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Immobilization of Chiral Ligands on Polymer Fibers by Electron Beam Induced Grafting and Applications in Enantioselective Catalysis

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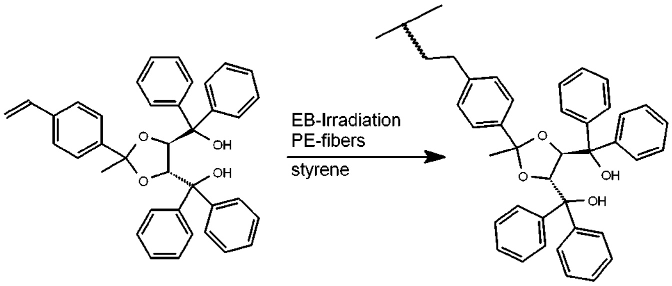
ABSTRACT



Styrenic TADDOL and L-prolinol-derived monomers were immobilized on polyethylene fibers by electron beam induced preirradiation grafting using styrene as comonomer. The polymer-supported chiral ligands were utilized as catalysts in the asymmetric addition of diethylzinc to benzaldehyde. Fiber-bound titanium TADDOLate gave a quantitative conversion of benzaldehyde to 1-phenylpropan-1-ol in a 97:3 *S*/*R* enantiomeric ratio. The catalyst was successfully regenerated and employed in subsequent reactions with retention of high enantioselectivities.

Covalent immobilization of homogeneous catalysts to insoluble polymer supports has received considerable attention in recent years.[1] Heterogenization facilitates the separation of the catalyst from reagents and products, simplifies the efficient recovery of the often expensive or toxic catalysts, and potentially allows the adaptation of the immobilized catalysts to continuous flow type processes. While the heterogenization of achiral catalysts is becoming standard practice, effective immobilization of asymmetric catalysts and auxiliaries remains as a particularly challenging target.[2] Immobilization of chiral catalysts often results in lower activities and enantioselectivities than observed for their homogeneous counterparts.[3] Evidently, architecture and properties of the polymeric support play an important role in determining the catalytic performance. The most common type of polymeric supports are cross-linked polystyrene beads prepared by suspension copolymerization of a polymerizable ligand together with styrene and a suitable cross-linker such

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(1) For reviews, see: (a) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217. (b) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21. (c) Sherrington, D. C. *Chem. Commun.* **1998**, 2275. (d) de Miguel, Y. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4213. (e) Itsuno, S. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 2, Chapter 21, p 945. (f) Bergbreiter, D. E. In *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A. Eds.; Wiley-VCH: Weinheim, 2000; Chapter 3, p 43. (g) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637.

(2) (a) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309. (b) Sung, D. W. L.; Hodge, P.; Stratford, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1463. (c) Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Salvador, R. V.; Vicent, M. J. *Tetrahedron* **1999**, *55*, 12987. (d) Angelino, M. D.; Laibnis, P. E. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 3888. (e) Canali, L.; Cowan, E.; Deleuze, H.; Gibson, C. L.; Sherrington, D. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2055. (f) Hu, J.; Zhao, G.; Yang, G.; Ding, Z. *J. Org. Chem.* **2001**, *66*, 303.

(3) For exceptions, see: (a) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147. (b) ten Holte, P.; Wijgergangs, J.-P.; Thijs, L.; Zwanenburg, B. *Org. Lett.* **1999**, *1*, 1095. (c) Wang, X.-W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295. (d) Sellner, H.; Faber, C.; Rheiner, P. B.; Seebach, D. *Chem. Eur. J.* **2000**, *6*, 3692. (e) Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 6929. (f) Hu, J.; Zhao, G.; Ding, Z. *Angew. Chem., Int. Ed.* **2001**, *40*, 1109.

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as divinylbenzene.[4] Alternatively, the ligands can be grafted to an existing cross-linked polystyrene resin containing properly functionalized reactive groups. The degree of cross-linking and the structure of the cross-linking agent strongly influence the activity and selectivity of the catalyst.

Practical drawbacks of cross-linked polystyrene supports are their low mechanical strength and restricted thermo-oxidative stability. If the spherical beads are not sufficiently stable to withstand stirring over a long period of time, their breakdown will result in the formation of a fine powder, which severely limits their handling during filtration and recycling of the supported catalyst. Likewise, grafting of functionalized ligands to chemically modified polystyrene resins may result in undesired side reactions and incomplete grafting; also functionalities may remain in the support material that could reduce the effectiveness of the polymeric catalyst. Thus, the development of new approaches for facile anchoring of chiral catalysts to mechanically stable, inert polymeric supports is of special interest. Fibrous supports have received very little attention in the present context.[5] Also, to our knowledge, radiation-induced grafting has not been employed previously for immobilization of chiral catalysts or auxiliaries on polymer supports. Nevertheless, electron beam accelerators are not only readily available but also widely used in the polymer processing industry.[6]

We report here the immobilization of chiral ligands on chemically inert, mechanically stable polyethylene fibers by electron beam induced preirradiation grafting using styrene as a comonomer.[7] Application of the resulting materials as effective and recyclable catalysts in enantioselective organic transformations is described.

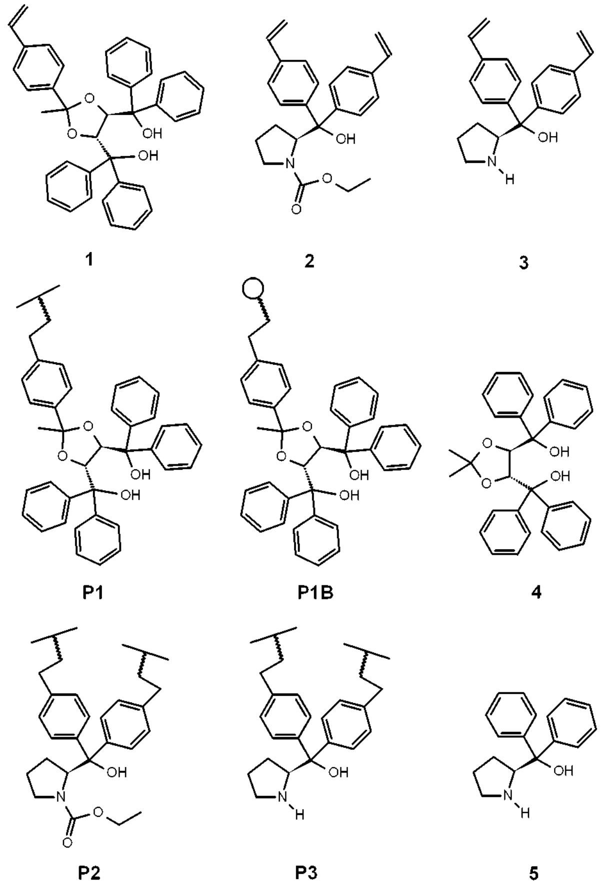

Figure 1. Monomeric ligands and model compounds **1**−**5** and the corresponding polymer-supported catalysts **P1**−**P3** of the present study.

The monomeric ligands selected for the present study together with the corresponding supported catalysts are depicted in Figure 1. The styrenic α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) derivative **1** was prepared as described previously by Seebach and co-workers.[8] The protected L-proline-derived ligand precursor **2** was prepared in 69% yield by addition of 4-(vinylphenyl)-magnesium chloride to L-proline *N*-ethylcarbamate methyl ester obtained by one-pot *N*,*O*-protection of L-proline.[9] Refluxing of **2** in KOH/MeOH gave the chiral amino alcohol **3** in 84% yield after purification by flash chromatography.[10] Ligand **1** was grafted on preirradiated polyethylene fibers with styrene comonomer to produce the polymeric catalyst **P1** with a loading of 0.15 mmol/g.[11] Reference catalyst **P1B** was prepared by supporting ligand **1** on polystyrene beads with a loading of 0.6 mmol/g by suspension copolymerization of **1** with styrene using divinylbenzene as a cross-linking agent.[8] The protected prolinol **2** was grafted in a fashion similar to that described for **1** to produce the fiber-supported catalyst **P2** with a loading of 0.2 mmol/g as confirmed by nitrogen analysis. The deprotected prolinol functionalized polymer **P3** with similar loading was obtained in quantitative yield by refluxing **P2** in KOH/MeOH followed by drying in vacuo. The homogeneous reference ligands **4** and **5** were purchased from commercial sources.

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(4) *Syntheses and Separations Using Functional Polymers*; Sherrington, D. C., Hodge, P., Eds.; Wiley: Chichester, 1988.

(5) Grafting of a phenolic TADDOL derivative to a chloromethylated ethylene−styrene copolymer has been described briefly, see: Altava, B.; Burguete, M. I.; Escuder, B.; Luis, S. V.; Salvador, R. V.; Fraile, J. M.; Mayoral, J. A.; Royo, A. J. *J. Org. Chem.* **1997**, *62*, 3126.

(6) McGinniss, V. D. In *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; Kroschwitz, J. I., Ed.; Wiley: New York, 1986; Vol. 4, p 418.

(7) (a) Stannett, V. T. *Radiat. Phys. Chem.* **1990**, *35*, 82. (b) Näsman, J. H.; Sundell, M. J.; Ekman, K. B. U.S. Patent 5 326 825, 1994.

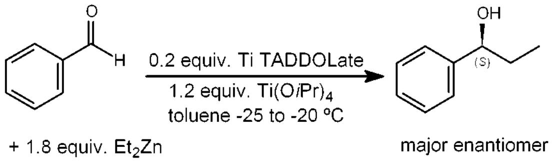
(8) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710.

(9) Bhaskar Kanth, J. V.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127.

(10) A low-yield synthesis of **3** from TMS-protected L-proline and its copolymerization with styrene to insoluble polymeric catalyst has been reported previously, see: (a) Itsuno, S.; Kamahori, K.; Watanabe, K.; Koizumi, T.; Ito, K. *Tetrahedron: Asymmetry* **1994**, *5*, 523. (b) Itsuno, S.; Watanabe, K.; Koizumi, T.; Ito, K. *React. Polym.* **1995**, *24*, 219. Polymer-supported **3** was employed as catalyst in the Diels−Alder reaction of methacrolein with cyclopentadiene, resulting in high yield and high exo-selectivity but a low level of asymmetric induction (ee = 25%).

(11) Loading of **P1** was approximated gravimetrically. In a typical grafting procedure, 10 g of cut PE fibers (0.7 Dtex) were irradiated under an inert atmosphere to a total dose of 200 kGy using an electron accelerator operating at an accelerator voltage of 175 kV and beam current of 5 mA. The irradiated fibers were immersed in a reaction mixture containing 15 g of styrene, 1.8 g of **1**, 40 mL of EtOH, and 20 mL of water. To the reaction mixture were additionally added 0.03 g of divinyl benzene and 0.155 g of a 25 wt % solution of dibenzoyl peroxide. The mixture was purged with N_2 before initiating the reaction and the grafting was allowed to continue to completion for approximately 6 h. The temperature was raised to 80 °C for 2 h, and the resulting fibers were subsequently filtered and washed with EtOH and dichloroethane. The weight gain of the recovered fibers was determined and the conversion of the monomers calculated to 80%.

Table 1. Comparison of the Fiber-Supported Titanium TADDOLate Derived from **P1** with **P1B** and **4** in the Addition of Et_2Zn to PhCHO



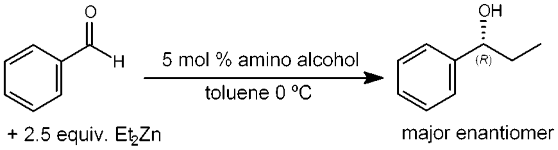
ligand	PhCHO (mmol/mL)[a]	pol. (g)[b]	loading (mmol/g)[c]	convn (%)[d]	*S*/*R*
4	0.13			quant.	99:1
P1	0.06	1.0	0.15	quant.	97:3
P1[e]	0.06	0.8	0.15	99	96:4
P1[f]	0.06	0.7	0.15	89	97:3
P1B	0.15	0.25	0.6	quant.	97:3
P1B[e]	0.15	0.23	0.6	90	97:3

[a] Concentration in mmol of PhCHO per mL of toluene. [b] Amount of polymer before loading with titanate. [c] Loading of the polymeric catalyst in mmol of TADDOL per g of polymer. [d] Conversion after 19 h by GC. [e] First regeneration of the polymeric catalyst. [f] Second regeneration.

The fiber-supported TADDOL **P1** was employed as a ligand in the titanium-catalyzed addition of diethylzinc to benzaldehyde[12] and its performance compared with those of previously described **P1B** and **4**. The results are summarized in Table 1. The enantioselectivity of the fibrous catalyst **P1** (es = 97%) was equally high compared with that of TADDOL **P1B** supported on beads and only slightly lower than that observed for the homogeneous system (es = 99%). Both polymer-supported catalysts were successfully recycled after quenching with HCl, filtration, and subsequent washings with H_2O, THF, and Et_2O.[8] Conversions decreased slightly upon regeneration whereas the enantioselectivities remained high. Performance of **P1B** was analogous to that reported earlier by Seebach.[8] The main difference between the two polymer-supported catalysts was the slower rate of reaction observed with the fibrous TADDOL **P1**, which may result from the different swelling characteristics, different loadings, and different accessibilities of the active sites between the two types of catalysts. These parameters are, however, subject to optimization, and studies along these lines are currently in progress.

Since the seminal work of Seebach and co-workers, TADDOLs and their closely related derivatives have become an extraordinarily versatile class of chiral auxiliaries with applications extending from utilization as stoichiometric reagents or chiral Lewis acids to catalytic enantioselective hydrogenations and stereoregular metathesis polymerizations.[13] In previous reports, TADDOLs have been heterogenized by incorporation or grafting onto Merrifield resin, polystyrene, controlled pore glass, dendritic macromolecules, and monolithic polymer rods.[5,8,14,15] Severe degradation of support morphology was observed in the present work when **P1B** was subjected to stirring, especially with longer reaction times. The fiber-supported TADDOL described here thus provides an attractive alternative as a mechanically stable, easily recyclable heterogeneous catalyst resulting in equally high enantioselectivities.

Table 2. Comparison of the Fiber-Supported Amino Alcohol **P3** with **3** and **5** as Catalysts in the Addition of Et_2Zn to PhCHO

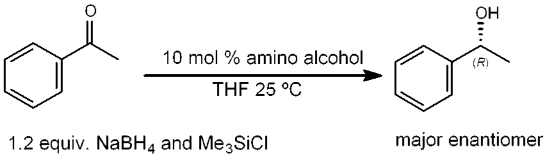


ligand	PhCHO (mmol/mL)[a]	pol. (g)[b]	loading (mmol/g)[c]	yield (%)[d]	*R*/*S*
5	0.38			97	84:16
3	0.38			70[e]	88:12
P3	0.52	1.0	0.21	36	62:38
P3[f]	0.56	0.8	0.21	33	60:40
P3[g]	0.49	0.7	0.21	30	61:39

[a] Concentration in mmol of PhCHO per mL of toluene. [b] Amount of polymer. [c] Loading of the polymeric catalyst in mmol of amino alcohol per g of polymer. [d] Yield after 24 h by GC. [e] Isolated yield by column chromatography. [f] First regeneration of the polymeric catalyst. [g] Second regeneration.

The fiber-supported chiral amino alcohol **P3** was employed as a catalyst in two types of reactions. The results of diethylzinc addition to benzaldehyde[12] using **P3** along with the homogeneous reference catalysts **3** and **5** are presented in Table 2. The reduction of benzophenone with $NaBH_4$/TMSCl using **P3**, **3**, and **5** is presented in Table 3.[16]

Table 3. Comparison of the Fiber-Supported Amino Alcohol **P3** with **3** and **5** as Catalysts in the Reduction of PhCOMe with $NaBH_4/Me_3SiCl$



ligand	PhCOMe (mmol/mL)[a]	pol. (g)[b]	loading (mmol/g)[c]	yield (%)[d]	*R*/*S*
5	0.5			quant.	98:2
3	0.5			98	97:3
P3	0.5	0.5	0.21	99	52:47

[a] Concentration in mmol of PhCOMe per mL of THF. [b] Amount of polymer. [c] Loading of the polymeric catalyst in mmol of amino alcohol per g of polymer. [d] Quenched 2 min after completed addition.

In the addition of diethylzinc to benzaldehyde, the performance of the styryl-substituted homogeneous catalyst **3** was comparable to that of the phenyl analogue **5**. Both catalysts resulted in high yields and moderate enantioselec-

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(12) For a review, see: Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, 757.

(13) For a review, see: Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92.

tivities (es = 84−88%), consistent with the literature data for proline-based ligands.[12] The polymer-supported catalyst **P3**, however, suffered from a considerable decrease in yield and a significant drop in enantioselectivity (es = 60%), as observed previously for other supported chiral amino alchols.[12] Recyclability of **P3** was, however, successful, and both enantioselectivity and conversion remained on the same level upon regeneration of the catalyst. Also the fibrous morphology of the support was retained.

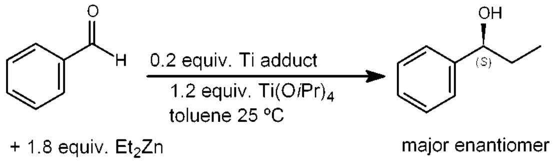
Supporting of the prolinol ligand from the phenyl substituents possibly decreases the flexibility of the chiral ligand, causing steric hindrance at the active site. In earlier reports, higher enantioselectivities have been obtained by immobilization of similar ligands via a flexible linker connected to the nitrogen atom.[12] A similar approach using the methodology described here may provide a feasible access to highly selective fiber-supported amino alcohols.

An even more dramatic decrease in enantioselectivity was observed in the reduction of benzophenone using **P3** in combination with $NaBH_4$ and trimethylchlorosilane (Table 3). Whereas both homogeneous catalysts **3** and **5** produced the chiral alcohol in high enantioselectivities (es = 97−98%) and nearly quantitative yields, the fiber-supported **P3** exhibited only marginal enantiocontrol (es = 52%) despite the retained yield. The performance of **5** was analogous to that described in the literature.[16]

The fiber-supported ethyl carbamate ligand **P2** was further employed as a catalyst in the titanium-catalyzed addition of diethylzinc to benzaldehyde in the same fashion as described for the TADDOL-based catalysts **P1** and **P1B**. The results are presented in Table 4. Both **P2** and the homogeneous reference catalyst **2** displayed moderate but significant enantioselectivities (es = 62−74%) with higher yields obtained under homogeneous conditions. Apparently the alcohol and/or keto functionalities of this ligand are accessible for coordination to titanium, generating a chiral environment resulting in enantiocontrol.[17]

In summary, we have shown that the combination of electron beam induced preirradiation grafting using styryl-substituted chiral ligands provides a facile high yield approach for immobilization of chiral catalysts on mechanically stable fibrous polymer supports. This method provides an attractive alternative to the traditional and predominant suspension copolymerization and grafting methods for heterogenization of chiral ligands and auxiliaries. High yields and high enantioselectives, as well as simple and efficient recyclabilities, are accessible with the fibrous catalysts, especially in combination with the TADDOL-based auxiliaries. While the loadings described here are relatively low, attempts to increase the degrees of functionalization will be addressed in future work.

Table 4. Titanium-Mediated Addition of Et_2Zn to PhCHO Using **P2** and **2**



ligand	PhCHO (mmol/mL)[a]	pol. (g)[b]	loading (mmol/g)[c]	yield (%)	*S*/*R*
2	0.10			87[d]	74:26
P2	0.11	2.25	0.21	55[e]	62:38

[a] Concentration in mmol of PhCHO per mL of toluene. [b] Amount of polymer before loading with titanate. [c] Loading of the polymeric catalyst in mmol of L-prolinol *N*-ethylcarbamate per g of polymer. [d] Yield after 26 h by GC. [e] Yield after 24 h.

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Supporting Information Available: Experimental procedures and analytical data for compounds **2** and **3** and polymeric catalysts **P1**−**P3** and the addition and reduction reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) See also: Takahashi, H.; Kawabata, A.; Higashiyama, K. *Chem. Pharm. Bull.* **1987**, *35*, 1604.