

Asymmetric aldol reactions in poly(ethylene glycol) catalyzed by L-proline[☆]

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Abstract—A rapid L-proline catalyzed direct aldol reaction between various aldehydes and acetone was achieved using PEG as the solvent with comparable enantioselectivities and yields to those obtained in other solvents. Recycling the catalyst and solvent (PEG) was possible 10 times without loss of activity.

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The asymmetric aldol reaction of an aldehyde and a modified/unmodified ketone is one of the most powerful C–C bond forming reactions.¹ This reaction yields β -hydroxy carbonyl compounds, which in turn have great potential in organic synthesis.² Even though several catalysts have been reported for this transformation, more emphasis recently has been given to nonmetallic small molecule chiral catalysts as they are more efficient and environment friendly.³ L-Proline is one such small molecule, which has given rich dividends in ee's and yields. However some of the protocols reported to date involve high boiling DMSO as the solvent and also require long reaction times.⁴ Recent work has attempted to overcome this by using a recyclable ionic liquid as the solvent,⁵ or buffered aqueous media,⁶ or a Zn–proline complex in aqueous media⁷ or aqueous micelles.⁸

We were particularly interested in developing an eco-friendly approach⁹ for the direct aldol reaction using PEG as the solvent for the following reasons. (a) PEG is biologically compatible.¹⁰ (b) The polymer is available at a very affordable price.¹¹ (c) The requirement for only a low concentration of catalyst. (d) A highly practical and simple workup procedure. Our results are presented herein.

First we examined the reaction of acetone (4 mmol), L-proline (10 mol% compared to 30 mol% in all the

earlier cases studied), PEG (2 g, 400 Da) and nitrobenzaldehyde (1 mmol) (Table 1, entry 1). To our satisfaction the reaction was complete in 30 min and yielded 94% of the product with 67% ee (Scheme 1). The reaction medium was diluted with anhydrous ether (5 mL), stirred for 5 min, allowed to separate out and the ether layer was decanted. This process was repeated twice to obtain the product in ether whereas the mother liquor (PEG + proline) was kept aside for further runs.

Encouraged by this result, we studied the reusability of the catalyst as well as the solvent. A second run was performed without any modification. The simple addition of nitrobenzaldehyde (1 mmol) and acetone (4 equiv) to the mother liquor with stirring for 30 min resulted in the aldol product in a 93% yield with similar enantioselectivity (68% ee) to first run. The efficient recycling of the reaction medium (catalyst and solvent) was then proved by additional experiments until a tenth run. Except for the third run, which showed a slight increase in enantioselectivity (71%), all the runs were similar in product yields and enantioselectivities.

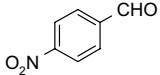
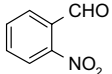
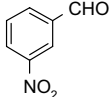
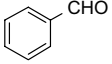
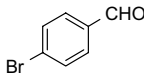
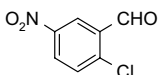
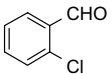
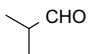
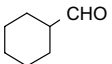
The efficiency of the transformation was examined by subjecting various aldehydes to an aldol reaction in PEG. All the examples studied gave similar results to those reported using conventional solvents and other methods. The 2- and 3-nitrobenzaldehydes (entries 11 and 12) underwent the aldol reaction smoothly giving the products in 90% and 88% yields with 64% and 70% ee's, respectively. Benzaldehyde (entry 13) gave the aldol product, which was comparable in yield and enantiomeric excess to that obtained with DMSO as the solvent. In the case of 4-bromobenzaldehyde (entry 14) there was

Keywords: Asymmetric aldol reaction; L-Proline; PEG; Reusability.

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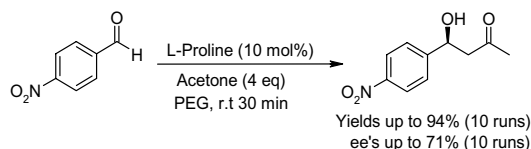
Table 1. L-Proline catalyzed asymmetric aldol reactions in PEG

Entry	Substrate	Time (min)	Yield ^a (%)	Ee (%)
1		30	94	67 ^b
2	2nd run	30	93	68 ^b
3	3rd run	30	90	71 ^b
4	4th run	30	89	67 ^b
5	5th run	30	90	66 ^b
6	6th run	30	88	64 ^b
7	7th run	30	87	67 ^b
8	8th run	30	88	65 ^b
9	9th run	30	86	67 ^b
10	10th run	30	84	66 ^b
11		30	90	64 ^b
12		30	88	70 ^b
13		30	58	58 ^b
14		30	85	65 ^b
15		30	90	61 ^b
16		30	88	60
17		120	90	84 ^c
18		180	65	71 ^c

^a Isolated yields after chromatography; the products were characterized by spectral data.

^b Ee% by chiral HPLC.

^c Ee% by optical rotation.

**Scheme 1.**

an increase in the yield (85%) of the product. Aliphatic aldehydes (entries 17 and 18) were also good substrates for the aldol reaction.

In conclusion poly(ethylene glycol) (PEG) has been shown to be a rapid and reusable reaction medium for L-proline catalyzed asymmetric aldol reactions. The reusability of this solvent was studied over 10 runs without loss of activity of either the catalyst or solvent.

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