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Effect of spacers on the activity of soluble polymer supported catalysts for the asymmetric addition of diethylzinc to aldehydes

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Abstract—A chiral Zn(II)–salen complex tethered with poly(ethylene glycol) (PEG) was synthesized. This *soluble* polymer-supported complex was found to catalyze the asymmetric addition of diethylzinc to a series of aromatic aldehydes in good yields and with good enantiomeric ratio (*er*). The PEG-supported catalyst could be recycled and reused up to three times. The reactivity and selectivity of the catalyst was dependent on the nature of the linker between the polymer and the complex.

In recent years, there have been intense efforts to develop methods to recover and reuse homogenous catalysts.[1] Amongst these methods, the use of low molecular weight soluble linear polymers or dendrimers as supports is attractive since the supported catalysts are in the same phase as the reactants.[2] The supported catalysts can be recovered by addition of a poor solvent, biphasic separation techniques or membrane filtration. In general, the reactivity and the selectivity of the supported catalysts tend to be lower than their unsupported analogs. This is often attributed to the inaccessibility of the catalytic sites to the substrates. In order to increase the accessibility of the catalytic sites, a spacer is often placed between the soluble polymer and the catalyst.[2e,3] The spacer units are mostly chosen to suit the chemistry of the end group on the polymer. We now show that these spacer units are not innocuous and that they do affect the reactivity and selectivity of the catalysts.

As a part of our research efforts to develop recyclable catalysts for important asymmetric reactions, we were interested in developing a soluble polymer supported catalysts for the enantioselective addition of dialkylzinc reagents to aldehydes. It is one of the most intensively studied asymmetric organic transformations and is an important synthetic route to chiral secondary alcohols, which are precursors to many functional organic molecules.[4] Despite the importance of this asymmetric transformation, there have been a few reported examples for the asymmetric addition of diethylzinc (Et_2Zn) to aldehydes employing soluble polymer-supported catalysts. In 1995, Wandrey and co-workers supported α,α-diphenyl-L-prolinol on a soluble co-polymer derived from 2-hydroxyethyl methacrylate and octadecyl methacrylate.[5] However, in order to achieve good selectivities, excess Et_2Zn was required. In 1999, Hodge and co-workers attached ephedrine and camphor derivatives as pendant groups on soluble linear polystyrene (LPS).[6] The selectivity of these catalysts were found to be largely dependent on the catalyst loading on the polymer and the degree of cross-linking. In 2001, Sasai explored the use of a soluble LPS-supported Ti-BINOLate complex for the asymmetric reaction of Et_2Zn with benzaldehyde.[7] However, upon recycling, the catalyst became insoluble and was unable to promote the reaction a second time. More recently Bolm and co-workers used ring-opening metathesis polymerization of *endo*-norbonene to synthesize a series of linear polymers with chiral prolinol and achiral lipophilic side chains.[8] The ratio between the chiral and achiral units along the polymer backbone was decisive for their catalytic activity.

Following the success in the early 1990s of the Jacobsen–Katsuki asymmetric epoxidation of olefins using chiral salen-type manganese(III) catalysts, there has been a growing interest in the application of these ligands as scaffolds for asymmetric catalysts.[9] In 1996, Cozzi and co-workers showed that a chiral salen ligand was capable of promoting the enantioselective addition of Et_2Zn to aldehydes.[10] Motivated by the importance of salen complexes in asymmetric catalysts,[11] we focused on developing a soluble polymer supported

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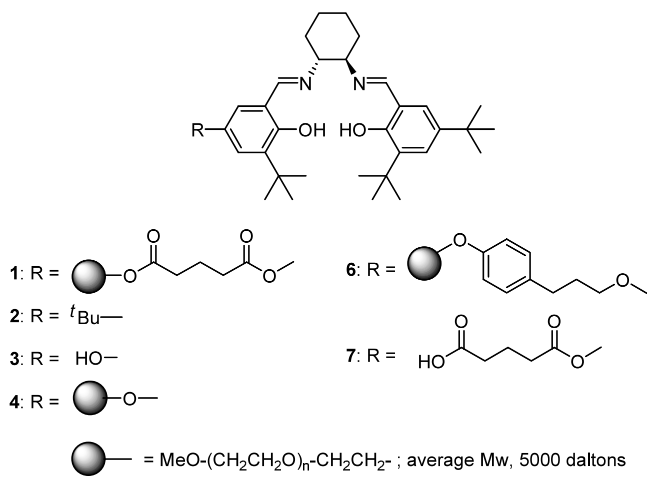
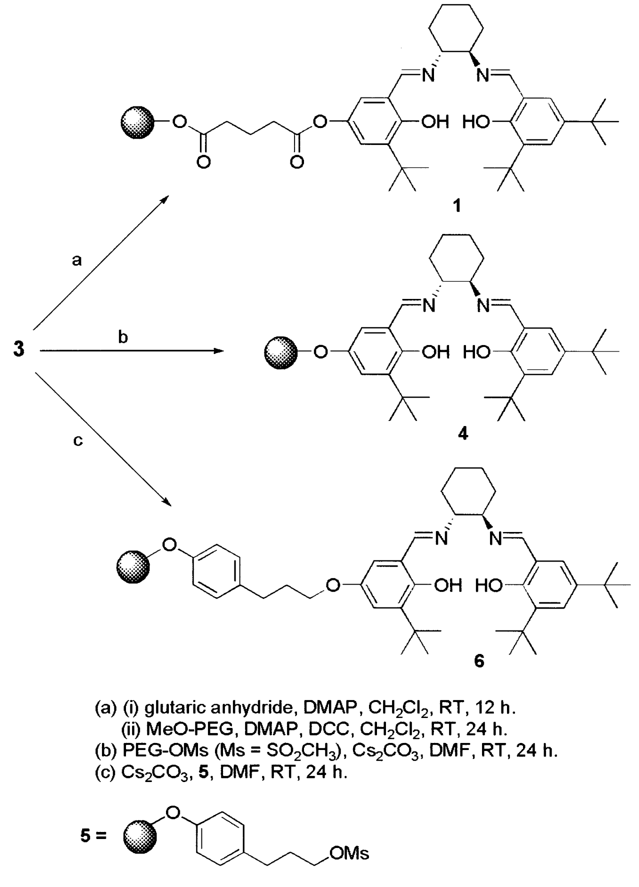
salen complex for the asymmetric addition of Et$_2$Zn to a series of aromatic aldehydes.



There are two main architectures for the attachment of a catalyst on linear polymers: as pendant groups and at the termini of the polymer chains. The later has been generally shown to yield more active polymeric catalysts with well-defined catalytic sites.[2d] With this in mind, we chose to attach a chiral salen ligand as an end group on monomethoxy-PEG (MeO-PEG). The unsymmetrical salen ligand **3** was synthesized in 55% yield following a previously reported procedure.[12] Reacting the unsymmetrical salen **3** with PEG mesylate[2b] in the presence of Cs$_2$CO$_3$ (3 equiv.) in DMF at rt for 24 h gave the PEG-supported salen **4** in 96% yield (Scheme 1). In order to explore the efficacy of the polymer-supported catalyst, 10 mol% of **4** (with respect to benzaldehyde) was treated with an equivalent amount of Et$_2$Zn in toluene and allowed to stir at rt for 1 h. To this solution, 2.3 equivalents of Et$_2$Zn was then added, followed by an equivalent of benzaldehyde. After 18 h the product, 1-phenyl-1-propanol, was obtained in 90% yield and in 66:34 *er*. Under similar reaction conditions, if salen **2** was used as the catalyst, the product was obtained in 93% yield and in 91:9 *er*, after 18 h.

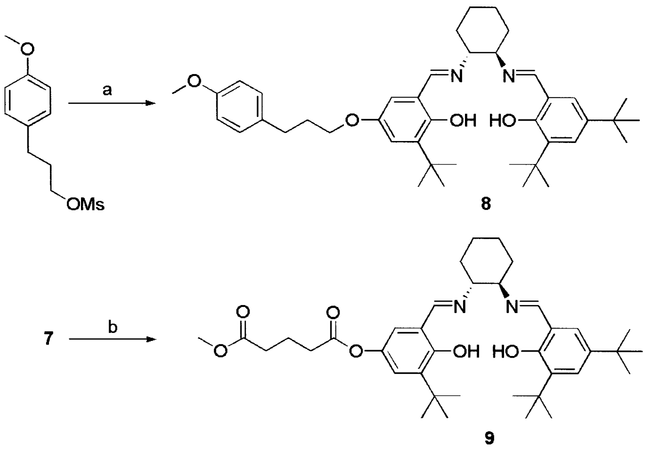


(a) (i) glutaric anhydride, DMAP, CH$_2$Cl$_2$, RT, 12 h.
(ii) MeO-PEG, DMAP, DCC, CH$_2$Cl$_2$, RT, 24 h.
(b) PEG-OMs (Ms = SO$_2$CH$_3$), Cs$_2$CO$_3$, DMF, RT, 24 h.
(c) Cs$_2$CO$_3$, **5**, DMF, RT, 24 h.

Scheme 1.

In order to explain the selectivity and reactivity differences between **4** and **2**, we surmised that the PEG support might be interfering with the active site of the catalyst. Hence, as a control experiment, we carried out the reaction of Et$_2$Zn with benzaldehyde and the catalyst **2**, in the presence of a catalytic amount of MeO-PEG. The product was obtained in 88% yield and in 91:9 *er*, after 18 h, indicating that the PEG as an additive had no adverse effect on the reactivity or selectivity of the catalyst. This led us to believe that the PEG support was affecting the microenvironment of the catalyst as a result of the covalent attachment of the polymer directly onto the salen ligand. We then synthesized the PEG-supported salen ligand **1** with a glutarate spacer between the ligand and the polymer using a previously reported literature procedure. This catalyst under aforementioned reaction conditions, furnished the product, 1-phenyl-1-propanol, in 90% yield and in 91:9 *er*, but in 32 h. This result showed while the spacer was effective in improving the selectivity of **1** over that of **4**, there was a decrease in the reactivity. In catalyst **1**, the salen ligand was tethered on the PEG through a glutarate spacer with an electron-withdrawing ester functionality on the C-5 position of the salen. Hence, we felt that introducing a spacer with an electron donating group would improve the reactivity *and* selectivity of the catalyst. We then synthesized the PEG-supported ligand **6** (Scheme 1) where the polymer is attached to the salen ligand through an ether functionality using a phenoxypropyl spacer. Treatment of the mesylate **5** with the salen **3** and Cs$_2$CO$_3$ in DMF at rt for 24 h gave the PEG-supported salen ligand **6** in 93% yield. Reaction of Et$_2$Zn and benzaldehyde with **6** as the catalyst gave the product in 91% yield in 18 h but only in 84:16 *er*. As we had expected, **6** was indeed more reactive than **1**. However, although there was a significant improvement in the selectivity of **6** compared to **4**, it was not as selective as **1**.

Often, the reduced reactivity of a polymer supported catalyst, when compared to its unsupported analog, is attributed to the inaccessibility of the substrate to all the catalytic sites on the polymer. In order to attest the applicability of this generalization to our catalyst system, we synthesized the unsupported analogs of **6** and **1**: catalysts **8** and **9**, respectively (Scheme 2). The synthesis of **8** was achieved in 78% yield by treating **3** with 3-(4-methoxyphenyl)-1-propylmesylate and Cs$_2$CO$_3$ in DMF at rt for 24 h. Catalyst **9** was synthesized by



Scheme 2.

reacting the unsymmetrical salen glutarate acid **7** with methanol in the presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimidehydrochloride (EDCI) and *N*,*N*-dimethylaminopyridine (DMAP). This gave the salen methyl glutarate in 69% yield. Catalyst **8** gave the product 1-phenyl-1-propanol in 94% yield and in 81:19 *er* after 18 h, whereas, catalyst **9** required 32 h to achieve a 91% yield and 91:9 *er*. Based on these results, we concluded that the reactivity and selectivity of **1** and **6** are similar to **8** and **9** (Table 1). Hence, *the difference in reactivity and selectivity clearly arises from the spacer unit and not as a result of the polymer support*. This raises the question as to whether or not the effect of the spacer on the selectivity and reactivity is of purely electronic origin (Table 2).

In 1998, Jacobsen and co-workers reported that there is a correlation between the enantioselectivity of epoxidation of alkenes and the σ_p values of the substituents 5,5′ position of the salen.[13] It was shown that electron donating groups at the 5,5′ positions increases the enantioselectivity of the epoxidation. However, in the only other reported example of a PEG-supported salen complex it was shown by Janda and co-workers in 2000, that the PEG supported Mn(III)-salen complex with glutarate spacer ($\sigma_p = 0.3$)[14] was as selective as the unsupported salen–Mn(III) complex with *tert*-butyl at the 5,5′ positions ($\sigma_p = -0.20$).[2e] If the effect of the glutarate spacer was purely electronic, then based on Jacobsen's correlation, the enantioselectivity of the epoxidation should have been considerably lower. Hence, based on the aforementioned studies and our observations, we conclude the effect of the spacer on reactivity and the selectivity of the catalyst cannot be correlated to the electronic effects in the unsupported catalyst.

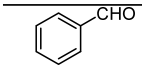
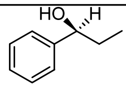
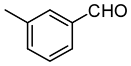
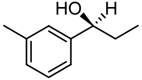
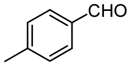
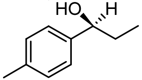
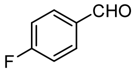
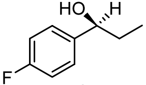
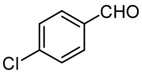
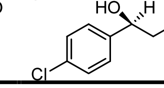
Table 1. Enantiomeric ratios of the secondary alcohol obtained by the addition of diethylzinc to benzaldehyde using PEG-supported catalysts

Catalyst	Time (h)	Conv. (%)[a]	*er*[b]
1	32	90	91:9
2	18	93	91:9
4	18	90	66:34
6	18	91	84:16
8	18	94	81:19
9	32	91	91:9

[a] Reactions were performed with benzaldehyde using 10 mol% catalysts and 2.3 equiv. of Et_2Zn.

[b] Determined by GC using Cyclosil-B column.

Table 2. Enantiomeric ratios and yields of secondary alcohol obtained by the addition of diethylzinc to aromatic aldehydes using catalyst **1**

Aldhehyde	Product	Isolated yield (%)	*er*
		90	91:9
		82	84:16
		87	76:24
		88	87:13
		75	88:12

[a] All reactions were carried out under nitrogen using 2.3 eq. of Et_2Zn.

[b] Determined by GC using Cyclosil-B column.

Since **1** provided the highest selectivity, it was used in the addition of Et_2Zn to a series of aromatic aldehydes to obtain the respective chiral secondary alcohols in good isolated yields (75–90%) and enantiomeric ratios (76:24–91:9).[†] In the absence of the catalyst, the addition of Et_2Zn to benzaldehyde gave marginal conversion to the product, 5%, even after 48 h. For the reaction of Et_2Zn with benzaldehyde, catalyst **1** was

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[†] **General procedure for the addition of diethylzinc to aldehydes**. The polymer-supported salen (0.1 mmol) was placed into a dry glass reaction tube, fitted with a magnetic stir bar and a rubber septum. The reaction tube was successively evacuated and then purged with nitrogen. The salen was then dissolved in dry toluene (3 mL) and Et_2Zn (0.1 mL, 1 M solution in hexanes, 0.1 mmol) was added dropwise. The yellow homogenous mixture was allowed to stir at rt for 1 h to form the (salen)Zn complex in situ. Next, Et_2Zn (2.3 mL, 1 M solution in hexanes, 2.3 mmol) was added to the reaction mixture and after 5 min, the aldehyde (1 mmol) was added and the reaction mixture at 0°C and then left to warm to rt. To monitor the reaction progress, 0.1 mL aliquots were taken from the reaction mixture, added to ether (0.5 mL), to precipitate the polymeric catalyst, quenched with 1N HCl and the ether layer subjected to GC analysis. Upon completion of the reaction, the mixture was then slowly triturated into cold stirring ether and the precipitate was collected by vacuum filtration, washed in *iso*-propanol and dried in vacuo. The filtrate was concentrated and treated with acetic anhydride (6 equiv.) and allowed to stand for 6 h after which it was washed in water (×1), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (1:4, ethyl acetate/hexanes) to yield the product phenyl acetate as a clear liquid.

recovered quantitatively, at the end of the reaction, by precipitation from diethyl ether. The catalyst was used in a second run to achieve a 91% yield and a 91:9 *er* of the product. This catalyst can be recycled up to three times without any significant loss in selectivity or reactivity.

In summary, we have shown that the reactivity and selectivity of this polymer-supported catalyst is dependent on the nature of the spacer. Using a glutarate spacer, we have synthesized a recylable, soluble polymer-supported salen catalyst that is capable of catalyzing the asymmetric addition of Et_2Zn to various aromatic aldehydes in good yields and enantiomeric ratios.

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