

Communications

Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Polymer-Supported Chiral Amino Thioacetates

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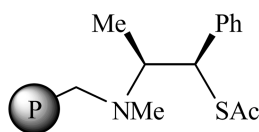
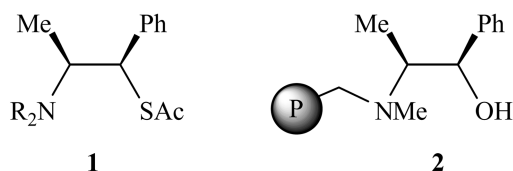
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Enantioselective addition of dialkylzinc to aldehydes in the presence of a catalytic amount of chiral ligands is known to be one of the most important methods for the synthesis of optically active secondary alcohols.¹ Much efforts have been made to search for efficient chiral ligands in the reaction.² Previously we showed the use of chiral amino thioacetate ligands **1** in the enantioselective addition.³ The ligands induced an efficient addition reaction with high ee's. The successful development of homogeneous ligands has been often followed by attempts to attach them onto an insoluble polymeric support.^{4,5} Immobilized ligands provide several advantages such as simplified workup procedures, easy recovery and reuse in successive reactions. In the case of expensive materials, their regeneration is attractive from an economical viewpoint. Our interest in the area led us to

prepare polymer-supported amino thioacetates **3** which may have such unique advantages over the homogeneous counterpart. We now report our preliminary results using them as chiral ligands for the enantioselective addition of diethylzinc to aldehydes.

Frechet and Soai have independently developed polymer-supported ephedrine **2** for the enantioselective addition of diethylzinc to aldehydes.^{5a,5b} According to the established experimental procedure, (1*R*,2*S*)-(-)-ephedrine was attached to 1% crosslinked partially chloromethylated polystyrene (1.0 mequiv/g, 100-200 mesh). The polymer **2** was then subjected to treatment with MsCl and Et₃N in CH₂Cl₂ at 0 °C for 2 h, followed by subsequent treatment with a 3-fold excess of potassium thioacetate in DMF-H₂O (1/1) at 65 °C for 24 h to yield polymer-supported amino thioacetate **3a**. The polymer **3b** was also prepared with 2% crosslinked chloromethylated polystyrene in the same procedure as for **3a**. The conversion of **2** to **3** seemed to be nearly quantitative from weight gain and elemental analysis (0.84 mmol of ligand per gram of polymer). The catalytic behavior of the polymer **3** was then tested in the addition of diethylzinc to aldehyde. The reaction conditions and results are summarized in Table 1. All the aldehydes were converted to the corresponding (*R*)-secondary alcohols with moderate to excellent optical purity in high yields. The amount of **3a** had a small effect on asymmetric induction. Increasing the amount of **3a** from 4 to 8% led to a small increase in the enantioselectivity and 6 mol% of **3a** was enough to give satisfactory enantioselectivity and reactivity. When the reaction was performed with 2% crosslinked polymer **3b**, somewhat low enantioselectivity was observed. The addition



3a: P = 1% crosslinked polystyrene

3b: P = 2% crosslinked polystyrene

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Table 1. Enantioselective Addition of Diethylzinc to Aldehydes

$$\text{RCHO} + \text{Et}_2\text{Zn} \xrightarrow[\text{hexane, RT}]{\text{Ligand}} \begin{array}{c} \text{OH} \\ | \\ \text{R}-\text{C}-\text{Et} \\ | \\ \text{H} \end{array}$$

Entry	R	Ligand	Time (h)	Yield (%) ^a	E.e. (%) ^b
1 ^c	C ₆ H ₅	2 (10%)	48	83	89
2	C ₆ H ₅	3a (4%)	18	80	90
3	C ₆ H ₅	3a (6%)	18	85	91
4 ^d	C ₆ H ₅	3a (6%)	18	82	90
5	C ₆ H ₅	3a (8%)	18	83	91
6	C ₆ H ₅	3b (6%)	24	84	82
7 ^d	C ₆ H ₅	3b (6%)	24	80	80
8 ^c	<i>p</i> -Cl-C ₆ H ₄	2 (10%)	48	78	83
9	<i>p</i> -Cl-C ₆ H ₄	3a (6%)	15	95	91
10 ^d	<i>p</i> -Cl-C ₆ H ₄	3a (6%)	15	92	90
11	<i>p</i> -Cl-C ₆ H ₄	3b (6%)	24	93	90
12 ^c	<i>o</i> -MeO-C ₆ H ₄	2 (10%)	48	79	51
13	<i>o</i> -MeO-C ₆ H ₄	3a (6%)	18	95	80
14	<i>o</i> -MeO-C ₆ H ₄	3b (6%)	18	93	77
15 ^c	<i>p</i> -MeO-C ₆ H ₄	2 (10%)	48	75	54
16	<i>p</i> -MeO-C ₆ H ₄	3a (6%)	24	72	90
17	<i>p</i> -MeO-C ₆ H ₄	3b (6%)	24	76	83
18 ^c	C ₆ H ₁₃	2 (10%)	48	71	21
19	C ₆ H ₁₃	3a (6%)	18	97	60
20	C ₆ H ₁₃	3b (6%)	18	95	56

^aIsolated yield. ^bEntries 1-17: Determined by HPLC analysis (chiralcel OD column). Entries 19-20: Determined by GC analysis (β -DEX 60 m capillary column). Absolute configuration was assigned by elution order from a chiral column. ^cPublished results, see ref. 5b. ^dRecycled polymer **3a** was used.

of diethylzinc to benzaldehyde and *p*-chlorobenzaldehyde in the presence of 6 mol% of **3a** took place with 91% ee's. Other aromatic aldehydes also underwent highly enantioselective additions. For an aliphatic aldehyde, heptanal, moderate enantioselectivity was recorded. It is noteworthy that the polymer-supported amino thioacetates **3** give higher reaction rate and better asymmetric induction than previously reported polymer amino alcohol **2**. The polymers were easily separated by filtration and the recycled polymers were found to be also effective.

A typical procedure for the present catalytic reaction is described as follows: Benzaldehyde (106 mg, 1.0 mmol) was added to a suspension of polymer **3a** (68 mg, 6 mol% based on ephedrine) in hexane (2.4 mL) at 0 °C. Diethylzinc (2

mL, 1.0 M in hexane) was then added dropwise. The mixture was stirred at room temperature for 15-24 h, observing the progress of the reaction by TLC. The reaction was quenched by the addition of dilute aqueous NH₄Cl. The polymer was removed by filtration and washed several times with CH₂Cl₂. The combined extracts were dried over anhydrous MgSO₄ and evaporated under reduced pressure. The residue was purified by column chromatography. The polymer was washed successively with water, MeOH and THF.

In summary, we have shown that polymer-supported chiral amino thioacetates **3** catalyze efficiently the enantioselective addition of diethylzinc to aldehydes. The chiral polymers could be reused without any significant loss in catalytic activity and enantioselectivity. Further studies are in progress to introduce different chiral ligands on polymeric supports.

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