Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6147–6149

Highly enantioselective aza-Morita–Baylis–Hillman reaction with a bisphenol-based bifunctional organocatalyst

Katsuji Ito,* Kanako Nishida and Takashi Gotanda

Department of Chemistry, Fukuoka University of Education, Akama, Munakata, Fukuoka 811-4192, Japan

Received 12 June 2007; revised 25 June 2007; accepted 26 June 2007
Available online 4 July 2007

Abstract—Newly developed phosphino-bisphenol **1c** was found to be an efficient organocatalyst for the aza-Morita–Baylis–Hillman reaction. High enantioselectivity up to 96% ee was obtained with catalyst loading of 1 mol %.

Chiral Lewis acid-catalyzed reactions are one of the most effective methods for synthesizing optically active compounds. The typical reaction involves the enantioselective addition of a nucleophile to carbonyl compounds in the presence of a chiral Lewis acid.[1] The carbonyl compound is activated through coordination of carbonyl oxygen atom to the Lewis acid and undergoes enantioselective nucleophilic addition. On the other hand, many biologic syntheses also include nucleophilic addition to carbonyl groups, however, the addition reactions are mostly non-metal catalyzed processes in which hydrogen bonding plays a pivotal role. Therefore, much effort has been directed toward the development of new organocatalysts bearing hydrogen-bond donor(s).[2] It has been demonstrated that appropriately oriented hydrogen-bond donors sufficiently activate carbonyl compounds through double or multiple hydrogen bonding.[2,3] Of the various organocatalysts reported to date, thiourea-based chiral organocatalysts have been the most successfully used for the activation of carbonyl, imine, and nitro groups through double hydrogen bonding.[3] It is well known that a phenolic hydroxy group also functions as a hydrogen-bond donor in some enzymes, such as L-fuculose 1-phosphate aldolase.[4] Although the successful application of chiral organocatalysts bearing phenolic hydroxy group(s) as a hydrogen-bond donor to enantioselective reactions is limited, it has been reported that the enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction that affords functionalized allylic amines in a single step can be promoted by this type of organocatalysts.[5,6] For example, quinidine derivatives,[6a,c,d,g] phosphinophenols,[6b,f,h] 3-substituted BINOLs,[6e,j,k] and thiourea Schiff bases[6i] have been developed to serve as the catalyst. Quite recently, Shi et al. reported that the chiral phosphine Lewis bases bearing multiple phenolic hydroxy groups were efficient catalysts for aza-MBH reactions.[6l] Although these reactions exhibited high enantioselectivities due to a sophisticated hydrogen bonding system (Fig. 1), relatively high catalyst loading (10 mol %) was required to obtain

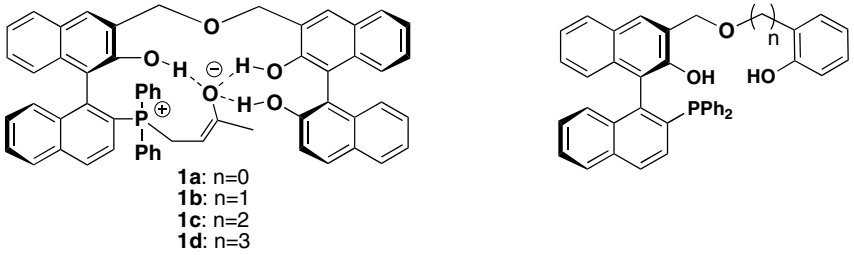


Figure 1. A hydrogen bonding structure proposed for the intermediate of aza-MBH reaction by Shi et al.

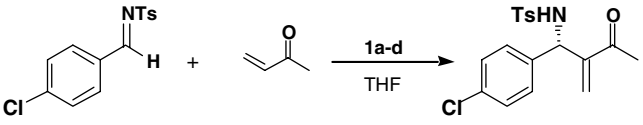
Keywords: Organocatalyst; Allyl amine; Aza-Morita–Baylis–Hillman reaction; Hydrogen bonding.
* Corresponding author. Tel.: +81 940 35 1367; fax: +81 940 35 1711; e-mail: itokat@fukuoka-edu.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.06.158

acceptable yields. Thus, the development of a new organocatalyst with a higher catalytic activity and more robustness is required. Shi et al. have proposed that both the naphthol parts take part in the activation of carbonyl groups, while the asymmetry is mostly induced by the chirality of the phosphinonaphthol part.[6l] Based on this proposal, we hypothesized that the carbonyl group should be sufficiently activated by two hydrogen bondings and that the replacement of the binaphthol unit with a simple phenol unit would facilitate substrate approach and enhance the catalyst activity. Thus, we synthesized new bifunctional phosphino-bisphenols **1** differing in the length of the spacer and examined their effect in the aza-MBH reaction.

Catalysts **1a–d** were prepared from phosphinophenol **2**[7] as follows (Scheme 1). Protection of the phenolic hydroxy group as MOM ether and subsequent MOM group-directed ortho-formylation gave aldehyde **3**. Reduction of the aldehyde with $NaBH_4$ followed by oxidation with urea·hydrogen peroxide adduct (UHP) afforded alcohol **4**. For the synthesis of **1a**, alcohol **4** was subjected to a Mitsunobu reaction[8] with mono-protected catechol to give **5a**. The other compounds **5b–d** were prepared in a similar manner to the syntheses of linked BINOL reported by Shibasaki et al.[9] The requisite alcohols **7b–d** were prepared from salicylaldehyde in a conventional manner. Reduction of the phosphinoyl group with PMHS in the presence of $Ti(O^iPr)_4$[10] and deprotection of the MOM group gave the desired phosphino-bisphenols **1a–d**. Deprotection of the MOM group in **5b** by Amberlyst 15 failed due to the instability of **1b** under the reaction conditions. Finally, compound **1b** was obtained by using *p*-toluenesulfonic acid, albeit in a very low yield.

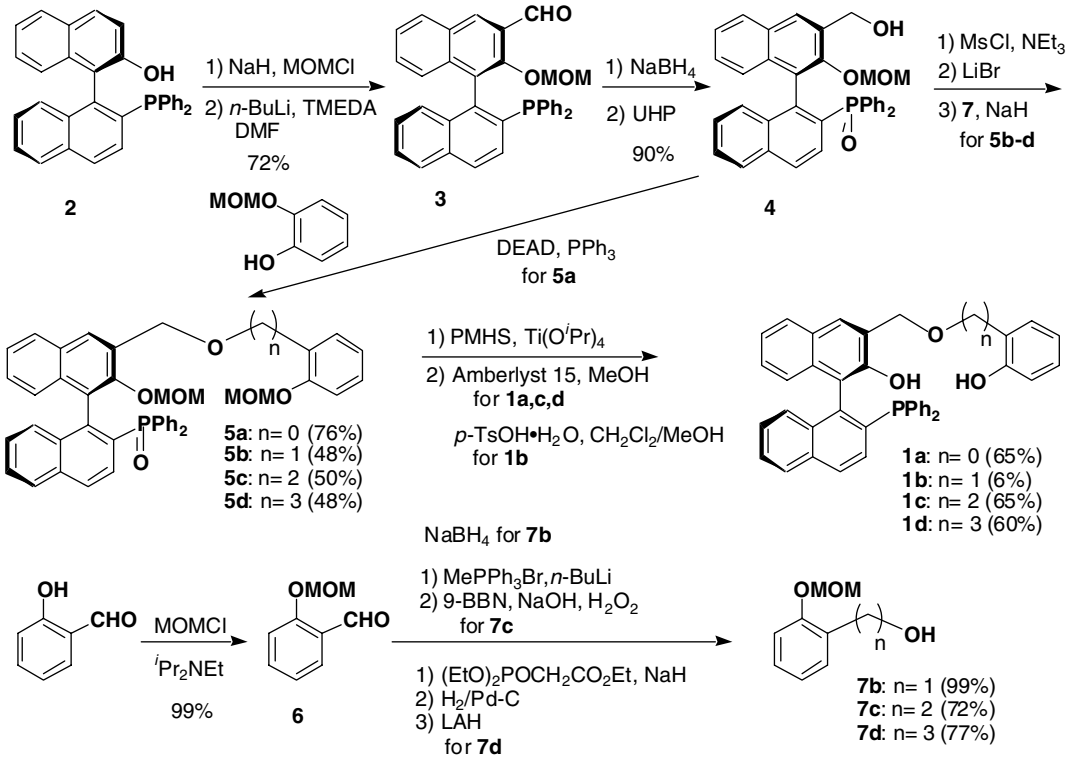
Table 1. Enantioselective aza-Morita–Baylis–Hillman reaction using **1a–d** as catalysts[a]



Entry	Catalyst	Catalyst loading (mol %)	Time (h)	Yield (%)	% ee[b]	Confign.[c]
1	**1a**	10	48	98	88	*S*
2	**1b**	10	2	93	95	*S*
3	**1c**	10	1.5	100	95	*S*
4	**1d**	10	1	99	93	*S*
5	**1c**	1	14	96	95	*S*
6	**1c**	0.5	96	95	95	*S*
7[d]	**1c**	1	48	100	95	*S*

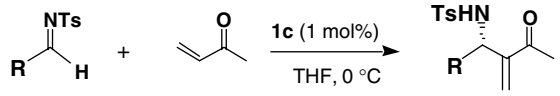
[a] All reactions were carried out at 0 °C in THF with molar ratio of imine/enone = 1:3 unless otherwise mentioned.
[b] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane/*i*-PrOH = 80:20).
[c] Determined by comparison of elution order of HPLC with the reported value (Ref. 6e).
[d] Reaction was performed at −15 °C.

With chiral phosphino-bisphenols **1a–d** in hand, we first examined the reaction of *p*-chlorophenyl *N*-tosylimine with methyl vinyl ketone in THF at 0 °C in the presence of **1a–d** (Table 1). The rate and the enantioselectivity of the reactions depended on the length of spacer in **1**. With **1a**, the reaction was completed after 48 h, and a good enantioselectivity of 88% ee was obtained (entry 1). The reaction rate and enantioselectivity were significantly improved when **1b** was used as the catalyst (entry



Scheme 1.

Table 2. Enantioselective aza-Morita–Baylis–Hillman reaction using **1c** as a catalyst[a]



Entry	R in *N*-tosyl imine	Time (h)	Yield (%)	% ee[b]	Confign.[c]
1	Phenyl	17	84	96	*S*
2	4-Fluorophenyl	17	100	95	*S*
3	4-Nitrophenyl	10	98	94	*S*
4	4-Methylphenyl	35	99	96	*S*
5	4-Methoxyphenyl	76	97	95	*S*
6	2-Naphthyl	17	100	95	*S*
7	(*E*)-Cinnamyl	164	71	87	*S*

[a] All reactions were carried out at 0 °C in THF with molar ratio of imine/enone/**1c** = 1:3:0.01.

[b] Determined by HPLC analysis using chiral stationary phase column according to the literature (Refs. 6e,f).

[c] Determined by comparison of elution order of HPLC with the reported value (Refs. 6e,f).

2). The most optimal result was obtained with **1c**, where the reaction was completed after 1.5 h with a high enantioselectivity of 95% ee (entry 3).[11] Although **1d** exhibited higher catalytic activity than **1c**, the enantioselectivity was somewhat decreased (entry 4). The high catalytic activity of **1c** allowed the reaction to be carried out at lower catalyst loading. To our delight, the catalyst loading could be reduced to 1 mol % without diminishing enantioselectivity (entry 5). The loading could be further reduced to 0.5 mol %, but the reaction was very slow (entry 6). Lowering the reaction temperature to −15 °C considerably retarded the reaction and no enhancement of the enantioselectivity was observed (entry 7).

Under the optimized conditions, we next examined the reactions of several other *N*-tosylimines (Table 2). Equally high enantioselectivities were obtained irrespective of the electronic nature of the aryl substituent, while the reaction rate was found to be dependent on the electronic nature such that the presence of an electron-donating group retarded the reaction (entries 4 and 5). The reaction of cinnamyl *N*-tosylimine was slow, and the enantioselectivity was decreased to 87% ee, although this is still good (entry 7).

In conclusion, we have demonstrated that newly developed phosphino-bisphenol **1c** is an efficient organocatalyst for the aza-MBH reaction. To the best of our knowledge, **1c** is the most active organocatalyst so far developed for the aza-MBH reaction. Further studies on the scope of the reaction and clarification of the reaction mechanism are currently under way in our laboratory.

Acknowledgments

The authors thank Dr. H. Furuno, Institute for Materials Chemistry and Engineering (IMCE), Kyushu University for measurement of NMR and HRMS.

References and notes

1. For reviews: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (b) *Catalytic Asymmetric Synthesis*; 2nd ed.; Ojima, I., Ed., Wiley-VCH: New York, 2000.
2. For reviews: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296; (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064; (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010; (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543.
3. Examples of bidentate or bifunctional metallic Lewis acids, see: (a) Maruoka, K. *Catal. Today* **2001**, *66*, 33–45; (b) Maruoka, K. *Pure Appl. Chem.* **2002**, *74*, 123–128; (c) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989–1999, and references cited therein.
4. For reviews: (a) Wong, C.-H.; Halcomb, R. H.; Ichikawa, Y.; Kajimoto, T. *Angew. Chem., Int. Ed.* **1995**, *34*, 412–432; (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374.
5. Reviews for the Morita–Baylis–Hillman reaction, see: (a) Iwabuchi, Y.; Hatakeyama, S. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 2–14; (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892; (c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628.
6. (a) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507–4510; (b) Shi, M.; Chen, L. H. *Chem. Commun.* **2003**, 1310–1311; (c) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103–3105; (d) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521–2524; (e) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680–3681; (f) Shi, M.; Chen, L. H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790–3800; (g) Shi, M.; Xu, Y.-M.; Shi, Y.-L. *Chem. Eur. J.* **2005**, *11*, 1794–1802; (h) Shi, M.; Li, C.-Q. *Tetrahedron: Asymmetry* **2005**, *16*, 1385–1391; (i) Rahhem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701–1705; (j) Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2006**, *17*, 578–583; (k) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761–765; (l) Liu, Y.-H.; Chen, L.-H.; Shi, M. *Adv. Synth. Catal.* **2006**, *348*, 973–979.
7. Uozumi, Y.; Tanahashi, A.; Lee, S. Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945–1948.
8. Mitsunobu, O. *Synthesis* **1981**, 1.
9. Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252–2260.
10. Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625–628.
11. Typical experimental procedure is exemplified by aza-MBH of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide with methyl vinyl ketone (MVK): To a solution of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide (58.8 mg, 0.2 mmol) and **1c** (1.2 mg, 2.0 μmol) in THF (0.4 ml), MVK (48.7 μl, 0.6 mmol) was added at 0 °C. After stirring for 14 h at 0 °C, the mixture was directly subjected to silica gel chromatography (hexane/ethyl acetate = 90:10–70:30), giving the desired product (70.0 mg, 96%). Enantiomeric excess of the product was determined to be 95% by HPLC using a chiral stationary phase column (Ref. 6e).