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Direct catalytic asymmetric cross-aldol reactions in ionic liquid media

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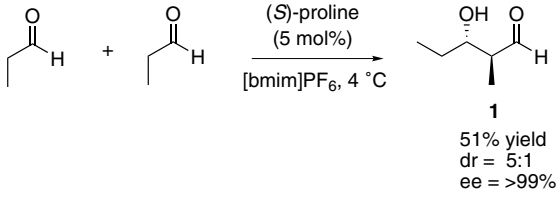
Abstract—Enantioselective proline-catalyzed direct asymmetric cross-aldol reactions with aldehydes were performed in ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate media, which simplified product isolation and catalyst recycling, affording 3-hydroxy aldehydes in high yield with excellent stereoselectivity. In addition, the enhanced reactivity of the asymmetric cross-aldol reactions in ionic liquid allowed the catalyst loading to be lowered significantly.

The employment of ionic liquids as solvents for chemical reactions has received increased attention in recent years.[1] These solvents are reusable, enhance the reactivity of chemical transformations, simplify product isolation and allow for catalyst recycling. The reduction of the amount of solvents needed for a chemical transformation enables the process to be more economical and environmentally benign.

Organocatalysis has recently experienced a renaissance in catalytic asymmetric synthesis.[2] Asymmetric transformations mediated by amino acids and their derivatives have been particularly successful. In our endeavours to mimick direct cross-aldol reactions that are catalyzed by the natural 5-phospho-deoxyribose aldolase,[3] we have investigated the use of unmodified aldehydes as nucleophiles and organic amino acid derivatives as catalysts for asymmetric reactions.[4] In addition, MacMillan, Jørgensen and co-workers have also reported elegant intermolecular cross-aldol reactions.[5–7] These results along with our research led us to envisage that there would be a possibility of performing these organocatalytic asymmetric reactions in ionic liquids. If successful, the reactions would be highly economical and allow for efficient reuse of the catalyst.

Herein, we present the first direct catalytic asymmetric cross-aldol reactions of aldehydes in ionic liquid media furnishing 3-hydroxy aldehydes in high yield and excellent enantioselectivity. The enantiomerically pure products are important building blocks for the synthesis of several natural product derivatives.

In an initial experiment, propionaldehyde (7.4 mmol) and a catalytic amount of (*S*)-proline (5 mol%) were mixed in the ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) (1 mL) (Eq. 1).[8]



1
51% yield
dr = 5:1
ee = >99%

(1)

After stirring for 16 h at 4 °C, the reaction was quenched by extraction with Et_2O (3×15 mL). The combined organic extracts were concentrated and the crude product purified by silica-gel column chromatography to afford β-hydroxy aldehyde **1** in 51% yield with dr 5:1 and >99% ee.[9] We found that the yield could be increased to 65% if the reaction was quenched after 6 h. Hence, the reaction was faster in the ionic liquid as compared to conventional organic solvents. In order to increase the yield further, we added DMF as a co-solvent to the ionic liquid. This almost completely inhibited the excessive oligomerization and increased the yield of **1** to 74% without affecting the selectivity of the reaction (Table 1, entry 1). We also tested recycling of the catalyst (Table 1). The reaction was readily performed five times

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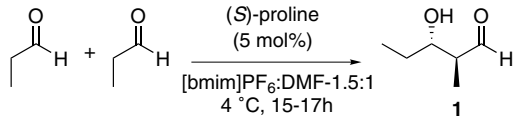
Table 1. Catalyst recycling studies

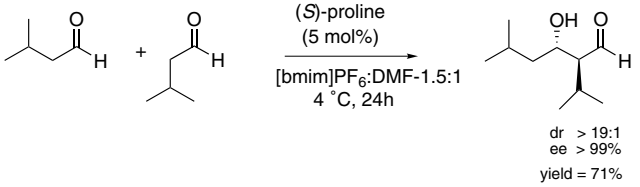


Entry	Recycle	Yield (%)[a]	Dr[b]	Ee (%)[c]
1		74	4:1	99
2	1st	76	5:1	99
3	2nd	71	4:1	99
4	3rd	77	4:1	99
5	4th	73	4:1	99

[a] Isolated yield after silica-gel column chromatography.
[b] Determined by NMR.
[c] Determined by chiral-phase GC.[9]

without affecting the yield or selectivity. Noteworthy, only 1–5 mol% of the catalyst was needed as compared to the previously reported 45–10 mol% used in conventional organic solvents.[4a,h,5,6]

Next, we investigated the cross-aldol reactions between different aldehydes in ionic liquid media (Table 2).[10] The reactions proceeded smoothly affording β-hydroxy aldehydes **1**–**5** in good yield with excellent enantioselectivity. The diastereoselectivity of the reaction increased for the α-substituted aliphatic acceptor aldehydes. For example, cross-aldol products **2**, **4** and **5** were isolated with dr > 19:1 and >99% ee, respectively.[9] The chemoselectivity of the transformation was high, for example, the reaction between propionaldehyde and *i*-valeraldehyde did not yield any products where *i*-valeraldehyde had been the nucleophile. However, proline was able to catalyze the self-aldol reaction of *i*-valeraldehyde affording the corresponding aldol adduct with >99% ee (Eq. 2).

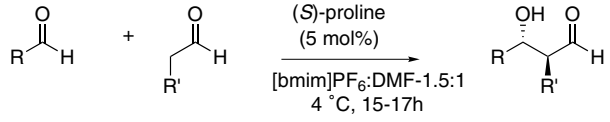


(2)

The reactivity of the reaction increased in ionic liquid media without decreasing the enantioselectivity of the reaction as compared to the cross-aldol reaction in DMF.[5] In addition, the absolute and relative configuration of the products did not change. Hence, (*S*)-proline afforded *anti*-(2*S*,3*S*)-2-alkyl-3-hydroxy-aldehydes. The sustainability and advantages of performing the reaction in an ionic liquid were also exhibited by performing entries 1, 2 and 4 in a row with the same (*S*)- or (*R*)-proline. In addition, the reactions were recycled more than five times without affecting the yield or the enantioselectivity of the cross-aldolizations.

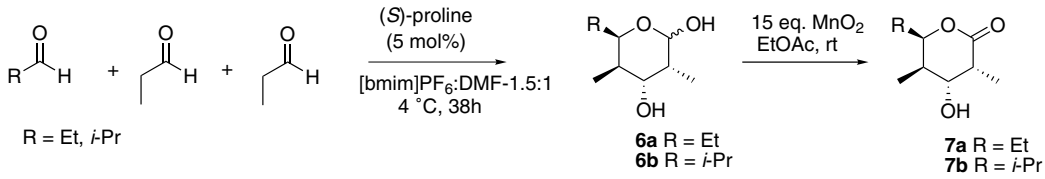
We also investigated the possibility of performing one-pot sequential cross-aldol reactions in ionic liquid media, which would assemble polyketide type sugars in a similar fashion to polyketide synthases and aldolase enzymes (Eq. 3).[11,12]

Table 2. Direct catalytic cross-aldol reactions in ionic liquid media



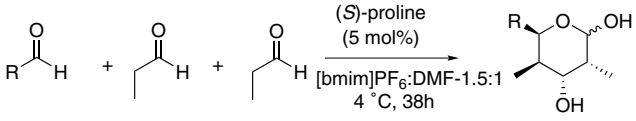
Entry	Recycle	R	R[1]	Yield (%)[a]	Dr[b]	Ee (%)[c]	Compound
1		Me	Me	73	4:1	99	**1**
2		*i*-Pr	Me	76	>19:1	>99	**2**
3	1st	*i*-Pr	Me	74	>19:1	>99	**2**
4	2nd	*i*-Pr	Me	78	>19:1	>99	**2**
5	3rd	*i*-Pr	Me	76	>19:1	>99	**2**
6	4th	*i*-Pr	Me	75	>19:1	>99	**2**
7		*i*-Bu	Me	69	3:1	99	**3**
8	1st	*i*-Bu	Me	71	3:1	99	**3**
9	2nd	*i*-Bu	Me	72	3:1	99	**3**
10	3rd	*i*-Bu	Me	70	3:1	99	**3**
11		*c*-Hexyl	Me	77	>19:1	>99	**4**
12	1st	*c*-Hexyl	Me	78	>19:1	>99	**4**
13	2nd	*c*-Hexyl	Me	75	>19:1	>99	**4**
14	3rd	*c*-Hexyl	Me	78	>19:1	>99	**4**
15		*i*-Pr	*n*-Bu	68	>19:1	>99	**5**
16	1st	*i*-Pr	*n*-Bu	70	>19:1	>99	**5**
17	2nd	*i*-Pr	*n*-Bu	69	>19:1	>99	**5**

[a] Isolated yield after silica-gel column chromatography.
[b] Determined by NMR.
[c] Determined by chiral-phase GC.[9]



(3)

Table 3. Catalyst recycling studies of the direct asymmetric assembly of pyranoses



Entry	Recycle	R	Yield (%)[a]	Dr[b]	Ee (%)[c]	Compound
1		Me	50	>19:1	49	**6a**
2	1st	Me	47	>19:1	48	**6a**
3	2nd	Me	48	>19:1	49	**6a**
4	3rd	Me	49	>19:1	49	**6a**

[a] Isolated yield after silica-gel column chromatography.
[b] Determined by NMR.
[c] Determined by chiral-phase HPLC analyses after conversion to **7a**.

Hence, the proline-catalyzed formation of **1** in [bmim]PF_6/DMF 1.5:1 (2 mL) from propionaldehyde (7.2 mmol) was continued after 16 h by slow addition of more propionaldehyde (21 mmol) in cold [bmim]PF_6/DMF 1.5:1 (2 mL) with a syringe pump at 4 °C. The reaction was quenched after 22 h by extraction with Et_2O (3×15 mL). Concentration of the combined organic layers and subsequent purification of the crude product by flash-column chromatography afforded dimer **1** in a 50% yield and pyranose **6a** in a 38% yield as a single diastereomer with an anomeric ratio of 1:2 (α:β). The pyranose **6a** was converted quantitatively to the corresponding δ-lactone **7a** by treatment with ab excess MnO_2 in EtOAc for 48 h. The lactone **7a** had an ee of 49% as determined by chiral-phase HPLC analysis.[13] In addition, lactone **7b** was synthesized in two steps as a single diastereomer with 25% ee.[14] Noteworthy the use of ionic liquid improved the ee as compared to the proline-catalyzed formation of **6a** and **6b** in DMF or dioxane.[4h] The proline-catalyzed direct asymmetric sequential aldol reactions were also recycled efficiently without affecting the yield or enantioselectivity of the reaction (Table 3).

In conclusion, we have reported the first catalytic direct asymmetric cross-aldol reactions in an ionic liquid, which simplify product isolation and catalyst recycling. The reactions furnish β-hydroxy aldehydes in high yield with excellent stereoselectivity. The reactions can be readily scaled-up and provide a low cost entry to either enantiomer of important building blocks for natural product synthesis.

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8. The ionic liquid [bmim]PF_6 was selected since it provided the best results as compared to [hmim]BF_4 and

[omim]bF$_4$. It has also been successfully used in aldol reactions with unmodified ketones see: Kotrusz, P.; Kmentová, I.; Gotov, B.; Toma, S.; Solcániová, E. *Chem. Commun.* **2002**, 2510; Loh, T.-P.; Feng, L.-C.; Yang, H.-Y.; Yang, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 8741.

9. The cross-aldol adducts were reduced quantitatively and the corresponding *anti*-1,3-diols converted to the 2,2-dimethylpropane-1,3-diols according to Ref. 5 and the ee determined by chiral-phase GC analysis. The racemic 2,2-dimethylpropane-1,3-diols derived by racemic proline-catalysis were checked as GC standards.
10. In a typical experiment, *i*-butyraldehyde (2 mmol) was added to a vial containing (*S*)-proline (5 mol%) in [bmim]PF$_6$/DMF 1.5:1 (2 mL) at 4 °C. Next, a cold solution of propionaldehyde (1 mmol) in [bmim]PF$_6$/DMF 1.5:1 (1.0 mL) was slowly added by syringe pump at 4 °C. After 16 h the reaction was quenched by extraction with Et_2O (3×15 mL). The remaining proline in the ionic liquid could be effectively reused for another cross-aldol reaction by simply adding DMF to obtain a [bmim]PF$_6$ to DMF ratio of 1.5:1. The combined organic extracts were concentrated and the crude product purified by silica-gel column chromatography (pentane/EtOAc 3:1) affording β-hydroxy aldehyde **2** in 76% yield with dr > 19:1 and >99% ee. All the structural and spectroscopical data were identical to the literature. See: Ref. 5 and Mahrwald, R.; Costrisella, B.; Guendogan, B. *Synthesis* **1998**, 26.
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13. **7a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 7.2$ Hz, 3H), 1.27 (d $J = 7.2$ Hz, 3H), 1.61 (m, 1H), 1.80 (m, 2H), 1.93 (br s, 1H), 2.67 (dq, $J = 7.2$, 3.6 Hz, 1H), 3.74 (t, $J = 3.6$ Hz, 1H), 3.76 (ddd, $J = 10.8$, 8.2, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.4$, 16.0, 26.1, 39.0, 41.78, 75.76, 82.61, 174.53. HRMS: $C_9H_{16}O_3Na$ (MNa^+): calcd 195.0992, found 195, 0993. $[\alpha]_D$ −14.0 (*c* 1.0, $CHCl_3$). The ee of δ-lactones **7a** and **7b** was determined by esterification of the alcohol group with 3,5-dinitro-benzoyl chloride according to Ref. 4h and subsequent chiral-phase HPLC-analysis of the corresponding 3,5-dinitrobenzoate ester.
14. **7b**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 7.2$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 1.07 (d $J = 6.8$ Hz, 3H), 1.26 (d, $J = 6.8$ Hz, 3H), 1.92 (m, 2H), 2.67 (dq, $J = 6.8$, 4.0 Hz, 1H), 3.74 (dd, $J = 11.2$, 2.0 Hz, 1H), 3.75 (t, $J = 3.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.2$, 14.6, 16.1, 20.0, 29.2, 38.8, 39.4, 75.7, 85.3, 174.7. HRMS: $C_{10}H_{18}O_3Na$ (MNa^+): calcd 209.1148, found 209.1146. $[\alpha]_D$ −11.2 (*c* 1.5, $CHCl_3$).