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Chiral bifunctional organocatalysts bearing a 1,3propanediamine 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 1,3propanediamine 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, 1,2ethanediamine (1a,b), 1,3-propanediamine (1c,d), 1,4-1,5-pentanediamine butanediamine (1e). (**1f**), 1,6hexanediamine (1g) derivatives were introduced onto the 3position of (S)-BINOL through a methylene or an ethylene spacer. The reaction of methyl vinyl ketone (2a) and 4bromophenyl 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 1,3propanediamine derivative 1c introduced onto the 3position 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

Me 2a	p-TsN + H Br 3a	(S)- 1 ► M CHCl ₃ ≥ 5 °C, 1 d	NHp-Ts Te (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	1σ	Trace	_

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



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, 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 11^8 (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 **11** efficiently promoted the reaction to

Table 2. Effect of reaction conditions using the organocatalyst 1c^a

	2a	+ 3a $\frac{(S)-1c(1)}{25}$	0 mol%) ┣━━━━ ℃	(R)- 4a	
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
10 T	1				

^a3 Equivalent of **2a**. ^bIsolated yield.

^cDetermined by HPLC (Daicel Chiralpak AD-H).

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

	2a + 3a 🛛 —	(U)-1	> 4a		
CHCl ₃ , 25 °C					
Entry	Catalyst (10 mol%)	Time (d)	Yield $(\%)^a$	Ee (%) ^b	
1	1h	4	73	58, R	
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, R	
6	11	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 , $R^2 = p$ -Br-C ₆ H ₄ , $R^3 = p$ -Ts	25	3	4a , 86	70
2	2a	3b , $R^2 = o$ -Br-C ₆ H 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 ₆ H ₄ , $R^3 = m$ -Ts	25	3	4d , 44	55
5	2a	3e , $R^2 = p$ -Cl-C ₆ H ₄ , $R^3 = o$ -Ts	25	3	4e , 51	20
6	2a	3f , $R^2 = p$ -Cl-C ₆ H ₄ , $R^3 = SO_2Ph$	25	3	4f , 44	69
7	2a	3g , $R^2 = p$ -CN-C ₆ H 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 , $R^2 = m - NO_2 - C_6 H_4$, $R^3 = p - Ts$	-25	2	4i , 97	60
10	2a	3j , $R^2 = p - F - C_6 H_4$, $R^3 = p - T_8$	5	2	4j , 83	71
11 ^a	2a	3k , $R^2 = p$ -Et-C ₆ H ₄ , $R^3 = p$ -Ts	25	5	4k , 88	72
12	2a	31 , $R^2 = p$ -MeO-C ₆ H ₄ , $R^3 = p$ -Ts	25	8	41 , 78	82
13	$2\mathbf{b}, \mathbf{R}^1 = \mathbf{O} \cdot 2 \cdot \mathbf{naphthyl}$	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**)



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.

Acknowledgements

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- Analytical data for (*S*)-11: $[\alpha]_D^{20} = -30.6$ (*c* 0.59, CHCl₃); IR 8. (neat) v (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 = 7.6Hz, 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); 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 $C_{35}H_{37}N_2O_2$ m/z = 517.2855 [(M+H)⁺]; found, m/z = 517 2849
- 9 General Procedure for Enantioselective aza-MBH Reaction Catalyzed by (S)-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. Absolute configurations of 4 were determined by comparing the optical rotation assignments with those in the literature.5,6