Asymmetric Direct Aldol Reaction of Cyclohexanone Catalyzed by (*N′*-Benzyl-*N′*-*D*-prolyl)-*trans*-4-hydroxy-*L*-proline Hydrazide

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A new proline catalyst, namely (*N′*-benzyl-*N′*-*D*-prolyl)-*trans*-4-hydroxy-*L*-proline hydrazide, has been prepared and proved to be a superior catalyst for the asymmetric aldol reaction of cyclohexanone and aromatic aldehydes, affording up to 98∶2 *dr* and 98% *ee*.

Keywords asymmetric aldol reaction, proline hydrazide, enantioselectivity, diastereoselectivity, cyclohexanone

Introduction

The asymmetric direct aldol reaction is one of the most powerful C—C bond forming reactions for the production of chiral 1,3-dioxygenated compounds.[1] The development of novel chiral organocatalyts for this transformation has recently been the subject of intense research[2] since List, Barbas and Lehner reported that *L*-proline could effectively catalyze the intermolecular direct aldol reaction.[3] A number of proline derivatives have emerged as highly efficient and stereoselective catalysts (for selected examples, see references 4—38). Among them, proline hydrazides, upon protonation with trifluoroacetic acid (TFA), behaved as highly efficient and enantioselective catalyst in the aldol reaction of aromatic aldehydes and ketones.[19] In previous studies, Sun *et al.*[20] has also proved that (*N′*-benzyl-*N′*-*L*-prolyl)-*trans*-4-hydroxy-*L*-proline hydrazide (**1**, Figure 1) was a good catalyst for the asymmetric aldol reaction of cyclohexanone with aromatic aldehydes, resulting in excellent diastereoselectivity (up to 99∶1 *dr*) and enantioselectivity (up to＞99% *ee*). In the catalysts cited above,[19,20] pyrrolidinyl groups are *L*-configuration. We speculated that new catalysts with different configuration of the pyrrolidinyl groups may have influence on the output in terms of both enantioselectivity and diastereoselectivity during catalyzing the aldol reaction. Herein, we report the preparation of one of the catalyst **1**'s diastereoisomers, (*N′*-benzyl-*N′*-*L*-prolyl)-*trans*-4-hydroxy-*L*-proline hydrazide's counterpart—(*N′*-benzyl-*N′*-*D*-prolyl)-*trans*-4-hydroxy-*L*-proline hydrazide (**2**, Figure 1) and its application as a catalyst for the aldol reaction of cyclohexanone and aromatic aldehydes. It proved to be an excellent catalyst, affording up to 98∶2 *dr* and 98% *ee*.

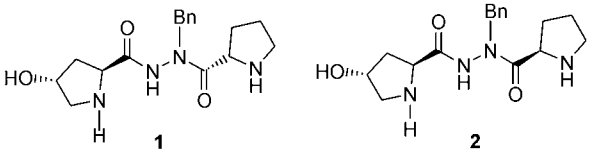

Figure 1 Structures of proline **1** and **2**.

Results and discussion

Preparation of organocatalysts (2, Scheme 1)[19]

To a solution of **2a** (935 mg, 8.8 mmol) in $PhCH_3$ (20 mL) was added benzaldehyde (935 mg, 8.8 mmol). The reaction mixture was stirred at room temperature for 24 h, and then concentrated under reduced pressure. The residue was dissolved in methanol (80 mL), then 5% Pd/C (0.2 g) was added into the reaction. After stirring under hydrogen (1.01×10^3 kPa) for 1 h, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified through column chromatography on silica gel [eluent: petroleum ether (PE)∶ethyl acetate (EtOAc)＝3∶1] to give **2b**.

To a solution of **2b** (2.0 mmol) in dimethylformamide (DMF, 20 mL) was added Boc-*D*-Pro (2.4 mmol), *N*,*N*-diisopropylethylamine (DIEA, 700 μL) and 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 922 mg, 2.4 mmol) at 0 ℃. The reaction mixture was stirred at room temperature for 24 h, then concentrated under reduced pressure. The residue was dissolved in EtOAc. The organic phase was then washed with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: PE∶EtOAc＝2∶1) to give a white solid, which

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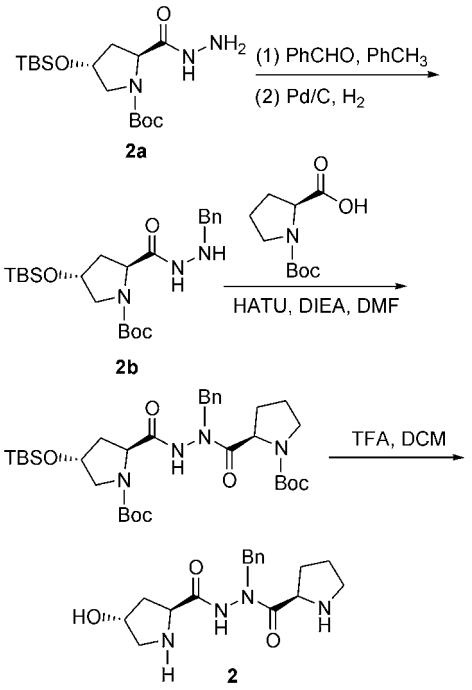
was then treated with a mixture of TFA: methylene dichloride (DCM) (*V*/*V*=1∶2, 20 mL). After stirring at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was subjected to chromatography on a H^+ ion-exchange resin column with NH_3•H_2O (3.0 mol•L^{-1}) as eluent to give a crude product, which was further purified through column chromatography on silica gel [eluent: DCM saturated with ammonia gas∶methanol (MeOH)=10∶1] to give the final product **2**, white solid, yield 50%; $[\alpha]_D^{25}$ +10.6 (*c* 0.246, MeOH); m.p. 128—130 ℃; ^{1}H NMR (CD_3OD, 600 MHz) δ: 1.69—1.84 (m, 4H), 2.02 (q, J = 7.86 Hz, 2H), 2.77—2.82 (m, 2H), 2.87—2.89 (br s, 1H), 3.13—3.17 (m, 1H), 3.83 (q, J= 9.00 Hz, 1H), 4.31 (brs, 1H), 4.65 (brs, 1H), 4.87 (brs, 1H), 7.29— 7.34 (m, 3H), 7.35—7.38 (m, 2H); ^{13}C NMR (CD_3OD, 150 MHz) δ: 25.6, 29.9, 39.3, 46.6, 48.4, 50.5, 54.7, 57.5, 58.1, 71.8, 127.6, 128.3, 128.9, 135.3, 174.4, 175.8; ESI HRMS for calcd $C_{17}H_{24}N_4O_3$ $[M+H]^+$ 333.1921, found 333.1926.

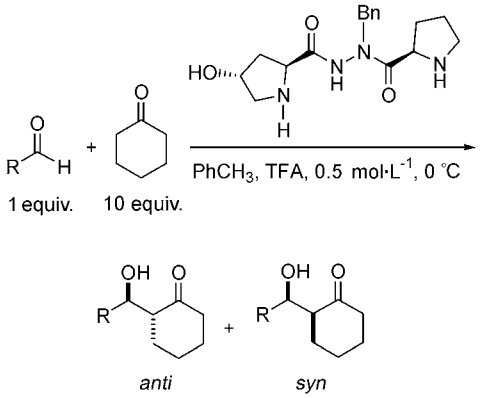
Scheme 1 Preparation of proline hydrazide **2**

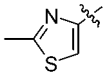


The direct aldol reaction of cyclohexanone catalyzed by organocatalyst 2

For the purpose of comparison with catalyst **1**, the established optimal condition, namely 20 mol% catalyst **2** and 20 mol% TFA, at 0 ℃, with toluene as solvent and the concentration of reaction 0.5 mol•L^{-1}, was directly used.[20] Under this condition, a range of aromatic aldehydes were reacted with cyclohexanone in the presence of organocatalyst **2**. As shown in Table 1, the reactions of benzaldehydes bearing electron-withdrawing groups on the benzene ring proceeded smoothly to furnish the aldol products in high yield (up to 99%, Entries 1—7) and excellent diastereoselectivity (up to 98/2 *dr* for the *anti*/*syn* isomers) and enantioselectivity (up to 98% *ee* for the major *anti* isomer). High *dr* and *ee* values were also obtained with the relatively electron-rich aldehydes (Entries 8—12), which, however, afforded moderate to high yields due to their attenuated reactivities. Not unsurprisingly, the heteroaromatic aldehydes also proved to be good substrates (Entries 13—16), which reacted well to give the corresponding aldol products in high diastereoselectivity and enantioselectivity (up to 98/2 *dr* and 98% *ee*). Decreasing the load-

Table 1 Direct aldol reactions of aldehydes with cyclohexanone catalyzed by **2**[a]



Entry	R	Time/h	Yieid[b]/%	*dr*[c] (*anti*/*syn*)	*ee*[d]/% (*anti*)
1	4-NO_2Ph	1	99	98/2	97
2	3-NO_2Ph	3	99	96/4	94
3	2-NO_2Ph	4	98	95/5	96
4	4-CNPh	3	95	97/3	95
5	4-ClC_6H_4	50	96	97/3	95
6	4-BrC_6H_4	50	98	98/2	95
7	2-ClC_6H_4	24	97	95/5	98
8	Ph	50	82	90/10	94
9	4-MeC_6H_4	72	71	95/5	93
10	4-$MeOC_6H_4$	50	58	95/5	92
11	3-$MeOC_6H_4$	50	68	96/4	93
12	1-naphthyl	72	68	94/6	93
13	4-Py	0.5	95	94/6	95
14	3-Py	3	97	98/2	98
15	2-furfuryl	50	82	98/2	97
16		50	71	95/5	94
17[e]	4-NO_2Ph	3	98	98/2	98
18[f]	4-NO_2Ph	6	98	98/2	97

[a] Unless specified otherwise, the reaction was carried out with catalyst **2** (20 mol%) and TFA (20 mol%). [b] Isolated yield based on the aldehyde. [c] Determined by chiral HPLC analysis of the mixture of the *anti*/*syn* product. [d] For the major *anti* isomer, determined by chiral HPLC. [e] In the presence of 10 mol% catalyst **2** and 10 mol% TFA. [f] In the presence of 5 mol% catalyst **2** and 5 mol% TFA.

ing of the catalyst to 10% or 5% merely slowed down the reaction to some extent but did not sacrifice either the yield or the selectivity (Entries 17—18). Notably, catalyst **2** proved to be ineffective for aliphatic aldehydes. The results showed that catalyst **2** had the same catalytic activity with catalyst **1**, which further proved that the pyrrolidinyl group closer to the hydrazide NH (on the left) plays the central role in the enamine formation in the course of the aldol reaction, whereas the other pyrrolidinyl group (on the right) mainly functions as a hydrogen-bond donor. Changing the configuration of this right-hand pyrrolidinyl group from *L* to *D* does not affect the diastereoselectivity and enantioselectivity of the aldol reaction.

Conclusions

In summary, we have demonstrated that *N'*-benzyl-*N'*-*D*-prolyl-*trans*-4-hydroxy-*L*-proline hydrazide (**2**) is also a superior catalyst similar to its counterpart **1**[20] for the asymmetric direct aldol reaction of cyclohexanone with aromatic aldehydes. In the presence of this catalyst, excellent diastereoselectivities (up to 98/2 *dr*) and enantioselectivities (98% *ee*) were obtained for a broad range of aromatic aldehydes, including heteroaromatic aldehydes. It is worth to be noted that the results obtained with catalyst **2** further verified the catalytic mechanism with proline hydrazides as proposed previously.[19] Further studies focusing on the mechanistic aspects and the full application scope of this catalyst system are currently underway and will be reported in due course.

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