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Novel Small Organic Molecules for a Highly Enantioselective Direct Aldol Reaction

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The great synthetic utility of the aldol reaction in organic synthesis has powered the rapid evolution of numerous highly enantioselective chiral catalysts.[1] The direct aldol reaction is atomically economic.[2] Shibasaki has reported the first example of a direct asymmetric aldol reaction catalyzed by heterobimetallic complexes.[3] Trost has designed a zinc complex for the direct catalytic asymmetric aldol reaction with high enantioselectivities.[4] Since the pioneering finding by List and Barbas III and their co-workers that L-proline could work as a catalyst in the intermolecular direct aldol reaction,[5] the concept of small organic molecules as catalysts has received great attention.[6,7] However, efficient organic catalysts other than chiral amino acids for asymmetric direct aldol reactions are scarce.[8] We seek to design small organic molecules with structural diversity for catalyzing organic transformations with high stereoselectivity and broad substrates. Here, we report on a novel class of organic catalysts, (*S*)-pyrrolidine-2-carboxamide with a terminal hydroxyl group, that efficiently catalyze the *direct aldol reactions of aromatic and aliphatic aldehydes in neat acetone with high enantioselectivities of up to >99% ee.*

The acid proton of proline is critical for the reactivity and stereoselectivity of the proline-catalyzed direct aldol reaction. L-Prolinamide (2-pyrrolidine-carboxamide) has been shown to be ineffective in catalyzing the direct aldol reaction.[6b] However, we found that L-prolinamides with a terminal hydroxyl group exhibited increased catalytic activity and enantioselectivity as compared with the parent L-prolinamide. This observation prompted us to study the direct aldol reaction catalyzed by L-prolinamides derived from L-proline and α,*β*-hydroxyamines, **1**−**3** (Figure 1). Compounds **1**−**3** were readily prepared from L-proline and corresponding *β*-amino alcohols by the known reaction sequences (see Supporting Information).

In the presence of 20 mol % **1**−**3**, the reaction of 4-nitrobenzaldehyde with neat acetone was examined under different conditions. Table 1 summarizes the results. This class of organic catalysts exhibited high catalytic efficiency. Chiral catalyst **1a** promoted the reaction with a high yield of 84% but a moderate enantioselectivity of 46% ee (entry 1), but it did not show an apparent difference in catalytic efficiency from its isomer **2a** (75% yield, 48% ee; entry 2). Compound **2b** afforded a superior level of stereocontrol to its diastereomer **1b** (entries 3 and 4). This indicates that the (*S*)-configuration of C_α (see **1** for labeling) matched the L-proline to enhance the stereochemical control. The catalysts **3c** and **3d** with (*S*)-conformation of C_α once again induced higher enantioselectivities (entries 7 and 8, 64% ee with **3c**; 69% ee with **3d**) than their diastereomers **3a** and **3b** (entries 5 and 6, 49% ee with **3a**; 44% ee with **3b**) that contain (*R*)-C_α. The (*S*)-configuration of C_β also contributed to the selection. The highest enantioselectivity of 69% ee was observed with (*S*,*S*,*S*)-pyrolidine-2-carboxylic acid (2′-hydroxyl-1′,2′-diphenyl-ethyl)-amine (**3d**) (entry 8). Upon the decrease of the reaction temperature, the yield was somewhat sacrificed, but the enantioselectivity increased significantly (entries 8−10). *High enantioselectivity of 93% ee was obtained for the reaction of 4-nitrobenzaldehyde with acetone at −25 °C (entry 10).*

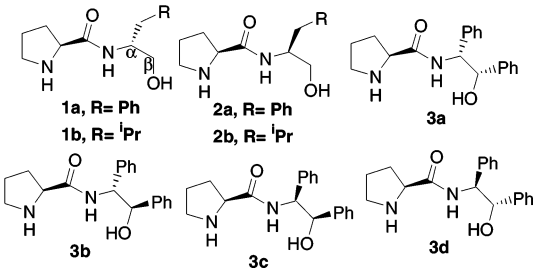

Figure 1. The small organic molecules evaluated in this study.

Table 1. Direct Aldol Reaction of 4-Nitrobenzaldehyde with Acetone Catalyzed by Organic Molecules **1**−**3**[a]

entry	catalyst	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	25	12	84	46
2	**2a**	25	12	75	48
3	**1b**	25	12	78	33
4	**2b**	25	12	89	52
5	**3a**	25	12	63	49
6	**3b**	25	12	77	44
7	**3c**	25	12	76	64
8	**3d**	25	12	89	69
9	**3d**	0	12	68	78
10	**3d**	**−25**	**24**	**66**	**93**

[a] The reaction was carried out in neat acetone with a concentration of 0.5 M. [b] Isolated yield. [c] The ee values were determined by HPLC, and the configuration was assigned as *R* by comparison of retention time.

The generality of catalyst **3d** in catalyzing direct aldol reactions with a variety of aldehydes including aromatic and aliphatic ones was examined under optimal conditions. The results are shown in Table 2. The aldol reactions of the aldehydes with acetone took place smoothly and were catalyzed by 20 mol % **3d** to give aldol adducts in moderate to high yields with high enantioselectivities of up to >99% ee. The observed enantioselectivities for both aromatic and aliphatic aldehydes appear to be systematically higher than those obtained with L-proline as the catalyst.[6a,9] This is attributed to the reduced temperature because of the high catalytic activity of **3d**. High enantioselectivities of up to 87% ee, but low yields, were given for α-unbranched aldehydes (entries 13 and 14).[10]

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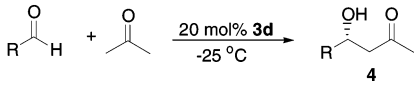
Table 2. Direct Aldol Reactions of Acetone with Aldehydes by Chiral Organic Catalyst **3d**[a]



entry	product	R	yield (%)[b]	ee (%)[c]
1	**4a**	4-NO_2Ph	66	93
2	**4b**	4-BrPh	77	90
3	**4c**	4-ClPh	75	93
4	**4d**	2-ClPh	83	85
5	**4e**	Ph	51	83
6	**4f**	α-naphthyl	76	81
7	**4g**	β-naphthyl	93	84
8	**4h**	4-MePh	48	84
9	**4i**	3-NO_2Ph	63	87
10	**4j**	*c*-C_6H_{11}	85	97
11	**4k**	*i*-Pr	43	98
12	**4l**	*t*-Bu	51	>99
13	**4m**	*n*-Pr	17	87[d]
14	**4n**	*n*-Bu	12	86[d]
15	**4j**	*c*-C_6H_{11}	77	98[e]
16	**4j**	*c*-C_6H_{11}	48	98[f]

[a] The reaction was carried out in neat acetone with a concentration of 0.5 M at −25 °C for 24−48 h (see Supporting Information). [b] Isolated yields. [c] Determined by HPLC. [d] Determined by GC. [e] Catalyzed by 10 mol % **3d**. [f] Catalyzed by 5 mol % **3d**.

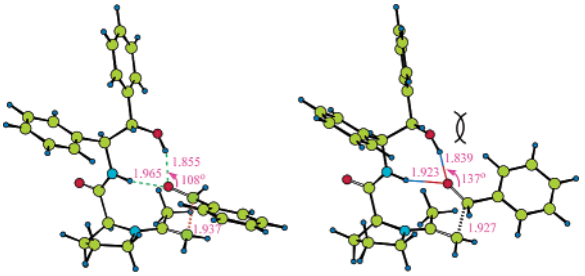


Figure 2. The calculated transition structure of the aldol reaction of benzaldehyde with acetone catalyzed by **3d**. The geometries were optimized with the HF/6-31G* method. The relative energies (kcal/mol) are with HF/6-31G* in ( ) and B3LYP/6-31G** in [ ].

It is noteworthy that the enantioselectivity of 98% ee was still provided for **4j** even with 5 mol % **3d** (entry 16).

Theoretical calculations have been carried out to understand the high enantioselectivity.[11] As shown in Figure 2, the best transition structures for the reaction of benzaldehyde with acetone are similar to those with proline as the catalyst,[12] except that here both the amide and the hydroxyl groups are hydrogen-bonded with the aldehyde to serve as the Lewis acid.[13,14] The hydroxyl group appears to be the better hydrogen-bond donor as indicated by the shorter hydrogen bond. The two phenyl groups of the hydroxylamine are in equatorial positions. **TS1**, which leads to the formation of the major product observed experimentally, is found to be much more stable than **TS2**. The phenyl group of benzaldehyde in **TS1** does not have steric interactions with anything. On the other hand, the phenyl group of benzaldehyde in **TS2** has a severe steric interaction with the hydroxyl group (H- - -H distance is only about 2.14 Å). The C═O- - -H(O) angle must open up to reduce the steric interaction.

In summary, we have presented the first successful example of using L-proline amino alcohol amides as catalysts for highly enantioselective direct aldol reactions of aldehydes with neat acetone. Catalyst **3d**, prepared from L-proline and (1*S*,2*S*)-diphenyl-2-aminoethanol, exhibits high enantioselectivities of up to 93% ee for aromatic aldehydes and up to >99% ee for aliphatic aldehydes. A theoretical study of transition structures demonstrates the important role of the terminal hydroxyl group in the catalyst in the stereodiscrimination. Our results suggest a new strategy in the design of new organic catalysts for direct asymmetric aldol reactions and related transformations because plentiful chiral resources containing multi-hydrogen bond donors, for example, peptides, might be adopted in the design. Research on such a strategy is now underway.[15]

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Supporting Information Available: Experimental procedures, NMR data for compounds **1**−**3**, HPLC spectra of **4a**−**c** and **4j**−**l**, GC spectra of **4m**,**n**, and Cartesian coordinates of **TS1** and **TS2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Dipeptide Pro-Thr-Me catalyzes the direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone in 69% ee at room temperature.

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