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Ionic-Liquid-Supported Organocatalyst: Efficient and Recyclable Ionic-Liquid-Anchored Proline for Asymmetric Aldol Reaction

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Abstract: Ionic-liquid-anchored (*2S,4R*)-4-hydroxyproline **12** catalyzes direct asymmetric aldol reactions with comparable enantioselectivities in DMSO, and with superior enantioselectivities in neat acetone or 2-butanone, than (*S*)-proline **(8)** (up to 28% *ee* difference) itself. Furthermore, the supported catalyst **12** can be easily recycled and reused for at least four times without significant loss of yields and enantioselectivity.

Keywords: asymmetric aldol reactions; catalysis; ionic liquids; proline; supported synthesis

Introduction

Catalysis of reactions, especially asymmetric reactions, by simple metal-free organic molecules (organocatalysis) has become an important area of research in recent years.[1] Among the organocatalysts developed thus far, the proline-catalyzed asymmetric aldol reaction is particularly interesting.[2] Proline catalyzes the aldol reaction, which is arguably one of the most important carbon-carbon bond-forming reactions in nature, by imitating the class I aldolase enzyme through an enamine mechanism.[3] The reaction generally produces moderate to good *ee* values in an atom-economical manner.[4] The extent of enantioselectivity in the reaction was found to be dependent on the solvent systems used. Dimethyl sulfoxide (DMSO) was reported to be the solvent of choice which made the reaction work-up and catalyst recycling difficult.[4] Some proline-based peptides have also been applied to the direct asymmetric aldol reactions where DMSO was again used as the reaction solvent.[5] Since the organocatalyst is usually used in substantial quantity (30 mol% in the proline case), the efficient recovery and reuse of the organocatalyst have become a major concern. Thus far, a number of ways have been explored to establish new process for the proline-catalyzed direct asymmetric aldol reactions so that the catalyst can be recovered readily. Two earlier attempts, by using proline-insoluble chloroform as solvent to get quantitative recovery of the catalyst through filtration, or by immobilizing (*S*)-proline on a silica gel column, all resulted in significant decrease in enantioselectivity.[4c] Using polyethylene glycol (PEG) as the soluble polymer support, PEG-supported (*2S,4R*)-4-hydroxyproline has successfully been applied to the asymmetric aldol reactions.[6] The reactions could be carried out under the desired homogeneous catalysis conditions in DMSO or DMF, and the catalyst could be recovered due to the insolubility of PEG in less polar solvents. Constant *ee* values were obtained during four cycles of reaction, but the yields diminished after the second recycle of the catalyst. The use of room temperature ionic liquids as reaction media has also been tested by several research groups as an approach for recycling and reuse of the catalyst.[7] Good yields and enantioselectivities, comparable to those from the reactions in DMSO, could be obtained in the first run of the reactions; but an obvious decrease of *ee* and yield was observed in some cases during the recycling and reuse of the catalyst system.[7b] Recently, the approach of 'supported ionic liquid asymmetric catalysis' has been developed.[8] An ionic liquid moiety is attached covalently in a monolayer to the surface of silica gel. The (*S*)-proline is then supported on the surface of the modified silica gels with or without additional adsorbed ionic liquid. Good yields and *ee* values have been obtained and the catalytic system can be recovered easily by simple filtration. The catalyst can be recycled by and reused for a number of times without any loss of activity. Nevertheless, the *ee* obtained in the aldol reaction was lower than that from homogeneous conditions in DMSO or in ionic liquids. There is, therefore, a need to develop new proline-based catalysts which are easily recyclable and preferably possess enhanced catalytic abilities.

In addition to being used as reaction media for organic reactions, functionalized ionic liquids have been

used for a variety of purposes and are sometimes referred to as 'task specific ionic liquids'.[9] Recently, we and others have developed the concept of ionic-liquid-supported synthesis (ILSS) based on the fact that the solubilities of ionic liquids can be tuned readily to get phase separation from organic as well as aqueous media by choosing different cations and anions. The ionic liquid moiety can therefore be used as soluble support for synthesis. Thus far, the ILSS strategy has been successfully applied to the synthesis of small molecules,[10] oligopeptides,[11] oligosaccharides[12] as well as oligonucleotides.[13] The applications of ionic-liquid-supported reagents[14] and catalysts[15] have also been explored. Chiral ionic liquids have also been examined as reaction media for several organic reactions, but the enantioselectivity has been relatively poor.[16] As far as we are aware, there is still no successful example on the use of ionic-liquid-supported chiral organocatalyst in asymmetric organic synthesis. One advantage of using an ionic-liquid-supported chiral catalyst is that the chiral catalyst can be recovered easily from the substrate, reagent and the product mixture simply by solubility difference as illustrated in Figure 1. We have now applied the idea to the proline-catalyzed direct asymmetric aldol reactions and report our results.

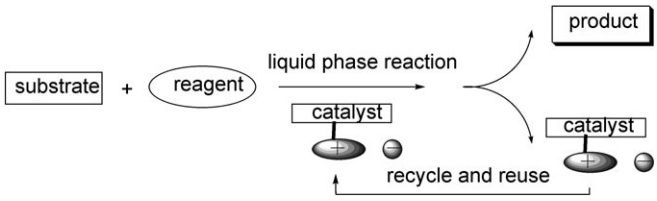
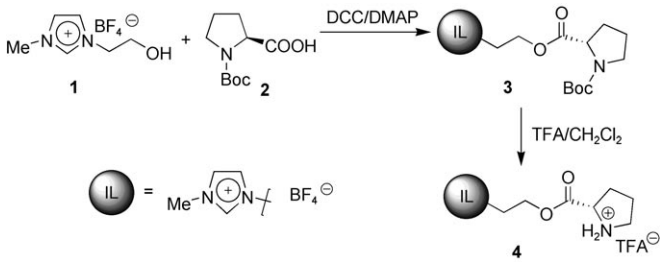


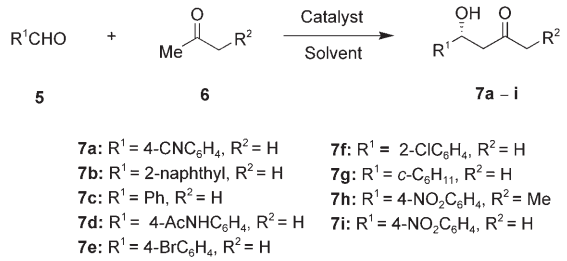
Figure 1. General concept of ionic-liquid-supported catalysis (ILSC).

Results and Discussion

It is well known from previous observations that the acidic proton in the proline is essential for efficient catalysis to occur.[4c] We were interested to know, however, if the imidazolium moiety can replace the role of the acidic proton, especially in view of the fact that the C-2 hydrogen of the imidazolium cation is fairly acidic. We thus started with the synthesis of the ionic-liquid-supported proline **4** according to Scheme 1. Coupling of the ionic liquid support **1**[10c,11] with commercially available Boc-Pro-OH under DCC/DMAP conditions afforded the ionic-liquid-supported Boc-proline **3** which, upon deprotection with trifluoroacetic acid, gave **4** in its TFA salt form. The catalytic activities of **4** were then examined by the direct asymmetric aldol reactions of 4-cyanobenzaldehdye with acetone (Scheme 2). When a mixture of 4-cyanobenzaldehyde (**5**, R^1 = 4-CNC_6H_4), **4** (30



Scheme 1. Preparation of ionic-liquid-supported proline **4**.



Scheme 2. Asymmetric aldol reactions.

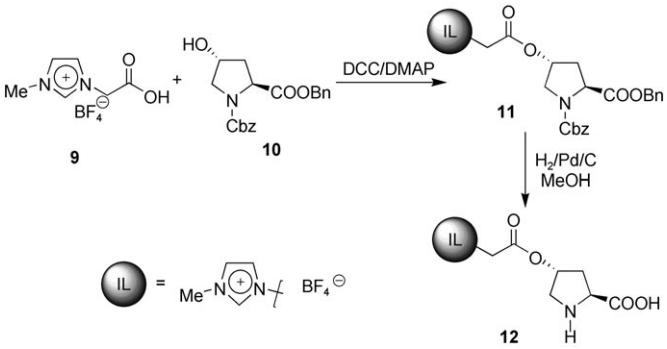
mol%) and 1 equivalent of *N*-methylmorpholine (NMM), in acetone (**6**, R^2 = H) was stirred at room temperature for 25 h, the aldol product **7a** was obtained, however, in only about 10% yield and 11% *ee* (Table 1, entry 1). The result was rather poor compared to that from the unsupported (*S*)-proline **8** which can give 49% yield and 56% *ee* under almost identical condition (no NMM base used) (Table 1, entry 2).

We then prepared the ionic-liquid-supported (*2S,4R*)-4-hydroxyproline **12**, which retains the free carboxylic acid group, according to Scheme 3. After coupling the ionic liquid carboxylic acid **9** with the readily available *N*-benzyloxycarbonyl-(*2S,4R*)-4-hydroxyproline benzyl ester **10**,[17] the supported proline **11** was then deprotected by hydrogenation to afford the ionic-liquid-supported proline **12** in very good yield and high purity. When **12** was applied as the catalyst to the direct asymmetric aldol reaction in acetone under the same conditions as before, **7a** was obtained in much better isolated yield (59%) and enantio excess (72% *ee*) (Table 1, entry 3). To test the general scope of the prepared ionic-liquid-supported (*2S,4R*)-4-hydroxyproline **12** as catalyst, a series of aldehyde acceptors including both aromatic and aliphatic aldehydes and two ketone donors, acetone and 2-butanone, were subjected to the same reaction conditions. For comparison, (*S*)-proline **8** catalyzed-reactions of the above substrates in neat ketone, as well as **8** and **12** catalyzed-reactions in DMSO were also carried out, and all the results are listed in Table 1.

We can see from Table 1 that in all cases, ionic-liquid-supported proline **12**-catalyzed reactions in neat ketone afforded similar yields of aldol products

Table 1. Ionic-liquid-supported catalysts **4**, **12** and (*S*)-proline **8** catalyzed asymmetric aldol reactions.

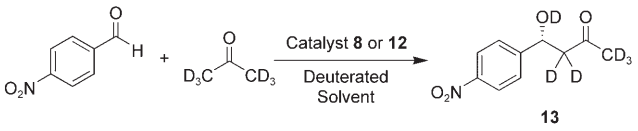
Entry	Aldehyde **5** (R^1)	Ketone **6** (R^2)	Catalyst	Solvent	Product	Isolated Yield [%]	*ee* [%]
1	4-CNC_6H_4	H	**4**	acetone	**7a**	10	11
2	4-CNC_6H_4	H	**8**	acetone	**7a**	49	56
3	4-CNC_6H_4	H	**12**	acetone	**7a**	59	72
4	4-CNC_6H_4	H	**8**	DMSO	**7a**	52	73
5	4-CNC_6H_4	H	**12**	DMSO	**7a**	46	72
6	2-naphthyl	H	**8**	acetone	**7b**	44	62
7	2-naphthyl	H	**12**	acetone	**7b**	50	80
8	2-naphthyl	H	**8**	DMSO	**7b**	48	76
9	2-naphthyl	H	**12**	DMSO	**7b**	47	79
10	C_6H_5	H	**8**	acetone	**7c**	51	48
11	C_6H_5	H	**12**	acetone	**7c**	50	76
12	C_6H_5	H	**8**	DMSO	**7c**	55	62
13	C_6H_5	H	**12**	DMSO	**7c**	52	60
14	4-$AcNHC_6H_4$	H	**8**	acetone	**7d**	40	56
15	4-$AcNHC_6H_4$	H	**12**	acetone	**7d**	40	64
16	4-$AcNHC_6H_4$	H	**8**	DMSO	**7d**	52	61
17	4-$AcNHC_6H_4$	H	**12**	DMSO	**7d**	50	63
18	4-BrC_6H_4	H	**8**	acetone	**7e**	62	63
19	4-BrC_6H_4	H	**12**	acetone	**7e**	58	73
20	4-BrC_6H_4	H	**8**	DMSO	**7e**	65	63
21	4-BrC_6H_4	H	**12**	DMSO	**7e**	60	75
22	2-ClC_6H_4	H	**8**	acetone	**7f**	92	57
23	2-ClC_6H_4	H	**12**	acetone	**7f**	92	71
24	2-ClC_6H_4	H	**8**	DMSO	**7f**	82	65
25	2-ClC_6H_4	H	**12**	DMSO	**7f**	83	70
26	*c*-C_6H_{11}	H	**8**	acetone	**7g**	42	72
27	*c*-C_6H_{11}	H	**12**	acetone	**7g**	43	85
28	*c*-C_6H_{11}	H	**8**	DMSO	**7g**	53	86
29	*c*-C_6H_{11}	H	**12**	DMSO	**7g**	49	86
30	4-$NO_2C_6H_4$	CH_3	**8**	acetone	**7h**	55	51
31	4-$NO_2C_6H_4$	CH_3	**12**	acetone	**7h**	51	71
32	4-$NO_2C_6H_4$	CH_3	**8**	DMSO	**7h**	53	70
33	4-$NO_2C_6H_4$	CH_3	**12**	DMSO	**7h**	56	75
34	4-$NO_2C_6H_4$	H	**8**	acetone	**7i**	68	71
35	4-$NO_2C_6H_4$	H	**12**	acetone	**7i**	64	85
36	4-$NO_2C_6H_4$	H	**8**	DMSO	**7i**	64	75
37	4-$NO_2C_6H_4$	H	**12**	DMSO	**7i**	60	87



Scheme 3. Preparation of ionic-liquid-supported proline **12**.

as unsupported (*S*)-proline **8**, but generally with better enantioselectivities. For benzaldehyde, the difference in *ee* value was up to 28% ee (entries 10 and 11). On the other hand, the aldol reactions catalyzed by the two catalysts in DMSO produced nearly similar yields and *ee* values (for examples, entries 8 and 9 or entries 12 and 13). An important advantage of using the ionic-liquid-supported catalyst **12** is that the use of DMSO as solvent can actually be avoided. The aldol reactions performed in pure ketone with **12** gave quite comparable or superior results to those obtained in DMSO (compare, for example: entries 3 and 5, entries 7 and 9, entries 11 and 13, etc.). In contrast, for (*S*)-proline **8**, the reaction results from neat ketone are much lower than those from DMSO (compare, for example: entries 2 and 4, entries 6 and 8, entries 10 and 12, etc) in term of enantioselectivities in agreement with reports by previous studies.[4] This renders the ionic-liquid-supported proline **12**-catalyzed aldol reactions much easier to work-up since acetone or butanone can be easily removed by simple distillation.

During our studies on the above catalytic aldol reactions, we noticed that the reactions from the supported proline **12** were generally faster than those from (*S*)-proline **8**. To have a clear comparison of the two catalysts, we have carried out the reactions of 4-nitrobenzaldehyde in deuterated acetone with **8** or **12** as catalyst, respectively, and monitored the reaction systems by proton NMR spectroscopic analysis (Scheme 4). As shown in Figure 2, both reactions



Deuterated Solvent: Neat acetone-d_6 or DMSO-d_6/acetone-d_6 = 4:1

Scheme 4. NMR studies of **8**- and **12**-catalyzed aldol reaction between 4-nitrobenzaldehyde and deuterated acetone.

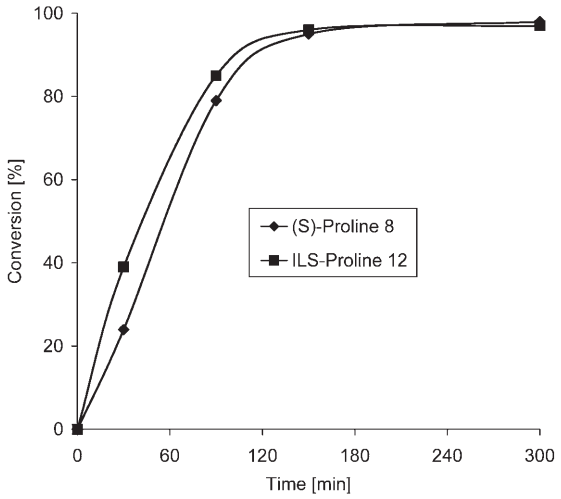


Figure 2. Comparison of **8**- and **12**-catalyzed aldol reaction between 4-nitrobenzaldehyde and neat deuterated acetone.

from **12** and **8** reached equilibrium at about the 2.5 h stage, with the conversions at 96% and 95% for **12**- and **8**-catalyzed reactions, respectively. However, at the initial stage before the reactions reached equilibrium, the one catalyzed by the ionic liquid-supported proline **12** was found to be faster than that catalyzed by (*S*)-proline **8**. For example, at the 0.5 h stage, the reaction conversions were 39% and 24% for **12** and **8**, respectively. We have also performed a similar study of **12**- and **8**-catalyzed aldol reactions in deuterated DMSO (data not shown) and found that the reactions could come to equilibrium much faster, within 30 min. Even so, we were able to show that at least at the stage of 10 min, the reaction conversion from **12** (87%) was slightly higher than that from **8** (83%). The results revealed here, plus those shown in the enantiomeric selectivity studies, seemed to suggest that the synthetic ionic-liquid-supported proline **12** is a more efficient organocatalyst than proline **8** itself. This suggests that the ionic moiety in **12** plays more than a silent or simply supporting role in the reaction.[6] Previously, it has been reported that reactions in ionic liquids are sometimes faster than in conventional organic solvents,[18] and ionic liquid itself has been shown to possess weak Lewis acidity that can serve as catalyst for organic reactions.[19] It is possible that when the ketone **6** forms an enamine intermediate with the catalyst **12**, as postulated for proline-catalyzed aldol reaction,[3] the enamine intermediate's reaction with the aldehyde **7** may be facilitated by the proximity of the ionic moiety.

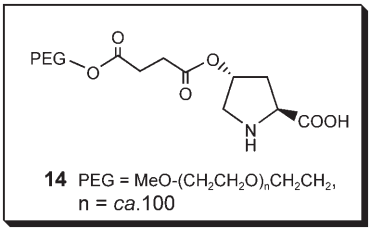
We have also examined the recyclability of the ionic-liquid-supported proline **12** as catalyst. We chose the reaction of 4-nitrobenzaldehyde in acetone as a model study. When the first run of the reaction was completed, the reaction mixture was concentrated and rinsed with dichloromethane for two times. After centrifuging, the clear dichloromethane solution was decanted, combined and concentrated to give the aldol product **7i**, whereas the residue contained the dichloromethane insoluble **12**. The recycled catalyst was dried under vacuum for 1 h and reused for the next cycle of reaction. The procedure was repeated for another three times and it was found that the aldol product **7i** could be obtained in comparable yield and *ee* value through the process (Table 2).

Table 2. Recycling studies of ionic-liquid-supported proline **12** catalyzed aldol reaction between 4-nitrobenzaldehyde and acetone.

Cycle	Catalyst	Isolated yield [%]	*ee* [%]
1	**12**	68	85
2	**12**	68	85
3	**12**	66	83
4	**12**	64	82

It is perhaps instructive to compare the use of ionic-liquid-supported proline **12** with the PEG-supported proline **14**[6] since both are designed to perform the same function as a homogeneous recyclable catalyst in the asymmetric aldol reaction.[20] Using 4-nitrobenzaldehyde and acetone as the common reaction, catalyst **14** was reported to give the adduct **7i** in DMSO in 36% yield (60% *ee*) in 20 h and in 73% yield (62% *ee*) in 48 h.[6] By comparison, catalyst **12** gave the adduct **7i** in DMSO in 60% yield (87% *ee*) in 25 h. On the other hand, when the same reaction was conducted in acetone, catalyst **14** was reported to give **7i** in 23% yield (21% *ee*) in 48 h whereas catalyst **12** gave **7i** in 64% yield (85% *ee*) in 25 h. In terms of recyclability, the yield of **7i** changed from 68% (77% *ee*) to 51% (75% *ee*) in four cycles for

catalyst **14**, whereas the yield of **7i** changed from 68% (85% *ee*) to 64% (82% *ee*) in four cycles for catalyst **12**. Finally, it should be pointed out that catalyst **14** requires a PEG of M_w 5000 for catalytic moiety, whereas the imidazolium moiety in **12** has a formal molecular weight of about 110. The lower molecular weight of **12** not only means less waste eventually, but also allows for easier monitoring of the reaction mixture throughout with conventional spectroscopy such as ^{1}H NMR (Figure 2).



14 PEG = MeO-$(CH_2CH_2O)_n CH_2CH_2$, n = *ca.*100

Conclusions

We have applied the concept of ionic-liquid-supported organocatalysis to proline-catalyzed direct asymmetric aldol reactions. The prepared ionic-liquid-supported proline **12** showed superior catalytic activities than proline **8** in neat ketone reaction systems, thus reducing the need to use DMSO or DMF as a solvent for the reaction. Furthermore, catalyst **12** can be easily recycled and reused with the same efficacies for four cycles.

Experimental Section

General Remarks

All reagents were obtained commercially and were used without further purification unless otherwise noted. Solvents were reagent grade and if necessary, were dried by standard procedures. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plastic backed plates and was visualized by irradiation with UV light and/or by dipping into a solution of ammonium molybdate (2.5 g) and ceric sulfate (1 g) in concentrated H_2SO_4/H_2O (10 mL/90 mL) and heated with a heat gun. Flash chromatography was performed by using silica gel 60 A (particle size 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz) or Mercury-400 (400 MHz) or 500 MHz spectrometers at 20 °C. Chemical shifts for protons are reported in parts per million and referenced to residual proton in deuterated chloroform (δ = 7.26), deuterium oxide (δ = 4.60) or acetone (δ = 2.06). The coupling constants, J are reported in Hz. Carbon chemical shifts are reported in parts per million relative to the carbon resonance of the methyl group of chloroform-d_1 (δ = 77.0) or acetone-d_6 (δ = 29.8, 206). Enantiomeric excess values of aldol products were determined by analytical HPLC using Daicel Chiralcel OD-H or Chiralpak AD analytical columns with 2-propanol in hexanes as the eluent. High resolution mass spectrometric analyses were preformed on a VG Micromass ZAB 2F HS spectrometer (FAB) or a Micromass Quattro II triple quadrupole mass spectrometer (Manchester, UK) equipped with an electrospray source (ESIMS). Ionic liquid support **1**,[10c,11] **9**,[21] and *N*-benzyloxycarbonyl-(2*S*,4*R*)-4-hydroxyproline benzyl ester **10**[17] were prepared according to literature procedures.

Preparation of Ionic-Liquid-Supported Boc-Proline 3

To a mixture of ionic liquid **1** (0.75 g, 3.5 mmol), Boc-(*S*)-proline (1.20 g, 5.6 mmol) and dimethylaminopyridine (0.05 g, 0.4 mmol) in dry acetonitrile (30 mL) was added dicyclohexylcarbodiimide (1 M in CH_2Cl_2, 7 mL, 7 mmol). The reaction mixture was stirred vigorously for 18 h at room temperature under nitrogen and then filtered through a plug of celite. The celite plug was rinsed with acetonitrile and the combined organic phase was concentrated under vacuum. The crude residue was washed firstly with ether (15 mL × 3), then dissolved in CH_2Cl_2 and washed with 2 M HCl (10 mL × 2). The organic phase was dried over Na_2SO_4 and concentrated to afford ionic-liquid-supported Boc-proline **3** as a pale yellow foam like solid; yield: 1.28 g (89%). ^{1}H NMR (400 MHz, acetone-d_6; 2 conformational isomers): δ = 9.02 and 8.99 (s, 1H), 7.80 and 7.78 (s, 1H), 7.70 (s, 1H), 4.72–4.43 (m, 4H), 4.25–4.23 (m, 1H), 4.05 (s, 3H), 3.44–3.35 (m, 2H), 2.28–1.83 (m, 4H), 1.44 and 1.30 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6; 2 conformational isomers): δ = 172.54 and 172.48, 154.29 and 153.25, 137.61 and 137.44, 124.17 and 124.03, 123.21, 79.56 and 79.24, 63.25 and 62.97, 59.29 and 59.04, 48.98 and 48.80, 46.93 and 46.58, 36.2, 30.9 and 29.9, 28.18 and 27.96 (3C), 24.6 and 23.8; HR-MS (ESI): m/z = 324.1913, calcd. for $C_{16}H_{26}N_3O_4^+$ (M^+): 324.1918.

Ionic-Liquid-Supported Proline TFA Salt 4

To a solution of ionic liquid supported Boc-proline **3** (0.82 g, 2 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL). The reaction mixture was stirred at room temperature under nitrogen for 0.5 h. After concentration under reduced pressure, the residue was washed twice with ether and dried on a vacuum line to afford the ionic-liquid-supported proline TFA salt **4** as a pale yellow foam like solid; yield: 0.91 g (98%). ^{1}H NMR (400 MHz, acetone-d_6): δ = 9.25 (s, 0.4H), 9.14 (s, 0.6H), 7.84 (s, 1H), 7.72 (s, 0.6H), 7.68 (s, 0.4H), 5.48 (t, J = 5.2 Hz, 1H), 4.78–4.62 (m, 4H), 4.29–4.13 (m, 2H), 4.05 (s, 1.8H), 4.04 (s, 1.2H), 3.58–3.41 (m, 1H), 2.56–2.20 (m, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ = 168.30 (0.4C) 167.10 (0.6C), 137.81 (0.4C), 137.56 (0.6C), 124.20 (0.6C), 124.05 (0.4C) 123.30 (0.6C), 123.20 (0.4C), 66.80 (0.6C), 65.11 (0.6C), 64.56 (0.4C), 59.50 (0.4C), 55.30 (0.6C), 48.60 (0.4C), 48.50 (0.6C), 45.97 (0.4C), 36.2 (0.6C), 36.1 (0.4C), 29.7 (0.6C), 28.1 (0.4C), 23.9 (0.4C), 23.3 (0.6C); HR-MS (ESI): m/z = 224.1391, calcd. for $C_{11}H_{18}N_3O_2^+$ (M^+): 224.1394.

Procedure for 4-Catalyzed Aldol Reaction of Acetone and 4-Cyanobenzaldehyde

To a mixture of 4-cyanobenzaldehyde (0.1 mmol), **4** (30 mol%) and acetone (1.0 mL) was added *N*-methylmorpholine (30 mol%) and the reaction mixture was stirred at room temperature for 25 h. After concentration under reduced pressure, the residue was subjected directly to flash silica gel column chromatography using hexanes/ethyl acetate as eluent to give the pure aldol product 4-(4-cyanophenyl)-4-hydroxy-2-butanone (**7a**). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.65$ (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 5.21 (m, 1H), 2.85 (m, 2H), 2.23 (s, 3H); HPLC (Daicel Chiralcel OD-H column, hexane/2-propanol = 95: 5, flow rate: 1 mL min^{-1}, $\lambda = 254$ nm), t_R (major) = 39.18 min, t_R (minor) = 46.37 min.

Preparation of Ionic-Liquid-Supported Proline Benzyl Ester 11

To a mixture of ionic liquid **9** (0.41 g, 1.8 mmol), *N*-benzyloxycarbonyl-(*2S,4R*)-4-hydroxyproline benzyl ester (0.75 g, 2.1 mmol) and dimethylaminopyridine (0.05 g, 0.4 mmol) in dry acetonitrile (20 mL) was added dicyclohexylcarbodiimide (1 M in CH_2Cl_2, 3.5 mL, 3.5 mmol). The reaction mixture was stirred vigorously for 18 h at room temperature under nitrogen and then filtered through a plug of celite. The celite plug was rinsed with acetonitrile and, the combined organic phase was concentrated under vacuum. The crude residue was washed firstly with ether (10 mL × 6), then dissolved in CH_2Cl_2 and washed with 2 M HCl (6 mL × 2). The organic phase was dried over Na_2SO_4 and concentrated to afford ionic-liquid-supported proline benzyl ester **11** as slightly yellow foam like solids; yield: 0.81 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.68$ (s, 1H), 7.34–7.15 (m, 12H), 5.33 (s, 1H), 5.15–4.90 (m, 6H), 4.48 (dt, $J = 16.4$ Hz, 7.6 Hz, 1H), 3.80 (s, 3H), 3.76–3.68 (m, 2H), 2.55–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$; 2 conformational isomers): $\delta = 172.1$ and 172.0, 166.1, 154.8 and 154.3, 137.7, 136.5 and 136.4, 135.6 and 135.4, 128.8 (4C), 128.7 and 128.6, 128.58 and 128.51, 128.4 (2C), 128.3 and 128.20, 128.00 and 127.90, 124.00 and 123.96, 123.49 and 123.44, 75.4 and 74.6, 67.6, 67.3, 58.4 and 57.9, 52.5 and 52.2, 50.0 36.6, 36.57 and 36.48; HR-MS (ESI): $m/z = 478.1963$, calcd. for $C_{26}H_{28}N_3O_6^+$ (M^+): 478.1973.

Ionic-Liquid-Supported Proline 12

To a solution of **11** (0.30 g, 0.53 mmol) in methanol (15 mL) was added palladium on charcoal catalyst (10%, 70 mg). The mixture was stirred under hydrogen at room temperature for 5 h. After filtration through cellulose and celite to remove the catalyst, the solvent was evaporated under vacuum to give ionic-liquid-supported proline **12** as a white solid; yield: 0.18 g (99%). ^{1}H NMR (500 MHz, D_2O): $\delta =$ 8.70 (s, 1H), 7.40 (s, 2H), 5.52 (s, 1H), 5.10 (s, 2H), 4.23 (t, $J = 8.5$ Hz, 1H), 3.82 (s, 3H), 3.63–3.49 (m, 2H), 2.54–2.26 (m, 2H); ^{13}C NMR (100 MHz, D_2O): $\delta = 172.9$ 167.10, 137.5, 123.7, 123.5, 76.0, 60.0, 50.8, 50.0, 36.2, 35.1; HR-MS (ESI): $m/z = 254.1139$, calcd. for $C_{11}H_{16}N_3O_4^+$ (M^+): 254.1135.

General Procedure for Ionic-Liquid-Supported Proline 12- and (*S*)-Proline 8-Catalyzed Aldol Reaction (no DMSO)

To a solution of aldehyde (0.1 mmol) in the ketone donor (1 mL) was added the catalyst (30 mol%) and the resulting mixture was stirred at room temperature for 25 h. After concentration under reduced pressure, the residue was subjected directly to flash silica gel column chromatography using hexanes/ethyl acetate as eluent to give the pure aldol products.

General Procedure for Ionic-Liquid-Supported Proline 12- and (*S*)-Proline 8-Catalyzed Aldol Reaction (in DMSO)

To a solution of aldehyde (0.1 mmol) in DMSO (0.8 mL) and the ketone donor (0.2 mL) was added the catalyst (30 mol%) and the resulting mixture was stirred at room temperature for 25 h. After evaporation of the volatile components under reduced pressure, the residue was subjected directly to flash silica gel column chromatography using hexanes/ethyl acetate as eluent to give the pure aldol products.

4-(2-Naphthyl)-4-hydroxy-2-butanone (7b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.82$ (m, 4H), 7.47 (m, 3H), 5.33 (m, 1H), 3.40 (s, br, 1H), 2.94 (m, 2H), 2.23 (s, 3H); HPLC (Daicel Chiralpak AD column, hexane/2-propanol = 92.5:7.5, flow rate: 1 mL min^{-1}, $\lambda = 254$ nm), t_R (major) = 18.65 min, t_R (minor) = 23.2 min.

4-Phenyl-4-hydroxy-2-butanone (7c): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.28$–7.18 (m, 5H), 5.06 (m, 1H), 2.77 (m, 2H), 2.11 (s, 3H); HPLC (Daicel Chiralpak AD column, hexane/2-propanol = 92.5:7.5, flow rate: 0.8 mL min^{-1}, $\lambda = 254$ nm), t_R (major) = 13.68 min, t_R (minor) = 15.00 min.

4-(4-Acetamidophenyl)-4-hydroxy-2-butanone (7d): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$ (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 5.10 (m, 1H), 2.83 (m, 2H), 2.23 (s, 3H); HPLC (Daicel Chiralpak AD column, hexane/2-propanol = 85:15, flow rate: 0.8 mL min^{-1}, $\lambda = 254$ nm), t_R (major) = 22.46 min, t_R (minor) = 24.44 min.

4-(4-Bromophenyl)-4-hydroxy-2-butanone (7e): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$ (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J =$ 8.4 Hz, 2H), 5.10 (m, 1H), 3.31 (s, br, 1H), 2.80 (m, 2H), 2.19 (s, 3H); HPLC (Daicel Chiralpak AD column, hexane/2-propanol = 92.5:7.5, flow rate: 0.8 mL min^{-1}, $\lambda = 254$ nm), t_R (major) = 12.69 min, t_R (minor) = 13.45 min.

4-(2-Chlorophenyl)-4-hydroxy-2-butanone (7f): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.63$–7.18 (m, 4H), 5.50 (m, 1H), 3.02–2.65 (m, 2H), 2.22 (s, 3H); HPLC (Daicel Chiralpak AD column, hexane/2-propanol = 92.5:7.5, flow rate: 0.8 mL min^{-1}, $\lambda = 254$ nm), t_R (major) = 11.14 min, t_R (minor) = 12.54 min.

4-Cyclohexyl-4-hydroxy-2-butanone (7g): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.82$ (m, 1H), 2.58 (m, 2H), 2.20 (s, 3H), 1.87–1.64 (m, 5H), 1.38–0.99 (s, 6H); HPLC (Daicel

Chiralpak AD column, hexane/2-propanol = 97.5:2.5, flow rate: 1.0 mL min^{-1}, λ = 280 nm), t_R (major) = 19.76 min, t_R (minor) = 23.69 min.

5-(4-Nitrophenyl)-5-hydroxy-3-pentanone (7h): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 5.27 (m, 1H), 3.65 (d, J = 3.6 Hz, 1H), 2.83 (m, 2H), 2.49 (q, J = 7.2 Hz, 2H), 1.10 (t, J = 7.2 Hz, 3H); HPLC (Daicel Chiralpak AD column, hexane/2-propanol = 95:5, flow rate: 0.8 mL min^{-1}, λ = 280 nm), t_R (major) = 35.42 min, t_R (minor) = 37.34 min.

4-(4-Nitrophenyl)-4-hydroxy-2-butanone (7i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 5.25 (m, 1H), 3.62 (s, br, 1H), 2.85 (m, 2H), 2.23 (s, 3H); HPLC (Daicel Chiralpak AD column, hexane/2-propanol = 90:10, flow rate: 0.8 mL min^{-1}, λ = 254 nm), t_R (major) = 22.20 min, t_R (minor) = 21.33 min.

Procedure for NMR Studies of Ionic-Liquid-Supported Proline 12- or (*S*)-Proline 8-Catalyzed Aldol Reactions in Deuterated Acetone (Acetone-d_6)

To a solution of 4-nitrobenzaldehyde (0.1 mmol) in acetone-d_6 (1 mL) was added the catalyst (30 mol%) and the resulting mixture was stirred at room temperature and examined at intervals by ^{1}H NMR.

Procedure for NMR Studies of Ionic-Liquid-Supported Proline 12- or (*S*)-Proline 8-Catalyzed Aldol Reactions in Deuterated Dimethyl Sulfoxide (DMSO-d_6)

To a solution of 4-nitrobenzaldehyde (0.1 mmol) in DMSO-d_6 (0.8 mL) and acetone-d_6 (0.2 mL) was added the catalyst (30 mol%) and the resulting mixture was stirred at room temperature and examined at intervals by ^{1}H NMR.

Procedure for the Recycle and Reuse of Ionic-Liquid-Supported Proline 12 in the Catalytic Aldol Reaction

To a solution of 4-nitrobenzaldehyde (0.25 mmol) in acetone (2.5 mL) was added catalyst **12** (30 mol%) and the resulting mixture was stirred at room temperature for 25 h. The volatile component was then removed under reduced pressure and the residue was rinsed with dichloromethane (15 mL × 2). After centrifuging, the clear dichloromethane solution was decanted, combined and concentrated to give the crude aldol product, which was further purified by flash column chromatograph using hexane/ethyl acetate as eluent. The dichloromethane insoluble catalyst **12** was dried under vacuum for 1 h and reused for the next cycle of reaction.

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