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Design of a C_2-symmetric chiral pyrrolidine-based amino sulfonamide: application to *anti*-selective direct asymmetric Mannich reactions

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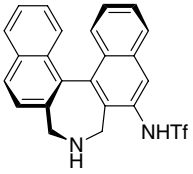
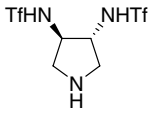
Abstract—The *anti*-selective direct asymmetric Mannich reaction was found to be efficiently catalyzed by the novel pyrrolidine-based amino sulfonamide (*R*,*R*)-**2** prepared from L-tartaric acid.

The development of highly stereoselective asymmetric reactions using organocatalysts has become a research area of great importance, and a number of new organocatalysts have been devised for this purpose.[1] Accordingly, we already designed several binaphthyl-based secondary amine catalysts for aldol and other reactions involving enamine intermediates in their transition state.[2] Among them, chiral binaphthyl-based amino sulfonamide (*S*)-**1** showed excellent reactivity, diastereo- and enantioselectivities in the *anti*-selective direct asymmetric Mannich reaction between aldehydes and α-imino esters.[2b,3,4] However, sterically hindered aldehydes gave the corresponding Mannich products in only moderate yields, probably due to the low nucleophilicity of (*S*)-**1**.[2b] In this context, we are interested in the possibility of designing a new chiral amino sulfonamide catalyst possessing the highly nucleophilic pyrrolidine core and acidic triflamide groups. Here we wish to report the synthesis of a new pyrrolidine-based amino sulfonamide (*R*,*R*)-**2** from L-tartaric acid as an inexpensive chiral starting material, and its application to the *anti*-selective direct asymmetric Mannich reaction.

Our catalyst design is based on the proposal of transition-state structures in the direct asymmetric Mannich reaction as shown in Scheme 1. When L-proline is used as a catalyst, the α-carboxyl group of L-proline controls

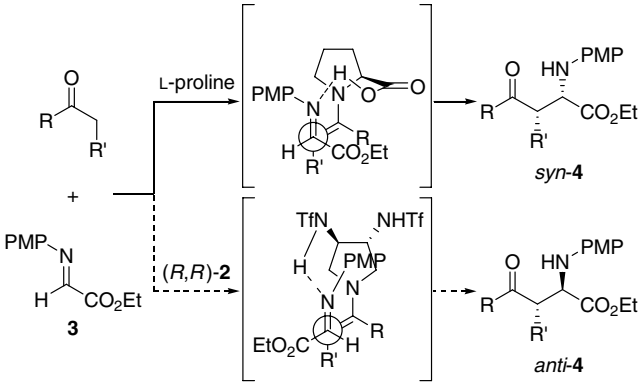


(*S*)-**1**



(*R*,*R*)-**2**

the orientation of the enamine moiety by the steric repulsion and the coordination pattern of α-imino ester **3** by the acid–base interaction, respectively, to furnish the *syn*-product **4** (Scheme 1).[5] On the other hand, the reaction using (*R*,*R*)-**2** would be expected to give the *anti*-product **4** as a result of the opposite facial orientation of α-imino ester **3**. In addition, the sterically less hindered (*R*,*R*)-**2** would be capable of reacting with



Scheme 1.

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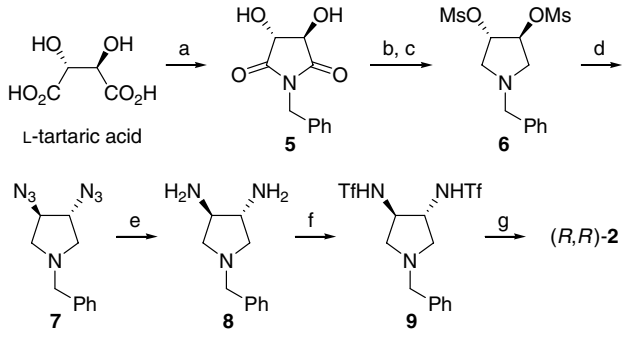
bulky aldehydes and ketones, which were found to be unsuitable substrates for the less nucleophilic (*S*)-**1**.

The requisite chiral pyrrolidine (*R*,*R*)-**2** was prepared in a seven-step sequence from L-tartaric acid as shown in Scheme 2. The direct condensation of the L-tartaric acid and benzylamine gave imide **5** almost quantitatively. The reduction of **5** with $NaBH_4$ and $BF_3{\cdot}OEt_2$, and the subsequent mesylation of hydroxyl groups afforded amino dimesylate **6** (61% yield in two steps), which was then converted with NaN_3 into diazide **7** in a 52% yield. The resulting azide groups were reduced in the presence of Pd/C under H_2 atmosphere to give triamine **8** in a 99% yield. The treatment of **8** with Tf_2O and *i*-Pr_2NEt gave bis(triflamide) **9** in a 76% yield. Finally, the reductive cleavage of the benzyl group provided the pyrrolidine-based amino sulfonamide (*R*,*R*)-**2** in a 93% yield, which was purified by an ion exchange resin.[6]

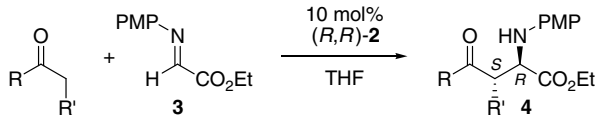
The new catalyst (*R*,*R*)-**2**, thus obtained, was utilized in the direct asymmetric Mannich reaction and the selected results are summarized in Table 1.[7] The Mannich reaction between butanal and α-imino ester **3** with 10 mol % of (*R*,*R*)-**2** proceeded smoothly in THF at −20 °C to give *anti*-product **4** predominantly (*anti*/*syn* = 16:1) in a high yield with excellent enantioselectivity (entry 1). The reaction with 3-methylbutanal also gave a satisfactory result (entry 2). While the use of a sterically more congested 3,3-dimethylbutanal resulted in the retardation of the reaction rate and slight decrease in enantioselectivity, the corresponding Mannich product was obtained in a good yield with a high *anti*- and enantioselectivity (entry 3). This result encouraged us to investigate the use of less reactive ketone substrates. The reaction of cyclohexanone gave satisfactory results in terms of both reactivity and selectivity even at lower catalyst loadings (entries 4–6). Even acyclic ketone such as 3-pentanone worked well with longer reaction time (entry 7).

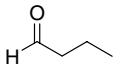
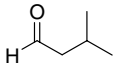
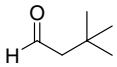
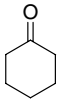
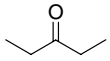
In summary, we have synthesized the pyrrolidine-based amino sulfonamide (*R*,*R*)-**2** from inexpensive and readily available L-tartaric acid, and have shown the efficiency of (*R*,*R*)-**2** for the *anti*-selective direct asymmetric Mannich reaction of sterically hindered aldehydes and ketones. Further investigations using this and related organocatalysts for other asymmetric reactions are currently underway.



Scheme 2. Reagents and conditions: (a) benzylamine, *o*-xylene, reflux, 99%; (b) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, reflux; (c) MsCl, Et_3N, CH_2Cl_2, rt, 61% over two steps; (d) NaN_3, DMF, 100 °C, 52%; (e) H_2, Pd/C, EtOH, rt, 99%; (f) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 76%; (g) H_2, Pd/C, AcOH, rt, 93%.

Table 1. *Anti*-selective Mannich reactions catalyzed by (*R*,*R*)-**2**[a]



Entry	Substrate	Conditions (°C, h)	% Yield[b] (*anti*/*syn*)[c]	ee[d] (%)
1		−20, 2	82 (16:1)	94
2		−20, 1	93 (11:1)	95
3		−20, 24	88 (18:1)	90
4		rt, 1	99 (>20:1)	95
5[e]		rt, 4	95 (>20:1)	95
6[f]		rt, 35	98 (>20:1)	93
7		rt, 70	56 (4.8:1)	92

[a] The reaction of a carbonyl compound (3 equiv) and α-imino ester **3** was carried out in THF in the presence of catalyst (*R*,*R*)-**2**.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] The enantiomeric excess of *anti*-isomer **4** was determined by HPLC analysis using chiral column (Chiralpak AS-H). The absolute configuration was determined by comparison of the HPLC retention times of **4** with the reported data.[3]
[e] Use of 2 mol % of (*R*,*R*)-**2**.
[f] Use of 0.5 mol % of (*R*,*R*)-**2**.

Acknowledgments

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References and notes

1. For reviews, see: (a) List, B. *Synlett* **2001**, 1675; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726; (c) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904; (d) List, B. *Tetrahedron* **2002**, *58*, 5573; (e) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858; (f) List, B. *Acc. Chem. Res.* **2004**, *37*, 548; (g) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570; (h) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580; (i) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (j) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719; (k) Berkessel, A.; Gröger, H. *Asymmetric*

Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis; Wiley-VCH: Weinheim, 2005.

2. (a) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055; (b) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408; (c) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046; (d) Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem. Asian J.* **2006**, *1*, 210.
3. *Anti*-selective direct asymmetric Mannich reactions with organocatalysts: (a) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 7749; (b) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296; (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) Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760; (e) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630.
4. *Anti*-selective direct asymmetric Mannich reactions with metal catalysts: (a) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712; (b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777; (c) Yoshida, T.; Morimoto, H.; Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3470; (d) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365; (e) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778.
5. (a) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866; (b) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624.
6. *(3R,4R)-3,4-Bis(trifluoromethylsulfonamido)pyrrolidine* (*R*,*R*)-**2**: ^{1}H NMR (400 MHz, CD_3OD) δ 3.98–3.95 (2H, m, C*H*NHTf), 3.51 (2H, dd, $J = 6.0$, 12.0 Hz, C*H*HNH), 3.13–3.09 (2H, dd, $J = 5.6$, 12.0 Hz, CH*H*NH) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 122.1 (q, $J_{C-F} = 325$ Hz), 61.4, 51.5 ppm.
7. *Typical procedure for the anti-selective direct asymmetric Mannich reaction with* (*R*,*R*)-**2**: To a stirred solution of chiral amino sulfonamide (*R*,*R*)-**2** (3.7 mg, 0.01 mmol) in THF (1 mL) were added 3-methylbutanal (32 μL, 0.3 mmol) and ethyl (4-methoxyphenylimino)acetate **3** (21 mg, 0.1 mmol) in this order at −20 °C. After stirring at −20 °C for 1 h, the reaction mixture was then quenched with brine, and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 2/1) to afford the corresponding Mannich adduct **4** (27 mg, 0.093 mmol, 93% yield, 95% ee).