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A first example of macromolecular Ti(IV) Lewis acid in the catalytic enantioselective Mukaiyama reaction

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Abstract

The preparation and characterization of a soluble copolymer **P1** between styrene, divinylbenzene (DVB) and the enantiomerically pure salicylaldimine ligand **3c** is described. The Lewis acid prepared from this macromolecular chiral ligand and $Ti(O^iPr)_4$ has been used in the catalytic Mukaiyama reaction to afford benzyl (R)-3-hydroxy-3-phenylpropanoate **7**. © 1998 Elsevier Science Ltd. All rights reserved.

The development of clean procedures for the preparation of organic molecules is a major challenge of modern organic chemistry in view of the environmental, practical and hence economic issues that the need of extensive purification of complex reaction mixtures raises.

Among the different approaches towards this goal, the use of soluble[1] or insoluble polymer-bound reagents and/or catalysts has already proved highly effective, allowing the easy separation of the product or the catalyst system by means of simple physical techniques, i.e. filtration or ultra filtration.[2] Following this route, notable progress has been achieved, in particular in the field of catalytic asymmetric synthesis, at least as far as asymmetric oxidation[3] and reduction[4] reactions are concerned. In contrast, the equally important enantioselective carbon–carbon bond forming processes are still awaiting comparably successful developments. Indeed a few reports concerning the catalysis of the asymmetric Diels–Alder reaction with insoluble polymer bounded boron[5] and titanium[6] chiral Lewis acids have appeared in the literature, leading to the cycloadducts in fair enantiomeric excess (25–65% e.e.). Better results in terms of enantioselectivity have been obtained in the case of dialkyl zinc addition to aldehydes, either using styrene copolymers bearing chiral amino alcohol pendant groups or inherently chiral soluble polybinaphthols.[7a] It is, however, worth noting that the latter materials have proved completely ineffective, in terms of enantioselectivity, as catalyst precursors for the Mukaiyama reaction:[7b] in fact, to our knowledge no attempt at *catalytic* asymmetric synthesis with a polymer-bound chiral Lewis acid in the addition of silyl enol ethers or silyl ketene acetals to carbonyl substrates, has met with any success to date.[8]

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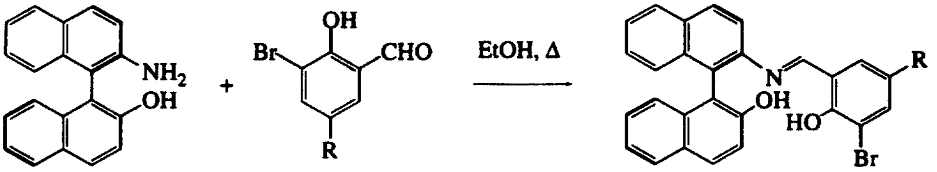
In this paper we wish to report the preparation and characterisation of a chiral salicyl aldimine/styrene/DVB soluble copolymer (R)-**P1** and its use as a macromolecular ligand in a first example of a catalytic enantioselective Mukaiyama reaction with a soluble polymeric Lewis acid.

As reported by Carreira and co-workers,[9] the reaction between aldehydes and silyl ketene acetals may be conveniently carried out in the presence of a catalytic amount (0.5–2 mol%) of a chiral Ti(IV) complex prepared from $Ti(O^iPr)_4$, the salicylaldimine ligand **3a** and 3,5-di-*tert*-butylsalicylic acid.

In order to introduce the structure of **3** into a polymeric chain, in the present study the modified salicylaldehyde **2c**, as well as the model compound **2b** were synthesised,[10] eventually allowing the preparation of the ligands (R)-**3b** and (R)-**3c** (Scheme 1).[9] In spite of the presence of two phenol groups in the latter compound, its radical copolymerization with styrene and DVB[11] afforded a macromolecular product (R)-**P1** that proved soluble in most of the common organic solvents, with the exception of aliphatic hydrocarbons and diethyl ether.



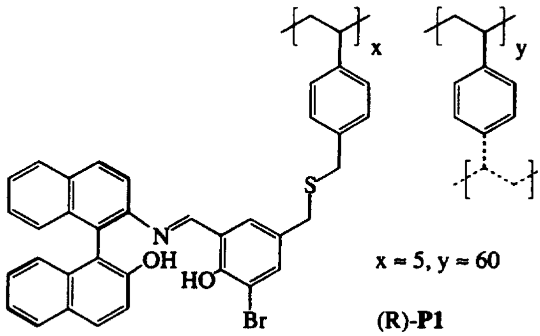
1

2.a R = Bu^t
2.b R = CH_2SCH_2Ph
2.c R = $CH_2SCH_2C_6H_4$-CH=CH_2

3.a R = Bu^t
3.b R = CH_2SCH_2Ph
3.c R = $CH_2SCH_2C_6H_4$-CH=CH_2

Scheme 1.

Gel permeation analysis of the material indicated a mean molecular weight $\langle M_n \rangle$ of 9600 (d=3.96) and also a glass transition at 147°C was evidenced by DSC. These data, as well as the solubility behaviour, allow us to conclude that **P1** is best viewed as a branched polymer instead of an extensively cross-linked one.



(R)-P1

P1 was further characterised by spectroscopic means: its UV spectrum is in practice superimposable on that of the low molecular weight compound **3b** in the region (280–430 nm) where the polystyrene backbone is transparent (Fig. 1a), suggesting, together with IR and NMR data, that the chemical identity of the chiral unit is preserved during the copolymerization. This conclusion also permitted the calculation of a salicylaldimine content in **P1** of 0.49 mmol/g, from the absorbance of the material at 325 nm.

Furthermore, the CD spectrum of (R)-**P1** closely resembles that of (R)-**3b** (Fig. 1b), supporting the hypothesis that the inclusion of the ligand in the polymeric chain occurs without any significant change in its conformational preferences.

The catalytic behaviour of the Ti(IV) Lewis acid prepared according to the published procedure[9] from

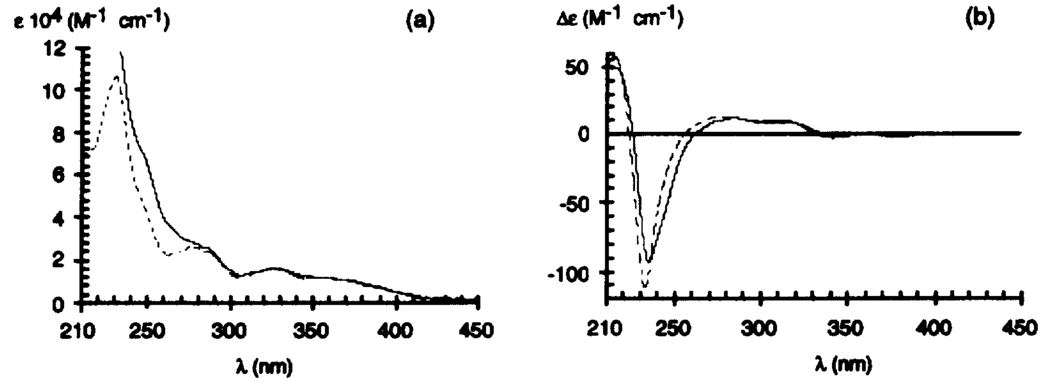
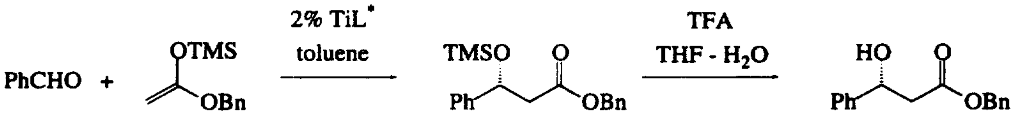


Fig. 1. (a) UV and (b) CD spectra of (R)-**P1** (solid line, arbitrary absorbance units) and (R)-**3b** (dashed line) in THF

the macromolecular ligand (R)-**P1** was then briefly evaluated in the reaction between benzaldehyde **4** and O-benzyl-O′-trimethylsilyl ketene acetal **5** (Scheme 2).[12] Despite the fact that the activity and enantioselectivity of (R)-**P1**-Ti (32% conversion and 26% e.e. in 36 h) was markedly lower than that reported for (R)-**3a**-Ti (conversion >95%, 96% e.e. in 4 h), it was encouraging to find that the polymeric Lewis acid was capable of a significant degree of asymmetric induction and that the prevailing enantiomer of **7** was (R) in either case. Moreover, at the end of the reaction the catalytic system was precipitated with pentane and easily removed from the reaction mixture by filtration, avoiding any need for chromatographic purification.



4 **5** **6** **7**

Scheme 2.

Although the poorer activity and enantioselectivity of (R)-**P1**-Ti with respect to (R)-**3a**-Ti may be partially ascribed to the polymeric nature of the former, it is likely that the presence of the sulphur atom and/or the reduced steric hindrance in the chiral monomeric unit could be responsible as well. In fact it is worth noting that even the catalytic system derived from the low molecular weight model (R)-**3b** affords the aldol product with just 48% conversion and 53% e.e. in 19 h.

The development of more effective macromolecular analogues of **3a**, the possibility of Lewis acid or ligand recycling and the evaluation of the scope of the present method are currently under investigation.

Acknowledgements

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10. Synthesis of **2b** and **2c**: 1.0 g of a 1:1 mixture of 5-chloromethyl- and 5-bromomethyl-3-bromo-2-hydroxybenzaldehyde (prepared by bromination of 5-chloromethyl-2-hydroxybenzaldehyde), 4.1 mmol of benzylthiol or 4-vinylbenzyl thiol and 0.4 mmol of $^{n}Bu_4NHSO_4$ in 7 ml of benzene were vigorously stirred for 24 h with 5% $KHCO_3$. After the usual work-up, the crude material was purified by chromatography, affording 60% **3b** (m.p. 70–72°C) and 75% **3c** (m.p. 76–78°C), respectively.
11. Preparation of (R)-**P1**: 413 mg of (R)-**3c**, 0.52 ml of styrene, 0.19 ml of 1,4-divinylbenzene, 30 mg of AIBN and 5 ml of degassed toluene were placed in a polymerisation vial and stirred at 80°C for 24 h. Thereafter, the polymeric material was precipitated by the slow addition of 5 ml of pentane, filtered and exhaustively extracted with Et_2O, until the UV analysis of the extracts showed the disappearance of the monomers. After drying, 513 mg of an orange material were obtained (39% of chiral ligand incorporation). ^{1}H-NMR ($CDCl_3$): δ 0.2–2.8 (br. m), 3.0–3.6 (br. s), 5.0–5.4 (br. s), 6.0–7.8 (br. m), 7.8–8.2 (br. s), 12.8–13.4 (br. s).
12. The reactions were carried out between 0°C and r.t., according to Ref. 9. The conversion was evaluated by GLC on the crude reaction mixture. The enantiomeric excess was determined by HPLC (Chiralcel OD, 0.5 ml/min hexane:^{i}PrOH=90:10) after desilylation of **6**.