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Design, Synthesis and Catalytic Property of L-Proline Derivatives as Organocatalysts for Direct Aldol Reaction

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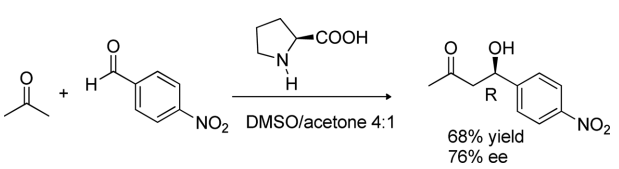
ABSTRACT. A series of chiral prolinamide compounds with pyridine-2, 6-dicarboxylic acid moieties derived from L-proline have been designed and synthesized, their catalytic properties for direct asymmetric aldol reactions were also studied in this article. These catalysts gave the aldol product in high yield (87%) and high enantioselectivity, up to 85%, of the anti-structure at room temperature but gave disappointing results at a lower temperature or when additive was added. Conditions, including solvents, temperature and additives were screened for the reactions. Moreover, the influence of presence of water on yield and stereoselectivity was also discussed.

Key words: Amides, Asymmetric catalysis, Asymmetric synthesis, Stereoselectivity, Stereoselective synthesis

INTRODUCTION

Aldol reactions play an important role in the development of organic synthesis-owing to their critical importance for the forming of carbon-carbon bond while concurrently one or two chiral centers come into beings. The first aldol reaction catalyzed by non-metal catalyst: Hajos-Parrish-Eder-Sauer-Wiechert reaction[1] discovered by Hajos, Parrish, etc. in 1970s, claimed the generation of organocatalyst for enantioselective aldol reaction. They took achirality triketone as substrate, which was treated with 30 mol% loading (*S*)-(−)-proline as catalyst, and got exciting results.[2]

The discovery that proline is a successful catalyst for aldol reaction lighted the interest in organocatalyst and it also has allowed previously difficult reactions to be successfully accomplished in a stereoselective manner. Moreover, the widespread presence of this functionality in natural products has made their construction a central focus of organic chemistry.[3] In 2000,[4,5] List and Barbas etc. performed direct aldol reaction between acetone and *p*-nitrobenzaldehyde, catalyzed by (S)-proline, resulting in 68% yield and 76% ee[6]. This reaction was called List-Barbas aldol reaction (*Scheme* 1), which is regarded as the real start of resurgence of organocatalysis.[7]



***Scheme* 1.** List-Barbas aldol reaction.

Proline has attracted significant attention in this area – particularly in the role of catalyzing aldol reactions.[8,9] Despite the utility of proline in facilitating aldol reactions, it's not without its shortcomings[13]: the reactivity and selectivity of some of these proline-catalyzed aldol reactions have serious limitations because of the difficulty in structurally modifying proline; a substoichiometric amount of proline is often necessary to achieve reasonable yields in the direct aldol reaction; proline is known to react with electron-deficient aromatic aldehydes to form iminium salts, which undergo decarboxylation, even at room temperature. Consequently, many organocatalysts (*Fig*. 1) derived from proline were discovered or synthetized, they have been created to provide an improved reactivity profile and are widely used in Aldol reaction, Mannich reaction and Michael reaction. Two commonly employed classes are the tetrazole **a**[10] and sulfonamides **b**$_1$–**b**$_3$[11], **c**$_1$–**c**$_3$.[12] Derivatives of 4-*trans*-hydroxyproline (e.g., *Fig*. 1, **b**$_1$–**b**$_3$) have been utilized in organocatalysis;[14] however, in actual synthesis of these organocatalysis, only one enantiomer of *trans*-hydroxyproline is readily available. It's also worth noting that most processes employed DMF or DMSO as reaction solvents, this obviously added the difficulty for

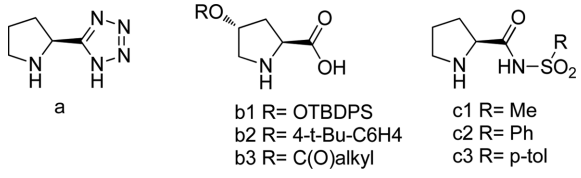
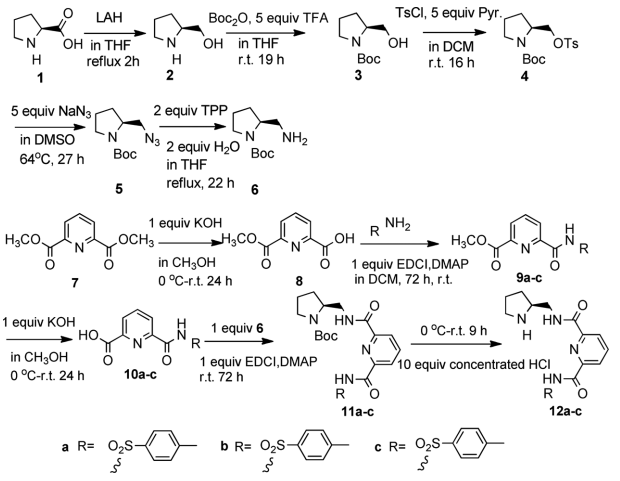


***Figure* 1.** Examples of proline-derived organocatalysts.



***Scheme* 2.** General synthesis route of designed organocatalysts **12a–c**.

product isolation. In response to these challenges, we designed and synthetized a series of organocatalysts **12a–c** (*Scheme* 2), and we hoped that they could provide improved results in the following test of catalytic performance.

The structures of designed catalysts **12a–c** are shown in *Scheme* 2. N-methylpicolinamide and N-sulfonyl amide groups were introduced because of the previous reports, N-methylpicolinamide was found to be a suitable group to bind a carboxyl molecule;[15,16] and the hydrogen bond between the aldehyde C–H and the sulfonamide S–O was considered as the key to the increased diastereoselectivity in "hua cat".[17,18] Their presence would theoretical possibly bring improvement in both reactivity and stereoselectivity. The introduction of alkyl group connecting with phenyl is expected to improve the solubility of the catalysts in commonly used organic solvents. Designed in this way, extra active sites were created; catalysts were estimated to perform in an enzyme-catalyzed manner. Catalytic effects of the catalysts that enhanced binding effects and improved stereoselectivity and solubility with small catalyst loading are aspired to acquire.

Dimethyl 2,6-pyridinedicarboxylate, a kind of inexpensive industrial product, is easily modified to bifunctional compound, so it's taken as the carrier of 2-N-methylpicolinamide and N-sulfonyl groups. Detailed procedures for preparing organocatalysts **12a–c** are outlined in *Scheme* 2.

Catalysts **12a–c** were synthesized in several steps starting from commercially available L-proline and Dimethyl 2,6-pyridinedicarboxylate. First, L-proline was reduced to N-Boc-(S)-2-aminomethyl-pyrrolidine, **6** through a very mature route.[20,21] The dimethyl ester was hydrolyzed selectively at only one of its two ester functions by 1.0 equiv KOH pellets in methanol at 0 °C to provide **8**, filtration procedure is avoided by an improved postprocedure comparing with the literature method.[22] The condensation reaction between **8** and corresponding amide provided **9a–c**. The other key intermidate **10a–c** was got by the hydrolysis of the remained ether function of **9a–c**. Combine **6** and **10a–c** by condensation reaction, then deprotect the N-Boc group of the resulted **11a–c**, the organocatalysts **12a–c** were finally obtained.

Aldol reaction between acetone or cyclohexanone and *p*-nitrobenzaldehyde is widely taken as template reaction to test the catalytic effects of catalyst newly synthetized.[23] Herein, we tested this series of catalysts in the reactions between *p*-nitrobenzaldehyde and cyclohexanone. The affection of catalyst, solvent, additive and the presence of water was respectively detected so as to optimize reaction condition and thus to get the best results. In view of the similarity of **12a–c**, only **12a** was taken to screen the factors in the experiments followed.

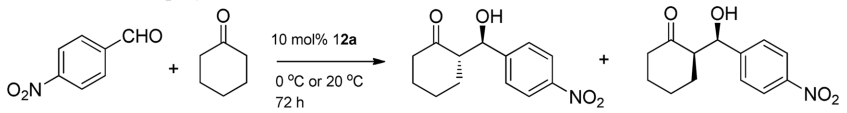
RESULTS AND DISCUSSIONS

Solvent employed in reaction was primary screened (*Table* 1) in order to simplify the following procedure.

As is shown in *Table* 1, variety of solvents resulted in enormous variation in yield and enantioselectivity: the adduct obtained in DCM, DCE, and solvent-free systems presented better results both in terms of diastereoselectivity and enantioselectivity than others, especially the value of dr in DCE, it's obviously higher than the others. Interestingly, enantiomeric excess for *syn*-diastereomer was remarkable when MeOH or water was used as reaction solvent, this phenomenon has been previously observed and reported,[24] so MeOH and water were also tested as solvents in the following experiments hoping to get higher enantiomeric excess for *syn*-diastereomer under optimized conditions. Lower temperature didn't lead to higher yield or enantioselecetivity as many workgroups reported. In view of these results, DCM, DCE, MeOH and water were taken as solvents in the following experiments (*Table* 2, 3) at 20 °C in which we would screen the best conditions for this system.

Addition of any of these additives didn't lead to higher yield or stereoselectivity, on the contrary, it lowered stereoselectivity by a great extent. The reaction process in MeOH or DCE was even restrained when $ZnCl_2$ was added, however, accelerated in DCM. The presence of water didn't bring any obvious alteration on both yield and stereoselectivity, so it's not considered as the affecting factors for

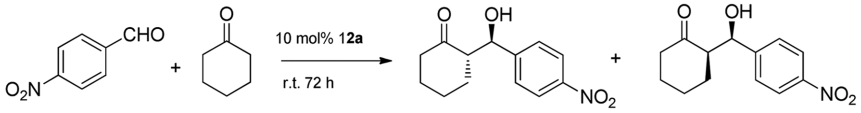
***Table* 1.** Primary selection of solvent employed in aldol reaction.[a]



Entry	Solvent	Time (h)	Temperature (°C)	Yield[b] (%)	Dr[c] (anti/syn)	Ee[c] (%) (anti)
1	MeOH	72	20	22	62:38	21(84)[d]
2	DCM	72	20	76	72:28	85
3	$CHCl_3$	72	20	26	74:26	48
4	DMF	72	20	19	68:32	28
5	DCE	72	20	54	87:13	68
6	Water	72	20	30	54:46	13(62)[d]
7	Neat	72	20	84	63:37	76
8	DMSO	72	20	43	49:51	47
9	*n*-hexane	72	20	Trace	–	–
10	DCM	120	0	57	69:31	80
11	DCE	120	0	44	66:34	75

[a]All the reactions were performed with 1.0 mmol of *p*-nitrobenzaldehyde, 1.0 mL of cyclohexanone, 10 mol.% catalyst **12a**, at 0 °C or 20 °C.
[b]Isolated yield.
[c]Determined by chiral HPLC for *anti*-diastereomer.
[d]Enantiomeric excess determined by chiral HPLC for *syn*-diastereomer.

***Table* 2.** Screening of various solvents and additives using catalyst 12a.[a]



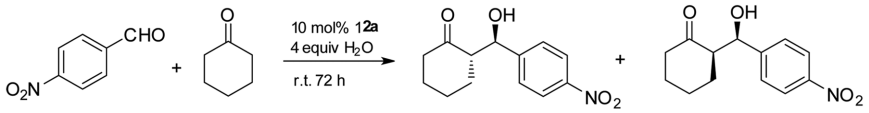
Entry	Additive	Solvent	Time (h)	Yield[b] (%)	Dr[c] (anti/syn)	Ee[d] (%)
1	Benzyl acid	Neat	72	99	68:32	43
2	Benzyl acid	Water	72	53	72:28	33(66)[e]
3	Benzyl acid	DCM	72	78	72:28	84
4	Benzyl acid	MeOH	72	Trace		
5	Benzyl acid	DCE	72	71	60:40	21
6	$ZnCl_2$	DCM	72	99	55:45	14
7	$ZnCl_2$	MeOH	72	Trace		
8	$ZnCl_2$	DCE	72	Trace		
9	Acetic acid	DCM	72	75	50:50	43
10	*o*-nitrobenzoic acid	DCM	72	87	83:17	45

[a]All the reactions were performed with 1.0 mmol of *p*-nitrobenzaldehyde, 1.0 mL of cyclohexanone, 10 mol % catalyst **12a**, 20 °C.
[b]Isolated yield.
[c]Determined by chiral HPLC.
[d]Determined by chiral HPLC for *anti*-diastereomer.
[e]Determined by chiral HPLC for *syn*-diastereomer.

this series of catalysts. What's disappointing, desired higher enantiomeric excess for *syn*-diastereomer reactions in MeOH or water by the addition of additives and (or) water was not observed.

The results for catalysts **12a–c** are presented in *Table* 4, moderate yield and high stereoselectivity (up to 85% ee and 72:28 dr for **12a** in DCM, up to 90:10 dr and 83% ee for **12c** in DCE) were obtained. Some exciting information with its own regularity was discovered that for any of the three catalysts, products obtained in DCM have general higher yield and enantioselectivity than that obtained in DCE. However, products obtained under the same conditions have general higher diastereoselectivity when DCE was employed as solvents. The variation of R-group didn't change the reaction mechanism, so the enantioselectivity of the products in *Table* 4 was similar to each other.

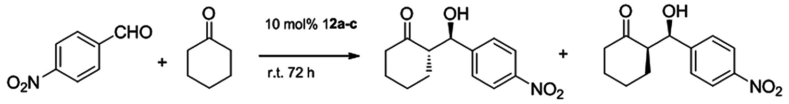
***Table* 3.** Effect of presence of water using catalyst 12a.[a]



Entry	Additive	Solvent	Time (h)	Yield[b] (%)	Dr[c] (anti/syn)	Ee[d] (%)
1	Benzyl acid	Neat/H_2O	72	99	66:34	76
2	Benzyl acid	DCM/H_2O	72	92	72:28	30
3	Benzyl acid	MeOH/H_2O	72	18	62:38	18(31)[e]
4	Benzyl acid	DCE/H_2O	72	73	60:40	2
5	$ZnCl_2$	DCM/H_2O	72	99	63:37	–44
6	$ZnCl_2$	MeOH/H_2O	72	Trace		
7	$ZnCl_2$	DCE/H_2O	72	Trace		
8	Acetic acid	DCM/H_2O	72	59	88:12	11
9	*o*-nitrobenzoic acid	DCM/H_2O	72	66	74:26	57

[a]All the reactions were performed with 1.0 mmol of *p*-nitrobenzaldehyde, 1.0 mL of cyclohexanone, 10 mol % catalyst **12a**, 4 equiv H_2O, 20 °C.
[b]Isolated yield.
[c]Determined by chiral HPLC.
[d]Determined by chiral HPLC for *anti*-diastereomer.
[e]Determined by chiral HPLC for *syn*-diastereomer.

***Table* 4.** Screening of various catalysts.[a]



Entry	Cat	Solvent	Time (h)	Yield [b] (%)	Dr[c] (anti/syn)	Ee[d] (%)
1	12a	DCM	72	76	72:28	85
2	12a	DCE	72	54	87:13	68
3	12b	DCM	72	81	66:34	81
4	12b	DCE	72	67	71:29	78
5	12c	DCM	72	87	82:18	83
6	12c	DCE	72	59	90:10	72

[a]All the reactions were performed with 1.0 mmol of *p*-nitrobenzaldehyde, 1.0 mL of cyclohexanone, 10 mol.% catalyst **12a–c**, without additive or water, 20 °C.
[b]Isolated yield.
[c]Determined by chiral HPLC.
[d]Determined by chiral HPLC for anti-diastereomer.

Synthesis Section

General

All reagents were commercial products. The reactions were monitored by TLC (thin layer chromatography). The column and preparative TLC purification were carried out using silica gel. Flash column chromatography was performed on silica gel (200–300 mesh). NMR spectra were recorded on a Bruker Avance 400 spectrometer at ambient temperature using $CDCl_3$ or DMSO-d_6 as solvents with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in ppm relative to TMS as the internal reference. Spectral patterns are designated as s = singlet; d = doublet; dd = doublet of doublets; q = quartet; t = triplet; br = broad; m = multiplet, coupling constant expressed in Hertz, integration, assignment of peak. FTIR spectra were recorded on a Varian 660-IR FTIR spectrometer and KBr discs were produced using a KBr press. Melting points were measured on a digital melting point apparatus. Optical rotations were measured on an AA series polAAr 20 automatic polarimeter. Analytical high performance liquid chromatography (HPLC) was carried out on Agilent 1200 instrument equipped with a diode array ultra-violet (UV) detector using Chiralpak AD (4.6 mm×250 mm).

Preparation and Characterization Data of Compounds 2–6[20,21]

Preparation of L-prolinol, 2.

Lithium aluminium hydride (7.6 g, 200 mmol) was placed in a 1 L reactor equipped with magnetic stirring, cooled to 0 °C. Then, dry, newly distilled THF (200 mL) was added and, after the temperature became stable again at 0 °C, L–proline (15 g, 130 mmol) was introduced portionwise as a solid, controlling the temperature to keep the system stay boiling without extra heat. The resulting mixture was refluxed for an hour and a half. After this time, the mixture was cooled to room temperature then 20% aqueous KOH solution (30 mL) was carefully added, and the mixture was filtered through Buchner funnel. The residue was refluxed with another 200 mL dry THF for 30 mins, then filtered through Buchner funnel. Filtrate was combined and concentrated under vacuum to afford clear oil (12.6 g, 127 mmol, 97% yield). The product was stored in the refrigerator without further purified until it was used.

Preparation of N-Boc-L-prolinol, 3.

L-prolinol (12.6 g, 127 mmol) was diluted with dry THF (160 mL) in a 400 mL flask and then a solution containing Boc_2O (27.3 g, 127 mmol) in THF (80 mL) was slowly added. The resulting mixture was stirred for 19 h at room temperature and then 20% aqueous citric acid solution (100 mL) was added. The layers were separated; the organic one was washed with saturated NaCl solvent (3×50 mL), dried with anhydrous sodium sulphate, filtered and concentrated under vacuum to afford a clear oil. The product was purified by flash chromatography through deactivated silica, eluting with methanol-dichloromethane (1:19) mixtures to obtain, after removal of the solvents, the title product as a faint yellow oil (23.3 g, 115 mmol, 91% yield). $[\alpha]_D^{20} = -39.7$ (c = 1.2, $CHCl_3$) The ^1H NMR was identical to the previously reported data[17]: ^1H NMR (400 MHz, $CDCl_3$): δ1.48 (s, 9H), 1.53 to 1.60 (m, 1H), 1.73 to 1.90 (m, 2H), 1.98 to 2.06 (m, 1H), 3.29 to 3.35 (m, 2H), 3.44 to 3.49 (m, 1H), 3.57 to 3.67 (m, 2H), 3.89 to 3.98 (br, 1H).

Preparation of (S)-tert-Butyl 2-(tosyloxymethyl)pyrrolidine-1-carboxylate, 4.

N-Boc-L-prolinol (9.7 g, 48 mmol) was dissolved in the mixture of 100 mL dichloromethane and 5 mL pyridine, cooled down to 0 °C. Then, *p*-toluenesulphonyl chloride (9.2 g, 48 mmol) was added, the mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was diluted with diethyl ether (150 mL) and washed with 1 M hydrochloric acid (3×100 mL), saturated sodium bicarbonate solution (3×100 mL) and, finally, water (2×100 mL). Then, the organic layer was dried with anhydrous sodium sulphate, filtered and concentrated under reduced pressure, affording a colorless oil. The crude product was purified by flash chromatography through deactivated silica, eluting with 15:1 dichloromethane-ethyl acetate mixture. After evaporation of the solvents, the title product was obtained as colorless oil (16.6 g, 47mmol, 97% yield). $[\alpha]_D^{20} = -39.7$ (c = 1.08, $CHCl_3$) The ^1H NMR was identical to the previously reported data[17]: ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 to 1.41 (br, 9H), 1.80 to 1.92 (m, 4H), 2.44 (s, 3H), 3.27 to 3.35 (m, 2H), 3.89 to 4.15 (m, 3H), 7.34 (br, 2H), 7.78 (d, 2H).

Preparation of (S)-tert-Butyl-2-(azidomethyl)pyrrolidine-1-carboxylate, 5.

(S)-tert-Butyl-2-(tosyloxymethyl)pyrrolidine-1-carboxylate (6.3 g, 17.7 mmol) was dissolved in dry DMSO (150 mL) and sodium azide (5.8 g, 90 mmol) was added. The reaction mixture was heated to 64 °C and stirred at this temperature for 27 h. After this time, the mixture was allowed to cool down to room temperature and it was diluted with diethyl ether (150 mL). The organic layer was washed with 3×80 mL water and 2×80 mL brine, dried with anhydrous sodium sulphate and concentrated under reduced pressure, to obtain the title product as a colorless oil (3.8 g, 16.8 mmol, 89% yield). The product was not further purified and was stored in the refrigerator until it was used. $[\alpha]_D^{20} = -45.4$ (c = 1.18, $CHCl_3$) The ^1H NMR was identical to the previously reported data[18]: ^1H NMR (400 MHz, d_6-DMSO): δ 1.45 (s, 9H), 1.74 to 1.82 (m, 2H), 1.86 to 1.93 (m, 1H), 1.98 to 2.05 (m, 1H), 3.26 (m, 1H), 3.36 to 3.41 (m, 2H), 3.49 (dd, 1H), 3.88 to 3.91 (m, 1H);

Preparation of N-Boc-(S)-2-aminomethylpyrrolidine, 6.

N-Boc-(S)-2-azidomethylpyrrolidine, **5** (3.2 g, 14 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL), triphenylphosphine (8.0 g, 30.5 mmol) and H_2O (0.5 mL) were added to it. The reaction mixture was heated to reflux temperature for 22 h until all starting material had been consumed (TLC monitoring). The organic solvent was then removed under reduced pressure and the remaining oil was dissolved in diethyl ether (200 mL). The pH of solution was adjusted to around 2 by using 1.0 mol/L HCl solution with vigorous stirring, and the aqueous phase was washed with diethyl ether (2×40 ml). The pH of the aqueous phase was adjusted to 13 by using 2.0 mol/L NaOH solution and extracted with CH_2Cl_2 (6×30 mL). The organic phase was dried with anhydrous sodium sulphate and concentrated under reduced pressure to afford the crude product **6** (2.3 g, 11.5 mmol, 82% yield) as colorless oil, which was not further purified for the further procedure. $[\alpha]_D^{20} = -56.2$

(c = 1.2, $CHCl_3$) The ^1H NMR was identical to the previously reported data[18]: ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.49 (m, 2H), 1.75 (m, 4H), 2.62(m, 1H), 2.77 (b, 1H), 3.26 (m, 2H), 3.75 (m, 2H).

Synthesis of 6-(methoxycarbonyl)pyridine-2-carboxylic acid, 8.[22]

Dimethyl 2,6-pyridinedicarboxylate (7.0 g, 36.0 mmol) was dissolved in methanol (150 mL), then the mixture was cooled to 0 °C and KOH (2.1 g, 36.0 mmol) was slowly added, the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 24 h. After that the solvent was removed under reduced pressure, and the residue was suspended in H_2O (100 mL), extracted with ethyl acetate (3×30 mL). The pH of aqueous layer was adjusted to about 2 with 1M HCl solution and extracted with chloroform (5×30 mL). The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure to provide the desired product **8** (4.3 g, 24 mmol, 66.5% yield) as a white solid: m.p. 144–146 °C. The ^1H NMR was identical to the previously reported data: ^1H NMR (400 MHz, DMSO-d_6): δ 8.12 to 8.24 (m, 3H), 3.93 (s, 3H); IR (KBr), ν/cm^{-1}: 3670-3073, 2964, 2852, 1725, 1581, 1325.

General synthesis of compounds 9a–c, 11a–c[26]

6-(methoxycarbonyl)pyridine-2-carboxylic acid, **8** was dissolved in dichloromethane, 1 equivalent of corresponding amine (for **11a–c**) or R-sulfamide (for **9a–c**), EDCI, DMAP was added consecutively. The reaction mixture was stirred at room temperature for 72 h. After that the solution was washed with 10% HCl solution and distilled water, the organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to provide an orange red oil, the crude product was purified by flash chromatography through deactivated silica, eluting with 19:1 dichloromethane-methanol mixture. After evaporation of the solvents, the title product was obtained as white solid.

Methyl 6-(tosylcarbamoyl)picolinate, 9a.

White solid, melting point 229–231 °C, 65% yield. ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H), 3.94 (s, 3H), 7.18 to 7.20 (b, 2H), 7.70 to 7.71(b, 2H), 8.05 to 8.19 (m, 2H), 8.17 to 8.19 (b, 1H); IR (KBr), ν/cm^{-1}: 3471–3267, 2924, 1754, 1596, 1340.

Methyl 6-((mesitylsulfonyl)carbamoyl)picolinate, 9b.

White solid, melting point 230–231 °C, 71% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H) 2.73 (s, 6H) 7.06 (s, 2H) 7.94 to 7.98 (t, 1H) 8.18 to 8.20 (b,1H) 8.35 to 8.37 (b, 1H).

Methyl 6-(((4-dodecylphenyl)sulfonyl)carbamoyl)picolinate, 9c.

White solid, melting point 189–191 °C, 69% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 0.63 to 0.79 (m, 6H) 0.97 to 1.17 (m, 13H) 1.51 to 1.57 (m, 4H) 2.45 to 2.47 (t, 2H) 3.95 (s, 3H) 7.17 to 7.20 (b, 2H) 7.38 to 7.40 (b, 2H) 7.94 to 7.98 (t, 1H) 8.18 to 8.19 (b, 1H) 8.35 to 8.36 (b, 1H).

(S)-*tert*-butyl 2-((6-(tosylcarbamoyl)picolinamido)methyl) pyrrolidine-1-carboxylate, 11a.

White solid, melting point 96–99 °C, 59% yield, $[\alpha]_D^{20}$ = –27.2 (c = 1.0, $CHCl_3$). ^1H NMR δ 1.45 (s, 9 H), 1.88 to 1.91 (m, 4H), 1.97 to 2.05(m, 2H), 2.47 (s, 3H) 3.37 to 3.50 (m, 1H), 3.51 to 3.57 (m, 1H), 3.91 to 4.11 (m, 2H), 7.25 to 7.30 (b, 2H), 7.97 to 8.01 (t, 1H) 8.08 to 8.11(b, 2H), 8.19 to 8.21 (b, 1H), 8.36 to 8.38 (b, 1H); IR (KBr), ν/cm^{-1}: 3595–3390,2974, 1708, 1658, 1186.

(S)-*tert*-butyl 2-((6-((mesitylsulfonyl)carbamoyl)picolinamido)methyl)pyrrolidine-1-carboxylate, 11b.

White solid, melting point 127–129 °C, 61% yield, $[\alpha]_D^{20}$ = –23.5 (c = 1.0, $CHCl_3$). ^1H NMR δ 1.48 (s, 9H), 1.87 to 1.90 (m, 4H), 1.98 to 2.16 (m, 2H), 2.31 (s, 3H), 2.74 (s, 6H), 3.38 to 3.51 (m, 1H), 3.53 to 3.58 (m, 1H), 4.43 to 4.45 (m, 2H), 6.94 (s, 2H), 7.95 to 8.00 (t, 1H), 8.18 to 8.21 (b, 1H), 8.35 to 8.36 (b, 1H).

(S)-*tert*-butyl 2-((6-(((4-dodecylphenyl)sulfonyl)carbamoyl)picolinamido)methyl)pyrrolidine-1-carboxylate, 11c.

White solid, melting point 58–60 °C, 52% yield, $[\alpha]_D^{20}$ = –19.7 (c = 1.0, $CHCl_3$). ^1H NMR δ 0.61 to 0.77 (m, 6H) 0.95 to 1.15 (m, 13H), 1.48 (s, 9H), 1.52 to 1.59 (m, 4H), 1.76 to 1.85 (m, 2H), 1.96 to 2.23 (m, 4H), 3.38 to 3.51 (m, 1H), 3.53 to 3.58 (m, 1H), 3.84 to 4.05 (m, 2H), 7.17 to 7.19 (b, 2H), 7.22 to 7.24 (b, 2H), 7.95 to 7.97 (t, 1H), 8.17 to 8.19 (b, 1H), 8.33 to 8.35 (b, 1H).

General synthesis of compounds 10a–c[25]

9a–c in mixed solvent (dichloromethane:methanol = 3:2) was cooled to 0 °C, 2equipment of 3M NaOH aqueous solution was added dropwise. The reaction mixture was stirred at 0 °C for 2 h, and then at room temperature for 12 h. The organic solvent was removed under reduced pressure and the residual was distilled with water. The aqueous solution was washed with ethyl acetate, after that pH of the aqueous layer was acided to 2 by 3M HCl solution, the resulted solvent was extracted repeatedly with dichloromethane, after that the organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure to provide the titled product as white solid.

6-(tosylcarbamoyl)picolinic acid, 10a.

White solid, melting point 234–235 °C, 92% yield. ^1H NMR δ 2.45 (s, 3H), 7.38 to 7.40 (b, 2H), 8.10 to 8.12 (t, 1H), 8.13 to 8.15 (b, 2H), 8.38 to 8.40 (b, 1H), 8.42 to 8.45 (b,

1H); IR (KBr), ν/cm^{-1}: 3466, 2956, 1711, 1580, 1331.

6-((mesitylsulfonyl)carbamoyl)picolinic acid, 10b.

White solid, melting point 229–231 ºC, 91% yield. ^{1}H NMR δ 2.30 (s, 3H), 2.75 (s, 6H), 7.08 (s, 2H), 8.08 to 8.10 (t, 1H), 8.27 to 8.30 (b, 1H), 8.41 to 8.43 (b, 1H).

6-(((4-dodecylphenyl)sulfonyl)carbamoyl)picolinic acid, 10c.

White solid, melting point 195–197 ºC, 82% yield. ^{1}H NMR δ 0.60 to 0.76 (m, 6H), 0.96 to 1.15 (m, 13H), 1.53 to 1.59 (m, 4H), 2.46 to 2.47 (t, 2H), 7.21 to 7.24 (b, 2H), 7.76 to 7.78 (b, 2H), 8.14 to 8.16 (t, 1H), 8.35 to 8.37 (b, 1H), 8.43 to 8.45 (b, 1H).

General Procedure of Aldol Reaction Between of *p*-nitrobenzaldehyde and Cyclohexanone[22,23]

1.51 g (1.0 mmol) *p*-nitrobenzaldehyde and 1.0 mL (9.6 mmol) cyclohexanone in 5 mL selected solvent was mixed in a 10 mL reaction flask, then 0.10 mmol catalyst (and 4 equiv water when needed) was added. The mixture was stirred for 72 h at given temperature. After that, solvent was removed under reduced pressure, the resulted residual was purified by flash chromatography through deactivated silica, eluting with 3:2 ethyl acetate-petroleum ether mixture. After evaporation of the solvents, the resulted adduct was obtained as white solid, melting point 147–149 ºC. ^{1}H NMR for *anti*, δ 1.31 to 1.45 (m, 1H), 1.51 to 1.67 (m, 3H), 1.78 to 1.87 (m, 1H), 2.06 to 2.17 (m, 1H), 2.36 (m, 1H), 2.45 to 2.65 (m, 2H), 4.09 (d, J=3.0 Hz, 1H, O*H*), 4.90 (br s, 1H, C*H*OH), 7.51(d, 2H), 8.21 (d, 2H); for *syn*, 3.20 (br, 1H, O*H*), 5.48 (br s, 1H, C*H*OH); IR (KBr), ν/cm^{-1}: 3730–3300, 2924, 1699, 1519, 1346, 854; Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 70:30), 20 ºC, 254 nm,0.5 mL/min, t_R (*syn* isomer) = 10.08 min (minor), 10.70 min (major); t_R (*anti* isomer) = 11.44 min (minor), 14.28 min (mayor).

General procedure of deprotection of 11a–c for 12a–c[22]

11a–c dissolved in dichloromethane was cooled to 0 ºC, 10 equiv of concentrated hydrochloric acid was added. The resulted mixture was stirred for 9 h, then the organic layer was removed under reduced pressure. The residual was diluted with dichloromethane and methanol (3:1), the pH of the solution was basified by ammonia to around 10. The mixture was concentrated under reduced pressure to obtain dry white solid, this crude product was purified by flash chromatography through deactivated silica, eluting with 15:5 dichloromethane-methanol mixture. After evaporation of the solvents, the title product was obtained.

(S)-N^2-(pyrrolidin-2-ylmethyl)-N^6-tosylpyridine-2, 6-dicarboxamide, 12a.

White solid, melting point 147–150 ºC, 99% yield, $[\alpha]_D^{20}$ = –27.1 (c = 1.0, $CHCl_3$). ^{1}H NMR δ 1.85 to 1.88 (m, 4H), 2.08 to 2.15 (m, 2H), 2.32 (s, 3H), 3.42 to 3.45 (m, 1H), 3.62 to 3.67 (m, 1H), 4.01 to 4.09 (m, 2H), 7.12 to 7.25 (b, 2H), 7.78 to 7.90 (t, 1H) 8.18 to 8.21(b, 2H), 8.24 to 8.25 (b, 1H), 8.33 to 8.35 (b, 1H); IR (KBr), ν/cm^{-1}: 3243, 2976, 2750 ,1708, 1670.

(S)-N^2-(mesitylsulfonyl)-N^6-(pyrrolidin-2-ylmethyl) pyridine-2,6-dicarboxamide, 12b.

White solid, melting point 165–167 ºC, 99% yield, $[\alpha]_D^{20}$ = –21.4 (c = 1.0, $CHCl_3$). ^{1}H NMR δ 1.88 to 1.90 (m, 4H), 1.90 to 2.14 (m, 2H), 2.30 (s, 3H), 2.77 (s, 6H), 3.42 to 3.44 (m, 1H), 3.64 to 3.68 (m, 1H), 4.01 to 4.04 (m, 2H), 7.12 to 7.24 (b, 2H), 7.78 to 7.91 (t, 1H) 8.17 to 8.21 (b, 2H), 8.24 to 8.25 (b, 1H), 8.34 to 8.35 (b, 1H).

(S)-N^2-((4-dodecylphenyl)sulfonyl)-N^6-(pyrrolidin-2-ylmethyl)pyridine-2,6-dicarboxamide, 12c.

White solid, melting point 128–130 ºC, 99% yield, $[\alpha]_D^{20}$ = –19.9 (c = 1.0, $CHCl_3$). ^{1}H NMR δ 0.62 to 0.77 (m, 6H) 0.96 to 1.16 (m, 13H), 1.53 to 1.59 (m, 4H), 1.76 to 1.85 (m, 2H), 1.99 to 2.43 (m, 4H), 3.24 to 3.26 (m, 1H), 3.36 to 3.40 (m, 1H), 3.82 to 4.04 (m, 2H),7.18 to 7.19 (b, 2H), 7.22 to 7.24 (b, 2H), 7.95 to 7.97 (t, 1H), 8.18 to 8.19 (b, 1H), 8.34 to 8.35 (b, 1H).

CONCLUSION

Generally, attempts to improve the enantioselectivity of catalyst **12a** by varying additive, water and temperature proved rewardless, for the best results were acquired under the original given condition. However the solvents were found to have significant effect on yield and stereoselectivity of the products.

The stereochemistry of the aldol reaction can be rationalized through the proposed transition state (*Fig.* 2). Here the carbonyl group of the aldehyde is activated by hydro-

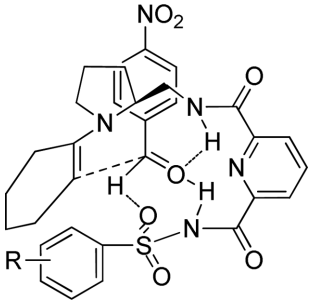


***Figure* 2.** Proposed transition state models for the aldol reaction catalyzed by **12a–c**.

gen-bonding with the amide N–H or sulfamide N–H, the enamine attacks the aldehyde on their face and leads to the formation of the favored *anti*-diastereomer as the major product. It's suggest that N–H of pyrrolidine and at least one of that between 2-N-methylpicolinamide and N-sulfonyl amide are vitally necessary to obtain desired enantioselectivity, the hydrogen bond between sulfonamide S–O and the aldehyde C–H along with the remained N–H promoted the improvement of enantioselectivity and assured high yield. It could be because that the pyrrolidin-2-ylmethyl moiety played a role of electron-donating group which possibly brought down the reactivity of the N–H of 2-N-methylpicolinamide, thus the reactivity of entire catalysts was lessened to some extent. Catalysts with unreduced proline moiety or introduction of electrophilic substituent groups in the α-position of (S)-pyrrolidin-2-ylmethanamine are being under consideration in order to increase the reactivity of target catalysts.

In conclusion, we have designed and synthesized a series of proline-derived compounds with Pyridine-2,6-dicarboxylic acid moieties **12a–c** as organocatalysts for asymmetric aldol reaction, bearing both N-methylpicolinamin and N-sulfonyl. These catalysts gave the aldol adduct in high yield (up to 87%) and high enantioselectivity (up to 85% ee) under mild conditions, they were also proved to have better solubility in most of commonly used solvents. Conditions, including temperature, additives and solvents were screened; however original given condition was finally proved to be most suitable for these catalysts. Conditions needed in this system that room temperature and absence of additive could be considered as an improvement since in several cases the reaction temperature usually was below 0 °C or even lower, and additives were commonly necessary. What's more important, the regular relationship of dr and ee, affected by solvent employed (DCE and DCM in this article), is reported for the first time.

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