

POLYACRYLIC CROSSLINKED RESINS WITH PENDANT CHIRALITY
AS AUXILIARY IN SUPPORTED ASYMMETRIC SYNTHESIS

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Abstract : A new approach is given in polymer assisted asymmetric synthesis, using a polyacrylic crosslinked polymer with pendant chirality as chiral auxiliary. The method is applied to the asymmetric synthesis of aminoacids.

Polymer assisted asymmetric synthesis is well documented^{1,2}. Chiral phases such as polyaminoacids³, polyamines⁴, acrylonitrile-cinchona alkaloid copolymers⁵, acrylic ester polymers⁶ have been used as either crosslinked or linear catalysts in different types of reactions. Other catalysts have been obtained by anchoring chiral molecules as alkaloids⁷, tertiary amines⁸, 3-hydroxyhydantoins⁹ to polystyrene. Asymmetric reduction has been shown to occur as well with polymeric amine-borane derivatives¹⁰ as with polystyrene-supported 1,4-dihydrinicotinamides¹¹, alcohol- AlLiH_4 ^{2,12} and prolinol-borane complexes¹³.

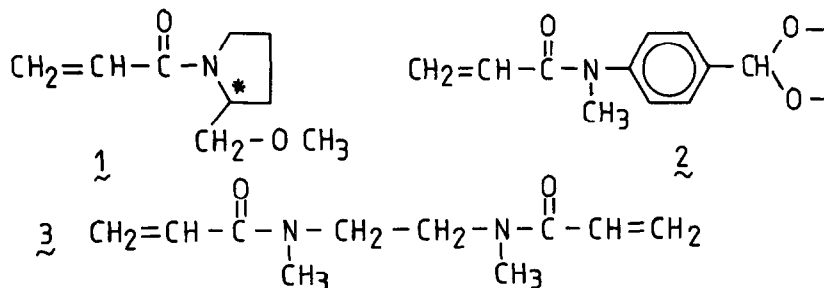
Asymmetric catalytic hydrogenations were also induced by polystyrene-supported optically active rhodium complexes¹⁴. Stille et al.¹⁵ have designed crosslinked polymeric chiral phosphines as rhodium ligands, allowing the enantiospecific reduction of dehydro-aminoacids. Polystyrene-supported chiral phosphine-nickel catalysts have been used in the asymmetric formation of single C-C bonds¹⁶.

Another possibility is outlined by the attempt to perform Meyers' synthesis of α -dialkylated acetic acids with optically active 2-oxazolines covalently bound to the polystyrene support^{17,18}. In the last type of polymer-assisted asymmetric synthesis, the prochiral substrate is covalently and reversibly linked to a polymer arm containing the chirality center¹⁹⁻²².

We have tried a totally different approach by using as unique chiral auxiliary a polyacrylic crosslinked polymer with pendant chirality. By shortening the arm length between the prochiral molecule and the support, we expected that such factors as proximity affects and steric crowding by the polymeric backbone, possible complexation with the chiral matrix, reduced mobility of the polymer-bound substrate would favourably affect the enantiospecificity.

To test the validity of this methodology, we have considered the asymmetric synthesis of aminoacids by alkylation of chiral Schiff's bases, which has been studied in solution by our group²³.

After some preliminary work, we obtained a convenient polyacrylic crosslinked resin of the type we have already developed²⁴ by radical copolymerisation of three monomers : (L)-1-acryloyl 2-methoxymethylpyrrolidine 1 as chiral matrix ; N-methyl N-acryloyl p-amino-benzaldehyde ethylene ketal 2 as functionalization reagent ; N,N'-dimethylethylenebisacrylamide 3 as crosslinking agent²⁵. Compound 1 (oil, $(\alpha)_D = -62^\circ$, C=1 benzene) was synthesized with an almost quantitative yield from L-prolinol. The (L)-2-methoxymethylpyrrolidine intermediate, already described by Seebach et al²⁶, was isolated with a three-fold increased yield by using the t-butyloxycarbonyl group as temporary protection in place of the formyl group and diazomethane in presence of $\text{BF}_3\text{-Et}_2\text{O}$ as alkylating agent. Compound 2 (oil ; NMR (CDCl_3) : 3.4 ppm (CH_3), 4.1 ppm (2 CH_2), 5.4-7.7 ppm (7H)) was isolated with a 90 % overall yield from p-methylamino benzaldehyde.²⁷



Radical copolymerisation of 1 (88.8 mmoles), 2 (33.3 mmoles) and 3 (12.8 mmoles) in 100 ml of buffered water (pH 7.5) was initiated with ammonium persulfate²⁴. After 1h stirring at room temperature, the polymer was filtered and washed with water. Hydrolysis of the ketal groups by digesting 6h at 20°C with 5% H_2SO_4 was followed by filtration, successive washings with water, alcohol, anhydrous ether, drying under vacuum at 20°C in presence of P_2O_5 , to give finally 20g of 9% crosslinked polymer 4, with a loading of 1.1 meq CHO/g as measured by Bryant and Smith's method²⁸. As shown in Fig.1 the idealized structure of this polymer is characterized by alternative chiral and functionalized pendants.

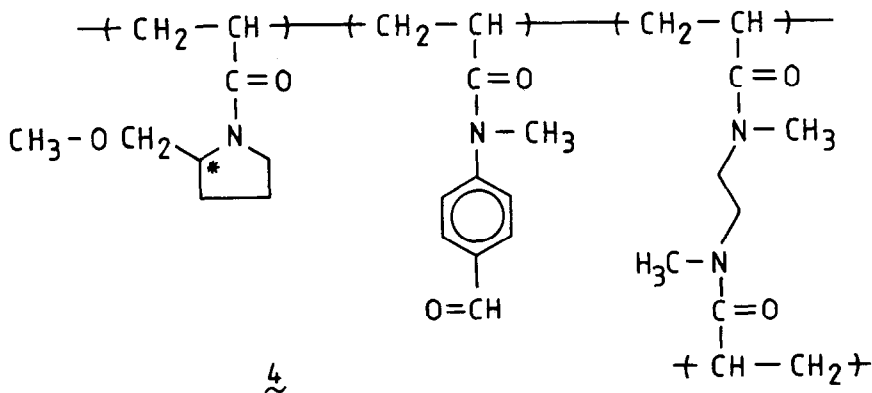
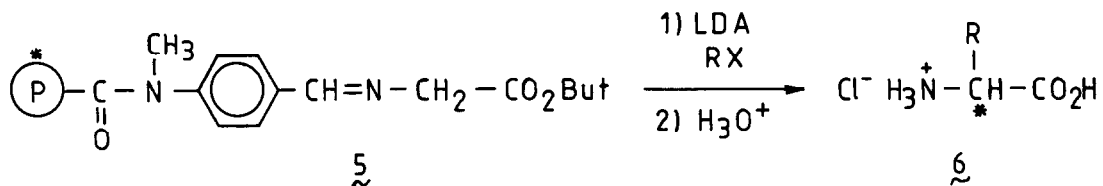


Fig. 1

Copolymer 4 (7g) and t-butyl glycinate (3g, 23 meq) in 100 ml of anhydrous benzene were heated under reflux during 2h in the presence of $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$, the water being removed by means of a Dean-Stark trap, to afford Schiff's base 5. To a slurry of 5 in anhydrous THF was added at -78°C 8 meq of LDA, then after 2h 8 meq of alkyl halide. After 2h stirring at -78°C and hydrolysis 4h at room temperature with 100 ml of 1N HCl, the regenerated polymer 4 was filtered and washed; filtrate and washings were concentrated under vacuum to give pure (S)-aminoacid hydrochlorides 6 after one crystallisation in methanol.



Chemical yields and enantioselectivities (table I) are only moderate, and work is now in progress to improve these values. Nevertheless these preliminary results demonstrate the practicability of this new approach. Moreover some specific advantages can be claimed. Copolymer 4 used as chiral auxiliary is easily synthesized and can be reused after recovery without any perceivable lowering of the enantioselectivity. There is no need to prevent secondary reactions as in the case of Merrifield's resin, with which it is often necessary to reduce remaining unaltered chloromethyl groups before completion of the synthetic pathway¹⁹. Finally by merely modifying the terminal function of monomer 2, it is hoped to show that our new methodology can also be applied to the synthesis of other chiral precursors.

Table I

RX	<u>6</u>	yield %	ee% [*]
ICH_3	Alanine	58	61
$\text{ICH}(\text{CH}_3)_2$	Valine	62	63
$\text{BrCH}_2\text{-C}_6\text{H}_5$	Phenylalanine	53	57

* determined by optical rotations

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