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Asymmetric aldol reactions in ketone/ketone systems catalyzed by ionic liquid-supported C_2-symmetrical organocatalyst

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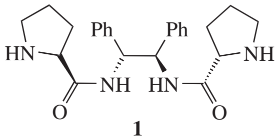
Ionic liquid-supported (1*S*,2*S*)- and (1*R*,2*R*)-1,2-bis[(*S*)-prolinamido]-1,2-diphenylethanes act as organocatalysts in asymmetric aldol reactions of acetone with α-keto esters or trifluoroacetophenone providing high yields and from moderate to high enantioselectivity. Recycling of the catalyst with a gradual decrease in conversion and *ee* values is possible.

Asymmetric organocatalysis is an intensely developing area of modern organic chemistry,[1] which allows one to synthesize complex polyfunctional compounds of high enantiomeric purity from simple prochiral precursors.[2] To facilitate purification of products and recovery of precious chiral catalysts, immobilized forms of organocatalysts tagged to polymers[3] or ionic groups[4] have been designed. They appeared efficient and recyclable catalysts in a number of asymmetric reactions which include intermolecular aldol reactions between aldehydes and ketones[5] and intramolecular aldol cyclizations of suitable triketones to afford Wieland–Miescher ketone analogues.[6] However, to the best of our knowledge, supported organocatalysts have not been so far applied to asymmetric intermolecular aldol reactions between two ketone molecules, in particular between acetone and α-keto esters, which are used for the synthesis of chiral α-hydroxy-γ-keto esters – valuable building blocks for the synthesis of biologically active compounds.[7] Among known catalysts of these useful asymmetric transformations,[8] C_2-symmetrical bisprolinamide derivative **1** is one of the most efficient.[8(a)] Herein we report novel ionic liquid-supported versions **2a** and **2b** of catalyst **1** and their application to intermolecular asymmetric aldol reactions between two different ketones.



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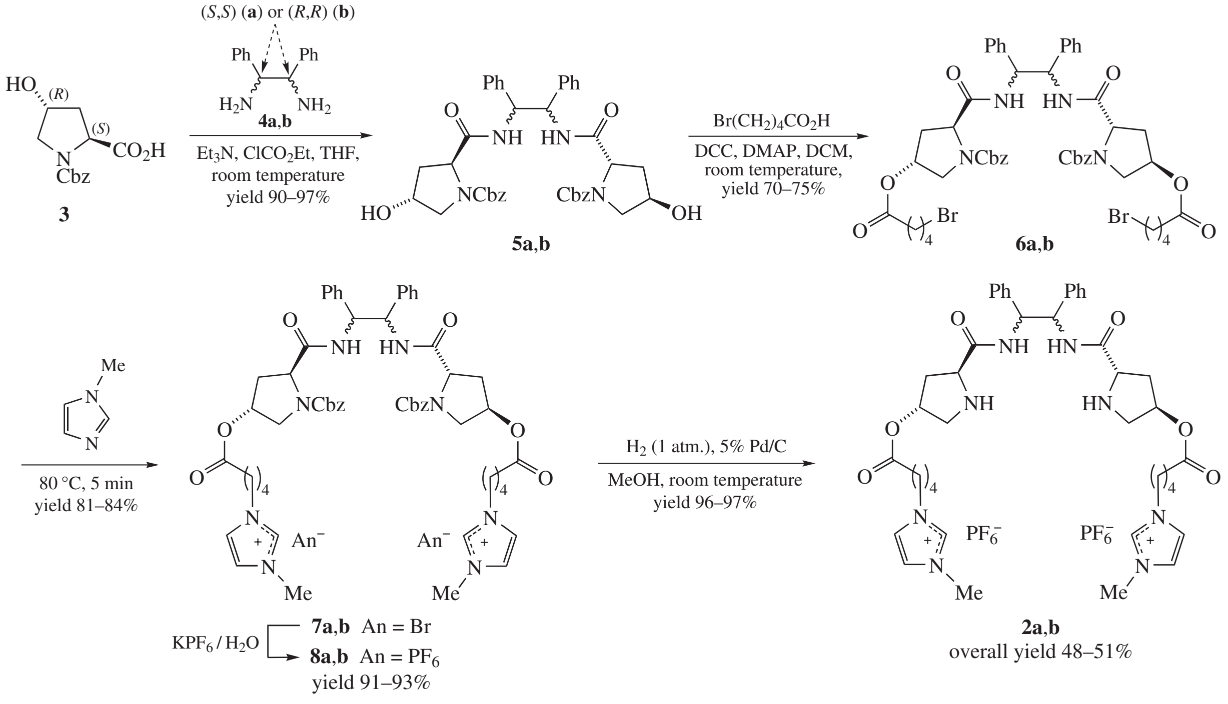
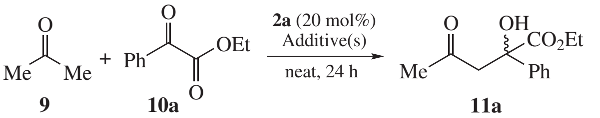
Catalyst **2a** was synthesized from protected (2*S*,4*R*)-4-hydroxyproline **3** by a synthetic scheme which included the reaction of **3** with (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine **4a** and $Et_3N/ClCO_2Et$, esterification of diamide **5a** with 5-bromovaleric acid in the presence of DCC/DMAP followed by N-alkylation of 1-methyl-1*H*-imidazole with dibromo ester **6a** to afford salt **7a** (Scheme 1). The synthesis of **2a** was accomplished by a replacement of bromide ions with PF_6^- ions and hydrogenative removal of Cbz-protection in compound **8a**. Diastereomer **2b** was prepared by a similar way from (1*R*,2*R*)-diamine **4b**.

Compounds **2a** and **2b** efficiently catalyzed the reaction of acetone **9** with ethyl 2-oxo-2-phenylacetate **10a** under similar



Scheme 1

Table 1 Optimization of model reaction conditions.



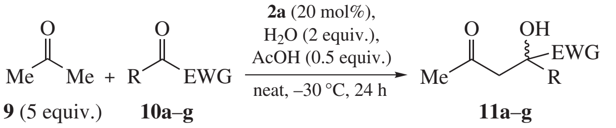
Entry	T/°C	Additive(s) (equiv.)	**9** (equiv.)	Conversion (%)[a]	*ee* of **11a** (%)[b]
1	room temperature	–	25	99 (99[c])	33 (9[c], 30[d], 25[e])
2	–5	–	25	99 (92[f])	51 (53[f])
3	–30	–	25	99	63
4	–30	H_2O (10)	25	99	67
5	–30	AcOH (0.5)	25	99	69
6	–30	H_2O (10), AcOH (0.5)	25	99	78
7	–30	H_2O (4), AcOH (0.5)	10	99	78
8	–30	H_2O (2), AcOH (0.5)	5	99	84

[a] Determined by ^{1}H NMR analysis of the crude product. [b] Determined by HPLC. [c] Catalyst **2b** (20 mol%) was used. [d] The loading of catalyst **2a** was 10 mol%. [e] The loading of catalyst **2a** was 5 mol%. [f] Reported data for catalyst **1** at 0 °C, the reaction product was *ent*-**11a**.[8(a)]

conditions to give aldol **11a** in high yield. However, of the two diastereomeric catalysts, **2a** induced a 15–24% higher enantioselectivity than **2b** (Table 1, entry 1). Reducing catalyst **2a** loading to 10 or 5 mol% exerted a negative impact on the *ee* value of aldol product. Luckily, enantiomeric purity of aldol **11a** grew up to 51–63% *ee* in experiments performed at –5 to –30 °C (entries 2 and 3) and up to 67–69% *ee* in catalytic systems where proton additives (H_2O or AcOH) were used (entries 4 and 5). The best enantioselectivity (up to 84% *ee*) was attained in the presence of cooperative catalytic system **2a**/H_2O (2 equiv.)/AcOH (0.5 equiv.) at the **9**/**10a** molar ratio of 5:1 (entries 6–8).

Under optimal conditions, acetone **9** reacted with α-aryl α-keto esters **10a–d** to afford corresponding aldols **11a–d** in high yields and with enantioselectivity of 63–84% *ee* (Table 2, entries 1,3–5).[†] Electron donating substituent (OMe group) in the aromatic ring slowed down the reaction without a notable effect on the *ee* value of product **11d**. When 2-oxopropionic (**10e**) or 2-oxobutyric (**10f**) esters were used as starting compounds, we obtained aldols **11e** and **11f** with enaniomeric enrichment of 62 and 65% *ee*, respectively (entries 6 and 7). Trifluoroacetophenone **10g** bearing electron withdrawing CF_3 group afforded the fluorinated aldol **11g** in quantitative yield and with 55% *ee* (entry 8). The absolute configuration of aldol **11a** was determined to be *S* by comparison with the literature data.[8(a)] Similar configurations were assigned to aldol products **11b–g** by analogy. Chiral α-hydroxy-γ-keto esters and polyfunctional trifluoromethylated carbonyl compounds are used in medicinal chemistry as precursors of α-hydroxy-γ-butyrolactones[10] and pharmaceutical ingredients to improve the metabolic property and bioavailability of drugs,[11] respectively.

Table 2 Bisprolinamide **2a**-catalyzed reactions between **9** and **10**.



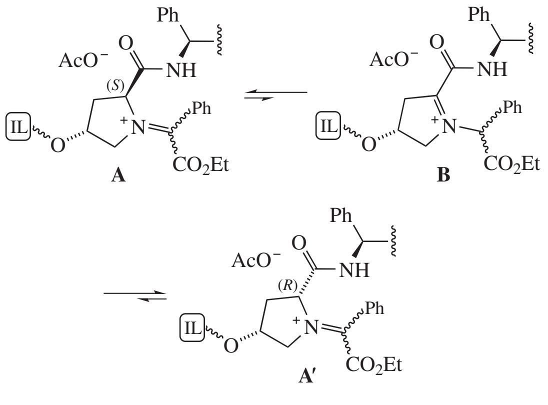
Entry	R	EWG	**11**	Conversion (%)[a]	*ee* (%)[b]
1	Ph	CO_2Et	**11a**	99 (93)[c]	84
2	Ph	CO_2Et	**11a**	98, 89, 77, 65[d]	81, 77, 74, 70[d]
3	Ph	CO_2Me	**11b**	99	79
4	2-ClC_6H_4	CO_2Me	**11c**	99 (91)[c]	63
5	4-$MeOC_6H_4$	CO_2Me	**11d**	12	72
6	Me	CO_2Bn	**11e**	99	62
7	Et	CO_2Bn	**11f**	99	65
8[e]	Ph	CF_3	**11g**	99	55

[a] Determined by ^{1}H NMR analysis of the crude product. [b] Determined by HPLC. [c] Yields after column chromatography. [d] Data for recycled catalyst in 2–5 cycles, respectively. [e] The reaction was carried out at room temperature.

Finally, we examined recyclability of catalyst **2a** in the model reaction between compounds **9** and **10a** (Table 2, entry 2). After completion of the reaction, aldol **11a** and acetone **9** were extracted with Et_2O, the residue was dried *in vacuo*, and new portions of reactants, water and AcOH were added to the remaining catalyst **2a**. Five-fold repetition of this procedure was possible, though with a notable decrease in conversion and *ee* values in each next cycle. The ^{1}H NMR spectra of recovered **2a** that had operated the reaction for five cycles were similar to that of freshly prepared catalyst sample (see Online Supplementary Materials) and this testified against irreversible changing of the catalyst backbone during the catalytic process.

Most likely, the observed deactivation of catalyst **2a** is caused by its leaching to organic solution during work-up. However, this cannot be responsible for the reduction of enantioselectivity. Apparently, catalyst **2a** reversibly reacted with highly electrophilic α-keto ester **10a** to give parasitic iminium cation **A** which generated isomeric iminium cation **B** and, ultimately, diastereomeric cation **A′** with opposite (*R*)-configuration of stereocenter C-2 in pyrrolidine ring (Scheme 2). This undesirable off-cycle equilibrium exerted a miserable impact on major aldol reaction in the first cycle. However, in a long run (multiple usage of the catalyst), it should lead to a deterioration of enantioselectivity.[12] This suggestion is in agreement with a notable decrease in specific optical rotation of **2a** ($[\alpha]_D^{20}$ reduced from –5.85 to –1.95 (*c* 2.0, MeCN) after a 120 h operation period) and with different *ee* values in aldol reactions catalyzed by diastereomers **2a** and **2b**.

In conclusion, novel ionic liquid-supported C_2-symmetrical prolinamides bearing the (*S*,*S*)- or (*R*,*R*)-1,2-diphenylethane-1,2-diamine units were synthesized and applied to asymmetric



Scheme 2 A plausible scheme for gradual epimerization of catalyst **2a**.

[†] *General procedure for asymmetric* **9** + **10** *aldol reaction*. A mixture of catalyst **2a** (20 mg, 19 μmol), ketone **10** (95 μmol), AcOH (2.8 μl, 48 μmol, 0.5 equiv. with respect to **10**) and water (3.5 μl, 200 μmol, 2 equiv. with respect to **10**) was cooled to –30 °C, then acetone **9** (35 μl, 475 μmol) was added and the mixture was stirred at –30 °C for 24 h. Aldol **11** was extracted with Et_2O (2×3 ml), the combined extracts were passed through a silica gel pad (1 g) and concentrated under reduced pressure (15 Torr). Conversions and *dr* values of aldols **11a–g** were measured by ^{1}H NMR spectroscopy, *ee* values were determined by HPLC (chiral phases: Chiralcel OD-H, OJ-H, or Chiralpak AD-H). The NMR and HPLC data for aldols **11a**,**b**,**d–g** are reported,[8(a),9] data for **11c** are given in Online Supplementary Materials.

aldol reactions in ketone–ketone systems to afford corresponding aldols in high yields and with moderate to high enantioselectivity. Catalyst **2a** can be recycled five times, though with a decrease in conversion and *ee* values of the product. The erosion of enantioselectivity was attributed to a gradual off-cycle epimerization of the catalyst during the catalytic process.

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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.2015.05.002.

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