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Chiral bifunctional organocatalysts bearing a 1,3-propanediamine unit for aza-MBH reaction

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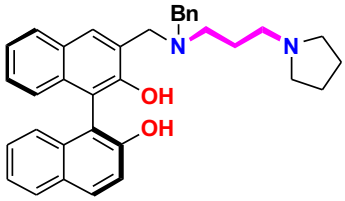

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Chiral bifunctional organocatalysts bearing a 1,3-propanediamine unit for aza-MBH reaction

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Abstract—The 1,3-propanediamine introduced onto the 3-position of (*S*)-BINOL through a methylene spacer could work as a chiral bifunctional organocatalyst for the aza-MBH reaction. The organocatalyst **1l** effected the aza-MBH transformation with high chemical yields and up to 82% ee.

The design and development of chiral organocatalysts possessing two or more reaction-promoting functionalities have attracted much attention in the recent asymmetric catalysis.[1] In the bi- or multifunctional organocatalysis, the acid-base moieties can activate the substrates and control the stereochemistry of reaction course to afford significant chiral induction.[2] A balance and location of acid and base units on the catalyst is important for the efficient activation of the substrates. In this communication, we report 1,3-propanediamine derivatives attached to the 3-position on (*S*)-BINOL through a methylene spacer can work as chiral bifunctional organocatalysts. The organocatalyst **1l**, as shown in Figure 1, effected the aza-Morita-Baylis-Hillman (aza-MBH) transformation with high chemical yields and up to 82% ee.

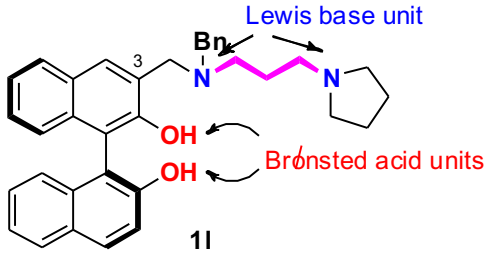

Figure 1. Chiral bifunctional organocatalyst **1l** bearing a 1,3-propanediamine unit for the aza-MBH reaction

aza-MBH reaction is recognized as one of the most useful and atom-economical carbon-carbon bond forming reactions between the α-position of enone and the carbonyl group of an imine catalyzed by nucleophilic amines or phosphines.[3] The products of the aza-MBH reaction are highly functionalized allylic amines, which prove to be valuable building blocks for biologically important compounds and natural products.[4] Obtaining efficient catalysts for the aza-MBH reaction has been a challenge in organic synthesis.[5]

We envisioned locating both acid and base units on one chiral binaphthyl skeleton thereby facilitating a synergistic cooperation on the aza-MBH reaction.[5b,k,6] To that end, tertiary diamine[7] as a strong Lewis base unit would be introduced onto the 3-position of BINOL as a chiral Brønsted acid using a spacer. As a step towards development of our bifunctional organocatalyst, 1,2-ethanediamine (**1a,b**), 1,3-propanediamine (**1c,d**), 1,4-butanediamine (**1e**), 1,5-pentanediamine (**1f**), 1,6-hexanediamine (**1g**) derivatives were introduced onto the 3-position of (*S*)-BINOL through a methylene or an ethylene spacer. The reaction of methyl vinyl ketone (**2a**) and 4-bromophenyl *N*-tosyl aldimine (**3a**) as prototypical substrates was attempted using the above organocatalysts **1** (Table 1). To our surprised, 48% yield and 61% ee of aza-MBH adduct **4a** was isolated when using 1,3-propanediamine derivative **1c** introduced onto the 3-position of (*S*)-BINOL through a methylene (entry 3). The analogous catalyst **1b** and **1d** bearing an ethylene spacer were prepared and applied to the reaction. The catalysts **1b** and **1d** also promote the reaction, but at a lower rates with lower enantioselectivities (entries 2 and 4) compared with that when the catalyst **1c** with a methylene spacer was utilized for the reaction. When **1a** and **1e-g** with various lengths (C_2 or C_4-C_6) of alkyldiamines through a methylene spacer were used as organocatalysts, low or no catalyst activity was observed (entries 1 and 5-7). These outcomes indicate that the exact positioning of the acid and base units on the catalyst dramatically improves the efficiency of bifunctional enantioselective catalysis.

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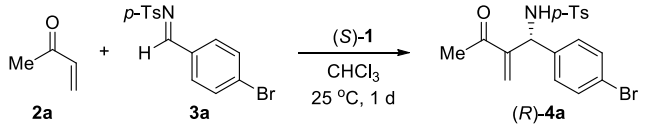
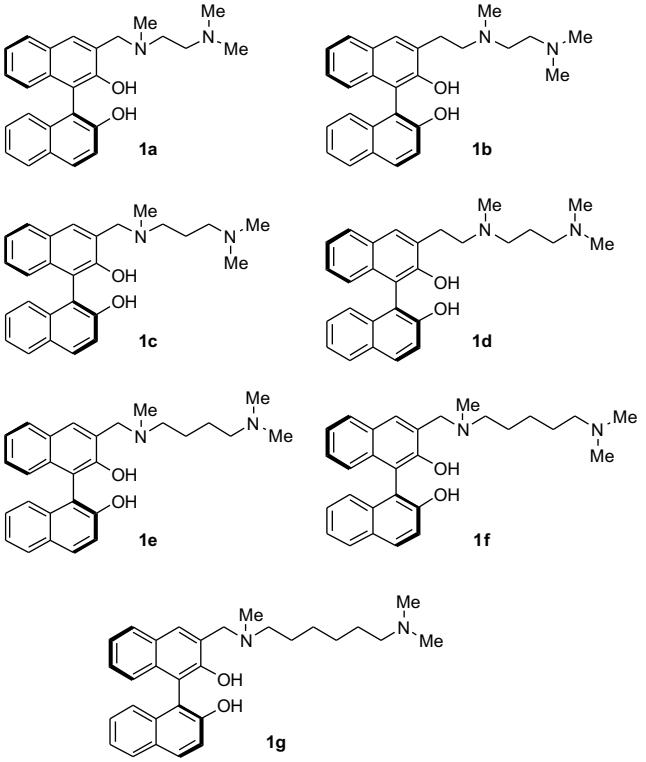
Table 1. Enantioselective aza-MBH reaction of **3a** with **4a** using organocatalysts **1**[a]



2a **3a** (*R*)-**4a**

Entry	Catalyst (10 mol%)	Yield (%)[b]	Ee (%)[c]
1	**1a**	16	4
2	**1b**	6	11
3	**1c**	48	61
4	**1d**	16	47
5	**1e**	8	7
6	**1f**	7	1
7	**1g**	Trace	-

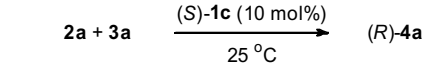
[a]0.5M (Substrate concentration of **3a**) and 3 equivalent of **2a**.
[b]Isolated yield.
[c]Determined by HPLC (Daicel Chiralpak AD-H).



Encouraged by these results, we went on to study the effects of solvent and concentration on the reaction of **2a** with **3a** (Table 2). In terms of enantioselectivites, $CHCl_3$ (entry 6) along with toluene (entry 3), THF (entry 4) and CH_2Cl_2 (entry 5) gave good results compared with protic solvents (entries 1 and 2). The concentration of **3a** was also important to promote the reaction in high yield with good enantioselectivity (entry 9). The most efficient process was cleared that organocatalyst **1l**[8] (R = Bn) with a pyrrolidine unit on the terminal was used under 0.5M concentration of **3a** (Table 3, entry 6).

As shown in Table 4,[9] when *N*-*p*-tosyl aldimines **3** prepared from the corresponding *p*- and *m*-substituted aryaldehydes were applied as substrates (entries 1, 3 and 7-12), organocatalyst **1l** efficiently promoted the reaction to

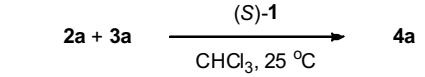
Table 2. Effect of reaction conditions using the organocatalyst **1c**[a]



Entry	Solvent	Conc. of **3a** (M)	Time (d)	Yield (%)[b]	Ee (%)[c]
1	MeOH	0.5	1	6	2
2	H_2O	0.5	1	16	6
3	toluene	0.5	1	18	42
4	THF	0.5	1	18	49
5	CH_2Cl_2	0.5	1	23	54
6	$CHCl_3$	0.5	1	48	61
7	$CHCl_3$	0.1	3	trace	-
8	$CHCl_3$	0.25	3	33	56
9	$CHCl_3$	0.5	3	85	64
10	$CHCl_3$	1.0	3	74	42

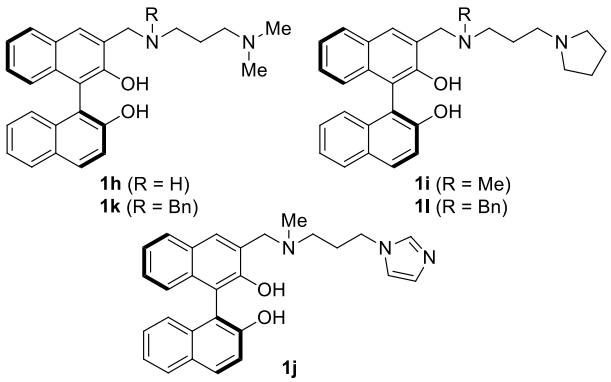
[a]3 Equivalent of **2a**.
[b]Isolated yield.
[c]Determined by HPLC (Daicel Chiralpak AD-H).

Table 3. Effect of *N*-substituents on bifunctional organocatalysts **1**[a]



Entry	Catalyst (10 mol%)	Time (d)	Yield (%)[a]	Ee (%)[b]
1	**1h**	4	73	58, *R*
2	**1c**	3	85	64, *R*
3	**1i**	4	65	70, *R*
4	**1j**	2	65	12, *S*
5	**1k**	3	86	63, *R*
6	**1l**	3	86	70, *R*

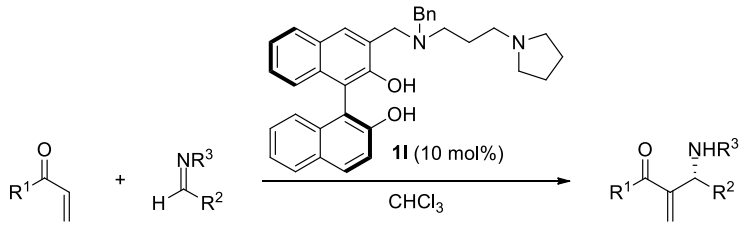
[a]0.5M (substrate concentration of **3a**) and 3 equivalent of **2a**.
[b]Isolated yield.
[c]Determined by HPLC (Daicel Chiralpak AD-H).



give the adduct **4** with high yields with good enantioselectivities. The reaction of **2a** and **3l** with organocatalyst **1l** afforded the best ee value (82% ee) of product (entry 12). The ketimine **3m** derived from a cyclic α-keto amide was a suitable substrate (Scheme 1, eq. 1),[5w] however, 2-naphthyl acrylate **2b** (Table 4, entry 13) and the aliphatic aldimine generated from **3n** in situ (Scheme 1, eq. 2) are not appropriate for this system.[5c,e,y]

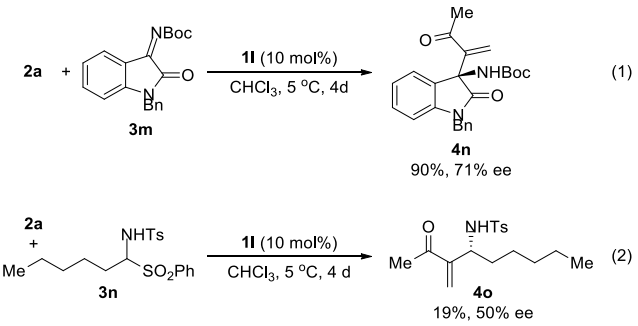
A diamine unit was found to be essential to promote the reaction because the monoamine derivatives **5** and **6** failed to undergo the reaction (Scheme 2). Based on these results and our early proposed transition state for the aza- MBH reaction catalyzed by (*S*)-3-(*N*-isopropyl-*N*-3-pyridinylami-

Table 4. Substrate scope[a]

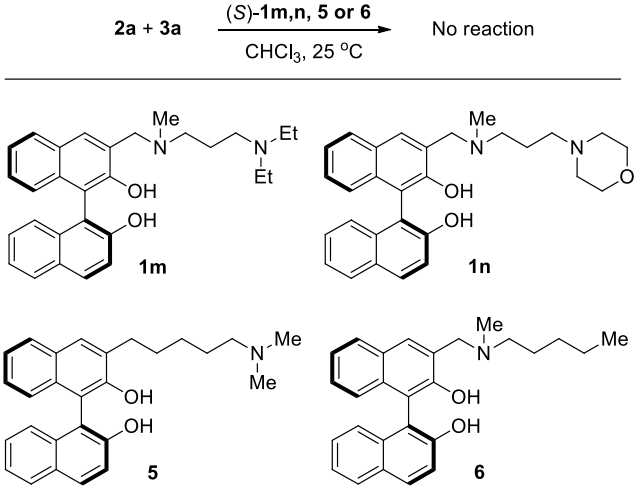


Entry	2	3	Temp. (°C)	Time (d)	Yield (%)[b]	Ee (%)[c]
1	**2a**, R^1 = Me	**3a**, R^2 = *p*-Br-C_6H_4, R^3 = *p*-Ts	25	3	**4a**, 86	70
2	**2a**	**3b**, R^2 = *o*-Br-C_6H_4, R^3 = *p*-Ts	25	3	**4b**, 83	39
3	**2a**	**3c**, R^2 = *p*-Cl-C_6H_4, R^3 = *p*-Ts	25	3	**4c**, 51 (85)[d]	74 (74)[d]
4	**2a**	**3d**, R^2 = *p*-Cl-C_6H_4, R^3 = *m*-Ts	25	3	**4d**, 44	55
5	**2a**	**3e**, R^2 = *p*-Cl-C_6H_4, R^3 = *o*-Ts	25	3	**4e**, 51	20
6	**2a**	**3f**, R^2 = *p*-Cl-C_6H_4, R^3 = SO_2Ph	25	3	**4f**, 44	69
7	**2a**	**3g**, R^2 = *p*-CN-C_6H_4, R^3 = *p*-Ts	0	1.5	**4g**, 88	67
8	**2a**	**3h**, R^2 = *p*-NO_2-C_6H_4, R^3 = *p*-Ts	0	1.5	**4h**, 92	64
9	**2a**	**3i**, R^2 = *m*-NO_2-C_6H_4, R^3 = *p*-Ts	-25	2	**4i**, 97	60
10	**2a**	**3j**, R^2 = *p*-F-C_6H_4, R^3 = *p*-Ts	5	2	**4j**, 83	71
11[a]	**2a**	**3k**, R^2 = *p*-Et-C_6H_4, R^3 = *p*-Ts	25	5	**4k**, 88	72
12	**2a**	**3l**, R^2 = *p*-MeO-C_6H_4, R^3 = *p*-Ts	25	8	**4l**, 78	82
13	**2b**, R^1 = O-2-naphthyl	**3h**	5	7	**4m**, 77	0

[a]0.5M (Substrate concentration of **3**) and 3 equivalent of **2a**.
[b]Isolated yield.
[c]Determined by HPLC (Daicel Chiralpak AD-H for **4a-k**; Daicel Chiralcel OD-H for **4l**; Daicel Chiralpak IB for **4m**; Daicel Chiralcel OD3 for **4n**; Daicel Chiralpak IA for **4o**)
[d]For 5 days



Scheme 1. aza-MBH reaction of **2a** with ketimine **3m**, or aliphatic aldimine generated from **3n** in situ.



Scheme 2. Catalyst screening of compounds **1m,n**, **5** and **6**

nomethyl)BINOL,[5b,6a,b] one acid-base pair (the 2-hydroxy group and the nitrogen atom on the benzyl position) could fix the conformation of organocatalyst through a hydrogen bonding, the other acid-base unit would activate substrate **2a** (Figure 2). When BINOL derivatives **1m,n** were applied for the reaction, no activity was observed, probably because of steric hindrance of terminal Lewis base unit (Scheme 2). The ^{1}H NMR (400MHz, $CDCl_3$) studies exhibited that the reaction mixture of catalyst **1c** and enone **2a** revealed the Me group of **2a** at δ 2.26 (3H, s) shifted to δ 2.07 (3H, s) and the phenolic hydroxy groups at δ 3.85 (2H, *J* = 3.2 Hz, d) in catalyst **1c** shifted to another place, attributable to the corresponding ammonium enolates.

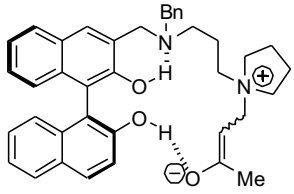


Figure 2. Our proposed intermediate

In conclusion, the chiral bifunctional catalyst **1l** was found to accelerate the aza-MBH reaction to afford the adduct in high yields with good enantioselectivities. The realization that BINOL as Brønsted acid units is compatible with a range of 1,3-propanediamine derivatives as Lewis base units has allowed the development of bifunctional catalysts for the aza-MBH reaction. Further studies aimed at elucidating the mechanism detail of the activation are currently in progress.

Acknowledgements

This study was supported by the CREST project of the Japan Science and Technology Corporation (JST), Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from The Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan and JST, Advanced Catalytic Transformation Program for Carbon Utilization (ACT-C). Y. Y. thanks JSPS Research Fellowships for Young Scientists. We acknowledge the technical staff of the Comprehensive Analysis Center of ISIR, Osaka University (Japan).

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8. Analytical data for (*S*)-**1l**: $[\alpha]_D^{20} = -30.6$ (*c* 0.59, $CHCl_3$); IR (neat) ν (cm^{-1}) 3056, 2928, 2821, 2346, 1736, 1620, 1596, 1509, 1431, 1342, 1244, 1211, 1148, 1107; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.70 (s, 1H), 7.37 (d, *J* = 8.9 Hz, 1H), 7.37-7.12 (m, 11H), 4.10 (d, *J* = 13.0 Hz, 1H), 4.02 (d, *J* = 13.7 Hz, 1H), 3.79 (d, *J* = 13.7 Hz, 1H), 3.65 (d, *J* = 13.0 Hz, 1H), 2.66-2.55 (m, 2H), 2.40-2.27 (m, 6H), 1.80-1.74 (m, 2H), 1.71-1.67 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.8, 151.6, 136.2, 133.8, 133.7, 129.7, 129.6, 129.2, 129.1, 128.6, 128.4, 128.2, 127.7 x 2, 126.8, 126.3, 125.1, 125.0, 124.5, 123.6, 123.1, 117.8, 115.3, 113.1, 58.5, 58.4, 54.1, 54.0, 51.4, 25.5, 23.3; HRMS (ESI) calcd for $C_{35}H_{37}N_2O_2$, m/z = 517.2855 [$(M+H)^+$]; found, m/z = 517.2849.
9. **General Procedure for Enantioselective aza-MBH Reaction Catalyzed by (*S*)-1l (Table 4)**: To a solution of organocatalyst **1l** (2.5 mg, 0.005 mmol) in a solvent $CHCl_3$ (0.3 mL) was added **2** (0.15 mmol) and imine **3** (0.05 mmol). The mixture was stirred until the reaction had reached completion with monitoring with TLC analysis. The mixture was directly purified by flash column chromatography (SiO_2, hexane:EtOAc = 3/1) to give the corresponding adduct **4** as a white solid. All adducts were characterized by ^{1}H, ^{13}C NMR, MS, and IR spectroscopy, and were identical in all respects with those reported data.[5,6] Absolute configurations of **4** were determined by comparing the optical rotation assignments with those in the literature.[5,6]