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4,4′-Disubstituted L-Prolines as Highly Enantioselective Catalysts for Direct Aldol Reactions

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Abstract: A new series of 4,4′-disubstituted prolines (**1a–h**) has been developed and tested as organocatalysts in the direct catalytic asymmetric aldol reaction of several aliphatic ketones with aldehydes. Catalyst **1g** affords the best enantioselectivities for this transformation. The reaction was carried out in DMF using a catalyst loading of 10 mol% at −10°C to give the aldol products in up to 97% *ee* for acetone. In the cases of cyclohexanone and cyclopentanone, the corresponding *anti*-products were obtained in 94% *ee*.

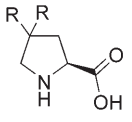
Keywords: direct aldol reaction; disubstituted L-prolines; enantioselectivity; organocatalysis

Introduction

The aldol reaction is recognized as one of the most fundamental tools for the construction of new carbon-carbon bonds in organic synthesis.[1] The great synthetic utility of the aldol reaction has prompted the rapid evolution of numerous highly enantioselective chiral catalysts.[2] In general, asymmetric catalytic aldol reactions are mainly classified into the following categories: a) chiral auxiliary-based aldol reactions; b) Lewis acid-catalyzed Mukaiyama-type and chiral Lewis base-catalyzed aldol reactions; and c) direct catalytic aldol reactions.[3] Among them, the direct aldol reaction is atom-economic.[4] On the other hand, although the proline-catalyzed intramolecular asymmetric aldol reaction (Hajos–Parrish–Eder–Sauer–Wiechert reaction) was discovered already in the 1970s,[5] the concept of organocatalysts has not received much attention until the pioneering studies on intermolecular catalytic direct asymmetric aldol reactions by List, Barbas III and their co-workers.[3,6] Since then, much effort has been made to develop new organocatalysts for this transformation.[7–12] Very recently, organocatalytic direct asymmetric aldol reactions in water were reported.[13] To date, most of the reported organocatalysts for the direct asymmetric aldol reactions and other closely related asymmetric reactions were designed by changing the carboxylic acid function of proline. However, less attention has been paid to the modification on five-membered ring of proline to improve the reactivity and enantioselectivity.[9f,g,14] Herein, we report the synthesis of 4,4′-disubstituted prolines, and their applications as catalysts in the direct asymmetric aldol reactions of several aliphatic ketones with aldehydes.

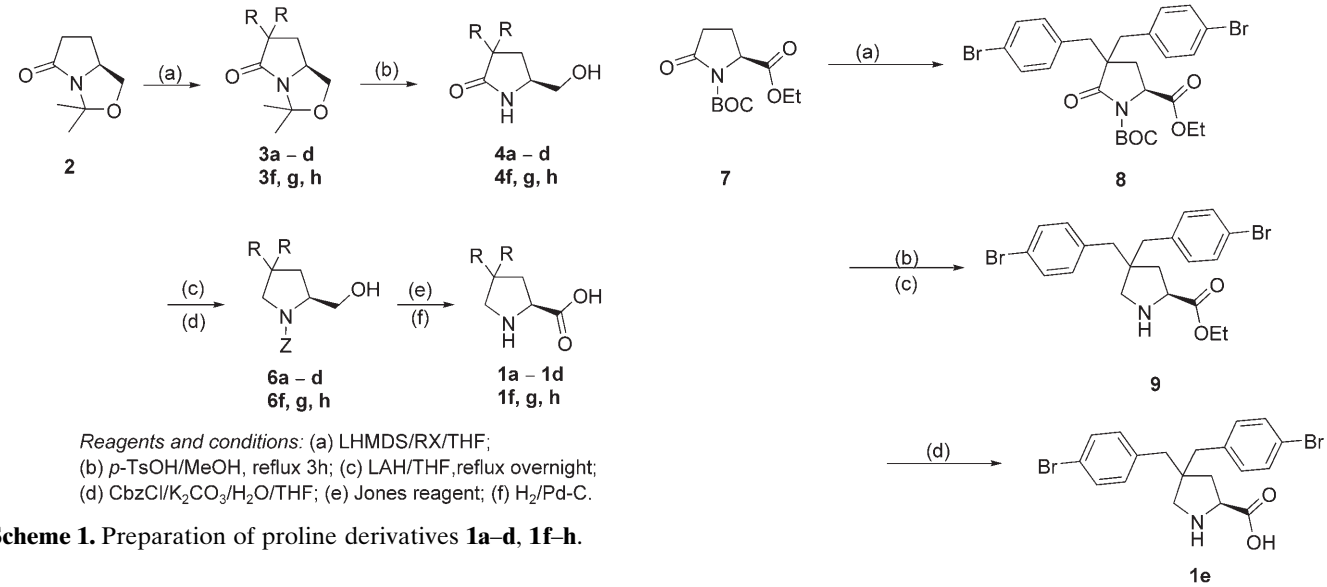
Results and Discussion

To study the steric and electronic effects of the 4,4′-disubstituted groups on the pyrrolidine ring, we firstly synthesized a new series of proline derivatives **1a–h** (Figure 1). The disubstituted lactams **4a–d** and **4f–g** were prepared from L-glutamic acid according to the reported procedure.[15,16] Scheme 1 depicts the sequence for the synthesis of proline derivatives **1a–d** and **1f–h**. Thus, double alkylation of **2** with alkyl halide followed by sequential deprotection, reduction, N-protection, oxidation of the alcohol and hydrogena-



1a R = CH_3 **1b** R = Benzyl
1c R = *p*-Fluorobenzyl **1d** R = *p*-Chlorobenzyl
1e R = *p*-Bromobenzyl **1f** R = *p*-Methoxybenzyl
1g R = 1-Methynaphthyl **1h** R = 2,4,6-Trimethylbenzyl

Figure 1. 4,4′-Disubstituted prolines.



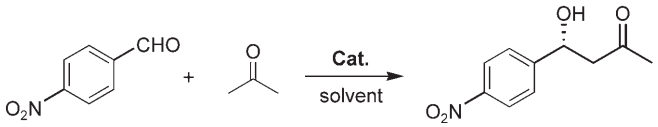
Scheme 1. Preparation of proline derivatives **1a–d**, **1f–h**.

Scheme 2. Preparation of proline derivative **1e**.

tion, furnished the disubstituted prolines **1a–d** and **1f**, **g**. Application of the same sequence did not give **1e** because a debromination reaction in the hydrogenation step occurred. The proline derivative **1e** was prepared in a different way from ethyl *N*-*tert*-butoxycarbonyl-L-pyroglutamate **7** as starting material.[17] Double alkylation of compound **7**, reduction of **8**, and acid hydrolysis of **9** gave the 4,4′-disubstituted proline **1e** (Scheme 2).[18]

Once the catalysts had been prepared, they were tested in the classical direct aldol reaction of acetone with *p*-nitrobenzaldehyde as model to examine their efficiency (Table 1). The reaction was initially per-

Table 1. Direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by proline derivatives **1a–h**.



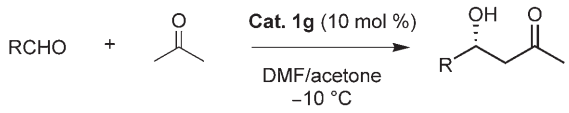
Entry	Catalyst	Loading [mol%]	Solvent	Time [h]	Temperature [°C]	Yield [%][a]	*ee* [%][b]
1	**1a**	10	Acetone	6	r.t.	89	75
2	**1b**	10	Acetone	1	r.t.	85	72
3	**1c**	10	Acetone	22	r.t.	90	79
4	**1d**	10	Acetone	5	r.t.	84	75
5	**1e**	10	Acetone	1	r.t.	78	71
6	**1f**	10	Acetone	16	r.t.	58	53
7	**1g**	10	Acetone	20	r.t.	86	90
8	**1g**	1	Acetone	120	r.t.	52	87
9[c]	Proline	30	DMSO/Acetone	4	r.t.	68	76[d]
10[c]	**1h**	10	DMSO/Acetone	7	r.t.	53	91
11[c]	**1g**	10	DMSO/Acetone	20	r.t.	60	95
12[c]	**1g**	5	DMSO/Acetone	20	r.t.	61	84
13[c]	**1g**	1	DMSO/Acetone	24	r.t.	7	83
14	**1g**	10	Acetone	20	0°C	82	86
15[e]	**1g**	10	DMF/Acetone	24	0°C	93	91
16[e]	**1g**	10	DMF/Acetone	48	-10°C	87	95

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] The reaction was carried out in DMSO/acetone (v/v: 4/1).
[d] Ref.[6].
[e] The reaction was carried out in DMF/acetone (v/v: 4/1).

formed in the presence of 10 mol% **1a–h** at room temperature for 1–22 h. Concerning the chemical yield and enantioselectivity, the catalysts **1a–h** (except **1f**) were more efficient than L-proline (Table 1). On decreasing the catalyst loading of **1g**, the enantioselectivity also decreased while the reaction time increased (Table 1, entries 8, 12 and 13). Changing the solvent to DMF and lowering the temperature to −10 °C, increased the *ee* up to 95%, with a reaction time of 48 h (Table 1, entry 16). Thus, 10 mol% of catalyst **1g** seems to be the appropriate catalyst loading to carry out the reaction.

After the best catalyst **1g** (10 mol%) and reaction conditions (DMF/acetone: 4:1, −10 °C) had been found, we used it in the reactions of acetone with different aldehydes, and the results are shown in Table 2.

Table 2. Direct aldol reactions of acetone with various aldehydes by catalyst **1g**.[a]

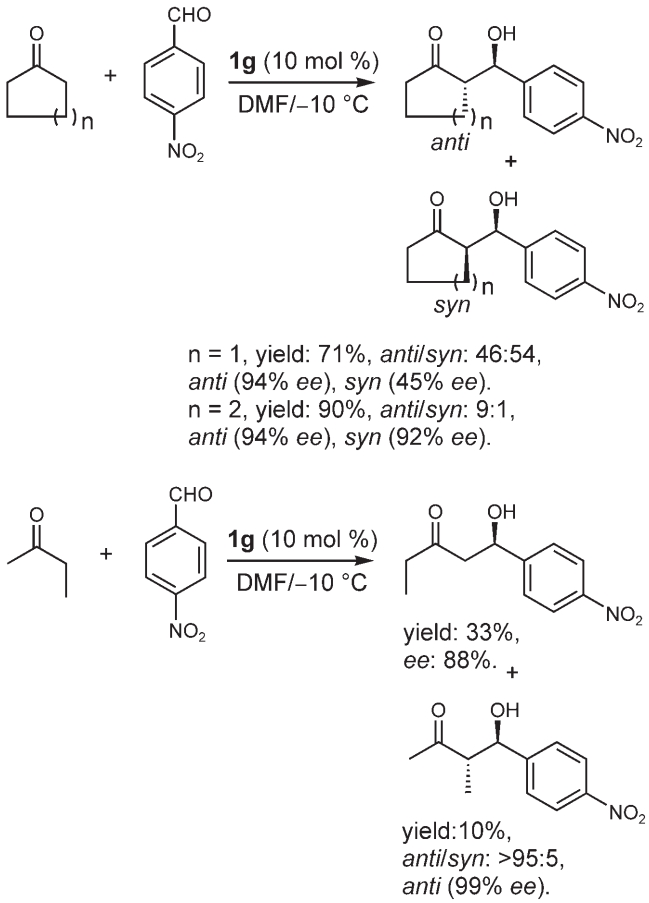


Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	4-$NO_2C_6H_4$	**10a**	87	95
2	4-BrC_6H_4	**10b**	96	96
3	4-ClC_6H_4	**10c**	97	92
4	4-$CF_3C_6H_4$	**10d**	62	94
5	4-FC_6H_4	**10e**	65	97
6	2,4-$Cl_2C_6H_3$	**10f**	77	90
7	Ph	**10g**	87	86
8	4-$MeOC_6H_4$	**10l**	31	84
9	α-naphthyl	**10h**	50	91
10	β-naphthyl	**10i**	70	88
11	*c*-C_6H_{11}	**10j**	70	92
12	*i*-Pr	**10k**	75	95

[a] The reaction was carried out in DMF/acetone (v/v: 4/1) at −10 °C for 48 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.

To our delight, high enantioselectivities for the electron-deficient aldehydes (Table 2, entries 1–6) were achieved, up to 97% *ee*. Less activated aldehydes, such as benzaldehyde, *p*-methoxybenzaldehyde, cyclohexanecarboxaldehyde or isobutyraldehyde also gave good to high enantioselectivities (Table 2, entries 7, 8, 11 and 12).

To demonstrate the scope of this aldol reaction, we probed reactions of cyclic ketones, such as cyclohexanone or cyclopentanone, promoted by 10 mol% **1g** in DMF at −10 °C (Scheme 3), cyclohexanone afforded a high diastereoselectivity (*dr* = 9/1) on using an activated aldehyde such as *p*-nitrobenzaldehyde. For both



Scheme 3. Aldol reaction of several aliphatic ketones with 4-nitrobenzaldehyde catalyzed by **1g**.

anti-isomer (major) and *syn*-isomer (minor), the achieved enantioselectivities were also very high, 94% *ee* and 92% *ee*, respectively. Cyclopentanone yielded a mixture of *anti*: *syn* products with lower diastereoselectivities (*dr* = 46/54), 94% *ee* and 45% *ee*, respectively. Then, an unsymmetrical ketone, 2-butanone, was tested; it gave a mixture of two regioisomers, and the major product was obtained with 88% *ee* while the minor product was obtained with > 99% *ee* (*anti*-isomer).

Conclusions

In summary, we have developed a series of new catalysts of the 4,4′-disubstituted proline family for an improved asymmetric direct aldol reaction. Catalyst **1g** gives good results for a range of substrates, furnishing the corresponding products in good yield with good to high enantioselectivities.

Experimental Section

(5*S*)-1-Aza-2,2-dimethyl-7,7-dimethyl-3-oxa-8-oxo-bicyclo[3.3.0]octane (3a)[15]

To a solution of **2** (10.0 g, 64.4 mmol) in dried THF (100 mL) was added LHMDS (128 mL, 135.7 mmol) at −78 °C and the mixture was stirred at that temperature for 2 h. Methyl iodide (30 mL, 160.4 mmol) was added and the resulting mixture was stirred for another 1 h. Then the reaction mixture was warmed to room temperature and stirred overnight. Saturated NH_4Cl solution (80 mL) was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (2×80 mL). The combined organic layer was washed with brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated to give a residue, flash column chromatography on silica gel (hexane:ethyl acetate = 5: 1) afforded **3a** as white solid; yield: 5.9 g (50 %).

(5*S*)-3,3-Dimethyl-5-hydroxymethylpyrrolidin-2-one (4a)[15]

To a stirred solution of **3a** (5.9 g, 32 mmol) in methanol (100 mL) at ambient temperature was added PTSA (0.38 mmol) in one portion and the reaction mixture was heated at reflux for 4 h. After cooling, the solvent was removed under vacuum and usual work-up afforded the essentially pure title compound **4a** as white solid; yield: 4.6 g (100 %).

(*S*)-(+)-(*N*-Benzyloxycarbonyl)-(4,4-dimethyl-pyrrolidin-2-yl)methan-1-ol (6a)

To a solution of LAH (7 g, 184 mmol) in dried THF (60 mL) was added slowly a solution of lactam **4a** (4.6 g, 32 mmol) in THF (60 mL) at 0 °C in a time of 45 min. After being stirred under reflux for 12 h and cooled to room temperature, the reaction mixture was slowly poured into a mixture of $Na_2SO_4{\cdot}10H_2O$ (300 g), H_2O (5 mL) and Et_2O (700 mL). The ether was concentrated to give **5a** as a yellow oil (4.6 g).

A solution of the oil **5a** (2.87 g, 22.5 mmol) without purification in THF (40 mL) was added to a solution of K_2CO_3 (1.9 g, 14 mmol) in water (10 mL) and the mixture was cooled in an ice/salt bath. Benzyloxycarbonyl chloride (4 mL 28 mmol) was added dropwise to the well-stirred reaction mixture in 30 min. The reaction mixture was stirred for 45 min in the ice/salt bath and then poured into crushed ice and water (50 mL). Sodium chloride was added to saturate the aqueous phase. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3× 30 mL). The combined organic phase was washed with 5 % aqueous HCl (20 mL), water (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated to obtain the crude product (red oil 6.40 g), which was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to give **6a** as a colorless oil; yield: 5.8 g (76 %).

4,4-Dimethyl-L-proline (1a)

A solution of product **6a** (5.8 g) in acetone (60 mL) was added slowly to a stirred solution of Jones reagent (17 mL) in acetone (50 mL) at −5 °C. After the addition was finished (3 h), the reaction mixture was stirred for 3 h at −5 °C. Methanol (10 mL) was added to the mixture, and it was stirred for 30 min. After being diluted with water 100 mL, the mixture was extracted with ethyl acetate (3×50 mL). The combined organic layer was successively washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated to give the crude product (colorless oil, 2.7 g). The crude acid (0.80 g) was dissolved in methanol (10 mL) and Pd/C (10 %, w/w) (0.25 g) was added. The mixture was stirred under 1 atm of hydrogen at room temperature. After 5 h, the catalyst was filtered, and the solvent was removed to obtain **1a** as a white solid; yield: 0.41 g (99 %).

Synthesis of Proline Derivative 1e

Ethyl (2*S*)-1-(*tert*-butoxycarbonyl)-4,4-di(*p*-bromobenzyl) pyroglutamate (8): To a solution of **7** (5.2 g, 20.1 mmol) in THF (50 mL) was added LHMDS (37.9 mL, 40.2 mmol) at −78 °C and the mixture was stirred at that temperature for 2 h. *p*-Benzyl bromide (10.25 g, 40.2 mmol) in THF (15 mL) was added and the mixture was stirred for another 1 h. Then it was warmed to room temperature and stirred overnight. Saturated ammonium chloride solution (80 mL) was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (2×80 mL). The combined organic layer was washed with brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated to give a residue, and flash column chromatography on silica gel (hexane: ethyl acetate = 20: 1) afforded **8** as a colorless oil; yield: 6.36 g (53.2 %).

Ethyl (2*S*)-4,4-di(*p*-bromobenzyl) prolinate (9): A 1.0 M solution of lithium triethylborohydride in THF (12.5 mL, 12.5 mmol) was added to a solution of **8** (6.23 g, 10.46 mmol) in THF (50 mL) at −78 °C under a nitrogen atmosphere in 20 min. After 40 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (12 mL) and warmed to 0 °C. H_2O_2 (30 %, 2.1 mL) was added and the mixture stirred at 0 °C. After 30 min the organic solvent was removed under vacuum and the aqueous layer extracted with CH_2Cl_2 (2×35 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was used without further purification. A solution of crude product and triethylsilane (1.80 mL, 11.27 mmol) in CH_2Cl_2 (60 mL) was cooled to −78 °C and boron trifluoride etherate (1.42 mL, 11.27 mmol) was then added dropwise under a nitrogen atmosphere. After 30 min, 1.80 mL of triethylsilane and 1.42 mL of boron trifluoride etherate were added. The resulting mixture was stirred for 2 h at −78 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL), extracted with CH_2Cl_2 (3×35 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 16: 1) afforded pure **9** as a colorless oil; yield: 3.18 g (65 % overall).

4,4′-Di(*p*-bromobenzyl)-L-proline (1e): To a solution of prolinate **9** in THF (30 mL) was added a solution of 6 N HCl (15 mL). The mixture was refluxed overnight. The resulting solution was evaporated to dryness, and the solid was triturated with acetone. Finally, the hydrochloride was dissolved in MeOH and an excess of propylene oxide was added. After evaporation of the solvent, the solid was triturated with ethyl ether and filtered; yield: 1.5 g (63 %).

General Procedure for Aldol Reaction of Ketone with Aldehyde

A mixture of aldehyde (0.5 mmol), catalyst (0.05 mmol) in neat acetone (2.25 mL) or in DMF/acetone (v:v = 4/1, 5 mL) was stirred at −10 °C (or in DMSO at room temperature). The reaction was monitored by TLC. It was then quenched with 5 mL saturated NH_4Cl solution, extracted with ethyl acetate (3 × 5 mL), and dried with over Na_2SO_4. Purification by flash chromatography afforded the corresponding pure products. The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AS, AD or OJ.

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