Polymer-Supported β-Amino Thioesters as Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes

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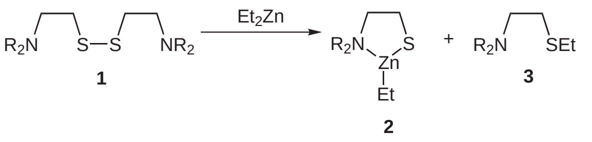
Abstract: A series of novel polymer-supported thioesters were prepared and found to be effective catalysts for the enantioselective addition of diethylzinc to benzaldehyde. These catalysts gave 1-phenylpropanol in up to 86% ee. The catalysts were fully recyclable and could be used in subsequent additions with retention of the enantioselectivity and efficiency levels.

Key words: asymmetric catalysis, ligands, nucleophilic additions, polymers, supported catalysis

The development of catalysts to effect the enantioselective addition of diorganozinc reagents to aldehydes has been a hugely fruitful area of research with many soluble and polymer-supported systems being reported.[2–4] While a great diversity of structural motifs have been described for these enantioselective catalysts, amino alcohols represent one of the largest group of compounds to be reported. However, there is growing interest in the replacement of the alcohol chelation site in amino alcohols with a sulfur atom because such amino sulfur catalysts offer improvements in enantioselectivity over their amino alcohol counterparts.[5] In this context, β-amino thiols, disulfides and thioacetates generally provide the best efficiencies and enantioselectivities.[1,6]

In the cases of β-amino disulfides (e.g. **1**)[5a,b] and thiols,[5f] the catalytically active species has been shown to be a thiazazincolidine **2** (in a dimer/monomer manifold). Kellogg and co-workers have elegantly established that the thiazazincolidine species **2** that are generated from β-amino disulfides **1** do so by cleavage of the disulfide bond by diethylzinc to give a thioether **3** and the thiazazincolidine **2** (Equation 1).[5a,b] The thioether **3** by-products are either catalytically unproductive[5a,b,7] or give less effective catalysis.[8] Therefore, in terms of stereochemical economy and efficiency, β-amino thiols would be more desirable catalysts than their disulfide counterparts. The disulfides may also suffer from the fact that the thioether by-products **3** may degrade the overall enantioselectivity. Thus, in terms of utilising stereochemical information and overall enantioselectivity, the amino thiols may be more advantageous catalysts. However, our observations concur with those of Kellogg and co-workers[5a,b] that β-amino thiols rapidly oxidise to the disulfides, even under carefully controlled storage conditions. In this context, we have reported the preparation and use of oxidatively stable tertiary amino thiols but found that the enantioselectivities were inferior (8–64% ee) in comparison with the corresponding primary aminothiol (67–99% ee).[9] We postulated that an alternative approach to oxidatively stable amino thiols might be to immobilise such systems via a polymer support. This would have the added advantage that the catalysts should also be fully recoverable and recyclable. To our knowledge, polymer-supported β-amino thiols or thioesters have not been prepared previously. However, van Koten and co-workers have prepared fluorous phase chiral arylzinc thiolates as catalysts for the enantioselective addition of diethylzinc to aldehydes.[10] Unfortunately, these fluorous phase systems were not recyclable and the ee dropped dramatically after two cycles of use. Consequently, herein, we report the first preparation of polymer-supported β-amino sulfur ligands and their use and recyclability in the enantioselective addition of diethylzinc to aldehydes.



Equation 1 Formation of thiazazincolidines and thioethers from disulfides

Initially, we investigated the possibilities of using a suitably functionalised supported hydroxy proline moiety as the source of the chiral discrimination. Such an approach had been successfully used by Lui and Ellman in the development of tetrahydropyranyl linked chiral amino alcohol catalysts.[11] Furthermore, at the outset we were keen to avoid attachment of the chiral discriminator via any of the crucial chelation centres (nitrogen and sulfur). However, employing hydroxyproline moieties and using dihydropyranyl resins, Rink acid resin or attachment via a benzyloxy linker with trichloroacetimidate[12] or TOPCAT[13] functionalised polymers, all failed either at the attachment step or in the subsequent functionalisation.

In the main, amino alcohols have been polymer-supported via attachment through the nitrogen atom. Given the foregoing problems with functionalised hydroxy proline, we chose to support (2*S*)-prolinol via the nitrogen. Accordingly, four different Merrifield resins **4** including three gel type **4a–c** (2% divinylbenzene with 1.74, 3.46 and 5.94

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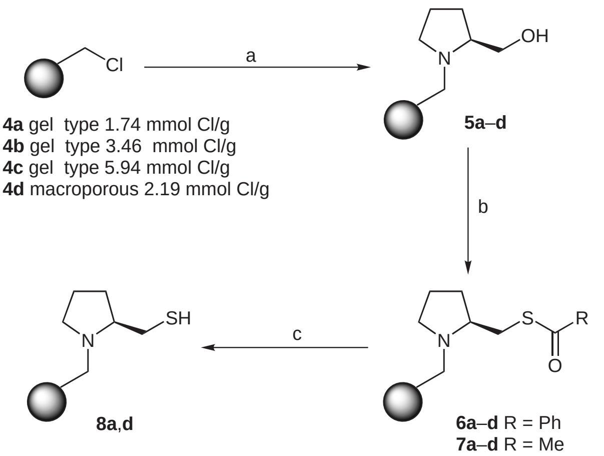
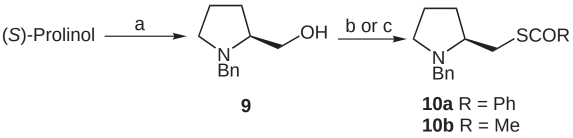
mmol Cl/g) and one macroporous type **4d** (80% divinylbenzene, 2.18 mmol Cl/g) were exhaustively treated, in duplicate, with (2*S*)-prolinol using the conditions of Lecavalier et al.[14] until no chlorine remained by microanalysis (Scheme 1). This afforded the polymer-supported prolinol systems **5a**–**d** (**5a** 77–85%; **5b** 79–81%; **5c** 67–69%; **5d** 90–95% as judged from microanalytical data). The lower yields of prolinol incorporation in the gel type polymers, and in particular the highly functionalised **4c** (5.95 mmol Cl/g), was attributed to some crosslinking of the active sites by the bifunctional prolinol. Subsequently, the prolinol-supported polymers **5a**–**d** were smoothly converted into the corresponding thiobenzoates **6a**–**d** by reaction with excess diethyl azodicarboxylate, triphosphine and thiobenzoic acid.[15] The efficiency of the conversions of the gel type polymers **5a**–**c** into the thiobenzoates **6a**–**c** (**6a** 80%; **6b** 69%; **6c** 30–43%) again probably reflected the higher level of prolinol crosslinking of the active sites and the decreased site accessibility. The lower conversion rate for the macroporous beads **6d** (33%) was attributed to reduced accessibility following derivatisation with prolinol residues and particularly to hindrance of sites in micropores. In order to investigate any steric problems with the thioester production the corresponding Mitsunobu reaction was repeated on the prolinol-supported resins **5a**–**d** using thioacetic acid.[15] This afforded the thioacetates **7a**–**d**. However, the conversion for polymer **5a** into **7a** (88–93%) was only marginally more efficient than for **6a** (80%). The conversion into the thioacetate macroporous resin **7d** (28–40%) showed no real improvement over the thiobenzoate **6d** (33%) and further supported the likelihood that only readily accessible sites in resin **5d** undergo reaction. In contrast, the conversions for the gel type resins **5b** and **5c** into thioacetates **7b** (31%) and **7c** (11%) were much lower than for the corresponding thiobenzoates **6b** (69%) and **6c** (30–43%) and may reflect the interaction of the aromatic backbone of the polymer with thiobenzoic acid but not with thioacetic acid.

Several attempts were made to convert the thiocarboxylate functionalities of resins **6** and **7** into the thiol moiety **8** without success (Red-Al, aq NH_3, NH_3/toluene, DIBALH, HCl/MeOH). However, using pyrrolidine[16] in toluene with thioacetates **7a** and **7d** efficiently afforded the corresponding thiols **8a** and **8d** as judged by sulfur/nitrogen microanalytical data and IR spectra (disappearance of the carbonyl group).

It was important to be able to compare the catalytic abilities (activity and selectivity) of the polymer-supported catalysts **6**–**8** with analogous solution phase systems. Accordingly, (*S*)-prolinol was converted into the corresponding *N*-benzyl derivative **9** in 87% yield using the method of Govindachari et al.[17] Subsequent Mitsunobu reaction with diethyl azodicarboxylate, triphosphine and thiobenzoic acid or thioacetic acid afforded the thiobenzoate **10a** or thioacetate **10b** in 82% and 57% yields, respectively (Scheme 2).



Scheme 1 Synthesis of polymer-supported thioester **6**, **7** and thiol catalysts **8**; *Reagents and conditions*: (a) excess (*S*)-prolinol, DMF, 60–70 °C; (b) excess DEAD, Ph_3P and PhCOSH or CH_3COSH; (c) pyrrolidine, DMF

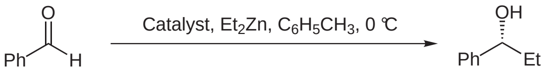


Scheme 2 Synthesis of solution-phase thioester catalysts **10a**,**b**. *Reagents and conditions*: (a) $PhCH_2Cl$, $C_6H_5CH_3$, Δ; (b) DEAD, Ph_3P, PhCOSH, $C_6H_5CH_3$ or (c) DEAD, Ph_3P, CH_3COSH, $C_6H_5CH_3$

With the polymer-supported catalysts **6**–**8** in hand together with the solution-phase analogues **10** the enantioselective addition of diethylzinc to benzaldehyde was investigated (Table 1).[18] To ensure that there was no appreciable background catalytic effect, the unfunctionalised chloromethyl polymer **4a** was used in a blank experiment in the addition of diethylzinc to benzaldehyde. The use of chloromethyl polymer **4a** gave racemic 1-phenylpropanol in only 17% yield (Table 1, entry 1). As a measure as to how effective the replacement of oxygen for sulfur was the prolinol-supported catalysts **5a** and **5d** were investigated. Both these systems showed very poor conversion (8–13%) and racemic 1-phenylpropanol was generated (entries 2 and 3). These latter two results are in contrast to the findings of Itsuno and Fréchet who found that a similar polymer-supported prolinol derived from 1–2% cross-linked chloromethylated polystyrene gave a 93% yield of 1-phenylpropanol in 24% ee.[19]

We were relieved to find that the polymer-supported thiobenzoates **6** were effective catalysts (entries 4–7). Surprisingly, gel type thiobenzoate **6c** with the highest initial loading of choloromethyl groups but the poorest incorporation of thiobenzoate groups (30%) gave the highest ee (entry 6, 86% ee). Similarly, the macroporous beads **6d** showed a poor incorporation of thiobenzoate groups (33%) but yet was still an effective catalyst (entry 7, 80% yield, 77% ee). Clearly, the unreacted amino alcohol sites do not detract from the overall enantioselectivity. These results are also in contrast to the findings of Hodge and coworkers with polystyrene-supported ephedrine where

Table 1 Catalytic Enantioselective Addition of Diethylzinc to Benzaldehyde



Entry	Catalyst	Catalyst concd (%)	Yield (%)[a]	ee (%)[b]
1	**4a**	10	17	0
2	**5a**	10	8	0
3	**5d**	10	13	1
4	**6a**	10	49	82
5	**6b**	10	47	82
6	**6c**	10	54	86
7	**6d**	5	80	77
8	**7a**	5	34	80
9	**7b**	10	13	34
10	**7c**	2.5	29	68
11	**7d**	10	59	78
12	**8a**	10	33	57
13	**8d**	10	57	49
14	**10a**	10	67	90
15	**10b**	10	82	91

[a] Isolated yield for purified material.

[b] Determined by chiral HPLC, Daicel Chiralcel OB, hexane–*i*-PrOH (97:3), 0.5 mL/min.

lower amino alcohol loading (<1 mmol catalyst sites per g) gave the best ee values.[20]

The results with the corresponding thioacetates **7** indicated that the lowest loading gel type **7a** (entry 8, 80% ee) and the macroporous thioacetate **7d** (entry 11, 78% ee) were the most enantioselective of the polymer-supported thioacetates. Apart from a slight drop in yield, the polymeric catalysts **6a**,**d** and **7a**,**d** are largely unaffected by replacement of the thiobenzoate functionality by a thioacetate (entries 4, 7, 8, 11). In the case of the solution-phase analogues the enantioselectivities were similar for the thiobenzoate **10a** (entry 14, 90% ee, 67%) and thioacetate **10b** (entry 15, 90% ee, 82%) but the efficiency was greater for the latter. The enantioselectivities of the solution-phase catalysts **10** (ca 90% ee) were superior to the polymer-phase analogues **6**–**8** (34–86% ee).

The results with the polymer-supported thiols **8a** (entry 12, 57% ee) and **8d** (entry 13, 49% ee) were quite poor in comparison to the corresponding thiobenzoates **6a** (entry 4, 82% ee) and **6d** (entry 7, 77% ee). It is conceivable that the thiol functionalities in **8** could interact to form a disulfide bridge. This would halve the number of catalytically competent sites as well as reducing the ability of the reagents to access these active sites.

In studies on polymer-supported ephedrine-based catalysts, Hodge and co-workers have shown that the level of cross-linking is important. Thus, these workers found that a 1% cross-linked polymer gave better enantioselectivities (85% ee) than the corresponding 2% cross-linked polymer (70% ee).[20] This was attributed to the more lightly cross-linked polymers being more easily swollen by the reaction solvent (toluene) so that the catalytic sites are more accessible. Accordingly, we prepared two 1% divinylbenzene thiobenzoates (1.24 and 1.78 mmol S/g) corresponding to **6a** and **6c**. However, these were much less effective than their 2% divinylbenzene counterparts giving 7% (0% ee) and 62% (54% ee) yields of 1-phenylpropanol, respectively.

The use of polymer-supported catalysts greatly facilitates the separation of the solid catalyst from reactants and products that should allow the catalyst to be recycled. To investigate this potential recyclability, the polymer-supported thiobenzoate **6b** was reused in a batch type process (Table 2). The method of polymer recycling was found to be important and any form of aqueous quench resulted in the loss of catalytic activity (Table 2, entries 2 and 3). Simply decanting the reaction solvent and washing with anhydrous toluene allowed the polymer-supported catalyst **6b** to be used in three successive runs without any loss of catalytic activity in terms of yield and enantioselectivity (Table 2, entries 4 and 5). After recycling three times the ee remained consistently high (80–84% ee) and, in principle, allow these catalysts to be used in continuous flow reactors.

In summary, a series of polymer-supported chiral β-aminothioesters **6** and **7** and thiols **8** were prepared along with solution-phase β-amino ester analogues **10**. Both the polymer-supported thioesters (≤86% ee) and solution-phase analogues (ca. 90% ee) were effective catalysts for the enantioselective addition of diethylzinc to benzaldehyde. These thioesters **6** (77–86% ee) and **7** (34–80% ee) were more enantioselective catalysts in diethylzinc addition to benzaldehyde in comparison with immobilised β-amino

Table 2 Polymer-Supported Catalyst Recycling for the Enantioselective Addition of Diethylzinc to Benzaldehyde by 10 mol% of Polymer-Supported Catalyst **6b**

Entry	Run	Recycling method[a]	Yield (%)	ee of 1-phenyl-1-propanol (%)
1	1	–	48	80
2	2	A	13	3
3	2	B	8	5
4	2	C	53	84
5	3	C	56	81

[a] Method A: the polymer-supported catalyst **6b** was filtered, then washed sequentially with H_2O, toluene, CH_2Cl_2 and dried (40 °C 0.1 mmHg). Method B: the polymer-supported catalyst **6b** was filtered, then washed sequentially with saturated aq NH_4Cl, H_2O, THF, toluene and dried (40 °C 0.05 mmHg). Method C: the solvent was decanted and **6b** was washed with three portions of anhyd toluene.

thiols **8** (49–57% ee). The polymer-supported thiobenzaldehyde **6b** was fully recyclable without diminishing the catalytic effectiveness in terms of enantioselectivities or efficiencies.

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(15) **Typical Procedure for the Synthesis of the Polymer-Supported Thioesters 6 and 7.**
To a stirred solution of [(2*S*)-1-(polystyrylmethyl)pyrrolidinyl]methanol (0.5008 g) and triphenylphosphine (0.5885 g) in anhyd toluene (10 mL) under nitrogen was added at r.t. a solution of DEAD (0.3912 g) in toluene (1 mL). After 3–5 min thiobenzoic acid (0.3012 g) in toluene (1 mL) was added. The resulting mixture was stirred for a further 45 h at r.t. At the completion of this period the polymer was filtered and rinsed with toluene, DMF and EtOH. The polymer beads were then transferred to a soxhlet apparatus and washed with THF for 1 d, rinsed with acetone and finally soxhlet extracted with Et_2O for 1 d. The beads were then dried in a drying pistol (40 °C, 0.05 mmHg) for 24 h to give 0.5639 g of polymer. IR (KBr): $\nu_{max} = 1664\ cm^{-1}$. Anal. Calcd: N, 2.08; S, 4.78. Found: N, 1.94; S, 3.82. Loading 1.19 mmol S/g and an 80% conversion based on sulfur microanalysis.

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(18) **Typical Procedure for the Enantioselective Addition of Diethylzinc to Benzaldehyde Catalysed by Polymer-Supported Catalysts 6–8.**
Diethylzinc (1.87 mL of a 1 M solution in hexane, 1.87 mmol) was added to a stirred solution of the catalyst (0.024 mmol, 0.048 mmol, or 0.096 mmol based on sulfur content) in anhyd toluene (5 mL) under a nitrogen atmosphere. After stirring at r.t. for 2 h the solution was cooled to –27 °C whereupon, freshly distilled benzaldehyde (0.937 mmol) was added and the resulting solution was stirred at 0 °C. After stirring for 19 h at this temperature additional diethylzinc was added (1.87 mL, 1.87 mmol) and the mixture stirred for a further 46 h at 0 °C. At the completion of this period there was no starting aldehyde, so HCl was added (1 M, 3 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and dried over Na_2SO_4. Evaporation of the solvent and silica column chromatography (hexane–EtOAc, 88:12) afforded (*R*)-(+)-1-phenyl-1-propanol as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 0.9$ (t, 3 H, $\mathrm{CH_2C}H_3$, $J = 7.4$ Hz), 1.65–2.00 (m, 3 H, $\mathrm{C}H_2\mathrm{CH_3}$, $J = 7.4$ Hz, $\mathrm{O}H$), 4.60 (t, 1 H, $\mathrm{C}H\mathrm{OH}$, $J = 6.6$ Hz), 7.30–7.40 (m, 5 H, $\mathrm{ArC}H$). The ee was determined by HPLC using a DAICEL chiralcel OB column with 3% *i*-PrOH in hexane (flowrate: 0.5 mL/min); $t_R = 25$ min for the *S*-isomer and 31 min for the *R*-isomer.

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