trans-4-Hydroxy-L-proline Hydrazide–Trifluoroacetic Acid as Highly Stereoselective Organocatalyst for the Asymmetric Direct Aldol Reaction of Cyclohexanone

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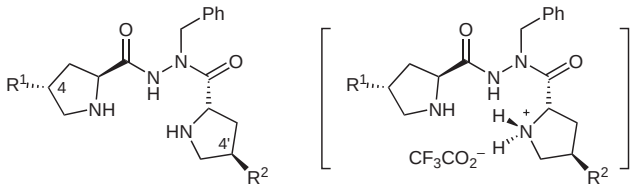
Abstract: Protonated *N*′-benzyl-*N*′-L-prolyl-*trans*-4-hydroxy-L-proline hydrazide has been found to be superior to the L-proline hydrazide counterpart as the catalyst for the asymmetric aldol reaction of cyclohexanone and aromatic aldehydes, resulting in excellent diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to >99% ee).

Key words: proline hydrazide, enantioselectivity, diastereoselectivity, cyclohexanone, asymmetric direct aldol reaction

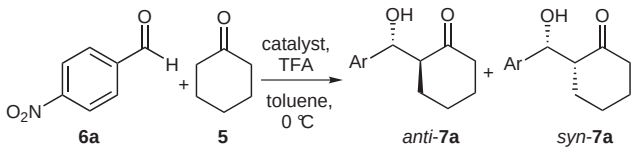
The asymmetric direct aldol reaction is one of the most powerful C–C bond-forming reactions for the production of chiral 1,3-dioxygenated compounds.[1] The development of novel chiral organocatalysts for this transformation has recently been the subject of intense research [2] since List, Barbas and Lerner 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.[4] In our previous report, we presented the first proline hydrazide, *N*′-benzyl-*N*′-L-prolyl-L-proline hydrazide (**1**; Figure 1) that, upon protonation with trifluoroacetic acid (TFA), behaved as a highly efficient and enantioselective catalyst in the aldol reaction of aromatic aldehydes and acetone.[5] This catalyst was also shown to efficiently catalyze the aldol reaction between cyclohexanone (**5**) and *p*-nitrobenzaldehyde (**6a**; Scheme 1). However, the resulting diastereomeric ratios (92:8 for the *anti*/*syn* products) and ee values (92% for the major *anti* isomer) are not excellent. Herein, we report that the analogous *N*′-benzyl-*N*′-L-prolyl-*trans*-4-hydroxy-L-proline hydrazide (**4**; Figure 1) proved to be a superior catalyst for the aldol reaction of cyclohexanone and aromatic aldehydes,[6] affording products in up to >99:1 dr and >99% ee.

Introduction of a *trans*-4-substituent, if appropriate, to the pyrrolidinyl backbone has recently proven to have some positive and profound impacts on the catalytic effects of the proline-based organocatalysts.[3b,4n,7] We were interested to investigate if there exists any such effect with the proline hydrazide catalyst system. Our previous studies have demonstrated that in the molecular structure of catalyst **1**, 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, upon protonation, to facilitate the formation of the hydrogen-bonding network in the transition state of the nucleophilic addition of the enamine to the aldehyde (see the structures of the protonated species inside the bracket in Figure 1).[5] We speculated that the introduction of a *trans*-4-substituent on C4 and C4′ might have different influences on the efficiency of the catalyst. Thus catalysts **2**–**4** (Figure 1) with a *trans*-hydroxyl group on C4 and/or C4′ were prepared starting from the easily accessible *trans*-4-hydroxy-L-proline and/or L-proline[8,9] and tested in the model aldol reaction of *p*-nitrobenzaldehyde and cyclohexanone (Scheme 1).



1 $R^1 = R^2 = H$ **2** $R^1 = H$, $R^2 = OH$
3 $R^1 = R^2 = OH$ **4** $R^1 = OH$, $R^2 = H$

Figure 1



Scheme 1

As illustrated in Table 1, catalysts **2**–**4** all exhibited significantly improved reactivity compared with the parent catalyst **1** (entries 4–6 vs entry 3), furnishing products with >90% yield in one hour. While **2** gave slightly decreased dr and ee values, **3** afforded a slightly improved dr and a significantly enhanced ee value. The best diastereoselectivity (99:1 dr for the *anti*/*syn* isomers) and enantioselectivity (98% ee for the major *anti* isomer) were obtained with **4**. These results clearly indicate that the existence of the *trans*-hydroxyl group on C4 is beneficial to

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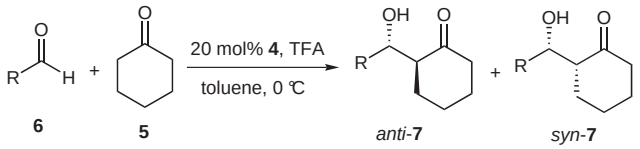
Table 1 Asymmetric Direct Aldol Reaction of 4-Nitrobenzaldehyde (**6a**) with Cyclohexanone (**5**) under Various Conditions[a]

Entry	Catalyst	C [M]	Molar ratio (**5**/**6a**)	Time (h)	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%, *anti*)[d]
1	**1**	0.2	20	24	98	92:8	92
2	**1**	0.2	10	24	96	98:2	93
3	**1**	0.5	10	1	73	97:3	86
4	**2**	0.5	10	1	94	95:5	84
5	**3**	0.5	10	1	99	98:2	95
6	**4**	0.5	10	1	99	99:1	98
7	**4**	0.5	5	1	51	98:2	95
8	**4**	0.2	10	5	94	99:1	98

[a] Unless specified otherwise, the reaction was carried out with catalyst (20 mol%) and TFA (20 mol%) in toluene at 0 °C.
[b] Isolated yield based on the aldehyde.
[c] Determined by chiral HPLC analysis of the mixture of the *anti*/*syn* product.
[d] Determined by chiral HPLC.

the reactivity, diastereoselectivity and enantioselectivity of the catalyst for the model aldol reaction, whereas the same group on C4′ only benefits the reactivity and has little impacts on diastereoselectivity and enantioselectivity.

We further investigated the influences of other reaction parameters on the performance of the most efficient catalyst **4** in the model reaction. Decreasing the molar ratio of cyclohexanone (**5**) to aldehyde **6a** from ten to five led to a much slower reaction rate (99% vs 51% yield, entry 6 vs 7, Table 1) and a decreased enantioselectivity (98% vs 95% ee) with an almost unchanged diastereoselectivity (99:1 vs 98:2 dr). Lowering the concentration of the reaction from 0.5 M to 0.2 M only slowed down the reaction to some degree (entry 6 vs 8), but had no effect on the dr and ee values.



Scheme 2

Having established the optimal reaction conditions, we next probed the general applicability of catalyst **4**.[10] A range of aromatic aldehydes **6a**–**p** were reacted with cyclohexanone in the presence of 20 mol% catalyst and an equal amount of TFA in toluene at 0 °C (Scheme 2). Table 2 summarizes the results. The reactions of benzaldehydes **6a**–**f** bearing an electron-withdrawing group on the benzene ring proceeded smoothly to furnish the aldol products in high yield (up to 99%, entries 1–6) and excellent diastereoselectivity (up to >99:1 dr for the *anti*/*syn* isomers) and enantioselectivity (up to >99% ee for the major *anti* isomer). High dr and ee values were also obtained with the relatively electron-rich aldehydes **6g**–**j** (entries 7–10), which, however, afforded low to moderate yields due to their attenuated reactivities. Not unsurprisingly, the heteroaromatic aldehydes **6k**–**p** also proved to be good substrates. In particular, the nitrogen-containing heteroaromatic aldehydes **6l**–**p** reacted well to give the corresponding aldol products in high diastereoselectivity and enantioselectivity (up to 99:1 dr and 99% ee, entries 12–16). These substrates, which could be problematic because the strong basicity of the nitrogen atom(s) could disturb the acid–base bifunctional catalysis, have rarely been used for the asymmetric organocatalytic aldol reaction.[4n] Notably, catalyst **4** proved to be ineffective for aliphatic aldehydes, for example, giving less than 10% conversion for isobutyraldehyde after one week.

In summary, we have demonstrated that *N*′-benzyl-*N*′-L-prolyl-*trans*-4-hydroxy-L-proline hydrazide (**4**) is a superior catalyst compared to the parent L-proline hydrazide counterpart **1** for the asymmetric direct aldol reaction of cyclohexanone with aromatic aldehydes. In the presence of this catalyst, excellent diastereoselectivities (up to >99:1 dr) and enantioselectivities (>99% ee) were obtained for a broad range of aromatic aldehydes, including heteroaromatic aldehydes. For comparisons to the other organocatalysts,[6] the remarkable features of this catalyst include: the high reactivity and the excellent diastereoselectivity and enantioselectivity, the requirement of the use of non-polar toluene as the solvent and the mild reaction conditions. Further studies focusing on the mechanistic aspects[11] and the full application scope of this catalyst system are currently underway and will be reported in due course.

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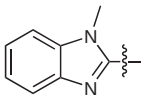
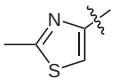
Table 2 Scope of the Aldehyde **6** for the Aldol Reaction with Cyclohexanone (**5**) Catalyzed by **4**

Entry	Aldehyde	Time (h)	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%)[d]
1	4-$NO_2C_6H_4$ (**6a**)	1	99	99:1	98
2	3-$NO_2C_6H_4$ (**6b**)	3	99	>99:1	>99
3	2-$NO_2C_6H_4$ (**6c**)	5	96	98:2	98
4	4-CNC_6H_4 (**6d**)	4	93	98:2	97
5	4-ClC_6H_4 (**6e**)	72	93	99:1	97
6	4-BrC_6H_4 (**6f**)	72	90	99:1	96
7	Ph (**6g**)	72	84	94:6	92
8	4-MeC_6H_4 (**6h**)	72	55	98:2	94
9	4-$OMeC_6H_4$ (**6i**)	72	39	96:4	93
10	1-Naphthyl (**6j**)	72	69	95:5	95
11	2-Furfuryl (**6k**)	72	69	99:1	97
12	4-Py (**6l**)	1	93	97:3	97
13	3-Py (**6m**)	3	95	99:1	99
14	2-Py (**6n**)	4	74	89:11	97
15	 (**6o**)	4	78	97:3	94
16	 (**6p**)	48	74	97:3	96

[a] The reaction was carried out with catalyst **4** (20 mol%) and TFA (20 mol%) in toluene at 0 °C.
[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.

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(8) **General Procedure for the Preparation of Catalysts 2−4:**
To a solution of Boc-L-Pro-$NHNH_2$ (for **2**) or *trans*-4-(*tert*-butyldimethylsilyloxy)-Boc-L-Pro-$NHNH_2$ (for **3** and **4**; 8.0 mmol) in toluene (20 mL) was added benzaldehyde (935 mg, 8.8 mmol). The reaction mixture was stirred at r.t. for 24 h, and then concentrated under reduced pressure. The residue was dissolved in MeOH (80 mL), and 5% Pd/C (0.2 g) was added. After stirring under hydrogen (1 atm) 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: PE−EtOAc, 3:1) to give *N*′-benzyl-Boc-L-proline hydrazide or *N*′-benzyl-*trans*-4-(*tert*-butyldimethylsilyloxy)-Boc-L-proline hydrazide.
To a solution of *N*′-benzyl-Boc-L-proline hydrazide or *N*′-benzyl-*trans*-4-(*tert*-butyldimethylsilyloxy)-Boc-L-proline hydrazide (2.0 mmol) in DMF (20 mL) were added Boc-L-Pro (for **4**) or *trans*-4-hydroxy-Boc-L-Pro (for **2** and **3**; 2.4 mmol), *N*,*N*-diisopropylethylamine (DIPEA, 700 μL) and HATU (922 mg, 2.4 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 24 h, and then concentrated under reduced pressure. The residue was dissolved in EtOAc. The organic phase was then washed with sat. aq $NaHCO_3$ and brine and dried over anhyd 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 was then treated with a mixture of TFA−CH_2Cl_2 (1:2, 20 mL). After stirring at r.t. 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 $NH_3 \cdot H_2O$ (3.0 M) as eluent to give a crude product, which was further purified

through column chromatography on silica gel (eluent: CH_2Cl_2 saturated with NH_3 gas−MeOH, 10:1) to give the final product.

(9) The following are the analytic data of catalyst **4**: $[\alpha]_D^{25}$ –43.2 (*c* = 0.206, MeOH); mp 59–62 °C. ^{1}H NMR (600 MHz, CD_3OD): δ = 1.57–1.72 (m, 4 H), 1.88−1.95 (m, 2 H), 2.66–2.71 (m, 2 H), 2.84–2.86 (dd, *J* = 3.90, 11.94 Hz, 1 H), 3.01–3.05 (m, 1 H), 3.71 (q, *J* = 8.46 Hz, 2 H), 4.21 (s, 1 H), 4.54 (br s, 1 H), 4.75 (br s, 1 H), 7.17–7.25 (m, 5 H). ^{13}C NMR (150 MHz, CD_3OD): δ = 25.6, 30.0, 39.4, 46.5, 50.5, 54.7, 57.5, 58.0, 71.8, 127.6, 128.3, 128.8, 135.4, 174.2, 175.6. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{25}N_4O_3$: 333.1921; found: 333.1915.

(10) **Typical Procedure for the Aldol Reaction of Aldehydes with Cyclohexanone:**
To a solution of **4** (12.6 mg, 0.04 mmol) in toluene (0.2 mL) were added cyclohexanone (210 μL) and TFA (3.1 μL, 0.04 mmol). After stirring at 0 °C for 15 min, aldehyde (0.2 mmoL) was introduced. The reaction was stirred at the same temperature until completion, and was then quenched with sat. aq solution of NH_4Cl. EtOAc was added to dilute the mixture. The organic layer was separated, washed with brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The residue was purified through column chromatography on silica gel (eluent: PE−EtOAc, 3:1) to yield the corresponding aldol products for further analysis.

(11) Further investigations, including computational studies, are needed to fully understand why catalyst **4** is superior to **1**. A plausible explanation is that the existence of the *trans*-4-hydroxyl group in **4**, which had no obvious effect on the solubility of the catalyst, favors the catalytic conformation that led to the major diastereomer and enantiomer.