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SCIENCE DIRECT®

Tetrahedron 59 (2003) 5823–5830

TETRAHEDRON

# Synthesis and preliminary studies on a novel class of soluble amino alcohol reagents based on methacrylate copolymers

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Received 11 April 2003; revised 27 May 2003; accepted 19 June 2003

**Abstract**—A class of soluble polymers containing chiral β-amino alcohol ligands, based on methacryate copolymers, are described. The use of copolymers permits the selective introduction of material to control the solubility and a functional group in a controllable ratio and polymer length. The application of the supported polymers to diethylzinc additions is described.


## 1. Introduction

Whilst homogeneous asymmetric catalysts benefit from a well-defined catalyst structure which can, to some extent, be predictably modified, they are often difficult to remove from reaction mixtures after use.[1] In cases where the catalyst contains a toxic metal, this presents a particular challenge to product purification. Heterogeneous asymmetric catalysts offer complimentary benefits and drawbacks, i.e. the catalyst is readily separable from the reagents and products, however, the selective modification of the catalyst is highly challenging.[2] The benefits of both methods may, in principle, be combined in an asymmetric homogeneous catalyst which has been converted to heterogeneous variant.[3] Such a combination may be achieved, for example, through the coupling of a catalyst or ligand to a solid support such as polymer (typically polystyrene) beads or silica. Although significant success has been achieved for a number of reactions, including diethylzinc additions to enones and asymmetric ketone reduction, a number of drawbacks and challenges remain to be addressed.[4] Most notable of these are the access of reagents to the active site, which is often limited by the permeability of the supports, as well as the mechanical stability of the materials used. As a result, reagents of this type are frequently of lower reactivity than the free ligands or catalysts.

An alternative approach to the 'heterogenisation' of homogeneous reagents is to convert them to a high molecular weight form which is fully soluble and homogeneous, yet separable from the bulk reaction by a process such as precipitation, or by filtration through a nanofiltration membrane.[5] In principle this also provides a means by which the catalysts may be recovered and reused. The attachment of a chiral ligand to a long polyethylene glycol chain, for example, provides a means for the separation of the catalyst from the reaction through precipitation upon addition of ether.[5a–d] In other approaches, functionalised dendrimers have been prepared in which several ligand or catalyst molecules are attached to a single high molecular-weight molecule.[5e,f] A nanofiltration membrane may then be used to separate the products from the catalyst at the end of the reaction. In this paper we describe the synthesis and preliminary studies on a new class of polymer-supported ligands for asymmetric catalysis, which also have the potential for use in a membrane reactor.

## 2. Results and discussion

In a project directed at the synthesis of a general class of polymer support for use in asymmetric catalysis, we reasoned that copolymers of methacrylates would represent an ideal class of material for this application (Figure 1). By combining two monomers in a known ratio in the presence of a chain transfer agent, both the polymer weight and the ratio of monomers can be controlled.[6] A judicious choice of monomers would permit the control of solubility whilst also incorporating a position for attachment of a ligand or catalyst.[7]

For our initial studies into the synthesis of a functionalised polymer, we investigated supported reagents for the catalysis of diethylzinc additions to aldehydes, a valuable asymmetric C–C bond-forming process which can be catalysed by an enantiomerically pure β-amino alcohol,

*Keywords*: soluble polymers; asymmetric; catalyst; ligand; dialkylzinc.
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0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00975-X

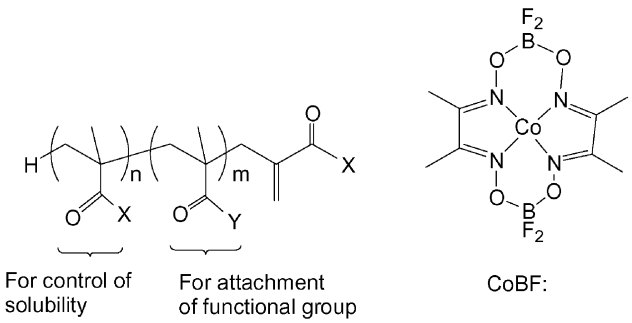
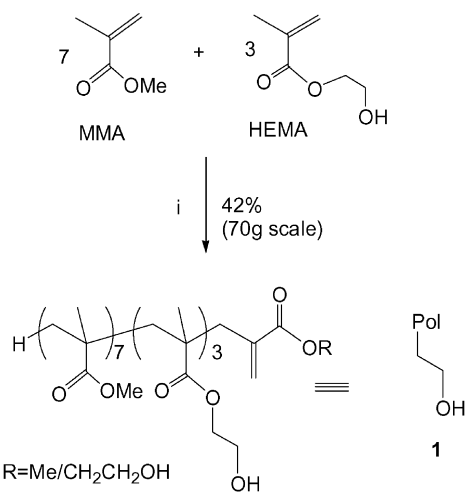



**Figure 1.** Copolymers of methacrylates.

such as a tertiary amine derivative of ephedrine.[8,9] As a polymer support, we examined the use of a copolymer of methyl methacryate (MMA) and 2-hydroxyethyl methacrylate (HEMA) (**1**). An established method was employed to prepare quantities of a 7:3 copolymer of MMA/HEMA using a cobalt-based chain transfer reagent (CoBF; ([bis[μ-[(2,3-butanedione dioximato)(2-)-O:O′]] tetraflurodiborato(2-)-*N*,*N*′,*N*″,*N*‴) to control the overall molecular weight of the product.[6]

Through the use of an appropriate amount of CoBF, it was possible to form polymers with a molecular weight average of ca. 5000 Da in large quantities (>100 g) in a reproducible manner (Scheme 1). As well as using GPC to determine the average molecular weight, the ready solubility of the polymer in a variety of organic solvents permitted a further direct check on its mass to be determined at each stage of the synthesis. Figure 1 illustrates the $^1$H NMR spectrum of a sample of polymer **1**. The peaks for the methylene groups in the HEMA unit are clearly visible, as are those for the methyl ester groups in the MMA, thus permitting a direct measurement of the ratio of monomers in the polymer to be determined. In addition, since the terminal alkene group is clearly visible and integratable on the $^1$H NMR spectrum, this provides a 'double check' on the overall molecular weight average.

The capacity of the polymer for analysis by $^1$H NMR spectroscopy also permits its subsequent functionalisation to be followed closely the same technique. The reaction of **1**




**Scheme 1.** *Reagents and conditions*: (i) cat. AIBN, sodium bis (2-ethylhexyl)sulfosuccinate, 0.06 mol% CoBF, 4 h, rt.

with tosyl chloride and triethylamine, for example, resulted in formation of the tosylated derivative **2**, which could be clearly characterised from the NMR spectrum (Figure 2). The migration of the methylene peak adjacent to the hydroxyl group to lower field following introduction of the electron-withdrawing function serves to indicate that the reaction has gone to completion. In the next step the reaction of **2** with an excess of the sodium salt of *p*-bromophenol resulted in clean substitution to give product **3**. At each stage the product was isolated by extractions in a sequence typical for any organic compound, without the requirement for specialised polymer isolation techniques.

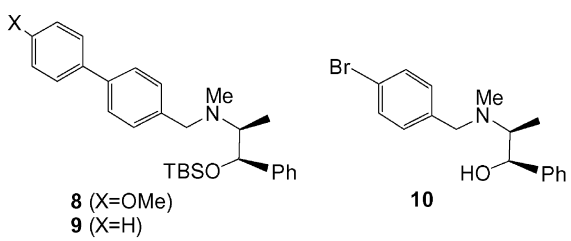
The attachment of a chiral ligand to polymer **3** was our next objective. In order to achieve this we envisaged the use of a palladium-mediated coupling process with the *p*-bromobenzyl derivative **4** of (−)-norephedrine **5**, which was prepared by the two-step route shown in Scheme 2.

Our rationale for the choice of linker was to introduce a separation between the ligand and the polymeric backbone, thus permitting the former to act unhindered by the latter. Following some experimentation (see below) we were able to achieve the coupling process to give **6** in a yield of 54%.[10] Removal of the TBS group from **6** was then completed in 80% yield, providing the required functionalised polymer **7** for use in catalytic reactions (Scheme 2).

As was the case for previous intermediates, the compound could be analysed by proton NMR spectroscopy and the structure confirmed (Figure 3 illustrates the $^1$H NMR spectrum of **6**). The attachment of the ephedrine to the polymer in **6** was supported by the ratio of peaks in the $^1$H NMR (i.e. relative of hydroxyethyl to ephedrine). In addition the spectrum of polymer **6** exhibited a sharp contrast to a spectrum of a 1:1 mixture of **3** with **4**. In the latter spectrum (Figure 4), the ephedrine peaks are clearly quite sharp and well defined, unlike the polymer-bound material in which the peaks are broad, as would be predicted.

Our coupling step was developed through experimentation directed at the synthesis of compounds **8** and **9** via palladium-coupling with **4**. These were formed in 38 and 40% yield respectively.

With polymer **7** in hand, we wished to examine its behaviour towards the control of asymmetric reactions. The reaction which we selected for this investigation was the addition of diethylzinc to benzaldehyde, a reaction which is known to be catalysed by β-amino alcohols, including derivatives of ephedrine (Scheme 3). Although other polymer-supported reagents have been reported for this application, including those of ephedrine, these have focussed on the preparation and use of alternative supported reagents.[9]



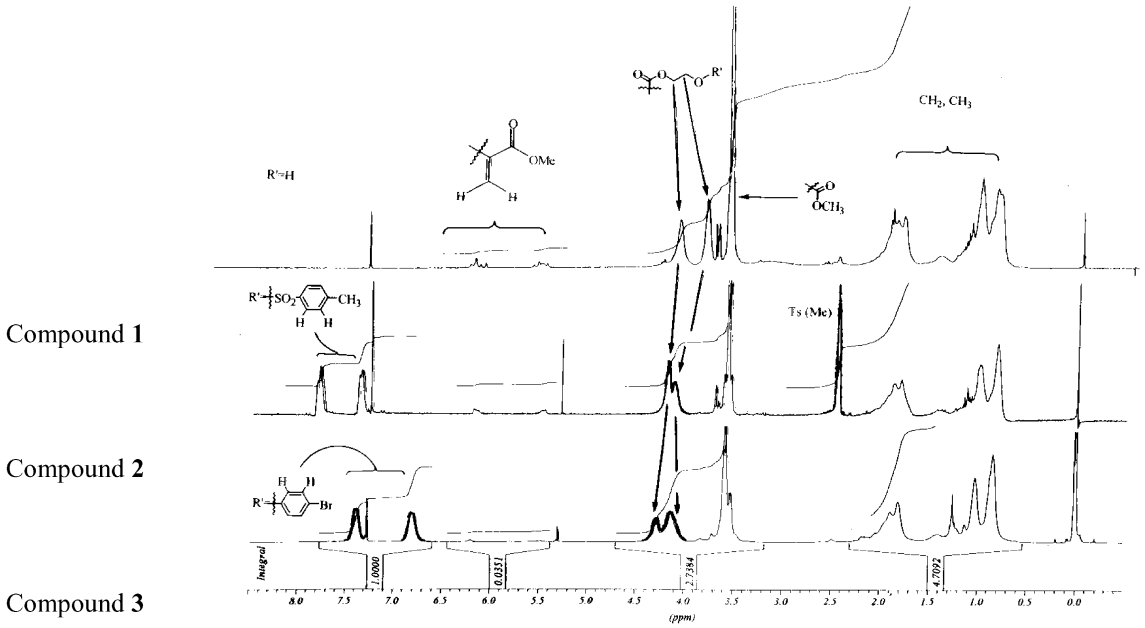
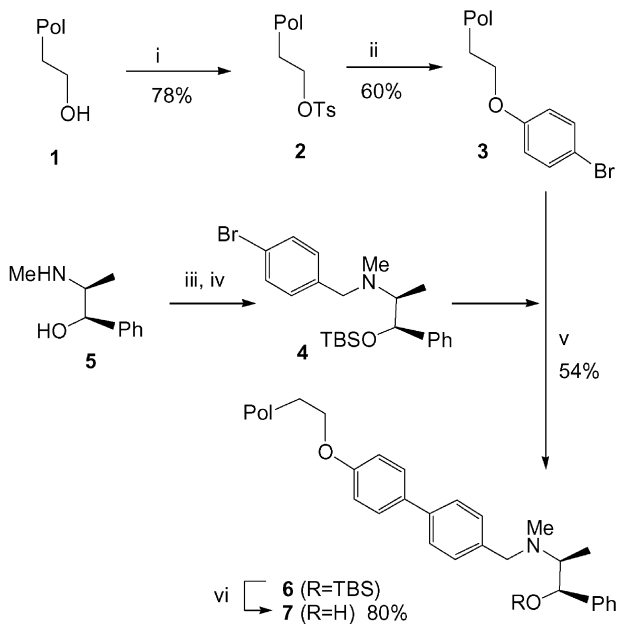



**Figure 2.** $^1$H NMR spectra of polymers.

In our studies, we chose to investigate the non-polymer supported reagents ephedrine **5**, and the desilylated derivative **10** of intermediate **4** to provide a baseline comparison with the supported ligand (Table 1). The initial studies proceeded as expected, with the tertiary amine **10** giving superior results over the secondary amine **5**. The ready solubility of **7** permitted the mol% loading with this material to be calculated relatively easily (details are given in Section 3).




**Scheme 2.** *Reagents and conditions*: (i) TsCl, $Et_3N$, DCM, DMAP, 2 days. (ii) 4-bromophenol, NaH, THF, reflux, o/n. (iii) TBSCl, Imidazole, DMF, reflux, 2 days 91%. (iv) $pBrC_6H_4CH_2Br$, $Et_3N$, THF, 2 days, 40%. (v) **4**, Pd(dppf)$Cl_2$·DCM, THF, KOAc, bis (pinacolato)diboron, 80°C, 2 h; then **3**, $Na_2CO_3$, Pd(dppf)$Cl_2$, THF, 80°C, o/n. (vi) TBAF, THF, 4 h, rt.

As expected, the reaction of diethylzinc with benzaldehyde clearly requires an amino alcohol additive for the reaction to take place. Appropriate control reactions were carried out to provide a baseline; significantly the N-benzylated ephedrine derivative **10** (prepared by desilylation of **4** in 70% yield) gave a product in high e.e. and yield after an overnight reaction, the enantioselectivity being comparable to that achieved with analogous reagents. Also, as predicted, the (1*R*,2*S*) enantiomer of ephedrine, which was used throughout, gave products of *R* configuration.[9] Ephedrine (**5**) itself was also effective but gave products with slightly lower enantioselectivity.

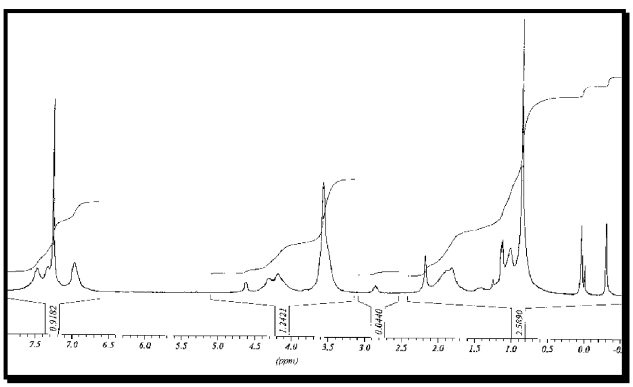
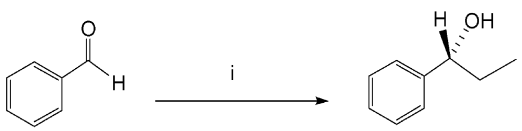



**Figure 3.** $^1$H NMR of **7**.




**Scheme 3.** *Reagents and conditions*: (i) $Et_2Zn$, hexane/toluene, ligand **4**, **5** or **7**, see Table 1.

**Table 1**. Asymmetric catalysis of diethylzinc addition to benzaldehyde

| Solvent | Ligand | Mol (%) ligand | Yield (%) | e.e. (%) | Notes |
|---|---|---|---|---|---|
| Hexane | None | – | 0 | 0 | 0°C o/n |
| Hexane | **5** | 6 | 76 | 23 (*R*) | rt, o/n |
| Hexane | **5** | 6 | 91 | 69 (*R*) | rt, o/n |
| Hexane | **5** | 6 | 74 | 67 (*R*) | rt, o/n |
| Hexane | **10** | 6 | 72 | 80 (*R*) | 0°C, 4 h |
| Hexane | **10** | 6 | 95 | 82 (*R*) | rt, o/n |
| Hexane | **10** | 10 | 94 | 81 (*R*) | rt, o/n (+DCM) |
| Hexane | **7** | 2 | 20 | nd | rt, 30 h |
| Hexane | **7** | 3 | 36 | nd | rt, 30 h |
| Toluene | **7** | 6 | 85 | 70 (*R*) | rt, 30 h |

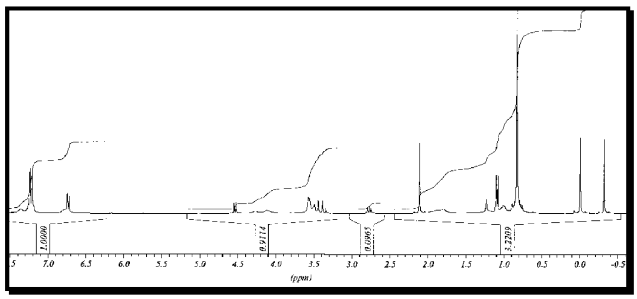


**Figure 4.** $^1$H NMR of **4**/polymer.

Use of the polymer was hindered by solubility problems when used in hexane. Although alcohol product was formed, the yield was low and the product essentially racemic, suggesting that the ligand is unable to interact effectively with the zinc reagent. The problem was less acute in toluene solvent, where an 85% yield of product was obtained in 30 h. The e.e. was low, however, at 70%. There is clearly still room for catalyst improvement, however, the later result does serve to underline the potential of this class of supported reagent in asymmetric catalysis.

In conclusion, in this paper we have described the successful synthesis of a novel type of supported ligand based on poly(methylmethacrylate) copolymers which may, in principle, be tuned for particular applications. Although the actual supported catalyst prepared in this paper is not optimal for the subject application, the results demonstrate the principle of the approach and in particular the ease of solubility and analysis of the products. Work is currently in progress towards the development of these reagents to specific applications.

## 3. Experimental

### 3.1. General

General experimental conditions have been described in a previous publication.[11]

**3.1.1. (1*R*,2*S*)-(−)-2-(Methylamino)-1-phenyl-[(*t*-butyl-dimethyl-silyl)oxy]-propane.** *t*-Butyldimethylsilyl chloride (9.85 g, 65.36 mmol) and imidazole (9.27 g, 136.17 mmol) were added to a solution of (1*R*,2*S*)-(−)-ephedrine (9.0 g, 54.47 mmol) dissolved in DMF (40 mL). The white cloudy reaction mixture was then heated at reflux for 2 days. The resulting yellow coloured reaction mixture was allowed to cool before diluting with diethyl ether (100 mL) and washed with water (200 mL). The water layer was extracted using diethyl ether (100 mL) and the combined organic extracts were dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified using column chromatography (EtOAc/hexane gradient) to give the pure product as a pale yellow oil (13.85 g, 91% yield). The following experimental data was in accordance with published data;[12] $\delta_H$ (250 MHz, $CDCl_3$) 7.52–7.44 (5H, m, Ar), 4.81 (1H, d, $J$=4.9 Hz, CH), 2.91–2.84 (1H, m, CH), 2.58 (3H, s, $CH_3$), 1.22 (3H, d, $J$=6.4 Hz, $CH_3$), 1.10 (9H, s, $CH_3$), 0.12 (6H, d, $J$=6.5 Hz, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 142.9 (*ipso* C), 128.0 (Ar), 127.2 (Ar), 126.8 (Ar), 77.4 ($CH^7$ or CH), 61.6 (CH), 34.0 ($CH_3$), 25.8 ($CH_3$), 18.2 (C), 14.6 ($CH_3$), −4.6 ($CH_3$); *m*/*z* (CI) 280 ($MH^+$), 222 ($MH^+-C(CH_3)_3$), 91, 58; $[\alpha]_D^{22}=-29$ ($c$=1, methanol), lit. $[\alpha]_D^{22}=-31$ ($c$=1, chloroform).[12]

**3.1.2. (1*R*,2*S*)-2-(Bromobenzylmethylamino)-1-phenyl-[(*t*-butyl-dimethylsilyl)oxy]-propane 4.** (1*R*,2*S*)-(−)-2-(Methyl-amino)-1-phenyl-[(*t*-butyldimethylsilyl)oxy]-propane, (12.40 g, 44.44 mmol) was dissolved in THF (50 mL). Triethylamine (8.98 g, 12.37 mL, 88.88 mmol) was added to the solution and stirred for 30 min. Bromobenzyl bromide (13.33 g, 53.33 mmol) was added to the reaction mixture and heated at reflux for 2 days. The resulting thick white reaction mixture was allowed to cool before diluting with EtOAc (200 mL). The reaction solution was then washed with water (150 mL) and the water extracted with EtOAc (100 mL). The combined organic extracts were dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified using column chromatography (EtOAc/hexane gradient) to give the product **4** as a pale yellow oil (7.28 g, 40% yield). $\delta_H$ (250 MHz, $CDCl_3$) 7.28–7.19 (7H, m, Ar), 6.73 (2H, d, $J$=8.3 Hz, Ar), 4.54 (1H, d, $J$=7.4 Hz, CH), 3.47 (1H, d, $J$=13.9 Hz, $CH_2$), 3.36 (1H, d, $J$=13.9 Hz, $CH_2$), 2.82–2.72 (1H, m, CH), 2.18 (3H, s, $CH_3$), 1.09 (3H, d, $J$=6.8 Hz, $CH_3$), 0.83 (9H, s, $CH_3$), −0.16 (6H, d, $J$=7.1 Hz, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 144.8 (*ipso* C), 139.3 (*ipso* C), 130.9 (Ar), 123.0 (Ar), 127.6 (Ar), 127.0 (Ar), 126.8 (Ar), 120.0 (*ipso* C), 77.4 (CH), 64.6 (CH), 58.3 ($CH_2$), 37.2 ($CH_2$), 25.8 ($CH_3$), 18.1 (C), 9.1 ($CH_3$), −4.4 ($CH_3$), −5.0 ($CH_3$); $\mu_{max}$ (liquid film)/$cm^{-1}$ 3088–2790 (CH stretch), 1947–1800, 1591, 1480–1450 (asymmetric CH bend), 1361 (symmetric CH bend), 1257, 1069, 1011; *m*/*z* (CI) 450 ($MH^+Br^{81}$), 448 ($MH^+Br^{79}$), 370 ($MH^+-Br$), 318 ($MH^+Br^{81}-OTBS$), 316 ($MH^+Br^{79}-OTBS$), 280 ($MH^+-C_7H_6Br$), 228 ($C_{10}H_{13}Br^{81}N$), 226 ($C_{10}H_{13}Br^{79}N$), 108, 83, 58; HRMS found $[M+H]^+$ 448.1671, requires 448.1671; $[\alpha]_D^{22}=+2$ ($c$=1, methanol).

**3.1.3. (1*R*,2*S*)-2-(Bromobenzylmethylamino)-1-phenyl-1-propanol 10.** TBAF (0.85 g, 2.68 mmol) was added to a solution consisting of (1*R*,2*S*)-2-(bromobenzylmethyl-amino)-1-phenyl-[(*t*-butyldimethylsilyl)oxy]-propane, **4**, (0.60 g, 1.34 mmol) dissolved in THF (20 mL). The reaction mixture was allowed to stir at room temperature overnight. The yellow reaction mixture was diluted with EtOAc (150 mL) and washed with water (200 mL). The

water layer was extracted using EtOAc (100 mL) and the combined organic extracts were dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified by column chromatography (EtOAc/hexane gradient) to give the pure product **10** as a white solid (0.31 g, 70% yield), mp 55–56°C; $\delta_H$ (250 MHz, $CDCl_3$) 7.41–7.24 (7H, m, Ar), 7.06 (2H, d, $J$=8.5 Hz, Ar), 4.84 (1H, d, $J$=5.2 Hz, CH), 3.54 (2H, s, $CH_2$), 2.96–2.86 (1H, m, CH), 2.17 (3H, s, $CH_3$), 0.99 (3H, d, $J$=6.7 Hz, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 142.6 (*ipso* C), 138.6 (*ipso* C), 131.3 (Ar), 130.2 (Ar), 128.1 (Ar), 127.1 (Ar), 126.2 (Ar), 120.6 (*ipso* C), 74.0 (CH), 63.5 (CH), 58.4 ($CH_2$), 38.5 ($CH_3$), 9.8 ($CH_3$); $\mu_{max}$ (nujol)/$cm^{-1}$ 3178 (OH stretch), 2000–1700, 1248, 1120, 1068; *m/z* (CI) 336 ($MH^+Br^{81}$), 334 ($MH^+Br^{79}$), 318 ($MH^+Br^{81}-H_2O$), 316 ($MH^+Br^{79}-H_2O$), 256 ($MH^+-Br$), 228 ($MH^+Br^{81}-C_7H_8O$), 226 ($MH^+Br^{79}-C_7H_8O$), 202, 200, 178, 148, 122, 108 ($C_7H_8O$); HRMS found $[M+H]^+$ 333.0745, requires 333.0728; $[\alpha]_D^{22}=-35$ ($c$=0.6, methanol).

**3.1.4. (1*R*,2*S*)-2-(4′-Anisylbenzylmethylamino)-1-phenyl-[(*t*-butyldimethylsilyl)oxy]-propane 8.** *Method 1.* (1*R*,2*S*)-2-(Bromobenzylmethylamino)-1-phenyl-[(*t*-butyldimethyl-silyl)oxy]-propane, **4**, (0.14 g, 0.33 mmol), methoxybenzeneboronic acid (0.13 g, 0.83 mmol), tetrabutylammonium bromide (0.11 g, 0.33 mmol) and palladium diacetate (0.004 g, 0.02 mmol) were added to a solution of potassium carbonate (0.11 g, 0.83 mmol) dissolved in water (5 mL). The reaction mixture was heated at reflux for 90 min.[13] The resulting black reaction mixture was allowed to cool before extracting with EtOAc (250 mL). The organic layer was dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified by column chromatography (EtOAc/hexane gradient) to give the pure product **8** as a pale yellow oil, (0.06 g, 38% yield). Experimental data can be found at the end of Method 2.

*Method 2.* (1*R*,2*S*)-2-(Bromobenzylmethylamino)-1-phenyl-[(*t*-butyldimethylsilyl)oxy]-propane, **4**, (0.10 g, 0.24 mmol) was dissolved in DMF (5 mL). To the stirred solution of ephedrine derivative was added dichloro[1,1-bis-diphenylphosphinoferrocene]-palladium(II)·DCM (0.005 g, 0.007 mmol), bis(pinacolato)diboron (0.07 g, 0.27 mmol) and potassium acetate (0.07 g, 0.73 mmol).[14] The orange reaction mixture was heated at 80°C for 2 h. The resulting black reaction mixture was allowed to cool before the addition of bromoanisole (0.09 g, 0.06 mL, 0.48 mmol), dichloro[1,1-bisdiphenylphosphino-ferrocene]palladium(II)·DCM (0.005 g, 0.007 mmol) and sodium carbonate (2 M, 5 mL, 0.66 g). The reaction mixture was then reheated at 80°C overnight.[14] The black reaction mixture was allowed to cool before extracting the product with diethyl ether (150 mL). The organic layer was then washed with water (100 mL) and a brine solution (100 mL). The organic layer was then dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a yellow oil. This was purified by column chromatography (EtOAc/hexane gradient) to give the pure product **8** as a pale yellow oil, (0.06 g, 48% yield); $\delta_H$ (250 MHz, $CDCl_3$) 7.44 (2H, d, $J$=8.7 Hz, Ar), 7.30 (2H, d, $J$=8.1 Hz, Ar), 7.24–7.16 (5H, m, Ar), 6.95–6.89 (4H, m, Ar), 4.58 (1H, d, $J$=7.0 Hz, CH), 3.78 (3H, s, $CH_3$), 3.55 (1H, d, $J$=13.8 Hz, $CH_2$), 3.45 (1H, d, $J$=13.9 Hz, $CH_2$), 2.86–2.77 (1H, m, CH), 2.14 (3H, s, $CH_3$), 1.09 (3H, d, $J$=6.6 Hz, $CH_3$), 0.82 (9H, s, $CH_3$), −0.17 (6H, d, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 158.9 (*ipso* C), 144.9 (*ipso* C), 138.9 (*ipso* C), 138.7 (*ipso* C), 133.7 (*ipso* C), 128.7 (Ar), 128.0 (Ar), 127.5 (Ar), 127.0 (Ar), 126.7 (Ar), 126.2 (Ar), 114.1 (Ar), 77.3 (CH), 64.6 (CH), 58.5 ($CH_2^{10}$), 55.3 (OMe), 37.4 ($CH_3$), 25.8 ($CH_3$), 18.1 (C), 9.0 ($CH_3$), −4.4 ($CH_3$); $\mu_{max}$ (liquid film)/$cm^{-1}$ 3028–2855 (CH stretch), 2054–1700, 1610, 1490–1463 (asymmetric CH bend), 1377 (symmetric CH bend), 1248, 1180, 1062; *m/z* (CI) 476 ($MH^+$), 280, 254, 197; HRMS found $[M+H]^+$ 476.2973, requires 476.2984; $[\alpha]_D^{22}=+9$ ($c$=0.4, chloroform).

**3.1.5. (1*R*,2*S*)-2-(4′-Phenylbenzylmethylamino)-1-phenyl-[(*t*-butyldimethyl silyl)oxy]-propane 9.** (1*R*,2*S*)-2-(Bromobenzylmethylamino)-1-phenyl-[(*t*-butyldimethyl-silyl)oxy]-propane, **4**, (0.88 g, 1.79 mmol), phenylboronic acid (0.54 g, 4.46 mmol), tetrabutylammonium bromide (0.60 g, 1.79 mmol) and palladium diacetate (0.02 g, 0.09 mmol) were added to a solution of potassium carbonate (0.62 g, 4.46 mmol) dissolved in water (20 mL). The resulting reaction mixture was then heated at reflux for 2 h. The resulting black reaction mixture was allowed to cool before extracting with EtOAc (250 mL). The organic layer was dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified by Kugelrohr distillation (0.5 torr, ~200°C) to give the product **9** as a clear oil, (0.35 g, 40% yield); $\delta_H$ (250 MHz, $CDCl_3$) 7.51 (2H, d, $J$=7.0 Hz, Ar), 7.36–7.33 (4H, m, Ar), 7.28–7.19 (6H, m, Ar), 6.97–6.94 (2H, d, $J$=8.3 Hz, Ar), 4.58 (1H, d, $J$=7.2 Hz, CH), 3.57 (1H, d, $J$=13.8 Hz, $CH_2$), 3.46 (1H, d, $J$=14.3 Hz, $CH_2$), 2.86–2.77 (1H, m, CH), 2.15 (3H, s, $CH_3$), 1.10 (3H, d, $J$=6.6 Hz, $CH_3$), 0.82 (9H, s, $CH_3$), −0.15 (6H, d, $J$=7.2 Hz, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 144.9 (*ipso* C), 141.1 (*ipso* C), 139.4 (*ipso* C), 139.3 (*ipso* C), 128.7 (Ar), 128.6 (Ar), 127.5 (Ar), 127.0 (Ar), 126.7 (Ar), 126.6 (Ar), 77.3 ($CH^7$ or $CH^8$), 64.6 (CH), 58.5 ($CH_2$), 37.4 ($CH_3$), 25.8 ($CH_3$), 18.1 (C), 9.0 ($CH_3$), −4.4 ($CH_3$); $\mu_{max}$ (liquid film)/$cm^{-1}$ 3060–2856 (CH stretch), 2000–1670, 1600, 1488–1452 (asymmetric CH bend), 1361 (symmetric bend), 1257, 1061; *m/z* (CI) 446 ($MH^+$), 314 ($MH^+$−OTBS), 280, 224, 198, 167; HRMS found $[M+H]^+$ 446.2886, requires 446.2880; $[\alpha]_D^{22}=+14$ ($c$=0.2, chloroform).

**3.1.6. HEMA/MMA soluble copolymer 1.**[6] Sodium bis(2-ethylhexyl) sulphosuccinate (2.0 g) was added to a 1 L flange flask glass reactor under a nitrogen atmosphere. Water (450 mL) was added to the reactor, heated to 80°C and stirred using a turbine impeller at 150 rpm. 4,4′-Azobis(4-cyanovaleric acid) (2.0 g) was added to the reaction mixture immediately prior to the monomer/catalyst feed. A solution of catalytic chain transfer agent (CoBF) (0.024 g, $6.2\times10^{-5}$ mol) in MMA (114 mL, 1.07 mol)) and HEMA (65 mL, 0.46 Mol) was fed from a Schlenk tube via a FMI pump set at a rate of 3.33 mL $min^{-1}$. The polymerisation was left for 4 h at which time 100% conversion was reached. The solvent was removed from the polymer using an oven set at 150°C to give the polymer **1** as a yellow solid which when ground appeared as a white powder (70.0 g, 42%). $\delta_H$ (250 MHz, $CDCl_3$) 6.18 (m, CH), 5.55 (m, CH), 4.12 (bs,

$CH_2$), 3.85 (bs, $CH_2$), 3.61 (bs, $CH_3'$), 2.01 (bs, $CH_2$), 0.99 (bs, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 178.0 (C═O), 176.8 (C═O), 66.7 ($CH_2$), 60.2 ($CH_2$), 54.2 (C), 51.7 ($CH_3$), 44.7 ($CH_2$), 44.4 ($CH_2$), 18.4 ($CH_3$), 16.5 ($CH_3$); $\mu_{max}$ (nujol)/$cm^{-1}$ 3434 (OH stretch), 1727 (C═O stretch), 1277, 1152, 1075; *m/z* (GPC) $M_n$=2940, PDi=1.78; $T_g$=59°C (inflection point), 49°C (onset), heated from 0 to 160°C at 20°C/min.

**3.1.7. Tosylated HEMA/MMA soluble copolymer 2.** Triethylamine (4.85 g, 6.68 mL, 48 mmol) was added to HEMA/MMA copolymer, **1**, (10.0 g, 3.4 mmol) which was dissolved in DCM (70 mL). Tosyl chloride (9.17 g, 48 mmol) and DMAP (0.50 g, catalytic) were added to the reaction mixture and the reaction was allowed to stir for 2 days. The orange/red solution was concentrated in vacuo to give a yellow solid. The yellow solid was transferred to a sinter funnel and washed with diethyl ether (200 mL) and hexane (100 mL). The pale yellow solid was redissolved in DCM (100 mL) and washed with water (300 mL), dried using magnesium sulfate and concentrated in vacuo to give a pale yellow solid. This was ground using a pestle/mortar and transferred to a sinter funnel and washed further with diethyl ether (200 mL), methanol (200 mL), hexane (100 mL) to give the product **2** as a white powder (10.60 g, 78% yield); $\delta_H$ (250 MHz, $CDCl_3$) 7.81 (bs, Ar), 7.39 (br d, *J*=14.0 Hz, Ar), 6.21 (bs, $CH_2$), 5.47 (bs, $CH_2$), 4.22 (bs, $CH_2$), 4.15 (bs, $CH_2$), 3.60 (bs, $CH_3$), 2.47 (bs, $CH_3$), 1.86 (bs, $CH_2$), 0.99 (bs, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 177.8 (C═O), 176.9 (C═O), 145.1 (*ipso* C), 132.8 (*ipso* C), 130.0 (Ar), 127.9 (Ar), 62.2 ($CH_2$), 62.0 ($CH_2$), 54.2 (C), 51.8 ($CH_3$), 44.9 ($CH_2$), 44.5 ($CH_2$), 21.7 ($CH_3$), 18.7 ($CH_3$), 16.7 ($CH_3$); $\mu_{max}$ (nujol)/$cm^{-1}$ 1730 (C═O), 1598, 1275, 1244, 1177, 1150, 923, 815, 748; *m/z* (GPC) $M_n$=4116, PDi=1.56; $T_g$=51°C (inflection point), 40°C (onset), heated from 0 to 160°C at 20°C/min.

**3.1.8. Synthesis of bromophenyl derivatised HEMA/MMA soluble copolymer 3.** Sodium hydride (0.45 g, 18.79 mmol) was added to THF (30 mL) and allowed to stir for 20 min before the addition of bromophenol (1.63 g, 9.39 mmol). Tosylated HEMA/MMA copolymer, **2**, (1.60 g, 0.40 mmol) was added to the reaction mixture and the reaction allowed to reflux for 48 h. The reaction mixture was allowed to cool before filtering through a sinter funnel and the filtrate concentrated in vacuo to give a pale brown solid. The pale brown solid was redissolved in EtOAc (100 mL) and washed with water (100 mL). The organic layer was dried using magnesium sulfate and concentrated in vacuo to give the crude product as a brown solid. This was triturated using diethyl ether (60 mL) to give the product **3** as a pale brown solid (0.95 g, 60% yield); $\delta_H$ (250 MHz, $CDCl_3$) 7.34 (bs, Ar), 6.82 (bs, Ar), 4.29 (bs, $CH_2$), 4.12 (bs, $CH_2$), 3.59 (bs, $CH_3$), 1.90–1.82 (bs, $CH_2$), 1.18 (bs, $CH_3$), 1.03 (bs, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 177.7 (C═O), 176.4 (C═O), 157.4 (*ipso* C), 132.2 (Ar), 117.2, 116.3, 113.2 (*ipso* C), 65.5 ($CH_2$), 63.1 ($CH_2$), 54.3 (C), 51.7 ($CH_3$), 44.8 ($CH_2$), 44.4 ($CH_2$), 18.6 ($CH_3$), 16.3 ($CH_3$); $\mu_{max}$ (nujol)/$cm^{-1}$ 2400–1800, 1729 (C═O stretch), 1591, 1489, 1273, 1245, 1150, 1066, 824; *m/z* (GPC) refractive index detector $M_n$=5192, PDi=1.36; UV detector $M_n$=4205, PDi=1.48; $T_g$=76°C (inflection point), 63°C (onset), heated from 0 to 160°C at 20°C/min.

**3.1.9. Suzuki coupling between bromophenyl derivatised HEMA/MMA 3 and bromoanisole to give 4′-methoxy-biphenyl functionalised HEMA/MMA copolymer.** This was carried out in order test the coupling process. Bromophenyl functionalised HEMA/MMA copolymer, **3**, (0.40 g, 0.1 mmol), palladium diacetate (0.015 g, 0.039 mmol), tetrabutylammonium bromide (0.25 g, 0.79 mmol) and methoxybenzeneboronic acid (0.30 g, 1.97 mmol) were added to a solution of potassium carbonate (0.27 g, 1.97 mmol) dissolved in water (10 mL). The reaction mixture was heated at 100°C for 90 min.[13] The black reaction mixture was allowed to cool before extraction with EtOAc (200 mL). The organic layer was dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a black solid. This was purified by the addition of methanol (2×100 mL) in which the product was stirred vigorously. The methanol was carefully removed to leave the pure product as a black solid (0.24 g, 57% yield); $\delta_H$ (250 MHz, $CDCl_3$) 7.47 (bs, Ar), 6.96 (bs, Ar), 6.19 (bs, $CH_2$), 5.47 (bs, $CH_2$), 4.31 (bs, $CH_2$), 4.19 (bs, $CH_2$), 3.84 (bs, $CH_3$), 3.59 (bs, $CH_3$), 1.89–1.81 (bs, $CH_2$), 0.84 (bs, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 177.8 (C═O), 176.9 (C═O), 158.7 (*ipso* C), 157.4 (*ipso* C), 133.8 (*ipso* C), 133.2 (*ipso* C), 132.3, 127.7, 116.4, 114.8, 114.2, 65.4 ($CH_2$), 63.4 ($CH_2$), 55.3 (MeO), 54.4 (C), 51.8 (MeO), 44.8 ($CH_2$), 44.5 ($CH_2$), 18.7 ($CH_3$), 16.4 ($CH_3$); $\mu_{max}$ (solid state)/$cm^{-1}$ 2948 (CH stretch), 1723 (C═O stretch), 1606, 1541, 1456, 1240, 1144, 822; *m/z* (GPC) refractive index detector $M_n$=7016, PDi=1.64; UV detector $M_n$=5476, PDi=1.72; $T_g$=69°C (inflection point), 61°C (onset), heated from 0 to 160°C at 20°C/min.

**3.1.10. Suzuki coupling between bromophenyl derivatised HEMA/MMA 3 and (1*R*,2*S*)-2-(bromobenzyl-methyl-amino)-1-phenyl-[(*t*-butyldimethylsilyl)oxy]-propane.** (1*R*,2*S*)-2-(bromobenzylmethylamino)-1-phenyl-[(*t*-butyldimethylsilyl)oxy]-propane, **4**, (0.20 g, 0.45 mmol) and dichloro[1,1-bisdiphenylphosphino ferrocene]-palladium(II)·DCM (0.01 g, 0.013 mmol) were dissolved in THF (10 mL). Potassium acetate (0.13 g, 1.34 mmol) and bis(pinacolato)diboron (0.12 g, 0.49 mmol) were added to the reaction mixture which was heated at 80°C for 2 h. The black coloured reaction mixture was allowed to cool before the addition of bromo derivatised HEMA/MMA copolymer, **3**, (0.30 g, 0.08 mmol), sodium carbonate solution (2 M, 0.53 g, 2.5 mL, 2.24 mmol) and dichloro[1,1-bisdiphenylphosphino-ferrocene]-palladium(II)·DCM (0.01 g, 0.013 mmol). The reaction mixture was then heated at 80°C overnight.[14] The black reaction mixture was allowed to cool before being concentrated in vacuo to give the crude product as a black/grey solid. This was redissolved in EtOAc (200 mL) and washed with water (100 mL). The organic layer was dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a black oil. Methanol (2×50 mL) was added to the crude product and stirred vigorously. The methanol extract was then carefully removed to leave the purified product **6** as a black solid (0.24 g, 54% yield); $\delta_H$ (250 MHz, $CDCl_3$) 7.48–6.98 (bs, Ar), 6.16 (bs, $CH_2$), 4.64 (bs, CH), 4.32 (bs, $CH_2$), 4.20 (bs, $CH_2$), 3.58 (bs, OMe), 2.87 (bs, CH), 2.17 (bs, $CH_3$), 1.86 (bs, $CH_2$), 1.13 (bs, $CH_3$), 1.03 (bs, $CH_3$), 0.87 (bs, $CH_3$), −0.13 (bs, d, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 177.7 (C═O), 176.9 (C═O), 157.8 (*ipso* C), 157.7 (*ipso* C), 144.9 (*ipso* C), 138.8 (*ipso* C), 134.0 (*ipso* C), 128.7,

128.0, 127.5, 126.9, 126.7, 126.2, 114.8, 65.3 ($CH_2$), 64.7 (CH), 63.4 ($CH_2$), 58.5 ($CH_2$), 54.4 (C), 51.8 (MeO), 44.7 ($CH_2$), 37.4 ($CH_3$), 25.8 ($CH_3$), 18.6 ($CH_3$), 18.1 (C), 16.4 ($CH_3$), 9.1 ($CH_3$), −4.7 ($CH_3$); $\mu_{max}$ (solid state)/$cm^{-1}$ 2949 (CH stretch), 1729 (C=O stretch), 1608, 1497, 1456, 1242, 1145, 1060, 832; $T_g$=107°C (inflection point), 99°C (onset), heated from 0 to 160°C at 20°C/min; *m/z* (GPC) sample insoluble in solvent system.

**3.1.11. Removal of the TBS group from the HEMA/MMA supported chiral ephedrine derivative.** HEMA/MMA supported TBS protected chiral ephedrine **6**, (0.10 g, 0.02 mmol) was dissolved in THF (6 mL) before the addition of tetrabutylammonium fluoride (0.35 g, 1.10 mmol). The reaction mixture was allowed to stir for 4 h at room temperature. The black reaction mixture was concentrated in vacuo to give the crude product as a black solid. The crude product was redissolved in EtOAc (150 mL) and washed with water (100 mL). The organic layer was dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a black solid. Methanol (2×50 mL) was added to the crude product and vigorously stirred. The methanol extract was then carefully removed from the sample to leave the pure product **7** as a black solid (0.07 g, 80% yield); $\delta_H$ (250 MHz, $CDCl_3$) 7.48–6.96 (bs, Ar), 4.90 (bs, CH), 4.31 (bs, $CH_2^?$), 4.20 (bs, $CH_2$), 3.58 (bs, MeO), 2.95 (bs, CH), 2.22 (bs, $CH_3$), 1.85 (bs, $CH_2$), 1.00–0.84 (bs, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 177.7 (C=O), 176.9 (C=O), 158.8 (*ipso* C), 157.4 (*ipso* C), 144.9 (*ipso* C), 138.8 (*ipso* C), 134.1 (*ipso* C), 128.7, 128.0, 127.6, 127.0, 126.7, 126.2, 114.8, 64.7 ($CH_2$), 63.2 (bs, CH), 63.0 (bs, $CH_2$), 58.5 (bs, $CH_2$), 54.3 (bs, C), 51.8 (bs, MeO), 44.5 (bs, $CH_2$), 37.8 (bs, $CH_3$), 18.1 (bs, $CH_3$), 16.5 (bs, $CH_3$), 9.1 (bs, $CH_3$); $\mu_{max}$ (solid state)/$cm^{-1}$ 3568 (OH stretch), 2948 (CH stretch), 1725 (C=O stretch), 1607, 1496, 1454, 1240, 1144, 1061, 821; *m/z* (GPC) refractive index detector $M_n$=6753, PDi=1.69; UV detector $M_n$=5155, PDi=1.79; $T_g$=117°C (inflection point), 112°C (onset), heated from 0 to 160°C at 20°C/min.

**3.1.12. Enantioselective addition of diethylzinc to benzaldehyde.** (General Experimental) The selected ligand was added to a cooled solution of diethylzinc (1.1 M in either toluene or hexane, 3 equiv., 2.83 mL, 2.83 mmol) at 0°C and allowed to warm to room temperature. The reaction mixture was allowed to stir at room temperature for 1 h before the addition of benzaldehyde (distilled, 0.10 g, 0.01 mL, 0.94 mmol) and allowed to react under conditions specified in Table 1.[8] On completion of the reaction, methanol (5 mL) was added to the reaction mixture and allowed to stir for 30 min. The resulting cloudy white reaction mixture was concentrated in vacuo to give a white solid. This crude product was redissolved in diethyl ether (150 mL) and washed with $NH_4Cl$ solution (100 mL). The diethyl layer was dried using magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a green oil. This was purified using column chromatography (EtOAc/hexane gradient) to give the pure 1-phenylpropan-1-ol as a pale green oil (mass and % yield for each run given in Table 1). The experimental data was in accordance with published data;[9] $\delta_H$ (250 MHz, $CDCl_3$) 7.39–7.23 (5H, m, Ar), 4.60–4.55 (1H, m, CH), 2.00 (1H, br, OH), 1.89–1.66 (2H, m, $CH_2$), 0.91 (3H, t, *J*=7.6 Hz, $CH_3$); $\delta_C$ (300 MHz, $CDCl_3$) 145.0 (*ipso* $C^6$), 128.8 (CH), 127.9 (CH), 126.4 (CH), 76.4 (CH), 32.3 ($CH_2$), 10.6 ($CH_3$); *m/z* (EI) 136 ($M^+$), 107 ($M^+-C_2H_5$), 91, 77, 59; $[\alpha]_D^{22}$=+47 (*c*=0.7, chloroform) which corresponds to an e.e. of 82%, lit. $[\alpha]_D^{22}$=−45 (*S*-isomer, *c*=5, chloroform).[9a] HPLC conditions, eluent: 5% EtOH/hexane+0.1%$Et_2NH$; wavelength, 254 nm; flow rate, 0.5 mL $min^{-1}$; retention times, $t_R$ for major peak=13.14, $t_R$ for minor peak=14.89. A racemic sample of product supplied by Aldrich was used as a reference.

## Acknowledgements

We thank the EPSRC and GlaxoSmithKline for CASE funding of this project (to C. W. E.) and Professor D. Games and Dr B. Stein of the EPSRC National Mass Spectroscopic service (Swansea) for HRMS analysis of certain compounds. We wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.[15]

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