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Asymmetric Organocatalysis

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Aims and Scope

The series *Topics in Current Chemistry* presents critical reviews of the present and future trends in modern chemical research. The scope includes all areas of chemical science, including the interfaces with related disciplines such as biology, medicine, and materials science.

The objective of each thematic volume is to give the non-specialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights of interest to a larger scientific audience are emerging.

Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5–10 years are presented, using selected examples to illustrate the principles discussed. A description of the laboratory procedures involved is often useful to the reader. The coverage is not exhaustive in data, but rather conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

Discussion of possible future research directions in the area is welcome.

Review articles for the individual volumes are invited by the volume editors.

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Enough Organocatalysis?

These are exciting times for asymmetric organocatalysis. During the last decade, the chemical community finally began considering the previously overlooked field as the third pillar of asymmetric catalysis, complementing only enzymes and chiral metal complexes. Now, countless academic groups around the world are entering the area. And with regard to industrial applications, the question is not anymore, *if* the pharmaceutical industry is going to use organocatalysis, but rather whether or not there are still companies actually *not* using it.

Organocatalysts are purely organic molecules that function by removing or donating electrons or protons from or to reaction substrates or transition states. This situation defines four distinct areas: Brønsted acid and base catalysis and Lewis acid and base catalysis. The field has roots back to the beginning of the 20th century with Bredig's now legendary studies on the use of natural alkaloids as enantioselective catalysts. This line of research has subsequently been continued by others, including Pracejus and Wynberg. Parallel studies by Hajos and Wiechert using proline as aldolization catalyst were inspired by the seminal work of Knoevenagel in the late 19th century. Few other organocatalysts were described during those decades but, like proline and quinine, they were considered exotic, isolated examples with a poorly understood mode of action. The situation changed only at the beginning of this millennium when it was shown that aminocatalysis, the activation of carbonyl compounds via enamine and iminium ion intermediates, is a *general* catalysis concept. This discovery finally opened the door to understanding and designing organocatalysts and to predicting their behavior. The concept of aminocatalysis has since been applied to dozens of reaction types and literally hundreds of variants. Moreover, the working principles of other Lewis base catalysts such as carbenes and tertiary amines as well as that of Brønsted acid and base catalysts is now appreciated and new reactions and catalysts are being designed and published on a daily basis. These are fascinating developments, especially in light of a previous opinion we organic chemists have convinced ourselves of, namely that new reactions can *only* be expected from the realm of transition metal chemistry. The current developments leave us to either accept the fact that our perception may not have been entirely correct or to continue to be "right" simply by arguing that organocatalysis is not truly novel (and yet researching it anyway). Undebatable though, at least in my opinion, is the success and usefulness of organocatalysis, the

enormous amount of activities in the field, and the resulting constant need for reflection and knowledge updates such as this volume.

So why the provocative title then? The term “organocatalysis” has been quite useful in initially highlighting and subsequently popularizing an underappreciated though fundamental catalysis principle. However, as time goes by and as more and more organic catalyst motifs and concepts are being developed, the term might become less and less accurate. In the field of transition metal catalysis, we speak of “palladium catalysts” or invent a new “iron-catalyzed reaction” rather than stating we are investigating “transition metal catalysis”. Similarly, in biocatalysis, we specify which particular class of enzyme is being studied. I suggest that a similar specification will ultimately take place in organocatalysis. We will find more and more publications using “a phosphoric acid catalyst” or describing a “secondary amine-catalyzed transformation” rather than an “organocatalytic reaction”. In that sense: Yes, enough organocatalysis! Still, there is little doubt that the field will continue to grow massively. It appears to me that there are still many ripe and delicious fruits to be picked by creative and intrepid minds.

All four areas of organocatalysis are covered in this volume, providing an overview of the field from experts in their areas. I would like to wholeheartedly thank all those who have contributed to making this volume such a wonderful and original source of knowledge. I hope it will inspire you to apply organocatalytic methods to solve some of your problems but possibly also to contribute solving some of the remaining challenges of organocatalysis.

Mülheim, Summer 2009

Benjamin List

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Noncovalent Organocatalysis Based on Hydrogen Bonding: Elucidation of Reaction Paths by Computational Methods

Kerstin Etzenbach-Effers and Albrecht Berkessel

Abstract In this article, the functions of hydrogen bonds in organocatalytic reactions are discussed on atomic level by presenting DFT studies of selected examples. Theoretical investigation provides a detailed insight in the mechanism of substrate activation and orientation, and the stabilization of transition states and intermediates by hydrogen bonding (e.g. oxyanion hole). The examples selected comprise stereoselective catalysis by bifunctional thioureas, solvent catalysis by fluorinated alcohols in epoxidation by hydrogen peroxide, and intramolecular cooperative hydrogen bonding in TADDOL-type catalysts.

Keywords Organocatalysis • hydrogen bonding • reaction mechanism on DFT level • oxyanion hole • bifunctional thiourea catalysis • catalytic solvents

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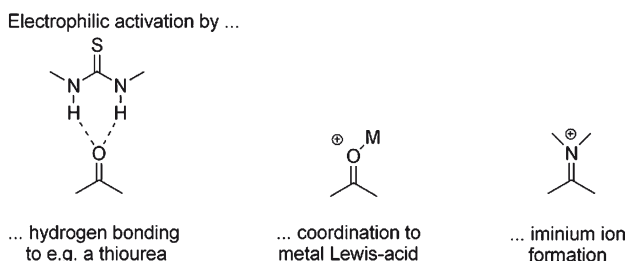
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1 Introduction

Organocatalysis has been a rapidly growing area of research over the last decade [1–3]. On a mechanistic basis, the vast array of organocatalytic transformations can be divided into the two subgroups “covalent organocatalysis” and “noncovalent organocatalysis.” In the former case, a covalent intermediate is formed between the substrate(s) and the catalyst within the catalytic cycle. Typical examples are proline-catalyzed aldol reactions which proceed via enamine intermediates [4], or cycloadditions, conjugate additions, etc. that proceed via iminium ions derived from enal substrates and amine catalysts [5]. In contrast, noncovalent organocatalysis relies solely on noncovalent interactions such as hydrogen bonding or the formation of ion pairs. Organocatalysis had its roots in “covalent” processes, such as the proline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert aldol condensation [6, 7]. However, the importance of hydrogen bonding for (stereo) selective organocatalysis has also been recognized early, and the recent past has seen tremendous development in this area as well [1, 8–10].

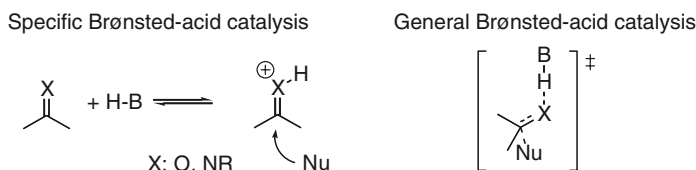
Hydrogen bonding to substrates such as carbonyl compounds, imines, etc., results in electrophilic activation towards nucleophilic attack (Scheme 1). Thus, hydrogen bonding represents a third mode of electrophilic activation, besides substrate coordination to, e.g., a metal-based Lewis acid, or iminium ion formation (Scheme 1). Typical hydrogen bond donors such as (thio)ureas are therefore often referred to as “pseudo-Lewis acids.”



Scheme 1 Three modes of carbonyl activation towards nucleophilic attack

Substrate activation by hydrogen bonding is related to, but different from Brønsted acid catalysis [1–3, 10]. In the latter case, proton transfer from the catalyst to the substrate(s) occurs. The terms “specific Brønsted acid catalysis” and “general Brønsted acid catalysis” are used, depending on whether proton transfer occurs to the substrate in its ground state, or to the transition state. In specific

Brønsted acid catalysis, the substrate electrophile is reversibly protonated in a pre-equilibrium step, prior to the nucleophilic attack (Scheme 2). In general acid catalysis, however, the proton is (partially or fully) transferred in the transition state of the rate-determining step (Scheme 2). Clearly, the formation of a hydrogen bond precedes proton transfer.



Scheme 2 Specific and general Brønsted-acid catalysis

Consequently, the processes most relevant to the topic of this chapter, i.e., “hydrogen bonds in organocatalytic transition states,” are (1) transition state stabilization by pure hydrogen bonding (without full proton transfer) and (2) general Brønsted acid/Brønsted base catalyzed reactions which are initiated by hydrogen bonding but move further to distinct proton transfer.

At this point of the introduction, seminal contributions to the development and understanding of organocatalysis by hydrogen bonding by Peter R. Schreiner and coworkers need to be acknowledged. Their contribution cited in reference [11–14] illustrate and highlight the concepts of electrophilic (i.e., Lewis acid like) substrate activation by hydrogen bonding [11, 12], as well as oxyanion stabilization by hydrogen bonding to organocatalysts [13, 14]. Furthermore, please note that hydrogen bonding as the basis of (mostly biologic) catalysis has been discussed and analyzed, although not by computational means, as early as the 1970s and 1980s by Jencks and Hine [15–17].

Up to now, only a few organocatalytic reactions of the above types have been investigated with post-Hartree–Fock methods.¹ Potential reasons are computational costs, spatial and conformational flexibility (ab initio methods do not necessarily find

¹The Hartree–Fock theory neglects correlations between electrons. This means that one single electron is only subjected to an average potential by the other electrons of a system. This leads, e.g., to errors in bond lengths and angles and dissociation energies. Therefore, more exact methods, the so-called post Hartree–Fock methods were developed which are either based on perturbation theory (e.g., second order Møller–Plesset–Perturbation theory, MP2), or on the variational principle (e.g., configuration interaction, CI or coupled cluster methods CC). Compared to the Hartree–Fock method, these techniques are very time consuming. Alternative approaches to electronic structure are density functional theory methods (DFT) in which the electron density distribution rather than the many electron wave function plays a central role. Difficulties in expressing the exchange part of the energy can be relieved by including a component of the exact exchange energy calculated from Hartree–Fock theory. Functionals of this type are known as hybrid functionals. Widely used for DFT-calculations is the hybrid functional B3LYP: a correlation functional developed by Becke combined with an exchange term from Lee, Yang and Parr [18–20]. It provides in many cases access to qualitatively good results at computational costs comparable to Hartree–Fock methods.

the absolute minimum, but the minimum closest to a given starting structure – which might turn out to be a relative minimum only), and the problem of properly treating solvent effects. Nevertheless, some examples for quantum mechanically analyzed reaction mechanisms exist and will be discussed in this chapter. They allow a detailed insight at atomic level into organocatalyst function, and provide an especially detailed view on the significance of hydrogen bonding. In the majority of current theoretical publications dealing with organocatalysis, Becke's [18, 19] three parameter hybrid functional B3 and the Lee, Yang, and Parr correlation functional [20] LYP are used in combination with standard split valence basis sets (for example 6-31G). In most cases, polarization functions which allow a greater flexibility of angle are added [for example, (d,p) means additional d-functions for second-row atoms, and additional p-functions for hydrogen atoms] [21]. In some cases, diffuse functions (abbreviated with +) are used as well, which allow an increased distance between nucleus and electron (one plus sign indicates additional diffuse functions for nonhydrogen atoms only; two plus signs indicate additional diffuse functions for hydrogen as well). They are recommended for negatively charged molecules or for the description of lone pair effects [21]. In this contribution, we focus solely on small metal free organocatalysts (including catalytically active solvents). We also exclude covalently catalyzed reactions, for example proline-catalyzed aldol reactions, although this reaction is well investigated at DFT-level [22–29], and although a hydrogen bond is involved (the carboxyl group of the proline catalyst activates the electrophile towards the attack by the enamine by hydrogen bonding).

Transition states are clearly the most interesting stages of a reaction path. Nevertheless, we also consider starting complexes and intermediates, provided that they contribute useful information about the mode of operation of hydrogen bond mediated catalysis.

2 Catalytic Functions of Hydrogen Bonds

2.1 *Hydrogen Bonds Can Preorganize the Spatial Arrangement of the Reactants*

In cases where hydrogen bond donor/acceptor functions are attached to a (chiral) scaffold, they can steer the assembly of a well defined catalyst–substrate complex. The positions of hydrogen bond donors and acceptors determine the stereoselectivity of the reaction.

2.2 *Hydrogen Bonds Can Activate the Reactants by Polarization*

The binding of substrates via hydrogen bonds (either as hydrogen bond acceptor or as donor) is necessarily associated with changes in electron densities. In catalytic systems, the resulting polarization leads to an activation of the reactants.

2.3 *Hydrogen Bonds Can Stabilize the Charges of Transition States and Intermediates*

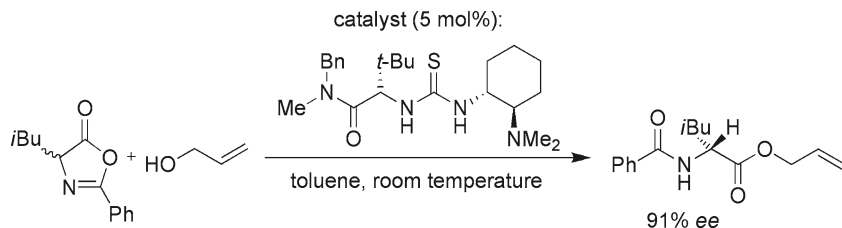
Hydrogen bonds are flexible with regard to bond length and angle. This feature is of utmost importance when charge separation occurs along the reaction pathway, and in particular in the transition state(s): hydrogen bonds have the ability to, e.g., contract and to thus stabilize developing (negative) charges. On the other hand, when the product stage is approached, the hydrogen bonds can expand again, and the product–catalyst complex can dissociate.

In hydrogen bond catalyzed reactions we find basically three different tasks that hydrogen bonds can perform. (1) There are hydrogen bonds which just stabilize charge in a transition state or intermediate. In these cases, the proton is shared between the donor and the acceptor during the transition state, and remains attached to the hydrogen bond donor afterwards. (2) In some transition states, however, a second type of hydrogen bond can be encountered, which is shorter and leads to a real proton transfer from the donor to the acceptor. By some authors this phenomenon is termed a low barrier hydrogen bond (LBHB) [30]. In particular the lifetimes and the binding energies of LBHBs still appear to be controversially discussed [31]. Apolar organic solvents as reaction media are reminiscent of hydrophobic binding pockets of enzymes. In such surroundings, hydrogen bonds between hetero atoms with matched pKs values can be very short and strong [30]. (3) A third class, the so-called “cooperative hydrogen bonds,” play another important role. The latter are typically *intramolecular* hydrogen bonds which can tune the *intermolecular* hydrogen bonding to, e.g., a substrate with regard to acidity (Brønsted acid assisted Brønsted acid catalysis (BBA)) [32] and they are often observed in diols as for example TADDOLs ($\alpha,\alpha',\alpha',\alpha'$ -tetraaryl-1,3-dioxolan-4,5-dimethanol) [33] or BINOL (1,1'-bi-2-naphthol)[34].

3 Case Studies

3.1 *Dynamic Kinetic Resolution (DKR) of Azlactones: Thioureas Can Act as Oxyanion Holes Comparable to Serine Hydrolases*

Our group recently reported that bifunctional (thio)urea – *tert*-amine organocatalysts catalyze the alcoholytic DKR of azlactones (Scheme 3). The method affords highly enantio-enriched N-protected α -amino acid esters [35–39]. We chose this transformation for a detailed computational study as the catalysis (both in terms of rate and stereoselectivity) is solely effected by hydrogen bonding: activation of the azlactone clearly hinges on H-bonding to the catalyst's thiourea moiety, whereas the binding/activation of the alcohol nucleophile occurs at the Brønsted-basic *tert*-amine.

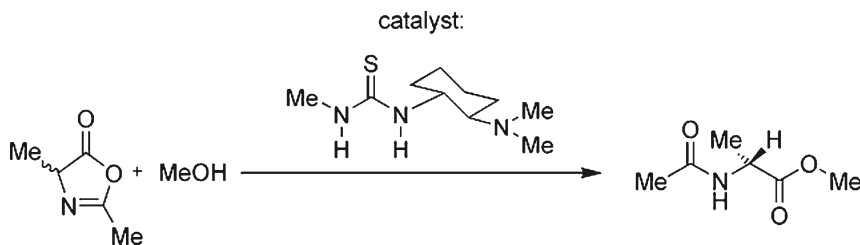


Scheme 3 Example for the dynamic kinetic resolution of azlactones

This reaction encompasses a number of interesting features (general Brønsted acid/Brønsted base catalysis, bifunctional catalysis, enantioselective organocatalysis, very short hydrogen bonds, similarity to serine protease mechanism, oxyanion hole), and we were able to obtain a complete set of DFT based data for the entire reaction path, from the starting catalyst–substrate complex to the product complex.

3.1.1 The Calculated Reaction Path of the Alcoholic Ring Opening of Azlactones

For the calculations we used a simplified model system in which all substituents were replaced by methyl groups (Scheme 4). Experimentally, the methyl substituted catalyst and methanol as nucleophile are active, but the enantiomeric excesses obtained fall below those obtained with the *tert*-leucine amide-derived catalyst in combination with allyl alcohol (Scheme 3).



Scheme 4 Model system for the DFT-calculations of the alcoholic ring opening of azlactones

The first step of the catalytic process is the hydrogen bond directed assembly and orientation of the reactants. In this example, the azlactone and methanol form a ternary *starting complex* with the organocatalyst (Fig. 1) [39]. The pseudo-Lewis acidic thiourea forms two bifurcated, nearly symmetric hydrogen bonds (2.147 Å, $\angle(\text{O},\text{H},\text{N})=155.5^\circ$ and 2.146 Å, $\angle(\text{O},\text{H},\text{N})=155.8^\circ$) to the carbonyl oxygen atom of the azlactone,

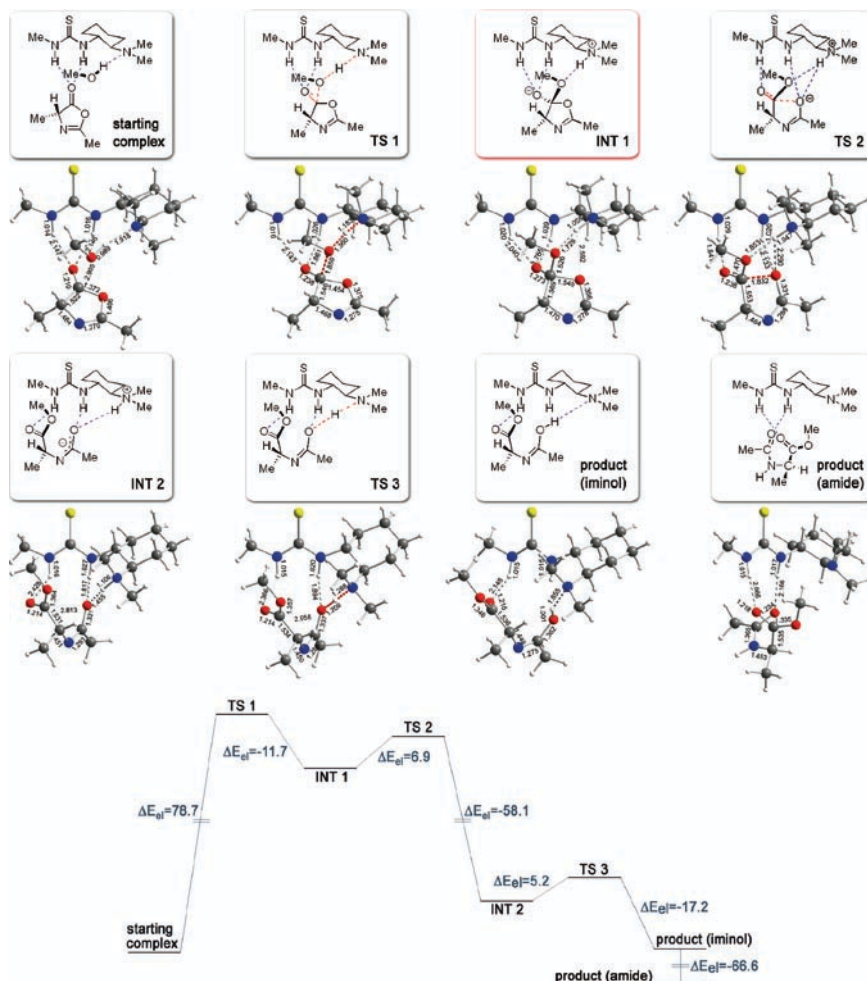


Fig. 1 The reaction path of the alcoholic ring opening of azlactones: geometries and relative electronic energies (kJ mol⁻¹) of the stationary points (B3LYP/6-311++G(d,p) // B3LYP/6-311++G(d,p), gas phase)

whereas the basic tertiary amino group binds the proton of the methanolic hydroxy function (1.918 Å, $\angle(\text{O},\text{H},\text{N}) = 166.5^\circ$). The position of these two groups is defined by the chiral scaffold of (1*R*, 2*R*)-cyclohexane-1,2-diamine (DACH).

As exemplified for the (*R*)-azlactone, in principle two modes of binding are possible with this hydrogen bonding pattern. The orientation of the azlactone in Fig. 1 (*starting complex*) leads to an attack to the *re*-side of the azlactone's carbonyl group. A 180° turn would result in a *si*-side attack, but this arrangement is disfavored

because of nonbonding interactions between the methyl group at the azlactone's center of chirality and the methyl group of the incoming alcohol nucleophile. An energetically preferred arrangement for the (*R*)-azlactone results when the alcohol is located at the *re*-site of the carbonyl group, preorganized for the subsequent nucleophilic attack.

Once the reactants are bound to the catalyst (*starting complex*),² polarization and activation by three hydrogen bonds takes place. This process is evidenced by the change of the natural charges of the *free* azlactone and methanol molecules compared to their charges in the *starting complex*. The negative NBO (natural bond order) charge of the carbonyl oxygen atom rises due to the bifurcated hydrogen bonds donated by the thiourea moiety (-0.068 e). As a consequence, the positive NBO charge of the carbonyl carbon atom increases ($+0.047$ e). Simultaneously, the electron density at the oxygen atom of the methanol molecule is increased (-0.057 e), due to the hydrogen bond between its hydroxy function and the tertiary amine moiety of the catalyst. In summary, the catalytic system is now perfectly orientated and activated by three hydrogen bonds for the following nucleophilic attack.

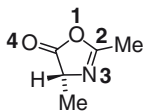
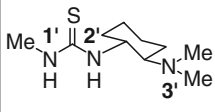
In the first transition state **TS1** (Fig. 1) the hydrogen bonds decrease the activation energy by stabilizing the increasing charges at the participating oxygen atoms. One of the bifurcated hydrogen bonds to the carbonyl oxygen atom is significantly shortened to 1.861 Å (-0.285 Å, $\angle(\text{O,H,N})=157.2^\circ$, adjacent to the cyclohexane ring). The negative charge of the attacking hydroxyl oxygen atom is stabilized by an even stronger contraction (-0.739 Å to 1.183 , $\angle(\text{O,H,N})=166.8^\circ$) of the hydrogen bond to the catalyst's tertiary amine. Here we see an example for a special type of hydrogen bond, as during nucleophilic attack, the proton is transferred along a nearly linear ($\angle(\text{O,H,N})=166.8^\circ$) hydrogen bond from the donor alcohol to the acceptor amine ("LBHB" with an O–H–N-distance of 1.360 Å (O–H) + 1.183 Å (H–N) = 2.543 Å (O–N)).

From the first transition state (**TS1**, Fig. 1), the reaction path leads to the tetrahedral intermediate **1** (**INT1**). In the latter, the proton transfer from methanol to the tertiary amine function is completed (from 1.183 to 1.059 Å), and the negative charge at the former carbonyl oxygen atom reaches its maximum. This charge is compensated by a further shortening of the bifurcated hydrogen bonds to 2.040 Å (-0.103 Å) and 1.765 Å (-0.096 Å) (Fig. 1). The thiourea moiety thus forms an "oxyanion hole" similar to the amide groups of the serine protease backbone [41].

In the following transition state **TS2**, the opening of the azlactone ring takes place. The bond between the carbonyl carbon and ether oxygen atoms is stretched from 1.545 to 1.832 Å. Negative charge is transferred from the carbonyl to the ether oxygen atom in transition state 2 (**TS2**) (change in natural charge -0.102 e; see Table 1 for a summary), and one of the bifurcated hydrogen bonds from the

²The formation of a ternary complex is entropically disfavoured relative to binary ones. However, kinetic and spectroscopic investigations [39] gave no indication of, e.g., a ping-pong mechanism, and/or the involvement of covalent intermediates

Table 1 NBO charges of the stationary points (black: natural charge, red: change to the previous stationary point B3LYP/6-31++G(d,p))

							
	O1	C2	N3	O4	N1'	N2'	N3'
Starting complex	-0.540	+0.571	-0.472	-0.614	-0.660	-0.659	-0.570
TS1	-0.590	+0.563	-0.504	-0.736	-0.655	-0.685	-0.538
	-0.050	-0.008	-0.032	-0.122	+0.005	-0.026	+0.032
INT1	-0.628	+0.564	-0.528	-0.834	-0.657	-0.699	-0.517
	-0.038	+0.001	-0.024	-0.098	-0.002	-0.014	+0.021
TS2	-0.735	+0.572	-0.567	-0.737	-0.656	-0.692	-0.520
	-0.107	+0.008	-0.039	+0.097	+0.001	+0.007	-0.003
INT2	-0.895	+0.614	-0.601	-0.629	-0.652	-0.683	-0.530
	-0.160	+0.042	-0.034	+0.108	+0.004	+0.009	-0.010
TS3	-0.860	+0.620	-0.578	-0.624	-0.656	-0.673	-0.552
	+0.035	+0.006	+0.023	+0.005	-0.004	+0.010	-0.022
Product(iminol)	-0.776	+0.609	-0.553	-0.632	-0.659	-0.661	-0.577
	+0.084	-0.011	+0.025	-0.008	-0.003	+0.012	-0.025
Product(amide)	-0.671	+0.701	-0.654	-0.645	-0.668	-0.648	-0.555
	+0.105	+0.092	-0.101	-0.013	-0.009	+0.013	+0.022

carbonyl oxygen to the thiourea moiety is cleaved. Two new bifurcated hydrogen bonds (2.133 and 2.290 Å) to the (former) azlactone ether oxygen atom are formed to stabilize the newly developing negative charge. As the ring opening proceeds, the negative charge at the (former) azlactone ether oxygen atom increases to its maximum (change in natural charge -0.162 e), and the intermediate 2 (**INT2**) is reached. In this intermediate, the catalyst's protonated tertiary amine and the NH-group adjacent to the cyclohexane ring together form a charge-stabilizing "oxyanion hole" (length of the hydrogen bonds 1.455 and 1.855 Å).

In the third transition state (**TS3**), the neutral catalyst is recovered by transferring the proton back from the catalyst to the substrate. In other words, the (former) azlactone ether oxygen atom deprotonates the tertiary ammonium ion. For proton transfer, again an "LBHB" is formed ($N-O$ distance 2.479 Å, $\angle(O,H,N)=166.2^\circ$). In the product complex, the catalyst is neutral and the *N*-acylamino acid ester is bound in its iminol form to the catalyst (**Product(iminol)**). Finally, an additional 66.6 kJ mol⁻¹ are gained by the subsequent iminol–amide tautomerization (**Product(amide)**) (Fig. 1).

Clearly, the strength of hydrogen bonds depends on the reaction medium. In practice, the nonpolar solvent toluene is routinely used. It can be considered to mimic a hydrophobic binding pocket of an enzyme and clearly supports the formation of moderate (1.5–2.2 Å) and even strong (1.2–1.5 Å) hydrogen bonds [42].

3.1.2 How Hydrogen Bonds Determine the Enantioselectivity of the Alcoholic Azlactone Opening

In order to explain the enantioselectivity of the alcoholic azlactone opening, we calculated the four possible ternary starting complexes (catalyst–azlactone–methanol) *re(R)*, *re(S)*, *si(R)*, and *si(S)* (Fig. 2), together with the first (and rate-determining) transition states. In the complexes *re(R)* and *si(S)*, the methyl group bound to the azlactone's center of chirality and the methyl group of the attacking methanol are located on

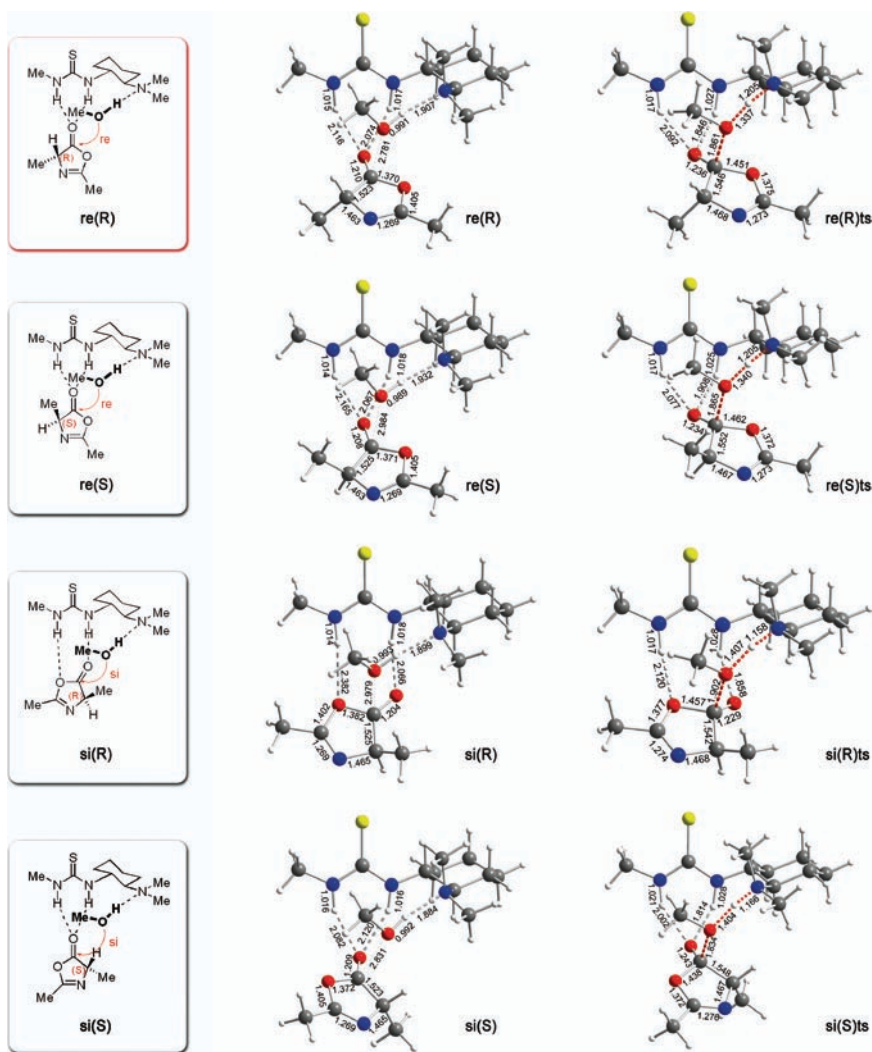


Fig. 2 Four possible ternary (*R/S*)-azlactone–methanol–catalyst complexes optimized with B3LYP/6-31+G(d)

opposite sides of the azlactone ring. As a consequence, there is no significant interaction between them. However, in the complexes *re(S)* and *si(R)*, where both methyl groups show significant steric interaction, there is pronounced nonbonding interaction between them. This fact is reflected in the activation energies, with one exception: the activation energy of *si(S)ts* is remarkably higher than that of *re(R)ts*, although the steric interaction of the methyl groups is comparable. This effect is due to unfavorable charge separation in the transition state. As the carbonyl oxygen atom develops a partial negative charge during the nucleophilic attack of the alcohol nucleophile, the charge separation is larger for *si(S)ts* (dipole moment of *re(R)ts*: 5.66 Debye, dipole moment of *si(S)ts*: 6.08 Debye). Additionally, in *re(R)ts*, a lone pair of the lactone oxygen atom points in the direction of the developing positive charge at the tertiary amine function of the catalyst. Overall, in *re(R)ts*, the negative charge is distributed and stabilized on the azlactone oxygen atoms more effectively than in *si(S)ts*.

In summary, the hydrogen bond pattern of the catalyst disfavors some principally possible arrangements due to steric interactions, and others due to a lack of charge distribution and charge stabilization. In this example, *re(R)ts* remains as the only favored transition state (see activation energies in Fig. 3).

Clearly, upon using the enantiomeric catalyst [(*S,S*) instead of (*R,R*)] the opposite enantioselectivity of the overall process results. However, this effect is also seen with catalysts that are of analogous configuration, but not derived from *trans*-1,2-diaminocyclohexane (DACH). For example, the pseudo-ephedrine derived catalyst shown in Scheme 5, having (*S*)-configuration at the centers of chirality, shows some preference for the (*S*)-azlactone kinetically favors the (*S*)-azlactone in alcoholic ring opening [37].

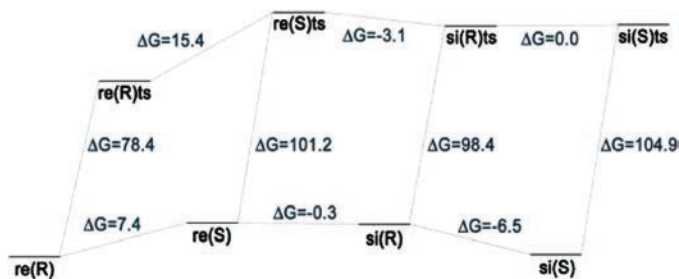
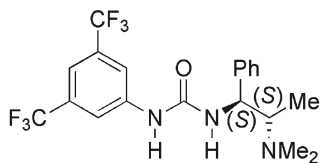


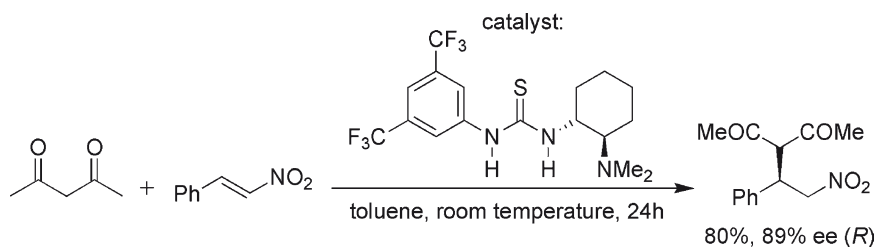
Fig. 3 Relative Gibbs free energies of the four ternary azlactone-methanol-catalyst complexes and the corresponding transition states at 298 K, gas phase (B3LYP/6-311++G(d,p)// B3LYP/6-31+G(d))

Scheme 5 Pseudo-ephedrine derived catalyst which favors the ring opening of (*S*)-azlactones



3.2 On the Bifunctionality of Chiral Thiourea: Tertiary-Amine Based Organocatalysts: Competing Routes to C–C Bond Formation in a Michael-Addition

Takemoto et al. were the first to report that bifunctional organocatalysts of the thiourea – *tert*-amine type efficiently promote certain Michael-reactions, e.g., the addition of β -dicarbonyl compounds to nitro olefins (Scheme 6) [43–45].



Scheme 6 Enantioselective Michael-addition of acetylacetone to nitrostyrene catalyzed by a bifunctional thiourea catalyst

Pápai et al. selected as model reaction the addition of 2,4-pentanedione (acetylacetone) to *trans*-(*R*)-nitrostyrene, catalyzed by the bifunctional thiourea catalyst shown in Scheme 6 [46]. The analogous Michael-addition involving dimethyl malonate and nitroethylene as substrates, and a simplified catalyst was calculated at the same level of theory by Liu et al. [47]. Himo et al. performed a density functional study on the related *cinchona*-thiourea catalyzed Henry-reaction between nitromethane and benzaldehyde [48].

As shown by Takemoto and coworkers, the nitro-Michael reaction shown in Scheme 6 proceeds efficiently (within 1 h) at room temperature, affording the Michael adduct in good yield (80%) and with high enantiomeric excess (89% ee, with (*R*)-configuration of the major enantiomer) [44]. The theoretical analysis by Pápai et al. revealed that both the nitroolefin (2.05 and 2.21 Å) (Fig. 4, left; adduct 1) and the enol form of acetylacetone (1.94 and 2.40 Å) (Fig. 4, right; adduct 2) can form two hydrogen bonds with the thiourea moiety of the catalyst. A proton transfer from the coordinated enol to the amino function of the catalyst can easily take place, as the transition state related to this process (TS2-3') represents only a relatively small energy barrier (6.6 kcal mol⁻¹) with respect to adduct 2 (see Fig. 4, 2) and the resulting ion pair (3') is predicted to be only 2.2 kcal mol⁻¹ (gas phase) above 2 (0.7 kcal mol⁻¹ in toluene) (see Fig. 5, 3').

The enolate anion in complex 3' is stabilized by three N–H···O bonds that involve the protonated amine moiety (1.68 and 2.28 Å) and one of the N–H groups (1.80 Å) of the thiourea. In complex 3'', the enolate is tilted from its original position to maximize the number of N–H···O bonds. In this arrangement, all three N–H units are involved in the hydrogen bond network.

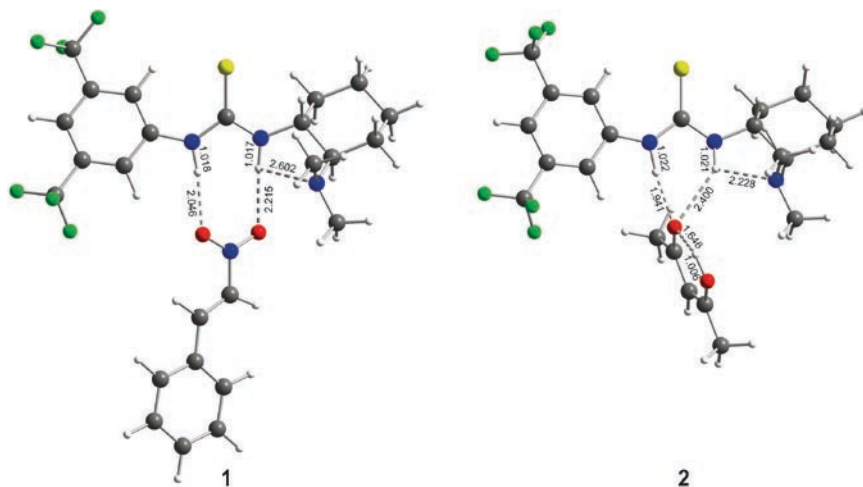


Fig. 4 Optimized structures (B3LYP/6-31G(d)) of the most stable catalyst–substrate adducts. Bond distances characteristic for hydrogen bonds are given in Ångstrom

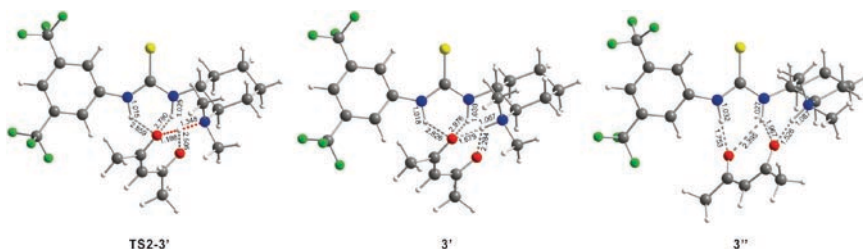
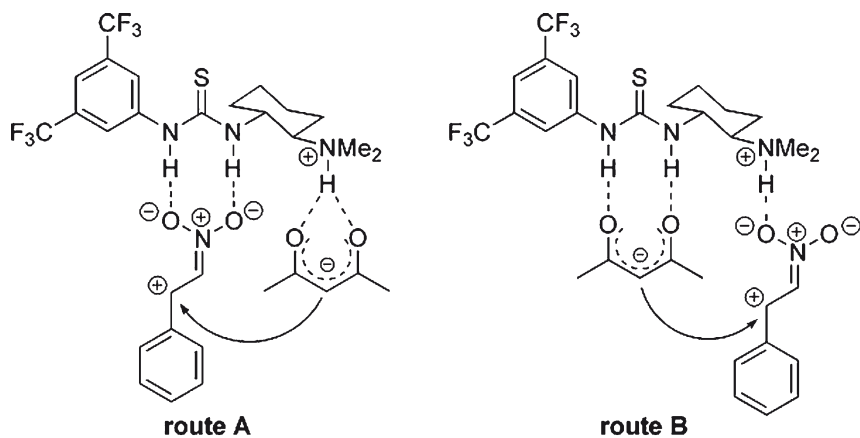


Fig. 5 Optimized structures (B3LYP/6-31G(d)) of the stationary points located for the proton transfer between the thiourea derived catalyst and the enol form of acetylacetone. Bond distances characteristic for hydrogen bonds are given in Ångstrom, bonds broken or formed are shown in red

Two distinct reaction pathways can be envisioned for the C–C bond formation step of this catalytic process (see Scheme 7). According to the mechanism proposed by Takemoto et al. [44], the nitroolefin interacts with the thiourea moiety of complex **3'** (Scheme 7, route A), forming a ternary complex, wherein both substrates are activated, and C–C bond formation can occur to produce the nitronate form of the addition product. Alternatively, the facile interconversion between **3'** and **3''** may allow an interaction of the nitroolefin with the cationic ammonium group of the protonated catalyst (Scheme 7, route B). In both cases, ternary complexes result which are the precursor for the C–C coupling step. On both routes, the hydrogen bonds to the nucleophilically attacked nitrostyrene are contracted to compensate the development of negative charge [route A: hydrogen bonds to the thiourea functionality: -0.160 and -0.316 Å (Fig. 6), route B: hydrogen bonds to the protonated amino group: -0.437 and -0.546 Å (Fig. 7)].



Scheme 7 Two alternative reaction routes for the organocatalytic Michael-addition of acetylacetone to nitrostyrene

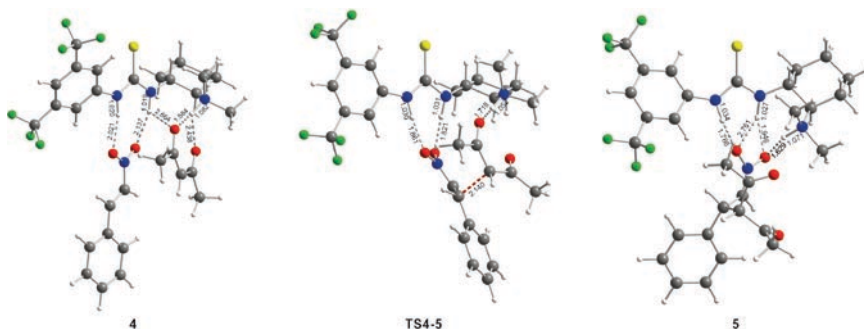


Fig. 6 Optimized structures (B3LYP/6-31G(d)) of the stationary points located along *route A*. Lengths of hydrogen bonds are given in Ångstrom, bonds broken or formed are indicated in red

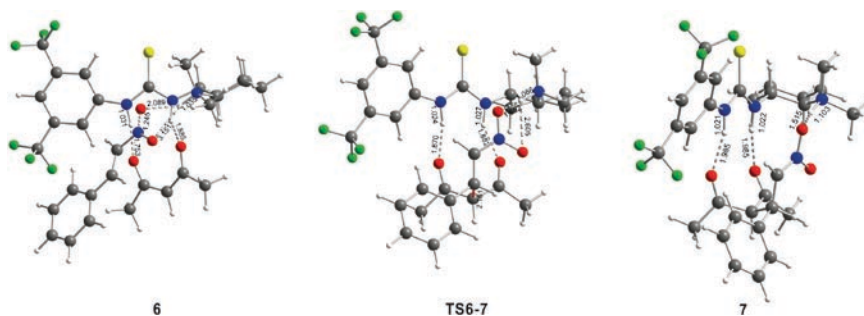


Fig. 7 Optimized structures (B3LYP/6-31G(d)) of the stationary points located along *route B*. Lengths of hydrogen bonds are given in Ångstrom, bonds broken or formed are indicated in red

Simultaneously, the hydrogen bonds to the nucleophile are stretched [route A: hydrogen bonds to the protonated amino group: +0.134 and +0.180 Å (Fig. 6), route B: hydrogen bonds to the thiourea functionality: +0.180 and −0.003 Å (Fig. 7)].

The C–C bond forming step also accounts for the enantioselectivity of the overall process. In the transition states affording the (*R*)-product [TS 4–5 (Fig. 6), TS 6–7 (Fig. 7)], the substrates are aligned in a staggered conformation along the forming C–C bond, thus minimizing nonbonding interactions. Such favorable orientation cannot be adopted in the transition states leading to the (*S*)-configured product: the electrophilic β -carbon atom of the Michael acceptor (nitrostyrene) is displaced from its ideal position when the nucleophile attacks its *si*-face. C–C Bond formation can only take place with a compromise of either the hydrogen bonding catalyst–substrate interactions, or the staggered geometry of the reacting molecules. These results underline the importance of the relative spatial arrangement of the hydrogen bond donor and acceptor in a bifunctional catalyst. To obtain best asymmetric induction, it should ideally be compatible only with the transition state geometry leading to the desired product stereoisomer (Fig. 8).

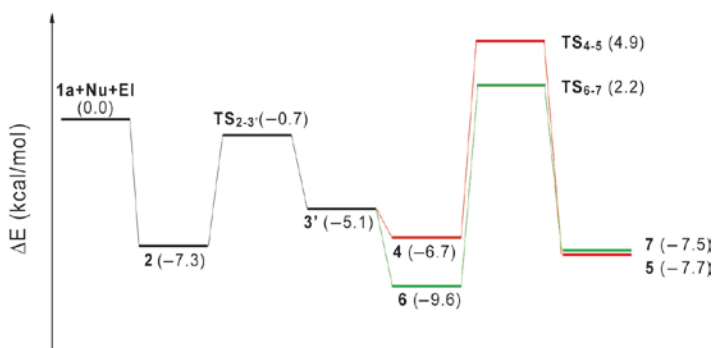
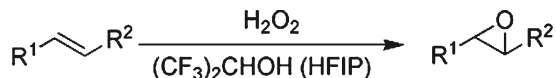


Fig. 8 Organocatalytic Michael-addition: Energy profiles of paths A and B, both leading to (*R*)-configured product, as obtained from gas phase calculations (B3LYP/6-311G(d,p)// B3LYP/6-31G(d))

3.3 Dramatic Acceleration of Olefin Epoxidation in Fluorinated Alcohols: Activation of Hydrogen Peroxide by Multiple Hydrogen Bond Networks

As a third example for an organocatalytic reaction, based on multiple hydrogen bonding and mechanistically investigated by DFT, we selected olefin epoxidation with hydrogen peroxide in fluorinated alcohol solvents, such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (Scheme 8). Here we encounter a new type of catalytic hydrogen bond: the cooperative hydrogen bond.



Scheme 8 Epoxidation of alkenes with hydrogen peroxide in HFIP as solvent

In this example the solvent – a fluorinated alcohol – forms higher order aggregates and activates H_2O_2 for the epoxidation of electron rich olefins. HFIP accelerates this oxidation reaction up to 100,000-fold (relative to that in 1,4-dioxane as solvent). Which hydrogen bond network involving H_2O_2 , olefin, and fluorinated alcohol gives rise to such spectacular accelerations?

3.3.1 Hydrogen Bond Donor Features of HFIP

For understanding the catalytic properties of HFIP, it is necessary to take a closer look at the hydrogen bond donor properties of HFIP, and the factors by which they are influenced [50]. The hydrogen bond donor ability of fluorinated alcohols, and in particular HFIP, is mainly dependent on two parameters: (1) the conformation of the alcohol monomer along the C–O bond [49, 50, 51] and (2) the cooperative aggregation to hydrogen bonded alcohol clusters [49, 50].

In a polarizable environment, the absolute minimum structure of HFIP carries the OH synclinal (sc) or almost synperiplanar (sp) to the adjacent CH (Fig. 9) [49]. On the basis of quantum-chemical considerations as well as single-crystal X-ray structures in which HFIP acts as hydrogen bond donor, HFIP always takes on such an sc or even sp conformation. In this conformation, the hydrogen bond donor ability of HFIP is significantly increased (Figs. 10 and 11) [49].

Furthermore, the hydrogen bond donor ability of an HFIP hydroxyl group is greatly enhanced upon coordination of a second or even third molecule of HFIP (Figs. 12 and 13). Aggregation beyond the trimer has no significant additional effect [49, 52].

Therefore, the following mechanistic investigation of the epoxidation of olefins with hydrogen peroxide is constrained to reaction pathways which (1) involve HFIP in an sc or even sp conformation and (2) to hydrogen bonded HFIP aggregates comprising up to four alcohol monomers.

3.3.2 The Catalytic Activity of HFIP in the Epoxidation Reaction

Kinetic investigations of the epoxidation of Z-Cyclooctene by aqueous H_2O_2 in HFIP show that the reaction follows a first order dependence with respect to the substrate olefin as well as to the oxidant, suggesting a monomolecular participation of these components in the rate-determining step [52]. On the other hand, a rate order of 2–3 with respect to the concentration of HFIP is observed for several cosolvents. The large negative $\Delta S^\ddagger$ of $-39 \text{ cal mol}^{-1} \text{ K}$ points to a highly ordered TS of the rate-determining reaction step: typical $\Delta S^\ddagger$ values for olefin epoxidations by peracids range from -18 to -30 cal mol^{-1} [53]. These experimental results provide the basis

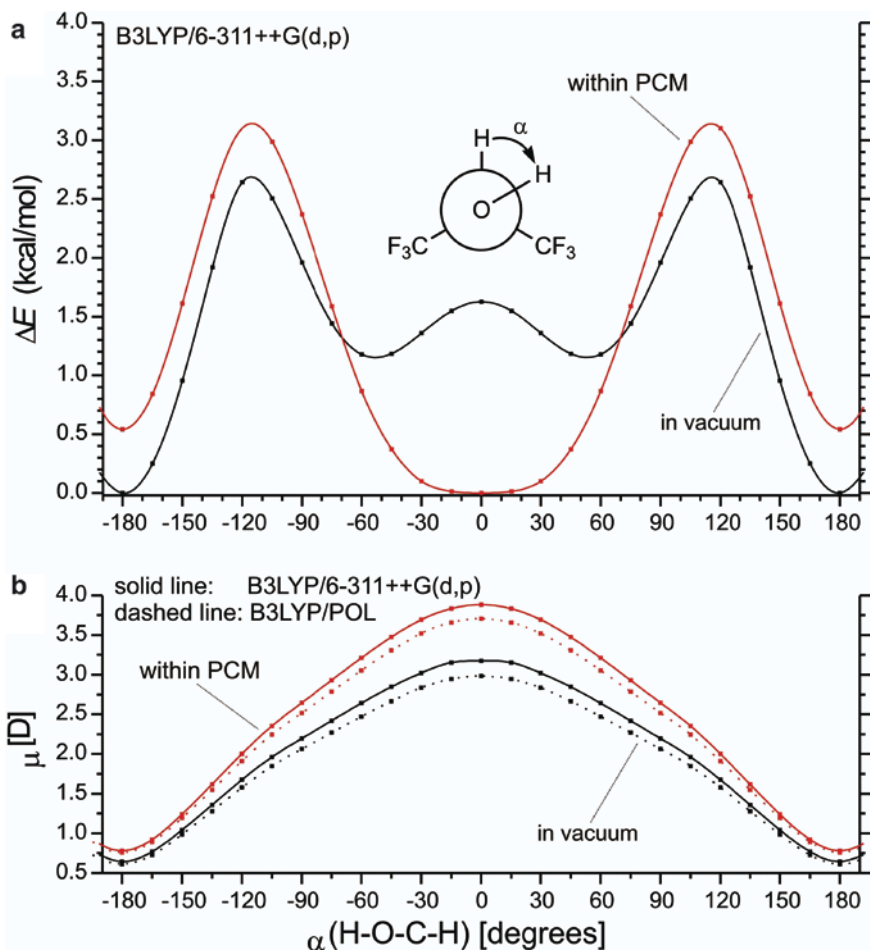


Fig.9 Potential energy (a) and dipole moment (b) of HFIP vs $\angle$ (HOCH) dihedral angle in vacuum (black) and within a PCM (red)

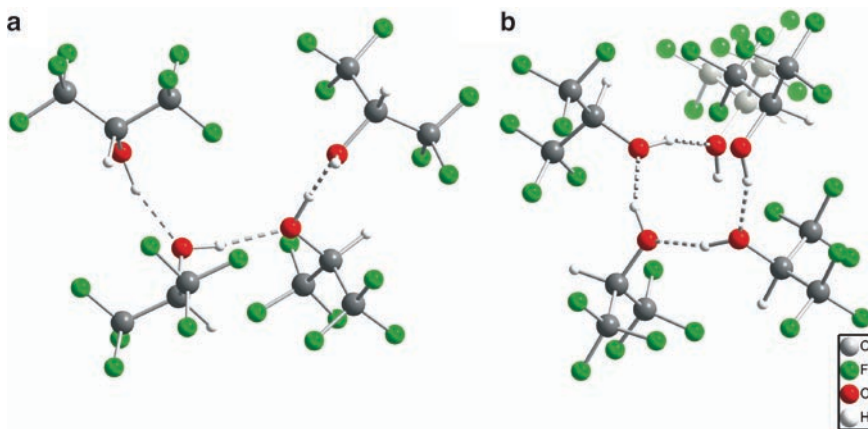


Fig. 10 Single-crystal X-ray structures of HFIP: (a) view perpendicular to the helix axis; (b) view along the helix axis

Fig. 11 Dependence of the properties of monomeric HFIP on the conformation along the CO bond

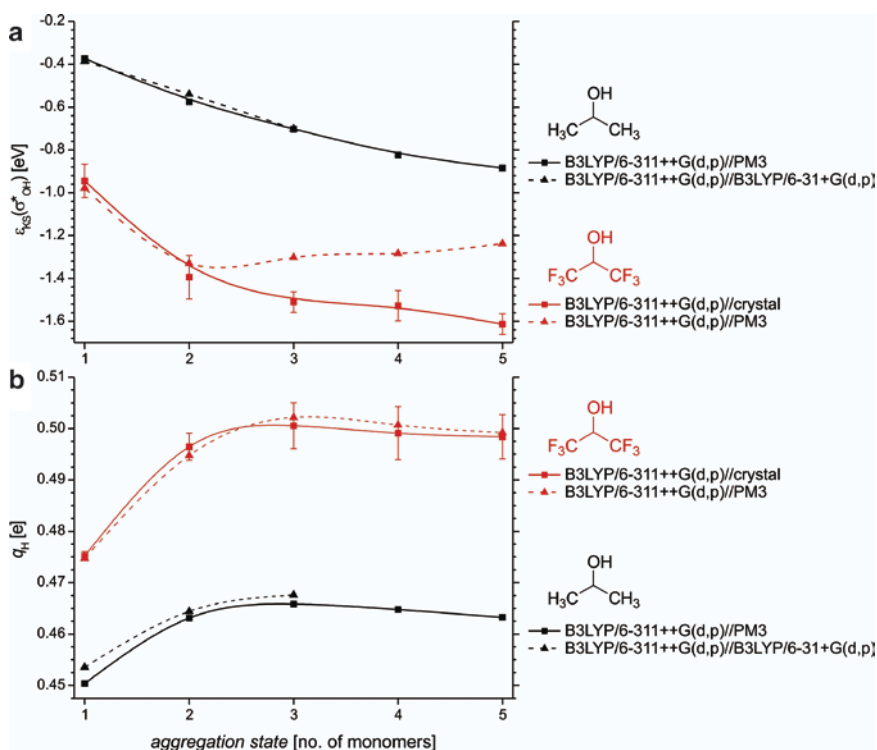
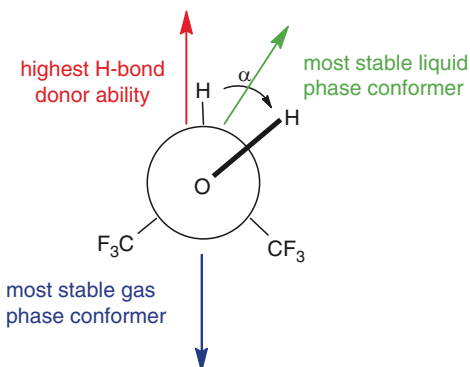


Fig. 12 LUMO energy (σ_{OH}^*) (a) and natural charge q_H of the hydroxyl proton (b) vs aggregation state of HFIP

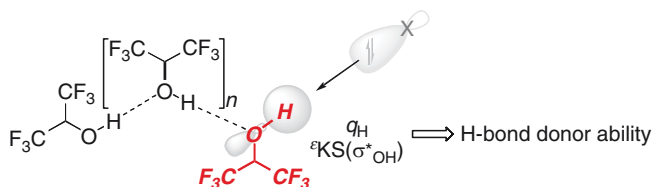


Fig. 13 Aggregation-induced hydrogen bonding enhancement of HFIP

for the calculations in which one to four molecules of HFIP are added to the transition state of the reaction.

The first quantum-chemical investigation of the mechanism of olefin epoxidation in fluoroalcohols was carried out by Shaik et al. [54]. In the absence of kinetic data, a *monomolecular* mode of activation by the fluorinated alcohols for all reaction pathways was assumed [54].

In this review, we compare the transition state which does not involve HFIP-participation [TS(e,0)] with single-HFIP involvement [TS(e,1) and TS(e,1)'] (Fig. 14). Particular emphasis is then put on the twofold HFIP-activated complex (Fig. 15) for a detailed inspection of the hydrogen bond assisted epoxidation. All relevant characteristics of higher order activation (as shown, e.g., in Fig. 16) are already present in the transition states **TS(e,2)** and **TS(e,2)'** (Fig. 15).

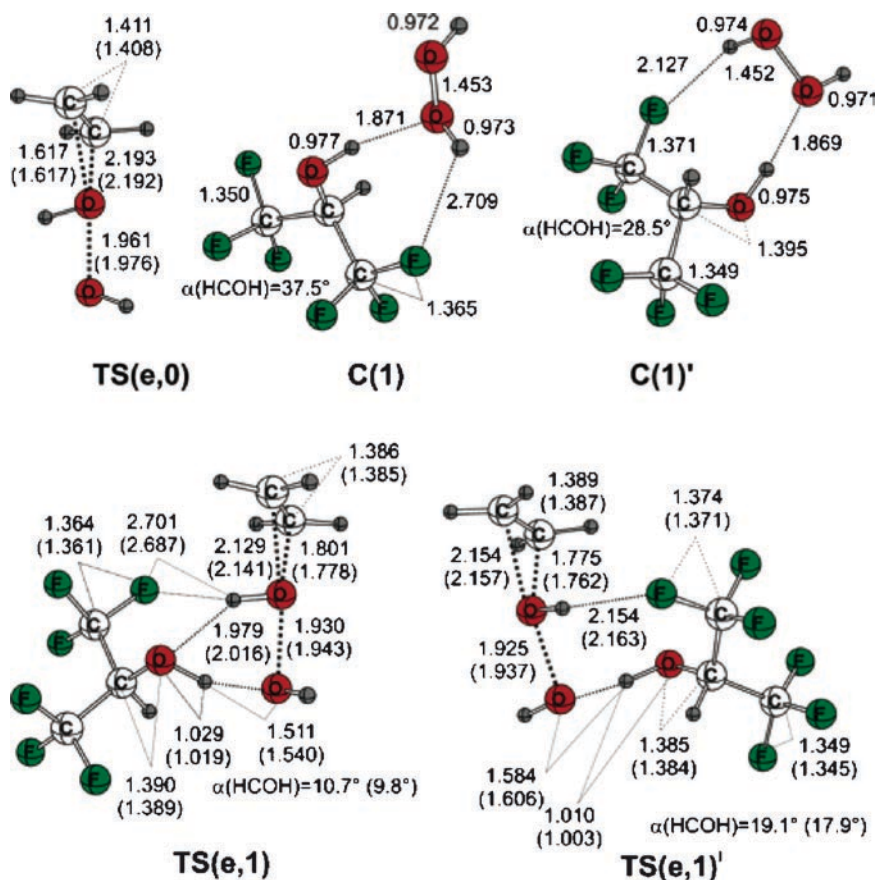


Fig. 14 Stationary-point structures for the epoxidation of ethene with hydrogen peroxide in the absence and in the presence of one molecule of HFIP, optimized at RB3LYP/6-31+G(d,p) (selected bond lengths in Å; RB3LYP/6-311++G(d,p) results in parentheses)

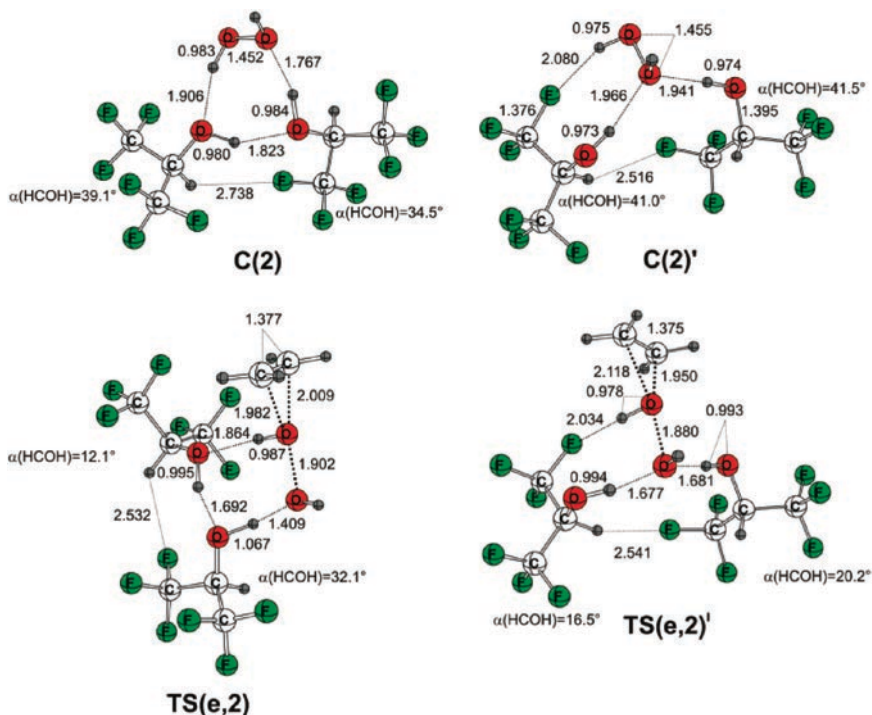


Fig. 15 Stationary-point structures for the epoxidation of ethene with hydrogen peroxide in the presence of two molecules of HFIP, optimized at RB3LYP/6-31+G(d,p)

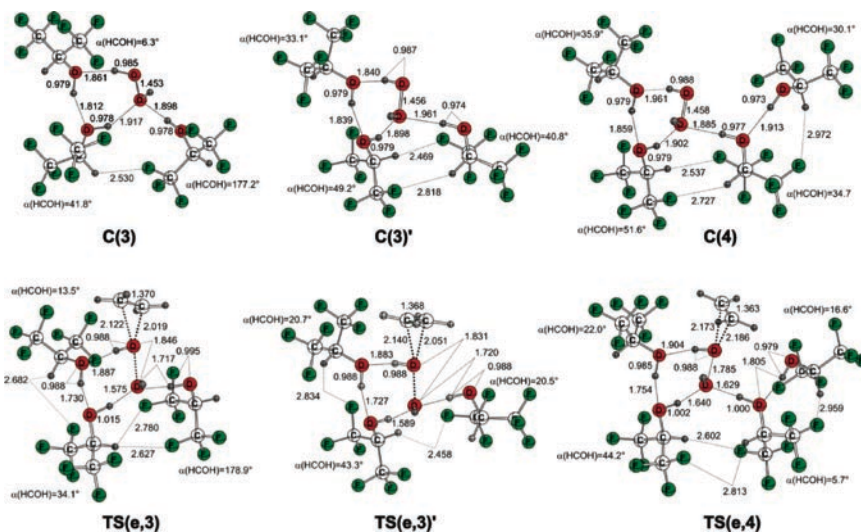


Fig. 16 Stationary-point structures for the epoxidation of ethene with hydrogen peroxide in the presence of three to four molecule of HFIP, optimized at RB3LYP/6-31+G(d,p)

In the 2:1 precomplex **C(2)** composed of HFIP and H_2O_2 , hydrogen peroxide is coordinated by the two alcoholic hydroxyl groups in a cyclic fashion, one HFIP acting as a hydrogen bond donor towards the leaving OH (hydrogen bond length 1.767 Å), and the other one as a hydrogen bond acceptor (hydrogen bond length 1.906 Å), deprotonating the hydroxyl group which is transferred to be the epoxide oxygen atom (**C(2)**, Fig. 15). The “internal” hydrogen bond between the two fluorinated alcohols (hydrogen bond length 1.823 Å) cooperatively increases the hydrogen bond donor ability of the alcohol molecule which activates the leaving OH-group. By this hydrogen bond pattern, a polarization of the O–O bond is achieved (the donated and accepted hydrogen bonds are not equal in length and angle), and an electron deficient oxygen is generated, ready for electrophilic attack on the olefinic double bond. In the corresponding transition state (**TS(e,2)**, Fig. 15) the shorter hydrogen bond (in which HFIP acts as H-bond donor) is extremely contracted to 1.409 Å (−0.358 Å) whereas the longer hydrogen bond (in which HFIP acts as acceptor) is slightly decreased in length to 1.864 Å (−0.042 Å). The acidity of the donor HFIP molecule is cooperatively increased by shortening of the HFIP internal hydrogen bond from 1.823 to 1.692 Å (−0.131 Å).

A second potential reaction path (**C(2)'**, **TS(e,2)'**, Fig. 15) for twofold HFIP activation was calculated, which differs from **TS(e,2)** with regard to the hydrogen bond from H_2O_2 to HFIP. Here, a fluorine atom of the trifluormethyl group serves as hydrogen bond acceptor, and not a second hydroxy function. Both transition states are similar in energy but the corresponding precomplex **C(2)'**, consisting of H_2O_2 and two HFIP molecules, lies 18.4 kJ mol^{−1} above **C(2)**.

An analysis of the hydrogen bonding parameters shows that, in all cases where HFIP donates a hydrogen bond to the oxidant, this hydrogen bond is significantly contracted in the transition state, usually by more than 0.3 Å. The result of this significant contraction is the formation of a *LBHB* [30], characterized by an increase in covalency which effectively exerts the pronounced stabilization of the highly polar transition states through charge transfer. Hydrogen bonds between two HFIP molecules show the same trend, being regularly shortened by ca. 0.1 Å. This effect clearly indicates a cooperative enhancement of hydrogen bonding. Additionally, we find a reduction of the $\angle(\text{HCOH})$ dihedral angles in 14 of the 16 HFIP molecules within the 7 calculated reaction pathways. This result is in agreement with the analysis of the hydrogen bonding properties of HFIP, as the hydrogen bond donor ability is maximized toward the *sp* conformation of the alcohol.

Proceeding from the transition states to the resulting products, IRC analysis demonstrates that along this reaction path, a subsequent and *barrier-free, cascade-like proton transfer* towards the formation of the epoxide and water takes place. Figure 17 shows the overall dependence of the activation parameters on the number of HFIP molecules involved. Interestingly, the activation enthalpy of the epoxidation decreases steadily from zero to fourth order in HFIP. As expected, the activation entropy $-T\Delta S^\ddagger$ shows a continuous increase with increasing numbers of specifically coordinated HFIP molecules. Due to the increasing entropic contribution, the value of $\Delta G^\ddagger$ approaches saturation when three or four HFIP molecules are involved. For methanol, however, no influence of explicit coordination of the solvent on the activation parameters of oxygen transfer could be found, so it seems to

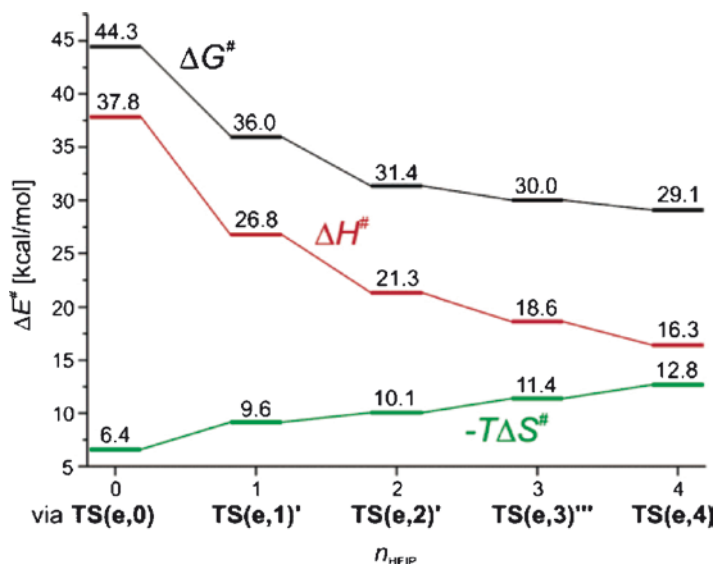


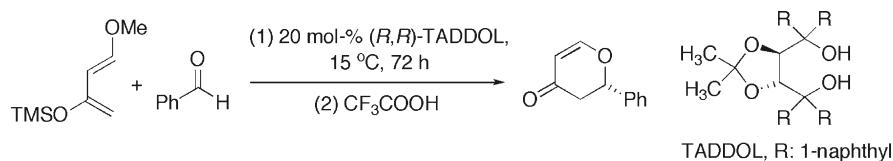
Fig. 17 Activation parameters vs number of HFIP molecules for the epoxidation of ethane within a solution model at 298 K (RB3LYP/6-311++G(d,p)//RB3LYP/6-31+G(d,p))

act solely as a polar reaction medium. In line with this result, no significant epoxidation catalysis results from the use of methanol as solvent.

3.4 *TADDOL-Promoted Enantioselective Hetero-Diels–Alder Reaction of Danishefsky’s Diene with Benzaldehyde: Another Example for Catalysis by Cooperative Hydrogen Bonding*

The enantioselective hetero-Diels–Alder (HDA) reaction of carbonyl compounds with 1,3-dienes represents an elegant access to optically active six-membered oxo-heterocycles. Since the pioneering work of Rawal et al. in 2003 [55], the enantioselective HDA reaction catalyzed by diols (such as TADDOLs) has become a flourishing field of research [56].

In the catalytic system shown in Scheme 9, a hydrogen bond between one hydroxy function of the diol catalyst and the carbonyl group of the substrate is regarded as the driving force of catalysis. Here, the spatial orientation of the bulky α -1-naphthyl substituents of the TADDOL ($\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolan-4,5-dimethanol) scaffold generates the chiral environment controlling the enantioselectivity of the reaction.



Scheme 9 Enantioselective hetero-Diels–Alder (HDA) reaction of Danishefsky’s diene with benzaldehyde

A similar Diels–Alder reaction was investigated at DFT-level by Houk and co-workers [57]. Instead of using TADDOL, they selected one methanol molecule, two methanol molecules and 1,4-butanediol in cooperative and bifurcated coordination as catalysts. It was found that cooperative catalysis is generally the favored route.

Ding, Wu et al. [58] used a model system consisting of benzaldehyde and a modified Danishefsky’s diene, in which the trimethylsilyl group was replaced by a methyl group. They varied the aryl substituents of the TADDOL catalyst, and the results for the most enantioselective 1-naphthyl substituted catalyst were presented in detail. The central feature of this computational analysis is the use of the ONIOM method [59, 60] for geometry optimization (Fig. 18): the substrates and the core of TADDOL were treated with B3LYP/6-31G(d), while the substituents of the catalyst were modeled using semi-empirical PM3 [61, 62] level. The energies of the optimized structures were determined by single point calculations with B3LYP/6-31G(d). X-ray crystal structures [33] of the TADDOLs investigated were taken as starting geometries.

In the starting complex, there are three principal possibilities of hydrogen bonding between TADDOL and benzaldehyde (Scheme 10). A bifurcated hydrogen bond between the two hydroxy functions and the carbonyl group can be excluded, as TADDOLs are well known to have an *intramolecular* hydrogen bond [33, 63]. Ding, Wu et al. found that structure optimizations resulted, without exception, in the *trans* configuration, even if the initial structure was *cis*. This observation is consistent with the crystal structures available for TADDOL adducts with carbonyl compounds [33, 63].

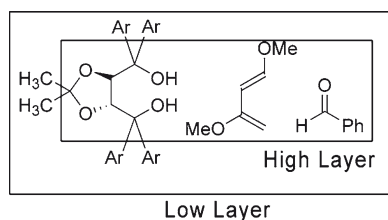
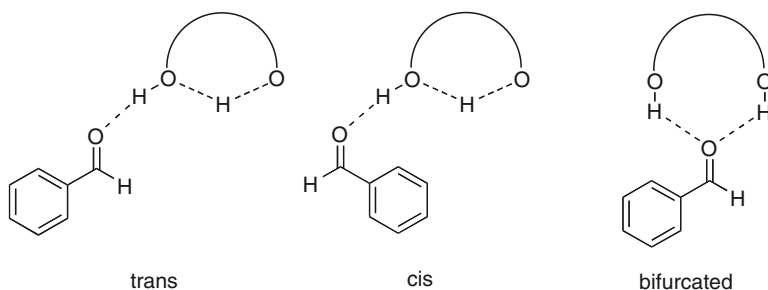


Fig. 18 Application of the ONIOM method to the model system of the reaction

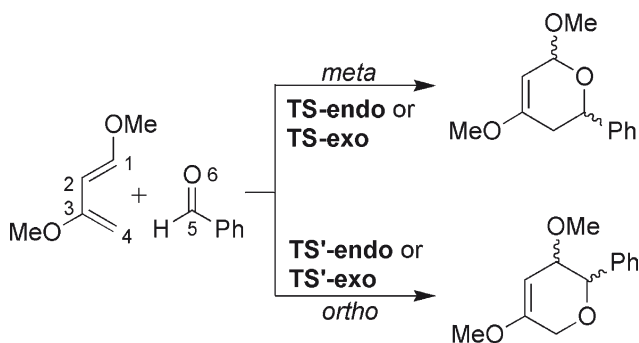


Scheme 10 Possible intermolecular hydrogen bonding patterns between benzaldehyde and TADDOL

Upon formation of the *trans* adduct of benzaldehyde with TADDOL, the *intramolecular* hydrogen bond is shortened by 0.128 Å, and the acidity of the substrate binding hydroxy function is increased. The length of the *intermolecular* hydrogen bond to the carbonyl group is 1.825 Å.

To rationalize the enantioselectivity of the TADDOL-catalyzed HDA reaction between Danishefsky's diene and benzaldehyde, eight possible diastereomeric transition states of different regio- and stereochemistry should in principle be considered for comprehensive analysis. The cycloaddition between the model diene and benzaldehyde can take place along two regio-isomeric “meta” (C1–O6, C4–C5 bond formation) and “ortho” (C1–C5, C4–O6 bond formation) reaction channels.³ For both of these pathways, an *exo*- and an *endo*-approach can be formulated (Scheme 11) [64].

The energy of the localized transition state for the “ortho” route (uncatalyzed reaction) is 14 kcal mol^{−1} higher than that of the “meta” channel. Therefore, the “ortho” channel can be excluded. Unlike the uncatalyzed transformation, the TADDOL-catalyzed HDA



Scheme 11 Regio- and stereoselectivity issues of the model hetero-Diels–Alder cycloaddition

³Please note that the “ortho/meta” terminology is used in a different way in ref. 58. The assignment used in here is based on the original formalism by Diels and Alder

reaction exhibited a clear energetic preference for the endo- over the exo-approach. Thus, only endo transition states were considered. The number of possible reaction paths/transition states is thus reduced from eight to two, namely endo-approach with *re*- or *si*-face attack of the model diene to the activated benzaldehyde.

As can be seen from Fig. 19, the activation energy of the reaction in the presence of the 1-naphthyl substituted TADDOL catalyst was reduced by 10.2 kcal mol⁻¹, in comparison with the uncatalyzed reaction (20.2 kcal mol⁻¹). The reaction proceeds via a concerted but asynchronous pathway, and no zwitterionic intermediate or transition state corresponding to a stepwise Mukaiyama-aldol type pathway could be located.

The partial charges of the aldehyde carbonyl group are stabilized by an intermolecular hydrogen bond to the TADDOL catalyst. In the organocatalytic reaction, the C–C bond formation has progressed further (due to the more positively polarized carbonyl carbon atom of the benzaldehyde) whereas the C–C bond formation lags behind in the uncatalyzed reaction. The NBO charges indicate that there is a considerable charge transfer of 0.49 e⁻ from the donor diene to the activated aldehyde acceptor in the transition state (**TS-(Si)-4b**), but in the uncatalyzed case the transferred charge does not exceed 0.27 e⁻ (*endo TS*). This is due to the fact that both the

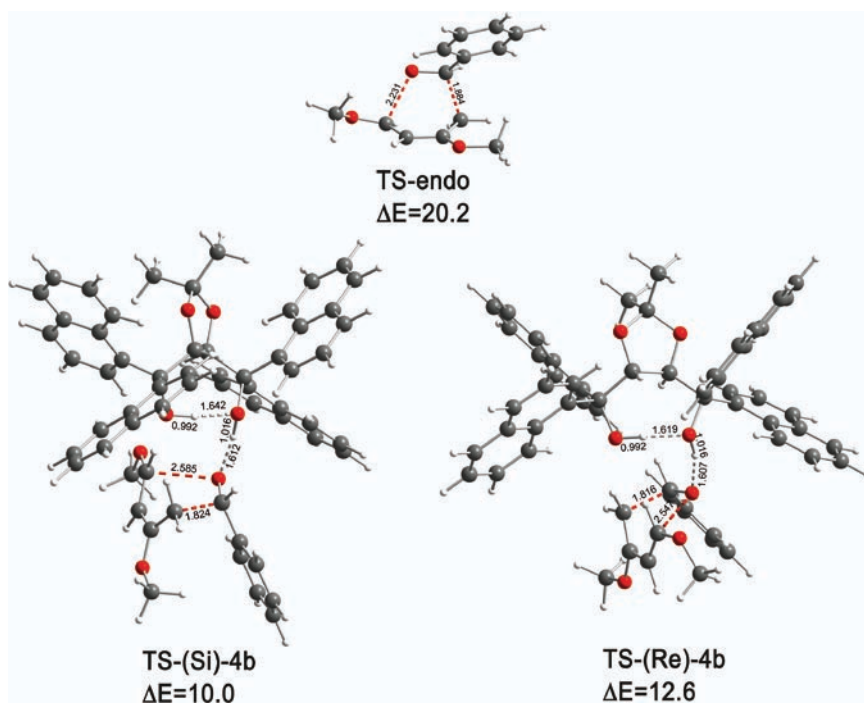


Fig. 19 Transition states involved in the cycloaddition (endo-mode) of the model diene with benzaldehyde, both in the absence (**TS-endo**) and the presence (**TS-(Si)-4b**, **TS-(Re)-4b**) of the TADDOL catalyst; corresponding activation energies [kcal mol⁻¹](B3LYP/6-31G(d)//B3LYP/6-31G(d):PM3)

cooperative intramolecular hydrogen bond (shortened by about 0.08 Å) and the intermolecular hydrogen bond to the substrate (shortened by about 0.2 Å) reinforce each other cooperatively in the transition state, and stabilize the developing negative charge at the carbonyl oxygen atom during nucleophilic attack. How can the energetic preference of **TS-(si)-4b** over **TS-(re)-4b** be rationalized? Obviously, nonbonding interactions of the 1-naphthyl groups of the TADDOL catalyst with the phenyl ring of benzaldehyde in the *re*-transition state effect the observed enantioselectivity.

4 Epilog

Multiple and specific hydrogen bonding has been recognized as a highly efficient motif not only in enzymatic catalysis, but nowadays also in organocatalysis. Much of our current mechanistic understanding is based on computational analysis of such processes, ideally in combination with kinetic and spectroscopic methods. It appears that naturally evolved catalytic motifs, such as the oxyanion hole, can be “side-tracked” to accelerate a number of “anthropogenic” reactions involving intermediates/transition states with a negatively charged oxygen atom. It is tempting to speculate which other types of enzymatic rate accelerations by hydrogen bonding might be suitable for adaptation to organocatalysis!

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Enamine Catalysis

Petri M. Pihko, Inkeri Majander, and Anniina Erkkilä

Abstract The reversible reaction of primary or secondary amines with enolizable aldehydes or ketones affords nucleophilic intermediates, enamines. With chiral amines, catalytic enantioselective reactions via enamine intermediates become possible. In this review, structure-activity relationships and the scope as well as current limitations of enamine catalysis are discussed.

Keywords Aldehydes and ketones • Alpha-functionalization • Amines • Enamine catalysis • Organocatalysis

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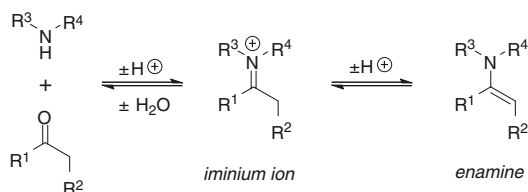
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1 Introduction

As nucleophiles, simple alkenes are typically so unreactive that only highly active electrophiles, such as carbocations, peroxides, and halogens will react with them. For the generation of carbon-carbon bonds, milder methods will often be required. Fortunately, it is possible to increase the reactivity of alkene-type π -nucleophiles by introducing electron-donating substituents. Substitution of one H with an OH or OR gives an *enol* or a *vinyl ether*, which are already much better nucleophiles. Using nitrogen instead of oxygen, one obtains even better nucleophiles, *enamines*. Enamines are among the most reactive neutral carbon nucleophiles, exhibiting rates that are even comparable to some charged nucleophiles, such as enolates [1, 2].

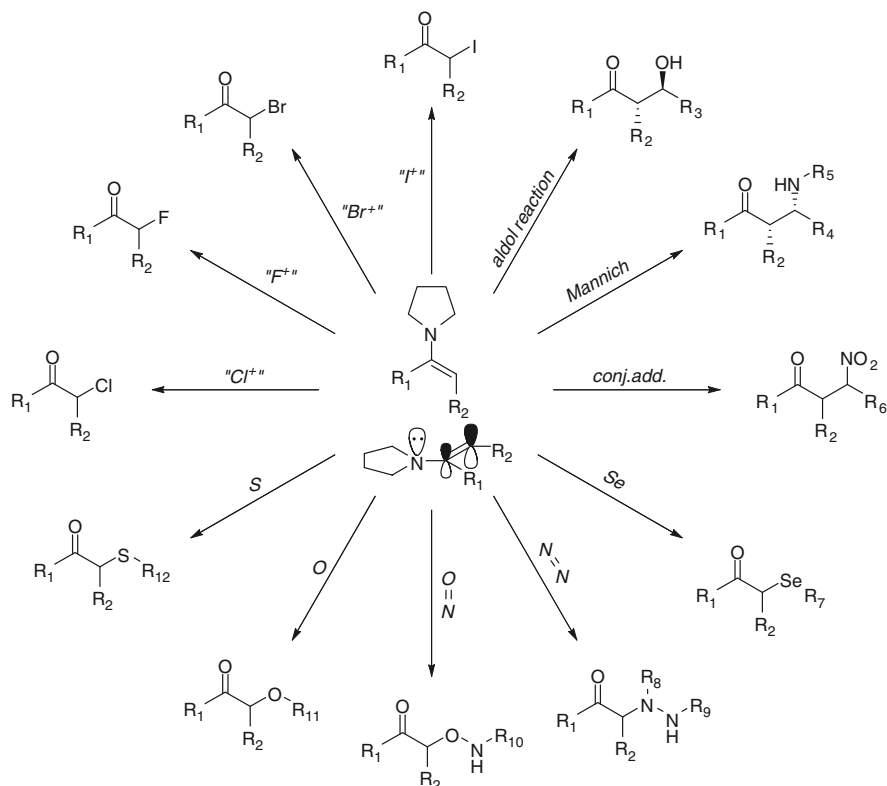
Most enamines, unfortunately, are sensitive to hydrolysis. The parent enamine, *N,N*-dimethylvinylamine, has in fact been prepared [3], but appears to be unstable. Enamines of cyclic ketones and many aldehydes can readily be isolated, however [4–7]. The instability of enamines might at first appear to diminish the utility of enamines as nucleophiles, but actually this property can be viewed as an added benefit: enamines can be readily and rapidly generated *catalytically* by using a suitable amine and a carbonyl compound. The condensation of aldehydes or ketones with amines initially affords an imine or iminium ion, which then rapidly loses a proton to afford the corresponding enamine (Scheme 1).



Scheme 1 Enamine formation

This catalytic enamine formation is limited to aldehydes and ketones as starting materials – it does not appear to be possible to prepare corresponding “enamines”, i.e. *N,O*-ketene acetals, from esters in this fashion. Nevertheless, the preparation of simple, reactive nucleophiles from normally electrophilic species, aldehydes and ketones, in a catalytic fashion sounds highly attractive. Furthermore, the catalytic nature of these reactions allows the use of *chiral amines*, and the further possibility that these reactions can be rendered enantioselective. Enamines react readily with a wide variety of electrophiles, and the range of reactions that can be catalyzed by enamine catalysis is summarized in Scheme 2.

As a catalytic concept, asymmetric enamine catalysis has been the subject of several recent reviews [8–23]. In this concept review, we will focus on some of the key aspects of this mode of activation, and probe the current limitations and possible future directions of enamine catalysis.



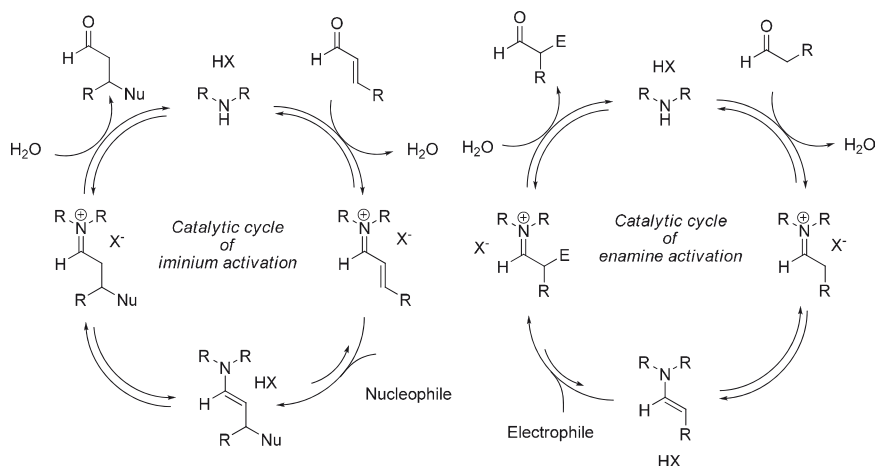
Scheme 2 A range of transformations can be promoted by enamine catalysis

2 Catalytic Formation of Enamines

2.1 A Brief History of Enamine Catalysis

The development of enamine catalysis parallels that of iminium catalysis ([Scheme 3](#)) [24]. Like iminium catalysis, the concept took a long time to mature, and also required a key discovery – the discovery of intermolecular proline-catalyzed aldol reactions by List and coworkers in 2000 [23] – to set the field in motion. The timeline of historical developments of enamine catalysis is outlined in [Scheme 4](#).

The word “enamine” was coined in 1927 by Wittig [27]. However, at that time, enamines were usually not considered as reactive intermediates. An early example of enamine catalysis that was not explicitly recognized as enamine-based reaction was the reaction of isatin with ketone nucleophiles (acetone and acetophenone), first published by Lindwall and coworkers in 1932 [28, 31]. Later, the interconversion of iminium ions and enamines in enzymatic reactions was recognized by Westheimer [32, 354]. The first person to propose a modern enamine-based



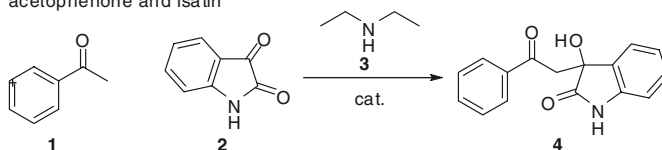
Scheme 3 Parallels between iminium and enamine catalysis

mechanism for a catalytic reaction was Rutter, who in 1964 suggested an essentially complete mechanism for aldolase reactions [29].

In stoichiometric enamine chemistry, the Stork group developed a range of highly useful transformations in the 1950s and 1960s [5]. The first really useful enantioselective enamine-catalyzed process, however, was the intramolecular aldol reaction known as the Hajos–Parrish–Eder–Sauer–Wiechert process [30, 33, 34]. Perhaps surprisingly, although the enamine-based mechanisms had been fully accepted for Nature's aldolase enzymes, the simple enamine mechanism for this reaction only became universally accepted in the 2000s. This was partly a result of conflicting data – in initial studies, Agami found a small nonlinear effect that would have required the presence of more than one molecule of proline in the transition state [35–40] but also partly due to the knowledge gap between organic chemists and biochemists of the time, a point eloquently made by Barbas [41]. It was only after the discovery of the intermolecular proline-catalyzed reaction in 2000 [23] and further studies by List and coworkers as well as several key modeling studies by the Houk group [42, 43] that the universality of the enamine catalysis concept became widely

1927 Wittig coins the term "enamine"

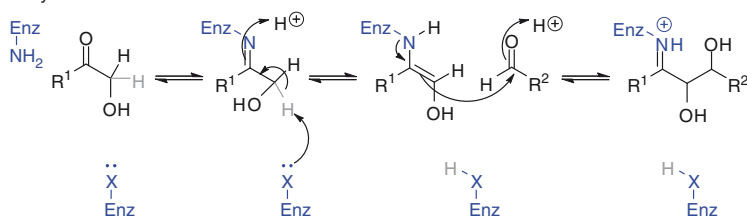
1932 Lindwall discovers secondary amine-catalyzed aldol reaction between acetophenone and isatin



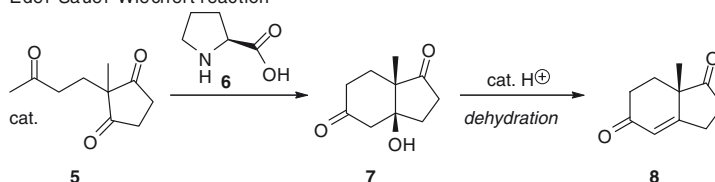
1954 Stork demonstrates that a variety of different α -acylations and α -alkylations are feasible with stoichiometric enamines

Scheme 4 Historical development of enamine catalysis [25–30]

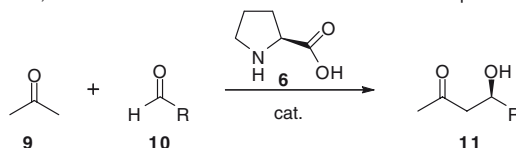
1964 Rutter proposes an essentially correct enamine-based mechanism for aldolase enzymes



1971 Discovery of the proline-catalyzed intramolecular aldol reaction - the Hajos-Parrish-Eder-Sauer-Wiechert reaction



2000 List, Barbas and Lerner discover the intermolecular proline-catalyzed aldol reaction



Scheme 4 (Continued)

accepted in the context of one of its oldest examples, the intramolecular aldol reaction. In retrospect, the simplicity of the enamine catalysis concept looks obvious, but as we all know, only in hindsight do we all have perfect vision.

2.2 Structural Requirements of Enamine Catalysis

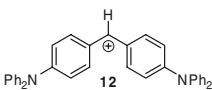
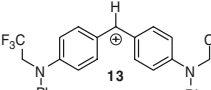
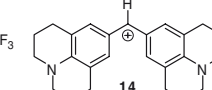
2.2.1 The Structure of the Amine and the Resulting Enamine

In general, the most nucleophilic enamines are those where the nitrogen lone pair is most effectively delocalized. This requires effective overlap of the lone pair with the $C = C$ π bond and maximum flattening (sp^2 hybridization) of the enamine nitrogen.

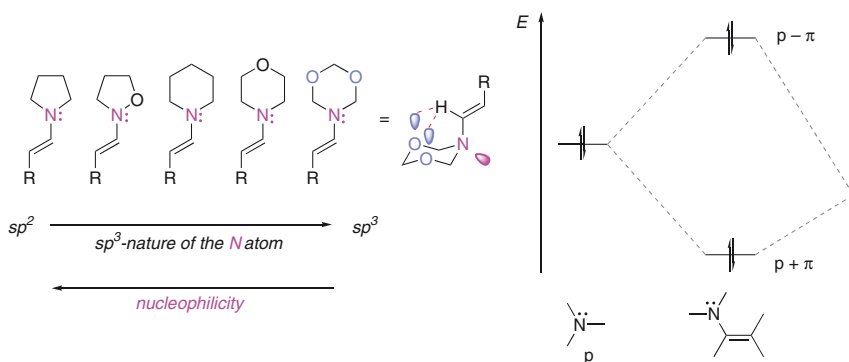
The structure of the amine component has a profound influence on the propensity to p - π delocalization. As an example, enamines derived from cyclic five-membered ring amines, such as pyrrolidine, are more than thousand times more nucleophilic than those derived from six-membered ring amines. In a series of fundamental studies, the Mayr group has determined nucleophilicities of different enamines, ranging from highly reactive pyrrolidine-derived amines to relatively

passive enaminones and pyrroles [44]. Differently substituted benzhydrylium ions (**12–14**, see Table 1) were used as reactivity probes. Some of these results are summarized in Table 1.

Table 1 Nucleophilicities of different enamines [44]

 12  13  14				
Enamine	Nucleophilicity parameter <i>N</i>	Rate constant <i>k</i> with 14	Rate constant <i>k</i> with 12	Rate constant <i>k</i> with 13
 15	15.91	3.32×10^5	—	—
 16	14.91	4.59×10^4	—	—
 17	15.06	4.57×10^4	—	—
 18	13.36	1.41×10^3	—	—
 19	11.40	3.35×10^1	3.38×10^5	—
 20	12.06	—	7.44×10^5	—
 21	8.52	—	—	2.02×10^4
 22	5.02	—	1.93	—

The high reactivity of pyrrolidine-derived enamines can be explained by the increased propensity of five-membered rings to accept sp^2 -hybridized atoms into the ring compared to the six-membered rings. This phenomenon was first formulated and explained by Herbert C. Brown and coworkers in 1954 [45]. A sp^2 hybridized nitrogen atom allows better overlap between the $C = C$ π system and the nitrogen lone pair and therefore better delocalization of the nitrogen lone pair. This increases the nucleophilicity of the enamine (a HOMO-raising effect, Scheme 5). As such, the reactivity of enamines follows the order pyrrolidine-



Scheme 5 Reactivity profile of enamines [2]

derived > acyclic amine-derived > piperidine-derived enamines [2, 44]. Additional oxygen substituents further reduce the reactivity of enamines, and therefore morpholine derivatives are even less reactive than piperidine derivatives.

Therefore it is perhaps not surprising at all that most of the successful enamine catalysts are based on the pyrrolidine skeleton. A constellation of typical enamine catalysts is presented in Fig. 1. Catalysts with a five-membered ring are clearly dominant, whereas other ring sizes are clearly less popular. In recent years, primary amines have emerged as interesting alternatives to the cyclic amine catalysts (top left cloud in Fig. 1).

2.2.2 Additional Assistance from Acids and Hydrogen Bonding

In enantioselective enamine catalysis, the enamine can control the approach of the electrophile either by the steric bulk of the enamine or by directing the electrophile with an activating group. As can be readily observed with relatively unreactive electrophiles, such as aldehydes, ketones or imines, additional assistance for catalysis can be provided by suitably positioned hydrogen bond donors and/or other acids (Scheme 6) [46].

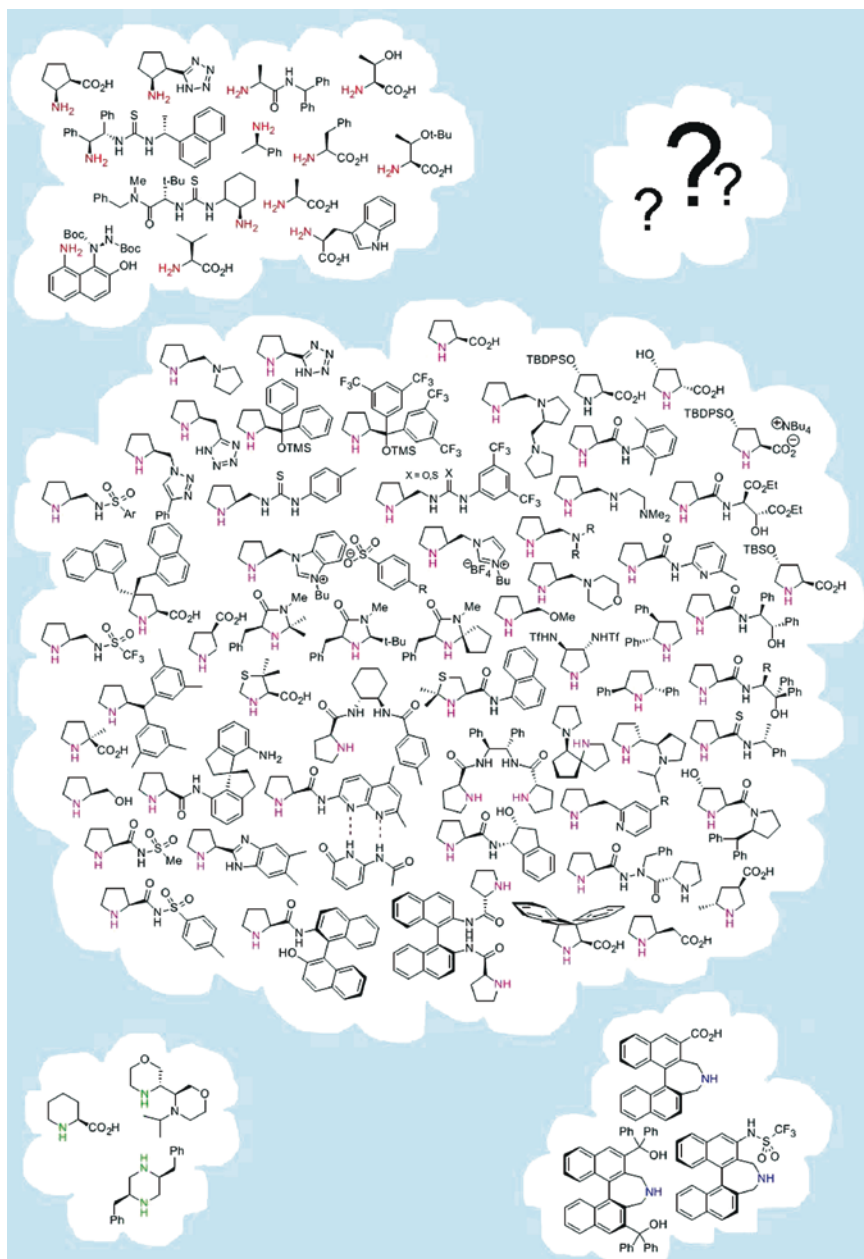
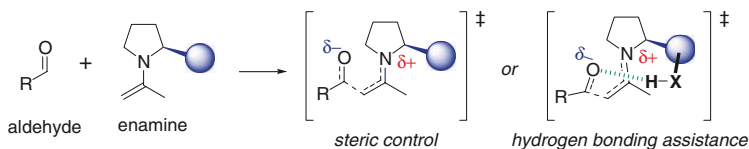
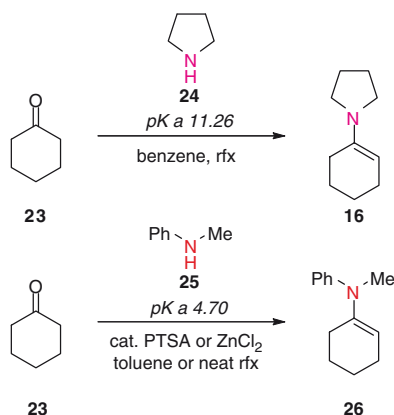


Fig. 1 Typical enamine catalysts



Scheme 6 Steric control vs hydrogen bonding control in enamine catalysis

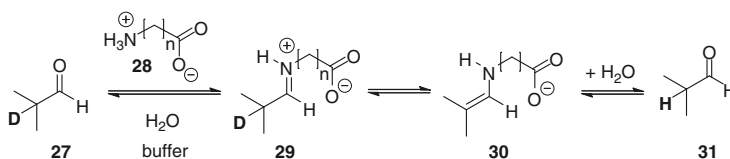
In addition, acid cocatalysts can assist the formation of the enamine. With very basic, nucleophilic amines, such as pyrrolidine and its derivatives, acid catalysis is not necessarily required for enamine formation. However, with less basic amines, Brønsted or Lewis acids are often used to assist in enamine formation ([Scheme 7](#)).



Scheme 7 Effect of pK_a on the enamine formation

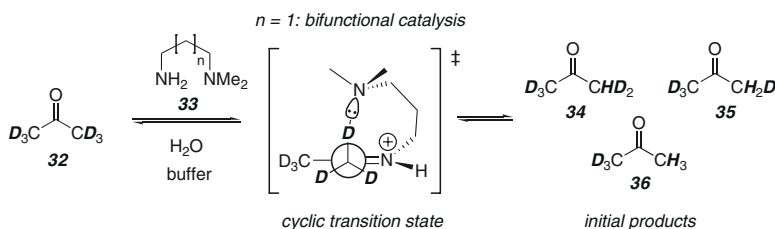
Enamine formation under acid catalysis has been extensively studied by several groups [47–61]. The abstraction of an α -proton from the initially formed iminium ion is a key step in the catalytic process. Whereas a strong acid cocatalyst has a strong stabilizing effect on the iminium ion and aids its formation, a basic cocatalyst will assist for the enamine forming step. Thus the basicity of the counteranion of the acid cocatalyst determines the rate of enamine formation. While a strong acid is beneficial in the first iminium forming step, its conjugate base has only a weak ability to remove the α proton. On the other hand, a relatively strong counter base would favor the formation of the enamine, but the initial formation of the iminium ion would be somewhat compromised. Hence both general acid and base cocatalysis has to be considered in enamine formation in addition to the choice of the catalytic amine species.

Hine has demonstrated that simple amino acids, such as glycine and β -alanine, are not capable of intramolecular deprotonation in the reaction with isobutyraldehyde-2-d (Scheme 8) [62]. Apparently, the carboxylate moiety in the iminium ion intermediate **29** is a relatively weak base and, as such, external bases, present in the buffer used (e.g. acetate ions), are largely responsible for the formation of the enamine intermediate **30**.



Scheme 8 Amino acid-catalyzed dedeuteration of isobutyraldehyde-2-d

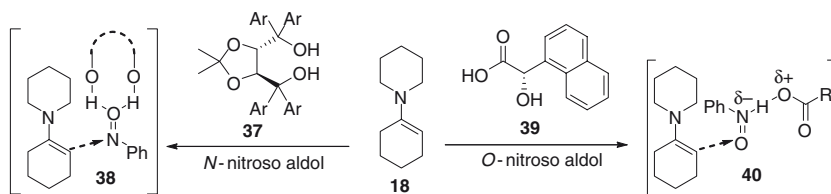
In contrast to amino acids, the Hine group demonstrated that certain 1,3-diamines are capable of bifunctional catalysis, as evidenced by the anomalously high rates of enamine formation compared to 1,2- and 1,4-diamines. They explained this result by invoking a cyclic transition state where the 3-dimethylaminopropylamine catalyst forms an iminium ion that is dedeuterated by the proximal dimethylamino group (Scheme 9). The deuterium exchange reactions with acetone- d_6 were first order in amine and led to the rapid formation of mono-, di- and triprotonated products. Apparently, the iminium ions undergo deuterium exchange and hydrolyze to acetone at almost comparable rates.



Scheme 9 Enamine formation via bifunctional catalysis

Momiyama and Yamamoto have recently demonstrated that acid cocatalysts can even influence the outcome of enamine-mediated reactions [63]. In their studies of the acid-catalyzed *O*- and *N*-nitroso aldol reaction, they found that the nature of the acid catalyst dictates the regioselectivity of the reaction between preformed enamine species. A carboxylic acid catalyst promoted the *O*-nitroso aldol reaction whereas a hydrogen bonding catalyst catalyzed the formation of an *N*-adduct, both in high enantioselectivities (Scheme 10).

Gryko and coworkers studied the influence of an acid additive in the aldol reaction catalyzed by a proline derivative equipped with an existing hydrogen bonding



Scheme 10 Different acid catalysts lead to opposite regioselectivity

functionality (thioamide) [64, 65]. They observed that the addition of one equivalent of acid per catalyst molecule enhanced the reaction rates significantly. A closer inspection revealed that the nature of the acid additive has strong influence on the reaction efficiency. A strong dependence was detected between the increasing strength of the acetic acid derivatives and both the reaction rate and enantioselectivity (Table 2). The catalyst salts of stronger inorganic acids as well as sulfonic acids failed to promote the reaction. By NMR studies, the authors were able to observe that the formation of iminium species between the catalyst salt and substrate correlated to high reaction efficiency. The iminium ion likely equilibrates with the reactive enamine and thus enhances the reaction rate. Additionally, the acid cocatalyst may stabilize the iminium ion of the formed product and push it towards hydrolysis instead of retroaldolization which might compromise the reaction selectivity. Other groups have reported that the addition of TFA cocatalyst to aldol reaction catalyzed by alternative proline derivatives affords similar results [66, 67].

Table 2 The influence of an acid additive in the L-prolinethioamide-catalyzed aldol reaction

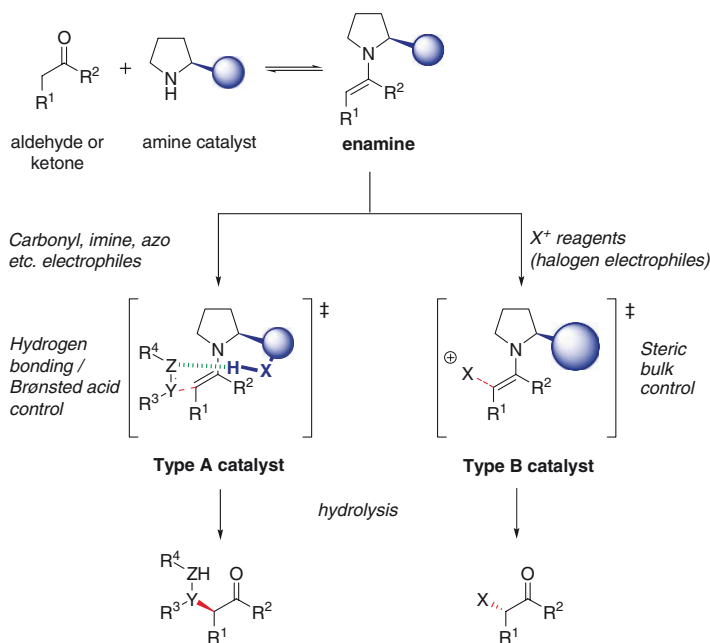
Entry	HX	pKa	Yield [%]	ee [%]
1	AcOH	4.76	20	86
2	HCO ₂ H	3.75	24	89
3	MIA	3.12	32	91
4	MBA	2.86	28	94
5	MCA	2.85	60	93
6	DCA	1.29	99	93
7	DFA	1.24	95	92
8	TFA	0.26	81	94

The effect of basic additive as well as water in proline catalyzed aldol reaction has been studied extensively [192]. Furthermore, Zhou and Shan disclosed that hydrogen bonding additives such as weak Brønsted acids successfully enhance both the efficiency and the selectivity of the reaction. They suggested that their hydrogen bonding BINOL additive enhanced the catalytic ability of proline by additional hydrogen bonding interactions between the catalyst, additive, and approaching substrate [68].

Only a few reactions with a purely external cocatalytic acid source have been published, and very few screening studies of the cocatalysts are available. Barbas and coworkers studied the effects of Lewis and Brønsted acids in the pyrrolidine-catalyzed aldol reaction [69]. They observed that acetic acid provided over twofold greater initial reaction rates compared to the same reaction without acid. Interestingly, stronger acids such as TfOH, PTSA and CSA gave slower reaction rates. Subsequently, Peng and coworkers disclosed beneficial effect of substituted phenols in the same reaction [70]. Decreasing acidity of the cocatalyst increased the reaction rates. These observations are consistent with the requirement of general acid catalysis for the iminium formation and the general base catalysis for the subsequent enamine formation.

2.2.3 Conclusion – Two Types of Enamine Catalysts

In conclusion, successful enantioselective enamine catalysts can be divided into two groups [16] (Scheme 11):

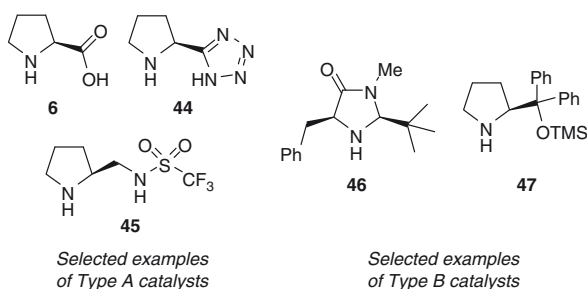


Scheme 11 The two modes of stereochemical steering with enamine catalysis

Type A: Includes an internal acid/hydrogen bond donor to orient the approach of the electrophile

Type B: A bulky, nonacidic group is used to orient the enamine and to block the approach of the electrophile from one side only

Type A enamine catalysts include simple amino acids, such as proline **6**, and most of their derivatives (such as the tetrazole **44** and various sulfonamides, e.g. **45**). They are typically used for aldol, Mannich, α -amination and α -oxygenation reactions – these are all reactions where the electrophile can readily be activated by hydrogen bonding (Scheme 12) [8, 9, 12, 46].



Scheme 12 Selected examples of Type A and Type B catalysts

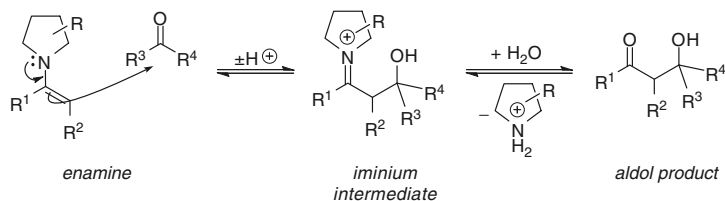
Type B enamine catalysts have been developed more recently. They include the diarylprolinol ethers (developed by the Hayashi and Jørgensen groups, e.g. **47** and its derivatives) [71–75] as well as the MacMillan imidazolidinone catalysts (e.g. **46**) [76–78]. They excel in reactions where hydrogen bonding assistance is either not required or is not essential, such as α -halogenation reactions as well as some conjugate addition reactions (Scheme 12).

3 Highlights of Enamine Catalysis

In the following discussion, key reactions of enamine catalysis are summarized. Present limitations of each method are also discussed. For more detailed treatment of the reactions, the original publications as well as recent comprehensive reviews [8–23] should be consulted.

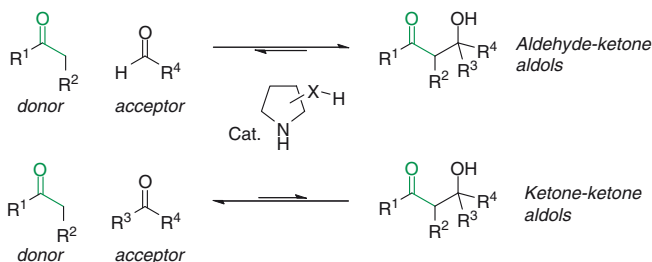
3.1 Aldol and Related Reactions

Among the electrophilic reaction partners of the enamine nucleophiles, aldehydes and ketones are arguably the most important class. The addition of an enamine to a carbonyl compound affords aldol products after hydrolysis (Scheme 13). In this process, one or two new stereogenic centers and one carbon-carbon bond are formed.



Scheme 13 Enamine-catalyzed aldol reaction

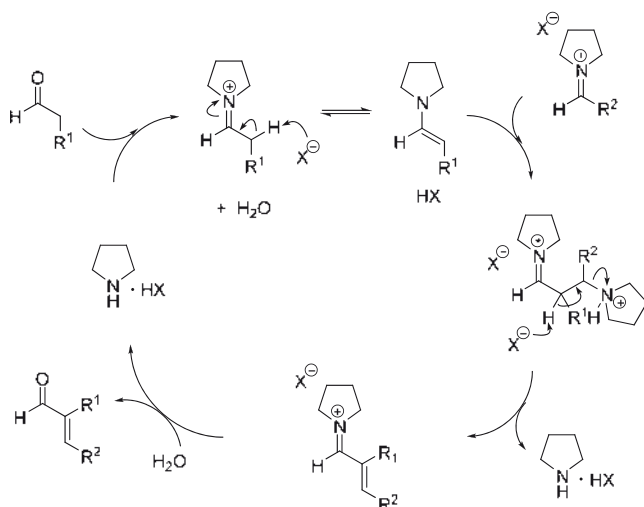
Usually, the component that forms the enamine is called *aldol donor*, and the electrophilic carbonyl component is called *acceptor* (Scheme 14).



Scheme 14 Equilibria in aldol reactions with ketone and aldehyde acceptors

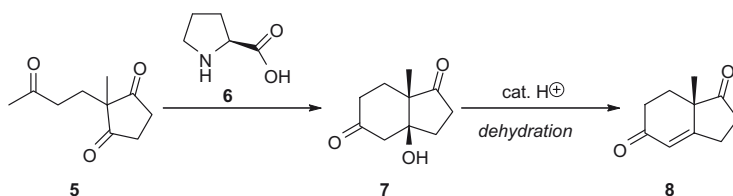
In spite of the attractiveness of the aldol manifold, there are several problems that need to be addressed in order to render the process catalytic and effective. The first problem is a thermodynamic one. Most aldol reactions are reversible. Furthermore, the equilibrium is also just barely on the side of the products in the case of simple aldehyde-ketone aldol reactions [79, 80]. In the case of ketone-ketone aldol reactions, the equilibrium generally lies on the side of starting materials (Scheme 14). Overall, this means that relatively high concentrations of starting materials should be used, and very often one of the components must be used in excess.

A second, even more worrying problem is the side reaction, the formation of condensation products. This process is essentially irreversible in most cases. The condensation products can arise either from the aldol product or directly through a Knoevenagel–Mannich type reaction where the enamine reacts with an iminium ion [26, 81, 82]. The condensation process requires only an external Brønsted acid, whereas the aldol process appears to require simultaneous activation of the carbonyl electrophile by an *internal* Brønsted acid/hydrogen bond donor (Scheme 15).



Scheme 15 Double activation of reaction components by an enamine/iminium mechanism [81]

The delicateness of the aldol protocol has perhaps been one of the factors why enamine catalysis of the aldol reaction did not emerge until the 1970s. The Hajos–Parrish–Eder–Sauer–Wiechert reaction [30] (Scheme 16) was an important early example of an *intramolecular* enamine-catalyzed aldol reaction. However, it was not until 2000 when List, Barbas and Lerner demonstrated that the same reaction can also be performed in an *intermolecular* fashion, using proline as a simple enamine catalyst [26].



Scheme 16 The Hajos–Parrish–Eder–Sauer–Wiechert reaction

Since 2000, remarkable advances in the utility of the enamine-catalyzed aldol reaction have been made [83]. A massive effort has been devoted to the development of more effective variants of proline [13, 26, 64, 68, 84–174]. In addition, alternative amino acids and peptides bearing primary amino groups [175–184] as

well as axially chiral amines [185–187], chiral imidazolidinones [188] and cinchona alkaloid-derived amines [189] have been used successfully as aldol catalysts. It should be noted, however, that most of these catalysts do not exceed proline in their efficiency. The rates as well as the diastereoselectivities of the reaction appear to be improved by the addition of water to the reaction mixture [190–193]. The Hayashi [96] and Barbas [141] groups have both demonstrated that aldol reactions can even be performed on water or in aqueous media using hydrophobic derivatives of proline.

For improvements in the enantioselectivity of the aldol reactions, the highly active catalysts developed by Gong and coworkers [194–196] as well as further improvements by Singh and coworkers [197] deserve to be mentioned (Fig. 2). These catalysts are one of the most active catalysts for the direct aldol reaction between acetone and various aldehydes, with very high enantioselectivities. The Gong group has also presented computational evidence [198] for an interesting double hydrogen bonding activation mode [199] with these catalysts.

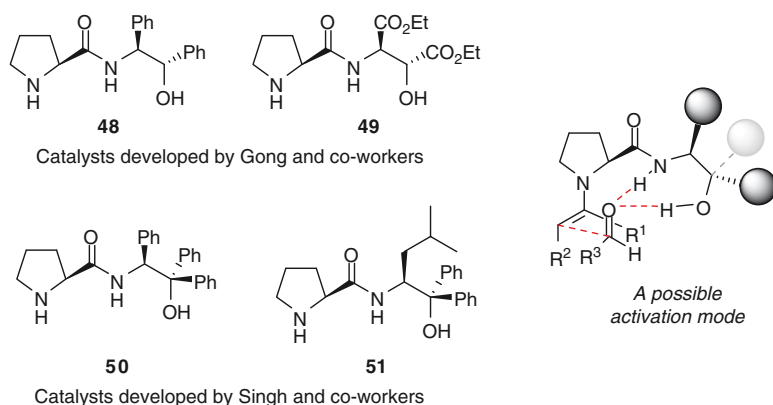
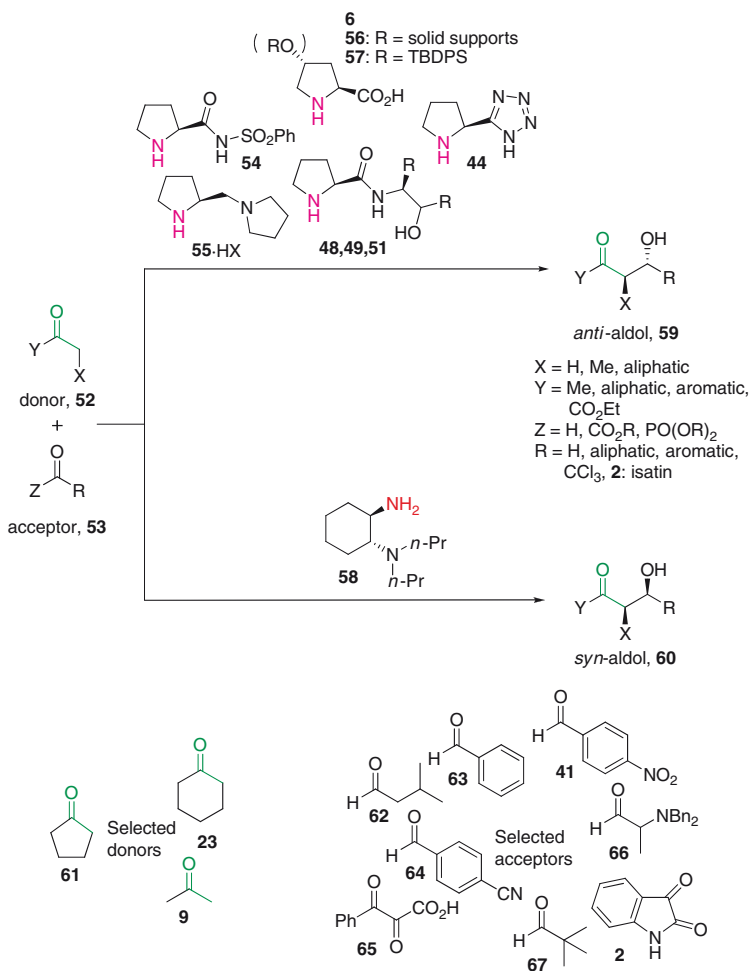


Fig. 2 Double hydrogen bonding enamine catalysts developed by Gong and Singh

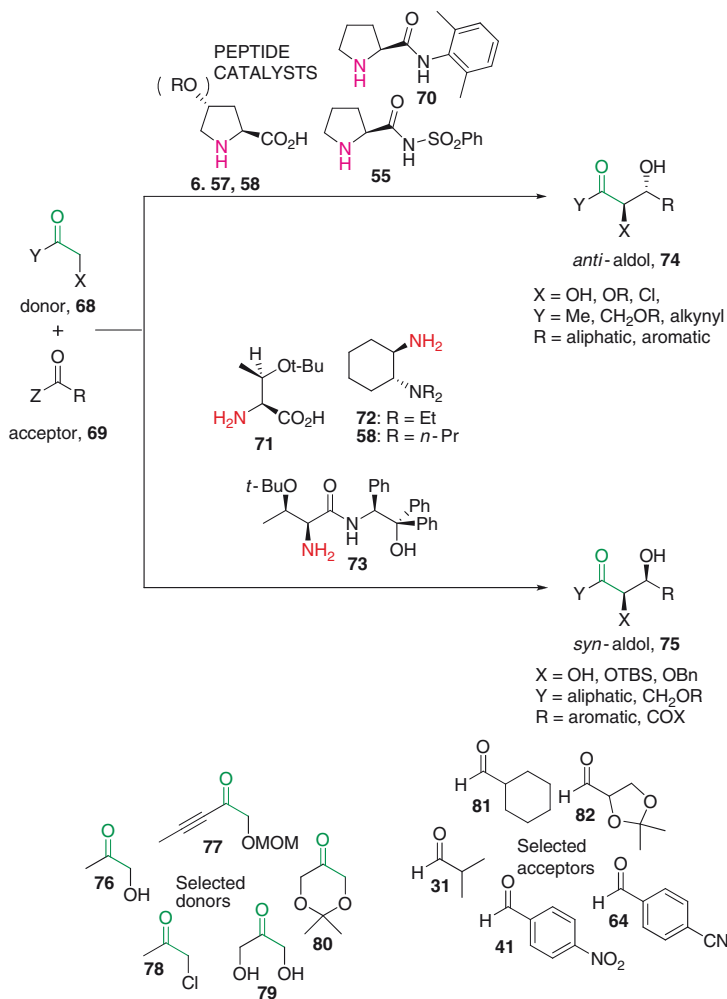
3.1.1 Ketone-Aldehyde and Ketone-Ketone Aldol Processes

Typical starting materials, catalysts, and products of the enamine-catalyzed aldol reaction are summarized in Scheme 17. In proline-catalyzed aldol reactions, enantioselectivities are good to excellent with selected cyclic ketones, such as cyclohexanone and 4-thianone, but generally lower with acetone. Hindered aldehyde acceptors, such as isobutyraldehyde and pivalaldehyde, afford high enantioselectivities even with acetone. In general, the reactions are *anti* selective, but there are already a number of examples of *syn* selective enamine aldol processes [200, 201] (Schemes 17 and 18, see below). However, *syn* selective aldol reactions are still rare, especially with cyclic ketones.



Scheme 17 Asymmetric aldol reactions with ketone donors

Ketone donors bearing α -heteroatoms are particularly useful donors for the enamine-catalyzed aldol reactions (Scheme 18). Both *anti* and *syn* aldol products can be accessed in remarkably high enantioselectivities using either proline or proline-derived amide, sulfonamide, or peptide catalysts. The *syn* selective variant of this reaction was discovered by Barbas [179]. Very recently, Luo and Cheng have also described a *syn* selective variant with dihydroxyacetone donors [201], and the Barbas group has developed improved threonine-derived catalysts **71** (Scheme 18) for *syn* selective reactions with both protected and unprotected dihydroxyacetone [202].

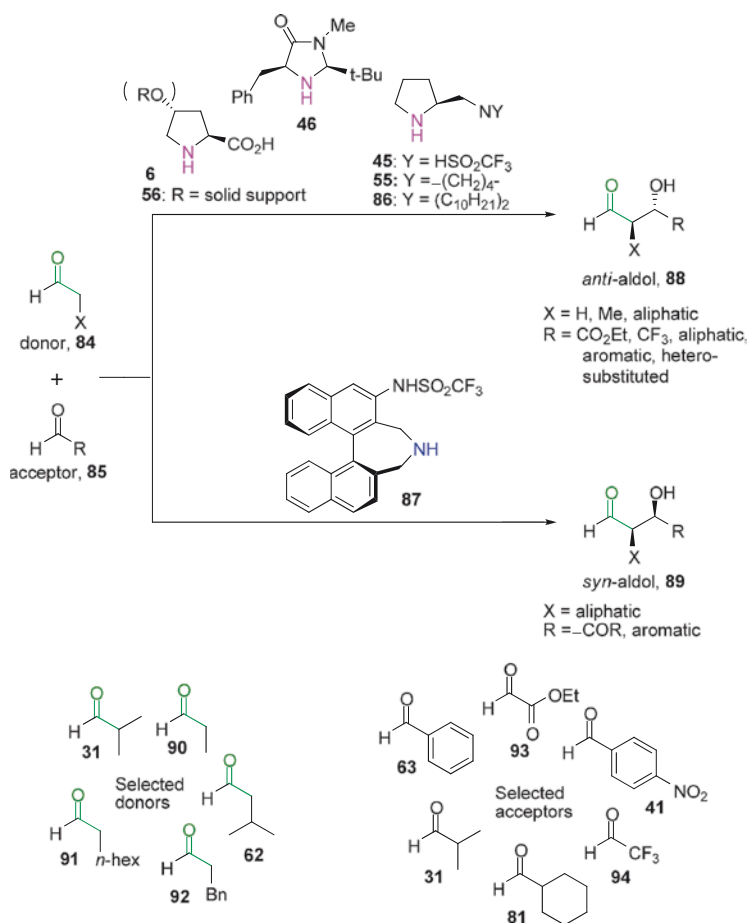


Scheme 18 Asymmetric aldol reactions with heterosubstituted ketone donors

3.1.2 Aldehyde-Aldehyde Aldol Processes

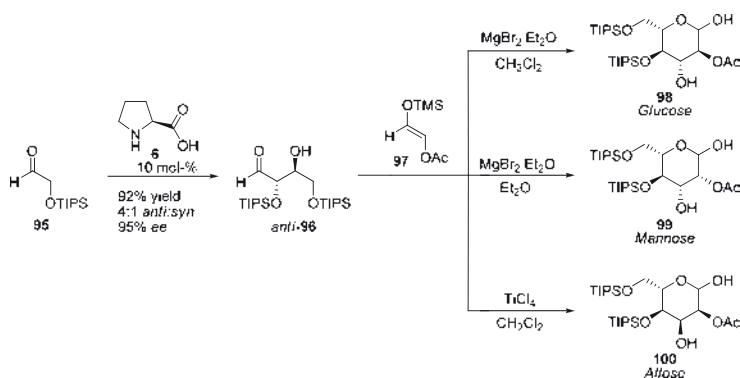
Unlike most enantio- and diastereoselective direct aldol processes, the enamine-catalyzed aldol reactions are also feasible with aldehyde donors. In a milestone paper, Northrup and MacMillan reported in 2002 that aldehyde-aldehyde aldol

reactions can be carried out with proline [145]. They demonstrated that a range of aliphatic aldehydes can be dimerized, with impressive enantioselectivities (>97% ee in most cases). Importantly, different combinations of aldehyde acceptors and donors were possible if the more reactive donor aldehyde was added via a syringe pump. Recently, Maruoka and coworkers also discovered a *syn* selective variant of the crossed-aldol reaction with aromatic and activated aldehydes as acceptors [187]. What remains to be discovered is the *syn* selective variant of the crossed aldol reaction with aliphatic aldehydes (Scheme 19).



Scheme 19 Asymmetric aldol reactions with aldehyde donors

As demonstrated by MacMillan and coworkers, α -oxygenated aldehydes are very good reaction partners in the aldehyde-aldehyde crossed-aldol reaction. The products are tetroses, and one further aldol step affords a range of hexoses, i.e. differentially protected monosaccharides, in a two-step synthesis (Scheme 20) [203].

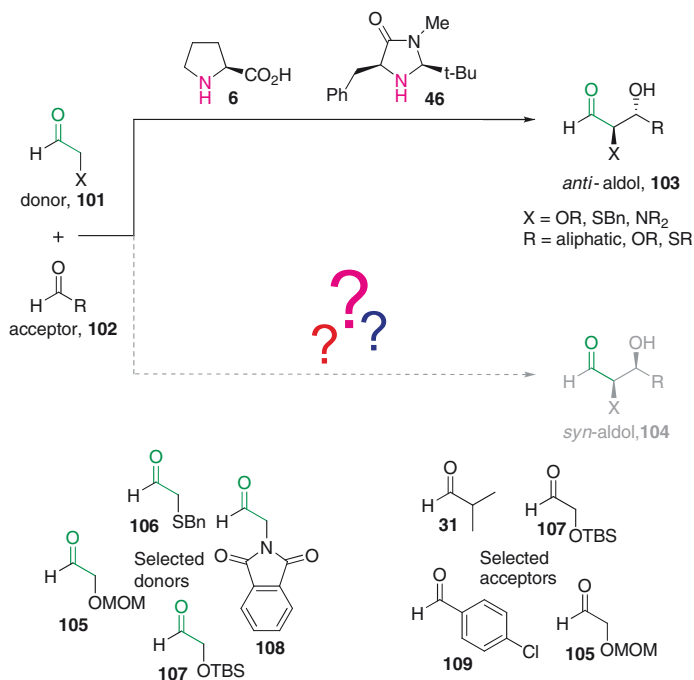


Scheme 20 A two-step aldol-based carbohydrate synthesis by Macmillan and co-workers

Aldehydes bearing α -hetero substituents also typically afford *anti* products, and the general solution to *syn* selective α -heteroatom substituted aldehyde-aldehyde aldol processes via enamine catalysis also still remains to be discovered. Nevertheless, the *anti* process is remarkably useful because a variety of highly substituted aldehydes can be accessed in a single operation using only very inexpensive catalysts, such as proline **6** or the phenylalanine-derived imidazolidinone **46** (Scheme 21) [114, 116, 117, 119–121, 188].

3.1.3 Substrate Scope and Current Limitations

A particularly acute problem in expanding the substrate scope of the reaction is the scope of the acceptors. The catalyst must somehow differentiate between the donor (to be activated via an enamine) and the acceptor (to be activated only by hydrogen bonding). It is a relatively trivial task to perform an aldol reaction with a nonenolizable acceptor, especially an aromatic aldehyde, and a good donor, such as acetone. However, the use of two substrates that are both capable of significant enolization is a considerably more difficult problem. In most cases, chemists circumvent this problem by generating the enolate in a separate enolizing step. This requires stoichiometric amounts of the enolizing reagent and therefore this tactic cannot be used under catalytic conditions.



Scheme 21 Asymmetric aldol reactions with heterosubstituted aldehyde donors

Ketones cannot generally be used as acceptors, at least not directly, due to unfavorable equilibrium between the aldol product and the starting ketones. However, highly reactive ketones [87, 88], such as isatin **2** [95] (Fig. 3) and α -keto phosphonates (e.g. **112**) [110] can readily be used as acceptors.

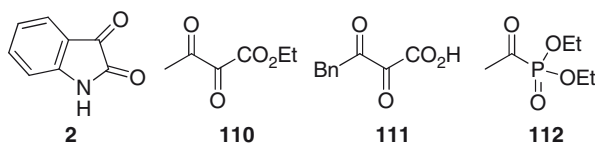
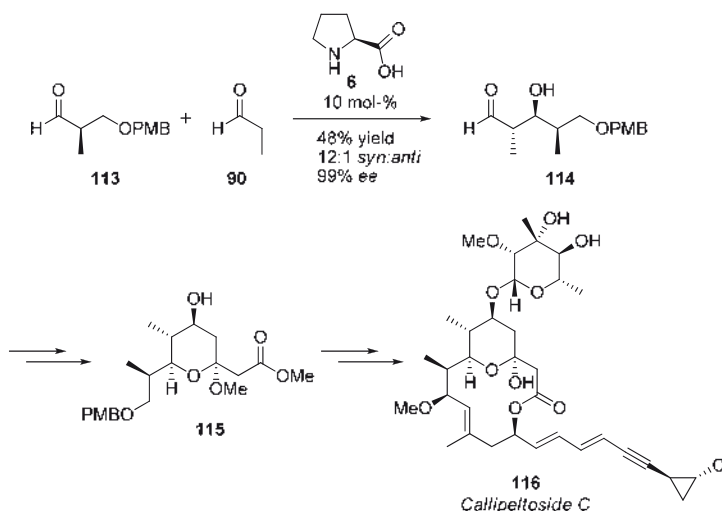


Fig. 3 Reactive ketones as acceptors in aldol processes

At present, most enamine-catalyzed aldol reactions are reliable only with electron-poor aromatic aldehyde acceptors. In addition, a handful of aliphatic aldehydes (e.g. isobutyraldehyde or pivalaldehyde) are often used as acceptors. The use of unbranched aldehyde acceptors is difficult, and generally only modest yields have been obtained. In addition, unsaturated aldehydes are curiously absent from the list of commonly used acceptors. On a positive side, it should be noted that even potentially racemizing α -chiral aldehydes have been employed as acceptors. As an example, in the recent synthesis of callipeltoside C, MacMillan and coworkers were able to employ protected Roche aldehyde **113** as a starting material (Scheme 22) [204].



Scheme 22 Proline-catalyzed aldol reaction in the synthesis of callipeltoside C

The simplest possible aldehyde donor, acetaldehyde, can also be used as the donor! Very recently, Hayashi and coworkers discovered how to use acetaldehyde in crossed-aldol reactions – the trick is to use diarylprolinol as the catalyst and to optimize the reaction conditions carefully to prevent oligomerization of acetaldehyde. However, so far the acetaldehyde aldol reactions appear to be limited to aromatic aldehyde acceptors [205].

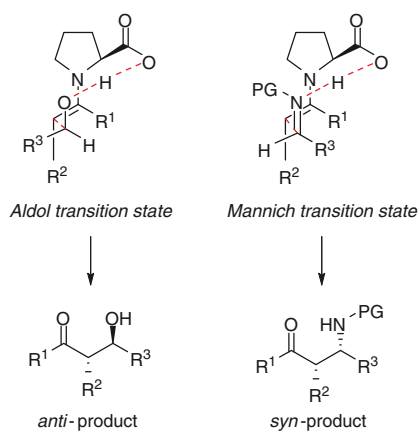
3.2 Mannich-Type Reactions

In enamine-catalyzed aldol reaction, the donor aldehyde or ketone first forms an enamine and then reacts with another aldehyde to form the aldol product. If imines instead of aldehydes are used as acceptors, the end result is the formation of a

β -amino carbonyl compound, and the reaction is now called the Mannich reaction [206, 207].

Although imines are less electrophilic than carbonyl compounds, they are also more readily activated by acids or hydrogen bonding. For this reason, Mannich reactions are often faster than the corresponding aldol reactions. It is not even necessary to use preformed imines. In a typical three-component Mannich reaction, the acceptor imine is generated from an aromatic or otherwise protected primary amine.

The first asymmetric enamine-catalyzed Mannich reactions were described by List in 2000 [208]. Paralleling the development of the enamine-catalyzed aldol reactions, the first asymmetric Mannich reactions were catalyzed by proline, and a range of cyclic and acyclic aliphatic ketones were used as donors (Schemes 24 and 25). In contrast to the aldol reaction, however, most Mannich reactions are *syn* selective. This is presumably due to the larger size of the imine acceptor, forcing the imine and the enamine to approach each other in a different manner than is possible with aldehyde acceptors (Scheme 23).

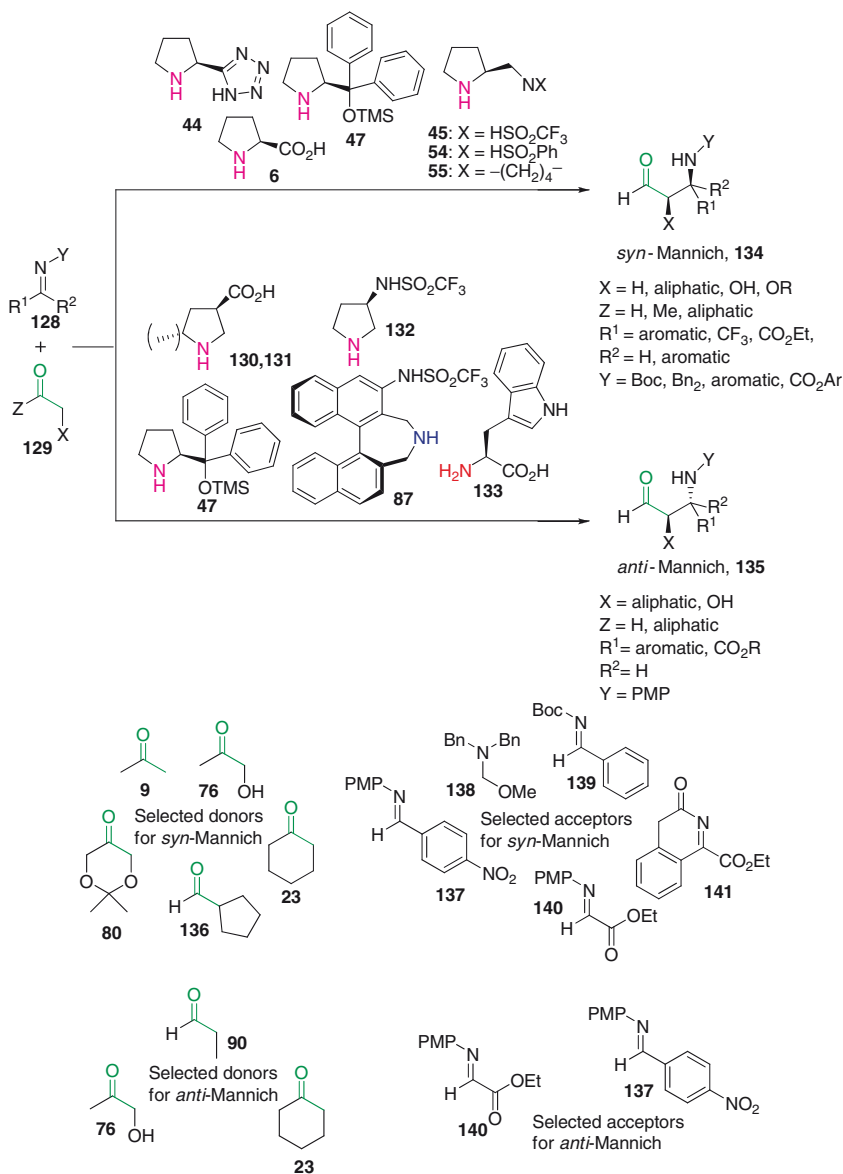


Scheme 23 Transition states in aldol and Mannich reactions

Since the initial studies, the substrate scope has expanded to include heteroatom-substituted ketones [208–216], cyclic ketones [217] and aldehydes [211, 218–226] as donors, and formaldehyde-derived imines [218, 227–232] as well as glyoxylate-derived imines [96, 220, 233–237] as acceptors. In addition, several alternative catalysts to proline have been pursued [238–242].

The amine-catalyzed Mannich reaction has also been a subject of special reviews [243, 244]. In general, yields and enantioselectivities of proline-catalyzed Mannich reactions are very high. Initially, the reactions were restricted to imines bearing an aromatic *N*-substituent, such as the *p*-methoxyphenyl (PMP) group. This restriction considerably limited the usefulness of the protocol, because relatively

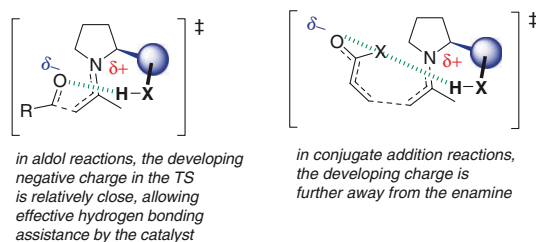
(Scheme 25). The *anti* selective reactions require somewhat more elaborate catalysts but the enantioselectivities and diastereoselectivities are excellent in both cases.



Scheme 25 Two-component Mannich reactions

3.3 Conjugate Addition Reactions

Enamine nucleophiles react readily with soft conjugated electrophiles, such as α,β -unsaturated carbonyl, nitro, and sulfonyl compounds [20–22]. Both aldehydes and ketones can be used as donors (Schemes 27 and 28). These Michael-type reactions are highly useful for the construction of carbon skeletons and often the yields are very high. The problem, however, is the enantioselectivity of the process. Unlike the aldol and Mannich reactions, where even simple proline catalyst can effectively direct the addition to the C = O or C = N bond by its carboxylic acid moiety, in conjugate additions the charge develops further away from the catalyst (Scheme 26):

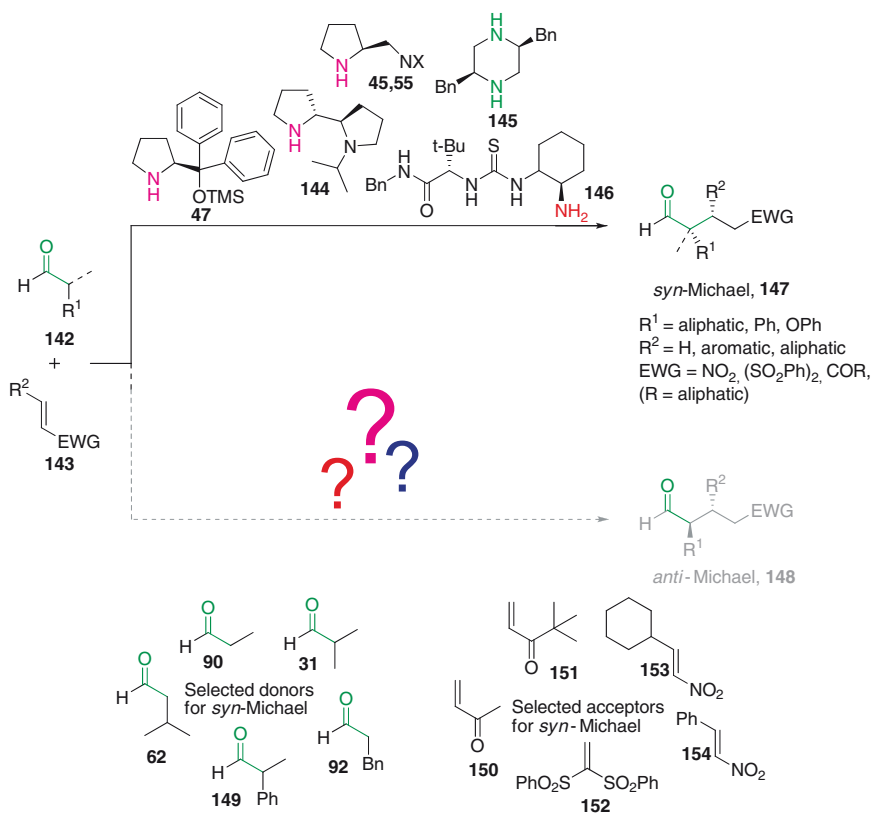


Scheme 26 Aldol and conjugate addition reactions require different types of stabilization for the transition state

Initially, proline and its analogues were used for the conjugate additions, with only modest results. In some reactions, proline was totally ineffective, and proline-derived diamines generally gave better selectivities [269, 270]. Good enantioselectivities were only obtained after the development of more sophisticated second-generation catalysts. Some of these catalysts include an additional hydrogen bond donor, such as thiourea moiety [271] or an acidic triflimide group [272], whereas some of them simply rely on steric control [273]. The diarylprolinol ethers, such as Jørgensen's catalyst **47**, perform very well in many conjugate addition reactions.

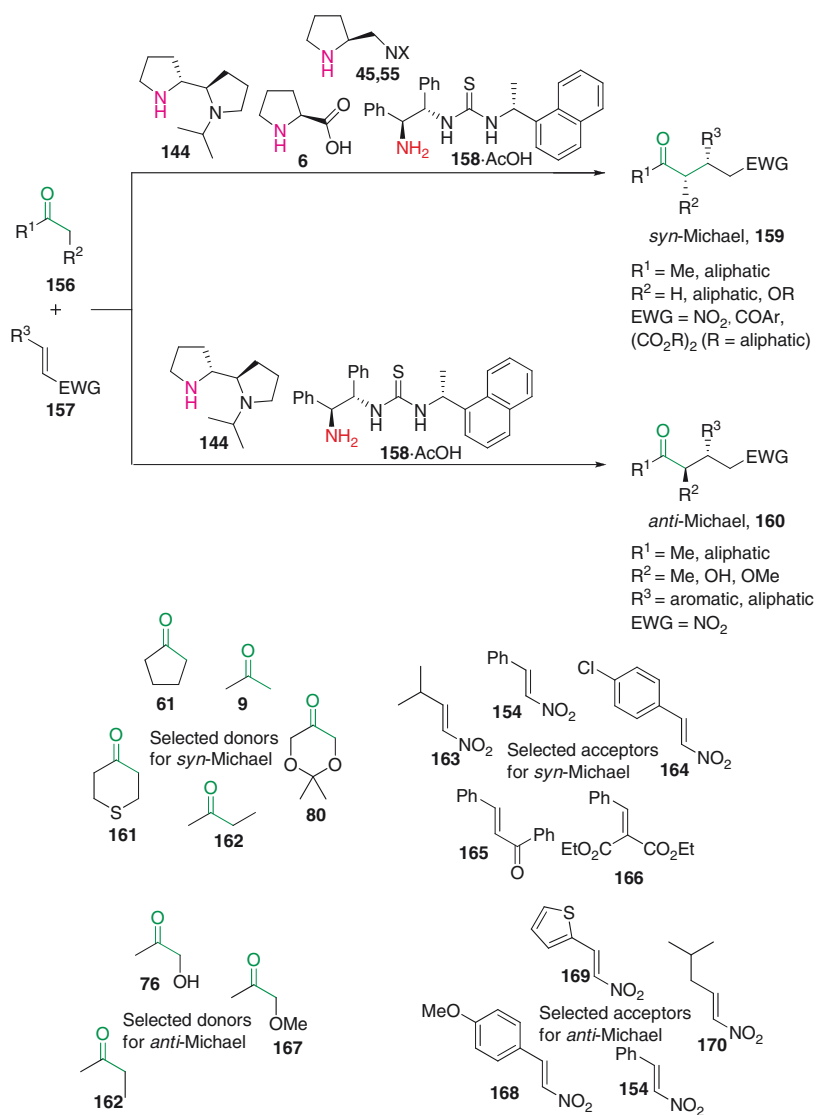
With aldehyde donors, the reactions are generally *syn* selective. A range of acceptors can be used, including α,β -unsaturated nitro compounds [72, 270, 274–281], α,β -unsaturated ketones [71, 282–285], vinyl phosphonates [286] and vinyl sulfones [287] etc. (Scheme 27). So far, no general *anti* selective

protocol for enamine-catalyzed conjugate additions with aldehyde donors has been published.

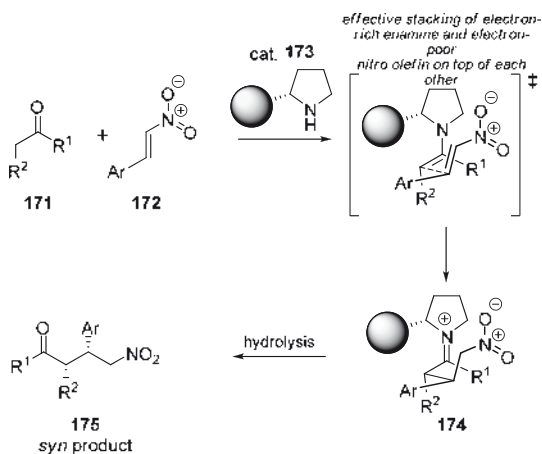


Scheme 27 Asymmetric enamine-catalyzed Michael additions with aldehyde donors

With ketone donors, both *syn* and *anti* selective reactions are possible. Typically, α,β -unsaturated nitro compounds are used as acceptors. The majority of these reactions are *syn* selective (Scheme 28) [94, 269, 271, 278, 279, 288–309]. This is a result of favored formation of the (*E*)-configured enamine and favorable electrostatic interactions between the nitro group and the enamine (Scheme 29) [290, 291, 310]. Of the known *anti* selective reactions, primary amine-thiourea catalysts such as **158** appear to perform best (Scheme 28) [271, 299, 301].



Scheme 28 Asymmetric enamine-catalyzed Michael additions with ketone donors



Scheme 29 Explanation for the typical *syn* selectivity observed in the enamine-catalyzed conjugate addition reactions

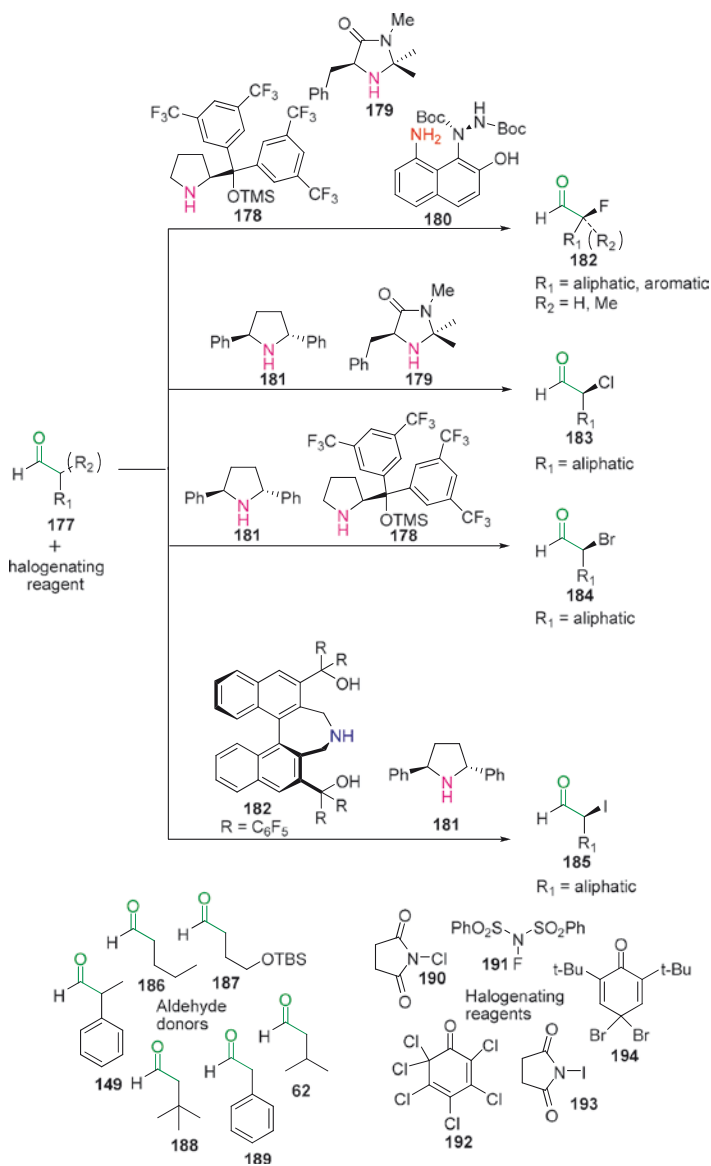
3.4 Heteroatom Functionalizations at the α -Carbon: α -Halogenations, Oxygenations and Other Transformations

A range of nitrogen, phosphorus, chalcogen (O, S, Se) and halogen electrophiles react with enamines, resulting in a net α -functionalization of the carbonyl compound. In the past five years, all of these reaction variants have been subjected to asymmetric enamine catalysis, with excellent results.

3.4.1 α -Halogenations

In α -halogenations, hydrogen bonding assistance does not play the same important role as it does in aldol and Mannich reactions. For this reason, proline and its amide variants are generally not highly enantioselective catalysts. The more hindered Jørgensen–Hayashi -type prolinol derivatives [71–74] as well as the MacMillan imidazolidinones [76, 311–313] are typically the most enantioselective catalysts for the halogenation of aldehydes (Scheme 30). The first enamine-catalyzed enantioselective α -halogenations of aldehydes were independently reported in 2004 by MacMillan and Jørgensen [74, 313].

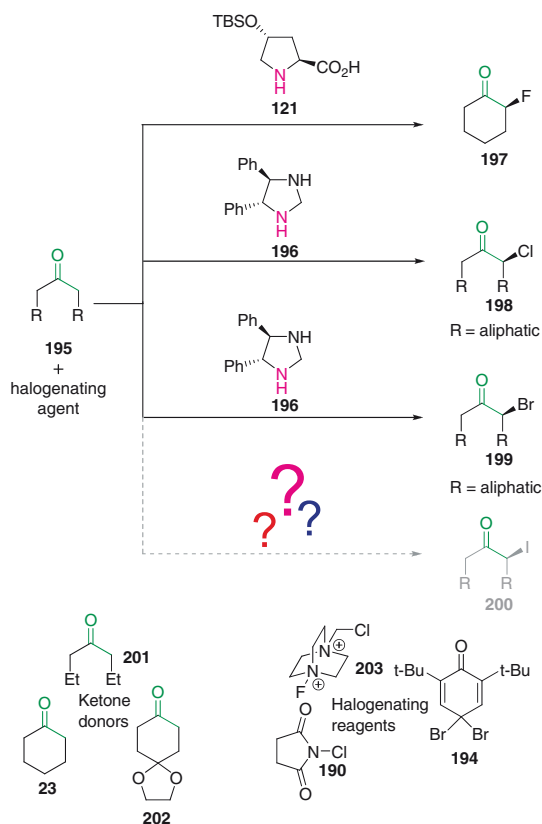
It should be noted that, in spite of the similarity of the mechanism, each of the halogenations appears to require its own optimal combination of catalyst and halo-



Scheme 30 α -Halogenations of aldehydes

genating agent [73, 74, 311, 313]. With the proper choice of halogenating agent and catalyst, the reactions are often highly enantioselective, typically in the range of 90–95% ee. The α -halogenation of aldehydes is often easier to achieve and affords higher enantioselectivities than α -halogenations of ketones. In addition to pyrrolidine-type [74, 314] or imidazolidinone secondary amine catalysts, an interesting rotationally restricted (atropisomerically pure) primary amine catalyst **180** has been described by Jørgensen for the α -fluorination reactions [315]. Very recently, the Maruoka group has described the use of axially chiral amine **182** for the α -iodination reaction in excellent enantioselectivities [316].

Successful solutions to the α -halogenation of ketones have also emerged, but here the problem is that sterically very hindered catalysts that work very nicely with aldehydes are not active with ketones. Some current solutions to this problem are summarized in Scheme 31 [314, 317, 318].



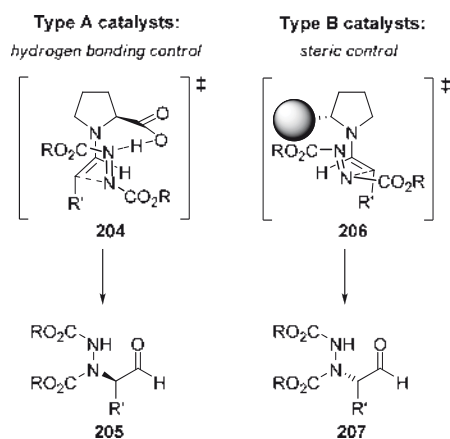
Scheme 31 α -Halogenations of ketones

3.4.2 α -Oxygenation and α -Amination Reactions

In contrast with α -halogenations, α -oxygenation and α -amination reagents are typically more Brønsted basic and therefore amenable to hydrogen bonding/Brønsted acid catalysis. Typical α -oxygenation and α -amination reactions as well as typical catalysts are summarized in Schemes 33 and 34. The prototype reagent for α -aminations are electrophilic azodicarboxylate esters (**210**), [285, 319–324] and for α -oxygenations, highly reactive nitrosobenzene **211** [325–327] is typically employed. Enantioselectivities are very high and the reactions are often very rapid (10–30 min).

The first α -amination reactions were reported simultaneously by List and Jørgensen in 2002, [328, 329] and the α -amination of ketones was reported by the Jørgensen group shortly thereafter [330]. Interestingly, although proline was initially used by both groups for the amination reactions, the Jørgensen group later used their own diaryl prolinol-derived catalyst **47** with very high enantioselectivities but with an opposite configuration [71]. This result underlines the mechanistic difference between Type A (hydrogen bonding) and Type B (steric control) enamine catalysts (Scheme 32). Type A and Type B catalysts with the same configuration lead to opposite enantiomers of product in amination reactions (Fig. 4).

The α -oxygenation of aldehydes is a highly versatile reaction that affords the oxygenated products in high yield and high enantioselectivity. In 2003, three different groups (Zhong [331], MacMillan [332], and Hayashi [333]) independently reported the use of nitrosobenzene for this reaction. The reaction is also applicable to ketones,



Scheme 32 Type A and Type B enamine catalysts afford opposite enantiomers in α -amination reactions

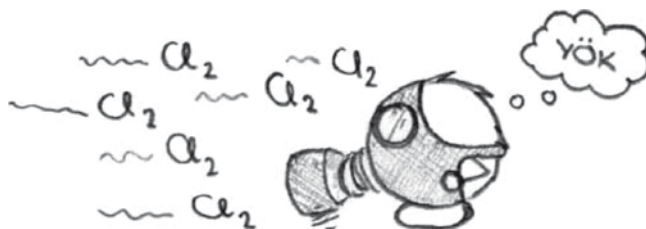
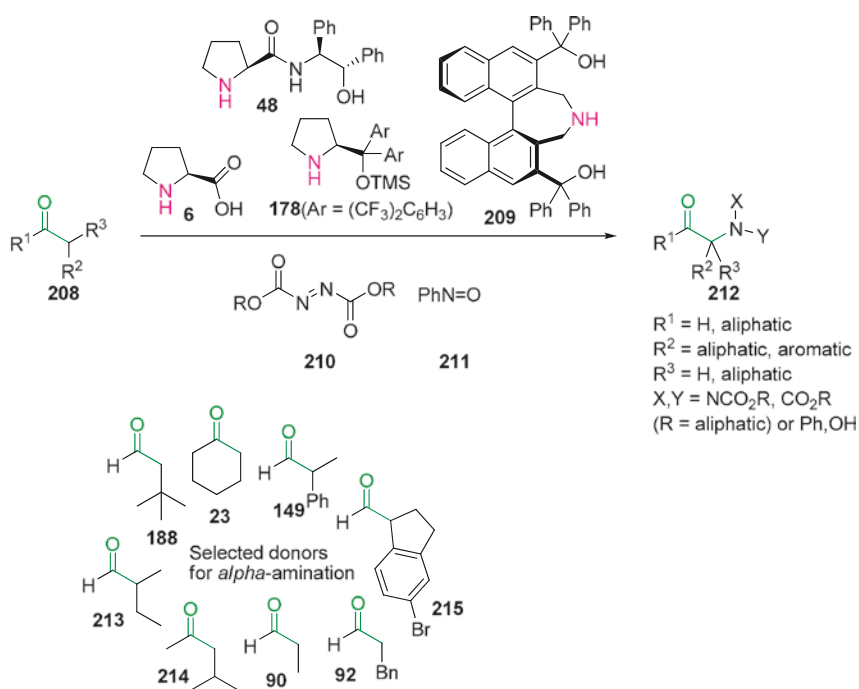


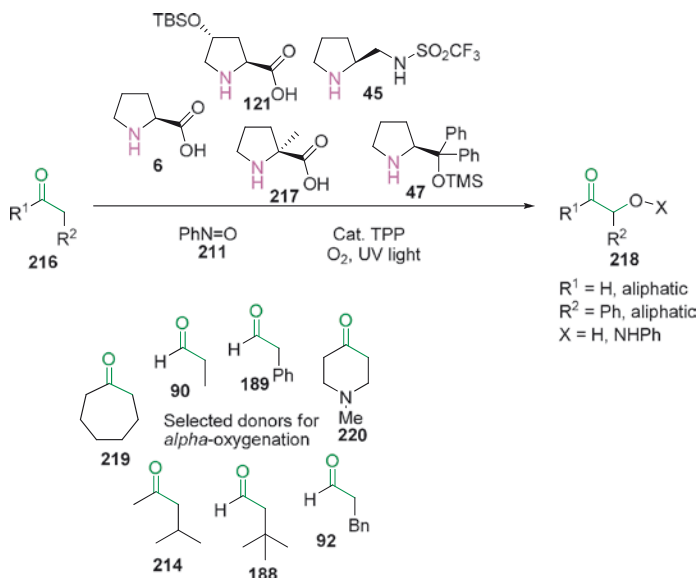
Fig. 4 α -Halogenations with elemental chlorine? Perhaps the next bold step in enamine catalysis

as reported by Hayashi [333–335] and later by Córdova [336, 337]. Different proline-derived catalysts have been reported by the Hayashi [338], Córdova [339], Wang [340], and Ley groups [341, 342].

As illustrated in Schemes 33 and 34, catalysts capable of hydrogen bonding or Brønsted acid activation (Type A catalysts) are generally highly effective and enantioselective catalysts for α -oxygenation and α -amination reactions. With nitroso-benzene, type A catalysts have so far been the only successful catalysts. The high reactivity of the reagents and the double activation mode of the catalyst both contribute to extremely high enantioselectivities typically observed in these processes.



Scheme 33 α -Aminations of aldehydes and ketones



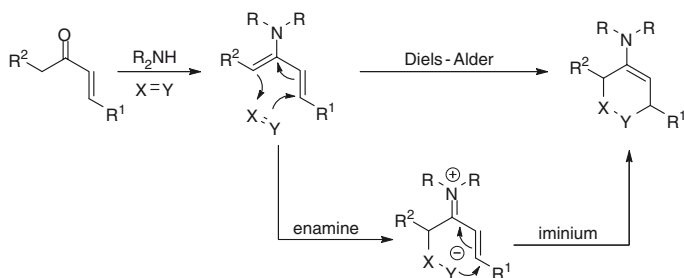
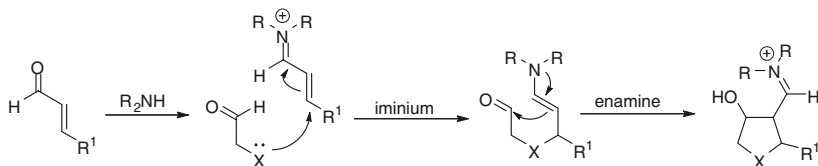
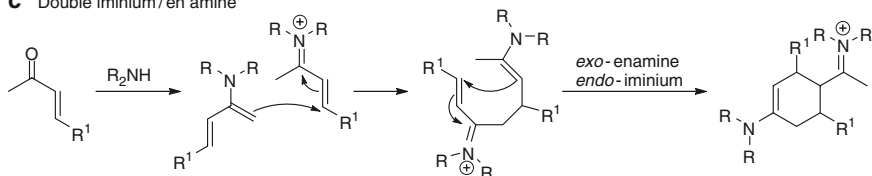
Scheme 34 α -Oxygenations of aldehydes and ketones

The drawback of many of these reactions is the relatively low atom economy of the reagents. Electrophilic nitrogen and oxygen reagents deliver only one or two N or O atoms, but these atoms are often attached to a much heavier carbon chain. A possible solution, at least in the case of oxygenations, is to use singlet oxygen. This elegant idea was first realized by Cordova and co-workers [343–345]. Although the yields and enantioselectivities are lower than those obtained with e.g. nitrosobenzene as the oxygen source, the method has obvious potential due to the low cost of the reagent and should be explored further. Interestingly, even the Type B diarylprolinol silyl ether catalysts (**47**) will work with singlet oxygen as the electrophile.

4 Enamine Catalysis in the Synthesis of Complex Molecules

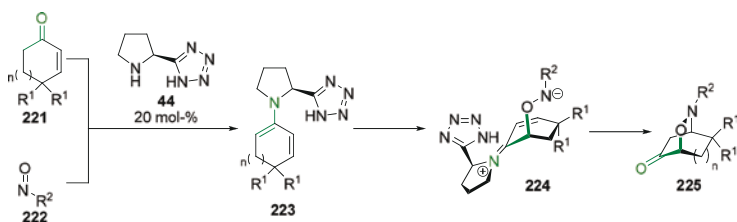
4.1 Domino Processes

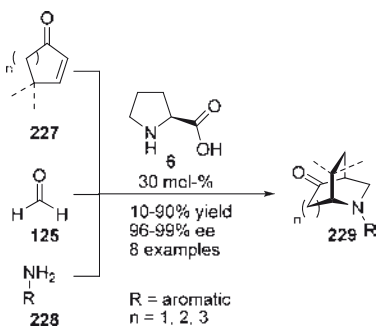
The dual nature of enamine-iminium pairs allows unique possibilities for domino processes. Reactions of enamines with electrophiles afford electrophilic iminium ions that are ready to react with another (internal or external) nucleophile. Conversely, reactions of unsaturated iminium ions with nucleophiles afford enamines. Examples of intramolecular enamine-catalyzed domino processes are depicted in Scheme 35. In all of these reactions, both enamine and iminium mediated steps can be distinguished.

a Generic reaction type: Enamine-iminium/Enamine-Diels-Alder**b** Generic reaction type: Iminium-enamine**c** Double iminium/enamine**Scheme 35** Enamines and iminium ions in organocatalytic domino reactions

In the following discussion, selected examples of domino processes with an enamine catalysis component are discussed. For further examples, several comprehensive reviews on the topic have recently appeared [8, 17, 24].

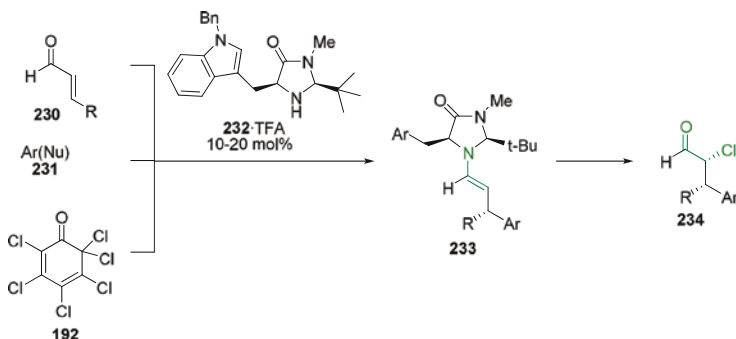
Yamamoto and coworkers described a highly enantioselective asymmetric domino *O*-nitroso aldol-conjugate addition sequence using cyclic enones **221** and aromatic nitroso compounds **222** as depicted in Scheme 36 [346]. A related reaction with imines was also reported by Córdova and coworkers (Scheme 37) [228].

**Scheme 36** Domino *O*-nitroso aldol-conjugate addition



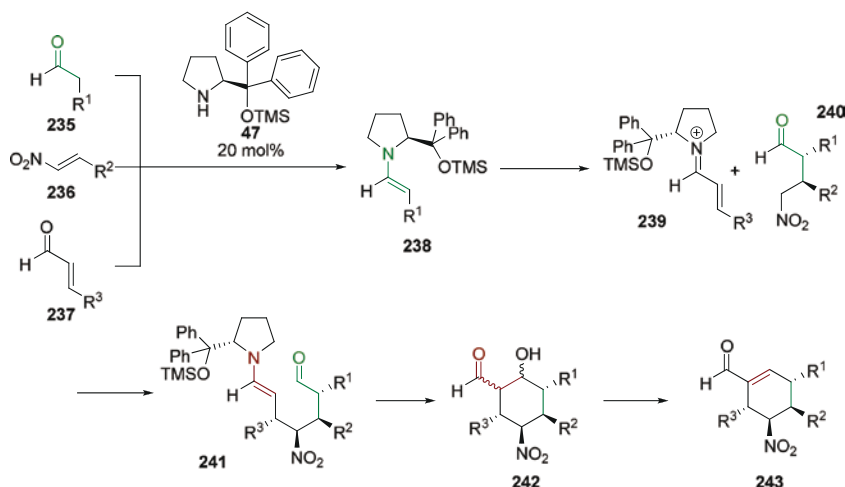
Scheme 37 Domino imine aldol-conjugate addition

Domino processes can also be performed on open-chain compounds. MacMillan and co-workers demonstrated this with their own imidazolidinone catalysts. Conjugate addition of a nucleophilic heterocycle **231** to the α,β -unsaturated enal **230** followed by α -chlorination of the resulting enamine led to the *syn* products **234** in very high enantioselectivities and good *syn:anti* diastereoselectivities (Scheme 38) [347]. Similar domino sequences, but with different nucleophile-electrophile partners, were also reported independently by Jørgensen [348].



Scheme 38 Domino conjugate addition-halogenation

Even triple domino sequences are possible. A beautiful demonstration was provided by Enders and co-workers, who start their cascade by an enamine-catalyzed conjugate addition of an aldehyde donor **235** to a α,β -unsaturated nitro compound **236** (Scheme 39). Following an iminium-catalyzed addition of the resulting nitro aldehyde **240** to the unsaturated iminium ion **239**, the resulting enamine **241** cyclizes and undergoes an aldol condensation reaction. Four contiguous stereogenic centers are generated in a single operation in this domino sequence [349].



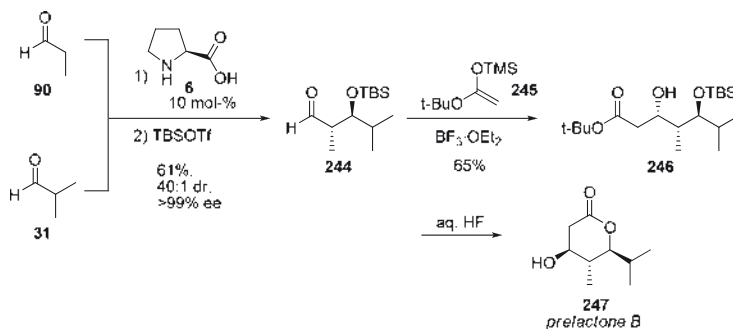
Scheme 39 A triple domino reaction from the Enders group

4.2 Total Syntheses

The ultimate test of any method lies in its applicability in challenging contexts, such as total synthesis of natural products and industrial settings. While the industrial applications of enamine catalysis are still mostly under development, asymmetric enamine catalysis has already been used in several instances for the synthesis of natural products. This area has been recently reviewed by Christmann [19].

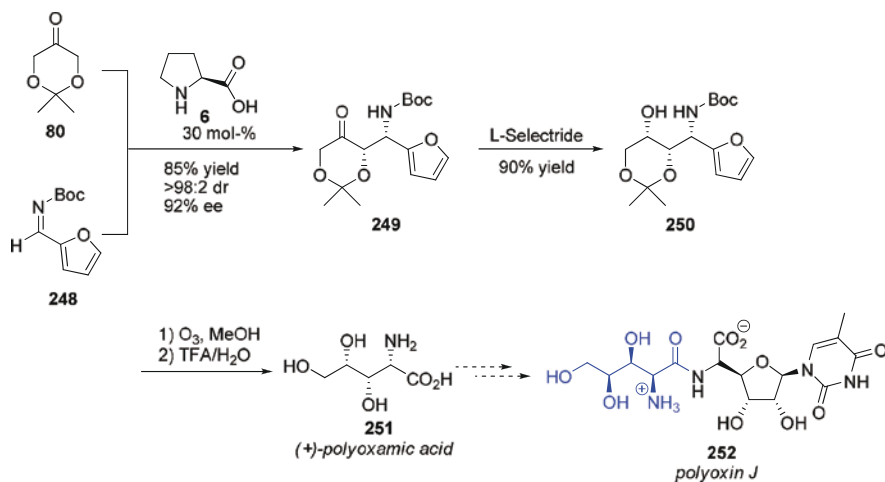
The following examples illustrate how different enamine-catalyzed reactions can lead to remarkably short and highly enantio- and diastereoselective routes to natural products.

The aldehyde-aldehyde aldol reactions were first used in a natural product synthesis setting by Pihko and Erkkilä, who prepared prelactone B in only three operations starting from isobutyraldehyde and propionaldehyde (Scheme 40). Crossed aldol reaction under proline catalysis, followed by TBS protection, afforded protected aldehyde **244** in >99% ee. A highly diastereoselective Mukaiyama aldol reaction and ring closure with aqueous HF completed the synthesis [112].



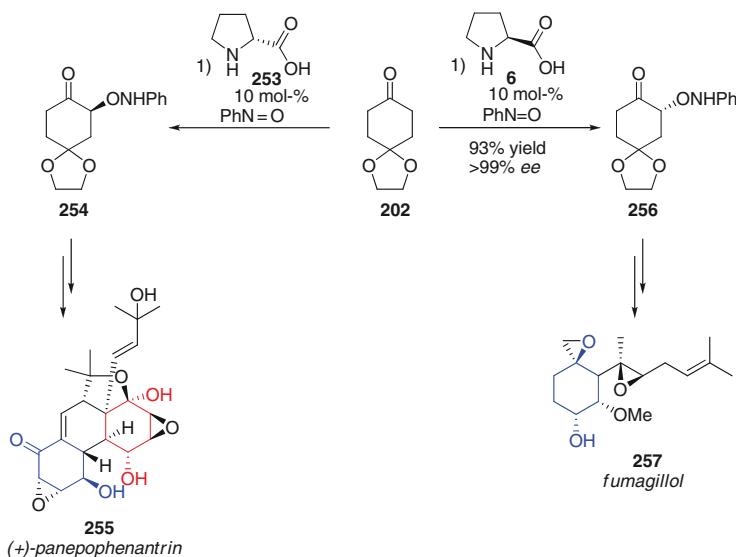
Scheme 40 Three-step synthesis of prelactone B

In nature, enamine catalysis is one of the most favored strategies for constructing carbohydrate skeletons. The use of proline-catalyzed aldehyde-aldehyde aldol reactions for carbohydrate synthesis was discussed in Sect. 3.1. Amino sugars can be similarly constructed using enamine-catalyzed Mannich reactions, as exemplified by the remarkably short synthesis of (+)-polyoxamic acid (and polyoxin J) by Enders and coworkers (Scheme 41) [245]. The initial proline-catalyzed Mannich reaction afforded the adduct **249** in 92% ee and >98:2 dr. Diastereoselective reduction with L-Selectride®, followed by oxidative cleavage of the furan ring and deprotection (TFA), afforded (+)-polyoxamic acid in only four steps. This synthesis also nicely demonstrates the advantages of the use of preformed Boc-imines in Mannich reactions.



Scheme 41 Synthesis of (+)-polyoxamic acid

Since many natural products, especially terpenoids, are highly oxygenated compounds, methods that allow direct insertion of oxygen into the structure are extremely useful. The proline-catalyzed α -oxygenation of aldehydes and ketones with nitrosobenzene is thus a highly valuable transformation, and it is not surprising that it has already found applications in total synthesis [350]. A particularly nice example is provided by the use of both L- and D-proline in two diverse total syntheses by the Hayashi group. Starting from achiral ketone **202**, they synthesized both panepophenantrin **255** [351] and fumagillol **257** [352] using either D- or L-proline catalysts. In both cases, the key starting materials **254** and **256** were furnished in >99% ee and excellent yield, using only 10 mol% of the inexpensive proline catalyst (Scheme 42).



Scheme 42 Syntheses of (+)-panepophenantrin and fumagillol

5 Directions for the Future

Over the past eight years, enantioselective enamine catalysis has expanded in scope more rapidly than perhaps any other field of asymmetric catalysis. From a handful of examples within the realm of aldol catalysis known in the beginning of 2000, the field enamine catalysis now comprises more than 50 different reactions, nearly 1000 different catalysts, and more than 1000 examples! Still, major challenges remain to be solved.

Although most enamine-catalyzed reactions are highly enantioselective, relatively high catalyst loadings are often required. Fortunately, this situation is improving, and most enamine catalysts are relatively inexpensive – especially proline and its simple derivatives – and as such even relatively high catalyst loadings could be tolerated. A more serious problem in enamine catalysis is the relatively narrow substrate scope, especially in aldol catalysis. As an example, at the time of writing (March 2008), it is still not possible to use enamine catalysis for the direct, chemoselective aldol reaction between acetaldehyde as the acceptor and propionaldehyde as the donor (or vice versa!), or to dimerize propionaldehyde to generate a *syn* aldol product in high ee and high diastereoselectivity. The three simplest aldehydes – formaldehyde, acetaldehyde, and propionaldehyde – have enormous potential in enamine catalysis, and their use as acceptors and donors should be explored more vigorously.

Enamine catalysis clearly affords shorter synthetic routes to a variety of natural product and drug targets [8, 19]. However, the full potential of enamine catalytic methods has yet to be realized in more complex settings. For example, the α -halogenations of aldehydes, in spite of their high importance, have only rarely been used in a total synthesis setting [353]. With so many attractive features – relatively benign reaction conditions, easy-to-handle catalysts, and high enantioselectivities – it is probably just a matter of time before the use of enamine catalysis in both academic total syntheses and industrial process chemistry becomes a matter of routine.

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Carbene Catalysts

Jennifer L. Moore and Tomislav Rovis

Abstract The use of *N*-heterocyclic carbenes as catalysts for organic transformations has received increased attention in the past 10 years. A discussion of catalyst development and nucleophilic characteristics precedes a description of recent advancements and new reactions using *N*-heterocyclic carbenes in catalysis.

Keywords Benzoin • Carbene • NHC • Nucleophilic Catalysis • Organocatalysis • Redox • Stetter • Transesterification • Umpolung

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Abbreviations:

Ac	acetyl
Ar	aryl
BAL	benzaldehyde lyase
BFD	benzoylformate decarboxylase
Bmin	butylmethylimidazolium
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[1.2.2]octane
DBU	1,8-diazabicyclo[2.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
HOAt	1-hydroxy-7-azabenzotriazole
<i>i</i> -Pr	isopropyl
KHMDS	potassium <i>bis</i> (trimethylsilyl)amide
KPi	buffer potassium phosphate buffer
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
LiHMDS	lithium <i>bis</i> (trimethylsilyl)amide
<i>n</i> -Bu	<i>normal</i> -butyl
<i>n</i> -Hex	<i>normal</i> -hexyl
<i>n</i> -Pr	<i>normal</i> -propyl
NHC	<i>N</i> -heterocyclic carbene
PEMP	pentamethylpiperidine
Ph	phenyl
Pr	propyl
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
ThDP	thiamin diphosphate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tol	<i>para</i> -tolyl
Ts	<i>para</i> -toluenesulfonyl (tosyl)

1 Introduction

Since the isolation and characterization of stable imidazolylidene carbenes by Arduengo in 1991 [1], chemists have been increasingly fascinated by their potential as modifying ligands on transition metals. The direct use of azolidine-based carbenes as catalysts in organic transformations, however, predates Arduengo's find by almost 50 years [2], not to mention the role that thiamin cofactor plays in modifying a number of biochemical transformations. Even asymmetric catalysis using chiral nucleophilic carbenes is over 40 years old, with Sheehan's seminal report appearing in 1966 [3]. That said, much of this early work attracted little attention from the chemical community as a whole, largely due to poor efficiency, selectivity or both. That situation has changed rather drastically in the past 10 years and the area has been reviewed both tangentially and specifically almost a dozen times [4–14].

This review will focus on the use of chiral nucleophilic *N*-heterocyclic carbenes, commonly termed NHCs, as catalysts in organic transformations. Although other examples are known, by far the most common NHCs are thiazolylidene, imidazolinylidene, imidazolylidene and triazolylidene, **I–IV**. Rather than simply presenting a laundry list of results, the focus of the current review will be to summarize and place in context the key advances made, with particular attention paid to recent and conceptual breakthroughs. These aspects, by definition, will include a heavy emphasis on mechanism. In a number of instances, the asymmetric version of the reaction has yet to be reported; in those cases, we include the state-of-the-art in order to further illustrate the broad utility and reactivity of nucleophilic carbenes.

2 Carbenes

Since the 1950s carbenes have shown great potential in the field of organic and organometallic chemistry [15–17]. These neutral molecules contain a divalent carbon atom with six electrons in its valence shell and exist in either a singlet or triplet state (Fig. 1a, b). Depending on the steric and electronic environment, carbene compounds can be electrophilic or nucleophilic. NHCs contain heteroatoms on either side of the carbene atom, which donate electron density into the vacant p-orbital to enhance thermodynamic stability. For example, in carbene **1** the nitrogen lone pairs donate electron density into the empty p-orbital of the carbene carbon perpendicular to the plane of the ring, allowing for 6π aromatic stabilization (Fig. 1c). The nitrogen atoms also stabilize the carbene via σ withdrawal of electron density from the carbene center. Steric hindrance contributes to kinetic stability. It is notable that no single characteristic is responsible for producing isolable carbenes; both electronic and steric factors are necessary for stability [16, 18].

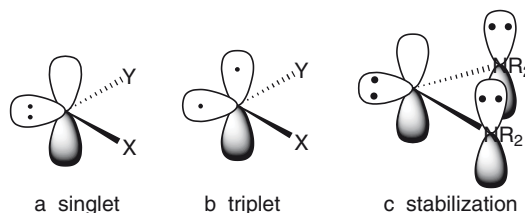
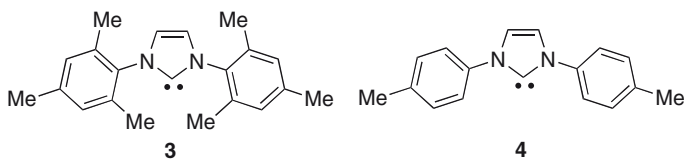


Fig. 1 Orbital representation of carbenes



Pioneering work by Wanzlick in the 1960s established nucleophilic saturated and unsaturated carbenes as reactive intermediates, although he was unable to isolate them due to their inherent reactivity [19]. Nearly 30 years later, Arduengo and Bertrand independently accomplished the first isolation of carbene species, **1** and **2**, respectively [1, 20]. The synthesis of bisadamantyl imidazolyldiene carbene **1** by Arduengo is considered by some to be the first isolated carbene and was unequivocally characterized by X-ray crystallography [4]. Since 1991, alkyl and aryl *N*-substituents have been documented to provide stable, isolable carbenes. There was concern that substituted aryl rings, which distort the plane of the carbene, would affect stability but Arduengo disproved this by synthesizing **3** and **4** [21]. The mesityl (Mes) substituted carbene prevents conjugation between the phenyl rings and the nitrogen centers, while *p*-tolyl substituents allow conjugation. Both share the same chemical characteristics and demonstrate that substitution of aryl rings has little effect on the stability of the carbene compound. Since the first isolation, many groups have reported the synthesis and isolation of imidazole-, thiazole-, and triazole-derived stable carbenes, some of which are stable enough to be bottled and occasionally even commercially available [22].

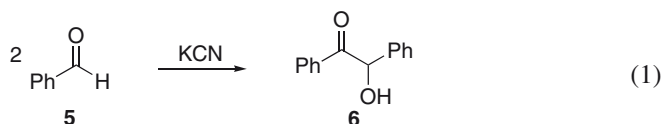


The similarity between *N*-heterocyclic carbenes and electron-rich organophosphines has been extensively studied and exploited in organometallic chemistry. NHC-metal complexes have been shown to outperform analogous phosphine-metal complexes in some organometallic transformations [23, 24]. Both compounds are σ -donors and exhibit little backbonding character. Most notable are the advances made in coordination chemistry, olefin metathesis, and cross-coupling reactions [25]. In addition to their use as ligands for transition metal catalysts, the use of NHCs as organocatalysts has experienced increased interest in the past 15 years and developed into a field of its own.

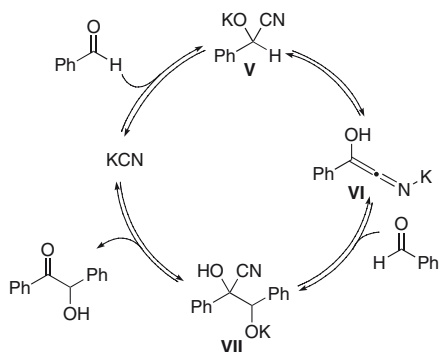
3 Benzoin Reaction

3.1 Mechanism and Catalyst Design

The benzoin reaction dates back to 1832 when Wöhler and Liebig reported that cyanide catalyzes the formation of benzoin **6** from benzaldehyde **5**, a seminal example in which the normal mode of polarity of a functional group was reversed (Eq. 1) [26]. This reversal of polarity, subsequently termed Umpolung [27], effectively changes an electrophilic aldehyde into a nucleophilic acyl anion equivalent.

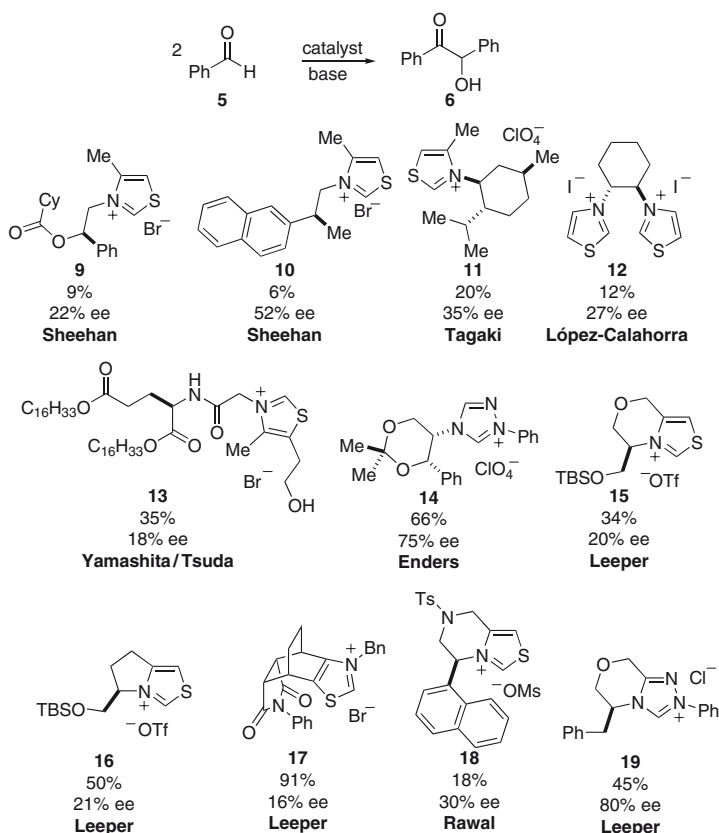


In 1903, Lapworth described his findings of the action of potassium cyanide on benzaldehyde [28]. He postulated that cyanide adds to benzaldehyde to form **V**, followed by proton transfer of the α -labile hydrogen, forming intermediate **VI** which is now referred to as an acyl anion equivalent. Addition to another molecule of benzaldehyde occurs to form **VII** (Scheme 1). The unstable cyanohydrin of benzoin **VII** then collapses to form benzoin and potassium cyanide. Additionally, Lapworth tested the reversibility of the addition of cyanide to benzaldehyde by first forming hydroxybenzyl cyanide (protonated variant of **V**) and subjecting it to benzaldehyde and base, in which benzoin was recovered.



Scheme 1 Lapworth's proposed mechanism of the benzoin reaction

In 1966, Sheehan and Hunneman reported the first example of an asymmetric benzoin reaction, using chiral thiazolium pre-catalyst **9** to yield benzoin **6** in 22% ee (Scheme 3) [3]. The next significant advance occurred in 1974, when Sheehan and Hara reported that adding steric bulk around the reactive site, **10**, leads to increased asymmetric induction in benzoin formation to 52% ee, although the yields remain low [31]. Many groups have attempted to improve the enantioselectivity of the thiazolylidene catalyzed benzoin reaction with modest success. In 1980, Tagaki and co-workers synthesized thiazolium salt **11** to study the benzoin reaction in a micellar two-phase media; despite the fact that the enantiomeric excess of 35% ee was achieved, only a slight increase in yield was observed [32]. López-Calahorra and co-workers designed the bis(thiazolin-2-ylidene) **12** in an effort to increase the rigidity of the active species, although the cyclohexyl tethered catalyst provides low yield and 27% ee [33]. Yamashita and co-workers synthesized lipid thiazolium salt **13** that produced benzoin in 18% ee [34].



Scheme 3 Catalyst development in the benzoin reaction

A breakthrough in the asymmetric benzoin reaction was achieved in 1996 when Enders and co-workers introduced chiral triazolinylidene carbenes instead of thiazolyli-dene carbenes. They utilized a variety of chiral triazolium salts that provided increased yields and enantioselectivities, outperforming all previous thiazolium pre-catalysts [35]. The most active of these triazolium salts is **14**, which affords benzoin in 75% ee and 66% yield. In 1997, Leeper and co-workers developed a series of rigid bicyclic thiazolium salts, **15–17**, that they hypothesized would increase enantioselectivities by restraining the rotation of the chiral side chain of the catalyst [36, 37]. Concurrently, Rawal and Dvorak increased the enantioselectivity of the benzoin reaction with bicyclic thiazolium salt **18** when compared to Leeper's chiral bicyclic thiazolium salts **15–17** [38]. The reactivity and enantioselectivity remained low until Leeper and co-workers exchanged the thiazolium framework for the more reactive triazolium pre-catalyst **19** and observed increased enantioselectivities, up to 80% ee [39]. In 2004, Takata and co-workers introduced the use of chiral rotaxanes as an asymmetric environment for the thiazolium catalyzed benzoin reaction, achieving modest enantioselectivities [40].

In 2002, Enders and co-workers took advantage of the bicyclic restriction first introduced by Leeper and Rawal to develop catalyst **20**. Use of this catalyst provides a number of benzoin derivatives **22a–h** in up to 95% ee (Table 1) [41]. The stereochemistry of the benzoin reaction catalyzed by thiazolium and triazolium pre-catalysts has subsequently been modeled by Houk and Dudding [42].

Table 1 Substrate scope of the asymmetric benzoin reaction [FX1]

Entry	22	Ar	Temp (°C)	Yield (%)	ee (%)
1	a	Ph	18	83	90
2	b	4-FC ₆ H ₄	18	81	83
3	c	4-FC ₆ H ₄	0	61	91
4	d	3-ClC ₆ H ₄	0	85	86
5	e	4-MeC ₆ H ₄	18	16	93
6	f	4-MeOC ₆ H ₄	18	8	95
7	g	2-Furyl	0	100	64
8	h	2-Furyl	–78	41	88

3.2 Cross-Benzoin Reaction

The benzoin reaction typically consists of the homocoupling of two aldehydes, which results in the formation of inherently dimeric compounds, therefore limiting the synthetic utility. The cross-benzoin reaction has the potential to produce four products, two homocoupled adducts and two cross-benzoin products. Several strategies have been employed to develop a selective cross-benzoin reaction, including the use of donor-acceptor aldehydes, acyl silanes, acyl imines, as well as intramolecular reactions.

Müller and co-workers have developed an enantioselective enzymatic cross-benzoin reaction (Table 2) [43, 44]. This is the first example of an enantioselective cross-benzoin reaction and takes advantage of the donor-acceptor concept. This transformation is catalyzed by thiamin diphosphate (ThDP) **23** in the presence of benzaldehyde lyase (BAL) or benzoylformate decarboxylase (BFD). Under these enzymatic reaction conditions the donor aldehyde **24** is the one that forms the acyl anion equivalent and subsequently attacks the acceptor aldehyde **25** to provide a variety of α -hydroxyketones **26** in good yield and excellent enantiomeric excesses without contamination of the other cross-benzoin products **27**. The authors chose 2-chlorobenzaldehyde **25** as the acceptor because of its inability to form a homodimer under enzymatic reaction conditions.

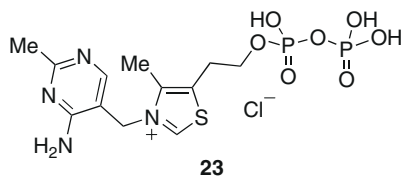
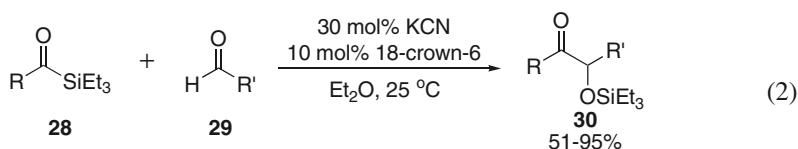


Table 2 Asymmetric enzymatic cross-benzoin reaction

Entry	26	R	Enzyme	Conversion (%)	ee (%)
1	a	3-CN	BFD H281 A	>99	90
2	b	4-Br	BFD H281 A	90	95
3	c	4-CF ₃	BFD H281 A	75	93
4	d	3,4-CH ₂ O ₂	BAL	98	>99
5	e	3,4,5-(CH ₃ O) ₃	BAL	82	>99
6	f	3,5-(CH ₃ O) ₂	BAL	>99	>99

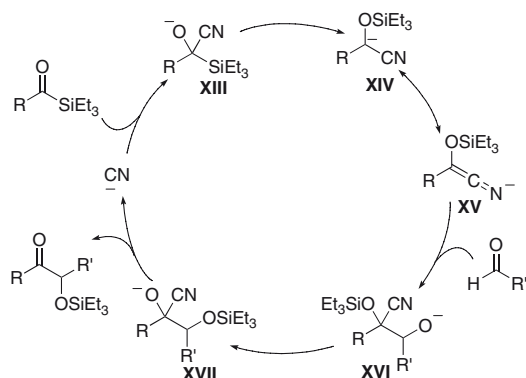
In an effort to circumvent a homodimerization event acyl silanes have been used to promote a cross-benzoin reaction. Initial reports by Johnson and co-workers employed potassium cyanide to catalyze the regiospecific cross silyl benzoin reaction to afford a single regioisomer in good yield (Eq. 2) [45–47].



The proposed mechanism is as follows: initial cyanation of the acyl silane followed by a [1,2]-Brook rearrangement yields acyl anion equivalent **XIV** (Scheme 4). Subsequent attack by the acyl anion equivalent **XV** to the aldehyde leads to

tetrahedral intermediate **XVI**. After a 1,4-silyl migration, cyanide is regenerated, and the desired α -siloxy ketone is formed.

Shortly after publishing the racemic cross silyl benzoin reaction, Johnson and co-workers reported an enantioselective variant utilizing metallophosphite catalysis [48]. The lithiophosphite adds to the acyl silane and proceeds through the remain-



Scheme 4 Proposed mechanism for the acyl silane cross-benzoin reaction

der of the mechanism in direct analogy to that observed with cyanide catalysis, with the added benefit of asymmetric induction. As illustrated in Table 3, good yields and enantioselectivities are achievable under these reaction conditions.

Table 3 Acyl Silane cross-benzoin reaction catalyzed by lithiophosphites

Entry	33	R	R'	Yield (%)	ee (%)
1	a	Ph	Ph	84	82
2	b	Ph	4-ClC ₆ H ₄	75	82
3	c	4-ClC ₆ H ₄	Ph	82	87
4	d	Ph	4-OMeC ₆ H ₄	87	91
5	e	4-ClC ₆ H ₄	4-OMeC ₆ H ₄	83	90
6	f	4-NMe ₂ C ₆ H ₄	Ph	86	86
7	g	<i>n</i> -hexyl	Ph	72	67

An alternative strategy to access cross-benzoin products is to tether the two reactive partners. This approach has the disadvantages inherent to intramolecular reactions, but it provides access to products produced by the coupling of aldehydes with ketones. In

In a report by Enders and co-workers, triazolium pre-catalysts **42–44** were shown to be competent in the cyclization of a variety of ketones (Table 5) [50]. Tetracyclic triazolium pre-catalyst **44** provides the enantioselectivities up to 98%.

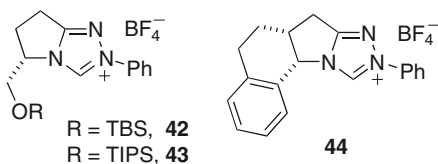
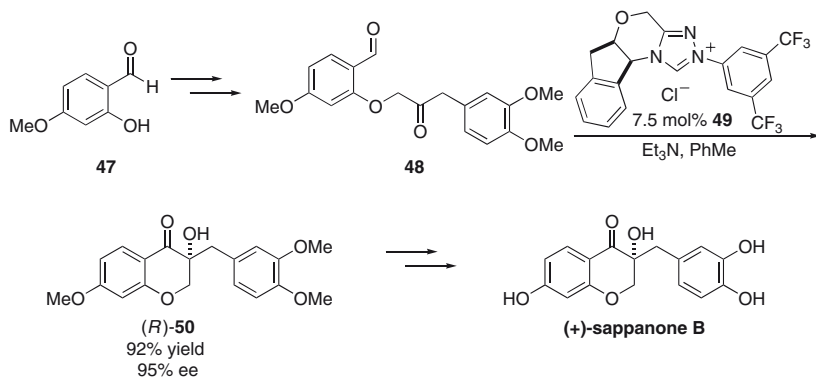


Table 5 Enders et al. enantioselective cross-benzoin reaction

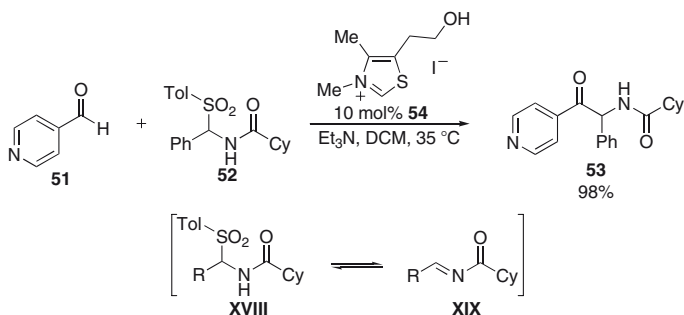
Entry	46	R	Yield (%)	ee (%)
1	a	Me	93	94
2	b	Et	90	95
3	c	<i>n</i> -Bu	85	98
4	d	<i>i</i> -Bu	91	98
5	e	Bn	43	93

Suzuki and co-workers have relayed this methodology into the synthesis of (+)-sappanone B (Scheme 5) [52]. The authors found that catalysts previously introduced by Rovis and co-workers led to inferior results; *N*-Ph catalyst **41** gave significant elimination while *N*-C₆F₅ gave low enantioselectivities. By tuning the electronics of the *N*-aryl substituent these workers identified **49** as providing the optimal mix of reactivity and enantioselectivity. Commercially available 2-hydroxy-4-methoxybenzaldehyde **47** was transformed into aldehyde **48**, which upon treatment with triazolium salt **49** in the presence of base was cyclized to afford (*R*)-**50** in 92% yield and 95% ee and subsequently transformed into (+)-sappanone B.



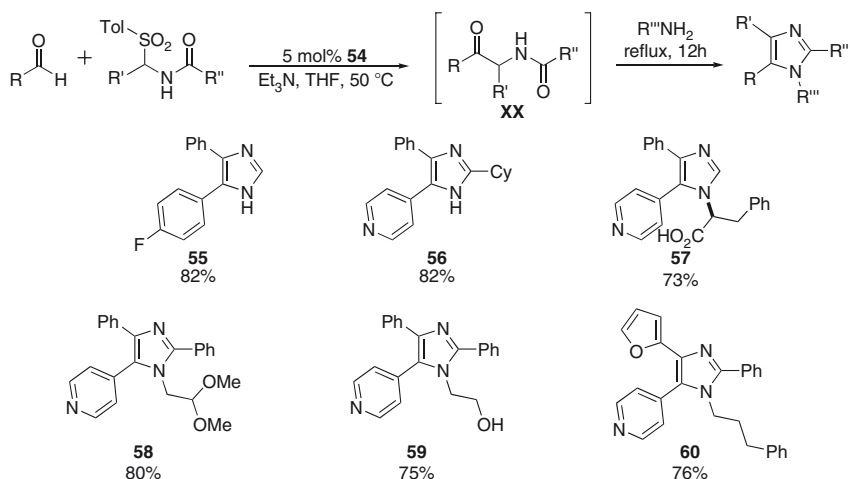
Scheme 5 Suzuki and co-workers synthesis of (+)-sappanone B

An additional means of performing a selective cross-benzoin was reported in 2001 when Murry and co-workers expanded benzoin methodology to include trapping of acyl imines **XIX** formed in situ (Scheme 6) [53]. The authors chose to use α -amido sulfones due to their stability and the relative ease of acyl imine liberation. The parent reaction combines pyridine 4-carboxaldehyde **51** and tosylamide **52** in 98% yield in the presence of pre-catalyst **54** and triethylamine (Scheme 6).



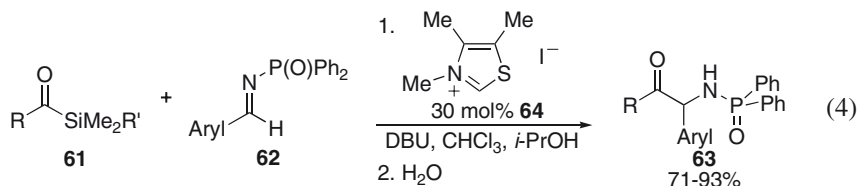
Scheme 6 Murry, Frantz and co-workers trapping of in situ formed imines

This method accommodates aryl aldehydes with both electron-deficient and electron-rich aryl substituents. Acetaldehyde is also a competent coupling partner, providing the corresponding amido ketone in 62% yield. Acyl substitution of the tosyl amide varies to include hydrogen, methyl, *tert*-butoxy, and phenyl producing the desired α -amido ketones in moderate to high yields. Expansion of this methodology to synthesize di- and tri-substituted imidazoles was reported by Murry and co-workers (Scheme 7) [54].

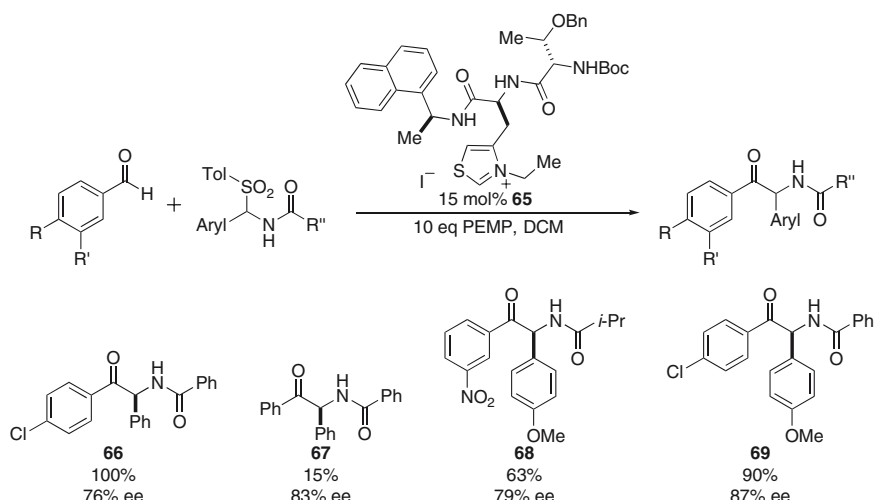


Scheme 7 Synthesis of imidazoles

Taking advantage of the acyl silane and imine methodologies, Scheidt and co-workers illustrated the use of acyl silanes **61** and *N*-diarylphosphinoylimines **62** to form α -amino ketones **63** (Eq. 4) [55]. Utilizing thiazolium pre-catalyst **64**, a variety of acyl silanes, both alkyl and aryl, can be coupled efficiently. The reaction conditions are tolerant of various aryl substitutions, providing high yields.



Miller and co-workers have reported the use of thiazolylalanine-derived catalyst **65** to render the aldehyde-imine cross-coupling enantioselective [56]. The authors comment on the time sensitivity of this transformation and found that racemization occurs when the reaction goes to complete conversion. Electron-deficient aldehydes are the most efficient coupling partners for various tosylamides leading to the corresponding products **66**, **68**, and **69** (Scheme 8).

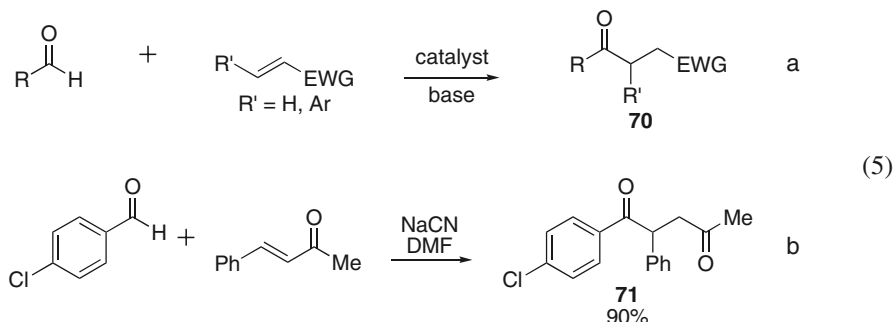


Scheme 8 Miller and co-workers aldehyde imine cross-coupling catalyzed by thiazolylalanine-derived catalysts

4 Stetter Reaction

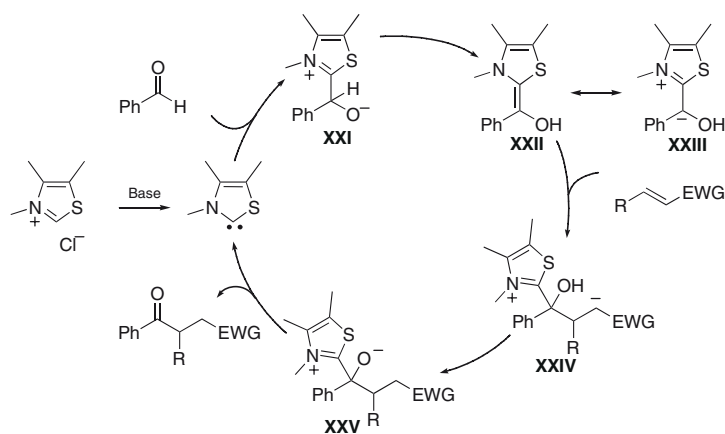
Stetter expanded Umpolung reactivity to include the addition of acyl anion equivalents to α,β -unsaturated acceptors to afford 1,4-dicarbonyls Eq. 5a [57–60]. Utilizing cyanide or thiazolylidene carbenes as catalysts, Stetter showed that a variety of aromatic and aliphatic aldehydes act as competent nucleophilic coupling partners with a wide range of α,β -unsaturated ketones, esters, and nitriles [61]. The ability to bring two different electrophilic partners

together and form a new carbon–carbon bond enhances the potential utility of this transformation. When $R' = H$, the reaction is quite versatile and provides high yields of **70**. Extensive work by Stetter and others in the development of this reaction revealed that the presence of a β -substituent on the Michael acceptor is a major limitation of this methodology; generally speaking, only the most activated Michael acceptors result in synthetically useful yields Eq. 5b. It has been shown that the reaction time can be decreased significantly with microwave irradiation [62]. Also, aldehydes can add to chalcone derivatives on solid support in moderate yields [63].



4.1 Mechanism

Since mechanistic studies modeling the Stetter reaction have not yet been reported, the proposed mechanism is based on that elucidated by Breslow for the thiazolium catalyzed benzoin reaction (Scheme 9). The carbene, formed in situ by deprotonation

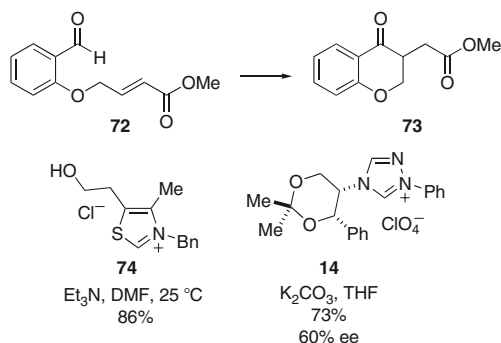


Scheme 9 Proposed mechanism for the Stetter reaction

of the corresponding azolium salt, adds to the aldehyde to form **XXI**, which undergoes proton transfer to form the acyl anion equivalent **XXIII**. Subsequent attack into the Michael acceptor forms a new carbon–carbon bond **XXIV** and is followed by a second proton transfer. Finally, tetrahedral intermediate **XXV** collapses to form the ketone, accompanied by liberation of active catalyst.

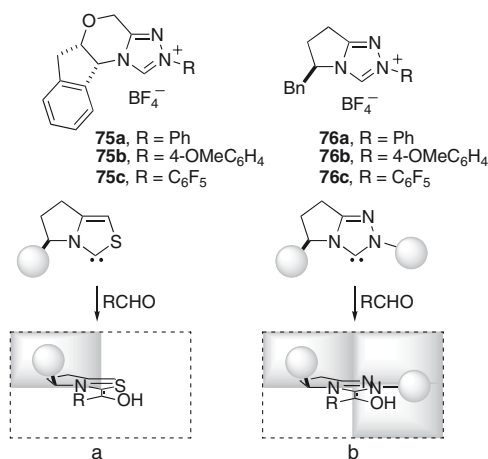
4.2 Intramolecular Stetter Reaction

Almost 20 years after the initial report of the Stetter reaction, Ciganek reported an intramolecular variant of the Stetter reaction in 1995 with thiazolium pre-catalyst **74** providing chromanone **73** in 86% yield (Scheme 10) [64]. This intramolecular substrate **72** has become the benchmark for testing the efficiency of new catalysts. Enders and co-workers illustrated the first asymmetric variant of the intramolecular Stetter reaction in 1996 utilizing chiral triazolinyldiene pre-catalyst **14** [65]. Despite moderate selectivity, the implementation of a chiral triazolinyldiene carbene in the Stetter reaction laid the foundation for future work.



Scheme 10 Intramolecular Stetter reaction

In 2002, Rovis and co-workers developed a series of triazolium pre-catalysts, **75** and **76**, and reported a highly enantioselective intramolecular Stetter reaction [66]. These tetracyclic structures bear a fused-ring system in order to restrict rotation, taking advantage of the concept first introduced by Leeper and Rawal, and further provide the ability to add steric bulk on both sides of the reacting site, blocking three of the four quadrants (Scheme 11, contrast Model **A** vs Model **B**) [67].



Scheme 11 Thiazolylidene vs triazolinylidene steric capacities

These catalysts induce enantioselectivities in the resulting chromanones and derivatives **78** in up to 97% ee (Table 6). A variety of heteroatom linkers on the aldehyde tether are compatible under the reaction conditions allowing for the synthesis of a variety of desired products in high yields and enantioselectivities.

Table 6 Variation of heteroatom linker in the intramolecular Stetter reaction

Entry	78	X	R	Catalyst	Yield (%)	ee (%)
1	a	O	H	75b	94	94
2	b	CH ₂	H	76a	90	92
3	c	O	2-Me	75b	80	97
4	d	S	H	75b	63	96
5	e	NMe	H	75b	64	82

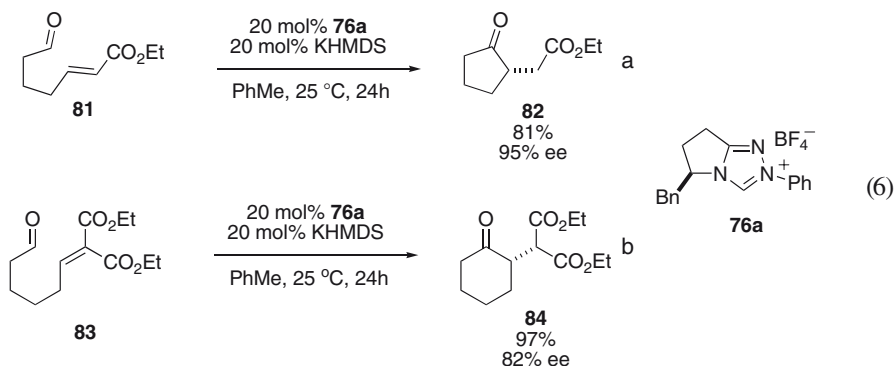
A wide range of α,β -unsaturated acceptors work well under standard reaction conditions with pre-catalyst **75c** (Table 7). Acceptors include α,β -unsaturated esters, amides, alkyl ketones, and phosphine oxides, many of which provide the products in greater than 90% ee [68, 69]. α,β -Unsaturated phenyl ketones, nitriles, and thioesters also work, albeit with lower enantioselectivity. The scope has been extended to include a variety of vinyl phosphonate precursors providing good chemical yields and moderate to high enantioselectivity (entries 9 and 10).

Table 7 Rovis and co-workers Michael acceptor scope of the intramolecular Stetter reaction

79 20 mol % 75c 20 mol % KHMDS toluene, 23 °C 80									
Entry	80	Product	Yield (%)	ee (%)	Entry	80	Product	Yield (%)	ee (%)
1	a		94	95	6 ^a	f		94	92
2 ^a	b		94	93	7	g		80	78
3 ^a	c		94	97	8	h		85	70
4 ^a	d		94	92	9	i		65	80
5	e		94	78	10	j		75	93

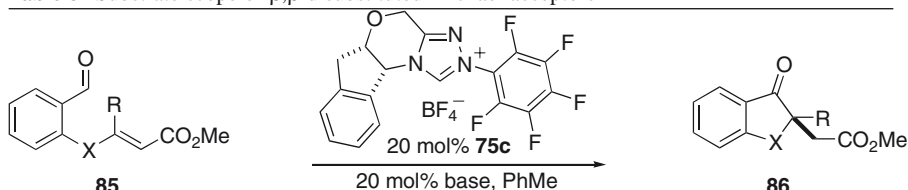
^aEnt-**75c** used as pre-catalyst

Aliphatic substrates also perform well, forming five membered rings in good yield and high enantioselectivity Eq. 6a. Typical Michael acceptors, however, are not sufficiently electrophilic to induce cyclization to form six-membered aliphatic rings. In order to effect this cyclization, use of a more electrophilic Michael acceptor, such as alkylidene malonate **83**, was required Eq. 6b [70]. The difference in reactivity is presumably due to the extra conformational freedom of the aliphatic linker compared to the fused aromatic linker of substrate **79** coupled with potential competing non-productive pathways.

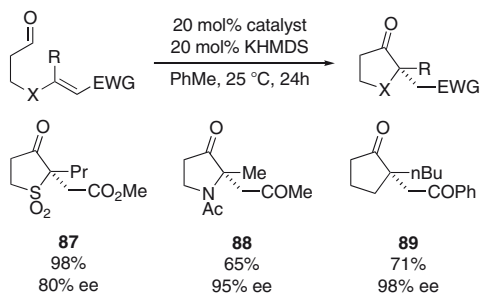


The scope of this methodology has been expanded to the synthesis of tetrasubstituted stereocenters by inducing the addition of aromatic and aliphatic aldehydes to β,β -disubstituted Michael acceptors [71, 72]. While a series of catalysts were examined, electron-deficient pre-catalyst **75c** was found to be the most efficient for this transformation (Table 8). Substrates with aromatic backbones readily undergo reaction, forming benzofuranones in high yields and enantioselectivities up to 99%. The scope includes oxygen, sulfur, and carbon linkers between the aldehyde and the α,β -unsaturated ester. Most notably, quaternary carbon centers are formed in 95% yield and 99% ee (entry 5).

Table 8 Substrate scope of β,β -disubstituted Michael acceptors

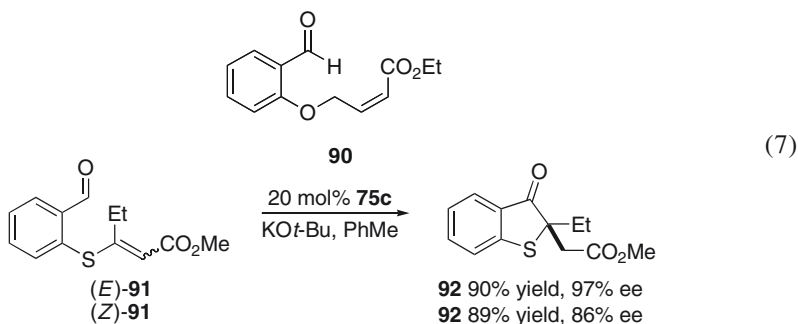
						
Entry	86	X	R	Base	Yield (%)	ee (%)
1	a	O	Et	Et ₃ N	96	97
2	b	S	Et	KOr-Bu	90	97
3	c	S	CH ₂ CH ₂ Ph	KOr-Bu	91	99
4	d	S	Ph	KOr-Bu	15	82
5	e	CH ₂	Me	Et ₃ N	95	99

Catalysts **75c** and **76a** also induce cyclization of a variety of aliphatic substrates for the construction of tetrasubstituted carbon centers in good yields and high enantioselectivities (Scheme 12). Despite the success of carbon, nitrogen and oxygen tethers, sulfide side chains have proven resistant to cyclization under optimized conditions. By changing the linker to a sulfone **87**, cyclization was accomplished in 98% yield, albeit 80% ee.

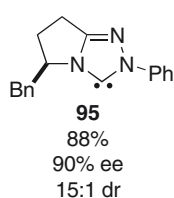
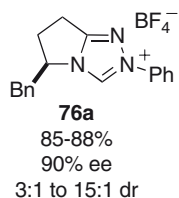
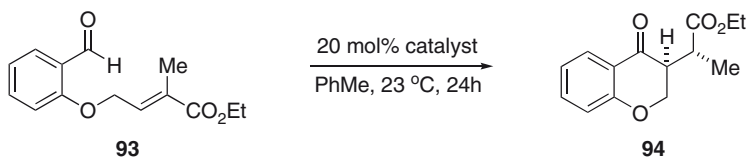


Scheme 12 Cyclization of β,β -disubstituted aliphatic substrates

The geometry of the Michael acceptor has been shown to play an important role in the intramolecular Stetter reaction [70, 72]. In the case of salicylaldehyde derived substrate **90**, which contains a *cis*-1,2-disubstituted alkene, no reaction occurs under standard reaction conditions. The same is not true with trisubstituted olefin acceptors. Cyclization of β,β -disubstituted substrate (*E*)-**91** provides cyclized product in high yield and 97% ee Eq. 7. The corresponding (*Z*)-isomer gives a similar yield although the enantioselectivity is decreased to 86%.



Utilizing prochiral α,α -disubstituted Michael acceptors, the Stetter reaction catalyzed by **76a** has proven to be both enantio- and diastereoselective, allowing control of the formation of contiguous stereocenters Eq. 8 [73]. It is noteworthy that a substantial increase in diastereoselectivity is observed, from 3:1 to 15:1, when HMDS, the conjugate acid formed upon pre-catalyst deprotonation, is removed from the reaction vessel. Reproducible results and comparable enantioselectivities are observed with free carbenes; for example, free carbene **95** provides **94** in 15:1 diastereoselectivity. The reaction scope is quite general and tolerates both aromatic and aliphatic aldehydes (Table 9).

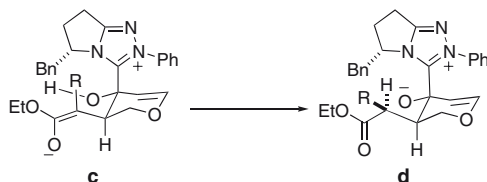


(8)

Table 9 Highly diastereoselective intramolecular Stetter reaction

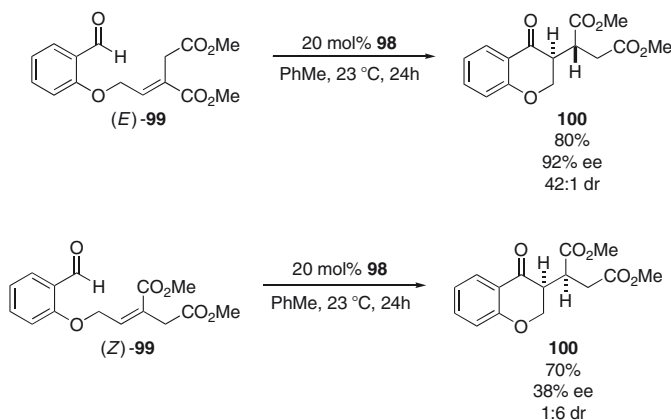
20 mol% 98 PhMe, 23 °C, 24h 96 → 97											
Entry	97	Product	Yield (%)	ee (%)	dr	Entry	97	Product	Yield (%)	ee (%)	dr
1	a		95	92	35:1	4	d		80	95	18:1
2	b		80	84	20:1	5	e		94	99	50:1
3	c		95	83	13:1	6	f		80	88	15:1

The observed diastereoselectivity of the protonation event may be explained by Model **C** (Scheme 13). In Model **C**, an intermolecular proton transfer would yield the minor diastereomer. Alternatively, the proton transfer may be intramolecular and occur from the more sterically hindered face of the enolate, providing **D**.



Scheme 13 Intramolecular protonation

The mechanistic hypothesis was tested with experiments involving a pair of substrates differing only in olefin geometry about the α,β -unsaturated ester. If the assumption that proton transfer occurs faster than the bond rotation of converting **C** to **D** is valid then the (*E*)- and (*Z*)-isomers are expected to produce opposite diastereomers. In the event, (*E*)-**99** provides 42:1 dr while (*Z*)-**99** provides 1:6 dr favoring the opposite diastereomer (Scheme 14).



Scheme 14 Complementary diastereoselectivity

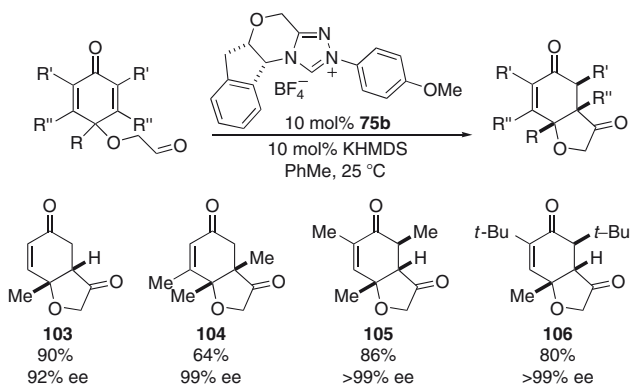
The influence of stereocenters in the backbone has been investigated [74]. A racemic substrate **101** can be subjected to standard Stetter reaction conditions leading to disubstituted cyclopentanones **102**. The reaction provides both *cis* and *trans* diastereomers in high enantiomeric excess but with very poor diastereoselectivity (Table 10). Adding steric bulk did not significantly change the outcome of the reaction (entry 2). The same trend was observed with substitution at the

3-position (entries 3 and 4). Alternatively, when substitution at 2-position is present there is little catalyst control over the diastereoselectivity and the *trans*-cyclopentanone is formed selectively in good yield (entry 5). Pre-existing stereocenters have little to no effect on the diastereoselectivity of a Stetter cyclization unless that center is alpha to the aldehyde, in which case a diminished enantioselectivity is observed (entry 5).

Table 10 Effect of a pre-existing stereocenter on the Stetter reaction

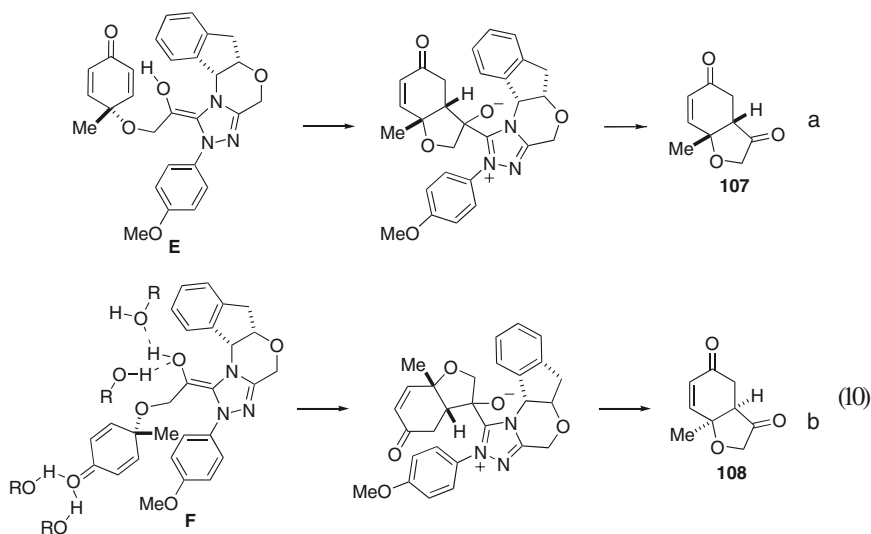
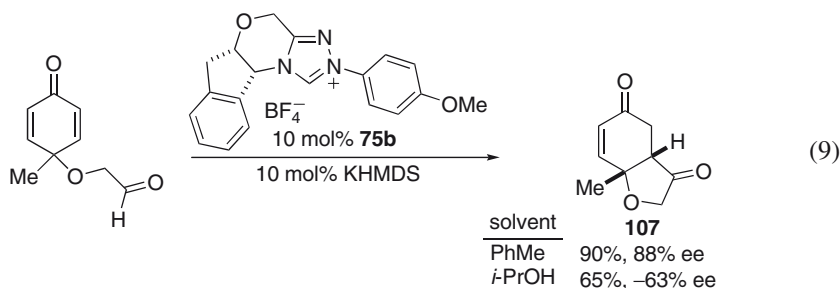
Entry	102	R	R'	R''	Catalyst	Yield (%)	<i>cis:trans</i>	ee (%)
1	a	Me	H	H	75a	90	50:50	95/90
2	b	<i>i</i> -Pr	H	H	76a	95	51:49	98/94
3	c	H	Me	H	75a	97	50:50	94/98
4	d	H	Ph	H	75a	96	50:50	96/98
5	e	H	H	Bn	75a	95	85:15	<5/<5

Rovis and Liu have accomplished the desymmetrization of cyclohexadienones by using triazolinyldene carbene **75b** (Scheme 15) [75, 76]. Multiple hydrobenzofuranones **103–106** were synthesized in good yields and excellent enantio- and diastereoselectivity. Generation of three contiguous stereocenters may be achieved in >99% ee and 80% yield.

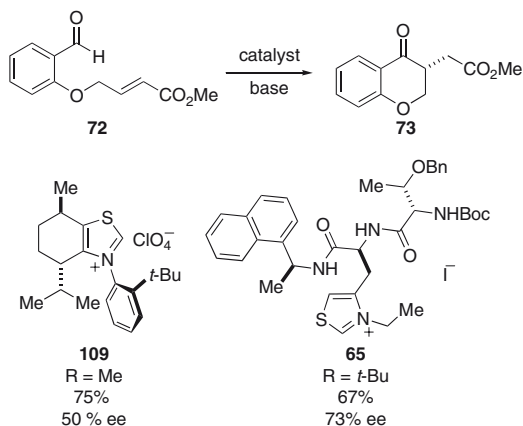


Scheme 15 Desymmetrization of cyclohexadienones

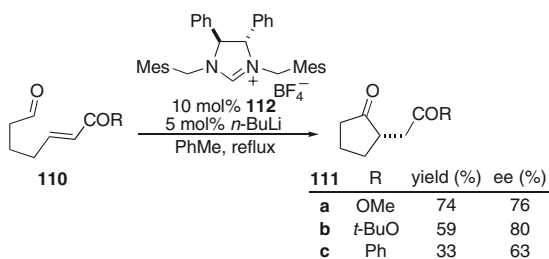
In this report the authors describe a surprising solvent effect on enantioselectivities. Alcoholic solvents afford the opposite enantiomer using the same enantiomeric series of catalyst Eq. 9. This profound effect is presumably due to hydrogen bonding in the transition state on the nucleophilic enol and/or the carbonyl acceptor Eq. 10. These electrostatic interactions can be visualized with Models **E** and **F**. Although the enantioselectivity is reversed the values remain lower than when toluene is used.



In 2004 and 2005, respectively, Bach and Miller independently described the use of chiral thiazolium salts as pre-catalysts for the enantioselective intramolecular Stetter reaction. Bach and co-workers employed an axially chiral *N*-arylthiazolium salt **109** to obtain chromanone **73** in 75% yield and 50% ee (Scheme 16) [77]. Miller and co-workers found that thiazolium salts embedded in a peptide backbone **65** could impart modest enantioselectivity on the intramolecular Stetter reaction [78]. In 2006, Tomioka reported a C_2 -symmetric imidazolinyldene **112** that is also effective in the aliphatic Stetter reaction, providing three examples in moderate enantioselectivities (Scheme 17) [79].



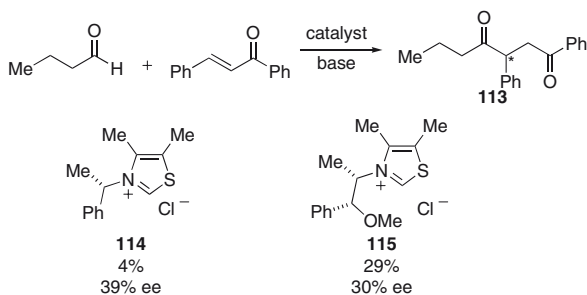
Scheme 16 Bach and Miller catalysts



Scheme 17 Tomioka's catalyst in the Stetter

4.3 Intermolecular Stetter Reaction

While catalysts and reaction protocols are well established for the enantioselective intramolecular Stetter reaction, asymmetric intermolecular Stetter products are much more difficult to obtain using known methodologies. A report by Enders and co-workers described the first asymmetric intermolecular Stetter reaction utilizing *n*-butanal and chalcone [4]. When thiazolium salt **114** is used in this system the reaction proceeds in 39% ee, albeit in 4% yield of **113**. The authors comment that both thiazolium and triazolium pre-catalysts perform poorly. The yield was increased to 29% yield with thiazolium pre-catalyst **115** although a loss in enantioselectivity was observed (Scheme 18) [80].



Scheme 18 Enders *et al.* intermolecular Stetter reaction

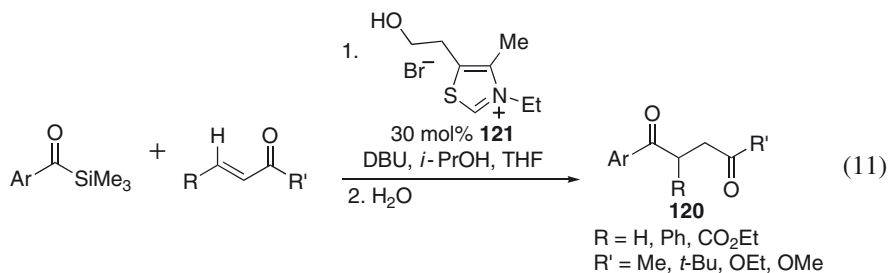
In a related process, Johnson and co-workers have developed an asymmetric metallophosphite-catalyzed intermolecular Stetter-like reaction employing acyl silanes [81, 82]. Acyl silanes are effective aldehyde surrogates which are capable of forming an acyl anion equivalent after a [1,2]-Brook rearrangement. The authors have taken advantage of this concept to induce the catalytic enantioselective synthesis of 1,4-dicarbonyls **118** in 89–97% ee and good chemical yields for α,β -unsaturated amides (Table 11). Enantioselectivities may be enhanced by recrystallization.

Table 11 Sila-Stetter reaction catalyzed by metallophosphites

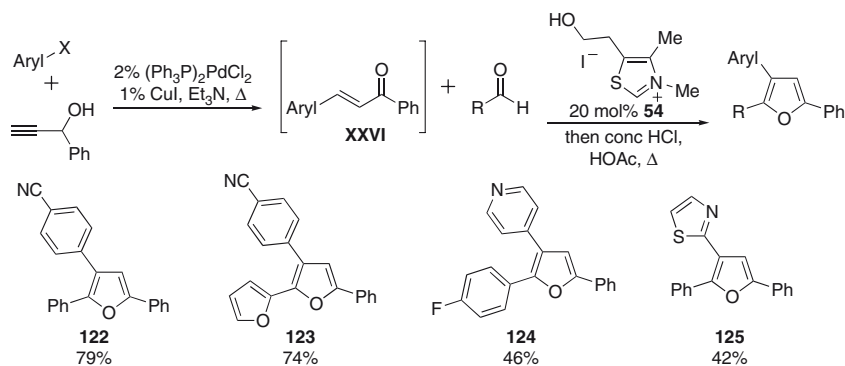
Entry	118	R	Yield (%)	ee ^a (%)	ee ^b (%)
1	a	Ph	68	90	99
2	b	3-MePh	67	93	99
3	c	4-ClPh	66	95	98
4	d	<i>N</i> -Tosylindol-3-yl	60	97	97
5	e	2-Naphthyl	66	89	97

^aBefore recrystallization ^bAfter recrystallization

Scheidt and co-workers have shown that acyl silanes behave analogously to aldehydes in the Stetter manifold, ultimately forming 1,4-dicarbonyls **120** in yields up to 75% [83, 84]. A range of acyl silanes are compatible in this reaction Eq. 11.



In an extension of traditional Stetter methodology, Müller and co-workers have used the Stetter reaction in a one-pot multicomponent reaction for the synthesis of furans and pyrroles (Scheme 19) [85, 86]. The α,β -unsaturated ketone **XXVI** is formed in situ and undergoes a Stetter reaction followed by a Paal-Knorr condensation.



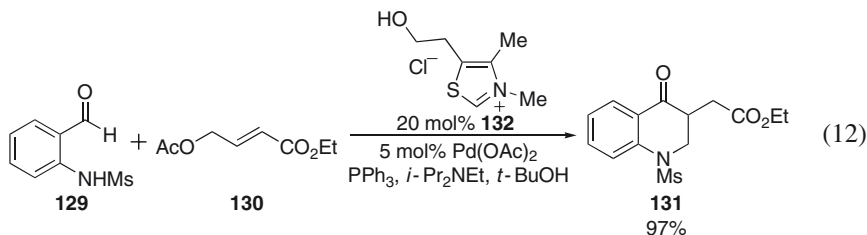
Scheme 19 Synthesis of furans via one-pot multicomponent reaction

Pyrrole synthesis has been shown to be more general than furan (Table 12). Scheidt and co-workers have subsequently shown that acyl silanes may again be used as aldehyde surrogates in this protocol [83, 87].

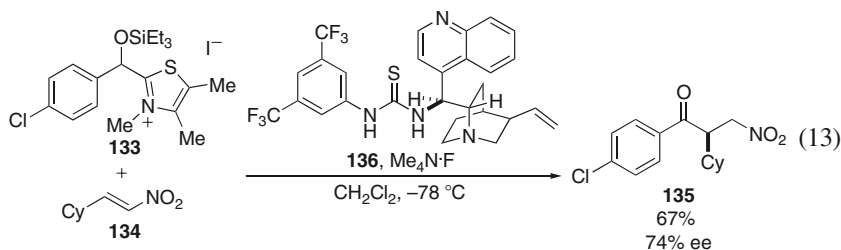
Table 12 Synthesis of pyrroles via multicomponent reaction

Entry	128	R	R'	Yield (%)	Entry	128	R	R'	Yield (%)
1	a	Ph	H	70	5	e	Ph	Bn	60
2	b	4-OMec ₆ H ₄	H	60	6	f	2-furyl	Bn	55
3	c	<i>n</i> -Pentyl	H	59	7	g	Ph	CH ₂ CO ₂ Et	54
4	d	(CH ₂) ₅ OH	H	53	8	h	Ph	CH ₂ CH ₂ OH	57

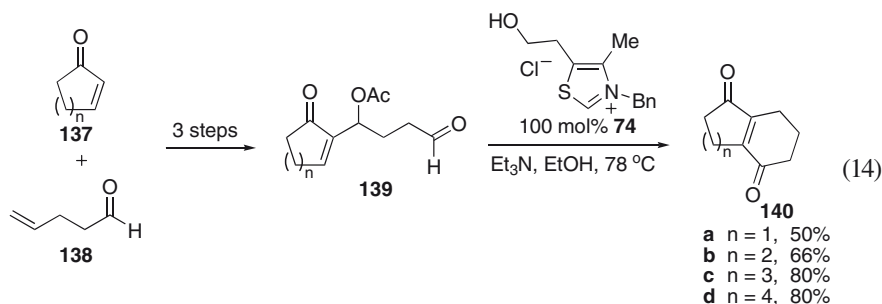
Recently, Hamada and co-workers utilized the Stetter reaction in a cascade sequence to produce dihydroquinolines, of type **131**, in excellent yields Eq. 12 [88]. Although the scope of this reaction is limited to unsubstituted aryl aldehydes, the compatibility of the carbene and palladium (0) catalysis is noteworthy.



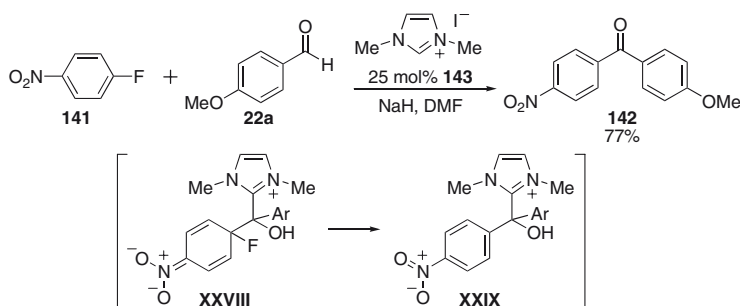
Scheidt and co-workers have reported the application of silyl-protected thiazolium carbinols as stoichiometric carbonyl anions for the intermolecular acylation of nitroalkenes [89]. While predominantly a discussion of racemic chemistry, a singular example illustrates that the newly formed stereocenter may be controlled by the addition of an equivalent of a chiral thiourea **136** with the desired product **135** formed in 74% ee Eq. 13.



Markó and co-workers utilized the Stetter reaction in the synthesis of bicycloenediones, proceeding in moderate yields using stoichiometric thiazolium pre-catalyst **74** Eq. 14 [90]. Morita-Baylis-Hillman adducts **139** were formed in three steps from commercially available starting materials 4-pentenal **138** and the corresponding cyclic enones **137**. The carbene induces a Stetter reaction followed by acetate elimination and alkene isomerization into conjugation. The best results were obtained with **139c** and **139d** providing 1,4-dicarbonyls **140c** and **140d**, respectively, in 80% yield.



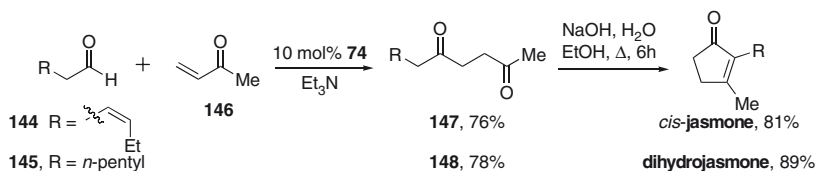
Suzuki and co-workers achieve aromatic substitution of fluoroarenes with a variety of aldehydes in good yields [91, 92]. Imidazolilydene carbene formed from **143** catalyzes the reaction between 4-methoxybenzaldehyde **22a** and 4-fluoronitrobenzene **141** to provide ketone **142** in 77% yield (Scheme 20). Replacement of the nitro group with cyano or benzoyl results in low yields of the corresponding ketones. The authors propose formation of the acyl anion equivalent and subsequent addition to the aromatic ring by a Stetter-like process forming **XXVIII**, followed by loss of fluoride anion to form **XXIX**.



Scheme 20 Aromatic substitution reaction catalyzed by NHCs

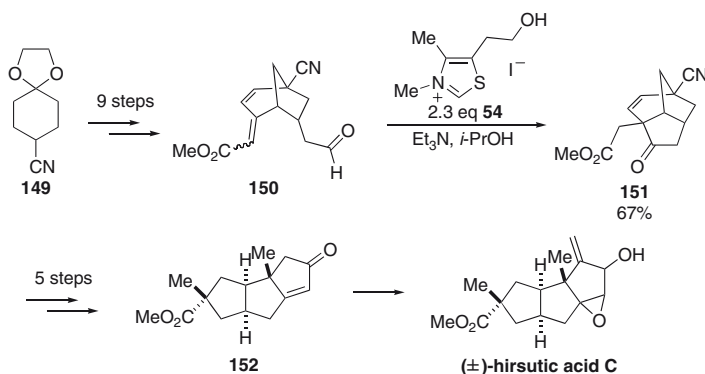
4.4 Applications in Total Synthesis

The first natural product synthesis that utilized the Stetter reaction was reported by Stetter and Kuhlmann in 1975 as an approach to *cis*-jasmonone and dihydrojasmonone (Scheme 21) [93]. Thiazolium pre-catalyst **74** was effective in catalytically generating the acyl anion equivalent with aldehydes **144** and **145**, then adding to 3-buten-2-one **146** in good yield. Cyclization followed by dehydration gives *cis*-jasmonone and dihydrojasmonone in 62 and 69% yield, respectively, over two steps. Similarly, Galopin coupled 3-buten-2-one and isovaleraldehyde in the synthesis of ($\pm$)-*trans*-sabinene hydrate [94].



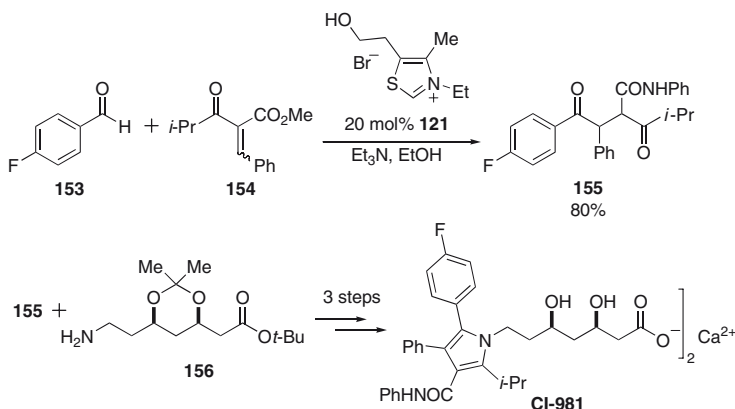
Scheme 21 Stetter and Kuhlmann's synthesis of *cis*-jasmonone and dihydrojasmonone

Trost and co-workers relied on the Michael and the Stetter reaction to set the relative stereochemistry for the core of hirsutic acid C (Scheme 22) [95]. The Stetter reaction was accomplished in 67% yield with 2.3 equiv. of 3,4-dimethyl-5-(2'-hydroxyethyl) thiazolium iodide **54** and 50 equiv. of triethylamine.



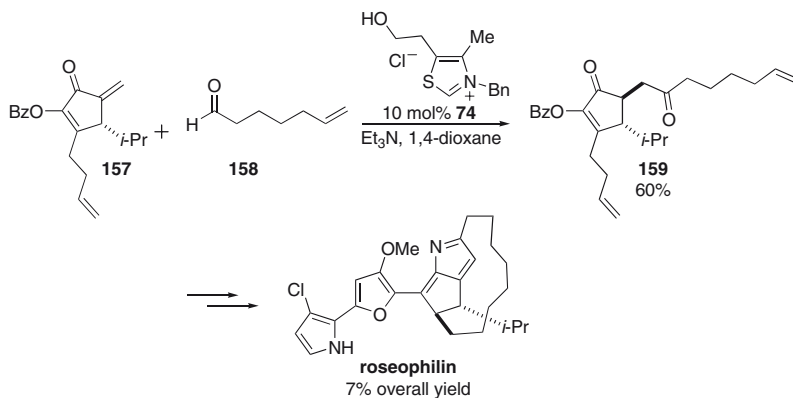
Scheme 22 Trost et al. synthesis of (±)-hirsutic acid C

The Stetter reaction has also been shown to be an important tool in the synthesis of CI-981, also known as LIPITOR® [96]. Roth and co-workers demonstrate the ability of commercially available starting materials **153** and **154** to couple in the presence of 20 mol% thiazolium pre-catalyst **121** (Scheme 23) [97, 98]. Amide **155** was obtained in 80% yield and allowed for the convergent synthesis of CI-981 in nine steps.



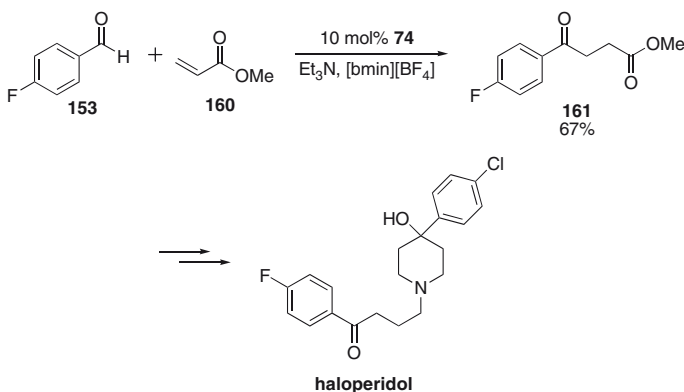
Scheme 23 Roth et al. synthesis of LIPITOR®

In the late 1990s, Tius and co-workers described a formal total synthesis of roseophilin [99, 100]. The Stetter reaction was well suited for the coupling of partners **157** and **158** in the presence of 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride (Scheme 24).



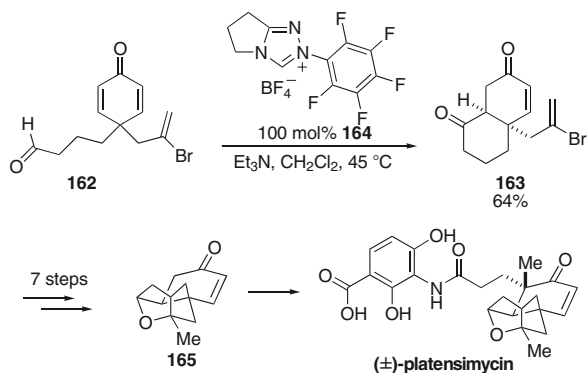
Scheme 24 Tius and co-workers synthesis of roseophilin

In the process of developing the Stetter reaction in ionic liquids, Grée and co-workers applied their methodology to the synthesis of haloperidol (Scheme 25) [101]. A variety of aromatic aldehydes react with methyl acrylate **160** when butyl-methylimidazolium tetrafluoroborate [bmim][BF₄] is used as solvent. In the synthesis of haloperidol, electron-deficient aldehyde **153** was subjected to standard reaction conditions with **160** to provide **161** in good yield.



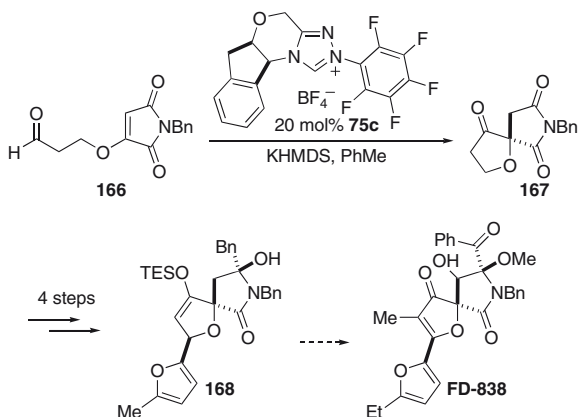
Scheme 25 Grée and co-workers synthesis of haloperidol

Nicolaou and co-workers recently published a formal synthesis of ($\pm$)-platensimycin utilizing Stetter methodology [102]. Aldehyde **162** was treated with achiral *N*-pentafluorophenyl pre-catalyst **164** and readily underwent cyclization to yield **163** as a single diastereomer (Scheme 26). After an additional seven steps late stage intermediate **165** was formed to complete the formal synthesis.



Scheme 26 Nicolaou et al. formal synthesis of ($\pm$)-platensimycin

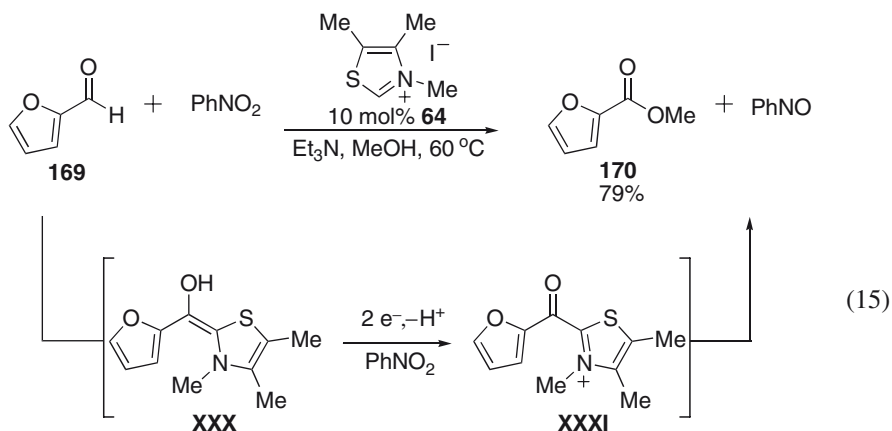
Rovis and Orellana have reported efforts toward the synthesis of FD-838 (Scheme 27) [103]. In four steps, the Stetter substrate **166** was obtained and underwent cyclization readily with aminoindanol derived pre-catalyst **75c** to produce spirocycle **167** in good yield and 99% ee.



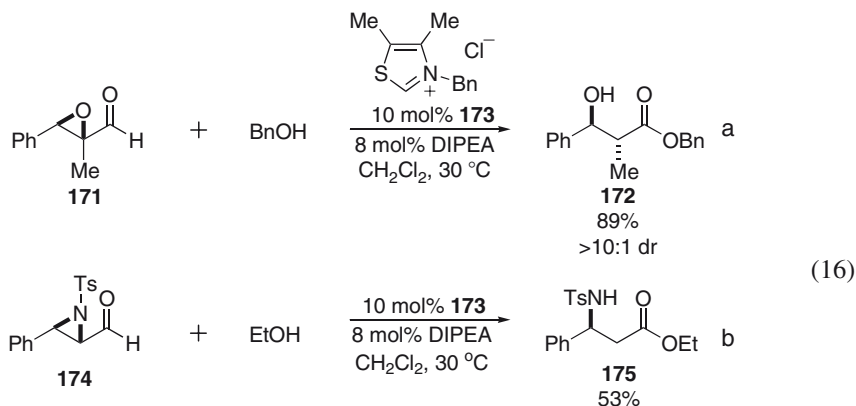
Scheme 27 Rovis and Orellana's efforts toward the synthesis of FD-838

5 Redox Reactions

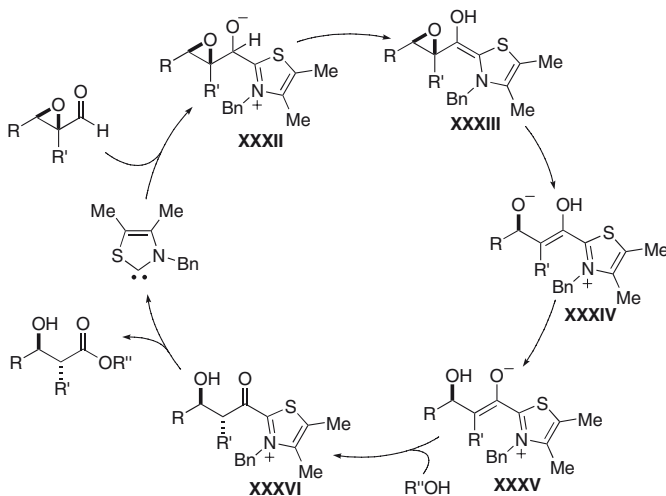
The catalytic preparation of esters and amides under mild and waste free reaction conditions using readily available starting materials is a desirable goal. The first redox process of this type using heterocyclic carbenes was reported by Castells and co-workers in 1977 in which aldehydes were oxidized to esters in one-pot in the presence of nitrobenzene [104]. Furfural **169** is converted into methyl 2-furoate **170** in 79% yield Eq. 15. Nitrobenzene is the presumed stoichiometric oxidant for the oxidation of the nucleophilic alkene **XXX** to the acyl azolium **XXXI** by successive electron transfer events. The authors observe nitrosobenzene as a stoichiometric byproduct. This type of reactivity is also observed when cyanide is used as the catalyst. Miyashita has expanded the scope of this transformation using imidazolidene carbenes [105–107].



In 2004, Bode and Rovis independently and concurrently reported the catalytic coupling of reducible aldehydes and alcohols. This mode of reactivity is most closely related to the work published by Wallach, who generated dichloroacetic acid from chloral under cyanide catalysis in aqueous media [108]. Bode and co-workers reported the catalytic, diastereoselective synthesis of β -hydroxy esters from α,β -epoxy aldehydes using thiazolium pre-catalyst **173** Eq. 16a [109]. MeOH , EtOH , and BnOH are effective nucleophiles providing upwards of $>10:1$ diastereoselectivity. Aziridinylaldehyde **174** has also been shown to provide the desired *N*-tosyl- β -aminoester **175** in 53% yield Eq. 16b.



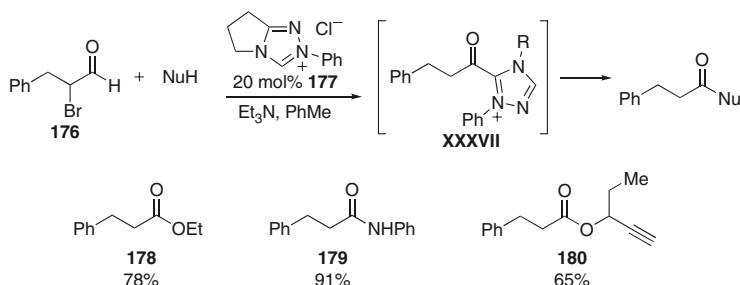
The proposed catalytic cycle for this reaction begins with the initial attack of the in situ generated thiazolyliidene carbene on the epoxyaldehyde followed by intramolecular proton transfer ([Scheme 28, XXXII–XXXIII](#)). Isomerization occurs to open the epoxide forming [XXXIV](#) which undergoes a second proton transfer forming [XXXV](#). Diastereoselective protonation provides activated carboxylate intermediate [XXXVI](#). Nucleophilic attack of the activated carboxylate regenerates the catalyst and provides the desired β -hydroxy ester.



Scheme 28 Proposed mechanism for the formation of β -hydroxy esters

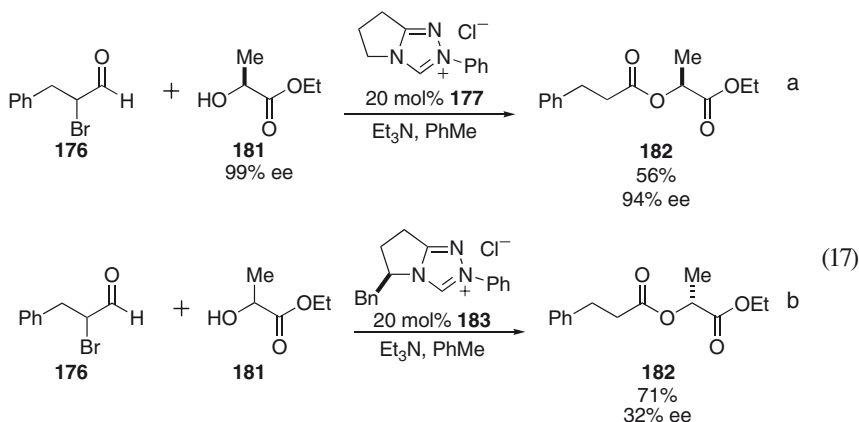
Concurrently with Bode's work, Rovis and co-workers reported an internal redox reaction of α -haloaldehydes to provide a variety of esters in good yields [110]. Triazolium salt [177](#) proved most effective for the transformation of

α -bromodihydrocinnamaldehyde **176** into the desired ester (Scheme 29). Activated carboxylate **XXXVII**, similar to **XXXVI** (Scheme 28), is the proposed intermediate. Secondary and tertiary bromoaldehydes are also useful electrophiles, along with secondary alcohols and phenols as nucleophilic partners in this acylation reaction.



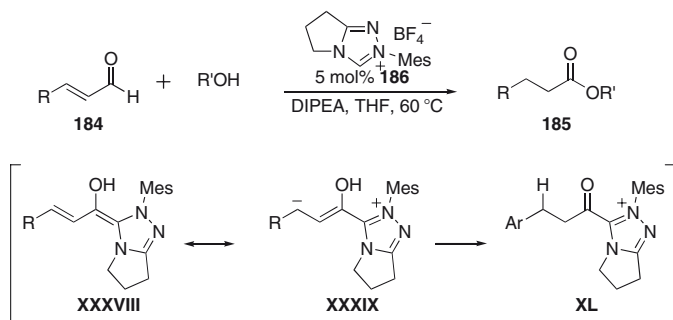
Scheme 29 Rovis and co-workers acylation reaction via activated carboxylate **XXXVII**

The reaction conditions are mild and generally tolerant of epimerizable stereocenters. For instance, the use of (*S*)-ethyl lactate **181** under the reaction conditions produces desired ester **182** in 94% ee (Eq. 17a). The subjection of racemic ethyl lactate **181** to standard reaction conditions with chiral pre-catalyst **183** provides ester **182** in 32% ee (Eq. 17b). This result suggests that the catalyst is intimately involved in the acylation event.



Bode and co-workers have shown that the outcome of internal redox reactions is uniquely dependent on the base [111]. When diisopropylethyl amine is used in the reaction of an enol and an alcohol, the initially generated homoenolate is protonated

more rapidly than the carbon–carbon bond formation of the homoenolate **XXXIX** to another equivalent of enol (**Scheme 30**). Thus this reaction serves as a direct conversion of an α,β -unsaturated aldehyde to the corresponding saturated ester **185** via **XL**.



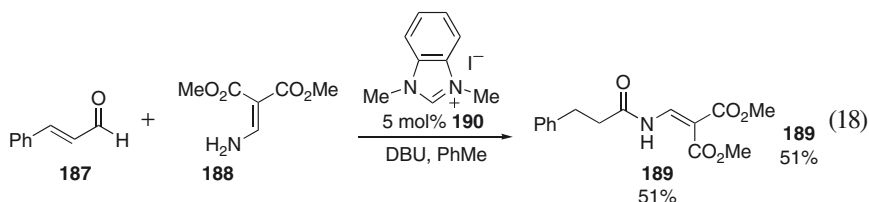
Scheme 30 Base dependent reactivity

Various aldehydes **184** and alcohols have been shown to be competent in the redox esterification of unsaturated aldehydes in the presence of the achiral mesityl triazolium pre-catalyst **186**. Both aromatic and aliphatic enals participate in yields up to 99% (**Table 13**). Tri-substituted enals work well (entry 3), as do enals with additional olefins present in the substrate (entries 4 and 7). The nucleophile scope includes primary and secondary alcohols as well as phenols and allylic alcohols. Intramolecular esterification may also occur with the formation of a bicyclic lactone (entry 8).

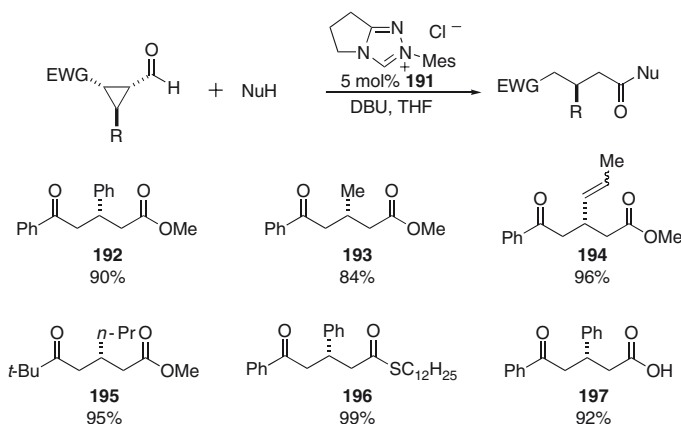
Table 13 Bode and co-workers redox esterification

Entry	185	Product	Yield (%)	Entry	185	Product	Yield (%)
1	a		97	5	e		86
2	b		86	6	f		79
3	c		72	7	g		63
4	d		85	8	h		89

Scheidt and co-workers have synthesized similar products using this reaction manifold [112]. While results are limited to primary and secondary alcohols, the authors provided a single example of the use of an amine nucleophile. The reaction of cinnamaldehyde **187** and β -amino alkylidene malonate **188** provide amide product **189**, albeit in moderate yield Eq. 18.



Bode and co-workers further extended redox esterification to include carbon–carbon bond breaking of formyl-cyclopropanes [113]. Both esters and thioesters are formed in high yield and good enantioselectivities (Scheme 31). The *N*-mesityl substituted triazolium salt **191** proved to be the most efficient pre-catalyst providing complete suppression of the benzoin reaction. Electron-deficient substituents, such as phenyl ketone, readily provide ester formation.



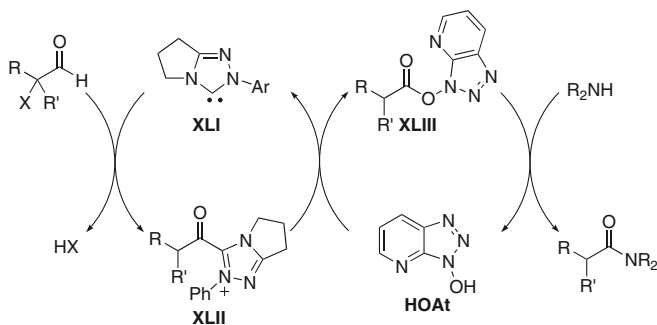
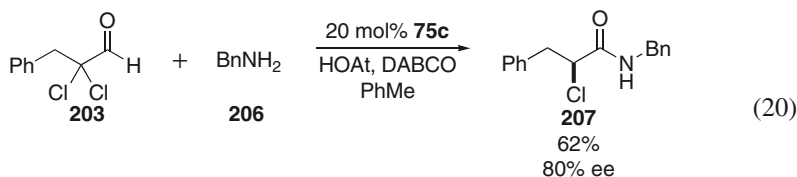
Scheme 31 Redox esterification of chiral enantioenriched formylcyclopropanes

In 2006, Zeitler demonstrated the use of alkynyl aldehydes in redox esterification [114]. As in previous examples, the author proposes the formation of an activated carboxylate that acts as an acylating agent Eq. 19. A variety of α,β -unsaturated carboxylic esters **199** are formed in moderate yields with *E*-selectivity up to >95:5.

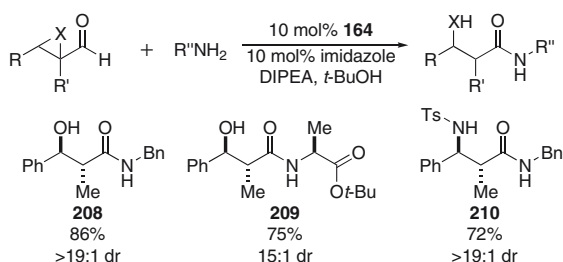
Table 15 Amine scope of the redox amidation of α,α -dichloroaldehydes

Entry	205	RR'NH	Yield (%)	Entry	205	RR'NH	Yield (%)
1	a	EtNH ₂	89	5	e	MeNHOMe	72
2	b	CyNH ₂	85	6	f	PhNH ₂	87
3	c	<i>t</i> -BuNH ₂	73	7	g	3-ClC ₆ H ₄ NH ₂	82
4	d	Et ₂ NH	89	8	h	4-OMeC ₆ H ₄ NH ₂	85

When 2,2-dichloro-3-phenylpropanal **203** is subjected to standard reaction conditions with chiral triazolium salt **75c**, the desired amide is produced in 80% ee and 62% yield Eq. 20. This experiment suggests that the catalyst is involved in an enantioselective protonation event. With this evidence in hand, the proposed mechanism begins with carbene addition to the α -reducible aldehyde followed by formation of activated carboxylate **XLII** (Scheme 32). Acyl transfer occurs with HOAt, presumably due to its higher kinetic nucleophilicity under these conditions, thus regenerating the carbene. In turn, intermediate **XLIII** then undergoes nucleophilic attack by the amine and releases the co-catalyst back into the catalytic cycle.

**Scheme 32** Proposed catalytic cycle of the redox amidation of α,α -dichloroaldehydes

As previously explored by Bode, other α -reducible substrates, such as α,β -epoxy aldehyde and aziridinylaldehyde, are competent partners for redox reactions. (Scheme 33) [109]. Various amines are compatible nucleophiles in this methodology in which β -hydroxy amides are furnished in good yield and excellent diastereoselectivity. A similar reaction manifold was discovered concurrently by Bode and co-workers using imidazole as co-catalyst [117].



Scheme 33 Synthesis of β -hydroxy amides catalyzed by NHCs

In a related transformation, Bode and co-workers have demonstrated the utility of homoeneolate protonation in an azadiene Diels-Alder reaction catalyzed by aminoindanol derived *N*-mesityl pre-catalyst **214** [118, 119]. The cyclization products **213** are obtained as a single diastereomer in excellent enantiomeric excess (Table 16). Electron-deficient enals are used in order to increase the electrophilicity and reactivity of the compounds. After protonation of the homoeneolate moiety, an inverse electron demand Diels-Alder is proposed to provide the desired cyclized product.

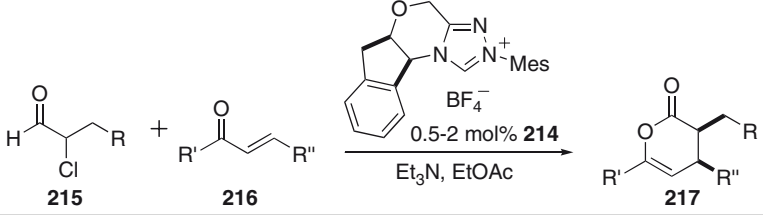
Table 16 Azadiene Diels-Alder reaction

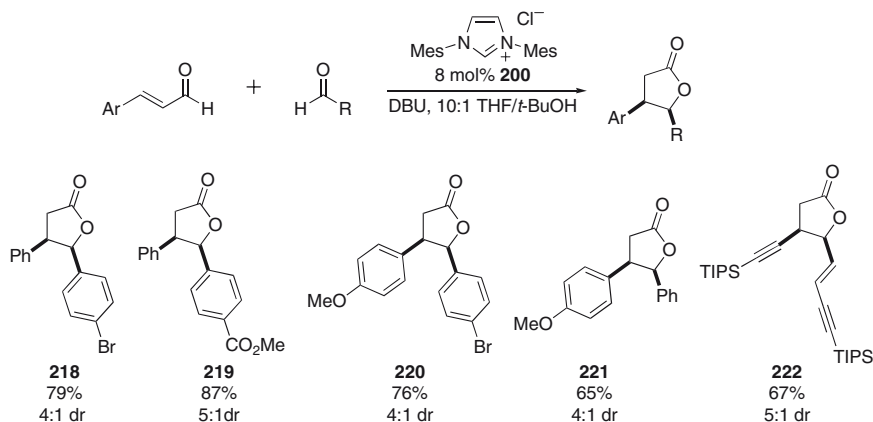
Entry	213	R	R'	Yield (%)	ee (%)
1	a	OEt	Ph	90	99
2	b	OEt	4-OMeC ₆ H ₄	81	99
3	c	OEt	4-COMeC ₆ H ₄	55	99
4	d	OEt	1-furyl	71	99
5	e	OEt	<i>n</i> -Pr	58	99
6	f	<i>Or</i> -Bu	Ph	70	97
7	g	Me	Ph	51	99
8	h	Me	<i>n</i> -Pr	71	98
9	i	Ph	4-OMeC ₆ H ₄	52	99

In continuing efforts at expanding the utility of NHCs, the synthesis of trisubstituted dihydropyran-2-ones employing chiral triazolium pre-catalyst was described by Bode and co-workers in 2006 [120]. In a mechanism distinct from earlier redox processes, this transformation proceeds via an enantioselective oxodiene Diels-Alder reaction to produce desired products in high yield and excellent enantiomeric excess (Table 17). The high selectivity, as well as the low catalyst loading and relatively fast reaction times, are impressive. The substrate scope is quite broad and includes varying substitution on the enone and aldehyde partners. Aromatic and aliphatic substitution is equally tolerated and provides excellent enantioselectivities. Diminished diastereoselectivity of aryl substitution is presumably due to epimerization of the *cis*-annulation product. This is further evidenced by the observation that the diastereomeric ratio is higher when the reaction is stopped before complete consumption of starting material.

Homoenolates generated catalytically with NHCs can also be employed for C-C and C-N bond formation. Bode and Glorius have independently accomplished the diastereoselective synthesis of γ -butyrolactones by annulation of enals and aldehydes [121, 122]. Bode and co-workers envisioned that increasing the steric bulk of the acyl anion equivalent would allow reactivity at the homoenolate position. While trying to suppress the competing benzoin and enal dimerization the authors comment on the steric importance of the catalyst. Thiazolium pre-catalyst **173** proved unsuccessful at inducing annulation. *N*-mesityl substituted imidazolium salt **200** was found to provide up to 87% yield and moderate diastereoselectivities (Scheme 34).

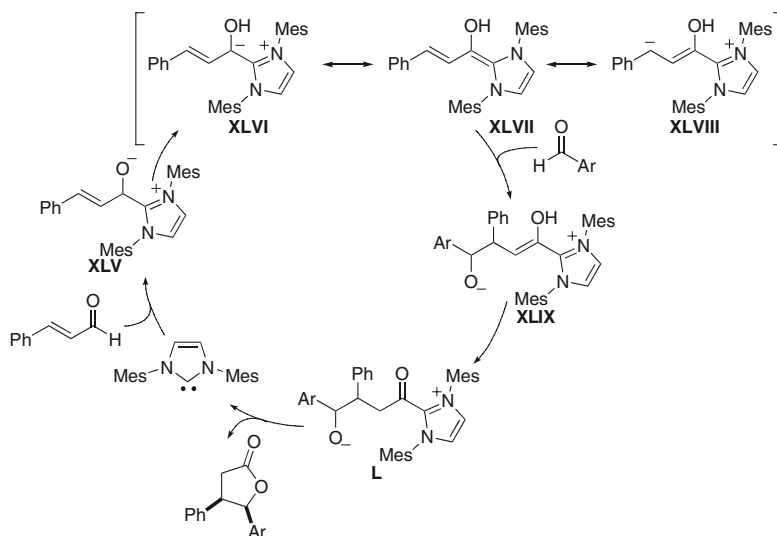
Table 17 Oxodiene Diels-Alder reaction

							
Entry	217	R	R'	R''	Yield (%)	ee (%)	dr
1	a	Ph	Me	CO ₂ Me	88	99	>20:1
2	b	Ph	4-BrC ₆ H ₄	CO ₂ Me	80	99	6:1
3	c	<i>n</i> -C ₉ H ₁₉	Me	CO ₂ Me	71	99	>20:1
4	d	OTBS	Ph	CO ₂ Me	80	97	3:1
5	e	Ph	CO ₂ Et	Cy	85	95	>20:1
6	f	OTBS	CO ₂ Et	<i>p</i> -Tol	70	99	>20:1



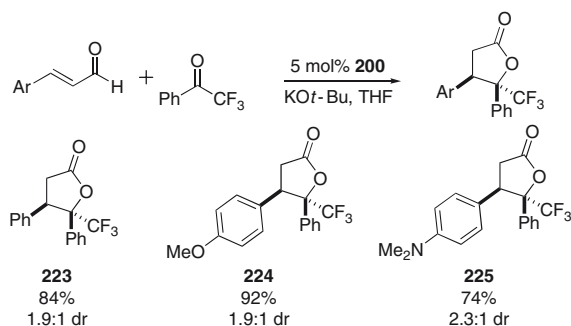
Scheme 34 Synthesis of γ -butyrolactones

The proposed catalytic cycle is shown in [Scheme 35](#) and begins with the imidazolylidene carbene adding to the enal. Proton transfer provides acyl anion equivalent **XLVII**, which may be drawn as its homoenolate resonance form **XLVIII**. Addition of the homoenolate to aldehyde followed by tautomerization affords **L** the precursor for lactonization and regeneration of the carbene.

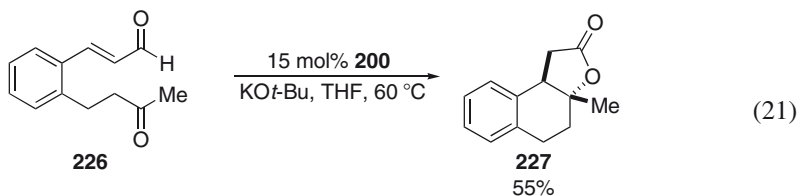


Scheme 35 Proposed mechanism of NHC catalyzed formation of γ -butyrolactone

Concurrently, Glorius and co-workers reported the synthesis of γ -butyrolactones under similar reaction conditions [122, 123]. Glorius has extended this reactivity to include trifluoromethyl ketones (Scheme 36). In addition to intermolecular reactions, intramolecular homoenolate additions are possible in modest yield Eq. 21 [123].



Scheme 36 Synthesis of γ -butyrolactones from trifluoromethyl ketones and enals

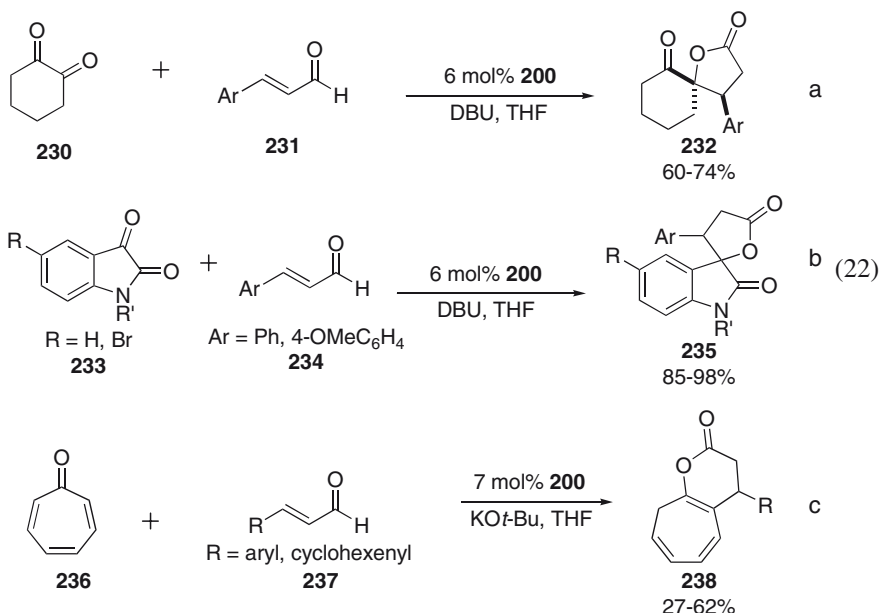


The synthesis of γ -lactams has been achieved under similar reaction conditions (Table 18) [124]. Initially, Bode and co-workers screened a variety of acyl imines in order to find suitable electrophiles. Control experiments provided evidence for carbene addition to the acyl imine, yielding a stable complex with complete inhibition of the desired reactivity. Reversibility of this addition was key to the success of the reaction. *N*-4-Methoxybenzenesulfonyl imines **212** proved to be the most efficient partners for lactamization with cinnamaldehydes **228** to provide γ -lactams **229** in moderate yields and good diastereoselectivities. Notably, no benzoin or Stetter products or their corresponding derivatives were observed during this reaction.

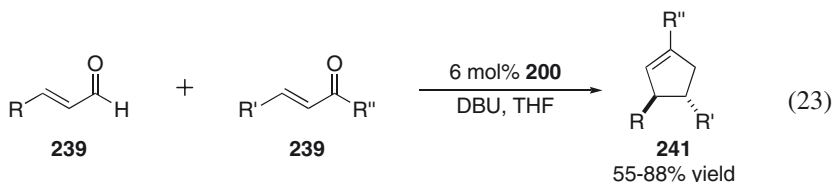
Nair and co-workers reported the diastereoselective synthesis of spiro γ -butyrolactones from 1,2-dicarbonyls [125]. The authors studied the reaction with 1,2-cyclohexane dione **230** which produces the desired lactone **232** in good yields Eq. 22a. Isatins **233** are more reactive, but the products **235** are obtained as a 1:1 separable mixture of diastereomers Eq. 22b. The Nair research group extended this methodology to include homoenolate addition to tropanone **236** to form bicyclic δ -lactones **238** Eq. 22c [126].

Table 18 NHC catalyzed annulation of enals and imines

Entry	229	R	R'	Yield (%)	dr
1	a	Ph	4-MeC ₆ H ₄	70	4:1
2	b	Ph	3-OMe	69	3:1
3	c	Ph	2-furyl	73	1.7:1
4	d	Ph		61	8:1
5	e		4-MeC ₆ H ₄	51	10:1



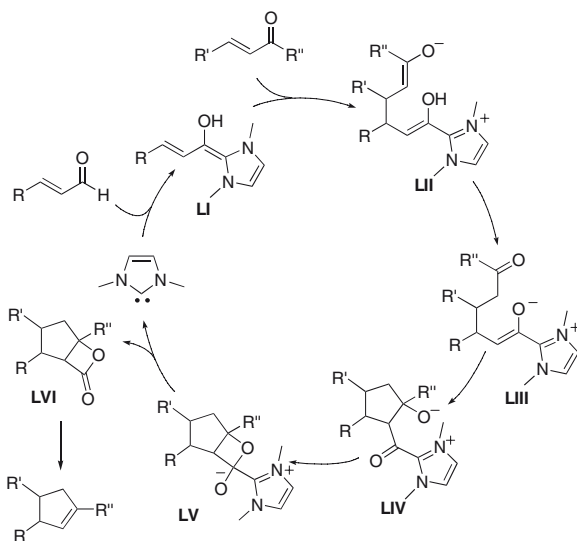
Nair and co-workers have continued their investigations into the catalytic reactivity of NHCs to include the synthesis of trisubstituted cyclopentenones [127]. Under mild reaction conditions the catalytically generated homoenolate adds conjugately to a chalcone derivative **240**, which then proceeds to furnish a cyclopentenone **241** as a single diastereomer in good yield Eq. 23. Compatible substituents include aryl groups, possessing electron-releasing and electron-withdrawing substitutions as well as one example where R and R' are methyl.



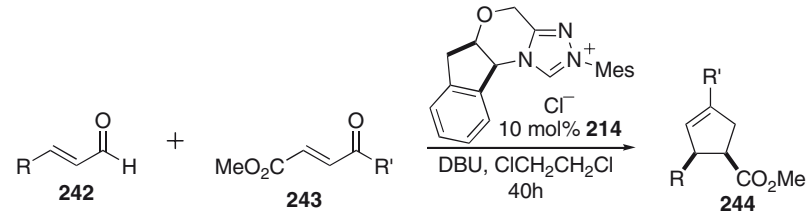
Upon formation of intermediate **LI**, conjugate addition to a chalcone and subsequent proton transfer is proposed to lead to enolate **LIII** (Scheme 37). An intramolecular aldol addition provides activated carboxylate **LIV** in which alkoxide acylation regenerates the catalyst and delivers β -lactone **LVI** which, upon decarboxylation, gives rise to a trisubstituted cyclopentene.

Bode and co-workers rendered this transformation asymmetric allowing access to *cis*-cyclopentenes **244** with high enantioselectivity (Table 19) [128]. Optimized reaction conditions include the use of *N*-methyl substituted aminoindanol derived triazolium catalyst **214**. When chalcone and derivatives were subjected to the reaction conditions, *cis*-cyclopentenes were formed selectively. Although the substrate scope is also limited to β -aryl substituted enals, *cis:trans* ratios of up to >20:1 are observed.

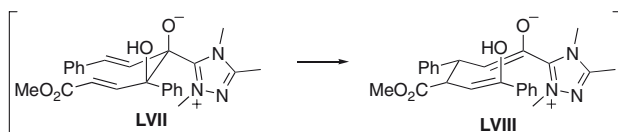
In contrast to Nair, Bode and co-workers propose that cross-benzoin adduct **LVII** is formed which then undergoes an oxy-Cope rearrangement to form **LVIII** (Scheme 38). Tautomerization and intramolecular aldol reaction occurs following the catalytic cycle proposed by Nair.



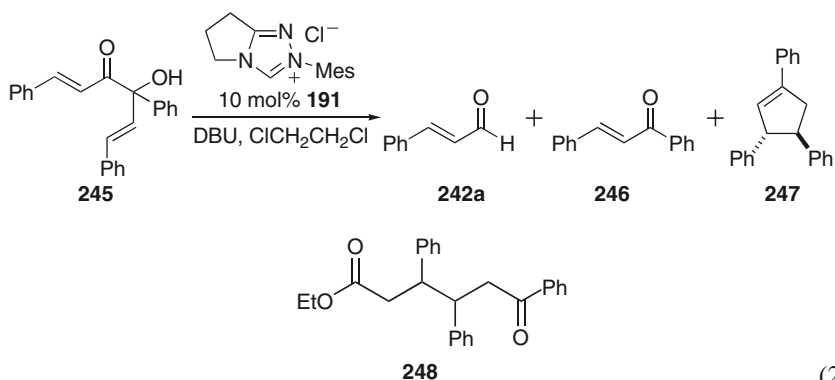
Scheme 37 Proposed mechanism of trisubstituted cyclopentene formation

Table 19 Scope and selectivity of cyclopentene formation


Entry	244	R	R'	yield(%)	cis:trans	ee(%)
1	a	Ph	Ph	78	11:1	99
2	b	Ph	4-MeOC ₆ H ₄	58	5:1	99
3	c	Ph	4-BrC ₆ H ₄	50	11:1	99
4	d	Ph	2-furyl	93	>20:1	98
5	e	4-BrC ₆ H ₄	Ph	58	6:1	99
6	f	4-CF ₃ C ₆ H ₄	Ph	68	4:1	98
7	g	2-furyl	Ph	53	5:1	99
8	h	<i>n</i> -Pr	Ph	25	14:1	96

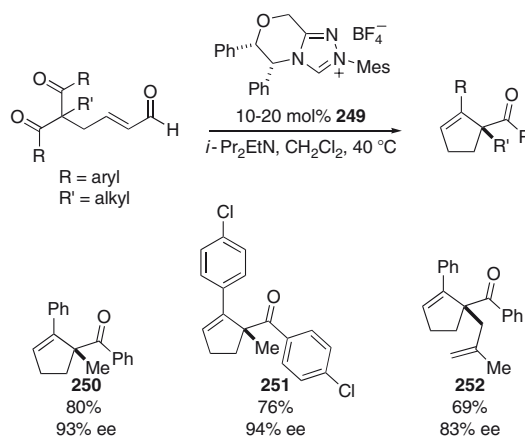
**Scheme 38** Proposed intermediates leading to *cis*-cyclopentenones

The authors describe a control experiment in which cross-benzoin product **245** was subjected to standard reaction conditions with achiral triazolium pre-catalyst **191** yielding retro-benzoin products, as well as cyclopentene product **247** Eq. 24. This result additionally demonstrates the reversibility of the benzoin reaction. When trimethylsilyl-protected **245** is treated under the same reaction conditions with ethanol as a nucleophile, ketoester **248** is formed along with retro silyl-benzoin and Stetter products. This result provides enough evidence that the cross-benzoin/oxy-Cope mechanism cannot be dismissed.



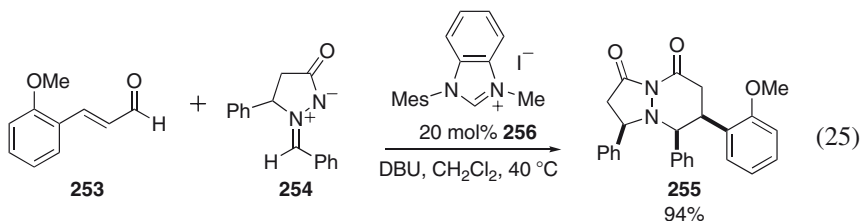
(24)

In 2007, Scheidt and co-workers reported the intramolecular desymmetrization of 1,3-diketones utilizing triazolium pre-catalyst **249** (Scheme 39) [129]. Generation of a homoenolate is followed by β -protonation and aldol reaction. In accordance with the proposed mechanism by Nair (Scheme 37), acylation occurs followed by loss of carbon dioxide. Cyclopentenones are formed in enantioselectivities up to 94% ee. The scope of this reaction is limited to aryl substitution of the diketone and alkyl substitution of R.



Scheme 39 Desymmetrization of 1,3-diketones

In a related paper, Scheidt and co-workers described a stereoselective formal [3 + 3] cycloaddition catalyzed by imidazolinylidene catalyst **256** Eq. 25 [130]. Ultimately this is an intermolecular addition of the homoenolate intermediate to an azomethine ylide followed by intramolecular acylation and presumably follows the same mechanistic path as described previously. Pyridazinones are obtained as single diastereomers in good to high yield from a number of aldehydes. Unfortunately no reaction occurs with the presence of electron-withdrawing groups on the aryl ring of the enal.

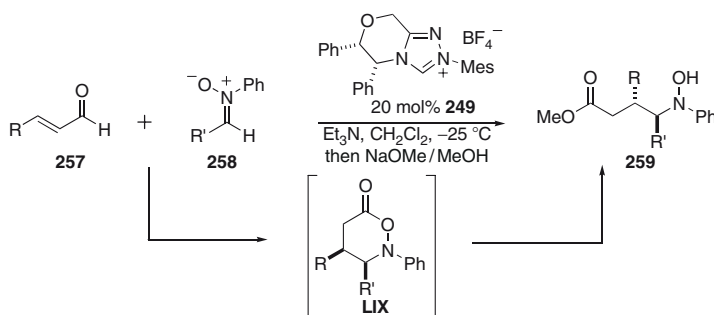


In related methodology, Scheidt and co-workers have also reported the homoenolate addition to nitrones to produce products of a formal [3 + 3]. Upon treatment with

basic methanol **LIX** opens to generate hydroxylamines in good to excellent enantio- and diastereoselectivities (Scheme 40) [131]. The scope of this reaction includes electron-rich and electron-deficient enals with little deviation in the overall yield.

Scheidt and co-workers have also illustrated the oxidation of activated alcohols to esters [132]. Oxidations of alcohols such as **260** provide the electrophile (acyl donor) for a nucleophilic alcohol **261**. Esters **262** are derived from propargylic, allylic, aromatic, and hetero-aromatic substrates (Table 20). The nucleophilic alcohol scope includes MeOH, *n*-BuOH, *t*-BuOH, 2,2,2-trichloroethanol, 2-methoxyethanol, and 2-(trimethylsilyl) ethanol.

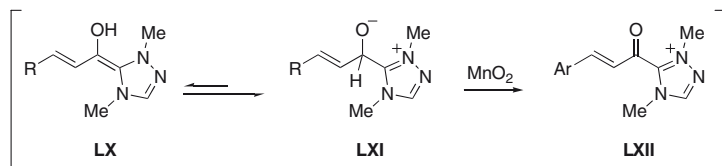
In this transformation, manganese(IV) oxide oxidizes allylic or benzylic alcohols to aldehydes followed by nucleophilic attack of the in situ formed triazolinyli- dene carbene (Scheme 41). The authors suggest the formation of an acyl anion equivalent **LX** is slow in MeOH compared to oxidation to allow for an activated carboxylate **LXII**.



Scheme 40 Scheidt and co-workers formal [3 + 3] of enals and azomethine

Table 20 Alcohol to ester oxidation catalyzed by NHC

$\text{R}-\text{CH}_2\text{OH} \quad \textbf{260} + \quad n\text{-BuOH} \quad \textbf{261} \xrightarrow[1.5 \text{ eq DBU, 15 eq MnO}_2]{\text{Mes-NHC-Mes} \quad \textbf{200} \quad 10\text{-}50 \text{ mol\%}} \quad \text{R}-\text{CO}-\text{O}n\text{-Bu} \quad \textbf{262}$							
Entry	262	R	Yield (%)	Entry	262	R	Yield (%)
1	a		93	4	d		87
2	b		91	5	e		65
3	c		85	6	f	2-BrC ₆ H ₄	70

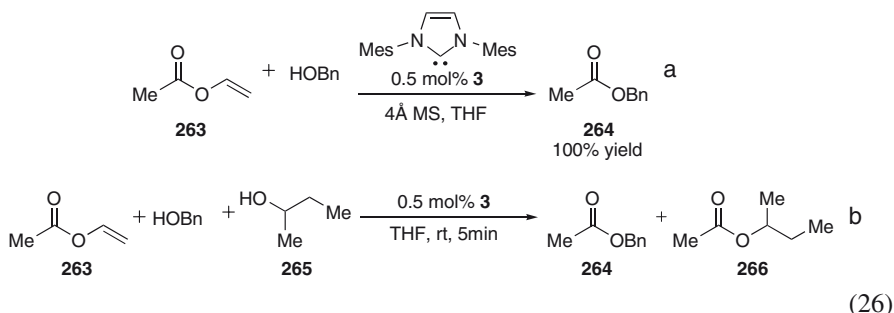


Scheme 41 Proposed intermediates leading to esters

6 Transesterification Reactions

The first examples of NHC catalyzed transesterification reactions were described independently by Nolan and Hedrick in 2002 [133, 134]. Transesterification reactions may appear trivial, but most methods are unselective between primary and secondary alcohols [135].

Nolan and co-workers found that in the presence of **3**, vinyl acetate acts as an acylating agent of benzyl alcohol in excellent yield with a reaction time of only 5 min (Eq. 26a). A range of imidazolium catalysts perform well in this reaction, as do strong inorganic bases. Employing NHCs as catalysts for acylation proved to be highly selective for primary over secondary alcohols. As shown in (Eq. 26b), a 1:1 mixture of primary and secondary alcohols resulted in a 20:1 ratio of the corresponding esters.



Mild reaction conditions and excellent selectivity provide a large scope of potential acylating agents that include a variety of alkyl and aryl methyl esters [133, 136]. As a further advantage over traditional methods, acid sensitive esters readily undergo transesterification in quantitative yield (Table 21, entry 2).

In the absence of primary alcohols, secondary alcohols participate in transesterification reactions to provide good yields for most alcohols. No significant electronic effect is observed when electron-releasing and electron-withdrawing substituents on aromatic secondary alcohols (Table 22, entries 2–4). A steric effect is observed with cyclohexanol derivatives. Increasing the α -substituent from hydrogen to methyl or *tert*-butyl dramatically decreases efficiency of transesterifi-

Table 21 NHC catalyzed transesterification

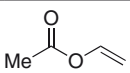
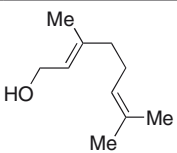
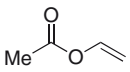
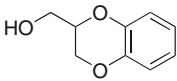
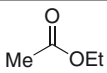
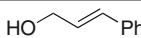
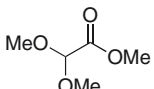
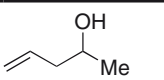
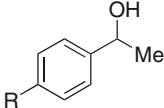
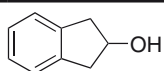
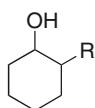
$ \begin{array}{c} \text{R} \\ \parallel \\ \text{O} \\ \text{R}' \end{array} \text{C} \text{OR}' \quad \text{267} + \text{HOR}'' \quad \text{268} \xrightarrow[4\text{\AA MS, THF}]{\text{Mes-N} \begin{array}{c} \diagup \diagdown \\ \vdots \\ \text{C} \\ \diagup \diagdown \\ \text{N-Mes} \end{array} \text{Mes} \quad 0.5 \text{ mol\% } \mathbf{3}} \begin{array}{c} \text{R} \\ \parallel \\ \text{O} \\ \text{R}'' \end{array} \text{C} \text{OR}'' \quad \text{269} $			
Entry	267	268	Yield (%)
1			99
2			100
Entry	267	268	Yield (%)
3			93
4			95

Table 22 NHC catalyzed transesterification with secondary alcohols

$ \begin{array}{c} \text{Me} \\ \parallel \\ \text{O} \\ \text{OMe} \end{array} \text{C} \text{OMe} \quad \text{270} + \text{HOR} \xrightarrow[4\text{\AA MS}]{\text{Cy-N} \begin{array}{c} \diagup \diagdown \\ \vdots \\ \text{C} \\ \diagup \diagdown \\ \text{N-Cy} \end{array} \text{Cy} \quad 5 \text{ mol\% } \mathbf{272}} \begin{array}{c} \text{Me} \\ \parallel \\ \text{O} \\ \text{OR} \end{array} \text{C} \text{OR} \quad \text{271} $			
Entry	271	HOR	Yield (%)
1	a		94
			
2	b	R = H	93
3	c	R = CF ₃	96
4	d	R = OMe	85
Entry	271	HOR	Yield (%)
5	e		92
			
6	f	R = H	93
7	g	R = Me	67
8	h	R = <i>t</i> -Bu	9

cation (Table 22, entries 6–8). Nolan and co-workers found that isolated 1,3-bis(cyclohexyl)-imidazol-2-ylidene performs more efficiently than the in situ generated carbene for this transformation.

Nolan and co-workers have extended the scope of transesterification reactions to include phosphonate esters as phosphorylating agents [137]. In this publication the authors use dimethyl methylphosphonate **273** and benzyl alcohol with a variety of imidazolylidene carbenes (Table 23). The use of molecular sieves to absorb methanol leads to increased conversion; however, longer reaction times lead to decreased

Table 23 NHC catalyzed transesterification of phosphonate esters

Entry	Catalyst	R	Time (h)	Yield (%)	274/275
1	272	Cy	2	71	90:10
2	272	Cy	8	90	75:25
3	1	Adamantyl	2	35	100:0
4	276	<i>t</i> -Bu	2	32	100:0
5	3	Mes	18	0	–

Table 24 Amidation of unactivated esters with alkyl amines

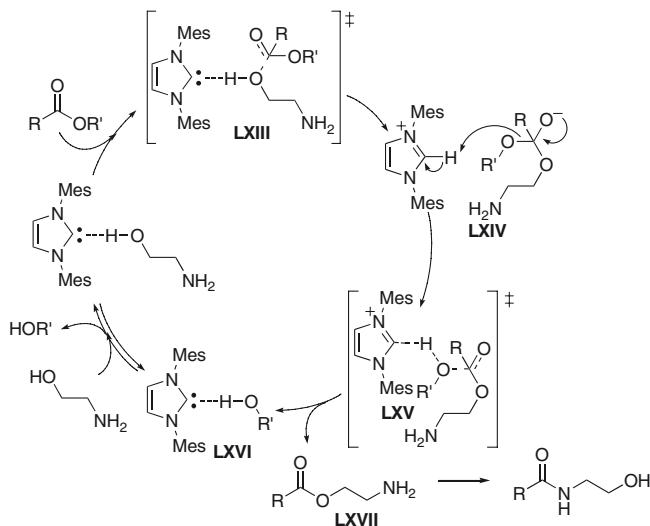
Entry	Ester	Amino alcohol	Yield (%)	Entry	Ester	Amino alcohol	Yield (%)
				8			66
1	R	R'		9			88
	Bn	Me	100				
2	Ph	Me	75	10			86
3	<i>p</i> -COMeC ₆ H ₄	Me	87				
4	<i>p</i> -CF ₃ C ₆ H ₄	Me	95	11			77
5	<i>p</i> -OMeC ₆ H ₄	Me	31				
6	Me	Me	99				
7	Me	Bn	95				

product selectivity, as more diesterified product is observed (Table 23, entry 2). This transformation is compatible with both in situ formed imidazolylidene carbene and preformed carbene.

Movassaghi and Schmidt reported that amidation of unactivated esters also occurs in the presence of carbene **3** when 1,2-amino alcohols are used [138]. A representative sample of the range of esters **277** and amino alcohols **278** is shown in Table 24. A few substrates proved problematic under standard reaction conditions,

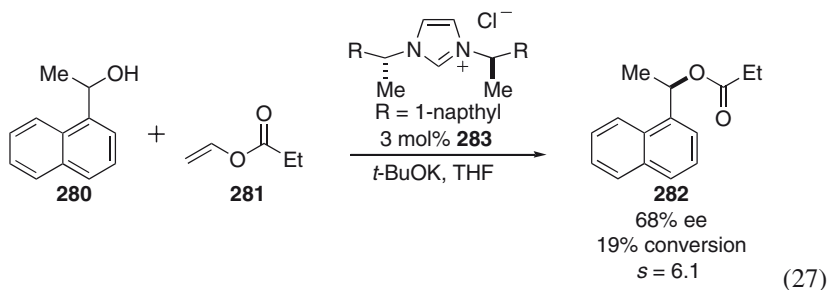
entry 5, but the addition of anhydrous LiCl as an additive increases the yields substantially.

A proposed mechanism for this transformation, provided in [Scheme 42](#), is based on the identification of alcohol-carbene complexes by Movassaghi and Schmidt. Mesityl substituted imidazolinyldine carbene acts as a Brønsted base as transesterification occurs to produce **LXVII**. Upon O $\rightarrow$ N acyl transfer, the observed product is formed. The evidence provided for this mechanism includes the control experiment in which **LXVII** is resubjected to the reaction conditions and proceeds with amide formation. A similar mechanism has recently been reported in a theoretical study of transesterification by Hu and co-workers [139]. In light of this work, it seems reasonable to suggest a similar that mechanism is operative in the transesterification reactions discussed throughout this section.



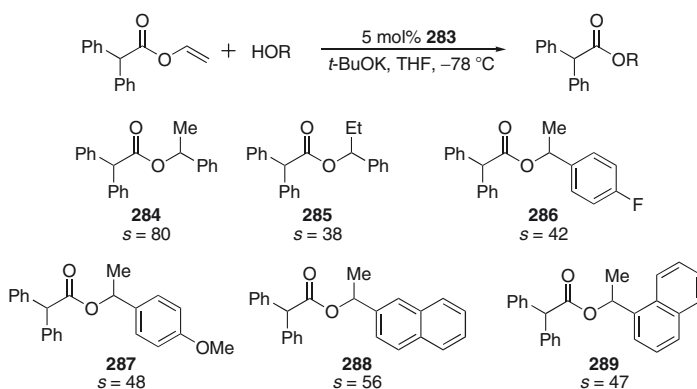
Scheme 42 Movassaghi et al. proposed catalytic cycle for amidation reaction

Suzuki and co-workers first published on the topic of enantioselective transesterification in 2004 [140, 141]. This process exploits C₂-symmetric imidazolium salts with various substitutions. When vinyl propionate **281** acts as the acyl donor, ester **282** is isolated in 68% ee at 19% conversion, corresponding to an *s* value of 6.1 (Eq. 27).



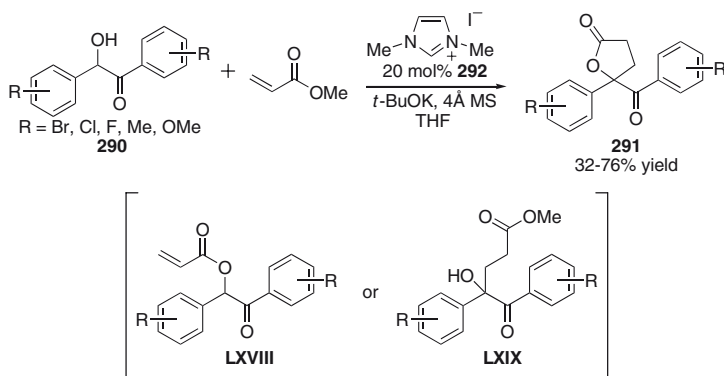
Concurrently, Maruoka and co-workers illustrated the same reaction manifold to produce the desired transesterification in high enantioselectivity [142]. Increasing enantioselectivities and corresponding s factors were observed by changing the acylating agent in the order of vinyl acetate, vinyl isobutyrate, vinyl pivalate, to the highest enantioselectivity being achieved with vinyl diphenylacetate. The range of aromatic substituted secondary alcohols that are competent nucleophiles include both electron-rich and electron-deficient alcohols and provide desired esters in good yields and very impressive s values up to 80 (Scheme 43).

NHCs have also been shown to promote the reaction of benzoin and methyl acrylate to produce γ -butyrolactones (Scheme 44) [143]. In the absence of dimethylimidazolium iodide, the reaction does not proceed. The mechanism is still under investigation, although the authors propose that the transformation may proceed via a tandem transesterification/intramolecular Michael addition **LXVIII** or Michael



Scheme 43 Maruoka et al. enantioselective acylation of secondary alcohols

addition/lactonization **LXIX** pathway. Aromatic aldehydes, for in situ benzoin formation, are suitable substrates in this reaction.

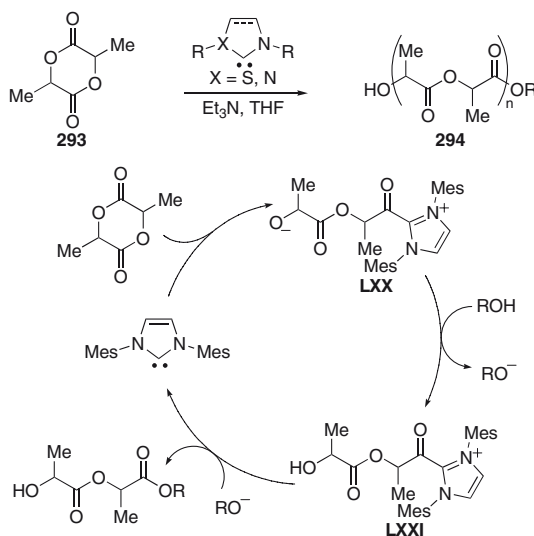


Scheme 44 NHC promoted synthesis of γ -butyrolactones

6.1 Ring Opening Polymerization

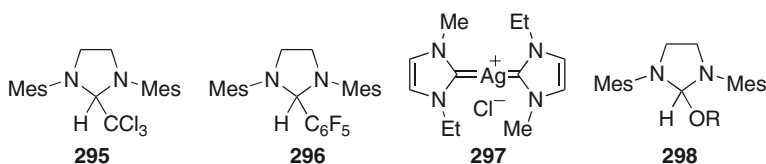
As mentioned previously, Hedrick and co-workers have done extensive work in the field of transesterification/ring opening polymerization (ROP). Their first report came in 2002 in which they showed imidazolinyldiene carbenes catalyze transesterification to form biodegradable polyesters [134]. These research groups have made contributions using NHCs to catalyze living polymerization of lactide and lactone with narrow polydispersity and predictable molecular weight [144, 145]. Thiazol-, imidazol- and imidazolinyldiene carbenes are competent catalysts although the thiazolyldiene carbene is the least active catalyst. The authors propose nucleophilic attack of lactide by the in situ generated or free carbene to deliver intermediate **LXX** (Scheme 45). Proton transfer occurs with the alcohol that acts as an initiator, followed by alkoxide addition and release of the carbene. Stereoselective polymerization has been accomplished using an imidazolyldiene catalyst [146].

The Hedrick and Waymouth groups have also studied methods for generating NHC catalysts in situ for ROP without an external base [147–150]. Thermal generation occurs readily with chloroform adduct **295** and pentafluorophenyl adduct **296** [147, 149]. Both compounds perform well as polymerization catalysts although **296** is stable at room temperature unlike **295**. (Imidazol-2-ylidene)

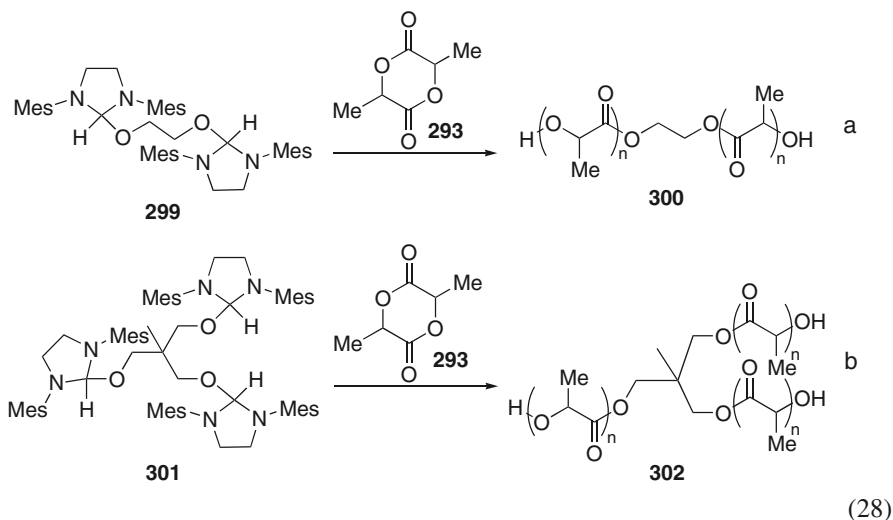


Scheme 45 Proposed mechanism for ROP

silver(I)chloride salts, such as **297**, are efficient catalysts for ROP [150]. Lactide polymerization has also been shown to occur with yttrium, titanium, and zinc complexes [151, 152].

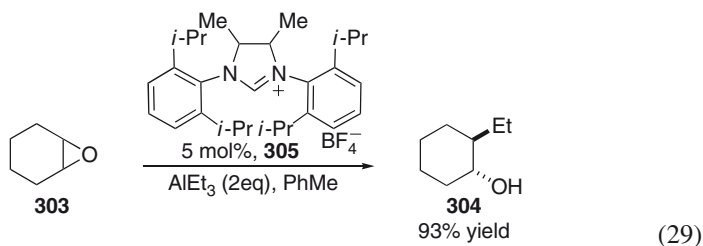


Most recently, Hedrick and co-workers have illustrated the use of alcohol adducts **298** as a sufficient catalyst/initiators for ROP, therefore eliminating the need for external alcohol [153]. These adducts undergo carbene formation at room temperature in THF. Additional advantages of these adducts, compared to free NHCs, is that they are not moisture sensitive and they provide the opportunity to synthesize more complex polymers (Eq. 28a). Star polyesters can be generated in one step (Eq. 28b).

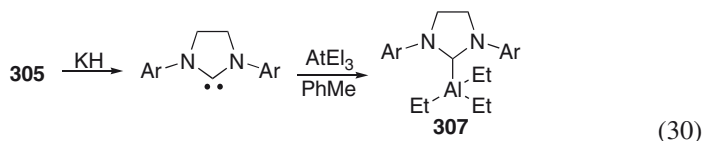


7 Nucleophilic Catalysis

Nguyen and co-workers have developed a method for the alkylation of *meso*-epoxides by a preformed NHC·AlEt₃ complex (Eq. 29) [117, 154]. This method is a natural extension of previous work utilizing triethylaluminum and catalytic phosphines for ring opening of epoxides [155].

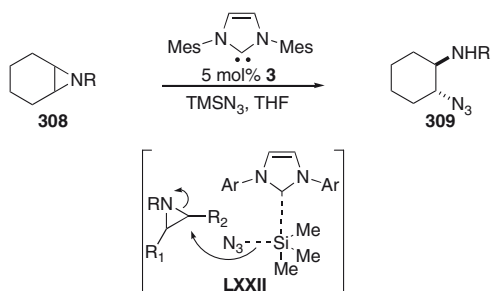


A difference in reaction efficiency was observed depending on the catalyst used. Imidazolium salt **305** provides the highest yield of desired product. When pre-formed complex **307** is subjected to the reaction conditions, *trans*-2-ethylcyclohexanol is detected by gas chromatography in 76% yield (Eq. 30). Alkylation starting with free carbene **306** results in only 28% yield of desired alkylated epoxide.



Wu et al. have added NHCs to their long list of methodologies for ring-opening of aziridines [156]. The substrate scope is somewhat limited, although non-activated aziridine, R = Bn, provides the desired product in 96% yield. TMSN₃, TMSI, and TMSCl prove to be competent nucleophiles (Scheme 46). The reaction time is reduced to less than 1 h with activated substrates, R = Ts, in nearly quantitative yield. The transformation is regioselective, providing attack of the nucleophile on the less substituted carbon of the aziridine. The authors suggest that a coordination of the NHC and trimethylsilyl azide forms a hypervalent silicon complex that opens the aziridine (LXXII, Scheme 46).

Additionally, Wu and co-workers have shown regioselective ring-opening of aziridines with acid anhydrides mediated by imidiazolynylidene **3** [157]. This pathway requires the use of an electron withdrawing tosylated aziridine **310** in order for the reaction to proceed. The mild reaction conditions allow for a variety of products to be formed in high yields (Table 25).

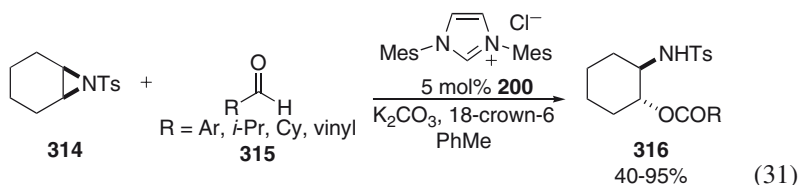


Scheme 46 Ring opening of aziridines catalyzed by NHCs

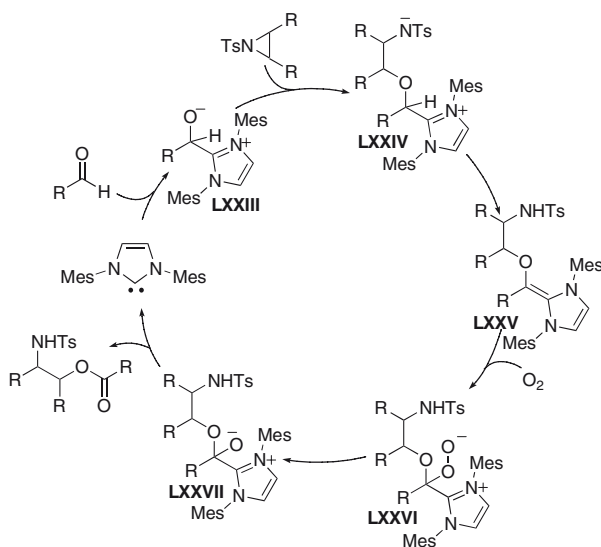
Table 25 NHC catalyzed acid anhydride ring opening of aziridines

Entry	312	Product	Yield (%)	Entry	312	Product	Yield (%) (306/307)
1	a		96	7	g		80
2	b	R = Me	96	8	h	R = Et	80
3	c	R = Ph	91	9	i	R = Ph	98
4	d		94	10	j	R = Me	70 (9:1)
5	e	R = Et	81	11	k	R = Ph	70 (10:1)
6	f	R = Ph	99				

In an attempt to use an acyl anion equivalent to open an aziridine, Wu and co-workers isolated an unexpected ring opened product **316** (Eq. 31) [158]. The authors found that the presence of oxygen was the determining factor between benzoin formation and ester formation. No desired ketones were ever formed. Various aromatic substituted aldehydes were treated under standard reaction conditions to afford esters in good yields. 4-Methoxybenzaldehyde provided product in only 40% yield, presumably due to the ease of aldehyde oxidation.

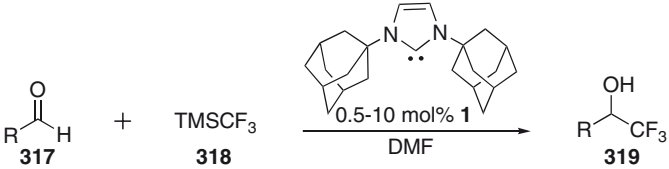
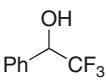
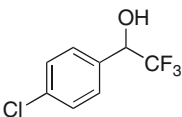
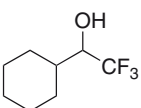
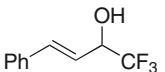
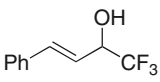
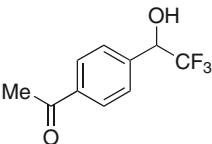
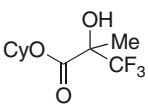
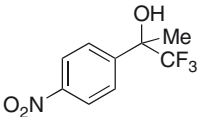


The authors' proposed mechanism involves initial attack of an in situ formed carbene onto the aldehyde to produce tetrahedral intermediate **LXXIII** (Scheme 47). Proton transfer would produce an acyl anion equivalent, but is inconsistent with product formation. Instead S_N2 displacement to produce ring opened intermediate **LXXIV** is proposed, followed by proton transfer. At this point, molecular oxygen apparently becomes involved to oxidize nucleophilic alkene **LXXV**. The active catalyst is then regenerated and observed product is formed.



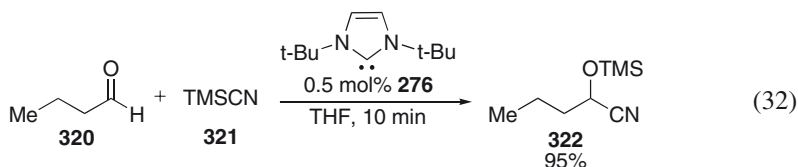
Scheme 47 Proposed mechanism of aziridine ring opening under aerobic reaction conditions catalyzed by NHC

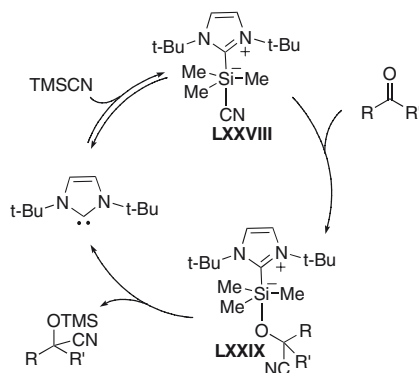
Table 26 Trifluoromethylation of aldehydes catalyzed by NHCs

			
Entry	319	Product	Yield (%)
1	a		73
2	b		86
3	c		81
4	d		89
4	e		84
5	f		85
6	g		62
7	h		85

Trifluoromethylation can be achieved with the use of imidazolyli-dene carbene **1** [159]. Song and co-workers found this transformation is tolerant of both electron-rich and electron-poor aldehydes (Table 26). Even enolizable aldehydes undergo trifluoromethylation in 81% yield (entry 3). Selective reaction occurs with an aldehyde in the presence of a ketone in the substrate (entry 5). The use of activated ketones as acceptors leads to tertiary alcohols in good yields (entries 7 and 8).

Song et al. extended this methodology to include cyanosilylation of aldehydes and ketones (Eq. 32) [160]. They propose that NHC **276** interacts with TMSCN to form complex **LXXVIII** followed by cyano group transfer to the aldehyde (Scheme 48). The carbene is then regenerated and the desired product is obtained when **LXXIX** fragments. Concurrently, Kondo, Aoyama and co-workers describe similar reaction conditions for the synthesis of cyanohydrins in high yields [161, 162], while Suzuki and co-workers reported a cyanosilylation of aromatic and aliphatic aldehydes in good yields [163].

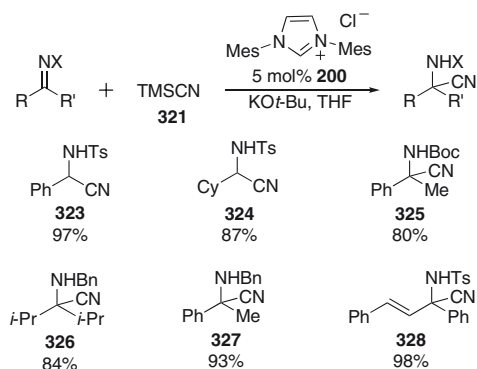




Scheme 48 Proposed mechanism for cyanosilylation of aldehydes and ketones

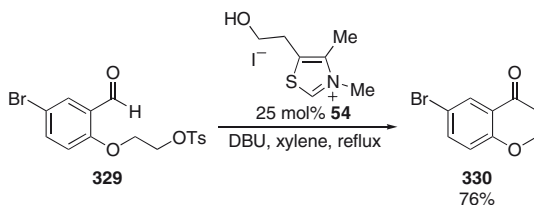
Kondo, Aoyama and co-workers expanded this chemistry to include aldimines and ketimines in good yields under mild reaction conditions (Scheme 49) [164, 165]. Maruoka and co-workers also report cyanosilylation of tosyl and benzyl imines [166].

She and co-workers took advantage of the acyl anion equivalent formed from the addition of an NHC to an aldehyde to catalyze the formation of benzopyranones via an intramolecular S_N2 displacement (Scheme 50) [167]. Various aromatic aldehydes provide alkylation products in moderate yields when the leaving group is either tosylate or iodide. No reaction was observed when phenyl or methyl was placed alpha to the leaving group.

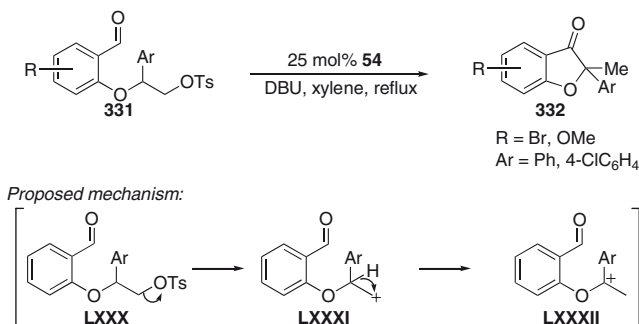


Scheme 49 Representative products formed via cyanation of aldehydes

When an aromatic group is placed $\sigma\psi$ to the leaving group, a new set of products is formed **332** (Scheme 51). Benzofuranones are formed in poor to good yields with no detection of the S_N2 product. The authors argue that carbocation intermediate **LXXXII** is formed due to stabilization at the benzylic position followed by formation and subsequent nucleophilic attack of the acyl anion equivalent.

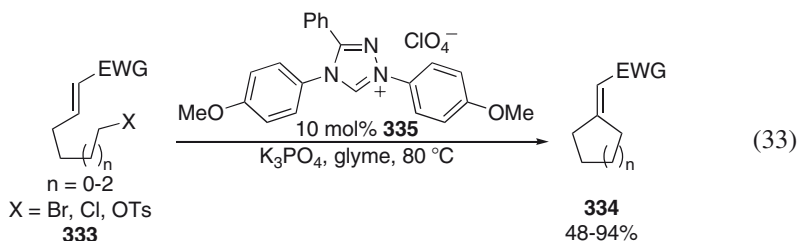


Scheme 50 Formation of benzopyranone via S_N2 reaction catalyzed by NHC

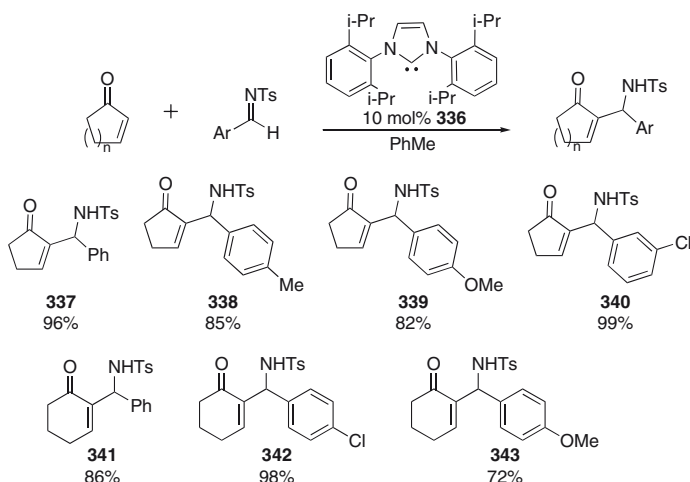


Scheme 51 NHC catalyzed substitution reaction

Fu and co-workers describe Umpolung reactivity of Michael acceptors catalyzed by triazolinyldene carbenes (Eq. 33) [168]. Nucleophilic addition followed by tautomerization renders the β position of the Michael acceptor nucleophilic, which subsequently undergoes alkylation. Compatible leaving groups include Br, Cl, and OTs. α,β -unsaturated esters, nitriles, and amides all provide good to excellent yields of cyclized products.

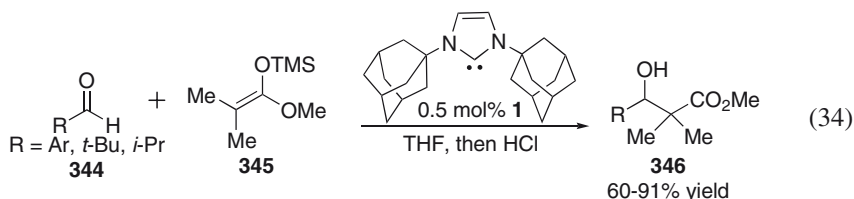


NHC catalyzed reactions have been expanded to include reactions such as aza-Morita-Baylis-Hillman and Mukaiyama aldol reactions. Ye and co-workers illustrate the utility of NHCs in a reaction that is traditionally catalyzed by amines and phosphines (Scheme 52) [169].

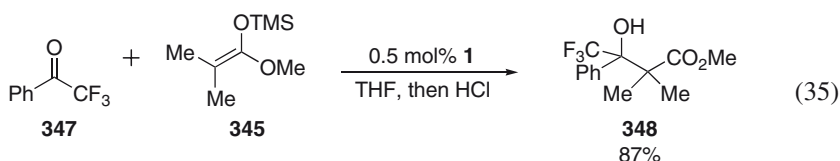


Scheme 52 Reaction scope of the aza-Morita-Baylis-Hillman catalyzed by NHCs

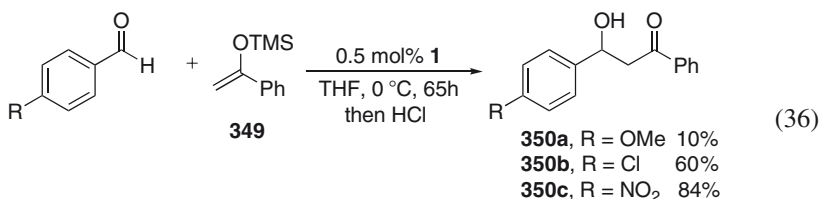
Song and co-workers have taken a variety of aldehydes **344** and treated them with *N*-adamantyl carbene **1** and trimethylsilyl ketene acetal **345** to produce Mukaiyama aldol products **346** in good yield (Eq. 34) [170]. The carbene presumably acts as a Lewis base to activate the silicon – oxygen bond in order to promote reactivity of the enol silane. The catalyst loading can be reduced to as low as 0.05 mol% without a change in yield.



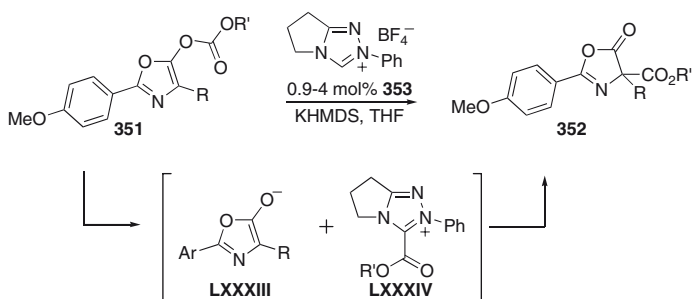
The authors presented one example of 2,2,2-trifluoroacetophenone as a coupling partner with **345** (Eq. 35), suggesting that the reaction proceeds through a pentavalent silicon complex similar to that in [Scheme 46](#).



Silyl enol ethers are inherently less reactive than silyl ketene acetals but are competent partners in this reaction with increased reaction times. Electron-deficient aldehydes provide the highest yields while 4-methoxybenzaldehyde proceeds in only 10% yield after 65 h (Eq. 36).

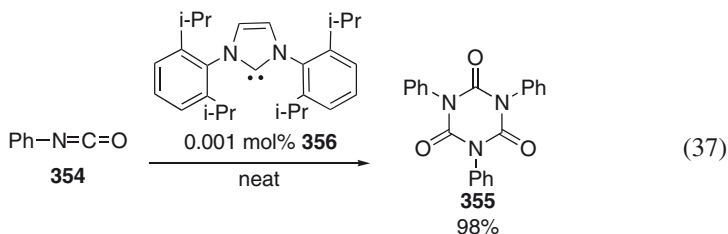


As shown in previous sections, NHCs promote acyl transfer in transesterification reactions. In a similar manner, O → C acyl transfer can be achieved with substrates such as **351** in the presence of 0.9–4 mol% of triazolium pre-catalyst **353** and KHMDS ([Scheme 53](#)). Moderate yields are obtained by varying substitution of the oxazole from R = Me, Ph, *i*-Bu, and *i*-Pr [171]. Deprotonation of the triazolium salt followed by nucleophilic addition to the carbonate moiety of the oxazole results in enolate intermediate **LXXXIII** and activated carboxylate **LXXXIV**. Enolate addition and regeneration of the active catalyst provides quaternary stereocenters **352**.



Scheme 53 NHC promoted O $\rightarrow$ C acyl transfer

Louie and co-workers have shown the utility of NHCs in the cyclotrimerization of isocyanates [172]. Isocyanurates were obtained in excellent yield with catalyst loading as low as 0.001 mol% (Eq. 37).



8 Conclusion

The use of stable nucleophilic carbenes as catalysts for organic transformations has come a long way since Ukai's original demonstration of their efficacy in the benzoin reaction. The last 10 years in particular have seen a tremendous explosion in interest in this area, with new reactivity manifolds having been developed across a range of reaction subtypes. It is clear that with many of these shortcomings remain – functional group compatibility, turnover frequency, turnover number and, naturally, expansion of substrate type. The inherent tunability of these catalysts promises great latitude in overcoming these issues. That, coupled with an increase in new reactivity, from Umpolung type reactivity best exemplified by the benzoin and Stetter reactions to redox catalysis, nucleophilic catalysis and even Morita-Baylis-Hilman reactivity, suggests that nucleophilic carbene catalysts will likely remain useful tools in organic synthesis for the foreseeable future.

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Brønsted Base Catalysts

Amal Ting, Jennifer M. Goss, Nolan T. McDougal, and Scott E. Schaus

Abstract Chiral organic Brønsted bases have emerged as highly efficient catalysts for enantioselective transformations. Since their early use in enantiomeric separation processes, chiral organic Brønsted base catalysis has advanced significantly to include both natural and designed catalysts. Insight into the mode of action of the organocatalysts has promoted modifications in catalyst structures to expand the application to numerous asymmetric reactions. Bifunctional catalysts, containing both Brønsted base and H-activating functionalities, have proven to be very applicable to an array of reaction types. The development of Brønsted base catalysts containing or not containing H-activating moieties, has greatly impacted asymmetric organocatalysis. This overview illustrates the recent developments in this emerging field.

Keywords Asymmetric organocatalysis • Bifunctional catalyst • Brønsted base • Chiral scaffold • *Cinchona* alkaloid • Cyclohexane-diamine • Guanidine

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1 Introduction

Chiral organic Brønsted bases have emerged as highly selective and efficient catalysts for enantioselective synthesis. Initially described in 1913 for enantioselective hydrocyanation to aldehydes [1] and later more broadly developed by Wynberg in the 1970s and 1980s [2], chiral organic Brønsted base catalysis has evolved as the result of mechanistic understanding and catalyst design to address challenges in synthetic methodology. Over the past two decades, new catalyst development has benefited significantly from mechanistic studies and insightful observations about Brønsted base and hydrogen bond donor activation of substrates [3–6]. Bifunctional catalyst design has been elegantly incorporated into catalyst design to activate *both* nucleophiles and electrophiles during the bond formation process. These advances in mechanistic understanding and catalyst design have resulted in an ever-increasing number of new methodologies and synthetic transformations (Fig. 1).

The advent of chiral Brønsted base catalysis began with the recognition that the *Cinchona* alkaloids serve as excellent catalysts [7–12] and privileged structures

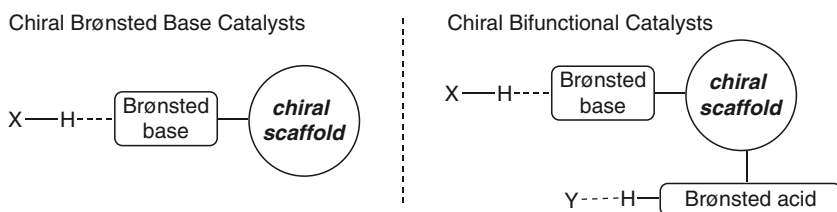


Fig. 1 Chiral Brønsted bases catalyst design

[13]. Systematic evaluation of structural variants led to a better understanding of the properties crucial for enantioselective catalysis. The importance of a rigid backbone with basic functionality and the absence or presence of a hydrogen-bond donor within the same catalyst structure has resulted from these studies. Such realizations have led to the synthesis of novel *Cinchona* alkaloid-based catalysts with modified hydrogen-bond donor capabilities and broadened the scope of their utility. Later developments have reinforced the understanding of this motif with the use of the cyclohexane diamine by Jacobsen [14] and Takemoto [15]. The development of these catalysts and the evolution of chiral organic Brønsted bases for enantioselective catalysis illustrate the importance of mechanistic insight achieved to date.

2 *Cinchona* Alkaloids

The direct role of *Cinchona* alkaloids in asymmetric synthesis proves its versatility in the field of chiral base catalysts, promoters, and ligands. Early studies up until the late 1980s on the use of *Cinchona* alkaloids in asymmetric synthesis were conducted by Pracejus [16, 17], Morrison and Mosher [18], and Wynberg [16, 17]. Key development of reactions at that time included ketene chemistry used in asymmetric β -lactone synthesis [19–23], and asymmetric induction in dihydroxylation and desymmetrization [24–27]. The first catalytic enantioselective conjugate addition was documented in Wynberg's [2] seminal work on *Cinchona* alkaloid-catalyzed addition of cyclic β -ketoesters to methyl vinyl ketone (MVK). The basicity of the quinuclidine nitrogen of *Cinchona* alkaloids combined with the Brønsted acidic C(9)–OH, confers a bifunctional catalytic property to *Cinchona* alkaloids (Fig. 2). Acting as a bifunctional organocatalyst or ligand, *Cinchona* alkaloids are key contributors in asymmetric reactions and enantioselective transformations of conjugate additions (Strecker, Baylis–Hillman, Michael, Mannich, Aldol, and Henry), cycloaddition reactions, phase-transfer reactions (PTC), β -lactone synthesis, aziridination, desymmetrization studies, decarboxylations, epoxidations, and hydrogenations [7].

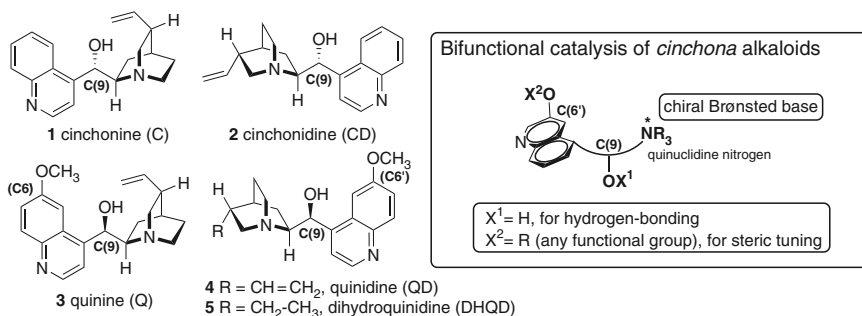


Fig. 2 *Cinchona* alkaloids as bifunctional catalysts

The notable mode of stereoselectivity of *Cinchona* alkaloids is presented by its pseudoenantiomeric pairs which can be employed to generate either enantiomer of chiral product. Key moieties that are central to *Cinchona* alkaloids are the quinuclidine nitrogen and the adjacent C(9)–OH (the N–C(8)–C(9)–OH moiety) (Fig. 2). In pseudoenantiomeric alkaloids in the natural open conformation, the torsion angle N–C(8)–C(9)–O are opposite in sign: Q and CD are (–), and thereby induce selectivity for one enantiomer, whereas QD and C are (+) and afford the other enantiomer [28, 29].

Cupreines and cupreidines are pseudoenantiomers of *Cinchona* alkaloids with the replacement of quinoline C(6')–OCH₃ with an OH-group. The result is availability of an additional hydrogen-bonding moiety.

The focus of this review is to discuss the role of *Cinchona* alkaloids as Brønsted bases in organocatalytic asymmetric reactions. *Cinchona* alkaloids are Lewis basic when the quinuclidine nitrogen initiates a nucleophilic attack to the substrate in asymmetric reactions such as the Baylis-Hillman (Fig. 3), β -lactone synthesis, asymmetric α -halogenation, alkylations, carbocyanation of ketones, and Diels-Alder reactions [30–39] (Fig. 4).

Lesser discussed is an equally significant and recent role of *Cinchona* alkaloids as Brønsted bases. *Cinchona* alkaloids are mechanistically categorized as Brønsted bases when the nitrogen moiety complexes to a proton (either via partial deprotonation or protonation), resulting in the chiral intermediate species essential to the stereodirecting and facial selectivity step. The earliest example is Hiemstra and Wynberg's [40] 1,4-addition of thiophenols to cyclohexenones. The quinuclidine nitrogen deprotonates the thiol in conjunction with stabilization of the enolate through hydrogen-bonding of the C(9)–OH moiety of the catalyst.

Modified *Cinchona* alkaloids catalysts have been developed in the last two decades to enhance further the bifunctional mode of the catalyst. Derivations at the C(9)–OH group, replacement of quinoline C(6')–OCH₃ with a hydroxyl group to enhance hydrogen bonding, syntheses of bis-*Cinchona* alkaloids, and development of thiourea-derived *Cinchona* alkaloids are most notable.

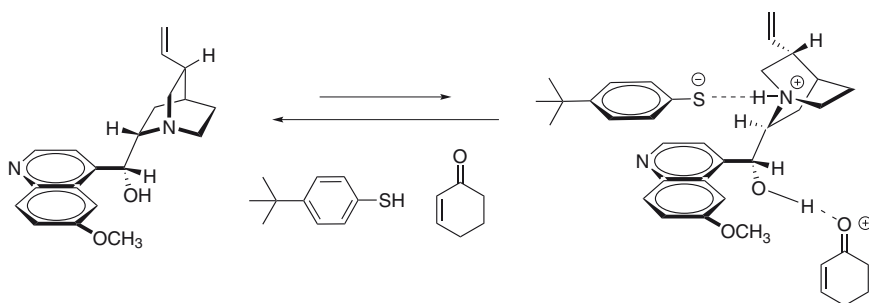


Fig. 3 *Cinchona* alkaloids as Lewis bases in the Baylis-Hillman reaction

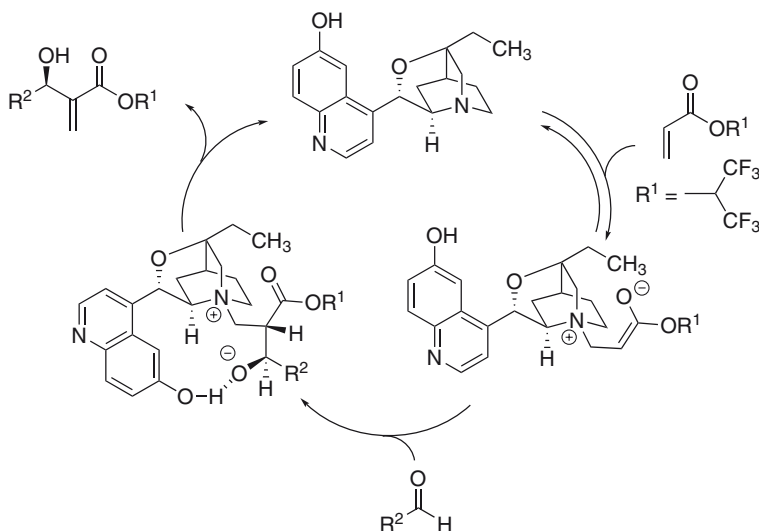


Fig. 4 *Cinchona* alkaloids as Brønsted base catalysts

2.1 *Cinchona Alkaloids in Asymmetric Transformations*

Asymmetric transformations that employ *Cinchona* alkaloids as Brønsted bases will be discussed. Acting as a chiral Brønsted base, the quinuclidine nitrogen together with hydrogen bonding moieties of the catalyst have promoted several remarkable enantioselective reactions. The reactions highlighted here will focus on asymmetric conjugate additions, subdivided into substrate categories of enones, imines, azodicarboxylates, nitroalkenes, sulfones, nitriles, and α -ketoesters.

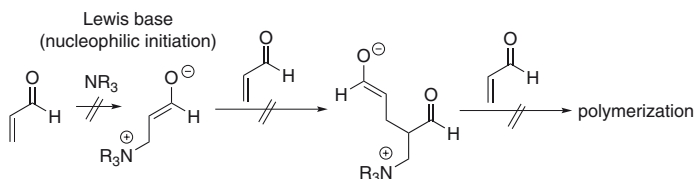
2.2 *Asymmetric Conjugate Addition with Enones and Enals*

The wide range of Michael donors and acceptors in 1,4-additions are of great utility. Consequently, further exploration on the addition of α -substituted β -ketoester addition to α,β -unsaturated ketones have captured the attention of many chemists. The transformation is a versatile methodology to access all-carbon quaternary stereocenters.

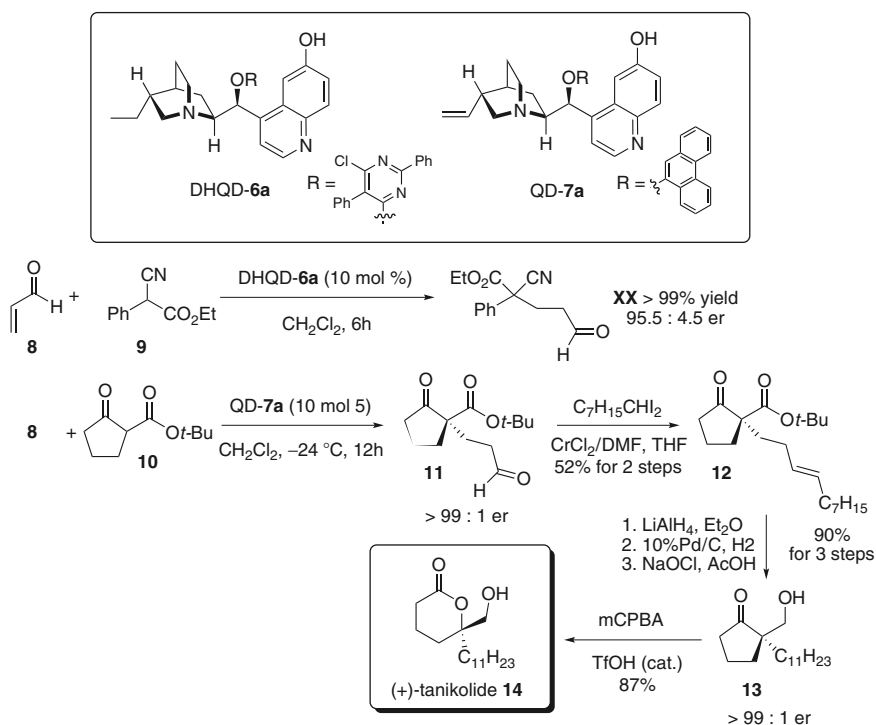
α,β -Unsaturated aldehydes are highly active towards nucleophilic reactions. Using *Cinchona* alkaloids-derived catalysts, Deng et al. investigated the viability of conjugate addition reactions with α,β -unsaturated aldehydes and 1,3-dicarbonyl donors [41].

Preliminary mechanistic studies show no polymerization of the unsaturated aldehydes under *Cinchona* alkaloid catalysis, thereby indicating that the chiral tertiary amine catalyst does not act as a nucleophilic promoter, similar to Baylis-Hillman type reactions (Scheme 1). Rather, the quinuclidine nitrogen acts in a Brønsted basic deprotonation-activation of various cyclic and acyclic 1,3-dicarbonyl donors. The conjugate addition of the 1,3-dicarbonyl donors to α,β -unsaturated aldehydes generated substrates with all-carbon quaternary centers in excellent yields and stereoselectivities (Scheme 2) Utility of these all-carbon quaternary adducts was demonstrated in the seven-step synthesis of (+)-tanikolide **14**, an antifungal metabolite.

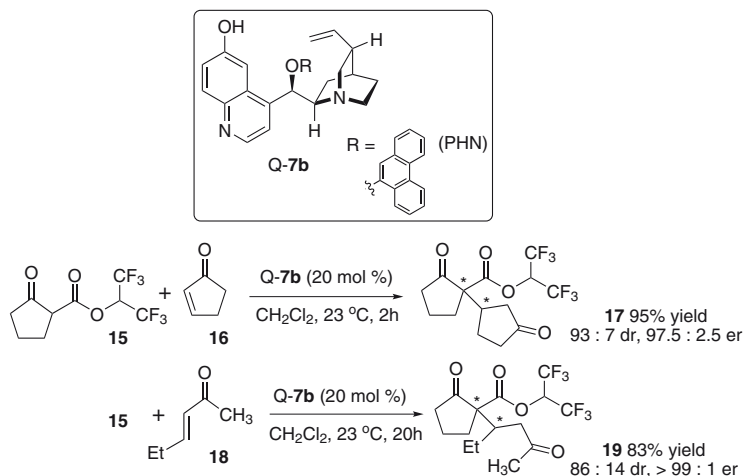
<No polymerization of acrolein observed. >



Scheme 1



Scheme 2



Scheme 3.

The first organocatalyzed conjugate addition of α -substituted β -ketoester to α,β -unsaturated ketones was presented by Deng et al. [42] (Scheme 3). Although traditional *Cinchona* alkaloids were efficient catalysts for conjugate addition of carbon nucleophiles to nitroalkenes and sulfones, replacement of the C(9)–OH with an ester group (**Q-7b**) showed great improvement in stereoselectivity. The reaction is applicable to a variety of cyclic and acyclic enones (**16**, **18**).

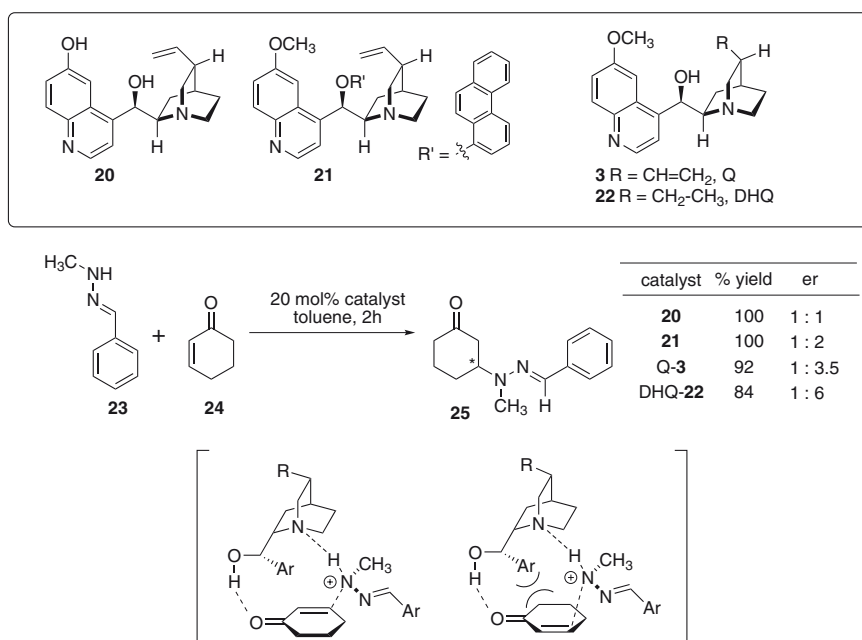
Enantioselective organocatalytic conjugate additions such as Michael and aldol reactions have been intensely studied under new catalysts. However, only a few organocatalyzed Michael reactions have been developed. The reaction involves construction of a new C–N bond that is very attractive for syntheses of molecules with biological properties.

The majority of the Michael-type conjugate additions are promoted by amine-based catalysts and proceed via an enamine or iminium intermediate species. Subsequently, Jørgensen et al. [43] explored the aza-Michael addition of hydrazones to cyclic enones catalyzed by *Cinchona* alkaloids. Although the reaction proceeds under pyrrolidine catalysis via iminium activation of the enone, and also with NEt_3 via hydrazone activation, both methods do not confer enantioselectivity to the reaction. Under a *Cinchona* alkaloid screen, quinine **3** was identified as an effective aza-Michael catalyst to give 92% yield and 1:3.5 er (Scheme 4).

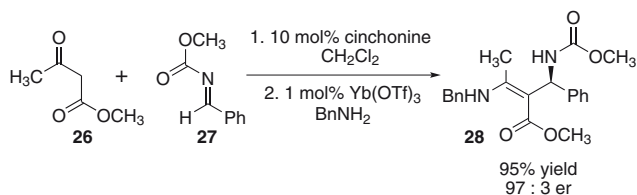
Substitution of the C(9)–OH with an ester (**21**) reduced selectivity to 1:2 er although yield was quantitative. Substitution of quinoline C(6')– OCH_3 (**20**) with OH resulted in quantitative yield but no enantioselectivity. Dihydroquinine (**22**) gave the highest er of 1:6 with 84% yield (Scheme 4).

2.3 Asymmetric Conjugate Additions with Imines

Highly enantioselective organocatalytic Mannich reactions of aldehydes and ketones have been extensively studied with chiral secondary amine catalysts. These secondary amines employ chiral prolines, pyrrolidines, and imidazoles to generate a highly active enamine or iminium intermediate species [44]. *Cinchona* alkaloids were previously shown to be active catalysts in malonate additions. The conjugate addition of malonates and other 1,3-dicarbonyls to imines, however, is relatively unexplored. Subsequently, Schaus et al. [45] employed the use of *Cinchona* alkaloids in the conjugate addition of β -ketoesters to *N*-acyl aldimines. Highly enantioselective multifunctional secondary amine products were obtained with 10 mol% cinchonine (Scheme 5).



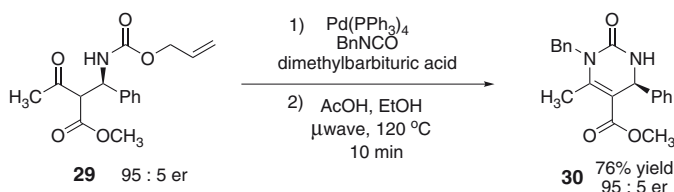
Scheme 4



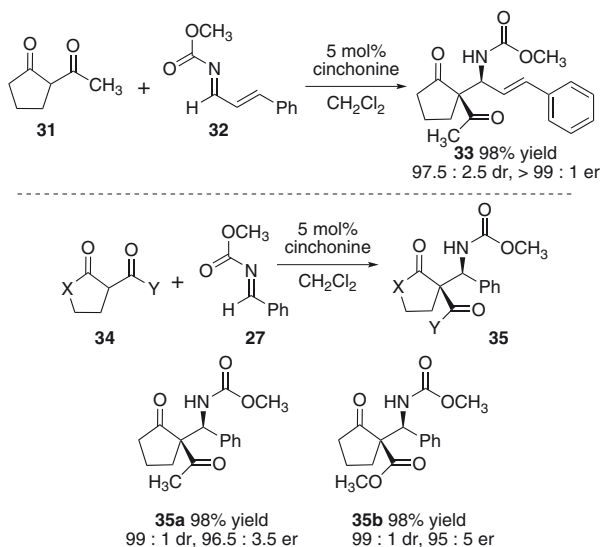
Scheme 5

The optically pure Mannich adducts were further converted to chiral dihydropyrimidones via two steps to offer 5-benzylpyrimidone in 96% yield and 95:5 er (Scheme 6).

Following the cinchonine-catalyzed results, Schaus et al. [46] reported the use of cyclic 1,3-dicarbonyl donors to access adjacent quaternary-tertiary stereogenic centers. Under similar reaction conditions cyclic β -ketoester and 1,3-diketones afforded the corresponding Mannich adducts in excellent yields and stereoselectivities (Scheme 7). The methodology was also applicable to aryl propenyl imines (**32**) – a class of novel aliphatic imines.



Scheme 6

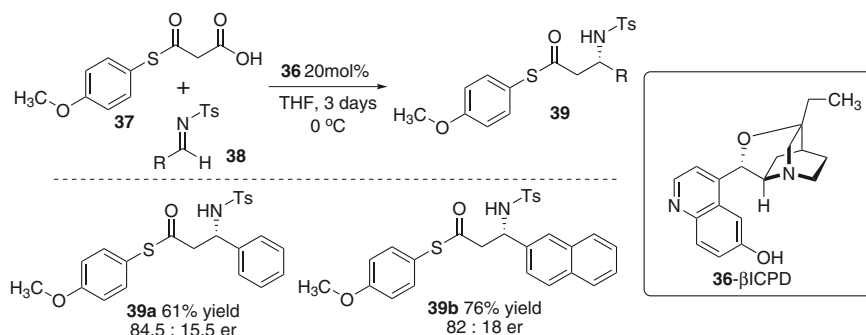


Scheme 7

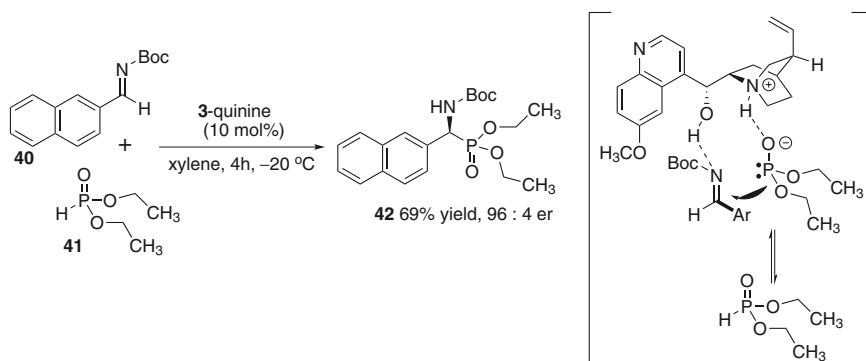
1,3-Dicarbonyl donors bearing a thioester has been applied in the Mannich reaction to *N*-tosyl imines. Ricci presented an enantioselective decarboxylative addition of malonic half thioester **37** to imine **38**. In the Mannich-type addition, catalyst **36** deprotonates the malonic acid thioester followed by decarboxylation to generate a stabilized thioacetate enolate. This stabilized anion reacts with facial selectivity to the imine due to steric-tuning from **36** [47] (Scheme 8).

Based on prior results where Ricci used *Cinchona* alkaloids as phase-transfer-catalysts, the group proceeded to look at hydrophosphonylation of imines [48]. Employing the chiral tertiary amine as a Brønsted base, α -amino phosphonates products were synthesized in high yields and good selectivities.

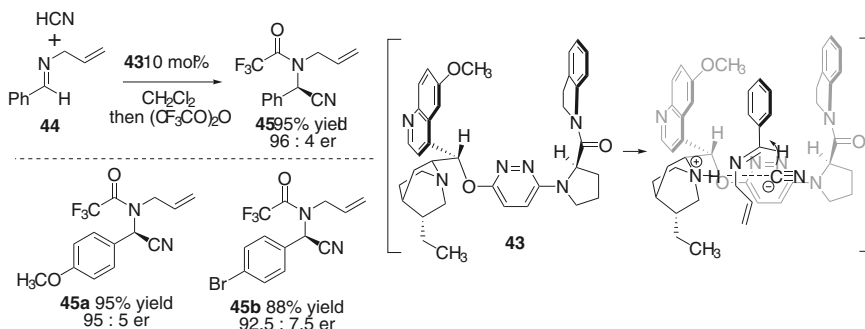
In the initial screening of various *Cinchona* alkaloids, the addition of diethyl phosphate **41** to *N*-Boc imine **40** in toluene revealed the key role of the free hydroxyl group of the catalyst. Replacing the C(9)-OH group with esters or amides only results in poor selectivity. Quinine (Q) was identified as an ideal catalyst. A mechanistic proposal for the role of quinine is presented. Hydrogen-bonding by the free C(9)-hydroxyl group and quinuclidine base activation of the phosphonate into a nucleophilic phosphite species are key to the reactivity of this transformation (Scheme 9).



Scheme 8



Scheme 9



Scheme 10

New catalyst design further highlights the utility of the scaffold and functional moieties of the *Cinchona* alkaloids. bis-*Cinchona* alkaloid derivative **43** was developed by Corey [49] for enantioselective dihydroxylation of olefins with OsO_4 . The catalyst was later employed in the Strecker hydrocyanation of *N*-allyl aldimines. The mechanistic logic behind the catalyst for the Strecker reaction presents a chiral ammonium salt of the catalyst **43** (in the presence of a conjugate acid) that would stabilize the aldimine already activated via hydrogen-bonding to the protonated quinuclidine moiety. Nucleophilic attack by cyanide ion to the imine would give an α -amino nitrile product (Scheme 10).

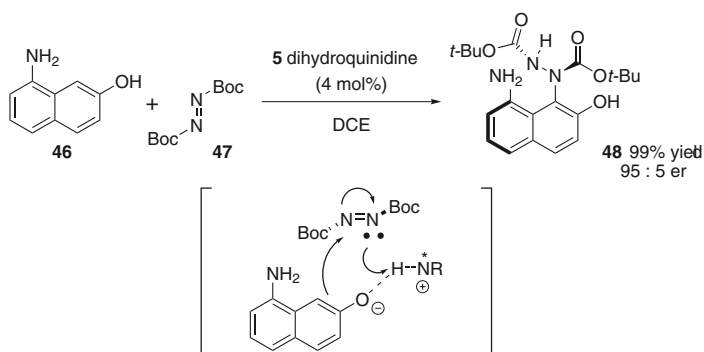
Molecular modeling of the reaction predicts attack of the CN^- ion on the *re* face of the *N*-allyl benzaldimine carbon to provide an (*S*)-adduct. The aromatic ring of the imine and the quinuclidine hydrogen bond stabilizes the iminium above the pyridazine, blocking the rear face of the imine bond. Nucleophilic attack by CN^- is therefore steered to attack from the *re* face.

2.4 Asymmetric Conjugate Addition with Diazo Substrates

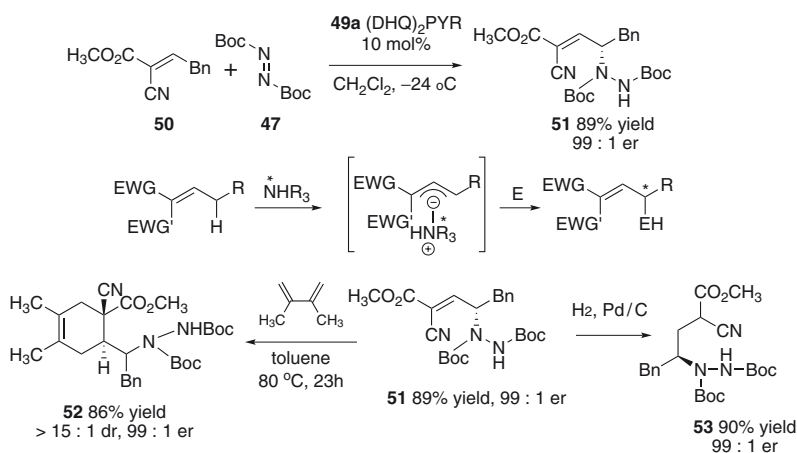
The use of diazodicarboxylates has been recently explored in *Cinchona* alkaloid catalyzed asymmetric reactions. Jørgensen [50] reported the synthesis of non-biaryl atropisomers via dihydroquinine (DHQ) catalyzed asymmetric Friedel-Crafts amination. Atropisomers are compounds where the chirality is attributed to restricted rotation along a chiral axis rather than stereogenic centers. They are useful key moieties in chiral ligands but syntheses of these substrates are tedious.

Amongst the class of aryl and biaryl atropisomers used in chiral ligand development, there are few reports where the nitrogen atom is directly attached to the aromatic ring. Jørgensen employed the use of chiral tertiary amines for deprotonation of the hydroxy group on 2-naphthol **46** followed by addition of *tert*-butyl-azodicarboxylate **47**. The corresponding aminated naphthol compound was obtained in 99% yield and 95:5 er with enantiomers that are readily separable by HPLC. The chiral product containing both an amino- and hydroxy-functionality were converted to chiral ureas and anilides in good yields without racemization (Scheme 11).

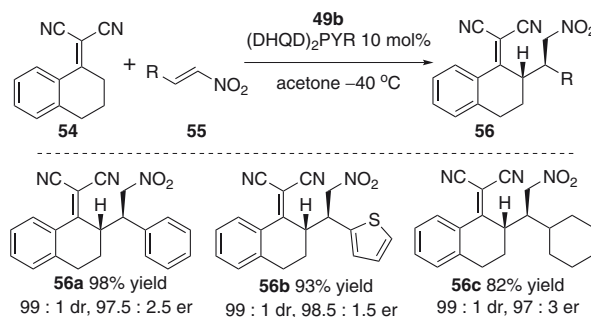
Another type of *Cinchona* alkaloid catalyzed reactions that employs azodicarboxylates includes enantioselective allylic amination. Jørgensen [51–53] investigated the enantioselective electrophilic addition to allylic C–H bonds activated by a chiral Brønsted base. Using *Cinchona* alkaloids, the first enantioselective, metal-free allylic amination was reported using alkylidene cyanoacetates with dialkyl azodicarboxylates (Scheme 12). The product was further functionalized and used in subsequent tandem reactions to generate useful chiral building blocks (**52**, **53**). Subsequent work was applied to other types of allylic nitriles in the addition to α,β -unsaturated aldehydes and β -substituted nitro-olefins (Scheme 13).



Scheme 11



Scheme 12



Scheme 13

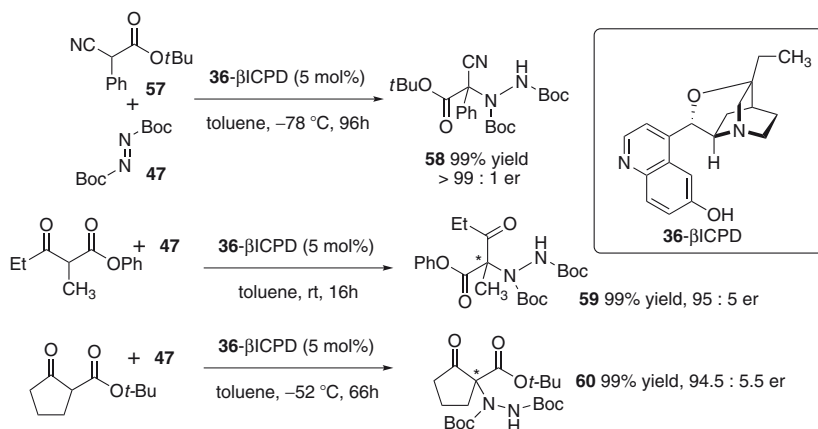
Construction of new C–N bonds via azodicarboxylates has also been explored in other types of reactions. In the conjugate addition to α -substituted α -cyanoacetates, new C–N bond formation also generates a chiral quaternary center. Using cupreidine as the catalyst, Deng [54] obtained excellent yields and selectivity in the reaction of *tert*-butyl azodicarboxylates with α -aryl α -cyanoacetates. At around the same time, Jørgensen [55] investigated the use of *Cinchona* alkaloids, including modified alkaloids cupreine, cupreidine, and β -isocupreidine (β -ICPD) (**36**) to carry out similar transformations.

β -Isocupreidines are *Cinchona* alkaloid derivatives with limited conformational flexibility and increased basicity and nucleophilicity due to the increased ring strain of the tricyclic skeleton. The C(6')–OH on β -ICPD offers two different sites of simultaneous activation of nucleophile and electrophile to enhance basicity and sterics of intermediate species.

Jørgensen's reactivity screen with various *Cinchona* alkaloids in the reaction of azodicarboxylate and α -aryl α -cyanoacetates showed almost quantitative yields with the catalysts, although β -ICPD **36** was superior in terms of enantioselectivity (Scheme 14). The types of esters on the azodicarboxylate had a significant impact on selectivity, the bulkier the ester group (*tert*-butyl), the higher the enantioselectivity. The reaction is robust enough towards other pro-nucleophiles such as acyclic and cyclic β -ketoesters to provide almost quantitative yields and 95:5 er (**59**, **60**). Aryl, heteroaryl, and aliphatic groups were all functionally tolerated, including varied electronic and steric properties.

2.5 Asymmetric Conjugate Addition with Nitroalkenes and Sulfones

Michael-type addition of stabilized carbon donors to electron-withdrawing α,β -unsaturated systems is an efficient method for C–C bond construction. The nitro-group



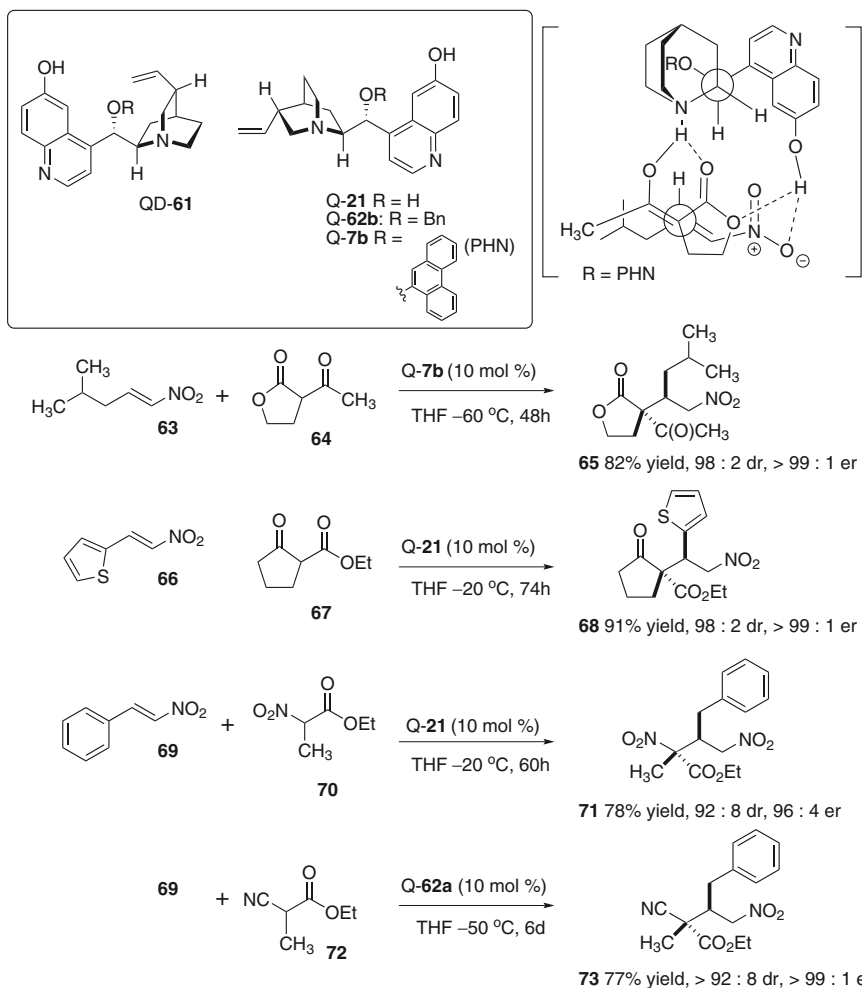
Scheme 14

has been a useful functionality in conjugate-type additions in terms of improving reactivity and also producing nitro-products for further derivations in syntheses.

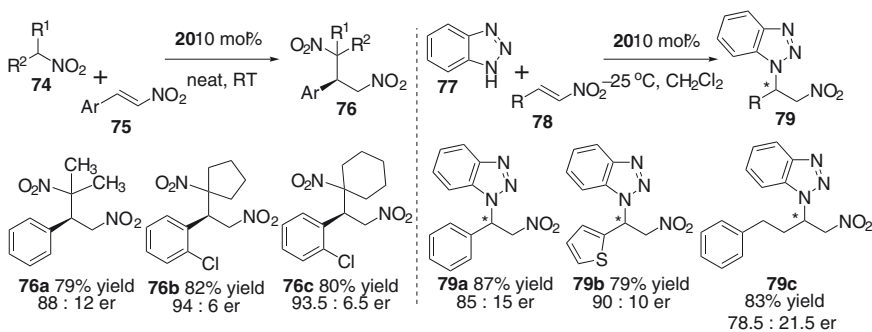
In addition to the efficient catalysis of cupreines and cupreidines in asymmetric reactions with azodicarboxylates, these catalysts also demonstrate keen selectivity with conjugate additions of nitroalkenes. Deng [56] reported high stereoselectivity for the conjugate addition of nitroalkenes to several classes of trisubstituted carbon nucleophiles (Scheme 15). The products include either carbon- or hetero-substituted quaternary and tertiary stereocenters. Various malonates, cyclic and acyclic β-ketoesters were investigated to offer excellent diastereo- and enantioselectivity. β-Substituted 1,3-diketones also gave similar results. Trisubstituted compounds that do not belong to the 1,3-dicarbonyl class also promised good results, such as various α-substituted α-cyanoacetate 72.

Wang and co-workers [57, 58] reported several Michael-type enantioselective additions with nitro-olefins. Under neat conditions, 1,3-dinitro compounds were generated in the 74 addition of nitroalkanes 75 to various β-substituted nitro-olefins (Scheme 15). Other Michael-type involving nitro-olefins reactions were illustrated using triazole donors 77 to offer good yields and high enantioselectivities (Scheme 16).

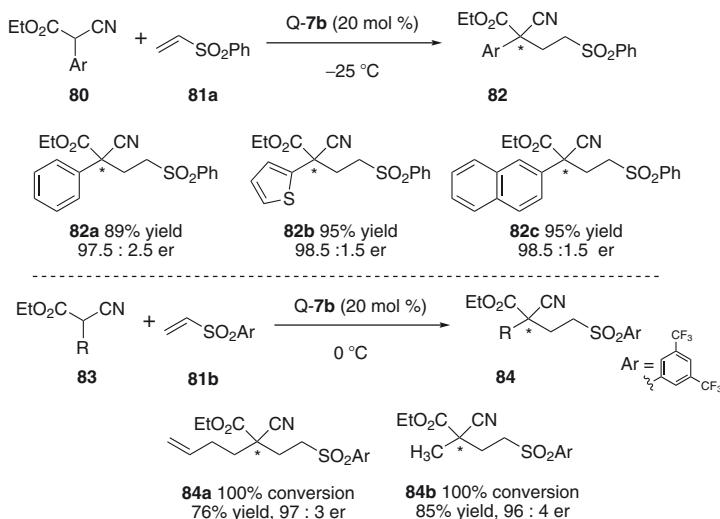
Mechanistically similar to nitroalkenes, vinyl sulfones in asymmetric conjugate additions to trisubstituted carbon nucleophiles give chiral adducts with all-carbon quaternary centers. Conjugate additions with α-substituted α-cyanoacetates (68) generate useful building blocks functionalized with the -CN and -NO₂ groups (s70, 72). Using the same modified *Cinchona* alkaloids for conjugate additions of nitroalkenes, Deng [59] reported the asymmetric conjugate addition of vinyl sulfones to α-aryl and α-aliphatic cyanoacetates (Scheme 17). Enantioselectivity was most evidently related to the types of *Cinchona* alkaloids use. *Cinchona* alkaloids with C(9)-OR and quinoline C(6')-hydroxy moieties gave significantly higher enantioselectivity than the traditional catalysts with C(9)-OH and quinoline C(6')-OCH₃.



Scheme 15



Scheme 16



Scheme 17

groups. α -Aliphatic α -cyanoacetates (**83**) which are less applied in conjugate additions (compared to aryl cyanoacetates) due to poor reactivity, proceeded relatively well in the addition to vinyl sulfones that have enhanced electrophilicity (**81b**).

2.6 Asymmetric Conjugate Addition of Nitriles

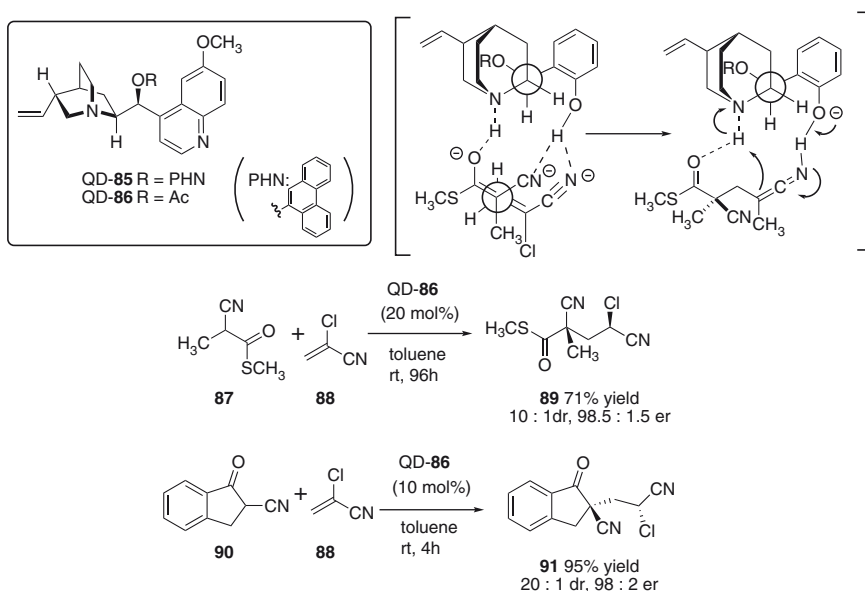
The efficiency with which modified *Cinchona* alkaloids catalyze conjugate additions of α -substituted α -cyanoacetates highlights the nitrile group's stereoselective role with the catalyst. Deng et al. [60] utilized this observation to develop a one-step construction of chiral acyclic adducts that have non-adjacent, 1,3-tertiary-quaternary stereocenters. Based on their mechanistic studies and proposed transition state model, the bifunctional nature of the quinoline C(6')-OH *Cinchona* alkaloids could induce a tandem conjugate addition-protonation reaction to create the tertiary and quaternary stereocenters in an enantioselective and diastereoselective manner (Scheme 18).

The 1,3-tertiary-quaternary stereocenter moiety is prevalent in natural products. Deng et al. [61] proceeded to investigate the conjugate addition of 2-chloroacrylonitrile **88** with trisubstituted carbon donors. α -Cyanoketones and β -ketoesters proceeded well to give products containing 1,3-tertiary-quaternary stereocenters in high yield. Depending on the type of substituent on C(9) of the catalyst, both cyclic and acyclic donors achieved high diastereo- and enantioselectivity.

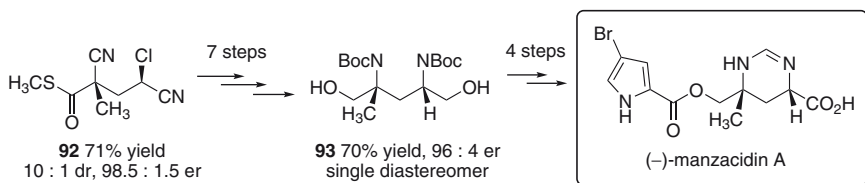
The utility of 1,3-tertiary-quaternary stereocenters was highlighted in the 7-step transformation of adduct **92** to diol **93**. Diol **93** was previously demonstrated used by Ohfuné [62] as a key intermediate in a 22-step syntheses of manzacidin A, a bromopyrrole alkaloid with interesting pharmacological profile as an α -adrenoreceptor blocker and serotonin antagonist (Scheme 19).

2.7 Asymmetric Conjugate Additions with α -Ketoesters

The nitroaldol reaction, particularly involving ketones has been relatively unexplored in the field of asymmetric organocatalysis. Employing cupreines and cupreidines as catalysts, Deng [63] presented an enantioselective nitroaldol reaction of α -ketoesters



Scheme 18



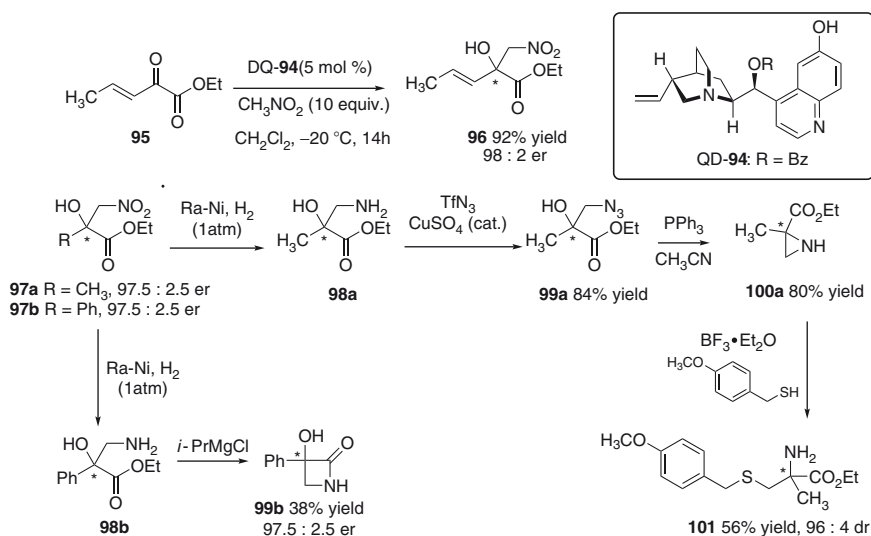
Scheme 19

(95). The all-carbon quaternary products formed are highly functionalized with a nitro group, hydroxyl group, and an ester functionality (Scheme 20). Utility of these substrates are demonstrated in subsequent functionalization in to chiral β -lactam **99b** and α -methylcysteine **101**, a key intermediate in the total syntheses of mirabazoles and thiagazole, natural products with antitumour and anti-HIV properties.

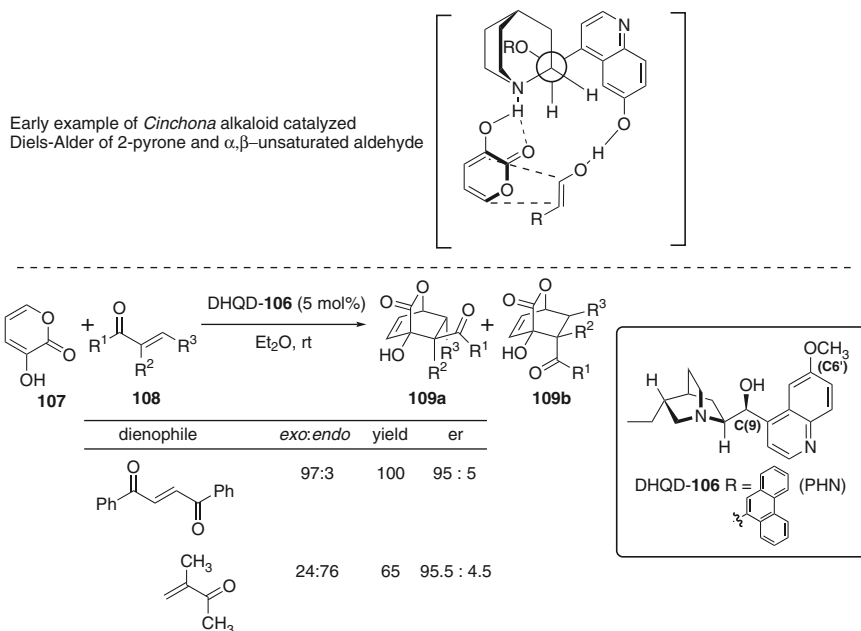
Toru and Shibata [64] investigated the use of fluorinated α -ketoester **103** in the enantioselective direct aldol-type reaction of oxindoles. The use of Corey's U-shaped bis-*Cinchona* alkaloid **102** was essential in achieving high enantioselectivities in the reaction, as compared to other modified *Cinchona* alkaloids. The methodology is a facile approach to generate oxindoles containing two stereogenic centers. The mechanistic model and stereodetermination of the transition state is based on Corey's model for (DHQD)₂ PHAL as discussed earlier in the chapter [49]. With the catalyst in open conformation, deprotonation of the oxindole by the quinuclidine nitrogen results in an enolate that could be stabilized via hydrogen bonding and p-stacking in the U-shaped pocket. The *si*-face of the oxindole is blocked by the quinoline ring, forcing the pyruvate to approach the *re*-face instead. This facial selectivity is further stabilized by hydrogen-bonding and through the quinuclidine nitrogen (Scheme 21).

2.8 Cycloaddition Reactions with 2-Pyrones

Diels-Alder reactions of 2-pyrones are efficient methods towards construction of bridged cyclohexene derivatives for natural product syntheses. Early studies by



Scheme 20

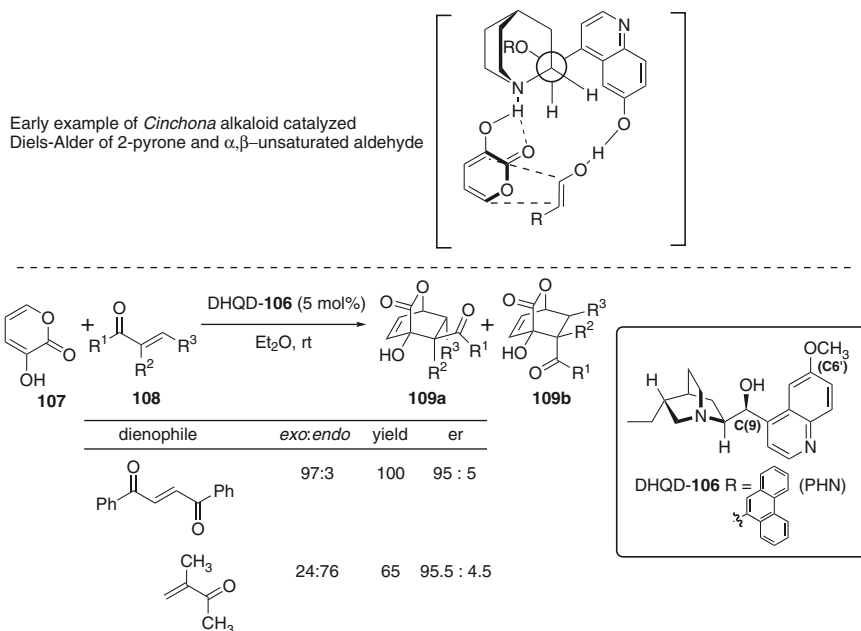


Scheme 21

Okamura and Nakatani [65] revealed that the cycloaddition of 3-hydroxy-2-pyrone **107** with electron deficient dienophiles such as simple α,β -unsaturated aldehydes form the *endo* adduct under base catalysis. The reaction proceeds under NEt_3 , but demonstrates superior selectivity with *Cinchona* alkaloids. More recently, Deng et al. [66], through use of modified *Cinchona* alkaloids, expanded the dienophile pool in the Diels-Alder reaction of 3-hydroxy-2-pyrone **107** with α,β -unsaturated ketones. The mechanistic insight reveals that the bifunctional *Cinchona* alkaloid catalyst, via multiple hydrogen bonding, raises the HOMO of the 2-pyrone while lowering the LUMO of the dienophile with simultaneous stereocontrol over the substrates (Scheme 22).

3 Chiral *Cinchona* Alkaloid-Derived Thiourea

Urea and thiourea derivatives have long been recognized for their hydrogen-bonding activity. Mechanistic studies of urea and thiourea catalysis were extensively studied by Kelly in Diels-Alder reactions [67], and Etter who further elucidated the role of chiral thioureas using crystallographic studies [68]. Jørgensen et al. further explored dual hydrogen-bonding activation in Diels-Alder and Claisen rearrangements [69, 70].



Scheme 22

After the initial elucidation of hydrogen bonding abilities of thiourea catalysts, utility of these catalysts were relatively limited in terms of enantioselectivity and application to reaction types. Subsequent modification to enhance stereodetermination via novel catalyst design was extensively explored by many groups, notably Jacobsen, Takemoto, Connon, Dixon, and Soós. Key modifications that significantly improve catalyst performance involved tethering *Cinchona* alkaloids and electron-withdrawing groups to construct a highly functionalized chiral thiourea.

Novel asymmetric conjugate-type reactions have been accomplished with *Cinchona* alkaloid-derived chiral thioureas, including less traditional reactions such as asymmetric decarboxylation [71]. In the following discussion, asymmetric reactions involving nitro-olefins, aldehydes and enones, and imines will be highlighted (Fig. 5).

3.1 Asymmetric Conjugate Addition of Nitro-Olefins

Using the addition of dimethyl malonate to nitro-olefins as the model reaction, Connon et al. [72] in 2005 reported a highly functionalized *Cinchona* alkaloid-derived chiral thiourea. Key functional groups were identified to enhance the catalyst's stereodirecting properties. Aside from the advantage of a bifunctional *Cinchona* alkaloid

tethered at the C(9) position to the thiourea, the thiourea *N*-aryl group was also significant. By using a non-Lewis basic, electron-withdrawing 3,5-bis(trifluoromethyl)-phenyl group, excellent yield and enantioselectivity was achieved (Scheme 23).

Other types of conjugate additions with chiral thioureas were also explored by Connon. β -Substituted nitro-olefins were used in the conjugate addition reaction with dimethyl chloromalonate **115** to generate chiral, functionalized nitrocyclopropanes **113**. Utility of the nitrocyclopropanes was demonstrated in the one-step modification towards other functionalized chiral building blocks (Scheme 24).

The conjugate addition of nitro olefins under chiral *Cinchona*-thiourea catalysis has shown promising results with a variety of Michael donors. Dixon conducted a screen of various chiral thioureas and identified catalyst **117** as a versatile catalyst that works well with β -substituted nitro-olefins (**78**) [74]. Aromatic, heteroaromatic

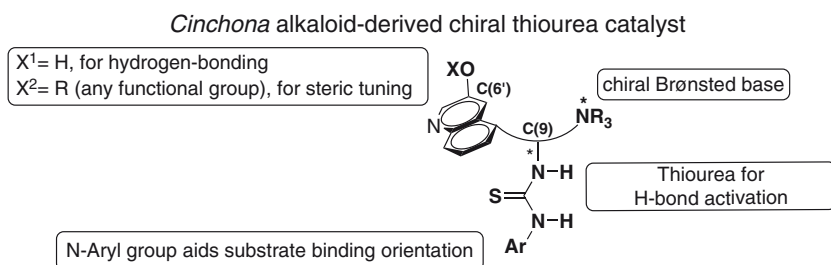
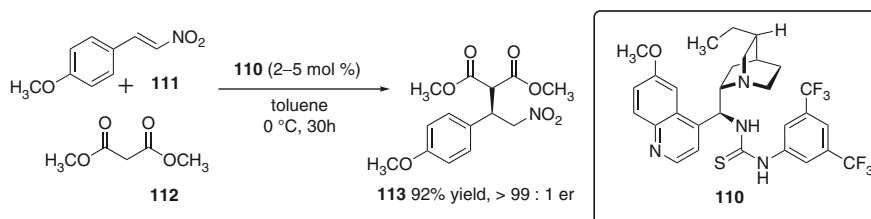
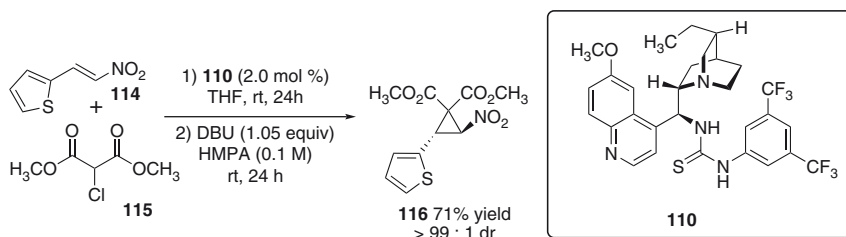


Fig. 5 Roles of *Cinchona* alkaloid-derived chiral thiourea catalyst



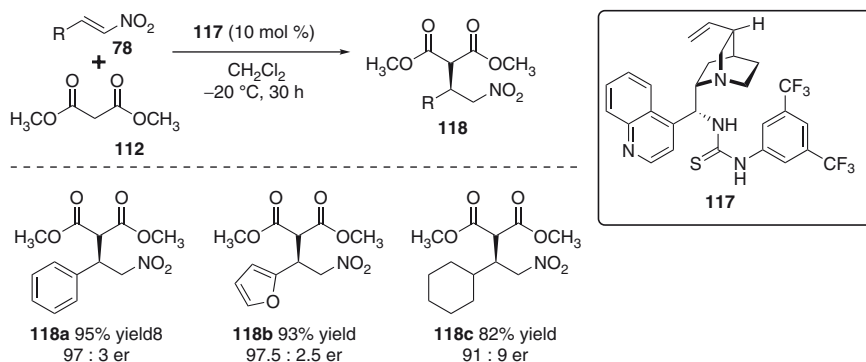
Scheme 23



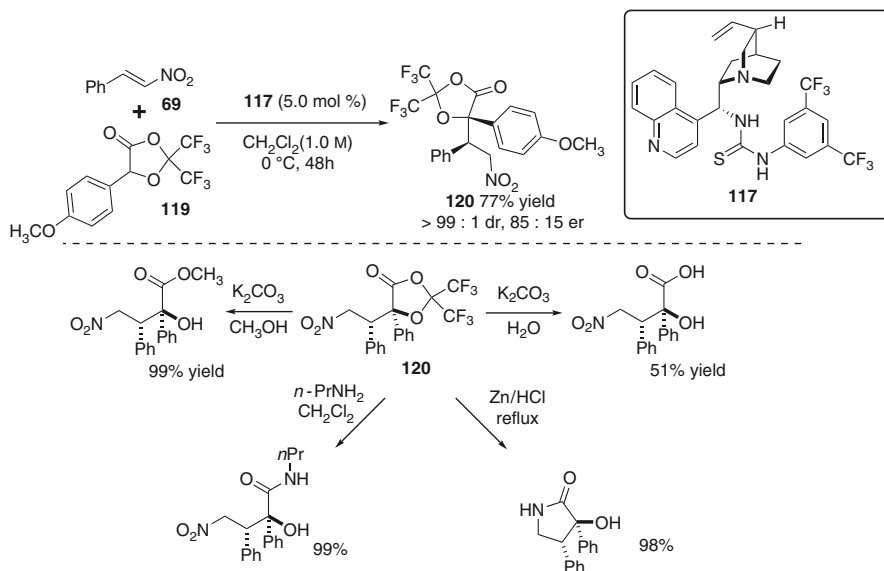
Scheme 24

and aliphatic nitro-olefins all demonstrated high enantioselectivities in good yields (Scheme 25). The strongly electron-withdrawing 3,5-bis(trifluoromethyl)-phenyl moiety was necessary to enhance enantioselectivity of the reaction.

Dixon [75] also investigated the use of unconventional carbon donors, such as the mandelic acid derivative **119** in the highly stereoselective addition to β -substituted nitro-olefins. The Michael product **120** was formed smoothly and can be converted in simple one-step procedures to generate various chiral building blocks for syntheses (Scheme 26).



Scheme 25



Scheme 26

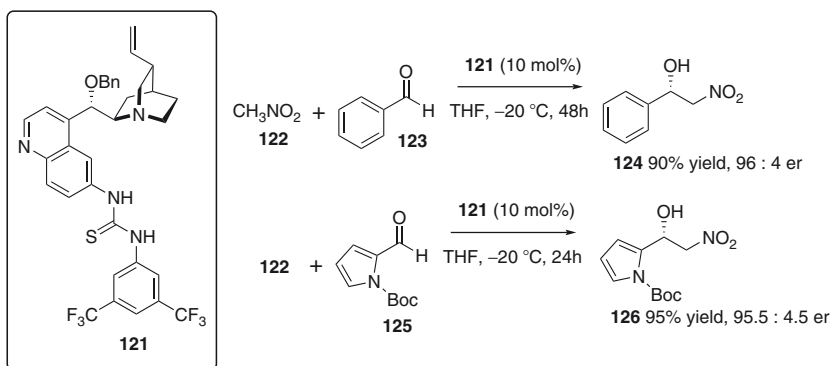
3.2 Asymmetric Conjugate Addition of Aldehydes and Enones

Nitroaldol (Henry) reactions of nitroalkanes and a carbonyl were investigated by Hiemstra [76]. Based on their earlier studies with *Cinchona* alkaloid derived catalysts, they were able to achieve moderate enantioselectivities between aromatic aldehydes and nitromethane. Until then, organocatalyzed nitroaldol reactions displayed poor selectivities. Based on prior reports by Soós [77], an activated thiourea tethered to a *Cinchona* alkaloid at the quinoline position seemed like a good catalyst candidate. Hiemstra incorporated that same moiety to their catalyst. Subsequently, catalyst **121** was used in the nitroaldol reaction of aromatic aldehydes to generate β -amino alcohols in high yield and high enantioselectivities (Scheme 27).

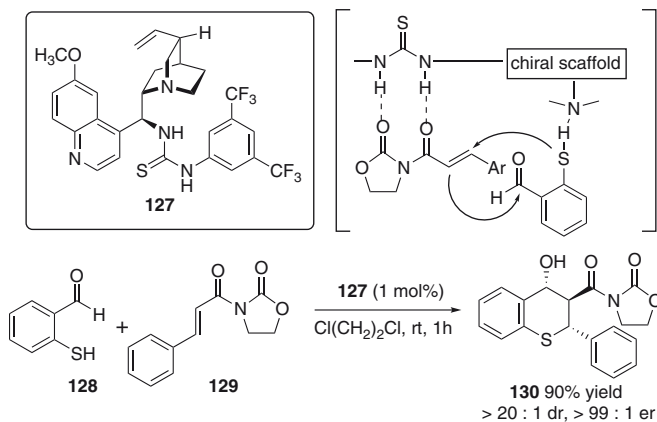
Novel aldol-type reactions under *Cinchona*-derived chiral thiourea catalysis was reported by Wang et al. [78]. In their report, a novel cascade Michael-aldol reaction was presented. The reaction involves a tandem reaction catalyzed via hydrogen-bonding with as little as 1 mol% catalyst loading to generate a product with three stereogenic centers (Scheme 28). In the reaction of 2-mercaptobenzaldehyde **128** and α,β -unsaturated oxazolidinone **129**, the desired benzothiopyran **130** was formed smoothly in high yield and excellent stereoselectivity.

1,3-Dicarbonyl donors are excellent Michael donors in asymmetric conjugate addition to α,β -unsaturated ketones. Wang and co-workers [79] applied chiral *Cinchona*-thiourea catalyst **131** to various carbon donors in the addition to aromatic enones. A diverse array of nucleophiles, mainly 1,3-dicarbonyls proceeded smoothly in the conjugate addition to α,β -unsaturated enone **132** (Scheme 29).

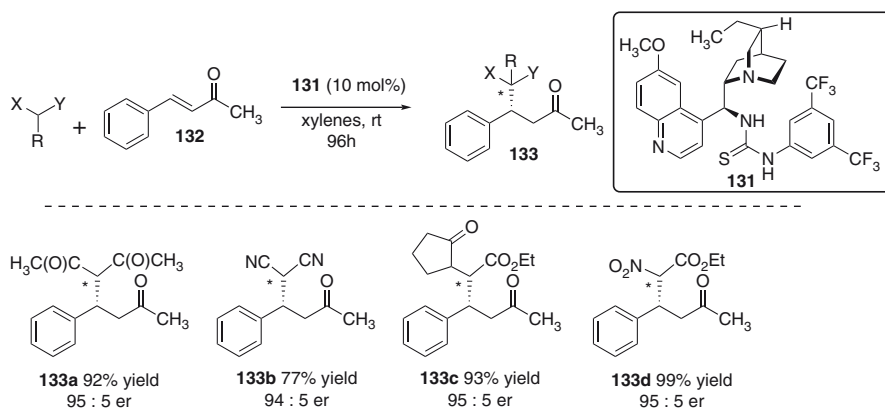
Soós [80] reported novel thiourea catalyst **134** in an efficient Michael reaction between nitromethane and chalcones to access chiral nitrocarbonyls in high enantioselectivity (Scheme 30).



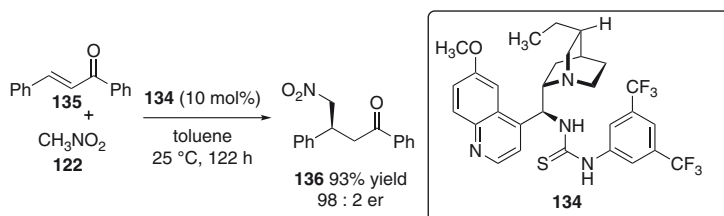
Scheme 27



Scheme 28



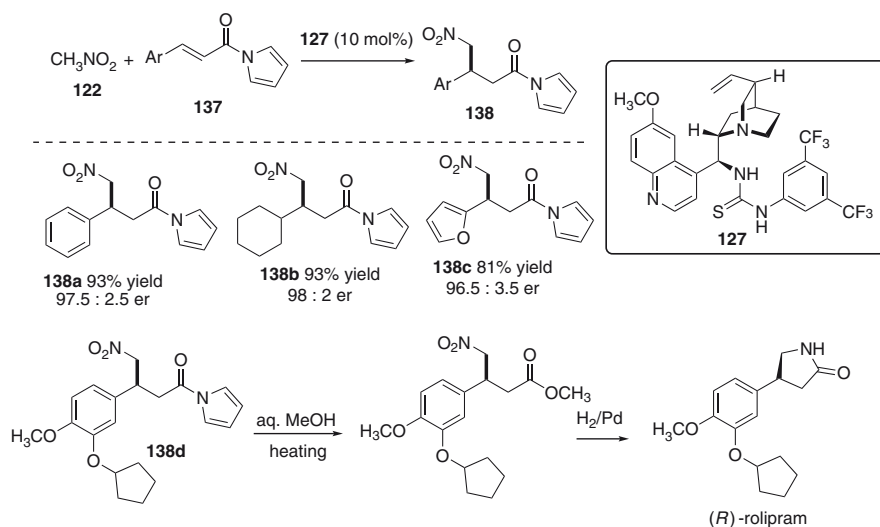
Scheme 29



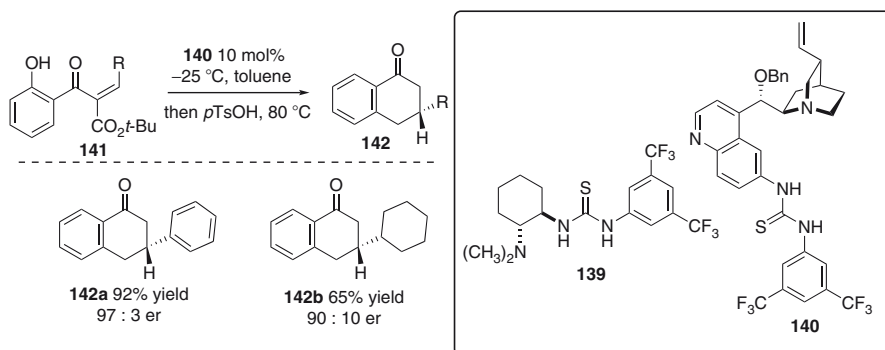
Scheme 30

Based on the results with chalcones, Soós expanded their substrate pool to look at α,β -unsaturated *N*-acyl pyrroles (**137**) as a chalcone derivative [81]. Utility of the products formed was demonstrated in the concise syntheses of the anti-inflammatory drug (*R*)-rolipram (Scheme 31).

Utility of *Cinchona*-alkaloid derived chiral thioureas were used in Scheidt's group [82] for the enantioselective syntheses of flavanones. The quinoline-tethered thiourea catalyst **140** displayed better stereodirecting properties than the corresponding thiourea that is tethered to a chiral cyclohexanediamine (**139**). Under optimized reaction conditions, flavanone **142** was obtained in 92% yield and 97:3 er; the best er using catalyst **139** was 90:10 under similar conditions (Scheme 32).



Scheme 31



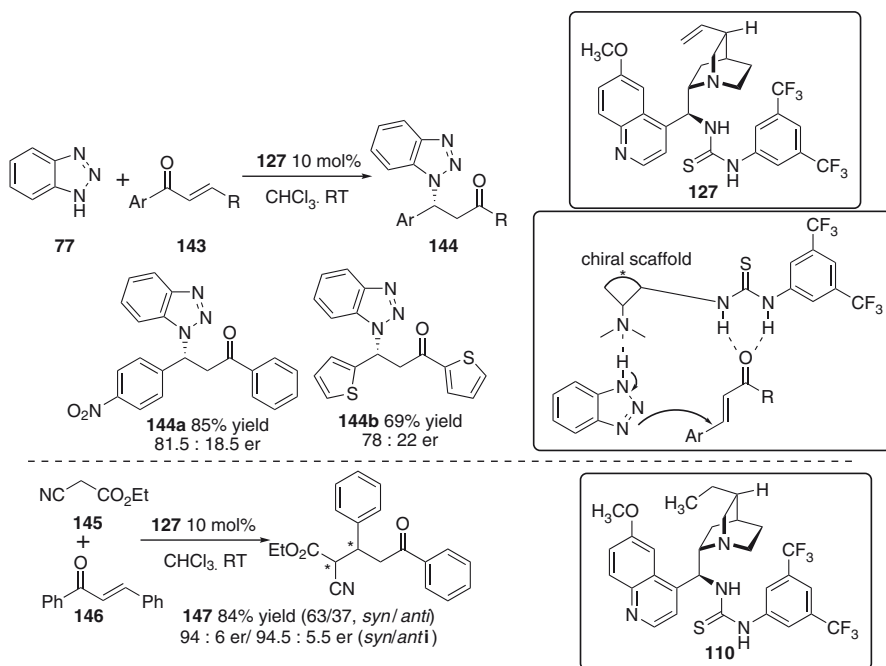
Scheme 32

Following work on Michael addition of triazoles to nitro-olefins (discussed in Sect. 2.5), bifunctional chiral thiourea catalysts were used in the addition of triazoles to chalcones [83]. The catalytic system was applicable to enones bearing aromatic groups of varying electronic natures to provide good yields and moderate selectivity. α -Cyanoacetates [84] were also applied in Michael addition to chalcones under similar catalytic conditions (Scheme 33).

3.3 Asymmetric Conjugate Addition with Imines

The aza-Henry reaction of imines to nitroalkanes promoted by modified *Cinchona* alkaloids has been investigated by several groups. Optically active β -nitroamine products are versatile functional building blocks. In 2005 and 2006, several reports regarding use of chiral thioureas emerged, using nitroalkanes in the aza-Henry reaction to various imines.

Ricci et al. [85] reported the use of a quinidine-derived chiral catalyst in the asymmetric addition of nitromethane to *N*-Boc imine **40**. At around the same time, Schaus and co-workers used a dihydroquinidine-derive chiral thiourea DHQD-134 applicable to nitromethane and nitroethane **149** [86]. The application of nitroethane conveniently generates a tertiary stereogenic center in the β -nitroamine product **151**. The methodology presented by Schaus is also applicable to novel

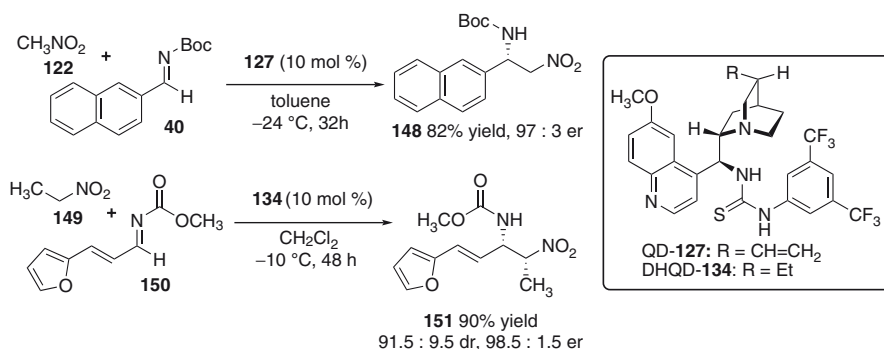


Scheme 33

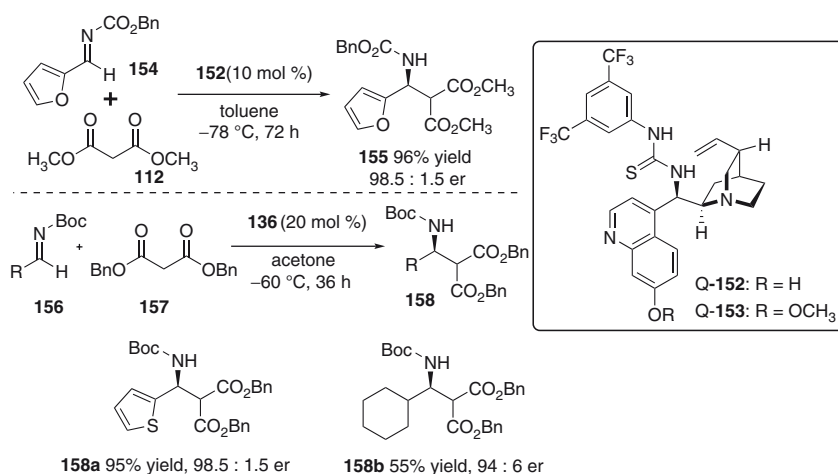
α,β -unsaturated, aliphatic imines (**150**). Application of similar reaction conditions to dimethyl malonate offered corresponding products in high enantioselectivity that were converted to β -amino esters under Nef conditions (Scheme 34).

At around the same time, other groups further reported the deprotonation-activation of malonates for the asymmetric addition to imines. Various malonates and aromatic *N*-acyl imines produced high yielding adducts with excellent stereoselectivities [87, 88].

Asides from the application of imines on conjugate addition reactions, Deng [87, 88] reported the first asymmetric chiral thiourea catalyzed Friedel-Crafts reaction of indoles with *N*-tosyl imines (Scheme 35). The reaction was receptive to various aromatic, heteroaromatic, and aliphatic imines in good yield and high enantioselectivity (Scheme 36).



Scheme 34



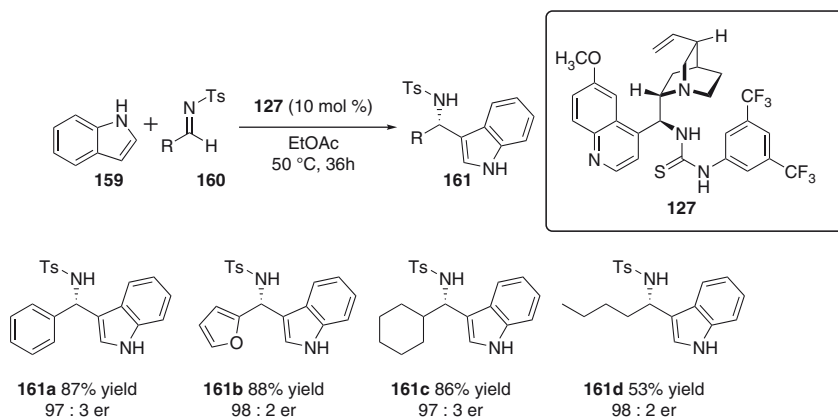
Scheme 35

4 Chiral Cyclohexane-Diamine Catalysts

Bifunctional catalysts have proven to be very powerful in asymmetric organic transformations [3]. It is proposed that these chiral catalysts possess both Brønsted base and acid character allowing for activation of both electrophile and nucleophile for enantioselective carbon–carbon bond formation [89]. Pioneers Jacobsen, Takemoto, Johnston, Li, Wang and Tsogoeva have illustrated the synthetic utility of the bifunctional catalysts in various organic transformations with a class of cyclohexane-diamine derived catalysts (Fig. 6). In general, these catalysts contain a Brønsted basic tertiary nitrogen, which activates the substrate for asymmetric catalysis, in conjunction with a Brønsted acid moiety, such as urea or pyridinium proton.

4.1 Discovery and Mechanism

In 1998, Jacobsen and co-workers synthesized and screened a library of peptide catalysts for the asymmetric Strecker reaction [14]. The peptide catalysts were



Scheme 36

Bifunctional Cyclohexane-Diamine Catalysts

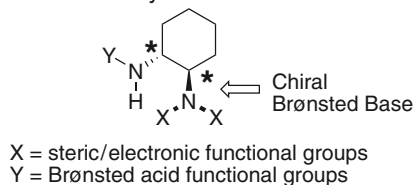


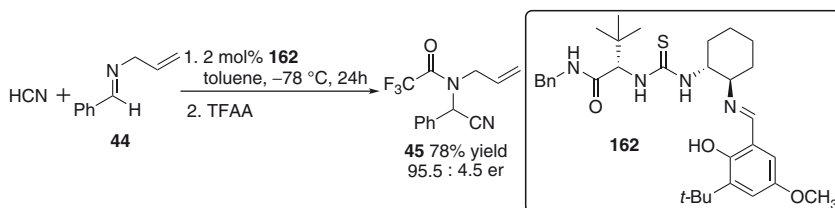
Fig. 6 Role of bifunctional cyclohexane-diamine catalysts

synthesized on solid support, implementing structural variation. The authors found that a particular library member, a thiourea imine chiral catalyst, promoted the asymmetric Strecker reaction in high yield and enantioselectivity (Scheme 37). Mechanistic and structural studies were conducted to investigate the mode of action of the new catalyst [90]. In rate studies of the asymmetric Strecker reaction, the authors found a first order dependence on both catalyst and HCN, and observed saturation kinetics for the imine, implicating reversible formation of an imine-catalyst complex. While the enantioselectivity of the reaction was largely attributed to the thiourea-imine hydrogen bonding interaction, it was recognized that HCN addition must take place away from the amino acid/amine portion. Similar to the dual activation of the bifunctional *Cinchona* alkaloids, this introduced the possibility that the HCN could be located near the imine portion of the catalyst, where a formal Brønsted base interaction could activate the HCN for nucleophilic addition.

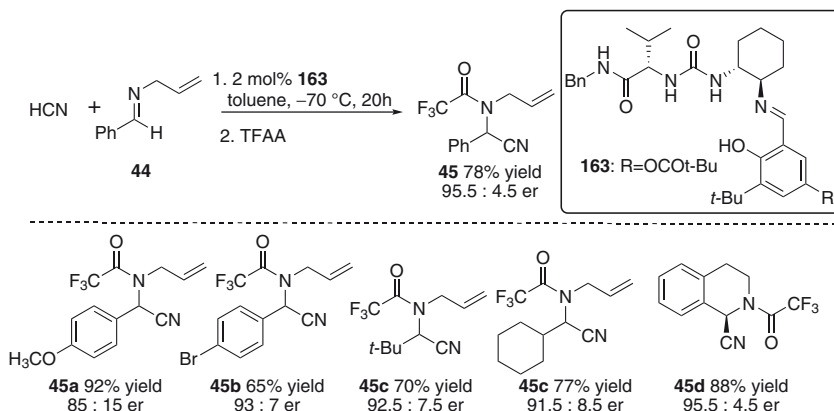
It was not long before the significance of the bifunctional catalyst was recognized. The chiral cyclohexane-diamine catalyst has promoted various asymmetric organic transformations including Strecker reactions, Michael additions, Mannich additions, aldol condensations and dynamic kinetic resolutions. Early work by Jacobsen et al. illustrated the scope of catalysis with the Strecker reaction [91]. A catalyst library of 70 small molecules was constructed, derivatives of a solid supported catalyst that had previously provided good results for the asymmetric Strecker reaction. Upon screening, analogue catalyst **163** provided optimal results for the addition of HCN to imines (Scheme 38). The broad scope of the reaction included aliphatic imines, and both electron-donating and electron-withdrawing imines. The authors were also able to promote the addition of HCN to cyclic isoquinoline (**45d**). The scope of the bifunctional catalysts was further illustrated with the Strecker reaction of HCN to ketoimines (Scheme 39), providing quaternary amino acids in high yield and enantiomeric excess [92]. The methodology was applied to the synthesis of α -methyl phenylglycine in quantitative yield. In addition, the authors found that the catalyst could be recycled without degradation of enantioselectivity.

4.2 Asymmetric Conjugate Additions

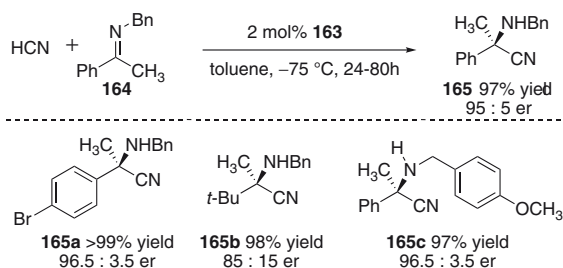
Takemoto and co-workers reported the use of a similarly structured bifunctional catalyst for the first enantioselective organocatalytic Michael addition of malonitrile to



Scheme 37



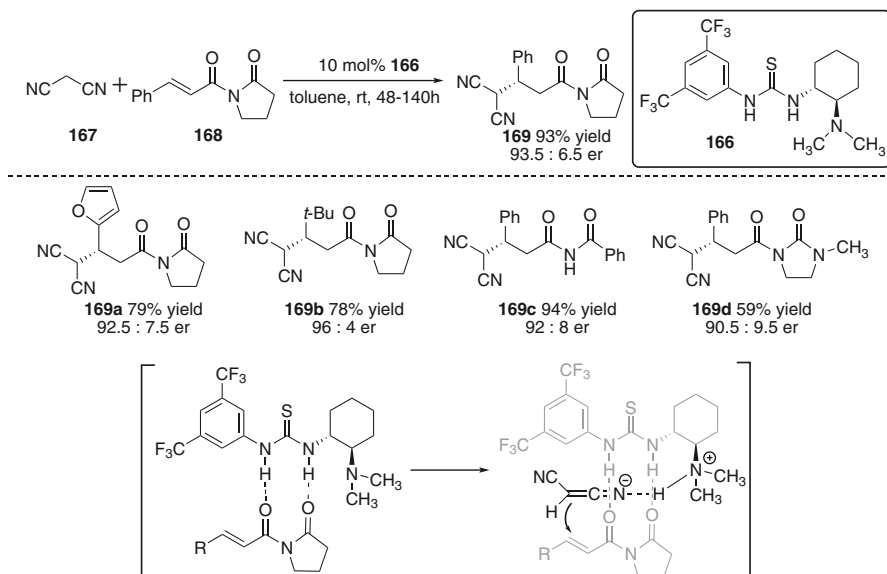
Scheme 38



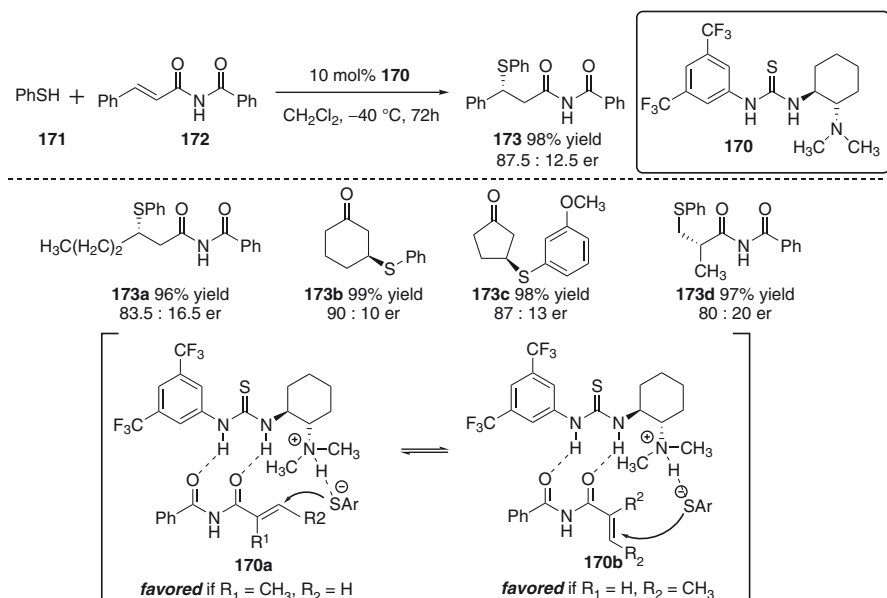
Scheme 39

α,β -unsaturated imides [93]. The catalyst of choice contained a 3,5-trifluoromethylphenylthiourea moiety, as well as a tertiary substituted amine. The asymmetric Michael addition was investigated with a variety of α,β -unsaturated imides (Scheme 40), and in general, both aliphatic and aromatic unsaturated imides were achieved with high enantioselectivities. Takemoto proposed that a Brønsted acid interaction existed between the diketone of the electrophile and the thiourea moiety. A Brønsted base interaction between the tertiary amine and the malonitrile tautomer provides the necessary pre-transition state for good reactivity and enantioselectivity [94].

The scope of Michael additions with catalysts containing cyclohexane-diamine scaffolds was broadened by Li and co-workers [95]. When screening for a catalyst for the addition of phenylthiol to α,β -unsaturated imides, the authors found that thiourea catalyst **170** provided optimal enantioselectivities when compared to *Cinchon* alkaloids derivatives (Scheme 41). Electrophile scope included both cyclic and acyclic substrates. Li attributed the enantioselectivity to activation of the diketone electrophiles via hydrogen-bonding to the thiourea, with simultaneous deprotonation of the thiol by the tertiary amine moiety of the diamine (**170a** and **170b**). Based on the observed selectivity, the authors hypothesized that the substrate-catalyst



Scheme 40



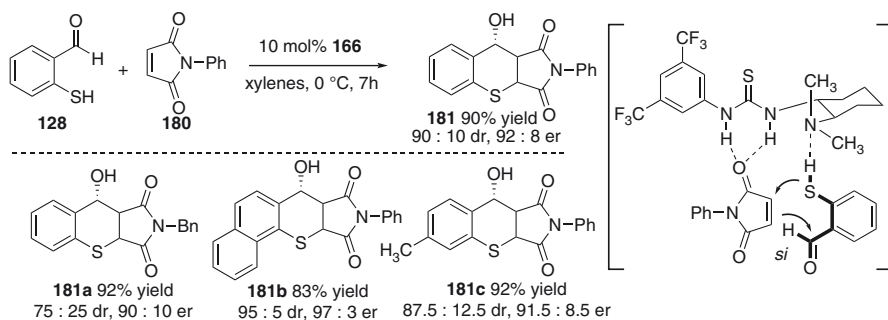
Scheme 41

Scheme 43

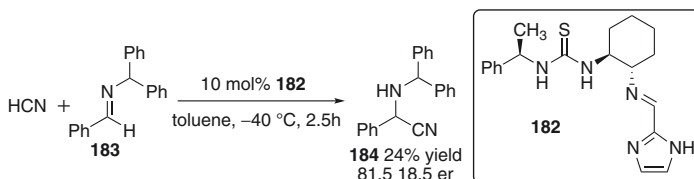
Michael-aldol for 2-mercaptobenzaldehydes and maleimides. Use of catalyst **166** provided a variety of fused heterocycles in high yield and high enantiomeric ratios (Scheme 44). The authors propose that the chiral catalyst simultaneously activates the thiol and the maleimide via Brønsted base and acid interactions. It was proposed that the pre-transition state arrangement of the catalyst and substrates determines the stereochemical outcome.

Tsogoeva and co-workers illustrated the utility of the cyclohexane-diamine bifunctional thiourea catalysts for both the asymmetric Strecker reaction and the nitro-Michael reaction [99]. Upon screening previously successful catalysts, the authors found that catalyst **182** catalyzes the asymmetric addition of HCN to various aldimines with moderate selectivity (Scheme 45). The imidazole catalysts also proved to be optimal in the Michael additions of acetone to β -substituted nitro-olefins (Scheme 46). A variety of electron-donating, electron-withdrawing and hetero- aromatic nitro-olefins were incorporated, all yielding products in high enantioselectivity. The authors hypothesized that the imidazole serves as a Brønsted base during catalysis, through coordinating to the acetone tautomer, while the thiourea functionality concurrently activates the nitro group through Brønsted acid interaction (**182a**).

Takemoto and co-workers designed a small library of thiourea cyclohexane-diamine derived catalysts for the Michael reaction of malonates to nitroolefins [15]. The authors observed an interesting trend in catalysis: the reaction only proceeded enantioselectively and in decent yields when the catalyst possessed both thiourea

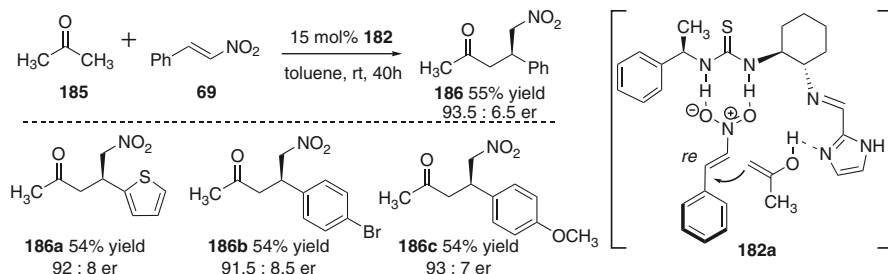


Scheme 44

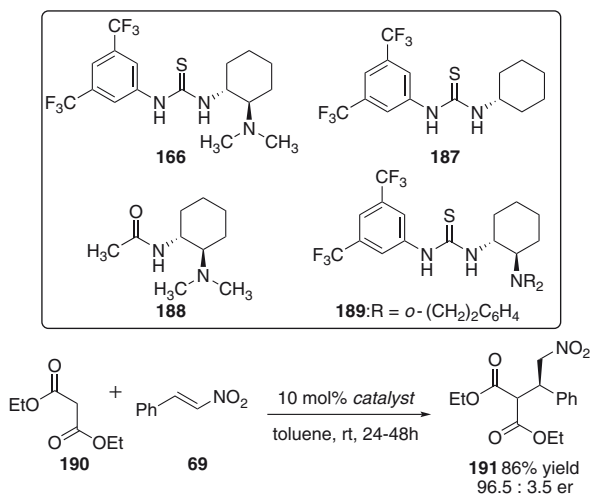


Scheme 45

and tertiary amine group moieties. When either functional group was removed, the selectivity and yield suffered immensely (Scheme 47, Table 1). This suggested a dual protonation-activation role from this class of catalysts characteristic of both Brønsted acidic and Brønsted basic properties.



Scheme 46



Scheme 47

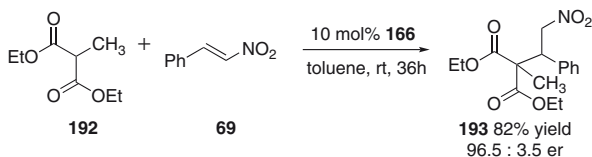
Table 1

Entry	Catalyst	Yield (%)	Er
1	NEt ₃	17	50:50
2	166	86	96.5:3.5
3	187 + NEt ₃	57	50:50
4	188	14	67.5:32.5
5	189	29	95.5:4.5

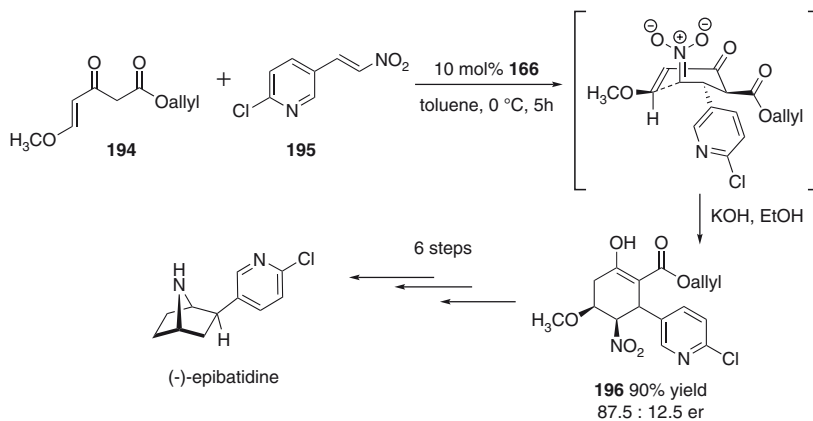
Using optimal bifunctional catalyst **166**, the reaction scope was expanded to aromatic, heteroaromatic, and aliphatic nitro-olefins. Catalyst **166** also promoted the addition of a β -phenyl nitro-olefin to α -CH₃- β -ketoester, achieving an asymmetric quaternary center in high yield and high enantiomeric ratio (Scheme 48).

The potential application of this catalytic system was illustrated by Takemoto in the application to a tandem conjugate addition towards the asymmetric synthesis of (–)-epibatidine, a biologically active natural product [100, 101]. The authors designed an enantioselective double Michael addition of an unsaturated functionalized β -ketoester to a β -aryl nitro-olefin. The asymmetric synthesis of the 4-nitro-cyclohexanones was achieved in both high diastereoselectivity and enantioselectivity, with the natural product precursor synthesized in 90% yield and 87.5:12.5 er (Scheme 49). The target (–)-epibatidine was subsequently achieved in six steps.

Chen and co-workers utilized the chiral bifunctional catalysts to directly access vinylogous carbon-carbon bonds via the asymmetric Michael addition of α,α -dicyano-olefins to nitro-olefins [102]. The scope of the reaction was explored with a variety of substituted α,α -dicyano-olefins and β -substituted nitro-olefins (Scheme 50). The authors propose the catalyst's tertiary amine functionality deprotonates the cyano-olefin, activating the nucleophile to add to the *si*-face of the pre-coordinated nitro-olefin.



Scheme 48

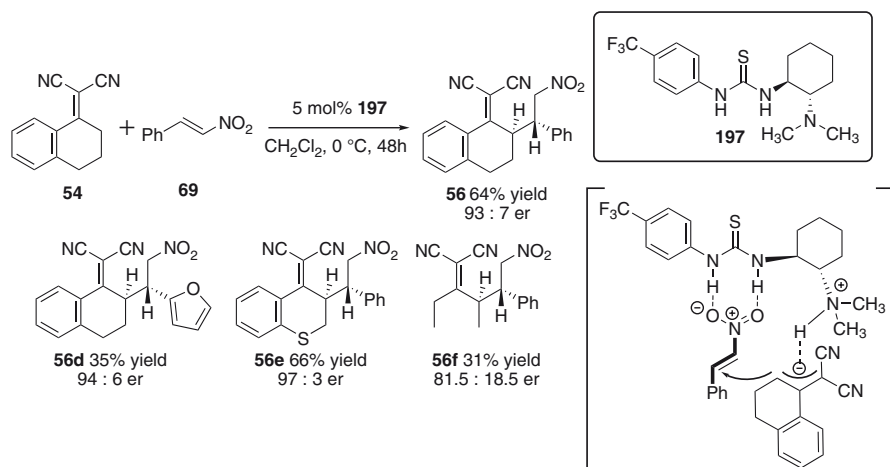


Scheme 49

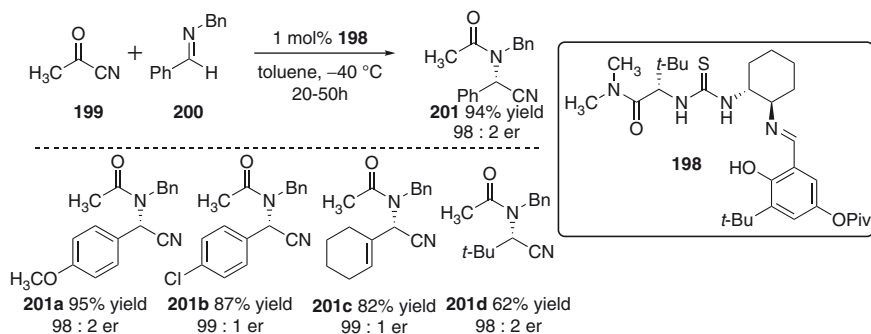
4.3 Asymmetric Mannich Additions

The asymmetric Mannich addition of carbon nucleophiles to imines catalyzed by the cyclohexane-diamine catalysts has developed significantly in the past decade. List and co-workers reported the asymmetric acyl-cyanation of imines catalyzed by a cyclohexane-diamine catalyst [103]. Using a derivative of Jacobsen's chiral urea catalyst, the authors optimized reaction conditions and obtained chiral *N*-acyl-aminonitriles in high yield and enantioselectivities (Scheme 51). The scope of the reaction was explored with both aliphatic and aromatic imines, providing good to high selectivities for a variety of substrates.

Takemoto and co-workers communicated that bifunctional organocatalyst **166** would promote aza-Henry reactions of phosphinoyl imines with nitroalkanes (Scheme 52) [104]. The catalytic additions provided high selectivities and yields



Scheme 50

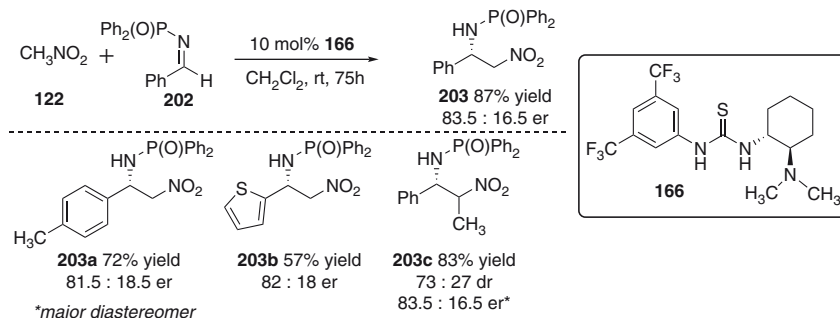


Scheme 51

for a range of aromatic imines. The scope of the reaction was extended to nitroalkanes, providing Henry-adducts in high yield, high diastereomeric ratios and high enantioselectivity.

The authors propose that the thiourea functionality of the catalyst would coordinate and activate the nitro-group via hydrogen bonding, while the catalyst's tertiary amine deprotonates the coordinated nucleophile to release active substrate for the asymmetric step (Fig. 7). Takemoto further expanded the scope and application of the methodology to the synthesis of CP-99,994, a neurokinin-1 (NK-1) receptor antagonist. The 2,3,6-trisubstituted piperidine core was achieved in 75% yield (Scheme 53). General methods were also developed to synthesize the piperidine derivatives in high yield and good stereoselectivity.

Johnston and co-workers designed a novel BisAmidinecatalyst (HQuin-BAM) for the asymmetric addition of nitroacetic acid derivatives to imines (Schemes 54 and 55) [105, 106]. The additions proceeded in high yield and high enantioselectivities for nitromethane and nitroalkanes to both electron-donating and electron-withdrawing aryl imines. While the mechanism of action is still undergoing investigation, the presence of the pyridinium proton is essential to the catalytic mode of



Scheme 52

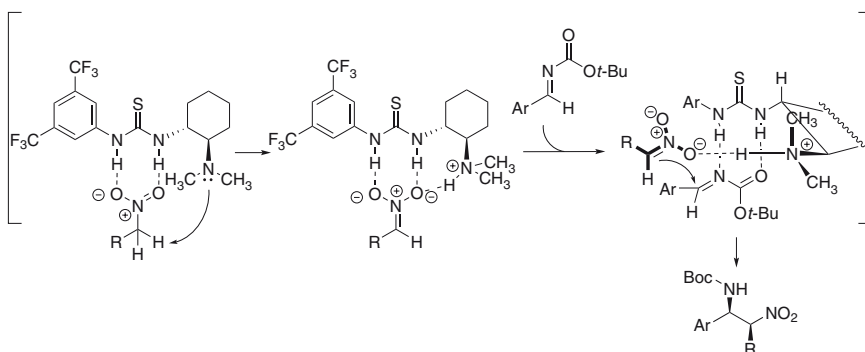
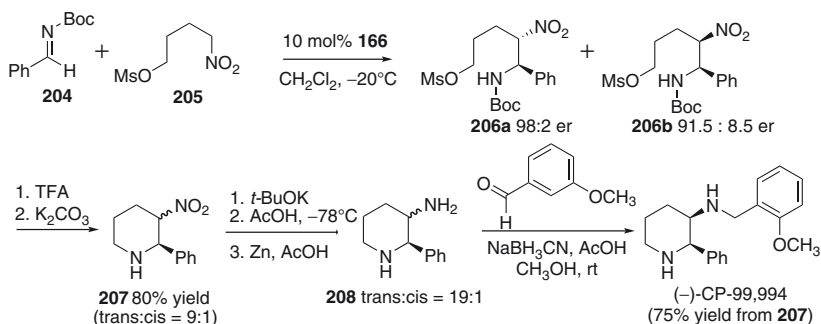
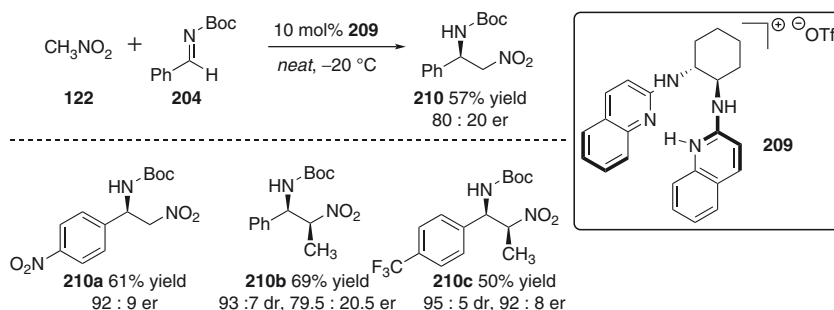


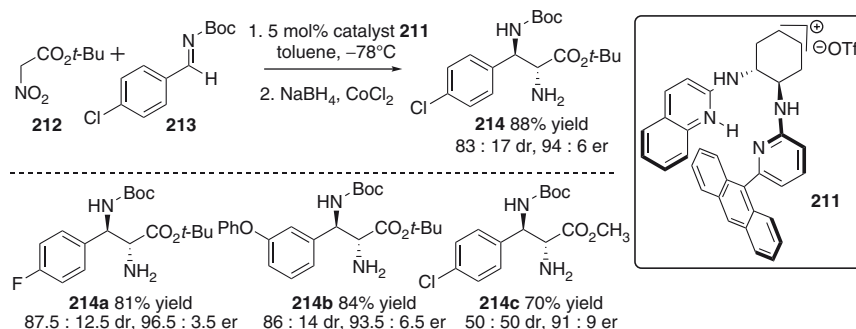
Fig. 7 Proposed role of cyclohexane-diamine thiourea **166** for the asymmetric aza-Henry reaction



Scheme 53



Scheme 54



Scheme 55

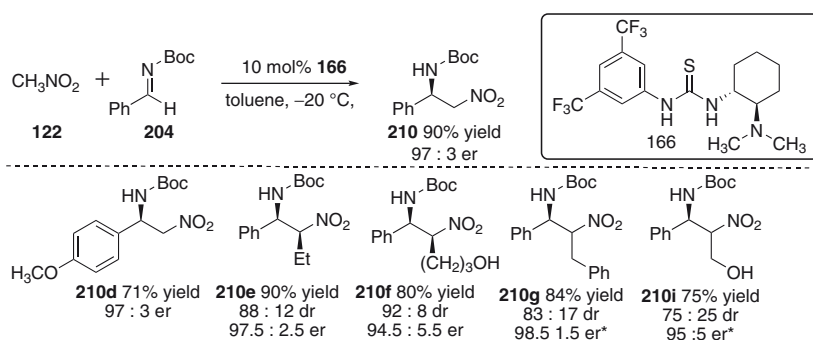
action. The reaction proceeds without external base additives or pre-activation of the nucleophile, presenting the possibility that the catalyst possesses bifunctional Brønsted acid and base interactions during catalysis.

Recently, Takemoto and co-workers reported the use of bifunctional thiourea catalyst **166** for the aza-Henry reaction of nitroalkanes to *N*-Boc imines [107, 108]. Using a

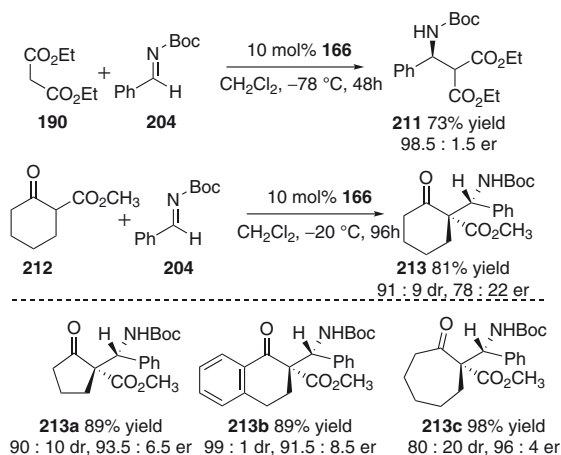
catalytic amount of the bifunctional catalyst provided the corresponding aza-Henry adducts in high yield and good enantiomeric ratio (Scheme 56). Both nitromethane and substituted nitroalkanes provided optimal results with catalyst **166**.

The scope of electrophiles was explored with malonates and β -ketoesters, providing chiral amine adducts in high yield and enantioselectivities (Scheme 57) [109]. Addition of cyclic β -ketoesters was also explored with hydrazines, providing cyclic and bicyclic chiral amines with quaternary centers in high enantiomeric ratios (Scheme 58).

Jacobsen et al. found that cyclohexane-diamine bifunctional catalyst **216** promoted the enantioselective hydrophosphonylation of *N*-benzyl imines [110]. Using a modified



Scheme 56

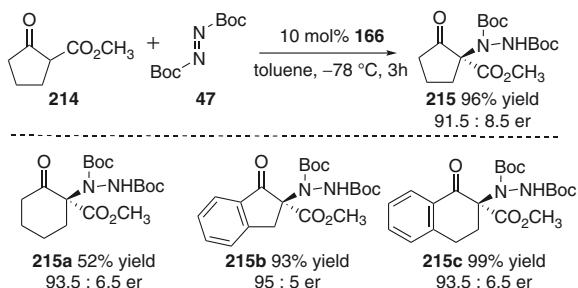


Scheme 57

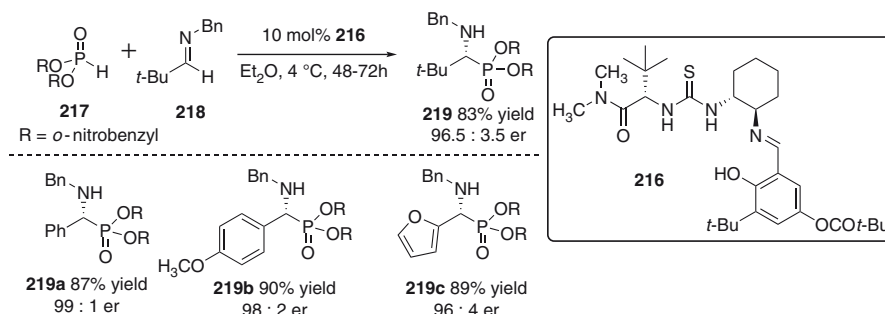
version of the bifunctional catalyst from their asymmetric hydrocyanation reaction, optimal results were achieved for the enantioselective phosphorylation of imines (Scheme 59). While the mechanism of the hydrophosphonylation is currently being investigated, it is necessary that strong electron-withdrawing groups be present on the phosphite for good reaction rate, suggesting that the imine moiety of the catalyst activates the phosphite via Brønsted base interaction.

4.4 Dynamic Kinetic Resolution

Berkessel and co-workers have demonstrated the utility of the bifunctional cyclohexane-diamine catalysts in the dynamic kinetic resolution of azalactones (Schemes 60 and 61) [111, 112]. The authors proposed that the urea/thiourea moiety of the catalyst coordinates and activates the electrophilic azlactone. The allyl alcohol nucleophilicity is increased due to the Brønsted base interaction with the tertiary amine of the catalyst.



Scheme 58

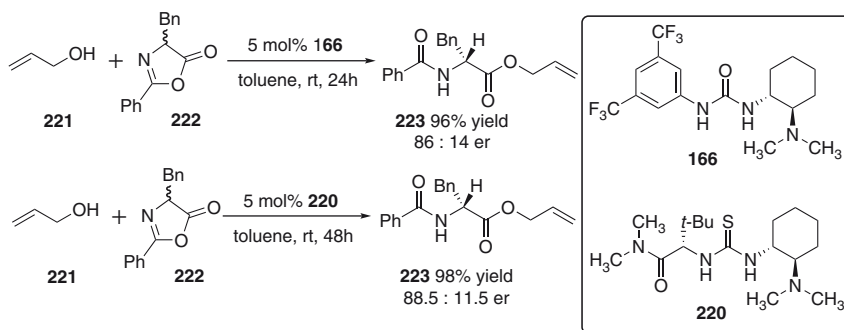


Scheme 59

The authors proposed that the Brønsted base interaction on the catalyst is imperative for reactivity. Catalysts lacking a basic amine moiety, specifically mono- and bis-ureas, did not promote the asymmetric catalytic addition well, if at all. In screening a variety of amine bases and bis-ureas, it became apparent that presence of a Brønsted base was necessary for catalytic activity (Scheme 61) [113]. The reactivity was extremely low in absence of Brønsted base (Table 2, entry 2), but slightly improved with presence of NEt_3 (Table 2, entry 1). Combined, a chiral Brønsted acid and Brønsted base increase conversion and showed some enantioselectivity (Fig. 8).

5 Chiral Guanidine Catalysts

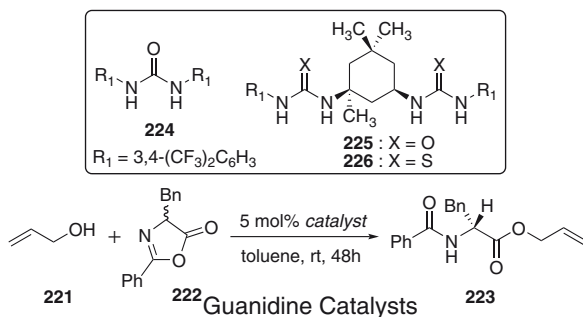
While the significance of the bifunctional Brønsted base catalysts has been illustrated in the previous sections, few examples rely solely on a Brønsted base interaction for asymmetric catalysis. However, in the past few decades, a novel catalyst system has emerged as a powerful promoter of chiral transformations. The guanidines have gained the reputation as super bases in organic transformations.



Scheme 60

Table 2

Entry	Catalyst	Conversion (%)	Er
1	NEt_3	14	—
2	224	4	—
3	224 + NEt_3	50	—
4	225 + NEt_3	50	<51:49
5	226 + NEt_3	33	55:45



Scheme 61

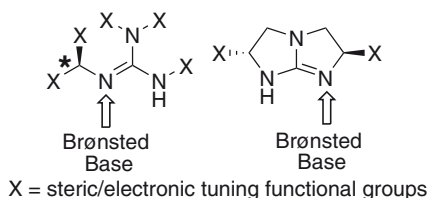


Fig. 8 Guanidine compounds as Brønsted base catalysts

Resonance stabilization of the conjugate acid of guanidine defines this class of molecules as some of the strongest bases in organocatalysis [114].

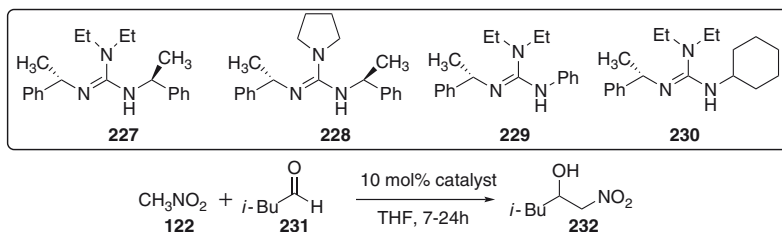
5.1 Discovery and Mechanism

It was not until 1994 that Chinchilla and co-workers identified a synthesized a chiral guanidine for asymmetric catalysis [115].

The authors reported the first chiral guanidine catalyzed addition of nitro-olefins to aldehydes (Scheme 62, Table 3). While reactivity and selectivity were not optimal, the discovery led to great developments in the field of asymmetric Brønsted base catalysis.

Shortly after Chinchilla's finding, Lipton and co-workers reported the use of a dipeptide guanidine for the asymmetric catalytic Strecker reaction [116]. The authors found that application of a dipeptide catalyst bearing an imidazole moiety provided very low reactivity. However, use of the same dipeptide catalyst bearing a more basic guanidine functional group provided high yields at low temperatures and very high enantioselectivities for aromatic imines (Scheme 63).

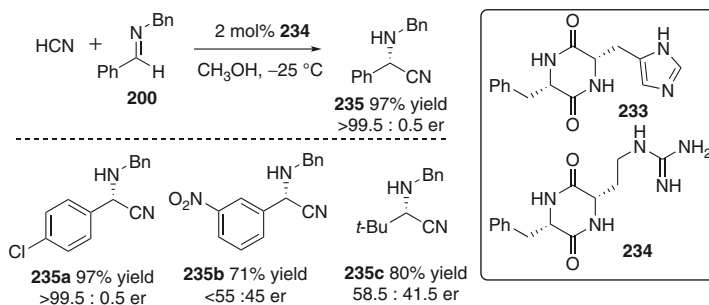
The chiral guanidine's role as a strong Brønsted base for the reactions of protic substrates has been proposed. In 1999, Corey developed a C_2 -symmetric chiral guanidine catalyst to promote the asymmetric Strecker reaction [117]. The addition of HCN to imines was promoted high yields and high enantioselectivities for both electron-withdrawing and electron-donating aromatic imines (Scheme 64).



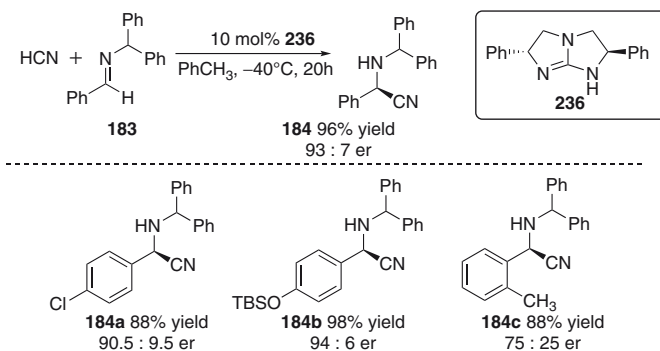
Scheme 62

Table 3

Entry	Catalyst	T (°C)	Yield (%)	Er
1	227	−45	40	67:33
2	227	−65	33	77:23
3	228	rt	77	53:47
4	229	rt	6	50:50
5	230	rt	60	52.5:47.5



Scheme 63



Scheme 64

The group proposed that the hydrocyanate underwent a formal Brønsted base interaction with the guanidine catalyst, thus activating the nucleophile for addition (Fig. 9). In contrast to the bifunctional catalysts, the guanidines are basic enough to activate the substrates without the need for secondary moieties.

5.2 Conjugate Additions

Tan and co-workers designed a guanidine catalyst similar to that of Corey's cyclic guanidine for the asymmetric addition of nitroalkanes to α,β -unsaturated ketones [118]. Michael adducts were achieved in decent yields and moderate selectivities (Scheme 65). The scope also included malonates as nucleophiles, providing γ -nitro adducts in high yields, although selectivities were degraded slightly (Scheme 66).

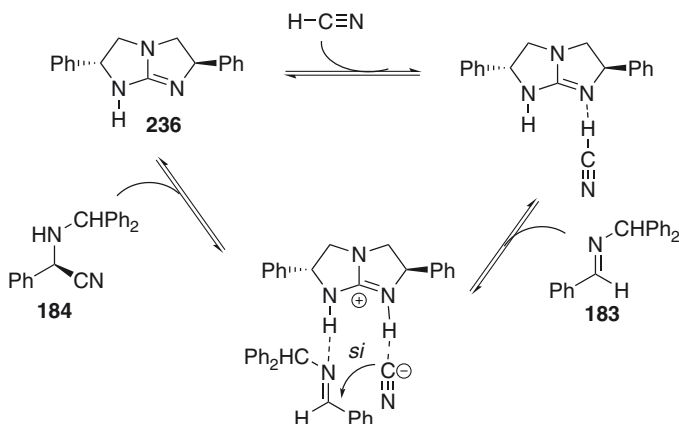
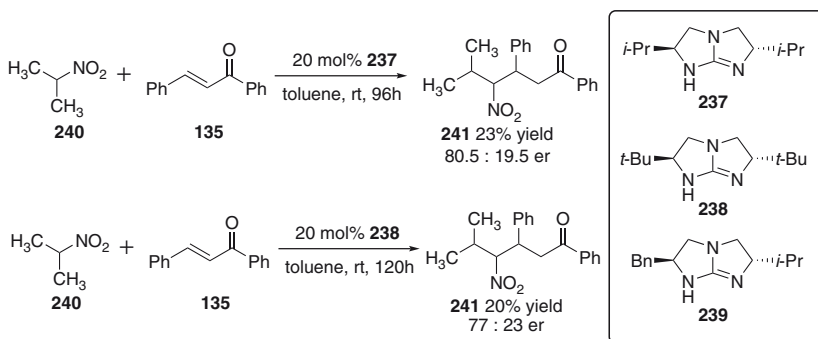


Fig. 9 Corey's proposed catalytic cycle for chiral guanidine promoted hydrocyanation

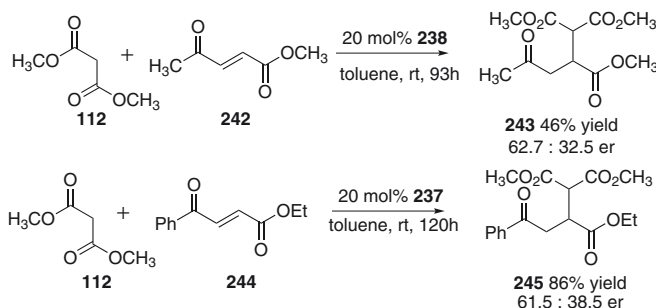


Scheme 65

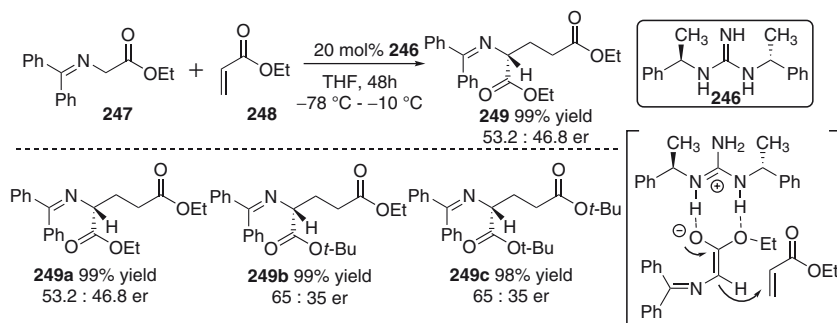
The degradation may be attributed to weaker interactions between the guanidine and malonate, as nitroalkanes are well known to form tightly bound ion pairs in non-polar solvents [119, 120]. The asymmetric induction may have been better for the nitroalkanes because of the tight coordination.

Ma and co-workers extended use of chiral guanidine catalysts to the addition of glycine derivatives to acrylates [121]. Addition products were achieved in high yield with modest enantioselectivity (Scheme 67). The *tert*-butyl glycinate benzophenone imines generally provided better enantiomeric ratios than the ethyl glycinate benzophenone imines. Based on this observation, the authors hypothesized that an imine-catalyst complex determines the stereochemical outcome of the product.

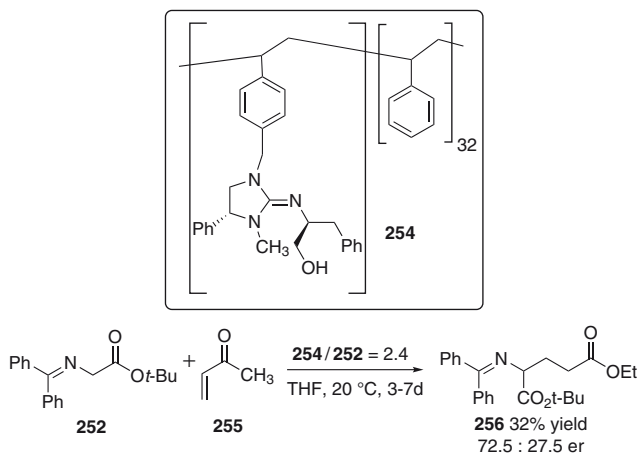
Another structurally modified guanidine was reported by Ishikawa et al. as a chiral superbases for asymmetric silylation of secondary alcohols [122]. Soon after, Ishikawa discovered that the same catalyst promoted asymmetric Michael additions of glycine imines to acrylates [123]. The additions were promoted in good yield and great asymmetric induction under neat reaction conditions with guanidine catalyst **250** (Scheme 68). The authors deduced that the high conversion and selectivity were due to the relative configuration of the three chiral centers of the catalyst in



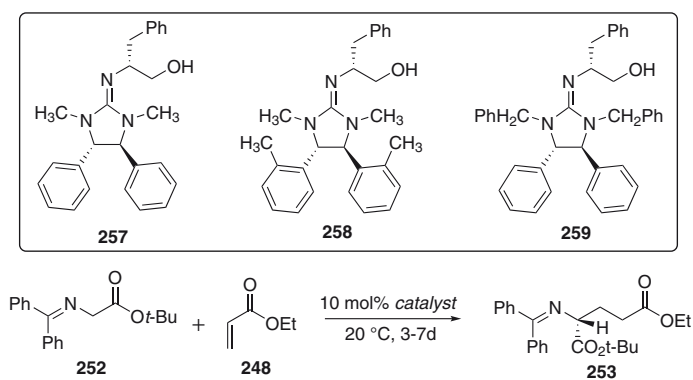
Scheme 66



Scheme 67



Scheme 69



Scheme 70

Table 4

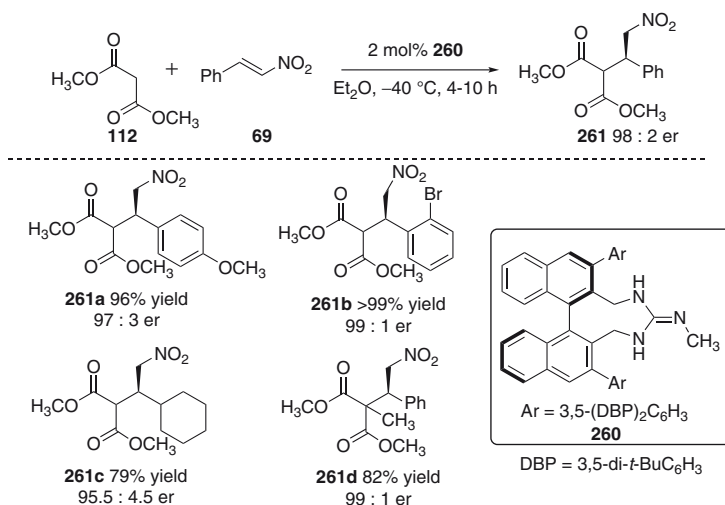
Entry	Catalyst	Solvent	Yield (%)	Er
1	257	THF	26	89.5:10.5
2	257	None	77	96.5:3.5
3	258	THF	62	95:5
4	258	None	79	98.5:1.5
5	259	THF	27	99:1
6	259	None	NR	—

More specifically, 3,5-di-*tert*-butylphenyl substitution on the 3,3'-position of the binaphthol backbone (**260**) provided overall best yields and selectivities. Using catalyst **260**, the authors expanded the scope of substrates to include aliphatic and aromatic nitro-alkenes, and α -substituted β -ketoesters, while maintaining good yields and enantiomeric ratios (Scheme 71).

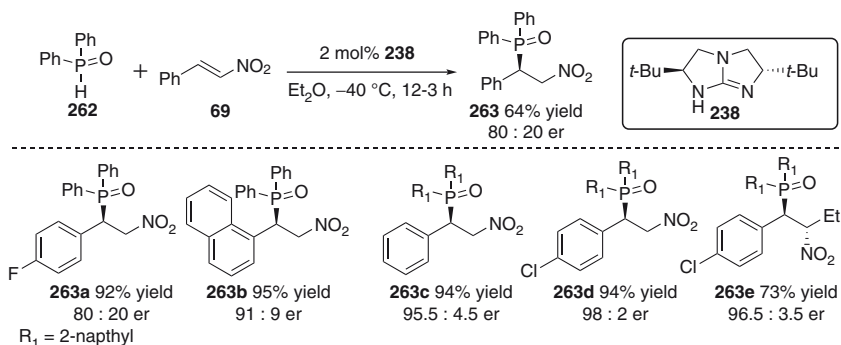
Chiral compounds containing phosphorus-carbon bonds have found significant roles in metal- and organo-based catalysis; therefore it is important to develop catalytic methods to access such substrates. Few organocatalytic phospho-Michael reactions exist, but recently Tan and co-workers reported an asymmetric addition of phosphine oxides to nitro-olefins [127]. Using a derivative of Corey's bicyclic guanidine catalyst, the authors achieved chiral amino-phosphines in high yield and high enantiomeric ratios (Scheme 72). The scope of the catalyst was illustrated with electron-withdrawing and electron-donating β -aryl-nitro-olefins.

Terada expanded the phospho-Michael reaction to include diphenyl-phosphites [128]. A novel binaphthol-derived guanidine catalyst promoted the addition in high yields and enantioselectivities (Scheme 73). Functionalizing the external nitrogen with a diphenylmethine moiety enhanced selectivities for a large scope of nitro-olefin derivatives.

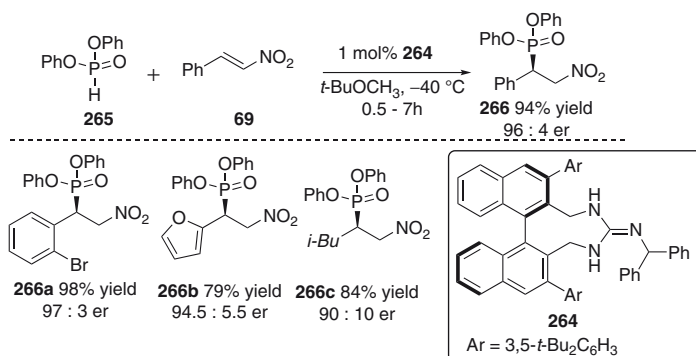
Tan and co-workers reported the Michael reactions of di-thiomalonates and β -keto-thioesters to a range of acceptors, including maleimides, cyclic enones, furanones and acyclic dioxobutenes [129]. Unlike dimethyl malonate, additions with acidic thioesters proceeded in higher yields, and overall better enantioselectivities (Scheme 74).



Scheme 71



Scheme 72



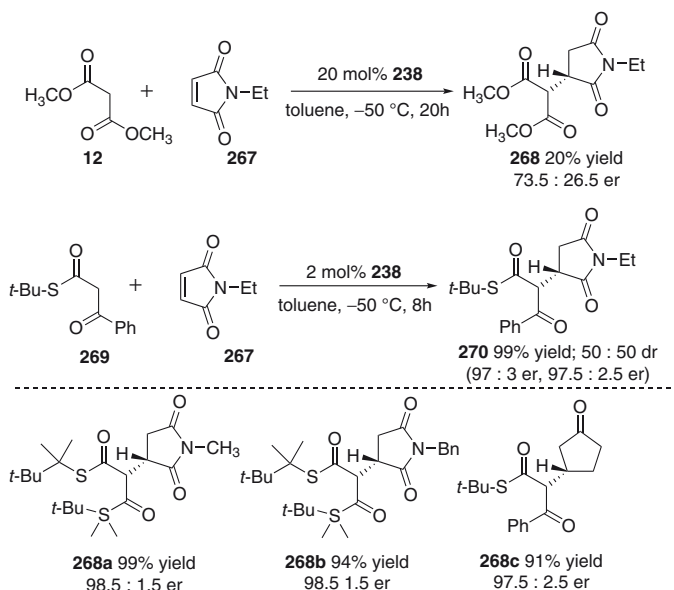
Scheme 73

5.3 Asymmetric Diels-Alder Reactions

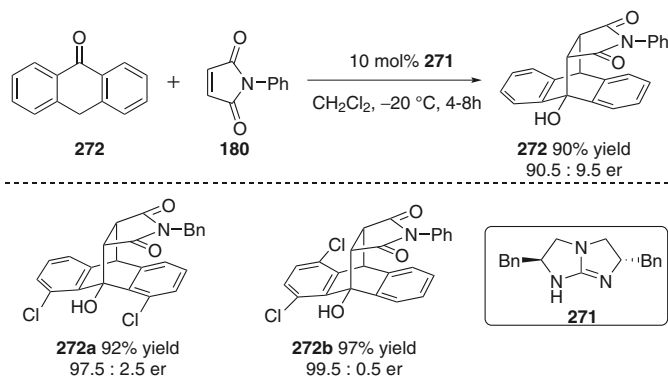
In 2006, Tan and co-workers reported the first asymmetric guanidine catalyzed Diels-Alder addition of anthrone to maleimides (Scheme 75) [130]. The authors observed very high yields and enantioselectivities using a derivative of Corey's C2-symmetric bicyclic guanidine catalyst. The addition of anthrones to maleimide also worked well for substituted anthrones. Interestingly, the authors observed the oxidized product when the anthrone was substituted at the *meta*-positions (Scheme 76).

6 Additional Brønsted Base Catalysts

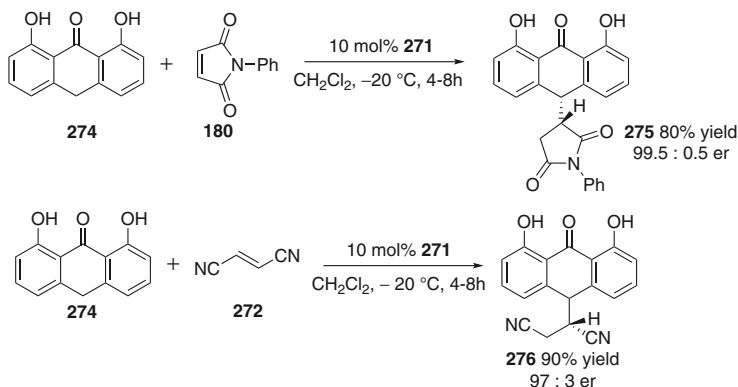
Many of the catalysts up until this point have been developed and applied to numerous organic transformations. While these discoveries have illustrated the importance of Brønsted base catalyzed asymmetric transformations, expanding the scope



Scheme 74



Scheme 75



Scheme 76

of base catalysis is always an ongoing effort. This section will highlight the development of new chiral Brønsted base catalysts undergoing development.

6.1 Chiral Binaphthyl-Derived Amine

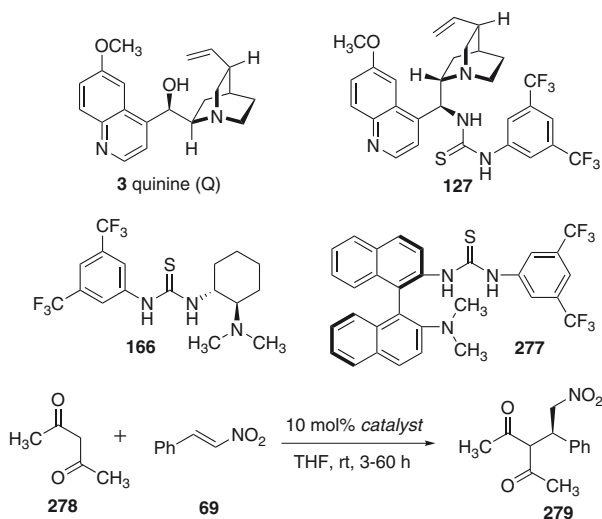
Wang and co-workers reported a novel class of organocatalysts for the asymmetric Michael addition of 2,4-pentandiones to nitro-olefins [131]. A screen of catalyst types showed that the binaphthol-derived amine thiourea promoted the enantioselective addition in high yield and selectivity, unlike the cyclohexane-diamine catalysts and *Cinchona* alkaloids (Scheme 77, Table 5).

The best reactivity and selectivity was illustrated with the binaphthol derived thiourea amine catalyst **277**. The substrate scope was explored primarily with β -aryl-nitro-olefins of both electron-donating and electron-withdrawing natures. Yields and selectivities were high for the majority of substrates (Scheme 78).

6.2 Chiral Paracyclophane-Derived Imine

Recently, Kunz et al. reported a new organocatalyst for the asymmetric Strecker reaction [132]. The paracyclophane-derived imine catalyst (**280**) promotes the hydrocyanation of various imines, both aromatic and aliphatic (Scheme 79).

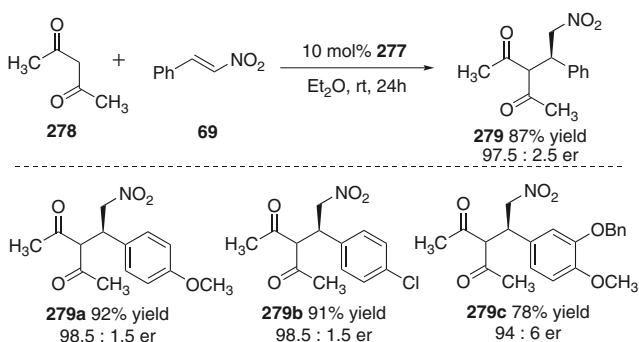
The authors identify the new paracyclophane derivative as a catalyst lacking a hydrogen bond donor, and propose that addition is catalyzed by the Brønsted basic imine moiety. Based on X-ray crystal data of the catalyst, it was hypothesized that



Scheme 77

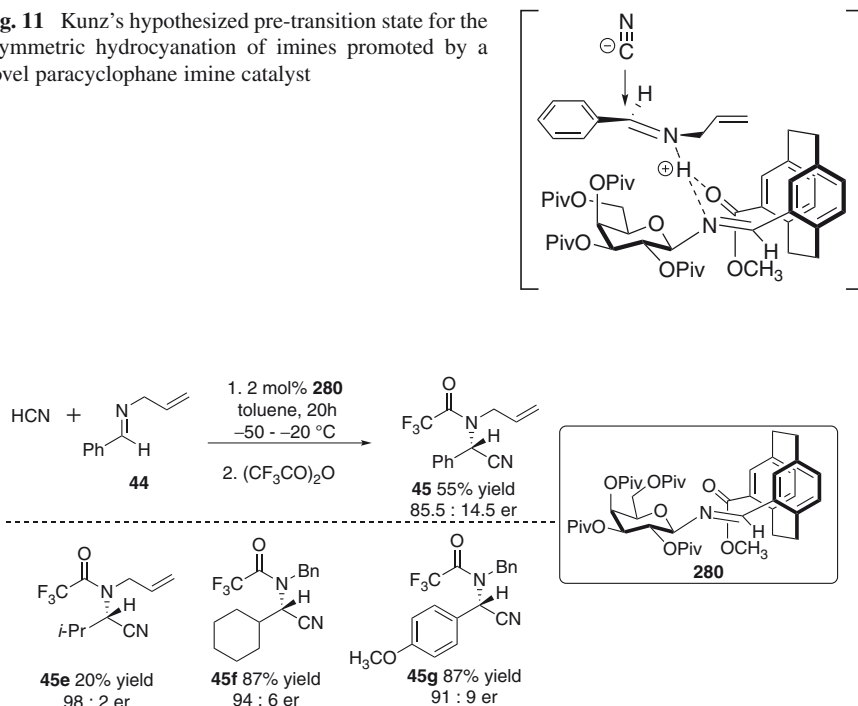
Table 5

Entry	Catalyst	Yield (%)	Er
1	3	52	58.5:41.5
2	127	47	98:2
3	166	92	92:8
4	277	93	97.5:2.5



Scheme 78

Fig. 11 Kunz's hypothesized pre-transition state for the asymmetric hydrocyanation of imines promoted by a novel paracyclophane imine catalyst



Scheme 79

the imine base moiety was key in coordination and deprotonation of HCN to create a Brønsted acid environment to trap the imine substrate (Fig. 11). The anionic CN^- would add to the imine over the *re* face, as the *si* is blocked by the catalyst bulk.

7 Conclusion

The utility of chiral organic Brønsted bases highlighted illustrates the evolution of the field and the catalyst design enabled through mechanistic understanding. The products afforded by the methods highlighted in this review provides a significant indication of how powerful the approach will be in providing ready access to chiral compounds for use in synthesis. Progress in catalyst design and method development has been the result of thoughtful mechanistic consideration of existing catalyst structures and creative catalyst modification to address limitations. Conceptual advances have been and will continue to be made as an increased emphasis is placed on the synthetic utility of the products afforded by new methods. The synthetic challenges in this area have resulted in the creation of novel catalysts and will continue to inspire the imaginations of chemists [133].

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Chiral Ketone and Iminium Catalysts for Olefin Epoxidation

O. Andrea Wong and Yian Shi

Abstract Organo-catalyzed asymmetric epoxidation has received much attention in the past 30 years and significant progress has been made for various types of olefins. This review will cover the advancement made in the field of chiral ketone and chiral iminium salt-catalyzed epoxidations.

Keywords Asymmetric epoxidation • Chiral iminium salt • Chiral ketone

Contents

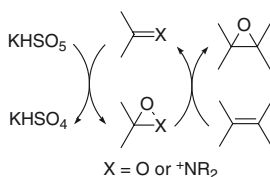
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1 Introduction

Asymmetric epoxidation of olefins is an effective approach for the synthesis of enantiomerically enriched epoxides. A variety of efficient methods have been developed [1, 2], including Sharpless epoxidation of allylic alcohols [3, 4], metal-catalyzed epoxidation of unfunctionalized olefins [5–10], and nucleophilic epoxidation of electron-deficient olefins [11–14]. Dioxiranes and oxaziridium salts have been proven to be effective oxidation reagents [15–21]. Chiral dioxiranes [22–28] and oxaziridium salts [19] generated in situ with Oxone from ketones and iminium salts, respectively, have been extensively investigated in numerous laboratories and have been shown to be useful toward the asymmetric epoxidation of alkenes. In these epoxidation reactions, only a catalytic amount of ketone or iminium salt is required since they are regenerated upon epoxidation of alkenes (Scheme 1).



Scheme 1 Ketone/iminium salt-catalyzed epoxidations

2 Chiral Ketone-Catalyzed Epoxidations

In 1984, Curci and coworkers reported asymmetric epoxidation of olefins with ketones **1** and **2** (Fig. 1), providing up to 12.5% ee for *trans*- β -methylstyrene [29]. Subsequently (in 1995), they reported that fluorinated ketones **3** and **4** were more reactive than **1** and **2** for epoxidations, and up to 20% ee was obtained for *trans*-2-octene [30]. Furthermore, these ketones are stable under epoxidation conditions and can be recovered with only minor losses (2–5%) after work-up of the reactions. In the same year, several other fluorinated ketones (**5**–**7**) were reported to be active for the epoxidation of some alkenes, such as, *trans*-stilbene, *trans*- β -methylstyrene, and 6-chloro-2,2-dimethyl-2*H*-1-benzopyran, but no enantioselectivity was observed [31].

2.1 *C*₂-Symmetric Binaphthyl-Based and Related Ketones

In 1996 Yang and coworkers reported a series of binaphthyl-derived *C*₂-symmetric ketones (**8**) as epoxidation catalysts (a few examples are shown in Fig. 2)[32–34].

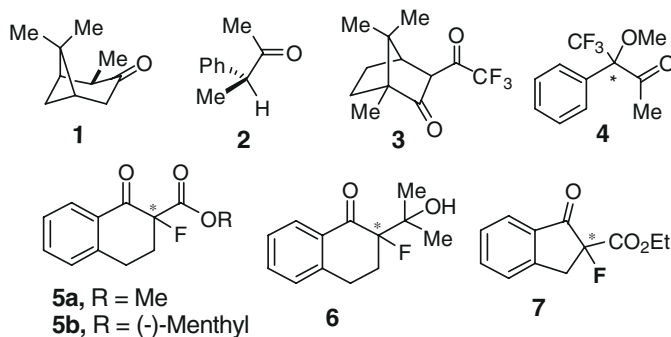


Fig. 1 Ketones 1–7

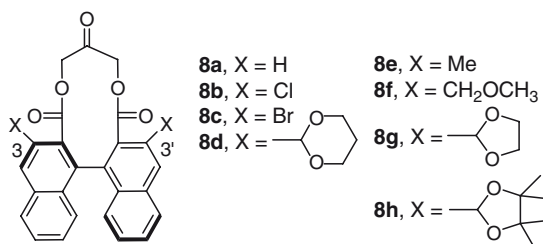


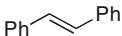
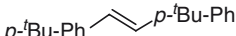
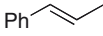
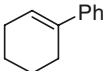
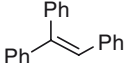
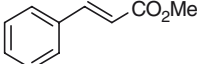
Fig. 2 Ketones 8

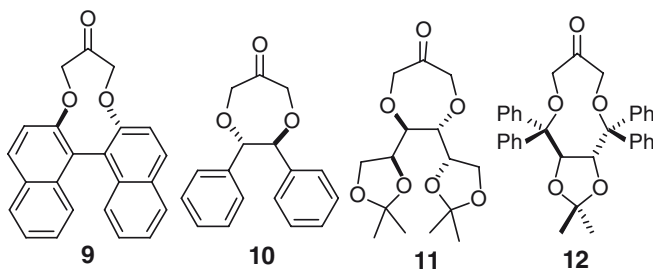
Ketone **8** epoxidizes a wide range of olefins in good yields. The steric hindrance and electronegativity of the substituents (X) at positions 3 and 3' greatly affect the epoxidation reactivity and enantioselectivity. In general, *para*-substituted *trans*-stilbenes are very effective substrates for the epoxidation using ketone **8** (Table 1, entries 1–8, 16–18). The enantioselectivity for the epoxidation increases as the size of the substituents increases. However, the size of the *meta*-substituents had little effect on enantioselectivity. Later, Seki and coworkers extended the epoxidation scope to cinnamates using ketone **8** (Table 1, entry 26) [35, 36].

Binaphthol- and biphenyl-derived ketones (**9** and **10**) were reported by Song and coworkers in 1997 to epoxidize unfunctionalized alkenes in up to 59% ee (Fig. 3, Table 1, entries 9, 10) [37, 38]. Ketones **9** and **10** were intended to have a rigid conformation and a stereogenic center close to the reacting carbonyl group. The reactivity of ketones **9** and **10** is lower than that of **8**, presumably due to the weaker electron-withdrawing ability of the ether compared to the ester. In the same year, Adam and coworkers reported ketones **11** and **12** to be epoxidation catalysts for several *trans*- and trisubstituted alkenes (Table 1, entries 11, 12). Up to 81% ee was obtained for phenylstilbene oxide (Table 1, entry 25) [39].

A series of fluorinated biaryl ketones (**13**) was reported by Denmark and coworkers in 1999 and 2002 (Fig. 4) [22, 40]. The introduction of fluorine atoms at the α -position of the reacting carbonyl increased the efficiency of the epoxidation. Fluorinated ketones **13b** and **13c** displayed high reactivity and good enantioselectivity

Table 1 Asymmetric epoxidation with ketones **8–16**

Entry	Substrates	Catalyst	Yield (%)	ee (%)
1		(R)-8a	91	47 (S,S)
2		(R)-8b	95	76 (S,S)
3		(R)-8c	92	75 (S,S)
4		(R)-8d	93	84 (S,S)
5		(S)-8e	93	56 (R,R)
6		(R)-8f	92	66 (S,S)
7		(R)-8g	90	77 (S,S)
8		(R)-8h	91	75 (S,S)
9		9	79	26 (S,S)
10		10	72	59 (S,S)
11		11	72 ^a	38 (R,R)
12		12	67 ^a	65 (R,R)
13		13b	46	94 (R,R)
14		15	27	30
15		16	93	64 (R,R)
16		(R)-8b	>90	91 (S,S)
17		(R)-8c	>90	93 (S,S)
18		(R)-8d	>90	95 (S,S)
19		13a	6 ^a	nd ^b
20		13b	80	88 (R,R)
21		13c	100 ^a	85
22		14a	100 ^a	86
23		14b	100 ^a	83
24		16	99	82 (R,R)
25		12	70 ^a	81
26		(R)-8a	75	74 (2R,3S)

^aConversion (%)^bNot determined**Fig. 3** Ketones **9–12**

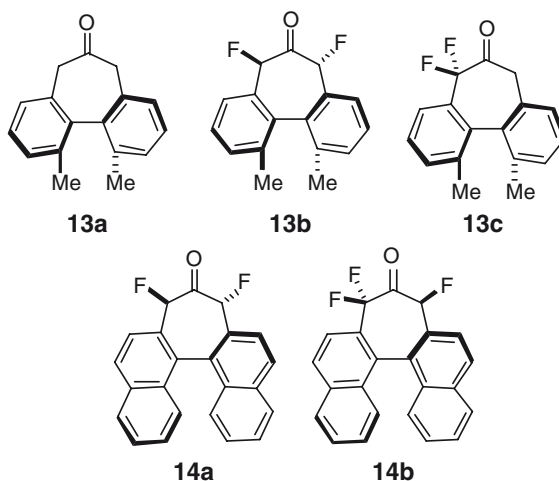


Fig. 4 Ketones 13–14

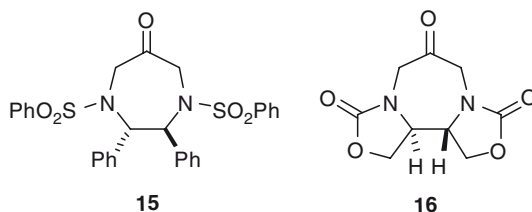


Fig. 5 Ketones 15–16

for *trans*-olefins (up to 94% ee was obtained for *trans*-stilbene oxide) (Table 1, entries 13, 19–21). Also in 2002, Behar and coworkers reported a series of structurally related fluorinated binaphthyl ketones (**14**) (Fig. 4) [41]. Among the ketones studied, difluorinated ketone **14a** and trifluorinated ketone **14b** were found to be the most reactive and enantioselective for the epoxidation of *trans*- β -methylstyrene (Table 1, entries 22, 23).

Tomioka and coworkers reported ketones **15** and **16** as asymmetric epoxidation catalysts (Fig. 5) [42, 43]. Ketone **15** was found to be prone to Baeyer–Villiger oxidation to the lactone, thus giving low yield for the epoxidation (Table 1, entry 14). Epoxidation results were much improved with tricyclic ketone **16** (Table 1, entries 15, 24).

2.2 Ammonium Ketones

Denmark and coworkers reported 4-oxopiperidinium salt **17** to be an effective catalyst under biphasic conditions (Fig. 6) [44, 45]. The choice of the alkyl groups on the nitrogen affects the lipophilicity of the ketone, thus influencing the partitioning

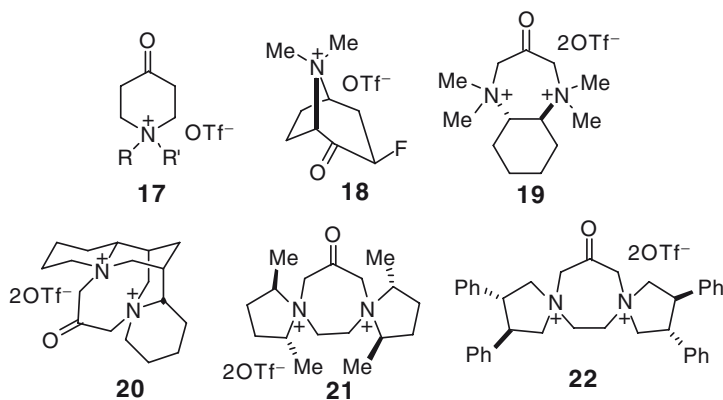


Fig. 6 Ketones 17–22

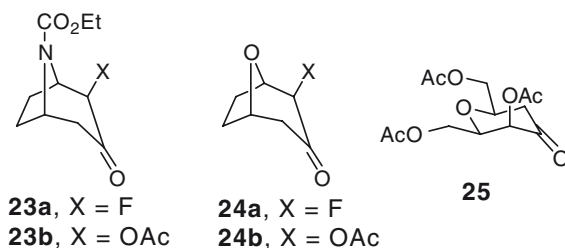


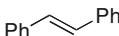
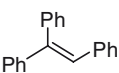
Fig. 7 Ketones 23–25

ability of the ketone and/or the dioxirane between the organic and aqueous phases. The oxidation efficiency is also dependent on the counterion, and triflate anion was found to be an effective one. Based on this study, a number of chiral ammonium ketones were studied (Fig. 6) [22, 40, 44, 46, 47]. Tropinone-based rigid ammonium ketone **18** showed good general reactivity, and up to 58% ee was obtained for *trans*-stilbene oxide with 10% mol catalyst loading. Bis(ammonium) ketones **19–22** were also found to be active epoxidation catalysts. *trans*- β -Methylstyrene can be epoxidized in up to 40% ee using ketone **20**.

2.3 Bicyclo[3.2.1]octan-3-ones and Related Ketones

In 1998, Armstrong and coworkers reported tropinone-based fluorinated ketone **23a** to give good enantioselectivities for several *trans*-olefins (Fig. 7) (Table 2, entries 1, 6) [48, 49]. The replacement of the fluorine atom with an acetate group

Table 2 Asymmetric epoxidation with ketones **23–25**

Entry	Substrates	Catalyst	Conv. (%)	ee (%)
1		23a	100	76 (R,R)
2		23b	100	86 ^a
3		24a	100	83 ^a
4		24b	85	93 ^a
5		25	100	81 (S,S)
6		23a	100	83 (R)
7		24b	71	98 ^a (R)

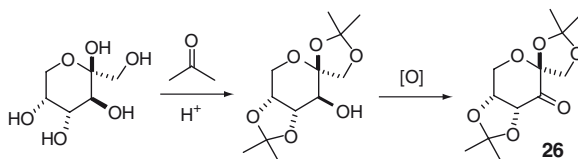
^aee_{max} 100(epoxide ee/ketone ee)

(**23b**) and/or the replacement of the bridgehead nitrogen with an oxygen atom (**24**) increased the enantioselectivity of the epoxidation [49–51]. Up to 98% ee_{max} was obtained for the epoxidation of phenylstilbene using ketone **24b** (Table 2, entries 2–4, 7). However, it appears that ketone **24b** is difficult to prepare in enantiomerically pure form. In 2006, enantiomerically pure tetrahydropyran-4-one **25** was investigated to evaluate the role of the bicyclic framework in ketones **23** and **24** [52]. Absence of the bicyclic framework results in the reduction of enantioselectivity in some cases. However, *trans*-stilbene can still be epoxidized in 81% ee. This result for ketone **25** suggested that the axial heteroatom plays an important role in enantioselectivity (Table 2, entry 5).

2.4 Carbohydrate-Based and Related Ketones

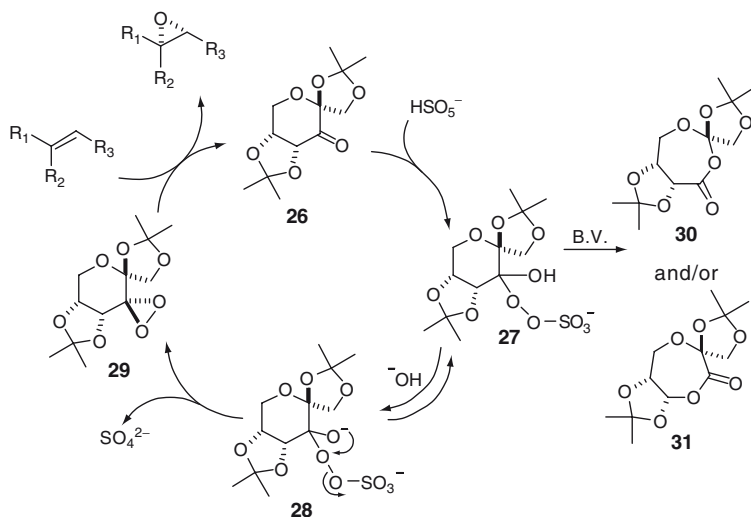
2.4.1 Catalyst Development for the Epoxidation of *trans*- and Trisubstituted Olefins

In 1996, ketone **26** was reported to be a highly effective epoxidation catalyst for a variety of *trans*- and trisubstituted olefins [53]. Ketone **26** can be readily synthesized from D-fructose by ketalization and oxidation (Scheme 2) [54–56]. The enantiomer of ketone **26** (*ent*-**26**) can be obtained by the same methods from L-fructose, which can be obtained from L-sorbose [57, 58].

**Scheme 2** Synthesis of ketone **26**

In ketone **26**, the chiral control elements are close to the reacting carbonyl, thus enhancing the stereochemical communications between the catalyst and the substrate. The fused ring or quaternary centers are placed at the α -position to the carbonyl group, which minimizes potential epimerization of the stereogenic centers. Electron-withdrawing oxygen substituents inductively activate the carbonyl.

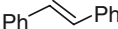
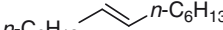
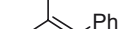
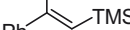
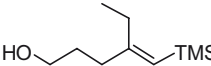
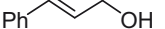
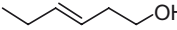
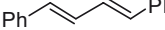
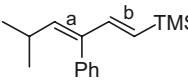
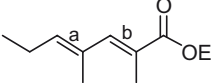
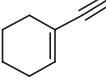
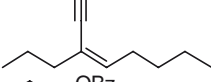
The epoxidation with ketone **26** was also found to be highly pH dependent. Earlier epoxidations using in situ generated dioxirane were usually carried out at pH 7–8, since Oxone rapidly autodecomposed at high pH value [59, 60]. In contrast, higher pH was found to be beneficial to the epoxidation with ketone **26**. For example, the substrate conversion increased from ca. 5% with pH being 7–8 to >80% with pH >10 for *trans*- β -methylstyrene. The optimal reaction pH value is around 10.5 [54, 61]. Because of the acidic nature of Oxone, the epoxidation with ketone **26** is performed in buffer and with the addition of either K_2CO_3 or KOH to maintain a steady pH throughout the reaction to ensure maximum conversion. Aqueous $Na_2B_4O_7 \cdot 10H_2O$ solutions or a mixture of acetic acid and aqueous K_2CO_3 are commonly used as buffers for this reaction. The increased epoxidation efficiency at higher pH is presumably due to the suppression of Baeyer-Villiger oxidation of the ketone catalyst (Scheme 3) and/or the increased nucleophilicity of Oxone toward the carbonyl group.



Scheme 3 Ketone **26** catalyzed epoxidation

A catalytic amount of ketone **26** was used to investigate the substrate scope of the asymmetric epoxidation. High enantioselectivities can be obtained for a wide variety of *trans*- and trisubstituted olefins (Table 3, entries 1–4) [54]. Simple *trans*-olefins, such as *trans*-7-tetradecene, can be epoxidized in high yield and enantiomeric excess, indicating that this asymmetric epoxidation is generally suitable for *trans*-olefins. 2,2-Disubstituted vinyl silanes are epoxidized in high ees (Table 3, entries 5, 6) and enantiomerically enriched 1,1-disubstituted epoxides can be

Table 3 Asymmetric epoxidation with ketone **26**

Entry	Substrates	Yield (%)	ee (%)
1		85	98 (R,R)
2		89	95 (R,R)
3		89	96 (R,R)
4		94	98 (R,R)
5		74	94 (R,R)
6		71	93 (R,R)
7		85	94 (R,R)
8		82	90 (R,R)
9		77	97
10 ^a		81	95
11 ^a		89	94
12		78	93 (R,R)
13		60	93 (R,R)
14		82	93 (R,R)
15		66	91 (2S,3R)

^aAlkene **a** is selectively epoxidized

obtained via the desilylation of these epoxides [62]. Allylic and homoallylic alcohols are also effective substrates (Table 3, entries 7, 8) [63]. Enantioenriched vinyl and propargyl epoxides can also be obtained in high ees by regio- and chemoselective epoxidations of conjugated dienes and enynes (Table 3, entries 9–13) [64–66]. The epoxidations of enol ethers and enol esters were also studied (Table 3, entries 14, 15) [67]. Enol esters generally gave higher enantioselectivities. The resulting epoxide can undergo stereoselective rearrangement to give optically active α -acyloxy ketones [68–70]. This rearrangement can operate through two different pathways when different Lewis acids are used, resulting in either retention or inver-

sion of configuration. The kinetic resolution of racemic enol ester epoxide using chiral Lewis acid was also examined. Good enantiomeric excess can be obtained for both α -acyloxy ketone and the unreacted enol ester epoxide using [(*R*)-BINOL]₂-Ti(O^{*i*}Pr)₄ as catalyst [69].

A high catalyst loading (typically 20–30 mol%) is usually required for the epoxidation with ketone **26** because Baeyer-Villiger oxidation presumably decomposes the catalyst during the epoxidation. The fused ketal moiety in ketone **26** was replaced by a more electron-withdrawing oxazolidinone (**32**) and acetates (**33**) with the anticipation that these replacements would decrease the amount of decomposition via Baeyer-Villiger oxidation (Fig. 8) [71, 72]. Only 5 mol% (1 mol% in some cases) of ketone **32** was needed to get comparable reactivity and enantioselectivity with 20–30 mol% of ketone **26** [71]. Since dioxiranes are electrophilic reagents, they show low reactivity toward electron-deficient olefins, such as α,β -unsaturated esters. Ketone **33**, readily available from ketone **26**, was found to be an effective catalyst towards the epoxidation of α,β -unsaturated esters [72].

While Oxone (2KHSO₅•KHSO₄•K₂SO₄) has been commonly used to generate dioxiranes from ketones, studies showed that epoxidation with ketone **26** can be carried out with a nitrile and H₂O₂ as the primary oxidant, giving high enantioselectivities for a variety of olefins (Scheme 4) [73–75]. Peroxyimide acid **34** is likely to be the active oxidant that reacts with the ketone to form dioxirane under the epoxidation conditions. Mixed solvents, such as CH₃CN-EtOH-CH₂Cl₂, improve the conversions for substrates with poor solubilities. No slow addition is necessary for the epoxidation with H₂O₂. Additionally, this epoxidation system is mild and greatly reduces the amount of solvent and salts involved.

Two extreme epoxidation modes, spiro and planar, are shown in Fig. 9 [33, 34, 53, 54, 76–85]. Baumstark and coworkers had observed that the epoxidation of *cis*-hexene of dimethyldioxirane was seven to nine times faster than the corresponding epoxidation of *trans*-hexene [79, 80]. The relative rates of the epoxidation of *cis/trans* olefins suggest that spiro transition state is favored over planar. In spiro transition states, the steric interaction for *cis*-olefin is smaller than the steric interaction for *trans*-olefin. In planar transition states, similar steric interactions would be expected for both *cis*- and *trans*-olefins. Computational studies also showed that the spiro transition state is the optimal transition state for oxygen atom transfer from dimethyldioxirane to ethylene, presumably due to the stabilizing interactions

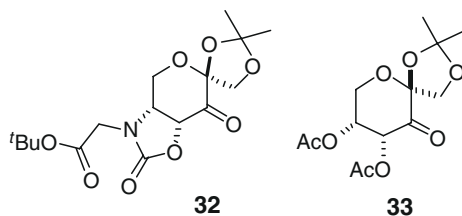
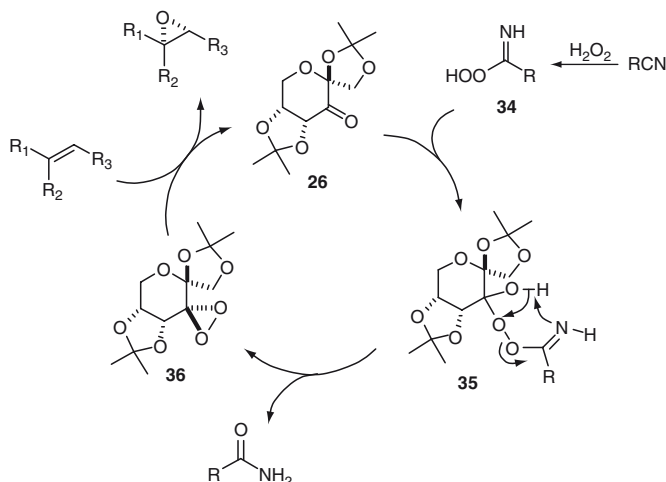


Fig. 8 Ketones **32–33**



Scheme 4 Ketone **26** catalyzed epoxidation with H_2O_2 as the oxidant

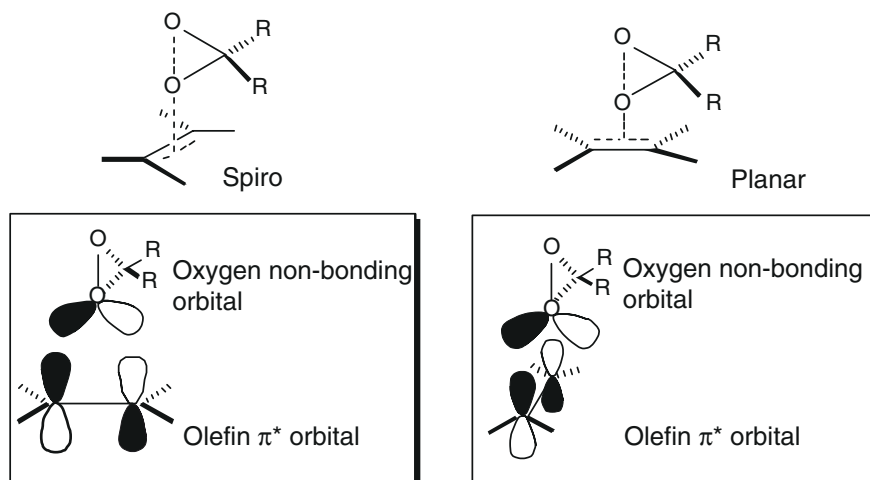


Fig. 9 The spiro and planar transition states for the dioxirane epoxidation of olefins

between the oxygen non-bonding orbital with the alkene π^* orbital in the spiro transition state [81–84].

The stereochemistry of the resulting epoxidation products using chiral ketones, such as ketone **26**, could provide new insights about the epoxidation transition states. Studies showed that the epoxidation of *trans*- and trisubstituted olefins with ketone **26** mainly goes through the spiro transition state (spiro **A**) (Fig. 10). Planar transition state **B** competes with spiro **A** to give the opposite enantiomer [53, 54]. Hence, factors that influence the competition between spiro **A** and planar **B** will also affect the enantiomeric excess of the resulting epoxides. Spiro **A** can be further

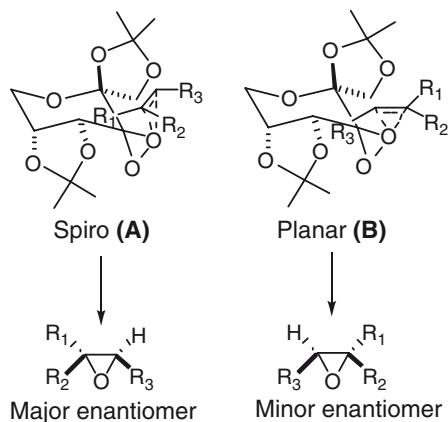


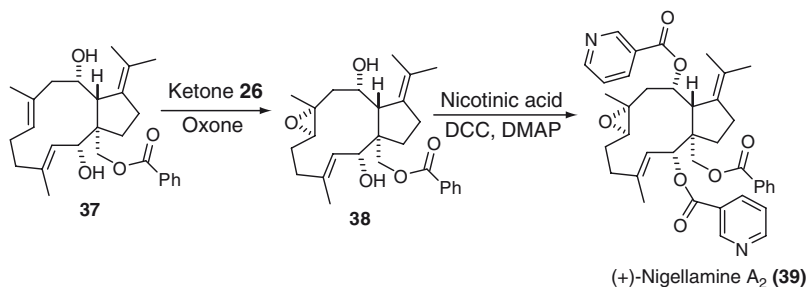
Fig. 10 The competing spiro and planar transition states for the epoxidation with ketone **26**

favored by conjugation of the alkene. Conjugation lowers the energy of the π^* orbital of the alkene and enhances the stabilizing interaction between the dioxirane and the olefin (Fig. 9). Decreasing the size of R_1 (further favoring spiro **A**) and/or increasing the size of R_3 (disfavoring planar **B**) can also result in higher ees for the epoxidation. The transition state modes for ketone **26** were further supported by results obtained from kinetic resolution of 1,6- and 1,3-disubstituted cyclohexenes [86] and desymmetrization of cyclohexadiene derivatives [87].

2.4.2 Synthetic Applications of Ketone **26**

The availability of ketone **26** and its effectiveness toward a wide variety of *trans*- and trisubstituted olefins make the epoxidation with this ketone a useful method. Other researchers have used ketone **26** in the synthesis of optically active complex molecules. Some of these studies will be highlighted in this section.

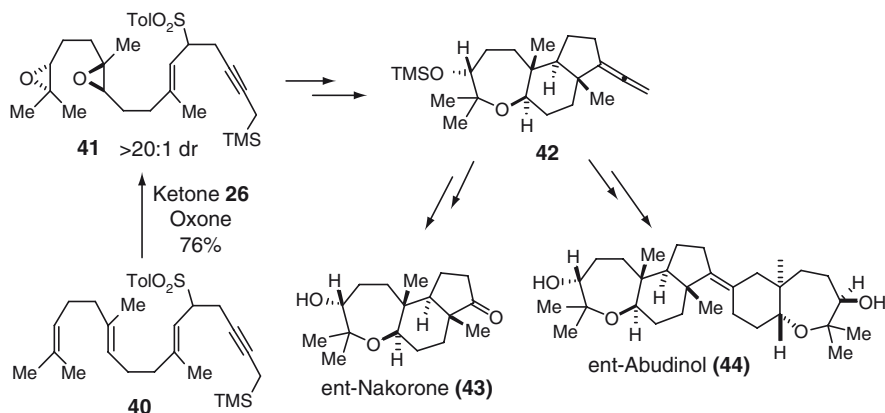
In the enantioselective total synthesis of nigellamine A_2 (**39**), Ready and coworkers reported the selective epoxidation of **37** to obtain **38** (Scheme 5) [88]. Compound



Scheme 5 Synthesis of nigellamine A_2

37 contains three double bonds; however, the desired one is preferentially epoxidized. In this case, the conformation of the substrate appears to be an important factor as to which face of the alkene gets epoxidized since the same diastereomer was generated using either ketone **26** or *ent*-**26** as the epoxidation catalyst.

Oxygenated triterpenoid marine natural products nakorone (**43**) and abudinol (**44**) were synthesized by McDonald and coworkers in 2007 (Scheme 6) [89].



Scheme 6 Syntheses of nakorone and abudinol

Stereocenters were introduced in the synthesis via asymmetric epoxidation of triene-yne **40**. Only two of the three more electron-rich alkenes were selectively epoxidized, leaving the alkene closest to the sulfone group unreacted.

Polycyclic oxasqualenoid glabrescol was synthesized by Corey and coworkers in order to confirm its structure. Several pentaoxacyclic compounds were synthesized via epoxidation with ketone **26** followed by cyclizations [90]. Finally, compound **48** was synthesized to match the properties of the naturally occurring glabrescol, leading to the determination of the stereochemistry of glabrescol (Scheme 7) [91].

McDonald and coworkers studied a series of tandem *endo*-selective and stereospecific oxacyclization of polyepoxides by reaction with Lewis acid [92–95]. Polyepoxides, such as **50**, can be obtained from the epoxidation of triene **49** with ketone **26** (Scheme 8). This cascade cyclization of polyepoxides provides an efficient method to synthesize substituted polycyclic ether structures, which are present in a number of biologically active marine natural products.

In recent studies, Jamison and coworkers reported the formation of tetrahydropyran via cascade epoxide-opening reactions in water (Scheme 9) [96]. In this study, polytetrahydropyran precursor, such as **53**, was synthesized from the epoxidation of polyalkene **52**.

2.4.3 Catalyst Development for the Epoxidation of *cis*-Olefins, Styrenes, and Other Olefins

In addition to the enantioselective epoxidation of *trans*- and trisubstituted olefins, efforts have also been made for the asymmetric epoxidation of *cis*- and terminal olefins. Glucose-derived ketone **55** was reported to be a highly enantioselective catalyst for the epoxidation of various *cis*-olefins and certain terminal olefins (Fig. 11, Table 4) [97–100]. The results of epoxidation with ketone **55** indicate that a π

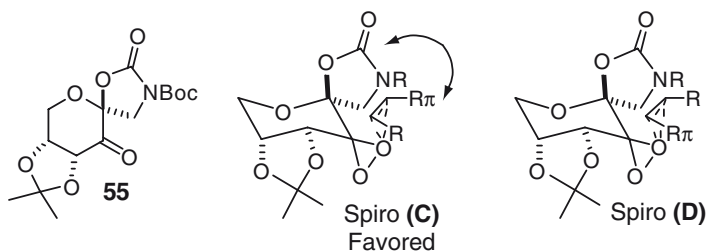
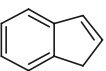
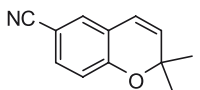
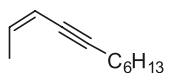
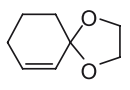
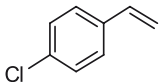


Fig. 11 The competing transition states for the epoxidation with ketone **55**

Table 4 Asymmetric epoxidation with ketone **55**

Entry	Substrates	Yield (%)	ee (%)
1		87	91 (1R,2S)
2		88	83 (1R,2S)
3		61	91 (3R,4R)
4		77	87 (2S,3R)
5		61	97
6		92	81 (R)
7		90	85 (R)

substituent on the substrate prefers to be proximal to the spiro oxazolidinone of ketone **55** in the transition state (spiro **C** favored over spiro **D**, Fig. 11). When epoxidation of 1-phenylcyclohexene was carried out with ketone **26**, the (*R,R*) epoxide was formed in 98% ee since spiro transition state **E** is favored over planar **F**. However, when the same epoxidation was carried out with ketone **55**, the epoxide with absolute configuration (*S,S*) was obtained instead (Fig. 12). This suggests an attraction between R_π of the olefin and the oxazolidinone is strong enough that planar **H** is favored over spiro **G**.

A carbocyclic analogue of ketone **55** (**56**) was synthesized as a catalyst for electronic and conformational studies (Fig. 13) [101]. Ketone **56** was found to epoxidize styrenes in higher ees (89–93% ee) and the opposite enantiomer for the epoxidation of 1-phenylcyclohexene as compared to ketone **55**. The X-ray structure showed that ketones **55** and **56** have similar conformations (at least in the solid state). These findings suggested that the replacement of the pyranose oxygen with a carbon influences the epoxidation transition states via an electronic effect rather than a steric effect. The replacement of the pyranose oxygen with a carbon may have increased the beneficial secondary orbital interaction (between the non-bonding

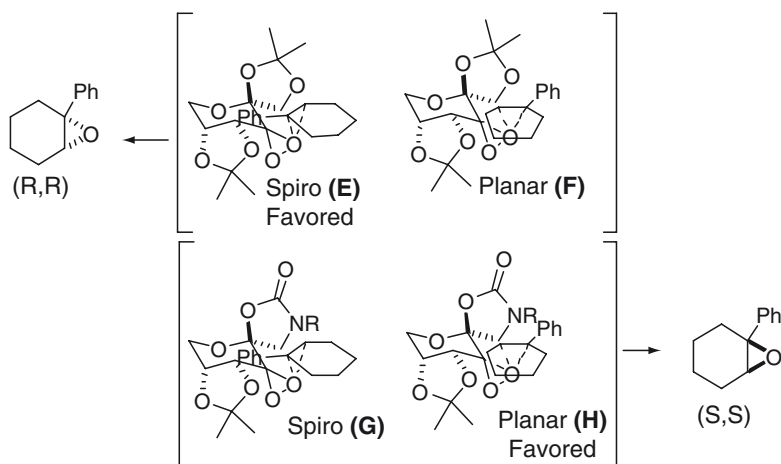


Fig. 12 The competing transition states for the epoxidation of 1-phenylcyclohexene with ketone **26** and ketone **55**

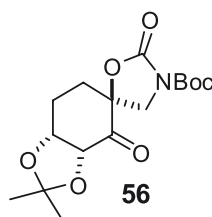


Fig. 13 Ketone **56**

orbital of the dioxirane and the π^* orbital of the alkene) by raising the energy of the non-bonding orbital of the dioxirane. Consequently, (*R,R*)-1-phenylcyclohexene oxide is produced from the epoxidation with ketone **56** because spiro **I** is favored over planar **J** (Fig. 14). In the case of styrene epoxidation with ketone **56**, both spiro transition states (desired spiro **K** and undesired spiro **L**) are further favored over planar **M** due to the increased secondary orbital interaction (Fig. 15). The reduced contribution of **M** leads to more enantioenriched styrene oxides.

The encouraging epoxidation results using ketone **55** led to the development of a series of more readily available catalysts (**57**) (Fig. 16) [102, 103]. Phenyl group substituted with hydrocarbons and electron-withdrawing groups gave better results than other substitutions such as halogens or ethers. Ketones **57** are synthesized in four steps from glucose and inexpensive anilines (Scheme 10), and large-scale syntheses of these ketones are feasible [104]. Preliminary results indicated that ketones **57** provide high enantioselectivity for a number of olefins, thus further substrate scope exploration was done with these ketones.

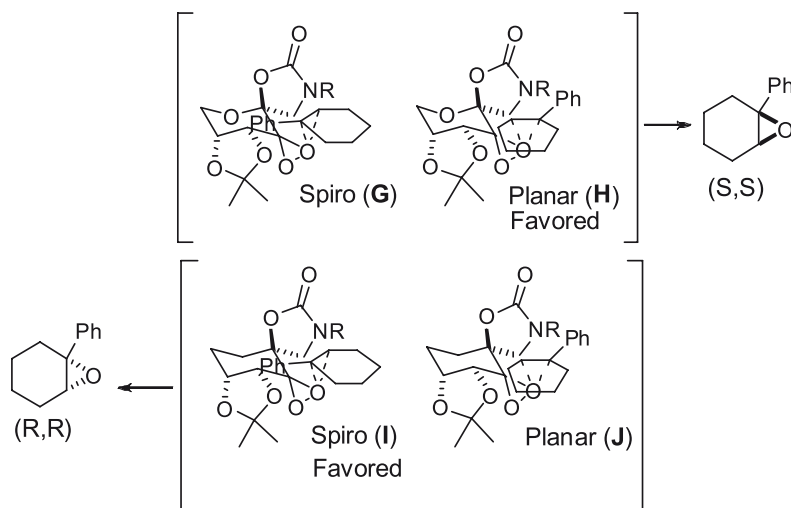


Fig. 14 The competing transition states for the epoxidation of 1-phenylcyclohexene with ketone **55** and ketone **56**

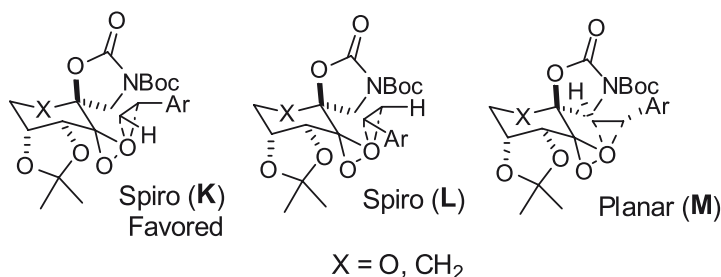
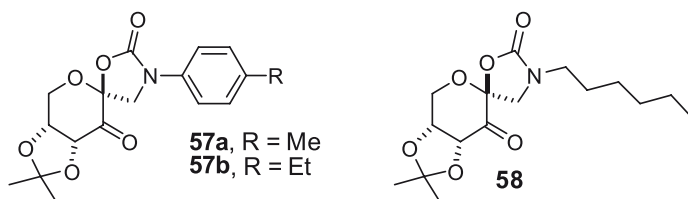
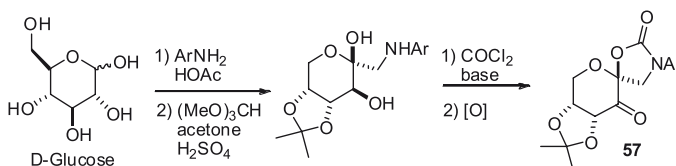


Fig. 15 The competing transition states for the epoxidation of styrenes

Fig. 16 Ketones **57–58**Scheme 10 Synthesis of ketone **57**

cis- β -Methylstyrenes were epoxidized in high conversion and ees (Table 5, entries 1, 2) [105]. The substrates bearing substituents are epoxidized with higher enantioselectivities presumably because the substituents further enhance the interaction between the phenyl group of the catalyst and the phenyl group of the olefin, thus further favoring spiro **N** over spiro **O** (Fig. 17). Subsequently, a series of 6- and 8-substituted chromenes were studied to further investigate this substituent effect [106]. For 6-substituted chromenes (e.g. Table 5, entries 5, 6), regardless of the substituent, the enantioselectivities increased compared to non-substituted chromenes. However, the ees increased for 8-substituted chromenes with electron-withdrawing groups (e.g. Table 5, entries 7, 8) and decreased with electron-donating groups. The substituents at the 8-position likely influence the enantioselectivity via electronic effect. The substituents at the 6-position might cause additional beneficial non-bonding interactions between the substrate and the catalyst, thus further favoring spiro **P** over **Q** (Fig. 18). However, such interaction is not feasible in the case of the 8-substituted chromenes (Fig. 18, spiro **R** and **S**). *N*-Alkyl substituted ketone **58** (Fig. 16) also gave good enantioselectivities for chromenes (Table 5, entries 4, 6, 8). This result suggested that van der Waal forces and/or hydrophobic effects are possibly important factors in the beneficial interaction between the substrate and the *N*-substituent of the catalyst.

Styrenes [103], conjugated *cis*-dienes [107], and *cis*-enynes [108] are also epoxidized with ketones **57** in high ees (Table 5, entries 9–14). No isomerization of the epoxides was observed; therefore only *cis*-epoxides were obtained from *cis*-olefins. Alkenes and alkynes appear to be effective directing groups to favor the desired transition states **T** and **V** (Fig. 19).

Trisubstituted and tetrasubstituted benzylidenecyclobutanes can be readily epoxidized and the resulting epoxides can be rearranged to 2-aryl cyclopentanones with either retention or inversion of configuration using LiI or Et₂AlCl, respectively (an example of trisubstituted benzylidenecyclobutane is shown in Scheme 11) [109, 110]. This method provides a convenient way to obtain optically active 2-aryl

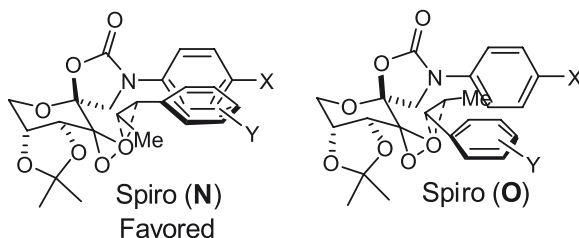


Fig. 17 The competing transition states for the epoxidation of β -methylstyrenes

cyclopentanones which have not been easily obtained otherwise. Furthermore, benzylidenecyclopropanes are epoxidized and rearranged to obtain optically active γ -aryl- γ -butyrolactones and γ -aryl- γ -methyl- γ -butyrolactones in good enantioselectivities (examples are shown in [Scheme 12](#)) [111]. Chiral cyclobutanones can also be obtained by suppressing Baeyer-Villiger oxidation with more catalyst and less Oxone. An epoxidation protocol with ketone **57** using H_2O_2 as primary oxidant was also developed [112].

2.4.4 Other Carbohydrate-Based Catalysts

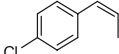
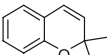
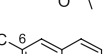
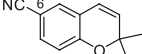
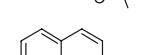
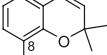
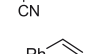
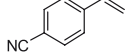
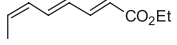
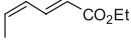
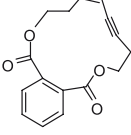
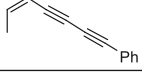
Shing and coworkers reported arabinose-derived uloses (**59**, **60**) as epoxidation catalysts, and phenyl stilbene can be epoxidized by **60** in up to 90% ee (Fig. 20) [113–115]. In 2003, Zhao and coworkers reported aldehyde **61** to epoxidize *trans*-stilbene in up to 94% ee [116].

2.5 Carbocyclic Ketones

A fused ring and a quaternary center α to the carbonyl group have been used as the chiral control elements in ketones such as **26**, **55–58** (Fig. 21). A series of pseudo C_2 -symmetric ketones (**62**), bearing two fused rings on each side of the reacting carbonyl, has been reported [117, 118]. A variety of olefins, including electron-deficient olefins, could be epoxidized using only 5–10 mol% ketones **62** in good yields and enantioselectivities ([Table 6](#), entries 1, 2, 15–18).

In 1998, Yang and coworkers reported a series of (*R*)-carvone derived ketones (**63**) containing a quaternary center at C_2 and various substituents at C_8 (Fig. 22) [119]. The ees of *trans*-stilbene oxide varied with different *para* and *meta* substituents when **63b** was used as the catalyst. The major contribution for the observed ee difference is from the n - π electronic repulsion between the Cl atom of the catalyst and the phenyl group of the substrate. The substitution at C_8 also influences the epoxidation transition state via an electrostatic interaction between the polarized C_8 -X bond and the phenyl ring on *trans*-stilbene ([Table 6](#), entries 3–7, 10–14). In 2000, Solladié-Cavallo and coworkers reported a series of fluorinated carbocyclic ketones

Table 5 Asymmetric Epoxidation with Ketone **57** and **58**

Entry	Substrates	Catalyst	Yield (%)	ee (%)
1		57a	99 ^a	84
2		57a	79 ^a	92
3		57b	100 ^a	84
4		58	100 ^a	84
5		57b	83 ^a	93 (R,R)
6		58	71 ^a	89 (R,R)
7		57b	95 ^a	88
8		58	87 ^a	89
9		57b	72	86 (R)
10		57b	86	90 (R)
11		57a	74	94
12		57a	64	94
13		57b	54	87
14		57a	76	93

^aConversion (%)

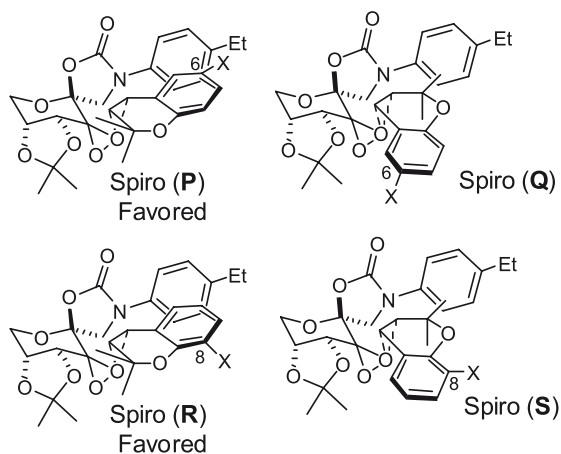


Fig. 18 The competing transition states for the epoxidation of 6- and 8-substituted chromenes

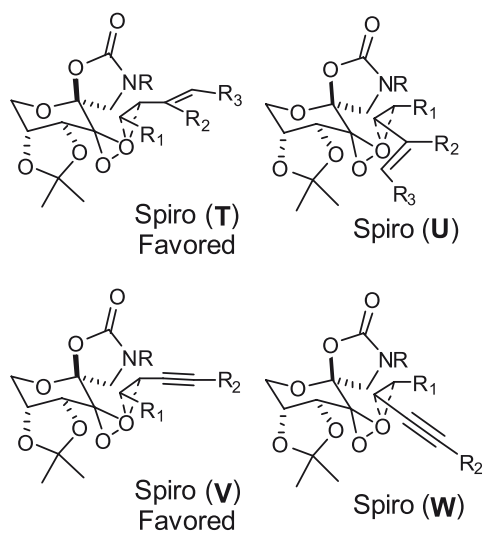
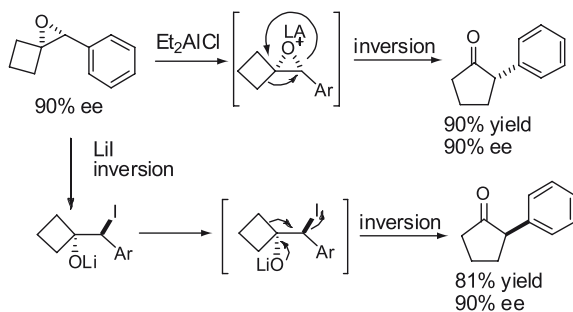
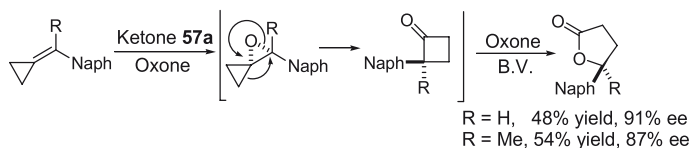


Fig. 19 The competing transition states for the epoxidation of dienes and enynes



Scheme 11 Rearrangement of benzyldenecyclobutane oxide



Scheme 12 Rearrangements of benzylidenecyclopropane oxides

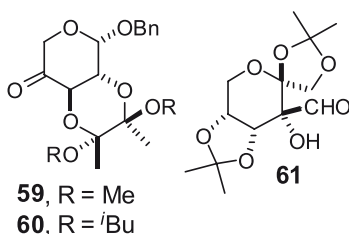


Fig. 20 Ketones **59–61**

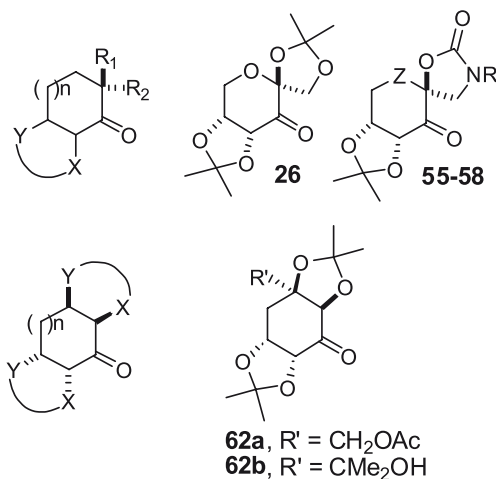
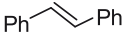
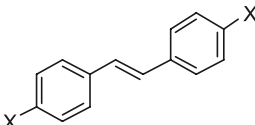
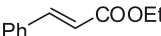
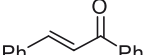
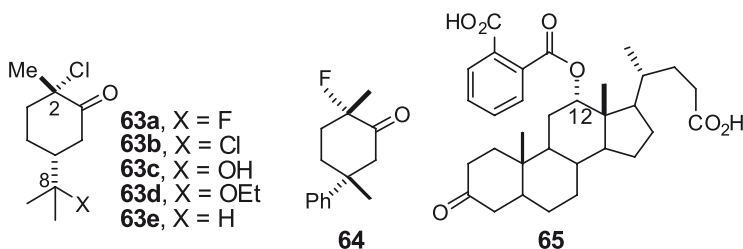


Fig. 21 Fused ring ketones **26**, **55–58** and pseudo C₂-symmetric ketones **62**

(an example, **64**, is shown in Fig. 22) [120–126]. Up to 90% ee can be obtained for the epoxidation of *trans*-stilbene with ketone **64** (Table 6, entry 8). Bortolini and coworkers reported asymmetric epoxidations using a series of keto bile acids as dioxirane precursors (an example is shown in Fig. 22). Ketone **65**, having substitution at C₁₂, epoxidizes *trans*-stilbene in up to 98% ee (Table 6, entry 9) [127].

Table 6 Asymmetric epoxidation with ketones **62–65**

Entry	Substrates	Catalyst	Yield (%)	ee (%)
1		62a	95	90 (R,R)
2		62b	91	96 (R,R)
3		63a	—	87.4
4		63b	—	85.4
5		63c	—	80.9
6		63d	—	73.8
7		63e	—	42.0
8		64	95 ^a	90 (S,S)
9		65	50	98 (R,R)
				
10	X = ^t Bu	63b	—	87.3
11	X = Me	63b	—	87.2
12	X = F	63b	—	78.5
13	X = Br	63b	—	74.8
14	X = OAc	63b	—	71.5
15		62a	34	86 (2S,3R)
16		62b	35	89 (2S,3R)
17		62a	80	94 (2S,3R)
18		62b	85	96 (2S,3R)

^aConversion (%)**Fig. 22** Ketones **63–65**

3 Chiral Iminium Salt-Catalyzed Epoxidations

In 1976, the synthesis of oxaziridinium salt **66** was reported by Lusinchi and coworkers (Fig. 23) [128–130]. Salt **66** was obtained by either methylation of the corresponding oxaziridine with FSO_3Me or oxidation of the corresponding iminium salt with peracid. Subsequently, Hanquet and coworkers prepared oxaziridinium salt **67** by methylation of the corresponding oxaziridine with Meerwein's salt ($\text{Me}_3\text{O}^+\text{BF}_4^-$) or oxidation of the *N*-methyl isoquinolinium fluoroborate salt with peracid [131, 132].

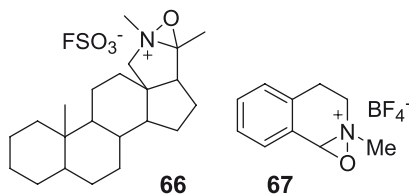
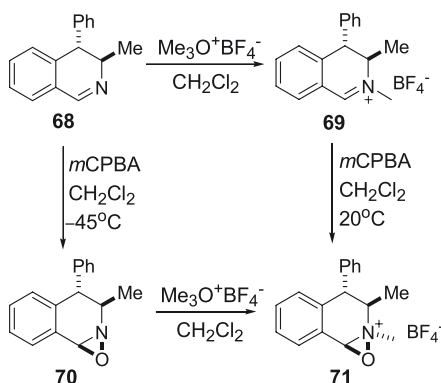


Fig. 23 Oxaziridinium salts **66–67**

Isolated or in situ generated oxaziridinium salt **67** efficiently epoxidizes various olefins in good yields [133–135].

3.1 Dihydroisoquinoline-Based Iminium Salts

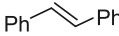
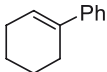
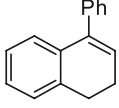
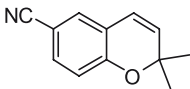
In 1993, Bohé and coworkers synthesized enantiomerically pure oxaziridinium salt **71** by methylation with Meerwein's salt and oxidation with *m*CPBA from dihydroisoquinoline **68** (Scheme 13) [136, 137]. Alternatively, **71** could also be produced by switching the reaction order. Epoxidations were carried out with either



Scheme 13 Synthesis of oxaziridinium salt **71**

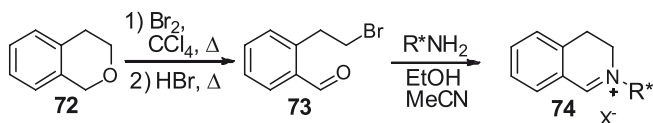
stoichiometric amounts of recrystallized **71** or catalytic amount of in situ generated **71**. *trans*-Stilbene was epoxidized with 5 mol% of in situ generated **71** using Oxone- NaHCO_3 in $\text{MeCN-H}_2\text{O}$ in 80–90% conversion and 35% ee (Table 7, entry 1). Studies showed that the transition states of such reaction have strong ionic character since the reaction rate increased in polar aprotic solvents such as nitrobenzene and nitromethane. In 2000, Rozwadowska and coworkers reported the synthesis of the enantiomer of iminium salt **69** (*ent*-**69**) [138, 139]. The enantioselectivity of epoxidations using *ent*-**69** are similar to those of **69**.

Table 7 Asymmetric epoxidation with iminium salts **71**, **74**, **76–82**

Entry	Substrates	Catalyst	Yield (%)	ee (%)
1		71	80–90 ^a	35 (R,R)
2		74a	78	73 (R,R)
3		74c^b	31	67 (R,R)
4		74a	68	40 (R,R)
5		74b	55	41 (S,S)
6		74c	100 ^a	39 (S,S)
7		74c^b	77	48 (R,R)
8		76	80	71 (R,R)
9		77	69	91 (S,S)
10		77^b	81	89 (S,S)
11		78	64 ^a	79 (S,S)
12		79	73	82 (S,S)
13		80	100 ^a	29 (R,R)
14		81	100 ^a	60 (S,S)
15		81^b	100 ^a	67 (S,S)
16		82	100 ^a	69 (S,S)
17		74a	73	63
18		74b	64	49 (1S,2R)
19		74c	100 ^a	47 (1S,2R)
20		74c^b	98	59 (1R,2S)
21		77	66	95 (1R,2S)
22		77^b	61	89 (1R,2S)
23		78	34 ^a	71 (1R,2S)
24		79	68	83 (1R,2S)
25		80	95 ^a	38 (1S,2R)
26		81	90 ^a	41 (1S,2R)
27		81^b	100 ^a	65 (1R,2S)
28		82	85 ^a	76 (1R,2S)
29		74c^b	59	97 (1S,2S)

^aConversion (%)^bNon-aqueous Conditions

In 1998, Page and coworkers reported a series of dihydroisoquinoline-related iminium salts which can be readily synthesized in three steps from a chiral amine (Scheme 14) [140–143]. Among the catalysts tested for asymmetric epoxidation, iminium salts **74** were found to be efficient catalysts (Fig. 24, Table 7, entries 2, 4–6, 17–19). Iminium salts **74a** can epoxidize 4-phenyl-1,2-dihydronaphthalene in up to 63% ee (Table 7, entry 17).



Scheme 14 Synthesis of iminium salt catalysts **74**

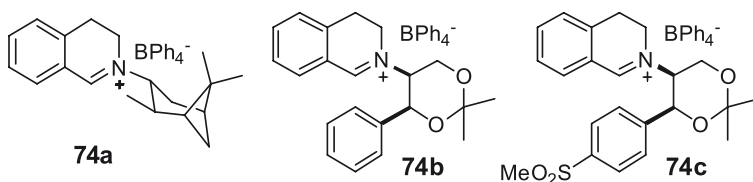
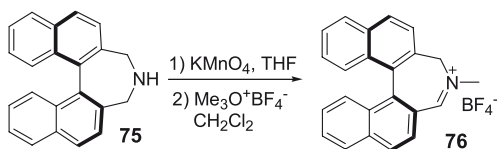


Fig. 24 Iminium salts **74**

Epoxidation reactions are normally carried out in aqueous conditions due to the low solubility of Oxone in organic solvents. In 2004, Page and coworkers developed a non-aqueous condition for the epoxidation of olefins using iminium salt **74** with organic solvent soluble oxidant tetraphenylphosphonium monoperoxsulfate (TPPP) [144–146]. Epoxidations can be carried out at lower temperatures in organic solvent since the reaction mixture usually freezes under $-8\text{ }^{\circ}\text{C}$ with aqueous conditions. Good enantioselectivities were obtained for the epoxidation of a number of *cis*-olefins (Table 7, entries 29), and up to 97% ee was obtained for the epoxidation of 2,2-dimethyl-6-cyanochromene by using iminium salt **74c** (Table 7, entry 29) [145].

3.2 Binaphthylazepinium-Based Iminium Salts

In 1996, Aggarwal and coworkers synthesized binaphthyl-based iminium salt **76** via oxidation and methylation from binaphthylamine (**Scheme 15**) [147]. Catalyst loading of 5 mol% is sufficient to catalyze the epoxidation of a number of olefins in good yield. Up to 71% ee can be obtained for 1-phenylcyclohexene oxide using this catalytic system (Table 7, entry 8).



Scheme 15 Synthesis of iminium salt catalyst **76**

In 2004, Page and coworkers reported binaphthyl-based iminium salt **77** to be a highly reactive and enantioselective catalyst for the epoxidation of trisubstituted olefins (Fig. 25, Table 7, entries 9, 21) [148, 149]. Catalyst loading can be as low as 0.1 mol% to get comparable results with 5 mol% for the epoxidation of 1-phenylcyclohexene. Iminium salt **77** was also employed in non-aqueous epoxidation reaction (Table 7, entries 10, 22) and up to 81% yield and 89% ee were obtained for 1-phenylcyclohexene oxide [150]. Lacour and coworkers reported iminium salts with TRISPHAT [tris(tetrachlorobenzenediolato)phosphate(V)] as counterions (**78**). The lipophilicity of TRISPHAT keeps the salt in the organic layer once it is dissolved. The addition of catalytic 18-crown-6 brings KHSO_5 into the organic layer and generally provides higher conversions (Table 7, entries 11, 23) [151]. Another set of binaphthalene-fused azepinium salts was also reported recently by Page [152]. Among the catalysts studied, **79** was found to give the best results (up to 83% ee for the epoxidation of 4-phenyl-1,2-dihydronaphthalene, Table 7, entry 24).

3.3 Biphenylazepinium-Based Iminium Salts

In 2002, Page and coworkers reported a series of biphenylazepinium-based iminium salts (**80**, **81**) to be reactive epoxidation catalysts (Fig. 26, Table 7, entries 13, 14, 25, 26) [143, 153]. Up to 60% ee could be obtained for the epoxidation of

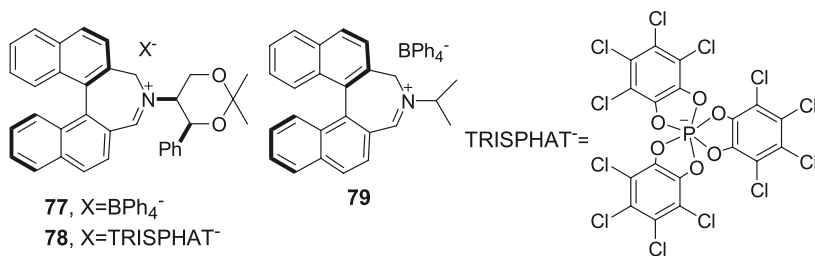


Fig. 25 Iminium salts **77**–**79**

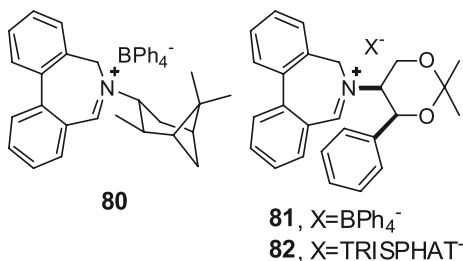


Fig. 26 Iminium salts **80**–**82**

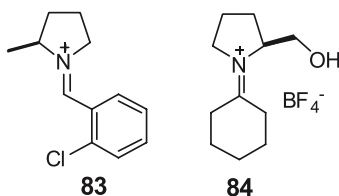


Fig. 27 Iminium salts **83**–**84**

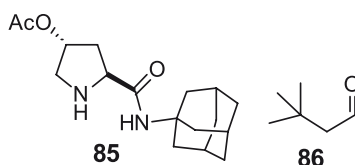


Fig. 28 Iminium salts **85**–**86**

1-phenylcyclohexene under aqueous conditions with iminium salt **81** (Table 7, entry 14). In some cases, the enantioselectivity can be improved by using non-aqueous epoxidation conditions (Table 7, entries 15, 27) [144, 150]. Iminium salt **82**, having TRISPHAT as counterion, also reported by Lacour and coworkers, gives higher enantioselectivity for the epoxidation of 4-phenyl-1,2-dihydronaphthalene (Table 7, entry 28) [151, 154, 155].

3.4 Acyclic Iminium Salts

While most of the iminium salts studied are cyclic, several acyclic iminium salts have also been investigated. In 1997, Armstrong and coworkers reported the use of acyclic iminium salt **83** as chiral epoxidation promoter (Fig. 27) [156, 157]. 1-Phenylcyclohexene oxide could be obtained in 100% conversion and 22% ee with stoichiometric amounts of **83**. In 2002 acyclic iminium salt **84**, prepared from L-prolinol, was investigated by Komatsu and coworkers, and cinnamyl alcohol was epoxidized in 70% yield and 39% ee (Fig. 27) [158].

In 2001, Yang and coworkers studied the use of in situ generated acyclic iminium salts as epoxidation catalysts [159]. Epoxidations of a number of alkenes proceed with 20–50 mol% of amine **85** and aldehyde **86** with Oxone as the primary oxidant (Fig. 28.) Methylstilbene can be obtained in 100% conversion and 59% ee.

4 Conclusion

Epoxidation of alkenes using chiral ketones and iminium salts has been extensively studied in numerous laboratories over the past 10 years. Significant progress has been made in this area. High enantioselectivities have been achieved for *trans*-,

trisubstituted, *cis*-, and certain terminal and tetrasubstituted olefins with chiral ketones. The extensive study of the ketone-catalyzed epoxidation transition states will provide a basis for the prediction of product stereochemistry and insight for the further development of new catalysts. Chiral iminium salt catalysts are proven to be highly active for the epoxidation of various olefins. Low catalyst loading and high enantioselectivity have been achieved in a number of cases. Further studies of the transition state model would be valuable for the development of chiral iminium salt catalysts.

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Amine, Alcohol and Phosphine Catalysts for Acyl Transfer Reactions

Alan C. Spivey and Stellios Arseniyadis

Abstract An overview of the area of organocatalytic asymmetric acyl transfer processes is presented including *O*- and *N*-acylation. The material has been ordered according to the structural class of catalyst employed rather than reaction type with the intention to draw mechanistic parallels between the manner in which the various reactions are accelerated by the catalysts and the concepts employed to control transfer of chiral information from the catalyst to the substrates.

Keywords Acylation • Asymmetric desymmetrisation • Esterification • Kinetic resolution • Nucleophilic catalysis

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Abbreviations

Ac	Acetyl
Alloc	Allyloxycarbonyl
ASD	Asymmetric desymmetrization
Bn	Benzyl (CH ₂ Ph)
Boc	<i>Tert</i> -butoxycarbonyl
C	Conversion
Cat	Catalyst
Cbz	Benzylloxycarbonyl
Cy	Cyclohexyl
(DHQ) ₂ AQN	Hydroquinine anthraquinone-1,4-diyl diether
(DHQD) ₂ AQN	Hydroquinidine anthraquinone-1,4-diyl diether
4-DMAP	4-(Dimethylamino)pyridine
E	Electrophile
<i>ee</i>	Enantiomeric excess
<i>ent</i>	Enantiomeric
<i>er</i>	Enantiomeric ratio
Fmoc	9-Fluorenylmethyloxylacrbonyl
GABA	γ-Aminobutyric acid
GC	Gas chromatography
HPLC	High pressure liquid chromatography
KR	Kinetic resolution
MS	molecular sieves
N/A	Not available
Nap	Naphthyl
NHC	<i>N</i> -heterocyclic carbenes
NMR	Nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	Nucleophile
PBO	<i>P</i> -aryl-2-phosphabicyclo[3.3.0]octane
Phe	(<i>S</i>)-Phenylalanyl
PIP	2-Phenyl-2,3-dihydroimidazo[1,2a]pyridine
PIQ	2-Phenyl-1,2-dihydroimidazo[1,2a]quinoline
PKR	Parallel KR
4-PPY	4-(Pyrrolidino)pyridine
<i>rec</i> SM	Recovered starting material
<i>s</i>	Selectivity factor

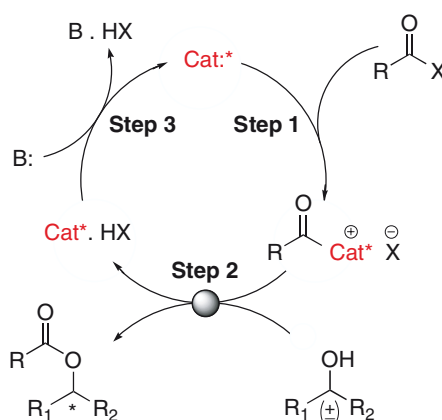
<i>sec</i>	Secondary
TADMAP	3-(2,2,-Triphenyl-1-acetoxyethyl)-4-dimethylamino)pyridine
TBDPS	<i>Tert</i> -butyldiphenylsilyl
TBS	<i>Tert</i> -butyldimethylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
Trt	Trityl (triphenylmethyl)
UNCA	Urethane-protected α -amino acid <i>N</i> -carboxy anhydride

1 Introduction

The preparation of stereochemically-enriched compounds by asymmetric acyl transfer using chiral nucleophilic catalysts has received significant attention in recent years [1–8]. One of the most synthetically useful and probably the most studied acyl transfer reaction to date is the kinetic resolution (KR) of *sec*-alcohols, a class of molecules which are important building blocks for the synthesis of a plethora of natural products, chiral ligands, auxiliaries, catalysts and biologically active compounds. This research area has been in the forefront of the contemporary ‘organocatalysis’ renaissance [9, 10], and has resulted in a number of attractive and practical KR protocols.

The mechanism by which chiral nucleophiles catalyze asymmetric acyl transfer in the KR of *sec*-alcohols can be seen as a three-step process (Scheme 1) [2].

The first step involves attack of the chiral nucleophile on an achiral acylating agent resulting in a chiral species which must be notably more reactive than the parent achiral acylating agent in order to undergo attack by either enantiomer of the racemic mixture of alcohols (step 2). This attack proceeds via two diastereomeric transition states which should be significantly different in energy for the resolution



NB. The  symbol indicates the stereochemistry determining step

Scheme 1 General catalytic cycle for the asymmetric acylation of *sec*-alcohols [2]

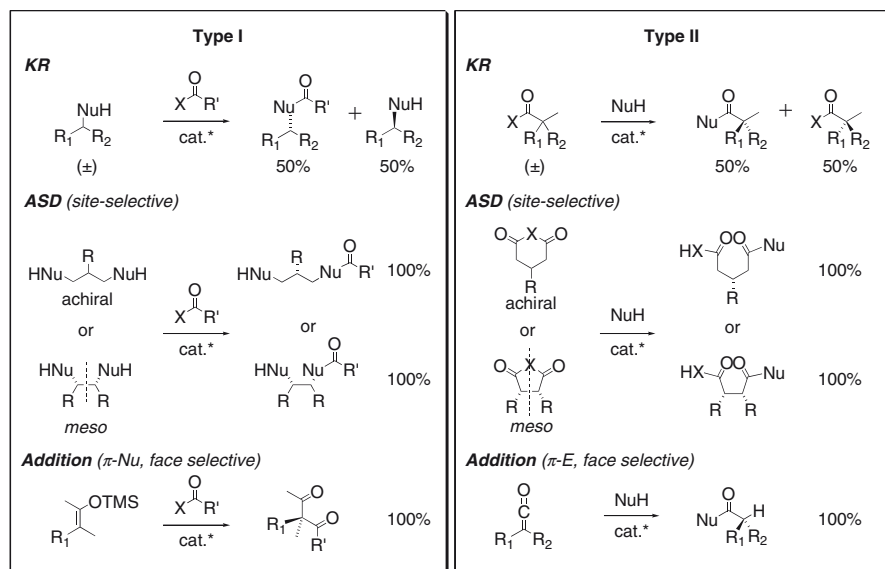
to occur. In the final step, the chiral nucleophile is regenerated, generally by the use of a stoichiometric amount of base, and re-engaged in the catalytic cycle (step 3).

The efficiency of such a process, and therefore of the catalyst, is expressed by the selectivity factor (s) which is defined as the ratio of the relative rate constants for the two reacting enantiomers (1) [11]:

$$\text{Selectivity} = \frac{\text{rate of fast-reacting enantiomer}}{\text{rate of slow-reacting enantiomer}} \quad (1)$$

Typically, a catalyst becomes synthetically useful when $s > 10$. Indeed, with such levels of selectivity one can isolate a synthetically usable amount of essentially enantiomerically pure unreacted starting material by driving the reaction past 50% conversion. With a process of high selectivity (e.g., $s > 50$), significant amounts of highly enantiomerically enriched both unreacted starting material and product can be isolated at close to 50% conversion. Unfortunately, the selectivity factor is not directly measurable [11]. Its determination is based on measurements of parameters such as the conversion (C), the enantiomeric composition of the substrate and product (enantiomeric excess, ee , or preferably [12], enantiomeric ratio, er) and the time elapsed (t) [13]. Its determination is also prone to error [14], notably if the enantiomeric purity of the catalyst is not absolute [15–18]. Despite these limitations in this review we have tried to record s and C values as well as ee/er values where available.

In general, catalytic asymmetric acyl transfer reactions can be classified into two main types depending on the nature of the nucleophile and the acyl donor (Scheme 2) [2].



Scheme 2 Classification of catalyzed asymmetric acyl transfer process [2]

Hence, a reaction of Type I will involve a racemic or achiral/*meso* nucleophile which will react enantioselectively with an achiral acyl donor in the presence of a chiral catalyst, while on the other hand, a reaction of Type II will associate an achiral nucleophile and a racemic or achiral/*meso* acyl donor in the presence of a chiral catalyst. In both cases, when a racemic component is implicated the process constitutes a KR and the maximum theoretical yield of enantiomerically pure product, given perfect enantioselectivity, is 50%. When an achiral/*meso* component is involved, then the process constitutes either a site-selective asymmetric desymmetrisation (ASD) or, in the case of π -nucleophiles and reactions involving ketenes, a face-selective addition process, and the maximum theoretical yield of enantiomerically pure product, given perfect enantioselectivity, is 100%.

Until the last decade or so, the only synthetically useful catalytic asymmetric acyl transfer processes involved the use of hydrolytic enzymes; particularly lipases and esterases [19–22]. However, the preparative use of enzymes can be associated with a number of well documented limitations, including their generally high cost, stringent operating parameters, low volumetric throughput, batch to batch irreproducibility, and availability in just one enantiomeric form. The significant interest in developing small molecule chiral organocatalysts capable of mediating these important asymmetric transformations over the past decade or so is in large part a consequence of researchers trying to overcome these limitations. Although interest in asymmetric acyl transfer by chiral nucleophiles can be traced back to Wegler in 1932 [23], it was only in 1996 that the groups of Vedejs [24] and Fu [25, 26] independently reported efficient asymmetric acyl transfer processes involving synthetic nucleophilic catalysts derived from an organophosphine and a pyrrole derivative, respectively. These two very different classes of nucleophiles have been further developed into ‘state-of-the-art’ asymmetric acylating agents of wide synthetic utility. As a direct consequence, the KR of a number of *sec*-alcohols has been demonstrated with selectivity factors approaching those of natural enzymes. These seminal discoveries inspired the development of many additional interesting chiral nucleophiles, many of which are capable of mediating asymmetric acyl transfer with synthetically useful levels of selectivity. All these systems will be covered in this review with emphasis being given to their proposed mechanism of action, the interactions that govern their selectivity and the strategies and hypotheses that were used to design the various catalyst topologies.

It should be noted that asymmetric acyl transfer can also be catalyzed by chiral nucleophilic *N*-heterocyclic carbenes [27–32] and by certain chiral Lewis acid complexes [33–37] but these methods are outside the scope of this review. Additionally, although Type I and Type II π -face selective acyl transfer processes have been reported to be catalyzed by some of the catalysts described in this review, these also lie outside the scope of this review.

2 Phosphine Catalysts

The accelerating influence of nucleophiles such as pyridine in acyl transfer processes has been known for over a century [38] and has led to the development of a wide variety of highly selective chiral catalysts incorporating this catalophore.

bicyclic phosphine **3** was totally detrimental to activity: no reaction was observed using these congeners. The use of catalysts **4** and **5**, however, did lead to good levels of conversion, although the selectivities were rather low [42]. These results suggested that the 5-membered ring was crucial for reactivity and therefore various modifications were considered in order to further improve the catalytic activity and selectivity. Hence, catalyst **5** was prepared with the idea that a larger bias in the steric environment around the phosphorous atom could be beneficial. Unfortunately, the selectivities observed with **5** were considerably lower than the ones observed with the parent catalyst **1**. The next structural modification consisted in removing one of the adjacent methyl substituents in order to improve access to the unshared electron pair of the phosphorous atom. However, while significant rate improvement was observed with catalyst **6**, the selectivity dropped ($s = 5.1$). Finally, replacing the methyl substituent by a *tert*-butyl (**7**) did lead to a slight increase in selectivity ($s = 5.6$), yet at the same time the reactivity dropped considerably (Fig. 1) [42].

Following these initial results, modelling studies were performed in order to identify the key structural features responsible for determining the selectivity in these systems. It appeared from these studies that the conformational/rotational flexibility of the *P*-phenyl substituent could be a crucial parameter. Indeed, catalysts that adopted a geometry where the phenyl ring was perpendicular to the ring system such as in **2** and **3** led to low selectivities, whereas catalysts that permitted the phenyl ring to be more flexible and thus turn away from the adjacent alkyl groups towards the neighbouring hydrogen atoms such as in **5**, **6**, and **7** were slightly more selective. These observations led to the design of a new family of catalysts derived from 2-phosphabicyclo[3.3.0]octane (PBO) containing a ring-fused *P*-aryl phosphine with a distinct geometry wherein the aryl ring is nearly coplanar with the 5-membered ring system. By placing the phosphorus atom in a bicyclic framework, the authors anticipated that they would maximise the relevant C–P–Ar bond angle and thus optimise the accessibility/nucleophilicity of the electron pair (Fig. 2) [16, 42–46].

The catalytic activity of phosphines **8** and **9** were first evaluated in the KR of *tert*-butyl phenylcarbinol using the electron-deficient *m*-chlorobenzoic anhydride as the achiral acylating agent. Interestingly, not only did these two catalyst display

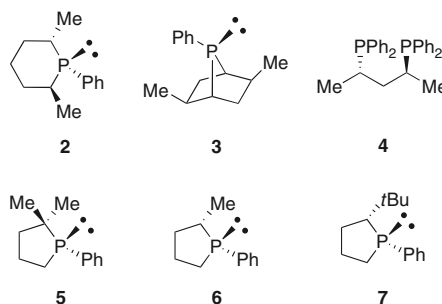


Fig. 1 Chiral phosphines screened by Vedejs as asymmetric acyl transfer catalysts [42]

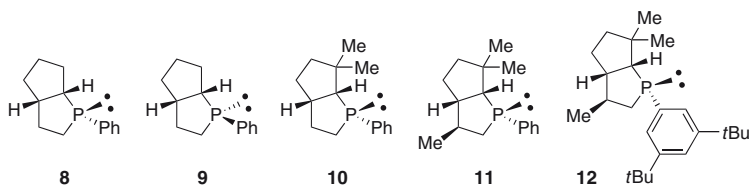


Fig. 2 Vedejs' PBO bicyclic phosphine catalysts [43–45]

>10-fold higher reactivity than the initial mono-cyclic phosphine **1**, but it appeared that the *endo* bicyclic phosphine **8** was significantly more reactive than the analogous *exo* compound **9**. The most promising derivatives were however the *gem*-dimethyl catalysts **10**, **11**, and **12** which were found to react >100 times faster than the original catalyst **1** while displaying high levels of selectivity. In particular, the 3,5-di-*tert*-butylphenyl derivative **12**, used in conjunction with isobutyric anhydride, was shown to induce *s* values of 42–369 for a wide range of aryl alkyl *sec*-alcohols (Table 1) [16]. These levels of selectivity are amongst the highest ever reported for non-enzymatic acylative KR and compare favourably with the selectivities observed when using enzymes.

Table 1 Vedejs' PBO catalyzed KR aryl alkyl *sec*-alcohols [16]

$$\text{Ar}-\text{CH}(\text{OH})-\text{R} + (i\text{Pr})_2\text{C}(\text{O})-\text{O}-\text{C}(\text{O})-\text{O}-i\text{Pr} \xrightarrow[\text{heptane}]{\text{12 (99.7\% ee)}} \text{Ar}-\text{CH}(\text{OH})-\text{R} + \text{Ar}-\text{CH}(\text{O}-i\text{Pr})-\text{R}$$

(±) (2.5 eq)

12

Entry	Ar	R	T(°C)	mol%		<i>ee</i> A (%)	<i>ee</i> E (%)	<i>s</i>
				cat.	C (%)			
1	Ph	Me	−20	2.5	29.2	3	93.3	42
2	Ph	Bu	−40	3.9	51.3	8	88.6	57
3	Ph ^{a,b}	<i>t</i> -Bu	−40	4.9	45.8	3	93.1	67
4	2-Tol	Me	−40	3.5	48.5	7	95.7	142
5	Mesityl ^{b,c}	Me	−40	12.1	44.4	0	98.7	369
6	1-Nap	Me	−40	3.9	29.8	2	97.0	99

^aBz₂O used in place of (*i*-PrCO)₂O

^bToluene used as solvent

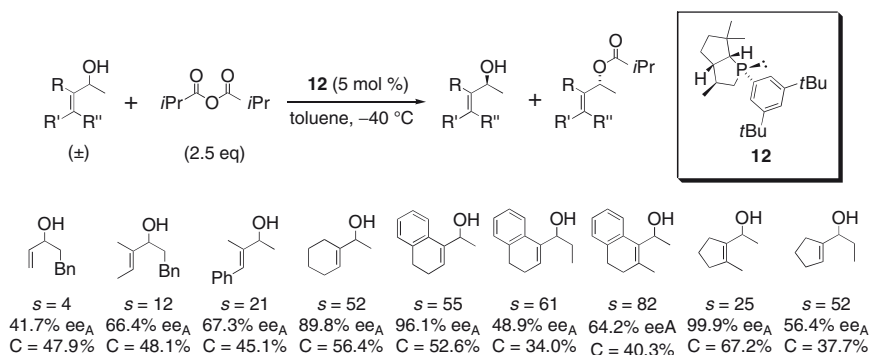
^cCatalyst of >99.9% *ee* used

Procedure for KR of an aryl alkyl *sec*-alcohol using catalyst **12**: KR of (±)-1-(2-methylphenyl)ethanol [16]

A solution of phosphine **12** (16 mg, 0.045 mmol; 99.7% *ee*) in deoxygenated *n*-heptane (74 mL) was added to an N₂-purged flask containing (±)-1-(2-methylphenyl)ethanol (1.02 g, 7.5 mmol). After cooling the mixture to −40 °C, (*i*-PrCO)₂O (3.05 mL, 18.4 mmol) was added via syringe. After stirring for 14 h at −40 °C the mixture was quenched by addition of isopropylamine (4 mL, 47 mmol). The solution was stirred at −40 °C for 10 min and the

flask was then allowed to warm to room temperature (ca. 1 h). After removal of the solvent in vacuo, the residue was purified by FC on silica gel (CH_2Cl_2 /hexanes, 2/3 $\rightarrow$ CH_2Cl_2) to yield the ester as an oil [725 mg, 48%, 95.7% ee by chiral-HPLC on the alcohol obtained by hydrolysis of an aliquot using NaOH/MeOH, 1/19] and the alcohol as an oil [482 mg, 46%, 90.2% ee by chiral-HPLC following additional purification by FC on silica gel (EtOAc/hexanes, 1/5)]. The calculated selectivity value at 48.5% conversion was $s = 142$.

Vedejs et al. subsequently extended the substrate scope of their 2,5-di-*tert*-butylphenyl PBO catalyst **12** to allylic alcohols for which they obtained moderate to good selectivities ($s = 4$ –82) (Scheme 4) [46].



Scheme 4 Vedejs' PBO catalyzed KR of *sec*-allylic alcohols [46]

Procedure for KR of a *sec*-allylic alcohol using catalyst **12**: KR of ($\pm$)-1-(3,4-dihydronaphthalen-1-yl)-ethanol [46]

1-(3,4-Dihydronaphthalen-1-yl)-ethanol (21 mg, 0.12 mmol) was added to a solution of phosphine **12** (1.97 mg, 0.006 mmol) in toluene (1.2 mL). The solution was cooled to -40 °C and (*i*-PrCO)₂O (50 mL, 0.3 mmol) was added via syringe. The reaction was stirred for 72 h, followed by quenching with *i*PrNH₂ (120 mL, 1.4 mmol). After stirring for 15 min at -40 °C the mixture was warmed to room temperature and concentrated in vacuo. ¹H-NMR (*d*₆-acetone) revealed that 51% conversion to the ester had occurred and confirmed that 5 mol% of catalyst had been used. Purification by FC on silica gel (CH_2Cl_2 /hexanes, 6/1) gave the ester (86.7% ee by chiral-HPLC on the alcohol obtained by hydrolysis using NaOH/MeOH, 1/19) and the alcohol (96.1% ee by chiral-HPLC). The calculated selectivity value at 51% conversion was $s = 55$.

3 *tert*-Amine Catalysts

As indicated in the introduction, Wegler and coworkers were the first to report successful asymmetric acylation using naturally occurring *tert*-amine-based alkaloids (e.g. brucine) in their KR studies on 1-phenylethanol [23]. While the selectivities achieved were rather modest, proof-of-concept was thereby established.

Although, from a historical standpoint the cinchona alkaloids also occupy a central position in the field owing to their use as catalysts for the alcoholative ASD of *meso* anhydrides (a Type II process, see Scheme 2), the past few years have witnessed an explosion of interest in the development of other classes of *tert*-amine-based catalysts primarily for Type I processes.

It is worth noting here that an understanding of the detailed kinetic and thermodynamic aspects of the catalytic cycles involved in both Type I and Type II processes has lagged significantly behind synthetic experimentation in this area [4]. However, this situation is rapidly being remedied by exciting physical organic and computational work by the groups of Zipse and Mayer in Munich. Zipse has published a series of detailed mechanistic analyses of alcohol acylation mediated by pyridine derivatives [47–49], including a theoretical analysis of a number of the stacking interactions postulated to mediate chirality transfer in some of the below described chiral acyl transfer catalytic systems [50]. Mayer and Zipse have also sought to establish new parameters for quantifying the nucleophilicities and carbon basicities of a wide range of nitrogen and phosphorus-based compounds to aid rationalisation of the relative reactivities of catalophores based on these units in all organocatalytic transformations [51–53].

3.1 Pyrrole-Based Catalysts

The first class of amine-based nucleophilic catalysts to give acceptable levels of selectivity in the KR of aryl alkyl *sec*-alcohols was a series of planar chiral pyrrole derivatives **13** and **14**, initially disclosed by Fu in 1996 [25, 26]. Fu and co-workers had set out to develop a class of robust and tuneable catalysts that could be used for the acylative KR of various classes of *sec*-alcohols. Planar-chiral azaferrocenes **13** and **14** seemed to meet their criteria. These catalysts feature of a reasonably nucleophilic nitrogen and constitute 18-electron metal complexes which are highly stable [54–58]. Moreover, by modifying the substitution pattern on the heteroaromatic ring, the steric demand and hence potentially the selectivity of these catalysts could be modulated.

Fu's strategy to introduce chirality into an initially achiral species such as pyrrole was based on the elimination of its two mirror planes – one mirror plane coplanar with the heteroaromatic ring and one perpendicular mirror plane that passes through the nitrogen and the mid-point of the C3–C4 bond. This was ingeniously achieved in a conceptually stepwise fashion through π -complexation of the pyrrole ring to a transition metal (ML_n) thus installing top-from-bottom differentiation, followed by the incorporation of a substituent in the 2-position of the heteroaromatic ring in order to enable left-from-right differentiation (Fig. 3).

These structural modifications provided a well-differentiated and highly tuneable chiral environment in the vicinity of the nucleophilic nitrogen as shown by the promising selectivities observed in the KR of 1-phenyl- and 1-naphthylethanol. Indeed,

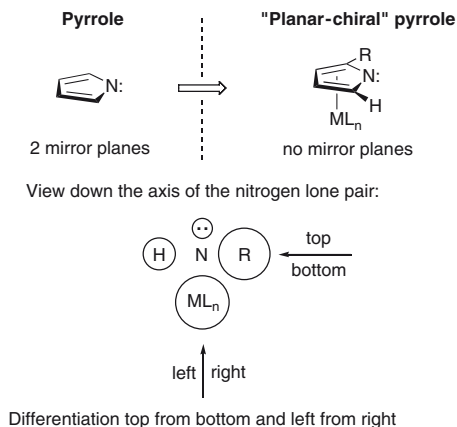


Fig. 3 Fu's design of a planar-chiral catalyst derived from pyrrole [69]

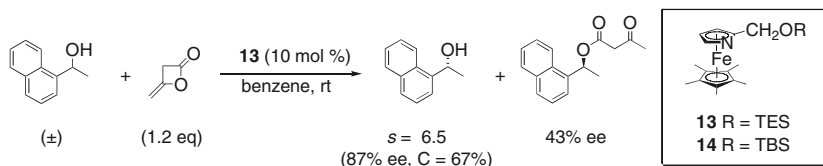
in this seminal study where diketene (1.2 eq) was employed as the acyl donor in the presence of 10 mol% of catalyst **13**, selectivities up to $s = 6.5$ were obtained (Scheme 5) [25].

3.2 (4-Dialkylamino)Pyridine-Based Catalysts

Based on their initial results using pyrrole-based catalysts, and also wanting to exploit the remarkable nucleophilic activity of 4-DMAP [59–63] first disclosed by Litvinenko [64] and Steglich [65] in the late 1960s as a potent acylation catalyst, Fu and co-workers set out to develop a second generation catalyst derived from a 4-DMAP framework but using the same chirality defining strategy described previously. However, as η^6 -complexation of a pyridine ring to an FeCp moiety (where 'Cp' is a cyclopentadienyl-derived ligand) would inevitably lead to a 19-electron metal complex, they decided to fuse a 5-membered ring to the pyridine framework and bind this second ring to the FeCp unit in a η^5 fashion (Fig. 4) [64]. Although this modification had the obvious consequence of moving the metal fragment away from the nucleophilic nitrogen, their hope was that the steric demand of the FeCp group might still furnish sufficient top-from-bottom differentiation to provide an effective chiral environment.

Hence, the group developed a series of planar chiral ferrocenyl 4-DMAP and 4-(pyrrolidino)pyridine (4-PPY) derivatives (**15–18**) that have proved to be highly versatile and efficient catalysts for many acyl transfer processes (Fig. 5) [25, 26, 66–82, 93, 99, 103, 105].

For example, a range of aryl alkyl *sec*-alcohols could be resolved in a highly efficient way using pentaphenylcyclopentadienyl 4-DMAP catalyst **16** (1–2 mol%) in conjunction with Ac_2O (0.75 eq) as the acyl donor and Et_3N (0.75 eq) as an auxiliary



Scheme 5 Fu's first generation planar-chiral catalyst for the KR of a *sec*-alcohol [25]

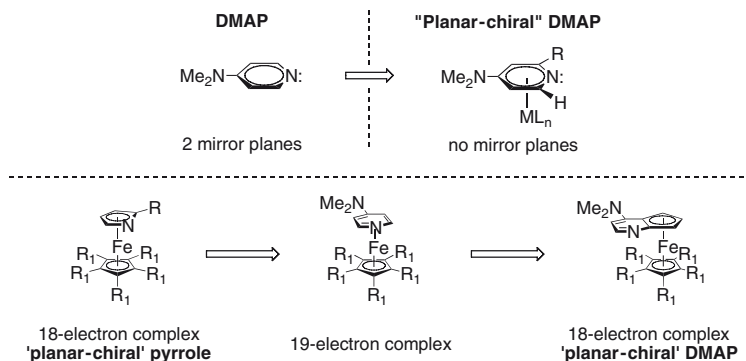


Fig. 4 Fu's concept for a 'planar-chiral' 4-DMAP catalyst based on his pyrrole 'planar-chiral' prototype [69]

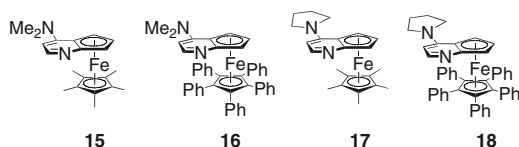
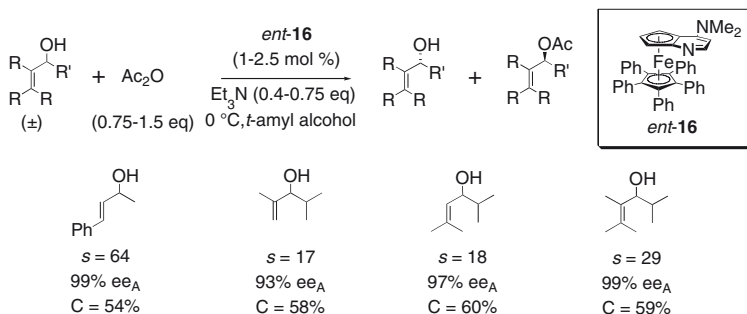


Fig. 5 Fu's planar chiral ferrocenyl 4-DMAP and 4-PPY catalysts [66, 83]

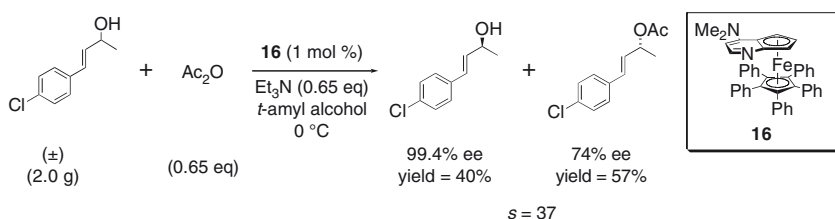
base [80, 81]. Interestingly, both the rate and the selectivity of this reaction were strongly solvent dependent. Indeed, the use of Et_2O as the solvent and 2 mol% of catalyst **16** provided s values of 12–52 at room temperature while the use of *tert*-amyl alcohol as the solvent in the presence of 1 mol% of catalyst **16** afforded s values of 32–95 at 0 °C (Table 2) [80, 81].

Procedure for KR of an aryl alkyl *sec*-alcohol using catalyst **16**: KR of ($\pm$)-1-(2-methylphenyl)ethanol [81]

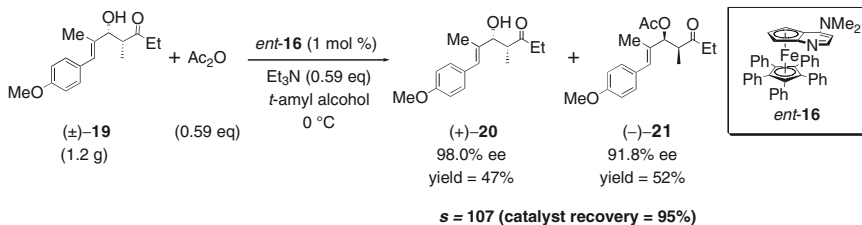
In a glove-box, 1-(2-methylphenyl)ethanol (1.11, 8.14 mmol), *tert*-amyl alcohol (16 mL), and Et_3N (0.67 mL, 4.8 mmol) were added to a flask containing **16** (27.7 mg, 0.0419 mmol). A septum was added and the flask was removed from the glove box. After some gentle heating to dissolve the catalyst, the flask was cooled to 0 °C. Ac_2O (0.46 mL, 4.9 mmol) was added dropwise and after 25.5 h the reaction was quenched with MeOH (5 mL).



Scheme 6 Fu's chiral planar ferrocenyl 4-DMAP catalyzed KR of *sec*-allylic alcohols [82]



Scheme 7 Preparation of a (-)-baclofen intermediate using Fu's planar chiral 4-DMAP [82]



Scheme 8 Preparation of an epothilone A intermediate using Fu's planar chiral 4-DMAP **ent-16** [82]

lyst **ent-16** (27.6 mg, 95%) from the alcohol/acetate mixture. The solution of alcohol and acetate was concentrated in vacuo and the residue purified by FC on silica gel (EtOAc/hexanes, 1/9 → 1/4) to afford the acetate **21** (0.70 g, 52%, 91.8% *ee* by chiral-HPLC) and the alcohol **20** (0.55 g, 47%, 98.0% *ee* by chiral-HPLC). The calculated selectivity value at 51.6% conversion was *s* = 107.

Fu's planar chiral ferrocenyl 4-DMAP derivative **16** is also the first organocatalyst that has been reported to efficiently perform the KR of certain propargylic *sec*-alcohols [83]. These KRs were achieved using 1 mol% of catalyst **16** and Ac₂O as the acylating agent in *tert*-amyl alcohol at 0 °C in the absence of a stoichiometric auxiliary base

(Et₃N was found to catalyze a non-selective background reaction). Under these conditions, moderate to good selectivities were achieved ($s = 3.8$ –20) depending on the nature of the substrate: an increase in the size of the alkyl group (R = Me → Et → *i*-Pr → *t*-Bu) lead to a dramatic decrease in selectivity with the best results being obtained with unsaturated groups at the remote position of the alkyne (Table 3) [86].

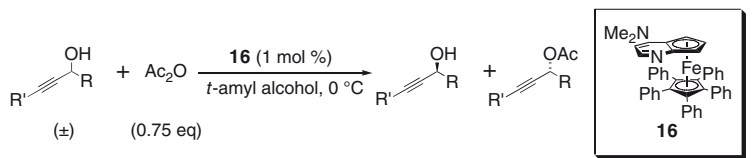
Procedure for KR of a propargylic *sec*-alcohol using catalyst **16**: KR of (±)-4-phenyl-3-butyn-2-ol [83]

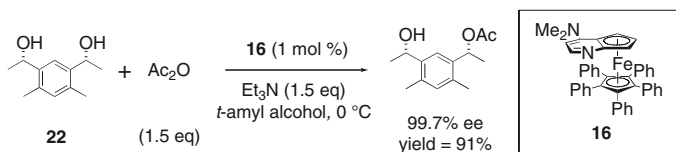
A vial containing (±)-4-phenyl-3-butyn-2-ol (73.0 mg, 0.500 mmol) and catalyst **16** (3.3 mg, 0.005 mmol) in *tert*-amyl alcohol (1.0 mL) was capped with a septum and sonicated to help dissolve the catalyst. The resulting purple solution was cooled to 0 °C, and Ac₂O (35.4 μL, 0.375 mmol) was added by syringe. After 49 h, the reaction mixture was quenched by the addition of a large excess of MeOH. After concentration in vacuo, the residue was purified by FC on silica gel (EtOAc/hexanes, 1/9 → 1/1 then EtOAc/hexanes/Et₃N, 9/9/2) to afford the (*R*)-acetate (68.6% *ee* by chiral-GC) and the (*S*)-alcohol (96.0% *ee* by chiral-GC on the acetate obtained following esterification). The calculated selectivity value at 58.3% conversion was $s = 20.2$.

Fu's planar chiral ferrocenyl 4-DMAP catalyst **16** was also shown to be effective for the ASD of *meso*-diols as illustrated for the case of unusual *meso*-diol **22** (Scheme 9) [81].

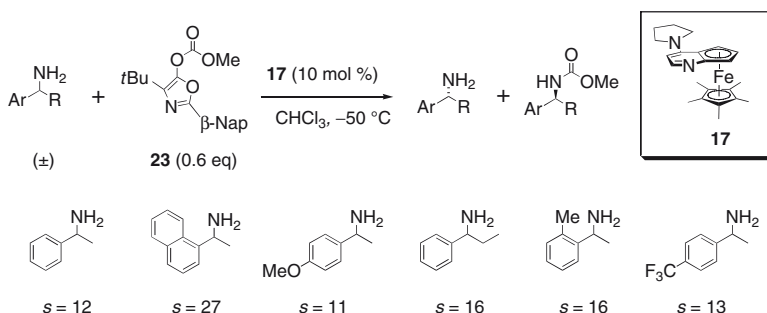
Although a number of methods have been recently reported for the asymmetric acylation of aryl alkyl *sec*-amines using stoichiometric amounts of chiral acylating agents, notably by Shibuya [84], Atkinson [85–90], Murakami [91], Krasnov [92], Fu [93], Arseniyadis [94–97], and Toniolo [98], the design of enantioselective acyl transfer catalysts suitable for use with amines is becoming a major focus of current interest for the synthetic community. This endeavour is particularly challenging due to the high nucleophilicity of most amines, which allows easy achiral acylation through direct reaction of these substrates with the achiral acyl source. Consequently, only one effective catalytic system has been reported to date by Fu. This organocatalytic system relies on the use of *O*-carbonyloxyazlactone **23** as the stoichiometric acyl donor in combination with 10 mol% of planar chiral ferrocenyl 4-PPY **17** as the catalyst. After optimization studies, a variety of racemic primary amines were successfully resolved with moderate to good selectivities ($s = 11$ –27) (Scheme 10) [99].

Table 3 Fu's planar chiral 4-DMAP catalyzed KR of *sec*-propargylic alcohols [83]

						
Entry	R	R'	s	<i>ee</i> A (%)	<i>ee</i> E (%)	C (%)
1	Me	Ph	20	96	6	58
3	<i>i</i> -Pr	Ph	11	93	5	63
4	<i>t</i> -Bu	Ph	3.8	95	5	86
5	Me	<i>n</i> -Bu	3.9	-	8	-



Scheme 9 ASD of *meso*-diols catalyzed by Fu's 4-DMAP catalyst **16** [81]



Scheme 10 Fu's planar chiral ferrocenyl 4-PPY catalyzed amine KR [99]

Advantageously, in the context of subsequent synthetic manipulation, the acylated products in these processes are carbamates (rather than amides). Fu proposed a mechanistic pathway that involves rapid initial reaction of the catalyst with the *O*-carbonyloxazylactone to form an ion pair, followed by slow transfer of the methoxycarbonyl group from this ion-pair to the amine in the enantioselectivity determining step (Fig. 6) [99].

Procedure for KR of an α -chiral primary amine using catalyst **17**: KR of (±)-1-phenylethylamine [99]

Catalyst **17** (5.2 mg, 0.014 mmol), (±)-1-phenylethylamine (17.0 mg, 0.14 mmol) and CHCl₃ (2.5 mL) were added to a Schlenk flask under argon. The resulting purple solution was cooled to -50 °C and a solution of *O*-carbonyloxazylactone **23** (13.5 mg, 0.042 mmol) in CHCl₃ (0.15 mL) was added by syringe. After 4 h, additional *O*-carbonyloxazylactone **23** (13.5 mg, 0.042 mmol) in CHCl₃ (0.15 mL) was added. After 24 h in total the solution was concentrated in vacuo and the residue purified by FC on silica gel (EtOAc/hexanes, 1/4) to afford the carbamate (7.3 mg, 29%, 79% ee by chiral-HPLC) and the amine which was immediately acylated (Et₃N, Ac₂O, CH₂Cl₂, room temperature) and then purified by FC on silica gel (EtOAc) to afford the acetamide (11.4 mg, 50%, 42% ee by chiral-GC). The calculated selectivity value at 35% conversion was *s* = 13.

Fu and co-workers expanded the scope of amine KR to include indolines [100]. However, as the initial conditions developed for aryl alkyl *sec*-amines were unsuccessful due to the low nucleophilicity of the catalyst, a few structural modifications were introduced. Hence, after screening various catalysts and achiral acyl donors, the use of a bulky pentacyclopentadienyl-derived catalyst in conjunction with an

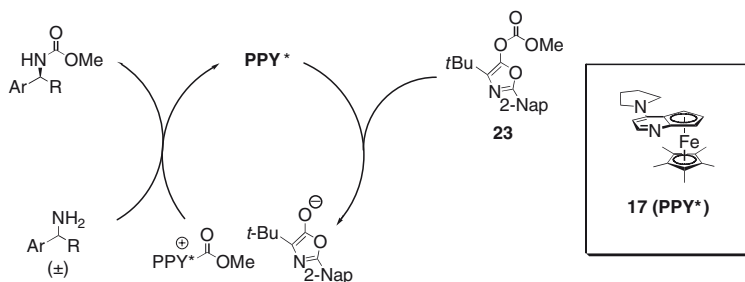


Fig. 6 Fu's proposed mechanism for the 4-PPY-catalyzed KR of amines [99]

O-carbonyloxyazlactone led to a more effective catalytic system that could achieve the desired KR with useful levels of selectivity; the best selectivities being obtained when using 4-PPY derivative **24** (Ar = 3,5-Me₂C₆H₃) (Scheme 11) [100].

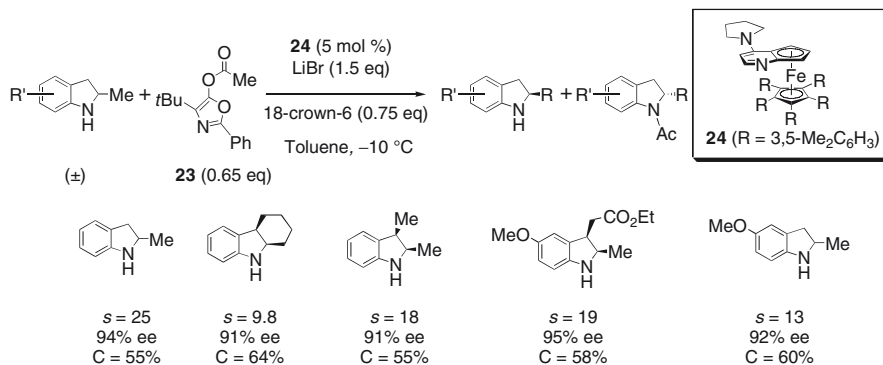
It is noteworthy that a safer and more efficient synthesis of catalysts **15** and **16** was recently developed involving a classical resolution of racemic **15** and **16** using commercially available tartaric acids [101].

In 1970, Steglich reported that 4-DMAP catalyzed the rearrangement of *O*-acylated azlactones to their *C*-acylated isomers ('the Steglich rearrangement') [60, 102]. This process effects C–C bond formation and concomitant construction of a quaternary stereocenter. Building upon this foundation, first Fu [103] and later Vedejs [104, 105], Johannsen [106] and Richards [107] have explored the utility of chiral 4-DMAP/4-PPY derivatives to effect this type of rearrangement. While Fu's planar chiral ferrocenyl 4-DMAP catalyst **17** and Vedejs' 3-(2,2-triphenyl-1-acetoxyethyl)-4-dimethylamino)pyridine (TADMAP) catalyst **25a** are very effective in giving products generally with *ee* values > 90% and in almost quantitative yields [103, 104], Richards' cobalt metallocenyl 4-PPY **26** and Johannsen's ferrocenyl 4-DMAP **27** give significantly lower levels of selectivity (25% and 45–67% *ee*, respectively) but have been less thoroughly investigated (Scheme 12) [107,105].

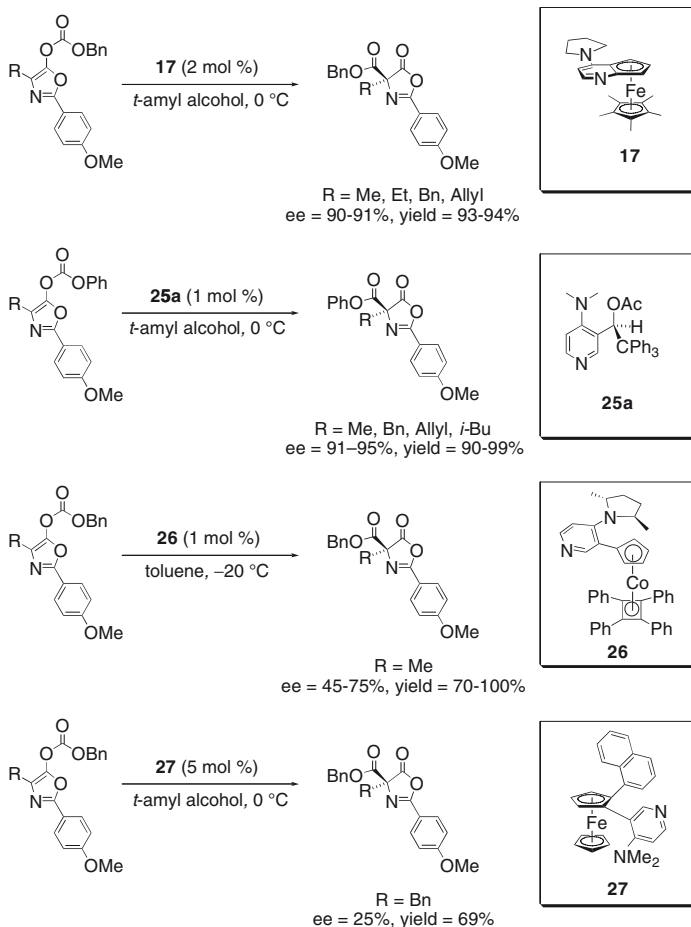
Gröger has also reported a preliminary study on enantioselective acetyl migration in the Steglich rearrangement using one of Fu's commercially available catalysts and Birman's tetramisole-based organocatalyst [108].

Analogous rearrangements have also been performed by both Fu [73] and Vedejs [105] on *O*-acyl benzofuranones and *O*-acyl oxindoles to provide synthetic intermediates potentially suitable for elaboration to diazonamide A and various oxindole-based alkaloids such as gelsemine respectively. Peris has also examined both Fu's and Vedejs' chiral 4-DMAP catalysts for effecting diastereoselective carboxyl migrations of 3-arylbenzofuranones [109].

In addition to the planar chiral ferrocenyl catalysts **15–18**, **24** developed by Fu, a number of other chiral derivatives of 4-DMAP and 4-PPY [4, 47, 48] have been explored by other groups as organocatalysts for KR of *sec*-alcohols. Contributions have been made by the groups of Vedejs [104, 105, 110, 111], Fuji and Kawabata



Scheme 11 Fu's planar chiral ferrocenyl 4-PPY catalyzed indoline KR [100]



Scheme 12 Fu's, Vedejs', Johannsen's and Richards' chiral DMAP-catalyzed rearrangements of *O*-acyl azlactones [103-107]

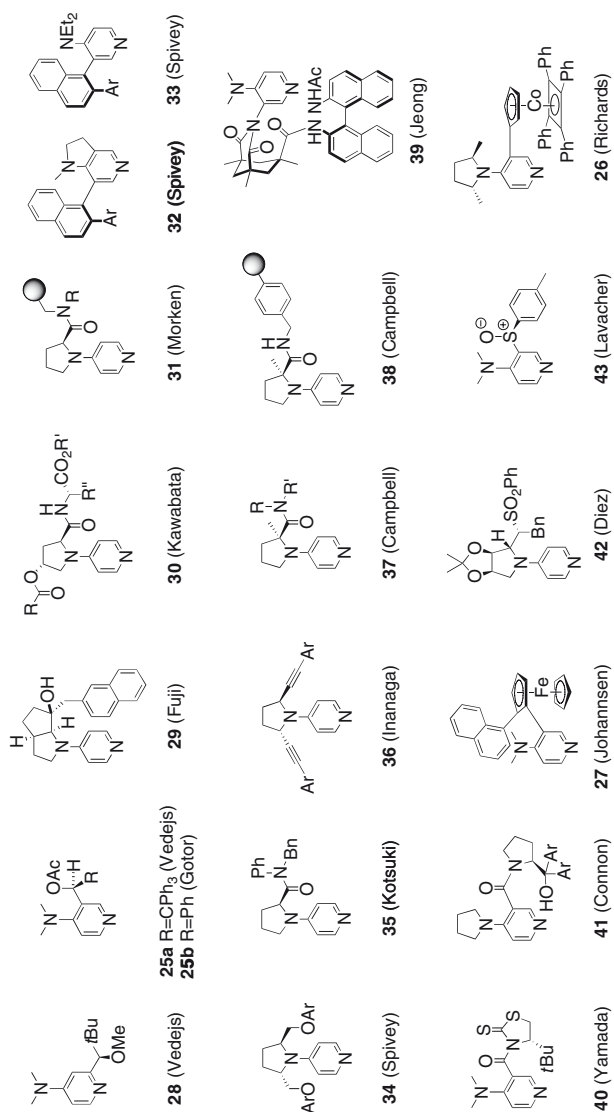


Fig. 7 Chiral Derivatives of 4-DMAP and 4-PPY

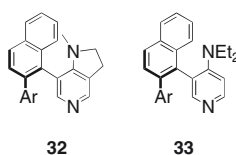
[112–115], Morken [116], Spivey [117–127], Kotsuki [128, 129], Inanaga [130], Campbell [131–134], Jeong [135], Yamada [136], Connon [137], Johannsen [106], Díez [138], Levacher [139], Richards [107] and Gotor [140, 141] (Fig. 7).

Spivey and coworkers reported in 1999 the use of axially chiral analogs of 4-DMAP **32** and **33**, which rely on the high barrier of rotation about an aryl–aryl bond at the 3-position of 4-DMAP to produce atropisomers that are selective in the acylation of *sec*-alcohols (Scheme 13) [117–127].

These catalysts show similar preferences to the Fu catalysts, but acylation selectivities are 3–5 times lower for the derivatives disclosed so far. They do, however, display higher catalytic activity than the analogous Fu catalysts which should provide a window of opportunity for increasing selectivity further and allow for KR of more intrinsically reactive substrates such as amines. *sec*-Alcohol KR can be carried out at $-78\text{ }^{\circ}\text{C}$ with 1 mol% catalyst. The high activity of these catalysts can be attributed at least in part to the relatively unencumbered environment of the nucleophilic pyridyl nitrogen and efficient conjugation between the 4-amino group lone pair and the pyridine ring.

The axially chiral biaryl 4-DMAP **32** developed by Spivey [117–127] is relatively readily prepared but only provides modest levels of selectivity for the KR of aryl alkyl *sec*-alcohols: $s \leq 30$ at $-78\text{ }^{\circ}\text{C}$ over 8–12 h or $s \leq 15$ at room temperature in ~20 min (Table 4) [119].

In the late 1990s, Fuji and Kawabata also set out to develop an efficient catalyst that would promote the enantioselective acylation of racemic alcohols. Their strategy was based on the use of a 4-PPY-derived catalyst that would mimic the induced-fit



Scheme 13 Spivey's axially-chiral analog of 4-DMAP in the KR of an alkyl aryl carbinol. [117–127]

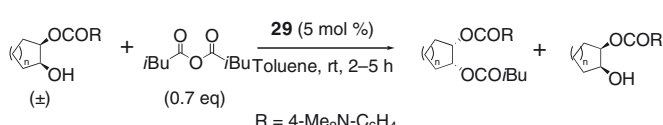
Table 4 Spivey's axially chiral 4-DMAP catalyzed KR of *sec*-alcohols [119]

32							
Entry	R	Ar	(<i>i</i> -PrCO) ₂ O	C (%)	<i>ee</i> A (%)	<i>ee</i> E (%)	<i>s</i>
1	Me	1-Nap	2 eq	17.2	18.6	89.3	21
2	Me	1-Nap	1 eq	22.3	26.3	91.4	29
3	Me	Ph	2 eq	39.0	49.9	78.1	13
4	Me	2-Tol	2 eq	41.4	60.7	86.0	25
5	<i>t</i> -Bu	Ph	2 eq	17.5	18.8	88.8	20

mechanism of enzymes by switching from an ‘open’ to a ‘closed’ conformation when activated. As the introduction of a sterically demanding asymmetric centre close to the nitrogen of the pyridine ring was known to reduce the catalytic activity, the authors decided to place the stereogenic centre at a remote position hoping for an induction through long-range chirality transfer. Catalyst **29** was thus synthesised and tested on various racemic mono-benzoylated *cis*-diol derivatives at room temperature [112]. These experiments were a success. Indeed, even though the selectivities observed were rather moderate ($s = 5.8$ – 10.1), they offered a proof-of-concept for the approach (Table 5) [113].

On the basis of NMR studies, Fuji and Kawabata proposed that catalyst **29** was selective despite the distance between the stereogenic centres and the acyl pyridinium carbonyl ‘active site’ as a result of a remote chirality transfer by face to face π – π stacking interactions between the naphthalene substituent and the pyridinium ring. Indeed, analysis of ^1H NMR chemical shifts and $n\text{Oe}$ measurements confirmed that catalyst **29** interconverted between two conformations (open and closed conformation) depending on whether it was in the ‘free’ or acyl pyridinium state. The authors also suggested that the relative orientation of the nucleophile was also ordered by π – π stacking interactions as *sec*-alcohol nucleophiles incorporating an electron rich aryl amide gave the highest selectivities (Fig. 8) [112].

Table 5 Fuji and Kawabata’s chiral 4-PPY catalyzed KR of racemic mono-benzoylated *cis*-diol derivatives [113]



29 (5 mol %)

$i\text{BuCOO}$ (0.7 eq)

$\text{R} = 4\text{-Me}_2\text{N-C}_6\text{H}_4$

Entry	N	Time	C (%)	<i>eeA</i> (%)	<i>s</i>
1	1	4	71	97	8.3
2	2	3	72	99	10.1
3	3	4	70	92	6.5
4	4	5	73	92	5.8

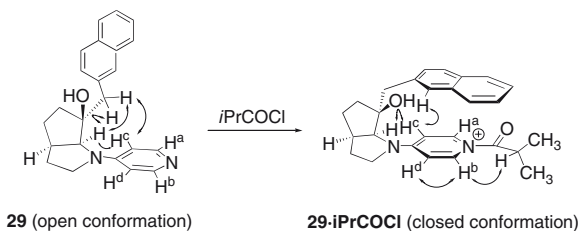


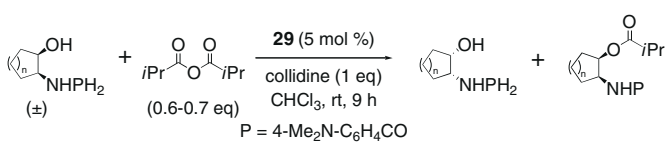
Fig. 8 ^1H NMR of Fuji’s and Kawabata’s catalyst and its acylpyridinium ion. Arrows designate $n\text{Oes}$ observed in open and closed conformations [112]

Fuji and Kawabata further demonstrated the utility of their catalyst by successfully achieving the KR of *N*-protected cyclic *cis*-amino alcohols [113]. Hence, by using 5 mol% of 4-PPY **29** in the presence of a stoichiometric amount of collidine in CHCl_3 at room temperature, a variety of cyclic *cis*-amino alcohol derivatives were resolved with moderate to good selectivities ($s = 10\text{--}21$) (Table 6) [113].

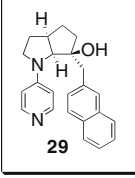
Kawabata has most recently turned his attention to the regioselective *O*-acylation of sugars using 4-PPY derivatives. Under appropriate conditions, 4-DMAP itself was found to catalyze *O*-isobutyrylation of octyl-6-*O*-methyl- and octyl-6-*O*-TBS- β -d-glucopyranoside at the 3-hydroxy position [142]. Using a chiral 4-PPY derivative it was possible to catalyze either 4- or 6-*O*-isobutyrylation of octyl- β -d-glucopyranoside with high levels of regioselectivity [143].

These pioneering insights into the possibilities offered by harnessing π - π ordering interactions to aid chirality transfer inspired many subsequent researchers in this area to design systems that could benefit from π - π , cation- π and related ordering interactions to achieve/enhance chirality transfer. In this context, Yamada and co-workers developed a new family of chiral catalysts derived from the 4-DMAP scaffold which achieved the KR of a range of *sec*-alcohols with interesting levels of selectivity (Scheme 14) [136, 144].

Table 6 Fuji and Kawabata's chiral 4-PPY catalyzed KR of cyclic *cis*-amino alcohol derivatives [113]

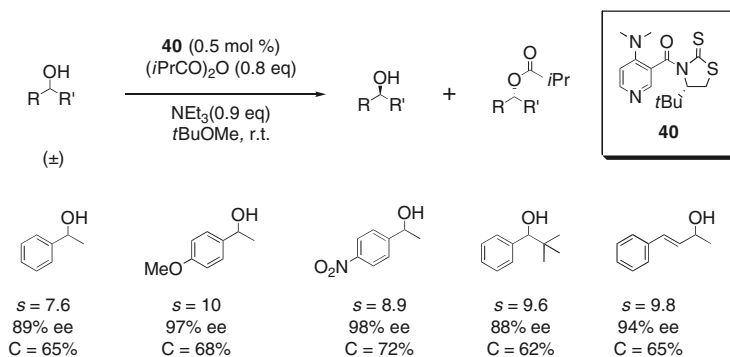


29



Entry	n	(<i>i</i> -PrCO) ₂ O	C (%)	<i>ee</i> A (%)	<i>ee</i> E (%)	<i>s</i>
1	2	0.6 eq	58	93	68	17
2	1	0.7 eq	69	>99	44	>12
3	3	0.7 eq	69	97	46	10

P = 4-Me₂N-C₆H₄CO



Scheme 14 Yamada's chiral 'conformation-switch' catalyst applied to the KR of aryl alkyl *sec*-alcohols [136, 144]

The design of these new catalysts was based on an early study by Yamada in which he had shown via ^1H NMR measurements, X-ray structural analyses and DFT calculations that upon *N*-acylation, 3-substituted 4-DMAPs underwent a conformational switch governed by an intramolecular cation– π interaction between the pyridinium ring and a thiocarbonyl group, thus providing a good facial control (Fig. 9) [145]. Yamada further applied catalyst **40** to the desymmetrization of various *meso*-diols with good selectivities using just 0.05–5 mol% of catalyst [145].

Most recently, Yamada et al. have applied their catalysts to the dynamic KR (DKR) of cyclic hemiaminals by acylation to give products in up to 88% *ee* and 99% yield [146].

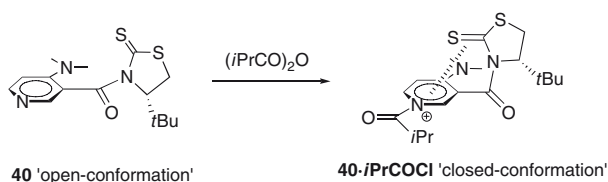


Fig. 9 Yamada's 'conformation-switch' catalyst [145]

Connon and co-workers [137, 147] also set out to develop a chiral catalyst which operates via an 'induced-fit' mechanism. Derived from a 3-substituted 4-PPY and possessing a pendant aromatic group, this new catalyst (**41**, Fig. 7) allowed moderate to good selectivities to be achieved for a wide range of aryl alkyl *sec*-alcohols. Connon [148] later showed that small improvements in selectivity could be obtained by introducing electron-deficient aryl groups. Finally, he was able to expand the substrate scope to include *sec*-alcohols obtained by Baylis–Hillman reaction [148].

Similarly, Díez [138] developed a series of chiral 4-PPY catalysts containing a sulfone side chain (**42**, Fig. 7); however, the selectivities obtained in the KR of ($\pm$)-1-phenylethanol were rather modest ($s < 2$).

Campbell et al. at GlaxoSmithKline developed a related family of chiral catalysts functioning through an 'induced-fit' mechanism. Based on a 4-(α -methyl)prolinopyridine scaffold, these new catalysts (**37**, Fig. 7) allowed the KR of *cis*-($\pm$)-(*p*-*N'*,*N'*-dimethylbenzoyl)cyclohexan-1,2-diol and other racemic alcohols with high selectivities [132, 149]. Interestingly, catalysts bearing a secondary amide in the side chain led to relatively high selectivities ($s = 8$ –13), whereas catalysts bearing a tertiary amide or an ester were rather inefficient ($s < 2$). In the light of these results, the authors suggested that hydrogen bonding was the key for obtaining good selectivities. Following these initial results, Campbell developed a solid-supported version of his catalyst (**38**, Fig. 7) with the advantage that it could be recycled. Unfortunately, the selectivities obtained were slightly lower than the ones obtained with the corresponding solution-phase catalyst [150, 151].

Kotsuki [128] reported a straightforward approach to the synthesis of chiral 4-PPY (**35**, Fig. 7) catalysts via high-pressure promoted nucleophilic aromatic

substitution of 4-chloropyridine and their application in the KR ($\pm$)-1-phenylethanol; however, the selectivities obtained were very poor (up to 20% *ee* at 12% conversion).

Finally, Inanaga's contribution to the development of chiral 4-dialkylaminopyridine based catalysts for enantioselective acyl transfer relied on the use of C_2 -symmetric 4-PPY derivative **36** (Fig. 7) [130]. This compound was obtained in an enantiopure form by selective cleavage of a carbamate intermediate using SmI_2 , and allowed the KR of various *sec*-alcohols with selectivity factors ranging from $s = 2.1$ to 14.

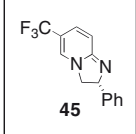
3.3 Dihydroimidazole-Based Catalysts

In 2004, Birman and coworkers set out to develop an easily accessible and highly effective acylation catalyst based on the 2,3-dihydroimidazo[1,2-*a*]-pyridine (DHIP) core. The first chiral derivative to be prepared and tested was (*R*)-2-phenyl-2,3-dihydroimidazo[1,2-*a*]-pyridine **44** (H-PIP) [152]. Derived from (*R*)-2-phenylglycinol, this catalyst afforded the KR of ($\pm$)-phenylethylcarbinol in 49% *ee* at 21% conversion ($s = 3.3$). In order to improve the reactivity of the catalyst, the authors decided to introduce an electron-withdrawing substituent on the pyridine ring that would increase the electrophilicity of the acylated intermediate. Hence, three new derivatives (Br-PIP, NO_2 -PIP and CF_3 -PIP) were synthesised and tested under rigorously identical conditions [152]. One of these easily accessible compounds, 2-phenyl-6-trifluoromethyl-dihydroimidazo[1,2-*a*]pyridine (**45**, abbreviated as CF_3 -PIP), proved to be particularly effective as, when combined with $(\text{EtCO})_2\text{O}$ and $i\text{Pr}_2\text{NEt}$, it resolved a variety of aryl alkyl *sec*-alcohols with good to excellent selectivities ($s = 26$ –85) (Table 7) [152].

Following these results, Birman suggested that the chiral recognition was dependent on the π – π stacking interactions between the reactive acylated intermediate and the aryl moiety in the substrate (Fig. 10) [152].

Table 7 Birman's CF_3 -PIP catalyzed KR of *sec*-alcohols [152]

$$\begin{array}{c} \text{OH} \\ | \\ \text{Ar}-\text{CH}-\text{R} \\ (\pm) \end{array} + \begin{array}{c} \text{O} \\ || \\ \text{Et}-\text{O}-\text{C}-\text{O}-\text{Et} \\ (0.75 \text{ eq}) \end{array} \xrightarrow[\text{CHCl}_3, 0^\circ\text{C}]{\begin{array}{c} \text{45 (2 mol \%)} \\ i\text{Pr}_2\text{NEt (0.75 eq)} \end{array}} \begin{array}{c} \text{OH} \\ | \\ \text{Ar}-\text{CH}-\text{R} \end{array} + \begin{array}{c} \text{O} \\ || \\ \text{Ar}-\text{O}-\text{C}-\text{O}-\text{Et} \end{array}$$



45

Entry	Ar	R	t (h)	C (%)	s
1	Ph	Me	8	32	26
2	Ph	Et	8	39	36
3	Ph	<i>i</i> -Pr	30	55	41
4	PH	<i>t</i> -Bu	52	48	85
5	1-Nap	Me	8	51	56
6	3-MeO-C ₆ H ₄	Me	8	40	34

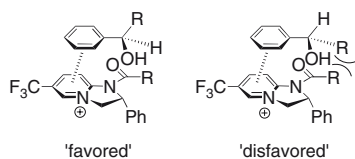


Fig. 10 π - π Stacking interactions in Birman's system [152]

Procedure for KR of an aryl alkyl *sec*-alcohol using catalyst **45**: KR of ($\pm$)-1-(1-naphthyl)-1-ethanol [152]

A solution of ($\pm$)-1-(1-naphthyl)-1-ethanol (2.416 g, 14.0 mmol), DIPEA (1.93 mL, 10.5 mmol) and catalyst **45** (74 mg, 0.28 mmol) in CHCl_3 (14 mL) was stirred at 0 °C for 15 min then treated with (*n*-PrO) $_2$ O (1.35 mL, 10.5 mmol). The mixture was stirred at 0 °C for 10 h, at which time it was quenched with MeOH (10 mL), allowed to warm slowly and left for 1 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 , washed twice with 1 M HCl, then twice with saturated aqueous NaHCO_3 , and dried (Na_2SO_4). The solution was concentrated in vacuo and purified by FC on silica gel (Et_2O /hexanes, 1/19 $\rightarrow$ 1/4) to give the ester (1.672 g, 52%, 82.5% *ee* by chiral-HPLC), and the alcohol (1.091 g, 45%, 98.8% *ee* by chiral-HPLC). The calculated selectivity value at 54.5% conversion was $s = 52.3$. The aqueous phase obtained during the work up was basified with 0.5 M NaOH and repeatedly extracted with CH_2Cl_2 (until the aqueous phase was pale-yellow), the extract was dried (Na_2SO_4), concentrated in vacuo, and purified by FC on silica gel (*i*-PrOH/hexanes, 1/19 $\rightarrow$ 1/9) to provide 50 mg of recovered catalyst **45** (68%).

In order to maximise this interaction, a second generation catalyst with an extended π -system was designed based on an (*R*)-2-phenyl-1,2-dihydroimidazo[1,2-*a*]quinoline (PIQ) core (Fig. 11) [153, 154].

The 7-chloro derivative (Cl-PIQ) **46** was found to provide even better selectivity and reactivity than CF_3 -PIP **45** for aryl alkyl *sec*-alcohols and, moreover, was effective for certain cinnamyl-based allylic *sec*-alcohol substrates ($s = 17$ –117, Scheme 15) [153, 154].

Procedure for KR of an aryl alkyl *sec*-alcohol using catalyst **46**: KR of ($\pm$)-1-(1-naphthyl)-1-ethanol [152]

A solution of ($\pm$)-1-(1-naphthyl)-1-ethanol (2.416 g, 14.0 mmol), DIPEA (1.93 mL, 10.5 mmol) and catalyst **46** (74 mg, 0.28 mmol) in CHCl_3 (14 mL) was stirred at 0 °C for 15 min then treated with (*n*-PrO) $_2$ O (1.35 mL, 10.5 mmol). The mixture was stirred for 0 °C for 10 h, at which time it was quenched with MeOH (10 mL), allowed to warm slowly and left for 1 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 , washed twice with 1 M HCl, then twice with saturated aqueous NaHCO_3 , and dried (Na_2SO_4). The solution was concentrated in vacuo and purified by FC on silica gel (Et_2O /hexanes, 1/19 $\rightarrow$ 1/4) to give the ester (1.672 g, 52%, 82.5% *ee* by chiral-HPLC), and the alcohol (1.091 g, 45%, 98.8% *ee* by chiral-HPLC). The calculated selectivity value at 54.5% conversion was $s = 52.3$. The aqueous phase obtained during the work up was basified with 0.5 M NaOH and repeatedly extracted with CH_2Cl_2 (until the aqueous phase was pale-yellow), the extract was dried (Na_2SO_4), concentrated in vacuo, and purified by FC on silica gel (*i*-PrOH/hexanes, 1/19 $\rightarrow$ 1/9) to provide 50 mg of recovered catalyst **46** (68%).

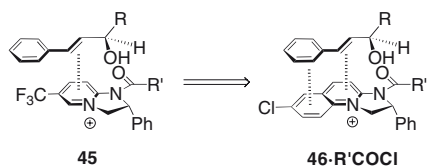
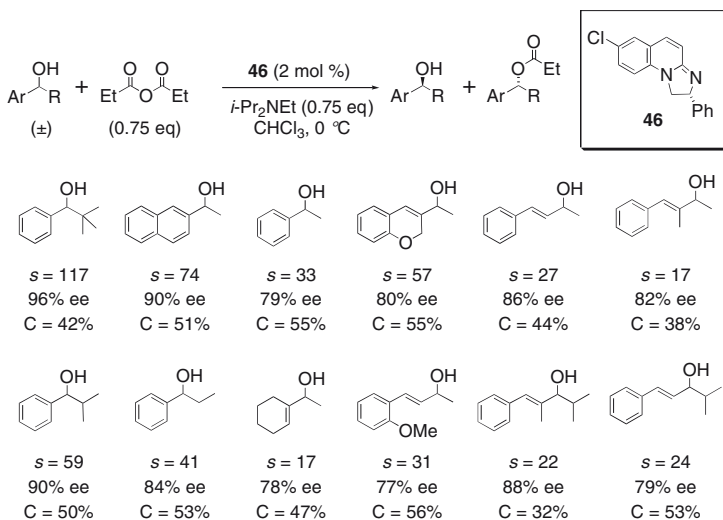


Fig. 11 Birman's second generation catalyst [153, 154]

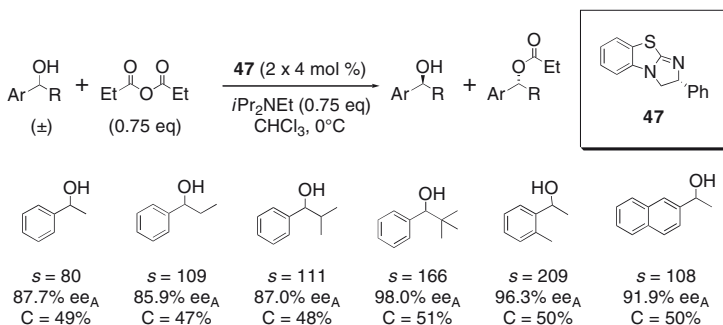


Scheme 15 Birman's Cl-PIQ catalyzed KR of *sec*-alcohols [153, 140]

Given that the Birman catalysts are readily prepared in just two steps from commercially available enantiomerically pure phenylalaninol, these catalysts constitute attractive alternatives to Fu's planar chiral ferrocenyl catalysts **15–18**.

Finally, while trying to evaluate the influence of the pyridine ring on the selectivity, Birman disclosed yet another family of catalysts for the acylative KR of *sec*-benzylic alcohols. Derived from commercially available tetramisole, benzotetramizole (BTM, **47**) led to outstanding selectivities on a wide range of alcohols ($s = 100\text{--}350$, Scheme 16) [155, 156].

It is noteworthy that BTM also allowed the KR of propargylic alcohols with unprecedented levels of selectivity ($s = 5.4\text{--}32$) [157], as well as the KR of 2-oxazolidinones through enantioselective *N*-acylation with selectivity values reaching $s = 450$ [158].



Scheme 16 Birman's BTM catalyzed KR of *sec*-alcohols [155, 156]

3.4 *N*-Alkylimidazole-Based Catalysts

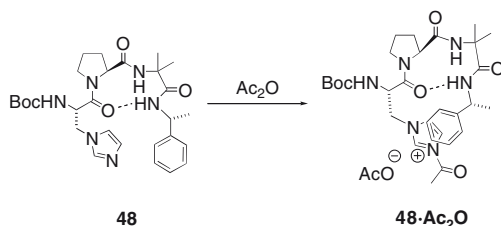
Miller and co-workers have taken a totally different approach to design an efficient catalyst for enantioselective acylation. Their strategy relied on the use of a peptide-based backbone incorporating a 3-(1-imidazolyl)-(*S*)-alanine unit as the catalytic core. Upon treatment with an achiral acyl source these 'biomimetic' enantioselective acyl transfer catalysts allow the formation of an acyl imidazolium ion in proximity to the chiral environment generated by the folding of the peptide [3, 159–174].

The first catalyst of this type to be reported by Miller was tripeptide **48** in 1998 which adopts a β -turn type structure possessing one intramolecular hydrogen bond [159]. In addition, this organocatalyst judiciously incorporates a *C*-terminal (*R*)- α -methylbenzylamide which prompts π - π stacking interactions (Scheme 17) [159].

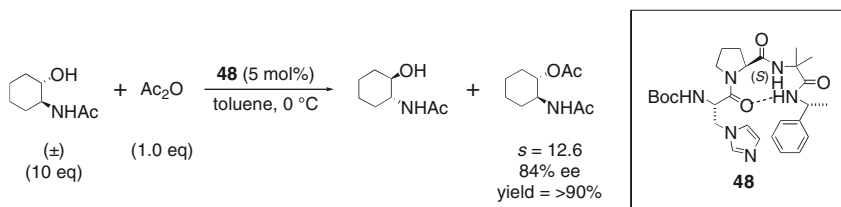
In order to increase the possibility of a kinetically significant peptide-substrate interaction (enzyme mimic) which could lead to improved stereoselection, initial KR experiments were performed on *trans*-1,2-acetamidocyclohexanol (Scheme 18) [159].

Interestingly, tripeptide **48** catalyzed the KR of this amide-containing *sec*-alcohol with moderate enantioselection ($s \leq 12.6$) and high solvent-dependency. Indeed, reactions that were carried out in polar solvents such as acetonitrile afforded lower selectivities ($s = 1.3$) than those performed in apolar solvents such as toluene ($s = 12.6$). Considering that apolar solvents usually favour the formation of intramolecular hydrogen bonds while polar solvents have a tendency to break these interactions leading to a more flexible conformation, these results indicate a significant correlation between conformational rigidity and degree of enantioselection. In addition, Miller and co-workers also observed that changing the configuration of the proline from (*S*) to (*R*) induces a complete reversal of selectivity along with an increase in the level of selectivity (Scheme 19) [160].

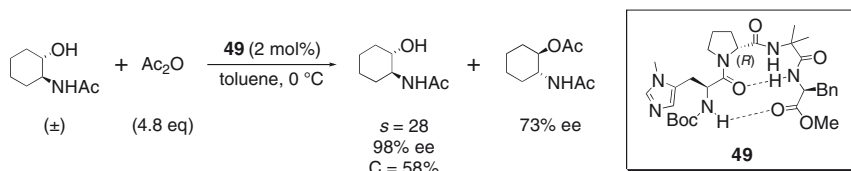
These results suggest not only that a single stereogenic centre can control the stereochemical outcome of the KR reaction, but also that the increase in overall



Scheme 17 Miller's first generation 3-(1-imidazolyl)-(*S*)-alanine containing peptide [159]



Scheme 18 Miller's tripeptide catalyzed KR of a cyclic *cis*-amino alcohol derivative [160]



Scheme 19 Miller's tetrapeptide catalyzed KR of a 1,2-amino alcohol derivative [160]

enantioselectivity can be attributed to an increase in the conformational rigidity of the catalyst.

In order to validate this hypothesis, a series of octapeptide catalysts known to possess four intramolecular hydrogen bonds [164] which confer conformational rigidity were synthesised and screened for activity in the KR of ($\pm$)-*trans*-1,2-acetamidocyclohexanol. Among them, (*R*)-proline containing octapeptide **50** (Fig. 12) was found to afford an excellent level of enantioselection ($s = 51$) while its (*S*)-proline analogue **51** (Fig. 12), which is structurally less well-defined, was substantially less selective ($s = 7$) [164].

Unfortunately, none of these catalysts displayed practical levels of selectivity in the KR of aryl alkyl *sec*-alcohols. Miller therefore embarked in the design of a third generation catalyst that could enable the KR of a larger number of substrates. In this context, he developed an elegant fluorescence-based activity assay which allowed rapid screening of a large number of structurally unique catalysts. This protocol based on proton-activated fluorescence led to the identification of octapeptide **52** as a highly selective catalyst for the KR of aryl alkyl *sec*-alcohols but also alkyl *sec*-alcohols

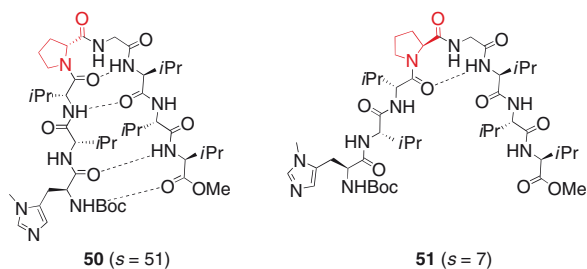


Fig. 12 Examples of octapeptide catalysts [164]

for which lipases and other organocatalysts invariably perform poorly (Scheme 20) [161, 164, 166, 167].

This strategy using rapid automated synthesis of libraries of peptides and fluorescent screening of reactivity has allowed Miller to identify specific peptide-catalysts for specific applications such as the KR of an intermediate en route to an aziridomitosane [165, 169], the KR of certain *tert*-alcohols [166], the regioselective acylation of carbohydrates [168], and finally the KR of *N*-acylated *tert*-amino alcohols with *s* values from 19 to >50 (Scheme 21) [166].

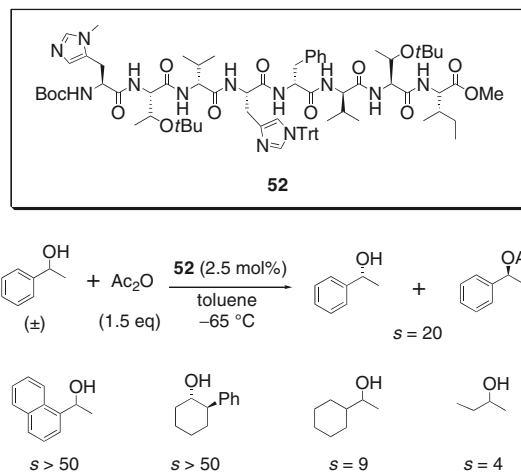
Miller also explored the ASD of glycerol derivatives through an enantioselective acylation process which relies on the use of a pentapeptide-catalyst which incorporates an *N*-terminal nucleophilic 3-(1-imidazolyl)-(*S*)-alanine residue [171]. Most recently, Miller has probed in detail the role of dihedral angle restriction within a peptide-based catalyst for *tert*-alcohol KR [172], site selective acylation of erythromycin A [173], and site selective catalysis of phenyl thionoformate transfer in polyols to allow regioselective Barton–McCombie deoxygenation [174].

Miller's biomimetic approach inspired Ishihara [234] to develop a 'minimal artificial acylase' for the KR of mono-protected *cis*-1,2-diols and *N*-acylated 1,2-amino alcohols. Derived from (*S*)-histidine, Ishihara's organocatalyst contains only one stereogenic centre and incorporates a sulfonamide linkage in place of a polypeptide chain to allow the NH group to engage as an H-bond donor with the substrates (Fig. 13) [234].

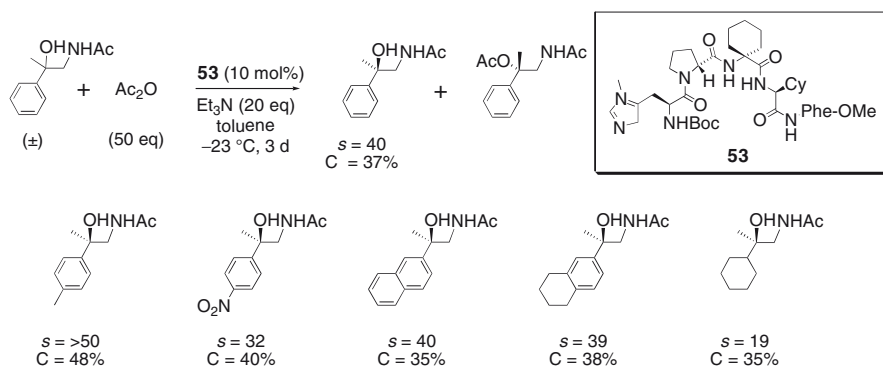
In order to design this artificial acylase, Ishihara and co-workers compared the catalytic activity of various imidazoles as well as the reactivity of carboxamides vs sulfonamides. Interestingly, the more acidic sulfonamide catalyst induced higher selectivities, thus suggesting that hydrogen-bonding may be a key factor for attaining a high level of KR.

Based on an X-ray crystal structure analysis of **54**, the authors proposed a transition-state where the conformation of the acylammonium salt generated from **54** would be fixed by an attractive electrostatic interaction between the acyl-oxygen and the imidazolyl-2-proton or a dipole minimization effect (Fig. 14) [177].

On the other hand, the H-bond between the sulfonylamino proton of the acylammonium salt and the carbamoyl oxygen preferentially promotes the acylation of the



Scheme 20 Miller's octapeptide catalyzed KR of *sec*-alcohols [164]



Scheme 21 Miller's tetrapeptide catalyzed KR of *tert*-alcohols [166]

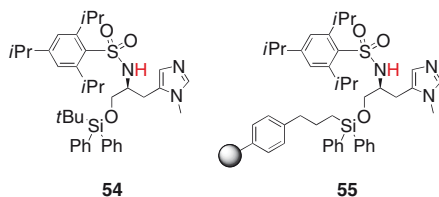


Fig. 13 Ishihara's minimal artificial acylase [234]

substrate by a proximity effect. Hence, catalyst **54** gave impressive levels of selectivity for a wide range of both cyclic and acyclic substrates (Scheme 22) [234].

Procedure for KR of a monoprotected-1,2-diol using catalyst **54**: KR of $(\pm)$ -*cis*-N-(2-hydroxycyclohexanoxycarbonyl)pyrrolidine [234]

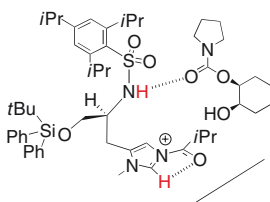
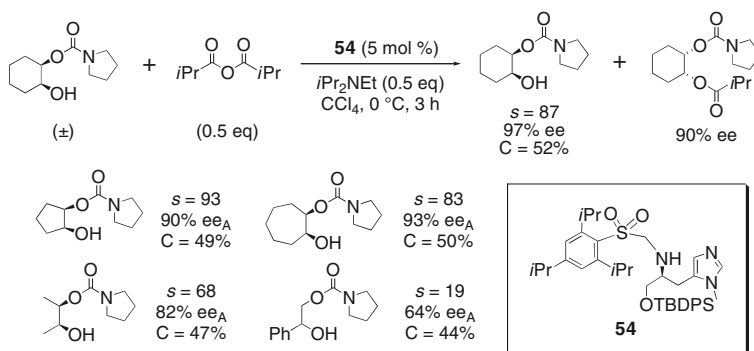


Fig. 14 Ishihara's model for enantioselective acylation [234]



Scheme 22 Ishihara's histidine derivative catalyzed KR of mono-protected *cis*-diols [234]

To a solution of (±)-*cis*-N-(2-hydroxycyclohexanoxycarbonyl)pyrrolidine (0.25 mmol) and catalyst **54** (0.0125 mmol) in CCl_4 (2.5 mL) was added $i\text{Pr}_2\text{NEt}$ (21.8 μL , 0.125 mmol) and $(i\text{PrCO})_2\text{O}$ (20.7 μL , 0.125 mmol). The reaction mixture was stirred at 0 °C for 3 h and then treated with 0.1 M aq. HCl and extracted with EtOAc. The organic layer was washed with sat. aq. NaHCO_3 , dried (Na_2SO_4) and concentrated to provide a crude mixture of the unreacted alcohol (97% *ee* by chiral-HPLC) and acylated product (90% *ee* by chiral HPLC). The calculated selectivity value at 51.9% conversion was *s* = 87.

3.5 1,2-Di(*tert*-amine)-Based Catalysts

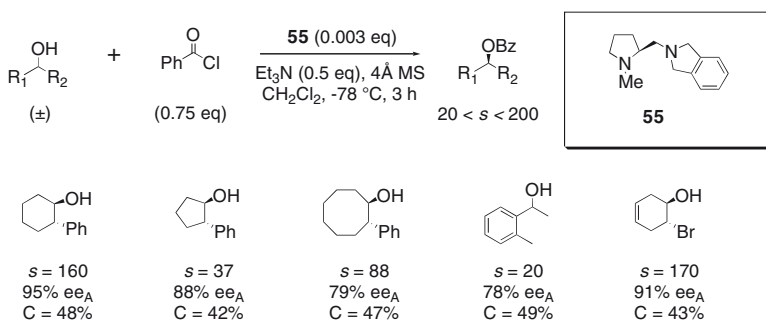
Oriyama [178–183] and co-workers developed yet another family of chiral catalysts. Derived from proline, these new catalysts were used in the KR of a number of cyclic alcohols (5- to 8-membered rings) with selectivity factors ranging from 37 to 170 with as low as 0.3 mol% of catalyst. While the exact reaction mechanism is not clear, the authors proposed, based on analysis of ^1H NMR chemical shift changes for signals from the catalyst upon addition of the achiral acylating agent, that the diamine coordinates in a bidentate fashion to the carbonyl carbon of the acid halide, which in turn leads to sufficient catalyst rigidity to account for the high enantioselectivities.

Although this non-classical bonding situation is highly unusual, catalyst **55** represents an extremely interesting catalyst class as it exhibits high selectivities whilst being extremely easy to prepare (Scheme 23) [178].

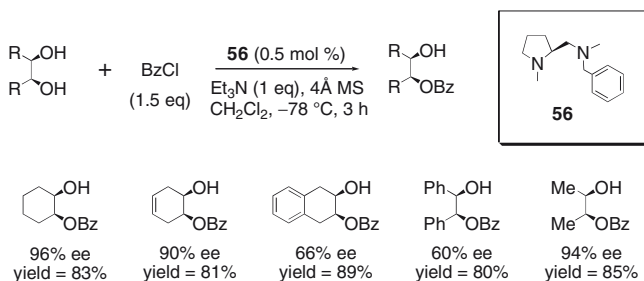
In addition, Oriyama was the first to provide a practical protocol for the ASD of *meso*-1,2-diols [179–182]. Thus, employing just 0.5 mol% of (*S*)-proline-derived chiral diamine **56** in conjunction with benzoyl chloride as the stoichiometric acyl donor in the presence of Et₃N, asymmetric benzylation of a variety of *meso*-diols could be achieved with good to excellent enantioselectivities (66–96% *ee*) and 80% yields (Scheme 24) [179–182].

Procedure for ASD of a *meso*-1,2-diol using catalyst **56**: ASD of *cis*-1,2-cyclohexanediol [180]

To 4 Å MS (400 mg) was added a solution of catalyst (*S*)-**56** (3.3 mg, 0.0151 mmol) in CH₂Cl₂ (2.5 mL) and the resulting reaction mixture was cooled to –78 °C. A solution of Et₃N (306 mg, 3.02 mmol) in CH₂Cl₂ (2.5 mL), a solution of *cis*-1,2-cyclohexanediol (351 mg, 3.02 mmol) in CH₂Cl₂ (20 mL) and a solution of BzCl (636 mg, 4.52 mmol) in CH₂Cl₂ (2.5 mL) were then added sequentially. After 3 h at –78 °C the reaction was quenched by the addition of a phosphate buffer (pH 7) and extracted with Et₂O. The combined organic



Scheme 23 Oriyama's proline derived diamine catalyst [178]



Scheme 24 Oriyama's proline diamine catalyzed ASD of *meso* diols [180]

extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by FC on silica gel (EtOAc/hexanes, 1/15) to afford *cis*-benzoyloxy-1-cyclohexanol (554 mg, 83%, 96% *ee* by chiral-HPLC).

Oriyama subsequently showed that this catalyst system was also effective for the KR of various classes of *sec*-alcohols, notably β -halohydrins [188] and also certain α -chiral primary alcohols such as glycerol derivatives [184]. A solid-supported version of Oriyama's catalyst developed by Janda was found to which induce comparable levels of selectivity [185–187].

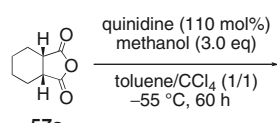
Most recently, Kündig has developed some related 1,2-di(*tert*-amine) catalysts which can be readily prepared from pseudo-enantiomeric quincoridines. These catalysts were shown to be more effective than those disclosed by Oriyama when applied to the ASD of a *meso*-diol complex derived from $[\text{Cr}(\text{CO})_3(\eta^6\text{-5,8-naphthoquinone})]$ [188, 189].

3.6 Quinine/Quinidine-Based Catalysts (e.g., Cinchona Alkaloids)

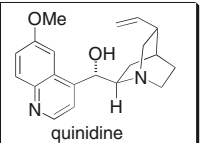
ASD of achiral and *meso*-anhydrides by ring opening with alcohols constitute Type II asymmetric acyl transfer processes which can be catalyzed by either chiral Lewis acids or bases [190–192]. Pioneering use of cinchona alkaloids as catalysts for these transformations was carried out by the groups of Oda [193, 194] and Aitken [195, 196] in the 1980s. This work provided the foundation for a significantly more enantioselective system for the ASD of cyclic *meso* anhydrides developed by Bolm employing a stoichiometric amount of the cinchona alkaloid quinidine (or its pseudoeoantiomer quinine) as the catalyst [197]. Reactions of bicyclic and tricyclic *meso*-anhydrides **57a–h** with methanol in the presence of 110 mol% of quinidine in a 1:1 toluene/ CCl_4 solvent system at -55°C provided the corresponding hemiesters with $\geq 93\%$ *ee* and $\geq 84\%$ yields. Use of quinine instead of quinidine generally provided *ent*-**57a–h** with similar levels of selectivity (Table 8). Mechanistically, it was initially assumed that amine-catalyzed acylative KR of *sec*-alcohols and ASD of achiral and *meso*-anhydrides involved nucleophilic attack by the amine onto the anhydride to afford a reactive acylammonium species. However, due to steric factors, neither the quinoline nor the quinuclidine nitrogens of the cinchona alkaloids are expected to be sufficiently nucleophilic to undergo such nucleophilic attack. In this context, Oda suggested that cinchona alkaloids catalyzed the acylative KR of *sec*-alcohols and the ASD of achiral and *meso*-anhydrides through a base activation even though a synergetic combination of both mechanisms could not be ruled out.

Following the reaction, simple extraction provided access to both the hemiester product and the alkaloid without chromatography and the recovered cinchona alkaloid could be reused with no deterioration in the *ee* or yield. This method has found use in the synthesis of β -amino alcohols and in natural product synthesis [198–201] and has recently been reported as an *Organic Syntheses* method [202].

Table 8 Bolm's quinidine/quinine promoted ASD of *meso*-anhydrides



57a



quinidine

57b

57c

57d

57e

57f

57g

57h

		Quinidin		Quinine ^a	
Entry	Anhydride	<i>ee</i> (%)	Yield (%)	<i>ee</i> (%)	Yield (%)
1	57a	93	98	87	91
2	57b	99	98	99	92
3	57c	96	96	93	94
4	57d	85	96	93	94
5	57e	95	97	93	99
6	57f	94	99	87	93
7	57g	95	93	93	99
8	57h	94	84	94	86

^aQuinine catalyzed reactions give enantiomeric products

Subsequently, Bolm developed a variant of this process which employed just a sub-stoichiometric quantity of cinchona alkaloid [203]. In this method, 10 mol% of quinidine was used in conjunction with a stoichiometric amount of pempidine to prevent sequestration of the cinchona alkaloid by the acidic hemiester product. The chiral hemiester products derived from various *meso*-anhydrides were obtained with $\geq 74\%$ *ee* and $\geq 94\%$ yields (Table 9) [203].

Although both quinidine and pempidine can be recovered and reused, it is noteworthy that pempidine is more expensive than quinidine and that this protocol requires very long reaction times.

Procedure for ASD of a cyclic *meso*-anhydride using quinidine: ASD of bicyclo [2.2.1] hept-5-ene-2,3-dicarboxylic acid endo *cis*-anhydride [204]

MeOH (0.122 mL, 3.0 mmol) was added dropwise to a stirred suspension of anhydride **57b** (164 mg, 1.0 mmol) and quinidine (0.357 g, 1.1 mmol) in a mixture of toluene and tetrachloromethane (1/1, 5 mL) at $-55\text{ }^{\circ}\text{C}$ under argon. The reaction mixture was stirred at this temperature for 60 h. During this period, the material gradually dissolved. Subsequently, the resulting clear solution was concentrated in vacuo to dryness, and the residue was dissolved in EtOAc. The solution was washed with 2N HCl and, after phase separation, followed by extraction of the aqueous phases with EtOAc; the organic layer was dried (MgSO_4), filtered and concentrated in vacuo to provide the corresponding hemiester (2*R*,3*S*)-3-endo-methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid as a white solid (192 mg, 98%, 99% *ee* by chiral-HPLC on the methyl 4-bromophenol diester). To recover the alkaloid, the acidic aqueous phase was neutralised with Na_2CO_3 and extracted with CH_2Cl_2 . The combined organic phases were dried (MgSO_4) and filtered. Evaporation of the solvent yielded the recovered alkaloid almost quantitatively.

Table 9 Bolm's quinidine catalyzed ASD of *meso*-anhydrides [203]

 57i	quinidine (10 mol%) MeOH (3.0 eq) pempidine (1.0 eq) toluene/CCl ₄ (1/1) -55 °C, 60 h	 H CO ₂ Me H CO ₂ H	 quinidine pempidine
Entry	Anhydride	<i>ee</i> (%)	Yield (%)
1	57b	90	98
2	57c	91	94
3	57e	89	96
4	57f	81	97
5	57i	74	98

Bolm has demonstrated the utility of the quinidine-mediated ASD of cyclic *meso*-anhydrides by developing protocols for the conversion of the hemiester products into enantiomerically enriched unnatural β -amino alcohols by means of Curtius degradation [204]. A particularly practical variant of this procedure utilises benzyl alcohol rather than methanol as the nucleophile in the quinidine-mediated ASD reaction, allowing, following Curtius degradation, for hydrogenolytic deprotection of both the benzyl ester and a *N*-CBz group to afford free β -amino alcohols in a single step [205]. The Bolm method can also be used under solvent-free conditions in a ball-mill [206].

In 2000, Deng was the first to report the use of readily available 'Sharpless ligands' to catalyze the enantioselective alcoholysis of *meso*-cyclic anhydrides [207]. Hence, the use of a catalytic amount of the bis-cinchona alkaloid (DHQD)₂AQN (5–30 mol%) in the alcoholysis of monocyclic, bicyclic and tricyclic succinic anhydrides as well as glutaric anhydrides at –20 to –30 °C and in the absence of a stoichiometric amount of an achiral base, provided the corresponding hemiesters in good to excellent yields (72–99%) and with excellent enantioselectivities (91–98% *ee*). Interestingly, the antipodal products could be easily obtained by employing the pseudo-enantiomeric (DHQ)₂AQN as the catalyst (Table 10) [208, 210].

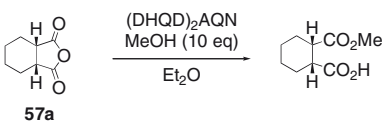
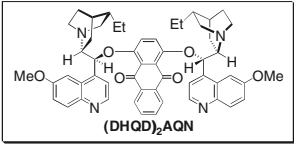
The synthetic utility of this methodology was further demonstrated in a formal synthesis of (+)-biotin by the same authors [211]. Following this work, various reusable immobilised analogues of (DHQD)₂AQN were reported to catalyze the desymmetrization of a number of *meso*-cyclic anhydrides with good selectivities [212–214].

Procedure for ASD of a cyclic *meso*-anhydride using (DHQD)₂AQN as catalyst: ASD of *cis*-cyclopentane-1,2-dicarboxylic acid anhydride [208–210]

Dry MeOH (32 mg, 40 μ L, 1.0 mmol) was added dropwise to a stirred solution of *cis*-cyclopentane-1,2-dicarboxylic acid anhydride **57e** (14 mg, 0.1 mmol) and (DHQD)₂AQN (95%, 72.2 mg, 0.08 mmol) in dry Et₂O (5 mL) under argon at –30 °C. The reaction mixture was stirred at –30 °C until the starting material was consumed (TLC, 71 h). The reaction was quenched by addition of HCl (1N, 3 mL) in one portion. The aqueous phase was extracted with EtOAc (2 $\times$ 10 mL) and the combined organic phases dried (MgSO₄) and concentrated in vacuo to afford the hemiester as a clear oil (17 mg, 99%, 95% *ee* by ¹H NMR on the diastereomeric amides formed by coupling the hemiesters to (*R*)-1-naphthalen-1-yl-ethylamine). The (DHQD)₂AQN catalyst was recovered quantitatively by basification (pH 11) of the aqueous phase with aqueous KOH (1N), extraction with Et₂O, drying of the Et₂O extracts (MgSO₄) and concentration in vacuo.

Deng also showed that (DHQD)₂AQN could catalyze the parallel KR (PKR) of a variety of monosubstituted succinic anhydrides via asymmetric alcoholysis [215]. The nature of the solvent was found to have a significant influence on the selectivity. Hence, increasing the size of the alcohol from methanol to ethanol resulted in increased levels of enantioselectivity, albeit with reduced reaction rates. In this context, 2,2,2-trifluoroethanol appeared to be the alcohol of choice as it allowed the ASD of 2-methyl succinic anhydride (**58a**) with a remarkable level of selectivity. Indeed, the use of (DHQD)₂AQN (15 mol%) provided a mixture of two regioisomeric hemiesters **59a** and **60a** in a ~1:1 ratio with 93 and 80% *ee* respectively.

Table 10 Deng's (DHQD)₂AQN catalyzed ASD of achiral/*meso*-anhydrides [208, 210]

 57a  (DHQD)₂AQN					
 57b 57e 57g 57j 57k 57l					
Entry	Anhydride	mol% cat ^a	T (°C) ^a	Yield (%) ^a	<i>ee</i> (%) ^a
1	57a	5(5)	–20(–20)	97(95)	97(93)
2	57b	10(20)	–30(–20)	82(82)	95(90)
3	57e	8(8)	–30(–30)	99(90)	95(93)
4	57g	7(7)	–20(–20)	95(92)	98(96)
5	57j	5(5)	–20(–20)	93(88)	98(98)
6	57k	30(30)	–40(–35)	70(56)	91(82)
7	57l	30(30)	–40(–35)	72(62)	90(83)

^a values in parentheses are for reactions using (DHQ)₂ AQN that give enantiomeric products

Similarly, a variety of 2-alkyl and 2-aryl succinic anhydrides (**58b–g**) were resolved with good to excellent enantioselectivities (66–98% *ee*) (Table 11) [216].

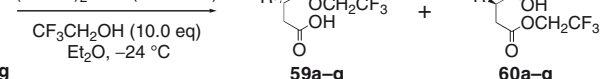
The synthetic utility of this PKR process was exemplified in a formal total synthesis of the γ -aminobutyric acid (GABA) receptor agonist (*R*)-baclofen [215].

Procedure for PKR of a monosubstituted succinic anhydride using (DHQD)₂AQN as catalyst: PKR of ($\pm$)-2-methylsuccinic anhydride [215]

2,2,2-Trifluoroethanol (0.73 mL, 10 mmol) was added to a solution of 2-methylsuccinic anhydride **58a** (114 mg, 1.0 mmol) and (DHQD)₂AQN (95%, 180 mg, 0.2 mmol) in Et₂O (50.0 mL) at –24 °C. The resulting reaction mixture was stirred at this temperature until the anhydride was consumed (TLC, 50 h). The reaction mixture was washed with aqueous HCl (1N, 3 $\times$ 10 mL). The aqueous phase was extracted with Et₂O (3 $\times$ 20 mL), the combined organic phases dried (MgSO₄) and then concentrated in vacuo. The residue was purified by FC on silica gel (cyclohexane/butyl acetate/acetic acid, 50/1/1) to afford hemiester **59a** (77 mg, 36%, 93% *ee* by chiral-HPLC on the diastereomeric amides formed by coupling the hemiesters to (*R*)-1-naphthalen-1-yl-ethylamine) and hemiester **60a** (88 mg, 41%, 80% *ee* by chiral-HPLC on the diastereomeric amides formed by coupling the hemiesters to (*R*)-1-naphthalen-1-yl-ethylamine). The (DHQD)₂AQN catalyst was recovered quantitatively by basification (pH 11) of the aqueous phase with aqueous KOH (2N), extraction with EtOAc (3 $\times$ 15 mL), drying of the EtOAc extracts (MgSO₄) and concentration in vacuo.

Deng also applied his (DHQD)₂AQN-catalyzed asymmetric alcoholysis to urethane-protected α -amino acid *N*-carboxy anhydrides (UNCAs) in order to access enantio-merically enriched α -amino acid derivatives [216]. Hence, the KR of a variety of alkyl and aryl UNCAs containing various carbamate protecting groups provided carbamate protected amino esters with selectivity values *s* ranging from 23 to 170 [217]. It is worth noting that when these reactions were performed at higher temperatures (such as room temperature), DKR could be achieved [218, 219]. Allyl alcohol was

Table 11 Deng's (DHQD)₂AQN catalyzed ASD of meso-anhydrides [216]



$(\pm)\text{-58a-g} \xrightarrow[\text{Et}_2\text{O}, -24^\circ\text{C}]{(\text{DHQD})_2\text{AQN (15 mol \%)}, \text{CF}_3\text{CH}_2\text{OH (10.0 eq)}} \text{59a-g} + \text{60a-g}$

Entry	R	59/60	<i>ee</i> (%)		Yield (%)	
			59	60	59	60

1a	Me (58a)	44/55	93	80	36	41
2	Et (58b)	40/60	91	70	38	50
3	<i>n</i> -C ₈ H ₁₇ (58c)	42/56	98	66	38	41
4	Allyl (58d)	46/53	96	82	40	49

5b	Ph (58e)	N/A	95	87	44	32
6b	3-MeO-C ₆ H ₄ (58f)	N/A	96	83	45	30
7b	4-Cl-C ₆ H ₄ (58g)	N/A	96	76	44	29

found to be the optimal nucleophile, allowing a variety of UNCAs to be resolved with high stereoselectivities (90–92% *ee*) and good yields (93–98%) [218]. The resulting allyl esters could then be converted to the corresponding α -amino acids via Pd-catalyzed deallylation (Table 12) [218].

The ready availability of the starting materials, the lack of special precautions to exclude air and moisture from the reaction mixtures and the ease of recovery of products make these DKR protocols attractive for the preparation of enantiomerically highly enriched *N*-protected- α -amino acids.

Procedure for DKR of a UNCA using (DHQD)₂AQN as catalyst: DKR of ($\pm$)-2,5-dioxo-4-phenyl-3-oxazolidine carboxylic acid phenylmethyl ester [218]

A mixture of UNCA **61a** (62.2 mg, 0.20 mmol) and 4 Å MS (20 mg) in anhydrous Et₂O (14.0 mL) was stirred at room temperature for 10 min and warmed to 34 °C, after which (DHQD)₂AQN (95%, 36.1 mg, 0.040 mmol) was added. The resulting mixture was stirred for a further 5 min and then a solution of allyl alcohol in Et₂O (1/99, 0.24 mmol) was introduced dropwise via a syringe over a period of 1 h. The resulting reaction mixture was stirred at 34 °C for 1 h, washed with aqueous HCl (2N, 2 $\times$ 3.0 mL) and brine (3.0 mL), dried (Na₂SO₄) and concentrated to provide a light yellow solid. Purification by FC on silica gel (EtOAc/hexanes, 1/9) gave (*R*)-allyl-(*N*-benzyloxycarbonyl)phenylglycinate **61a** as a white solid (63 mg, 97%, 91% *ee* by chiral-HPLC). The (DHQD)₂AQN catalyst was recovered quantitatively by washing the combined aqueous extracts with Et₂O (2 $\times$ 2.0 mL) and then basifying first with KOH ($\rightarrow$ pH $\sim$ 4) and then with Na₂CO₃ ($\rightarrow$ pH $\sim$ 11). The resulting solution was extracted with EtOAc (2 $\times$ 5.0 mL) and the combined organic extracts washed with brine (2.0 mL), dried (Na₂SO₄) and concentrated in vacuo.

Table 12 Deng's (DHQD)₂AQN catalyzed DKR of UNCAs [218]



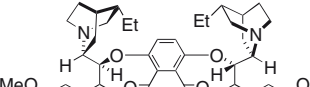
(±)-61a-f

1) (DHQD)₂AQN (20 mol %)
allyl alcohol (1.2 eq)
Et₂O, 4 Å MS

2) Pd(PPh₃)₄ (0.1 eq)
morpholine (10.0 eq)
THF, 23 °C, 10 min



(R)-62a-f



(DHQD)₂AQN

Entry	R	T (°C) ^a	t (h) ^a	(R)-62a-f	
				<i>ee</i> (%)	Yield (%)
1	aPh	23(34)	1(1)	90	91
2	b 4-F-C ₆ H ₄	23	1	90	93
3	c 4-Cl-C ₆ H ₄	23	1	92	92
4	d 4-CF ₃ -C ₆ H ₄	23	1	90	88
5	e 2-Thienyl	−30	2	92	93
6	f 2-Furyl	23(−30)	0.5(1)	89	86

^aValues in parentheses are for reactions using (DHQ)2AQN and give enantiomeric products

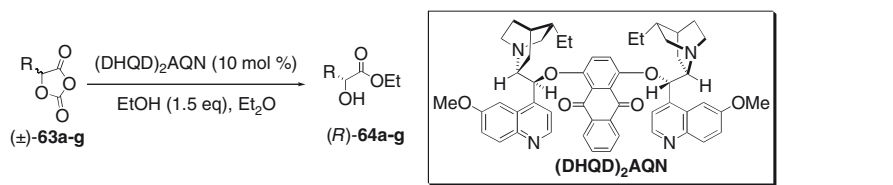
This methodology was also applied to substituted 1,3-dioxolane-2,4-diones which represent potential precursors to enantiomerically enriched α -hydroxy acid derivatives. Hence, Deng found that the alcoholative KR of α -alkyl-1,3-dioxolane-2,4-diones using (DHQD)₂AQN as the catalyst provides chiral α -hydroxy esters with excellent selectivities ($s = 49$ –133) [219]. As for the UNCAs, Deng found that under appropriate conditions 1,3-dioxolane-2,4-diones could also be induced to undergo DKR, sometimes at -78 °C although temperatures up to -20 °C proved optimal for certain substrates. Thus, for a range of α -aryl-1,3-dioxolane-2,4-diones **63a–g**, (DHQD)₂AQN (10 mol%) catalyzed DKR to the corresponding esters **64a–g** with excellent stereoselectivities (91–96% *ee*) and good yields (65–85%) (Table 13) [219].

Procedure for DKR of an α -aryl-1,3-dioxolane-2,4-dione using (DHQD)₂AQN as catalyst: DKR of ($\pm$)-5-phenyl-1,3-dioxolane-2,4-dione [219]

A mixture of 5-phenyl-1,3-dioxolane-2,4-dione (**63a**) (178 mg, 1.0 mmol) and 4 Å MS (100 mg) in anhydrous Et₂O (50 mL) was stirred at room temperature for 15 min, then cooled to -78 °C, after which (DHQD)₂AQN (95%, 90.2 mg, 0.1 mmol) was added to the mixture. The resulting mixture was stirred for a further 5 min and then EtOH (1.5 eq) was added dropwise over 10 min by syringe. The resulting reaction mixture was stirred at -78 °C for 24 h. HCl (1N, 5.0 mL) was added to the reaction dropwise and the resulting mixture was allowed to warm to room temperature. The organic phase was collected, washed with aqueous HCl (1N, 2×5.0 mL) and the aqueous phase was extracted with Et₂O (2×5.0 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated in vacuo. Purification by FC on silica gel (EtOAc/hexanes, 1/4) gave (*R*)-ethyl mandalate (**64a**) as a white solid (128 mg, 71%, 95% *ee* by chiral-HPLC).

The mechanism by which cinchona-based catalyst systems effect such selective ring-opening of anhydrides and related systems has been the subject of extensive

Table 13 Deng's (DHQD)₂AQN catalyzed DKR of 1,3-dioxolane-2,4-diones [219]

					
Entry	R	T (°C)	t (h)	Yield (%)	<i>ee</i> (%)
1	a Ph	-78	24	71	95
2	b 4-Cl-C ₆ H ₄	-78	24	70	96
3	c 4-CF ₃ -C ₆ H ₄	-78	24	85	93
4	d 4- <i>i</i> -Pr-C ₆ H ₄	-20	8	68	91
5	e 1-Nap ^a	-40	14	74	91
6	f 2-Cl-C ₆ H ₄	-60	10	66	62
7	g 2-Me-C ₆ H ₄	-20	4	61	60

^aTHF used as solvent and *n*-PrOH in place of EtOH

debate in the literature, and although a consensus has yet to emerge as to whether nucleophilic or general base catalysis is primarily operational the current weight of evidence seems to support the latter [190].

In line with this mechanistic interpretation, recently Connon [220] and Song [222] have independently described the highly enantioselective ASD of cyclic *meso*-anhydrides using a bifunctional thiourea-based organocatalyst **65** derived from a cinchona alkaloid core. The choice of this catalyst was based on the premise that it might selectively bind and activate the anhydride electrophile by hydrogen bonding to the thiourea moiety and subsequently encourage attack at a single anhydride carbonyl moiety through general-base catalysis mediated by the suitably positioned chiral quinuclidine base (Fig. 15) [221].

Fujimoto has also described an asymmetric benzoylation system that is effective for ASD of cyclic *meso*-1,3- and 1,4-diols and which employs phosphinite derivative of quinidine **66** as the catalyst (Fig. 15) [224, 225].

The development of predictive transition state models for the interpretation of selectivity data pertaining to the use of cinchona alkaloid derivatives in all the processes described above is challenging due to the complex conformational behaviour of these natural scaffolds (for example, it is well known that *O*-acylated quinidines undergo major conformational changes upon protonation) [223]. Consequently, hypotheses regarding the details of chirality transfer in these systems are notably absent.

3.7 Imidazolone-Based Catalysts

Uozumi has explored a series of (2*S*,4*R*)-4-hydroxyproline-derived 2-aryl-6-hydroxy-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolones as potential alternatives to cinchona alkaloid-based catalysts for the alcoholative ASD of *meso*-anhydrides (Fig. 16) [226]. Uozumi screened a small library of catalysts prepared by a four-step, two-pot reaction sequence from 4-hydroxyproline in combination with an aldehyde and an aniline. The most selective member, compound **67**, mediated the methanolytic ASD of *cis*-hexahydrophthalic anhydride in 89% *ee* when employed at the 10 mol% level for 20 h at -25°C in toluene [226].

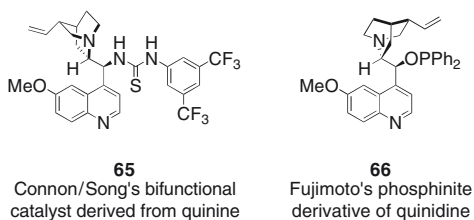


Fig. 15. Connon/Song's and Fujimoto's catalysts for alcoholative ASD of cyclic *meso*-anhydrides and mono benzoylation of *meso*-diols respectively [220–225]

3.8 Piperidine-Based Catalysts

Irie has described the use of an optically active tripodal amine, (2*S*,6*S*)-2,6-bis(*o*-hydroxyphenyl)-1-(2-pyridylmethyl)piperidine (**68**) as a potent catalyst for methanolytic ASD of cyclic *meso*-anhydrides (Fig. 16) [227]. This catalyst was envisaged to adopt a helical conformation thereby providing a highly asymmetric environment for the nucleophilic *tert*-amine lone pair whilst also allowing activation of the anhydride substrate by the phenolic hydroxyl groups. In the event, *ees* up to 81% were obtained for the methanolytic ASD of a cyclic *meso*-anhydride when employed at the 5 mol% level for 20 h at 0 °C in toluene [227].

3.9 Sulfonamide-Based Catalysts

Nagao has disclosed bifunctional chiral sulfonamide **69** as being effective for the *thiol*ytic ASD of *meso*-cyclic anhydrides in up to 98% *ee* when employed at the 5 mol% level for 20 h at room temperature in ether [228]. Catalyst **69** is a 1,2-diamine derivative in which one of the nitrogens presents as an acidic NH group (part of an electron deficient aryl sulfonamide) and the other as a nucleophilic/basic *tert*-amine group with the intention to act synergistically in activation of the substrate carbonyl function and thiol nucleophile respectively (Fig. 16) [228].

4 Alcohol Catalysts

4.1 Trifluoromethyl-*sec*-Alcohol-Based Catalysts

Oxygen-based nucleophiles can also be employed for the catalysis of acyl transfer. For example, pyridine-*N*-oxide derivatives such as 4-DMAP-*N*-oxide have long been known as such catalysts although, interestingly, these catalophores are reportedly particularly efficient at mediating sulfonyl and phosphoryl transfer [229–230].

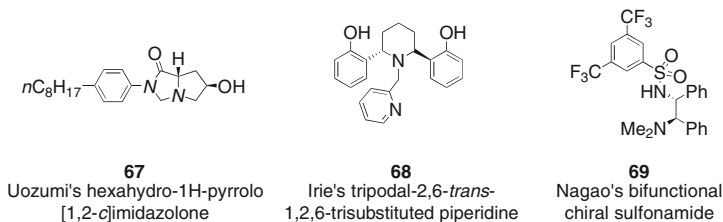
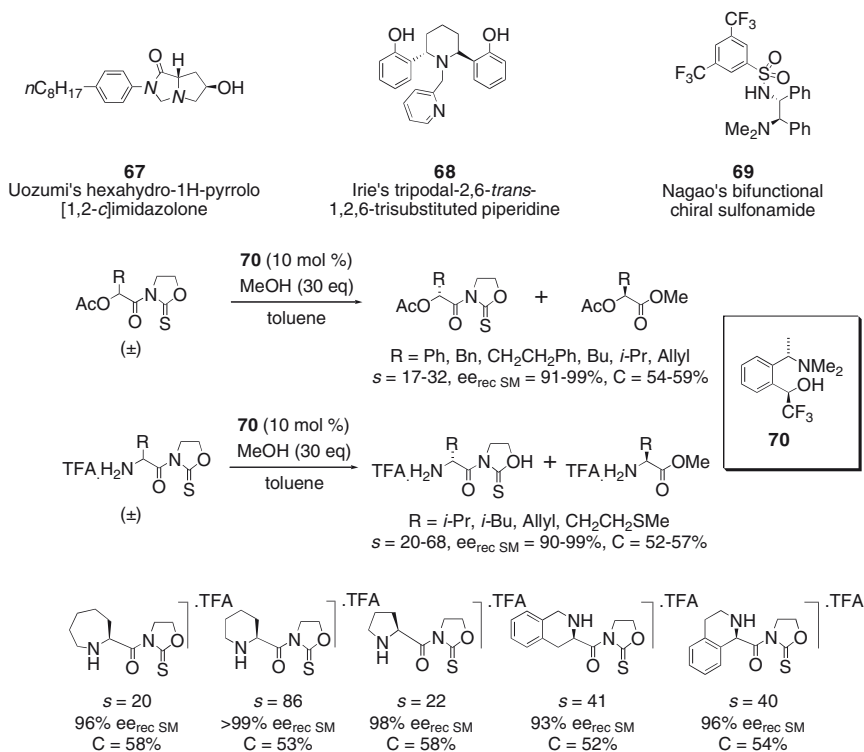


Fig. 16 Uozumi's, Irie's and Nagao's catalysts for alcoholative ASD of cyclic *meso*-anhydrides [226–228]

Sammakia has developed a unique chiral *O*-nucleophilic acyl transfer catalyst **70** and shown that it is effective for the KR of a series of α -hydroxy acid [231] and α -amino acid [232] derivatives. He found that by employing this catalyst at the 10 mol% level in toluene at -26 to 0°C it was possible to resolve α -acetoxy-*N*-acyloxazolidinethiones with *s* values in the range 17–32 and α -(*N*-trifluoroacetyl)-*N*-acyloxazolidinethiones with *s* values in the range 20–86 (Scheme 25) [231, 232].

The stereoselectivity-determining step is believed to involve attack of the hydroxyl group of the catalyst on the active ester of the substrate with concomitant general base catalysis from the proximal nitrogen of the catalyst to form an acyl catalyst intermediate. Attack of methanol on this intermediate, again with base catalysis from the proximal nitrogen provides the ester product and regenerates the catalyst. The trifluoromethyl group is essential to modulate the acidity of the alcohol; the corresponding methyl substituted alcohol is ~ 37 times less active [233]. This KR method is notable for its success with cyclic amino acid derivatives making it nicely complementary to the above described approach of Deng to acyclic amino acids. Sammakia has also shown that the recovered oxazolidinethiones can be used directly in peptide coupling reactions using (*i*-Pr)₂EtN and HOBt.



Scheme 25 Sammakia's chiral alcohol catalyzed KR of α -acetoxy- and α -(*N*-trifluoroacetyl) amino acid-*N*-acyloxazolidinethiones [231, 232]

5. Concluding Remarks

Since the pioneering work of Vedejs and Fu using chiral phosphines and pyrrole derivatives, respectively, a plethora of topologically diverse chiral nucleophilic acylating agents incorporating many different catalytic cores have been developed in laboratories across the globe. As a result, efficient systems have been developed for the acylative KR and ASD of a range of *sec*-alcohols, *meso*-diols, *sec*-amines and *meso*-anhydrides. In some cases, results can be compared favourably with hydrolytic enzymes, usually with the advantage of ready access to enantiomeric catalysts.

However, much progress remains to be made; for example *tert*-alcohols remain formidable substrates as do most classes of amine. Moreover, the development of related chiral nucleophile catalyzed reaction manifolds for asymmetric silylation [234–236], sulfonylation [237] and phosphorylation [238] remains relatively unexplored. For success to be achieved with these and other substrate/reaction classes and for the efficiencies and selectivities of all the types of transformations discussed in this review to be optimised, additional mechanistic insight needs to accrue. Structural detail relating to the nature of the interactions which are decisive in orchestrating chirality transfer between the catalyst and substrate including H-bonding and stacking interactions need to be understood in intimate detail and to this end it is hoped that the focus brought to bear on these transformations in this review may help to galvanise synthetic effort towards this goal.

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Secondary and Primary Amine Catalysts for Iminium Catalysis

John B. Brazier and Nicholas C.O. Tomkinson

Abstract Formation of iminium ions from the condensation of chiral secondary or primary amines with α,β -unsaturated aldehydes or ketones can be used as an effective platform for the acceleration of a wide variety of catalytic asymmetric cycloaddition and conjugate addition reactions. The reversible formation of the active iminium ion species simulates the π -electronics and equilibrium dynamics traditionally associated with Lewis acid activation of α,β -unsaturated carbonyl compounds lowering the energy level of the LUMO associated with the π -system and activating subsequent reaction. Importantly, these iminium ion catalysed processes offer the opportunity to conduct reactions in the presence of both moisture and air greatly adding to the practicality and general applicability of the chemistry described. Proposed catalytic cycles and transition state models for the induction of asymmetry provide reliable and robust predictive tools for the outcome of reactions and high functional group tolerance suggests this class of transformation will have broad application in the arena of synthetic organic chemistry as the area matures. This review describes the rapid expansion of iminium ion catalysis over recent years from its conceptual introduction to the development of a whole new arsenal of highly practical and effective methods with which to approach challenging and fundamental bond construction processes.

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Keywords Aminocatalysis • Conjugate addition • Cycloaddition • Iminium ion • Organocatalysis

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Abbreviations

Alloc	Allyloxycarbonyl
DCA	Dichloroacetic acid
DIPEA	<i>N,N</i> -Diisopropylethylamine
DNBA	2,4-Dinitrobenzoic acid
F-SPE	Fluorous solid phase extraction
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
IMDA	Intramolecular Diels–Alder reaction
LUMO	Lowest unoccupied molecular orbital
Ns	4-Nitrophenylsulfonyl
PMP	4-Methoxyphenyl
TCA	Trichloroacetic acid
TES	Triethylsilyl
TIPBA	2,4,6-Triisopropylbenzenesulfonic acid
TRIP	3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate

1 Basic Principles

1.1 Introduction

At the heart of synthetic chemistry is the drive to develop novel, cleaner, more efficient and selective transformations. To this end there has been a recent explosion of interest in the use of metal-free processes to carry out functional group transformations, due to the potential for academic, industrial, economic and environmental benefit. Of particular note in this area has been the use of small organic molecules to catalyse a number of fundamental reactions that are an integral part of the synthetic organic chemist's toolkit [1]. The broader area of organocatalysis has caught the imagination of the synthetic community over the past decade and development of this fast paced and exciting field of contemporary research has been astounding.

One of the most prolific and successful areas of research within the subject of organocatalysis has been in the use of secondary and primary amines to accelerate transformations via iminium ion and enamine catalysis [2]. This review will focus on the use of iminium ion intermediates as a simple and effective method to activate α,β -unsaturated aldehydes and ketones towards cycloaddition and conjugate addition processes. First, reactions that can be accelerated using iminium ion intermediates generated from chiral secondary and primary amines are discussed. The use of secondary and primary amines in conjunction with chiral anions is then described. Exploitation of the methodology within synthesis is explored, highlighting some of the real advantages made available to the synthetic chemist by this technology. Finally, the mechanistic, structural and theoretical contributions to the field that aid in the understanding of mechanism, origin of asymmetric induction and reactivity are presented.

1.2 Iminium Ion Catalysis: The Concept

The broad spectrum of reactivity for α,β -unsaturated carbonyl compounds has bestowed them a central role within synthesis. Depending upon the reaction conditions adopted they can undergo nucleophilic addition reactions in a 1,2- or 1,4-manner as well as cycloadditions across either of the π -bonds. Each of these processes can introduce new chiral centres into the molecule and significantly increase complexity, highlighting their importance. Acceleration of these reactions is traditionally sought about with a Lewis acid which complexes to the carbonyl group, lowering the energy of the LUMO associated with the π -system, thus increasing reactivity. The fundamental concept of iminium ion catalysis, reported in a seminal paper by MacMillan in 2000 [3], involves the reversible condensation of a secondary amine salt **2** with an α,β -unsaturated aldehyde **1** to give the corresponding iminium ion **3** (Fig. 1). Formation of this iminium ion simulates the π -electronics and equilibrium dynamics traditionally associated with Lewis acid activation lowering the energy of the LUMO of the π -system and promoting subsequent reaction. Significantly, along with formation of the imin-

ium ion this equilibrium also results in a molecule of water **4**. Consequently, unlike many Lewis acid catalysed processes the reactions are inherently tolerant of both moisture and air which has major ramifications for their simplicity and practicality. The ability to generate C–C, C–O, C–N, C–S, C–P and C–H bonds (the daily challenges of the synthetic chemist) under such mild conditions in high yield and optical purity explains the exponential growth of organocatalysis in such a short space of time.

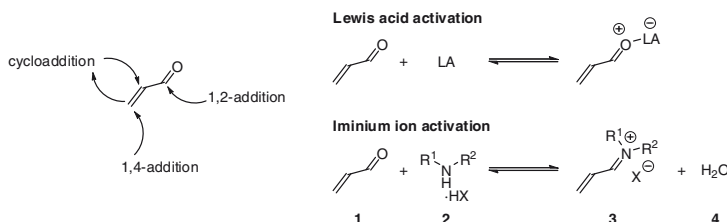


Fig. 1 The concept of iminium ion activation

The proposed catalytic cycles for the iminium ion catalysed Diels–Alder cycloaddition and conjugate addition reactions are outlined in Fig. 2. The general principles of these catalytic cycles can be used to understand each of the reactions described within this review which all follow a similar mechanistic pathway. The catalytic cycle consists of three principle steps:

Step 1: Iminium ion formation

Step 2: Key bond forming reaction (i.e. cycloaddition or conjugate addition)

Step 3: Iminium ion hydrolysis

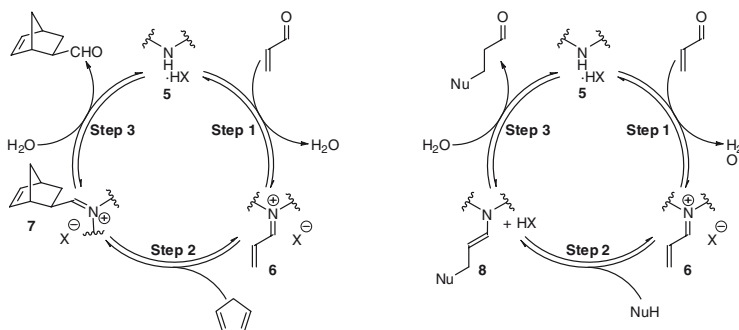


Fig. 2 Catalytic cycles for the iminium ion activated Diels–Alder and conjugate addition reactions

Along with the secondary (or primary) amine **5** an equimolar amount of a co-acid HX is also used in these reactions. This proton source facilitates iminium ion formation and hydrolysis and in most cases is essential for catalytic activity. Formation of the active iminium ion **6** (Step 1) is an equilibrium, generating a molecule of water which forms an integral part of the catalytic cycle. On formation, the iminium ion can undergo the key bond forming reaction (Step 2). Cycloaddition results in an iminium ion intermediate (**7**) and conjugate addition results in an enamine (**8**). These intermediates (**7** and **8**) are then hydrolysed with a molecule of water to give the observed product and regenerate active amine **5** turning over the catalytic cycle (Step 3).

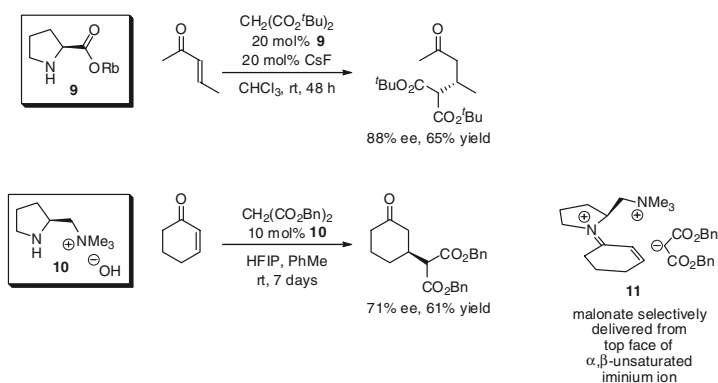
1.3 Perspective and History

Given the importance of the field it is not surprising there have been a significant number of reviews on organocatalysis. Several reviews [4–10] and highlights [2, 11–13] on the general area of organocatalysis have been published which are relevant to the current discussion. More specialised reports on organocatalytic multi-component [14], domino [15], tandem [16], conjugate addition [17–19] and Morita–Baylis–Hillman reactions [20] also contain some details of iminium ion catalysed processes. Polymer-supported immobilisation of many organic catalysts has also been comprehensively reviewed [21]. An excellent review by de Figueiredo and Christmann elegantly places the significance of organocatalysis within the field of synthesis by showcasing the many uses of the reactions developed in the preparation of drugs and bioactive natural products [22]. Specifically related to the current discussion, MacMillan has written an outstanding and personal review on the advent and development of iminium ion activation which clearly sets out the scope and future challenges in the area [23]. Most recently, a comprehensive review of the area has been provided by Pihko including many insightful historical perspectives [24].

The use of iminium ion activation in cycloaddition reactions has some precedent with synthetic and biogenetic examples. Baum showed that acetylinic iminium compounds underwent facile [4+2] and [3+2] cycloaddition reactions and describes them to be “*among the best partners within these reactions*” [25]. Baldwin has also proposed an iminium ion accelerated [4+2] cycloaddition in the biosynthesis of the *Galbulimina* type I alkaloids, highlighting the facile nature of these stoichiometric reactions [26–28].

In a series of reports between 1991 and 1997 Yamaguchi showed that rubidium salts of L-proline (**9**) catalysed the conjugate addition of both nitroalkanes [29, 30] and malonates [31–33] to prochiral α,β -unsaturated carbonyl compounds in up to 88% ee (Scheme 1). Rationalisation of the selectivities observed involved initial formation of an iminium ion between the secondary amine of the catalyst and the α,β -unsaturated carbonyl substrate. Subsequent deprotonation of the nucleophile by the carboxylate and selective delivery using ion pair

control gave the observed products after hydrolysis of the resulting enamine. A truly organocatalytic approach using a similar catalyst scaffold and transition state model was disclosed by Karwara and Taguchi who reported that L-proline derived ammonium salt **10** (10 mol%) catalysed the conjugate addition of malonates to both cyclic and acyclic α,β -unsaturated ketones in up to 71% ee [34]. The transition state model proposed within this work suggests the malonate is selectively delivered from one face of the iminium ion **11** leading to enantioenriched products. Unfortunately, the scope of this process was not explored to any significant extent and no subsequent reports have been disclosed; however, the results certainly stand as a tantalising prelude to more recent discoveries.



Scheme 1 Iminium ion catalysed conjugate addition using proline derivatives

2 Secondary Amines as Catalysts

2.1 Cycloaddition

2.1.1 [4+2] Cycloaddition

Since its original discovery in 1928 [35] the Diels–Alder [4+2] cycloaddition has evolved to become an integral transformation that is routinely exploited in the art of total synthesis [36]. Development of asymmetric variants of this reaction has received great attention and literature within the area is vast [37–40] providing many of the guiding principles which are now adopted in catalyst design. Given the importance and history of this reaction it is not surprising that it was also used as a learning-ground for the development of iminium ion catalysis.

In the initial report by MacMillan, use of the imidazolidinonium salt **12**·HCl to generate iminium ion intermediates identified a new catalytic strategy for the activation of α,β -unsaturated carbonyl compounds towards cycloaddition [3]. Inherent

to the enantiofacial discrimination of substrates using this catalyst is the formation of a single iminium ion upon condensation with an aldehyde. Of the two possible iminium ions (**13** and **14**) from reaction of **12** with cinnamaldehyde, only **13** is observed due to steric interactions between the geminal dimethyl group of the catalyst and the α -carbon of the substrate disfavoured **14** (Fig. 3). The benzyl arm of the catalyst blocks one diastereoface of the activated substrate and thus renders subsequent transformations asymmetric. These simple, rational and creative factors in catalyst design make understanding this chemistry extremely accessible heightening its great appeal.

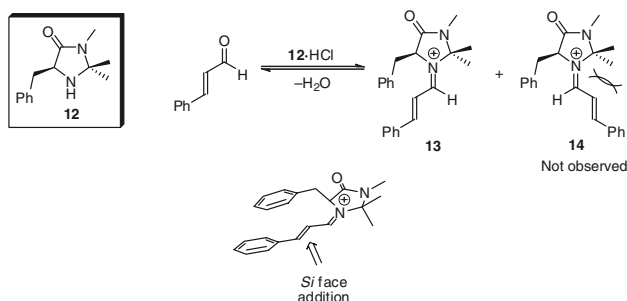
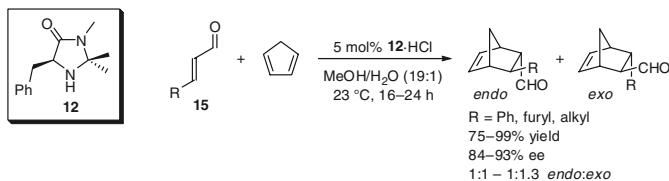


Fig. 3 Mode of action for imidazolidinone catalyst **12**

The imidazolidinonium salt **12**·HCl was shown to be an excellent catalyst for the Diels–Alder reaction of α,β -unsaturated aldehydes **15** (Scheme 2) [3]. Using just 5 mol% of the catalyst at room temperature in a methanol/water mixture (19:1), adducts were obtained in excellent yield (75–99%) and enantiomeric excess (84–93%). The simplicity of these transformations, operating at room temperature in the presence of moisture and air without the need for rigorous purification of solvents and reagents, makes these procedures highly practical and opened up a new area for further research.

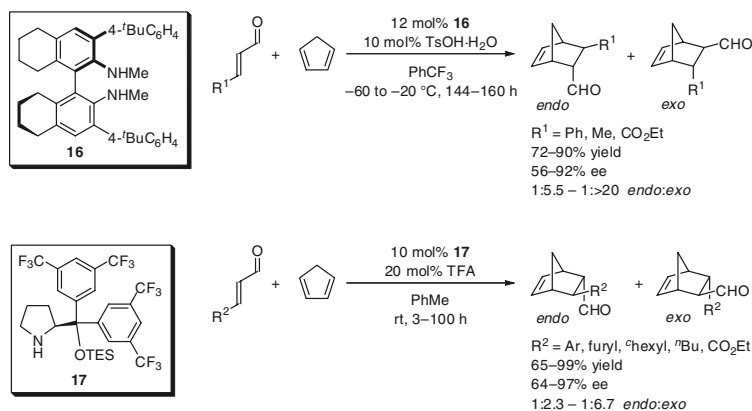


Scheme 2 [4+2] Cycloaddition of α,β -unsaturated aldehydes using imidazolidinone **12**

The absolute stereochemistry of the products was shown to be consistent with a transition state model in which the benzyl arm of the catalyst blocked the *Re*-face of the dienophile from approach of the diene (Fig. 3). An attractive face–face π – π

interaction between the catalyst and substrate was proposed to stabilise this transition state. Other cyclic and acyclic dienes were also shown to be effective in the Diels–Alder reaction of acrolein and crotonaldehyde catalysed by **12** (72–90% yield; 85–96% ee).

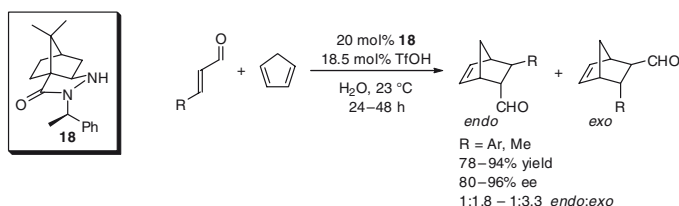
The major deficiency in the use of **12** was the low levels of diastereoselectivity observed within these transformations; typical *endo:exo* ratios being in the range from 1:1 to 1:1.3. Improvements in these levels have been achieved using biaryl catalyst **16** and diarylprolinol silyl ether **17** (Scheme 3). Using **16** (12 mol%) as the catalyst in the Diels–Alder reaction between cyclopentadiene and cinnamaldehyde allows impressive *endo:exo* selectivities of up to 1:13 to be achieved (92% ee *exo*-adduct) [41, 42]. It should be noted that to achieve these levels of selectivity, reactions must be performed at $-20\text{ }^{\circ}\text{C}$ for 160 h in trifluoromethyl benzene, adding an additional 4 equivalents of the diene through the course of the reaction, which detracts from the practicality of the procedure. Use of **17** is significantly more convenient, the reactions progressing at room temperature with all but the most electron rich substrates being complete in less than 30 h showing *endo:exo* ratios up to 1:6.7 [43]. The *exo*-selectivity observed in these reactions is significant, in that it complements the *endo*-selectivity observed in Lewis acid catalysed Diels–Alder reactions of β -substituted unsaturated aldehydes. The precise origin of this selectivity is unknown, but an understanding may allow further enhancement.



Scheme 3 Improved *exo*-selectivity using **16** and **17**

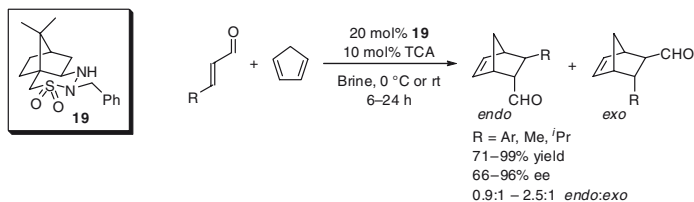
Based on the observation that the majority of secondary amines shown to be effective in iminium ion catalysed transformations were cyclic five-membered nitrogen containing heterocycles, it was postulated that a highly nucleophilic nitrogen was central to catalytic activity [44]. This proposal was reinforced by the discovery that secondary amines with α -heteroatoms (α -effect nucleophiles) provided an effective platform for the acceleration of iminium ion catalysed

transformations [44, 45]. This concept was elegantly applied by Ogilvie to a series of conformationally rigid hydrazide catalysts which were shown to accelerate the Diels–Alder cycloaddition using iminium ion activation. Although catalytic activity of these systems was low compared with that of the imidazolidinone catalysts, reactions proceeded at room temperature using water as the solvent [46, 47] providing the adducts with excellent levels of asymmetric induction. For example, hydrazide **18** was shown to be effective at catalysing the reaction between cyclopentadiene and a series of β -substituted aldehydes (78–94% yield; 80–96% ee) (Scheme 4). Ogilvie has also used these hydrazide catalysts to perform a series of qualitative kinetic and mechanistic studies which suggest that iminium ion formation and hydrolysis are both rapid and it is the Diels–Alder cycloaddition within the catalytic cycle which is the overall rate-determining step (see Sect. 6 for further discussion) [48]. This should prove to be a crucial factor in the design of more active catalysts for these transformations.



Scheme 4 Ogilvie hydrazide catalyst

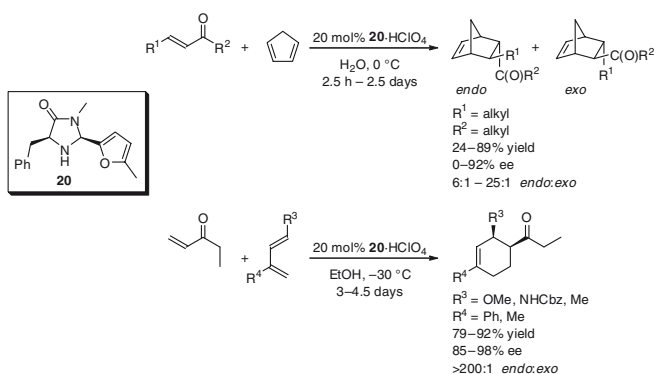
Lee has shown that the structurally related sulfonyl hydrazine **19** provides a more active catalyst scaffold. Reactions proceed to completion in brine at 0 °C–rt in under 24 h, with respectable yields and enantioselectivities in many cases (71–99% yield; 66–86% ee for *endo*; 83–96% ee for *exo*) however, diastereoselectivities were once again poor (0.9:1–2.5:1 *endo:exo*) (Scheme 5) [49].



Scheme 5 Lee sulfonyl hydrazine catalyst

Modifications to the architecture of the imidazolidinone catalyst provided the furyl derivative (**20**) which proved to be a powerful catalyst for the catalytic asymmetric Diels–Alder cycloaddition of simple α,β -unsaturated ketones [50]. Although

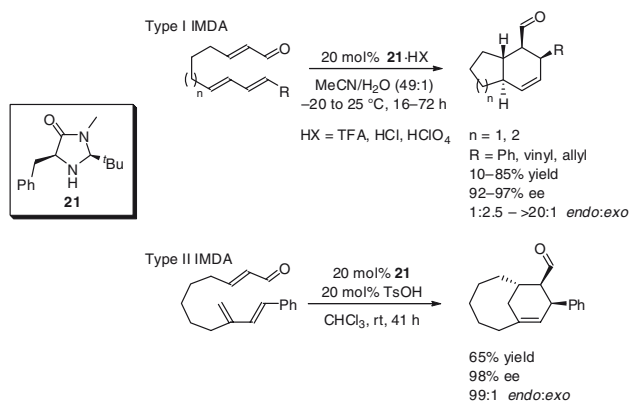
the scope of the α,β -unsaturated ketone was limited, the chemical challenge of selectively forming a single tetra-substituted iminium ion is significant and this report provides excellent insight into the key-problems faced in the design of catalysts to recognise these substrates. Using 20 mol% of catalyst **20** as its perchlorate salt, high levels of diastereoselectivity and enantioselectivity were achieved with a series of diene and dienophile substrates (Scheme 6). It is of note that, in contrast to the reactions of α,β -unsaturated aldehydes, the system favours formation of the *endo* products. The system was also found to be efficient in the Diels–Alder cycloaddition of cyclopentadiene with unsubstituted cyclic enones, although room for improvement in the enantioselectivity still exists for the dienophiles cyclopentenone (48% ee) and cyclohexenone (63% ee).



Scheme 6 Diels–Alder cycloaddition of α,β -unsaturated ketones

Application to both Type I and Type II intramolecular Diels–Alder cycloaddition has also met with appreciable success, the most efficient catalyst for these reactions being imidazolidinone **21** (Scheme 7) [51, 52]. The power of the intramolecular Diels–Alder reaction to produce complex carbocyclic ring structures from achiral precursors has frequently been exploited in synthesis to prepare a number of natural products via biomimetic routes. It is likely that the ability to accelerate these reactions using iminium ion catalysis will see significant application in the future.

Although the imidazolidinone catalysts used within these transformations are simple, cheap, readily accessible and in some cases recyclable using acid/base extraction, considerable efforts have been made to examine alternative methods to separate and recycle the catalyst with good success. Examination of the structure of imidazolidinone **22** shows two convenient points for the introduction of a polymer or fluorous support, R^1 and R^2 , both of which have been examined (Fig. 4). Curran has shown that identical reactivity, diastereoselectivity and enantioselectivity can be obtained using a fluorous tag (**23**) [53]. The catalyst can easily be recovered and recycled using F-SPE with excellent yield, purity and levels of activity. Polymer- (**24**) and silica-supported (**25**) imidazolidinones reported by Pihko [54] (R^1 substitution)



Scheme 7 Imidazolidinone catalysed Type I and Type II IMDA reactions

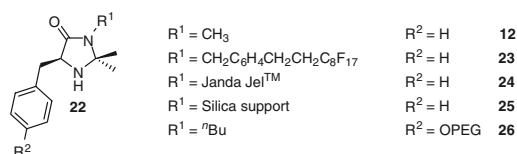


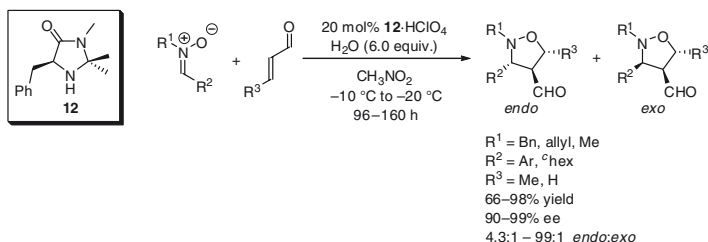
Fig. 4 Supported imidazolidinones

and Benaglia (**26**) [55] (R² substitution) are also equally efficient and can be recovered and reused by simple filtration. The use of siliceous and polymer coated meso-cellular foams have also been investigated [56] (R² substitution). Ionic liquids are also an effective means to recover and recycle the parent imidazolidinone catalyst [57].

2.1.2 [3+2] Cycloaddition

The [3+2] cycloaddition strategy provides an effective method to access valuable intermediates for the construction of biologically important alkaloids, amino acids, amino carbohydrates and β -lactams [58–62]. The reaction involves the concerted pericyclic addition of a dipole and a dipolarophile and considerable efforts have been made to render these reactions asymmetric using Lewis acid catalysis and chiral auxiliaries [63].

The first report of an enantioselective organocatalytic [3+2] cycloaddition between nitrones and α,β -unsaturated aldehydes was reported by MacMillan and co-workers who showed that iminium ion activation was effective in this reaction (Scheme 8) [64]. After a survey of seven catalysts the imidazolidinonium salt **12**·HClO₄ emerged as the most efficient system. The reactions were conducted in a mixture of nitromethane and water at –20 °C in the presence of 20 mol% catalyst



Scheme 8 [3+2] Cycloaddition using the MacMillan imidazolidinone **12**

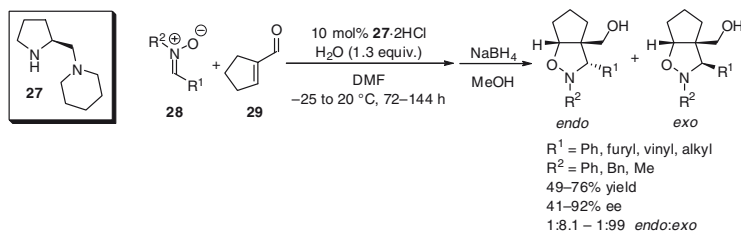
giving the products in excellent yield (66–98%) with ee (90–99%). The transformations proved to be slow with reaction times varying between 96 and 160 h to deliver the products in the yields observed. In an analogous fashion to that described for the [4+2] cycloaddition, the transition state model to explain the sense of asymmetric induction involved blocking of the *Re*-face of the α,β -unsaturated carbonyl group by the benzyl arm of the catalyst (c.f. Fig. 3).

In a similar manner to the [4+2] cycloaddition, Benaglia has shown that a polyethylene glycol supported imidazolidinone leads to similar levels of enantioselectivity in the [3+2] cycloaddition of nitrones with α,β -unsaturated aldehydes when compared to a non-supported catalyst, however, significantly lower chemical yields were obtained, which deteriorated upon catalyst recycling [65].

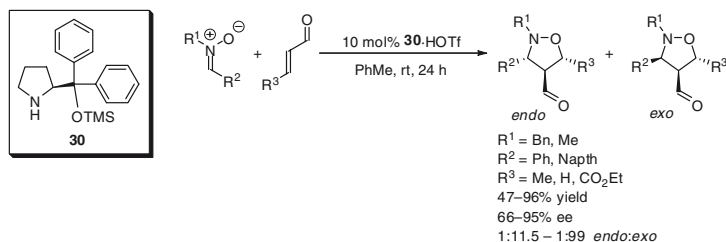
In addition, Ogilvie has shown his hydrazide catalyst **18** (and derivatives) to be effective for the [3+2] cycloaddition reaction [66].

Karlson and Högborg surveyed an interesting series of structurally diverse chiral secondary amines in the [3+2] cycloaddition of nitrones **28** with 1-cycloalkene-1-carboxaldehyde **29**, during which proline derivative **27** emerged as the best catalyst (Scheme 9) [67, 68]. The reaction selectively delivered the *exo*-product with ees observed in the range 41–92%. Although reactions were once again slow (72–144 h), only 1 equivalent of each of the reaction partners was used together with 10 mol% of the catalyst **27**.

Prolinol derived catalyst **30** has also been used in the [3+2] cycloaddition of nitrones with α,β -unsaturated aldehydes (Scheme 10) [69]. Importantly, the reactions proceed at room temperature in just 24 h, showing excellent levels of catalyst activity, with uniformly high *endo:exo* ratios (11.5:1–99:1) and enantioselectivity



Scheme 9 [3+2] Cycloaddition of nitrones with 1-cyclopentene-1-carboxaldehyde

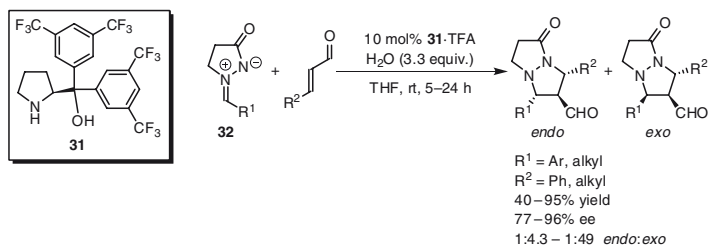


Scheme 10 [3+2] Cycloaddition using the diarylprolinol **30**

for the *endo*-adduct (66–95% ee). Examination of catalyst **30**·HOTf in a reaction using cyclopentene carboxaldehyde **29** as the dipolarophile showed lower levels of activity but an interesting preference for the *endo*-adduct, providing a complementary strategy to the work of Karlson and Högberg [67, 68]. Within this report it was also disclosed that, of the six secondary amines examined, MacMillan imidazolidinone **21** proved to be a significantly more efficient catalyst for the [3+2] cycloaddition of *N*-benzylidenebenzylamine *N*-oxide with crotonaldehyde (20 mol% catalyst, $\text{CH}_2\text{Cl}_2/\text{PrOH}$ (85:15), 4 °C, 12 h, 98:2 *endo:exo*, 97% ee); however, the scope of this catalyst has yet to be described in the primary literature.

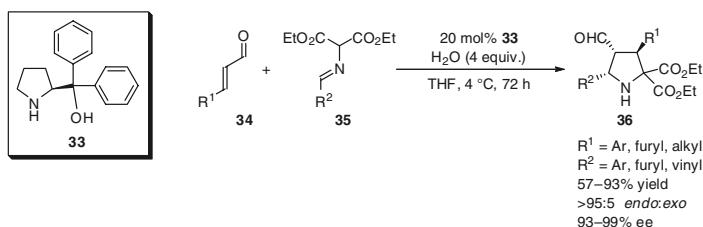
The [3+2] cycloaddition has also been shown to be effective in the reaction of azomethine imines **32** with α,β -unsaturated aldehydes by Chen and co-workers [70]. A survey of seven catalysts revealed some interesting trends, with the diarylprolinol derivative **31** giving the highest yields and selectivities (40–95% yield; *endo:exo* 1:4.3–1:49; 77–96% ee for *exo*) with short reaction times (5–24 h) and low catalyst loading (10 mol%) (Scheme 11). The reaction was particularly sensitive to the amount of water present in the reaction medium and the choice of co-acid. This phenomenon is a reoccurring theme in many of the publications in the area of iminium ion catalysis and, as yet, no general explanation has been proposed to account for these observations.

A final class of dipole shown to be effective in iminium ion catalysed [3+2] cycloadditions are azomethine ylides derived from **35** [71] (Scheme 12). Vicario showed that 20 mol% of diarylprolinol **33** catalysed the cycloaddition between α,β -unsaturated aldehydes **34** and imines **35** (THF, 4 °C, 72 h) to give the densely



Scheme 11 [3+2] Cycloaddition of azomethine imines with α,β -unsaturated aldehydes

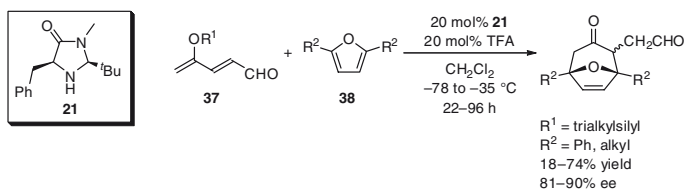
functionalised pyrrolidine skeleton **36** with excellent yield and selectivity (57–93% yield, >19:1 *endo:exo*; 93–99% ee). Addition of water (4 equivalents) was found to significantly accelerate the reaction, and the presence of a free hydroxyl group within the catalyst structure was essential for the high selectivities observed. An understanding of these intriguing observations should pave the way for further development of this reaction.



Scheme 12 [3+2] Cycloaddition of azomethine ylides with α,β -unsaturated aldehydes

2.1.3 [4+3] Cycloaddition

In comparison to the preceding classes of cycloaddition, the [4+3] process has received far less attention, despite representing a powerful strategy with which to access seven-membered rings. Harmata showed that imidazolidinone **21** could be used to catalyse the reaction of substituted furans **38** and silyloxypentadienals **37** with high levels of enantioselectivity (Scheme 13) [72]. These high levels of selectivity were not maintained for unsubstituted furans and much opportunity remains to further develop this as a robust synthetic strategy.

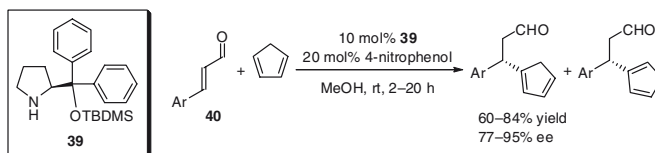


Scheme 13 [4+3] Cycloaddition using the imidazolidinone **21**

2.1.4 Ene Reaction

An unexpected and potentially useful mode of reactivity was observed in the reaction of cinnamaldehyde and cyclopentadiene catalysed by diarylprolinol silyl ether **39** [73]. Rather than observing a Diels–Alder adduct, the products resulting from an ene reaction were isolated in excellent yield. The transformation was found to be general for a series of β -aryl acroleins (**40**) with routinely excellent levels of

enantioselectivity. The reactions proceeded most efficiently when 4-nitrophenol was used as the co-catalyst (Scheme 14). These findings are in marked contrast to those reported by the same authors for the related diarylprolinol silyl ether **17** (Scheme 3) [43], showing that subtle changes in the structure of the catalyst can lead to marked differences in the reaction outcome, suggesting that other significant and interesting nuances in reactivity remain to be discovered.



Scheme 14 Ene reaction of cyclopentadiene and β -aryl acroleins

2.2 Conjugate Addition

The conjugate addition reaction involves the attack of nucleophiles to electron deficient double and triple bonds. The reaction leads to the formation of one, two or even three new stereogenic centres and so considerable efforts have been made to develop asymmetric methods, particularly under the influence of an external chiral ligand or chiral catalyst. Transition metal catalysed methods have been developed for the addition of carbon-, nitrogen-, oxygen-, sulfur- and hydride based nucleophiles and these areas are well documented [74–81]. Given the propensity of α,β -unsaturated aldehydes and ketones to undergo conjugate addition processes with a broad range of nucleophiles a number of methods have also been developed for the addition of nucleophiles via iminium ion activation. These processes follow similar principles to those described in the cycloaddition section, leading to a series of powerful new methods with which to perform these important reactions. Recent advances in organocatalytic conjugate addition reactions using many different methods of activation have recently been reviewed [17–19].

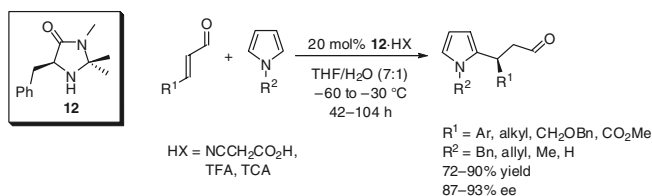
2.2.1 C–C Bond Formation: Aromatic and Vinylic Alkylations

Formation of C–C bonds remains the ultimate challenge to the synthetic chemist. The employment of new synthetic methods in complex target synthesis can be frustrated by a lack of functional group tolerance and substrate specificity. These problems can be somewhat alleviated within conjugate addition reactions by the use of secondary amine catalysts where a number of important and highly selective methods have been developed. Two principle classes of nucleophile have been shown to be effective in the iminium ion activated conjugate addition of carbon nucleophiles to α,β -unsaturated carbonyl systems: aryl, heteroaromatic and vinyl

nucleophiles, which undergo Friedel–Crafts type alkylation; and C–H acids such as 1,3-dicarbonyl compounds and nitroalkanes. Conjugate additions of this type of nucleophile have emerged as reliable methods to form new C–C bonds in an efficient and highly enantioselective manner which is exemplified by the numerous applications of this synthetic strategy in target synthesis (Sect. 5).

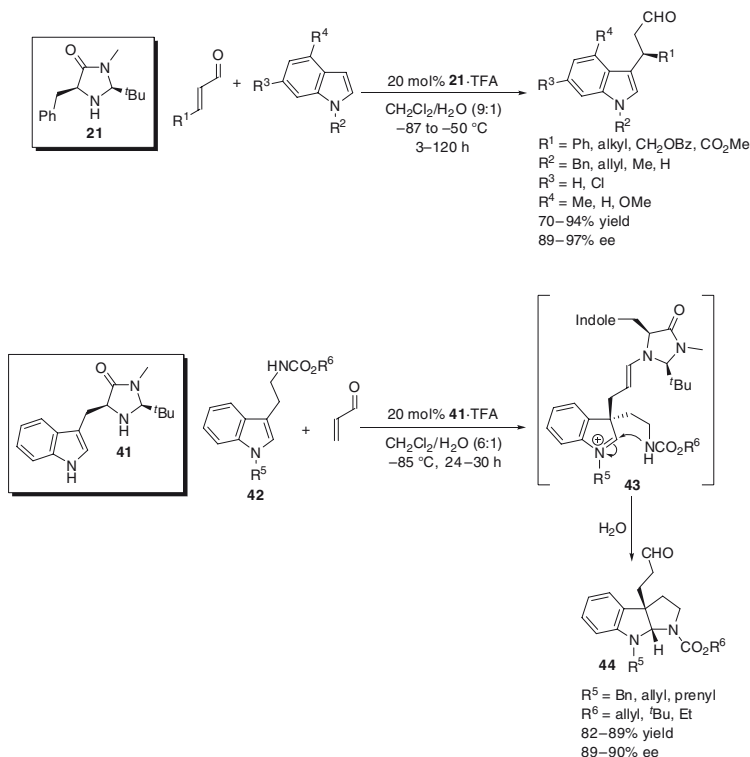
In a series of important papers, MacMillan described the alkylation of electron rich aromatic and heteroaromatic nucleophiles with α,β -unsaturated aldehydes, using catalysts based upon the imidazolidinone scaffold, further establishing the concept and utility of iminium ion activation. In line with the cycloaddition processes described above, the sense of asymmetric induction of these reactions can be rationalised through selective (*E*)-iminium ion formation between the catalyst and the α,β -unsaturated aldehyde substrate, with the benzyl arm of the catalyst blocking one diastereoface of the reactive π -system towards nucleophilic attack (Fig. 3).

The initial report within this area described the regiospecific alkylation of pyrroles using imidazolidinone **12** (20 mol%) as the catalyst [82]. A mixture of THF and water provided optimal reaction conditions, but low temperatures ($-60\text{ }^{\circ}\text{C}$ to $-30\text{ }^{\circ}\text{C}$) were required to ensure the chemospecificity of the reaction. The functional group tolerance at the β -position of the substrate and *N*-substitution on the pyrrole nucleophile was explored (Scheme 15). It was noticed that subtle changes in the nature of the co-acid altered selectivities and this had to be modified depending on the substrates adopted.



Scheme 15 Conjugate addition of pyrrole nucleophiles using imidazolidinone **12**

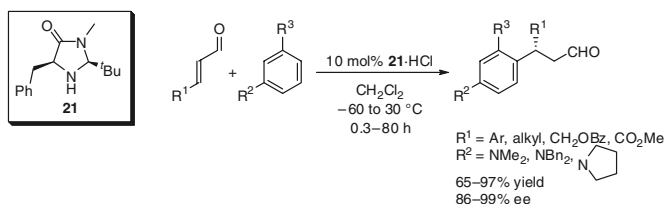
It was subsequently found that this strategy was also applicable to indole nucleophiles, which reacted regiospecifically through the 3-position. Use of the pivaldehyde derived imidazolidinonium salt, **21**·TFA provided the highest rate increases, and a series of conjugate additions to α,β -unsaturated aldehydes provided the products in excellent yield (70–94%) with enantiomeric excess (89–97%) (Scheme 16) [83]. In an interesting extension to this work, MacMillan found that using 3-substituted indoles as the nucleophile (e.g. **42**) allowed intramolecular trapping of the intermediate iminium species **43** by either nitrogen or oxygen nucleophiles, thus providing a convergent cascade process for the preparation of architecturally complex heterocyclic structures. For example, reaction of a series of tryptamine derived indoles (**42**) with acrolein catalysed by imidazolidinone **41** directly gave pyrroloindolines **44** in one step with excellent levels of absolute stereocontrol [84]. Within the report this method was further exemplified by the preparation of the



Scheme 16 Imidazolidinone catalysed alkylation of indoles

marine natural product (–)-flustramine B. Recently, Xiao has shown that catalyst **21** can be applied to an intramolecular ring closing alkylation of indole tethered α,β -unsaturated aldehydes [85].

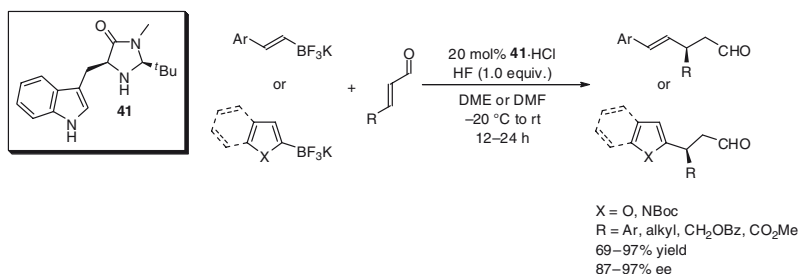
Addition of electron rich aromatic rings provides a particularly useful addition to this portfolio of alkylative processes (Scheme 17) [86]. The presence of amine directing groups on the aromatic nucleophile was found to be essential for the successful outcome of these reactions. This directing group could be removed after the conjugate addition step through an *N*-alkylation/reduction sequence. The most efficient couplings were between electron deficient α,β -unsaturated aldehydes and



Scheme 17 Conjugate addition of electron rich benzenes to α,β -unsaturated aldehydes

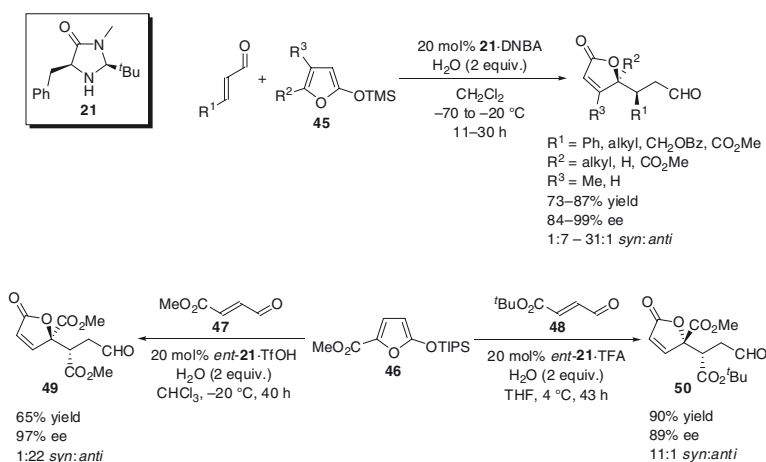
non-sterically demanding aromatics. In these cases where the donor and acceptor were matched, catalyst loadings could be reduced down to just 1 mol% (40 h) without erosion of either yield (87%) or ee (88%).

A major limitation of these alkylation reactions has been the regioselectivity and/or need for directing groups of the nucleophile. MacMillan has overcome this and expanded the scope of the reaction to include alkene nucleophiles by using trifluoroborate salts (Scheme 18) [87]. This approach enables alkylation of the 2-position of indoles, complementing the 3-selective alkylation shown in Scheme 16. One equivalent of hydrogen fluoride was found to be necessary in the reaction in order to sequester the boron trifluoride generated.



Scheme 18 Conjugate addition of trifluoroborate activated π -nucleophiles

As a further example of the addition of electron rich heteroaromatics to electron deficient alkenes, MacMillan has shown that γ -butenolides can be prepared in one-step by the addition of silyloxyfurans (**45**) to α,β -unsaturated aldehydes (Scheme 19) [88]. Reactions were tolerant to substitution at the 4- and 5-positions of the furan



Scheme 19 Organocatalytic preparation of γ -butenolides

ring **45** as well as at the β -position of the enal and proceeded with good levels of relative and absolute stereocontrol (*syn:anti* 1:7–31:1; 84–99% ee). Depending upon the steric bulk at the β -position of the enal substrate and the co-acid adopted, the diastereoselectivity of the conjugate addition could be altered, the reactions still proceeding with excellent ees. For example, addition of silyloxyfuran **46** to either enal **47** or **48** catalysed by an imidazolidinonium salt of *ent*-**20** gave *anti*-**49** (97% ee) and *syn*-**50** (89% ee) products respectively. The later was readily converted into the fermentation product spiculisporic acid.

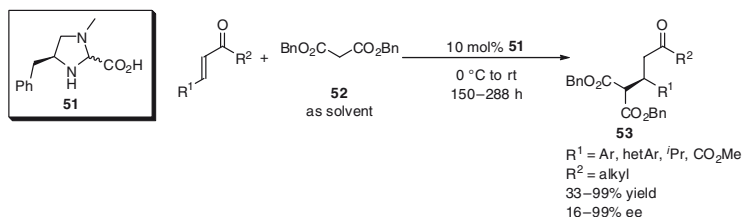
Once again, a notable advantage provided by the alkylations described within this section is the reactions are tolerant to air and proceed in wet solvents. This offers significant operational simplicity over organometallic alternatives. Additionally, each of the catalysts described is available in two synthetic steps, increasing the accessibility of this chemistry. Expansion of the substrate scope with respect to the enal coupling partner would further improve the utility of these reactions.

2.2.2 C–C Bond Formation: C–H Acids

As previously noted (Scheme 1), prior to the explosion of interest in iminium ion catalysis as a platform for the activation of α,β -unsaturated carbonyl compounds in 2000, Yamaguchi [29–33] and Taguchi [34] showed that proline derived bi-functional catalysts could provide an effective platform for the ion-pair controlled conjugate addition of malonates and nitroalkanes to α,β -unsaturated ketones with good levels of stereocontrol.

The majority of recent contributions for the conjugate addition of C–H acids to α,β -unsaturated carbonyl compounds catalysed through iminium ion intermediates have come from the laboratories of Jørgensen. The ease with which 1,3-dicarbonyl compounds and nitroalkanes can be deprotonated, together with the soft nature of the nucleophile mean this is a particularly facile reaction which conveniently leads to useful precursors for further synthetic manipulation.

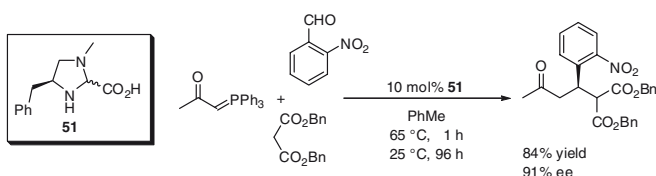
The addition of malonates to α,β -unsaturated ketones provides a simple and rapid entry to δ -ketoesters and tetrahydroquinolines. After surveying a series of potential donors and acceptors it was found that the addition of dibenzyl malonate (**52**) to α,β -unsaturated ketones catalysed by imidazolidine **51** gave the products (**53**) with exceptional yields and levels of enantioselectivity [89]. A thorough examination of the scope and limitations of the process showed a variety of substitution on the acceptor α,β -unsaturated ketone was tolerated apart from steric bulk around the reactive carbonyl centre (Scheme 20). In order to achieve the results reported, reactions were performed using the nucleophile as the solvent. Despite this excess of dibenzyl malonate the reactions were slow (150–288 h) showing the challenging nature of these substrates. In line with the imidazolidinone catalysts described above, selectivities could be explained through selective (*E*)-iminium ion formation, with the benzyl arm of the catalyst blocking the top face, forcing the nucleophile to approach from the *Si*-face. Catalyst **51** was prepared in three steps from phenyl alanine [90] as a mixture of diastereoisomers and was used as this mixture within the transformations described.



Scheme 20 Conjugate addition of dibenzyl malonate to α , β -unsaturated ketones

Application of this work to a domino process using **51** involves Michael addition of β -ketoesters [91], β -diketones or β -ketosulfones [92] to α , β -unsaturated ketones followed by an intramolecular aldol reaction provides highly functionalised cyclohexanone building blocks with up to four contiguous chiral centres. Gryko has also reported examples of this domino Michael/intramolecular aldol reaction in the coupling of 1,3-diketones and methyl vinyl ketone using L-proline as catalyst [93].

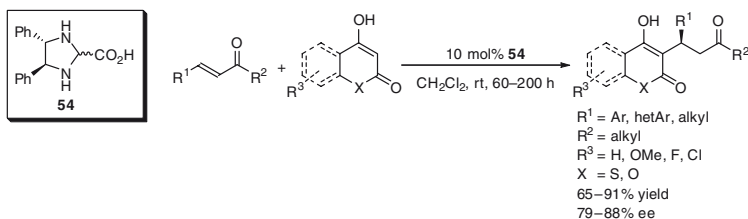
Barbas developed this procedure further by introducing an asymmetric three-component Michael reaction that should be applicable to many other conjugate addition reactions. He used a Wittig olefination to prepare, in situ, an α , β -unsaturated ketone that subsequently underwent a conjugate addition with malonates (Scheme 21) [94]. The rate of the conjugate addition process was observed to be considerably faster than the analogous reaction reported by Jørgensen which was attributed to the presence of triphenylphosphine oxide within the reaction mixture.



Scheme 21 Asymmetric three-component Michael reactions

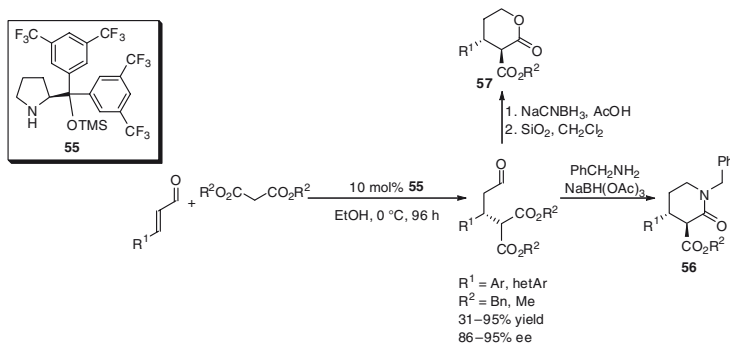
Extension to cyclic Michael donors also met with marked success using imidazolidine catalyst **54** (10 mol%) (Scheme 22) [95]. Conveniently, the reactions proceeded at room temperature using dichloromethane as the solvent and 1.05 equivalents of the Michael donor, representing a substantial improvement in the atom efficiency of the process. The synthetic utility of this transformation was exemplified by the one-step preparation of the anticoagulant (*S*)-warfarin ($R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{H}$; 90% yield; 80% ee) which could be recrystallised to optical purity (>99.9% ee) from acetone/water.

Use of α , β -unsaturated aldehydes as the substrate allows for a more efficient conjugate addition of malonates, reaction times being reduced to 96 h. The optimal reaction conditions involved addition of the malonate (1.0 equivalents) to an ethanolic solution of the α , β -unsaturated aldehyde (2.0 equivalents) at 0 °C in the



Scheme 22 Conjugate addition of cyclic 1,3-dicarbonyl compounds to α,β -unsaturated ketones

presence of diarylprolinol derivative **55** (31–95% yield; 86–95% ee) (Scheme 23) [96]. Simple conversion of the products to lactams **56**, lactones **57** and piperidines as single stereoisomers exemplifies the synthetic utility of this conjugate addition process. Extension of this work to the addition of dinitropropanes allowed for the formation of highly substituted cyclohexane ring systems generating five contiguous stereocentres in one-pot with excellent levels of selectivity [97].

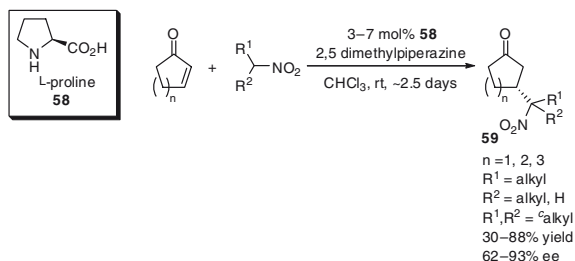


Scheme 23 Conjugate addition of malonates to α,β -unsaturated aldehydes

Rueping has further developed this theme by showing that diarylprolinol ether **55** efficiently catalyses the addition of hydroxyquinones to a variety of α,β -unsaturated aldehydes as a method for the preparation of both 1,4- and 1,2-naphthoquinones with remarkable levels of enantioselectivity [98].

Jørgensen has also developed a one-pot three component coupling of 1,3-dicarbonyl compounds, α,β -unsaturated aldehydes and primary amines to give a series of Hantzsch ester analogues [99].

Hanessian described the facile addition of cyclic and acyclic nitroalkanes to cyclic α,β -unsaturated ketones using L-proline **58** as the catalyst (3–7 mol%) in the presence of 2,5-dimethylpiperazine [100]. The reactions proceeded efficiently at room temperature and consistently provided adduct **59** with increased levels of enantioselectivity when compared with the rubidium prolinates method disclosed by Yamaguchi [29] (Scheme 24). The presence of trace amounts of water in the reaction was found to be essential, suggesting a hydrolytic step is involved in the catalytic



Scheme 24 Conjugate addition of nitroalkanes to α,β -unsaturated ketones

cycle, however, a substantial nonlinear effect with respect to the ee of the proline suggests a complex chiral catalytic system that requires further investigation to reveal the precise mechanistic details of the reaction.

More recently, this class of reaction has been extended to encompass acyclic α,β -unsaturated ketones as substrates using catalysts **60** and **51** (Fig. 5) [90, 101]. Although in general these reactions proceed well for the addition of symmetrically α -disubstituted nitroalkanes a substantial challenge that remains is the addition of non-symmetrical α -substituted nitroalkanes where low levels of diastereoselectivity in the addition product are observed (frequently 1:1). The histidine derived imidazolidinone **61** was examined in the conjugate addition of nitroalkanes to α,β -unsaturated aldehydes [102]. Although some encouraging enantioselectivities were observed, the reaction was shown to be highly substrate specific and competing 1,2-addition of the nucleophile was found to be a substantial problem.

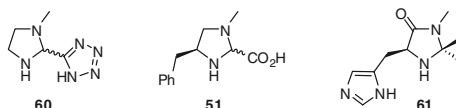
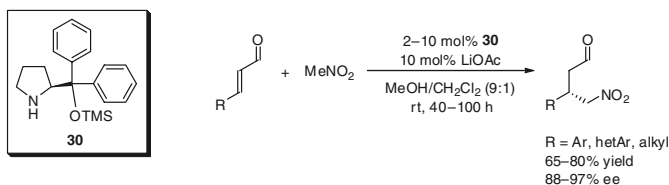


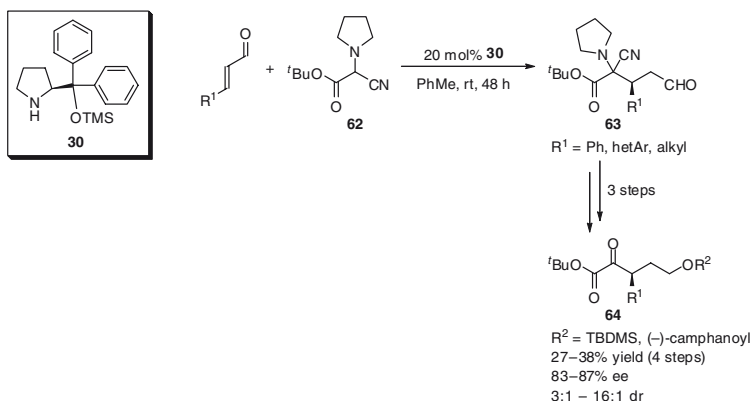
Fig. 5 Catalysts for the conjugate addition of nitroalkanes to acyclic Michael acceptors

Suitable conditions for the highly selective conjugate addition of nitromethane to α,β -unsaturated aldehydes were developed by Ye and co-workers [103]. Catalyst loadings as low as 2 mol% were found to be effective with a range of substrates (65–80% yield; 88–97% ee) (Scheme 25).



Scheme 25 Conjugate addition of nitromethane to α,β -unsaturated aldehydes

A synthetically more challenging C–H acid that represents a method for the glyoxylation of α,β -unsaturated aldehydes is aminonitrile **62** [104]. Conjugate addition of **62** catalysed by diarylprolinol ether **30** (20 mol%) provides adducts **63**. Reduction, protection and hydrolysis of these adducts leads to the glyoxylates **64** showing the impressive functional group tolerance of these transformations (Scheme 26).

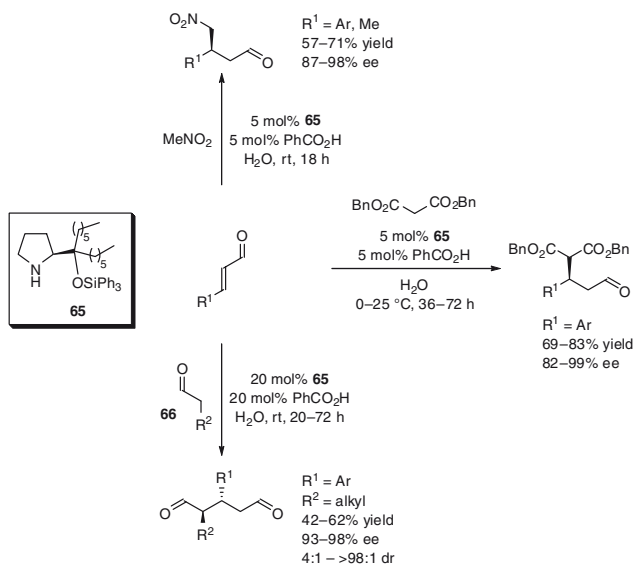


Scheme 26 Organocatalytic asymmetric nucleophilic glyoxylation

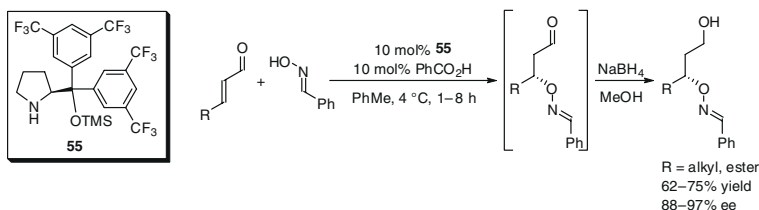
A promising new catalyst recently reported in this area is the novel dialkylprolinol ether **65** which was shown to be efficient for the addition of nitromethane, dibenzyl malonate and even simple aldehydes (Scheme 27) [105], the majority of reactions proceeding at room temperature using water as the solvent in the presence of just 5 mol% catalyst. Of particular significance is the ability to use aldehydes **66** as the Michael donor to give 1,5-dicarbonyl compounds in reasonable yield (42–62%) and high enantioselectivity (93–98% ee) given the challenging nature of the transformation. No self-condensation of the aldehyde was reported.

2.2.3 C–O Bond Formation

1,3-Dioxygenated patterns are ubiquitous in nature and thus addition of an oxygen nucleophile should provide a strategy of broad utility in target synthesis. Reports of this addition using iminium ion catalysis are limited, probably because of the hard nature of the oxygen nucleophile resulting in competing 1,2-addition to the carbonyl or derived iminium ion. Jørgensen conveniently circumvented this problem using aryl oximes as the nucleophile and provided a simple and effective route to the 1,4-addition product using diarylprolinol ether **55** as the catalyst (Scheme 28) [106]. The hydroxyl functionality was easily unmasked under standard hydrogenation conditions to reveal the synthetically important 1,3-diol functionality. A limitation of this protocol was aryl containing α,β -unsaturated aldehydes were unreactive under these conditions.

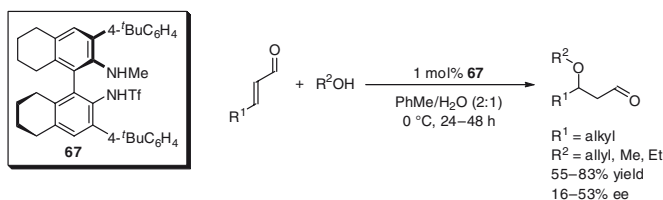


Scheme 27 Dialkylprolinol ether **65** for the organocatalytic Michael reaction



Scheme 28 Conjugate addition of aryl oximes

Maruoka has found that simple alcohols can also be used in the oxy-Michael reaction [107]. Using the axially chiral biaryl catalyst **67** (1 mol%) the conjugate addition of methanol, ethanol and allyl alcohol to α,β -unsaturated aldehydes was examined (Scheme 29). Despite moderate yields (55–83%) and enantioselectivities (16–53% ee), the high activity of this catalyst suggests that further optimisation

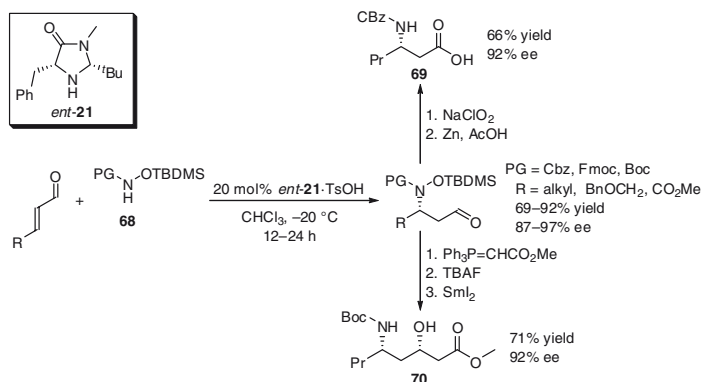


Scheme 29 Conjugate addition of alcohols to α,β -unsaturated aldehydes

might prove fruitful. Disappointingly, the absolute sense of asymmetric induction within these transformations was not determined preventing the development of a working transition state model.

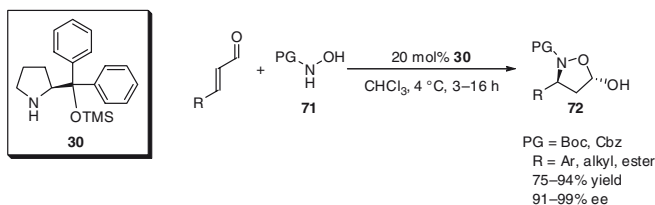
2.2.4 C–N Bond Formation

MacMillan expanded the portfolio of donors that could be used in the iminium ion activated conjugate addition to encompass nitrogen nucleophiles [108]. The synthetic challenge that needed to be overcome to achieve this transformation was differentiation of the amine nucleophile inherent to the structure of the catalyst and the amine nucleophile of the reagent. This dichotomy was circumvented by use of *N*-silyloxycarbamates **68**, which, in conjunction with the imidazolidinonium salt *ent*-**21**·TsOH gave the 1,4-addition products in 69–92% yield and 87–97% ee (Scheme 30). The strength of this protocol was further established by conversion of a conjugate addition product to the *N*-protected β -amino acid **69** in two steps (66% yield; 92% ee), and to the β -hydroxy- δ -amino ester **70** in three steps (71% overall yield; 92% ee). Related products of the conjugate addition of *O*-methyl-*N*-hydroxycarbamates have also been used to provide effective substrates for Mannich and aldol reactions revealing an important extension to this methodology [109].



Scheme 30 Conjugate addition of *N*-silyloxycarbamates using iminium ion catalysis

Córdoba has shown that using unprotected *N*-hydroxycarbamates **71** as the nucleophile with diarylprolinol ether **30** as catalyst gave direct access to 5-hydroxyisoxazolidines **72** (91–99% ee) which are convenient precursors to β -amino alcohols and β -amino acids (Scheme 31) [110]. Interestingly, these reactions proceed efficiently (3–16 h) without the need for an additional co-acid unlike the majority of other iminium ion catalysed transformations, an unexpected result which highlights the need for further mechanistic understanding.

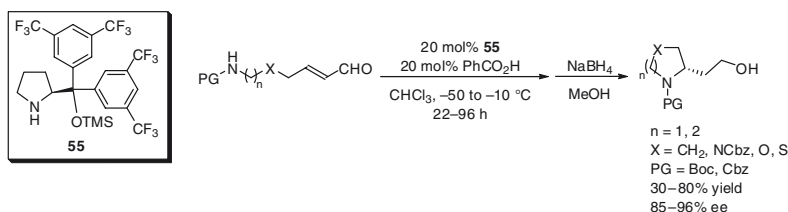


Scheme 31 Direct preparation of 5-hydroxyisoxazolidines using diarylprolinol ether **30**

Jørgensen [111] and Vicario [112] independently described the conjugate addition of both triazole and tetrazole based nucleophiles to α,β -unsaturated aldehyde substrates as an alternative method for C–N bond formation. These reactions were catalysed by the diarylprolinol and imidazolidinone scaffolds with equal efficiency showing the complementarity and efficacy of both these catalyst architectures. In addition, Jørgensen has also shown succinimide to be an effective Michael donor (see Sect. 2.3.5 Scheme 49 for further details) [113].

Takasu examined a series of five imidazolidinone catalysts in the intramolecular conjugate addition of amides to α,β -unsaturated aldehydes to prepare a series of tetrahydroisoquinolines [114]. Although yields were high for these organocatalytic transformations (70–90%), enantiomeric excesses were low (18–53%) showing further optimisation with regards to the co-acid and solvent are necessary to bring this potentially useful transformation in line with other reactions of this class.

Fustero has devised an intramolecular version of the iminium ion catalysed conjugate addition of nitrogen in the preparation of a series of simple pyrrolidine and piperidine derivatives [115]. The reactions proceed in chloroform to give the target heterocycles in good yield and excellent levels of stereocontrol (Scheme 32).

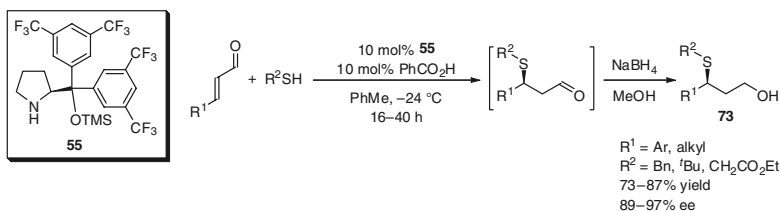


Scheme 32 Organocatalytic intramolecular aza-Michael reaction

2.2.5 C–S Bond Formation

Despite the prevalence of the C–S bond in nature and the importance of the sulfur group in many biological processes the organocatalysed formation of C–S bonds has received significantly less attention than C–N, C–O and C–C construction.

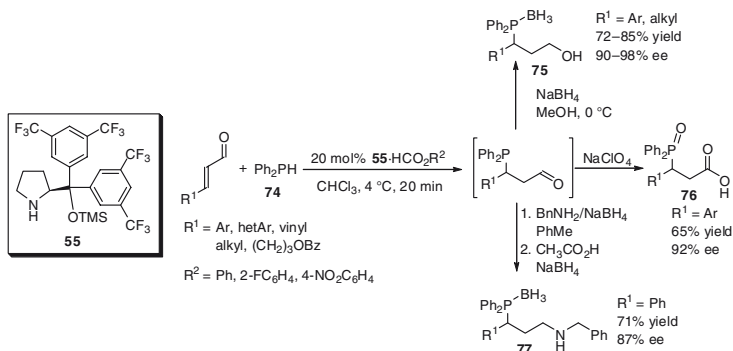
However, formation of this bond through the conjugate addition of a soft sulfur nucleophile to α,β -unsaturated aldehydes is efficiently catalysed using iminium ion catalysis [116]. Using diarylprolinol silyl ether **55** the addition of a series of sulfur based nucleophiles to a variety of α,β -unsaturated aldehydes was shown to be effective (73–87% yield; 89–97% ee). The products were isolated as their β -hydroxy sulfide derivatives **73** after in situ reduction of the products (Scheme 33).



Scheme 33 Conjugate addition of sulfur based nucleophiles

2.2.6 C–P Bond Formation

Simultaneous publication of the iminium ion catalysed hydrophosphination of α,β -unsaturated aldehydes by Melchiorre and Córdova showed diarylprolinol silyl ether **55** was effective in the conjugate addition of diphenylphosphine **74** [117, 118]. Direct transformation of the products allowed for one-pot methods for the preparation of β -phosphine alcohols **75** (72–85% yield; 90–98% ee), β -phosphine oxide acids **76** (65% yield; 92% ee) and 3-amino phosphines **77** (71% yield; 87% ee) (Scheme 34). These reports represent the first examples of the addition of P-centred nucleophiles and the resulting highly functionalised products may well have further use in asymmetric catalysis.



Scheme 34 Addition of P-centred nucleophiles to α,β -unsaturated aldehydes

Jørgensen has shown that phosphites also act as effective phosphorous based nucleophiles in the conjugate addition to a range of α,β -unsaturated aldehydes

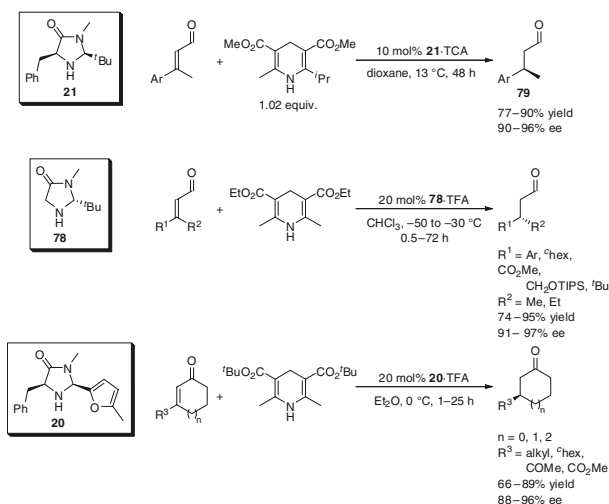
using diarylprolinol silyl ether **55** as the catalyst [119]. The products were readily transformed into the corresponding phosphinic acid derivatives and glutamic acid analogues suggesting this work might have applications in medicinal chemistry.

2.2.7 C–H Bond Formation

The majority of chemical methods for the asymmetric hydrogenation of unsaturated systems rely on the use of transition metal catalysts or stoichiometric amounts of metal hydride. The chemical importance of this transformation has led to the development of some of the most powerful and efficient methods in catalytic asymmetric synthesis. Routinely used on the milligram to multi-tonne scale, they represent one of the biggest success stories of asymmetric catalysis [120].

Biochemical hydride-reduction using the cofactor NADH provided the inspiration for the development of a Hantzsch ester mediated organocatalytic reduction of both enal [121–123], and enone [124] substrates using imidazolidinone catalysts, providing a new and efficient context in asymmetric hydrogenations (Scheme 35) [125–127]. These reactions are particularly mild and provide the products with excellent levels of absolute stereocontrol. Three imidazolidinones, **21**, **78** and **20**, have been shown to be effective at catalysing this transformation using similar reaction conditions. Many functional groups that are not compatible with transition metal catalysed hydrogenations are tolerated within these reactions (e.g. CN, NO₂), exemplifying the way in which iminium ion catalysed reactions can both complement and augment many existing processes.

A fascinating observation within these transformations was that with certain substrates, regardless of the stereochemical purity of the starting α,β -unsaturated aldehyde, identical levels of asymmetric reduction were observed within the reaction. For example, starting with either (*E*)-**80**, (*Z*)-**80** or a 1:1 mixture of the two



Scheme 35 Imidazolidinone catalysed hydride reduction of α,β -unsaturated aldehydes and ketones

stereoisomers, similar yields (83, 80, and 81% respectively) of (*R*)-**79** were isolated in 94% ee. Both (*E*)-**80** and (*Z*)-**80** can form the corresponding iminium ions **81** and **83** by condensation with an imidazolidinone. These iminium ions can then interconvert through the common dienamine intermediate **82**. Faster conjugate reduction of the more stable iminium ion (**81**) accounts for the outcome of this reaction (Fig. 6). During the reaction of prochiral unsaturated systems stereochemical purity of the reactant is usually essential in order to observe high levels of asymmetry in subsequent transformations. As preparation of geometrically pure starting materials can frequently represent one of the toughest challenges within synthesis, as a chemical tool, this stereoconvergent method represents a unique and important strategy.

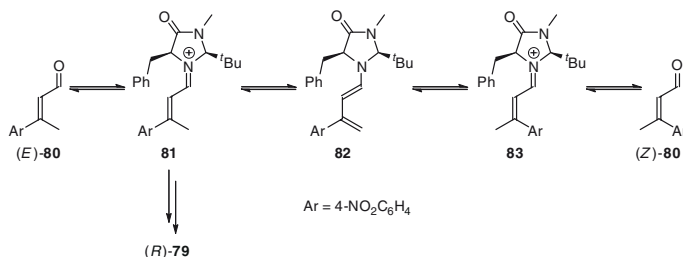


Fig. 6 Imidazolidinone catalysed hydride reduction of diastereoisomeric α,β-unsaturated aldehydes

2.3 Using the Enamine Intermediate

In the proposed catalytic cycle for iminium ion accelerated conjugate addition reactions (Fig. 2), the intermediate derived from the addition process is an enamine (**8**), which is hydrolysed under the reaction conditions to deliver the product and regenerate the catalytically active secondary amine **5**. A useful synthetic strategy involves the exploitation of this reactive intermediate by subsequent reaction with a variety of electrophiles providing a cascade process for the formation of two new bonds (Fig. 7). The iminium ion (**84**) that results from trapping of the enamine is hydrolysed under the reaction conditions to reveal the densely functionalised product **85** and release the amine (**5**) back into the catalytic cycle. The high levels of enantioselectivity observed from conjugate additions (see Sect. 2.2) make this method even more powerful. Exploitation of the enamine intermediate in the construction of C–O, C–N, C–C and C–X bonds by trapping with electrophiles in an intra- and inter-molecular fashion is described below.

2.3.1 Epoxide Formation

Of the numerous catalytic asymmetric methods developed for the functionalisation of alkenes, epoxidation has emerged as one of the most versatile and reliable methods

to aid in chemical synthesis. Since the pioneering work of Sharpless on allylic epoxidation [128], sustained research efforts have delivered organometallic [129, 130] and organocatalytic [131–133] strategies to epoxidise the majority of electron rich alkenes [134]. More recently, catalytic asymmetric methods have also been realised for the epoxidation of electron deficient systems [135–142]. These overall transformations are also accessible through iminium ion catalysed procedures using a variety of stoichiometric oxidants, the strategy for which is outlined below (Fig. 8). Conjugate addition of a nucleophilic oxygen incorporating a suitable leaving group (87) to an active

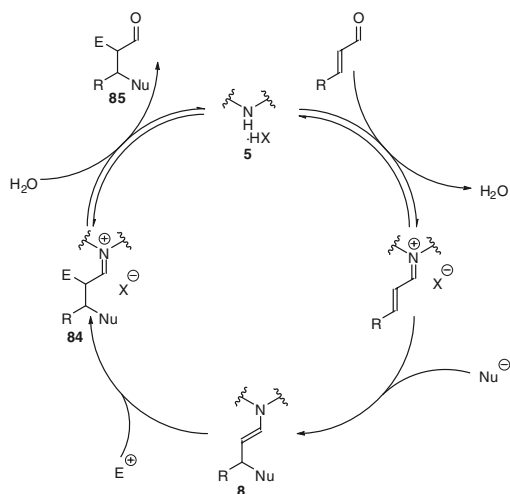


Fig. 7 Proposed catalytic cycle for the amino catalytic conjugate addition enamine trapping sequence

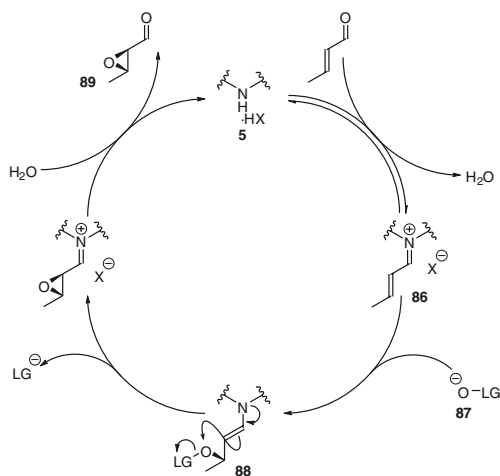
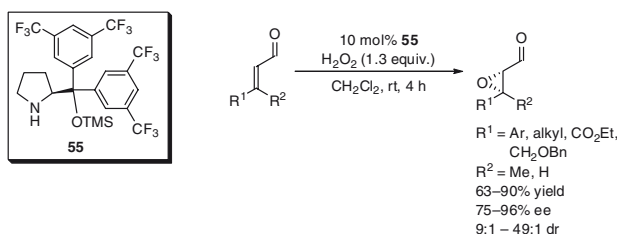


Fig. 8 Proposed catalytic cycle for the epoxidation of αβ-unsaturated aldehydes

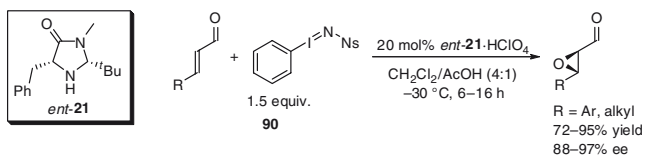
iminium ion (**86**) results in an intermediate enamine (**88**). Intramolecular trapping of this enamine with expulsion of the oxygen tethered leaving group followed by iminium ion hydrolysis results in the epoxidation product (**89**). The processes described here all adopt this strategy and differ in the oxidant and catalyst used.

Jørgensen made the first contribution to the area using diarylprolinol ether **55** [143]. Hydrogen peroxide (35 wt% in H₂O) emerged as the most effective oxidant for the epoxidation of cinnamaldehyde in dichloromethane. Application of the optimal reaction conditions to a series of α,β -unsaturated aldehydes showed equal efficiency in both yield (63–90%) and enantiomeric excess (75–96%) using just 10 mol% of catalyst **55** (Scheme 36). These high selectivities were achieved at room temperature in the presence of 10 mol% of the catalyst in just 4 h, providing a highly practical process that should find many applications. Jørgensen has subsequently disclosed that the reactions can also be performed in an ethanol/water mixture (3:1), although yields are substantially reduced (34–56%) and reaction times extended to 16 h [144].



Scheme 36 Epoxidation of α,β -unsaturated aldehydes using hydrogen peroxide as oxidant

An alternative oxidant that has also been shown to be effective for the epoxidation of α,β -unsaturated aldehydes is iminoiodinane **90**, which acts as an in situ source of iodosobenzene [145]. In a careful and thorough mechanistic investigation using a ¹⁵N labelled catalyst it was shown that iodosobenzene bought about slow catalyst degradation; however, use of **90** in the presence of acetic acid provided a slow release of iodosobenzene to undergo the epoxidation process. Reactions proceeded at –30 °C in the presence of 20 mol% *ent*-**21** as its perchlorate salt using 1.5 equivalents of the oxidant (Scheme 37). Most reactions reported gave the products as single diastereoisomers highlighting a benefit of this methodology.



Scheme 37 Imidazolidinone promoted epoxidation of α,β -unsaturated aldehydes

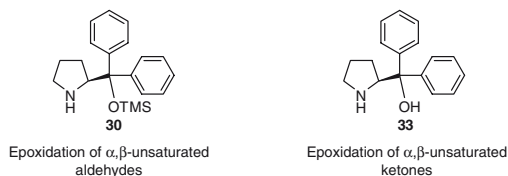


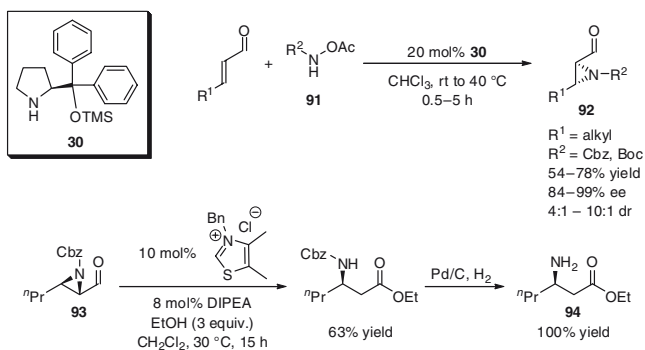
Fig. 9 Alternative catalysts for organocatalytic asymmetric epoxidation

Córdoba has also shown hydrogen peroxide to be an effective oxidant in the epoxidation of α,β -unsaturated aldehydes using diarylprolinol ether **30** as the catalyst (Fig. 9) [146, 147]. Within these reports it was also shown that the resulting epoxy aldehydes could be used directly in either Wittig or Mannich reactions, providing synthetically useful one-pot protocols to prepare densely functionalised building blocks for further elaboration.

It is worth noting that use of unprotected diarylprolinol **33** provides an effective platform for the epoxidation of α,β -unsaturated ketones [148, 149]. Within these reports it was proposed that an alternative mode of activation of the substrate could be taking place. Hydrogen bonding catalysis, rather than iminium ion formation, could explain the results and would be consistent with the non-polar reaction medium adopted within these reactions.

2.3.2 Aziridine Formation

Aziridines represent an important class of building block within synthesis. This structural motif is also embedded within a number of biologically significant natural products, and thus robust and efficient methods for their construction represent an important contribution to the synthetic toolkit. Córdoba reported an enantioselective aziridination of α,β -unsaturated aldehydes catalysed by diarylprolinol ether **30** using protected hydroxylamine **91** as the nitrogen source (Scheme 38) [150]. The reaction was proposed to proceed via iminium ion formation followed by



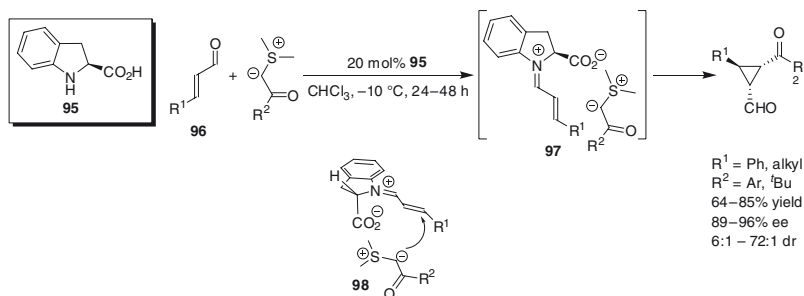
Scheme 38 Organocatalytic aziridination of α,β -unsaturated aldehydes

conjugate addition of an *O*-acyl hydroxylamine, the resultant enamine then underwent an intramolecular 3-*exo*-tet cyclisation, eliminating acetate, to give the observed aziridine after hydrolysis. The products (**92**) were found to be sensitive to column chromatography and extended reaction times, however, reasonable yields and excellent levels of enantioselectivity could be obtained. A simple two-step sequence could also convert formyl aziridine **93** to the corresponding β -amino ester (**94**), further adding to the applicability of this work.

2.3.3 Cyclopropane Formation

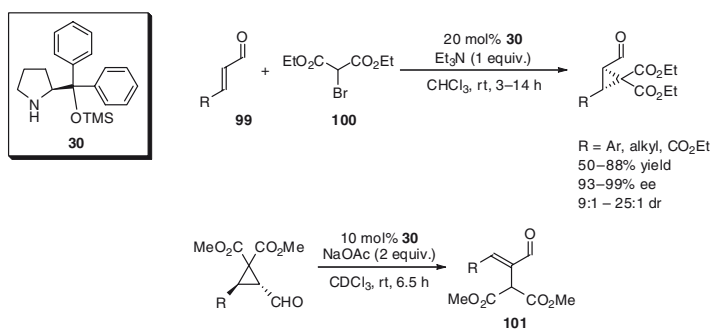
The cyclopropane moiety is a fundamental class of functional group present in both natural products and numerous therapeutic agents. It has provided the impetus for significant breakthroughs in the use of metal carbenoids [151] and organocatalytic ylide intermediates [152, 153] such that reliable methods exist for most disconnection strategies on this ring system.

In the context of iminium ion catalysed approaches to the formation of cyclopropanes, it has been shown that α,β -unsaturated aldehydes activated with secondary amines can be used as substrates for cyclopropanation processes. The pioneering work in this area was reported by MacMillan and co-workers, who showed that the commercially available dihydroindole-2-carboxylic acid **95** efficiently accelerated the reaction of α,β -unsaturated aldehydes **96** and stabilised sulfur ylides. Various subtle factors within the catalyst's design were found to be essential for attaining the high levels of enantioselectivity observed [154]. It was reasoned that only the (*Z*)-iminium ion **97** was formed to minimise van der Waals interactions that could occur with the C-7 proton on the aromatic ring of the catalyst. The approach of the incoming sulfur ylide was directed by an electrostatic interaction with the carboxylate of the catalyst causing the ylide to approach from the bottom face of the iminium intermediate **98**. Conjugate addition followed by ring closure with the expulsion of dimethyl sulfide provided the cyclopropyl products in good yield (64–85%) and with excellent levels of enantioselectivity (89–96% ee) (Scheme 39). It was reported that one of the reactions was undertaken on a 1 mmol scale without loss of yield or enantioselectivity, showing the robust nature of this work.



Scheme 39 Iminium ion catalysed cyclopropanation reactions

More recent reports from Córdova [155] and Wang [156] have described the cyclopropanation of α,β -unsaturated aldehydes **99** with diethyl bromomalonates **100** and 2-bromo ethyl acetoacetate catalysed by a series of diarylprolinol derivatives. Both describe **30** as being the most efficient catalyst in many cases and optimal reaction conditions are similar. Some representative examples of this cyclopropanation are shown in Scheme 40. The transformation results in the formation of two new C–C bonds, a new quaternary carbon centre and a densely functionalised product ripe for further synthetic manipulation. Triethylamine or 2,6-lutidine are required as a stoichiometric additive in order to remove the HBr produced during the reaction sequence. The use of sodium acetate (4.0 equivalents) as an additive led to subsequent stereoselective ring opening of the cyclopropane to give α,β -unsaturated aldehydes **101**. It can be envisioned that these highly functionalised materials may prove useful substrates in a variety of iminium ion or metal catalysed transformations.



Scheme 40 Iminium ion catalysed cyclopropanation using 2-bromoacetoacetate esters

Diarylprolinol ether **30** has also been used to accelerate the cyclopropanation of α,β -unsaturated aldehydes with arsonium ylides with excellent levels of asymmetric induction (95–98% ee) [157].

2.3.4 Other Electrophiles Intramolecular

Application of an organocatalytic domino Michael addition/intramolecular aldol condensation to the preparation of a series of important heterocycles has recently received much attention [158] with methods being disclosed for the preparation of benzopyrans [159–161], thiochromenes [162–164] and dihydroquinolidines [165, 166]. The reports all use similar conditions and the independent discovery of each of these reactions shows the robust nature of the central concept. A generalised catalytic cycle which defines the principles of these reports is outlined in Fig. 10. Formation of iminium ion **102** is followed by an intermolecular Michael addition of an oxygen, sulfur or nitrogen based nucleophile (**103**) to give an intermediate

enamine (**104**). Intramolecular aldol condensation of this enamine with an aldehyde and hydrolysis of the resulting iminium ion leads to the observed products (**105**) in high yield and selectivity. Each process uses the structurally similar diarylprolinol derivatives **30**, **106**, or **55** to afford the products. It is also worth noting that in the preparation of benzopyrans ($X = O$), the addition of 4 Å molecular sieves was found to lead to higher yields and selectivities despite the fact that water is intimately involved within the proposed catalytic cycle [159–161].

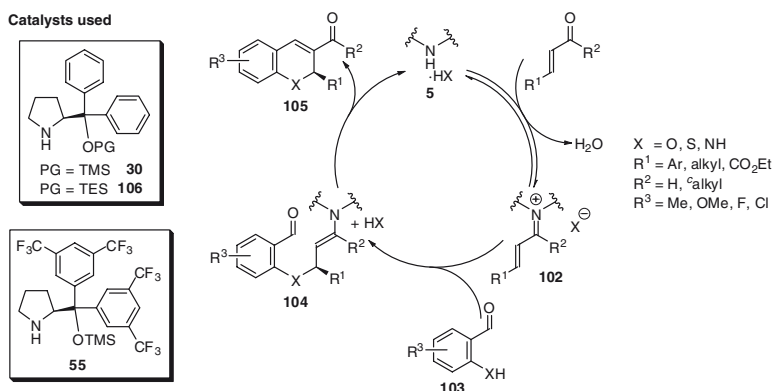
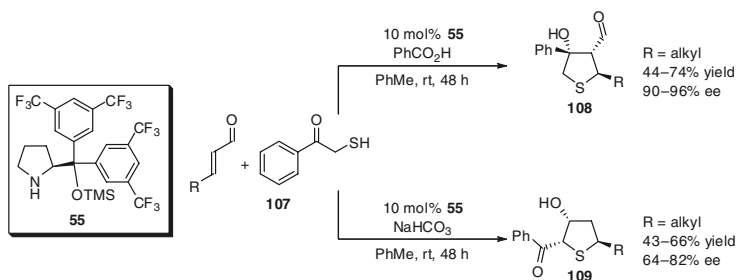


Fig. 10 Catalytic cycle for the organocatalytic domino Michael/intramolecular aldol condensation

Córdova has shown that it is also possible to isolate benzothiopyrans (71–98% yield; 96–99% ee) prior to the elimination of water by using 2-mercaptoacetophenone as the starting material [167].

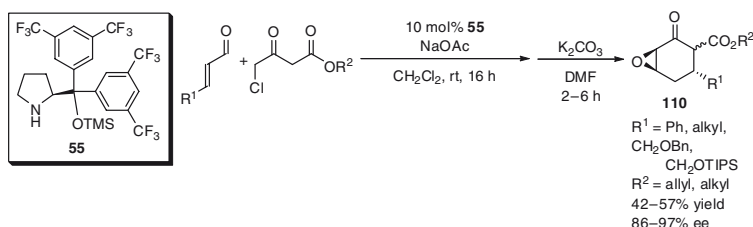
Jørgensen has reported a domino Michael/intramolecular aldol reaction of 2-mercapto-1-phenyl ethanone (**107**) and α,β -unsaturated aldehydes to give tetrahydrothiophenes [168]. Depending upon the reaction conditions adopted the regiochemical outcome could be controlled using the same catalyst (**55**) to give products **108** or **109** simply by changing the additive used (Scheme 41). Using benzoic acid as additive, tetrahydrothiophenes **108** were isolated in reasonable



Scheme 41 Divergent domino Michael/aldol reaction

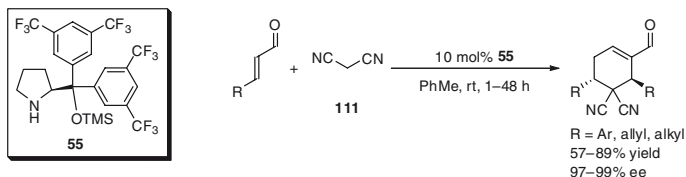
yield and excellent levels of enantiomeric excess (44–74% yield; 90–96% ee). Under the same reaction conditions (PhMe, rt, 48 h), but using sodium bicarbonate as the additive, regioisomeric adducts **109** were the major products (43–66% yield; 64–82% ee). Rationalisation of this result invoked two separate catalytic cycles. When benzoic acid was added, the catalyst **55** was involved in both the iminium ion mediated conjugate addition and the enamine promoted aldol reaction. Use of a base within the reaction mixture (NaHCO_3) proceeded by an iminium ion catalysed conjugate addition followed by hydrolysis and base catalysed intramolecular aldol reaction. This important observation offers additional divergent properties of iminium ion catalysed transformations that can be applied to further reaction design.

Using diarylprolinol ether **55** in conjunction with an additional base, a domino Michael/aldol/intramolecular S_N2 process has been developed that led to highly functionalised epoxycyclohexanones **110**, with excellent control of three of the chiral centres generated (Scheme 42) [169]. Despite the apparent complexity, these reactions proceed at room temperature in less than 24 h and the products contain significant potential for a host of further transformations.



Scheme 42 Organocatalytic domino Michael/aldol/intramolecular S_N2 reactions

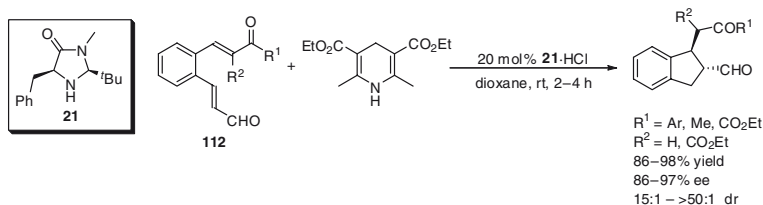
Jørgensen has also reported a sequential Michael/Michael/aldol condensation for the three component coupling of malonitrile **111** and α,β -unsaturated aldehydes that involves two iminium ion catalysed Michael additions followed by an intramolecular aldol condensation (Scheme 43) [170]. Using diarylprolinol ether **55** (10 mol%) in a concentrated toluene solution of malonitrile **111** and 3 equivalents of α,β -unsaturated aldehyde the reaction products can be isolated in just 1–48 h (57–89% yield; 97–99% ee). The atom efficiency of this three component reaction is remarkable and the ability to prepare these complex products under



Scheme 43 Multicomponent Michael/Michael/aldol condensation reaction

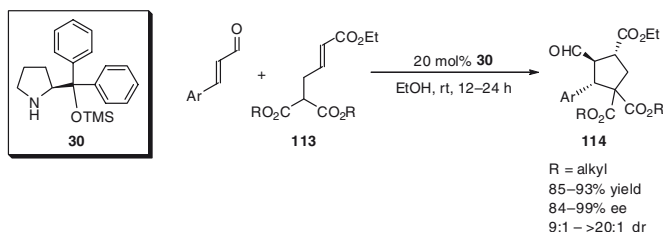
such mild reaction conditions is outstanding. Preliminary attempts to introduce two different α,β -unsaturated aldehydes selectively into this reaction sequence through appropriate choice of α,β -unsaturated aldehyde substrates were highly successful (for example: $R = ^i\text{Pr}$ and Ph gave 52% yield; >99% ee) and provide an important proof of concept for the ultimate development of a general three component coupling procedure.

List has reported a catalytic asymmetric reductive Michael cyclisation for the formation of five- and six-membered rings and the generation of two contiguous chiral centres [171]. Using imidazolidinonium salt **21**·HCl (20 mol%) and a Hantzsch ester (1.1 equivalents), substrates **112** smoothly underwent reductive Michael cyclisation (dioxane, rt, 2–4 h) with excellent yields, diastereoisomeric ratios and enantioselectivities (Scheme 44). This sequence was also applied to the formation of *trans*-disubstituted cyclopentanes and cyclohexanes. The reaction proceeds via an achiral conjugate reduction followed by an asymmetric Michael cyclisation. Given the exceptional levels of enantioselectivity observed in the conjugate reduction of β,β -disubstituted enals [121–123], it seems likely that this methodology could be used in an asymmetric conjugate reduction resulting in the formation of three contiguous chiral centres.



Scheme 44 Catalytic asymmetric reductive Michael cyclisation

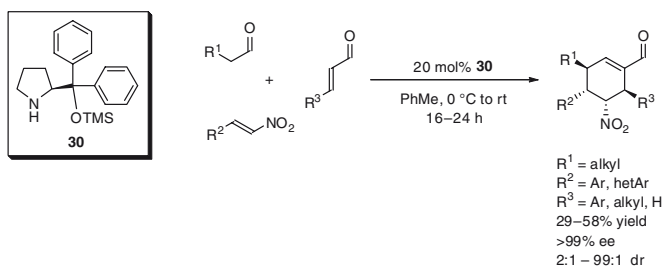
Wang identified a series of Michael/Michael and Michael/aldol sequences catalysed by diarylprolinol ethers that led directly to densely functionalised five-membered rings [172–174]. For example, highly diastereoselective and enantioselective double Michael addition reactions were achieved by treatment of α,β -unsaturated aldehydes with triester **113** catalysed by **30** (Scheme 45). Initial conjugate addition



Scheme 45 Catalytic asymmetric Michael/Michael reactions

of the malonate gives an enamine intermediate that undergoes conjugate addition onto the acrylate acceptor to give cyclopentane adducts **114** (85–93% yield; 9:1–>20:1 dr; 84–99% ee) at ambient temperature in ethanol.

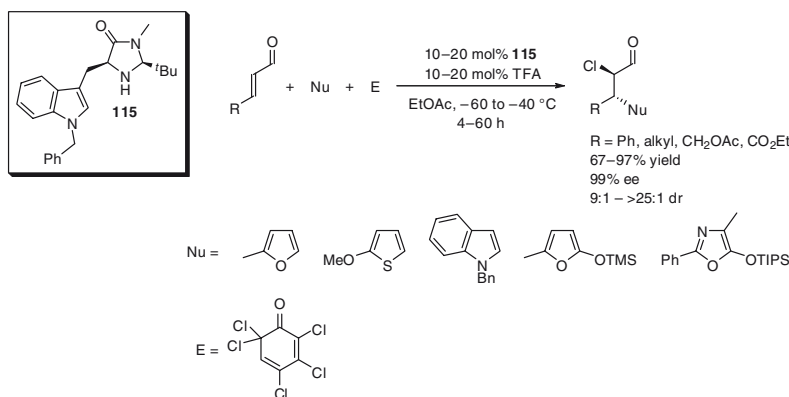
In a collection of insightful pieces of work Enders has incorporated an iminium ion conjugate addition of nitroalkanes to α,β -unsaturated aldehydes into a triple cascade reaction generating up to four contiguous stereocentres in one pot, again indicative of the complexity attainable from superficially simple catalysts and techniques [175–177] (Scheme 46).



Scheme 46 Enders triple cascade reaction

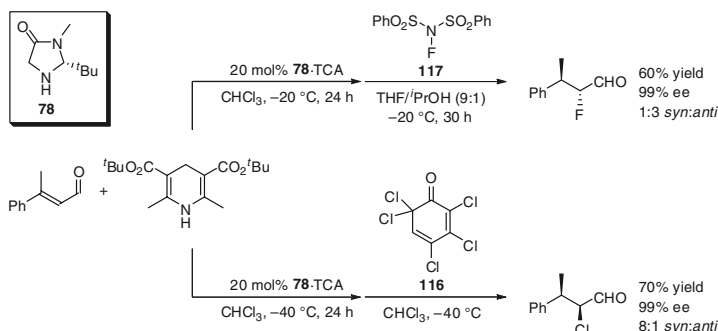
2.3.5 Other Electrophiles Intermolecular

In each of the tandem iminium ion/enamine cascade processes described above, the enamine is trapped in an intramolecular fashion. The ability to perform the trapping sequence in an intermolecular manner would allow for the one-pot introduction of three points of diversity. MacMillan has realised this goal and described a series of secondary amine catalysed conjugate addition–enamine trapping sequences with α,β -unsaturated aldehydes using tryptophan derived imidazolidinone **115** to give the products in near perfect enantiomeric excess (Scheme 47) [178].



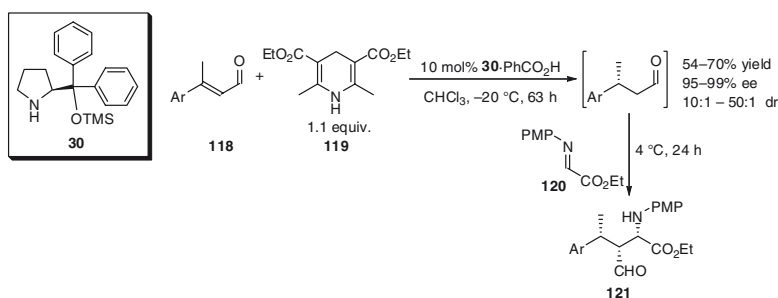
Scheme 47 Intermolecular organo-cascade catalysis

Combination of the Hantzsch ester mediated transfer hydrogenation together with chlorine (**116**) or fluorine (**117**) electrophiles allows for the formal addition of HCl or HF across a double bond in a catalytic asymmetric manner (Scheme 48) [178]. Within this paper the reactions were further refined by the use of two cycle-specific secondary amines which effectively operated independently within the same reaction mixture. Impressively, this allowed access to either diastereoisomer of the product depending upon the absolute configuration of the catalyst used in the second step of the sequence.



Scheme 48 Catalytic asymmetric formal addition of HCl or HF across a double bond

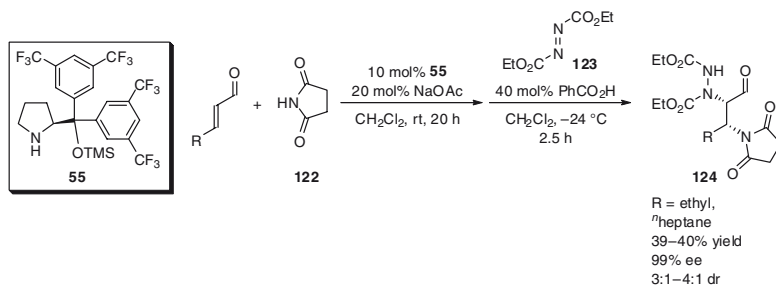
Córdova has described a reductive Mannich protocol that proceeds with high chemo-, diastereo- and enantioselectivity [179]. Conjugate reduction of β,β -disubstituted enal **118** with Hantzsch ester **119** in the presence of **30** (10 mol%) and benzoic acid (10 mol%) (63 h, $-20\text{ }^{\circ}\text{C}$) followed by addition of α -iminoglyoxylate **120** and stirring for a further 24 h gave the product (**121**) with excellent levels of relative and absolute stereocontrol (10:1–50:1 dr; 95–99% ee) (Scheme 49).



Scheme 49 Organocatalytic asymmetric reductive Mannich reaction

Jørgensen reported the first catalytic asymmetric diamination procedure using an iminium ion/enamine method [113]. Treatment of an α,β -unsaturated aldehyde with succinimide **122** in the presence of diarylprolinol ether **55** (10 mol%) gave the conjugate

addition product (65–74%; 78–89% ee). Direct treatment of the crude reaction mixture with DEAD (**123**) led to diamination product **124** with near perfect enantioselectivities (39–40%; 99% ee) clearly showing the power of these transformations (Scheme 50).



Scheme 50 *syn*-Selective diamination of α,β -unsaturated aldehydes

It is clear that, as understanding of the underlying principles of both iminium ion and enamine catalysis improves, the true power of these cascade sequences will be fully exploited. It can be expected that introduction of subsequent independent catalytic cycles will add to the complexity and applicability of these processes and provide highly regulated cascades that mimic the power of enzymatic pathways.

2.3.6 Morita–Baylis–Hillman Reaction

Since its original discovery the Morita–Baylis–Hillman reaction has received considerable attention due to its potential as a powerful carbon–carbon bond forming process [180]. The intriguing multi-step mechanism has provided the driving force for the invention of a variety of catalytic asymmetric methods to accelerate this reaction; however, there is still room for improvement with regards substrate scope and reaction generality. Shi showed an iminium ion/enamine catalysed process was viable for the coupling of methyl vinyl ketone (**125**) and a series of aromatic aldehydes (**127**) accelerated by a dual catalyst mixture of L-proline and imidazole [181]. The proposed catalytic cycle is outlined in Fig. 11. Iminium ion formation followed by conjugate addition of imidazole gives intermediate enamine **126** which reacts with an aldehyde to give **128**. Elimination of imidazole and iminium ion hydrolysis gives the Morita–Baylis–Hillman product (**129**) and releases both catalysts for further reaction. Although 30 mol% of each catalyst was needed and the products were isolated with low to negligible ee, this proof of concept provided excellent precedent for further investigation. In the absence of either proline or imidazole the reaction was reported to be ineffective showing that both these catalysts are critical to catalytic activity.

Improvements in the enantioselectivities were observed using benzodiazepine **130** and L-proline (**58**) which catalysed the reaction of methyl vinyl ketone and a small

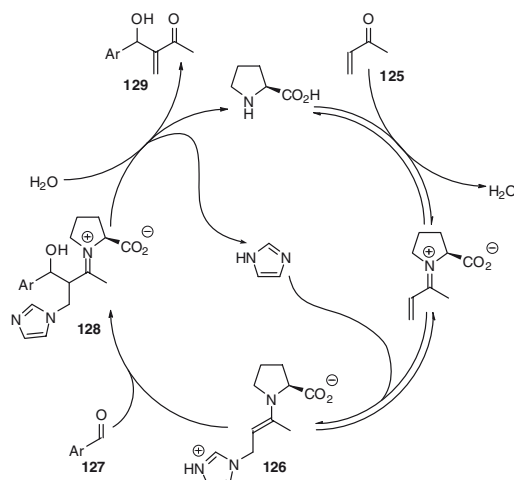
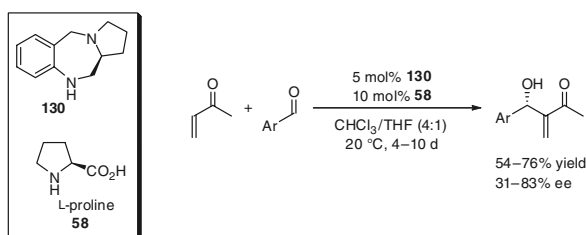


Fig. 11 Proposed catalytic cycle for the Morita–Baylis–Hillman reaction

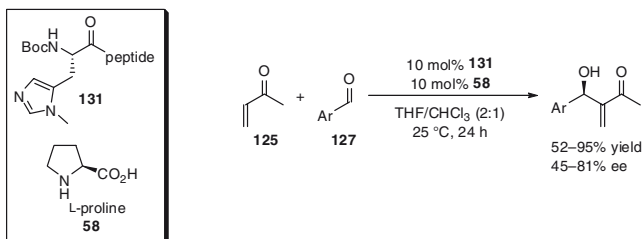
series of aromatic aldehydes (54–76% yield; 31–83% ee) (Scheme 51) [182]. Although the levels of enantioselectivity are short of those required for this technology to be taken up as a general method, it might be expected that improvements are possible.



Scheme 51 Morita–Baylis–Hillman reaction using the dual catalysts **130** and **58**

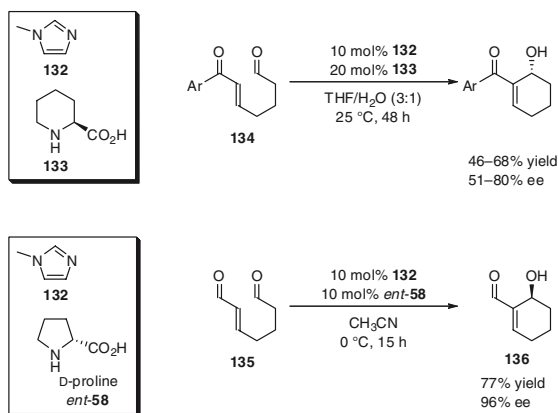
The most efficient catalyst system for the Morita–Baylis–Hillman reaction of methyl vinyl ketone has been reported by Miller [183, 184]. Use of L-proline (**58**) (10 mol%) in conjunction with the *N*-methyl imidazole containing hexapeptide **131** (10 mol%) provided an efficient platform for the reaction of **125** with a series of aromatic aldehydes **127** (52–95% yield; 45–81% ee) (Scheme 52). Importantly, it was shown that the absolute configuration of the proline catalyst was the major factor in directing the stereochemical outcome of the reaction and not the complex peptide backbone.

Intramolecular versions of the Morita–Baylis–Hillman reaction have also met with success using a dual Lewis acid/Lewis base catalyst system. Miller has shown that a combination of *N*-methyl imidazole (**132**) (10 mol%) and



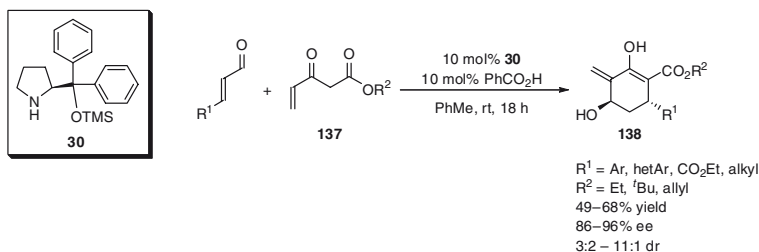
Scheme 52 Optimal catalyst system for the Morita–Baylis–Hillman reaction of methyl vinyl ketone

pipecolic acid (**133**) (20 mol%) accelerates the intramolecular cyclisation of α,β -unsaturated ketones **134** which proceeds at room temperature in a THF/water mixture (46–68% yield; 51–80% ee) (Scheme 53) [185]. These highly practical reaction conditions using commercially available catalysts suggests that this should become a particularly useful method for the construction of these highly functionalised products. Hong has also described an intramolecular reaction of α,β -unsaturated aldehyde **135** which gives the cyclic product **136** (77% yield; 96% ee) [186]. Expansion or reduction of the ring size led to a substantial decrease in both yield and enantioselectivity observed, however, this example shows excellent potential.



Scheme 53 Intramolecular Morita–Baylis–Hillman reaction

An interesting alternative intramolecular cyclisation was discovered by Jørgensen and co-workers [187]. Although not strictly exploiting an enamine intermediate, the transformation represents a secondary amine catalysed Morita–Baylis–Hillman reaction leading to a series of highly functionalised cyclohexene products. Reaction of the Nazarov reagent **137** with α,β -unsaturated aldehydes in the presence of the diarylprolinol ether **30** led to the cyclohexene products **138** (49–68% yield; 86–96% ee) via a tandem Michael/Morita–Baylis–Hillman reaction (Scheme 54).



Scheme 54 Organocatalytic Michael/Morita–Baylis–Hillman reaction

Although the precise mechanisms for each of these examples have yet to be determined, a pathway involving iminium ion intermediates appears reasonable. Further optimisation of the complex dual catalyst systems may well lead to a general and robust procedure that will prove of considerable use in synthesis.

2.4 1,2-Addition – An Important Consideration

2.4.1 Condensation Reactions

A less developed but substantial opportunity for reaction of iminium ions is the direct 1,2-addition of a nucleophile. Although this can reduce opportunities for developing a catalytic procedure because of mechanistic considerations, appropriate choice of substrates and reaction conditions has provided a number of successful methods that adopt this mode of reactivity.

Barbas, one of the pioneers of enamine catalysis, has incorporated iminium ion intermediates in complex heterodominic reactions. One particularly revealing example that uses the complementary activity of both iminium ion and enamine intermediates is shown in Fig. 12 [188]. Within this intricate catalytic cycle the catalyst, L-proline (**58**), is actively involved in accelerating two iminium ion catalysed transformations: a Knoevenagel condensation and a retro-Michael/Michael addition sequence, resulting in epimerisation.

It can be expected that inclusion of 1,2-addition reactions catalysed by iminium ion intermediates will allow for further rapid introduction of architectural diversity into simple building blocks through similar domino type processes addressing one of the critical objectives in contemporary synthetic chemistry.

Care must also be taken when choosing the reaction partners within reactions. Nucleophiles that have been reported to be effective in conjugate addition processes can also undergo 1,2-addition reactions and these possibilities must be addressed in reaction design. For example, aldehydes and ketones have been shown to undergo a bis-indole alkylation sequence in the presence of achiral amine **139** (42–84% yield; 1–10 mol% catalyst) [189]. This additional reactivity was exploited in the

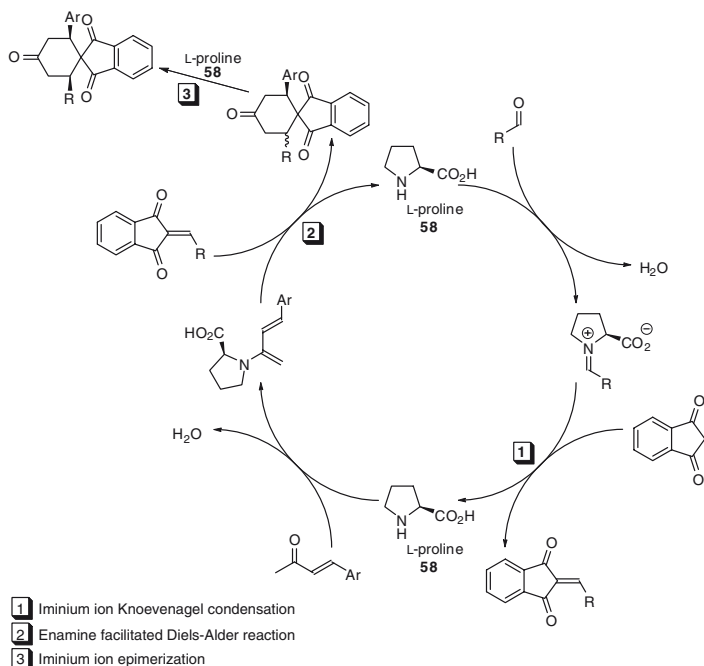
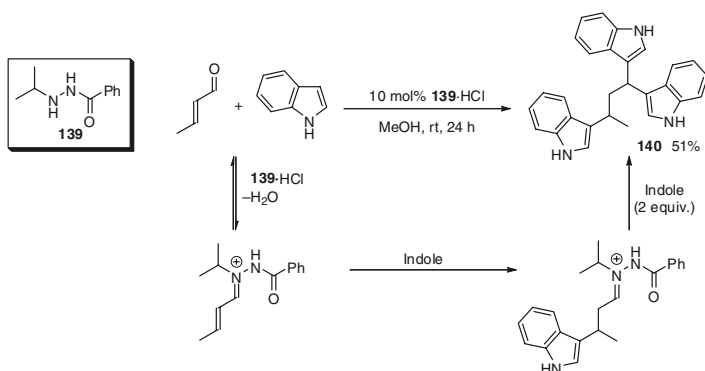


Fig. 12 Organocatalytic heterodomino reactions

synthesis of the naturally-occurring tris-indole **140** which was prepared directly by the reaction of crotonaldehyde with 3 equivalents of indole (Scheme 55). It was proposed this reaction proceeded via iminium ion formation followed by conjugate addition of the first molecule of indole. Conversion of the resulting enamine back to the iminium ion followed by the 1,2-addition of 2 further equivalents of indole gave the observed product **140** in a respectable 51% isolated yield after three C–C bond-forming reactions.



Scheme 55 1,2-Addition of indole to an iminium ion

Although condensation reactions usually result in achiral products they represent important additional reactivity of the active iminium ion which must be considered. Design of condensation reactions into cascade processes will provide further intriguing catalytic sequences.

3 Primary Amines as Catalysts

The majority of transformations reported within the literature using the concept of LUMO energy lowering iminium ion activation have used secondary amines as the catalyst. Under the aqueous acidic reaction conditions inherent to this mode of activation it is also possible to use primary amines as efficient catalysts where the active species is the protonated imine **141** (Fig. 13). Although this is a somewhat less explored avenue of research, initial results suggest it will become an equally fruitful area with broad application.

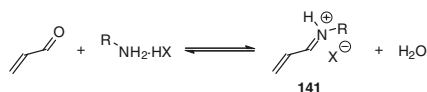


Fig. 13 Iminium ion activation using primary amines

In particular, the reduced steric bulk around the catalytic nitrogen has allowed for expansion of the scope of these reactions to more hindered substrates such as α -substituted acroleins and, importantly, α,β -unsaturated ketones, augmenting the chemistry described in Sect. 2 of this report (Fig. 14).

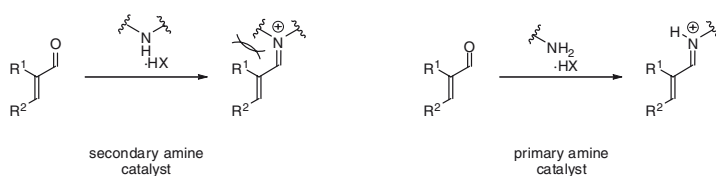
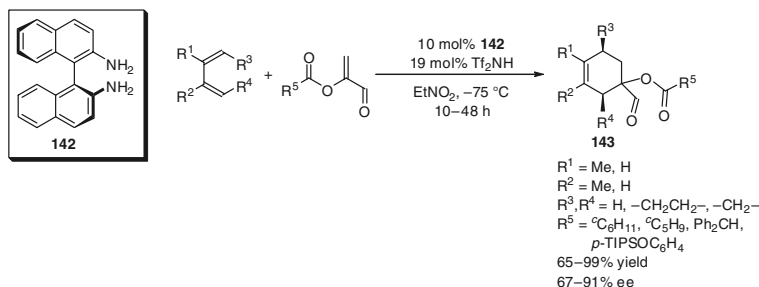


Fig. 14 Activation of α -substituted acroleins using primary and secondary amines

3.1 [4+2] Cycloaddition

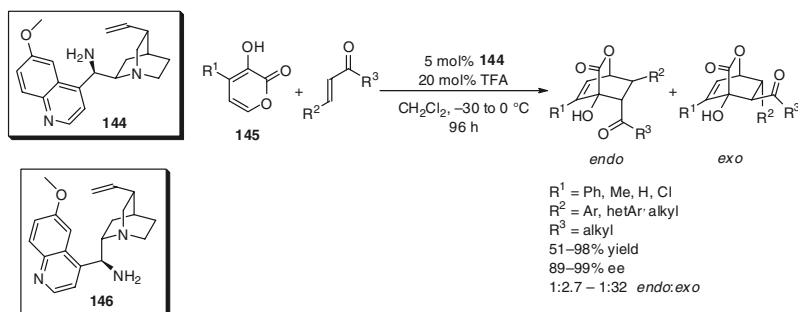
Ishihara and Nakano reported a complex triamine catalyst which was effective for the enantioselective Diels–Alder reaction of α -acyloxyacroleins [190]. They have subsequently described binaphthyl catalyst **142** which gave higher yields and enantioselectivities within the same transformation [191, 192]. Reaction of a range of dienes and α -acyloxyacroleins in the presence of **142** (10 mol%) and

bis(trifluoromethanesulfonyl)amine (19 mol%) gave Diels–Alder adducts **143** (65–99% yield) in 67–91% ee (Scheme 56). In order to achieve these levels of selectivity, reactions were performed at $-75\text{ }^{\circ}\text{C}$ for up to 48 h, revealing further opportunities for improvement within this challenging area of research.



Scheme 56 Diels–Alder reaction of α -acyloxyacroleins catalysed by binaphthylamine **142**

An interesting expansion to the scope of dienes that could be adopted as partners within the Diels–Alder cycloaddition was reported by Deng (Scheme 57) [193]. Reaction of 3-hydroxypyrones **145** with a broad range of α,β -unsaturated ketones in the presence of the primary cinchona alkaloid **144** (5 mol%) provided the Diels–Alder adducts with exceptional levels of asymmetric induction (up to 99% ee). Within this report it was also shown that the related alkaloid **146** provided access to the enantiomeric adducts with similar levels of asymmetric induction.

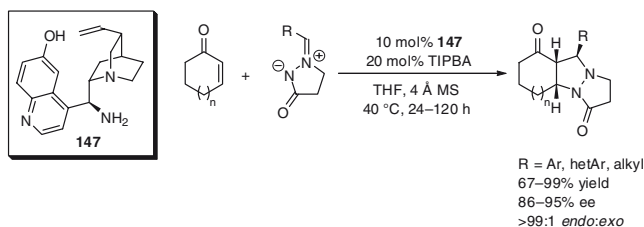


Scheme 57 [4+2] Cycloaddition of 3-hydroxypyrones and α,β -unsaturated ketones

3.2 [3+2] Cycloaddition

Chen extended the scope of his iminium ion catalysed [3+2] cycloaddition with azomethine imines (see Sect. 2.1.2) to encompass cyclic α,β -unsaturated ketone substrates using primary amine **147** as the catalyst [194]. Interestingly, the presence

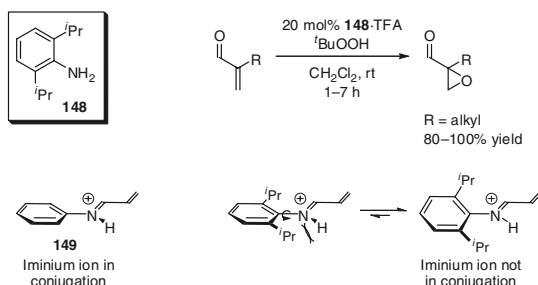
of molecular sieves improved the enantiomeric excesses obtained for the adducts, despite the fact that water is an integral part of the catalytic cycle. This may provide a reason for the long reaction times required (up to 120 h). Despite this, impressive levels of asymmetric induction (86–95% ee) and high yields (up to 99%) were achieved in these reactions (Scheme 58).



Scheme 58 [3+2] Cycloaddition of azomethine imines with α,β -unsaturated ketones

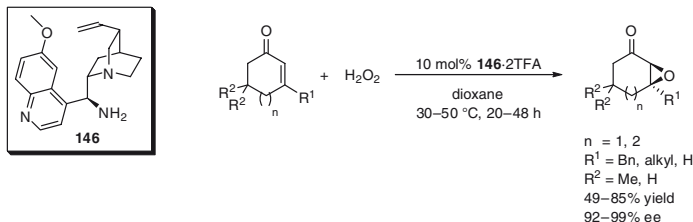
3.3 Epoxide Formation

Pihko reported that effective turnover could be obtained using hindered primary anilines as the catalyst for iminium ion accelerated processes. It was reasoned that an iminium ion derived from aniline would be conjugated with the aromatic ring slowing catalytic turnover (**149**). Use of a bulky *o*-substituted aniline **148** would prevent this conjugation and lead to faster catalyst turnover providing a new platform for design of novel catalytic architectures for challenging substrates such as α -substituted acroleins (Scheme 59) [195]. This hypothesis was shown to be correct with the simple achiral aniline salt **148**·TFA which efficiently catalysed the epoxidation of a series of α -substituted α,β -unsaturated aldehydes using *tert*-butylhydroperoxide as the oxidant. Asymmetric versions of this and related transformations based on this catalyst design will certainly augment this area.



Scheme 59 Epoxide formation using primary anilines as catalysts

List has provided access to chiral epoxides derived from cyclic α,β -unsaturated ketones using the primary amine salt **146**·2TFA [196]. Treatment of cyclohexenone or cycloheptenone derivatives with the catalyst (10 mol%) and hydrogen peroxide (1.5 equivalents) in dioxane (30–50 °C) gave the corresponding epoxide (92–99% ee) (Scheme 60). Deng has subsequently reported that the same catalyst system **146**·2TFA is also effective in the epoxidation of acyclic α,β -unsaturated ketones using 1-methyl-1-phenylethylhydroperoxide as the oxidant with similar high levels of asymmetric induction (96–97% ee) [197].

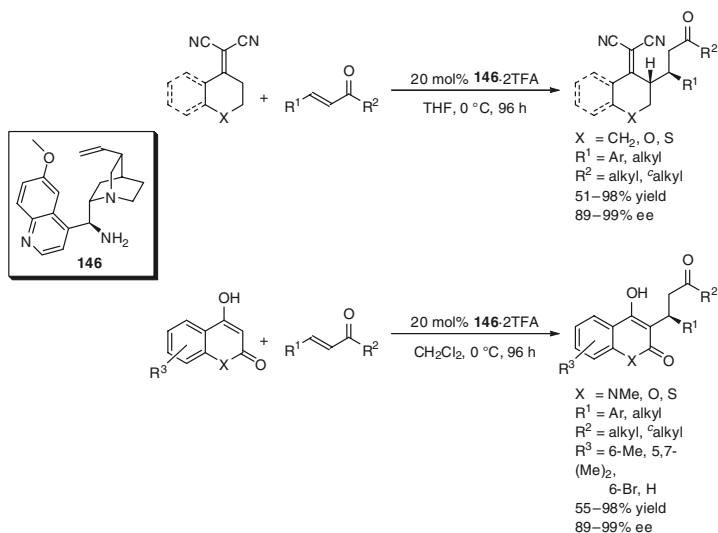


Scheme 60 Catalytic asymmetric formation of epoxides from α,β -unsaturated ketones

3.4 Conjugate Addition

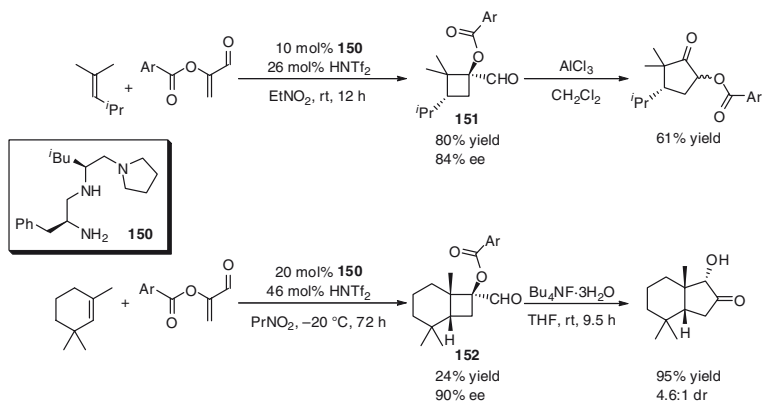
The conjugate addition of carbon nucleophiles to α,β -unsaturated ketones using a primary amine as the catalyst has recently met with success and broadens the substrate scope using iminium ion activation. In an improved procedure from earlier work [198] Deng found that the primary quinine derived amine **146** was effective for the intermolecular conjugate addition of α,α -dicyanoalkenes to α,β -unsaturated ketones to give the Michael adducts (51–98% yield; 89–99% ee) (Scheme 61) [199]. Deng has since shown this reaction is equally effective using malononitrile as the nucleophile [200]. This amine (**146**) has also been found to catalyse the addition of cyclic 1,3-dicarbonyl compounds to α,β -unsaturated ketones (55–98% yield; 89–99% ee) [201]. Use of the pseudo-enantiomeric cinchonine derived analogue leads to the opposite sense of asymmetric induction with similar levels of enantiomeric excess being reported. Although both these reactions are slow (96 h at 0 °C), the high yields and levels of stereocontrol suggest that further exploitation of this amine in iminium ion activated processes should be fruitful. Exploitation of this amine (**146**) in the C-3 alkylation of indole with α,β -unsaturated ketones has also been shown to be effective with reasonable enantioselectivities (16–99% yield; 47–89% ee). Catalyst loadings for this transformation were high (30 mol%) and low temperatures were frequently required (0 to –20 °C) [202].

Ishihara has reported an unusual enantioselective [2+2] cycloaddition of unactivated alkenes with α -acyloxyacroleins catalysed by triamine **150** [203]. Although the precise mechanistic details of this transformation are unclear at present, a possible



Scheme 61 Conjugate addition of C-based nucleophiles to α,β -unsaturated ketones

stepwise pathway involves iminium ion formation with the primary amine which facilitates enantioselective conjugate addition of the electron rich alkene. Subsequent intramolecular cyclisation of the resulting enamine onto the tertiary carbocation then provides the observed products **151** and **152**. These cycloadducts can be efficiently ring expanded to the corresponding cyclopentanone by treatment with either aluminium trichloride or TBAF, leading to an overall formal [2+3] cycloaddition process (Scheme 62).

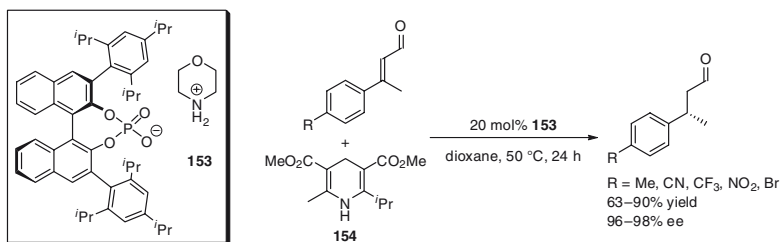


Scheme 62 Enantioselective [2+2] cycloaddition of unactivated alkenes

4 Chiral Anions Using Secondary and Primary Amines as Catalysts

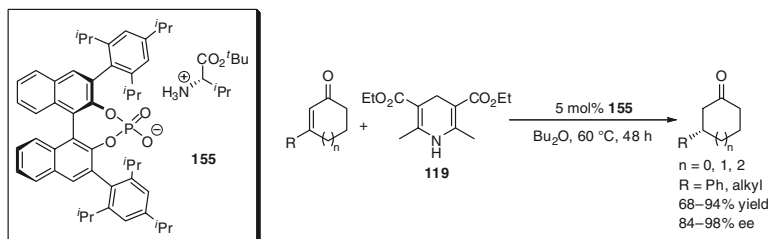
A recent concept introduced into the field of iminium ion activation that shows great promise for expanding the scope of both substrates and transformations is the use of a chiral anion in association with a primary or secondary amine. The use of non-reactive chiral anions as effective tools for the introduction of asymmetry in transition metal, phase-transfer, Brønsted acid and organocatalysed processes is currently receiving significant attention [204–208]. These isolated reports highlight the potential strength of this organocatalytic methodology which will certainly increase in scope.

List was the first to explore this possibility, examining the Hantzsch ester mediated reduction of α,β -unsaturated aldehydes [209]. Using 20 mol% of the binaphthyl derived phosphonate salt of morpholine (**153**) in dioxane at 50 °C, a series of β -aryl α,β -unsaturated aldehydes underwent transfer hydrogenation with Hantzsch ester **154** with excellent levels of absolute stereocontrol (96–98% ee) (Scheme 63). The method was also applied to the aliphatic substrates (*E*)-citral and farnesal to give the mono-reduced products in 90% and 92% ee, respectively. Significantly, in line with many of the chiral secondary amine catalysed transformations described above the reactions follow a simple and practical procedure without the need for exclusion of moisture and air.



Scheme 63 Asymmetric counteranion-directed catalysed transfer hydrogenation

Subsequently, List reported that although the method described above was not applicable to the reduction of α,β -unsaturated ketones, use of a chiral amine in conjunction with a chiral anion provided an efficient and effective procedure for the reduction of these challenging substrates [210]. Transfer hydrogenation of a series of cyclic and acyclic α,β -unsaturated ketones with Hantzsch ester **119** could be achieved in the presence of 5 mol% of valine *tert*-butyl ester phosphonate salt **155** with outstanding levels of enantiomeric control (Scheme 64). A simple mechanistic model explains the sense of asymmetric induction within these transformations allowing for reliable prediction of the reaction outcome. It should also be noted that matched chirality in the anion and amine is necessary to achieve high levels of asymmetric induction.



Scheme 64 Enantioselective transfer hydrogenation of α,β -unsaturated ketones

In conjunction with the chiral anion TRIP (**156**) (10 mol%), diamine **157** (10 mol%) can be used in the catalytic asymmetric epoxidation of α,β -unsaturated ketones (>90% ee) [196], while the secondary amine **158** (10 mol%) can be used for the epoxidation of both di- and trisubstituted α,β -unsaturated aldehydes (92–98% ee) (Fig. 15) [211]. The facile nature of these reactions, using commercially available peroxides as the stoichiometric oxidant, together with the synthetic utility of the epoxide products suggests application in target oriented synthesis.

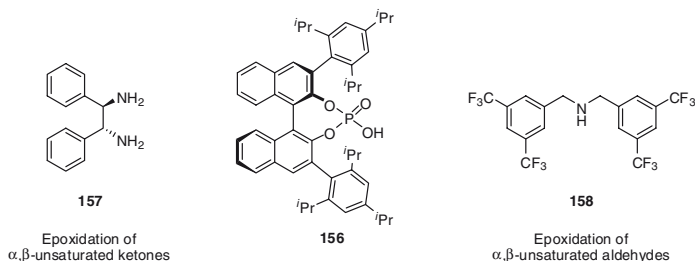
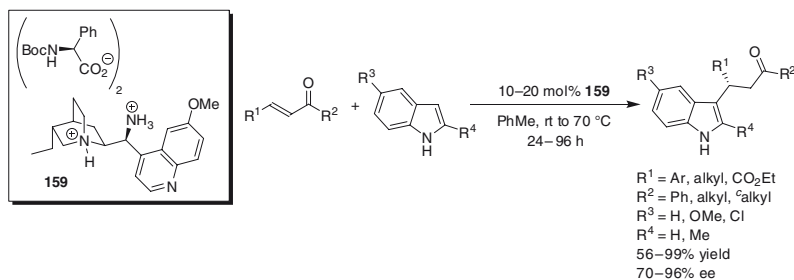


Fig. 15 Amines used in conjunction with TRIP for the epoxidation of enones and enals

A further example of the use of a chiral anion in conjunction with a chiral amine was recently reported by Melchiorre and co-workers who described the asymmetric alkylation of indoles with α,β -unsaturated ketones (Scheme 65) [212]. The quinine derived amine salt of phenyl glycine (**159**) (10–20 mol%) provided the best platform with which to perform these reactions. Addition of a series of indole derivatives to a range of α,β -unsaturated ketones provided access to the adducts with excellent efficiency (56–99% yield; 70–96% ee). The substrates adopted within these reactions is particularly noteworthy. For example, use of aryl ketones ($R^2 = Ph$), significantly widens the scope of substrates accessible to iminium ion activation. Expansion of the scope of nucleophiles to thiols [213] and oximes [214] with similar high levels of selectivity suggests further discoveries will be made.



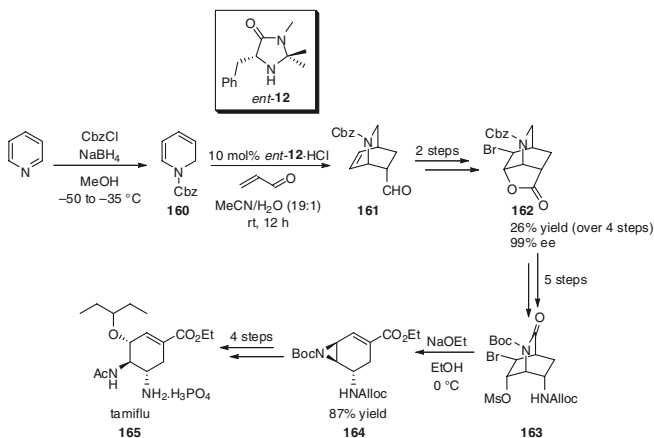
Scheme 65 Alkylation of indoles using a chiral anion/chiral amine combination

5 Applications in Synthesis

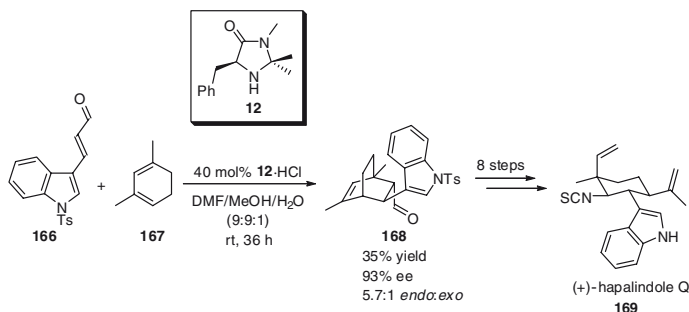
A true test for the applicability of any methodology is not only the level of its uptake by the general synthetic community, but also its use in the synthesis of natural products and molecules of biological significance. To this end there have been a number of applications in natural product synthesis of the iminium ion catalysed reactions discussed within this review. This can be put down to the mild, efficient and user friendly reaction conditions possible for many of the transformations, the ease of accessibility of the catalysts reported (many are even commercially available) and the high functional group tolerance, all features eminently compatible with complex target synthesis. A comprehensive review encompassing a variety of organocatalytic transformations in the synthesis of drugs and bioactive natural products has been reported [22]. Within this section a selected group of syntheses are described that serve to illustrate applications of cycloaddition and conjugate addition processes. Additionally, each of these syntheses increase the substrate scope compatible with iminium ion mediated transformations and expand the horizon of the chemistry accessible using simple chiral amines as catalysts.

Tamiflu ((-)-oseltamivir phosphate, **165**) is a potent inhibitor of neuraminidase which has been stockpiled by governments worldwide as a precautionary measure against a possible influenza pandemic. Fukuyama reported an efficient synthesis of this compound which commenced with an iminium ion catalysed Diels–Alder reaction of acrolein and dihydropyridine **160** catalysed by imidazolidinone *ent*-**12** expanding the scope of the dienes accessible using this chemistry. The crude product from the Diels–Alder reaction (**161**) was converted into bromolactone **162** in two further steps (26% overall yield; 99% ee). Functional group manipulation and Curtius rearrangement gave the highly substituted bi-cycle **163** which was hydrolysed to give aziridine **164**. This was then converted to tamiflu (**165**) by a four-step sequence (Scheme 66) [215].

The scope of the dienophile partner within the Diels–Alder reaction was further expanded in an insightful synthesis of (+)-hapalindole Q by Kerr and co-workers [216]. Cycloaddition of *N*-protected indole **166** and substituted diene **167** catalysed by imidazolidinium salt **12**·HCl (40 mol%) gave the densely functionalised Diels–Alder adduct **168** (35% yield; 93% ee), which was converted to the target alkaloid (**169**) in eight steps (Scheme 67).



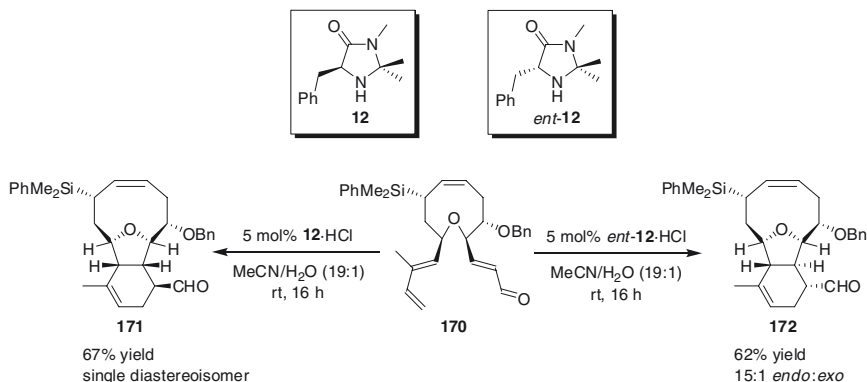
Scheme 66 Iminium ion catalysed Diels–Alder reaction in the synthesis of tamiflu



Scheme 67 Iminium ion catalysed Diels–Alder reaction in the synthesis of (+)-hapalindole Q

The majority of syntheses reporting organocatalytic transformations use the high levels of asymmetric induction frequently obtained to set key stereocentres in the early stages of the synthesis. Burton and Holmes have reported a diastereoselective IMDA in the late stages of the synthesis of the core of eunicellin revealing further opportunities using the reported catalysts [217]. Treatment of the homo chiral α,β -unsaturated aldehyde **170** (prepared in 18 steps from 2-deoxyribose) with **12** (5 mol%; CH₃CN/H₂O; rt) leads to the *exo* isomer **171** (67%) which represents the core of the target natural product (Scheme 68). Complimentary to this result, the use of *ent*-**12** leads selectively to the *endo* isomer **172** (62%; 15:1 *endo*:*exo*). The complexity and high selectivity observed pays tribute to the robust nature of the imidazolidinone catalysts.

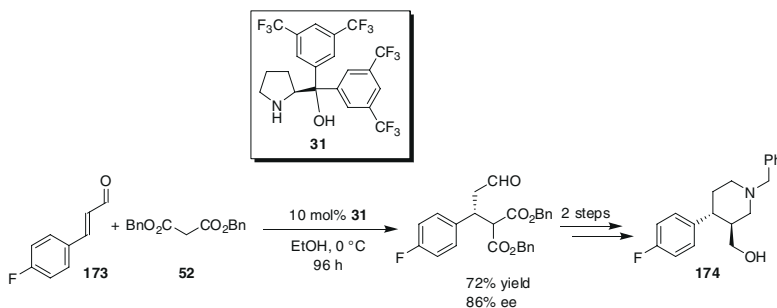
The power of intramolecular Diels–Alder reactions have also been exploited in the synthesis of a number of natural products. MacMillan reported a concise and highly practical synthesis of solanpyrone D [51, 218] and Koskinen described an



Scheme 68 Stereoselective iminium ion catalysed IMDA

IMDA strategy to access the core structure of amaminol A [52]. More recently, Jacobs and Christmann reported the synthesis of amaminol B [219].

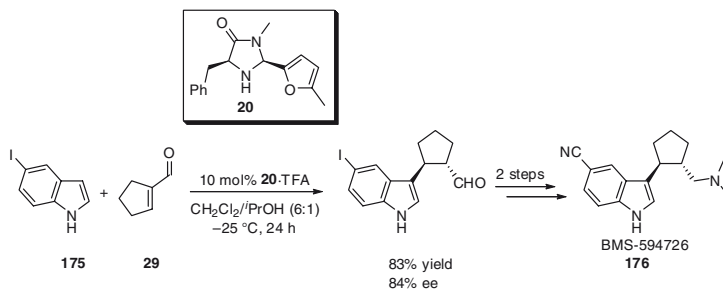
Jørgensen has exploited the conjugate addition reactions developed within his laboratories in a highly effective one-step synthesis of warfarin [95] and the preparation of the antidepressant (–)-paroxetine [96] both using diarylprolinol **31**. For example, conjugate addition of dibenzyl malonate **52** to substituted cinnamaldehyde **173** (10 mol% **31**; 72% yield; 86% ee) followed by reductive amination and reduction gave piperidine **174** which represents a formal synthesis of (–)-paroxetine (Scheme 69) [220]. Other examples of conjugate addition reactions that have been exploited in synthesis include Liang and Ye's conjugate addition of nitromethane to α,β -unsaturated aldehydes in the preparation of (*R*)-baclofen [103] and Fustero's addition of nitrogen nucleophiles en route to (+)-sedamine, (+)-allosdamine and (+)-coniine [115].



Scheme 69 Iminium ion catalysed conjugate addition in the synthesis of paroxetine

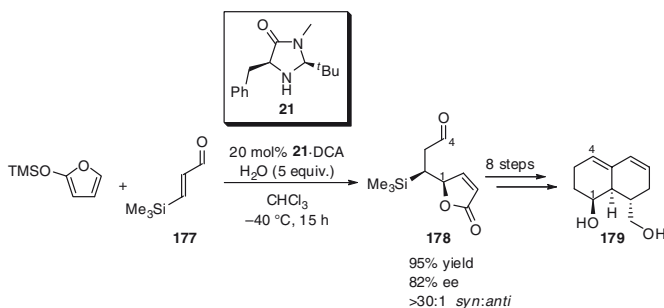
The powerful enantioselective alkylation methodology developed by MacMillan for the addition heteroaromatics and anilines to α,β -unsaturated

aldehydes was originally exploited in a synthesis of (–)-flustramine B [84]. The preparation of the serotonin reuptake inhibitor BMS-594726 (**176**) also used indole alkylation, significantly extending the scope of this reaction to include α,β -disubstituted aldehydes as substrates [221]. The strength of the method was highlighted by undertaking the synthesis on a 20g scale, the product from the conjugate addition of indole **175** to enal **29** being isolated in an excellent 83% yield (84% ee) (Scheme 70). The alkylation of pyrroles with α,β -unsaturated aldehydes in an intramolecular fashion was developed by Banwell in the synthesis of (–)-tashiromine [222]. The conjugate addition of electron rich aromatics to α,β -unsaturated aldehydes has also been exploited in the synthesis of the antitumour agent (+)-curcuphenol [223].



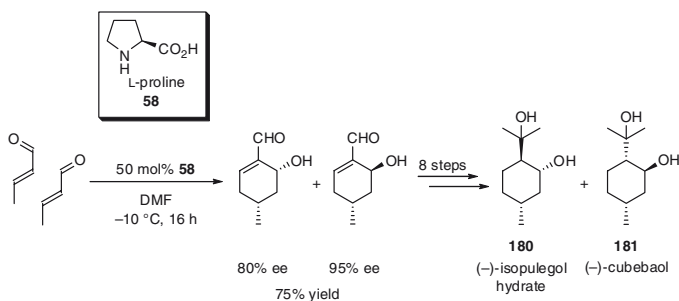
Scheme 70 Iminium ion catalysed conjugate addition of indoles in the synthesis of BMS-594726

MacMillan reported a short and effective synthesis of spiculisporic acid which elegantly exemplified his Mukaiyama–Michael addition of silyloxyfurans to α,β -unsaturated aldehydes [88]. Robichaud and Tremblay augmented this in a formal synthesis of compactin [224]. Within this report it was shown that low enantioselectivities were obtained in the conjugate addition to acrolein. Use of β -silyl acrolein **177** circumvented this and gave butenolide **178** in 95% yield and 82% ee. Conversion of adduct **178** to the decalin (**179**) in eight steps resulted in a formal synthesis (Scheme 71).



Scheme 71 Iminium ion catalysed Mukaiyama–Michael reaction in the synthesis of compactin

Hong and co-workers have described a formal [3+3] cycloaddition of α,β -unsaturated aldehydes using L-proline as the catalyst (Scheme 72) [225]. Although the precise mechanism of this reaction is unclear a plausible explanation involves both iminium ion and enamine activation of the substrates and was exploited in the asymmetric synthesis of (–)-isopulegol hydrate **180** and (–)-cubebaol **181**. This strategy has also been extended to the trimerisation of acrolein in the synthesis of montiporyne F [226].



Scheme 72 Iminium ion catalysed [3+3] addition in the synthesis of isopulegol hydrate and cubebaol

6 Mechanistic and Structural Investigations

One of the most compelling features of iminium ion catalysis is the proposed mechanistic rationale for the transformations, which leads to highly predictable reaction outcomes. Despite impressive advances and the plethora of reactions reported efforts to provide a detailed mechanistic understanding of the catalytic cycle are limited. The reported work has focussed on the Diels–Alder cycloaddition and has provided useful indicators that could be used in design of more active catalysts.

Ogilvie monitored the Diels–Alder reaction between cinnamaldehyde and cyclopentadiene by ^1H NMR using his hydrazone catalyst **18** and was able to conclude that under the reaction conditions adopted (**18**·TfOH 100 mol%; $\text{CD}_3\text{NO}_2/\text{D}_2\text{O}$ (19:1); 0.1 M) cycloaddition was the rate limiting step of the catalytic cycle, iminium ion formation and hydrolysis being rapid [48]. In addition, it was also shown that under these reaction conditions the key cycloaddition step was reversible. Although this unexpected reversibility was slow, the possibility of exploiting this in a dynamic resolution procedure appears tempting.

Platts and Tomkinson reported a detailed quantitative study of the iminium ion catalysed Diels–Alder reaction between cyclopentadiene and cinnamaldehyde catalysed by trifluoromethyl pyrrolidine salt **182**·HPF₆ [227]. This combination of secondary amine, co-acid and dienophile allowed the isolation and structural elucidation of the reactive iminium ion intermediate. As a result it was possible to

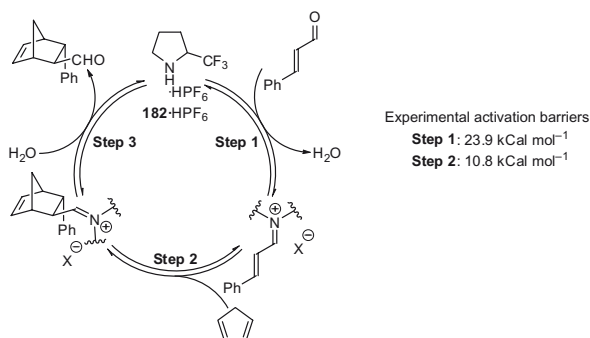


Fig. 16 Kinetics of iminium ion catalysis using trifluoromethyl pyrrolidine

examine both iminium ion formation (step 1) and Diels–Alder cycloaddition (step 2) independently (Fig. 16). In line with Ogilvie’s observations it showed iminium ion formation ($k_{293} = (2.65 \pm 0.35) \times 10^{-3} \text{ dm}^{-3} \text{ mol}^{-1} \text{ s}^{-1}$) and hydrolysis to be rapid with Diels–Alder cycloaddition being rate limiting ($k_{293} = (3.74 \pm 0.02) \times 10^{-4} \text{ dm}^{-3} \text{ mol}^{-1} \text{ s}^{-1}$). From this study it was concluded that design of more active catalysts should target lowering the energy level of the iminium ion LUMO. This could conveniently be predicted through theoretical calculations prior to experimental investigation and should prove of great use to those working in the field.

X-Ray crystal structures of the MacMillan imidazolidinones **12**·HCl and *ent*-**12**·HCl have been reported [228]. Iminium ions derived from a hydrazide [47] and trifluoromethyl pyrrolidine [227] have also been characterised through crystallography.

7 Theoretical Investigations

Despite the impact of iminium catalysis on the synthetic community, theoretical investigations to understand the mechanism of the catalytic cycle, origins of asymmetric induction and reactivity of catalysts have been limited.

Computational investigations have mainly focussed on examining the reactivity of iminium ions (e.g. Diels–Alder reactions, conjugate additions etc.), although some efforts have been made towards modelling the formation of iminium ions (Fig. 2, Step 1). Platts studied the formation of iminium ions between acrolein and a series of secondary ammonium chloride salts at the B3LYP/6–31+G(d,p) level using an Onsager solvent model [229]. The model included an explicit molecule of water and the results suggest that this is intimately involved in the reaction pathway, acting as a ‘proton shuttle’. Based on these calculations Platts proposed that deprotonation of the amine is the rate determining step in iminium ion formation. This differs from the traditional view of imine formation where attack on the carbonyl is

thought to be rate determining [230], but does suggest a reason why the choice of solvent and the strength of the co-acid have such an impact on iminium catalysed processes.

Diels–Alder cycloaddition reactions of iminium ions (Sect. 2.1.1) could take place with either the C=N bond or the C=C bond acting as the dienophile. This potential dual reactivity was investigated by Zora using the AM1 semi-empirical method [231]. The results showed not only the preferred C=C reactivity (activation barrier is 4.20 kCal mol⁻¹ lower than for reaction with the C=N bond) but also suggested that the reaction was stepwise.

The conjugate addition of nitroalkanes to α,β -unsaturated aldehydes (Sect. 2.2.2) has been investigated by Uggerud, who compared the uncatalysed, proton catalysed and iminium ion catalysed additions [232]. The results suggested that protonated acrolein was more activated towards addition than the iminium ion catalysed process and also indicated that an intermediate oxazolidin structure **183**, unobserved experimentally, may be involved in the reaction pathway (Fig. 17) with the transition state resembling that of a [3+2] cycloaddition process.

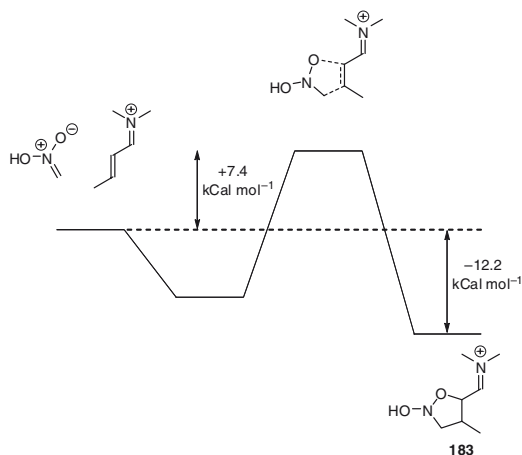


Fig. 17 Potential energy diagram for the addition of nitromethane to crotonaldehyde

The primary aim of the investigation and, perhaps, its greatest contribution, was to evaluate the accuracy of the popular and computationally inexpensive DFT method, B3LYP/6-31G(d), for investigating these reaction pathways. Comparisons of the results with those obtained using a high level ab initio benchmark (G3) showed that B3LYP/6-31G(d) performed exceptionally well with near quantitative agreement for the energies of all intermediates and transition structures.

Studies using this method to investigate iminium ions and their reactions have been undertaken by Houk who has concentrated principally on systems derived from the imidazolidinones of MacMillan (Schemes 2 and 6). His investigations into the geometries of iminium ions confirmed the predicted high selectivity for (*E*)-

iminium ions (Fig. 3) [233]. Intriguingly, the lowest energy iminium ion geometry differs from that proposed by MacMillan (Fig. 3). This calculated structure shows the phenyl ring of the benzyl group sitting above the imidazolidinone ring. The conformation proposed by MacMillan is 0.3 kcal mol⁻¹ higher in energy and the lowest energy (*Z*)-isomer a further 0.9 kcal mol⁻¹ above that (Fig. 18).

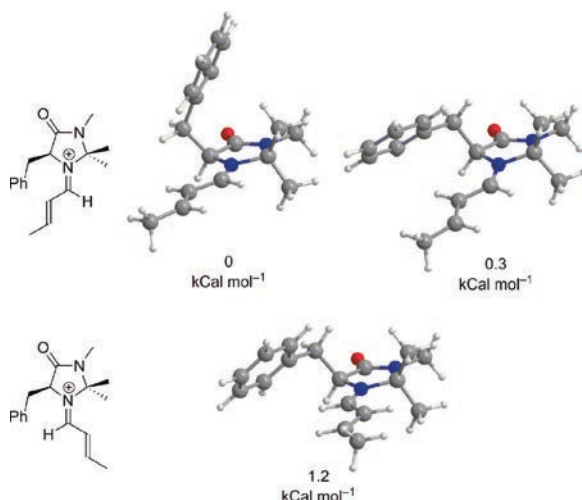


Fig. 18 The three lowest energy iminium ion conformations obtained by Houk

Additionally, investigations into imidazolidinone catalysed Diels–Alder reactions (Schemes 2 and 6) [234] have shown that iminium ions of α,β -unsaturated aldehydes and ketones have lower activation barriers for the Diels–Alder reaction with cyclopentadiene than the parent compound (13 and 11 kcal mol⁻¹, respectively). It was also noted that transition structures show the formation of the bonds is concerted but highly asynchronous.

Houk has also considered the alkylation reactions of pyrroles and indoles using the same class of catalyst. The report addresses the fact that while catalyst **12** provides high ees in the alkylation of pyrroles (Scheme 15), the same is not true of indoles and catalyst **21** is required instead (Scheme 16). A thorough examination of the accessible transition states for the reaction of iminium ion **184** with pyrrole and with indole led to the conclusion that the two reactions occur through different transition states. Pyrrole adopts a closed transition state reminiscent of that of the Diels–Alder reaction whereas indole adopts an open transition state (Fig. 19) [233].

Using this information in conjunction with a study into the preferred conformations of iminium ions generated from catalysts **12** and **21**, Houk suggests that the additional steric bulk of the *tert*-butyl group causes the benzyl arm of the catalyst to shield better the Si face of the C=C double bond – a requirement for high ees in an open transition state. For both the Diels–Alder and pyrrole/indole alkylation

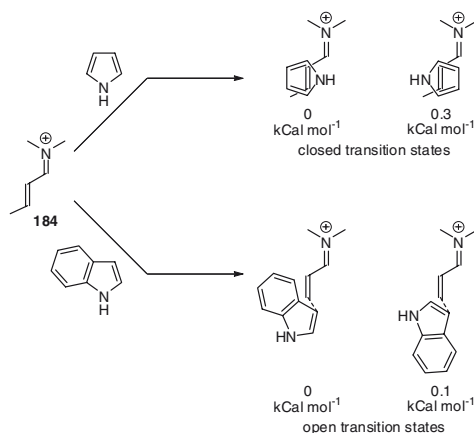


Fig. 19 Lowest energy transition states for the addition of pyrrole and indole to iminium ions

reactions, the computational studies have enabled a rationalisation of the selectivities observed by experiment and have given an insight into the accessible conformations of the iminium ions.

In order to understand better the catalysis of the conjugate addition of heteroatom nucleophiles to α,β -unsaturated aldehydes by the diarylprolinol ether **55**, Jørgensen used DFT calculations (B3LYP/6-31G(d)) to investigate the intermediates and transition states involved in such reactions. For a triazole nucleophile, the calculations predicted an ee of 90%, which was in good agreement with that observed experimentally (92% ee) [111]. Most significantly, investigation of the reaction pathway indicated that protonation of the enamine intermediate occurs by water assisted proton transfer from the triazole nitrogen atom (Fig. 20). In the case of phosphite nucleophiles, the study led to an understanding of the enantiocontrol in the reaction allowing rationalisation of the conditions required for optimal selectivity [119].

To date, the use of computational methods to investigate iminium ion catalysis has been limited. The focus has been on rationalising the diastereo- and enantioselectivities observed in the laboratory, but this has largely been retrospective and the clear potential of these models as predictive tools for the design of improved catalysts or even entirely new scaffolds has yet to be realised. There are few examples of solid kinetic data in the literature making evaluation of the models difficult.

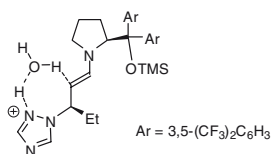


Fig. 20 Water assisted proton transfer in an enamine intermediate

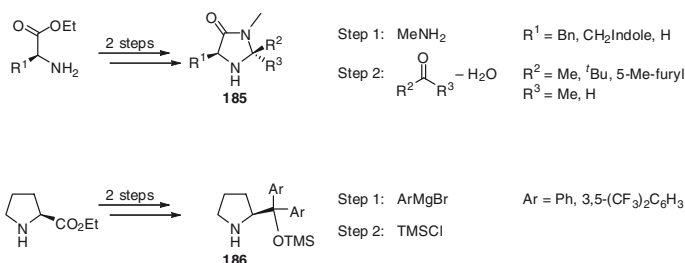
While the information has certainly advanced the understanding of the form of the transition structures, the issues of counterion and explicit solvent effects have yet to be addressed, largely as a result of limitations of the computational methods so far employed.

8 Conclusions and Perspectives

The area of iminium ion catalysis has been an exciting and vibrant area of research in recent years. Exploitation of this mode of activation for α,β -unsaturated aldehydes and, to a lesser extent, ketones has provided methods to catalyse a variety of standard synthetic procedures in high yield and enantiomeric excess. Two principle classes of catalyst have emerged from these investigations which are robust, reliable and non-reaction specific: the imidazolidinones **185** and the diarylprolinol ethers **186**. Many of these catalysts are available from commercial sources which will undoubtedly accelerate their uptake over the coming years. Additionally, both architectures are readily accessible in both enantiomeric forms from commercially available starting materials, thus adding to their attraction. The general reaction sequence to access these is outlined in Scheme 73 [3, 50, 145, 235, 236].

The key advantage that this class of catalysis offers to the synthetic community lies in the true practicality of the transformations. The ability to carry out reactions at room temperature in the presence of both moisture and air in high yield and optical purity can be viewed as the Holy-Grail of the synthetic chemist. Iminium ion catalysis makes significant inroads into meeting these targets. Additionally, the ability to apply this technology to tandem, cascade and multicomponent coupling reactions allows for the formation of densely functionalised molecules from simple achiral precursors in a single step [237]. The strategies and methods described within this review form the basis of a simple and effective mode of activation for key chemical building blocks and it can be expected that exciting advances will continue to be disclosed.

Despite rapid progress in iminium ion catalysis it is still a maturing field and significant challenges remain if it is to become a bench-mark method of choice. The



Scheme 73 Preparation of imidazolidinone and diarylprolinol catalysts

obstacles to this advancement are becoming more apparent and key chemical challenges can be summarised as follows:

- Substrate scope – can a universal catalyst be developed for the activation of any α,β -unsaturated aldehyde and ketone with multiple substitutions?
- Catalyst activity – can the activity of catalysts be increased to achieve similar levels of yield and asymmetric induction with reduced catalyst loading?
- Catalyst activity – why are many of the selectivities and activities reported sensitive to subtle changes in the amount of water present in the reaction medium and the nature of the co-acid additive?

Although these are lofty goals, it can be certain that the synthetic community has the drive, ambition and capabilities to rise to these challenges and the impetus to continue development of the area is clear. An important factor in the realisation of these goals will come from a more intimate understanding of mechanism and mode of action which have remained under explored to date and certainly offer great opportunity to those entering this competitive field of research.

In conjunction with both metal catalysed and other organocatalytic methods the power of the synthetic chemist to construct more complicated targets will only increase and have profound beneficial effects on society.

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Lewis Acid Organocatalysts

Oksana Sereda, Sobia Tabassum, and René Wilhelm

Abstract The term Lewis acid catalysts generally refers to metal salts like aluminium chloride, titanium chloride and zinc chloride. Their application in asymmetric catalysis can be achieved by the addition of enantiopure ligands to these salts. However, not only metal centers can function as Lewis acids. Compounds containing carbenium, silyl or phosphonium cations display Lewis acid catalytic activity. In addition, hypervalent compounds based on phosphorus and silicon, inherit Lewis acidity. Furthermore, ionic liquids, organic salts with a melting point below 100 °C, have revealed the ability to catalyze a range of reactions either in substoichiometric amount or, if used as the reaction medium, in stoichiometric or even larger quantities. The ionic liquids can often be efficiently recovered. The catalytic activity of the ionic liquid is explained by the Lewis acidic nature of their cations. This review covers the survey of known classes of metal-free Lewis acids and their application in catalysis.

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1 Introduction

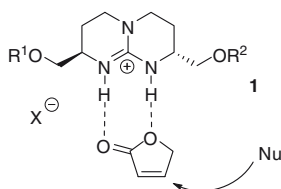
Until recently the most popular method in asymmetric catalysis was the application of metal complexes. This is not surprising, since the use of different metals, ligands and oxidation states makes it possible to tune selectivity and perform asymmetric induction very easily. Thus, the concept of asymmetric catalysis has become almost synonymous with the use of metals coordinated by chiral ligands [1,2]. In many examples the metal is a Lewis acid [3].

Roles that are normally associated with metals as Lewis acids and as redox agents [4,5], can be emulated by organic compounds. This review will introduce the reader to the research field of Lewis acid organocatalysts. This field, compared to other types of organocatalysts, which are highlighted in the other chapters of this volume, is still limited. The number of asymmetric catalyzed examples is small, and the obtained enantiomeric excess is sometimes low. Therefore, this review will also cover a number of reactions promoted by achiral catalysts. Nevertheless, due to the broad variety of possible reactions, which are catalyzed by Lewis acids, this research field possesses a large potential.

Compounds containing carbenium, silyl or phosphonium cations can act as Lewis acids. In addition, phosphorus- and silicon-based hypervalent compounds display a Lewis acid catalytic activity. Furthermore, ionic liquids, organic salts with a melting point below 100 °C, have shown the ability to catalyze a group of reactions either in substoichiometric amount or, if used as the reaction medium, in stoichiometric or even larger quantities. The solvents can be efficiently recovered after the reaction. Each type of these compounds will be discussed in a separate section.

This review will concentrate on metal-free Lewis acids, which incorporate a Lewis acidic cation or a hypervalent center. Lewis acids are considered to be species with a vacant orbital [6,7]. Nevertheless, there are two successful classes of organocatalysts, which may be referred to as Lewis acids and are presented in other chapter. The first type is the proton of a Brønsted acid catalyst, which is the simplest Lewis acid. The enantioselectivities obtained are due to the formation of a chiral ion pair. The other type are hydrogen bond activating organocatalysts, which can be considered to be Lewis acids or pseudo-Lewis acids.

There are some types of organic cations which cannot be placed under the heading of Lewis acid organocatalyst. For example, one type is the chiral guanidinium salt **1** which has been used as a catalyst [8] in the Michael reaction. Due to the mode of activation as shown in Scheme 1, this salt belongs to the hydrogen bond activating organocatalysts. In this example, **1** gave only a racemic product (Scheme 1). In addition, a chiral amidinium salt [9], which catalyzed the Diels-Alder reaction with significant enantiomeric excess, would also belong to the class of hydrogen bond activating organocatalysts.



Scheme 1 Michael reaction

Another type would be ammonium cations of the types RNH_3^+ , R_2NH_2^+ or R_3NH^+ which could be considered to be Brønsted acids or hydrogen bond activating organocatalysts. Fully substituted ammonium cations, R_4N^+ , could interact with a carbonyl group, lowering the electron density of its carbon atom. Yet, since the ammonium cation does not possess an empty orbital to take up an electron pair, it is not a Lewis acid. However, enantiopure ammonium salts have been used very efficiently in asymmetric phase transfer catalysis, which has been reviewed [10–19].

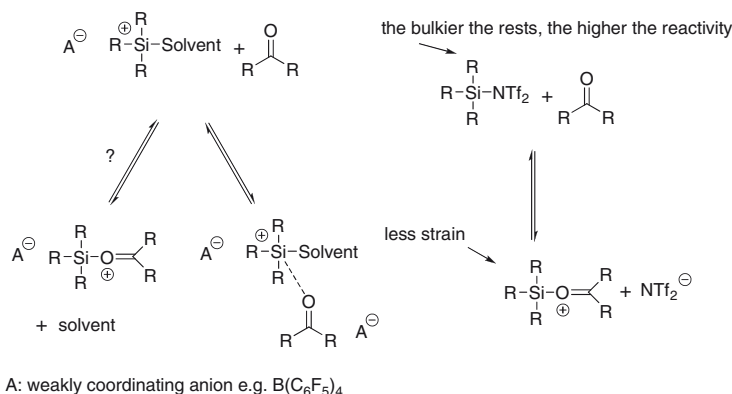
One section in this review will deal with silyl cations, another with hypervalent silicon compounds. The concept of hypervalent silicon compounds belongs, strictly speaking, to the class of Lewis base catalysis. However, since a Lewis base forms in situ with a silicon containing reagent or SiCl_4 an intermediate, which functions as a Lewis acid to activate substrates during the reaction, we would also present a few examples in this review. Since silicon is a semimetal we leave it up to the reader to decide whether silicon catalysts should be considered as organocatalysts.

Another semimetal is boron, which has been used for a long time as a Lewis acid, e.g. BF_3 , and of which enantiopure derivatives have been applied very successfully. Asymmetric boron catalysts have been reviewed [20–23] and will not be a part of this article.

2 Silyl Cation-Based Catalysts

Silicon-based Lewis acids have been known for some time, and the related chemistry in catalysis has recently been reviewed [24]. Most examples in the literature are mainly based on achiral species and will be discussed only briefly in this section. In general, a broad variety of reactions can be catalyzed with compounds like Me_3SiOTf , $\text{Me}_3\text{SiNTf}_2$ or $\text{Me}_3\text{SiClO}_4$. One advantage over some metal Lewis acids is that they are compatible with many carbon nucleophiles like silyl enol ethers, allyl organometallic reagents and cuprates.

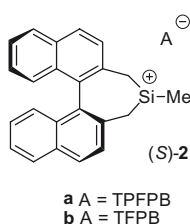
Overall, it is possible to divide the silyl Lewis acids into two groups, depending on how strong the counter anion interacts with the silicon atom as shown in Scheme 2. In the case where a very weakly coordinating anion is part of the compound, one could consider that a free silyl cation is present. However, the silyl cation is very strong and will be coordinated by solvent molecules like acetonitrile or toluene [25, 26]. This complex could activate, for example, a carbonyl group. Whether the carbonyl group replaces the solvent molecule is not known. In the case



Scheme 2 Silyl based Lewis acid catalysis

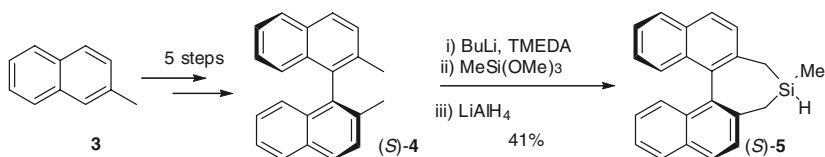
where a more coordinating anion is present, a neutral silicon molecule should be postulated. A carbonyl oxygen could perform an exchange with the $[\text{NTf}_2]$ ligand. The larger the three alkyl rests around the silicon atom are, the better the exchange takes place, due to the release of strain, replacing the larger $[\text{NTf}_2]$ substituent with a smaller carbonyl ligand [27–29].

In 1998 the groups of Jørgensen and Helmchen reported the preparation of the chiral silyl cationic salt **2** (Scheme 3) [30]. This was the first time that a chiral silyl cation was used as a catalyst in an enantioselective reaction. In order to ensure that the silyl salt had a high reactivity, the almost chemically inert and non-coordinating anions tetrakis[pentafluorophenyl]borate [TPFPB] and tetrakis[3,5-bis (trifluoromethyl)phenyl]borate [TFPB] were chosen as counter anions.

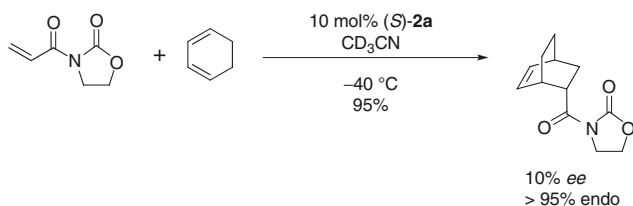


Scheme 3 Axial chiral silyl salt

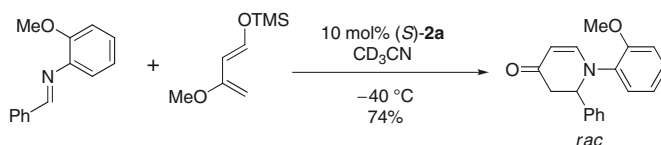
The salt precursor was prepared according to the following route as shown in Scheme 4. The desired enantiopure binaphthyl compound (*S*)-**4** was made from 2-methylnaphthalene (**3**) over five steps, which also included a resolution step [31–33]. The final precursor (*S*)-**5** was obtained in 41% yield via a deprotonation of (*S*)-**4** followed by the reaction with methyltrimethoxysilane and a subsequent reduction.

**Scheme 4** Preparation of **5**

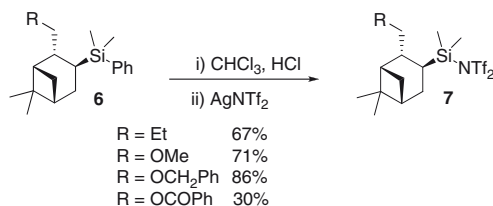
Since silyl cations are highly reactive and moisture sensitive, the salts (*S*)-**2a** and (*S*)-**2b** were prepared *in situ* from the air and moisture stable precursor (*S*)-**5** via a hydride transfer [34, 35] with trityl tetrakis[3,5-bis(trifluoromethyl)phenyl]borate [Tr][TFPB] or trityl tetrakis[pentafluorophenyl]borate [Tr][TPFPB]. The authors showed by ^{29}Si -NMR studies that the desired salts were formed. The silyl salt (*S*)-**2a** was then tested in the Diels-Alder reaction as shown in Scheme 5. A good reactivity was found, and the product was obtained in 95% yield with higher than 95% *endo* selectivity at -40°C in 1 h. However, only 10% ee was achieved.

**Scheme 5** Diels-Alder reaction

In addition, it was possible to show that salt (*S*)-**2a** could catalyze the aza-Diels-Alder reaction as presented in Scheme 6. Benzyldiene-2-methoxyaniline and Danishefsky's diene in the presence of 10 mol% catalyst at -40°C gave the desired product in 74% yield in just 2 h. Unfortunately, the obtained product was racemic.

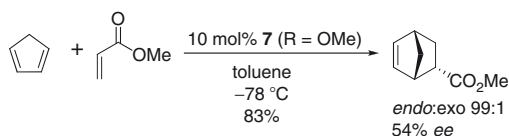
**Scheme 6** aza-Diels-Alder reaction

A second example of an enantiopure silicon-based catalyst was reported by the group of Ghosez [27]. They concluded from the results of Simchen and Jonas [28] as described above, that R_3SiNTf_2 compounds, bearing bulky chiral groups, should possess a good catalytic activity. Silylated sulfonimides from readily available (–)-myrtenal were obtained in few steps to give the desired precursors **6** shown in Scheme 7. The salts were prepared *in situ* by transforming silane **6** to the corresponding silyl chloride with HCl in CHCl_3 followed by the treatment with AgNTf_2 .



Scheme 7 Preparation of catalysts **7**

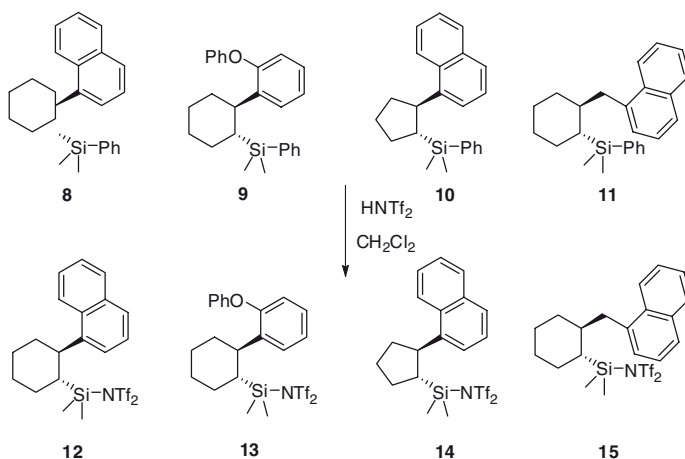
The catalysts were tested in the Diels-Alder reaction of cyclopentadiene and methyl acrylate. The best result is given in Scheme 8. Catalyst **7** (R = OMe), bearing an oxygen atom, which can stabilize the silicon center through coordination, gave the product in 83% yield with an ee of 54% in favour of the *endo* product in 1.5 h. In case of **7** (R = Et) without an oxygen atom, a significantly lower ee of 7% was observed. Next to toluene, solvents like ether, propionitrile or CH₂Cl₂ were tested, but gave no desired product.



Scheme 8 Diels-Alder reaction

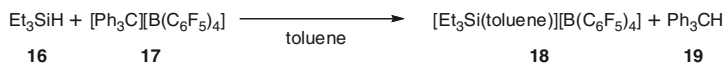
The same group reported the synthesis of enantiopure cycloalkylsilyl triflimides [36]. Some examples are presented in Scheme 9. The precursors were prepared from cyclohexenones and cyclopentanones, which were transferred in three steps into racemic 2-aryl- and arylmethyl-3-dialkylphenylsilyl cycloalkanones. These were resolved by preparative chiral HPLC. Next, the carbonyl function was removed to give the desired precursors to the silyl triflimides. The latter were obtained in situ directly by the treatment with HNTf₂. The formation of these compounds could be followed by ¹H-NMR due to the signals of the methyl groups connected to the silicon atom. The signals shifted from 0.20 ppm to 0.60 ppm. In addition a signal at 7.36 ppm appeared due to the formation of benzene during the course of the reaction.

The salts were afterwards tested in the Diels-Alder reaction of methyl acrylate and cyclopentadiene as depicted in Scheme 8. In contrast to the previous investigation [27], CH₂Cl₂ was found to be a good solvent for the reactions. A 10 mol% catalyst was prepared in situ, and the reaction was performed at -78°C in the presence of 2,6-di-*tert*-butyl-4-methylpyridine to trap any residual HNTf₂. The best result was obtained with compound **12** giving the product in high *endo* selectivity in 96% yield and 50% ee. When -100°C was chosen as the reaction temperature, 94% yield and 59% ee were reached in less than 2 h. Contrary to the previous example, catalyst **13** containing an oxygen atom, gave poor results with low *endo* selectivity and 35% ee. The cyclopentane-based analogue **14** gave an ee of 56%; however, the *endo/exo* selectivity was 32%. The results with catalyst **15** showed that an insertion of a methylene group between the cyclohexene ring and the 1-naphthyl group gave a significant lower ee of 7% due to the higher conformational mobility in this catalyst.



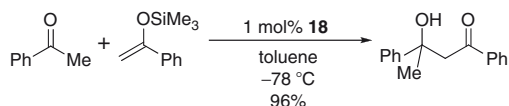
Scheme 9 Preparation of catalysts **12–15**

Further on, Sawamura et al. [37] investigated the influence of different counter anions on the catalytic activity of cationic silicon Lewis acids. In the studies an achiral salt was used. In previous cases [30] acetonitrile was used as a solvent, which is known to coordinate strongly the silicon cation species. Therefore, the application of toluene as a solvent was investigated with a silicon cationic species. Although even toluene coordinates a silicon cation [25, 38], an enhanced activity compared to other solvents, was found. The achiral salt was prepared in situ from triethylsilane and $[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$ (**17**) as depicted in Scheme 10.



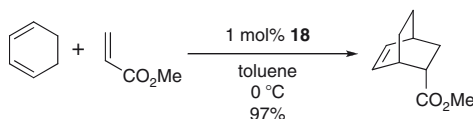
Scheme 10 Preparation of salt **18**

The salt **18** was explored in the Mukaiyama aldol reaction with acetophenone, and a yield of 96% was obtained after 1 h at -78°C (Scheme 11). When Me_3SiOTf was used as a catalyst, a yield of 0% was observed. $\text{Me}_3\text{SiNTf}_2$ and $\text{Et}_3\text{SiNTf}_2$ resulted in 12% and 8% yield, respectively.



Scheme 11 Mukaiyama aldol reaction

In addition, the Diels-Alder reaction was found to be catalyzed by salt **18** giving the *endo*-product in 97% yield in 1 h. Application of Me_3SiOTf resulted in no product formation, while $\text{Me}_3\text{SiNTf}_2$ and $\text{Et}_3\text{SiNTf}_2$ gave a yield of 6 and 13%, respectively (Scheme 12). Both reactions proceeded in the same way in the presence of the proton scavenger 2,6-di-*tert*-butylpyridine with salt **18**, which should rule out a proton promoted reaction.

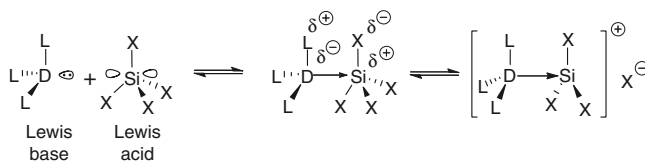


Scheme 12 Diels-Alder reaction catalyzed with salt **18**

In summary, due to the low ees so far obtained with silyl-based Lewis acids, there is still much room for optimization. The latter is a promising and worthwhile task, considering the large number of reactions catalyzed by the achiral analogues and their advantages over metal Lewis acids.

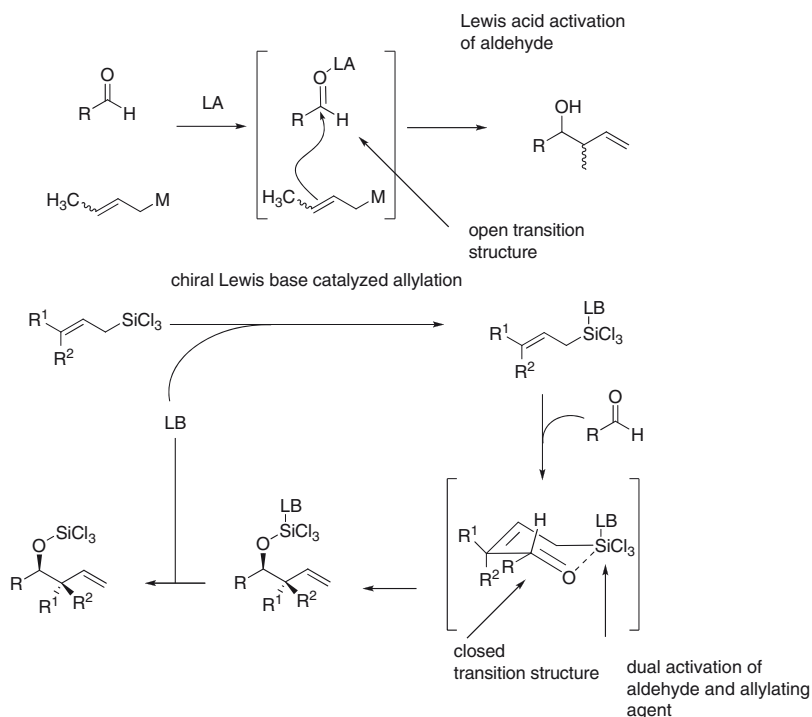
3 Hypervalent Silicon-Based Catalysts

Lewis bases in combination with silicon containing reagents can form in situ a Lewis acid center, which can activate a substrate. Therefore, a few examples would be presented in this section, although this type of catalysis is mainly considered to be part of Lewis base catalysis. Due to the valence shell expansion capability of silicon, Lewis bases tend to interact with vacant orbitals residing on the silicon. This interaction of Lewis bases increases the electron density on the most labile ligand of the silicon atom. Once the ligand is ionized or partially ionized, a positively charged silicon complex is formed, which acts as a Lewis acid due to its free 3d-orbitals responsible for many organic transformations [24, 39–44] (Scheme 13).



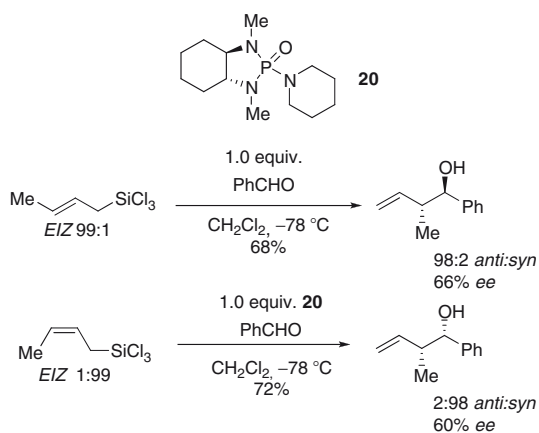
Scheme 13 Lewis base-Lewis acid pair

First, a few examples with silicon atom in one of the reaction partners will be discussed. The asymmetric allylation of carbonyl compounds with an allylating agent leads to homoallylic alcohols with two consecutive stereocenters along with a carbon-carbon bond formation. The traditional method for this is the use of Lewis acids that activate an electrophilic aldehyde towards nucleophilic attack of an allyl metal reagent (Scheme 14) [2]. The use of the latter gives high enantioselectivity, but lacks diastereoselectivity. This is because of the non-rigid transition state in the reaction. In contrast, chiral Lewis base catalyzed allylations provide a dual mechanism of activation, which involves binding of the Lewis base with a nucleophile (trichlorosilane), thus generating a reactive hypercoordinated silicate species, which further coordinates with aldehydes. Since the reactions proceed in the close assembly of allyltrichlorosilane, aldehyde and chiral Lewis base, a high degree of diastereoselectivity and enantioselectivity can be achieved [40].



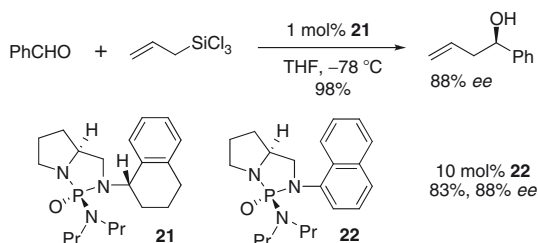
Scheme 14 Chiral Lewis base catalyzed allylation

The first example of a chiral Lewis base promoted allylation was given by Denmark and coworkers in 1994 [45]. Stoichiometric amounts of chiral phosphoramidate (*R,R*)-**20** facilitated the enantioselective allylation (Scheme 15). There was a complete stereochemical correlation between the geometry (*E/Z*) of allylsilane and the diastereomeric ratio (*syn/anti*) of the products.



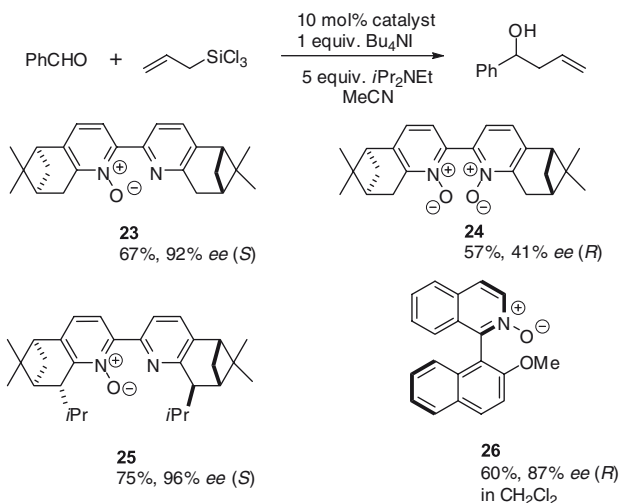
Scheme 15 Lewis base **20** catalyzed allylation

Similar results were reported by the Barret group by using stoichiometric amounts of an enantiopure 2-(2-pyridinyl)-2-oxazoline [46]. In 1996, Iseki and Kobayashi achieved a catalytic version of the asymmetric allylation [47]. They applied proline-based chiral HMPA derivatives for the allylation. The catalyst **21** proved to be the best one regarding catalyst loading down to 1 mol% (Scheme 16) [48].



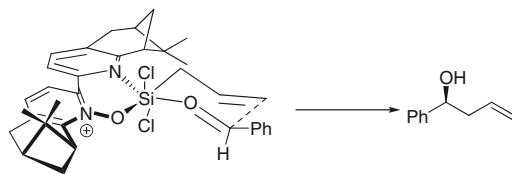
Scheme 16 Lewis base **21** catalyzed allylation

Amine *N*-oxides, possessing the property of Lewis basicity, have also been exploited in an enantioselective allylation. Malkov and Kočovský prepared a series of chiral *N*-oxide catalysts and found, that ligands **23** and **25** afforded good yield and stereoselectivity (Scheme 17) [49–51].



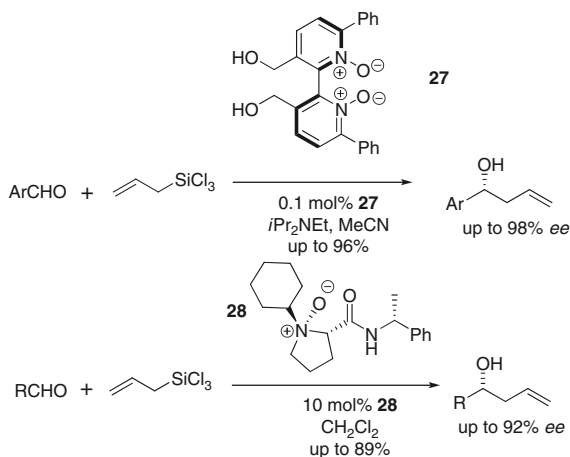
Scheme 17 Enantioselective Allylation with axial chiral *N*-oxides

Mechanistic analysis suggests that the *N*-oxide activates the trichlorosilane functionality and the other nitrogen atom stabilizes the complex by chelation, thus leading to closed chair-like transition state [49, 52]. Scheme 18 shows the possible transition state.



Scheme 18 Proposed Intermediate

Hayashi et al. achieved high catalytic activity by using axially chiral *N*-oxide catalyst **27**. As compared to other organic catalysts, the reaction proceeded much faster, and high enantioselectivities were obtained with 0.01–0.1 mol% catalyst loading [53–55]. In 2005, Hoveyda and Snapper used a novel proline-based aliphatic *N*-oxide **28** for an asymmetric allylation (Scheme 19) [56].



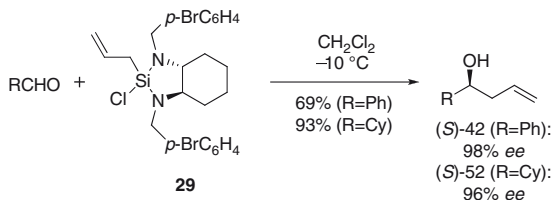
Scheme 19 Allylation catalyzed with Lewis base **27** and **28**

In addition, Iseki et al. reported a highly enantioselective allylation reaction with aliphatic and unconjugated aldehydes. They used chiral DMF derivatives and observed a dramatic increase in the yield and enantioselectivity of the reaction, when a stoichiometric amount of HMPA was employed [57, 58].

Next, enantiopure silicon allylation reagent will be presented, which already inherits Lewis acidity. It is accepted that Lewis acidity of silicon, as well as its high tendency to expand valence shell, increases [59, 60] if it is tetravalent and incorporated into strained four- or five-membered ring systems (strain-release Lewis acidity) [61]. This corresponds to smaller energy gaps between sp^3 and dsp^3 orbitals of a strained system as compared to an acyclic species.

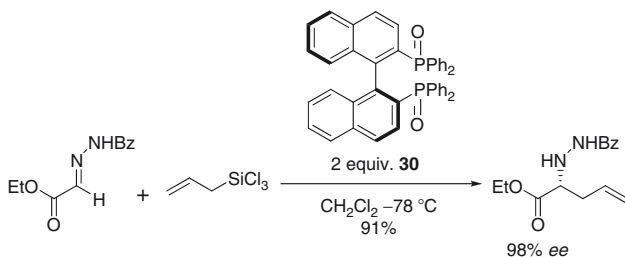
Leighton has combined this concept of *strained silacycles* [62–66] with the asymmetric allylation chemistry in a series of publications [60, 67–70]. Leighton's allylic silacyclopentane **29** [67] (Scheme 20) works equally for allylation of aromatic and aliphatic aldehydes in the absence of additional Lewis bases (promoter activator) or Lewis acids with high yield and enantioselectivity. The mechanism of

the reaction is not completely understood, but it likely involves a cyclic transition state with a trigonal bipyramidal geometry at a pentacoordinated silicon [59, 70].



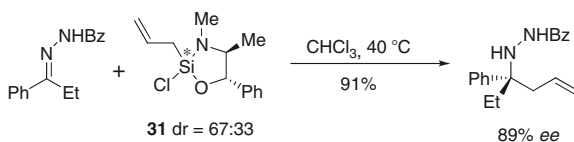
Scheme 20 Allylation with reagent **29**

Furthermore, next to aldehydes, acylhydrazones have been used in the allylation reaction. Kobayashi and coworkers found that achiral phosphineoxides catalyze the allylation of acylhydrazone [71, 72]. Next, a method for an asymmetric allylation of *N*-acylhydrazone with chiral BINAP dioxide **30** was developed (Scheme 21) [71, 72].



Scheme 21 Allylation with Lewis base **30**

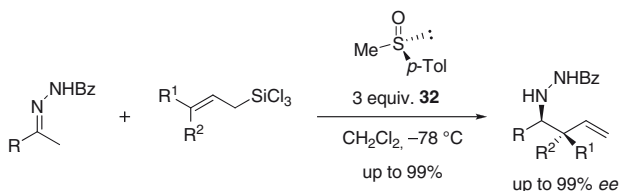
The synthesis of tertiary carbinamines is an important goal in organic synthesis. Leighton reported allylation of benzoylhydrazone by using the allylic silane reagent **31** giving tertiary carbinamines with high enantioselectivity in 24 h (Scheme 22) [70]. This reaction is exceptional, since high enantioselectivity was achieved with the diastereomeric mixture of the allylating reagent **31**. There may be two possible explanations [60]. First, by using 1.5 equiv. excess of **31**, only the major diastereomer transfers an allyl group and the minor remains unreactive. Second, the reaction proceeds through a hypervalent silicon intermediate, which is prone to a pseudorotational process. More likely the stereogenic silicon fast epimerizes and only one diastereomeric intermediate transfers the allyl group.



Scheme 22 Allylation with reagent **31**

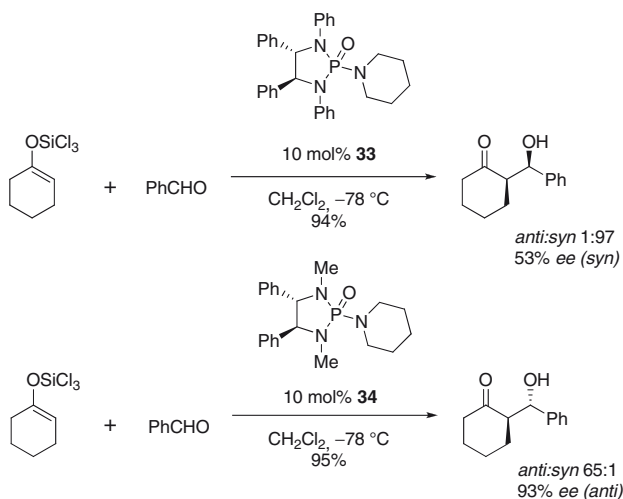
Imidazoles/benzimidazoles and chiral carbinamines are of particular importance [73, 74]. Recently, Leighton et al. developed a method for enantioselective imidazole directed allylation of aldimines and ketimines [75] with an analogue of **31**.

Next to P(O) or N(O) Lewis bases, there are very rare cases where enantiopure sulfoxides are used in combination with silanes. Kobayashi and coworkers reported a highly diastereoselective and enantioselective allylation of hydrazones with chiral sulfoxide **32** (Scheme 23) [76]. Massa [77, 78] and Barness [79] reported the asymmetric allylation of aldehydes with enantiopure sulfoxides, respectively, with moderate selectivity.



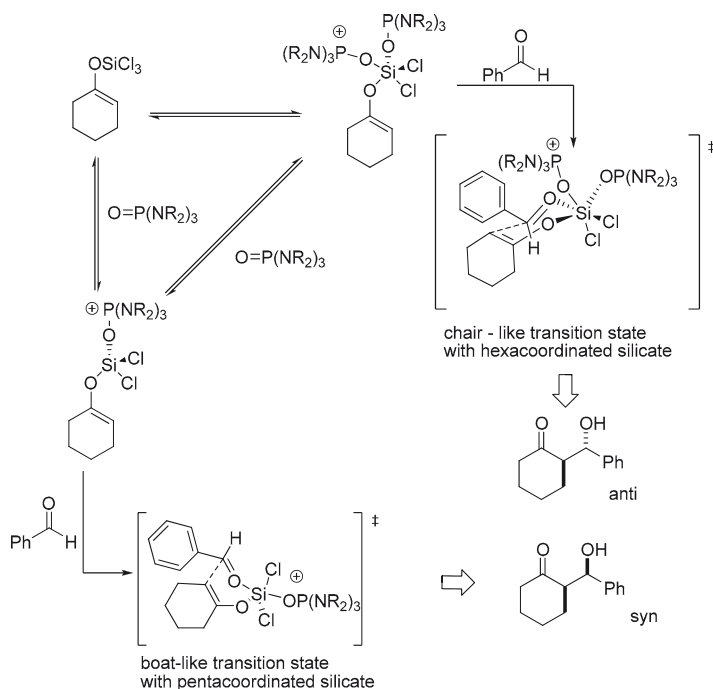
Scheme 23 Allylation with sulfoxide **32**

In the following a few examples of the asymmetric aldol reaction are given. Silyl enol ethers (O-Si) resemble very much allylsilanes (C-Si) in terms of structure and mode of action. That is why Lewis base catalyzed aldol reactions of silyl enol ethers have been extensively studied. The first example of Lewis base catalyzed asymmetric aldol reaction of trichlorosilyl enol ether with chiral phosphoramidate [80–91] was reported by Denmark et al. (Scheme 24).



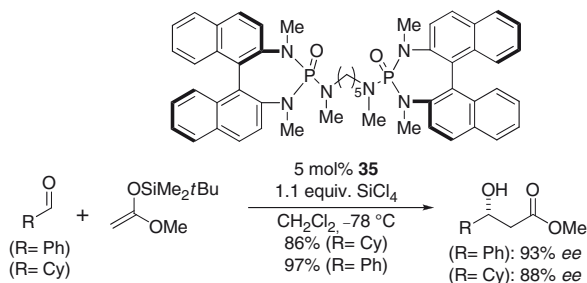
Scheme 24 Lewis base catalyzed aldol reaction

The coordination state of the silyl enol ether in the transition state strongly influences the diastereoselectivity (*syn/anti*). If a ligand is sterically demanding, like phosphoramidate **33**, a boat-like transition state with a pentacoordinated silicate is formed and affords the *syn* product in the reaction of trichlorosilyl enol ether with benzaldehyde. In contrast, the less hindered ligand **34** gave the *anti* product through a chair-like transition state with a hexacoordinated silicate (Scheme 25).

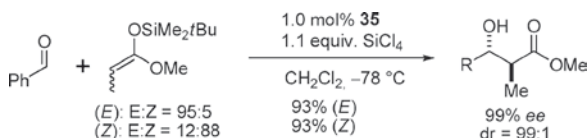


Scheme 25 Proposed mechanism

Denmark utilized chiral base promoted hypervalent silicon Lewis acids for several highly enantioselective carbon-carbon bond forming reactions [92–98]. In these reactions, a stoichiometric quantity of silicon tetrachloride as achiral weak Lewis acid component and only catalytic amount of chiral Lewis base were used. The chiral Lewis acid species desired for the transformations was generated in situ. The phosphoramidate **35** catalyzed the cross aldolization of aromatic aldehydes as well as aliphatic aldehydes with a silyl ketene acetal (Scheme 26) [93] with good yield and high enantioselectivity and diastereoselectivity.

**Scheme 26** Cross aldolization

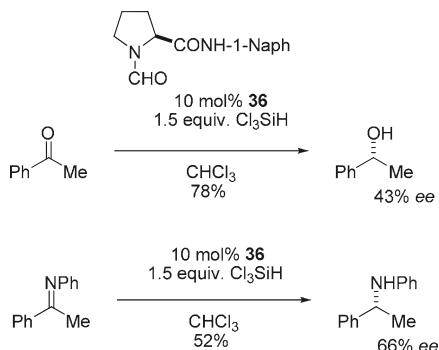
It was found that benzaldehyde reacts with *E* and *Z* configured silyl ketene acetals to furnish identical aldol products [93] with high enantioselectivity. Neither diastereoselectivity nor enantioselectivity were affected by double bond geometry of the silyl ketene acetal. This is an evidence for an acyclic transition state (Scheme 27).

**Scheme 27** Cross aldolization with trisubstituted silyl ketene acetals

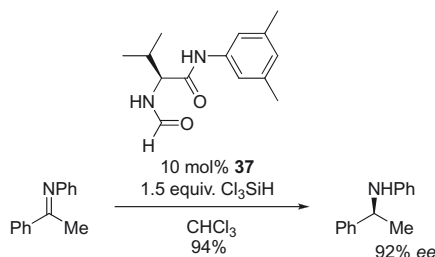
Catalytic amounts of **35** (1 mol%) also promoted the reaction of aromatic aldehydes with silyl ethers [94], vinylogous silicon enolates [95] and even with isocyanates in the presence of stoichiometric amount of SiCl_4 [98]. The products were isolated in high yield and enantioselectivity.

Next to phosphoramides, Denmark reported an axially chiral *N*-oxide to catalyze the asymmetric aldol reaction of trichlorosilyl enol ethers with ketones [99]. Hashimoto reported an aldol reaction with 3 mol% of another axially chiral *N*-oxide [100] which gave good yields and enantioselectivities.

Next, a few examples of asymmetric reductions with trichlorosilane are presented. An asymmetric reduction of ketones and imines was reported by Matsumura and coworkers by using trichlorosilane as reductant and *N*-formyl pyrrolidine derivative **36** as ligand (Scheme 28) [101, 102].

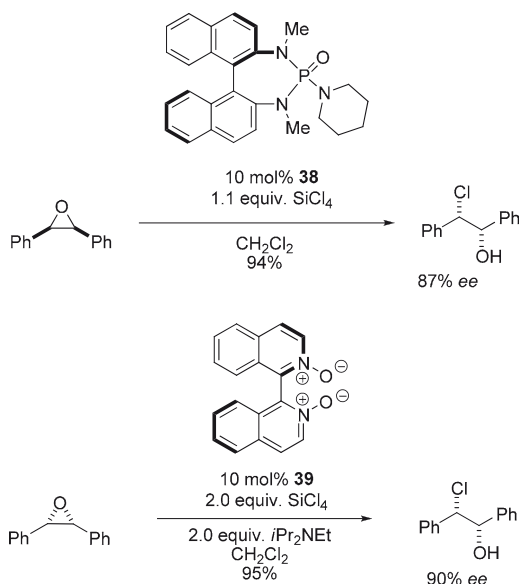
**Scheme 28** Reduction of ketones and imines

Later, Malkov and Kočovský reported the asymmetric reduction of imines with *N*-methyl L-valine derivative **37** with high yield and enantioselectivity (Scheme 29) [103].



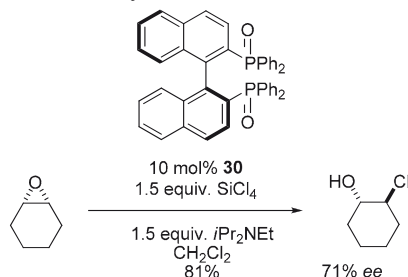
Scheme 29 Reduction with catalyst **37**

Next to the above presented use of SiCl_4 for the in situ preparation of a Lewis acid catalyst with a Lewis base for the aldol reaction, it is possible to apply this compound as a reagent in the ring opening of epoxides leading to chlorinated alcohols. Denmark [104] reported that the chiral phosphoramidate **38** catalyzed the asymmetric ring opening reaction of meso-epoxides in the presence of tetrachlorosilane. Similar examples were provided by Hashimoto in 2002 [105], applying the *N*-oxide **39** as catalyst (Scheme 30).



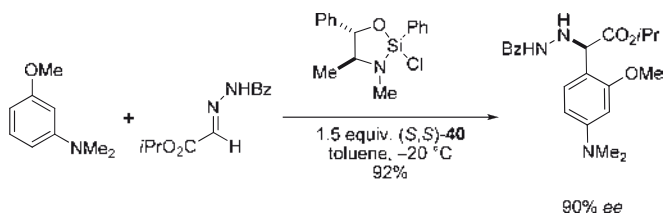
Scheme 30 Epoxide ring opening

Later in 2005, Hashimoto [106] reported the asymmetric ring opening reaction of cyclohexane oxide with catalyst **30** and afforded the corresponding chlorohydrin in high yield and enantioselectivity (Scheme 31).



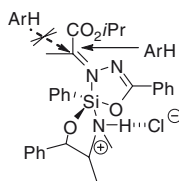
Scheme 31 Epoxide ring opening catalyzed with Lewis base **30**

Extending the application of his *strained silacycle* reagents, Leighton et al. described a method for the enantioselective Friedel-Crafts alkylation with benzoylhydrazones, catalyzed by an extraordinarily simple chiral silane Lewis acid. The salient features of the chiral silane are: it can be prepared in bulk in a single step from (*S,S* or *R,R*) pseudoephedrine and PhSiCl_3 , and after employing it in a reaction, pseudoephedrine can be recovered in nearly quantitative yield during the workup. The best example is shown in Scheme 32 in which, by employing chiral silane **40**, 92% yield and 90% ee of the product were achieved in 48 h [107].



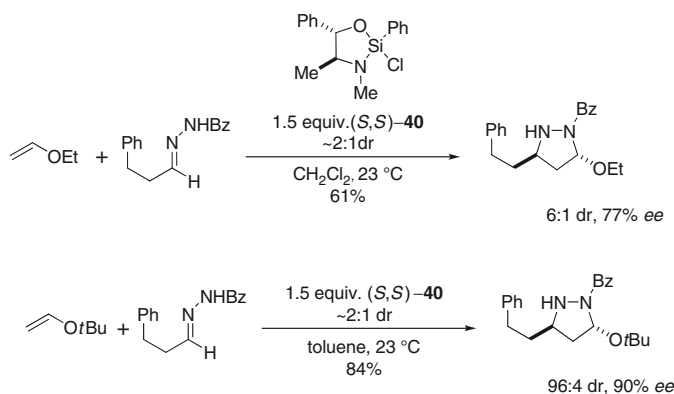
Scheme 32 Enantioselective Friedel-Crafts alkylation

The catalyst, although applied in 1.5 equiv., also worked well with heteroarenes in the alkylation reactions. A simple and most plausible mode for the enantioselectivity of the Friedel-Crafts reaction has been shown in Scheme 33. It is evident from the model that the arene would approach from the front (*Si*) face, as the back (*Re*) face is blocked by the phenyl group present on the silicon.



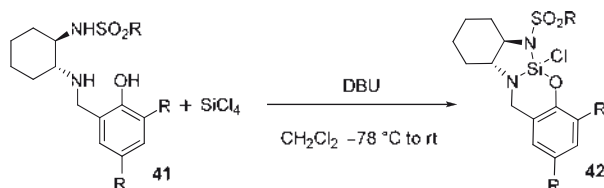
Scheme 33 Proposed mechanism

Inspired by the previous results, Leighton et al. reported the enantioselective [3 + 2] acylhydrazone-enol ether cycloaddition reaction by employing the same pseudoephedrine-based chiral silane. The pyrazolidine product was obtained in 61% yield with 6:1 dr and 77% ee in 24 h. The use of *tert*-butyl vinyl ether led to an improvement in both diastereoselectivity and enantioselectivity as shown in Scheme 34 [108].



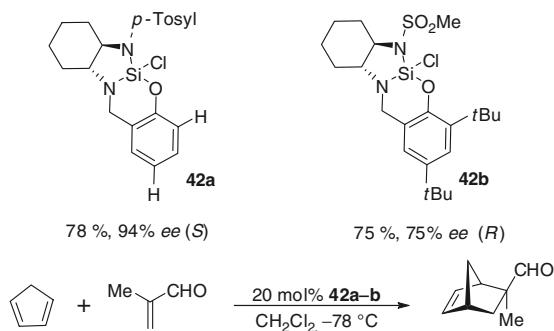
Scheme 34 Enantioselective [3+2] cycloaddition

In 2006 Leighton et al. reported that a chiral ligand carrying three functional groups for attachment to tetrachlorosilane, proved to be a good ligand for the efficient silane catalyst **42** in the cycloaddition reaction of enals with cyclopentadiene. The catalyst was generated in situ by treatment of **41** with SiCl_4 and DBU in 4 h (Scheme 35) [109]. It was possible to assign the relative configuration of compound **42** at the silicon center by the observation of NOE interactions (Scheme 37).

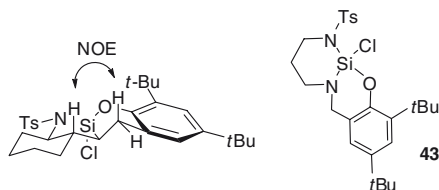


Scheme 35 Preparation of **42**

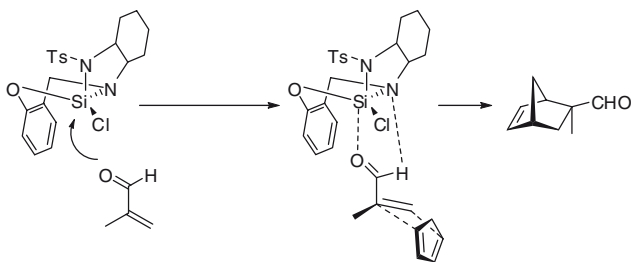
Simple changes to a sulphonamide group and substituents on the phenols produced a dramatic effect on the enantioselectivity in the reaction (Scheme 36).

**Scheme 36** Diels-Alder reaction catalyzed by **42**

It was proven that a five-membered strained ring is an essential component for the Lewis acidity. Thus silane **43**, being six-membered, is strain free and showed no catalytic activity under identical reaction conditions (Scheme 37).

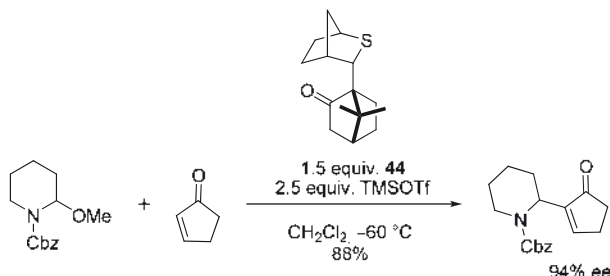
**Scheme 37** Determining ring strain

The proposed mechanism is depicted in Scheme 38. The aldehyde is activated due to coordination on the silicon atom. A hydrogen bond between the aldehyde function and the benzyl substituted tertiary nitrogen atom stabilizes the transition state, and the benzyl group ensures that the cyclopentadiene attacks the dienophile only from one side.

**Scheme 38** Proposed mechanism

Finally, a few examples of the Morita-Baylis-Hillman reaction are provided, where a silyl species functions as a Lewis acid co-catalyst. These examples could have been presented in the previous section about silyl cation-based catalysts. Since the enantiomeric induction originated in the present examples from a Lewis base, we have listed these examples in this section.

The promoters of the so-called chalcogenide Morita-Baylis-Hillman reaction are Kataoka and co-workers who employed sulfide and TiCl_4 for dual Lewis acid-base activation. Later, in 1996 the ability of the combination of sulfide/TBDMSOTf to promote the reaction was reported [110]. Asymmetric version of the Baylis-Hillman reaction has been achieved by using chiral sulfide in place of SMe_2 . The best ee was 94% in combination with a high yield of 88% in 5 h (Scheme 39) [111].

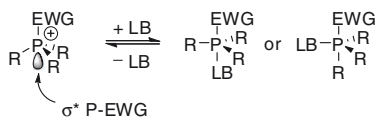


Scheme 39 Sulfide 44 catalyzed Morita-Baylis-Hillman reaction

In summary, it is possible to state that the field of the Lewis base catalyzed reactions involving silane reagents is very well established and high enantioselectivities can be obtained for several examples. As pointed out above, the research field has been only briefly discussed in this review, since it is considered to be a Lewis base catalyzed domain. Since the reactive intermediate is a Lewis acid, it was decided to discuss it in the context of this article. Considering the examples where the silane reagent was replaced by SiCl_4 to generate in situ an active Lewis acid catalyst, one could argue that it is also possible to place the reactions under the category of Lewis acid catalyzed reactions. The presented example of the catalyzed Diels-Alder reaction with strained five-membered silanes belongs undoubtedly to the field of Lewis acid organocatalysts.

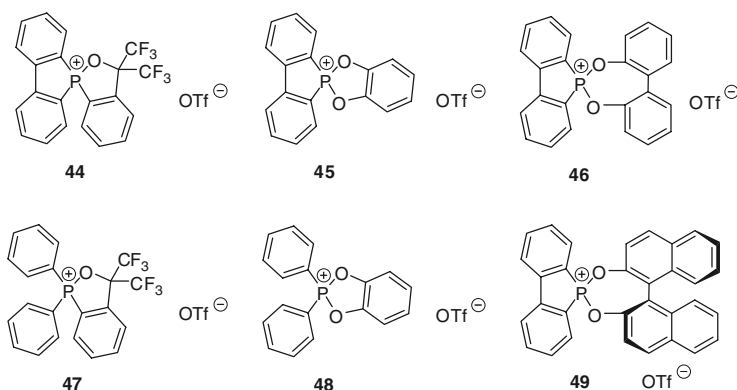
4 Phosphonium Cation-Based Catalysts

In 2006 Terada and Kouchi reported the investigation of phosphonium salts in catalysis [112]. A pentacoordinated phosphorus atom is a hypervalent [113] atom, which has a formal valence shell of more than eight electrons. As shown in Scheme 40, it is possible for the lower lying σ^* orbital of a P^+ -EWG (Electron Withdrawing Group) bond to take up a free electron pair of a Lewis base, in order to form a new bond. If the new formed bond is *trans* to the EWG, the formed complex is more stable.



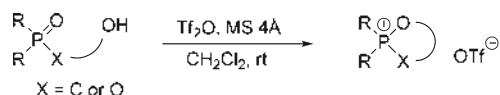
Scheme 40 Hypervalent phosphorus atom

The authors prepared a series of different phosphonium salts of which a few examples are given below. All incorporated electron withdrawing groups as shown in Scheme 41.



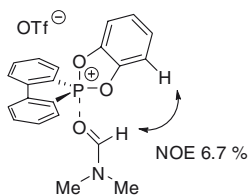
Scheme 41 Phosphonium salts

The salts were prepared from hydroxy phosphine oxides or phosphinates as depicted in Scheme 42 after 1 h. The reactions were carried out with trifluoromethanesulfonic anhydride in the presence of 4Å molecular sieves, and it was shown by ^{31}P -NMR due to downfield shifts that the phosphonium salts were formed. However, the salts could not be isolated and were prepared in situ for NMR studies and for the application in catalysis.



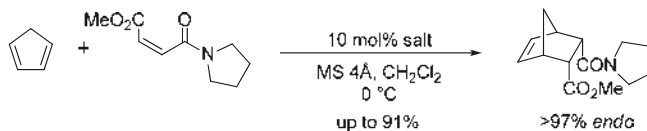
Scheme 42 Preparation of phosphonium salts

In NMR investigations of the salts with DMF, it was possible to observe a shift change in the case of salts **45** and **48**. The other salts revealed no change. It appeared that the five-membered ring of the catechol substituent is crucial for a high reactivity. It is known that cyclic five-membered phosphorus compounds possess an enhanced reactivity [114, 115]. Salt **45**, incorporating two 5-membered rings, showed a stronger interaction with DMF than salt **48**. As shown in Scheme 43, an NOE was found between the C3-proton of the catechol moiety and the formyl proton of DMF.



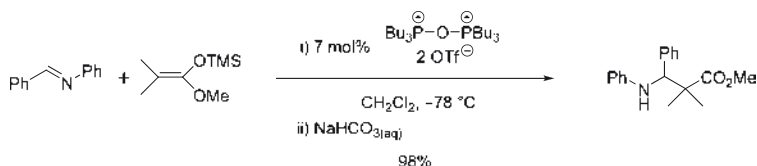
Scheme 43 Mode of activation

The authors investigated the salts in the Diels-Alder reaction. In analogy to the NMR experiments similar reactivities were found. As presented in Scheme 44, the salts gave up to 91% yield in high *endo*-selectivity with cyclopentadiene and an unsaturated amide in 4 h. The highest yield was obtained with salt **45**, while for example salt **47** gave only 7% and salt **49** gave only traces.



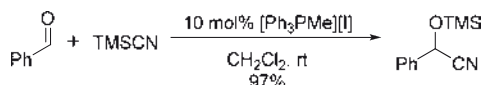
Scheme 44 Phosphonium salt catalyzed Diels-Alder reaction

By 1989 Mukaiyama had already explored the behaviour of phosphonium salts as Lewis acid catalysts. It was possible to show that the aldol-type reaction of aldehydes or acetals with several nucleophiles and the Michael reaction of α,β -unsaturated ketones or acetals with silyl nucleophiles gave the products in good yields with a phosphonium salt catalyst [116]. In addition, the same group applied bisphosphonium salts as shown in Scheme 45 in the synthesis of β -aminoesters [117]. High yields up to 98% were obtained in the reaction of *N*-benzylideneaniline and the ketene silyl acetal of methyl isobutyrate. Various analogues of the reaction partners gave similar results. The bisphosphonium salt was found to be superior to Lewis acids like TiCl_4 and SnCl_4 , which are deactivated by the resulting amines.



Scheme 45 A bisphosphonium salt catalyzed reaction

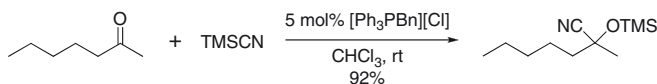
Furthermore, phosphonium salts have been applied as catalysts in the TMSCN addition to aldehydes [118] and ketones [119]. Methyltriphenylphosphonium iodide [118] was found to be a reasonably active catalyst for the addition of TMSCN to aldehydes at room temperature by the group of Plumet. In general, the yields varied between 70% and 97% in 24 h, depending on the aldehyde, applied in the reaction (Scheme 46). However, the salt did not support the addition of TMSCN to ketones, with one exception, when the highly reactive cyclobutanone was applied in the reaction [120].



Scheme 46 TMSCN addition to aldehydes

In order to extend the reaction to further ketones, it was found by the group of Tian [119], that benzyltriphenylphosphonium chloride was a suitable phosphonium

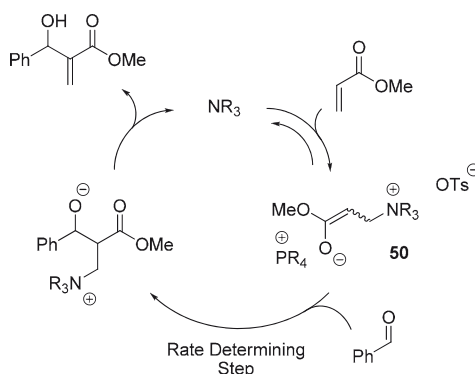
salt-based catalyst which gave the desired product in 92% yield in the reaction of 2-heptanone with TMSCN in 24 h (Scheme 47). The authors could show that it was essential to apply the chloride salt in the reaction. In the case where a bromide analogue was used, only a yield of 2.6% was found.



Scheme 47 TMSCN addition to ketones

In the phosphonium iodide and chloride salt catalyzed TMSCN addition on aldehydes and ketones, a double activation should exist. Not only the activation of the ketones or aldehydes with the phosphonium cation is necessary, but also the activation of the TMSCN by the soft Lewis base [I] or the harder Lewis base [Cl], which can form a pentavalent silicon intermediate [121].

Phosphonium salts have also been used as co-catalysts in the DABCO catalyzed Baylis-Hillman reaction of methyl acrylate with benzaldehyde [122]. Good results were obtained with triethyl-*n*-butylphosphonium tosylate with up to quantitative yields in some cases. The authors proposed that the phosphonium salt is rather stabilizing the intermediate **50**, shown in Scheme 48, and increasing therefore its concentration rather than activating the benzaldehyde.



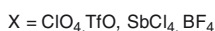
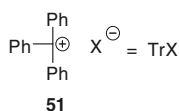
Scheme 48 Phosphonium Salts as co-catalysts in the Baylis-Hillman reaction

Finally, achiral phosphonium salts have been applied as Lewis acid catalysts in some other reactions. The examples will be listed here but not discussed in more detail. Phosphonium salts have been used as catalysts for the *N,N*-dimethylation of primary aromatic amines with methyl alkyl carbonates giving the products in good yields [123]. In addition acetonyltriphenylphosphonium bromide has been found to be a catalyst for the cyclotrimerization of aldehydes [124] and for the protection/deprotection of alcohols with alkyl vinyl ethers [125, 126]. Since the pK_a of the salt is 6.6 [127–130], the authors proposed that, next to the activation of the phosphonium center, a Brønsted acid catalyzed pathway is possible.

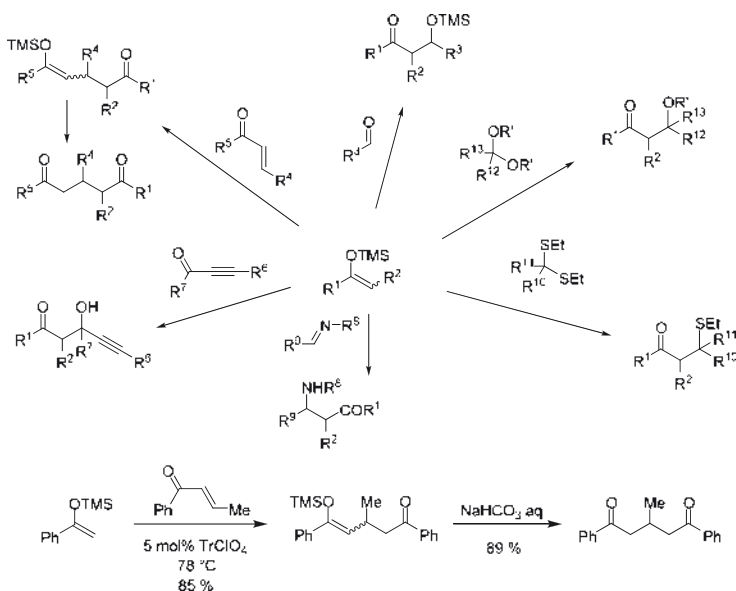
In summary, there are now several examples of phosphonium salt-based Lewis acids as catalysts known, which have shown a good catalytic activity. However, an asymmetric catalyzed reaction with an enantiopure phosphonium salt has not been reported yet.

5 Carbocation-Based Catalysts

During the past decades, the scope of Lewis acid catalysts was expanded with several organic salts. The adjustment of optimal counter anion is of significant importance, while it predetermines the nature and intensity of catalytic Lewis acid activation of the reactive species. Discovered over 100 years ago and diversely spectroscopically and computationally investigated [131–133], carbocations still remain seldom represented in organocatalysis, contrary to analogous of silyl salts for example. The first reported application of a carbenium salt introduced the trityl perchlorate **51** (Scheme 49) as a catalyst in the Mukaiyama aldol-type reactions and Michael transformations (Scheme 50) [134–142].



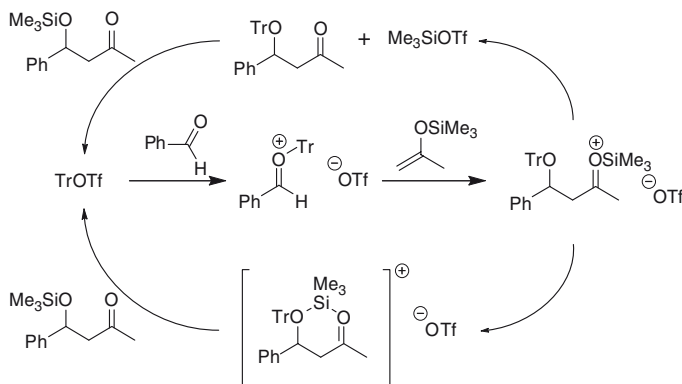
Scheme 49 Carbocation based salt **51**



Scheme 50 Carbocation catalyzed reactions

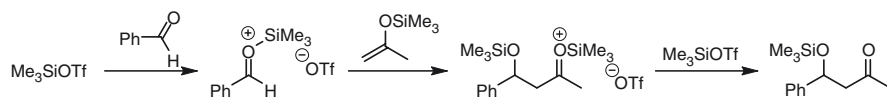
The reactions proceeded efficiently under mild conditions in short time. The silyl enol ethers reacted with the activated acetals or aldehydes at $-78\text{ }^{\circ}\text{C}$ to give predominant erythro- or threo-products [136, 137] respectively. In the same manner, the aldol reaction of thioacetals, catalyzed by an equimolar amount of catalyst, resulted in γ -ketosulfides [139] with high diastereoselectivity. In the course of this investigation, the interaction of silyl enol ethers with α,β -unsaturated ketones, promoted by the trityl perchlorate, was shown to proceed regioselectively through 1,2- [141] or 1,4-addition [138]. The application of the trityl salt as a Lewis acid catalyst was spread to the synthesis of β -aminoesters [142] from the ketene silyl acetals and imines resulting in high stereoselective outcome.

The undefined mechanism of the aldol-type Mukaiyama and Sakurai allylation reactions arose the discussion and interest in mechanistic studies [143–145]. The proposed mechanism was proved to proceed through the catalytic activation of the aldehyde and its interaction with the silyl ketene acetal or allylsilane producing the intermediate. From that point the investigation is complicated with two possible pathways that lead either to the release of TMS triflate salt and its electrophilic attack on the trityl group in the intermediate or to the intramolecular transfer of the TMS group to the aldolate position resulting in the evolution of the trityl catalyst and the formation of the product (Scheme 51). On this divergence, series of experimental and spectroscopic studies were conducted.



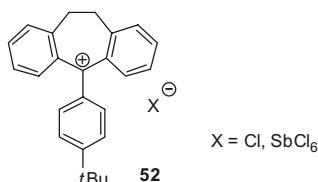
Scheme 51 Proposed mechanism

The valuable and versatile study was conducted by the group of Bosnich [143]. The defined nature and amounts of by-products in the reaction mixture allowed to judge about the possible mechanism of the catalysis. It was proved that the aldolization and allylation reactions proceed with the evolution of TMS salt that is itself a strong Lewis acid and can catalyze the reaction in high rate (Scheme 52). The possible sources of the TMS salt production in the reaction medium were investigated. The utilization of a hindered base suppressed the influence of the silyl salt, and the rate of the reaction was dramatically diminished. This consequence was considered to confirm that the TMS salt can catalyze the reaction even in the undetectable quantities of 10^{-7} mol.



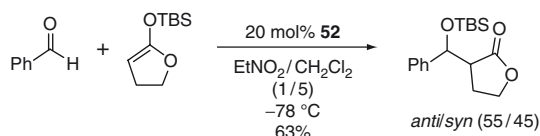
Scheme 52 Trimethylsilyl catalyzed reaction

The further investigation of functionalized trityl cations with different counter anions and TMS or TBS enolates, conducted by Chen [145], introduced the dibenzozuberone-derived salt **52** [146] as a catalyst (Scheme 53).



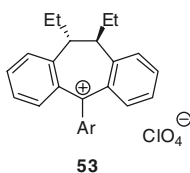
Scheme 53 Salt **52**

The TBS ketene acetal was proposed to be the preferable silyl component, while the rate of the TBS transfer to the aldolate group of the product decreased and did not overtake the slow-acting carbenium catalysis (Scheme 54).



Scheme 54 Salt **52** catalyzed Mukaiyama aldol reaction

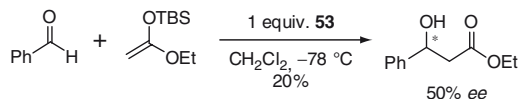
The next investigation conducted by the group of Chen [147], involved the chiral trityl salt **53** and thus brought clearness to a certain extent in the understanding of the mechanism of the catalysis (Scheme 55). Since enantiomeric excess was achieved, the carbenium-mediated catalysis should not be disregarded. The correlation of the results manifested the concurrence of the catalytic species and dependence of their participation in the catalysis on the silyl substituents and counter ions in the trityl salts.



Scheme 55 Enantiopure carbocation based salt **53**

Over a reaction period of 3–6 h (Scheme 56) the enantioselectivity of the aldolization catalyzed by **53** decreased from 24% to 11% along with the increase of yield from 52% to 99%. The decrease of the enantioselectivity with prolongation of reaction time indicates the prevailing of the silyl-mediated catalysis, due to the slow

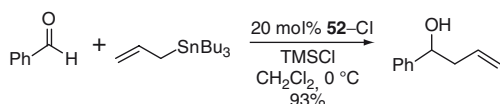
metathesis between tritylated aldolate and silyl salt. The best enantioselectivity of 50% together with just 22% yield was achieved when 1 equiv. of catalyst **53** was used. This experiment points out the slow consumption of trityl ions as well as the low rate of the silyl substitution of the trityl aldolate.



Scheme 56 Asymmetric Mukaiyama aldol reaction

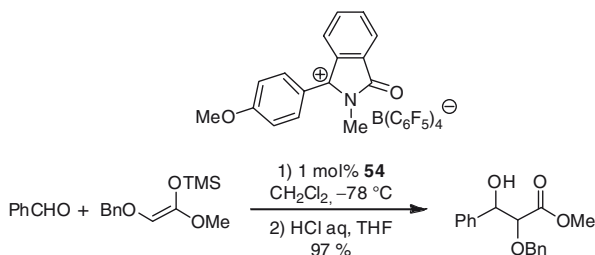
The estimation of the conditions, suppressing the silyl-mediated catalysis and preferable for the carbenium-promoting catalysis, is of significant importance to introduce the chiral information in the product. Since it was observed that a carbenium salt promoted the reaction and thus provided the enantioselectivity in the outcome, the rigid conformation and the enhanced reactivity of the carbocation may be the key requirement for the productive enantioselective carbenium catalysis in the aldol-type additions.

The catalytic activity of the trityl moiety was unobjectionably adjusted in the addition reaction of the allylstannanes to aldehydes [148]. In this allylation process the trityl chloride **52**, due to its disposition to partially ionic character of the halogen bonding, was employed as a catalyst in the complementary tandem with weak Lewis acid TMSCl (Scheme 57). The excess of the silyl component was necessary in order to release the trityl catalyst from the intermediate to complete the catalytic cycle. The achieved yield was 93%, when trityl chloride **52** was used.



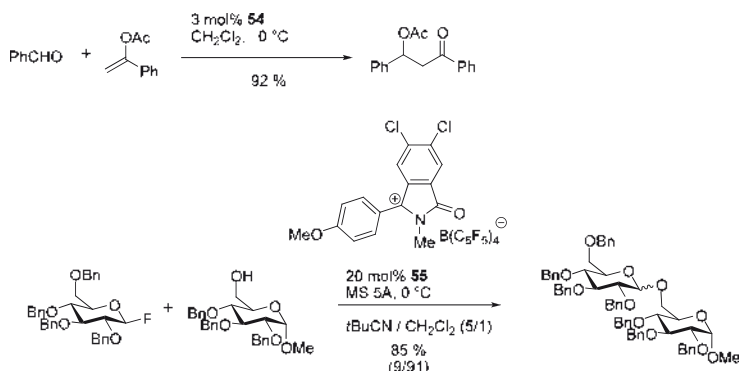
Scheme 57 Salt **52** catalyzed allylation

In order to enhance the catalytic activity of a carbocationic center, the novel Lewis acid **54** was designed by Mukaiyama [149–152]. The 1-oxoisindolium-based carbenium salt **54** [149], possessing a weak coordinating borate counter anion, proved to be a very active catalyst in the aldolization (Scheme 58) [150]. The Mukaiyama aldol reaction was catalyzed by 1 mol% of salt **54** and proceeded in up to 97% yield in 30 min.



Scheme 58 Salt **54** catalyzed Mukaiyama aldol reaction

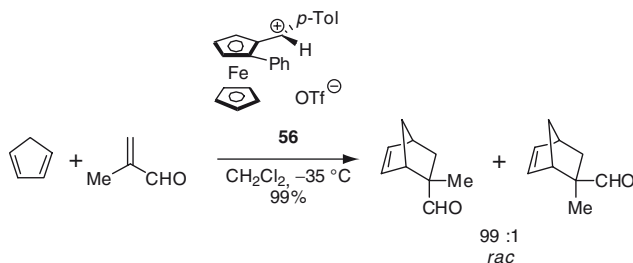
The catalytic activity of the oxoisindolium salt **54** and **55** was compared to that of trityl tetrakis[pentafluorophenyl]borate salts in the addition reaction of enol acetate to benzaldehyde and glycosylation reaction (Scheme 59) [151, 152].



Scheme 59 Carbocation based salt **55** catalyzed glycosylation reaction

The utilization of compound **54** in the aldolization showed higher yield of the product (92%) after 30 min, compared to that (73%) of a trityl catalyzed reaction. The similar results were obtained in the glycosylation reaction: 85% (α/β ratio 9:91) and 72% (α/β ratio 10:90) respectively. The application of the highly hindered tetrakis[pentafluorophenyl]borate anion is remarkably advantageous for the stabilization of the positive charge in the carbocation **54** and at the same time promotion of its accessibility to the interaction with a carbonyl species.

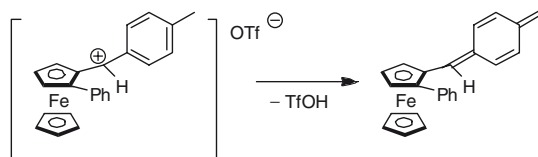
The development of the stable α -ferrocenyl carbocations **56** prompted the further investigation of the carbenium salts in the Lewis acid catalyzed reactions (Scheme 60). The group of Kagan [153–155] designed the *o*-substituted ferrocenyl scaffold that allowed to avoid the placement of two aryl groups on the carbocation and provided the stabilization and asymmetry, preventing the isomerization by the facile rotation about the carbenium center. Being exploited in the Diels-Alder reaction of cyclopentadiene with methacrolein, the catalyst **56** displayed a perfect *exolendo* diastereoselectivity of up to 99:1 in the presence of 4 Å MS resulting in nearly quantitative yield (Scheme 60).



Scheme 60 Ferrocene based salt **58** catalyzed Diels-Alder reaction

In contrast to these results, the group of Sammakia [156] reported that the reaction can be actually catalyzed by the protic acid TfOH, released either by the decomposition of the carbenium salt or by the nucleophilic attack of the diene on the cation center with evolution of the proton.

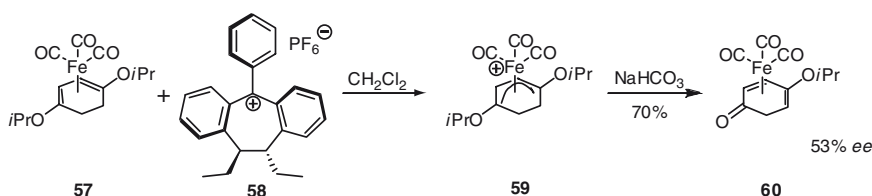
Supplementary studies of the mechanism were conducted. The dependence of the reaction rate on the nature of environment at the cationic carbon has shown that the concurrent formation of the protic acid proceeds, if the substituents can undergo the isomerization (Scheme 61), and thus the carbenium catalysis is utterly negligible. It was shown that the reaction was still catalyzed, even when a base was added in order to rule out a TfOH catalyzed reaction. Obviously, the protonated base was then a catalyst.



Scheme 61 Release of TfOH

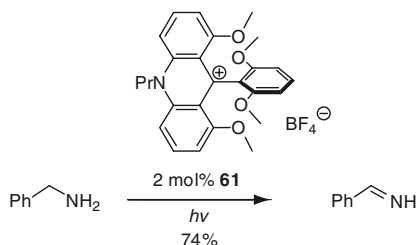
While the ambiguity of the catalysis of the Diels-Alder reaction needs to be carefully elucidated, the application of the ferrocenyl carbocations in the Mukaiyama aldolization turned out evidently to be unrealisable due to their interaction with the TMS enol ether that produces TMSOTf , which proved readily to catalyze the aldolization [154].

Due to the extensively represented oxidative behaviour of the carbenium ions as hydride abstractor or one-electron oxidant [157], attempts were made to employ the carbocations as reagents. Recently the enantioselective outcome in a hydride transfer reaction was reported [158, 159]. The abstraction of the *exo* hydrogen atoms from the tricarbonyliron complex **57** resulted in a yield up to 70% and enantioselectivity of 53% (Scheme 62) [158].



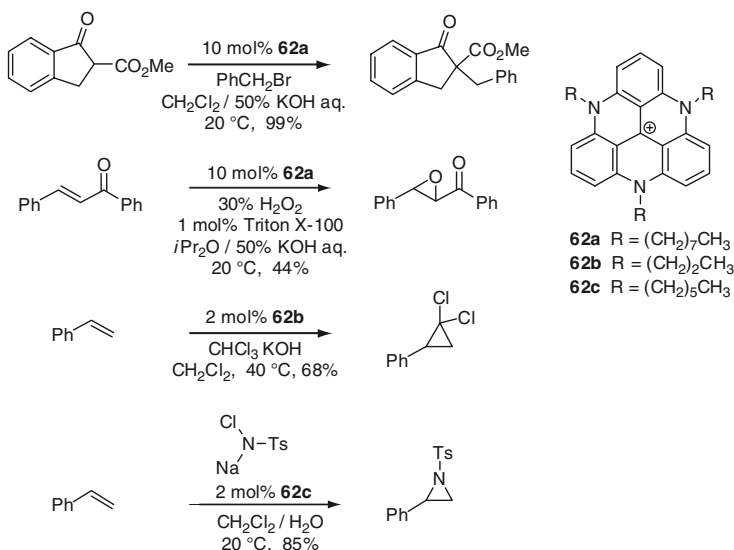
Scheme 62 Enantioselective hydride transfer reaction

The oxidative behaviour of the acridinium carbocations **61** was also explored by the group of Lacour in the photoinduced electron transfer reaction [160]. In the amount of 2 mol%, the achiral hindered acridinium salt **61** catalyzed the aerobic photooxidation of the primary benzylic amine to benzylimine in the yield of 74% (Scheme 63).



Scheme 63 Photo-oxidation catalyzed by salt **61**

Finally, one example of trityl salt analogues in the phase-transfer catalysis is presented. The highly stable triazatriangulenium cations **62** [161, 162] were just recently introduced to the phase-transfer chemistry [163]. Persistent to strongly basic and nucleophilic conditions, these salts revealed efficient catalytic activity in addition reactions (Scheme 64). Modification of the alkyl side chains on nitrogen allowed matching the fair hydro/lipophilicity with the optimised conditions in the alkylation, epoxidation, aziridination and cyclopropanation reactions. The results are comparable to those of tetrabutylammonium salts and in some cases showed even a better outcome.



Scheme 64 A stable triazatriangulenium based salt as phase-transfer catalyst

So far, there has been only one example of a successful asymmetric catalyzed reaction with an enantiopure carbocation-based salt. In this section it was possible to learn, that a good understanding of a catalyzed reaction is necessary and that possible achiral side reactions have a critical negative influence. Nevertheless, carbocations can be highly active catalysts. However, this makes their application

sometimes difficult. One exception was the last presented example resembling a moisture, base and nucleophilic stable trityl cation. In the next section ionic liquids will be discussed, some of which can be also classified as carbocation-based salts. However, they are far more stable but on the other hand possess a lower catalytic activity.

6 Ionic Liquids

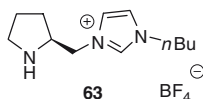
Ionic liquids, having per definition a melting point below 100 °C, and especially room temperature ionic liquids (RTIL) have attracted much interest in recent years as novel solvents for reactions and electrochemical processes [164]. Some of these liquids are considered to be “green solvents” [165]. The scope of ionic liquids based on various combinations of cations and anions has dramatically increased, and continuously new salts [166–168] and solvent mixtures [169] are discovered. The most commonly used liquids are based on imidazolium cations like 1-butyl-3-methylimidazolium [bmim] with an appropriate counter anion like hexafluorophosphate [PF₆]. Salts with the latter anion are moisture stable and are sometimes called third generation ionic liquids.

The so-called second generation ionic liquids were prepared from organic cations and AlCl₃ anions [170]. Since AlCl₃ was present in these liquids, they were used as catalysts in Lewis acid catalyzed reactions. Also many of the third generation ionic liquids have been used as solvents for catalytic reactions [171–174]. However, it is also known that third generation ionic liquids are capable of catalyzing reactions, either in substoichiometric amounts or as reaction medium. This will be discussed in this section.

There have been recently several reviews about the preparation and application of chiral enantiopure ionic liquids [172, 175–177]. Unfortunately, often the evaluation of the growing number of enantiopure ionic liquids concentrated more on their behavior as chiral discrimination agents. Hence, the number of examples of reactions catalyzed by enantiopure ionic liquids is rather small, and therefore this section will also give an overview over catalyzed reactions with achiral ionic liquids, rather than giving examples of enantiopure ionic liquids, which have not been evaluated as reaction medium yet.

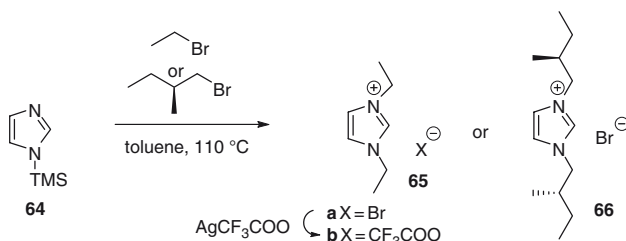
Examples, like the application of enantiopure ionic liquids in the copper catalyzed enantioselective 1,4-addition of diethyl zinc to enones giving up to 76% ee, will not be presented [178], since here the chiral ionic liquid, CIL, acts as a ligand for a metal catalyzed reaction.

Furthermore, to clarify the difference between task specific ionic liquids (or also called functionalized ionic liquids) and chiral ionic liquids, one very successful example of a task specific ionic liquid **63** is presented in Scheme 65. This catalyst with a loading of 15 mol% under neat conditions gave up to 100% yield and 99% ee in the Michael addition of cyclohexanones to nitroolefins [179]. This catalyst belongs to the field of the proline catalyzed reactions.



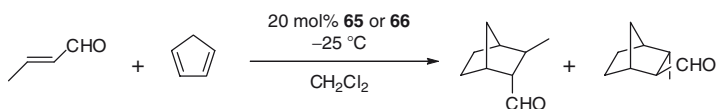
Scheme 65 A task specific ionic liquid

In 1997 Howarth [180] reported the preparation of ionic liquids **65** and **66**. They reported that imidazolium cations can be used as Lewis acid centers in catalytic amount rather than as solvent (Scheme 66). The bromide salts **65a** and **66** were prepared by a literature procedure [181] from TMS protected imidazole **64** and ethyl bromide or (*S*)-1-bromo-2-methylbutane in refluxing toluene in 46 and 21% yield, respectively. Salt **65a** was converted into salt **65b** with AgCF_3COO in 89% yield.



Scheme 66 Preparation of chiral salt **66**

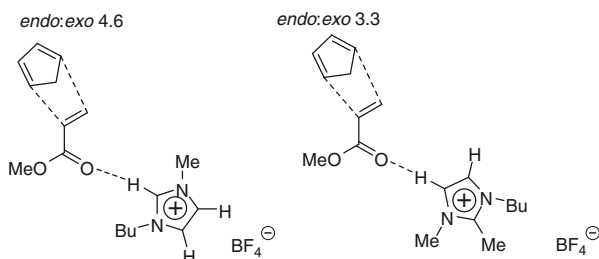
The salts were investigated in the Diels-Alder reaction of crotonaldehyde with cyclopentadiene (Scheme 67). The yields obtained were between 35% and 40% with an *endo:exo* ratio of 90:10. The control reaction without the salt at -25°C gave no product. The observed ee with the enantiopure salt **66** was less than 5%. Nevertheless, this was the first example which showed, that imidazolium-based ionic liquids can be used in substoichiometric amounts as Lewis acid catalysts.



Scheme 67 Ionic liquid catalyzed Diels-Alder reaction

Also the use of moisture stable ionic liquids as solvents in the Diels-Alder reaction has been carried out, and in all examples an enhanced reaction rate was observed [182, 183]. The application of pyridinium-based ionic liquids allowed the utilization of isoprene as diene [184]. The chiral ionic liquid [bmim][L-lactate] was used as a solvent and accelerated the reaction of cyclopentadiene and ethyl acrylate, however, no enantiomeric excess was observed [183]. In addition several amino acid based ionic liquids have been recently tested in the Diels-Alder reaction. Similar *exo:endo* ratios were found but the product was obtained as racemate. The ionic liquids were prepared by the addition of equimolar amounts of HNO_3 to the amino acids [185]. Furthermore, an enantiopure imidazolium salt incorporating a camphor motive was tested in the Diels-Alder reaction. No enantiomeric excess was found [186].

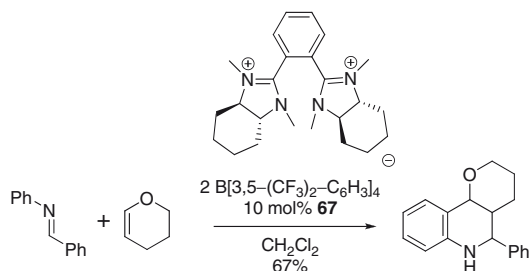
In order to investigate the origin of the catalytic activity of imidazolium-based ionic liquids, the group of Welton [187] performed further studies, and it was proposed that hydrogen bond activation plays an important part in the activation of a dienophile in the Diels-Alder reaction. This was proposed due to observed hydrogen bonds between the imidazolium cation and the corresponding counter anion in the salt. The reaction of methyl acrylate in the ionic liquid [bmim][BF₄] with cyclopentadiene gave the product in 72 h at 25 °C in 85% yield. When the C2-methylated salt [bm₂im][BF₄] was applied as solvent, a similar yield of 84% was obtained; however, the *endo:exo* ratio changed from 4.6 to 3.3. This was attributed to weaker hydrogen bond formation with the C4 and C5 protons compared to the C2 proton in the first salt (Scheme 68).



Scheme 68 Possible mode of activation

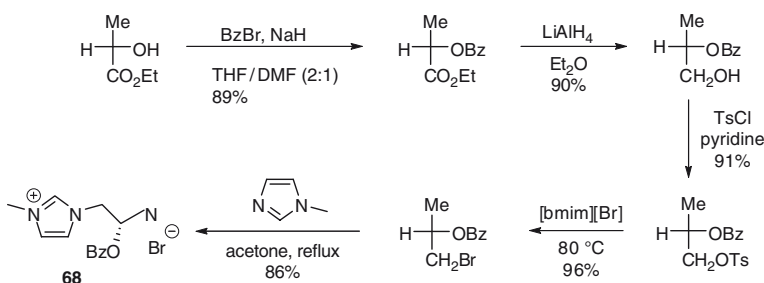
This would place imidazolium-based ionic liquids more to the hydrogen bond activator organocatalysts. However, further studies by the group of Dyson showed that when salt analogues with [NTf₂] as the counter anion were used in the reaction, the salt with a methyl group at the C2 position gave a better *exo:endo* selectivity, indicating that hydrogen bonding capability is not the only reason for the activity of the imidazolium ionic liquids, and other variables, like π -orbital interactions have to be taken into account [188]. Recent calculations for an imidazolium salt showed that the hydrogen bond of a C2-H of the imidazolium cation with a corresponding counter anion is considerably different from that of conventional hydrogen bonds and not as strong as previously considered. The charge-charge interaction of the ion pair was proposed to be the dominant interaction [189].

The ionic liquid [bmim][BF₄] is known to catalyze the aza-Diels-Alder reaction in the synthesis of pyrano- and furanoquinolines [190]. This reaction was also catalyzed by the enantiopure bis-imidazolium salt **67** in 67% yield with an *endo:exo* ratio of 60:40 (Scheme 69) [191]. The product was obtained as a racemate. In addition the aza-Diels-Alder reaction with imines and Danishefsky's diene was catalyzed by the salt **67** giving racemic product. The salt and its analogues could be easily prepared via the oxidation of the corresponding amins [192]. Investigation of the influence of the counter anion in achiral C2-substituted imidazolium salts, which can be also described as 4,5-dihydroimidazolium or saturated imidazolium salts, in the aza-Diels-Alder reaction showed, that the catalytic activity increased, the more lipophilic the counter anion and therefore the more hydrophobic the salt was [193].



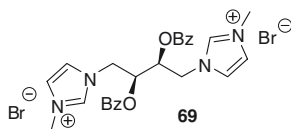
Scheme 69 aza-Diels-Alder reaction catalyzed with salt **67**

The chiral salt **68** has been recently prepared as shown in Scheme 70 in an overall yield of 60% from L-(-)ethyl lactate [194].



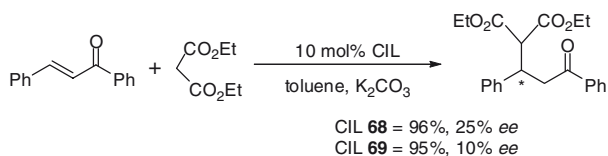
Scheme 70 Preparation of Salt **68**

The salt **69** was also prepared in a similar way from L-(+)-diethyl tartrate in an overall yield of 44% (Scheme 71).



Scheme 71 Ionic liquid **69**

The chiral ionic liquids **68** and **69** were tested in the Michael addition (Scheme 72) [194].

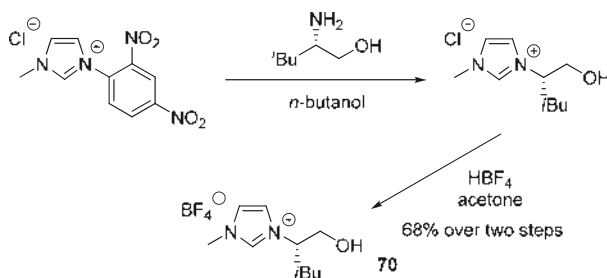


Scheme 72 Ionic liquid catalyzed Michael reaction

The salt **68** under solid phase transfer conditions gave a yield of 96% and 25% ee at room temperature. Since the melting point of the CIL was over 40 °C, toluene

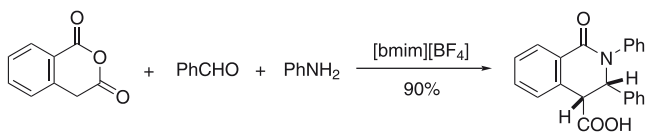
was used as a solvent. The influence of different anions in the salt was very low. Compared to the [Br] counter anion, [PF₆] resulted in 23% ee and [BF₄] gave an ee of 24%. When the polar solvents DMSO and DMF were investigated, a decrease of the ee to 17 and 16% ee was observed. Salt **69** gave a lower ee of 10%. The enantiomeric excess was determined by optical rotation.

Recently another enantiopure ionic liquid was tested in this reaction, and an ee up to 15% was obtained with the ionic liquid **70** which was prepared in an overall yield of 68% in two steps as shown in Scheme 73 [195].



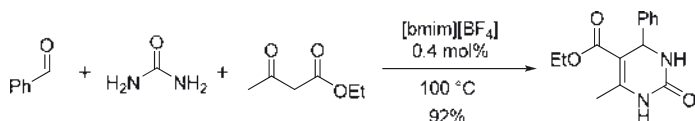
Scheme 73 Preparation of ionic liquid **70**

The achiral ionic liquid [bmim][BF₄] was able to catalyze the three component reaction of benzaldehyde, aniline and homophthalic anhydride in 90% yield. Next to the major *cis*-isomer, 10% *trans*-isomer was isolated after 3 h (Scheme 74) [196]. Control reactions in CH₂Cl₂ with 10 mol% [bmim][BF₄] and without catalyst showed that in the presence of the ionic liquid a high conversion in a short time was observed. Application of polar solvents like methanol or acetonitrile made it necessary to increase the reaction temperature to 70–80 °C, and the product was obtained in only 45–60% yield in a prolonged reaction time of 8–15 h. Further control reactions with [*n*Bu₄N][Cl] or [bmim][Cl] showed that the anion played a comparable important role as the cation, since no product was formed. The author could demonstrate the generality of the reaction by the application of a broad variety of benzaldehyde and aniline derivatives.



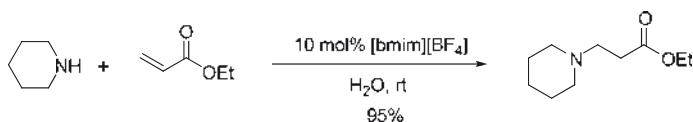
Scheme 74 Ionic liquid catalyzed three component reaction

The Biginelli reaction is also known to be catalyzed by the ionic liquids [bmim][BF₄] and [bmim][PF₆] under solvent-free conditions [197]. One example is shown in Scheme 75. While a control reaction without ionic liquid gave no product, the addition of just 0.4 mol% afforded a yield of 92% in 30 min. [Bmim][Cl] resulted only in a yield of 56%, while [*n*Bu₄N][Cl] gave no yield. This indicated that both the cation and the anion have an influence in catalyzing the reaction.



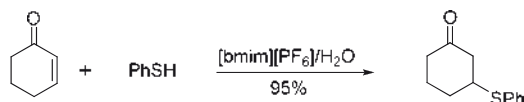
Scheme 75 Ionic liquid catalyzed Biginelli reaction

The imidazolium-based ionic liquid $[\text{bmim}][\text{BF}_4]$ has been used as a catalyst in the aza-Michael reaction of various aliphatic amines to unsaturated compounds with different electron withdrawing groups in good yields as shown in Scheme 76. Water was used as the solvent in order to obtain up to 98% yield in 7 h. In the presented example, 95% yield in 7 h was achieved [198]. The ionic liquid could be recovered and reused five times without loss of activity.



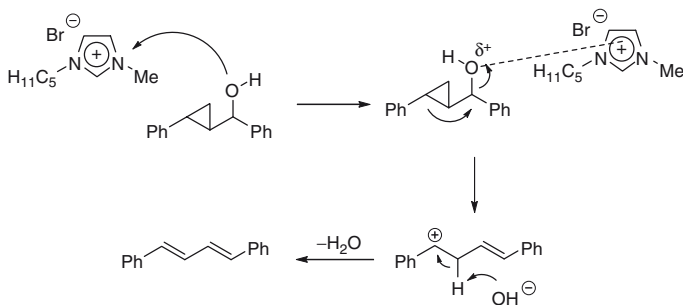
Scheme 76 Ionic liquid catalyzed aza-Michael reaction

The addition of thiols to α,β -unsaturated ketones with $[\text{bmim}][\text{PF}_6]$ in water was investigated. It was found that product could be obtained in up to 95% yield in 10 min (Scheme 77) [199].



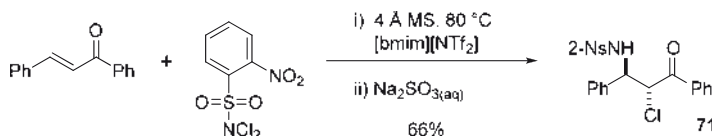
Scheme 77 Ionic liquid catalyzed thiol addition to α,β -unsaturated ketones

In addition, a Lewis acid behaviour was proposed in the cyclopropyl carbonyl rearrangement catalyzed by $[\text{pmim}][\text{Br}]$ as depicted in Scheme 78 [200]. The products were obtained in good yields up to 95% when stirred at rt in the ionic liquid. By the application of sonication, the reaction time was decreased to 0.75 h.



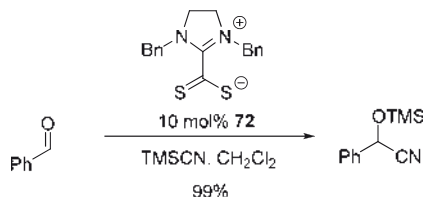
Scheme 78 Ionic liquid catalyzed rearrangement

The ionic liquid [bmim][NTf₂] catalyzed the aminohalogenation of electron-deficient alkenes in good yields. This is the first time that this reaction was performed in the absence of a metal catalyst. A representative example is presented in Scheme 79. The authors found that the major regiomer was **71** [201].



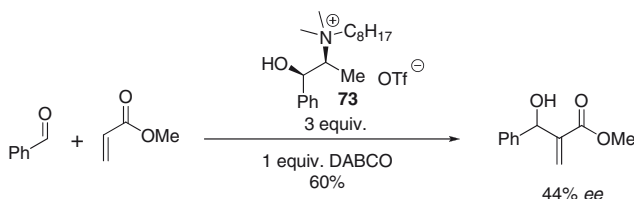
Scheme 79 Ionic liquid catalyzed aminohalogenation of electroneficient alkenes

The TMSCN addition on aldehydes has been reported to be catalyzed by the ionic liquid [omim][PF₆] [202]. The influence of the counter anion in activating the TMSCN cannot be neglected, since the TMSCN addition on aldehydes can be also catalyzed by a Lewis base. The imidazolinium-dithiocarboxylate **72** has been recently shown to catalyze the reaction also in good yields up to 99% (Scheme 80) [203]. One could assume, that the zwitterion incorporates a Lewis acid and Lewis base center. The reaction did not proceed in the absence of the catalyst.



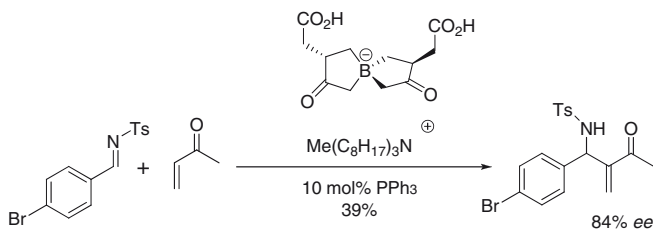
Scheme 80 TMSCN addition to aldehydes catalyzed with zwitterion **72**

Ionic liquids have been also explored in the Baylis-Hillman reaction [204–206]. The application of the enantiopure ionic liquid **73** in the Baylis-Hillman reaction by Vo-Thanh [207] resulted in an enantiomeric excess of up to 44% with 1 equiv. of the Lewis base catalyst DABCO (Scheme 81). It was shown that it was essential to have a hydroxy group incorporated in the ionic liquid in order to obtain significant ee.



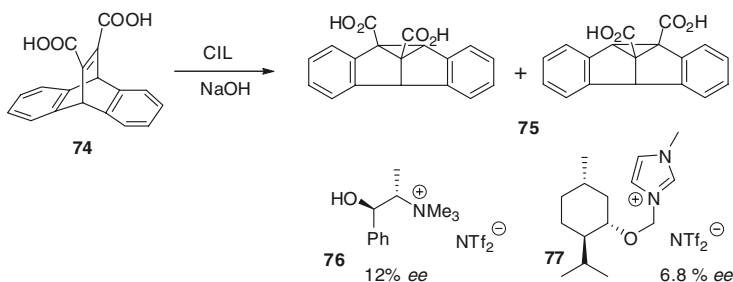
Scheme 81 Enantioselective Baylis-Hillman reaction in chiral ionic liquid **73**

Recently the group of Leitner was able to achieve high enantioselectivities in the aza-Baylis-Hillman reaction by the application of enantiopure ionic liquid with a chiral anion (Scheme 82) [208].



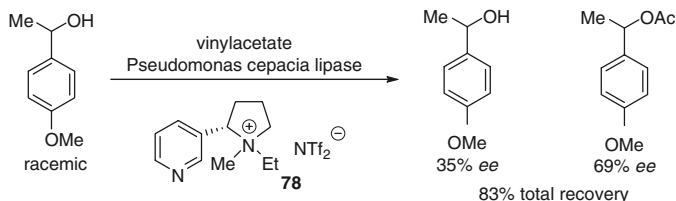
Scheme 82 Enantioselective aza-Baylis-Hillman reaction in a chiral anion based ionic liquid

Recently the group of D. W. Armstrong exploited the enantiopure ionic liquid **76** in the photoisomerization of dibenzobicyclo[2.2.2]octatrienes, and up to 12% ee was reported (Scheme 83). The obtained ee was possible due to the addition of base in order to deprotonate the carboxylic acid function of **74** resulting in a strong anion–chiral cation interaction. In the absence of a base, lower values of ee were obtained, and in the case that ester functions instead of carboxylic acid groups were present in the molecule, only racemic product was found. Ionic liquid **77** gave up to 6.8% ee.



Scheme 83 A Photoisomerization in chiral ionic liquids **76** and **77**

The enantiopure nicotinium-based ionic liquid **78** has been explored in the biocatalyzed kinetic resolution of 1-(4-methoxyphenyl)-ethanol with pseudomonas cepacia lipase (Scheme 84) [209]. The ee obtained at room temperature without any other co-solvent however was lower compared to other systems.



Scheme 84 Kinetic resolution in chiral ionic liquid **78**

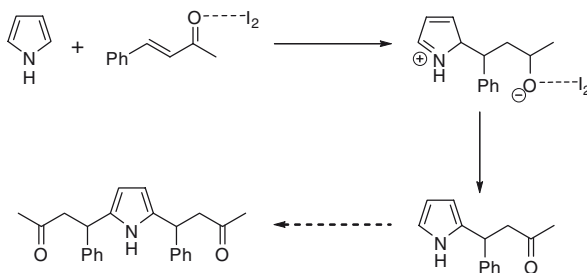
Ionic liquids also showed a catalytic activity for the cyclocondensation of α -tosyloxyketones with 2-aminopyridine [210], the nucleophilic substitution

of α -tosylketones with potassium salts of aromatic acids [211], the synthesis of aryl hydrazones [212], the nucleophilic substitution reactions of highly functionalized allyl halides [213], the alkylation of isobutene with 2-butene [214], the Nazarov cyclization [215], the Pictet-Spengler reaction [216], the demethylation of *N,N*-dimethylanilines with phenyl chloroformate [217], the alkylation of ammonium salts [218], the aza-Michael reaction [219], the aza-Markovnikov's addition with *N*-heterocycles and vinyl esters [220], the ring opening of epoxides with thiophenols [221], the α -halogenation of β -dicarbonyl compounds and cyclic ketones with *N*-halosuccinimides [222], and the ring opening of epoxides with TMSCl [223]. The listed examples were all carried out with achiral ionic liquids and will not be described in further detail, since the presented achiral examples so far have already displayed in general the catalytic activity of ionic liquids for different types of reactions.

Although the number of enantiopure ionic liquids as successful asymmetric catalytic reaction media is still very limited, the research field has attracted considerable attention. Due to the large number of possible applications in combination with the advantages of easy recoverability, the further development of the field is very important. However, it shall be mentioned here that some reported examples of catalytic activities of ionic liquids have to be investigated in more detail. In particular, ionic liquids incorporating $[\text{BF}_4]$ and $[\text{PF}_6]$ have to be very pure and normally should not be used with water for a prolonged time, since the anions could decompose and release HF, which could be itself the cause of the observed activity [164].

7 Miscellaneous Catalysts

Iodine has been reported to possess a mild Lewis acidity and can activate carbonyl groups. It can for example catalyze the addition of pyrroles to α,β -unsaturated ketones (Scheme 85) [224]. A mixture of pyrrol and 3 equiv. of ketone gave disubstituted products in up to 92% yield in 10 min with 10 mol% of iodine. In cases when only 1.1 equiv. of ketone was applied in the reaction, mono- and disubstituted products were isolated in few minutes in up to 95% yield in a ratio between 1:1 and up to 1:5. *N*-Alkylated pyrroles also participated in the reaction in good yields.



Scheme 85 Iodine catalyzed reaction

In addition, iodine successfully catalyzed the electrophilic substitution reaction of indoles with aldehydes and ketones to bis(indonyl)methanes [225], the deprotection of aromatic acetates [226], esterifications [227], transesterifications [227], the chemoselective thioacetalization of carbon functions [228], the addition of mercaptans to α,β -unsaturated carboxylic acids [229], the imino-Diels-Alder reaction [230], the synthesis of *N*-Boc protected amines [231], the preparation of alkynyl sugars from D-glycals [232], the preparation of methyl bisulfate [233], and the synthesis of β -acetamido ketones from aromatic aldehydes, enolizable ketones or ketoesters and acetonitrile [234].

Iodine is known to catalyze the condensation of aldehydes, benzyl carbamate and allyltrimethylsilane to homoallylic amines. However, in this case the involvement of an in situ prepared $[\text{Me}_3\text{Si}]$ species was suggested to be the active catalyst [235]. An iodine catalyzed acetalization of carbonyl compounds was reported, where the active catalyst was believed to be hydroiodic acid [236].

Very recently, Ishirihara et al. [237] reported the application of a “chiral iodine atom” through the reaction of NSI and a chiral nucleophilic phosphoramidite for the halocyclization of homo(polyprenyl)arenes.

Next to iodine there is also another class of neutral Lewis acids known. Tetracyanoethylene, dicyanoketene acetals and derivatives can catalyse reaction due to their π -Lewis acid properties. They promoted the alcoholysis of epoxides [238], tetrahydropyranylation of alcohols [239], monothioacetalization of acetals [240], and carbon-carbon bond formation of acetals [241,242] and imines [243] with silylated carbon nucleophiles.

Recently, Denmark reported, based on the Lewis base activation of Lewis acids concept, a Lewis base catalyzed selenolactonization [244].

While the research filed of selenium catalyzed reactions appears to be promising, the application of iodine as a catalyst is of course limited, since the development of an asymmetric version is not possible. Furthermore, much care has to be taken, that the iodine is the active catalyst and not traces of HI.

8 Conclusion

It has been shown that metal-free Lewis acids have been applied as catalysts in a broad variety of reactions. However, in several cases the asymmetric induction in the reactions has to be improved. While many of the highly active salts are moisture sensitive, ionic liquids with the right choice of cation and anion, are quite stable. Therefore their catalytic Lewis acidic activity is weak. The research field presented still has much room for improvement and further investigations and results are continuously reported in the literature in an increasing number due to the large potential of metal-free Lewis acids.

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Chiral Brønsted Acids for Asymmetric Organocatalysis

Daniela Kampen, Corinna M. Reisinger, and Benjamin List

Abstract Chiral Brønsted acid catalysis is an emerging area of organocatalysis. Since the pioneering studies of the groups of Akiyama and Terada in 2004 on the use of chiral BINOL phosphates as powerful Brønsted acid catalysts in asymmetric Mannich-type reactions, numerous catalytic asymmetric transformations involving imine activation have been realized by means of this catalyst class, including among others Friedel–Crafts, Pictet–Spengler, Strecker, cycloaddition reactions, transfer hydrogenations, and reductive aminations. More recently, chiral BINOL phosphates found application in multicomponent and cascade reactions as for example in an asymmetric version of the Biginelli reaction. With the introduction of chiral BINOL-derived *N*-triflyl phosphoramides in 2006, asymmetric Brønsted acid catalysis is no longer restricted to reactive substrates. Also certain carbonyl compounds can be activated through these stronger Brønsted acid catalysts. In dealing with sensitive substrate classes, chiral dicarboxylic acids proved of particular value.

Keywords Asymmetric catalysis • BINOL • Dicarboxylic acids • *N*-Triflyl phosphoramides • Phosphoric acids • Strong chiral Brønsted acids

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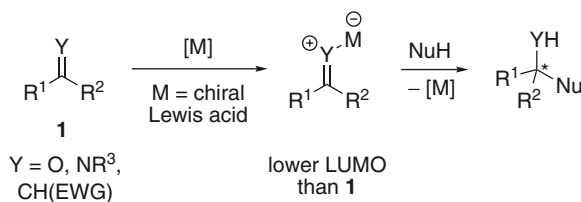
Abbreviations

Ac	Acetyl
All	Allylic substituent
Ar	Aromatic substituent
BHT	Butylated hydroxytoluene
BINAM	2,2'-Diamino-1,1'-binaphthyl
BINOL	1,1'-Binaphthol
bmim	1-Butyl-3-methylimidazolium
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
Bs	Brosyl
<i>t</i> Bu	<i>tert</i> -Butyl
BV	Baeyer–Villiger
Bz	Benzoyl
cat	Catalytic
Cbz	Benzyloxycarbonyl
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DA	Diels–Alder
DBU	1,5-Diazabicyclo[1.4.0]undec-5-ene
DCE	1,2-Dichloroethane
DFT	Density functional theory
DHP	1,4-Dihydropyridine
DHPM	3,4-Dihydropyrimidin-2-(1 <i>H</i>)-one
DMAP	4-Dimethylaminopyridine
<i>dr</i>	Diastereomeric ratio
<i>ee</i>	Enantiomeric excess
equiv	Equivalent(s)
Et	Ethyl
EWG	Electron-withdrawing group
h	Hour(s)
HX	Brønsted acid
HX*	Chiral Brønsted acid
k	Rate constant
M	Metal
MCR	Multicomponent reaction
Me	Methyl
Mes	Mesityl
min	Minute(s)
MS	Molecular sieves
NADH	Nicotinamide adenine dinucleotide
Np	Naphthyl
NuH	Nucleophile

<i>p</i>	<i>Para</i>
Pent	<i>n</i> -Pentyl
Ph	Phenyl
PMB	<i>para</i> -Methoxybenzyl
PMP	<i>para</i> -Methoxyphenyl
cPr	Cyclopropyl
cPr	Isopropyl
R	Organic substituent
rac	Racemic
RT	Room temperature
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -Tetraaryl-1,3-dioxolane-4,5-dimethanol
<i>tert</i>	Tertiary
Tf	Triflyl (trifluoromethanesulfonyl)
TMS	Trimethylsilyl
TS	Transition state
Ts	Tosyl
VAPOL	4,4'-Dihydroxy-2,2'-diphenyl-3,3'-biphenanthryl

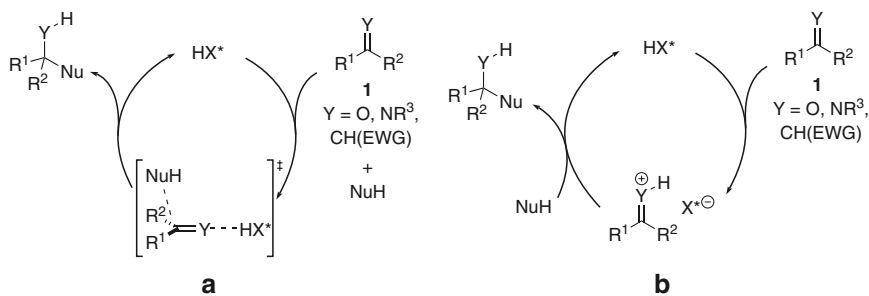
1 Introduction

Chiral Lewis acid catalysts are powerful tools for asymmetric synthesis, combining a metal or metalloid central atom with a chiral ligand [1, 2]. Such chiral Lewis acids activate electrophiles **1** for a nucleophilic attack. Various metals can be used as the center element (Scheme 1).

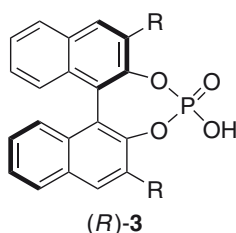
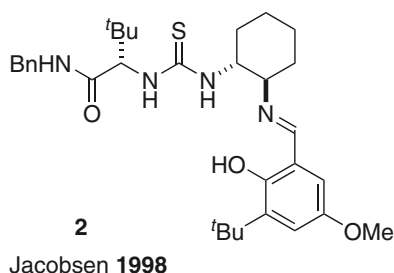


Scheme 1 Lewis acid catalysis

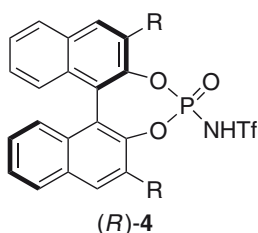
Hydrogen would be the simplest center element. Indeed, chiral Brønsted acids have emerged as a new class of organocatalysts over the last few years [3–13]. The field of asymmetric Brønsted acid catalysis can be divided into general acid catalysis and specific acid catalysis. A general acid activates its substrate (**1**) via hydrogen bonding (Scheme 2, **a**), whereas the substrate (**1**) of a specific acid is activated via protonation (Scheme 2, **b**).



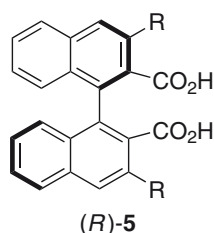
Scheme 2 Asymmetric Brønsted acid catalysis



Akiyama, Terada 2004



Yamamoto 2006



Maruoka 2007

Fig. 1 Chiral Brønsted acids

Brønsted acids such as thiureas **2** represent hydrogen-bonding catalysts. Phosphoric acids **3**, *N*-triflyl phosphoramides **4**, and dicarboxylic acids **5** are examples of stronger specific Brønsted acids (Fig. 1).

In this review, we present asymmetric reactions catalyzed by stronger Brønsted acids. The scope and limitations of chiral phosphoric acids, *N*-triflyl phosphoramides, and dicarboxylic acids are described considering articles published until the middle of 2008. Although the mechanisms of a few transformations have been investigated in some detail, they are not the focus of this review.

2 Chiral Phosphoric Acids

2.1 Pioneering Studies

Mannich reactions give rise to β -amino carbonyl compounds which are amenable to further synthetic manipulations. Numerous stereoselective variants have been achieved by means of different types of catalysts including both metal complexes and organic molecules. In 2004, the groups of Akiyama and Terada independently selected this transformation as a model reaction for the introduction of a novel chiral motif to asymmetric catalysis [14, 15].

Axially chiral phosphoric acid **3** was chosen as a potential catalyst due to its unique characteristics (Fig. 2). (1) The phosphorus atom and its optically active ligand form a seven-membered ring which prevents free rotation around the P–O bond and therefore fixes the conformation of Brønsted acid **3**. This structural feature cannot be found in analogous carboxylic or sulfonic acids. (2) Phosphate **3** with the appropriate acid ity should activate potential substrates via protonation and hence increase their electrophilicity. Subsequent attack of a nucleophile and related processes could result in the formation of enantioenriched products via sterenchemical communication between the cationic protonated substrate and the chiral phosphate anion. (3) Since the phosphoryl oxygen atom of Brønsted acid **3** provides an additional Lewis basic site, chiral BINOL phosphate **3** might act as bifunctional catalyst.

Phosphoric acids **3** bearing different aromatic substituents at the 3,3'-positions can be synthesized in a few steps starting from commercially available BINOL (**6**) (Scheme 3). The key step involves a palladium-catalyzed cross-coupling of boronic acid **7** and the respective aryl halide. Both the electronic and steric properties of potential catalyst **3** can be tuned by a proper choice of the substituents at the 3,3'-positions. Besides a simple phenyl group, Akiyama et al. introduced monosubstituted phenyl derivatives as well as a mesityl group, whereas Terada and coworkers focused on substituents such as biphenyl or 4-(2-naphthyl)-phenyl.

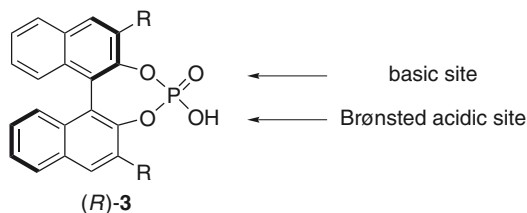
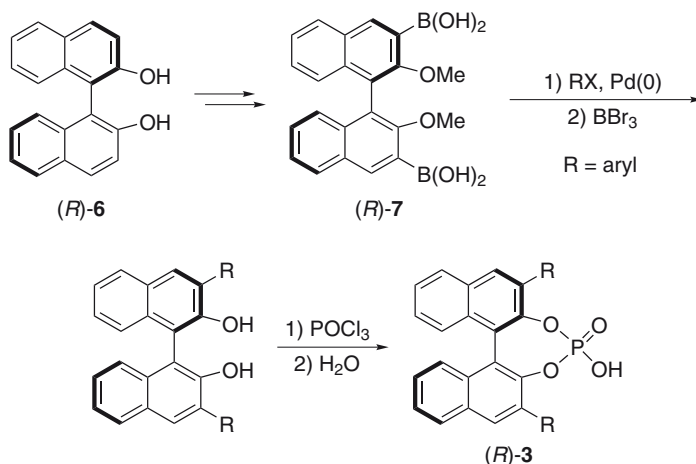
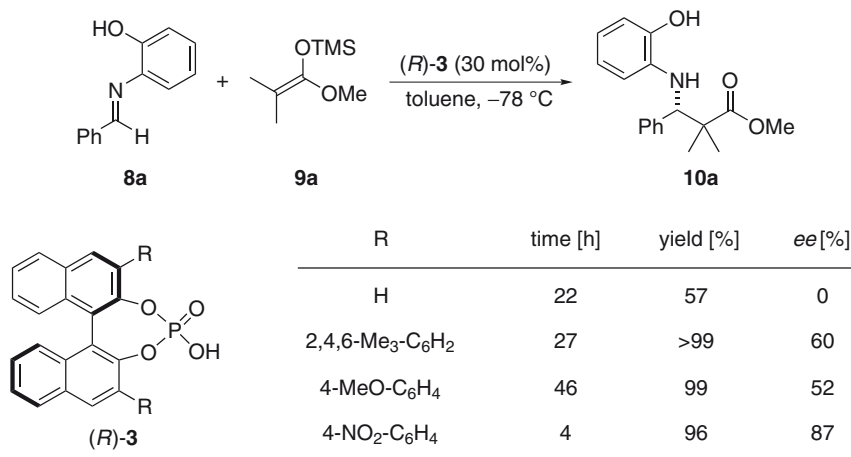


Fig. 2 Brønsted acidic and basic sites of BINOL phosphates



Scheme 3 Synthesis of BINOL phosphates according to Akiyama and Terada

The Akiyama group tested various BINOL phosphates **3** as catalysts for the indirect Mannich reaction of aldimines **8** derived from 2-aminophenol with silyl ketene acetals **9** (Scheme 4). All of these Brønsted acids furnished β -amino ester **10a** in (nearly) quantitative yields. Both the reaction rates (4–46 h) and the enantioselectivities (27–87% *ee*) were strongly dependent on the nature of the substituents at the 3,3'-positions.



Scheme 4 Screening of catalysts

Phosphoric acid **(R)-3d** (10 mol%, R = 4-NO₂-C₆H₄, Fig. 3) bearing *p*-nitrophenyl substituents turned out to be the most powerful catalyst. It provided the desired products **10** in good yields (65 to >99%), *syn*-diastereoselectivities (6:1 to >99:1) and enantioselectivities (81–96% *ee*) (Scheme 5) [14].

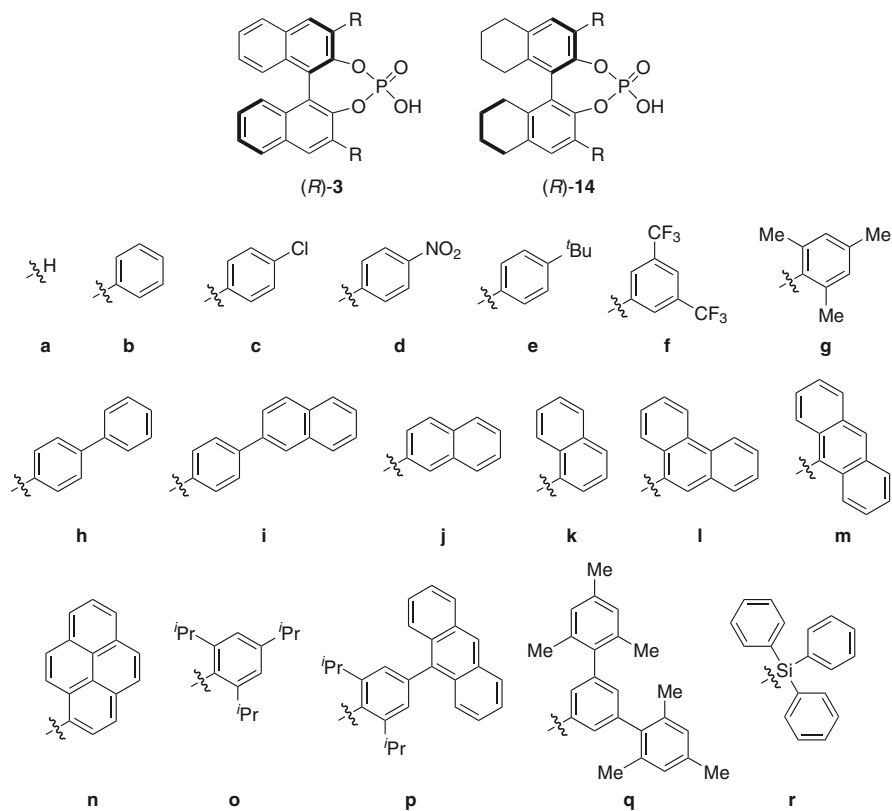
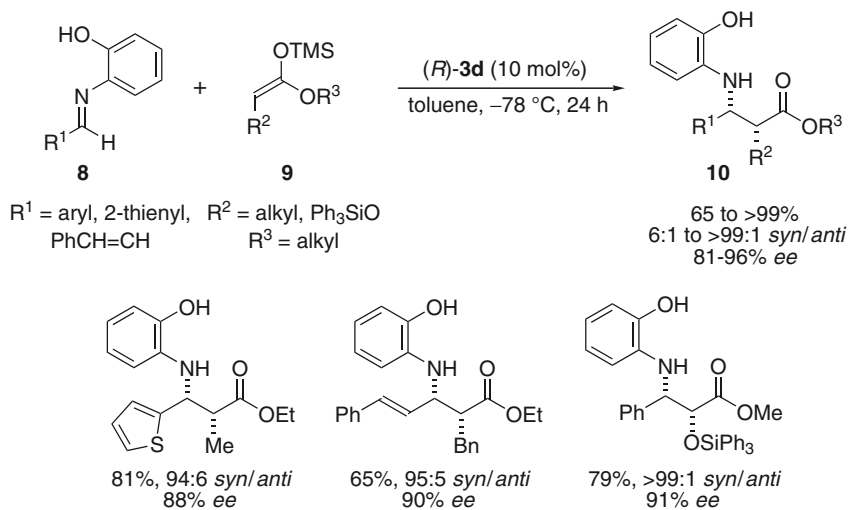


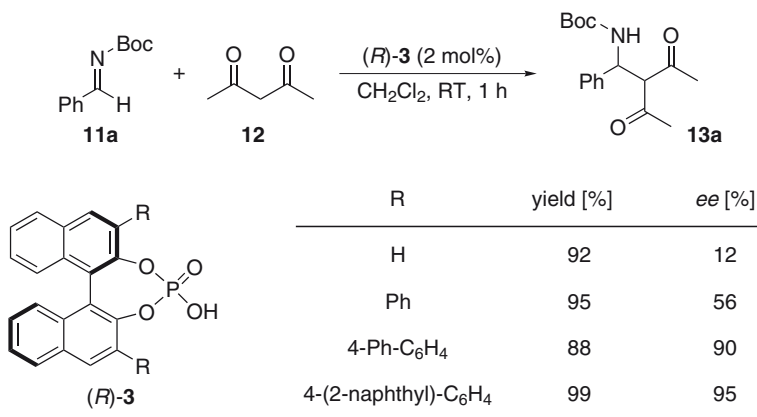
Fig. 3 Phosphoric acids derived from BINOL and H_8 -BINOL



Scheme 5 Mannich reaction of silyl ketene acetals

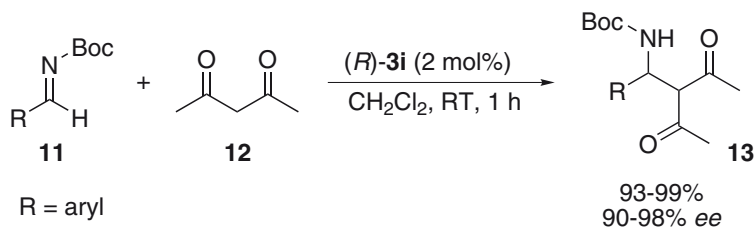
Detailed mechanistic investigations based on DFT computational studies were disclosed by Yamanaka and Akiyama et al. in 2007 [16].

Terada et al. found the direct Mannich reaction between *N*-Boc-protected aldimines **11** and acetyl acetone (**12**) to be catalyzed by different phosphoric acids **3** (Scheme 6). Varying the aromatic groups at the 3,3'-positions influenced the yields slightly (88–99%), but the enantioselectivities to a high degree (12–95% *ee*).



Scheme 6 Screening of catalysts

Sterically demanding BINOL phosphate **(R)-3i** (2 mol%, R = 4-(2-naphthyl)-C₆H₄, Fig. 3) led to superior results. It gave protected β -amino ketones **13** in high yields (93–99%) and enantioselectivities (90–98% *ee*) (Scheme 7) [15].



R	yield [%]	<i>ee</i> [%]
4-Br-C ₆ H ₄	96	98
2-Me-C ₆ H ₄	94	93
1-naphthyl	99	92

Scheme 7 Mannich reaction of acetyl acetone

After having proven that BINOL phosphates serve as organocatalysts for asymmetric Mannich reactions, Akiyama and Terada et al. reasoned that the concept of electrophilic activation of imines by means of chiral phosphoric acids might be applicable to further asymmetric transformations. Other groups recognized the potential of these organocatalysts as well. They showed that various nucleophiles can be used. Subsequently, chiral phosphates were found to activate not only imines, but also other substrates.

2.2 Overview of Phosphoric Acids

The development of new asymmetric transformations calls for the synthesis of new chiral catalysts with different electronic and steric properties (Fig. 3). BINOL phosphates **3** bearing aromatic substituents or a triphenylsilyl group at the 3,3'-positions as well as its partially hydrogenated analogs **14** were prepared according to the pioneers' protocol or slightly modified procedures. While most of the substituents are introduced by a Suzuki cross-coupling, the introduction of a few groups requires a Kumada cross-coupling. The synthesis of Brønsted acids **3r** and **14r** bearing triphenylsilyl substituents involves an O-silyl to C-silyl rearrangement as the key step.

Furthermore, phosphoric acids **15**, **16**, **17**, and **18** derived from TADDOL,[17] VAPOL, BINAM[18] or a bis-BINOL as well as a bisphosphoric acid **19** were synthesized according to modified protocols (Fig. 4).

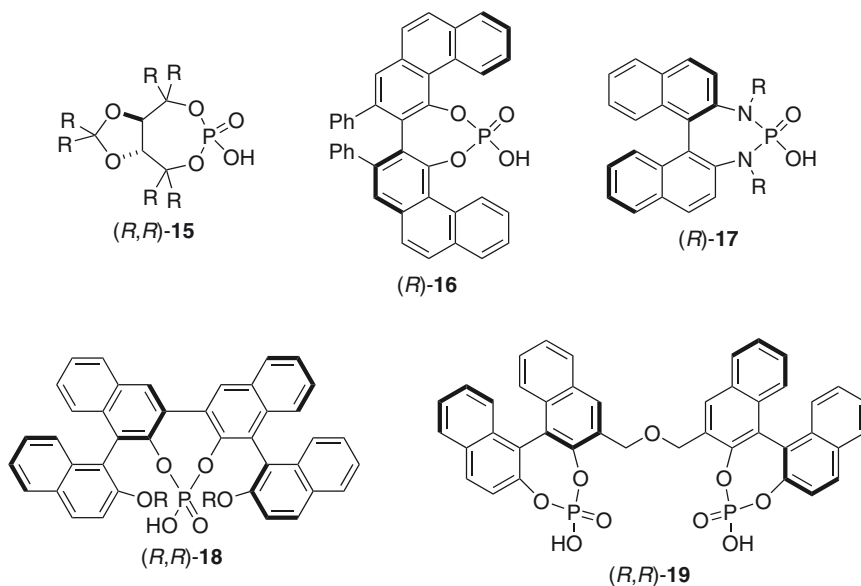


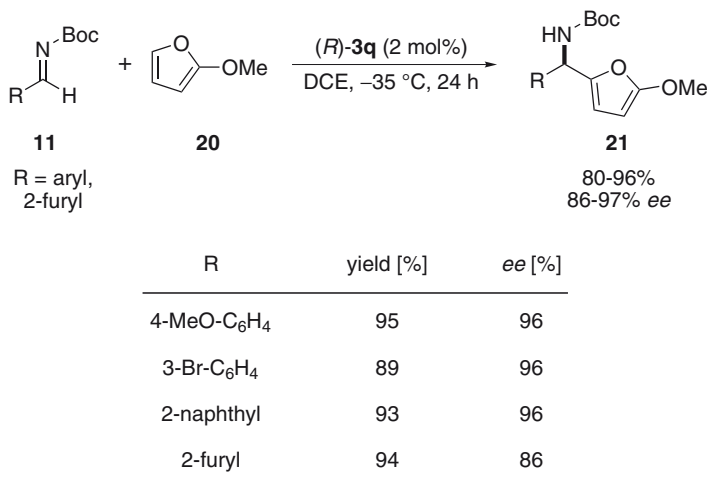
Fig. 4 Other phosphoric acids

2.3 Imines as Substrates

2.3.1 Friedel–Crafts and Related Reactions

The Friedel–Crafts reaction is one of the most important and versatile tools for the formation of carbon–carbon bonds in the synthesis of substituted aromatic and heteroaromatic compounds present in numerous natural products and drugs. Catalytic asymmetric variants using either metal complexes or organic molecules attracted considerable attention over the last few years.

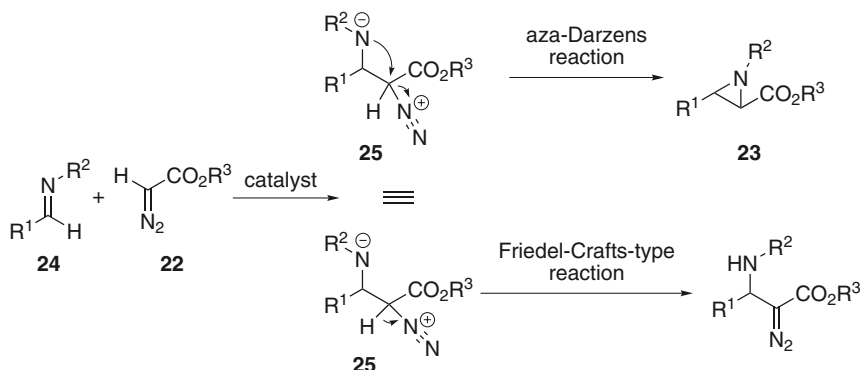
In 2004, Terada and coworkers reported the first asymmetric phosphoric acid-catalyzed Friedel–Crafts alkylation (Scheme 8). Aldimines **11** reacted with commercially available 2-methoxy furan (**20**) in the presence of BINOL phosphate (*R*)-**3q** (2 mol%, $R = 3,5\text{-Me}_2\text{-C}_6\text{H}_3$) to provide access to *N*-Boc-protected 2-furyl amines **21** in high yields (80–96%) and enantioselectivities (86–97% *ee*) [19].



Scheme 8 Friedel–Crafts alkylation of 2-methoxy furan

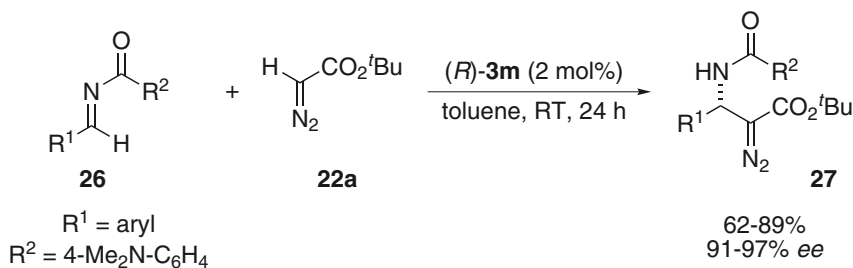
Noteworthy, the reaction could be carried out on a 1-g scale employing only 0.5 mol% of catalyst **3q** without a considerable loss in reactivity and selectivity (one example: 95% yield, 97% *ee*).

Diazoesters **22** have an electronically unique α -carbon atom. (Scheme 9) They are commonly used for the formation of aziridines **23** from imines **24**. The intermediate (**25**) resulting from the addition of α -diazoesters **22** to the latter (**24**) can undergo elimination of the proton at the α -position prior to extrusion of molecular nitrogen. This interrupted aza–Darzens reaction allows for the direct alkylation of diazoesters **22** via cleavage of a carbon–hydrogen bond.



Scheme 9 Mechanism of a Friedel–Crafts-type alkylation of α -diazoesters

In conjunction with their Friedel–Crafts alkylation, Terada et al. found phosphoric acid (*R*)-**3m** (2 mol%, R = 9-anthryl) bearing a bulky 9-anthryl group to mediate the asymmetric Friedel–Crafts-type reaction of α -diazoester **22a** with *N*-acylated aldimines **26** (Scheme 10). α -Diazo- β -amino esters **27** were obtained in moderate yields (62–89%) and very good enantioselectivities (91–97% *ee*) [20].

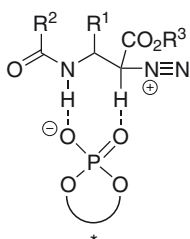


R^1	yield [%]	<i>ee</i> [%]
4-F-C ₆ H ₄	74	97
4-Ph-C ₆ H ₄	71	97
2-MeO-C ₆ H ₄	85	91

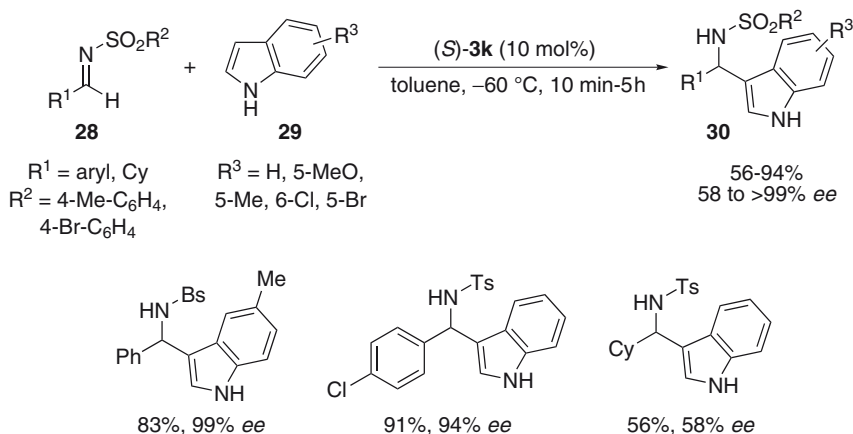
Scheme 10 Friedel–Crafts-type alkylation of α -diazoesters

While its precise role remains unclear, the catalyst **3m** is supposed not only to activate the electrophile (**26**), but also to lower the nucleophilicity of the amide nitrogen atom (Fig. 5). The latter interaction may account for a chemoselective Friedel–Crafts-type alkylation versus an aza-Darzens reaction.

Fig. 5 Possible transition state



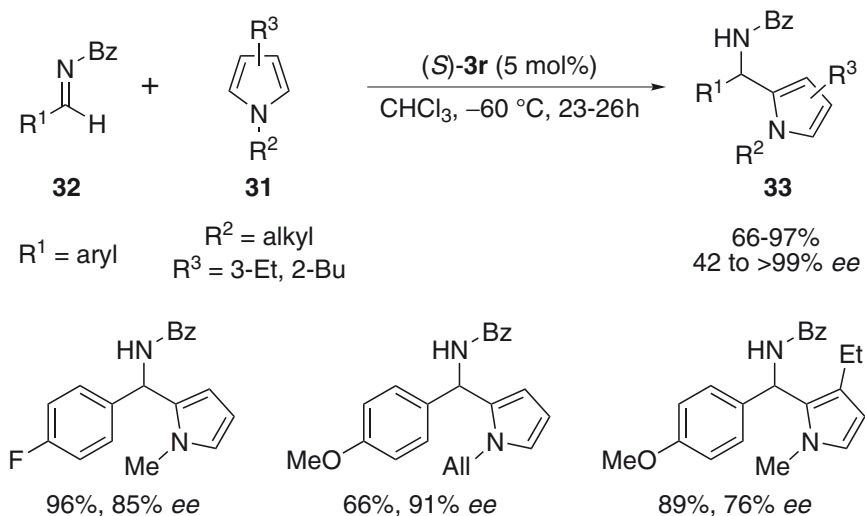
Two years after the discovery of the first asymmetric Brønsted acid-catalyzed Friedel–Crafts alkylation, the You group extended this transformation to the use of indoles as heteroaromatic nucleophiles (Scheme 11). *N*-Sulfonylated aldimines **28** are activated with the help of catalytic amounts of BINOL phosphate (*S*)-**3k** (10 mol%, R = 1-naphthyl) for the reaction with unprotected indoles **29** to provide 3-indolyl amines **30** in good yields (56–94%) together with excellent enantioselectivities (58 to >99% *ee*) [21]. Antilla and coworkers demonstrated that *N*-benzoyl-protected aldimines can be employed as electrophiles for the addition of *N*-benzylated indoles with similar efficiencies [22]. Both protocols tolerate several aryl imines and a variety of substituents at the indole moiety. In addition, one example of the use of an aliphatic imine (56%, 58% *ee*) was presented.



Scheme 11 Friedel–Crafts alkylation of indoles

Moreover, phosphoric acid (*S*)-**3r** (5 mol%, R = SiPh₃) bearing a bulky triphenylsilyl group turned out to be a suitable catalyst for the asymmetric Friedel–Crafts alkylation of *N*-alkyl pyrroles **31** with *N*-benzoyl-protected aldimines **32** (Scheme 12) [23]. 2-Pyrrolyl amines **33** were obtained in high yields (66–97%) and moderate to high enantioselectivities (42 to >99% *ee*).

The incorporation of a CF₃ group into organic molecules often leads to significant changes in physical, chemical, and biological properties of the parent

**Scheme 12** Friedel–Crafts alkylation of pyrroles

compound. Therefore, trifluoromethylated compounds have attracted considerable attention in organic synthesis, medicinal and agrochemistry. In 2008, Ma et al. applied imines **34** generated in situ from trifluoroacetaldehyde methyl hemiacetal (**35**) and aniline **36** to an asymmetric Friedel–Crafts alkylation of unprotected indoles **29** catalyzed by phosphoric acid (*S*)-**3o** (10 mol%, $R = 2,4,6\text{-}i\text{-Pr}_3\text{-C}_6\text{H}_2$) bearing 2,4,6-trisopropylphenyl substituents at the 3,3'-positions of the binaphthyl scaffold (Scheme 13) [24]. A range of substituted indoles **29** furnished the

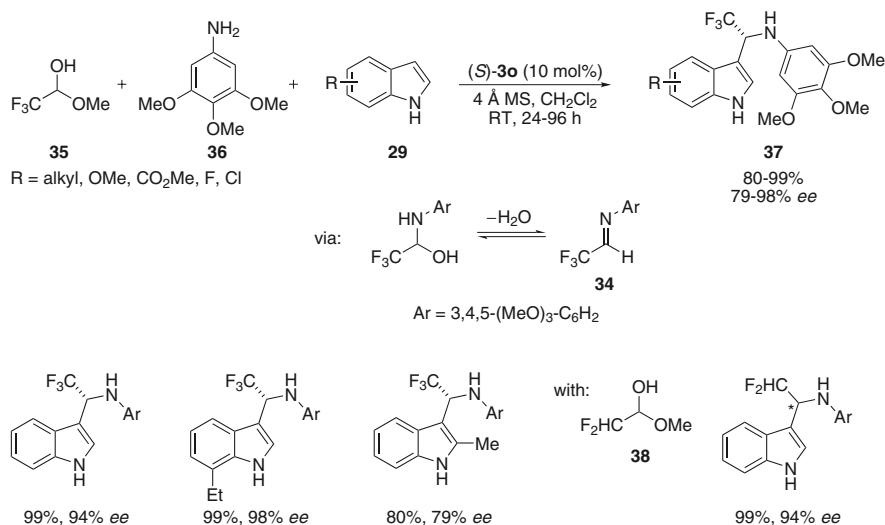
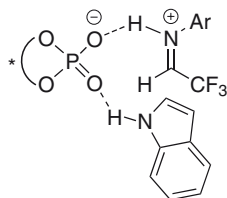
**Scheme 13** Three-component Friedel–Crafts alkylation of indoles

Fig. 6 Proposed transition state

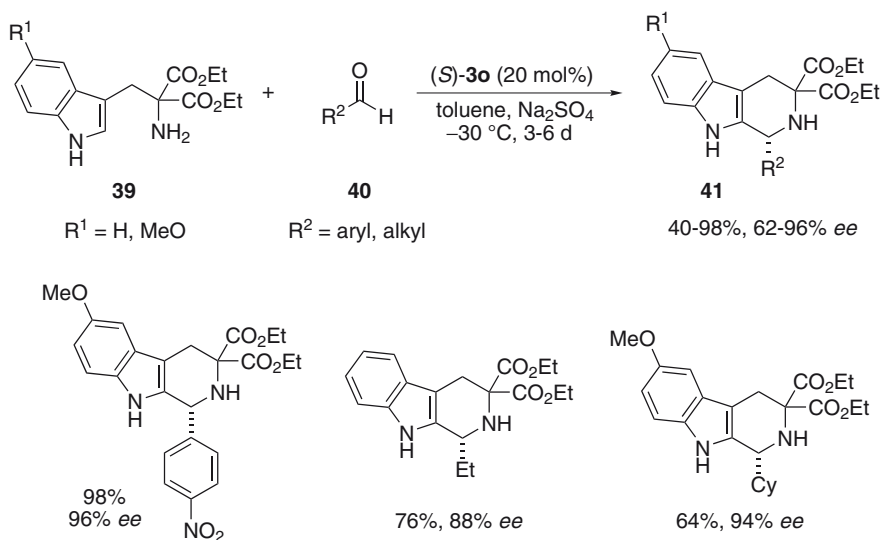
corresponding trifluoromethyl-containing 3-indolyl amines **37** in high yields (80–99%) along with good to excellent enantioselectivities (79–98% *ee*). The methodology was further extended to the use of difluoroacetaldehyde methyl hemiacetal (**38**).

Notably, the aminoalkylation reaction did not occur with *N*-protected indoles revealing the crucial role of the free N–H group for the activation by the phosphoric acid. This prompted the authors to postulate the transition state model depicted in Fig. 6.

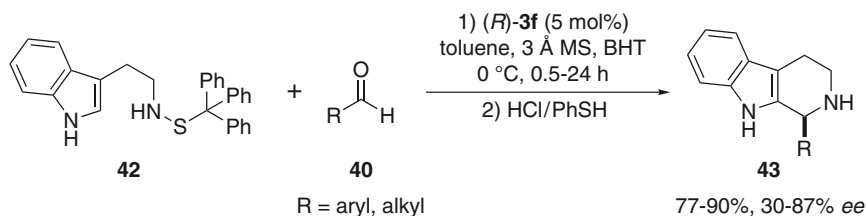
2.3.2 Pictet–Spengler Reactions

The Pictet–Spengler reaction is the method of choice for the preparation of tetrahydro- β -carbolines, which represent structural elements of several natural products such as biologically active alkaloids. It proceeds via a condensation of a carbonyl compound with a tryptamine followed by a Friedel–Crafts-type cyclization. In 2004, Jacobsen et al. reported the first catalytic asymmetric variant [25]. This acyl-Pictet–Spengler reaction involves an *N*-acyliminium ion as intermediate and is promoted by a chiral thiourea (general Brønsted acid catalysis).

List and coworkers reasoned that BINOL phosphates (specific Brønsted acid catalysis) could be suitable catalysts for an asymmetric direct Pictet–Spengler reaction [26]. Preliminary experiments revealed that unsubstituted tryptamines do not undergo the desired cyclization. Introduction of two geminal ester groups rendered the substrates more reactive which might be explained by electronic reasons and a Thorpe–Ingold effect. Tryptamines **39** reacted with aldehydes **40** in the presence of phosphoric acid (*S*)-**30** (20 mol%, R = 2,4,6-*i*Pr₃-C₆H₂) bearing 2,4,6-triisopropyl-phenyl substituents to provide tetrahydro- β -carbolines **41** in high yields (40–98%) and enantioselectivities (62–96% *ee*) (Scheme 14). The requirement of the geminal diester functionality constitutes a limitation of this method. However, the corresponding products **41** are amenable to further synthetic manipulations via diastereoselective functional group differentiations.

**Scheme 14** Direct Pictet–Spengler reaction

In 2007, Hiemstra et al. established a catalytic asymmetric Pictet–Spengler reaction that proceeds via *N*-sulfenyliminium ions (Scheme 15) [27]. Treatment of *N*-sulfenylated tryptamines **42** with aldehydes **40** and BINOL phosphate (*R*)-**3f** (5 mol%, $R = 3,5\text{-(CF}_3)_2\text{-C}_6\text{H}_3$) afforded tetrahydro- β -carboline. After completion of the cyclization the sulfenyl group was cleaved by the use of HCl. This one-pot



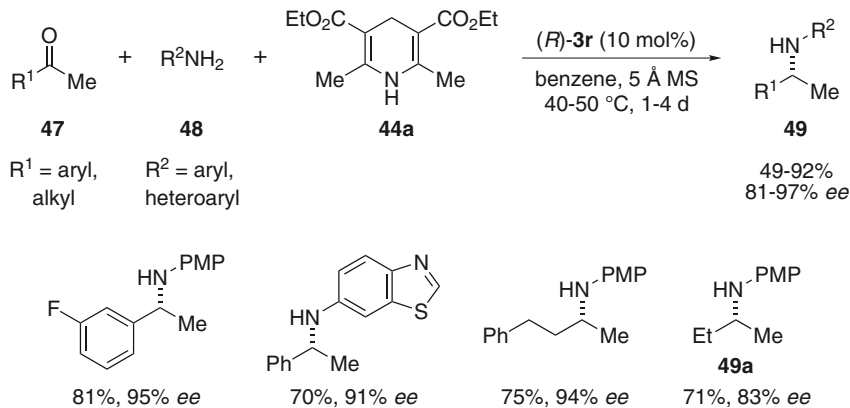
R	yield [%]	<i>ee</i> [%]
Ph	77	82
Bn	90	87
Pent	87	84
<i>i</i> Pr	77	78

Scheme 15 Pictet–Spengler reaction via *N*-sulfenyliminium ions

Scheme 16 Transfer hydrogenation of ketimines

phosphoric acid (*S*)-**3o** ($R = 2,4,6\text{-}i\text{-Pr}_3\text{-C}_6\text{H}_2$) bearing 2,4,6-triisopropylphenyl substituents, which led to superior results. *N*-PMP-protected amines **46** can now be obtained in higher yields (80–98%) with improved enantioselectivities (80–93% *ee*) under milder reaction conditions [31]. The remarkably low catalyst loading (1 mol%) was up to that time unprecedented in asymmetric Brønsted acid catalysis.

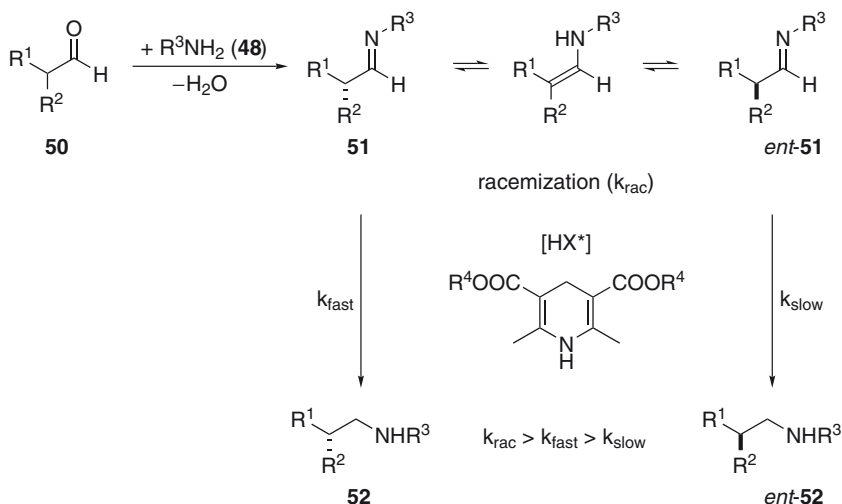
The catalytic asymmetric reductive amination is a powerful transformation for the coupling of carbonyl compounds and amines and provides rapid access to stereogenic C–N bonds. Despite its potential for the union of complex fragments, only a few enantioselective protocols have been described. The first example of a phosphoric acid-catalyzed reductive amination of acetophenone with Hantzsch ester **44a** followed by removal of the protecting group to furnish the corresponding free amine (81% overall yield, 88% *ee*) was presented by the List group [31]. In 2006, MacMillan et al. established a reductive amination in the presence of the new phosphoric acid (*R*)-**3r** (10 mol%, $R = \text{SiPh}_3$) bearing bulky triphenylsilyl substituents using the same hydride source (**44a**) (Scheme 17) [32]. Various aryl–alkyl as well as alkyl–alkyl ketones **47** in combination with aromatic and heteroaromatic amines **48** were converted into the corresponding α -branched amines **49** in good yields (49–92%) and high enantioselectivities (81–97% *ee*). Computational studies revealed that torsionally constrained BINOL phosphate **3r** should be generally selective for the transfer hydrogenation of iminium ions derived from methyl ketones **47**. Particularly, reductive amination of 2-butanone (**47a**, $R^1 = \text{Et}$) provided 2-amino butane (**49a**) in 71% yield and 83% *ee*.



Scheme 17 Reductive amination of ketones for the preparation of α -branched amines

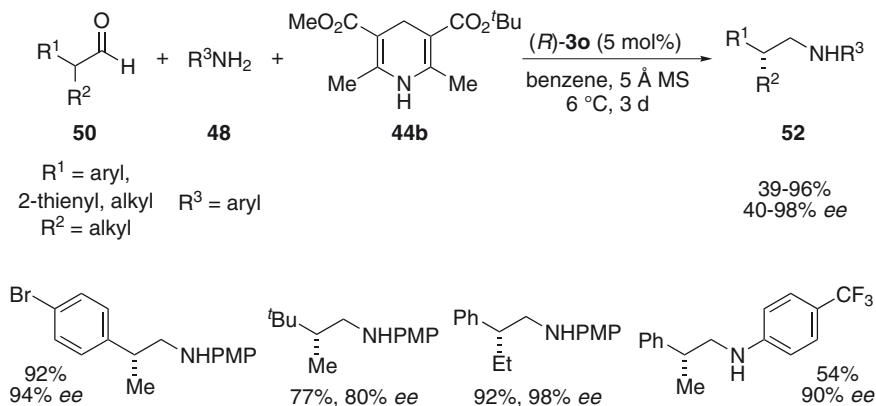
Since imines derived from alkyl–alkyl ketones are relatively unstable, reductive amination may be more practical compared to imine reduction. Compared to the reductive amination, which employs three equivalents of the ketone substrate, the in situ imine generation/one-pot reduction protocol has the significant advantage that it does not require an excess of the carbonyl compound.

The List group came up with a novel concept for a catalytic asymmetric reductive amination, which involves enolizable aldehydes (Scheme 18) [33].



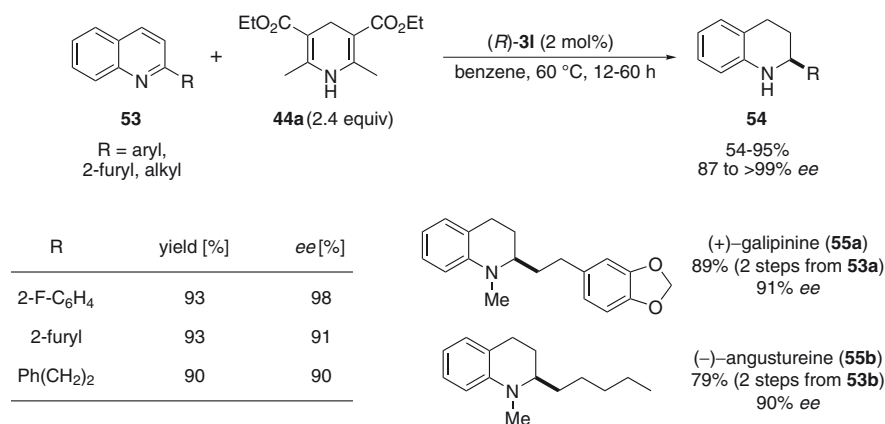
Scheme 18 Dynamic kinetic resolution of enolizable aldehydes

In the presence of a primary amine (**48**) and chiral phosphoric acid (*R*)-**3o** (5 mol%, $R = 2,4,6\text{-}i\text{Pr}_3\text{-C}_6\text{H}_2$), α -branched aldehydes **50** undergo a quick racemization via an imine/enamine tautomerization. Brønsted acid-catalyzed transfer hydrogenation of one enantiomer (**51**) is faster than of the other (*ent*-**51**), which results in the differentiation of the two enantiomers and therefore leads to the formation of enantioenriched β -branched amines **52**. This dynamic kinetic resolution could be applied to a broad range of 2-substituted propionaldehydes **50** and electronically different anilines **48** (Scheme 19). Unsymmetrical Hantzsch dihydropyridine **44b** was required to obtain high yields (39–96%) and enantioselectivities (40–98% *ee*). Interestingly, an ethyl substituent at the α -position of precursor **50** was tolerated as well.



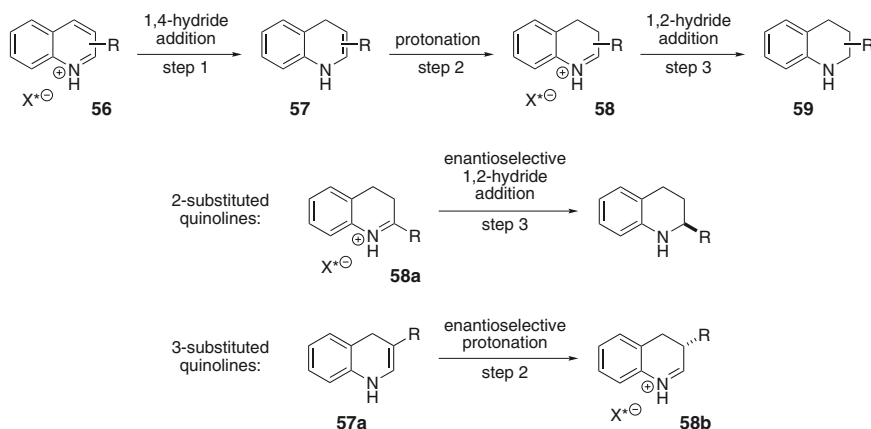
Scheme 19 Reductive amination of α -branched aldehydes for the preparation of β -branched amines

After having proven that simple ketimines can be subjected to phosphoric acid-catalyzed transfer hydrogenations yielding optically active amines, Rueping and coworkers extended this principle to more complex molecules in 2006. They described the first enantioselective organocatalytic reduction of heteroaromatic compounds as well as its application to natural product synthesis (Scheme 20) [34]. Treatment of 2-substituted quinolines **53** with 2.4 equivalents of Hantzsch ester **44a** and catalytic amounts of sterically demanding BINOL phosphate (*R*)-**31** (2 mol%, R = 9-phenanthryl) gave tetrahydroquinolines **54** in excellent yields (54–95%) and enantioselectivities (87 to >99% *ee*). The utility of the partial reduction of readily available quinolines **53** was demonstrated by the preparation of biologically active alkaloids such as (+)-galipinine (**55a**) and (–)-angustureine (**55b**) in only two steps. At a later date, the same group expanded the scope of the cascade transfer hydrogenation of heteroaromatic compounds to 3-substituted quinolines [35] and 2,3,6-substituted pyridines [36]. The biomimetic reduction of 2- and 2,3-substituted quinolines was also studied by the Du group to test their newly developed bis-BINOL-derived phosphoric acid **18** (Fig. 4) [37].



Scheme 20 Transfer hydrogenation of 2-substituted quinolines

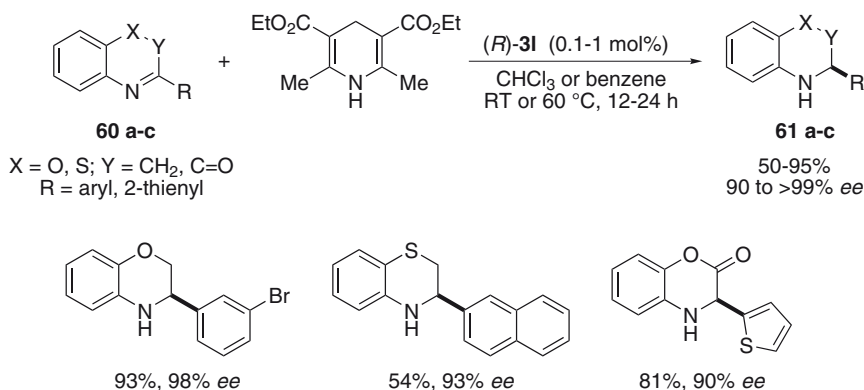
Mechanistically, the Brønsted acid-catalyzed cascade hydrogenation of quinolines presumably proceeds via the formation of quinolinium ion **56** and subsequent 1,4-hydride addition (step 1) to afford enamine **57**. Protonation (step 2) of the latter (**57**) followed by 1,2-hydride addition (step 3) to the intermediate iminium ion **58** yields tetrahydroquinolines **59** (Scheme 21). In the case of 2-substituted precursors enantioselectivity is induced by an asymmetric hydride transfer (step 3), whereas for 3-substituted ones asymmetric induction is achieved by an enantioselective proton transfer (step 2).



Scheme 21 Mechanism of the transfer hydrogenation of quinolines

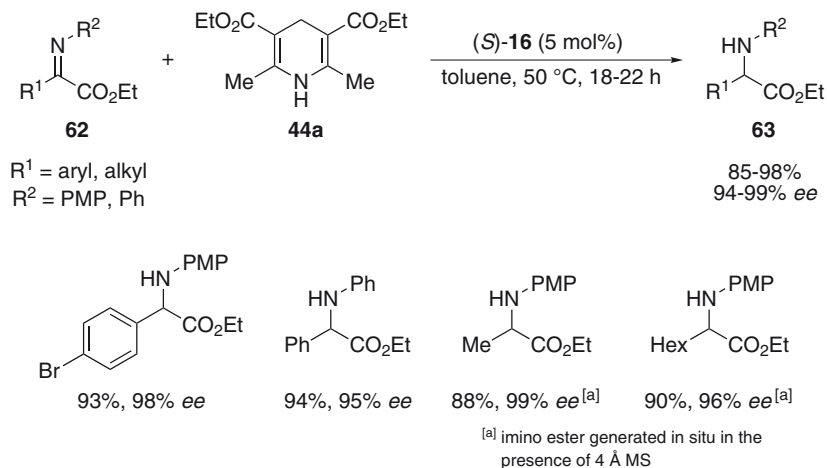
Furthermore, Rueping et al. applied phosphoric acid (*R*)-**3I** (0.1 or 1 mol%, *R* = 9-phenanthryl) bearing 9-phenanthryl substituents to the asymmetric reduction of benzoxazines **60a** (*X* = O, *Y* = CH₂), benzothiazines **60b** (*X* = S, *Y* = CH₂) and benzoxazinones **60c** (*X* = O, *Y* = CO) in good yields (50–95%) and excellent enantioselectivities (90 to >99% *ee*) (Scheme 22) [38]. The corresponding architectures **61** represent structural elements of numerous natural products and pharmaceuticals. In particular, the organocatalytic approach to enantioenriched dihydrobenzothiazines **61b** (*X* = S, *Y* = CH₂) complements metal-mediated hydrogenations, since some metal catalysts are poisoned by sulfur-containing compounds.

Remarkably, the catalyst loading could be decreased to 0.01 mol% without a considerable loss in reactivity and selectivity (one example: 90% yield, 93% *ee*). A substrate/catalyst ratio of 10,000 to 1 has not been achieved in asymmetric metal-free catalysis before.



Scheme 22 Transfer hydrogenation of benzoxazines, benzothiazines and benzoxazinones

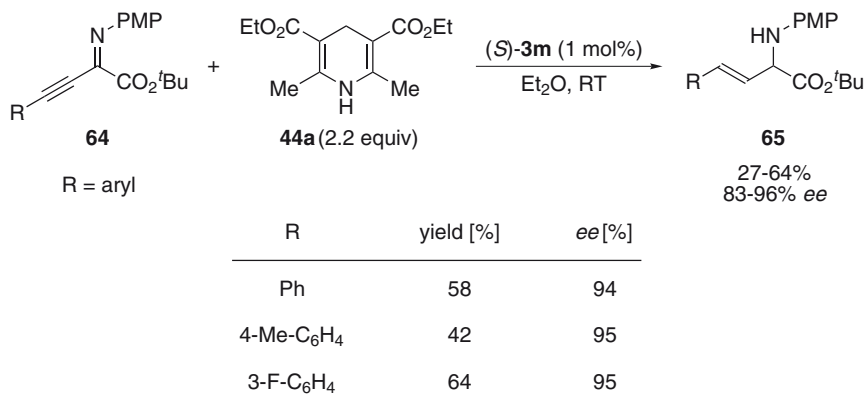
In 2007, Antilla and coworkers disclosed the first asymmetric organocatalytic reduction of acyclic α -imino esters (Scheme 23) [39]. Chiral VAPOL phosphate (**S**)-**16** (5 mol%) served as a catalyst for the transfer hydrogenation of the latter (**62**) employing commercially available dihydropyridine **44a** to give both aromatic and aliphatic α -amino esters **63** in very high yields (85–98%) and enantioselectivities (94–99% *ee*).



Scheme 23 Transfer hydrogenation of α -imino esters

While aromatic substrates are preformed, aliphatic precursors are generated in situ from the corresponding α -keto esters and *p*-anisidine. The use of in situ-generated α -imino esters generally gave identical enantioselectivities, but lower yields. Products **63** can be readily transformed into α -amino acids. You et al. found chiral phosphoric acid (*S*)-**3m** (1 mol%, R = 9-anthryl) bearing 9-anthryl groups to mediate the transfer hydrogenation of α -imino esters of type **62** [40]. Moreover, their catalyst turned out to be suitable for the asymmetric reduction of β,γ -alkynyl α -imino esters **64** using 2.2 equivalents of Hantzsch ester **44a** (Scheme 24) [41]. The corresponding *trans*-alkenyl α -amino esters **65** were obtained in moderate yields (27–64%) along with good enantioselectivities (83–96% *ee*). Mechanistic investigations revealed that the carbon-carbon triple bond is hydrogenated faster than the carbon-nitrogen double bond. Although alkenyl α -amino esters **65** are amenable to synthetic manipulations, they cannot be reduced further under the present reaction conditions.

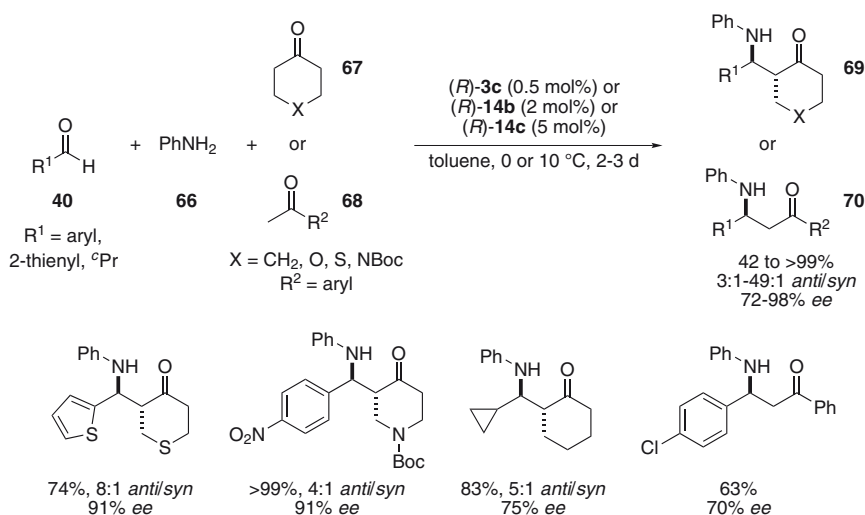
Detailed mechanistic investigations of transfer hydrogenations with Hantzsch ester by means of DFT computational studies were carried out by the groups of Goodman and Himo [42, 43].



Scheme 24 Transfer hydrogenation of β,γ -alkynyl α -imino esters

2.3.4 Mannich Reactions

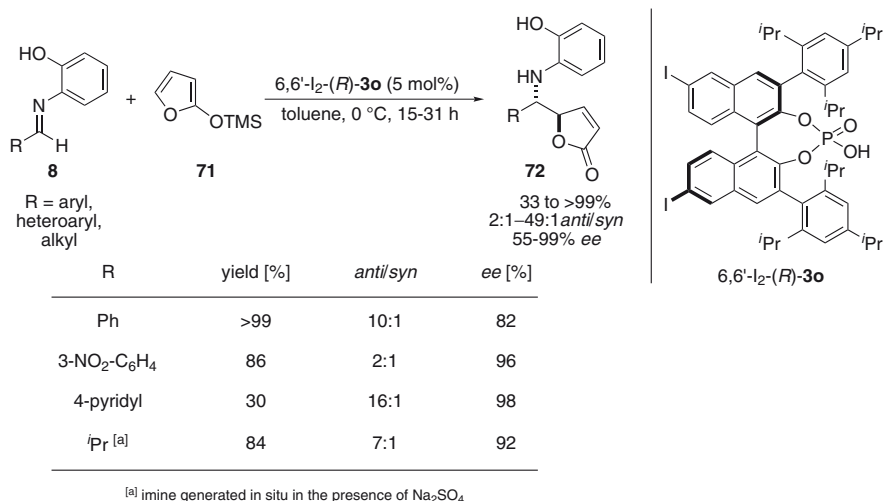
Three years after the discovery of the asymmetric BINOL phosphate-catalyzed Mannich reactions of silyl ketene acetals or acetyl acetone, the Gong group extended these transformations to the use of simple ketones as nucleophiles (Scheme 25) [44]. Aldehydes **40** reacted with aniline (**66**) and ketones **67** or **68** in the presence of chiral phosphoric acids (*R*)-**3c**, (*R*)-**14b**, or (*R*)-**14c** (0.5–5 mol%, R = Ph, 4-Cl-C₆H₄) to give β -amino carbonyl compounds **69** or **70** in good yields (42 to >99%), *anti*-diastereoselectivities (3:1–49:1), and enantioselectivities (72–98% *ee*).



Scheme 25 Mannich reaction of simple ketones

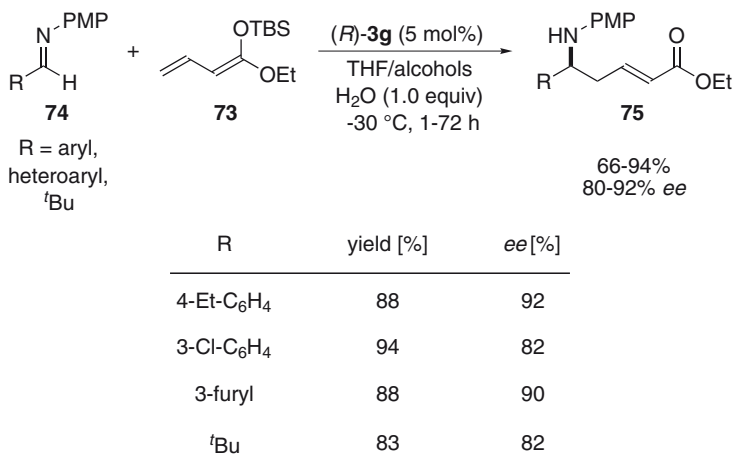
This protocol complements Akiyama's method which provides β -amino carbonyl compounds as *syn*-diastereomers [14]. It tolerated aromatic, heteroaromatic, and aliphatic aldehydes. Cyclic ketones, acetone, as well as acetophenone derivatives could be employed. The use of aromatic ketones as Mannich donors was up to that time unprecedented in asymmetric organocatalysis. Rueping et al. independently expanded the scope of the asymmetric Brønsted acid-catalyzed Mannich reaction of acetophenone [45].

In 2008, Akiyama and coworkers introduced a new chiral BINOL phosphate bearing 2,4,6-trisopropylphenyl groups at the 3,3'-positions as well as an iodine atom at the 6,6'-positions for a vinylogous Mannich reaction (Scheme 26) [46]. Aldimines **8** derived from 2-aminophenol were treated with 2-(trimethylsiloxy) furan (**71**) and catalytic amounts of phosphoric acid 6,6'-I₂-(*R*)-**3o** (5 mol%, R = 2,4,6-*i*-Pr₃-C₆H₂) to furnish γ -butenolides **72** in high yields (30 to >99%), *anti*-diastereoselectivities (2:1–49:1), and enantioselectivities (55–99% *ee*). The iodine substituents have an effect on the stereoselectivity. Compared to catalyst **3o**, its iodine-substituted analog 6,6'-I₂-**3o** increases the enantioselectivity (82% *ee* instead of 74% *ee*), but decreases the diastereoselectivity (10:1 instead of 13:1). Interestingly, calculations revealed that BINOL phosphates **3o** and 6,6'-I₂-**3o** exhibit the same dihedral angle (53°). Thus, the observed difference in stereoselectivities might be explained by rather electronic than steric effects.



Scheme 26 Vinylogous Mannich reaction of 2-(trimethylsiloxy)furan

The Schneider group independently reported an asymmetric vinylogous Mannich reaction (Scheme 27) [47]. Addition of silyl dienolates **73** to *N*-PMP-protected imines **74** was promoted by phosphoric acid (*R*)-**3g** (5 mol%, R = Mes) with mesityl substituents to afford *trans*- α,β -unsaturated δ -amino esters **75** in high yields (66–94%) together with good enantioselectivities (80–92% *ee*).

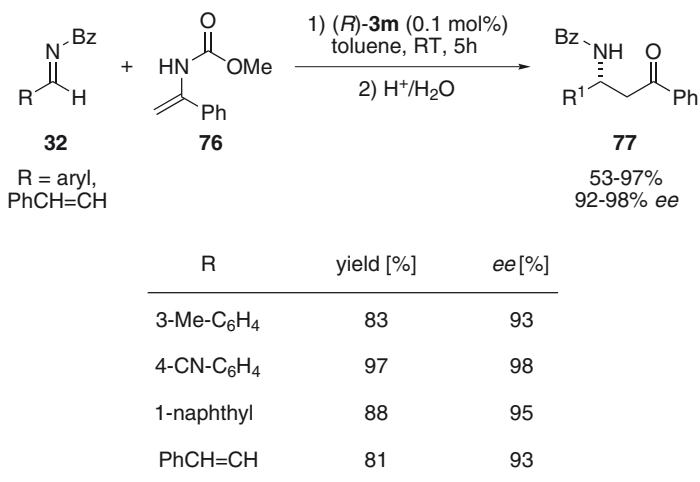


Scheme 27 Vinylous Mannich reaction of silyl dienolates

2.3.5 Aza-Ene-Type Reaction

In 2004, Kobayashi et al. introduced enecarbamates as nucleophiles to asymmetric catalysis [48]. The addition of enecarbamates to imines in the presence of a chiral copper complex provides access to β -amino imines which can be hydrolyzed to the corresponding β -amino carbonyl compounds [49].

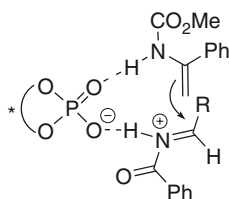
Two years later, Terada and coworkers described an asymmetric organocatalytic aza-ene-type reaction (Scheme 28) [50]. BINOL phosphate (*R*)-**3m** (0.1 mol%, R = 9-anthryl) bearing 9-anthryl substituents mediated the reaction of *N*-benzoylated aldimines **32** with enecarbamate **76** derived from acetophenone. Subsequent hydrolysis led to the formation of β -amino ketones **77** in good yields (53–97%) and excellent enantioselectivities (92–98% *ee*). A substrate/catalyst ratio of 1,000:1 has rarely been achieved in asymmetric Brønsted acid catalysis before.



Scheme 28 Aza-ene-type reaction

Noteworthy, the reaction can be conducted on a 1 g scale in the presence of only 0.1 mol% of catalyst **3m** without a considerable loss in reactivity and selectivity (one example: 89% yield, 95% *ee*). The authors' mechanistic proposal relies on the dual function of the phosphoric acid moiety and invokes a simultaneous activation of both reaction partners through a hydrogen bonding network (Fig. 7).

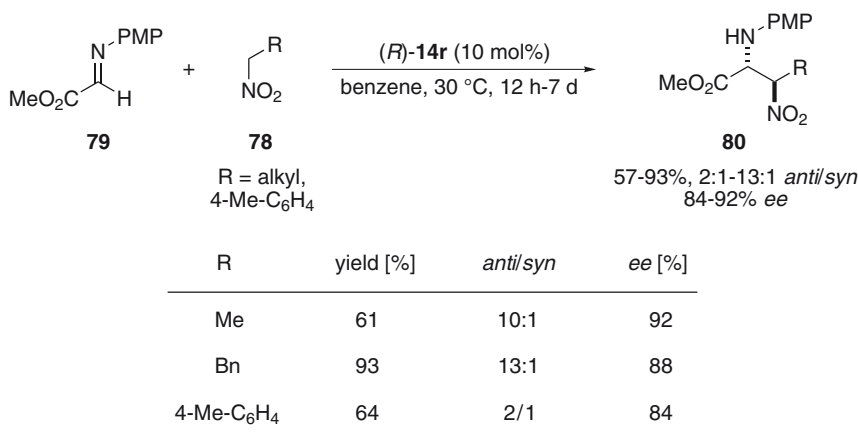
Fig. 7 Working hypothesis



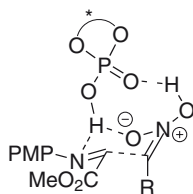
2.3.6 Aza-Henry Reaction

The aza-Henry reaction is an important tool for the preparation of compounds bearing vicinal nitrogen-containing functional groups. Catalytic asymmetric methods using either metal complexes or organic molecules were disclosed over the last years. While metal-free variants employing imines as substrates are well-established, the corresponding aza-Henry reaction of α -imino esters is less advanced. The latter furnishes valuable intermediates for the synthesis of biologically active α,β -diamino acids.

In 2008, the Rueping group reported the addition of nitroalkanes **78** to *N*-PMP-protected α -imino esters **79** in the presence of chiral phosphoric acid (*R*)-**14r** (10 mol%, R = SiPh₃) (Scheme 29) [51]. This transformation provided β -nitro- α -amino esters **80** in good yields (57–93%), *anti*-diastereoselectivities (2:1–13:1) and enantioselectivities (84–92% *ee*).



Scheme 29 Aza-Henry reaction

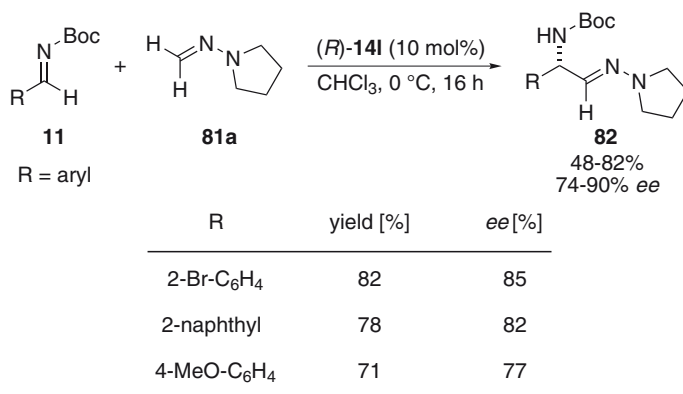
Fig. 8 Possible transition state

Mechanistically, the aza-Henry reaction presumably proceeds via a six-membered transition state. Brønsted acid **14r** is expected to activate both the electrophile and the nucleophile (Fig. 8).

2.3.7 Addition of a Hydrazone

N,N-Dialkyl hydrazones derived from formaldehyde serve as powerful formyl anion equivalents. Their asymmetric addition to imines gives rise to optically active α -amino hydrazones which are amenable to further synthetic manipulations.

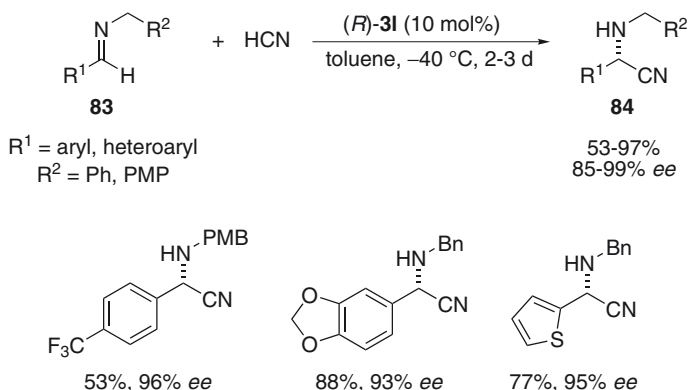
In 2007, Rueping et al. found chiral H_8 -BINOL phosphate (*R*)-**14l** (10 mol%, *R* = 9-phenanthryl) with 9-phenanthryl groups to mediate the reaction of aldimines **11** with *N*-methylenepyrrolidin-1-amine (**81a**) (Scheme 30) [52]. *N*-Boc-protected α -amino hydrazones **82** were obtained in satisfactory yields (48–82%) and enantioselectivities (74–90% *ee*).

**Scheme 30** Addition of a hydrazone to imines

2.3.8 Strecker Reactions

One of the most important approaches to α -amino acids is based on the Strecker reaction. Although there are already a number of catalytic asymmetric variants, the cyanation of imines still challenges modern organic chemists.

In 2006, the Rueping group showed that chiral phosphoric acid (*R*)-**31** (10 mol%, R = 9-phenanthryl) with 9-phenanthryl substituents promoted the addition of HCN to *N*-benzylated aldimines **83** (Scheme 31) [53]. α -Amino nitriles **84** were obtained in good yields (53–97%) along with high enantioselectivities (85–99% *ee*) and could be transformed into the corresponding α -amino acids.



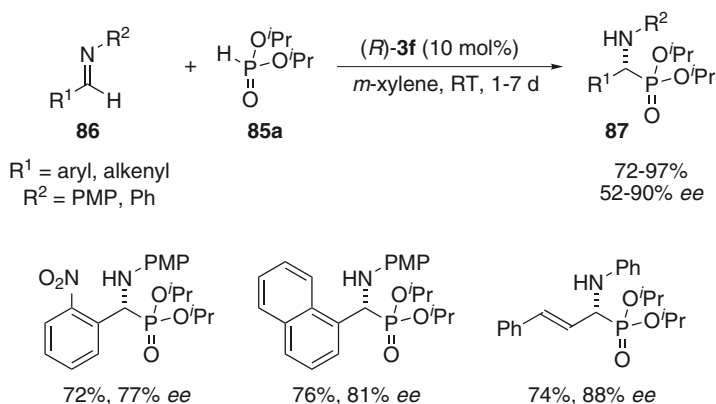
Scheme 31 Strecker reaction

Furthermore, Rueping and coworkers applied their reaction conditions to the cyanation of ketimines [54]. The use of *N*-benzylated imines derived from aryl-methyl ketones generally gave comparable yields, but lower enantioselectivities. However, this method furnished Strecker products bearing a quaternary stereogenic center, which are valuable intermediates for the preparation of optically active α,α -disubstituted α -amino acids.

2.3.9 Hydrophosphonylations

α -Amino phosphonic acids and their esters are of great value due to their function as α -amino acid mimics in medicinal chemistry. They act as inhibitors of proteases and phosphatases as well as exhibit antibacterial and antifungal activity. Consequently, their catalytic asymmetric preparation has attracted considerable attention. A powerful approach to α -amino phosphonates involves the hydrophosphonylation of preformed imines. The direct combination of an aldehyde with an amine and a phosphite is referred to as the Kabachnik–Fields reaction.

Akiyama et al. disclosed an asymmetric hydrophosphonylation in 2005 (Scheme 32) [55]. Addition of diisopropyl phosphite (**85a**) to *N*-arylated aldimines **86** in the presence of BINOL phosphate (*R*)-**3f** (10 mol%, R = 3,5-(CF₃)₂-C₆H₃) afforded α -amino phosphonates **87** in good yields (72–97%). The enantioselectivities were satisfactory (81–90% *ee*) in the case of imines derived from α,β -unsaturated aldehydes and moderate (52–77% *ee*) for aromatic substrates.



Scheme 32 Hydrophosphonylation of preformed imines

Mechanistically the reaction is proposed to proceed via a nine-membered transition state with the chiral phosphoric acid simultaneously activating the imine by protonation and the phosphite by coordinating to the hydroxyl group (Fig. 9).

Three years later, List and coworkers extended their phosphoric acid-catalyzed dynamic kinetic resolution of enolizable aldehydes (Schemes 18 and 19) to the Kabachnik–Fields reaction (Scheme 33) [56]. This transformation combines the differentiation of the enantiomers of a racemate (**50**) (control of the absolute configuration at the β -position of **88**) with an enantiotopic face differentiation (creation of the stereogenic center at the α -position of **88**). The introduction of a new sterically congested phosphoric acid led to success. BINOL phosphate (*R*)-**3p** (10 mol%, R = 2,6-*i*Pr₂-4-(9-anthryl)-C₆H₂) with anthryl-substituted diisopropylphenyl groups promoted the three-component reaction of α -branched aldehydes **50** with *p*-anisidine (**89**) and di-(3-pentyl) phosphite (**85b**). β -Branched α -amino phosphonates **88** were obtained in high yields (61–89%) and diastereoselectivities (7:1–28:1) along with good enantioselectivities (76–94% *ee*) and could be converted into

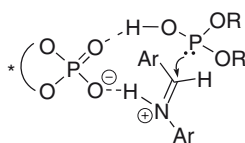
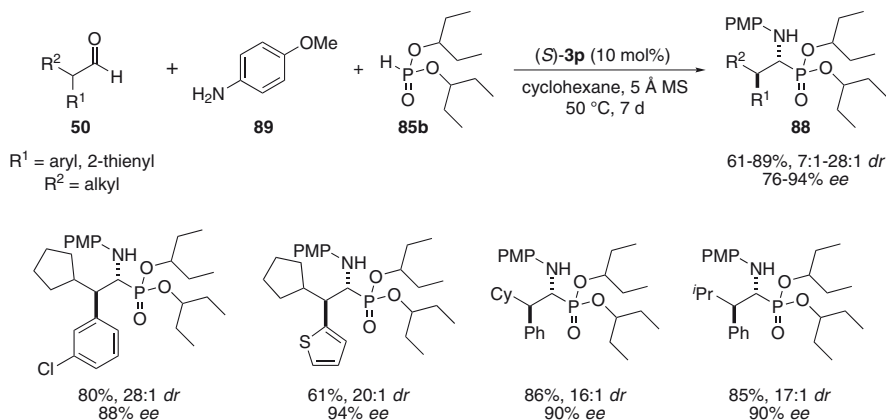


Fig. 9 Proposed activation mode

the corresponding α -amino phosphonic acids. The protocol is limited to 2-aryl acetaldehydes bearing a bulky alkyl substituent such as cyclohexyl, cyclopentyl or isopropyl at the α -position. By contrast, a methyl group at the α -position resulted in poor stereoselectivities.

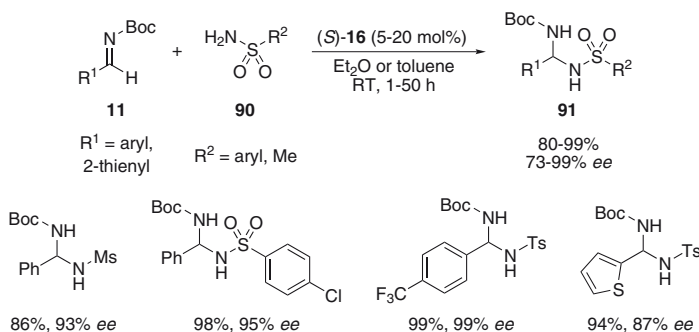


Scheme 33 Kabachnik–Fields reaction

2.3.10 Addition of Sulfonamides or Alcohols

The addition of sulfonamides or alcohols to imines gives rise to amins which represent structural elements of natural products and drugs. Recently, Antilla et al. reported the first catalytic asymmetric variants of both transformations.

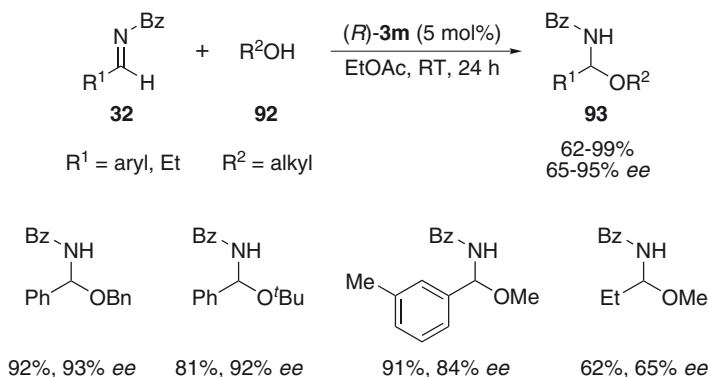
In 2005, they found chiral VAPOL phosphate (*S*)-**16** (5–20 mol%) to mediate the reaction of *N*-Boc-protected aldimines **11** with sulfonamides **90** (Scheme 34) [57]. *N,N*-amins **91** were obtained in high yields (80–99%) and enantioselectivities (73–99% *ee*).



Scheme 34 Synthesis of *N,N*-amins by addition of sulfonamides to imines

Three years later, the same group showed that oxygen-containing nucleophiles can also be used (Scheme 35) [58]. *N*-Benzoylated aldimines **32** were treated with alcohols **92** in the presence of chiral BINOL phosphate (*R*)-**3m** (5 mol%, R = 9-anthryl) to provide *N,O*-aminals **93** in high yields (62–99%) and good enantioselectivities (65–95% *ee*).

In general, enantioenriched aminals are prone to decompose or racemize in the presence of a Brønsted acid. Remarkably, *N,N*-aminals **91** as well as *N,O*-aminals **93** are stable under Antilla's reaction conditions.

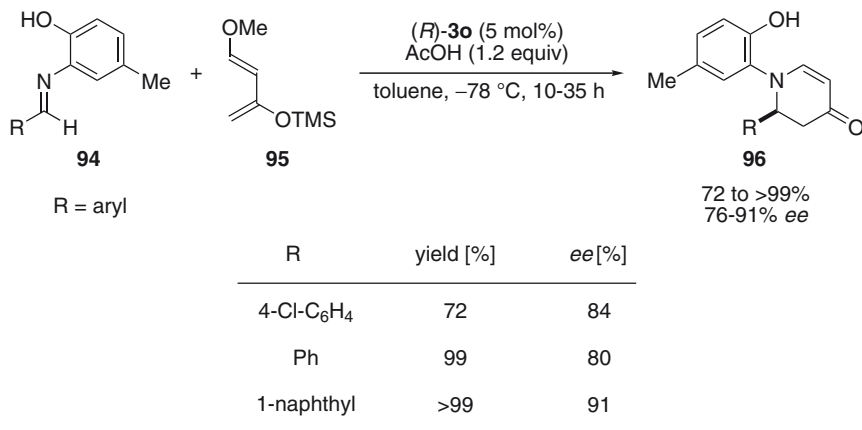


Scheme 35 Synthesis of *N,O*-aminals by addition of alcohols to imines

2.3.11 Aza-Diels–Alder Reactions

The aza-Diels–Alder reaction is an important and versatile tool for the preparation of nitrogen-containing heterocycles present in numerous natural products and drug candidates. It involves the [4 + 2] cycloaddition of either an imine with an electron-rich diene or an azabutadiene with an electron-rich alkene (inverse electron demand). Catalytic asymmetric variants employing not only metal complexes, but also organic molecules were disclosed over the last few years.

In 2006, Akiyama and coworkers established an asymmetric Brønsted acid-catalyzed aza-Diels–Alder reaction (Scheme 36) [59]. Chiral BINOL phosphate (*R*)-**3o** (5 mol%, R = 2,4,6-*i*Pr₃-C₆H₂) bearing 2,4,6-triisopropylphenyl groups mediated the cycloaddition of aldimines **94** derived from 2-amino-4-methylphenol with Danishefsky's diene **95** in the presence of 1.2 equivalents of acetic acid. Piperidinones **96** were obtained in good yields (72 to >99%) and enantioselectivities (76–91% *ee*). While the addition of acetic acid ($\text{p}K_{\text{a}} = 4.8$) improved both the reactivity and the selectivity, the use of benzenesulfonic acid ($\text{p}K_{\text{a}} = -6.5$) as an additive increased the yield, but decreased the enantioselectivity. A strong achiral Brønsted acid apparently competes with chiral phosphoric acid **3o** for the activation of imine **94** and catalyzes a nonasymmetric hetero-Diels–Alder reaction. The role of acetic acid remains unclear.



Scheme 36 Aza-Diels–Alder reaction of Danishefsky's diene

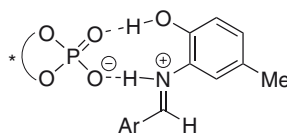
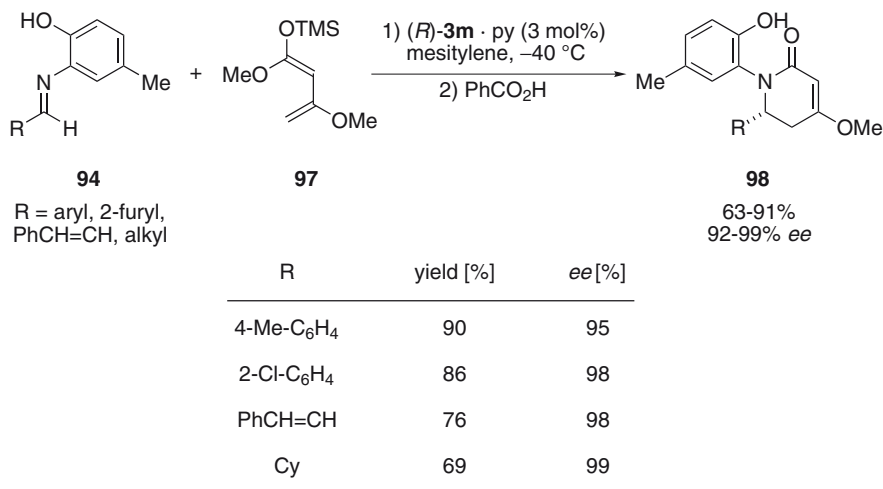


Fig. 10 Proposed catalyst-imine interaction

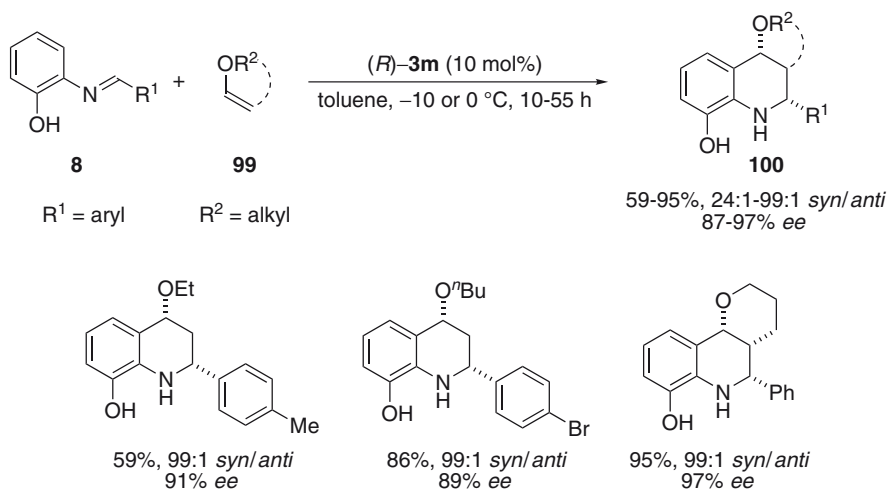
The authors suggested the catalyst-imine interaction depicted in Fig. 10 for the present Diels–Alder reaction. Imine **94** features a free hydroxyl group appropriate for binding to the phosphoryl oxygen of the phosphoric acid moiety by hydrogen bonding.

The same group expanded the scope of the aza-Diels–Alder reaction of electron-rich dienes to Brassard's diene **97** (Scheme 37) [60]. In contrast to Danishefsky's diene, it is more reactive, but less stable. Akiyama et al. found chiral BINOL phosphate (*R*)-**3m** (3 mol%, R = 9-anthryl) with 9-anthryl substituents to promote the [4 + 2] cycloaddition of *N*-arylated aldimines **94** and Brassard's diene **97**. Subsequent treatment with benzoic acid led to the formation of piperidinones **98**. Interestingly, the use of its pyridinium salt (3 mol%) resulted in a higher yield (87% instead of 72%) along with a comparable enantioselectivity (94% ee instead of 92% ee). This method furnished cycloadducts **98** derived from aromatic, heteroaromatic, α,β -unsaturated, and aliphatic precursors **94** in satisfactory yields (63–91%) and excellent enantioselectivities (92–99% ee). NMR studies revealed that Brassard's diene **97** is labile in the presence of phosphoric acid **3m** (88% decomposition after 1 h), but comparatively stable in the presence of its pyridinium salt (25% decomposition after 1 h). This observation can be explained by the fact that the pyridinium salt is a weak Brønsted acid compared to BINOL phosphate **3m**.



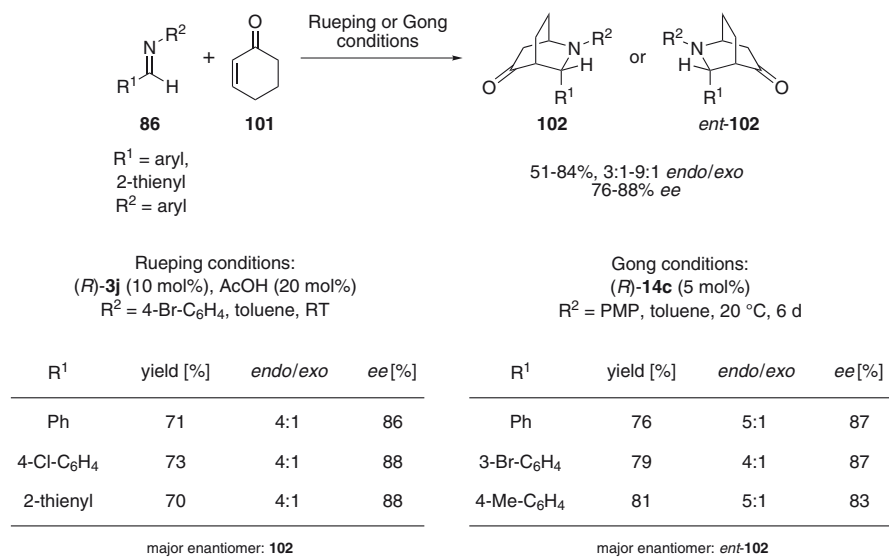
Scheme 37 Aza-Diels–Alder reaction of Brassard's diene

Furthermore, Akiyama and coworkers applied phosphoric acid (*R*)-**3m** (10 mol%, R = 9-anthryl) to the asymmetric inverse-electron-demand hetero-Diels–Alder reaction of *N*-2-hydroxyphenyl-protected aldimines **8** with vinyl ethers **99** (Scheme 38) [61]. Tetrahydroquinolines **100** were obtained in good yields (59–95%), excellent *syn*-diastereoselectivities (24:1–99:1), and high enantioselectivities (87–97% *ee*).



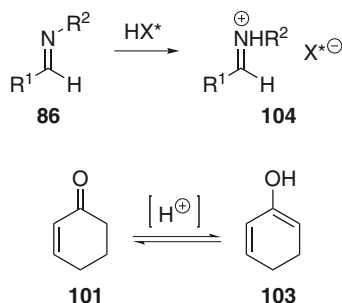
Scheme 38 Inverse-electron-demand aza-Diels–Alder reaction

In 2006, two groups independently developed an asymmetric Brønsted acid-catalyzed aza-Diels–Alder-type reaction of *N*-aryl aldimines **86** with cyclohexenone **101** to provide isoquinuclidines **102** in good yields (51–84%), *endo*-diastereoselectivities (3:1–9:1), and enantioselectivities (76–88% *ee*) (Scheme 39).



Scheme 39 Aza-Diels–Alder-type reaction of cyclohexenone

On the one hand, Rueping's protocol involved a combination of chiral BINOL phosphate (R) -**3j** (10 mol%, $R = 2\text{-naphthyl}$) bearing 2-naphthyl substituents and achiral acetic acid (20 mol%) [62]. While stronger Brønsted acid **3j** is expected to activate electrophile **86**, the weaker Brønsted acid is proposed to facilitate the keto–enol tautomerism of nucleophile **101** (Scheme 40)¹. On the other hand, Gong

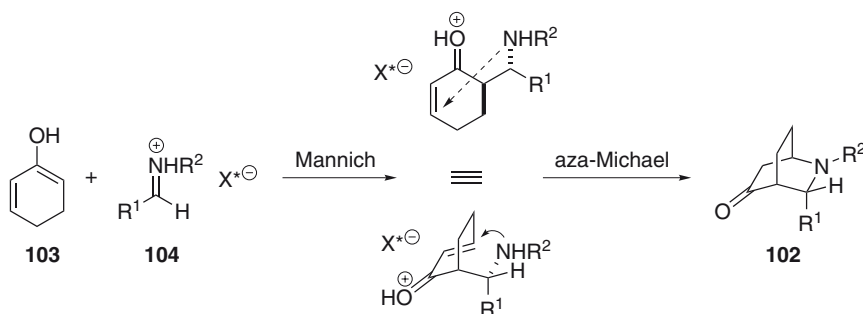


Scheme 40 Activation of both the electrophile and the nucleophile by Brønsted acids

¹ pK_a (dimethyl phosphate) = 1.29, pK_a (acetic acid) = 4.76

found H₈-BINOL phosphate (*R*)-**14c** (5 mol%, R = 4-Cl-C₆H₄) with a 4-chlorophenyl group to be sufficient to obtain comparable results [63]. Both methods are limited to aromatic or heteroaromatic imines.

Mechanistically, the present transformation probably comprises two steps. Mannich reaction of in situ-generated cyclohexadienol **103** with iminium ion **104** is followed by an intramolecular aza-Michael reaction to furnish isoquinuclidine **102** (Scheme 41). Three stereogenic centers are created in this process.



Scheme 41 Mechanism of the aza-Diels–Alder-type reaction of cyclohexenone

2.3.12 1,3-Dipolar Cycloaddition

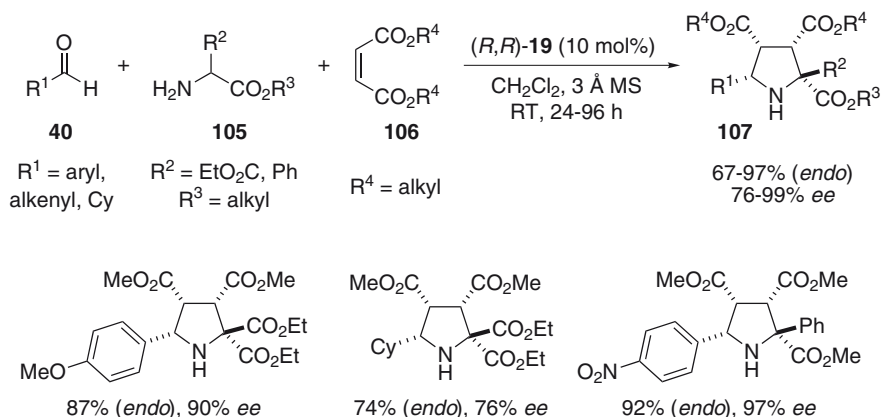
The 1,3-dipolar cycloaddition of azomethine ylides with olefins gives rise to pyrrolidines which represent structural elements of organocatalysts, natural products, and drug candidates. Asymmetric metal-catalyzed variants attracted considerable attention over the last few years [64]. Recently, Vicario et al. reported an organocatalytic [3 + 2] cycloaddition of azomethine ylides and α,β -unsaturated aldehydes mediated by a chiral secondary amine [65].

In 2008, Gong and coworkers introduced a new chiral bisphosphoric acid **19** (Fig. 4) that consists of two BINOL phosphates linked by an oxygen atom for a three-component 1,3-dipolar cycloaddition (Scheme 42) [66]. Aldehydes **40** reacted with α -amino esters **105** and maleates **106** in the presence of Brønsted acid **19** (10 mol%) to afford pyrrolidines **107** as *endo*-diastereomers in high yields (67–97%) and enantioselectivities (76–99% *ee*). This protocol tolerated aromatic, α,β -unsaturated, and aliphatic aldehydes. Aminomalonates as well as phenylglycine esters could be employed as dipolarophiles.

Mechanistically, the [3 + 2] cycloaddition presumably proceeds via a dipole coordinated by catalyst **19** (Fig. 11).

2.3.13 Multicomponent and Cascade Reactions

A multicomponent reaction (MCR) represents a sequence of bimolecular events leading to products that incorporate essentially all atoms of three or more starting materials. MCRs allow for the rapid and facile access to complex target structures



Scheme 42 1,3-Dipolar cycloaddition

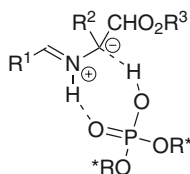


Fig. 11 Possible activation mode

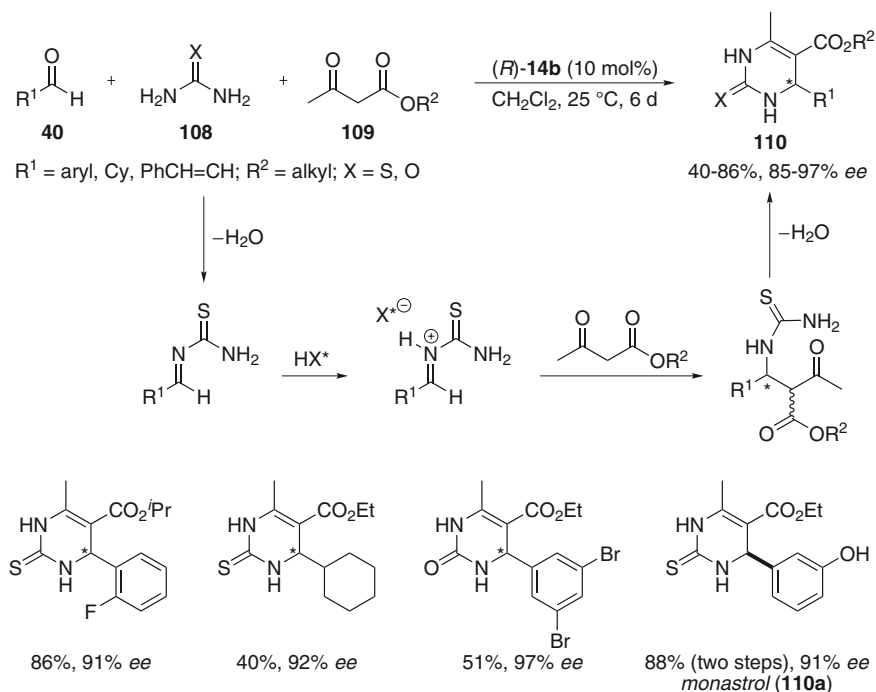
in one step. The combination of enantioselective organocatalysis and MCRs has created a powerful synthetic tool as exemplified by several intriguing applications [67].

Recently, several research groups reported on the use of chiral BINOL phosphates as Brønsted acid catalysts in MCRs involving imine activation.

Biginelli Reaction

In 2006, Gong and coworkers described the first highly enantioselective organocatalytic Biginelli reaction (Scheme 43). Starting from an aldehyde **40**, thiourea or urea **108**, and acetoacetates **109**, the Biginelli reaction furnished multifunctionalized 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) **110** or the respective thio-analogs. H_8 -BINOL-based chiral phosphoric acid (*R*)-**14b** (10 mol%, $R = \text{Ph}$) exhibited the highest catalytic efficiency and afforded the heterocyclic products **110** in moderate to good yields (40–86%) with high enantioselectivities (85–97% *ee*) [68].

Simple phenyl substituents at the 3,3'-positions were sufficient to achieve high levels of enantiocontrol, which is in contrast to the substitution effect of many other BINOL phosphate-catalyzed reactions. Indeed, increasing the size of the 3,3'-substituents resulted in both decreased yields and enantioselectivities. The synthetic utility of the catalytic asymmetric Biginelli reaction was demonstrated by the preparation of the active pharmaceutical ingredient monastrol (**110a**) in two steps



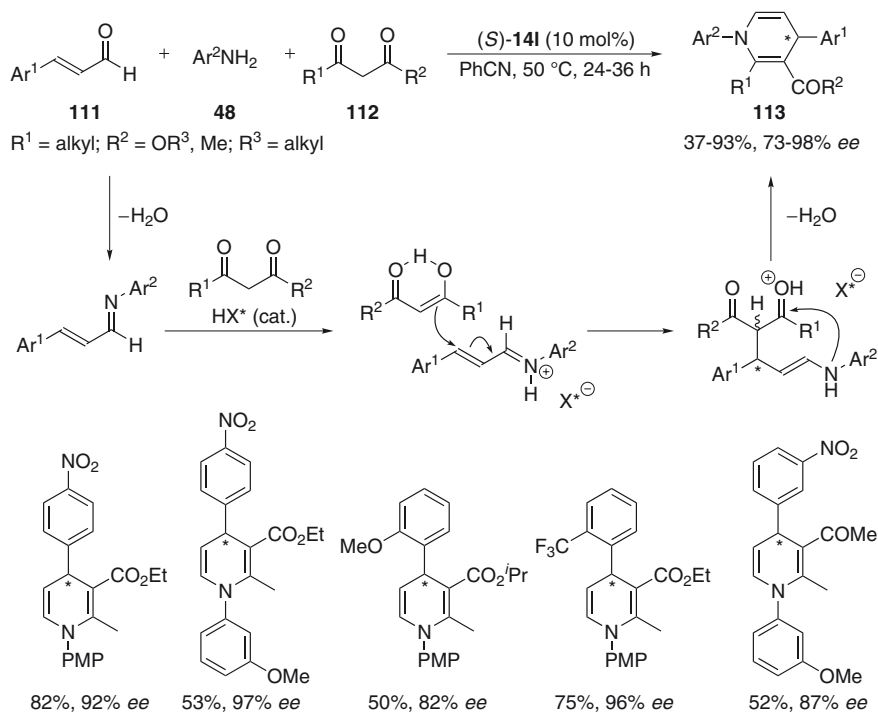
Scheme 43 Biginelli reaction: scope and proposed reaction pathway

and high optical purity (91% *ee*) from TBS-protected 3-hydroxy benzaldehyde, thiourea, and ethyl acetoacetate. Importantly, the individual enantiomers of monastrol show distinct pharmaceutical properties.

Dihydropyridine Syntheses

In 2008, the same group developed an asymmetric three-component cyclization reaction of cinnamaldehydes **111** and aromatic primary amines **48** with 1,3-dicarbonyl compounds **112** in the presence of a catalytic amount of H_8 -BINOL-based chiral phosphate (*S*)-**14l** (10 mol%, $\text{R} = 9$ -phenanthryl) (Scheme 44). Enantiomerically enriched 4-aryl-substituted 1,4-dihydropyridines (DHPs) **113** were rapidly assembled in moderate to high yields by means of this method (37–93%, 73–98% *ee*) [69]. DHPs exhibit a broad range of pharmaceutical activities. Most prominent among them is their role as an important class of organic calcium-channel modulators for the treatment of cardiovascular diseases.

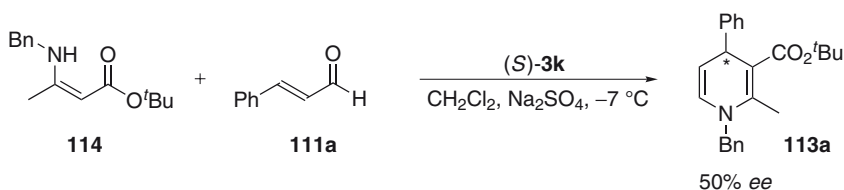
The scope was illustrated with 35 examples using various β -ketoesters as well as acetylacetone as 1,3-dicarbonyl compound. The use of aliphatic α,β -unsaturated aldehydes resulted in low yield and inferior enantioselectivity. Transformation of the DHP products into other optically active heterocyclic



Scheme 44 Three-component cyclization to 4-substituted DHPs: scope and proposed reaction pathway

compounds, like tetrahydropyridines and piperidines, demonstrated their utility as synthetic intermediates.

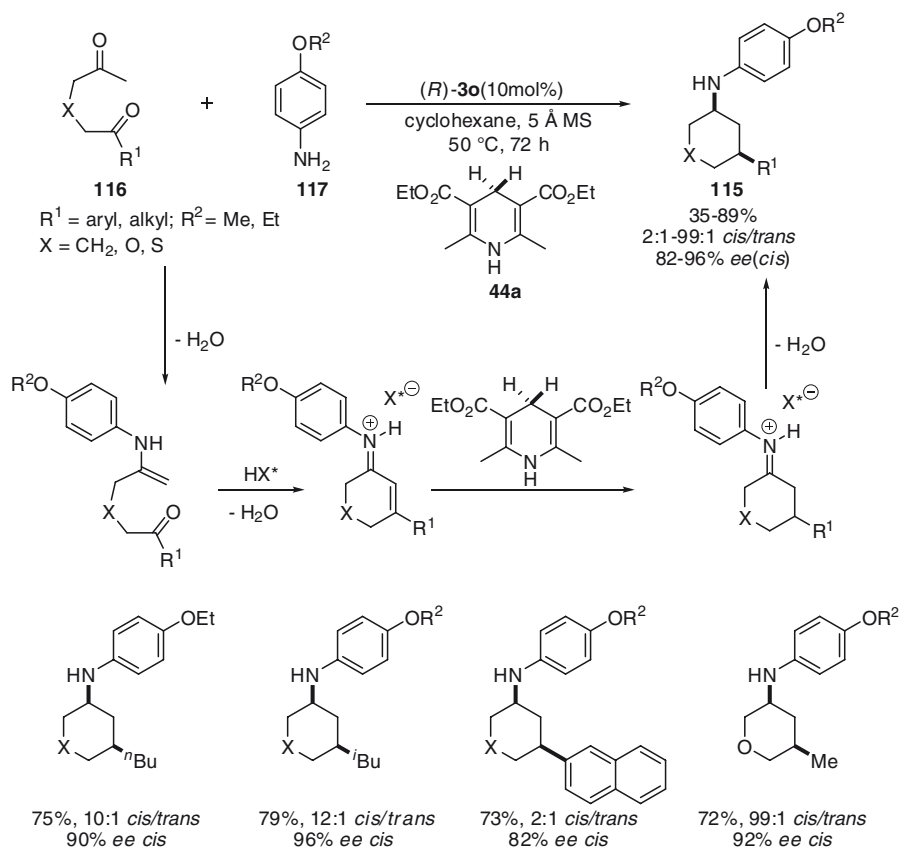
Prior to this work, Renaud and coworkers described an alternative phosphoric acid-catalyzed approach to DHPs **113** commencing with β -enaminoesters such as **114** and cinnamaldehydes **111**. Besides developing a catalytic nonasymmetric protocol, the authors attempted a BINOL phosphate (*S*)-**3k**-catalyzed (R = 1-naphthyl) asymmetric version attaining moderate enantioselectivity (50% *ee*) (Scheme 45) [70].



Scheme 45 DHP synthesis from a β -enaminoester and cinnamaldehyde

Reaction Cascades

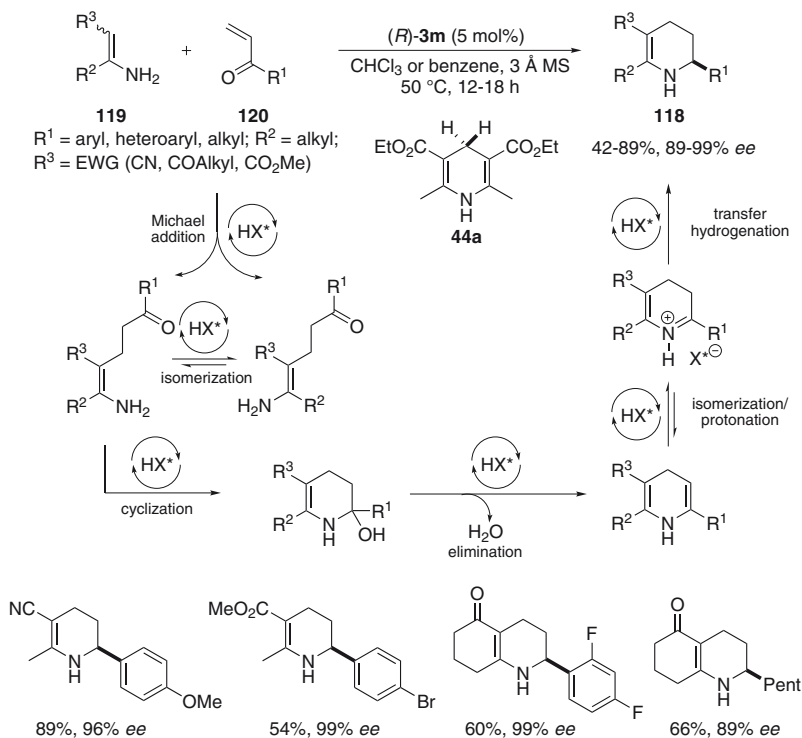
In 2007, Zhou and List described a reaction cascade to substituted cyclohexylamines **115** starting from various 2,6-diketones **116** and *p*-alkoxyanilines **117** in the presence of Hantzsch ester **44a** and chiral phosphoric acid (*R*)-**3o** (10 mol%, $R = 2,4,6\text{-}i\text{-Pr}_3\text{-C}_6\text{H}_2$). The *cis*-3-substituted (hetero)cyclohexylamines **115** were obtained in good to high yields (35–89%) along with high enantioselectivities in case of aliphatic substituents (90–96% *ee*) and with somewhat lower enantioselectivity in case of aromatic R^1 groups (82% *ee* for $R^1 = 2\text{-naphthyl}$). The cascade reactions proceeds via sequential aldolization-dehydration-conjugate reduction-reductive amination steps and merges asymmetric Brønsted acid catalysis with enamine and iminium catalysis. It is catalyzed by the chiral phosphoric acid and accelerated by the achiral amine substrate **117**, which is ultimately incorporated into the product.



Scheme 46 Multiple-reaction cascade to 3-substituted cyclohexylamines: scope and proposed reaction pathway

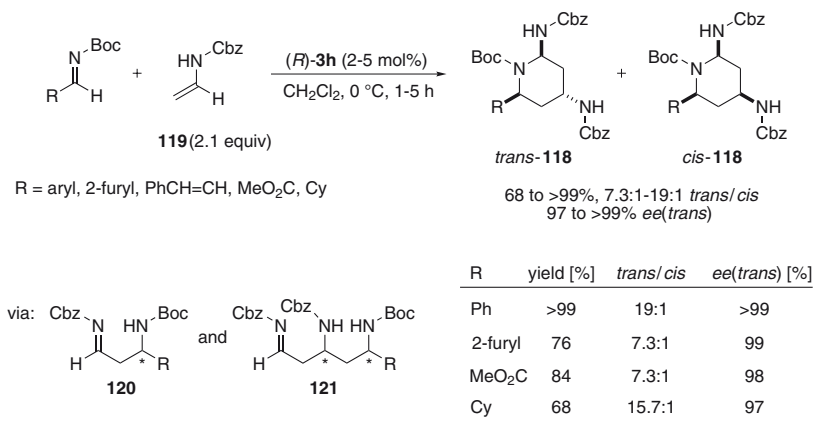
A direct entry to valuable enantiomerically enriched tetrahydropyridines and azadecalinones **118** was provided by the Rueping group in 2008 [71]. A mixture of enamines

119 and vinyl ketones **120** in the presence of BINOL phosphate (*R*)-**3m** (5 mol%, R = 9-anthryl) and Hantzsch dihydropyridine **44a** furnished the desired products in good yields (42–89%) along with excellent enantioselectivities (89–99% *ee*) by means of a multiple-reaction cascade comprising a Michael addition, isomerization, cyclization, elimination, isomerization, and asymmetric transfer hydrogenation (Scheme 47). Each step of the six-step sequence is catalyzed by phosphoric acid **3m**.



Scheme 47 Multiple-reaction cascade to tetrahydropyridines and azadecalones: scope and proposed reaction pathway

In 2007, Terada et al. extended their previously described chiral phosphoric acid-catalyzed aza-ene-type reaction of *N*-acyl aldimines with disubstituted enecarbamates (Scheme 28) to a tandem aza-ene-type reaction/cyclization cascade as a one-pot entry to enantioenriched piperidines **121** (Scheme 48). The sequential process was rendered possible by using monosubstituted **122** instead of a disubstituted enecarbamate **76** to produce a reactive aldimine intermediate **123**, which is prone to undergo a further aza-ene-type reaction with a second enecarbamate equivalent. Subsequent intramolecular cyclization of intermediate **124** terminates the sequence. The optimal chiral BINOL phosphate (*R*)-**3h** (2–5 mol%, R = 4-Ph-C₆H₄) provided the 2,4,6-substituted *N*-Boc-protected piperidines **121** in good to excellent yields (68 to > 99%) and accomplished the formation of three stereogenic centers with high diastereo- and excellent enantiocontrol (7.3:1 to 19:1 *trans/cis*, 97 to > 99% *ee(trans)*) [72].

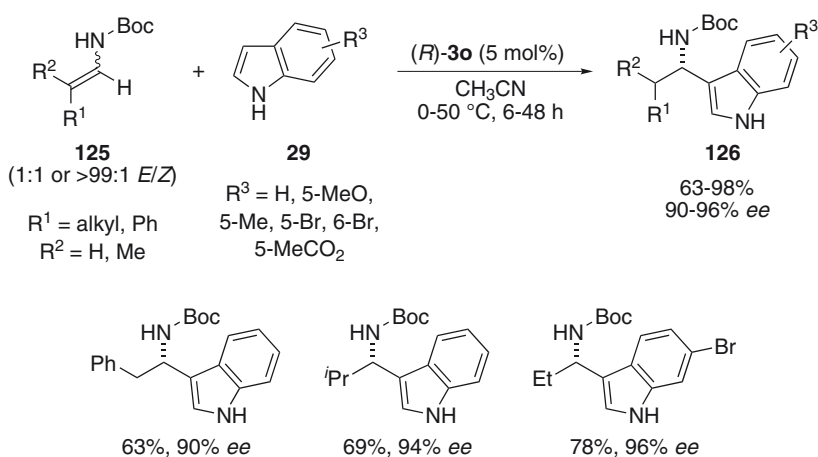


Scheme 48 Tandem aza-ene-type reaction/cyclization cascade: scope and reaction intermediates

2.4 Other Substrates

2.4.1 Imine Surrogates

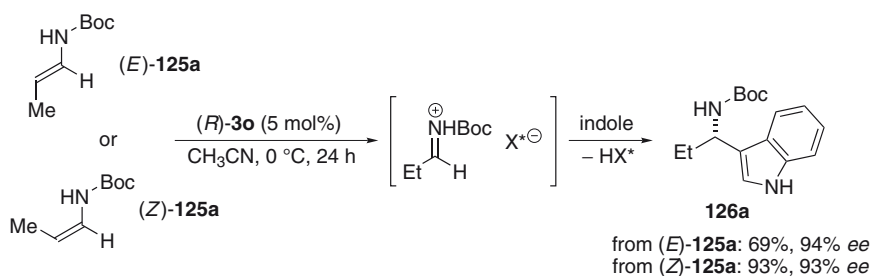
In 2007, two groups independently described asymmetric phosphoric acid-catalyzed Friedel–Crafts alkylations of indoles. While You et al. chose the conventional approach and employed imines as substrates (Scheme 11), Terada and coworkers came up with a different concept and used electron-rich alkenes as precursors (Scheme 49) [73]. Encarbamates **125** reacted with indoles **29** in the presence of BINOL phosphate (*R*)-**3o** (5 mol%, R = 2,4,6-*i*-Pr₃-C₆H₂) bearing 2,4,6-triisopropylphenyl substituents to provide *N*-Boc-protected 3-indolyl amines **126** in high yields (63–98%) and enantioselectivities (90–96% *ee*).



Scheme 49 Friedel–Crafts reaction of encarbamates and indoles

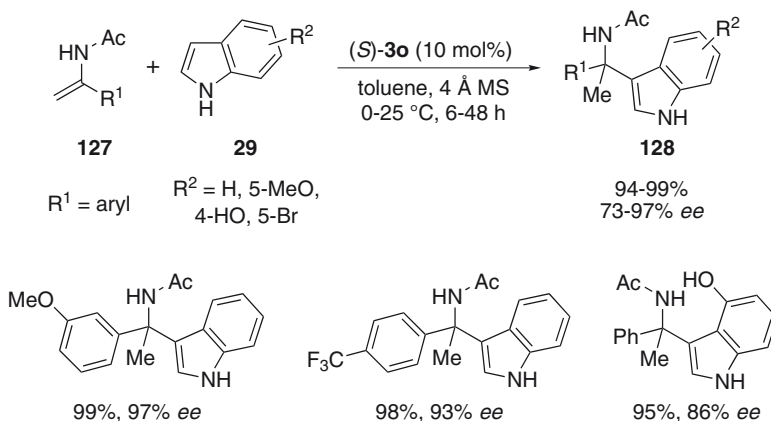
The geometry of the double bond of electron-rich alkene **125a** plays an important role. Starting from (*E*)- and (*Z*)-enecarbamate **125a** respectively, product **126a** was obtained in comparable enantioselectivities (94% *ee* instead of 93% *ee*), but different yields (69% instead of 93%) (Scheme 49).

These results suggest that both reactions proceed through the same intermediate composed of an aldimine and BINOL phosphate **3o** (Scheme 50). Protonation of either (*E*)- or (*Z*)-enecarbamate **125a** to furnish an iminium ion via ionic transition states is considered as the rate-determining step. This mechanism is supported by the observation that polar, but protophobic acetonitrile is a powerful solvent in terms of reactivity. A significant advantage of Brønsted acid-catalyzed transformations of enecarbamates derived from aliphatic aldehydes is the in situ generation of the corresponding imines since the latter are difficult to isolate. Terada's approach allows for the preparation of alkyl 3-indolyl amines and thus complements You's synthesis of mainly aryl ones.



Scheme 50 Friedel–Crafts alkylation of indoles with (*E*)- or (*Z*)-enecarbamates

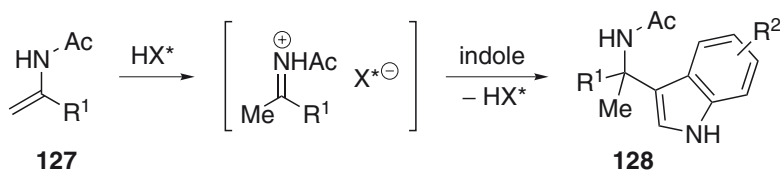
Shortly after the discovery of the first asymmetric phosphoric acid-catalyzed transformation of enecarbamates, Zhou et al. expanded the scope of the Friedel–Crafts alkylation of indoles **29** with electron-rich alkenes to enamides **127** (Scheme 51) [74].



Scheme 51 Friedel–Crafts reaction of enamides and indoles

BINOL phosphate (*S*)-**3o** (10 mol%, R = 2,4,6-*i*-Pr₃-C₆H₂) turned out to be the catalyst of choice and gave *N*-acetylated 3-indolyl amines **128** bearing a quaternary stereogenic center in excellent yields (94–99%) with high enantioselectivities (73–97% *ee*). Enamides derived from aryl-methyl ketones as well as indoles with various substituents could be employed.

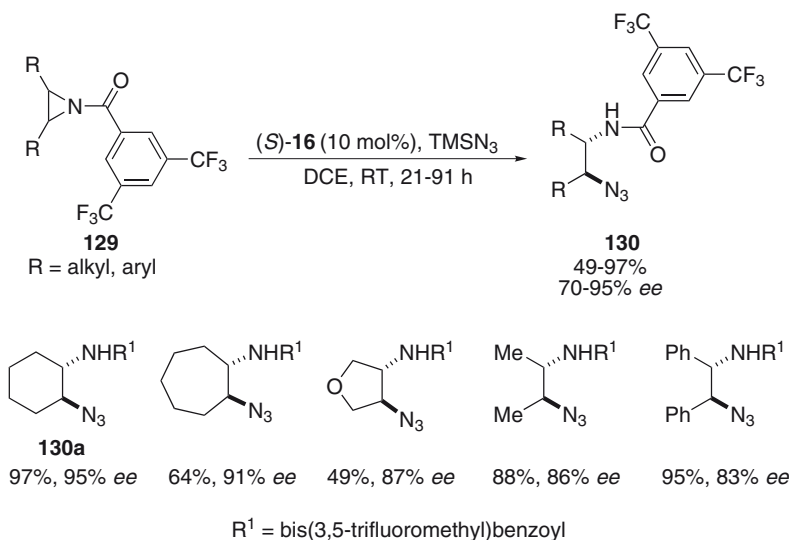
Mechanistically, the Brønsted acid-catalyzed Friedel–Crafts reaction presumably involves a tautomerism of enamide **127** to the corresponding *N*-acetyl-protected imine. Subsequent addition of indole **29** affords amide **128** (Scheme 52).



Scheme 52 Mechanism of the Friedel–Crafts reaction of enamides and indoles

2.4.2 Aziridines

In 2007, Antilla and coworkers described the Brønsted acid-catalyzed desymmetrization of *meso*-aziridines giving vicinal diamines [75]. In recent years, chiral phosphoric acids have been widely recognized as powerful catalysts for the activation of imines. However, prior to this work, electrophiles other than imines or related substrates like enecarbamates or enamides have been omitted. In the presence of VAPOL-derived phosphoric acid catalyst (*S*)-**16** (10 mol%) and azidotrimethylsilane as the nucleophile, aziridines **129** were converted into the corresponding ring-opened products **130** in good yields and enantioselectivities (49–97%, 70–95% *ee*) (Scheme 53).

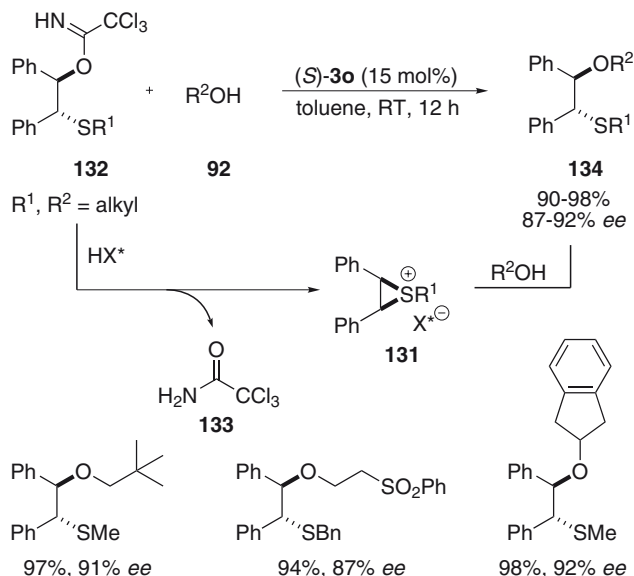


Scheme 53 Desymmetrization of *meso*-aziridines

The proper choice of the nitrogen substituent at the aziridine moiety was found to be crucial. Whereas both Boc and Cbz protecting groups resulted in the formation of the ring-opened product as the racemate in moderate yield, use of the 3,5-bis(trifluoromethyl)benzoyl group afforded product **130** in high yield and 95% *ee*. The authors' preliminary mechanistic studies suggest a silyl phosphate as the catalytically active species, which is likely generated by displacement of the azide in the first step of the reaction.

2.4.3 Trichloroacetimidates (Episulfonium Ion Precursors)

In 2008, Toste and coworkers reported the desymmetrization of *meso*-episulfonium ions **131** generated in situ from ring closure of sulfides **132** featuring a β -trichloroacetimidate leaving group [76]. Chiral BINOL-derived phosphoric acid (*S*)-**3o** (15 mol%, R = 2,4,6- $\text{Pr}_3\text{-C}_6\text{H}_2$) triggered the formation of the intermediate *meso*-episulfonium ions **131** through protonation of the trichloroacetimidate **132**, followed by liberation of trichloroacetamide (**133**) and concurrent ring closure. Ring opening of the *meso*-episulfonium cations **131** paired with the resultant chiral phosphate counteranion by various alcohols **92** occurred in excellent yields of *trans*- β -alkoxy sulfides **134** (90–98%) with high asymmetric induction (87–92% *ee*). Subsequent proton transfer completes the catalytic cycle and regenerates the phosphoric acid catalyst **3o** (Scheme 54). Although phosphate **3o** initiates this transformation by protonation, it is mechanistically distinct from reactions where an imine is activated by a Brønsted acid.



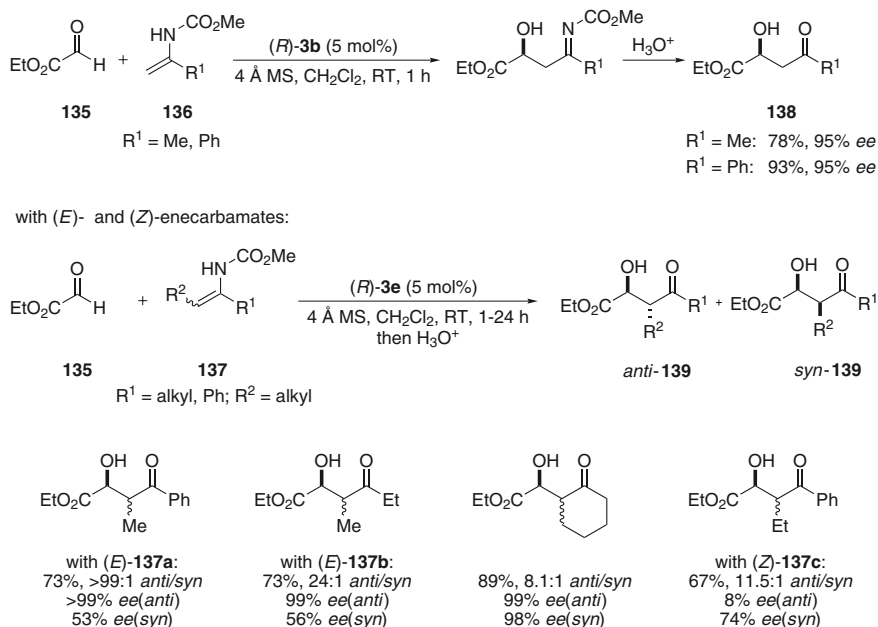
Scheme 54 Desymmetrization of *meso*-episulfonium ions

2.4.4 Carbonyl Compounds

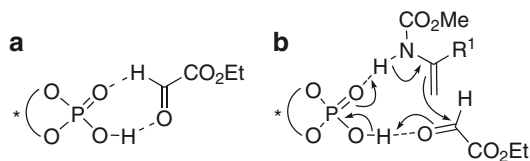
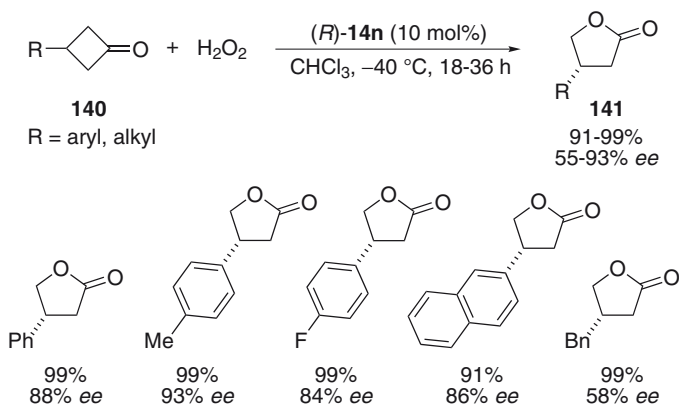
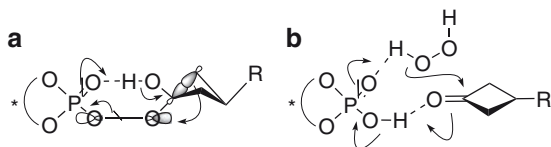
In 2008, Terada et al. developed an aza-ene-type reaction between ethyl glyoxylate **135** and various enecarbamates **136** and **137** catalyzed by BINOL phosphates (*R*)-**3b** or (*R*)-**3e** (5 mol%, R = Ph or 4'-Bu-C₆H₄) (Scheme 55) [77]. Whereas simple enecarbamates **133** and (*E*)-enecarbamates **137** furnished the products **138** and **139** in high yields with high enantio- and diastereoselectivities (73–93%, 8.1:1 to >99:1 *anti/syn*, 95 to >99% *ee(anti)*), (*Z*)-isomers **137** gave poor results (11–74%, 1:1–11.5:1 *anti/syn*, 8–28% *ee(anti)*, 69–88% *ee(syn)*).

DFT computational studies suggest the presence of a double hydrogen bond between the catalyst and ethyl glyoxylate (Fig. 12, a). On this basis the authors rationalized the experimental observation that sterically demanding aryl groups at the 3,3'-positions of the binaphthyl core decrease the catalytic efficiency with regard to activity as well as enantioselectivity. However, an alternative mechanism involving bifunctional catalysis can also be envisaged (Fig. 12, b) [78]. This report constitutes the first example of aldehyde activation by a BINOL-derived phosphoric acid and is – although restricted to glyoxylates as reactive aldehydes – important in this respect.

In the same year, chiral phosphoric acids were found to catalyze the enantioselective Baeyer–Villiger (BV) oxidation of 3-substituted cyclobutanones **140** with aqueous



Scheme 55 Aza-ene-type reaction between ethyl glyoxylate and various enecarbamates

**Fig. 12** Proposed activation modes**Scheme 56** Baeyer–Villiger oxidation of 3-substituted cyclobutanones**Fig. 13** Proposed working models

hydrogen peroxide (30%) as the oxidant by Ding and coworkers (Scheme 56) [79]. H_8 -BINOL-derived phosphoric acid (*R*)-**14n** (10 mol%, R = 1-pyrenyl) bearing bulky 1-pyrenyl groups at the 3,3'-positions proved to be effective giving high yields of γ -lactone products **141** (91–99%) with good enantioselectivities (82–93% ee) in case of 3-aryl-substituted cyclobutanones. γ -Lactones resulting from the BV oxidation of 3-alkyl-substituted substrates were still obtained in high yields (99%) albeit with moderate enantioselectivities (55–58% ee).

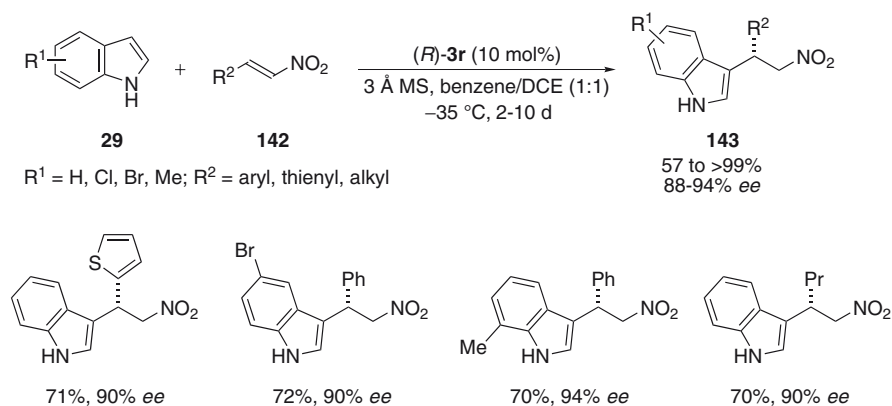
The authors propose a working model relying on the commonly accepted mechanism for BV reactions (Fig. 13, **a**). Thus the sense of asymmetric induction is determined by the conformation of the Criegee intermediate, which is dictated by the chiral environment created by the catalyst. However, an alternative noncovalent, bifunctional mechanism may be considered (Fig. 13, **b**) [80]. This work

represents the first example of a Brønsted acid-catalyzed asymmetric BV reaction and features the highest enantioselectivity values attained in catalytic BV reactions of 3-substituted cyclobutanones with chemical catalysts.

2.4.5 Alkenes

Akiyama and coworkers extended the scope of electrophiles applicable to asymmetric Brønsted acid catalysis with chiral phosphoric acids to nitroalkenes (Scheme 57). The Friedel–Crafts alkylation of indoles **29** with aromatic and aliphatic nitroalkenes **142** in the presence of BINOL phosphate (*R*)-**3r** (10 mol%, R = SiPh₃) and 3-Å molecular sieves provided Friedel–Crafts adducts **143** in high yields and enantioselectivities (57 to >99%, 88–94% *ee*) [81]. The use of molecular sieves turned out to be critical and significantly improved both the yields and enantioselectivities.

N-Methyl indole gave inferior results under the optimized conditions (11%, 0% *ee*). Therefore, the authors assume the reaction to proceed via a nine-membered transition state with the phosphoric acid activating the nitroalkene and at the same time binding the indole through a hydrogen bond to the indole N–H moiety (Fig. 14).



Scheme 57 Friedel–Crafts alkylation of indoles with nitroalkenes

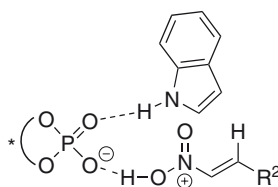
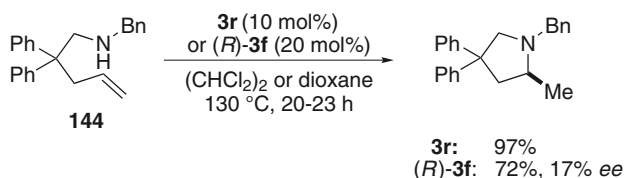


Fig. 14 Proposed activation mode

In 2008, the Ackermann group reported on the use of phosphoric acid **3r** (10 mol%, $R = \text{SiPh}_3$) as a Brønsted acid catalyst in the unprecedented intramolecular hydroaminations of unfunctionalized alkenes alike **144** (Scheme 58) [82]. BINOL-derived phosphoric acids with bulky substituents at the 3,3'-positions showed improved catalytic activity compared to less sterically hindered representatives. Remarkably, this is the first example of the activation of simple alkenes by a Brønsted acid. However, the reaction is limited to geminally disubstituted precursors **144**. Their cyclization might be favored due to a Thorpe–Ingold effect. An asymmetric version was attempted by means of chiral BINOL phosphate (*R*)-**3f** (20 mol%, $R = 3,5\text{-(CF}_3)_2\text{-C}_6\text{H}_3$), albeit with low enantioselectivity (17% *ee*).



Scheme 58 Intramolecular hydroamination of an unfunctionalized alkene

3 Chiral *N*-Triflyl Phosphoramides

Until 2006, a severe limitation in the field of chiral Brønsted acid catalysis was the restriction to reactive substrates. The acidity of BINOL-derived chiral phosphoric acids is appropriate to activate various imine compounds through protonation and a broad range of efficient and highly enantioselective, phosphoric acid-catalyzed transformations involving imines have been developed. However, the activation of simple carbonyl compounds by means of Brønsted acid catalysis proved to be rather challenging since the acidity of the known BINOL-derived phosphoric acids is mostly insufficient. Carbonyl compounds and other less reactive substrates often require a stronger Brønsted acid catalyst.

Replacement of an $X = \text{O}$ moiety by a strong electron acceptor, such as $X = \text{NTf}$, is known to enhance significantly the acidity of a Brønsted acid (Fig. 15) [83].

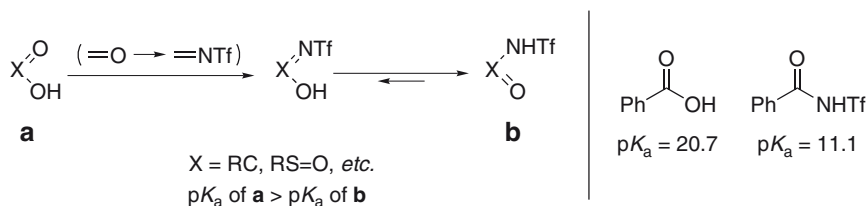
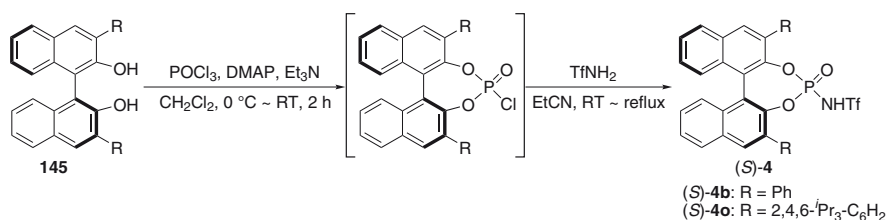


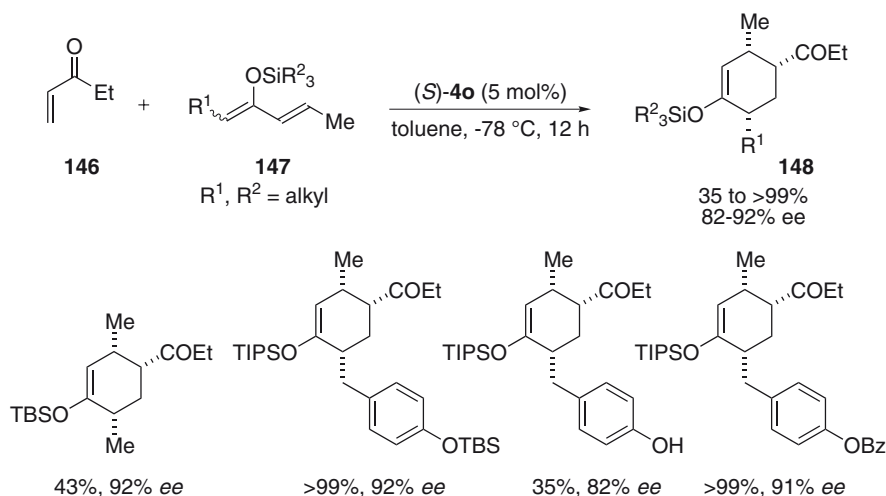
Fig. 15 Enhancement of the acidity of a Brønsted acid by a strong electron acceptor

In 2006, Yamamoto and Nakashima picked up on this and designed a chiral *N*-triflyl phosphoramidate as a stronger Brønsted acid catalyst than the phosphoric acids based on this concept. In their seminal report, they disclosed the preparation of new chiral BINOL-derived *N*-triflyl phosphoramidates and their application to the asymmetric Diels–Alder (DA) reaction of α,β -unsaturated ketones with silyloxydienes [83]. As depicted in Scheme 59, chiral *N*-triflyl phosphoramidates of the general type **4** are readily synthesized from the corresponding optically active 3,3'-substituted BINOL derivatives **145** through a phosphorylation/amidation route.



Scheme 59 Preparation of chiral BINOL-derived *N*-triflyl phosphoramidates

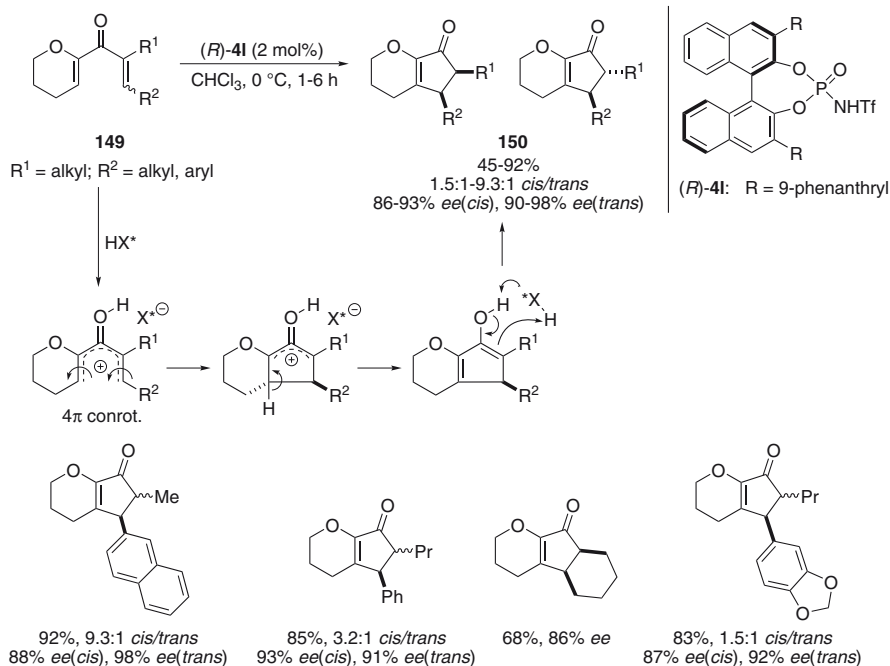
Whereas the established phosphoric acids showed no catalytic activity, *N*-triflyl phosphoramidate (*S*)-**4o** (5 mol%, R = 2,4,6-*i*-Pr₃-C₆H₂) proved to be a highly effective catalyst for the DA reaction of ethyl vinyl ketone (**146**) with various silyloxydienes **147** giving ready access to highly enantioenriched *endo*-DA products **148** in good yields (35 to >99%, 82–92% *ee*) (Scheme 60).



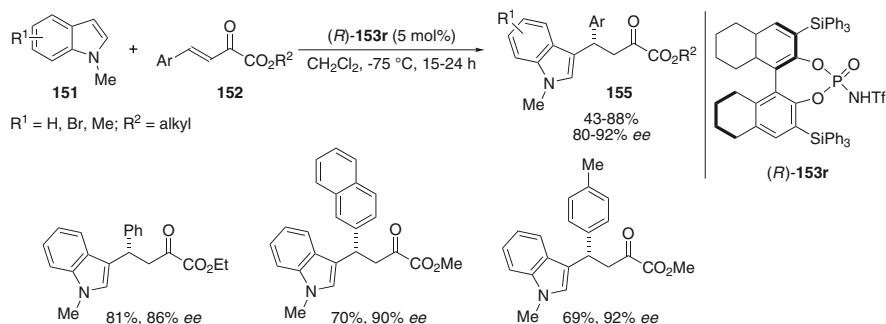
Scheme 60 Diels–Alder reaction of ethyl vinyl ketone with silyloxydienes

The authors observed a significant difference in reactivity between *N*-triflyl phosphoramides **4a** and **4b**. Catalyst **4b** (*R* = Ph) furnished only a trace amount of the desired DA product probably due to its rapid deactivation through silylation by the silyloxydiene. In a control experiment, preformed silylated **4b** turned out to be no longer catalytically active. This observation confirms the crucial role of the bulky 2,4,6-triisopropylphenyl substituents at the 3,3'-positions of the binaphthyl scaffold of **4a** to suppress silylation under the reaction conditions. The Brønsted acid-catalyzed DA reaction showed high functional group compatibility, tolerating even free hydroxyl groups in contrast to metal Lewis acid-catalyzed versions.

In 2007, Rueping and coworkers developed a Brønsted acid-catalyzed asymmetric Nazarov cyclization, which is one of the most versatile methods for the synthesis of cyclopentenones [84]. This report constitutes the first example of an enantioselective organocatalytic electrocyclic reaction (Scheme 61). Various BINOL phosphates were found to mediate the cyclization of dienones **149** and furnished the corresponding products **150** in good enantioselectivities (up to 82% *ee*). However, improved reactivity, diastereo- and enantiocontrol was achieved by using *N*-triflyl phosphoramidate (*R*)-**4l** (2 mol%, *R* = 9-phenanthryl) as the catalyst. Thus, alkyl, aryl- as well as dialkyl-substituted cyclopentenones **150** were obtained in good yields and diastereoselectivities (45–92%, 1.5:1–9.3:1 *cis/trans*) along with high enantioselectivities (86–93% *ee*(*cis*), 90–98% *ee*(*trans*)) within short reaction times.

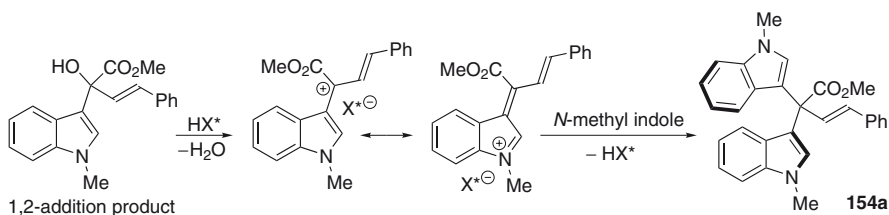


Scheme 61 Nazarov cyclization of dienones



Scheme 64 Conjugate addition of indoles to β,γ -unsaturated α -ketoesters

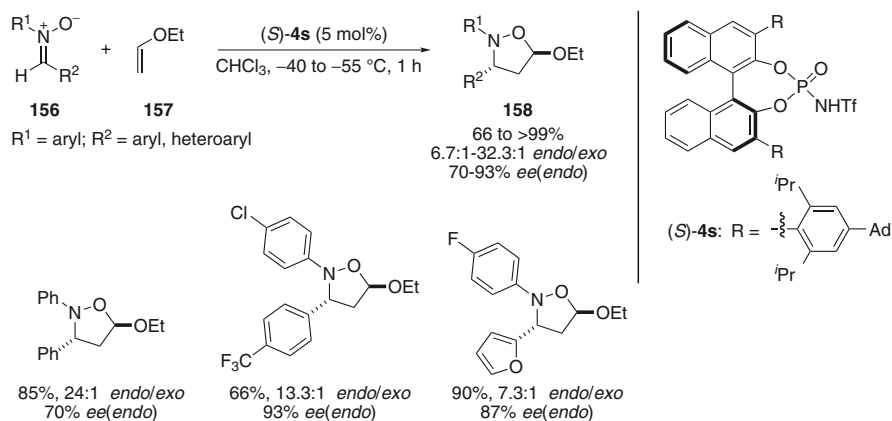
An intriguing feature is that the previously unknown bisindoles **154** display atropisomerism as a result of the rotation barrier about the bonds to the quaternary carbon center. With the use of *N*-triflyl phosphoramidate (*R*)-**4l** (5 mol%, *R* = 9-phenanthryl), bisindole **154a** could be obtained in 62% *ee*. Based on their experimental results, the authors invoke a Brønsted acid-catalyzed enantioselective, nucleophilic substitution following the 1,2-addition to rationalize the formation of the bisindoles **154** (Scheme 65).



Scheme 65 Proposed mechanism for the formation of the bisindole products

In 2008, Yamamoto et al. disclosed an asymmetric 1,3-dipolar cycloaddition of diarylnitrones **156** with ethyl vinyl ether (**157**) (Scheme 66). Under the influence of the bulky chiral *N*-triflyl phosphoramidate (*S*)-**4s** (5 mol%, *R* = 2,6-*i*-Pr₂-4-Ad-C₆H₂), the *endo*-products **158** were formed as the major diastereomers in good yields and enantioselectivities (66 to >99%, 7:1–32:1 *endo/exo*, 70–93% *ee*(*endo*)) [86]. High asymmetric induction was achieved only with electron-deficient aryl groups on the nitrones.

A previously reported AlMe-BINOL catalyzed version features *exo*-selectivity. In this respect, the present *endo*-selective process is in sharp contrast and shows



Scheme 66 1,3-Dipolar cycloaddition of diarylnitrones with ethyl vinyl ether **154**

how asymmetric Brønsted acid and metal Lewis acid catalysis can complement one another. The authors rationalized the observed diastereoselectivity by means of transition state (TS) structures **a** and **b**. Additional hydrogen bonding may stabilize the *endo*-selective TS **a** whereas TS **b**, which leads to the *exo*-product, seems to be disfavored because of steric repulsion (Fig. 16).

In the same year, Enders and coworkers reported an asymmetric one-pot, two-step synthesis of substituted isoindolines **159** in the presence of chiral *N*-triflyl phosphoramidate (*R*)-**4e** (10 mol%, R = 4-NO₂-C₆H₄) (Scheme 67) [87]. The cascade was triggered by a Brønsted acid-catalyzed aza-Friedel–Crafts reaction of indoles **29** and *N*-tosyliminoenoates **160** followed by a DBU-mediated aza-Michael cyclization of intermediates **161** to afford the isoindolines **159** in high yields (71–99%) and short reaction times (10 min to 4 h) along with good enantioselectivities (52–90% *ee*). Longer reaction times (16 h to 10 days) caused increasing formation of the bisindole byproduct **162** (Scheme 68) along with amplified optical purity of isoindolines **159**.

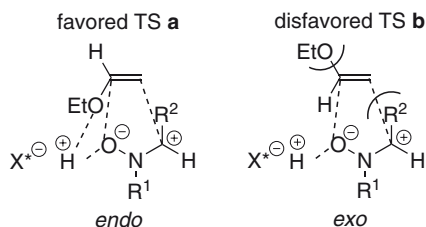
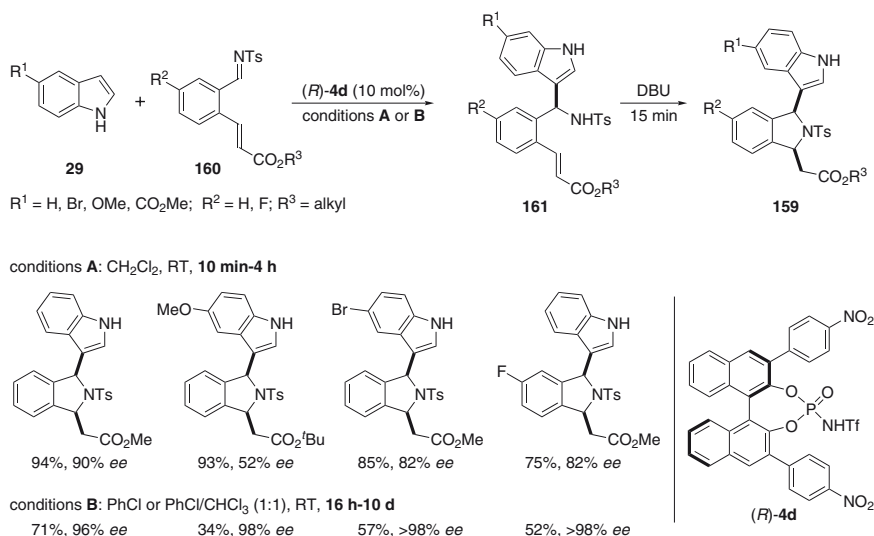


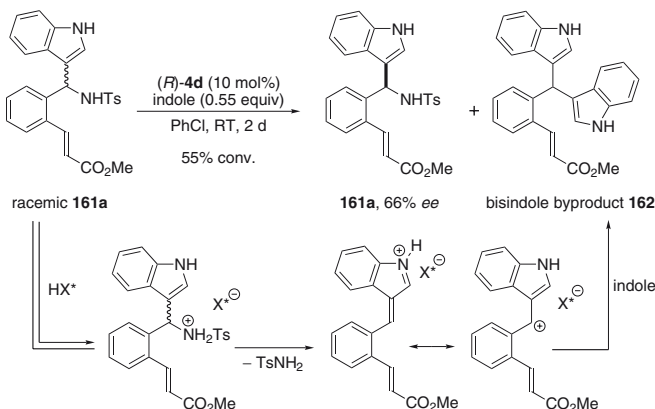
Fig. 16 Proposed transition state structures



Scheme 67 One-pot, two-step synthesis of substituted isoindolines

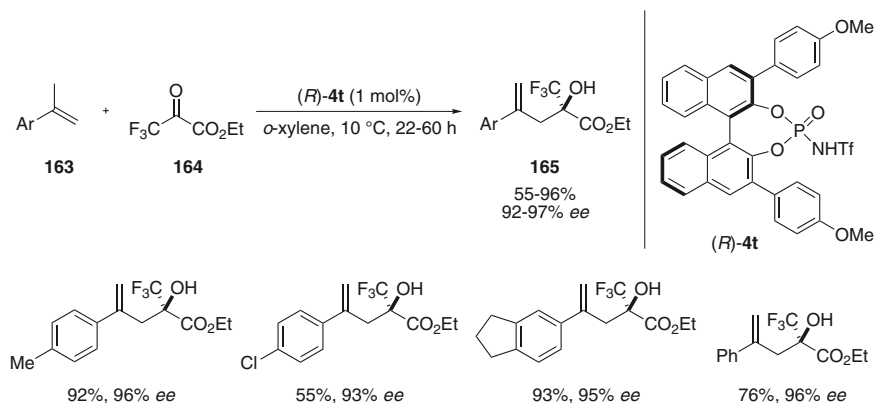
Thus, isoindolines **159** could be obtained in excellent enantioselectivities albeit with decreased yield (31–71%, 96 to >98% *ee*).

This observation denotes a stereoablative kinetic resolution taking place during the acid-catalyzed step, which was confirmed in experiments with racemic intermediate **161a** giving scalemic Friedel–Crafts product **161a** at 55% conversion upon treatment with *N*-triflyl phosphoramidate (*R*)-**4d** and indole (Scheme 68).



Scheme 68 Stereoablative kinetic resolution

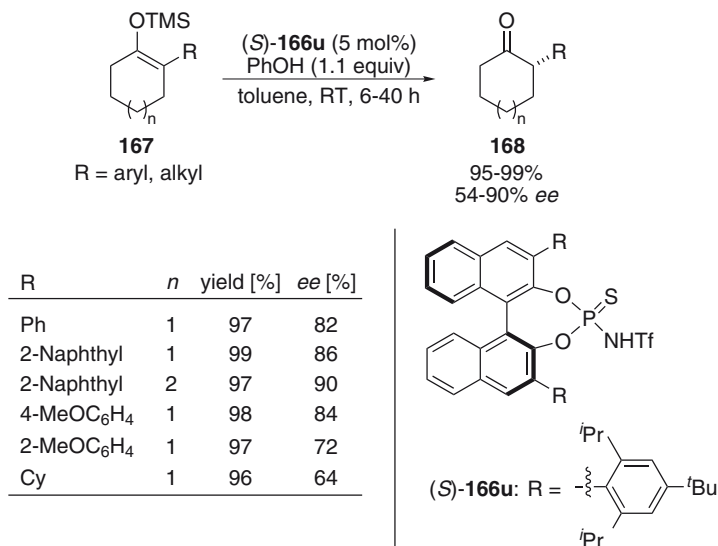
An asymmetric intermolecular carbonyl-ene reaction catalyzed by 1 mol% of chiral *N*-triflyl phosphoramidate (*R*)-**4t** (1 mol%, R = 4-MeO-C₆H₄) was developed by Rueping and coworkers (Scheme 69) [88]. Various α -methyl styrene derivatives **163** underwent the desired reaction with ethyl α,α,α -trifluoropyruvate **164** to afford the corresponding α -hydroxy- α -trifluoromethyl esters **165** in good yields along with high enantioselectivities (55–96%, 92–97% *ee*). The presence of the trifluoromethyl group was crucial and the use of methyl pyruvate or glyoxylate instead of **164** resulted in lower reactivities or selectivities.



Scheme 69 Carbonyl-ene reaction of α -methyl styrenes and ethyl α,α,α -trifluoropyruvate

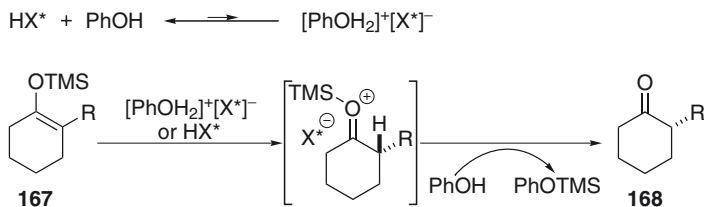
In 2008, Yamamoto et al. further modified the parent chiral *N*-triflyl phosphoramidate structure by substitution of the oxygen in the P=O bond with sulfur or selenium. This should increase the acidity and reactivity of the Brønsted acid according to the general rule that acidity increases as it descends in a column of the periodic table due to better stabilization of the conjugate base in a larger size atom². Various *N*-triflyl thio- or selenophosphoramidates were synthesized from optically active BINOL derivatives by thio- or selenophosphorylation with PSCl₃ or PSeCl₃ followed by oxidation with selenium powder and amidation of the intermediate thio- or selenophosphoryl chlorides with TfNH₂. Among all the catalysts tested, chiral *N*-triflyl thiophosphoramidate (*S*)-**166u** (5 mol%, R = 4-*t*Bu-2,6-*i*Pr₂-C₆H₂) showed the best catalytic potential in the asymmetric protonation reaction of various six- and seven-membered cyclic silyl enol ethers **167** with phenol as an achiral proton source (Scheme 70) [89]. α -Substituted cyclic ketones **168** were obtained in excellent yields (95–99%) with good enantioselectivities (54–90% *ee*), particularly in case of aryl-substituted silyl enol ethers.

²for example: pK_a (PhOH) = 18.0, pK_a (PhSH) = 10.3, pK_a (PhSeH) = 7.1



Scheme 70 Enantioselective protonation of silyl enol ethers

Cycloheptanones attained better enantioselectivity values than their six-membered analogs and the use of alkyl-substituted silyl enol ethers resulted in only moderate enantioselectivities. Indeed, replacement of P=O by P=S or P=Se in the phosphoramidate catalyst led to improved results in terms of reactivity as well as enantioselectivity. The catalyst loading could be decreased to 0.05 mol% without a deleterious effect on the enantioselectivity (one example). Optimization experiments revealed the critical influence of the achiral proton source on the reactivity and enantioselectivity. This observation suggests a two-step mechanism for the protonation reaction (Scheme 71).

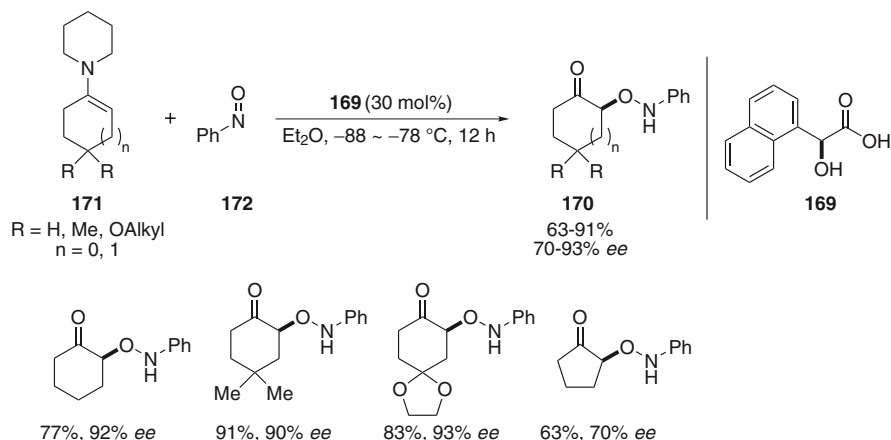


Scheme 71 Proposed reaction path

4 Chiral Carboxylic Acids

The key feature of Brønsted acid catalysis is often the choice of a catalyst with the appropriate acidity for particular substrate classes. Whereas less reactive substrates require stronger Brønsted acids than the widely used phosphoric acids for activation, acid-sensitive substrates tend to decompose under strongly acidic conditions. Thus, weaker Brønsted acid catalysts may prove beneficial.

In 2005, Yamamoto and Momiyama reported on the use of chiral carboxylic acids in asymmetric nitroso aldol reactions of achiral enamines (Scheme 72) [90]. Catalytic amounts of (*S*)-1-naphthyl glycolic acid ((*S*)-**169**) (30 mol%) led to the selective formation of *O*-nitroso aldol products **170** in good yields with high enantioselectivities (63–91%, 70–93% *ee*) using piperidine-derived enamines **171** and nitrosobenzene (**172**) as an electrophile. The conformational rigidity of catalyst **169** may result from an internal hydrogen bond between the carboxylic acid moiety and the oxygen lone pair of the hydroxyl group and accounts for the good selectivities observed.

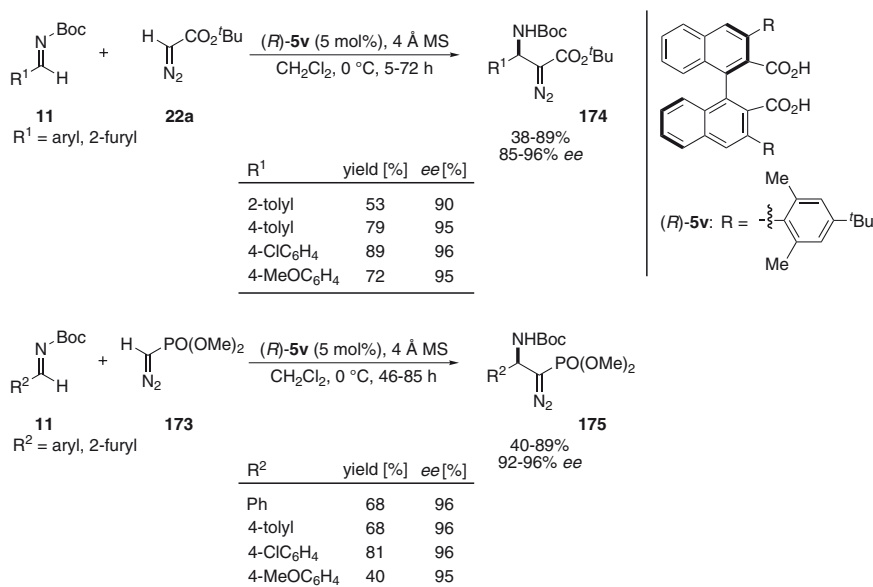


Scheme 72 Asymmetric nitroso aldol reactions of achiral enamines

Exclusive formation of the *N*-nitroso aldol product from similar starting materials was observed in the presence of 1-naphthyl TADDOL (30 mol%) in toluene (63–81%, 65–91% *ee*; $n = 1, 2$).

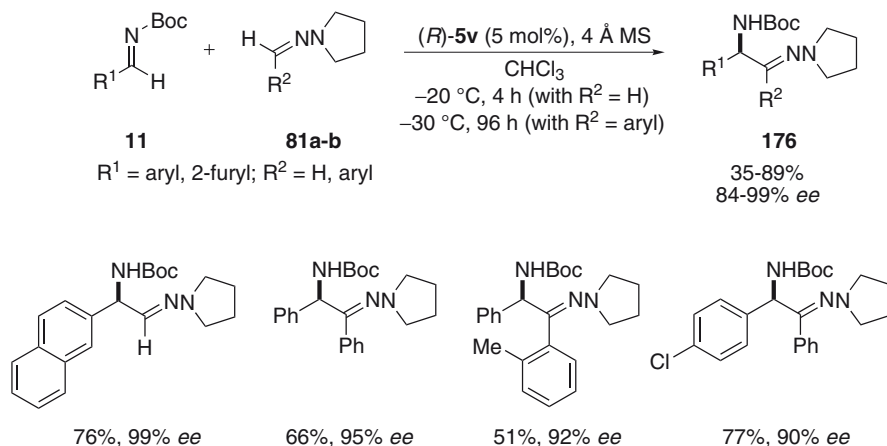
In 2007, Maruoka et al. introduced chiral dicarboxylic acids consisting of two carboxylic acid functionalities and an axially chiral binaphthyl moiety. They applied this new class of chiral Brønsted acid catalyst to the asymmetric alkylation of diazo compounds with *N*-Boc imines [91]. The preparation of the dicarboxylic acid catalysts bearing aryl groups at the 3,3'-positions of the binaphthyl scaffold follows a synthetic route, which has been developed earlier in the Maruoka laboratory [92].

Dicarboxylic acid (*R*)-**5v** (5 mol%, $R = 4\text{'Bu-2,6-Me}_2\text{-C}_6\text{H}_2$) in the presence of 4 Å molecular sieves displayed the optimal conditions for the investigated Friedel–Crafts-type reactions of various arylaldehyde-derived *N*-Boc imines **11** with *tert*-butyldiazoacetate **22a** or dimethyl diazomethylphosphonate **173** (Scheme 73). In both cases the corresponding products **174** and **175** were obtained in good yields with high enantioselectivities (38–89%, 85–96% *ee*). Notably, the reaction of *N*-Boc imine **11a** ($R^1 = \text{Ph}$) with **22a** in the presence of phosphoric acid **3a** (10 mol%, $R = \text{H}$) furnished beside the α -diazo- β -amino esters **174a** ($R^1 = \text{Ph}$) a considerable amount of the *E/Z* isomers of the corresponding enecarbamate.



Scheme 73 Friedel–Crafts-type alkylation of diazo compounds with *N*-Boc imines

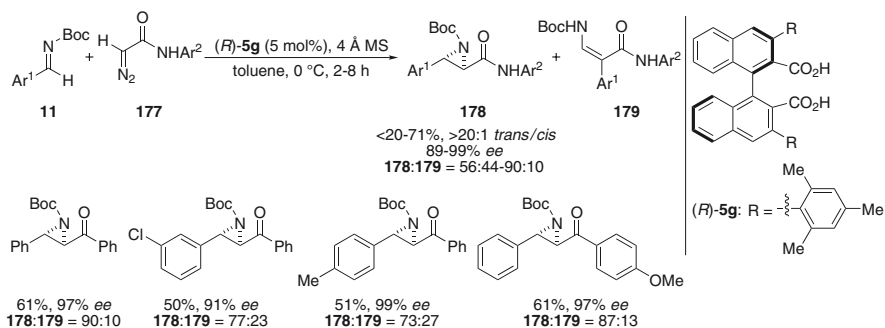
In 2008, the same group employed chiral dicarboxylic acid (*R*)-**5v** (5 mol%, $R = 4\text{'Bu-2,6-Me}_2\text{-C}_6\text{H}_2$) as the catalyst in the asymmetric addition of aldehyde *N,N*-dialkylhydrazones **81** to aromatic *N*-Boc-imines **11** in the presence of 4 Å molecular sieves to provide α -amino hydrazones **176**, valuable precursors of α -amino ketones, in good yields with excellent enantioselectivities (35–89%, 84–99% *ee*) (Scheme 74) [93]. Aldehyde hydrazones are known as a class of acyl anion equivalents due to their aza-enamine structure. Their application in the field of asymmetric catalysis has been limited to the use of formaldehyde hydrazones (Scheme 30). Remarkably, the dicarboxylic acid-catalyzed method applied not only to formaldehyde hydrazone **81a** ($R^1 = \text{H}$) but also allowed for the use of various arylaldehyde hydrazones **81b** ($R^1 = \text{Ar}$) under slightly modified conditions. Prior to this



Scheme 74 Addition of aldehyde hydrazones to *N*-Boc-imines

report, this class of practical acyl anion equivalents was completely unexplored in asymmetric synthesis. In the present transformation dicarboxylic acid **5v** featured higher catalytic efficiency in terms of both activity and asymmetric induction compared to phosphoric acid (*R*)-**14j** earlier employed by the Rueping group [52].

Chiral dicarboxylic acid (*R*)-**5g** (5 mol%, $\text{R} = \text{Mes}$) bearing simpler mesityl-substituents at the 3,3'-positions was found to catalyze efficiently the *trans*-selective asymmetric aziridination of *N*-aryl-monosubstituted diazoacetamides **177** and aromatic *N*-Boc imines **11** (Scheme 75) [94]. In sharp contrast to previous reports on this generally *cis*-selective sort of aziridination, this method exhibited unique *trans*-selectivity and afforded exclusively the *trans*-aziridines **178** in moderate to good yields along with excellent enantioselectivities (<20–71%, 89–99% *ee*). The 1,2-aryl shift products **179** were observed as side products in varying ratios (**178**:**179** = 56:44–90:10). Diazoacetamides were chosen instead of diazoesters. Due

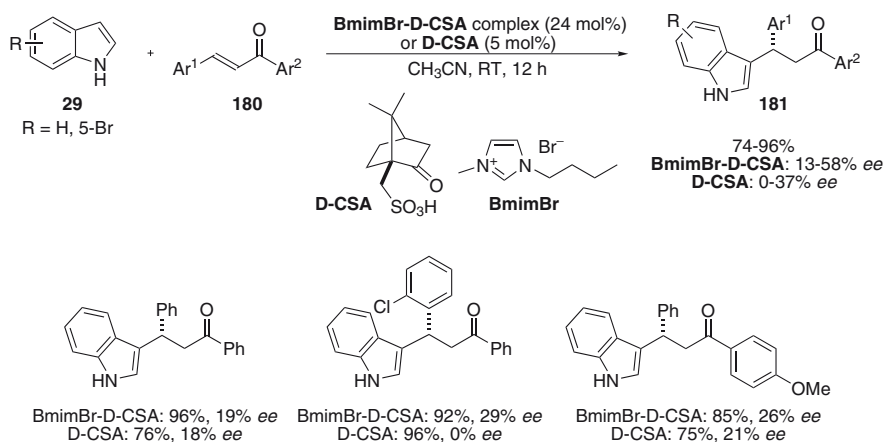


Scheme 75 Aziridination of diazoacetamides and *N*-Boc imines

to their inherent lower α -acidity they are capable of resisting proton abstraction in the course of the reaction, which renders aziridine formation via the aza-Darzens route possible. The intervention of a different mechanism is reflected in the inverted enantiofacial selectivity compared to the previously reported dicarboxylic acid-catalyzed Mannich reactions of diazoesters [91].

5 Chiral Sulfonic Acids

In 2006, Xu and Xia et al. revealed the catalytic activity of commercially available D-camphorsulfonic acid (CSA) in the enantioselective Michael-type Friedel–Crafts addition of indoles **29** to chalcones **180** attaining moderate enantiomeric excess (75–96%, 0–37% *ee*) for the corresponding β -indolyl ketones **181** (Scheme 76) [95]. This constitutes the first report on the stereoselectivity of D-CSA-mediated transformations. In the course of their studies, the authors discovered a synergistic effect between the ionic liquid BmimBr (1-butyl-3-methyl-1*H*-imidazolium bromide) and D-CSA. For a range of indoles **29** and chalcone derivatives **180**, the preformed BmimBr-CSA complex (24 mol%) gave improved asymmetric induction compared to D-CSA (5 mol%) alone, along with similar or slightly better yields of β -indolyl ketones **181** (74–96%, 13–58% *ee*). The authors attribute the beneficial effect of the BmimBr–D-CSA combination to the catalytic Lewis acid activation of Brønsted acids (LBA). Notably, the direct addition of BmimBr to the reaction mixture of indole, chalcone, D-CSA in acetonitrile did not influence the catalytic efficiency.



Scheme 76 Michael-type Friedel–Crafts addition of indoles to chalcones

6 Summary and Outlook

Specific Brønsted acid catalysis is a popular field within the domain of asymmetric organocatalysis. Since the introduction of stronger chiral Brønsted acids as powerful catalysts for enantioselective synthesis in 2004, numerous asymmetric Brønsted acid-catalyzed transformations have been developed.

Chiral phosphoric acids mediate the enantioselective formation of C–C, C–H, C–O, C–N, and C–P bonds. A variety of 1,2-additions and cycloadditions to imines have been reported. Furthermore, the concept of the electrophilic activation of imines by means of phosphates has been extended to other compounds, though only a few examples are known. The scope of phosphoric acid catalysis is broad, but limited to reactive substrates. In contrast, chiral *N*-triflyl phosphoramides are more acidic and were designed to activate less reactive substrates. Asymmetric formations of C–C, C–H, C–O, as well as C–N bonds have been established. α,β -Unsaturated carbonyl compounds undergo 1,4-additions or cycloadditions in the presence of *N*-triflyl phosphoramides. Moreover, isolated examples of other substrates can be electrophilically activated for a nucleophilic attack. Chiral dicarboxylic acids have also found utility as specific acid catalysts of selected asymmetric transformations.

Given the wide range of chiral catalysts with different acidities and structures, we anticipate new asymmetric transformations to arise in the near future. One challenge that is likely to be addressed includes the Brønsted acid-catalyzed activation of new substrate classes such as unactivated carbonyl compounds or simple olefins, which will presumably require the design of even stronger chiral acids. There will probably be further advances in the area of Brønsted acid-catalyzed multicomponent and cascade reactions for the construction of complex molecules such as natural products or pharmaceuticals. Although stronger chiral Brønsted acids are mainly used as catalysts for asymmetric synthesis in academia, it is likely that they will ultimately be employed in industry as well. Furthermore, mechanistic studies along with computational methods will presumably be applied to aid in the understanding and discovery of new asymmetric Brønsted acid-catalyzed processes. It will definitely be quite exciting to follow the development of the field over the next years.

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