Enantioselective Aldol Condensations Catalyzed by Poly(ethylene glycol)-Supported Proline

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Dedicated to Professor Mauro Cinquini on the occasion of his 60th birthday

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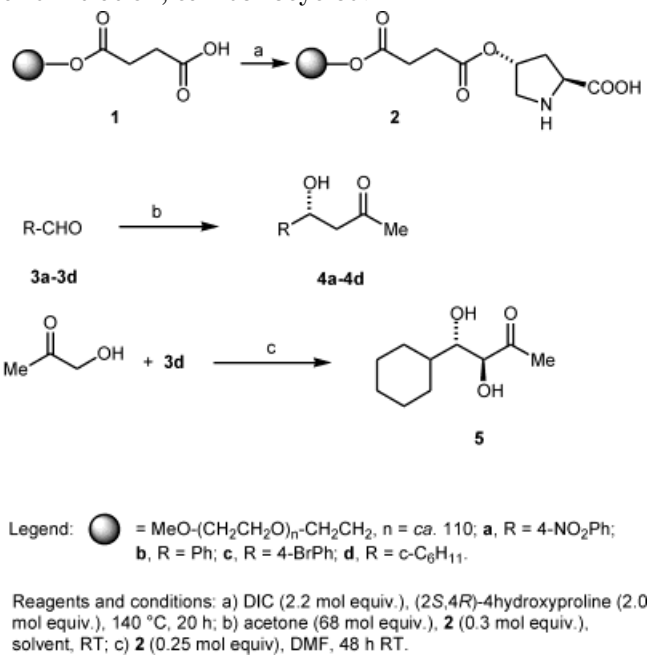
Asymmetric catalysis has witnessed a tremendous growth in recent years.[1] While homogeneous processes generally secure best enantioselection, heterogeneous catalysis allows simple product purification and, in principle, catalyst recovery and recycling. In order to combine the advantages of homogeneous and heterogeneous processes, catalyst immobilization on polymer matrixes has been investigated.[2] In this context, the ideal polymer support should be soluble in some solvents, for the catalyzed reaction to be carried out under best performing conditions, and insoluble in other solvents, so that the supported catalyst, easily isolated and recovered by precipitation and filtration, can be recycled.[3]



Scheme 1. Synthesis of PEG-supported catalyst **2** and enantioselective aldol condensations

Inexpensive and readily functionalized poly(ethylene glycol)s (PEGs) of $M_w \geq 2000$ Da feature the desired solubility profile.[4] We recently reported that a PEG-supported ammonium salt is an efficient, recoverable, and recyclable phase-transfer catalyst.[5] Here we report that immobilization of (2*S*,4*R*)-4-hydroxyproline on PEG_{5000} monomethyl ether (MeOPEG) by means of a succinate spacer afforded a recyclable catalyst that promoted the enantioselective aldol condensation of acetone and hydroxyacetone with various aldehydes.[6,7]

By reacting MeOPEG monosuccinate **1** (Scheme 1) with diisopropylcarbodiimide (DIC, 2.2 mol equiv.) and (2*S*,4*R*)-4-hydroxyproline (2.0 mol equiv.) at 140 °C for 20 h in the absence of solvent, diester **2** was obtained in 87% yield.[8] This product was employed as catalyst (0.3 mol equiv.) for the aldol condensation between acetone (68 mol equiv.) and aldehydes **3a**–**3d** (1.0 mol equiv.) to give aldols **4a**–**4d** (Scheme 1 and Table 1).[6a]

The synthesis of **4a** was selected to establish optimum reaction conditions (entries 1–6). These involved the use of DMF as solvent, and a reaction time ≥48 h at RT (entry 2). Under these conditions, product **4a** was obtained in 68% isolated yield and 77% enantiomeric excess (ee, by chiral HPLC). These values nicely compare to those obtained when the reaction was carried out with (2*S*,4*R*)-4-acetoxyproline as catalyst in DMSO (same reagent ratio) to give **4a** in 70% yield and 74% ee.[6a] In our case the use of DMSO instead of DMF (entry 3) gave a higher yield (73%) but a lower ee (62%) The use of acetone, CH_2Cl_2, and toluene slowed down the reaction rate (entries 4–6). Aldols **4b** and **4c** were also obtained in yields and ee comparable to those reported (entries 7 and 8).[6a] Remarkably, the reaction could be extended to aliphatic aldehyde **3d**. Aldol **4d**[9] was

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Table 1. Catalytic enantioselective synthesis of aldols **4a–d**

Entry	Aldehyde	Solvent/Time [h]	Product	Yield (%)[a]	ee (%)[b]
1	**3a**	DMF/24	(*R*)-**4a**	35	67
2	**3a**	DMF/48	(*R*)-**4a**	68	77
3	**3a**	DMSO/48	(*R*)-**4a**	73	62
4	**3a**	Acetone/48	**4a**	23	undetermined
5	**3a**	CH_2Cl_2/48	**4a**	8	undetermined
6	**3a**	Toluene/48	**4a**	15	undetermined
7	**3b**	DMF/60	(*R*)-**4b**	45	59
8	**3c**	DMF/60	(*R*)-**4c**	55	63
9	**3d**	DMSO/130	(*R*)-**4d**	81	≥98
10[c]	**3a**	DMF/48	(*R*)-**4a**	63	77
11[d]	**3a**	DMF/48	(*R*)-**4a**	58	77
12[e]	**3d**	DMSO/130	(*R*)-**4d**	77	98

[a] Yields of isolated products. For each aldehyde the highest yields were average values of triplicate experiments run on different scales. The variations in yield were ≤4%.
[b] As determined by HPLC on a chiral stationary phase or by comparison of optical rotation values. Ee values for the highest yielding reactions were average values of triplicate experiments. The variations in ee were ≤2%.
[c] Carried out with a catalyst sample recycled after use in entry 2.
[d] Carried out with a catalyst sample recycled after use in entries 2 and 10.
[e] Carried out with a catalyst sample recycled after use in entry 8.

obtained in 81% yield and ≥98% ee (DMSO, RT, 130 h, entry 9).

Entries 10 and 11 showed that the supported catalyst **2**, recovered by precipitation and filtration, could be recycled two times and employed in the synthesis of **4a**, with only marginal loss of the catalytic activity and no erosion of the enantioselectivity. When the condensation between acetone and aldehyde **3d** was performed in DMSO with a catalyst sample recycled from the synthesis of **4c** carried out in DMF (entry 8), aldol **4d** was obtained in 77% yield and 96% ee (entry 12), thus showing the generality of catalyst recovery and recycling.

In subsequent experiments it was found that catalyst **2** (0.25 mol equiv.) also promoted the enantio- and diastereoselective condensation of hydroxyacetone with aldehyde **3d** (Scheme 1). Thus, *anti*-aldol **5** (*anti/syn* ratio >20/1) was obtained (DMF, RT, 48 h) in 48% yield and ≥98% ee. With non-supported proline as catalyst (same reagent ratio, DMSO as solvent) this reaction gave **5** in 60% yield, >99% ee, and *anti/syn* ratio >20/1.[6b]

In conclusion, these results showed that a modified PEG is a convenient catalyst support for a synthetically relevant enantioselective aldol condensation process. The PEG-supported catalyst secured high level of stereocontrol (up to ≥98% ee), very similar to those obtained with the non-supported catalyst. Very simple catalyst recovery and recycling was also demonstrated. These findings can be useful in designing practical enantioselective catalytic reactions with continuous catalyst recycle. The generality of the use of PEG as a "harmless" chiral catalyst support in other enantioselective transformations is currently being investigated in our laboratories.

Experimental Section

Synthesis of Catalyst 2

To a mixture of **1** (3.0 g, 0.6 mmol, loading 0.196 meq/g), previously dried under vacuum at 90 °C for 1 h, and (*2S*,*4R*)-4-hydroxyproline (0.156 g, 1.2 mmol) kept at 140 °C under N_2, DIC (0.204 mL, 1.32 mmol) was added dropwise. After 20 h stirring at 140 °C, the thick mixture was cooled at RT, dissolved in CH_2Cl_2 (5 mL), and poured dropwise in Et_2O (200 mL). The precipitated pale brown solid was filtered, washed first with Et_2O (150 mL) and then with ice-cold absolute EtOH (150 mL), and dried under vacuum to give **2** (2.67 g, 0.52 mmol, loading 0.191 meq/g). ^{1}H-NMR (300 MHz, $CDCl_3$, with pre-saturation of the PEG methylene signals at δ = 3.63; relaxation delay: 6 s; acquisition time: 4 s): δ = 5.58–5.67 (1H, m, H-C4 of proline), 4.25 (2H, t, *J* = 4.4 Hz, PEG-CH_2OCO), 4.00–4.17 (1H, m, H-C2 of proline), 3.30 (3H, s, CH_3O), 2.66 (2H, t, *J* = 6.8 Hz, CH_2COO-proline), 2.58–2.70 (2H, m, H_2C3 of proline), 2.44 (2H, t, *J* = 6.8 Hz, *CH_2*CH_2COO-proline).

General Procedure for the Aldol Condensation

The synthesis of **4a** is illustrative of the procedure. To a stirred solution of catalyst **2** (0.160 g, 0.0306 mmol), previously dried under vacuum at 90 °C for 1 h, in dry DMF (2 mL) and acetone (0.5 mL, 6.8 mmol), 4-nitrobenzaldehyde (0.0151 g, 0.1 mmol) was added in one portion. The mixture was stirred at RT for 48 h and then poured in Et_2O (100 mL). The precipitated **2** was filtered off, and the solid was washed with Et_2O (50 mL). Average recovery of catalyst ranged from 70 to 80% (0.110 to 0.130 g) when the reaction was run on the above-mentioned scale, and increased to ≥90% when the reaction was run on a doubled or an even larger scale. The filtrate was washed twice with water, and the Et_2O phase was dried and concentrated. The residue was purified by flash chromatography with a 1 : 1 hexanes: Et_2O mixture as eluant to give the product (0.010 g, 68%), that had ^{1}H-NMR data in

agreement with those reported. The ee was determined by HPLC (Daicel Chiralpack AS, hexane/*i*-PrOH = 70:30, flow rate 0.8 mL/min, $\lambda = 270$): t_R: 13.285 min (major) and 15.942 min (minor). $[\alpha]_D^{25}$: + 55.3° (*c* 0.2, in $CHCl_3$).

Aldols **4a**–**4d** and **5** were known compounds. They had spectral data in agreement with those reported. Their absolute configuration was assigned on the basis of comparison of optical rotation sign.

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