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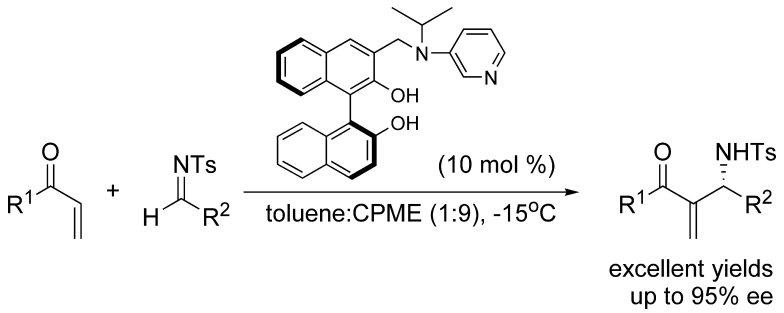

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Bifunctional Organocatalysts for Enantioselective aza-Morita−Baylis−Hillman Reaction

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Catalytic asymmetric reactions provide one of the most powerful approaches to a variety of enantiomerically pure and useful compounds. In particular, the design and development of catalysts possessing two or more reaction-promoting functionalities are of ongoing interest in asymmetric synthesis.[1] A synergistic activation by the functionalities on the catalyst can lead to specific control of the transition state structure, resulting in products with high enantioselectivity. Bifunctional organometallic catalysts, developed by the present authors, are representative examples of this type.[1a,b] The immobilized bifunctional catalysts have also been investigated by several research groups.[2] However, in general, the practical use of immobilized organometallic catalysts is difficult due to the leaching of the metal, which results in the deactivation of the catalyst and/or contamination of the product resulting from the catalytic reaction. Therefore, the development of asymmetric systems without using any metal salt has been of great importance for organic chemists. In this study, we report a new class of bifunctional metal-free catalysts for enantioselective aza-Morita-Baylis-Hillman (aza-MBH) reaction of α,β-unsaturated carbonyl compounds with *N*-tosylimines. The aza-MBH reaction is a C−C bond-forming reaction of activated alkenes with imines catalyzed by Lewis bases, such as amines, to form highly functionalized allylic amines, which are valuable building blocks for medicinal chemistry.[3,4] To date, excellent systems utilizing the quinidine-derived catalyst have been reported independently by Shi,[4a] Adolfsson,[4b] and Hatakeyama[4c] for this asymmetric process. Shi also reported a chiral phosphinyl BINOL to promote aza-MBH reaction.[4d] Obtaining efficient catalysts for an aza-MBH reaction has been a challenge in organic synthesis.[4] We designed a catalyst in which chiral Brønsted acid units are connected with a Lewis base unit via spacer (Figure 1).

If both Brønsted acid and Lewis base units could be appropriately positioned on one chiral molecule, the acid unit could activate a carbonyl group of α,β-unsaturated carbonyl compounds, and subsequently, the Lewis base unit would react with the β-position of the substrate to facilitate the Michael addition of the base (Scheme 1). The chiral Michael intermediate **I** generated by cooperative interaction between each component on the organocatalyst could furnish the product through the aldol and *retro*-Michael reaction.

In our own work directed toward the development of efficient bifunctional organocatalysts for the reaction, (*S*)-BINOLs bearing 4-(dimethylamino)pyridine were first designed (Figure 2, compound **1**). Although a mixed reagent, (*S*)-BINOL (10 mol %) and 4-(dimethylamino)pyridine (4-DMAP; 10 mol %) promoted the reaction of methyl vinyl ketone (**3a**) with phenyl *N*-tosylimine (**4a**) quite smoothly to give the product **5a**;[5] the organocatalysts **1**, which attached the pyridine ring directly to the 3-position of BINOL, resulted in no or low activities. The catalytic deficiency of **1** would be attributable to the inappropriate position of Lewis base on the catalyst. Next, the organocatalysts **2**, which attached 3-, 2-, or 4-aminopyridine derivatives through methylene spacer, were synthesized. Although organocatalyst **2b** which possesses 2-aminopyridine unit was ineffective, the catalyst **2a** bearing 3-aminopyridine unit afforded **5a** in 41% yield with 73% ee. In contrast, the reaction mediated by a mixed reagent, (*S*)-BINOL (10 mol %) and 3-(dimethylamino)pyridine (3-DMAP; 10 mol %), produced **5a** in 48% yield with low enantioselectivity (3% ee). The organocatalyst **2c** with 4-aminopyridine unit, for which the facilitation of the Michael addition of the attached base in an intramolecular manner would be impossible, did not promote the reaction. These results obviously

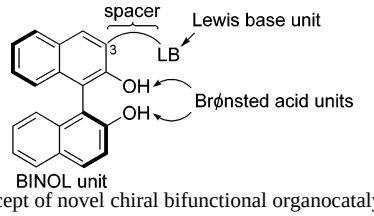
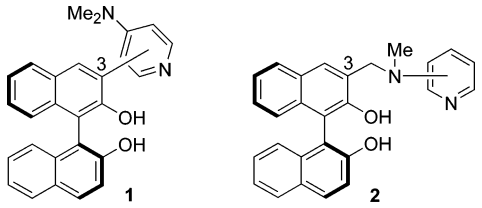


Figure 1. Concept of novel chiral bifunctional organocatalysts for an aza-MBH reaction.



1a: (*S*)-3-[4-(dimethylamino)pyridin-2-yl]BINOL
1b: (*S*)-3-[4-(dimethylamino)pyridin-3-yl]BINOL
2a: (*S*)-3-(*N*-methyl-*N*-3-pyridinylaminomethyl)BINOL
2b: (*S*)-3-(*N*-methyl-*N*-2-pyridinylaminomethyl)BINOL
2c: (*S*)-3-(*N*-methyl-*N*-4-pyridinylaminomethyl)BINOL

Figure 2. Chiral bifunctional organocatalysts for an aza-MBH reaction.

Scheme 1. Proposed Catalytic Cycle for the Bifunctional Organocatalyst-Mediated aza-MBH Reaction

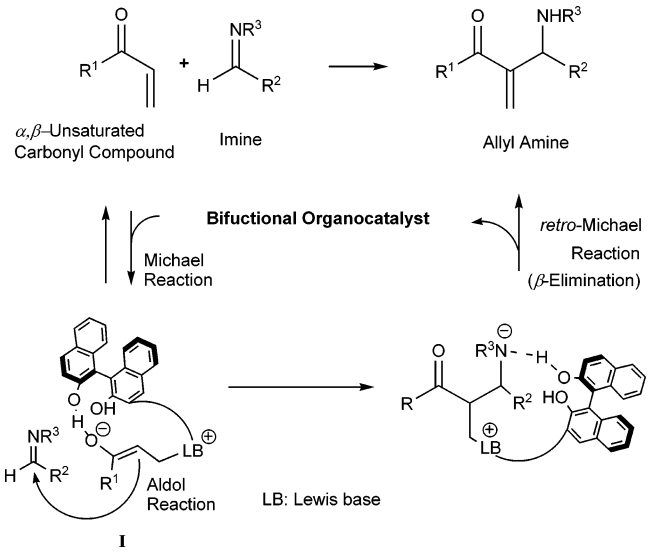


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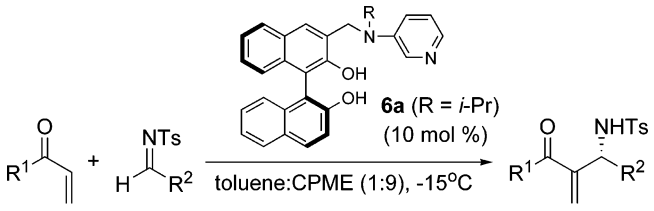
Table 1. Enantioselective aza-MBH Reaction of **3** with **4** Catalyzed by **6a**



3 **4** **5**

entry	**3**: R^1	**4**: R^2	time (h)	yield (%)[a]	ee (%)[b]
1	Me (**3a**)	Ph (**4a**)	168	**5a**, 93	87
2	Me (**3a**)	*p*-Cl−C_6H_4 (**4b**)	60	**5b**, 96	95
3	Me (**3a**)	*m*-Cl−C_6H_4 (**4c**)	72	**5c**, 93	93
4	Me (**3a**)	*p*-Br−C_6H_4 (**4d**)	36	**5d**, 93	94
5	Me (**3a**)	*p*-MeO−C_6H_4 (**4e**)	132	**5e**, 93	94
6	Me (**3a**)	2-furyl (**4f**)	48	**5f**, quant	88
7	Me (**3a**)	2-naphthyl (**4g**)	108	**5g**, 94	91
8	Me (**3a**)	*p*-NO_2−C_6H_4 (**4h**)	12	**5h**, 91	91
9	Et (**3b**)	*p*-NO_2−C_6H_4 (**4h**)	96	**5i**, 88	88
10	H (**3c**)	*p*-NO_2−C_6H_4 (**4h**)	36	**5j**, 95	94

[a] Isolated yield. [b] Determined by HPLC (DAICEL CHIRALPAK AD-H or OD-H).

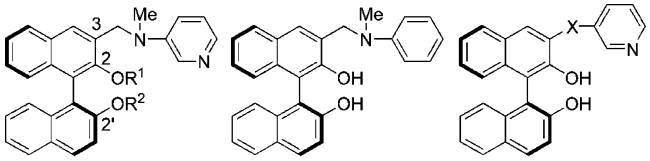
indicate that the exact position of active units on the catalyst dramatically improves the efficiency of bifunctional asymmetric organocatalysis.

Having been encouraged by these results, we studied the effects of solvent and temperature on the reaction. The best result (93% yield, 87% ee) was obtained at −15 °C with a mixed solvent system consisting of toluene and cyclopentyl methyl ether (CPME) in a 1:9 ratio.

The primary organocatalyst **6a** was established with the *i*-Pr substituent on the amino group.[6] Next, we investigated the substrate scope of this bifunctional asymmetric catalysis under optimal conditions (Table 1). Whether the aromatic substituent R^2 of **4** is electron-withdrawing or electron-donating, the organocatalyst **6a** efficiently promoted the reaction with high enantioselectivity (entries 1−5 and 8). 2-Furyl and 2-naphthyl tosylimines were also suitable substrates (entries 6 and 7). The reaction of methyl or ethyl vinyl ketone and acrolein produced corresponding adducts with 91, 88, and 94% ee, respectively (entries 8−10).

Both the catalysts **2a** and **6a** possess two phenolic hydroxy groups and two nitrogen atoms. To clarify the role of each unit on the reaction, the monoprotected catalyst **7a** with the 2′-OMe group, **7b** with the 2-OMe group and the aniline derivative **8**, the pyridine derivative **9a**,**b** with varying chain length of the spacer, and **9c** with the oxygen atom linker were examined. Although the catalyst **7a** was not effective in promoting the reaction (**5a**, 5% yield, 24% ee), **7b** showed a slightly decreased activity (**5a**, 85% yield, 79% ee) compared to the parent catalyst **2a**. Interestingly, **8** and **9** did not promote the reaction. These results and the significant enantioselectivity of **6a** are consistent with the notion that our designed organic molecules can act as bifunctional catalysts utilizing both the phenolic 2′-hydroxy group and the pyridine moiety to activate the substrate. Since one pair of acid−base unit fixes the conformation of the organocatalyst **6a**, the other pair of acid−base unit appears to be able to activate substrate **3** with high enantiocontrol, though the nucleophilicity of the pyridinyl nitrogen of **2a** (or **6a**) is low compared to that of **2b** or **2c**.[7] The molecular orbital calculation of **6a** also supported the conformation.[8]

In summary, an efficient and novel bifunctional organocatalyst for the enantioselective aza-MBH reaction has been established with (*S*)-3-(*N*-isopropyl-*N*-3-pyridinylaminomethyl)BINOL for the first time. The reaction proved to be deeply influenced by the position



of the Lewis base attached to BINOL. The acid−base-mediated functionalities for the activation of the substrate and the fixing of conformation of the organocatalyst are harmoniously performed to promote the reaction with high enantiocontrol.

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Supporting Information Available: A complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The product **5a** was obtained in 60% yield with 2% ee (CH_2Cl_2, room temperature, 8 h).

(6) Results of the reaction of **3a** with **4c** promoted by organocatalysts **6** with various substituents on the nitrogen atom. **6b**: R = H (62% yield, 87% ee, 240 h), **6c**: R = Et (90% yield, 91% ee, 132 h), **6d**: R = *t*-Bu (72% yield, 83% ee, 240 h), **6e**: R = Bn (quant, 93% ee, 144 h).

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(8) See Supporting Information.

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