Multifunctional Chiral Phosphine Organocatalysts in Catalytic Asymmetric Morita-Baylis-Hillman and Related Reaction
Introduction

• 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.

• 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.

_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._
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.
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.
The Proposed Mechanism of MBH Reaction
Introduction

Multifunctional chiral phosphine Lewis base catalyst, LBBA bifunctional catalytic system: LB, Lewis base; BA, Brønsted acid.
In 1993, Hayashi first synthesized the chiral phosphorus compound CP1 as a chiral monodentate phosphine ligand:

$$\text{CP1}$$
In 2002, Min Shi first demonstrated that this 1,1′-bi-2,2′-naphthol (BINOL)-derived chiral LBBA bifunctional phosphine \( CP1 \) (\( \text{LB} \) PPh\(_3\), \( \text{BA} \) Ph-OH).

![Diagram](https://via.placeholder.com/150)

\[
\begin{align*}
\text{LBBA: chiral bifunctional phosphine} \\
\text{Ar-CH=NTs} + \text{R} \quad \rightarrow \quad 10 \text{ mol\%} \\
\text{solvent, 12–36 h} \\
\text{TsHN} \quad \rightarrow \quad \text{Ar-R} \\
\text{Yields: } 60–97\% \text{ with } 52–94\% \text{ ee} \\
\text{with MS: } 82–96\% \text{ yields, } 79–92\% \text{ ee}
\end{align*}
\]

\( \text{Ar} = \text{C}_6\text{H}_5, 4-\text{MeC}_6\text{H}_4, 4-\text{EtC}_6\text{H}_4, 3-\text{FC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 3-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 3-\text{NO}_2\text{C}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, \) \\
\( \text{R} = \text{Me, OPh} \)

Min Shi* and Lian-Hui Chen *CHEM. COMMUN.*, 2003, 1310–1311
Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

Mechanistic speculation on the chiral Lewis base CP1
The asymmetric induction of CP1 catalyst is comparable to that of the quinidinium derivatives.

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<td>95</td>
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</table>

[a] Yields of isolated products.
The presence of a phenolic hydroxyl group in catalyst CP1 seems crucial for good yield and high ee.
Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

$^{31}P$ NMR of CP1

$^{31}P$ NMR of the mixture of CP1 and methyl vinyl ketone

$^{31}P$ NMR of the mixture of CP1 and imine

$^{31}P$ NMR of the mixture of CP1, methyl vinyl ketone and imine
Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

![NMR Spectra](image)

OH: δ 4.6

1H NMR of CP1

OH: δ 9.7

1H NMR of phosphonium bromide
Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

The chiral catalyst \textbf{CP1} did not induce any racemization on a similar time scale.

\[
\begin{align*}
\text{EtO} & \quad \text{N}^\text{Ar} \\
\text{R} = \text{Me}, \text{Et} \\
\text{EtO}_2 & \quad \text{R} \\
\text{MS 4Å, LB (10 mol%)} & \quad \text{EtO}_2, -10^\circ \text{C}, 48-60 \text{ h} \\
\end{align*}
\]

53%-99% yields, 66%-97% ee

\text{(R)-LB1} 
\text{(S)-HB-LB2}
Multifunntional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

However, catalyst CP1 could not give good enantiomeric excess in the reaction of $N$-arylmethylenediphénylphosphinamides with activated alkenes such as MVK, acrylonitrile, or phenyl acrylate.

Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

\[
\text{C}_6\text{H}_5\text{-CHN-Ph}_2 + \text{C}_6\text{H}_5\text{O}PPh_2 \xrightarrow{10\text{ mole}\%\text{ Catalyst}} \text{C}_6\text{H}_5\text{O}PPh_2\text{NH} \text{C}_6\text{H}_5\text{O}PPh_2
\]

chiral nitrogen Lewis base TQO

chiral phosphine Lewis base

Table 18. Catalytic, asymmetric aza-Baylis–Hillman reactions of N-benzylidene diphenylphosphinamide (1a; 1.0 equiv.) with MVK (1.2 equiv.) in the presence of chiral phosphine and nitrogen catalysts (10 mol%).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp. °C</th>
<th>Time [h]</th>
<th>Yield [%]</th>
<th>ee [%]</th>
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<td>ND</td>
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<td>ND</td>
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<td>26</td>
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<td>+8.9</td>
</tr>
</tbody>
</table>

* Yields of isolated products.
* Determined by chiral HPLC.
* Measured in chloroform at 20 °C.
* Calculated by comparing the optical rotation.
* Not determined.
(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.
Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

Organocatalysis mediated by (thio) urea derivatives

Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

In Baylis-Hilman reaction previously used organocatalyst which has thio urea functional group and give quantitative yield and high ee.

\[
\text{EWG} + \text{RCHO} \xrightarrow{20 \text{ mol}\% \text{cat. base}} \text{neat, 10 }^\circ\text{C} \rightarrow \text{RCH(OH)}\text{EWG}
\]

up to quant yield
up to 96% ee

Albrecht Berkessel,* Katrin Roland, Org. Lett., Vol. 8, No. 19, 2006
The chiral thiourea-phosphine \textbf{CP2} in combination with benzoic acid was a very successful catalytic system for the aza-MBH reaction of \textit{N}-tosyl imines with MVK, PVK, EVK.

First reported about synthesis and application

$$R^1CH=NTs + \text{aldehyde} \rightarrow R^1CH=CHCOH$$

\textbf{CP2} 10 mol\%  
5 mol\% PhCO$_2$H, CH$_2$Cl$_2$, rt, 3–80 h

\[R^1 = \text{cinnamyl and various aryl groups.}\]
\[R^2 = H, Me, Et, Ph.\]

61–98% yields up to 97% ee

Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

A new kind of bifunctional (thio)ureaphosphine catalyst.

A plausible reaction mechanism.
In order to further improve the catalytic activity and enantioselectivity, designed and synthesized a series of bifunctional chiral phosphine amides.

\[
\text{CP3: } R = \text{SO}_2\text{CH}_3; \quad \text{CP4: } R = \text{SO}_2\text{CF}_3, \\
\text{CP5: } R = \text{SO}_2\text{C}_6\text{H}_4\text{CH}_3-\text{p}; \quad \text{CP6: } R = \text{COC}_6\text{H}_5; \\
\text{CP7: } R = \text{COCH}_3; \quad \text{CP8: } R = \text{CO}_2\text{CH}_3; \quad \text{CP9: } R = \text{PO(C}_6\text{H}_5)_2
\]
**Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:**

![Chemical Structures and Reactions](image)

### Table 1: Reaction Conditions and Results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
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<th>Yield (%)</th>
<th>ee (%)</th>
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### Table 2: Reaction Conditions and Results (continued)

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**L1:** R = SO₂CH₃  
**L2:** R = SO₂CF₃  
**L3:** R = SO₂C₆H₄CH₂-p  
**L4:** R = COCl₂H₅  
**L5:** R = COCH₃  
**L6:** R = CO₂CH₃  
**L7:** R = PO(C₆H₅)₂

![Structures](image)
Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

![Chemical Reaction Diagram](image)

<table>
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<th>Entry</th>
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<td>51</td>
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Three sterically congested bifunctional chiral phosphane-amides, synthesized in order to evaluate the steric effect for asymmetric induction.

Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

The chiral sterically congested phosphane-amide bifunctional phosphanes


\[ \text{p-ClC}_6\text{H}_4\text{CH}=\text{NTs} + \overset{\text{L4 (20 mol-%)}}{\text{O}} \rightarrow \text{TsHN} + \overset{\text{p-ClC}_6\text{H}_4}{\overset{\text{2c, 84% yield, 78% ee}}{\text{O}}} \]

\[ \text{p-ClC}_6\text{H}_4\text{CH}=\text{NTs} + \overset{\text{L5 (20 mol-%)}}{\text{O}} \rightarrow \text{no reaction} \]
The nucleophilicity of the phosphorus center in the catalyst may affect catalytic activity.

The nucleophilicity of the phosphorus center in the catalyst may affect catalytic activity.

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

A few reports have demonstrated that introducing a longchainalkyl group in a variety of chiral ligands could improve the catalytic activity and enantioselectivity in homogeneous asymmetric.

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

catalyst CP19 was more effective in the aza-MBH reaction of \( N\)-tosyl imines with MVK than the previously reported original chiral phosphine CP1. Up to 88% yield, and 82% ee.
Another approach to improve the catalytic activity and enantioselectivity is to increase the number of hydrogen bond donors in the bifunctional chiral phosphines.
Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

\[
\begin{align*}
\text{p-ClC}_6\text{H}_4-\text{CH}=\text{NTs} + \text{CPLB (10 mol\%)} &\rightarrow \text{TsHN} \quad \text{TsOH} \\
&\quad \text{p-ClC}_6\text{H}_4 \\
12 \text{ h, yield: } 98\%, \text{ ee: } 92\% \\
\end{align*}
\]

\[
\begin{align*}
(R,R)\cdot\text{CPI R1} \\
(R,S)\cdot\text{CPI R2} \\
12 \text{ h, yield: } 90\%, \text{ ee: } 90\% \\
\end{align*}
\]

\[
\begin{align*}
(R,R)\cdot\text{CPLB3} \\
(R)\cdot\text{CPLB4} \\
(R)\cdot\text{CPLB5} \\
12 \text{ h, yield: } 64\%, \text{ ee: } 92\% \\
12 \text{ h, yield: } 96\%, \text{ ee: } 91\% \\
12 \text{ h, yield: } 86\%, \text{ ee: } 84\% \\
\end{align*}
\]
The 31P NMR measurements for CP20 and the mixture of CP20 and MVK

Multifunctional Chiral Phosphine Catalysts in Aza-Morita-Baylis-Hillman Reaction:

Catalyst **CP21 could effectively** catalyze asymmetric aza-MBH reaction of *N-tosyl imines with vinyl ketones*

\[
\text{Ar-CH=NTs} + \text{R-C=O} \xrightarrow{10 \text{ mol\% CP21}} \text{tBuOMe, -20 °C, 2-12 d, 85-100\% yields} \Rightarrow \text{R-C=OAr} \quad 82-94\% \text{ ee}
\]

\[
\text{Ar} = \text{C}_6\text{H}_5, 4-\text{MeOC}_6\text{H}_4, 4-\text{EtC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 2\text{-furyl}, 1\text{-naphthyl}, 2\text{-naphthyl}
\]

\[
\text{R} = \text{Me, Et, Ph}
\]

Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* 2006, 761–765
The aza-MBH reaction promoted by asymmetric bifunctional catalysts
biphenol-based bifunctional catalyst **CP22** for aza-MBH reaction of N-tosyl imines with MVK has high enantioselectivity up to 96% ee was achieved by **CP22** with catalyst loading of 1 mol %.

![Chemical structure of CP22](image)

\[
\text{Ar-CH=NR + } \xrightarrow{\text{CP22 (1 mol%)} \text{ THF, 0 °C, 10–164 h, 71–100% yields}} \xrightarrow{87–96\% \text{ ee}} \text{Ar-CH=CH-R}
\]

**Ar = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-MeOC_6H_4, 4-NO_2C_6H_4, 2-Naphthyl, (E)-Cinnamyl**

**R = Ts**

In order to recycle the catalyst, immobilized CP1 on a series of dendrimers. It was found that the dendrimerimmobilized catalyst CP23 was more effective than catalyst CP1 for the aza-MBH reaction of N-sulfonylimines with MVK, EVK, or acrolein.

Dendrimer immobilized phosphine-phenol type of multifunctional chiral phosphines

It was used for the first time to catalyze aza-Morita–Baylis–Hillman reactions between N-tosylimines and methyl vinyl ketone with fast reaction rates and good enantioselectivity at room temperature.
CP25 catalyzed MBH reaction between 4-pyridinecarboaldehyde and methyl acrylate

Phosphane-Hydroxy-Type Multifunctional Chiral Phosphine-Catalyzed Asymmetric MBH Reaction

Wenge Li, Zhaoguo Zhang, Dengming Xiao, and Xumu Zhang* J. Org. Chem. 2000, 65, 3489-3496
Multifunctional Chiral Phosphine Catalysts in Morita-Baylis-Hillman Reaction

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

\[
\text{R-CH}=\text{O} + \text{CH} = \text{CH}_2 \xrightarrow{\text{THF, 10 }^\circ\text{C, 3–7 d, 16–71% yields}} \text{R-H} \_\text{CH}=\text{CH}_2
\]

\[
\text{R} = \text{C}_6\text{H}_5, 4-\text{ClC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 2-\text{NO}_2\text{C}_6\text{H}_4, 3-\text{NO}_2\text{C}_6\text{H}_4, \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2
\]

4–39% ee

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.

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

Phosphane-Phenol-Type Multifunctional Chiral Phosphine-Catalyzed Asymmetric MBH Reaction of Aldehydes with R₁-Unsaturated Ketones

Recently, Wu's group reported a series of chiral phosphino(thio)ureas CP31-CP36 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.

\[
\begin{align*}
\text{CP31: } X &= S, R = C_6H_5 \\
\text{CP32: } X &= O, R = C_6H_5 \\
\text{CP33: } X &= S, R = 3,5-(CF_3)_2C_6H_3 \\
\text{CP34: } X &= S, R = 4-ClC_6H_4 \\
\text{CP35: } X &= S, R = 4-MeOC_6H_4 \\
\text{CP36: } X &= S, R = c-Hexyl
\end{align*}
\]

**CP31** is the best catalyst for the MBH reaction. *Products with excellent enantiomeric excesses*

Since 2007, bifunctional chiral phosphines can be applied in reactions beyond MBH/aza-MBH reaction, such as enantioselective [3 + 2] cycloaddition reactions.

More recently, Jacobsen developed a series of bifunctional phosphorus thiourea derivatives for highly enantioselective synthesis of chiral dihydropyrroles via imine-allene [3 + 2] cycloaddition.

\[
\begin{align*}
\text{Ar} & = C_6H_5, 4-FC_6H_4, 4-MeC_6H_4, 4-PhC_6H_4, \\
& 2-NO_2C_6H_4, 3,4,5-(MeO)_3C_6H_2, 2-BrC_6H_4,
\text{3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl}
\end{align*}
\]

CP38 as the best catalyst

Interestingly, 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.

\[
\begin{align*}
\text{R}^1 &= \text{aromatic group or C}_3\text{H}_7, \text{R}^2 = \text{Me, Et, OMe} \\
\text{45-98% yields} & \quad 71-96\% \text{ ee}
\end{align*}
\]

Multifunctional Chiral Phosphine Catalysts in Other Reactions

The proposed Mechanism

Multifunctional Chiral Phosphine Catalysts in Other Reactions

Chiral Phosphine-Catalyzed Regio- and Enantioselective Allylic Amination of Morita-Baylis-Hillman Acetates


\[ R^1 = H, m-NO_2, p-Cl, m-Cl, o-Cl, p-Br, p-F, p-CF_3, p-CN, p-Me, m-Me, p-NO_2, R^2 = Me, Et \]

70-91% yields
34-58% ee
the product in good yields with moderate ee

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.

The reactivities and enantioselectivities 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.
Thank you

Mahodand Lake; Pakistan