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Asymmetric aldol reactions catalyzed by new spiro diamine derivatives

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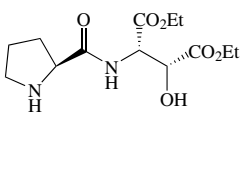
Abstract—Two new organocatalysts derived from L-proline and a novel chiral spiro diamine bearing a C_2 symmetric backbone, were introduced for an asymmetric aldol reaction in moderate to good asymmetric induction in up to 76% ee and high yields.

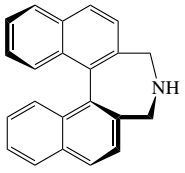
1. Introduction

The asymmetric aldol reaction, which is a basic C–C bond-forming method, constitutes a great challenge in synthetic chemistry. Among the different kinds of catalysts used, organocatalysis have contributed one of the most exciting advances in recent years.[1]

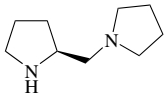
Proline has been found to be efficient in many asymmetric catalysis, such as dehydration, α-amination of aldehydes, Baylis–Hillman reaction, Michael addition, and α-alkylation of aldehydes.[2–9] In the case of the aldol reaction, List first reported the utility of this amino acid catalyst in 2000 with the highest ee of 96% for acetone with 2-methylpropanal. Similar to the reported enamine based mechanism with aldolase antibodies,[8] L-proline activates both the donor and acceptor, which are a ketone and aldehyde, respectively, during the reaction. High catalytic efficiency obtained indicates a convergence of biological and chemical approaches.[1] Meanwhile, many other organocatalysts containing a similar structure to proline or its derivatives have been developed, some of which exhibited high chiral inductions of 99%, 95%, and 83% ee with catalysts **1**,[10,11] **2**,[12] and **3**,[13] respectively. In a continuation of our studies on transition metal catalyzed synthetic transformation, we herein report a new chiral source bearing a rigid spiro diamine[14] named (*S*)-1,1′-spirobiindane-7,7′-diamine **6** to form two catalysts with L-proline for an aldol reaction.



1



(*S*)-**2**



(*S*)-**3**

2. Results and discussion

2.1. Preparation of organocatalysts 4 and 5

The procedure for the synthesis of the catalysts **4** and **5** is shown in Scheme 1 according to the reported method[10] but with the exception that the amino alcohol was replaced by the new chiral diamine. As expected, these two new catalysts could be obtained individually in one pot with the ratio determined by the amount of reactants used; increasing the amount of proline used, benefited the formation of catalyst **8**. Furthermore, when the ratio of reactants *N*-(*tert*-butoxy carbonyl)-L-proline and diamine **6** remained constant at 2:1, the ratio of products **7** and **8** relied on the reaction time and temperature. The formation of **8** was dominant if the reaction was kept for a further 3 h under refluxing conditions. Furthermore, using our procedure, acyl

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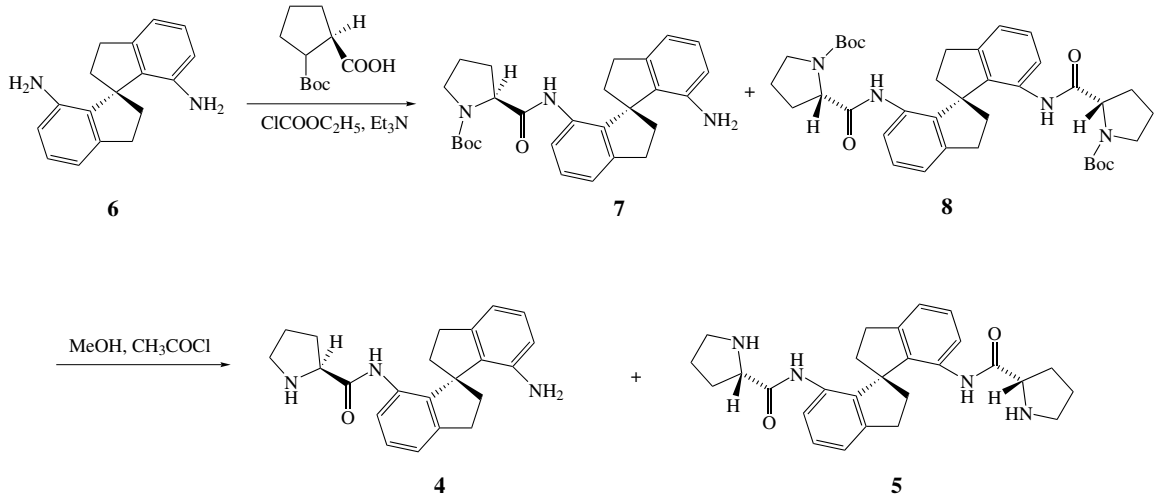


6 7 8 4 5

Scheme 1.

chloride in methanol was used instead of the Pd/C reagent to remove the BOC group.

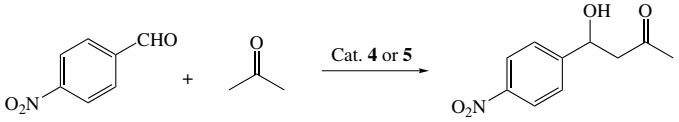
2.2. Optimization of reaction conditions

The influences of reaction conditions such as temperature, solvents, and amount of catalyst used were optimized in the catalytic aldol reaction of *p*-nitrobenzaldehyde and acetone, and the results are listed in Table 1.

In general, the reactions proceeded smoothly with higher yields than using the reported L-prolinamides.[10] Furthermore, in our case, it proved that solvents were not good for asymmetric induction as reported. In fact, 33% ee was obtained without solvents, while only 7–14% ee were found with either polar or apolar solvents (entries 1–7). Thus, the ensuing reactions were performed without solvents.

For the effects of reaction temperature, a lower temperature seemed to benefit the results.[1] For example, enantioselectivities increased from 33%, 38%, 45% to 52% when the reaction temperature decreased from 25, 0, −15 to −25 °C, respectively (entries 7–10). A lower temperature of −40 °C seemed to be unnecessary due to the unchanged results obtained, while longer reaction time was needed (entry 11). On the other hand, under the same reaction temperature, similar results were found when the catalyst loadings were decreased from 20%, 10%, 5%, 2% to 1% (entries 10, 12–15). It indicated the high catalytic activity of this new catalyst, while 20%

Table 1. Asymmetric aldol reaction of *p*-nitrobenzaldehyde with acetone catalyzed by **4** or **5**



Entry	Solvent	Temp (°C)	Time (h)	Cat.	Cat. loading (%)	Yield (%)[a]	ee (%)[b]
1	CH_3CN	25	3	**4**	10	75	14
2	DMF					70	12
3	CH_2Cl_2					73	11
4	Toluene					70	8
5	DMSO					70	8
6	Dioxane					70	7
7	None					92	33
8	None	0	3.5			90	38
9	None	−15	4			88	45
10	None	−25	4.5			87	52
11	None	−40	5			82	55
12	None	−25	4.5		20	87	53
13	None	−25			5	85	52
14	None	−25			2	81	51
15	None	−25			1	80	51
16	None	−25		**5**	1	70	48
17	None	−25			1	75	52

[a] Isolated yield based on aldehyde.
[b] Ee values were determined by HPLC, and the configuration was assigned as *R* by comparison of retention time reported.[10]

catalyst was needed to be used in the literature. Catalyst **5** was also synthesized and applied in this reaction to give similar results (entries 16 and 17).

2.3. Asymmetric Aldol reactions with other aldehydes

Asymmetric aldol reactions with other aldehydes were carried out under the optimized reaction conditions by **4**. As shown in Table 2, moderate to good selectivities were obtained for aromatic aldehydes with better results for alkyl analogues. The highest ee of 76% was observed for the reaction of cyclohexanecarboxaldehyde with acetone (entry 7).

3. Conclusion

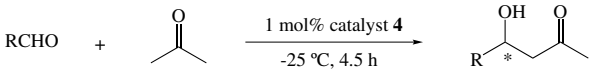
C_2 Symmetric spirocyclic chiral rigid diamine was introduced to form two new organocatalysts with L-proline for the intermolecular asymmetric direct aldol reaction in moderate enatiomeric selectivity (76% ee).

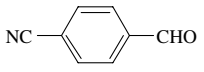
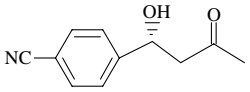
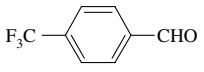
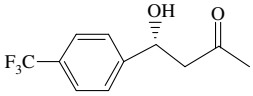
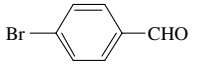
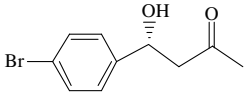
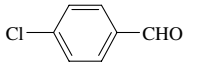
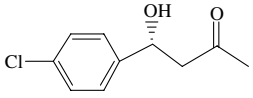
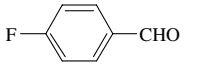
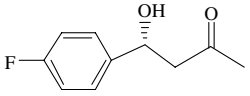
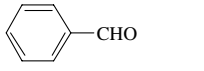
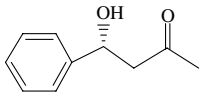
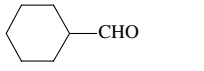
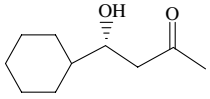
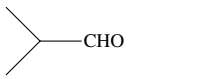
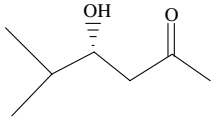
4. Experimental

4.1. Instrument and materials

^{1}H NMR spectra were recorded on a Bruker-300 MHz spectrometer with $CDCl_3$ as solvent. MS spectra were recorded on a Finnigan MAT 95 mass spectrometer. Elemental analysis was carried out using Carlo Erba-1106 Analyzer. Optical rotations were measured on Auto V Polarimeter at $\lambda = 589$ nm. Melting points were determined on a Yanaco microscopic melting point instrument without adjustment. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump), Chiralpak AS, AD columns were purchased from Daicel Chemical Industries Ltd. Acetone was purified by $KMnO_4$ and then dried over anhydrous K_2CO_3. Petroleum ether and ethyl acetate for column chromatography were distilled before use. Other materials were purchased from Aldrich or Acros. The procedure for the asymmetric aldol reaction was carried out according to a described

Table 2. Asymmetric aldol reaction of acetone with other aldehydes catalyzed by **4**[a]



Entry	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1			68	48
2			68	46
3			63	32
4			87	27
5			70	25
6			72	19
7			56	76
8			50	73

[a] The reactions were carried out under −25 °C for 4.5 h in the presence of 1 mol % catalyst **4**.
[b] Isolated yield based on aldehyde.
[c] The ee values were determined by HPLC. An (*R*)-configuration was assigned by comparison of the retention time.

method and the products were determined to be identical with those reported.[10]

4.2. Preparation of organocatalysts

Compound **7**: *N*-(*tert*-Butoxy carbonyl)-L-proline (0.43 g, 2 mmol) and triethylamine (0.28 mL, 2 mmol) were dissolved in THF (10 mL). The solution was cooled down to 0 °C. To the mixture was added ethyl chloroformate (0.19 mL, 2 mmol) dropwise for 15 min. After stirring for 30 min, chiral diamine **6** (0.25 g, 1 mmol) was added. The resulting mixture was stirred at room temperature for 5 h, and then diluted with ethyl acetate. After filtration and removal of solvent under reduced pressure, the crude product of **7** was obtained as a solid without further purification for next step. MS: 447 (M^+).

Compound **8** was prepared according to the same method described for **7** except that the final reaction temperature was 65 °C and the reaction time changed to 12 h. The crude product was also obtained with mass spectrum of 644 (M^+).

Compound **4** (*S*,*S*)-1,1′-spirobiindane-7-amine-7′-(pyrrolidine-2-carboxylic acid amide): **7** was added to a methanol solution containing a few drops of acyl chloride at 0 °C, the mixture was kept stirring at room temperature overnight. Methanol was then removed under reduced pressure, and the residue dissolved in ethyl acetate, after washing with saturated sodium carbonate solution. The organic solvent was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (dichloromethane–methanol = 80:1) to give white solid organocatalyst **4**. Yield: 85%. Mp 168–170 °C. $[\alpha]_D^{25} = -123.7$ (*c* 0.27, CH_2Cl_2). ^{1}H NMR δ (ppm) 1.25–1.68 (m, 4H), 2.12–2.27 (m, 6H), 2.59 (m, 1H), 2.93–3.03 (m, 4H), 3.30 (br s, 2H), 3.54 (m, 1H), 6.41 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.2 Hz, 1H), 7.02 (t, J = 7.8 Hz, 2H), 7.24 (m, 1H), 8.13 (d, J = 8.1 Hz, 1H), 9.31 (br s, 1H). MS (EI): 347 ($M^{+\cdot}$). Anal. Calcd for $C_{22}H_{25}N_3O$: C, 76.08; H, 7.20; N, 12.10. Found: C, 75.82; H, 7.48; N, 11.76.

Compound **5** (*S*,*S*,*S*)-1,1′-spirobiindane-7,7′-bis(pyrrolidine-2-carboxylic acid amide): **5** was prepared according to the same method described for **4**, except that **8** was used instead of **7** to give white solid. Yield 92%. Mp 234–236 °C. $[\alpha]_D^{25} = -92.2$ (*c* 0.27, CH_2Cl_2). ^{1}H NMR δ (ppm) 1.33–1.65 (m, 8H), 2.01 (m, 4H), 2.22 (m, 4H), 2.55 (m, 2H), 2.98 (m, 4H), 3.51 (m, 2H), 7.03 (d, J = 7.2 Hz, 2H), 7.23 (t, J = 7.8 Hz, 2H), 8.22 (d, J = 8.0 Hz, 2H), 9.28 (br s, 2H). MS (EI): 444 ($M^{+\cdot}$). Anal. Calcd for $C_{27}H_{32}N_4O_2$: C, 72.97; H, 7.21; N, 12.61. Found: C, 72.52; H, 7.47; N, 12.76.

4.3. General procedure for the aldol reaction

To a mixture of anhydrous acetone (1 mL) was added the corresponding aldehyde (0.5 mmol) and catalyst (0.005 mmol) and the reaction mixture stirred at −25 °C for 4.5 h. The reaction mixture was then treated with saturated ammonium chloride solution, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified through flash column chromatography on silica gel (eluent: PET–ethyl acetate = 2:1) to give pure products.

Acknowledgments

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