ACCOUNTS
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Multifunctional Chiral Phosphine Organocatalysts in Catalytic Asymmetric Morita–Baylis–Hillman and Related Reactions

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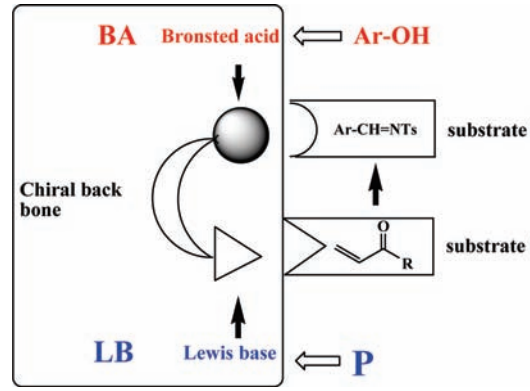
RECEIVED ON NOVEMBER 24, 2009

CONSPECTUS

Catalytic asymmetric synthesis has received considerable attention over the past few decades, becoming a highly dynamic area of chemical research with significant contributions to the field of organic synthesis. In the development of new catalysts, the concept of multifunctional catalysis described by Shibasaki and co-workers, namely, the combination of more than one functional group within a single molecule to activate the transformation, has proved a powerful strategy in the design of efficient transition metal-containing catalysts.



A variety of reactions have since been addressed with multifunctional organocatalysts. One example is the Morita–Baylis–Hillman (MBH) reaction, in which a carbon–carbon bond is created between the α-position of an activated double-bond compound and a carbon electrophile. The seminal report on this reaction in 1972 described the prototypical couplings of (i) ethyl acrylate with acetaldehyde and (ii) acrylonitrile with acetaldehyde; the reaction is promoted by the conjugate addition of a nucleophilic catalyst to the α,β-unsaturated aldehyde. Many variations of the MBH reaction have been reported, such as the aza-MBH reaction, in which an *N*-tosyl imine stands in for acetaldehyde. Recent innovations include the development of chiral molecules that catalyze the production of asymmetric products. In this Account, we describe the refinement of catalysts for the MBH and related reactions, highlighting a series of multifunctional chiral phosphines that we have developed and synthesized over the past decade. We also review similar catalysts developed by other groups.

These multifunctional chiral phosphines, which contain Lewis basic and Brønsted acidic sites within one molecule, provide good-to-excellent reactivities and stereoselectivities in the asymmetric aza-MBH reaction, the MBH reaction, and other related reactions. We demonstrate that the reactivities and enantioselectivies of these multifunctional chiral phosphines can be adjusted by enhancing the reactive center's nucleophilicity, which can be finely tuned by varying nearby hydrogen-bonding donors.

Artificial catalysts now provide highly economic access to many desirable compounds, but the general adaptability and reactivity of these platforms remain problematic, particularly in comparison to nature's catalysts, enzymes. The multifunctional organocatalysts described in this Account represent another positive step in the synthetic chemist's efforts to profitably mimic nature's catalytic platform, helping develop small-molecule catalysts with enzyme-like reactivities and selectivities.

1. Introduction

A wide variety of enantioselective chemical transformations are now performed with only a catalytic amount of chiral promoters, providing highly economic access to desired compounds, although the performance of most artificial catalysts is still far from satisfactory in terms of generality and reactivity.[1] During the past two decades, the research on chiral catalysts has been particularly

Published on the Web 03/16/2010 www.pubs.acs.org/acr
10.1021/ar900271g

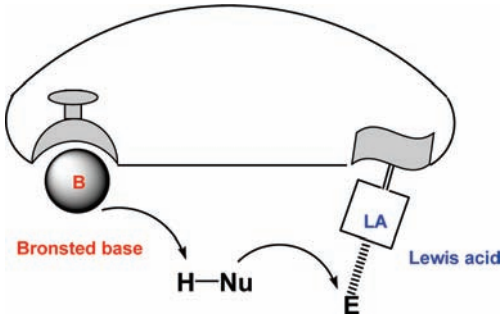


FIGURE 1. Multifunctional catalysts employing the synergistic function of a Lewis acid and a Brønsted base: LA, Lewis acid; B, Brønsted base; E, electrophile; Nu-H, nucleophile.

active in both metal catalysis and organocatalysis. In metal catalysis, Shibasaki et al. have developed the concept of multifunctional catalysis,[2] wherein the catalysts exhibit both Lewis acidity and Brønsted basicity (Figure 1), using lanthanide complexes.[1a,3] Furthermore, a variety of asymmetric transformations have been realized by carefully choosing the metal elements according to the reaction type, consistent with the above-mentioned concept. An ideal set of multifunctional chiral catalysts should conceptually contain Brønsted base, Brønsted acid, Lewis base, and Lewis acid as active sites to synergistically activate the substrates in a controlled chiral environment (Figure 2). The catalysts including bi/multifunctions enable effectively asymmetric transformations that have never been achieved by using conventional catalysts employing only Lewis acidity or Lewis basicity. Therefore, multifunctional catalyst systems have drawn and will continue to attract much attention.

On the other hand, organocatalysts combining multifunctional sites in a single structure have been applied recently in a variety of organic reactions.[4,5] One of the important reactions employing multifunctional/bifunctional chiral catalysts is the Morita−Baylis−Hillman (MBH) reaction and its aza-counterpart. MBH reaction is described as the coupling between the α-position of an activated double bond and an sp^2 electrophilic carbon using an appropriate catalyst, normally Lewis bases. Great progress has been made in the execution of the MBH reaction, since the seminal report in 1972 described the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO).[6,7] During the long-term of research in this area, many versions of the MBH reaction have been discovered, including the aza-MBH reaction (reported by Perlmutter and Teo), the chalcogenide-mediated MBH reaction (reported by Kataoka et al.), the $TiCl_4$-mediated MBH reaction (reported by Taniguchi et al. and Oshima et al. using a $TiCl_4$−Bu_4NI system and Li et al.), and the intramolecular MBH reaction reported by Murphy et al.[8] Recently the asymmetric versions of the MBH/aza-MBH reaction have also been well exploited.[9] The most recent notable advances are in catalytic asymmetric MBH reactions;[10] however the catalytic asymmetric MBH reactions are limited to specialized α,β-unsaturated ketones or acrylates such as ethyl vinyl ketone (EVK, 71% ee),[10a] 2-cyclohexen-1-one (96% ee),[10b] or 1,1,1,3,3,3-hexafluoroisopropyl acrylate (99% ee).[10c] MBH reactions involving simple Michael acceptors such as methyl vinyl ketone (MVK) or methyl acrylate are notoriously characterized by poor enantioselectivity, which motivates people to design more efficient and enantioselective catalysts to broaden the scope of this general class of reactions. Undoubtedly, mechanistic studies of MBH have provided a solid basis and inspired the design of new catalysts. The commonly accepted mechanism of MBH reaction is depicted in Scheme 1.[11] The catalytic cycle is initiated by the conjugate addition of a nucleophilic catalyst to an α,β-unsaturated carbonyl compound, leading to the formation of a zwitterionic enolate **I**, which subsequently attacks the aldehyde to afford the zwitterionic alkoxide **II**. At this point, the mechanism is considered to diverge into two distinct pathways leading to the observed products. In the first pathway, proton transfer in **III** or with promotion of hydrogen-bonding additives or solvents (MeOH/*t*-BuOH/H_2O/phenol), followed by elimination of the catalyst, completes the catalytic cycle. The second pathway

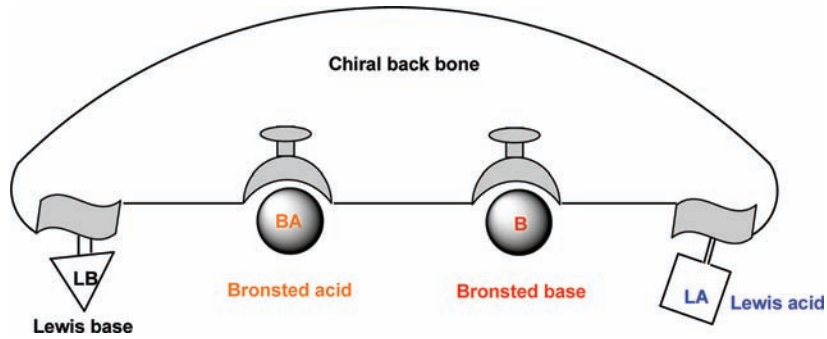
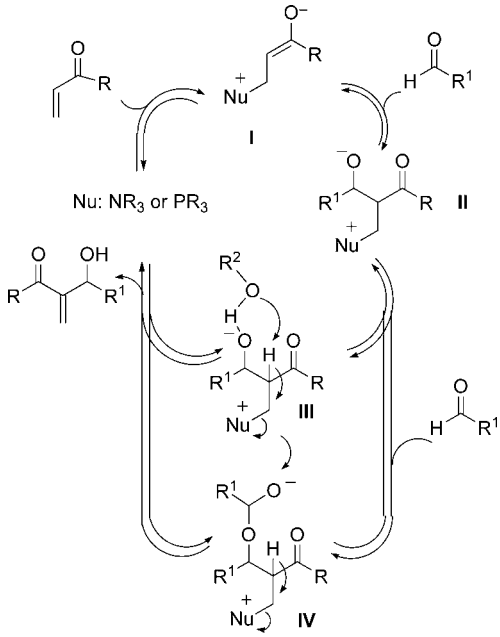


FIGURE 2. Ideal multifunctional chiral catalysts containing Lewis acid, Brønsted base, Brønsted acid, and Lewis base as active catalytic sites: LA, Lewis acid; B, Brønsted base; BA, Brønsted acid; LB, Lewis base.

SCHEME 1. The Proposed Mechanism of MBH Reaction



involves attack of the alkoxide **II** on a second molecule of aldehyde, which leads to the formation of the zwitterionic hemiacetal **IV**. This intermediate facilitates proton transfer and subsequent elimination of the catalyst. Recently, the theoretical studies of mechanisms of MBH reactions have shown that the proton transfer step in the zwitterionic aldolate intermediate is the rate-determining step. Thus the addition of hydrogen-bonding substituents to a specific catalyst may provide a good opportunity to accelerate the crucial proton transfer step and influence the overall reaction rate and selectivity. Bifunctional chiral amine catalysts have shown good reactivity and selectivity for asymmetric MBH/aza-MBH reaction.[12] Because phosphines are effective nucleophilic organocatalysts for MBH/aza-MBH reaction and other reactions,[13] it appears straightforward that one expects to develop bifunctional chiral phosphines for asymmetric MBH/aza-MBH reactions. However,

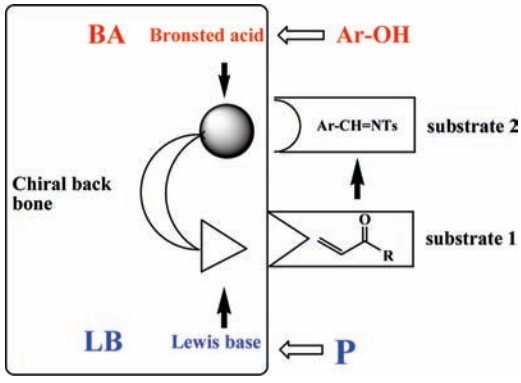
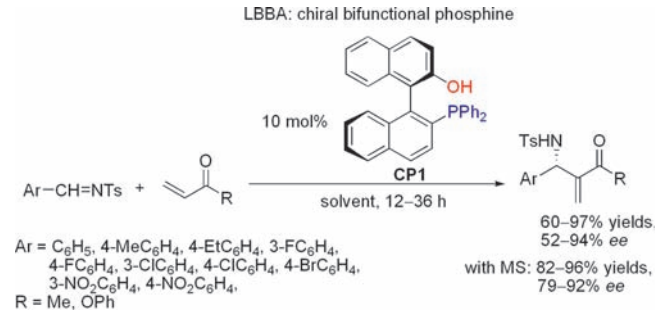


FIGURE 3. Multifunctional chiral phosphine Lewis base catalyst, LBBA bifunctional catalytic system: LB, Lewis base; BA, Brønsted acid.

SCHEME 2. Phosphine and Phenolic Hydroxyl Group Type of Multifunctional Chiral Phosphine-Catalyzed Asymmetric Aza-MBH Reaction



the research on a phosphine version of bifunctional organocatalysts has been less explored, compared with that on bifunctional chiral amine catalysts.

Inspired by the concept of multifunctional catalysis and based on understanding the mechanism of MBH reaction, we have employed the strategy of multifunctional catalysis to design LBBA (Lewis base and Brønsted acid) bifunctional chiral phosphine organocatalysts (Figure 3) for MBH/aza-MBH and related reactions. Our developed bifunctional chiral phosphine organocatalysts have afforded the corresponding adducts in high yields with good to excellent ee's in MBH/aza-MBH and related reactions. This Account will summarize the origin and development in the application of multifunctional/bifunctional chiral phosphine organocatalysts in catalytic asymmetric MBH/aza-MBH and related reactions.

2. Multifunctional Chiral Phosphine Catalysts in Aza-Morita–Baylis–Hillman Reaction

In 1993, Hayashi first synthesized the chiral phosphorus compound **CP1** as a chiral monodentate phosphine ligand.[14] In 2002, our group first demonstrated that this 1,1′-bi-2,2′-naphthol (BINOL)-derived chiral LBBA bifunctional phosphine **CP1** (LB = PPh_3, BA = Ph–OH) could be used as an effective catalyst in asymmetric aza-MBH reaction of *N*-tosyl imines with MVK and phenyl acrylate, providing the corresponding adducts in good yields with high ee's (Scheme 2).[15] The asymmetric induction of this catalyst is comparable to that of the quinidine derivatives.[16] The presence of a phenolic hydroxyl group in catalyst **CP1** seems crucial for good yield and high ee since replacing the phenolic hydroxyl group with a methoxyl or an ethyl group gave the product in much lower yield and ee. Then, we first conducted the mechanistic studies of the bifunctional chiral phosphine catalysis in the aza-MBH reaction through the ^1H and ^{31}P NMR spectroscopic tracing experiments, which revealed the bifunctional role of catalyst

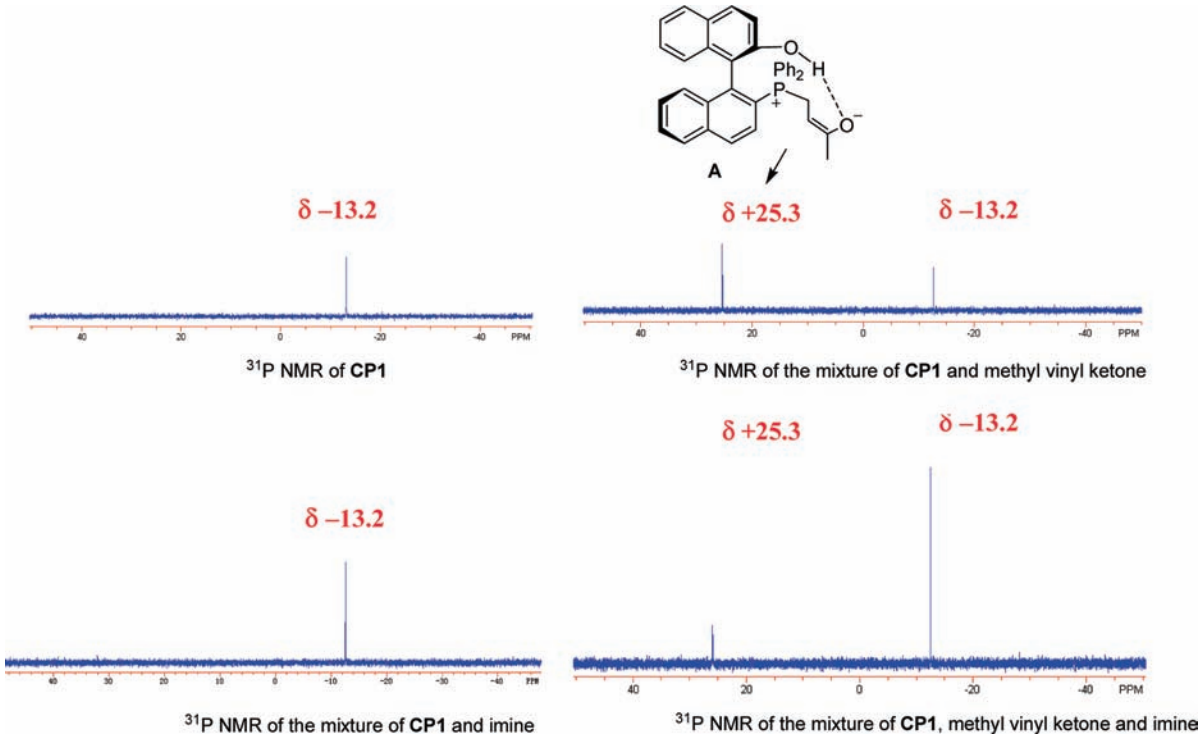


FIGURE 4. ^{31}P NMR tracing experiment.

CP1.[17] The ^{31}P NMR spectroscopic data of **CP1** with MVK elucidated a new signal at +25.30 ppm, which was believed to correspond to the phosphonium enolate intermediate **A** (Figure 4). The ^{1}H NMR spectra clearly showed that the phenolic hydroxy group at 4.62 ppm in **CP1** shifted to another place with the addition of MVK, which indicated the existence of a hydrogen-bonding interaction (Figure 5). For comparison, the phosphonium bromide salt was prepared, and its ^{1}H NMR spectrum was measured and showed that the signal of the phenolic hydroxy group dramatically shifted to 9.78 ppm (Figure 5; for a more detailed discussion on the preparation procedure and NMR measurements, please see ref 17). This further strongly suggests that there is an intramolecular hydrogen bonding between the phenolic hydroxy group and oxygen atom of carbonyl group to stabilize the in situ formed phosphonium enolate. We then proposed a detailed mechanism to rationalize the reaction outcomes of stereochemistry of adducts. The phosphorus center acts as a Lewis base (LB) to initiate the reaction, and the phenolic OH group acts as a Brønsted acid (BA) utilized to stabilize the in situ formed key enolate intermediate **A** and the reaction intermediate **B** through hydrogen bonding; subsequently one of **B**′s diastereomers is the most favorable for the subsequent proton transfer and β-elimination, leading to the desirable enantioselective adduct (Scheme 3). Subsequently, Leitner et al. observed that triphenylphosphine either alone or in combination with protic additives could cause racemization of the aza-MBH product.[18] To our delight, the chiral catalyst **CP1** did not induce any racemization on a similar time scale. The phenolic hydroxyl group in the catalyst might play an important role in preventing the racemization of the product. Catalyst **CP1** also shows good asymmetric induction for the aza-MBH reactions of ethyl (arylimino)acetates with MVK and EVK.[19] However, catalyst **CP1** could not give good enantiomeric excess in the reaction of *N*-arylmethylidenediphenylphosphinamides with activated alkenes such as MVK, acrylonitrile, or phenyl acrylate.[20]

Having identified the catalyst **CP1** as an efficient catalyst for aza-MBH reaction, we hypothesized that replacing the phenol group in catalyst **CP1** with other groups such as a (thio-)urea group might also give high catalytic activity and good asymmetric induction, because the acidic NH protons provide good opportunity to form a hydrogen bond, which may stabilize certain intermediates.[21] Indeed it was found that the chiral thiourea-phosphine **CP2** in combination with benzoic acid was a very successful catalytic system for the aza-MBH reaction of *N*-tosyl imines with MVK, PVK, EVK, or acrolein (Scheme 4).[22] To the best of our knowledge, this was the first report about the synthesis and application of chiral phosphinothiourea catalysts in asymmetric catalysis.

Subsequently, in order to further improve the catalytic activity and enantioselectivity, we designed and synthesized a series of bifunctional chiral phosphine amides, **CP3**−**CP9** (Figure 6), which may serve as efficient catalysts because they

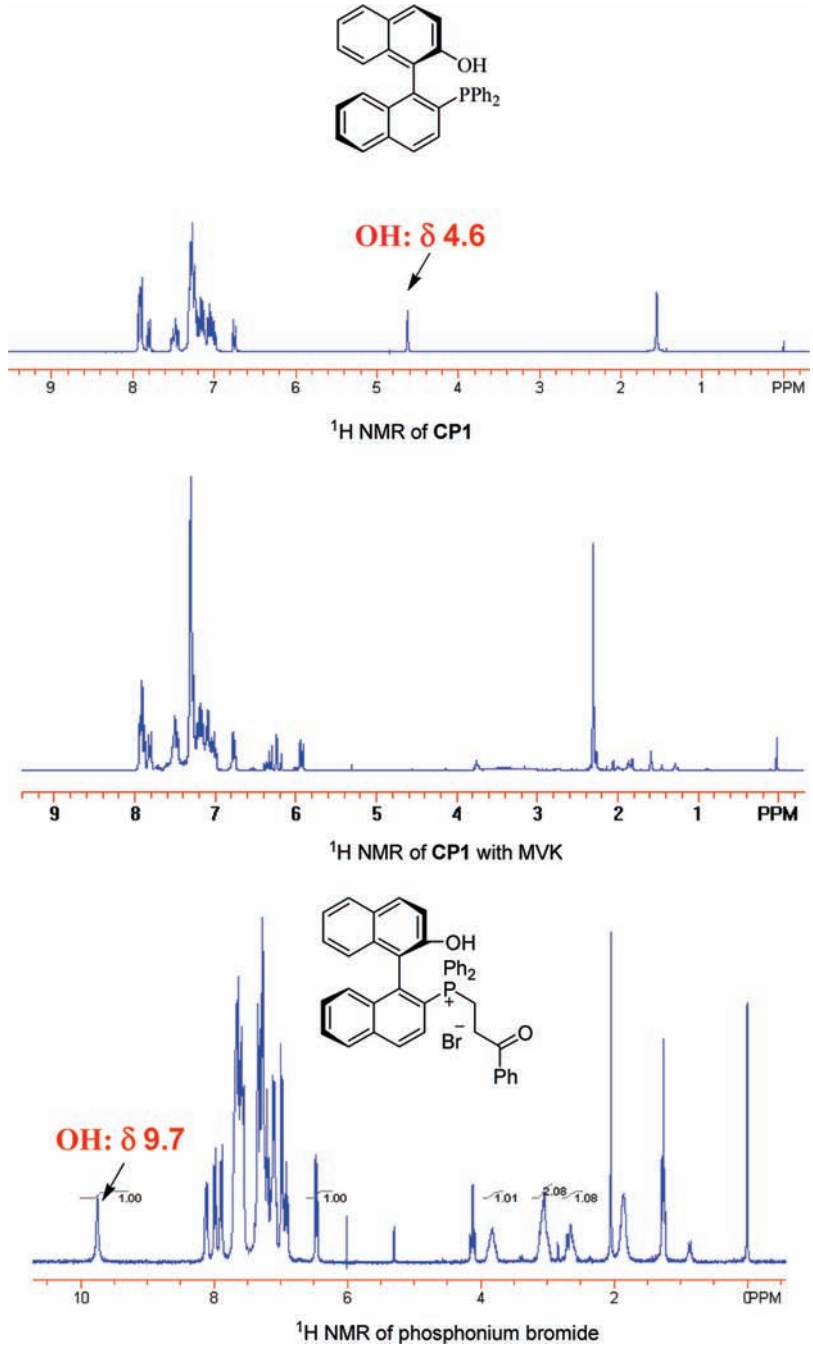
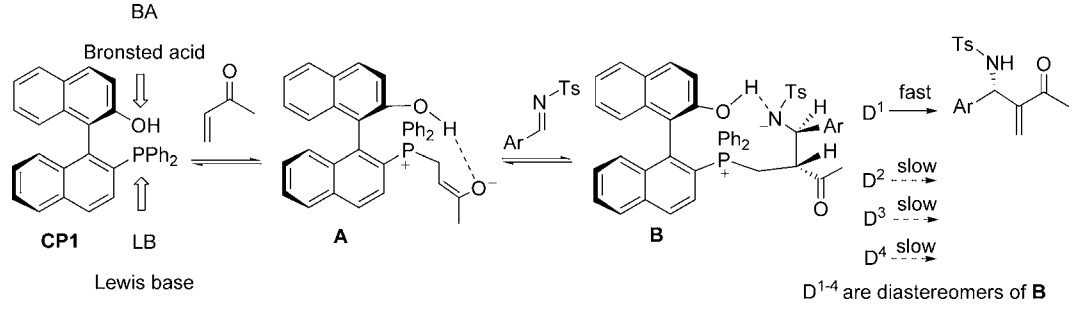
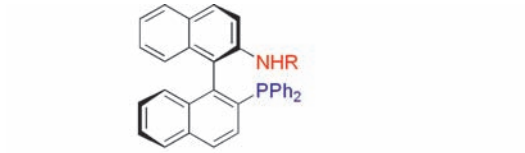


FIGURE 5. ^{1}H NMR spectra.

SCHEME 3. A Plausible Mechanism of Bifunctional Chiral Phosphine Catalyzed Aza-MBH Reaction

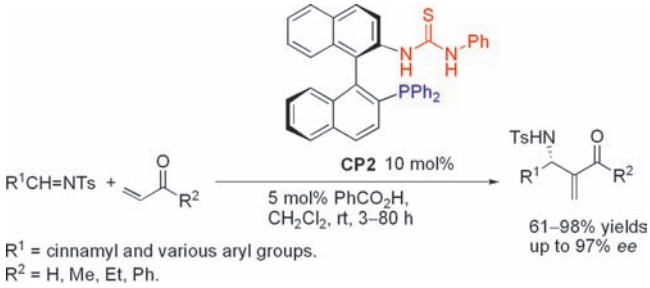




CP3: R = SO_2CH_3; **CP4**: R = SO_2CF_3,
CP5: R = $SO_2C_6H_4CH_3$-*p*; **CP6**: R = COC_6H_5;
CP7: R = $COCH_3$; **CP8**: R = CO_2CH_3; **CP9**: R = $PO(C_6H_5)_2$

FIGURE 6. Structures of phosphine-amide-type bifunctional chiral phosphines.

SCHEME 4. Multifunctional Chiral Phosphinothiourea-Catalyzed Asymmetric Aza-MBH Reaction



have a unique chiral environment and their acidic amide proton may act as an efficient hydrogen-bonding donor to interact with substrate. Interestingly, it was observed that the acetamide-phosphine **CP7** with a moderately acidic amide proton displayed the best asymmetric induction for the aza-MBH reaction of *N*-tosyl imines with MVK or EVK, affording high yield up to 99% and excellent ee up to 91%.[23] However, the catalyst **CP4** having a stronger acidic amide proton could not give any product. Presumably, the strong acidic amide proton is transferred to zwitterionic enolate **I** mentioned in Scheme 1, leading to some inactive intermediate, which cannot facilitate the catalytic cycle.

Later on, three sterically congested bifunctional chiral phosphane-amides, **CP10**–**CP12** (Figure 7) were further synthesized in order to evaluate the steric effect for asymmetric induction. It was found that this type of catalyst has similar chiral induction for the aza-MBH reaction of *N*-tosyl imines with MVK at room temperature as catalyst **CP1** at −30 °C. Catalysts **CP11** and **CP12** are indeed more effective than the less sterically hindered phosphane-monobenzamide **CP6**.[24]

The nucleophilicity of the phosphorus center in the catalyst may affect catalytic activity. Thus catalyst **CP13** was designed to test the nucleophilicity effect by changing the phenyl groups in catalyst **CP1** with methyl groups. The derived catalyst **CP13** was examined in the aza-MBH reaction of *N*-tosyl imines with less reactive olefins of 2-cyclohexen-1-one or 2-cyclopenten-1-one (Scheme 5), which could not be catalyzed by **CP1**. The desired adducts were obtained in good yields and moderate enantiomeric excess.[25] This indicates that increasing the nucleophilicity of the reactive center improves the catalytic reactivity.

Having established the nucleophilicity effect, we further designed and developed a series of bifunctional chiral phosphine Lewis bases, **CP14**–**CP17** (Figure 8), bearing an alkyl group on the phosphorus atom to tune the nucleophilicity of the phosphorus center and the steric hindrance.[26] We were pleased to find that catalysts **CP14**–**CP17** were very effective in the aza-MBH reaction of various *N*-tosyl imines with MVK under mild and concise conditions to produce the corresponding adducts in good-to-excellent yields within relatively short reaction times. Especially, **CP16** was the most effective catalyst to give the corresponding adducts in good-to-excellent yields and moderate-to-good enantioselectivities

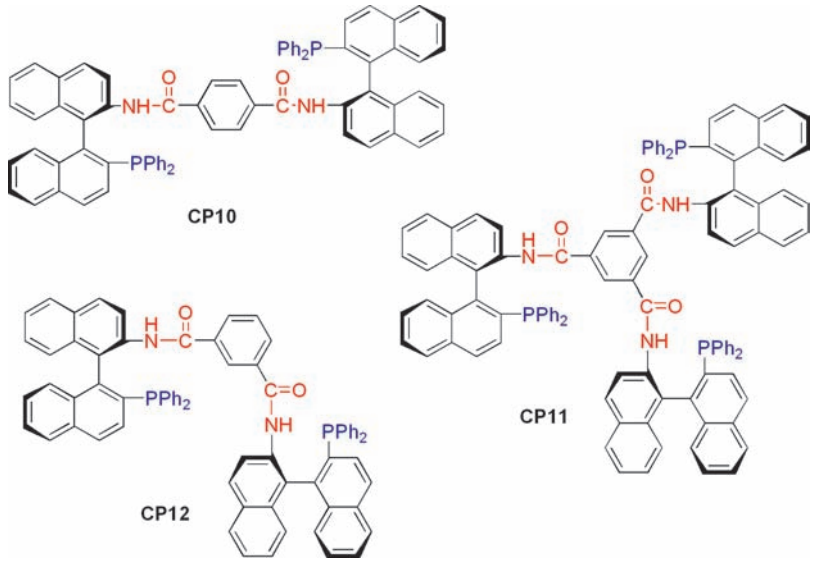
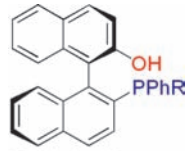
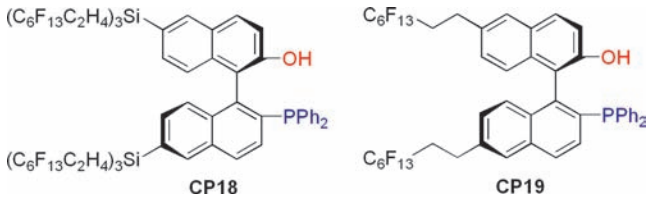


FIGURE 7. Sterically congested phosphine-amide-type bifunctional chiral phosphines.



CP14: R = Et
CP15: R = *i*Pr
CP16: R = *n*Bu
CP17: R = Cy

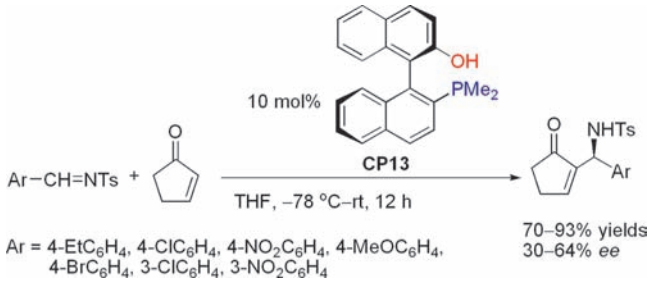
FIGURE 8. Structures of more nucleophilic phosphane-phenol type bifunctional chiral phosphines.



CP18 **CP19**

FIGURE 9. Phosphane-phenol-type bifunctional chiral phosphines bearing perfluoroalkane chains.

SCHEME 5. More Nucleophilic Phosphane-Phenol-Type Bifunctional Chiral Phosphines in the Asymmetric Aza-MBH Reaction of *N*-Sulfonated Imine with Cyclic Enone



within only 1−5 h under mild conditions.[26] To the best of our knowledge, this is the fastest asymmetric aza-MBH reaction reported thus far.

A few reports have demonstrated that introducing a long-chain alkyl group in a variety of chiral ligands could improve the catalytic activity and enantioselectivity in homogeneous asymmetric catalysis.[27] Inspired by these reports, we have introduced the so-called "pony tails", long perfluoroalkane chains, at the naphthalene framework and synthesized the catalysts **CP18** and **CP19** (Figure 9). Indeed, the catalyst **CP19** was more effective in the aza-MBH reaction of *N*-tosyl imines with MVK than the previously reported original chiral phosphine **CP1**.[28] The performance of **CP18** was not so impressive, presumably due to the steric bulkiness.

Another approach to improve the catalytic activity and enantioselectivity is to increase the number of hydrogen bond donors in the bifunctional chiral phosphines. The working hypothesis is that chiral phosphine Lewis base, such as chiral phosphinyl BINOL, bearing multiple phenol groups, can accelerate the reaction rates and overcome the drawback of the limited substrates in catalytic asymmetric aza-MBH reaction

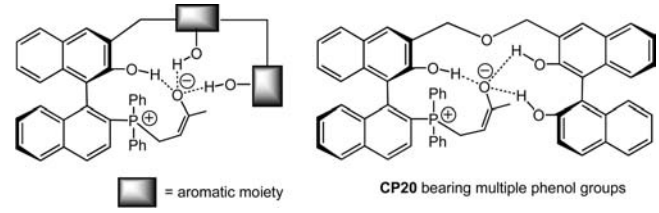
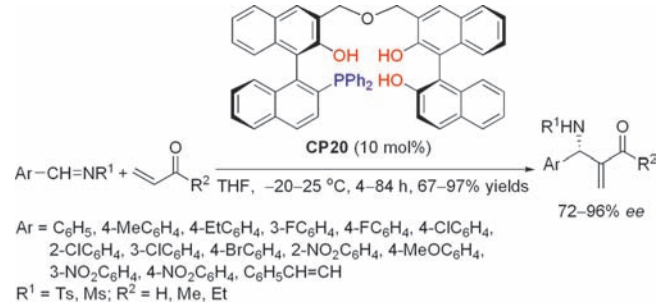


FIGURE 10. A proposed hydrogen-bonding structure in chiral phosphine Lewis bases bearing multiple phenol groups.

SCHEME 6. Asymmetric Aza-MBH Reaction Catalyzed by Chiral Phosphines Bearing Multiple Phenolic Hydroxyl Groups



because these hydrogen bond donating groups can significantly stabilize the key phosphonium enolate and then produce the corresponding adducts in good yields and high ee (Figure 10). Thus, **CP1** was modified to incorporate multiple phenol groups, and it was found that catalyst **CP20** gave the best asymmetric induction. The corresponding adducts could be obtained in >90% ee and good to excellent yields at −20 °C or room temperature (25 °C) in THF for most substrates using MVK, EVK, or acrolein as a Michael acceptor (Scheme 6).[29] We also carried out the ^{31}P NMR measurements for **CP20** and the mixture of **CP20** and MVK in order to provide some evidence for our working hypothesis. It was observed that the ^{31}P NMR spectrum of **CP20** showed a signal at −12.07 ppm, and then a new signal appeared quickly at +26.36 ppm, while the signal at −12.07 ppm almost vanished after addition of MVK (Figure 11). The signal at +26.36 ppm was considered to be the chemical shift corresponding to a key phosphonium enolate intermediate generated in situ from equilibrium. It is notable that under the same conditions, the aforementioned ^{31}P NMR spectrum of the mixture of **CP1** and MVK (see Figure 4) showed two signals at +25.3 ppm and −13.2 ppm in a ratio of almost 1:1. These results indicated that multiple phenol groups, namely, more hydrogen bond donors, can drive the equilibrium largely to the formation of the phosphonium enolate intermediate and stabilize the intermediate strongly via intramolecular hydrogen bonding, which may be employed to rationalize the high enantioselectivities and yields achieved by **CP20**.

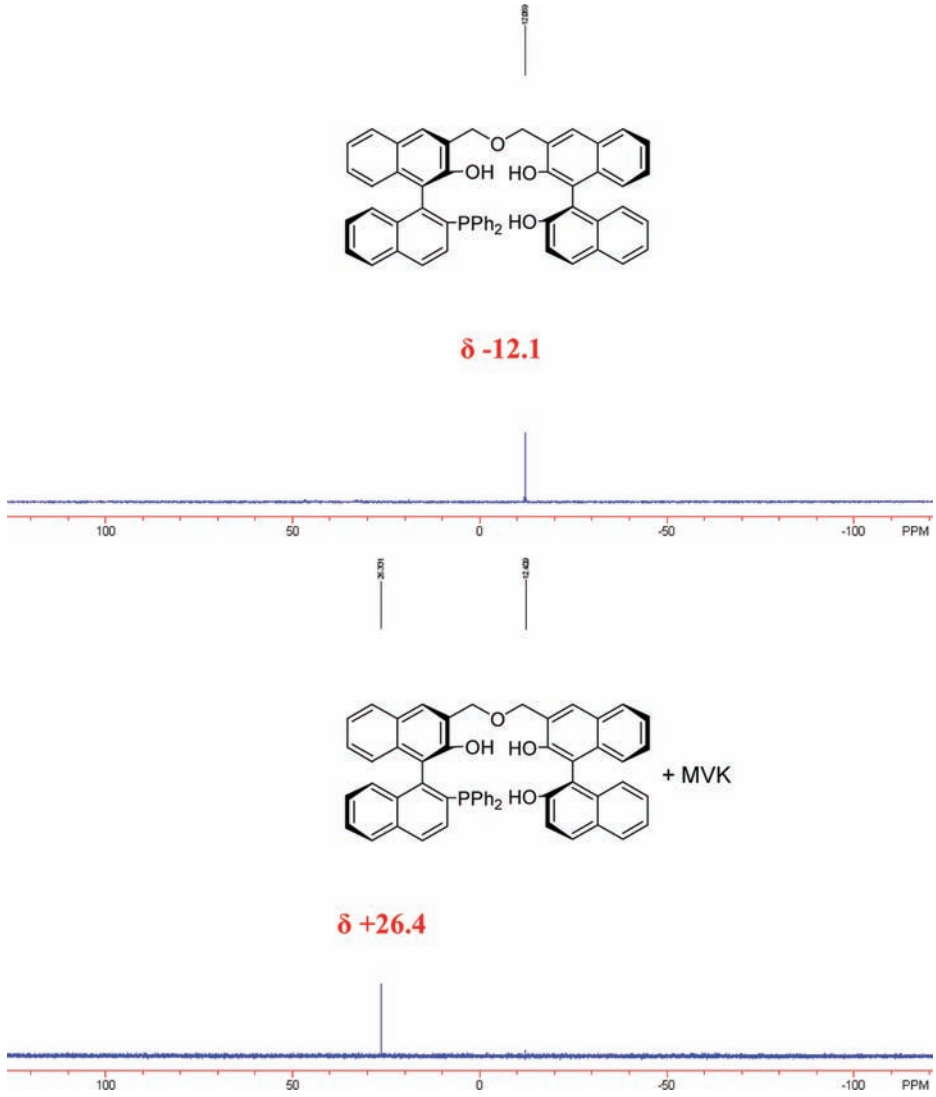
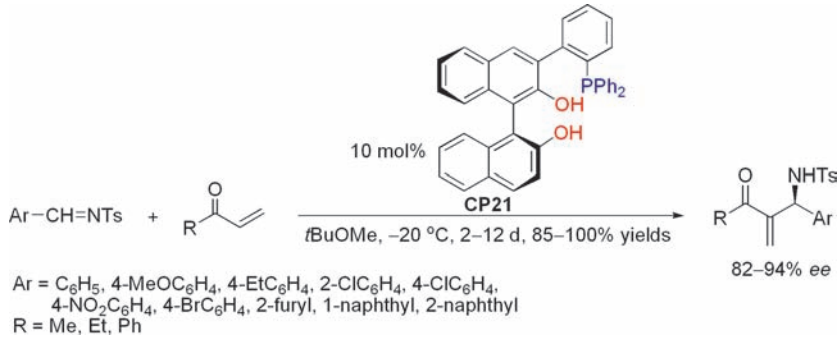


FIGURE 11. ^{31}P NMR of **CP20** and the mixture of **CP20** and MVK.

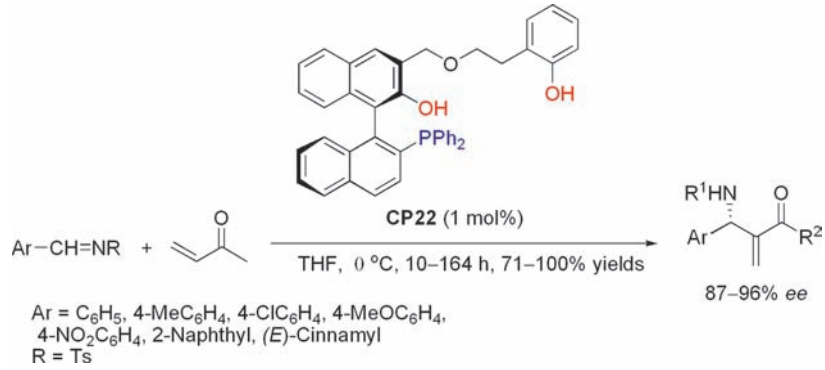
SCHEME 7. Multifunctional Chiral Phosphines in Asymmetric Aza-MBH Reaction



On the basis of the same working hypothesis, Sasai et al. functionalized the 3-position of BINOL with a series of aryl phosphines. It was found that catalyst **CP21** could effectively catalyze asymmetric aza-MBH reaction of *N*-tosyl imines with vinyl ketones (Scheme 7).[30] More recently, Ito et al. also reported biphenol-based bifunctional catalyst **CP22** for aza-MBH reaction of *N*-tosyl imines with MVK (Scheme 8).[31] High enantioselectivity up to 96% ee was achieved by **CP22** with catalyst loading of 1 mol %.

In order to recycle the catalyst, we immobilized **CP1** on a series of dendrimers.[32] It was found that the dendrimer-immobilized catalyst **CP23** (Figure 12) was more effective

SCHEME 8. Biphenol-Based Bifunctional Catalyst in Asymmetric Aza-MBH Reaction



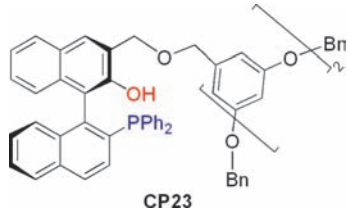
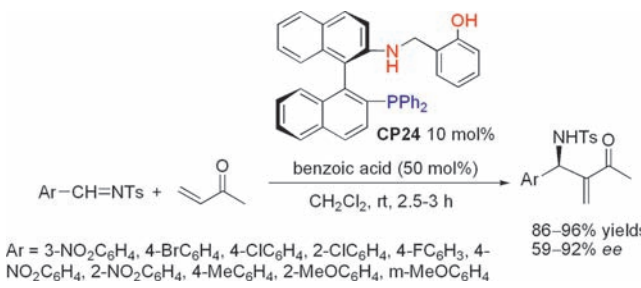


FIGURE 12. Dendrimer immobilized phosphine-phenol type of multifunctional chiral phosphines.

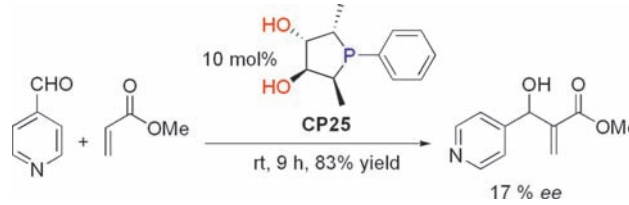
than catalyst **CP1** for the aza-MBH reaction of *N*-sulfonyl imines with MVK, EVK, or acrolein. The catalyst could be easily separated from the reaction mixture by simple filtration after the reaction and reused without obvious loss of activity.[33]

More recently, Liu and co-workers reported trifunctional organocatalyst-promoted counterion catalysis for aza-MBH reactions at ambient temperature.[34] Fast and enantioselective aza-MBH reactions between electron-deficient or electron-rich aromatic *N*-tosyl imines and MVK were achieved at ambient temperature using asymmetric counterion-directed catalysis promoted by trifunctional organocatalysts with a Brønsted base as the activity switch after protonation with benzoic acid (Scheme 9).

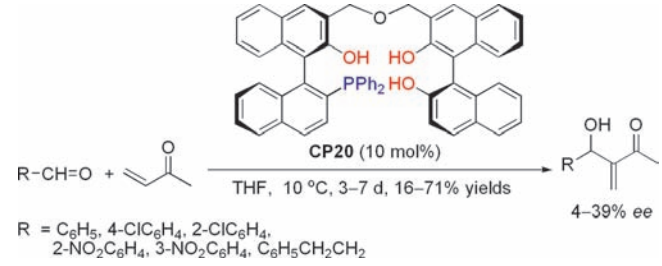
SCHEME 9. Trifunctional Phosphine Organocatalyst-Promoted Aza-MBH Reaction



SCHEME 10. Phosphane-Hydroxy-Type Multifunctional Chiral Phosphine-Catalyzed Asymmetric MBH Reaction



SCHEME 11. Phosphane-Multiphenol Groups of Chiral Phosphines in Asymmetric MBH Reaction of Aldehydes with MVK



3. Multifunctional Chiral Phosphine Catalysts in Morita−Baylis−Hillman Reaction

We have demonstrated that bifunctional chiral phosphines are efficient enantioselective catalysts in aza-MBH reactions. Besides aza-MBH reactions, we and other groups found that they can also be applied in MBH reaction of aldehydes with various activated alkenes. In 2000, Zhang reported that hydroxyl phospholane **CP25** catalyzed MBH reaction between 4-pyridinecarboaldehyde and methyl acrylate. If the hydroxyl group in the phospholane was protected, a lower reaction rate was observed (Scheme 10).[35]

As an effective catalyst in aza-MBH reaction, catalyst **CP20** bearing multiple phenol groups is also effective for the MBH reaction of aldehydes with MVK (Scheme 11).[36] If the two phenol groups on the second binaphthalene moiety were changed to methoxy groups, the resulting chiral phosphine could not catalyze the reaction under identical conditions. It

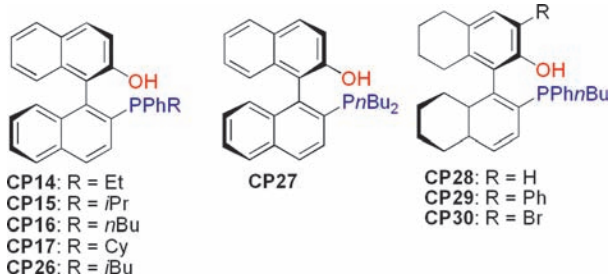


FIGURE 13. Structures of more nucleophilic phosphine-phenol-type bifunctional chiral phosphines.

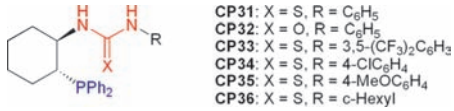
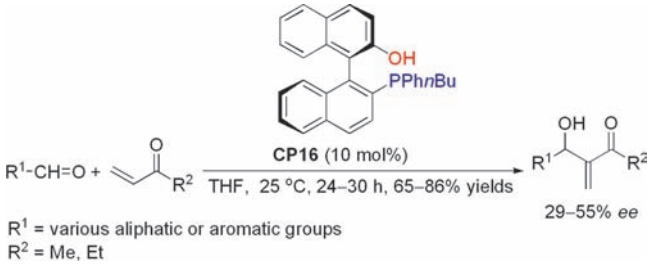


FIGURE 14. Structures of phosphine-(thio)urea multifunctional chiral phosphines.

SCHEME 12. Phosphane-Phenol-Type Multifunctional Chiral Phosphine-Catalyzed Asymmetric MBH Reaction of Aldehydes with α,β-Unsaturated Ketones

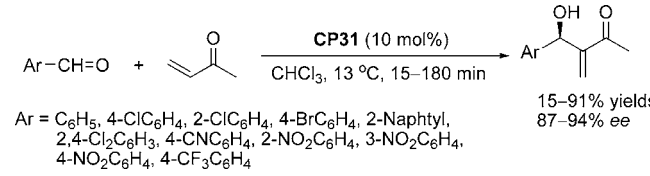


could be deduced that the multiple phenol groups played a significant role in accelerating the reaction rates, which is in line with our observations in aza-MBH reaction.

In order to investigate whether previously synthesized catalysts **CP14**−**CP17** were still effective for MBH reaction, we tested them in the reaction of aldehydes with activated alkenes. For comparison, the catalyst **CP1** and newly designed catalysts **CP26**−**CP30** were also examined (Figure 13). Unfortunately, the effective catalyst **CP1** for aza-MBH reaction did not show catalytic activity for the reaction of 3-phenylpropanal and MVK. **CP16** was still the most effective catalyst with respect to a wide range of substrates, affording the corresponding products in good yields with moderate ee's (Scheme 12).[37]

Recently, Wu's group reported a series of chiral phosphino(thio)ureas **CP31**−**CP36** (Figure 14) derived from *trans*-2-amino-1-(diphenylphosphino)cyclohexane. **CP31** was the best catalyst for the MBH reaction of various aromatic aldehydes with MVK giving the products with excellent enantiomeric excesses under mild conditions in relative short reaction time (Scheme 13).[38]

SCHEME 13. Phosphine-(thio)urea Multifunctional Chiral Phosphine-Catalyzed Asymmetric MBH Reaction



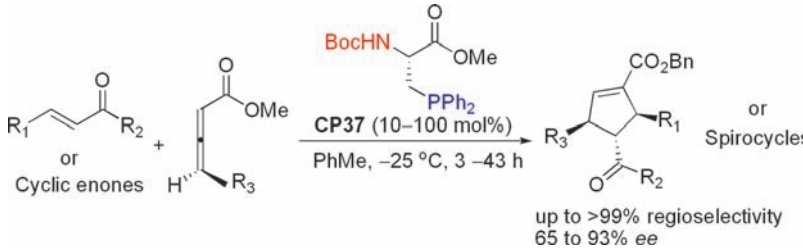
4. Multifunctional Chiral Phosphine Catalysts in Other Reactions

Since 2007, several elegant papers have reported that bifunctional chiral phosphines can be applied in reactions beyond MBH/aza-MBH reaction, such as enantioselective [3 + 2] cycloaddition reactions.[39,40] Miller's group developed α-amino acid derived chiral phosphines that can catalyze [3 + 2] cycloaddition between allenic ester and α,β-unsaturated ketones. Both cyclic and acyclic enones were applicable for this reaction, giving the corresponding cyclopentenes with high enantioselectivities (Scheme 14).[41] The hydrogen atom in the amide moiety of **CP37** was considered to be pivotal as the hydrogen bond donor to stabilize the transition state accounting for asymmetric induction.

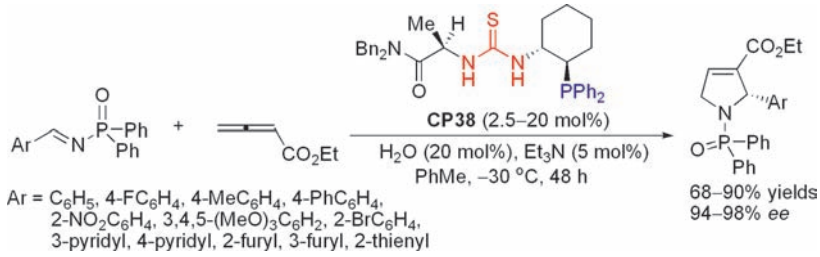
More recently, Jacobsen developed a series of bifunctional phosphorus thiourea derivatives for highly enantioselective synthesis of chiral dihydropyrroles via imine-allene [3 + 2] cycloaddition. They identified the simplified alanine-derived chiral phosphinothiourea **CP38** as the best catalyst (Scheme 15) and found that the amino amide plays a secondary role relative to the aminophosphine component of the catalyst with respect to enantioinduction but is nonetheless important for catalyst activity.[42] The hydrogen bonding of thiourea to the oxygen atom of the phosphinyoyl group is proposed to make the imine adopt an *s*-cis conformation that is critical to furnish an effective chiral environment. The $\pi-\pi$ stacking between the amide portion of the catalyst and the diphenyl portion of the imine may also provide additional selective stabilization of the lowest energy transition state.

Interestingly, our previously developed catalyst **CP7** for aza-MBH reaction has a new application. Catalyst **CP7** achieved high yield and excellent ee for the reaction of MBH acetates with 2-trimethylsilyloxy furan, which is an effective approach for the asymmetric synthesis of γ-butenolides (Scheme 16).[43] The experimental observations reveal that the active amide proton in **CP7** is crucial to the catalytic reactivity and enantioselectivity. The proposed mechanism is illustrated in Scheme 17, which suggests that the active amide proton in **CP7** as a hydrogen donor to form intramolecular

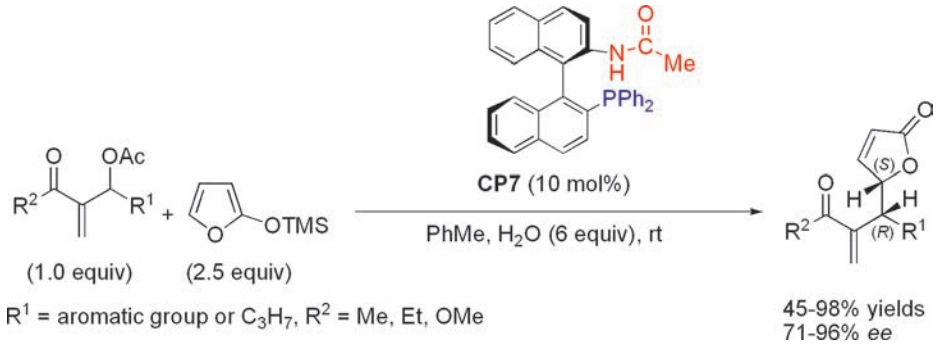
SCHEME 14. Phosphine-amide-Type Multifunctional Chiral Phosphine Catalyzed Asymmetric [3 + 2] Cycloaddition Reaction



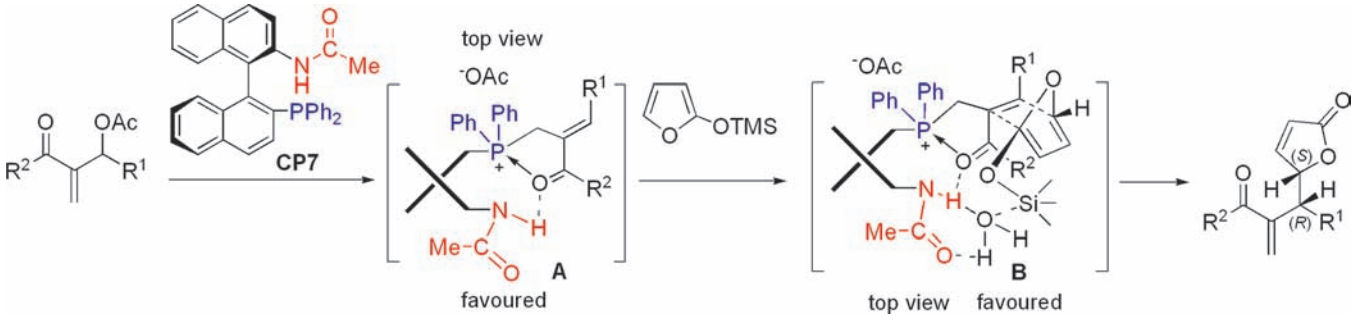
SCHEME 15. Phosphane-Amide-Type Multifunctional Chiral Phosphine Catalyzed Asymmetric [3 + 2] Cycloaddition Reaction of Activated Imines with Allenic Ester



SCHEME 16. Phosphane-Amide-Type Multifunctional Chiral Phosphine Catalyzed Allylic Substitution of Various MBH Acetates with 2-Trimethylsilyloxy Furan



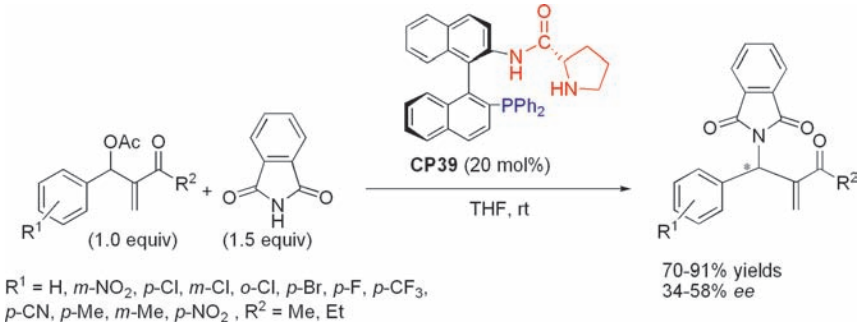
SCHEME 17. A Plausible Reaction Mechanism



hydrogen bonding stabilizes the intermediate, leading to excellent enantioselectivity.

In 2004, Krische and co-workers reported the first example of phosphine-catalyzed intermolecular allylic substitution reactions of MBH acetates,[44] and then the asymmetric version was reported by Hou using planar chiral [2.2]paracyclophane monophosphines as catalyst, affording the allylic amination products in high regioselectivities and in modest enantioselectivities with respect to limited substrates.[45] To further extend the substrate scope of this reaction, we developed a series of L-proline-derived chiral phosphine-amide catalysts and examined their performance. Using catalyst **CP39**, we were pleased to obtain the product in good yields with moderate ee, which could not be achieved successfully in previ-

SCHEME 18. Phosphine-Amide-Type Multifunctional Chiral Phosphine Catalyzed Asymmetric Allylic Amination Reaction of MBH adducts



ous studies (Scheme 18).[46] Our results reveal that the chirality of the proline moiety has a certain impact on the reaction outcome but do not show any significant match/mismatch between the chirality of binaphthol and proline. Replacing the active amino proton of proline with an *N*-Boc group did not decrease the yield and enantioselectivity significantly, suggesting that the active amino proton of the proline moiety might be dispensable in this reaction.

5. Conclusion

In conclusion, multifunctional/bifunctional chiral phosphine organocatalysts have established themselves as efficient enantioselective catalysts in catalytic asymmetric MBH and related reactions due to the combination of a hydrogen-bonding motif with a highly nucleophilic phosphorus center within one molecule. We have also demonstrated that the reactivities and enantioselectivies of these multifunctional/bifunctional chiral phosphine organocatalysts can be finely tuned through enhancing the reactive center's nucleophilicity and varying and increasing hydrogen bond donors. Multifunctional catalysis will remain as a powerful strategy to inspire the design of new efficient and selective catalysts.

We thank the Shanghai Municipal Committee of Science and Technology (Grants 06XD14005, 08dj1400100-2), National Basic Research Program of China (Grant (973)-2010CB833302), and the National Natural Science Foundation of China (Grants 20872162, 20672127, 20821002, and 20732058) for financial support.

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Yin Wei was born in Henan, China. She received her Ph.D. from Ludwig-Maximilians-Universität in München (Germany) in 2009 under the direction of Professor Hendrik Zipse. Subsequently she joined Professor Min Shi's group at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, as an Assistant Professor. She is currently working on theoretical studies of organocatalysis.

FOOTNOTES

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REFERENCES

1 (a) Shibasaki, M.; Sasai, H.; Arai, T. Asymmetric Catalysis with Heterobimetallic Compounds. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236–1256. (b) Shibasaki, M.; Yoshikawa, N. Lanthanide Complexes in Multifunctional Asymmetric Catalysis. *Chem. Rev.* **2002**, *102*, 2187–2209. (c) Saito, S.; Yamamoto, H. Design of Acid-Base Catalysis for the Asymmetric Direct Aldol Reaction. *Acc. Chem. Res.* **2004**, *37*, 570–579. (d) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; Mcdaid, P.; Deng, L. Asymmetric Organic Catalysis with Modified Cinchona Alkaloids. *Acc. Chem. Res.* **2004**, *37*, 621–631. (e) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. Cupreines and Cupreidines: An Emerging Class of Bifunctional Cinchona Organocatalysts. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496–7504.

2 For reviews of multifunctional catalysis, see: (a) Sawamura, M.; Ito, Y. Catalytic Asymmetric Synthesis by Means of Secondary Interaction between Chiral Ligands and Substrates. *Chem. Rev.* **1992**, *92*, 857–871. (b) Steinhagen, H.; Helmchen, G. Asymmetric Two-Center Catalysis - Learning from Nature. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2339–2342. (c) van den Beuken, E. K.; Feringa, B. L. Bimetallic Catalysis by Late Transtition Metal Complexes. *Tetrahedron* **1998**, *54*, 12985–13011. (d) Rowlands, G. J. Ambifunctional Cooperative Catalysts. *Tetrahedron* **2001**, *57*, 1865–1882.

3 For reviews, see: (a) Shibasaki, M.; Sasai, H.; Arai, T.; Iida, T. Heterobimetallic Asymmetric Catalysts. Developments and Applications. *Pure Appl. Chem.* **1998**, *70*, 1027–1034. (b) Shibasaki, M.; Iida, T.; Yamada, Y. M. A. Development of Multifunctional Asymmetric Catalysts and Their Application to Practical Organic Synthesis. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 344–356. (c) Shibasaki, M. Multifunctional Asymmetric Catalysis. *Chemtracts: Org. Chem.* **1999**, *12*, 979–998. (d) Shibasaki, M. Multifunctional Asymmetric Catalysis. *Enantiomer* **1999**, *4*, 513–527.

4 For selected reviews concerning organocatalysis, see: (a) Dalko, P. I.; Moisan, L. Enantioselective Organocatalysis. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748. (b) Benaglia, M.; Puglisi, A.; Cozzi, F. Polymer-Supported Organic Catalysts. *Chem. Rev.* **2003**, *103*, 3401–3430. (c) Berkessel, A.; Gröger, H. *Metal-Free Organic Catalysis in Asymmetric Synthesis.* Wiley-VCH, Weinheim, Germany, 2004. (d) Special Issue: Asymmetric Organocatalysis. *Acc. Chem. Res.* **2004**, *37*, 487−631.

5 For reviews, see: (a) List, B. Asymmetric Aminocatalysis. *Synlett* **2001**, 1675–1686. (b) List, B. Proline-Catalyzed Asymmetric Reactions. *Tetrahedron* **2002**, *58*, 5573–5590. (c) List, B. Enamine Catalysis Is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents. *Acc. Chem. Res.* **2004**, *37*, 548–557. (d) Movassaghi, M.; Jacobsen, E. N. The Simplest "Enzyme". *Science* **2002**, *298*, 1904–1905.

6 (a) Baylis, A. B.; Hillman, M. E. D. Ger. Offen 2,155,113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q; Hillman, M. E. D.; Baylis, A. B. U. S. Patent 3,743,669, 1973. (b) Morita, K.; Suzuki, Z.; Hirose, H. A Tertiary Phosphine-Catalyzed Reaction of Acrylic Compounds with Aldehydes. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815–2815. For recent reviews on MBH reaction, see: (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Recent Advances in the Baylis-Hillman Reaction and Applications. *Chem. Rev.* **2003**, *103*, 811–892. (d) Basavaiah, D.; Rao, K. V.; Reddy, R. J. The Baylis-Hillman Reaction: A Novel Source of Attraction, Opportunities, and Challenges in Synthetic Chemistry. *Chem. Soc. Rev.* **2007**, *36*, 1581–1588. (e) Singh, V.; Batra, S. Advances in the Baylis-Hillman Reaction-Assisted Synthesis of Cyclic Frameworks. *Tetrahedron* **2008**, *64*, 4511–4574.

7 For reviews on *aza*-MBH reaction, see: (a) Shi, Y.-L.; Shi, M. Aza-Baylis-Hillman Reactions and Their Synthetic Applications. *Eur. J. Org. Chem.* **2007**, 2150–2155. (b) Declerck, V.; Martinez, J.; Lamaty, F. Aza-Baylis-Hillman reaction. *Chem. Rev.* **2009**, *109*, 1–46. For reviews on enantioselective MBH reaction, see: (c) Langer, P. New Strategies for the Development of an Asymmetric Version of the Baylis-Hillman Reaction. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049–3052. (d) Masson, G.; Housseman, C.; Zhu, J. The Enantioselective Morita-Baylis-Hillman Reaction and Its Aza Counterpart. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628.

8 Ma, G.-N.; Jiang, J.-J.; Shi, M.; Wei, Y. Recent Extensions of the Morita-Baylis-Hillman Reaction. *Chem. Commun.* **2009**, 5496–5514, and references therein.

9 For some representative reports on the asymmetric MBH/aza-MBH reaction, see: (a) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. The Asymmetric Baylis-Hillman Reaction. *J. Am. Chem. Soc.* **1997**, *119*, 4317–4318. (b) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A.; Adams, H. The Use of Enantiomerically Pure *N*-sulfinimines in Asymmetric Baylis-Hillman Reactions. *Tetrahedron Lett.* **2002**, *43*, 1577–1580. (c) Shi, M.; Xu, Y.-M. Diastereoselective Baylis-Hillman Type Reactions of Chiral Non-Racemic *N*-Sulfinimines with Cyclopent-2-en-1-one. *Tetrahedron: Asymmetry* **2002**, *13*, 1195–1200. (d) Li, G.; Wei, H.-X.; Whittlesey, B. R.; Batrice, N. N. Novel Asymmetric C−C Bond Formation Process Promoted by Et_2AlCl and Its Application to the Stereoselective Synthesis of Unusual β-Branched Baylis−Hillman Adducts. *J. Org. Chem.* **1999**, *64*, 1061–1064. (e) Krishna, P. R.; Sachwani, R.; Reddy, P. S. Asymmetric Baylis-Hillman Reaction: An Enchanting Expedition. *Synlett* **2008**, 2897–2912.

10 (a) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. Asymmetric Baylis-Hillman Reactions: Catalysis Using a Chiral Pyrrolizidine Base. *Chem. Commun.* **1998**, 2533–2534. (b) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. Chiral Amine-Catalyzed Asymmetric Baylis−Hillman Reaction: A Reliable Route to Highly Enantiomerically Enriched (α-Methylene-β-hydroxy)esters. *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220. (c) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. Dual Catalyst Control in the Amino Acid-Peptide-Catalyzed Enantioselective Baylis−Hillman Reaction. *Org. Lett.* **2003**, *5*, 3741–3743.

11 For recent mechanistic studies on MBH reaction: (a) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. Probing the Mechanism of the Baylis-Hillman Reaction by Electrospray Ionization Mass and Tandem Mass Spectrometry. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330–4333. (b) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. Baylis−Hillman Mechanism: A New Interpretation in Aprotic Solvents. *Org. Lett.* **2005**, *7*, 147–150. (c) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. Reevaluation of the Mechanism of the Baylis-Hillman Reaction: Implications for Asymmetric Catalysis. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706–1708. (d) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. Mechanism of the Morita−Baylis−Hillman Reaction: A Computational Investigation. *J. Am. Chem. Soc.* **2007**, *129*, 15513–15525.

12 (a) Matsui, K.; Takizawa, S.; Sasai, H. Bifunctional Organocatalysts for Enantioselective Aza-Morita−Baylis−Hillman Reaction. *J. Am. Chem. Soc.* **2005**, *127*, 3680–3681. (b) Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H. Conformational Lock in a Brønsted Acid-Lewis Base Organocatalyst for the aza-Morita-Baylis-Hillman Reaction. *Tetrahedron: Asymmetry* **2006**, *17*, 578–583.

13 For reviews of phosphine catalysis, see: (a) Glueck, D. S. Catalytic Asymmetric Synthesis of Chiral Phosphanes. *Chem.—Eur. J.* **2008**, *14*, 7108–7117. (b) Methot, J. L.; Roush, W. R. Nucleophilic Phosphine Organocatalysis. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050. (c) Lu, X.; Zhang, C.; Xu, Z. Reactions of Electron-Deficient Alkynes and Allenes under Phosphine Catalysis. *Acc. Chem. Res.* **2001**, *34*, 535–544.

14 Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. Synthesis of Optically Active 2-(Diary1phosphino)-1,1′-binaphthyls, Efficient Chiral Monodentate Phosphine Ligands. *J. Org. Chem.* **1993**, *58*, 1945–1948.

15 Shi, M.; Chen, L.-H. Chiral Phosphine Lewis Base Catalyzed Asymmetric Aza-Baylis-Hillman Reaction of *N*-sulfonated Imines with Methyl Vinyl Ketone and Phenyl Acrylate. *Chem. Commun.* **2003**, 1310–1311.

16 Shi, M.; Xu, Y.-M. Catalytic, Asymmetric Baylis-Hillman Reaction of Imines with Methyl Vinyl Ketone and Methyl Acrylate. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507–4510.

17 Shi, M.; Chen, L.-H.; Li, C.-Q. Chiral Phosphine Lewis Bases Catalyzed Asymmetric Aza-Baylis−Hillman Reaction of N-Sulfonated Imines with Activated Olefins. *J. Am. Chem. Soc.* **2005**, *127*, 3790–3800.

18 Buskens, P.; Klankermayer, J.; Leitner, W. Bifunctional Activation and Racemization in the Catalytic Asymmetric Aza-Baylis−Hillman Reaction. *J. Am. Chem. Soc.* **2005**, *127*, 16762–16763.

19 Shi, M.; Ma, G.-N.; Gao, J. Chiral Bifunctional Organocatalysts in Asymmetric Aza-Morita−Baylis−Hillman Reactions of Ethyl(arylimino)acetates with Methyl Vinyl Ketone and Ethyl Vinyl Ketone. *J. Org. Chem.* **2007**, *72*, 9779–9781.

20 Shi, M.; Zhao, G.-L. Aza-Baylis-Hillman Reactions of *N*-(Arylmethylene)diphenylphosphinamides with Activated Olefins in the Presence of Various Lewis Bases. *Adv. Synth. Catal.* **2004**, *346*, 1205–1219.

21 For (thio)urea derivatives catalyzed reactions, see: (a) Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis by Chiral Hydrogen-bond Donors. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543. (b) Connon, S. J. Organocatalysis Mediated by (Thio)Urea Derivatives. *Chem.—Eur. J.* **2006**, *12*, 5418–5427. (c) Berkessel, A.; Roland, K.; Neudörfl, J. M. Asymmetric Morita−Baylis−Hillman Reaction Catalyzed by Isophoronediamine-derived Bis(thio)urea Organocatalysts. *Org. Lett.* **2006**, *8*, 4195–4198.

22 Shi, Y.-L.; Shi, M. Chiral Thiourea-Phosphine Organocatalysts in the Asymmetric Aza-Morita-Baylis-Hillman Reaction. *Adv. Synth. Catal.* **2007**, *349*, 2129–2135.

23 Qi, M.-J.; Ai, T.; Shi, M.; Li, G. Asymmetric Catalytic Aza-Morita-Baylis-Hillman Reaction Using Chiral Bifunctional Phosphine Amides as Catalysts. *Tetrahedron* **2008**, *64*, 1181–1186.

24 Guan, X.-Y.; Jiang, Y.-Q.; Shi, M. Chiral Sterically Congested Phosphane-Amide Bifunctional Organocatalysts in Asymmetric Aza-Morita-Baylis-Hillman Reactions of *N*-sulfonated Imines with Methyl and Ethyl Vinyl Ketones. *Eur. J. Org. Chem.* **2008**, 2150–2155.

25 Shi, M.; Li, C.-Q. Catalytic, Asymmetric Aza-Baylis-Hillman Reaction of *N*-Sulfonated Imines with 2-Cyclohexen-1-one and 2-cyclopenten-1-one in the Presence of a Chiral Phosphine Lewis Base. *Tetrahedron: Asymmetry* **2005**, *16*, 1385–1391.

26 Lei, Z.-Y.; Ma, G.-N.; Shi, M. A Fast Catalytic Asymmetric Aza-Morita-Baylis-Hillman Reaction of *N*-Sulfonated Imines with Methyl Vinyl Ketone in the Presence of Chiral Bifunctional Phosphane Lewis Bases. *Eur. J. Org. Chem.* **2008**, 3817–3820.

27 Han, J.-W.; Hayashi, T. Preparation of a New MOP Ligand Containing a Long-Chain Alkyl Group and Its Use for Palladium-Catalyzed Asymmetric Hydrosilylation of Cyclic 1,3-Dienes. *Chem. Lett.* **2001**, 976–977.

28 Shi, M.; Chen, L.-H.; Teng, W.-D. Asymmetric Aza-Morita-Baylis-Hillman Reaction of *N*-Sulfonated Imines with Methyl Vinyl Ketone Catalyzed by Chiral Phosphine Lewis Bases Bearing Perfluoroalkanes as "Pony Tails". *Adv. Synth. Catal.* **2005**, *347*, 1781–1789.

29 Liu, Y.-H.; Chen, L.-H.; Shi, M. Asymmetric Aza-Morita-Baylis-Hillman Reaction of *N*-Sulfonated Imines with Activated Olefins Catalyzed by Chiral Phosphine Lewis Bases Bearing Multiple Phenol Groups. *Adv. Synth. Catal.* **2006**, *348*, 973–979.

30 Matsui, K.; Takizawa, S.; Sasai, H. A Brønsted Acid and Lewis Base Organocatalyst for the Aza-Morita-Baylis-Hillman Reaction. *Synlett* **2006**, 761–765.

31 Ito, K.; Nishida, K.; Gotauda, T. Highly Enantioselective Aza-Morita-Baylis-Hillman Reaction with a Bisphenol-based Bifunctional Organocatalyst. *Tetrahedron Lett.* **2007**, *48*, 6147–6149.

32 For dendrimeric phosphines in asymmetric catalysis, see: Caminade, A.-M.; Servin, P.; Laurent, R.; Majoral, J.-P. Dendrimeric Phosphines in Asymmetric Catalysis. *Chem. Soc. Rev.* **2008**, *37*, 56–67.

33 Liu, Y.-H.; Shi, M. Dendritic Chiral Phosphine Lewis Bases-Catalyzed Asymmetric Aza-Morita-Baylis-Hillman Reaction of *N*-Sulfonated Imines with Activated Olefins. *Adv. Synth. Catal.* **2008**, *350*, 122–128.

34 (a) Garnier, J.-M.; Anstiss, C.; Liu, F. Enantioselective Trifunctional Organocatalysts for Rate-Enhanced Aza-Morita-Baylis-Hillman Reactions at Room Temperature. *Adv. Synth. Catal.* **2009**, *351*, 331–338. (b) Garnier, J.-M.; Liu, F. Trifunctional Organocatalyst-Promoted Counterion Catalysis for Fast and Enantioselective Aza-Morita-Baylis-Hillman Reactions at Ambient Temperature. *Org. Biomol. Chem.* **2009**, *7*, 1272–1275.

35 Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. Synthesis of Chiral Hydroxyl Phospholane from D-manitol and Their Use in Asymmetric Catalytic Reactions. *J. Org. Chem.* **2000**, *65*, 3489–3496.

36 Shi, M.; Liu, Y.-H.; Chen, L.-H. Asymmetric Catalysis of Morita-Baylis-Hillman Reactions by Chiral Phosphine Lewis Bases Bearing Multiple Phenol Groups. *Chirality* **2007**, *19*, 124–128.

37 Lei, Z.-Y.; Liu, X.-G.; Shi, M.; Zhao, M. Binfunctional Chiral Phosphine-Containing Lewis Base Catalyzed Asymmetric Morita-Baylis-Hillman Reaction of Aldehydes with Activated Alkenes. *Tetrahedron: Asymmetry* **2008**, *19*, 2058–2062.

38 Yuan, K.; Zhang, L.; Song, H.-L.; Hu, Y.; Wu, X.-Y. Chiral Phosphinothiourea Organocatalyst in the Enantioselective Morita-Baylis-Hillman Reactions of Aromatic Aldehydes with Methyl Vinyl Ketone. *Tetrahedron Lett.* **2008**, *49*, 6262–6264.

39 For other [3 + 2] cycloaddition reactions, see: (a) Wilson, J. E.; Fu, G. C. Synthesis of Functionalized Cyclopentenes through Catalytic Asymmetric [3 + 2] Cycloadditions of Allenes with Enones. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426–1429. (b) Jean, L.; Marinetti, A. Phosphine-Catalyzed Enantioselective [3 + 2] Annulations of 2,3-Butadienoates with Imines. *Tetrahedron Lett.* **2006**, *47*, 2141–2145. (c) Lu, Z.; Zheng, S.; Lu, X. An Unexpected Phosphine-Catalyzed [3 + 2] Annulation. Synthesis of Highly Functionalized Cyclopentenes. *Org. Lett.* **2008**, *10*, 3267–3270 For some similar works on the phosphine-catalyzed [4 + 2] annulation between imines and allenoates, see: (d) Zhu, X.-F.; Lan, J.; Kwon, O. An Expedient Phosphine-Catalyzed [4 + 2] Annulation: Synthesis of Highly Functionalized Tetrahydropyridines. *J. Am. Chem. Soc.* **2003**, *125*, 4716–4717.

40 For mechanistic study on [3 + 2] cycloaddition reactions, see: Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. An Unexpected Role of a Trace Amount of Water in Catalyzing Proton Transfer in Phosphine-Catalyzed (3 + 2) Cycloaddition of Allenoates and Alkenes. *J. Am. Chem. Soc.* **2007**, *129*, 3470–3471.

41 Cowen, B. J.; Miller, S. J. Enantioselective [3 + 2]-Cycloadditions Catalyzed by a Protected, Multifunctional Phosphine-Containing α-Amino Acid. *J. Am. Chem. Soc.* **2007**, *129*, 10988–10989.

42 Fang, Y.-Q.; Jacobsen, E. N. Cooperative, Highly Enantioselective Phosphinothiourea Catalysis of Imine−Allene [3 + 2] Cycloadditions. *J. Am. Chem. Soc.* **2008**, *130*, 5660–5661.

43 Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. Chiral Phosphine-Catalyzed Enantioselective Construction of γ-Butenolides through Substitution of Morita−Baylis−Hillman Acetates with 2-Trimethylsilyloxy Furan. *J. Am. Chem. Soc.* **2008**, *130*, 7202–7203.

44 (a) Cho, C.-W.; Kong, J.-R.; Krische, M. J. Phosphine-Catalyzed Regiospecific Allylic Amination and Dynamic Kinetic Resolution of Morita−Baylis−Hillman Acetates. *Org. Lett.* **2004**, *6*, 1337–1339. (b) Cho, C.-W.; Krische, M. J. Regio- and Stereoselective Construction of γ-Butenolides through Phosphine-Catalyzed Substitution of Morita-Baylis-Hillman Acetates: An Organocatalytic Allylic Alkylation. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689–6691.

45 Zhang, T.-Z.; Dai, L.-X.; Hou, X.-L. Enantioselective Allylic Substitution of Morita-Baylis-Hillman Adducts Catalyzed by Planar Chiral [2.2]paracyclophane Monophosphines. *Tetrahedron: Asymmetry* **2007**, *18*, 1990–1994.

46 Ma, G.-N.; Cao, S.-H.; Shi, M. Chiral Phosphine-Catalyzed Regio- and Enantioselective Allylic Amination of Morita-Baylis-Hillman Acetates. *Tetrahedron: Asymmetry* **2009**, *20*, 1086–1092.