DOI: 10.1002/ejoc.200700021

Recent Advances in the Catalytic Asymmetric Nitroaldol (Henry) Reaction

Claudio Palomo,*[a] Mikel Oiarbide,[a] and Antonio Laso[a]

Keywords: Henry reaction / Asymmetric catalysis / Nitro compounds / C–C bond formation

Catalyst-controlled enantioselective nitroaldol (or Henry) reactions are presented. These reactions represent powerful C–C bond-forming tools and the resulting nitro alcohol (nitroaldol) products can be transformed into a number of nitrogen- and oxygen-containing derivatives (nitroalkenes, amino alcohols, amino acids etc.). In addition to substrate-controlled nitroaldol reactions (not covered), catalytic systems that provide good stereoselectivity have been developed in recent years. Through the use of preformed silyl nitronates as activated substrates, catalytic systems involving metallic Lewis acids or tetraalkylammonium salts have been deployed in fluoride-mediated nitroaldol reactions. In a further advance, catalytic systems capable of promoting direct nitroaldol reactions between unmodified nitroalkanes and aldehydes (ketones) with high yields and stereoselectivities have been developed. To this end, ambifunctional systems based on La, Zn, Cu, Co and Mg metal species are described, together with some organocatalysts.

Introduction

The nitroaldol or Henry reaction consists of the addition of a nitroalkane compound to the carbonyl group of an aldehyde or ketone. The reaction involves a reactive nitronate species, which can be generated in situ as part of

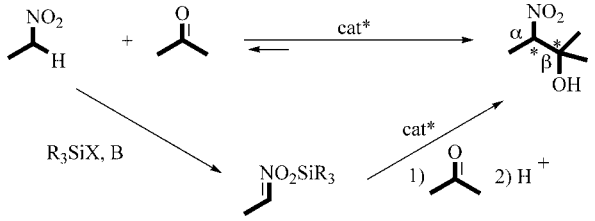
[a] Departamento de Química Orgánica I, Facultad de Química, Universidad del País Vasco,
Apdo. 1072, 20080 San Sebastián, Spain
Fax: +34-943015270
E-mail: claudio.palomo@ehu.es

Claudio Palomo was born in Barcelona in 1951. He studied chemistry at the Instituto Químico de Sarriá in Barcelona, where he received his Chemical Engineering Degree in 1975. He obtained his Licenciatura in chemistry in 1979 at the University of Barcelona. In the same year he joined the Organic Chemistry Department at the University of the Basque Country with Prof. R. Mestres. In 1983 he took his Ph.D. in Organic Chemistry and after two years of postdoctoral work at the same university, he became associate Professor. In 1989 he was promoted to full Professor in Organic Chemistry and two years later he joined the research group of Prof. H. Rapoport at the University of California at Berkeley as visiting professor. He has published more than 190 papers and reviews. Topics he is now interested in include asymmetric catalysis in organic synthesis, and the design and implementation of molecular entities with biological properties.

Mikel Oiarbide was born in 1963 and studied chemistry at the University of the Basque Country. He obtained his Licenciatura in 1986 and completed his Doctorate in 1991 with Prof. Palomo. After a two-year postdoctoral stay with Prof. H. Rapoport at the University of California at Berkeley, he joined the Department of Organic Chemistry at San Sebastián, where he was made associate Professor in 1994. In 2004 he was promoted to full Professor. His work main focus is asymmetric catalysis.

Antonio Laso was born in 1977 and studied chemistry at the University of the Basque Country. He obtained his Licenciatura in 2001 and completed his Ph.D. in 2006 with Prof. Palomo on the topic of asymmetric Henry and aza-Henry reactions. He is currently a postdoctoral associate in Prof. M. Shibasaki's group at the University of Tokyo.

the catalytic cycle through the action of a suitable catalyst. Alternatively, preformed nitronates, particularly silyl nitronate species, can be used (Scheme 1).[1,2] The principal interest of the nitroaldol products stems from the potential offered by nitro compounds for transformation into other compound families.[2c]



Scheme 1. Direct catalytic nitroaldol (Henry) reaction and its variant using trialkylsilyl nitronates (general pictogram).

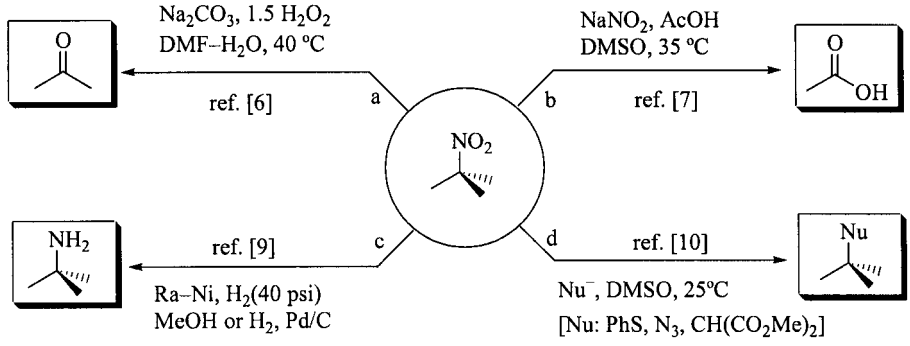
For many applications, nitro alcohol adducts are subjected either to subsequent dehydration reactions to afford conjugate nitroalkenes, which are important building blocks in synthesis,[3] or to oxidation of the carbinol group to provide the corresponding ketone, so stereogenicity at either C^{α} or C^{β} or at both positions is lost. In these instances the stereochemical outcome of the nitroaldol reaction becomes irrelevant. For many other applications, however, in which the newly formed C^{β} and/or C^{α} stereocentres are retained in the target molecules, control of the configuration at those stereocentres is crucial during the nitroaldol reaction. In particular, the nitro group offers versatile routes to other functionalities. The CH–NO_2 moiety in a nitroaldol product can thus be converted (Scheme 2) into the corresponding ketone, aldehyde or carboxylic acid[4] through Nef oxidation[5] (paths a[6] and b[7]), into an amino compound[8] through reduction (path c),[9] or into other derivatives through substitution of the nitro group by various carbon- and heteroatom-centred nucleophiles (path d).[10]

From a formal point of view, the nitroaldol reaction very closely resembles the aldol reaction, and the two are comparable in several aspects. Nevertheless, they have important distinguishable features that justify their unequal degrees of development. In particular, the field of stereoselective nitroaldol reactions has remained less studied in comparison with the wealth of methods for stereocontrolled aldol reactions.[11] An inherent limitation of the nitroaldol reaction in this respect is the lack of trivial points for covalent attachment of chiral auxiliaries in either the nitroalkane (nucleophile) or the carbonyl (electrophile) component.[12] Additional issues that often erode stereocontrol are the reversible natures of many nitroaldol reactions and the relatively ease with which racemisation of the carbon stereocentre located α to the nitro group can occur. Not surprisingly, catalyst-controlled asymmetric versions of the nitroaldol reaction were essentially undocumented until 1992, while three main reviews on catalytic asymmetric Henry reactions covering the literature up to 2003 have been published.[13] Since then, a meaningful number of papers dealing with new catalysts and concepts have appeared, making an update timely. The aim of this short review is to summarise these methods, from already well established systems to the most recent contributions in the field.

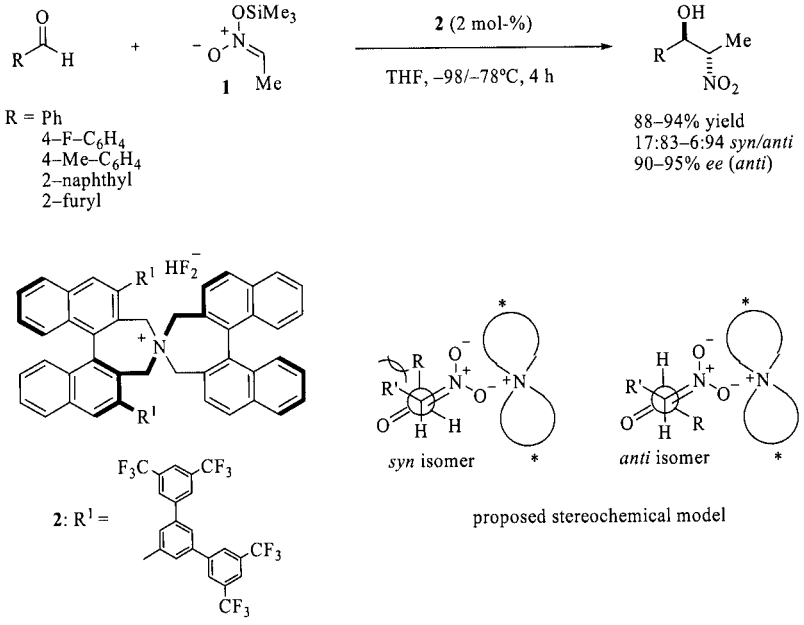
The use of chiral catalysts has advantages over substrate- or auxiliary-controlled reactions, since lower loadings of the (usually expensive) chiral nonracemic inductor are required. The catalytic methods so far documented in this context adhere to two different strategies: (i) those involving preactivation of the nitroalkane species in a previous step through irreversible and quantitative formation of the corresponding silyl nitronate, and (ii) direct nitroaldol reactions between unmodified nitroalkanes and aldehydes (ketones).

Catalyst-Controlled Asymmetric Nitroaldol Reactions of Preformed Silyl Nitronates

As a prior step to the nucleophilic attack of the nitro compound on the carbonyl group of an aldehyde or ketone, generation of the activated nitronate species is needed. In this respect, it was shown many years ago[14] that quantitative formation of a trialkylsilyl nitronate and subsequent treatment with an aldehyde in the presence of a fluoride ion source irreversibly gives the nitroaldol product. This approach offers a good platform for asymmetric implementation. Following this principle, Maruoka and co-workers[15] have shown quite recently that quaternary ammonium salt fluorides are effective promoters of reactions between silyl nitronates **1** and aldehydes. With use of only 2 mol-% of the chiral ammonium salt **2** (Scheme 3) the reactions between silyl nitronate **1** and aromatic aldehydes in THF at –98/–78 °C preferentially gave the *anti* nitroaldol adducts (up to



Scheme 2. The nitro group as a versatile source of other compound families.



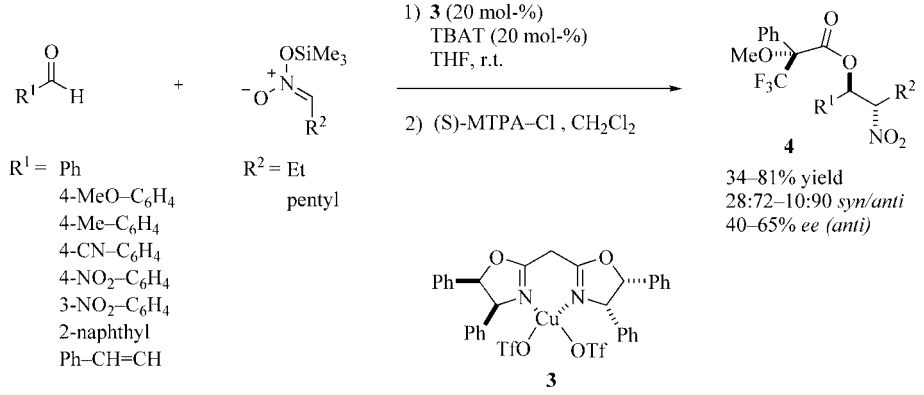
Scheme 3. Chiral nitroaldol reactions between nitroethane-derived silyl nitronates and aldehydes catalysed by ammonium salts.[15]

6:94 *syn*/*anti* ratios) in high yields and *ee* values, although aliphatic aldehydes did not give acceptable levels of diastereo- and enantioselectivity. Importantly, the nature of the trialkylsilyl group has a strong influence both on chemical yield and on selectivity: while trimethylsilyl (and triethylsilyl) nitronates gave very good results, the bulky *tert*-butyldimethylsilyl nitronates showed reduced efficiency. An acyclic transition state model predicting the formation of the *anti* adduct from the approaching reactant that displays the fewest *gauche* interactions has been proposed by the authors.

At almost the same time, Jørgensen[16] described *anti*-selective catalytic nitroaldol reactions between trimethylsilyl nitronates and aromatic aldehydes triggered by a combination of an achiral fluoride ion source and chiral metal complexes (Scheme 4). The catalytic system consists of a Cu^{II}–bis(oxazoline) complex as the chiral Lewis acid (20 mol-%), together with 20 mol-% of tetrabutylammonium triphenylsilyldifluorosilicate (TBAT) as fluoride ion source. The promoting system was able to function at room temperature and high *anti*/*syn* ratios were obtained, but both yields and *ee* values were only moderate. In order to avoid epimerization and retro-Henry reactions, adducts were transformed in situ into the corresponding Mosher esters **4**. Both Maruoka's and Jørgensen's methods are suitable for nitro compounds other than nitromethane, considerably expanding the potential of the Henry methodology.

Catalyst-Controlled Direct Asymmetric Nitroaldol Reactions

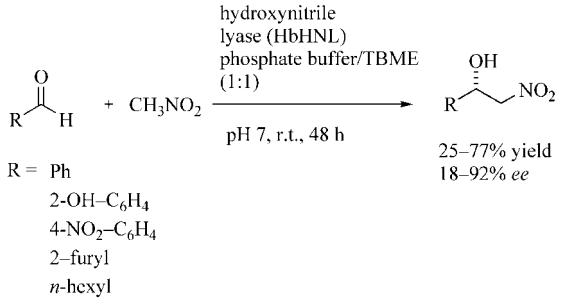
Methods that use unmodified nitroalkanes and acceptor carbonyls (aldehydes or ketones) to produce the product nitro alcohols in a single synthetic operation through the action of a catalytic species are preferable for obvious reasons. In these methods, nitroalkane activation by base-promoted hydrogen transfer must necessarily be part of the catalytic cycle, together with the activation of the acceptor



Scheme 4. Asymmetric nitroaldol reactions between nitropropane-derived trimethylsilyl nitronate and aromatic aldehydes catalysed by combined Cu^{II}–BOX and TBAT.[16]

carbonyl through coordination to an acidic centre. The breakthrough in this area came from Shibasaki's laboratory in 1992[17] and was based on bifunctional multimetallic catalysis.[18] In more recent years, purely organic molecules capable of catalysing chemical transformations (organocatalysis), usually working in the context of a cooperative activation principle model,[19] have also appeared. Both approaches – metal catalysis and organocatalysis – have been successfully applied in nitroaldol reactions, and the main contributions in this field follow. Methods belonging to the metal-catalysed group are categorised according to the metal involved.

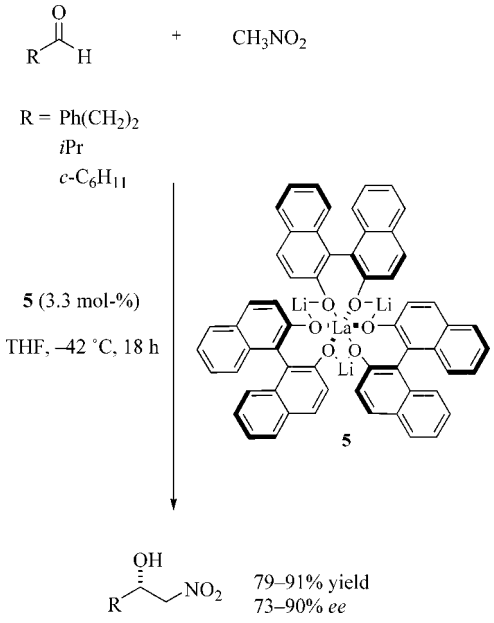
While no substantial research has been conducted on biocatalytic Henry reactions, a recent example by Griengl[20] described lyase-catalysed nitroaldol reactions between nitromethane or nitroethane and some aromatic aldehydes (Scheme 5). As often customary for processes involving enzymes, yields and selectivity were highly substrate-dependent, ranging from high enantioselectivities (92% and 89% *ee* values for benzaldehyde and *tert*-pentanal, respectively) to low (18% and 28% *ee* values for *m*-hydroxybenzaldehyde and *o*-nitrobenzaldehyde, respectively).



Scheme 5. Lyase-catalysed nitroaldol reactions in buffered media.[20]

Rare Earth Catalysis

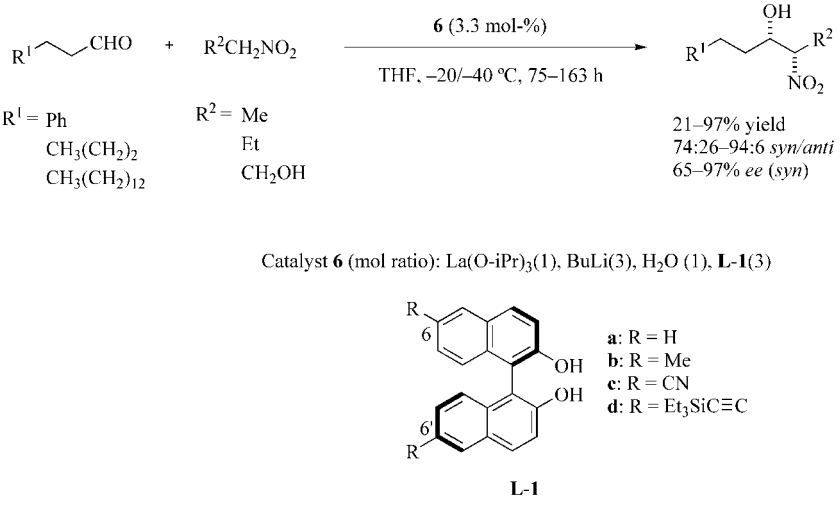
The first catalyst of this category to be designed was complex **5**, which promoted nitroaldol reactions of both nitromethane and other nitroalkanes with a variety of aldehydes with generally good or very good yields and enantioselectivities (Scheme 6).[17] It is believed that the lanthanum and the phenoxy-Li groups act in concert as the Lewis acid and the Brønsted base centres, respectively.[17c]



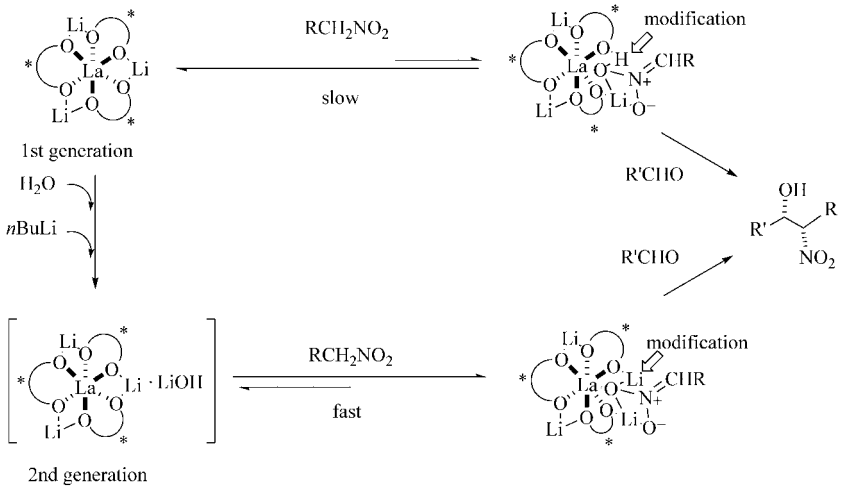
Scheme 6. Nitroaldol reactions catalysed by a heterodimetallic ambifunctional catalyst.[17a]

Further refinement of the catalyst was achieved through the insertion of substituents at the 6,6′-positions of the BINOL skeleton in **L-1**,[21] which resulted in improved enantio- and *syn*/*anti* selectivities (Scheme 7).[22] In this respect, insertion of Me groups at the 6,6′-positions (catalyst **6b**) did not afford any improvement, while insertion of groups such as CN (catalyst **6c**) and especially $R_3SiC{\equiv}C$ (catalyst **6d**) provided *syn*/*anti* ratios of up to 94:6 and *ee* values of up to 97%.

In subsequent studies it was found that alteration of the complex catalyst by addition of H_2O and BuLi, which



Scheme 7. Shibasaki's second-generation lanthanum-based catalysts for the Henry reaction.[22]



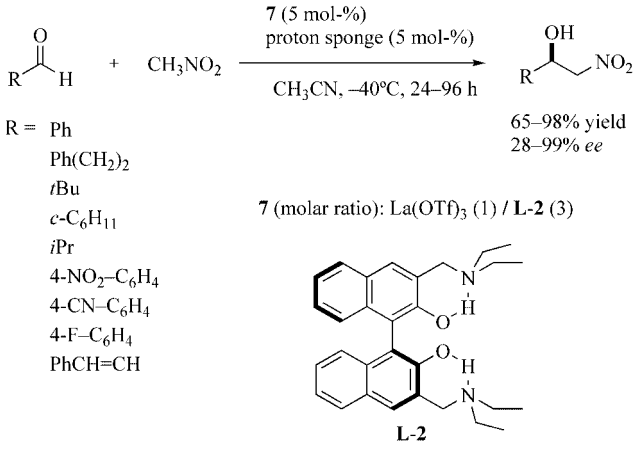
catalyst	R'	*T*(°C)	yield(%)	*syn:anti*	*ee*(%)
1st gen.	Me	–30	25	70:30	62
2nd gen.	Me	–30	83	89:11	94
1st gen.	Et	–40	<5	---	---
2nd gen.	Et	–40	84	95:5	95

Scheme 8. Explanation of the differential activities/selectivities of Shibasaki's first- and second-generation catalysts.[23]

forms LiOH, gave a more active catalyst, resulting in shorter reaction times.[23] This rate enhancement is attributed to faster nitronate formation through hydrogen transfer, which is believed to be the rate-limiting step of the catalytic cycle (Scheme 8).

More recently (Scheme 9), Saá and co-workers[24] have described the lanthanum-based bifunctional catalyst **7** for nitroaldol reactions, with the catalyst consisting of central La coordinated to three BINOL ligands that have been modified by attachment of aminoalkyl side chains at the 3,3′-positions. Although these complexes alone were able to catalyse the reactions, the authors found that addition of external strong bases, preferentially DBU and proton sponge, increased both reaction rate and selectivity. In general, aliphatic aldehydes gave the best yields and enantioselectivities (typically above 90%), while aromatic and α,β-unsaturated aldehydes were less efficient.

The development of nitroaldol methodologies well suited for ketones as carbonyl acceptors is more challenging, because of the attenuated reactivity of ketones and the strong tendency toward retro-nitroaldol reactions under basic conditions. Some favourable ketones such as α-keto esters, which are especially active, and in addition bear two coordinating atoms, have been investigated in the context of the catalytic Henry reaction[25] (vide infra). However, the implementation of methods suitable for simple ketones is particularly difficult even in racemic variants.[26] Recently, Shibasaki and Matsunaga have reported the first promising results in the area, involving the kinetic resolution of tertiary nitroaldols with BINOL/biphenol mixed La–Li heterobimetallic complexes as the catalytic resolution agent (Scheme 10).[27] Apparently, the best suited ketone nitro

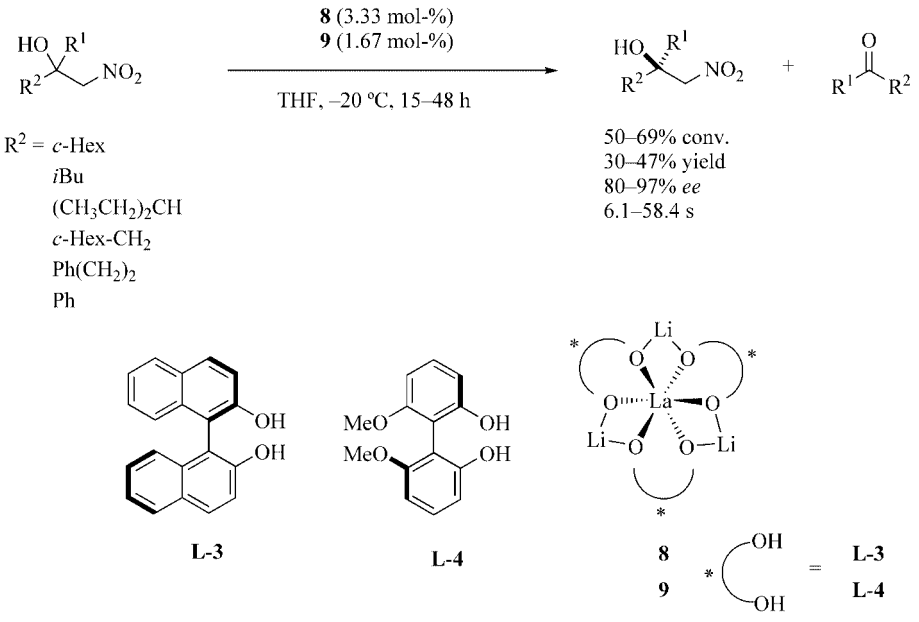


Scheme 9. BINOL ligands bearing aminomethyl side arms for the lanthanum-catalysed asymmetric nitroaldol reaction.[24]

alcohols are those with one (R^1) methyl group and another (R^2) branched chain alkyl group. The selectivity of the resolution process is also very sensitive with respect to the ratio of the complexes **8/9** added.

Zinc(II)-Based Catalysis

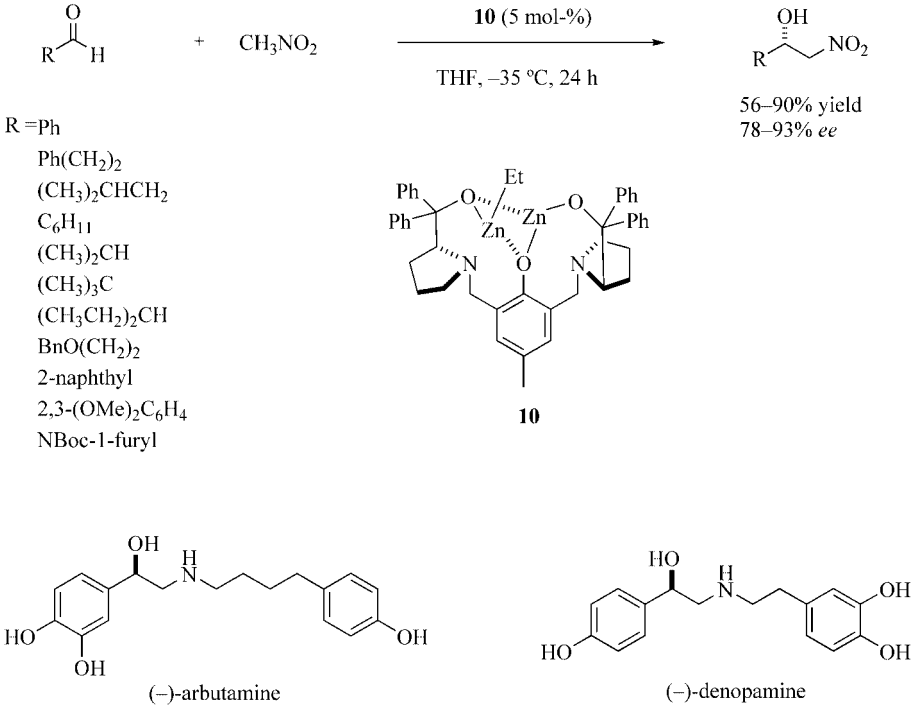
Zinc-centred metal complexes of ambifunctional character represent another family of efficient catalysts in the context of the asymmetric nitroaldol reaction. Such catalytic species parallel class II aldolase enzymes[28] in that both rely on Zn^{2+}; this feature makes them especially attractive as potential for implementation in aqueous media might be



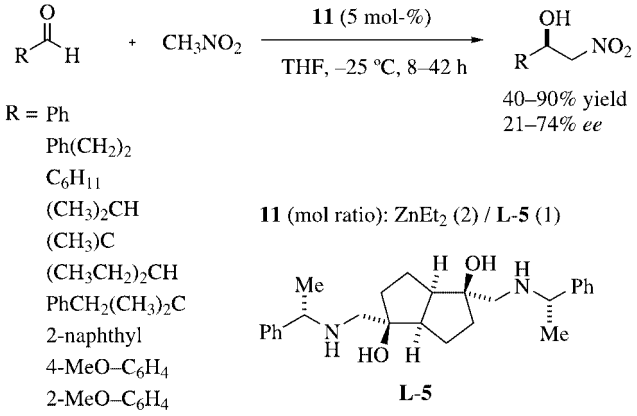
Scheme 10. Catalytic kinetic resolution of nitro alcohols. An enantioselective route to ketone-derived nitro alcohols.[27]

foreseen. Trost[29] has designed a very effective catalyst of this group (Scheme 11), consisting of a dinuclear zinc complex with a chiral semi-azacrown ligand. High levels of enantioselection are regularly achieved in nitroaldol reactions catalysed by 5 mol-% **10** with a broad range of aliphatic and aromatic aldehydes. Of additional interest, the preparation of the chiral C_2-symmetric semi-azacrown ligand present in **10** is straightforward from proline and is amenable for structural and electronic tuning. This technology has been applied to the synthesis of the β-receptor agonists (–)-arbutamine and (–)-denopamine.

Other Zn-centred bifunctional metal complexes with applications in catalytic nitroaldol methodology have been documented as displaying somewhat more limited results.[30] The complex formed upon admixture of Et_2Zn and the dimeric chiral amino alcohol ligand **L-5** has been reported to produce nitroaldol products with low to moderate enantioselectivities (Scheme 12).[30b]

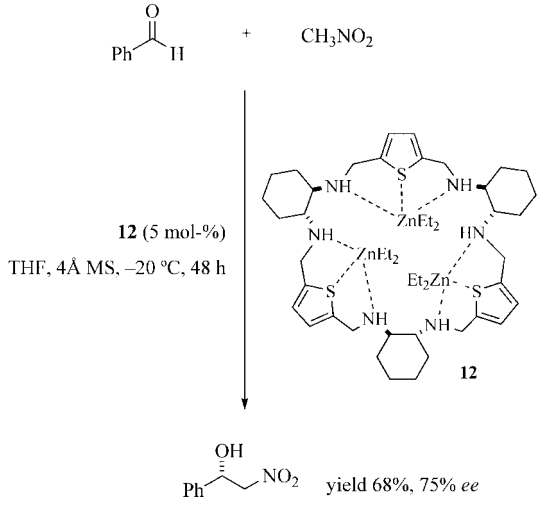


Scheme 11. Trost's dinuclear Zn complex's performance in catalytic asymmetric Henry reactions and some synthetic targets approached.[29]



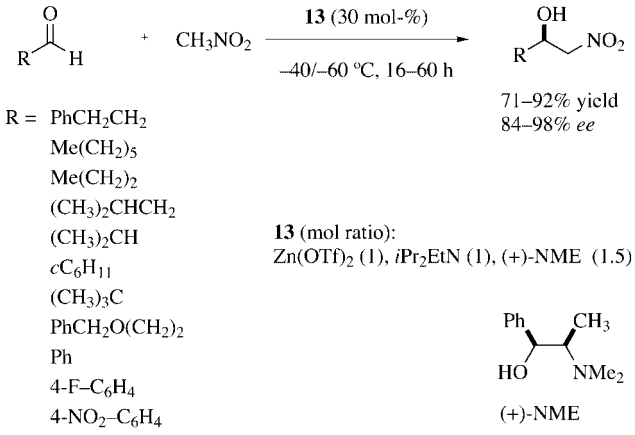
Scheme 12. A synthetic amino alcohol dimer as a ligand for the Zn-catalysed Henry reaction.[30b]

In the same context, Martell[31] has reported catalysis of the nitroaldol reaction between nitromethane and benzaldehyde by a trinuclear zinc complex obtained from a trimeric thioaza macrocyclic ligand and diethylzinc to provide 68% yield and 75% *ee* (Scheme 13). Unfortunately, no data for assessment of substrate generality are available.



Scheme 13. Thioazacrown ligands for the Zn^{II}-mediated Henry reaction between benzaldehyde and nitromethane.[31]

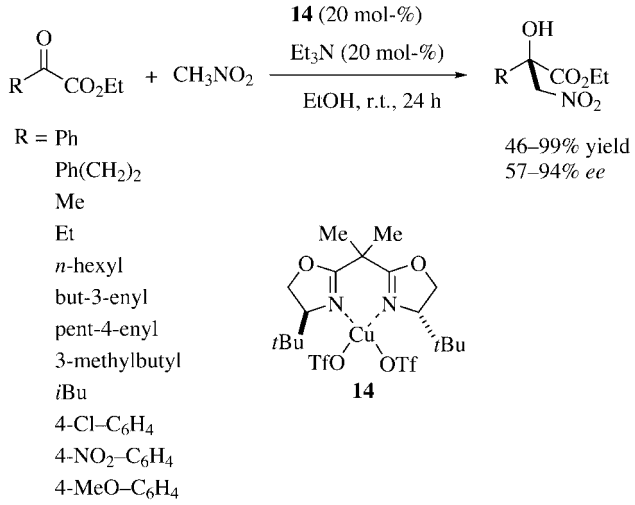
Palomo and co-workers have described a practical system that combines a simple Zn^{II} salt, a chiral amino alcohol ligand and an amine base (Scheme 14).[32] In this design, the acid and the basic centres, which are presumed concurrently to activate the electrophilic aldehyde and the pronucleophilic nitroalkane, respectively, are not integrated in the same molecular entity. This distinguishing feature facilitates straightforward screening of different combinations of metal salts, amine bases and chiral ligands. Among the chiral amino alcohols tested, *N*-methylephedrine (NME) showed the best results, regularly giving *ee* values above 90% for all aliphatic aldehydes tested and slightly below 90% for aromatic aldehydes. The system exhibited a positive nonlinear effect, which fits well with Kagan's two-ligand model (ML_2).[33] Of practical importance, essentially quantitative recovery of the chiral amino alcohol used is easy to carry out from the crude reaction product by simple acid/basic workup.



Scheme 14. Enantioselective Henry reactions catalysed by the commercially available triad system $Zn(OTf)_2$/*N*-methylephedrine/DIPEA.[32]

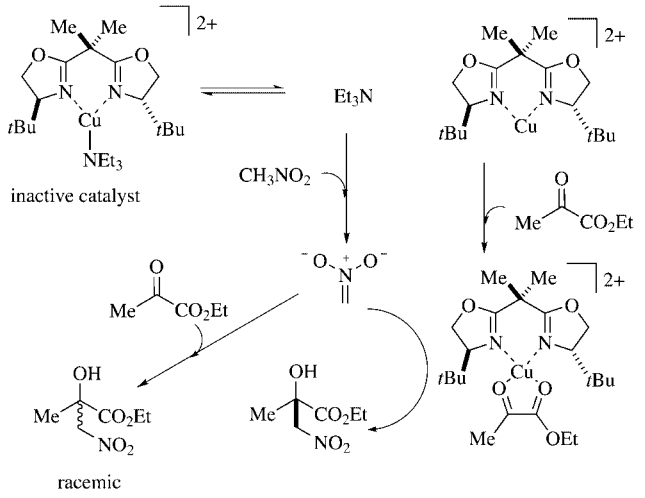
Copper-Based Catalysis

Chiral complexes of copper, particularly Cu^{II}–bis(oxazoline) complexes,[34] have found wide application in the general context of catalytic asymmetric transformations. The first application of these type of organometallics to the asymmetric nitroaldol reaction was reported by Jørgensen[35] and involves reactions between nitromethane and α-keto esters in the presence of chiral Cu^{II}–BOX complexes and triethylamine as the co-catalyst, working at room temperature (Scheme 15). The newly formed quaternary stereocentre is obtained with selectivities generally above 90% for aliphatic and electron-poor aromatic aldehydes, but significantly lower *ee* values are attained with neutral or electron-rich aromatic congeners.



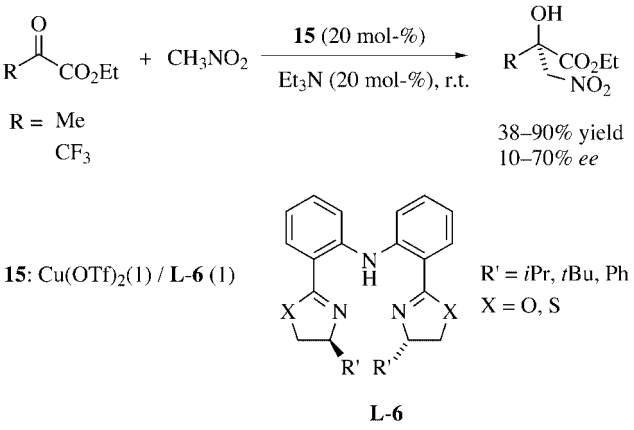
Scheme 15. Henry reactions between α-keto esters and nitromethane catalysed by Cu^{II}–BOX complex and triethylamine base, affording tertiary alcohols.[35]

In this method, the optimum loading of the two catalytic components – Cu^{II} complex and triethylamine – is 20 mol-% each (1:1 ratio); ratios above this value give lower selectivity, ratios below show lower yields. Bases other than triethylamine also gave detrimental yields and/or selectivity. A reaction model that considers both racemic and asymmetric pathways, with triethylamine as an active participant, has been proposed (Scheme 16).



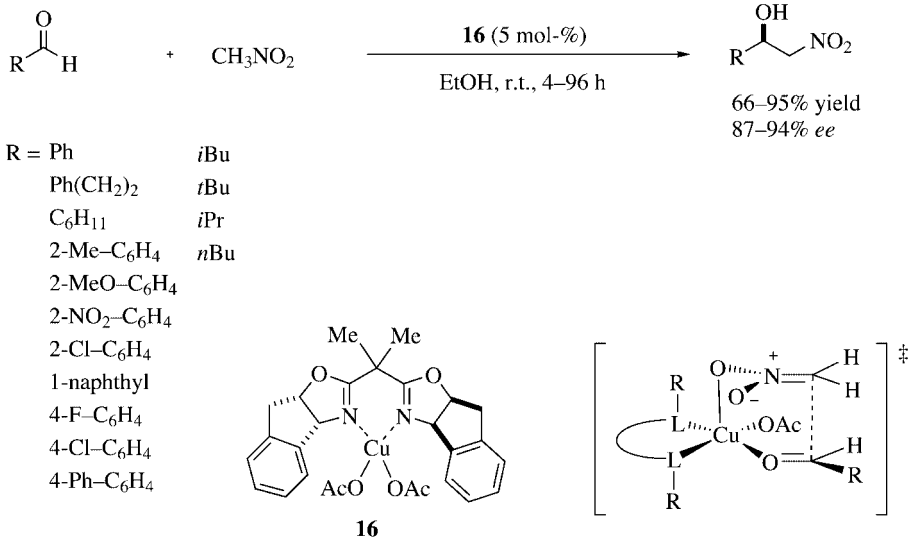
Scheme 16. Double role played by triethylamine co-catalyst as the reaction promoter and deactivator of the Lewis acid catalyst.[35]

In a related work, Du has reported[36] the use of tridentate bisoxazoline and thiazoline ligands **L-6** in combination with $Cu(OTf)_2$ salts as catalysts, providing the corresponding (*R*)-configured nitro alcohol products with somewhat inferior selectivity (Scheme 17). The best suited catalyst incorporates the bis(thiazoline) ligand bearing *tert*-butyl substituents (X = S, R′ = *t*Bu, *ee* values up to 70%). The complex formed from the same type of ligands (20 mol-%) and $ZnEt_2$ (50 mol-%) also promoted the reactions in hexane at 0 °C, but predominantly affording products of opposite configuration.[36b] Interestingly, in the latter instance, the bis(oxazoline) ligands with R′ = benzyl gave the best results, providing fairly good selectivities (up to 85% *ee* values).



Scheme 17. Tridentate bis(oxazoline) ligands for Cu^{II}-catalysed Henry reactions of α-keto esters.[36]

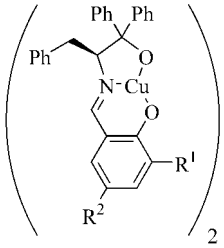
A more efficient Cu^{II} catalyst, which is active at loading levels of 5 mol-%, has been described by Evans[37] for nitroaldol reactions between nitromethane and aldehydes (Scheme 18). The method is quite general for a range of both aliphatic and aromatic aldehydes and works under very mild reaction conditions (EtOH, room temperature). The catalyst design required a weakly acidic metal complex bearing moderately basic charged ligands that would facilitate deprotonation of nitroalkanes, and the $Cu(OAc)_2$–BOX complex **16** was found to fulfil the requirements best. A transition state model involving a Jahn–Teller effect on copper coordination and positioning of reactants in the most favourable orientations according to steric and electronic considerations has been proposed. Copper is thus coordi-



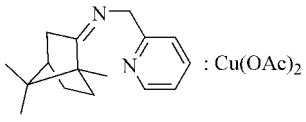
Scheme 18. Bifunctional $Cu(OAc)_2$–BOX catalyst for broad-scope enantioselective Henry reactions developed by Evans, together with the proposed TS model.[37]

nated both to the nitronate and to the aldehyde carbonyl, producing a preferential boat conformation that correctly predicts the observed stereochemistry.

Other Cu^{II} catalysts for the Henry reaction that apparently work on an activation principle similar to that described by Evans have also been described. Zhou has reported[38] a Cu^{II} dinuclear complex **17** bearing chiral imino alcohol ligands. The dimeric nature of the catalytic complex was demonstrated by X-ray structure determination. Unfortunately, while good chemical yields were obtained, enantioselectivities were only modest, particularly with aliphatic aldehydes (typically 45–64% *ee* values). On the other hand, Pedro has described[39] catalysis of the Henry reaction between nitromethane and *o*-anisaldehyde by complexes formed from camphor-derived iminopyridine ligands and $Cu(OAc)_2$. Again, under reaction conditions similar to those developed by Evans, good yields but modest selectivities were obtained. The best result was obtained with complex **18**, which gave a product with 86% *ee* (Figure 1).



17

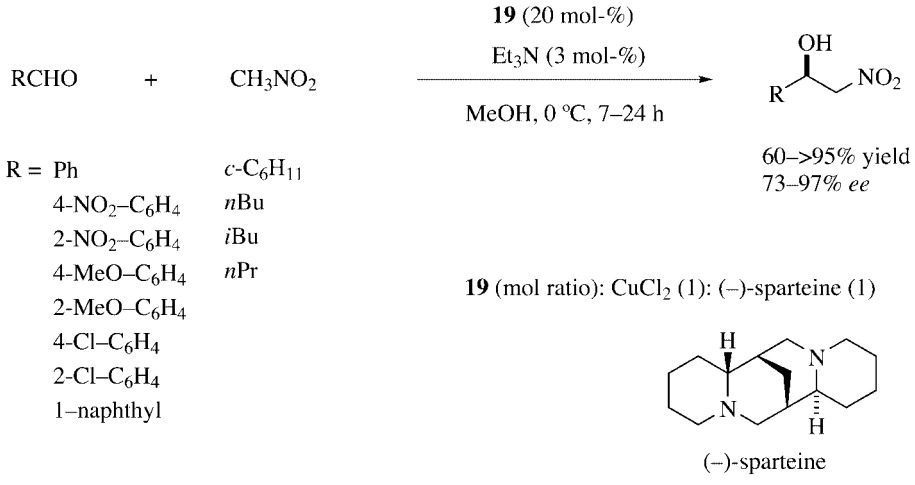


18

Figure 1. Catalytic Cu^{II}–imine complexes tested against the Henry reaction.

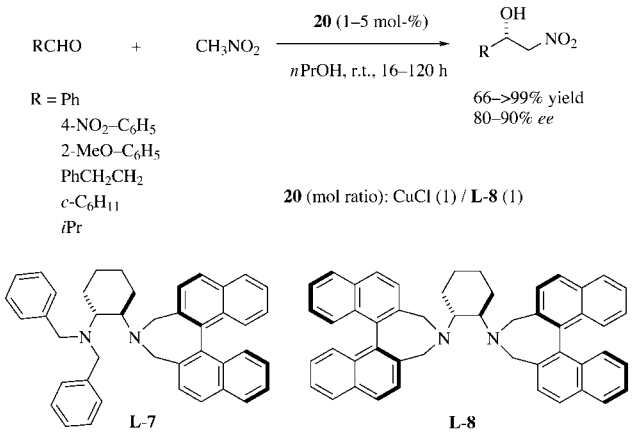
Chiral Cu^{II}–diamine complexes have also very recently been shown to act as useful catalysts in Henry reactions.[40] In view of the well known stereochemical biases of Cu^{II}–sparteine complexes, and their conformational rigidity, complexes of both $CuCl_2$ and $Cu(OAc)_2$ with (–)-sparteine were screened against Henry reactions between nitromethane and a range of representative aromatic and aliphatic aldehydes. Interestingly, while the $Cu(OAc)_2$–(–)-sparteine complex was able to catalyse the reaction without any need for external base, essentially racemic products were obtained. On the other hand, the $CuCl_2$–(–)-sparteine complex alone was inefficient in promoting the reaction, but a smooth reaction took place in the presence of a small quantity of triethylamine, with *ee* values in the 80's (Scheme 19). The authors found the quantity of triethylamine added to be very influential: an increase in the amount of triethylamine base beyond the 3 mol-% level lowered the enantioselectivity. Also noteworthy is the requirement for methanol as solvent, since other solvents such as dichloromethane or THF gave poor results. The experimentally observed differences between the complexes derived from $Cu(OAc)_2$ and from $CuCl_2$ were explained on the basis of the significant differences in the bond angles and torsion angles around the copper(II) site as determined in the solid state.

After an innovative system for high-throughput screening of catalyst efficiencies, new chiral diamine ligands for Cu^{I}-mediated Henry reactions were identified.[41] The new monitoring tool uses circular dichroism (CD) peaks' intensities as a means of quantifying the efficiency of an asymmetric catalyst. This measurement is sensitive both to the reaction yield and to the enantioselectivity, and so only those catalysts fulfilling both criteria give rise to high-intensity peaks in the CD spectra. With the assistance of this technique, complexes formed from diamines **L-7** and **L-8** and CuCl were found to be very active catalysts for Henry reactions between nitromethane and several representative aldehydes. In particular, the C_2-symmetric catalyst **20** regularly gave



Scheme 19. A combined Cu^{II}–(–)-sparteine/Et_3N catalytic system for Henry reactions of nitromethane.[40]

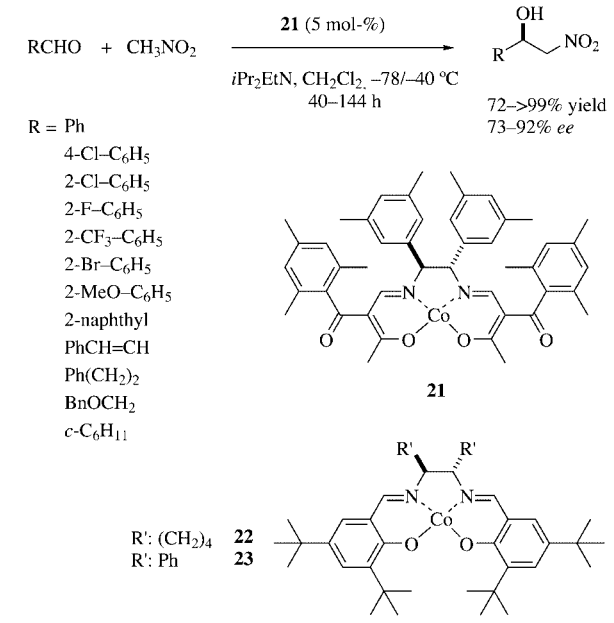
high yields and enantioselectivities even at loadings as low as 1 mol-% at room temperature in *n*-propanol as solvent (Scheme 20).



Scheme 20. Ligands designed through CD-based high-throughput screening. Highly efficient chiral diamine ligands for Cu-catalysed Henry reactions.[41]

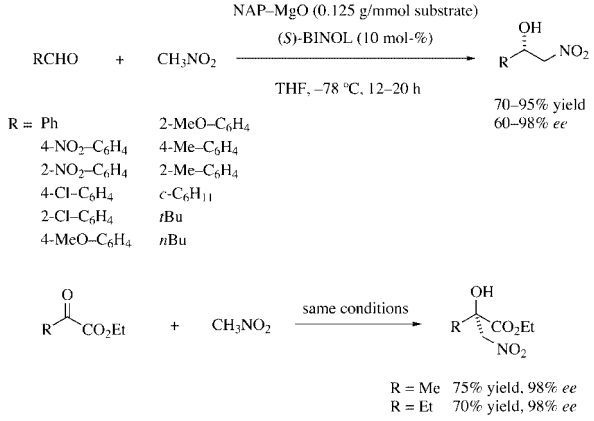
Other Metal-Based Catalysts

Yamada and co-workers have found[42] Co^{II}-ketoimine and Co^{II}-SALEN complexes to be good catalysts of the Henry reaction in the presence of 1 mol equivalent of Hünig's base (Scheme 21). Catalyst **21** in combination with stoichiometric diisopropylethylamine, for instance, afforded the corresponding nitroaldol products with very high yields and enantioselectivities, usually in the 73–92% range for an array of aliphatic and aromatic aldehydes. A notable exception was *p*-anisaldehyde, which gave a poor 11% yield and only 53% *ee*.[42a] Structurally similar complexes **22** and **23** are also promoters of the reaction, although their aldehyde scope seems to be somewhat more limited.[42b]



Scheme 21. Co-based enantioselective catalytic Henry reaction using imino-enol ligands.[42]

Using nanocrystalline magnesium oxide (NAP–MgO) as a heterogeneous catalyst with defined shape and size, Choudary has reported[43] enantioselective Henry reactions involving BINOL as the catalytic chiral ligand (Scheme 22). The reactions between nitromethane and a range of aromatic and aliphatic aldehydes at –78 °C were reported to proceed with high yields and selectivities fluctuating between 60% and 98% *ee*. The heterogeneous catalytic system is equally effective in promoting Henry reactions of α-keto esters, giving rise to tertiary alcohols in a remarkable 98% *ee*.

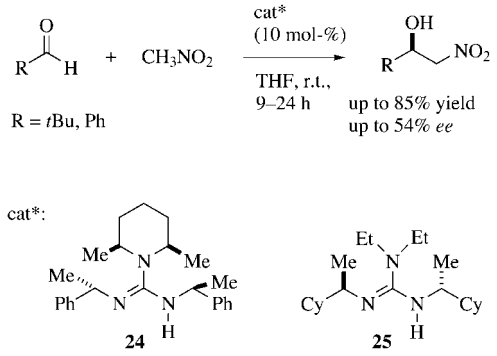


Scheme 22. Enantioselective Henry reactions triggered by a nanocrystalline MgO–BINOL system.[43]

Organocatalysis

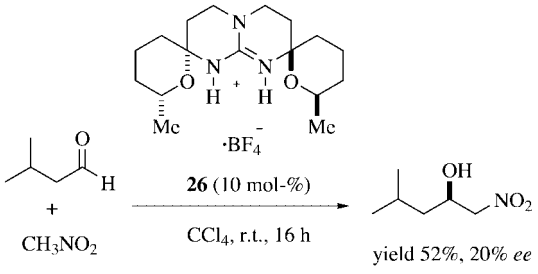
The search for small organic molecules capable of promoting a chemical transformation catalytically (organocatalysis) has attracted considerable attention over the last few years.[44] In this context, some selected organocatalysts have demonstrated high chemical and stereochemical efficiency in nitroaldol reactions. Common requirements for these organocatalysts structures for achieving good performance appears to be the presence of: (1) a basic unit (or, alternatively, an external base will be required as co-catalyst), (2) some unit capable of binding the nitro (or nitronate) group either through hydrogen bonding or through purely electrostatic interactions, and (3) some unit capable of forming a hydrogen bond with the acceptor carbonyl.

Among the units that meet requirement (2), guanidine units[45] appear to be some of the best suited. Nájera has thus documented[46] the synthesis of several guanidines with C_1 and C_2 symmetry, such as **24** and **25**, and their application to the reactions between nitromethane and both isovaleraldehyde and benzaldehyde in THF at room temperature (Scheme 23). While the yields were generally good, only modest enantioselectivities were observed (*ee* ≤ 54%).



Scheme 23. Chiral guanidine species as organocatalysts for the Henry reaction.[46]

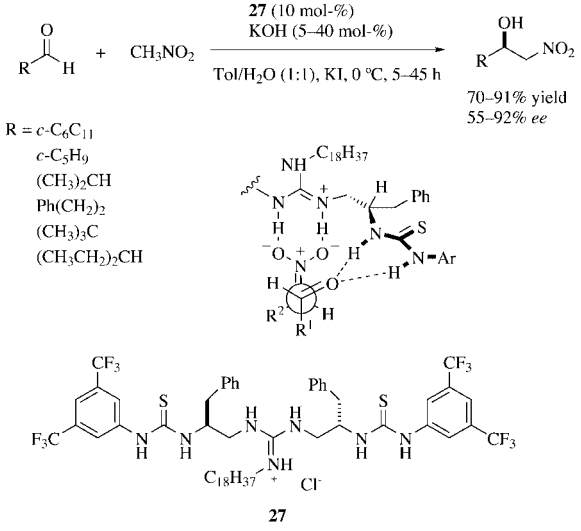
Similarly, guanidine tetrafluoroborate salt **26** has been reported to promote the nitroaldol reaction between nitromethane and isovaleraldehyde with some enantioselectivity (Scheme 24).[47] No data have been reported with other aldehydes.



Scheme 24. Chiral guanidinium tetrafluoroborate salt in the enantioselective Henry reaction.[47]

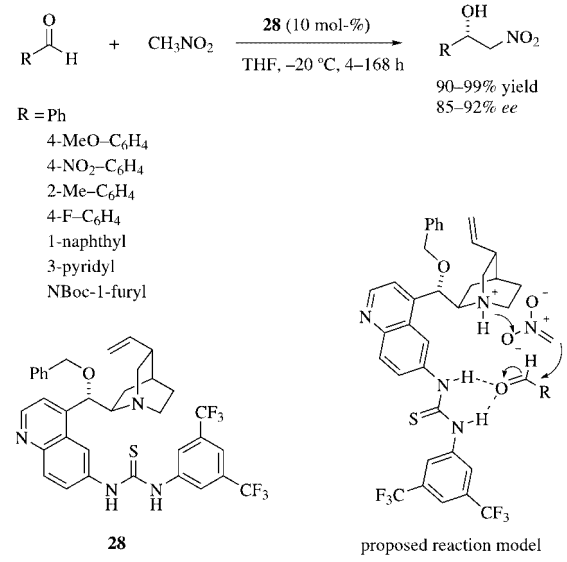
Through the integration of a quaternised guanidine unit and a thiourea unit in the same catalyst molecule, and by working under PTC with the assistance of KOH base, Nagasawa has reported[48] an improved catalyst for the nitroaldol reaction (Scheme 25). In the working model, while the nitronate group is ion paired with the guanidinium moiety, the thiourea should be able to bind to the carbonyl group through H-bonding. Good yields and acceptable enantioselectivities are obtained in reactions between nitromethane and branched-chain aliphatic aldehydes. It seems that aromatic and aliphatic unbranched aldehydes are less well tolerated. While a similar limitation in aldehyde scope is seen in reactions with nitroethane, some remarkably high *syn*/*anti* selectivities and *ee* values are obtained.[48b] The improved performance of this catalyst with higher nitroalkanes rather than with nitromethane is explained on the basis of an open transition state in which the Me (R^2) group of the nitroalkane controls orientation.

The minimum requirement for effective catalytic activity in a nitroaldol reaction is also met by organic molecules bearing both a thiourea and an amine residue.[49] Hiemstra,[50] for instance, has reported compound **28** as an efficient catalyst for nitroaldol reactions of nitromethane, providing very high yields and *ee* values in the 85–92% range for a series of aromatic aldehydes. In this instance, the model proposed to explain the reaction outcome implies



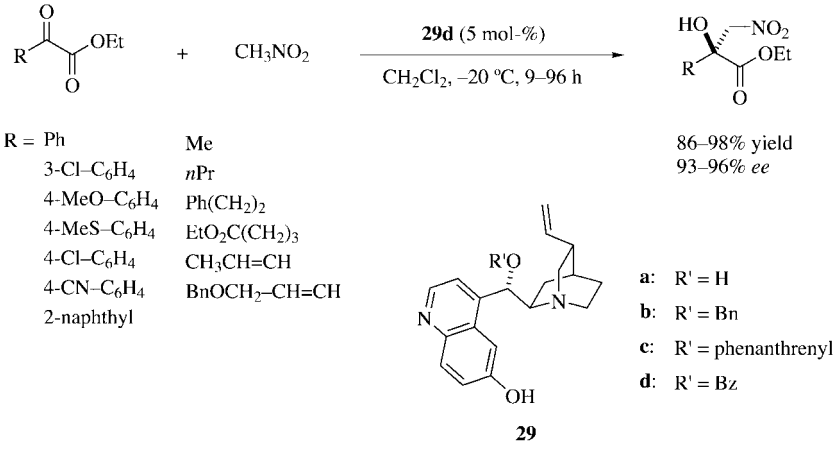
Scheme 25. Guanidinium–thiourea molecule as an efficient bifunctional PTC catalyst for Henry reactions between nitromethane and aldehydes.[48]

hydrogen bonding between the thiourea moiety and the acceptor carbonyl, together with ion pairing between the protonated quinuclidine and the nitronate group in the transition state (Scheme 26).



Scheme 26. A bifunctional amine-thiourea organocatalyst derived from cinchona alkaloids and its performance in Henry reactions.[50]

An efficient organocatalyst that lacks both the guanidinium/amidinium and the thiourea moieties has recently been reported by Deng[51] for highly efficient nitroaldol reactions between nitromethane and α-keto esters (Scheme 27). The new cinchona catalyst family is easily available from natural sources,[52] and the most effective member, the cupreidine derivative[53] **29d**, provided outstanding performances for a series of ethyl keto esters[54] bearing aromatic, aliphatic, or functionalized alkyl side chains, under very practical reaction conditions (CH_2Cl_2, –20 °C, 5 mol-% catalyst loading). Mechanistic studies on



Scheme 27. A simple cinchone derivative as efficient organocatalyst for Henry reactions of α-keto esters.[51]

the catalytic activity indicated that these molecules could serve as acid-base bifunctional catalyst through hydrogen-bonding interactions with the acceptor and donor components of the reactions through the quinuclidine nitrogen and the C6′–OH, respectively.

Phosphanes have also been used as organocatalysts of the Henry reaction, but attempts to obtain enantioselection have so far been unsuccessful.[55]

Conclusions

The catalytic asymmetric nitroaldol (or Henry) reaction has attracted considerable interest in the last few years. A meaningful number of conceptually different catalytic systems that have successfully triggered such reactions under mild conditions have been identified. From pioneering efforts involving direct methods based on ambifunctional lanthanum catalytic complexes and indirect methods based on preformed silyl nitronates, current possibilities include zinc, copper and cobalt catalytic complexes. In addition, organocatalysts – particularly thiourea-guanidine and thiourea–quinuclidine systems – appear to offer great promise in the field. Despite these advances, important limitations remain. Most catalytic systems provide uniformly high chemical yields and enantioselectivities but for too narrow substrate variation. While simple aldehydes are tolerated quite well, functionalized aldehydes and ketones (α-keto esters being a remarkable exception) represent two compound families that need further studies. With respect to the nitroalkane tolerance, most direct methods are limited to nitromethane. Direct methods involving higher nitroalkanes, in which the *syn*/*anti* diastereocontrol is an open question, are almost unexplored. Neither has the issue of double stereodifferentiation by use either of chiral aldehydes or chiral nitroalkanes been properly addressed yet. Models that account for activation of substrate nitro and carbonyl compounds, as well as reaction diastereo- and enantiocontrol, have been proposed for most cases. However, more robust proposals are still needed, since data relating to reaction kinetics or characterization of intermediates are scarce, while computational studies are fundamentally lacking.[56] Several applications of these catalytic methods to solving of relevant synthetic problems have appeared in the literature and new contributions can be anticipated. From these observations, the development of improved and more general catalytic systems and their increasing utility in synthetic plans can be foreseen for the near future.

Note Added in Proof (March 9, 2007): After completion of the manuscript, the following papers appeared: Review: a) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326. Cobalt: b) S. Tsuchiya, T. Sunazuka, T. Hirose, R. Mori, T. Tanaka, M. Iwatsuki, S. Ōmura, *Org. Lett.* **2006**, *8*, 5577–5580. Copper: c) Y. Xiong, F. Wang, X. Huang, Y. Wen, X. Feng, *Chem. Eur. J.* **2007**, *13*, 829–833; d) K. Ma, J. You, *Chem. Eur. J.* **2007**, *13*, 1863–1871; e) M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi, C. Ventrinci, *Chem. Commun.* **2007**, 616–618. Cupreine: f) T. Mandal, S. Samanta, C.-G. Zhao, *Org. Lett.* **2007**, *9*, 943–945. Lipase: g) P. Vongvilai, M. Angelin, R. Larsson, O. Ramström, *Angew. Chem. Int. Ed.* **2007**, *46*, 948–950.

Acknowledgments

The authors thank The University of the Basque Country (UPV/EHU) and the Ministerio de Educación y Ciencia (MEC), Spain, for financial support.

[1] L. Henry, *Compt. Rend. Hebd. Seances Acad. Sci.* **1895**, *120*, 1265–1267.
[2] For general reviews, see: a) G. Rosini in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, New York, **1991**, vol. 2, pp. 321–340; b) F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915–945; c) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**.
[3] O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894.
[4] G. M. Coppola, H. F. Schuster, *α-Hydroxy Acids in Enantioselective Syntheses*, VCH, Weinheim, **1997**.
[5] For a review on the Nef oxidation, see: R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047.
[6] C. Narayana, N. K. Reddy, G. W. Kabalka, *Synth. Commun.* **1992**, *22*, 2587–2592.
[7] C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234–235.
[8] For a review on vicinal amino alcohols, see: S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576.

[9] M.-A. Poupart, G. Fazal, S. Goulet, L. T. Mar, *J. Org. Chem.* **1999**, *64*, 1356–1361.

[10] R. Tamura, A. Kamimura, N. Ono, *Synthesis* **1991**, 423–434.

[11] Reviews; a) E. M. Carreira in *Comprehensive Asymmetric Catalysis*, vol. 3 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto) Springer, Heideberg, **1999**, pp. 997–1065; b) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, *33*, 65–75; c) *Modern Aldol Reactions*, vol. 1–2 (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2005**.

[12] For examples of chiral auxiliaries-controlled asymmetric Henry reactions involving α-keto acid derivatives, see: a) A. Solladié-Cavallo, N. Khiar, *J. Org. Chem.* **1990**, *55*, 4750–4754; b) I. Kudyba, J. Raczko, J. Jurczak, *Tetrahedron Lett.* **2003**, *44*, 8681–8683; c) I. Kudyba, J. Raczko, J. Jurczak, *J. Org. Chem.* **2004**, *69*, 2844–2850. For Henry reactions involving chiral α-amino and α-oxy aldehydes, including sugar derivatives, see ref.[2b].

[13] a) M. Shibasaki, H. Gröger in *Comprehensive Asymmetric Catalysis*, vol. III (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 1075–1090; b) M. Shibasaki, H. Gröger, M. Kanai in *Comprehensive Asymmetric Catalysis, Supplement 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **2004**, pp. 131–133; c) C. Palomo, M. Oiarbide, A. Mielgo, *Angew. Chem. Int. Ed.* **2004**, *43*, 5442–5444.

[14] E. W. Colvin, D. Seebach, *J. Chem. Soc., Chem. Commun.* **1978**, 689–691.

[15] T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055.

[16] T. Risgaard, K. V. Gothelf, K. A. Jørgensen, *Org. Biomol. Chem.* **2003**, *1*, 153–156.

[17] a) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420; b) H. Sasai, T. Suzuki, N. Itoh, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 851–854; c) H. Sasai, T. Suzuki, N. Itoh, K. Tanaka, T. Date, K. Okamura, M. Shibasaki, *J. Am. Chem. Soc.* **1993**, *115*, 10372–10373.

[18] Reviews: a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187–2209; b) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989–1999; c) *Multimetallic Catalysts in Organic Synthesis* (Eds: M. Shibasaki, Y. Yamamoto), Wiley-VCH, Weinheim, **2004**; d) M. Shibasaki, M. Kanai, S. Matsunaga, *Aldrichim. Acta* **2006**, *39*, 31–39.

[19] For reviews on ambifunctional catalysis, see: a) Ref.[18]; b) G. J. Rowlands, *Tetrahedron* **2001**, *57*, 1865–1882; c) J.-A. Ma, D. Cahard, *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583.

[20] T. Purkarthofer, K. Gruber, M. Gruber-Khadjawi, K. Waich, W. Skranc, D. Mink, H. Griengl, *Angew. Chem. Int. Ed.* **2006**, *45*, 3454–3456.

[21] For reviews about catalysts based on modified BINOL, see: a) M. Shibasaki, S. Matsunaga, *Chem. Soc. Rev.* **2006**, *35*, 269–279; b) Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155–3211; c) H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1924–1942. For a review about catalysts with lanthanide metals, see: d) K. Mikami, M. Terada, H. Matsuzawa, *Angew. Chem. Int. Ed.* **2002**, *41*, 3554–3571.

[22] a) K. Iseki, S. Oishi, H. Sasai, M. Shibasaki, *Tetrahedron Lett.* **1996**, *37*, 9081–9084; b) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388–7389; c) H. Sasai, T. Suzuki, N. Itoh, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 851–854.

[23] T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, *Chem. Eur. J.* **1996**, *2*, 1368–1372.

[24] J. M. Saá, F. Tur, J. González, M. Vega, *Tetrahedron: Asymmetry* **2006**, *17*, 99–106.

[25] One example using 2,2,2-trifluoroacetophenone to give the product with low *ee* (21%) has been reported: Y. Misumi, R. A. Bulman, K. Matsumoto, *Heterocycles* **2002**, *56*, 599–605.

[26] P. B. Kisanga, J. G. Verkade, *J. Org. Chem.* **1999**, *64*, 4298–4303.

[27] S.-y. Tosaki, K. Hara, V. Gnanadesikan, H. Morimoto, S. Harada, M. Sugita, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 11776–11777.

[28] For a review, see: D. Machajewski, C.-H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1374.

[29] a) B. M. Trost, V. S. C. Yeh, *Angew. Chem. Int. Ed.* **2002**, *41*, 861–863; b) B. M. Trost, V. S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* **2002**, *4*, 2621–2623.

[30] a) G. Klein, S. Pandiaraju, O. Reiser, *Tetrahedron Lett.* **2002**, *43*, 7503–7506; b) Y.-W. Zhong, P. Tian, G.-Q. Lin, *Tetrahedron: Asymmetry* **2004**, *15*, 771–776; c) U. Köhn, M. Schulz, H. Görls, E. Anders, *Tetrahedron: Asymmetry* **2005**, *16*, 2125–2131.

[31] J. Gao, A. E. Martell, *Org. Biomol. Chem.* **2003**, *1*, 2801–2806.

[32] C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884.

[33] a) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959; b) H. B. Kagan, *Adv. Synth. Catal.* **2001**, *343*, 227–233.

[34] Reviews: a) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; b) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain, J. Thorhauge, *Acc. Chem. Res.* **1999**, *32*, 605–613; c) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; d) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151–4202; e) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.

[35] a) C. Christensen, K. Juhl, K. A. Jørgensen, *Chem. Commun.* **2001**, 2222–2223; b) C. Christensen, K. Juhl, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4875–4881.

[36] a) S.-F. Lu, D.-M. Du, S.-W. Zhang, J. Xu, *Tetrahedron: Asymmetry* **2004**, *15*, 3433–3441; b) D.-M. Du, S.-F. Lu, T. Fang, J. Xu, *J. Org. Chem.* **2005**, *70*, 3712–3715.

[37] D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693.

[38] C. Gan, G. Lai, Z. Zhang, Z. Wang, M.-M. Zhou, *Tetrahedron: Asymmetry* **2006**, *17*, 725–728.

[39] G. Blay, E. Climent, I. Fernández, V. Hernández-Olmos, J. M. Pedro, *Tetrahedron: Asymmetry* **2006**, *17*, 2046–2049.

[40] H. Maheswaran, K. L. Prasanth, G. G. Krishna, K. Ravikumar, B. Sridhar, M. L. Kantam, *Chem. Commun.* **2006**, 4066–4068.

[41] T. Arai, M. Watanabe, A. Fujiwara, N. Yokoyama, A. Yanagisawa, *Angew. Chem. Int. Ed.* **2006**, *45*, 5978–5981.

[42] a) Y. Kogami, T. Nakajima, T. Ashizawa, S. Kezuka, T. Ikeno, T. Yamada, *Chem. Lett.* **2004**, 614–615; b) Y. Kogami, T. Nakajima, T. Ikeno, T. Yamada, *Synthesis* **2004**, 1947–1950.

[43] B. M. Choudary, K. V. S. Ranganath, U. Pal, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2005**, *127*, 13167–13171.

[44] a) P. L. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**.

[45] T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, 737–752.

[46] R. Chinchilla, C. Nájera, P. Sánchez-Agulló, *Tetrahedron: Asymmetry* **1994**, *5*, 1393–1402.

[47] M. T. Allingham, A. Howard-Jones, P. J. Murphy, D. A. Thomas, P. W. R. Caulkett, *Tetrahedron Lett.* **2003**, *44*, 8677–8680.

[48] a) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.* **2005**, *347*, 1643–1648; b) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Eur. J. Org. Chem.* **2006**, 2894–2897.

[49] For reviews, see: a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; b) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; c) P. M. Pihko, *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064; d) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296.

[50] T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931.

[51] H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732–733.

[52] For use of cinchona alkaloids in asymmetric synthesis, see: a) H. M. R. Hoffmann, J. Frackenpohl, *Eur. J. Org. Chem.* **2004**, 4293–4312; b) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621–631; c) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506–517; d) K. Kacprzak, J. Gawronski, *Synthesis* **2001**, *7*, 961–998.
[53] Use of cupreines and cupreidines as bifunctional organocatalysts: T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504.
[54] With benzaldehydes as electrophiles, catalyst **29b** has been shown to display limited enantioselection, see: a) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Synlett* **2005**, 2817–2819; b) ref.[50]
[55] J. A. Weeden, J. D. Chisholm, *Tetrahedron Lett.* **2006**, *47*, 9313–9316.
[56] For a theoretical discussion of *syn*/*anti* selectivity in Henry reactions, see: B. Lecea, A. Arrieta, I. Morao, F. P. Cossío, *Chem. Eur. J.* **1997**, *3*, 20–28.

Received: January 10, 2007
Published Online: March 16, 2007

