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

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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 **11** 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 **11**, 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 **11** 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 diamine⁷ 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

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	-

^a0.5M (Substrate concentration of **3a**) and 3 equivalent of **2a**.

^bIsolated yield.

^cDetermined 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 enantioselectivities, CHCl₃ (entry 6) along with toluene (entry 3), THF (entry 4) and CH₂Cl₂ (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 arylaldehydes 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 ₂ O	0.5	1	16	6
3	toluene	0.5	1	18	42
4	THF	0.5	1	18	49
5	CH ₂ Cl 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

^a3 Equivalent of **2a**.

^bIsolated yield.

^cDetermined 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, <i>R</i>
2	1c	3	85	64, <i>R</i>
3	1i	4	65	70, <i>R</i>
4	1j	2	65	12, <i>S</i>
5	1k	3	86	63, <i>R</i>
6	1l	3	86	70, <i>R</i>

^a0.5M (substrate concentration of **3a**) and 3 equivalent of **2a**.

^bIsolated yield.

^cDetermined 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 = <i>p</i> -Br-C ₆ H ₄ , R ³ = <i>p</i> -Ts	25	3	4a , 86	70
2	2a	3b , R ² = <i>o</i> -Br-C ₆ H ₄ , R ³ = <i>p</i> -Ts	25	3	4b , 83	39
3	2a	3c , R ² = <i>p</i> -Cl-C ₆ H ₄ , R ³ = <i>p</i> -Ts	25	3	4c , 51 (85) ^d	74 (74) ^d
4	2a	3d , R ² = <i>p</i> -Cl-C ₆ H ₄ , R ³ = <i>m</i> -Ts	25	3	4d , 44	55
5	2a	3e , R ² = <i>p</i> -Cl-C ₆ H ₄ , R ³ = <i>o</i> -Ts	25	3	4e , 51	20
6	2a	3f , R ² = <i>p</i> -Cl-C ₆ H ₄ , R ³ = SO ₂ Ph	25	3	4f , 44	69
7	2a	3g , R ² = <i>p</i> -CN-C ₆ H ₄ , R ³ = <i>p</i> -Ts	0	1.5	4g , 88	67
8	2a	3h , R ² = <i>p</i> -NO ₂ -C ₆ H ₄ , R ³ = <i>p</i> -Ts	0	1.5	4h , 92	64
9	2a	3i , R ² = <i>m</i> -NO ₂ -C ₆ H ₄ , R ³ = <i>p</i> -Ts	-25	2	4i , 97	60
10	2a	3j , R ² = <i>p</i> -F-C ₆ H ₄ , R ³ = <i>p</i> -Ts	5	2	4j , 83	71
11 ^a	2a	3k , R ² = <i>p</i> -Et-C ₆ H ₄ , R ³ = <i>p</i> -Ts	25	5	4k , 88	72
12	2a	3l , R ² = <i>p</i> -MeO-C ₆ H ₄ , R ³ = <i>p</i> -Ts	25	8	4l , 78	82
13	2b , R ¹ = O-2-naphthyl	3h	5	7	4m , 77	0

^a0.5M (Substrate concentration of **3**) and 3 equivalent of **2a**.^bIsolated yield.^cDetermined 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**)^dFor 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 ¹H NMR (400MHz, CDCl₃) 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 **11** 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.

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- Analytical data for (S)-**11**: [α]_D²⁰ = -30.6 (c 0.59, CHCl₃); IR (neat) ν (cm⁻¹) 3056, 2928, 2821, 2346, 1736, 1620, 1596, 1509, 1431, 1342, 1244, 1211, 1148, 1107; ¹H-NMR (400 MHz, CDCl₃): 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, 1H), 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); ¹³C-NMR (100 MHz, CDCl₃): 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 C₃₅H₃₇N₂O₂, *m/z* = 517.2855 [(M+H)⁺]; found, *m/z* = 517.2849.
- General Procedure for Enantioselective aza-MBH Reaction Catalyzed by (S)-11 (Table 4):** To a solution of organocatalyst **11** (2.5 mg, 0.005 mmol) in a solvent CHCl₃ (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 (SiO₂, hexane:EtOAc = 3/1) to give the corresponding adduct **4** as a white solid. All adducts were characterized by ¹H, ¹³C 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}