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New polymer anchored chiral amino oxazolines as effective catalysts for enantioselective addition of diethylzinc to aldehydes

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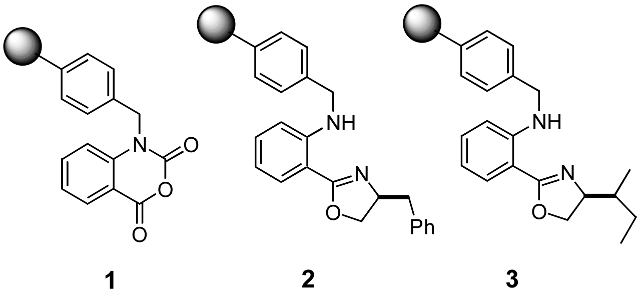
Abstract—The application of a new type of polymer anchored chiral amino-oxazolinyl ligand as catalyst for the enantioselective addition of diethylzinc to aldehydes is reported. The catalyst is effective at a low ligand concentration and can be reused with minimal loss of activity. © 2002 Published by Elsevier Science Ltd.

Several chiral ligands have proven extremely successful in catalytic enantioselective nucleophilic addition of dialkylzinc to aldehydes,[1] probably the most widely studied asymmetric carbon–carbon bond forming reaction. Since the pioneering work of Noyori[2,3] using (−)-3-*exo*-dimethylaminoisoborneol for highly enantioselective catalytic addition of dimethylzinc to benzaldehyde, a large number of different types of chiral amino alcohols have been prepared and utilized as catalysts for this reaction. In comparison a very few successful examples of diamine catalysts[1c,4] have been reported for this conversion. Optically active catalysts with an oxazoline moiety have a unique place in the rapidly growing field of enantioselective conversions mainly due to their simple preparation from natural amino acids and suitable structural features. Ferrocene-based oxazolines[5] as well as other oxazolinyl catalysts[6] have been found to be effective in catalyzing the asymmetric addition of diethylzinc and diarylzinc[5d] to various aldehydes.



Scheme 1.

The strategy of attaching a chiral ligand onto a polymer has been widely used to prepare heterogeneous, immobilized catalysts for enantioselective conversions.[7] This approach is advantageous compared to the classical homogeneous version due to: (1) the ease of separation of the expensive chiral catalyst from the reaction system, and hence the possibility of reutilizing the catalyst for successive reactions, (2) convenient operation in flow reactors or flow membrane reactors for continuous production and (3) for the development of environmentally safe processes for the production of fine chemicals. Reports of several polymer-supported chiral ligands have been documented[1c,8] for the specific reaction of the catalytic asymmetric addition of dialkylzinc to aldehydes.

The chelation of diethylzinc with ligands is crucial in increasing its nucleophilicity and, hence, its reactivity towards aldehydes. The chiral environment of the ligand is responsible for determining the stereochemical outcome of the addition reaction. A few chiral hydroxy-oxazolines have been used as ligands in this reaction but we believe that amino-oxazolines could be better chelates due to the higher nucleophilicity of the amino group compared to alcohols. This enhanced chelating ability may help to overcome the problem of low reactivity of heterogeneous polymer-supported chiral ligands. With this concept, we have prepared a new type of polymer-anchored oxazoline and wish to present our results of screening as catalysts in the addition of diethylzinc to aldehydes.

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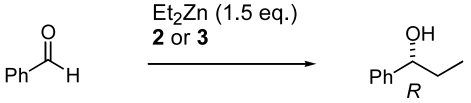
The polymer supported isatoic anhydride **1** was exposed to the chiral amino alcohol in the presence of acidic clay to furnish the polymer anchored amino-oxazolines.[9] We have prepared two catalysts, **2** with (*S*)-(−)-2-amino-3-phenyl-1-propanol, and **3** with (*S*)-(+)-isoleucinol as the amino alcohol (Scheme 1). Preparation of the polymeric ligands was monitored by IR spectroscopy and they were characterized by elemental analysis.[9]

The catalytic activity of these polymer-supported amino-oxazolines was first studied using the standard reaction of diethylzinc with benzaldehyde. It is important to note that we were able to alkylate successfully the aldehyde without any additives, such as a Lewis acid. The bead shaped heterogeneous catalyst was easily separated and the secondary alcohol was isolated in satisfactory yield. This reaction was tested in a toluene–dichloromethane mixture at different temperatures and results are summarized in Table 1. The catalyst **3** was marginally more selective than **2**, while a mixture of 20 % dichloromethane in toluene at 0°C was found to be the optimum reaction conditions. The presence of dichloromethane helps the swelling of polymer which is essential for the satisfactory accessibility of the ligand by the substrate.[8b]



The catalytic activity of our new polymer anchored amino alcohols in successive reactions was investigated by performing the three cycles of addition of diethylzinc to benzaldehyde. It can be seen from the results in Table 2 that the catalyst **3** survives the reaction conditions, work-up procedure and retains its activity.

Having established the catalytic reaction conditions, a number of different aldehydes were subjected to the standard reaction using **3** as catalyst and the results are presented in Table 3. We observed high chemical conversion and moderate to high enantioselectivity for a range of substrates demonstrating the generality of these amino-oxazolines as catalysts.

The addition of diethylzinc to some aromatic aldehydes was effectively catalyzed by **3** with moderate to high enantioselectivity. The secondary alcohols were obtained with the *R* configuration at the newly formed chiral center. It is worthwhile to note that other types of aldehyde such as allylic and aliphatic aldehydes were also successfully alkylated using **3** as the catalyst, see, for example, *trans*-cinnamaldehyde (entry 4, Table 3) and nonyl aldehyde (entry 8, Table 3), which gave products in moderate yield and enantioselectivity.

Thus, we have presented some applications of a new type of polymer-supported chiral amino oxazoline for catalytic asymmetric addition of diethylzinc to aromatic aldehydes, which also works well with aliphatic and allylic aldehydes. The catalyst is easy to prepare, quite effective at very low ligand concentration and with a wide range of aldehydes. The catalyst can be effectively recycled for a successive set of reactions, which is a prerequisite for this type of heterogeneous asymmetric catalysis to be useful.

Experimental

A suspension of polymer **3** (110 mg; 0.175 mmol/g) in a mixture of dry toluene (12 mL) and dichloromethane (3 mL) was stirred slowly at ambient temperature for 4 h to allow the polymer to swell. This mixture was cooled to 0°C and diethylzinc (15 mL of a 1 M solution in hexane, 15 mmol) was added slowly over 15 min. This was followed by the addition of benzaldehyde (1.06 g, 10.0 mmol) and the mixture was stirred for 24 h at 0°C. The reaction mixture was quenched with water and the resin was removed by filtration. The resin was washed with dichloromethane (3×10 mL) while the aqueous

Table 2. The enantioselective addition of diethylzinc to benzaldehyde using recycled polymer-supported catalyst **3**

Cycle	Isolated yield (%)	% ee[a]
1	90	89
2	86	84
3	87	85

[a] The reactions were performed with conditions similar to entry 6, Table 1. The optical purity was determined by HPLC analysis using a *R*,*R*-Whelk-O column.

Table 1. The enantioselective addition of diethylzinc to benzaldehyde employing catalyst **2** or **3**

Entry	Ligand	Solvent [temp. in °C]	Isolated yield (%)	% ee (config.)[a]
1	**2**	Toluene–Hexane (1:1) [−78]	46	21 (*R*)
2	**3**	Toluene–Hexane (1:1) [−78]	52	36 (*R*)
3	**2**	Toluene–Hexane (1:1) [−10]	60	34 (*R*)
4	**3**	Toluene–Hexane (1:1) [0]	72	38 (*R*)
5	**2**	20% CH_2Cl_2 in Toluene [0]	80	84 (*R*)
6	**3**	20% CH_2Cl_2 in Toluene [0]	90	89 (*R*)
7	**2**	20% CH_2Cl_2 in Toluene [30]	74	24 (*R*)
8	**3**	20% CH_2Cl_2 in Toluene [30]	75	50 (*R*)
9	**3**	Toluene [0]	81	84 (*R*)

[a] The optical purity and configuration was determined by comparison of the specific rotation with reported values and HPLC analysis using a Chiralcel OD or an *R*,*R*-Whelk-O column.

Table 3. Enantioselective addition of diethylzinc to aromatic aldehydes using polymer supported catalyst **3**

Entry	Aldehyde	Isolated yield (%)	% ee[a] (config.)[b]
1	*p*-Chlorobenzaldehyde	92	83 (*R*)[10a]
2	*p*-Methoxybenzaldehyde	86	68 (*R*)[10a]
3	*o*-Methoxybenzaldehyde	70	43 (*R*)[10b]
4	*trans*-Cinnamaldehyde	75	53 (*R*)[10c]
5	*p*-*N*,*N*-Dimethylaminobenzaldehyde	87	76 (*R*)[10d]
6	9-Anthraldehyde	90	84 (*R*)[10e]
7	3,4,5-Trimethoxybenzaldehyde	86	90 (*R*)[10e]
8	Nonyl aldehyde	68	52 (*R*)[10f]

[a] The optical purity determined by comparison of specific rotation with reported values.

[b] Literature reference for optical rotation.

layer was extracted with the same solvent (3×25 mL). The combined organic layer was dried over anhydrous sodium sulphate, concentrated and the products were purified by column chromatography. The isolated alcohols were characterized by the usual spectroscopic analysis while the optical purity was determined by chiral phase HPLC analysis and specific rotation. The recovered catalyst was washed with different solvents (THF, methanol, acetone, and dichloromethane), dried and recycled for successive reactions with very little loss of activity (see Table 2).

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