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(*L*)-Prolinamide imidazolium hexafluorophosphate ionic liquid as an efficient reusable organocatalyst for direct asymmetric aldol reaction in solvent-free condition

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Abstract: We have designed a new hydrophobic ionic liquid derived from bromoester of *trans*-4-hydroxy-(*L*)-prolinamide and N-methylimidazole. (*L*)-Prolinamide imidazolium hexafluorophosphate ionic liquid (2 mol%) found to be an excellent organocatalyst for direct asymmetric aldol reaction between 4-nitrobenzaldehyde and cyclohexanone using acetic acid (2 mol%) as an additive at -15°C in solvent-free condition, the aldol product was afforded in excellent yield with diasteromeric ratio (*anti/syn*; 97:3) and 94% *ee* of *anti*-aldol product. Ionic liquid can catalyze the direct aldol reaction between benzaldehyde derivatives and cycloalkanones and best dr (*anti/syn*; 99.9/0.01) and 99% *ee* was obtained for aldol product of 2-trifluoromethyl benzaldehyde and cyclohexanone. (*L*)-Prolinamide imidazolium hexafluorophosphate ionic liquid was reused up to 6 continuous cycles without decrease in the conversion of the product with 92% *ee* and found to be superior than its counterpart *trans*-4-hydroxy-(*L*)-prolinamide. Continuous cycle experiments do not require isolation of the catalyst after each cycle. The results of reusability of the ionic liquid catalyst were found to be better than most of other reported reusable catalysts.

Keywords: Organocatalysis/ Direct asymmetric aldol reactions / (*L*)-Prolinamide / Ionic liquid / Continuous cycles

Introduction

The aldol reaction is recognized as one of the most powerful carbon-carbon bond-forming reactions in modern organic synthesis. It provides an atom-economic approach to β-hydroxyl carbonyls, which make up a large family of chiral intermediates for the synthesis of biologically active substances and natural product.[1] Since the early reports in the 1970s that the *L*-proline catalysed intramolecular aldol reactions[2a,b] later the pioneering work by List et al. in 2000.[2c,d] After these reports numerous proline-derived organocatalysts such as proline analogues,[3] acyclic amino acids,[4] different types of prolinamides,[5–13] prolinethioamides,[14] sulfonamides,[15] chiral amines,[16] organic salts[17] were exploited as organocatalysts for direct asymmetric aldol reaction. The organocatalyst is usually used for direct asymmetric aldol reaction in a substantial quantity, in some cases up to 30 mol%, its recovery and reuse is vital for reduce the cost and to facilitate the separation of the product from the catalyst. Several research groups are attentive to develop a recoverable organocatalysts for direct asymmetric aldol reaction.[18] Immobilization of modified proline derivatives are desirable due to their non-commercial viability and their high reactivity.

In our ongoing research on development of organocatalyst for asymmetric Diels-alder reaction and direct asymmetric aldol reaction.[19] We recently reported the *trans*-4-hydroxy-(*L*)-prolinamide (**1**) as organocatalyst for aldol reaction between aromatic aldehydes and cycloalkanes under solvent free conditions.[20] Herein, we wish to report synthesis of imdidazolium ionic liquids from bromoester of *trans*-4-hydroxy-(*L*)-prolinamide and *N*-methylimidazole and their catalytic activity in direct asymmetric aldol reaction.

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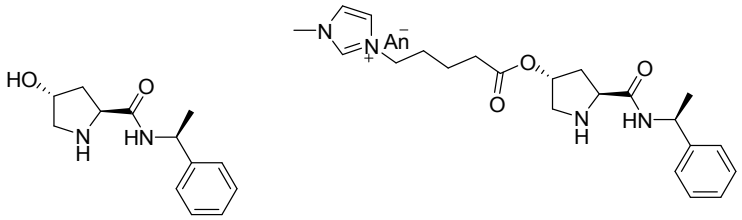

Figure 1. Prolinamide catalysts for direct asymmetric aldol reaction.

Results and discussion

Prolinamide imdazolium ionic liquids **2** and **3** were synthesized according to scheme 1. First, *trans*-4-hydroxy-(*S*)-proline **4** was protected as *N*-boc protecting group in quantitative yield. *N*-Boc-*trans*-4-hydroxy-(*S*)-proline **5** was treated with (*S*)-1-phenylethylamine, in presence of triethylamine and ethylchloroformate, gave corresponding *N*-boc-prolinamide **6** in 81% yield. The esterification of compound **6** with 5-bromovleric acid in the presence of DCC and DMAP in dichloromethane gave the product **7** in a 94% yield. The compound **8** was synthesised by the reaction of *N*-methyl imidazole and compound **7**, which affords N-boc protected imidazolium bromide **8** in 97% yield. The bromide anion of the ionic liquid **8** was exchanged by KPF_6 to hexafluorophosphate anion in 86% yield. Deprotection of *N*-boc group in compounds **8** and **9** by TFA in dichloromethane at room temperature gave ionic liquid (**IL**) **2** and **3**.

In our initial investigation, the direct asymmetric aldol reaction between 4-nitrobenzaldehyde **10** and cyclohexanone using ionic liquid **3** (10 mol %) and acetic acid (10 mol %) as additives at room temperature gave >99 % conversion and 29% enantiomeric excess (*ee*) of product *anti* **11** with poor diastereoselectivity (Table 1, entry 1). Decreasing of the reaction temperature to -15°C, improved the diastereomeric ratio (*dr*; *anti/syn*; 94:6) and *ee* (96%) of the product *anti*-**11** (Table 1, entries 2). We also varied the catalyst loading and even though at low catalyst loading (2 mol%) with additive acetic acid (2 mol%), product *anti*-**11** was obtained in excellent yield with 94% *ee* and *dr* (*anti*/*syn*; 97:3) after 24 h (Table 1, entry 3-4). We also compared the catalytic result with organocatalyst **1** with ionic liquid **3** (**IL 3**) under identical conditions and the organocatalyst **1** was found to be more reactive but better *ee* for product *anti*-**11** was observed with **IL 3** (Table 1, entry 5). **IL 2** gave the aldol product in poor yield (39%) with 76% *ee* of *anti*-**11** (Table 1, entry 6).

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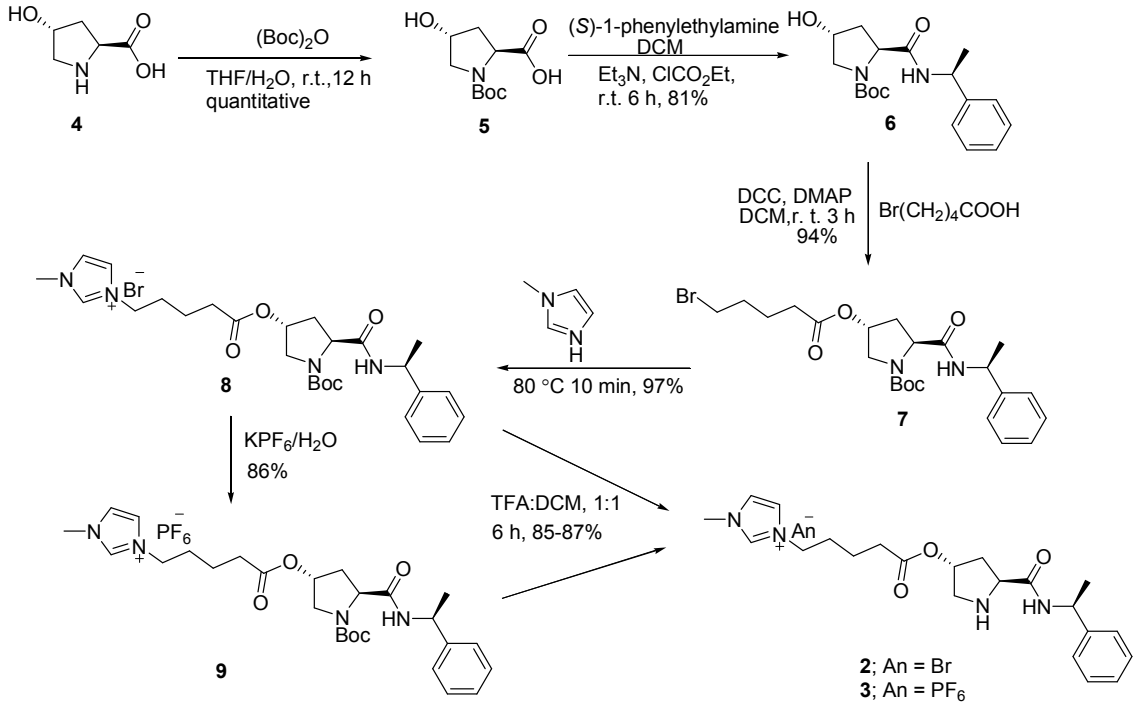
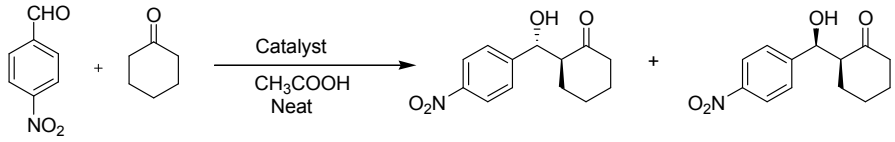


Scheme 1. Synthesis of ionic liquids (**IL**) **2** and **3**.

Table 1. Optimization of reaction conditions for direct asymmetric aldol reaction.[a]



10 **11-*anti*** **11-*syn***

Entry	Organocatalyst	Catalyst loading (mol %)	Time (h)	Yield[b] (%)	*dr* (*anti:syn*) [c]	*ee* (%) (*anti*)[d]
1	3	10	6	>99	59:41	29[e]
2	3	10	12	>99	94:6	96
3	3	5	12	>99	96:4	91
4	3	2	24	99	97:3	94
5	1	2	8	>99	93:7	92
6	2	2	24	39	85:15	76

[a] Organocatalyst (2-10 mol %), CH_3COOH (2-10 mol %), cyclohexanone (3 mmol) and 4-nitrobenzaldehyde (1 mmol) were stirred at − 15 °C for specified time.

[b] Conversion was determined by HPLC using response factor for 4-nitrobenzaldehyde **10** and product **11**.

[c] Diastereomeric ratio (*dr*) (*anti/syn*) and enantiomeric excess (*ee*) were determined by HPLC using chiralpak AD-H column.

[d] The absolute configuration was determined by comparing the specific rotation of product *anti*-**11** with literature values and found to be (1'*S*, 2*R*).

[e] Reaction carried out at room temperature.

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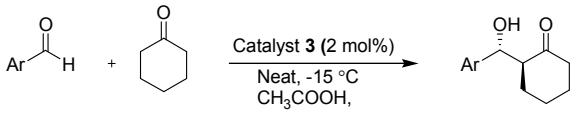
We also compared our organocatalyst **IL 3** with other reusable organocatalysts reported in literature for the direct asymmetric aldol reaction between 4-nitrobenaldehyde and cyclohexanone are shown in SI Table 1. The results show that **IL3** was found to be better catalyst in terms of catalyst loading and turnover frequency than the most of the reported reusable catalysts.

We have investigated the asymmetric direct aldol reaction between substituted benzaldehydes and cyclohexanone catalyzed by **IL 3** (2 mol%) and additive CH_3COOH (2 mol%) at − 15 °C in solvent-free conditions. All the benzaldehyde derivatives gave the *anti* diastereomer as major product. Benzaldehyde afforded aldol product in a 60% yield with diastereomeric ratio of *anti:syn* (91/9) with 98% *ee* of *anti* diastereomer and bulkier naphthaldehyde improved the *anti:syn* ratio but *ee* was slightly decreased (Table 2, entry 1 and 2). Electron withdrawing group (EWG) such as nitro on benzaldehyde improved the reactivity and 2-nitrobenzaldehyde gave 97% *ee* (Table 2, entry 3). 4-Halogenated benzaldehydes were found to be less reactive with excellent *ee* and *dr*. The order of reactivity of 4-halogenated benzaldehydes (F<Cl<Br) was increasing when electronegativity of halogen is decreasing due to enhancement of electrophilicity of carbonyl carbon of halobenzaldehydes (Table 2, enties 5, 7, and 9). 2-Halobenzaldehydes gave the corresponding aldol products in 88-90% yields and 91-97% *ee* (Table 2, entries 4, 6, and 8). Electron donating group (EDG) like methoxy on benzaldehyde, found to be less reactive compared to derivatives of EWG. The EWG's enhance the electrophilicity of carbonyl carbons in aldehydes which facilitate the reaction, while EDG's lessen the electrophilicity of carbonyl carbons. 4-Methoxybenzaldehyde was found to be least active and afforded only 5% of the product but by increasing the catalyst loading was increased to 5 mol% and 25% yield of the product was obtained (Table 2, entries 11 and 12). In case of 2-(trifluoromethyl)benzaldehyde, exclusively afforded *anti* product in 99% *ee* (Table 2, entry 13).

Table 2. Aldol reaction of cyclohexanones with substituted benzaldehydes catalysed by **IL 3**.[a]



Entry	Ar	Time [h]	Yield[b] (%)	*dr* (*anti:syn*) [c]	*ee* (%) (*anti*)[d]
1	Phenyl	24	60	91:9	98
2	1-Napthyl	48	25	98:2	93
3	2-$NO_2C_6H_4$	17	87	96:4	97
4	2-FC_6H_4	18	88	97:3	91
5	4-FC_6H_4	24	49	98:2	93
6	2-ClC_6H_4	18	90	95:5	97
7	4-ClC_6H_4	26	74	98:2	97
8	2-BrC_6H_4	18	90	97:3	97
9	4-BrC_6H_4	26	84	97:3	98
10	2-$OMeC_6H_4$	40	23	99:1	91

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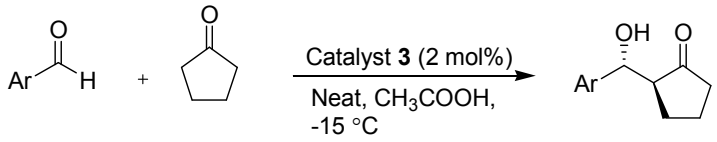
11	4-$OMeC_6H_4$	48	5	63:37	ND
12	4-$OMeC_6H_4$	48	25	99.8:0.2	52[e]
13	2-$CF_3C_6H_4$	17	69	100: 0	99
14	4-$CF_3C_6H_4$	17	87	97:3	91

[a] IL **3** (0.02 mmol, 2 mol%), CH_3COOH (0.02 mmol, 2 mol%), cyclohexanone (3 mmol) and substituted benzaldehyde (1 mmol) were stirred at -15 °C for specified time.
[b] Isolated yield after purification by column chromatography.
[c] Diastereomeric ratios (*dr*) were determined by ^{1}H-NMR of crude products.
[d] Enantiomeric excess (*ee*) was determined by HPLC using chiralpak AD-H and chiralcel OD-H columns.
[e] 5 mol% catalyst was used.

We have also studied the direct asymmetric aldol reaction between 2- and 4-substituted benzaldehydes with cyclopetanone catalyzed by **IL 3** (2 mol%) at -15 °C in solvent-free conditions (Table 3). The reactivity of benzaldehydes having EWG's was faster than the EDG's. In case of 4-substituted benzaldehydes *anti* aldol products were obtained as major diastereomers while *syn* diastereomers were obtained with 2-substituted benzaldehydes except 2-nitrobenzaldehyde (Table 3, entries 1-8). The better *ee* was obtained for *anti* diasteromers of the aldol products than *syn* diastereomers. The reactivity of 4-methoxy was found to be poor and but by increasing the catalyst loading to 5 mol% increased the yield (Table 3, entries 8 and 9).

Table 3. Aldol reaction of cyclopentanone with substituted benzaldehydes catalysed by **IL 3**.[a]



Entry	Ar	Time (h)	Yield[b] (%)	*dr* (*anti:syn*)[c]	*ee* (%) (*anti/syn*)[d]
1	2-$NO_2C_6H_4$	30	71	55:45	99/28
2	4-$NO_2C_6H_4$	30	66	50:50	66/40
3	2-FC_6H_4	40	76	43:57	81/26
4	4-FC_6H_4	40	69	72:28	82/20
5	2-ClC_6H_4	38	37	40:60	99/45
6	4-ClC_6H_4	38	72	54:46	84/26
7	2-$OMeC_6H_4$	48	33	21:79	97 /33
8	4-$OMeC_6H_4$	48	7	72:28	70/20
9	4-$OMeC_6H_4$	44	64	44:56	81/8[e]

[a] **IL 3** (0.02 mmol, 2 mol%), CH_3COOH (0.02 mmol, 2 mol%), cyclopentanone (3 mmol) and 4-nitrobenzaldehyde (1 mmol) were stirred at -15 °C for specified time.
[b] Isolated yield after purification by column chromatography.
[c] Diastereomeric ratios were determined by ^{1}H-NMR of crude products.
[d] The *ee* was determined by HPLC using chiralpak AD-H, and chiralcel OD-H columns.
[e] Reaction carried out using 5 mol% of the catalyst

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The reusability performance of the **IL 3** (2 mol%) was carried out for the asymmetric aldol reaction of 4-nitrobenzaldehyde **10** (1 mmol) and cyclohexanone (3 mmol) using acetic acid (2 mol%) as additive at -15°C (Table 4). The reaction was monitored on TLC and HPLC, after complete conversion of 4-nitrobenzaldehyde **10,** 4-nitrobenzaldehyde **10** (1 mmol) and cyclehexanone (3 mmol) were added to the reaction mixture without any additive and catalyst. This procedure was repeated for 6 continuous cycles and afforded aldol products in overall >99% conversion of the product with *anti/syn* 96:4 with 92% *ee* of product **11-*anti*** and total turnover number (TON) of the catalyst was found to be more than 346 (Table 4, entry 7 and Figure 2). The advantages of continuous cycle for the reuse of the catalyst are: (i) **IL3** and catalytic product of the aldol reaction are polar so it's difficult to separate catalyst from the product by using the different solvents therefore use of continuous cycle is beneficial, (ii) It enhances economic viability of the process because it does not require separation of the catalyst after completion of each cycle which save the cost of the manpower and solvents and (iii) the product is stable during the reaction even though we are stirring the reaction up to 7 cycles. Similar strategy was used by List and co-workers in cyanosilylation of aldehydes.[20] We also compared the catalysis of **IL3** in low loading (0.4 mol%) in identical reaction conditions and afforded product in >99% yield and *anti/syn* 95:5 with 85% *ee* of product **11**-*anti* after 4.5 days and these results are found to be poor in terms of *ee* than the continuous use of the **IL 3**. We also conducted the aldol reaction using catalyst **1** (2 mol%) under identical conditions to compare the reusability in continuous cycle. Catalyst **1** afforded the desired product ***anti-11*** in 97% yield and 96% *ee* but reaction took 65 h for completion of a 4th continuous cycle. The overall TON and TOF was found to be better for the catalyst **3** compared to the catalyst **1**. The hydrophobic nature of the ionic liquid unit of the catalyst **3** maintains the catalytic activity at dilution of the catalyst concentration in continuous cycle.

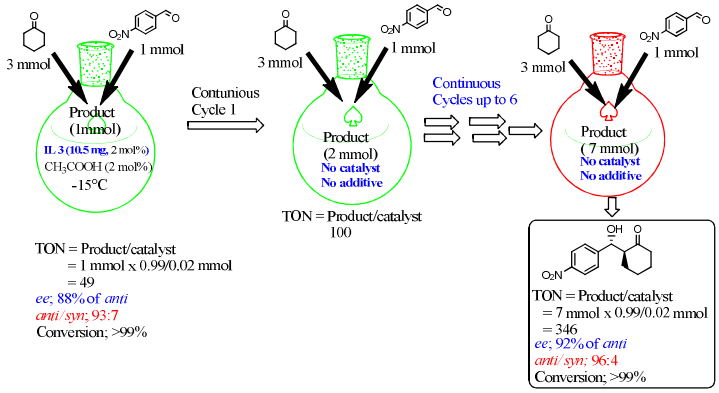

Figure 2. Reusability of **IL 3** in continuous cycle

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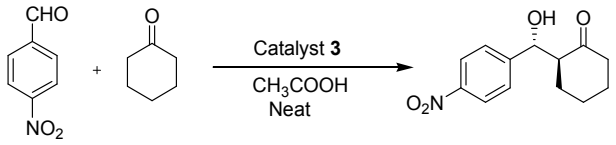
Table 4. Reusability of **IL 3** in continuous cycle for asymmetric aldol reaction.[a]



10 **11-*anti***

Cycle	Time (h)	Conversion (%)[b]	*dr (anti:syn)*[c]	*ee* (%) (*anti*)[c,d]
1	20 (8)[e]	>99 (>99)	97:3 (93:7)	88 (92)
2	20 (24)	>99 (96)	91:9 (95:5)	88 (93)
3	20 (48)	>99 (96)	95:5 (96:4)	93 (96)
4	24 (65)	>99 (97)	96:4 (96:4)	92 (96)
5	24	>99	96:4	92
6	24	>99	96:4	92
7	24	>99	96:4	92

[a]Catalyst 3 (0.02 mmol, 2 mol%), CH_3COOH (0.02 mmol, 2 mol%), cyclopentanone (3 mmol) and 4-nitrobenzaldehyde (1 mmol) were stirred at -15 °C for specified time.

[b]Conversion was determined by HPLC using response factor for 4-nitrobenzaldehyde **10** and product **11**.

[c]Diastereomeric ratio (*dr*) and enantiomeric excess (*ee*) were determined by HPLC using chiralpak AD-H column.

[d]The absolute configuration was determined by comparing optical rotation of product **11**-*anti* with literature and found to be (1'*S*, 2*R*).

[e]Results in parenthesis are for catalyst **1** under identical reaction conditions.

[f] Turn over frequency (TOF) for catalyst **3** = 2.22 h^{-1} and for catalyst **1** = 1.34 h^{-1}; turn over number (TON) for catalyst **3** = 346 and for catalyst **1** = 194.5.

Experimental Section

General

Benzaldehyde derivatives, cyclohexanone and cyclopentanone were purchased from commercial source and used as such. Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR, respectively) were recorded on 400 MHz (operating frequencies: 1H, 400.13 MHz; 13C, 100.61 MHz) Jeol-FT-NMR spectrometers at ambient temperature. The chemical shifts (□) for all compounds are listed in parts per million (ppm) downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform ($CDCl_3$) were 7.26 and 77.00 ppm for ^1H and ^{13}C NMR spectra, respectively. HRMS analysis was carried out using QSTAR XL Pro system microTOF-Q-II. The reaction was monitored by thin layer chromatography was carried out using Merck Kieselgel 60 F254 silica gel plates. Compounds were purified by column chromatography separations were performed using silica gel 230–400 mesh. The enantiomeric excess was determined on Shimadzu LC-2010HT using chiralcel OD-H, and chiralpak AD-H columns. Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer. Optical rotations were taken using Rudolph digipol polarimeter. (*2S,4R*)-*1-(tert*-Butoxycarbonyl)-4-

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hydroxypyrrolidine-2-carboxylic acid (**5**) and (2*S,* 4*R*)-*tert*-butyl-4-hydroxy-2-((*S*)-1-phenylethylcarbamoyl)pyrrolidine-1-carboxylate (**6**) were synthesised according to our earlier report.[19a] All the unknown compounds were characterized by ^{1}H, ^{13}C NMR and HRMS. Aldol products were characterized by ^{1}H-NMR and compared compared with our earlier report.[19a] Copy of ^{1}H-NMR, ^{13}C-NMR and HPLC chromatogram are given in supporting information.

(2*S*,4*R*)-*tert*-Butyl2-((*S*)-1-phenylethylcarbamoyl)-4-(5-bromopentanoyloxy)pyrrolidine-1-carboxylate (7)

5–bromovaleric acid (0.712 g, 3.94 mmol) was added to a solution of DCC (0.812 g, 3.94 mmol) and DMAP (0.0356 g, 0.292 mmol) in CH_2Cl_2 24 mL) at 0 °C and compound **6** (1.02 g, 3.07 mmol) was added in 10 min. The reaction mixture was stirred at 0 °C for 1h. The reaction progress was monitored by TLC. The combined organic washings were evaporated, the residue was purified by column chromatography on silica gel (*eluent*: EtOAc/Hexane 8/2) to afford the ester **7**as colourless liquid. Yield 1.52 g (94 %); $[\alpha]_D^{25}$= −55.1 (*c* 1.2, $CHCl_3$);IR (K Br): 3297, 2975, 1735, 1698, 1405, 1163 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.24–7.19 (m, 5H), 5.20–5.17 (m, 1H), 5.09–4.96 (m, 1H), 4.27 (t, *J* = 7.63 Hz, 1H), 3.58–3.48 (m, 1H), 3.34 (t, *J* = 6.10 Hz, 2H), 2.48 (t, *J* = 6.87 Hz, 1H), 2.27 (t, *J* = 7.63 Hz, 2H), 1.86–1.68 (m, 6H), 1.42 (s, 9H), 1.33–1.20 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.75, 170.21, 154.89, 142.70, 127.91 (2C), 126.38, 125.27 (2C), 80.07, 72.30, 68.79, 59.69, 57.74, 51.76, 48.21, 32.56, 32.46, 31.25, 27.66, 22.77 ppm. HRMS (ESI): m/z $[M+H]^+$calcd for $C_{23}H_{34}BrN_2O_5$: 497.1651; found: 497.1661.

(*2S,4R*)-*tert*-Buty*l2-((S*)-1-phenylethylcarbamoyl)-4-(pentanoyloxy)pyrrolidine-1-carboxylate (1-methyl-1H-imidazol-3-ium) bromide (8)[2]

A mixture of ester **7** (3.04 g, 6.14mmol) and 1-methyl-1H-imidazole (2.28 g, 27.8mmol) was heated at 80 °C for 10 min, cooled to r.t. and washed thoroughly with Et_2O (5×40 mL). The residue was dissolved in MeOH (6 mL), then Et_2O (60 mL) was added to the solution. The separated oil was dried under reduced pressure for 1 h to afford bromide **8** as colourless liquid. Yield 3.44 g (97%); $[\alpha]^D_{20}$ = −69.6 (*c* 0.6, $CHCl_3$); IR (K Br): 3302, 2927, 1728, 1691, 1408, 1053, 842 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.33 (brs, 1H), 7.43 (s, 1H), 7.33–7.16 (m, 7H), 5.17–5.13 (m, 1H), 5.07–4.95 (m, 1H), 4.43 (t, *J* = 7.63 Hz, 2H), 4.38–4.28 (m, 1H), 4.01 (s, 3H), 3.70–3.49 (m, 2H), 2.53–2.33 (m, 4H), 1.93 (quin, *J* = 7.63 Hz, 2H), 1.62 (quin, *J* = 6.87 Hz, 2H), 140 (s, 9H), 1.35–1.31 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =172.14, 170.92, 154.38, 143.57, 137.06, 128.33 (2C), 126.28, 125.95 (2C), 123.32, 122.23, 80.52, 72.50, 58.88, 52.07, 52.07, 49.35, 48.83, 36.43, 33.09, 29.29, 28.10, 22.17, 21.13 ppm. HRMS (ESI): m/z $[M]^+$calcd for $C_{27}H_{39}N_4O_5^+$: 499.2915; found: 499.2916.

(*2S,4R*)-*tert*-Buty*l*-2-*((S*)-1-phenylethylcarbamoyl)-4-(pentanoyloxy)pyrrolidine-1-carboxylate (1-methyl-1H-imidazol-3-ium)hexafluorophosphate (9)

A solution of KPF_6 (552 mg, 3mmol) in water (3 mL) was added to a stirred solution of bromide **8 (**1.73 g, 3.0mmol) in water (9 mL). The precipitate was filtered off, washed with water (3×9 mL) and dried under reduced pressure (0.5 Torr) for 1 h to afford

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hexafluorophosphate **9** as colourless solid. Yield 1.66 g (86 %); $[\alpha]_D^{25} = -39.7$ (*c*1.5, $CHCl_3$); IR (K Br): 3294, 2931, 1727, 1655, 1449, 1199, 841cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (s, 1H), 7.26–7.15 (m, 8H), 5.17–5.12 (m, 1H), 5.02–4.91 (m, 1H), 4.33–4.24 (m, 1H), 4.05 (t, *J* = 7.63 Hz, 2H), 3.77 (s, 3H), 3.67–3.39 (m, 2H), 2.28–2.26 (m, 3H), 1.85–1.80 (m, 3H), 1.54 (t, *J* = 7.63 Hz, 2H), 1.40 (s, 9H), 1.35–1.31 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.26, 171.14, 154.24, 143.43, 135.56, 128.34 (2C), 126.91, 125.71 (2C), 123.44, 122.05, 80.61, 72.51, 59.02, 53.36, 49.17, 48.71, 36.47, 35.80, 34.07, 32.83, 27.92, 21.89, 20.81 ppm.^{19}F NMR (376 MHz): $\delta = -71.63$ (d, $J_{P\text{-}F}$ = 710.62 Hz) ppm; ^{31}P NMR (161 MHz): δ = −143.64 (heptet, $J_{P\text{-}F}$= 715.50 Hz) ppm. HRMS (ESI): m/z $[M]^+$calcd for $C_{27}H_{39}N_4O_5^+$: 499.2915; found: 499.2917.

(*2S,4R*) -*2-((S)*-1-Phenylethylcarbamoyl)-4-(pentanoyloxy)pyrrolidine (1-methyl-1H-imidazol-3-ium)bromide (2)[1]

The bromide **8** (1.79 g, 3.1mmol) was dissolved in dry dichloromethane (2.5 mL) and trifluoroacetic acid (2.5 mL) was added, then stirred at room temperature for 6 h. Reaction mixture was concentrated *in vacuo,* dissolved in H_2O (10 mL), and the pH was adjusted to ~ 8 by adding 10% NaOH. The product was then extracted with dichloromethane (3x10 mL), dried over $MgSO_4$, and concentrated *in vacuo* yielding hydroscopic colourless liquid **(2)**. Yield 1.48 g (87%); $[\alpha]_D^{25}$= −18.6 (*c*1.8, CH_3OH); IR (K Br): 3419, 2924, 1684, 1457, 1052, 842 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (brs, 1H), 9.42 (s, 1H), 7.35—7.32 (m, 7H), 5.23–5.12 (m, 1H), 4.91–4.71 (m, 2H), 4.20–4.15 (m, 2H), 3.88 (s, 3H), 3.56–3.40 (m, 2H), 2.35–2.28 (m, 2H), 2.10–2.03 (m, 1H), 1.86–1.78 (m, 3H), 1.66–1.54 (m, 2H), 1.39 (d, *J* = 6.87 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.32, 165.90, 143.50, 137.02, 128.01 (2C), 126.52, 125.39 (2C), 123.00, 121.83, 72.79, 57.93, 51.74, 50.61, 49.39, 48.75, 35.69, 32.75, 28.67, 21.88, 20.47 ppm. HRMS (ESI): m/z $[M]^+$calcd for $C_{22}H_{31}N_4O_3^+$: 399.2391; found: 399.2385.

(*2S,4R*)-*2-((S)*-1-phenylethylcarbamoyl)-4-(pentanoyloxy)pyrrolidine (1-methyl-1H-imidazol-3-ium)hexafluorophosphate (3)[1]

The compound **9** (1.35 g, 2.1 mmol) was dissolved in dry dichloromethane (2.0 mL) and trifluoroacetic acid (2.0 mL) was added, then stirred at room temperature for 6 h. Reaction mixture was concentrated *in vacuo,* dissolved in H_2O (10 mL), and the pH was adjusted to ~ 8 by adding 10% NaOH. The product was then extracted with dichloromethane (3x10 mL), dried over $MgSO_4$, and concentrated *in vacuo* yielding hydroscopic colourless liquid **(3)**. Yield 0.969 g (85%); $[\alpha]_D^{25}$= −72.1 (*c* 0.69, CH_3OH); IR (KBr): 3436, 2927, 1677, 1046, 841 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17−9.15 (bs, 2H), 7.76 (d, *J* = 1.53 Hz, 1H), 7.03 (s, 1H), 7.33—7.21 (m, 5H), 5.24 (t, *J* = 4.20 Hz, 1H), 4.93 (quintet, *J* = 7.63 Hz, 1H), 4.41 (m, 1H), 4.17 (t, *J* = 7.63 Hz, 2H), 3.84 (s, 3H), 3.56–3.52 (m, 1H), 3.38–3.31 (m, 1H), 2.54–2.49 (m, 1H), 2.34 (t, *J* = 7.63 Hz, 2H), 2.03–1.96 (m, 1H), 1.80 (quintet, *J* = 7.63 Hz, 2H), 1.49 (quintet, *J* = 7.63 Hz, 2H), 1.38 (d, *J* = 7.63 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.04, 166.19, 144.05 (CH), 136.69 (CH), 128.48 (2xCH), 126.96 (CH), 125.77 (2xCH), 123.72 (CH), 122.33 CH), 73.07 (CH), 58.03 (CH), 50.62 (CH_2), 48.77 (CH), 48.46 (CH_2), 35.77 (CH_3), 35.51 (CH_2), 32.57 (CH_2), 28.79 (CH_2), 22.46 (CH_3), 20.70 (CH_2) ppm.^{19}F

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NMR (376 MHz):δ= −72.30 (d, $J_{P\text{-}F}$ = 710.34 Hz) ppm;^{31}P NMR (161 MHz): δ= −144.12 (heptet, $J_{P\text{-}F}$= 708.44 Hz) ppm. HRMS (ESI): m/z $[M]^+$calcd for $C_{22}H_{31}N_4O_3^+$: 399.2391; found: 399.2390.

General procedure for asymmetric aldol reaction

The organocatalyst (**IL-3)** (10.8 mg, 0.02 mmol), cyclohexanone (0.310 mL, 3 mmol) and acetic acid (1.1 μL, 0.02 mmol) was stirred for 20 min at −15 °C, then 4-nitrobenzaldehyde **10** (151 mg, 1 mmol) was added. The reaction mixture was stirred for a specified reaction time period at same temperature. The crude aldol product was purified by flash column chromatography on silica gel (hexane/ethyl acetate (3/1)). The diastereomeric ratio was determined by ^{1}H-NMR of the crude product. The *ee* of the aldol product was determined by HPLC using chiral column (chiralpak AD-H and OD-H) using hexane/2-propanol as mobile phase.

(*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone (11) [19a]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 4.84 (dd, J = 7.60, 3.2 Hz, 1H), 4.12 (s, OH, 1H), 2.64–2.52 (m, 1H), 2.48–2.41 (m, 1H), 2.34–2.26 (m, 1H), 2.08–2.02 (m, 1H), 1.81–1.78 (m, 1H), 1.66–1.45 (m, 3H), 1.36–1.26 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.93, 148.49, 147.68, 127.88 (2C), 123.44 (2C), 73.97, 57.20, 42.66, 30.75, 27.71, 24.69 ppm. HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm, 25 °C): t_{minor} = 22.6 min, t_{major} = 30.9 min, *ee*: 94%.

Conclusions

In summary, we designed a new, efficient, and reusable organocatalyst for the direct asymmetric aldol reaction. **IL 3** was synthesised in 55% of overall yield in 6 steps. Only 2 mol% of hydrophobic **IL 3** was efficiently catalysed the reaction at -15°C in solvent-free conditions. The scope and limitations of the catalyst was investigated for the reaction between benzaldehyde derivatives and cycloalkanes, gave corresponding aldol products in 25-90% yields with up to 99% *ee* of *anti* diastereomer. Poor yield of the aldol product was obtained with methoxy-benzaldehyde which can be improved by increasing the catalyst loading. The isolation of the product from the catalyst is difficult by precipitation for this reaction. We have used alternative method for resuse of organocatalyst (**IL 3**) and the catalyst was successfully reused up to 6 continuous cycles with excellent yields of the aldol product with 92% *ee* and shown better activity in continouos cycles compared to the *trans*-4-hydroxy-(L)-prolinamide (**1**).

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