Tetrahedron: *Asymmetry* 24 (2013) 1189–1192

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

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

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ARTICLE INFO

Article history:
Received 6 July 2013
Accepted 6 August 2013

ABSTRACT

The introduction of a 1,3-propanediamine unit at the 3-position of (*S*)-BINOL using a methylene spacer led to the formation of a chiral bifunctional organocatalyst for the aza-Morita–Baylis–Hillman (aza-MBH) reaction. The organocatalyst **1k** mediated aza-MBH transformations with high chemical yields and with up to 82% ee.

1. Introduction

The design and development of chiral organocatalysts possessing two or more reaction-promoting functionalities have attracted much attention in the field of asymmetric catalysis.[1] In bi- and multifunctional organocatalysis, acid–base moieties can activate substrates and control the stereochemistry of reactions to afford significant chiral induction.[2] The balance and appropriate location of acid and base units in a catalyst are important for the efficient activation of substrates. Herein we report that (*S*)-BINOL substituted at the 3-position with appropriate 1,3-propanediamine derivatives using a methylene spacer works as an effective chiral bifunctional organocatalyst. The organocatalyst **1k** (Fig. 1) mediates aza-Morita–Baylis–Hillman (aza-MBH) transformations in high chemical yields and with up to 82% ee.

2. Results and discussion

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

We envisioned locating both an acidic and a basic unit on one chiral binaphthyl skeleton, thereby facilitating synergistic cooperation in the aza-MBH reaction.[5b,k,6] To that end, it was proposed to introduce a tertiary diamine[7] (a strong Lewis base unit) at the 3-position of BINOL (a chiral Brønsted acid) using a spacer. A tertiary diamine moiety could be used to easily adjust Lewis basicity via the introduction of substituents onto the nitrogen atom and the distance between the acid–base units with an alkyl chain of appropriate length. As a step toward the development of such a bifunctional organocatalyst, 1,2-ethanediamine **1a**,**b**, 1,3-propanediamine **1c**,**d**, 1,4-butanediamine **1e**, 1,5-pentanediamine **1f**, and 1,6-hexanediamine **1g** were introduced at the 3-position of (*S*)-BINOL using a methylene or ethylene spacer. Next, 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). The aza-MBH adduct **4a** was isolated in 48% yield with 61% ee when using 1,3-propanediamine derivative **1c** with a methylene linker (entry 3). The analogous catalysts **1b** and **1d** bearing an ethylene spacer were then prepared and applied to the reaction. These catalysts also promoted the reaction but at lower rates with lower enantioselectivities (entries 2 and 4) compared with those obtained using catalyst **1c** with the

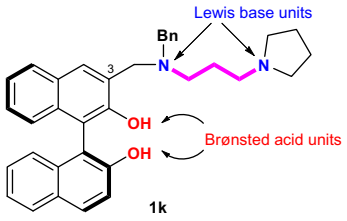

Figure 1. Chiral bifunctional organocatalyst **1k** bearing a 1,3-propanediamine unit for the aza-MBH reaction.

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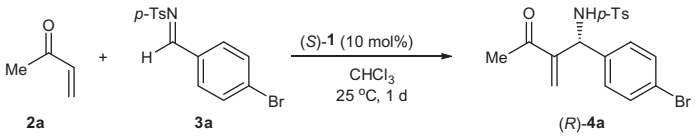
http://dx.doi.org/10.1016/j.tetasy.2013.08.005

Table 1
Enantioselective aza-MBH reaction of **2a** with **3a** using organocatalysts **1**[a]

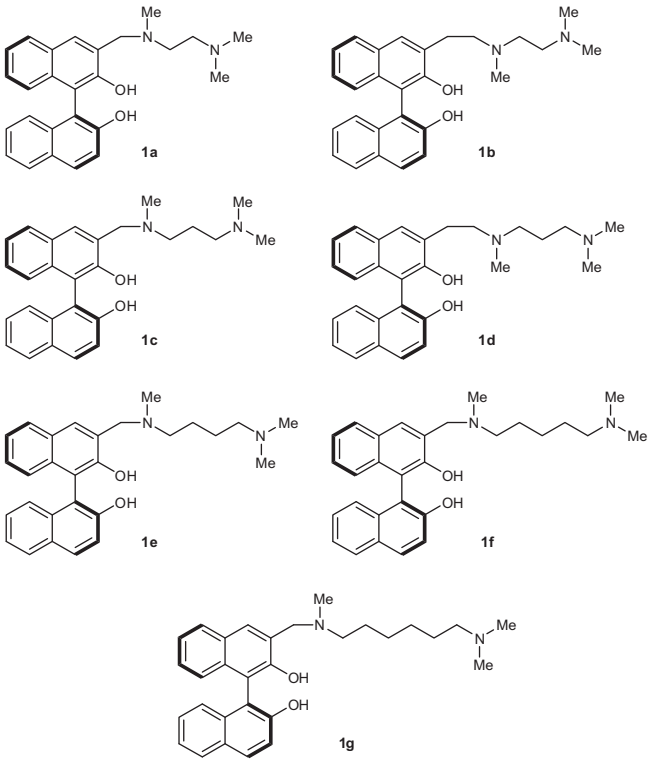


2a **3a** (*R*)-**4a**

Entry	Catalyst	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	—

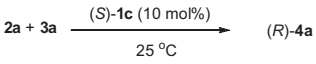
[a] 0.5 M (substrate concentration of **3a**) and 3 equiv of **2a**.
[b] Isolated yield of product **4a**.
[c] Determined by HPLC (Daicel Chiralpak AD-H).

methylene spacer. Alkyldiamines with various chain lengths (C_2 and C_4–C_6 for **1a** and **1e**–**g**, respectively) were then incorporated using a methylene spacer, and the resulting compounds were used as organocatalysts. In these cases, low or no catalytic activity was observed (entries 1 and 5–7). These results indicate that the exact positioning of the acid and base units on the catalyst dramatically affects the efficiency of bifunctional enantioselective catalysis.



Encouraged by these results, the effects of solvent and concentration on the reaction of **2a** with **3a** (Table 2) were then investigated. In terms of enantioselectivity, $CHCl_3$ (entry 6), toluene (entry 3), THF (entry 4), and CH_2Cl_2 (entry 5) gave good results compared with those obtained with protic solvents (entries 1 and 2). The appropriate concentration of **3a** was also important for promoting the reaction in high yields with good enantioselectivity (entry 9).

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



Entry	Solvent	Concd 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 Equiv of **2a**.
[b] Isolated yield of product **4a**.
[c] Determined by HPLC (Daicel Chiralpak AD-H).

Table 3
Effect of the *N*-substituents in the bifunctional organocatalysts **1**[a]

Entry	Catalyst (10 mol %)	Time (d)	Yield[b] (%)	ee[c] (%)
1	**1c**	3	85	64 (*R*)
2	**1h**	4	73	58 (*R*)
3	**1i**	3	86	63 (*R*)
4	**1j**	4	65	70 (*R*)
5	**1k**	3	86	70 (*R*)
6	**1l**	2	65	12 (*S*)
7	**1m**	2	NR[d]	—
8	**1n**	2	NR[d]	—

[a] 0.5 M (substrate concentration of **3a**) and 3 equiv of **2a**.
[b] Isolated yield of product **4a**.
[c] Determined by HPLC (Daicel Chiralpak AD-H).
[d] No reaction.

The most efficient process was observed with organocatalyst **1k**[8] (R = Bn) bearing a terminal pyrrolidine unit and a concentration of **3a** <0.5 M (Table 3, entry 5). When BINOL derivatives **1m** and **1n** were applied in the reaction, no activity was observed probably owing to the steric hindrance of the terminal Lewis base unit or electronic influence of the oxygen atom on the morpholine to the terminal nitrogen-Lewis base region.

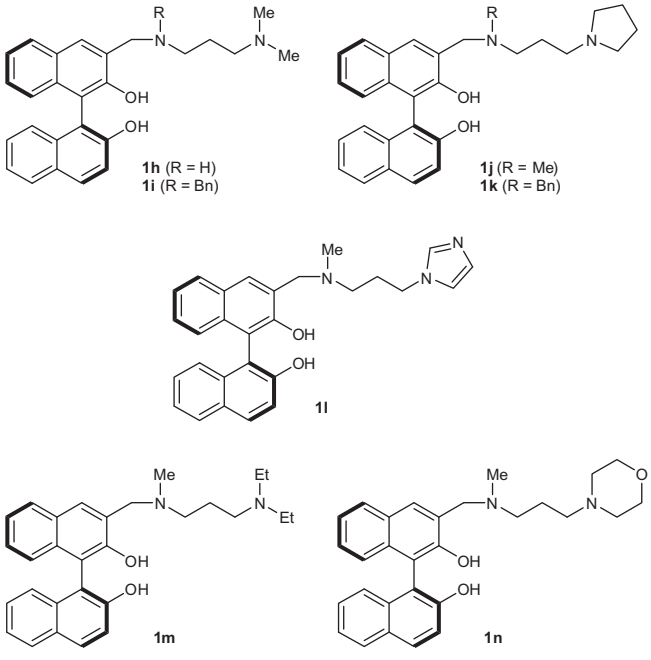
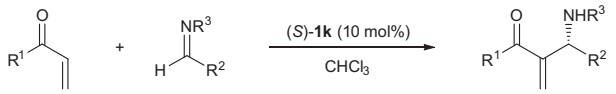
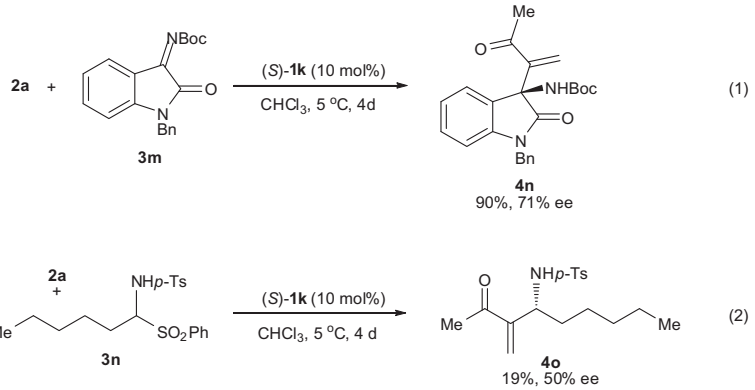


Table 4
Substrate scope[a]



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[f]
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[e]	**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 = 2-naphthoxy	**3h**	5	7	**4m**, 77	0

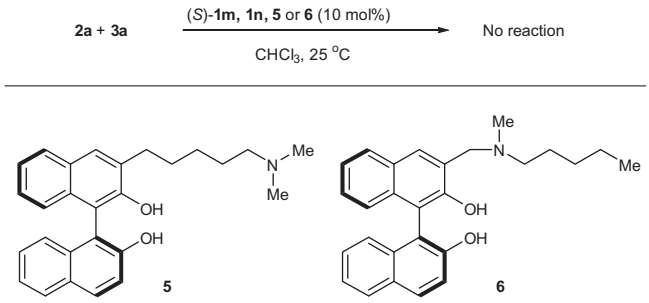
[a] 0.5 M (substrate concentration of **3**) and 3 equiv of **2**.
[b] Isolated yield.
[c] Determined by HPLC (Daicel Chiralpak AD-H for **4a–k**; Daicel Chiralcel OD-H for **4l**; Daicel Chiralpak IB for **4m**; Daicel Chiralcel OD-3 for **4n**; Daicel Chiralpak IA for **4o**).
[d] For 5 days.
[e] 20 mol % of **1k** was used.
[f] (*S*)-Configuration product was obtained.



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

With the optimized conditions in hand, the reaction scope was explored.[9] As can be seen in Table 4, 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 **1k** efficiently promoted the reaction with **2a** to give adducts **4** in high yields and with good enantioselectivities. The reaction of **2a** and **3l** with organocatalyst **1k** proceeded with the highest ee (82%) (entry 12). It should be noted that while the ketimine **3m** derived from a cyclic α-keto amide was found to be a suitable substrate (Scheme 1, Eq. 1),[5w] 2-naphthyl acrylate **2b** (Table 4, entry 13) and the aliphatic aldimine generated in situ from **3n** (Scheme 1, Eq. 2) were not appropriate for this system.[5c,e,y]

Furthermore, it was confirmed that a diamine unit is essential for promoting the transformation; the monoamine derivatives **5** and **6** failed to undergo the reaction (Scheme 2). Given these results and considering our previously proposed transition state for the aza-MBH reaction catalyzed by (*S*)-3-(*N*-isopropyl-*N*-3-pyridinylaminomethyl)-1,1′-bi(2-naphthol),[5b,6a,b] it was thought that one acid–base pair (the 2-hydroxy group and the nitrogen atom on the benzylic position) fixed the conformation of the organocatalyst via hydrogen bonding, while the other acid–base unit activates substrate **2a** (Fig. 2). Notably, the ^{1}H NMR (400 MHz, $CDCl_3$) studies showed that in the reaction mixture consisting of



Scheme 2. Catalyst screening of compounds **5** and **6**.

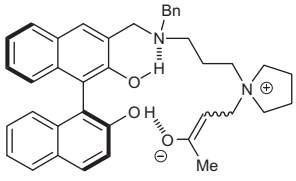


Figure 2. Our proposed intermediate.

catalyst **1c** and enone **2a**, the peak for the Me group of **2a** at δ 2.26 (3H, s) shifted to δ 2.07 (3H, s), and the peaks for the two phenolic hydroxy groups at δ 4.12 (1H, s) and δ 4.00 (1H, s) in catalyst **1c** also shifted to 3.96 (2H, br s) due to the formation of the corresponding ammonium enolates. A chiral bifunctional organocatalyst bearing a 1,3-propanediamine unit would provide a flexible chiral pocket resulting in the formation of the aza-MBH adducts with moderate to good enantioselectivities.

3. Conclusion

In conclusion, the chiral bifunctional catalyst **1k** was found to accelerate the aza-MBH reaction to afford the desired adducts in high yields with up to 82% ee. The realization that BINOL as a Brønsted acid unit 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 for elucidating the detailed activation mechanism are currently in progress.

Acknowledgments

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)*-**1k**: $[\alpha]_D^{20} = -30.6$ (*c* 0.59, $CHCl_3$); IR (neat) ν (cm^{-1}) 3056, 2928, 2821, 2346, 1736, 1620, 1596, 1509, 1431, 1342, 1244, 1211, 1148, 1107; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.9 Hz, 1H), 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), 7.33–7.12 (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 × 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 the enantioselective aza-MBH reaction catalyzed by (S)*-**1k** (Table 4): To a solution of organocatalyst **1k** (2.5 mg, 0.005 mmol) in $CHCl_3$ (0.3 mL) were added **2** (0.15 mmol) and imine **3** (0.05 mmol). The mixture was stirred until the reached completion as determined by 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 ^1H, ^{13}C NMR, MS, and IR spectroscopy, and were identical in all respects with the reported data.[5,6] The absolute configurations of **4** were determined by comparing the specific rotation assignments with those in the literature.[5,6]