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Efficient Novel Prolinamide-Based Organocatalysts for Aldol Reactions in Aqueous Media

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New and novel prolinamide organocatalysts were synthesized from L-proline and *trans*-4-hydroxy-L-proline under optimized conditions (93%–97% yield). The catalytic potential of both catalysts was assessed in direct aldol condensation reactions between cyclohexanone and 4-nitrobenzaldehyde. Different solvents were used to study the solvent effect to generate good yields. Water was found to be the most effective solvent, giving the highest yield of 81%. Enantioselectivities and diastereoselectivity of the aldol products formed through the use of the synthesized catalysts gave moderate to good yields and stereoselectivity.

Key words: Aldol reaction; organocatalyst; proline; enantioselectivity; prolineamide

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Aldol condensation is an important asymmetric reaction that creates β-hydroxycarbonyl compounds, which are found in biologically active natural and pharmaceutical compounds[1]. List *et al*. (2000) had successfully used L-proline as the organocatalyst to facilitate aldol reaction in constructing large molecules from smaller molecules. Since its discovery, L-proline-catalysed aldol reactions have generated many interests among synthetic chemists. Nevertheless, there are numerous drawbacks in the use of proline as catalyst, including moderate stereoselectivities and dehydration of by-products[2]. In addition, L-proline catalysis of aldol reactions in water may lead to racemic products[3].

Water tends to inhibit the catalytic activity or alter the enantioselectivity by interrupting the ionic interactions and hydrogen bonds among molecules, which is critical for stabilizing the transition state of a reaction[4]. Furthermore, non-polar organic compounds are less soluble in water. Water is made of small molecules, however, it has high polarity. Its three-dimensional hydrogen bonded network system provides some unique properties, which include large cohesive energy density, high surface tension, and hydrophobic effect[5].

Considering these facts, proline derivatives, such as prolinamides, have been studied and designed to give high enantioselectivities and diastereo-selectivity of reactions[6]. In this study, L-prolinamide derivatives bearing an apolar substituent and amine catalysts bearing the hydrophobic region were introduced to investigate their capability as catalysts. It was predicted that such prolinamide derivatives could act as ideal models to be used in aqueous media.

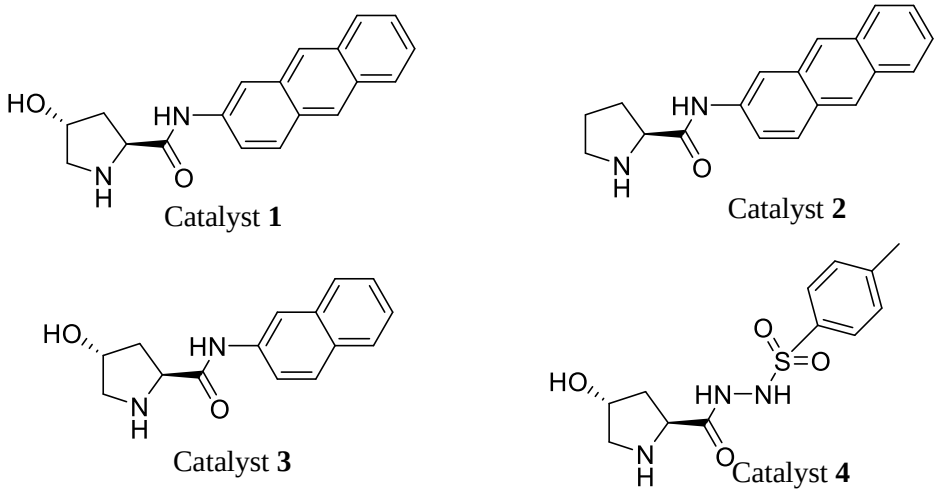

Figure 1. Structures of synthesized organocatalysts

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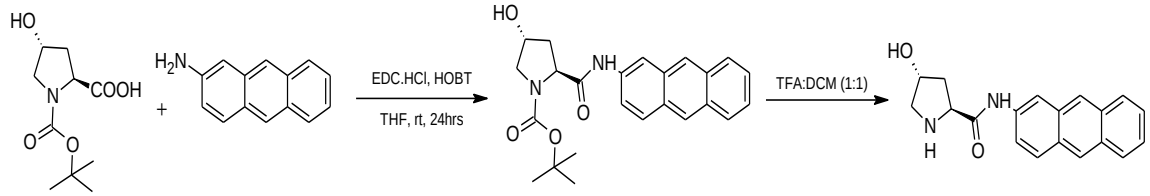
Two factors that appear crucial for the development of an efficient organocatalyst in an aqueous environment are its hydrophobic/hydrophilic properties and acidity[7]. By introducing 2-aminoanthracene into proline moiety, it was postulated that the prolinamide containing aromatic groups would increase the efficiency of the catalyst and isolate the transition state from water. In addition, the amidic-NH group is key to forming the hydrogen bond by activating the substrate[8,9]. As for the amine substituent, it acts as a nucleophilic catalyst in water and becomes increasingly effective with decreasing base strength of the amine catalyst[10].

For comparison purposes, *trans*-4-hydroxy-L-proline was needed to evaluate the effectiveness of hydrogen bonding and the capability of steric interactions of both organocatalysts. The study aimed to assess the role of hydrophobic (bulky area of benzene ring) and hydrophilic functions of designated prolinamide in increasing the enantioselectivities and diastereoselectivity of aldol reactions.

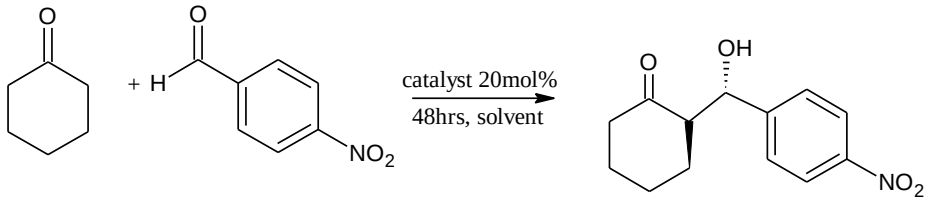
RESULTS AND DISCUSSION

Catalysts **1** and **2** were prepared from the commercially available 2-aminoanthracene and the corresponding BOC-*trans*-4-hydroxy-L-proline and BOC-L-proline. Preparation of catalyst **1** is shown in Scheme 1. The reactions gave high yields of 97% and 93% for Catalyst **1** and Catalyst **2**, respectively. The BOC protecting group was removed from these compounds using a 1:1 ratio of TFA:DCM, which gave the quantitative yields. Further purification was done by column chromatography, as required. The structures of these catalysts was fully characterized by ^{1}H and ^{13}C-NMR, whereby they were found to be in full agreement with the proposed structures. In accordance to the high yields of Catalysts 1 and 2, Catalysts 3 and 4 were prepared using the same method and reaction conditions. Catalyst 3 was obtained from the reaction between BOC-*trans*-4-hydroxy-L-proline and 2-aminonaphtalene, which resulted in 93% yield. Catalyst 4 (94% yield) was successfully synthesized using BOC-*trans*-4-hydroxyproline and *p*-toluenesulfonylhydrazide.



Scheme 1. Synthetic route for the preparation of Catalyst **1**

Table 1. Catalytic performances of Catalysts **1** and **2** in aldol reactions in various solvents for 48 h[a]



Entry	Catalyst	Solvent	Yield[b] (%)	anti:syn[c]	ee[d] (%)
1	1	H_2O	81	46:54	79
2	1	H_2O /EA	76	39:61	78
3	1	MeOH	71	44:56	73
4	1	DMSO	78	46:54	81
5	1	EA	30	47:53	85
6	1	THF	78	71:29	100
7	1	DCM	26	68:32	74
8	2	H_2O	80	44:56	84
9	2	H_2O /EA	75	13:87	61
10	2	MeOH	53	63:37	82
11	2	DMSO	53	67:33	70
12	2	EA	35	56:44	71
13	2	THF	68	60:40	70
14	2	DCM	33	45:55	49

[a]The reactions were conducted with *p*-nitrobenzaldehyde (0.5 mmol), cyclohexanone (1 mmol), catalyst (0.10 mmol), and solvent (2 ml).
[b]Isolated yield
[c]Determined by ^{1}H-NMR
[d] Determined by HPLC (Chiralcel OD-H)

Table 2. Catalytic performances of Catalysts **3** and **4** in aldol reactions in various solvents for 48 h[a]

Entry	Catalyst	Solvent	Yield[b] (%)	anti:syn[c]	Ee[d] (%)
1	3	H_2O	60	29:71	89
2	3	H_2O /EA	58	32:68	92
3	3	MeOH	54	36:64	90
4	3	DMSO	64	45:55	87
5	3	EA	70	37:63	75
6	3	THF	54	55:45	89
7	3	DCM	67	43:57	86
8	4	H_2O	25	35:65	61
9	4	H_2O /EA	37	41:59	69
10	4	MeOH	72	33:67	80
11	4	DMSO	60	40:60	92
12	4	EA	61	52:48	76
13	4	THF	68	49:51	81
14	4	DCM	57	53:47	68

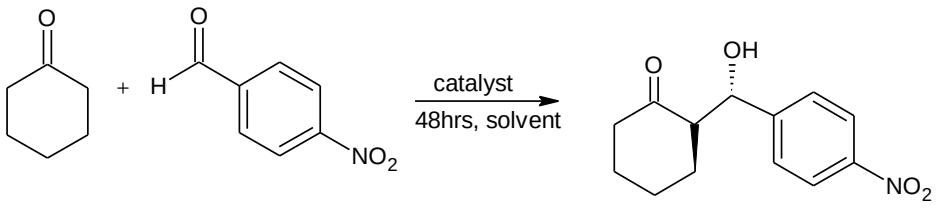
[a]The reactions were conducted with *p*-nitrobenzaldehyde (0.5 mmol), cyclohexanone (1 mmol), catalyst (0.10 mmol) and solvent (2 ml).
[b]Isolated yield
[c]Determined by ^{1}H-NMR
[d]Determined by HPLC (Chiralcel OD-H and Chiralpak IG)

Aldol reactions of 4-nitrobenzaldehyde and cyclohexanone were utilized to evaluate the catalysts in different solvents (Tables 1 and 2). In these model reactions, the major product was the anti-isomer with *2R*,1'*S*-configuration[11]. Both Catalysts **1** and **2** were homogenous in methanol (MeOH), dimethyl sulfoxide (DMSO), and tetrahydrofuran (THF); but heterogenous in water, dichloromethane (DCM), and ethyl acetate (EA). These conditions resulted in significant differences in enantiomeric excess and diastereomeric ratio of the aldol products when Catalyst **1** was utilized but not so much (difference) in the use of Catalyst **2**. Reactions with Catalyst **1** exhibited good yields and enantioselectivity in protic solvents (Table 1; Entries 1, 2, and 3) and aprotic solvents (Table 1; Entries 4 and 6) but low diastereoselectivity in solvents EA and DCM. However, THF portrayed an unexpectedly excellent enantioselectivity and good diastereoselectivity. Meanwhile, DCM displayed moderately good enantiomeric excess and diastereomeric ratio. Reactions with Catalyst **2** revealed good yields in water, water/EA, and THF. On the other hand, moderately good enantioselectivity and diastereoselectivity could be seen in water and MeOH. Catalyst **1** showed higher yields in most solvents, since the presence of the hydroxy moiety provided more sites for hydrogen bonding with the solvents than that of Catalyst **2**.

Catalyst **3**, on the other hand, has notably a similar structure with Catalyst **1** with one less benzene ring; however, there were some dissimilarities in their results. When reactions proceeded with Catalyst **3**, moderate yields were obtained in both polar protic and polar aprotic solvents, where EA presented the highest yield of 70%, followed by DCM with 67% yield, and DMSO with 64% yield (Table 2; Entries 5, 7, and 4). In terms of diastereoselectivity, significant difference could be seen with H_2O and H_2O/EA as solvents (Table 2; Entries 1 and 2), having moderate diastereomeric ratio. Enantioselectivity of the products using Catalyst **3** varied from moderate to high, where H_2O/EA gave the highest ee of 92%.

It was hypothesized that the presence of more N-H moiety in Catalyst **4** could create more sites for hydrogen bonding and provide excellent results[12]. Unfortunately, Catalyst **4** performed poorly in H_2O and H_2O/EA, giving low yields in diastereoselectivity and enantioselectivity (Table 2; Entries 8 and 9). However, when MeOH, THF, and DMSO were used as solvents, good enantioselectivity was shown, with 80%, 81%, and 92%, respectively. With these results in hand, further studies were performed by evaluating the catalyst loading and the addition of trifluoroacetic acid as an additive to increase the acidity of the organocatalyst (Table 3).

Table 3. The effects of catalyst loading and TFA loading in aldol reactions[a]



Entry	Catalyst	Solvent	Catalyst loading (mol%)	TFA loading (mol%)	Yield[c] (%)	anti:syn[d]	ee[e] (%)
1	1	H_2O/EA	10	-	80	48:52	82
2	1	H_2O/EA	5	-	45	43:57	76
3	1	DCM	10	-	38	77:23	88
4	1[b]	-	20	-	34	51:49	76
5	1	H_2O/EA	20	10	27	48:52	68
6	1	H_2O/EA	20	5	76	56:44	68
7	1	DCM	20	5	8	48:52	37
8	2	H_2O/EA	10	-	80	47:53	77
9	2	H_2O/EA	5	-	82	67:33	88
10	2[b]	-	20	-	70	44:56	73
11	3[b]	-	20	-	78	32:68	92

[a]The reactions were conducted with *p*-nitrobenzaldehyde (0.5 mmol), cyclohexanone (1 mmol), and solvent (2 ml).
[b]Neat condition
[c]Isolated yield
[d]Determined by ^{1}H-NMR
[e]Determined by HPLC (Chiralcel OD-H)

Firstly, Catalyst **1** loading was lowered to 10% in water/EA, which revealed higher enantiomeric excess value (82%) but no improvement in the diastereomeric ratio. Nevertheless, reducing Catalyst **1** loading to 5% demonstrated low yield and low stereo-selectivity. Based on previous results, DCM showed an unexpectedly good diastereo-selectivity, thus the further investigation on the reduction of Catalyst **1** loading. Notably, the yield and stereoselectivity increased satisfactorily. In contemplation to obtain excellent activity of the organocatalyst, trifluoroacetic acid was introduced, as it was reported to give dramatically high yield and enantioselectivity[13]. Surprisingly, the results showed a significant deviation when a catalytic amount of TFA (10%–5%) was added; the yield and enantioselectivity of the organocatalyst also decreased. In order for high efficiency reactions, TFA acidity should be strong enough to improve the yield but not too strong to assist the catalyst for enantiocontrol.As for Catalyst **2**, decreasing the catalyst loading from 10% to 5% exhibited higher yield from 80% to 82%. Although the enantiomeric excess was good, the diastereoselectivity was barely satisfactory.

From the above-mentioned observations, the transition state presented in Figure 2 was suggested, which considered the stearic factor of the atomic model. In particular, hydrogen-bonding interactions have the ability to tautomerize the keto–enol form[13]. The pyrrolidine moiety activated the ketone through the formation of a chiral enamine intermediate[14]. The electrophilicity of aromatic aldehydes had also increased by a strong hydrogen bond involving amide N–H hydrogen atom and protic solvents[15]. It was anticipated that the π–π interaction between the aldehyde and aromatic rings of the catalyst in the transition state may play an important role in the selectivity and gave rise to a rigid transition state. However, the enamine was able to attack at both Re-facial and Si-facial forms, which eventually exhibited a moderate diastereoselectivity.

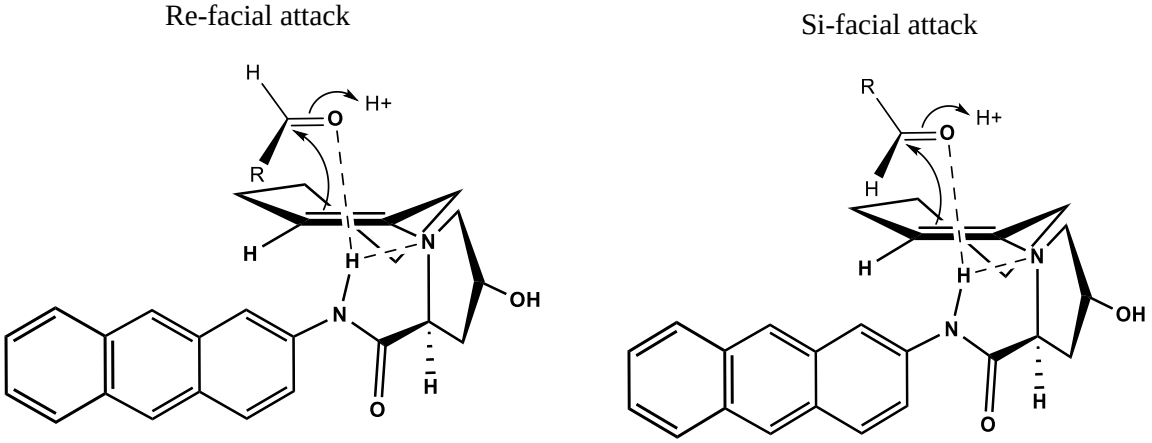


Figure 2. Proposed transition state

EXPERIMENTAL SECTION

General procedure

Chemicals and solvents were purchased from commercial suppliers and used without further purification. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using Silica gel 60 F254 aluminium precoated plates from Merck (0.25 mm), and the compounds were visualized by UV light irradiation. Column chromatography was performed on Silica gel (MN Kieselgel 60 M, 0.063–0.200 mm, 70–230 mesh). Both the ^{1}H and ^{13}C-NMR spectra were recorded on JEOL 400 MHz spectrometer. Chemical shifts were reported in ppm (parts per millions) according to residual solvent signals of $CDCl_3$ (^{1}H-NMR; d¼7.26 ppm, ^{13}C-NMR; d¼77.0 ppm), DMSO-d_6 (^{1}H-NMR; d¼2.50 ppm, ^{13}C-NMR; d¼39.43 ppm) and CD_3OD (^{1}H-NMR; d¼3.30 ppm, ^{13}C-NMR; d¼49.0 ppm). All spectra were acquired and processed using JEOL Delta 5.1.1. The enantiomeric ratio of products was determined by Chiral HPLC analysis using Agilent Technologies instrument (Chiralcel OD-H or Chiralpak AS-H, 4.6 mm × 250 mm columns).

Synthesis of catalysts

Dry THF (10 ml) was added to BOC-*trans*-4-hydroxy-L-proline (0.25 g, 1.08 mmol), N-(3-dimethylamino propyl)-N′-ethylcarbodiimide hydro-chloride (0.21 g, 1.08 mmol, 1 equiv), and hydroxybenzotriazole (0.03 g, 0.02 mmol, 0.19 equiv) at 0°C under nitrogen (N_2) atmosphere. The reaction mixture was stirred for 30 min at 0°C, and 2-aminoanthracene was added and stirred at room temperature overnight. The reaction was quenched with saturated sodium hydrogen carbonate. The organic layer was separated, where the aqueous layer was extracted with dichloromethane and the combined organic layer was dried over anhydrous sodium sulphate, filtered, and evaporated. Further purification was done through column (hexane:ethyl acetate ratio of 3:1) to give the yellow powder of BOC-(4*R)-N*-(anthracen-2-yl)-4-hydroxy pyrrolidine-2-carboxamide **1** at 97% yield. A similar procedure was used to prepare Catalyst **2**.

BOC-(4*R)-N*-(anthracen-2-yl)-4-hydroxypyrrolidine-2-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) (ppm): 1.35(s, 5H), 1.42 (s, 4H), 2.14-2.18 (m, 1H), 2.29-2.31 (m, 1H), 3.53-3.66 (dd, 2H) 4.46-4.4.59 (m, 2H), 7.38-7.53 (m, Ar), 7.9-7.95(m, Ar), 8.28-8.43 (m, Ar); ^{13}C-NMR (400 MHz, $CDCl_3$) (ppm): 27.44, 39.21, 48.77, 68.11, 57.44, 106.21, 115.25, 123.00, 124.55, 123.22, 127.55, 128.99, 130.22, 131.98, 142.84, 178.21.

BOC-(4*R)-N*-(anthracen-2-yl)-pyrrolidine-2-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) (ppm): 1.32 (s, 5H), 1.46 (s, 4H), 2.02-2.04 (m, 1H),2.05-2.06 (m, 2H) 2.31-2.34 (m, 1H), 3.46-3.58(dddd, 2H), 4.31-4.34 (d, 1H), 7.39-7.52 (m, Ar), 7.93-7.97 (m, Ar), 8.32-8.40 (m, Ar). ^{13}C-NMR (400 MHz, $CDCl_3$)(ppm):28.83, 37.24, 55.82, 68.51,69.77, 105,90, 120.08, 124.95,125.33, 124.46, 125.84, 127.56, 127.90, 129.03, 129.03, 129.40, 131.49, 131.75, 132.39, 134.60, 172.79.

BOC-(2*R*,4R)-4-hydroxy-*N*-(naphthalen-2-yl) pyrrolidine-2-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) (ppm): 1.31 (s, 5H), 1.37 (s, 4H), 2.12-2.16 (m, 1H), 2.27-.92 (m, 1H), 3.524-3.54 (d, 1H), 3.61-3.62 (dd, 1H)44.45-4.47 (m, 2H), 7.34-7.42 (m, 2H), 7.56-7.58 (d, 1H), 7.75-7.78 (dd, 3H), 8.19-8.21 (d, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$)(ppm): 28.40, 37.41, 52.11, 63.12, 68.35, 79.82, 116.54, 119.69, 120.52, 123.54, 125.41, 133.56, 135.87, 175.12.

BOC-(2*R*,4R)-4-hydroxy-*N*-(4-methylbenzene-1-sulfonyl)pyrrolidine-2-carbohydrazide

^{1}H-NMR (400 MHz, $CDCl_3$) (ppm):1.41 (s, 1H), 1.98

(s,2H), 2.38 (s,3H), 3.28-3.412(dddd, *J*=3.35Hz, 2H), 4.06-4.22 (m, *J*=4.14Hz, 3H), 7.29-7.32 (m, *J*= 7.31Hz, 2H), 7.74-7.76 (t, *J*= 7.74Hz, 2H); ^{13}C-NMR (400 MHz, $CDCl_3$)(ppm): 13.22,19.66, 20.33, 27.21, 27.41, 38.25, 39.14, 47.55, 47.76, 54.43, 57.10, 57.34, 60.27, 68.56, 69.18, 80.10, 80.30, 80.58, 128.04, 128.30,128.18, 129.73,135.17, 135.24, 144.19, 144.35, 154.37, 154.87, 171.71, 172.15, 172.43.

BOC-deprotection

Initial BOC-(4*R)*-*N*-(anthracen-2-yl)-4-hydroxypyrrolidine-2-carboxamide was dissolved in dichloromethane (CH_2Cl_2). Trifluoroacetic acid (1 mmol sample: 5 ml) was added. The reaction mixture was stirred at room temperature for 3 h. Next, CH_2Cl_2 was evaporated and replaced by anhydrous toluene, which was then evaporated to azeotrope excess trifluoroacetic acid. This process was repeated three times to yield the yellow powder, which was dried in vacuo. The prolineamide was used without further purification.

(4*R)*-*N*-(anthracen-2-yl)-4-hydroxypyrrolidine-2-carboxamide

^{1}H-NMR (400 MHz, CDCl3) (ppm): 2.16-2.21 (dd, 1H), 2.54-2.66 (t, 1H), 3.21-3.46 (m, 1H), 3.52 (dd, 1H), 4.61-4.79 (m, 2H), 7.53-7.61 (m, Ar), 7.90-8.01 (m, Ar), 8.31-8.52 (t, Ar); ^{13}C-NMR (400 MHz, $CDCl_3$) (ppm): 32.82, 47.04, 47.25, 47.46, 47.67, 47.89, 48.10, 48.32, 59.42, 70.02, 116.02, 120.10, 124.96, 125.34, 125.46, 125.84, 127.57, 127.90, 129.03, 129.42, 131.51, 131.73, 132.39, 134.54, 166.89.

(4*R)*-*N*-(anthracen-2-yl)-pyrrolidine-2-carboxamide

^{1}H-NMR (400 MHz, CDCl3) (ppm): 2.16-2.21 (dd, 1H), 2.08-2.22 (m, 1H), 2.51-2.60 (m, 1H), 3.52 (m, 2H), 4.45-4.61 (m, 1H), 7.37-7.47 (m, Ar), 7.93-8.01 (m, Ar), 8.31-8.52 (t, Ar); ^{13}C-NMR (400 MHz, $CDCl_3$)(ppm):23.83, 29.84,47.24, 60.51, 115,90, 120.08, 124.95,125.33, 124.46, 125.84, 127.56, 127.90, 129.03, 129.03, 129.40, 131.49, 131.75, 132.39, 134.60, 166.79.

(2*R*,4R)-4-hydroxy-*N*-(naphthalen-2-yl)pyrrolidine-2-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) (ppm): 2.14-2.21(tt, 1H), 2.55-2.60 (dd, 1H), 3.28-3.29(m, 1H), 3.34-3.46 (dd, 1H), 4.62-4.67 (dd, 2H), 7.39-7.44 (m, 2H), 7.57-7.58 (dd, IH), 7.77-7.82 (m, 3H), 8.22-8.233 (d, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$)(ppm):38.78, 53.96, 69.97, 116.74, 119.50, 125.05, 126.37, 127.25, 127.32, 128.49, 131.01, , 133.78, 135.20, 166.70.

(2*R*,4R)-4-hydroxy-*N*-(4-methylbenzene-1-sulfonyl) pyrrolidine-2-carbohydrazide

^{1}H-NMR (400 MHz, $CDCl_3$) (ppm): 1.41 (s, 1H), 1.98 (s,2H), 2.38 (s,3H), 3.28-3.412(dddd, *J*=3.35Hz, 2H), 4.06-4.22 (m, *J*=4.14Hz, 3H), 7.29-7.32 (m, *J*= 7.31Hz, 2H), 7.74-7.76 (t, *J*= 7.74Hz, 2H)1.19-1.35 (m, 2H); ^{13}C-NMR (400 MHz, $CDCl_3$)(ppm): 20.21, 38.66, 47.88, 69.84, 69.58, 128.09, 129.37, 129.85, 144.59.

General procedure for the enantioselective aldol reaction

For the organic solvent (2.5 mL) and catalyst (0.2 mmol), cyclohexanone (5 mmol) was added at room temperature, and the mixture was allowed to stir for five minutes, followed by the addition of 4-Nitrobenzaldehyde (1 mmol). The reaction mixture was stirred for 48 h and monitored with TLC at regular intervals. Upon completion of the reaction, water (5 mL) was added to it and the reaction mixture was extracted with dichloromethane (3–10 mL). The organic layer was separated, dried over anhydrous sodium sulphate, filtered, and evaporated to obtain the crude aldol product. The ^{1}H-NMR of the crude product was recorded to determine the diastereomeric excess. The column chromatography on silica gel then exhibited the pure aldol product.

2-[hydroxy(4-nitrophenyl)methyl]cyclohexanone

Yield: 92%; anti/syn = 94:6; enantiomeric excess: 95% determined by HPLC (Daicel Chiralpak AS-H, hexane/i-PrOH 85:15; flow rate 0.3 mL min^{-1}, k = 254 nm; tR (syn, major) = 43.86 min, tR (anti, major) = 48.23, tR (anti, minor) = 59.0 min, tR (syn, minor) = 66.56 min; ^{1}H-sNMR (CDCl3, 300 MHz): d 1.53–1.85 (m, 4H, CH2), 2.05– 2.13 (m, 1H, CH2), 2.33–2.56 (m, 4H, CH2 and CH), 3.90–4.20 (br s, 1H, OH), 4.85–4.88 (d, 1H, J = 9 Hz, CH (anti)), 5.48 (s, 1H, CH (syn)), 7.45–7.49 (m, 2H, ArH), 8.15–8.19 (m, 2H, ArH); ^{13}C-NMR (CDCl3, 300 MHz): d 24.5, 24.6, 25.8, 27.5, 27.6, 30.6, 42.4, 42.5, 56.7, 57.0, 69.9, 73.8, 123.3, 123.4, 126.5, 127.8, 147.4, 148.3, 149.2, 213.9, 214.6.4.3.2.

2-[Hydroxy(3-nitrophenyl)methyl]cyclohexanone

Yield: 83%; anti/syn = 88:12; enantiomeric excess: 86% determined by HPLC (Diacel Chiralpak AD-H, hexane/i-PrOH 95:5, flow rate 0.8 mL/min; k = 254 nm; tR (syn, major) = 35.09 min, tR =(syn, minor) = 40.14 min, tR (anti, major) = 43.79 min, tR (anti, minor) = 56.53 min; ^{1}H-NMR (CDCl3, 300 MHz): d 1.57–1.74 (m, 5H, CH2), 1.98–2.10 (m, 1H, CH2), 2.39–2.46 (m, 2H, CH2), 2.61–2.70 (m, 1H, CH),

3.20–3.32 (br s, 1H, OH (syn)), 4.13–4.30 (br s, 1H, OH (anti)), 4.92–4.95 (d, 1H, J = 9 Hz, CH (anti)), 5.47–5.48 (d, 1H, J = 2.4 Hz, CH (syn)), 7.49–7.56 (m, 1H, ArH), 7.69–7.70 (m, 1H, ArH), 8.06–8.22 (m, 2H, ArH); ^{13}C-NMR (CDCl3, 300 MHz): d 24.5, 25.8, 27.5, 27.7, 30.6, 42.5, 56.6, 57.0, 69.7, 73.9, 120.8, 122, 122.7, 129, 129.2, 131.9, 133.1, 143.2, 148.1, 214.7.

CONCLUSION

Novel prolinamide-based organocatalysts were developed, and it was learned that they can easily be prepared in high yields. Good yields and enantioselectivities were observed in direct asymmetric aldol reactions in water. However, further studies in the reaction mechanism and wider scope application of the novel catalyst are in progress.

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