Protonated *N*′-benzyl-*N*′-prolyl proline hydrazide as highly enantioselective catalyst for direct asymmetric aldol reaction†

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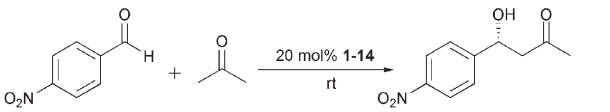
Protonated *N*′-benzyl-*N*′-L-prolyl-L-proline hydrazide has been developed as a highly enantioselective catalyst for the asymmetric direct aldol reaction of aromatic aldehydes with ketones.

Proline catalysis in the asymmetric direct intermolecular aldol reactions[1,2] has recently received extraordinary attention due to its fundamental importance to the evolution of so-called organocatalysis.[3] The acidic proton of the carboxylic acid group of proline was shown to be critical for both the reactivity and stereoselectivity.[1b] However, such an acidic proton has been proven to be not indispensable by the finding that chiral aminoalcohol derived proline amides catalyze the same aldol reactions with high efficiency and excellent enantioselectivity.[4] A new window has thus been opened for developing new proline-based organocatalysts through modifying its carboxylic acid function. For such a kind of proline amide catalysts,[5] the hydrogen-bonding in the transition state involving the amide NH and the terminal hydroxyl group was demonstrated to be the key to their catalytic effectiveness in the aldol reactions. Along the same principle, we envisioned that properly substituted proline hydrazides could potentially also be developed into effective organocatalysts for the same aldol reactions. The additional nitrogen atom in the hydrazides should provide the catalysts with an excellent open site to anchor hydrogen-bonding elements. Here we describe the first example of chiral proline hydrazides as highly enantioselective catalysts for the direct intermolecular aldol reactions.

We first screened a series of easily prepared *N*′-substituted L-proline hydazides (**1–14**,Fig. 1) as the catalysts (20 mol%) in the model reaction of *p*-nitrobenzaldehyde with neat acetone. As shown in Table 1, the reactions with most of these catalysts were found to be sluggish, affording the product in low to moderate ee values. Interestingly, the catalyst with an *N*′-L-prolyl group that bears a free cyclic secondary amine (**12** in Fig. 1) stood out with much higher efficiency than the others (entry 14, Table 1). The conversion reached over 95% after 24 hours at room temperature. The reaction time was further shortened to 8 hours if one equivalent (based on the catalyst) of trifluoroacetic acid (TFA) was added (entry 15). Due to some side reactions,[6] only around 65% of isolated yield was obtained in both cases. On the other hand, catalyst **12** exhibited only moderate enantioselectivity (51%) in the absence of Brønsted acid, which was, however, significantly lifted to 83% in the presence of TFA (entry 15 *vs* 14). It should be noted that capping the secondary amine of the *N*′-prolyl group (see catalysts **13** and **14** in Fig. 1) was found to be detrimental to the reactivity of the catalyst (entries 16–18) even though the enantioselectivity was slightly enhanced (entries 16 and 17 *vs* 14

Table 1 Screening L-proline hydrazides as the catalysts in the direct aldol reaction of *p*-nitrobenzaldehyde with acetone[a]



Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1**	24	16	54
2	**2**	24	<5	n.d.[d]
3	**3**	24	<10	54
4[e]	**3**	24	<10	20
5	**4**	24	29	48
6	**5**	24	28	42
7	**6**	24	32	59
8	**7**	24	<10	17
9[e]	**7**	24	41	77
10	**8**	24	<10	n.d.
11	**9**	24	<10	n.d.
12	**10**	24	<10	n.d.
13[e]	**11**	24	<10	n.d.
14	**12**	24	67[f]	51
15[e]	**12**	8	65[f]	83
16	**13**	24	10	70
17[e]	**13**	24	30	90
18	**14**	24	<10	58

[a] Unless specified otherwise, the concentration of aldehyde is 0.1 M in neat acetone. [b] Isolated yield based on the aldehyde. [c] The ee values were determined by HPLC and the configuration was assigned as *R* by comparison of retention time. [d] Not detected. [e] 20 mol% TFA was added. [f] Conversion is more than 95%.

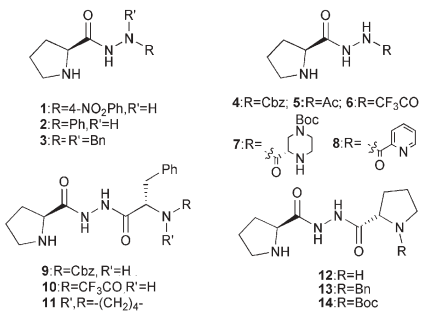


Fig. 1 L-Proline hydrazides evaluated in this study.

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and 15, respectively). Apparently, the existence of the $[HN\cdots H]^+$ group of the protonated *N′*-prolyl group of catalyst **12** is crucial to both the reactivity and enantioselectivity. To further optimize the structure of the catalyst, we thus fixed this protonated *N′*-prolyl substituent and turned our attention to the CO–NH–NH–CO unit of the hydrazide. Gratifyingly, installation of a benzyl group on the *N′*-position of **12** led to an excellent catalyst (**15** in Fig. 2), of which the catalysis in the model aldol reaction afforded excellent reactivity, enantioselectivity and isolated yield (entry 13 in Table 2).

Catalyst **15** was first examined for the model reaction in acetone at room temperature in the presence of an equal molar amount of TFA. The reaction was found to complete in 3 hours, affording 92% ee (entry 2). Again, due to the side reactions, only 54% isolated yield was obtained. As expected, both the reactivity and enantioselectivity of the catalyst sharply dropped in the absence of TFA (entry 1). Thus pre-mixed equal molar amounts of **15** and TFA (**15.TFA**) were used for further optimization of the reaction conditions.[7]

A survey of solvents with 20 mol% catalyst **15.TFA** revealed that most of the low boiling-point solvents with relatively low polarity are friendly to this catalytic system (Table 2). Consistently high ee values were obtained with all of the solvents listed in the table except DMF and DMSO, in either of which the reaction was extremely sluggish (entries 3 and 4). While the highest ee of 94% was obtained in either Et_2O or THF at room temperature (entries 8 and 9), the yield in the latter was slightly better than in the former. Up to 98% ee was achieved at −20 °C in THF with 88% isolated yield. Toluene turned out to be the best solvent to suppress the side reactions and in the meantime maintain high reactivity and enantioselectivity (entries 12–15). With this solvent, lowering the temperature from room temperature to 0 °C increased the ee of the product from 90% to 96% and more importantly, completely suppressed the side reactions, affording 95% isolated yield (entry 13). Lowering the temperature further to −20 °C had little effect on the ee whereas the reaction rate was strikingly decreased (entry 14). Under the optimal reaction condition, namely 20 mol% catalyst **15.TFA**, at 0 °C and with toluene as solvent, the model reaction was completed in *7 hours, affording 95% yield and 96% ee*. Decreasing the loading of the catalyst to 5% merely slowed down the reaction to some extent but didn't sacrifice either the yield or the enantioselectivity (entry 15).

Other aldehydes were also examined to expand the substrate scope of catalyst **15.TFA** under the optimal condition. As shown in Table 3, excellent enantioselectivities and yields were consistently obtained for the aromatic aldehydes with an electron-withdrawing group (entries 1–5). However, for the aromatic aldehydes with an electron-donating group or without any substitution, the reactions were much slower and less than 20% of isolated yields were obtained after 72 hours under the optimal conditions (entry 6 and 7). Interestingly, the ee values of the products remained at high levels. On the other hand, this catalytic system was proven to be totally ineffective for aliphatic aldehydes. Thus the present

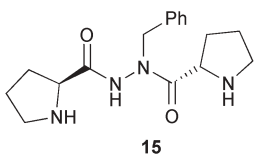

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Fig. 2 Structure of the optimised catalyst.

Table 2 Optimizing the reaction conditions with **15**[a]

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	Acetone	20	12	54	7
2	Acetone	20	3	54	92
3	DMF	20	24	<10	n.d[e]
4	DMSO	20	24	<10	n.d
5	DCM	20	11	69	90
6	DCE	20	3	73	89
7	CH_3CN	20	11	49	91
8	Et_2O	20	3	66	94
9	THF	20	3	70	94
10	THF	0	5	86	97
11	THF	−20	72	88	98
12	$PhCH_3$	20	3	84	90
13	**$PhCH_3$**	**0**	**7**	**95**	**96**
14	$PhCH_3$	−20	40	97	97
15[f]	$PhCH_3$	0	70	95	96

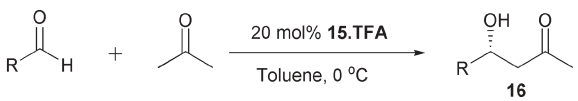
[a] Unless specified otherwise, 20 mol% **15.TFA** was used as the catalyst, the concentration of aldehyde is 0.1 M, and v/v of acetone/solvent is 1/4. [b] Isolated yield based on the aldehyde. [c] The ee values were determined by HPLC and the configuration was assigned as *R* by comparison of retention time. [d] No TFA was added. [e] Not detected. [f] 5 mol% catalyst was used.

hydrazide catalyst seems to be substrate-specific, and its application scope is limited to relatively electron-deficient aromatic aldehydes.

We also investigated some other ketone substrates (Scheme 1). With the catalysis of **15.TFA**, cyclohexanone gave a dr of 92 : 8 for the *anti*/*syn* products; with an ee of 92% for the major *anti* isomer. Cyclopentanone yielded a dr of 25 : 75 for the *anti*/*syn* products; with ee value of 67% and 74%, respectively.

Theoretical calculations have been performed to understand the high enantioselectivity with catalyst **15.TFA**.[8] As shown in Fig. 3, in the enamine intermediate, the optimal CO–N–N–CO dihedral angle was found to be nearly perpendicular. This is consistent with the observations from early computational studies on diacylhydrazines[9] and from our X-ray analyses of the single crystal of **12**.[10] When the aldehyde was added, a simple rotation of the protonated pyrrolidine (up left) could allow its NH to form a strong hydrogen bond with the hydrazide NH and the aldehyde (see **TS1** and **TS2**). The phenyl of the *N*-benzylic group in the enamine is reaching out towards the reaction center to avoid the steric interaction with the two carbonyl groups in the back. In **TS1**, which leads to the

Table 3 Aldol reactions catalyzed by **15.TFA**[a]



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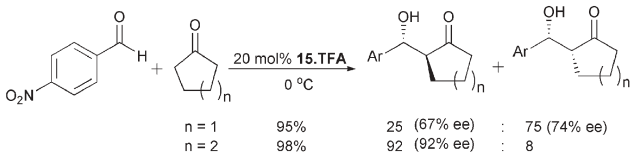
Entry	Product	R	Time (h)	Yield (%)[b]	ee (%)[c]
1	**16a**	4-NO_2Ph	7	95	96
2	**16b**	2-NO_2Ph	5	97	96
3	**16c**	3-NO_2Ph	5	86	96
4	**16d**	4-CNPh	21	97	92
5	**16e**	2-ClPh	24	75	96
6	**16f**	4-MePh	72	15	87
7	**16g**	Ph	72	17	90

[a] The concentration of aldehyde is 0.1 M, and v/v of acetone/toluene is 1/4. [b] Isolated yield based on the aldehyde. [c] The ee values were determined by HPLC and the configuration was assigned as *R* by comparison of retention time.



Scheme 1 Aldol reactions of 4-nitrobenzaldehyde with some ketones catalyzed by **15.TFA**.

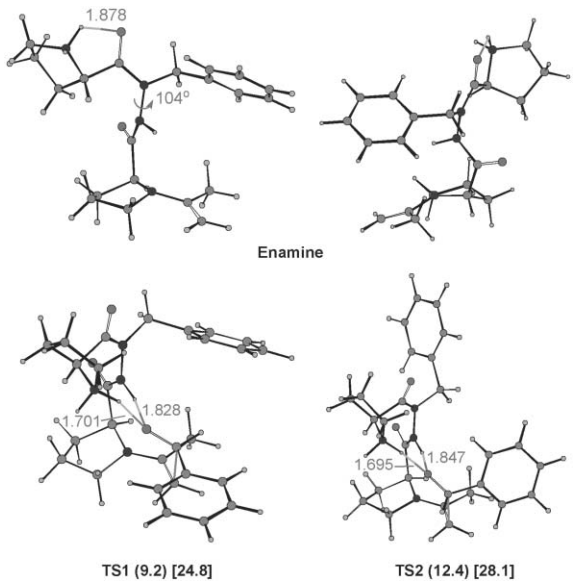


Fig. 3 The optimized structures of the enamine intermediate (in two views) and the transition states. The geometries were optimized with the HF/6-31G* method. The relative energies (kcal mol^{-1}) are from the B3LYP/6-311+G** method and the IEFPCM[13] solvation model. The activation enthalpies are in ( ) and the activation Gibbs free energies in [ ].

formation of the major product observed experimentally, this phenyl group is far away from the phenyl group of the aldehyde. However, in **TS2** this phenyl group has to turn back to make space for the phenyl group of benzaldehyde substrate, causing the structure to be less stable than **TS1** by about 3.3 kcal mol^{-1}. When the *N*-benzyl group is replaced by a hydrogen to model the situation of catalyst **12**, a much smaller preference of **TS1** over **TS2** ($\Delta\Delta G$ = 1.2 kcal mol^{-1}) is predicted by our calculations (see Supporting Information†) because of the absence of the above mentioned steric interaction. It should be noted that the secondary amine of the prolyl on the right-hand side of **15** should also be able to form enamine with acetone.[11] However, the catalytic effect of **15** in the aldol reactions was unambiguously proven not to result from the enamine formation with this prolyl but with the one on the left-hand side by the fact that *N*-benzylation of the former only slightly affects the reactivity and enantioselectivity[12] whereas *N*-benzylation of the latter totally deactivates the catalyst.

In conclusion, we have developed proline hydrazides as highly enantioselective catalysts for the asymmetric direct intermolecular aldol reactions. Catalyst **15.TFA** catalyzed the reactions of aromatic aldehydes and acetone with 87–96% ee. A theoretical study revealed that both the CO–N–N–CO group and protonated prolyl group are important for the reactivity of the catalyst and the benzyl substituent has certain contribution to the stereoselectivity.

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Notes and references

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6 Side reactions, especially dehydration of the product, is a common problem encountered with proline and most of its derivatives catalyzed intermolecular aldol reactions.

7 Addition of 0.5 equivalent of TFA significantly decreased both the reactivity and enantioselectivity. Addition of 1.5 equivalent of TFA also significantly decreased the reactivity, but didn't affect the enantioselectivity.

8 All calculations were performed with the *Gaussian03* program. *GAUSSIAN 03 (Revision C.02)*, Gaussian, Inc., Wallingford, CT, 2004. See ESI for full reference†.

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10 Crystal data for **12**: $C_{10}H_{18}N_4O_2$ (286 K). M = 226.28, orthorhombic, space group $P2_12_12_1$, a = 9.705 (1) Å, b = 7.660 (1) Å, c = 7.818 (1) Å, $\alpha = \beta = \gamma = 90°$, V = 581.23 (17) $Å^3$, Z = 2, ρ_{calc} = 1.293 mg m^{-3}, absorption coefficient = 0.093 mm^{-1}, F (000) = 244, total reflections collected 939, unique 823 (R_{int} = 0.0095), final R indices [$I > 2\sigma(I)$] were R_1 = 0.0351, wR_2 = 0.0751, GOF = 0.963. CCDC 281902. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511992h.

11 Both prolyl units of **15** were found to be iso-propylated when **15.TFA** was treated with excess acetone and $NaBH(OAc)_3$.

12 In the model reaction of *p*-nitrobenzaldehyde and acetone with the corresponding **Catalyst.TFA**, 79% of yield and 93% of ee were obtained under the same optimal reaction conditions.

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