Morita–Baylis–Hillman Reaction

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The Enantioselective Morita–Baylis–Hillman Reaction and Its Aza Counterpart

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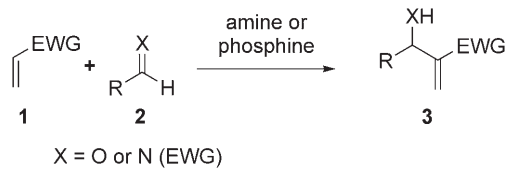
The development of asymmetric Morita–Baylis–Hillman (MBH) reactions has evolved dramatically over the past few years, parallel to the emerging concept of bifunctional organocatalysis. Whereas organocatalysis is starting to compete with metal-based catalysis in several important organic transformations, the MBH reaction belongs to a group of prototypical reactions in which organocatalysts already display superiority over their metal-based counterparts. This Minireview summarizes recent mechanistic insights and advances in the design and synthesis of small organic molecules for enantioselective MBH and aza-MBH reactions.

1. Introduction

The Morita–Baylis–Hillman (MBH) reaction can be broadly defined as a condensation of an electron-deficient alkene and an aldehyde catalyzed by a tertiary amine or phosphine.[1] Imines can also participate in the reaction if they are appropriately activated, and in this case the process is commonly referred to as the aza-Morita–Baylis–Hillman (aza-MBH) reaction (Scheme 1). These operationally simple and atom-economic reactions afford α-methylene-β-hydroxycarbonyl or α-methylene-β-aminocarbonyl derivatives **3**, which comprise a contiguous assembly of three different functionalities. Popularized by the work of Drewes and Emslie[2] and Hoffmann and Rabe at the beginning of the 1980s,[3] these highly valuable building blocks have found wide applications in the synthesis of medicinally relevant compounds as well as complex natural products.[4]



Scheme 1. A generic Morita–Baylis–Hillman (MBH) reaction. EWG: electron-withdrawing group.

Earlier efforts have addressed the intrinsic drawbacks associated with the MBH reaction, including low reaction rates, poor conversion, and limited substrate scope. These issues have now been partially resolved by applying physical or chemical methods.[5] However, the progress of the much sought after enantioselective version of the MBH reaction is slow despite a considerable amount of efforts devoted to the field. It is fair to say that only very few efficient catalytic enantioselective MBH reactions were known up to the year 2000, with the disclosure of Hatakeyama's catalyst (β-isocupreidine; see Section 3.1.1) in 1999 being a notable exception.[6] The complexity of the reaction sequence and the oversimplified mechanistic view probably misled the working direction and could be responsible for the slow development.

The use of small organic molecules as catalysts to perform asymmetric transformations has received increasing attention over the past decade.[7] Being a prototypical nucleophile-induced transformation, the MBH/aza-MBH reactions are indeed ideal (though challenging) candidates for the development of organocatalysts. Since 2000, chiral multifunctional organocatalysts have been designed with much higher "hit" rates in promoting successful enantioselective MBH/aza-MBH processes. This Minireview will focus on the development of this exciting field, including recent mechanistic studies and their implication on future catalyst development.

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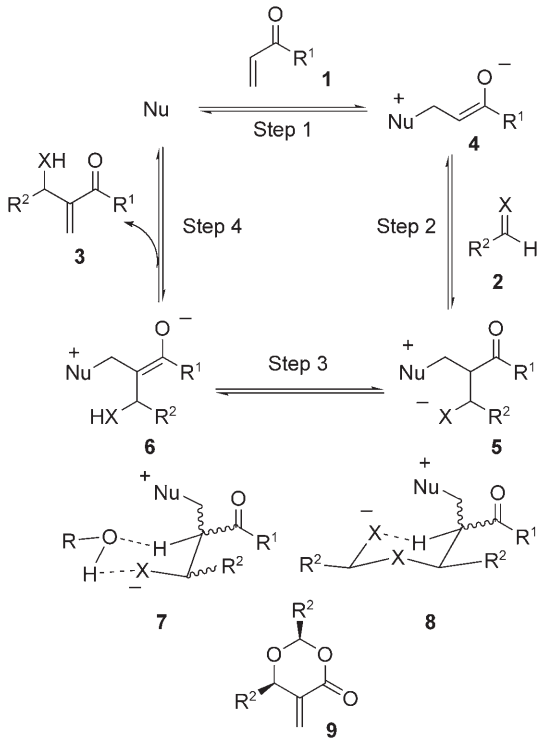
2. Recent Mechanistic Insights

The MBH reaction involves formally a sequence of Michael addition, aldol reaction, and β elimination. A commonly accepted mechanism is depicted in Scheme 2. A



Scheme 2. Proposed mechanism for the MBH reaction.

reversible conjugate addition of the nucleophilic catalyst to the Michael acceptor **1** generates an enolate **4** (step 1), which can intercept the aldehyde or the acylimine **2** to afford the second zwitterionic intermediate **5** (step 2). A proton shift from the α-carbon atom to the β-alkoxide/amide (step 3) followed by β elimination affords then the MBH adduct **3** with concurrent regeneration of the catalyst (step 4).[8]

The aldol reaction between **4** and **2** generates two stereogenic centers (step 2) and has for a long time been considered as the rate-determining step (RDS). However, this view was recently challenged and refined thanks to the detailed mechanistic studies carried out by the group of Aggarwal et al.[9] and McQuade and co-workers[10] on the MBH reaction and by Leitner and co-workers[11] and Jacobsen and Raheem[12] on the aza-MBH reaction. Key factors and conclusions are summarized as follows:

a) On the basis of the initial rate measurement, the 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed reaction between methyl acrylate and *p*-nitrobenzaldehyde showed a significant primary kinetic isotope effect (KIE, $K_H/K_D = 2.2–5.2$ depending on the solvent used) when α-deuteriomethyl acrylate was used, and a large inverse isotope effect ($K_H/K_D = 0.72–0.80$) when α-deuterio-*p*-nitrobenzaldehyde was employed. Similarly, a prominent KIE ($K_H/K_D = 3.81$) for the reaction between methyl acrylate and *N*-(*p*-nitrobenzenesulfonyl)imine was observed. These results strongly suggested that deprotonation of the α-H(D) atom of **5** (step 3) was rate-limiting. While the intramolecular proton transfer from the α-carbon atom to the vicinal alkoxide/amide anion is not impossible, it is not a particularly facile process especially in the case of the *anti* stereomer **5**, as a result of geometric constraints. Two alternative transition states (**7** and **8**, Scheme 2) have been proposed to account for the proton shift.[9,10] The involvement of **7** was supported by the fact that the reaction was accelerated in the presence of protic solvents[5,13] and that it can be autocatalytic.[14] The possible implication of hemiacetal **8** in aprotic solvent was, on the other hand, in accord with the observation that the MBH reaction was second order with respect to the aldehyde. The frequent isolation of dioxanone as the side product of the MBH reaction also credited this hypothesis.

b) The stereogenic center of the MBH adduct is created in step 2, which is formally an aldol reaction. In light of the formidable achievements in the enantioselective aldol process,[15] one might expect that a highly enantioselective MBH reaction should be easily achievable. However, the

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MBH reaction seems to be more complicated than this oversimplified mechanistic view. Indeed, even a diastereoselective MBH reaction was difficult to realize when a chiral aldehyde or chiral Michael acceptor was used as reaction partner.[16] On the basis of their mechanistic studies, Aggarwal et al.[9] and Jacobsen and Raheem[12] suggested in accord with Hatakeyama's earlier rationale (see Section 3.1.1) that in designing chiral catalysts for MBH and aza-MBH reactions, one has to consider not only the enantioselectivity and the diastereoselectivity of the aldol condensation (step 2) but also the different fate of the diastereomers in the subsequent proton-shift step (step 3). If a catalyst was designed such that it could favor (promote) the proton shift of one of the four diastereomers, then a highly enantioselective MBH reaction may result as step 2 is reversible.

c) In the phosphine-catalyzed aza-MBH reaction, racemization may take place through a deprotonation/protonation sequence.[11]

Most of the efficient catalysts developed during the past five years are based on a working hypothesis that may not be in line with these most recent mechanistic considerations. Notwithstanding this fact, the deeper mechanistic insight and better understanding we now have of the basic factors that control the reactivity and selectivity of this reaction will certainly have an impact on future catalyst development.

3. Chiral Lewis Base Catalysts

The MBH reaction is catalyzed by a nucleophile, either an unhindered tertiary amine or a trialkylphosphine. It is thus not surprising that earlier efforts focused on the use of chiral nucleophiles.

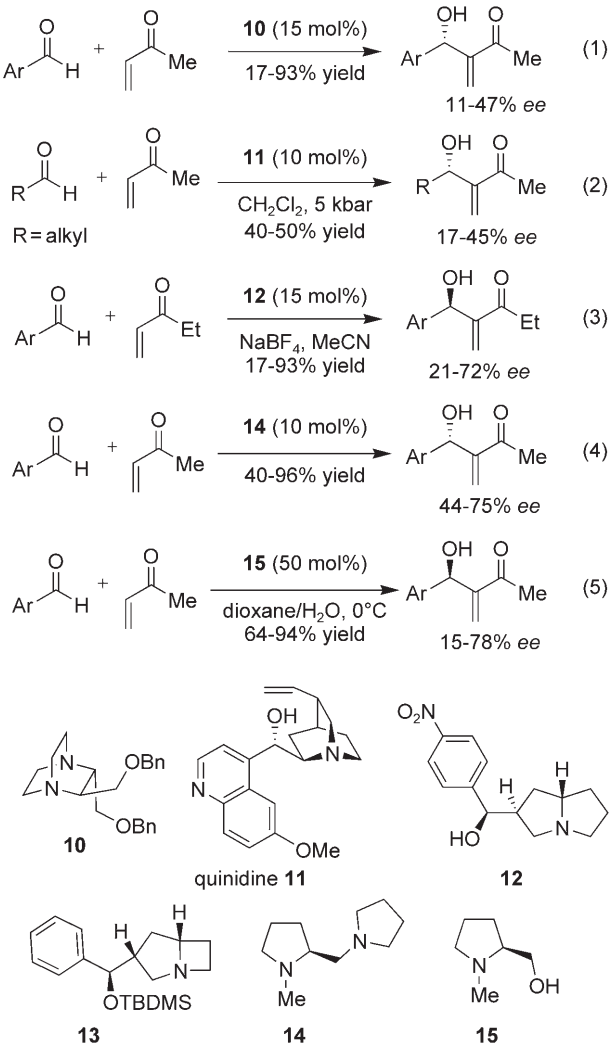
3.1. Nucleophilic Chiral Tertiary Amine Catalysis

3.1.1. Bifunctional Catalysts Derived from Pyrrolidines and Cinchona Alkaloids

Chiral amines have been extensively used in the field of asymmetric synthesis as chiral ligands, but quite recently they have emerged as effective organocatalysts for enantioselective transformations.[17]

Hirama et al. prepared the enantiopure DABCO derivative, the C_2-symmetric 2,3-bis(benzyloxymethyl)-1,4-diazabicyclo(2.2.2)octane (**10**) and found that the highest *ee* value (47%) was obtained when the reaction was run at high pressure (Scheme 3, equation 1).[18] The parent compound 2,3-bis(hydroxymethyl)-1,4-diazabicyclo(2.2.2)octane was not examined in this study.

Cinchona alkaloids have been widely used as resolving agents, as ligands for metal-mediated processes, as phase-transfer catalysts,[19] and as organocatalysts.[20] Several of these alkaloids bear acidic hydroxy groups besides the basic amine functionality, suggesting that they could act as bifunctional catalysts.[21] Markó et al. were the first to use quinidine **11** as catalyst for the MBH reaction. Under optimized conditions



Scheme 3. Early examples of chiral Lewis base catalyzed enantioselective MBH reactions. Bn: benzyl; TBDMS: *tert*-butyldimethylsilyl.

(CH_2Cl_2, 25 °C, 5 kbar), the reaction between aliphatic aldehydes and methyl vinyl ketone (MVK) afforded the allylic alcohol (R = cyclohexyl) with 45% *ee* (*S* configuration; Scheme 3, equation 2).[22] The presence of the free hydroxy group in **11** is important as no enantioselectivity was observed when *O*-acetylquinidine was used as catalyst. Other β-amino alcohols such as *N*-methylprolinol and *N*-methylephedrine afforded the MBH adduct with notably low enantioselectivity under otherwise identical conditions.

Barrett et al. developed chiral bicyclic pyrrolizidine derivatives **12** as asymmetric catalysts for the MBH reaction of ethyl vinyl ketone (EVK) and electron-deficient aldehydes (Scheme 3, equation 3).[23] The advantage of this catalyst is that the MBH reaction can be performed at atmospheric pressure with reasonable chiral induction. Addition of a Lewis acid ($NaBF_4$ or $NaBPh_4$) was found to be beneficial to the enantioselectivity, leading to the MBH adduct (*R* configuration) with up to 72% *ee*. The same group also designed and synthesized a chiral bicyclic azetidine derivative **13** based on the consideration that **13** should be more reactive than the pyrrolizidine **12** as a result of the increased pyramidalization

of nitrogen in the former catalyst. Indeed, significant rate acceleration was observed when **13** was used instead of **12** as a catalyst. Unfortunately, the *ee* value of the MBH adduct remained low (26% *ee*). Note that the hydroxy group in **13** was protected as a TBDMS ether, which could be responsible for the reduced enantioselectivity.

More recently, Hayashi et al. reported that chiral diamine **14**, easily prepared from L-proline, catalyzed the MBH reaction to afford the product with up to 75% *ee* (*S* configuration, Scheme 3, equation 4).[24] On the other hand, Krishna et al. used *N*-methylprolinol **15** as a chiral bifunctional catalyst to catalyze the MBH reaction between ethyl acrylate or methyl vinyl ketone with aromatic aldehydes (Scheme 3, equation 5).[25] The reaction is best performed in protic solvent (dioxane/water), and the presence of the primary alcohol in **15** was found to be important for both the reactivity and the enantioselectivity of the catalyst. Note that *N*-methylprolinol **15** was previously examined by Markó et al and found to be ineffective when the reaction was performed in dichloromethane.[22]

The ability of a hydroxy group to enhance the rate of the MBH reaction is well documented. Both Markó and Barrett have proposed a similar ternary complex in which the hydroxy group is bonded to the aldehyde through either a hydrogen bond (**16**) or a metal–oxygen bond (**17**, Figure 1). In both

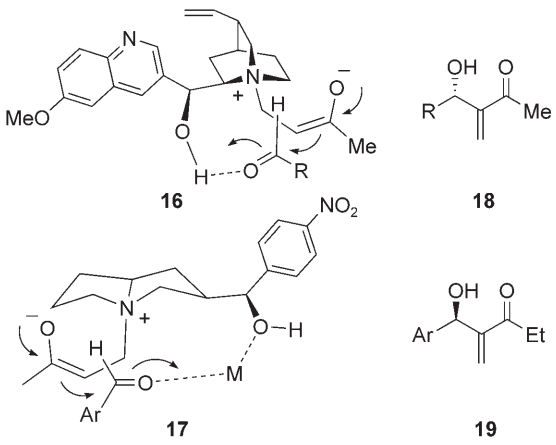
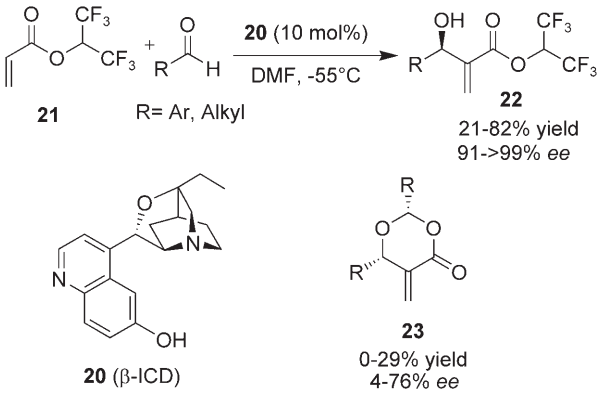


Figure 1. Proposed transition states for a chiral hydroxylated Lewis base catalyzed MBH reaction.

transition states, the geometry of the incipient enolate was assumed to be *Z*, which indeed could be stabilized by electrostatic interactions.[16a] With **16**, addition of an enolate to the *Re* face of the aldehyde would give the *S* adduct **18** as the major enantiomer, whereas with **17** the enolate would attack the aldehyde from the *Si* face to afford the *R* adduct **19**. Although these models explained well the experimental outcome, they were probably oversimplified if we take into consideration the recent mechanistic studies as discussed in Section 2.

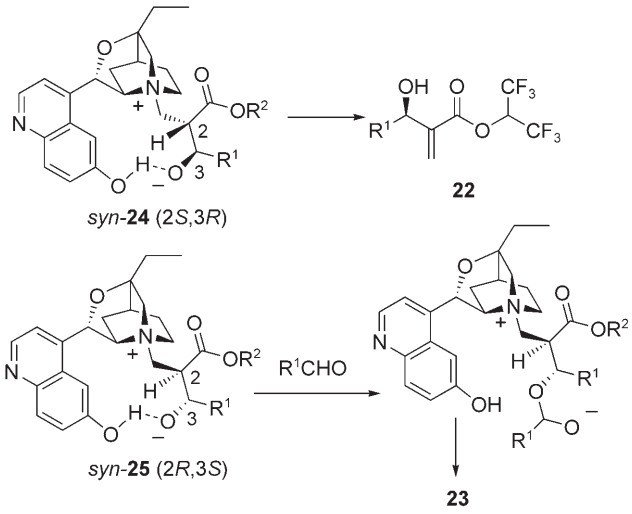
A breakthrough came in 1999 when Hatakeyama et al. discovered that β-isocupreidine (β-ICD, **20**) is an efficient catalyst for the MBH reaction (Scheme 4).[26] In the presence of 10 mol% of catalyst **20**, the reaction of highly reactive



Scheme 4. β-Isocupreidine (β-ICD; **20**): the first highly efficient catalyst for enantioselective MBH reactions. DMF: *N*,*N*-dimethylformamide.

1,1,1,3,3,3-hexafluoroisopropyl (HFIP) acrylate **21** with various aromatic and aliphatic aldehydes at −55 °C afforded *R*-allylic alcohols **22** in moderate yield and with excellent enantioselectivity (up to 99% *ee*). Interestingly, the dioxanone **23** isolated in some cases has the opposite absolute configuration to **22**.

The opposite configurations of compounds **22** and **23** is intriguing. It is assumed that both *syn* diastereomers were produced from the aldol reaction; *syn*-**24** (2*S*,3*R*) was apt for rapid β elimination leading to (*R*)-**22**, whereas *syn*-**25** (2*R*,3*S*) was less prone to this process owing to steric constraints and underwent condensation with the second molecule of aldehyde to afford the hemiacetal intermediate that is subsequently converted into the dioxanone **23** (Scheme 5). It was speculated that both diastereomers **24** and **25** are stabilized by

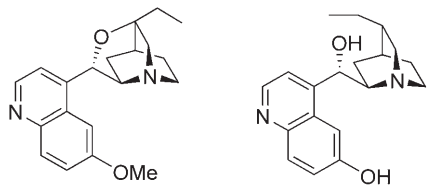


Scheme 5. Hatekeyama's rationalization on the formation of **22** and **23**.

intramolecular hydrogen bonding between the oxy anion and the phenolic hydroxy group, although this would produce a 13-membered cyclophane with high ring strain. Nevertheless, the formation of postulated hydrogen-bonding intermediates

24 and **25** could be assisted by the conformational preorganization of β-ICD.[27] Indeed, both solution and solid-phase structures showed that the nitrogen atom and phenol are in close proximity in their low-energy conformations. A few additional comments on Hatakeyama's catalyst are listed below:

a) Both the rigid tricyclic structure and the phenolic OH group are indispensable for obtaining a high degree of asymmetric induction as well as rate acceleration. Thus, neither *O*-methyl-β-isocupreidine (**26**) nor the *O*-demethylated hydroquinidine **27** that lacks the tricyclic cage structure is effective for the asymmetric MBH reaction. Overall, the nucleophilic nitrogen atom in the quinuclidine moiety of **20** acts as a Lewis base to initiate the MBH reaction, whereas the phenolic OH group acts as a Lewis acid to stabilize and organize the enolate intermediate and also to promote the subsequent aldol addition. Consequently, β-isocupreidine (**20**) is considered to be a typical bifunctional chiral organocatalyst.



26 **27**

b) The HFIP ester **21** is not only responsible for rate acceleration but also is essential for the high enantioselectivity of the process. Methyl acrylate[28] and other linear fluorine-containing acrylates[29] afforded the MBH adduct with negligible *ee* values under otherwise identical conditions. Highly reactive α-naphthyl acrylate[30] was also examined and found to give the MBH adduct with moderate to good selectivity.[28]

c) Importantly from a practical point of view, the one-step synthesis of β-isocupreidine (**20**) from quinidine has recently been improved by simply prolonging the reaction time from 5 days to 10 days. Under optimized conditions (10 equiv KBr, 85% H_3PO_4, 100 °C, 10 days), β-ICD (**20**) can now be isolated in over 60% yield. The higher reactivity of azeotropically dried β-ICD over "undried" β-ICD (β-ICD co-crystallizes with a molecule of water and a molecule of MeOH) was also noted.[29]

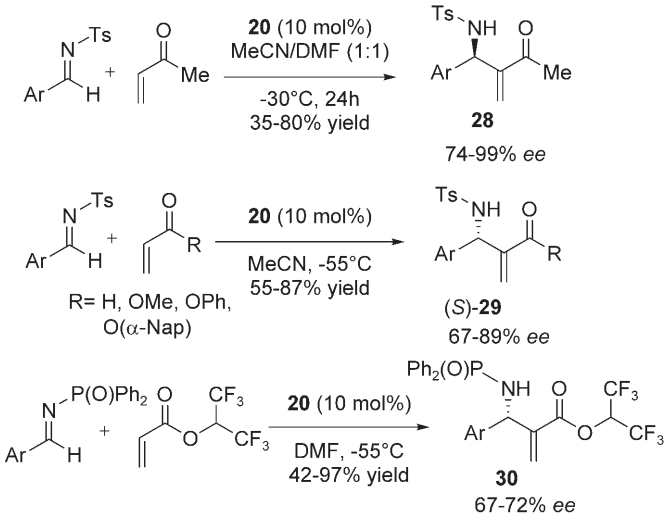
Hatakeyama and co-workers subsequently applied their catalyst to the development of an efficient asymmetric synthesis of (−)-mycestericin E[31] and epopromycin B which involve a β-ICD-catalyzed MBH reaction as a key step.[32]

The aza-MBH reaction between a preformed imine and methyl acrylate was first reported by Perlmutter and Teo in 1984.[33] Since then, a number of reports have been disclosed, including diastereoselective versions.[34] However, the enantioselective aza-MBH reaction was notably missing until Shi et al.,[35] Adolfsson and Balan,[36] and Hatakeyama and co-workers[37] independently discovered that β-ICD (**20**) is an efficient catalyst for the asymmetric aza-MBH reaction. The results from these studies are summarized as follows:

a) Only those imines that have a nitrogen atom attached to electron-withdrawing groups (benzoyl, mesyl, tosyl, and diphenylphosphonyl) were reactive enough to participate in the aza-MBH reaction, and only the *N*-acyl imines derived from aromatic aldehydes were used as reaction partners in these reports.

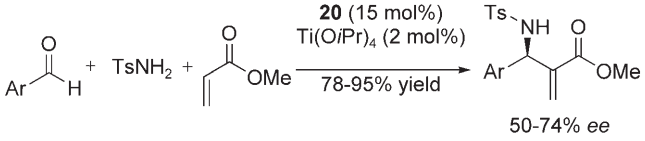
b) The reaction is not limited to HFIP acrylate, but the sense of asymmetric induction is very sensitive to the structure of electron-poor alkenes. With β-ICD (**20**), the reaction of methyl (or ethyl) vinyl ketone with *N*-tosylimine afforded the *R*-enriched allylamine as in the case of the aldehyde. However, when acrylate derivatives (HFIP, methyl, phenyl, and α-naphthyl esters), acrylonitrile, and acrolein were used as substrates, the *S*-enriched allylamine was obtained.

c) The reaction medium affects significantly the enantioselectivity, and the best solvent system varied according to the structure of the alkene (Scheme 6).



Scheme 6. β-ICD-catalyzed enantioselective aza-MBH reactions. Ts: *p*-toluenesulfonyl; Nap: naphthyl.

d) By combined use of a catalytic amount of $Ti(OiPr)_4$ and β-ICD, a three-component reaction of aryl aldehyde, tosylamine, and methyl acrylate was developed by Adolfsson and Balan (Scheme 7).[36] The absolute configuration was assigned as *R* by analogy to the MBH reaction. However, note that the reaction between methyl acrylate and the preformed acylimine afforded the *S*-configured allylamine according to Hatakeyama and co-workers.[37]

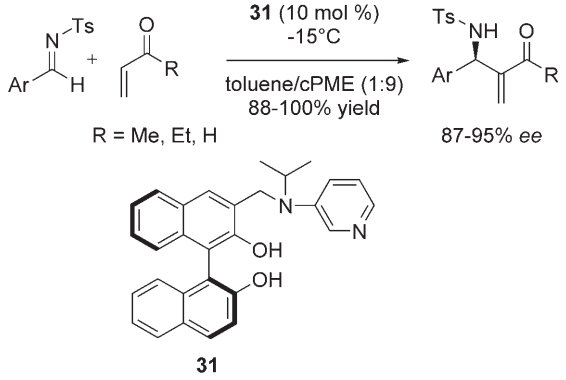


Scheme 7. A β-ICD-catalyzed enantioselective three-component aza-MBH reaction.

The β-ICD catalyst **20** was the first effective catalyst for the MBH reaction, and in our opinion it remains one of the most efficient catalysts in the field. One drawback is that its enantiomer is difficult to access.[38] Recently, a 20-step synthesis of its pseudo-enantiomer from quinine was developed.[39] The reaction between HFIP acrylate **21** and aldehydes catalyzed by the pseudo-enantiomer of β-ICD afforded the allylic alcohol (*S*)-**22** as expected.

3.1.2. Binol-Based Bifunctional Catalysts

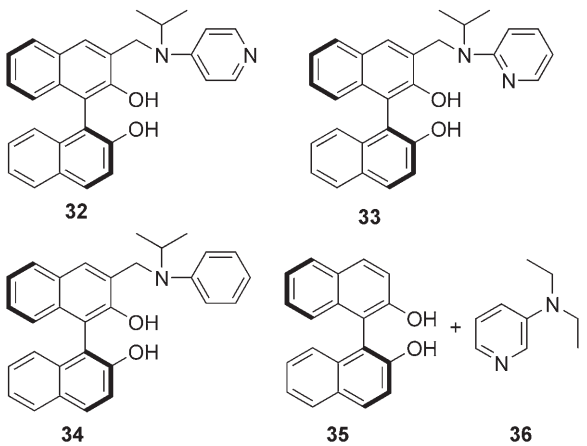
Sasai and co-workers designed and synthesized 1,1′-bi-2-naphthol (binol)-based bifunctional organocatalyst **31** and demonstrated that it acts as an efficient catalyst for the aza-MBH reaction (Scheme 8).[40] The best results were obtained



Scheme 8. A chiral binol-based bifunctional organocatalyst for the aza-MBH reaction. cPME: cyclopentyl methyl ether.

when the reaction was performed in a mixed solvent of toluene and cyclopentyl methyl ether at −15 °C. Under these conditions, the reaction between alkyl vinyl ketones and *N*-tosylimines derived from both electron-rich and electron-poor aldehydes provided the allylamine in high yield and with excellent enantioselectivity.

Sasai noted that the proper combination of two reactive functions, namely the amine and the binol, on the catalyst is of utmost importance for it to act as a bifunctional catalyst. In fact, binol derivatives **32** and **33** were ineffective, as was **34** in which the pyridine nucleus was replaced by a phenyl ring. The advantage of using bifunctional catalysts is also illustrated by the fact that the same reaction promoted by combined use of binol (**35**) and 3-*N*,*N*-diethylaminopyridine (**36**) provided the adduct with 3% *ee* only.

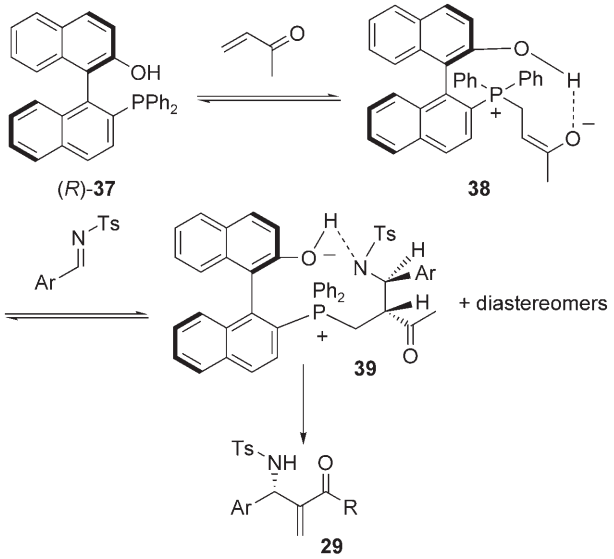


Catalyst **31** is as efficient as Hatakeyama's catalyst (**20**) for catalyzing the aza-MBH reaction. The potential advantage of Sasai's catalyst is that the enantiomer of **31** should be easily accessible.

3.2. Chiral Tertiary Phosphine Catalysts

A plethora of chiral phosphines are commercially available and are widely used as ligands in transition-metal-catalyzed asymmetric syntheses.[41] As triaryl- or trialkylphosphines are effective catalysts for the MBH reaction, it appears logical that one expects to develop an enantioselective version by using chiral phosphines. Unfortunately, of the many chiral phosphines that have been screened only a few of them displayed reasonable catalytic activity to afford, with limited substrate scope, the desired product with low to moderate enantioselectivity.[42]

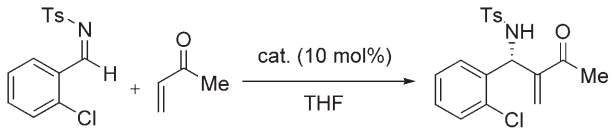
Shi and co-workers developed one of the most efficient chiral bifunctional phosphine-based catalysts for the aza-MBH reaction.[43] The reaction of N-sulfonylated imines with various activated alkenes in the presence of binol derivative **37** afforded the corresponding adducts in good yields and with good to excellent *ee* values. Both ^{31}P and ^{1}H NMR spectroscopic studies indicated the bifunctional role of the catalyst. The phosphine acts as a Lewis base to initiate the reaction sequence, whereas the phenolic OH group serves as a Lewis acid to activate the electrophile and to stabilize the enolate intermediate through hydrogen bonding (**38**, Scheme 9). A Mannich reaction between the enolate **38** and tosylimine would afford possibly four diastereomers. However, only one of them may adopt a conformation wherein proton transfer



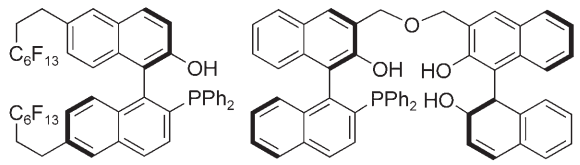
Scheme 9. Working hypothesis for chiral phosphine-based bifunctional catalysts.

and the subsequent β elimination could occur without introducing significant steric interaction. When (*R*)-**37** was used as catalyst, the *S*-enriched allylamine was produced preferentially. The reaction involving vinyl ketones (MVK, EVK) or acrolein is best performed in THF at −30 °C in the presence of 4-Å molecular sieves, while that involving phenyl acrylate is best carried out in dichloromethane at 40 °C. Interestingly, note that only low enantioselectivity was observed when methyl acrylate was used as the activated alkene (< 20 % *ee*). Although the yield remained moderate in some cases (26–97 %), the MBH adduct is generally obtained with good to excellent enantioselectivity (52–94 % *ee*).

To fine tune the reactivity and enantioselectivity of catalysts, Shi devised and synthesized chiral phosphine ((*R*)-**40**) with a "ponytail"[44] and (*R*,*R*)-**41** bearing multiple phenol groups.[45] Both catalysts **40** and **41** turned out to be more effective than the parent phosphine **37**. While the *S*-allylamine is generally obtained from the reaction catalyzed by **37**, **40**, and **41**, the reaction between MVK and tosylimines derived from *ortho*-substituted benzaldehydes catalyzed by **41** displayed the opposite selectivity, affording the *R* adduct preferentially (Scheme 10).



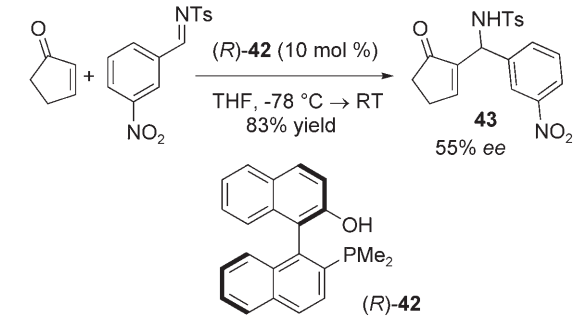
Entry	cat.	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]
1	**37**	-30	24	85	61 (*S*)
2	**40**	-20	48	90	89 (*S*)
3	**41**	-20	36	85	90 (*R*)



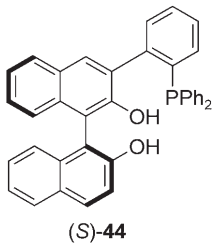
Scheme 10. Further structure refinement of chiral phosphine-based bifunctional catalysts.

Shi et al. also demonstrated that a more nucleophilic chiral phosphine catalyst, (*R*)-**42**, is capable of catalyzing the reaction between cyclopentenone (and to a lesser extent, cyclohexenone) and tosylimine to afford the corresponding MBH adduct **43** in excellent yield and with moderate *ee* values (Scheme 11).[46] The parent phosphine (*R*)-**37** was inactive for this reaction.

Along the same lines, Sasai and co-workers have developed another binol-based chiral phosphine catalyst, (*S*)-**44**.[47] The reaction between MVK (or EVK) and tosylimine catalyzed by (*S*)-**44** afforded the corresponding *S*-allylamine in excellent yield and with excellent enantioselectivity (82–95 % *ee*) irrespective of whether the tosylimine was derived from electron-rich or electron-poor aromatic aldehydes. Note that the absolute configuration of the allylamines obtained with catalyst (*S*)-**44** is opposite to that obtained with (*S*)-**31**, although the axial chirality of both catalysts is identical.



Scheme 11. Aza-MBH reactions of *N*-tosylimines and cyclopentenone catalyzed by chiral Lewis base (*R*)-**42**.



4. Chiral Acid Catalysis

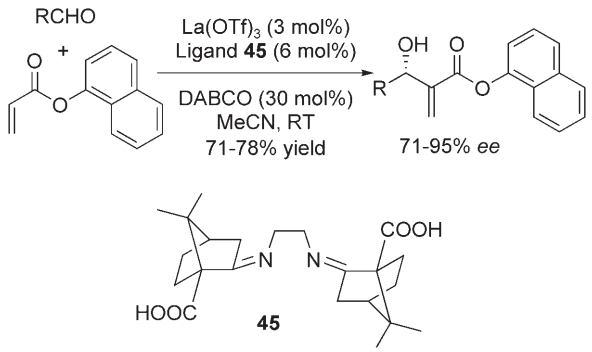
The MBH process involves a reaction between an α,β-unsaturated carbonyl derivative and an aldehyde. Consequently, it is logical to exploit the electrophile-activation approach by employing a chiral acid as catalyst. Indeed, a number of attractive chiral Lewis acid or Brønsted acid catalysts have recently been developed for the asymmetric MBH reaction.

4.1. Lewis Acid Catalysts

Investigations on Lewis acid catalyzed enantioselective processes have met with great success over the past quarter of a century.[48] An especially fruitful and thoroughly investigated process is the aldol reaction, which is highly relevant to the MBH reaction. Nonetheless, there have been very few successful examples of metal-based Lewis acid catalyzed enantioselective MBH reactions, illustrating the challenges associated with it. The obligatory coexistence of a Lewis base and a Lewis acid in this approach could potentially complicate the catalyst design. In fact, both tertiary amines and tertiary phosphines are good ligands for most of the transition metals. Any coordination of the achiral Lewis base to the chiral Lewis acid could modify the chiral environment and reduce the nucleophilicity of the Lewis base, consequently decreasing or even stopping completely the catalytic cycle.

Aggarwal et al. examined the enantioselective MBH reaction between acrylates and aldehydes in the presence of lanthanide ions and a chiral ligand. Unfortunately, with a range of polydentate chiral ligands such as salen, aminodiols, aminotriols, bisoxazoline, and diisopropyltartrate, the MBH

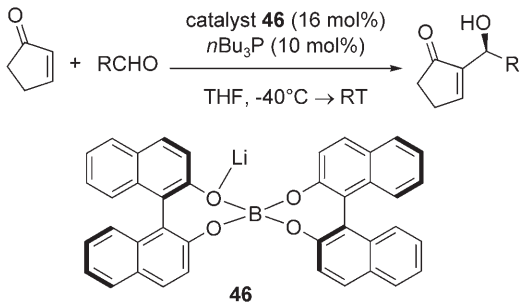
adduct was obtained with only 5% *ee* at best.[49] Recently, Chen and co-workers showed that a chiral catalyst formed in situ from dimeric camphor-derived ligand **45** and $La(OTf)_3$ can catalyze, in combination with DABCO, the MBH reaction with good to excellent enantioselectivity (Scheme 12).[50]



Scheme 12. A chiral Lewis acid catalyzed, DABCO-mediated enantioselective MBH reaction. Tf: trifluoromethanesulfonyl.

Both aliphatic aldehydes and aromatic aldehydes with different electronic properties participated in the reaction, and the reaction was complete within 20 min when highly reactive α-naphthyl acrylate was used as the reaction partner.

By combining chiral heterobimetallic complex **46** and tri-*n*-butylphosphine, Sasai and co-workers synthesized enantiomerically enriched allylic alcohols in good to excellent yields, although a long reaction time was required (Scheme 13).[51]



Scheme 13. An enantioselective MBH reaction in the presence of a chiral heterobimetallic catalyst and tri-*n*-butylphosphine.

The reaction worked particularly well with α-branched aliphatic aldehydes, but it provided the MBH adduct with low *ee* values when benzaldehyde was used.

4.2. Brønsted Acid Catalysts

The ability of carboxylic acids to accelerate the cycloaddition of cyclopentadiene and benzoquinone was reported by Wassermann in 1942,[52] however, this finding lay dormant for almost half a century in the arsenal of chiral catalysis design probably as a result of the conceived low tunability of chiral protic acids and low organization power of hydrogen bonds. However, the resurgence of interest since the late 1990s in chiral Brønsted acids is dramatically changing this view and enantioselective transformations catalyzed by chiral hydrogen-bond donors has emerged as a very active research field.[53,54]

According to Steiner, "*An X–H···A interaction is called a "hydrogen bond" if 1) it constitutes a local bond, and 2) X–H acts as proton donor to A*".[55] Two modes of activation of carbonyl compounds and/or imines by a Brønsted acid are frequently encountered (Figure 2): 1) double hydrogen bonding (ureas, thioureas, guanidinium, and amidinium ions, capable of simultaneously donating two hydrogen bonds, are emerging as a class of privileged catalyst structures)[56] and 2) single hydrogen bonding (taddol[57a] and binol[57b] belong to a family of Brønsted acid assisted Brønsted acid catalysts[58] and act as single hydrogen-bond donors, although they have two appropriately positioned acidic protons[59]). Both types of chiral Brønsted catalysts have been used in the development of enantioselective MBH reactions.

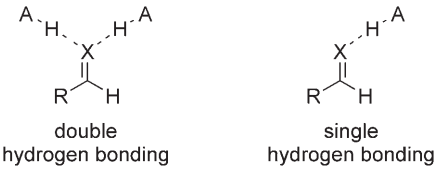
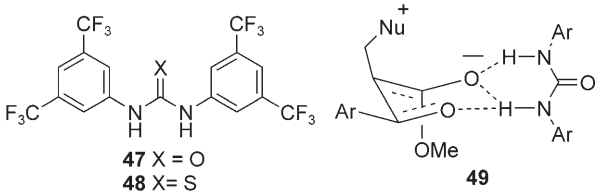


Figure 2. Modes of hydrogen bonding.

As the MBH reaction is promoted by a nucleophilic Lewis base, such as a tertiary amine or a phosphine, its compatibility with Brønsted acid catalysts needs to be carefully considered to avoid any possible acid–base quench leading to inactive catalysts. Fortunately, strong protic acids are not required for the reactions promoted by general-acid catalysts and, indeed, the most effective Lewis acids developed for the MBH reaction are not acidic enough to protonate the common nucleophilic Lewis bases used in the reaction.

4.2.1. (Thio)ureas

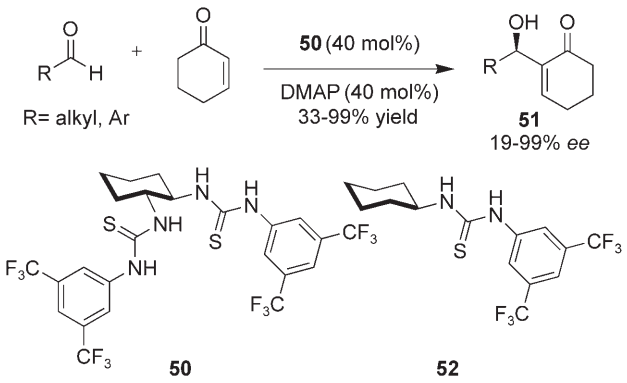
The ready availability, excellent stability, high conformational rigidity, and affinity towards carbonyl and imine functions have made (thio)ureas popular organocatalysts through efficient double-hydrogen-bonding interactions.[20,60,61] Connon and Maher were the first to demonstrate that urea **47** is capable of accelerating the DABCO-promoted MBH reaction between methyl acrylate and aromatic aldehydes.[62] Interestingly, thiourea **48**, which is a stronger



hydrogen-bond donor, is a less efficient catalyst than **47** in this reaction.

Methyl acrylate is a better hydrogen-bond acceptor than aromatic aldehydes, thus at first glance it is reasonable to postulate that urea is going to speed up the Michael addition by direct activation of the methyl acrylate. However, this step (see Section 2; step 1 in Scheme 2) is not the rate-determining step of the MBH reaction and should thus not be expected to influence the overall reaction rate. The intermediate **49**, in which the urea stabilizes the zwitterion **5** (see Scheme 2) and at the same time activates the aldehyde by hydrogen bonding, could be an attractive explanation of the rate-enhancement effect of urea.

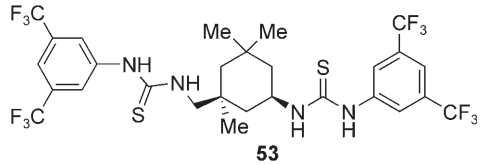
Around the same time as Connon's report, Nagasawa and co-workers reported that thiourea is prone to form hydrogen bonds with both cyclohexenone and aldehydes.[63] This observation prompted them to synthesize the *trans*-(1*R*,2*R*)-1,2-diaminocyclohexane-derived bis-thiourea **50** (Scheme 14). In combination with DMAP, **50** was capable of



Scheme 14. An enantioselective MBH reaction catalyzed by a C_2-symmetric bis-thiourea. DMAP: 4-(*N*,*N*-dimethylamino)pyridine.

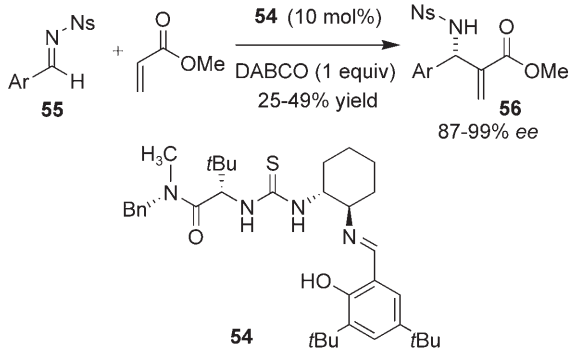
promoting the MBH reaction between cyclohexenone and aldehydes. Although aromatic aldehydes were generally poor substrates in terms of enantioselectivity, the aliphatic aldehydes were converted to MBH adducts (*R*)-**51** with moderate to excellent enantioselectivity (up to 99% *ee*). Simultaneous activation of both cyclohexenone and the aldehyde has been proposed to account for the observed rate acceleration and stereoselectivity. This dual-activation mode was supported by the fact that the mono-thiourea **52** is an ineffective catalyst.

Berkessel et al. prepared chiral bis(thio)urea **53** from isophoronediamine (IPDA), a readily available 1,4-diamine produced industrially on a multiton scale.[64] The reaction between cyclohexenone (4 equiv) and an aliphatic aldehyde (1 equiv) in the presence of 20 mol% of **53** and DABCO



under solvent-free conditions afforded the corresponding allylic alcohol **51** with good to excellent enantioselectivity (up to 96% *ee*). Aromatic aldehydes in general afford the MBH adduct with lower *ee* values. The same reaction using cyclopentenone instead of cyclohexenone afforded the corresponding adduct with a lower *ee*.

Jacobsen and co-workers uncovered that thiourea **54** is an efficient Brønsted acid catalyst for the DABCO-mediated aza-MBH reaction between *N*-(*p*-nitrobenzenesulfonyl)imine (*N*-nosylimine) and methyl acrylate (Scheme 15).[12] For the

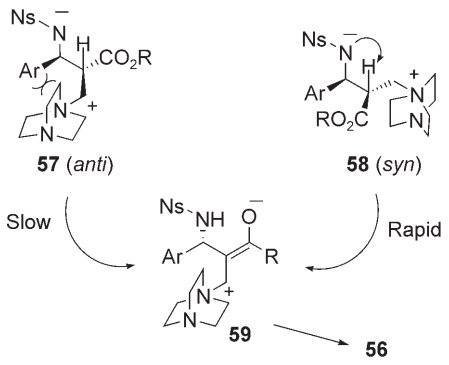


Scheme 15. An enantioselective aza-MBH reaction catalyzed by a chiral thiourea. Ns: *p*-nitrobenzenesulfonyl.

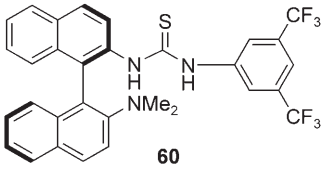
success of this reaction, the use of the *N*-nosyl function was essential as other N-protecting groups such as Boc, phosphonyl, *p*-toluenesulfonyl, and alkyl imines afforded the MBH adduct with only marginal enantioselectivity. Other factors such as solvent and concentration have also been carefully examined, and the highest *ee* value was obtained in nonpolar solvents such as diethyl ether and xylene. Under optimized conditions (0.1 equiv **54**, 1.0 equiv DABCO, 3-Å molecular sieves, xylene, 4°C), the aza-MBH adduct **56**, irrespective of the electronic properties of the Ar group, was obtained with over 90% *ee*, although the yield remained moderate.

A pronounced inverse relationship between conversion and *ee* was observed. Careful analysis of the reaction course allowed the authors to isolate and identify, for the first time, a zwitterion intermediate *anti*-**57** that precipitated from the reaction mixture. It was proposed that unfavorable steric interactions in the eclipsed conformation of *anti*-**57** that is required for an intramolecular proton transfer may slow down the proton-transfer process (Scheme 16). As the aldol addition leading to *anti*-**57** is reversible, the reduced rate of proton transfer may ultimately reduce the *ee* value of **56**. On the other hand, *syn*-**58** suffered less steric interaction in its eclipsed conformation and underwent rapid proton transfer/β elimination to generate **56** with high *ee* values.

Wang and co-workers developed a bifunctional binaphthyl-derived amino-thiourea, **60**.[65] It was speculated that the 2-dimethylamino group would serve as a Lewis base to initiate the reaction sequence, whereas the thiourea function at C2′ would serve as a Lewis acid to activate the electrophilic carbonyl group. Indeed, under optimum conditions (0.1 equiv **60**, MeCN, 0°C), the reaction of cyclohexenone (5.0 equiv)



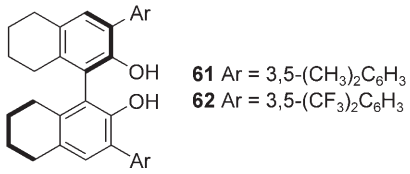
Scheme 16. Isolation of a zwitterionic intermediate: mechanistic implication.



and aliphatic aldehyde (1.0 equiv) afforded the corresponding allylic alcohol (*R*)-**51** (see Scheme 14) in good yield and with excellent enantioselectivity (80–94% *ee*). Remarkably, even with *ortho*-chlorobenzaldehyde, the corresponding adduct was obtained in 55% yield and with 60% *ee*.

4.2.2. Binol Catalysts

The ability of phenol and binol to co-catalyze the triphenylphosphine-mediated MBH reaction of cyclic enones with aldehydes was reported by Ikegami and Yamada.[13h] On the basis of this observation, Schaus and McDougal developed a highly enantioselective MBH reaction by a synergistic effect of binol-derived Brønsted acids **61** (or **62**) and



triethylphosphine.[66] The binol derivatives **61** (or **62**) were found to be optimum co-catalysts in the PEt_3-mediated MBH reaction. The reaction between cyclohexenone (2 equiv) and aliphatic aldehydes (1.0 equiv) under optimized conditions (0.1 equiv **61**, 2 equiv PEt_3, THF, −10 °C) afforded the allylic alcohol (*S*)-**51** (see Scheme 14) in excellent yield and with enantiomeric purity (> 82% *ee*).

The presence of bulky substituents at the 3,3′-positions and the two hydroxy groups in **61**/**62** were essential for the enantioselectivity. Interestingly, the Lewis base also played a key role in the enantioselectivity, as the MBH adduct was obtained in similar yields but with significantly reduced *ee* values when trimethyphosphine (PMe_3) or tri-*n*-butylphosphine ($PnBu_3$) was used as co-promoter under otherwise identical conditions.

By using this enantioselective MBH reaction as a key step, Schaus and Rodgen have developed an efficient synthesis of the *trans*-decalin core of clerodane.[67]

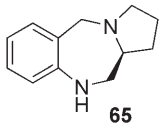
4.2.3. Proline as Co-Catalyst

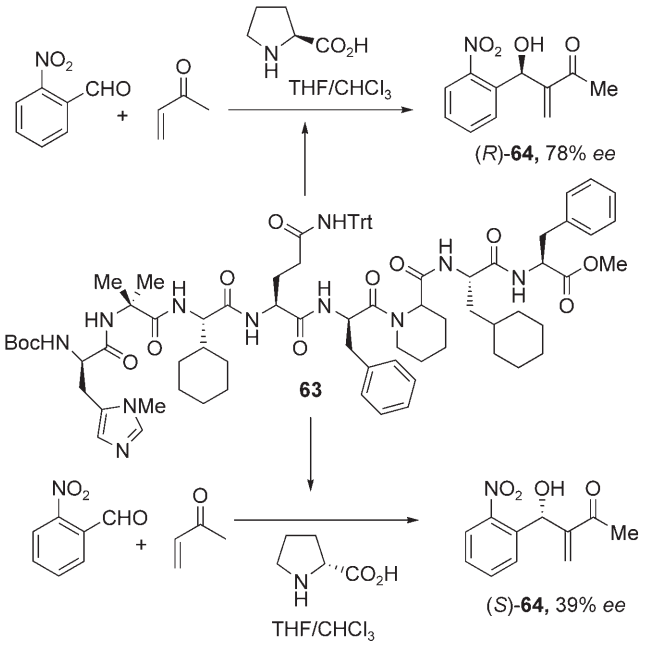
Proline, which bears both an acidic carboxyl group and a basic secondary amine moiety, is an efficient chiral bifunctional catalyst.[68] Shi et al. observed a remarkable synergistic effect of imidazole and L-proline in catalyzing the MBH reaction between MVK and aryl aldehydes. Although an obvious rate acceleration of the reaction was observed, the enantioselectivities of the reaction remained low (< 10% *ee*).[69] The combination of L-proline and Hatakeyama's catalyst has also been investigated and affords the adducts with up to 31% *ee* for the MVK-based MBH reaction.[29]

On the basis of their extensive work on peptide-based catalysts for asymmetric transformations,[70] Miller and coworkers found that the nucleophile-loaded peptide **63** is an efficient co-catalyst of proline for the reaction between MVK and electron-deficient aromatic aldehydes.[71] The reaction is nevertheless limited in scope as aliphatic aldehydes and non-activated aromatic aldehydes, such as *o*-tolualdehyde and cinnamaldehyde, did not participate in this reaction. Phenyl vinyl ketone, *tert*-butyl vinyl ketone, and other non-ketone-based α,β-unsaturated compounds such as acrylate and acrylonitrile were also unreactive under the established conditions ($CHCl_3$/THF = 1:2, c = 0.5 M, 0.1 equiv each of proline and peptide **63**, RT).

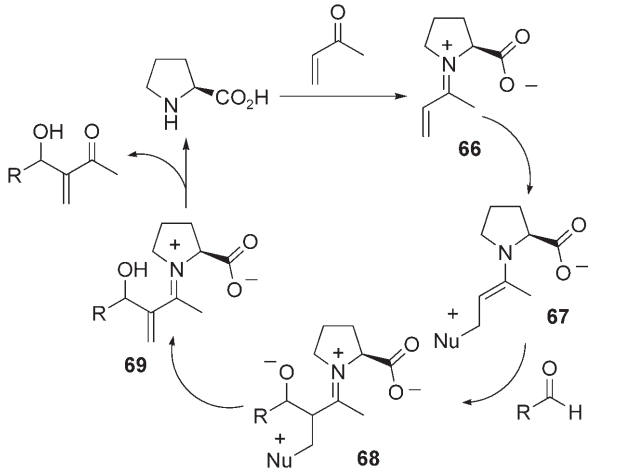
As both catalysts are chiral and neither of them is capable of promoting the reaction individually, the question of double stereoselection (matched/mismatched) was raised. Indeed, whereas the combination of L-proline and octapeptide **63** promoted the reaction between *o*-nitrobenzaldehyde and MVK to afford (*R*)-**64** in 78% *ee*, the catalyst pair of D-proline and **63** yielded predominantly the opposite enantiomer (*S*)-**64** with 39% *ee* (Scheme 17). These results suggested that a phenomenon of matched/mismatched stereoselection is operating and that the absolute sense of asymmetric induction is dictated by the stereochemistry of proline.

Most recently, Zhao, Zhou, and coworkers reported that chiral benzodiazepine **65** in combination with L-proline catalyzed the MVK-based MBH reaction to afford the corresponding adduct with a moderate *ee* value.[72] However this catalyst system seemed to be limited to electron-deficient aldehyde. While the exact role of proline in this catalytic process has yet to be determined, it may act not only as a Brønsted acid. One attractive proposal involves the formation of iminium intermediate **66** between MVK and proline (Scheme 18). The Michael addition of a Lewis base onto **66** would afford enamine **67**, which then undergoes aldol condensation to produce a highly charged intermediate **68**. Proton transfer followed by elimination would provide the iminium **69** with the concurrent regeneration of the Lewis





Scheme 17. Asymmetric MBH reactions catalyzed by L-proline and nucleophile-loaded octapeptide **63**: matched versus mismatched cases. Trt: trityl; Boc: *tert*-butyloxycarbonyl.



Scheme 18. Proposed mechanism for the L-proline-catalyzed, Lewis base promoted MBH reaction.

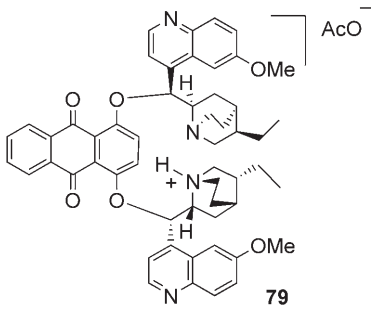
base catalyst. Hydrolysis of **69** would then yield the MBH adduct as well as proline, thus completing the catalytic cycle. The fact that the catalyst combination of Lewis base and proline did not promote the acrylate- and acrylonitrile-based MBH reaction is in accord with this proposal.

A proline-catalyzed intramolecular reaction of hep-2-enedial (**70**) leading to 6-hydroxycyclohexenecarbaldehyde (*S*)-**71** was developed by Hong and co-workers (Scheme 19).[73] Mechanistically, it was proposed that preferential condensation of proline with the enal instead of the non-conjugated aldehyde would afford the conjugated iminium **72** that tautomerizes to enamine **73**. The Stork enamine aldol reaction proceeded through the Zimmerman–Traxler transition state **73b** to furnish (*S*)-**71**. The alternative transition state **73a** is considered to be energetically unfavorable.[74] Interestingly, Hong discovered that in the presence of imidazole, the reaction rate was accelerated to provide the oppositely configured product (*R*)-**71** with excellent enantioselectivity. The cyclization of enedial **70** co-catalyzed by the imidazole/proline pair is a typical intramolecular MBH reaction.[75] It is proposed that imidazole traps the iminium intermediate **72** from the *Si* face (directed by a hydrogen bond between the carboxylic acid and imidazole) to afford the enamine **74**. Owing to the pronounced 1,3-diaxial interaction in **74a**, the conformation **74b** is preferred that leads to the formation of the *R*-enriched allylic alcohol **71**.

Independently, Miller and co-workers reported that pipecolic acid (**76**) and *N*-methylimidazole (**75**) co-catalyzed efficiently the intramolecular MBH reaction (Scheme 20).[76] The reaction was best carried out in protic solvents (THF/$H_2O = 3:1$) to avoid dimerization of the starting materials.

4.2.4. Ammonium Salts

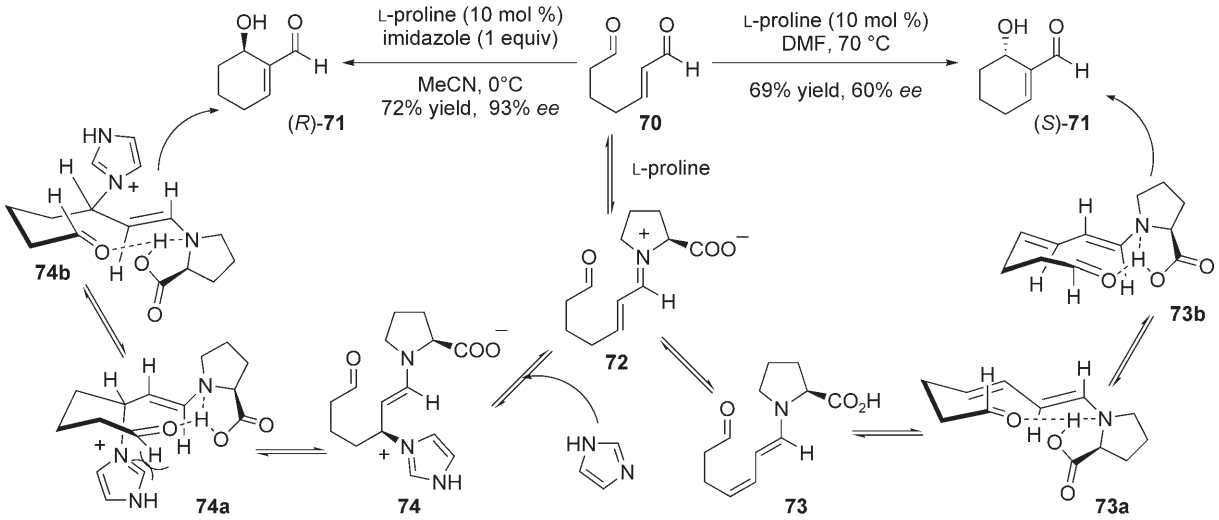
Perhaps the most striking bifunctional catalyst is the ammonium salt **79** prepared by Warriner and Mocquet.[77] The



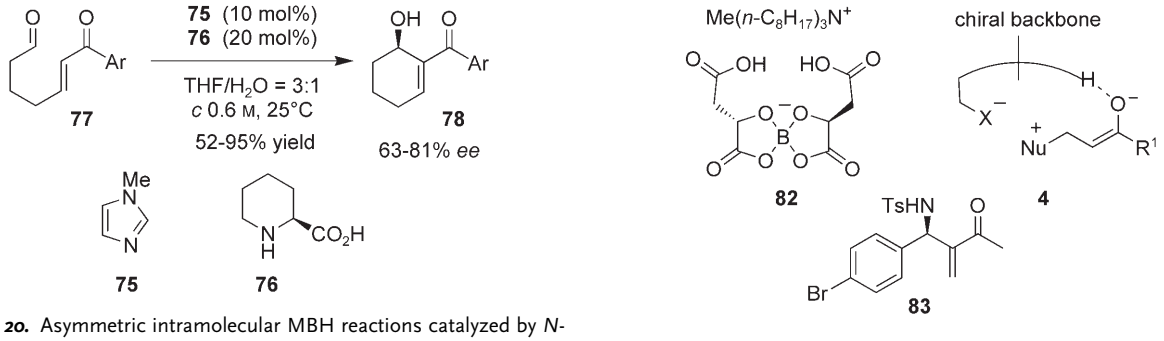
design principle was that one quinuclidine unit in **79** would act as a nucleophile to initiate the MBH reaction whilst a second protonated quinuclidine could act as a Brønsted acid. The ammonium salt **79**, formed in situ from Sharpless ligand hydroquinidine(anthraquinone-1,4-diyl) diether ($(DHQD)_2$-AQN) and one equivalent of acetic acid, is indeed capable of promoting the reaction between *p*-nitrobenzaldehyde and methyl acrylate to afford the corresponding adduct with up to 60% *ee*. However, the conversion remained low and the isolated yield of the MBH adduct was less then 10%. Initial experiments clearly indicated that the proton of the ammonium salt played a key role in the rate acceleration and enantioselectivity of this transformation.[78]

5. Chiral Ionic liquids as Reaction Media

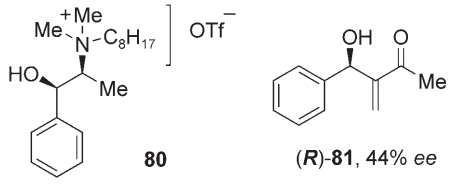
Vo-Thanh and co-workers were the first to examine chiral ionic liquids as chiral inducers for the asymmetric MBH reaction.[79] They synthesized the *N*-octyl-*N*-methylephedrinium trifluoromethanesulfonate salt **80** and demonstrated that chirality transfer can indeed occur when it is used as a solvent. The allylic alcohol (*R*)-**81** was obtained with 44% *ee* when a DABCO-mediated reaction of methyl acrylate and



Scheme 19. Intramolecular Stork enamine aldol reaction of **70** versus the intramolecular MBH reaction.



Scheme 20. Asymmetric intramolecular MBH reactions catalyzed by *N*-methylimidazole (**75**) and pipecolic acid (**76**).



benzaldehyde (30 °C, 7 days, 60 % yield) was performed in **80** (3 equiv).

Recently, Leitner and co-workers devised and synthesized a chiral ionic liquid **82**, with a chiral anion that contains terminal carboxylic acid functions.[80] It was expected that **82** would complex the zwitterion intermediate **4** (see Scheme 2) through ion-pair and hydrogen-bond formation. Such interactions would not only stabilize **4** but also create a chiral environment for the subsequent aldol addition, accounting for the asymmetric induction.

Chiral dimalatoborate **82** was easily synthesized from malic acid in two steps. The PPh_3-mediated aza-MBH reaction between *N*-(4-bromobenzylidene)-4-toluenesulfonamide and MVK in **82** (concentration of imine, $c = 0.125$ M) afforded allylic **83** with 84 % *ee* (39 % conversion). Control experiments showed that the presence of the carboxylic acids is essential for the enantioselectivity and that no asymmetric induction was observed when **82** was used as an additive only. Therefore, the use of **82** as a reaction medium is crucial for effective chirality transfer.[81]

6. Summary and Outlook

Much effort has been devoted to the development of enantioselective MBH reactions over the past 10 years, and a number of effective catalyst systems have been uncovered from these studies. However, a catalyst that is applicable to a wide range of substrates to generate the MBH adduct in high yield with a predictable high *ee* remains illusive. Notably, the enantioselective MBH reaction of methyl acrylate that would generate a versatile synthetic intermediate is still missing.[82]

A trend that can be recognized from these studies is that chiral Brønsted acids can act as efficient chiral inducers in combination with an achiral Lewis base. On the other hand, a chiral Lewis base alone can barely transfer its chirality to the MBH adduct unless this catalyst is armed with an appropriately positioned acidic proton, that is, a bifunctional catalyst. Interestingly, the recent achievements in enantioselective MBH reactions coincided with the emergence of the concept of organocatalysis and indeed most of the effective chiral

catalysts for MBH reactions known to date are small organic molecules. As it is a reaction that involves two electrophilic substrates and a nucleophilic catalyst, the MBH reaction is indeed intrinsically suitable for the development of organocatalysts and especially bifunctional catalysts. To date, the MBH reaction is among the very few reactions wherein chiral organocatalysts give better results than metal-based chiral catalysts.

From a structural point of view, most of the bifunctional catalysts known to date have a rigid backbone structure. Although double hydrogen bonding is not an obligation especially when an intramolecular hydrogen bond exists within the catalyst framework, the bi- or multidentate catalyst–substrate interaction should amplify the catalytic effectiveness by restricting the degree of conformational freedom. Note also that the binding interactions need not be excessively strong as is the case for traditional Lewis acids because this could potentially lead to product inhibition or acid/base quenching. After all, of primary importance in designing a bifunctional catalyst would naturally be the synergistic action of both functions. Such a cooperative effect should not only increase the mutual chemical reactivity of substrates but also organize the three-dimensional structure of the transition state for achieving better stereochemical communication. Although remarkable progress has been made in the development of asymmetric MBH reactions, there remains room for more developments in this challenging field.

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