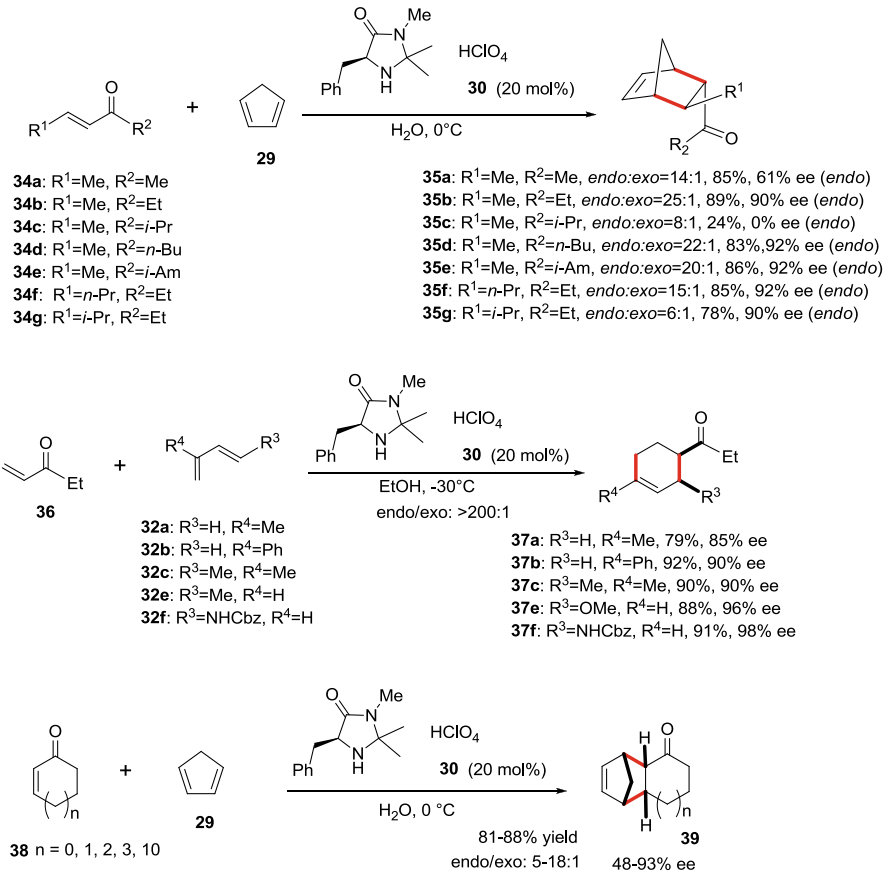
Scheme 3.8 Organocatalyzed Diels-Alder cycloadditions between cyclopentadiene and α,β-unsaturated aldehydes



Scheme 3.9 Organocatalyzed Diels-Alder reaction between acrolein and dienes

[4+2] cycloadditions. The enantioselectivity was rationalized by the fact that selective formation of the (*E*)-iminium isomer to avoid nonbonding interactions between the substrate olefin and the geminal methyl substituents and the benzyl group on the catalyst framework which effectively shields the *re* face of the dienophile, leaving the *si* face exposed to cycloaddition.

Later in 2002, MacMillan reported the first organocatalytic enantioselective Diels-Alder reaction of dienes with α,β-unsaturated ketones **34**, Scheme 3.10 [20].

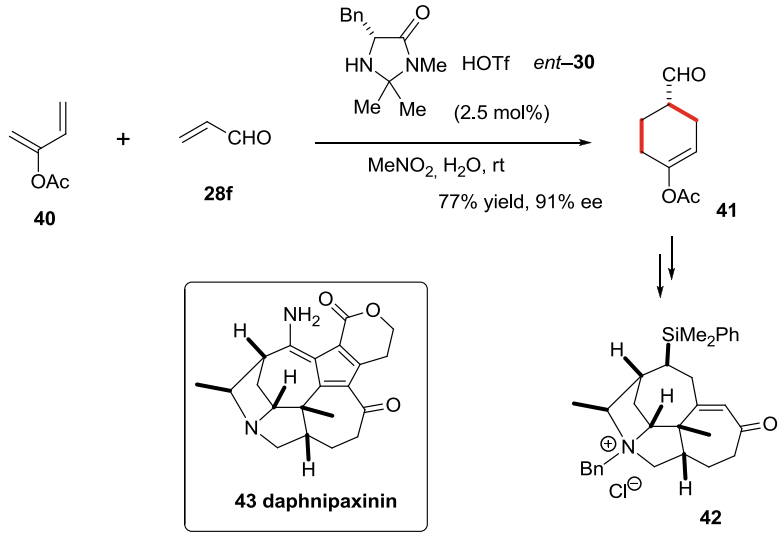


Scheme 3.10 Organocatalyzed Diels-Alder cycloadditions between α,β-unsaturated carbonyl compounds and dienes

The enantioselectivity of this reaction was rationalized by MM3 calculation of the (*Z*)- and (*E*)-iminium intermediate. Noteworthy, the imidazolidinone catalyst **30** was working well also in aqueous media or ethanol.

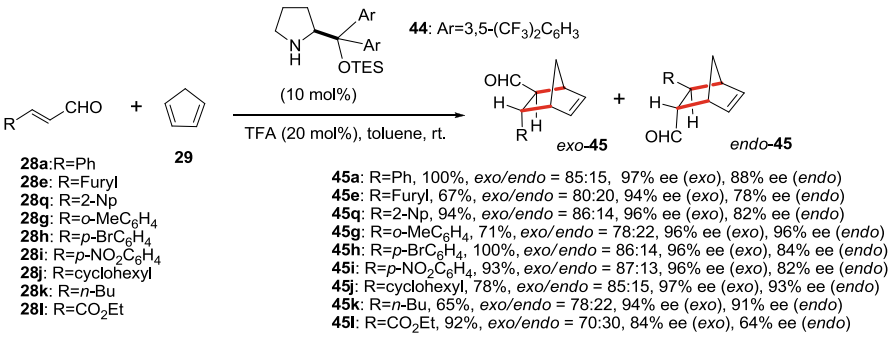
Recently, Overman, et al. reported an organocatalytic Diels-Alder reaction of 2-acetoxy-1,3-butadiene **40** and acrolein (**28f**) by MacMillan catalyst, *ent*-**30**–HOTf, Scheme 3.11 [21]. It was noteworthy to use water-saturated nitromethane as the reaction solvent. The adduct **41** was transformed to a tetracycle with the skeleton of the ring A–D of daphnicyclidin-Type alkaloids (**42**).

Hayashi and co-workers have reported an unusual and interesting case of stereoselectivity in organocatalyzed Diels–Alder reaction. Catalyst **44**–CF_3CO_2H was



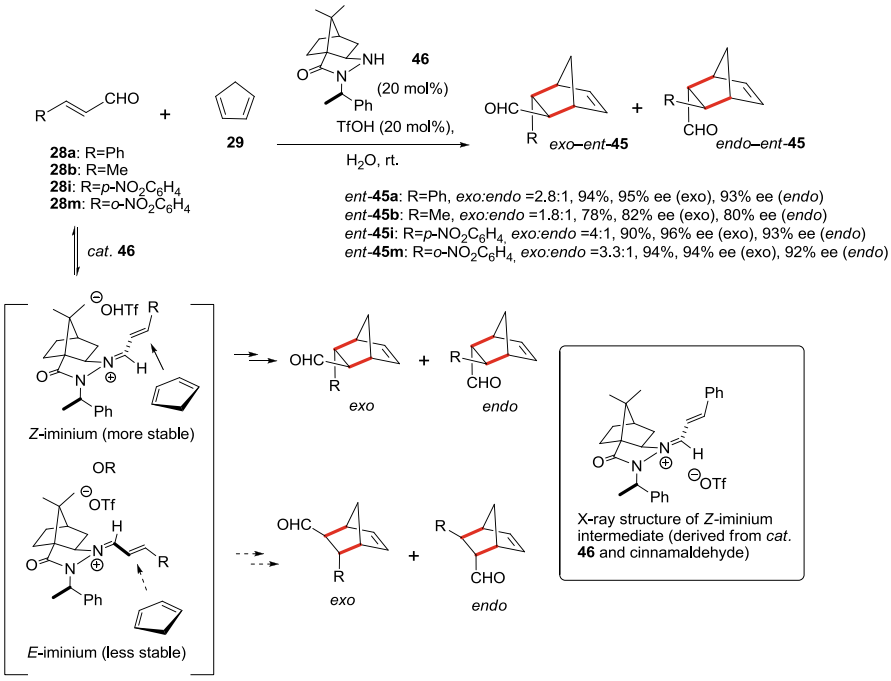
Scheme 3.11 Synthesis of (*S*)-cyclohexenecarboxyaldehyde via the organocatalytic Diels-Alder reaction

found to be an effective *exo*-selective organocatalyst for the enantioselective Diels–Alder reaction of α,β-unsaturated aldehydes (**28**) and cyclopentadiene, Scheme 3.12 [22]. Later, the authors reported the organocatalytic enantioselective Diels–Alder reaction in the presence of water and provides adducts with high *exo*- selectivities and excellent enantioselectivities. The reaction was done by completely organic solvent-free procedures, including the purification step. Moreover, it was observed that water accelerates the reaction as well as increases the enantioselectivity [23]. More recently, a kinetic study of the Diels-Alder reaction of cyclopentadiene and cinnamaldehyde with iminium ion catalysis was reported by Platts, et al. [24].



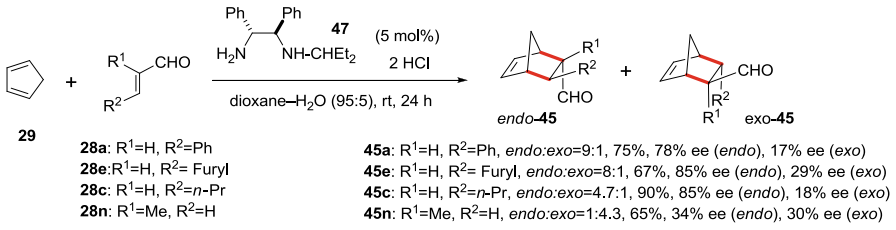
Scheme 3.12 Enantioselective Diels-Alder reaction between α,β-unsaturated aldehydes and cyclopentadiene catalyzed by diarylprolinol silyl ether **44**

Designed by Oglivie and his co-workers, the conformationally rigid hydrazide organocatalyst **46** was utilized as catalyst for asymmetric Diels-Alder reaction of cyclopentadiene and α,β-unsaturated aldehydes, Scheme 3.13 [25]. In addition, the first crystal structure of a key iminium intermediate, derived from catalyst **46** and cinnamaldehyde was presented by the authors. In the initial step of the Diels-Alder reaction, condensation of catalyst **46** and aldehydes (for example, cinnamaldehyde) results in the formation of iminium ions that can adopt one of the two key geometries (*Z*- or *E*-iminium), which was accounted for the enantioselectivity observed in the reaction. *Z*-iminium, which is more stable than *E*-iminium, leads to the major enantiomer through bottom-face approach of the diene. The steric bulk of camphor bridgehead methyl groups provided stereochemical bias that impairs top-face approach of the diene.



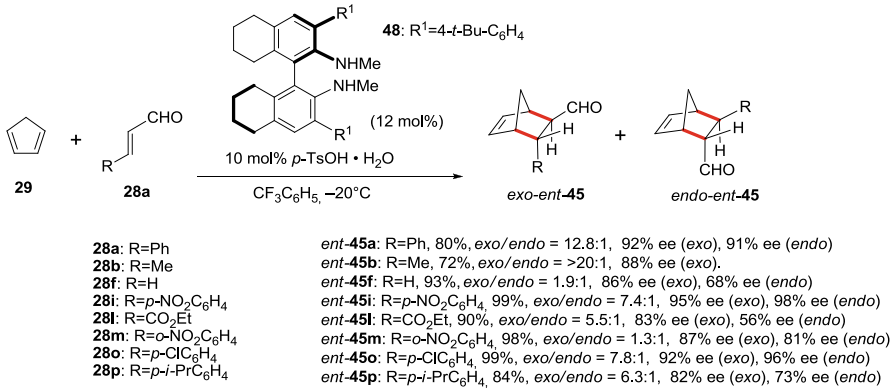
Scheme 3.13 Asymmetric Diels–Alder reaction of α,β-unsaturated aldehydes and cyclopentadiene by hydrazide catalyst **46**

Organocatalyzed asymmetric Diels–Alder reaction of cyclopentadiene and α,β-unsaturated aldehyde by protonated 1,2-diamino-1,2-diphenylethane (**47**, DPEN) was reported by Ha et al., Scheme 3.14 [26].



Scheme 3.14 Asymmetric Diels–Alder reaction of cyclopentadiene and α,β–unsaturated aldehydes by catalyst **47**

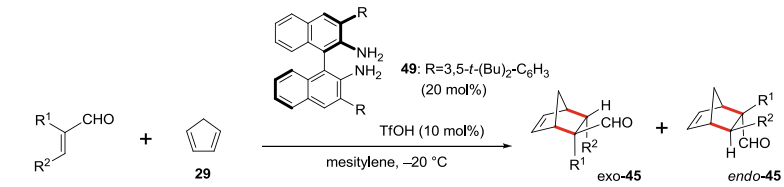
Maruoka, et al. reported unprecedented high exo-selectivity in the asymmetric Diels-Alder reaction of α,β-unsaturated aldehydes by a protonic acid-(*R*)-binaphthyl-based diamine salt catalyst **48**, Scheme 3.15 [27]. On the other hand, the Diels-Alder reaction of cyclopentadiene and cinnamaldehyde via enantioselective catalysis over mesocellular foams was reported by Ying and his co-workers [28].



Scheme 3.15 *exo*-Selective asymmetric Diels–Alder reaction of cyclopentadiene and α,β–unsaturated aldehydes by catalyst (*R*)-**48**

Lately, Maruoka, et al. reported an organocatalytic Diels–Alder reaction of α-substituted α,β-unsaturated aldehydes with cyclopentadiene, Scheme 3.16 [29]. Usually, the organocatalytic Diels–Alder reactions were not applicable to α-substituted acroleins due to serious steric repulsion between the substituent of aldehyde and the secondary amine catalyst. A binaphthyl-based primary amine, catalyst **49**, was designed for the reaction, and a plausible mechanism for the stereoselectivity reaction was presented.

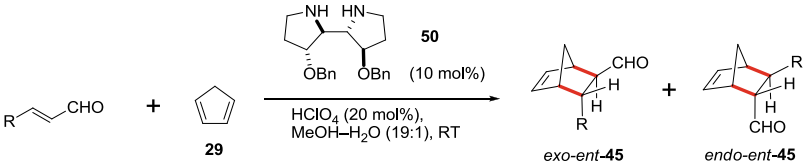
A new class of C_2-symmetric 3,3′-dialkoxy-2,2′-bipyrrolidines (*e.g.*, **50**) have been designed and developed by Zhang and his co-workers. The catalysts were used in asymmetric organocatalytic Diels–Alder reactions of α,β-unsaturated aldehydes **28** and dienes, Scheme 3.17 [30].



28o: R^1=Me, R^2=H
28s: R^1=Et, R^2=H
28t: R^1=Pr, R^2=H
28u: R^1=allyl, R^2=H
28v: R^1=Bn, R^2=H
28w: R^1=$BnOCH_2CH_2$, R^2=H
28x: R^1=$AcOCH_2$ R^2=H
28y: R^1=Me, R^2=Me

45o: R^1=Me, R^2=H, *exo/endo*>20:1, 51%, 55% ee (*exo*)
45s: R^1=Et, R^2=H, *exo/endo*>20:1, 68%, 92% ee (*exo*)
45t: R^1=Pr, R^2=H, *exo/endo*>20:1, 67%, 91% ee (*exo*)
45u: R^1=allyl, R^2=H, *exo/endo*>20:1, 86%, 94% ee (*exo*)
45v: R^1=Bn, R^2=H, *exo/endo*>20:1, 79%, 91% ee (*exo*)
45w: R^1=$BnOCH_2CH_2$, R^2=H, *exo/endo*>20:1, 90%, 89% ee (*exo*)
45x: R^1=$AcOCH_2$ R^2=H, *exo/endo*>20:1, 89%, 86% ee (*exo*)
45y: R^1=Me, R^2=Me, *exo/endo*>20:1, 89%, 66% ee (*exo*)

Scheme 3.16 Asymmetric Diels–Alder reaction of cyclopentadiene and α-substituted α,β-unsaturated aldehydes by catalyst (*R*)-**49**

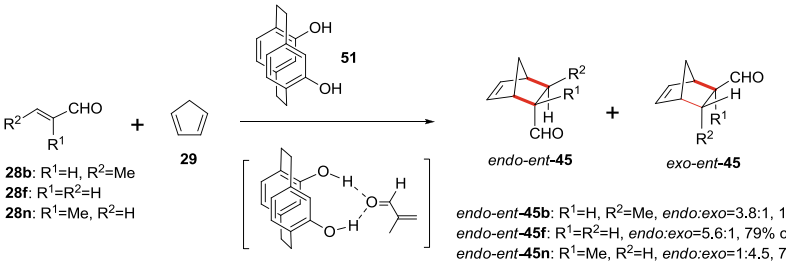


28a: R=Ph
28c: R=Pr
28h: R=*p*-BrC_6H_4
28i: R=*p*-$NO_2C_6H_4$
28l: R=CO_2Et
28m: R=*o*-$NO_2C_6H_4$
28o: R=*p*-ClC_6H_4
28r: R=*o*-$OMeC_6H_4$

ent-**45a**: R=Ph, 93%, *exo/endo* = 2.5:1, 91% ee (*exo*), 83% ee (*endo*)
ent-**45c**: R=Pr, 95%, *exo/endo* = 1.1:1, 82% ee (*exo*), 85% ee (*endo*)
ent-**45h**: R=*p*-BrC_6H_4, 95%, *exo/endo* = 2.1:1, 84% ee (*exo*), 83% ee (*endo*)
ent-**45i**: R=*p*-$NO_2C_6H_4$, 94%, *exo/endo* = 2.0:1, 83% ee (*exo*), 77% ee (*endo*)
ent-**45l**: R=CO_2Et, 95%, *exo/endo* = 1.5:1, 84% ee (*exo*), 83% ee (*endo*)
ent-**45m**: R=*o*-$NO_2C_6H_4$, 75%, *exo/endo* = 0.9:1, 85% ee (*exo*), 91% ee (*endo*)
ent-**45o**: R=*p*-ClC_6H_4, 95%, *exo/endo* = 2.2:1, 89% ee (*exo*), 88% ee (*endo*)
ent-**45r**: R=*o*-$OMeC_6H_4$, 55%, *exo/endo* = 2.7:1, 89% ee (*exo*), 83% ee (*endo*)

Scheme 3.17 Asymmetric Diels–Alder reaction of cyclopentadiene and α,β–unsaturated aldehydes by catalyst bipyrrolidine **50**

Braddock and his co-workers reported planar chiral PHANOLs as organocatalysts for Diels–Alder reaction of α,β-unsaturated aldehydes (e.g., **28** or α,β-unsaturated ketones) with cyclopentadiene, via double hydrogen-bridges to a carbonyl group, Scheme 3.18 [31].

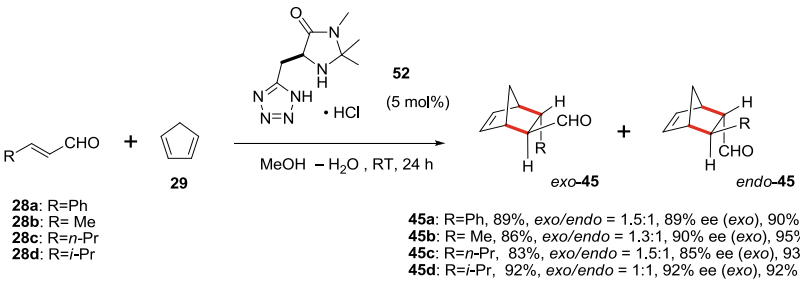


28b: R^1=H, R^2=Me
28f: R^1=R^2=H
28n: R^1=Me, R^2=H

endo-ent-**45b**: R^1=H, R^2=Me, *endo:exo*=3.8:1, 17% conversion
endo-ent-**45f**: R^1=R^2=H, *endo:exo*=5.6:1, 79% conversion
endo-ent-**45n**: R^1=Me, R^2=H, *endo:exo*=1:4.5, 74% conversion

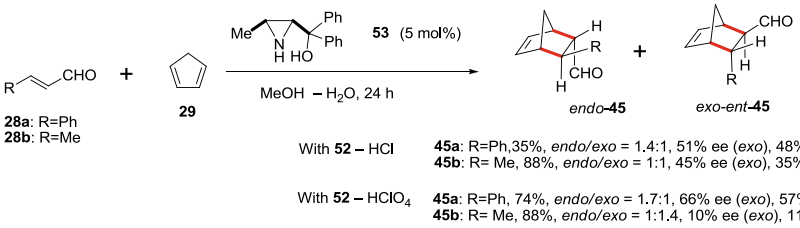
Scheme 3.18 Asymmetric Diels–Alder reaction of cyclopentadiene and α,β–unsaturated aldehydes by catalyst PHANOL **51**

Arvidsson and his co-workers synthesized a 1*H*-tetrazol containing catalyst and used it in the enantioselective organocatalyzed Diels–Alder reactions with good enantioselectivities (up to 95% ee), Scheme 3.19 [32].



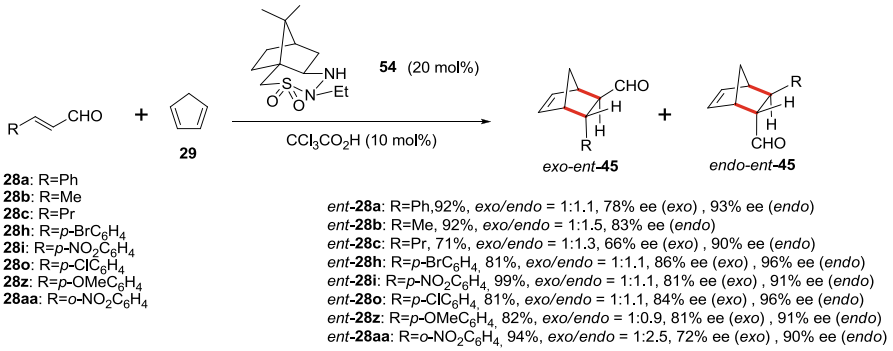
Scheme 3.19 Asymmetric Diels–Alder reaction of cyclopentadiene and α,β–unsaturated aldehydes by catalyst 1*H*-tetrazol **52**

A series of enantiomerically pure aziridin-2-yl methanols (e.g., **53**) have been used as organocatalysts in Diels–Alder reactions of cyclopentadiene and α,β-unsaturated aldehydes by Bonini, et al. Scheme 3.20 [33]. However, moderate ees were obtained.



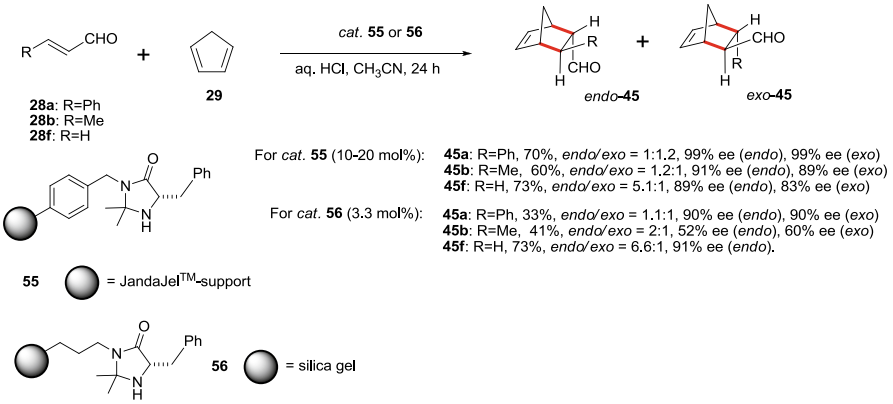
Scheme 3.20 Asymmetric Diels–Alder reaction of cyclopentadiene and α,β–unsaturated aldehydes by catalyst **53**

Lee and co-workers reported camphor sulfonyl hydrazines **54** as organocatalysts in enantioselective Diels-Alder reactions of cyclopentadiene and α,β–unsaturated aldehydes, Scheme 3.21 [34]. On the other hand, a similar Diels–Alder cycloaddition reactions with camphor-derived sulfonylhydrazines and $HClO_4$ in $MeNO_2$ were also developed by Langlois, et al. [35].



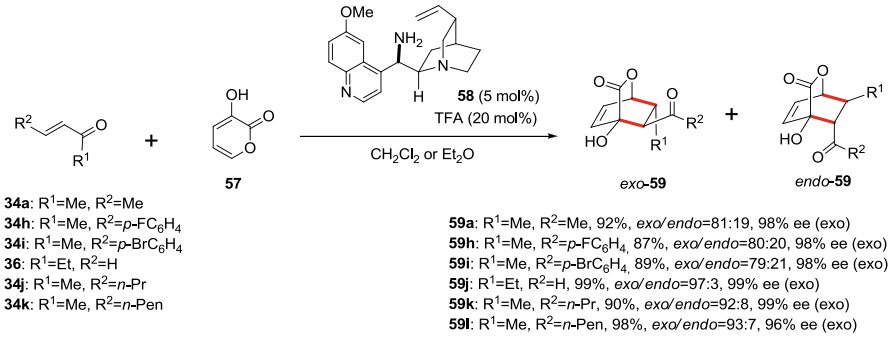
Scheme 3.21 Asymmetric Diels–Alder reaction of cyclopentadiene and α,β–unsaturated aldehydes by catalyst **54**

Pihko and co-workers reported asymmetric organocatalytic Diels-Alder reactions on solid support (JandaJel™-supported or *n*-propyl-functionalized silica gel) with the advantage of easy recovery and reuse, Scheme 3.22 [36]. For example, synthesized polymer- and silica-supported chiral imidazolidinone catalysts **55** and **56** were demonstrated to be efficient catalyst for the enantioselective Diels-Alder reactions of cyclopentadiene and cinnamaldehyde.



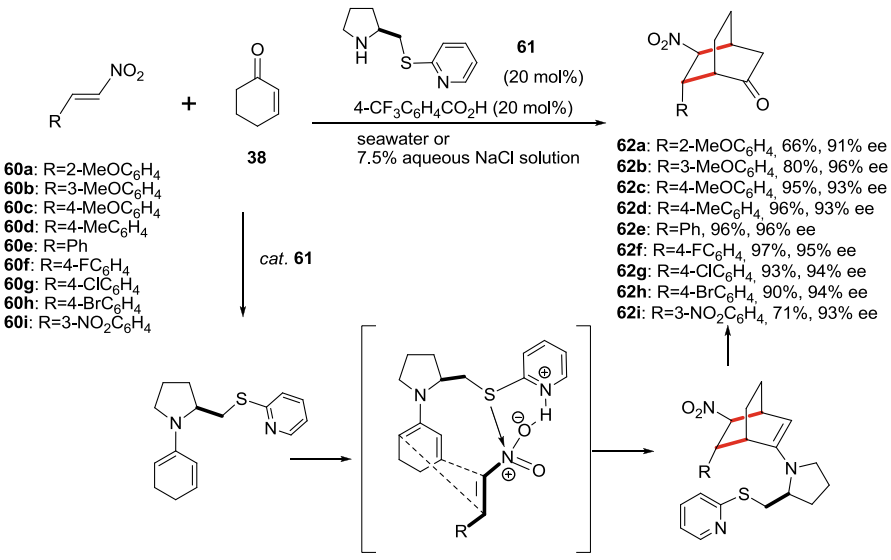
Scheme 3.22 Asymmetric Diels–Alder reaction of cyclopentadiene and α,β–unsaturated aldehydes by catalyst **55** and **56**

An asymmetric Diels – Alder reaction of 2-pyrones **57** and α,β-unsaturated ketones **34** with a bifunctional organic catalyst, *e.g.*, cinchona alkaloid derivative **58**, was reported by Deng, et al. Scheme 3.23. [37].



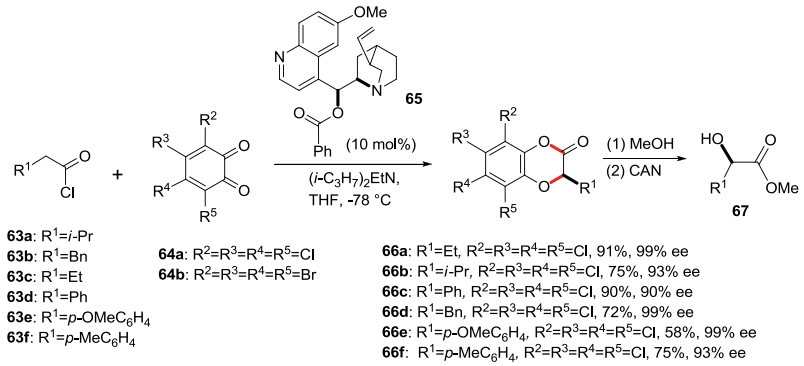
Scheme 3.23 Enantioselective Diels–Alder reaction of α,β-unsaturated ketones and 2-pyrones with cinchona alkaloid catalyst **58**

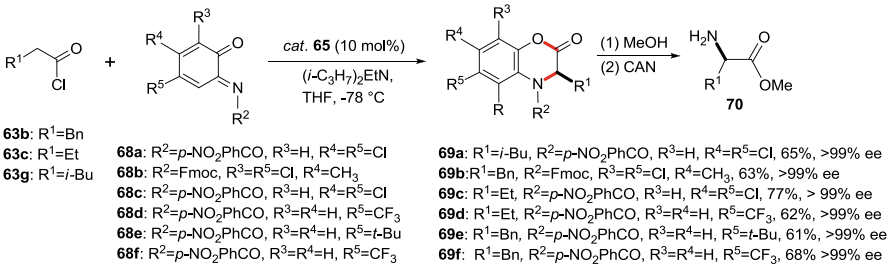
Xu, et al. developed an asymmetric organocatalytic Diels–Alder reaction of cyclohexenones (e.g., **38**) with aromatic nitroolefins **60** in seawater and brine with excellent chemo-, regio- and stereoselectivities, Scheme 3.24 [38]. The study suggested that seawater or brine play a role in stabilizing the transition state through a hydrogen-bonding interaction and the cyclization is involved in the one-step concerted addition pathway rather than a sequence of the Michael–Michael mechanism.



Scheme 3.24 Diels–Alder reactions of cyclohexenones with nitroolefins promoted by catalyst **61** in seawater and brine

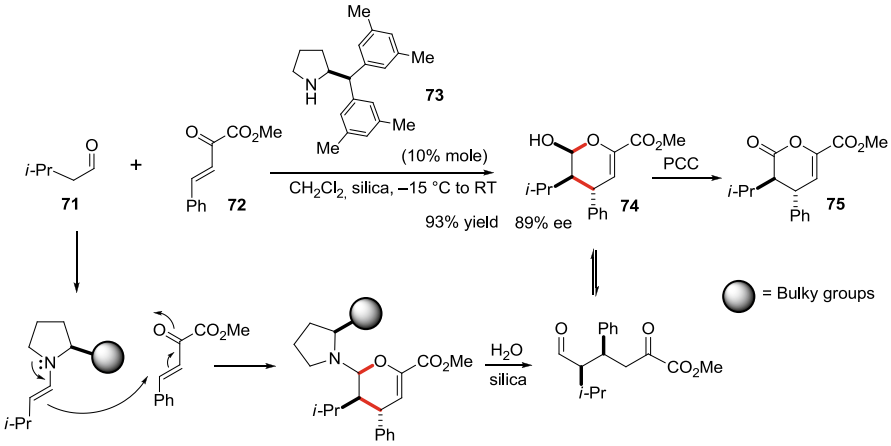
Organocatalytic and enantioselective [4 + 2]-cycloadditions of ketene enolates and *o*-quinones **64** providing benzo[*b*][1, 4]dioxin-2(3*H*)-ones **66** were developed by Lectka, et al., Scheme 3.25 [39]. The reactions were catalyzed by cinchona alkaloid **65** and the yields were improved by using Hünig's base instead of triethylamine. The *o*-chloranil-derived cycloadducts **66** has converted to chiral α-oxygenated carboxylic acid derivatives, such as (+)-methylmandelate, by methanolysis and CAN oxidation. The same methodology was applied in the synthesis of 1,4-benzoxazinones **69**, prepared from the reaction of acylchloride **63** and 6-alkyliminocyclohexa-2,4-dienone **68**, and followed by the conversion to α-amino acids derivatives **70** [40].





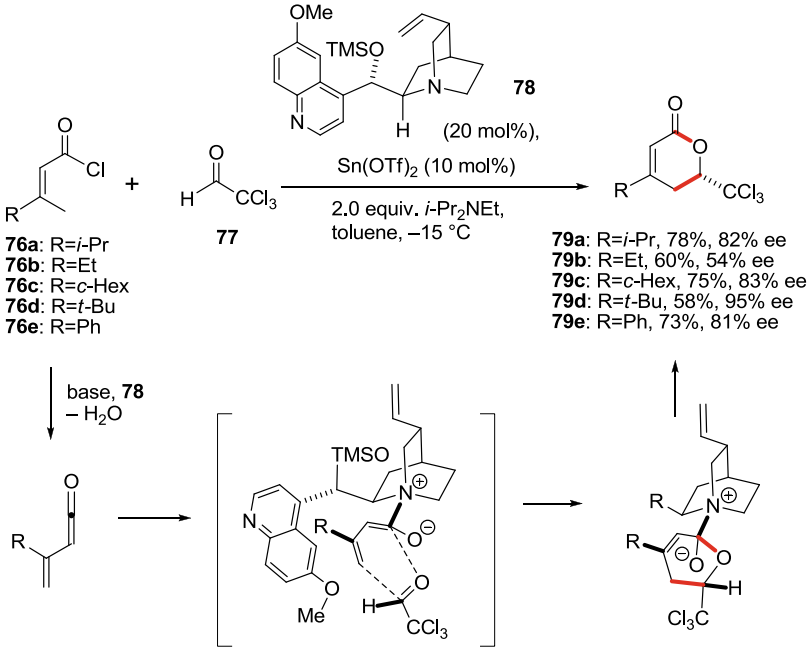
Scheme 3.25 Enantioselective [4 + 2]-cycloadditions of ketene enolates and *o*-quinones

Jørgensen and Juhl reported the first organocatalytic enantioselective inverse-electron-demand hetero-Diels–Alder reaction of aldehydes (e.g., **71)** and enones (e.g., **72)** with excellent diastereo- and enantioselectivity, Scheme 3.26 [41]. The reaction utilizes a chiral enamine intermediate as an alkene in catalytic asymmetric cycloaddition reactions.



Scheme 3.26 Enantioselective inverse-electron-demand Hetero-Diels–Alder reaction of aldehyde and enone

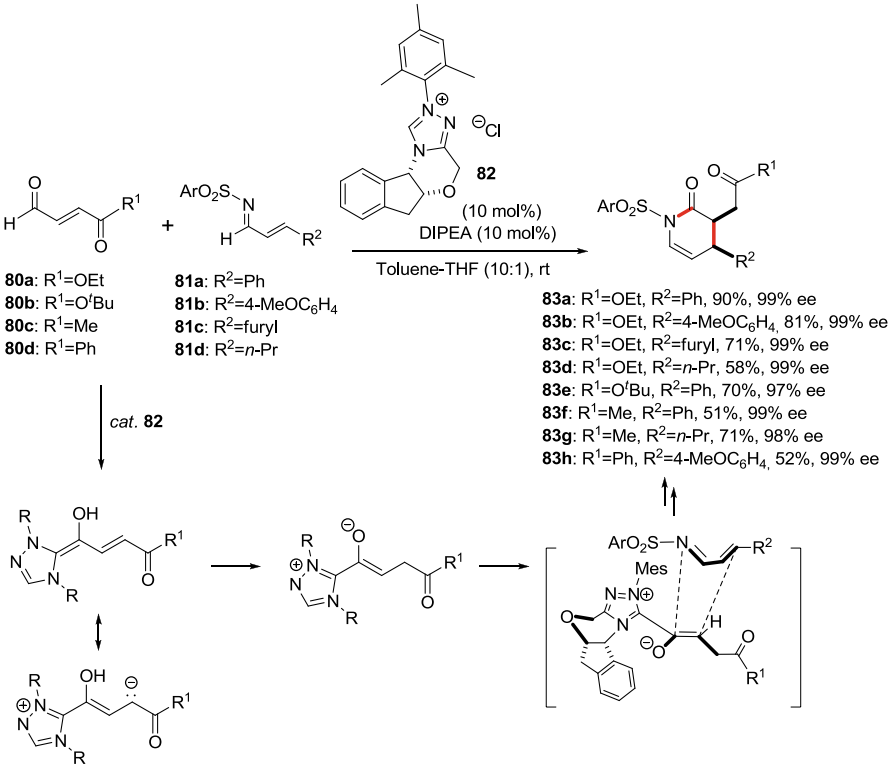
Peters and co-workers developed a tertiary amine-catalyzed enantioselective [4+2] cycloaddition of α,β-unsaturated acid chlorides **76a–e** and electron-poor aldehyde chloral (**77**) to provide *δ*-lactones **79a–e**, Scheme 3.27 [42]. Vinylketene, which was formed in situ by dehydrohalogenation of α,β-unsaturated acid chloride



Scheme 3.27 [4+2] Cycloaddition of zwitterionic dienolates, generated from α,β-unsaturated acid chlorides, and trichloroacetaldehyde

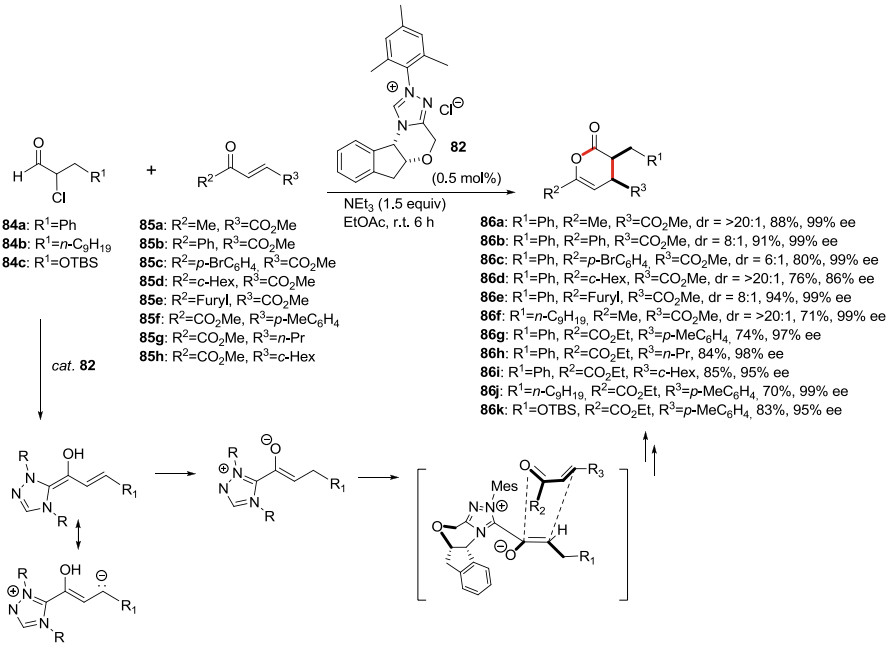
76, was trapped and activated as a zwitterionic dienolate by the enantiopure tertiary amine (*cat.* **78**). Preferring in an *cis*-conformation, the zwitterionic dienolate undergo [4+2] cycloadditions with aldehydes from the less-hindered *si* face since the *re* face is shield by quinoline and OTMS groups. As the general trend in this study, the larger the steric bulk of R, the better enantioselectivity was obtained, thus imply that R and the CCl_3 group should point away from each other to avoid steric interaction during the transition state.

Bode, et al. developed a highly enantioselective azadiene Diels-Alder reactions catalyzed by chiral *N*-heterocyclic carbenes, Scheme 3.28 [43]. Reactions of alkyl *trans*-4-oxo-2-butenoate **80** with *N*-sulfonyl imines **81** and catalyst **82** (10–15 mol%), DIPEA (10 mol%) in toluene-THF (10:1) at room temperature afforded the dihydopyridinones **83** in excellent diastereo- and enantioselectivity (>50:1 *cis*-diastereoselectivity, 99% ee). The $LUMO_{diene}$-controlled inverse electron demand Diels-Alder cycloaddition was facilitated by NHC-carbene catalyst **82**. Similar reactions without the catalyst would require high pressure (12 bar) or high temperature. The high *cis*-diastereoselectivity which would arise from (*Z*)-enolate reacting with the dienophile is rationalized as depicted in Scheme 3.28.

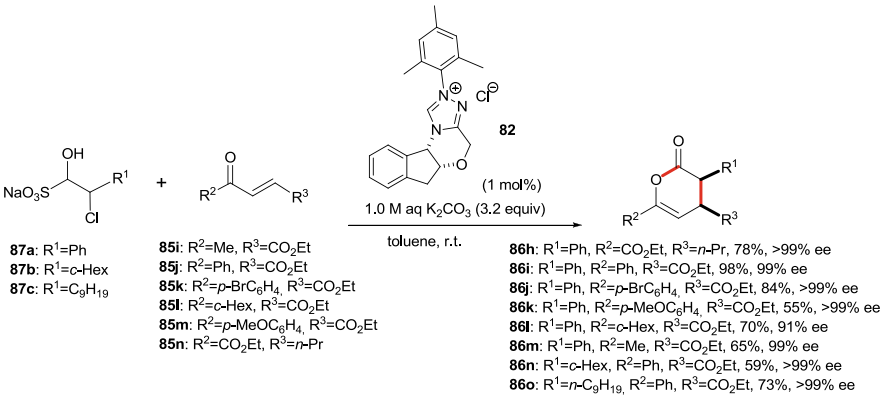


Scheme 3.28 NHC-catalyzed azadiene Diels-Alder reactions of 4-oxo-2-butenoate with *N*-sulfonyl imines

Subsequently, an enantioselective oxodiene Diels-Alder reactions with low organocatalyst loading (0.5 mol%) was developed by Bode, et al., Scheme 3.29 [44]. The enantioselective reaction of α-chloroaldehyde **84** and β,γ-unsaturated-α-ketones **85** (or methyl-4-oxo-pent-2-enoate) was achieved by catalyst **82**, affording the *δ*-lactones **86**. Later on, the α-chloroaldehyde surrogates, α-chloroaldehyde bisulfide adducts **87**, were employed in the chiral NHC-catalyzed hetero-Diels-Alder reaction with oxodienes **85** under biphasic reaction and aqueous condition with high enantioselectivity, Scheme 3.30 [45]. In addition, the methodology provides an



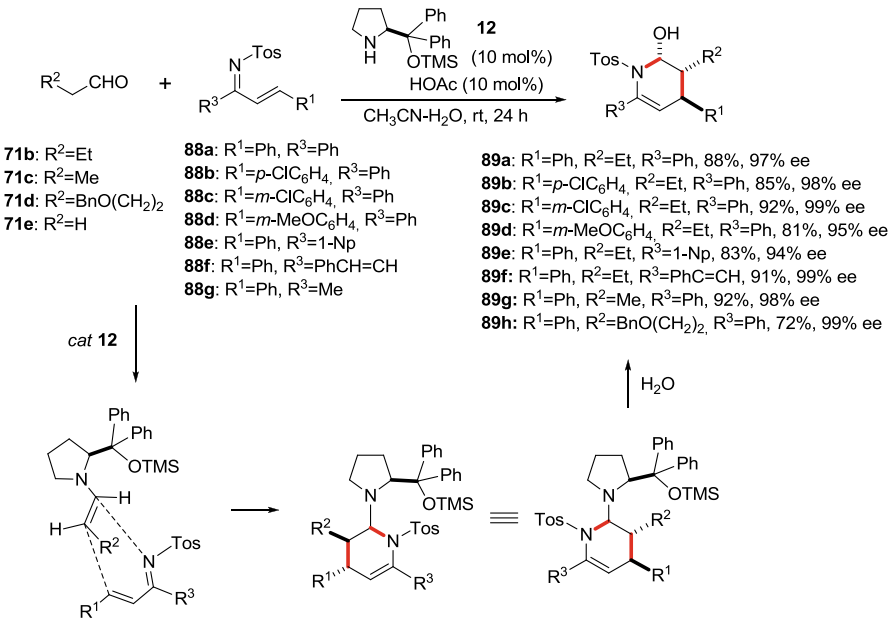
Scheme 3.29 NHC-catalyzed [4 + 2] reactions of unsaturated α-Ketoesters



Scheme 3.30 NHC-catalyzed biphasic Diels-Alder reactions of chloroaldehyde bisulfite salts with oxodienes

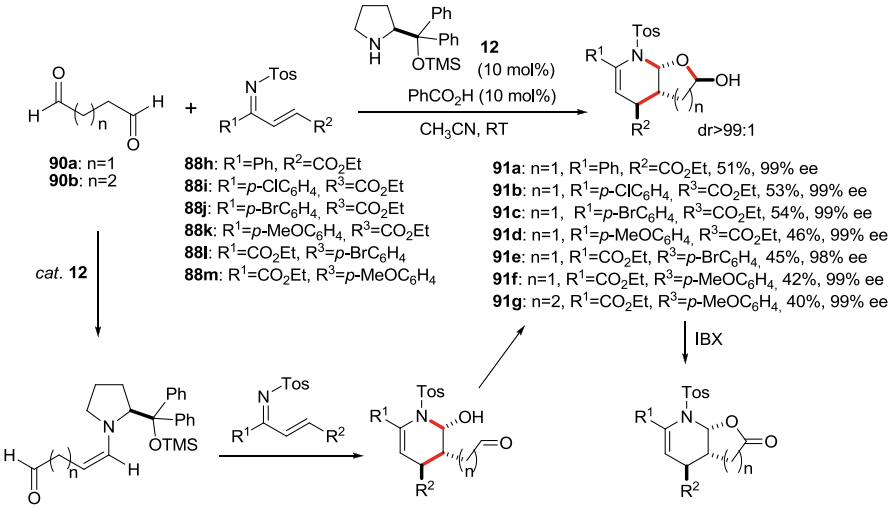
innovative example to employ commodity chemical of preactivate and protective reactant, as well as the example of water-tolerant NHC-catalyzed reaction.

A highly enantioselective inverse-electron-demand aza-Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes **88** and aldehydes **71** was reported by Chen and his co-workers, Scheme 3.31 [46]. Few chiral piperidine derivatives **89** were prepared via this methodology. The addition of water in the reaction media led to a dramatic acceleration of the reaction. Presumably, water is helpful for the hydrolysis of the catalyst-incorporated intermediate to release the catalyst and thus enable the catalytic turnover. Noteworthy, replacement of acetic acid to stronger acid, *e.g. p*-toluenesulfonic acid, resulted in no reaction.



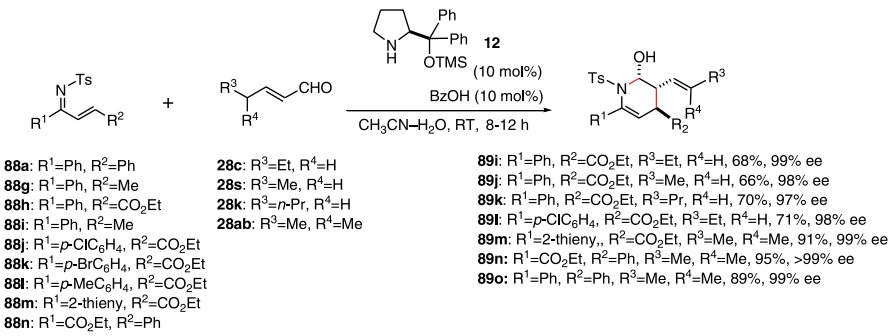
Scheme 3.31 Organocatalytic asymmetric inverse-electron-demand aza-Diels–Alder reaction of *N*-Sulfonyl-1-aza-1,3-butadienes and aldehydes

Later, the group reported a highly enantioselective construction of δ- and γ-lactone[2,3-*b*]piperidine skeletons by a tandem aza-Diels–Alder–hemiacetal formation–oxidation process from *N*-tos-1-aza-1,3-butadienes **88** and aliphatic dialdehydes **90**, Scheme 3.32 [47].



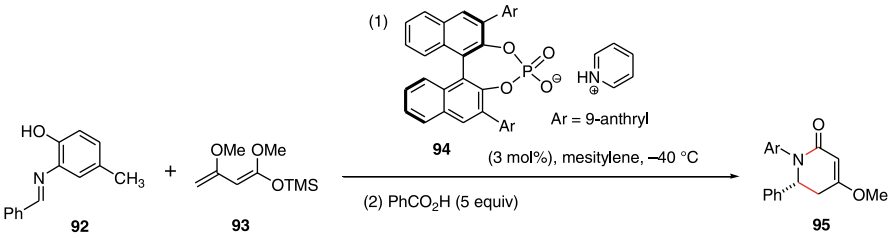
Scheme 3.32 Enantioselective construction of lactone[2,3-*b*]piperidine skeletons via organocatalytic tandem aza-Diels–Alder–hemiacetal formation–oxidation process

More recently, Chen and co-workers reported an organocatalytic regio- and stereoselective inverse-electron-demand aza-Diels–Alder reaction of α,β-unsaturated aldehydes **28** and *N*-tosyl-1-aza-1,3-butadienes **88**, providing the enantiomerically pure piperidine derivatives **89**, Scheme 3.33 [48].



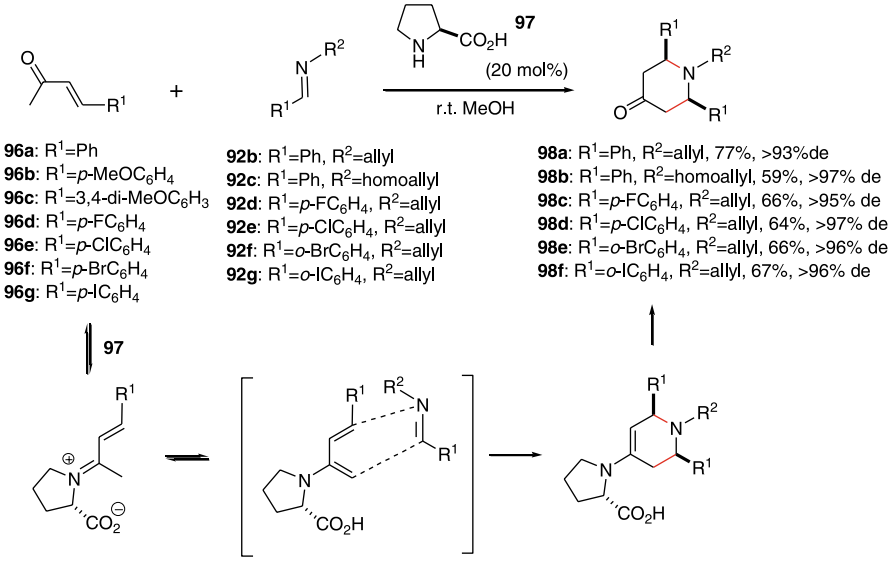
Scheme 3.33 Asymmetric aza-Diels–Alder reaction of *N*-tosyl-1-aza-1,3-butadienes and α,β-unsaturated aldehydes

Akiyama and his co-workers developed the aza-Diels–Alder reaction of Brassard's diene **93** with imines **92**, catalyzed by a chiral Brønsted acid **94** derived from (*R*)-BINOL, to give dihydropyridone derivatives **95** with excellent enantioselectivities, Scheme 3.34 [49]. To demonstrate the utility of the methodology, an experiment was performed on a gram scale.



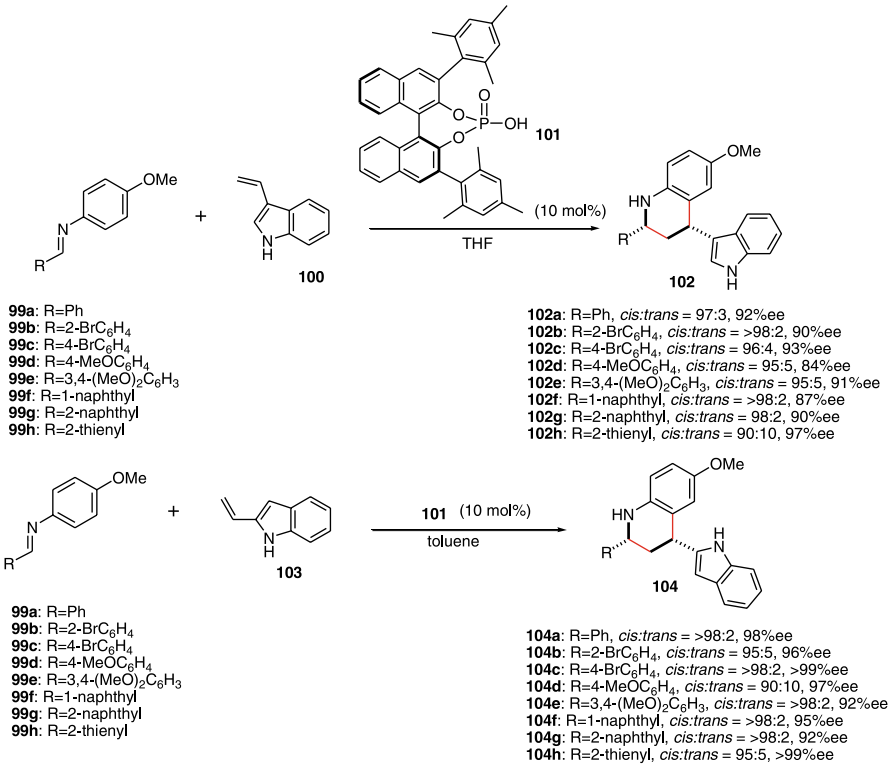
Scheme 3.34 Aza-Diels–Alder reaction of Brassard's diene **93** with imines **92**

Aznar, et al. reported a proline-catalyzed imino-Diels-Alder reactions of acyclic α,β-unsaturated ketones **96** with imines **92** for the synthesis of *meso*-2,5-diaryl-4-piperidones **98**, Scheme 3.35 [50]. The 2-amino-1,3-butadiene was generated *in situ* by the reaction of α,β-unsaturated ketones **96** with L-proline, followed by Diels-Alder cycloaddition with imine **92** to provide tetrahydropyridine adduct which was then hydrolyzed to the 4-piperidone **98**.



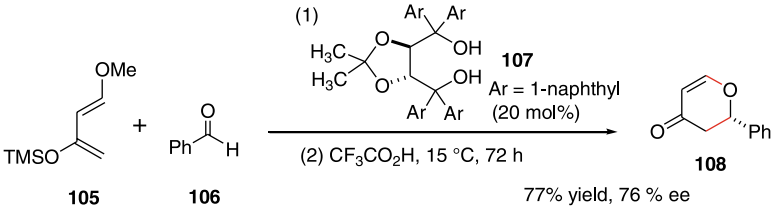
Scheme 3.35 Proline-catalyzed imino-Diels–Alder reactions of α,β-unsaturated ketones with imines

The asymmetric Povarov-reaction of *N*-arylimines **99** with 2- and 3-vinylindoles (**100** and **103**) was developed by Bernardi, Ricci and co-workers with a chiral phosphoric acid catalyst ((*S*)-TRIP, **101**) and provided highly enantioenriched indole derivatives (Scheme 3.36) [51].



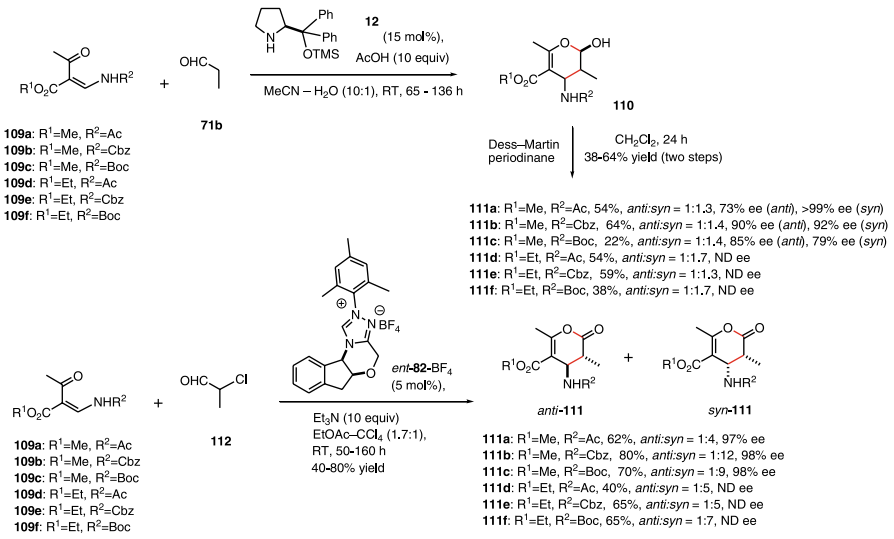
Scheme 3.36 Organocatalytic Povarov reactions of 4-methoxyaniline derived imines with 2- and 3-vinylindoles

Wu and his co-workers reported an experimental and theoretical study on the hydrogen-bond-promoted enantioselective hetero-Diels-Alder reaction (HAD) of Danishefsky's diene **105** with benzaldehyde **106**, Scheme 3.37 [52]. The reaction was achieved catalytically by a series of α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) derivatives through hydrogen-bonding activation and afforded 2-phenyl-2, 3-dihydro-4*H*-pyran-4-one **108** in good enantioselectivity.



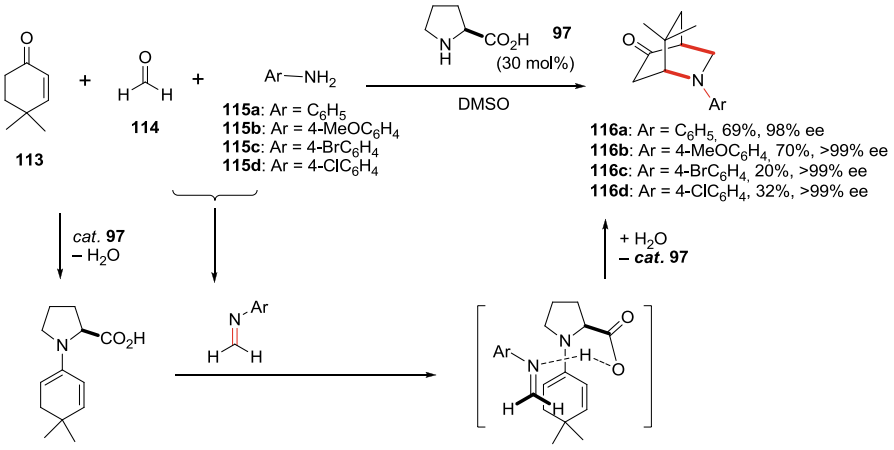
Scheme 3.37 Hetero-Diels-Alder reaction of Danishefsky's diene with benzaldehyde

Kobayashi et al. reported an organocatalytic enantioselective cycloadditions of oxodienes **109** and propanal **71b** providing nitrogen-substituted dihydropyran-2-ones **111**, Scheme 3.38 [53]. Also, their investigation showed that chiral triazonium salt **82** gave rise to excellent asymmetric induction with high 3,4-*syn* stereoselectivity**.** The product was a versatile intermediate in the synthesis of 1β-methylcarbapenem antibiotics.



Scheme 3.38 Asymmetric cycloaddition of oxodienes and aldehydes

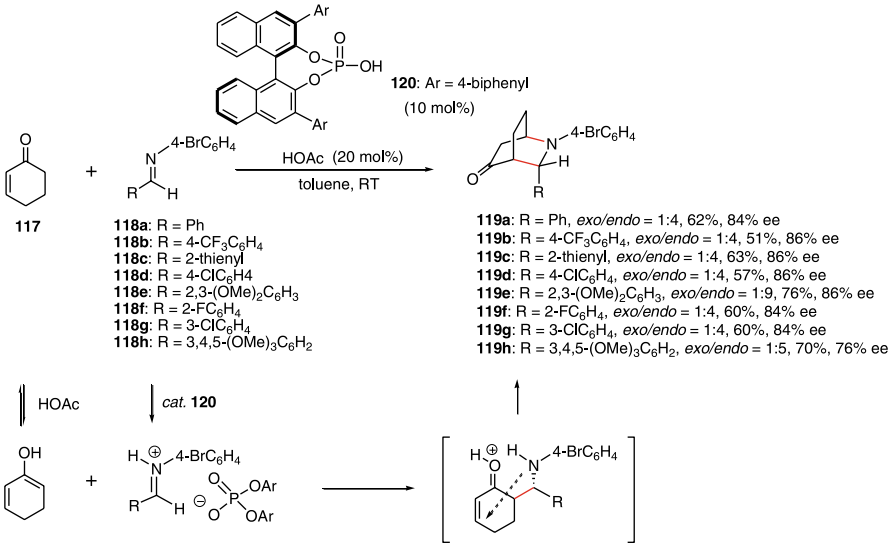
Córdova, et al. reported a one-pot three component direct catalytic enantioselective aza-Diels–Alder reaction of α,β-unsaturated ketones, Scheme 3.39 [54]. The reaction was catalyzed by proline with excellent regio-, and stereoselectivity. The



Scheme 3.39 Proline-catalyzed three-component enantioselective aza-Diels–Alder reaction of 4,4-dimethylcyclohex-2-enone (**113**) with different anilines

mechanism involved the proline-catalyzed formation of chiral enamine from α,β-unsaturated ketone, followed by the reaction with imine of formaldehyde.

Rueping and Azap developed an effective interplay of two Brønsted acids in the asymmetric synthesis of isoquinuclidines, Scheme 3.40 [55]. The key element for the success of this process is the fine-tuning of both Brønsted acid catalysts.



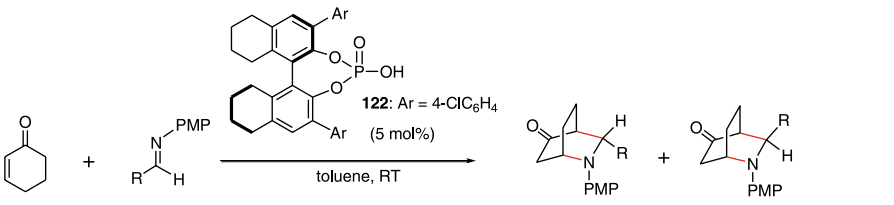
117

118a: R = Ph
118b: R = 4-$CF_3C_6H_4$
118c: R = 2-thienyl
118d: R = 4-ClC_6H4
118e: R = 2,3-$(OMe)_2C_6H_3$
118f: R = 2-FC_6H_4
118g: R = 3-ClC_6H_4
118h: R = 3,4,5-$(OMe)_3C_6H_2$

119a: R = Ph, *exo/endo* = 1:4, 62%, 84% ee
119b: R = 4-$CF_3C_6H_4$, *exo/endo* = 1:4, 51%, 86% ee
119c: R = 2-thienyl, *exo/endo* = 1:4, 63%, 86% ee
119d: R = 4-ClC_6H_4, *exo/endo* = 1:4, 57%, 86% ee
119e: R = 2,3-$(OMe)_2C_6H_3$, *exo/endo* = 1:9, 76%, 86% ee
119f: R = 2-FC_6H_4, *exo/endo* = 1:4, 60%, 84% ee
119g: R = 3-ClC_6H_4, *exo/endo* = 1:4, 60%, 84% ee
119h: R = 3,4,5-$(OMe)_3C_6H_2$, *exo/endo* = 1:5, 70%, 76% ee

Scheme 3.40 Enantioselective Bronsted acid catalyzed synthesis of isoquinuclidines

Independently, Gong, et.al reported the same reaction with similar chiral Brønsted acids, a chiral phosphoric acid derived from 3,3-di(4-chlorophenyl)-H_8-binol **122** with fairly good yields and enantioselectivities, Scheme 3.41 [56].



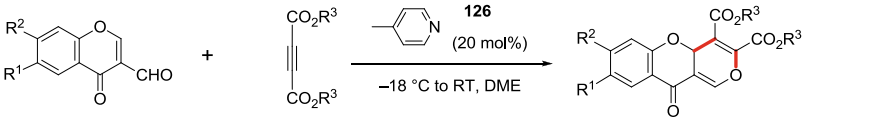
117

121a: R = Ph
121b: R = 3-ClC_6H_4
121c: R = 4-ClC_6H_4
121d: R = 2-ClC_6H4
121e: R = 4-FC_6H_4
121f: R = 4-CN_6H_4
121g: R = 4-MeC_6H_4

123a: R = Ph, *endo/exo* =84:16, 76%, 87% ee (endo)
123b: R = 3-ClC_6H_4, *endo/exo* =81:19, 74%, 83% ee (endo)
123c: R = 4-ClC_6H_4, *endo/exo* =82:18, 82%, 85% ee (endo)
123d: R = 2-ClC_6H_4, *endo/exo* =81:19, 73%, 77% ee (endo)
123e: R = 4-FC_6H_4, *endo/exo* =80:20, 72%, 85% ee (endo)
123f: R = 4-CN_6H_4, *endo/exo* =83:17, 70%, 76% ee (endo)
123g: R = 4-MeC_6H_4, *endo/exo* =83:17, 81%, 83% ee (endo)

Scheme 3.41 Organocatalytic asymmetric Diels–Alder reaction of cyclohexenone with aldimines

Stephanidou-Stephanatou and co-workers reported a 4-picoline-catalyzed hetero-Diels–Alder type cycloadditions of chromone-3-carboxaldehydes **124** with acetylenedicarboxylates **125**, providing an one-pot synthesis of pyrano[4,3-*c*] chromenes**127**, Scheme 3.42 [57].



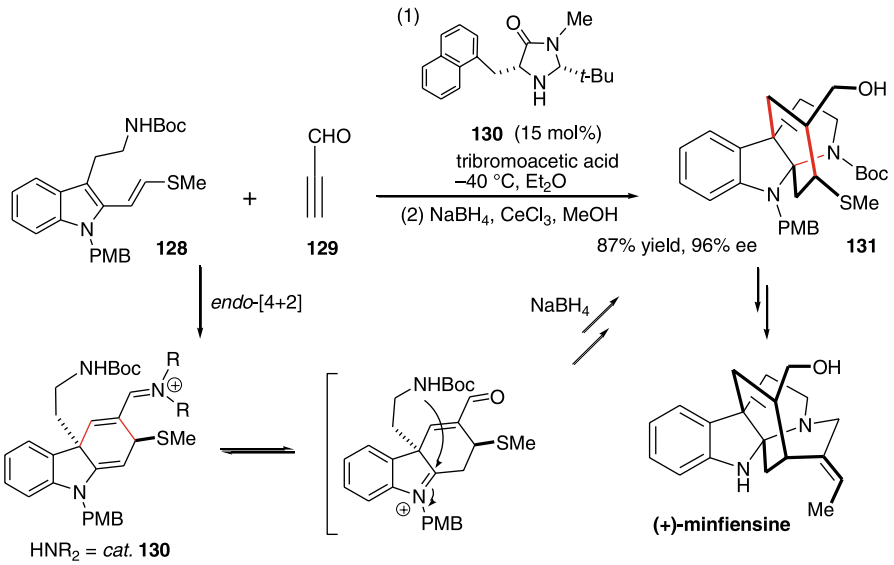
124a: R^1=R^2=H
124b: R^1=Me, R^2=H
124c: R^1=CH(Me)$_2$, R^2=H
124d: R^1=Cl, R^2=H
124e: R^1=Cl, R^2=Me

125a: R^3=Me
125b: R^3=Et

127a: R^1=R^2=H, R^3=Me, 42% yield
127b: R^1=Me, R^2=H, R^3=Me, 47% yield
127c: R^1=CH(Me)$_2$, R^2=H, R^3=Me, 48% yield
127d: R^1=Cl, R^2=H, R^3=Me, 39% yield
127e: R^1=Cl, R^2=Me, R^3=Me, 41% yield
127f: R^1=Me, R^2=H, R^3=Et, 45% yield
127g: R^1=CH(Me)$_2$ R^2=Me, R^3=Et, 51% yield
127h: R^1=Cl, R^2=H, R^3=Et, 38% yield

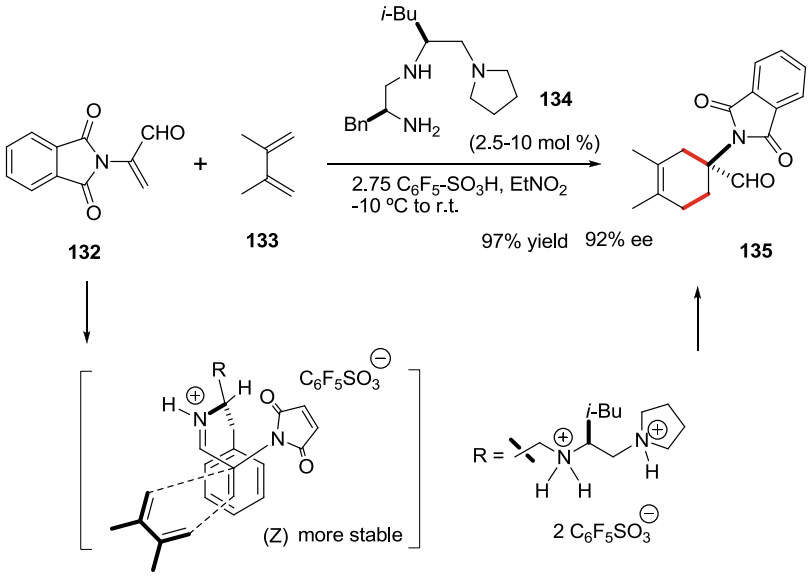
Scheme 3.42 4-Picoline-catalyzed hetero-Diels–Alder cycloadditions of chromone-3-carboxaldehydes with acetylenedicarboxylates

Recently, MacMillan reported a nine-step enantioselective total synthesis of (+)-minfiensine via the key step reaction of organocatalytic Diels-Alder-cascade cyclization, Scheme 3.43 [58].



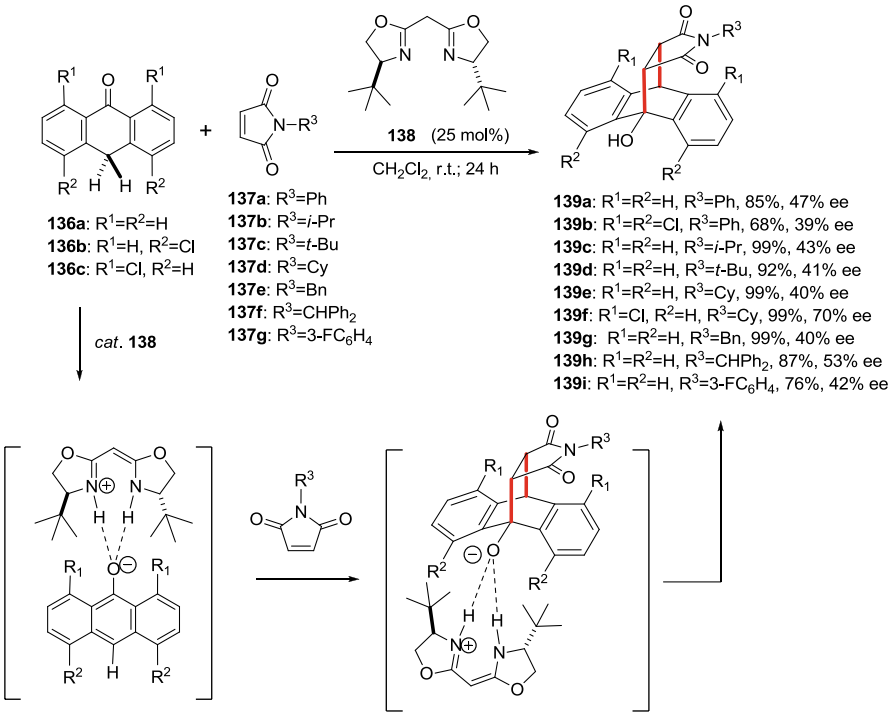
Scheme 3.43 Enantioselective total synthesis of (+)-minfiensine via the key step reaction of organocatalytic Diels-Alder-cascade cyclization

Ishihara, et al. reported an organocatalytic enantioselective Diels-Alder reaction of dienes α-(*N*,*N*-diacylamino)acroleins, Scheme 3.44 [59]. DFT calculation (with B3LYP) of catalyst revealed that the (*Z*)-aldiminium salt derived from α-(*N*,*N*-diacylamino)acrolein and catalyst has 2.8 kcal/mol lower energy than the *E*-form conformer. Based on this fact, diene should approach enantiomerically the *Si* face of the electron-deficient enimide to give the *endo*-(2*S*)-adduct as a major product. Earlier, catalyst **134**–Tf_2NH as well as 1,1′-binaphthyl-2,-2′-diammonium salt (catalyst–Tf_2NH) were used in the enantioselective Diels-Alder reaction with α-acyloxyacroleins [60].



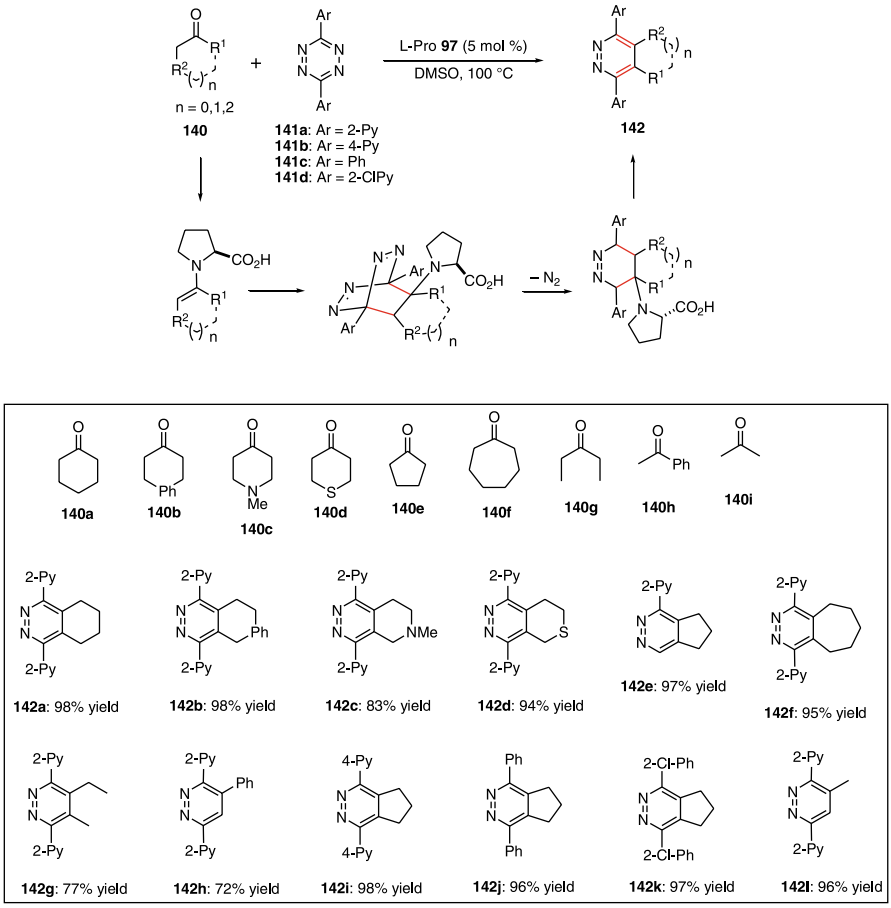
Scheme 3.44 Enantioselective Diels-Alder reaction of α-phthalimidoacroleins with 2,3-dimethylbuta-1,3-diene

Metal-free bisoxazolines catalyzed Diels-Alder reaction of *N*-substituted maleimides **137** with anthrone **136** derivatives was achieved by Göbel, et al. Scheme 3.45 [61]. With the photoelectron spectra and other studies, the Brønsted-base catalysis is assumed to be involved with formation of an ion pair between the protonated catalyst **138** and the anthrone enolate, acting as diene.



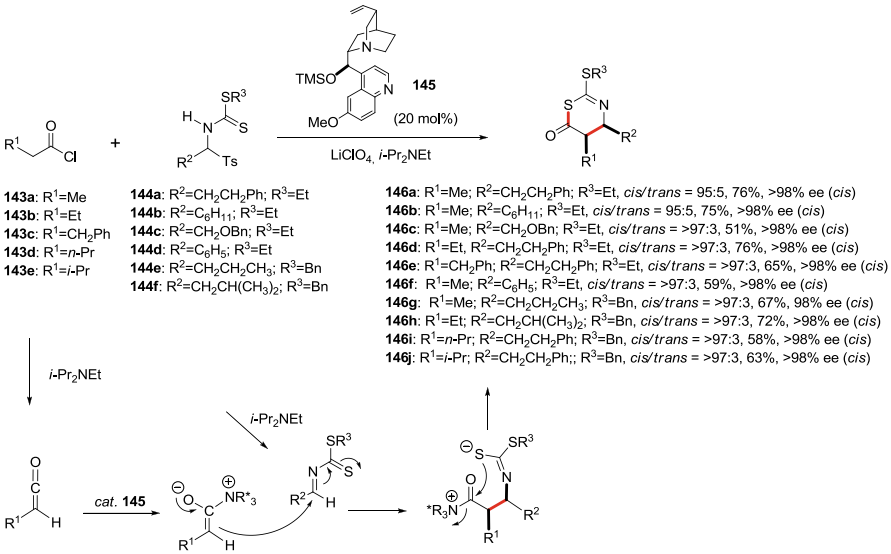
Scheme 3.45 Bisoxazoline-catalyzed Diels–Alder reaction

Wang, et al. reported an organocatalytic direct inverse electron demand Diels-Alder reaction of ketones **140** with 1,2,4,5-tetrazines**141**, Scheme 3.46 [62]. Examination of the results of catalyst screening revealed that L-proline seems to be the best organocatalyst tried in this process. Several steps were involved in the cascade reactions: inverse electron demand Diels-Alder reaction of 1,2,4,5-tetrazines **141** with the enamines, derived from ketones and L-proline, followed by a subsequent retro-Diels-Alder process to extrude N_2 and elimination to afford pyridazines **142**.



Scheme 3.46 L-Proline catalyzed inverse-electron-demand Diels–Alder reaction of ketones **140** and 1,2,4,5-tetrazine **141**

Nelson and co-workers reported cinchona alkaloid-catalyzed [4+2] cycloaddition of ketenes and *N*-thioacyl imine, affording the 4,5-*cis*-disubstituted 1,3-thiazin-6-one derivatives **146** with high enantioselectivities (≥95% ee) and diastereoselectivities (≥95:5 *cis*:*trans*), Scheme 3.47 [63]. Ketene, *in situ* generated from acyl halide **143** and base, followed by addition to imine which was generated *in situ* via basic elimination of α-amido sulfone **144**, providing the ketene-imine addition pathway toward the cycloadducts.



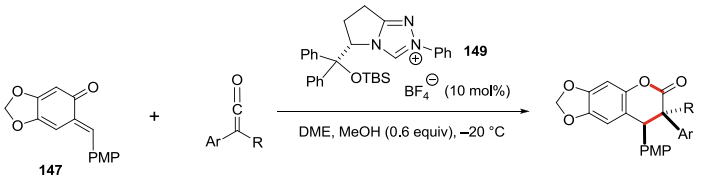
143a: R^1=Me
143b: R^1=Et
143c: R^1=CH_2Ph
143d: R^1=*n*-Pr
143e: R^1=*i*-Pr

144a: R^2=CH_2CH_2Ph; R^3=Et
144b: R^2=C_6H_{11}; R^3=Et
144c: R^2=CH_2OBn; R^3=Et
144d: R^2=C_6H_5; R^3=Et
144e: R^2=$CH_2CH_2CH_3$; R^3=Bn
144f: R^2=$CH_2CH(CH_3)_2$; R^3=Bn

146a: R^1=Me; R^2=CH_2CH_2Ph; R^3=Et, *cis*/*trans* = 95:5, 76%, >98% ee (*cis*)
146b: R^1=Me; R^2=C_6H_{11}; R^3=Et, *cis*/*trans* = 95:5, 75%, >98% ee (*cis*)
146c: R^1=Me; R^2=CH_2OBn; R^3=Et, *cis*/*trans* = >97:3, 51%, >98% ee (*cis*)
146d: R^1=Et, R^2=CH_2CH_2Ph; R^3=Et, *cis*/*trans* = >97:3, 76%, >98% ee (*cis*)
146e: R^1=CH_2Ph; R^2=CH_2CH_2Ph; R^3=Et, *cis*/*trans* = >97:3, 65%, >98% ee (*cis*)
146f: R^1=Me; R^2=C_6H_5; R^3=Et, *cis*/*trans* = >97:3, 59%, >98% ee (*cis*)
146g: R^1=Me; R^2=$CH_2CH_2CH_3$; R^3=Bn, *cis*/*trans* = >97:3, 67%, 98% ee (*cis*)
146h: R^1=Et; R^2=$CH_2CH(CH_3)_2$; R^3=Bn, *cis*/*trans* = >97:3, 72%, >98% ee (*cis*)
146i: R^1=*n*-Pr; R^2=CH_2CH_2Ph; R^3=Bn, *cis*/*trans* = >97:3, 58%, >98% ee (*cis*)
146j: R^1=*i*-Pr; R^2=CH_2CH_2Ph;; R^3=Bn, *cis*/*trans* = >97:3, 63%, >98% ee (*cis*)

Scheme 3.47 Cinchona alkaloid-catalyzed [4+2] cycloadditions of ketenes with α-amido sulfone

Ye and his co-workers reported an enantioselective synthesis of 3,3,4-trisubstituted 3,4-dihydrocoumarins **150** via *N*-heterocyclic carbene-catalyzed cycloaddition of ketenes **148** and *o*-quinone methides **147**, Scheme 3.48 [64]. Noteworthy, it was found that the additive methanol was crucial for the high yields and enantioselectivities. However, the rationalization for the use of the additive methanol remains unclear.

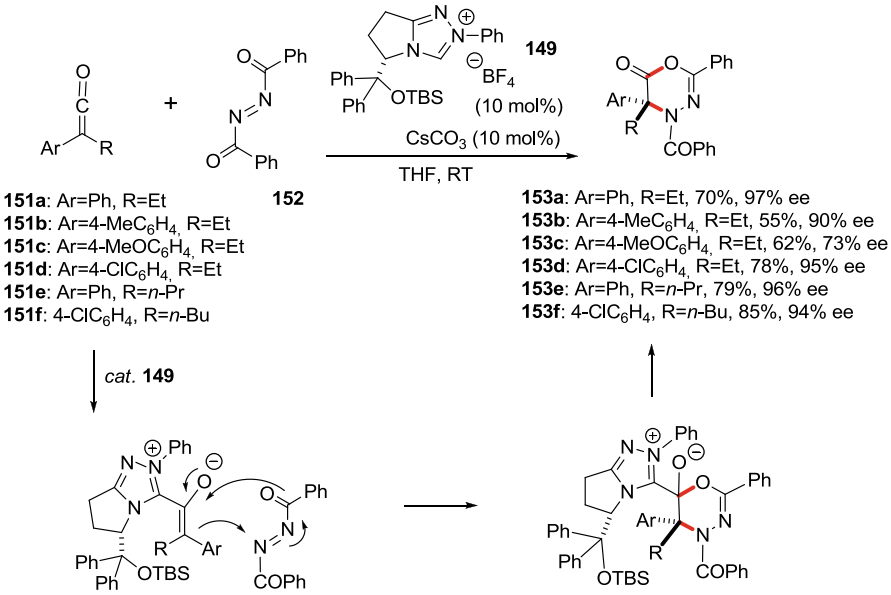


148a: Ar= Ph, R=Et
148b: Ar= Ph, R=Me
148c: Ar= Ph, R=*n*-Pr
148d: Ar= Ph, R=*n*-Bu
148e: Ar= 4-MeC_6H_4, R=Et
148f: Ar=4-$MeOC_6H_4$, R=Et
148g: Ar=4-BrC_6H_4, R=Et
148h: Ar=4-ClC_6H_4, R=Et

150a: Ar= Ph, R=Et, *cis*/*trans* = 7:1, 96%, 99% ee (*cis*), 96% (*trans*)
150b: Ar= Ph, R=Me, *cis*/*trans* = 2:1, 92%, 51% ee (*cis*)
150c: Ar= Ph, R=*n*-Pr, *cis*/*trans* = 9:1, 90%, 98% ee (*cis*), 85% (*trans*)
150d: Ar= Ph, R=*n*-Bu, *cis*/*trans* = 4:1, 67%, 97% ee (*cis*), 96% (*trans*)
150e: Ar= 4-MeC_6H_4, R=Et, *cis*/*trans* = 6:1, 94%, 98% ee (*cis*), 86% (*trans*)
150f: Ar=4-$MeOC_6H_4$, R=Et, *cis*/*trans* = 4:1, 80%, 96% ee (*cis*)
150g: Ar=4-BrC_6H_4, R=Et, *cis*/*trans* = 7:1, 96%, 99% ee (*cis*)
150h: Ar=4-ClC_6H_4, R=Et, *cis*/*trans* = 7:1, 90%, 99% ee (*cis*)

Scheme 3.48 Organocatalytic enantioselective synthesis of 3,3,4-trisubstituted 3,4-dihydrocoumarins

Ye reported a [4+2] cycloaddition of ketenes **151** with *N*-benzoyldiazenes **152** catalyzed by *N*-heterocyclic carbene**149**, affording 1,3,4-oxadiazin-6-ones **153**, Scheme 3.49 [65].

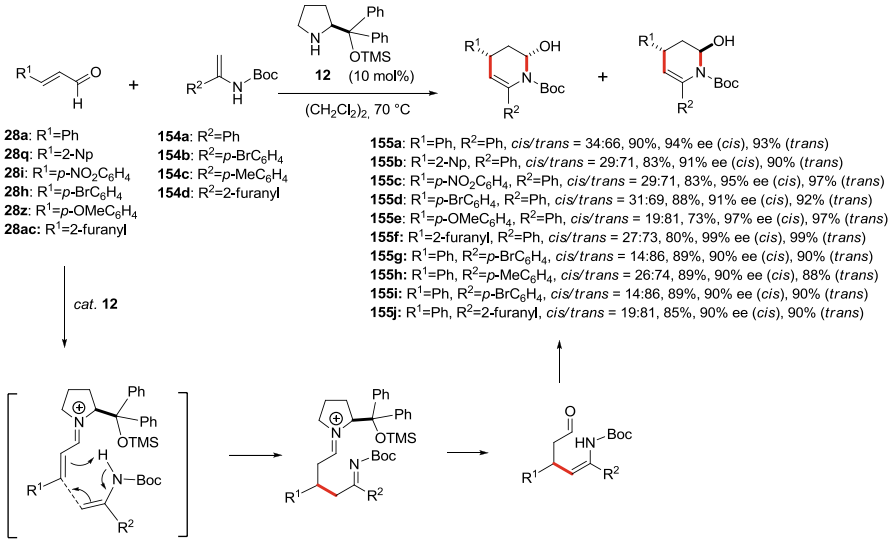


Scheme 3.49 Organocatalytic cycloaddition of ketenes with *N,N′*-dibenzoyldiazenes

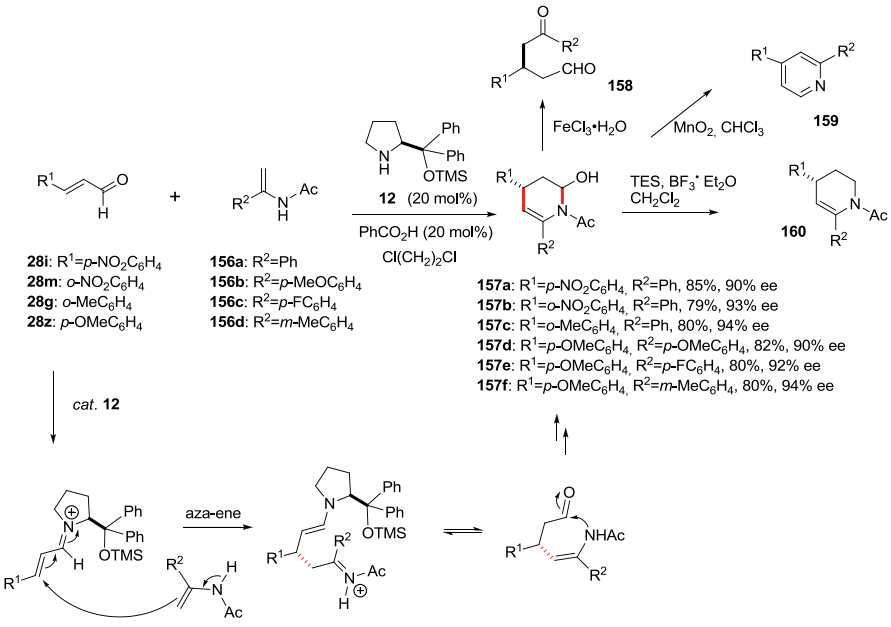
3.3.2 Ene Reaction

Hayashi, et al. developed an enantioselective formal aza [3+3] cycloaddition of α,β-unsaturated aldehydes and enamide (enecarbamate) providing tetrahydropyridin-2-ol in excellent enantioselectivities and yield, Scheme 3.50 [66]. The reaction comprised four consecutive reactions: ene reaction, isomerization of imine to enecarbamate, hydrolysis and hemiacetal formation. Noteworthy, examples of α,β-unsaturated aldehydes acting as enophile in intermolecular catalytic enantioselective ene reaction are rare, and the reaction developed by Hayashi represents one of the successful example in such category.

Shortly later, within 2 months, a similar reaction, the enantioselective cascade aza-ene-type cyclization reactions of α,β-unsaturated aldehydes **28** and enamide **154**, was also reported by Wang et al. In addition, the reaction product hemiaminal **157** was converted to ketoaldehyde **158**, pyridine **159** and enamide **160**, Scheme 3.51 [67]. Similarity, the reaction mechanism started from a nucleophilic attack of enamide (an aza-ene-type reaction), followed by reversible enamine-iminium transformation and hydrolysis to provide the hemiaminal.



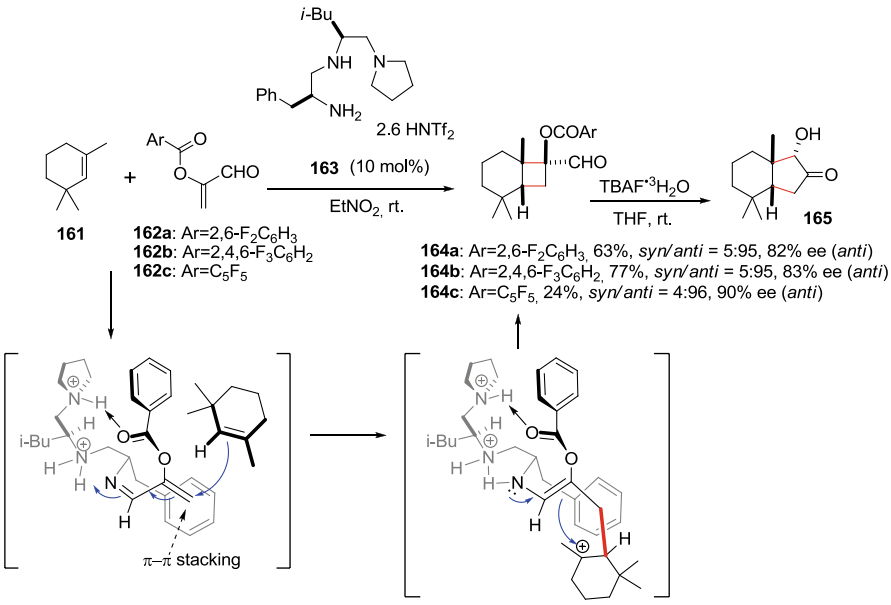
Scheme 3.50 Organocatalytic formal aza [3+3] cycloaddition reactions of enecarbamates and α,β-unsaturated aldehydes



Scheme 3.51 Organocatalytic cascade aza-ene-type reactions of α,β-unsaturated aldehydes with enamides and the subsequent transformations.

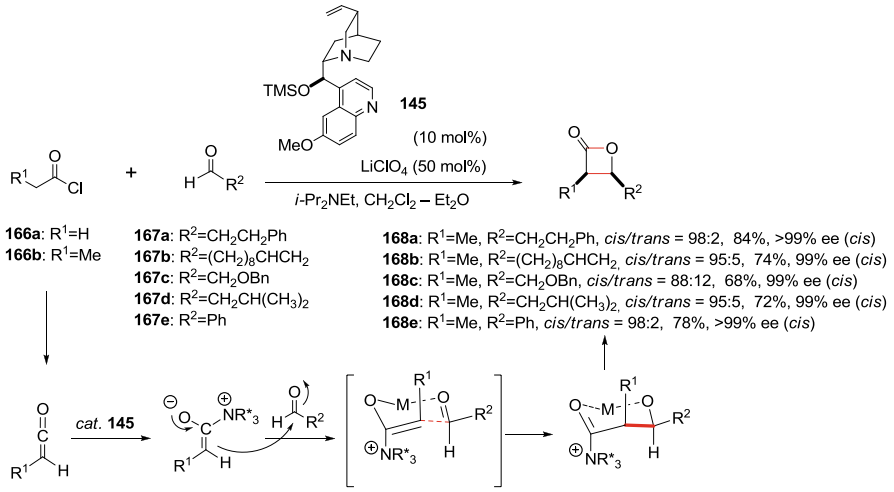
3.3.3 [2+2] Cycloadditions

Ishihara, K. et al. reported an enantioselective [2+2] cycloaddition of unactivated alkenes (e.g., **161**) with α-acyloxyacroleins **162**, catalyzed by chiral organoammonium salts, catalyst **163**, Scheme 3.52 [68]. A possible stepwise mechanism was proposed by authors to account for the stereoselectivity, which includes initial Michael addition of alkene to (*Z*)-iminium enal intermediate and intramolecular cyclization to afford the cycloadducts. The proposed transition states were stabilized by aromatic π-π stacking and intramolecular hydrogen-bonding interaction.



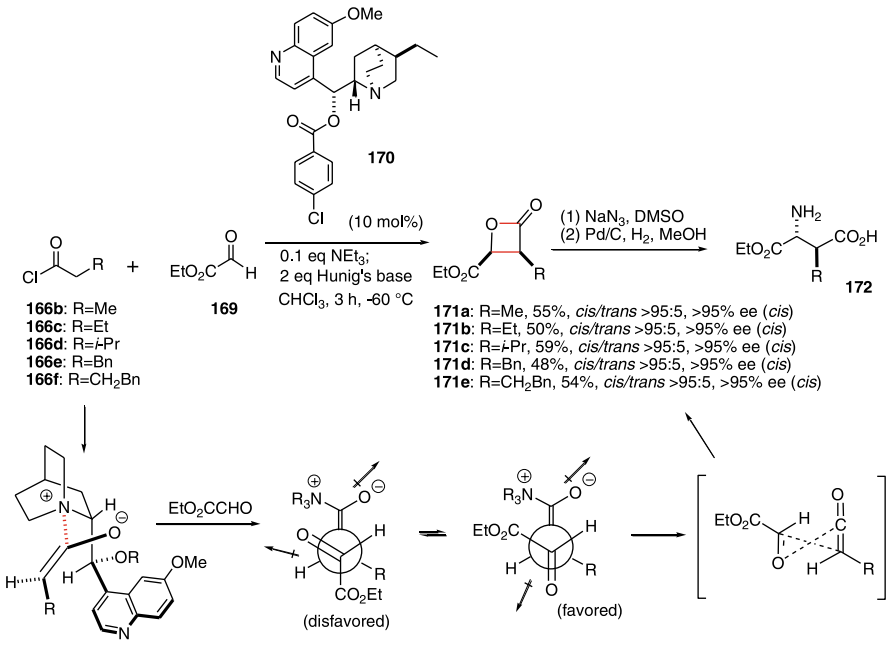
Scheme 3.52 Organocatalytic enantioselective [2+2] cycloaddition of 1,3,3-trimethylcyclohex-1-ene **161** and α-acyloxyacroleins

Nelson and co-workers reported a cinchona alkaloid-Lewis acid-catalyzed acycl chloride aldehyde reaction, an extension of ketene–aldehyde cycloaddition, providing 3,4-*cis*-β-lactones **168** with excellent enantioselectivities (up to >99% ee) and diastereoselectivities (>96% de), [69]. The methodology was later applied by the group in the enantioselective total synthesis of (−)-pironetin (Scheme 3.53).



Scheme 3.53 Cinchona alkaloid **145**/$LiClO_4$-catalyzed ketene-aldehyde cycloadditions

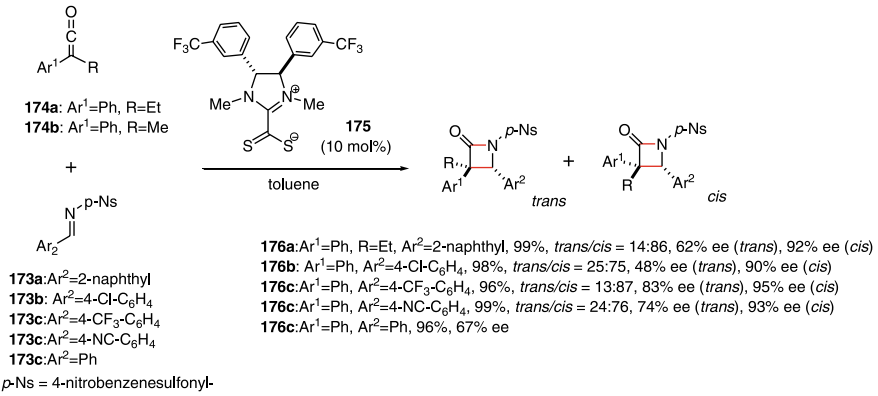
Later, Armstrong, et al. reported a similar methodology. Cinchona alkaloid-catalyzed reaction of ethyl glyoxylate **169** with substituted ketenes, formed in situ, gave β-lactones, which was underwent ring opening by sodium azide, reduction and ester hydrolysis to afford β-alkyl aspartates **172**, Scheme 3.54 [70]. Noteworthy in



Scheme 3.54 Enantioselective ketene–glyoxylate [2+2] cycloadditions

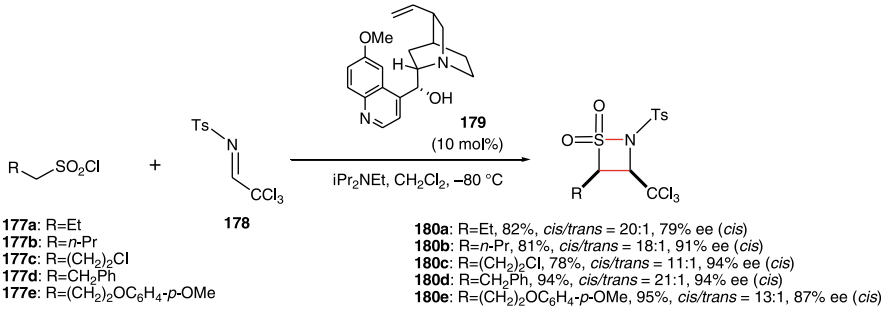
the reaction conditions, the mixture of tertiary amine bases was necessary in the reactions since the rate of ketene formation was too slow with Hünig's base alone.

An enantioselective Staudinger reaction of ketene **174** and imine **173** with imidazolinium-dithiocarboxylate catalyst (**175**) was developed by Wilhelm, et al., Scheme 3.55 [71].



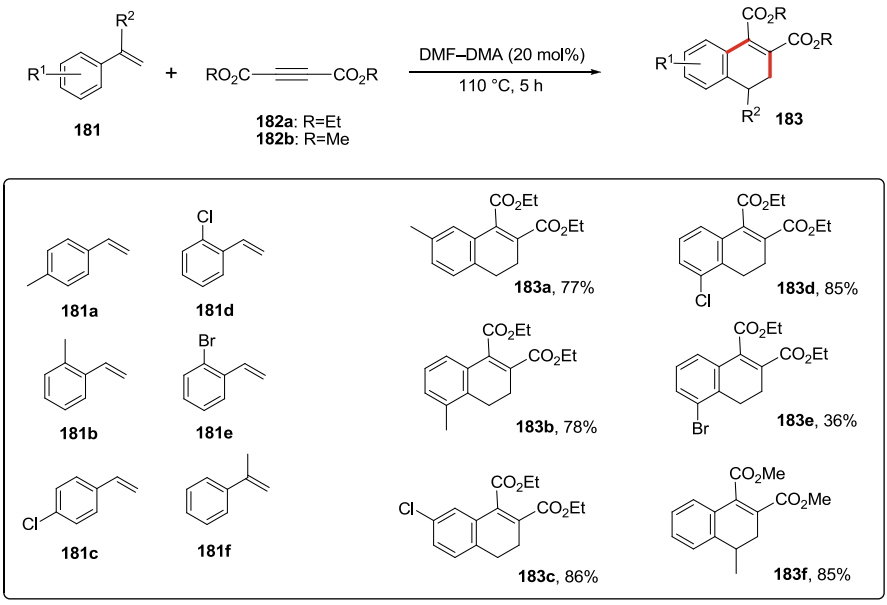
Scheme 3.55 Enantioselective Staudinger reaction of ketene and imine with imidazolinium-dithiocarboxylate catalyst

Peters and Zajac reported the cinchona alkaloids, e.g. quinine, catalyzed formal [2+2] cycloadditions of sulfonylchlorides **177** and highly reactive non-nucleophilic imines**178**, affording the β-sultams **180**, Scheme 3.56 [72].



Scheme 3.56 Organocatalytic enantioselective [2+2] cycloadditions of imine and sulfonyl chlorides

Hua and his co-workers reported a highly efficient cycloaddition of vinylarenes **181** with electron-deficient alkynes **182**, affording 1,2-disubstituted-3,4-dihydronaphthalenes **183**, in the presence of DMF•DMA (N,N-dimethylformamide dimethyl acetal) as organocatalyst, Scheme 3.57 [73]. The mechanism for the

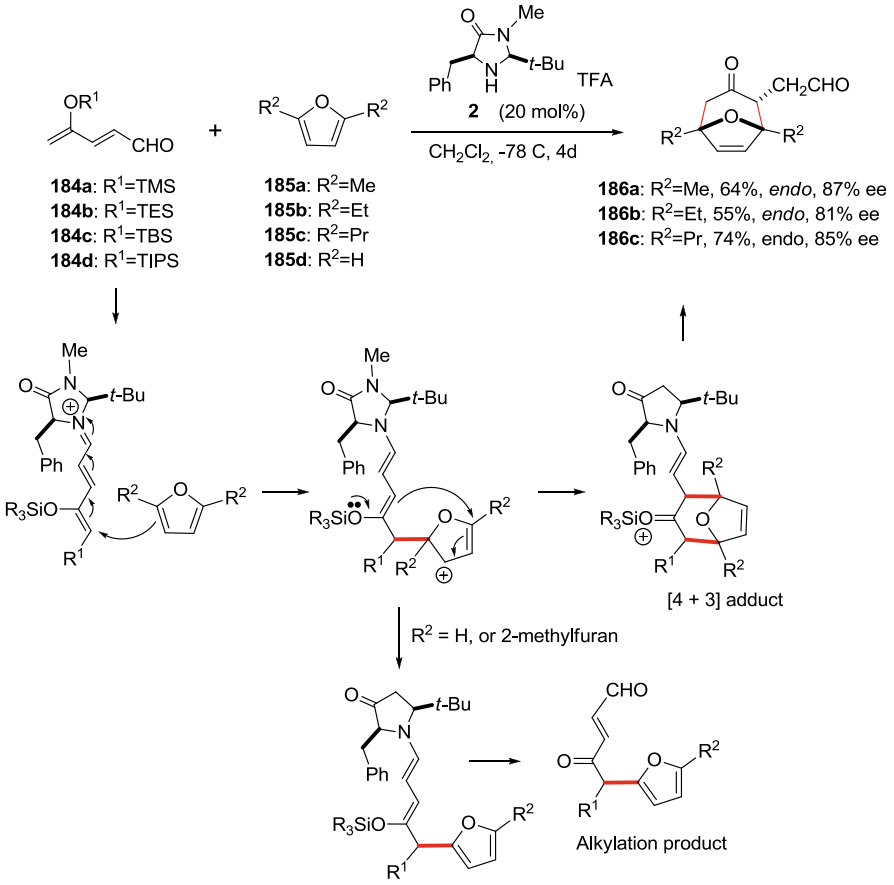


Scheme 3.57 Organocatalyzed [4 + 2] reaction of styrene with acetylenedicarboxylate

cycloaddition of is not clear. It is possible that the formation of adduct by [2 + 2] cycloaddition of alkenes with electron-deficient alkynes followed by rearrangement to afford the more stable six-membered ring products. The other possible pathway for the present reaction is the DMF•DMA-catalyzed Diels–Alder cycloaddition of vinylarene with acetylenedicarboxylate, followed by aromatization. However, according to authors' claim, there is no successful Diels–Alder reaction in which vinylarene acts as a diene. Therefore, the reaction via the Diels–Alder reaction pathway seems to be very unfavorable.

3.3.4 [4 + 3] Cycloaddition

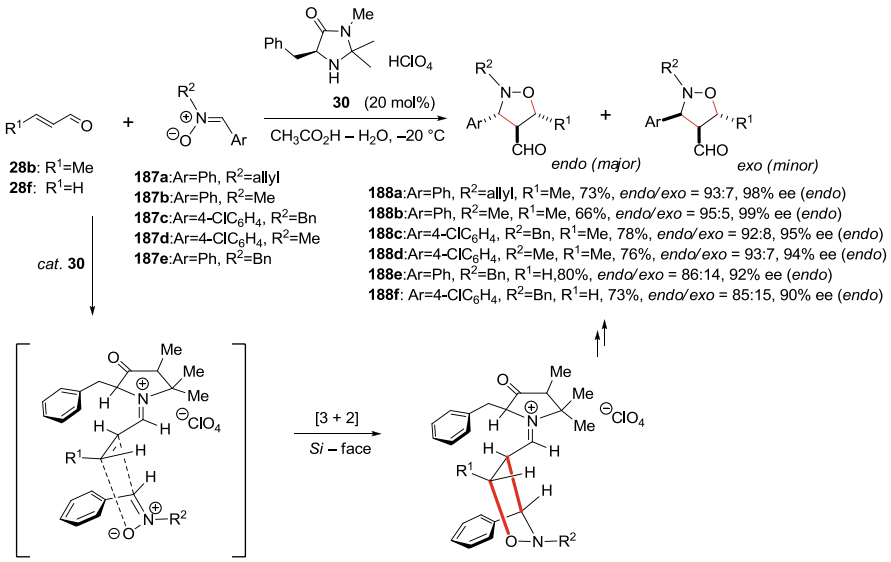
Harmata and co-workers reported an asymmetric organocatalytic [4 + 3] cycloadditions of (*E*)-4-trialkylsilyloxypenta-2,4-dienal **184** and furans **185** by catalyst **2**, [74]. The same reaction condition with 2-methylfuran or furan, instead of 2,5-dialkylfurane, afforded complicated mixtures or products derived from alkylation. The result suggested that the cycloaddition could be stepwise, and implied that the way to circumventing the formation of substitution product (by losing a proton) is to use disubstituted furans, since the conformer needed for ring closure would be significantly populated and the barriers to rotate to achieve the conformer for cyclization would be reduced (Scheme 3.58).



Scheme 3.58 Organocatalytic enantioselective [4+3] cycloaddition reactions of substituted furans and dienes

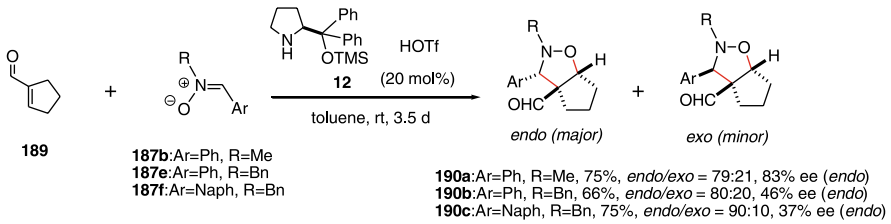
3.3.5 [3+2] or 1,3-Dipolar Cycloaddition

In 2000, MacMillan and his co-workers presented the first enantioselective organocatalytic 1,3-dipolar cycloaddition of nitrones **187** and α,β-unsaturated aldehydes **28** (dipolarphiles) to afford the *endo*-(4*S*)-isoxazolidine adducts **188**, Scheme 3.59 [75]. With the LUMO-lowering activation of α,β-unsaturated aldehydes **28** and enforced formation of (*E*)-iminium isomer, the $HClO_4$-salt of catalyst **30** effectively promote cycloaddition of the dipolarphile. In addition, *endo*-cycloaddition effectively alleviated nonbonding interaction between the nitrone phenyl group and the neopentyl methyl substituent on the catalyst framework. Later, in 2002, Karlsson and Högberg reported the organocatalytic enantioselective 1,3-dipolar cycloaddition of



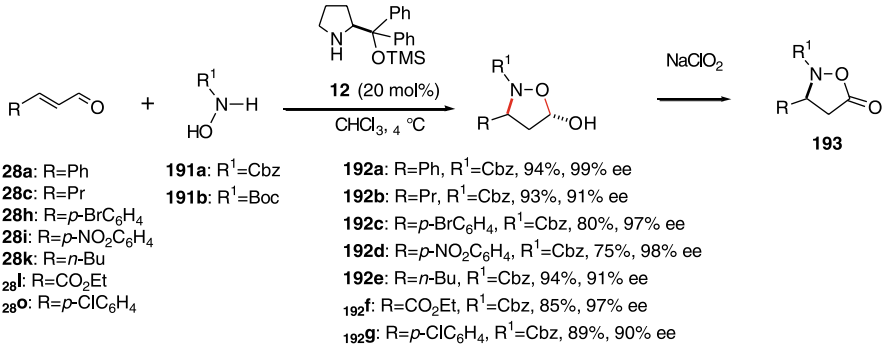
Scheme 3.59 Organocatalyzed dipolar cycloadditions between nitrones and dipolarophiles

nitrones to cyclopent-1-enecarbaldehyde [76]. More recently, the similar reaction was reported by Nevalainen et al., and the catalyst **12**-HOTf was applied in reaction of cyclopentene carbaldehyde **189** and nitrones **187** to give the isoxazolidine adducts **190** with moderate enantioselectivities, Scheme 3.60 [77].



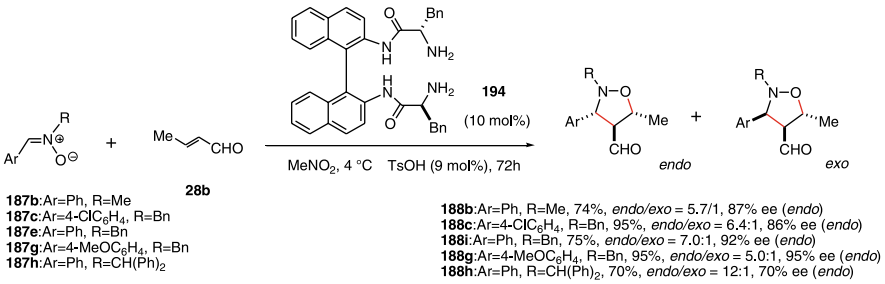
Scheme 3.60 Organocatalytic 1,3-dipolar cycloadditions of nitrones to cyclopent-1-enecarbaldehyde

In 2006, Córdova and his co-workers reported the organocatalytic asymmetric reaction of *N*-Boc-protected hydroxylamine **191** and α,β-unsaturated aldehyde **28**. The reaction provided access to 5-hydroxyisoxazolidines **192** and β-amino acids, Scheme 3.61 [78].



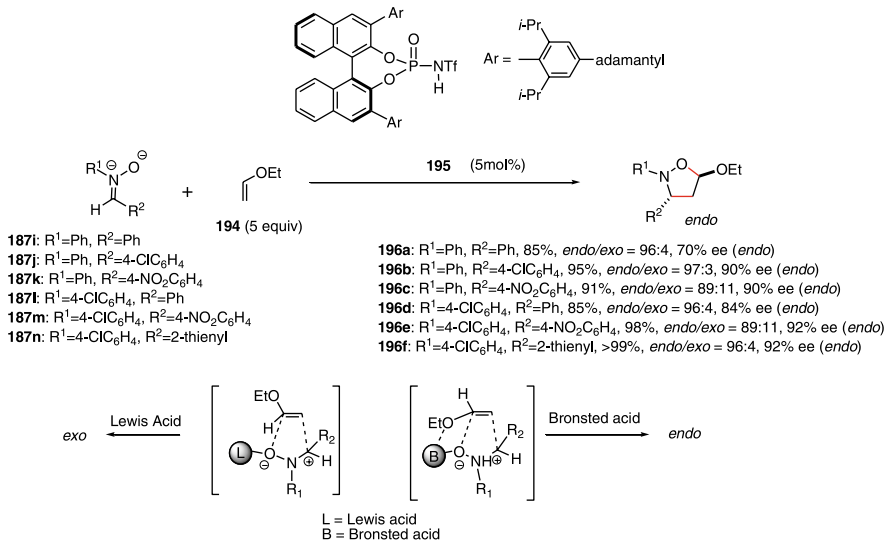
Scheme 3.61 Organocatalytic asymmetric reaction of *N*-Boc-protected hydroxylamine **191** and α,β-unsaturated aldehyde **28**

Jurczak and co-workers reported hybrid diamines derived from 1,1′-binaphthyl-2,2′-diamine and α-amino acids as organocatalysts for 1,3-dipolar cycloaddition of aromatic nitrones **187** to (*E*)-crotonaldehyde **28b**, Scheme 3.62 [79]. The L-phenylalanine-based 1,1′-binaphthyl-2,2′-diamine (BINAM) catalyst **194**, with trifluoromethanesulfonic acid as an additive, afforded the optimal results with good endo-diastereoselectivity and enantioselectivity up to 95% ee.



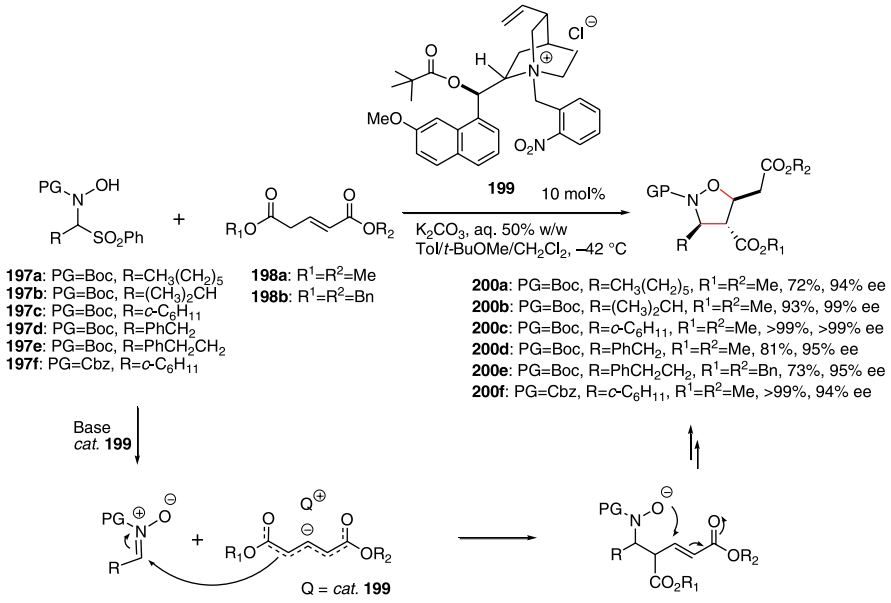
Scheme 3.62 Organocatalytic 1,3-dipolar cycloaddition of nitrones to crotonaldehyde

An enantioselective 1,3-dipolar cycloaddition of nitrones **187** with ethyl vinyl ether **194** catalyzed by Brønsted acid catalyst **195** was reported by Yamamoto and co-workers, Scheme 3.63 [80]. Only 5 mol% of this air-stable catalyst was used, and the reactions were completed within 1 h. The *endo*-selectivity of this cycloaddition is different to the previously reported *exo*-selectivity of the aluminum-catalyzed reaction (Lewis acid catalysis).



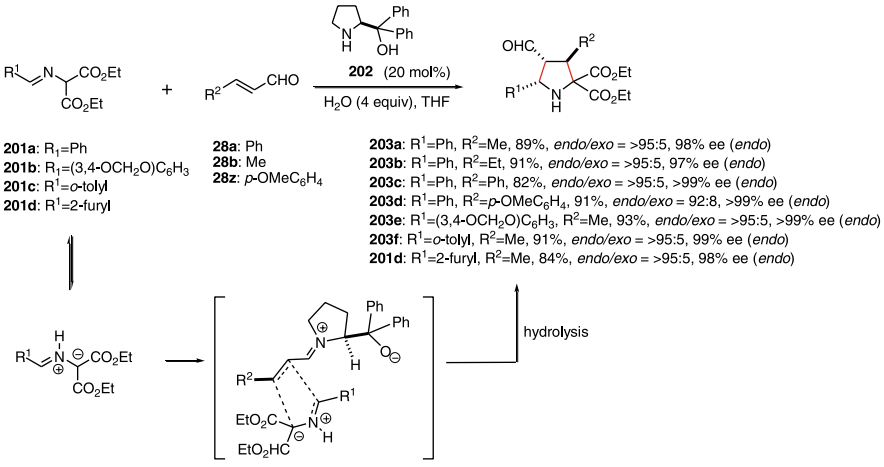
Scheme 3.63 Organocatalytic 1,3-dipolar cycloadditions of diaryl nitrones and ethyl vinyl ether

An organocatalytic enantioselective [3 + 2] cycloaddition of α,β-unsaturated esters **198** with in situ-generated *N*-carbamoyl nitrones was reported by Fini and their co-workers, Scheme 3.64 [81]. The process provided the *N*-Boc- and *N*-Cbz-protected isoxazolidines in good yields and enantioselectivities.



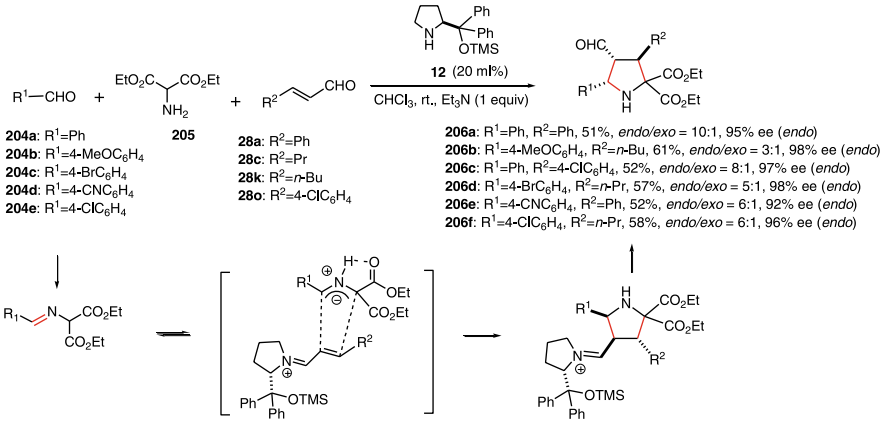
Scheme 3.64 Organocatalytic [3 + 2] cycloaddition of glutaconates with in situ-generated *N*-carbamoyl nitrones

Vicario, et al. reported the first organocatalytic enantioselective [3+2] cycloaddition reaction between α,β-unsaturated aldehydes **28** and azomethine ylides, generated in situ from imines **201**, Scheme 3.65 [82]. Efficient shielding of the *Si* face of the iminium intermediate by the bulky group of catalyst **202** lead to a stereoselective *Re*-face and *endo*-type approach of the (*E*)-1,3-dipole, and provide pyrrolidine **203** with high diastereoselectivity and enantioselectivity.

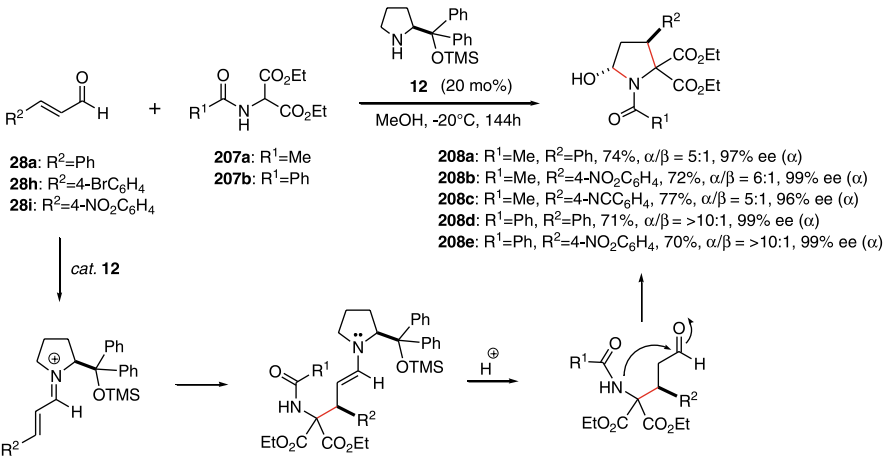


Scheme 3.65 Organocatalytic enantioselective [3+2] cycloaddition of azomethine ylides and α,β-unsaturated aldehydes

Subsequently, the one-pot organocatalytic [C+NC+CC] coupling reaction between aldehydes **204**, dialkyl-2-aminomalonate **205** and α,β-unsaturated aldehydes **28** was achieved with highly chemo-and enantioselectivity by Córdova, et al., Scheme 3.66 [83]. The mechanism involved the 1,3-dipolar cycloaddition of azomethine ylide and chiral iminium intermediate, via *re*-facial and *endo*-addition to give the pyrrolidine derivatives. Later, the authors reported a similar approach to 5-hydroxypyrrolidine **208** from acylaminomalonates **207** and α,β-unsaturated aldehydes **28**, Scheme 3.67 [84].

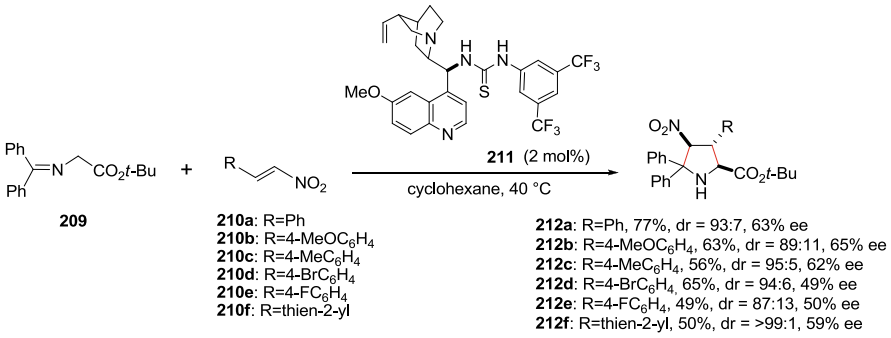


Scheme 3.66 Organocatalytic asymmetric multi-component synthesis of highly functionalized pyrrolidine derivatives



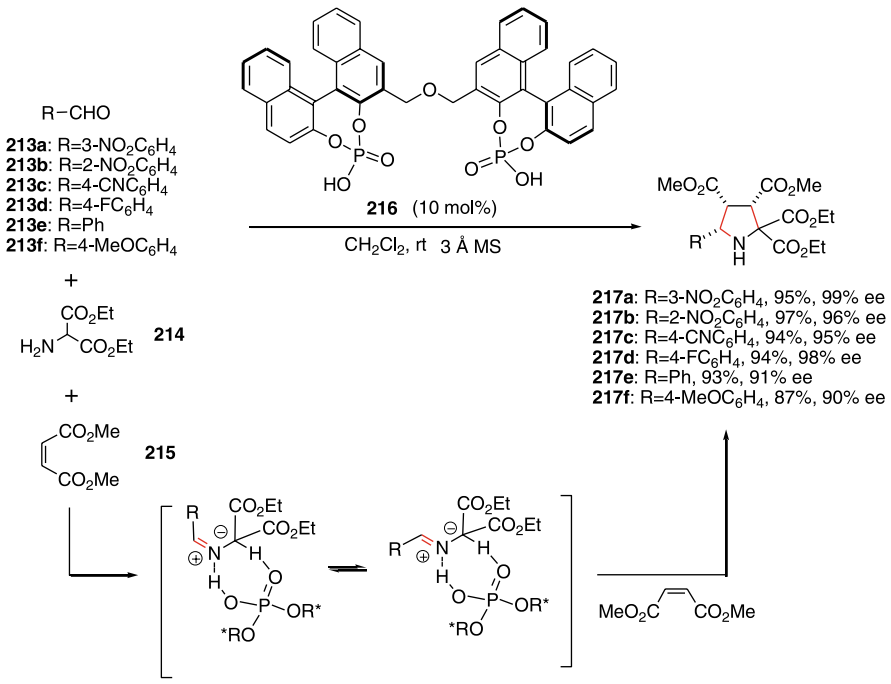
Scheme 3.67 Enantioselective organocatalytic [3+2] reaction between 2-acylaminomalonates and α,β-unsaturated aldehydes

The first chiral thiourea-catalyzed stereoselective 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes **210** was reported by Gong, et. al., Scheme 3.68 [85]. This reaction afforded highly substituted pyrrolidines **212** with high diastereoselectivities and moderate enantioselectivities.



Scheme 3.68 Organocatalytic 1,3-dipolar cycloadditions of azomethine ylide generated from imine **209** with nitroalkenes

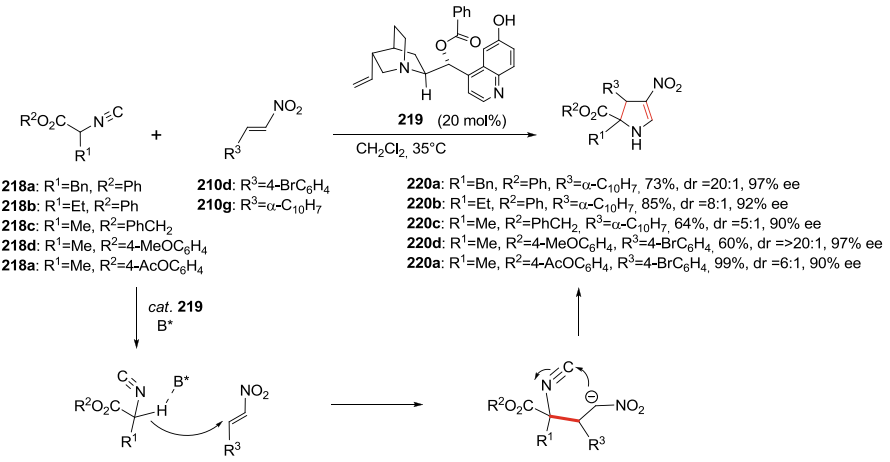
Also, Gong and co-workers reported a Brønsted acid catalyzed three-component asymmetric 1,3-dipolar cycloaddition reactions between aldehydes **213**, amino esters **214**, and dipolarphiles **215** by catalyst **216**, providing pyrrolidines **217** in high yields with excellent enantioselectivity, Scheme 3.69 [86]. The methodology introduced a concept that stereochemistry can be controlled by use of a chiral Brønsted acid (BH), *e.g.*, phosphoric acid. The chiral BH provided sufficient acidity



Scheme 3.69 Organocatalytic three-component 1,3-dipolar cycloaddition

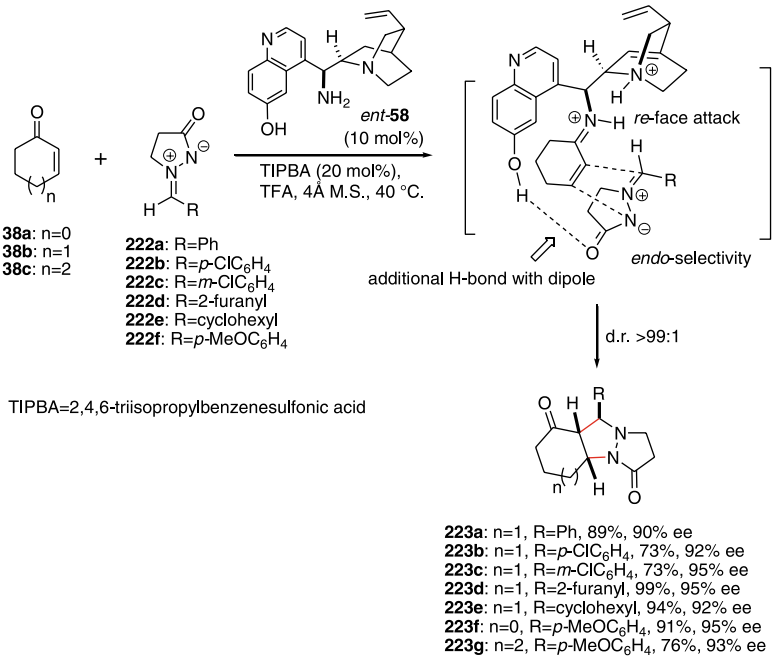
required for forming a chiral azomethine ylide dipole with an azomethine compound (generated *in situ*), which underwent the enantioselective 1,3-dipolar cycloaddition with dipolarphiles. The methodology provides a rapid diversity-oriented synthesis of chiral pyrrolidine derivatives.

An organocatalytic asymmetric formal [3 + 2] cycloaddition reaction of isocyanoesters **218** to nitroolefins **210** leading to highly optically active dihydropyrroles **220** was reported by Gong, et al., Scheme 3.70 [87]. The proposed mechanism is depicted in Scheme 3.70; the cinchona alkaloid chiral base **219** promote an asymmetric Michael addition of isocyanoesters to electron-deficient olefins (nitroolefins), and subsequent intramolecular cyclization of the intermediate to afford the dihydropyrroles **220**.

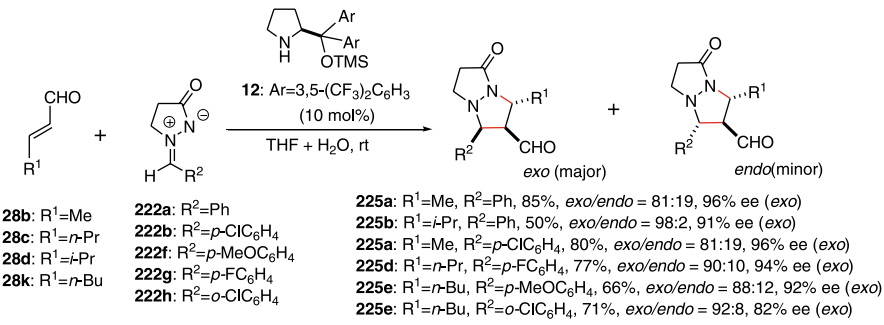


Scheme 3.70 Organocatalytic [3 + 2] cycloadditions of α-substituted isocyanoesters with nitroolefins

Chen, et al., developed the organocatalytic and enantioselective 1,3-dipolar cycloaddition of cyclic enones **221** and azomethine imines **222**, by employing multifunctional primary amine catalysts derived from cinchona alkaloids, Scheme 3.71 [88]. The essential factor for excellent stereoselectivity is the synergic hydrogen-bonding interaction of catalyst and 1,3-dipole during the addition steps. The methodology provided the first example of the organocatalytic enantioselective [3 + 2] cycloaddition of enones. Previously, Chen and his co-workers have reported the organocatalytic and stereoselective [3 + 2] cycloaddition of azomethine imines with α,β-unsaturated aldehydes, Scheme 3.72 [89].

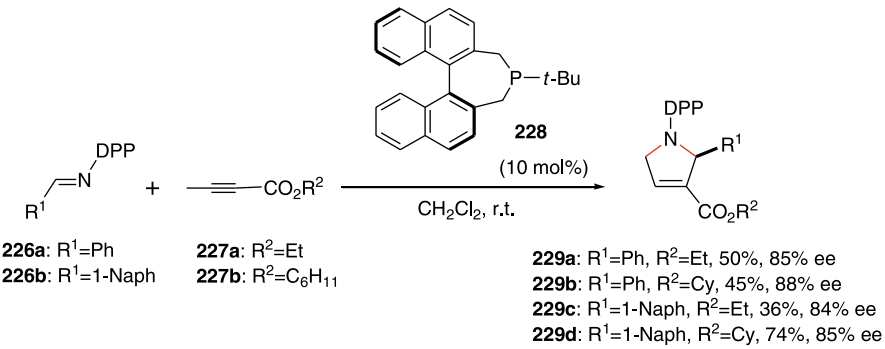


Scheme 3.71 Organocatalytic and enantioselective 1,3-dipolar cycloaddition of cyclic enones and azomethine imines



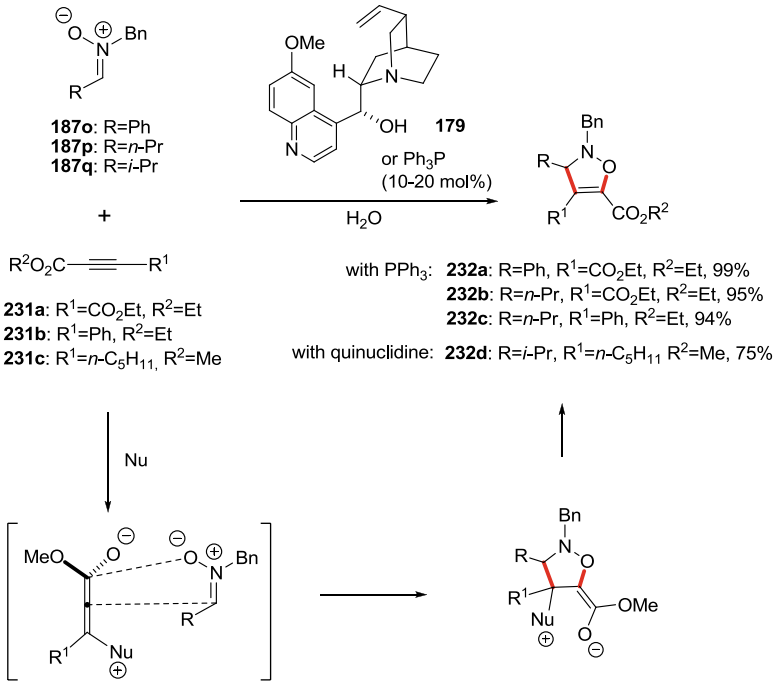
Scheme 3.72 Organocatalytic enantioselective [3+2] cycloaddition of azomethine imines with α,β-unsaturated aldehydes

An enantioselective [3+2] cycloaddition of *N*-DPP-imines **226** with 2-butynoates **227** promoted by (*S*)-binaphthophosphepine (*cat*. **228**), affording the pyrrolines **229** was reported by Marinetti, et al. Scheme 3.73 [90].



Scheme 3.73 Enantioselective [3 + 2] cycloaddition of N-DPP-imines and 2-butynoates promoted by binaphthosphepine (DPP – diphenylphophinoyl)

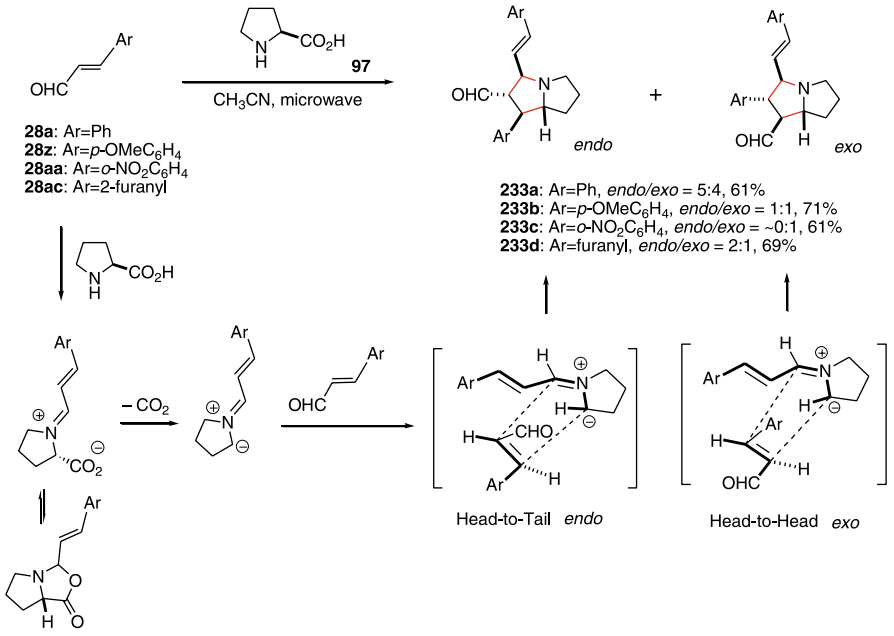
García-Tellado and his coworkers have reported an organocatalyzed 1,3-dipolar cycloaddition of alkynoate **231** and nitrones **230** in the presence of triphenylphosphane, quinine or quinuclidine "on water" [91], affording 2,3-dihydroxazoles **232**, Scheme 3.74 [92]. Initial addition of the organocatalyst (e.g., quinine, quinuclidine or Ph_3P) to alkynoate **231** generated the zwitterionic allenolate. Regioselective



Scheme 3.74 Organocatalyzed 1,3-dipolar cycloaddition reactions between conjugated alkynoates and nitrones "on water"

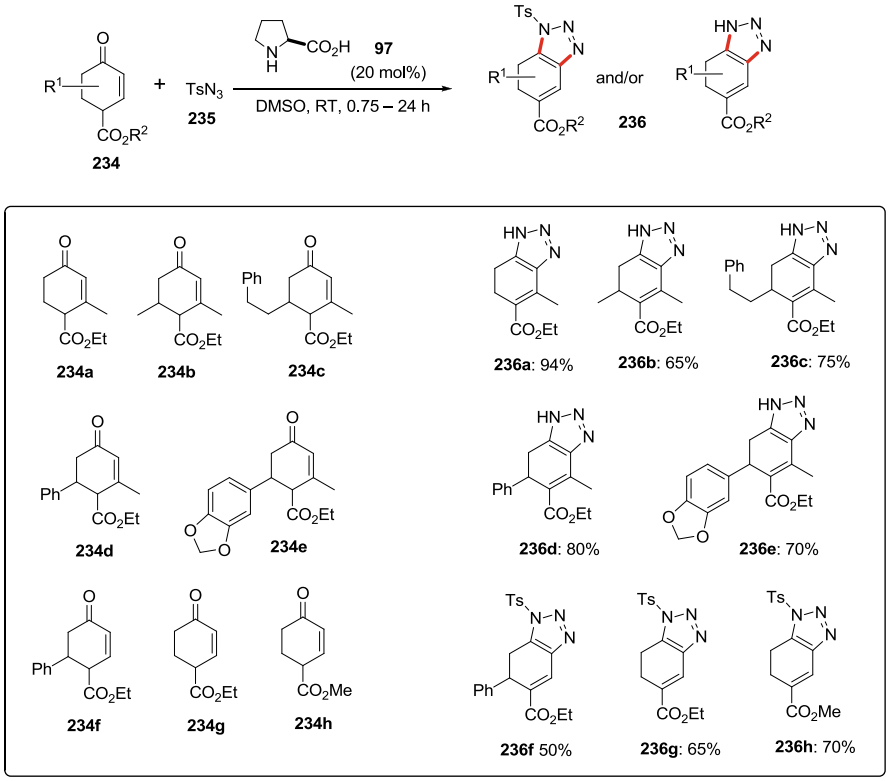
1,3-dipolar cycloaddition (1,3-DCR) of this dipolarphile intermediate and nitrone provided the adducts **232**. However, no enantioselectivity data were provided in the papers. In addition, the reactions with methyl propiolate, an acyclic adduct, propargylic *N*-hydroxylamine, arising from the 1,2-addition reaction, was obtained along with the 1,3-DCR adduct. A detail study in revealing the reaction mechanistic cycles was presented in that paper.

A proline-mediated dimerization of cinnamaldehyde via 1,3-dipolar decarboxylative cycloaddition reaction with azomethine ylides was reported by Hong, and his co-workers, Scheme 3.75 [93]. The method provides an efficient route to highly functionalized hexahydro-1*H*-pyrrolizine **233**. The high diastereoselectivity (two out from the eight possible diastereoisomers) of this dipolar cycloaddition can be realized as illustrated by a plausible mechanism in Scheme 3.75. Initial formation of iminium or oxazolidinone by reaction of α,β-unsaturated aldehyde **28** and proline provide a non-stabilized cyclic azomethine ylides, followed by 1,3-dipolar cycloaddition with another α,β-unsaturated aldehyde **28** to give the adducts **233**. The dipole approaches cinnamaldehyde in that way, where all substituents, including CHO, CH=CHPh, and Ph tend to be away from each other but aligned with H on the same side for less steric hindrance, giving the two adducts.



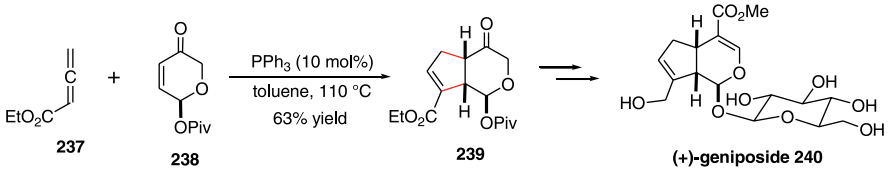
Scheme 3.75 Proline-mediated dimerization of cinnamaldehyde via 1,3-dipolar decarboxylative cycloaddition reaction with azomethine ylides

Ramachary and his co-workers reported a proline-catalyzed cascade [3+2]-cycloaddition/hydrolysis reactions for the synthesis of highly functionalized *N*H-1,2,3-triazoles, Scheme 3.76 [94].



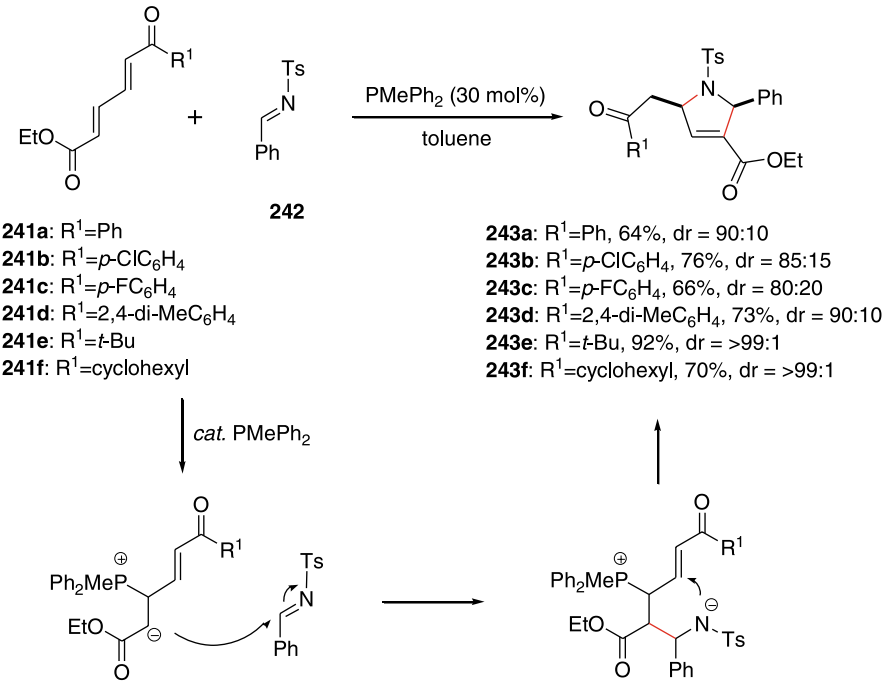
Scheme 3.76 Organocatalyzed cascade [3 + 2] cycloadditions for the synthesis of *N*H-1,2,3-triazoles

The phosphane catalyzed [3 + 2] cycloaddition between allenoates and activated alkenes have attracted extensive attention since its discovery [95, 96]. Recently, in 2009, Krische and his co-worker reported a phosphane-catalyzed [3 + 2] cycloaddition of ethyl-2,3-butadienoate **237** with an enone **238** to give the *cis*-fused cyclopenta[*c*]pyran **239**. They applied this methodology to the total synthesis of the iridoid β-glucoside (+)-geniposide **240**, Scheme 3.77 [97]. Alternatively, phosphane-catalyzed [3 + 2] annulation of allenoates with aldehydes, affording 2-alkylidenetetrahydrofurans, was reported by He and his co-workers [98].



Scheme 3.77 Phosphane catalyzed [3 + 2] cycloaddition between allenoates and activated alkenes.

Likewise, a highly diastereoselective access to trisubstituted 3-pyrrolines by alkylphosphane-promoted [3+2] annulation of conjugate diene **241** and *N*-tosylbenzaldimine **242** was reported by Marinetti and his co-workers, Scheme 3.78 [99].

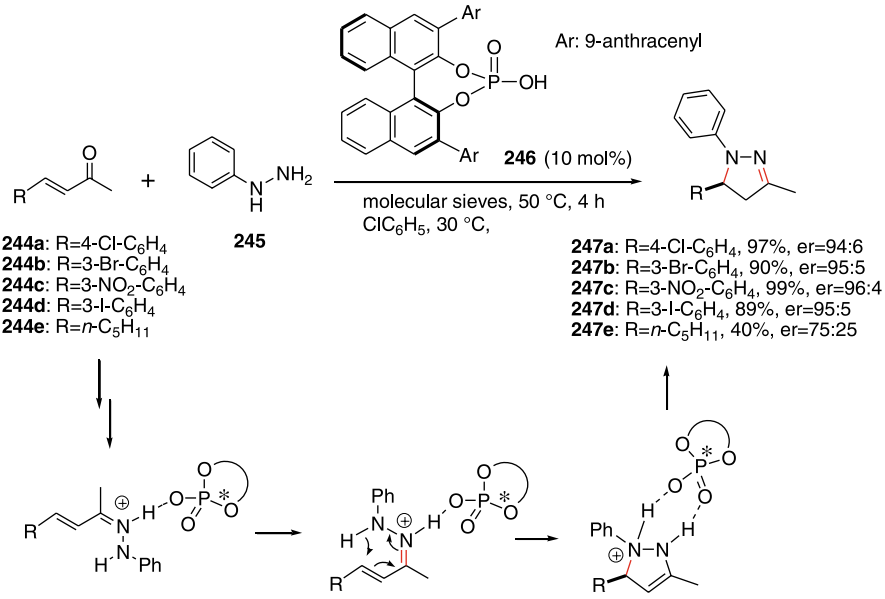


Scheme 3.78 Phosphane catalyzed [3+2] cycloaddition of 6-oxodienoates and imine

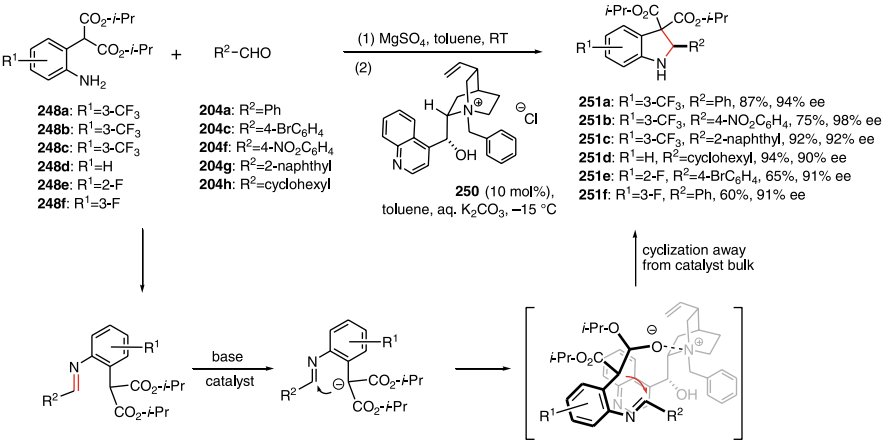
3.4 Electrocyclization

List and Müller reported a Brønsted acid catalyzed asymmetric 6π electrocyclization of benzylideneacetone-derived phenylhydrazone. These compounds were prepared *in situ* from α,β-unsaturated enones **244** and phenylhydrazine **245**, to give 2-pyrazolines **247** in high yields and enantioselectivities, Scheme 3.79 [100].

Smith, et al. developed an organocatalyzed 6π electrocyclization of benzaldimines, as precursors to 2-aza-pentadienyl anions, prepared *in situ* from anilines **248** and aldehydes **249**, to give functionalized indolines in high yields and enantioselectivities, Scheme 3.80 [101].



Scheme 3.79 Enantioselective synthesis of 2-pyrazolines starting from α,β-unsaturated ketones and phenylhydrazine

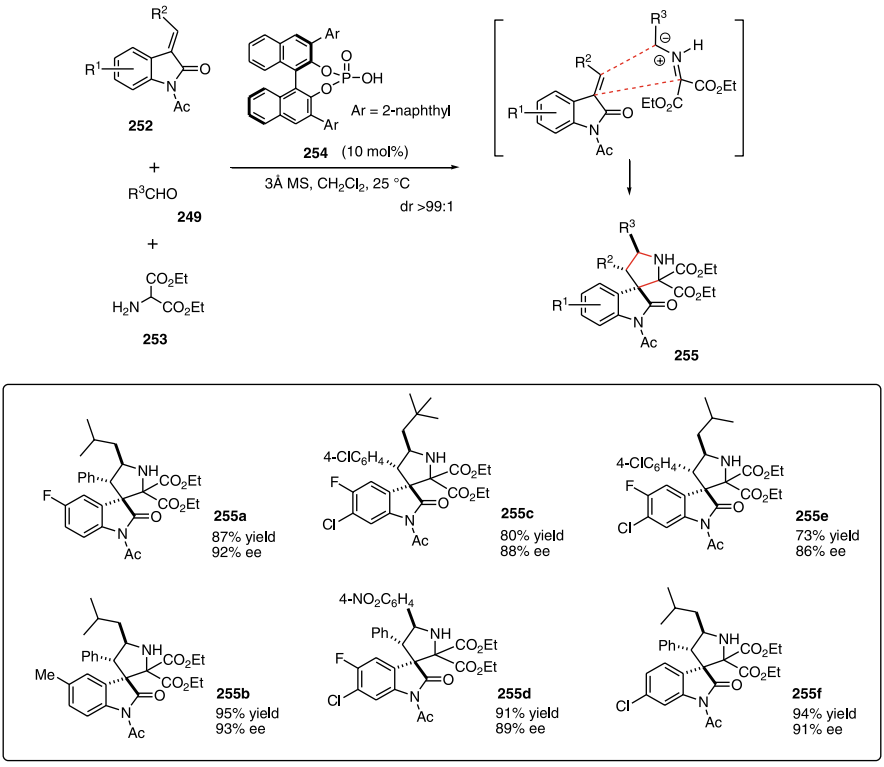


Scheme 3.80 Organocatalytic asymmetric 6π electrocyclization

3.5 Multicomponent Reactions [102]

An asymmetric organocatalytic three-component 1,3-dipolar cycloaddition of methyleneindolinones **252** with aldehydes **249** and amino malonates **253**, catalyzed by phosphoric acid **254**, affording compounds **255** with spirooxindole skeleton was

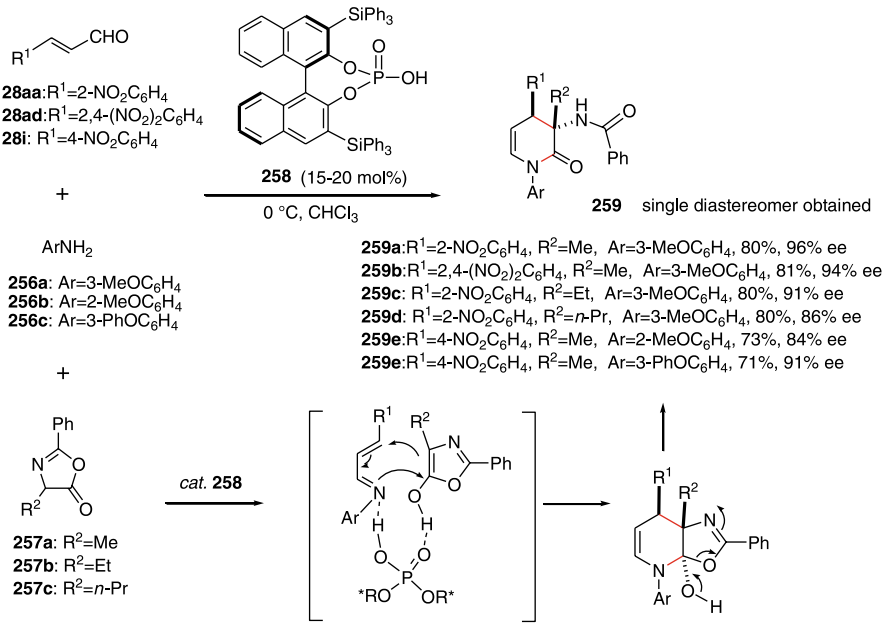
developed by Gong and his co-workers, Scheme 3.81 [103]. Theoretical calculations of the reaction revealed that both the azomethine ylide and the methyleneindolinone are hydrogen-bonded with the phosphoric acid, which resulted in the high enantio- and regioselectivity.



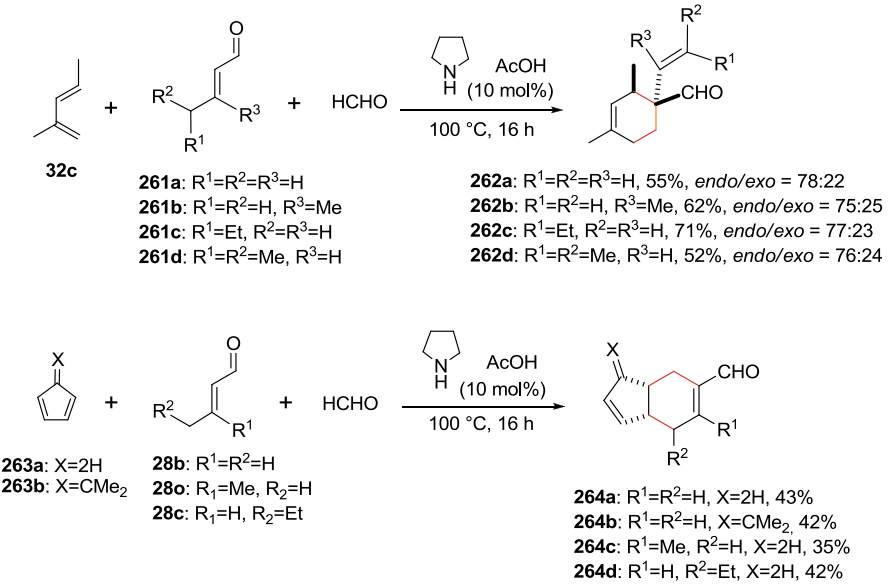
Scheme 3.81 1,3-Dipolar cycloaddition reactions for synthesis of spiro[pyrrolidin-3,3′-oxindole] derivatives

Gong, et al. reported a phosphoric acid derivative **258** catalyzed asymmetric three-component formal [4 + 2] cycloaddition reaction of azlactones **257**, α,β-unsaturated aldehydes **28**, and primary amines **256** to give the 3-amino-3, 4-dihydropyridinones **259** with high enantioselectivities (up to 96% ee), Scheme 3.82 [104].

An organocatalytic diastereoselective multicomponent α-methylenation/Diels-Alder reaction to 4-vinylcyclohexenecarbaldehyde derivatives **262** was reported, Scheme 3.83 [105].

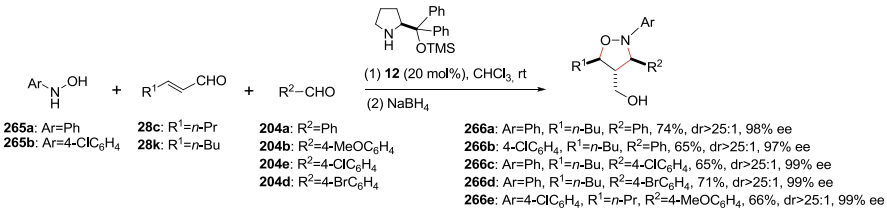


Scheme 3.82 Asymmetric three-component [4+2] cycloaddition reaction of azlactones, α,β-unsaturated aldehydes, and primary amines



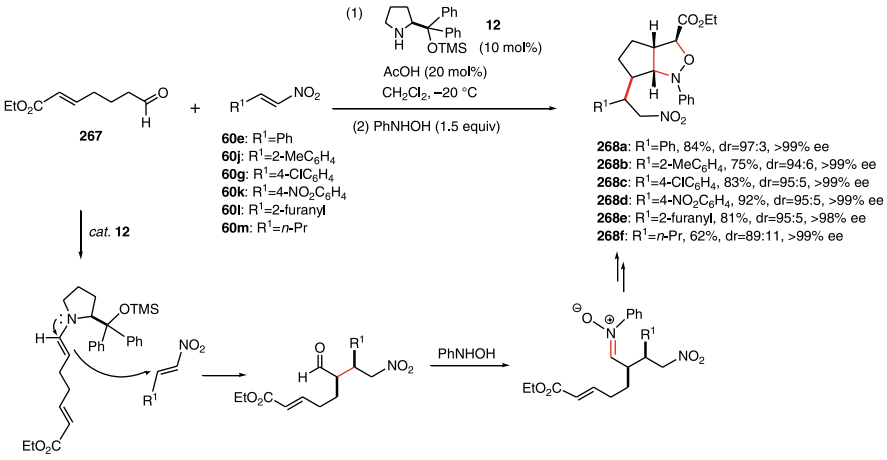
Scheme 3.83 Organocatalytic domino α-methylenation/Diels–Alder reactions of α,β-unsaturated aldehydes with dienes and formaldehyde

Córdova and co-workers developed a highly enantioselective three-component synthesis of isoxazolidines **266.** The reactions were carried out between *N*-arylhydroxylamines, aldehydes and α,β-unsaturated aldehydes, Scheme 3.84 [106].



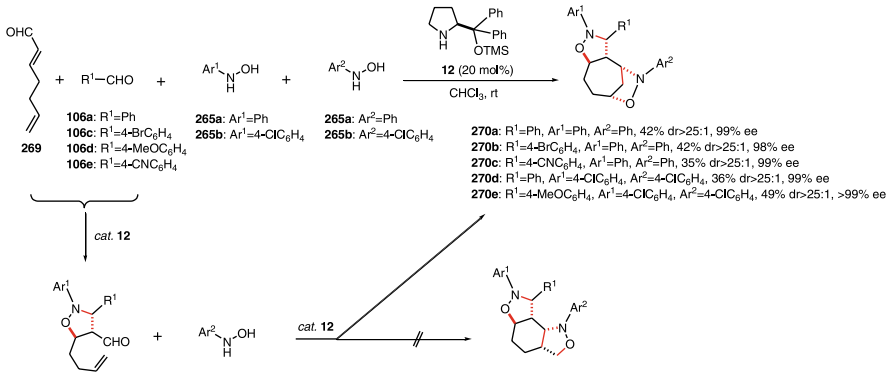
Scheme 3.84 Organocatalytic three-component synthesis of isoxazolidines

A one-pot synthesis of bicyclic isoxazolidines with five stereogenic centers by catalyst **12** was reported by Zhong and his co-workers, Scheme 3.85 [107]. This domino sequence involved Michael reaction of 7-oxohept-2-enoate **267** to nitroolefins **60** [108] and subsequent intramolecular nitrone [3+2] cycloaddition to give enantiopure bicyclic isoxazolidines **268**. The methodology can be applied to the synthesis of α-hydroxy-γ-amino acid derivatives.



Scheme 3.85 Organocatalytic one-pot asymmetric synthesis of bicyclic isoxazolidines by domino Michael addition/in situ condensation/intramolecular nitrone [3+2] cycloaddition sequence

Recently, Córdova and co-workers revealed a regiospecific, highly chemo-, diastereo-, and enantioselective one-pot organocatalytic domino reaction of α,β-unsaturated aldehydes **269**, aromatic aldehydes **106**, and phenylhydroxyamine **265**, providing cycloheptane derivatives **270**, Scheme 3.86 [109]. The tandem multicomponent [2+3]/[3+2] cycloaddition afforded six new bonds and five new



Scheme 3.86 One-pot organocatalytic cascade synthesis of bis-oxazolidines

stereogenic centers in one-pot reaction. The seven-membered carbocycles were predominated over the six-membered carbocycles in these reactions due to a combination of steric and substitution effects of the [3 + 2] cycloaddition.

3.6 Conclusions

The organocatalyzed cycloaddition reactions summarized in this review are remarkable examples of stereoselective reactions. It is encouraging that most of the reactions were catalyzed by simple small organic molecules. Some products generated through a series of cascade, domino or tandem reactions, with the construction of multiple bonds and chiral centers in a one-pot operation. All these transformations have been dedicated to the complex reactions with carefully designed of the catalysts as well as the functional groups on the reaction substrates. Nevertheless, much works still need to be invested in developing better cycloaddition reactions with highly enantioselective multi-bond formations, and the applications in efficient synthesis of biologically interest natural and unnatural molecules. It is without any doubt that this subject will continue to thrive for years to come.

Acknowledgements Financial support from the National Science Council, Taiwan, is gratefully acknowledged.

References

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Chapter 4
Enantioselective Intermolecular Aldol Additions and Related Morita-Baylis-Hillman Processes

Gabriela Guillena, Carmen Nájera, and Diego J. Ramón

Abstract Since the thriving use of simple (*S*)-proline as organocatalyst in the intermolecular direct aldol reaction in 2000, new reaction conditions have been investigated with this molecule to overcome the initial reaction inconveniences such as slow reaction rate, high catalyst loading, need of high polar solvents and huge excesses of reagents. At the same time, an arsenal of new catalytic systems have been designed to improve the early reported proline efficiency, increasing the substrate scope of the reaction and facilitating their application to a large scale or natural product synthesis. Throughout this chapter these new inputs for this well-known process as well as the related C-C bond formation Morita-Baylis-Hillman reaction, in which the last step of the overall reaction is also an aldol process, will be discussed.

4.1 Introduction

One of the most ancient C-C bond transformation in organic chemistry is the useful aldol reaction [1, 2], originally reported by Wurtz in 1872 [1b]. Years before this process was described, Kane discovered the related aldol condensation [1a]. In this case, α,β-unsaturated carbonyl compound was obtained by dehydration of the former aldol product. In the aldol reaction, a nucleophile, generally an enolizable carbonyl compound, reacts with itself or with another carbonyl compound acting as electrophile to give a β-hydroxy carbonyl compound

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known as aldol product. This process normally is catalyzed by either basic or acidic compounds. Additionally to the new C-C bond formed, one or more stereogenic centers can also be generated.

In nature, aldolase enzymes use this transformation to produce enantiomerically pure compounds [3]. Other biochemical methods such as the use of antibodies [4] have provided a practical methodology for the synthesis of chiral aldol products. However, both methodologies have a shortage of substrate scope.

Obviously, the application of catalytic enantioselective methods to perform this transformation would enlarge the substrate scope [5], with the discovery of the Mukaiyama-aldol reaction [6] being a definitely boost for the development of this research area. In this procedure, the use of stoichiometric amounts of bases and silylating reagents for the generation of the required silyl enol ether (or chemical equivalent) is mandatory, thus hampering the achievement of high atom efficiencies [7]. The development of the enantioselective direct aldol reaction [8] has eluded the use of performed enolates and therefore enhanced the efficiency of the process, with organocatalytic methods [9] being in the vanguard of this methodologies.

Another important and useful C-C bond process is the Morita-Baylis-Hillman reaction (MBH-reaction) [10], which can be defined as a reaction of a α,β-unsaturated carbonyl compound, acting as an α-acyl anion, with an aldehyde catalyzed by a tertiary amine or phosphine, providing the access to α-methylene-β-hydroxycarbonyl compounds. This reaction involves a sequence of a nucleophilic attack of the catalyst to the Michael acceptor, an aldol reaction of the zwitterionic intermediate with the aldehyde, which generates two stereogenic centers and finally a β-elimination with regeneration of the catalyst. Therefore, a great effort has been made to achieve the corresponding asymmetric α-methylene-β-hydroxycarbonyl products [11], being several organocatalyst successfully applied to perform this task.

The aim of this chapter is revised the use of enantioselective organocatalytic aldol reactions [12] and the related MBH-reaction giving an comprehensive overview of the catalysts, as well as protocols, results and disadvantages providing a useful tool to find the best solution to a precise process and devise unexplored areas of study.

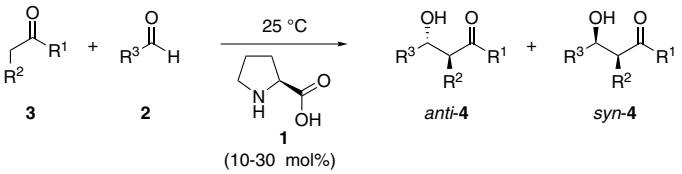
4.2 Proline as Organocatalyst

Probably (*S*)-proline (**1**) is the most used organocatalyst, being applied in ample spectra of asymmetric reactions with excellent results in a variety of reaction conditions. Its application in the intermolecular direct aldol reaction marked a breakthrough in the organocatalysis research area. In this section the use of proline in different aldol processes will be divided according to the nature of the nucleophilic and electrophilic partner used.

4.2.1 Ketones as Source of Nucleophile

4.2.1.1 Aldehydes as Electrophiles

Although the use of proline as catalyst in the intramolecular aldol reaction was known since 1971 [13], its use in the intermolecular aldol reaction between ketones **3** and aldehydes **2** to give aldol adducts **4** was not reported until the beginning of this century (Scheme 4.1) [14]. In order to prevent several side reactions such as self-condensation of aldehyde, or the formation of the oxazolidinone derived from proline and the aldehyde, a great excess of ketones **3** was used. This high amount of ketone also moves the whole process, which consist in a series of equilibriums, to the aldol product. Best results were obtained in the reaction between α-substituted aldehydes such as isobutyraldehyde (**2a**), but when linear aldehydes such as *n*-valeraldehyde (**2c**) were used a significant amounts of the side-product enone were obtained. The use of cyclic ketones such as cyclohexanone (**3b**) and cyclopentanone as source of nucleophile gave modest diastereoselectivities (*ca.* 60%) and similar enantioselectivities, with the *anti*-isomer **4** being the main diastereoisomer. The reaction took place at the less substituted position, when asymmetric ketones such as butanone were used. Under these reaction conditions, the reaction with dialkyl ketones such as 3-pentanone, cyclohexyl methyl ketone, isopropyl methyl ketone, 3-methyl-2-butanone and cyclopropyl methyl ketone with *p*-nitrobenzaldehyde failed [14c].



3a: R^1 = Me, R^2 = H **2a**: R^3 = *i*-Pr
3b: R^1,R^2 = $(CH_2)_4$ **2b**: R^3 = 4-$NO_2C_6H_4$
2c: R^3 = $CH_3(CH_2)_4$

4a: R^1 = Me, R^2 = H, R^3 = *i*-Pr, 97%, 96% ee
4b: R^1 = Me, R^2 = H, R^3 = 4-$NO_2C_6H_4$, 68%, 78% ee
4c: R^1 = Me, R^2 = H, R^3 = $CH_3(CH_2)_4$, 35%, 73% ee
4d: R^1,R^2 = $(CH_2)_4$, R^3 = 4-$NO_2C_6H_4$, 65%, 63% de, 86% ee

Scheme 4.1 L-Proline intermolecular aldol reaction

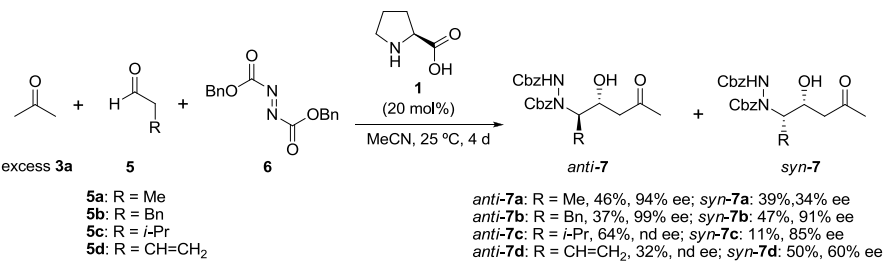
4-Methyl-4-hydroxy-2-pentanone (diacetone alcohol) could be used as nucleophile instead of acetone (**3a**) [15], giving the expected aldol products **4** (R^2 = H) with lower enantioselectivities (48–86% ee). A tandem organo- and biocatalytic process has been designed [16], with the aim of improving the achieved enantioselectivities for the α-hydroxy ketones **4** (R^2 = H), using *Pseudomonas cepacia* lipase (Amano I) as catalyst for the kinetic resolution of the mixture of aldol adducts obtained after the proline-catalyzed reaction.

The scope of aldehydes as electrophiles has been extensively studied. For instance, aqueous formaldehyde reacted with only two equiv. of cyclic ketones

catalyzed by **1** (10 mol%), providing the expected products with moderated yield (25–45%) and high enantioselectivity (95–99%) [17]. The use of perfluoroalkyl aldehyde ethyl hemiacetals as electrophiles in the aforementioned reaction has permitted the synthesis of α-hydroxy- α-perfluoroalkyl ketones with good diastereoselectivities for cyclic ketones (88–98% de) and moderated to good enantioselectivities (37–93% ee) [18], using the nucleophilic ketone also as reaction solvent. More complex 1-(phenylsulfanyl)cycloalkanecarbaldehydes reacted with a large excess of aliphatic ketones in DMSO using proline (**1**, 20 mol%) as catalyst to give the corresponding aldol products **4** with yields ranging from 21% to 80% and excellent enantiomeric excesses (up to 99%). After carbonyl reduction and an acid-catalyzed cyclization process, the obtained chiral aldol adducts were further transformed into the corresponding *cis*-fused spirocyclic tetrahydrofurans and cyclopentanones [19].

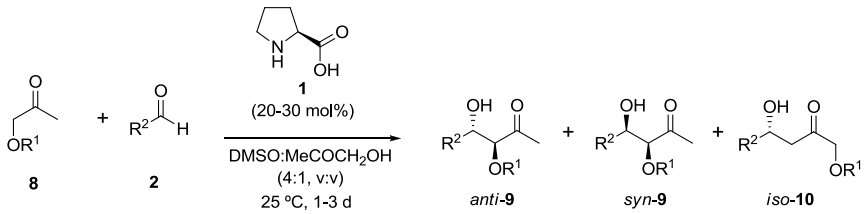
Electrophilic aldehydes have been also generated through a rhodium catalyzed hydroformylation process of alkenes, which has been combined with the aldol addition catalyzed by proline (**1**, 30 mol%) in a tandem reaction sequence, providing the aldol products **4** in good yields (59–86%) and enantioselectivities (71–83%), but with low diastereoselectivities [20].

A more complex process was the multicomponent reaction [9u, 21] between acetone (**3a**), benzyl azodicarboxylate (**6**) and enolizable aldehydes **5** (Scheme 4.2) [22] catalyzed by substoichiometric amounts of (*S*)-proline (**1**). The higher reactivity of the aldehydes over acetone (about 100-fold) towards the azodicarboxylate, led to the formation of an α-amino aldehyde derivative which was the electrophilic partner for the further aldol reaction. The low diastereomeric ratio (*ca.* 1:1) of the products **7** was attributed to the easy and fast racemization of the initial formed α-amino aldehyde, compare to its reaction with acetone. Notwithstanding, this strategy has been used in the synthesis of a rennin inhibitor.



Scheme 4.2 Multicomponent reaction catalyzed by L-proline

The scope of ketones as nucleophilic source has been also extensively investigated. Thus, the use of α–functionalized ketones such as an excess of α-hydroxyacetone (**8a**: R^1 = H, 29.2 equiv. in Scheme 4.3) has permitted the access to chiral compounds with a high interest. When α-substituted aliphatic aldehydes were used as electrophiles, the *anti*-**9** isomer was the main/only isolated product, with excellent regio-, diastereo- and enantioselectivities (up to 99%) being obtained. Aromatic,



8a: R^1 = H
8b: R^1 = TBS
8c: R^1 = Me

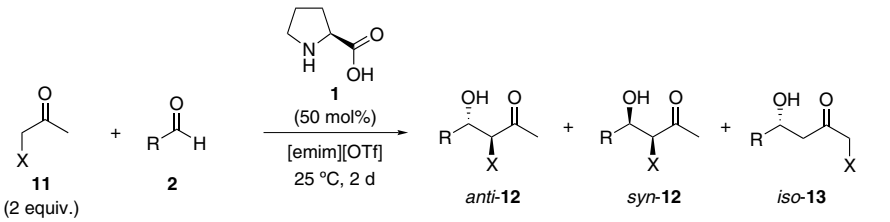
2a: R^2 = *i*-Pr
2d: R^2 = 2-ClC_6H_4
2e: R^2 = $(CH_3)_3CHCH_2$
2f: R^2 = 4-ClC_6H_4

9a: R^1 = H, R^2 = *i*-Pr, 62%, 90% de, > 99% ee
9b: R^1 = H, R^2 = *i*-Pr, 95%, 20% de, 67% ee
9c: R^1 = H, R^2 = $(CH_3)_3CHCH_2$, 38%, 26% de, 97% ee
9d: R^1 = TBS, R^2 = 4-ClC_6H_4, 77%, 14% de, 72% ee

Scheme 4.3 L-Proline aldol reaction between α-alkoxyketones and aldehydes

linear aliphatic aldehydes, and chiral (*R*)-glyceraldehyde derivatives led to significant lower results, being the regioisomeric product *iso*-**10** only detected in low yields. A known *anti*-**9** D-tagatose derivative was obtained using (*R*)-2,3-*O*-(isopropylidene) glyceraldehyde as electrophile (40%, 66% de, > 97% ee) [14, 23]. Under the same reaction conditions, [*tert*-butyl(dimethyl)silyloxy]acetone (**8b**: R^1 = TBS, Scheme 4.3) reacted with several aromatic aldehydes giving mainly product *anti*-**9** with enantioselectivities ranging from 28% to 95% [24]. Unexpectedly, the regioisomeric compound *iso*-**10** was the major product when α-substituted–α,β-unsaturated aldehydes were used as electrophiles (10–95% ee).

Generally a high excess of ketone was used in all these processes. This was not an economical or practical problem when simple and volatile ketones were used as nucleophiles, but could be a severe drawback when more sophisticated ketones were used. The use of ionic liquid such as 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate ([emim][OTf]) [25] has allowed to reduce the amount of ketones used. Thus, the reaction of α–hydroxyacetone (**8a**: R^1 = H), as well as α-methoxyacetone (**8c**: R^1 = Me) with *p*–(trifluoromethyl)benzaldehyde derivatives gave a mixture of three possible isomers of type **9** and **10** with mediocre diastereoselectivities (no enantioselectivities were reported). Under this reaction conditions, α-chloro- (**11a**) and α-fluoroacetone (**11b**) were used as source of nucleophile (Scheme 4.4),



11a : X = Cl
11b : X = F

2g: R = Ph
2h: R = 4-$CF_3C_6H_4$

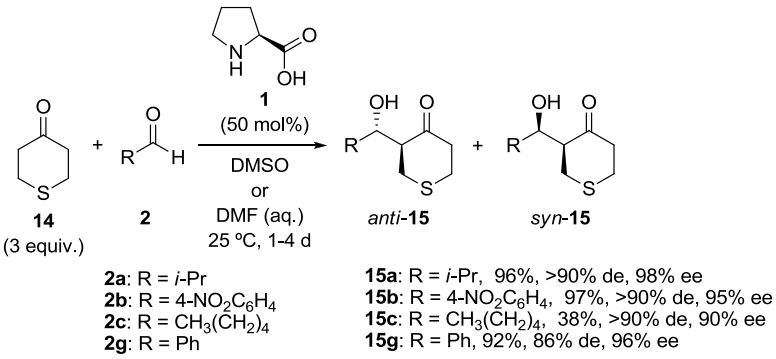
12a: X = Cl, R = Ph, 21%, 62% de, 70% ee
12b: X = Cl, R = 4-$CF_3C_6H_4$, 86%, 70% de, 75% ee
12c: X = F, R = 4-$CF_3C_6H_4$, 41%, 56% de, nd ee

Scheme 4.4 L-Proline aldol reaction between α-halogenated ketones and aldehydes

giving a mixture of two isomers **12**. The corresponding (3*R*,4*S*)-*trans*-epoxides were obtained by treatment with triethylamine of the mixture of isomers **12a** (X = Cl) in yields from 69% to 83% and enantioselectivities around 70%, with the related *cis*-epoxides being not detected.

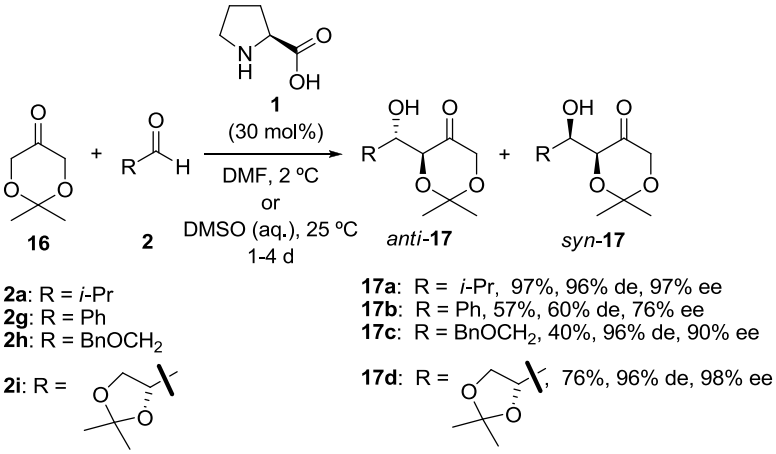
The addition of hexa- and pentasubstituted guanidinium salts as ionic liquids has improved the chemical yields obtained in the reaction between acetone and various aliphatic and aromatic aldehydes catalyzed by proline (**1**, 20 mol%) at −25°C. The corresponding aldol products **4** were obtained with yields ranging from 33% to 82% and enantioselectivities from 48% to 99% [26].

As mentioned before [14c], the use of 3-pentanone as nucleophiles in the direct aldol reaction with aldehydes failed. As an alternative, tetrahydro-4*H*-thiopyran-4-one (**14**) can be used to give mainly the expected products *anti*-**15** (Scheme 4.5), giving after reductive desulphurization using Raney nickel (W-2), the corresponding 5-hydroxy-4-methylpentanone [27].



Scheme 4.5 Aldol reaction between tetrahydro-4*H*-thiopyran-4-one and aldehydes

The use of 2,2-dimethyl-1,3-dioxan-5-one (**16**), a protected dihydroxyacetone, as nucleophile in the aldol reaction with aldehydes allowed the successful enantioselective synthesis of carbohydrates (Scheme 4.6) [28]. While the use of aliphatic α-branched aldehydes as electrophiles and one equiv. of ketone **16** in DMF at 2°C [29], gave good yields, diastereo- and enantioselectivities for product **17**, lower chemical yield was encountered for α-unsubstituted and aromatic aldehydes. When (*R*)-2,3-*O*-(isopropylidene)glyceraldehyde or (*S*)-Garner aldehyde were used as electrophiles, excellent diastereoselectivities were obtained in reactions using (*S*)-proline (**1**) as the catalyst. Thus, proline and these chiral aldehydes represent the match pair. However, the use of sterically demanding or α,α-unsaturated aldehydes, as well as aqueous formaldehyde led to unsuccessful results. This synthetic strategy has been applied for the preparation of partly orthogonal protected aldopentoses and derivatives using ketone **16** with α,α-dimethoxyacetaldehyde as starting materials [29c]. Changing the reaction conditions to aqueous DMSO at 25°C and using 2 equiv. of ketone **16** led to similar results [30]. However, the use of other protected of



Scheme 4.6 Aldol reaction between protected dihydroxyacetone and aldehydes

dihydroxyacetone, such as 1,3-dioxan-5-one or 1,5-dioxaspiro[5.5]undecan-3-one gave lower results [31].

Following this biomimetic route, several ulosonic acid precursors and azasugars (iminocyclitols) have been prepared. Thus, the aldol reaction catalyzed by proline (**1**) between pyruvic aldehyde dimethyl acetal and several aldehydes provided a direct entry for the synthesis of ulosonic and sialic acids, albeit in modest results [32]. The diastereoselective aldol reaction between ketone **16** and chiral protected 3-amino-2,4-dihydroxypentanal gave the corresponding aldol product, which after simple manipulations, such as deprotection and reduction could be transformed into iminocyclitols [33]. In a similar way, the diastereoselective *syn*-aldol reaction of 2-*tert*-butyl-2-methyl-3-dioxan-2-one and (*S*)-isoserinal hydrate, followed by reductive amination and cyclization provided a useful tool for the synthesis of interesting azasugars [34].

In order to avoid some of the general drawbacks of the enantioselective aldol reaction catalyzed by proline such as: (a) the usually required high catalyst loading, (b) the huge excess of starting ketone needed and (c) the long reaction times, some variations from the standard protocols have been reported.

First, the impact of additives in the reaction media was investigated. Although proline-catalyzed aldol reactions (20 mol%) between an excess of ketone and aldehydes were possible in aqueous media [35] using 0.01 M phosphate buffer (pH = 7.4) in the presence of sodium dodecyl sulfate (0.1 equiv.) at 25°C, the expected aldol product **4** was obtained as nearly racemic mixture. In this early study, a shorter reaction time (16–24 h) compared with that registered in only organic medium (1–2 days) was need for the reaction completion. However, the use of mixtures of water and organic solvents as reaction media allowed the synthesis of optically active aldol product. Thus, the reaction of acetone (**3a**) with *p*-nitrobenzaldehyde (**2b**) in DMSO:H_2O (9:1, v:v) gave product **4b** (Scheme 4.1) in 40% ee, whereas the reaction

performed in DMF:H_2O (10:1, v:v) led to the product in 35% ee and carrying the reaction on 1,4-dioxane:H_2O (10:1, v:v), 63% ee was achieved in shorter reaction times. These acceleration allowed to reduce the excess of ketone to a stoichiometric amount. The addition of 100–500 mol% of water to dry DMF afforded the aldol products **4** using only stoichiometric amount of all reagents (**2** and **3**), without interfering on the achieved diastereo- or enantioselectivity [36].

Recently, kinetic and spectroscopic studies gave a mechanistic explanation of the role of water in the aldol reaction with aromatic aldehydes. While the addition of water increases the catalyst concentration by suppression the formation of parasitic species such as the oxazolidinone, decreases the relative concentration of key minimum intermediates by Le Châtelier's principle, shifting the equilibrium towards proline (**1**). The net effect on the reaction rate of these opposing roles would differ when different substrates are used in the reaction, with the intrinsic rate per active catalysts species within the cycle being suppressed by the added water in the aldol reaction of acetone with aromatic aldehydes [37].

The addition of Brønsted/Lewis acids in the aldol reaction has been studied. When chiral camphorsulfonic acid (10 mol%) and proline (20 mol%) were used in a mixture of acetone:water (4:1, v.v; 54.4 equiv. of **3a**) with *p*-nitrobenzaldehyde as electrophile, the expected aldol product **4b** was obtained in 74% yield and 61% ee after only 1 day (compare with results in Scheme 4.1). The same procedure was also applied to reaction**s** of cyclic ketones giving the corresponding products with good enantioselectivities (44–99% ee) [38]. Other additives, such as pyridinium *p*-toluenesulfonate (100 mol%) or lithium chloride (150 mol%) in reactions of ketone **16** and several aldehydes improved ee values from 66% to 92% [39]. Conversely, the presence of either acids, such as acetic and trifluoroacetic acid, or bases, such as DBU or triethylamine, did not produce any substantial improvement when the reaction was performed using acetone in DMF (**3a**, 27.3 equiv.). Notwithstanding the addition of water (100–500 mol%), particularly for cyclic ketones, under these conditions accelerated the reaction and only a slight increase of the observed enantioselectivities were observed [40].

The use of chiral diols as co-catalyst in aldol reaction led to an improvement of the achieved results [41]. Thus, when acetone (**3a**, 8.18 equiv.) was reacted with benzaldehyde (2 h) in DMSO at 0°C catalyzed by (*S*)-proline (30 mol%) the expected product **4** was obtained in 72% ee, while a 96% ee was achieved in the presence of (*R*)-BINOL (0.5 mol%). A hypothetical explanation from the authors for this effect is the possible template effect of the chiral diol which may activate and ordered the aldehyde and enamine nucleophile. The same reason was claimed for the beneficial effect achieved by addition of a 10 mol% of (3,5-bistrifluoromethylphenyl)thiourea in the aldol reaction between cyclohexanone (**3b**) and several aromatic aldehydes catalyzed by proline (**1**, 10 mol%) in hexane a 25°C [42]. In this case, reaction times, yields as well as diastereo- and enantioselectivities were improved (75–98%, 76–88% de, 98–99% ee), with these results being also attributed to the enhancement of the proline solubility by the formation of a host-guest proline-thiourea complex.

Also, the addition of a small amount of ionic liquid such as 1-ethyl-3-methylimidazoliun trifluoroacetate ([emim][CF_3COO], 30 mol%) to the reaction

catalyzed by proline (**1**, 30 mol%) between cyclic ketones and aromatic aldehydes using [bmim][BF_4] (1-*n*-butyl-3-methylimidazolium tetrafluoroborate) as solvent at 25°C in the presence of 10 equiv of water improved the achieved selectivities [43]. The corresponding aldol products were obtained in low to good yields (trace-89%), moderated diastereoselectivities (20–76% de) and high enantioselectivities for the major *anti*-**4** isomer (74–97% ee). Recycling of catalysts and solvent was carried out up to four times without detrimental on the achieved results.

Due to the negative activation volume of the proline-catalyzed aldol reaction, high pressure conditions have been applied. Thus, when 0.2 GPa was used in the reaction between acetone (**3a**) as source of nucleophile and *p*-nitrobenzaldehyde (**2b)** in the presence of proline (**1**, 30 mol%) at 25°C the only observed consequence was the suppression of the formation of the condensation by-product. But, for other aldehydes a slightly improvement on the observed enantioselectivity was produced [44a]. Analogous results were found by inducing high pressure (0.2 GPa) using water-freezing conditions at −20°C [44b].

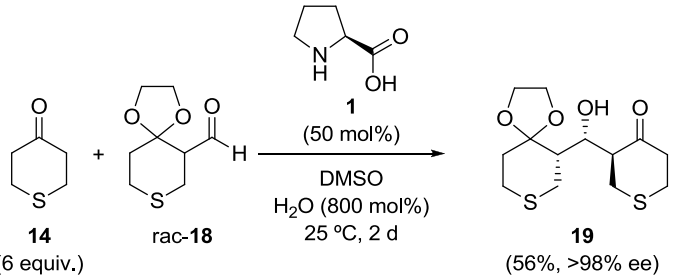
Very short reaction times (15–60 min) were encountered when the aldol reaction was performed under microwave conditions (15 W) with external cooling, affording the aldol products **4** with similar results to those achieved under standard conditions [45].

Recently, ethylene and propylene carbonates have been tested as a sustainable solvents to perform the aldol reaction of acetone and cyclohexanone with aromatic aldehydes under (*S*)-proline (10 mol%) catalysis, giving yields ranging from 12% to 99%, diastereoselectivities up to 100% and enantioselectivities up to 99% [46].

Probably the most convenient modification done for this reaction was the introduction of solvent-free conditions (which differs with the use of a large excess of ketone as source of nucleophile and solvent at the same time, known as neat conditions). The application of ball-milling technique [47] allowed to perform the aldol reaction using only one equiv. of ketone **3** and 10 mol% of (*S*)-proline, in shorter reaction time and in some cases with improved enantioselectivity [48]. Using a conventional magnetic stirring process under solvent-free conditions, 5 equiv. of ketones **3** and 30 mol% of catalyst **1** were required, to give the corresponding aldol products **4** in longer reaction times but with similar enantioselectivities, with the addition of a small amount of water (up to 5 equiv.) having a benign effect on the diastereo- and enantioselectivities. For instance, by reaction of cyclohexanone (**3b**) and *o*-chlorobenzaldehyde without water, the aldol adduct was obtained with 75% de and 84% ee, while 93% de and 97% ee was found adding 500 mol% of water to the reaction mixture [49].

Dynamic kinetic resolution processes (DKR) [50] have been also carried out successfully using (*S*)-proline as catalyst. Thus, racemic atropisomeric *N,N*-diisopropyl-2-formylbenzamide derivatives reacted with excess of acetone (27.3 equiv.) in DMSO at room temperature to gave mixtures of diastereoisomers from 36% to 78% de, with the major diastereoisomer reaching up to 95% ee [51]. In a similar way, DKR of racemic 1,4-dioxa-8-thia-spiro[4.5]decane-6-carbaldehyde (**18**) was performed with an excellent enantioselectivity using ketone **14** as the source of nucleophile (Scheme 4.7) [52]. The protocol has been successfully extended to the related 6,10-dicarbaldehyde, as a mixture of racemic and *meso*-compounds.

Recently, 4-substituted prochiral cyclohexanones (10 equiv.) have been efficiently desymmetrized by their reaction with aromatic aldehydes catalyzed by (*S*)-proline (**1**, 20 mol%) in the presence of 3,5-dimethylphenyl 3,5-bisfluoromethylphenyl thiourea as co-catalyst (20 mol%) in toluene at 25°C [53], affording the corresponding aldol products in good yields (68–87%), diastereoselectivities up to 78% de and in high enantioselectivities (94–99% ee).



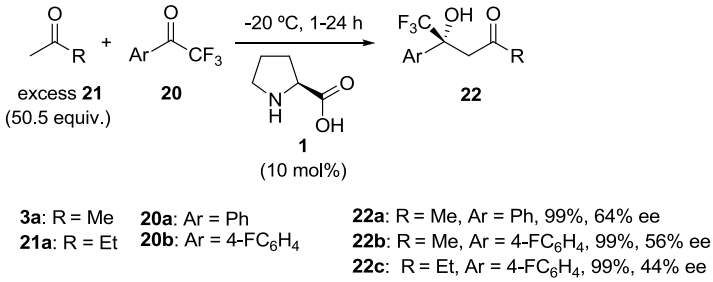
Scheme 4.7 Dynamic kinetic resolution of aldehyde **18** by reaction with ketone **14**

Finally, the organocatalyzed intermolecular aldol reaction using ketones as nucleophiles and aldehydes as electrophiles has been applied to the enantioselective synthesis of compounds with biological interest such as epothilones A-D [54], pheromones derived from chiral 5-hexadecanolide [55], sphingoids [56], antibiotic linezolid [57], the synthesis of a C13-C23 fragment of iriomoteolide-1a [58] and (*S*)-[*n*]-gingerols [59]. A diastereoselective approach of this reaction has been also used starting from chiral aldehydes, such as protected sugars, protected α-aminoaldehydes, 4-formyl-2,2-dimethyloxazolidine (Garner aldehyde), and 4-oxoazetidine-2-carboxaldehydes in order to prepare possible biologically active compounds [60], in the construction of steroid brassinolide side [61] and for the synthesis of carbasugar 1-*epi*-(+)-MK7607 [62].

4.2.1.2 Ketones as Electrophiles

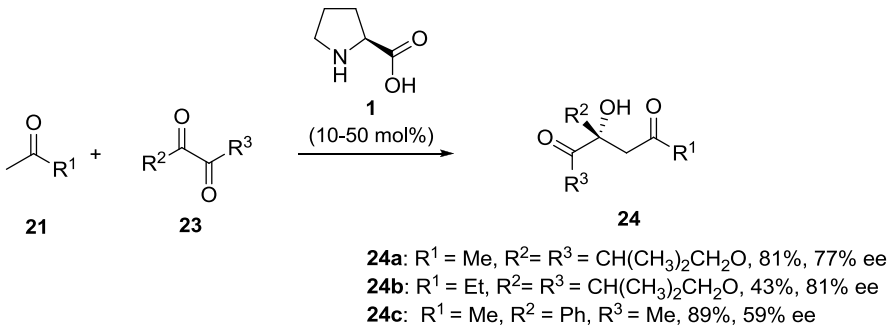
The poor electrophilic character of ketones has hampered their use for the aldol reaction. For this transformation very high active non-enolizable ketones have been used as electrophiles giving chiral compounds bearing tertiary alcohols [63].

α,α,α–trifluoroacetophenones **20** reacted with a huge excess of alkyl methyl ketones **21**, which acted at the same time as source of nucleophile and as solvent, in the presence of substoichiometric amounts of (*S*)-proline (**1**), leading to the expected trifluoromethyl aldol products **22** with modest enantioselectivities (Scheme 4.8). The success of the reaction was determined by nature of the substitution at the aromatic ring of **20** with the presence of an electron-donating group at the *para*-position making the reaction failed, whereas electron-withdrawing groups facilitating it [64].



Scheme 4.8 L-Proline catalyzed aldol reaction between ketones **20** and alkylmethyl ketones

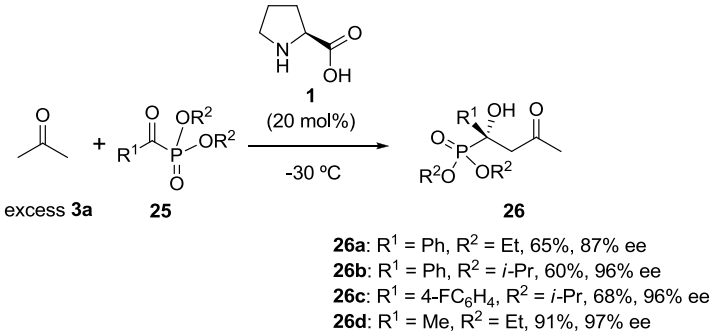
α-Keto carbonyl compounds are adequate to be used as electrophilic partner in this transformation (Scheme 4.9). Acyclic α-keto ester derivatives gave disappointing enantioselectivities, but the results were increased up to 81% ee when the reaction was performed using alkyl methyl ketones **21** (67 equiv.) as source of nucleophile (and as solvent) and α-oxolactones **23a**, **b** [65a]. 1,2-Diketone derivatives **23c** gave better results when were used as electrophiles using DMSO as solvent, with cyclic ketones such as cyclohexanone providing up to 99% ee [65b].



Scheme 4.9 Aldol reaction between α-oxolactones or 1,2-diketones with alkyl methyl ketones

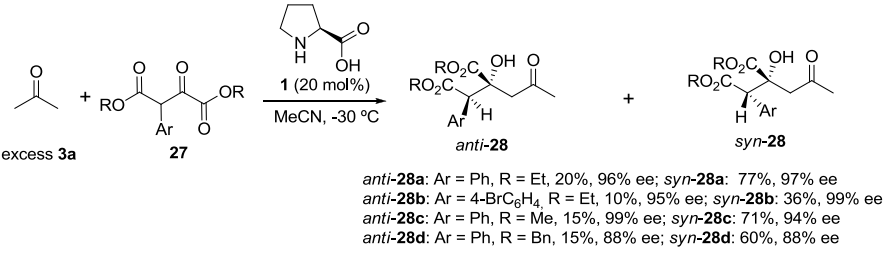
The enantioselective synthesis of α-hydroxy phosphonates **26** could be accomplished with excellent results independently on the nature of ketone substituent R^1 by reaction of acetone (**3a**) with α-keto phosphonates **25** (Scheme 4.10). The size of ester moiety R^2 had a little effect, with the best enantioselectivities being achieved for isopropyl derivatives [66].

It has been described the reaction between acetone (13.6 equiv.) with α-fluoro and α,α-difluoro β-keto esters catalyzed by (*S*)-proline (20 mol%) in DMSO at 25°C [67], with good yield (87%), low diastereoselectivity (11% de) and high enantioselectivity (81%) being obtained in the reaction of ethyl 2-fluoroacetoacetonate.



Scheme 4.10 L-Proline promoted aldol reaction between acetone and α-keto phosphonates

The dynamic kinetic resolution of 2-oxo-3-arylsuccinate derivatives **27** by reaction with acetone (**3a**, 17 equiv.) in acetonitrile (Scheme 4.11) gave a mixture of diastereomers with excesses never higher than 60%. The major *syn*-**28** diastereoisomer was achieved in high ee, being the absolute configuration determined by X-ray [68a]. Following a similar procedure, racemic 2,4-dioxo-3-methyl-4-aryl butanoates were resolved achieving consistently good yields (51–81%) and high diastereo- and enantioselectivities (60–98% de, 85–97% ee) [68b].



Scheme 4.11 Dynamic kinetic resolution of 2-oxo-3-arylsuccinate derivatives **27**

Ketones have been also used as electrophiles for the synthesis of natural products. Thus, the partial synthesis of oxybutynin (ditropan) has been accomplished by the aldol reaction between cyclohexanone (**3b**) and ethyl phenylglyoxylate (**23**, R^1 = Ph, R^2 = EtO, Scheme 4.9) [69]. Also using a diastereoselective approach the synthesis of 3-functionalized 3-hydroxy-β-lactams has been achieved with good yields and total diastereoselectivity [70].

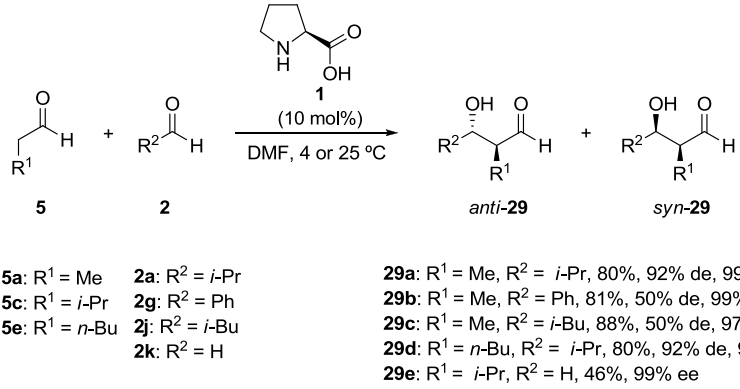
4.2.2 Aldehydes as Source of Nucleophile

The use of aldehydes as source of nucleophiles was introduced short after the first reported organocatalytic intermolecular aldol reaction catalyzed by proline.

4.2.2.1 Aldehydes as Electrophiles

The intermolecular aldol reaction between aldehydes can be classified in two types: the homo-aldol dimerization process of a single aldehyde and the cross-aldol process between two different aldehydes. The later is a more demanding transformation, since the two possible cross-aldol processes have to differentiated and the two possible homo-aldol dimerization processes must be prevented.

(*S*)-Proline (**1**) has showed to be a effective catalyst for both the homo-aldol and the cross-aldol reactions (Scheme 4.12). Thus, the homo-aldol process using propionaldehyde (R^1 = Me in **5a** and R^2 = Et in **2**) afforded the expected α-hydroxyaldehyde in an excellent enantioselectivity for the major *anti*-**29**. Under similar reaction conditions, the cross-aldol reaction between propionaldehyde as source of nucleophile (**5**, R^1 = Me) and other different aliphatic and aromatic aldehydes has been performed, giving the *anti*-**29** isomer as the main diastereoisomer [71]. This reaction course has been explained due to the steric hindrance as well as the kinetic inaccessibility of the hydrogen for some α,α-disubstituted aldehydes which leads, in both cases, to a very thermodynamic unstable corresponding nucleophilic enamine intermediate.



Scheme 4.12 Homo-aldol reaction catalyzed by L-proline

Other electrophilic aldehydes such as 1,3-dithianyl-2-carboxaldehyde [72] or aqueous formaldehyde [17] (Scheme 4.12) have been applied successfully in the proline cross-aldol reaction.

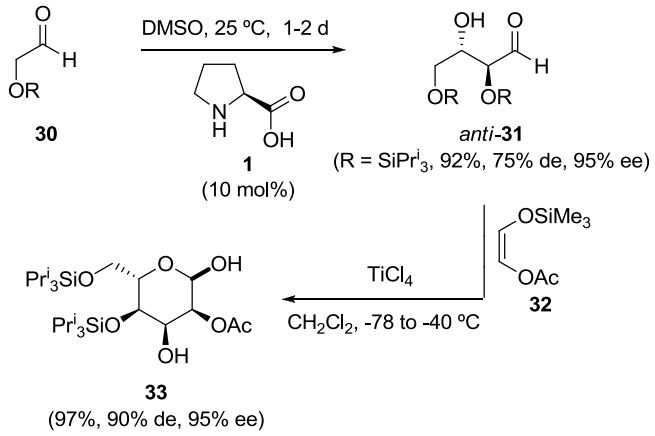
The cross-aldol reaction can be also performed using an excess of aldehyde (**5**, 500 mol%) acting both as the source of nucleophile and solvent in the presence of water (300 mol%) with the obtained enantiomeric excess being increased [49].

Chiral 1,3-diols can be obtained, with in general modest diastereoselectivities, from aldehydes *anti*-**29** by indium mediated allylation reaction [73]. Also, aldehydes *anti*-**29** can be converted in different δ-lactone derivatives by Horner-Wadworth-Emmons reaction with methyl 2-(diethoxyphosphoryl)acetate followed by dihydroxylation using osmium tetraoxide and final cyclization [74].

Optically active tetrahydropyran derivatives can be obtained by domino cross aldol/acetal cyclization reaction of aromatic aldehydes with glutaraldehyde generated from the inexpensive tetrahydro-2*H*-pyran-2,6-diol under equilibrium conditions, in yields ranging from 42% to 78% and good diastereo- (60–75% de) and enantioselectivities (93–99% ee) [75].

The cross-aldol reaction between propionaldehyde (**5a**, R^1 = Me in Scheme 4.12) and *p*-nitrobenzaldehyde gave the corresponding compound *anti*-**29** (> 88% yield, 88% de and 99% ee), which has been used as the asymmetric key step in the synthesis of trichostatin A [76]. In a similar way, using propionaldehyde (**5a**, R^1 = Me in Scheme 4.12) and an excess isobutyraldehyde (4 equiv, R^2 = *i*-Pr) catalyzed by proline (10 mol%), product *anti*-**29** (98% de and 99% ee) was obtained. Subsequent diastereoselective Mukaiyama aldol reaction followed by lactonization gave prelactone B [77]. The synthesis of (−)-enterolactone has been achieved by a cross-aldol reaction between methyl 4-oxobutyrate and 3-methoxybenzaldehyde catalyzed by proline (20 mol%) as a key step [78].

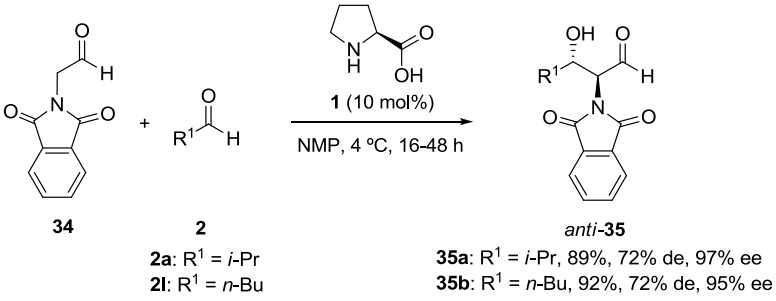
Polyol architectures can be easily obtained by the homo-aldol reaction of α-alkoxyacetaldehydes **30** with the choice of the appropriate protecting group being crucial to predict the role of the aldehyde. When the aldehyde **30** is protected as alkyl or silyl moiety takes the role of nucleophile in its reaction with α,α-disubstituted aldehydes, while behaves as electrophile, in its reaction with simple aliphatic aldehydes. In both cases, products were obtained with good yields (33–84%), good diastereoselectivities (60–78%) and excellent enantioselectivities for the *anti*-aldol **31** (94–99%) [79]. The homo-aldol reaction of α-(triisopropylsilyloxy)acetaldehyde [**30**, R = $SiO(i\text{-}Pr)_3$] led to the corresponding aldehyde *anti*-**31** with a 75% diastereoselectivity, with the obtained product being used as a key intermediate in the synthesis of callipeltoside C [80]. When product *anti*-**31** reacted in turn with the silyl enol ether **32** in the presence of titanium tetrachloride [81] gave the corresponding allose **33** (Scheme 4.13) [82]. The use of $MgBr_2$ as



Scheme 4.13 Two-step synthesis of allose by selective homo-aldol reaction

Lewis acid for this last Mukaiyama-aldol reaction afforded the diastereomeric mannose derivative with similar results. The homo-aldol reaction depicted in Scheme 4.13 showed a positive non-linear effect [83], which was attributed to the formation of the inactive imidazolidinone derivative of both enantiomers of proline with *anti*-**31** (R = Bn) in the different reaction rates, resulting in a kinetic resolution of proline by the final product. The cross-aldol reaction between α-silyloxyacetaldehydes of type **30** with propanal has been used in the synthesis of one key fragment for the preparation of (+)-spongistatin 1 [84].

Other α-functionalized aldehydes such as glycine aldehyde derivative **34** have been used as source of nucleophile. Its reaction with an excess of different aldehydes **2** led to *anti*-α-hydroxy-α-amino aldehyde **35** as the main product, with excellent results (Scheme 4.14). Their subsequent oxidation allowed the synthesis of corresponding amino acids [85].



34 **2** *anti*-**35**

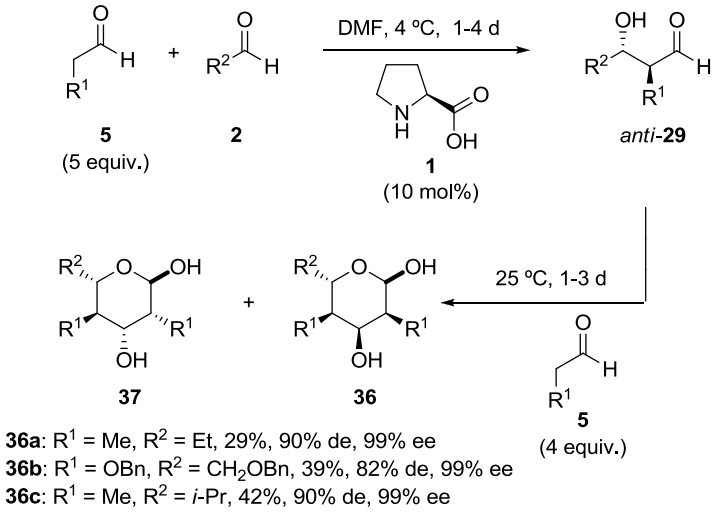
2a: R^1 = *i*-Pr
2l: R^1 = *n*-Bu

35a: R^1 = *i*-Pr, 89%, 72% de, 97% ee
35b: R^1 = *n*-Bu, 92%, 72% de, 95% ee

Scheme 4.14 Synthesis of chiral *anti*-α-hydroxy-α-amino aldehyde catalysed by L-Proline

Additionally, trimers can be obtained by the homo-aldol reaction catalyzed (*S*)-proline (**1**), giving directly polyketide derivatives. The trimerization of acetaldehyde was performed in a THF:acetaldehyde mixture (4:1) at 0°C, to give (5*S*)-hydroxy-2-hexenal in low yield (12%) but with high ee (84%) [86]. The slow addition of acetaldehyde to the in situ formed dimer of type *anti*-**29** permitted an improvement of the results. Thus, a mixture of diastereoisomers **36** and **37** (78% de) in a 53% yield was obtained by trimerization of propionaldehyde (R^1 = Me, R^2 = Et in Scheme 4.15) catalyzed by (*S*)-proline (**1**, 10 mol%) in DMF after 3 days reaction time [87]. Starting from isobutyraldehyde a single diastereoisomer **36** (R^1 = Me) was formed but with low yields and enantioselectivity, this last fact being attributed to the mismatch pair of intermediate *anti*-**29** and (*S*)-proline. Performing the reaction in a stepwise manner, using (*S*)-proline for the first aldol process and (*R*)-proline for the final aldol reaction between isolated *anti*-**29** and aldehyde **5**, the enantioselectivity was improved up to 99% [88, 89].

Using benzyloxyacetaldehyde in the trimerization process, the corresponding allose derivative **36** (R^1 = OBn, R^2 = CH_2OBn) was obtained in 39% yield and 99% ee, with an important non-linear effect being detected [90]. This fact has been permitted the dynamic kinetic resolution processes of compounds of type *anti*-**29** by



Scheme 4.15 Synthesis of polyketide structures by aldehyde-aldehyde aldol reaction

reaction with aldehydes [91]. The homo-aldol reaction of benzyloxy-acetaldehyde (**30**, R = CH_2Ph in Scheme 4.13), using (*R*)-proline (*ent*-**1**) gave the corresponding diastereoisomer *anti*-**31** in 78% yield and 98% ee [92], being this a key intermediate for the synthesis of brasoside and littoralisone.

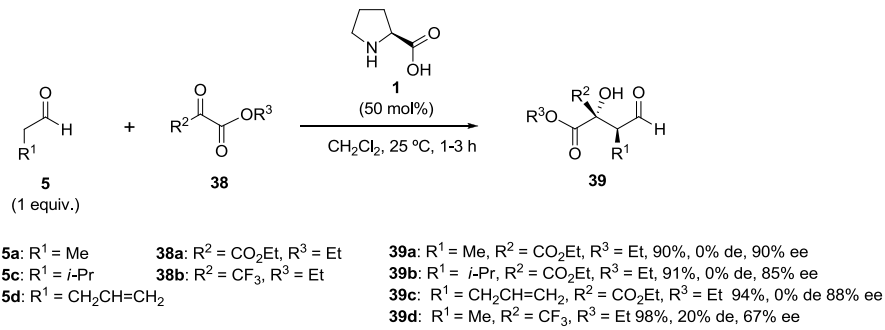
Using water as solvent for the trimerization process led to a dramatic decrease on the achieved enantioselectivity, point out the high relevance of the hydrophobic environment in the transition state [89].

An evident acceleration of the reaction time was achieved using ionic liquid as reaction media for the above di- and trimerization processes, simplifying the product isolation and catalyst recycling. For instance, the dimerization of propionaldehyde can be performed in a 1.5:1 mixture of 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmin][PF_6]) and DMF with only 5 mol% of (*S*)-proline to give the product *anti*-**29** (R^1 = Me and R^2 = Et) in 74% yield with a 60% de and 99% ee. The reaction can be repeated five cycles without changing the achieved yields or enantioselectivities. This media was also used in the one-pot sequential polyketide synthesis of **36** (R^1 = Me and R^2 = Et), affording the expected product in 38 yield% after only 22 h (49% ee)[93].

4.2.2.2 Ketones as Electrophiles

The most challenging combination for this transformation is the use of an aldehyde as source of nucleophile and a ketone as electrophile. This reaction has been successfully achieved by using several aldehydes **5** with high electrophilic ketones (**38**), such as diethyl ketomalonate or ethyl trifluoropyruvate, in the presence of

(*S*)-proline. The desired aldol products **39** were obtained in good chemical yields, enantioselectivities and poor diastereoselectivities (Scheme 4.16). The lability of compound **39**, towards work-up and purification process, forced their transformation either to the corresponding ketals by reaction with ethylene glycol [94] or to nitrones by reaction with substituted *N*-hydroxylamines [95]. This last class of products could be also achieved through the reaction of nitrones with ketones **38** catalyzed by (*S*)-proline [96].



Scheme 4.16 L-Proline promoted aldol reaction using electrophilic ketones

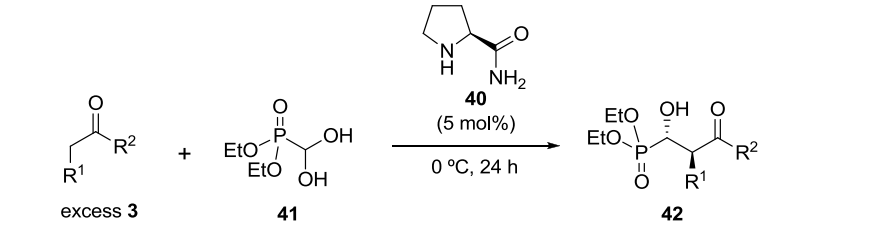
4.3 Prolinamide Derivatives

Prolinamides are probably the most large group of (*S*)-proline (**1**) derivatives used in the intermolecular aldol reaction, due to their easy preparation, stability of the amide linkage and the enough acidity of the NH-moiety able to activate electrophiles by hydrogen bonding.

4.3.1 Ketones as Source of Nucleophile

4.3.1.1 Aldehydes as Electrophiles

Although the use of simple prolinamide-catalyzed intermolecular aldol reaction in high polar organic media failed [14a], it has been reported its use as catalyst (20 mol%) using water as solvent affording the corresponding racemic aldol products **4** in high yields (32–98%) and diastereoselectivities highly depending of the starting ketone [97]. This prolinamide **40** catalyzed efficiently the aldol reaction between ketones **3** and diethyl formylphosphonate (**41**), to give the expected secondary α-hydroxyphosphonates **42** (Scheme 4.17) [98], with the use of the ketone as both source of nucleophile and solvent rendering the best results.



Scheme 4.17 Cross aldol reaction between phosphonate hydrate and ketones

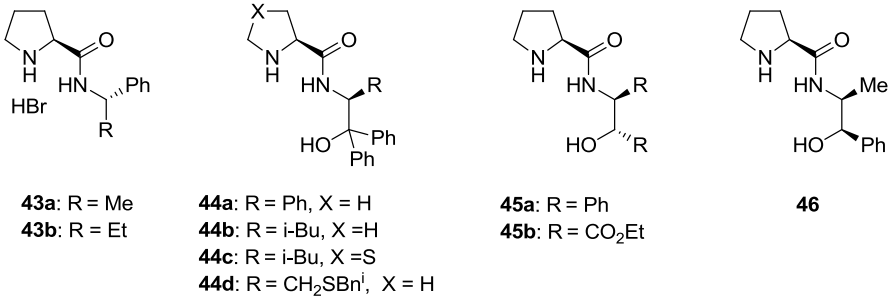


Fig. 4.1 Chiral amines and aminoalcohols derived prolinamide

Several prolinamides with different structural motifs have been synthesized and used in the intramolecular aldol reaction. Thus, simple *N*-alkyl prolinamide derivatives, such as compounds **43** (20 mol%, Fig. 4.1), has been used in the presence of water to perform the reaction between aromatic aldehydes **2** with acetone (**3a**, 10 equiv.) to give the corresponding aldol product **4**. The best results in terms of yields (19–96%) were found for those aldehydes possessing electron-withdrawing groups, with the *ortho*-substituted aromatic aldehydes giving higher enantioselectivities than the related *para*-substituted ones (21–62% ee). The use of diastereomeric amide derived from (*R*)-1-phenyl-1-propylamine showed higher reactivity but lower enantioselectivity [99].

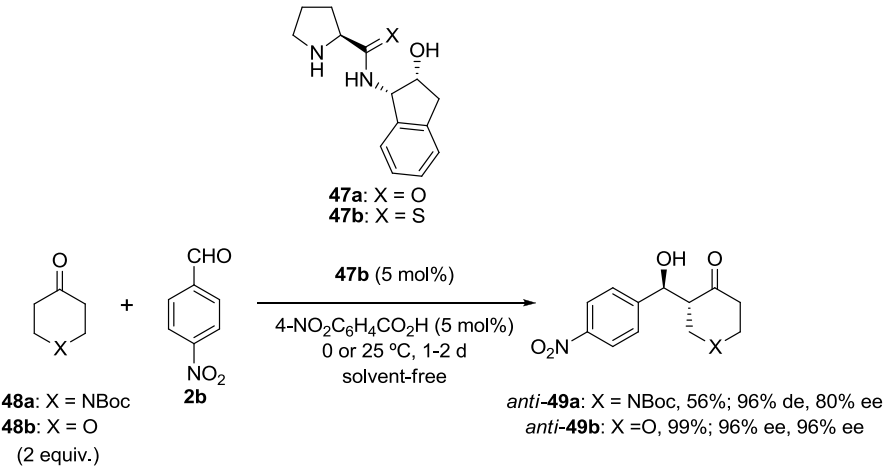
The results obtained in this transformation using 1,2-aminoalcohols derived prolinamides have been more rewarding. For instance, prolinamides **44a** and **44b** (5 mol% or 10 mol% respectively, Fig. 4.1) were very efficient in the reaction between aliphatic and aromatic aldehydes with acetone (**3a**, 13 equiv.) at −40°C, achieving products **4** with good results (52–88%, 80–99% ee). Changing the diphenyl or di-isobutyl moieties by other less hindered alkyl groups or by hydrogen decreased strikingly the achieved enantioselectivities. This effect is associated with a more restricted conformation, to a stronger hydrogen bonding aptitude and to a higher solubility of compounds **44a**, **b**. Worse results were obtained by using the

corresponding diastereomeric amides [100a]. Even better results were obtained by using both catalytic species (**44a**,**b**, 0.5 mol%) in the reaction between cyclohexanone (**3b**) and aromatic aldehydes performing the reaction in brine at −5°C (69–85%, 72–98% de, 85–99% ee) [100b]. The effect of the presence of an heteroatom in the pyrrolidine ring, which enhances the hydrophobicity of the catalyst, was evaluated using compound **44c** (1 mol%) as catalysts for the reaction of acetone (**3a**) and cyclic ketones with aromatic aldehydes at 0°C in brine affording the aldol product **4** with improved diastereo-(88–98% de) and enantioselectivities (91–99% ee) [100c]. Lower results (35–83%, 61–94% ee) were encountered by using cysteine derived prolinamide **44d** (10 mol%) at −15°C in the reaction between acetone (**3a**, 13.6 equiv.) with different aromatic aldehydes [101].

The use of the hindered amide derived from (*S*,*S*)-1,2-diphenyl-2-aminoethanol **45a** (20 mol%, Fig. 4.1) in the reaction between acetone (**3a**, 27.2 equiv.), acting as nucleophile and solvent, and different aromatic aldehydes at −25°C gave good yields and enantioselectivities (48–93% yield and 81–93% ee) and modest yields and excellent enantioselectivities for aliphatic aldehydes (12–77% yield and 86–99% ee) [102]. For alkyl methyl ketones **21**, such as butanone, the reaction took place mainly through the methyl group leading to the corresponding *iso*-regioisomer derivative with moderated yields and high enantiomeric excesses [102b]. The reaction could be perform using ionic liquid ([bmin][BF_4]) as reaction media, giving aldol product **4** with improved results (for example, 82% yield and 94% ee for aldol **4b** compared to 66% yield and 93% ee in acetone as solvent) and permitting the catalyst recycling twice without losing its activity [102c]. The replacement of the phenyl groups in catalyst **45a** by a more electron-withdrawing groups such as ethoxycarbonyl gave a new organocatalyst **45b** with stronger acidity, and therefore stronger ability for hydrogen bond formation [103]. This catalyst (**45b**, 2 mol%, Fig. 4.1) gave slightly enhanced results than **45a** for the reaction between acetone (**3a**, 27.2 equiv.) and aldehydes at −25°C, with excellent enantiomeric excess being obtained for α-branched aldehydes (41–99%, 96–99% ee). When butanone was used as nucleophile, mainly the *iso*-regioisomer derivative was achieved (43–62% yield) with excellent enantiomeric excess (98–99%), together with a minor amount of *anti*-**4** isomer (21–42%, 98% de and 98–99% ee). The results were also good for cyclic ketones although the diastereomeric excess depended on the ring size (90% de for the case of cyclohexanone and 0% de for cyclopentanone) [103a]. This high active catalyst has permitted its use in the reaction of less reactive ketones. Thus, α-hydroxyacetone (**8a**, 15 equiv.) in THF:H_2O (2:1 v:v) at −15°C gave only regioisomers *iso*-**10** in good results. Similar results were found for the related α-fluoroacetone (X = F in **11**). Conversely, using α-fluoroacetone and carrying the reaction in THF, the main product was *anti*-**12** (X = F) achieving in general good results (89–96% yield, 33–60% de, 94–98% ee) [103b]. The use of α-(methylsulfanyl)acetone (X = MeS in **11**) led only to the formation of regioisomers *iso*-**13** with up to 99% ee [103c].

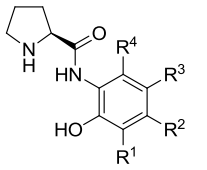
The use of norephedrine derivative **46** (20 mol%, Fig. 4.1) in the reaction of different aldehydes **2** in neat acetone at −40°C gave modest results (22–67% yield and 60–80% ee) [104].

More successful have been the use of (*R*)-1-aminoindonone prolinamide or prolinethioamide (**47**, Scheme 4.18) as catalyst under solvent-free or in the presence of water aldol reaction between aliphatic ketones (2 equiv.) and aromatic aldehydes [105]. Prolinethioamide **47b** (5 mol%) was a more effective catalyst for the intermolecular aldol reaction between cyclic ketones such cyclohexanone (**3b** in Scheme 4.1), tetrahydro-4*H*-thiopyran-4-one (**14** in Scheme 4.5) or heterocyclic cyclohexanones (**48** in Scheme 4.18) with aldehydes affording mainly the *anti*-aldol products in good yield (40–93%), diastereo- (90–96% de) and enantioselectivities (80–96%), with the use of *p*-nitrobenzoic acid (20 mol%) being required as co-catalyst when less reactive ketones or aldehydes were used. For the case of cyclopentanone, a nearly 1:1 mixture of both diastereoisomers were achieved with 92% ee for the *syn*-**4** isomer. The reaction with *p*-nitrobenzaldehyde could be extended to acyclic ketones, such as acetone (**3a**), butanone or α-alkoxyketone (**8**, R^1 = Me or Bn in Scheme 4.3), giving for this later case the corresponding *anti*-**9** isomer as a major products in good diastereo- (60–80% de) and enantioselectivity (87–94% ee). Generally, better selectivity were obtained under solvent-free condition than using water as solvent.

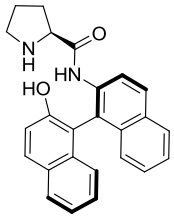


Scheme 4.18 (*R*)-1-aminoindonone prolinamide or prolinethioamide aldol catalyzed reaction

The use of more acidic aminophenol framework instead of hydroxy group, allows the tuning of the steric and electronic properties of the prolinamide by the different substitution on the aromatic rings. Therefore, while the results obtained in water with catalyst **50a** (20 mol%) using acetone (**3a**, 27.2 equiv.) and *p*-nitrobenzaldehyde were moderated (16%, 68% ee), the use of a large excess of cyclohexanone (11.7 equiv.) led to higher yields and selectivity [106a]. The introduction of electron-withdrawing groups at the aromatic ring as in catalyst **50b** improved the achieved reaction outcome. Thus, using catalyst **50b** (10 mol%) for the reaction between cyclohexanone with aromatic aldehydes in water at 30°C



50a: $R^1 = R^3 = t\text{-Bu}^t$, $R^2 = R^4 = H$
50b: $R^1 = Cl$, $R^3 = F$, $R^2 = R^4 = H$
50c: $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$



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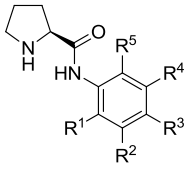


52a: $R^1 = R^3 = R^5 = Me$, $R^2 = R^4 = H$
52b: $R^2 = NO_2$, $R^1 = R^3 = R^4 = R^5 = H$
52c: $R^1 = R^3 = R^5 = NO_2$, $R^2 = R^4 = H$
52d: $R^1 = R^2 = R^3 = R^4 = R^5 = F$

Fig. 4.2 *N*-aryl derived prolinamides

afforded the expected products in high yield (65–91%), diastereo- (76–94% de) and enantioselectivities (9097% ee) [106b]. Lower results were encountered using catalyst **50c** (10 mol%) in DMSO at 25ºC, with a correlation between the enantiomeric ratios and the Hammet constants being found [106c].

NOBIN-prolinamide derivative **51** (5 mol%) was an efficient catalyst for the aldol reaction under unusual conditions such the use of hexane as reaction media or the use of only 3 equiv. of ketone [107], giving the aldol product by reaction of acetone and aromatic aldehydes in high yields (51–99%) and moderated selectivities (53–70% ee). The related methyl ether derivative gave very low results showing the important role of phenolic hydroxyl group. Improved results (26–99%, 12–99% de, 70–95% ee) were achieved when the reaction was performed in dioxane as solvent in the presence of water as additive (1.1 equiv.) allowing to enlarge the substrate scope to cyclic ketones and α-functionalized ketones such compounds **8** and **11** [107b]. Also, catalyst **51** (10 mol%) in combination with trifluoroacetic acid has been used in pure water to perform the aldol reaction between cyclic ketones (only 2 equiv. used) and aromatic aldehydes achieving good results (53–99% yield, 40–98% de, 62–97% ee) [107c] (Fig. 4.2).

Simple *N*-aryl prolinamides has been also used as catalyst in the direct intermolecular aldol reaction, with the different substitution on the aromatic rings affecting the steric and electronic properties of the prolinamide and therefore the catalysts efficiencies. For instance, the use of simple amide **52a** as catalyst in the reaction between α-chloroacetone (X = Cl in **11** in Scheme 4.4) and aromatic aldehydes led to mainly the compound *anti*-**12** (18–57% yield, 66–94% de, 91–98% ee) with a minor amount of *iso*-**13** (X = Cl) being detected [108]. 3-Nitroaniline derived prolinamide **52b** (20 mol%) has been used in the reaction between several cyclic ketones and butanone (5 equiv.) at 27°C with aromatic aldehydes in water providing the corresponding aldol products **4** in good yields (35–92%), diastereo- (4–99% de) and enantioselectivities (50–98% ee). Surprisingly, also 3-pentanone could be used as nucleophilic source, under these reaction conditions, affording the expected aldol in 21% yield, as a 1:1 diastereomeric mixture with 48% enantiomeric excess for the *anti*-isomer. A careful study of the influence of the pH in the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde showed that the best diastereo- and enantioselectivity (84% de and 96% ee) was achieved in a optimal pH range 4–5, with the

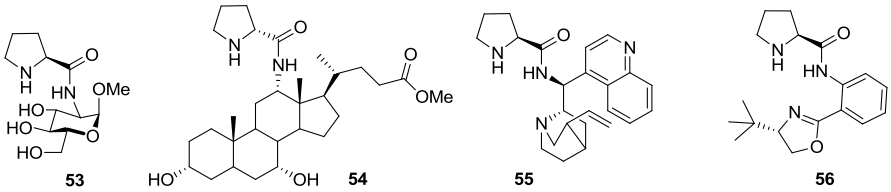


Fig. 4.3 Prolinamides derived for chiral compounds bearing one or more stereogenic centers

protonating acid for that pH range having a marginal effect of the obtained selectivity [109]. Less effective was the use of *(S)*-proline-2,4,6-trinitroanilide (**52c**, 20 mol%) as catalyst in the reaction of acetone and aromatic aldehydes in HMPA/water as reaction media at 25°C, giving only good results for aldehydes bearing electron-withdrawing groups (48–90% yield, 78–89% ee) [110]. *N*-(pentafluorophenyl) prolinamide (**52d**, 20 mol%) was more efficient in the reaction of several cyclic ketones and acetone (20 equiv.) with aromatic aldehydes in the presence of TFA (10 mol%) as catalyst in DMF at 3°C (42–90% yield, 28–98% de, 90–98% ee). This catalysts can be employed also in non-polar solvents such as cyclohexane or high polar solvents such as brine affording similar results [111].

Prolinamides derived from several chiral compounds bearing one or more stereogenic centers have been prepared and tested in the intramolecular aldol reaction (Fig. 4.3). Thus, glucopyranoside derived prolinamide **53** (30 mol%) gave the aldol product **4b** in 69% yield and 61% ee using a huge excess of acetone (90 equiv.) in the presence of a 5 vol.% of water. Increasing the amount of water led to an improved yield but a decrease of the achieved enantioselectivity. Changing the absolute configuration of the proline gave to the enantiomeric aldol product with similar results [112]. A proline derivative from a bile acid such as compound **54** has been evaluated in the aldol reaction between acetone (13.6 equiv.) and *p*-nitrobenzaldehyde. These results showed that the activity and enantioselectivity depended not only on the absolute configuration of the proline but also on the position where it was linked onto the steroid backbone, with derivative **54** (10 mol%) with proline linked to the 12-position of the cholestanic backbone and with free hydroxy groups in the 3 and 7 positions of the cholic acid achieving the best conversion (99%) and enantioselectivity (80% ee) in DMF/H_2O as solvent at –40°C [113a]. Catalyst **54** (5 or 1 mol% in water or in CH_2Cl_2, respectively) have been also used in the reaction between cyclohexanone or cyclopentanone with several aromatic aldehydes at 0°C. For the case of cyclohexanone consistently good conversions, diastereo- and enantioselectivities were achieved (46–98%, 26–94% de; 62–90% ee), while cyclopentanone gave the corresponding aldol products as a diastereomeric mixture (6–44% de) highly dependent on the aromatic aldehyde and on the reaction conditions used, with generally good conversion and high enantiomeric excesses for the *anti*-isomer being obtained [113b]. The combination of cinchona alkaloids and proline led to chiral catalyst **55** (10 mol%), which proved to be very efficient (61–96%, 77–93% ee) in the reaction between acetone (45.5 equiv.), used both as nucleophile and solvent, and aromatic aldehydes in the presence of acetic acid (20 mol%) as co-catalysts.

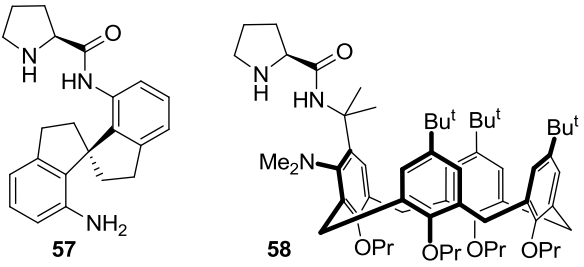


Fig. 4.4 Prolinamides derived for chiral compounds bearing a stereogenic axis

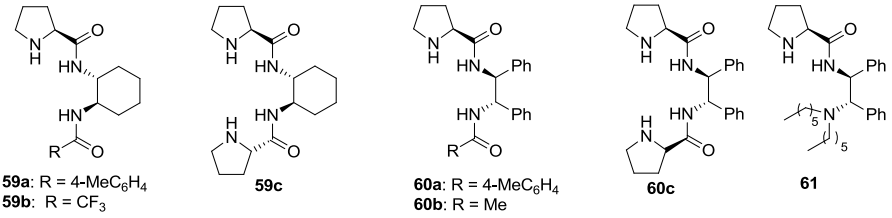


Fig. 4.5 Chiral diamines derived prolinamides

This combination of catalysts **55**-AcOH (20 and 40 mol%, Fig. 4.3) was also applied for the reaction of 2-butanone and aromatic aldehydes, occurring the reaction preferentially at the methylene position to give mainly the *anti*-isomer in high diastereo- (86–88% de) and enantioselectivities (92–98% ee) [114]. Other well-known chiral molecules are oxazolidines. Their combination with proline gave compound of type **56** (30 mol%) which has been tested as catalyst in the reaction between cyclohexanone and several aromatic aldehydes in DMSO and in the presence of 10 equiv. of water at 25°C giving moderated results (59–95% yield, 50–90% de, 7–84% ee) [115].

Also, the use of prolinamide derivatives bearing a stereogenic axis such as in the spiro compound **57** (Fig. 4.4) has been further explored in the reaction of acetone (26.5 equiv.) with several aliphatic and aromatic aldehydes at −25°C. Although its high activity permitted to reduce the amount of catalyst to only 1 mol%, the results were in general modest (50–87% yield, 19–76% ee) [116]. More complicated chiral calix[4]-arene based prolinamide **58** (10 mol%) required the use of acetic acid (20 mol%) as co-catalyst to give the aldol products derived from cyclohexanone (7.3 equiv.) and several aromatic aldehydes, with moderated yields and selectivities (35–93% yield, 66–88% de, 50–79% ee) [117].

Other prolinamides derived from chiral diamines have been synthesized and employed as catalyst in the intermolecular aldol reaction. Thus, diamide **59a** (20 mol%, Fig. 4.5) containing only one unit of proline has been used in the aldol reaction of cyclohexanone (19.2 equiv.) with different aromatic aldehydes. The use of 20 mol% of acetic acid is required to enhance the catalytic activity [118a, b]. It seems that both NH group of diamide stabilized the transition state, activating the electrophile. Changing the R group in catalyst **59**, would influence the acidity of the

NH group and therefore could have an important impact on the activity and selectivity of the reaction. For instance, catalyst **59b** (20 mol%, Fig. 4.5), which has a lower pK_a, has been used in the reaction of *N*-Boc-4-piperidone (**48a**) with different aromatic and heteroaromatic aldehydes in THF, with acetic acid (40 mol%) as co-catalyst at −20°C, giving mainly the isomer *anti*-**49** with diastereoselectivities higher than 90% in good yields and enantioselectivities (32–96% yield, 86–99% ee). However, catalyst **59a** gave better results in the related reaction using tetrahydro-4*H*-pyran-4-one (**48b**) [118c]. Bisprolinamide **59c** (10 mol%, Fig. 4.5) was also effective using (1-butyl-3-methylimidazolium)tetrafluoroborate ([bmim][BF_4])-water as reaction media in the reaction between acetone and cyclohexanone with aromatic aldehydes, affording the corresponding aldol products in high yields (68–99%) and moderated diastereo- and enantioselectivities (60–80% de, 26–82% ee). Under these reaction conditions the catalyst can be recycled up to five times without affecting to the achieved results [118d].

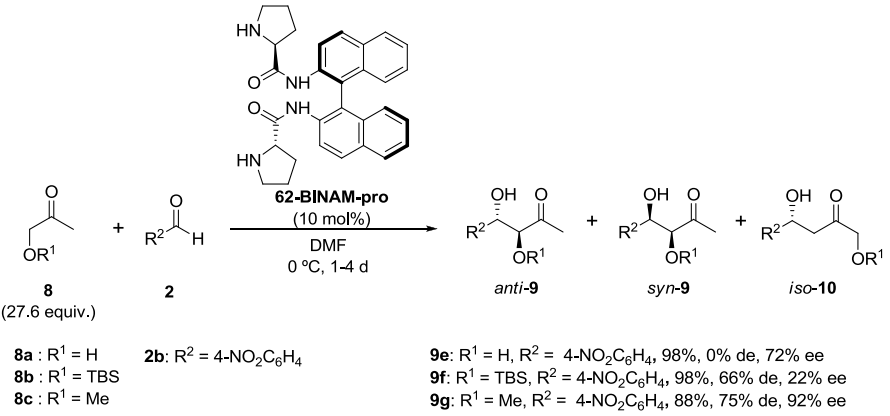
Excellent results were achieved using catalyst **60a** (20 mol%, Fig. 4.5) in the aldol reaction between tetrahydro-4*H*-thiopyran-4-one (**14**) and aldehydes, affording the product *anti*-**15** in 37–99% yield, 78–99% de and 90–99% ee [118c]. The presence of two units of proline in these derivatives increased the catalytic activity. In fact, the reaction between acetone (**3a**, 27.2 equiv.) and *p*-nitrobenzaldehyde (**2b**) at −35°C catalyzed by amide **60c** (10 mol%, Fig. 4.5) gave the expected compound **4b** with an excellent result (75% yield, 98% ee) in only 5 h. This result could be extended with other aldehydes independently on the nature of aromatic or aliphatic electrophilic aldehyde used, with worse results being encountered with catalyst **60b** [119].

Related prolinamide **61** (Fig. 4.5) bearing two highly hydrophobic groups in one of the nitrogens of the diamine showed to be highly efficient as catalyst (1 mol%) in the aldol reaction between acetone (**3a**, 10 equiv.) and aromatic aldehydes in brine as reaction media at 25°C, being the addition of 2,4-dinitrophenol (1 mol%) essential to achieve good yields and selectivities (17–97%, 77–94% ee). These reaction conditions were also applied for the reaction of cyclohexanone with several aromatic aldehydes, with electron-deficient aldehydes giving better results than the electron-rich ones (10–99% yield, 26–96% de, 77–97% ee) [120].

The use of bisprolinamide derived from 1,1'-binaphthyl-2,2'-diamine (BINAM) **62** have been specially interesting for the intermolecular aldol reaction. Two different research groups, almost simultaneously, reported it use as an efficient catalyst in the aldol reaction between ketones **3** and aldehydes **2**, with the matched combination of chiral units being (*S*)-proline and (S_a)-BINAM [121a, b]. However, the applied reaction conditions were quite different. While the mixture 1,4-dioxane/ketone **3** (4:1, v:v) at 4°C were used to obtain the corresponding aldol **4** with yields ranging from 9% to 79% and enantiomeric excess from 50% to 88% [121a], using DMF:water (1:1, v:v) at 0°C or DMF at 25°C the corresponding products **4** were achieved with slightly better results (52–99% yield, 78–95% ee) [121b]. Under these last conditions, when 2-butanone was used as source of nucleophile, the reaction took place nearly exclusively at the methyl position, whereas when cyclohexanone was used as the starting reagent the corresponding isomer *anti*-**4** was mainly obtained. Under these conditions, catalyst **62** can be easily recovered by

aqueous acidic-basic extraction, and reused at least during three-fold cycles, without any detrimental effect on the obtained yields and enantioselectivities [121b]. Alternative, other reported reaction conditions, such as $CHCl_3$:ketone **3** (1:1, v:v) at −27°C, gave lower results than previously reported ones [121c].

Catalyst **62** has been used in the reaction between α-alkoxyketones **8** and aldehydes **2** (Scheme 4.19) to give mainly regioisomers **9**, with small amounts of corresponding *iso*-**10**. The nature of R^1 group determined the diastereoselectivity of the reaction. Generally compound *anti*-**9** was as the main product being obtained with enantioselectivity up to 99% [122]. When α-hydroxyacetone (**8a**) was used as source of nucleophile, the best reaction conditions were DMSO at 25°C, affording *anti*-**9** in a 80% ee. The results obtained with catalyst **62** were compared with those obtained using (*S*)-proline (**1**) under similar reaction conditions, showing that catalyst **62** gave comparable or in some cases, better results.



Scheme 4.19 Aldol reaction catalyzed by BINAM-bisprolinamide **62**

The reaction catalyzed by **62** was accelerated by the addition of substoichiometric amounts of carboxylic acids. Among all tested acid, benzoic acid emerged as the best one, with its addition (20 mol%) reducing the reaction time from original 3 days to only 1.5 h, maintaining the high enantioselectivity for **4b**. After decreasing the reaction temperature from 25°C to −20°C the corresponding enantioselectivity was increased (86–99% ee). Furthermore, the use of benzoic acid allowed to perform the reaction using only water as solvent achieving similar results [123a]. Other carboxylic acids have been proposed as an alternative. Using acetic acid as co-catalyst in toluene at −40, aldol products **4** were obtained (45–91% yield, 40–96% de, 67–95% ee) but in longer reaction times (2–3 days) [123b]. Using water and micellar agent stearic acid (20 mol%) as co-catalyst at 2°C, the amount of ketone **3** could be reduced to 3 equiv. [123c]. Under these conditions, compounds **4** were obtained (61–99% yield, 58–93% ee) in 12 h.

The combination of catalyst **62** (10 mol%) and benzoic acid (20 mol%) in either DMF or pure water allowed the use of less reactive ketones such as α-(methylsulfanyl)

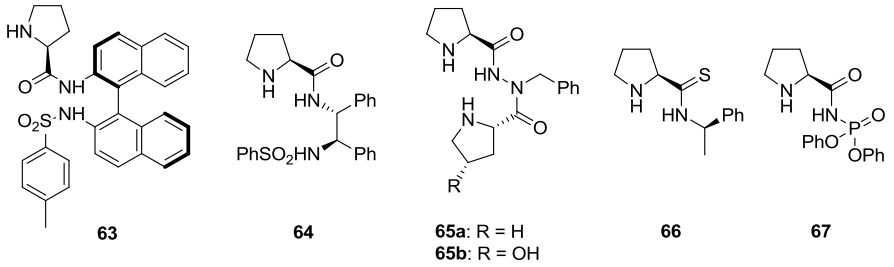


Fig. 4.6 Other prolinamides used as catalysts in the aldol reaction

acetone (X = MeS in **11**) in the reaction with *p*-nitrobenzaldehyde (**2b**), to yield *iso*-**13** as the main product in either DMF/water or pure water with an excellent 93% ee [124a]. The reaction of α-alkoxyketones **8** as nucleophilic source, under these reaction conditions, gave similar results but in shorter reaction times (3–24 h) compared to those achieved in the absence of acid. When the reaction of chloroacetone (X = Cl in **11**) with aromatic aldehydes was performed catalyzed by amide **62** (10 mol%) and benzoic acid (20 mol%), the isomer *anti*-**12** was obtained as the main product (27–96% yield, 50–98% de and 40–97% ee). Compound *anti*-**12** (X = Cl) was easily converted into the corresponding chiral (3*R*,4*S*)-*trans*-epoxides by treatment with triethylamine with excellent enantioselectivities [124b].

A further improvement of the reaction conditions was possible by the use of catalyst **62** (5 mol%) and benzoic acid (10 mol%) under solvent-free conditions in the aldol reaction between different cycloalkyl, alkyl and α-functionalized ketones and aromatic aldehydes [125]. For these purpose, three different procedures were assayed: simple conventional magnetic stirring, magnetic stirring after previous dissolution in THF and evaporation, and ball mill technique, with the first one being superior to the others. All these procedures allowed to reduce the amount of the required ketone to 2 equiv, giving the corresponding aldol products **4** in high yields (54–98%), diastereo- (40–98% de) and enantioselectivities (16–97% ee). Generally *anti*-**4** isomers were obtained, with exception of cyclopentanone, which gave mainly the *syn*-**4** with the lowest diastereoselectivity (40% de). When unsymmetrical ketones were used as nucleophiles, the reaction took almost regioselectively on the methylene site, with the exception of the case of α-(methylsulfanyl)acetone (X = MeS in **11**), which yielded product *iso*-**13** as the main product. This aldol process using catalyst **62** was studied by using positive ESI-MS technique, providing the evidence of the formation of the corresponding enamine-iminium intermediates [125b].

Replacement of one of the proline residues in catalyst **62**, by a more acidic moiety such as sulfonamide would led to the preparation of a bifunctional catalyst such as **63** (Fig. 4.6) [123b, 126] in which the acceptor aldehyde can be activated by a hydrogen bond through the sulfonamide group. The use of this catalytic system **63** (5 mol%) permitted to reduce the amount of benzoic acid co-catalyst to 1 mol%, giving under solvent-free conditions, in absence or in the presence of water, the corresponding aldol products with excellent results (27–98% yield, 26–98% de, 78–98% ee) [126a]. Remarkably, compound **63** proved to be an

excellent catalyst, even more efficient than proline and other organocatalytic systems, for the synthesis of Wieland-Miescher ketone analogues through an aldol intramolecular process [126b].

Prolinamide **64** (Fig. 4.6) bearing a sulphonamide moiety was synthesized by regio- and enantioselective ring opening of chiral aziridines with azide anions [127]. Compound **64** (2 or 5 mol%) was tested as catalysts in brine at −5°C in the reaction between several ketones (4 equiv.) such as acetone (**3a**) cyclohexanone (**3b**) and tetrahydrothiopyran-4-one (**14**) with aromatic aldehydes providing the corresponding aldol products with good results (60–99% yield, 80–96% de, 67–99% ee). Surprisingly, a extremely high diastereoselectivity (96% de) in favor of the *anti*-isomer was encountered in the reaction between cyclopentanone and *p*-nitrobenzaldehyde, with also an excellent enantioselectivity being achieved (93% ee). The obtained chiral aldol products were further derivatized to chiral azetidine rings with multiple applications in organic synthesis.

Other tested catalytic systems are hydrazide derivatives and thioamides. The additional nitrogen atom at the hydrazide derivatives **65** would provide a new hydrogen-bonding site, which may improve the activity. Thus, using catalyst **65a** (20 mol%) and trifluoroacetic acid (20 mol%) in the reaction between cyclohexanone (27.2 equiv.) with different aldehydes in toluene at 0°C, the expected aldol product were obtained with good enantioselectivities (17–95% yield, 87–96% ee), with the yields being lower when aromatic aldehydes bearing electron-donating groups being used [128a]. The use of the hydroxy derivative **65b** under the same reaction conditions led to similar results [128b].

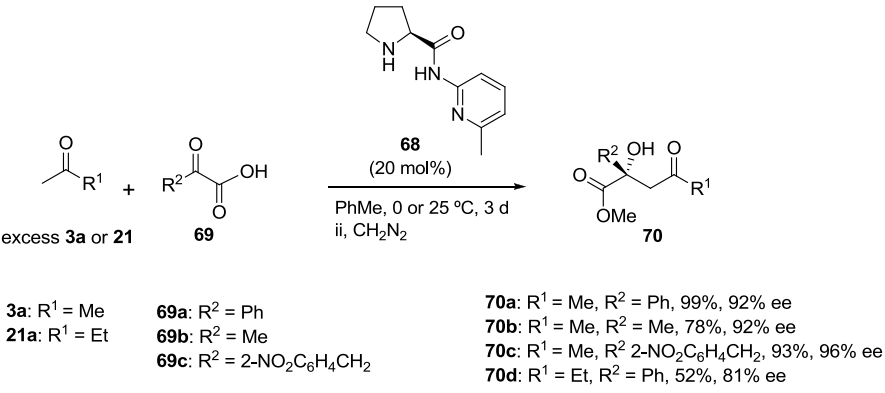
As it has been point out before, the conversion of amide moiety into the corresponding thioamide would increase the acidity of NH hydrogen allowing the formation of stronger hydrogen bonds and favoring its catalytic activity. Thus, catalyst **66** (20 mol%) was prepared and tested in the intermolecular aldol reaction [129a, b], between acetone (**3a**, 27.2 equiv.) and *p*-nitrobenzaldehyde (**2b**) at 4°C in the presence of trifluoroacetic acid (20 mol%) affording the expected compound **4b** in 81% yield and 94% ee. When aromatic aldehydes bearing strong electron-withdrawing groups were used, the achieved results proved that thioamides are more selectively than the related amides. However, the reaction with less reactive aldehydes gave lower enantioselectivities. Other tested thioamides as well as other acidic catalysts gave lower or similar results. For instance, while the use of acids with similar pK_a such as trifluoro-, difluoro- or dichloroacetic acid gave similar result, the use of stronger acids than trifluoroacetic acid led to the inactivation of catalyst **66** [129c]. The aldol reaction between cyclic ketones and aromatic aldehydes catalyzed by thioamide **66** (10 mol%) and dichloroacetic acid (10 mol%) has been also performed in brine as reaction media and using only 1.2–3 equiv. of ketone as a source of the nucleophile. The corresponding products *anti*-**4**, *anti*-**15** and *anti*-**49** were obtained with moderate to good results (32–97% yield, 20–90% de, and 68–98% ee) [129d].

The catalytic efficiency of L-proline-based phosphoric acid esters such as compound **67** (10 mol%) has been also evaluated in the aldol reaction between acetone (**3a**, 6 equiv.) and several aromatic aldehydes. The reaction was performed in THF at 25°C in the presence of *N*-methylmorpholine (10 mol%) as a base, yielding the aldol products in good yields and enantioselectivities (52–81% yield, 52–74% ee). When

these reaction conditions were applied in the reaction between cyclohexanone and aromatic aldehydes, low yields, diastereo- and enantioselectivities were found. However, performing the reaction in DMSO as solvent and in the presence of base, the diastereo- and enantioselectivities were improved (64–92% de, 83–99% ee) [130]

4.3.1.2 Ketones as Electrophiles

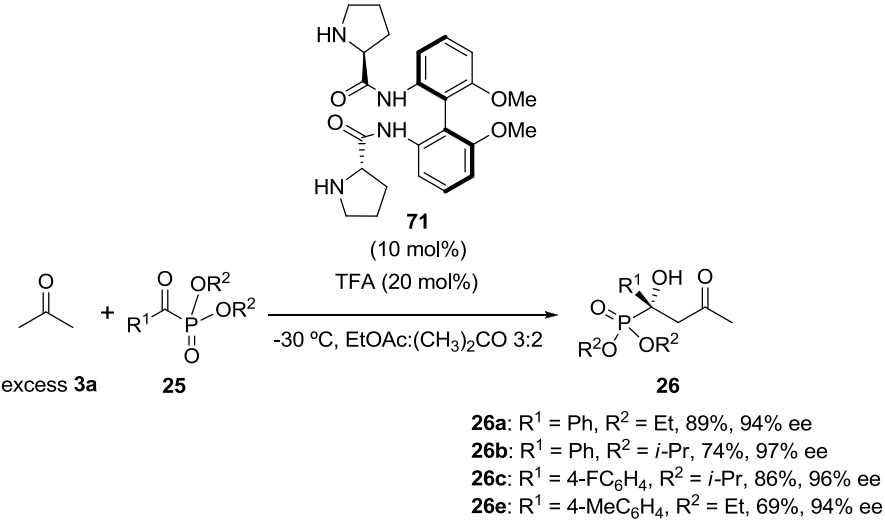
The use of ketones as electrophilic partner of the aldol reaction is a more demanding process. However, using the amide catalyst **68** (20 mol%, Scheme 4.20), the reaction between methyl ketones such as 2-butanone (**21a**) or acetone (**3a**) and other acyclic aliphatic ketones with a wide range of α-keto acids have been accomplished in a excellent manner. Experimental and theoretical studies attributed this success to the presence of an strong interaction between the hydrogen from the carboxylic moiety and the keto oxygen of the α-keto acids with the basic nitrogen atom of pyridine ring and the hydrogen of the amide, which facilities the recognition and approach of reagents [131]. Therefore, when either the ester derivative **38** or non-heteroaromatic ring catalyst was used, a strong detrimental effect on the yields and enantioselectivities was observed. The reaction could be also performed using cyclopentanone, but slightly lower enantioselectivity was encountered. A linear correlation of the enantiomeric excess of the catalyst with that of the aldol product (**70**) was observed, indicating that only a single molecule of catalyst is involucrate in the reaction. Furthermore, catalyst **68** could be recovered and reused three-fold just by aqueous acidic-basic extraction.



Scheme 4.20 Aldol reaction between ketones and α-keto acids

Aromatic α-keto esters (**38**) have been also used as electrophilic partner in this transformation. Thus, catalyst *ent*-**60c** (15 mol%) combined with acetic acid (150 mol%) allowed the reaction between acetone (**3a**, 27.3 equiv.) and several α-keto esters affording the corresponding chiral tertiary alcohols (**70**) in good results. When other ketones such as cyclohexanone, 3-pentanone or 2-butanone were used, the products were obtained albeit in low yields [132].

α-Hydroxy phosphonates **26** could be synthesized efficiently by reaction of acetone (**3a**) with aryl α-keto phosphonates **25** (Scheme 4.21), by using C_2-bisprolinamide **71** (10 mol%) as catalyst in the presence of trifluoroacetic acid (20 mol%) at −20°C in a mixture of ethyl acetate/acetone as solvent [133].

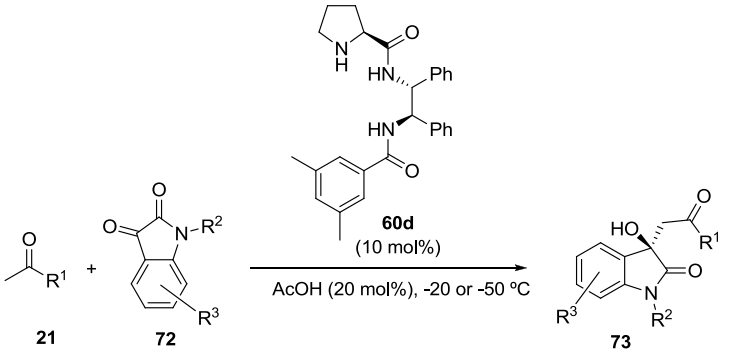


Scheme 4.21 Aldol reaction between acetone and α-hydroxy phosphonates

The use of bifunctional catalyst **60d** (10 mol%) has permitted the synthesis of several 3-alkyl-3-hydroindolin-2-ones (**73**) by reaction of acetone (13.6 equiv.) or butanone with a variety of isatins **72** (Scheme 4.22). The addition of acetic acid (20 mol%) as co-catalyst was required to achieve good results. For the case of the reaction with butanone, the process was highly regioselective affording mainly product **73d** and **73e**. Convolutamydine A, an alkaloid isolated from floridian marine bryozoan *Amathia convolute*, was prepared by reaction of acetone (**3a**) with 4,6-dibromoisatin (R^3 = 4,6-Br_2 and R^2 = H in **72**) catalyzed by compound **60d** under similar conditions, with product of type **73** being isolated in practical quantitative yield and 60% ee [134].

4.3.2 Aldehydes as Source of Nucleophile

Although prolinamides have shown their versatility in the aldol reaction between ketones and aldehydes, their application towards the reaction between the cross or homo-aldol reaction between aldehydes have been scarcely studied. The homo-aldol dimerization reaction between neat propionaldehyde (**5**, R^1 = Me and **2**, R^2 = Et in Scheme 4.23) catalyzed by (*S*)-prolinamide (**40**, 20 mol%) in the presence of

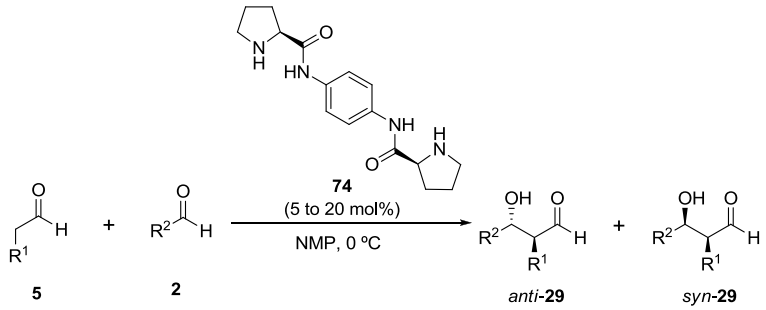


3a: R^1 = Me
21b: R^1 = Et

72a: R^2 = H, R^3 = H
72b: R^2 = Me, R^3 = H
72c: R^2 = H, R^3 = 5-Me

73a: R^1 = Me, R^2 = R^3 = H, 99%, 88% ee
73b: R^1 = Me, R^2 = Me, R^3 = H, 85%, 88% ee
73c: R^1 = Me, R^2 = H, R^3 = 5-Me, 99%, 88% ee
73d: R^1 = Et, R^2 = R^3 = H, 98%, 74% ee
73e: R^1 = Et, R^2 = H, R^3 = 5-Me, 99%, 72% ee

Scheme 4.22 Aldol reaction between isatins and ketones



5a: R^1 = Me
5c: R^1 = *i*-Pr
5e: R^1 = *n*-Bu

2b: R^2 = 4-$NO_2C_6H_4$
2h: R^2 = Ph

29a: R^1 = Me, R^2 = 4-$NO_2C_6H_4$, 99%, 50% de, 95% ee
29b: R^1 = *i*-Pr, R^2 = 4-$NO_2C_6H_4$, 87%, 60% de, 97% ee
29c: R^1 = *n*-Bu, R^2 = 4-$NO_2C_6H_4$, 99%, 84% de, 99% ee
29d: R^1 = *n*-Bu, R^2 = Ph, 88%, 60% de, 98% ee

Scheme 4.23 Cross aldol reaction catalyzed by prolinamide **74**

20 equiv. of water has been reported, affording the expected product *syn-anti*-configured aldol adducts **29** as a 1.3:1 diastereoisomeric mixture. After reduction with $NaBH_4$, the enantiomeric excess for both diols was practically identical (78 and 74% ee for *anti*- and *syn*-configured diols of **29**, respectively) [135].

The cross-aldol reaction between propionaldehyde (**5**, R^1 = Me) and several aromatic aldehydes (**2**, R^2 = Ar) under dry or wet solvent-free conditions has been accomplished using BINAM-prolinamides **62** (5 mol%) or **63** (10 mol%) in the presence of benzoic acid as catalyst (10 and 5 mol%, respectively). After reduction

with $NaBH_4$ the corresponding chiral diols were obtained in good results (45–96% yields 56–78% de, 40–94% ee) [125, 126a].

Another bisprolinamide which has been successfully applied in the cross aldol reaction between aldehydes was compound **74** (5–20 mol%, Scheme 4.23). Good enantioselectivities were obtained for linear and branched aliphatic aldehydes (**5**). A linear correlation between the enantiomeric excess of the catalyst and that of the product was obtained indicating that a single catalyst molecule was involved in the process [136].

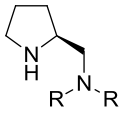
4.4 Prolinamine Derivatives

4.4.1 Ketones as Source of Nucleophile

4.4.1.1 Aldehydes as Electrophiles

Several diamines derived from proline combined with protic acids were tested in the aldol reaction between acetone (**3a**) and aldehydes **2** [137]. Among the screened catalysts, the best results were obtained with prolinamines bearing a tertiary amine group, with slower reaction being encountered as the above moiety become bulkier. When catalyst **75a** (3 mol%, Fig. 4.7) was used as catalyst in the reaction of acetone (source of nucleophile and solvent) with aldehydes in the presence of carboxylic acids and, for instance, using trifluoroacetic acid (3 mol%), the aldol compound **4b** was obtained after 2 h at 30°C in moderate result (51% yield and 82% ee), but together with the corresponding α,β-unsaturated compound. Trying to minimize the amount of this by-product, the amount of carboxylic acid was reduced, but the decrease of by-reaction was marginal. Other ketones, such as cyclic ketones and, surprisingly 3-pentanone, were used in this reaction giving as the main diastereoisomer *anti*-**4** with lower enantioselectivities (81–97% yield, 84–96% de and 8–48% ee). Catalyst **75a** was also effective in the intramolecular aldol reaction [137c].

The combination of hydrophobic catalyst **75b** (10 mol%) with trifluoroacetic acid (10 mol%) has been designed and used in the intermolecular aldol reaction between ketones (2 equiv.) and aromatic aldehydes in pure water as solvent. The expected aldol products **4** were obtained with good yields (46–99%). When high electrophilic aldehydes were used, very low to good diastereoselectivities (8–82%) and enantioselectivities (22–99%) were obtained. The presence of carboxylic acid was crucial, since the reaction in absence of trifluoroacetic acid gave the product as a racemic mixture. The reaction media was, in fact, an emulsion mixture under carboxylic acid catalysis, what permitted the easy isolation of products just by centrifugal separation of water [138a]. The addition of a long chain fatty acid (1 mol%) such as stearic acid or erucic acid permitted to reduce the catalyst loading (1 mol%) achieving similar results (12–99% yield, 4–76% de, 38–92% ee). This enhanced reactivity was attributed to the small particle size of the emulsion (less than 1 μm) showed by dynamic light scattering (DLS) analyses [138d].



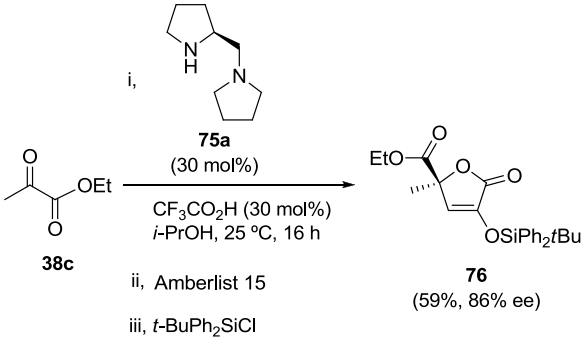
75a: R,R = -$(CH_2)_4$-
75b: R = $(CH_2)_9CH_3$

Fig. 4.7 Prolinamine type organocatalysts

After the publication of these results and other articles related with the use of water as reaction media, a deep discussion about of the water-media concept began [139]. The beneficial effect of the addition of water in the intermolecular aldol reaction was early recognized, since at least one water molecule participates in the catalytic cycle [36]. However, in many of these reaction protocols, water is mere a co-solvent of an organic media (aqueous reactions). In other protocols, water is the only solvent used but a huge amount of source of nucleophile was also used which makes these processes to be recognized as an aqueous reaction, since the excess of reagent play the role of organic solvent media for the reaction. The use of pure water as the only solvent is considered, in general, of high interest owing to water is a cheap, safe and environmental benign solvent. However, to be fair claiming for the environmental beneficial effects of using water as solvent, several demands should be addressed [140]. The green perspective of such processes is clearly in doubt if either a great excess of one reagent is used or a surfactant/micellar agent is added. Pure water should be considered as a green solvent only if it can be directly discharged to a biological effluent plant. Moreover, the work-up of the reaction should be counted to look the whole process as a green approach, with the extraction having to be performed by using minimal amounts of environmental friendly organic solvent, such as ethyl acetate.

4.4.1.2 Ketones as Electrophiles

The use of ethyl pyruvate (**38c**), as both source of nucleophile and electrophile, in the aldol reaction catalyzed by catalyst **75a** (Scheme 4.24) led to the formation of the isotetronic acid derivative **76** with good enantioselectivity. Although, initially

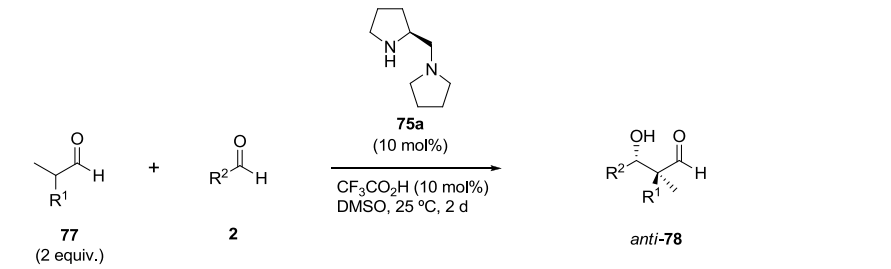


Scheme 4.24 Homo-aldol reaction of ethyl pyruvate catalyzed by prolinamine **75a**

the reaction gave a complicate mixture of different products derived from the aldol process, the use of polymer-supported sulfonic acid Amberlist 15, to eliminate the catalyst, and the final treatment of reaction mixture with a silylating agent permitted the isolation of product **76** in reasonable yields [141].

4.4.2 Aldehydes as Source of Nucleophile

The combination of catalyst **75a** with trifluoroacetic acid has allowed the cross-aldol reaction between α-methylaldehydes **77** and aromatic aldehydes in DMSO at 25°C (Scheme 4.25), affording mainly *anti*-**78** as product, but in moderated diastereoselectivity (24–70% de) [142]. Although the enantioselectivity was highly homogeneous, independently on size of R^1 group and on the electronic nature of substituent at the aromatic ring of electrophilic aldehyde, the chemical yields were lower when aldehydes bearing electron-donating groups were used as nucleophiles.



Scheme 4.25 Cross aldol reaction catalyzed by prolinamine **75a**

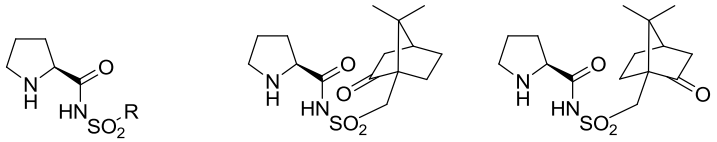
4.5 Sulfur Proline Derivatives

4.5.1 Ketones as Source of Nucleophile

4.5.1.1 Aldehydes as Electrophiles

The use of (*S*)-proline sulfonamide derivatives provide a catalytic system in which the acidic, steric and electronic properties could be adjusted, changing the sulfonyl moiety. Thus, several catalysts of type **79** or **80** were prepared and tested in the aldol reaction (Fig. 4.8).

Sulfonamide **79a** (30 mol%) gave better results in the preparation of compound **4b** performed in DMSO at 25°C (96% yield, 94% ee), than simple (*S*)-proline [143].



79a: R = 4-MeC$_6$H$_4$
79b: R = Me
79c: R = Ph
79d: R = 4-C$_{12}$H$_{25}$C$_6$H$_4$

80a **80b**

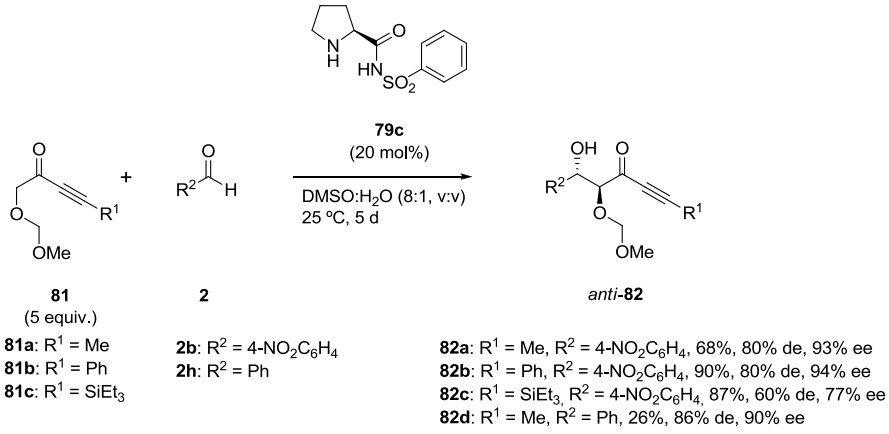
Fig. 4.8 (S)-Proline sulfonamide derivatives

This result was attributed to a better shielding of one of the two possible enantiotopic faces of aldehyde by the aryl ring. When the reaction was carried out using ionic liquid ([bmim][BF_4]) as solvent, aldol product **4b** was obtained in similar yield but slightly decreased enantioselectivity (96% yield, 84% ee) [144]. When catalyst **79a** was recycled and reused under these conditions, a decrease in the yield and enantioselectivity was observed with the reaction cycles, probably due to a possible leaching of catalyst during product extraction from the ionic liquid. Modest results were obtained with catalyst **79b** and **79c** (20 mol%) in the reaction of acyclic and cyclic ketones with *p*-nitrobenzaldehyde in dichloromethane as solvent at −20°C (42–88% yield, 20–36% de, 23–94% ee) [145]. However, excellent selectivities, specially using cyclic ketones as nucleophiles (5 equiv, 84–99% de, 59–99% ee), were achieved in the aldol reaction catalyzed by sulfonamide **79d** (20 mol%) in 1,2-dichloroethane as solvent in the presence of 1 equiv. of water at 4°C. While yields were consistently high using aromatic aldehydes bearing electron-withdrawing groups, lower reaction outcome was found using electron-rich aromatic aldehydes (16–98% yield). For the case of the reaction between cyclohexanone with aromatic aldehydes, the catalyst loading could be reduced to only 2 mol% performing the reaction under neat conditions. Under these conditions, 1 mol scale of aldol product **4d** could be prepared in 88% yield, 97% de and 97% ee [146].

The use of more sophisticated diastereomeric camphorsulfonamide derivatives **80a**, **b** (20 mol%) as catalyst in the reaction between acetone (**3a**) and *p*-nitrobenzaldehyde (**2b**) in a DMF/acetone 4/1 mixture at 25ºC, gave lower results (47 and 78% yield, 63 and 60% ee, respectively) [147].

The aldol reaction between ynones **81**, as source of nucleophile, and aromatic aldehydes have been successfully performed using catalyst **79c**, giving as the main product *anti*-**82** with good diastereo- and enantioselectivities (Scheme 4.26). The best results were obtained for the less bulky ynone (**81a**, R^1 = Me) [148]. The instability of compounds **82** led to their transformation to the corresponding 3-oxotetrahydrofuranone derivative by addition of an alkoxy moiety at the α-position of the triple carbon-carbon bond, catalyzed by phosphane compounds.

Other sulfur-proline derivatives have been prepared and screened as catalysts in the intramolecular aldol reaction. Remarkably, sulfonamide **83a** (10 mol%, Fig. 4.9) was an efficient catalyst for the aldol reaction between aryl methyl ketones



Scheme 4.26 Aldol reaction between ynones and aromatic aldehydes

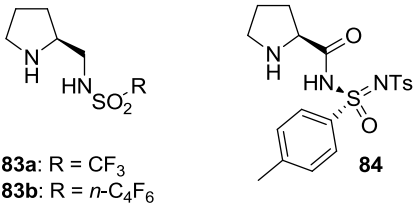


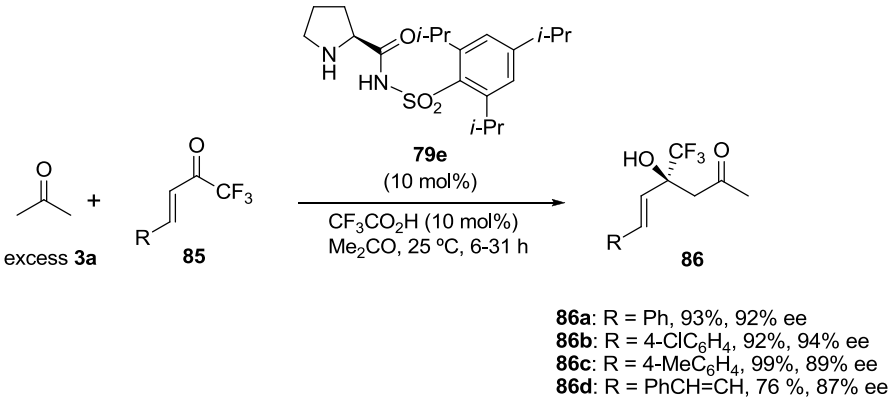
Fig. 4.9 Other sulfur-proline type derived organocatalysts

and aromatic aldehydes providing the corresponding aldol products with good results (18–91% yield, 71–91% ee). Low yields were obtained in reactions between acetophenone and benzaldehyde. It should be pointed out that other catalyst such as proline, prolinamides or thiourea-proline derivative, failed in this process. The reaction was carried out in DMSO at solvent at 25°C in the presence of 1 equiv. of water as additive [149]. Sulfonamide catalyst **83a** (20 mol%) promoted the reaction between α-methyl substituted aldehydes **77** (10 equiv.) and aromatic aldehydes **2** in DMSO at 25°C to afford products *anti*-**78** with high yields (81–97%), and enantioselectivities (91–97%), with the diastereomeric excesses being about 85% [150]. The use of recyclable fluoro-sulfonamide **83b** (10 mol%) in water at 0°C for the reaction between acyclic and cyclic ketones (5 equiv.) with aromatic aldehydes to prepared the corresponding aldol products (73–93% yield, 0–90% de, 70–97% ee), permitted its recovery by simple fluorous solid-phase extraction and its reuse up to seven reaction cycles with a slightly decrease in the achieved yields and enantioselectivities [151].

A more complex sulfur-proline catalyst is sulfoimidamide of type **84** (Fig. 4.9). This catalyst, together with its diastereoisomer, have been tested in the aldol reaction between cyclohexanone (**3b**, 5 equiv.) and aromatic aldehydes to afford the corresponding aldol products, with best yields and selectivities being obtained using compound **84** (10 mol%) under ball-mill solvent-free conditions (22–84% yield, 84–92% de, 89–98% ee) [152].

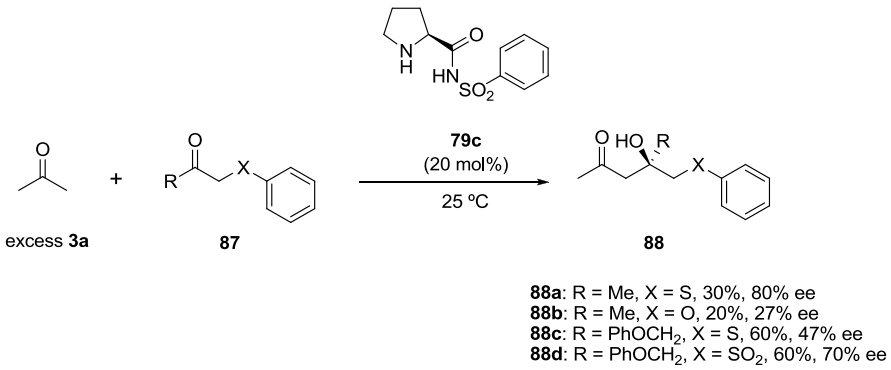
4.5.1.2 Ketones as Electrophiles

High electrophilic ketones, such as compounds **85** reacted with acetone (**3a**) using very bulky sulfonamide **79e** in combination with trifluoroacetic acid (10 mol%) as catalysts (Scheme 4.27). Also different methyl alkyl ketones could be used with similar results, taking part the reaction always at the methyl group. The absolute configuration of final aldol was determined in basis of crystallographic determinations [153].



Scheme 4.27 Aldol reaction between acetone and high electrophilic ketones **85**

The aldol reaction between acetone (**3a**) and α-phenoxy and phenylsulfanylmethyl ketones **87** was possible by using catalyst **79c** (Scheme 4.28) affording tertiary alcohols **88** albeit in moderated yields and enantioselectivities, with acetone acting both as nucleophile and solvent. Also, compounds **87** reacted as source of the nucleophile with different aromatic aldehydes using (*S*)-proline (20 mol%) as catalyst in DMSO at 25°C. Whereas α-phenoxy ketones gave the regioisomer from the reaction



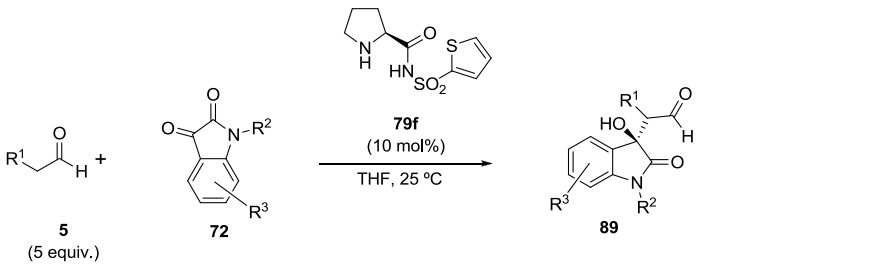
Scheme 4.28 Aldol reaction between acetone and α-phenoxy and phenylsulfanylmethyl ketones **87**

of the methylene group giving mainly the corresponding *anti*-aldol in moderated yields and good diastereo- and enantioselectivities (66–70% yield, 50–92% de, 64–99% ee), α-phensulfanylmethyl ketones reacted mainly over the methyl group in low yields and moderated enantioselectivities (27–40%, 68–95% ee) [154].

Finally, sulfonamide **79f** (5 mol%) has shown to be effective in the aldol reaction between acetone (**3a**, 200 equiv.) and isatins (**72**) in the presence of 10 equiv. of water at 25°C, yielding the corresponding aldol products **89** in good results (59–99% yield, 92–97% ee), with exception for product **73a** which was obtained in high yield (99%) but nearly as racemic mixture [155].

4.5.2 Aldehydes as Source of Nucleophile

Sulfonamide **79f** (10 mol%, Scheme 4.29) allowed the enantioselective synthesis of convolutamydine E (**89c**) and derivatives, by the reaction of isatins (**72**) and acetaldehyde (**5f**) in THF at 25°C, followed by reduction with $NaBH_3CN$. As in the previous cases, isatin **72a** gave the corresponding alcohol in moderated yield (60%) and nearly as a racemic mixture. Other linear aldehydes different from acetaldehyde, gave alcohols **89** with good results, while the reaction with α-branches aldehydes failed [156].



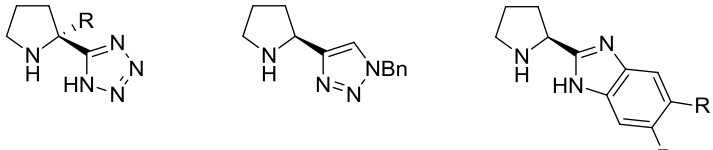
Scheme 4.29 Synthesis of convolutamydine E (**89c**) by organocatalyzed aldol reaction

4.6 Heteroaromatic Pyrrolidine Derivatives

4.6.1 Ketones as Source of Nucleophile

4.6.1.1 Aldehydes as Electrophiles

The pk_a of tetrazole in DMSO (8.2) is higher than acetic acid (12.3), although both have a similar aqueous pK_a values [157]. Furthermore, tetrazoles due to their higher solubility, lipophilicity and metabolic stability than analogous carboxylic acids are



90a: R = H
90b: R = Me

91

92a: R = H
92b: R = Me

Fig. 4.10 Heteroaromatic pyrrolidine derivatives

frequently used as their bioisosters. Thus, the reaction between different ketones **3** (2 equiv.) and chloral monohydrate (**2**, $R^3 = CCl_3$, Scheme 4.1) has been catalyzed by chiral tetrazole **90a** (5 mol%, Fig. 4.10) in acetonitrile affording the expected products **4** in high yields (35–88%) and enantioselectivities (36–97%) [158a]. As in other cases, the reaction with cyclopentanone yielded the isomer *syn*-**4** as the main product (80% de), whereas using cyclohexanone *anti*-configured aldol adduct **4** (92% de) was observed as the main product. Other ketones, even aryl methyl ketones, as well as aldehydes (trifluoroacetaldehyde monohydrate or aqueous formaldehyde) were used successfully in this process. In the case of alkyl methyl ketones, the reaction took place always at the methylene position of the ketone. Tetrazole **90a** (20 mol%) was also a efficient catalyst in the reaction between acetone (**3a**, 34 equiv.) and several aromatic or aliphatic aldehydes in a DMSO:Me_2CO mixture (4:1, v.v), achieving products **4** with good yields and enantioselectivities (65–82% yield, 63–99%) in very short reaction times (10 min to 13 h). The high solubility displayed by catalyst **90a** permitted the use of other solvents to perform this reaction, even in the presence of 10 mol% of water [158b, c]. The high activity of catalyst **89a** for this aldol reaction has allowed its use in a continuous-flow reactor. For this purpose, a 1 mL glass microreactor, equipped with a mixing zone and a rectangular residence channel, in which the reagents were separately introduced through two inlets, was used. The reaction was conducted using a 5 mol% of catalyst using 1 mol of *p*-nitrobenzaldehyde (**2b**) and 2 mL of 1:1 DMSO/acetone mixture at 60°C, with the temperature being monitored using a thermal sensor close to the reactor and maintained constant. After 10 min, 79% of product **4b** was formed in 76% ee. The applicability of this method was demonstrated by using other aromatic aldehydes, affording aldol adducts **4** in moderated yields and enantioselectivities (36–79% yields, 57–76% ee) in short reaction times (20–30 min), with lower yields being obtained for benzaldehyde and 3-naphthylcarbaldehyde due to a competing dehydration process. This protocol was extended to reaction between cyclohexanone (9.6 equiv.) and 4-cyanobenzaldehyde to give after 40 min a 86% of a 1:1 diastereomeric mixture of both possible aldol adducts, with 81% ee for the a*nti*-isomer [158d].

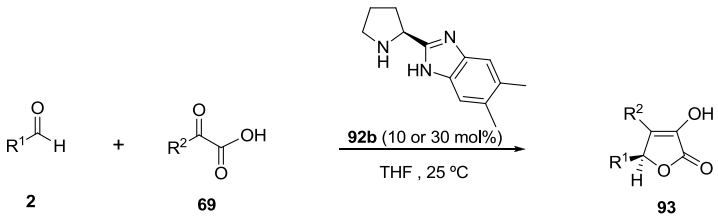
Tetrazole derivative **90a** catalyzed the DKR of compound *rac*-**18** by reaction with ketone **14** (2 equiv.), in wet DMSO, giving the expected product **19** in 75% yield and more than 98% ee. The compound **19** was converted, after radical dehydroxylation and reductive desulfurization, in the corresponding ethylene ketal of natural serricornin, a beetle sex pheromone [159].

With the aim of improving the stereoselectivity displayed by catalyst **90a**, compound **90b** (20 mol%, Fig. 4.10) was tested in the aldol reaction between acetone

(**3a**, 27 equiv.) and aromatic aldehydes in DMSO at 25°C. But lower yields (11–72%, 70–91% ee), compared to those obtained with **90a**, were achieved due to the formation of dehydration products [160].

Chiral pyrrolidine-triazole **91** (10 mol%), obtained by "click chemistry", was used as catalyst in combination with TFA (1.5 mol%) in the aldol reaction between cyclohexanone (10 equiv.) and several aldehydes under solvent-free conditions at 0°C, affording the aldol products in good yields and diastereoselectivities (86–93% yield, 84–92% de) albeit with low enantioselectivities (23–28% ee) [161].

Benzoimidazol derivatives **92** were screened in the classical aldol reaction between acetone and aromatic aldehydes. While catalyst **92a** (15 mol%) afforded the corresponding aldol products in high yields (65–93%) but low enantioselectivities (27–49% ee) in *N*-methylpyrrolidone as solvent at 25°C [162]. Compound **92b** (2 mol%) combined with trifluoroacetic acid (20 mol%) gave good results [163a], achieving product **4b** in 67% yield and 82% ee using equimolecular amounts of acetone (**3a**) and *p*-nitrobenzaldehyde (**2b**) in THF at −5°C. The catalyst loading could be reduced to 2 mol% without detrimental on the achieved enantioselectivity by using acetone as solvent and source of nucleophile, improving the yield to 87%. Similar reaction conditions were applied in the aldol reaction between cyclic ketones or 3-pentanone with *p*-nitrobenzaldehyde to give the corresponding aldol products in good yields and enantioselectivities (65–99% yield, 80–99% ee), although low diastereoselectivities were obtained [163b]. Catalyst **92b** (10 or 30 mol%) was also efficient in the synthesis of isotetronic acids obtained by reaction of an equimolecular mixture of pyruvic acid **69** with aliphatic or aromatic aldehydes **2** (Scheme 4.30). The reaction could be either performed in THF or water as solvent, affording product **93** with good results [163c].



2

2a: R^1 = *i*-Pr
2h: R^1 = Ph
2l: R^1 = 4-$MeOC_6H_4$

69

69b: R^2 = Me

93

93a: R^1 = *i*-Pr, R^2 = Me, 44%, 76% ee
93b: R^1 = Ph, R^2 = Me, 90%, 70% ee
93c: R^2 = 4-$MeOC_6H_4$, R^2 = Me, 10%, 36% ee

Scheme 4.30 Organocatalyzed synthesis of isotetronic acids **93**

4.6.2 Aldehydes as Source of Nucleophile

Isatins **72** reacted with α-methyl aldehydes (**77a**) catalyzed efficiently by tetrazole **90a** (15 mol%) in the presence of 1 equiv. of water and using phosphoric acid (15 mol%) as co-catalyst at 0°C in isopropanol, to afford the corresponding aldol

products in which two contiguously quaternary centers were smoothly created (50–92% yield, 49–84% ee). This reaction conditions could be also applied to linear aldehydes giving products **89** with good results (69–80% yield, 16–78% de, 90–98% ee) [164].

4.7 4-Hydroxyproline Derivatives

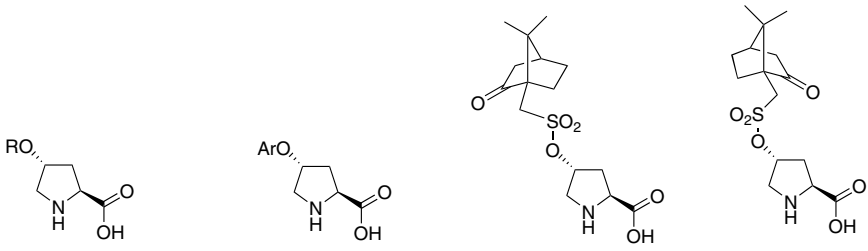
Although it is a less common amino acid, 4-hydroxyproline have been extensively used in asymmetric synthesis, because is cheap and that the additional hydroxy group offers new possibilities of structural modification.

4.7.1 Ketones as Source of Nucleophile

4.7.1.1 Aldehydes as Electrophiles

Different 4-hydroxyproline derivatives have been prepared by modification of the hydroxy group in order to improve their efficiencies and to facilitate their recovery and recyclability properties (Fig. 4.11).

The use of protected 4-hydroxyproline **94a** (10 mol%) as catalyst in the reaction between cyclopentanone and cyclohexanone (5 equiv.) and different aromatic aldehydes, bearing electron-withdrawing groups, in the presence of water (18 equiv.) at room temperature, afforded mainly the corresponding *anti*-**4** isomer in good yields (78–92%), diastereoselectivities (64–90%) and excellent enantioselectivities (95–99%). Besides acetone (**3a**), other aliphatic ketones such as butanone have been used as source of nucleophile achieving the aldol products in moderate yields. Also moderated yields (21–76%), albeit good diastereo- and enantioselectivities were obtained using either aromatic aldehydes bearing electron-donating moieties or aliphatic aldehydes, including aqueous formaldehyde. Oxygen-containing ketones such as hydroxyacetone (**8a**, Scheme 4.3) or 2,2-dimethyl-1,3-dioxan-5-one (**16**) gave worse results. Remarkably, the amount of catalyst **94a** and water could be reduced to 1 mol% and 3 equiv. respectively, without affecting yields and enantioselectivities, but increasing the corresponding reaction times. These later reaction conditions were applied for a large-scale preparation of the aldol product coming from the reaction between cyclohexanone (2 equiv.) and benzaldehyde, including the purification steps using a minimal amount of organic solvents. In this way, 10 g of aldol product **4** in 70% yield, 82% de and 99% ee using only 60 mL of ethyl acetate [165b]. A temperature study on the stereoselectivity of the aldol reaction between 3-pyridinecarbaldehyde and cyclohexanone catalyzed by **94a** (10 mol%) in water, showed a non-linear behaviour of the Eyring plot of the diastereomeric ratio *anti*/*syn* with the presence of an inversion temperature (T_{inv}), which disclosed dynamic solvation effects in water. However, enantioselectivity was not influenced by temperature [166].



94a: R = Bu^tMe_2Si
94b: R = $CH_3(CH_2)_{11}$
94c: R = $CH_3(CH_2)_nCO$
94d: R = $C_8F_{17}(CH_2)_2$

95a: Ar = Ph
95b: Ar = 4-$(CH_3)_3CC_6H_4$
95c: Ar = 2-Naphthyl

96a **96b**

Fig. 4.11 4-Hydroxyproline derived catalysts

4-Hydroxyproline derivative **94b** (5 mol%) at 0°C was tested in the aldol reaction between acetone and cyclohexanone, and aromatic aldehydes to give the corresponding aldol adducts in good results (82–99% yield, 30–96% de, 59–96% ee). However, when the reaction was performed in water as solvent, acetone gave poor results, while cyclohexanone provided the aldol products in excellent yields (67–99%), diastereo- (64–98% de) and enantioselectivities (83–99% ee), with the relation 1:2 water:ketone being the optimal. This fact was reasoned by the greater lipophilic character of cyclohexanone compare to acetone, which increased the hydrophobic interaction with the aldehyde and therefore formed an aggregated organic phase in which the reaction occurred [167]. Another proline derivative used as catalyst in the aldol reaction was compound **94c** (n = 10, 15 mol%). In the reaction between cyclohexanone and several aromatic aldehydes at 25°C, the formation of metastable emulsion droplets of size about 0.1–0.2 μm, determined by dynamic light scattering, was observed. The catalyst acted as a surfactant, maintaining the emulsion droplets and therefore providing a high interfacial surface area, which may be responsible of the high reactivity observed. In addition, the high yields (40–98%) and selectivities achieved (74–92% de, 90–98% ee) were reasoned by the formation of a well-ordered and two-dimensional chiral surface by the catalyst in emulsion [168].

Catalyst **94d** (25 mol%), which has a polyfluorous tail anchored to the hydroxyl group was used in the reaction between acetone (**3a**, 27.2 equiv.) and *p*-nitrobenzaldehyde (2b, Scheme 4.1) in a biphasic trifluoromethylbenzene:acetone system (4:1) affording the expected product **4b** with similar results to those obtained using proline (**1**) in DMSO (72% yield, 73% ee). Decreasing the amount of catalyst **94d** to 7 mol% resulted in an important deleterious effect on yields and enantioselectivity of the product [169].

The use of catalyst **95a** (5 mol%) permitted to carried out the reaction in either classical organic solvents such as acetone (27.2 equiv.) or ionic liquid ([bmim] PF_6) [170], with similar results for product **4b** (75 and 81% yield, 76 or 75% ee, respectively). However, using ionic liquid as solvent, the catalyst could be reused

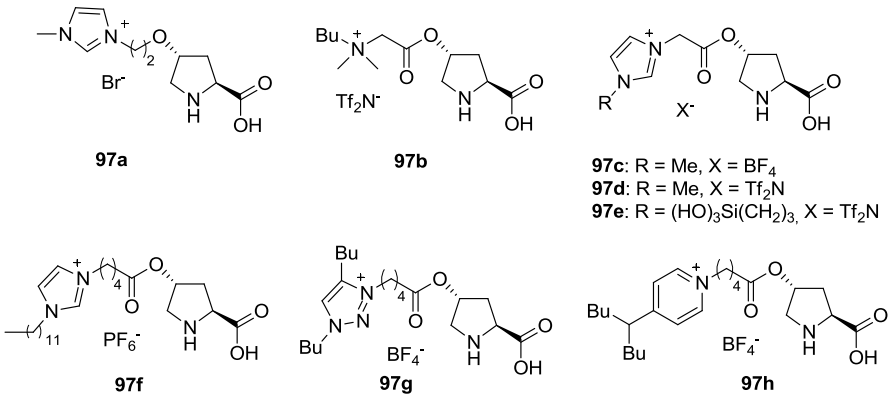


Fig. 4.12 Ion tagged 4-hydroxy proline derivatives

at least four-fold without detrimental on the initials results. Similar yields and enantioselectivities were achieved using aromatic aldehydes bearing electron-withdrawing groups, meanwhile results were accountable lower when benzaldehyde or *p*-methylbenzaldehyde were used. 4-*tert*-Butylphenoxyproline **95b** (2 mol%) catalyzed efficiently at 25°C, the reaction between cyclohexanone (1 equiv.) and aromatic aldehydes using sulfated β-cyclodextrin as an inverse phase-transfer reagent allowing the water-insoluble molecules to react in water, affording the expected aldol products **4** in good yields (62–100%) and with both excellent diastereo- (68–98%) and enantioselectivities (96–99%) [171]. In order to increase the solubility of catalyst of type **95** in common solvents, compound **95c** (5 mol%) was tested in the reaction between acetone and aromatic aldehydes. The reaction had to be performed at low temperature (−25°C) to improve the enantioselectivities (82–90% ee), with lower chemical yield being achieved (45–81%) [172].

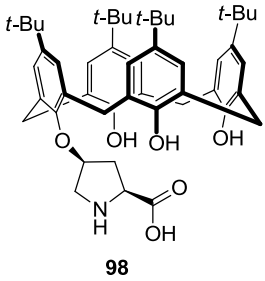
Very hindered catalysts **96a, b** (20 mol%) permitted to reach very good level of enantioselectivity (74–91% ee) in the reaction of acetone with aromatic aldehydes using a DMF/acetone mixture as reaction media at 25°C, with the camphorsulfonyl derivative **96b** giving better results even using only 10 mol% of catalyst [173].

The use of ion tagged 4-hydroxyproline derivatives such as catalysts **97** allowed to perform the reaction under ionic liquid phase conditions with in some cases very good results (Fig. 4.12). Thus, catalyst **97a** (10 mol%) was used for the aldol reaction between acetone and several aromatic aldehydes in a mixture 1:1 of ionic liquid [bmim]BF_4:acetone, giving the aldol products in good results (53–94% yield, 65–93% ee). The use of such conditions permitted six-fold recycling process with the enantioselectivity being constant, but a minor decrease in the chemical yield being suffered [174]. Similar results were encountered using catalyst **97b** in [bmim]Tf_2N as ionic liquid for the same aldol process, with catalyst loading being reduced to 5 mol%. These reaction conditions were applied to other ketones such as cyclohexanone or -methoxyacetone giving the aldol products in moderated yields (35–78%) and diastereoselectivities (34–70% de) and good enantioselectivities for the major

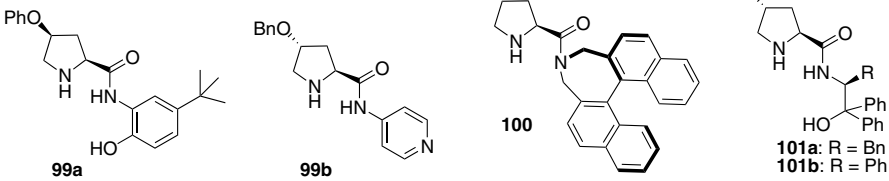
anti-isomer (75–94% ee). However, the recycling of this catalyst was possible only once. A significant drop in the catalytic efficiency was observed after the third cycle [175]. The use of higher catalyst loading (30 mol%) of compound **97c**, in the reaction between acetone or butanone with aromatic aldehydes in DMSO or acetone as solvent, allowed the recyclability of the system up to four cycles without lost the catalytic activity. Aldol products were obtained in yields ranging from 40% to 92% and enantiomeric excess reaching up to 87% [176]. Changing the counteranion to a more lipophilic Tf_2N, 5 mol% of catalyst **97d** showed to be extremely efficient in the reaction between cyclohexanone (5 equiv.) and aromatic aldehydes in water at 25°C (41–98% yield, 82–96% de, 96–99% ee). Excellent diastereo- and enantioselectivities (99% de, 99% ee) and lower yields were achieved using aliphatic aldehydes as electrophiles (52–60%), with worse results being obtained when the reaction was performed in ionic liquid as solvent. Under these conditions, the catalyst could be recovered and reused up to five times without deleterious effect on the results. The catalyst loading could be further decreased to 0.1 mol% for the case of using high electrophilic aromatic aldehydes, without compromising the achieved enantioselectivities [177]. Catalyst **97e** (10 mol%), having a hydrophilic cation and lipophilic anion, was completely insoluble in ether and highly soluble in water, therefore it was designed to improve the recycling properties. Although its catalytic efficiency in the reaction between cyclohexanone (4 equiv.) and aromatic and aliphatic aldehydes was good (50–98% yield, 90–99% de, 99% ee). Yields were highly influenced after the third reaction cycles, albeit the stereochemical performance was maintained up to five runs [178]. Better recyclability was displayed by amphiphilic catalyst **97f**, which could be recovered from the reaction performed in water and reused up to five times without being detrimental on the achieved results. A high catalyst loading (30 mol%) was necessary to afford aldol products from reaction between cyclic ketones and aromatic aldehydes with good results (20–95% yield, 710–94% de, 80–99% ee) [179]. 1,2,3-Triazolium-tagged system **97g** (20 mol%) was used as catalyst in the solvent-free aldol reaction between acetone, cyclopentanone and cyclohexanone (5 equiv.) with aromatic aldehydes at 25°C, with good results being obtained specially with cyclohexanone (79–99% yield, 24–98% de, 72–94% ee). Similar results were obtained when the reaction was performed in ionic liquids as solvent. Unfortunately, the recycling of the catalyst under all the tested reaction conditions gave a substantial decrease on the achieved enantioselectivity [180]. The highest recyclability was displayed by using compound **97h** (15 mol%) as catalyst in the aldol reaction between a range of cyclic ketones (**3b**, **14** or **48**, 3 equiv.) and aromatic aldehydes in water at 25°C, giving good yields (38–97%) and excellent diastereo- and enantioselectivities (60–94% de, 92–99% ee). This system was reused up to 8 cycles without affecting the achieved results [181].

Also calix[4]arene has been incorporated to the hydroxy moiety of 4-hydroxyproline to give compound **98** (Fig. 4.13). This system (2 mol%) have been applied as catalyst in the aldol reaction between cyclohexanone with different aromatic aldehydes in water at 25°C. Generally, moderate yields, diastereo- and enantioselectivities were obtained, being highly dependent on the aromatic substitution. Whereas electron rich aromatic aldehydes afforded mainly the *syn*-aldol, the

Fig. 4.13 Calix[4]arene 4-hydroxyproline derivative



98



99a **99b** **100** **101a**: R = Bn **101b**: R = Ph

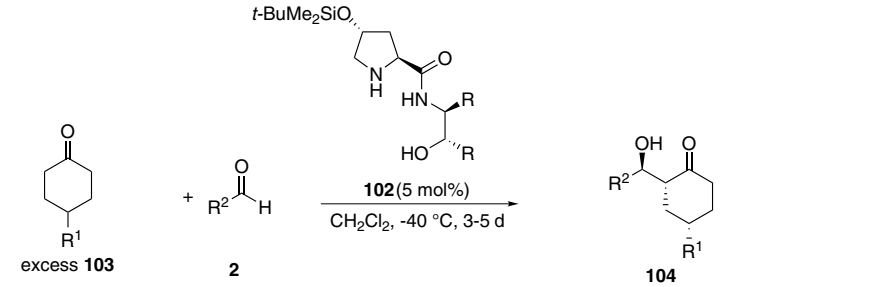
Fig. 4.14 4-Hydroxyproline amide type derivatives

use of opposite electron-poor derivatives led to the *anti*-isomer (23–73% yield, 0–80% de, 63–99% ee). Surprisingly, when cyclopentanone was reacted with p-nitrobenzaldehyde under similar reaction conditions, the corresponding aldol product was obtained in 99% yield, 24% de and 99% ee for the *syn*-isomer [182].

Several amide derivatives from 4-hydroxyproline (Fig. 4.14) have been used as catalysts in the aldol reaction using different ketones and aldehydes. Thus, catalyst **99a** (10 mol%) in combination with trifluoroacetic acid, was used in water at 25°C for the reaction between cyclohexanone and several aromatic aldehydes displaying an excellent performance (65–99% yield, 80–98% de, 84–97% ee). The scope of the reaction was expanded to the use of cyclopentanone and acetone [183]. *p*-Dodecylbenzenesulfonic acid (DBSA, 10 mol%) was required as surfactant in the aldol reaction catalyzed by compound **99b** (10 mol%) between several cyclohexanone derivatives with aromatic aldehydes in water at 25°C in order to achieve good results (74–99% yield, 82–96% de, 90–99% ee). The reaction seemed to proceed in micelles formed in the good colloid dispersion obtained by mixing reagents and substrates in water [184]. Compound **100** (10 mol%) having an axial stereoelement was used as catalyst in the reaction between cyclic ketones **3**, **14** and **48** with several aromatic aldehydes bearing electron-withdrawing groups, affording the corresponding aldol adducts **4**, *anti*-**15** and *anti*-**49** with moderate to high yields and diastereoselectivities (37–99% yield, 12–94% de) and good enantioselectivities (84–99% ee). The presence of molecular sieves as water scavengers in the reaction performed in THF at −20°C was compulsory to control background processes [185]. 4-Hydroxyprolinamide alcohols **101** (5 mol%), having three noncovalent binding sites, two hydroxy groups and the NH of the amide, which can activate the aldehyde through hydrogen bonding displayed a good activity in the reaction between acetone, used as solvent and nucleophile, and aromatic aldehydes at −25°C (48–95%

yield, 97–99% ee). The scope of the reaction could be expanded to the reaction of cyclohexanone or cyclic ketones such compound **14** and **48b** (3 equiv.) with aromatic aldehydes achieving good results in methanol at −10°C (43–77% yield, 66–98% de, 90–98% ee) [186].

Although the results using catalyst **102a** (5 mol%, R = Ph) in the reaction of acyclic ketones were good (for instance, compound **4b** was obtained in 57% yield and 91% ee in CH_2Cl_2 at −40°C) [187b], better results were obtained when used with cyclic ketones such as cyclohexanone, tetrahydro-4*H*-thiopyran-4-one and tetrahydro-4*H*-pyran-4-one, giving in all cases the corresponding isomer *anti*-**4**, **15** and **49b**, respectively. More interesting was its use in the enantioselective desymmetrization of cyclic ketones **103** by aldol reaction with aromatic aldehydes (Scheme 4.31), which gave



Scheme 4.31 Desymmetrization of cyclic ketones by aldol reaction with aldehydes

isomer **104** as the main compound. A molecule with three different stereogenic centers was created by only one synthetic operation [187a]. Very efficient catalyst was compound **102b** (R = CO_2Et) performing the aldol reaction between acyclic and cyclic ketones with aromatic aldehydes in water at 25°C with excellent results (50–99% yield, 80–99% de, 71–98% ee) using only 1 mol% of catalyst loading [187c].

The assembly of 4-hydroxyproline, well-defined camphanic scaffold and the thiourea group gave compound **105** (Fig. 4.15) in which a synergistic activation of both nucleophile and electrophile was expected to occur. Thus, catalyst **105** (20 mol%) in the presence of DBSA (*p*-Dodecylbenzenesulfonic acid, 20 mol%) as surfactant was used in water at 25°C to perform the aldol reaction between cyclohexanone (2 equiv.) and aromatic aldehydes, affording the expected aldol adducts in moderated to good results (16–87% yield, 4–98% de, 24–98% ee), highly depending on the nature and position of the substituent in the aromatic ring. Other ketones such as cyclopentanone or 2–butanone were also tested as substrates in the reaction with *p*-nitrobenzaldehyde under these conditions to give the corresponding aldols in moderate yields and diastereoselectivities and good enantioselectivities [188]. Highly efficient catalysts are compounds **106a, b** where a combination of a sulfonamide moiety with 4-hydroxyproline skeleton was

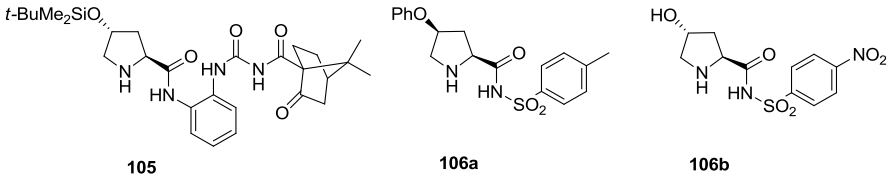


Fig. 4.15 Other 4-hydroxyproline derived organocatalysts

designed to improve the performance of aldol reaction. For instance, when catalyst **106a** (10 mol%) was used in the typical reaction between cyclohexanone and aromatic aldehydes in water as solvent, good yields (56–99%) and excellent diastereo- and enantioselectivities (70–99% de, 85–99% ee) was achieved [189a]. Using more acidic catalyst **106b**, the loading could be decreased to 3 mol% to give, under similar reaction conditions, the expected aldol products in yields ranging from 97% to 99%, diastereoselectivities from 86% to 99% and enantioselectivities around 99% for nearly every case. Under these reaction conditions, also a good performance was obtained using cyclopentanone as source of nucleophile to yield mainly the *anti*-isomer (94–99% yield, 76–84% de 96–99% ee) [189b].

4.7.1.2 Ketones as Electrophiles

Aromatic α,β-unsaturated trifluoromethyl ketones **85** (Scheme 4.27) were reacted with acetone (**3a**) in the presence of catalyst **94e** (R = $Si(SiMe_3)_3$, Fig. 4.11, 5 mol%) in DMF at −20°C, affording aldol products **86** in good yields (49–99%) and high enantiomeric excesses (74–91%). Significant effects of the type of substitution at the aromatic ring to the achieved results was not observed [190].

Compound **94f** (R = $OSiPh_2Bu^t$, 15 mol%) was able to catalyzed the reaction between aromatic α,β-unsaturated keto esters **38** and cyclic ketones such compounds **3b**, **14** and **48** (5–10 equiv.) in water at 25°C, yielding the corresponding tertiary alcohols in good results (41–99% yield, 98–99% de, 81–99% ee). Although the reaction was performed with acetone giving the expected aldol product in 85% yield and 45% ee, other aliphatic ketones failed [191].

4.7.2 Aldehydes as Source of Nucleophile

Hydroxyproline derivative **94c** (n = 8, 10 mol%) emerged as the best catalyst among other related ester derivatives for the homo-aldol reaction of enolizable aldehydes **5** (5 equiv.) and water (18 equiv.) as additive. The main product was the isomer *anti*-**29**, which was isolated after reduction to the corresponding 1,3-diol (29–97% yield, 60–90% de, 77–99% ee). Using related catalyst bearing longer or shorter alkyl chains, lower results were obtained showing the important role of the length of alkyl chain which was correlated with the emulsion character of the reaction [192].

Ion tagged hydroxyproline derivative **97h** (15 mol%) efficiently catalyzed cross-aldol reaction between aldehyde **77a** (3 equiv.) and p-nitrobenzaldehyde (**2b**) giving product **78a** in 40% yield and 99% enantiomeric excess [181].

4.8 Proline Peptide Derivatives

Short-chain peptide containing (*S*)-proline would provide a catalyst that offer many sites for structural and functional modification resembling an asymmetric environment similar to that existing in most of enzymes.

4.8.1 Ketones as Source of Nucleophile

4.8.1.1 Aldehydes as Electrophiles

Several structurally different *N*-terminal proline-dipeptides have been prepared and used in the aldol reaction (Fig. 4.16). Among them, simple dipeptide **107a** (40 mol%) was used as catalyst in combination with trifluoroacetic acid (40 mol%) and *N*-methylmorpholine (NMM, 100 mol%), in a mixture of DMSO:acetone (4:1) at 25°C giving aldol **4b** in almost quantitative yield albeit in a discrete enantioselectivity (46% ee) [193]. This result was slightly improved by increasing the peptide sequence to a tetrapeptide. From seven different *N*-terminal proline-based dipeptide set tested in the aldol reaction, compound **107b** (30 mol%) gave the best results as far as enantioselectivity concerns (87% yield, 77% ee) [194]. Similar performance was obtained by using catalyst **107c** (20 mol%). *N*-methylmorpholine (100 mol%) and propylene glycol methyl ether (PGME-5000, 5 mol%) were required as additives in order to obtain good yields and enantioselectivities (96% yield, 73% ee) [195]. Under these reaction conditions several aromatic and aliphatic aldehydes afforded aldol products **4** in high yields (62–96%) and good enantioselectivities (53–99%). Dipeptide **107d** (20 mol%) in the presence of NMM (20 mol%) and sodium dodecyl sulfate (SDS, 5 mol%) in water as solvent catalyzed the aldol reaction between cyclic ketones with several aromatic aldehydes giving the expected products **4** in good yields (67–94%) and enantioselectivities (72–95%). As occurred with prolinamides, the major diastereoisomer was *anti*-**4** for the case of cyclohexanone (50–99% de), whereas diastereoisomer *syn*-**4** was mainly obtained (18–30% de) for the case of cyclopentanone [196]. Partially protected dipeptide **107e** (20 mol%) was efficient in the aldol reaction between acetone (4 equiv.) and several aromatic and aliphatic aldehydes in chloroform as solvent at 4°C. The corresponding aldol products **4** were obtained in good yield (72–91%) and moderated enantioselectivities (65–85% ee) regardless on the nature of the aldehyde [197].

The product of the aldol reaction of methyl glyoxal **108a** and acetone (**3a**) is known as Henze's ketol (**109**). It synthesis has been studied via organocatalytic

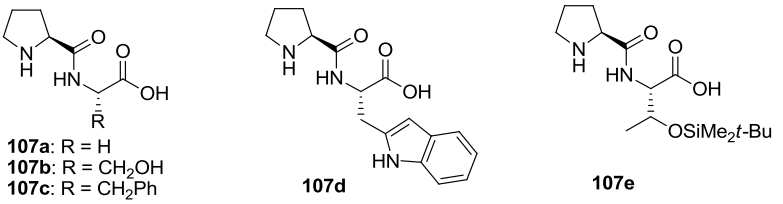
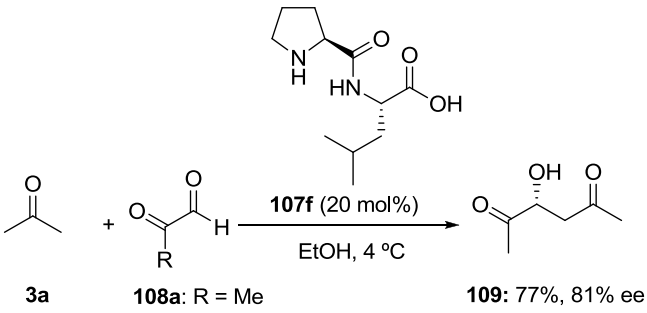


Fig. 4.16 *N*-Terminal proline-dipeptides as organocatalysts in the aldol reaction

methods using different proline derivatives with prolinamide **40** (20 mol%) in neat acetone at −24°C giving higher yields and enantioselectivities (83% yield, 71% ee) compared to those obtained in other solvents. Better enantioselectivity for aldol **109** were encountered when the reaction was performed using dipeptide **107f** (20 mol%) in ethanol at 4°C (Scheme 4.32) [198]. Product **109** was prepared under simulated physiological conditions at microscale, pointing out that this reaction might be also performed in living organisms.



Scheme 4.32 Aldol reaction between methyl glyoxal (**108a**) and acetone

The *C*-terminal carboxylic acid group of different *N*-terminal proline based dipeptide has been converted into several other functionalities (Fig. 4.17). Thus, the *C*-terminal carboxylic acid group of seven different dipeptides was transformed into several amides, which were tested in the aldol reaction between cyclohexanone and aromatic ketones. Compound **110** (20 mol%) gave the best results (27–98% yield, 72–98% de, 52–97% ee) in chloroform as solvent at - 20°C with the addition of acetic acid or 2-methylbenzoic acid (20 mol%) being required [199]. These conditions were applied also to the reaction with acyclic ketones achieving similar yields but lower enantioselectivities. Several sulphonamides salts derived from dipeptide proline-phenylalanine were screened as catalyst in the aldol reaction between acetone and *p*-nitrobenzaldehyde under different reaction conditions and in the presence of several additives. The optimal results (82% yield, 82% ee) were obtained with catalyst **111**(20 mol%) in the presence of NMM (20 mol%) in dichloromethane at −20°C [200]. The conversion the *C*-terminal carboxylic acid group in a tetrazole group would increase their solubility in typical organic solvents. Thus, the tetrazolic

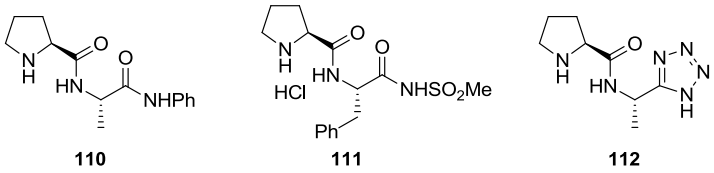


Fig. 4.17 Other *N*-terminal proline based dipetide catalysts

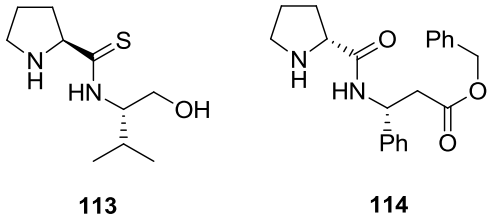
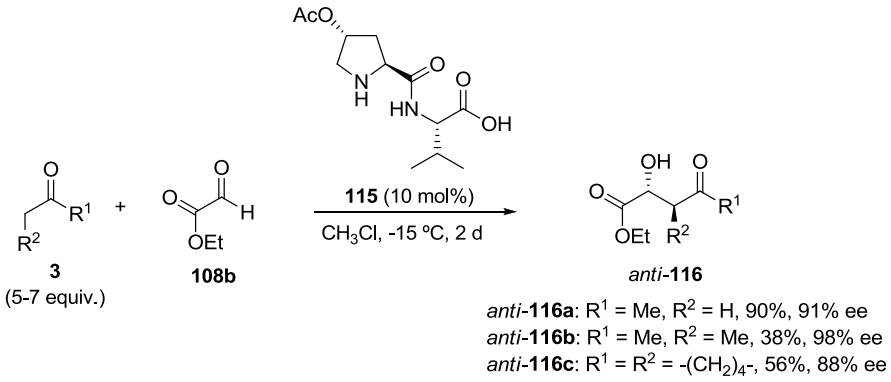


Fig. 4.18 Dipeptide derived from proline and β^3-homophenylglycine

catalyst **112** (10 mol%), in the presence of triethylamine (10 mol%), was effective in the aldol reaction between acetone (**3a**, 10.9 equiv.) and several high electrophilic aldehydes in DMF, affording the corresponding aldol adducts **4** with good yields (48–69%) and enantioselectivities (74–96%). However, when used with poor electrophilic aldehydes, such as benzaldehyde or aromatic aldehydes bearing electron-donating groups the reaction failed [201].

Further structurally modified dipeptides were used in the intramolecular aldol reaction (Fig. 4.18). Proline-valinol thioamide **113** (2 mol%) in the presence of 10 mol% of benzoic acid were efficient catalyst in the reaction between acetone and cyclohexanone with aromatic aldehydes [202]. Whereas the reaction with acetone was performed in a mixture of ketone with DMSO as solvent, affording aldol adducts **4** in moderated yields (20–87%) and good enantioselectivities (78–96%), the reaction with cyclohexanone was carried out in water at 0–25°C giving mainly *anti*-configured aldol adduct **4** in good results (36–95%, 90–98% de, 92–97% ee). The use of aliphatic aldehydes as a electrophile failed under both conditions. Dipeptide derived from proline and β^3-homophenylglycine **114** (10 mol%) was tested in reaction of hydroxyacetone (**8a**) with two aromatic aldehydes in DMSO at 25°C, giving surprisingly *syn*-configured aldol adduct **9** in good results (96–98% yield, 46–60% de, 86–89% ee). The results with a tripeptide, containing a further unit of β^3-homophenylglycine, were similar [203].

Several peptides having different pyrrolidine motifs have been used as catalyst for the intermolecular aldol reaction between ketones and aldehydes. Thus, ethyl glyoxylate (**108b**, Scheme 4.33) reacted with different aliphatic ketones **3** promoted by the *N*-terminal acetoxyproline dipeptide **115**, to give the corresponding hydroxy ester derivative, mainly as the *anti*-isomer **116**, in general, with moderated diastereoselectivities (20–90%) and good enantioselectivities (74–98%). When 2-pentanone or 4-methyl-2-pentanone were used, the main product obtained was the one obtained by reaction at the methylene position, giving the corresponding *anti*-**116** [204].



Scheme 4.33 Enantioselective synthesis of secondary α-hydroxy-carboxylates

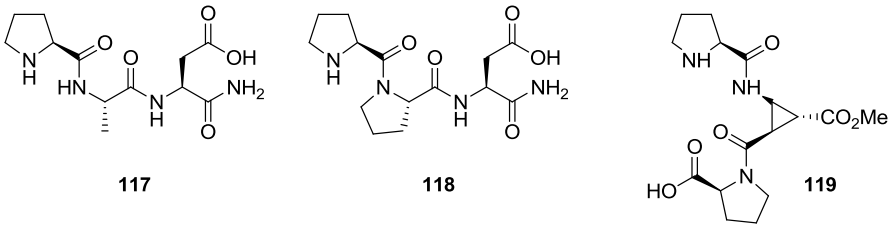
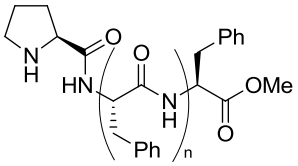


Fig. 4.19 Tripeptide type derived organocatalysts

The development of a combinatorial screening method of "catalyst-substrate co-immobilization" permitted the identification of two main consensus sequences tripeptides **117** and **118** which are catalysts for the aldol reaction (Fig. 4.19). Thus, a library of 3375 different tripeptides linked to a TentaGel resin by means of a bifunctional lysine linker, which was functionalized at the other end with a ketone derived from levulinic acid was allowed to react with a dye-marked benzaldehyde derivative at 25°C, with only 1 mol% of the beads being bright red colored. This fact indicated that these beads might catalyze the aldol reaction, since they were able to form iminium salts. Structures **117** and **118** having a proline residue at the *N*-terminal position, and a carboxylic acid moiety, were isolated from these beads. Peptides without any of these two peptides or even having these moieties but at different positions gave lower activities. Conformational analysis of these two peptides showed a preferred turn-like structure, in which the secondary amine of proline was very close to the carboxylic acid moiety of the aspartic acid residue. Catalyst **117** (1 mol%) was 30-fold more active than compound **118**, affording aldol products **4**, by reactions between acetone and aromatic and aliphatic aldehydes in the presence of trifluoroacetic acid (1 mol%) and NMM (1 mol%) as additives. Yields are ranging from 24 to in 99% and enantiomeric excesses from 70% to 91%. Remarkably, the absolute configuration of product **4a,b** was opposite to that obtained using (*S*)-proline (**1**) and also to that obtained using catalyst **117**. A possible explanation for this



120a: n = 2
120b: n = 3

Fig. 4.20 *N*-terminal proline peptide derivatives used as organocatalysts

behavior was given by the fact that catalyst **117** is a left-handed turn peptide structure, whereas catalyst **118** is a right-handed one, behaving almost as mirror image as far as the aspartame acid residue concerns, and therefore changing the configurative outcome of the reaction [205]. Short peptides, containing restricted *cis*-β-aminocyclopropyl carboxylic acid units as turn inducing elements, such as **118**, were screened as catalyst in the aldol reaction between acetone and *p*-nitrobenzaldehyde. Compound **119** (20 mol%) was one of the most effective when was used in a mixture 10:1 acetone/water at 25°C. Under these reaction conditions, acetone reacted with several aromatic aldehydes and cyclohexanecarbaldehyde to give the corresponding aldol adducts **4** in good yields (43–89%) and enantioselectivities (41–91%). The scope of the reaction was expanded to the use of cyclic ketones, affording the expected product with moderated to good results (50–96% yield, 33–99% de, 46–98% ee) [206].

The aldol reaction between functionalized ketones, such as hydroxyacetone (**8a**, 29.2 equiv.) with high electrophilic aldehydes, was possible using different *N*-terminal proline peptide derivatives (10–20 mol%) in mixtures of THF:water at 0°C. Among ten screened different di-, tri-, tetra-, penta- and hexapeptides, catalysts **120a**, **b** (Fig. 4.20) with lipophilic phenylalanine residues gave the best performance, providing mainly regioisomers *iso*-**10** (Scheme 4.3, $R^1 = H$) in 82 and 76% yield, and 82 and 87% ee, respectively [207].

4.8.1.2 Ketones as Electrophiles

From a set of 15 different dipeptides bearing α- or β-amino acid residues, dipeptide derivative **113** was selected (10 mol%) as an efficient catalyst in reactions between acetone (**3a**, source of nucleophile and solvent) and isatins **72**, giving the corresponding product **73** in good yields (90–99%) and moderated enantioselectivities (73–77%) [208a]. Under these reaction conditions convolutamydine A was synthesized, in practical quantitative yield and 68% ee, with the enantiomeric excess reaching up to >99% just by a recrystallization process [208b]. The addition of small quantities of water to this reaction increased the enantioselectivity, while the addition of large quantities (>40 equiv.) caused a detrimental effect on the results. Also, a small increase in the enantioselectivity was found as the yield increased. A DFT study involving water in the transition state, showed two energy minimum transition states, where one water molecule passively participated [208c].

4.9 Other Pyrrolidine Derivatives

In this section, pyrrolidine containing systems as substructures will be introduced.

4.9.1 Ketones as Source of Nucleophile

The C_2-symmetry (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (**121**, 30 mol%, Fig. 4.21) in the presence of triethylamine (30 mol%) was used in aldol reaction between acetone (**3a**, 36 equiv.) and different aromatic aldehydes to achieve the expected aldol products **4** with good yields (40–99%) and moderated enantioselectivities (47–73% ee). Similar results were obtained using hydroxyacetone (**8a**) as source of the nucleophile. Surprisingly, the use of cyclohexanone gave *syn*-**4** as the main product, albeit with low diastereoselectivities [209]. Although using 20 mol% of either β-proline (**122**) or bicyclic compound **123** as catalysts in DMSO, aldol product **4b** was obtained in good yields and low enantioselectivities for both catalysts (5 and 32% ee, respectively) [210b]. However, previous DFT studies predicted that bicyclic catalyst **123** and related structures would be more effective than proline [210a], further DFT computational calculations rationalized the poor results achieved [210b]. Moderated yields (5–73%) were obtained with (*S,S,S*)-perhydroindolic acid (**124**, 10 mol%) in the reaction between acetone (**3a**, 28 equiv.) and aromatic aldehydes, with the best enantioselectivities being obtained for aromatic aldehydes possessing electron-withdrawing groups (38–87% ee). In this case, the addition of water to the reaction media has a deleterious effect not only on the enantioselectivities, but also on the reaction rates [211]. (*S*)-*cis*-4-(Pyrrolidin-1-yl)proline (**125**, 20 mol%) in combination with trifluoroacetic acid (20 mol%) were more efficient in the reaction of cyclohexanone (**3b**, 19.2 equiv.) with aromatic and heteroaromatic aldehydes in DMF at 0°C affording the expected *anti*-configured **4** aldol products with good to excellent results (28–99% yield, 88–99% de, and 97–99% ee). The proximity of the *cis*-substituent to the carboxylic moiety in the transition state has a beneficial steric and electronic effect. When these conditions were applied with aliphatic aldehydes, the reaction failed. As previously, the presence of water was detrimental for the achieved yields and enantioselectivities [212].

Proline derivatives **126** (20–100% mol, Fig. 4.22) were tested for the synthesis of aldol **4b** in DMSO at 25°C with disappointing results (11–40% yield, 71–85% ee) [213]. More successful was the use of highly sterically hindered (*S*)-4,4-di(naphtha-1-ylmethyl)proline (**127**, 10 mol%) as catalyst. In the reaction between acetone (**3a**, 27.2 equiv.) and *p*-nitrobenzaldehyde (**2b**) in DMF at −10°C giving product **4ab** with good results (87% yield and 95% ee). Similar results were obtained using other aromatic or aliphatic aldehydes [214]. Slightly lower results concerning to selectivity were obtained when used with the more substituted amino acid **128** [215].

Peptidic catalyst derived from γ-amino acids **129** (15 mol%, Fig. 4.23) have been also tested in the reaction of acetone (**3a**, 54.4 equiv.) and *p*-nitrobenzaldehyde (**2b**)

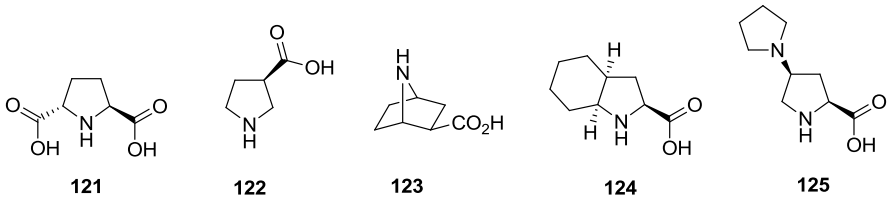


Fig. 4.21 Several pyrrolidine derivatives used as organocatalysts in the aldol reaction

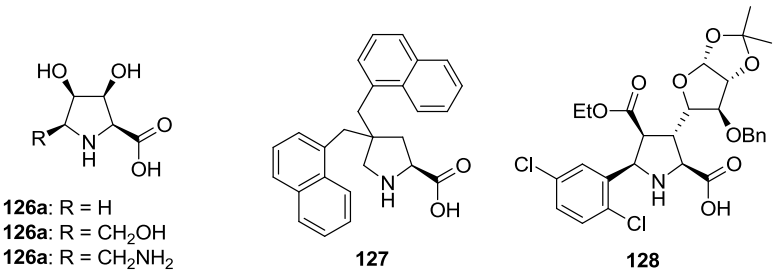


Fig. 4.22 Highly substituted proline derivatives

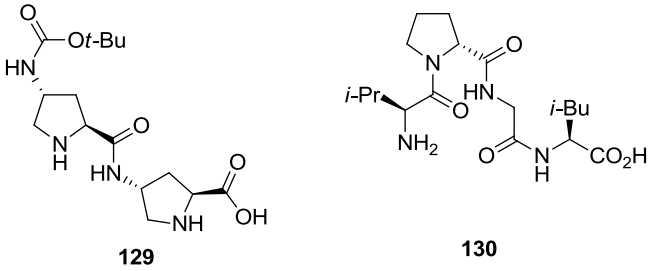


Fig. 4.23 Proline containing peptidic catalysts

in DMSO:acetone mixture (4:1, v:v) at 25°C, affording the expected aldol **4b** in only 62% yield and 75% ee [216]. Several conformational β-turn restricted tetrapeptides, containing a terminated primary amine have screened in the aldol reaction. The best results were achieved with peptide **130** (20 mol%), with different conditions being used depending on the ketone as the nucleophile source. In reactions of acetone, cyclohexanone and cyclopentanone with aromatic aldehydes in the presence of benzoic acid (40 mol%) in methanol as solvent aldol adducts **4** were obtained in moderated yields (10–84%), diastereoselectivities (6–33%) and good enantioselectivities (37–96%). When used with hydroxyacetone (**8a**) as nucleophile, (*S*)-BINOL (20 mol%) is required as additive. The reaction was performed in acetonitrile at −10°C, to afford mainly *anti*-configured products **9** (42–99% yield, 6–48% de, 62–91% ee) [217].

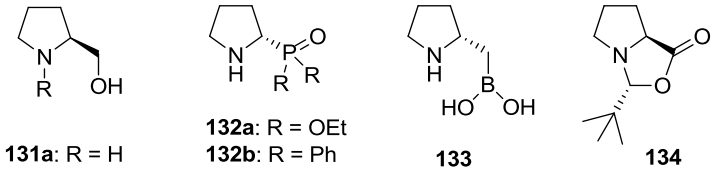


Fig. 4.24 Other pyrrolidine ring containing organocatalysts

Not only pyrrolidine ring containing the carboxylic acid moiety and its related amide have been tested in this transformation, but also other moieties has been screened as catalysts (Fig. 4.24). Thus, simple prolinol (**131a**, 35 mol%) promoted the reaction between fluoroacetone (**11**, X = F, 27.7 equiv.) and different aromatic and aliphatic aldehydes in DMSO at 25°C giving a mixture of all possible isomers (29–82%, 50–82% de, 79–87% ee). While diastereoisomers *anti*:*syn*-**12** were the major regioisomer for most of aldehydes, for glyoxylate derivative (**108c**, R = 4-$CH_3CONHC_6H_4CH_2O$) the compound of type *iso*-**13** was the main product [218]. Only 5 mol% of the highly reactive aminophosphonate **132a** was needed in the aldol reaction between cyclic ketones (**3**, **14** and **48b**, 2 equiv.) with aldehydes to afford the corresponding *anti*-aldol products **4**, **15** and **49** in moderated yields (36–79%), diastereoselectivities (0–80% de), and excellent enantioselectivities (89–98%) [219]. The reaction between 4-*tert*-butylcyclohexanone (**103**: R^1 = *t*-Bu, Scheme 4.31) and *p*-nitrobenzaldehyde (**2b**) gave a 1:1 mixture of corresponding isomers *anti-trans* and *syn-trans*-**104**. Phosphinyl oxide **132b** (20 mol%) in combination with acetic acid (20 mol%) was tested in the aldol reaction between cyclic ketones (**3**, **14** and **48**, 5 equiv.) with aromatic aldehydes giving mainly *anti*-aldol products **4**, **15** and **49** in comparable results to those obtained using **132a** [220]. The in situ generated catalyst **133** was used in the reaction of acetone and *p*-nitrobenzaldehyde to give aldol adduct **4b** in 94% yield and 82% ee. When the same protocol was performed under anhydrous conditions, using molecular sieves, the enantioselectivity was improved to 90% with lower reactivity being achieved (58% yield) [221]. Highly soluble oxazolidinone **134** (30 mol%) was used as catalyst in the reaction of acetone, cyclohexanone and hydroxyacetone with aldehydes providing the corresponding aldol products mainly as *anti*-isomer in good results (72–80% yields, 66–99% ee). 20 Equiv. of ketone were necessary to shift the equilibrium exchange between compound **134** to the required oxazolidinone intermediate which provides the aldol product [222].

Other more complex functionalities attached to the pyrrolidine ring have been used as catalysts in the aldol reaction (Fig. 4.25). Different prolinamines have incorporated into the ionic liquid motif to improve the initial reaction conditions. Hence, a library of functionalized ionic liquid have been tested as organocatalyst, with compounds **135a, b** bearing a pyrrolidine ring giving the best performance. Imidazolium derivative **135a** (X = BF_4, 20 mol%) in the presence of water (100 mol%) and acetic acid (5 mol%) gave mainly *anti*-**4** or *syn*-**4** using cyclohexanone or cyclopentanone (10 equiv.) with aromatic aldehydes, respectively, with good yields (66–92%), moderated diastereoselectivities (0–66%) and poor enantioselectivities (5–63%). When used with 10 mol% of non-covalent bifunctional catalysts **135b**

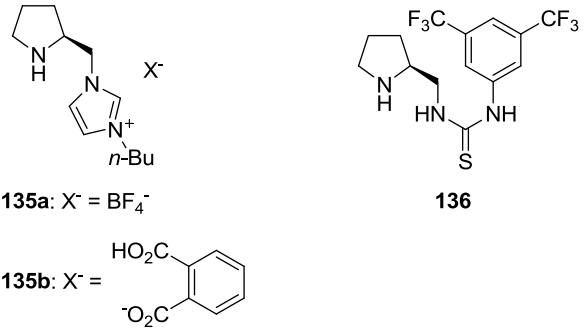


Fig. 4.25 Pyrrolidine ring containing complex functionalities

(X = 2-$HCO_2C_6H_4$-1-CO_2) was used in aldol reaction between cyclohexanone and aromatic aldehydes aldol products **4** mainly as *anti*-isomer were obtained in moderate results (66–94% yield, 23–40% de, 50–95% ee) [223]. Catalyst **135a** was recovered and reused six-fold obtaining similar enantiomeric excess but lower yields and diastereoselectivities.

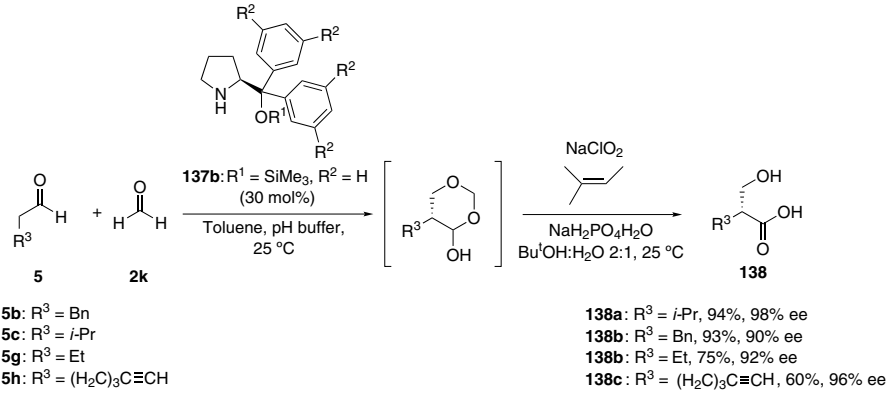
Pyrrolidine thiourea derivative **136** (50 mol%) afforded the best results (49% yield, 33% de, 85% ee), among several proline derivatives, in aldol reaction of α-ketoester and 4-pentenal, which was a key step in the total synthesis of (+)-trachyspic acid [224].

4.9.2 Aldehydes as Source of Nucleophile

4.9.2.1 Aldehydes as Electrophiles

The use of acetaldehyde (**5e**, R = H, Scheme 4.2) in aldol reaction has been reported only recently, probably due to the problems associated with some side-reactions such as polyaldolization, dehydratation, Tischenko-type processes and oligomerization [225]. However, catalyst **137a** (R^1 = H, R^2 = CF_3, Scheme 4.34) has permitted its use in the homo-aldol dimerization process [226a], and even in the cross-aldol reaction between aromatic and heteroaromatic aldehydes and acetone (**2**, electrophile) [226b]. In both cases, 10 mol% of catalyst and the in situ reduction with $NaBH_4$ to the corresponding diols, were required. Whereas the best results for the homo-dimerization process were obtained in NMP at 4°C affording the corresponding diol in 56% yield and 82% ee, the cross aldol reaction gave best performance in DMF at 23 or 4°C (50–91% yield, 96–99% ee).

Additionally, diphenylprolinol derivative **137b** (30 mol%, Scheme 4.34) was able to catalyze the hydromethylation of several aldehydes, including functionalized ones, with excellent results. The reaction proceeds using 3 equiv. of aqueous formaldehyde to give cyclic hemiacetals, which were difficult to handle and therefore were converted through Pinnick oxidation to the corresponding acid derivatives **138**. Aldehydes **5** bearing aromatic rings, oxygen or other functionalities at the α-position have a detrimental effect in the hydromethylation process. The synthesis



Scheme 4.34 Cross aldol reaction between aldehydes and aqueous formaldehyde

of compound **138d** was carried out in a large-scale without compromising the achieved results. Furthermore, this methodology was use as a key-step for the synthesis of (−)-rasfonin [227].

4.9.2.2 Ketones as Electrophiles

Several *N*-substituted isatins were reacted with acetaldehyde **5f** (5 equiv.) to afford products of type **89** promoted by catalyst **137a** (30 mol%), *N*-triisopropylsiloxymethyl protected isatin **72g**, ($R^2 = CH_2OSi[CH(CH_3)_2]_3$) affording the best result (73% yield, 85% ee). Different products **89** were prepared with similar yields and enantioselectivities performing the reaction in the presence of chloroacetic acid (60 mol%) as co-catalyst in DMF as solvent at 4°C. This procedure was applied in the total synthesis of *ent*-convolutamydine E [228].

4.10 Other Organocatalysts

As well as proline, its derivatives and other catalysts containing the pyrrolidine motif have been used in the aldol reaction, with astonishing results being achieved in some cases.

4.10.1 Ketones as Source of Nucleophile

4.10.1.1 Aldehydes as Electrophiles

In the early stage of the organocatalyzed intermolecular aldol reaction, the use of other α-amino acids different from proline failed [14a, c]. However, choosing the

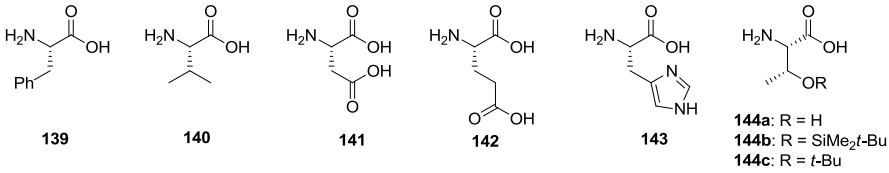


Fig. 4.26 Several α-amino acids used as organocatalysts for the aldol reaction

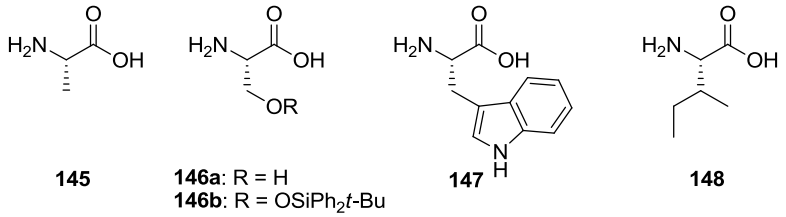


Fig. 4.27 Other proteogenic α-amino acids used as catalysts for the aldol reaction

right reaction conditions, several of these compounds have shown their effectiveness in this process (Fig. 4.26). Thus, six different α-amino acids such as (*S*)-phenylalanine (**139**), (*S*)-valine (**140**), (*S*)-aspartic acid (**141**), (*S*)-glutamic acid (**142**), (*S*)-histidine (**143**) and (*S*)-threonine (**144a**: R = H) were screened in the aldol reaction between acetone (**3a**, 13.6 equiv.) and *p*-nitrobenzaldehyde (**2b**) in DMSO:Me_2CO (3:1, v:v) at 35°C in the presence of 1 equiv. of water, giving product **4b** with modest results (25–58% yield and 12–53% ee) [229], compound **140** being the most active catalyst. Other aromatic aldehydes were used in DMF as solvent, improving the initial results up to 50–87% yield and 42–72% ee.

Other α-amino acids have been tested in the reaction of cyclohexanone with *p*-nitrobenzaldehyde (Fig. 4.27). (*S*)-Alanine (**145**, 30 mol%) was an excellent catalyst for reaction of these substrates performed in DMSO as solvent and in the presence of a small amount of water, affording a mixture of compounds *anti*:*syn*-configured aldol adduct **4** with good results (95% yield, 88% de, 99% ee). When applied these reaction conditions to protected dihydroxyacetone **16** and different aldehydes the expected aldol products **17** and **103** were isolated with general good yields (42–95%), diastereoselectivities (66–90%) and enantioselectivities (97–99%) [230]. All proteogenic α-amino acids have been studied and compared as catalysts (30 mol%) in the reaction between ketones and aromatic aldehydes in DMSO and aqueous DMSO, with most of them promoting the reaction. A positive water effect was observed in the diastereoselectivity of the reaction with most of the amino acids, while only proline (**1**), serine (**146a**) and histidine (**143**) showed a water positive effect on the enantioselectivity. Besides proline, valine (**140**) and isoleucine (**148**) gave the best results in aqueous DMSO in the aldol reaction with cyclohexanone, whereas poor results were encountered with acyclic ketones [231].

α-Amino acids containing hydroxy groups have also screened as catalysts for the reaction between cyclohexanone and aromatic aldehydes. Thus, serine derivative

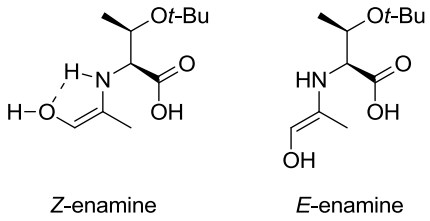
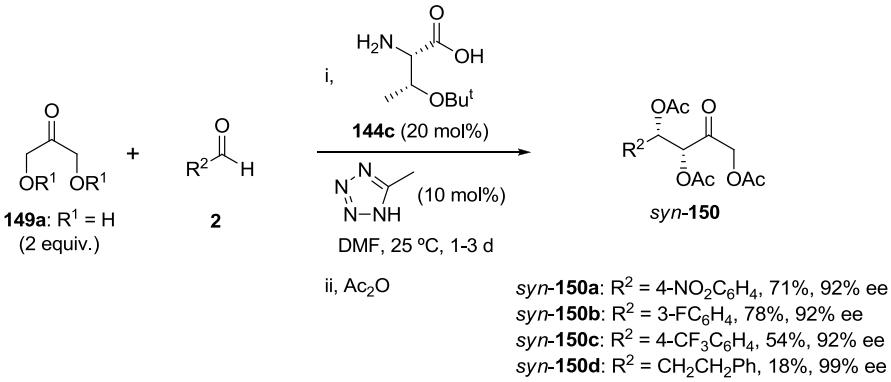


Fig. 4.28 Preferential formation of *Z*-enamine in the catalytic cycle of serine derived catalysts

146b (130 mol%, Fig. 4.27) [232a] and threonine derivative **144b** (R = $SiMe_2Bu^t$, 2 mol%, Fig. 4.26) [233a] in a mixture of cyclohexanone and water at 25°C, gave mainly compound *anti*-**4d** with excellent results (95 and 99% yield, 74 and 82% de, 98 and 96% ee, respectively). However, lower chemical yields were found when the reaction was performed using aromatic aldehydes with electron-donor groups. The catalyst **146b** has been used also under other reaction conditions. Thus, catalysts loading could be reduced to 10 mol% using ionic liquid [bmim][BF_4] as reaction media, yielding in this case the corresponding *anti*-aldol adducts **4** coming from the reaction between cyclohexanone and aromatic aldehydes in good yields and diastereoselectivities (40–96% yield, 62–76% de, 88–92% ee). The catalyst was recycled in this media four times, with some loss of activity being observed after the third cycle [232b]. If water was used as reaction media with the same amount of catalyst, slightly better results in terms of yields, diastereo- and enantioselectivities was achieved (64–90% yield, 60–84% de, 74–94% ee) [232c], while the use of brine afforded worse results [232d]. Threonine derivatives **144** (Fig. 4.26) have been used as catalyst in the reaction between several functionalized ketones with aldehydes. Thus, using *o-tert*-butyldiphenylsilyl derivative **144b** (R = $SiMe_2Bu^t$, 2 mol%) in a mixture of water:**8a** (2:1, v:v) at 25°C gave, conversely to the results obtained with proline derivatives, mainly isomer *syn*-**9** in good results (76–92% yield, 50–78% de and 91–98% ee) [233a]. Similar results were obtained when *tert*-butyl ether derivative **144c** (R = Bu^t, 20 mol%) was used as catalyst in the reaction of α-hydroxyacetone (**8a**, 2 equiv.) in a mixture of NMP:water (9:1, v:v) at 4°C [233b]. This unusual diastereoselectivity was explained due to the preferential formation of *Z*-enamine in the catalytic cycle owing to the formation of stabilizing hydrogen bonds (Fig. 4.28).

The use of unprotected α,α′-dihydroxyacetone (**149a**, R = H, Scheme 4.35) as source of nucleophile in the reaction with aromatic, heteroaromatic and aliphatic aldehydes was very interesting (Scheme 4.35). Threonine derivatives **144c** catalyzed this reaction in DMF and 5-methyl-1*H*-tetrazole to give mainly the isomer *syn*-**150** (66–94% de) with excellent results, after the acetylation process [233c]. Lowest yields were encountered for aliphatic aldehydes whereas the enantioselectivity was uniform independently of nature of aldehydes used. Also benzyl- or *tert*-butyldimethylsilyl-protected α,α'-dihydroxyacetone (**149,** R = Bn or $SiMe_2Bu^t$) could be used as source of nucleophile in this transformation. The reaction was carried out in NMP as solvent and in the presence of water at 25°C, affording the expected product in good results (65–94% yield, 60–75% de, 93–98% ee).



Scheme 4.35 Aldol reaction of unprotected α,α'-dihydroxyacetone and aldehydes

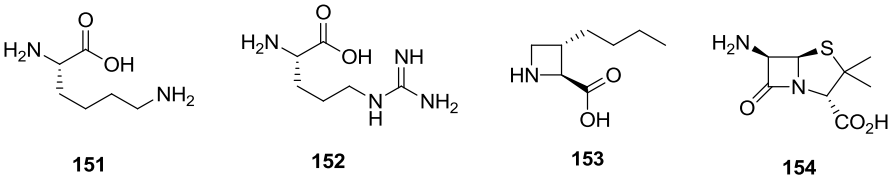


Fig. 4.29 Lysine, arginine and other cyclic amino acids used as organocatalysts

Also, aromatic α-amino acids were useful as catalyst in the aldol reaction. So, (*S*)-tryptophan (**147**, 10 mol% or 20 mol%, Fig. 4.27) has been used in the reaction of cyclohexanone and aromatic aldehydes. While the use of a mixture ketone:water gave mainly *anti*-**4** in good yield, moderated diastereoselectivity, and high enantioselectivity (42–79% yield, 72–96% de, 82–92% ee) [234a], the application of pure water resulted in lower yield and enantioselectivity [234b]. This procedure was also used with pyranone **48b**, giving **49b** in 74% yield, 24% de and 42% ee. However, the reaction failed using either the thia-derivative **14**, acyclic ketones or non-aromatic aldehydes. (*S*)-Histidine (**143**, 30 mol%, Fig. 4.26) catalyzed the aldol reaction between acyclic and cyclic ketones and aromatic aldehydes on water, although the presence of a micellar agent as sodium dodecyl sulfate (SDS) was required to achieve good yields (64–95%). However, the diastereoselectivity and enantioselectivity were low (4–66% de, 27–53% ee). Changing the reaction media to poly(ethylene glycol) (PEG-500) has an important and beneficial effect on the results (12–96% yield, 0–98% de, and 26–88% ee) [235].

The side chain protonation of lysine (**151**) and arginine (**152**) allowed their use as catalysts (Fig. 4.29) in the aldol reaction of cyclic ketones and aromatic aldehydes in ionic liquids such as *N*-butyl-*N*-methylpyrrolidinium triflate ([bmpy][TfO]) and in DMSO. Thus, catalysts **151** or **152** as their *p*-toluenesulfonic salts (10 mol%) afforded the aldol products **4** mainly as *anti*-isomer in good results (38–89% yield, 34–86% de, 76–94% ee). Catalyst **151** could be recycled by liquid/liquid extraction and reused only for three runs with similar results [236].

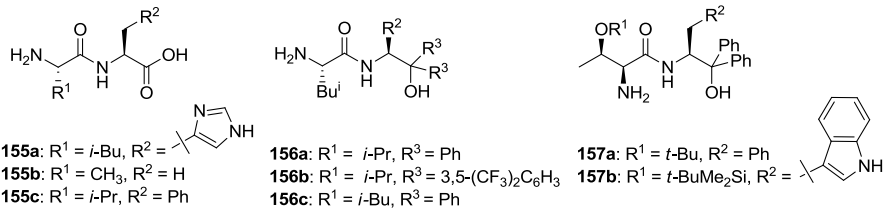


Fig. 4.30 Different peptides without containing *N*-terminal proline residues

Not only proteogenic amino acids are useful catalyst to promote the aldol, but also other cyclic amino acids served as catalysts for this reaction (Fig. 4.29). For instance, cyclic azetidine derivative **153** (10 mol%) catalyzed the reaction between acetone (**3a**, 27.2 equiv.) and aldehyde **2b** giving the expected aldol compound **4b** with 62% yield and 59% ee [237]. Also, moderated results were obtained when 6-aminopenicillanic acid (6-APA, **154**, 10 mol%) was used in the reaction between cyclohexanone and aromatic aldehydes affording mainly the *syn*-isomer (43–86% yield, 2–14% de, 18–23% ee) [238].

Different peptides without containing *N*-terminal proline residues have been also used as catalysts in the intermolecular aldol reaction (Fig. 4.30). Thus, leucine and histidine derived dipeptide **155a** (30 mol%) was tested in the reaction between acetone (**3a**, 27.2 equiv.) and different aldehydes **2** in DMSO:acetone (4:1, v:v) at 25°C, giving aldol products **4** in moderated yields and enantiomeric excesses (55–86% yield, 50–76% ee). The addition of *trans*-2,5-dimethylpiperazine (10 mol%) as co-catalyst, increased the reaction rate, but decreased the enantioselectivity (in the case of compound **4b** from 71% to 55% ee) [239a]. Alanine derived dipeptide **155b** (30 mol%) catalyzed the reaction between cyclic ketones (3 equiv.) and aromatic or aliphatic aldehydes using wet DMSO (10 equiv. of water), giving the expected *anti*-configured isomers **4** in good results (50–88% yields, 32–84% de, and 92–99% ee) [230, 239b]. Valine and phenylalanine derived dipeptide **155c** did not produce any important improvement in the previous results [239c]. Compounds **156a** and **156b** derived from leucine and β-amino alcohols were efficient for the synthesis of *syn*-aldol products [240]. Catalyst **156a** (20 mol%) gave a good performance in the reaction between α-fluoro, α-chloroacetone (**11a**) or 3-pentanone with aromatic aldehydes in dichloromethane at 25°C. However, better results were obtained using aliphatic linear ketones and α,α′-dihydroxyacetone (**149a**) as source of nucleophile performing the reaction in the presence of *p*-nitrobenzoic acid (20 mol%) in brine at 25°C (65–98% yield, 60–98% de, 73–99% ee). On the other hand, catalyst **156b** (5 mol%) was able to perform the reaction between α-hydroxyacetone (**8a**) and aromatic and aliphatic ketones with excellent results (45–97% yield, 82–98% de, 94–98% ee). Leucine derived dipeptide **156c** (20 mol%) in the presence of 2,4-dinitrophenol catalyzed the reaction between acyclic, cyclic and α-hydroxy ketones, acting both as nucleophile source and solvent, with aromatic aldehydes proving the corresponding *syn*-aldol products in yields ranging from 26% to 89% and in good diastereo-and enantioselectivities (33–99% de, 88–99% ee) [241]. The reaction between free or silylated α,α′-dihydroxyacetone (**149**) and aliphatic, aromatic

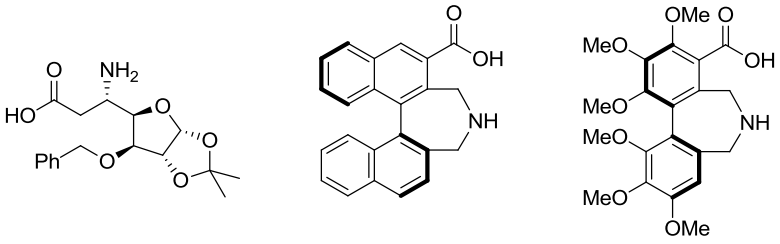


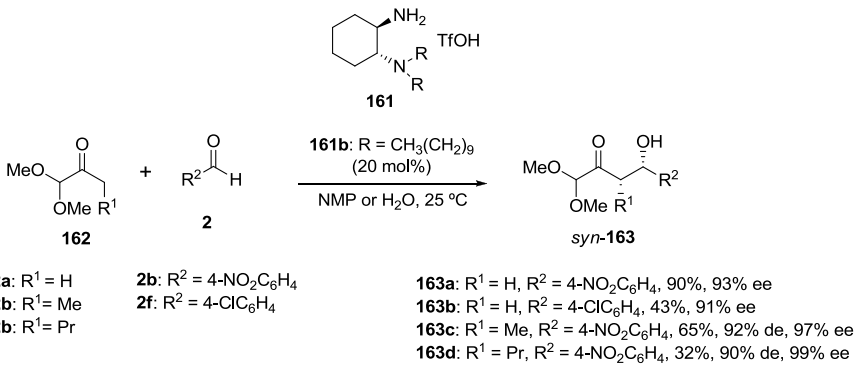
Fig. 4.31 Other amino acids type organocatalysts

aldehydes and even glyoxylated derivatives **108** was efficiently catalyzed by compound **157a** [242]. While α,α′-dihydroxyacetone (**149a**, R = H) required the use of 5-methyl-1*H*-tetrazole (10 mol%) as additive in DMF at 25°C to provide *syn*-**150** in moderated yields and diastereoselectivities (62–78% yield, 33–78% de) and good enantioselectivities (92–99% ee), protected α,α′-dihydroxyacetone gave better results in brine as solvent. Moderate results were also obtained using catalyst **157b** (4 mol%) in the reaction of hydroxyacetone (**8a**) and aromatic aldehydes in toluene or xylene as solvent (68–91% yield, 50–80% de, 76–82% ee) [243]. Polyleucines, of different commercial sources and therefore with different degree of polymerization, has been also tested as catalyst in the aldol reaction between cyclohexanone and aromatic aldehydes. In all cases, the major product was the *anti*-isomer, albeit in low yields. Generally, the selectivities displayed for all these catalysts were low and dependent on the aromatic aldehyde and the type of polyleucine used [244].

A glycosyl-β-amino acid **158** (20 mol%, Fig. 4.31) has been successfully used in the aldol reaction between acetone (**3a**, 40.8 equiv.) and different aldehydes, reaching up to 90% ee [245]. γ-Amino acid derived catalysts such as **159** and **160** were very effective in the aldol reaction [246]. Catalyst **159** (5 mol%) promoted the reaction between acetone (**3a**, 27.2 equiv.) with aromatic and heteroaromatic aldehydes in DMF:acetone (4:1, v:v), affording the corresponding products **4** with moderate to good yields (22–91%) and excellent enantioselectivities (90–95%). When cyclic ketones, such as cyclohexanone (**3b**), tetrahydro-4*H*-thiopyran-4-one (**14**) and tetrahydro-4*H*-pyran-*4*-one (**48b**) were used, the best solvent was DMSO. The *anti*-configured aldol adduct was the main product (38–98% yield, 76–90% de and 95–99% ee). However, comparable reactions with cyclopentanone gave only poor results (30% yield, 0% de, 75% ee). Remarkably, the reaction using alkyl methyl ketones took place mainly at the methylene position. Methoxylated derivative **160** was designed in order to increase the nucleophilicity of the amine and therefore its activity [246c]. The catalyst loading could be reduced to only 0.5 mol% for the reaction of acetone (**3a**, 136 equiv.) with different aliphatic and aromatic aldehydes (**2**), giving the expected products **4** in good yields (50–95%), excellent enantioselectivities (91–96%) and reaction rates similar to those described for catalyst **159**.

Diamine **161a** (R = Pr, 10 mol%, Scheme 4.36) in the presence of triflic acid (10 mol%) and *m*-nitrobenzoic acid (10 mol%) catalyzed the reaction of different ketones **3** (20 equiv.) and aromatic aldehydes, giving surprisingly *syn*-configured

compounds **4** as the main isomers. The results were in general very good (21–99% yield, 60–84% de and 85–98% ee), with the lowest chemical yields being obtained for the reaction using a rich aromatic aldehyde [247a]. Under similar reaction conditions, but using hexane as solvent, compound **161a** was also efficient in the reaction between hydroxyacetone (**8a**) and aromatic aldehydes, providing the *syn*-**9** as main product with good results. If dihydroxyacetone (**149a**) was used as source of nucleophile, the best performance was achieved by using the combination of catalyst **161b** (10 mol%, Scheme 4.36) as its triflic acid salt and *m*-nitrobenzoic acid (10 mol%) in DMF as solvent (40–97% yield, 84–96% de, 94–99% ee). However, deployment of protected dihydroxyacetone (**16**), required the use of catalyst **161c** (R = Et) to afford *anti*-**17** in good yields, diastereo- and enantioselectivities (40–99%, 60–82% de, 65–95% ee) [247b]. Also catalyst **161b** (Scheme 4.36) showed to be very efficient in the reaction between pyruvic aldehyde acetal **162** and aromatic aldehydes to give mainly *syn*-configured product **163** in moderated to good results [247c].



Scheme 4.36 Aldol reaction between pyruvic aldehyde acetal **162** and aromatic aldehydes

Other chiral diamines derivatives have shown their usefulness in the asymmetric aldol reaction (Fig. 4.32). For instance, compound **164** (10 mol%) was used in combination with trifluoroacetic acid in water as solvent for the reaction between hydroxyacetone (**8a**) or cyclic ketones such as **3b**, **14** and **48b** with aromatic aldehydes in good results (76–90% yield, 94–98% de, 90–99% ee). Whereas products **9** were obtained mainly as *syn*-isomers, the reaction with cyclic ketones gave *anti*-aldol adducts as major products [248]. Compound **165** (5 mol%) was evaluated in the aldol reaction between cyclic ketones such as **3b** and **16**, in a mixture of THF/water as solvent at 25°C, affording mainly *anti*-aldols as main products in yields depending on the nature of the aromatic aldehydes used (25–99% yield) and in high diastereo- and enantioselectivities (66–99% de, 76–99% ee). Remarkably, by changing the 1,4-position in catalyst **165** opposite configuration in aldol adducts were obtained [249]. High performance (23–96% yield, 60–99% de, 87–98% ee) was also obtained using catalyst **166** (3.5 mol%), bearing a group with an axial chirality.

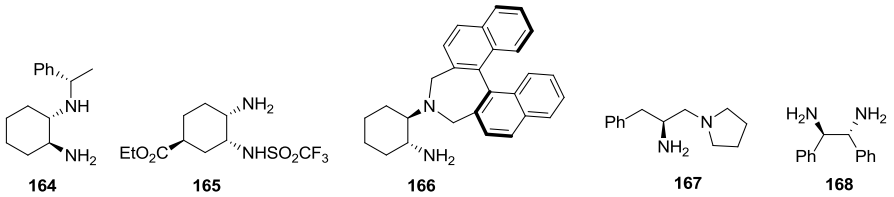


Fig. 4.32 Other chiral diamines derivatives as organocatalysts in the aldol reaction

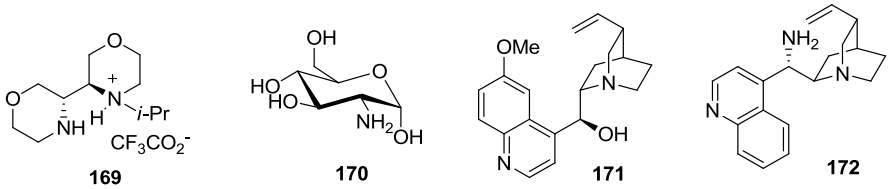


Fig. 4.33 Other chiral amines used as organocatalysts

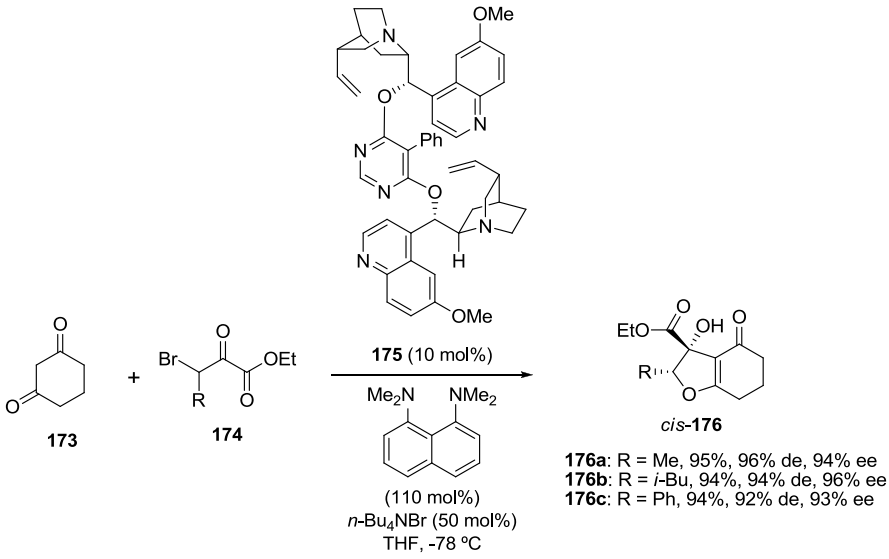
The aldol reaction of cyclic ketones and acetone with aromatic aldehydes were carried out in combination with triflic acid in water at 25°C [250]. Other chiral primary-tertiary diamine catalyst such as compound **167** (20 mol%) was used in combination with solid polyoxometalate acid support (6.67% mol) in the aldol reaction between dihydroxyacetone (**149a**) and aromatic aldehydes in NMP as solvent at 25°C to afford mainly *syn*-aldol products in good yields (59–97%) and high diastereo- and enantioselectivities (78–99% de, 84–99% ee). The combination of catalyst **167** with triflic acid was used in the reaction of acyclic ketones and α-hydroxyketones **8** with aromatic aldehydes also with good results [251]. Simple chiral diamine **168** (10 mol%) in the presence of triflic acid (20 mol%) was applied as catalyst in the reaction between acetone and cyclohexanone with aromatic aldehydes in water at 25°C, giving aldol adducts **4** in low yields (15–58%) and moderate diastereo- and enantioselectivities (50–98% de, 45–93% ee) [252].

Bimorpholine derivative **169** (30 mol%, Fig. 4.33), which was highly active in the intramolecular aldol reaction, was also able to promote the intermolecular version of acetone (**3a**, 27.2 equiv.) and different aromatic aldehydes, with results depending strongly on the nature of aldehydes. While aromatic aldehydes bearing electron-withdrawing groups gave *ent*-**4b** in good yields (48–91%), other aromatic aldehydes led to very poor yields (10–18%). However, the enantioselectivities were independent on the nature of the aldehyde (76–94% ee) [253]. Natural amines such as glucosamine **170** (10 mol%) were tested as catalyst in water in the standard aldol reaction of acetone and aromatic aldehydes giving poor results [254]. *Cinchona* alkaloids such as compound **171** and **172** have been used as catalysts in this process**.** Quinidine (**171**, 10 mol%) was used in the reaction of hydroxyacetone (**8a**) and aromatic aldehydes yielding mainly *syn*-**9** with moderate results (11–96% yield,

0–80% de, 23–44% ee) [255a]. Better performance has been showed with cinchonine derived amine **172** (10 mol%) in the presence of trifluoroacetic acid (15 mol%) in the reaction between cyclic ketones and aromatic aldehydes (19–99% yield, 0–80% de, 56–99% ee) [255b]

4.10.1.2 Ketones as Electrophiles

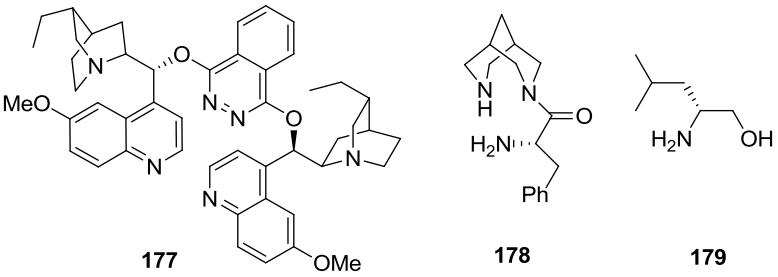
Some systems of different structure have shown their ability to catalyze the formation of a new carbon-carbon bond by reaction of two ketones. The enantioselective aldol reaction between 1,3-cyclohexanedione (**173**) and different α-bromoketo esters **174** followed by final cyclization gave as the main compound *cis*-configured **176**. Several *Cinchona* alkaloid derivatives were tested in this transformation, with the dimeric catalyst system **175** in the presence of a proton sponge and an ammonium salt affording the best results (Scheme 4.37) [256]. Also dimeric *cinchona*



Scheme 4.37 Aldol reaction between 1,3-cyclohexanedione with different α-bromoketo esters

derivative $(DHQ)_2PHAL$ (**177**, 10 mol%, Fig. 4.34) was able to promote the reaction of isatins **72** with highly reactive ethyl trifluoropyruvate (**38b**), yielding the corresponding oxindole products with two contiguous asymmetric quaternary centers in good yields (61–99%) and high diastereo- and enantioselectivities (66–94% de, 79–99% ee) [256b].

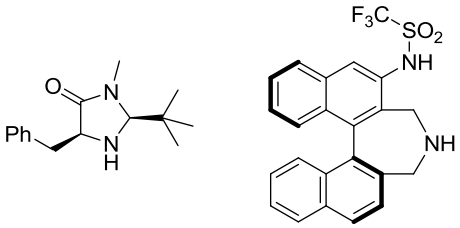
The enantioselective synthesis of α-hydroxy phosphonates **26** was accomplished with bispidine derivative **178** (5–30 mol%) in the presence of formic acid (20 mol%) performing the reaction in acetone as solvent, in good yields (35–97%)



177 178 179

Fig. 4.34 Organocatalysts able to promote the aldol reaction between two ketones

Fig. 4.35 Organocatalysts used for the homo-cross-aldol reaction between aldehydes



180 181

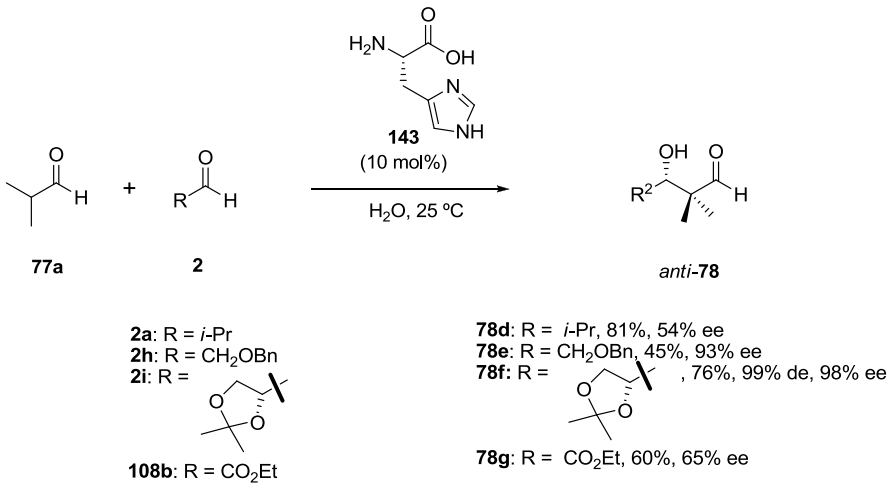
and enantioselectivities (82–98% ee), regardless on electronic and steric nature of the α-keto phosphonate used as electrophile [257]. Simple leucinol (**179**, 20 mol%) was used for the enantioselective synthesis of convolutamydine A by reaction of acetone (**3a**) with 4,6-dibromoisatin (**72**: R^3 = 4,6-Br_2) in dichloromethane at 25°C in 88% yield and 94% enantiomeric excess [258].

4.10.2 Aldehydes as Source of Nucleophile

The imididazolidinone **180** (10–20 mol%, Fig. 4.35) catalyzed the homo-aldol dimerization process of an aldehyde and also the cross-aldol reaction between enolizable aldehydes (**5**, source of nucleophile, 10 equiv.) and aromatic aldehydes (**2**, electrophile). For both cases, the yields were high (58–90%), the *anti*-diastereoselectivity was moderated (60–86% de) and the enantioselectivity was excellent (91–97% ee). To prevent a hemiacetal reaction of the initial aldol product **29** with another equivalent of aldehyde, the reaction was quenched by a methanolysis process to form the corresponding dimethyl acetal [259].

Chiral binaphthylsulfonamide derivative **181** (5 mol%) promoted successfully the cross-aldol reaction of aldehydes, using only 2 equiv. of the source of the nucleophile in NMP. Conversely the main diastereoisomers obtained were *syn*-configured **29** in good results (22–99% yield, 40–90% de, 92–99%) [260].

Recently, it has been reported the use of histidine (**143**, 10 mol%) as promoter in water for the cross aldol reaction between two enolizable aldehydes (Scheme 4.38).

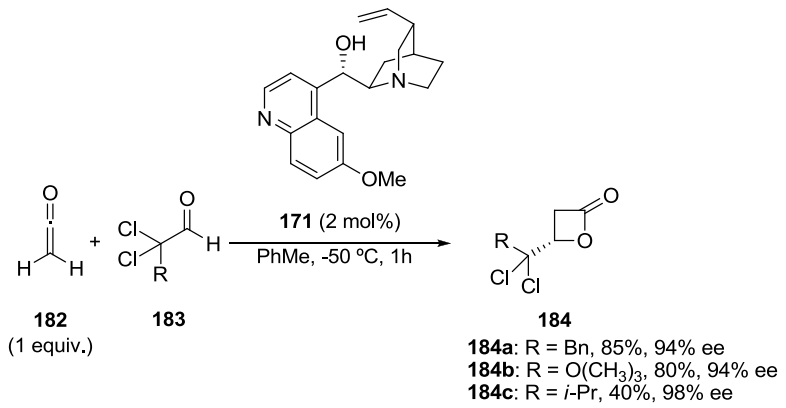


Scheme 4.38 Cross-aldol reaction between enolizable aldehydes catalyzed by histidine

The catalyst was able to differentiate and control the reactivity of both used aldehydes, allowing the synthesis of chiral β-hydroxy aldehydes bearing a quaternary stereocenter in good results (40–95%, 50–99% de, 41–98% ee) [261]. By using this reaction protocol, the total synthesis of branched-chain natural products such as pantolactone or lyxose derivatives were successfully accomplished.

4.10.3 Ketenes as Source of Nucleophile

Quinidine (**171**) was used as catalyst in the reaction of ketene **182** (acting as acetic acid equiv.) and different α,α-dichloroaldehydes **183** to give after cyclization process the corresponding α-lactones **184** with in general good results (Scheme 4.39)



Scheme 4.39 Synthesis of chiral α-lactones by organocatalyzed aldol reaction

[262]. In situ prepared ketene by dehydrochlorination of the corresponding acyl chloride with Hünig's base, afforded similar results [262c]. A further modification was the dimerization of ketenes **182** in situ formed from different alkanoyl chlorides to afford 3,4-dialkyl-*cis*-α-lactone derivatives [262d].

4.11 Supported Organocatalysts

In this section, different examples of supported catalyst will be presented following the criteria outlined in the content section. In this context, proline and its derivatives, as well other organocatalyst, have been incorporated to inorganic or organic supports to give new catalytic systems, which can be used under homogeneous or heterogeneous conditions, with the aim of recovering and reusing the catalytic species. Although some of the following examples are not small organic molecules, they have considered and covered here because the attached polymer or support only plays a marginal role in the catalytic process, although the activity could be modulated somehow, rendering different results to those using the so-called free catalyst.

(*S*)-Proline (**1**, 10 mol%) have reused performing the aldol reaction between acetone (**3a**, 4 equiv.) with different aromatic or aliphatic aldehydes at 25°C in recyclable media such as polyethylene glycol PEG-400 which is a non-toxic solvent [263]. Under these conditions, aldol adducts **4** were obtained with good results (58–94% yield and 58–84% ee). The products were isolated just by diethyl ether extraction from the poly(ethylene glycol) medium, which contained the organocatalyst **1**. The reaction media (including catalyst) could be reused ten-fold with a slightly decrease of yields, maintaining the enantioselectivity. The use of ionic liquid media such as 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmin] PF_6) as solvent allowed the recycling of proline (**1**, 30 mol%) in the reaction of acetone (**3a**, 27.2 equiv.) with aromatic or aliphatic aldehydes [264]. Aldol adducts **4** were obtained with moderated results (58–83% yield and 67–71% ee), together with a considerable amount of aldol condensation by-product (10–23% yield of the corresponding α,β-unsaturated ketone). Only a slightly decrease on the results was observed when the reaction media was reused four-fold. Remarkably, the chemical yields of reaction could be increased just by decreasing the ketone amount to seven equiv, as the reaction media being recycled without detrimental on the previous results [264b]. Different silica gel containing ionic liquid tails (3-methylimidazolium motif), has been tested in the aldol reaction. The ionic liquid containing proline (30 mol%) was adsorbed to the modified silica, promoting the reaction of acetone (**3a**, 27.2 equiv.) and *p*-nitrobenzaldehyde (**2b**) at 25°C, to give aldol **4b** in 83% yield and 48% ee [265], together with aldol condensation by-product. The structure of ionic liquid had an important effect on the enantioselectivity, with the best anion and cation partner being BF_4 and 1-*n*-butyl-3-methylimidazolium, respectively [265b]. This system could be recycled three-fold without important variations on the results. Also the structure of the linker used to attach the ionic liquid to the silica was evaluated, with modified silica gel bearing more sterically demanding aryl-alkyl

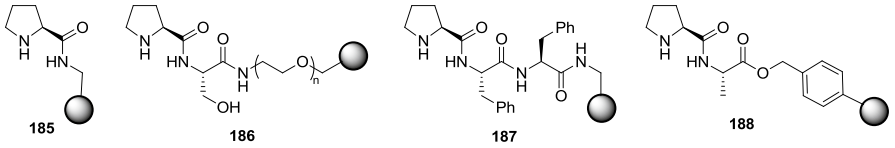


Fig. 4.36 Solid resins L-proline supported derivatives

linker having better performance. Tripeptide **118** was also supported in these last ionic liquid modified silica gel, providing better results to that encountered with proline under similar reaction conditions [265c]. Inorganic layered double hydroxides (LDH) have been used as heterogeneous support for proline [266]. These systems consist of stacks of positively charged mixed metal hydroxide layers that require the presence of interlayer of proline anions, to maintain the overall charge neutral. When a Mg-Al-NO_3 LDH-(*S*)-proline system was used as catalyst (1 mol%) in the reaction between acetone (27.2 equiv.) and benzaldehyde in acetone:heptane (1:4, v:v), aldol adduct **4** was obtained with good chemical yield (95%) but low enantioselectivity (6%) [266a]. The related system derived from Mg-Al-CO_3 LDH showed a better behavior reaching up to 94% ee when 35 mol% of proline was the charge of system [266b]. Instead of an inorganic cationic support, an organic cationic polymer has been used to immobilize proline. Thus, proline was adsorbed in poly(diallyldimethylammonium) and used as catalyst (15 mol%) for the reaction between acetone (**3a**, 30 equiv.) and benzaldehyde to give the expected aldol product with moderated results (53–59% yield and 66–69% ee), independently on the molecular mass of support as well as its anionic counter ion (Cl, BF_4 or PF_6). These polymeric systems have been recycled six-fold without losing enantioselectivity [266c].

Also, proline derivatives have been introduced into different supports to facilitate their recovery and reuse. For instance, proline and several short peptides have been incorporated to solid resins and tested in the aldol reaction (Fig. 4.36). Thus, polystyrene resin with an amino group terminal has been coupled to proline, affording the corresponding catalyst **185** (20 mol%), which gave product **4** in the reaction between acetone (**3a**, 68 equiv.) and aliphatic aldehydes, with good results (55–100% yield and 54–86% ee). This catalyst could be recovered up to three-fold and reused with important detrimental effect on the results [267]. Different *N*-terminal proline peptides have been attached to a PEG-polystyrene resin. Among then, resin **186** (13 mol%) emerged as the best catalyst in the reaction between acetone (160 equiv.) and *p*-nitrobenzaldehyde (**2b**) at −25°C, yielding the expected compound **4b** (98%, 82% ee), with the removal of PEG-linker (dipeptide directed bound to the aminopolystyrene resin) lessening the results (**4b**: 26%, 60% ee) [268]. The resin bounded tripeptide **187** did not produced any important advantage [269]. Merryfield supported dipeptide **188** (10 mol%) was used in the reaction between cyclohexanone, tetrahydro-4*H*-thiopyran-4-one (**14**), acetone and hydroxyacetone with several aromatic aldehydes, affording the corresponding aldol products in good yields (52–98%), moderate diastereoselectivities (20–80%) and good enantioselectivities (75–95%). The recyclability of this catalyst was proved, with seven reaction cycles being performed with only a slightly decreased in the achieved yields [270].

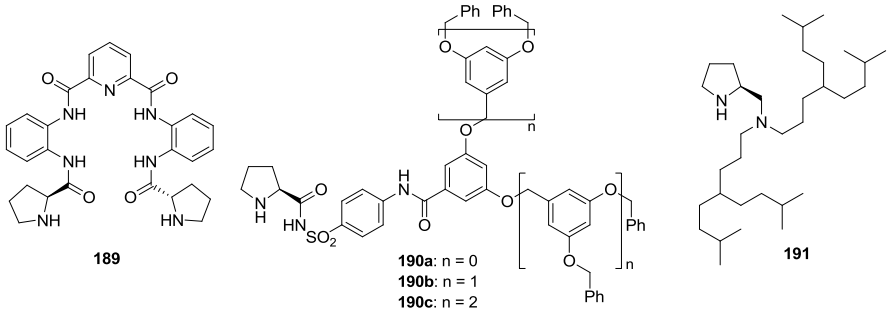


Fig. 4.37 Dendronized proline derivatives used as organocatalysts

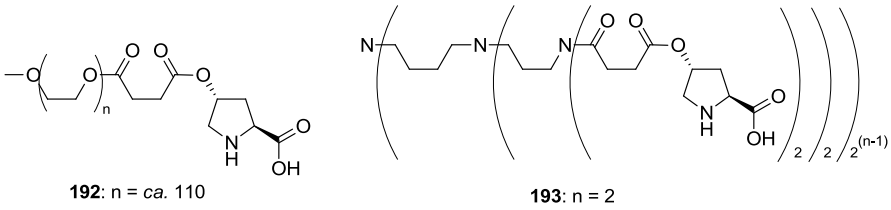


Fig. 4.38 4-Hydroxy proline supported in PEG-500 monomethyl ether and diaminobutane poly(propyleneimine) dendrimers

The attachment of proline and proline derivatives to dendrons was a further strategy used to attempt their recycling (Fig. 4.37). Thus, "compact" and "expanded" dendrimers functionalized with prolinamide units at the periphery such as system **189** were used in the aldol reaction of cyclopentanone and cyclohexanone with *p*-nitrobenzaldehyde, with a possible dendritic effect that increased the stereoselectivities observed with simple *N*-benzylprolinamide and G1 dendron **189** [271].

Attachment of sulfonamide to a Fréchet dendritic wedges provided catalysts **190a–c** (10 mol%), which have been tested as catalysts in the reaction between cyclohexanone (**3b**, 2 equiv.) and *p*-nitrobenzaldehyde (**2b**) in pure water as solvent at 25°C, affording mainly the isomer *anti*-configured **4d** with excellent results (86–92% yield, 94–98% de and 98–99% ee). Catalyst **190b** (n = 1) gave the best results due to the hydrophobic effect of the dendritic wedges. This catalyst was recovered by precipitation using a *n*-hexane:ethyl acetate mixture and reused five-fold without any detriment on the results [272]. Dendritic amphiphilic catalyst having a proline-derived core and one or two nonpolar hydrocarbon dendrons were used as catalysts in the aldol reaction between cyclohexanone and aromatic aldehydes, with good results (5–95% yield, 28–66% de, 35–93% ee) being obtained with the first generation catalyst **191** and second generation dendrimer (10 mol%), which formed stable emulsions, in the presence of trifluoroacetic acid (10 mol%) in water at 23°C [273].

4-Hydroxyproline has been incorporated to a PEG-500 monomethyl ether polymer by means of a succinate spacer rendering catalyst **192** (30 mol%, Fig. 4.38),

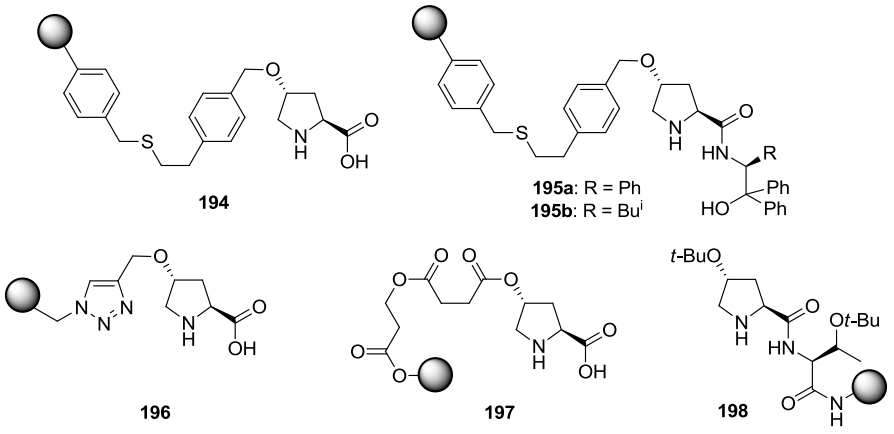


Fig. 4.39 4(*R*)-Hydroxyproline supported in solid resins

which was used in the aldol reaction between acetone (68 equiv.) and different aromatic and aliphatic aldehydes giving the expected aldol compounds **4** in modest yield and enantioselectivities (8–81%, 59–98% ee). While the best chemical yields were achieved in DMSO as solvent, the highest enantioselectivity was obtained by using DMF as solvent. When hydroxyacetone (**8a**, 66 equiv.) was used as source of nucleophile in the reaction with cyclohexanecarbaldehyde, the expected product *anti*-**9** was obtained in low yield (48%, 90% de and 96% ee). The catalyst could be recovered by filtration and reused twice with a marginal variation [274]. 4-Hydroxyproline have been also supported in the commercial available diaminobutane poly(propyleneimine) dendrimers, containing different numbers of free amino groups (4, 8, 16, 32 and 64) at the surface of structure giving homogenous catalysts of type **193** [275]. Among five dendrimers tested, second generation compound **193** (n = 2, 26.5 mol%), bearing eight α-amino acid units, gave the best result in the reaction between acetone (27.2 equiv.) with *p*-nitrobenzaldehyde (**2b**) in DMF:acetone (4:1, v:v) at 25°C (61% yield, 65% ee). When used with water comparable enantioselectivities were obtained. A negative dendritic effect, which is caused by a steric hindrance between proline units at the surface of nanomolecular compound, was observed for dendrimers of high generation, giving lower enantioselectivities.

4(*R*)-Hydroxyproline motif has been incorporated into a resin following different synthetic strategies (Fig. 4.39). Grafting the styrylmethylmercapto derivative of 4(*R*)-hydroxyproline to polystyrene gave polymer **194**, which has been used as catalyst (10 mol%) in the aldol reaction between cyclohexanone (5 equiv.) with different aromatic aldehydes in the presence of water (2 mol%) without solvent giving mainly *anti*-configured isomer **4** with good chemical yields (71–98%), diastereoselectivities (84–92%), and excellent enantioselectivities (90–98%) [276]. The scope of the reaction has been extended to other cyclic ketones affording similar results. However, when acetone was used as source of nucleophile low yields were encountered.

The resin could be recovered just by simple filtration and reused four-fold with highly reproducible enantioselectivities but with a slightly decrease on the yield. The same synthetic strategy has permitted the grafting of prolinamides such as **195** to a polystyrene resin. Both polymers (10 mol%) were able to promote he aldol reaction between acetone and cyclohexanone in a mixture of chloroform:water as solvent at 25°C in good results (14–98% yield, 82–96% de, 80–99% ee), with their regeneration by treatment with formic acid being needed in order to assure their recyclability. In this manner these catalyst species could be reused up to 16 times without being detrimental on the achieved results [277].

Catalyst system **196** was prepared from azide-substituted Merrifield resin through a 1,3-dipolar cycloaddition reaction with the corresponding *O*-propargylic hydroxyproline derivative [278]. This resin (10 mol%) was used in the aldol reaction between alkyl ketones (**3**, 5 equiv.) with different aromatic aldehydes in the presence of water and poly(ethylene glycol) dimethyl ether (DiMePEG-2000, 10 mol%) rendering the expected aldol compounds **4** (70–97% yield, 64–94% de, and 93–97% ee). The presence of water was compulsory to achieve a good performance, suggesting that the reaction took place at the interphase between polymer and the aqueous phase, with DiMePEG-2000 facilitating the diffusion of reagents from solvent to the resin interphase. The resin **196** could be reused three-fold without detrimental results. Free-radical copolymerization of 4-hydroxyproline derived methacrylates or acrylates gave acrylic polymer beads such as compound **197**, which were used as catalysts (5–10 mol%) in water for the enantioselective synthesis of aldol adduct **4d** with similar results for all the different polymeric structures tested (65–85% yield, 76–96% de, 97–98% ee). Worse results were obtained when a soluble ketone such as acetone was used as source of nucleophile [279]. TentaGel-bound resin was used as support for hydroxyproline-threonine dipeptides such as polymer **198**, which were used in the aldol reaction between methyl ketones **21** and aromatic aldehydes to afford the corresponding aldol products in moderate yields (65–79%) and high enantioselectivities (94–98% ee). The application of this system could be extended to the aldol reaction between aromatic methyl ketones to 3-methylcyclohexanone, giving the corresponding aldol products, which after an intramolecular cyclization process permitted the synthesis of chromanones in good results [280].

System **199** having a long inert spacer placed between the resin and the catalytic site of the reaction in order to minimize the negative influence of resin surface was prepared (Fig. 4.40).

Among three prepared dendritic resins, second generation compound **199** (30 mol%) gave the best performance (90% yield and 84% ee) in the reaction between acetone (27.2 equiv.) with *p*-nitrobenzaldehyde (**2b**) in DMSO:acetone (4:1, v:v) at 25°C, with lower generation systems giving lower enantioselectivities. The reuse of catalyst produced a sharp decrease on the chemical yield obtained for compound **4b**, maintaining the enantioselectivity [281]. The synthesis of simple models of this supported dendritic catalysts, based on linear or more complex partially dendritic spacers, showed that the proximity of the proline units was crucial to achieve good results [281b]. Using this type of catalyst the formation of any by-products was not observed. However, high amounts of cyclic by-products were obtained when dendronized

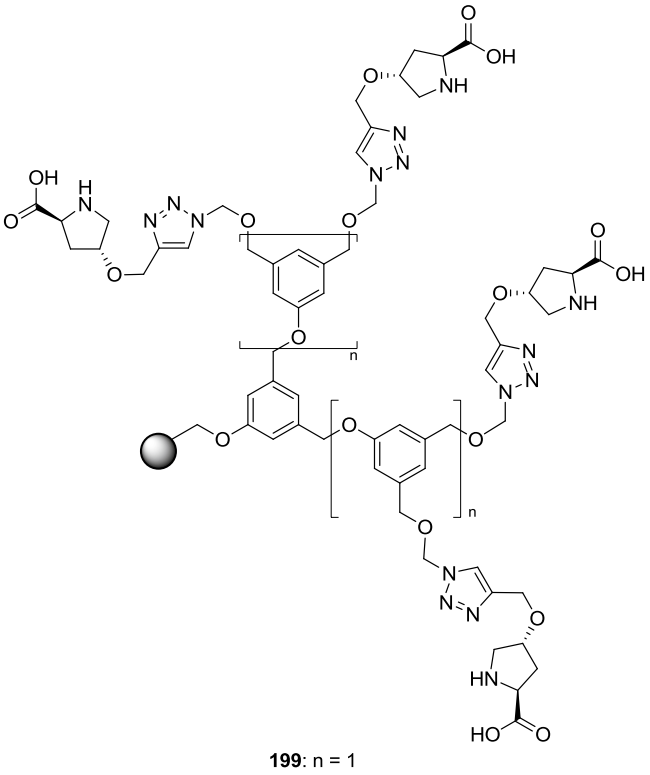


Fig. 4.40 Dendronized 4(*R*)-Hydroxyproline derivative

polystyrene resins attached to a proline unit through the carboxylate moiety and having an additional guanidine unit in other dendron arm were used as catalyst in the aldol reaction between acetone and aromatic aldehydes [281c].

4-hydroxyproline has been also incorporated to silica via a sol-gel process, through an ether or a carbamate linker to give systems **200**, with different molar ratios of silica oxides per hydroxyproline derivative (y). These systems (30 mol%) were tested as catalysts in aldol reaction between acetone and *p*-nitrobenzaldehyde. Catalyst **200b** afforded good conversions but with low enantioselectivities for all tested cases [282]. The 4(*S*)-aminoproline motif has been incorporated to different mesoporous and lamellar siliceous materials with different topologies and screened as catalyst in the aldol reaction between hydroxyacetone (**8a**, 29.2 equiv.) and aliphatic and aromatic aldehydes. The best performance was obtained with catalyst **201** (20 mol%) in DMSO:hydroxyproline (1.6:1, v,v) at room temperature, yielding aldol products **9** with moderate to good results (55–60% yield, 16–90% de, and 70–99% ee). Using microwave conditions to perform the reaction, decreased the reaction times from 1–3 days to 10–30 min. Surprisingly, aliphatic aldehydes afforded the expected *anti*-configured isomer **10** as main product of the reaction,

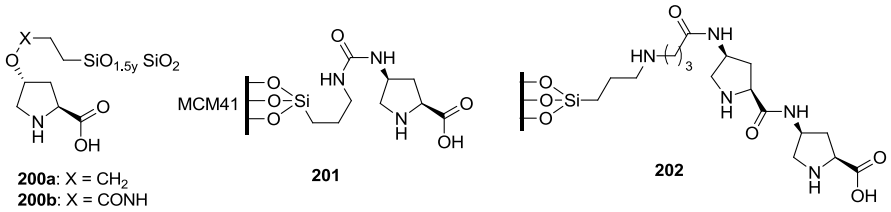


Fig. 4.41 Proline derivatives immobilized in several silica supports

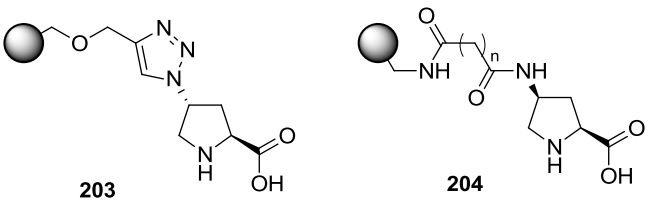
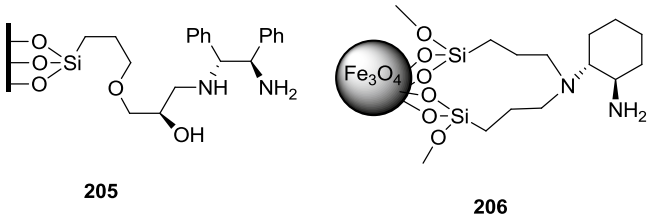


Fig. 4.42 4-Aminoproline moiety supported in solid resins

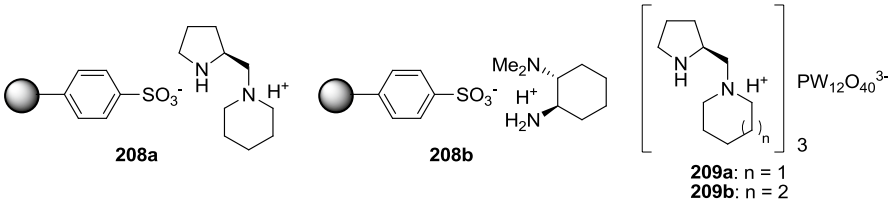
while the reaction with benzaldehyde afforded the corresponding *syn*-configured isomer **10** [283a]. This mesoporous catalyst (30 mol%) was used in the aldol reaction between protected dihydroxyacetone **16** and *p*-nitrobenzaldehyde, giving *anti*-configured **17** as a main product, with lower conversion but moderate enantioselectivities. They were achieved in non-polar solvents such as toluene. Good conversion but poor enantioselectivity were obtained in polar solvent such DMF [283b]. Also proline based peptides have been supported in silica. Thus, in the presence of catalyst **202** (5 mol%), the aldol reaction between acetone and several aldehydes in acetone/DMSO as solvent mixture gave the corresponding aldol products in good yields (55–97%) and enantioselectivities (64–96%). This catalytic system could be recovered for the reaction media by filtration and reused up to five times without loss of reactivity [284] (Fig. 4.41).

The 4-aminoproline moiety has been supported in polystyrene resins (Fig. 4.42). Thus, 4(*R*)-aminoproline was bounded to polystyrene through a 1,2,3-triazole linker to afford polymer **203**, which swelled perfectly in water forming a gel-like single phase. Resin **203** (10 mol%) was used as catalyst in the aldol reaction between cyclohexanone and aromatic aldehydes, giving mainly *anti*-configured **4** aldol isomers in good results (16–98% yields, 68–94% de, 94–98% ee). Lower catalyst loading (1 mol%) was permitted in the homo-aldol reaction of propanal (R = Me in **5a**) to achieve a complete conversion affording *anti*-configured **29** in 66% de and 97% ee [285]. 4(*S*)-Aminoproline has been incorporated to a polystyrene resin through a flexible spacer, giving polymers **204** (n = 2 or 4,% mol%), which were tested in the aldol reaction of cyclohexanone and aromatic aldehydes to afford, in DMF/water media, *anti*-configured **4** in similar yields ranging from 46% to 94% and good



205 206

Fig. 4.43 Other chiral diamines incorporated to a solid supports



208a 208b

209a: n = 1
209b: n = 2

Fig. 4.44 Nonconvalently supported organocatalysts

diastereo- and enantioselectivities (66–90% de, 84–96% ee). Lower yields and diastereoselectivities were obtained when same reaction conditions were applied to acyclic ketones (acetone or 2-butanone) and aromatic aldehydes, albeit the enantioselectivities levels were maintained. The polymeric resins could be reused up to five times with a slightly decreased on the reactivity [286].

Not only prolines but also chiral diamines have been incorporated to a solid support and tested in asymmetric aldol reaction (Fig. 4.43). Polysiloxanes have served as support for a chiral primary amine rendering catalyst **205** (20 mol%), which was used in the reaction between cyclic ketones (10 equiv.) and aromatic aldehydes in the presence of triflic acid or 4-nitrobenzoic acid to give mainly the corresponding *anti*-configured isomers **4** in good yields (53–97%), moderate to good diastereoselectivities (33–99%) and excellent enantioselectivities (65–99%) [287]. Magnetic nanoparticles have been used to immobilized chiral 1,2-cyclohexyldiamine giving system **206** (20 mol%) which has a good performance (53–98% yield, 33–84% de, 84–98% ee) in the presence of trifluoracetic acid in water at 25°C. The catalytic system could be recovered from the reaction media using a simple magnet and reused up seven cycles with unchanged activity. TEM Images of the catalytic system showed that the nanospheric dimensions as well as the silica coating were maintain after these reaction cycles, but a slight aggregation was observed [288].

Nonconvalently supported organocatalyst have shown their efficiency in the aldol process (Fig. 4.44). The noncovalent immobilization of a prolinamine through acid-base interaction in a solid acid polystyrene sulfonic acid resin gave catalytic systems which were tested in preparation of the aldol **4d**. The catalytic system **208a** (10 mol%) afforded the best results among the proline systems

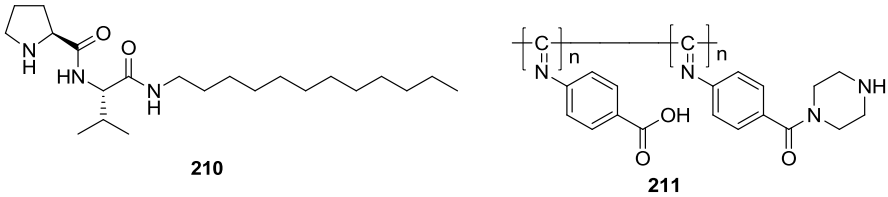


Fig. 4.45 L-Proline hydrogel supramolecular structure and chiral poly(phenyl isocyanides) used in the aldol reaction

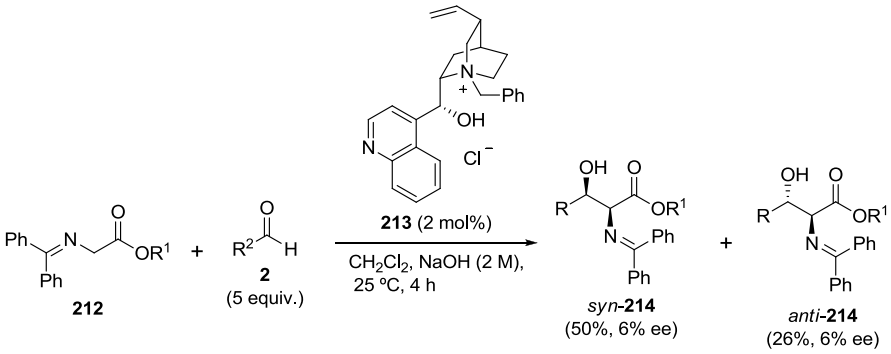
screened in dichloromethane as solvent. Another chiral diamine were also used as cationic part of this system with catalysts **208b** giving the best performance (67–99% yield, 66–86% de, 89–97% ee) under similar reaction conditions. This catalytic system could be recovered and reused five times with a sharp decrease in the yield obtained in the fifth run. Washing the catalysts with HCl/dioxane and recharging with chiral diamine led to the recovery of the catalytic activity [289]. Solid acid-proline hybrids were explored as catalyst in the aldol reaction between acetone and *p*-nitrobenzaldehyde, with systems **209** proving the best results. Only 0.33 mol% of catalyst loading was required to perform the reaction between acetone, 2-butanone, cyclohexanone or cyclopentanone with aromatic aldehydes using the ketone as source of nucleophile and solvent giving good yields (11–99%) and enantioselectivities (87–99%), but moderate diastereoselectivities (50–80%). Similar results were achieved under aqueous conditions. Under the last conditions, the recyclability of the catalysts was studied. Catalyst **209b** was reused up to six times with only a slightly decrease on the achieved yields [290].

Finally, the hydrogel supramolecular structure, formed from L-proline compound **210** (Fig. 4.45) was tested as catalyst (20 mol%) at 5°C in the enantioselective aldol addition. Aldol adduct **4d** was isolated with 98% yield, 88% de and 88% ee. The hydrogel was obtained by dissolving above concentration of 2 mM in hot water and sudden cooled at 25°C. After decantation of the organic phase, the macroscopic structure of the hydrogel seemed not to be affected, with its reused being possible for two additional reaction cycles with the same results [291]. Chiral poly(phenyl isocyanides) partially modified with achiral amines, such as piperazine **211**, maintained their chiral helicity and were applied as catalysts (100 mol%) in the aldol reaction between acetone or cyclohexanone with *p*-nitrobenzaldehyde giving low yields (11–44%) and poor enantioselectivities (6–12%) [292].

4.12 Phase-Transfer Catalysis

Enantioselective phase-transfer catalysis (PTC) has been extensively applied for the alkylation, epoxidation, conjugate addition and related process, with the use of chiral ammonium salts being the typical transfer agent [293]. However, the related aldol

process has been scarcely investigated. The first example of this type of process was the reaction of glycine derivatives **212** with different aldehydes **2** using cinchonidium salt **213** as catalyst (Scheme 4.40) [294]. A disappointed 1:1 diastereomeric mixture of products **214** with very low enantiomeric has been reported. However, the great interest of β-hydroxy-α-amino acids for the pharmaceutical industry lead to important efforts to improve this process.



Scheme 4.40 Phase-transfer catalysis of chiral β-hydroxy-α-amino acids

Cinchonidium salt of type **215** (Fig. 4.46) were essayed as catalysts for this transformation [295]. While derivative **215a** gave practically negligible enantioselectivity, using catalyst **217b** (17 mol%), an excess of aldehyde (4 equiv.) and *tert*-butyliminotris(pyrrolidino)phosphorane (BEMP) as organic base (1. 7 equiv.), the expected products **214** were achieved in moderated results (34–78% yield, 0–14% de, and 52–83% ee for *syn*-**214**). Compounds **214** were very unstable in the chromatography isolation. Therefore, they were transformed by hydrolysis of the imine and acylation to the more stable amide derivative. The reduction of the amount of the phosphazene base used led to a lower yield but a higher enantiomeric excess. Aromatic aldehydes gave better results, with those bearing neutral or poor electron-withdrawing groups providing the best enantioselectivities. The catalyst **215b** has been also used as catalyst in the aldol reaction between α-alkoxy acetophenone derivatives using sodium hydroxide as base [296], with enantioselectivities below 22% ee. Catalyst **216** (17 mol%) was used under similar conditions to those previously mentioned using BEMP (2.5 equiv.) as organic base to gave compounds **214** in similar results (38–86% yield, 0–82% de and 2–43% ee for *anti*-**214**) but with the *anti*-**214** isomer being the major product in many cases [297]. Astonishing performance was achieved using a very sophisticated salt **217** (2 mol%) and 1% aqueous NaOH and toluene at 0°C, since the reaction of glycinate **212** ($R^1 = Bu^t$) and aliphatic aldehydes (2 equiv.) afforded in short reaction times the expected product **214** with good chemical yield, diastereoselectivities (39–84% and 33–95%, respectively) and excellent enantioselectivities for the main isomer *anti*-**214** (80–98% ee) [298]. The increase in the reaction time led to the reverse of the diastereoselectivity,

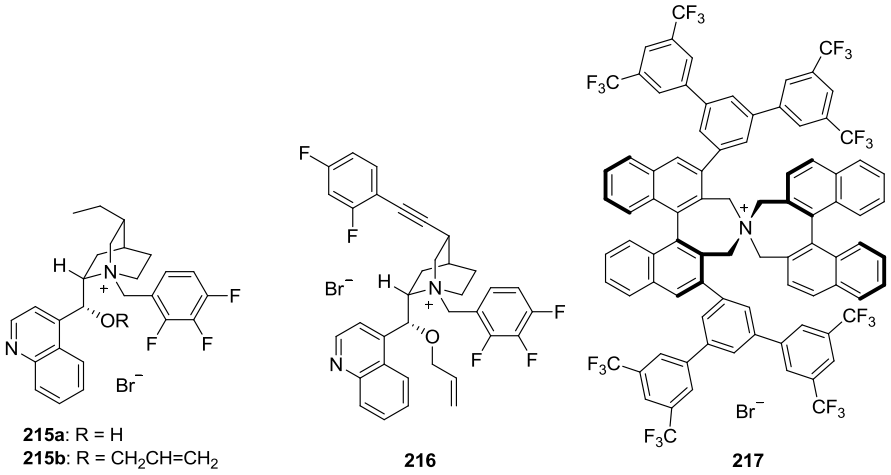
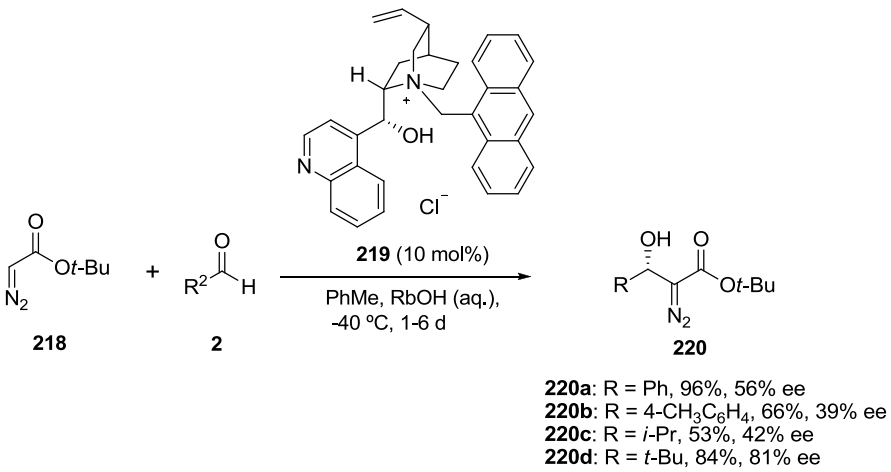


Fig. 4.46 Phase-transfer catalysts tested for the synthesis of chiral β-hydroxy-α-amino acids

the decrease of the ee of *anti*-**214**, while the ee of *syn*-**214** remained unchanged. These facts were attributed to the existence of a retro-aldol process in which the chiral catalyst played an important role. To minimize this retro-aldol process, the amount of aqueous base should be decreased, adding inorganic salts (NH_4Cl) to control the pH of the overall process.

The enantioselective PTC-aldol process between aromatic aldehydes and diazo-ester derivatives **218** has been successfully accomplished by cinchonidium salt catalyst **219** (Scheme 4.41). From all bases tested RbOH provided the best results, with

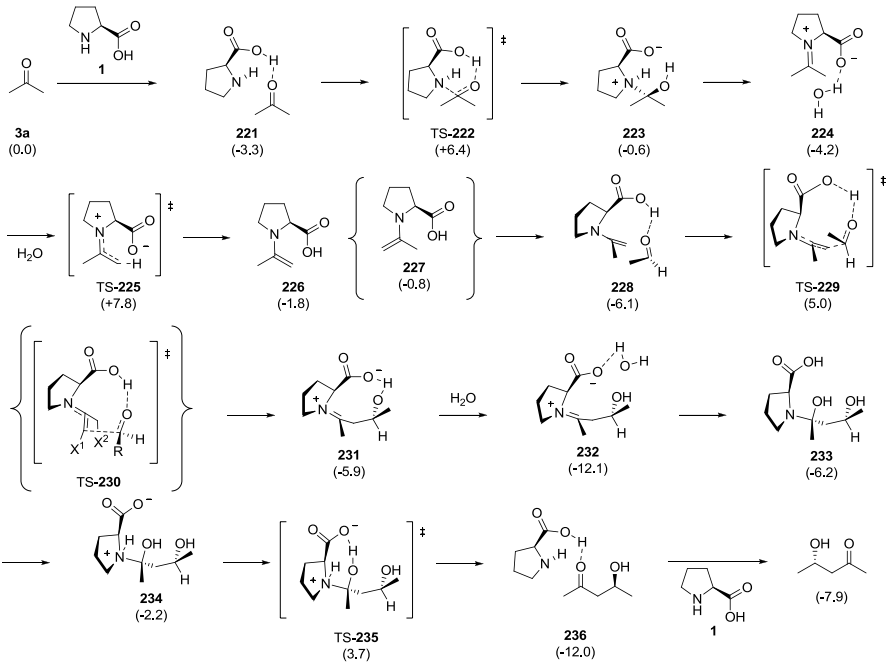


Scheme 4.41 PTC-aldol process between aromatic aldehydes and diazo-ester derivatives

the enantiomeric excess being influenced strongly by the electronic character of substituent of aldehyde. Thus, aromatic aldehydes with strong electron-donor substituent gave racemic mixtures of compounds **220**, while aliphatic aldehydes gave moderated results except in the case of pivaldehyde ($R^2 = Bu^t$ in **2**), which reached 81% ee [299].

4.13 Mechanistic Studies

A great effort has been done in order to elucidate the possible mechanism pathway of the aldol reaction catalyzed by proline-type. The initial computational calculation of all possible different steps of the intermolecular reaction process [300] showed a similar profile to that disclosed for the intramolecular one (Scheme 4.42). Gas-phase conditions calculations led to an initial complexation of acetone (**3a**) by the proline (**1**) to give very stable species. However, under DMSO conditions, the stability of **221** is not so high. The formation of enamine **226** follows the expected steps. At this point, different alternative pathways were given by different authors. The original study implies the complexation of this *syn*-conformer (active methylene group relative to carboxylic acid one) in a *cis*-mode, to form intermediate **228**, which through transition state **229** rise to zwitterionic intermediate **231**, liberating the catalyst **1** and expected aldol product after the usual steps.



Scheme 4.42 Possible calculated mechanistic steps of the intermolecular reaction process

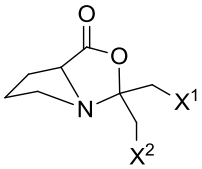


Fig. 4.47 Intermediate heterocyclic oxazolidinone formed by reaction of proline **1** with ketone

For this initial pathway, the enamine formation was the rate-determining step with the asymmetric transition step having a similar energetic level. Alternatively, the *anti*-conformer **227** has been proposed, since the energetic difference between both possible enamine conformers is only 1 kcal/mol and the rotation around single C-N bond could take place very easily [301]. In fact, when the quantum mechanical calculation of the possible transition states for the reaction with acetone (TS-**230**: $X^1 = X^2 = H$) or cyclohexanone [TS-**230**: $X^1–X^2 = (CH_2)_3$] with acetaldehyde, benzaldehyde or isobutyraldehyde were reevaluated [302], the transition state with lower calculated energy was of type TS-**230** in all cases (*anti*-enamine, *re*-carbonyl and carboxylic activation or *cis*-mode), implying the C-N bond rotation previous to the reaction with the electrophile. The stability of this transition state was rationalized, as above, due to the favorable hydrogen bonding interaction between the hydrogen of the nitrogen in the pyrrolidine ring with the oxygen of the reactive carbonyl group. Accurate reaction enthalpies and sources of errors in DFT thermochemistry applied for the aldol reaction and other organocatalyzed processes have been performed, showing the satisfactory application of such calculation for these processes [303].

Intermediates of type **223**, **227** (**226**), **231** and **234** could be detected either as the protonated specie or as the sodium complex using electrospray ionization mass spectrometry confirming the above reaction profile [304].

Further calculations have been done for other proline derivatives. Thus, results encountered with prolinamide **40** corroborated this mechanism [103b], while the initial calculation results for the case of tetrazole **90a** were not conclusive [158b]. However, a further study was concordant with previous calculations showing that, although, the related *anti*-enamine intermediate had only 0.37 kcal/mol more than the corresponding *syn*-conformer (compare conformers **226** and **227**), the corresponding transition state (*anti*-enamine, *re*-carbonyl and tetrazole activation, compare with TS-**230**) was 1.99 kcal/mol more stable than any other possibilities [305]. Moreover, similar calculation studies performed for alanine catalyst (**145**), showed again the initial formation of corresponding *syn*-conformer, which rotates to the *anti*-one, with the postulated more stable transition stated being related with TS-**230** [306]. Finally, DFT calculations explained the opposite *syn* versus *anti* diastereoselectivities found with catalysts **156a**, **b** and compounds **45a**, **b**, with this difference arising from the steric repulsion of the enamine nitrogen (hydrogen for derivatives **156a**, **b** and methylene in derivatives **45a**, **b**) with the substituent in the nucleophilic ketone of the *Z*-enamine [307].

An alternative process has been postulated occurring through the formation of corresponding heterocyclic oxazolidinone (see Fig. 4.47) by reaction of proline

1 and ketone **3** (clearly detected by NMR studies, isolated for some proline derivatives and their structures evidently confirmed by X-ray diffraction experiments) [308]. The deprotonation process rises to the expected *syn*-conformer **226**, which reacts in a *trans*-mode (respected to carboxylic group) with the corresponding electrophilic carbonyl compound. In a simultaneous process, one oxygen atom of carboxylic acid moiety reacts to regenerate the initial oxazolidinone ring.

This whole picture is still more complicated due to the partial solubility of α-amino acids in the reaction media [309]. The crystallization of racemic mixtures can give three different type of crystals. The most common situation is the formation of a racemate-crystal, in which both enantiomers are forming part of the unit cell by symmetry. More strange is the case of conglomerate-crystal, in which a physical mixture of both enantiomerically pure crystals is achieved. The last possibility is the solid-solution-crystal, in which the enantiomers are randomly distributed. However, the prediction of whether a given compound will form crystal of a concreted type is impossible in practice. Thus, for example when proline was solved in chloroform in the presence of small quantities of ethanol, a large non-linear effect was observed [310]. The initial enantiomeric excess was 10% and after a triturating process in the above solvent mixture, the enantiomeric excess raised up to 99%, with the highly selective dissolution of one enantiomer being cause not by a simple extraction of the excess enantiomer but by the following dissolution and recrystallization mechanism. In this context, the use of a co-solvent could modify the expected crystal structure for the racemic mixture, and therefore changes this non-linear effect.

Under certain conditions has been observed that proline with different enantiomeric excess catalyzed the intermolecular aldol reaction with the same enantioselectivity. The phase study of this process, showed that proline formed two solid phases at equilibrium (conglomerate-crystals), forming an eutectic point. At this stage, the same composition for the solved proline independently of the composition of the initial mixture of both enantiomers was obtained [311]. The concentration of the excess enantiomer at the eutectic point depends on the solvent and temperature, even on the presence of doping agents [312], and corresponds closely to the solubility of the pure enantiomer. However, the solid-solution equilibrium is not always reached for many reactions and the expected eutectic conditions could not be applied. For instance, α-amino acid proline during this transient period has a higher solubility than in equilibrium conditions. This fact could modified the enantioselectivity of the aldol reaction. This high proline solution concentration under non-equilibrium conditions has been explained as a function of the higher solubility of conglomerate-crystals at the eutectic point to the enantiopure phase than racemate-crystals [313]. All these effects could lead to erroneous interpretation for non-linear effect as a result of two or more chiral molecules acting in the transition state [314].

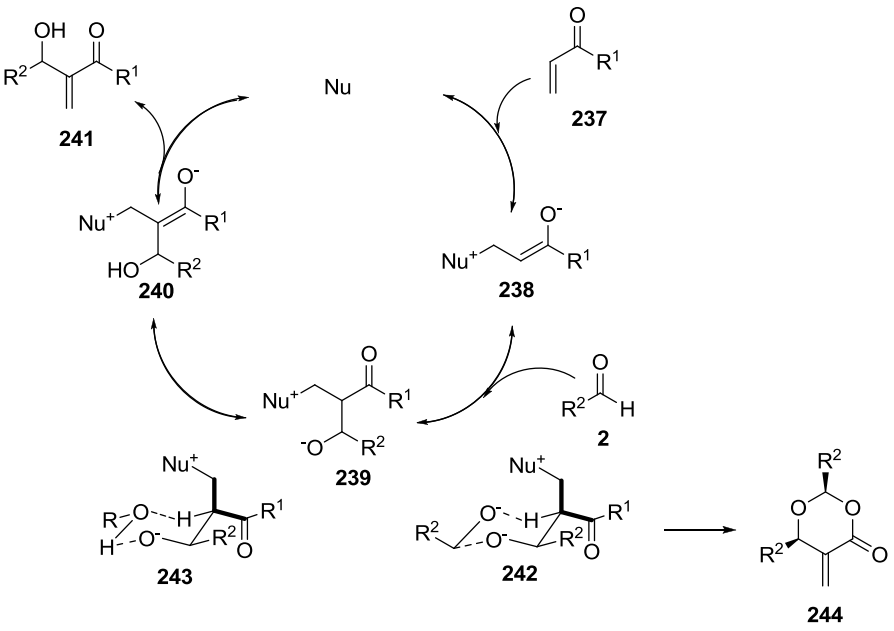
Finally, kinetic studies for the aldol reaction showed that this process was characterized by a well-behaved positive order kinetics, conversely to that observed in other related organocatalytic processes [315].

4.14 Enantioselective Morita-Baylis-Hillman (MBH) Processes

As it was commented in the introduction part, the Morita-Baylis-Hillman reaction allows the synthesis of highly functionalized α-methylene-β-hydroxycarbonyl compounds through a carbon-carbon bond formation process by addition to an aldehyde to an α,β-unsaturated compound, with an active nucleophile (generally and amine or phosphine) being required. The reaction begins by the addition of the nucleophile to the enone, giving an enolate, which adds to the electrophilic aldehyde, leading to the formation of a new stereogenic center. The formation of this new stereocenter could be controlled by either the use of a chiral α,β-unsaturated compound or chiral aldehyde (diastereoselective MBH reaction) or either by the use of a chiral catalyst. In this enantioselective version of the process, chiral organocatalysts to which this section is devoted to, has successfully used in the last decade [11c].

4.14.1 Mechanistic Considerations

As it has been pointed out before, the mechanism of the organocatalyzed aldol reaction have been extensively studied. Conversely to this situation, the related MBH mechanism (Scheme 4.43) has been scarcely investigated probably due to the complexity of the reaction sequence.



Scheme 4.43 MBH proposed mechanism

Formally, the MBH reaction involves a sequence of Michael addition, aldol reaction and β-elimination. The commonly proposed mechanism consists in a reversible conjugate addition of the nucleophile to the starting enone **237**, generating an intermediate enolate **238**. This enolate reacts with the electrophilic aldehyde in an aldol-type process, in which two stereogenic centers are formed, to give **239**, which suffers an intramolecular acid-base equilibrium to give another enolate **240**. From this intermediate, the β-elimination of the nucleophile provides the MBH product **241** with the recovery of the catalyst. For a long time, the aldol process leading to the formation of zwitterionic intermediate **239** was considered the rate determining step. However, detailed mechanistic studies for this and the related aza-MBH process [316], showed that the acid-base equilibrium was the rate limiting step, which is a difficult process in **239** due to geometric constrains. Two transition states **242** and **243** have been proposed to facilitate this process. The difference between them was the participation of a molecule of protic solvent. In the case of aprotic media, transition state **242** takes place as is confirmed by the frequent formation of by-product **244**. Thus, a chiral catalyst should control the diastereo- and enantioselectivity at the aldol step and the acid-base equilibrium by differentiation of the four possible diastereoisomers.

Recently, the use of ESI-MS technique had permitted the detection of several of these proposed intermediates such as **238** and **239** in the MBH reaction in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) and an achiral thiourea. The presence of thiourea molecule being crucial for the stabilization of such intermediates [317b]. DFT calculations also showed that thiourea accelerates [317a] the MBH process by decreasing the transition states energies through bidentate hydrogen bonding [317b].

4.14.2 Chiral Lewis Base Catalyst

4.14.2.1 Tertiary Amines as Organocatalysts

As expected from the depicted mechanism, early attempts to control the stereoselectivity of the MBH reaction was focused on the application of chiral amines (Fig. 4.48). Thus, using high pressure conditions (5 kbar) to accelerate the reaction and a C_2-symmetric DABCO derivative **245** (15 mol%), product **241a** (R^1 = Me, R^2 = 4-$NO_2C_6H_4$), was obtained in 45% yield and 47% ee (1 mol% hydroquinone, THF, 30°C) [318]. When used with pyrrolizidine derivative **246** (10 mol%, acetonitrile, –40°C) improved results (17–93% yield, 39–72% ee) were obtained in reactions between methyl or ethyl vinyl ketone (**237a**: R^1 = Me and **237b**: R^1 = Et) and aromatic aldehydes. The presence of $NaBF_4$ as co-catalyst was required to achieve these results, due to the coordination of aldehyde and hydroxy group of the catalyst to the alkali metal, which fixed the orientation for the attack of the nucleophile to the electrophile in the transition state [319].

Other, proline derivatives have been tested in this reaction. Thus *N*-methyl prolinol **131b** (R = Me, 50 mol%) was used as catalyst in 1,4-dioxane:water mixture at 0°C. In this case, besides the use of compound **237a**, the scope of the reaction was

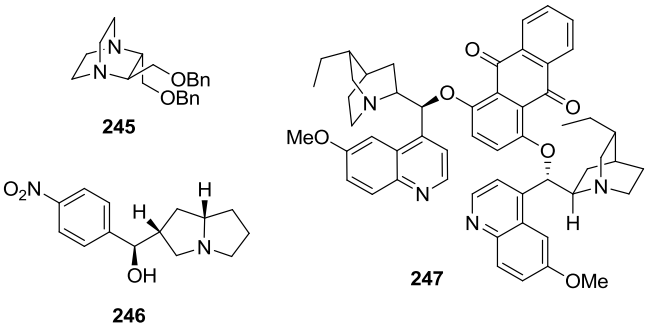
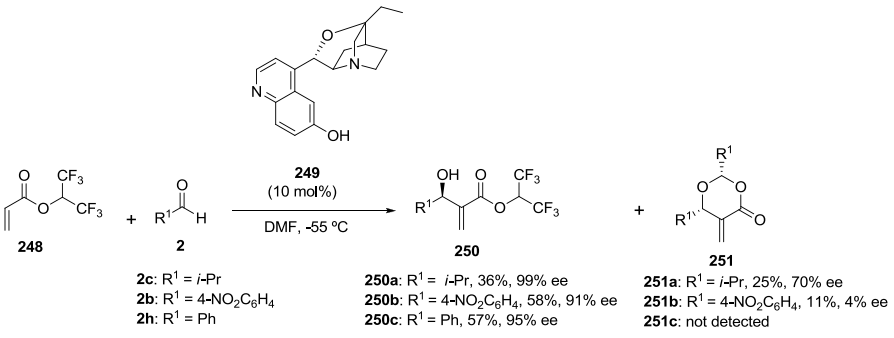


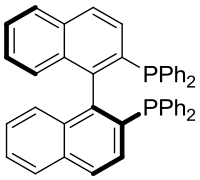
Fig. 4.48 Tertiary amines as organocatalysts for the MBH reaction

extended to the use of ethyl acrylate **237c** (R^1 = OEt), affording the corresponding products in good yields (64–94%) and moderate enantioselectivities (15–78% ee) [320]. Similar yields were obtained using pyrrolidine **75a** (30 mol%) in ethanol at 0°C to perform the reaction of methyl ketone (**237a**: R^1 = Me) with aromatic aldehydes. As in previous cases, better yields and enantioselectivities (44–75% ee) were obtained using electron-deficient aldehydes, with benzaldehyde leading poor results and electron-rich or aliphatic aldehydes failing in this process [321]. From these results, the use of *cinchona* alkaloids as catalyst for the MBH reaction would be envisaged as a promising candidates. In fact, 45% ee (*S*-configuration for **241**) was obtained in the reaction between **237a** and cyclohexanecarbaldehyde promoted by quinidine **171** (10 mol%) using high pressure conditions (3 kbar) in dichloromethane at 25°C [322]. The opposite (*R*)-enantiomer with up to 72% ee, albeit with very low yields, was obtained by using dimeric catalyst **247** (10 mol%) in a solution of 0.1 M propionic acid in THF [323].

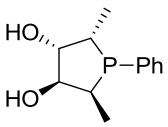
A real progress in this area was achieved by the use β-isocupreidine **249** (10 mol%) [324] as catalysts for the reaction of highly reactive 1,1,1,3,3,3-hexaflouro isopropyl acrylate (HFIPA, **248**) with aromatic and aliphatic aldehydes in DMF at −55°C leading to products **250** with moderate yields and outstanding enantioselectivities (Scheme 4.44), along with variable amount of dioxanone **251** [324a].



Scheme 4.44 β-isocupreidine (**249**) as catalyst for the MBH reaction



252



253

Fig. 4.49 Tertiary phosphines as organocatalysts for the MBH reaction

In order to achieve the reported results, catalyst **249** has to be azeotropically dried, otherwise water bounded to it caused partial hydrolysis of compound **248** leading to slightly worse results [324f]. These results have allowed the application of this catalyst to the key step in the synthesis of natural products (−)-mycestericin E [324b] and epopromycin B [324c]. The application of a pseudoenantiomer of β-isocupreidine, synthesized from quinine, permitted the preparation of *ent*-**250** with slightly lower yields and enantioselectivities [324e]. Also, catalyst **249** was able to promote the related aza-MBH process with good results [324d]. Accountable lower yields (17–71%) and enantioselectivities (33–92% ee) were achieved by using catalyst **249** (10 mol%) in THF at −20°C for the reaction of 1-naphthyl acrylate and aromatic aldehydes [325].

4.14.2.2 Tertiary Phosphines as Organocatalysts

Chiral phosphines, which are widely used in enantioselective synthesis, have been also explored in the MBH-reaction (Fig. 4.49). Thus, (*S*)-BINAP **252** (20 mol%) have been used as catalyst in the reaction of several alkyl acrylates **237** (R^1 = alkoxides) with pyrimidine derived aldehydes in chloroform at 20°C, providing the expected products in low yields (8–26%) and moderate enantioselectivities (9–44% ee) [326]. Although better yield (83%) was encountered by using phospholane **253** (10 mol%) using methyl acrylate as starting material and solvent at 25°C, product **241** was obtained in only 17% ee [327].

4.14.3 Chiral Brønsted Acid Catalysts

Another strategy to perform the MBH-reaction in a enantioselective manner is the activation of the electrophile by interaction with a chiral acid. Whereas the use of chiral Lewis acid always implies the presence of metals and therefore are excluded for this section, the use of some Brønsted acids as organocatalyst have led to excellent performances in this transformation.

The combination of proline (**1**) and imidazole as catalyst for the MBH-reaction led to the increase of the achieved results in reduced reaction times. Very low enantioselectivity (<10% ee) was observed in the intermolecular version of this reaction

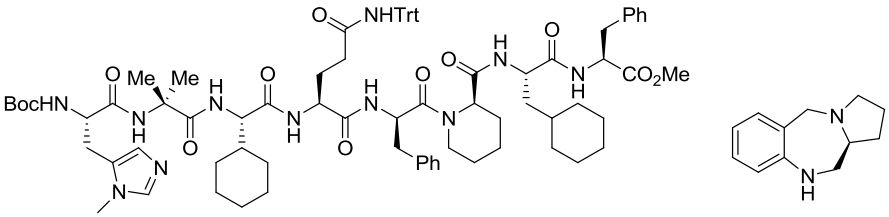
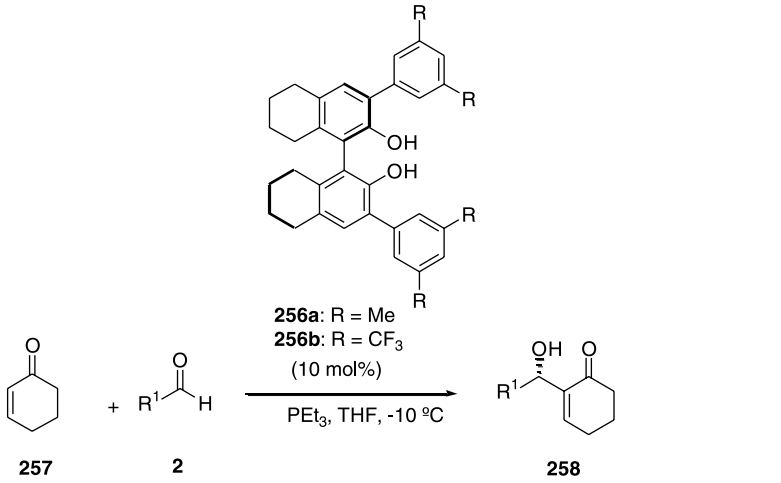


Fig. 4.50 Chiral Brønsted Acid Catalysts for the MBH reaction

[325a], whereas moderate enantioselectivities were detected in intramolecular versions [328]. Despite these disappointing previous results, a library of 105 peptides, biased towards β-hairpin scaffolds, in combination with proline were tested in the MBH-reaction, showing that the most active peptide was octapeptide **254** (Fig. 4.50). Thus, the combination of this catalyst (10 mol%) with proline (10 mol%) used for the reaction of methyl vinyl ketone (**237a**: $R^1 = Me$) and several aromatic aldehydes in chloroform:THF solvent mixture at 25°C, afforded (*R*)-configured product **241** in good yields and enantioselectivities (52–95% yield, 45–81% ee) [329]. Also, pipecolinic acid (20 mol%) and *N*-methylimidazole catalyzed intramolecular MBH-reaction has been reported. In order to enhance the enantioselectivity, kinetic resolution of products by acylation in the presence of an octapeptide of similar structure has been performed [330]. Also, the combination of proline and chiral benzodiazepine **255** has allowed the synthesis of product **241a** in 83% ee [331].

The application of BINOL derivatives **256** in the MBH-reaction of cyclohexenone **257** with aldehydes has been more interesting (Scheme 4.45). Triphenyl phosphine (100 mol%) was used as a nucleophilic promoter in THF at 0°C. Optimal yields and enantioselectivities were achieved using aliphatic aldehydes, while the use of benzaldehyde or *p*-nitrobenzaldehyde led to worse results [332].

Probably the highest achievement in the development of the enantioselective MBH-process is given by the application of chiral thioureas as promoters (Fig. 4.51). Remarkably, using catalyst **259** (40 mol%) in the presence of 4-dimethylaminopyridine (DMAP, 40 mol%) and molecular sieves, products *ent*-**258** were obtained with good results (33–99% yield, 44–90% ee), even when linear, branched or cyclic aliphatic aldehydes were used as electrophiles [333]. A dual-activation mode of both cyclohexanone and aldehydes was proposed to explain the rate acceleration and the observed stereoselectivity. This is confirmed by the fact that a monothiourea of related structure was an ineffective catalyst. Almost similar results were obtained using BINAM-derived thioureas **260** [334] and **261** [335]. While only a 10 mol% of catalyst **260** in acetonitrile at 0°C was enough to promote the reaction of cyclohexanone with aliphatic and aromatic aldehydes with enantioselectivities up to 92% ee, 20 mol% of compound **261** in the presence of DABCO (20 mol%) in toluene at 25°C was required to perform the reaction of **257** and aromatic aldehydes. Also



Scheme 4.45 BINOL derivative as catalyst in the MBH-reaction

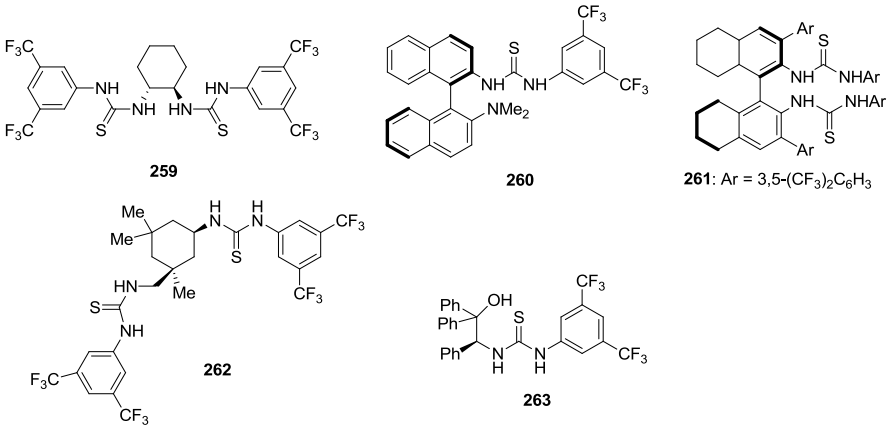


Fig. 4.51 Chiral thioureas as promoters for the MBH reaction

thiourea **262** (20 mol%) required the use of a base as co-catalysts, with DABCO giving the best results [336]. Under this conditions (10°C), enone **257** reacted with aromatic aldehydes affording products *ent*-**258** in good yields (79–99%) and moderate enantioselectivities (50–77%), while aliphatic aldehydes gave lower yields but higher enantioselectivities (up to 96%). Worse results were obtained when

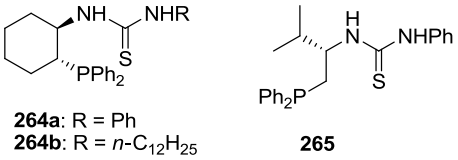


Fig. 4.52 Catalysts to perform the MBH-reaction bearing a thiourea and phosphane group

cyclopentenone or ethyl acrylates were used under these reaction conditions. Amino alcohol derived thiourea **263** (20 mol%) was used for the reaction between cyclohexanone and aromatic aldehydes in the presence of triethylamine under solvent free conditions providing the corresponding products in high yields and enantioselectivities (up to 88% ee) [337].

The combination of thiourea motif with a phosphane group in the same molecule has allowed to perform the related MBH-reaction of acyclic enones **237** and aldehydes avoiding the use of additional bases as co-catalysts (Fig. 4.52). Thus, catalyst **264a** (10 mol%) gave good enantioselectivities (87–94%) and moderate yields (40–75%) in the reaction of methyl vinyl ketone (**237a**, R^1 = Me) with aromatic aldehydes [338a] (chloroform, 13°C). Compound **264b** (8 mol%) showed a better performance for the reaction of acrylates such as ethyl acrylate (**237c**, R^1 = OEt) with aldehydes in THF at 25°C [338b]. Slightly lower yields (28–93%) and enantioselectivities (50–81%) were encountered using valine-derived phosphinothiourea **265** in the reaction of acrylates with aldehydes under the same reaction conditions [339].

4.15 Conclusions and Outlook

Although asymmetric organocatalysis is now considered as a powerful tool for the synthesis of chiral compounds this research field experimented its own revolution. It was restricted after the seventies only to the use of simple α-amino acids as catalyst for the Robinson annulations and above all with the application of proline to the enantioselective intermolecular aldol reaction.

Whereas the intermolecular processes using ketones as source of nucleophile and aldehydes as electrophiles have been extensively studied, other reactions, using either ketones or aldehydes as electrophiles, have been less studied, with reactions implying the use of aldehydes as source of nucleophile and ketones as electrophiles having scarcely investigated. Also the use of poor reactive ketones such as α,β-unsaturated ketones or even alkyl aryl ketones is still elusive.

In the area of enantioselective MBH-reactions, although a considerable effort have been done in the last decade in the field, a catalyst with a wider substrate scope still to be developed. Also, the application of other substrates different from α,β-unsaturated ketones or esters is still unexplored.

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Chapter 5
Organocatalyzed Asymmetric Mannich Reactions

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Abstract The organocatalytic asymmetric Mannich reaction and the related aza-Morita-Baylis-Hillman have been reviewed. The activities in this field have been subdivided based on the types of catalysts that have been utilized, which includes catalysis by enamine-forming chiral amines, chiral Brønsted bases, chiral Brønsted acids, and phase-transfer catalysts.

5.1 Introduction

Near the end of the past millennium, asymmetric organocatalysis was rediscovered as a viable strategy for producing enantiomerically pure building blocks. For a long time only isolated examples of organocatalytic reactions existed [(a) Eder U, Sauer G, Wiechert R (1971) Angew Chem Int Edit 10:496; (b) Hajos ZG, Parrish DR (1974) J Org Chem 39:1615; (c) Hiemstra H, Wynberg H (1981) J Am Chem Soc 103:417], but during the past decade numerous more generally applicable organocatalytic enantioselective reactions have been developed [(a) Berkessel A, Gröger H (2005) Asymmetric organocatalysis, Wiley-VCH, Weinheim; (b) Dalko PI (2007) Enantioselective organocatalysis, Wiley-VCH, Weinheim (c) List B (2007) Chem Rev 107:5413]. In this review, we aim to address organocatalytic asymmetric versions of the well-known Mannich reaction [Arend M, Westermann B, Risch N (1998) Angew Chem Int Edit 37:1044], as well as organocatalyzed asymmetric versions of the related aza-Morita-Baylis-Hillman reaction [Shi Y, Shi M (2007) Eur J Org Chem 18:2905]. Throughout the past few years, several reviews have appeared on organocatalyzed asymmetric Mannich reactions [(a) Marques MMB (2006) Angew Chem Int Edit 45:348; (b) Ting A, Schaus SE (2007) Eur J Org Chem 35:5797; (c) Verkade

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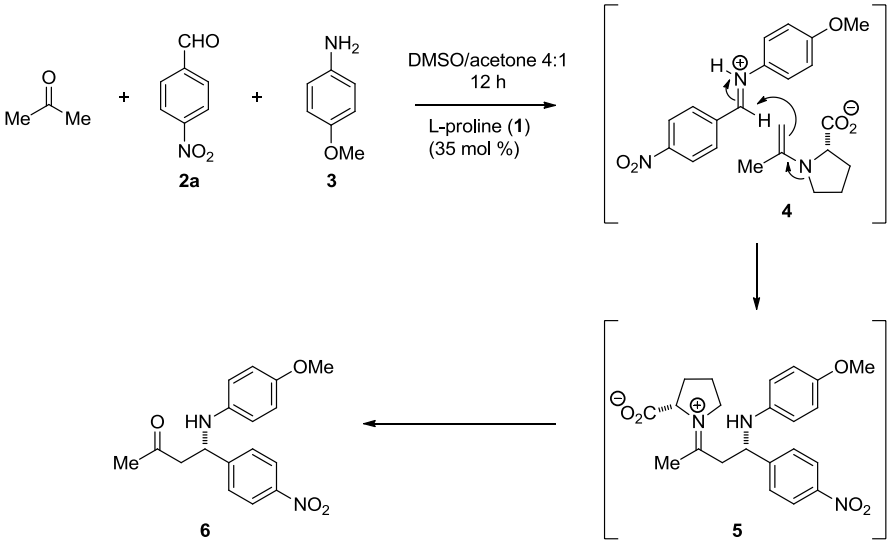
R. Mahrwald (ed.), *Enantioselective Organocatalyzed Reactions II: Asymmetric C-C Bond Formation Processes*, DOI 10.1007/978-90-481-3867-8_5,

JMM, van Hemert LJC, Quaedflieg PJLM, Rutjes FPJT Chem Soc Rev (2008) 37:29; (d) Gómez Arrayás R, Carretero JC (2009) Chem Soc Rev 38:1940]. The overview of the activities in this field is subdivided following the different types of catalysts that have been utilized. This includes catalysis by enamine-forming chiral amines, chiral Brønsted bases, chiral Brønsted acids, and phase-transfer catalysts.

5.2 Catalysis by Enamine-Forming Chiral Amines

5.2.1 Syn-Selective Approaches

Chiral amines can react with so-called Mannich donors such as ketones or aldehydes. The resulting chiral enamines will then attack a Mannich acceptor, usually a prochiral aldimine, thereby introducing one or two chiral centers in the Mannich product. This usually is a β-aminoaldehyde or β-aminoketone, optionally substituted at the α-position. Inspired by their work on proline-catalyzed asymmetric aldol reactions [1], the List group envisioned that the related Mannich reactions might also be carried out with a catalytic amount of an enantiomerically pure chiral amine. This led in 2000 to the first direct catalytic asymmetric organocatalyzed Mannich reaction, catalyzed by L-proline (**1**, Scheme 5.1) [2].



Scheme 5.1 First direct catalytic asymmetric organocatalyzed Mannich reaction

By using a three-component system of acetone, 4-nitrobenzaldehyde (**2a**) and *p*-anisidine (**3**), an electrophilic imine was formed, which reacted with the *in situ* formed proline-derived chiral enamine **4** to form the adduct **5**. Subsequent iminium hydrolysis then led to the Mannich product **6** and regeneration of the organocatalyst. Hydrogen bonding interactions between the carboxylate of the enamine **4** and the

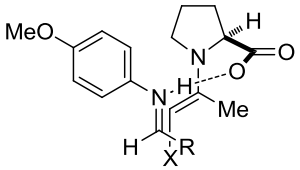
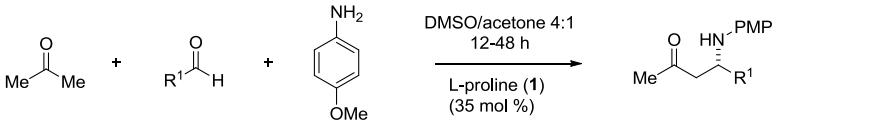


Fig. 5.1 Transition state conformation of L-proline catalyzed Mannich reaction

iminium ion were thought to give rise to a transition state conformation that would explain the highly enantioselective outcome of the reaction (Fig. 5.1).

In these first experiments, starting from several aldehyde acceptor molecules **2a-c**, the Mannich products **8a-c** were obtained in moderate to good yields and generally high enantioselectivity after 12 h of stirring in a mixture of acetone and DMSO (Scheme 5.2). Some side-products were also formed due to competing aldol reactions and subsequent condensations thereby accounting for the somewhat lower yields.



7a **2** **3** **8**

2a: R^1= 4-NO_2-C_6H_4
2b: R^1= *i*-Pr-CH_2
2c: R^1= *n*-Bu

8a: R^1= 4-NO_2-C_6H_4, 50%, 94% ee
8b: R^1= *i*-Pr, 90%, 93% ee
8c: R^1= *n*-Bu, 74%, 73% ee

Scheme 5.2 Aldehyde acceptors in the three-component Mannich reaction

In a successive study, the scope of the methodology was expanded by varying the different components in the three-component reaction, including the ketone, aldehyde and amine components as well as the catalyst and reaction media [2]. It appeared that the catalyst loading could be reduced to 10 mol%, while still obtaining the product in good yield (>90%) and a reasonable reaction time (<5 h). The amount of ketone-component could also be reduced from 26 to as low as 1.3 equiv, while reaction rates remained virtually unaffected. Three different ketones **7b-d** including butanone, methoxyacetone, and hydroxyacetone were reacted with *p*-nitrobenzaldehyde (**2a**) and *p*-anisidine (**3**) to furnish the desired Mannich products **9b-d** in high yields (92–96%) and ee's of up to >99% (Scheme 5.3). Furthermore,

7 **2a** **3** **9**

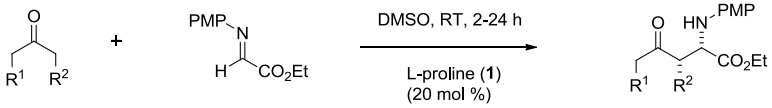
7a: R^1= H
7b: R^1= Me
7c: R^1= OMe
7d: R^1= OH

9a: R^1= H, 50%, >94% ee
9b: R^1= Me, 69%, >95% de, 99% ee
9c: R^1= OMe, 93%, >95% de, 98% ee
9d: R^1= OH, 92%, >95% de, >99% ee

Scheme 5.3 Various ketone donors in the three-component Mannich reaction

these reactions all proceeded in a highly diastereoselective fashion, giving rise to the *syn*-configuration in >95% de. Moreover, various structurally diverse aldehydes, including α-unbranched aldehydes were found to give good results under these conditions (not shown). Conclusively, *p*-anisidine, which introduces the *p*-methoxyphenyl (PMP) group into the product, was indisputably the best amine component.

Not long after List published his three-component methodology, the group of Barbas reported a fairly similar procedure [3]. Besides L-proline (**1**), a penicillamine derivative appeared to effectively catalyze the reaction. Later on, various ketone donors **7b, 7e-g** were successfully subjected to the preformed *N*-PMP-protected α-imino ethyl glyoxylate **10a** as imine acceptor, thereby yielding γ-oxo-α-amino acid derivatives **11a-d** as the products (Scheme 5.4). Analogous to the results of List, the reactions proceeded smoothly resulting in Mannich products with excellent *syn*-selectivity in complete enantiomerically pure form [4].



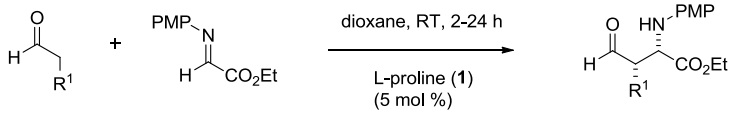
7 **10a** **11**

7b: R^1= H, R^2= Me
7e: R^1= Me, R^2= Me
7f: R^1= H, R^2= Allyl
7g: R^1= Me, R^2= OH

11a: R^1= H, R^2= Me, 72%, >19:1 dr, >99%
11b: R^1= Me, R^2= Me, 47%, >19:1 dr, >99%
11c: R^1= H, R^2= Allyl, 79%, >19:1 dr, >99%
11d: R^1= Me, R^2= OH, 62%, >19:1 dr, >99%

Scheme 5.4 A preformed *N*-PMP-protected α-imino ethyl glyoxylate as imine acceptor

The Barbas group were also the first to report similar reactions with unmodified aldehydes **2b, 2d-g** as donors [5]. In all cases, the reaction proceeded in excellent ee, albeit not always with satisfactory diastereoselectivity. More specifically, an increase in bulkiness of the aldehyde substituent led to the corresponding β-amino acids **12a-e** in significantly improved diastereomeric ratio (Scheme 5.5).



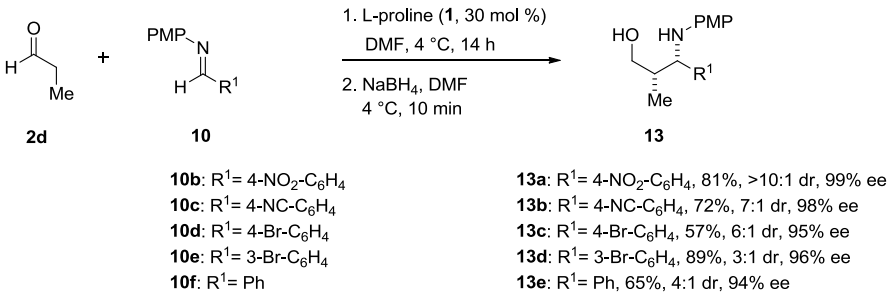
2 **10a** **12**

2b: R^1= *i*-Pr
2d: R^1= Me
2e: R^1= Et
2f: R^1= *n*-Bu
2g: R^1= *n*-pent

12a: R^1= *i*-Pr, 81%, >19:1 dr, 93% ee
12b: R^1= Me, 72%, 3:1 dr, 99% ee
12c: R^1= Et, 57%, 7:1 dr, 99% ee
12d: R^1= *n*-Bu, 81%, >19:1 dr, 99% ee
12e: R^1= *n*-pent, 81%, >19:1 dr, >99% ee

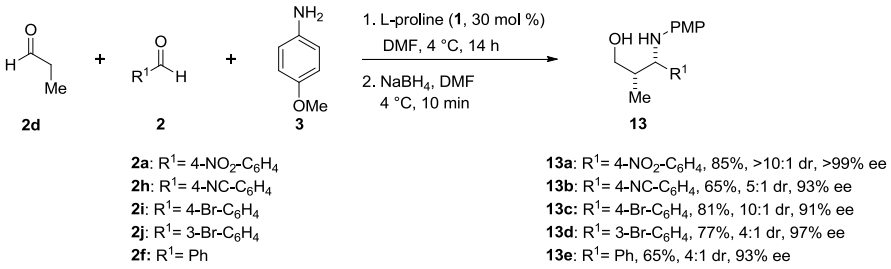
Scheme 5.5 Unmodified aldehydes as donors

The scope was broadened by subjecting a set of different *p*-anisidine-derived aromatic imines **10b-f** to propionaldehyde (**2d**) to afford the corresponding aromatic β-amino aldehydes (Scheme 5.6). Due to their instability at room temperature and tendency to epimerize on the silica gel column, they were immediately reduced to give the β-amino alcohols **13a-e**.



Scheme 5.6 A set of different *p*-anisidine-derived aromatic amines as acceptor

The groups of Barbas [6], Córdova [7] and Hayashi [8] more or less simultaneously showed that also challenging three-component cross-Mannich reactions are possible involving two different aldehydes. In such reactions it is crucial to prohibit the formation of cross-aldol and self-Mannich products since these processes are likely to occur. As an example, the solution lies in careful addition of propionaldehyde (**2d**) to a mixture of 4-nitrobenzaldehyde (**2a**), *p*-anisidine (**3**), and L-proline (**1**, 30 mol%) in DMF at 4°C. This afforded β-amino alcohol **13a** in 85% yield, high ee (>99%) and good diastereoselectivity (> 10:1 dr (*syn*/*anti*)) after *in situ* reduction. The employment of other aromatic aldehydes led to comparable good results, albeit in slightly lower yields as compared to the reactions with preformed imines (Scheme 5.7). Interestingly, when the reaction was carried out in absence of the aldehyde acceptor, formation of the self-Mannich product took place.



Scheme 5.7 Aromatic aldehydes employed in the three-component Mannich reaction

In 2006, Córdova and co-workers suggested that L-proline-catalyzed three-component Mannich reactions with dihydroxyacetone-protected mimetic **14** would offer a potential one-step entry into the orthogonally protected amino sugars **15** [9]. In an initial experiment with formaldehyde as acceptor, the desired *syn*-amino sugar **15b** was produced within 24 h in good yield, dr and ee (77% yield, 16:1 dr, >99% ee). DMSO seemed to be the solvent of choice. Subsequently, a small library was constructed by varying the acceptor aldehydes **2f, 2k-n** (Scheme 5.8). The discovery was made that addition of five equiv of water greatly enhanced reaction rates and contributed to better yields.

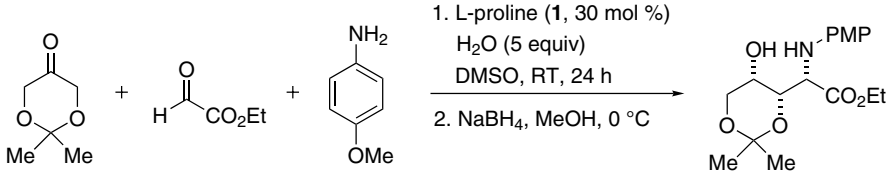
14 **2** **3** **15**

2f: R^1= Ph
2k: R^1= H
2l: R^1= EtO_2C
2m: R^1= $BnOCH_2$
2n: R^1= *i*-Pr

15a: R^1= Ph, 80%, 3:1 dr, 76% ee
15b: R^1= H, 84%, >99% ee
15c: R^1= EtO_2C, 77%, 16:1 dr, >99% ee
15d: R^1= $BnOCH_2$, 70%, 6:1 dr, 98% ee
15e: R^1= *i*-Pr, 60%, 4:1 dr, 48% ee

Scheme 5.8 One-step entry into orthogonally protected *syn*-amino sugars

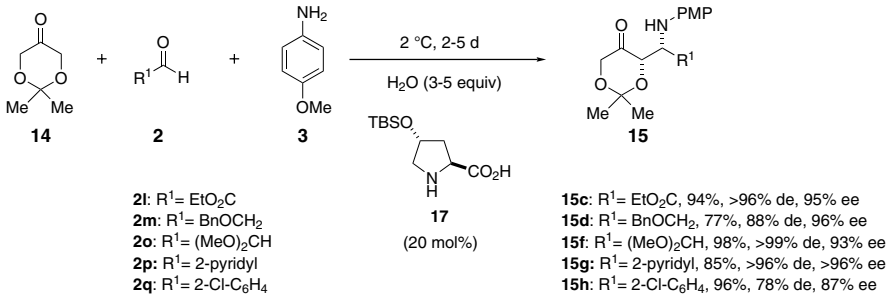
The group also applied the former protocol to synthesize hydroxylated α-amino acid **16**. The procedure involved addition of ketone **14** to ethyl glyoxylate **2l** in wet DMSO, followed by *in situ* reduction with $NaBH_4$. The amino alcohol **16** was formed in 30% yield, excellent ee (>99%) and a dr of 8:1 in favor of the *syn*-adduct (Scheme 5.9).



14 **2l** **3** **16**

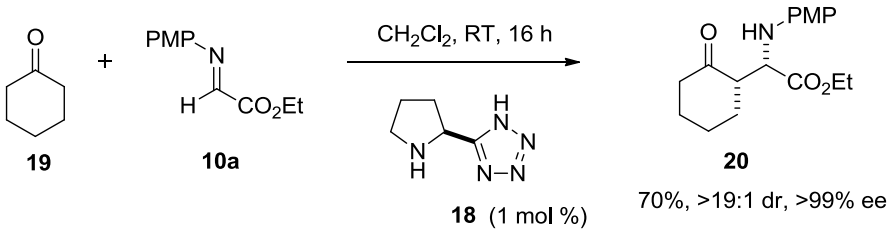
Scheme 5.9 Two-step synthesis to α-amino acid derivative **16**

Enders et al. also reported direct asymmetric Mannich reactions starting from the protected ketone **14** [10]. Several protected carbohydrates and amino sugars were assembled in a three-component reaction. Alongside L-proline (**1**) they employed the L-hydroxyproline-based catalyst **17** (Scheme 5.10). This catalyst proved to be beneficial in terms of reaction rate due to superior solubility properties. Remarkably, the addition of water had a positive effect on the stereoselectivity in case catalyst **17** was employed.



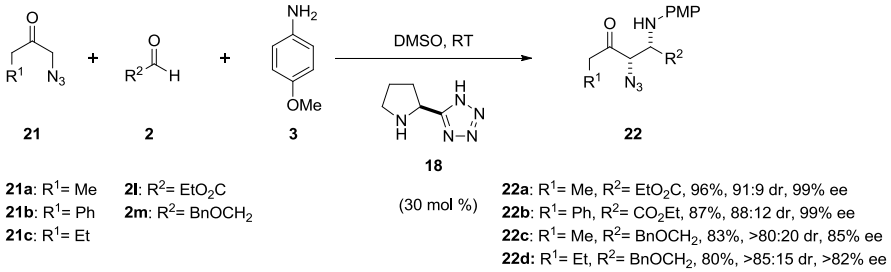
Scheme 5.10 Enhanced reaction rate due to superior solvability of new catalyst **17**

Up till now most examples concerning organocatalyzed asymmetric Mannich reactions showed the utilization of L-proline (**1**) as the catalyst. The employment of other amino acids can be imagined as well, but these are less effective. Nevertheless, there are some limitations to the use of proline as well. For instance, proline-catalyzed reactions are typically conducted in solvents such as DMF and DMSO due to the low solubility of proline in regular solvents. Additionally, high levels of catalyst loading (10–30%) are usually required. Therefore, Ley et al. developed tetrazole **18** and related acylsulfonamide organocatalysts with the aim to catalyze the asymmetric Mannich reaction more effectively [11]. Indeed, use of these catalysts allowed reactions to be conducted in CH_2Cl_2 and other non-polar solvents. For example, the reaction of cyclohexanone (**19**) with *N*-PMP-protected glyoxylate ester **10a** provided the Mannich-base **20** by using only 1 mol% of catalyst **18** without affecting the yield or selectivity (Scheme 5.11).



Scheme 5.11 Tetrazole-based catalyst allowing non-polar solvents as reaction medium

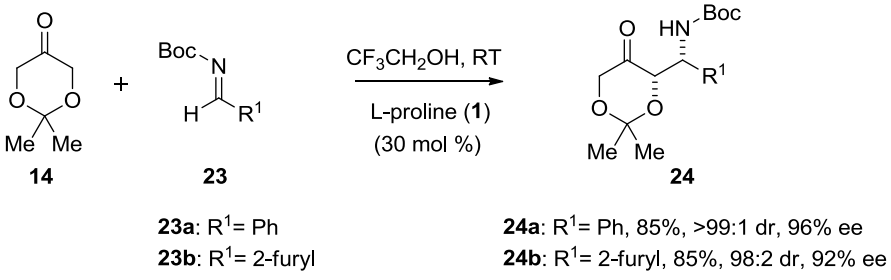
Barbas and co-workers employed the new tetrazole-functionalized catalyst **18** in the reaction of protected 2-aminoketones with *N*-PMP-protected imines [12]. As an example, after optimizing the reaction conditions, a set of azidoketones **21** was reacted with *p*-anisidine (**3**) and aldehydes **2l-m** to afford the corresponding α-azido-β-aminoketones **22a-d** in high yield and selectivity (80–96%, 91:9 dr (*syn*/*anti*), 80–99% ee, Scheme 5.12).



Scheme 5.12 Tetrazole-based catalyst facilitates the formation of α-azido-β-aminoketones

Most of the efforts so far in the field of organocatalyzed Mannich reactions had focused on the use of aryl-protected imines, of which the PMP-protecting group in particular gave optimal results. In many publications it is claimed that use of ceric ammonium nitrate (CAN) leads to convenient removal of the PMP group [13]. This deprotection proceeds via oxidation of the anisidine moiety into the corresponding iminoquinone, followed by aqueous imine hydrolysis to liberate the amine. More recently, cleaner and cost-efficient methods have been developed, involving (i) electrochemistry [14], (ii) chemical reagents such as periodic acid or trichloroisocyanuric acid (TCCA) [15, 16], and (iii) enzymes in the form of alcalases, sometimes in combination with mediators to enhance electron transport [17]. Nevertheless, in order to be more flexible in deprotection strategies and further explore the scope of the Mannich reactions, other protecting groups were evaluated. Several groups then reported the use of the *tert*-butoxycarbonyl (Boc) as a viable carbamate protecting group in asymmetric Mannich reactions. Enders et al. were the first to report Boc as the imine protecting group in proline-catalyzed Mannich reactions (Scheme 5.13) [18]. Employing protected dihydroxyacetone **14** as the donor and imines **23a-b** as the acceptor molecule, the resulting products **24a-b** were formed in good yields, excellent ee and *syn*-selectivity.

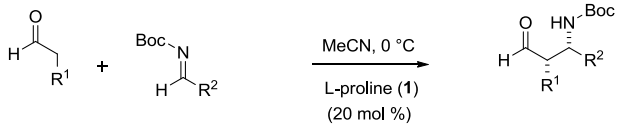
Not much later, Córdova and List almost simultaneously reported extensive studies on the use of N-Boc imines as Mannich acceptors. The Córdova group reported that



Scheme 5.13 *tert*-Butoxycarbonyl as viable imine protecting group

proline, but also (4*R*,5*S*)-4-hydroxyproline, was able to catalyze Mannich reactions of aryl-substituted *N*-Boc imines with aliphatic aldehydes in high yields and selectivities (dr >19:1, ee up to >99%) [19].

List also reported on the synthesis of *N*-Boc protected aldimines employing proline as the catalyst, and found that acetone could be used as Mannich donor (73% yield, ee >98%) [20]. The latter group nicely exemplified the viability of using Boc-protected aldimines **23a-e** in Mannich reactions with aldehydes **2b, 2d, 2f** to prepare a series of β-aminoaldehydes **25a-g** in high yield and excellent selectivities (Scheme 5.14) [21]. An important difference with the *N*-aryl-protected imines **10** is that due to the more difficult formation of *N*-acylated imines, preformation of the imines is required and that three-component Mannich reactions are not possible.



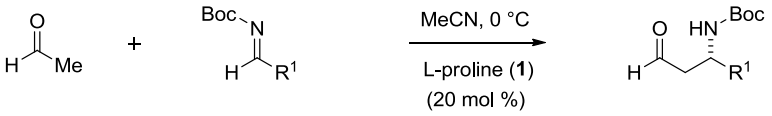
2: **2b**: R^1= *i*-Pr; **2d**: R^1= Me; **2f**: R^1= *n*-Bu

23: **23a**: R^2= Ph; **23b**: R^2= 2-furyl; **23c**: R^2= 4-MeO-C_6H_4; **23d**: R^2= 4-Cl-C_6H_4; **23e**: R^2= 2-naphthyl

25: **25a**: R^1= *i*-Pr, R^2= Ph, 88%, dr >99:1, 99% ee; **25b**: R^1= *i*-Pr, R^2= 2-furyl, 74%, dr 97:3 dr, 98% ee; **25c**: R^1= *i*-Pr, R^2= 4-MeO-C_6H_4, 80%, dr >99:1, 99% ee; **25d**: R^1= *i*-Pr, R^2= 4-Cl-C_6H_4, 59%, dr 99:1, 98% ee; **25e**: R^1= *i*-Pr, R^2= 2-naphthyl, 82%, dr >99:1, 99% ee; **25f**: R^1= Me, R^2= Ph, 91%, dr >99:1, 99% ee; **25g**: R^1= *n*-Bu, R^2= Ph, 75%, dr >99:1, 99% ee

Scheme 5.14 Boc-protected aldimines in the Mannich reaction with aldehydes

One year later, the List group reported Mannich reactions involving the use of acetaldehyde **2r** as the Mannich donor, which due to its reactive nature, is a very difficult substrate. Albeit not in high yields, they showed that under carefully controlled conditions such Mannich reactions could proceed in excellent selectivity, even in case of the aliphatic Boc-protected imines **23i** and **j** (Scheme 5.15) [22].



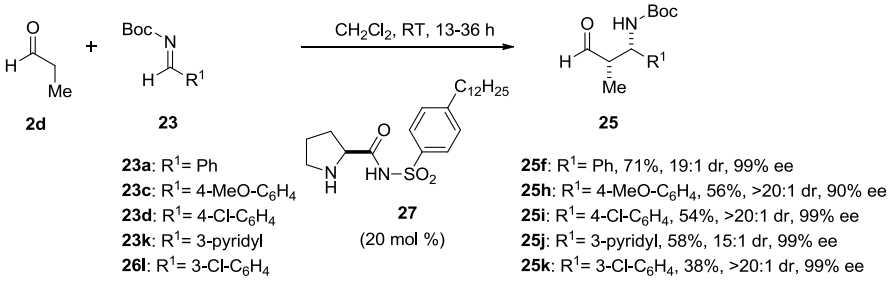
2r

23: **23a**: R^1= Ph; **23b**: R^1= 2-furyl; **23e**: R^1= 2-naphthyl; **23f**: R^1= 4-Me-C_6H_4; **23g**: R^1= 4-CF_3-C_6H_4; **23h**: R^1= 3-NO_2-C_6H_4; **23i**: R^1= *i*-Bu; **23j**: R^1= Et

26: **26a**: R^1= Ph, 54%, >98% ee; **26b**: R^1= 2-furyl, 30%, 98% ee; **26c**: R^1= 2-naphthyl, 40%, >98% ee; **26d**: R^1= 4-Me-C_6H_4, 58%, 96% ee; **26e**: R^1= 4-CF_3-C_6H_4, 42%, 98% ee; **26f**: R^1= 3-NO_2-C_6H_4, 42%, >98% ee; **26g**: R^1= *i*-Bu, 55%, >98% ee; **26h**: R^1= Et, 23%, >98% ee

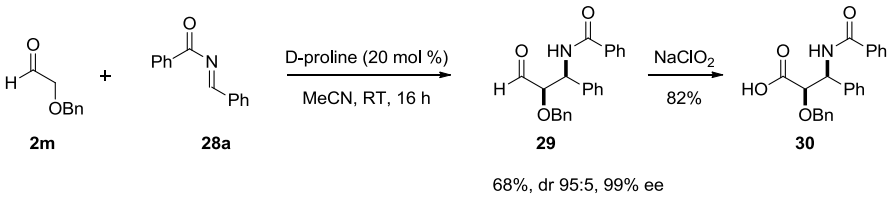
Scheme 5.15 Mannich reactions involving acetaldehyde as the substrate

In 2009, Carter and Yang reported the construction of the novel proline-based catalyst **27**, which is soluble in most solvent systems, including industrially attractive solvents such as 2-Me-THF, and is readily made from inexpensive starting materials [23]. Several experiments were conducted to validate the scope of this new catalyst (Scheme 5.16). For instance, propionaldehyde (**2d**) was reacted with *N*-Boc-protected aldimine **23k** to provide the Mannich product **25j** in excellent selectivity (15:1 dr *syn*/anti, 99% ee), while L-proline (**1**) furnished the same product in rather poor diastereoselectivity (1.2:1 dr (*syn*/*anti*), 99% ee). Similar results were obtained for differently substituted aldimines **23a**, **23c-d** and **23l** as well.



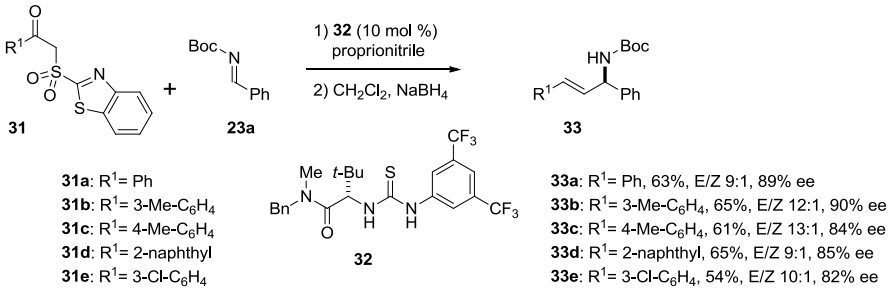
Scheme 5.16 Novel proline-based catalyst **27**

Somewhat in contrast to these results, the Córdova group reported excellent results of using D-proline for reaction between aldehyde **2m** and the *N*-acylated imine **28a** (Scheme 5.17). This specific application led to the Mannich adduct **29** in excellent stereoselectivity, which via subsequent Pinnick oxidation provided the Taxol side chain (**30**) in 82% yield [24].



Scheme 5.17 Excellent results with D-proline as catalyst

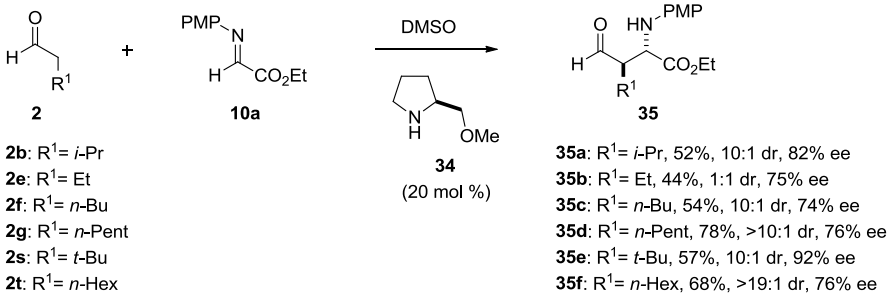
Another interesting application involved the formation of allylic amines **33a-e** in enantiomerically pure form as published by the Jørgensen group (Scheme 5.18) [25]. This Mannich reaction was conducted between the benzothiazolesulfonyl-derived aldehydes **31a-e** and the Boc-protected aldimine **23a**. After the initial Mannich reaction, a subsequent reduction with $NaBH_4$ was carried out to give rise to the allylic amines **33a-e** in moderate yields, but high E/Z-ratios and enantioselectivity.



Scheme 5.18 Formation of allylic amines in high *E*/*Z* ratios

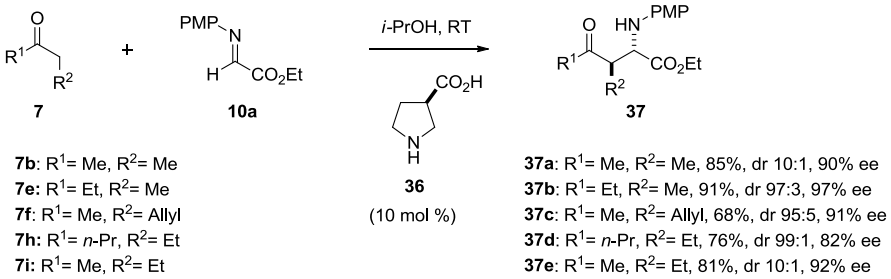
5.2.2 *Anti-Selective Approaches*

Thus far only procedures to acquire the *syn*-Mannich adducts have been described. Equally valuable and perhaps more appealing are protocols that broaden the versatility of the former methodology by providing the Mannich bases in a highly *anti*-selective manner. The preparation of *anti*-Mannich adducts was initially conducted by Barbas et al. by means of a direct (*S*)-2-methoxymethylpyrrolidine (**34**, SMP) catalyzed asymmetric Mannich-type reaction [26]. A variety of unmodified aliphatic aldehydes **2** were treated with *N*-PMP-protected iminoglyoxylate **10a** in DMSO to afford the β-formyl-functionalized amino acid derivatives **35a-f** in moderate to good ee's and with a dr that increased with the bulkiness of the aldehyde (Scheme 5.19).



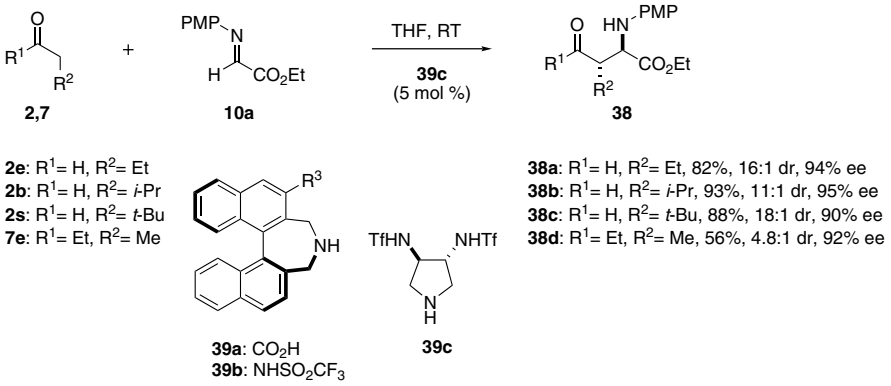
Scheme 5.19 Preparation of *anti*-Mannich adducts

Unfortunately, these results could not be readily reproduced in related reactions. Further studies by the same group led to the design of the pyrrolidine-derived catalyst **36** to catalyze the reaction of ketones **7** with *N*-PMP-protected glyoxylate ester **10a** (Scheme 5.20) [27]. The corresponding β-formyl-functionalized amino acid derivatives **37** were produced in high yields and excellent *anti*-selectivities.



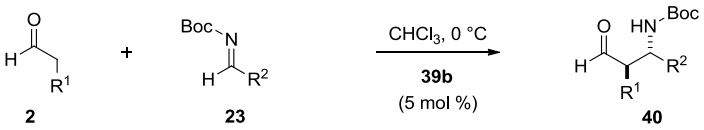
Scheme 5.20 Pyrrolidine-derived catalyst to react ketones with *N*-PMP-protected glyoxylate ester **10a**

Maruoka and co-workers constructed the novel axially chiral amine organocatalysts **39a,b** to afford the *anti*-Mannich product **38** from alkyl aldehydes and *N*-PMP-protected glyoxylate esters **10a** [28]. The reaction of 2-pentanone **7e** with α-imino ester **10a** and catalyst **39a** resulted in poor yield without any diastereoselectivity. However, when aminosulfonamide **39b** was employed excellent yields and *anti*-selectivities were observed (not shown). Catalyst **39b** has a highly acidic triflamide group to activate electrophiles and a less nucleophilic dibenzylic secondary amine moiety as compared to pyrrolidine-type catalysts. These properties were thought to suppress undesired side reactions such as aldol reactions and other follow-up reactions of the Mannich product. Remarkably, 1 mol% of catalyst loading was adequate to facilitate reactions with primary alkyl aldehydes. Later, excellent results were reported by the same group when the sterically hindered aldehydes **2a, 2b, 2s** and less reactive ketones (e.g. **7e**), were subjected to the newly designed pyrrolidine-based catalyst **43c**, thereby affording *anti*-adducts **38a-d** (Scheme 5.21) [29].



Scheme 5.21 Excellent results with catalysts **39b-c**

In 2009, the Maruoka group used the previously discussed aminosulfonamide catalyst **39b** to facilitate the reaction of various aldehydes **2** with *N*-Boc-protected imines **23a-b, 23m** to afford the *N*-Boc-protected *anti*-β-amino-β-aryl aldehyde **40a-f** in high yield and *anti*-selectivity and excellent ee (Scheme 5.22) [30].



2

2d: R^1= Me
2b: R^1= *i*-Pr
2u: R^1= *i*-Bu
2v: R^1= Bn

23

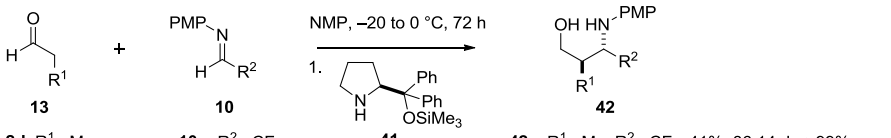
23a: R^2= Ph
23b: R^2= 2-furyl
23m: R^2= 2-pyridyl

40

40a: R^1= Me, R^2= Ph, 92%, dr 7.7:1, 99% ee
40b: R^1= *i*-Pr, R^2= Ph, 77%, dr 8.8:1, 99% ee
40c: R^1= Bu, R^2= Ph, 93%, dr 16:1, 99% ee
40d: R^1= Bn, R^2= Ph, 80%, dr 15:1, 99% ee
40e: R^1= Bu, R^2= 2-furyl, 88%, dr 7.5:1, 99% ee
40f: R^1= Bu, R^2= 3-pyridyl, 92%, dr 16:1, 99% ee

Scheme 5.22 The catalyst's properties are thought to suppress side reactions

Fustero et al. noticed that fluorinated imines **10g-h** had received little attention so far in literature. In particular, the synthesis of the corresponding *anti*-Mannich adducts had never been explored previously. By employing Jørgensen's diphenylprolinol derivative **41**, highly enantioselective one-pot reactions between aldehydes **2** and the fluoroaldimines **10g-h** were conducted [31], leading to the fluorinated β-alkyl-γ-amino alcohols **42a-e** in a highly selective *anti*-manner (Scheme 5.23).



13

2d: R^1= Me
2e: R^1= Et
2v: R^1= Bn
2w: R^1= Allyl

10

10g: R^2= CF_3
10h: R^2= CF_2CF_3

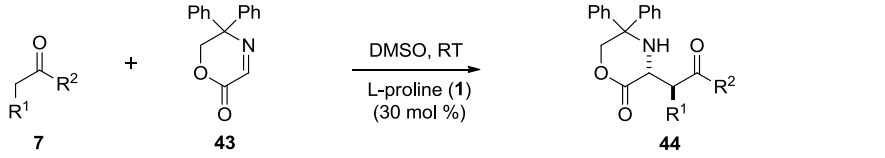
41

42

42a: R^1= Me, R^2= CF_3, 41%, 86:14 dr, >99% ee
42b: R^1= Et, R^2= CF_3, 57%, 80:20 dr, 49% ee
42c: R^1= Bn, R^2= CF_3, 50%, 92:8 dr, 98% ee
42d: R^1= Allyl, R^2= CF_3, 60%, 95:5 dr, 97% ee
42e: R^1= Et, R^2= CF_3CF_2, 22%, 93:7 dr, >99% ee

Scheme 5.23 Highly enantioselective Mannich reactions with fluoroaldimines

So far, the general strategy to obtain *anti*-Mannich adducts proceeded through identification of appropriately designed organocatalysts. Inversely, Glorius et al. reported the *anti*-selective Mannich reaction of the unmodified ketones **7a**, **7d-e**, **7j-l** with the cyclic imine acceptor **43** simply using L-proline (**1**) as the catalyst (Scheme 5.24) [32]. The 5,5-diphenyl-substituted imine acceptor **43** can be readily synthesized and is obviously locked in the Z-configuration. The presence of the diphenylethylene moiety and the change in configuration of the imine double bond



7 **43** **44**

7b: R^1= Me, R^2= Me
7d: R^1= OH, R^2= Me
7e: R^1= Me, R^2= Et
7j: R^1= R^2= -$(CH_2)_3$-
7k: R^1= R^2= -$(CH_2)_4$-
7l: R^1= R^2= -$(CH_2)_5$-

44a: R^1= Me, R^2= Me, 70%, dr 20:1, 99% ee
44b: R^1= OH, R^2= Me, 84%, dr 10:1, 98% ee
44c: R^1= Me, R^2= Et, 73%, dr 12:1, 99% ee
44d: R^1= R^2= -$(CH_2)_3$-, 30%, dr 20:1, 99% ee
44e: R^1= R^2= -$(CH_2)_4$-, 91%, dr 20:1, 99% ee
44f: R^1= R^2= -$(CH_2)_5$-, 60%, dr 20: 1, 97% ee

Scheme 5.24 First *anti*-selective Mannich reaction using L-proline

are thought to account for the high *anti*-selectivity. Reactions were performed in dry DMSO and cleanly afforded the corresponding *N*,*O*-protected 1,4-morpholin-2-ones **44a-f** in excellent dr and ee. The diphenylethylene protecting group were easily cleaved by hydrogenolysis in aqueous ethanol to yield the free α-amino-acids.

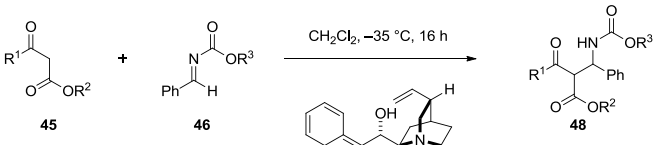
5.3 Catalysis by Chiral Brønsted Bases

In the previous section, secondary chiral amines were employed that give rise to enamine formation upon reaction with ketones or aldehydes. Chiral tertiary amines, unable to form enamines, are nevertheless capable of inducing enantioselectivity in case substrates are used that contain sufficiently acidic protons such as aldehydes, ketones or active methylene compounds [33]. The cinchona alkaloids, by far the most versatile source of Brønsted base catalysts, have played a prominent role in various types of asymmetric organocatalytic reactions [34], which is also true for the Mannich reaction.

Schaus and co-workers envisioned the application of cinchona alkaloids **47a-d** as chiral Brønsted base catalysts in the asymmetric Mannich reaction of acetoacetates **45** with *N*-acylimines **23a**, **46a-c** (Scheme 5.25) [35]. Promising results were reported when the chiral base cinchonine (**47a**) was employed, while the cinchona alkaloid quinine (**47b**) gave considerably lower selectivities. Opposite selectivities were observed when the *pseudo*-enantiomers cinchonidine (**47c**) and quinidine (**47d**) were used.

The scope of the methodology was expanded by the same group involving Mannich reactions of cyclic 1,3-dicarbonyl compounds **49a-d** with different types of *N*-acylimines such as **50a-b** to afford the corresponding adducts **51a-g**, containing an asymmetric quaternary carbon atom. These products were obtained in generally excellent yields, good de's and ee's of up to 99% (Scheme 5.26) [36].

Computational studies and experimental observations led to the discovery that the enol tautomer coordinates to the catalyst through hydrogen-bond interactions with the catalyst's hydroxyl group and tertiary amine. In this chiral nucleophile, the quinoline ring is effectively blocking the *si*-face of the enol, thus giving rise to a highly selective reaction (Fig. 5.2).



45a: R^1= Me, R^2= Allyl
45b: R^1= Me, R^2= Me

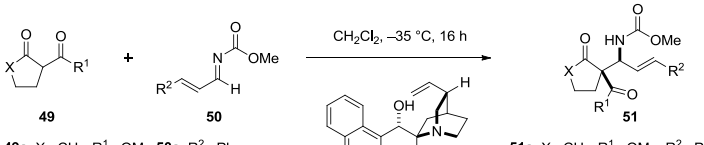
23a: R^3= *t*-Bu
46a: R^3= Et
46b: R^3= Me
46c: R^3= Allyl

(10 mol %)

47a: cinchonine
47b: quinine
47c: cinchonidine
47d: quinidine

48a: R^1= Me, R^2= Allyl, R^3= *t*-Bu, **47a**, 85%, 3:1 dr, 80% ee
48a: R^1= Me, R^2= Allyl, R^3= *t*-Bu, **47b**, 86%, 1:1 dr, 60% ee
48b: R^1= Me, R^2= Allyl, R^3= Et, **47a**, 91%, 2:1 dr, 86% ee
48c: R^1= Me, R^2= Allyl, R^3= Me, **47a**, 99%, 3:1 dr, 92% ee
48c: R^1= Me, R^2= Allyl, R^3= Me, **47c**, 96%, 2:1 dr, 90% ee
48c: R^1= Me, R^2= Allyl, R^3= Me, **47b**, 90%, 1:1 dr, 60% ee
48c: R^1= Me, R^2= Allyl, R^3= Me, **47d**, 95%, 1:1 dr, 65% ee
48d: R^1= Me, R^2= Me, R^3= Me, **47a**, 99%, 20:1 dr, 94% ee
48d: R^1= Me, R^2= Me, R^3= Me, **47c**, 95%, 20:1 dr, 90% ee
48d: R^1= Me, R^2= Me, R^3= Me, **47b**, 97%, 4:1 dr, 60% ee
48d: R^1= Me, R^2= Me, R^3= Me, **47d**, 98%, 5:1 dr, 65% ee
48e: R^1= Me, R^2= Me, R^3= Allyl, **47a**, 91%, 2:1 dr, 90% ee

Scheme 5.25 Cinchona alkaloids as chiral Brønsted-base catalysts



49a: X= CH_2, R^1= OMe
49b: X= Me, R^1= OEt
49c: X= CH_2, R^1= Me
49d: X= O, R^1= Me

50a: R^2= Ph
50b: R^2= 2-furyl

(5 mol %)

51a: X= CH_2, R^1= OMe, R^2= Ph, 98%, 90% de, 99% ee
51b: X= Me, R^1= OEt, R^2= Ph, 98%, 94% de, 98% ee
51c: X= CH_2, R^1= Me, R^2= Ph, 98%, 95% de, 99% ee
51d: X= O, R^1= Me, R^2= Ph, 88% 38% de, 98% ee
51e: X= CH_2, R^1= OMe, R^2= 2-furyl, 98%, 99% de, 99% ee
51f: X= Me, R^1= OEt, R^2= 2-furyl, 98%, 98% de, 93% ee
51g: X= CH_2, R^1= Me, R^2= 2-furyl, 98%, 94% de, 98% ee

Scheme 5.26 Mannich reactions of cyclic 1,3-dicarbonyl compounds with *N*-acylimines

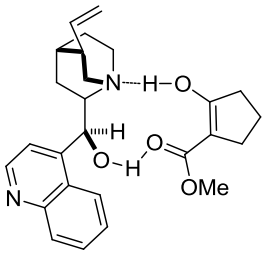
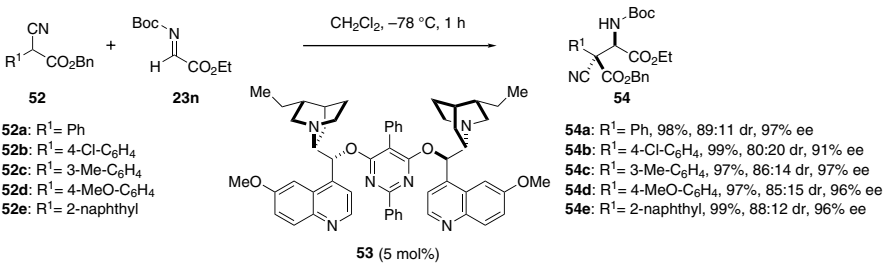


Fig. 5.2 Transition state conformation of cinchonine-catalyzed Mannich reaction

The first enantio- and diastereoselective Mannich reactions of benzyl α-aryl cyanoacetates **52a-e** with α-imino ester **23n** were reported by the group of Jørgensen [37]. After extensive screening, the commercially available chiral amine base $(DHQD)_2PYR$ (**53**) appeared to be the most promising candidate, giving rise to the corresponding Mannich products **54a-e** in good diastereoselectivities and excellent ee's (Scheme 5.27). The opposite enantiomers of the same Mannich adducts



52a: R^1= Ph
52b: R^1= 4-Cl-C_6H_4
52c: R^1= 3-Me-C_6H_4
52d: R^1= 4-MeO-C_6H_4
52e: R^1= 2-naphthyl

54a: R^1= Ph, 98%, 89:11 dr, 97% ee
54b: R^1= 4-Cl-C_6H_4, 99%, 80:20 dr, 91% ee
54c: R^1= 3-Me-C_6H_4, 97%, 86:14 dr, 97% ee
54d: R^1= 4-MeO-C_6H_4, 97%, 85:15 dr, 96% ee
54e: R^1= 2-naphthyl, 99%, 88:12 dr, 96% ee

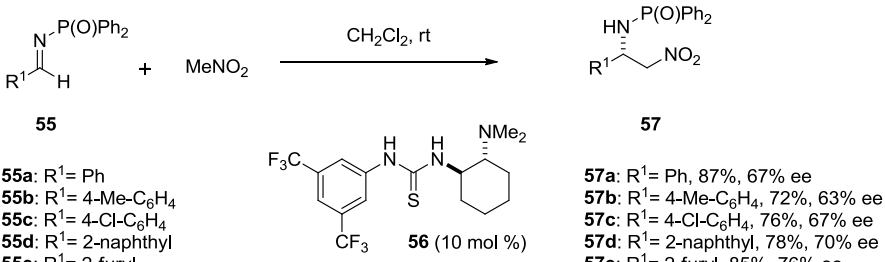
Scheme 5.27 $(DHQD)_2PYR$ in reaction of benzyl α-aryl cyanoacetates **52** with α-imino ester **23n**

were obtained with comparable selectivities when the commercially available *pseudo*-enantiomeric catalyst $(DHQ)_2PYR$ was utilized.

In many examples of Brønsted base catalysis, the combination of a chiral tertiary amine and a hydrogen-bonding donor, such as a urea or thiourea moiety, significantly enhances the selectivity of the formation of carbon-carbon bonds. Catalysts possessing this combination of functional groups have proven useful due to their ability to simultaneously stabilize and activate both electrophilic and nucleophilic components.

Takemoto et al. reported the application of such a catalyst (**56**) in the enantioselective addition of nitromethane to various phosphinoylimines **55a-f** resulting in the corresponding *β*-nitroamines **57a-f** in generally moderate enantioselectivity (Scheme 5.28) [38, 39]. They reasoned that a nitronate was formed from nitromethane *via* hydrogen-bonding activation by the thiourea group and subsequent deprotonation by the neighboring tertiary amine group. As a result the nitronate would be in a fixed position to facilitate the aza-Henry (nitro-Mannich) reaction in an enantioselective manner (Fig. 5.3).

A very similar approach was followed by the Jacobsen group using the slightly different thiourea-based catalyst **58** [40]. It was shown that using nitroethane highly *syn*-selective nitro-Mannich products **59a-g** could be obtained in high yield and impressive ee (Scheme 5.29).



55a: R^1= Ph
55b: R^1= 4-Me-C_6H_4
55c: R^1= 4-Cl-C_6H_4
55d: R^1= 2-naphthyl
55e: R^1= 2-furyl
55f: R^1= 2-pyridyl

57a: R^1= Ph, 87%, 67% ee
57b: R^1= 4-Me-C_6H_4, 72%, 63% ee
57c: R^1= 4-Cl-C_6H_4, 76%, 67% ee
57d: R^1= 2-naphthyl, 78%, 70% ee
57e: R^1= 2-furyl, 85%, 76% ee
57f: R^1= 2-pyridyl, 91%, 68% ee

Scheme 5.28 Bifunctional catalyst **56** facilitates the nitro-Mannich reaction in an enantioselective manner

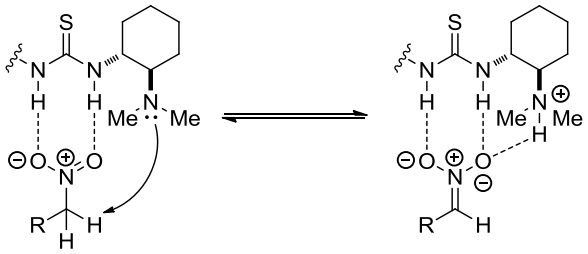
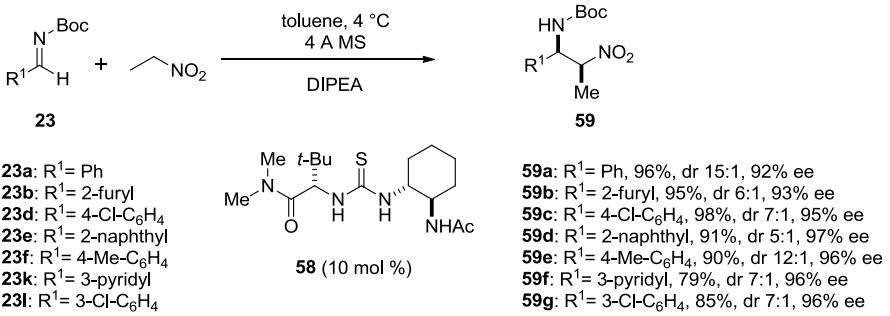
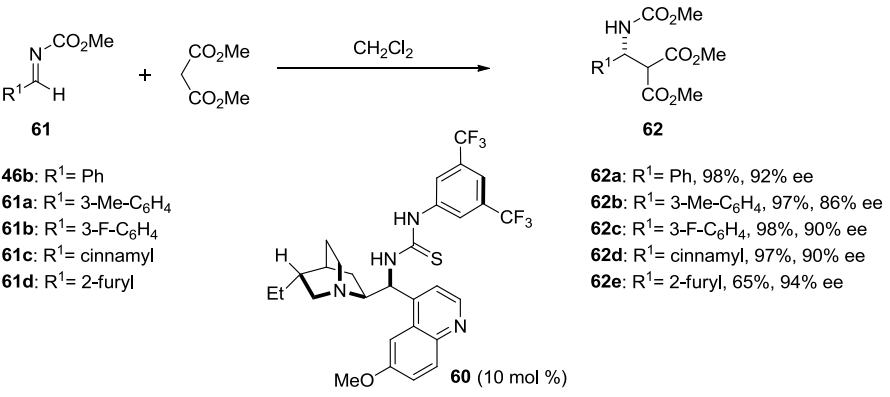


Fig. 5.3 Transition state conformation involving catalyst **56**



Scheme 5.29 Highly *syn*-selective nitro-Mannich products with bifunctional catalyst **58**

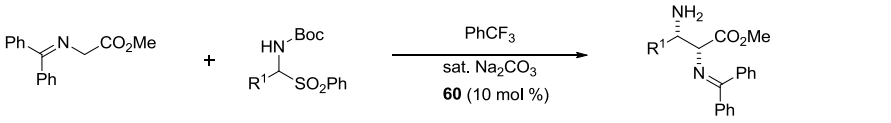
Later Schaus and co-workers used the cinchona alkaloid-derived thiourea catalyst **60** to catalyze the nucleophilic addition of both nitroalkanes (not shown) and dimethyl malonate to the *N*-carbamoyl protected imines **46b**, **61a-d** to produce the corresponding Mannich adducts **62** in excellent yields and high enantioselectivities (Scheme 5.30) [41]. The level of selectivity observed in these reactions is indicative of a catalyst-associated complex with a high degree of coordination. Modelling



Scheme 5.30 Nucleophilic addition of dimethyl malonate to *N*-carbamoyl-protected imines

studies suggested anion stabilization *via* a chiral ion pair with the hydroquinine moiety, while the thiourea part facilitated hydrogen-bonding with the same anion.

Barbas et al. described highly enantio- and diastereoselective organocatalytic Mannich reactions of the glycine-derived Schiff base **63** with *in situ* generated aromatic *N*-Boc-protected imines from **64** (Scheme 5.31) [42]. Several thiourea-



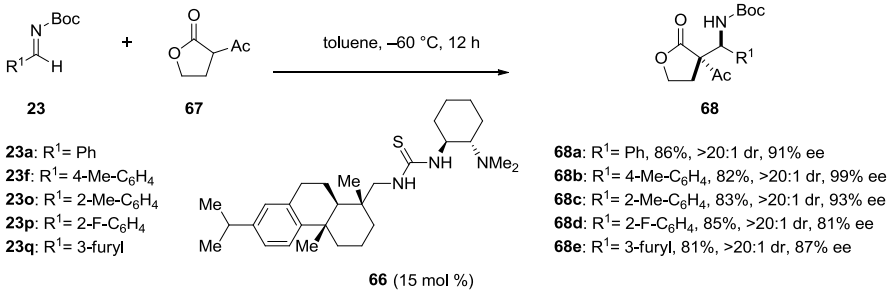
64a: R^1= Ph
64b: R^1= 4-MeO-C_6H_4
64c: R^1= 4-NO_2-C_6H_4
64d: R^1= 4-Cl-C_6H_4
64e: R^1= 2-furyl

65a: R^1= Ph, 73%, 99% ee
65b: R^1= 4-MeO-C_6H_4, 62%, 98% ee
65c: R^1= 4-NO_2-C_6H_4, 86%, 94% ee
65d: R^1= 4-Cl-C_6H_4, 87%, >99% ee
65e: R^1= 2-furyl, 74%, >99% ee

Scheme 5.31 Enantioselective addition of glycine-derived Schiff base **63** to in situ generated *N*-Boc-aldimines

containing catalysts were screened and the previously described bifunctional catalyst **60** proved to be the most promising one. It was suggested that the tertiary amine of catalyst **60** activates the Schiff base forming a nucleophile, while the thiourea portion activates the *N*-Boc-protected imine as an electrophilic acceptor through hydrogen-bonding to the imine nitrogen. Reactions were performed in trifluorotoluene ($PhCF_3$) and yielded the chiral α,β-diamino acid derivatives **65** in good yields with outstanding diastereo- and enantiocontrol (95–99% ee, dr > 99:1).

Recently, the formation of Mannich products via reaction of lactones with a variety of *N*-Boc-aldimines, catalyzed by the bifunctional rosin-derived amine thiourea catalyst **66**, was reported by the Wang group (Scheme 5.32) [43]. The formation of



23a: R^1= Ph
23f: R^1= 4-Me-C_6H_4
23o: R^1= 2-Me-C_6H_4
23p: R^1= 2-F-C_6H_4
23q: R^1= 3-furyl

68a: R^1= Ph, 86%, >20:1 dr, 91% ee
68b: R^1= 4-Me-C_6H_4, 82%, >20:1 dr, 99% ee
68c: R^1= 2-Me-C_6H_4, 83%, >20:1 dr, 93% ee
68d: R^1= 2-F-C_6H_4, 85%, >20:1 dr, 81% ee
68e: R^1= 3-furyl, 81%, >20:1 dr, 87% ee

Scheme 5.32 Catalyst **66** in the formation of quaternary Mannich adducts

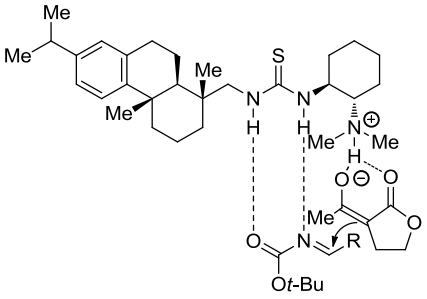
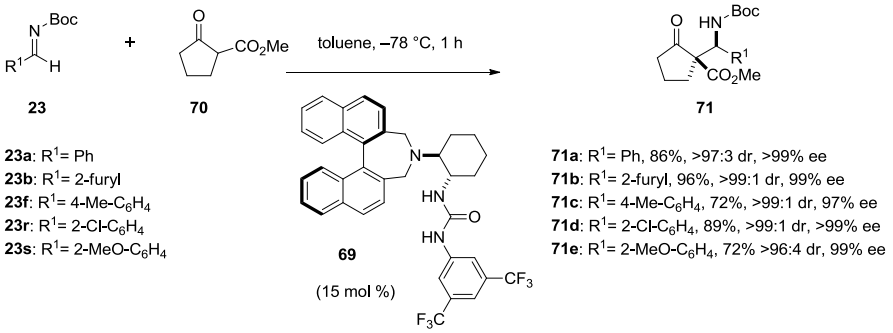


Fig. 5.4 Ternary intermediate complex

the quaternary stereogenic center in Mannich products **68** was accomplished with high levels of enantio- and diastereoselectivity when the acetyl-substituted lactone **67** was subjected to different aromatic *N*-Boc-aldimines **23** (80–92% yield, 75–99% ee, dr>20:1). In contrast, similar benzoyl-substituted lactones showed very poor enantioselectivity in identical conversions. To account for the observed selectivity, it was postulated that a ternary intermediate complex was formed, generated by coordination of the enolate to the chiral tertiary amine moiety and hydrogen-bond formation of the *N*-Boc-aldimine with the thiourea part of the catalyst (Fig. 5.4).

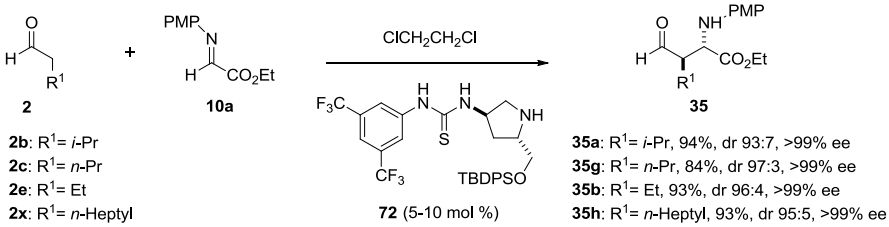
Earlier on, Kim et al. reported results wherein similar reagents were investigated [44]. Excellent results were obtained by using the bifunctional urea catalyst **69** to facilitate the reaction of the cyclic β-ketoesters **70** with *N*-Boc-aldimines **23**. The downside of this method was that the reactions took several days to reach completion. Very high ee's (>95%) and superb diastereoselectivities were reported in those reactions (Scheme 5.33).



Scheme 5.33 Bifunctional urea catalyst **69** providing quaternary Mannich adducts

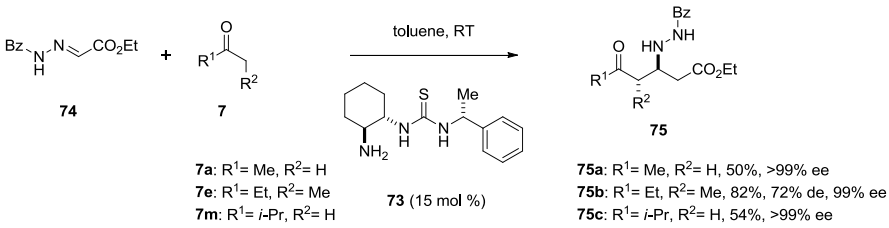
The utilization of bifunctional thiourea catalyst containing a chiral secondary amine was first reported by Peng and co-workers [45]. The prolinol-derived thiourea catalyst **72** has been successfully applied to the *anti*-selective direct asymmetric

Mannich reaction of unmodified aldehydes **2** (and cyclic ketones, not shown) with glyoxylimine **10a** to obtain the α-amino esters **35** (Scheme 5.34). In general, these products were formed in excellent enantio- and diastereoselectivity. In order to rationalize the observed selectivity, it was proposed that the reaction mechanism involved the formation of an enamine from the chiral secondary amine moiety of the catalyst and the unmodified aldehyde or ketone. The bulky TBDPS-group could effectively shield the *re*-face of the enamine double bond thereby rendering the *si*-face available for attack to give the observed major enantiomer. The hydrogen bonding between both thiourea protons and the nitrogen of the α-imino ethylglyoxylate **10a** may have served to activate the imine effectively and guide the electrophile in the right position for nucleophilic attack.



Scheme 5.34 First bifunctional thiourea catalyst bearing a secondary amine moiety

Tsogoeva et al. described the use of the primary amine thiourea-based organocatalyst **73** in an asymmetric Mannich-type reaction of unmodified aldehydes and ketones **7** with readily available and stable α-hydrazonoesters **74** (Scheme 5.35) [46]. Moderate to good yields and excellent enantioselectivities (90–99% ee) were reported. However, the *anti*-diastereoselectivity appeared generally poor (8–72% de).

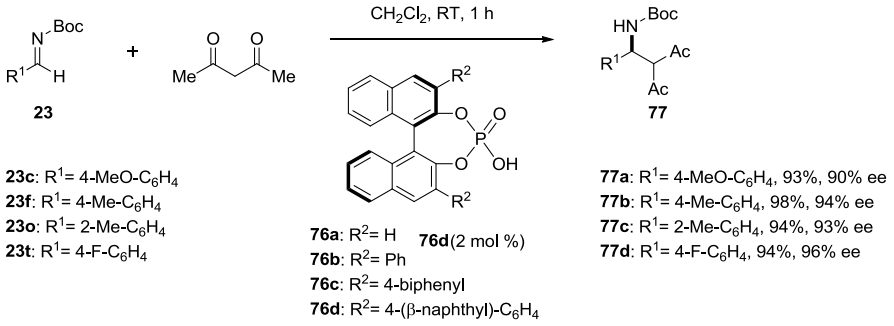


Scheme 5.35 Employment of primary amine thiourea catalyst **73**

5.4 Catalysis by Chiral Brønsted Acids

Instead of using Brønsted bases, chiral Brønsted acids can also be utilized to enantioselectively acquire Mannich products. The acidic catalyst assists in the Mannich reaction by protonating the imine, thereby forming an iminium ion to which the deprotonated Brønsted acid catalyst coordinates. This chiral counterion directs the incoming nucleophile and leads to an optically active Mannich product.

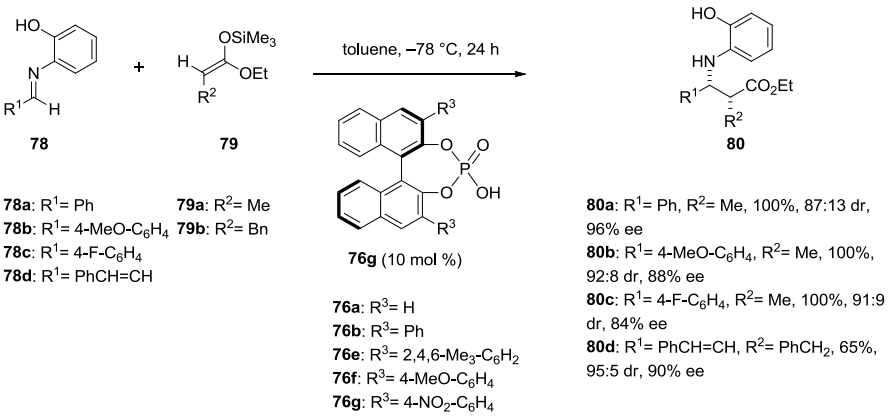
In 2004, Terada et al. studied a new family of chiral Brønsted acid catalysts [47]. These (*R*)-BINOL-based phosphoric acids **76** efficiently catalyzed the enantioselective direct addition of acetyl acetone to the *N*-Boc-protected aldimines **23** providing the corresponding β-aminoketones **77** under mild conditions (Scheme 5.36). It was anticipated that the phosphoric acids **76** would be excellent Brønsted acid catalysts, since the cyclic phosphoric acid moiety restricts rotation and at the same time provides highly efficient ionic hydrogen bonding sites. Additionally, the phosphoryl oxygen could function as a Lewis basic site. Of the (*R*)-BINOL-based phosphoric acids screened, catalyst **76d** gave the most encouraging results.



Scheme 5.36 BINOL-based phosphoric acid in the addition of acetyl acetone to *N*-Boc-protected aldimines

Concurrently, the group of Akiyama reported the use of the rather similar (*R*)-BINOL-based phosphoric acid catalyst **76g** [48]. A selection of aldimines **78a-d** was reacted with silyl ketene acetals **79a-b** to give rise to the β-amino esters **80a-d** in good dr (>86:14 *syn*-selectivity) and high ee (up to 96%, Scheme 5.37).

More recently, Akiyama and Yamanaka proposed a mechanism for the above-mentioned reaction [49]. Calculations revealed that a two-point hydrogen bonding interaction is governing the reaction. It proceeds through protonation of the imine, followed by nucleophilic attack *via* a zwitterionic and nine-membered cyclic TS (Fig. 5.5). The hydrogen-bonding moiety and π-stacking interaction between the aromatic moiety on the Brønsted catalyst and *N*-aryl protecting group contribute considerably to a fixed geometry of the aldimine, which accounts for the observed *re*-facial selectivity.



Scheme 5.37 Variety of BINOL-based catalysts

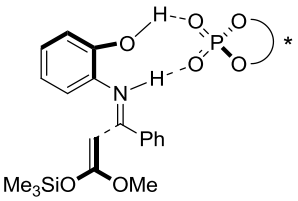
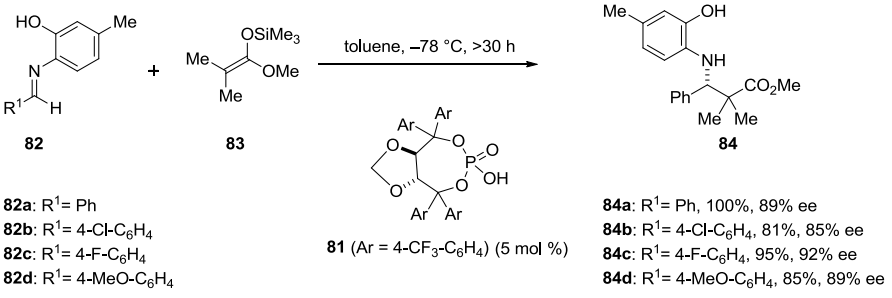


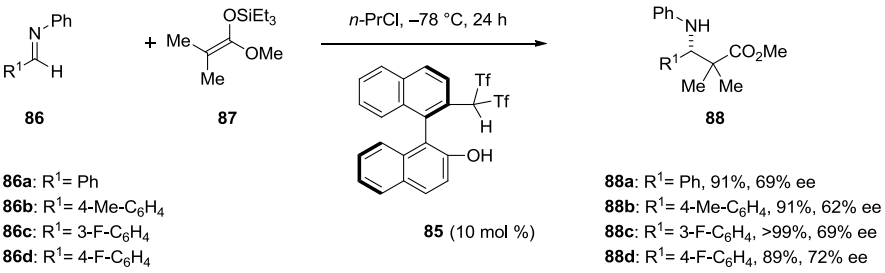
Fig. 5.5 Proposed nine-membered cyclic transition state

A novel chiral Brønsted acid (**81**) based on the so-called TADDOL-scaffold was also prepared by the Akiyama group [50]. The catalyst was optimized by varying the aryl and alkyl groups on the acetal moiety. By employing this new Brønsted acid, Mannich-type reactions of aldimines **82a-d** with silyl ketene acetals **83** were efficiently catalyzed at lower catalyst loadings. On top, the resulting β-amino esters **84a-d** were obtained in higher ee than with the previously mentioned catalysts **76** (Scheme 5.38).



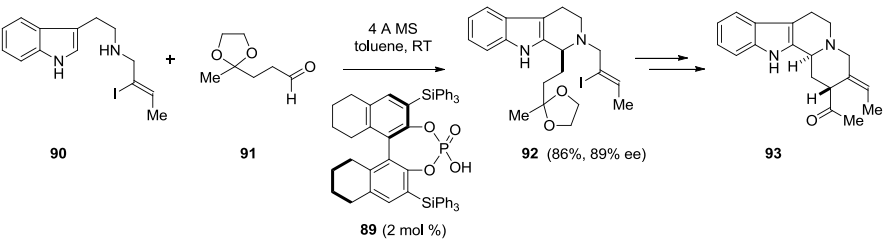
Scheme 5.38 Novel chiral Brønsted acid-based on TADDOL scaffold

Yamamoto and Ishihara designed a so-called Brønsted acid-assisted chiral Brønsted acid (BBA) catalyst **85** bearing a bis(triflyl)methyl group for the Mannich-type reaction of aldimines **86a-d** with silyl ketene acetals **87** (Scheme 5.39) [51]. The BBA catalyst **85** carries two acidic protons. It was suggested that in order to stabilize the configuration of the chiral transition state, both intermolecular hydrogen-bonding between the bis(triflyl)methyl proton and aldimine nitrogen and intramolecular hydrogen-bonding between the hydroxyl proton and the catalyst's triflyl-groups take place. The conformation of the protonated aldimines may also be fixed by π-stacking interactions between the naphthyl group of the catalyst and the aryl group of the aldimine. The reactivity was improved by adding a stoichiometric achiral proton source to complete the catalytic cycle of the chiral Brønsted acid catalysts. The β-amino esters **88a-d** were obtained in high yields, but generally moderate ee.



Scheme 5.39 Brønsted acid-assisted chiral Brønsted acid catalysis

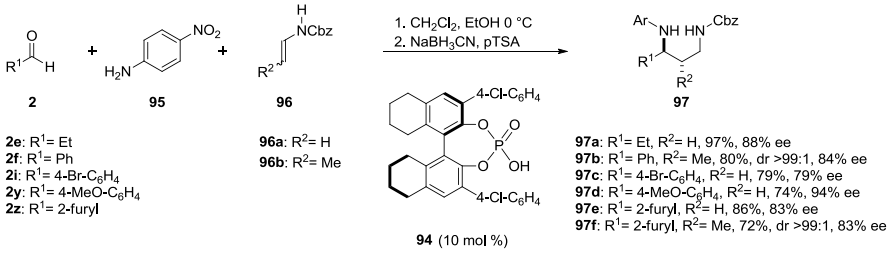
Besides the aforementioned Mannich reactions, several groups have reported related reactions in which iminium ions also serve interesting as intermediates in carbon-carbon bond formation. Specific examples include organocatalytic asymmetric Pictet-Spengler reactions, which have been studied by several groups [52–54]. An interesting extension of their previous work on Brønsted-acid catalyzed asymmetric Pictet-Spengler reactions [55], was the application of Hiemstra et al. of such a reaction in a total synthesis of the alkaloid (–)-arboricine (**93**, Scheme 5.40) [56]. In this case, treatment of tryptamine derivative **90** with aldehyde



Scheme 5.40 Brønsted-acid catalyzed asymmetric Pictet-Spengler reaction

91 in the presence of 2 mol% of phosphoric acid **89** provided the Pictet-Spengler product **92** in good yield and very high ee. The latter product was then converted in a few steps into the natural product (–)-arboricine (**93**).

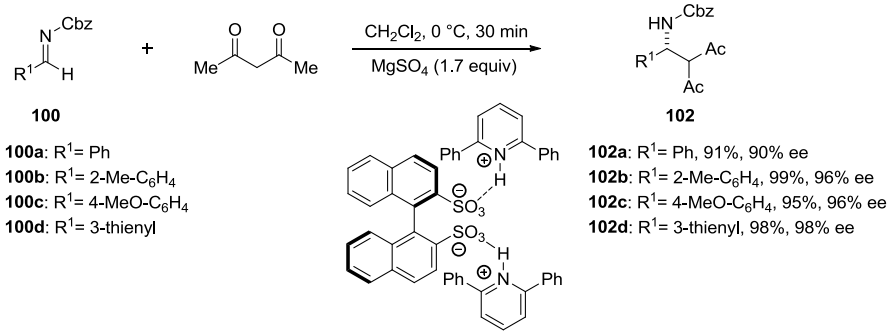
The (*R*)-BINOL-based phosphoric acid catalyst **94** was recently applied in a related three-component Mannich-type reaction of aldehydes **2** with *p*-nitroaniline **95** and enecarbamates **96a-b** by Masson and Zhu to obtain the corresponding amino-substituted N,O-acetals, which were reduced *in situ* to the *anti*-1,2-disubstituted 1,3-diamines **97a-f** (Scheme 5.41) [57]. The reduced Mannich products were obtained in moderate to high yields (62–97%) and good to excellent ee.



Scheme 5.41 (*R*)-BINOL-based phosphoric acid catalyst in three-component Mannich reaction

Acid-base combination chemistry is a promising and upcoming approach in modern asymmetric catalysis. This often involves salts, which due to a combination of a basic and an acidic site can activate and coordinate both the substrate and an acidic pronucleophile. A possible advantage is that they are generally more flexible in design than single-molecule catalysts.

Ishihara et al. used the chiral sulfonic acid **98** in the direct Mannich reaction of *N*-Cbz-protected phenylaldimines **100a-d** and acetylacetone (Scheme 5.42) [58].



Scheme 5.42 Application of chiral Brønsted-acid-base combined salt catalyst in new Mannich reactions

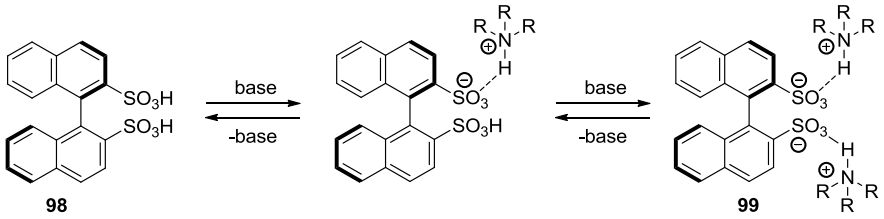


Fig. 5.6 Formation of chiral Brønsted-acid-base combined salt catalyst

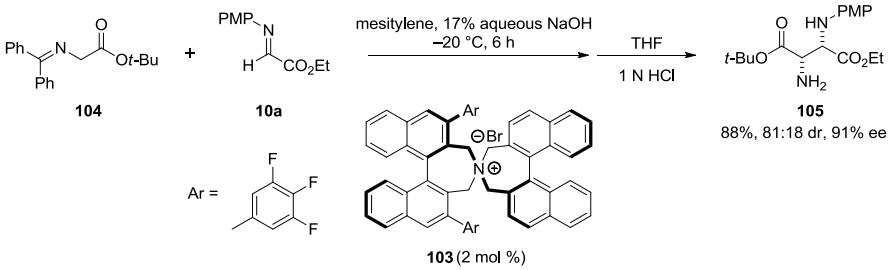
The corresponding Mannich base was obtained in good yield, however, the enantioselectivity was rather poor (17% ee). Hence, several salts **99** were prepared *in situ* by combining sulfonic acid **98** with various organic amines and subsequently employed the resulting chiral Brønsted acid-base salts as catalysts in the aforementioned reaction (Fig. 5.6).

The combination with 2,6-diphenylpyridine (**101**) appeared highly effective, leading to product **102a** in 74% yield and 92% ee. This was further improved by adjusting the molar ratio of sulfonic acid **98** (1 mol%) and pyridine **101** (2 mol%) to attain both a high conversion and enantioselectivity. In the end, several *N*-Cbz-protected aldimines **100a-d** were screened to give the Mannich adducts **102a-d** in high yield (> 91%) and ee (84–98%, Scheme 5.42). The concept of combining acids and bases was further elaborated by the same group amongst others by also invoking Lewis acids in combination with Brønsted bases and application of these new catalysts in Mannich reactions [59].

5.5 Phase-Transfer Catalysts and Quaternary Salts

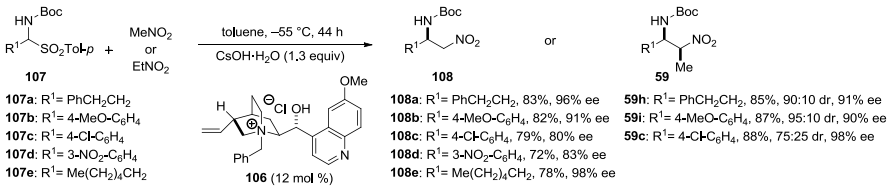
Over the past decades, quaternary ammonium- and phosphonium salts have been widely employed as effective phase-transfer catalysts in reactions between substances located in different immiscible phases. Recently, efforts have been made to unlock the full potential of chiral non-racemic onium salts as versatile catalysts for asymmetric carbon-carbon bond formation. These reactions can be conducted under mild biphasic conditions and the phase-transfer catalysts can often be derived from readily available naturally occurring alkaloids. The reaction proceeds since the catalyst forms a well-defined chiral ion pair with the electrophile. As a result one enantiotopic face is shielded and enantioselective carbon-carbon bond formation can be realized.

In 2004, the group of Maruoka reported the direct asymmetric Mannich reaction of glycinate Schiff base **104** with α-imino ester **10a** catalyzed by *N*-spiro-C_2-symmetric chiral quaternary ammonium bromide **103** to provide the protected 3-aminoaspartate **105** in 88% yield (81:18 dr, 91% ee) [60]. The latter was afterwards converted into a precursor of the streptothricin antibiotics core structure (Scheme 5.43).



Scheme 5.43 *N*-spiro-C_2-symmetrical chiral quaternary ammonium bromide in the Mannich reaction

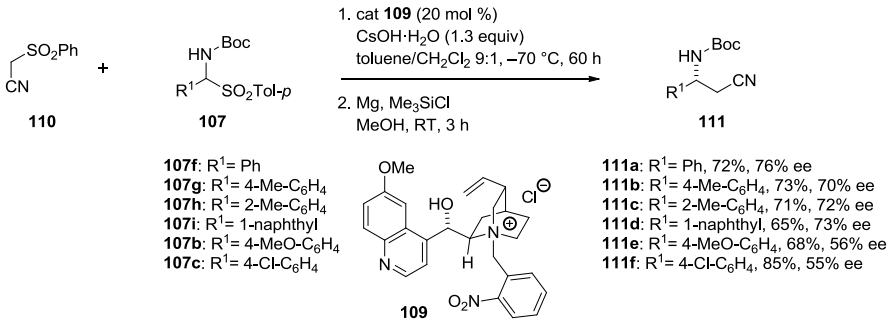
The group of Palomo screened several commercially available chiral quaternary ammonium salts and inorganic bases for the nitro-Mannich reaction of α-amidosulfones **107a** and nitromethane in toluene [61]. A combination of $CsOH{\cdot}H_2O$ and the quinine-derived catalyst **106** proved to give the best results. To extend the scope of the methodology, a variety of α-amidosulfones **107a-e** were reacted with both nitromethane and nitroethane (Scheme 5.44). The corresponding products **108a-e** and **59c**, **59h-i** were obtained in good yield and stereoselectivity (80–98% ee, 72:25 to 95:5 dr (*syn*/*anti*)).



Scheme 5.44 Quinine-derived PTC in the addition of nitroalkanes to *in situ* formed aldimines

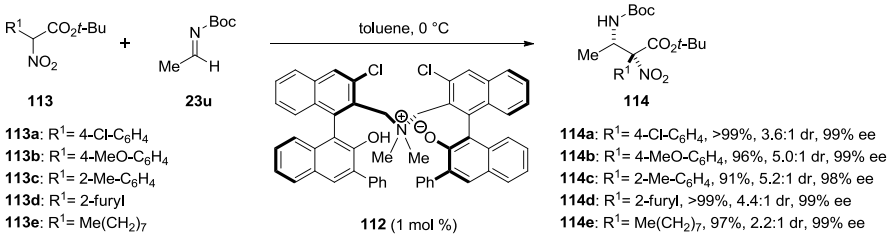
In 2010 the Palomo group used the related quinidine-derived phase-transfer catalyst **109** to facilitate the addition of sulfonylacetonitrile **110** to either *N*-Boc-protected α-amidosulfones **107** or imines (not shown) in order to obtain – upon subsequent treatment with Mg in MeOH – the enantioenriched α-unsubstituted β-aminonitriles **111a-f** (Scheme 5.45) [62]. The latter compounds were obtained in moderate to good yields (65–85%) and moderate ee (55–76%).

The new chiral ammonium betaine **112** was developed and utilized by Ooi et al. as a bifunctional organic base catalyst for Mannich-type reaction of α-nitrocarboxylates [63]. This quaternary ammonium compound is an internal salt, unlike the aforementioned intermolecular ion-pairing ammonium salts. Consequently, the anion could act as a Brønsted base and deprotonate a pronucleophile. The resulting



Scheme 5.45 Enantioenriched α-unsubstituted β-aminonitriles involving quinidine-based PTC **109**

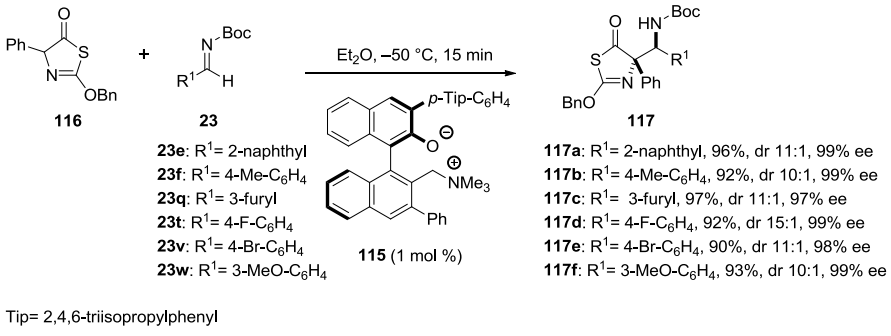
acidic proton could assist in directing the counterionic nucleophile to the cationic pocket through hydrogen-bonding interactions and retain its position, a benefit that intermolecular ion-pairing ammonium salts do not share. To examine the competence of the catalyst, α-substituted α-nitrocarboxylates **113** and the *N*-Boc aldimines **26u** were evaluated to form the α-substituted β-amino acids **114** (Scheme 5.46). Excellent yields and ee's were observed. However, the dr was generally modest (2:0 to 5.2:0 (*syn*/*anti*)).



Scheme 5.46 Chiral ammonium betaine **112** as a bifunctional organic base catalyst

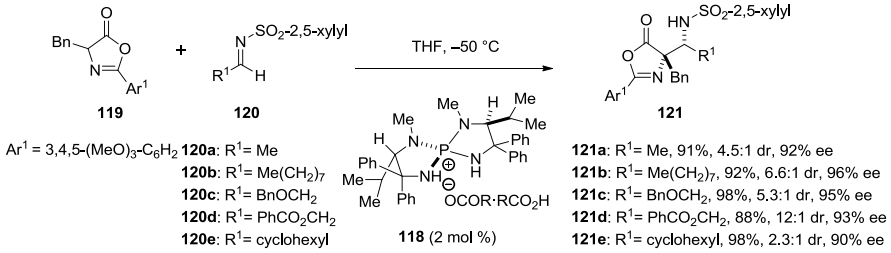
More recently, the same group moved to a simpler catalyst design, also containing an internal ion pair. A series of catalysts were evaluated, eventually leading to **115** as the best performing one [64]. The catalyst was shown to efficiently catalyze the addition of thiazolone **116** onto the aldimines **23** providing the corresponding Mannich products **117a-f** in high *anti*-selectivity and excellent ee (Scheme 5.47).

A few months later, the Ooi group published another paper concerning organic ion-pair catalysis [65]. Up till now the focus of these catalysts had primarily been on the cation part of the quaternary salt, since the anion was hardly associated with overall efficiency and stereoselectivity. Hence, they looked into the development



Scheme 5.47 Bifunctional organic base catalyst by the Ooi group

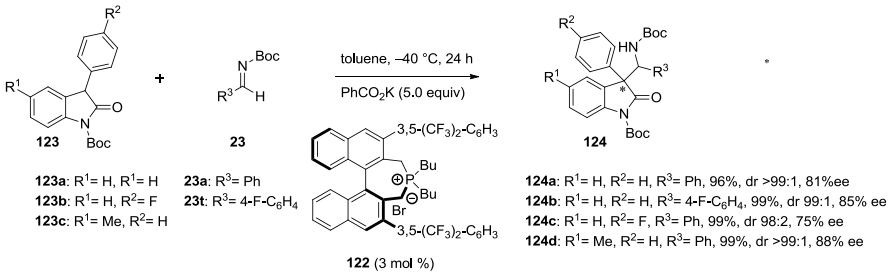
and application of a novel quaternary ammonium salt catalyst complemented by a useful organic anion. In initial studies the [5,5]-*P*-spirocyclic tetraaminophosphonium framework **118** as a primary structure of the key onium ion and different carboxylates as organic counteranions were screened in the direct Mannich-type reaction of azlactone **119** with *N*-sulfonylimine **120** (Scheme 5.48). Changing the anionic component from formate to acetate to pivalate resulted in a dramatic rate enhancement, albeit that stereoselectivity remained unaffected. Altering the aromatic substituent on both **119** and **120** led to a further improvement of selectivity. In the end, various α,β-diamino acid derivatives **121a-e** were obtained in excellent yield (>90%) and enantioselectivity (>90%). Unfortunately, the observed diastereoselectivity was not too impressive (2.3:1 to 12:1(*syn*/*anti*)).



Scheme 5.48 Novel quaternary onium salt catalyst complemented by useful organic anion

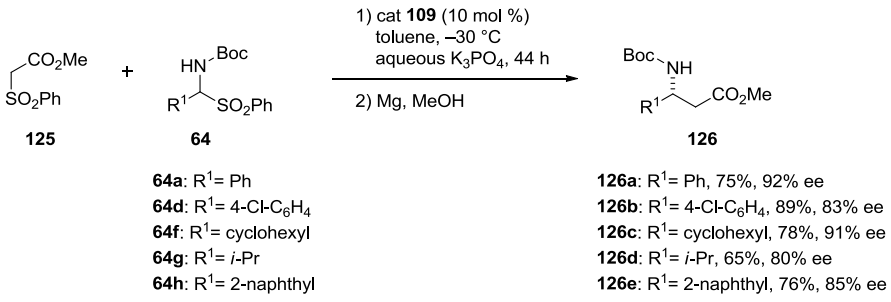
In 2009, the phosphonium-derived catalyst **122** was utilized by Maruoka and co-workers [66]. The group aimed to construct chiral quaternary carbon centers and set out to explore the scope of these particular phase-transfer catalysts, since they successfully employed chiral quaternary phosphonium salts before. The catalyst

was initially designed to facilitate the enantioselective Michael-addition of 3-aryloxindoles, but was also found to effectively catalyze the Mannich reaction of 3-aryloxindoles **123a-c** onto activated imines **23a**, **23t** in excellent diastereo- and good enantioselectivity (Scheme 5.49).



Scheme 5.49 Construction of chiral quaternary carbon centers with phosphonium-derived catalyst **122**

Bernardo and Ricci reported the first employment of arylsulfonylacetates in a catalytic asymmetric setting [67]. Arylsulfonylacetate **125** was reacted with *N*-carbamoyl imines generated *in situ* from α-amidosulfones **64a**, **64d**, **64g-h** to yield the Mannich-adducts (not shown) under phase transfer conditions (Scheme 5.50). Of all the phase-transfer catalysts tested, derivative **109** was one of the most promising in terms of enantioselectivity. Subsequent chemistry allowed for the conversion of the Mannich adducts into the corresponding β-aminoesters **126a-e**. Moderate to good overall yields (65–89%) and high enantioselectivities (77–94%) were reported.

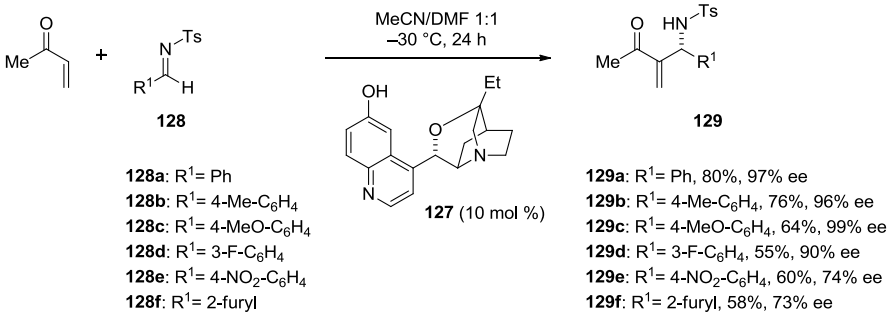


Scheme 5.50 First employment of arylsulfonyl acetates in catalytic asymmetric reaction

5.6 The Aza-Morita-Baylis-Hillman Reaction

The aza-Morita-Baylis-Hillman (AMBH) reaction involves the reaction of imines with zwitterionic enolates, generated through conjugate addition of tertiary amines or phosphines onto α,β-unsaturated esters, aldehydes or ketones, eventually resulting in allylic amines. One can envision that if chiral tertiary amines or phosphines are used, the AMBH reaction may proceed in an enantioselective fashion, giving rise to the optically active products. Due to the similarity to the Mannich reaction, organocatalyzed versions of the AMBH reaction are reviewed in this chapter as well [68].

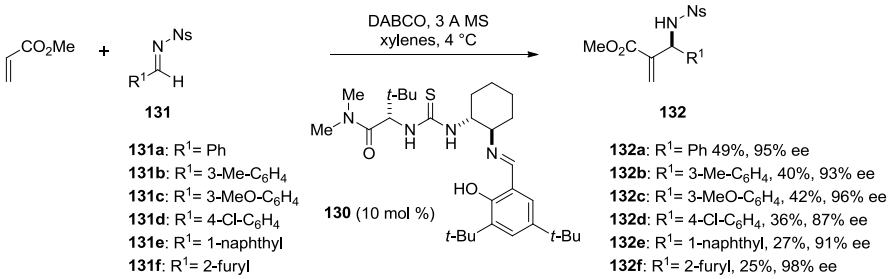
One of the earliest examples of the organocatalyzed asymmetric AMBH was reported by the group of Shi (Scheme 5.51) [69]. The imines **128a-f**, suitably activated with the strongly electron-withdrawing tosyl group, were reacted with methyl vinyl ketone under the influence of 10 mol% of catalyst **127**. This provided the corresponding allylic amines **129a-f** in moderate to good yields and often excellent enantioselectivity.



Scheme 5.51 Early example of organocatalyzed asymmetric AMBH reaction

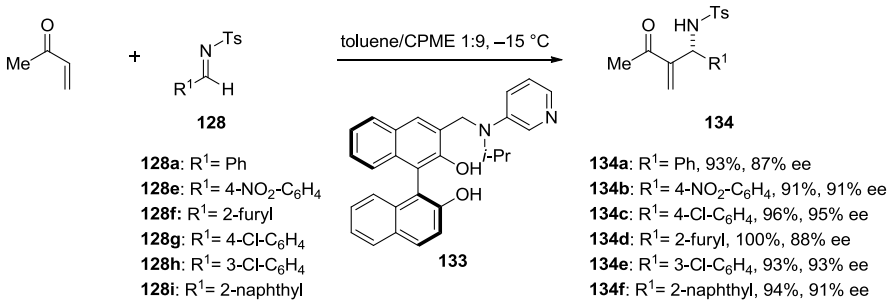
Fairly similar reactions with organocatalyst **127** were carried out by Balan and Adolfsson with *in situ* generated tosyl imines from tosylamide and the corresponding aldehyde in the presence of a catalytic amount of $Ti(O\text{-}iPr)_4$ [70]. Although the yields of these three-component reactions were generally very high, the enantioselectivity appeared often moderate (50–74%). Another early example with catalyst **127** was published by Hatakeyama et al., who successfully performed AMBH reactions with hexafluoroisopropyl esters of acrylates [71].

The Jacobsen group reported the use of thiourea-derived catalyst **130** to efficiently catalyze the formation of allylic amines **132a-f** from methyl acrylate and the nosylated imines **131a-f** (Scheme 5.52) [72]. Remarkably, this catalyst was used in combination with DABCO, yet leading to usually high ee's, albeit in often moderate yields. An advantage of the nosyl protecting group is that the products can be readily deprotected using thiolate anions.



Scheme 5.52 Use of bifunctional thiourea catalyst **130** in the AMBH reaction

The group of Shi later on were the first to show that that BINOL-derived catalysts can also successfully be utilized to react methyl vinyl ketone with *N*-tosylated imines in an highly enantioselective fashion [73]. This example inspired various other groups to come up with similar catalysts, all giving rise to highly enantiopure allylic amines in the same AMBH reaction. As a particular example, the Sasai group used BINOL-derivative **133** in the reaction of methyl vinyl ketone with *N*-tosyl imines **128** to yield the corresponding AMBH products **134** in excellent yields and very high ee's (Scheme 5.53) [74]. In a later stage, this reaction was further explored by the same group focusing on enlarging the scope, and elucidation of the exact mechanism of the reaction including the origin of the enantioselectivity [75, 76].



CMPE= cyclopentylmethylether

Scheme 5.53 BINOL-derivative **133** yields AMBH products in excellent yields and selectivities

As mentioned before, various group used fairly similar catalyst to report excellent results on this particular asymmetric organocatalyzed AMBH reaction. Some of the catalysts used are shown in Fig. 5.7. Organocatalyst **135** is the one originally used by Shi [73], as was **136** at a later stage in the same reaction [77]. Liu and co-workers

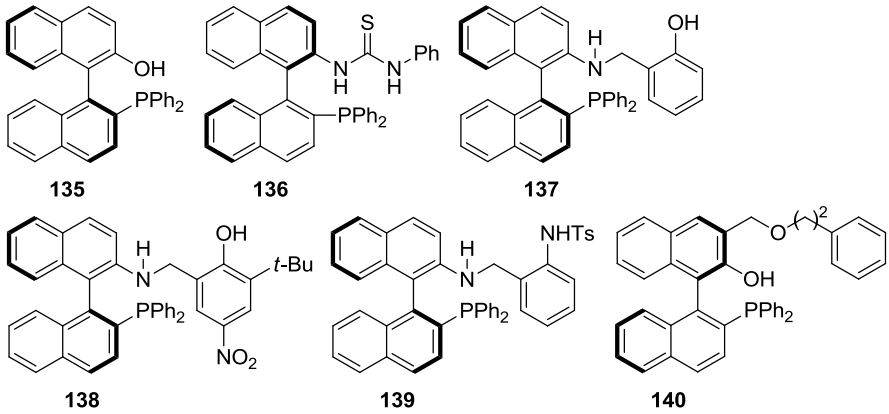
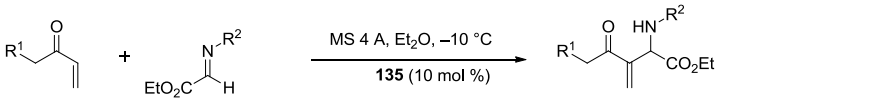


Fig. 5.7 BINOL-derivatives generally are successful catalysts in the AMBH reaction

were working with the strongly related catalysts **137**–**139** all applied successfully in this AMBH reaction [78–80], the same holds for Ito et al. using BINOL derivative **140** [81].

The scope of catalyst **135** was also extended by work from the Shi group by showing that it could also be successfully applied on other imines such as *N*-aryl imines (Scheme 5.54) [82, 83]. As an example, ethyl and methyl vinyl ketone were coupled to imines **141a-f** to yield the AMBH products **142a-g** in high yield and high to excellent ee.



141

142

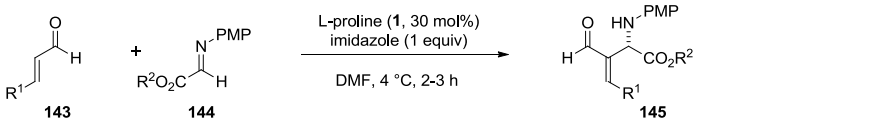
R^1= Me, Et

141a: R^2= 4-Me-C_6H_4
141b: R^2= 4-Br-C_6H_4
141c: R^2= 4-Cl-C_6H_4
141d: R^2= Ph
141e: R^2= 4-MeO-C_6H_4
141f: R^2= 4-CF_3-C_6H_4

142a: R^1= Me, R^2= 4-Me-C_6H_4, 99%, 94% ee
142b: R^1= H, R^2= 4-Br-C_6H_4, 65%, 90% ee
142c: R^1= Me, R^2= 4-Br-C_6H_4, 69%, 94% ee
142d: R^1= H, R^2= 4-Cl-C_6H_4, 76%, 90% ee
142e: R^1= Me, R^2= 4-Cl-C_6H_4, 60%, 88% ee
142f: R^1= H, R^2= Ph, 92%, 91% ee
142g: R^1=Me, R^2= Ph, 89%, 92% ee

Scheme 5.54 Various *N*-imines successful in the AMBH reaction

Barbas and co-workers used α,β-unsaturated aldehydes **143** as donors in the AMBH reaction in combination with the PMP-protected imines **144** (Scheme 5.55). Interestingly, this reaction was successfully catalyzed by L-proline (**1**), leading to the corresponding AMBH products **145** in moderate yields, but high *E*/*Z*-ratios and excellent enantioselectivity [84].



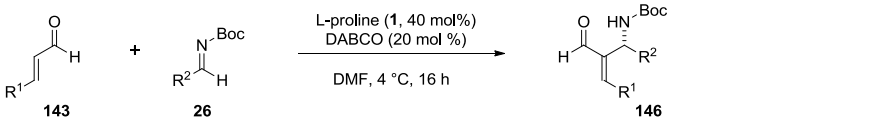
143a: R^1= Me
143b: R^1= Et
143c: R^1= *n*-Pr
143d: R^1= *i*-Pr

144a: R^2= *i*-Pr
144b: R^2= Et

145a: R^1= Me, R^2= *i*-Pr, 68%, E/Z 16:1, 99% ee
145b: R^1= Et, R^2= Et, 58%, E/Z 10:1, 99% ee
145c: R^1= *n*-Pr, R^2= Et, 50%, E/Z 8:1, 97% ee
145d: R^1= *i*-Pr, R^2= Et, 40%, E/Z 4:1, 98%

Scheme 5.55 α,β-Unsaturated aldehydes as donors in L-proline catalyzed AMBH reaction

Similar aldehydes **143a-b**, **143e** were also applied by the Córdova group, this time in combination with Boc-protected imines **23a**, **23c-d** (Scheme 5.56). Again, L-proline **1** was successfully utilized to yield the allylic Boc-protected amines **146** in reasonable yield and E/Z selectivity, but excellent enantioselectivity (all >99% ee) [85].



143a: R^1= Me
143b: R^1= Et
143e: R^1= 3-butenyl

23a: R^2= Ph
23c: R^2= 4-MeO-C_6H_4
23d: R^2= 4-Cl-C_6H_4

146a: R^1= Me, R^2= Ph, 45%, E/Z 4:1, 99% ee
146b: R^1= Et, R^2= Ph, 51%, E/Z 9:1, 99% ee
146c: R^1= 3-butenyl, R^2= Ph, 47%, E/Z 8:1, >99% ee
146d: R^1= Et, R^2= 4-MeO-C_6H_4, 56%, E/Z 9:1, 99% ee
146e: R^1= Et, R^2= 4-Cl-C_6H_4, 61%, E/Z 9:1, 99%

Scheme 5.56 Boc-protected aldimines in combination with α,β-unsaturated aldehydes

5.7 Conclusions

Since the advent of organocatalysis at the end of the past century, asymmetric organocatalyzed Mannich and related reactions have become firmly established as an important area of research within the field of organic synthesis. What started some decades ago with a few isolated examples, has grown into a respectable field and opened up numerous new possibilities for (asymmetric) carbon-carbon bond formation. Hence, a large variety of amino-substituted building blocks has become readily accessible in enantiomerically pure form, and not unimportantly in a highly practical manner, making often use of cheap and environmentally benign organic molecules and running reactions at room temperature.

If one considers what enormous progress has been made in only 10 years time, one can also conceive that there will be many new reactions discovered in the years to come.

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Index

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