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A New Polymer-Anchored Chiral Catalyst for Asymmetric Michael Addition Reactions[†]

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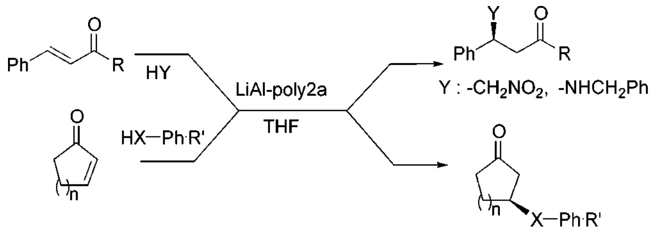
ABSTRACT



Monomer (*R*,*R*)-3-aza-3-(*p*-vinylbenzyl)-1,5-diphenyl-1,5-dihydroxypentane (2) when polymerized with styrene and divinylbenzene affords polymers, onto which lithium and aluminum are incorporated via reaction with lithium aluminum hydride. The resulting insoluble polymers containing chiral lithium and aluminum active centers are quite effective for asymmetric Michael addition of nitro compounds, thiols, and amines. The optimized reaction conditions yield Michael adducts in good yield with high enantiomeric excesses.

Asymmetric Michael addition reactions using chiral Lewis base catalysts have been the subject of intensive research in recent years[1] A practical difficulty in performing conventional homogeneous catalytic reactions lies in separating the product from the catalyst. Also, the possibility of oligomerization of the catalyst that may be unavoidable in some cases could mean lower activity and a decrease in the enantiomeric excess (ee). Such aggregations can, however, be restricted by supporting the catalyst onto a polymer backbone.[2]

Chiral polymers have been used in the chromatographic separation of enantiomers,[3] as chiral auxiliaries in phase-transfer catalysis,[4] or as chiral polymer catalysts in hydrogenation,[5] hydroformylation,[6] alkylation,[7] hydrosilation,[8] epoxidation,[9] dihydroxylation,[10] and Diels−Alder[11] reactions. The advantages of this method are the ease of purification of the reaction mixture and reusability of the catalyst, and as these polymers have bulkier groups, they may provide a respectively small space for the reactions, enhancing stereoselectivity. The last point might bring out some general resemblance to the reactive sites such as those found in enzymes.[12]

We have shown earlier that the heterobimetallic catalyst based on a chiral C_2-symmetric (*R*,*R*)-3-aza-3-benzyl-1,5-

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[†] Dedicated to Professor Ronald Sauers on the occasion of his 65th birthday.

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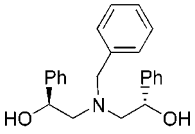
dihydroxy-1,5-diphenylpentane (**1**) is capable of inducing asymmetry in Michael addition reaction of malonates and thiophenols with cyclic and acyclic enones.[13]



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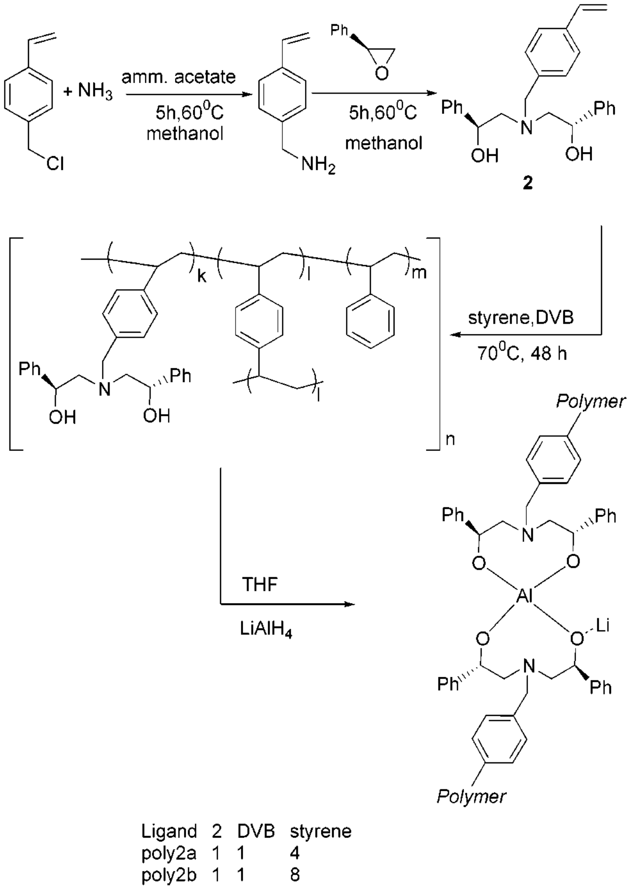
In view of the above-mentioned reports on the positive aspects of polymer anchored chiral catalysts, we decided to synthesize and evaluate the efficiency of the polymer chiral ligand incorporating the crucial C_2-symmetric aminodiol **1** onto a macromolecular backbone. The results obtained are detailed in this letter.

Accordingly, ligand **2** carrying a polymerizable vinyl tether, was synthesized by refluxing *p*-vinylbenzylamine with 2 equiv of *R*-(+)-styrene epoxide in 30% yield[14] with a high coproduction of dimer and other oligomers. The chiral polymers (**poly2a** and **poly2b**) were synthesized[15] by free radical copolymerization of the corresponding chiral monomer with *p*-divinylbenzene and styrene as cross-linking reagent and comonomer in ratio of 1:1:4.[16] (Scheme 1). The TGA of the resulting polymer indicated the start of the weight loss at 175 °C and reaching a maximum weight loss at 447 °C. DSC measurements suggested the glass transition temperature (T_g) of the polymer to be 175 °C.

Scheme 1. Synthesis of Polymer Chiral Ligand



Changes in the chemical and structural properties of the polymer are sure to affect the efficiency of the polymer-anchored catalysts wherein the catalytic activity may depend on the degree of immobilization.[2,17] With this objective we changed the relative ratios of the monomer **2**, divinylbenzene, and styrene to 1:1:8 and obtained **poly2b**. Both these polymers were used for anchoring the metal centers for promoting asymmetric Michael addition reactions.

The polymeric chiral catalyst **LiAl-poly2A** was prepared by the reaction of excess polymer chiral ligand **poly2A** with $LiAlH_4$ in THF under an inert atmosphere. The amount of hydrogen gas evolved was measured and found to be in agreement with the value calculated for a complete reaction of the hydride. The inductively coupled plasma (icp) analysis of the product showed the presence of lithium and aluminum in the polymer chiral catalyst with expected amounts for a complete incorporation of the metals. Scanning electron microscopy (SEM) was used to observe qualitatively and

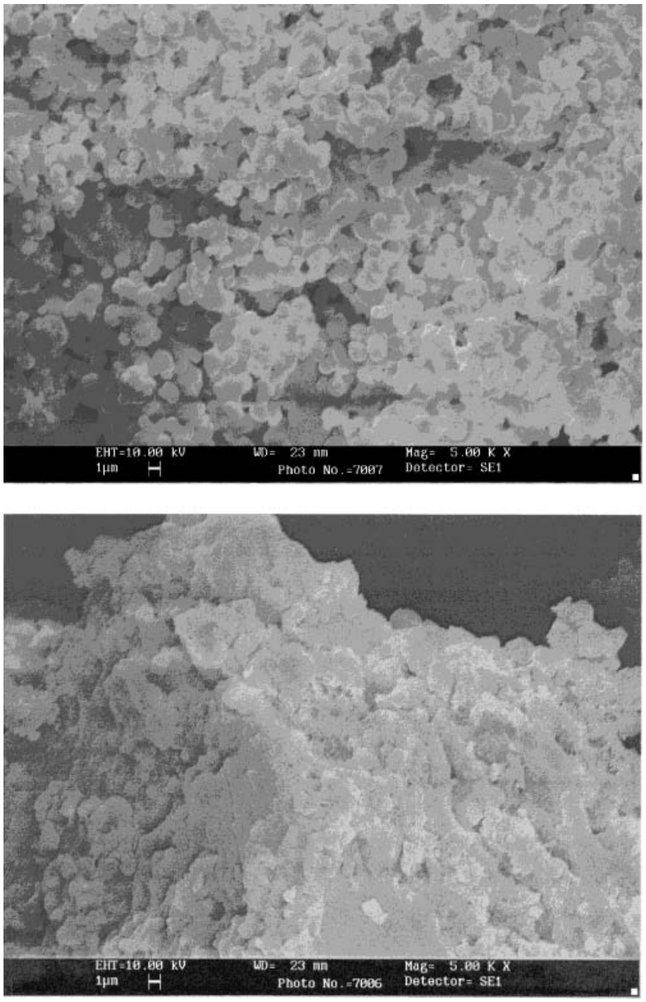
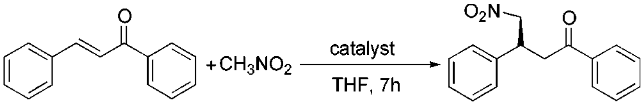


Figure 1. SEM microphotographs of the surface structure of polymer chiral ligand **poly2a** (top) and that of the polymer chiral catalyst **LiAl-poly2a** (bottom).

pictorially the changes in the specific morphologies of **poly2A** as such and on the **LiAl-poly2A**. In **poly2A** a well-developed system of microspheres are seen (Figure 1, top photograph) forming large fused aggregates of microgel particles.[18] The large pore sizes seen in these polymers may facilitate the penetration of the reactants into the polymer matrix. By SEM we also observed the changing morphology of **LiAl-poly2A** where the microspheres get hidden indicative of the agglomeration of microspheres with aluminum and lithium metals (Figure 1, bottom photograph). On the basis of our earlier studies on the structure of the heterobimetallic catalyst[13] LiAl-**1**, we suggest that the polymer chains entangle to attain a similar structure (Scheme 1)

Both **poly2a** and **poly2b** were used for promoting asymmetric Michael addition reactions of nitromethane to the chalcone (Table 1). The very reaction catalyzed by chiral alkaloids was done earlier under high pressure and for a longer time.[19] But here the reaction could be completed at atmospheric pressure and for lesser reaction time of 6 h. Moreover, the purification process is simple which is just a quick filtration of the reaction mixture separating the catalyst from the organics.[20]

Table 1. Michael Addition of Nitromethane with Chalcone Using Different Ligands



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catalyst : Li, Al, and ligand*

ligand*	% of amino diol in catalyst[a]	yield (%)	ee (%)
1	100	92	5.3
Poly2a	41	90	51
Poly2b	28	90	11.5

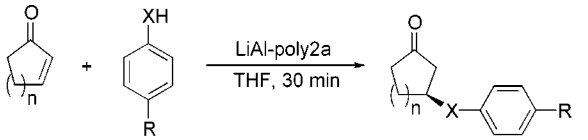
[a] In all cases the ratio, [Al]/[Michael acceptor] was kept at 0.5.

On using the amino diol **1** as ligand, we could obtain just 5.3% ee of the Michael adduct, whereas on using **poly2A** as the ligand the ee of the product rose to 51%. But with **poly2b**, where the chain length space was increased by higher styrene incorporation, the ee of the product fell to 11.5% (Table 1).

From this we may infer that the polymer chiral catalyst **LiAl-poly2a** is more stereospecific compared to **1**, and the drop in the specificity is dramatic on increasing the chain length with varying amount of styrene. We can explain the significantly enhanced enantioselectivity for **poly2a**-promoted Michael addition as follows. The entangling of polymer chains to reach the suggested composition of heterobimetallic would concomitantly impose high steric restriction for the reactants, and this might be responsible for the observed high asymmetric induction. For **poly2b**, however, as the chain length space was higher, the formation of such heterobimetallic may be incomplete resulting in lower ee.

In an earlier report we had noted that the Michael addition of thiols to enones gets completed in seconds and that the stereospecificity is optimum.[13] We attempted the same reaction with **LiAl-poly2A** catalyst and found that here the reactions were comparatively slow, 30 min, but the ee's were slightly higher (Table 2).

Table 2. Michael Addition of Thiols to Cycloalkenones



no.	n	R	X	yield (%)	ee %[a]	ee%[b]
4	1	H	S	95	41	32
5	2	H	S	90	57	45
6	1	CH_3	S	90	52	26
7	2	CH_3	S	90	33	40
8	1	H	CH_2S	85	52[c]	-
9	2	H	CH_2S	90	76[c]	-

[a] On using **LiAl-poly2a**. [b] On using amino diol **1**. [c] By HPLC chiralcel-OD column.

Cyclopentenone and cyclohexenone were also used as Michael acceptors, and the Michael donors were thiophenol, *p*-methylthiophenol, and benzyl mercaptan. The yields and the ee's are in general high when compared with other methods.

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(14) To a cooled solution of vinyl benzylamine (5 mmol) in 2 mL of methanol was added (*R*)-(+)-styrene epoxide (10 mmol) in 4 mL of methanol at 0 °C and stirred for 1 h. It was then refluxed for 4 h. After completion of the reaction, the solvent was then removed under reduced pressure to give a syrupy mass which upon column chromatography (alumina) using ethyl acetate:hexane (10:90) as eluent gave the product (yield 30%).

(15) To 1 mol of (*R*,*R*)-3-aza-3-(*p*-vinylbenzyl)-1,5-diphenyl-1,5-dihydroxypentane were added 1 mol of divinylbenzene and 4 mol of styrene in the presence of 10 mg of benzoyl peroxide, and it was sealed in a nitrogen atmosphere. Then the reaction mixture was heated at 70 °C for 48 h.

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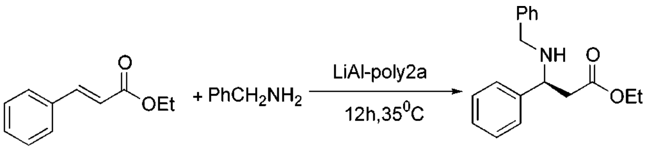
(20) General procedure for the Michael addition reaction: To the polymer chiral ligand (250 mg) in THF was added slowly a solution of $LiAlH_4$ (10 mg, 0.268 mmol) in dry THF, drop by drop at 0 °C. The mixture was stirred for 30 min, the mixture was warmed to room temperature, and the Michael acceptor and donor were added subsequently. After the reaction was over, it was quenched with 1 N HCl and mixture extracted with ethyl acetate. The organic layer was washed successively with saturated $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a syrupy mass, which upon flash column chromatography gave the product.

Asymmetric Michael addition of benzylamine to α,β-unsaturated ester group has also been studied recently.[21] Here we also report asymmetric Michael addition of benzylamine with ethyl cinnamate using **LiAl-poly2A** catalyst (Table 3).

Table 3. Michael Addition of Benzylamine to Ethyl Cinnamate



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serial no.	complex	yield (%)	ee %
1	**LiAl-poly2a**	60	80.9
2	**LiAl-poly2a**+ $Nd(O^iPr)_3$	75	81.6
3	**LiAl-poly2a** + $Nd(O^iPr)_3$ + mol sieves	75	81.6

On using the aminodiol **1** as the chiral ligand, we obtained 60% ee for this reaction. With **LiAl-poly2A** as the chiral ligand, the ee was found to be higher at 80%. Shibasaki has noted that the ee's of a chiral Mannich reaction promoted by lithium−aluminum heterobimetallic get enhanced when equimolar amounts of rare earth alkoxides or molecular sieves are added.[22] We found that here addition of neodymium isopropoxide resulted in some increase in the yield, and there was no change in the ee. Similarly with the addition of molecular sieves we found no perceptible change in the ee (Table 3).

In all these reactions the recovered polymer can be reactivated by addition of lithium aluminum hydride and used for same asymmetric addition reactions, but we have found some decrease in the ee.[23] Another disadvantage in using the polymer chiral catalyst is that while stirring, the beads get broken into powders and this makes it difficult to recycle. In general, the polymer chiral catalyst would require careful handling.

To conclude, we have developed a novel polymer chiral ligand **poly2** and polymer-anchored chiral catalyst **LiAl-poly2A** and used it as a promoter for Michael addition reaction of nitromethane to chalcone with good yield and high enantioselectivity. Addition of thiophenols to unsaturated cycloalkenones also shows acceleration in the presence of this catalyst, resulting in greater yield and moderate enantioselectivity. Optical yields varied depending on the styrene content in copolymers. The purification involes simple filtration, and the polymer chiral ligand can be reused by washing with 1 N hydrochloric acid.

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Supporting Information Available: Experimental details and characterization of all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.

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[23] The polymer chiral ligand when reused two times for this reaction changed ee from 80% to 60% to 58%. But in a separate experiment, the unquenched catalyst, filtered from the reaction mixture, was found to be ineffective with a lower yield (40%) and lower ee (4%) for the Michael adduct. We suggest that this could be due to the leaching out of Li^+ as the enolate, thus reducing the number of active chiral catalyst centers.