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1(*R*),2(*R*)-Bis[(*S*)-prolinamido]cyclohexane/[bmim][BF_4] ionic liquid as an efficient catalytic system for direct asymmetric aldol reactions

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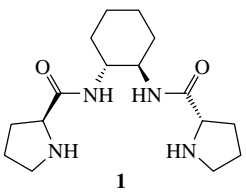
A direct asymmetric aldol reaction between unmodified ketones and aldehydes was achieved for the first time using the 1(*R*),2(*R*)-bis[(*S*)-prolinamido]cyclohexane/[bmim][BF_4] ionic liquid catalytic system.

A direct asymmetric aldol reaction between unmodified aldehydes and ketones is used for the synthesis of chiral β-hydroxy carbonyl compounds, which are valuable intermediates in organic synthesis.[1(a)–(c)] Native amino acids, in particular, (*S*)-proline,[2(a)] (*S*)-tryptophan[2(b)] *etc.*,[2(c)] are generally employed as catalysts. As a rule, a 20- to 30-fold excess of a ketone is required to complete the process, which limits the scope of reaction applications (acetone and simple cycloalkanones) and hampers the product isolation.

(*S*)-Proline containing amides[3(a)–(g)] and peptides[4] are more active catalysts of the asymmetric aldol reaction. They enhance enantioselectivity by running the reaction at lower temperatures (to –40 °C). The reaction rate grew further when an ionic liquid was used as a solvent.[5]

Here, we report the first application of the proline amide/ionic liquid catalytic system in the direct asymmetric aldol reaction between unmodified ketones and aldehydes taken in a ratio of 3:1 (Scheme 1).

1(*R*),2(*R*)-Bis[(*S*)-prolinamido]cyclohexane **1** obtained from available and inexpensive reagents [1(*R*),2(*R*)-diaminocyclohexane and *N*-benzyloxycarbonyl-(*S*)-proline] by a known scheme[6] was used as an organocatalyst. First, we compared the activities of amide **1** and (*S*)-proline **2** (10 mol% each) in a model reaction between *p*-nitrobenzaldehyde **3a** (1 equiv.) and acetone **4a** (3 equiv.) in the 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) (4 equiv.) media. Noticeably higher conversions of **3a** at different reaction stages were achieved in the reaction catalysed by amide **1** than in the respective reaction catalysed by amino acid **2**. These are indicative of a higher efficiency of the chosen catalyst (Figure 1). Reduction of the **4a**:**3a** molar ratio down to 2:1 resulted in a decrease of the conversion of **3a** by ~10% in 60 min, even though active catalyst **1** was used.



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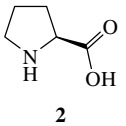

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Next, we investigated the influence of ionic liquid nature on the reaction of asymmetric aldol between *p*-nitrobenzaldehyde **3a** (1 equiv.) and acetone **4a** (3 equiv.) catalysed by amide **1**.

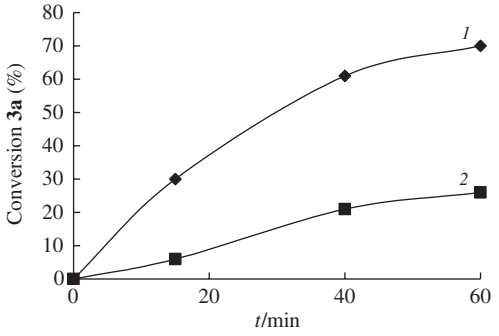


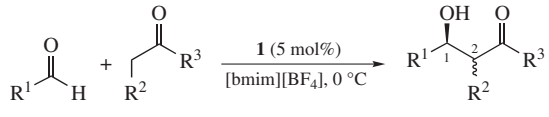
Figure 1 Activities of organocatalysts **1** (curve *1*) and **2** (curve *2*) in the asymmetric aldol reaction between *p*-nitrobenzaldehyde **3a** and acetone **4a** in [bmim][BF_4]. *Reagents and conditions*: **1** and **2** (0.013 mmol each), **3a** (0.13 mmol), **4a** (0.40 mmol), ionic liquid (0.1 ml), 20 °C.

Apart from [bmim][BF_4], we studied [bmim][PF_6], [bmim][NTf_2] and 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim][BF_4]) ionic liquids (Table 1). The reactions were run at 0 °C, the catalyst amount was 5 mol% and the **3a**/ionic liquid molar ratio was 1:4. The highest yield of aldol **5a** (83%) with moderate *ee* (50%) was achieved in [bmim][BF_4].

Table 1 Asymmetric aldol reaction between **3a** and **4a** catalysed by amide **1** in ionic liquids.[a]

Entry	Iolic liquid	Cycle	τ/h	Isolated yield of **5a** (%)	*ee* (%)[b]
1	[bmim][PF_6]	1	15	76	47
2	[bmim][NTf_2]	1	15	70	36
3	[bdmim][BF_4]	1	15	79	48
4	[bmim][BF_4]	1	15	83	50
5		2	15	84	50
6		3	25	70	51

[a]*Reagents and conditions*: **1** (0.006 mmol), **3a** (0.13 mmol), **4a** (0.40 mmol), ionic liquid (0.54 mmol), 0 °C. [b]HPLC, chiral phase Chirapak OJ-H, $\tau(R)$ 20.73 min, $\tau(S)$ 24.93 min.



3a–c **4a–f** **5a–h**

Scheme 1

Table 2 Synthesis of β-hydroxycarbonyl compounds **5** catalysed by the **1**/[bmim][BF_4] system.[a]

Entry	Reagents	Product	R^1	R^2	R^3	τ/h	Isolated yield (%)	*dr* (%)		*ee* (%)[b]	
								syn	*anti*	*syn*	*anti*
1	**3a**, **4a**	**5a**	4-$NO_2C_6H_4$	H	Me	15	83	—		60	
2	**3a**, **4b**	**5b**	4-$NO_2C_6H_4$	H	Et	35	56	—		42	
3	**3a**, **4c**	**5c**	4-$NO_2C_6H_4$	H	cyclopropyl	50	54	—		45	
4	**3a**, **4d**	**5d**	4-$NO_2C_6H_4$	H	$(CH_2)_2CH{=}CMe_2$	60	38	—		52	
5	**3a**, **4e**	**5e**	4-$NO_2C_6H_4$	$(CH_2)_3$		30	43	72	28	54	70
6	**3a**, **4f**	**5f**	4-$NO_2C_6H_4$	OH	Me	30	63	30	70	6	42
7	**3b**, **4a**	**5g**	3-$NO_2C_6H_4$	H	Me	15	80	—		52	
8	**3c**, **4a**	**5h**	η-$CpMn(CO)_3$	H	Me	40	62	—		40	

[a]*Reagents and conditions*: **1** (0.013 mmol), **3** (0.26 mmol), **4** (0.80 mmol), [bmim][BF_4] (1.08 mmol), 0 °C. [b]Determined by HPLC.

The **1**/[bmim][BF_4] system was further examined in asymmetric aldol reactions between aromatic aldehydes **3** and ketones **4**.† The reactions were carried out under the same conditions. In all the instants aldols **5** were synthesised in moderate to high yields and with reasonable *ee* (Scheme 1, Table 2). Asymmetric ketones **4b–d** reacted regioselectively at the methyl group adjacent to the carbonyl group affording respective aldols **5b–d** (Table 2, entries 2–4). Aldols **5e**,**f** with substituents at C^2 (Scheme 1) were produced in reactions of aldehydes **3a**,**b** with cyclopentanone **4e** and hydroxyacetone **4f** (Table 2, entries 5, 6). A diastereomeric ratio in products **5e**,**f** depended on the ketone structure. According to ^{1}H NMR (coupling constants between H^1 and H^2), a *syn*-diastereomer prevailed in aldol **5e** ($J_{H^1–H^2}$ 2 Hz), whereas an *anti*-diastereomer dominated in aldol **5f** ($J_{H^1–H^2}$ 5 Hz).

Note that aldol **5b** was only reported as a product of the native aldolase-catalysed asymmetric aldol reaction between **3a** and **4b**.[7] Compounds **5c**,**d**,**h** have not been synthesised so far, assumingly, because of low activity of the employed organocatalysts (ketones **4b–d** do not react with aldehydes **3** under the studied conditions even in the presence of 30 mol% of **2**). Furthermore, given a high catalytic activity of the **1**/[bmim][BF_4] system we managed to synthesise for the first time chiral aldol **5h**, bearing an organometal moiety, from cymantrene aldehyde **3c** and acetone **4a** (Table 2, entry 8).

The catalytic system **1**/[bmim][BF_4] can be used repeatedly. After each reaction cycle, aldol **5** was extracted with an organic solvent (EtOAc) and fresh portions of reagents **3** and **4** were added to the remaining catalyst. At least triple catalyst recycling was possible without a significant activity and enantioselectivity loss (Table 1, entries 4–6).

As a result, a new highly active recoverable catalytic system of 1(*R*),2(*R*)-bis[(*S*)-prolinamido]cyclohexane **1**/[bmim][BF_4] was developed to perform an asymmetric aldol reaction between unmodified ketones and aldehydes in a ratio of 3:1, which is much lower than that required in respective (*S*)-proline-catalysed reactions.

† NMR spectra were recorded on Bruker AM 300 (300.13 MHz {^{1}H}) and Bruker DRX 500 instruments (500.13 {^{1}H}, 125.76 {^{13}C} in $CDCl_3$). ^{1}H and ^{13}C chemical shifts were recorded relative to Me_4Si and $CDCl_3$, respectively. Optical yields of aldols **5** were determined using HPLC (Daicel Chirapak OJ-H and OD-H columns). Ionic liquids [bmim][PF_6],[8] [bmim][NTf_2],[9] [bdmim][BF_4][10] and [bmim][BF_4][11] were synthesised by reported methods and dried at 70 °C (2 Torr) for 4 h. Ionic liquid purity was controlled by ^{1}H, ^{13}C and ^{19}F NMR spectra. Residual water content was not determined, in [bmim][NTf_2] according to reported data[9] it is 0.03%.

General procedure. Aldehyde **3** (0.26 mmol) and ketone **4** (0.80 mmol) were added to a stirred suspension of catalyst **1** (4.0 mg, 0.013 mmol) in ionic liquid (1.08 mmol). The reaction mixture was stirred for 15–60 h at 0 °C and extracted with EtOAc (3×5 ml). Combined extracts were evaporated at a reduced pressure (30 °C, 15 Torr), aldols **5** were isolated by column chromatography on silica gel (0.060–0.200 nm, Acros); eluent, *n*-hexane–EtOAc (3:1). Compounds **5a**,**b**,**e**,**f**,**g** were identified by their ^{1}H NMR spectra compared with the reported data.[3(a)–(e),7] ^{1}H, ^{13}C NMR and HPLC [τ(*R*) (major enantiomer), τ(*S*)] data for newly synthesised compounds **5c**,**d**,**h** are given below. Yields, *ee* and *dr* of compounds **5** are summarised in Tables 1 and 2.

1-Cyclopropyl-3-hydroxy-3-(4-nitrophenyl)propan-1-one **5c**: ^{1}H NMR, δ: 1.01 (m, 2H), 1.13 (m, 2H), 1.93 (m, 2H), 3.74 (s, 1H), 5.20 (m, 1H), 7.56 (d, 2H, *J* 8.3 Hz), 8.23 (d, 2H, *J* 8.3 Hz). ^{13}C NMR, δ: 11.5, 21.8, 51.0, 68.9, 123.8, 126.5, 147.3, 150.2, 210.9. HPLC: Chirapak OJ-H, *n*-hexane/Pr^{i}OH, 85:15 (0.5 cm^3 min^{-1}), τ(*R*) 20.51 min, τ(*S*) 27.19 min.

1-Hydroxy-7-methyl-1-(4-nitrophenyl)oct-6-en-3-one **5d**: ^{1}H NMR, δ: 1.63 (s, 3H), 1.69 (s, 3H), 2.30 (m, 2H), 2.46 (m, 2H), 2.81 (m, 2H), 3.60 (br. s, 1H), 5.05 (m, 1H), 5.27 (t, 1H, *J* 5.4 Hz), 7.53 (d, 2H, *J* 8.8 Hz), 8.20 (d, 2H, *J* 8.8 Hz). ^{13}C NMR, δ: 17.2, 23.6, 25.6, 44.1, 52.0, 71.1, 121.0, 123.5, 128.3, 136.2, 147.9, 148.4, 210.1. HPLC: Chirapak OJ-H, *n*-hexane/Pr^{i}OH 85:15 (1 cm^3 min^{-1}), τ(*R*) 13.73 min, τ(*S*) 14.94 min.

4-Hydroxy-4-(η-cyclopentadienylmanganese)butan-2-one **5h**: ^{1}H NMR, δ: 2.22 (s, 3H), 2.81 (m, 2H), 3.20 (br. s, 1H), 4.68 (m, 2H), 4.78–4.92 (m, 3H). ^{13}C NMR, δ: 30.6, 51.3, 63.9, 80.9, 81.1, 82.0, 82.1, 107.5, 207.8. HPLC: Chirapak OD-H, *n*-hexane/Pr^{i}OH 90:10 (1 cm^3 min^{-1}), τ(*S*) 20.92 min, τ(*R*) 19.91 min.

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