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PERSPECTIVE

Bioinspired organocatalytic asymmetric reactions

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Several small organic molecule catalysts are reminiscent of natural enzymes in their mode of action and substrate interaction/activation. This striking similarity has been a great source of inspiration for the development of new organocatalytic asymmetric processes. A few representative examples, mostly dealing with catalysts interacting through multiple hydrogen-bonds (synthetic oxyanion holes), are highlighted in this perspective.

Introduction

Catalytic technologies occupy a prominent role in the development of sustainable synthetic chemistry.[1] Catalysis is not however a human invention, as catalytic transformations have occurred in Nature for millions of years. Evolution through natural selection has indeed provided living beings with an astounding set of catalysts, mostly macromolecular entities such as enzymes. The mimicking of enzymatic catalysis by artificial structures is one of the most fascinating and provocative challenges presented by Nature to chemists. Examination of chemical building blocks, modes of substrate activation, and biosynthetic pathways in Nature provide insights for achieving similar transformations.[2] Even the renaissance of organocatalysis can partly be ascribed to efforts made to develop synthetic low molecular weight catalysts that mimic the characteristic of enzymes and biomolecules.[3] This branch of research may therefore be coined, according to Schreiner, with the notion 'hunt for the smallest enzymes'. This paper highlights various bioinspired approaches towards mostly hydrogen-bond directed organocatalysis, and their applications to name reactions in organic chemistry, emphasizing the way in which the operational mode of various kinds of organocatalytic species relates to that of their biocatalytic equivalents.

Synthetic oxyanion holes

A commonly accepted paradigm in biocatalysis is the ability of enzymes to bind transition states and intermediates in preference to either starting materials or products.[4] An emblematic example is given by the ubiquitous enzymatic oxyanion holes. A typical feature in many enzyme-catalyzed reactions, such as hydrolase, lipase, protease and esterase, is that a high-energy tetrahedral intermediate bearing a negatively charged oxygen ("oxyanion") must be stabilized by hydrogen-bonding in the active site. For this task a simultaneous donation of two (or more) hydrogen-bonds has proven to be highly successful, as shown in Scheme 1 for a serine protease. The mechanism of these enzymes involves an Asp–His–Ser catalytic triad, and an oxyanion hole formed by protons of amide moieties in the backbone pointing into the active site cavity.[3i,5]

In simple terms, an enzymatic oxyanion hole binds an oxyanion through multiple hydrogen-bonds, stabilizing it. For decades artificial receptors have been developed exploiting the same principles for the recognition of anions (*i.e.* multiple weak interactions giving geometrically defined, strongly bound complexes). The rationalisation of the similarities between the mode of action of organic hydrogen-bond donor catalysts and natural oxyanion hole containing enzymes made it possible for chemists to utilise a wide range of synthetic receptors matching the requirements for anion binding, providing the basis for the development of new organocatalytic species.[3l,6] In particular, due to their capability to simultaneously donate two hydrogen-bonds and to their favourable geometrical arrangement, species such as (thio)ureas,[7] guanidinium ions[8] and squaramides[9] have been proven to possess high potential as privileged (chiral) catalyst structures.[10]

Exploiting some of these synthetic oxyanion hole analogues, the mimicking of the active site of hydrolytic enzymes leads to the synthesis of catalysts featuring outstanding activity and turnover. For example, the trifunctional organocatalyst **1** reminiscent the active site of serine lipase has been designed and synthesized in which a hydroxyl group acting as a nucleophile, a pyridine moiety as a base, and a (thio)urea group as an oxyanion hole to stabilize the carbonyl oxyanion in the transition state are present (Scheme 2).[11] Organocatalyst **1** shows high catalytic activity *via* the acyl-catalyst intermediate CF_3CO_2-**1**, with up to a 3 700 000-fold acceleration and high turnover in the acyl-transfer reactions from vinyl trifluoroacetate to alcohols with the three functional groups working cooperatively to stabilize the transition state and accelerating the reaction.

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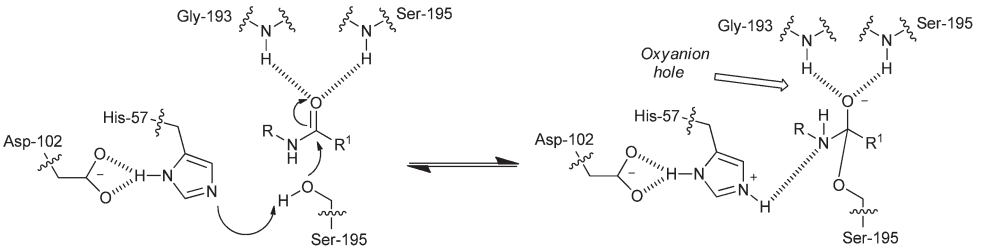
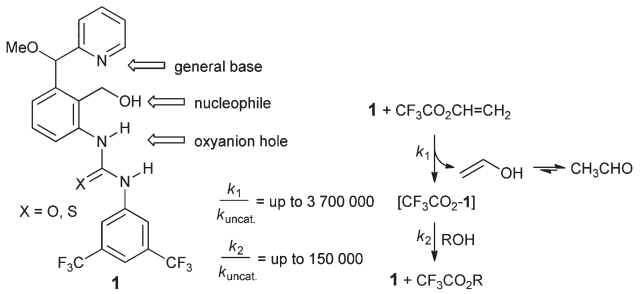


Scheme 1 The oxyanion hole in the active site of serine protease enzymes.



Scheme 2 Mimicking the active site of serine protease enzymes.

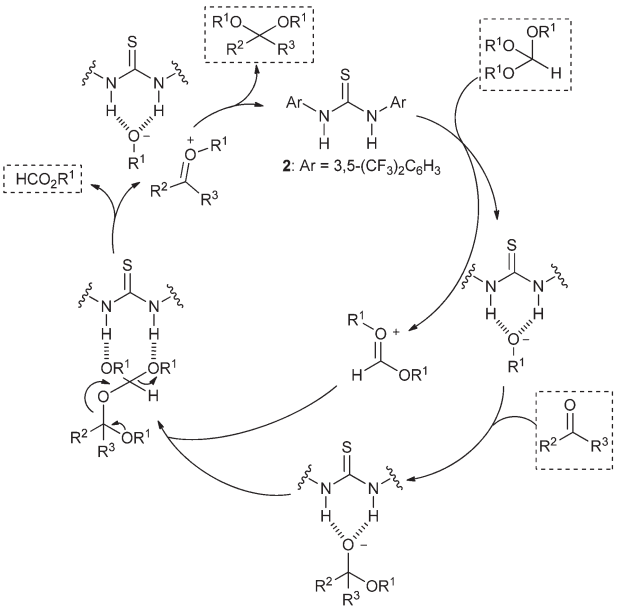
One important reason for the success of this class of catalysts lies in their hydrogen-bond ability not only to carboxylic or carbonylic oxyanions but also to a variety of reactants and intermediates. For example, the hydrogen-bond ability of thiourea to different oxyanions has been clearly demonstrated in a highly efficient thiourea-catalyzed acetalization of carbonyl compounds proceeding through thiourea **2** assisted orthoester hydrolysis and multiple oxyanion stabilization, as shown in Scheme 3.[12] A considerable high turnover frequency around 600 h^{-1} and catalyst loading down to 0.01 mol% are assets of this reaction. The proposed mechanism clearly marks the departure from the frequently implied concept of carbonyl or imino activation through hydrogen-bonding catalysts and expands the 'oxyanion stabilization' concept suggesting both hydrogen-bond assisted generation of the free anionic nucleophile, as well as counterion binding of the electrophile.[13]

On the other hand, after pioneering studies by Jacobsen and coworkers established its effectiveness and generality,[7b,14] the appropriate incorporation of the (thio)urea motifs as well as of other double hydrogen-bond donors in acylic and cyclic chiral frameworks has become one of the prevailing strategies in the design of a number of organocatalytic species for asymmetric transformations. In particular, the introduction of basic moieties, typically tertiary amines, suitable to convey a dual activation mechanism (Fig. 1) has also proved to be highly successful for the development of new catalytic asymmetric transformations.

The recognition, besides the oxyanion, of different anions such as nitronate, carboxylate and enolate by these organocatalytic species allows the accomplishment of a range of highly enantioselective reactions taking place under mild conditions and simple operational modes.[15]

Decarboxylative additions

In Nature, malonic acid half thioesters (MAHTs) serve as thioester enolate equivalents and are used in the biosynthesis of fatty



Scheme 3 Thiourea **2** catalyzed acetalization.

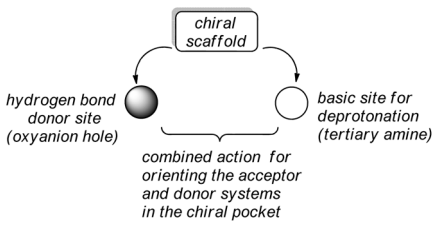
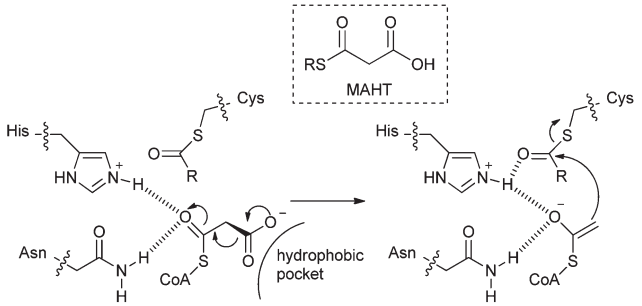


Fig. 1 Oxyanion holes embedded in a bifunctional catalytic system.

acids and polyketides in all kingdoms of life. The activation and reaction of MAHTs is achieved by polyketide synthases (PKSs) which lack metal ions and have in common amino acids such as cysteine, histidine and asparagine in their active sites. Within the catalyst triad, the activation of the CoA-bound deprotonated MAHT that reacts upon decarboxylation with a second cysteine-bound thioester, is performed by the histidine–asparagine motif, which binds the thioester and stabilizes the enolate, combined with a lipophilic pocket embedding and destabilizing the carboxylate (Scheme 4).[16] In order to delocalise the developing negative charge into the π-system of the thioester, decarboxylation requires a specific conformation of MAHTs. Remarkably, in the enzymatic machinery this conformation triggering CO_2 loss is reached only when the electrophile is also present in the active site.



Scheme 4 PKS Claisen condensation.

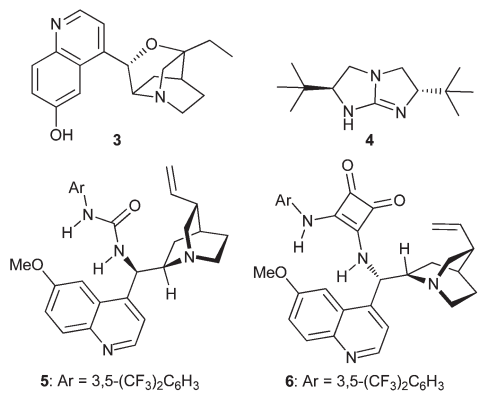


Fig. 2 Bifunctional catalysts used in MAHT organocatalytic reactions.

Resorting to decarboxylation, instead of deprotonation, PKSs exploit the thermodynamic driving force provided by the loss of CO_2 to generate enolates under mild conditions, overcoming the low acidity of acetate thioesters.[17] The potential of this strategy has been appreciated by synthetic chemists for many years,[18] and has also been applied in asymmetric catalysis using chiral Lewis acids.[19] It was only more recently that this mechanism of activation of MAHTs in the active site of PKSs, inspired several attempts aimed at designing metal-free catalysts able to mimic the biological process. The formation in the presence of bifunctional catalysts **3–6** (Fig. 2) of tight chiral ion pairs and the recognition of the reaction partners by the hydrogen-bond donor sites, co-operate to achieve the formation of an activated highly organized chiral environment in which weak interactions play a major role.

In particular, Mannich,[20] Michael,[21] amination[20b] and aldol[22] reactions have been developed delivering a range of synthetically useful products in enantioenriched form, with variable results in terms of yields and enantioselectivities (Scheme 5). The first examples, appearing already in 2007, described a Mannich[20a] and a Michael[21a] addition to nitroalkenes. Both reports are limited to α-unsubstituted MAHTs and use *Cinchona* alkaloid derived catalysts **3** and **5**. More recently, both scope (*i.e.* use of α-substituted MAHTs) and stereoselectivity in the Mannich reaction could be consistently improved by using the more basic chiral guanidine **4** as the catalyst, which was also successfully applied to the first catalytic asymmetric amination reaction.[20b] The employment of the squaramide derivative **6** allowed instead a substantial improvement in the Michael addition to nitroalkenes,[21b] together with the development of the first aldol reactions using isatins as acceptors.[22]

It was initially assumed an operational mode of these organocatalytic species closely paralleling the mechanism proposed for PKSs, *i.e.* decarboxylative enolate formation followed by addition (Schemes 4 and 6).

This hypothesis was based on the observation of substantial MAHT decarboxylation in the absence of an electrophile, and of the lack of reactivity of both an esterified MAHT and *S*-phenylthioacetate.[20a]

However, more recent kinetic and computational studies strongly indicate a divergent pathway for organocatalytic decarboxylative reactions, at least for aldol and Mannich type additions.[20b,23] In this newly proposed scenario, which parallels the mechanism of Lewis acid catalyzed transformations of MAHTs,[19] a fast and possibly reversible addition is followed by a slow, irreversible decarboxylative step (Scheme 7).

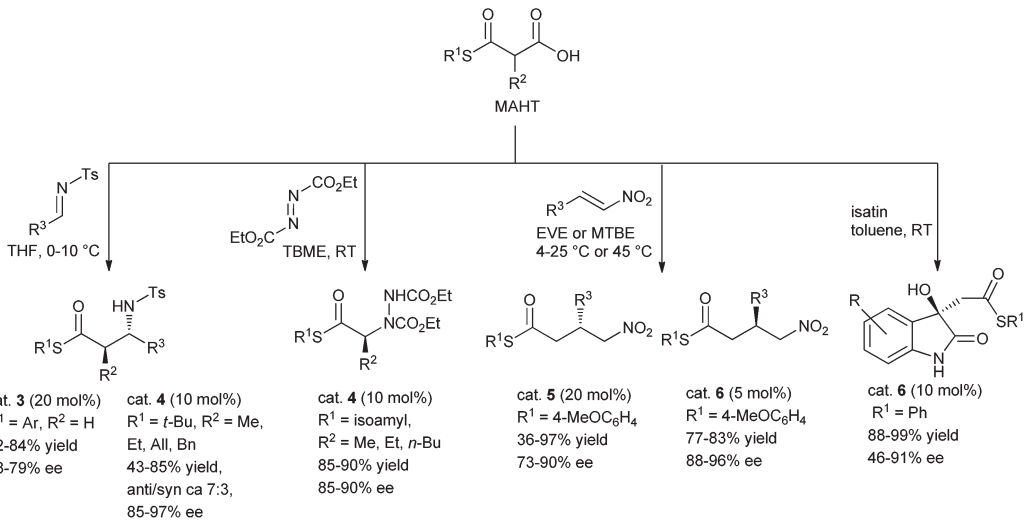
It is worth noting that substituents at the 2-position of MAHTs seem to have a major impact on reaction pathway, possibly accelerating the decarboxylative step.[24] Furthermore, electronic tuning of the substituent at this position can eliminate the necessity of resorting to decarboxylation for enolate generation with an organic base. The pK_a of some α-aryl thioesters is in fact low enough (*ca.* 16–18) to allow their direct use in organocatalytic protocols.[25]

Pericyclic reactions

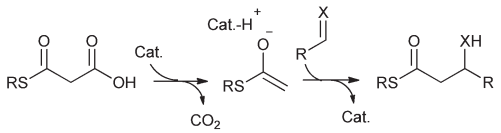
Diels–Alder cycloadditions

Speculations about the origin of many natural compounds and metabolites have lead to propose the [4 + 2] Diels–Alder cycloaddition reaction as a key transformation in their biosynthesis.[26] Theoretical support to the feasibility of this pericyclic reaction in biological settings has also been provided through the theozyme approach.[27] However, mechanistic ambiguities in some presumed Diels–Alderase catalyzed reactions,[28] together with the multi-catalytic activity shown by (often impure) putative Diels–Alderase,[29] has rendered elusive until very recently[30] the unambiguous detection and identification of an enzyme tailored for the catalysis of this [4 + 2] pericyclic reaction.

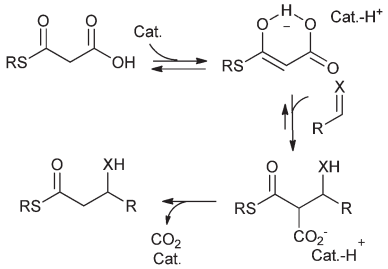
Diels–Alder reactions proceed through highly ordered transition state involving a large negative $\Delta S^{\ddagger}$ (*ca.* −30 to −40 kcal mol^{-1}).[31] Therefore, despite the mentioned elusivity, enzymes should be proficient in its promotion, as their ability to bind the substrates steering them in the right conformation for reactivity results in a large $\Delta S^{\ddagger}$ gain.[32] These considerations have in fact led to the development of artificial biomolecules (ribozymes,[33] catalytic antibodies,[34] and more recently a *de novo* developed enzyme[35]), able to efficiently catalyze Diels–Alder reactions. Initially chosen for its synthetic utility and the accessibility of a suitable hapten mimicking the reaction transition state,[36] the cycloaddition between *N*-carbamoyl-1-azadienes and *N*,*N*-dimethylacrylamide has been the benchmark for antibody catalyzed Diels–Alder reactions (Scheme 8). Besides the entropy gain, it was soon recognised that hydrogen-bond interactions giving transition state stabilization are essential for antibody activity. X-ray structure of an inhibitor-bound antibody,[37] and computational modeling on small models combined with flexible



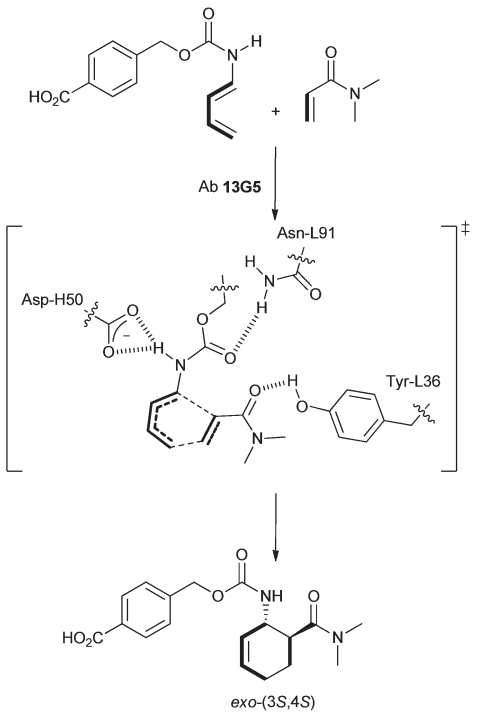
Scheme 5 Organocatalytic asymmetric decarboxylative reactions using MAHTs.



Scheme 6 Initially assumed reaction pathway.



Scheme 7 Plausible reaction pathway.



Scheme 8 Antibody **13G5** catalyzed *exo*-Diels–Alder reaction.

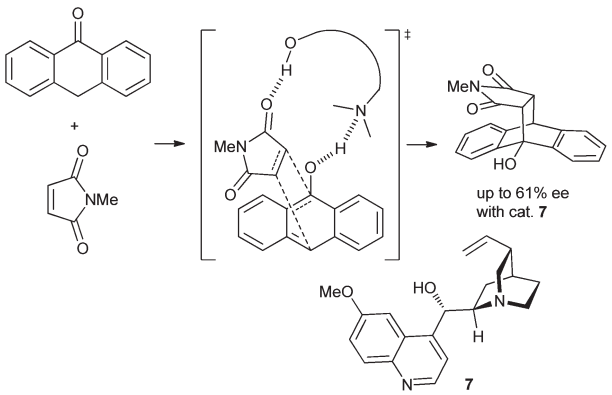
docking,[38] led to envisage a cooperative multiple hydrogen coordination to both diene and dienophile. As exemplified for *exo*-Ab **13G5**, in the transition state, the Brønsted acidic phenol of Tyr-L36 residue stabilizes the negative charge at the acrylamide, while the carboxylate of Asp-H50 binds the positively charged carbamate proton (Scheme 8). Similar considerations have been used as a starting working hypothesis for the remarkable *de novo* preparation of an artificial Diels–Alderase enzyme.[35]

As a rough picture, antibodies catalyze Diels–Alder reactions by simultaneously raising the HOMO of the diene and lowering the LUMO of the dienophile through a bifunctional acid–base mechanism. This binding is particularly relevant in the transition state, wherein charges are much more pronounced and thus interactions are strengthened. Often unconsciously, the same concept has been used in the past few years in several organocatalytic asymmetric Diels–Alder reactions.[39] It is worth noting that the conventional approach to catalytic enantioselective Diels–Alder reactions has been the exclusive activation of the dienophile through the use of a (chiral) Lewis acid, without considering diene activation/coordination.[40]

The challenge in the development of organocatalytic Diels–Alder reactions proceeding through this bifunctional activation has been in fact the identification of suitable diene systems.[41] Anthrones possess the right requisites. It has long been recognised that organic bases can promote their reaction with maleimides, proceeding through a [4 + 2] cycloaddition pathway.[42] Based on these observations, natural *Cinchona* alkaloids such as quinidine **7** and synthetic catalysts as chiral bases were later explored, giving the corresponding cycloadducts with moderate

stereoselectivities (Scheme 9).[43] Already from the first examples, it was understood that a bifunctional activation, due to hydroxy moieties in the catalyst, was operative in these reactions.

Only more recently, along with the flourishing of bifunctional organocatalysis, have two efficient catalytic processes for this cycloaddition reaction been developed.[44] In both reports the pericyclic nature of the reaction was demonstrated, and the cycloadducts were obtained with excellent stereoselectivities from anthrone and a range of maleimides. The optimal catalyst was the bicyclic guanidine **8** in one case, and the thiourea derivative **9** in the other (Fig. 3). The possible occurrence of divergent reaction pathways (*i.e.* Michael additions) when maleimides were substituted with less symmetrical electrophiles such as nitroalkenes was also studied.



Scheme 9 Diels–Alder reaction of anthrones with maleimides.

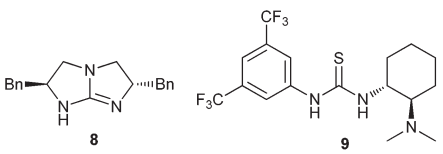


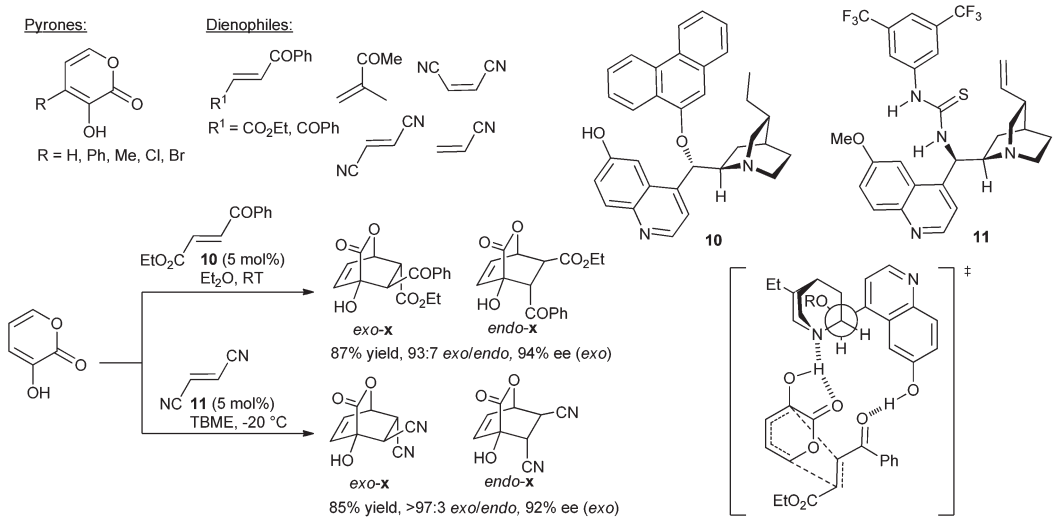
Fig. 3 Most efficient catalysts for the Diels–Alder cycloaddition of anthrones with maleimides.

Another class of dienes suitable for base coordination/activation are 3-hydroxy-2-pyrones and the related pyridones. As for anthrones, although reports from the mid 90s had demonstrated their potential in asymmetric base catalyzed cycloaddition using natural *Cinchona* alkaloids,[45] it was not until 2007 that a truly synthetically useful catalytic asymmetric protocol appeared in the literature.[46] The reported protocol is effective for several diene–dienophile combinations, encompassing different ketones and nitrile activated double bonds (Scheme 10). The catalysts derived from *Cinchona* alkaloids need however to be tuned depending on the class of substrate used, as shown for two representative examples in Scheme 10. On the basis of literature precedents and on reaction stereospecificity, a concerted [4 + 2] reaction pathway delivering the *exo* adduct was proposed, involving bifunctional activation of both diene and dienophile, at least in the case of ketone acceptors. In contrast, a more recent report on the cycloaddition reaction of the same 3-hydroxy-2-pyrones with nitroalkenes, catalyzed by a similar catalytic system, was found to proceed through a stepwise pathway (*i.e.* addition followed by cyclization).[47]

A catalytic asymmetric protocol was also developed for the related 3-hydroxy-2-pyridones.[48] The catalyst of choice turned out be the aminoindanol derivative **12**, which was able to promote the Diels–Alder cycloaddition between different pyridones and maleimides or vinylketones, delivering the corresponding products with very good results (Scheme 11).

Exclusively the *endo* cycloadducts were obtained when maleimides were employed, whereas *endo*/*exo* mixtures were observed in the reactions with vinylketones. Interestingly, the same catalyst could also be successfully used in the *endo*-cycloaddition of 3-hydroxy-2-pyrones with maleimides.

The catalytic asymmetric cycloaddition reaction of 3-vinylindoles[49] with activated dienophiles, such as maleimides and quinones, was also reported (Scheme 12).[50] Exclusively *endo* cycloadducts were obtained, in generally good yields and enantioselectivities. Simple product manipulations, such as H-shift

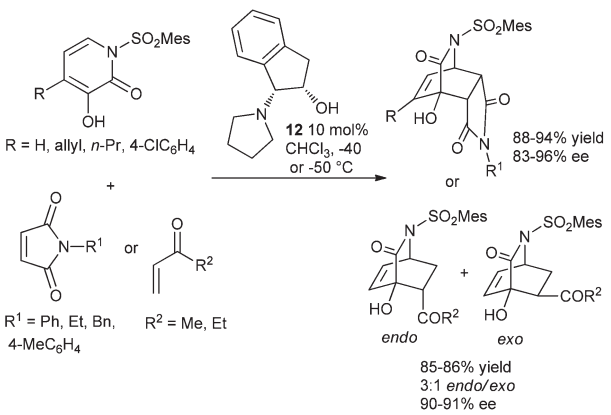


Scheme 10 Diels–Alder reactions of 3-hydroxy-2-pyrones catalyzed by **10** or **11**.

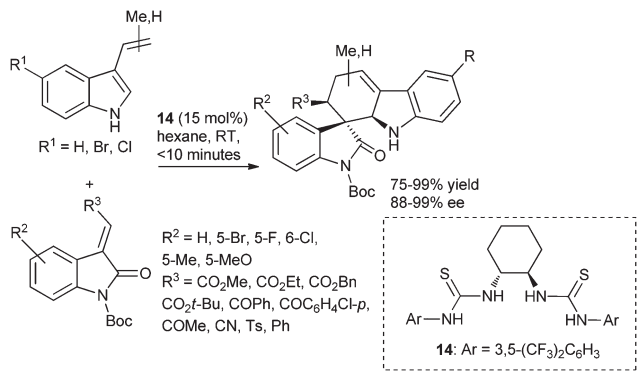
giving rearomatisation on the cycloadduct, reduction of the double bond, or H-shift followed by decarboxylation under forcing conditions, were also performed delivering enantioenriched indolines and tetrahydrocarbazoles. Based on the very low enantioselectivity observed when swapping the indole N–H proton for a Boc or a tosyl group, a multicentre coordination/stabilization of the reaction transition state by the bifunctional catalyst **13** was postulated.

The dienes described before (anthrones, pyrones and pyridones) possess a rather acidic hydroxy enol-like proton. It can be assumed that the coordination of a base to this proton renders these dienes reactive enough for the cycloaddition, in a way which is reminiscent of an enolisation process. Indeed, many of these processes can be catalyzed by simple bases (*e.g.* Et_3N),[41] without requiring an acidic activation. In this respect, the Diels–Alder cycloaddition reaction of 3-vinylindoles is substantially different. This very electron-rich diene cannot be subjected to base activation in its ground state, and cannot thus be coordinated by the catalyst prior to the cycloaddition reaction. Reacting with dienophiles through a late transition state, cycloaddition reactions of this diene bear considerable resemblance to antibody catalyzed Diels–Alder reactions of 1-azadienes (Scheme 8).[51] Similarly to antibody **13G5**, the bifunctional thiourea catalyst **13** has coordinating moieties (the tyrosine and the aspartate residues in Ab **13G5**, the thiourea and the tertiary amine in **13**) with the right geometry to interact with one of the two enantiomeric transition states. Incidentally, both dienes feature the same atom connectivity.

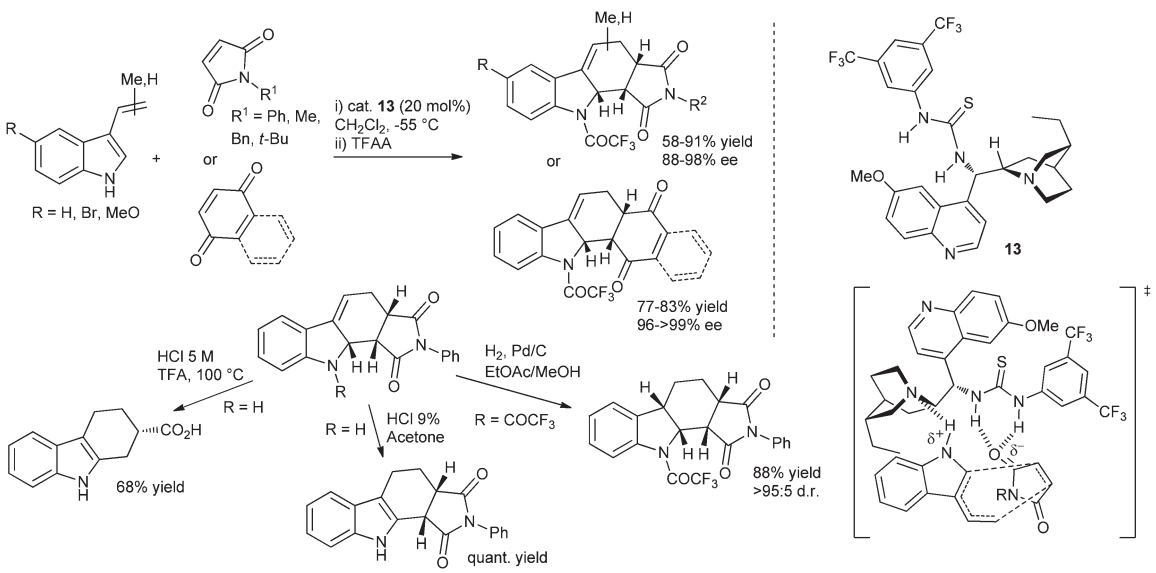
However, it was recently reported that even a catalyst at first sight lacking a basic moiety, such as the bis-thiourea **14**, is able to promote very efficient Diels–Alder reactions of 3-vinylindoles.[52] In particular, cycloadditions with methyleneindolinones furnished biologically interesting spirocyclic oxindoles with excellent enantioselectivities (Scheme 13). Remarkably, reactions were performed at room temperature and went to completion in just a few minutes. Despite the apparent monofunctional character of the catalyst **14**, the indole N–H was again found to be essential for enantioselectivity. A reliable model justifying the reaction outcome could thus not be defined.



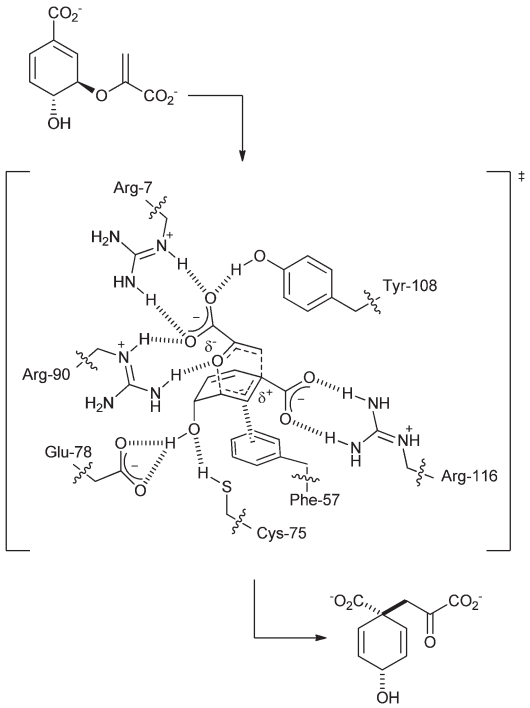
Scheme 11 Diels–Alder reactions of 3-hydroxy-2-pyridones.



Scheme 13 Diels–Alder reactions of 3-vinylindoles with methyleneindolinones.



Scheme 12 Diels–Alder reactions of 3-vinylindoles with maleimides and quinones.



Scheme 14 Claisen rearrangement by chorismate mutase enzymes.

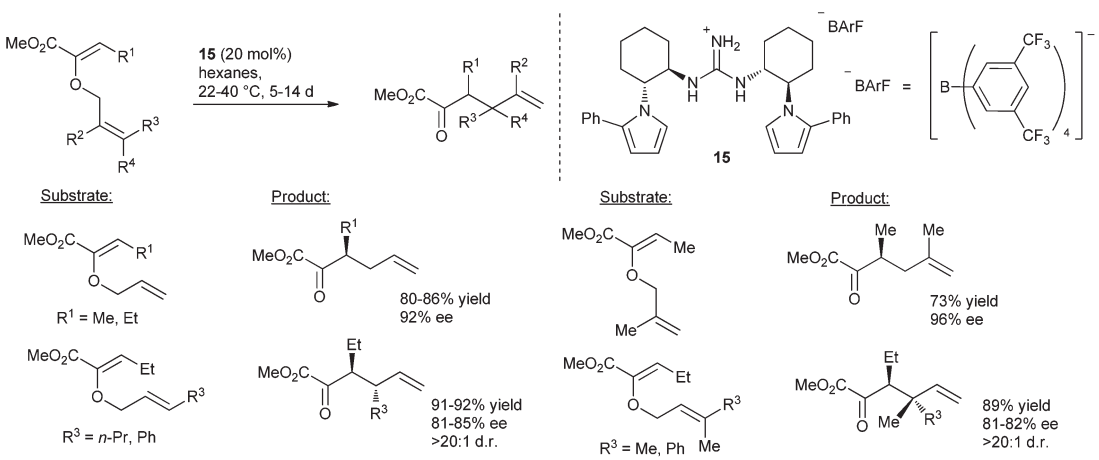
Claisen rearrangements

As part of the Shikimate pathway, the [3,3]-sigmatropic Claisen rearrangement of chorismate to prephenate is catalyzed by chorismate mutases (Scheme 14). The outstanding rate acceleration provided by these enzymes (10^6) has been proposed to derive from multiple non-covalent interactions, which not only coordinate and position the substrate in the right conformation for rearrangement, but are also able to stabilize developing charges in the transition state.[53] Transition state stabilization is due to positively charged arginine residues and, intriguingly, to the phenyl group of a phenylalanine giving a π-interaction with the positively charged double bond. Remarkably, organocatalytic Claisen rearrangements involve a catalyst featuring a guanidinium ion in combination with an aromatic system, as summarised below.

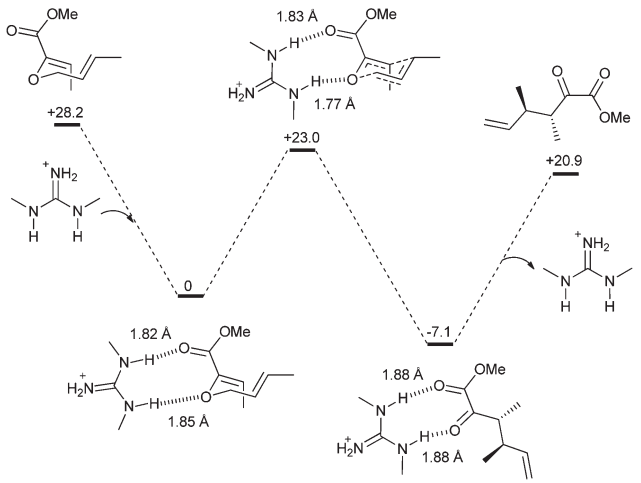
In 2008, the first catalytic enantioselective Claisen rearrangement based on hydrogen-bond donor catalysts was reported.[8g] Considering the known rate acceleration of Claisen rearrangement by protic solvents[54] and by stoichiometric amounts of ureas,[55] a study was undertaken on the use of chiral double hydrogen-bond donors such as thioureas as catalysts for this reaction.

However, it was not until the focus was moved to guanidinium ions bearing non coordinating counterions as hydrogen-bond donors, that a significant catalytic effect in model Claisen rearrangements was observed. Ester substituted allyl vinyl ethers turned out to be suitable substrates for the development of an enantioselective version of this rearrangement. Employing the guanidinium catalyst **15** in hexanes, several rearranged products could be obtained with moderate to good enantioselectivities. The pericyclic nature of the Claisen rearrangement, wherein a chair-like transition state is highly favoured, gives complete diastereocontrol when terminal asymmetrically substituted allyl moieties are used (Scheme 15).

To understand the origin of the activity and selectivity displayed by the guanidinium catalyst **15**, a detailed mechanistic investigation was undertaken.[56] Kinetic studies indicated a first-order dependence on the total catalyst concentration and saturation behaviour in the substrate. A 2.3 kcal mol^{-1} lowering of the activation free energy at 328 K by the catalyst in the Claisen rearrangement could also be estimated from these data, corresponding to about 250-fold rate acceleration. Computational studies (DFT) on a simplified model catalyst suggested the following reaction pathway (Scheme 16). Coordination of the catalyst to carbonyl and ether oxygens favours the s-*cis* conformation, which undergoes rearrangement. Interestingly, the calculated length of the hydrogen-bond between the catalyst and the ether oxygen shortens in the chair-like transition state (1.77 *vs.* 1.85 Å), strongly suggesting electrostatic stabilization of the developing negative charge at this oxygen. Besides, product binding is only slightly disfavoured, compared to the substrate. A small catalyst inhibition effect by the product was in fact observed.



Scheme 15 Catalytic asymmetric Claisen rearrangement: representative examples.



Scheme 16 Calculated pathway with a simplified catalyst. Energies are given in kcal mol^{-1}.

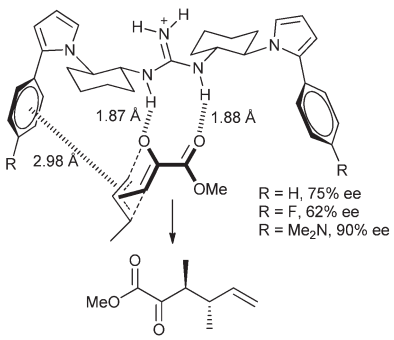
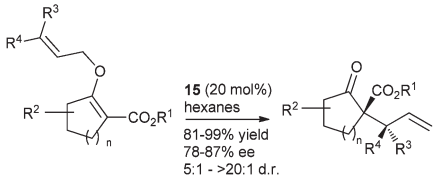


Fig. 4 Calculated transition state and phenyl substituent effect. Distances refer to the structure with R = H.



Scheme 17 Claisen rearrangement of β-ketoester derivatives.

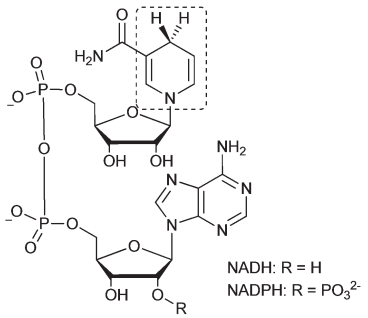


Fig. 5 NADH and NADPH cofactors.

A catalytic enantioselective Claisen rearrangement of another class of substrates, delivering 2-allyl β-ketoesters, was developed using the parent guanidinium catalyst **15** (Scheme 17).[58] The method proved to be very general, as a broad range of cyclic β-ketoesters featuring different ring sizes and substitution patterns could be employed. More importantly, the pericyclic nature of the rearrangement, giving a chair-like six-member transition state leading to predictable diastereoselectivities, was exploited for the preparation of several branched allylated β-ketoesters, not readily obtainable in a regio- and diastereo-controlled fashion through standard allylation processes (*i.e.* R^3 and/or $R^4 \neq H$ in Scheme 17).

After the binding of the substrate in its ground state was defined by NMR, a model justifying the stereoselectivity observed was targeted by computational means considering the full catalyst structure. The computed model involves stabilization of the transition state delivering the product with the observed stereochemistry, not only thanks to the coordination of the guanidinium ion with the oxygen atoms, but also to a π-interaction between the phenyl pyrrole substituent of the catalyst and the positively charged allyl fragment (Fig. 4). This additional interaction is not present in the transition state leading to the disfavoured enantiomeric product. It provides approximately 0.7 kcal mol^{-1} energy stabilization contributing to the overall 2.29 kcal mol^{-1} calculated energy difference between the two stereoisomeric transition states. The similarity between the mode of action of this catalyst in the Claisen rearrangement, and the description of chorismate mutase activity (Scheme 14), is remarkable. To further prove the role of this unusual π-interaction,[57] structural modifications at this aryl group of the catalysts were experimentally investigated. Indeed, better enantioselectivities were observed by increasing the electron-donating properties of this moiety, as expected, thus ultimately leading to the disclosure of a more selective catalyst.

Hydride reductions

In Nature, transfer hydrogenation processes are ubiquitous, and are typically mediated by the dihydropyridine-containing co-factor NADH (nicotinamide adenine dinucleotide) or by its phosphate analogue NADPH (Fig. 5), associated with enzymes. Aromatisation to the corresponding pyridine (NAD^+ or $NADP^+$) is the thermodynamic driving force promoting the hydride transfer. However, as for MAHTs, these cofactors are kinetically stable and require an enzymatic system for their activation.

Nature's hydrogenation mechanism involving NADH can be exemplified by the glutamate dehydrogenase-catalyzed reductive amination of 2-ketoglutarate, which represents one of the most powerful transformations for the rapid introduction of stereogenic C–N bonds. The catalytic active site of the enzyme contains different amino acids. Asp-165 has a fundamental role in the reduction process, by coordinating the α-iminoglutarate formed from ammonia and 2-ketoglutarate (Fig. 6).[59] The possibility that the conceptual blueprint of biochemical transfer hydrogenation might be employed in a chemical asymmetric reduction wherein enzymes and co-factors are replaced by small

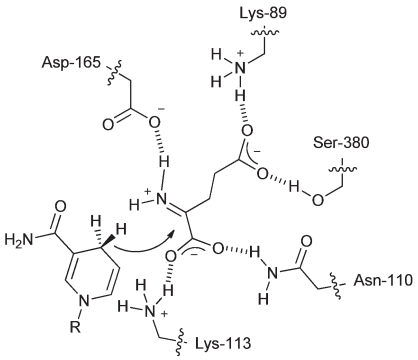


Fig. 6 Enzymatic reductive amination of 2-ketoglutarate.

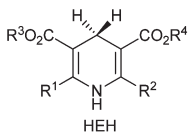


Fig. 7 Hantzsch ester structure.

molecules organocatalysts and reagents has been taken into consideration.

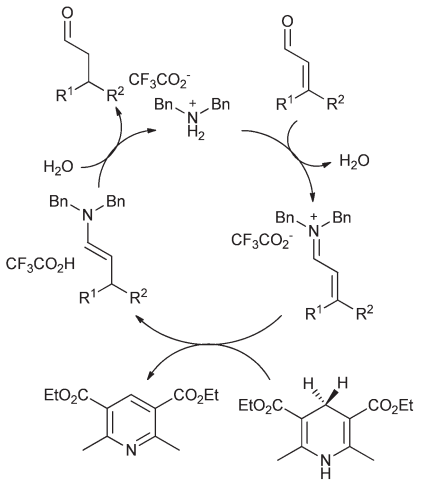
Analogous to Nature's NADH, Hantzsch esters (HEHs)[60] (Fig. 7) have been shown to serve the role of small molecule NADH analogues given that the dihydropyridine system participates in hydride delivery with electrophilic π-systems in a variety of non catalytic processes. Also due to their rapid synthetic access, HEHs have served as a powerful platform for the development of a large number of reductive organocatalytic processes in the last few years, and perhaps represent the most successful and broadly applied example of a bioinspired catalytic manifold. A detailed description of the many organocatalytic reactions involving these dihydropyridines is however beyond the scope of this perspective.[61]

Despite the analogies between HEHs and NADH cofactors, the first employment of HEHs in organocatalytic settings dealt with a transformation which does not have a close biological counterpart, such as the metal-free reduction of α,β-unsaturated aldehydes.[62]

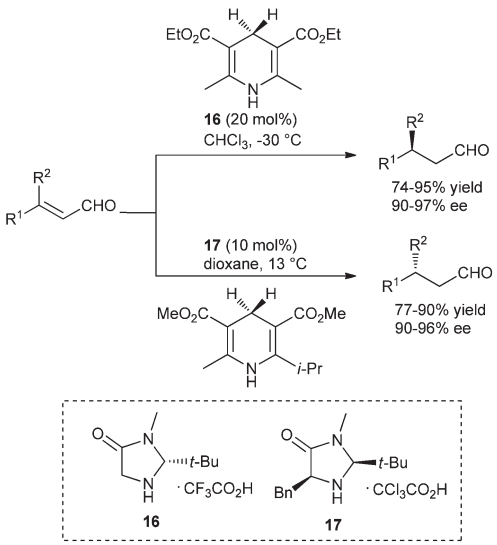
As shown in Scheme 18 for the non-asymmetric version of this reaction,[62a] exploiting the *in situ* formation of the corresponding iminium ion,[63] it was possible to devise the metal-free HEH mediated reduction of α,β-unsaturated aldehydes, in which an ammonium trifluoroacetate salt was applied as an activating agent lowering the LUMO of the acceptor.

Employment of enantiopure secondary amines, such the trichloro and trifluoroacetate salts **16** and **17** led to the development of asymmetric versions of this transformation (Scheme 19).[62b,c]

HEH reduction served also as a platform for the realisation of a novel mode of iminium activation termed asymmetric counteranion-directed catalysis (ACDC),[64] wherein the source of the asymmetry is located on the chiral anionic counterion, that residing in close contact with the activated iminium intermediate can provide a selective shielding to one of the two prochiral faces of the LUMO-lowered iminium system, followed by



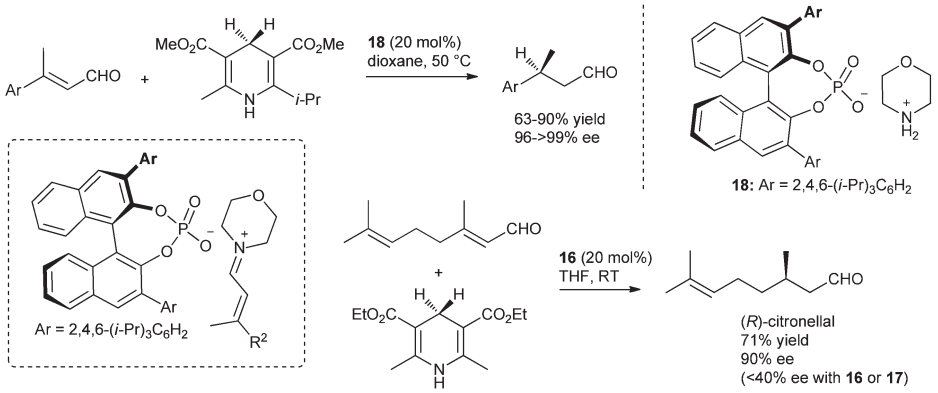
Scheme 18 Metal-free reduction of α,β-unsaturated aldehydes with HEH.



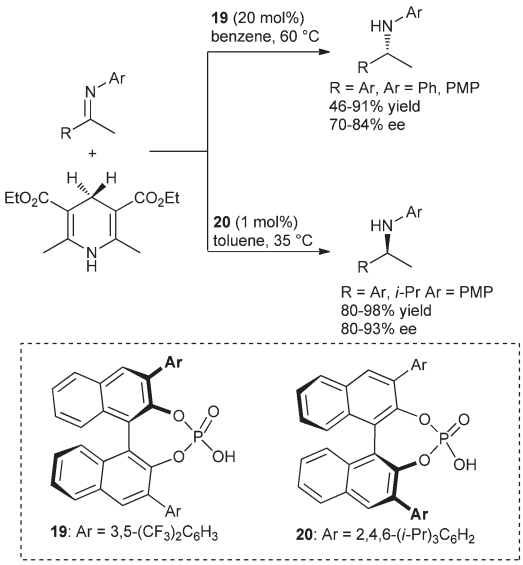
Scheme 19 Catalytic asymmetric reductions of α,β-unsaturated aldehydes.

enantioselective interception of a hydride from the HEHs. To this purpose, the most effective secondary amine–chiral counterion resulted from the combination of a BINOL phosphoric acid[65] and morpholine (salt **18**, Scheme 20). Remarkably, with some substrates such as the citronellal precursor, catalyst **18** proved to be more enantioselective than the chiral secondary amines **16** and **17** previously employed.

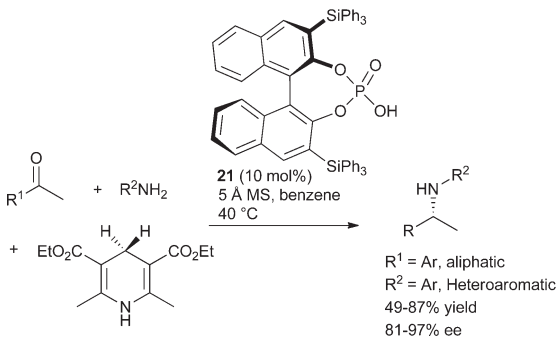
Several HEH-based approaches have been used for the metal-free asymmetric hydrogenations of C=N bonds. The reductive amination reaction represents one of the most widely utilised transformations for the rapid introduction of stereogenic C–N bonds. Nature has perfected this reaction as a powerful *in vivo* chemical tool for the enantioselective synthesis of essential amino acids *via* selective reduction of hydrogen-bond activated pyruvate-derived ketimines, as shown for the reduction of 2-ketoglutarate imine described above (Fig. 6). Biomimetic organocatalytic reductions of C=N double bonds based on the



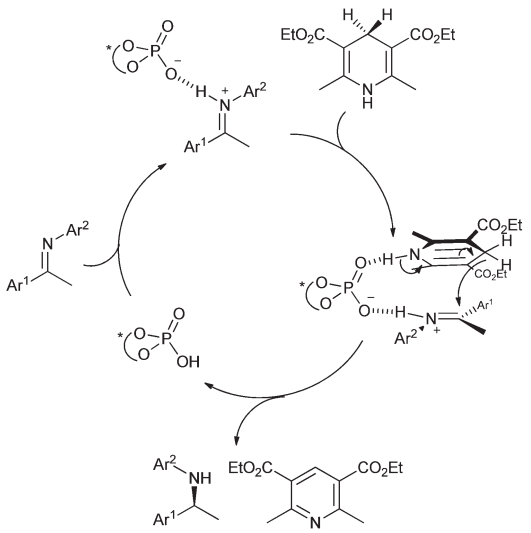
Scheme 20 Asymmetric counterion-directed catalysis (ACDC) in the reduction of α,β-unsaturated aldehydes.



Scheme 21 Biomimetic asymmetric reduction of ketimines.



Scheme 22 Reductive amination catalyzed by **21**.



Scheme 23 Reaction pathway in the biomimetic reduction of ketimines.

conceptual blueprints displayed in the corresponding biochemical process were devised (Scheme 21).[65c,66] The action in NADH of the nucleosidic element that enables molecular recognition of a specific enzymatic environment wherein selective reaction might occur, in the biomimetic process was effected by Brønsted acid catalysts such as **19** and **20**, and HEH was used as an NADH analogue (Scheme 21).

A reductive amination strategy, avoiding imine preformation, was also developed.[67] While thiourea and taddol based organocatalysts failed to induce reductive amination, the BINOL phosphoric acid **21** afforded in high yields and moderate to excellent enantioselectivities the products of reductive amination in the reaction between a wide range of ketones and aromatic or heteroaromatic amines (Scheme 22).

Concerning the mechanism, a very close pathway with respect to that used in Nature's reductive amination by glutamate dehydrogenase was proposed[66] for the asymmetric transfer hydrogenation of C═N bonds in *N*-protected ketimines with HEHs using chiral BINOL-derived phosphoric acid catalysts (Scheme 23). Later computational studies[68] suggested the fundamental importance of a coordination by the phosphoryl oxygen, acting as a Lewis base, to the HEH NH proton, in order to achieve a highly organised transition state and consequently good stereocontrol.

The biomimetic organocatalyzed process, inspired by Nature's dehydrogenase, in which small molecules of organic catalysts and NADH analogues replace enzymes and co-factors can therefore be successfully applied to the asymmetric reduction of imines and activated olefins. Using HEHs as the hydride source

and organocatalytic species whose activation modes include hydrogen-bonding as well as iminium ion activation, various medicinally relevant amines, nitrogen-containing heterocycles as well as natural and bioactive products can be synthesized.

Conclusions

Many organic catalysts operate exploiting the same principles as enzymatic catalysis. For example, synthetic catalysts embedding double hydrogen-bond donors, such as (thio)ureas, guanidinium ion and squaramides, able to bind anions, are very proficient in the stabilization of negatively charged transition states and intermediates, in a similar way to oxyanion holes in natural enzymes. It is thus not surprising that substantial research has been directed at mimicking useful transformations taking place in biological settings, for the disclosure of tailored substrate–reagent–organocatalyst sets reflecting their natural substrate–cofactor–enzyme counterparts. Some representative examples are highlighted in this review. Since the employment of efficient oxyanion hole mimics is a relatively new field, a flourishing of new bioinspired transformations can be expected. Some newly developed hydrogen-shift processes, such as a catalytic asymmetric olefin isomerisation[69] reminiscent of ketosteroid isomerase, and an enantioselective transamination reaction inspired from α-amino acid biosynthesis[70] are significant in this respect. Besides, a large number of in-depth investigations on the mechanism of enzymatic transformations is available. This large amount of detailed information might give useful hints for better understanding reaction pathways and substrate coordination modes in the corresponding organocatalytic reactions.[71]

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