Chiral Brønsted Acid−Catalyzed Direct Asymmetric Mannich Reaction

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · MAY 2007

Impact Factor: 12.11 · DOI: 10.1021/ja068236b · Source: PubMed

6 AUTHORS, INCLUDING:

Qi-Xiang Guo
Southwest University in Chongqing
16 PUBLICATIONS **554** CITATIONS
SEE PROFILE

Chang Guo
University of Münster
13 PUBLICATIONS **537** CITATIONS
SEE PROFILE

Shi-Wei Luo
University of Science and Technology of China
35 PUBLICATIONS **1,459** CITATIONS
SEE PROFILE

J|A|C|S
COMMUNICATIONS

Published on Web 03/15/2007

Chiral Brønsted Acid-Catalyzed Direct Asymmetric Mannich Reaction

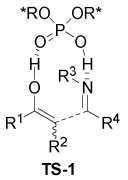
Qi-Xiang Guo,[†,§] Hua Liu,[†,§] Chang Guo,[‡] Shi-Wei Luo,[‡] Yi Gu,[‡] and Liu-Zhu Gong*[,†,‡]

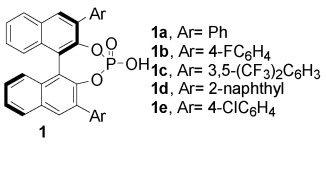
Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026 China, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences (CAS), Chengdu, 610041 China, and Graduate School of Chinese Academy of Sciences, Beijing, China

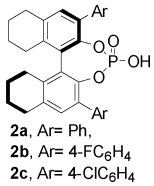
Received November 17, 2006; E-mail: gonglz@ustc.edu.cn

The asymmetric catalytic Mannich reaction is a powerful synthetic method for the preparation of enantioenriched β-amino carbonyl molecules, an important class of chiral building blocks of pharmaceutically relevant compounds.[1,2] Due to its atom-economy, the direct asymmetric Mannich reaction has been receiving increasing attention.[3−7] Of diastereo- and enantioselective organocatalytic direct Mannich reactions, *syn*-selective variants have been obtained for a wide scope of both imine acceptors and ketone/aldehyde donors.[3,6] Recently, *anti*-selective direct Mannich reactions of *N*-PMP-protected α-imino esters with simple ketones and aldehydes have also been performed with excellent diastereo- and enantioselectivities using reasonably designed chiral organocatalysts.[7a−d] However, there has been no report of an *anti*-selective asymmetric direct Mannich reaction of an aldimine other than α-imino ester with a simple ketone[7e] and an organocatalytic direct asymmetric Mannich reaction using an aromatic ketone as the donor. Nevertheless, the organocatalysts so far used for direct Mannich reactions involving simple ketones as donors are designed on the basis of enamine catalysis[6,7] and require a high loading (10−30 mol %) with the exception of those designed by Maruoka and Barbas.[7b−d]

Chiral phosphoric acids have currently been catalysts of choice for the activation of imines, leading to a number of asymmetric additions of various nucleophiles to imines.[8,9] However, the chiral phosphoric acids were only investigated for catalyzing an indirect Mannich reaction[9b,d] and a direct Mannich reaction of a β-dicarbonyl compound with *N*-Boc-protected aldimines, in which simple ketones were not reported as Mannich donors.[9a] The mechanistic proposal for the Brønsted acid-catalyzed Mannich reaction[10] indicates that a carbonyl compound possessing α-hydrogens will enolize in acid, and the formed enol will attack the protonated aldimine generated in situ from an aldehyde and a primary amine in the presence of the acid. Thus, we speculated that chiral phosphoric acids were potentially capable of promoting asymmetric direct Mannich reaction via **TS-1**.[11] Herein, we will report our findings that a catalytic amount of a chiral phosphoric acid is sufficient to promote an *anti*-selective direct asymmetric Mannich reaction of cycloketones with high diastereo- (*anti*/*syn*= 98:2) and enantioselectivity (up to 98% ee) and Mannich reactions between aldimines and aromatic ketones with fairly good enantioselectivity.

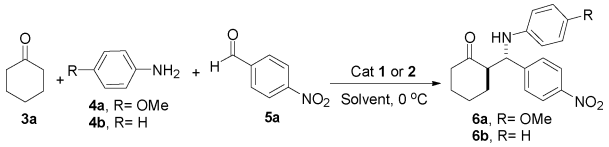






The primary experiment of a one-pot direct Mannich reaction between cyclohexanone (**3a**), *para*-methoxylphenylamine (PMP-NH_2), and *para*-nitrobenzaldehyde was carried out with 5 mol % of **1a** in CH_2Cl_2. As expected, the reaction was successful, affording the product **6a** in 49% yield. To our delight, *anti*-**6a** was favorably formed with 72/28 dr and 50% ee. The survey of the H_8-BINOL- and BINOL-based phosphoric acids revealed that **2a** turned out to be promising catalysts in terms of yield, diastereo-, and enantioselectivity (Table 1, entries 1−8). The enantioselectivity increased to 84% ee when the reaction was conducted in toluene (entry 9). The structure of the amine component has a considerable effect on the reaction (see Supporting Information). Accordingly, the employment of phenylamine further enhanced the enantioselectivity and reactivity (entry 10). Importantly, 0.5 mol % of **2a** or **1e** is sufficient to catalyze the reaction, furnishing *anti*-Mannich product **6b** with high enantioselectivity (90% ee with **2a** and 92% ee with **1e**) and fairly good diastereoselectivity (entries 11 and 12).

Table 1. Screening Catalysts and Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	4	solvent	yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%)[d]
1	**1a** (5)	**4a**	CH_2Cl_2	49	72/28	50
2	**1b** (5)	**4a**	CH_2Cl_2	91	80/20	67
3	**1c** (5)	**4a**	CH_2Cl_2	74	65/35	21
4	**1d** (5)	**4a**	CH_2Cl_2	48	81/19	53
5	**1e** (5)	**4a**	CH_2Cl_2	>99	88/12	63
6	**2a** (5)	**4a**	CH_2Cl_2	87	82/18	70
7	**2b** (5)	**4a**	CH_2Cl_2	93	84/16	64
8	**2c** (5)	**4a**	CH_2Cl_2	90	90/10	69
9	**2a** (5)	**4a**	toluene	93	80/20	84
10	**2a** (5)	**4b**	toluene	>99	72/28	88
11	**2a** (0.5)	**4b**	toluene	90	89/11	90
12	**1e** (0.5)	**4b**	toluene	90	82/18	92

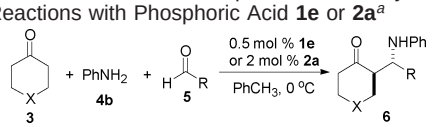
[a] Reaction conditions: a solution of 4-nitrobenzaldehyde (0.2 mmol), cyclohexanone (2.0 mmol), **4a** or **4b** (0.22 mmol), and a catalyst in a solvent (5 mL) was stirred at 0 °C for 48 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Enantiomeric excess of *anti*-product was determined by HPLC.

The optimized protocol was then expanded to a wide variety of aldehydes and cyclohexanone derivatives (Table 2). Direct Mannich reactions between the various aldehydes, phenylamine, and cyclohexanone proceeded smoothly in the presence of as little as 0.5 mol % of **1e** to yield *anti*-selective Mannich adducts mostly with excellent enantioselectivities (entries 1−9). The stereochemical outcome depends significantly on the electronic properties of the substituent on benzaldehyde. Electron-donating groups had a deleterious effect on the enantioselectivity (entry 6). An aliphatic aldehyde smoothly underwent the Mannich reaction with 84/16 dr and 75% ee (entry 7). Tetrahydropyran- and *N*-Boc-protected piperidin-4-ones (**3b** and **3c**) are both highly reactive toward the imine generated in situ from *para*-nitrobenzaldehyde and phenyl-

[†] Chengdu Institute of Organic Chemistry.
[‡] University of Science and Technology of China.
[§] Graduate School of Chinese Academy of Sciences.

10.1021/ja068236b CCC: $37.00

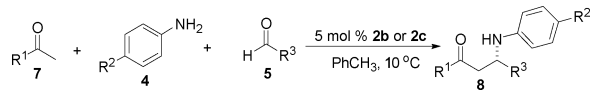
Table 2. *anti*-Selective Three-Component Direct Asymmetric Mannich Reactions with Phosphoric Acid **1e** or **2a**[a]



entry	X	R	6	yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%)[d]
1	CH_2	4-$CF_3C_6H_4$	**6c**	90	77/23	94
2	CH_2	4-CNC_6H_4	**6d**	92	86/14	91
3	CH_2	4-BrC_6H_4	**6e**	99	83/17	91
4	CH_2	4-ClC_6H_4	**6f**	99	85/15	93
5	CH_2	4-FC_6H_4	**6g**	67	81/19	95
6	CH_2	4-MeC_6H_4	**6h**	84	81/19	80
7	CH_2	$(CH_2)_2CH$	**6i**	83	84/16	75
8	CH_2	3,5-$Br_2C_6H_3$	**6j**	91	89/11	95
9	CH_2	3-FC_6H_4	**6k**	94	84/16	89
10	O	4-$NO_2C_6H_4$	**6l**	94	92/8	90
11	BocN	4-$NO_2C_6H_4$	**6m**	>99	80/20	91
12	S	4-$NO_2C_6H_4$	**6n**	97	92/8	95[e]
13	S	3,5-$Br_2C_6H_3$	**6o**	90	97/3	98[e]
14	S	3,5-$F_2C_6H_3$	**6p**	85	98/2	92[e]
15	S	4-$CF_3C_6H_4$	**6q**	82	92/8	95[e]
16	S	4-ClC_6H_4	**6r**	90	93/7	92[e]
17	S	3-Cl-4-FC_6H_3	**6s**	79	94/6 (100/0)[f]	83[e] (>99)[f]
18	S	2-thiophenyl	**6t**	74	89/11	91[e]

[a] The reaction was performed on 0.4 mmol scale for 48 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Enantiomeric excess of *anti*-product was determined by HPLC. [e] Catalyzed by 2 mol % of **2a**. [f] After recrystallization.

Table 3. Direct Asymmetric Mannich Reactions of Acyclic Ketones[a]



entry	**7** (R^1)	R^2	R^3	**8**	yield (%)[b]	ee (%)[c]
1	**7a** (CH_3)	CO_2Me	4-$NO_2C_6H_4$	**8a**	61	86[d]
2	**7a** (CH_3)	CO_2Me	4-MeC_6H_4	**8b**	76	72[d]
3	**7b** (Ph)	H	4-$NO_2C_6H_4$	**8c**	68	80[e]
4	**7b** (Ph)	H	4-BrC_6H_4	**8d**	69	79[e]
5	**7b** (Ph)	H	4-ClC_6H_4	**8e**	63	70[e]
6	**7c** (4-$CF_3C_6H_4$)	H	4-$NO_2C_6H_4$	**8f**	42	78[e]

[a] The reaction was performed on 0.4 mmol scale. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC. [d] 5 mol % of **2b**, at 0 °C, and 48 h. [e] 5 mol % of **2c** and 72 h.

amine, leading to the formation of *anti*-Mannich products with 90 and 91% ee, respectively (entries 10 and 11). Tetrahydrothiopyran-4-one (**3d**) is seemingly less reactive than its analogues. Consequently, 2 mol % of catalyst **2a** was required to ensure a complete Mannich reaction (entries 12−18). Excellent enantioselectivities (up to 98% ee) resulted from Mannich reactions involving tetrahydrothiopyran-4-one. The diastereoselectivity was highly dependent on the structures of both the aldehydes and the cyclic ketones. Accordingly, diastereomeric ratios ranging from 77/23 to 98/2 were observed. The relative and absolute configurations of the two contiguous stereogenic carbons in **6s** were determined by X-ray crystallographic analysis (see Supporting Information).

Acyclic ketones were also examined as Mannich donors (Table 3). Fairly good enantioselectivities were afforded for an aliphatic ketone in the presence of **2b** (entries 1 and 2).[12] Importantly, aromatic ketones such as **7b,c** could smoothly occur in the Mannich reaction with good enantioselectivities catalyzed by 5 mol % of phosphoric acid **2c** (entries 3−6). To the best of our knowledge, this is the first organocatalytic asymmetric Mannich reaction using aromatic ketones as donors.[13]

In summary, we have developed a Brønsted acid-catalyzed direct asymmetric Mannich reaction. The presence of 0.5 mol % of the phosphoric acid **1e** or 2 mol % of **2a** could effectively catalyze the reactions of a range of aldimines with cyclohexanone derivatives, giving *anti*-β-amino carbonyls in high yields with excellent enantioselectivities (up to 98% ee) and high diastereomeric ratios (up to 98/2 dr). The one-pot Mannich reaction involving aromatic ketones catalyzed by **2c** gave β-amino carbonyls in high yields with fairly good enantioselectivities.

Acknowledgment. We are grateful for financial support from NSFC (20472082, 203900505, and 20325211) and CAS.

Note Added after ASAP Publication: On March 15, 2007, after the initial ASAP publication, the Table 3 footnotes were amended.

Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; pp 923−961.
(2) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
(3) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.
(4) (a) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (b) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (c) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (d) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525.
(5) (a) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (b) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896. (c) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (d) Tillman, A. L.; Ye J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191.
(6) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (c) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (d) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (e) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2003**, *44*, 1923. (f) Watanabe, S.-i.; Córdova, A.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2002**, *4*, 4519. (g) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677. (h) Cobb, J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (i) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528. (j) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (k) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077. (l) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079.
(7) (a) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 7749. (b) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. (c) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040. (d) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630. (e) During revision of this paper, Barbas reported an *anti*-selective Mannich reaction of aromatic aldimines with ketones catalyzed by primary amino acids: Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288.
(8) For recent excellent reviews, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909. (c) Akiyama, A.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal*. **2006**, *348*, 999.
(9) For pioneering works, see: (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. For recent examples, see: (c) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (d) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254. (e) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617. (f) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193. (g) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368. (h) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (i) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (j) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (k) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796. (l) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074. (m) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802.
(10) (a) Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647. (b) Akiyama, T.; Matsuda, K.; Fuchibe, K. *Synlett* **2005**, 322.
(11) (a) Liu, H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 6023. (b) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832.
(12) The *syn*-Mannich product was mainly observed for a similar reaction of 3-pentanone (50% yield, 86/14 dr, 20% ee) probably due to the favorable formation of the *Z*-enol during reaction.
(13) For similar reactions catalyzed by transition metals, see: Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307 and refs 4b,c.

JA068236B