# Organocatalytic direct asymmetric α-heteroatom functionalization of aldehydes and ketones

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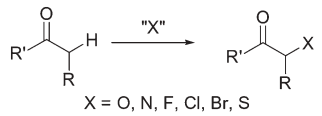
The direct enantioselective introduction of a stereogenic carbon–heteroatom bond adjacent to a carbonyl functionality leads to optically active compounds of significant importance for *e.g.* the life-science industry. Organocatalytic enantioselective amination, oxygenation, fluorination, chlorination, bromination and sulfenylation of aldehydes and ketones, using chiral amines as the catalysts, are reviewed in this feature article. Furthermore, a few other transformations are also outlined. The scope, potential and application of these organocatalytic asymmetric reactions are presented and the mechanistic aspects discussed.

## Introduction

The stereochemical control of the transformation of a C–H bond into a stereogenic C–X (X = O, N, F, Cl, Br, S) bond adjacent to a carbonyl functionality (eqn (1)) is a fundamental challenge and of importance in chemistry. The importance of these optically active α-heteroatom substituted carbonyl compounds is due their application in ''nearly all fields of organic chemistry''.




(1)

The great importance of optically active α-heteroatom substituted carbonyl compounds has led to an intensive effort in trying to develop procedures for the formation of these compounds by applying asymmetric catalysis using carbonyl compounds, or equivalents, as substrates. Several catalytic asymmetric approaches can be considered for the C–H to C–X transformation in eqn (1), of which chiral Lewis acid- and organo-catalysis are methods which have attracted considerable attention in recent years.

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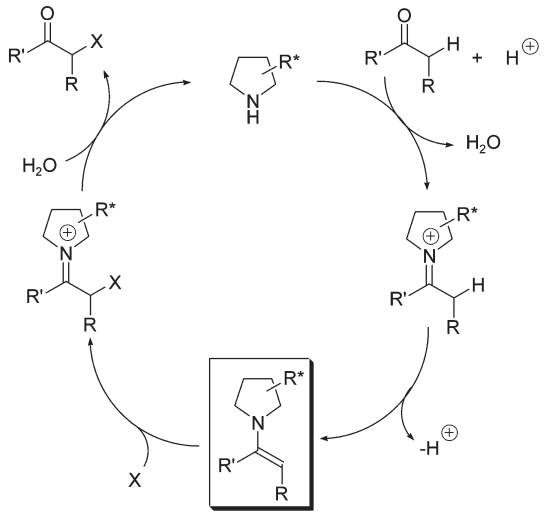
In this feature article we will discuss the development and application of direct organocatalytic α-heterofunctionalization of aldehydes and ketones catalyzed by ''small chiral amines''.[1] The following C–H to C–X transformations will be considered: amination, oxygenation, halogenation (fluorination, chlorination, bromination) and sulfenylation. Furthermore, we will also briefly discuss other organocatalytic approaches for the formation of a stereogenic C–X bond adjacent to a carbonyl functionality. We will try to give an overview of the recent developments of organocatalytic enantioselective α-heterofunctionalization of aldehydes and ketones, but also discuss why these reactions are important due to the useful products obtained. Furthermore, we will also present selected mechanistic details for some of the transformations discussed.

## Mechanistic considerations

The basic concept in the activation of a C–H bond adjacent to a carbonyl group and its transformation into a C–X bond using small chiral amines as the catalyst can be accounted for by the formation of an enamine intermediate as highlighted in the mechanism outlined in Scheme 1. The first step in the catalytic cycle is the reaction of a carbonyl compound with the chiral amine to form an iminium intermediate. Cleavage of the C–H bond, by an iminium to enamine transformation, leads to the formation of an enamine intermediate, having a nucleophilic carbon atom which reacts with the electrophile X forming the C–X bond. Hydrolysis of the intermediate releases the chiral amine, which can then undergo a new catalytic cycle to give the α-heteroatom substituted carbonyl compound.

The chirality of the stereogenic center formed during the catalytic cycle in Scheme 1 is determined by the substituent R* in the chiral amine. Two types of interactions are operating in these reactions leading to the face-selectivity: electronic and steric. To the left in Fig. 1 is the face-selectivity caused by the electronic interaction[2] outlined. This face-selectivity is here exemplified by hydrogen-bonding of the acidic hydrogen atom of *e.g.* a carboxylic acid or tetrazole group, of the chiral substituent in the 2-position in a pyrrolidine ring, with a basic



**Scheme 1** Enamine mechanism for the catalytic enantioselective α-heteroatom functionalization of aldehydes and ketones.

lone pair in the heteroatom (Y) of the electrophile. This type of interaction normally takes place when the reagent has a double bond, such as azodicarboxylates (–N=N–) and nitrosobenzene (–N=O). The face-selectivity of the electrophilic addition of heteroatom X thus takes place from the same face as the orientation of the chiral substituent, due to the hydrogen-bonding interaction. This characteristic of the catalytic system leads to an approach to the *Re*-face of the enamine–carbon atom.

The face-selectivity originating from steric shielding is presented to the right in Fig. 1. The chiral substituent in *e.g.* the 2-position of the pyrrolidine ring shields the *Re*-face of the enamine carbon atom forcing an approach of the electrophile from the opposite site of the chiral substituent (*Si*-face approach).

The absolute configuration of the chiral carbon atom formed in the α-position of the carbonyl functionality is thus dependent on the type of interaction between the electrophile and the catalyst. Catalysts with the same absolute configuration will, by electronic or steric interactions, give the opposite absolute configuration in the optically active product formed.

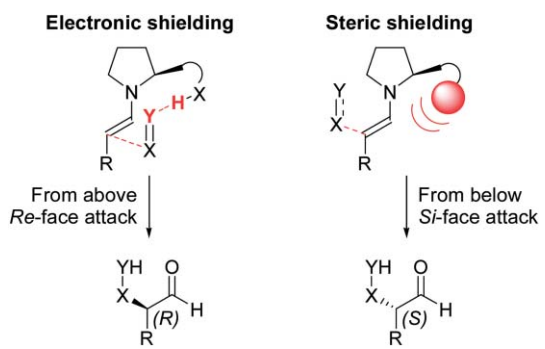
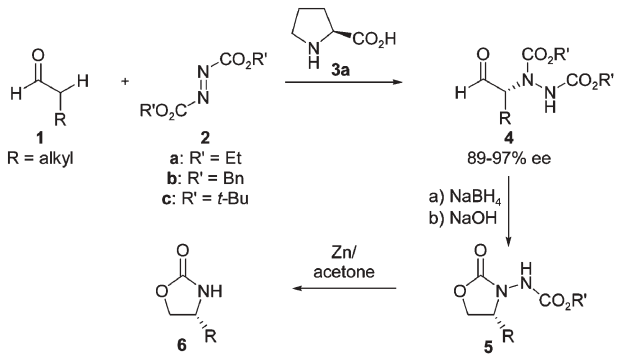



**Fig. 1** The two types of interactions – electronic and steric – in the approach of the electrophile to the nucleophilic carbon atom in the chiral enamine intermediate.

## Amination reactions

The direct stereoselective introduction of a nitrogen atom functionality in the α-position of aldehydes and ketones leads to valuable optically active synthetic targets such as α-amino acids and amino alcohols, which have great potential in various fields of life-science molecules.[3]

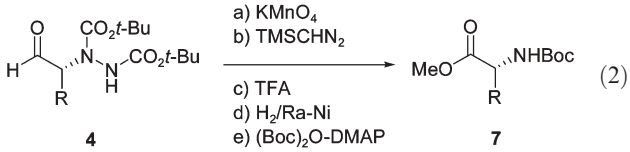
The first direct α-heteroatom functionalization was presented in 2002 when we[4] and List[5] independently submitted a very simple procedure for the direct α-amination of aldehydes: a solution of the aldehyde **1** and diethyl-, dibenzyl- or di-*tert*-butyl azodicarboxylate **2a–c**, either neat or in a protic solvent, in the presence of L-proline **3a** (5–10 mol%) as the catalyst gave the α-hydrazino aldehydes **4** with *R*-configuration in moderate to good yields and with excellent enantioselectivities (89–97% ee) (Scheme 2).




**Scheme 2** L-Proline catalyzed direct enantioselective α-amination of aldehydes and further transformations to optically active oxazolidinones.

The α-hydrazino aldehydes **4** are prone to racemization and it was found to be advantageous to reduce the aldehydes directly with $NaBH_4$ to stereochemical stable compounds which, in a one-pot process, by treatment with NaOH, can cyclize to form the *N*-amino oxazolidinones **5**. Reductive cleavage of the *N*-amino group in **5** with Zn/acetone gives the corresponding oxazolidinone **6**.

Optically active α-amino acid derivatives **7** are accessible by oxidation of the aldehyde functionality in the α-hydrazino aldehydes **4**, to the corresponding carboxylate, with $KMnO_4$, followed by esterification and reductive hydrazine cleavage (eqn (2)).[4]




(2)

The formation of the *R*-enantiomer of the α-hydrazino aldehydes **4** in the L-proline catalyzed α-amination of aldehydes (Scheme 2) is due to an electronic-shielding mechanism (Fig. 1 and *vide infra*) in the stereoselective C–N bond forming reaction. The *S*-enantiomer of the α-hydrazino aldehydes **4** can of course be formed using D-proline as the catalyst. However, recently a novel and very general organo-catalyst, (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine **3b**, has been presented for *e.g.* the enantioselective α-heteroatom functionalization of aldehydes,

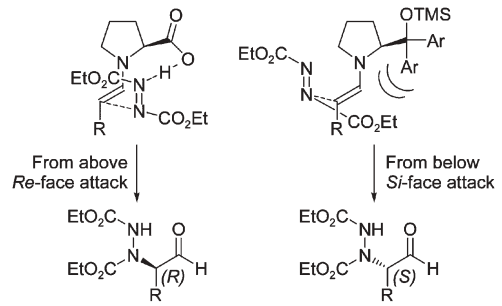
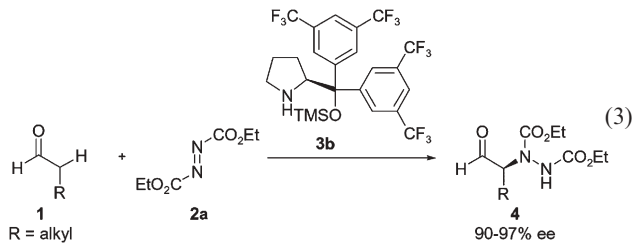



**Fig. 2** Transition-state models for L-proline **3a** (*S*)-2-[bis(3,5- bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine **3b** catalyzed α-amination of aldehydes.

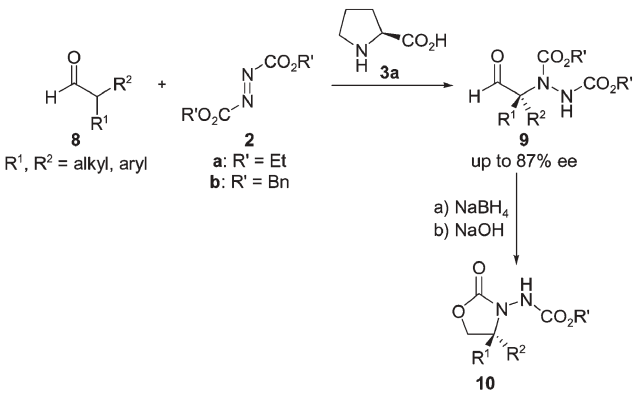
based on the steric-shielding mechanism (Fig. 2 and *vide infra*).[6] The α-amination of aldehydes **1** with diethyl azodicarboxylate **2a** takes place in 15 min at room temperature using **3b** as the catalyst (10 mol%) to give **4** with *S*-configuration in good yields and with excellent enantioselectivities (90–97% ee) (eqn (3)) – in some cases higher than the ones obtained with L-proline.




(3)

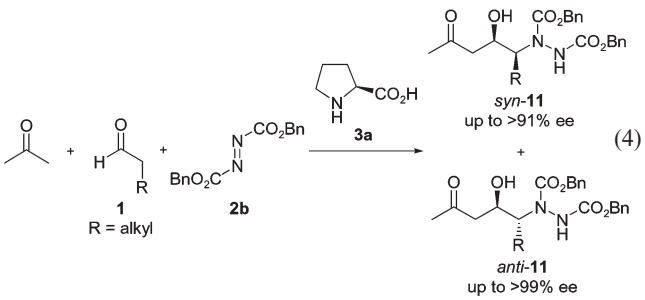
The L-proline-catalyzed direct amination of aldehydes has been extended to also include α,α-disubstituted aldehydes **7** using azodicarboxylates as the electrophilic nitrogen source (Scheme 3).[7]

The direct α-amination of α,α-disubstituted aldehydes **8** is especially well-suited for α-alkyl-α-aryl aldehydes which gave the optically active products in moderate to good yields and up to 87% ee. The –N–N– bond in **10** was cleaved by hydrogenation using Pd/C in MeOH–AcOH, followed by treatment with $NaNO_2$ in AcOH–HCl.



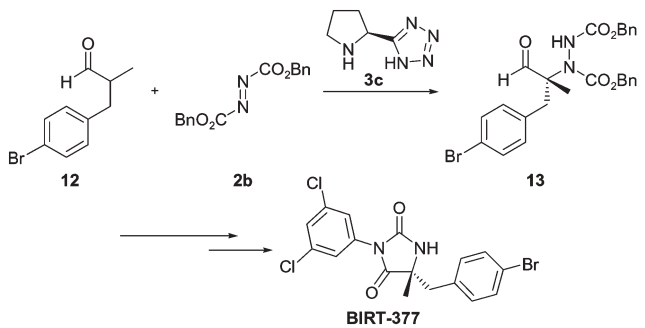

**Scheme 3** L-Proline catalyzed direct enantioselective α-amination of α,α-disubstituted aldehydes and further transformations to optically active oxazolidinones.

The direct amination of aldehydes has been applied in a series of papers by Barbas and co-workers.[8] By combining acetone, various aldehydes **1** and dibenzyl azodicarboxylate **2b** and using L-proline **3a** as the catalyst a one-pot synthesis of functionalized β-amino alcohols **11** was achieved (eqn (4)).[8a] The scope of the reaction turned out to be quite general for various aldehydes and the optically active β-amino alcohols **11** were obtained in high yields with low diastereoselective control. However, excellent enantioselectivity of especially the *anti*-adducts were obtained.



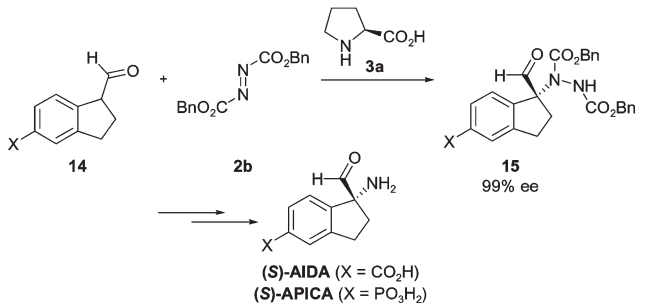

(4)

For the enantioselective total synthesis of the cell-adhesion inhibitor BIRT-377, the organocatalytic construction of the quaternary stereocenter was essential.[8b] The direct α-amination of 3-(4-bromophenyl)-2-methylpropanal **12** with dibenzyl azodicarboxylate **2b** catalyzed by L-proline **3a** required 5 d reaction time to provide the amino aldehyde **13** in 90% yield, but with moderate enantioselectivity (44% ee). However, the use of the L-proline-derived tetrazole catalyst **3c** turned out to be a good choice for this enantioselective α-amination reaction, as the desired optically active **13** now was formed in 95% yield and with 80% ee. From the optically active α-aminated aldehyde **13**, BIRT-377 was synthesized by standard transformations (Scheme 4).




**Scheme 4** Enantioselective total synthesis of the cell-adhesion inhibitor BIRT-377 using the organocatalytic α-amination reaction of 3-(4-bromophenyl)-2-methylpropanal **12**.

The proline-catalyzed direct α-amination has been applied to the synthesis of AIDA and APICA (Scheme 5), which are known antagonists of metabotropic glutamate receptors and G-protein-coupled receptors associated with various neurodegenerate diseases.[8c] Both, indane carbaldehyde and analogous compounds having an ester functionality (leading to AIDA) or a phosphonate substituent (APICA), all reacted with dibenzyl




**Scheme 5** Total synthesis of AIDA and APICA known antagonists of metabotropic glutamate and G-protein-coupled receptors using L-proline catalyzed enantioselective α-amination reaction of **14**.

azodicarboxylate **2b** in the presence of L-proline as the catalyst and the products **15** having a quaternary stereocenter were obtained with excellent enantioselectivity (99% ee).

Due to the low yield in the cleavage of the –N–N– bond with the previously mentioned procedures, an alternative route based on $SmI_2$ was utilized. The authors first applied a one-pot trifluoroacetylation-selective benzyloxycarbonyl deprotection protocol giving the trifluoro hydrazine. The –N–N– bond cleavage was then carried out with $SmI_2$.

The direct α-amination of carbonyl compounds catalyzed by L-proline has been further developed to also include ketones.[9] Using diethyl azodicarboxylate **2a** and L-proline (10 mol%) as the catalyst the amination reaction proceeded with excellent enantioselectivities – for acyclic ketones in the range of 94–98% ee, while cyclohexanone gave 84% ee. Furthermore, the reaction is highly regioselective and takes place at the more substituted carbon atom. The stereocenter formed in the α-amination of ketones was found to be less prone to racemization compared to the aldehydes. The synthetic utility of the optically active α-aminated ketones was *e.g.* demonstrated by the diastereoselective reduction of the ketone: reduction with $NaBH_4$ gave the corresponding *syn*-α-amino alcohol, while the use of $Et_3SiH$–$TiCl_4$ provided the corresponding *anti*-α-amino alcohol.[9]

Based on the absolute configuration of the α-aminated aldehydes and ketones and the observation that L-proline **3a** and (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine **3b**, having identical absolute configuration promoted the formation of products with opposite absolute configuration at the α-carbon stereocenter the two transition states presented in Fig. 2 have been proposed.[6]

Further insight into the mechanism of the L-proline catalyzed α-amination of aldehydes has been provided by Blackmond and co-workers.[10] A combination of kinetic experiments and DFT-calculations led to clues about the possible nature of the species in the catalytic cycle. It was postulated that at the end of the reaction, when the products begin to separate from the catalyst, a series of hydrogen-bonding interactions can take place. These interactions are *e.g.* between the product –N–H group and the carboxylic oxygen atom which tethers the carboxylic group. This positions the proline nitrogen atom such that its lone-pair electrons are accessible for attack on the incoming aldehyde substrate, which in turn can be activated by a developing interaction with the carboxylic acid proton.

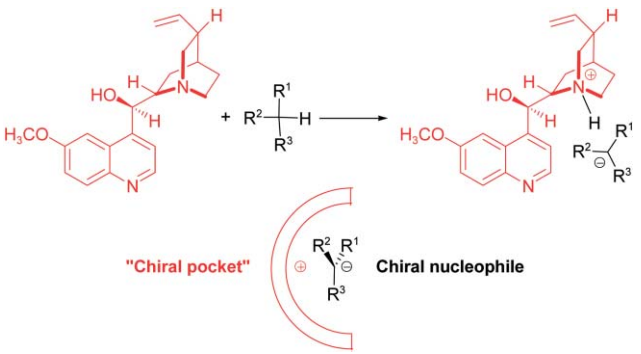



**Fig. 3** Reaction between a cinchona alkaloid (quinine) and a substrate having an acidic proton.

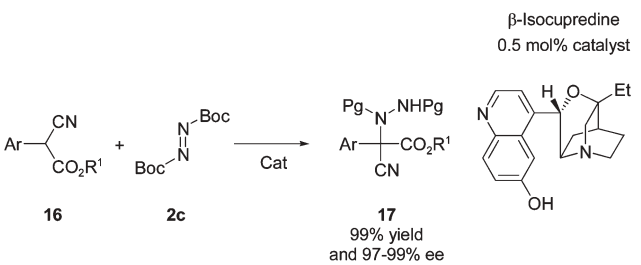
The organocatalytic direct α-amination of carbonyl compounds has been further developed to also include cinchona alkaloids as catalysts. The concept is outlined in Fig. 3 with quinine as the chiral catalyst. Quinine reacts as a base with the substrate having an acidic hydrogen atom, *i.e.* using a substrate which has electron-withdrawing substituents that generates the acidic C–H bond. The reaction between the chiral base and the substrate catalytically generates a chiral nucleophile in a "chiral pocket" as outlined in Fig. 3.

Applying the concept in Fig. 3, it has been reported that the quinidine-derived alkaloid β-isocupridine (β-ICD) is an efficient catalyst for the direct α-amination of α-cyanoacetates **16** (Scheme 6) and β-dicarbonyl compounds.[11] The substrates are highly acidic and the reaction probably proceeds as an enolate with a chiral β-ICD-$H^+$ counterion as the intermediate. The β-ICD-catalyzed α-amination of α-cyanoacetates with di-*tert*-butyl azodicarboxylate **2c** is a highly efficient process that proceeds with 0.5 mol% of β-ICD to give the expected products **17** having a stereogenic quaternary carbon center in excellent yields and with excellent levels of enantioselectivity for a variety of aryl-substituted α-cyanoacetates (Scheme 6), while the β-dicarbonyl compounds give slightly lower enantioselectivity (83–90% ee).

Deng and co-workers followed up on the α-amination of α-cyanoacetates **16** (Scheme 6) by showing that 6′-OH-modified cinchona alkaloids that are accessible from either quinine or quinidine were also effective catalysts for the reaction leading to the optically active products in 71–99% yield and up to 99% ee.[12]

## Oxygenation reactions

The α-oxycarbonyl group is a common feature of many natural and biologically active compounds. Furthermore, this



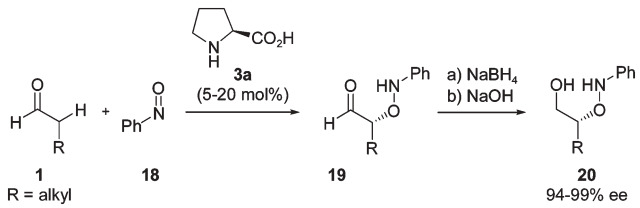

**Scheme 6** Cinchona-alkaloid catalyzed amination of α-cycnoacetates.

functionality is an obvious precursor in the synthesis of other important building blocks such as diols.

In 2003, Yamamoto and co-workers introduced the use of nitrosobenzene as an electrophilic source of oxygen in the asymmetric metal-catalyzed oxidation of tin enolates.[13]

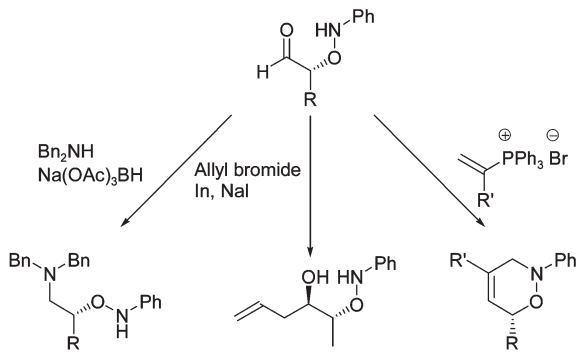
Following this inspiring discovery, almost contemporaneously, three different groups used nitrosobenzene for the direct functionalization of aldehydes using L-proline as the organocatalyst.

Zhong,[14] MacMillan's[15] and Hyashi's group[16] reported independently within a very short time, the ability of L-proline to control both the O/N-selectivity, as well as, the enantioselectivity in a variety of solvents and reaction conditions (Scheme 7).




**Scheme 7** L-Proline catalyzed direct enantioselective α-oxidation of aldehydes using nitrosobenzene as the oxygen donor.

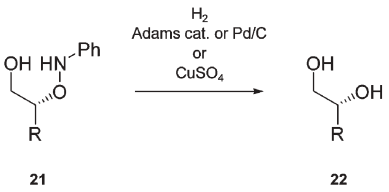
The product **19** of the organocatalytic oxidation was found to be relatively unstable and it was conveniently reduced *in situ* in the presence of $NaBH_4$. Nevertheless, other transformation can be performed directly on the crude reaction mixture maintaining the high optical purity, as reported by MacMillan and co-workers[15] and later by Zhong[17] and the group of Ley (Scheme 8).[18]




**Scheme 8** Synthetic transformation of optically active α-oxidized aldehydes.

It was also demonstrated that the –O–N– bond in **21** could be efficiently cleaved using $CuSO_4$ or alternatively, by hydrogenolysis on Pd/C or using Adam's catalyst (Scheme 9).[14–16]

The described strategy for the α-oxidation of aldehydes was later further extended to the use of ketones as nucleophiles. A considerable effort was made to optimize the reaction conditions since different problems arose, such as lower reaction rate and yields, because of the formation of the di-addition product at the two enolizable carbon atoms and lower O/N-selectivity.




**Scheme 9** Cleavage of the O–N bond in optically active α-oxidized aldehydes.

The groups of Hyashi[19] and Cordova[20] minimized these problems by using a relatively large excess of ketone and by applying the slow addition method. In this way good chemical yields (44–91%) and nearly enantiopure products were obtained (96–99% ee). The addition of nitrosobenzene to ketones catalyzed by proline was also applied by Ramachary and Barbas in the desymmetrization of *meso*-cyclohexanone derivatives.[21] Due to the importance of the products obtained, different research groups investigated the catalytic properties of other secondary amines (**3c–f**) in this transformation (Fig. 4).[22] Catalyst **3c** turned out to be particularly successful since the same high yields and enantioselectivities could be obtained in the case of aldehydes and ketones, but with a lower catalyst loading and shorter reaction times.

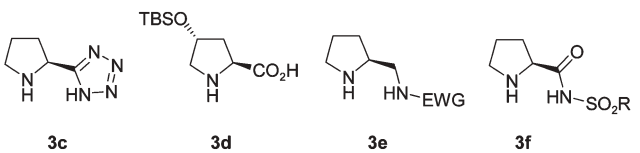



**Fig. 4** Alternative organocatalysts for the α-aminooxylation of aldehydes and ketones.

The common feature to all these catalysts is the acidic proton in the group in the 2-position of the pyrrolidine ring. The role of this functionality is not only to control the enantioselectivity as in other related proline-catalyzed reactions (see Fig. 1), but also to control the regioselectivity of the reaction. Both Córdova *et al.*[20b] and Cheong and Houk[23] performed quantum mechanical computational studies in attempts to understand the mechanism and to explain the greater electrophilicity of the oxygen atom over the nitrogen atom of nitrosobenzene under these specific reaction conditions.

The higher energy for the *N-anti* transition state accounts for the excellent O/N-selectivity observed (Fig. 5).[23] The preferential protonation of the nitrogen atom is a consequence

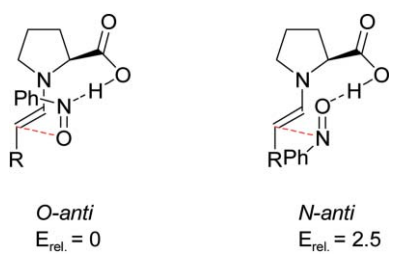



**Fig. 5** Rationalization of the O/N selectivity.

of its higher basicity and this fact leads to the electrophilic attack of the enamine at the oxygen atom.

The two alternative transition states proposed by Zhong[14] with the enamine nitrogen atom mediating the proton transfer from the carboxylic acid to the nitrogen atom of nitrosobenzene, and by MacMillan and co-workers,[15] in which a zwitterionic species is present (Fig. 6), were suggested to be unlikely due to the significantly higher energies involved. Other possibilities involving for example (*Z*)-enamines or a nitrosobenzene dimer as the electrophile were also examined and discarded due to the much higher energies involved.

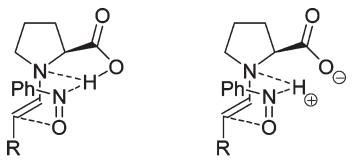


**Fig. 6** Proposed alternative transition states.

The mechanism of the reaction was studied also by the group of Blackmond.[24] In the absence of a long pre-equilibration period of proline with an excess of aldehyde, the aminoxylation reaction showed a very interesting kinetic profile and the authors observed a positive non-linear effect and accelerating rate of the reaction. These observations suggest the possibility for alternative and more complex catalytic cycles. One the other hand, Córdova *et al*. observed no-non-linear effect for the related reaction of ketones.[20b]

In 2004 Cordova *et al*.[25] reported that L-α-methylproline could incorporate molecular oxygen in the α-position of an aldehyde. The presence of TPP as sensitizer was necessary to promote the formation of singlet molecular oxygen as the electrophilic species. Although, the enantioselectivities obtained were only moderate (54–66% ee), this represents undoubtedly a very intriguing alternative to the use of nitrosobenzene in this kind of reactions.

The direct enantioselective α-hydroxylation of activated ketones,[26] specifically cyclic β-dicarbonyl compounds, can be performed using dihydroquinine as the chiral catalyst and simple commercially available peroxides as the oxidant. The use of cumyl hydroperoxides led to the α-hydroxylation of β-ketoesters in high yields and moderate to good enantioselectivities (66–80% ee). These products could be transformed into *anti*-diols with excellent diastereoselectivity (99:1) using $BH_3$-4-ethylmorpholine as the reducing agent.

## Halogenation reactions

Optically active halogen compounds are important in various fields of science, either for use in further manipulations or because the stereogenic C–halogen center has a unique property which is of specific importance for a given molecule. The involvement of these functional groups for further stereospecific manipulations and their increasing importance in medicinal chemistry and material sciences have led to an increased search for catalytic asymmetric C–halogen bond-forming reactions.[27]

The use of organocatalysis for the asymmetric α-halogenation of carbonyl compounds has opened up new aspects for the formation of stereogenic C–halogen centers and in the following the enantioselective fluorination, chlorination and bromination reactions will be discussed.

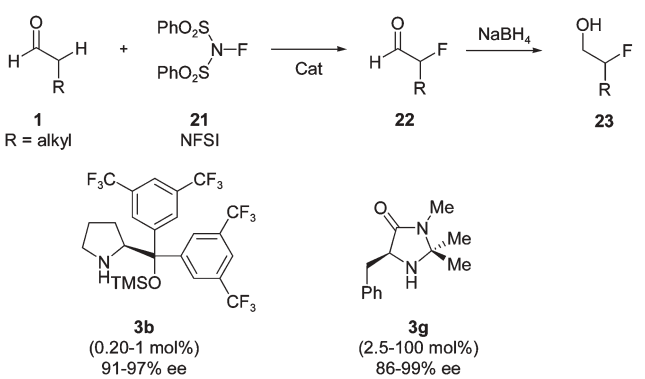
### Fluorination

The catalytic direct enantioselective α-fluorination of aldehydes was presented within a few weeks in 2005 by four different research groups. Enders and Hüttl,[28a] us,[28b] Barbas and co-workers[28c] and Beeson and MacMillan.[28d]

The work by the group of Enders focussed on the use of Selectfluor for the α-fluorination of both aldehydes and ketones. For the aldehydes no enantiomeric excess was reported using L-proline as the catalyst.[28a] In the attempt to perform direct enantioselective α-fluorination of ketones, cyclohexanone was used as the substrate and a number of chiral amines were tested for their enantioselective properties; however, the enantiomeric excess was rather low and in the range of 0–36% ee.

The three other approaches to direct enantioselective α-fluorination of aldehydes used *N*-fluorobenzenesulfonimide (NFSI)[21] as the fluorination reagent. Our approach was based on the application of (*S*)-2-[bis(3,5-bistrifluoromethylphenyl) trimethylsilanyloxymethyl]pyrrolidine **3b** as the catalyst (Scheme 10).[28b] Various aldehydes were α-fluorinated in a highly enantioselective manner (91–97% ee) in methyl *tert*-butyl ether as the solvent and the corresponding α-fluoroalcohols[23] were obtained in moderate to good yields after reduction with $NaBH_4$.

The work by Barbas and co-workers and Beeson and MacMillan was based on the same catalytic concept – a chiral imidazolidinone **3g** (Scheme 10).[28c,d] In the work presented by the former group, a large number of catalysts were evaluated and under catalytic conditions (30 mol%) up to 88% ee was obtained for linear aldehydes, however, the conversion was rather low. The scope of the reaction was demonstrated for various linear and branched aldehydes and an equimolar amount of catalyst was needed in order to obtain moderate to good yields of the optically active α-fluorinated compounds.[28c] The MacMillan group used the imidazolidinone compound (**3g**) in a catalytic amount by applying the salt of the catalyst




**Scheme 10** Organocatalytic enantioselective α-fluorination of aldehydes.

and in this case also the addition of 10% i-PrOH.[28d] This approach led to a highly enantioselective α-fluorination of linear aldehydes in moderate to high yields and enantioselectivities in the range of 91–99% ee. It was also demonstrated that the reaction could proceed with 2.5 mol% catalyst loading, still giving excellent enantioselectivity.

Mechanistic and computational investigations[6] of the direct enantioselective α-fluorination of aldehydes using (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl] pyrrolidine **3b** as the catalyst have been performed. In these studies the structure of the energetically lowest intermediate showed that the 3,5-trifluoromethyl phenyl and TMS groups efficiently shield the α-proton in (*S*,*S*)-**24** thereby protecting it from abstraction preventing enamine formation (Fig. 7). On the other hand, for the diastereoisomer (*R*,*S*)-**24**, the α-proton is placed on the open face and is more accessible towards abstraction (Fig. 7). This has been used to account for some of the observations found for the reaction under various conditions such as: kinetic resolution of racemic α-fluoroaldehydes, non-linear effects and mono- *vs*. di-fluorination.

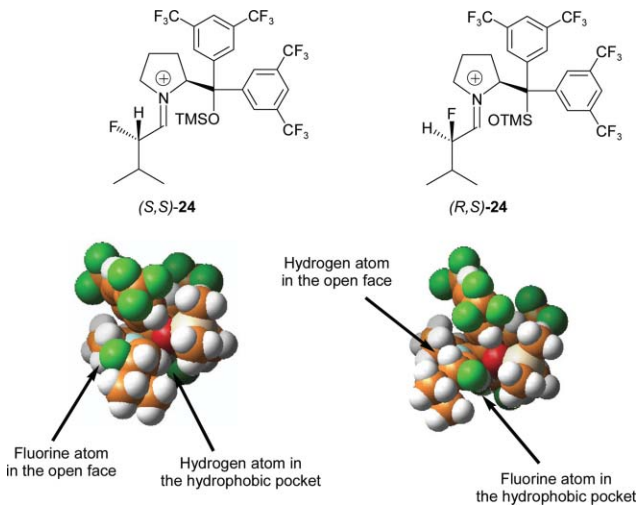
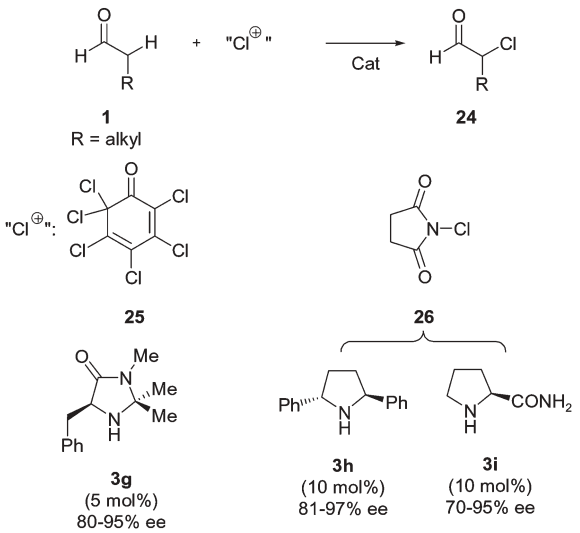



**Fig. 7** DFT-optimized structures of the iminium-ion intermediates (*S*,*S*)-**24** and (*R*,*S*)-**24**.

The direct enantioselective organocatalytic α-fluorination can also take place using cinchona alkaloids as the catalyst under phase-transfer reaction conditions.[29] The fluorination reaction of α-ketoesters, readily enolizable substrates, generated a stereogenic quaternary C–F bond in high yields and with enantioselectivities up to 69% ee.

## Chlorination

The direct enantioselective α-chlorination of aldehydes was also developed independently by two groups and published within very short time in 2004. MacMillan *et al*. applied the salt of the chiral imidazolidinone **3g** as the catalyst, as L-proline turned out to be a poor chiral catalyst for the electrophilic chlorination of the electron-rich enamine intermediate (Scheme 11).[30a] Various chlorinating reagents were tested and it was found that the perchlorinated quinone **25** gave the best enantioselectivity. The reaction proceeded in a




**Scheme 11** Organocatalytic enantioselective α-fluorination of aldehydes.

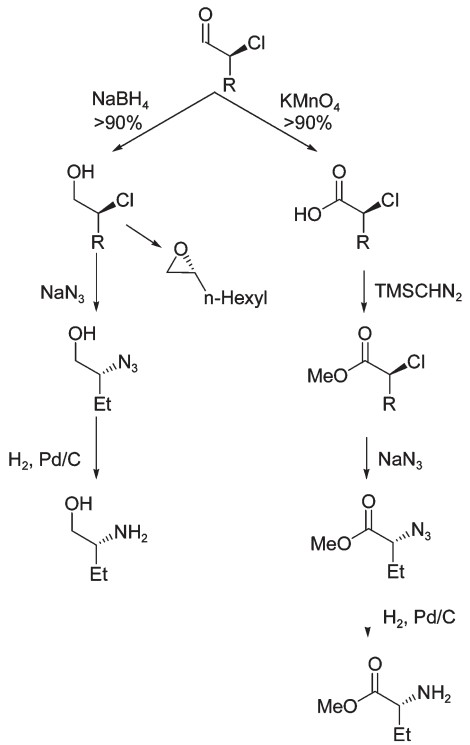
variety of different solvents and it was demonstrated that a number of linear aldehydes could successfully be α-chlorinated in good to high yields and with enantioselectivities in the range of 80–95% ee.

The other development for the direct enantioselective α-chlorination of aldehydes reported by us differed from the first one in several ways: the catalysts used for the α-chlorination reaction were the $C_2$-symmetric (2*R*,5*R*)-diphenylpyrrolidine **3h** and L-proline amide **3i** and the electrophilic chlorinating reagents was *N*-chlorosuccinimide (Scheme 11).[30b] Both chiral amines were effective catalysts for the α-chlorination reaction and the optically active products **24** were obtained in high yields with **3h** giving the highest enantiomeric excess (81–97% ee) compared to **3i** (70–95% ee).

The synthetic utility of the organocatalytic α-chlorination of aldehydes was demonstrated by the preparation of chiral building blocks by a variety of different transformations (Scheme 12).[30b] The α-chloroaldehydes could be reduced to the corresponding optically active α-chloroalcohols in more than 90% yield maintaining the enantiomeric excess using $NaBH_4$. It was also shown that optically active 2-aminobutanol, a key intermediate in the synthesis of tubercolustatic ethambutol, could be obtained in high yields by standard transformations from 2-chlorobutanol. Furthermore, the synthesis of an optically active terminal epoxide was demonstrated. The 2-chloroaldehydes could also be oxidized to α-chlorocarboxylic acids in high yields without loss of optical purity and further transformations were also presented.

The mechanism for the $C_2$-symmetric (2*R*,5*R*)-diphenylpyrrolidine **3h** catalyzed α-chlorination of aldehydes has been investigated from both an experimental and theoretical point of view.[31] One reason for these investigations was that the DFT-optimized chiral enamine intermediate **27** shown in Fig. 8 did not provide any face-shielding.

In an attempt to account for the high enantioselectivity observed in these α-chlorination reactions it was postulated that the reaction might proceed *via* an initial kinetically controlled *N*-chlorination giving **28** followed by a




**Scheme 12** Various transformation of optically active α-chloroaldehydes.

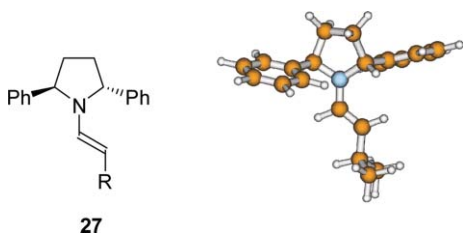
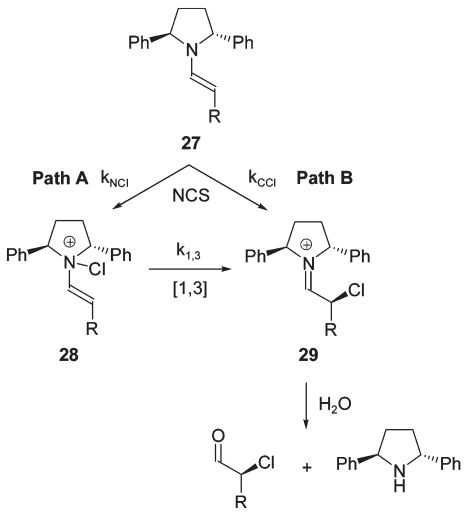



**Fig. 8** DFT-optimized structure of enamine intermediate in the organocatalytic α-chlorination of aldehydes using **3g** as the catalyst (R = *i*-Pr).

[1,3]-sigmatropic shift leading to the energetically favourable catalyst-iminium intermediate **29** (path A in Scheme 13), rather than the direct formation of **29** (path B in Scheme 13).[31] Based on a series of DFT-calculations of transition states structures, it was shown that *e.g.* the [1,3]-sigmatropic rearrangement was favoured for the formation of the observed absolute configuration of the α-chlorinated product. Furthermore, a series of experimental investigations, which included labelling studies of the enamine intermediate, kinetic studies, chlorination with various electrophilic chlorinating reagents and non-linear investigations, showed that the reaction mechanism outlined as path A in Scheme 13 could not be excluded.[31]

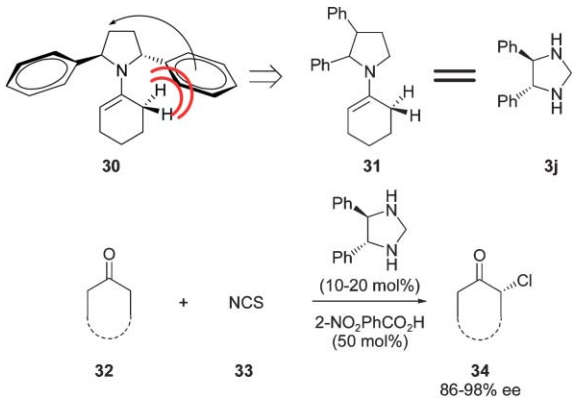
Several attempts were performed to extend the knowledge from the α-chlorination of aldehydes to ketones. However, the use of the most successful catalysts, (2*R*,5*R*)-diphenylpyrrolidine **3h** and L-proline amide **3i**, gave for the latter moderate yield and 81% ee due to polychlorination, while no conversion was observed for the former catalyst.[32] A possible explanation for the unsuccessful results for the $C_2$-symmetric catalyst could



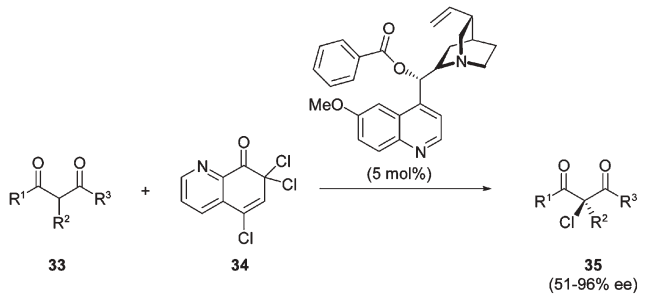

**Scheme 13** Possible mechanism(s) for the α-chlorination of aldehydes catalyzed by $C_2$-symmetric (2*R*,5*R*)-diphenylpyrrolidine **3h** *via* intermediate **27**.

be that the formation of the enamine intermediate **30** (Scheme 14) is not possible due to steric repulsion between the α-hydrogen atoms and the phenyl ring in the catalyst. It was demonstrated that moving the phenyl ring as indicated in Scheme 14 could solve the problem and the application of the $C_2$-symmetric 4,5-diphenylimidazoline **3j**, in combination with 2-nitrobenzoic acid as a rate-accelerating additive, gave a catalytic system which proved to be very useful for the α-chlorination of both cyclic and acyclic ketones (Scheme 14).[32] The scope of the direct enantioselective α-chlorination showed that the optically active α-chloroketones were obtained in 86–98% ee, with the highest enantioselectivity for the cyclic ketones.

Various transformations of the optically active α-chloroketones were presented;[32] *e.g.* 2-chlorocyclohexanone (92% ee) underwent a Baeyer–Villiger oxidation to the corresponding lactone in 81% yield maintaining the enantiomeric excess, and the ketone functionality was selectively reduced to the corresponding *syn*-α-chloroalcohol with high diastereomeric ratio.




**Scheme 14** Model for the development of the catalyst for the α-chlorination of ketones.




**Scheme 15** Organocatalytic α-chlorination of β-ketoesters using benzoylquinidine as the catalyst.

Bartoli, Melchiorre *et al*. have used cinchona alkaloids as the catalyst and trichloroquinolinone **34** as the chlorinating reagent for the direct α-halogenation of 1,3-dicarbonyl compounds **33** (Scheme 15).[33] This reaction is based on the same concept outlined in Scheme 3. Various acyclic and cyclic β-dicarbonyl compounds could be α-chlorinated in moderate to good yield. The enantioselectivity was very dependent on the substrate with the cyclic β-ketoesters giving the highest enantiomeric excess (90–96% ee), while the acyclic β-ketoesters and β-dicarbonyl compounds gave enantioselectivities in the range of 51–89% ee. The best catalyst was benzoylquinidine and the reaction scope was further extended to also include enantioselective bromination using tribromoquinolinone as the brominating reagent.

The formation of stereogenic C–Cl, as well as C–Br bonds in the α-position to a carbonyl functionality can also be carried out in an indirect manner *via* a ketene, which is accessed from acyl chlorides using a resin-bound phosphazene base, a chiral nucleophilic organocatalyst, in the form of a cinchona alkaloid and a halogenation agent such as **25**.[34] This procedure developed by Lectka and co-workers is an ingenious reaction process for the formation of α-chloro-, as well as, α-bromoesters with excellent enantioselectivity.

An interesting approach to the formation of optically active α-chloroesters has been presented by Reynolds and Rovis.[35] It was discovered that 2,2-dichloroaldehydes reacted with phenols in the presence of chiral triazolinylidenecarbenes to form the α-chloroesters in good yields and with high enantioselectivities.

### Bromination

Aldehydes and ketones can also be directly α-brominated using the catalytic concepts presented in Schemes 11 and 14.[36] For the bromination, the easily synthesized and air-stable 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone turned out to be the best reagent for the functionalization of aldehydes (enantioselectivities in the range from 68–96% ee) and for preparation of the optically active α-bromoketones (73–94% ee).

It should be noted that (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine **3b** was also found to be a very efficient catalyst for the α-bromination of aldehydes using 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone as the brominating reagent.[6] Various aldehydes were α-brominated in good yield and in 94–95% ee.

## Sulfenylation reactions

Chiral compounds having a free thiol functionality are very interesting because often they are potent inhibitors of zinc-containing enzymes.[37] One of the possible strategies for the preparation of α-sulfenylated compounds is the $S_N2$ reaction of thiols with α-halogenated carbonyl compounds. However, the preparation of optically active α-sulfenylated aldehydes has been always the result of multistep procedures.

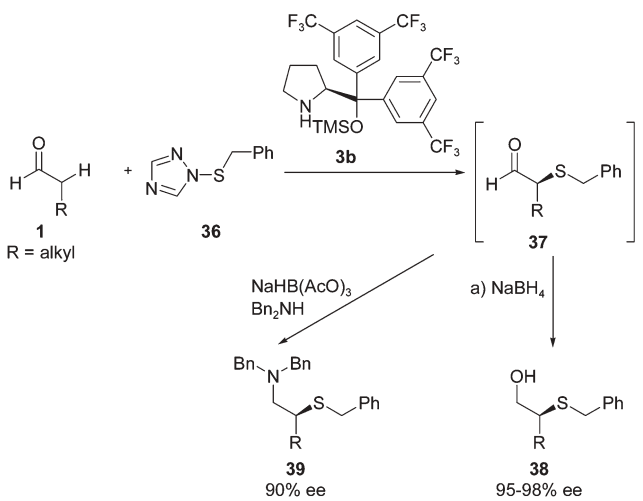
Obviously, a direct catalytic enantioselective approach to these synthetic targets would be preferable but it has been until recently neglected. In 2004, Wang *et al.* using catalyst **3e** achieved an achiral sulfenylation of aldehydes and ketones using commercially available electrophilic sulfur sources.[38]

Almost contemporarily, we presented the first enantioselective version of this transformation.[39] For a simpler optimization of the reaction conditions and an easier manipulation of the products, we extended the list of existing sulfenylating agents by preparing 1-benzylsulfanyl-1,2,4-triazole **36**. Application of (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine **3b** to the reaction of **36** with aldehydes **1** resulted in a highly enantioselective process (Scheme 16)[39] and the absolute configuration of the products was in agreement with the model previously discussed.

The products of the reaction could be quantitatively transformed into compounds **38** by reduction with $NaBH_4$. The optically active aminothiol precursor **39** was instead isolated after application of the conditions used by MacMillan and co-workers[15] for the reductive amination of the sulfenylated products **37** even if a partial racemization was observed. The preparation and use of **36** was justified by the simple deprotection of the benzyl group that led to the free thiol functionality using $Na/NH_3(l)$.

The more sterically demanding α,α-disubstituted aldehydes could be efficiently sulfenylated but with lower enantiomeric excess (61% ee) when the same catalyst was used.

Compound **36**, along with some other structurally related sulfenylating agents, has also been found to be useful for the functionalization of 1,3-dicarbonyl compounds. Lactones and



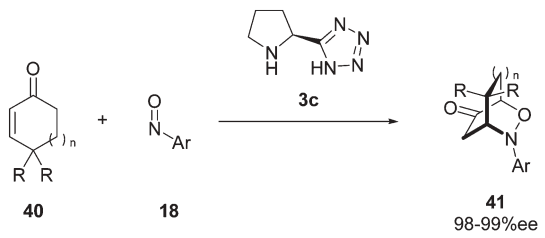

**Scheme 16** Organocatalytic enantioselective α-sulfenylation of aldehydes.

β-dicarbonyl compounds were α-sulfenylated in the presence of $(DHQD)_2PYR$ in high yields and moderate to good enantioselectivities (51–89% ee).[40]

## Miscellaneous reactions

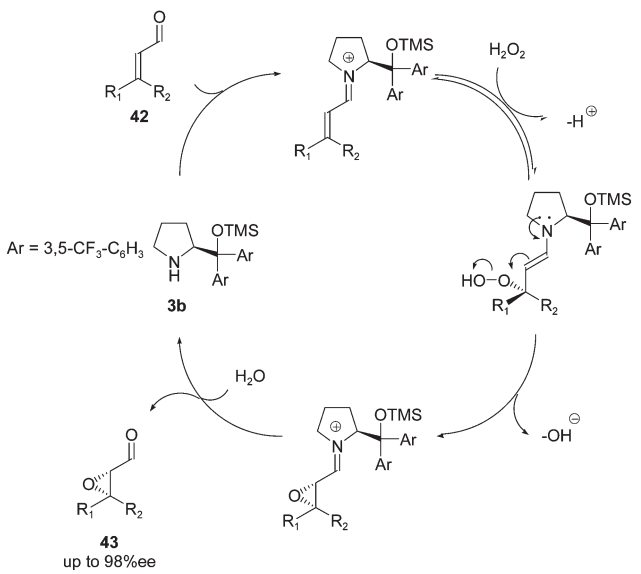
In this section of the feature article we will introduce how the formation of a stereogenic C–X bond adjacent to a carbonyl functionality can be controlled through multicomponent/domino reactions that lead to more complex products.

Yamamoto *et al.*[41] made another important contribution to the chemistry of nitrosobenzene by disclosing a new enantioselective hetero-Diels–Alder reaction of **40** (Scheme 17). The reaction was suggested to occur by a stepwise process. First, the catalyst controls the *O*-nitroso-aldol reaction by forming an enamine intermediate and then activates the intermediate for an intramolecular Michael reaction. The bicyclic product **41** was obtained in remarkably high enantiomeric excess using alternatively catalyst **3c** or L-proline **3a**.




**Scheme 17** Organocatalytic *O*-nitroso aldol/Michael reaction of α,β-unsaturated enones.

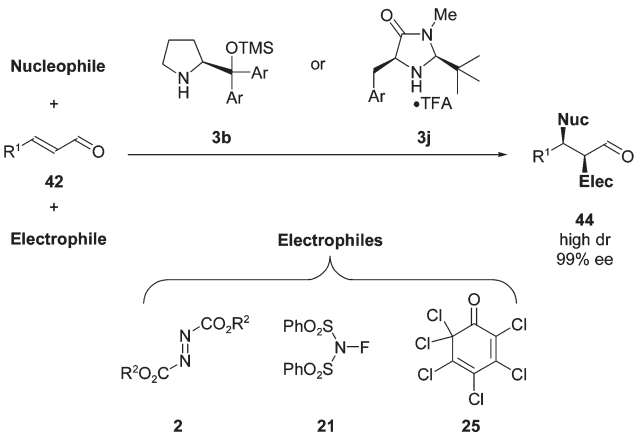
Recently, we developed a related strategy for the achievement of a highly diastereo- and enantioselective epoxidation of α,β-unsaturated aldehydes **42** (Scheme 18).[42] The reaction works well in a variety of organic solvents, but it is interesting to underline the fact that excellent enantioselectivities can also be achieved in particularly benign conditions such as $H_2O$–EtOH mixtures.[42b]




**Scheme 18** Organocatalytic epoxidation reaction of α,β-unsaturated aldehydes with hydrogen peroxide.

The mechanism of the reaction deserves particular attention since catalyst **3b** controls the formation of both stereocenters fixing the geometry of the intermediates and providing a very efficient face-shielding. In the first step, hydrogen peroxide acts as the nucleophile in the conjugated addition to the acrolein derivatives **42** activated by the catalyst through an iminium-ion intermediate. The final product was obtained after the intramolecular nucleophilic attack by the enamine intermediate to the electrophilic peroxygen atom.

MacMillan's group[43] and we[44] have also recently produced contemporaneous reports on the application of this sequential activation to multicomponent/domino reactions (Scheme 19).




**Scheme 19** Organocatalytic multicomponent/domino reactions of α,β-unsaturated aldehydes with different nucleophiles and electrophiles.

We demonstrated that catalyst **3b** was able to promote the reaction of α,β-unsaturated aldehydes **42** with a variety of thiols and with azodiazocarboxylate **2** as an electrophilic nitrogen source. MacMillan *et al.* successfully applied catalyst **3j** to the same type of transformations, choosing for example different aromatic π-nucleophiles or the Hantzsch ester for the conjugate addition step, and the electrophilic halogen sources **21** or **25** for the α-heteroatom functionalization.

It is important to highlight that in all the cases, using any of the two catalysts presented in the two distinct articles, in a variety of solvents and conditions, the optical purity of the product is essentially always as high as 99% ee. This fact certainly suggests that catalyst **3b** or **3j** could be useful for an even larger number of combinations of nucleophiles and electrophiles.

In summary, this feature article has demonstrated the tremendous developments in direct organocatalytic α-heterofunctionalization of carbonyl compounds which have taken place in the last few years. It is now possible to perform the direct amination, oxidation, fluorination, chlorination, bromination and sulfenylation with very high enantioselectivities. Furthermore, it has also been shown that the optically active compounds formed in these reactions can be used for the formation of important chiral building blocks and in the synthesis of important biologically active compounds. Moreover, the next stage in organocatalysis has also been

presented – the use of chiral amines to control multi-component/domino reactions with very high stereoselectivities.

## Acknowledgements

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