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► **To cite this version:**

Mccort-Tranchepain Isabelle, Petit Morgane, Dalko Peter I. Organocatalysis. Paul Anastas. Handbook of Green Chemistry, 1, Wiley, 2010, <10.1002/9783527628698.hgc009>. <hal-04254661>

HAL Id: hal-04254661

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Submitted on 6 Nov 2023

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Organocatalysis

Isabelle McCort-Tranchepain, Morgane Petit, and Peter I. Dalko

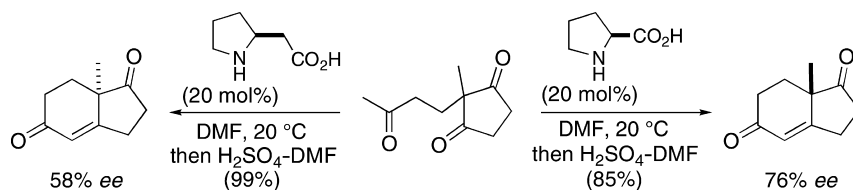
9.1

Introduction

Organocatalysis is a way of accelerating chemical reactions with a catalytic amount of an organic compound without the presence of a metal, metal salt or other metal derivatives. The development of organocatalytic methods of wide synthetic scope is of real scientific, economic and environmental interest [1–3]. Organocatalytic reactions can be performed usually under (very) simple experimental conditions, under an aerobic atmosphere and in wet solvents; Catalysts are inexpensive and also they are more stable than metal-based or bioorganic analogs; recovery is simpler than with metal-based or bioorganic catalysts; they can be anchored to a solid support and reused; and there are fewer toxicity and environmental problems associated than with metal catalysts (this only applies when dealing with the more notorious metals; it should be pointed out that little is known about the toxicity of many of the organic catalysts).

Despite the steadily growing number of catalysts and more and more selective transformations that are appearing, applications to more complex systems in multistep synthesis seem to be following these spectacular advances reluctantly. Are organocatalytic systems suitable for a broad range of transformations with high levels of reliability and generality? Organocatalytic reactions are often characterized by narrow substrate scope and low reactivity. An often encountered difficulty also arises from the almost complete lack of a mechanism-based predictive power of the underlying mechanistic pathway compared with most metal-mediated reactions. As an example, the variation of the enantioselectivity in the venerable Hajos–Wiecher reaction, using L-proline and L-homoproline [(pyrrolidin-2-yl)acetic acid], can be cited (Scheme 9.1). While the fact is well precedented from the early days of proline catalysis, this puzzling observation has not responded to rationalization attempts in the literature until very recently [4, 5].

This chapter attempts to highlight asymmetric organocatalytic transformations of general synthetic scope illustrating the generality of the transformation in multistep synthesis [6]. The selection that will treat additions to C=O, C=N and C=C bonds and also discusses domino and cascade reactions is not intended to be exhaustive as it is limited by space restrictions: more specialized reviews may complete the reading.



Scheme 9.1 The Hajos–Wiecher reaction, using L-proline and L-homoproline ((pyrrolidin-2-yl)acetic acid).

9.2

Catalysts

Most currently used efficient organocatalyst are bi- or multifunctional catalysts, commonly having Brønsted acid and Lewis base centers. Hence their structures incorporate known hydrogen bond donor motifs such as thiourea, 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) or phosphoric acid and different nucleophile-activating groups. According to the common organocatalytic concept, these functions may be able to activate one or both of the reagents in the same transition state (TS). Such cooperative activation gives rise to well-organized TSs and results in a considerable rate acceleration. Interactions between the catalyst and the substrates are assured by passive and/or dynamic binding and also via hydrogen bonding. The passive binding includes hydrophobic, van der Waals and electrostatic interactions whereas dynamic binding refers to interactions between catalyst and substrate at the reaction center. Hydrogen bond interactions constitute a major driving force in the formation of specific molecular and complex geometries. Thus, protein and nucleic acid secondary and tertiary structural elements and also many natural and artificial host–guest complexes are partly based on the directive power of intra- and intermolecular hydrogen bond formation.

The molecular events in organocatalytic reactions can be remarkably complex, as has been demonstrated in a very limited number of mechanistic studies [5, 7, 14]. Structural variations of any of the reacting partners may fine tune interconnecting mechanistic pathways that are dependent on the plethora of experimental parameters and, not least, on whether the reactions are run under homogeneous or heterogeneous conditions.

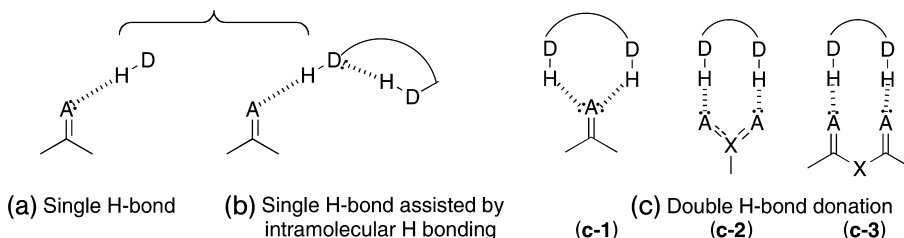
9.2.1

Catalyst Functions

9.2.1.1 Brønsted Acids [8]

Proton is the most abundant Lewis acid existing in Nature. In solutions, there are countless variations in hydrogen bond strengths and geometric orientations and they may change even within the same bond partners. Formation of a hydrogen bond to the electrophile (typically a carbonyl or imine) occurs through either a one-point or two-point interaction. Some of the principal modes of coordination are depicted in

Scheme 9.2: (a) single H bond; (b) single H-bond assisted by an intramolecular H-bonding increasing Brønsted acidity of the hydroxyl proton which coordinates to the electrophile; (c) double H-bond, with one (c-1) or two (c-2, c-3) heteroatoms. The bonding results in lowering of the LUMO energy of the electrophile, increasing the electrophilicity, thereby making it more reactive to the second reactant, such as a nucleophile or a diene.



Scheme 9.2 Different modes of activation by H-bonding.

Mild *and* moderately strong Brønsted acid catalysts having single or multiple H-donor ability have been extensively tested for organocatalytic reactions. Among the protic functions, carboxylic and phosphoric acids, tertiary alcohols, phenols, activated amides including thioureas and sulfonamides were developed. Protonated tertiary amines are also efficient H donors. The match between the Brønsted acidity of the catalyst and the substrate is a determinant factor both in the selectivity and in the reactivity of the system.

In hydrogen bonding activation, the solvent participates directly or indirectly in the structure of the TS complex and thus influences substantially the enantioselectivity. Non-polar solvents avoid hydrogen bond competition with the electrophile that could be formed in polar or protic solvents.

Proton can be provided not only by the catalyst but also by achiral protic additives such as water or other Brønsted acid co-catalysts used generally in stoichiometric amounts with respect to the catalyst. Beyond the fact that electrophilic assistance may activate the reagent(s) by LUMO lowering and also help to organize the TS via extensive H-bonding, the protic additive may play further key roles, e.g. (i) it increases the ligand instability of covalently bonded catalysts, resulting in overall rate acceleration and in increased conversion; (ii) it allows efficient asymmetric proton transfer to the substrate; (iii) it avoids base-catalyzed undesired secondary reactions; and (iv) it avoids catalyst deactivation by hydrolyzing inactive dead-end complexes. Although reaction conditions compatible with water as solvent were devised [9], the presence of large amounts of water and in particular water as solvent usually results in a lower reaction rate or complete suppression of the reactivity of the catalyst.

9.2.1.2 Lewis acids

Typical Lewis acid (LA) functions can be emulated by covalently linked functions such as iminium (see below) or by forming donor–acceptor complexes with metalloids such as boron and silicon derivatives. Iminium activation is chemically equivalent to the electrophile activation of the parent carbonyl compound resulting in LUMO

lowering. Also, among the typical Lewis acids, chiral oxazaborolidines and hypervalent boron and silica derivatives have found wide application in enantioselective organocatalytic transformations.

9.2.1.3 Brønsted Bases

Asymmetric organocatalytic reactions can be mediated by general-base catalysts, provided that experimental conditions for the formation of a tight ion pair between the achiral anion (substrate) and the chiral cation can be found. The most frequently used organic bases are chiral quinuclidines derived from cinchona alkaloids. General-base-mediated reactions can be conducted under homogeneous conditions or under phase-transfer (PT) conditions.

9.2.1.4 Lewis Bases

As metals form Lewis acids easily, non-metallic elements are more prone to form Lewis bases. Among the various organic Lewis bases, the most common are amines, but also P-, O- and, less frequently, S-compounds that proceed through diverse mechanisms to convert the substrates in either activated nucleophiles or electrophiles. Nucleophilic carbenes (NHC) are a recent addition to the synthetic arsenal and represent a dynamic area of current research [10]. The reactive intermediate species involved in catalysis are typically enamines/imines, ammonium enolates, acylammonium ions, carbenes and ylides.

Amine catalysts, due to their natural abundance, are more readily available than phosphorus catalysts. There is no natural P-containing chiral substrate for catalytic use. The particular advantage of phosphorus-based catalysts is their ability to act as both a nucleophilic *and* a stereogenic reaction center. Furthermore, the diminished Brønsted basicity of the phosphorus atom compared with the amine function may be advantageous in avoiding base-mediated secondary reactions.

9.2.2

Catalyst Structures

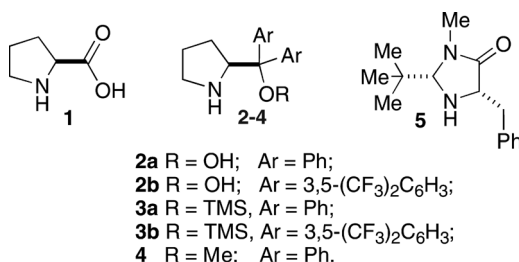
The great majority of organic catalyst are derived either from 'privileged' catalyst structures (privileged catalysts may promote high enantioselectivity in mechanistically distinct reactions) or are assembled by sequential manner from chiral organic building blocks such as peptides, peptide analogs or more recently nucleotides as well as other accessible chiral organic units.

9.2.2.1 Privileged Catalysts

The Pyrrolidine Class [11–13]

L-Proline (**1**) (Scheme 9.3) is probably the best known organocatalyst that mediates essentially enamine- or iminium-type asymmetric reactions: many of the derivatives have also proven to be very useful catalysts [15]. The high, often exceptional, enantioselectivity of proline-mediated reactions has been subject to considerable mechanistic interest [5, 14], and will be discussed briefly later. Although proline

continues to play a central role in aminocatalysis, synthetic analogs may offer better reactivity and selectivity in a number of reactions [15]. In particular, diarylprolinol ether derivatives **2–4** emerged as potentially general enamine/iminium organocatalysts [16]. The parent alcohol **1** that was developed earlier as a chiral ligand, although generally inefficient in organocatalytic reactions, trimethylsilyl (TMS) ethers **3** and methyl ether **4** derivatives were seen as generally more efficient [17].

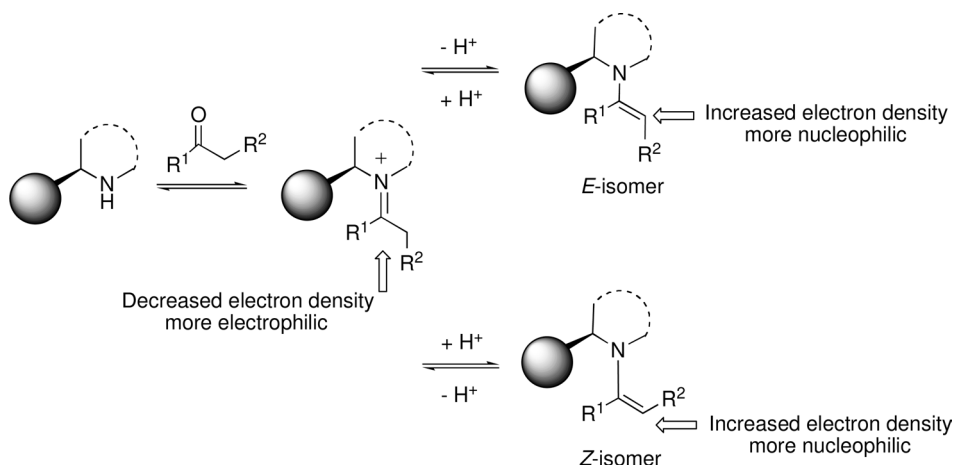


Scheme 9.3 L-Proline, diarylprolinol and imidazolidinone derivatives as organic catalysts.

The pyrrolidine ring can be replaced advantageously in a number of transformations by other five-membered nitrogen-containing chiral saturated heterocycles. The structurally related MacMillan's imidazolidinone catalysts are highly selective in a number of enamine- or iminium-type transformations: salts of **5** was identified as one the most reactive and versatile amine catalysts, acting preferentially via iminium formation [18].

Amino Catalysis with Pyrrolidine Derivatives [19]

The condensation of amine catalysts with ketones or aldehydes gives rise to enamines and/or iminium intermediates. The former structure results in increased electron density at the reaction center(s); the latter corresponds to a decreased electron density of the reaction center(s) (Scheme 9.4). A feature of this type of chemistry is the facile



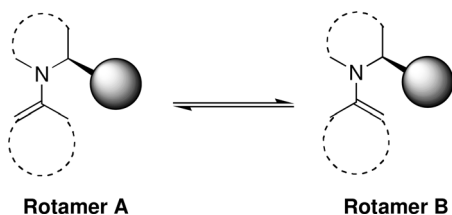
Scheme 9.4 The interconversion of the *Z/E* geometry of enamines.

equilibrium between these two, electron-rich and electron-deficient, states (i.e. the acid–base form) of the same center. Like protonation–deprotonation, this may activate the reagent and contribute to the kinetic lability of the ligand. The notable feature of this activation is the fact, that due to this equilibrium process, the same center may act as a Lewis acid or a Lewis base, depending on the reaction conditions. More importantly, the same catalyst may promote the complementary nucleophile–electrophile activation (i.e. promoting reactions via enamine and iminium intermediates, respectively) in the same reaction pot in a domino sequence [20].

Catalysis by Enamine Formation

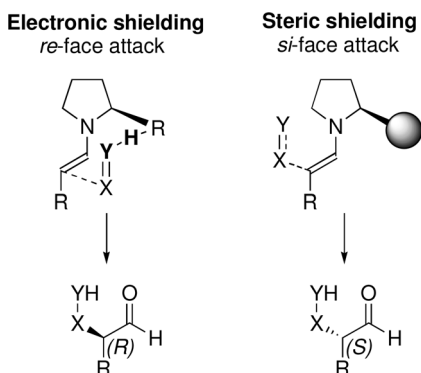
The partial steps of the aminocatalytic reactions are in dynamic equilibrium, hence products are formed under thermodynamic control. This is also reflected in the geometry of the enamine intermediates, which can be either *E* or *Z* (Scheme 9.4), leading to the product. The geometry of the enamine depends essentially on the catalyst structure and to a lesser extent on the substrate. Whereas proline-catalyzed reactions with α -alkyl-substituted ketones preferentially form the *E*-isomer, enamines derived from pipercolic acid afford an approximately 1 : 1 mixture of *E*- and *Z*-isomers [21].

Noteworthy, the relative stability and the reactivity of the rotamers such as **A** and **B** (Scheme 9.5) have a determinant role in the facial selectivity of the addition.



Scheme 9.5 Enamine rotamers as factors in stereocontrol of catalysts.

Finally, the acceptor (electrophile) may approach the enamine by two different routes, as depicted in Scheme 9.6. Stabilizing interactions such as hydrogen bonding

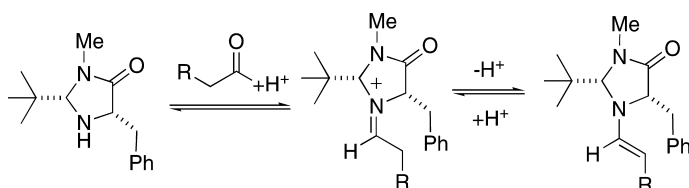


Scheme 9.6 The guiding and shielding TSs.

or electrostatic interactions between the catalyst and the alkene may offset repulsive (steric) interactions. In the latter (shielding) scenario, it is considered that the acceptor approaches the enamine via an acyclic synclinal TS, as suggested by Seebach and Golinski [22].

Catalysis via Iminium Activation

A great number of secondary amine catalysts provide rate acceleration via iminium formation. In the case of the imidazoline catalyst **5**, according to the computational model, the π -facial differentiation of enamine–iminium intermediates can be rationalized by the concerted shielding of the *re* face of the benzyl and *tert*-butyl groups. The selective formation of the (*E*)-iminium isomer in the TS, and also the preferred *E* geometry of the enamine, can be attributed to the minimized non-bonding interactions with the bulky *tert*-butyl group (Scheme 9.7).

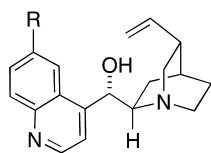


Scheme 9.7

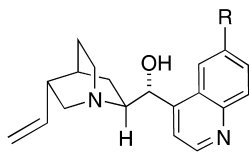
The analysis of these simplified conditions reveals that in aminocatalytic reactions there are a number of viable alternative reaction paths leading to different TSs and rendering possible the formation of a number regio- and stereoisomers. It is astonishing and difficult to understand thus the often very high regio- and stereo-selectivity of many of the pyrrolidine-class mediated reactions.

Cinchona Alkaloids [23]

The readily available and inexpensive cinchona alkaloids having pseudoenantiomeric forms, such as quinine and quinidine or cinchonine and cinchonidine, are among the most efficient catalysts (Scheme 9.8). The range of reaction types over which the cinchona alkaloids impart high enantioselectivity is astonishing. The key structural feature responsible for their synthetic utility is the presence of the tertiary quinuclidine nitrogen, which complements the proximal polar hydroxyl function of the natural compound that may be easily transformed into a variety of chemical functions. The modification of the cinchona backbone resulted notoriously in the past in a decrease in or loss of selectivity and such derivatives were disregarded as catalysts. The major event that pushed cinchona alkaloids to the center of interest was the development of dimeric cinchona alkaloid ligands for asymmetric dihydroxylation of simple alkenes [24]. The presence of the Brønsted acidic (H-bonding) and Lewis basic (quinuclidine nitrogen) sites in the natural compounds makes them bifunctional catalysts.



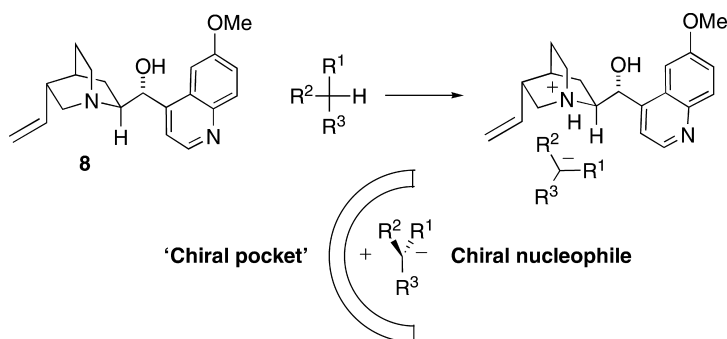
6: R = OMe, (+)-quinidine
7: R = H (+)-cinchonine



8: R = OMe, (-)-quinine
9: R = H (-)-cinchonidine

Scheme 9.8 Cinchona alkaloids.

Moreover, the Brønsted basicity of the quinuclidine moiety makes cinchona alkaloids one of the strongest organic bases. Deprotonation of relatively acidic substrates forming a chiral ion pair is an efficient way to promote asymmetric reactions (Scheme 9.9).



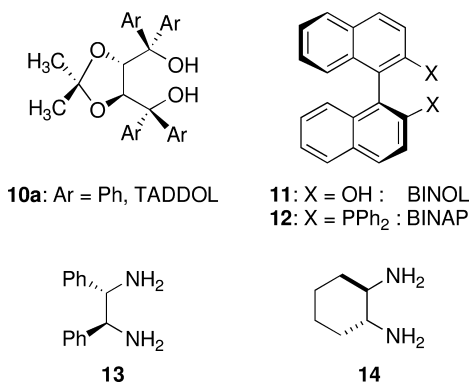
Scheme 9.9 Cinchona alkaloids allowing the formation of chiral ion pairs.

Noteworthy, the same principle operates in phase-transfer catalysis (PTC), where the chiral cinchonium forms tight ion pairs with one of the charged substrates, ensuring asymmetric induction [25].

Axially Chiral Diols and Diamines

TADDOL and Derivatives [26]

TADDOL (**10**) is one of the oldest and most extraordinarily versatile chiral auxiliary catalysts (Scheme 9.10). The design of TADDOL was driven by practical considerations, because it is derived from tartaric acid, the least expensive chiral starting material with two-fold symmetry available from natural sources. The genuine molecule has two conveniently oriented hydroxyl functions that can act as a double hydrogen bond donor catalyst and also gives a wide scope for further derivatizations.



Scheme 9.10 Axially chiral catalysts.

Binaphthol Derivatives [27]

The enantiomeric atropoisomers of 1,1'-binaphthyl-2,2'-diol (**11**) (BINOL) and bis-diphenylphosphonate derivatives **12** (BINAP) are completely synthetic molecules developed to exploit the axial dissymmetry induced by the restricted rotation of the biaryl bond (Scheme 9.10). These compounds are among the most widely used ligands in catalytic asymmetric transformations. A great number of analogs and derivatives have been developed in the last decade.

Chiral *C*₂-Symmetric 1,2-Diamines [28]

Chiral vicinal diamines such as 1,2-diaminocyclohexane (**13**) and *threo*-diphenylethylenediamines (**14**) (Scheme 9.10) have proven valuable tools as ligands in asymmetric metal-mediated reactions and have found rich applications as building blocks for the construction of chiral organocatalysts.

9.2.2.2 Synthetic Oligopeptides and Peptide Analogs [29]

Synthetic oligopeptides and peptide analogs are highly modular catalyst platforms. While some oligopeptide sequences may be considered as 'privileged' catalyst structures, the main advantage of the 'oligopeptide approach' is that the catalyst can be improved by varying the nature of the amino acids using combinatorial synthetic methods. Combinatorial synthesis and screening have made it possible to test the large structural and functional diversity of peptides to select the best candidates. The flexibility of the method is of great use since it is possible to prepare a peptide sequence that can eventually produce the opposite enantiomer or its diastereoisomer, a hardly amenable process with enzymes. Moreover, this oligopeptide approach may provide a solution to the reactivity versus selectivity problem, in particular when the steric hindrance of the chiral appendage compromises the reactivity of the catalyst. The strategy consists of building a simplified version of a complex chiral environment around the catalytic site, in a similar way to enzymes, where the chiral handle is thus distant from the active site. Such artificial enzymes may comprise a short oligopeptide sequence including an active site (such as imidazole) and a basic secondary structure: α/β turn or α/β hairpin, for example.

It is interesting to contemplate that, with the spectacular increase in the molecular weight and complexity of many catalyst structures, not only the selectivity but also the kinetic profile of the catalyst is sharply ameliorated.

9.3

Reactions

9.3.1

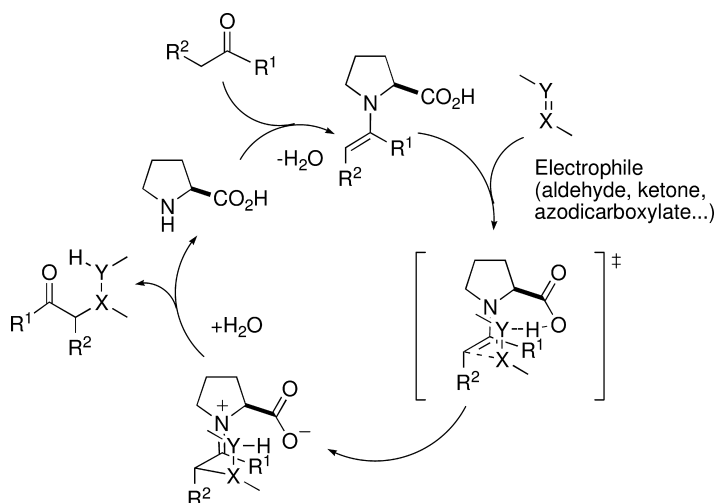
Nucleophilic Additions to C=O

9.3.1.1 Aldol- and Knoevenagel-type Additions

Cross-aldol Reactions of Unmodified Aldehydes and Ketones [19]

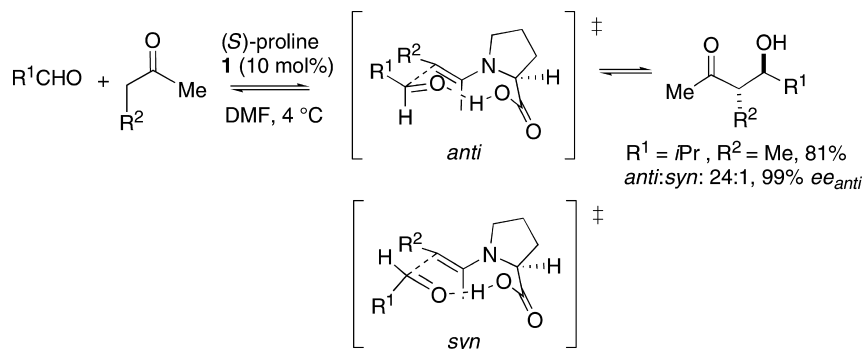
Aminocatalytic aldol reactions have matured into synthetically useful tools in organic chemistry. Intermolecular cross-aldol reactions allowing the preparation of both *syn* and *anti* isomers have been developed for aromatic and aliphatic substrates.

The design of a cross-aldol reaction is far to be trivial. The success of the reaction relies on the difference in reactivity of the reagents with regard to the catalyst forming an enamine (donor) selectively and the acceptor (Scheme 9.11). Such a difference can be found between ketone and aldehyde reagents, enolizable and non-enolizable carbonyls, and alkyl and heteroatom-substituted alkyl (oxyketone) donors. In cross-aldol reactions, it is often required that the donor aldehyde be added slowly to the acceptor and catalyst or one of the reagents be used in large (5–10-fold) excess. Although this transformation has probably attracted the largest amount of synthetic and mechanistic interest in organocatalytic transformations, many facets of the reaction remains puzzling [5, 14].



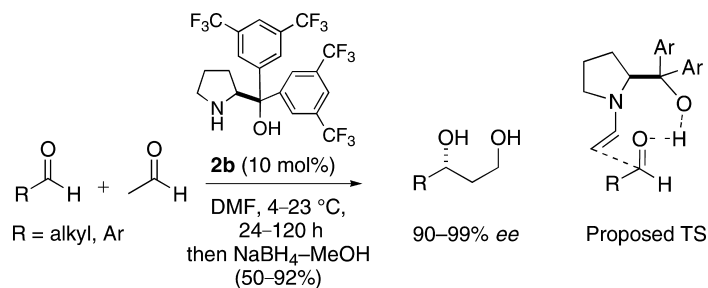
Scheme 9.11 The generalized enamine cycle

Using (*S*)-proline (**1**) as catalyst, the reaction proceeds preferentially via the (*E*)-enamine intermediate. The predominant structural factor that determines stereoselectivity is assumed to be the activation of the electrophilic reactant by an intramolecular H-bond between the proline COOH group and the carbonyl O-atom of an aldehyde in a nine-membered H-bonded ring. A second determinant is the *s-trans* arrangement of the enamine and carbonyl double bonds relative to the position of the COOH group. It is noteworthy that unsymmetrical ketones, in the simplest case 2-butanone, are reported to give regioselectively β -hydroxy ketones on the higher substituted α -C-atom (Scheme 9.12).



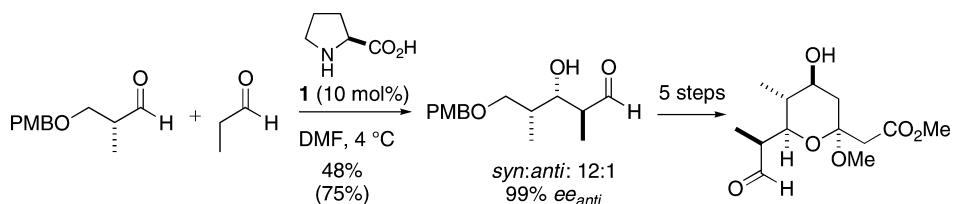
Scheme 9.12 Cross-aldol reaction of unmodified aldehydes and ketones.

The reaction affords satisfactory results for α -branched aliphatic aldehydes, whereas the enantiomeric excess (*ee*) decreases with aromatic aldehydes to the range 60–70%. The range of donors can be extended to butanone, 2-pentanone, cycloalkanones and α -hydroxy ketones, whereas simple ketones such as acetophenone and 3-pentanone are inert and acetaldehyde affords a mixture using proline as catalyst. This last transformation can be best mediated by diarylprolinol as catalyst (Scheme 9.13) [30].



Scheme 9.13 Cross-aldol reaction of acetaldehydes with aldehyde acceptors.

An elegant application of the proline-mediated cross-aldol reaction is the synthesis of the tetrahydropyran fragment of callipeltoside C (Scheme 9.14) [31].

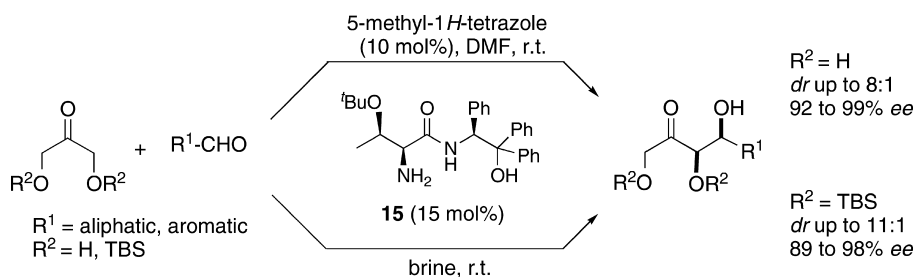


Scheme 9.14 Application of the cross-aldol reaction in the synthesis of the tetrahydropyran fragment of callipeltoside C.

Usually proline-mediated aldol reactions are tolerant to small amounts of tertiary amine bases. Weak acids or water as an *additive* were beneficial for the overall selectivity and efficiency of the transformation, whereas the reaction was inhibited by the presence of a strong acid [32].

Noteworthy, the usually long reaction time can be shortened by applying microwave irradiation without loss of selectivity [33]. Polymer-supported catalysts were also prepared and tested [11, 12, 34]. Poly(ethylene glycol)-supported proline derivatives [34] allowed the convenient reuse of the catalyst (10 runs).

Although proline derivatives dominate the organocatalytic field, primary amino acids [35], short oligopeptide catalysts and axially chiral bisaryl derivatives are emerging as alternatives, allowing usually complementary stereoselectivity and affording preferentially the *syn*-aldol products (in addition to *anti*-Mannich reactions; see below). The preference for *syn* selectivity can be attributed to the preferred formation of the (*Z*)-enamine that generates the *syn* product via the TS similar to that discussed above and also to the cooperativity between the catalyst and the acceptor resulting in a more organized TS. Amide catalysts having an amino alcohol such as **15** (Scheme 9.15) activate the electrophilic aldehyde of the aldol reaction by forming two hydrogen bonds, from both the amide and the hydroxy functionalities, with the carbonyl (Scheme 9.2c-1) [36, 37].



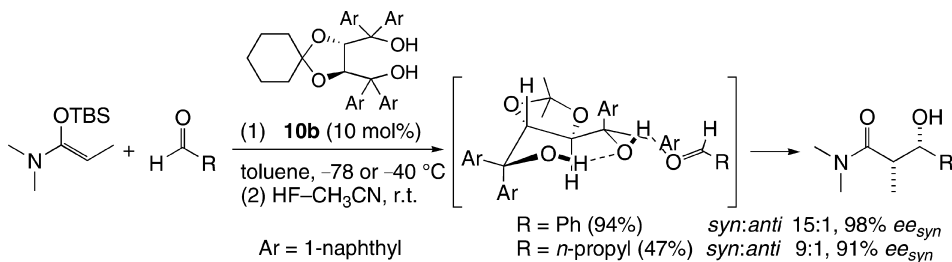
Scheme 9.15 *Syn*-selective cross-aldol reaction of unmodified aldehydes and ketones.

Noteworthy, other basic nitrogen compounds such as pyridine and tertiary amines, may also promote cross-aldol additions [38], some of them with high *syn*-selective internal stereocontrol [38b].

Aldol- and Knoevenagel-type Reactions with Preformed Enolates

Brønsted Acid Activation

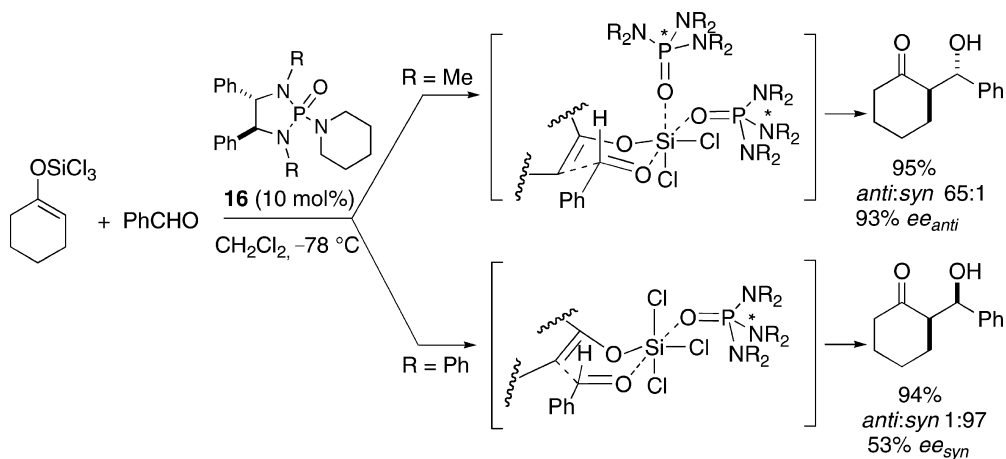
Mukaiyama-type asymmetric aldol and Knoevenagel-type reactions can be mediated by asymmetric proton catalysts such as TADDOL and cinchona-derived chiral salts that promote selective addition of *N,O*-silyl ketene acetal with various aromatic and heteroaromatic aldehydes (Scheme 9.16). According to Rawal's selectivity model [39], the aldehyde carbonyl is activated by a single-point intermolecular hydrogen bond to the internally hydrogen-bonded TADDOL (Scheme 9.2b) and is further organized through electrostatic interactions with an aryl (naphthyl) ring of TADDOL.



Scheme 9.16 Chiral Brønsted-acid-catalyzed Mukaiyama-type asymmetric Knoevenagel-type reactions

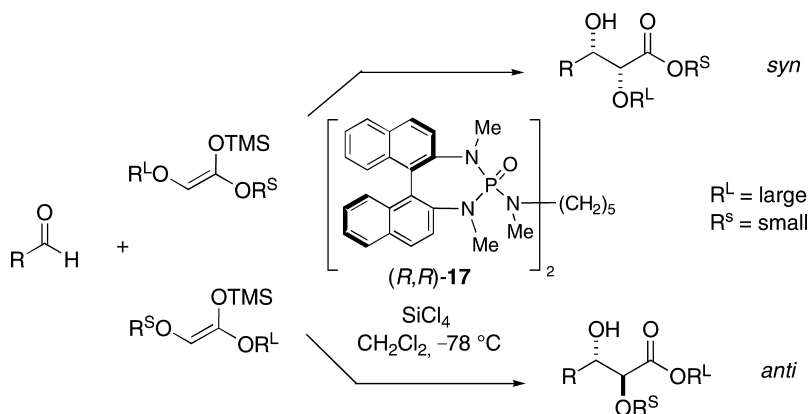
Lewis Acid Activation with Lewis Bases in Aldol-type Additions [40]

Lewis bases typically activate silicon atoms in electron donors such as silyl enolates or allylsilanes, as conventional Lewis acid catalysts activate heteroatoms in electron acceptors such as carbonyl groups. In these reactions, the asymmetric activation relies on the formation of a tightly binding chiral complex between the Lewis base catalyst such as alkoxides, HMPA, *N*-oxides or its asymmetric analogs and the silicon compounds, effecting rate acceleration. The enantio- and diastereoselectivity (*syn:anti* ratio) depends strongly on the structure of the chiral phosphoramidate that affects the coordination state of the silicon atom of the silyl enol ether in the TS, as was demonstrated in the aldol reaction of cyclohexanone trichlorosilyl enol ether and benzaldehyde [40]. The more selective path with hexacoordinated silicate requires two sterically less demanding phosphoramidate ligands (*R* = Me), leading to a chair-like TS with hexacoordinate silicate and affording the *anti* adduct. In contrast, the sterically demanding phosphoramidate (*R* = Ph) forms a pentacoordinate silicate, which leads to a boat-like TS and affords the *syn* adduct (Scheme 9.17). The enantioselectivity of the reaction is sensitive to the enolate structure, with larger groups providing lower enantioselectivities. A marked effect of the aldehyde structure on the rate of the addition was noted since aliphatic and hindered aldehydes were less reactive.



Scheme 9.17 Different stereochemical courses of the mono- and bis-coordinated hypervalent silica in the chiral HMPA-activated addition of cyclohexanone trichlorosilyl enol ether to benzaldehyde.

The bis-coordinated path was optimized in preparing dimeric phosphoramidate catalysts. These catalysts were also effective in mediating the cross-aldol reaction of various silyl ether enolates and in the Mukaiyama-reaction of various *exo*-TMS-enolates to aromatic aldehydes [41]. Moreover, a general and selective addition of glycolate-derived silyl ketene acetals to a wide range of aryl- and alkylaldehydes has been developed using silicon tetrachloride and the chiral Lewis basic bisphosphoramidate catalyst [42]. The sense of diastereoselectivity can be modulated by changing the size of the R substituents on the silyl ketene acetals (Scheme 9.18). In general, the trimethylsilyl ketene acetals derived from methyl glycolates with a large protecting group on the oxygen provide enantiomerically enriched (*R*)- α,β -dihydroxy esters with high *syn* diastereoselectivity, whereas the *tert*-butyldimethylsilyl ketene acetals

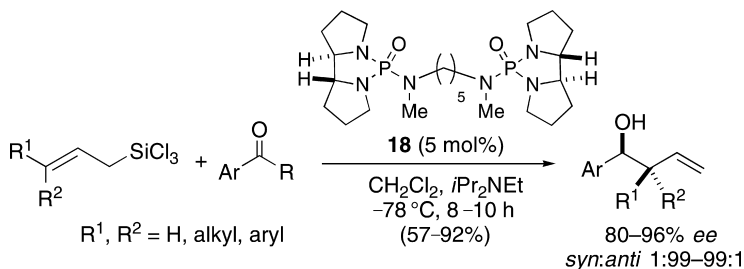


Scheme 9.18 Substrate control in the dimeric chiral HMPA-mediated addition of trimethylsilyl ketene acetals to aldehydes.

derived from bulky esters of methoxyacetic acid provide enantiomerically enriched (*R*)- α,β -dihydroxy esters with high *anti* diastereoselectivity.

9.3.1.2 Allylation Reactions

Tethered bis-phosphoramidates catalyze the addition of either allyltrichlorosilane (*E*)- or (*Z*)-2-butenyltrichlorosilane to unsaturated aldehydes (Scheme 9.19) [43]. Noteworthily, chiral bidentate imidodiphosphoric tetramides and pyridine-*N*-oxides were also efficient in the allylation of aromatic aldehydes [44].



Scheme 9.19

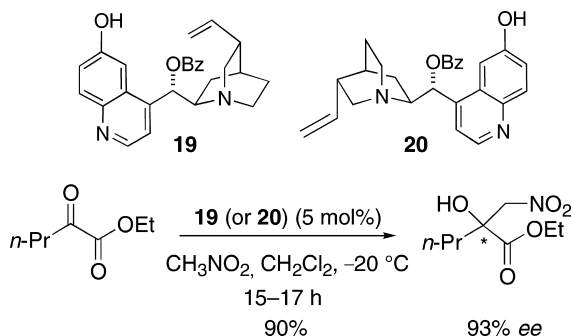
This method has also been applied to the synthesis of chiral quaternary centers (R^1 , $\text{R}^2 = \text{alkyl and/or aryl}$) and to the synthesis of the serotonin antagonist LY426965 [45].

9.3.1.3 Nitroaldol (Henry) Reactions [46]

Direct Nitroaldol Reactions

Nitroaldol (Henry) Reactions via General-base Catalysis and Contact Ion-pair Formation Under Homogeneous Conditions

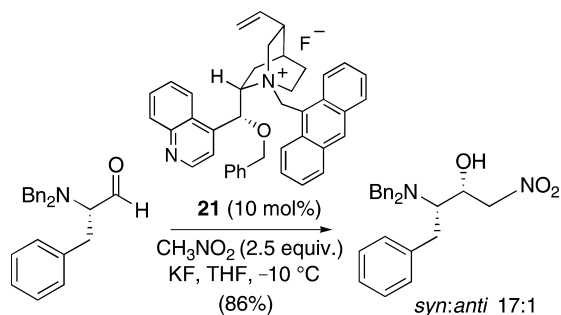
Chiral bases such as benzoylcupreidine (**19**) and benzoylcupreine (**20**) mediate the reaction of α -keto esters with nitromethane and provide easy access to functionalized compounds (Scheme 9.20) that feature a quaternary stereocenter such as aziridines, β -lactams and α -alkylcysteines [47].



Scheme 9.20 Benzoylcupreidine (**19**) and benzoylcupreine (**20**)-mediated addition of nitromethane to α -keto esters.

Nitroaldol (Henry) Reactions via General-base Catalysis and Contact Ion-pair Formation Under Phase-transfer Conditions [48]

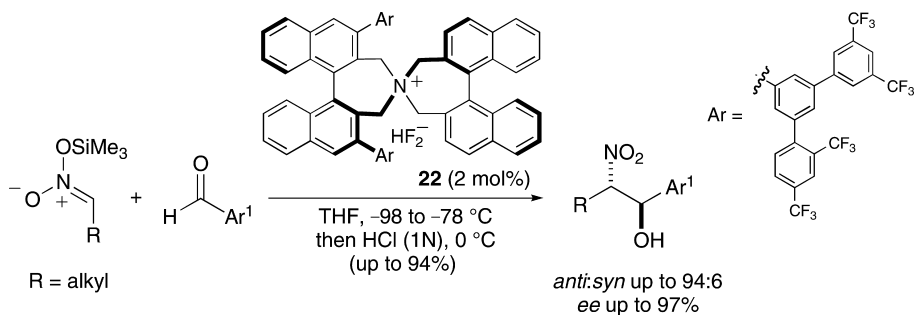
The face-selective nitroaldol reaction of nitromethane with protected (*S*)-phenylalanine was effected under PT conditions using the functionalized 9-anthracenylmethyl cinchona catalyst **21**. The reaction afforded the key intermediate of the second-generation HIV protease inhibitor amprenavir in good yield and with remarkable stereoselectivity (Scheme 9.21) [49].



Scheme 9.21 9-Anthracenylmethyl cinchona (**21**)-catalyzed addition of nitromethane to aldehyde under PT conditions in the synthesis of amprenavir.

Nitroaldol (Henry) Reaction of Silyl Nitronates

Chiral ammonium fluoride salt **22** was engineered for the asymmetric nitroaldol reaction of silyl nitronates with aromatic aldehydes (Scheme 9.22) [50]. High enantio- and *anti* diastereoselectivity were observed when a radially extended 3,3'-aryl-substituted catalyst was used.

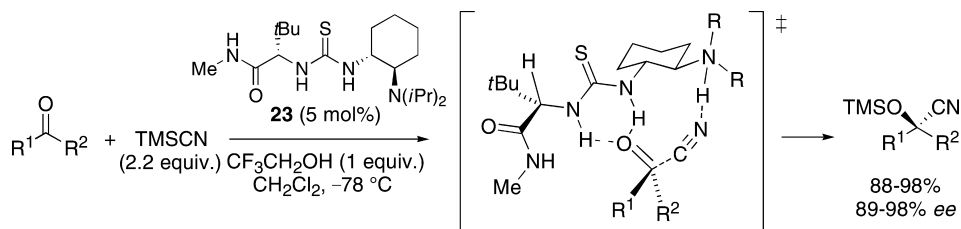


Scheme 9.22 Chiral quaternary ammonium-catalyzed addition of silyl nitronates to aryl aldehydes.

9.3.1.4 Hydrocyanation

Most of the organocatalysts developed to date for hydrocyanation are limited in substrate scope [51]. Chiral diketopiperazine-imidazoles and diaminocyclohexane-derived salem catalysts are efficient in the asymmetric hydrocyanation of aromatic

aldehydes, whereas dihydroquinyl (DHQ) and dihydroquinidyl (DHQD) derivatives can be used for the hydrocyanation of ketones [52]. Tertiary aminothiourea catalysts have, however, remarkably broad substrate compatibility as they can be used for both aldehydes and ketones bearing one sp^2 -hybridized substituent. The HCN is generated *in situ*, from TMS-CN and trifluoroethanol, affording the addition products in high yields and *ee* (Scheme 9.23) [53]. In the **23**-mediated hydrocyanation, both the thiourea and the tertiary amine of the catalyst are involved productively in the rate-limiting cyanide addition step, as depicted in Scheme 9.23 [54]. According to this cooperative mechanism, the enantioselectivity arises from direct interactions between the ketone substrate and the amino-acid derived portion of the catalyst (Scheme 9.2c-1).



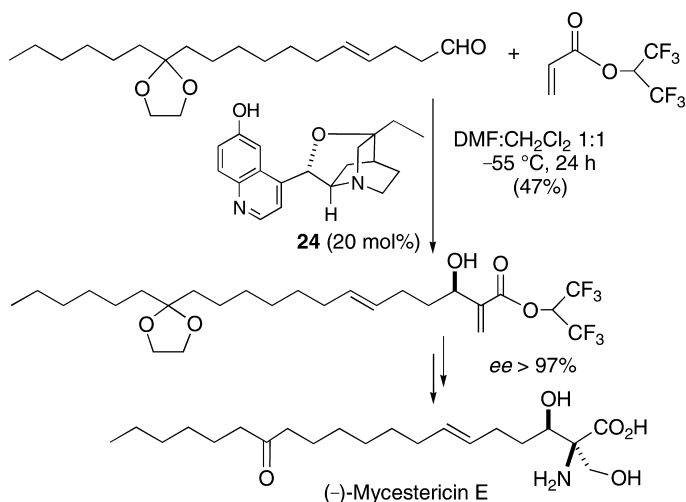
Scheme 9.23 Enantioselective cyanosilylation of ketones catalyzed by tertiary aminothiourea catalysts **23**.

9.3.1.5 The Morita–Baylis–Hillman (MBH) Reaction [55]

The addition of aldehydes to enones or α,β -unsaturated esters, the so-called Morita–Baylis–Hillman (MBH) reaction, requires both nucleophile and proton catalysts either in the same structure or in separate catalysts. The action of the Brønsted co-catalyst is at least two-fold: (i) it promotes the conjugate addition by binding to the zwitterionic enolate and stabilizes these intermediates; and (ii) it ensures efficient proton transfer in the rate- and stereo-determining proton abstraction step [7]. Among the number of catalysts that have been developed for the MBH reaction, β -isocupreidine, chiral thiourea and phosphine–BINOL-type catalysts have shown high selectivity and a relatively wide substrate range.

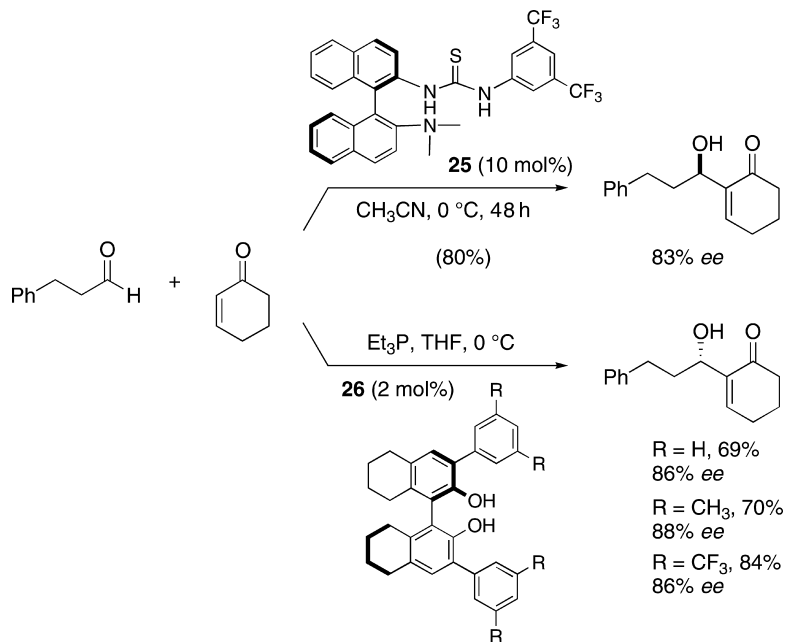
The quinidine-derived β -isocupreidine catalyst (β -ICD) (**24**) mediated the addition of the acrylate to a variety of aromatic and aliphatic aldehydes even at $-55\text{ }^\circ\text{C}$ in DMF (up to 99% *ee*). The 1,1,1,3,3,3-hexafluoroisopropyl acryl ester (HFIPA) displayed an almost 200-fold rate acceleration compared with methyl acrylate under identical reaction conditions. Limitations were observed with bulky aldehydes such as butyraldehyde, where dimerization of the acrylate was observed. The β -ICD catalyst **24** was used in the synthesis of epopromycin B, a plant cell wall synthesis inhibitor [56], and in the synthesis of mycestericin E, a potent immunosuppressor (Scheme 9.24) [57].

Enones usually provide less selective additions and the scope of the MBH reaction with this class of substrates remains narrow. Chiral (thio)urea–amine catalysts **25** [58]



Scheme 9.24 The asymmetric MBH reaction in the synthesis of $(-)$ -mycestericin E.

and the combination of PPh_3 with partially saturated BINOL derivatives such as **26** offered high chemical yield and enantioselectivity in the addition of cyclohexenone with hindered aliphatic aldehydes (Scheme 9.25) [59]. Conjugated and aromatic aldehydes resulted in low yields and enantioselectivities.

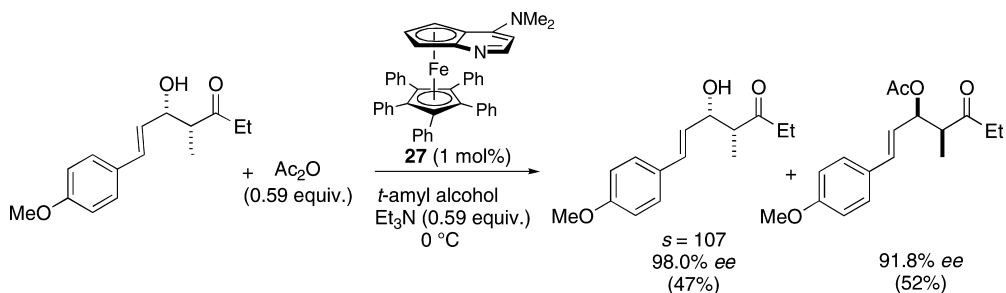


Scheme 9.25 Bifunctional thiourea–amine and achiral phosphine–chiral binaphthol-derived Brønsted acid-catalyzed MBH reactions of cyclohexenone and dihydrocinnamaldehyde.

9.3.1.6 Asymmetric Acyl Transfer Reactions [60]

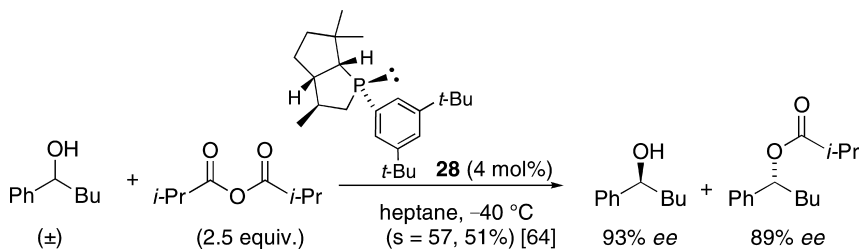
Kinetic Resolution of Secondary Alcohols

Among the great number and variety of DMAP-derived acyl transfer agents, the planar chiral ferrocenyl DMAPs proved to be highly versatile and efficient catalysts for many acyl transfer processes (Scheme 9.26) [60b, e, f]. In particular, the catalyst **27** was found to be efficient in the kinetic resolution of aryl, alkyl and allyl *sec*-alcohols and was the only organocatalyst that has been shown to be generally effective for the kinetic resolution of propargylic *sec*-alcohols [60b, e, f]. The synthetic utility of this catalyst was demonstrated in multistep synthesis; the following example is taken from the kinetic resolution protocol of a racemic aldol intermediate in the Sinha–Lerner synthesis of epothilone A (Scheme 9.26) [61]. It is considered that a π – π stacking interaction between the catalyst and the substrate in the TS is crucial to the observed enantioselectivity [62].



Scheme 9.26 Preparation of an epothilone A intermediate using the planar chiral DMAP **27**.

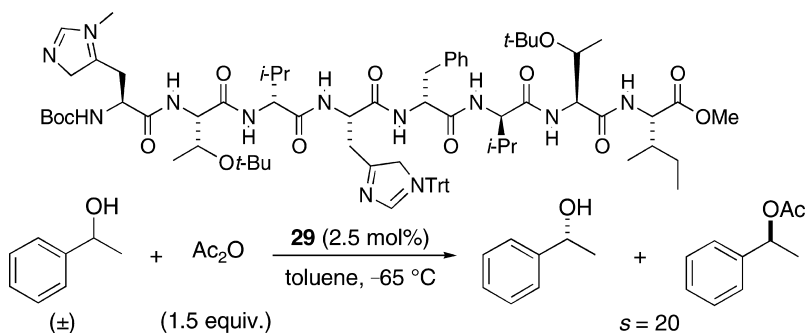
Among the phosphine-derived catalysts, chiral *P*-aryl-2-phospha-bicyclo[3.3.0]octanes (PBO) [63] were shown to be remarkably selective in acylation for a broad range of arylalkyl *sec*-alcohols (Scheme 9.27) [65].



Scheme 9.27 The kinetic resolution of arylalkyl *sec*-alcohols using chiral PBO catalyst.

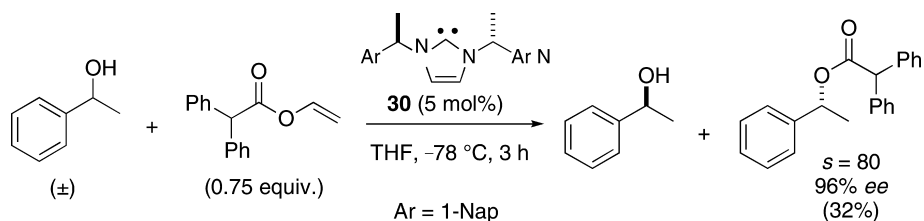
Engineered oligopeptides such as **29** are efficient for the acylative kinetic resolution of *sec*-alcohols [29, 66]. The substrate scope includes not only arylalkyl

sec-alcohols but also alkyl *sec*-alcohols with which lipases and other organocatalysts invariably perform poorly (Scheme 9.28) [67].



Scheme 9.28 Miller's octapeptide **29**-catalyzed kinetic resolution of *sec*-alcohols.

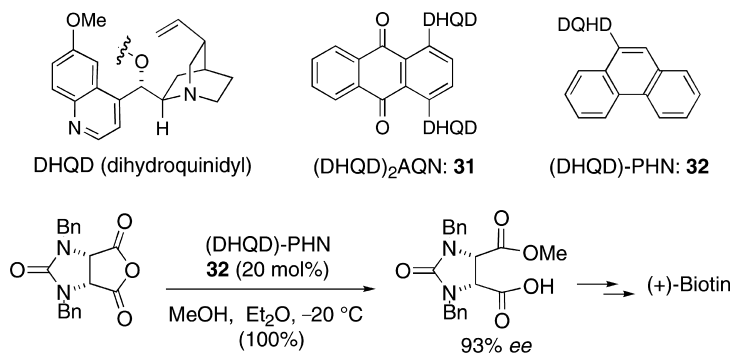
The kinetic resolution of arylalkyl *sec*-alcohols using various chiral nucleophilic *N*-heterocyclic carbenes (NHCs) has also recently been achieved by the groups of Suzuki [68] and Maruoka [69] (Scheme 9.29). These studies build on an emerging body of work showing that achiral NHCs are extremely efficient nucleophilic organocatalysts for transesterification.



Scheme 9.29 Maruoka's chiral NHC-catalyzed kinetic resolution of *sec*-alcohols.

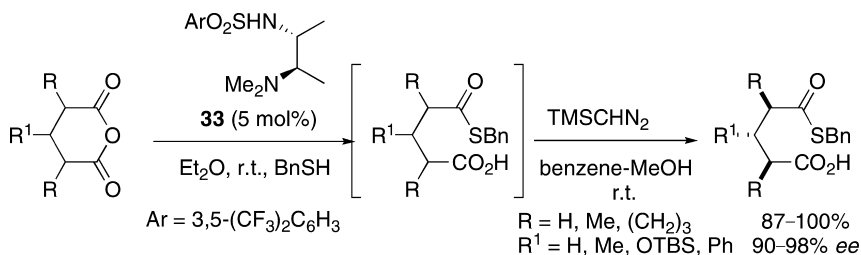
Asymmetric Desymmetrization of Achiral/*meso* cyclic Anhydrides [23a, 60d, 70]

Asymmetric desymmetrization (ASD) of achiral and *meso* cyclic anhydrides by nucleophilic ring opening with alcohols or thiols can be catalyzed by either chiral Lewis acids or bases. One of the most selective classes of catalyst in this type of transformation is Sharpless ligands. Reaction of a variety of mono-, bi- and tricyclic succinic anhydrides with methanol in diethyl ether and a catalytic amount of the bisquinoline alkaloid (DHQD)₂AQN (**31**) provided the corresponding hemiesters with excellent enantioselectivities (91–98%) and good to excellent yields (72–99%) [71, 72]. The synthetic utility of this approach has been demonstrated in a formal total synthesis of (+)-biotin (Scheme 9.30) [73].



Scheme 9.30 Cinchona-derived (DHQD)–PHN catalyst-mediated asymmetric desymmetrization of a *meso* anhydride in the synthesis of (+)-biotin.

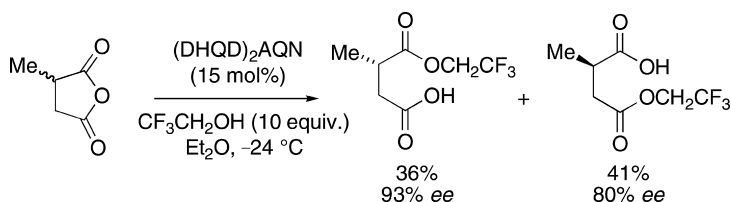
Cinchona-derived catalysts are not the only efficient systems for the ASD of *meso* anhydrides; the bifunctional chiral sulfonamide–amine organocatalyst **33** can also be used for the highly enantioselective catalytic thiolysis of prochiral cyclic anhydrides (Scheme 9.31) [74].



Scheme 9.31 Chiral sulfonamide–amine organocatalyst **33**-mediated asymmetric desymmetrization of achiral and *meso*-anhydrides.

Alcoholative Kinetic Resolution of Racemic Anhydrides

Further application of (DHQD)₂AQN-catalyzed asymmetric alcoholysis can be illustrated by the kinetic resolution of monosubstituted succinic anhydrides [75]. A variety of 2-alkyl- and 2-arylsuccinic anhydrides were resolved via this process with good to excellent enantioselectivities (Scheme 9.32).



Scheme 9.32 Deng's (DHQD)₂AQN-catalyzed ASD of *meso* anhydrides.

9.3.2

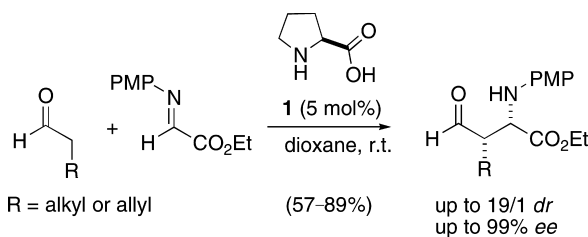
Nucleophilic Additions to C=N

9.3.2.1 Mannich-type Reactions [76]

The Organocatalytic Direct Mannich Reaction

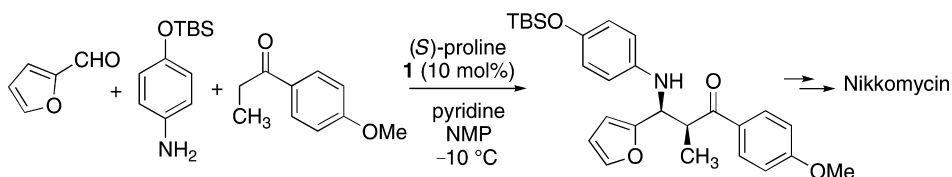
Organocatalytic Mannich reactions have been described either under three-component (one-pot) reaction conditions or involving preformed (protected) imines and aldol donors. Proline was found to catalyze both versions, usually in good yields and in high selectivity. Using L-proline (**1**) as catalyst, the stereochemistry of the reaction is catalyst controlled and independent of the chiral centers present in the substrate. The original Mannich reaction provided the highest selectivities with aromatic aldehydes.

Historically, the one-pot, three-component Mannich reaction between a ketone, aldehyde and anisidine was developed first, which also provided practical access to a number of enantiomerically enriched β -aminocarbonyls. The use of preformed imines, such as *N*-PMP-protected α -iminoethyl glyoxylates, is more recent (Scheme 9.33). The advantage of this modification is that under these conditions the potential side-reactions are minimized and both ketones and aldehydes can be used as aldol donors.



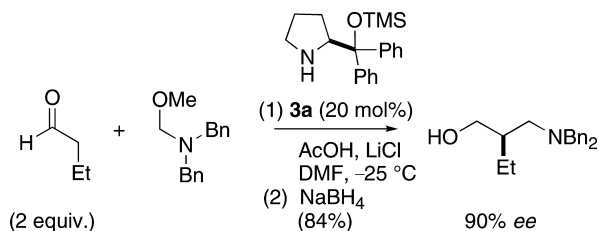
Scheme 9.33 Two-component Mannich reaction between *N*-PMP-protected α -iminoethyl glyoxylates and aldehydes.

Intriguingly, the cross-Mannich reaction using ‘unmodified’ aldehydes proceeds faster than the competing cross-aldol reaction (Scheme 9.34). The three-component cross-Mannich reaction at temperatures below 0 °C exhibits both higher stereo- and chemo-selectivity ($k_{\text{cross-Mannich}} > k_{\text{cross-aldol}}$). With electron-rich aromatic acceptor aldehydes, the use of a syringe pump was not necessary and the catalyst loading could be reduced. The example in Scheme 9.34 is taken from the formal synthesis of nikkomyacin [77].



Scheme 9.34 The application of the three-component cross-Mannich reaction in the synthesis of nikkomyacin.

The direct Mannich reaction can also be mediated by proline analogs [78]. In particular, TMS-diphenylprolinol derivatives **3a** were seen efficient for the aminomethylations of various aldehydes (Scheme 9.35) [79].

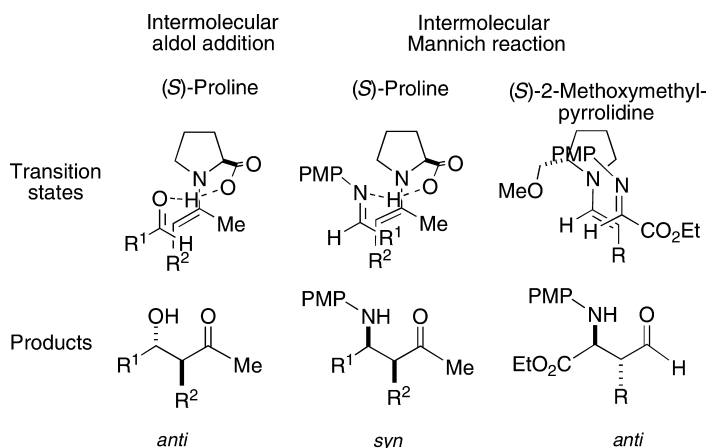


Scheme 9.35 Aminomethylations of aldehydes via direct Mannich reaction.

As proline and proline analogs provide preferentially the *syn* isomer, the *anti*-selective Mannich reactions between unmodified α -hydroxy ketones, arylamines and aldehydes can be realized by L-threonine or L-tryptophan-derived amino acids [80].

The lengthy reaction times, which characterize both the proline and other chiral amine-catalyzed Mannich reactions, can be considerably shortened (up to 4–50 times) by replacing standard organic solvents by ionic liquids such as [bmim].BF₄ or [bmim].PF₆ [81]. This modification may also permit the use of as little as 1 mol% of catalyst while retaining reasonable reaction times (~2 h). The reaction usually affords higher yields than in organic solvents and provides similar enantioselectivity. The enhanced rates may result from ionic liquid-based activation of the imine electrophile.

The proline-catalyzed Mannich reaction shows opposite diastereo- and enantioselectivity to those of the related aldol reactions as the *syn* adducts being obtained as major isomers. In contrast, *anti* addition between *N*-PMP-protected α -iminoethyl



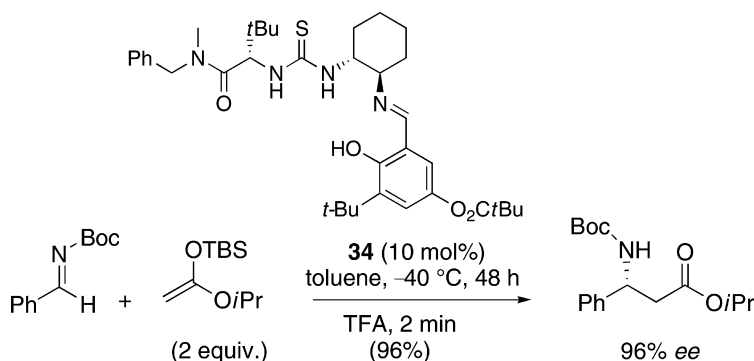
Scheme 9.36 The rationale of the observed difference in the stereoselectivity of (*S*)-proline- and (*S*)-2-methoxymethylpyrrolidine-mediated aldol and Mannich reactions.

glyoxylate and aldehydes was observed using a bulky pyrrolidine catalyst where the acid function was suppressed, such as (*S*)-2-methoxymethylpyrrolidine (SMP). The differences in the reversal of selectivity of the proline-catalyzed Mannich reaction can be explained by the differences in the preferred conformations in the TS of the substrates. As the aldehyde substituents assume a pseudoequatorial conformation in the aldol reaction, the substituents are forced into a pseudoaxial arrangement in the Mannich reaction since the (*E*)-imine is more stable than the (*Z*)-imine (Scheme 9.36).

Mannich-type Reactions with Preformed Enolates and Enolate Equivalents

Brønsted Acid Catalysis

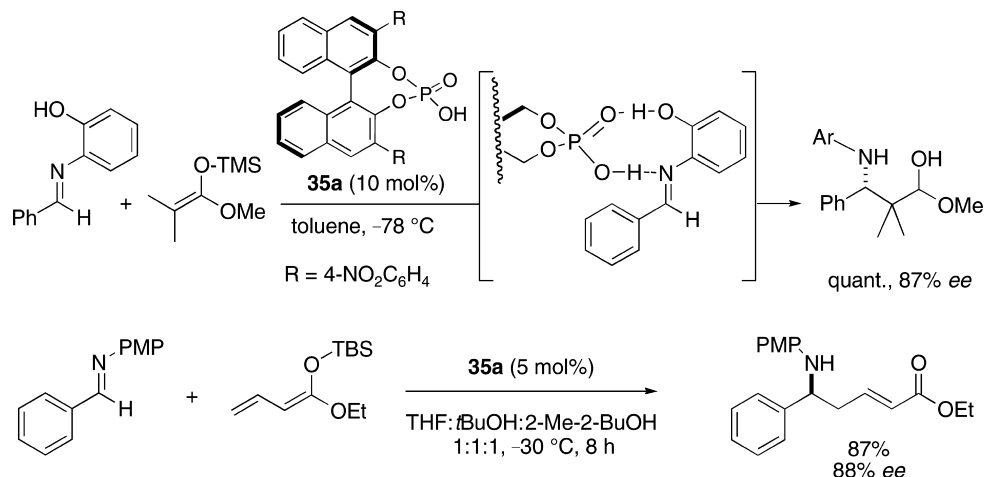
Highly enantioselective Mannich reactions were developed with chiral thiourea-derived Brønsted acid catalysts by Jacobsen's group (Scheme 9.37) [82]. Likewise, bifunctional thiourea catalysts mediated the direct asymmetric vinylogous Mannich reaction of α,α -dicyanoalkenes and *tert*-butyloxycarbonyl (Boc)-protected imines with complete γ -regioselectivity and excellent enantioselectivities [83].



Scheme 9.37 Chiral thiourea catalyst-mediated Mannich reaction of ketenesilyl acetals and arylimines.

One of the more promising classes of catalysts for a broad range of highly enantioselective imine addition reactions is the 2,2'-dihydroxy-1,1'-binaphthyl (BINOL)-based phosphoric acid catalysts that involve chiral contact ion pairs generated *in situ* [8f]. Such a chiral phosphoric acid diester catalyst was developed for the asymmetric Mannich-type addition of silylketene acetals to arylaldimines. The catalyst mediated the addition in favor of the *syn* isomer [84, 85]. In this transformation, the *N*-2-hydroxyphenyl group of aldimine was found to be essential for the high selectivity as the reaction proceeds via a dicoordination pathway through the zwitterionic and nine-membered cyclic TS consisting of the aldimine and the phosphoric acid (Scheme 9.38). The *re*-facial selectivity was rationalized by the aromatic stacking interaction between the 4-nitrophenyl group and the *N*-aryl group that fix the geometry of aldimine in the TS, where the *si*-facial attacking TS is less favored by the steric hindrance of the 3,3'-aryl substituents. Noteworthy, the BINOL-based phosphoric acid catalyst was also efficient in the vinylogous Mukaiyama–Mannich reaction of

acyclic silyl dienolates and imines. The reaction proceeds also with complete regioselectivity in favor of the δ -product [86].



Scheme 9.38 The BINOL-based phosphoric acid-mediated Mukaiyama–Mannich and vinylogous Mukaiyama–Mannich reactions of silylketene acetals and arylimines.

General-base Catalysis and Contact Ion-pair Formation Under Phase-transfer Conditions

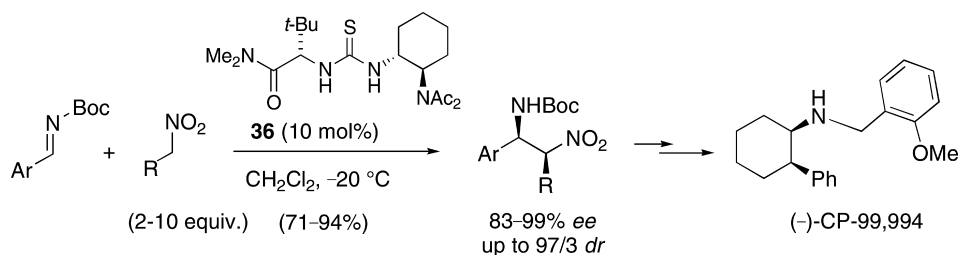
Similar transformations can be successfully conducted under phase-transfer conditions with a chiral pyrrolidinium salt in up to 95% ee [87].

9.3.2.2 The Nitro-Mannich (Aza-Henry) Reaction

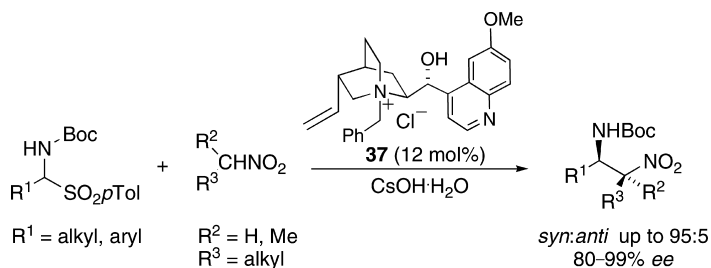
A highly effective thiourea-based catalyst was developed for the nitro-Mannich (aza-Henry) reaction that mediated the *syn*-selective addition of a range of nitroalkanes to aromatic *N*-Boc-imines [88]. The sense of imine enantioface selectivity is the same as that observed in thiourea-catalyzed Strecker, Mannich and hydrophosphonylation reactions, suggesting a common mechanism of imine activation. However, thiourea derivatives are also known to bind and modulate the reactivity of nitronate anions; therefore, the role of the catalyst in this transformation could be either activation of the nitroalkane component or dual activation of both reaction partners. The scope of the transformation can be illustrated by the synthesis of the potent neurokinin-1 receptor antagonists (–)-CP-99,994 (Scheme 9.39).

General-base Catalysis and Contact Ion-pair Formation Under Phase-transfer Conditions [89]

A remarkably general cinchona-derived ammonium catalyst-mediated nitroaldol reaction was developed between nitroalkanes and α -amidosulfones by using CsOH.H₂O as base under phase-transfer conditions. The reaction that generates the reactive imine component *in situ* can be applied to either non-enolizable or enolizable aldehyde-derived azomethines and to nitroalkanes, other than nitromethane, for the production of β -nitroamines (Scheme 9.40).



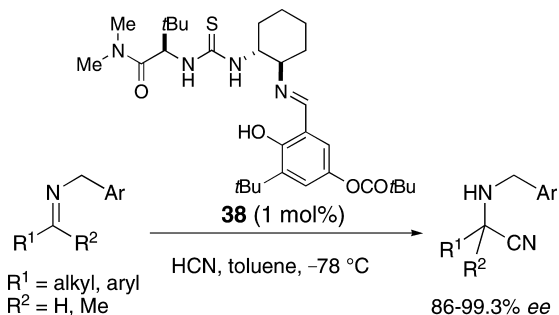
Scheme 9.39 Chiral thiourea-mediated *syn*-selective nitro-Mannich (aza-Henry) reaction in the synthesis of the (-)-CP-99,994.



Scheme 9.40 Cinchona-derived ammonium catalyst-mediated nitroaldol reaction between azomethines and nitroalkanes under PT conditions.

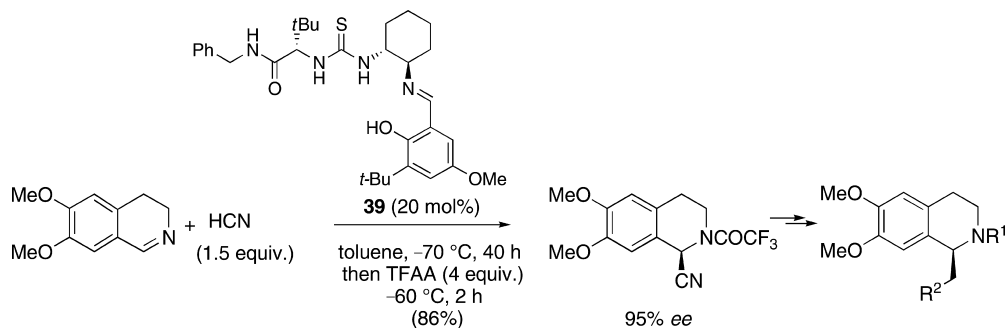
9.3.2.3 The Asymmetric Strecker Reaction [90]

Chiral peptide-like urea catalysts have been the subject of considerable study [91]. Surprisingly, the same class of catalyst can be used in asymmetric cyanation reactions of aldimines and methylketimines and in asymmetric Mannich reaction of *N*-Boc-aldimines with silylketene acetals (Scheme 9.41). The thiourea **38** mediated hydrocyanation reactions with a remarkably broad generality: the same catalyst affords >95% *ee* for all aldimines examined, ranging from aromatic to bulky aliphatic such as *tert*-butyl, to small aliphatic such as *n*-pentyl. It is worth noting that ketimines can be used likewise. This level of generality is still unusual in asymmetric catalysis [82b].



Scheme 9.41 Chiral thiourea-mediated asymmetric Strecker reaction of aldimines and ketimines.

The imine–catalyst complex forms reversibly a hydrogen bond between the imine nitrogen having a *Z* configuration and the acidic proton of the urea. Factors which account for the high enantioselectivity of the reactions are as follows: the steric demand of the substituents flanking the imine group should be markedly different; the *N*-substituent should favor the formation of the *Z* isomer of the imine; and the HCN addition takes place from the diaminocyclohexane side of the catalyst. The reaction was used for the preparation of optically enriched isoquinoline alkaloids, precursors of natural compounds (*R*)-(-)-calycotmine ($R^1 = \text{H}$, $R^2 = \text{OH}$), (*S*)-(-)-salsolidine ($R^1 = R^2 = \text{H}$) and (*S*)-(-)-carnegine ($R^1 = \text{Me}$, $R^2 = \text{H}$) (Scheme 9.42) [2].

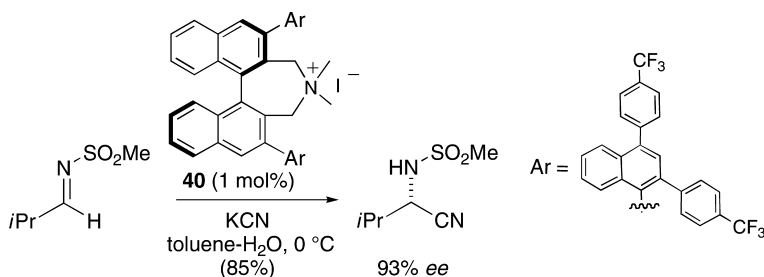


Scheme 9.42 The asymmetric Strecker reaction in the synthesis of isoquinoline alkaloids.

Other Brønsted acid catalysts such as chiral BINOL phosphate-derived catalysts [3] and Lewis base catalysts such as the axially chiral biquinoline *N,N'*-dioxide catalysts used in the presence of trimethylsilyl cyanides showed less general substrate scope.

Strecker Reactions Under Phase-transfer Conditions

Under heterogeneous conditions, the chiral binaphthol-derived quaternary ammonium salts efficiently promotes the Strecker reaction of aldimines when aqueous potassium cyanide is used (Scheme 9.43) [4].

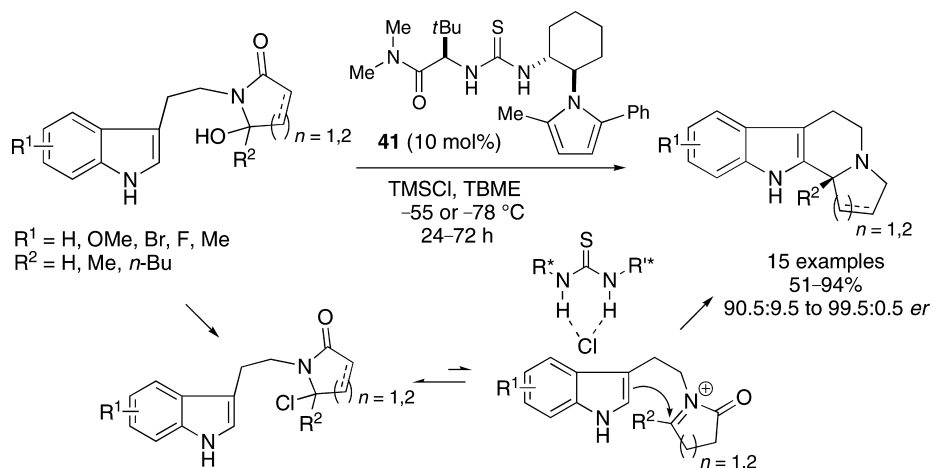


Scheme 9.43 The Strecker reaction of aldimines under PT conditions.

9.3.2.4 Pictet–Spengler-type Cyclizations

Brønsted acid catalysts and in particular chiral thiourea catalysts may promote enantioselective Pictet–Spengler reactions (Scheme 9.44) [5]. In the following

example the iminium ions were generated from tryptamine-derived hydroxylactams using TMSCl [5]. Substituent and counterion effect studies pointed to rate-limiting anion abstraction and binding by the thiourea by hydrogen bonding to the putative iminium ion intermediate.



Scheme 9.44 The preparation of enantioenriched indolizone and quinolizone products by chiral thiourea-promoted Pictet-Spengler reaction.

9.3.2.5 Reduction of Ketimines [6]

Chiral formamides have been developed for the enantioselective reduction of *N*-aryl- and *N*-cycloalkylketimines with trichlorosilane [7]. Among the catalysts developed, pipercolic acid derivative **42** was shown to be comparable with both alkyl- and arylketimines, whereas the valine-derived *N*-methyl-substituted formamide **43** was active in the reduction of arylketimines (Scheme 9.45) [98].

A conceptually different approach for the reduction of ketimines is the use of Hantzsch esters **I** as hydrogen donors that can be used in the presence of a chiral phosphoric acid catalyst (Scheme 9.46). This method can be used for the reduction of both alkyl- and arylketimines [99].

9.3.3

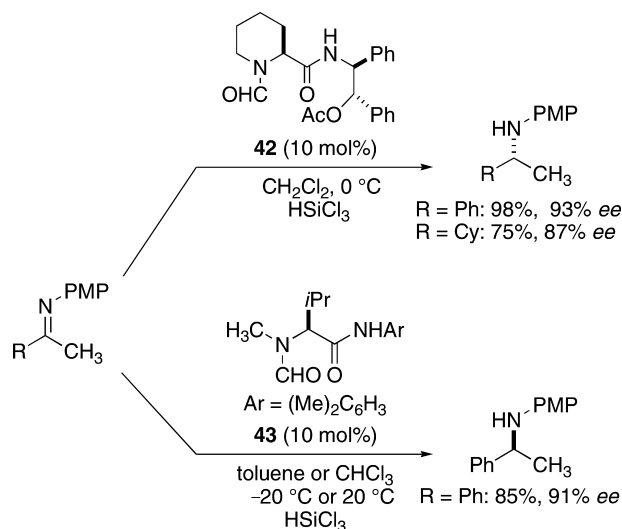
Additions to Alkenes

9.3.3.1 Michael Addition [19e, 100]

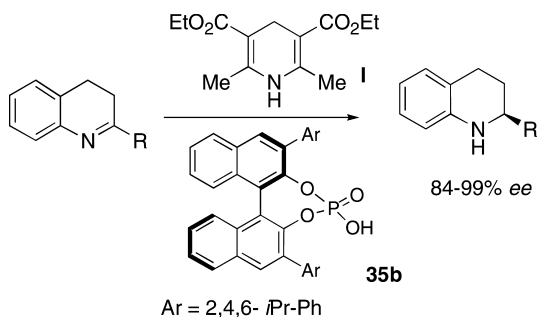
Aminocatalytic Direct Addition of Aldehydes and Ketones to Nitroalkenes

Enamine Activation

Pyrrolidine-derived catalysts promote *syn*-selective additions of nitroalkenes with aldehydes and also with ketones [1, 101]. While high levels of diastereo- and enantio-

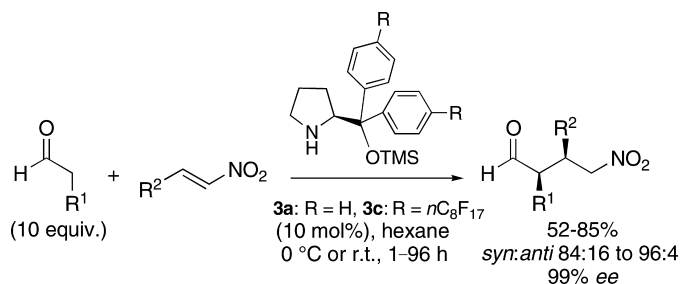


Scheme 9.45 Asymmetric reduction of *N*-aryl- and *N*-cycloalkylketimines by trichlorosilane and chiral formamide catalysts.



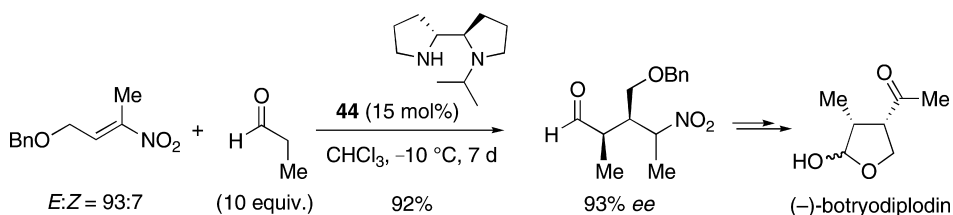
Scheme 9.46 Chiral phosphoric acid catalyst-mediated asymmetric reduction of ketimines in the presence of Hantzsch esters.

electivity can be obtained in selected cases and in particular with cyclohexanone, the reactions are usually substrate dependent. The diphenylprolinol silyl ether catalyst **3a** is remarkably efficient for the addition of α -unbranched aldehydes to aryl- and alkyl-substituted nitroalkenes [17a] and also to nitroethylene in the presence of a carefully selected acidic co-catalyst [102]. The diphenylprolinol silyl ether catalyst **3a** and the perfluoroalkyl derivative **3c** [103] afford high yields, excellent diastereoselectivity and nearly perfect enantioselectivity with a broad range of aldehydes. Moreover, the perfluoroalkyl catalyst **3c** can also be used in aqueous media [104]. The bulky diphenylsilyloxymethyl group probably plays a dual role in promoting the selective formation of the (*E*)-enamine and in providing efficient shielding of the *re*-face of the enamine (Scheme 9.47).



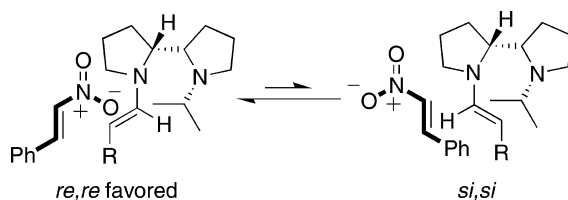
Scheme 9.47 The diphenylprolinol silyl ether-catalyzed Michael addition of aldehydes to nitroalkenes.

α -Substituted nitroalkenes can be used as substrates in bispyrrolidine-catalyzed additions. The efficiency of the catalyst **44** was demonstrated in the synthesis of (–)-botryodiplodin (Scheme 9.48). The addition of propionaldehyde to nitroalkene led to a roughly 2 : 3 mixture of *anti* and *syn* isomers in high yield and *ee* (92 and 93%, respectively) [105].



Scheme 9.48 Alexakis's (–)-botryodiplodin synthesis.

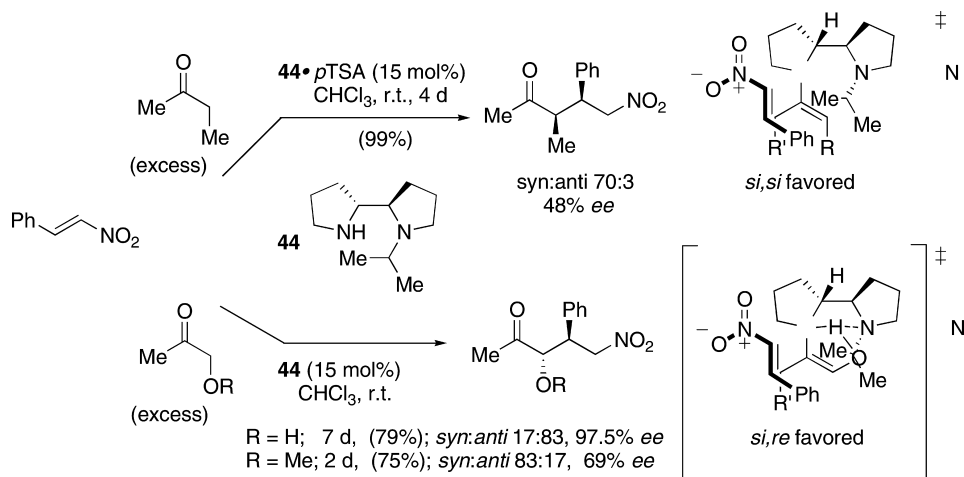
Interestingly, the same catalyst induces opposite selectivity with aldehydes compared with ketones. This can be rationalized by the difference in the steric demand of the enamine forms in the TS. As depicted in Scheme 9.49, the equilibrating conformers give rise to product via the less congested TS, forming the thermodynamic product.



Scheme 9.49 Rationale of enantioselectivity of the pyrrolidine catalyst-mediated additions of aldehydes to nitroalkenes.

Alkylation of asymmetric acyclic ketones takes place regioselectively on the most substituted carbon, affording the *syn* isomers as the major products. α -Hydroxy ketones showed *anti*-selective additions similar to that observed in related aldol-type

additions, but the mechanistic rationale is different (Scheme 9.50). The selectivity is due to the preferred formation of the (*Z*)-enamine intermediate, stabilized by intramolecular hydrogen bonding between the hydroxy group and the tertiary amine of the catalyst [106].



Scheme 9.50 Variation of the *syn/anti* diastereoselectivity of the conjugate addition as a function of the substrate.

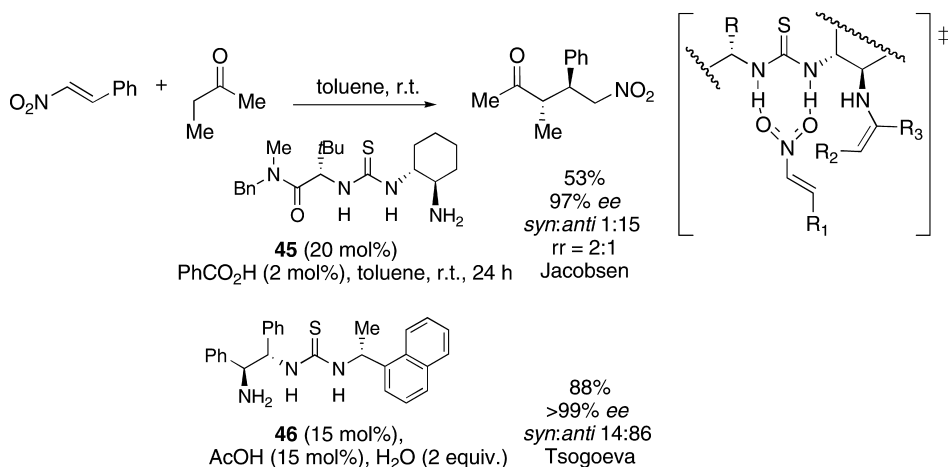
Short oligopeptides such as H-D-Pro-Pro-Asp-NH₂ and the homologous and more soluble H-D-Pro-Pro-Glu-NH₂ catalyst bearing an additional methylene group also showed remarkable selectivity in the addition of nitroethylene to a great variety of aldehydes [107, 108]. Notably, the product of a homoaldol reaction of the aldehyde that is often observed with other amine-based organocatalysts was not detected.

Amine–Thiourea Catalysts

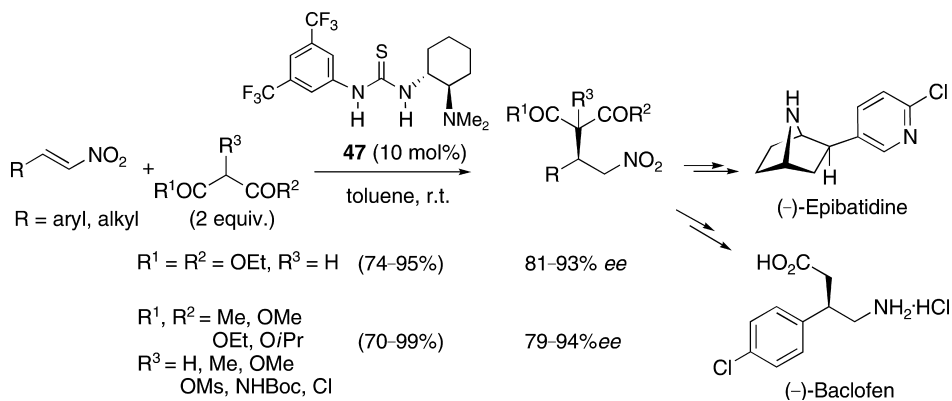
The bifunctional thiourea catalyst combined with a nucleophilic amine mediates the addition of ketones to nitroalkenes at room temperature in the presence of a weak acid co-catalyst, such as benzoic acid, *n*-butyric acid or acetic acid (Scheme 9.51) [109]. The acid additive allows double alkylation to be avoided and also increases the reaction rate. The *anti* selectivity of the addition is attributed to the preferred (*Z*)-enamine geometry in the TS. The catalyst also activates the acceptor and orientates in space. The regioselectivity of the alkylation of non-symmetric ketones is the consequence of this orientation.

General-base Activation: Addition of Esters, Amides and Nitriles to Nitroalkenes

A number of tertiary amine–thiourea catalyst combinations have been developed for the conjugate addition to nitroalkenes with malonates and with various 1,3-dicarbonyl compounds such as diesters and chiral keto esters. Among them, cinchona-derived bifunctional catalysts, where the hydroxy group at C-9 was replaced by an arylthiourea [110, 111], and thiourea derived from binaphthyl [112] are noteworthy.



Scheme 9.51 Thiourea–amine catalysts mediated addition of acyclic ketones to nitrostyrenes.



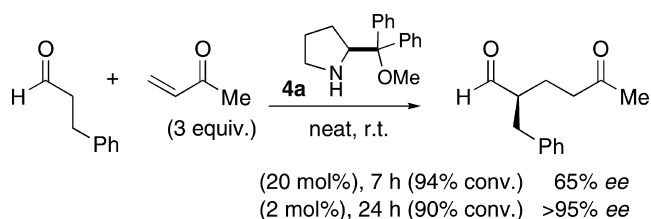
Scheme 9.52 Synthesis of (–)-baclofen and (–)-epibatidine by chiral 1,2-diaminocyclohexane-derived thiourea-mediated conjugate addition to nitroalkenes.

Chiral 1,2-diaminocyclohexane-derived thioureas are also efficient catalysts and were used in the synthesis of (–)-baclofen [113], an analog of GABA used as an antispastic agent, and (–)-epibatidine (Scheme 9.52) [114].

Aminocatalytic Addition of Aldehydes and Ketones to Enones

Enamine Activation

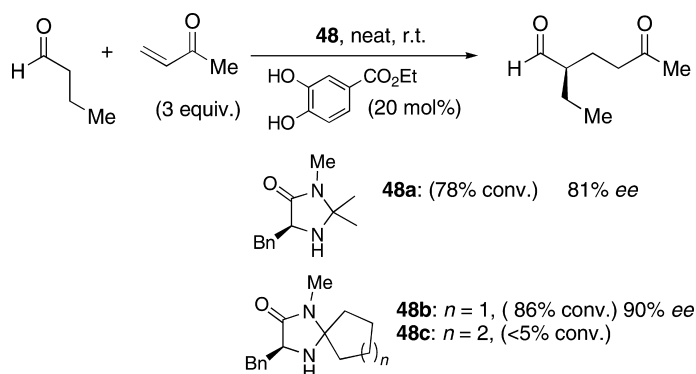
Among the pyrrolidine-derived catalysts, (*S*)-2-[bis(phenyl)methyl]pyrrolidine derivatives such as **4a** allowed good conversion and enantioselectivity in the addition of linear aldehydes to MVK (up to 85 % *ee*) (Scheme 9.53) [115]. Cyclic enones and β -substituted enones afforded no or poor results.



Scheme 9.53 4a-catalyzed addition of dihydrocinnamaldehyde to MVK.

The observed small negative non-linear effect suggested the participation of more than one catalyst molecule in the enantiodifferentiating step. This may be a consequence of the simultaneous activation of the nucleophile (enamine formation) and the electrophile partners (iminium formation) [116].

MacMillan's organocatalyst **48a**, which is used typically for electrophilic activation, was also found to be efficient in promoting conjugate addition via enamine formation (Scheme 9.54) [117]. The proof of the enamine pathway was furnished by NMR studies.



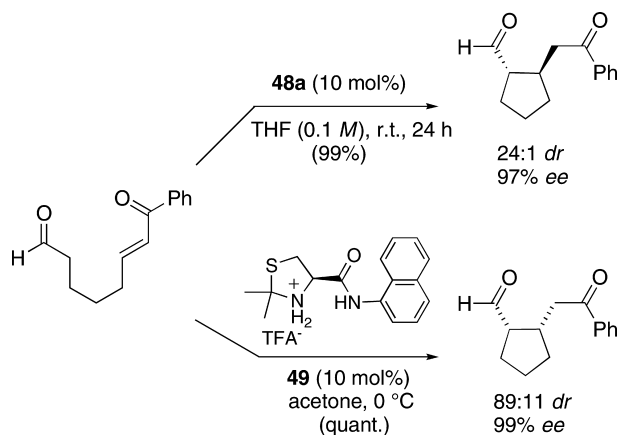
Scheme 9.54 Organocatalyzed asymmetric addition of butyraldehyde to MVK.

Intramolecular Conjugate Additions

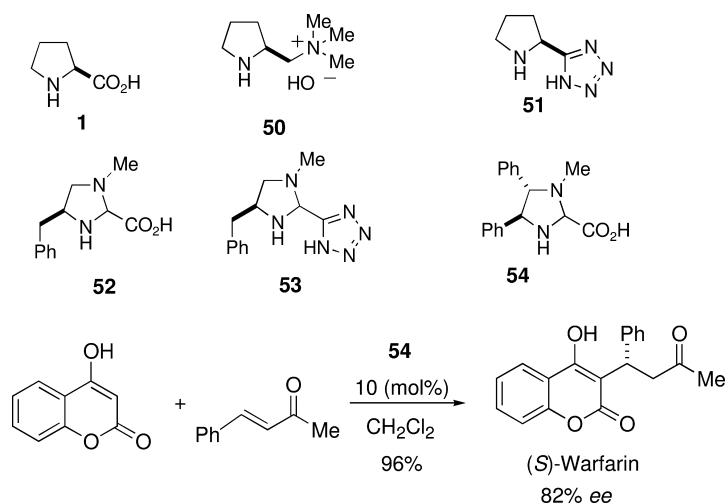
The intramolecular addition of aldehydes to enones could also be promoted with iminium catalysts (Scheme 9.25). The cyclization is highly *trans* selective, with the imidazolidinone catalyst forming 1,2-disubstituted cyclopentanes [118]. The reaction tolerates aryl and alkyl substituents on the enone and can be carried out with enals, and also in the presence of heteroatoms (Scheme 9.55). Inverse (*cis*) diastereoselectivity was obtained in the intramolecular Michael addition with the cysteine-derived prolinamide analog **49** (Scheme 9.55) [119].

Activation of Enones via Iminium Formation

Chiral pyrrolidine and imidazolidinone catalysts have been successfully employed in inter- and intramolecular Michael reactions including conjugate reduction, Friedel–Crafts alkylations and cycloadditions (Scheme 9.56). In 1,4-addition, central to these



Scheme 9.55 Intramolecular addition of aldehydes to enones.



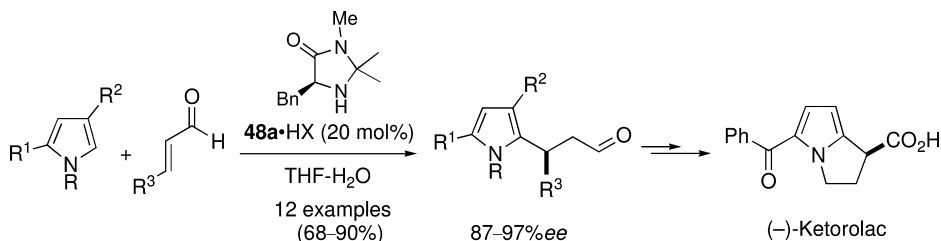
Scheme 9.56 Chiral pyrrolidine and imidazolidinone catalysts and the one-step preparation of warfarin.

reactions is the activation of an α,β unsaturated carbonyl compound by forming an iminium ion, which is activated to nucleophilic attack at the γ -carbon. Iminium activation is chemically equivalent to the electrophilic activation of the parent carbonyl compound resulting in LUMO lowering. The effectiveness of this approach is illustrated by the elegant enantioselective one-step preparation of one of the most widely used anticoagulants, warfarin (Scheme 9.56) [120].

Friedel–Crafts Alkylations

1,4-Additions of electron-rich aromatics and heteroaromatics to α,β -unsaturated aldehydes were developed with iminium catalysts. In particular, pyrrole, indole and

aniline derivatives were used as donors. The reaction is general with respect to the pyrrole architecture as far as incorporation of substituents at the C-2- or C-3-pyrrole positions provide regioselective alkylations at the C-5 and C-2 positions, respectively. The utility of this approach has been highlighted by the short and straightforward preparation of (–)-ketorolac (Scheme 9.57) [121].



Scheme 9.57 Friedel–Crafts alkylations via iminium activation: synthesis of (–)-ketorolac.

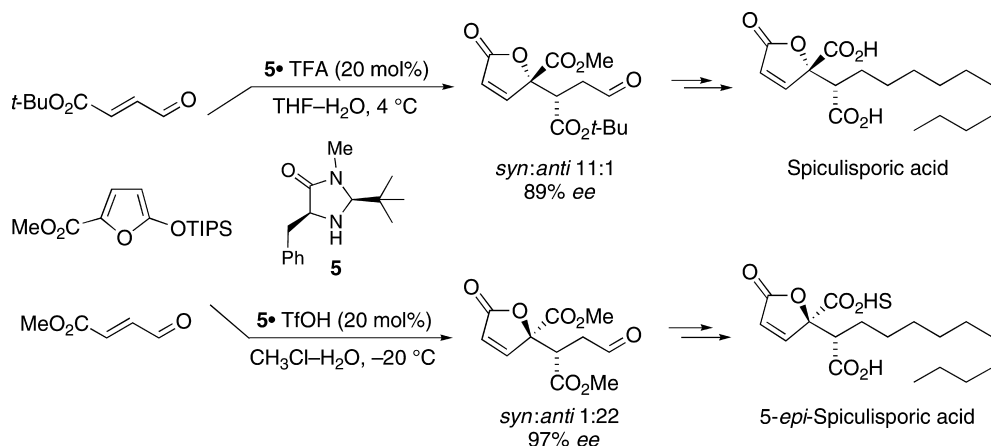
Mukaiyama–Michael Reactions

Chiral imidazolidinone catalyst **5** can also catalyze the addition of silyloxyfurans to α,β -unsaturated aldehydes to provide γ -butenolides [122]. Remarkably, whereas similar Lewis acid-catalyzed transformations give almost exclusively 1,2-addition products (Mukaiyama–aldol reaction), the organocatalyzed variant affords only 1,4-adducts (Mukaiyama–Michael reaction), thus providing a new strategy for the catalytic preparation of enantiomerically enriched butenolides [123]. Treatment of 2-silyloxyfurans with a variety of α,β -unsaturated aldehydes afforded the desired products in good enantiomeric purity with predominantly *syn* selectivity. Significantly, the use of different reaction conditions, namely changing the co-catalyst and solvent, provided butenolide adducts of opposite sense of diastereoselection, while retaining high levels of enantiocontrol. In a demonstration of the utility of this protocol, a four-step synthesis of spiculisporic acid, a *Penicillium spiculisporum* fermentation adduct which has found commercial application as a bio-surfactant for metal decontamination processes and fine polymer production, and its 5-*epi*-diastereomer has been accomplished (Scheme 9.58) [123].

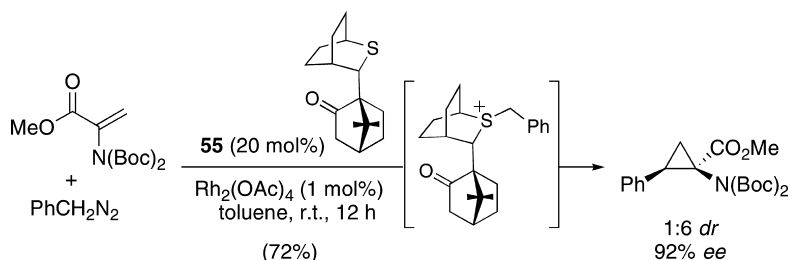
9.3.3.2 Cyclopropanation

Ylide reactions have been developed as one of the powerful approaches for the synthesis of small-ring compounds. Among the vast array of asymmetric methods for the preparation of enantiomerically enriched cyclopropanes, few examples concern organocatalysis; worth mentioning are the pioneering work by the groups of Aggarwal, Gaunt and MacMillan.

Sulfur ylide-mediated cyclopropanation was developed by Aggarwal's group [124]. A sulfur ylide is generated *in situ* from a chiral sulfide catalyst and phenyldiazomethane in the presence of a transition metal catalyst (Scheme 9.59). A modified procedure was introduced by Aggarwal and co-workers which utilized the generation of the diazo compounds *in situ* from tosyl hydrazone salts at 40 °C in the presence of a phase-transfer catalyst.



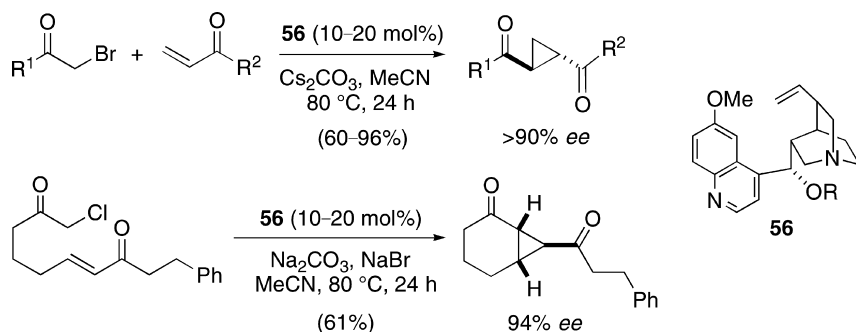
Scheme 9.58 Enantioselective addition of 2-silyloxyfurans to α,β -unsaturated aldehydes via iminium activation.



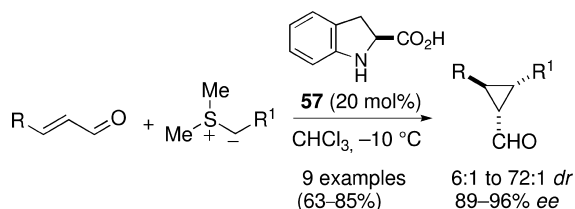
Scheme 9.59 Sulfur ylide-mediated enantioselective cyclopropanation.

Ammonium ylides were generated using cinchona alkaloids by Gaunt and co-workers [125]. Mechanistically, the nucleophilic catalyst forms an ammonium salt with an α -bromocarbonyl species. The pK_a lowering effect of the salt readily effects deprotonation with a mild base to form the ylide, which subsequently undergoes conjugate addition and ring closure to form the cyclopropane as a single diastereomer. The reaction also works in an intermolecular fashion, forming bicycloalkanes in excellent yields and *ees* (Scheme 9.60).

Another way of directing the stereoselectivity of the cyclopropanation reaction was described by Kunz and MacMillan, who applied the iminium catalysis concept effectively to activate alkene substrates [126]. α,β -Unsaturated aldehydes were converted in the presence of stabilized ylides and dihydroindole-2-carboxylic acid catalyst (**57**) to enantioenriched cyclopropanes (Scheme 9.61). The atypical reactivity and the stereocontrol were rationalized by a mechanistic postulate in which the chiral carboxylic acid catalyst allows the control of the iminium geometry and also by a direct electrostatic effect that activates the approaching sulfonium ylides.



Scheme 9.60 Cinchona alkaloid-catalyzed cyclopropanation of activated alkenes.



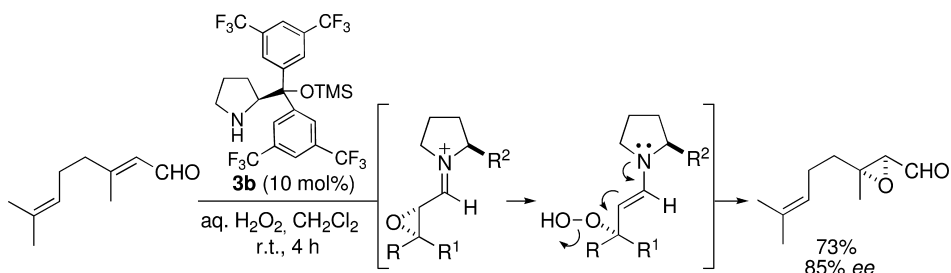
Scheme 9.61 Asymmetric cyclopropanation of activated alkenes via iminium catalysis.

9.3.3.3 Epoxidation of Alkenes

Although the greatest part of current methodology for the catalytic asymmetric epoxidation of alkenes relies on the use of chiral metal complexes [127], organocatalytic methods are taking a more and more important place [128]. Here a brief summary is given of the preparation of enantiomerically enriched epoxides from alkenes and alternative organocatalytic methods including the addition of chiral sulfur ylides to aldehydes [129].

Epoxidation of Electron-deficient Alkenes with Hydrogen Peroxide

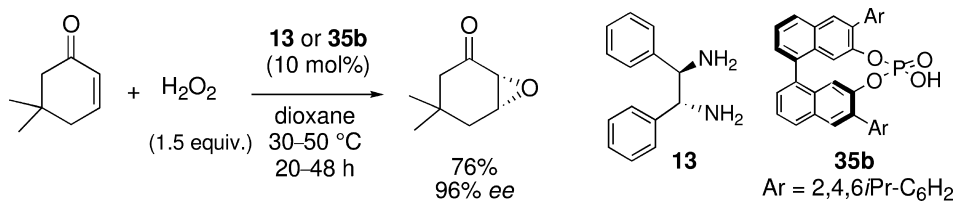
Jørgensen and co-workers developed an asymmetric approach allowing the conversion of enals to epoxides. The best catalyst in this transformation was the chiral pyrrolidine **3b** and H_2O_2 as oxidant. The reaction follows the concept of iminium catalysis as depicted in Scheme 9.62 [130]. Importantly, the reaction conditions are



Scheme 9.62 Asymmetric epoxidation of enals by H_2O_2 .

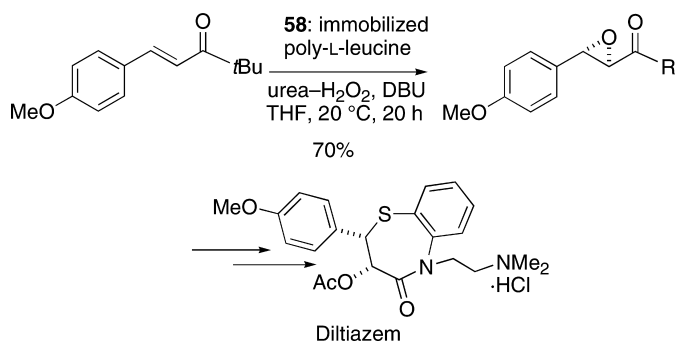
tolerant to a variety of functionalities and this chemical transformation proceeds in different solvents with no loss of enantioselectivity.

Cyclic enones can be oxidized likewise using hydrogen peroxide as oxidant and chiral diamine catalysts such as 1,2-diphenylethane-1,2-diamine (DPEN) TFA salt or with a chiral phosphate co-catalyst (TRIP) [131]. The DPEN salts proved to be both active and highly enantioselective catalysts for the oxidation of unsubstituted cyclohexanones when the diamine catalyst was obtained with DPEN mono-TRIP salt, although the TFA salt gave a high yield and enantioselectivity. As in the preceding transformation, the reaction is believed to proceed via an iminium ion intermediate. The second basic amine site of the catalyst may organize the TS by directing the attack of hydrogen peroxide towards one enantioface of the double bond.



Scheme 9.63 Asymmetric epoxidation of cyclic enones.

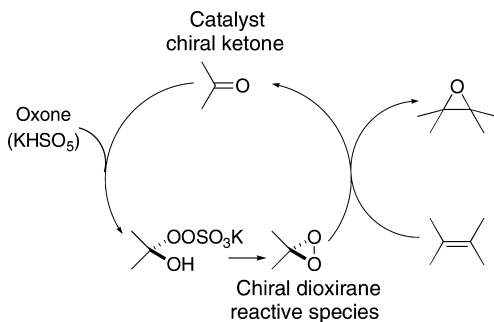
The polyleucine-mediated epoxidation, the so-called Julia–Colonna reaction, includes biphasic reaction systems (e.g. use of DBU in THF along with urea–H₂O₂ as oxygen source), which can give shorter reaction times and improved scope [132, 133]. Most of the enones used in this chemistry have aryl, heteroaryl or alkenyl substituents in the β-position, but alkyl substituents can be tolerated in the α'-position. α-Substituted enones are generally unreactive, with the exception of some examples where the alkene is exocyclic to a cyclic ketone, which is suggested to be due to the need for an *s-cis*-enone conformation for the reaction to occur. Most of the enantioselectivities obtained are excellent (>90% ee). The synthetic utility of the products has been demonstrated by application to target synthesis; the preparation of the blood pressure-lowering agent diltiazem (Scheme 9.64) illustrates a common tactic since epoxidation of enone is followed by Baeyer–Villiger reaction to give the desired epoxy ester [134].



Scheme 9.64 Polyleucine-mediated epoxidation in the synthesis of diltiazem.

Epoxidation of Alkenes via Chiral Dioxirane Intermediates [128b–d]

Isolated alkenes can be oxidized by the triple salt Oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$), of which the active constituent is KHSO_5 . Interaction of Oxone with the ketone precursor produces the reactive dioxirane that transfers oxygen to alkenes in a concerted (although possibly asynchronous) manner, resulting in stereospecific epoxidation (i.e. retention of the alkene geometry of the starting alkene). Importantly, the starting ketone or iminium salt is regenerated and so in principle can be used in sub-stoichiometric quantities (Scheme 9.65).



Scheme 9.65 General mechanism of the ketone-catalyzed alkene epoxidation.

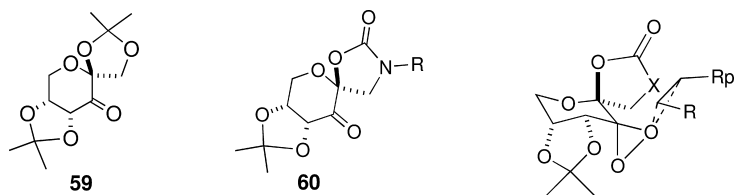
Among the chiral ketones developed for asymmetric oxidation, the fructose-derived Shi catalyst and also the binaphthol-derived Yang catalysts have attracted particular attention (Scheme 9.66).

Both oxidation systems have found applications in total synthesis [128b, c] [135]. Particularly attractive are examples in which it has been used to establish the stereochemistry of polyepoxides that can undergo cascade cyclizations to polyether products, mimicking possible biosynthetic pathways. An example is the construction of the tetrahydrofuran rings of the natural product glabrescol via highly stereoselective formation of the tetraepoxide from the polyene (Scheme 9.67). [136].

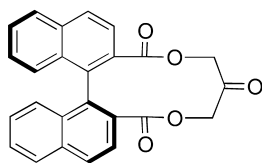
The replacement of the acetonide function in **59** by a diacetate slows the Baeyer–Villiger decomposition of the catalyst and enables **62** to convert *trans*- and trisubstituted α,β -unsaturated esters to the corresponding epoxides (Scheme 9.68) [137]. In contrast, the catalyst **62** does not allow high *ee* to be obtained for *trans*-aliphatic α,β -unsaturated esters and *cis*-cinammates.

Epoxidation of Alkenes via Acyl Peroxide Intermediates

Oligopeptide catalysts were engineered for the transformation of allylic carbamates to chiral epoxides. The peracid, generated catalytically by H_2O_2 or by the use of hydrogen peroxide–urea clathrate (UHP) from the γ -carboxylic acid function of L-aspartate incorporated into a tripeptide, provided the chiral environment necessary for asymmetric transformation (Scheme 9.69) [138, 139].

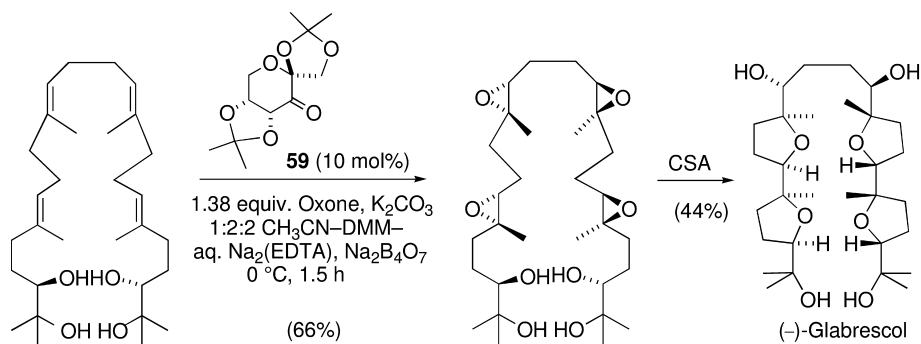


R = H, Me, Ph, *p*MeSO₂Ph, Boc

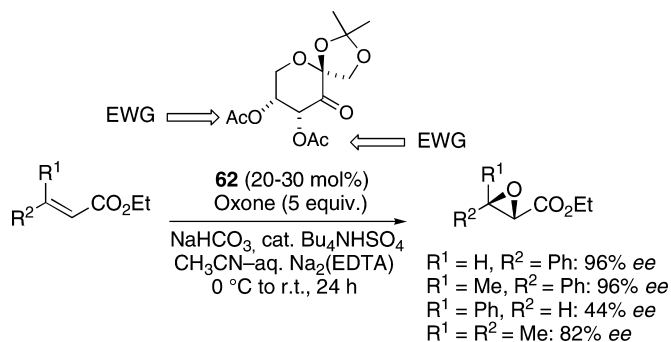


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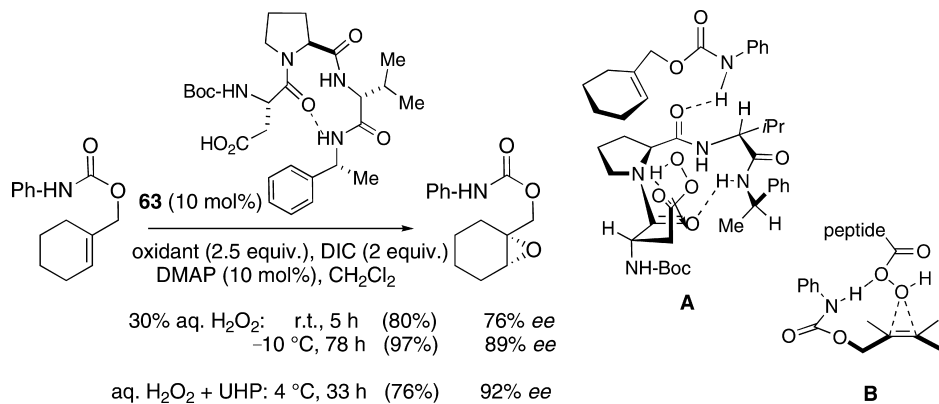
Scheme 9.66 The first- (59) and second-generation (60) Shi catalysts with the proposed selectivity model and the Yang catalyst (61).



Scheme 9.67 Shi epoxidation in the total synthesis of (-)-glabrescol.



Scheme 9.68 Asymmetric oxidation of electron-poor olefins using modified Shi catalyst.



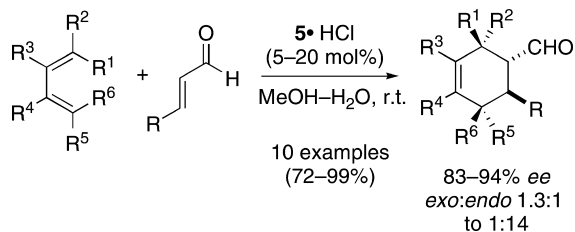
Scheme 9.69 Oligopeptide catalyst-mediated epoxidation of allylic carbamates.

9.3.3.4 Cycloaddition reactions

[4 + 2] Additions

[4 + 2] Additions via Iminium Activation

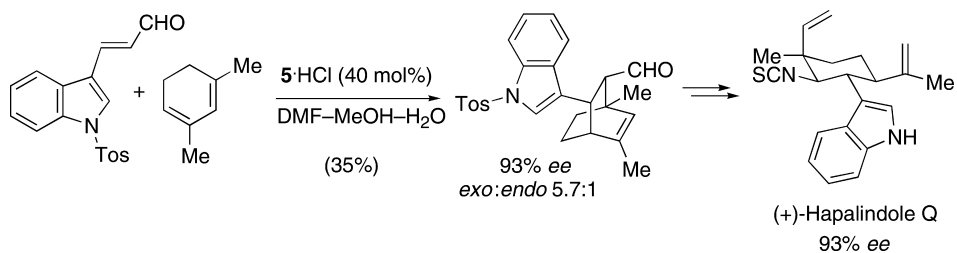
A MacMillan's iminium catalyst such as **5** was used for the addition of a range of α,β -unsaturated aldehydes (dienophiles) to a variety of symmetrical and unsymmetrical dienes (Scheme 9.70). This chemistry has been highlighted in a number of excellent reviews [18].



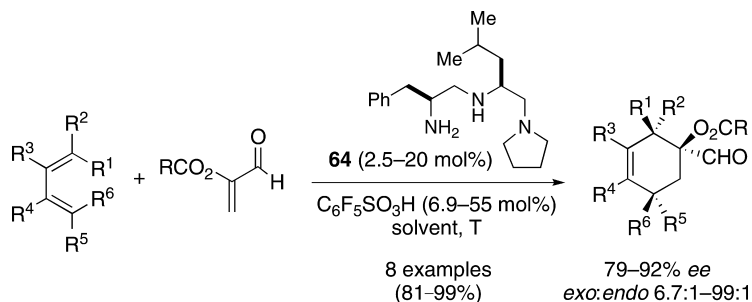
Scheme 9.70 MacMillan's imidazolidinone-mediated [4 + 2] reaction between dienes and α,β -unsaturated aldehydes.

The reaction probably takes place via an asynchronous mechanism where the attack of the diene on the β -carbon atom of the iminium ion is the rate-limiting step and the π - π interaction between the phenyl ring of the catalyst benzyl group and the alkeneic π -system of the iminium ion accounts for the selectivity of the reaction. The reaction was used in the synthesis of (+)-hapalindole Q, a tricyclic alkaloid natural product containing four contiguous stereocenters (Scheme 9.71).

MacMillan's imidazoline catalysts are inefficient for the activation of α -substituted enones. The scope of this formal [4 + 2] cycloaddition was extended to α -substituted α,β -unsaturated aldehydes as dienophiles by using a primary amine organocatalyst, **64** [140] (Scheme 9.72).

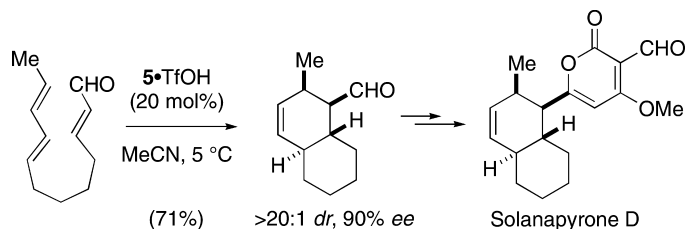


Scheme 9.71 Synthesis of (+)-hapalindole Q via iminium-mediated formal [4 + 2] cycloaddition.



Scheme 9.72 The formal [4 + 2] cycloaddition of α -substituted α,β -unsaturated aldehydes.

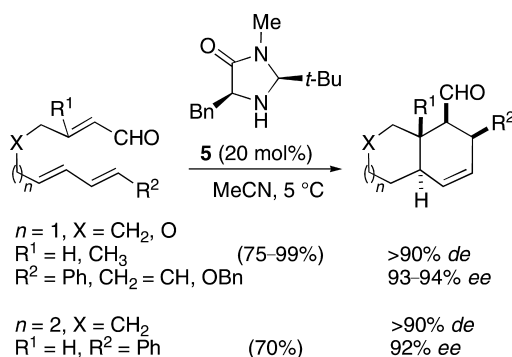
The iminium activation strategy was applied in an intramolecular Diels–Alder reaction [141]. This LUMO-lowering iminium activation strategy allowed the preparation of various cycloadducts incorporating ether and quaternary carbon functionalities (Scheme 9.73). The synthetic potential of this methodology was demonstrated by the total synthesis of the marine metabolite solanapyrone D.



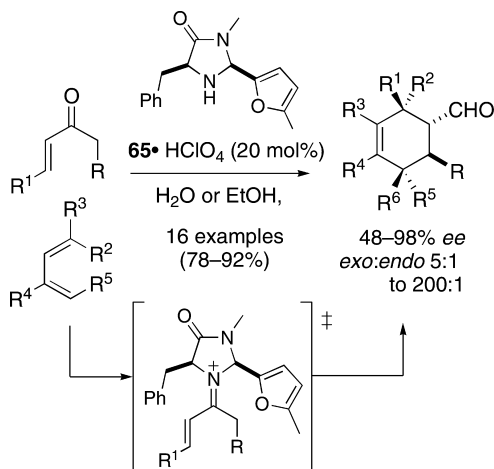
Scheme 9.73 The asymmetric intramolecular Diels–Alder reaction in the synthesis of solanapyrone D.

A similar strategy was used by Selkälä and Koskinen to prepare other bicyclo[4.3.0]nonanes and was applied to the synthesis of amaminol A, a cytotoxic agent against murine leukemia cells (Scheme 9.74) [142].

Imidazolidinone catalyst **65** was identified for Diels–Alder transformations using simple ketone dienophiles (Scheme 9.75) [143]. This reaction is fairly general with respect to diene structure, allowing enantioselective access to a broad range of alkyl-, alkoxy-, amino- and aryl-substituted cyclohexenyl ketones.



Scheme 9.74 The asymmetric intramolecular Diels–Alder reaction in the synthesis of amininol A.



Scheme 9.75 Formal Diels–Alder reaction of simple ketone dienophiles via iminium activation.

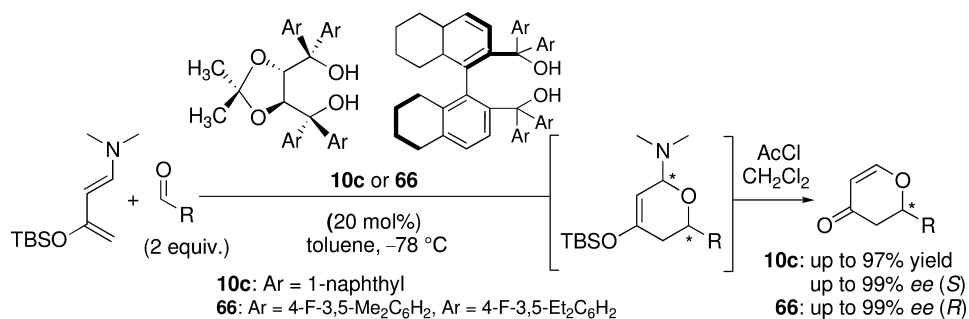
Hetero-Diels–Alder Reactions via Brønsted Acid Catalysis

Since the discovery by Huang and Rawal that hetero-Diels–Alder (HDA) reactions between 1-amino-3-silyloxybutadiene and unactivated aldehydes and ketones are considerably accelerated in protic solvents [144], chiral alcohol **3b** has been investigated, in addition to new hydrogen-bonding catalysts derived from TADDOL and binaphthyl (BAMOL) (**5e**) [145] (Scheme 9.76). The acceleration of the reactions is promoted by hydrogen bonding interaction between the diol catalyst and the carbonyl group, as depicted in Scheme 9.2b.

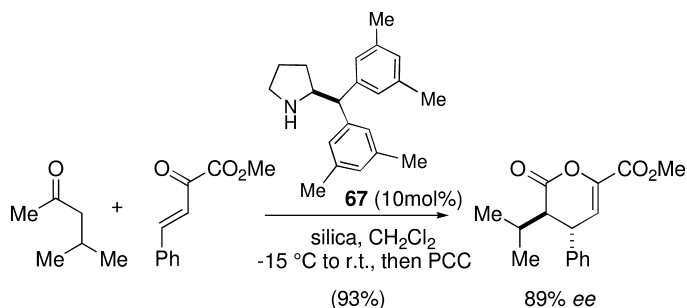
Organocatalyzed aza-Diels–Alder reactions using arylaldimines were also developed in the presence of chiral phosphoric acids as catalysts [146, 147]. These transformations usually provided less selective additions.

Hetero-Diels–Alder Reactions via Enamine Activation

Enamine activation can be used for mediating inverse electron demand [4 + 2] reactions. Chiral secondary amines such as depicted in Scheme 9.77 generate the



Scheme 9.76 Chiral Brønsted acid-catalyzed hetero-Diels–Alder reaction.



Scheme 9.77 Chiral pyrrolidine-mediated formal [4 + 2] inverse electron demand cycloaddition.

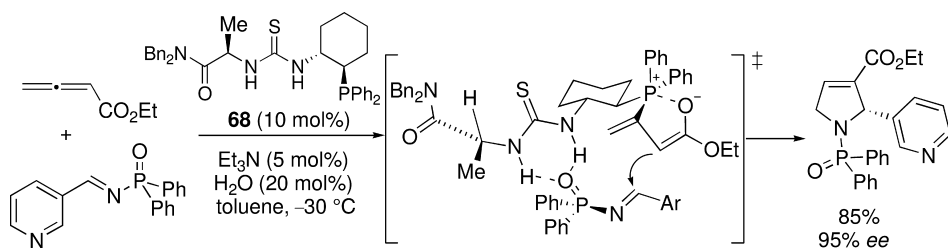
electron-rich enamines from aldehydes, which react subsequently with the enone [148].

[3 + 2] Cycloadditions

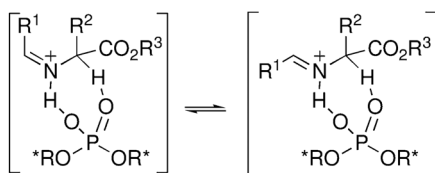
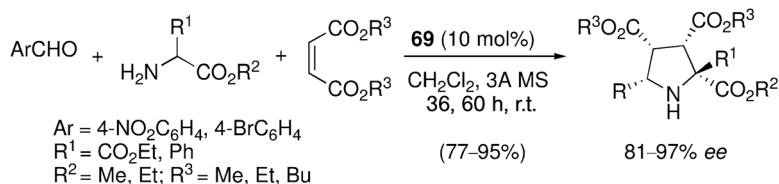
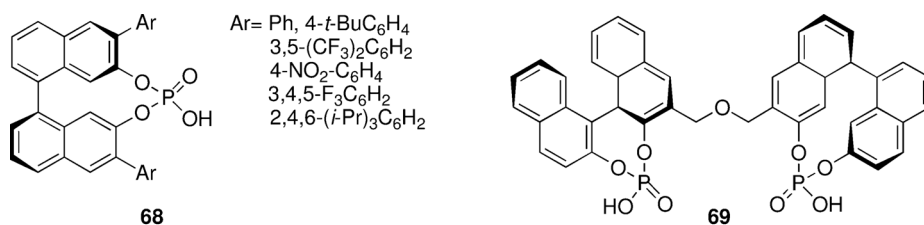
[3 + 2] Cycloadditions via Brønsted Acid Activation

N-Protected aryl- and heteroarylaldimines add to electron-deficient allene in the presence of phosphinthiourea catalysts and provide 2-aryl-2,5-hydropyrroles via a [3 + 2] cycloaddition (Scheme 9.78) [149]. The presence of both H₂O and Et₃N as additives was found to be important for achieving optimal rates. Dual activation of both nucleophile and electrophile by the bifunctional catalyst is invoked to account for the observed high reactivity and enantioselectivity. According to the rationale, the thiourea binds and activates the imine by association with the oxygen atom of the phosphinoyl group (Scheme 9.2c-1) and the delivery of the phosphonium ion enolate takes place from the imine *re* face with the thiourea catalyst.

The three-component asymmetric 1,3-dipolar addition reaction between aldehydes, amino esters and dipolarophiles can be promoted by BINOL-derived chiral phosphoric or bisphosphoric acid [150]. As in the former example, the stereoselectivity is controlled by a chiral Brønsted acid bonded to the azomethyne complex (Scheme 9.79). This procedure allows a rapid diversity-oriented synthesis of poly-functionalized chiral pyrrolidine derivatives.



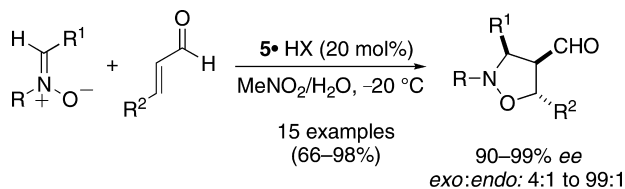
Scheme 9.78 Phosphinthiourea-mediated addition of aldimines to electron-deficient allenes.



Scheme 9.79 Chiral phosphoric acid-catalyzed three-component asymmetric 1,3-dipolar addition reaction between aldehydes, amino esters and dipolarophiles.

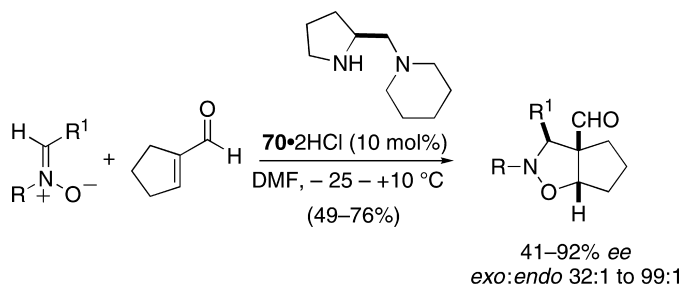
Lewis Acid (Iminium) Activation in [3 + 2] Addition

The addition of several α,β -unsaturated aldehydes to a variety of *N*-alkylated nitrones in the presence of catalytic amounts of imidazolidinone **5** afforded the corresponding isoxazolidines (Scheme 9.80). While the reaction tolerates relatively large functionalization on the nitron, only limited variation of the dipolarophile can be achieved: crotonaldehyde ($\text{R}^2 = \text{Me}$) and acrolein ($\text{R}^2 = \text{H}$) generate cycloadducts in good yields and selectivities, but other β -substituted enals are largely unsuccessful due to the sluggish nature of these reactions.



Scheme 9.80 The MacMillan imidazolidinone-catalyzed addition of α,β -unsaturated aldehydes to *N*-alkylated nitrones.

The scope of the reaction was expanded to the 1,3-dipolar cycloaddition of nitrones to cyclic α,β -unsaturated aldehydes, allowing the formation of fused bicyclic isoxazolidines (Scheme 9.81). Noteworthily, the use of catalyst **5** resulted in almost no reaction, whereas a proline-based diamine (**70**) afforded high levels of enantio- and diastereoselectivity [151].

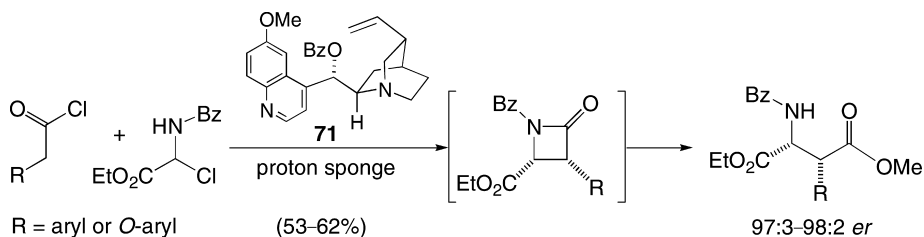


Scheme 9.81 Prolinamide salt-catalyzed asymmetric 1,3-dipolar cycloaddition of nitrones to cyclic α,β -unsaturated aldehydes.

[2 + 2] Cycloadditions

The β -Lactam Synthesis

The best-performing chiral catalysts to date in the dimerization of ketenes, and also in related cycloadditions between ketenes and C=O or C=N compounds, are cinchona alkaloids. Ketenes can be formed from acyl chlorides under homogeneous conditions by using proton-sponge or phosphazine as base (BEMP), but also under heterogeneous conditions using K_2CO_3 , NaH, $NaHCO_3$ or a resin-bound variant of BEMP. The cycloaddition reaction can be performed without epimerization of the formed stereocenters when non-pyrolytic methods are used for the preparation of the ketene reagents and also when *O*-functionalized quinine or quinidine derivatives such as *O*-Bz (**39**), *O*-*n*-Pr or *O*-TMS analogs are used [152]. Aldehydes form β -lactones with ketenes in high selectivity and chemical yield [76c]. This reaction was also extended to the addition of ketenes to imines affording β -lactams. A short application of this reaction was described in the preparation of β -substituted aspartic acid derivatives via a cinchona-catalyzed [2 + 2] enantioselective cycloaddition one-pot synthesis (Scheme 9.82).

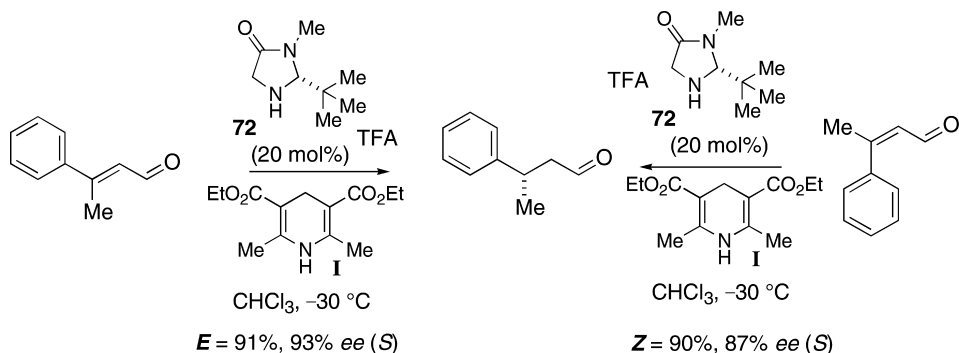


Scheme 9.82 Cinchona alkaloid-catalyzed [2 + 2] enantioselective cycloaddition of *in situ*-generated ketenes to imines.

Although the reaction depicted in Scheme 9.82 proceeds without a Lewis acid co-catalyst, the reaction is far more efficient in its presence. For example, Nelson and co-workers reported that lithium perchlorate assisted the cinchona alkaloid-catalyzed addition of ketenes (generated *in situ* from acid chlorides) to aldehydes to form β -lactones in excellent yields, *dr*s and *ees* [153]. Lectka and co-workers also reported that the indium(III) complex of a salicylquinine derivative effectively forms the corresponding β -lactam structure from the reaction of ketenes and imines also with excellent stereoselectivities [154].

9.3.3.5 Transfer Hydrogenation of Alkenes

Organocatalytic transfer hydrogenation relies on a similar mechanism to NADH or FADH₂ reduction of substrates in combination with enzymes. MacMillan's imidazolidinone catalyst permits LUMO-lowering activation in combination with dihydropyridine (Hantzsch ester I) analogs. The method was used for the selective reduction of various α,β -unsaturated aldehydes [155], and also of β -aryl- β -methyl α,β -unsaturated aldehydes [156]. Importantly, in the latter case an enantioconvergent process was observed when the mixtures of (*E*)- and (*Z*)-alkene substrates could be hydrogenated with comparable enantioselectivities, providing identical enantiomers as the major product (Scheme 9.83).



Scheme 9.83 Enantioconvergent reduction of β -aryl- β -methyl α,β -unsaturated aldehydes in the presence of MacMillan's imidazolidine **72** and Hantzsch ester **I**.

9.3.4

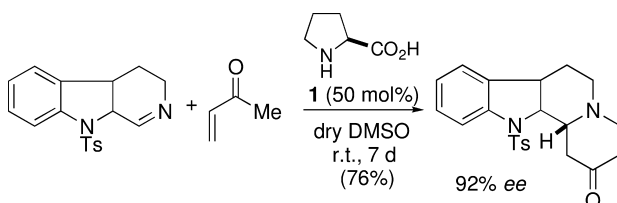
Organocatalytic Multicomponent and Cascade Reactions [157]

Organocatalytic reactions are particularly well suited for sequential transformations, providing easy access to structurally complex skeletons from simple starting materials.

9.3.4.1 Single Catalyst-mediated Domino Reactions

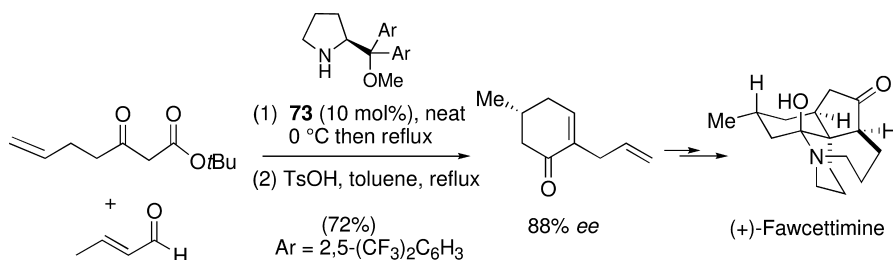
The Addition–Cyclization Strategy

Probably the simplest way to generate multiple bonds in a single reaction is to take advantage of the difference in reactivity between inter- and intramolecular reactions. Such a sequence can be realized by an (*S*)-proline-catalyzed asymmetric Mannich-type addition of methyl ketones to form β -carbolines [158]. The reaction was used in the synthesis of the tetracyclic precursor of yohimbine and deserpidine (Scheme 9.84).



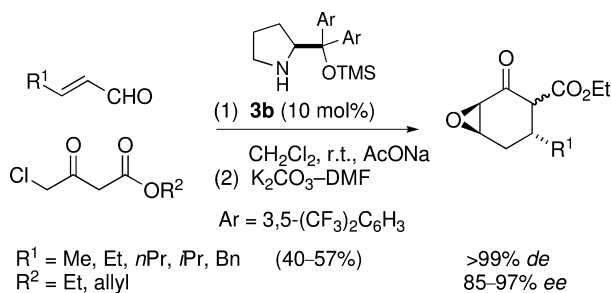
Scheme 9.84 (*S*)-Proline-catalyzed asymmetric synthesis of β -carbolines.

Another example is drawn from the synthesis of (+)-fawcettimine involving a catalytic 1,4-addition–intramolecular aldolization as a key step to prevent heteroatom-substituted hydrianoes from participating in the cross-coupling reaction (Scheme 9.85) [159]. Using an organocatalytic Robinson annulation, reaction between a keto ester and crotonaldehyde gave 2-allylcyclohexanone in 88% *ee* and 72% yield.



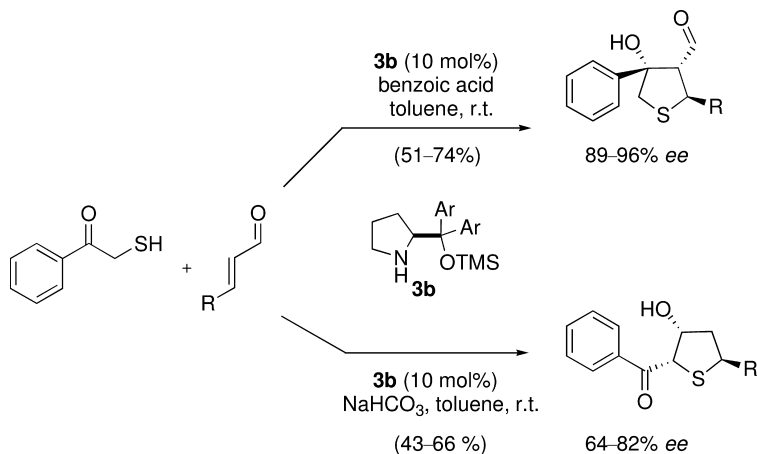
Scheme 9.85 Asymmetric 1,4-addition–Robinson annulation sequence in the synthesis of (+)-fawcettimine.

A one-pot Michael addition Darzens-type domino reaction of α,β -unsaturated aldehydes and γ -chloro- β -keto esters was realized in preparing highly functionalized cyclohexanone oxides (Scheme 9.86) [160]. After decarboxylation, the products were isolated as a single diastereoisomer.



Scheme 9.86 One-pot Michael addition Darzens-type domino reaction of α,β -unsaturated aldehydes and γ -chloro- β -keto esters.

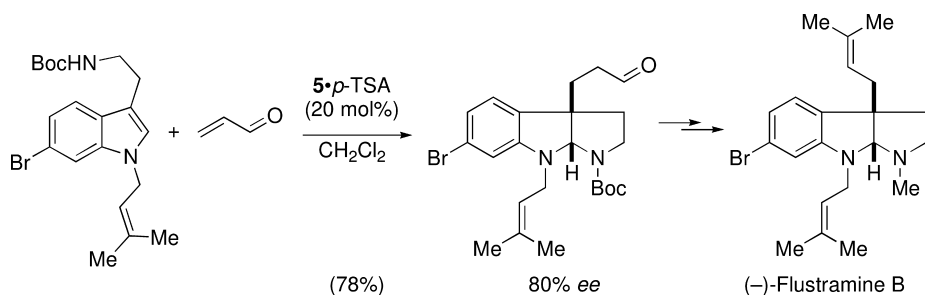
A similar Michael addition–aldol condensation sequence has been devised for the synthesis of chiral tetrahydrothiophenes containing three stereocenters starting from various enals and 2-mercapto-1-phenylethanone and employing a TMS-protected proline derivative (**3b**) as catalyst (Scheme 9.87). It is possible to control the regioselectivity of this domino reaction by varying the pH; indeed, diastereomerically pure (tetrahydrothiophen-2-yl)phenylmethanones were obtained on adding NaHCO_3 , whereas the same reaction performed with benzoic acid led to tetrahydrothiophene carbaldehydes having one quaternary center [161].



Scheme 9.87 Michael reaction–aldol condensation sequence in the synthesis of chiral tetrahydrothiophenes.

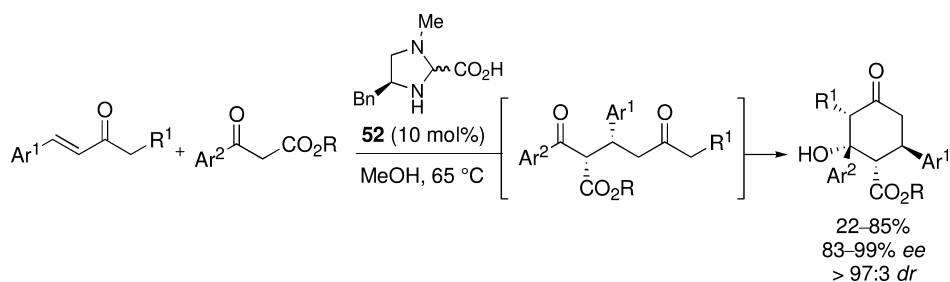
The power of the iminium activation protocol was demonstrated by the synthesis of (–)-flustramine B (Scheme 9.88) [162]. In this sequence, the intermediate iminium is intercepted by intramolecular addition forming the tetrahydropyrrolidine backbone.

An imidazolidine catalyst can promote the tandem Michael reaction–aldol sequence between α,β -unsaturated ketones and a variety of aromatic and heteroaromatic β -keto esters to provide cyclohexanones containing three or four contiguous



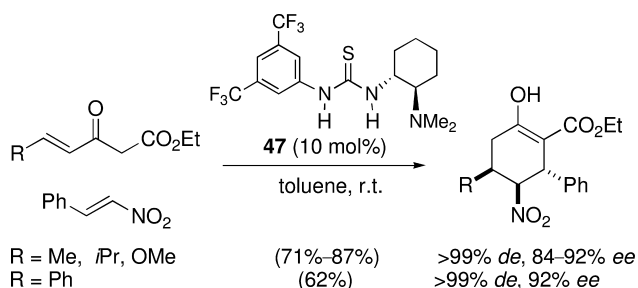
Scheme 9.88 Synthesis of (-)-flustramine B via an addition–cyclization protocol.

stereogenic centers with excellent enantio- and diastereoselectivity (Scheme 9.89) [163]. The first step consists in an intermolecular Michael addition, followed by an intramolecular aldol condensation forming the elaborated cyclohexanone. The whole reaction takes place thanks to a triple role of the catalyst, which first activates the Michael acceptor by formation of an iminium ion, then generates the active Michael donor deprotonating the β -keto ester and finally acts as a base in the intramolecular aldol reaction.



Scheme 9.89 Chiral cyclohexanone synthesis by tandem Michael reaction–aldol sequence between α,β -unsaturated ketones and aromatic and heteroaromatic β -keto esters.

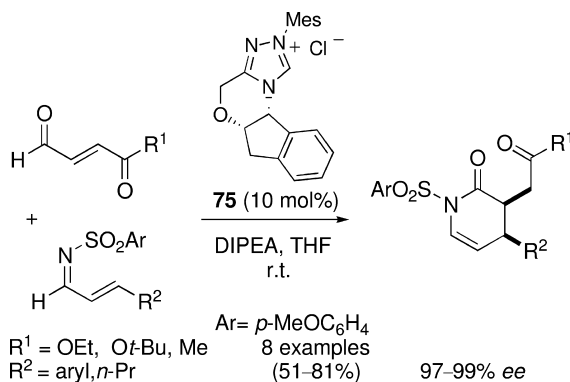
The two-fold domino Michael addition of γ,δ -unsaturated β -keto esters to nitroalkenes catalyzed by a bifunctional thiourea gives rise to highly functionalized cyclohexanones (Scheme 9.90) [164]. The three contiguous stereogenic centers of the



Scheme 9.90 Two-fold domino Michael addition sequence in the synthesis of functionalized cyclohexanes.

products were constructed with high diastereo- and enantioselectivity. This sequence was further applied to the total synthesis of (–)-epibatidine.

A chiral carbene derived from aminoindanol triazolium salts mediated the addition of α,β -unsaturated aldimines to electron-deficient alkenes in azadiene Diels–Alder reactions (Scheme 9.91) [165]. This strategy, mediated by an *N*-heterocyclic carbene, involved the generation of a highly reactive dienophile that participated in LUMO diene-controlled Diels–Alder cyclizations with α,β -unsaturated imines.

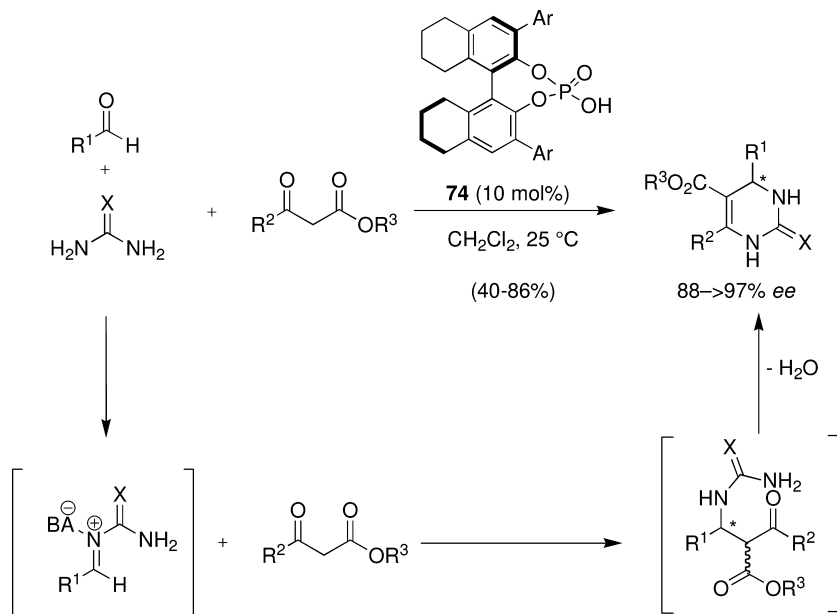


Scheme 9.91 Michael reaction–aldol condensation sequence in the synthesis of chiral tetrahydrothiophenes.

Multicomponent Reactions

Catalysts may promote the assembly of different organic elements. The acid-catalyzed three-component one-pot condensation of an aldehyde, a β -keto ester and (thio) urea, the so-called Biginelli reaction, was realized with a chiral phosphoric acid catalyst (74) [166]. The partial steps of the transformation involve a condensation of the urea with the aldehyde, yielding an iminium intermediate that undergoes aldol-type reaction with the keto ester followed by cyclization under the reaction conditions and affords chiral DHMP (Scheme 9.92).

The interconversion of enamines and iminium intermediates was also exploited synthetically in sequential transformations. As the 1,4-addition to iminium-activated enones gives rise to enamines and, in turn, the reaction of enamines gives rise to iminium intermediates, these intermediates can be intercepted with suitable reagents. In seminal work, Enders *et al.*'s three-component domino reaction between excess of aldehyde, nitroalkene and a nearly stoichiometric amount of α,β -unsaturated aldehyde afforded tetrasubstituted cyclohexene carbaldehydes in good yields, high diastereoselectivity and in almost complete enantioselectivity (Scheme 9.93) [167]. The first step of the catalytic cycle involves the conjugate addition via enamine formation of aldehyde and the nitroalkene followed by a Michael addition between the nitroalkane and the α,β -unsaturated aldehyde via an iminium intermediate. The third step of the domino sequence is an intramolecular aldol reaction of the enamine and a subsequent dehydration gives rise to the polyfunctional cyclohexene. The



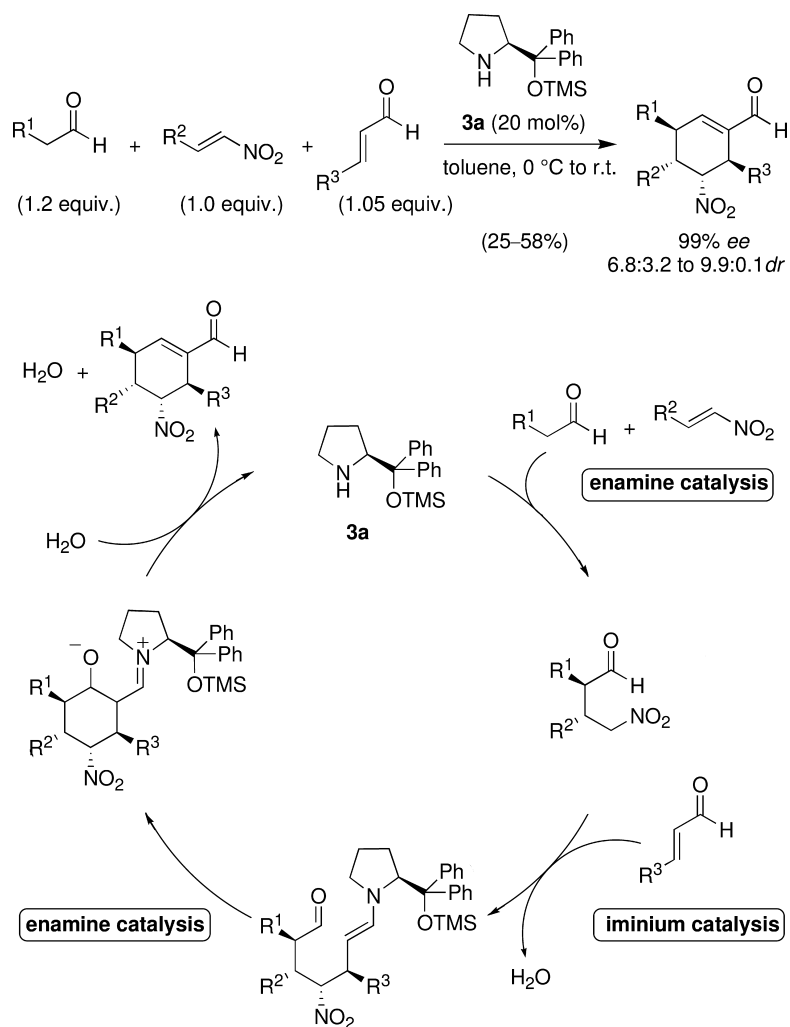
Scheme 9.92 Chiral phosphoric acid-catalyzed Biginelli reaction.

overall high stereoselectivity of the transformation is the consequence of the high selectivity of the first Michael addition; the resulting intermediate presumably dictates the stereochemistry of the reaction.

A catalytic enantioselective strategy was developed in which substituted phenols are directly converted to complex non-racemic molecular architectures (Scheme 9.94) [168]. The process involves oxidative dearomatization of substituted phenols followed by a desymmetrizing secondary amine-catalyzed asymmetric intramolecular Michael addition and forms a range of highly functionalized polycyclic molecules with excellent selectivity.

A domino Mannich–Wittig olefination reaction was devised allowing easy entry to functionalized α,β -unsaturated esters (Scheme 9.95) [169]. A subsequent diastereoselective dihydroxylation of the products allowed the corresponding amino- and iminosugar derivatives to be obtained stereoselectively in two steps (Scheme 9.95).

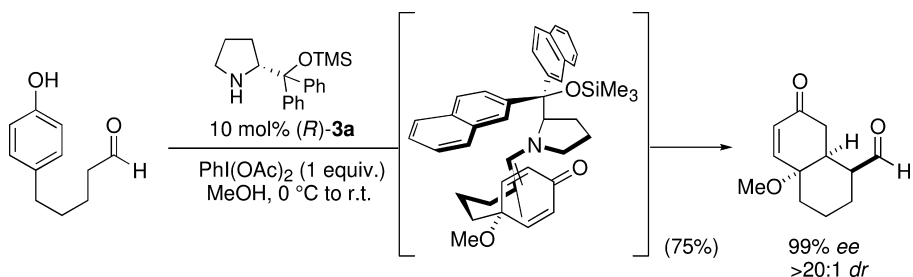
MacMillan's catalyst **5** allowed the combination of the domino 1,4-hydride addition followed by intramolecular Michael addition (Scheme 9.96) [20a]. The reaction is chemoselective, as the hydride addition takes place first on the iminium-activated enal. The enamine product of the reaction is trapped in a rapid intramolecular reaction by the enone, as depicted in Scheme 9.96. The intramolecular trapping is efficient and no formation of the saturated aldehyde can be observed. The best results were obtained with MacMillan's imidazolidinium salt **5** and Hantzsch ester **I** as hydride source. As was the case in the cyclization reaction, the reaction affords the thermodynamic *trans* product in high selectivity. Interestingly, an opposite sense of asymmetric induction was noted compared with the transformation discussed in Scheme 9.80.



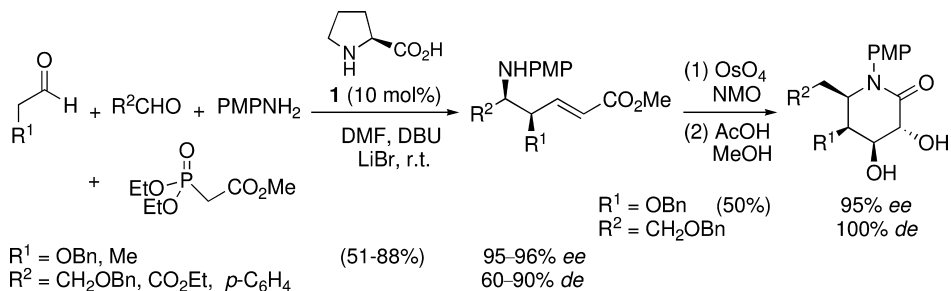
Scheme 9.93 Enders *et al.*'s three-component catalytic asymmetric domino reaction.

9.3.4.2 Multicatalyst Cascade Reactions

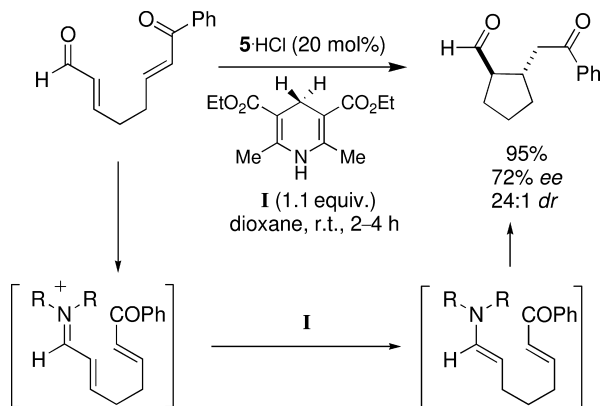
Polyfunctionalized tricyclic carbon frameworks containing up to eight stereogenic centers were realized in a single pot by relaying Enders *et al.*'s cyclohexenal synthesis with an intramolecular Diels–Alder (IMDA) strategy (Scheme 9.97) [170]. In this case the cyclohexene carbaldehyde product bears a diene moiety able to undergo subsequent cycloaddition. The one-pot synthesis was performed by dilution of the mixture with dichloromethane after complete consumption of the starting materials and adding an excess of dimethylaluminum chloride at $-78\text{ }^\circ\text{C}$. In this new Michael–Michael–aldol condensation–IMDA process, five new C–C bonds and eight



Scheme 9.94 The oxidative dearomatization–intramolecular Michael addition strategy in the synthesis of functionalized polycyclic molecules.

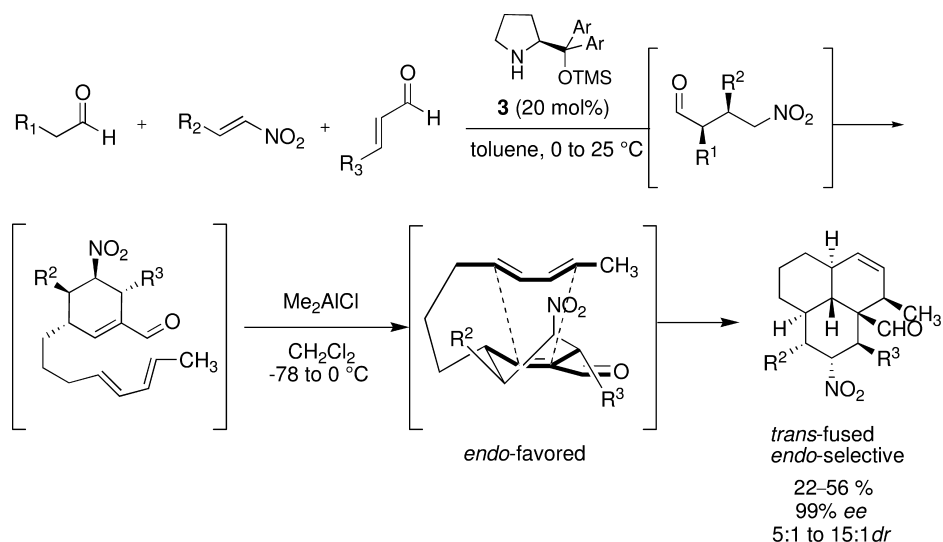


Scheme 9.95 The domino Mannich–Wittig olefination sequence.



Scheme 9.96 Domino 1,4-hydrate addition followed by intramolecular Michael addition.

stereogenic centers were formed with complete enantioselectivity in four steps (>99%). The *endo* approach is favored due to kinetic control and steric interactions in the TS. In this way, decahydroacenaphthylene and decahydrophenalene cores are obtained, which are advanced precursors of biologically active natural products.



Scheme 9.97 Michael–Michael–aldol condensation–intramolecular Diels–Alder strategy in the synthesis of polycyclic compounds.

9.4

Conclusion

Asymmetric organocatalytic reactions offer synthetically viable alternatives to metal complex-mediated reactions. Most of the major enantioselective transformations have found organocatalytic alternatives, but reaction scopes usually remain below those of metal complex-mediated reactions. Bifunctional cooperative chiral catalysts having both nucleophilic Lewis base and Brønsted acid sites were found to be the most efficient. While many important factors that govern reactions have been uncovered, our understanding of the basic factors controlling reactivity and selectivity remains only partial. Although substrate dependence remains an important issue, there are more and more transformations that reach the standards of current asymmetric reactions.

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