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Catalytic asymmetric Henry reaction

Joshodeep Boruwa, Naminita Gogoi, Partha Pratim Saikia and Nabin C. Barua*

Natural Products Chemistry Division, Regional Research Laboratory (CSIR), Jorhat 785 006, Assam, India

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Dedicated to Dr. Anil C. Ghosh on his 70th birthday

Abstract—The classical Henry reaction, the coupling of a nitroalkane with a carbonyl compound in the presence of a base, is an important C–C bond forming reaction in organic chemistry giving β-nitroalcohols, which are useful synthons in organic synthesis. However, an asymmetric version of the reaction, that has been developed recently, gives a new dimension to the classical Henry reaction whereby the control of stereochemistry of two newly generated carbon centres has become possible. In this review, the various catalytic methods for this purpose are discussed.

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* Corresponding author. Tel.: +91 376 2370121x2360; fax: +91 376 2370011; e-mail addresses: ncbarua12@rediffmail.com; ncbarua2000@yahoo.co.in

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1. Introduction

Among the various C–C bond forming reactions, the nitroaldol or Henry reaction is one of the classical named reactions in organic synthesis. Essentially the coupling of the nucleophile generated from a nitroalkane with a carbonyl electrophile is a widely used transformation, since its discovery in 1895.[1] The resulting product of this reaction is a β-nitroalcohol, which is a versatile intermediate in synthetic organic chemistry. However, the wide applicability of this transformation, until recently, was impaired due to the nonavailability of suitable catalysts for imparting a definite stereochemistry to the newly generated stereogenic centres.

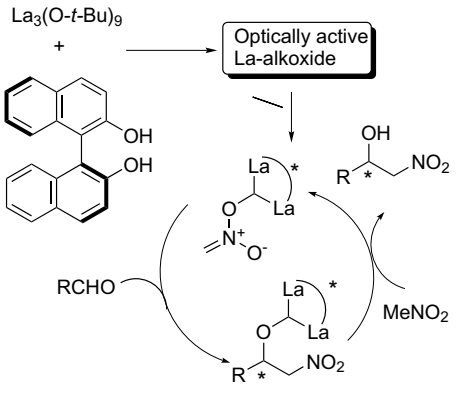
The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992.[2] Since then, interest in this area has been expanded upon considerably and various reports have been continuously appearing in the literature on development of various metal and nonmetal based catalysts for the asymmetric Henry reaction.

In this review, we intend to focus on various catalyst systems for the Henry reaction, noting their advantages, scope and limitations. Based on the literature reports, the discussion is divided into two categories: metal/chiral ligand complex-based reactions and organocatalytic reactions.

2. Metal based chiral catalysts

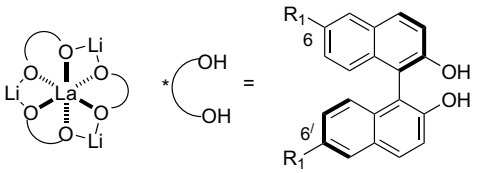
2.1. Rare earth–BINOL complexes

Shibasaki et al. observed that rare earth alkoxides are sufficiently basic due to the low ionisation potential (ca. 5.4–6.4 ev) and electronegativity (1.1–1.3) of the rare earth elements. During this study, it was observed that optically active rare earth alkoxides such as $La_3(O\text{-}t\text{-}Bu)_9$ promote the nitroaldol reactions with ee up to 90%. These authors suggested that the first step of the reaction is the ligand exchange between the binaphthol and nitromethane (Scheme 1).[2]

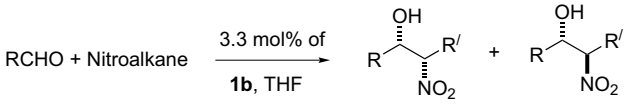


Scheme 1.

Shibasaki's Rare earth–BINOL catalyst has been shown to have structure **1** (Fig. 1) based on ^1H, ^{13}C and X-ray crystallographic data.[3] This catalyst afforded nitroalcohols in 79–91% yield and with 86:14–95.5 er from aliphatic aldehydes and nitromethane.



1a R_1 = H
1b R_1 = OTES



Syn *Anti*

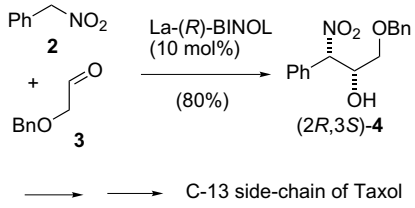
R	nitroalkane	yield	*syn:anti*	ee of *syn*
$PhCH_2H_2$	$CH_3CH_2NO_2$	70	89:11	96
$PhCH_2CH_2$	$CH_3(CH_2)_2NO_2$	85	93:7	98
$PhCH_2CH_2$	$OH(CH_2)_2NO_2$	97	92:8	98
$CH_3(CH_2)_4$	$OH(CH_2)_2NO_2$	95	92:8	98

Figure 1.

To expand the scope of this reaction, Shibasaki et al. applied this catalyst system to complex nitroalkanes in which the catalyst is required to control the enantioselectivity as well as its diastereoselective outcome.

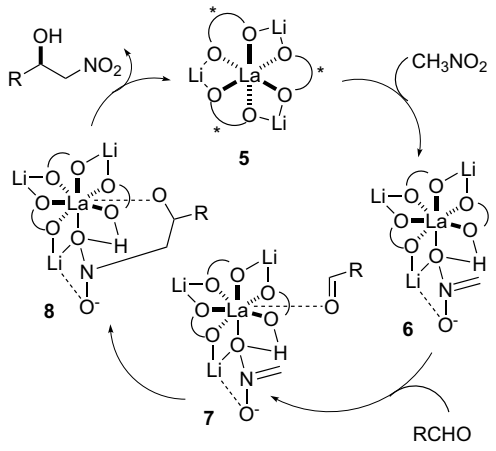
The introduction of two TES groups at the 6- and 6′-position of the binapthol turned out to make a good catalyst **1b**, which led to the generation of β-nitroalcohols with better diastereoselectivity with the *syn*-isomer as the predominant product.[4]

In our hands, coupling of phenyl nitromethane with benzyloxy acetaldehyde in the presence of catalyst **1a** afforded nitroalcohol (2*R*,3*S*)-**4** in 80% yield and 95:5 er, which was further elaborated to C-13 side chain of taxol with 33% overall yield (Scheme 2).[5]



Scheme 2.

The catalytic cycle initially proposed by Shibasaki et al. was later modified (Scheme 3) upon.[6] It is suggested that the lanthanum metal in LLB **5** acts as a Lewis acid to acti-



Scheme 3. Proposed mechanism for heterobimetallic complexes; (H_2O is omitted for clarity).

vate the aldehyde, and the lithium binapthoxide moiety functions as a Brönsted base to deprotonate the nitroalkane to form lithium nitronate **6**. This nitronate complex then activates the aldehyde to form complex **7**, which undergoes nucleophilic addition to generate complex **8**. Subsequent release of the nitroalcohol regenerates the catalyst.

The heterobimetallic complexes containing a rare earth metal, three alkali metals and three 1,1′-bi-2-naphthols (BINOLs) abbreviated as REMB offer a versatile framework for asymmetric catalysis (Fig. 2).[7] The synergistic effect of the two metal centres enables various transformations that are otherwise difficult to carry out using monometallic catalysts possessing only Lewis acidity.

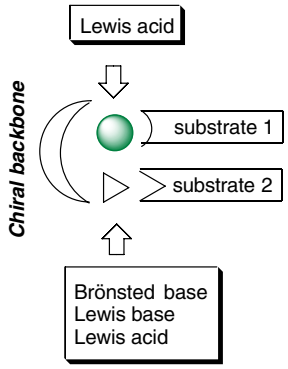
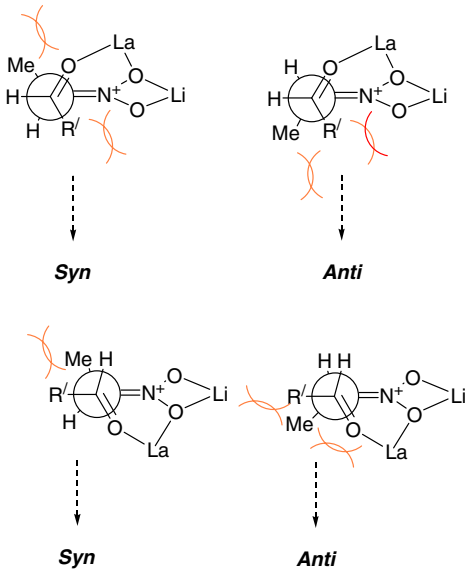


Figure 2. Bifunctional asymmetric catalysts.

The *syn*-selectivity in this reaction can be explained as arising from steric hindrance in the bicyclic transition state, as can readily be seen in the Newman projection (Scheme 4).[7]

These authors further observed that the enantiomeric excess of the nitroaldol products was dependent on the ionic radius of the lanthanides.[8] The best lanthanides differed according to the substrates used in the reaction. This observation made it possible to optimise the reaction by simply choosing the lanthanide based on the substrate. A more



Scheme 4. Newman projections of an intermediate for the diastereoselective nitroaldol reaction.

prominent substrate effect was detected with α-haloaldehydes, where there was a reversal of the enantiotopic facial selectivity. This reversal was also observed with both α-oxo aldehydes and α,α-difluoro aldehydes.[9,10] These effects could be due to the hydrogen bonding between the α-heteroatom and the BINOL formed from protonation of binaphthyl alkoxide during nitronate formation. Alternatively, the effect could result from Lewis acid/Lewis base interactions between the α-heteroatom and a lithium cation.

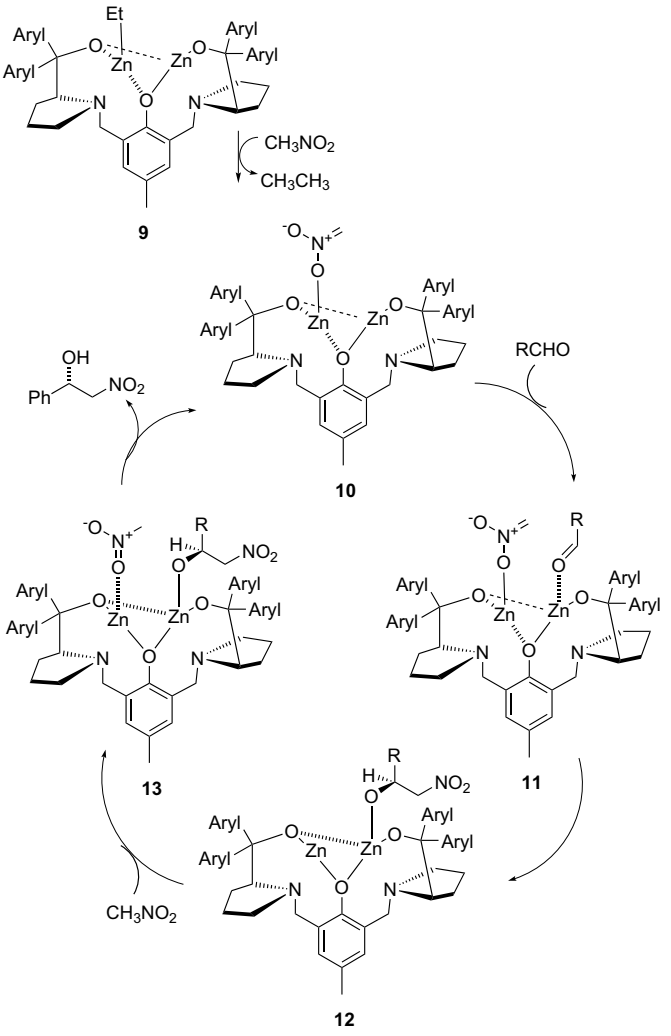
2.2. Dinuclear Zn catalysts

Trost et al. have recently revealed[11] a new class of dinuclear zinc complex **9** for the asymmetric Henry reaction.

This catalyst system, which apparently functions along a route of cooperative activation, similar to Shibasaki's catalyst, efficiently converts α-branched aldehydes to the corresponding β-nitroalcohol (up to 93% ee). However, the yields and enantioselectivities were lower with unbranched aldehydes. By using a lower temperature and more equivalents of nitromethane, researchers were able to increase the selectivity, although their attempts to improve the selectivity by modification of the ligand with phenols of different pKa value were not successful. The catalytic cycle proposed by Trost et al. is believed to proceed through activation of both the nitromethane and the aldehyde by Zn (Scheme 5).

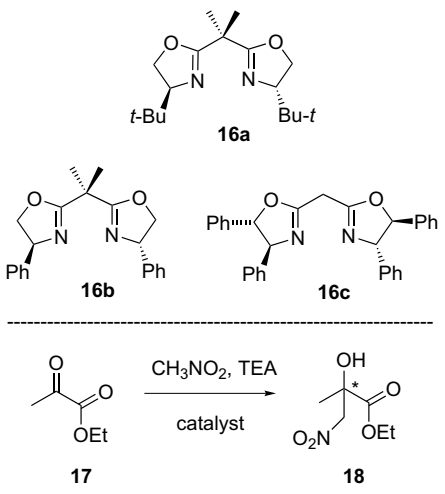
2.3. Cu-Bis(oxazoline) (BOX) catalysts

In general, ketones react more slowly than aldehydes, and their Henry reactions with nitroalkanes tend to be reversible. In addition, enantioface differentiation is rather challenging because of the greater similarity of the two entities flanking the carbonyl group. In a remarkable exception, Jørgensen et al. developed a series of bis(oxazoline)-



Scheme 5. Proposed catalytic cycle for dinuclear zinc complexes.

complexes which in combination with a triethyl amine catalysed the reaction of nitromethane with α-keto esters, (pyruvates) give optically active β-nitro-α-hydroxy esters in high yield and excellent enantiomeric excess (Scheme 6).[12a]

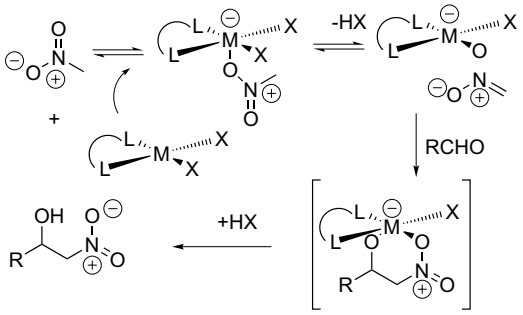


Scheme 6.

The important aspect of this reaction is that it allows the synthesis of enantiomerically pure tertiary alcohols, which are otherwise difficult to prepare. A survey of bis(oxazoline) ligands **16a**, **16b** and **16c** and Lewis acid in the presence of Et_3N revealed that ligand **16a** and $Cu(OTf)_2$ are the best combination for this transformation. This provided the corresponding β-nitro-α-hydroxy ester in 95% yield and 92% ee. However, use of other Brönsted bases resulted in lower ee than equimolar amounts of Et_3N. Interestingly, use of $Zn(OTf)_2$ as Lewis acid effected a reversal of enantioface selection but with low ee. This reaction is very sensitive to the ratio of the reagents used. To rationalise this the authors hypothesised that the reaction proceeds through a series of equilibria.[12b]

To account for the (*R*)-configuration of the product, Jørgensen et al. proposed that a square pyramidal intermediate **19** is initially formed through coordination of an α-keto ester and nitromethane to the copper-centre. The nitronate then formed can approach the ketone only from the *re*-face through a chair like transition state **20**, as the *si*-face is shielded by the *tert*-butyl group of the ligand (Scheme 7).[12b]

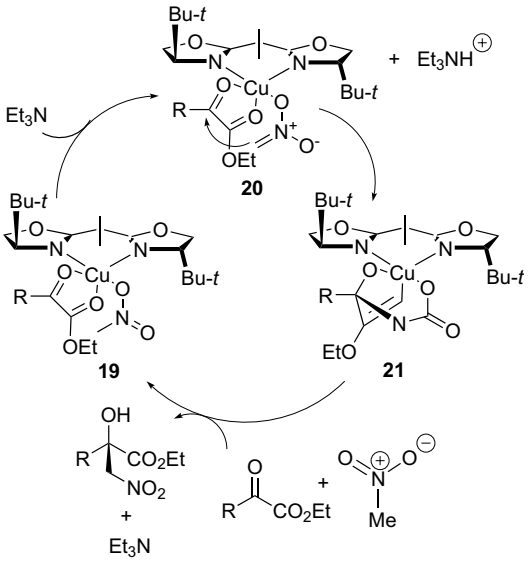
In another important recent report, Evans et al. developed a novel Cu-bis(oxazoline) catalyst which could effect the asymmetric nitroaldol reaction with a variety of aldehydes in excellent yield and enantiomeric excess.[13] Unlike Jørgensen's catalyst, no external base is required for this system. The designing of this catalyst is based on the concept that weakly Lewis acidic metal complexes bearing a moderately charged ligand (X) facilitate the deprotonation of the nitroalkane (Eq. 1) as a prelude to the aldol addition process (Eq. 2).



In this event, the acetate anion displaced from the metal centre of catalyst **22** (Fig. 3) by nitromethane coordination deprotonates the nitroalkane.

2.4. Dual Lewis acid/amine chiral amino alcohol ligand

To circumvent certain inherent difficulties of the metal based bifunctional catalysts such as chemical incompatibility of Lewis acids and Brönsted bases[14] and the occurrence of nonselective base initiated Henry side reactions,[15] Palomo and co-workers recently developed a relatively simple protocol for asymmetric Henry reaction triggered by a



Scheme 7. The catalytic cycle proposed by Jørgensen et al.

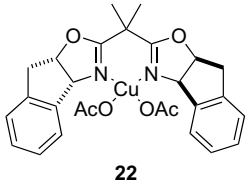
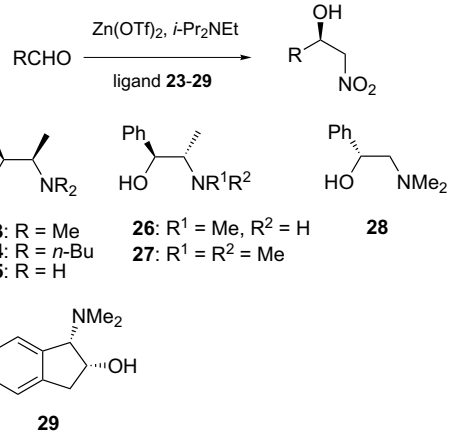


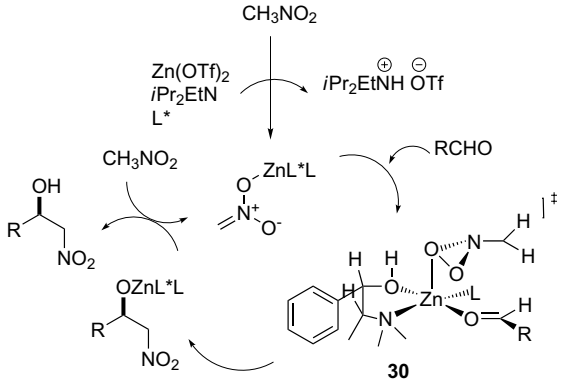
Figure 3.

combination of Zn(II) salt, an amine base and a chiral amino alcohol ligand.[16]

These authors utilised discrete Lewis acids and Brönsted bases as structurally independent entities[17] for concurrent activation of the aldehyde and the nitroalkane. Screening of a series of commercially available amino alcohol ligands for this purpose (Scheme 8) led to the finding that (+)-NME (*N*-methyl epihedrine) **23** in combination with $Zn(OTf)_2$ and *i*-Pr_2EtN and in a molar ratio of 1.5:1:1 provides the best result (90% yield, 90% ee). This optimised condition works well for essentially all aliphatic aldehydes, including some branched and hindered aldehydes in ee up to 98%. However, for aromatic aldehydes, the enantioselectivities were comparatively moderate under the typical reaction temperature (−20 °C). Further lowering of the temperature to −40 °C or to −60 °C resulted in an enhanced enantioselectivity. Although not conclusive, the reaction is proposed to proceed through transition model **30** (Scheme 9).



Scheme 8.



Scheme 9. Proposed reaction pathway and transition state **30**. L* = (+)-NME.

2.5. Tridentate-bis(thiazole) and bis(tetrazole) ligands

The C_2 symmetric tridentate bis(oxazoline)ligands **31** to **33** (Fig. 4) are another important class of ligands, which are supposed to form deeper chiral pocket around the metal centre. These ligands are applied in various asymmetric reactions.[17]

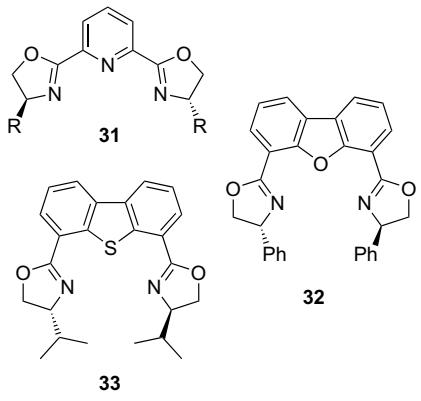
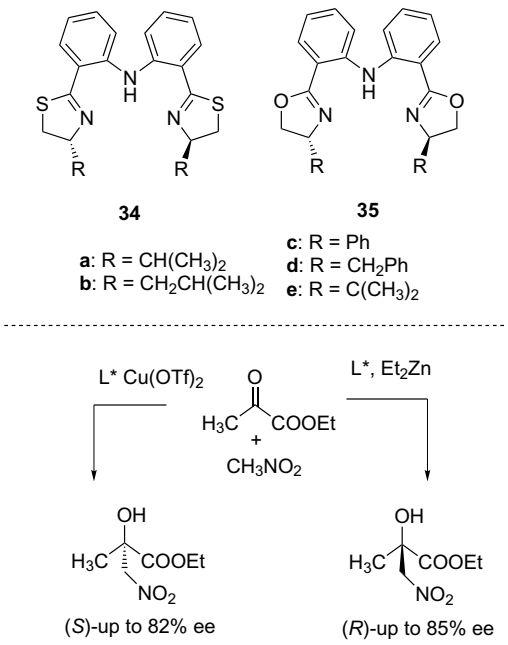


Figure 4.

Working in this line, Xu et al. designed some C_2 symmetric tridentate bis(oxazoline)ligands and bis(thiaxazoline)-ligands[18] **34** to **35** with a diphenylamine backbone for the asymmetric Henry reaction between nitromethane and ethyl pyruvate (Scheme 10).[19] The authors observed that bis(thiaxazoline)ligands gave better enantioselectivity (up to 70% ee) in comparison with bis(oxazoline)ligands

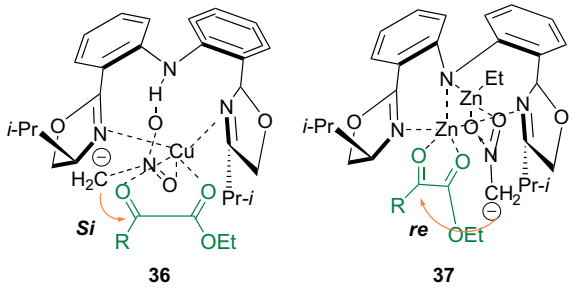


Scheme 10.

(60% ee). Although significant improvements in enantioselectivity were observed in halogenated solvents, the chemical yields were low.

The most appealing feature of this reaction is the reversal of enantioselectivity that can be achieved simply by changing the Lewis acid. Also the role of the amino group in this ligand is very crucial in controlling the enantiofacial selectivity.

From a mechanistic point of view, the authors suggested that since the NH group positioned between the two phenyl groups cannot be deprotonated by Et_3N, it remains available to act as a hydrogen bond donor to orient nitronate **36** (Scheme 11). Under the chiral environment formed by the tridentate ligand and the copper atom, the nucleophile can only approach the α-ketoester from the *si*-face, resulting in the (*S*)-enantiomer. In the Et_2Zn catalysed system, diethyl zinc causes the deprotonation of the NH group and a dinuclear zinc catalyst is formed through coordination of **37**. The reaction proceeds by nucleophilic attack of the nitronate on the α-ketoester from the *re*-face, under this chiral environment, to afford the (*R*)-enantiomer.



Scheme 11.

2.6. Diethyl zinc triggered reactions

Zinc based catalysts are especially interesting because they are compatible with aqueous system as zinc enolates have been identified as intervening species in aldol reactions catalysed by type II aldoses.[20]

Following Trost's work of dinuclear zinc catalyst, Reiser et al. disclosed in detail that the Henry reaction can be promoted by Et_2Zn in the assistance of either diamine or amino alcohols.[21] Working in this area Lin and co-workers synthesised a new class of β-amino alcohol ligands with a bicyclo[3,3,0]octane scaffold for enantioselective Henry reactions.[22] Under optimal conditions, the complex formed in situ between 5 mol % of **38** (Fig. 5) and 10 mol % of Et_2Zn catalysed Henry reaction between nitromethane and a variety of aldehydes in moderate enantioselectivity.

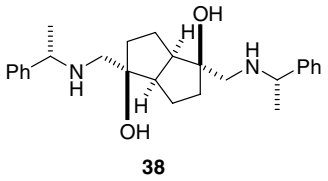


Figure 5. β-Amino alcohol ligand developed by Lin et al.

In another report, Martell et al. synthesised some new macrocyclic thioaza ligands with specific metal binding and asymmetric catalytic properties.[23] The trimeric chiral ligand **39** (Fig. 6) has been shown to be an efficient chiral auxiliary for the enantioselective Henry reaction triggered by Et_2Zn. Although the study is still underway, the trimeric chiral domino macrocycle may provide an opportunity to observe the cooperative mechanism.

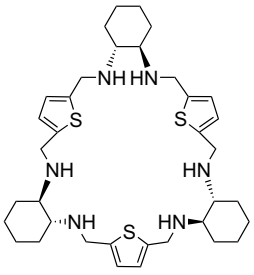


Figure 6. N_6S_3-Donor macrocyclic ligand.

2.7. Ketoamino cobalt complexes

Ketoamino cobalt complexes are known to have considerable catalytic potential due to their Lewis acidic nature.[24] These types of complexes are usually prepared in aqueous solution and their axial sites are occupied either by water or by oxygen containing compounds such as THF, still these complexes act as Lewis acids and are compatible with Lewis bases such as water, nitrone and amines.[25] Based on this idea, Yamada et al. synthesised some chiral ketoamino

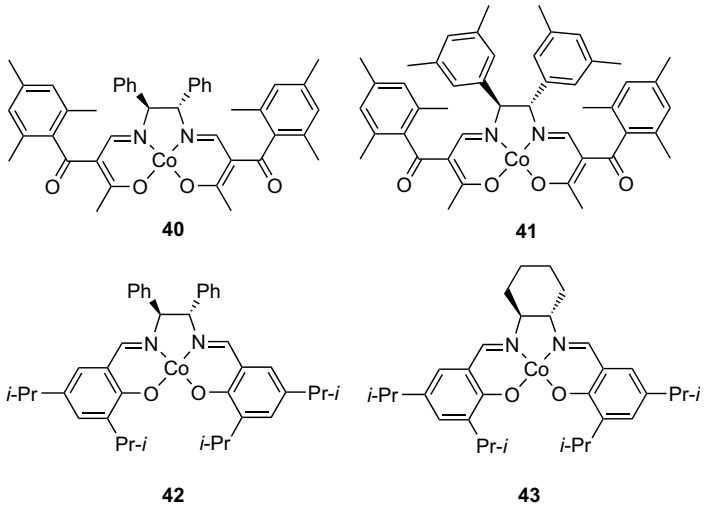


Figure 7.

cobalt complexes and employed them in the asymmetric Henry reaction.[26] Investigation of the catalytic activity of these complexes revealed that in the presence of *i*-Pr_2EtN, 2 mol % of cobalt complexes with optically active 1,2-diarylethylene diamines **40** and **41** (Fig. 7) can mediate the reaction between nitromethane and aldehyde in ee up to 84%. For *ortho*-halo substituted aldehydes, these complexes showed enhanced enantioselectivity (up to 92%); however, the reason for this is not clear.

As the cobalt salen complexes developed for HKR are also compatible with nucleophilic compounds such as phenol and water,[27] in subsequent studies Yamada et al. employed commercially available cobalt salen complexes **42** and **43** (Fig. 7) for the enantioselective Henry reaction.[28] In the presence of *i*-Pr_2EtN, as little as 2 mol % of the cobalt salen complexes promotes condensation of nitromethane with aromatic aldehydes with enantioselectivity ranging from 62% to 98%. In this instance, also improved enantioselectivity was noticed for the *ortho*-halo substituted aldehydes.

2.8. Metal complexes on solid support

In order to derive and achieve advantages, such as simplification of the work-up, easy separation of reaction mixture, reuse and possibility to design continuous flow process, Abadi et al. anchored chiral BINOL ligand on silica and mesoporous MCM-41.[29]

These anchored ligands **44** with a lanthanum content of 0.12–0.18 mmol/g (Fig. 8) catalyse the Henry reaction with ee 55–84%. The solid catalysts can be reused several times without much loss in activity.

2.9. Other metal complexes

Sedlák et al. recently reported some copper(II) complexes of *N*,*N*-bidentate ligands derived from 2-(4-isopropyl-4-methyl-4,5-dihydro-1*H*-imidazole-5-one-2-yl)pyridines. These complexes, which exist as a monomer as well as a dimer in various proportions in gas phase and in solution phase (Scheme 12), catalyse the condensation between 4-nitro benzaldehyde and nitromethane in good to moderate yield. Unfortunately the asymmetric induction was poor (4–19% ee).[30]

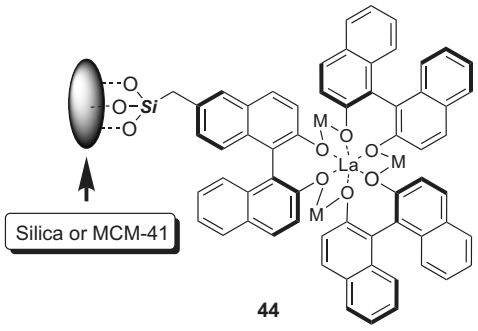
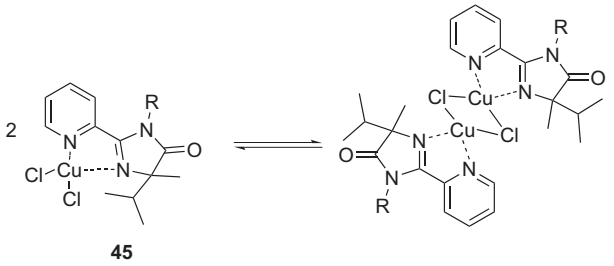
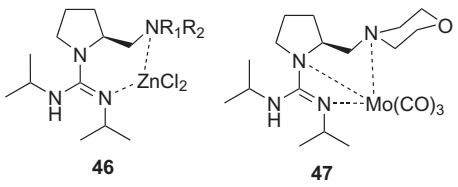


Figure 8.



Scheme 12.

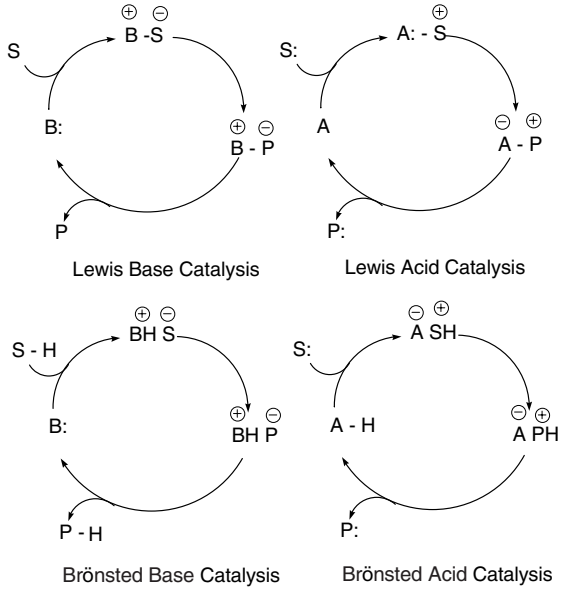
In another report, Anders et al. synthesised some zinc guanidine complexes in which chiral guanidine units bis coordinate the zinc centres and a molybdenum complex in which the chiral guanidines act as a tridentate ligand (Scheme 13). However, the results of the asymmetric nitro-aldol condensation using these catalysts were insignificant (2% ee).[31]



Scheme 13.

3. Organocatalytic Henry reaction

In recent years, it has been established that small organic molecules can also be highly selective and efficient catalysts such as biocatalysts (enzymes) and metal complexes in asymmetric C–C bond forming reactions. Although discovered long ago,[32] the area of enantioselective organocatalysis became the focus of research recently. List et al. broadly classified the organocatalysis as Lewis bases, Lewis acids, Brönsted bases and Brönsted acids and also suggested simplified catalytic cycles for these catalysts (Scheme 14).[33]



Scheme 14. Organocatalytic cycles proposed by List et al.

As shown, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrate (S:) in a similar manner. Brönsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively. However, the major drawback of the mechanistic classification approach is the typical lack of information on the mechanisms of most organocatalytic reactions.

3.1. Guanidine derived organocatalysts

3.1.1. Enantiopure guanidine catalysts. In 1994 Najera et al. reported the first organocatalytic asymmetric Henry reaction using enantiomerically pure guanidines with or without C_2-symmetry (Fig. 9).[34] Although enantiomeric excess not higher than 54% was achieved in the condensation between nitromethane and aromatic or aliphatic aldehydes, this brought forward a new concept to the asymmetric Henry reaction. Almost ten years later, Allingham et al. reported the synthesis of some C_2-symmetric guanidinium salts for the asymmetric Henry reaction, but the results were less significant (20% ee).[35]

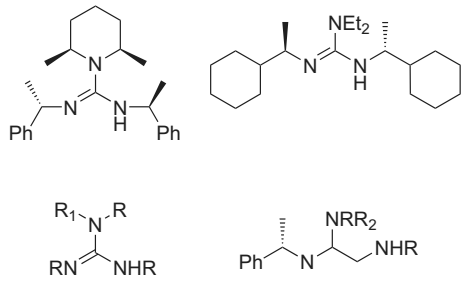
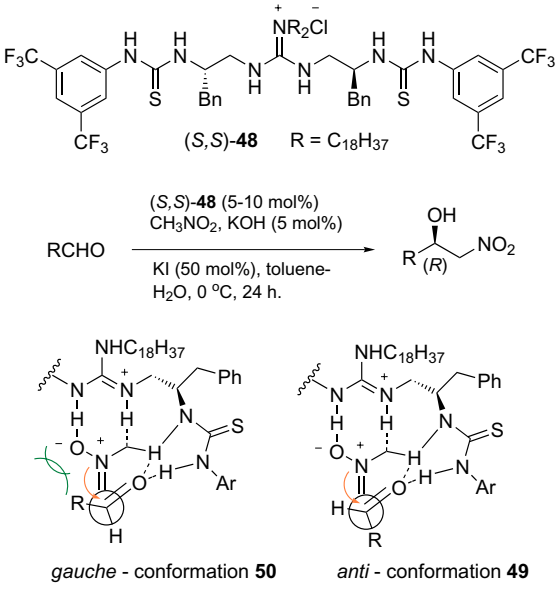


Figure 9. Catalyst developed by Najera et al.

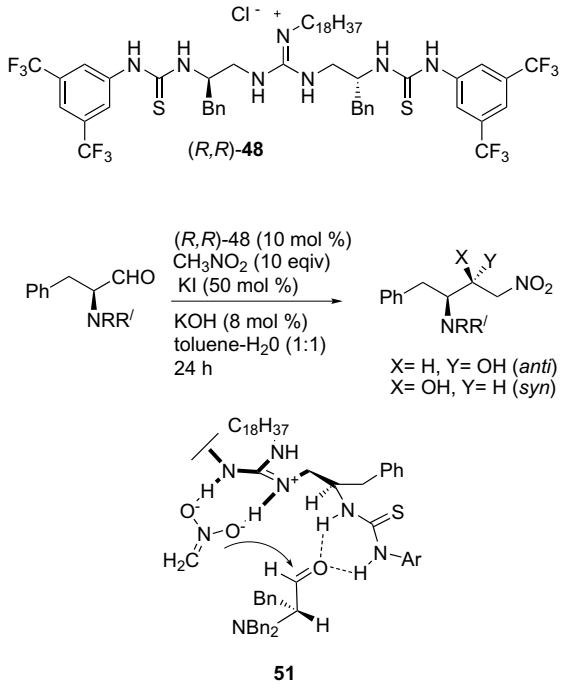
3.1.2. Guanidine based bifunctional catalysts. In a significant recent advance in this area, Nagasawa et al. reported some broadly effective linear guanidine–thiourea based bifunctional catalysts, with guanidine and thiourea groups linked to a chiral spacer (phenylalanine) for an enantio- as well as diastereoselective Henry reaction.[36] Under the optimal conditions, 10 mol % of the octadecyl substituted catalyst **48** in the presence of KI as additive in a biphasic system of toluene and aqueous KOH promotes condensation between nitromethane and aliphatic α-branched aldehydes in 70–91% yield and 82–92% ee. However, for aliphatic unbranched aldehydes the ee was much lower (55%). To account for the (*R*)-configuration of the newly generated asymmetric centre, these researchers reasoned that the reaction proceeds through the favourable



Scheme 15.

anti conformational transition state **49** rather than the *gauche* conformation **50** (Scheme 15).

Further exploration on the applicability of this catalyst showed that under similar conditions, this catalyst works remarkably well in the reaction between α-amino- or hydroxyl-aldehydes and nitromethane to afford the *anti* nitroalcohol as the major product (Scheme 16).[37]



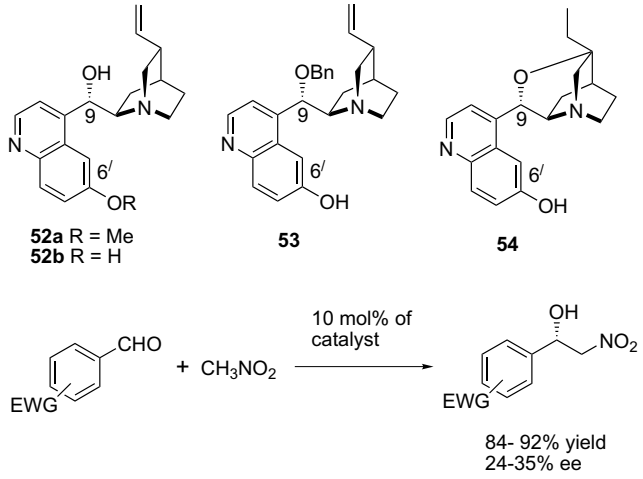
Scheme 16.

The matched combination for this catalytic system was found to be an (*S*)-aldehyde and (*R*,*R*)-**48**, which can be explained in terms of transition state **51**. A year later the same group disclosed that a Henry reaction of prochiral nitroalkane, such as nitroethane and a variety of aldehydes under the influence of (*S*,*S*)-**48**, gives predominantly the *syn*-nitroalcohols (diastereoselectivity 86:14 to 99:1) and ee in the range of 84–99%.[38] The newly generated stereochemistry of the product was found to be consistent with the already proposed transition state.

3.2. Cinchona alkaloid derived organocatalysts

In general, cinchona alkaloids are known to act as a chiral Brönsted base by creating an effective asymmetric environment (Fig. 10).[39]

In 2005, Hiemstra et al. introduced cinchona derived bifunctional catalysts **52**, **53** and **54** for a reaction between activated aromatic aldehyde and nitromethane (Scheme 17).[40]



Scheme 17.

Although the scope and enantioselectivities were modest, the authors made an important discovery that a hydrogen bond donor at C6′ is mandatory for asymmetric induction. Since the phenol moiety and the basic quinuclidine nitrogen atom can be in reasonable proximity in solution, the enantioselectivity could arise from a double activation of both the nucleophile and the electrophile.[41]

In an attempt to improve this catalyst, these authors envisioned that replacement of the phenol moiety with a better hydrogen bond donor could result in a more powerful and more enantioselective catalyst. Thus, in a modification, bench stable catalyst **55** was prepared on a multigram scale. This catalyst works remarkably well under the optimised condition for the condensation of nitromethane with

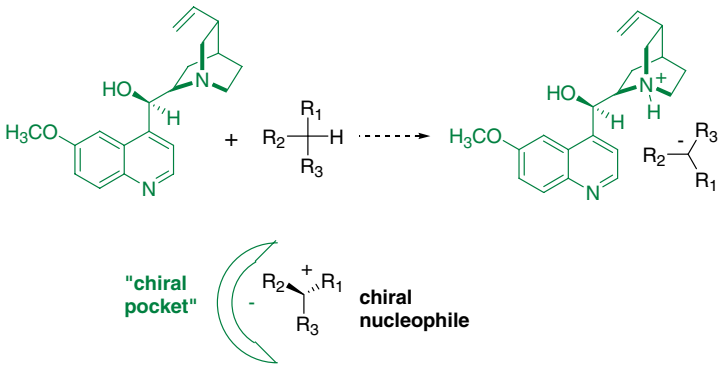
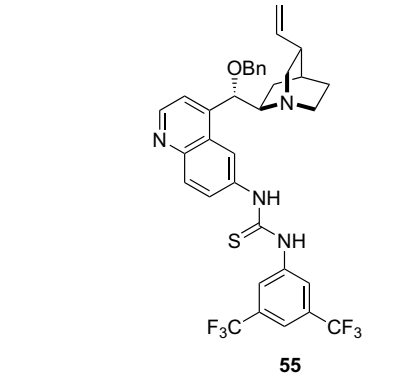
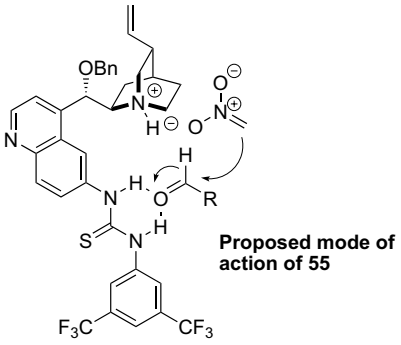


Figure 10. Reaction between cinchona alkaloid and a compound having an acidic proton.

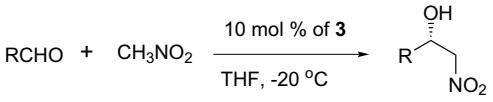


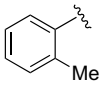
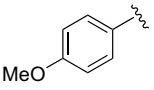
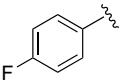
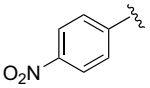
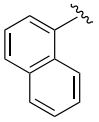
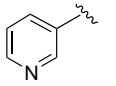
55



56

Proposed mode of action of 55



R	Yield (%)	ee (%)	t (h)
	90	92	48
	97	91	96
	94	89	168
	99	85	24
	91	86	4
	99	92	48
	91	86	24
	91	95	24

Scheme 18.

aromatic and heteroyclic aldehydes to give the nitroalcohol in consistently high yield and enantioselectivity (Scheme 18).[42] On the other hand, the pseudo enantiomer of **55** also gave excess nitroalcohol with an opposite configuration and comparable ee. Although not conclusive transition model **56** is invoked for this reaction, where the thiourea moiety activates the aldehyde through double hydrogen bonding, while the basic quinuclidine nitrogen activates the nitromethane.

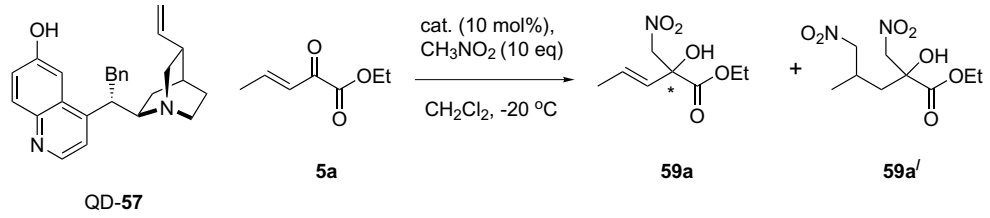
Nitroaldol reactions in alkenyl α-ketoesters are particularly challenging since these substrates can engage in 1,2- as well as 1,4-addition with nitroalkane. Deng et al. developed cinchona alkaloid derived catalysts **57a**–**d**, which can engage in a hydrogen bonding interaction with a range of nucleophiles and electrophiles either through the quinuclidine nitrogen or through the 6′-OH.[43] These catalysts act reasonably well for the chemoselective addition of nitromethane to **58a** to afford nitroalcohol **59a** with high ee (Scheme 19).

Catalysts QD-**57d** and Q-**57d** are particularly noteworthy, since these can promote reactions between a broad range of aryl and alkyl α-ketoesters with a relatively low loading (5 mol %) of the catalyst.

3.3. Silyl nitronates as activated nitroalkanes

The fluoride ion promoted Henry reaction of silyl nitronates has been known in the literature for some time.[44] An asymmetric version of this reaction was first reported by Jørgensen et al. using bisoxazoline ligands **16a**–**c** (20 mol %) with tetrabutylammonium triphenylsilyl difluorosilicate (TBAT 20 mol %) as the fluoride source.[45] Unfortunately, the coupling of propyl- and hexyl-silylnitronates with various aldehydes resulted only in moderate yields and enantioselectivities. Since the products were prone to retro-Henry reactions, they were immediately converted into the Mosher ester. The *anti* products were obtained preferentially, but in general, both yields (30–80%) and enantioselectivities (40–65%) were less impressive. Maruoka et al. reported better results with the use of a catalytic chiral fluoride source.[46] The addition of trimethyl silyl nitronate **60** to aromatic aldehydes in the presence of 2 mol % of the chiral quarternary ammonium fluoride salt **62** gave **61** with *anti*:*syn* ratios usually higher than 90:10 with more than 90% ee (Scheme 20).

However, poorer results were obtained when aliphatic aldehydes were involved, the observed *anti* selectivity can be explained on the basis of an extended transition state model,



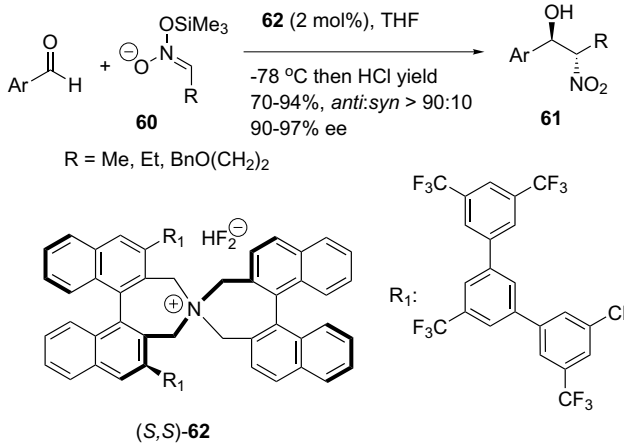
QD-**57**

a R = H
b R = Bn
c R = PHN
d R = Bz

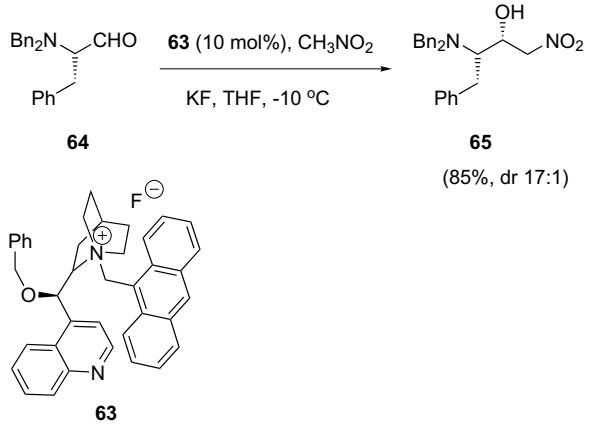
Q-**57**

catalyst	conv. (%)	**59a**/**59a'**	ee (%)
Et_3N	>95	80/20	
QD	91	>95/5	-17
DHQD-PHN	74	>95/5	59
$(DHQD)_2AQN$	>95	>95/5	40
beta-ID	>95	>95/5	61
QD-**57a**	>95	>95/5	86
QD-**57b**	93	>95/5	70
QD-**57c**	93	>95/5	93
QD-**57d**	>95	>95/5	97
Q-**57d**	>95	>95/5	-97

Scheme 19.



Scheme 20.



Scheme 21.

which involves a chiral ammonium nitronate as active species.

3.4. Miscellaneous

A special case worth commenting on is the Henry reaction of α-amino aldehydes to provide the corresponding nitroaldol product. Corey et al. used quartenary ammonium salt **63** in the presence of finely divided KF for a highly diastereoselective condensation of *N*,*N*-dibenzyl-(*S*)-phenyl alanine and nitromethane to afford the *syn* nitroalcohol **65** as the predominant product (dr 17:1) (Scheme 21).[47] This product was then transformed into HIV protease inhibitor Amprenavir in a few steps.

Matsumoto et al. have found that no added catalyst is needed for the reaction to proceed in high diastereoselectivity and little or no racemisation if high pressure (8 kbar) is applied.[48] The implicit concept is that the substrate itself may act as a catalytic chiral base, an idea that might be extended to other types of reaction. For a diastereoselective Henry reaction of α and β hydroxy aldehydes, we found that Shibasaki's heterobimetallic complex works reasonably well. This reaction was then successfully used in the total synthesis of natural products (+)-boronolide[49] and (+)-preussin.[50]

4. Conclusion

In this review, we have attempted to cover the different catalyst systems used for carrying out asymmetric Henry reaction, although details on the synthetic applications of these methodologies are not included here. From the current degree of development, it is understandable that most of the catalysts developed so far are substrate dependent, and nitroalkanes other than nitromethane have been less studied. Some principles have already been set to understand the mechanisms of reactant activation and stereocontrol, yet much effort is needed for a complete understanding of the basis of reactivity and selectivity. Nevertheless, the asymmetric Henry reaction is a rapidly growing area that

without doubt will continue to yield exciting results in the coming years.

Acknowledgement

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