Direct asymmetric three-component organocatalytic *anti*-selective Mannich reactions in a purely aqueous system†

Lili Cheng,[a] Xiaoyu Wu[a] and Yixin Lu*[a,b]

Received 1st February 2007, Accepted 5th February 2007
First published as an Advance Article on the web 14th February 2007
DOI: 10.1039/b701579h

The direct three-component Mannich reactions of *O*-benzyl hydroxyacetone with *p*-anisidine and aromatic or aliphatic aldehydes in the presence of an L-threonine-derived catalyst afforded *anti*-1,2-amino alcohols in good-to-excellent yields and with enantioselectivities of up to 97%. This study is the first demonstration that direct three-component Mannich reactions can be promoted by a primary amino acid in water.

The asymmetric Mannich reaction[1] is one of the most powerful carbon–carbon bond-forming reactions for the construction of optically enriched β-amino carbonyl compounds and their derivatives. Recently, the groups of Trost,[2] Shibasaki,[3] and Jorgensen[4] reported direct Mannich-type reactions between ketones and preformed imines, whereby chiral zinc or copper complexes were utilized as catalysts. Because of the versatility of the synthons obtained from Mannich reactions, it is highly desirable to obtain either *syn*- or *anti*-products with high enantioselectivity. While *syn*-selective Mannich reactions are common, enantioselective *anti*-selective Mannich reactions are considerably more challenging.[2b,3b,5] The ideal Mannich reaction would involve a catalytic process employing directly the unmodified carbonyl donor, amine and acceptor aldehyde in one pot.

Asymmetric reactions catalyzed by metal-free organic molecules have become increasingly popular in recent years.[6] The first direct asymmetric three-component Mannich reaction catalyzed by proline was reported by List and co-workers,[7] followed by excellent contributions from Barbas *et al.*[8] Cordova and co-workers also reported asymmetric three-component Mannich reactions catalyzed by acyclic chiral amines or amino acids.[9] Water is an ideal solvent for chemical reactions due to its low cost, safety and environmentally benign nature,[10] and it has recently been shown by the groups of Takabe, Barbas and Hayashi that direct asymmetric aldol reactions and Michael reactions can be catalyzed by proline-derived hydrophobic catalysts in water.[11] We have previously disclosed direct aldol reactions in water promoted by hydrophobic primary amino acids.[12] Herein, we report the first highly enantioselective, direct three-component *anti*-selective Mannich reactions in water promoted by organocatalysts derived from threonine (Fig. 1).

We have been particularly interested in the development of direct asymmetric three-component Mannich reactions in a purely aqueous system. Hydroxyacetone is a very useful donor, and its Mannich reactions could furnish chiral 1,2-amino alcohols. In our initial screening, we examined the reactions of hydroxyacetone, *p*-nitrobenzaldehyde, *p*-anisidine and various organocatalysts in the presence of water (Table 1). Virtually no desired product was obtained when hydroxyacetone was used directly as a donor (entry 1), but silyl protection of the hydroxyl group resulted in donor reactivity in aqueous media. Threonine-derived organocatalysts (**2a–c**) (entries 7–9) were more effective than those derived from serine (**1a–c**) (entries 3–5). In the absence of water, the enantiomeric excess was lower (entry 6). Tryptophan and catalysts **4–7** were ineffective (entries 2 and 10–13). Hayashi's catalyst[11b] only afforded modest ee (entry 14). The combination of benzyl protection and the utilization of **2b** as catalyst led to the best diastereoselectivity and enantioselectivity (entry 16).

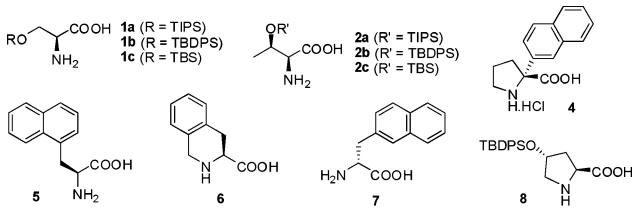


Fig. 1 Structures of the catalysts screened.

The optimized reaction conditions were applied to Mannich reactions employing various aromatic aldehydes (Table 2). The reactions were *anti*-selective and the Mannich products were obtained in excellent yields and with excellent enantioselectivities in most cases. However, the result was less satisfactory in the case of an electron-rich aromatic aldehyde (entry 10).

Mannich reactions involving aliphatic aldehydes were also investigated (Table 3). Our methods proved to be remarkably versatile, affording the Mannich products with excellent enantioselectivities for both branched and linear aliphatic aldehydes.

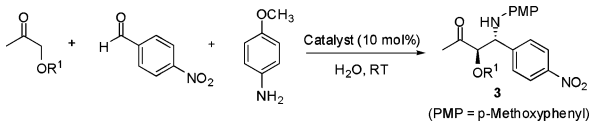
The relative and absolute configurations of the products were established by converting the amino alcohols into their corresponding Boc-protected oxazolidinones,[7b] and comparison with the enantiomerically pure commercially available compounds. To account for the stereochemical outcome, we propose that the reaction follows the enamine mechanism and involves a transition state as depicted in Fig. 2. The geometry of the enamines resulting from *O*-benzyl hydroxyacetone and *O*-(*tert*-butyldiphenylsilyl) threonine is *Z*, likely due to the hydrophobic interactions of hydrophobic moieties or π–π stacking of the aromatic components.

In summary, we have demonstrated for the first time that direct asymmetric three-component Mannich reactions can be carried out in one pot in a purely aqueous system. The reactions

[a]*Department of Chemistry, National University of Singapore, 3 Science Drive 3, 117543, Republic of Singapore. E-mail: chmlyx@nus.edu.sg; Fax: +65 6779-1691; Tel: +65 6516-1569*
[b]*The Medicinal Chemistry Program, Office of Life Sciences, National University of Singapore, Republic of Singapore*

† Electronic supplementary information (ESI) available: Experimental data. See DOI: 10.1039/b701579h

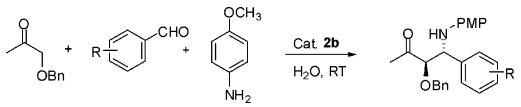
Table 1 Screening of organocatalysts[a]



Entry	Catalyst	R^1	Time/h	Yield[b] (%)	*Anti*:*syn*[c]	ee[d] (%)
1	**2c**	H	24	<5	—	—
2	L-Trp	TBS	24	—	—	—
3	**1a**	TBS	24	90	1 : 1	51
4	**1b**	TBS	24	77	1 : 1	48
5	**1c**	TBS	24	72	2 : 3	41
6[e]	**2c**	TBS	24	76	1 : 1	57
7	**2a**	TBS	24	76	7 : 2	95
8	**2b**	TBS	24	91	2 : 1	90
9	**2c**	TBS	24	82	1 : 1	71
10	**4**	TBS	40	85	1 : 3	0
11	**5**	TBS	120	<30	1 : 2	12
12	**6**	TBS	120	<30	1 : 3	0
13	**7**	TBS	120	<30	1 : 2	16
14	**8**	TBS	29	90	1 : 5	41 (75[f])
15	**2a**	Bn	24	92	4 : 1	81
16	**2b**	Bn	24	90	6 : 1	93

[a] The reactions were performed with *p*-nitrobenzaldehyde (0.1 mmol), *p*-anisidine (0.11 mmol), hydroxyacetone (0.3 mmol), and catalyst (0.01 mmol) in water (1 mmol) at room temperature. [b] Isolated yield. [c] The *anti*-to-*syn* ratio was determined by ^{1}H NMR analysis of the crude product. [d] The ee of the *anti*-isomer was determined by chiral HPLC analysis. [e] Neat. [f] The ee of the *syn*-isomer.

Table 2 Direct three-component Mannich reactions with aromatic aldehydes promoted by organocatalyst **2b** in water[a]

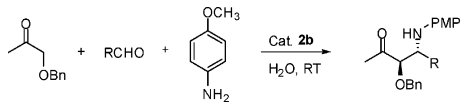


Entry	Product	Time/h	Yield[b] (%)	*Anti*:*syn*[c]	ee[d] (%)
1	**9** (R = 4-CN)	20	88	6 : 1	94
2	**10** (R = 4-Br)	25	73	4 : 1	86
3	**11** (R = 2-NO_2)	30	95	20 : 1	97
4	**12** (R = 2-naphthyl)	36	92	3 : 1	87
5	**13** (R = 3-NO_2)	26	90	7 : 1	88
6	**14** (R = 4-CF_3)	25	80	4 : 1	86
7	**15** (R = 4-pyridyl)	5	98	13 : 1	97
8	**16** (R = 3-pyridyl)	6	90	8 : 1	90
9	**17** (R = 2-Cl,4-Cl)	24	90	6 : 1	88
10	**18** (R = 4-Me)	36	87	3 : 2	62

[a] The reactions were performed with aldehyde (0.1 mmol), *p*-anisidine (0.11 mmol), *O*-benzyl hydroxyacetone (0.3 mmol), and catalyst (0.01 mmol) in water (1 mmol) at room temperature. [b] Isolated yield. [c] The *anti*-to-*syn* ratio was determined by ^{1}H NMR analysis of the crude product. [d] The ee of the *anti*-isomer was determined by chiral HPLC analysis.

promoted by the threonine-derived hydrophobic organocatalysts are *anti*-selective and highly enantioselective, and applicable to both aromatic and aliphatic aldehydes. Mechanistic studies and the full extension of the reaction scope are currently being investigated in our laboratory, and will be reported in due course.

Table 3 Direct three-component Mannich reactions with aliphatic aldehydes promoted by organocatalyst **2b** in water[a]



Entry	Product	Time/h	Yield[b] (%)	*Anti*:*syn*[c]	ee[d] (%)
1	**19** (R = *i*-Pr)	23	57	3 : 1	92
2	**20** (R = *i*-Bu)	22	70	2 : 1	90
3	**21** (R = cyclohexyl)	20	63	5 : 1	93
4	**22** (R = *n*-Pr)	23	53	3 : 1	91
5	**23** (R = *n*-Bu)	20	52	2 : 1	91
6	**24** (R = *n*-hexyl)	24	54	3 : 2	84
7	**25** (R = phenylethyl)	20	50	3 : 1	86

[a] The reactions were performed with aldehyde (0.1 mmol), *p*-anisidine (0.11 mmol), *O*-benzyl hydroxyacetone (0.3 mmol), and catalyst (0.01 mmol) in water (1 mmol) at room temperature. [b] Isolated yield. [c] The *anti*-to-*syn* ratio was determined by ^{1}H NMR analysis of the crude product. [d] The ee value of the *anti*-isomer was determined by chiral HPLC analysis.

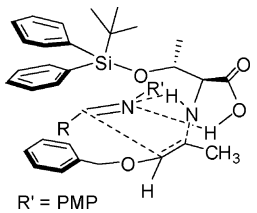


Fig. 2 The proposed transition state.

Acknowledgements

We thank the National University of Singapore for generous financial support.

Notes and references

1 (*a*) C. Mannich and W. Krosche, *Arch. Pharm. (Weinheim, Ger.)*, 1912, **250**, 647. For excellent reviews, see: (*b*) S. E. Denmark and O. J.-C. Nicaise, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Heidelberg, 1999, pp. 923–961; (*c*) M. Arend, B. Westermann and N. Risch, *Angew. Chem., Int. Ed.*, 1998, **37**, 1044; (*d*) S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069; (*e*) A. Cordova, *Acc. Chem. Res.*, 2004, **37**, 102.

2 (*a*) B. M. Trost and L. Terrell, *J. Am. Chem. Soc.*, 2003, **125**, 338; (*b*) B. M. Trost, J. Jaratjaroonphong and V. Reutrakul, *J. Am. Chem. Soc.*, 2006, **128**, 2778.

3 (*a*) S. Matsunaga, N. Kumagai, N. Harada, S. Harada and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 4712; (*b*) T. Yoshida, H. Morimoto, N. Kumagai, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **44**, 3470; (*c*) S. Harada, S. Handa, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4365.

4 (*a*) K. Juhl, N. Gathergood and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2001, **113**, 3840; (*b*) L. Bernardi, A. S. Gothelf, R. G. Hazell and K. A. Jorgensen, *J. Org. Chem.*, 2003, **68**, 2583.

5 (*a*) S. Kobayashi, H. Ishitani and M. Ueno, *J. Am. Chem. Soc.*, 1998, **120**, 431; (*b*) T. Hamada, K. Manabe and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 7768; (*c*) S. Matsunaga, T. Yoshida, H. Morimot, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 8777; (*d*) T. Kano, Y. Yamaguchi, O. Tokuda and K. Maruoka, *J. Am. Chem. Soc.*, 2005, **127**, 16408; (*e*) S. Misunori, H. Zhang, P. H.-Y. Cheong, K. N. Houk, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 1040; (*f*) I. Ibrahem and A. Cordova, *Chem. Commun.*, 2006, 1760; (*g*) H. Zhang, M. Mifsud, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 9630.

6 (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*b*) A. Berkssel and H. Groger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005.
7 (*a*) B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336; (*b*) B. List, P. Pojarliev, W. T. Biller and H. J. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 827.
8 (*a*) W. Notz, K. Sakthivel, T. Bui, G. Zhong and C. F. Barbas, III, *Tetrahedron Lett.*, 2001, **42**, 199; (*b*) A. Cordova, W. Notz, G. Zhong, J. M. Betancort and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2002, **124**, 1842; (*c*) W. Notz, S. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancort, F. Tanaka and C. F. Barbas, III, *Adv. Synth. Catal.*, 2004, **346**, 1131.
9 (*a*) A. Cordova, *Synlett*, 2003, 1651; (*b*) I. Ibrahem, W. Zou, M. Engqvist, Y. Xu and A. Cordova, *Chem.–Eur. J.*, 2005, **11**, 7024.
10 (*a*) For excellent reviews, see: U. M. Lindstrom, *Chem. Rev.*, 2002, **102**, 2751; (*b*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095; (*c*) *Organic Synthesis in Water*, ed. P. Grieco, Blackie, London, 1998; (*d*) C.-J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997.
11 (*a*) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 734; (*b*) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima and M. Shoji, *Angew. Chem., Int. Ed.*, 2006, **45**, 958; (*c*) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 4966; (*d*) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya and M. Shoji, *Angew. Chem., Int. Ed.*, 2006, **45**, 5527. For recent research, see: (*e*) A. P. Brogan, T. J. Dickerson and K. D. Janda, *Angew. Chem., Int. Ed.*, 2006, **45**, 8100; (*f*) Y. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 8103.
12 (*a*) Z. Jiang, Z. Liang, X. Wu and Y. Lu, *Chem. Commun.*, 2006, 2801; (*b*) X. Wu, Z. Jiang, H.-M. Shen and Y. Lu, *Adv. Synth. Catal.*, 2007, DOI: 10.1002/adsc.200600564.

