Direct catalytic asymmetric *anti*-selective Mannich-type reactions†

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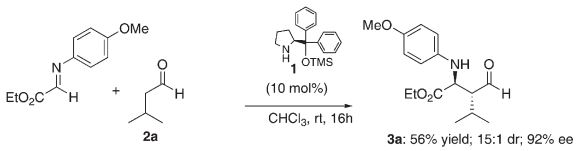
The simple chiral pyrrolidine catalyzed asymmetric *anti*-selective Mannich-type reaction is presented; the reaction gives the corresponding amino acid derivatives with 10 : 1−>19 : 1 dr and 97–99% ee.

The development of direct catalytic Mannich reactions has received considered attention in recent years.[1] It is used for the enantioselective synthesis of amino acids, β-lactams, amino sugars, imino sugars and amino alcohols.[1–12] The synthetic utility of these products have created a demand for catalytic highly enantioselective Mannich reactions that are either *syn*- or *anti*-selective.[2] Several catalysts have been developed for the catalysis of *syn*-selective direct asymmetric Mannich reactions. For instance, organometallic La-,[3] Zn-,[4] Cu-[5] and In-complexes[6] catalyze the reaction with excellent *syn*- and enantioselectivity. Moreover, organocatalysts such as Brønsted acids,[7] chincona alkaloids,[8] proline and its derivatives,[9] proline tetrazoles,[10] and amino acids catalyze[11] the direct Mannich reaction with high *syn*- and enantioselectivity. However, there are only a few examples of *anti*-selective direct catalytic asymmetric Mannich-type reactions.[12] Thus, the development of direct catalytic asymmetric *anti*-selective Mannich reactions is important and challenging.[13] Herein, we report a highly *anti*- and enantioselective Mannich-type reaction with aldehydes as nucleophiles that is catalyzed by a simple diphenylprolinol derivative.

In the proline, hydroxyproline and proline tetrazole-catalyzed Manich reactions, the *Si*-facial attack on the imine with a *trans* configuration by the *Si*-face of the chiral enamine gives the corresponding Mannich product with a *syn* relative configuration (Fig. 1).[9,10] However, we believed that efficient shielding of the *Si*-face of the chiral enamine by the employment of a bulky chiral amine catalyst would switch the facial selectivity of the reaction (Fig. 1) and thus change the stereochemical outcome of the reaction and make it *anti*-selective. To test this we investigated the chiral pyrrolidine-catalyzed Mannich-type reaction between ethyl *N*-*p*-methoxyphenyl (PMP)-protected α-iminoglyoxylate and *iso*-valeraldehyde **2a** (eqn (1)). We found that several bulky pyrrolidine derivatives catalyzed the reaction with moderate to good *anti*-selectivity. To our delight we found that the readily available TMS-protected α,α-diphenyl-2-pyrrolidinemethanol[14] (diphenylprolinol, **1**) catalyzed the direct catalytic asymmetric Mannich-type reaction with high *anti*- and enantioselectivity and the corresponding β-formyl-α-amino acid **3a** was furnished in 56% yield with >19 : 1 dr (*anti* : *syn*) and 92% ee.



(1)

Encouraged by this result, we performed a solvent screen with protected diphenylprolinol **1** as the catalyst (Table 1).

The reaction proceeded smoothly with high *anti*- and enantioselectivity in all the solvents tested. The highest enantioselectivity was obtained in $CHCl_3$ and CH_3CN. Notably, the reaction was highly stereoselective in water: the amino acid derivative **3a** was formed with 12 : 1 dr and 98% ee. In fact, this is the first example of a direct catalytic asymmetric Mannich-type reaction in water. Based on the results from the solvent screen we chose to investigate the chiral pyrrolidine **1** catalyzed *anti*-selective reaction between different aldehydes and *N*-PMP-protected α-iminoglyoxylate in $CHCl_3$ and CH_3CN (Table 2).

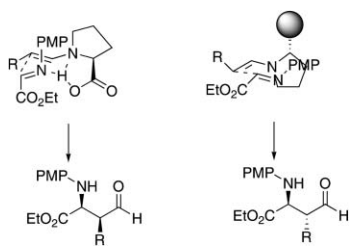
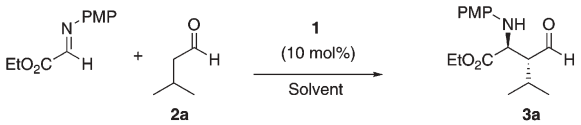


Fig. 1 The stereochemical outcome of the (*S*)-proline direct asymmetric catalyzed Mannich reaction and a plausible bulky chiral amine catalyzed Mannich-type reaction.

Table 1 Solvent screen for the direct catalytic asymmetric *anti*-selective formation of **2a**



Entry	Solvent	Time (h)	Temp. (°C)	Yield (%)[a]	dr[b]	ee (%)[c]
1	*t*-BuOH: H_2O-1:1	16	rt	35	>19 : 1	96
2	CH_3CN	17	rt	50	>19 : 1	99
3	$CHCl_3$	16	rt	56	>19 : 1	92
4	$CHCl_3$	24	4	68	>19 : 1	98
5	Toluene	16	rt	43	14 : 1	88
6	EtOH	16	rt	32	>19 : 1	82
7	H_2O	16	4	35	12 : 1	98

[a] Isolated yield of the pure products after silica-gel chromatography. [b] *Anti*:*syn* ratio as determined by NMR analyses. [c] Determined by chiral-phase HPLC analyses. PMP = *p*-methoxyphenyl.

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Table 2 Direct catalytic *anti*-selective asymmetric Mannich-type reactions

Entry	R	Cond.	Prod	Time (h)	Yield (%)[a]	dr[b]	ee (%)[c]
1	*i*-Pr	A	**3a**	24	68	>19 : 1	98
2	*n*-pent	A	**3b**	18	63	>19 : 1	99
3	Me	A	**3c**	14	45 (35)[d]	14 : 1 (15 : 1)[d]	99 (90)[d]
4	Me	B	**3c**	17	75	15 : 1	99
5	CH_2OBn	A	**3d**	16	67 (30)[d]	14 : 1 (10 : 1)[d]	97 (90)[d]
6	CH_2Ph	A	**3e**	16	67	19 : 1	99
7	*i*-Pr	A	**3a**	16	45[e]	>19 : 1[e]	99[e]

[a] Isolated yield of the pure products after silica-gel chromatography. [b] *Syn*:*anti* ratio as determined by NMR analyses. [c] Determined by chiral-phase HPLC analyses. [d] Reaction performed in H_2O at 4 °C, 1 h reaction time. Bn = benzyl, PMP = *p*-methoxyphenyl. [e] TMS protected di(2-naphthyl)prolinol (10 mol%) was used as the catalyst. A = $CHCl_3$, 4 °C. B = CH_3CN, 4 °C.

The diphenylprolinol **1**-catalyzed direct Mannich-type reactions were highly enantioselective and amino acid derivatives **3** were isolated in moderate to high yields with 97–99% ee. The reactions were highly *anti*-selective (14 : 1−>19 : 1). For instance, α-amino acid **3e** was furnished in 67% yield with 19 : 1 dr and 99% ee. Moreover, the chiral amine-catalyzed asymmetric reaction with α-benzyloxyacetaldehyde as the donor was highly stereoselective and gave **3d** in 67% yield with 14 : 1 dr and 97% ee. Amino sugar **3d** with an *anti*-configuration is an important chiral synthon and can be used in the *de novo* synthesis of C-6 amino- and iminosugars.[9l] Thus, the catalytic asymmetric *anti*-selective Mannich-type reaction opens up the possibility of synthesizing all the different diastereomers of amino and imino sugar derivatives. We also investigated the organocatalytic asymmetric Mannich-type reactions in water with aldehydes **2** as nucleophiles. The reactions were very fast due to the hydrophobic effect[15] and the product together with the starting imine formed an organic precipitate within 1 h, which upon isolation gave the corresponding products **3** with high enantioselectivity (90–98% ee) but low conversion (<40%). Moreover, TMS protected di(2-naphthyl)prolinol catalyzed the asymmetric Mannich reaction with excellent *anti*- and enantioselectivity to give **3a** with >19 : 1 dr and 99% ee.

The absolute stereochemistry of the Mannich products was established by comparison with the epimerized (2*S*,3*S*)-*syn*-**3a** and **3d** Mannich products obtained by (*S*)-proline catalysis.[9g,i,l] Hence, (*S*)-diphenylprolinol **1** catalyzed the asymmetric formation of (2*S*,3*R*)-amino acid derivatives **3**. The stereochemical outcome of the reaction was explained by the proposed transition state I (Fig. 2). Thus, attack on the *Si*-face of the imine with a *trans*-configuration by the *Re*-face of the chiral enamine gives the amino acid derivative **3**.

Stabilization of the *trans*-configuration and efficient shielding of the *Si*-face of the chiral enamine can explain the high stereoselectivity of the reaction. In addition, plausible stabilization by coulombic interactions between the amine atom of the imine and the δ^+ on the nitrogen of the pyrrolidine moiety of the chiral enamine, which is generated during the nucleophilic attack,

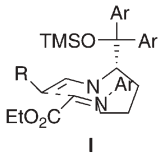

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Fig. 2 Proposed transition state for the protected diarylprolinol catalyzed direct asymmetric *anti*-selective Mannich-type reaction.

contributes to the stabilization of the *Si*-facial attack on the electrophile.[16]

In summary, we have developed a highly *anti*- and enantioselective direct catalytic asymmetric Mannich-type reaction. The asymmetric Mannich-type reactions are catalyzed by simple diphenyl- and di(2-naphthyl)prolinol derivatives that are prepared in one step and furnish amino acid derivatives in high yields with 14 : 1−>19 : 1 dr and up to 99% ee. The reaction is also highly stereoselective in water (90–98% ee). Further studies on the development of direct catalytic *anti*-selective Mannich reactions and their application in catalytic asymmetric domino- and tandem-reactions are ongoing.

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Notes and references

1 A. Córdova, *Acc. Chem. Res.*, 2004, **37**, 102.
2 (*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. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069; (*d*) S. Kobayashi, R. Matsubara, Y. Nakamura, H. Kitagawa and M. Sugiura, *J. Am. Chem. Soc.*, 2003, **125**, 2507.
3 S. Yamasaki, T. Iida and M. Shibasaki, *Tetrahedron Lett.*, 1999, **40**, 307.
4 (*a*) S. Matsunaga, N. Kumagai, N. Harada, S. Harada and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 4712; (*b*) B. M. Trost and L. M. A. Terrell, *J. Am. Chem. Soc.*, 2003, **125**, 338.
5 K. Juhl, N. Gathergood and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 2995.
6 S. Harada, S. Handa, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **43**, 4365.
7 T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566; D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356.
8 S. Lou, B. M. Taoka, A. Ting and S. Schaus, *J. Am. Chem. Soc.*, 2005, **127**, 11256.
9 (*a*) B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336; (*b*) A. Córdova, *Chem.-Eur. J.*, 2004, **10**, 1987; (*c*) A. Córdova, *Synlett*, 2003, 1651; (*d*) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji and K. Sakai, *Angew. Chem., Int. Ed.*, 2003, **42**, 3677; (*e*) A. Münch, B. Wendt and M. Christmann, *Synlett*, 2004, 2751; (*f*) W. Zhuang, S. Saaby and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2004, **43**, 4476; (*g*) A. Córdova, S.-I. Watanabe, F. Tanaka, W. Notz and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2002, **124**, 1866; (*h*) S. Fustero, D. Jimenez, J. F. Sanz-Cervera, M. Sanchez-Rosello, E. Esteban and A. Simon-Fuentes, *Org. Lett.*, 2005, **7**, 3433; (*i*) A. Córdova and C. F. Barbas, III, *Tetrahedron Lett.*, 2002, **43**, 7749; (*j*) B. Westermann and C. Neuhaus, *Angew. Chem., Int. Ed.*, 2005, **44**, 4077; (*k*) I. Ibrahem and A. Córdova, *Tetrahedron Lett.*, 2005, **46**, 2839; (*l*) W. -W. Liao, I. Ibrahem and A. Córdova, *Chem. Commun.*, 2006, 674; (*m*) D. Enders, C. Grondal, M. Vrettou and G. Raabe, *Angew. Chem., Int. Ed.*, 2005, **44**, 4079.
10 A. J. A. Cobb, D. M. Shaw and S. V. Ley, *Synlett*, 2004, 558; A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold and S. V. Ley, *Org. Biomol. Chem.*, 2005, **3**, 84.
11 I. Ibrahem, W. Zou, M. Engqvist and Y. Xu, *Chem.-Eur. J.*, 2005, **11**, 7024.
12 (*a*) T. Yoshida, H. Morimoto, N. Kumagai, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **44**, 3470; (*b*) T. Kano,

Y. Yamaguchi, O. Tokuda and K. Maruoka, *J. Am. Chem. Soc.*, 2005, **127**, 16408; (*c*) S. Mitsumori, H. Zhang, P. H.-Y. Cheong, K. N. Houk, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 1040; (*d*) B. M. Trost, J. Jaratjaroonphong and U. Reutrakul, *J. Am. Chem. Soc.*, 2006, **128**, 2778.
13 M. M. B. Marques, *Angew. Chem., Int. Ed.*, 2006, **45**, 348.
14 (*a*) E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551; (*b*) E. J. Corey, *Angew. Chem., Int. Ed.*, 2002, **41**, 1650. Both enantiomers of α,α-Diphenylprolinol and α,α-di(2-naphthyl)prolinol are commercially available and TMS protected in one-step see; (*c*) M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 794; (*d*) M. Marigo, D. Fielenbach, A. Braunton, A. Kjaersgaard and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 3703; (*e*) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjaersgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 18296; (*f*) M. Marigo, T. Schulte, J. Franzén and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 15710; (*g*) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212; (*h*) H. Sundén, I. Ibrahem and A. Córdova, *Tetrahedron Lett.*, 2006, **47**, 99.
15 (*a*) R. Breslow, *Acc. Chem. Res.*, 1991, **21**, 159; (*b*) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275.
16 V. Vinkovic and V. Sunjic, *Tetrahedron*, 1997, **53**, 689.

