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Poly(ethylene-glycol)-supported proline: a recyclable aminocatalyst for the enantioselective synthesis of γ-nitroketones by conjugate addition

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Dedicated to Professor Renato Ugo on the occasion of his 65th birthday

Abstract

A poly(ethylene-glycol)-supported proline was used as the catalyst for two enantioselective conjugate addition reactions leading to γ-nitroketones. In both cases the chemical yield and the stereochemical efficiency of the processes greatly depended on the reaction conditions. In the additions of ketones (cyclohexanone, cyclopentanone, and acetone) to 2-nitrostyrene, fair yields (up to 60%) and good diastereoselectivity (up to 95/5 *syn*/*anti* ratios) were observed. The enantiomeric excesses (up to 40%) were lower than those obtained with non-supported proline (e.e. up to 57%). In the addition of 2-nitropropane to cyclohexenone the use of the sodium salt of supported proline allowed to almost match the e.e. of the adduct obtained with rubidium prolinate as the catalyst (50% e.e. versus 59% e.e.) in comparable yields. Examples of recovery and recycling of the supported catalysts in both types of processes were also reported.

Keywords: Aminocatalysis; Asymmetric catalysis; Conjugate addition; Polymer-supported catalysts; Soluble polymers

1. Introduction

Enantioselective organic catalysis is currently the subject of an intense research activity aimed to develop "metal-free" alternatives to established "metal-based" catalytic processes [1]. In this respect, catalysis by enantiomerically pure amines (aminocatalysis) [2] is receiving considerable interest due to the ubiquitary presence and ready availability of these compounds in the chiral pool.

As a part of a project aimed to the improvement of homogeneous enantioselective catalytic processes by immobilization of organic catalysts on soluble polymer supports [3], we recently developed the poly(ethylene-glycol)-supported proline **1** (PEG-Pro, Fig. 1) that was shown to be an effective, enantioselective, and recyclable promoter for the aldol and iminoaldol condensations of ketones with aldehydes and imines [4]. In the context of these reactions, the choice of the monomethylether of poly(ethylene-glycol) of M_W 5000 Da ($MeOPEG_{5000}$) as the support was

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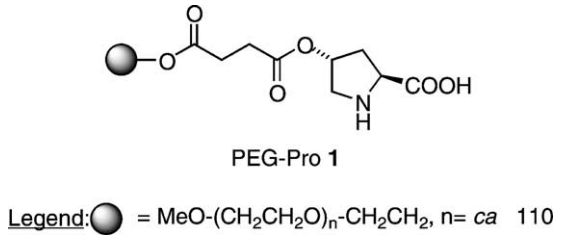


Fig. 1. Structure of PEG-Pro.

particularly successful. This commercially available, inexpensive polymer, being soluble in many organic solvents and insoluble in a few other solvents [5], is a convenient catalyst support allowing, in principle, to run a reaction under homogeneous (and likely best performing) conditions, and to recover and recycle the catalyst as if it were bounded to a solid support (for a recent review on the use of PEG as catalyst support see [6]; on the use of other soluble polymers as catalyst supports see [7]; for another example of PEG-supported enantioselective catalyst see [8]).

In extending the use of PEG-Pro to other reactions, we reasoned that this supported proline can in principle facilitate enantioselective conjugate addition processes, either by inducing ketones (by enamine formation) to act as Michael donors (A, Fig. 2), or by activating α,β-unsaturated ketones (by iminium ion formation) to act as Michael acceptor (B, Fig. 2) [2]. Here, we report the results of this study.

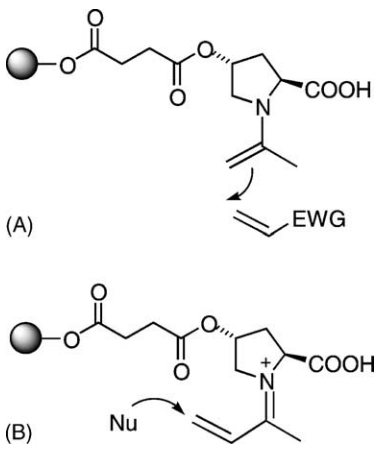


Fig. 2. Activation of conjugate addition processes by PEG-Pro **1**.

2. Experimental

General: ^{1}H NMR spectra were recorded at 300 MHz in chloroform-d ($CDCl_3$) and were referenced to tetramethylsilane (TMS) at 0.00 ppm. Optical rotations were measured at the Na-D line in a 1 dm cell at 22 °C. IR spectra were recorded on thin films or as CH_2Cl_2 solutions. Compound **1** was prepared as described [4] and was dried under vacuum at 80–90 °C before use. Adducts **3** [9], **5** [10], **7** [9], and **10** [11] were known compounds that gave ^{1}H NMR and IR data in agreement with those reported in the literature. The relative and absolute configuration of compound **3**, and the absolute configuration of compound **10** were assigned by comparison of signs of optical rotation. In the case of compound **5** the assignment was based on the assumption of an identical reaction pathway to that followed with cyclohexanone and from common characteristic NMR patterns with related known compounds [12].

2.1. Addition of ketones to 2-nitrostyrene: general procedure

The reaction of cyclohexanone is illustrative of the procedure. To a solution of PEG-Pro **1** (0.472 g, 0.09 mmol) in the appropriate solvent (1.2 ml, see Table 1) kept under a nitrogen atmosphere, 2-nitrostyrene (0.090 g, 0.60 mmol) and cyclohexanone (0.621 ml, 6 mmol) were added in this order. After stirring at RT for the appropriate time (see Table 1), the solvent was evaporated under vacuum and the residue was dissolved in CH_2Cl_2 (2 ml). This solution was poured into ice cold Et_2O (60 ml), whereupon the catalyst precipitated and was filtered off and recovered. The filtrate was concentrated under vacuum and the residue was analyzed by ^{1}H NMR spectroscopy to assess the diastereoisomeric ratio. To this end, the signals at ca. 4.00 ppm (*anti*) and 3.75 ppm (*syn*) were exploited. Flash chromatographic purification (90:10 and then 80:20 hexanes:AcOEt mixtures as eluants) afforded the pure product in the yields reported in Table 1. The e.e. were determined by HPLC analysis on a Chiracel ODH column with a hexanes:EtOH 95:5 mixture as eluant (flow rate 1 ml/min); t_R: of the major enantiomer 11.89 min; of the minor enantiomer 11.32 min.

Table 1
Stereoselective addition of cyclohexanone to 2-nitrostyrene catalyzed by PEG-Pro **1**

Entry	Solvent	Time (h)	Yield (%)[a]	*syn*/*anti*[b]	e.e. (%)[c]
1	DMF	18	23	90/10	22
2[d]	DMF	40	12	90/10	21
3	DMSO	40	10	Undetermined	Undetermined
4	DMSO	72	26	70/30	15
5	MeOH	40	46	95/05	35
6	MeOH	72	60	95/05	35
7[d]	MeOH	72	48	90/10	23
8[e]	MeOH	72	23	90/10	23
9[f]	MeOH	72	23	90/10	20
10[g]	MeOH	72	18	90/10	20

[a] Isolated yields.
[b] As determined by 300 MHz ^{1}H NMR analysis of the crude reaction products.
[c] Reported values refer to the *syn* isomer and were determined by HPLC on a chiral stationary phase.
[d] Carried out with 30 mol eq. of cyclohexanone.
[e] Carried out with a catalyst sample recycled after use in entry 6.
[f] Carried out with a catalyst sample recycled after use in entries 6 and 8.
[g] Carried out with a catalyst sample recycled after use in entries 6, 8, and 9.

2.2. Addition of 2-nitropropane to cyclohexenone: general procedure

To a solution of PEG-Pro **1** (0.472 g, 0.09 mmol) in the appropriate solvent (4.5 ml, see Table 2) kept under a nitrogen atmosphere, a 0.5 M solution of NaOH in the reaction solvent indicated in Table 2 (40.5 μl, 0.081 mmol) or the equivalent amount of solid NaOH (or one of the bases reported in Table 2) was added. After 1 h stirring at RT, cyclohexenone (0.057 ml, 0.9 mmol) and 2-nitropropane (0.162 ml, 0.6, 1.8 mmol) were added in this order. After stirring at RT for the appropriate time (see Table 2), the solvent was evaporated under vacuum and the residue was dissolved in CH_2Cl_2 (2 ml). This solution was poured into ice cold Et_2O (60 ml), whereupon the catalyst precipitated and was filtered off and recovered. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography (90:10 and then 80:20 hexanes:AcOEt mixtures as eluants) to afford the pure product in the yields reported in Table 2. The e.e. were determined by HPLC analysis on a Chiracel OB column with a hexanes:EtOH 80:20 mixture as eluant (flow rate 1 ml/min); t_R: of the major enantiomer 11.67 min; of the minor enantiomer 13.07 min.

Table 2
Stereoselective addition of 2-nitropropane to cyclohexenone catalyzed by alkali metal salts of PEG-Pro **1**

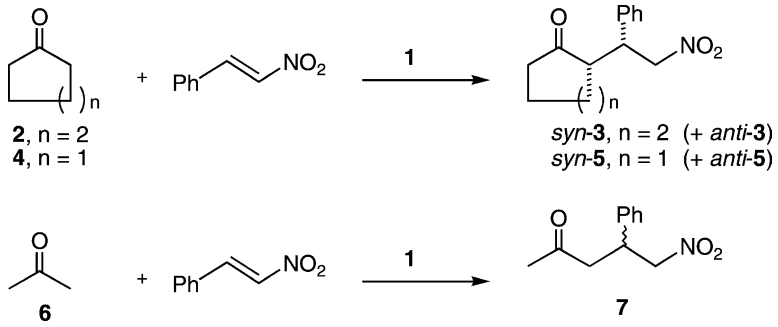
Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]	e.e. (%)[b]
1	**1**/RbOH	$CHCl_3$	40	62	5
2	**1**/NaOH	$CHCl_3$	60	38	33
3	**1**/NaOH	DMSO	60	36	10
4	**1**/NaOH	MeOH	60	86	10
5	**1**/NaOH	2-PrOH	60	65	42
6	**1**/NaOH	2-PrOH	5	36	50
7	**1**/Bu_4NOH	2-PrOH	60	98	16
8	**1**/Bu_4NOH	2-PrOH	5	22	20
9	**1**/Bu_4NOH	2-PrOH	12	50	16
10	**1**/NaOH[c]	2-PrOH	60	65	46
11	**1**/NaOH[d]	2-PrOH	60	64	38
12	**1**/NaOH[e]	2-PrOH	60	65	32

[a] Isolated yields.
[b] As determined by HPLC on a chiral stationary phase.
[c] With a catalyst sample recovered from the reaction of entry 5 and recycled.
[d] With a catalyst sample recovered from the reactions of entries 5 and 10 and recycled.
[e] With a catalyst sample recovered from the reaction of entries 5, 10, and 11 and recycled.

3. Results and discussion

3.1. Diastereo- and enantioselective addition of ketones to 2-nitrostyrene

The well-known ability of proline to activate ketones by enamine formation has led to the de-



Scheme 1. Addition of ketones to 2-nitrostyrene.

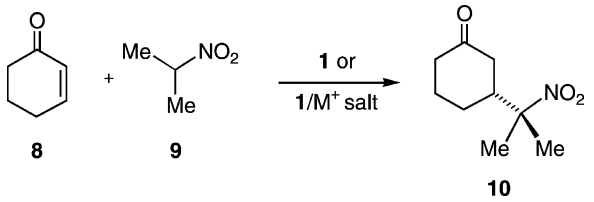
velopment of a variety of enantioselective catalytic processes including Robinson annulation [13,14], aldol condensations [15,16], and Mannich type reactions [17,18]. Recently, List reported the conjugate addition of symmetric ketones to nitroalkenes carried out in the presence of proline (0.15 mol eq.). Working with 2-nitrostyrene and cyclohexanone in DMSO for 24 h at room temperature, the product was obtained in high yield (94%), excellent *syn* diastereoselectivity (*syn*/*anti* ratio ca. 20/1), but modest enantioselectivity (23%) [9]. More recently, Enders and Seki improved the stereochemical outcome of this process by employing a slightly higher catalyst loading (0.20 mol eq.), methanol as the solvent, and longer reaction time (96 h). Under these conditions the product was isolated in 79% yield, 32/1 *syn*/*anti* diastereoselectivity, and 57% e.e. [19].

This same reaction (Scheme 1) was investigated by us working with 1.0 mol eq. of 2-nitrostyrene, 0.15 mol eq. of PEG-Pro **1**, and 10 mol eq. of cyclohexanone **2** in different solvents (**2**/solvent (v/v) ratio = 0.5). The data, reported in Table 1, showed that MeOH was the solvent of choice for this reaction (entries 5 and 6), allowing to isolate adduct **3** in yield (up to 60%), *syn* diastereoselectivity (*syn*/*anti* ratio up to 19/1), and e.e. (35%) higher than those observed in more polar solvents such as DMF (entries 1 and 2) and DMSO (entries 3 and 4).[1] The use of a long reaction time was beneficial for the yield (entry 5 versus entry 6) but not for the stereoselectivity. Independently of the solvent, the use of a larger excess of cyclohexanone depressed both the yield and the stereocontrol (entries 2 and 7).

By comparing the present results to those obtained for the same reaction with non-supported proline [9,19], it can be concluded that the supported catalyst is less efficient in term of chemical yield than the non-supported one both in MeOH and in DMSO. As far as the stereoselectivity of the reaction is concerned on the other hand, the results obtained with the supported and the non-supported catalyst in DMSO [9] are very similar (with PEG-Pro: *syn*/*anti* = 9/1, e.e. 22%; with proline: *syn*/*anti* > 20/1, e.e. 23%), whereas the use of proline in MeOH leads to higher e.e. (57% versus 35%) [19]. The observation of somewhat lower chemical yields seems to be a common feature of the PEG-Pro catalyzed reactions [4] with respect to their proline-catalyzed counterparts [13–18]. On the contrary, the lower enantioselectivty observed was more surprising and unprecedented in previous works, where PEG-Pro performed stereochemically as well as proline [4].

One of the main reasons for developing a polymer-supported catalyst resides in the possibility of exploiting the polymer support as a solubility device for catalyst recovery and recycling [3,6,7]. This issue was addressed with the experiments described in entries 8 through 10 of Table 1. From the reaction of entry 6, PEG-Pro was readily recovered by precipitation with diethylether followed by filtration (average recovery yields ranged from 85 to 90%), and employed to promote three additional runs. As can be seen from the reported data, a decrease both in chemical yield (from 60 to 23%) and e.e. (from 35 to 23%) was observed for the

[1] Other solvents tested without success were: chloroform, toluene, cyclohexanone, nitromethane, and 2,2,2-trifluorethanol. Yields and ee were lower than 15%.



Scheme 2. Addition of 2-nitropropane to 2-cyclohexenone.

second run, after which the catalyst performed at the same level of efficiency for two other runs. Also this behavior is in contrast with that observed in the case of other PEG-Pro catalyzed reactions [4] where the decrease in chemical yields was much slower (some 8% per run) and no erosion of enantioselectivity was reported up to the fourth cycle.

Finally, extension of the use of catalyst **1** to the reactions of different ketones was attempted. Replacement of cyclohexanone with cyclopentanone **4** (under the conditions of entry 7, Table 1) gave adduct **5** in 40% yield as a 60/40 mixture of *syn*/*anti* diastereoisomers having 40 and 30% e.e., respectively. A recycled sample of catalyst promoted the same reaction affording **5** in lower yield (26%) but identical diastereo- and enantioselectivity (*syn*/*anti* ratio 60/40; e.e. of *syn* isomer 40%, of *anti* isomer 32%). The use of acetone **6** led to racemic adduct **7** in 92% yield.

3.2. Enantioselective addition of 2-nitropropane to 2-cyclohexenone

The possibility of exploiting PEG-Pro **1** to activate α,β-unsaturated ketones by iminium ion formation toward the addition of nucleophiles (**B**, Fig. 2) was examined by studying the reaction reported in Scheme 2. According to a recent literature report by Hanessian and Pham [20], compound **10** could be obtained in 88% yield and 93% e.e. by running the reaction between 2-cyclohexenone **8** and 2-nitropropane **9** in the presence of a stoichiometric amount of 2,5-dimethylpiperazine and a catalytic amount (0.03–0.07 mol eq.) of proline in chloroform (62 h, room temperature). This results improved a previous procedure by Yamaguchi et al. [11] that was described to afford the same product in 81% yield and 59% e.e. when 0.05 mol eq. of rubidium prolinate was used to catalyze the reaction in chloroform (24 h, room temperature). It is worth mentioning that in both Hanessian's and Yamaguchi's procedures the catalysts were poorly soluble in the reaction solvent.

While attempts to replicate Hanessian's results with PEG-Pro were not very successful,[2] Yamaguchi's method, or modifications thereof, proved to be much more amenable to the use of the supported catalyst (Table 2). Indeed, the in situ generated sodium salt of PEG-Pro (**1**/Na) catalyzed the synthesis of **10** in 2-propanol in 65% yield and 42% e.e. (entry 5). Shortening the reaction time to 5 h (entry 6) improved the e.e. of **10** to 50%, a value close to Yamaguchi's one (59%). It seems likely that the reversible nature of the reaction can account for the dependence of the e.e. on the reaction time.

Also the role of the solvent was found to be important. Indeed, when the reaction was performed with **1**/Na, a high yield was observed in MeOH (entry 4, e.e. 10%), while the reaction is sluggish both in DMSO (36% yield and 10% e.e., entry 3) and in chloroform (38% yield and 33% e.e., entry 2).

The possibility that the polyethyleneoxy chain of PEG could interact with the alkali metal of the prolinate salt,[3] led us to investigate the use of different bases to generate the catalytically active species.[4] The use of an in situ generated sample of the rubidium salt of PEG-Pro in chloroform (reaction time 40 h) led to compound **10** in 62% yield and 5% e.e. (entry 1). Pre-formation of the Rb-catalyst depressed the chemical yield to less than 10%. The use of

[2] Repetition of Hanessian's experiment using PEG-Pro instead of proline afforded a 94% yield of virtually racemic **10** in MeOH, and a 68% yield of a 20% ee sample of the product in 2-propanol. Other solvents tested were: chloroform (15% yield, racemic); DMSO (28% yield, racemic); EtOH (65% yield, racemic); hexane (42%, racemic) and acetonitrile, THF, and toluene in which no product was obtained. It must be noted that the reaction carried out under Hanessian's conditions in the presence of the bismethylether of PEG of M_W 2000 Da afforded the product in 60% isolated yield and 70% ee, both values being inferior than those obtained in the absence of PEG (88% yield, 93% ee). This clearly showed that the polymer influenced the outcome of this reaction, likely because of its solubilizing properties (see later).

[3] That a PEG/Rb+ interaction can indeed play a role in the reaction was suggested by the fact that when Yamaguchi's procedure was repeated in the presence of the bismethylether of PEG of M_W 2000 Da, adduct **10** was obtained in 54% yield and only 15% ee.

[4] Other alkali metals tested were: lithium (no product obtained), potassium (20% yield, 10% ee of the opposite enantiomer), caesium (10% yield, undetermined ee).

tetrabutylammonium hydroxide as the PEG-Pro carboxylate generating reagent (entry 7) afforded the product in excellent yield (98%) but unacceptably low e.e. (16%). Under these conditions, a slight improvement in the e.e. was observed at a much shorter reaction times (entry 8).

In attempting an explanation for the results obtained in the PEG-Pro catalyzed synthesis of compound **10**, it is worth mentioning that the aggregation state of the catalyst seems to play an important role in determining the outcome of both the Hanessian's and Yamaguchi's reactions. In this respect it is worth mentioning that under Hanessian's conditions, proline is not soluble and a nonlinear relation between the e.e. of proline and that of the product was observed [20]. With PEG-Pro on the other hand, the solubilising presence of the PEG portion of **1** can obliterate catalyst's surface effects that seem to be important in achieving high e.e.. Similarly, the presence of PEG can prevent proline aggregation around the alkali metal, a structural feature that very recently was shown to be an important factor for the efficiency of Yamaguchi's catalyst [21].

The recovery and recycling of **1**/Na was studied with the experiments described in entries 10–12, Table 2. The catalyst recovered from the reaction of entry 5 was employed for three additional cycles, affording the product in constant yields (60–65%). On the other hand, the e.e. remained in the 40% range until the third run, and dropped to 32% at the fourth cycle. This behavior was reminiscent of that observed upon recycling PEG-Pro in the aldol- and iminoaldol reactions [4], and clearly different from that observed for **1** in the conjugate addition of ketones to 2-nitrostyrene (entries 8–10, Table 1).

4. Conclusions

In conclusions, the use of a poly(ethylene-glycol)-supported proline as a catalyst for two types of enantioselective conjugate addition reactions leading to γ-nitroketones was investigated. In the additions of ketones to 2-nitrostyrene, fair yields (up to 60%), good diastereoselectivity (up to 95/5 *syn*/*anti* ratios), but e.e. (up to 40%) lower than that observed with proline were observed. In the addition of 2-nitropropane to cyclohexenone the use of the sodium salt of supported proline allowed to almost match the e.e. of the adduct obtained with rubidium prolinate as the catalyst (50% e.e. versus 59% e.e.) in comparable yields. Examples of supported catalyst recovery and recycling were reported for both processes (four cycles), when the two catalysts were shown to behave differently.

The data collected for the two PEG-Pro catalyzed Michael-type addition processes here described seem to indicate a strong dependence of the efficiency of the supported catalyst on the type of the reaction in which the catalyst is employed. Differently from the aldol-type processes, where PEG-Pro [4] behaved as well as non-supported proline [13–18], in the present cases the PEG-supported catalyst is less efficient than the non-supported one. Therefore, as more general conclusion, these results showed that the identification of an ideal support of wide applicability in the field of supported catalysis remains an elusive goal that will require more work to be achieved.

Acknowledgements

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