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Asymmetric organocatalysis

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In loving memory of Cyril and Valérie Pellissier

Contents

Abbreviations: Ac, acetyl; Ar, aryl; BINOL, 1,1′-bi-2-naphthol; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bu, butyl; Bz, benzoyl; Cbz, benzyloxycarbonyl; CPME, cyclopentyl methyl ether; Cy, cyclohexyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBAB, dibenzylazodicarboxylate; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DBP, 3,5-di-*tert*-butylphenyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; de, diastereomeric excess; DIPEA, diisopropylethylamine; DKR, dynamic kinetic resolution; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DPEN, 1,2-diamino-1,2-diphenylethane; ee, enantiomeric excess; Et, ethyl; EWG, electron-withdrawing; Fmoc, 9-fluorenylmethoxycarbonyl; Fu, furanyl; Hex, hexyl; Hept, heptyl; HFIAP, 1,1,1,3,3,3-hexafluoroisopropyl acrylate; IPDA, isophoronediamine; Me, methyl; Mes, mesyl; MTBE, methyl *tert*-butyl ether; naph, naphthyl; Nf, nonaflamide; NFSI, *N*-fluorobenzenesulfonimide; NMO, 4-methylmorphine-*N*-oxide; NMP, *N*-methyl-2-pyrrolidone; Non, nonyl; Ns, nosyl; Oct, octyl; PEG, poly(ethylene glycol); PEMP, pentamethylpiperidine; Pent, pentyl; Ph, phenyl; Phth, phthalimido; Piv, pivaloyl; PMP, *p*-methoxyphenyl; PNBA, *p*-nitrobenzoic acid; Pr, propyl; py, pyridyl; TADDOL, α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol; TBAB, tetra-*n*-butylammonium bromide; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; THF, tetrahydrofuran; TIPS, triisopropylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; TMG, tetramethylguanidine; TMS, trimethylsilyl; Tol, tolyl; TPP, tetraphenylporphyrin; Troc, 2,2,2-trichloroethoxycarbonyl; Ts, 4-toluenesulfonyl (tosyl).

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1. Introduction

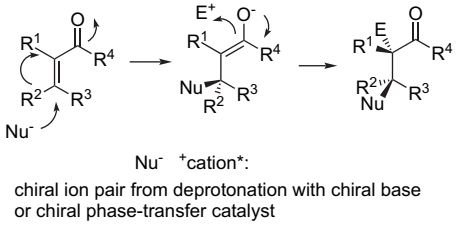
The enantioselective production of compounds is a central theme in current research. The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Until a few years ago, it was generally accepted that transition-metal complexes and enzymes were the two main classes of very efficient asymmetric catalysts. Synthetic chemists have scarcely used small organic molecules as catalysts throughout the last century, even though some of the very first asymmetric catalysts were purely organic molecules. Indeed, already in 1912, Bredig reported a modestly enantioselective alkaloid-catalysed cyanohydrin synthesis. In the 1960s, Pracejus showed that organocatalysts could give significant enantioselectivities. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using the simple amino acid proline as the catalyst. The cinchona alkaloids and proline stood as the only familiar organocatalysts for some time. In contrast to the relative inattention paid to organocatalysts by chemists, biological evolution has led to metal catalysis and organocatalysis in equal measure. While the end of the last century has been dominated by the use of metal catalysts,[1] a change in perception has occurred during the last few years, when several reports confirmed that relatively simple organic molecules could be highly effective and remarkably enantioselective catalysts of a variety of fundamentally important transformations. This rediscovery has initiated an explosive growth of research activities in organocatalysis, both in industry and in academia. As the realisation grows that organic molecules not only have ease of manipulation and a green advantage, but also can be very efficient catalysts, asymmetric organocatalysis may begin to catch up with the spectacular advances in enantioselective transition-metal catalysis. Thus, it was demonstrated that, besides the well-established asymmetric metal-complex-catalysed syntheses and biocatalysis, the use of pure organic catalysts turned out to be an additional efficient tool for the synthesis of chiral building blocks. Although the first examples were reported several decades ago,[2] the area of enantioselective organocatalysis became a main focus of research only recently. The last decade has seen an exponential growth in the field of asymmetric organocatalysis, and iminium-, enamine- and phosphoramide-based organocatalysis now allows cycloadditions, Michael additions, aldol reactions, nucleophilic substitutions and many other reactions with excellent enantioselectivities. The last few years have witnessed an explosive and impressive growth in the field, with new catalysts, novel methodologies for epoxidation, imine reduction or acylation, and mechanistic studies of aldol condensation, Mannich-type reactions, Michael addition, aza-Henry and Baylis–Hillman reactions and phase-transfer processes.

Organocatalysis, by now, has definitively matured to a recognised third methodology, of potentially equal status to organometallic and enzymatic catalysis. Organocatalysts have several important advantages, since they are usually robust, inexpensive, readily available and non-toxic. Because of their inertness towards moisture and oxygen, demanding reaction conditions, e.g., inert atmospheres, low temperatures, absolute solvents, etc., are, in many instances, not required. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination such as pharmaceutical products. A collection of chiral organocatalysts has already been involved in asymmetric

synthesis, such as the prototypical example of proline, cinchona alkaloids such as quinine and various sugar-, amino acid- or peptide-derived compounds. Indeed, this type of catalysis has several serious advantages when compared to biocatalysis or to the use of transition-metal complexes as catalysts. The catalysts are usually more stable, less expensive and readily available, and can be applied in less-demanding reaction conditions. This type of catalyst can be easily incorporated onto a support, facilitating their recovery and recycling. Moreover, the absence of using a transition metal makes this type of reaction an attractive tool for the synthesis of agrochemical and pharmaceutical compounds, in which the presence of hazardous metallic traces are inadmissible in the final product. In this strategy, these factors contribute to superior atom efficiency, avoiding the protection of the substrate and deprotection of the products, and allowing the direct synthesis of structurally complex molecules, even through asymmetric multicomponent reactions[3] as well as domino,[4] tandem[5] or cascade transformations.[6] Consequently, this methodology will be important in industry, due to its versatility and its favourable environmental impact. This review is an update of the important use of such chiral metal-free organic catalysts in numerous reaction types, such as nucleophilic substitutions, and addition reactions as well as cycloadditions and redox reactions. Asymmetric organocatalysis was previously reviewed by List[7] and Dalko,[8] covering the literature up to the end of 2004. In 2006, List reported a personal account focusing on asymmetric aminocatalysis.[9] In addition, a book was published in 2005 by Berkessel and Gröger, ranging from the biomimetic concepts to applications in asymmetric synthesis of asymmetric organocatalysis.[10] The goal of the present review is to cover the recent advances in the use of chiral organocatalysts in asymmetric synthesis, focusing on those published since the beginning of 2005. This review is subdivided into 10 sections, according to the different types of reactions based on the use of chiral organocatalysts, such as nucleophilic additions to electron-deficient C=C double bonds, nucleophilic additions to C=O double bonds, nucleophilic additions to C=N double bonds, nucleophilic additions to unsaturated nitrogen, nucleophilic substitutions at aliphatic carbon, cycloaddition reactions, oxidations, reductions, kinetic resolutions and miscellaneous reactions. The vast majority of organocatalytic reactions are amine-based reactions.[11] In this asymmetric aminocatalysis, amino acids, peptides, alkaloids and synthetic nitrogen-containing molecules have been used as chiral catalysts.

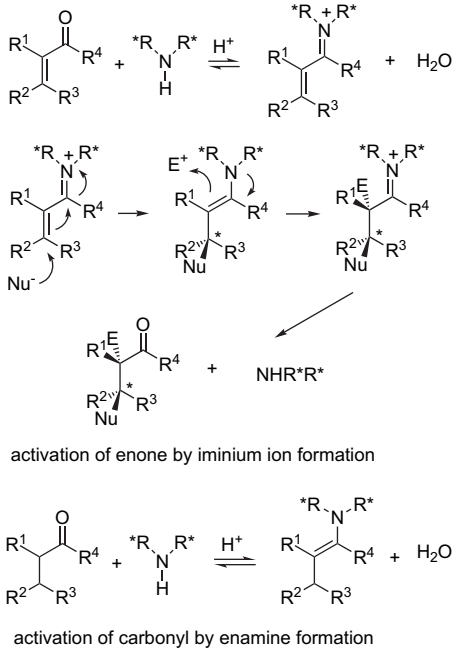
2. Nucleophilic additions to electron-deficient C=C double bonds

In the Michael addition, a nucleophile Nu^- is added to the β-position of an α,β-unsaturated acceptor. The active nucleophile Nu^- is usually generated by deprotonation of the precursor NuH. The mechanistic scheme implies that enantioface differentiation in the addition to the β-carbon atom of the acceptor can be achieved in two ways, either deprotonation of NuH with a chiral base, resulting in a chiral ion pair, which can be expected to add to the acceptor asymmetrically, or phase-transfer catalysis in which deprotonation of NuH is achieved in one phase with an achiral base and the anion Nu^- is transported into the organic phase by a chiral phase-transfer catalyst, also resulting in a chiral ion pair from which asymmetric β-addition may proceed. These methods of providing a chiral environment for the attacking nucleophile can be regarded as the classical ways of approaching asymmetric organocatalysis of Michael additions (Scheme 1).



Scheme 1. Use of chiral bases and phase-transfer catalysis in Michael reactions.

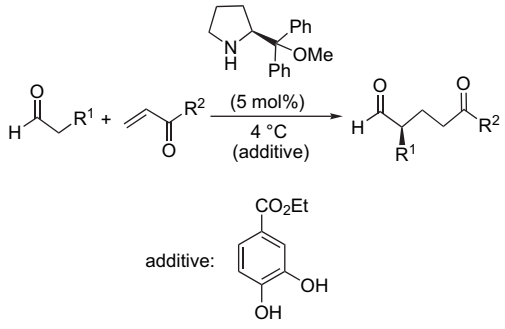
Two highly efficient and very practical alternatives have emerged in recent years (Scheme 2). One of these approaches consists of activating the acceptors by reversible conversion into a chiral iminium ion. Thus, the reversible condensation of an α,β-unsaturated carbonyl compound with a chiral secondary amine provides a chiral α,β-unsaturated iminium ion. A face-selective reaction with the nucleophile provides an enamine, which can either be reacted with an electrophile and then hydrolysed, or just hydrolysed to a β-chiral carbonyl compound. The second approach is the enamine pathway. If the nucleophile is an enolate anion, it can be replaced by a chiral enamine, formed reversibly from the original carbonyl compound and a chiral secondary amine. It is apparent that enamine and iminium catalyses are based on the same origin. Enamine catalysis proceeds via iminium ion formation and almost always results in iminium ion formation. In an opposing, but complementary, fashion, iminium catalysis typically results in the formation of an enamine intermediate. The two catalytic intermediates are opposite, yet interdependent, and they consume and support each other.



Scheme 2. Enamine and iminium catalysis in Michael reactions.

2.1. Intermolecular Michael additions

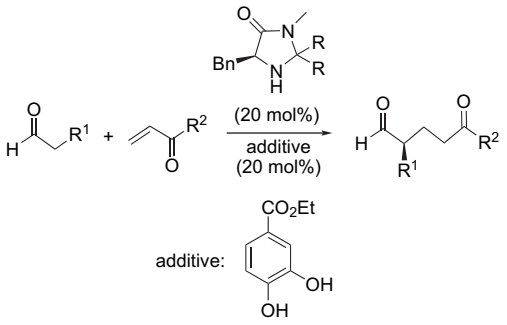
2.1.1. Intermolecular Michael additions of *C*-nucleophiles. The first part of this section deals with Michael additions of *C*-nucleophiles evolving via enamine or iminium ion intermediates. The most successful catalyst for enamine-type reactions is the cheap, natural, simple, and readily available amino acid L-proline, which has been defined in the recent past as a 'universal catalyst'. Proline can react as a nucleophile with carbonyl groups or Michael acceptors to form iminium ions or enamines. The high enantioselectivities generally observed in proline-mediated reactions can be rationalised by the capacity of this molecule to promote the formation of highly organised transition states with extensive hydrogen-bonding networks. Many successes have been realised by applying organocatalysts such as proline derivatives to highly reactive Michael donors or acceptors. In contrast, Michael additions of simple aldehydes to simple enones have received little attention. In 2005, Gellman and Chi reported that diphenylprolinol methyl ether could catalyse intermolecular Michael addition of simple aldehydes to relatively non-activated enones with the highest enantioselectivities reported to date (95–99% ee) and significantly lower catalyst loading (1–5 mol %) than has been typical in this arena (Scheme 3).[12] Although some of these reactions proceeded well with only the chiral pyrrolidine as a catalyst, others required the use of a catechol as a co-catalyst, which was supposed to electrophilically activate the enone via hydrogen-bond donation to the carbonyl oxygen.



R^1,R^2	Additive (mol%)	Yield (%)	ee (%)
Me,Me	20	82	97
Et,Me	0	75	97
n-Pr,Me	0	69	> 95
i-Pr,Me	0	65	98
n-Hex,Me	0	85	> 95
Bn,Me	0	82	> 95
Me,Et	20	70	99
Et,Et	20	68	95
n-Pr,Et	20	69	> 95
i-Pr,Et	20	60	99
n-Hex,Et	20	87	> 95
Bn,Et	20	87	> 95

Scheme 3. Diphenylprolinol methyl ether-catalysed Michael additions of aldehydes to simple enones.

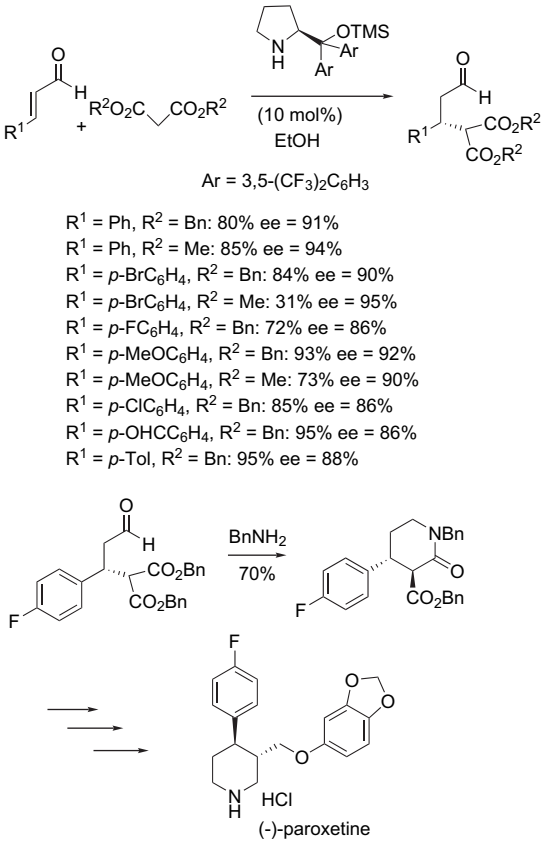
Although proline continues to play a central role in aminocatalysis, its supremacy is being challenged by new synthetic analogues such as chiral imidazolidinones first introduced in asymmetric organocatalysis by MacMillan et al.[13] As an example, in 2005, Gellman et al. developed intermolecular aldehyde–enone Michael addition reactions catalysed by a MacMillan imidazolidinone catalyst in the presence of an appropriate hydrogen-bond-donating co-catalyst, the same catechol as depicted in Scheme 3.[14] The authors have isolated an imidazolidinone-derived enamine and shown it to be a competent nucleophile, whereas most prior reports of imidazolidinone-catalysed Michael additions have involved electrophilic activation of α,β-unsaturated aldehydes via iminium ion formation.[15] Therefore, the results depicted in Scheme 4 support the recent suggestions that imidazolidinones can serve as organocatalysts by nucleophilic activation of carbonyl compounds,[16] in addition to their well-precedented role as electrophilic activators (via iminium formation). This study has provided the first clear evidence for an imidazolidinone-derived enamine.



R^1,R^2	R,R	Yield (%)	ee (%)
Me,Me	$(CH_2)_4$	84	90
Me,Et	$(CH_2)_4$	79	92
Et,Et	$(CH_2)_4$	68	92
Bn,Me	$(CH_2)_4$	62	89
Bn,Et	$(CH_2)_4$	54	92
Et,Me	$(CH_2)_4$	86	90
Et,Me	Me,Me	85	81

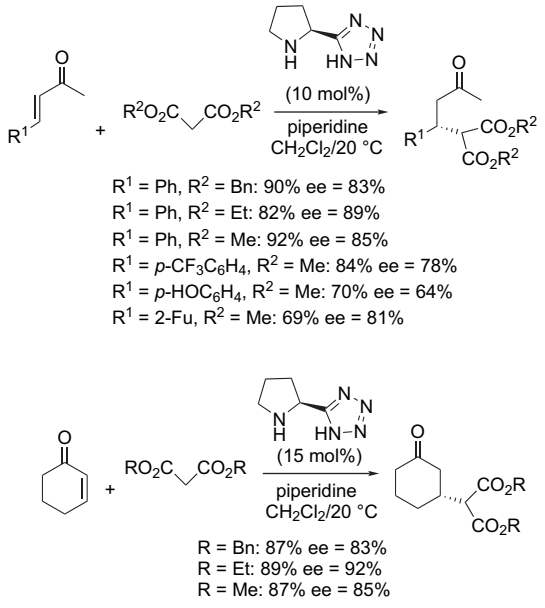
Scheme 4. Imidazolidinone-catalysed Michael additions of aldehydes to simple enones.

On the other hand, most organocatalysed Michael additions of stabilised carbon nucleophiles have used either nucleophiles or electrophiles that are highly activated. As an example, Michael additions of highly activated nucleophiles such as malonates[17] or nitroalkanes[18] to simple enones have been reported; alternatively, relatively unactivated ketones or aldehydes have been used with highly activated Michael acceptors such as nitroalkenes.[19] Malonates that use iminium ion activation have been successfully added enantioselectively to α,β-unsaturated ketones[20] and, more recently, to α,β-unsaturated aldehydes, thus creating a simple approach to chiral lactams and lactones.[21] This methodology was recently applied to the synthesis of (−)-paroxetine, a selective serotonin reuptake inhibitor used in the treatment of depression.[21] An L-proline derivative, (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine, was involved as the catalyst of the Michael addition of several malonates to various α,β-unsaturated aldehydes, providing the corresponding addition products in good yields and very good-to-excellent enantioselectivities, as depicted in Scheme 5.



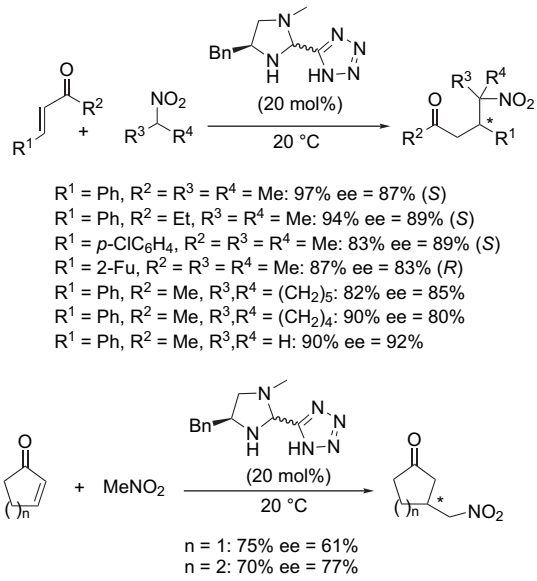
Scheme 5. Michael additions of malonates to α,β-unsaturated aldehydes catalysed by an L-proline derivative.

The same group has demonstrated that another derivative of proline, 5-pyrrolidin-2-yltetrazole, was a useful catalyst for the Michael additions of malonates to a wide range of enones, both cyclic and acyclic, providing excellent enantioselectivities in the presence of an additive such as piperidine (Scheme 6).[22]



Scheme 6. 5-Pyrrolidin-2-yltetrazole-catalysed Michael additions of malonates to enones.

In 2005, Jorgensen et al. reported the Michael addition of nitroalkanes, another valuable source of stabilised carbanions, to acyclic and cyclic enones catalysed by a novel, more soluble chiral imidazolidin-2-yltetrazole catalyst, giving access via an iminium intermediate to the corresponding 1,4-adducts with enantioselectivities of up to 92% ee (Scheme 7).[23]

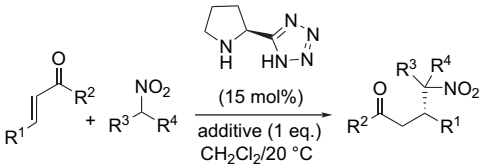


Scheme 7. Michael additions of nitroalkanes to enones catalysed by an L-imidazolidine-tetrazole catalyst.

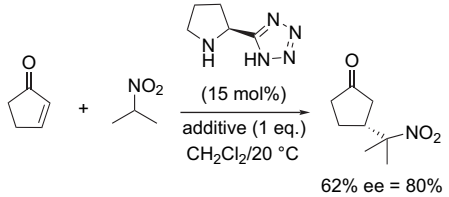
Similar Michael additions of nitroalkanes to unsaturated cyclic and acyclic ketones were developed by Ley et al., using the tetrazole analogue of proline, 5-pyrrolidin-2-yltetrazole, as a catalyst, giving again better results for acyclic enones relative to cyclic precursors.[24] The use of *trans*-2,5-dimethylpiperazine as a stoichiometric base additive proved to give the best enantiomeric excesses of up to 98% (Scheme 8). The mechanism of these reactions has not been rigorously established, although it is plausible that the catalyst initially forms an iminium complex with the enone.

In 2006, Deng et al. reported the first highly regio-, chemo-, diastereo- and enantioselective direct vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes, employing readily available chiral α,α-diarylprolinol salts as iminium organocatalysts.[25] This reaction, allowing the production of multifunctional products bearing two vicinal chiral tertiary carbon centres, gave the best enantioselectivities when diphenylprolinol was employed in the presence of *p*-nitrobenzoic acid (PNBA). As depicted in Scheme 9, only the *anti*-products were detected for all the reactions tested, and the higher ee values were obtained in the reactions of linear or branched alkyl- and aryl-, or heteroaryl-substituted α,β-unsaturated aldehydes with cyclic and aromatic α,α-dicyanoolefins. In contrast, probably due to the formation of unreactive hemiaminal species, the results catalysed by free prolinols in the literature were generally poorer than those obtained using their etherified analogues.[26]

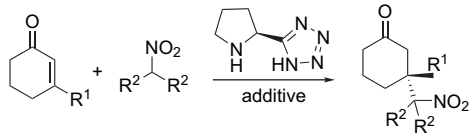
In order to develop a new access to three-membered chiral carbocyclic rings, MacMillan and Kunz have successfully



R^1 = Ph, R^2 = Et, R^3 = R^4 = Me: 78% ee = 78%
R^1 = CO_2Me, R^2 = Me, R^3 = R^4 = Me: 96% ee = 82%
R^1 = Ph, R^2 = Me, R^3 = R^4 = H: 45% ee = 89%
R^1 = Ph, R^2 = Me, R^3 = R^4 = Me: 65% ee = 72%
R^1 = Ph, R^2 = Me, R^3,R^4 = $(CH_2)_5$: 80% ee = 73%

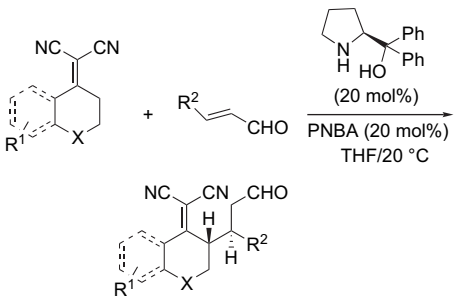


62% ee = 80%



R^1 = Me, R^2 = H: 64% ee = 91%
R^1 = H, R^2 = Me: 870% ee = 98%
R^1 = H, R^2,R^2 = $(CH_2)_5$: 63% ee = 94%

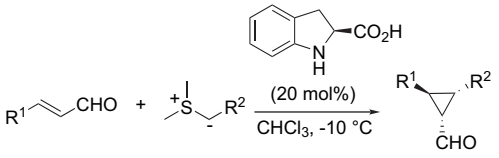
Scheme 8. 5-Pyrrolidin-2-yltetrazole-catalysed Michael additions of nitroalkanes to enones.



R^1 = H, X = CH_2, R^2 = Me: 61% ee = 95%
R^1 = H, X = CH_2, R^2 = *n*-Pr: 58% ee = 94%
R^1 = H, X = CH_2, R^2 = *n*-Bu: 51% ee = 93%
R^1 = H, X = CH_2, R^2 = Ph: 80% ee = 89%
R^1 = H, X = O, R^2 = Me: 83% ee = 95%
R^1 = H, X = O, R^2 = *n*-Pr: 78% ee = 95%
R^1 = H, X = O, R^2 = *n*-Bu: 80% ee = 94%
R^1 = H, X = O, R^2 = *i*-Pr: 69% ee = 98%
R^1 = H, X = O, R^2 = Ph: 83% ee = 92%
R^1 = H, X = O, R^2 = *p*-$MeOC_6H_4$: 63% ee = 92%
R^1 = H, X = O, R^2 = 2-Fu: 71% ee = 95%
R^1 = H, X = S, R^2 = Me: 91% ee = 92%
R^1 = H, X = S, R^2 = *n*-Pr: 75% ee = 93%
R^1 = H, X = S, R^2 = *n*-Bu: 71% ee = 92%
R^1 = H, X = S, R^2 = *i*-Pr: 55% ee = 94%
R^1 = H, X = S, R^2 = Ph: 90% ee = 86%
R^1 = OMe, X = CH_2, R^2 = Me: 48% ee = 95%

Scheme 9. Diphenylprolinol-catalysed Michael additions of α,α-dicyanoolefins to α,β-unsaturated aldehydes.

condensed stabilised sulfonium ylides onto α,β-unsaturated aldehydes in the presence of chiral 2-carboxylic acid dihydroindole as catalyst.[27] As revealed in Scheme 10, this novel catalyst design plan was successful to furnish the corresponding chiral cyclopropanes with excellent levels of induction and reaction efficiency. The authors have postulated a mechanism based upon the concept of directed electrostatic activation, rationalising that the catalyst-derived iminium and the ylide might readily engage in electrostatic association via their pendant carboxylate and thionium substituents. In doing so, the ylide carbanion and the iminium β-carbon would be transiently activated while in close proximity, thereby facilitating carbon–carbon bond formation. Moreover, it was observed that this reaction could be conducted with enals, but not with electron-deficient olefins, such as unsaturated nitrile, nitro or alkylidene malonate systems, which lends support for an iminium-mediated pathway. Moreover, N-methylation of the carboxylic dihydroindole framework, a step that removes the possibility of iminium formation, leads to a complete loss of catalytic activity.

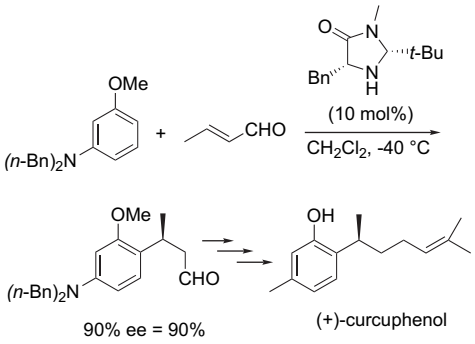


R^1 = *n*-Pr, R^2 = Bz: 85% de = 94% ee = 95%
R^1 = CH_2Oallyl, R^2 = Bz: 77% de = 90% ee = 91%
R^1 = Me, R^2 = Bz: 67% de > 90% ee = 90%
R^1 = CH_2=CH-$(CH_2)_4$, R^2 = Bz: 74% de = 92% ee = 96%
R^1 = Ph, R^2 = Bz: 73% de = 94% ee = 89%
R^1 = *n*-Bu, R^2 = Bz: 63% de = 96% ee = 96%
R^1 = *n*-Pr, R^2 = COC_6H_4*p*-Br: 67% de = 98% ee = 92%
R^1 = *n*-Pr, R^2 = COC_6H_4*p*-OMe: 64% de > 84% ee = 93%
R^1 = *n*-Pr, R^2 = CO*t*-Bu: 82% de = 72% ee = 95%

Scheme 10. 2-Carboxylic acid dihydroindole-catalysed Michael additions of sulfonium ylides to α,β-unsaturated aldehydes.

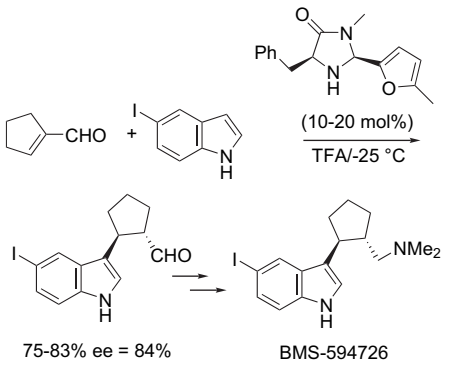
The asymmetric addition of heteroaromatic compounds to α,β-unsaturated aldehydes, the asymmetric Friedel–Crafts-type Michael reaction, is an important reaction in asymmetric organic chemistry, because valuable synthetic building blocks are obtained by this aromatic electrophilic substitution proceeding via iminium ion catalysis.[28] In 2005, Kim et al. reported the enantioselective Friedel–Crafts-type addition of *N*,*N*-dibenzyl-3-anisidine and crotonaldehyde using an imidazolidinone chiral catalyst, providing the corresponding alkylated product in 90% yield with an ee of 90% (Scheme 11).[29] This product was further used in a total synthesis of (*S*)-(+)-curcuphenol, a bioactive sesquiterpene phenol.

In the same context, King et al. developed, in 2005, an enantioselective alkylation of the indole nucleus with an α-branched α,β-unsaturated aldehyde such as 1-cyclopentene-1-carboxaldehyde using a MacMillan imidazolidinone catalyst, which constituted the key step of a total synthesis of the highly potent and selective serotonin reuptake inhibitor, BMS-594726 (Scheme 12).[30] The extension of the reaction to acyclic α-branched α,β-unsaturated aldehydes allowed the synthesis of a variety of chiral



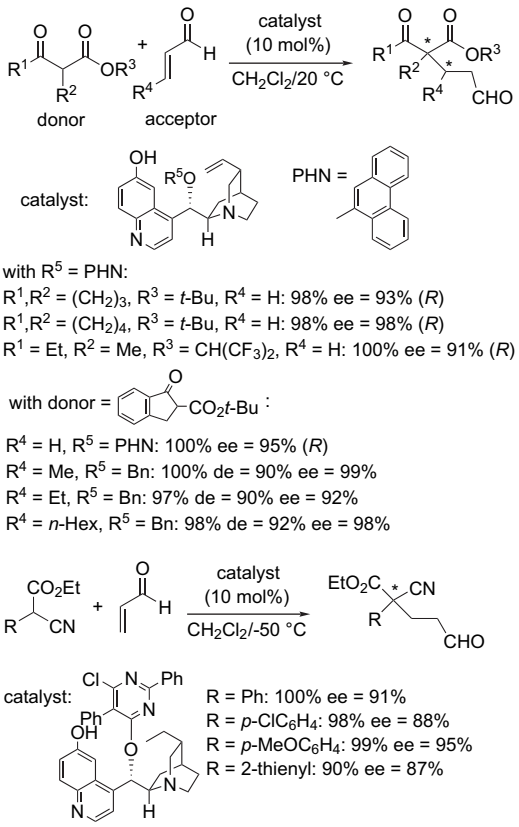
Scheme 11. Friedel–Crafts-type Michael reaction of *N*,*N*-dibenzyl-3-anisidine with crotonaldehyde catalysed by an imidazolidinone catalyst.

3-(indol-3-yl)-propionaldehydes with up to 90% ee's. In 2006, Xiao et al. applied similar conditions to the reaction of indoles with α,β-unsaturated ketones, providing promising results with 52% yield and 28% ee in the case of 5-methyl-3-hexen-2-one.[31]



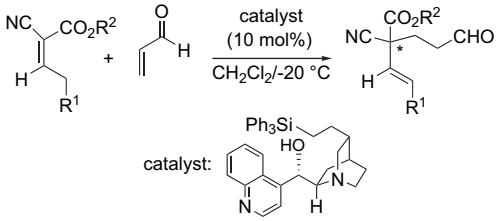
Scheme 12. Friedel–Crafts-type Michael reaction of 5-iodoindole with 1-cyclopentene-1-carboxaldehyde catalysed by an imidazolidinone catalyst.

The second part of this section deals with Michael additions of *C*-nucleophiles involving chiral bases or phase-transfer catalysis. In 2006, Deng et al. reported the use of cinchona alkaloids as catalysts in the enantioselective conjugate addition of carbonyl donors such as cyclic and acyclic α-substituted β-keto or α-cyano esters to α,β-unsaturated aldehydes.[32] The corresponding chiral aldehydes were obtained in quantitative yields and excellent enantioselectivities, as depicted in Scheme 13. This elegant method of construction of tetrasubstituted carbon stereocentres was applied to the enantioselective synthesis of the biologically active natural product, (+)-tanikolide. This methodology was applied by the same authors to the general conjugate addition of a wide range of α-substituted β-keto esters to an extraordinarily wide range of vinyl ketones.[33] Using the same cinchona alkaloid catalysts as in Scheme 13, the reaction provided the corresponding 1,4-adducts in almost quantitative yields and excellent enantioselectivity levels ranging from 90 to 98% ee. Moreover, this reaction was extended to the use of cyclic, as well as acyclic, β-substituted enones, providing under the same conditions the corresponding products with very high enantioselectivities (up to 99% ee) and diastereoselectivities (up to 92% de) combined with excellent yields (up to 99%).



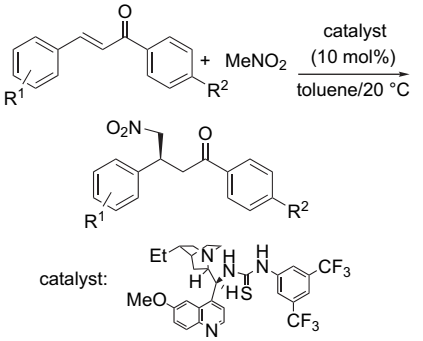
Scheme 13. Cinchona alkaloid-catalysed Michael reactions of carbonyl donors to α,β-unsaturated aldehydes.

A new class of 6′-hydroxy cinchona alkaloids, with a non-biaryl atropisomeric functionalisation at position 5′ of the quinoline core, was reported by Jorgensen et al. in 2006. The corresponding aminated cinchona alkaloids proved to be effective organocatalysts for the Michael addition of β-keto esters to acrolein and methyl vinyl ketone, in up to 93% ee.[34] The same authors have reported the deconjugative Michael addition of a range of activated alkylidene cyanoacetates to acrolein in the presence of catalysts derived from cinchonine, giving access, in spite of modest enantioselectivities, to highly functionalised chiral aldehydes bearing a quaternary stereocentre, arising from the exclusive attack from the α-position of the anion (Scheme 14).[35]



Scheme 14. Cinchona alkaloid-catalysed Michael reactions of alkylidene cyanoacetates to acrolein.

Over the last decade the potential for chiral (thio)urea derivatives to serve as active organocatalysts for a wide range of synthetically useful asymmetric reactions has begun to be realised.[36] In this context, Soos et al. have prepared cinchona alkaloid-derived chiral bifunctional thiourea organocatalysts and applied them in the Michael addition between nitromethane and chalcones with high ee's and chemical yields (Scheme 15).[37]

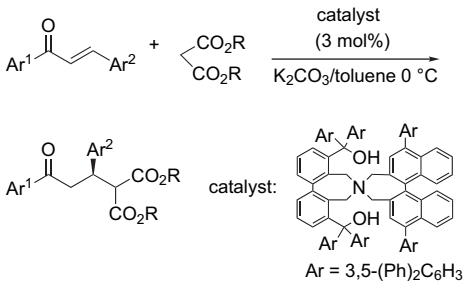


R^1 = *p*-Cl, R^2 = H: 94% ee = 95%
R^1 = *p*-F, R^2 = H: 94% ee = 98%
R^1 = *o*-Me, R^2 = H: 93% ee = 89%
R^1 = H, R^2 = *p*-MeO: 80% ee = 96%

Scheme 15. Cinchona-based thiourea-catalysed Michael reactions of nitromethane to chalcones.

Phase-transfer catalysis is an attractive alternative for organic reactions in which charged intermediates are involved. The reactions are usually carried out in two- or three-phase system, most commonly in vigorously stirred aqueous/apolar solvent mixtures. An inorganic base, such as K_2CO_3 or Cs_2CO_3, is used to form the reactive enolate. The role of the catalyst is primarily that of an ion shuttle. Chiral organocatalysts have been used to act as templates to direct the approach of the reagent. Asymmetric phase-transfer-catalysed reactions were firstly carried out with cinchona alkaloids. On the other hand, a considerable amount of work has been devoted to the development of ammonium catalysts from either natural compounds such as tartaric acid, or synthetic compounds such as 1,1′-(2,2′-binaphthol), for use in asymmetric phase-transfer reactions. As an example, in 2005, Maruoka et al. developed highly enantioselective Michael additions of malonates to chalcone derivatives under mild phase-transfer conditions by the successful use of an *N*-spiro C_2-symmetric chiral quaternary ammonium bromide as a catalyst, which possessed diarylhydroxymethyl functionalities as a recognition site for the prochiral electrophile (Scheme 16).[38] The reaction process was found to be quite effective for various chalcones including those with heteroaromatic substituents. The scope of the reaction could be extended to the use of malononitrile as a nucleophile, providing the corresponding chiral Michael adduct in 98% yield and 81% ee in the presence of 1,3-diphenyl-1-propen-3-one.

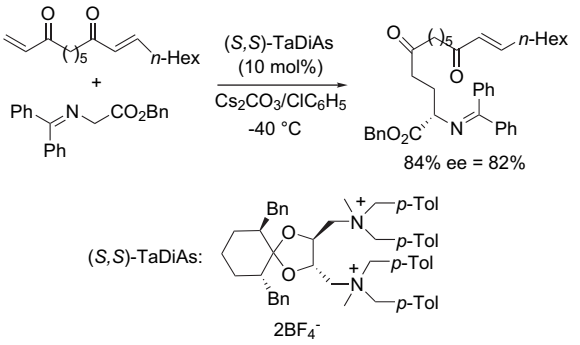
Tartrate-derived catalysts have also been shown to be efficient in mediating phase-transfer Michael additions. Therefore, Shibasaki et al. reported, in 2006, a total synthesis of an antitumour compound, (+)-cylindricine C, based on a catalytic asymmetric Michael reaction of a glycine Schiff base



Ar^1 = Ar^2 = Ph, R = Me: 99% ee = 84%
Ar^1 = Ar^2 = Ph, R = Et: 99% ee = 90%
Ar^1 = Ar^2 = Ph, R = *i*-Pr: 99% ee = 74%
Ar^1 = Ph, Ar^2 = 2-naph, R = Et: 94% ee = 91%
Ar^1 = Ph, Ar^2 = *p*-$MeOC_6H_4$, R = Et: 99% ee = 87%
Ar^1 = Ph, Ar^2 = *p*-ClC_6H_4, R = Et: 99% ee = 85%
Ar^1 = *p*-ClC_6H_4, Ar^2 = Ph, R = Et: 97% ee = 86%
Ar^1 = Ph, Ar^2 = 2-py, R = Et: 99% ee = 90%
Ar^1 = Ph, Ar^2 = 2-thienyl, R = Et: 99% ee = 94%
Ar^1 = 2-thienyl, Ar^2 = Ph, R = Et: 99% ee = 94%

Scheme 16. Michael additions of malonates to chalcones catalysed by C_2-symmetric phase-transfer catalyst.

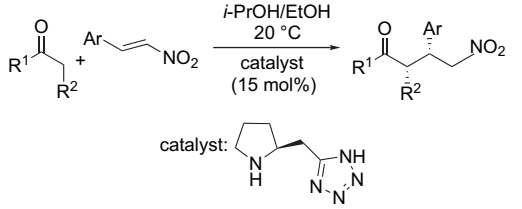
to a dienone, which was catalysed by TaDiAS, a tartrate-derived diammonium salt (Scheme 17).[39]



Scheme 17. TaDiAS-catalysed Michael addition of a glycine Schiff base to a dienone.

2.1.2. Intermolecular nitro-Michael additions of *C*-nucleophiles. In the last two years, a large number of results have been reported dealing with the asymmetric organocatalysed conjugate addition of carbonyl compounds to nitroolefins. Hayashi et al. reported, in 2005, the use of (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine (depicted in Scheme 5) in a highly enantioselective Michael reaction of various aldehydes and nitroalkenes.[40] The use of this catalyst, easily prepared from commercially available diphenylprolinol in a single step, allowed the products to be obtained in nearly optically pure form in almost all cases examined. Other derivatives of proline have been involved in nitro-Michael reactions such as the tetrazole analogue of proline, 5-pyrrolidin-2-yltetrazole, as depicted in Scheme 8. Ley et al. have demonstrated that this catalyst gave better yields (up to 100%) and enantioselectivities (up to 65% ee) than L-proline in the Michael reaction of cyclohexanone with various nitroolefins.[41] Higher enantioselectivities were obtained by the same group using a new homoproline tetrazole derivative, particularly with

cyclohexanone, where they were consistently high, showing that the nature of the nitro-Michael acceptor has less effect on the stereoselective outcome of the reaction than the ketone (Scheme 18).[42] In 2005, the usefulness of (*S*)-homoproline was exploited by Oriyama et al. as a catalyst of nitro-Michael additions of ketones to β-nitrostyrenes, providing the corresponding Michael adducts in a highly diastereoselective and enantioselective manner (>90% ee).[43] More recently, Gong et al. have prepared a novel chiral triamine bearing three pyrrolidine moieties and obtained up to 98% ee for the nitro-Michael addition of cyclic ketones.[44]

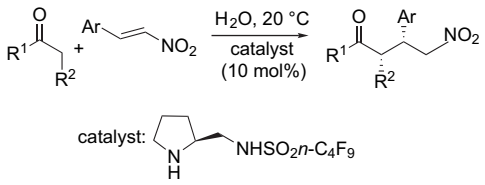


$R^1,R^2 = (CH_2)_4$, Ar = *m*-$O_2NC_6H_4$: 59% de > 90% ee = 93%
$R^1,R^2 = (CH_2)_4$, Ar = *p*-$MeOC_6H_4$: 74% de = 100% ee = 93%
$R^1,R^2 = (CH_2)_4$, Ar = thienyl: 51% de > 90% ee = 90%
$R^1,R^2 = (CH_2)_2$-S-CH_2, Ar = Ph: 61% de > 90% ee = 90%
R^1= Me, R^2 = H, Ar = Ph: 68% ee = 42%
R^1= Me, R^2 = OH, Ar = Ph: 52% de = 42% ee = 52%
R^1= H, R^2 = *i*-Pr, Ar = Ph: 39% de > 90% ee = 37%

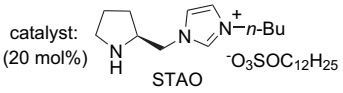
Scheme 18. Nitro-Michael additions of ketones catalysed by homoproline tetrazole.

In 2005, Wang et al. developed nitro-Michael reactions of a wide range of aldehydes and ketones catalysed by (*S*)-pyrrolidine trifluoromethanesulfonamide, proceeding with high levels of enantioselectivity (up to 99% ee) and diastereoselectivities (up to 96% de).[45] This methodology was applied to an efficient synthesis of the potent H_3 agonist, Sch 50917, with potential use for the treatment of a variety of diseases such as obesity or Alzheimer's disease. In order to perform the nitro-Michael reaction in aqueous media, the same authors synthesised a more hydrophobic pyrrolidine sulfonamide containing a more lipophilic and strongly electron-withdrawing *n*-C_4F_9 group.[46] This easily recoverable catalyst promoted highly enantio- and diastereoselective nitro-Michael reactions of carbonyl compounds in water (Scheme 19). Moreover, Luo et al. have developed a surfactant-type asymmetric organocatalyst (STAO), as depicted in Scheme 19, which was demonstrated to be highly efficient for the nitro-Michael reaction of cyclohexanone in pure water.[47] In addition, functionalised chiral ionic liquids (CILs) have been investigated by the same group in the presence of a catalytic amount of TFA in neat mixtures. Therefore, the exchange of $^-O_3SOC_{12}H_{25}$ for Br^- in the structure of catalyst STAO, depicted in Scheme 19, gave rise to a re-usable CIL catalyst, which provided excellent levels of enantioselectivity (up to 99% ee) when applied to the nitro-Michael addition of cyclohexanone.[48]

Moreover, a nitro-Michael reaction was performed in brine in the presence of a diamine catalyst bearing dodecyl alkyl chains, providing, in the presence of TFA, excellent reactivities, diastereoselectivities and enantioselectivities without the addition of organic solvents (Scheme 20).[49]

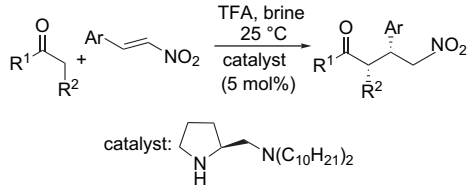


$R^1,R^2 = (CH_2)_4$, Ar = Ph: 95% de = 92% ee = 90%
$R^1,R^2 = (CH_2)_4$, Ar = *p*-$MeOC_6H_4$: 95% de = 88% ee = 89%
$R^1,R^2 = (CH_2)_4$, Ar = *o*-$MeOC_6H_4$: 92% de = 96% ee = 91%
$R^1,R^2 = (CH_2)_4$, Ar = *o*-$CF_3C_6H_4$: 90% de = 96% ee = 93%
$R^1,R^2 = (CH_2)_2$-O-CH_2, Ar = Ph: 56% de = 96% ee = 95%
R^1= H, R^2 = *n*-Hept, Ar = Ph: 98% de = 60% ee = 81%



$R^1,R^2 = (CH_2)_4$, Ar = Ph: 93% de = 94% ee = 97%
$R^1,R^2 = (CH_2)_4$, Ar = *o*-ClC_6H_4: 99% de = 98% ee = 98%
$R^1,R^2 = (CH_2)_4$, Ar = *o*-BrC_6H_4: 99% de = 98% ee = 98%
$R^1,R^2 = (CH_2)_4$, Ar = *p*-Tol: 90% de = 94% ee = 95%
$R^1,R^2 = (CH_2)_4$, Ar = *p*-$MeOC_6H_4$: 84% de = 98% ee = 94%
$R^1,R^2 = (CH_2)_4$, Ar = *m*-$O_2NC_6H_4$: 83% de = 94% ee = 97%
$R^1,R^2 = (CH_2)_4$, Ar = 2-naph: 84% de = 94% ee = 96%

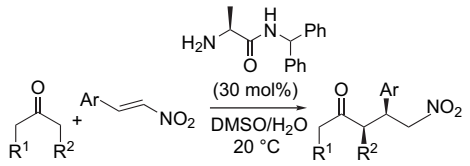
Scheme 19. Nitro-Michael additions of carbonyl compounds catalysed by pyrrolidines in water.



$R^1,R^2 = (CH_2)_4$, Ar = Ph: 93% de = 90% ee = 89%
$R^1,R^2 = (CH_2)_3$, Ar = Ph: 75% de = 54% ee = 80%
$R^1,R^2 = (CH_2)_4$, Ar = Ph: 93% de = 90% ee = 89%
$R^1,R^2 = (CH_2)_2$-S-CH_2, Ar = Ph: 67% de = 94% ee = 87%
$R^1,R^2 = (CH_2)_4$, Ar = *o*-$MeOC_6H_4$: 98% de = 92% ee = 83%
$R^1,R^2 = (CH_2)_4$, Ar = 2-Fu: 94% de = 92% ee = 86%
$R^1,R^2 = (CH_2)_4$, Ar = 2-naph: 99% de = 96% ee = 97%

Scheme 20. Nitro-Michael additions of cyclic carbonyl compounds catalysed by diamine catalyst in brine.

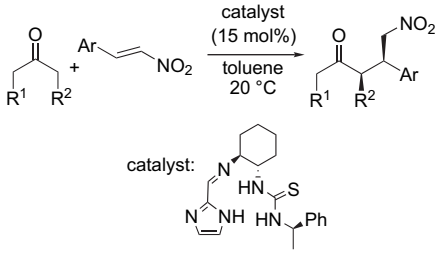
In 2006, Cordova et al. demonstrated that simple chiral primary amines derived from acyclic aliphatic amino acids were able to mediate nitro-Michael additions of ketones.[50] As an example, the primary amine derived from (*S*)-alanine catalysed the nitro-Michael reaction of a set of ketones in high yields, with up to 94% de and 99% ee (Scheme 21). As an extension of these studies, the same group has shown that small, readily prepared di- and tripeptides, derived from alanine, catalysed the nitro-Michael addition of ketones with up to 98% de and 98% ee.[51] In one example, the addition of cyclohexanone to *trans*-β-nitrostyrene gave, in the presence of the dipeptide, (*S*)-alanine–(*S*)-alanine, in DMSO, a 58% yield of the corresponding *syn*-adduct with 98% de and 93% ee. This study demonstrated that small peptides with increased structural complexity, as compared to the parent amino acid, mediated the Michael reaction with superior reactivity and enantioselectivity.



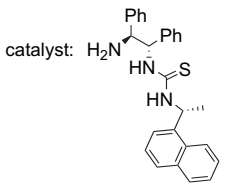
$R^1,R^2 = (CH_2)_3$, Ar = Ph: 92% de = 92% ee = 93%
$R^1,R^2 = (CH_2)_3$, Ar = 2-naph: 75% de = 92% ee = 98%
$R^1,R^2 = (CH_2)_3$, Ar = *p*-$MeOC_6H_4$: 82% de = 90% ee = 90%
$R^1,R^2 = (CH_2)_3$, Ar = *p*-$O_2NC_6H_4$: 82% de = 94% ee = 96%
R^1= Me, R^2 = Et, Ar = Ph: 945% de = 966% ee = 67%
$R^1,R^2 = CH_2SCH_2$, Ar = Ph: 45% de = 94% ee = 99%
$R^1,R^2 = CH_2OCH_2$, Ar = Ph: 63% de = 94% ee = 90%

Scheme 21. (*S*)-Alanine derivative-catalysed nitro-Michael additions of ketones.

Chiral thiourea derivatives have also been used as bifunctional catalysts for Michael additions of ketones to nitroolefins. Tsogoeva et al. obtained up to 87% ee for the Michael addition of acetone to nitroolefins in the presence of a novel imidazole-based chiral thiourea catalyst (Scheme 22).[52] Even better results (90–99% ee's) were obtained by the same group in 2006 by using a new thiourea-amine bifunctional catalyst (Scheme 22).[53] A transient activation of the ketone through formation of an enamine on the primary or secondary amino group was anticipated. Furthermore, the neighbouring thiourea was supposed to interact, via hydrogen bonding, with the nitro group of the nitroolefin and enhance its electrophilicity. In addition, the chiral arylethyl moiety adjacent to the thiourea probably shielded one side of the activated nitroolefin.



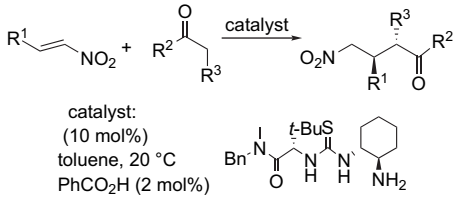
R^1 = Me, R^2 = H, Ar = Ph: 55% ee = 87%
R^1 = Me, R^2 = H, Ar = *p*-BrC_6H_4: 62% ee = 83%
R^1 = Me, R^2 = H, Ar = *p*-$MeOC_6H_4$: 46% ee = 86%
R^1 = Me, R^2 = H, Ar = 2-thienyl: 57% ee = 84%



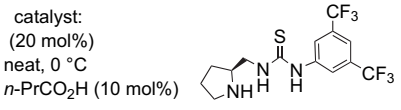
R^1 = Me, R^2 = H, Ar = Ph: 98% ee = 91%
R^1 = Me, R^2 = H, Ar = *p*-BrC_6H_4: 99% ee = 90%
R^1 = Me, R^2 = H, Ar = *p*-$MeOC_6H_4$: 84% ee = 91%
R^1 = Me, R^2 = H, Ar = 2-thienyl: 98% ee = 90%
$R^1 = R^2$ = Me, Ar = Ph: 88 de = 72% ee > 99%
$R^1,R^2 = (CH_2)_3$, Ar = Ph: 82% de = 60% ee = 96%
$R^1,R^2 = (CH_2)_2S$, Ar = Ph: 89% de = 66% ee = 98%

Scheme 22. Nitro-Michael additions of ketones catalysed by thiourea bifunctional catalysts.

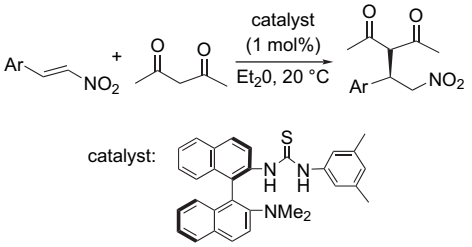
Another chiral primary amine thiourea catalyst was described in 2006 by Jacobsen and Huang, providing high yields and enantioselectivities (up to 99% ee) for the nitro-Michael addition of various ketones to a range of nitroalkenes (Scheme 23).[54] Similar results were obtained by Tang et al., in 2006, by involving a pyrrolidine-thiourea, easily prepared from L-proline, as catalyst for the Michael addition of cyclohexanone to both aryl and alkylnitroolefins and *n*-butyric acid (Scheme 23).[55] Modest enantioselectivities were observed in the case of other ketones and aldehydes. In addition, the first nitro-Michael addition of 1,3-diketones such as 2,4-pentanedione was reported by Wang et al., employing a novel binaphthyl-derived amine thiourea as catalyst, which provided remarkably high enantioselectivities (Scheme 23).[56]



R^1 = Ph, R^2 = Me, R^3 = H: 93% ee = 99%
R^1 = *p*-$MeOC_6H_4$, R^2 = Me, R^3 = H: 88% ee = 99%
R^1 = *p*-Tol, R^2 = Me, R^3 = H: 87% ee = 97%
R^1 = 2-Fu, R^2 = Me, R^3 = H: 88% ee = 99%
R^1 = 2-thienyl, R^2 = Me, R^3 = H: 94% ee = 96%
R^1 = *i*-Bu, R^2 = Me, R^3 = H: 81% ee = 94%
R^1 = Ph, R^2 = Et, R^3 = Me: 65% de = 90% ee = 99%
R^1 = Ph, R^2 = *n*-Pr, R^3 = Me: 67% ee = 97%
R^1 = *i*-Bu, R^2 = Me, R^3 = OMe: 78% de = 82% ee = 86%



R^1 = Ph, R^2, $R^3 = (CH_2)_4$: 93% de = 92% ee = 90%
R^1 = 2-naph, $R^2,R^3 = (CH_2)_4$: 93% de = 98% ee = 95%
R^1 = 2-Fu, $R^2,R^3 = (CH_2)_4$: 99% de = 82% ee = 90%
R^1 = *o*-$O_2NC_6H_4$, $R^2,R^3 = (CH_2)_4$: 95% de = 92% ee = 97%
R^1 = *p*-BrC_6H_4, $R^2,R^3 = (CH_2)_4$: 90% de = 90% ee = 95%
R^1 = *i*-Pr, $R^2,R^3 = (CH_2)_4$: 63% de > 98% ee = 94%

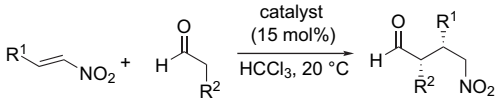


Ar = Ph: 87% ee = 95%
Ar = *p*-$MeOC_6H_4$: 92% ee = 97%
Ar = *p*-BrC_6H_4: 89% ee = 95%
Ar = *o*-$MeOC_6H_4$: 92% ee = 97%

Scheme 23. Nitro-Michael additions of ketones and 2,4-pentanedione catalysed by thiourea bifunctional catalysts.

In 2006, Barros and Phillips developed a new class of chiral amines with a cyclic 1,2-diacetal skeleton derived from (2*R*,3*R*)-(+)-tartaric acid, which were tested as organocatalysts for the nitro-Michael addition of cyclohexanone to

trans-β-nitrostyrene, giving the expected adducts with good diastereoselectivity (84% de), albeit with moderate optical purity (30% ee).[57] Another new class of more efficient bicyclic six-membered-ring organocatalysts was designed by Alexakis et al. in 2006.[58] Indeed, these *N*-alkyl-3,3′-bimorpholine derivatives (e.g., *i*PBM, where alkyl= isopropyl) were revealed to be efficient catalysts for the nitro-Michael addition of aldehydes to various nitroolefins (Scheme 24). Moreover, the same group has demonstrated the impact of microwave activation in the nitro-Michael reaction where *N*-*i*-Pr-2*S*,2′*S*-bipyrrolidine (*i*PBP) was used as catalyst.[59] In all cases, the reaction time was dramatically shortened without loss of selectivity, and the catalyst loading could be decreased from 15 to 5 mol % while maintaining good reactivity (Scheme 24).



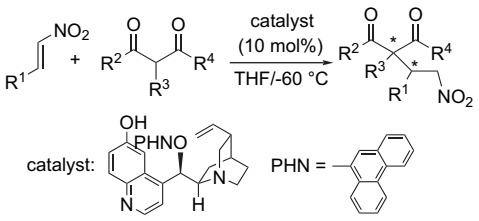
with *i*PBM:
R^1 = Ph, R^2 = *i*-Pr: 85% de = 88% ee = 88%
R^1 = Ph, R^2 = *n*-Pr: 88% de = 74% ee = 89%
R^1 = Ph, R^2 = Cy: 85% de = 90% ee = 90%
R^1 = Ph, R^2 = Me: 86% de = 80% ee = 80%
R^1 = 2-thienyl, R^2 = Me: 89% de = 78% ee = 79%
with *i*PBP:
R^1 = Ph, R^2 = OH: 83% de = 78% ee = 98%
R^1 = Ph, R^2 = *i*-Pr: 97% de = 80% ee = 78%

*i*PBM *i*PBP

Scheme 24. *i*PBM- or *i*PBP-catalysed nitro-Michael additions of aldehydes.

1,3-Dicarbonyl compounds have been recently condensed onto nitroolefins in the presence of various organocatalysts such as cinchona alkaloids. Among these is the catalyst depicted in Scheme 13, already involved in the Michael addition of malonates to α,β-unsaturated aldehydes. Application of this cinchona alkaloid to the nitro-Michael addition of various cyclic and acyclic β-keto esters gave high enantioselectivities and diastereoselectivities combined with excellent yields (Scheme 25).[60] Similarly high enantioselectivities were also observed for 2-substituted 1,3-diketones.

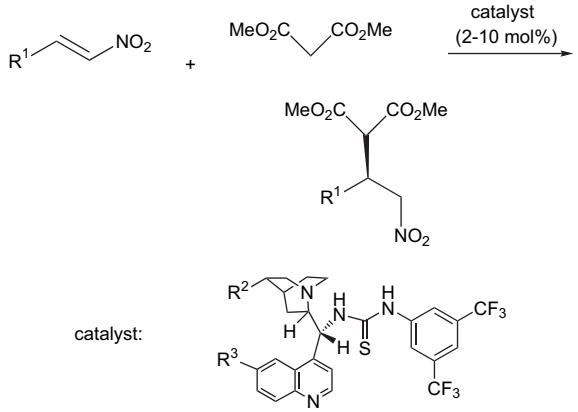
In 2005, Takemoto et al. reported similar reactions performed in the presence of bifunctional catalysts bearing a thiourea moiety and an amino group on a chiral scaffold. Among these, a thiourea bearing 3,5-bis(trifluoromethyl)-benzene and dimethylamino groups was revealed to be highly efficient for the asymmetric nitro-Michael addition of malonates.[61] Furthermore, this reaction was applied to the total synthesis of (*R*)-(−)-baclofen, an antispastic agent. The possibility of modifying the privileged cinchona alkaloid structural backbone by substituting the hydroxyl group at C-9 with an arylthiourea moiety with the aim of augmenting the rigidity, tunability and hydrogen-bond-donating proclivity of these materials was simultaneously developed by Connon[62] and Dixon.[63] This new class of catalysts, which



R^1 = Ph, R^2,R^3 = $(CH_2)_3$, R^4 = CO_2Me:
97% de = 88% ee > 99%
R^1 = *p*-BrC_6H_4, R^2,R^3 = $(CH_2)_4$, R^4 = CO_2Et:
96% de > 96% ee = 99%
R^1 = Ph, R^2 = R^3 = Me, R^4 = CO_2Et:
70% de = 64% ee = 99%
R^1 = *p*-ClC_6H_4, R^2,R^3 = $O(CH_2)_2$, R^4 = Me:
92% de = 94% ee = 98%
R^1 = Ph, R^2,R^3 = $(CH_2)_3$, R^4 = Me:
70% de = 76% ee = 98%

Scheme 25. Cinchona alkaloid-catalysed nitro-Michael additions of 1,3-dicarbonyl compounds.

was also successfully applied, in its natural stereochemistry, in the Michael addition of nitromethane to chalcones (Scheme 15), gave rise to high enantioselectivities for the nitro-Michael addition of malonates (Scheme 26).



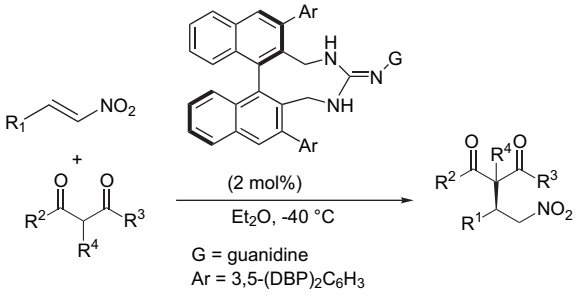
in CH_2Cl_2 at -20 °C:
R^1 = Ph, R^2 = $CH{=}CH_2$, R^3 = H: 95% ee = 94%
R^1 = *o*-ClC_6H_4, R^2 = $CH{=}CH_2$, R^3 = H: 99% ee = 94%
R^1 = *o*-BrC_6H_4, R^2 = $CH{=}CH_2$, R^3 = H: 95% ee = 92%
R^1 = *p*-$MeOC_6H_4$, R^2 = $CH{=}CH_2$, R^3 = H: 96% ee = 92%
R^1 = *m*-$MeOC_6H_4$, R^2 = $CH{=}CH_2$, R^3 = H: 96% ee = 91%
R^1 = *o*-$MeOC_6H_4$, R^2 = $CH{=}CH_2$, R^3 = H: 96% ee = 97%
R^1 = 2-Fu, R^2 = $CH{=}CH_2$, R^3 = H: 93% ee = 95%

in toluene at 0 °C or -20 °C:
R^1 = *o*-BrC_6H_4, R^2 = Et, R^3 = OMe: 94% ee = 93%
R^1 = *o*-$O_2NC_6H_4$, R^2 = Et, R^3 = OMe: 91% ee = 90%
R^1 = 2-thienyl, R^2 = Et, R^3 = OMe: 94% ee = 95%
R^1 = *o*-Tol, R^2 = Et, R^3 = OMe: 95% ee = 94%
R^1 = *p*-Tol, R^2 = Et, R^3 = OMe: 90% ee = 91%
R^1 = *p*-$MeOC_6H_4$, R^2 = Et, R^3 = OMe: 92% ee = 99%

Scheme 26. Cinchona-based thiourea-catalysed nitro-Michael additions of malonate.

In 2006, an axially chiral guanidine was found to be a remarkable enantioselective base catalyst for the nitro-Michael addition of various 1,3-dicarbonyl compounds such as malonates, 1,3-diketones and β-keto esters (Scheme

27),[64] whereas bis(3,5-dimethylphenyl)[(*S*)-pyrrolidin-2-yl]-methanol, easily prepared from L-proline, gave modest enantioselectivities for the addition of malonates (up to 56% ee).[65]

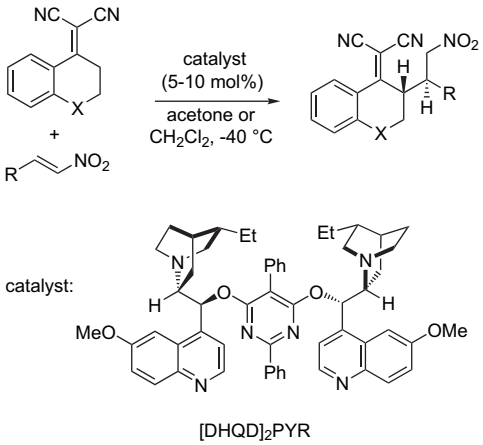


R^1 = *o*-$MeOC_6H_4$, R^2 = R^3 = OMe, R^4 = H: 98% ee = 97%
R^1 = *m*-BrC_6H_4, R^2 = R^3 = OMe, R^4 = H: 99% ee = 98%
R^1 = *p*-$MeOC_6H_4$, R^2 = R^3 = OMe, R^4 = H: 94% ee = 94%
R^1 = *p*-ClC_6H_4, R^2 = R^3 = OMe, R^4 = H: 99% ee = 95%
R^1 = 2-Fu, R^2 = R^3 = OMe, R^4 = H: 90% ee = 94%
R^1 = naph, R^2 = R^3 = OMe, R^4 = H: 99% ee = 96%
R^1 = *i*-Bu, R^2 = R^3 = OMe, R^4 = H: 99% ee = 86%
R^1 = Cy, R^2 = R^3 = OMe, R^4 = H: 79% ee = 91%
R^1 = Ph, R^2 = R^3 = OMe, R^4 = Me: 82% ee = 98%
R^1 = Ph, R^2 = R^3 = Me, R^4 = H: 88% ee = 91%
R^1 = Ph, R^2 = Me, R^3 = OMe, R^4 = H: 98% ee = 91%

Scheme 27. Nitro-Michael additions of malonates catalysed by axially chiral guanidine.

Deng and Jorgensen have studied the nitro-Michael addition of another type of *C*-nucleophiles, electron-deficient vinyl malononitriles, to alkyl and aryl nitroalkenes.[66] These new transformations were performed in the presence of a chiral modified cinchona alkaloid, $[DHQD]_2PYR$, which led to the formation of a chiral ion-pair intermediate. These reactions exhibited exclusive γ-selectivity and high diastereo- and enantioselectivity, providing multifunctional products bearing two vicinal chiral centres (Scheme 28).

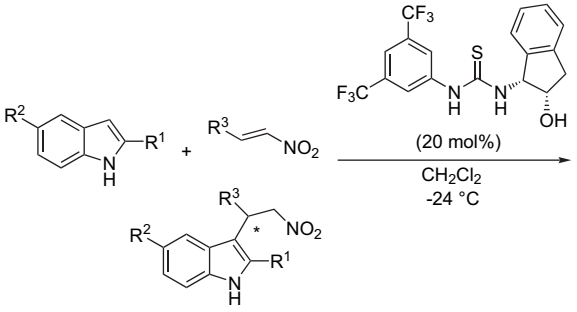
A novel entry to important hydroxyl-substituted pyrrolidines or aza sugars was developed in 2006 by Cordova et al. on the basis of a nitro-Michael addition of dihydroxyacetone to *trans*-β-nitrostyrene catalysed by L-proline, but, however, only low enantioselectivity was obtained (11% ee, 72% de, 40% yield).[67] On the other hand, Dixon and Richardson have condensed aryl methyl ketone-derived enamines to nitroalkenes in good-to-excellent yields and moderate enantioselectivities (up to 60% ee) in the presence of a tetraphenylphthalimide-derived thiourea as catalyst.[68] In addition, catalytic enantioselective Friedel–Crafts alkylations of indoles with nitroalkenes have been studied by several groups such as that of Ricci, who used a simple thiourea-based organocatalyst, which provided the corresponding chiral 2-indolyl-1-nitro derivatives in fairly good yields and enantioselectivities (Scheme 29).[69] Similar reactions were investigated by Connon et al. in the presence of catalytic amounts of novel axially chiral bis-arylthioureas, having the advantage of compatibility with challenging nitroolefin substrates incorporating β-aliphatic substituents, but providing modest enantioselectivities (up to 50% ee).[70] In addition, chiral vicinal diamine derivative-bis-sulfonamides were shown to be effective catalysts for similar reactions, producing the



R = Ph, X = CH_2: 98% de > 98% ee = 95%
R = *p*-Tol, X = CH_2: 90% de = 100% ee = 90%
R = *p*-ClC_6H_4, X = CH_2: 91% de = 100% ee = 90%
R = *p*-$MeOC_6H_4$, X = CH_2: 97% de > 98% ee = 98%
R = *p*-$(Me)_2NC_6H_4$, X = CH_2: 91% de = 100% ee = 93%
R = 2-thienyl, X = CH_2: 93% de > 98% ee = 97%
R = *p*-$MeOC_6H_4$, X = O: 93% de = 100% ee = 70%
R = Ph, X = O: 95% de > 98% ee = 74%
R = *p*-$MeOC_6H_4$, X = S: 95% de = 100% ee = 86%
R = *p*-$O_2NC_6H_4$, X = CH_2: 99% de > 98% ee = 95%
R = *p*-BrC_6H_4, X = CH_2: 96% de > 98% ee = 96%
R = Cy, X = CH_2: 82% de > 98% ee = 96%
R = Ph, X = $(CH_2)_2$: 96% de = 88% ee = 92%

Scheme 28. $[DHQD]_2PYR$-catalysed nitro-Michael additions of vinyl malononitriles.

corresponding Friedel–Crafts adducts in high yields and with enantioselectivities of up to 64% ee.[71]

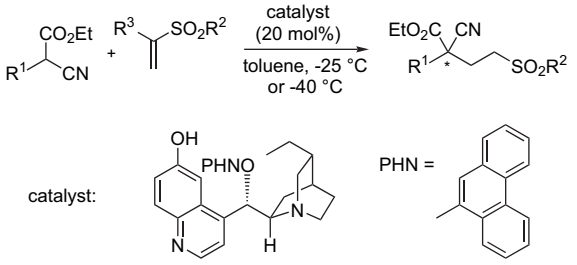


R^1 = R^2 = H, R^3 = Ph: 78% ee = 85%
R^1 = Me, R^2 = H, R^3 = Ph: 82% ee = 74%
R^1 = H, R^2 = OMe, R^3 = Ph: 86% ee = 89%
R^1 = R^2 = H, R^3 = 2-Fu: 88% ee = 73%
R^1 = R^2 = H, R^3 = 2-thienyl: 70% ee = 73%
R^1 = R^2 = H, R^3 = *n*-Pent: 76% ee = 83%
R^1 = R^2 = H, R^3 = *i*-Pr: 37% ee = 81%

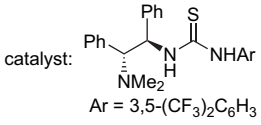
Scheme 29. Thiourea-catalysed Friedel–Crafts alkylations of indoles with nitroalkenes.

2.1.3. Intermolecular Michael additions of *C*-nucleophiles to vinyl sulfones and α,β-unsaturated imides. Compared to the extensively studied α,β-unsaturated carbonyl compounds or nitroolefins, the enantioselective catalytic reaction of vinyl sulfones is still in its infancy. Deng et al. reported, in 2005, the first highly enantioselective catalytic conjugate addition of α-alkyl- or α-aryl-α-

cyanoacetates to vinyl sulfones employing a cinchona alkaloid catalyst (Scheme 30).[72] In the same context, Chen et al. demonstrated, in 2006, that the bifunctional thiourea tertiary amine derivatives of simple chiral diamines served as highly enantioselective catalysts for similar reactions, giving another efficient protocol for the construction of an all-carbon-substituted quaternary stereocentre (Scheme 30).[73]



$R^1 = R^2 = Ph$, $R_3 = H$: 89% ee = 95%
$R^1 = p$-Tol, $R^2 = Ph$, $R_3 = H$: 96% ee = 93%
$R^1 = p$-$MeOC_6H_4$, $R^2 = Ph$, $R_3 = H$: 92% ee = 94%
$R^1 = p$-ClC_6H_4, $R^2 = Ph$, $R_3 = H$: 95% ee = 94%
$R^1 = p$-BrC_6H_4, $R^2 = Ph$, $R_3 = H$: 95% ee = 94%
$R^1 = m$-ClC_6H_4, $R^2 = Ph$, $R_3 = H$: 96% ee = 93%
R^1 = 2-naph, $R^2 = Ph$, $R_3 = H$: 96% ee = 97%
R^1 = 2-thienyl, $R^2 = Ph$, $R_3 = H$: 95% ee = 97%
R^1 = allyl, R^2 = 3,5-$(CF_3)_2C_6H_3$, $R_3 = H$: 76% ee = 94%
$R^1 = Me$, R^2 = 3,5-$(CF_3)_2C_6H_3$, $R_3 = H$: 85% ee = 92%

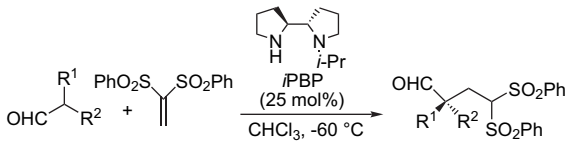


Ar = 3,5-$(CF_3)_2C_6H_3$

$R^1 = R^2 = Ph$, $R_3 = H$: 83% ee = 94%
$R^1 = p$-ClC_6H_4, $R^2 = Ph$, $R_3 = H$: 90% ee = 95%
$R^1 = p$-BrC_6H_4, $R^2 = Ph$, $R_3 = H$: 93% ee = 96%
$R^1 = p$-FC_6H_4, $R^2 = Ph$, $R_3 = H$: 92% ee = 93%
$R^1 = m$-$CF_3C_6H_4$, $R^2 = Ph$, $R_3 = H$: 92% ee = 91%
$R^1 = p$-$MeOC_6H_4$, $R^2 = Ph$, $R_3 = H$: 73% ee = 94%
R^1 = 2-thienyl, $R^2 = Ph$, $R_3 = H$: 96% ee = 95%
$R^1 = Me$, $R^2 = Ph$, $R_3 = SO_2Ph$: 96% ee = 73%
$R^1 = n$-Bu, $R^2 = Ph$, $R_3 = SO_2Ph$: 98% ee = 82%
R^1 = Bn, $R^2 = Ph$, $R_3 = SO_2Ph$: 98% ee = 72%
$R^1 = (EtO)_2CH_2$, $R^2 = Ph$, $R_3 = SO_2Ph$: 52% ee = 96%

Scheme 30. Cinchona alkaloid- and thiourea-catalysed Michael additions of cyanoacetates to vinyl sulfones.

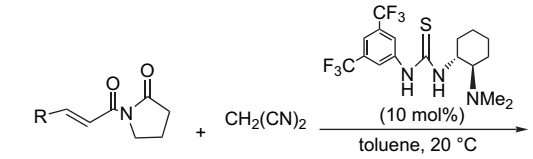
In 2006, Alexakis et al. reported the first condensation of aldehydes onto vinyl sulfones catalysed by *N*-*i*-Pr-2*S*,2′*S*-bipyrrolidine (*i*PBP).[74] The corresponding 1,4-adducts were obtained in good yields and enantioselectivities (Scheme 31).



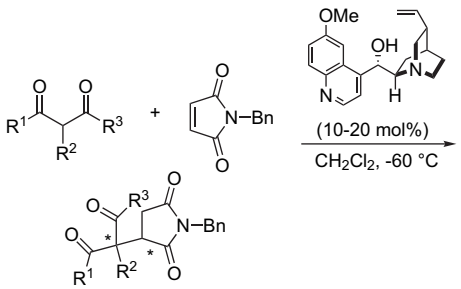
$R^1 = i$-Pr, $R^2 = H$: 71% ee = 75%
$R^1 = t$-Bu, $R^2 = H$: 78% ee = 80%
$R^1 = Cy$, $R^2 = H$: 71% ee = 70%
$R^1 = n$-Pr, $R^2 = H$: 76% ee = 53%

Scheme 31. *i*PBP-catalysed Michael additions of aldehydes to vinyl sulfones.

In 2005, the enantioselective organocatalysed Michael addition methodology could be extended to another type of α,β-unsaturated acid derivative such as α,β-unsaturated imides by the use of a bifunctional thiourea as catalyst.[75] The Michael addition of malononitrile to α,β-unsaturated imides bearing a pyrrolidinone moiety gave the best results in terms of both the yields and enantioselectivities (Scheme 32). In 2006, Bartoli et al. showed that cinchona alkaloids were also highly efficient catalysts for the Michael addition of 1,3-dicarbonyl compounds to maleimides (Scheme 32).[76]



R = p-ClC_6H_4: 85% ee = 89%
R = p-FC_6H_4: 99% ee = 88%
R = p-$MeOC_6H_4$: 77% ee = 85%
R = 1-naph: 93% ee = 88%
R = 2-Fu: 79% ee = 85%
R = $BnCH_2$: 96% ee = 88%
R = *t*-Bu: 78% ee = 92%

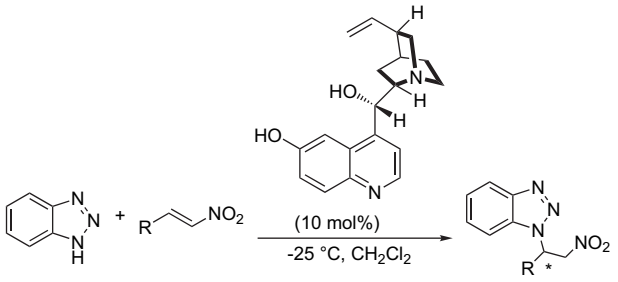


R^1,$R^2 = (CH_2)_3$, R^3 = OEt: 99% de = 74% ee = 98%
R^1,$R^2 = O(CH_2)_2$, R^3 = Me: 91% de = 96% ee = 93%
R^1 = Me, R^2 = Bn, R^3 = OEt: 63% de = 54% ee = 85%
R^1,$R^2 = (CH_2)_3$, R^3 = Me: 99% de = 84% ee = 91%

Scheme 32. Thiourea- and cinchona alkaloid-catalysed Michael additions of *C*-nucleophiles to α,β-unsaturated imides.

2.1.4. Intermolecular Michael additions of *N*-, *S*- and *O*-nucleophiles. Enantioselective conjugate addition reactions of nitrogen-centred heterocyclic nucleophiles to electron-deficient olefins constitute a powerful preparative method in the area of asymmetric heterocyclic chemistry, but, to date, reports of this reaction are sparse. As an example, Wang et al. reported, in 2006, a method for the Michael addition of *N*-heterocycles such as 1*H*-benzo[*d*][1,2,3]-triazole to nitroolefins promoted by a cinchona alkaloid derivative, giving the corresponding Michael adducts in moderate-to-high enantioselectivities (Scheme 33).[77] The reactivity of other nitrogen heterocycles such as 1*H*-[1,2,3]triazole and 5-phenyl-1*H*-tetrazole was evaluated in conjugate additions to *trans*-β-nitrostyrene. Good yields (65 and 76%, respectively) were obtained, combined with high ee's (84 and 85%, respectively) and excellent regioselectivities. Unfortunately, the process was not efficient when applied to purines. In addition, a variety of chiral pyrrolidinium salts were found to catalyse the 1,4-conjugate addition of *N*-methylpyrrole to cyclopent-1-ene carbaldehyde with, according to the

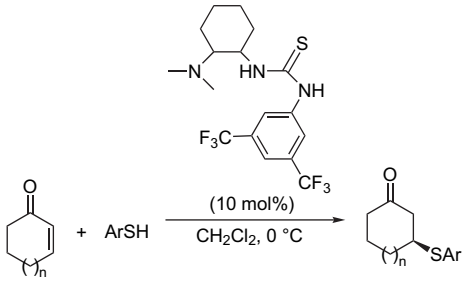
reaction conditions, high diastereo- and enantioselectivities (up to 99% de and 66% ee). Indeed, parameters such as water activity, choice of acidic co-catalyst $(HX)_n$ and amount of co-catalyst used turned out to be crucial for the diastereo- and enantioselectivity of the reaction.[78] Three other enantioselective organocatalytic conjugated additions of thiols to α,β-unsaturated aldehydes were recently reported by Jorgensen,[79] Cordova[80] and Wang,[81] but, since they belong to the class of domino reactions, they are detailed in Section 2.2.



R = Ph: 87% ee = 70%
R = *p*-$BnOC_6H_4$: 73% ee = 78%
R = *o*-$BnOC_6H_4$: 87% ee = 92%
R = *o*-$(PhCO_2)C_6H_4$: 75% ee = 94%
R = 2-thienyl: 79% ee = 80%
R = 2-(*N*-Cbz)-pyrrole: 80% ee = 94%
R = *n*-Bu: 67% ee = 68%

Scheme 33. Cinchona alkaloid-Michael additions of *N*-heterocycle.

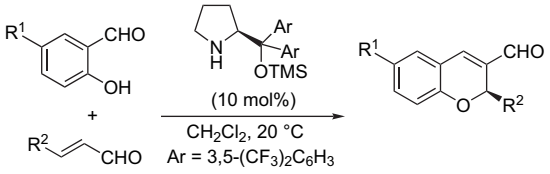
Bifunctional chiral organocatalysts comprising thiourea and tertiary amine groups were prepared by Chen et al. and used to promote the enantioselective Michael addition of arylthiols to α,β-unsaturated carbonyl compounds.[82] The involvement of α,β-unsaturated imides gave rise to enantioselectivities of up to 73% ee, whereas the addition onto enones provided up to 85% ee (Scheme 34). Another *S*-nucleophile such as thioacetic acid was applied to the enantioselective Michael reaction. Therefore, this acid was used in addition reactions to a range of *trans*-β-nitrostyrenes upon catalysis by a chiral amine thiourea catalyst.[83] The processes took place in high yields with up to 70% ee. Although these reactions are actually domino reactions, it was decided to situate them in this section and not in Section 2.2., since they constitute the sole example of Michael additions of *O*-nucleophiles.



Ar = Ph, n= 1: 97% ee = 85%
Ar = naph, n = 1: 98% ee = 71%
Ar = *m*-$MeOC_6H_4$, n = 1: 99% ee = 77%
Ar = Ph, n = 0: 97% ee = 68%
Ar = naph, n = 0: 96% ee = 63%
Ar = *m*-$MeOC_6H_4$, n = 0: 98% ee = 74%

Scheme 34. Thiourea-catalysed Michael additions of arylthiols to enones.

Moreover, the first organocatalysed asymmetric synthesis of chiral benzopyrans, considered as a privileged scaffold in medicinal chemistry, was reported in 2006 by Arvidsson et al.[84] The benzopyran unit was constructed through a domino reaction involving an oxa-Michael attack of salicylic aldehyde derivatives onto α,β-unsaturated aldehydes, activated through iminium ion formation with the organocatalyst (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine, followed by an intramolecular aldol reaction and subsequent elimination of water. This overall reaction sequence provided benzopyrans with aromatic C-2 substituents in up to 60% yield and 60% enantioselectivity, while the C-2 aliphatic analogues could be obtained in up to 90% ee, but with only low yields (Scheme 35).



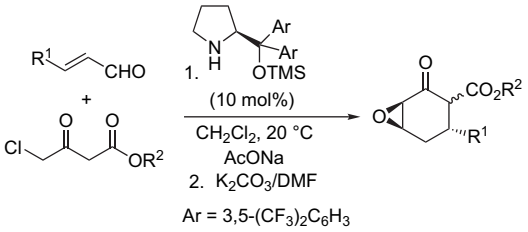
R^1 = H, R^2 = Ph: 90% ee = 60%
R^1 = OMe, R^2 = *n*-Pr: 15% ee = 90%
R^1 = H, R^2 = *n*-Pr: 25% ee = 69%

Scheme 35. Oxa-Michael reactions catalysed by L-proline derivative.

2.2. Domino Michael reactions

In the last two years, several groups have developed highly efficient enantioselective organocatalytic domino Michael reactions, among which are reactions predominantly catalysed by L-proline derivatives. Gryko reported, in 2005, the domino Michael aldol reaction of 1,3-diketones with methyl vinyl ketone in the presence of L-proline, furnishing the corresponding highly substituted cyclohexanones in a regio- and stereocontrolled manner.[85] When the reaction was performed in NMP as solvent, high yields (up to 93%) and enantioselectivities (up to 80%) were observed. In 2006, Jorgensen et al. developed a simple and versatile organocatalytic strategy for the preparation of structurally complex molecules having up to four stereocentres on the basis of a one-pot Michael addition aldol S_N2 domino reaction of α,β-unsaturated aldehydes and γ-chloro-β-keto esters.[86] The process, involving (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine as catalyst, led to the formation of the polysubstituted 7-oxa-bicyclo[4.1.0]-heptan-2-one ring system in excellent diastereo- and enantioselectivities (Scheme 36). These values were determined after decarboxylation of the products, due to the fact that the stereocentre between the two electron-withdrawing groups (ketone and ester) was not configurationally stable. Nevertheless, after decarboxylation, only one diastereoisomer could be detected (>99% de) in all cases, implying perfect control of the relative configuration of the three stable chiral centres.

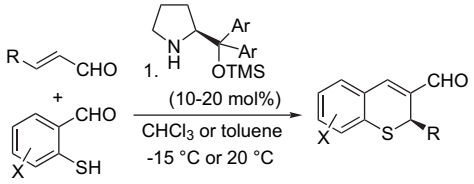
The same catalyst was applied, in 2006, to the development of two enantioselective domino thia-Michael adol reactions (Scheme 37).[80,81] The reaction starts with iminium activation of the aldehyde by the chiral pyrrolidine catalyst. The



R^1 = Me, R^2 = Et: 57% de > 99% ee = 86%
R^1 = Me, R^2 = allyl: 56% de = 99% ee = 85%
R^1 = R^2 = Et: 53% de > 99% ee = 92%
R^1 = Et, R^2 = allyl 46% de > 99% ee = 92%
R^1 = *n*-Pr, R^2 = allyl: 48% de > 99% ee = 91%
R^1 = *i*-Pr, R^2 = allyl: 44% de > 99% ee = 97%
R^1 = *i*-Pr, R^2 = Me: 50% de > 99% ee = 97%
R^1 = Bn, R^2 = allyl: 40% de = 99% ee = 92%

Scheme 36. Domino Michael addition aldol S_N2 reactions catalysed by L-proline derivative.

efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups leads to stereoselective *Re*-facial nucleophilic conjugate attack on the β-carbon by the thiol, resulting in a chiral enamine intermediate. Next, the chiral enamine undergoes an intramolecular 6-*exo trig* aldol addition, followed by hydrolysis of the resulting iminium intermediate to give the aldol product. Finally, elimination of water gives the corresponding thiochromene-3-carbaldehyde.

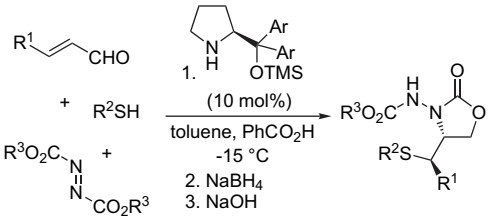


R = Ph, X = H: 85% ee = 94%
R = *o*-$MeOC_6H_4$, X = H: 96% ee = 94%
R = *p*-BrC_6H_4, X = H: 93% ee = 98%
R = *p*-$O_2NC_6H_4$, X = H: 95% ee = 92%
R = *p*-NCC_6H_4, X = H: 80% ee = 98%
R = Et, X = H: 81% ee = 95%
R = *n*-Pr, X = H: 96% ee = 94%
R = *n*-Pent, X = H: 94% ee = 93%
R = Me, X = 5-MeO: 80% ee = 93%
R = Me, X = 5-Me: 97% ee = 90%
R = Me, X = 4,6-$(MeO)_2$: 96% ee = 89%
R = *n*-Bu, X = H: 70% ee = 96%

Scheme 37. Domino thia-Michael aldol reactions catalysed by L-proline derivative.

The first asymmetric domino thia-Michael electrophilic amination reaction was described by Jorgensen using the same L-proline derivative.[79] Highly functionalised oxazolidinones in nearly enantiopure form were prepared by the reaction between an α,β-unsaturated aldehyde, a thiol and an azodicarboxylate, as depicted in Scheme 38.

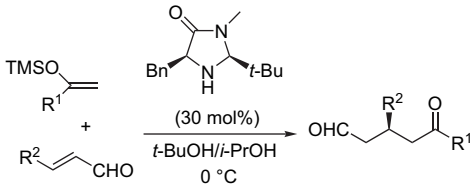
Organocatalysts other than proline derivatives have been used in order to promote new asymmetric domino reactions.[87] An enantioselective domino Mukaiyama Michael



R^1 = Me, R^2 = Bn, R^3 = Et: 72% de = 86% ee > 99%
R^1 = R^3 = Et, R^2 = Bn: 63% de = 90% ee > 99%
R^1 = Me, R^3 = R^2 = Bn: 44% de = 78% ee > 99%
R^1 = Me, R^2 = Et, R^3 = Bn: 51% de = 76% ee > 99%
R^1 = R^2 = Et, R^3 = Bn: 38% de = 90% ee = 97%

Scheme 38. Domino thia-Michael amination reactions catalysed by L-proline derivative.

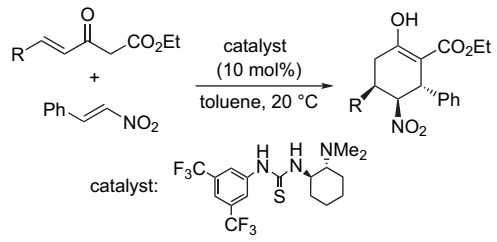
addition reaction of silyl enol ethers to α,β-unsaturated aldehydes was catalysed by a MacMillan chiral imidazolidinone, affording the corresponding δ-keto aldehydes in high yields (56–87%) and enantioselectivities (85–97% ee).[88] The reaction could be applied to a wide range of silyl ethers and aldehydes, as depicted in Scheme 39. Other enantioselective domino reactions have been developed using this type of catalyst. MacMillan et al. have reported reactions between an α,β-unsaturated aldehyde, an aromatic nucleophile such as furan, thiophene, indole or butenolide and a chlorinated quinone, providing the corresponding chiral 3,3′-disubstituted 2-chloroaldehydes in high yields (up to 86%), diastereoselectivities (up to 92% de) and enantioselectivities (up to 100% ee).[89]



R^1 = R^2 = Ph: 75% ee = 90%
R^1 = *p*-Tol, R^2 = Ph: 62% ee = 95%
R^1 = *p*-$MeOC_6H_4$, R^2 = Ph: 56% ee = 97%
R^1 = *p*-Tol, R^2 = *p*-FC_6H_4: 71% ee = 92%
R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-FC_6H_4: 63% ee = 95%
R^1 = Ph, R^2 = *p*-NCC_6H_4: 59% ee = 90%
R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-NCC_6H_4: 61% ee = 94%
R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-$MeOC_6H_4$: 63% ee = 90%

Scheme 39. Domino Mukaiyama Michael reactions catalysed by MacMillan imidazolidinone.

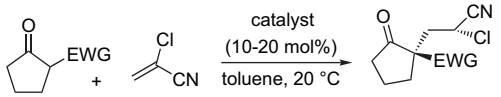
In 2006, Takemoto et al. reported an enantioselective domino Michael addition reaction of γ,δ-unsaturated β-keto esters to nitroalkenes catalysed by a bifunctional thiourea, giving rise to highly functionalised cyclohexanones in good yields (Scheme 40).[90] The three contiguous stereogenic centres of the products were constructed with high diastereo- and enantioselectivity. This reaction was further applied to the total synthesis of (−)-epibatidine, a potent nicotinic acetylcholine receptor agonist and a non-opiate analgesic approximately 200-fold more potent than morphine.



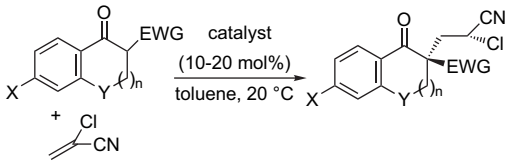
R = Me: 87% de > 99% ee = 92%
R = *i*-Pr: 71% de > 99% ee = 88%
R = Ph: 62% de > 99% ee = 92%
R = OMe: 79% de > 99% ee = 84%

Scheme 40. Thiourea-catalysed domino Michael reactions.

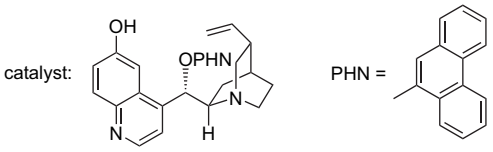
In order to provide a highly versatile catalytic approach for the asymmetric creation of 1,3-tertiary–quaternary stereocentres, Deng et al. developed, in 2006, a novel asymmetric domino Michael protonation reaction catalysed by a cinchona alkaloid.[91] This reaction occurred in the presence of a cyclic or acyclic Michael donor and 2-chloroacrylonitrile, producing the corresponding adduct containing the 1,3-tertiary–quaternary stereocentres (Scheme 41). The synthetic value of this approach was illustrated by the development of a concise and highly stereoselective route to (−)-manzacidin A, a natural bromopyrrole alkaloid.



EWG = CN: 93% de = 76% ee = 93%
EWG = $CO_2CH(CF_3)_2$: 71% de = 80% ee = 94%



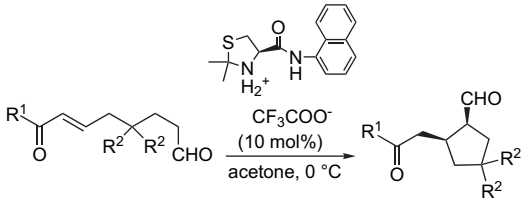
X = H, Y = CH_2, n = 0, EWG = CN : 95% de = 90% ee = 96%
X = H, Y = CH_2, n = 1, EWG = CN : 87% de = 84% ee = 91%
X = H, Y = CH_2, n = 2, EWG = CN : 88% de = 92% ee = 95%
X = H, Y = CH_2, n = 0, EWG = CN : 95% de = 90% ee = 96%
X = H, Y = CH_2, n = 0, EWG = $CO_2CH(CF_3)_2$: 71% de = 80% ee = 94%
X = H, Y = CH_2, n = 0, EWG = CO_2t-Bu : 94% de = 88% ee = 98%
X = Cl, Y = CH_2, n = 0, EWG = CO_2t-Bu : 81% de = 90% ee = 99%
X = H, Y = O, n = 0, EWG = CO_2t-Bu : 75% de = 90% ee = 98%



Scheme 41. Cinchona alkaloid-catalysed domino Michael protonation reactions.

2.3. Intramolecular Michael additions

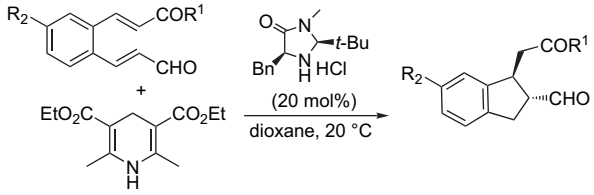
In 2005, MacMillan and Mangion achieved the total syntheses of two biologically active natural products, (−)-brasoside and (−)-littoralisone, based on an intramolecular Michael addition of a formyl-enal catalysed by L-proline in DMSO, providing the corresponding chiral lactol in 91% yield and 82% de.[92] On the other hand, a naphthylamide catalyst derived from cysteine was developed to act as an efficient organocatalyst of asymmetric intramolecular Michael reactions such as those implicating formyl enones, which led to the stereoselective formation of cis-disubstituted cyclopentane skeletons (Scheme 42).[93] These compounds, containing two contiguous chiral centres, were formed in good yield with high diastereoselectivities and excellent enantioselectivities. A noteworthy feature of this reaction was the unexpected stereoselective formation of the cis-isomer.



R^1 = Ph, R^2 = H: 100% de = 78% ee = 99%
R^1 = Ph, R^2 = CO_2Me: 95% de = 82% ee = 97%
R^1 = Ph, R^2,R^2 = S-$(CH_2)_3$-S: 93% de > 90% ee = 99%
R^1 = Me, R^2,R^2 = S-$(CH_2)_3$-S: 93% de > 90% ee > 99%

Scheme 42. Intramolecular Michael reactions catalysed by cysteine-derived catalyst.

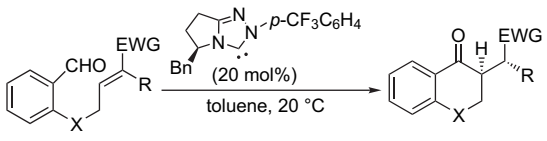
A MacMillan imidazolidinium salt was used by List et al. to promote a reductive Michael cyclisation of enal enones in the presence of a Hantzsch ester as a hydrogen donor, leading to the formation of the corresponding keto aldehydes with high selectivity (Scheme 43).[94] It was assumed that the reaction proceeded via an iminium catalytic conjugate reduction followed by an in situ enamine catalytic asymmetric Michael cyclisation.



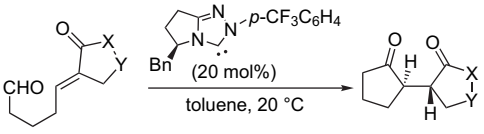
R^1 = Ph, R^2 = H: 98% de = 88% ee = 96%
R^1 = 2-naph, R^2 = H: 94% de = 96% ee = 94%
R^1 = Me, R^2 = H: 91% de > 96% ee = 91%
R^1 = Ph, R^2 = F: 95% de = 90% ee = 97%

Scheme 43. Intramolecular reductive Michael reactions catalysed by imidazolidinium salt.

The Stetter reaction, where a Michael acceptor traps the acyl anion equivalent generated by nucleophilic attack of the catalyst, offers an alternative approach to the well-established conjugate addition reaction manifold.[95] In 2005, Rovis and Read de Alaniz described a highly enantioselective intramolecular Stetter reaction of trisubstituted Michael acceptors, resulting in a highly enantioselective Michael addition and a diastereoselective proton transfer in the presence of a chiral pyrrolidinone-based catalyst (Scheme 44).[96]



X = O, R = Me, EWG = CO_2Et: 94% de = 94% ee = 95%
X = O, R = Et, EWG = CO_2Et: 95% de = 94% ee = 92%
X = O, R = *n*-Bu, EWG = CO_2Et: 53% de = 84% ee = 94%
X = O, R = Bn, EWG = CO_2Et: 80% de = 90% ee = 84%
X = O, R = allyl, EWG = CO_2Me: 95% de = 86% ee = 83%
X = O, R, EWG = $(CH_2)_2OCO$: 95% de = 82% ee = 94%
X = O, R, EWG = $(CH_2)_3CO$: 80% de = 90% ee = 95%
X = O, R = Me, EWG = COMe: 85% de = 82% ee = 55%



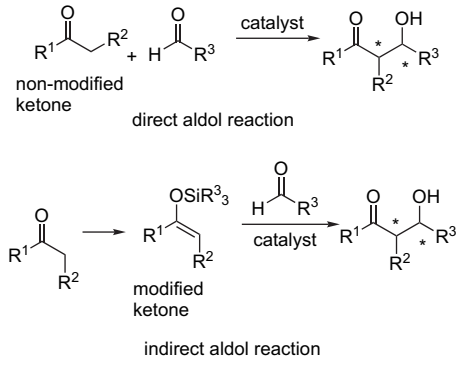
X = O, Y = CH_2: 94% de = 96% ee = 99%
X = NPh, Y = CO: 80% de = 88% ee = 88%

Scheme 44. Intramolecular Stetter reactions catalysed by pyrrolidinone catalyst.

3. Nucleophilic additions to C═O double bonds

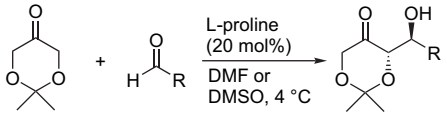
3.1. Aldol reactions

The asymmetric aldol reaction is one of the most important topics in modern catalytic synthesis and one of the most advanced types of synthesis in the field of organocatalysis. During the last few years, several new concepts have been developed, which are based on the use of organocatalysts in which unmodified ketones or enolates can be used as aldol donors. Asymmetric aldol reactions are classified into indirect and direct aldol reactions. The former reactions require a modified ketone such as an enolate prepared in a previous step as starting material, whereas the latter involve a ketone in a non-activated form as nucleophile (Scheme 45).



Scheme 45. Direct and indirect aldol reactions.

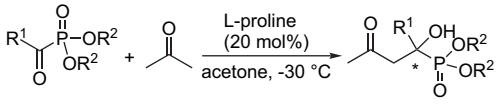
3.1.1. Direct aldol reactions catalysed by proline derivatives. During the last two years the organocatalysed intermolecular direct aldol reactions have grown most remarkably, especially those which involve chiral proline derivatives as catalysts.[9,97] Surprisingly, the catalytic potential of proline in asymmetric aldol reactions was not explored further, until recently, in spite of the discovery, in the early 1970s, of the first proline-catalysed intramolecular aldol reaction. The List and Barbas approaches, applying proline as the organocatalyst, are surely among the most efficient and general asymmetric catalytic aldol reactions yet discovered.[98] There are several reasons why proline has become an important molecule in asymmetric catalysis, e.g., it is an abundant chiral molecule, which is inexpensive and available in both enantiomeric forms. Additionally, there are various chemical reasons that contribute to proline's role in catalysis. Proline is bifunctional, with a carboxylic acid and an amine function, which can both act as an acid or base, allowing chemical transformations in concert, in a similar manner to enzymatic catalysis. Recently, some interesting extensions of the enantioselective proline-catalysed aldol reaction have been reported. As an example, aldol reactions between aldehydes and dihydroxyacetone variants such as 2,2-dimethyl-1,3-dioxan-5-one have been developed by several groups, providing a biomimetic asymmetric synthesis of various carbohydrate scaffolds[99] in a fashion analogous to aldolase enzymes (Scheme 46).[100]



R = CH_2OAc: 60% de > 88% ee = 98%
R = *i*-Bu: 75% de = 82% ee = 98%
R = $(CH_2)_4$: 67% de = 98% ee = 97%
R = $CH(OMe)_2$: 60% de = 90% ee = 98%
R = *p*-$O_2NC_6H_4$: 72% de = 90% ee = 93%
R = Ph: 80% de = 0% ee = 97%
R = CH_2OBn: 85% de > 90% ee = 98%
R = *i*-Pr: 97% de > 96% ee = 94%
R = *n*-$C_{14}H_{29}$: 60% de > 99% ee = 95%

Scheme 46. L-Proline-catalysed direct aldol reactions of dihydroxyacetone variant.

On the other hand, a highly enantioselective cross-aldol reaction of α-ketophosphonates and ketones was reported by Zhao and Samanta, in 2006, giving rise to chiral tertiary α-hydroxyphosphonates (Scheme 47).[101]

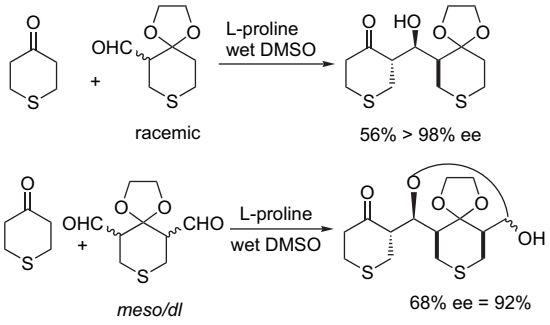


R^1 = Ph, R^2 = Et: 65% ee = 87%
R^1 = Ph, R^2 = Me: 66% ee = 95%
R^1 = Ph, R^2 = *i*-Pr: 60% ee = 96%
R^1 = *p*-ClC_6H_4, R^2 = Et: 68% ee = 91%
R^1 = *p*-ClC_6H_4, R^2 = *i*-Pr: 63% ee = 95%
R^1 = *p*-FC_6H_4, R^2 = *i*-Pr: 68% ee = 96%
R^1 = *p*-BrC_6H_4, R^2 = Et: 66% ee > 99%
R^1 = *p*-IC_6H_4, R^2 = Et: 67% ee = 94%
R^1 = Me, R^2 = Et: 91% ee = 97%
R^1 = Bn, R^2 = Et: 86% ee = 92%

Scheme 47. L-Proline-catalysed direct cross-aldol reactions with α-ketophosphonates.

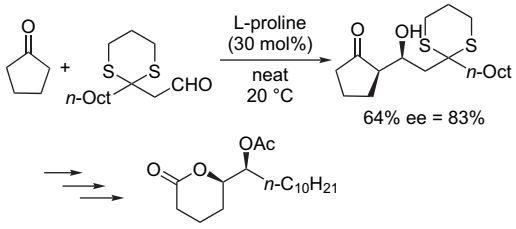
The scope of the enantioselective direct aldol reaction was significantly extended by Ward et al., who, in 2005, showed

that proline-catalysed reactions of tetrahydro-4*H*-thiapyranone with racemic 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde and with *meso*/*dl* 1,4-dioxa-8-thia-spiro[4.5]decane-6,10-dicarboxaldehyde proceeded with dynamic kinetic resolution and gave single adducts with excellent enantioselectivities (Scheme 48).[102] The high enantiotopic group selectivity results from the high intrinsic diastereofacial selectivity of the aldehydes.



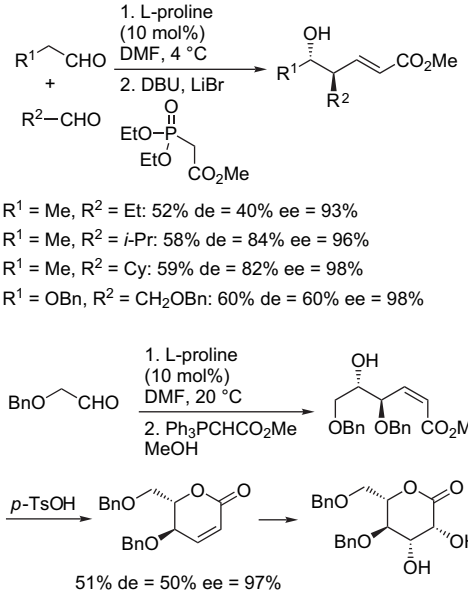
Scheme 48. L-Proline-catalysed direct aldol reactions of tetrahydro-4*H*-thiapyranone.

In 2006, Pihko et al. studied the effect of additives on proline-catalysed ketone–aldehyde aldol reactions.[103] While the reactions appeared to be relatively tolerant to small amounts of tertiary amine bases or weak acids, they stopped completely with strong acids. The use of water as an additive had a highly beneficial effect on the reactions that were conducted with a stoichiometric ratio of ketone to aldehyde, especially with cyclic ketones. This allowed the efficient use of more precious ketones such as 4-thianone as donors in the direct enantioselective aldol reaction with a wide range of aldehydes and facilitated the purification. Excellent enantio- and diastereoselectivities were obtained with this ketone (up to 99% ee and 90% de). Moreover, proline-catalysed intermolecular aldol reactions of acetone with various aldehydes have recently been successfully performed, both with proline and poly(ethylene glycol)-supported derivative (PEG-400) as a recyclable medium.[104] Recycling of the catalyst and solvent (PEG) was possible for up to 10 runs without loss of catalytic activity. L-Proline was also found to be an efficient catalyst for the asymmetric transfer aldol reaction between various aldehydes and diacetone alcohol under the same conditions. Good yields (up to 94%) and enantioselectivities (up to 84% ee) were observed with both methods. In addition, Alexakis and Mosse have demonstrated that microwave irradiation in aldol reactions of acetone with aldehydes allowed the reaction time to be dramatically shortened without loss of selectivity.[59] In 2005, Maruoka et al. reported the total synthesis of (*S*)-oxybutynin, a potent muscarinic receptor antagonist, on the basis of an L-proline-catalysed aldol reaction between cyclohexanone and ethyl glyoxylate, providing, in mild conditions (DMSO, 20 °C), the key intermediate bearing a tetrasubstituted carbon centre with 96% ee and 79% yield.[105] The L-proline-catalysed aldol methodology was also applied by List et al. to the total synthesis of a natural mosquito attractant pheromone, depicted in Scheme 49. Li's synthesis was based on the aldol reaction of cyclopentanone with undecanal, giving rise to the corresponding β-hydroxy cyclopentanone with 80% yield, 70% de and 96% ee.[106] Another synthesis, reported in 2006 by Kotsuki et al., involved as the key step the aldol reaction of cyclopentanone with a straight-chain aliphatic aldehyde bearing a 1,3-dithiane moiety at the β-position (Scheme 49).[107]



Scheme 49. L-Proline-catalysed synthesis of pheromone.

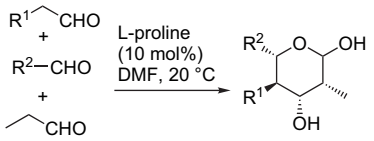
In addition to serving as acceptors in proline-catalysed aldol reactions, aldehydes can also act as donors. In this context, asymmetric domino cross-aldol Horner–Wittig–Emmons reactions were developed in 2006 by Cordova et al.[108] These processes furnished chiral polyketide and carbohydrate derivatives (Scheme 50).



Scheme 50. Domino L-proline-catalysed cross-aldol Horner–Wittig–Emmons reactions.

In addition, two iterative L-proline-catalysed aldol reactions with three aldehydes were performed by the same authors, providing the corresponding L- or D-sugar in most cases with >99% ee. This novel iterative aldol reaction methodology allowed the creation of four contiguous stereocentres with excellent stereocontrol (Scheme 51).[109]

In addition to the use of L-proline in the organocatalysed aldol reaction, a number of proline derivatives have been investigated as catalysts for this reaction in the last two years. As an example, a series of 4-substituted prolines were prepared by Kokotos and Bellis and evaluated for aldol reactions. Using (2*S*,4*R*)-4-camphorsulfonyloxy-proline, the aldol products were obtained in much higher enantiomeric excesses in comparison to those observed using proline. Therefore, up to 90% ee was obtained for the aldol reaction between acetone and 4-nitrobenzaldehyde in the presence of

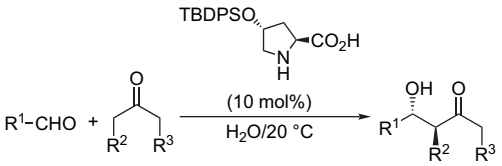


R^1 = Me, R^2 = Et: 29% ee = 99%
R^1 = Me, R^2 = *i*-Pr: 42% ee > 99%
R^1 = OBn, R^2 = CH_2OBn: 39% ee > 99%
R^1 = Me, R^2 = CH_2OBn: 29% ee > 99%
R^1 = Me, R^2 = *i*-Bu: 24% ee > 99%
R^1 = Me, R^2 = Cy: 41% ee > 99%

Scheme 51. Domino L-proline-catalysed aldol reactions.

10 mol % loading of the 4-substituted proline, whereas a similar reaction did not occur with such a loading of L-proline and gave a 69% ee with a 20 mol % loading. In addition, the improved solubility of these new catalysts in organic solvents permitted their use in lower, sub-stoichiometric amounts, compared to proline.[110] In the same context, a novel proline derivative, (4*R*)-4-(β-naphthalenyl)methoxy-(*S*)-proline, was shown to efficiently catalyse the asymmetric aldol reaction of various benzaldehydes with acetone in an excess of acetone as the solvent, giving the corresponding aldol products in good yields with up to 90% ee.[111] In 2006, Wu et al. reported similar reactions performed in the presence of (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (30 mol %) and an equimolar amount of Et_3N.[112] By using this novel catalyst, the direct aldol condensation products were obtained in reasonable yields and up to 90% ee. On the other hand, reactions in which water is used as the solvent have attracted a great deal of attention, because water is an environmentally friendly, safe medium, which avoids the problems of pollution that are inherent with organic solvents.[113] The first organocatalysed aldol reaction performed in water without the use of an organic solvent was reported in 2006 by Hayashi et al., using 4-*tert*-butyldiphenylsiloxyproline as catalyst (Scheme 52).[114] In the same context, a combined proline–surfactant organocatalyst was developed by the same group and applied to the highly diastereo- and enantioselective aqueous cross-aldol reaction of aldehydes.[115] Indeed, this result has opened up a new method for the development of asymmetric organocatalysis in water. In addition, 4-hydroxyproline has been recently anchored to a polystyrene resin through click chemistry, and the resulting catalyst has been successfully applied to the aldol reaction in water (up to 96% ee).[116] Similarly, in 2007, a polystyrene-supported proline was used to catalyse the aldol reaction between cyclohexanone and substituted benzaldehydes in water, allowing enantioselectivities of up to 98% ee to be obtained.[117] On the other hand, protonated chiral proline amide derivatives have been shown to be useful catalysts in water for aldol processes with high yield and good enantioselectivity.[118]

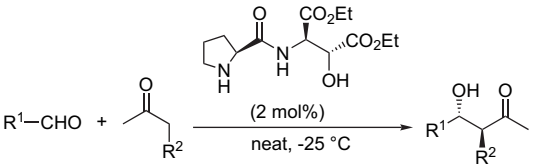
L-Proline amides bearing substituents of various electronic nature at their stereogenic centres have been prepared and evaluated by Gong et al. for their ability to catalyse the aldol reaction between 4-nitrobenzaldehyde and ketones such as acetone or butanone.[119] The presence of only 2 mol % of catalyst, such as that depicted in Scheme 53, allowed the formation of the corresponding β-hydroxy ketones with very high



R^1 = Ph, R^2,R^3 = $(CH_2)_3$: 78% de = 86% ee > 99%
R^1 = Ph, R^2,R^3 = $(CH_2)_2$: 74% de = 80% ee > 99%
R^1 = *p*-$O_2NC_6H_4$, R^2,R^3 = $(CH_2)_3$: 86% de = 90% ee > 99%
R^1 = Cy, R^2,R^3 = $(CH_2)_3$: 76% de > 90% ee > 99%
R^1 = *i*-Pent, R^2,R^3 = $(CH_2)_3$: 54% de > 90% ee > 99%
R^1 = *p*-BrC_6H_4, R^2,R^3 = $(CH_2)_3$: 80% de = 90% ee = 97%
R^1 = 2-Fu, R^2,R^3 = $(CH_2)_3$: 79% de = 64% ee = 97%
R^1 = *p*-$O_2NC_6H_4$, R^2,R^3 = H: 63% ee = 67%
R^1 = 2-naph, R^2,R^3 = $(CH_2)_3$: 89% de = 90% ee = 97%

Scheme 52. 4-*tert*-Butyldiphenylsiloxyproline-catalysed aldol reactions in water.

enantioselectivities, ranging from 96 to 99% ee. The same authors have shown that similar catalysts could be employed in ionic liquids, giving up to 99% ee for the reaction of acetone with both aromatic and aliphatic aldehydes.[120]

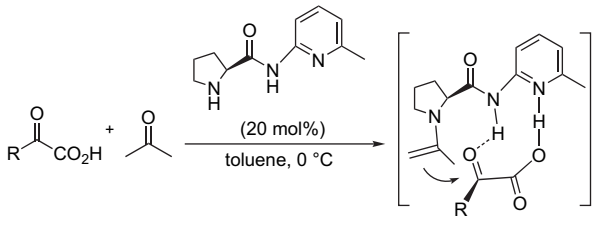


R^1 = *p*-$O_2NC_6H_4$, R^2 = Me: 42% de > 98% ee = 99%
R^1 = *p*-ClC_6H_4, R^2 = Me: 36% de > 98% ee = 98%
R^1 = *p*-$O_2NC_6H_4$, R^2 = H: 62% ee = 99%
R^1 = *p*-ClC_6H_4, R^2 = H: 84% ee = 99%
R^1 = *o*-ClC_6H_4, R^2 = H: 99% ee = 96%
R^1 = Ph, R^2 = H: 68% ee = 98%
R^1 = 2-naph, R^2 = H: 63% ee = 97%
R^1 = *t*-Bu, R^2 = H: 71% ee > 99%
R^1 = *i*-Pr, R^2 = H: 75% ee > 99%
R^1 = Cy, R^2 = H: 80% ee = 99%

Scheme 53. L-Proline amide-catalysed aldol reactions.

Despite the substantial variety of aldol acceptors, the range of donors has remained narrow. Whereas acetone, hydroxyacetone and some enolisable aldehydes are excellent nucleophiles, a variety of other donors remain neglected. Gong et al. reported, in 2006, the use of α-keto acids in direct aldol reactions of ketones in the presence of a chiral proline amide as catalyst, affording the corresponding β-hydroxy carboxylic acids with a tertiary stereogenic centre with excellent enantioselectivities of up to 98% ee (Scheme 54).[121] In addition, the use of 30 mol % (*S*)-pyrrolidine-2-carboxylic acid (2,4,6-trimethyl-phenyl)-amide was shown to catalyse the aldol reaction of chloroacetone with a range of aldehydes to give *anti*-α-chloro-β-hydroxy ketones with regio-, diastereo- and enantioselectivity (up to 98% ee).[122]

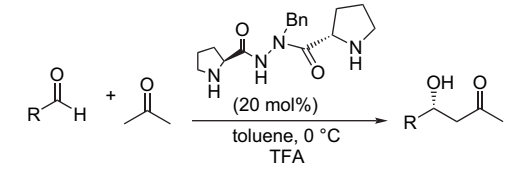
In 2005, Gryko and Lipinski demonstrated for the first time that a series of novel L-proline thioamides were efficient organocatalysts for the aldol reaction of acetone with aromatic aldehydes, giving the corresponding aldol products with high ee's (up to 100%) and moderate yields (20–86%).[123]



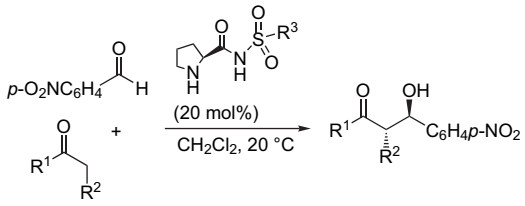
R = Ph: > 99% % ee = 93%
R = 2-Fu: > 99% % ee = 93%
R = 2-thienyl: 78% % ee = 93%
R = Bn: 75% ee = 98%
R = Me: 78% ee = 92%
R = Et: 85% ee = 95%
R = *i*-Bu: 96% ee = 96%

Scheme 54. Proline amide-catalysed aldol reactions of α-keto acids.

Other derivatives of L-proline such as chiral pyrrolidine imides,[124] *N*′-benzyl-*N*′-prolyl proline hydrazide[125] or acyl sulfonamides[41] gave good results in direct aldol reactions, as depicted in Scheme 55.



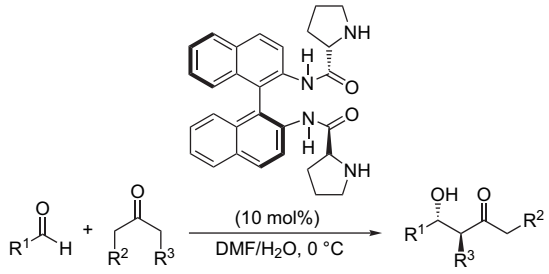
R = *p*-$O_2NC_6H_4$: 95% ee = 96%
R = *o*-$O_2NC_6H_4$: 97% ee = 96%
R = *m*-$O_2NC_6H_4$: 86% ee = 96%
R = *p*-NCC_6H_4: 97% ee = 92%
R = *o*-ClC_6H_4: 75% ee = 96%



$R^1 = R^2 = R^3$ = Me: 78% ee = 79%
R^1 = Et, $R^2 = R^3$ = Me: 42% ee = 76%
$R^1 = R^2 = R^3$ = Me: 78% ee = 79%
$R^1 = R^2$ = Me, R^3 = Ph: 100% ee = 92%
R^1 = Et, R^2 = Me, R^3 = Ph: 48% ee = 77%
R^1,R^2 = CH_2, R^3 = Ph: 21% ee = 86%
R^1,R^2 = $(CH_2)_3$, R^3 = Ph: 35% ee = 63%

Scheme 55. Aldol reactions catalysed by L-proline hydrazide or acyl sulfonamide.

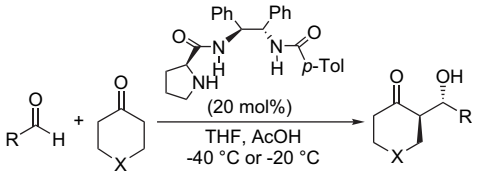
The catalytic activity of the proline amide-type catalysts may also be improved by introducing an additional proline amide moiety into the catalyst, while the enantioselectivity can still be maintained or further improved. Therefore, a series of C_2-symmetric bisproline amides have been evaluated for the direct aldol reaction by several groups.[126] As an example, new proline amides derived from 2,2′-diamino-1,1′-binaphthalene (BINAM) were studied by Gryko et al. and by Najera et al. for their ability to catalyse aldol reactions between aldehydes and aliphatic ketones including α-alkoxyacetones (Scheme 56).[127]



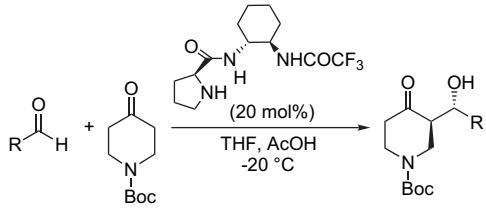
R^1 = *p*-$O_2NC_6H_4$, $R^2 = R^3$ = H: 99% ee = 79%
R^1 = *o*-ClC_6H_4, $R^2 = R^3$ = H: 98% ee = 95%
R^1 = *p*-$O_2NC_6H_4$, R^2 = H, R^3 = Me: 96% ee = 96%
R^1 = *o*-$O_2NC_6H_4$, R^2 = H, R^3 = CH_2OMe: 96%
de = 75% ee > 99%

Scheme 56. BINAM proline amide-catalysed aldol reactions.

On the other hand, non-symmetric bifunctional diamides, sterically and electronically tunable, have been used by Xiao et al. to achieve direct aldol reactions of heterocyclic ketones with various aldehydes, affording more than 30 compounds with enantioselectivities ranging from 94 to >99% (Scheme 57).[128]



R = *p*-$O_2NC_6H_4$, X = O: 91% de > 98% ee = 99%
R = *m*-$O_2NC_6H_4$, X = O: 96% de = 94% ee > 99%
R = *o*-$O_2NC_6H_4$, X = O: 94% de = 98% ee > 99%
R = *p*-NCC_6H_4, X = O: 81% de = 94% ee = 99%
R = *p*-BrC_6H_4, X = O: 89% de = 90% ee > 99%
R = Ph, X = O: 80% de = 98% ee = 99%
R = 2-Fu, X = O: 89% de > 98% ee > 99%
R = 2-thienyl, X = O: 67% de > 98% ee > 99%
R = *p*-$O_2NC_6H_4$, X = S: 91% de = 98% ee = 99%
R = *m*-$O_2NC_6H_4$, X = S: 88% de = 84% ee = 99%
R = *o*-$O_2NC_6H_4$, X = S: 93% de = 96% ee = 99%
R = *p*-NCC_6H_4, X = S: 98% de = 96% ee = 99%
R = *p*-BrC_6H_4, X = S: 90% de = 98% ee = 97%
R = 2,4-$(Cl)_2C_6H_3$, X = S: 99% de = 94% ee = 99%

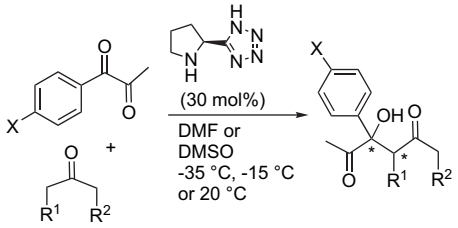


R = *p*-$O_2NC_6H_4$: 90% de = 92% ee = 96%
R = *m*-$O_2NC_6H_4$: 91% de = 92% ee = 93%
R = *o*-$O_2NC_6H_4$: 80% de = 92% ee = 92%
R = *p*-BrC_6H_4: 86% de = 94% ee = 95%
R = *m*-$O_2NC_6H_4$: 80% de = 98% ee = 96%
R = *i*-Pr: 58% de = 94% ee = 98%

Scheme 57. Aldol reactions of heterocyclic ketones catalysed by L-proline-derived diamides.

The tetrazolic acid analogue of L-proline, widely employed in the literature, has been found to be significantly more

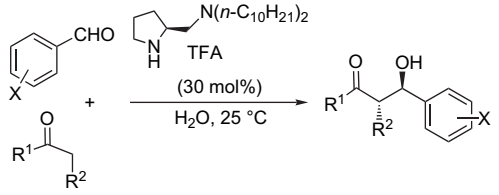
reactive and sometimes more stereoselective than L-proline in various aldol reactions of acetone with both aromatic and aliphatic aldehydes.[129] In 2006, Zhao and Samanta reported the use of this catalyst for the cross-aldol reactions of ketones with 1,2-diketones, which yielded the corresponding 2-hydroxy-1,4-diketones in high regioselectivity, diastereoselectivity and good enantioselectivity (Scheme 58).[130] The scope of the reaction could be extended to cyclic 1,2-diketones such as 1,2-cyclohexanedione and 9,10-phenanthrenequinone, which gave, by reaction with acetone, the corresponding adducts in 66 and 86% ee's, respectively.



$R^1 = R^2 = X = H$: 83% ee = 83%
$R^1 = R^2 = H$, $X = NO_2$: 75% ee = 84%
$R^1 = R^2 = H$, $X = CF_3$: 59% ee = 85%
$R^1, R^2 = (CH_2)_3$, X = H: 43% ee = 80%
$R^1 = R^2 = X = H$: 83% ee = 83%

Scheme 58. 5-Pyrrolidin-2-yltetrazole-catalysed cross-aldol reactions of 1,2-diketones.

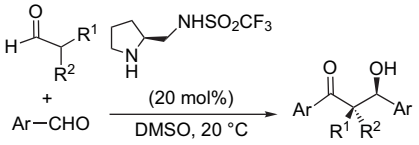
A chiral diamine derived from L-proline was recently shown to catalyse the direct aldol reaction of aromatic aldehydes with various ketones in water without addition of organic solvents (Scheme 59).[131]



$R^1 = R^2 = (CH_2)_4$, X = *p*-CN: 99% de = 72% ee = 87%
$R^1 = R^2 = (CH_2)_4$, X = *p*-CO_2Me: 89% de = 80% ee = 91%
$R^1 = R^2 = (CH_2)_4$, X = H: 46% de = 80% ee = 99%
$R^1 = R^2 = (CH_2)_4$, X = *m*-NO_2: 99% de = 80% ee = 99%
$R^1 = R^2 = (CH_2)_4$, X = *o*-NO_2: 98% de = 78% ee = 98%
R^1 = H, R^2 = *i*-Pr, X = *p*-NO_2: 99% de = 100% ee = 91%
$R^1 = R^2 = (CH_2)_3$, X = *p*-NO_2: 98% de = 22% ee = 87%

Scheme 59. L-Proline-derived diamine-catalysed aldol reactions in water.

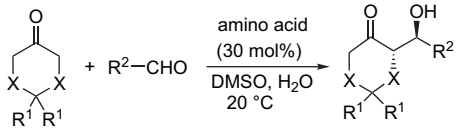
In addition, Wang et al. have developed aldol reactions of α,α-dialkyl aldehydes with aromatic aldehydes catalysed by a pyrrolidine sulfonamide, producing quaternary carbon-containing β-hydroxy carbonyl compounds with high enantioselectivities (Scheme 60).[132] More recently, high enantioselectivities (up to 99% ee) were also achieved by Amedjkouh and Diner by using chiral α-amino phosphonates such as (2*S*)-pyrrolidin-2-ylphosphonic acid, an analogue of D-proline, in the aldol reaction of various substituted cyclohexanones with benzaldehydes.[133] Several organic bases such as DBU, DBN and TMG were used together with the α-aminophosphonate in the reaction and were found to favour *syn*-selectivity.



$R^1 = R^2$ = Me, Ar = *p*-$O_2NC_6H_4$: 83% ee = 91%
$R^1 = R^2$ = Me, Ar = *p*-$F_3CC_6H_4$: 83% ee = 95%
$R^1 = R^2$ = Me, Ar = *p*-ClC_6H_4: 96% ee = 94%
$R^1 = R^2$ = Me, Ar = *p*-NCC_6H_4: 95% ee = 95%
$R^1 = R^2$ = Me, Ar = *p*-$MeO_2CC_6H_4$: 93% ee = 94%
$R^1 = R^2$ = Me, Ar = *p*-$OHCC_6H_4$: 97% ee = 97%
R^1 = Me, R^2 = Et, Ar = *p*-$O_2NC_6H_4$: 85% ee = 93%

Scheme 60. Aldol reactions of α,α-dialkyl aldehydes catalysed by a pyrrolidine sulfonamide.

3.1.2. Direct aldol reactions catalysed by non-proline derivatives. In 2005, Cordova et al. showed that linear amino acids and their derivatives were able to catalyse direct aldol reactions. In one example, the use of alanine, valine,[134] aspartate, isoleucine, alanine tetrazole and serine as catalysts of the aldol reaction furnished the corresponding β-hydroxy ketones in high yield and up to >99% ee (Scheme 61).[135] It was shown that the presence of water accelerated the reaction. On the other hand, tryptophan, a cyclic and natural amino acid bearing a primary amino function, was shown to catalyse aldol reactions between various cyclic ketones and aromatic aldehydes in water with high enantioselectivity (up to 96% ee).[136]

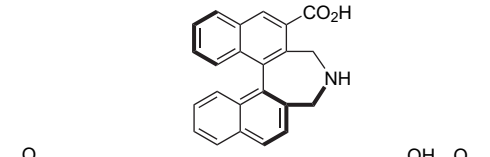


with L-alanine:
R^1 = H, R^2 = *p*-$O_2NC_6H_4$, X = CH_2: 95% de = 88% ee = 99%
R^1 = H, R^2 = *p*-ClC_6H_4, X = CH_2: 42% de = 90% ee > 99%
R^1 = Me, R^2 = *p*-NCC_6H_4, X = O: 75% de = 72% ee > 99%
R^1 = Me, R^2 = *p*-ClC_6H_4, X = O: 75% de = 66% ee = 98%
R^1 = Me, R^2 = CH_2OBn, X = O: 41% de > 90% ee = 99%
with L-valine:
R^1 = H, R^2 = *p*-ClC_6H_4, X = CH_2: 98% de = 94% ee > 99%
with L-isoleucine:
R^1 = H, R^2 = *p*-ClC_6H_4, X = CH_2: 82% de = 82% ee > 99%
with L-serine:
R^1 = H, R^2 = *p*-ClC_6H_4, X = CH_2: 80% de = 72% ee > 99%

Scheme 61. Linear amino acid-catalysed aldol reactions.

Most successful organic catalysts are derived from chiral natural products such as amino acids and, therefore, there are certain limitations on possible structural modifications, especially in the design of more efficient catalysts. In this regard, the preparation and use of a novel and artificial axially chiral amino acid with a binaphthyl backbone as catalyst opened up the possibility of developing structurally and electronically novel catalysts that gave good reactivities and high enantioselectivities (up to 95% ee) when applied

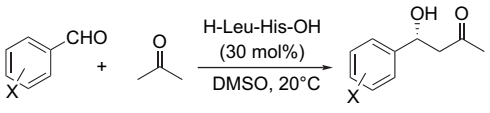
to the aldol reaction of acetone (Scheme 62).[137] In addition, Enders and Gries have described the synthesis of substituted azetidine-type α- and β-amino acids and screened their catalytic activities for the aldol reaction of acetone and *p*-nitrobenzaldehyde, showing good yields and moderate enantioselectivities (up to 59% ee), compared to proline.[138]



R = *p*-$O_2NC_6H_4$: 82% ee = 95% (*R*)
R = *p*-NCC_6H_4: 80% ee = 95% (*R*)
R = *o*-ClC_6H_4: 91% ee = 95% (*R*)
R = *o*-$TfOC_6H_4$: 81% ee = 94% (*R*)
R = CH=CH-CH=N-CH=CH-: 76% ee = 95% (*R*)
R = C(Cl)=CH-Ph: 73% ee = 90% (*R*)
R = C(Me)=CH-CO_2Et: 81% ee = 96% (*R*)

Scheme 62. Binaphthyl-based amino acid-catalysed aldol reactions.

Peptides offer many sites for functional and structural diversity that can be used to generate optimised catalysts and constitute an ideal compromise between small rigid organocatalysts and enzymes. Several di- and tripeptides have recently been applied to the catalysis of the aldol reaction. In 2005, Tsogoeva and Wei studied the structure–activity relationships for some (*S*)-histidine-based dipeptide catalysts in direct aldol reactions between acetone and aromatic aldehydes.[139] The reactivities and stereoselectivities were shown to be dependent upon the intramolecular cooperation of side-chain functional groups and the presence of a suitable combination and sequence of amino acids. Good yields and enantioselectivities were obtained with electron-deficient aromatic aldehydes in the presence of H-Leu–His-OH as catalyst (Scheme 63).

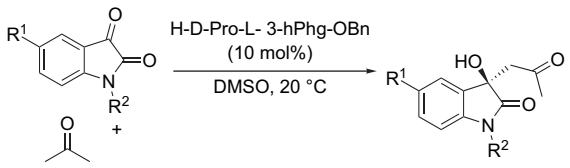


X = *p*-O_2N: 87% ee = 71%
X = *o*-O_2N: 62% ee = 72%
X = *o*-Cl: 96% ee = 76%
X = *p*-Br: 65% ee = 68%
X = *p*-Cl: 67% ee = 60%

Scheme 63. Aldol reactions catalysed by H-Leu–His-OH dipeptide.

The aldol condensation of acetone with isatin and *N*-alkylated isatins was developed by Tomasini et al., in 2005, by using dipeptides containing N-terminal proline residues as catalysts.[140] This reaction enabled the formation of a quaternary stereogenic centre with good enantioselectivity when the dipeptide H-D-Pro–L-β^3-hPhg-OBn was used as catalyst (Scheme 64).

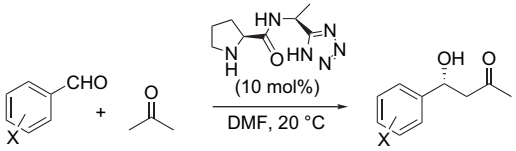
In 2006, a series of new N-terminal prolyl-dipeptide derivatives have been synthesised by Zhang et al. and evaluated as organocatalysts for the aldol reaction of acetone with



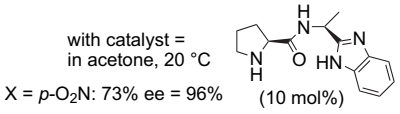
R^1 = H, R^2 = Me: 100% ee = 77%
R^1 = H, R^2 = Et: 92% ee = 74%
R^1 = H, R^2 = Bn: 90% ee = 74%
R^1 = Br, R^2 = H: 100% ee = 73%

Scheme 64. Aldol reactions of isatins catalysed by H-D-Pro–L-β^3-hPhg-OBn dipeptide.

electron-deficient aromatic aldehydes.[141] The corresponding aldol adducts were obtained with modest-to-excellent enantiomeric excesses of up to 96% (Scheme 65).



X = *p*-O_2N: 60% ee = 92%
X = *o*-O_2N: 69% ee = 82%
X = *p*-CN: 62% ee = 86%
X = *p*-Cl: 46% ee = 83%
X = *p*-Br: 49% ee = 84%



Scheme 65. Aldol reactions catalysed by N-terminal prolyl-dipeptide catalysts.

Other simple dipeptides, having a primary amino group at the N-terminus and based on the amino acids alanine and valine have been investigated by Cordova et al., furnishing the corresponding aldol products with up to 99% ee with a variety of ketones and aldehydes (Scheme 66).[142] This process could be successfully performed in water with excellent enantioselectivities (up to 86% ee).[143]

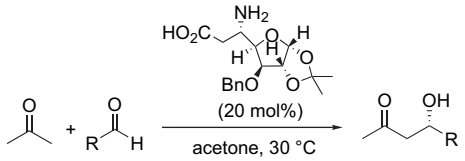
with catalyst = L-ala-L-ala:
R^1,R^2 = $(CH_2)_3$, R^3 = *p*-$O_2NC_6H_4$: 73% de = 78% ee = 91%
R^1,R^2 = $(CH_2)_3$, R^3 = *p*-BrC_6H_4: 86% de = 34% ee = 96%
R^1,R^2 = $(CH_2)_3$, R^3 = *p*-ClC_6H_4: 67% de = 34% ee = 98%
R^1,R^2 = OCH_2O, R^3 = *p*-$O_2NC_6H_4$: 70% de = 50% ee = 99%
R^1,R^2 = OCH_2O, R^3 = *p*-CNC_6H_4: 65% de = 86% ee = 99%
R^1,R^2 = OCH_2O, R^3 = *i*-Pr: 50% de = 34% ee = 97%
with catalyst = L-ala-L-phe:
R^1,R^2 = OCH_2O, R^3 = *p*-$O_2NC_6H_4$: 88% de = 66% ee = 99%
R^1,R^2 = $(CH_2)_3$, R^3 = *p*-BrC_6H_4: 88% de = 34% ee = 99%

Scheme 66. Dipeptide-catalysed aldol reactions.

On the other hand, tripeptides containing a secondary amine and a carboxylic acid in a specific relative orientation have been shown to be more efficient catalysts for aldol reactions than proline.[144] Therefore, the aldol reaction between

cyclohexylcarboxaldehyde and acetone gave the corresponding aldol product in 66% yield and 82% ee (*S*) in the presence of 1 mol % of H-L-Pro-L-Pro-L-Asp-NH_2. The enantioselectivity of the peptidic catalysts could be changed from (*R*) to (*S*) by simple modifications of the secondary structure and, therefore, the same reaction gave the corresponding (*R*)-product in 56% yield and 83% ee when performed in the presence of 10 mol % of H-L-Pro-D-Ala-D-Asp-NH_2. In addition, Davis and Andreae have reported the heterogeneous catalysis of the asymmetric aldol reaction by solid-supported proline-terminated peptides.[145] Peptides with prolyl N-termini, attached to a PEG–polystyrene (TG) synthesis resin, were shown to catalyse the aldol reaction between acetone and *p*-nitrobenzaldehyde. In particular, the dipeptide, H-Pro–Ser-NH-TG, in which proline is combined with serine, allowed the achievement of 82% ee.

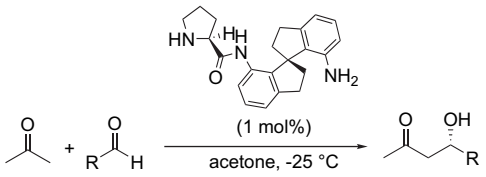
In 2006, the aldol reactions of acetone with aldehydes were performed by Tripathi et al., using glycosyl-β-amino acids as a new class of organocatalysts.[146] As depicted in Scheme 67, high enantioselectivities were obtained when a 5-amino-5-deoxy-β-L-*ido*-(α-D-*gluco*)-heptofuranuronic acid was employed as catalyst of the aldol reaction of acetone with different aldehydes.



R = *m*-$O_2NC_6H_4$: 65% ee = 90%
R = *o*-$O_2NC_6H_4$: 67% ee = 99%
R = *p*-$O_2NC_6H_4$: 60% ee = 86%
R = *p*-FC_6H_4: 57% ee = 76%
R = *p*-ClC_6H_4: 45% ee = 77%

Scheme 67. Glycosyl-β-amino acid-catalysed aldol reactions.

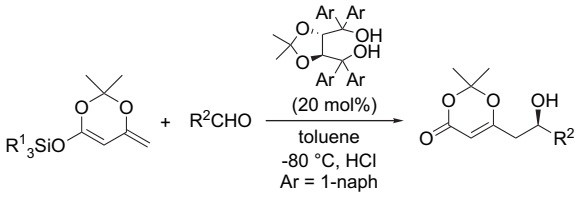
In 2006, Zhou et al. reported a new chiral source bearing a rigid spiro diamine, (*S*)-1,1′-spirobiindane-7,7′-diamine, to form a catalyst with L-proline for an aldol reaction between acetone and various aldehydes.[147] The use of this novel chiral spiro diamine bearing a C_2-symmetric backbone led to the formation of the aldol products in high yields and up to 76% ee (Scheme 68).



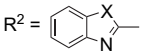
R = *p*-NCC_6H_4: 68% ee = 48%
R = *p*-$F_3CC_6H_4$: 68% ee = 46%
R = Cy: 56% ee = 76%
R = *i*-Pr: 50% ee = 73%

Scheme 68. Spiro diamine-catalysed aldol reactions.

3.1.3. Indirect aldol reactions. The vinylogous Mukaiyama aldol reaction has proved to be a powerful method for complex molecule synthesis, as it provides rapid access to polyketide derivatives. In 2005, Rawal et al. reported the successful use of 1-naphthyl-TADDOL as catalyst in the enantioselective vinylogous Mukaiyama aldol reaction of silyldienol ethers with a range of aldehydes, giving regiospecifically the addition products in good-to-excellent yields and ee values as high as 90% (Scheme 69).[148]



R1 = *n*-Bu, R2 = CO_2Et: 60% ee = 87%
R1 = *n*-Bu, R2 = CO_2*t*-Bu: 54% ee = 84%
R1 = *n*-Bu, R2 = CH=CH-CO_2Et: 66% ee = 71%
R1 = *n*-Bu, R2 = *o*-$O_2NC_6H_4$: 58% ee = 75%
R1 = *n*-Bu, R2 = F_5C_6: 57% ee = 67%
R1 = Me, R2 = CO_2Et: 82% ee = 81%



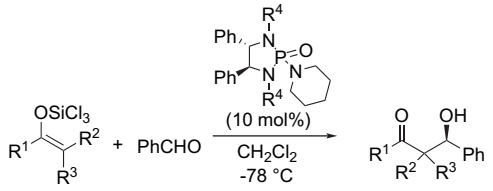
R1 = *n*-Bu, X = O: 55% ee = 83%
R1 = *n*-Bu, X = S: 73% ee = 90%

Scheme 69. TADDOL-catalysed vinylogous Mukaiyama aldol reactions.

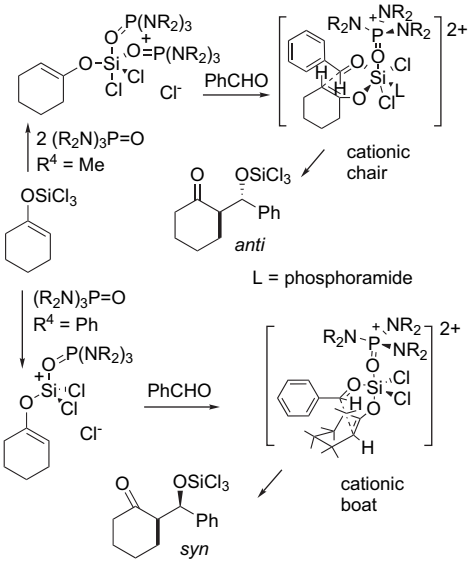
Trichlorosilyl enolates have been used as nucleophiles in the indirect aldol reaction. Such enolates are highly activated ketone derivatives and react spontaneously with aldehydes in the presence of organocatalysts such as chiral phosphoramides.[149] The mechanism of the reaction has been investigated and this has allowed the formulation of a unified mechanistic rationale to explain the origin of rate enhancements and mode of stereoselectivity for the phosphoramide-catalysed aldol additions of trichlorosilyl enolates to aldehydes (Scheme 70). Structure–activity–selectivity relationships were developed for a variety of phosphoramides, detailing the propensity for bulky phosphoramides to participate via a 1:1 phosphoramide/enolate pathway through boat-like transition structures centred around a five-coordinate cationic siliconate. Likewise, smaller phosphoramides are able to engage the trichlorosilyl enolate in a 2:1 manner, reacting through a six-coordinate, chair-like transition structure.

Chiral bis-sulfonamides, such as bis-nonaflamides of vicinal diamines were demonstrated to be promising catalysts for the enantioselective Mukaiyama aldol reaction of *p*-nitrobenzaldehyde with silyl ketene acetals (Scheme 71).[150] The scope of the reaction could be extended to heteroaromatic aldehydes, with both 2- and 4-pyridinecarboxaldehydes giving the aldol products in high yields and up to 56% ee.

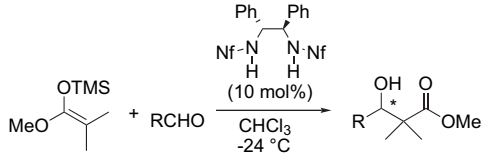
In 2005, chiral bipyridine bis-*N*-oxide catalysts were used to catalyse the additions of methyl trichlorosilyl ketene acetal to a wide range of ketones, yielding the corresponding β-*tert*-hydroxy esters in excellent yields with most substrates (Scheme 72).[151] Chiral 2,2′-bipyridyl bis-*N*-oxides bearing various substituents at the 3,3′- and 6,6′-positions also provided excellent yields of the aldol products with variable enantioselectivities ranging from 87% ee for aromatic ketones to near-racemic for aliphatic ketones.



$R^1 = R^2 = R^3 = H$, $R^4 = Me$: 88% ee = 84%
$R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Me$: 92% ee = 86%
$R^1,R^3 = (CH_2)_4$, $R^2 = H$, $R^4 = Me$: 94% *anti:syn* > 50:1 ee = 91%
$R^1,R^3 = (CH_2)_4$, $R^2 = H$, $R^4 = Ph$: 94% *syn:anti* = 97:1 ee = 91%

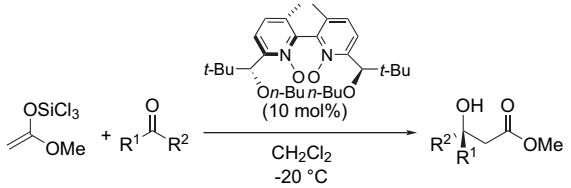


Scheme 70. Phosphoramide-catalysed aldol additions of ketone trichlorosilyl enolates.



R = p-$O_2NC_6H_4$: 90% ee = 43%
R = Ph: 41% ee = 30%
R = 2-py: 87% ee = 30%
R = 4-py: 85% ee = 56%

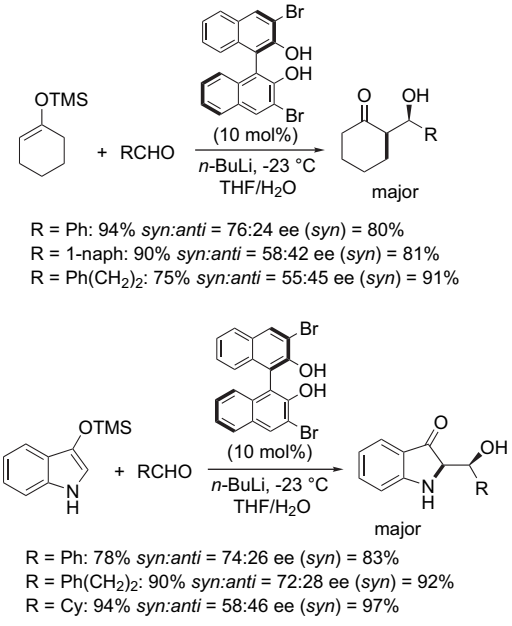
Scheme 71. Bis-nonaflamide-catalysed Mukaiyama aldol addition reactions of silyl ketene acetal.



R^1 = Ph, R^2 = Me: 91% ee = 87%
R^1 = Ph, R^2 = Et: 90% ee = 80%
R^1 = Ph, R^2 = CCH: 89% ee = 86%
R^1 = p-$F_3CC_6H_4$, R^2 = Me: 91% ee = 76%
R^1 = p-$MeOC_6H_4$, R^2 = Me: 94% ee = 68%
R^1 = *t*-Bu, R^2 = Me: 87% ee = 46%

Scheme 72. Bipyridine bis-*N*-oxide-catalysed aldol addition reactions of methyl trichlorosilyl ketene acetal to ketones.

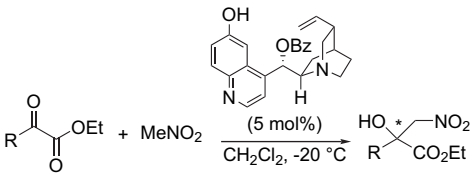
In 2006, the first example of an aldol reaction of trimethoxysilyl enol ethers catalysed by a chiral base such as lithium binaphtholate was reported by Nakajima et al.[152] The aldol reaction of the trimethoxysilyl enol ether derived from cyclohexanone under anhydrous conditions predominantly afforded the *anti*-aldol adduct with moderate enantioselectivity, whereas the reaction under aqueous conditions predominantly resulted in the *syn*-adduct and the enantioselectivity of the *syn*-adduct was considerably improved. The best enantioselectivity was obtained in the reaction of the trimethoxysilyl enol ether derived from 1-indanone with cyclohexanecarboxaldehyde (Scheme 73).



Scheme 73. Aldol reactions of trimethoxysilyl enol ethers catalysed by BINOL derivative.

3.1.4. Nitroaldol reactions. In addition to the classic aldol reaction, several modified versions have been reported. These methods are based on the use of nucleophiles related to the standard ketones. In particular, nitromethane is an interesting carbon nucleophile in aldol reactions and the use of this type of substrate has been investigated in aldol reactions catalysed by organocatalysts. The asymmetric catalytic nitroaldol reaction, also known as the asymmetric Henry reaction, is another example of an aldol-related synthesis of considerable general interest. In this reaction, nitromethane (or a related nitroalkane) reacts in the presence of a chiral catalyst with an aldehyde, forming the optically active β-nitro alcohols. The β-nitro alcohols are valuable intermediates in the synthesis of a broad variety of chiral building blocks such as β-amino alcohols. Actually, there are very few examples of catalytic asymmetric metal-free Henry reactions. In one example, cinchona alkaloids have been employed as bifunctional catalysts in the reaction of nitromethane with activated aromatic aldehydes, giving enantiomeric excesses of up to 92%.[153] The scope of the reaction was even more successfully extended, in 2006, to the nitroaldol addition of nitromethane to α-ketoesters (Scheme 74).[154]

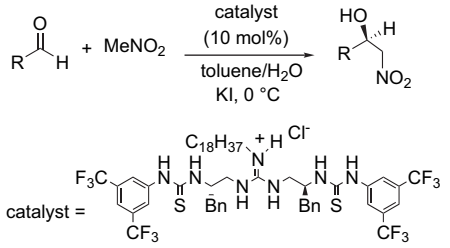
On the other hand, novel bifunctional catalysts having guanidine and thiourea functional groups were developed by



R = CH=CHMe: 92% ee = 96%
R = $CH=CHCH_2OBn$: 98% ee = 94%
R = Ph: 96% ee = 95%
R = *p*-ClC_6H_4: 98% ee = 97%
R = *p*-NCC_6H_4: 96% ee = 94%
R = *m*-ClC_6H_4: 91% ee = 95%
R = 2-naph: 96% ee = 94%
R = Me: 89% ee = 95%
R = *n*-Pr: 90% ee = 93%
R = $Ph(CH_2)_2$: 88% ee = 95%
R = $EtO_2C(CH_2)_3$: 87% ee = 94%

Scheme 74. Cinchona alkaloid-catalysed nitroaldol reactions.

Nagasawa et al.[155] Various structural developments of the catalyst revealed that the compound having an octadecyl-substituted guanidine and thiourea groups linked with a chiral spacer derived from phenylalanine efficiently promoted the Henry reaction. Therefore, high asymmetric inductions were obtained with aliphatic cyclic aldehydes and branched aliphatic aldehydes (Scheme 75). More recently, the scope of this process was extended to the use of various α-substituted aldehydes, providing diastereoselectively the corresponding Henry products with up to 98% de and up to 99% ee.[156]

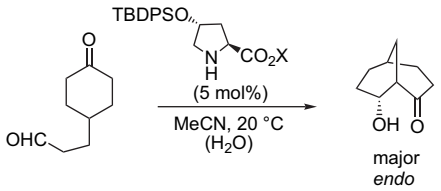


R = Cy: 91% ee = 92%
R = *c*-Pent: 76% ee = 82%
R = *t*-Bu: 85% ee = 88%
R = *i*-Pr: 88% ee = 83%
R = *i*-Pent: 70% ee = 88%

Scheme 75. Nitroaldol reactions catalysed by guanidine-thiourea catalyst.

3.1.5. Intramolecular aldol reactions. The asymmetric proline-catalysed intramolecular aldol cyclisation, also called the Hajos–Parrish–Eder–Sauer–Wiechert reaction, has been applied to several substrates since its discovery over 35 years ago.[2,157] A series of proline derivatives were recently studied as organocatalysts for the intramolecular aldolisation of σ-symmetric substrates by Iwabuchi et al.[158] A high enantioselectivity and a high catalytic efficiency have been exhibited by (4*R*,2*S*)-tetrabutylammonium 4-TBDPSoxy-prolinate in the aldolisation of 3-(4-oxocyclohexyl)propionaldehyde to give highly enantiomerically enriched (1*S*,5*R*,8*R*)-8-hydroxybicyclo[3.3.1]nonan-2-one (Scheme 76). This new methodology offered a new entry to chiral bicyclo[3.*n*.1]alkanones.

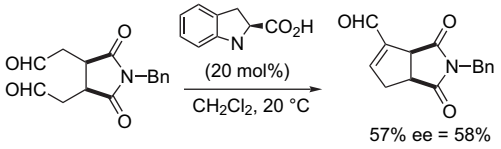
In 2005, Afonso and Kurteva reported an intramolecular asymmetric aldol cyclodehydration of *meso*-3,4-disubstituted-1,6-dialdehydes to the corresponding cyclopentene carbaldehydes by using chiral aromatic amino acids such



X = CO_2NBu_4: 77% de = 98% ee = 94%
X = H: 81% de = 99% ee = 95% (with 10 eq. H_2O)

Scheme 76. Intramolecular aldol reactions of σ-symmetric keto aldehyde.

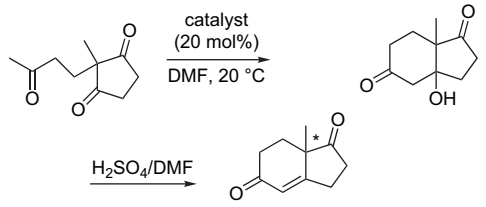
as (*S*)-(−)-2-indolinecarboxylic acid as organocatalysts (Scheme 77).[159]



57% ee = 58%

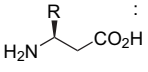
Scheme 77. Intramolecular aldol reaction of 1,6-dialdehyde.

Amino acids other than those derived from L-proline have received scant attention as organocatalysts for the intramolecular aldol reaction. As an example, Limbach demonstrated, in 2006, that β^3-homoamino acids catalysed the intramolecular aldol reaction of 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione, providing the corresponding cycloadduct with enantioselectivities similar to that of proline (Scheme 78).[160]



catalyst = L-proline: 85% ee = 76% (*S*)

catalyst =  : 99% ee = 58% (*R*)

catalyst = 

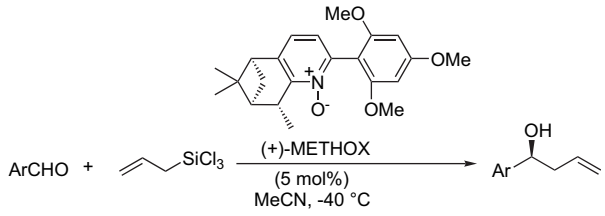
R = Bn: 64% ee = 75% (*R*)
R = Me: 49% ee = 78% (*R*)
R = *i*-Bu: 29% ee = 83% (*R*)
R = (*R*)-CH(Me)Et: 54% ee = 75% (*R*)

Scheme 78. β^3-Homoamino acid-intramolecular aldol reactions.

3.2. Allylation reactions

The enantioselective allylation of aldehydes is another C–C bond-forming reaction of wide interest. The resulting unsaturated alcohols are used as versatile intermediates in the construction of many interesting molecules. A broad variety of organocatalysts have been found to catalyse the enantioselective allylation of aldehydes with allyltrialkylsilanes,[161] such as optically active urea derivatives, phosphoramides, *P*-oxides, *N*-oxides and bis-sulfoxides. Amine *N*-oxides are good electron-pair donors, and this property has been exploited in organocatalytic reactions in a chiral environment. In particular, chiral pyridine *N*-oxide catalysts have been

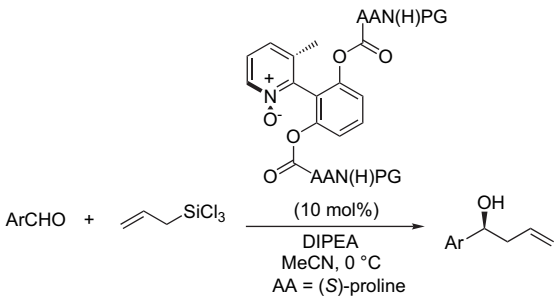
studied by several groups to promote the asymmetric allylation of aldehydes with allyltrichlorosilane. As an example, pyridyl *N*-oxide-substituted helically chiral poly(methacrylate)s were found to be active organocatalysts in the allylation of benzaldehyde with allyltrichlorosilane, although the enantiomeric excess observed in the product was rather low (19% ee).[162] On the other hand, high enantioselectivities were obtained by Malkov et al. by using a new terpene-derived pyridine *N*-oxide, METHOX, as an organocatalyst for similar reactions (Scheme 79).[163]



Ar = Ph: 95% ee = 96%
Ar = *p*-$F_3CC_6H_4$: 86% ee = 93%
Ar = *p*-$MeOC_6H_4$: 95% ee = 96%
Ar = *o*-$MeOC_6H_4$: 95% ee = 89%

Scheme 79. METHOX-catalysed allylations of aldehydes.

A series of more structurally simple pyridine *N*-oxides have been assembled from inexpensive amino acids and these were shown by Benaglia et al. to promote the allylation of aldehydes with satisfactory stereocontrol (Scheme 80).[164] In particular, the L-proline-based catalysts afforded the products derived from aromatic aldehydes in fair-to-good yields and in up to 84% ee, whereas the allylation of heteroaromatic, unsaturated and aliphatic aldehydes was less satisfactory.

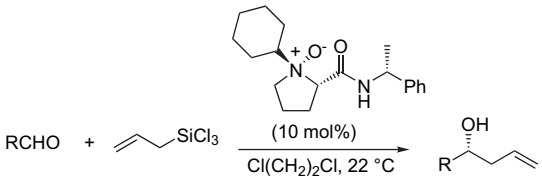


Ar = Ph, PG = Boc: 87% ee = 62%
Ar = *p*-Tol, PG = Cbz: 65% ee = 71%
Ar = *m*-$O_2NC_6H_4$, PG = Cbz: 60% ee = 84%
Ar = *p*-$O_2NC_6H_4$, PG = Boc: 60% ee = 76%
Ar = *p*-$O_2NC_6H_4$, PG = Cbz: 38% ee = 76%

Scheme 80. Allylations of aldehydes catalysed by pyridine *N*-oxide.

Similar reactions were developed by Hoveyda et al. on the basis of the use of a proline-based *N*-oxide as an effective catalyst, giving rise, under mild reaction conditions (22 °C), to the corresponding homoallylic alcohols in up to 92% ee (Scheme 81).[165] This chiral catalyst was easily prepared from L-proline in three simple steps and 60% overall yield. The scope of the reaction was extended to the use of α,β-unsaturated aldehydes.

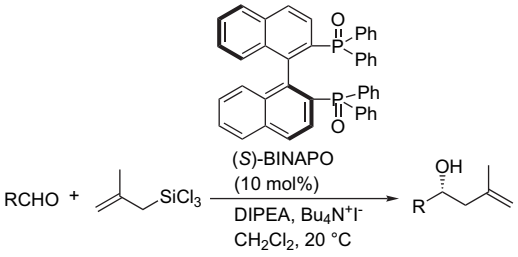
In 2005, Nakajima et al. showed the effectiveness of a chiral phosphine oxide, BINAPO, as a catalyst for similar



R = Ph: 82% ee = 87%
R = *m*-BrC_6H_4: 81% ee = 82%
R = *p*-ClC_6H_4: 74% ee = 85%
R = *p*-$MeOC_6H_4$: 81% ee = 88%
R = 1-naph: 89% ee = 79%
R = 2-naph: 89% ee = 83%
R = 3-Fu: 64% ee = 82%
R = CH=CH-Ph: 79% ee = 71%
R = C(Me)=CH-Ph: 62% ee = 76%

Scheme 81. Allylations of aldehydes catalysed by proline-based *N*-oxide.

reactions, in which a combination of diisopropylethylamine and tetrabutylammonium iodide as additives was crucial for accelerating the catalytic cycle (Scheme 82).[166]



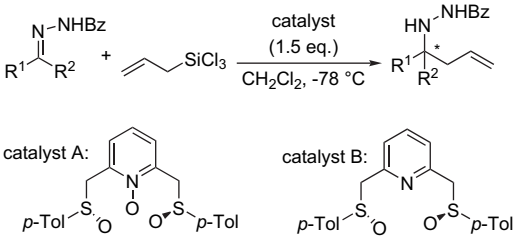
R = Ph: 73% ee = 66%
R = *p*-ClC_6H_4: 77% ee = 65%
R = 2-Fu: 53% ee = 63%
R = 2-naph: 75% ee = 62%
R = 3,5-$(Me)_2C_6H_3$: 70% ee = 79%
R = 3,5-$(F_3C)_2C_6H_3$: 65% ee = 56%
R = 3,4,5-$(MeO)_3C_6H_2$: 61% ee = 57%

Scheme 82. BINAPO-catalysed allylations of aldehydes.

In 2005, Oyama et al. developed polymeric catalysts having phosphoramide structures as the ring substituents of polystyrene for the Lewis base-catalysed asymmetric addition of allyltrichlorosilane to benzaldehyde.[167] The polymeric catalysts showed higher catalytic activity and enantioselectivity than the corresponding low-molecular-weight analogues. The polymer effect made the coordination of two (or more) chiral phosphoramides to the silicon atom favourable, and this would improve the enantioselectivity (up to 63% ee) and the yields (up to 84%) of the reactions. Unlike P(O) or N(O) Lewis bases, which are excellent catalysts, chiral sulfoxides have seldom been used, since synthetically useful yields were only observed when excess sulfoxide was used.[168] As an example, novel C_2-symmetric bis-sulfoxides were employed in 2006 by Juaristi et al. to promote the asymmetric allylation of *N*-benzoylhydrazones derived from aldehydes and ketones (Scheme 83).[169]

3.3. Morita–Baylis–Hillman reactions

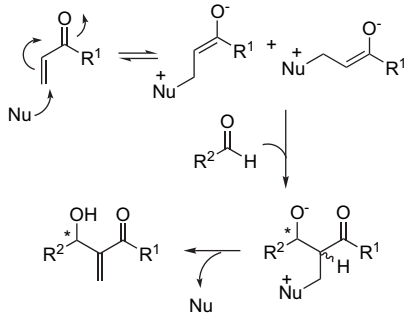
The Morita–Baylis–Hillman reaction is a powerful transformation in organic synthesis, consisting of the formation of



R^1 = Ph, R^2 = H, catalyst A: 89% *R*:*S* = 12:88
R^1 = Ph, R^2 = H, catalyst B: 73% *R*:*S* = 20:80
R^1 = *p*-$MeOC_6H_4$, R^2 = H, catalyst A: 80% *R*:*S* = 14:86
R^1 = *p*-$MeOC_6H_4$, R^2 = H, catalyst B: 72% *R*:*S* = 30:70
R^1 = *m*-$MeOC_6H_4$, R^2 = H, catalyst A: 93% *R*:*S* = 18:82
R^1 = *m*-$MeOC_6H_4$, R^2 = H, catalyst B: 68% *R*:*S* = 30:70
R^1 = Ph, R^2 = Me, catalyst A: 82% *R*:*S* = 20:80
R^1 = Ph, R^2 = Me, catalyst B: 30% *R*:*S* = 87:13
R^1 = 2-Fu, R^2 = H, catalyst A: 84% *R*:*S* = 16:84
R^1 = 2-Fu, R^2 = H, catalyst B: 54% *R*:*S* = 45:55

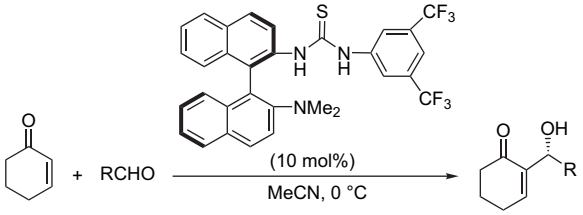
Scheme 83. C_2-Symmetric bis-sulfoxide-catalysed allylations of *N*-benzoylhydrazones.

α-methylene-β-hydroxy carbonyl compounds by the addition of aldehydes to α,β-unsaturated carbonyl compounds such as vinyl ketones, acrylonitriles or acrylic esters.[170] For the reaction to occur, the presence of catalytically active nucleophiles is required. The reaction is initiated by the addition of the catalytically active nucleophile to the enone. The resulting enolate adds to the aldehyde, establishing the new stereogenic centre by proton transfer from the α-position of the carbonyl moiety to the alcoholate oxygen atom, with concomitant elimination of the nucleophile, which is available for the next catalytic cycle (Scheme 84).



Scheme 84. Morita–Baylis–Hillman reaction.

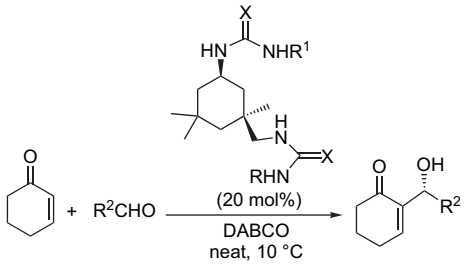
A considerable amount of effort has been devoted to the development of catalytic, enantioselective versions of the processes. Discovering catalytic systems for asymmetric Morita–Baylis–Hillman reactions has proved to be a synthetic challenge and, to date, few successful chiral organocatalysts such as chiral nucleophilic amines or phosphines have been demonstrated for this process. Among these, a new bifunctional binaphthyl-derived amine thiourea organocatalyst was shown to promote the Morita–Baylis–Hillman reaction of cyclohexenone with a wide range of aldehydes.[171] The process, catalysed by the amine thiourea, afforded synthetically valuable chiral allylic alcohol building blocks in high yields and high enantioselectivities (Scheme 85).



R = $BnCH_2$: 80% ee = 83%
R = *i*-Bu: 72% ee = 80%
R = *i*-Pr: 63% ee = 94%
R = *c*-Pent: 71% ee = 90%
R = Cy: 67% ee = 92%
R = *n*-Hept: 74% ee = 82%
R = *n*-Hex: 71% ee = 80%
R = *n*-Pent: 75% ee = 81%
R = *o*-ClC_6H_4: 55% ee = 60%

Scheme 85. Binaphthyl-derived amine thiourea-catalysed Morita–Baylis–Hillman reactions.

In 2006, Berkessel et al. reported the synthesis of very active bis(thio)urea catalysts prepared in one step from the readily available chiral 1,4-diamine, isophoronediamine (IPDA).[172] These catalysts were further successfully applied to the Morita–Baylis–Hillman reactions of enones and acrylates with aldehydes, providing the best results in the reaction of cyclohexenone with cyclohexanecarbaldehyde (Scheme 86).

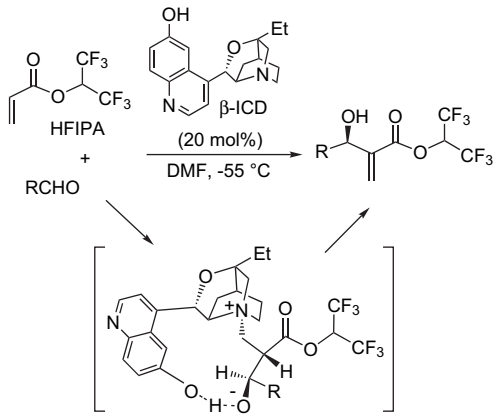


R^1 = 3,5-$(F_3C)_2C_6H_3$, R^2 = Cy, X = S: 75% ee = 96%
R^1 = 3,5-$(F_3C)_2C_6H_3$, R^2 = Ph, X = S: 100% ee = 60%
R^1 = Ph, R^2 = Cy, X = O: 65% ee = 77%
R^1 = Ph, R^2 = *i*-Pr, X = O: 62% ee = 90%
R^1 = 3,5-$(F_3C)_2C_6H_3$, R^2 = $BnCH_2$, X = S: 52% ee = 69%

Scheme 86. IPDA-derived bis(thio)urea-catalysed Morita–Baylis–Hillman reactions.

Asymmetric Morita–Baylis–Hillman reactions of aldehydes with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) have been performed by Hatakeyama et al., using β-isocupreidine (β-ICD) as a chiral Lewis base catalyst.[173] This process had remarkable advantages in terms of high enantioselectivity, broad applicability and availability of both β-ICD and HFIPA. The authors speculated that hydrogen bonding between the oxy anion and the phenolic OH should play a crucial role during the enantio-controlling event, as depicted in Scheme 87.

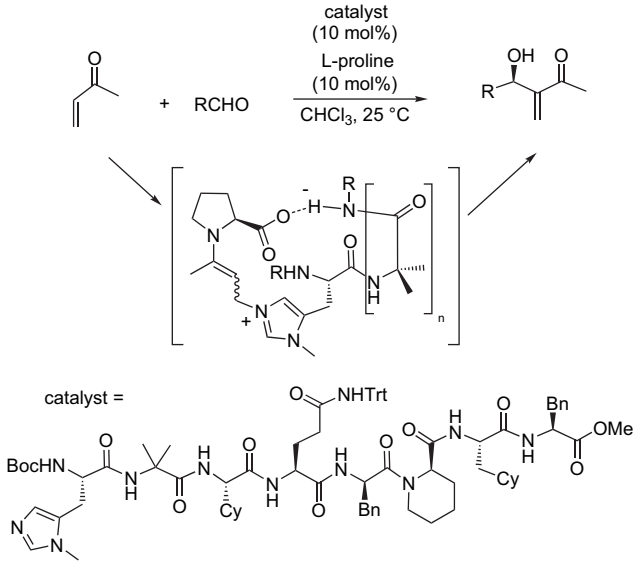
In 2006, Miller et al. reported a novel catalyst system involving a peptide-based catalyst in the presence of proline as co-catalyst.[174] This co-catalyst combination was applied to the Morita–Baylis–Hillman reaction of methyl vinyl ketone with a variety of aromatic aldehydes, affording enantioselectivities in up to 81% ee. The stereoselectivity of the reaction was correlated with a specific peptide–proline co-catalyst



R = p-$O_2NC_6H_4$: 58% ee = 91%
R = Ph: 75% ee = 97%
R = (*E*)-PhCH=CH: 64% ee = 94%
R = p-$MeOC_6H_4$: 27% ee = 95%
R = 1-naph: 23% ee = 97%
R = 2-naph: 82% ee = 97%
R = $BnCH_2$: 38% ee = 98%
R = Cy: 36% ee = 99%
R = *t*-Bu: 0%

Scheme 87. β-ICD-catalysed Morita–Baylis–Hillman reactions of HFIPA with aldehydes.

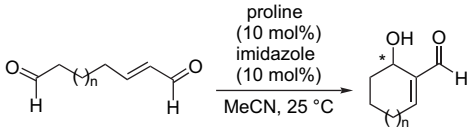
interaction, shown in the possible cohesive transition state assembly depicted in Scheme 88. This transition state could be stabilised by hydrogen bonding of the peptide backbone with the carboxylic acid of proline.



R = o-$O_2NC_6H_4$: 81% ee = 78%
R = p-$O_2NC_6H_4$: 81% ee = 69%
R = o-$F_3CC_6H_4$: 52% ee = 71%
R = 1-Fu: 95% ee = 63%
R = 1,3-$(O_2N)_2C_6H_3$: 89% ee = 63%
R = 1,3-$(O_2N)(MeO)C_6H_3$: 88% ee = 81%
R = o-FC_6H_4: 55% ee = 65%
R = Ph: 55% ee = 41%

Scheme 88. Proline–peptide-catalysed Morita–Baylis–Hillman reactions.

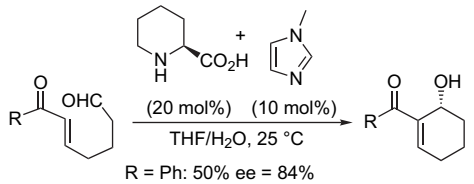
A class of Morita–Baylis–Hillman reactions, where enantioselective catalysis has been nearly unexplored, is the intramolecular version. As an example, Hong et al. reported, in 2005, the proline-catalysed intramolecular Morita–Baylis–Hillman reaction of hept-2-enedial (Scheme 89).[175] The best result was obtained in the presence of imidazole as an additive, which resulted, surprisingly, in an unusual inversion of selectivity.



with L-proline: 73% ee = 80% (*R*)
with D-proline: 74% ee = 98% (*S*)

Scheme 89. Proline-catalysed intramolecular Morita–Baylis–Hillman reactions.

In 2005, Miller et al. reported another example of an intramolecular Morita–Baylis–Hillman reaction achieved with unprecedented levels of enantioselectivity.[176] Using a co-catalyst system involving pipecolinic acid and *N*-methylimidazole, cyclic Morita–Baylis–Hillman products were obtained with up to 84% ee (Scheme 90). In addition, the reactions could be carried out with a kinetic resolution quench, involving acetic anhydride and an asymmetric acylation peptide catalyst such that ee enhancement occurred to deliver the products with >98% ee.



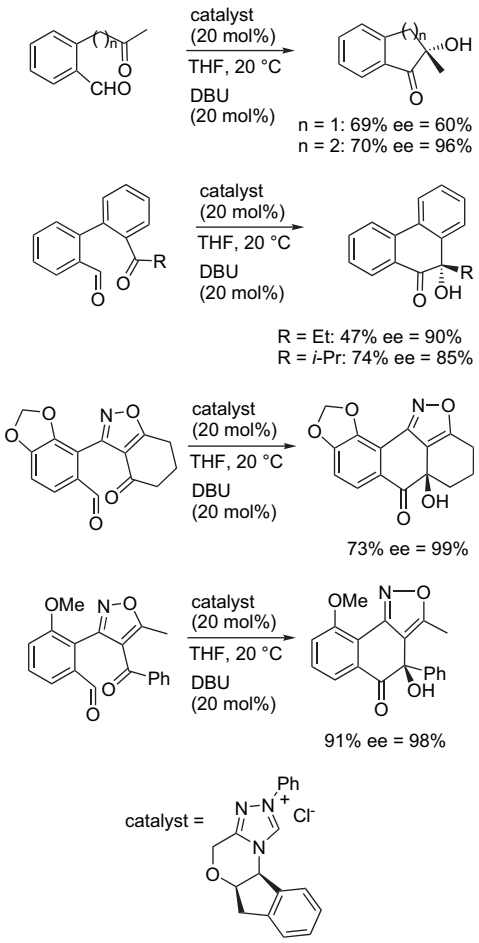
R = Ph: 50% ee = 84%
R = p-ClC_6H_4: 92% ee = 79%
R = p-BrC_6H_4: 88% ee = 79%
R = o-Tol: 94% ee = 51%
R = 1-thienyl: 83% ee = 74%

Scheme 90. Co-catalysed intramolecular Morita–Baylis–Hillman reactions.

3.4. Miscellaneous reactions

The benzoin condensation is a nucleophilic acylation of great synthetic utility, involving the addition of an acyl anion equivalent to an aldehyde, resulting in the formation of a 2-hydroxyketone.[177] Heteroazolium salts in the presence of a base are the most frequently used catalysts for the umpolung of an aldehyde for an asymmetric addition to another aldehyde or an imine. In 2006, Suzuki et al. reported an intramolecular aldehyde–ketone benzoin reaction catalysed by a chiral aminoindanol-derived triazolium salt.[178] This exceptional organocatalyst allowed up to 99% ee to be obtained for the enantioselective aldehyde–ketone benzoin cyclisation of a wide variety of substrates (Scheme 91). Despite the exceptionally long history of the benzoin reaction in the toolbox of organic methodology, it has found only limited use in the synthesis of complex molecules. This new methodology could, however, be applied to the asymmetric synthesis of 4-chromanones, key structural motifs in natural products such as (−)-eucomol. At the same time, Enders et al. reported the asymmetric synthesis of other

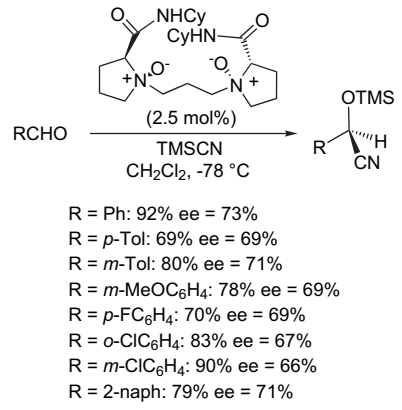
α-hydroxy-α-alkyl tetralones with up to 98% ee through similar intramolecular aldehyde–ketone benzoin cyclisations catalysed by another tetracyclic triazolium salt in the presence of KO*t*-Bu as a base.[179]



Scheme 91. Intramolecular benzoin reactions catalysed by triazolium salt.

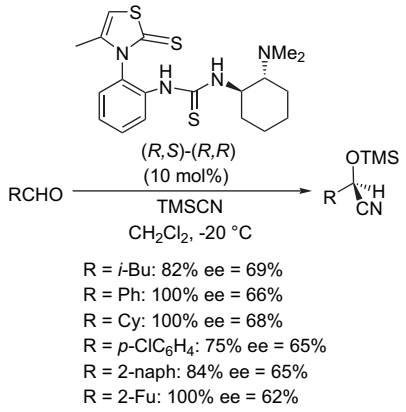
The asymmetric cyanation of aldehydes is an important and well-documented reaction, due to the fact that the product cyanohydrins are important intermediates for the synthesis of α-hydroxy acids, α-amino acids and β-amino alcohols. Hydrocyanation is actually one of the first examples of asymmetric organocatalysis in general. As early as 1912, Bredig reported that the addition of HCN to benzaldehyde was accelerated by the alkaloids, quinine and quinidine, and that the resulting cyanohydrins were optically active.[180] There are, however, very few examples of organocatalysed cyanide addition to aldehydes. As an example, a novel proline-based *N*,*N*′-dioxide was used, in 2005, as an effective catalyst for the enantioselective cyanosilylation of aldehydes in up to 73% ee (Scheme 92).[181] Attractive features of the method included the ease of catalyst preparation and the low catalyst loading (2.5 mol %).

Similar reactions were reported in 2006 by Roussel et al. by using a diastereomeric mixture of atropisomeric thioureas, giving, in the presence of a range of aldehydes, quantitative yields and moderate enantioselectivities (up to 69% ee).[182] Surprisingly, the best results were achieved using a



Scheme 92. Proline-based *N*,*N*′-dioxide-catalysed cyanosilylations of aldehydes.

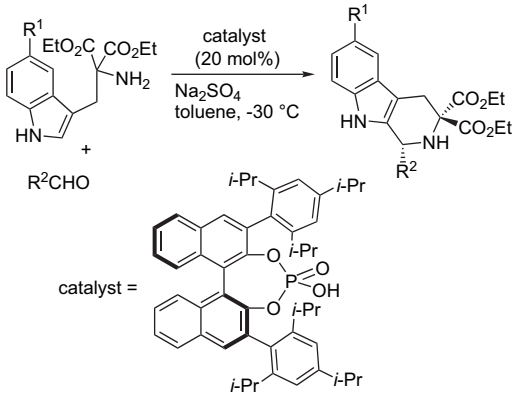
diastereomeric mixture of the (*R*,*R*)-thiourea instead of one or other of the single diastereomers (Scheme 93).



Scheme 93. Cyanosilylations of aldehydes catalysed by an (*R*,*S*)-(*R*,*R*)-thiourea catalyst.

The Pictet–Spengler reaction is an important acid-catalysed transformation frequently used in organic synthesis, as well as by various organisms for the synthesis of tetrahydro-β-carbolines or tetrahydroisoquinolines from carbonyl compounds and phenyl ethylamines or tryptamines, respectively.[183] In 2006, List et al. reported an elegant organocatalytic Pictet–Spengler reaction of both aromatic and aliphatic aldehydes with tryptamines, furnishing the corresponding chiral tetrahydro-β-carbolines in the presence of a chiral phosphoric acid catalyst (Scheme 94).[184]

The Darzens reaction is the base-promoted generation of epoxides from aldehydes (or ketones) and alkyl halides, the latter carrying an electron-withdrawing group in the α-position. The mechanism of this reaction involves deprotonation of the C–H acidic halide to form an enolate anion, which adds to the aldehyde, affording the anion of a β-halohydrin, which ring closes to the product epoxide. Most of catalytic enantioselective versions of the Darzens condensation are based on the use of chiral phase-transfer agents such as chiral ammonium salts. Different azacrown ethers derived from sugars have, however, been proposed as an alternative, but in neither case was the enantiomeric excess higher than 74%.[185]



R^1 = OMe, R^2 = Et: 96% ee = 90%
R^1 = OMe, R^2 = *n*-Pr: 98% ee = 88%
R^1 = OMe, R^2 = *n*-Bu: 90% ee = 87%
R^1 = H, R^2 = *n*-Bu: 91% ee = 87%
R^1 = OMe, R^2 = Cy: 64% ee = 94%
R^1 = OMe, R^2 = *p*-$O_2NC_6H_4$: 98% ee = 96%
R^1 = OMe, R^2 = *p*-NCC_6H_4: 60% ee = 80%

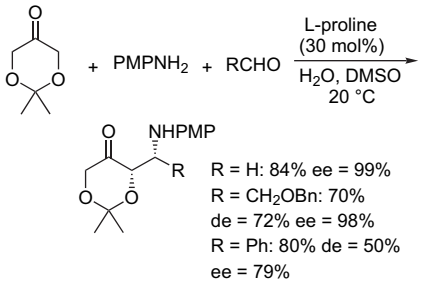
Scheme 94. Pictet–Spengler reactions catalysed by phosphoric acid catalyst.

4. Nucleophilic additions to C=N double bonds

Chiral α-branched amines are common substructures within biologically active materials and hence attract broad interest, particularly in the areas of synthetic methodology, bioorganic and medicinal chemistry and natural product synthesis. Additions of carbon fragments to C=N bonds of imines and related compounds build up the carbon framework in the same operation as asymmetric induction, so this approach is one of the more attractive entries to chiral amines.[186]

4.1. Mannich reactions

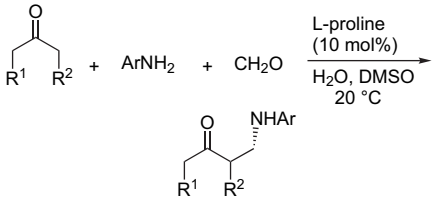
The Mannich reaction, a widely applied means of producing β-amino carbonyl compounds starting from cheap and readily available substrates, involves an aldehyde, an amine and a ketone reacting in a three-component, one-pot synthesis.[187] As an alternative, the reaction can be performed as a nucleophilic addition of a *C*-nucleophile to a preformed imine, which is prepared starting from the aldehyde and an amine source. The Mannich reaction tolerates a wide range of acceptors, donors and amine reagents, and can be carried out in a large variety of polar solvents. Organocatalytic Mannich reactions can be carried out either as three-component, one-pot reactions or as reactions of preformed imines with aldol donors. Among a wide variety of organocatalysts that have been used in the asymmetric Mannich reaction, the most widely used is proline. As an example, in 2005, Westermann and Neuhaus developed L-proline-catalysed Mannich reactions of dihydroxyacetone acetonide to aldimines in order to gain access to unusual aminosugars with very good stereoselectivities (up to 99% ee).[188] Moreover, Enders et al. have found that derivatives of L-proline such as *trans*-*O*-TBS-protected β-hydroxyproline could be effective catalysts for these reactions, allowing similar diastereo- and enantioselectivities to those of L-proline (up to 98% de and 96% ee).[189] The three-component versions of these reactions were successfully performed by Cordova et al. in the presence of *p*-anisidine as a precursor of the in situ-generated imines (Scheme 95).[67,100c]



R = H: 84% ee = 99%
R = CH_2OBn: 70%
de = 72% ee = 98%
R = Ph: 80% de = 50%
ee = 79%

Scheme 95. Direct L-proline-catalysed Mannich reactions of dihydroxyacetone acetonide.

In 2006, the scope of this methodology was extended to the use of various ketones in the presence of aqueous formaldehyde and aromatic amines, furnishing the desired Mannich bases in high yields with up to 99% ee (Scheme 96).[190] Moreover, methyl alkyl ketones were regioselectively α-aminomethylated at the methylene carbon, affording the corresponding Mannich products with up to 99% ee, whereas α-ethyl glyoxylate reacted under the same conditions to give the corresponding amino acid derivative in 77% yield, 88% de and >99% ee.[67]

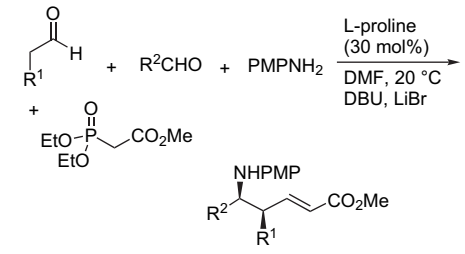


Ar = *p*-$MeOC_6H_4$, R^1,R^2 = $(CH_2)_3$: 90% ee > 99%
Ar = *p*-$MeOC_6H_4$, R^1,R^2 = $OC(Me)_2O$: 84% ee > 99%
Ar = *p*-$MeOC_6H_4$, R^1,R^2 = $CH_2CH(Me)CH_2$: 85% ee > 99%
Ar = *p*-$MeOC_6H_4$, R^1 = Me, R^2 = $(CH_2)_2CH{=}CH_2$: 94%
de = 60% ee = 84%
Ar = *p*-$MeOC_6H_4$, R^1 = Me, R^2 = *n*-Oct: 72%
de = 72% ee > 99%
Ar = *p*-BrC_6H_4, R^1,R^2 = $(CH_2)_3$: 71% ee > 99%
Ar = Ph, R^1,R^2 = $(CH_2)_3$: 92% ee > 99%

Scheme 96. Direct L-proline-catalysed Mannich reactions of ketones.

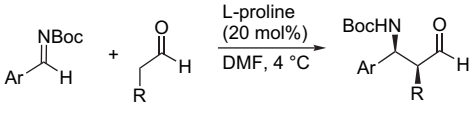
The development of Mannich reactions between two different unmodified aldehydes provided a significant advance in the synthetic methodology. The use of an aldehyde as the Mannich donor and another aldehyde as the Mannich acceptor, however, has associated problems such as finding the right reaction conditions which favour the Mannich reaction and equilibrium rather than the side pathways such as cross-aldol, self-aldol, self-Mannich and enamine formation. In 2005, the direct L-proline-catalysed asymmetric syntheses of α-oxy-β-amino aldehydes were reported by Cordova et al. on the basis of a direct Mannich reaction occurring with excellent enantioselectivities between unmodified α-oxyaldehydes and anilines.[191] In 2006, the same authors elaborated an elegant domino Mannich Wittig olefination reaction on the basis of the preceding methodology.[192]

A subsequent diastereoselective dihydroxylation of the thus-formed products allowed the corresponding amino- and iminosugar derivatives to be stereoselectively obtained in two steps (Scheme 97).



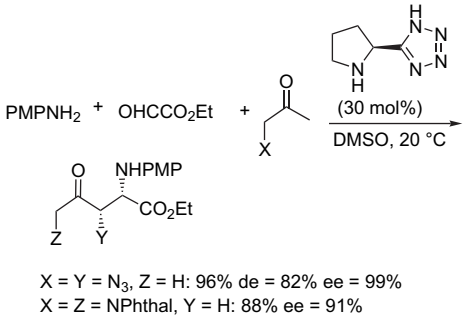
Scheme 97. L-Proline-catalysed domino Mannich Wittig olefination reactions.

In 2006, Bolm and Rodriguez studied thermal effects on the L-proline-catalysed Mannich reactions between cyclohexanone, formaldehyde and various anilines.[193] These authors have shown that, with only 0.5 mol % of catalyst, the corresponding Mannich products were obtained in high yields (up to 96%) with up to 98% ee after a short period of time in reactions performed under microwave irradiation at 65 °C. On the other hand, an intense study of organocatalytic indirect Mannich reactions such as the highly enantioselective additions of unmodified aldehydes to *N*-Boc-protected imines reported in 2007 by Cordova et al. is underway.[194] These reactions proceeded with excellent chemo- and enantioselectivities combined with high yields, as depicted in Scheme 98. Similarly, Fustero et al. have developed a highly enantioselective synthesis of acyclic γ-fluorinated β-amino alcohols through L-proline-catalysed Mannich reactions between fluorinated aldimines and aliphatic aldehydes, followed by reduction of the crude mixture with sodium borohydride.[195] Although the reaction yields were only moderate (up to 50%), the ease of this methodology made it the procedure of choice for the preparation of chiral fluorinated α-alkyl β-amino acid derivatives with excellent diastereoselectivities (up to 99% de) and enantioselectivities (up to 99% ee).



Scheme 98. L-Proline-catalysed Mannich reactions of aldehydes with *N*-Boc-protected imines.

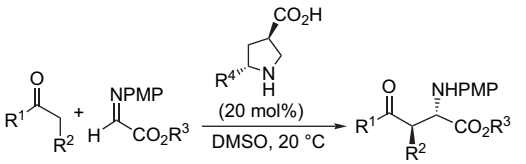
One of the drawbacks of using proline as the catalyst is the limited choice of solvent, since only polar solvents such as DMSO or DMF can be used. In this context, several derivatives of proline have been screened to catalyse the Mannich reaction. Among the catalysts tested, an L-imidazolidine-tetrazole catalyst was found by Ley et al. to catalyse the Mannich reaction of cyclohexanone and *N*-PMP-protected α-imino ethyl glyoxalate with high enantioselectivity and high yield.[41] This catalyst was compatible with organic solvents such as CH_2Cl_2 and THF and required low catalyst loadings (1 mol %), without affecting the enantioselectivity (up to 99% ee). In 2006, Barbas et al. reported a regioselective synthesis of chiral 1,2- or 1,4-diamine through a Mannich reaction pathway using the same catalyst.[196] Protected α-phthalimido ketones furnished 1,4-diamines through selective enamine formation via catalysis with the L-proline-derived tetrazole, whereas α-azido ketones produced the complementary regioisomer (Scheme 99).



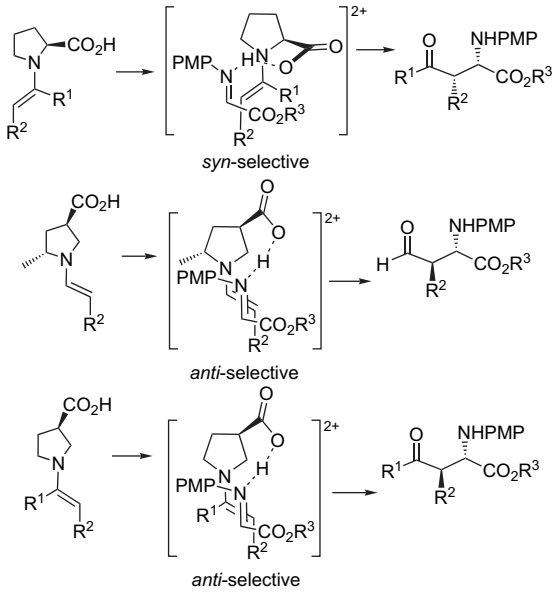
Scheme 99. L-Imidazolidine-tetrazole-catalysed Mannich reactions of protected amino ketones with imines.

In contrast to L-proline, which provided *syn*-adducts, the closely related catalyst, (3*R*,5*R*)-5-methyl-3-pyrrolidine-carboxylic acid, depicted in Scheme 100, was reported by Barbas et al. to produce the *anti*-Mannich products selectively.[197] With the carboxylic acid in the pyrrolidine 3-position and the methyl steric directing group at the 5-position, the control of the enamine C–N rotamer in the transition state was proposed to have a dihedral angle 180° from that the corresponding transition state with proline, thus reversing the stereocontrol. The use of several alkyl aldehydes with *N*-PMP-protected α-imino esters produced diastereomeric ratios of 94:6 and higher. An analogous reaction with ketones was much slower, and this was corrected by simply dispensing with the extra methyl substituent, to arrive at a catalyst without the methyl group at the 5-position.[198] Only the C–N rotamer shown was hypothesised to be capable of forming the required hydrogen bond with the 3-carboxylate. In the context of this scenario, ketones gave enhanced reactivity using this catalyst, while maintaining excellent *anti*-selectivity and control of absolute configuration. In 2007, several primary amine-containing amino acids, derived from L-threonine or L-tryptophan, were successfully employed by the same group to catalyse the three-component *anti*-Mannich reaction between unmodified α-hydroxyketones, $PMPNH_2$ and various aldehydes.[199] This new process constituted a simple and efficient route to highly enantiomerically enriched *anti*-1,2-amino alcohols (up to 98% ee).

Another *anti*-selective Mannich reaction was achieved by Cordova and Ibrahem with the use of TMS-protected

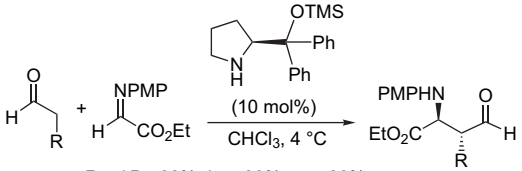


R^1 = H, R^2 = *i*-Pr, R^3 = Et, R^4 = Me: 85% de = 96% ee = 99%
R^1 = H, R^2 = *n*-Bu, R^3 = Et, R^4 = Me: 71% de = 94% ee = 99%
R^1 = H, R^2 = *n*-Pent, R^3 = Et, R^4 = Me: 80% de = 94% ee > 99%
R^1 = H, R^2 = R^3 = *i*-Pr, R^4 = Me: 92% de = 94% ee = 98%
R^1 = H, R^2 = *n*-Pent, R^3 = *i*-Pr, R^4 = Me: 85% de = 92% ee > 99%
R^1 = R^3 = Et, R^2 = Me, R^4 = H: 91% de = 94% ee = 97%
R^1 = Et, R^2 = Me, R^3 = *t*-Bu, R^4 = H: 93% de > 98% ee = 95%
R^1 = R^2 = Me, R^3 = Et, R^4 = H: 81% de > 99% ee = 99%
R^1 = Me, R^2 = allyl, R^3 = Et, R^4 = H: 85% de > 90% ee = 91%
R^1,R^2 = $(CH_2)_4$, R^3 = allyl, R^4 = H: 95% de > 98% ee = 95%
R^1,R^2 = $(CH_2)_4$, R^3 = *t*-Bu, R^4 = H: 92% de > 98% ee = 95%



Scheme 100. *anti*-Mannich reactions catalysed by 3-pyrrolidinecarboxylic acids.

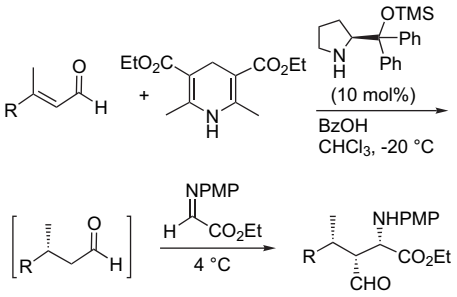
diphenylprolinol as catalyst, which lacks the H-bond donor functionality of proline.[200] A range of substituted aldehydes were tested with *N*-PMP-protected α-imino esters, producing high diastereoselectivities (up to 90% de) with moderate yields and outstanding enantiocontrol (Scheme 101). Similar reactions were successfully performed in MeCN by Jorgensen et al. by using a closely related catalyst, (*S*)-2-[bis-(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]-pyrrolidine, giving rise to the corresponding *anti*-Mannich products with up to 84% de and 98% ee.[201]



R = *i*-Pr: 68% de > 90% ee = 98%
R = *n*-Pent: 63% de > 90% ee = 99%
R = Me: 75% de = 88% ee = 99%
R = Bn: 67% de = 90% ee = 99%

Scheme 101. *anti*-Mannich reactions catalysed by TMS-protected diphenylprolinol.

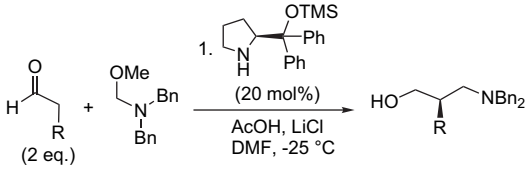
The catalyst depicted in Scheme 102 was also applied to the catalysis of a domino reductive Mannich reaction that allowed for the formation of three contiguous stereocentres with high chemo-, diastereo- and enantioselectivity in one step (Scheme 102).[202]



R = Ph: 69% de = 88% ee = 99%
R = *p*-Tol: 54% de > 82% ee = 96%
R = *p*-BrC_6H_4: 58% de = 82% ee > 95%
R = 2-naph: 70% de = 96% ee = 97%

Scheme 102. Domino reductive Mannich reactions catalysed by TMS-protected diphenylprolinol.

In addition, TMS-protected diphenylprolinol was used as a catalyst in Mannich reactions involving a formaldehyde-derived iminium species in situ.[203] These aminomethylations of aldehydes provided chiral β-amino aldehydes, which were immediately reduced to the corresponding β-substituted γ-amino alcohols to avoid epimerisation (Scheme 103). This process constituted a new and efficient access to β^2-amino acids.



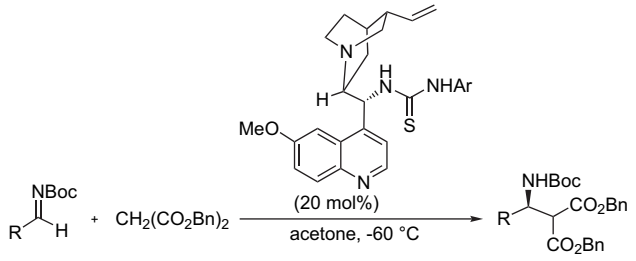
R = Et: 84% ee = 90%
R = *n*-Pr: 87% ee = 92%
R = *i*-Pr: 86% ee = 91%
R = *n*-Bn: 81% ee = 92%
R = CH_2CO_2Me: 65% ee = 90%

Scheme 103. Aminomethylations of aldehydes catalysed by TMS-protected diphenylprolinol.

A series of amino acids other than proline have been studied by Cordova et al. to catalyse three-component Mannich reactions.[204] Simple acyclic chiral amino acids such as alanine tetrazole, alanine, valine and serine successfully promoted the Mannich reactions between unmodified ketones, *p*-anisidine and aldehydes with high chemo- and stereoselectivity, furnishing the corresponding Mannich bases with up to 99% ee. This study demonstrated that the whole range of amino acids in nature, as well as non-proteogenic amino acid derivatives, could be considered in the design and tuning of novel, inexpensive organocatalysts for the direct asymmetric Mannich reaction.

Cinchona alkaloids and their thiourea conjugates have been introduced as organocatalysts for the Mannich reaction by

several groups.[205] Schaus et al. have developed highly stereoselective Mannich reactions of 1,3-dicarbonyl compounds with acyl imines catalysed by cinchona alkaloids such as cinchonine and cinchonidine.[205a,b] In particular, cyclic 1,3-dicarbonyl compounds afforded α-quaternary carbon-bearing reaction products in yields of up to 98%, diastereomeric excesses of ≥90% and enantioselectivities of up to 99% ee. In 2006, Deng et al. demonstrated that a quinidine-derived bifunctional catalyst, depicted in Scheme 104, delivered malonates to *N*-Boc-protected aromatic imines with outstanding stereocontrol.[205c] Aliphatic imines gave lower yields, whereas the enantioselectivity remained quite high. A further decarboxylation of the Mannich products furnished the corresponding *N*-Boc-protected β-amino acids. A similar methodology was successfully applied by Dixon et al. to the Mannich reactions of *N*-Cbz aldimines with a range of malonate esters.[205d]



R = Ph: 99% ee = 96%
R = *o*-Tol: 98% ee = 99%
R = *m*-Tol: 99% ee = 98%
R = *p*-Tol: 92% ee = 97%
R = *p*-FC_6H_4: 99% ee = 99%
R = *p*-ClC_6H_4: 98% ee = 99%
R = *p*-$CF_3C_6H_4$: 81% ee = 97%
R = 2-Fu: 99% ee = 97%
R = *p*-$MeOC_6H_4$: 98% ee = 97%
R = 3,4-$(OCH_2O)C_6H_3$: 99% ee = 98%

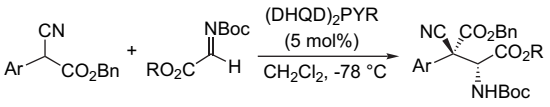
Scheme 104. Mannich reactions of malonates with imines catalysed by a thiourea cinchona alkaloid.

In 2005, Jorgensen et al. reported highly enantioselective Mannich reactions of α-substituted α-cyanoacetates with α-imino esters catalysed by a chiral modified cinchona alkaloid, $(DHQD)_2PYR$ (Scheme 105).[206] Diastereomeric ratios were generally modest, whereas excellent enantioselectivity was observed for a series of aromatic precursors in addition to glyoxylate *N*-(Boc)imine.

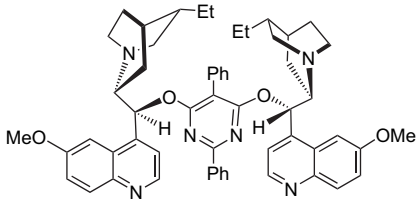
Chiral phosphoric acids are powerful organocatalysts for asymmetric addition reactions to imines.[207] In 2006, Terada et al. developed phosphorodiamidic acids derived from binaphthyl diamine as novel structural motifs of Brønsted acid catalysts for Mannich reactions of *N*-acyl imines with 1,3-dicarbonyl compounds.[208] Therefore, this chiral catalyst led to addition of acetylacetone to imines with modest enantioselectivity (Scheme 106).

In 2005, Maruoka et al. designed a novel axially chiral amino sulfonamide catalyst, allowing highly *anti*-selective asymmetric Mannich reactions between aldehydes and imines with excellent enantioselectivity (Scheme 107).[209]

An enantioselective Mannich-type reaction of ketene silyl acetals with aldimines was recently reported by Yamamoto

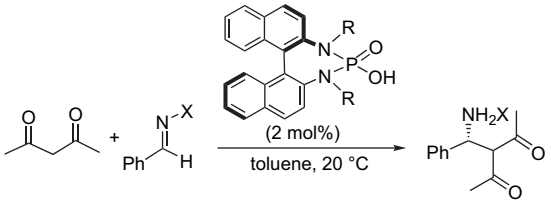


Ar = Ph, R = Et: 98% de = 78% ee = 97%
Ar = *p*-ClC_6H_4, R = Et: 99% de = 66% ee = 94%
Ar = *m*-Tol, R = Et: 97% de = 72% ee = 97%
Ar = *p*-$MeOC_6H_4$, R = Et: 97% de = 70% ee = 96%
Ar = 2-naph, R = Et: 99% de = 76% ee = 96%
Ar = 3,4-$(MeO)_2C_6H_3$, R = Et: 97% de = 70% ee = 97%
Ar = *o*-BrC_6H_4, R = *i*-Pr: 98% de = 70% ee = 98%
Ar = *o*-BrC_6H_4, R = *t*-Bu: 99% de = 96% ee = 98%



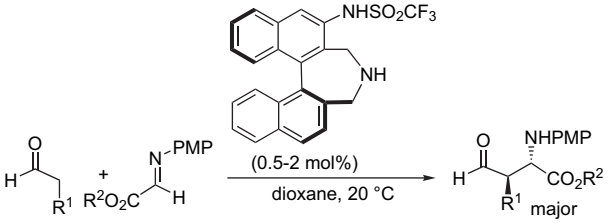
$(DHQD)_2PYR$

Scheme 105. $(DHQD)_2PYR$-catalysed Mannich reactions of α-cyanoacetates with imines.



R = 2-naphthylsulfonyl, X = Bz: 42% ee = 56%
R = *p*-tosyl, X = Boc: 97% ee = 19%

Scheme 106. Mannich addition reactions of acetylacetone to imines catalysed by phosphorodiamidic acids.

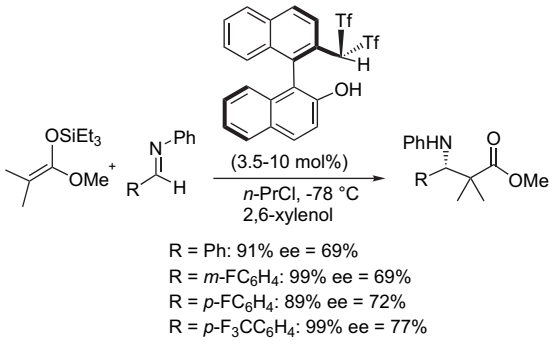


R^1 = Me, R^2 = Et: 93% de = 86% ee > 99%
R^1 = Bu, R^2 = Et: 93% de > 90% ee = 99%
R^1 = *i*-Pr, R^2 = Et: 93% de > 90% ee > 99%
R^1 = *t*-Bu, R^2 = Et: 42% de > 90% ee > 99%
R^1 = *i*-Pr, R^2 = allyl: 99% de = 88% ee > 99%
R^1 = *i*-Pr, R^2 = *t*-Bu: 99% de = 88% ee > 99%

Scheme 107. *anti*-Mannich reactions catalysed by an amino sulfonamide.

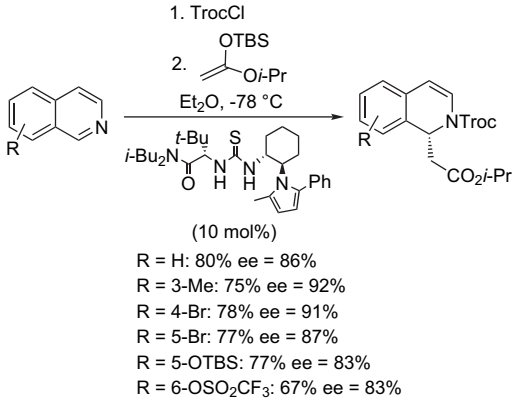
et al., involving a new Brønsted acid-assisted chiral Brønsted acid catalyst, obtained by substitution of a hydroxyl group of optically active 1,1′-bi(2-naphthol) with a stronger Brønsted acidic group such as bis(trifluoromethanesulfonyl)methyl (Scheme 108).[210] The addition of a stoichiometric achiral proton source such as 2,6-xylenol was required to accomplish the catalytic cycle of the chiral Brønsted acid catalyst.

On the other hand, Jacobsen et al. have described an acyl-Mannich reaction catalysed by a chiral thiourea derivative,



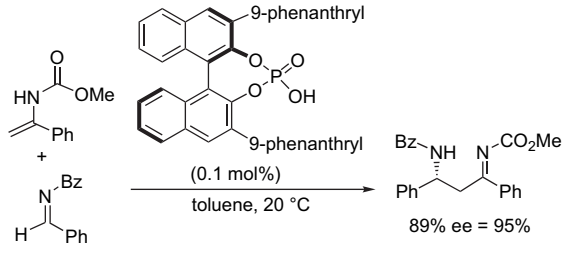
Scheme 108. Mannich-like reactions of ketene silyl acetals with aldimines.

providing access to useful chiral dihydroisoquinoline building blocks.[211] This process was the first example of a catalytic addition of enolate equivalents to heteroaromatic electrophiles (Scheme 109).



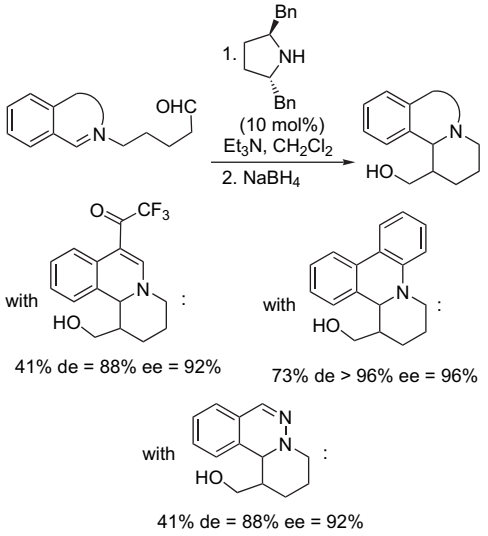
Scheme 109. Thiourea-catalysed acyl-Mannich reactions of isoquinolines.

In addition, a Mannich-like aza–ene-type reaction was reported by Terada et al.,[212] involving enamide addition to an *N*-acyl imine acceptor using a chiral Brønsted acid (depicted in Scheme 110). This chiral acid was presumed to hydrogen bond with the imine acceptor by donating the activating proton, and to the hydrogen of the enamide nucleophile. The yield and selectivity with a methyl carbamate enamide were high, using just 2 mol % of the chiral Brønsted acid, and remained high even with a 0.05 mol % catalyst loading (85%, 93% ee).



Scheme 110. Mannich-like aza–ene-type reaction.

In 2005, Jorgensen et al. published an interesting variation on the amine-catalysed asymmetric Mannich reaction in a stereoselective annulation (Scheme 111).[213] Intramolecular addition of an aldehyde functionality to various aromatic iminium ions resulted in the formation of two new stereogenic centres with stereocontrol derived from a C_2-symmetric (2*S*,5*S*)-2,5-dibenzylpyrrolidine catalyst.



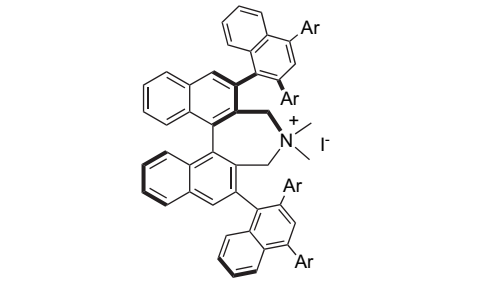
Scheme 111. Intramolecular Mannich-like reactions.

4.2. Strecker reactions

The Strecker reaction starting from an aldehyde, ammonia and a cyanide source is an efficient method for the preparation of α-amino acids and their derivatives. A popular version for asymmetric purposes is based on the use of preformed imines and a subsequent nucleophilic addition of HCN or TMSCN in the presence of a chiral catalyst.[214] Intense investigation of the asymmetric Strecker-type reaction has continued over many years, due to the importance of α-amino acid building blocks in medicinal chemistry.[215] Interestingly, a number of completely different types of chiral organocatalysts have been found to have catalytic hydrocyanation properties. Among these molecules are chiral quaternary ammonium salts. Maruoka et al. reported, in 2006, highly enantioselective Strecker reactions of aldimines using aqueous potassium cyanide by phase-transfer catalysis of chiral quaternary ammonium salts bearing a tetranaphthyl backbone (Scheme 112).[216]

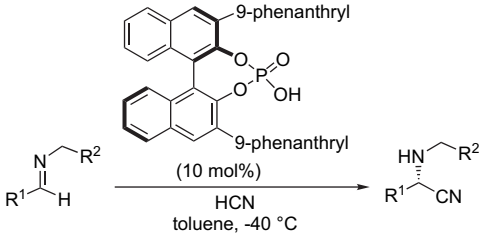
A successful application of chiral BINOL phosphate-derived Brønsted acids to catalysis of the Strecker reaction of a range of aromatic and heteroaromatic imines was reported by Rueping et al. in 2006.[217] As shown in Scheme 113, the use of a catalyst having a phenanthryl-substituted binaphthyl framework allowed the highest enantioselectivities for the addition of HCN to be obtained.

The thiourea catalysis concept[218] has been applied to the Strecker reaction. As an example, Tsogoeva et al. have studied several thiourea-based non-nucleoside inhibitors of HIV reverse transcriptase as catalysts in the Strecker addition of HCN to aldimines.[219] It was shown that the incorporation of an imidazolyl moiety in place of a pyridyl group attached to the thiourea nitrogen resulted in a new thiourea derivative that displayed a much higher catalytic activity (100% conversion), whereas a low enantioselectivity was generally



R = *c*-Oct: 88% ee = 97%
R = *i*-Pr: 85% ee = 93%
R = $BnCH_2$: 81% ee = 90%
R = *t*-Bu: 94% ee = 94%
R = $Ph(Me)_2C$: 95% ee = 98%

Scheme 112. Phase-transfer-catalysed Strecker reactions of aldimines.



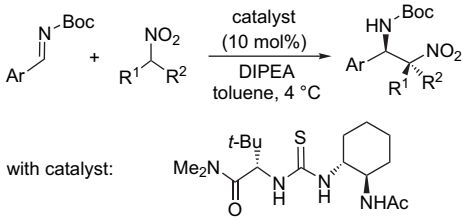
R^1 = p-$F_3CC_6H_4$, R^2 = Ph: 75% ee = 97%
R^1 = p-$F_3CC_6H_4$, R^2 = p-AcC_6H_4: 53% ee = 96%
R^1 = 2,4-$(F)_2C_6H_3$, R^2 = Ph: 59% ee = 98%
R^1 = 2-naph, R^2 = Ph: 71% ee = 85%
R^1 = Ph, R^2 = p-AcC_6H_4: 87% ee = 89%
R^1 = p-$MeOC_6H_4$, R^2 = Ph: 97% ee = 93%
R^1 = p-Tol, R^2 = Ph: 55% ee = 87%

Scheme 113. Strecker reactions of imines catalysed by BINOL phosphate.

observed (ee's $\leq$31%).[52] In addition, Kunz et al. have recently synthesised novel diketopiperazines containing a guanidino-functionalised side chain and investigated them as potential organocatalysts of enantioselective Strecker reactions, but without success.[220]

4.3. Aza-Henry reactions

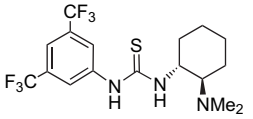
Nitroalkyl anions can serve as the nucleophile component in addition to imino compounds, and these nitro-Mannich or Aza-Henry reactions, afford adducts with an orthogonal nitrogen functionality on neighbouring carbons having some interesting synthetic utility.[11] In a very impressive expansion of asymmetric aza-Henry reactions, Takemoto et al. have introduced a bifunctional thiourea catalyst, depicted in Scheme 114, which incorporated both a thiourea H-bond donor and a basic nitrogen.[221] This construct was hypothesised to not only activate the acceptor for addition, but also to act as the base to produce the nitroalkyl nucleophile. The reactions were tested with a wide range of acceptors, with *N*-(Boc)imines showing optimal yields and selectivities, and the optimised conditions were applied in additions of nitromethane to a series of aromatic aldimines. The mild conditions enabled the reaction to tolerate additional electrophilic sites in the nitroalkane precursor including, remarkably, mesylate, triflate and acrylate functionalities. In the same context, Jacobsen and Yoon reported an application of another thiourea catalyst, depicted in Scheme 114, to aza-Henry reactions of four different nitroalkyl components and several aromatic *N*-(Boc)aldimines.[222]



with catalyst:

Ar = Ph, R^1 = H, R^2 = Et: 99% de = 75% ee = 95%
Ar = Ph, R^1 = R^2 = H: 87% ee = 92%
Ar = Ph, R^1 = R^2 = Me: 87% ee = 92%
Ar = Ph, R^1 = $TBSOCH_2$, R^2 = H: 85% de = 60% ee = 95%
Ar = Ph, R^1 = H, R^2 = Me: 96% de = 88% ee = 92%
Ar = p-$MeOC_6H_4$, R^1 = H, R^2 = Me: 95% de = 88% ee = 96%
Ar = p-Tol, R^1 = H, R^2 = Me: 90% de = 84% ee = 96%
Ar = 2-Fu, R^1 = H, R^2 = Me: 95% de = 72% ee = 93%

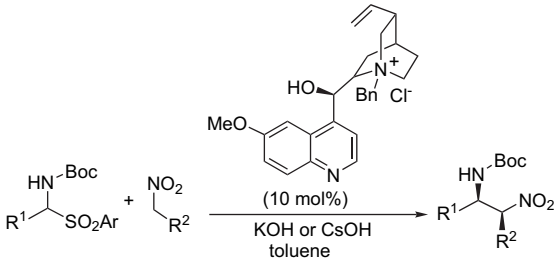
with catalyst:



with R^1 = R^2 = H: 71-90% ee = 83-98%
with R^1,R^2 = alkyl: 75-94% de = 50-94% ee = 89-99%

Scheme 114. Aza-Henry reactions of *N*-(Boc)imines with nitroalkanes.

A number of reports outline the utility of phase-transfer catalysis for aza-Henry reactions. As an example, a catalyst incorporating a quininium salt was examined by Herrera et al. for addition to in situ-generated *N*-Boc- or *N*-Cbz-protected imines (Scheme 115).[223] Phase transfer of the nitronate

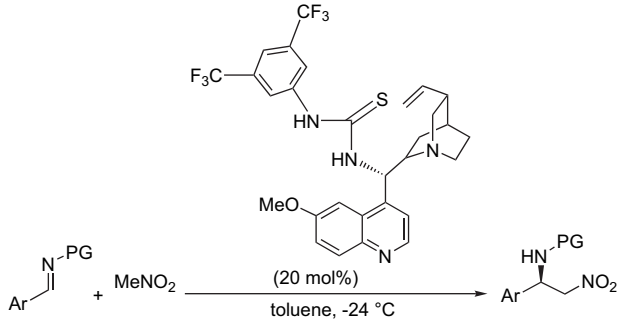


R^1 = $BnCH_2$, R^2 = Me: 83% ee = 96%
R^1 = Et, R^2 = Me: 80% ee = 96%
R^1 = *n*-Hex, R^2 = Me: 78% ee = 98%
R^1 = *i*-Pr, R^2 = Me: 81% ee = 95%
R^1 = Cy, R^2 = Me: 77% ee = 98%
R^1 = Ph, R^2 = Me: 79% ee = 91%
R^1 = p-$MeOC_6H_4$, R^2 = Me: 82% ee = 91%
R^1 = p-$MeOC_6H_4$, R^2 = Et: 87% de = 90% ee = 90%
R^1 = p-ClC_6H_4, R^2 = Et: 88% de = 50% ee = 98%
R^1 = $BnCH_2$, R^2 = Et: 85% de = 80% ee = 91%
R^1 = Ph, R^2 = Et: 88% de = 86% ee = 94%
R^1 = 1-naph, R^2 = Me: 95% ee = 84%
R^1 = R^2 = Me: 86% ee = 92%

Scheme 115. Phase-transfer-catalysed aza-Henry reactions.

quininium ion pair from the KOH solid phase to toluene was critical for the asymmetric induction. Concurrently, the same approach was reported by Palomo et al.,[224] in this case with the use of CsOH as a base; nitroethane was also found to be a suitable nucleophilic component (Scheme 115).

In 2006, Ricci et al. reported a survey of a range of modified cinchona alkaloids as organocatalysts for the aza-Henry reaction, culminating in an optimal structure, depicted in Scheme 116, bearing a thiourea functionality, which produced a highly effective catalyst.[225] Various *N*-protected imines were examined as substrates such as *N*-Boc-, *N*-Cbz- and *N*-Fmoc-protected imines, which gave the best results in terms of yields and enantioselectivities. At the same time, a closely related cinchona alkaloid-derived thiourea catalyst was used by Schaus et al. to promote the aza-Henry reaction of various nitroalkanes with acyl imines, affording the corresponding β-nitroamines in good yields with enantioselectivities of 90–98% ee and diastereoselectivities of up to 97% de.[226] The scope of the reaction also included dimethyl malonate as a nucleophile to access β-amino esters in high enantiopurity.



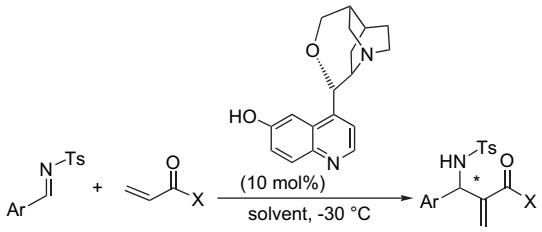
Ar = 1-naph, PG = Boc: 87% ee = 88%
Ar = 2-naph, PG = Boc: 82% ee = 94%
Ar = *p*-ClC_6H_4, PG = Boc: 77% ee = 94%
Ar = *p*-ClC_6H_4, PG = Cbz: 58% ee = 90%
Ar = *o*-BrC_6H_4, PG = Boc: 82% ee = 88%
Ar = Ph, PG = Fmoc: 60% ee = 90%

Scheme 116. Cinchona alkaloid-catalysed aza-Henry reactions.

4.4. Aza-Morita–Baylis–Hillman reactions

The aza-Morita–Baylis–Hillman reaction is a C–C bond-forming reaction of activated alkenes with imines. In 2005, Shi et al. reported that the aza-Morita–Baylis–Hillman reaction of *N*-sulfonated imines with activated olefins could be catalysed by quinidine-derived chiral amines (Scheme 117).[227] A range of activated olefins such as alkyl vinyl ketones, acrolein and acrylates led to the formation of the corresponding adducts in good yields and high enantioselectivities (up to 99% ee).

The same group also reported the use of a chiral phosphinyl BINOL catalyst to promote analogous aza-Morita–Baylis–Hillman reactions between *N*-sulfonated imines and various activated olefins (Scheme 118).[228] In the same context, Sasai et al. have shown that (*S*)-3-(*N*-isopropyl-*N*-3-pyridinylaminomethyl)BINOL was also an efficient bifunctional organocatalyst for analogous reactions, giving rise to excellent enantioselectivities, as depicted in Scheme 118.[229]



with solvent = MeCN/DMF:
Ar = Ph, X = Me: 80% ee = 97% (*R*)
Ar = *p*-Tol, X = Me: 80% ee = 96% (*R*)
Ar = *p*-$MeOC_6H_4$, X = Me: 67% ee = 99% (*R*)
Ar = Ph, X = Et: 54% ee = 94% (*R*)
with solvent = THF:
Ar = Ph, X = H: 58% ee = 85% (*S*)
Ar = *p*-BrC_6H_4, X = H: 72% ee = 89% (*S*)
Ar = *m*-ClC_6H_4, X = H: 65% ee = 99% (*R*)
with solvent = CH_2Cl_2:
Ar = Ph, X = OMe: 62% ee = 83% (*S*)
Ar = *p*-Tol, X = OMe: 67% ee = 80% (*S*)
Ar = *m*-FC_6H_4, X = OMe: 87% ee = 83% (*S*)
Ar = PhCH=N-NTs, X = OMe: 60% ee = 83% (*S*)
Ar = *m*-FC_6H_4, X = OPh: 83% ee = 82% (*S*)
with solvent = MeCN:
Ar = Ph, X = O(1-naph): 85% ee = 80% (*S*)

Scheme 117. Aza-Morita–Baylis–Hillman reactions catalysed by quinidine-derived amine.

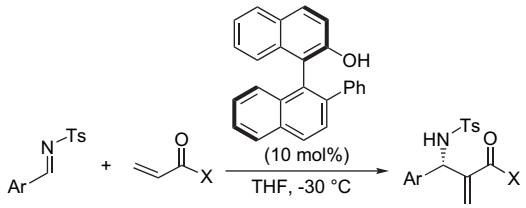
4.5. Miscellaneous reactions

In 2005, Miller et al. developed a thiazolylalanine-derived catalyst for the enantioselective intermolecular aldehyde–imine cross-coupling.[230] Indeed, the peptide-catalysed reactions between aldehydes and tosylamides delivered, in the presence of a base such as pentamethylpiperidine (PEMP), the corresponding α-amido ketones with up to 87% ee (Scheme 119). The authors have proposed the possibility of a bifunctional mechanism involving a covalent catalysis that benefited from simultaneous activation of the acyl anion equivalent derived from the aldehyde, with H-bond activation of the *N*-acyl imine component derived from the sulfinamide precursor.

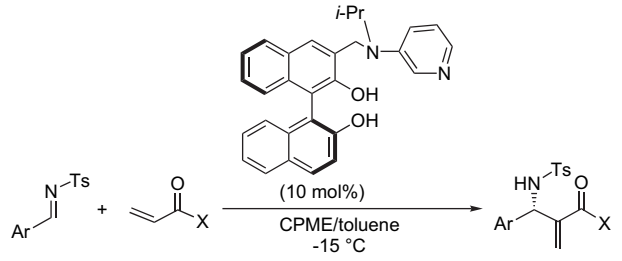
In 2006, Deng et al. developed the first highly enantioselective organocatalysed Friedel–Crafts reaction of indoles with imines, providing a direct and broadly useful catalytic enantioselective approach towards 3-indolyl methanamines, thus facilitating the asymmetric synthesis of a number of biologically interesting indole compounds (Scheme 120).[231] Its unique applicability to alkyl imines should open up new possibilities in the total synthesis of indole alkaloids and their analogues.

The first organocatalysed reaction of neutral aza-enamines to imines was reported in 2005 by Dixon and Tillman, using a novel 3,3′-bismethanol-2,2′-binaphthol catalyst (BIMBOL) easily synthesised via a three-step sequence from (*S*)-BINOL.[232] The corresponding versatile products were obtained in moderate-to-good yields and enantioselectivities (Scheme 121).

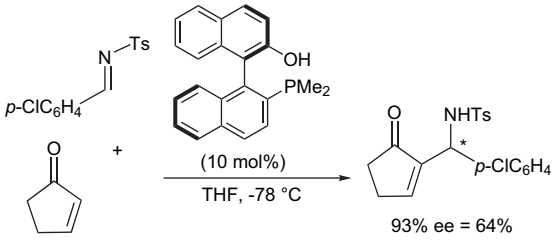
Another derivative of BINOL, VAPOL (vaulted biphenanthrol)-derived phosphoric acid, was shown to provide excellent enantioselectivities for imine amidation reactions,



Ar = *p*-ClC_6H_4, X = Me: 72% ee = 94%
Ar = *p*-FC_6H_4, X = Me: 84% ee = 81%
Ar = *m*-ClC_6H_4, X = Me: 62% ee = 88%
Ar = *p*-$O_2NC_6H_4$, X = Me: 60% ee = 94%
Ar = Ph-CH=CH, X = Me: 94% ee = 95%
Ar = *p*-BrC_6H_4, X = Et: 78% ee = 85%
Ar = *p*-BrC_6H_4, X = OPh: 85% ee = 77%
Ar = *p*-ClC_6H_4, X = H: 91% ee = 83%
Ar = Ph, X = H: 88% ee = 86%
Ar = *p*-FIC_6H_4, X = H: 86% ee = 84%



Ar = *p*-ClC_6H_4, X = Me: 96% ee = 95%
Ar = *p*-$MeOC_6H_4$, X = Me: 93% ee = 94%
Ar = *p*-$O_2NC_6H_4$, X = Me: 91% ee = 91%
Ar = *p*-$O_2NC_6H_4$, X = Et: 88% ee = 88%
Ar = *p*-$O_2NC_6H_4$, X = H: 95% ee = 94%
Ar = 2-naph, X = Me: 94% ee = 91%
Ar = Ph, X = Me: 93% ee = 87%



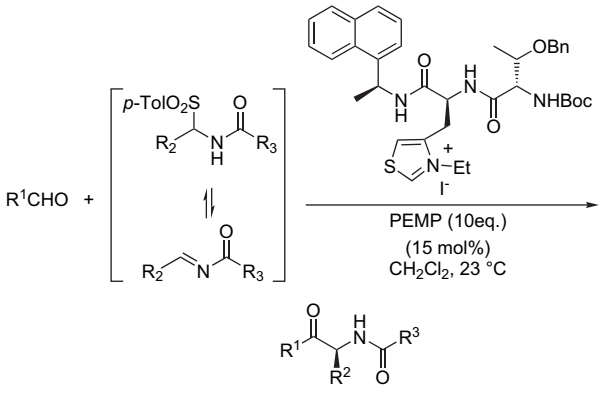
93% ee = 64%

Scheme 118. Aza-Morita–Baylis–Hillman reactions catalysed by BINOL derivatives.

involving a variety of aromatic *N*-Boc-protected imines (Scheme 122).[233]

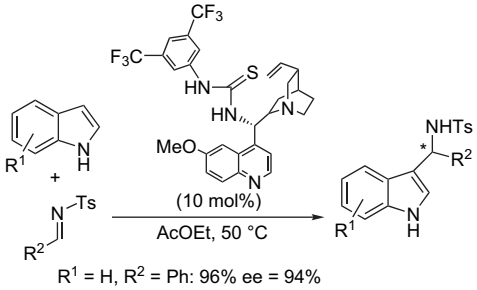
The bifunctional nature of the phosphoric acid moiety was also exploited by Terada et al. by developing novel organocatalysed reactions between *N*-acyl imines and α-diazoesters.[234] Therefore, a new binaphthol monophosphoric acid catalyst was used to catalyse direct alkylations of α-diazoesters, via C–H bond cleavage, providing β-amino-α-diazoesters which constituted highly functionalised and useful synthetic precursors for various types of β-amino acids (Scheme 123).

Asymmetric catalytic hydrophosphonylation is an attractive approach for the synthesis of chiral α-amino phosphonates. In 2005, Akiyama et al. reported the use of a cyclic phosphoric acid derivative derived from (*R*)-BINOL as catalyst for hydrophosphonylations of aldimines with diisopropyl phosphite.[235] The process afforded α-amino phosphonates in



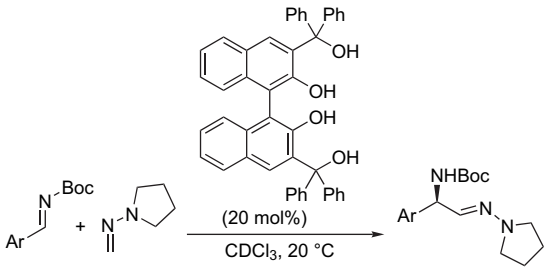
R^1 = *p*-ClC_6H_4, R^2 = R^3 = Ph: 100% ee = 76%
R^1 = *p*-ClC_6H_4, R^2 = *p*-$MeOC_6H_4$, R^3 = Ph: 90% ee = 87%
R^1 = *m*-$O_2NC_6H_4$, R^2 = *p*-$MeOC_6H_4$, R^3 = Ph: 77% ee = 82%
R^1 = *p*-ClC_6H_4, R^2 = Ph, R^3 = *i*-Pr: 97% ee = 75%

Scheme 119. Aldehyde–imine cross-couplings catalysed by thiazolylalanine-derived catalyst.



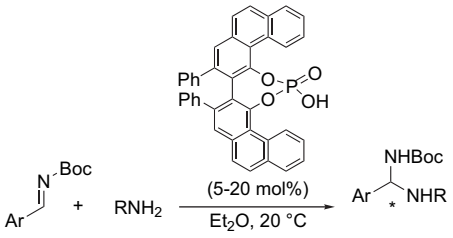
R^1 = H, R^2 = Ph: 96% ee = 94%
R^1 = 6-Br, R^2 = Ph: 86% ee = 95%
R^1 = 6-MeO, R^2 = Ph: 89% ee = 92%
R^1 = 4-MeO, R^2 = Ph: 88% ee = 91%
R^1 = H, R^2 = *p*-ClC_6H_4: 98% ee = 94%
R^1 = H, R^2 = *o*-BrC_6H_4: 98% ee = 93%
R^1 = H, R^2 = *p*-$F_3CC_6H_4$: 97% ee = 96%
R^1 = H, R^2 = 2-Fu: 88% ee = 96%
R^1 = H, R^2 = Cy: 86% ee = 94%
R^1 = H, R^2 = *i*-Pr: 85% ee = 94%
R^1 = H, R^2 = *i*-Bu: 85% ee = 95%
R^1 = H, R^2 = *n*-Bu: 53% ee = 96%
R^1 = H, R^2 = CH_2OBn: 65% ee = 96%

Scheme 120. Cinchona alkaloid-catalysed Friedel–Crafts reactions of indoles with imines.



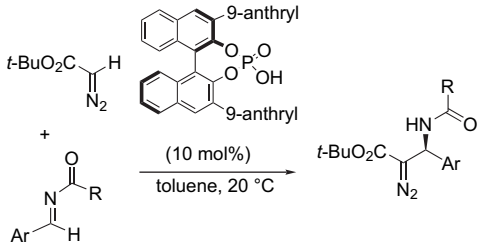
Ar = Ph: 87% ee = 63%
Ar = 2-naph: 81% ee = 43%
Ar = *o*-Tol: 50% ee = 75%
Ar = *o*-BrC_6H_4: 44% ee = 44%

Scheme 121. BIMBOL-catalysed reactions of methyleneaminopyrrolidine imines.



Ar = Ph, R = Ts: 95% ee = 94%
Ar = Ph, R = Mes: 86% ee = 93%
Ar = *p*-ClC_6H_4, R = Ts: 88% ee = 94%
Ar = *p*-BrC_6H_4, R = Ts: 96% ee = 92%
Ar = *p*-$F_3CC_6H_4$, R = Ts: 99% ee = 99%
Ar = *p*-$MeOC_6H_4$, R = Ts: 92% ee = 90%
Ar = 2-thienyl, R = Ts: 94% ee = 87%

Scheme 122. VAPOL-catalysed imine amidation reactions.



Ar = R = Ph: 59% ee = 90%
Ar = Ph, R = *o*-Tol: 84% ee = 90%
Ar = Ph, R = *o*-$MeOC_6H_4$: 77% ee = 92%
Ar = Ph, R = *m*-$MeOC_6H_4$: 76% ee = 91%
Ar = Ph, R = *p*-Tol: 72% ee = 91%
Ar = Ph, R = *p*-$MeOC_6H_4$: 73% ee = 93%
Ar = Ph, R = *p*-$Me_2NC_6H_4$: 81% ee = 97%
Ar = Ph, R = 2-naph: 82% ee = 90%
Ar = *p*-FC_6H_4, R = *p*-$Me_2NC_6H_4$: 74% ee = 97%
Ar = *o*-FC_6H_4, R = *p*-$Me_2NC_6H_4$: 89% ee = 91%
Ar = *m*-FC_6H_4, R = *p*-$Me_2NC_6H_4$: 84% ee = 93%
Ar = *o*-$MeOC_6H_4$, R = *p*-$Me_2NC_6H_4$: 85% ee = 91%

Scheme 123. Alkylations of α-diazoester with *N*-acyl imines.

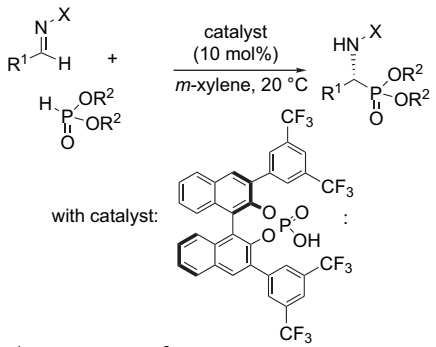
good-to-high enantioselectivities (Scheme 124). In the same context, Pettersen et al. developed the hydrophosphonylation of *N*-Boc-protected imines with diethyl phosphite by using quinine as catalyst, which allowed up to 94% ee to be obtained (Scheme 124).[236]

5. Nucleophilic additions to unsaturated nitrogen

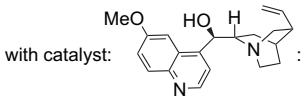
The direct introduction of either a nitrogen or an oxygen atom adjacent to a carbonyl group in a catalytic, enantioselective manner using a chiral organocatalyst has been described only recently. The chiral products of these reactions represent fundamental building blocks for the construction of complex natural products and other important bioactive molecules.[237,238]

5.1. Nucleophilic additions to N=N double bonds

A large variety of natural products and drugs are nitrogen-containing molecules. The enantioselective construction of molecules bearing a carbon–nitrogen bond via direct α-amination using readily available starting materials is one of the



R^1 = *o*-$O_2NC_6H_4$, R^2 = *i*-Pr, X = *p*-$MeOC_6H_4$: 72% ee = 77%
R^1 = PhCH=CH, R^2 = *i*-Pr, X = *p*-$MeOC_6H_4$: 92% ee = 84%
R^1 = *p*-$TolC_6H_4CH$=CH, R^2 = *i*-Pr, X = *p*-$MeOC_6H_4$: 88% ee = 86%
R^1 = *p*-ClC_6H_4CH=CH, R^2 = *i*-Pr, X = *p*-$MeOC_6H_4$: 97% ee = 83%
R^1 = *o*-ClC_6H_4CH=CH, R^2 = *i*-Pr, X = *p*-$MeOC_6H_4$: 82% ee = 87%
R^1 = *o*-$O_2NC_6H_4CH$=CH, R^2 = *i*-Pr, X = *p*-$MeOC_6H_4$: 92% ee = 88%
R^1 = *o*-$F_3CC_6H_4CH$=CH, R^2 = *i*-Pr, X = *p*-$MeOC_6H_4$: 86% ee = 90%
R^1 = PhCH=CH, R^2 = *i*-Pr, X = Ph: 74% ee = 88%

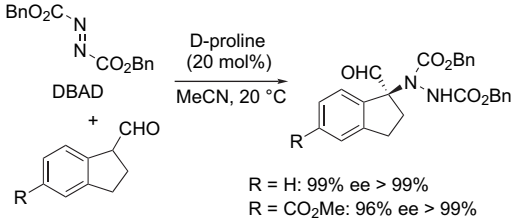


R^1 = Ph, R^2 = Et, X = Boc: 83% ee = 80%
R^1 = 2-naph, R^2 = Et, X = Boc: 69% ee = 92%
R^1 = *m*-Tol, R^2 = Et, X = Boc: 61% ee = 94%
R^1 = *p*-Tol, R^2 = Et, X = Boc: 62% ee = 93%
R^1 = *p*-$MeOC_6H_4$, R^2 = Et, X = Boc: 57% ee = 94%

Scheme 124. Hydrophosphonylations of aldimines with dialkyl phosphites.

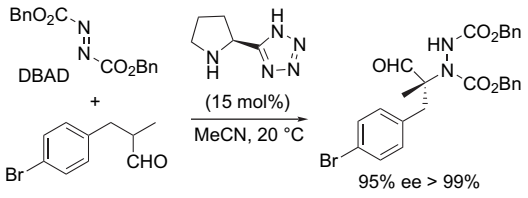
many challenges for organic chemists, this being one of the simplest and straightforward strategies to access important chiral molecules such as α-amino acids, aldehydes and alcohols. In contrast to the large number of addition reactions to C=O, and C=N double bonds, only a few examples of nucleophilic addition to N=N double bonds have been investigated. The use of azodicarboxylates as the electrophilic nitrogen source and proline as the catalyst has been reported recently. This methodology has been successfully applied to the synthesis of important medicinal amino acids such as (*S*)-AIDA and (*S*)-APICA, which are metabotropic glutamate receptor ligands used in the treatment of several neurodegenerative diseases. Barbas et al. reported, in 2005, the D-proline-catalysed amination reaction of functionalised indane carboxaldehydes with dibenzylazodicarboxylate (DBAD), giving, in all cases, only one enantiomer, which was further converted into (*S*)-AIDA and (*S*)-APICA (Scheme 125).[239]

5-Pyrrolidin-2-yltetrazole has been shown to be superior to proline as a catalyst in the reaction of 3-(4-bromophenyl)-2-methylpropanal with DBAD, yielding the corresponding



R = H: 99% ee > 99%
R = CO_2Me: 96% ee > 99%
R = Br: 75% ee > 99%

Scheme 125. D-Proline-catalysed reactions of indane carboxaldehydes with DBAD.

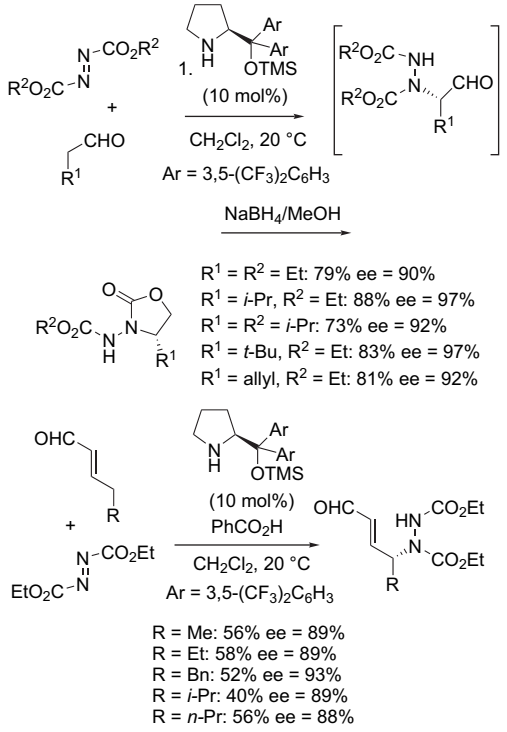


Scheme 126. Tetrazole proline-catalysed reaction of 3-(4-bromophenyl)-2-methylpropanal with DBAD.

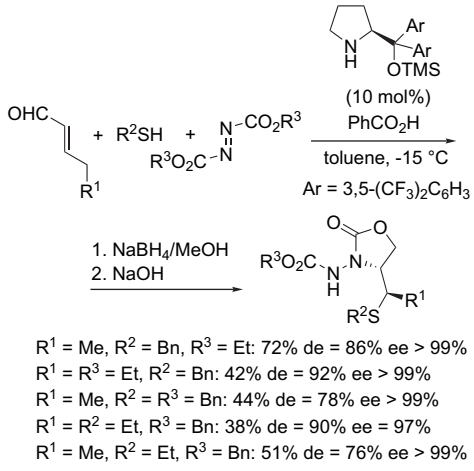
α-amino aldehyde with good enantioselectivity (Scheme 126). Indeed, in the case of using L-proline, the enantiomeric excess was only 44%. The higher reactivity of this catalyst was attributed to its lower pK_a value and its higher steric hindrance. The thus-formed aldehyde was used as an intermediate in the total synthesis of a cell adhesion inhibitor, BIRT-377.[240]

In 2005, Jorgensen et al. demonstrated that (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine, used as a catalyst of reactions between aldehydes and azodicarboxylates, gave results matching those obtained with L-proline (Scheme 127).[201] Indeed, the α-aminated products were isolated in high yields and very high enantioselectivities as the corresponding oxazolidinones after reduction of the aldehyde moiety and subsequent cyclisation. Remarkably, the absolute configuration of the final products was opposite that obtained using L-proline. In 2006, the scope of this methodology was extended to a range of α,β-unsaturated aldehydes, enabling a direct γ-amination of the carbonyl compound with high enantioselectivities (Scheme 127).[241]

The same catalyst as that described above allowed the synthesis of highly functionalised molecules having two adjacent



Scheme 127. α,α-Diarylprolinol silyl ether-catalysed reactions of aldehydes with azodicarboxylates.

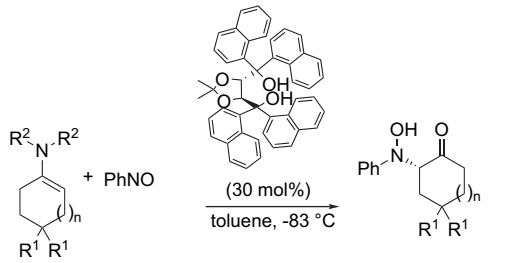


Scheme 128. α,α-Diarylprolinol silyl ether-catalysed three-component domino reactions.

stereocentres, as depicted in Scheme 128, through a multicomponent domino conjugated nucleophilic addition electrophilic amination reaction, followed by reduction and basic treatment.[79] The mechanistic pathway appears to proceed via the formation of the corresponding chiral α,β-unsaturated iminium intermediate, which reacts with the soft nucleophilic thiol in a Michael-type process, to form the corresponding enamine, which, in turn, reacts with the diazo compound. Further reduction and basic treatment gave the final oxazolidinones with a high enantioselectivity (only one enantiomer in many cases) and high diastereoselectivities.

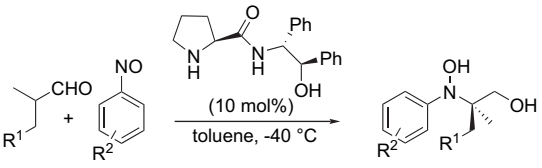
In 2006, Greck et al. reported α-aminations of carbonyl compounds in the presence of DBAD, using L-azetidinecarboxylic acid as catalyst.[242] Generally, if the yields were comparable to those obtained by using L-proline, the enantiomeric excesses were increased for substrates such as cyclohexanone and propanal. The enantioselective α-amination of various aliphatic aldehydes and ketones with diethyl azodicarboxylate has also been carried out in ionic liquids as reaction media, in which the re-use of the catalyst could be performed.[243] Of several chiral organocatalysts tested, L-proline and L-thiazoline-2-carboxylic acid gave the highest enantioselectivities (up to 94% ee) combined with good yields (up to 85%). The best results were obtained by using [bmim]PF_6 and [hmim]BF_4 as ionic liquids. On the other hand, the α-amination of carbonyl compounds has also been accomplished by using a Brønsted acid catalyst such as a TADDOL derivative (Scheme 129). The reaction of different enamines with nitrosobenzene gave exclusively the *N*-regioisomers in a highly enantioselective manner.

In 2006, Jiang et al. showed that this amination could be performed without the preformed enamine by using the proline amide catalyst depicted in Scheme 130.[244] The involvement of this catalyst contributed to the formation of the *O*-regioisomer. This reaction was the first direct organocatalysed enantioselective α-hydroxyamination reaction of α-branched aldehydes with a variety of nitrosobenzenes The reason for this unusual behaviour could be attributed to the low acidity of the proton of the proline amide, which was unable to protonate the nitrogen atom, but could protonate the



R^1,R^1 = H, R^2,R^2 = $(CH_2)_4$, n = 1: 69% ee = 70%
R^1,R^1 = H, R^2,R^2 = $(CH_2)_5$, n = 1: 77% ee = 92%
R^1,R^1 = OCH_2CH_2O, R^2,R^2 = $(CH_2)_5$, n = 1: 83% ee = 93%
R^1,R^1 = H, R^2,R^2 = $(CH_2)_6$, n = 1: 89% ee = 91%
R^1,R^1 = Me, R^2,R^2 = $(CH_2)_5$, n = 1: 78% ee = 82%
R^1,R^1 = H, R^2,R^2 = $(CH_2)_5$, n = 2: 67% ee = 65%

Scheme 129. TADDOL-catalysed *N*-nitroso aldol reactions.

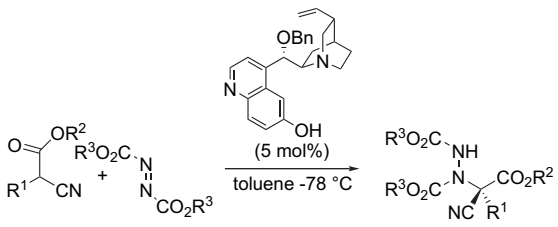


R^1 =  , R^2 = *o*-Br: 76% ee = 64%
R^1 =  , R^2 = *p*-Cl: 63% ee = 63%
R^1 =  , R^2 = *p*-Me: 66% ee = 59%
R^1 = *p*-*t*-BuC_6H_4, R^2 = H: 69% ee = 59%
R^1 = Et, R^2 = H: 55% ee = 46%

Scheme 130. L-Proline amide-catalysed nitroso aldol reactions.

oxygen atom of the nitroso derivative, therefore making the nitrogen atom more electrophilic.

Since the catalytic construction of nitrogen-substituted quaternary stereocentres is an important and challenging task in asymmetric synthesis, Deng et al. have developed highly enantioselective aminations of α-substituted α-cyanoacetates using 6′-OH-modified cinchona alkaloids derived from either quinine or quinidine as catalysts (Scheme 131).[245]



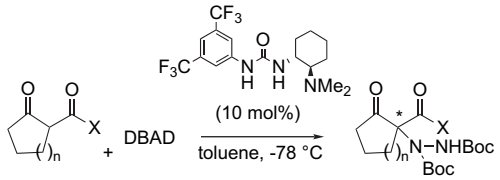
R^1 = Ph, R^2 = Et, R^3 = *t*-Bu: 92% ee = 97%
R^1 = 1-naph, R^2 = Et, R^3 = *t*-Bu: 99% ee = 93%
R^1 = *p*-$MeOC_6H_4$, R^2 = Et, R^3 = *t*-Bu: 96% ee = 94%
R^1 = *p*-BrC_6H_4, R^2 = Et, R^3 = *t*-Bu: 99% ee = 93%
R^1 = *p*-FC_6H_4, R^2 = Et, R^3 = *t*-Bu: 97% ee = 94%
R^1 = *p*-Tol, R^2 = Et, R^3 = *t*-Bu: 96% ee = 94%

Scheme 131. Cinchona alkaloid-catalysed aminations of α-substituted α-cyanoacetates.

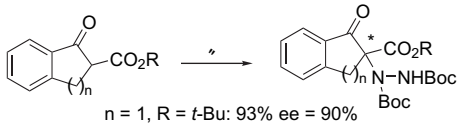
In 2006, Takemoto et al. studied the α-hydrazination of 1,3-dicarbonyl compounds such as β-keto esters and 1,3-diketones using a bifunctional urea as catalyst and azodicarboxylates as electrophiles.[246] Scheme 132 shows that the reactions proceeded in high yields and gave the chiral products in up to 91% ee.

The first example of a highly enantioselective organocatalysed allylic amination was reported by Jorgensen in 2005.[247] A cinchona alkaloid derivative $(DHQ)_2PYR$ was used to catalyse the addition of DBAD to alkylidene cyanoacetates and malononitriles. The reaction took place at the allylic position with excellent enantioselectivities, as shown in Scheme 133. The same catalyst was also successfully applied to the α-amination of α-cyanoacetates and β-dicarbonyl compounds.[248]

In addition, this catalyst was recently applied to an unprecedented example of organocatalysed Friedel–Crafts amination of 2-naphthols.[249] Scheme 134 shows the good enantioselectivities obtained with a series of different 2-naphthol derivatives.

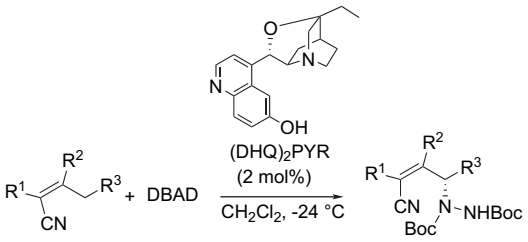


n = 1, X = *i*-Pr: 98% ee = 91%
n = 1, X = *t*-Bu: 96% ee = 91%
n = 1, X = Me: 97% ee = 80%
n = 2, X = OMe 52% ee = 87%
n = 3, X = O*t*-Bu: 90% ee = 90%



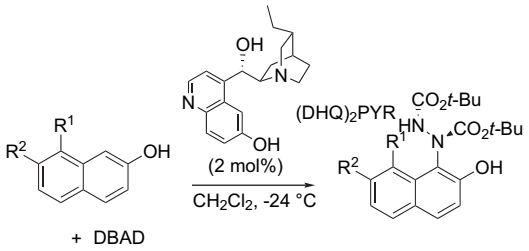
n = 1, R = *t*-Bu: 93% ee = 90%
n = 2, R = Me: 99% ee = 87%

Scheme 132. Urea-catalysed hydrazinations of 1,3-dicarbonyl compounds with DBAD.



R^1 = CO_2Me, R^2 = H, R^3 = Et: 84% ee = 98%
R^1 = CO_2Me, R^2 = H, R^3 = *n*-Hex: 90% ee = 99%
R^1 = CO_2Me, R^2 = H, R^3 = *i*-Pr: 87% ee = 90%
R^1 = CO_2Me, R^2 = H, R^3 = *n*-Bn: 89% ee = 98%
R^1 = CO_2Me, R^2 = H, R^3 = allyl: 85% ee = 96%
R^1 = CN, R^2 = H, R^3 = Et: 65% ee = 91%
R^1 = CN, R^2 = Ph, R^3 = Me: 85% ee = 86%
R^1 = CN, R^2 = Ph, R^3 = Bn: 84% ee = 88%

Scheme 133. Cinchona alkaloid-catalysed allylic aminations of alkylidene cyanoacetates.



$R^1 = NH_2$, R^2 = H: 90% ee = 88%
R^1 = NHBn, R^2 = H: 98% ee = 48%
R^1 = NH*n*-Pent, R^2 = H: 98% ee = 78%
$R^1 = NH_2$, R^2 = Br: 96% ee = 80%

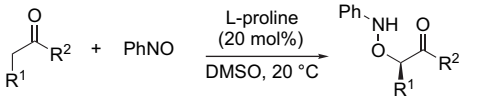
Scheme 134. Cinchona alkaloid-catalysed Friedel–Crafts aminations of 2-naphthols.

5.2. Nucleophilic additions to N=O double bonds

The α-oxycarbonyl group is a common feature of many natural and biologically active compounds. Furthermore, this functionality is an obvious precursor in the synthesis of other important building blocks such as diols. Among the already existing methods for the asymmetric synthesis of chiral α-hydroxy carbonyl compounds, the direct organocatalysed enantioselective α-amino-oxylation of carbonyl compounds is one of the most important strategies for achieving this purpose. Nitroso compounds such as nitrosobenzene are useful electrophiles for performing this type of reaction, although its nitrogen versus oxygen reactivity should be carefully controlled through the selection of appropriate catalysts and reaction conditions.[250] The ability of L-proline to control both the O/N-selectivity, as well as the enantioselectivity, in a variety of solvents and reaction conditions during the catalysis of the direct functionalisation of carbonyl compounds by nitroso compounds has been well documented. Although double amino-oxylation can take place with ketones which have two enol forms, the double attack can be circumvented by the slow addition of the nitroso electrophile, combined with the use of a relatively large excess of ketone.[251] In this context, Hayashi et al. reported, in 2006, the L-proline-catalysed reaction of 1,4-cyclohexanedione monoethylene ketal with nitrosobenzene, providing the expected ketone in 94% yield and as only one enantiomer (Scheme 135).[252] This reaction was the key step in the total synthesis of several inhibitors of angiogenesis such as fumagillol, RK-805, FR65814, ovalicin and 5-demethylovalicin. The scope of the reaction was extended to several aliphatic ketones.

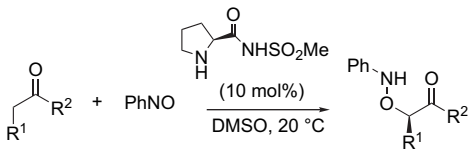
The L-proline-catalysed addition of nitrosobenzene to ketones was also applied by Barbas and Ramachary to the enantioselective desymmetrisation of *meso*-cyclohexanone derivatives with up to 99% ee.[253] In 2006, Kim et al. reported the synthesis of the pheromones, (+)-*exo*- and (−)-*endo*-brevicomin, and their derivatives on the basis of an α-amino-oxylation of aldehydes catalysed by L-proline, followed by an in situ indium-mediated allylation and a final olefin cross-metathesis.[254] In spite of obtaining excellent enantioselectivities (98–99% ee's), the *syn*/*anti* diastereoselectivities observed for the formation of the intermediate diols were moderate (20% de). Due to the importance of the products obtained, the catalytic properties of several derivatives of L-proline were investigated by different research groups. Cordova et al. have studied the proline-derived *N*-sulfonylcarboxamide-catalysed enantioselective α-oxidation of ketones and aldehydes with nitrosobenzene.[255] The corresponding α-amino-oxylated products were obtained in good yields with up to >99% ee (Scheme 136).

Different chiral dihydro-1,2-oxazine derivatives were obtained when the enantioselective α-amino-oxylation reaction was catalysed by the tetrazole proline catalyst (Scheme 137), in which the in situ-formed aldehyde reacted subsequently with a vinylphosphonium salt derivative. The possible mechanistic pathway involved a Michael-type addition of a nitrogen atom of the aldehyde intermediate on the phosphonium salt to form the corresponding ylide derivative, which, in turn, reacted with the carbonyl moiety to form the corresponding cyclic product.[256] The scope of this methodology was extended to the use of various ketones and trisubstituted vinylphosphonium bromides, giving rise to the corresponding tetrasubstituted 1,2-oxazines with complete diastereoselectivity and excellent enantioselectivity (99% ee).[257]



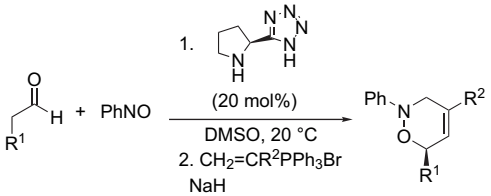
$R^1 = R^2$ = Me: 75% ee > 99%
R^1 = Me, R^2 = Et: 65% ee = 99%
R^1 = allyl, R^2 = Me: 68% ee > 99%
R^1 = *i*-Pr, R^2 = Me: 58% ee > 99%
$R^1,R^2 = (CH_2)_4$: 68% ee > 99%
$R^1,R^2 = CH_2C(OCH_2CH_2O)(CH_2)_2$: 94% ee > 99%

Scheme 135. L-Proline-catalysed α-amino-oxylations of ketones.



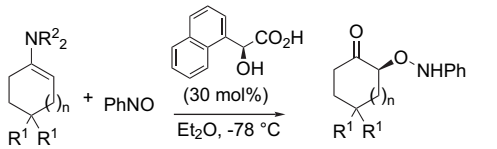
$R^1,R^2 = (CH_2)_4$: 80% ee > 99%
$R^1,R^2 = CH_2C(OCH_2CH_2O)(CH_2)_2$: 74% ee = 98%
$R^1,R^2 = (CH_2)_2CH(Me)(CH_2)_2$: 54% ee > 99%
R^1 = Me, R^2 = H: 66% ee > 99%

Scheme 136. α-Amino-oxylations of carbonyl compounds catalysed by L-proline derivative.

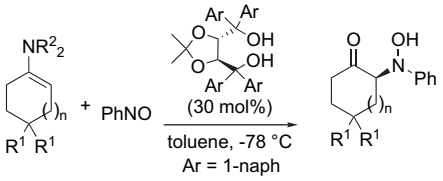


R^1 = *i*-Pr, R^2 = H: 71% ee = 99%
R^1 = *t*-Bu, R^2 = H: 82% ee = 99%
R^1 = *i*-Pr, R^2 = Me: 53% ee = 99%
$R^1 = (CH_2)_3CO_2Me$, R^2 = H: 50% ee = 99%
$R^1 = CH_2CH{=}CHEt$, R^2 = H: 50% ee = 99%

Scheme 137. Synthesis of dihydro-1,2-oxazines catalysed by L-pyrrolidinyl-tetrazole.



R^1 = H, R^2,R^2 = $(CH_2)_4$, n = 1: 69% ee = 70%
R^1 = H, R^2,R^2 = $(CH_2)_5$, n = 0: 63% ee = 70%
R^1 = H, R^2,R^2 = $(CH_2)_5$, n = 1: 77% ee = 92%
R^1 = Me, R^2,R^2 = $(CH_2)_5$, n = 1: 91% ee = 90%
R^1,R^1 = OCH_2CH_2O, R^2,R^2 = $(CH_2)_5$, n = 1: 83% ee = 93%
R^1 = H, R^2,R^2 = $(CH_2)_6$, n = 1: 64% ee = 83%

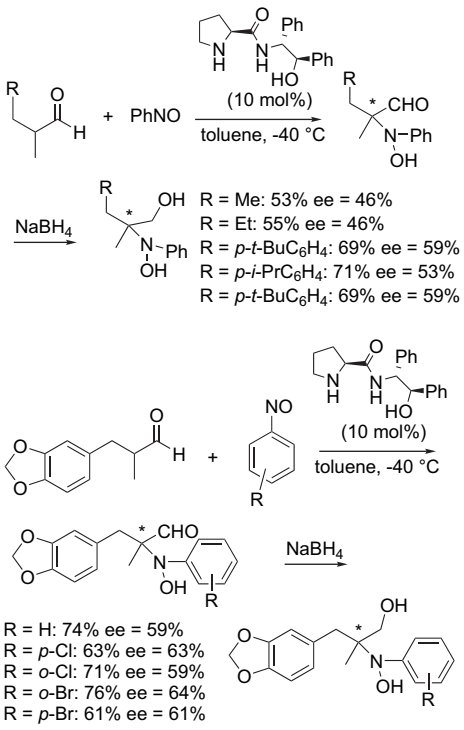


R^1 = H, R^2,R^2 = $(CH_2)_5$, n = 1: 81% ee = 83%
R^1 = Me, R^2,R^2 = $(CH_2)_5$, n = 1: 78% ee = 82%
R^1,R^1 = OCH_2CH_2O, R^2,R^2 = $(CH_2)_5$, n = 1: 63% ee = 91%
R^1 = H, R^2,R^2 = $(CH_2)_2O(CH_2)_2$, n = 1: 91% ee = 79%
R^1 = H, R^2,R^2 = $(CH_2)_2S(CH_2)_2$, n = 1: 88% ee = 77%

Scheme 138. *O*- and *N*-nitroso aldol reactions of enamines with PhNO.

On the other hand, Yamamoto and Momiyama have used organocatalysts other than proline derivatives such as 1-arylglycolic acids to catalyse the enantioselective nitroso aldol reaction.[258] The selectivity was significantly influenced by the choice of solvent. The piperidine enamine of cyclohexanone reacted with nitrosobenzene with >90% enantioselectivity in Et_2O in the presence of (*S*)-1-naphthylglycolic acid as catalyst (Scheme 138). It was shown that the use of (*S*,*S*)-1-naphthyl TADDOL as catalyst led selectively to the *N*-nitroso aldol reaction products (Scheme 138).

In 2006, Gong et al. reported another enantioselective *N*-nitroso aldol reaction involving α-branched aldehydes and a variety of nitrosobenzenes catalysed by an L-proline amide derivative.[259] The high ability to control the regioselectivity of the L-proline amide catalyst only allowed for the formation of α-hydroxyamination products in good yields with up to 64% ee (Scheme 139).



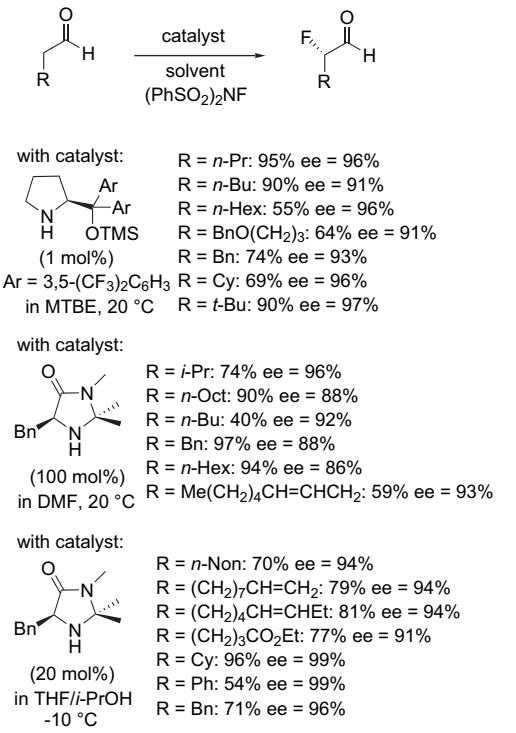
Scheme 139. L-Proline amide-catalysed *N*-nitroso aldol reactions.

6. Nucleophilic substitutions at aliphatic carbon

6.1. α-Halogenations of carbonyl compounds

Halogenated compounds are useful intermediates in organic synthesis, due to the fact that this functionality serves as a lynchpin for further transformations. Indeed, chiral halogen compounds are important in various fields of science, either for use in further manipulations or because the stereogenic C–halogen centre has a unique property which is of specific importance for a given molecule. The involvement of these functional groups for further stereospecific manipulations and their increasing importance in medicinal chemistry and material sciences have led to an increased search for catalytic asymmetric C–halogen bond-forming reactions.[238,260] Therefore, the enantioselective formation of these compounds is a deserved objective in asymmetric synthesis, with organocatalysis having shown its potential in this type of transformation. All organocatalytic halogenations reported to date are α-halogenations of carbonyl compounds.

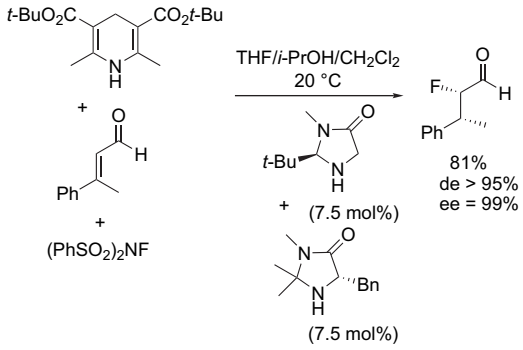
6.1.1. Fluorination reactions. Fluorine is the most electronegative element in the periodic table and its incorporation in organic compounds alters, sterically and electronically, the properties of molecules, affecting their pK_a, dipole moment and hydrogen-bonding capacity. Furthermore, the carbon–fluorine bond is strong, conferring a special stability and reactivity to fluorinated compounds. All these facts, together with their high metabolic stability, make these compounds ideal candidates for applications in medicinal chemistry.[261] Indeed, a wide range of fluorinated compounds are applied as pharmaceuticals and agrochemicals. Therefore, the enantioselective organocatalysed synthesis of fluorinated products represents an interesting synthetic challenge. Several groups have shown that L-proline and its derivatives were able to catalyse the fluorination of carbonyl compounds. As an example, Enders and Hüttl have focussed on the use of Selectfluor, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2,2,2]octane bis(tetrafluoroborate), as the electrophilic source of fluorine for the L-proline-catalysed α-fluorination of both aldehydes and ketones.[262] For the aldehydes, no enantiomeric excess was reported using L-proline as catalyst, whereas the use of the 3-hydroxy derivative of L-proline as catalyst of the fluorination of cyclohexanone gave rise to the expected α-fluorinated ketone with 56% yield and 36% ee. The fluorination of aldehydes has, however, been more successful with the almost simultaneously reported studies by Jorgensen et al., Barbas et al. and MacMillan et al. In all cases, the selected fluorinating agent was the stable, easily handled and commercially



Scheme 140. α-Fluorinations of aldehydes catalysed by TMS-protected diarylprolinol or imidazolidinone.

available *N*-fluorobenzenesulfonimide. The first group has selected the TMS-protected diarylprolinol, depicted in Scheme 140, as the best catalyst for the α-fluorination of a range of aldehydes, providing good chemical yields and excellent enantioselectivities when methyl *tert*-butyl ether was used as the solvent.[201,263] The work of Barbas' group was based on the same catalyst concept, since a chiral imidazolidinone (Scheme 140) was selected after evaluation of a large number of catalysts mostly derived from L-proline.[264] Under these conditions (30 mol % of catalyst) up to 88% ee was obtained for linear and branched aldehydes, in spite of a low conversion. An equimolecular amount of catalyst was needed to obtain moderate-to-good yields of the optically active α-fluorinated compounds with up to 96% ee. The same imidazolidinone derivative, as previously depicted, was also used with the reaction medium being mixtures of THF and isopropanol at −10 °C, achieving good chemical yields and excellent enantioselectivities for the corresponding fluorinated aldehydes (Scheme 140).[265] Although the standard catalyst loading used in this study was 20 mol %, this amount could be reduced to 2.5 mol % without a decrease in the enantioselectivity, but with a detrimental effect on the reaction time (12 h vs 30 min). This protocol permitted the fluorination of different aldehydes with a broad range of functionalities, maintaining the very high enantioselectivity (up to 99% ee).

In addition, MacMillan et al. have demonstrated that a combination of two imidazolidinone catalysts also permitted the synthesis of α-fluorinated aldehydes with excellent results (Scheme 141).[89] The mechanistic pathway could be defined as a tandem process involving, for the first time, a hydride transfer from the Hantzsch ester to the iminium intermediate, previously formed by the reaction of the starting α,β-

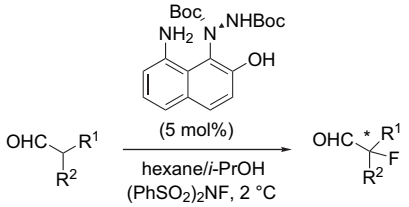


Scheme 141. α-Fluorination of aldehyde catalysed by combination of two imidazolidinone catalysts.

unsaturated aldehyde and the least substituted chiral amine catalyst, followed by hydrolysis to render an aliphatic intermediate. The second step was the fluorination, which took place by the reaction of *N*-fluorobenzenesulfonimide with the enamine formed by a previous reaction of the aliphatic aldehyde intermediate and the most substituted chiral amine catalyst. The final hydrolysis gave the expected aldehyde with a diastereomeric excess higher than 95%.

In 2006, Jorgensen et al. studied a non-biaryl atropisomeric naphthol as a catalyst to promote the enantioselective fluorination of 2-phenylpropanal by NFSI.[34] Surprisingly, it was noted that the reaction worked in all tested solvents, with good conversions and moderate-to-good enantioselectivities, irrespective of the polarity of the solvent. Therefore, the best result (95%, 86% ee) was obtained when hexane was used as solvent. Unfortunately, not all substrates were sufficiently soluble in hexane, and hence, a solvent mixture of hexane/*i*-PrOH (9:1) was used, in order to extend the scope of the reaction to other aldehydes (Scheme 142).

6.1.2. Chlorination and bromination reactions. Chiral α-chloro carbonyl compounds are especially versatile organic compounds, due to their potential for further synthetic transformations. For instance, chiral α-chloro aldehydes are good substrates for the synthesis of chiral amino acid derivatives, epoxides and amino alcohols by simple transformations without racemisation. A double process of enantioselective chlorination and esterification of acyl chlorides was developed by Lectka et al. In this process, a column-based flow system was present in which a cinchona alkaloid-based

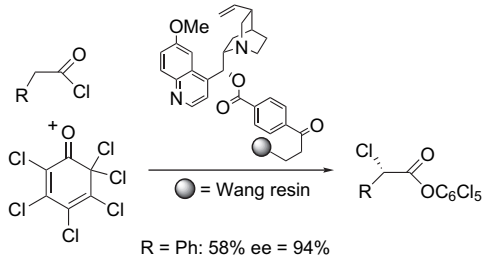


Scheme 142. α-Fluorinations of aldehydes catalysed by a naphthol catalyst.

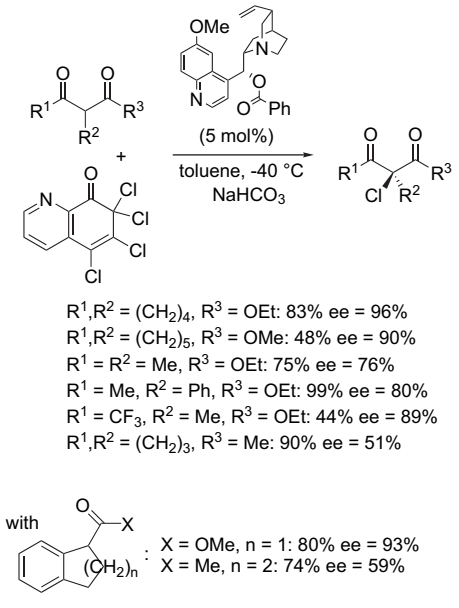
reagent/catalyst promoted, in the solid phase, the α-chlorination of acid chlorides to afford highly optically active α-chloroesters in high enantioselectivities and good yields.[266] Quinine was anchored to a Wang resin to give the catalyst depicted in Scheme 143, which was then used as a stoichiometric base in the chlorination process in a column-based flush-and-flow system. The alkaloid-derived beads could be easily regenerated by flushing Hünig's base through the column. This methodology was applied to the synthesis of a precursor of the metalloproteinase inhibitor, BMS-275291, used for the treatment of cancer.

In 2005, Bartoli et al. reported the α-chlorination of 1,3-dicarbonyl compounds using a cinchona alkaloid, benzoylquinidine, as catalyst and a trichloroquinolinone as the chlorinating reagent (Scheme 144).[267] The enantioselectivity was very dependent upon the substrate, giving the highest enantioselectivities (90–96% ee) with the cyclic β-keto esters, while the acyclic β-keto esters and β-diketones gave enantioselectivities in the range 51–89%.

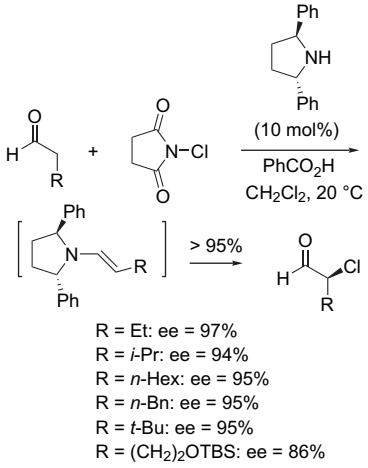
Aldehydes could also serve as substrates for the highly enantioselective α-chlorination process in the presence of



Scheme 143. α-Chlorinations of acyl chlorides using a polymer-bound quinine catalyst.



Scheme 144. Cinchona alkaloid-catalysed α-chlorinations of β-keto esters.

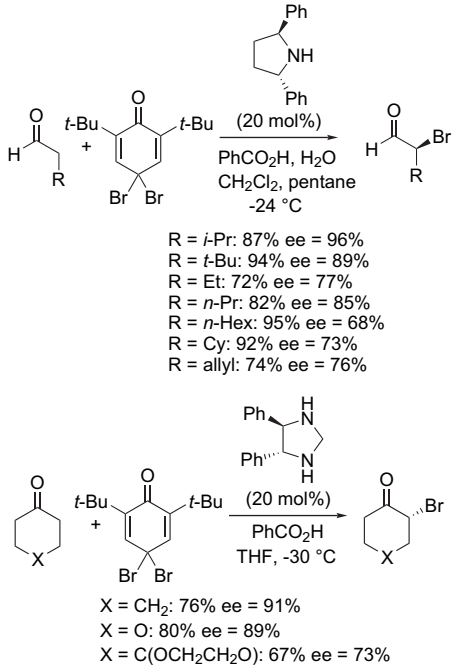


Scheme 145. (2*R*,5*R*)-Diphenylpyrrolidine-catalysed α-chlorinations of aldehydes.

C_2-symmetric (2*R*,5*R*)-diphenylpyrrolidine as catalyst (Scheme 145).[268] The mechanism of the reaction involved an initial *N*-chlorination of the chiral catalyst–substrate complex, followed by a 1,3-sigmatropic shift of the chlorine atom to the intermediate enamine carbon atom. This hypothesis was tested by an investigation of the possible presence of isotope effects, kinetics and by DFT calculations. The scope of the methodology could not be extended to less reactive starting carbonyl compounds such as ketones, since no conversion was observed under similar conditions, whereas the use of L-proline amide as catalyst allowed moderate yields and up to 81% ee to be obtained, due to polychlorination.

In addition, the formation of stereogenic C–Cl, as well as C–Br, bonds in the α-position to a carbonyl functionality can also be carried out in an indirect manner via a ketene, which is accessed from acyl chlorides using a resin-bound phosphazene base, a chiral organocatalyst in the form of a cinchona alkaloid and a halogenation agent such as perchlorinated quinine. This procedure, developed by Lectka et al., is an ingenious reaction process for the formation of α-chloro- and α-bromoesters with excellent enantioselectivity.[260b] Another interesting approach to the formation of chiral α-chloroesters was presented by Reynolds and Rovis,[269] who discovered that 2,2-dichloroaldehydes reacted with phenols in the presence of chiral triazolinylidene-carbenes to form the α-chloroesters in good yields and with high enantioselectivities.

Surprisingly, only two chiral organocatalysts have been employed by Jorgensen et al. for the α-bromination of aldehydes and ketones.[270] Indeed, the use of a C_2-symmetric diphenylpyrrolidine catalyst allowed the α-brominated aldehydes to be obtained in good yields and up to 96% ee, while ketones were α-brominated by using a C_2-symmetric imidazolidine catalyst in up to 94% ee (Scheme 146). The air-stable 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone turned out to be the best brominating agent. Furthermore, the organocatalytic enantioselective iodination of aldehydes was also demonstrated to proceed with up to 89% ee.

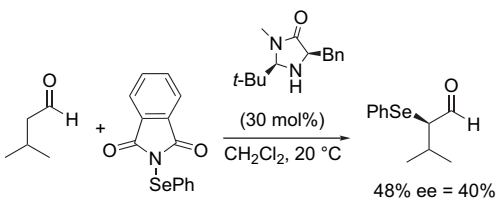


Scheme 146. α-Brominations of carbonyl compounds catalysed by C_2-symmetric pyrrolidine or imidazolidine catalyst.

6.2. Miscellaneous reactions

The enantioselective α-selenenylation of carbonyl compounds is still in its infancy. Actually, there is only one example of an organocatalysed version of this reaction reported by Wang et al. who used a chiral imidazolidinone to promote the reaction between isovaleraldehyde and *N*-(phenylseleno)phthalimide, yielding the expected α-selenenylated aldehyde with moderate results (Scheme 147).[271] This result could be slightly improved upon by the use of chiral 2-(tosylaminomethyl)pyrrolidine, which gave up to 60% ee. This catalyst was also applied to the α-selenenylation of cyclohexanone, giving the corresponding α-seleno cyclohexanone with 88% yield, but very low enantioselectivity (18% ee).

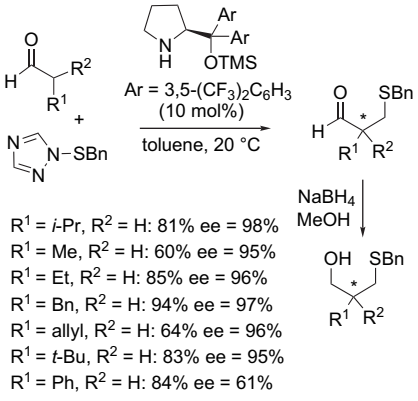
In addition, Gruttadauria et al. have reported, very recently, an α-selenenylation of aldehydes catalysed by polystyrene-supported proline and proline amide.[117] Both proline and proline amide resins gave high yields (65–98%), but recycling studies showed that the proline resin gave better results than the proline amide resin. Unfortunately, the enantioselectivity was low (unspecified), as was that observed under homogeneous conditions, as depicted above.



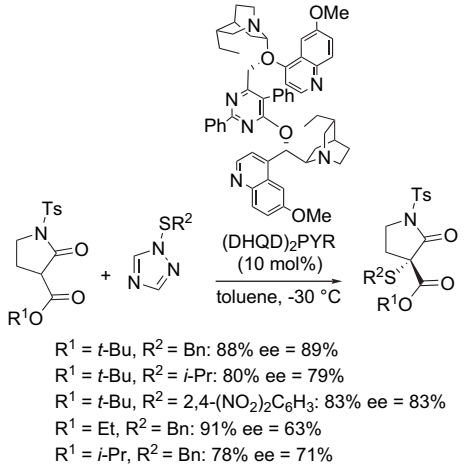
Scheme 147. α-Selenenylation of isovaleraldehyde catalysed by imidazolidinone catalyst.

Despite the synthetic potential of α-sulfenylated carbonyl compounds, their asymmetric synthesis generally involved the use of chiral auxiliaries. Therefore, the development of enantioselective protocols, avoiding the use of poisonous transition metals, is still highly desirable. This goal was achieved in 2005 by Jorgensen et al., who reported the reaction of aldehydes with an electrophilic sulfur source triazole in the presence of sub-stoichiometric amounts of a TMS-protected diarylprolinol as catalyst, providing, after final reduction and hydrolysis, the corresponding chiral 2-benzylsulfanyl alcohols with excellent results (Scheme 148).[272] To facilitate the work up, the reaction products were isolated as the corresponding alcohols, after in situ reduction of the aldehyde moiety with $NaBH_4$, without loss of enantiomeric excess.

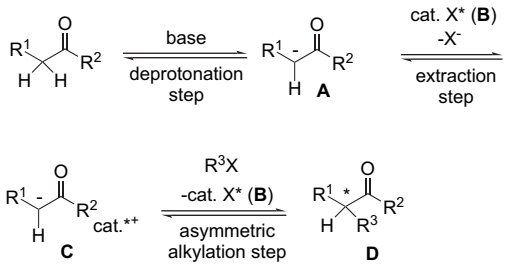
In 2005, a second example of enantioselective α-sulfenylations of carbonyl compounds was described by Jorgensen et al., using a cinchona alkaloid as catalyst.[273] In this work, activated C–H bonds of lactones, lactams and 1,3-dicarbonyl compounds were reacted with the sulfur electrophile reagent, 1-benzylsulfanyl[1,2,4]triazole, affording the corresponding chiral α-sulfenylated products in moderate-to-high yields (up to 95%) and enantioselectivities of up to 91% ee. Scheme 149 summarises the



Scheme 148. α-Sulfenylations of aldehydes catalysed by proline derivative.



Scheme 149. $(DHQD)_2PYR$-catalysed α-sulfenylations of cyclic β-keto esters.



Scheme 150. Nucleophilic substitution at aliphatic carbon.

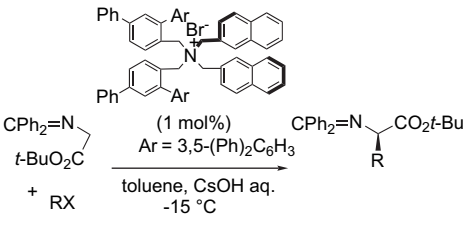
results obtained for the reaction of cyclic β-keto esters catalysed by $(DHQD)_2PYR$. It was shown that the nature of the R^2 substituent borne by the sulfur reagent did not have any important effect on the enantioselectivity of the reaction, whereas the bulkiness of the ester moiety of the β-keto ester had an accountable effect, since, the more crowded the ester moiety, the higher the enantioselectivity.

Enantioselective catalytic alkylation is a versatile method for the construction of stereogenic carbon centres. Typically, phase-transfer catalysts are used and these form a chiral ion pair **C** as a key intermediate (Scheme 150). In the first step, an anion **A** is formed via deprotonation with an achiral base; this is followed by extraction in the organic phase via formation of a salt complex **C** with the phase-transfer organocatalyst **B**. Subsequently, a nucleophilic substitution reaction furnishes the optically active alkylated product **D**, with the recovery of the catalyst **B**. An overview of this process concept is depicted in Scheme 150.

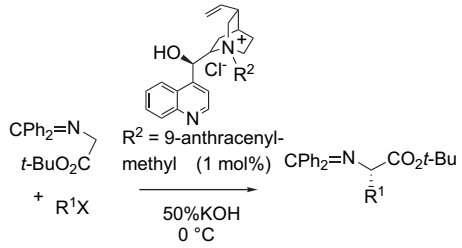
In 2006, Maruoka et al. designed and prepared novel conformationally flexible, *N*-spiro chiral quaternary ammonium bromides incorporating a modular achiral biphenyl structure as a conceptually new chiral phase-transfer catalyst.[274] Among these salts, one catalyst was particularly efficient to catalyse the enantioselective phase-transfer alkylation of *tert*-butyl glycinate benzophenone Schiff base with various alkyl halides (Scheme 151). Similar reactions were performed by Takabe et al. in aqueous media without any organic solvent in the presence of a cinchona alkaloid catalyst, providing similar results under mild conditions (Scheme 151).[275]

In 2005, Jorgensen et al. reported an efficient organocatalytic nucleophilic aromatic substitution reaction between activated aromatic compounds and 1,3-dicarbonyl compounds using phase-transfer catalysis.[276] This new reaction catalysed by a cinchona alkaloid afforded functionalised chiral products bearing a quaternary stereocentre in high enantioselectivity and excellent yields (Scheme 152).

In 2007, the same group developed the first organocatalytic enantioselective α-alkynylation of β-keto esters and 3-acyl oxindoles catalysed by a chiral phase-transfer cinchona alkaloid, affording the corresponding alkynylated products in high yields and excellent enantioselectivities (Scheme 153).[277] The scope of the reaction was extended

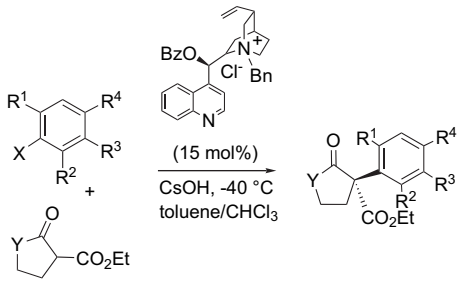


R = *p*-FC_6H_4, X = Br: 83% ee = 95%
R = *p*-Tol, X = Br: 83% ee = 96%
R = *p*-$AcC_6H_4CH_2$, X = Br: 90% ee = 90%
R = allyl, X = Br: 85% ee = 93%
R = CH_2=C(Me)CH_2, X = Br: 85% ee = 96%
R = Et, X = I: 61% ee = 93%



R^1 = *p*-$FC_6H_4CH_2$, X = Br: 84% ee = 93%
R^1 = Bn, X = Br: 96% ee = 85%
R^1 = allyl, X = Br: 87% ee = 82%
R^1 = $HCCCH_2$, X = Br: 87% ee = 90%
R^1 = Me, X = I: 83% ee = 84%
R^1 = Et, X = I: 81% ee = 92%
R^1 = *p*-$ClC_6H_4CH_2$, X = Br: 97% ee = 91%

Scheme 151. Phase-transfer alkylations of a glycinate Schiff base.

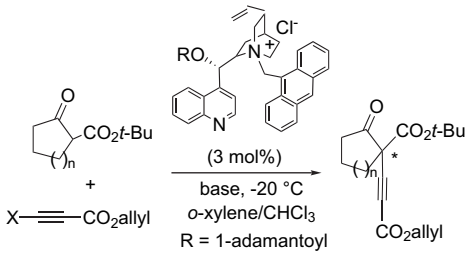


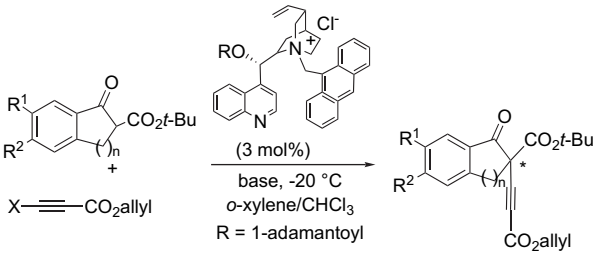
R^1 = R^4 = NO_2, R^2 = R^3 = H, X = F, Y = NBoc: 93% ee = 85%
R^1 = R^4 = NO_2, R^2 = H, R^3 = Br, X = F, Y = CH_2: 96% ee = 92%
R^1 = H, R^2 = CN, R^3 = X = F, R^4 = NO_2, Y = CH_2: 81% ee = 86%
R^1 = R^4 = NO_2, R^2 = H, R^3 = X = F, Y = CH_2: 81% ee = 87%
R^1 = H, R^2 = CN, R^3 = X = F, R^4 = NO_2, Y = NBoc: 76% ee = 75%

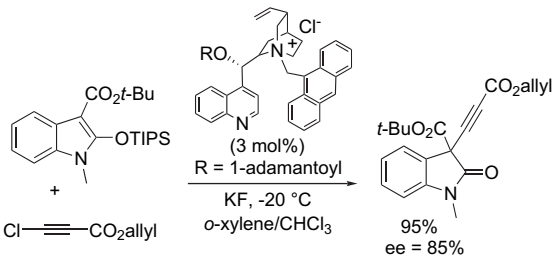
Scheme 152. S_NAr reactions catalysed by phase-transfer cinchona alkaloid.

to a large number of cyclic β-keto esters with various ring sizes.

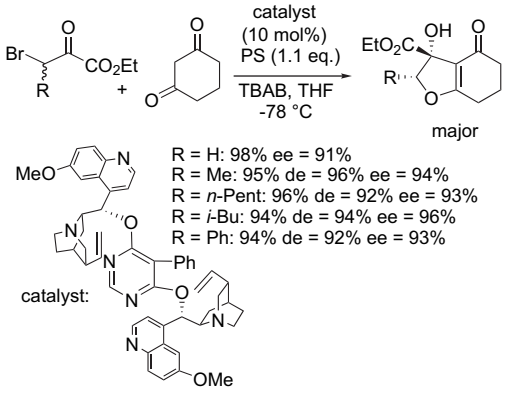
The Feist–Bénary reaction involves the condensation of β-dicarbonyl compounds with α-haloketones to produce hydroxydihydrofurans, followed by elimination to form furans. When the reaction is stopped at the intermediate hydroxydihydrofurans, it is called the interrupted Feist–Bénary reaction. In 2005, Calter et al. reported an enantioselective version of this reaction catalysed by a cinchona alkaloid, providing high enantioselectivity in the presence of TBAB and proton sponge (PS), as shown in Scheme 154.[278]







Scheme 153. α-Alkynylations of cyclic β-keto esters by phase-transfer cinchona alkaloid.



Scheme 154. Interrupted Feist–Bénary reactions catalysed by cinchona alkaloid.

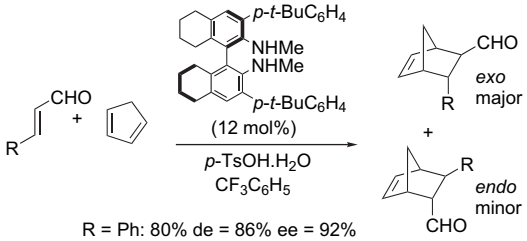
7. Cycloaddition reactions

7.1. Diels–Alder reactions

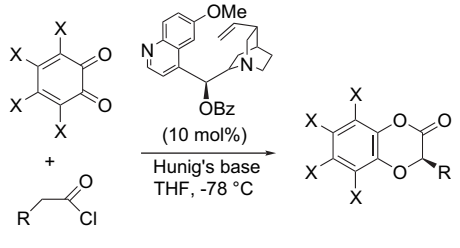
The asymmetric Diels–Alder reaction is one of the most important organic transformations and has proved to be a versatile means of synthesis of a large number of important chiral building blocks and intermediates in the total synthesis of natural products.[279] For a long time, it was not known that organocatalysts could be used to catalyse the Diels–Alder reactions and base-catalysed Diels–Alder reactions, in particular, were regarded as uncommon. In recent years, several different organocatalysts have been developed. As an example, Maruoka et al. reported, in 2006, the design and synthesis of a novel binaphthyl-based diamine,[280] the *p*-Tosyl salt of which had the advantage of exhibiting an unprecedentedly high *exo* selectivity in the asymmetric Diels–Alder reaction of cyclopentadiene with α,β-unsaturated aldehydes (Scheme 155).

In 2006, a cinchona alkaloid-based catalyst was successfully employed by Lectka et al. to promote enantioselective Diels–Alder reactions between ketene enolates, generated from the corresponding acyl chlorides, and *o*-quinones, providing an efficient entry to chiral α-oxygenated carboxylic acid derivatives (Scheme 156).[281]

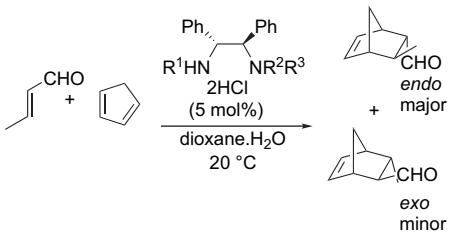
On the other hand, Ha et al. have demonstrated that the bis-ammonium salts of mono-*N*-alkylated chiral 1,2-diamino-1,2-diphenylethane (DPEN) could be used in the catalytic Diels–Alder reaction between cyclopentadiene and crotonaldehyde.[282] Hence, the *N*-3-pentyl diamine·2HCl catalyst showed high *endo*/*exo*-selectivity and *endo*-enantioselectivity for the cycloaddition, and this organocatalyst was the first example of the use of a chiral 1,2-diamine to generate an imine intermediate, which was activated by an internal ammonium Brønsted acid for the cycloaddition in a wet solvent



Scheme 155. Diels–Alder reactions catalysed by binaphthyl-based diamine salt.



Scheme 156. Diels–Alder reactions catalysed by cinchona alkaloid.



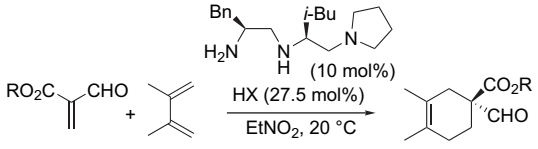
$R^1 = R^2 = H$, $R^3 = i$-Pr: 97% de = 72% ee = 86%
$R^1 = R^2 = H$, R^3 = Cy: 96% de = 74% ee = 85%
$R^1 = R^2 = H$, $R^3 = i$-Pent: 97% de = 78% ee = 91%
$R^1 = R^2 = H$, $R^3 = n$-Non: 94% de = 76% ee = 87%
$R^1 = H$, R^2,$R^3 = (CH_2)_4$: 98% de = 74% ee = 84%
$R^1 = R^2 = i$-Pr, $R^3 = H$: 77% de = 44% ee = 19%
$R^1 = R^2 = H$, $R^3 = i$-Pent: 94% de = 62% ee = 78%

Scheme 157. Diels–Alder reactions catalysed by bisammonium salts of DPEN.

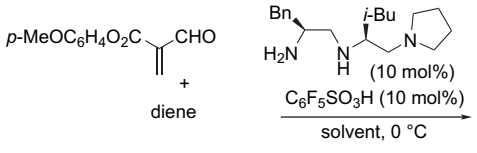
(Scheme 157). This successful reaction was, however, restricted to the use of β-substituted α,β-enals as the dienophiles.

In the same context, the ammonium salt of a chiral triamine bearing a primary amino group was involved by Ishihara and Nakano to catalyse the Diels–Alder reactions of α-acyloxyacroleins.[283] The results are summarised in Scheme 158.

In 2005, Ogilvie and Lemay disclosed the design and synthesis of a new structural class of organic catalysts functioning in water.[284] A hydrazide was employed as the catalytic machinery in a compact camphor-derived framework that imparted facial selectivity to Diels–Alder reactions. Kinetic evidence suggested that the reaction involved a rapid iminium formation, as shown in Scheme 159. It was demonstrated that the catalyst functioned best in water, providing an environmentally benign reaction that gave excellent yields and enantioselectivities, with a preference for the *exo* isomer.

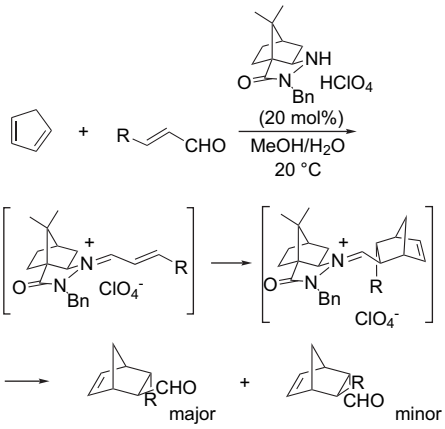


R = *p*-$MeOC_6H_4$, X = $C_6F_5SO_3$: > 99% ee = 90%
R = Ph, X = $C_6F_5SO_3$: 97% ee = 87%
R = Me, X = 2,4-$(NO_2)_2C_6H_3SO_3$: 97% ee = 87%



DA adducts
diene = cyclopentadiene, solvent = THF:
99% *exo:endo* = 87:13 ee = 83%
diene = cyclohexadiene, solvent = $EtNO_2$:
84% *exo:endo* = 7:93 ee = 91%
diene = isoprene, solvent = $EtNO_2$:
90% *exo:endo* = 99:1 ee = 88%
diene = 2,3-dimethylbutadiene, solvent = $EtNO_2$:
92% ee = 92%

Scheme 158. Diels–Alder reactions catalysed by ammonium salt of triamine.

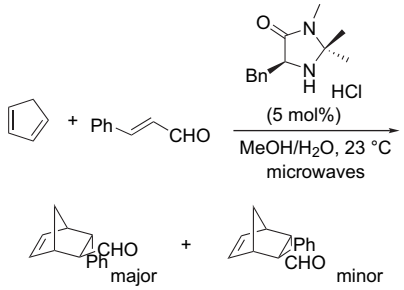


R = Ph: 96% *exo:endo* = 66:34 ee = 90%
R = *p*-$O_2NC_6H_4$: 93% *exo:endo* = 69:31 ee = 92%
R = *p*-ClC_6H_4: 92% *exo:endo* = 67:33 ee = 90%
R = *p*-*i*-PrC_6H_4: 84% *exo:endo* = 63:37 ee = 90%
R = *o*-$O_2NC_6H_4$: 90% *exo:endo* = 55:45 ee = 87%
R = *m*-$O_2NC_6H_4$: 88% *exo:endo* = 85:15 ee = 94%
R = *i*-Pr: 84% *exo:endo* = 72:28 ee = 85%
R = *n*-Pr: 83% *exo:endo* = 62:38 ee = 81%

Scheme 159. Diels–Alder reactions catalysed by hydrazide catalyst in water.

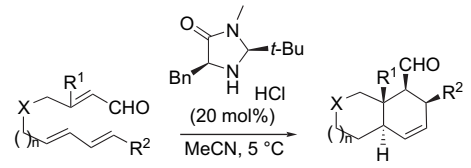
MacMillan's chiral imidazolidinones have also been successfully used to catalyse Diels–Alder reactions. Alexakis and Mosse described, in 2006, the first microwave-assisted organocatalysed enantioselective Diels–Alder reaction between cyclopentadiene and cinnamaldehyde, ingeniously discovered by MacMillan.[59] The combination of microwaves with a MacMillan imidazolidinium salt allowed an excellent yield and enantioselectivity to be obtained, as shown in Scheme 160.

In 2006, Houk and Gordillo studied the Diels–Alder reactions of cyclopentadiene with α,β-unsaturated aldehydes and ketones catalysed by MacMillan's imidazolidinones on the basis of B3LYP/6-31G(d) density functional theory.[285] The DFT calculations have demonstrated that secondary amines decreased the activation energies of the Diels–Alder reactions of cyclopentadiene with α,β-unsaturated aldehydes and ketones by 13 and 11 kcal/mol, respectively. The formation of an iminium complex produced a much more reactive dienophile. Although a number of different conformers of iminium intermediates and transition states were located, there was a preference for attack in



99% *exo:endo* = 57:43 ee (*exo*) = ee (*endo*) = 93%

Scheme 160. Diels–Alder reaction catalysed by MacMillan salt and microwaves.



R^1 = H, R^2 = Ph, X = CH_2, n = 1: 85% de > 90% ee = 93%
R^1 = H, R^2 = CH=CH_2, X = CH_2, n = 1: 75% de > 90% ee = 94%
R^1 = Me, R^2 = Ph, X = CH_2, n = 1: 76% de > 90% ee = 94%
R^1 = H, R^2 = Ph, X = O, n = 1: 84% de > 90% ee = 93%
R^1 = H, R^2 = Ph, X = CH_2, n = 2: 70% de > 90% ee = 92%
R^1 = H, R^2 = OBn, X = CH_2, n = 1: 99% de > 98% ee = 72%

Scheme 161. Intramolecular Diels–Alder reactions catalysed by MacMillan catalyst.

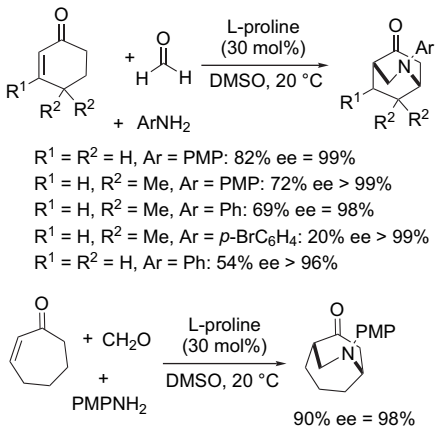
a sterically unencumbered fashion that led to a family of preferred transition structures and high stereoselectivity. The iminium activation strategy was applied by MacMillan et al. to the development of the first example of an organocatalytic intramolecular Diels–Alder reaction.[286] This powerful new catalytic variant of the intramolecular Diels–Alder reaction, using the LUMO-lowering iminium activation strategy, has allowed the preparation of various cycloadducts incorporating ether and quaternary carbon functionalities (Scheme 161). Moreover, the synthetic utility of this protocol was demonstrated via the total synthesis of the marine metabolite, solanapyrone D, a phytotoxic polyketide. The same methodology was used by Koskinen and Selkälä to prepare other bicyclo[4.3.0]nonanes and was applied to the synthesis of amaminol A, a cytotoxic agent against murine leukaemia cells.[287]

On the other hand, several groups have developed organocatalysed asymmetric hetero-Diels–Alder reactions, such as aza-Diels–Alder reactions, which constitute one of the most powerful C–C bond-forming reactions for the preparation of nitrogen-containing compounds, such as piperidine and quinolidine derivatives. As an example, in 2005, Cordova et al. reported the first one-pot, three-component direct catalytic enantioselective aza-Diels–Alder reaction.[190,288] This reaction, catalysed by L-proline, yielded the corresponding products with excellent stereoselectivity, as shown in Scheme 162.

In 2006, Akiyama et al. showed that Danishefsky's diene and aldimines underwent aza-Diels–Alder reactions under the influence of a chiral phosphoric acid derived from (*R*)-BINOL to afford piperidinone derivatives in good-to-high enantioselectivities (Scheme 163).[289]

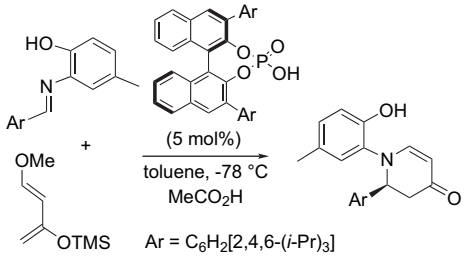
A chiral aminoindanol-derived triazolium salt, already depicted in Scheme 91, was also used by Bode et al. as an efficient catalyst of azadiene Diels–Alder reactions.[290] This strategy, mediated by an *N*-heterocyclic carbene, involved the generation of a highly reactive dienophile that participated in $LUMO_{diene}$-controlled Diels–Alder cyclisations with α,β-unsaturated imines. This new triazolium precatalyst afforded the dihydropyridinone products in >99% ee's for a wide range of substrates (Scheme 164).

In 2005, Yamamoto et al. found the axially chiral 1,1′-biaryl-2,2′-dimethanol (BAMOL) scaffold to be highly effective



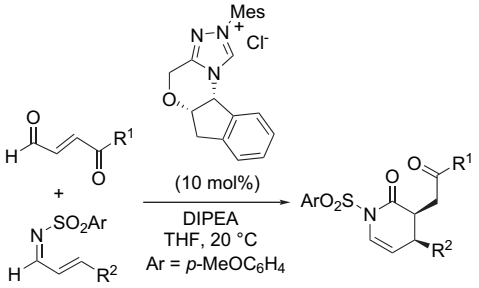
R^1 = R^2 = H, Ar = PMP: 82% ee = 99%
R^1 = H, R^2 = Me, Ar = PMP: 72% ee > 99%
R^1 = H, R^2 = Me, Ar = Ph: 69% ee = 98%
R^1 = H, R^2 = Me, Ar = *p*-BrC_6H_4: 20% ee > 99%
R^1 = R^2 = H, Ar = Ph: 54% ee > 96%

Scheme 162. L-Proline-catalysed three-component aza-Diels–Alder reactions.



Ar = Ph: 99% ee = 80%
Ar = *p*-IC_6H_4: 86% ee = 84%
Ar = *p*-BrC_6H_4: 100% ee = 84%
Ar = *p*-ClC_6H_4: 72% ee = 84%
Ar = *p*-$CF_3C_6H_4$: 82% ee = 81%
Ar = *o*-BrC_6H_4: 96% ee = 80%
Ar = 1-naph: 100% ee = 91%

Scheme 163. Aza-Diels–Alder reactions catalysed by BINOL derivative.



R^1 = OEt, R^2 = Ph: 90% ee = 99%
R^1 = OEt, R^2 = *p*-$MeOC_6H_4$: 81% ee = 99%
R^1 = OEt, R^2 = *p*-AcC_6H_4: 55% ee = 99%
R^1 = OEt, R^2 = *n*-Pr: 58% ee = 99%
R^1 = O*t*-Bu, R^2 = Ph: 70% ee = 97%
R^1 = Me, R^2 = Ph: 51% ee = 99%
R^1 = Me, R^2 = *n*-Pr: 71% ee = 98%
R^1 = Ph, R^2 = *p*-$MeOC_6H_4$: 52% ee = 99%

Scheme 164. Azadiene Diels–Alder reactions catalysed by *N*-heterocyclic carbene.

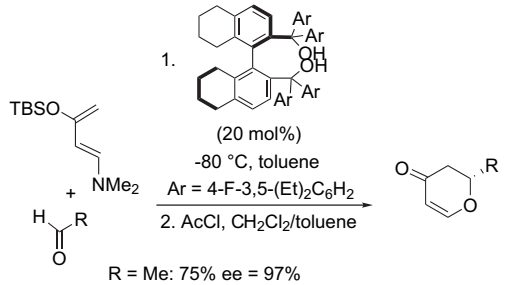
for the catalysis of the hetero-Diels–Alder reactions of a wide range of aliphatic and aromatic aldehydes.[291] This new scaffold shared with TADDOLs the bis(diarylhydroxymethyl) functionality, in which the steric and electronic

properties were readily tunable. Useful yields and excellent enantioselectivities were obtained for the hetero-Diels–Alder reactions between 1-amino-3-siloxydiene and a wide variety of unactivated aldehydes (Scheme 165). In 2007, Deslongchamps et al. studied the reverse docking of a TADDOL catalyst to rigid transition state models of catalyst-free reactions for the same reactions as described above.[292]

Chiral bis-trifluoromethanesulfonylamides have been shown to work as efficient organocatalysts for the hetero-Diels–Alder reactions between Danishefsky's diene and glyoxylate or phenylglyoxal, presumably through double hydrogen bonding (Scheme 166).[293] Among these bis-triflylamides, (*R*,*R*)-1,2-*N*,*N*′-bis-(trifluoromethanesulfonylamino)-1,2-diphenylethane (DPENTf) gave the highest enantioselectivity (87% ee). In addition, Jorgensen et al. have developed similar reactions catalysed by a bis-nonaflamide of the same chiral diamine described above, which gave enantioselectivities of up to 73% ee (Scheme 166).[150]

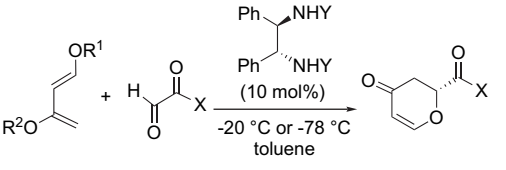
7.2. Miscellaneous cycloadditions

In 2005, Hsung et al. reported an intramolecular aza-[3+3] cycloaddition catalysed by an L-proline-based amine salt.[294] A detailed study of various secondary amine salts was undertaken, showing a dependence of enantioselectivity on the structural features of these chiral amine catalysts. This study also revealed a very interesting reversal of the stereochemistry in the respective cycloadducts obtained using C_1- and C_2-symmetric amine salts. The best results are summarised in Scheme 167.



R = Me: 75% ee = 97%
R = Ph: 84% ee = 98%
R = *m*-$MeOC_6H_4$: 86% ee = 98%
R = *o*-$O_2NC_6H_4$: 93% ee = 98%
R = 1-naph: 67% ee = 97%
R = 2-Fu: 96% ee > 99%

Scheme 165. BAMOL-catalysed hetero-Diels–Alder reactions.

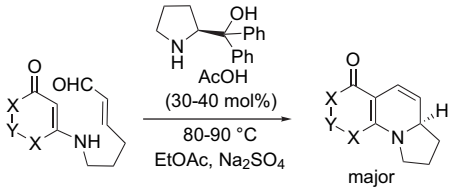


R^1 = *t*-Bu, R^2 = TMS, X = *n*-Bu, Y = Tf: 23% ee = 23%
R^1 = Me, R^2 = TIPS, X = Ph, Y = Tf: 67% ee = 87%
R^1 = Me, R^2 = TIPS, X = *p*-$F_3CC_6H_4$, Y = Tf: 74% ee = 78%
R^1 = Me, R^2 = TIPS, X = *p*-$MeOC_6H_4$, Y = Tf: 46% ee = 77%
R^1 = Me, R^2 = TIPS, X = *n*-Bu, Y = Tf: 87% ee = 86%
R^1 = Me, R^2 = TBS, X = *n*-Bu, Y = Tf: 55% ee = 58%
R^1 = Me, R^2 = TMS, X = *n*-Bu, Y = Tf: 43% ee = 55%

Scheme 166. Bis-sulfonamide-catalysed hetero-Diels–Alder reactions.

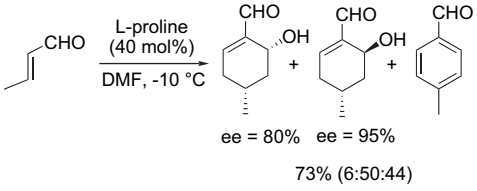
L-Proline was used by Hong et al. to promote an enantioselective [3+3] cycloaddition of α,β-unsaturated aldehydes, providing a practical tool for the rapid and efficient access to six-membered ring systems (Scheme 168).[295] Using this methodology, crotonaldehyde was converted into 6-hydroxy-4-methylcyclohex-1-enecarbaldehyde, which was used in the synthesis of (−)-isopulegol hydrate and (−)-cubebaol.

In 2006, Terada et al. developed a highly efficient enantioselective aza–ene-type reaction of *N*-benzoylimines with enecarbamates, using an extremely low loading (0.1 mol %) of a binaphthol-derived monophosphoric acid catalyst (Scheme 169).[296] This methodology provided a practical route to synthetically useful β-amino-imine

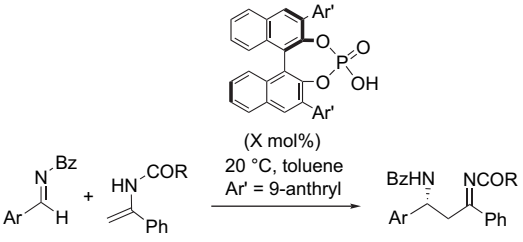


X = NMe, Y = C=O: 65% de = 60%
X = CH_2, Y = $C(Me)_2$: 61% de = 46%
X = Y = CH_2: 44% de = 20%

Scheme 167. Intramolecular aza-[3+3] cycloadditions catalysed by L-proline-based amine salt.



Scheme 168. L-Proline-catalysed [3+3] cycloaddition of crotonaldehyde.



Ar = Ph, R = Me, X = 2: 90% ee = 86%
Ar = Ph, R = O*t*-Bu, X = 2: 94% ee = 60%
Ar = Ph, R = OBn, X = 2: 55% ee = 83%
Ar = Ph, R = OMe, X = 2: 85% ee = 95%
Ar = *p*-Tol, R = OMe, X = 0.1: 90% ee = 95%
Ar = *m*-Tol, R = OMe, X = 0.1: 83% ee = 93%
Ar = *o*-Tol, R = OMe, X = 0.1: 84% ee = 93%
Ar = *p*-$MeOC_6H_4$, R = OMe, X = 0.1: 82% ee = 92%
Ar = *p*-BrC_6H_4, R = OMe, X = 0.1: 89% ee = 96%
Ar = *m*-BrC_6H_4, R = OMe, X = 0.1: 85% ee = 95%
Ar = *p*-FC_6H_4, R = OMe, X = 0.1: 89% ee = 95%
Ar = *p*-NCC_6H_4, R = OMe, X = 0.1: 97% ee = 98%
Ar = 1-naph, R = OMe, X = 0.1: 88% ee = 95%
Ar = 2-naph, R = OMe, X = 0.1: 91% ee = 95%
Ar = Ph-CH=CH, R = OMe, X = 0.1: 81% ee = 93%

Scheme 169. Aza–ene-type reactions catalysed by BINOL-derived monophosphoric acid.

derivatives, which could be readily transformed into 1,3-diamine derivatives of synthetic and biological importance.

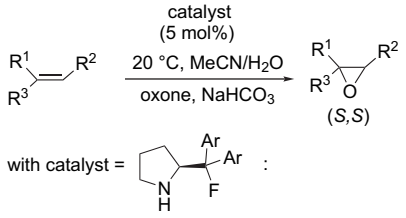
8. Oxidations

8.1. Epoxidations of alkenes

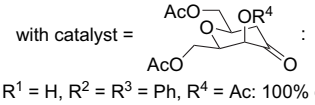
Asymmetric epoxidation is an extremely useful methodology to generate chiral compounds, because chiral epoxides are versatile building blocks in organic synthesis.[297] In addition, many biologically active compounds and natural products contain epoxide functionalities.[298] In 2005, Yang et al. synthesised a series of chiral cyclic secondary amines having different substitution patterns and screened them as organocatalysts for the asymmetric epoxidation of olefins using oxone (Scheme 170).[299] The best result occurred for the epoxidation of 1-phenylcyclohexene catalysed by a cyclic secondary amine bearing a fluorine atom at the β-position relative to the amino centre. The experimental results provided support to the notion that the amine played a dual role as a phase-transfer catalyst and an oxone activator. The slightly acidic reaction conditions obviated the need to preperform ammonium salts, which were the actual catalysts that mediated the epoxidations. In 2006, Armstrong and Tsuchiya reported that similar reactions could be catalysed by tetrahydropyran-4-one catalysts, affording epoxides with up to 83% ee (Scheme 170).[300] In addition, asymmetric epoxidation of 1-phenylcyclohexene could be performed in non-aqueous conditions in the presence of iminium salt organocatalysts and by using monoperoxybisulfate as the oxidant, providing up to 50% ee.[301]

8.2. Epoxidations of enones

Although methods for the enantioselective epoxidation of alkenes have been admirably performed over the last 30 years, achievements in the epoxidation of electron-poor alkenes, such as enones, with good results have been less developed.



Ar = *p*-Tol, R^1,R^2 = $(CH_2)_4$, R^3 = Ph: 92% ee = 61%
R^1,R^2 = $(CH_2)_4$, R^3 = Ar = Ph: 87% ee = 50%
R^1 = H, R^2 = R^3 = Ar = Ph: 80% ee = 28%
R^1 = Me, R^2 = R^3 = Ar = Ph: 88% ee = 33%
R^1 = H, R^2 = Ar = Ph, R^3 = Me: 86% ee = 15%
R^1,R^2 = $(CH_2)_4$, R^3 = *m*-FC_6H_4, Ar = Ph: 95% ee = 48%



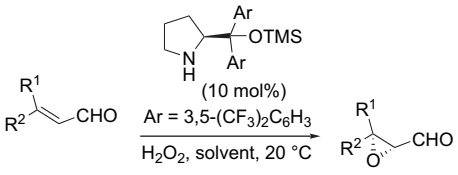
R^1 = H, R^2 = R^3 = Ph, R^4 = Ac: 100% ee = 81%
R^1 = H, R^2 = R^3 = Ph, R^4 = Piv: 43% ee = 43%
R^1 = H, R^2 = R^3 = Ph, R^4 = Bz: 91% ee = 83%
R^1 = R^2 = R^3 = Ph, R^4 = Bz: 53% ee = 82%

Scheme 170. Organocatalysed epoxidations of olefins with oxone.

In this case, a nucleophilic oxygen-donor molecule is necessary for carrying out this transformation. Recently, a number of useful combinations of different types of organocatalysts and oxidative reagents have been elaborated. As an example, Jorgensen et al. have recently introduced the use of an L-proline-derived amine as a soluble catalyst for the enantioselective epoxidation of α,β-unsaturated aldehydes to give the corresponding epoxides in excellent enantioselectivities (Scheme 171). As far as the oxidants were concerned, similar results could be obtained not only with H_2O_2, but also with urea–hydrogen peroxide, and even with organic peroxides. Moreover, the reactions could be performed in solvents other than CH_2Cl_2 with only a slight decrease in the enantioselectivity, even in the case of using an environmentally safe water–ethanol mixture.[302] The proposed mechanism consisted of the formation of the corresponding iminium ion by condensation of the amine catalyst with the aldehyde, which suffered nucleophilic attack of the peroxide derivative at the β-position, leading to an enamine. The intramolecular nucleophilic attack of this enamine on the peroxide moiety gave the corresponding iminium epoxide, which, after hydrolysis, liberated the final epoxide and the regenerated catalyst.

The use of other organocatalysts, such as various chiral pyrrolidine derivatives, proline and amino acid-derived imidazolidinones, under similar conditions to those described above, did not improve the original results.[303] A change of the oxidant to either solid sodium percarbonate or *tert*-butyl hydroperoxide, as well as the solvent to $CHCl_3$, however, allowed the enantioselectivity to reach higher than 98% ee. In one example, TMS-protected α,α-diphenyl-2-prolinol catalysed the formation of 2-epoxy-aldehydes in 81–95% yield with up to 92% de and 98% ee.

In 2005, Lattanzi applied other α,α-diaryl-2-prolinols as organocatalysts in the enantioselective epoxidation of different chalcones, using *tert*-butyl hydroperoxide as oxidant and non-polar solvents such as hexane, to afford the expected chiral epoxides with good results (up to 94% ee).[304] This study has shown that stereoelectronic substitution on the



solvent = CH_2Cl_2:
R^1 = Ph, R^2 = H: 80% de = 86% ee = 96%
R^1 = *o*-$O_2NC_6H_4$, R^2 = H: 90% de = 82% ee = 97%
R^1 = *p*-ClC_6H_4, R^2 = H: 63% de = 90% ee = 98%
R^1 = Et, R^2 = H: 90% de = 94% ee = 96%
R^1 = CH_2OBn, R^2 = H: 84% de = 92% ee = 94%
R^1 = CO_2Et, R^2 = H: 60% de = 80% ee = 96%
R^1 = R^2 = Me: 65% ee = 75%
solvent = EtOH:H_2O (3:1):
R^1 = Ph, R^2 = H: 43% de = 72% ee = 92%
R^1 = *p*-ClC_6H_4, R^2 = H: 40% de = 68% ee = 96%
R^1 = *p*-$O_2NC_6H_4$, R^2 = H: 56% de = 66% ee = 90%
R^1 = CO_2Et, R^2 = H: 53% de = 62% ee = 88%

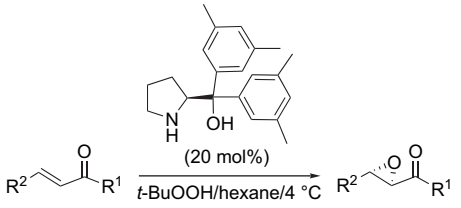
Scheme 171. Epoxidations of α,β-unsaturated aldehydes catalysed by L-proline derivative.

aryl moiety of the diaryl-2-pyrrolidinemethanols significantly affected the efficiency with respect to the previously reported (*S*)-diphenyl-2-pyrrolidinemethanol.[304a] Improved reactivity and enantioselectivity were achieved with bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol at reduced catalyst loading (20 mol %) with ee's of up to 92% for chalcone epoxides under mild reaction conditions, whereas (*S*)-diphenyl-2-pyrrolidinemethanol afforded a maximum ee of 80%. Interestingly, this methodology was applicable to the epoxidation of more challenging aliphatic or enolisable enones with good control of the asymmetric induction (Scheme 172).

In the same context, Bako et al. have used a D-mannose-based azacrown ether to catalyse similar reactions in toluene, in a liquid–liquid two-phase system, employing 20% aqueous NaOH as base.[185] The results are summarised in Scheme 173.

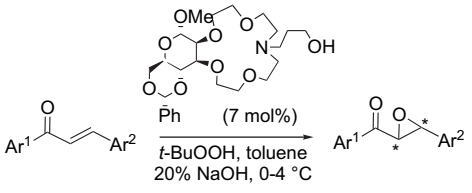
In 2005, Jew et al. developed highly enantioselective epoxidations of 2,4-diarylenones by using dimeric cinchona phase-transfer catalysts, and demonstrated an enhancement of the enantioselectivity by surfactants.[305] The best results were obtained with Span 20, in the presence of a dimeric catalyst, hydrogen peroxide and aqueous KOH (Scheme 174).

Enantioselective organocatalytic epoxidations of α,β-unsaturated aldehydes using hypervalent iodine reagents, such as



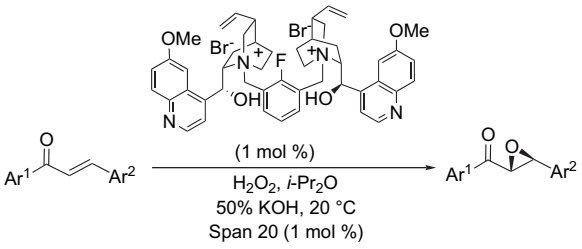
$R^1 = R^2$ = Ph: 90% ee = 91%
R^1 = *p*-BrC_6H_4, R^2 = Ph: 81% ee = 92%
R^1 = *m*-Tol, R^2 = Ph: 98% ee = 89%
R^1 = Ph, R^2 = *p*-$MeOC_6H_4$: 70% ee = 90%
R^1 = Ph, R^2 = *p*-ClC_6H_4: 81% ee = 92%
R^1 = Ph, R^2 = *p*-$O_2NC_6H_4$: 90% ee = 82%
R^1 = Me, R^2 = Ph: 60% ee = 87%
R^1 = 2-Fu, R^2 = Ph: 80% ee = 91%
R^1 = Ph, R^2 = $BnCH_2$: 87% ee = 79%

Scheme 172. Bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol-catalysed epoxidations of chalcones.



$Ar^1 = Ar^2$ = Ph: 47% ee = 82%
Ar^1 = Ph, Ar^2 = *p*-Tol: 37% ee = 55%
Ar^1 = *p*-Tol, Ar^2 = Ph: 40% ee = 61%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = Ph: 37% ee = 54%
Ar^1 = *p*-ClC_6H_4, Ar^2 = *p*-ClC_6H_4: 38% ee = 64%
$Ar^1 = Ar^2$ = *p*-Tol: 40% ee = 50%

Scheme 173. Epoxidations of chalcones catalysed by D-mannose-based azacrown ether.



$Ar^1 = Ar^2$ = Ph: 95% ee > 99%
Ar^1 = Ph, Ar^2 = *p*-FC_6H_4: 94% ee = 98%
Ar^1 = Ph, Ar^2 = *p*-Tol: 96% ee = 97%
Ar^1 = Ph, Ar^2 = *p*-$MeOC_6H_4$: 95% ee > 99%
Ar^1 = Ph, Ar^2 = 2-naph: 96% ee > 99%
Ar^1 = *o*-FC_6H_4, Ar^2 = Ph: 97% ee > 99%
Ar^1 = *m*-FC_6H_4, Ar^2 = Ph: 96% ee = 98%
Ar^1 = *m*-Tol, Ar^2 = Ph: 95% ee = 97%

Scheme 174. Phase-transfer catalytic epoxidations of chalcones.

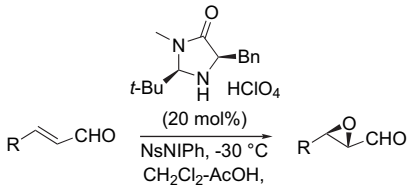
[(nosylimino)iodo]benzene (NsNIPh), have been developed by MacMillan and Lee, using a chiral imidazolidinone salt as an iminium activation catalyst.[306] Scheme 175 summarises the results obtained for a range of aldehydes.

In addition, a practical procedure has been developed for grafting a poly(amino acid) on silica gel as an efficient and recoverable catalyst in the asymmetric epoxidation of chalcones.[307] Hence, a silica-grafted poly-(L)-leucine could act as an efficient chiral organocatalyst in the epoxidation of various chalcones with the percarbonate protocol to yield the corresponding epoxy ketones in high enantioselectivities of up to 93% ee (Scheme 176).

8.3. α-Oxidations of carbonyl compounds

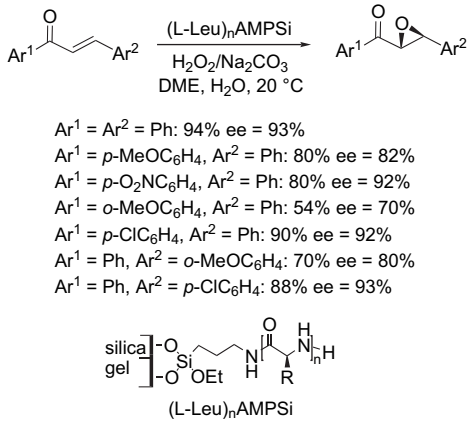
In 2005, Cordova et al. reported the first examples of organocatalytic asymmetric α-oxidation of ketones using oxidants such as iodosobenzene and *N*-sulfonyloxaziridines.[308] Scheme 177 shows the results obtained for the L-proline-catalysed α-oxidation of ketones with iodosobenzene, yielding the corresponding α-hydroxylated ketones with up to 77% ee.

In 2006, an enantioselective α-oxidation of aldehydes was performed by Cordova et al. by using molecular oxygen as

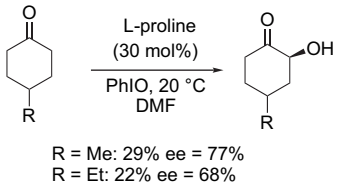


R = Me: 88% ee = 93%
R = *n*-Pr: 72% ee = 88%
R = Cy: 77% ee = 92%
R = CH_2=CH-$(CH_2)_3$: 95% ee = 92%
R = $BzOCH_2$: 89% ee = 85%
R = $CO_2Me(CH_2)_2$: 86% ee = 90%
R = Ph: 92% ee = 92%
R = *p*-$O_2NC_6H_4$: 89% ee = 97%
R = *p*-BrC_6H_4: 93% ee = 93%

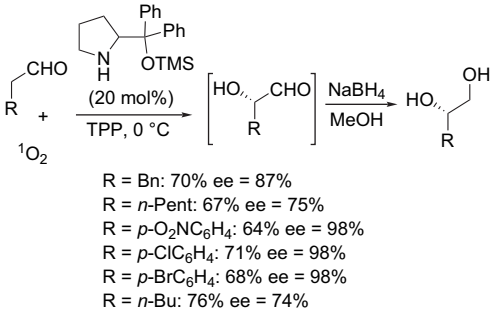
Scheme 175. Epoxidations of α,β-unsaturated aldehydes catalysed by MacMillan imidazolidinone catalyst.



Scheme 176. Epoxidations of chalcones by silica-grafted poly-(L)-leucine catalyst.



Scheme 177. L-Proline-catalysed α-oxidations of ketones with PhIO.



Scheme 178. α-Oxidations of aldehydes with molecular oxygen catalysed by TMS-protected α,α-diphenyl-2-prolinol.

a green oxidant.[309] TMS-protected α,α-diphenyl-2-prolinol catalysed these reactions with singlet molecular oxygen with high enantioselectivity to furnish the corresponding diols, after in situ reduction, in high yield with up to 98% ee (Scheme 178). Electrophilic singlet molecular oxygen was photo- or chemically generated $^1O_2$.

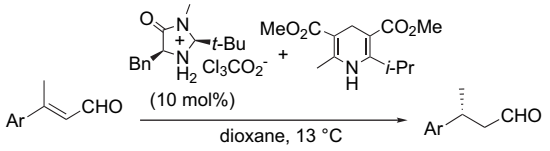
9. Reductions

Asymmetric hydrogenation of unsaturated organic compounds is currently becoming a standard procedure in both academic laboratories and industrial applications.[310]

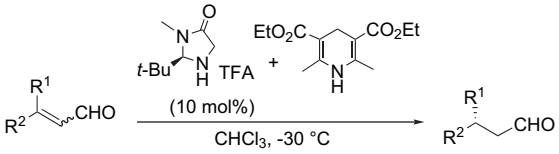
9.1. Hydrogenations of α,β-unsaturated carbonyl compounds

Until recently, all the methods developed for the reduction of organic compounds have been dominated by the use of metal catalysts surrounded by proper stereodiscriminating chiral ligands. A shift of this paradigm was, however, recently made by the discovery that simple ammonium salts of secondary amines were able to catalyse the chemoselective reduction of α,β-unsaturated aldehydes in the presence of a dihydropyridine as the hydride donor.[311] In biological systems, reductions are performed in cascade reactions that involve metalloenzymes and organic hydride reduction cofactors, such as nicotinamide adenine dinucleotide (NADH) or flavin adenine dinucleotide ($FADH_2$). Inspired by the way that natural systems perform reduction reactions, List et al. have recently reported that Hantzsch ester worked as a good NADH mimic in the hydride-transfer reaction to the iminium ion formed from 2-nitrocinnamyl aldehyde and a catalytic amount of dibenzylammonium trifluoroacetate.[311] In 2005, the same group found that, upon treating aromatic, trisubstituted α,β-unsaturated aldehydes with a slight excess of dihydropyridine and a catalytic amount of a MacMillan imidazolidinone salt, the corresponding saturated aldehydes were obtained in high yields and excellent enantioselectivities (Scheme 179).[312] Hence, these results constituted the first completely metal-free catalytic asymmetric transfer hydrogenations.

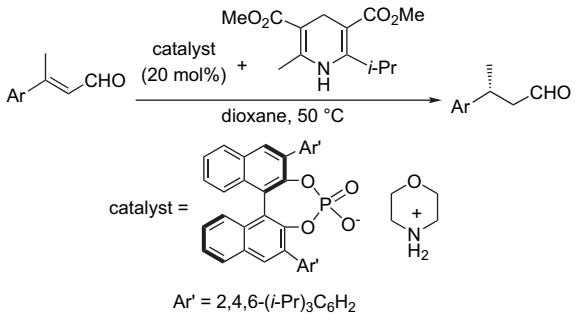
Concurrently, the group of MacMillan has developed similar reactions based on the use of catalysts having the same imidazolidinone skeleton, but differing only in the ring substituents. In this context, this group has reported that superior levels of enantiomeric excess could be obtained by employing an amine triflate salt, depicted in Scheme 180,[15] in $CHCl_3$ at −30 °C. Most interestingly, regardless of whether an *E* or a *Z* olefin was used as the substrate, they both converged into the same *S* enantiomer of the product, probably



Scheme 179. Hydrogenations of α,β-unsaturated aldehydes catalysed by a MacMillan imidazolidinone salt.



Scheme 180. Hydrogenations of α,β-unsaturated aldehydes catalysed by another MacMillan imidazolidinone salt.



Ar = *p*-Tol: 87% ee = 96%
Ar = *p*-NCC_6H_4: 84% ee = 98%
Ar = *p*-$O_2NCC_6H_4$: 90% ee = 98%
Ar = *p*-BrC_6H_4: 67% ee = 96%
Ar = *p*-$F_3CC_6H_4$: 63% ee = 98%
Ar = 2-naph: 72% ee > 98%

Scheme 181. Asymmetric counterion-mediated organocatalytic transfer hydrogenations of α,β-unsaturated aldehydes.

due to a fast *E*–*Z* isomerisation reaction mediated by the catalyst prior to the selective reduction of the *E*-olefin.

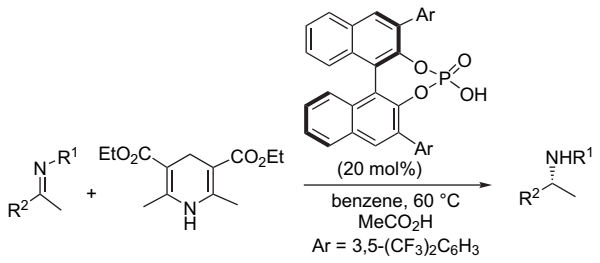
In 2006, List and Mayer hypothesised that catalytic salts of achiral amines combined with chiral phosphoric acids could induce asymmetry in the same process as that described above.[313] Indeed, these authors have developed a new catalyst salt, depicted in Scheme 181, which consisted of an achiral ammonium ion and a chiral phosphate anion, which catalysed highly enantioselective transfer hydrogenations of α,β-unsaturated aldehydes to the corresponding saturated derivatives.

9.2. Reductions of imines

The enantioselective reduction of imines to obtain chiral amines still represents a challenging topic. Although many highly enantioselective hydrogenations of ketones and alkenes are known, only less effective reductions of imines are available. Indeed, the development of efficient catalysts giving high enantioselectivity has proved to be much more difficult in the case of imines, compared with alkenes and ketones. In 2005, Rueping et al. reported the first enantioselective organocatalysed hydrogenation of ketimines.[314] This reaction, involving a Hantzsch dihydropyridine as the hydrogen source and a chiral phosphoric acid derived from (*R*)-BINOL as the catalyst, allowed an attractive approach to chiral amines under mild conditions (Scheme 182).

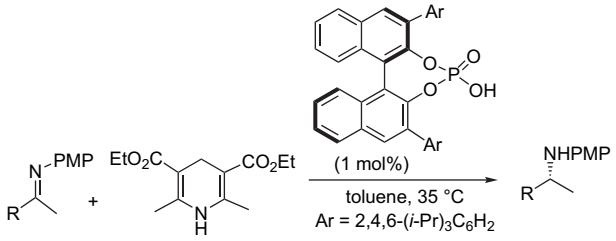
The same reactions described above were also developed by List et al., using a closely related catalyst, as depicted in Scheme 183.[315] The remarkable features of this process included its generally high yields and enantioselectivities, its scope, including both aliphatic and aromatic amines, and its remarkably low catalyst loading (1 mol %).

In 2006, Sun et al. developed a highly efficient organocatalyst for the enantioselective reduction of *N*-aryl imines with trichlorosilane.[316] This new catalyst was easily prepared from the commercially available, L-pipecolinic acid, and promoted the reduction of a broad range of *N*-aryl imines in high yields and excellent ee values under mild conditions (Scheme 184). The broad substrate spectrum of this



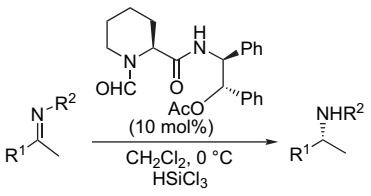
R^1 = PMP, R^2 = 2-naph: 82% ee = 94%
R^1 = Ph, R^2 = 2-naph: 69% ee = 68%
R^1 = PMP, R^2 = *p*-$F_3CC_6H_4$: 71% ee = 72%
R^1 = Ph, R^2 = *p*-$F_3CC_6H_4$: 58% ee = 70%
R^1 = PMP, R^2 = Ph: 76% ee = 74%
R^1 = R^2 = Ph: 71% ee = 72%
R^1 = PMP, R^2 = *o*-FC_6H_4: 82% ee = 84%
R^1 = PMP, R^2 = 2,4-$(Me)_2C_6H_3$: 91% ee = 78%
R^1 = PMP, R^2 = *p*-$MeOC_6H_4$: 76% ee = 72%

Scheme 182. Reductions of ketimines catalysed by a BINOL derivative.



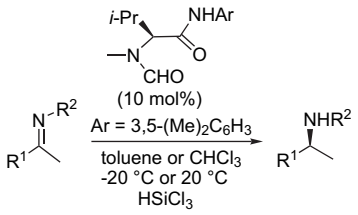
R = Ph: 96% ee = 88%
R = *p*-NCC_6H_4: 87% ee = 80%
R = *i*-Pr: 80% ee = 90%
R = 2,4-$(Me)_2C_6H_3$: 88% ee = 92%
R = *o*-Tol: 91% ee = 93%
R = 3,5-$(MeO)_2C_6H_3$: 84% ee = 89%
R = *p*-Tol: 98% ee = 88%
R = *o*-FC_6H_4: 95% ee = 85%

Scheme 183. Reductions of ketimines catalysed by another BINOL derivative.



R^1 = R^2 = Ph: 97% ee = 95%
R^1 = *p*-$O_2NC_6H_4$, R^2 = Ph: 96% ee = 95%
R^1 = *p*-BrC_6H_4, R^2 = Ph: 98% ee = 95%
R^1 = *p*-$MeOC_6H_4$, R^2 = Ph: 95% ee = 93%
R^1 = 2-naph, R^2 = Ph: 92% ee = 93%
R^1 = Ph, R^2 = *p*-$MeOC_6H_4$: 98% ee = 92%
R^1 = Ph, R^2 = *p*-ClC_6H_4: 98% ee = 93%
R^1 = Ph, R^2 = *p*-Tol: 90% ee = 95%
R^1 = Cy, R^2 = *p*-$MeOC_6H_4$: 75% ee = 87%
R^1 = Cy, R^2 = *p*-BrC_6H_4: 80% ee = 95%
R^1 = *i*-Pr, R^2 = Ph: 86% ee = 91%
R^1 = Ph-CH=CH, R^2 = Ph: 81% ee = 87%

Scheme 184. Reductions of *N*-aryl imines with $HSiCl_3$ catalysed by L-pipecolinic acid derivative.



$R^1 = R^2 = Ph$: 94% ee = 92%
$R^1 = p\text{-}MeOC_6H_4$, $R^2 = Ph$: 85% ee = 90%
$R^1 = p\text{-}F_3CC_6H_4$, $R^2 = Ph$: 95% ee = 89%
$R^1 = o\text{-}Tol$, $R^2 = Ph$: 90% ee = 92%
$R^1 = Ph$, $R^2 = p\text{-}MeOC_6H_4$: 85% ee = 91%
$R^1 = Ph$, $R^2 = p\text{-}MeOC_6H_4$: 85% ee = 91%
$R^1 = Ph\text{-}CH{=}CH$, $R^2 = Ph$: 64% ee = 81%

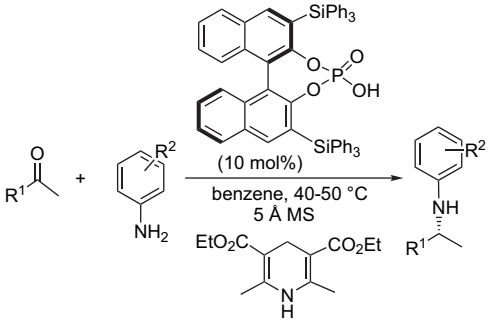
Scheme 185. Reductions of aromatic ketimines with $HSiCl_3$ catalysed by valine-derived bisamide.

catalyst was unprecedented in asymmetric imine reduction catalysis.

In addition, Kocovsky et al. have shown that similar reactions to those described above could be catalysed by formamides derived from *N*-methyl amino acids with a high enantioselectivity of up to 92% ee.[317] The structure–reactivity investigation has shown that the product configuration was controlled by the nature of the side chain of the catalyst scaffold, so that catalysts of the same absolute configuration could induce the formation of the opposite enantiomers of the product. The results obtained with a valine-derived bisamide as catalyst are summarised in Scheme 185.

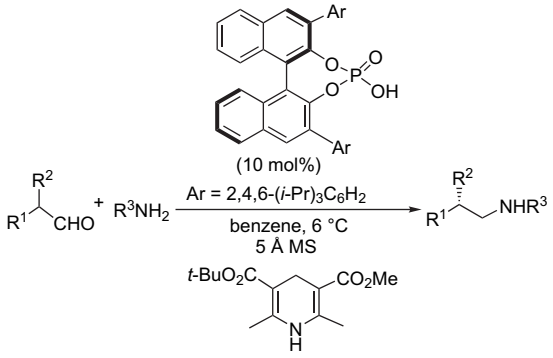
9.3. Reductive aminations of carbonyl compounds

Catalytic asymmetric reductive aminations of carbonyl compounds are useful for the synthesis of chiral amines and also powerful C–N bond-forming fragment coupling



$R^1 = Ph$, $R^2 = p\text{-}MeOC_6H_4$: 87% ee = 94%
$R^1 = p\text{-}Tol$, $R^2 = p\text{-}MeOC_6H_4$: 79% ee = 91%
$R^1 = p\text{-}O_2NC_6H_4$, $R^2 = p\text{-}MeOC_6H_4$: 71% ee = 95%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = p\text{-}MeOC_6H_4$: 75% ee = 95%
$R^1 = p\text{-}FC_6H_4$, $R^2 = p\text{-}MeOC_6H_4$: 75% ee = 94%
$R^1 = m\text{-}FC_6H_4$, $R^2 = p\text{-}MeOC_6H_4$: 81% ee = 95%
$R^1 = 2\text{-naph}$, $R^2 = p\text{-}MeOC_6H_4$: 73% ee = 96%
$R^1 = n\text{-Hex}$, $R^2 = p\text{-}MeOC_6H_4$: 72% ee = 91%
$R^1 = CH_2Bn$, $R^2 = p\text{-}MeOC_6H_4$: 75% ee = 94%
$R^1 = CH_2allyl$, $R^2 = p\text{-}MeOC_6H_4$: 60% ee = 90%
$R^1 = R^2 = Ph$: 73% ee = 93%
$R^1 = Ph$, $R^2 = p\text{-}F_3CC_6H_4$: 55% ee = 95%

Scheme 186. Reductive aminations of ketones catalysed by BINOL-derived phosphoric acid.



$R^1 = Ph$, $R^2 = Me$, $R^3 = PMP$: 87% ee = 96%
$R^1 = p\text{-Tol}$, $R^2 = Me$, $R^3 = PMP$: 86% ee = 94%
$R^1 = p\text{-}MeOC_6H_4$, $R^2 = Me$, $R^3 = PMP$: 81% ee = 94%
$R^1 = p\text{-}BrC_6H_4$, $R^2 = Me$, $R^3 = PMP$: 92% ee = 94%
$R^1 = o\text{-}FC_6H_4$, $R^2 = Me$, $R^3 = PMP$: 89% ee = 94%
$R^1 = m\text{-}FC_6H_4$, $R^2 = Me$, $R^3 = PMP$: 84% ee = 94%
$R^1 = 1\text{-naph}$, $R^2 = Me$, $R^3 = PMP$: 85% ee = 98%
$R^1 = 2\text{-naph}$, $R^2 = Me$, $R^3 = PMP$: 96% ee = 96%
$R^1 = Ph$, $R^2 = Et$, $R^3 = PMP$: 92% ee = 98%
$R^1 = R^3 = Ph$, $R^2 = Me$: 78% ee = 94%
$R^1 = t\text{-Bu}$, $R^2 = Me$, $R^3 = PMP$: 77% ee = 80%
$R^1 = CF_3$, $R^2 = Me$, $R^3 = PMP$: 40% ee = 80%

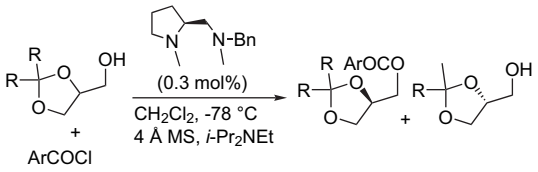
Scheme 187. Reductive aminations of aldehydes catalysed by BINOL-derived phosphoric acid.

reactions.[318] Surprisingly few laboratory methods are known for enantioselective reductive amination. In 2006, MacMillan et al. reported the first organocatalytic reductive amination, a biomimetic reaction that allowed the asymmetric coupling of complex fragments using a BINOL phosphoric acid catalyst and Hantzsch esters.[319] The scope of the reaction was extended to a wide range of ketones in combination with aryl and heterocyclic amines, as summarised in Scheme 186.

In 2006, List et al. extended the scope of the previous reactions to aldehydes.[320] Hence, an efficient enantioselective reductive amination of α-branched aldehydes with aromatic amines was developed via dynamic kinetic resolution. This process was broad in scope, since both aromatic and aliphatic aldehydes could be used, although enantiomeric ratios were, typically, lower with simple aliphatic aldehydes, as shown in Scheme 187.

10. Kinetic resolutions

The kinetic resolution of racemic alcohols via asymmetric acylation has been widely used to construct various useful chiral building blocks in the synthesis of complex natural products.[321] Most methods reported to date have employed enzymes, such as lipase or esterase. The challenge of developing easily accessible and effective non-enzymatic asymmetric acylation catalysts has attracted many research groups over the last decade.[322] The asymmetric acylation of alcohols using molecular catalysts has emerged as a viable alternative to the well-established enzyme-catalysed acylation. As an example, Oriyama et al. reported, in 2005, the first organocatalytic kinetic resolution of racemic primary



R = Me, Ar = Ph: 44% ee = 56% + 33% ee = 69%
R = *n*-Pr, Ar = Ph: 49% ee = 60% + 37% ee = 64%
R = *n*-Bu, Ar = Ph: 52% ee = 54% + 41% ee = 71%
R = *i*-Pr, Ar = Ph: 52% ee = 59% + 39% ee = 75%
R = Cy, Ar = Ph: 54% ee = 51% + 43% ee = 82%
R = $(CH_2)_5$, Ar = Ph: 49% ee = 53% + 41% ee = 65%
R = *i*-Pr, Ar = *m*-Tol: 54% ee = 51% + 37% ee = 79%
R = *i*-Pr, Ar = *p*-Tol: 48% ee = 68% + 43% ee = 81%
R = *i*-Pr, Ar = *p*-*t*-BuC_6H_4: 55% ee = 57% + 36% ee = 84%
R = *i*-Pr, Ar = 1-naph: 47% ee = 77% + 46% ee = 68%

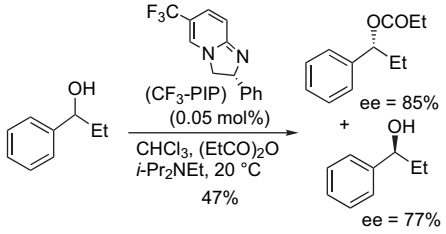
Scheme 188. Kinetic resolutions of primary alcohols catalysed by L-proline-derived diamine.

alcohols, using a chiral 1,2-diamine derived from L-proline, and attaining high enantioselectivities (Scheme 188).[323]

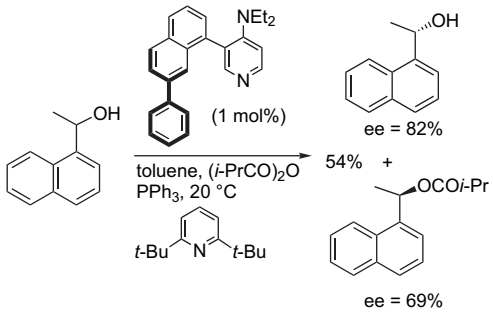
In 2006, a new class of chiral nucleophilic catalysts based on dihydroimidazo[1,2-*a*]pyridine (DHIP) was studied by Birman et al. for the kinetic resolution of acyclic secondary benzylic alcohols.[324] After examining the influence of several steric and electronic factors on the activity and enantioselectivity of a series of catalysts derived from the DHIP core, the authors selected CF_3-PIP as the best DHIP-based catalyst (Scheme 189).

Other catalysts, such as 4-dialkylaminopyridines containing terphenyl groups, have been recently developed by Spivey et al. and evaluated for kinetic resolution of aryl alkyl secondary alcohols.[325] Optimisation of the conditions for conducting the kinetic resolutions at room temperature using a 1 mol % level of catalyst indicated that the use of PPh_3 as an additive was beneficial for selectivity and allowed kinetic resolution of (±)-1-(naphthyl)ethanol to occur in <30 min to give 40% of recovered alcohol with >95% ee (Scheme 190).

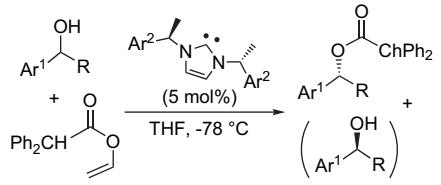
In 2005, Maruoka et al. established that chiral *N*-heterocyclic carbenes could serve as a new class of catalysts for the enantioselective acylation of a range of secondary alcohols with vinyl diphenylacetate (Scheme 191).[326] An important feature of this catalyst system was that the C_2-symmetric chiral imidazolium salts, precursors of these chiral carbene catalysts, could be readily synthesised from commercially available chiral amines, paraformaldehyde, glyoxal and tetrafluoroboric acid in one step. More recently, Suzuki et al. reported similar reactions performed in the presence of other



Scheme 189. CF_3-PIP-catalysed kinetic resolution of 1-(phenyl)propanol.



Scheme 190. Kinetic resolution of 1-(naphthyl)ethanol catalysed by 4-dialkylaminopyridine.

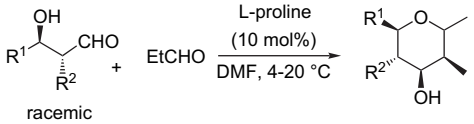


Ar^1 = Ph, Ar^2 = 1-naph, R = Me: 32% ee = 96%
Ar^1 = Ar^2 = Ph, R = Me: 33% ee = 93%
Ar^1 = Ph, Ar^2 = 1-naph, R = Et: 33% ee = 92%
Ar^1 = *p*-FC_6H_4, Ar^2 = 1-naph, R = Me: 39% ee = 91%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = 1-naph, R = Me: 30% ee = 94%
Ar^1 = 2-naph, Ar^2 = Ph, R = Me: 35% ee = 93%
Ar^1 = 2-naph, Ar^2 = 1-naph, R = Me: 27% ee = 95%
Ar^1 = Ph-CH=CH, Ar^2 = Ph, R = Me: 27% ee = 84%
Ar^1 = Ph-CH=C(Me), Ar^2 = Ph, R = Me: 33% ee = 87%

Scheme 191. Kinetic resolutions of secondary alcohols catalysed by *N*-heterocyclic carbenes.

acyl donors, such as vinyl acetate or vinyl propionate.[327] In one example, this acyl donor led, in the presence of 1-(1-naphthyl)ethanol, to the corresponding acylated product in up to 68% ee.

In addition, Cordova and Reyes have found that amino acids could catalyse highly chemo-, diastereo- and enantioselective dynamic kinetic asymmetric transformations of racemic β-hydroxy aldehydes.[328] The remarkably high selectivity of L-proline was used in the novel one-step synthesis of deoxy- and polyketide sugars with up to 99% ee (Scheme 192). The proline-mediated dynamic kinetic asymmetric transformation (DYKAT) process was a combination of an L-proline-mediated racemisation of the β-hydroxyaldehyde acceptor



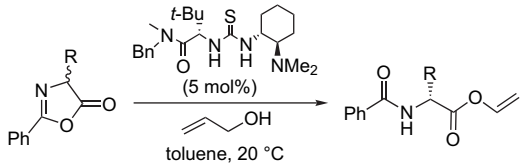
R^1 = *i*-Pr, R^2 = Me: 21% de > 90% ee = 98%
R^1 = Et, R^2 = Me: 9% de > 90% ee = 94%
R^1 = *i*-Bu, R^2 = Me: 19% de > 90% ee = 93%
R^1 = Cy, R^2 = Me: 19% de > 90% ee = 90%
R^1 = CH_2OBn, R^2 = OBn: 22% de > 90% ee = 99%

Scheme 192. L-Proline-catalysed DYKAT of β-hydroxy aldehydes.

via retro-aldol and aldol additions, and a subsequent L-proline-catalysed direct stereoselective aldol addition to the racemic β-hydroxy-aldehyde acceptor with an aldehyde nucleophile.

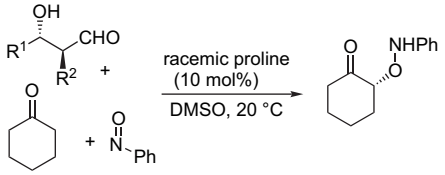
In 2005, Berkessel et al. reported the highly enantioselective alcoholytic dynamic kinetic resolution of azalactones catalysed by a thiourea-based bifunctional organocatalyst (Scheme 193).[329] This novel methodology provided a direct access to a wide range of protected natural and non-natural α-amino acids in high enantiomeric excesses.

In 2006, Cordova et al. reported a sugar-assisted kinetic resolution of amino acids such as proline.[330] This process provided a mechanism in which a racemic mixture of proline could catalyse the formation of an optically active organic molecule, in the presence of a sugar product, of even low enantiomeric excess (Scheme 194). Thus, the authors have found that the optical enrichment of products derived by amino acid catalysis may be influenced by the action of simple sugars and amino acids. The symbiotic behaviour of these additives, in combination with the likely presence of each in the prebiotic milieu, suggests that their cooperative action could have contributed to the early achievement of highly enantio-enriched products under prebiotic conditions and may be an explanation for the origin of homochirality, where the initial asymmetry may have been set by an amino acid or sugar.



R = Bn: 98% ee = 78%
R = Me: 94% ee = 80%
R = *i*-Pr: 89% ee = 92%
R = *t*-Bu: 28% ee = 95%
R = *i*-Bu: 77% ee = 91%

Scheme 193. Thiourea-catalysed dynamic kinetic resolutions of azalactones.



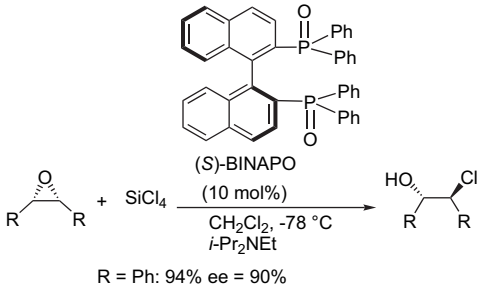
R^1 = Et, R^2 = Me, de = 60%, ee = 98%: 57% ee = 27%
R^1 = Et, R^2 = Me, de = 60%, ee = 86%: 55% ee = 24%
R^1 = Et, R^2 = Me, de = 60%, ee = 70%: 41% ee = 20%
R^1 = Et, R^2 = Me, de = 50%, ee = 48%: 67% ee = 10%
R^1 = Et, R^2 = Me, de = 50%, ee = 15%: 72% ee = 3.5%
R^1 = CH_2OBn, R^2 = OBn, de = 60%, ee = 98%: 51% ee = 66%
R^1 = *i*-Bu, R^2 = Me, de = 60%, ee = 99%: 26% ee = 5%
R^1 = *i*-Pr, R^2 = Me, de > 90%, ee > 99%: 48% ee = 10%
R^1 = *i*-Pr, R^2 = Me, de > 90%, ee > 99%: 55% ee = 27%

Scheme 194. Sugar-assisted in situ kinetic resolutions of proline.

11. Miscellaneous reactions

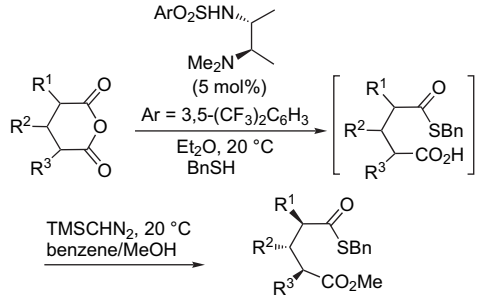
The asymmetric ring opening of *meso*-epoxides is a versatile method for preparing optically active chlorohydrins.[331] Various organocatalysts, such as phosphoramides or *N*-oxides, have been reported to be effective for the ring opening of *meso*-epoxides with tetrachlorosilane. In 2005, the first example of the use of a chiral phosphine oxide, BINAPO, was reported by Nakajima et al. furnishing the corresponding chlorohydrins in high enantioselectivities of up to 90% ee (Scheme 195).[332]

Asymmetric differentiation between two identical carbonyl groups of prochiral σ-symmetric dicarboxylic acid derivatives is a rational and useful strategy for the asymmetric synthesis of chiral products. Recent efforts in this field have been directed towards the development of methods for the catalytic desymmetrisation of prochiral cyclic dicarboxylic anhydrides, such as enantioselective ring opening with nucleophiles in the presence of a chiral organocatalyst.[333] As an example, Nagao et al. reported, in 2005, a highly enantioselective catalytic thiolysis of prochiral cyclic anhydrides, using a bifunctional chiral sulfonamide as organocatalyst for the first time (Scheme 196).[334]



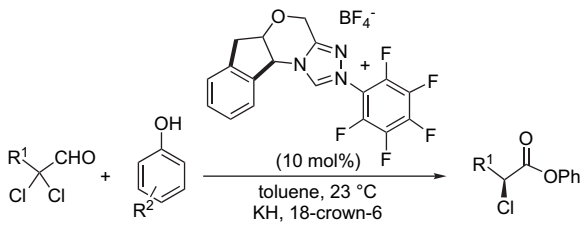
R = Ph: 94% ee = 90%
R = CH_2OBn: 97% ee = 31%
R,R = $CH_2N(Ts)CH_2$: 95% ee = 34%
R,R = CH_2OCH_2: 73% ee = 39%
R,R = $(CH_2)_4$: 81% ee = 71%
R,R = $(CH_2)_6$: 81% ee = 50%

Scheme 195. BINAPO-catalysed desymmetrisations of *meso*-epoxides.



R^1 = R^3 = H, R^2 = Ph: 95% ee = 91%
R^1 = R^3 = H, R^2 = Me: 87% ee = 91%
R^1 = R^3 = Me, R^2 = H: 100% ee = 90%
R^1 = R^3 = H, R^2 = OTBS: 88% ee = 93%
R^1 = R^3 = $(CH_2)_3$, R^2 = H: 90% ee = 98%

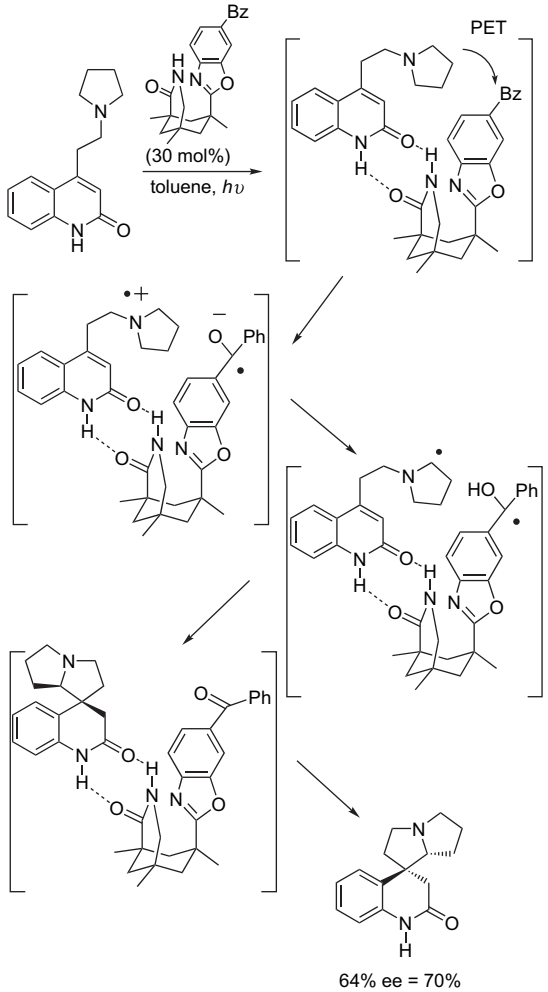
Scheme 196. Desymmetrisations of prochiral cyclic dicarboxylic anhydrides catalysed by sulfonamide.



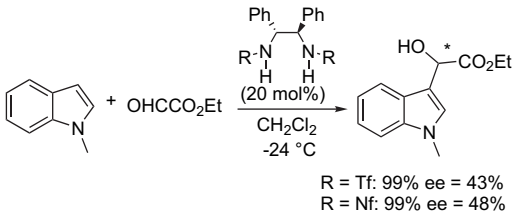
R^1 = Bn, R^2 = H: 79% ee = 93%
R^1 = CH_2(*p*-$MeOC_6H_4$), R^2 = H: 76% ee = 90%
R^1 = CH_2Bn, R^2 = H: 73% ee = 85%
R^1 = $(CH_2)_3$Ph, R^2 = H: 68% ee = 89%
R^1 = CH_2CH=CH-*n*-Pent, R^2 = H: 74% ee = 90%
R^1 = $(CH_2)_4$CH=CHEt, R^2 = H: 71% ee = 88%
R^1 = CH_2Cy, R^2 = H: 65% ee = 93%
R^1 = $(CH_2)_7CO_2Me$, R^2 = H: 75% ee = 84%
R^1 = Bn, R^2 = *p*-Me: 65% ee = 82%
R^1 = Bn, R^2 = *p*-OMe: 85% ee = 76%
R^1 = Bn, R^2 = *o*-Me: 80% ee = 89%

Scheme 197. Enantioselective protonations catalysed by azolium salt.

In 2005, Rovis and Reynolds demonstrated a unique synthesis of α-chloroesters, based on an enantioselective protonation of in situ-generated chiral α-chloroenolates.[335]



Scheme 198. Organocatalysed enantioselective photochemical cyclisation.



Scheme 199. Bis-sulfonamide-catalysed Friedel–Crafts reactions of *N*-methyl indole with ethyl glyoxylate.

Indeed, 2,2-dichloroaldehydes reacted with phenols in the presence of a chiral triazolinylidene carbene, generated in situ upon deprotonation of the corresponding azolium salt by base, to form the corresponding α-chloroesters in good yield and enantioselectivity (Scheme 197).

In contrast to the extensive knowledge concerning enantioselective catalysis in thermal organochemical reactions, it is astonishing that so little is known about catalytic enantioselective photochemical reactions.[336] In 2005, Bach et al. reported the photochemical asymmetric cyclisation of a (pyrrolidinylethyl)quinolone into the corresponding chiral spiro product in the presence of a photoelectron acceptor organocatalyst, depicted in Scheme 198.[337] The key step of this reaction was supposed to be a photo-induced electron transfer (PET) in an intermediate complex from the nitrogen atom of the tertiary amine to the excited benzophenone chromophore of the catalyst with the formation of a radical anion/radical cation pair. A proton transfer subsequently occurred, providing a radical pair. An attack of the pyrrolidin-2-yl radical moiety on the C–C double bond of the quinolone proceeded preferably from the left side and the product complex was formed by hydrogen back-transfer (Scheme 198).

Enantioselective Friedel–Crafts reactions of indoles with α-dicarbonyl compounds have been performed by Jorgensen et al. by using chiral bis-sulfonamides as organocatalysts.[150] As an example, the organocatalysed reaction of *N*-methyl indole with ethyl glyoxylate, performed in the presence of a bis-triflamide or a bis-nonaflamide catalyst, led to the formation of the corresponding product in moderate enantioselectivity (Scheme 199).

12. Conclusions

This review clearly demonstrates the diversity and power of asymmetric organocatalysed reactions in the field of synthetic organic chemistry. Enantioselective organocatalytic processes have reached maturity in recent years with an impressive and steadily increasing number of publications, regarding the applications of this type of reactions, which paint a comprehensive picture for their real possibilities in organic synthesis. Even though transition-metal-catalysed enantioselective reactions will certainly continue to play a central role in synthetic organic chemistry in the future, the last few years have, however, seen an increasing trend in the use of metal-free catalysts. The reasons are the often high costs of transition metals and the problems that their residues, mainly in pharmaceutical products, can cause. Hence,

the application of chiral organocatalysts has permitted the preparation of a number of very valuable chiral products with the exclusion of any trace of hazardous metals and with several advantages from an economical and environmental point of view.

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Biographical sketch

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