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Polystyrene-supported proline and prolinamide. Versatile heterogeneous organocatalysts both for asymmetric aldol reaction in water and α-selenenylation of aldehydes

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Abstract—A simple and efficient synthesis of polystyrene-supported proline and prolinamide has been carried out. Polystyrene-supported proline has been used as organocatalyst in the asymmetric aldol reaction between cyclohexanone and substituted benzaldehydes in water without any additive. High yields, diastereoselectivities and ee values have been observed. The versatility of this resin was demonstrated in the α-selenenylation of aldehydes. Both proline and prolinamide resins gave high yields. Recycling studies showed that the proline resin gave better results than prolinamide resin.

In the last years organocatalysis has emerged as a powerful methodology.[1] The development of small organic molecules which do not contain a metal atom as useful catalysts for enantioselective reactions is attracting much interest. The advantage of using an organocatalyst can be higher if an efficient recovery and reuse of the catalyst can be carried out.[2] From an economical point of view this aspect is important since in several cases organocatalysts are used up to 30 mol %, but also in order to avoid wastes, so improving the greenness of the process.

In addition to these aspects, a very recent development has been the use of water as solvent for organocatalytic asymmetric reactions. Indeed, water is a desirable solvent in terms of safety, cost and environmental concerns. Excellent results for the aldol reaction in water have been obtained using a diamine, derived from pyrrolidine, containing a large apolar group in the presence of an additive (TFA),[3] or proline derivatives containing a large apolar group too[4] or protonated prolinamide derivatives.[5] Good results have been observed using tryptophan in water.[6] Also a simple dipeptide has been used as a catalyst in the reaction between cyclohexanone and *p*-nitrobenzaldehyde in water, using α-cyclodextrin as an additive, with interesting results.[7] Very recently, a paper dealing with asymmetric aldol reaction in water using a polystyrene-supported proline appeared.[8] The L-proline was anchored to a polystyrene resin through a 1,2,3-triazole moiety. This catalyst was used for the aldol reaction in water giving high stereoselectivities, whereas yields were increased by using a 10 mol % of DiMePEG as an additive. A debate is now open as to whether some of these reactions really are 'all wet'.[9]

Our efforts have been devoted to the recycling studies of the organocatalyst. Such investigations have led us to interesting achievements. We prepared an ionic liquid-modified silica gel in which the L-proline is supported as useful and recyclable catalyst for aldol reaction between acetone and several aldehydes.[10] Our approach has advantages in terms of yields, enantiomeric excess values and recyclability. Moreover, since the proline was supported by adsorption, the spent catalyst was easily regenerated and reused. However, this aspect represents a disadvantage too. Indeed, the use of a solvent more polar than acetone can cause the desorption of the proline from the surface support. Then we started a study to overcome this inconvenience. In order to reach this goal we carried out the covalent immobilization of

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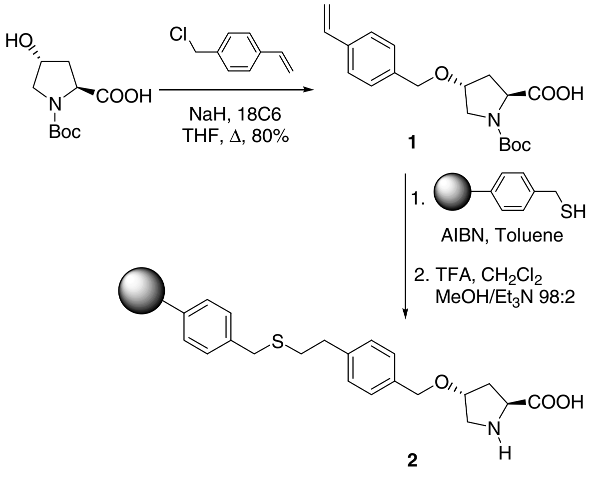
L-proline. Recently, covalently immobilization of L-proline has been carried out on soluble poly(ethyleneglycol) (PEG)[11] or mesoporous silica.[12] Such proline-modified materials gave good results for the asymmetric aldol reaction in organic solvents.

Our first aim was the preparation of a L-proline-modified material that can be used for the asymmetric aldol reaction in more polar solvents than acetone and even in water. Moreover, since proline is able to catalyze many reactions, we decided to use the same material to investigate the α-selenenylation of aldehydes catalyzed by proline or prolinamide.[13] Indeed, stereoselective synthesis using organoselenium compounds is another area of interest in our laboratory.[14]

To reach our goals we decided to immobilize the L-proline on a polystyrene resin. The polystyrene support was chosen in order to have an insoluble catalytic material that can be easily recovered. Moreover, since polystyrene may be regarded as a large apolar substituent, this material may be useful for asymmetric aldol reaction in water.

Commercially available *trans*-*N*-Boc-4-hydroxy-L-proline was used for proline immobilization since its hydroxyl group can be easily functionalized. As support we have chosen the commercially available mercaptomethyl polymer-bound (1% cross-linked with DVB, spherical beads, particle size 100–200 mesh, 2.5 mmol/g loading). The anchorage of L-proline was accomplished in two steps accordingly to Scheme 1: (a) synthesis of styrene derivative **1** of hydroxy-L-proline; (b) radical reaction between the polystyrene and **1** followed by the deprotection of proline moiety. The removal of *tert*-butoxycarbonyl group was carried out with TFA/CH_2Cl_2 20/80 followed by treatment with Et_3N/MeOH 2/98.

This procedure gave the polystyrene-supported L-proline in a high yield and in a very simple way (proline loading ca. 1.5 mmol/g, determined by elemental analysis and weight gain). Moreover, this approach is flexible, allowing the synthesis of polystyrene-supported L-proline possessing different linkers and can be used for the immobilization of different organic molecules.



Scheme 1. Synthesis of polystyrene-supported proline.

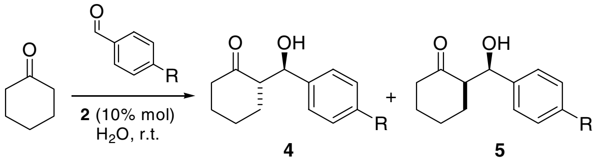
First we carried out a reaction between acetone and benzaldehyde at room temperature using a 30 mol % of catalyst. We checked the reaction after 2 h. Both conversion (30%) and ee value (61%) were not good.

Then we turned our attention to the reaction using water as the sole solvent, since the insoluble apolar polystyrene resin may act as artificial aldolase.[8] We investigated the reaction between cyclohexanone and several substituted benzaldehydes.[15] The results are reported in Table 1. We were delighted to find that the catalyst works well in water.

Yields are quite good whichever was the aldehyde. Reaction times are ranging from 22 to 90 h. Diastereoselectivities were high, comparable[4a] or even better[3] than those obtained with proline derivatives in water. Also ee values were comparable. We also carried out the reaction with *p*-nitrobenzaldehyde using DiMePEG as the additive.[8] In our case both *anti*/*syn* ratio and ee value were identical to those obtained without additive, but the isolated yield was lower (55%). The crucial role played by water was evident when the reaction was carried out under neat conditions (Table 1, entry 9). We hypothesize that the hydrophilic proline moiety lies in the interface (resin/H_2O). This facilitates the formation of a hydrophobic core on the inner surface of the resin. Such microenvironment promotes the aldol reaction with a high stereoselectivity.[17]

The performance of the resin was also checked using it several times. The reactions were quenched by filtration. After each cycle the resin was washed with EtOAc and acetone then dried. The resin was used four times using *p*-cyanobenzaldehyde. Each cycle gave reproducible

Table 1. The catalytic asymmetric aldol reaction in water catalyzed by polystyrene-supported proline **2**



Entry	*R*	Time [h]	Conv.[a] [%]	*anti*/*syn*[b]	ee[c] [%]
1	H	60	71	95/5	93
2	Br	90	85	96/4	96[d]
3	NO_2	22	85	95/5	90
4	CF_3	48	74	96/4	94
5	CN cycle 1	22	98	92/8	98
6	Cycle 2	22	79	96/4	98
7	Cycle 3	22	65	95/5	98
8	Cycle 4	22	62	95/5	98
9[e]	CN	22	<5	nd	nd

[a] Yields >98% (based on conversion).
[b] Determined by the ^1H NMR of the crude product.
[c] Determined by HPLC using a chiral column (Daicel AS-H).
[d] Determined by optical rotation (see Ref. 16).
[e] Reaction carried out without water.

anti/*syn* ratio and ee values. However, a decrease in conversion was observed.

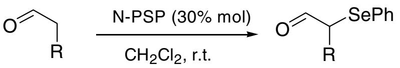
In order to check the versatility of the resin, we used it in the α-selenenylation of aldehydes by reaction with *N*-(phenylseleno)-phthalimide (NPSP).[18] In our first attempt we used resin **2** (30% mol) and decanal in dichloromethane. The reaction was quenched by filtration with EtOAc after 1 h (see Table 2). We were pleased to find a very clean reaction and an interesting isolated yield (65%). The resin was dried for a few minutes then reused in a second cycle using the same aldehyde. In the second cycle the reaction time was 2.5 h. In this case the yield was higher (85%). We decided to carry out reactions using a 30 mol % of resin **2** for 2.5 h. Fresh resin **2** was used in the reaction with 3-methylbutanal. Three cycles were carried out. Each cycle gave a high isolated yield. Excellent yields were observed using hexanal. In this case four cycles were performed.

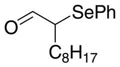
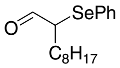
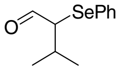
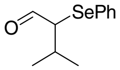
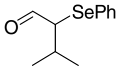
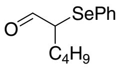
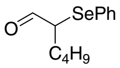
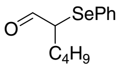
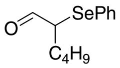
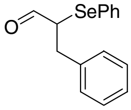
Finally, we used 3-phenylpropanal, also in this case a high yield was obtained. Even if proline is able to catalyze the α-selenenylation of aldehydes in good yields, it has been reported that prolinamide is more efficient.[13] For this reason we decided to prepare the L-prolinamide-supported resin **7**. The synthesis was straightforward (see Scheme 2). The resin was obtained starting from the *trans*-*N*-Boc-4-hydroxy-L-proline in three steps (prolinamide loading 2.5 mmol/g). The prolinamide derivative **6** was easily prepared by reaction of compound **1** with ammonium hydrogen bicarbonate, pyridine and Boc_2O in MeCN.[19] Selenenylation of hexanal was carried out for 2.5 h using a 10 mol % of resin **7** instead of 30% of resin **2**. The yield was excellent. The reaction was also carried out using less amount of resin for different times (Table 3, entries 2–4).

Again, after 2.5 h, but using a 5% mol of catalyst **7**, an excellent yield was obtained. Resin **7** was used in the reaction with other aldehydes (Table 3, entries 5–7) giving high yields. As for catalyst **2**, hexanal was used as substrate for recycling studies. Resin **7** was used four times. However, in this case resin **7** gave the α-phenylselenoaldehyde with a decreased conversion after four cycles. The ee values of α-phenylselenoaldehydes obtained were low as those observed under homogeneous conditions.[13]

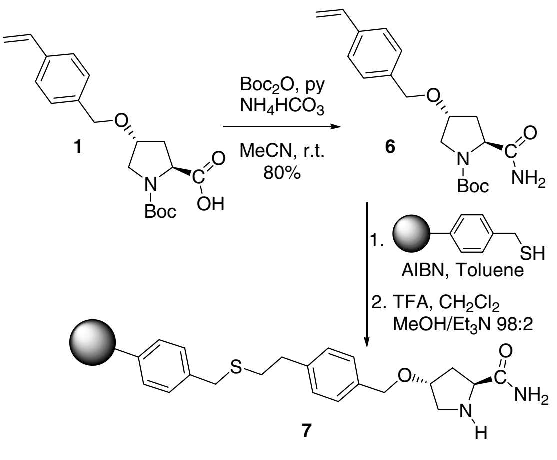
In conclusion we have reported the straightforward synthesis of the polystyrene-supported proline and polystyrene-supported prolinamide. It has been showed that the proline resin is a useful catalyst both in the aldol reaction in water as the sole solvent without any additive and in the α-selenenylation of aldehydes. Moreover, the proline resin is recyclable and reusable at least for four cycles with excellent results especially in the case of the α-selenenylation of aldehydes. As observed under homogeneous conditions, even the prolinamide-supported resin is more efficient than the corresponding

Table 2. The catalytic α-selenenylation of aldehydes catalyzed by polystyrene-supported proline **2** (30% mol)



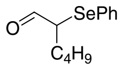
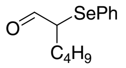
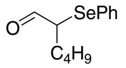
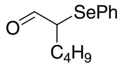
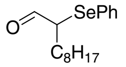
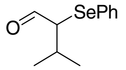
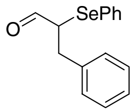
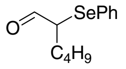
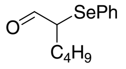
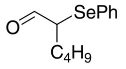
Entry	Product	Time [h]	Conv.[a] [%]
1	 cycle 1	1	65
2	 cycle 2	2.5	85
3	 cycle 1	2.5	88
4	 cycle 2	2.5	90
5	 cycle 3	2.5	89
6	 cycle 1	2.5	96
7	 cycle 2	2.5	97
8	 cycle 3	2.5	97
9	 cycle 4	2.5	97
10		2.5	85

[a] Yields >98% (based on conversion).



Scheme 2. Synthesis of polystyrene-supported prolinamide.

Table 3. The catalytic α-selenenylation of aldehydes catalyzed by polystyrene-supported prolinamide **7**

Entry	Product	Catalyst [% mol]	Time	Conv.[a] [%]
1		10	2.5 h	98
2		5	5 min	52
3		5	1 h	63
4		5	2.5 h	96
5		5	2.5 h	84
6		5	2.5 h	86
7		5	2.5 h	87
8	 cycle 2	5	2.5 h	94
9	 cycle 3	5	2.5 h	70
10	 cycle 4	5	2.5 h	40

[a] Yields >98% (based on conversion).

proline resin. The former catalyst showed a diminished activity in subsequent runs. These data represent the first examples of heterogeneous catalytic α-selenenylation of aldehydes.

Further investigations are in progress with different substrates in order to study the scope and limitation of this methodology.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.040.

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15. *Typical procedure for aldol reaction*: To a mixture of the corresponding benzaldehyde (0.5 mmol) and cyclohexanone (2.5 mmol) in distilled water (0.18 ml), catalyst **2** was added (0.05 mmol) and the reaction mixture was stirred at rt for the time indicated in Table 1. The reaction was quenched by adding ethyl acetate and, upon filtration, the catalyst was washed thoroughly with ethyl acetate, acetone and ethyl ether. The organic layers were collected and, after evaporation of solvents, the crude product was purified by chromatography (petroleum ether/ethyl acetate).

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17. Lindström, U. M.; Andersson, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 548–551.
18. *Typical procedure for α-selenenylation of aldehydes*: To a mixture of the corresponding aldehyde (0.5 mmol) and *N*-(phenylseleno)-phthalimide (0.6 mmol) in freshly distilled CH_2Cl_2 (3.0 ml), catalyst **2** or **7** was added (0.15 mmol or 0.025 mmol, respectively) and the reaction mixture was stirred at rt for 2.5 h. A usual work-up gave the corresponding α-phenylselenoaldehydes.
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