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Ionic liquid supported 4-HO-Pro-Val derived organocatalysts for asymmetric aldol reactions in the presence of water

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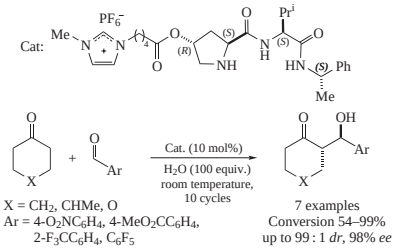
Novel (4*R*)-HO-(2*S*)-Pro-(*S*)-Val derivative tagged to 1-methylimidazolium cation and PF_6^- anion efficiently catalyzes asymmetric aldol reactions of cyclic ketones with aromatic aldehydes in aqueous environment to afford the corresponding aldols in high yield with moderate to high *anti*-diastereo- (*dr* up to 99 : 1) and enantioselectivity (up to 98% *ee*). The catalyst was recycled 9 times in the same reaction without any decrease in selectivity values.



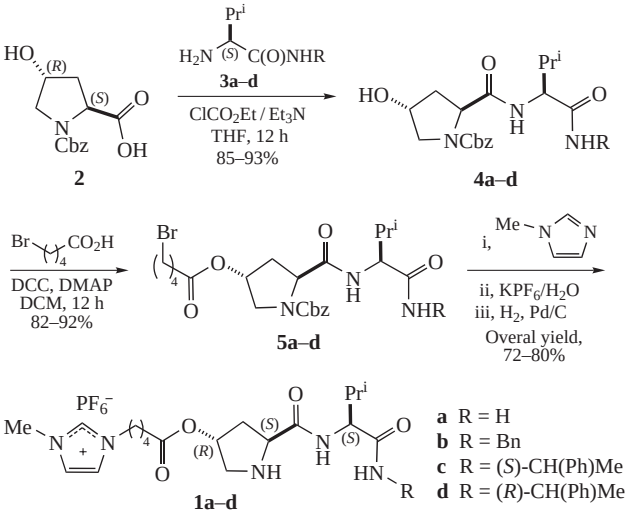
Low-molecular peptides, simple analogues of natural enzymes (aldolases, decarboxylases, *etc*.), belong to a perspective class of organocatalysts for asymmetric synthesis.[1–3] Like a number of other bifunctional amino catalysts,[4–7] they activate carbonyl component *via* the formation of enamine or iminium intermediates and properly locate the second reactant in the active complex by means of 3D-hydrogen bonding. Hydrogen bonds may also induce conformational changes and/or self-association of low peptide molecules that significantly contribute to the stereoselection process.[8] In the presence of di- and tripeptide-derived catalysts, asymmetric aldol, Michael, Morita–Baylis–Hillman, hydrogenation, acylation and some other useful reactions proceed with high diastereo- and enantioselectivity.[9–16] Furthermore, potentially suitable to industrial application heterogeneous versions of di- and tripeptides attached to organic or inorganic polymers (in particular, polystyrene,[17] PEG/polystyrene co-polymer,[18] or silica[19]) have been designed over the past decade. This modification significantly simplifies recovery of precious chiral catalysts and allows one to perform efficient screening of their libraries to identify most efficient of them.[20]

Another promising immobilization strategy is based on tagging organocatalysts to ionic groups (ionic liquid moieties).[21,22] This approach allows one to increase the number of active sites per mass unit as compared with polymeric catalysts. Moreover, this brings an opportunity to tune catalytic performance by varying cation and/or anion nature and study modified catalysts by conventional NMR and HRMS methods.[23] Hybrid catalysts[24] incorporating ionic groups are particularly suitable to asymmetric reactions in aqueous media[25,26] where similar enzymatic reactions occur in Nature[27] in which a proper balance between hydrophilic and hydrophobic properties of the catalyst is very important for the reaction outcome. However, to the best of our knowledge, dipeptide-based organocatalysts tagged to ionic groups have not been reported so far.

We chose catalysts bearing (4*R*)-HO-(2*S*)-Pro-(*S*)-Val backbone with terminal amide group as research objects since they are composed from available natural amino acids and contain properly located bulky Pr^i group and two H-bonding amide units, which may favorably contribute to stereoselection in the transition state of asymmetric catalytic reactions [for representative examples of asymmetric catalysis with similar dipeptide derivatives see refs. 18(*a*), 28].

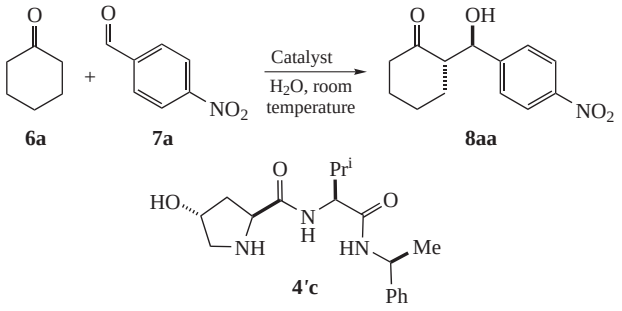
Herein, we describe an efficient synthesis of novel (4*R*)-HO-(2*S*)-Pro-(*S*)-Val dipeptides **1a–d** modified with imidazolium cation and PF_6^- anion. The synthetic scheme includes reactions of N-protected 4-(*R*)-hydroxy-(*S*)-proline **2** with (*S*)-valinamides **3a–d** and esterification of dipeptide derivatives **4a–d** with 4-bromovaleric acid in the presence of DCC/DMAP. The resulting bromo esters **5a–d** were converted to target imidazolium salts by a sequence of alkylation, anion exchange and catalytic hydrogenation one-pot reactions (Scheme 1).

One of the most popular organocatalytic reactions is asymmetric aldol reaction which is a powerful tool for enantioselective formation of C–C bonds in organic compounds.[29] Catalytic



Scheme 1

Table 1 Testing of catalysts **1a–d** and **4′c** in the model reaction.



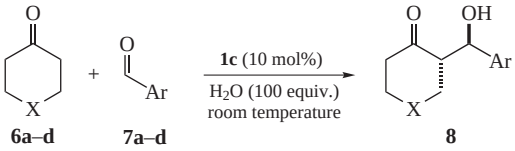
Entry	Catalyst (mol%)	H_2O (equiv.)	*t*/h	Conversion (%)	*dr* (*anti*:*syn*)	*ee* (*anti*) (%)
1	**1a** (10)	100	20	60	91:9	99
2	**1b** (10)	100	20	99	92:8	94
3	**1c** (10)	100	20	99	92:8	98
4	**1d** (10)	100	20	99	92:8	96
5	**1c** (5)	100	20	80	69:31	97
6	**1c** (1)	100	48	76	50:50	95
7	**1c** (10)	75	20	99	86:14	97
8	**1c** (10)	50	20	99	87:13	98
9	**1c** (10)	25	20	99	85:15	98
10	**4′c** (10)	100	20	98	90:10	96

performance of compounds **1a–d** was examined in the model reaction between cyclohexanone **6a** and 4-nitrobenzaldehyde **7a** in the presence of water [**6a**:**7a** = 3:1, **1** (10 mol%), 20 °C] (Table 1). High diastereoselectivities (*anti*:*syn* 91:9–92:8) and *ee* values (98–99%) of aldol **8aa** were attained in dipeptide **1a** and **1c** catalyzed reactions. However, of the two dipeptides, compound **1c** bearing terminal (*S*)-1-phenylethyl group was more active catalyst under the studied conditions (entry 3). Diastereoisomeric catalyst **1d** displayed a somewhat lower enantioselection than **1c** (entry 4). Reduction of catalyst **1c** loading or amount of water exerted a negative impact on conversion and/or diastereoselectivity (entries 5–9). Dipeptide catalyst **4′c** that did not contain ionic group exhibited similar catalytic performance in the model reaction (entry 10). However, it got lost during work-up due to significantly higher solubility in diethyl ether used for extraction of aldol product from the reaction mixture.

Six-membered cyclic ketones **6a–c** and various benzaldehydes **7a–d** appeared suitable substrates.† The corresponding aldols **8** were generated under proposed conditions in high yield and with moderate to high *anti*-diastereo- and enantioselectivities (Table 2). In the case of cyclopentanone **6d**, diastereo- and enantioselectivity values were noticeably lower.

Sustainability and recoverability of catalyst **1c** was demonstrated in the reaction of cyclohexanone **6a** with methyl 4-formylbenzoate **7d**. Once the reaction completed, aldol **8ad** was extracted from the reaction mixture with diethyl ether, fresh portions of reactants **6a** and **7d** were added to the remaining suspension of catalyst **1c** in water, and the reaction was re-performed. Nine iterations of this procedure did not result in a reduction of diastereo- or enantioselectivity. A gradual decrease in the product yield may be attributed to partial leaching of the catalyst to organic solution during extraction procedure (Table 3).

Table 2 Dipeptide **1c**-catalysed asymmetric aldol reactions in the presence of water.



Entry	**6**	**7**	*t*/h	**8**, conversion (%)	*dr* (*anti*:*syn*) (%)	*ee* (*anti*) (%)
1	**6a** (X = CH_2)	**7a** (Ar = 4-$O_2NC_6H_4$)	20	**8aa**, 99	92:8	98
2	**6a**	**7b** (Ar = 2-$F_3CC_6H_4$)	20	**8ab**, 98	81:19	94
3	**6a**	**7c** (Ar = C_6F_5)	20	**8ac**, 99	>99:1	70
4	**6a**	**7d** (Ar = 4-$MeO_2CC_6H_4$)	20	**8ad**, 97	86:14	96
5	**6b** (X = O)	**7d**	48	**8bd**, 54	86:14	89
6	**6c** (X = CHMe)	**7d**	48	**8cd**, 75	80:20	90
7	**6d** (X = none)	**7d**	20	**8dd**, 97	50:50	76 (*anti*) 42 (*syn*)

Table 3 Recycling of catalyst **1c** in the reaction between **6a** and **7d** in the presence of water.

Cycle	Conversion of **7d** (%)	*dr* (*anti*:*syn*) of **8ad**	*ee* (*anti*) (%)
1	96	86:14	96
2	92	89:11	96
3	88	91:9	97
4	85	87:13	95
5	80	91:9	96
6	75	91:9	96
7	71	90:10	96
8	65	91:9	98
9	56	91:9	97

In conclusion, novel (4*R*)-HO-(2*S*)-Pro-(*S*)-Val derived ionic liquid-supported organocatalyst for asymmetric aldol reactions between cyclic ketones and aromatic aldehydes in the presence of water was synthesized. Under proposed conditions, the corresponding aldols are generated with high diastereo- and enantioselectivity. The catalyst can be readily recovered and reused over 8 times without any decrease in selectivity values, though its catalytic efficiency gradually diminished in each next cycle.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.09.007.

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† *General procedure for asymmetric aldol reaction.* A mixture of catalyst **1c** (8.5 mg, 0.013 mmol), ketone **6** (0.40 mmol), aldehyde **7** (0.13 mmol) and water (0.23 ml, 13 mmol, 100 equiv. with respect to **7**) was stirred for 20–48 h. Aldol **8** was extracted with Et_2O (2×5 ml), the combined extracts were passed through a silica gel pad (1 g) and evaporated under reduced pressure (15 Torr). The *dr* values of aldols **8** were measured by ^{1}H NMR spectroscopy of the crude reaction mixture, *ee* values were determined by HPLC (chiral phases: Chiralcel OD-H, OJ-H, or Chiralpak AD-H).

Recycling of catalyst **1c**. After extraction of aldol **8ad**, fresh portions of reactants **6a** (0.40 mmol) and **7d** (0.13 mmol) were added to the remaining suspension of catalyst **1c** in water, and the reaction was re-performed as described above.

For detailed experimental procedures and characteristics of compounds **1**, **4** and **5**, see Online Supplementary Materials.

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