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Polystyrene-Supported Hydroxyproline: An Insoluble, Recyclable Organocatalyst for the Asymmetric Aldol Reaction in Water

Daniel Font,[†] Ciril Jimeno,[†] and Miquel A. Pericàs*[,†,‡]

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans, 16. 43007 Tarragona, Spain, and Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain

mapericas@iciq.es

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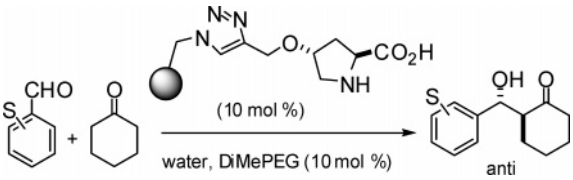
ABSTRACT



4-Hhydroxyproline has been anchored to a polystyrene resin through click chemistry, and the resulting catalyst has been successfully applied to the direct aldol reaction in water. The high hydrophobicity of the resin and the presence of water are key to ensuring high stereoselectivity, whereas yield can be increased by using catalytic amounts of DiMePEG. This effect has been further demonstrated by the inefficiency of a homogeneous, more polar analogue.

It has been recently shown[1,2] that asymmetric direct aldol reactions can be efficiently carried out in water as the sole solvent[3] using as catalysts proline derivatives that contain large apolar groups and behave as aldolase mimics.[4] From a practical perspective, the use of water as the solvent for these reactions is a very favorable characteristic, but it would be even more desirable to be able to efficiently recycle and reuse the catalysts that perform the reaction in that media.[5,6] Following initial attempts to immobilize proline,[7] excellent results have been achieved using soluble poly(ethylene glycol) (PEG),[8] or mesoporous silica[9] supported proline in organic solvents. However, attempts to work in water with peptides supported on PEG-PS resins have led only to low enantioselectivities.[10]

We thought that polystyrene (PS) could be a suitable support for L-proline for this application, and that the high hydrophobicity of the polymer chain could favor stereocontrol of the direct aldol reaction in water. Readily available 3-hydroxyproline was chosen as the monomer catalyst, since it can be anchored to the polymer chain with minimal perturbation of the catalytically active α-amino acid moiety.[11]

[†] ICIQ.
[‡] U.B.

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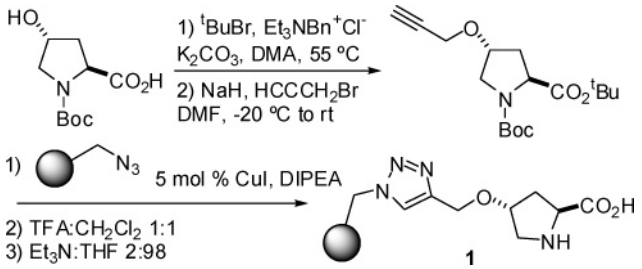
In this event, a novel strategy for the anchoring of the catalyst, involving 1,3-dipolar cycloaddition[12] of an azide-substituted Merrifield resin with an *O*-propargyl hydroxyproline derivative was envisaged. With respect to common S_N2 anchoring, this strategy offers the advantages of being compatible with the introduction of structural diversity on the monomer and of increasing spatial separation between the polymer backbone and the active site, while no negative effects on reactivity or stereocontrol were expected from the rather inert 1,2,3-triazole moiety.[13]

Click-proline resin **1**[14] was prepared uneventfully as shown in Scheme 1 (see the Supporting Information for experimental details).

Scheme 1. Preparation of Polystyrene-Supported Hydroxyproline



Optimal conditions for the use of resin **1** were first determined working on the aldol reaction of cyclohexanone with benzaldehyde. Since resin swelling would likely be key for catalysis, attention was paid to the determination of the optimal composition in solvent−water mixtures for the reaction (Table 1).

Very interestingly, the reaction worked nicely in water, yielding the aldol product in high diastereoselectivity and high ee for the major *anti* diastereomer (entry 1). On the other hand, the diastereoselectivity was lost and ee for *anti* diastereomers deteriorated when good resin-swelling solvents such as DMF and DMSO (entries 2 and 10) were used in the reaction. However, overall yield increased noticeably in these reactions. Increasing the water content in these solvents improved the diastereo- and enantioselectivities, but at the expense of lower reactivity. Without solvent, the reaction proceeded sluggishly (entry 10). Thus, water appears as the optimal media for the reaction, and this strongly suggests

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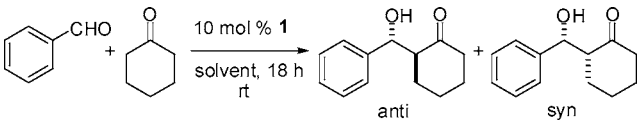
(14) Patent pending.

Table 1. Solvent Effects on the Aldol Reaction of Cyclohexanone with Benzaldehyde Catalyzed by Resin **1**

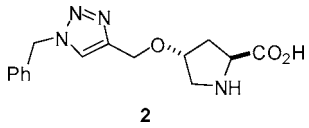


entry	solvent	yield[a] (%)	*anti*/*syn*[b]	ee *anti*[c] (%)	ee *syn*[c] (%)
1	water	26	95:5	96	61
2	DMF[d]	90	50:50	44	87
3	DMF/water 94:6	30	84:16	92	90
4	DMF/water 71:29	48	93:7	96	84
5	DMF/water 50:50	28	95:5	96	85
6	DMSO[d]	95	50:50	84	89
7	DMSO/water 94:6	90	82:18	91	90
8	DMSO/water 71:29	73	91:9	95	95
9	DMSO/water 50:50	55	93:7	96	87
10	neat	<5	nd	nd	nd

[a] Isolated yield. [b] Determined by ^{1}H NMR of the crude product. [c] Determined by HPLC using a chiral stationary phase. [d] Synthesis grade.

that the reaction takes place at the interface between the polymer and the aqueous phase.

In favor of a beneficial contribution of the polymer backbone to the overall outcome of the reaction, when monomer **2** (Figure 1) was tested in the reaction under the



2

Figure 1. Monomer ligand **2**.

conditions of entry 1, *anti*/*syn* ratio was reduced to 63:37, and ee for the *anti* diastereomer was only 83%.

To improve the aldol yield, reaction time was increased and a catalytic amount of water-soluble DiMePEG (MW ~2000) was added with the hope of facilitating difusion to the resin.[15]

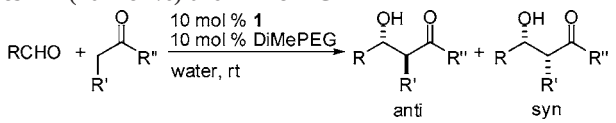
The results are summarized in Table 2. Clearly, improved yields can be obtained at shorter reaction times (compare

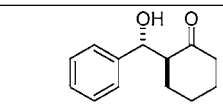
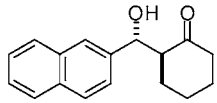
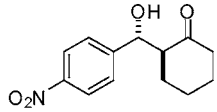
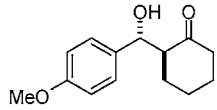
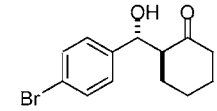
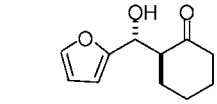
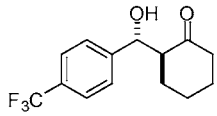
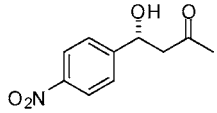
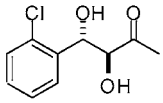
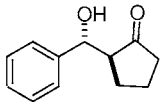
Table 2. DiMePEG Effect on the Aldol Reaction of Cyclohexanone with Benzaldehyde Catalyzed by Resin **1** (10 mol % in Water)

entry	additive (10 mol %)	yield[a] (%)	time (h)	*anti*/*syn*[b]	ee *anti*[c] (%)
1	none	67	84	95:5	95
2	DiMePEG	46	18	95:5	96
3	DiMePEG	75	60	96:4	96
4	DiMePEG[d]	70	60	92:8	91

[a] Isolated yield. [b] Determined by ^{1}H NMR of the crude product. [c] Determined by HPLC using a chiral stationary phase. [d] 5 mol % of **1** used.

Table 3. Asymmetric Aldol Reactions in Water Catalyzed by Resin **1** (10 mol %) and DiMePEG



entry	product	yield[a] [%]	time [h]	anti/sin[b]	yield[c] [%]
1		75	60	96:4	96
2		70	84	95:5	95
3		85	18	98:2	97
4		18	108	90:10	93
5		90	84	96:4	95
6		92	65	82:18	94
7		97	60	97:3	96
8[d]		24	60	-	59
9		42[e]	144	58:42	45
10		97	60	83:17	87

[a] Isolated yield. [b] Determined by ^{1}H NMR of the crude product. [c] Determined by HPLC using a chiral stationary phase. [d] 25 equiv of acetone was used. [e] Estimated by ^{1}H NMR.

entries 1 and 3, and entry 2 with entry 1 in Table 1). Reducing the amount of catalytic resin **1** to 5 mol % still allowed the isolation of the aldol in good yield, but with somewhat diminished stereocontrol (entry 4).

Next, a representative set of aldehydes and ketones was examined under the optimized reaction conditions (10 mol % of **1**, 10 mol % of DiMePEG, water, rt) to check the scope of the catalyst (Table 3). Interestingly, aromatic aldehydes reacted with cyclohexanone with diastereoselectivities higher than those recorded for monomeric proline derivatives in water.[1,2] Moreover, the ee for the major isomers practically did not deteriorate with respect to those catalysts. In *difficult* examples involving other ketones (entries 8−10), a similar behavior was observed.

In addition to these characteristics, the robustness of resin **1** is noteworthy. Thus, after the reactions were quenched by filtration, the resin was washed with AcOEt and simply dried for reuse. No decrease in its performance was observed after three uses of the same sample (see the Supporting Information), and in fact, the results in Table 3 were obtained with recycled samples of resin **1**.

In summary, we have shown for the first time that click chemistry is a most suitable strategy for immobilizing a hydroxyproline derivative to a Merrifield resin for organocatalysis purposes, and we have shown that the resulting catalyst promotes direct asymmetric aldol reactions in water with similar or even better performance than their monomeric counterparts.

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Supporting Information Available: Experimental procedures and characterization of **1** and **2**. Experimental procedures for aldol reactions and HPLC data for aldol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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