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(2*S*,5*S*)-Pyrrolidine-2,5-dicarboxylic acid, an efficient chiral organocatalyst for direct aldol reactions

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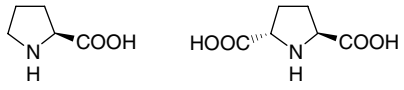
Abstract—Enantioselective aldol reaction of ketones with aldehydes catalyzed by (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid in the presence of an equal molar amount of Et_3N was described. By using the new chiral organocatalyst, the direct aldol condensation products were obtained in reasonable yields and up to 90% ee.

1. Introduction

Since the pioneering finding by List et al. that L-proline could catalyze the direct intermolecular aldol reaction,[1] proline-catalyzed aldol, Mannich, Michael, amination, and related reactions have been extensively studied.[2,3] Proline is so useful that it has been defined as a 'universal catalyst'. At the same time, various proline derivatives and structural analogues, such as small peptides,[4–6] diamines,[7,8] proline-amides,[9–11] pyrrolidinyltetrazoles,[12–14] sulfonamides,[15,16] prolinethio-amides,[17] proline hydrazides,[18] and α,α-diphenylprolinol silyl ethers[19] have been investigated and comparable or even better results were obtained in some cases.

The mechanism of proline-catalyzed aldol and related reactions has been studied by Houk et al. using computational methods.[20–22] These studies showed that the L-proline-catalyzed aldol reaction took place through an enamine intermediate, which was similar to an enzymatic process. It was proposed that the hydrogen-bonding between proline and electrophiles is crucial for achieving high asymmetric induction. For example, L-prolinamide (pyrrolidine-2-carboxamide) was ineffective in catalyzing a direct aldol reaction,[23] while proline-amides derived from β-amino alcohols promoted direct aldol reactions in high enantioselectivities.[9] A theoretical study of the transition state also demonstrated that the terminal hydroxyl group in the proline-type organocatalyst was vital to the stereodiscrimination.[9]

One of the proline derivatives (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid **1**[24] is C_2 symmetric and has two carboxylic acid groups. The C_2 symmetry of compound **1** could limit the number of transition states and reduce the possible routes during the approach of the enamine intermediate to the substrate, and improve the enantioselectivity in the aldol reaction. On the other hand, the additional carboxylic acid group might be beneficial to the formation of hydrogen-bonding and make the catalyst more efficient. Herein we report the preliminary results of our investigation on the direct asymmetric aldol reaction catalyzed by (2*S*,5*S*)-pyrroline-2,5-dicarboxylic acid **1**.



L-proline **1**

2. Results and discussion

Initially, the reaction of acetone and 4-nitrobenzaldehyde was studied as a model reaction. In the presence of catalyst **1** (30 mol %), 4-nitrobenzaldehyde was reacted with excess amount of acetone in DMSO at room temperature for 48 h, to afford the aldol product in an (*R*)-configuration in 22% yield and 63% ee (Table 1, entry 1). The addition of triethylamine dramatically speeded up the reaction rate

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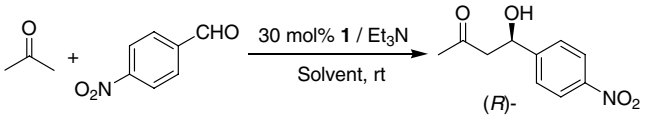
Table 1. Direct aldol reaction of acetone with 4-nitrobenzaldehyde catalyzed by organic molecule **1**



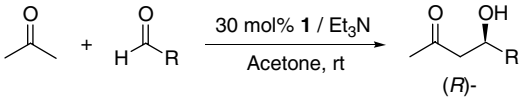
Entry	Et_3N (mol %)	Solvent[a]	Time (h)	Yield (%)[b]	ee (%)[c]
1	0	DMSO	48	22	63
2[d]	30	DMSO	72	NR	—
3	30	DMSO	3	60	62
4	15	DMSO	3	52	65
5	60	DMSO	3	50	65
6	30	Acetone	30	91	65
7[e]	30	Acetone	45	75	63
8[f]	30	Acetone	30	86	65
9	30	DMF	10	66	65
10	30	CH_3CN	48	62	63
11	30	CH_2Cl_2	48	79	57
12	30	THF	48	81	62

[a] Solvent/acetone = 4:1.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC using Chiralcel OJ column.
[d] Without catalyst **1**.
[e] Reaction temperature is 0 °C.
[f] Recovered catalyst was used.

and increased the yield of aldol product, while the enantioselectivity remained unchanged. For example, when 30 mol % of Et_3N was used, the reaction was accomplished in only 3 h, and the aldol product was obtained in 60% yield with 62% ee (entry 3). Other bases tested including pyridine, piperidine, and diethylamine, did not have a positive influence on the reaction. Houk et al. suggested that the rate-determining step is the formation of the enamine intermediate and the enantioselectivity-determining step is aldol addition.[21,25] The addition of Et_3N in our reaction might improve the reaction rate by promoting the enamine formation, which did not vary the ee value of the product. Although different solvents can be used in the aldol reaction catalyzed by catalyst **1**, the highest yield was achieved in pure acetone (entry 6). Decreasing the reaction temperature to 0 °C did not improve the enantioselectivity of the reaction, but dropped the yield of the desired product from 91% to 75% (entry 7). Thus acetone at room temperature is the most suitable condition regarding yield and enantioselectivity. We also investigated the recovery and reuse of catalyst **1**. After the reaction, catalyst **1** was filtered out and directly used in the second run of the reaction, resulting in only a slightly lower yield and the same level of enantioselectivity (entry 8).

Under the optimized reaction conditions, a variety of aldehydes were reacted with acetone. As illustrated in Table 2, the aldol reactions of the aromatic aldehydes with acetone proceeded smoothly, to furnish aldol adducts in moderate to high yields with ee values ranging from 47% to 73%. The aldehydes with an electron-withdrawing group on the phenyl ring were more active and gave higher yields (Table 2, entries 2–8), while those with an electron-donating group at the *para*-position of the phenyl ring were less active (entries 9–11). The yields achieved by the catalyst **1** for the aldol reaction of aromatic aldehydes in this work

Table 2. Direct aldol reaction of acetone with different aldehydes catalyzed by organic molecule **1**



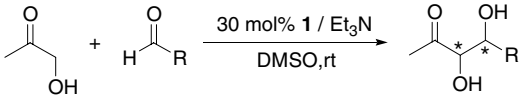
Entry	R	Time (h)	Yield (%)[a]	ee (%)[b]
1	C_6H_5	72	74	56
2	4-$NO_2C_6H_4$	30	91	65
3	2-$NO_2C_6H_4$	30	82	73
4	3-$NO_2C_6H_4$	30	95	60
5	4-ClC_6H_4	72	68	57
6	2-ClC_6H_4	48	99	55
7	3-ClC_6H_4	72	81	61
8	4-BrC_6H_4	72	74	55
9	4-MeC_6H_4	96	40	48
10	4-$MeOC_6H_4$	96	43	47
11	2-Naphthyl	72	56	54

[a] Isolated yield after column chromatography.
[b] Determined by chiral HPLC using Chiralcel AD-H column, except for entry 1, which was determined using Chiralcel OJ column.

were apparently higher than those obtained with the L-proline catalyst.[1,23] The higher activity of catalyst **1** might be attributed to the fact that both of its carboxylic hydroxyl groups could form hydrogen-bonds with the aldehyde. Unfortunately, catalyst **1** showed a very low activity in the reaction of aliphatic aldehydes with acetone (yields <10%).

Furthermore, hydroxyacetone could be used as a donor in the direct asymmetric aldol reaction with aldehydes. The 1,2-diol unit occurs frequently in natural products. Sharpless asymmetric dihydroxylation of (*E*)-olefins[26] and proline-catalyzed aldol reaction[27] could afford *syn*-1,2-diols and *anti*-1,2-diols, respectively. As shown in Table 3, the 2,3-dihydroxyketones were formed in good yields with up to 90% ee in the aldol reaction of hydroxyacetone and aromatic aldehydes by using catalyst **1**, although the diastereoselectivities were poor (dr ranges from 1:1 to 1.5:1).

Table 3. Direct aldol reaction of hydroxyacetone with aldehydes catalyzed by organic molecule **1**

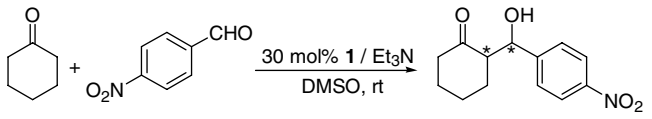


Entry	R	Time (h)	dr[a]	Yield (%)[b]	ee (%)[c]
1	C_6H_5	48	1.5:1	53	90/38
2	4-$NO_2C_6H_4$	10	1.4:1	68	79/84
3	3-$NO_2C_6H_4$	5	1.0:1	77	75/87
4	4-ClC_6H_4	48	1.3:1	60	85/60
5	2-ClC_6H_4	48	1.0:1	60	28/87

[a] The dr was determined by ^1H NMR spectroscopy.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC using Chiralpak AD-H column.

Cyclohexanone was also examined as a donor in the asymmetric aldol reaction. In the presence of catalyst **1**, cyclohexanone reacted with 4-nitrobenzaldehyde to generate

an aldol adduct in moderate yield. The diastereomeric ratio (*syn*/*anti*) is 3:2 according to ^{1}H NMR analysis. The enantiomeric excesses were 88% for the *syn*- and 87% for the *anti*-isomer, where L-proline provided 67% ee for the *syn*- and 89% ee for the *anti*-isomer.[23] It was reported that there were 24 reasonable transition states in the reaction of cyclohexanone enamines with aldehydes.[20] To a certain degree, the higher enantioselectivity proved that the C_2 symmetry of catalyst **1** could limit the number of transition states and improve the enantioselectivity.



55% yield, *syn* / *anti* = 3 /2
88% ee (*syn*), 87% ee (*anti*)

3. Conclusion

In conclusion, we have developed a new organocatalyst **1**, which was efficient for direct asymmetric aldol reaction in the presence of an equal molar of Et_3N. Further refinement of the catalyst structure and extension of the utility of this new organocatalyst to other organic processes, such as the Mannich reaction, are under active investigation.

4. Experimental

4.1. General

Acetone was dried from anhydrous K_2CO_3. DMSO and DMF were dried over CaH_2 and distilled under reduced pressure. THF was distilled from sodium-benzophenone. Dichloromethane and acetonitrile were distilled from CaH_2. ^{1}H NMR spectra were recorded on a Brucker-500 MHz spectrometer, $CDCl_3$ as solvent and TMS as the internal standard ($\delta = 0$ ppm). HPLC analysis was performed on Waters 510 with 2487 detector using Daicel Chiralcel OJ, OD-H or Chiralpak AD-H column. (2*S*,5*S*)-Pyrrolidine-2,5-dicarboxylic acid was prepared according to Yamamoto's method.[24] All starting materials were obtained commercially and used directly.

4.2. General procedure for the catalytic asymmetric aldol reaction of acetone and aldehydes

To a suspension of (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (12 mg, 0.075 mmol) and Et_3N (10 μL, 0.075 mmol) in 2.5 mL acetone was added 4-nitrobenzaldehyde (38 mg, 0.25 mmol). The resulting mixture was stirred at room temperature for 30 h (monitored by TLC). After removing the solvent and purifying by column chromatography on silica gel, the desired product was obtained (46 mg, 91%), $[\alpha]_D^{20} = +35.0$ (*c* 0.2, $CHCl_3$). ^{1}H NMR: 8.14 (d, $J = 8.6$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 2H), 5.19–5.21 (m, 1H), 3.56 (s, 1H), 2.78–2.79 (m, 2H), 2.15 (s, 3H); Enantiomeric excess: 65%; determined by HPLC (Daicel Chiralcel OJ, hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, UV 254 nm): t_R 15.63 min for the (*R*)-isomer (major), and t_R 17.44 min for the (*S*)-isomer (minor).

The results for other aldehydes (0.25–0.5 mmol scale) according to the same procedure are summarized in Table 2, and their spectral data are in accordance with those reported in the literature.[23,28–30]

4.3. General procedure for the catalytic asymmetric aldol reaction of hydroxyacetone and aldehydes

To the solution of (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (24 mg, 0.15 mmol) and Et_3N (20 μL, 0.15 mmol) in 4 mL of anhydrous DMSO were added hydroxyacetone (1.0 mL) and aldehyde (0.5 mmol), and the resulting mixture stirred at room temperature (monitored by TLC). The reaction mixture was treated with saturated ammonium chloride solution, the layer was separated, and the aqueous layer extracted with ethyl acetate. The combined organic phases were washed with brine and dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel to afford the desired diol. The ratio of diastereomers was determined by ^{1}H NMR analysis, and the enantiomeric excesses were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH, UV 254 nm). The results are summarized in Table 3.

4.3.1. 3,4-Dihydroxy-4-phenyl-butan-2-one[31] (entry 1). Yield: 53%, dr = 1.5:1. Major isomer (*syn*-): ^{1}H NMR 7.33–7.30 (m, 4H), 7.26–7.24 (m, 1H), 4.93–4.91 (m, 1H), 4.40 (d, $J = 4.4$ Hz, 1H), 3.40 (br, 2H), 1.88 (s, 3H); Enantiomeric excess: 90%, hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, t_R 10.58 min (major) and 10.13 min (minor). Minor isomer (*anti*-): 7.33–7.30 (m, 4H), 7.26–7.24 (m, 1H), 4.93–4.91 (m, 1H), 4.29 (d, $J = 3.2$ Hz, 1H), 3.40 (br, 2H), 2.14 (s, 3H); Enantiomeric excess: 38%, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, t_R 39.62 min (major) and 60.81 min (minor).

4.3.2. 3,4-Dihydroxy-4-(4-nitrophenyl)-butan-2-one[32] (entry 2). Yield: 68%, dr = 1.4:1. Major isomer (*syn*-): ^{1}H NMR: 8.20–8.18 (m, 2H), 7.56–7.54 (m, 2H), 5.16 (d, $J = 2.4$ Hz, 1H), 4.35 (d, $J = 2.4$ Hz, 1H), 2.96 (br, 2H), 2.30 (s, 3H); Enantiomeric excess: 79%, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, t_R 29.99 min (major) and 43.99 min (minor). Minor isomer (*anti*-): ^{1}H NMR: 8.20–8.18 (m, 2H), 7.56–7.54 (m, 2H), 5.02 (d, $J = 4.6$ Hz, 1H), 4.40 (d, $J = 4.6$ Hz, 1H), 2.96 (br, 2H), 1.96 (s, 3H); Enantiomeric excess: 84%, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, t_R 21.52 min (minor) and 25.19 min (major).

4.3.3. 3,4-Dihydroxy-4-(3-nitrophenyl)-butan-2-one (entry 3). Yield: 77%, dr = 1.0:1. Major isomer: ^{1}H NMR: 7.77–7.73 (m, 2H), 7.57–7.54 (m, 2H), 5.22 (d, $J = 2.3$ Hz, 1H), 4.41 (d, $J = 2.3$ Hz, 1H), 2.62 (br, 2H), 2.07 (s, 3H); Enantiomeric excess: 75%, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, t_R 27.40 min (major) and 38.60 min (minor). Minor isomer: ^{1}H NMR: 8.30 (s, 2H), 8.18–8.16 (m, 2H), 5.04 (d, $J = 4.7$ Hz, 1H), 4.45 (d, $J = 4.7$ Hz, 1H), 2.62 (br, 2H), 2.34 (s, 3H); Enantiomeric excess: 87%, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, t_R 22.73 min (major) and 24.13 min (minor).

4.3.4. 3,4-Dihydroxy-4-(4-chlorophenyl)-butan-2-one[33] (entry 4). Yield: 60%, dr = 1.3:1. Major isomer: ^{1}H NMR: 7.38–7.37 (m, 4H), 5.03 (d, $J = 3.0$ Hz, 1H), 4.36 (d, $J = 3.0$ Hz, 1H), 2.97 (br, 2H), 2.29 (s, 3H); Enantiomeric excess: 85%, hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, t_R 9.66 min (major) and 8.79 min (minor). Minor isomer: ^{1}H NMR 7.38–7.37 (m, 4H), 4.99 (d, $J = 4.5$ Hz, 1H), 4.45 (d, $J = 4.5$ Hz, 1H), 2.97 (br, 2H), 2.29 (s, 3H); Enantiomeric excess: 60%, hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, t_R 10.65 min (major) and 14.20 min (minor).

4.3.5. 3,4-Dihydroxy-4-(2-chlorophenyl)-butan-2-one[27] (entry 5). Yield: 60%, dr = 1.0:1. Major isomer: ^{1}H NMR 7.57–7.55 (m, 1H), 7.34–7.20 (m, 3H), 5.30 (d, $J = 4.1$ Hz, 1H), 4.64 (d, $J = 4.1$ Hz, 1H), 2.98 (br, 2H), 1.81 (s, 3H); Enantiomeric excess: 28%, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, t_R 18.90 min (major) and 17.86 min (minor). Minor isomer: ^{1}H NMR: 7.46–7.45 (m, 1H), 7.34–7.20 (m, 3H), 5.47 (d, $J = 1.6$ Hz, 1H), 4.41 (d, $J = 1.6$ Hz, 1H), 2.98 (br, 2H), 2.34 (s, 3H); Enantiomeric excess: 87%, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, t_R 14.52 min (major) and 16.06 min (minor).

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