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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 1I 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. 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. 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 1I, as shown in Figure 1, effected the aza-Morita-Bayliss-Hillman (aza-MBH) transformation with high chemical yields and up to 82% ee.

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

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 enone and the carbonyl group of an imine catalyzed by nucleophilic amines or phosphines. The products of the aza-MBH reaction are highly functionalized aliphatic amines, which prove to be valuable building blocks for biologically important compounds and natural products. Obtaining efficient catalysts for the aza-MBH reaction has been a challenge in organic synthesis.

We envisioned locating both acid and base units on one chiral binaphthyl skeleton thereby facilitating a synergistic cooperation on the aza-MBH reaction. To that end, tertiary amine 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 (C₂ or C₅-C₆) 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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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 1f (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, 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 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),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.

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-pyrindylamino-
Table 4. Substrate scope

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<th>Ec (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<sup>a</sup>0.5M (Substrate concentration of 3) and 3 equivalent of 2a.
<sup>b</sup>Isolated yield.
<sup>c</sup>Determined by HPLC (Daicel Chiralpak AD-H for 4a-k; Daicel Chirace OD-H for 4l; Daicel Chiralkap IB for 4m; Daicel Chiralcel OD3 for 4n; Daicel Chiralpak IA for 4o)
<sup>d</sup>For 5 days

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

$$
\text{2a} + \text{3m} \xrightarrow{11(10\text{ mol\%})} \text{4m} \quad (1)
$$

$$
\text{2a} + \text{MeNHTsSO_2Ph} \xrightarrow{11(10\text{ mol\%})} \text{4o} \quad (2)
$$

Scheme 2. Catalyst screening of compounds 1m,n, 5 and 6 nonmethylBINOL<sup>5h,6a,b</sup> 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 <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) studies exhibited that the reaction mixture of catalyst 1c and enone 2a revealed the Me group of 2a at <sup>δ</sup> 2.26 (3H, s) shifted to <sup>δ</sup> 2.07 (3H, s) and the phenolic hydroxy groups at <sup>δ</sup> 3.85 (2H, <sup>J</sup> = 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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References and notes


