Short Communication

Ligand-exchange chromatography of alkenes on stationary phases containing palladium(II) complexes

Enantiomeric separation of *trans*-1,2-divinylcyclohexane

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ABSTRACT

Alkenes can be separated from alkanes and alkenes with terminal double bonds from other alkenes using palladium(II) complexes of chelating N,O-ligands supported on polystyrene–divinylbenzene. A palladium complex containing a polymer-bound chiral aminoalcohol has been shown to separate the enantiomers of *trans*-1,2-divinylcyclohexane with a separation factor of 1.3. The resolution is, however, still not satisfactory.

INTRODUCTION

The present high demand for chiral compounds has stimulated the development of chromatographic techniques for the separation of enantiomeric compounds on both analytical and preparative scales [1,2]. Of the various techniques developed, ligand-exchange chromatography, using the complexing properties of grafted metal complexes, has proven particularly useful for the separation of amino acids and their derivatives and for other molecules containing polar functional groups, most commonly on copper(II)-containing resins [3,4]. Considerably less attention has been paid to the separation of enantiomeric alkenes. The separation of such compounds is important in organic chemistry as many biologically active compounds, such as terpenoids and pheromones, contain alkene groups as the only functionality.

A number of examples of enantiomeric separations of simple alkenes by gas chromatography have been reported [5–8], but this technique is often unsatisfactory as a result of the decomposition of compounds that may occur at the higher temperatures required. Therefore the development of liquid chromatographic methods is desirable. To the authors' knowledge, the only examples of the direct separation of the enantiomers of chiral alkenes use acetylated microcrystalline cellulose [9,10] and chiral polyacrylate [11]. Other reported methods rely on the separation of preformed diastereomeric metal complexes, which require subsequent decomplexation [12–16]. Separation on a preparative scale is often required, which is usually more convenient using liquid chromatography. It has now been found that palladium complexes of chiral chelating ligands supported on cross-linked polystyrene can be used for the enantioseparation of alkenes.

EXPERIMENTAL

The structures of the numbered compounds discussed are given in Fig. 1.

Resin 1 [17] and polystyrene functionalized with chiral non-racemic epoxy groups [18] were prepared as described previously using Bonopore (a macroporous styrene–divinylbenzene polymer) beads with an average particle size of 100 μm. Reaction mixtures containing this polymer were shaken to minimize particle breakdown. After each reaction step the polymers were dried under vacuum at ambient temperature for at least 15 h. Tetrahydrofuran (THF) was freshly distilled from benzophenone ketyl radical. IR spectra (KBr) were recorded on a Perkin-Elmer 1710 FT spectrophotometer.

Preparation of stationary phases

Preparation of 3. Polystyrene–divinylbenzene substituted with α-methoxy-β-tosyloxyethyl groups[a] (1.76 g), containing approximately 0.4 mmol of tosyl groups per gram of polymer, was treated with 2-cyano-8-hydroxyquinoline (340 mg) and anhydrous potassium carbonate (312 mg) in N,N-dimethyl formamide (DMF) at 85°C under nitrogen for 48 h. The polymer was filtered off, washed [methanol, water, methanol–water (1:1), acetone, dichloromethane, methanol] and dried. This procedure gave 1.80 g of a polymer (IR 2237 cm^{-1}, weak, CN) of which 1.76 g was treated with a mixture of sulphuric acid (1.2 ml), acetic acid (13 ml) and water (1.2 ml) at 80°C for 24 h and then washed [water, methanol–water (1:1), methanol] and dried to give 1.72 g of quinaldic acid containing polymer 3 (IR 1735 cm^{-1}, COOH).

Preparation of 5. A polymer containing approximately 2 mmol/g (R)-styrene oxide groups [18] (3.83 g) was reacted with (S)-α-phenethylamine (3.57 g) in refluxing methanol for five days, washed (methanol, methanol–water, dichloromethane, methanol) and dried, resulting in 4.20 g of a polymer containing amino alcohol units. To a suspension of this poly-

mer (1.5 g) and sodium hydride (54 mg) in THF was added a solution of *tert*-butanol (133 mg) in THF. This mixture was left to react for 4.5 h at ambient temperature under an atmosphere of nitrogen. Methyl iodide (1.7 g) was added and the mixture left for a further 17 h. The polymer was filtered off, washed (methanol, water, methanol, dichloromethane, methanol) and dried to give 1.50 g of polymer 5.

Preparations of polymer-supported palladium complexes. General procedure. The functionalized polymers were treated with a slight excess of Pd (OAc)$_2$ in THF under nitrogen for 20, 6.5 and 72 h for polymers 2, 4 and 6, respectively, then washed (THF) under nitrogen and dried. All operations were performed in a Schlenck apparatus to avoid the presence of air. The amount of palladium was determined by elemental analyses to be 0.39 and 0.58 mmol/g for resins 2 and 6, respectively, whereas that of resin 4 was estimated to be about 0.1 mmol/g by the increase in weight during the preparation of the complex.

Chromatographic instrumentation

An Omni glass chromatography column (150 mm × 6.6 mm) was used, together with an FMI RPG-400 pump. The sample was injected directly into the PTFE tubing leading to the column and eluted with *n*-hexane–methylene chloride (4:1). No detector was used; the collected fractions were analysed by gas chromatography using a DB-wax column (30 m × 0.25 mm I.D., J&W Scientific). The enantiomeric composition of *trans*-1,2-divinylcyclohexane was determined using a fused-silica capillary Cyclodex-B column (permethylated β-cyclodextrin–DB-1701, 30 m × 0.25 mm I.D., J&W Scientific, column temperature 90°C, carrier gas 120 kPa helium, internal standard *n*-nonane).

The polymeric palladium complex 2 (1.5 g) was allowed to swell in methylene chloride and the slurry was then packed onto the column; complexes 4 and 6 (1.2 and 1.4 g, 10.5 cm, respectively) were dry-packed onto the column.

Liquid chromatographic separation of n-dodecane, trans-5-decene and 1-decene

Complex 2. A solution (0.4 ml) of *trans*-5-decene and 1-decene (1 μl of each compound in 1 ml of solvent) was injected. Fractions of 60 drops were

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[a] Obtained by opening of polymer-supported (R)-styrene oxide (90% enantiomeric excess) with methanol under the influence of boron trifluoride etherate and subsequent treatment with *p*-toluenesulphonyl chloride. This reaction sequence is under further study and will be described in more detail elsewhere.
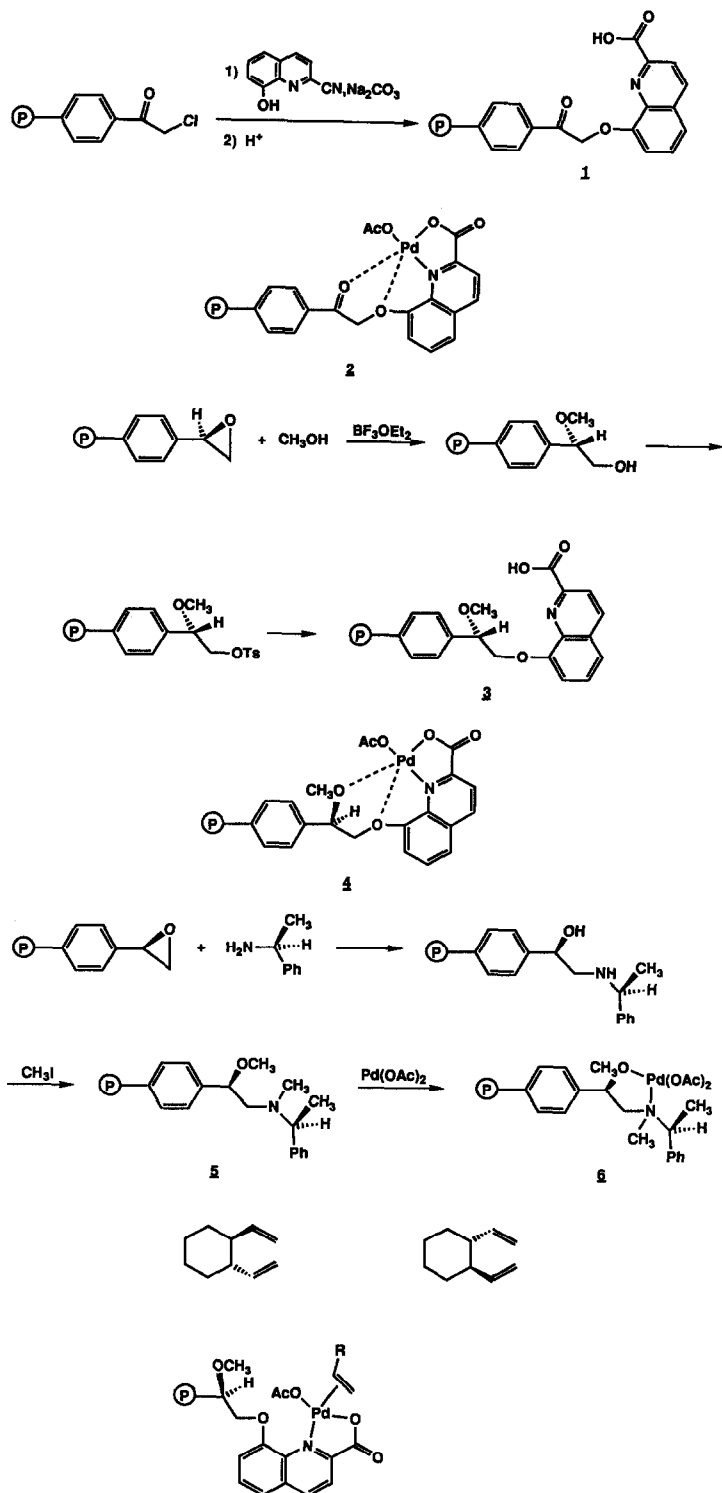
Fig. 1. Structures of compounds 1–6. Ac = Acetyl; Et = ethyl.

collected at a flow-rate of 0.2 ml/min. The retention volumes were: V (trans-5-decene), about 700 drops; V (1-decene), about 800 drops; V (dodecane, obtained independently), about 300 drops.

Complex 4. A solution (0.4 ml) of n-dodecane, trans-5-decene and 1-decene (0.5 µl of each compound in 1.6 ml of solvent) was injected. Fractions of 20 drops were collected at a flow-rate of 0.4 ml/min. V (dodecane), 170 drops; V (trans-5-decene), 210 drops; V (1-decene), 350 drops.

Complex 6. A solution (0.4 ml) of n-dodecane, trans-5-decene and 1-decene (0.5 µl of each compound in 0.8 ml of solvent) was injected. Fractions of 20 drops were collected at a flow-rate of 0.3 ml/min. V (dodecane), 180 drops; V (trans-5-decene), 190 drops; V (1-decene), 270 drops.

Liquid chromatographic separation of trans-1,2-divinylcyclohexane

Complex 4. A solution (0.4 ml) of trans-divinylcyclohexane and n-dodecane (0.5 µl of each compound in 1.6 ml of solvent) was injected. Fractions of 60 drops were collected at a flow-rate of 0.4 ml/min. V (dodecane), 185 drops, V (divinylcyclohexane), 500 drops.

Complex 6. A solution (0.1 ml) of trans-divinylcyclohexane and n-dodecane (2 µl of each compound in 1.6 ml of solvent) was injected. Fractions of 0.1 ml (5 drops) were collected at a flow-rate of 0.4 ml/min. V (dodecane), 178 drops; V (1), 228 drops; V (2), 243 drops, yielding an α-value of 1.3 [V_o = V(dodecane)].

RESULTS AND DISCUSSION

Macroporous polystyrene–divinylbenzene with pendant chloroacetyl groups was reacted with 2-cyano-8-hydroxyquinoline and hydrolysed according to a previously described procedure to yield the polymeric ligand 1 [17]. Treatment of this polymeric ligand with palladium(II) acetate gave a palladium complex, which probably has a square planar structure (2) in which the carboxylate oxygen, the quinoline nitrogen, one of the two remaining oxygen atoms of the ligand and one acetate group take part in the co-ordination to the metal ion. When this polymer was used as a stationary phase for column liquid chromatography, 1-decene was eluted after 5-decene, which in turn was eluted after n-dode-

cane, demonstrating the ability of complex 2 to co-ordinate alkenes, thus offering a method complementary to argentation chromatography [19,20].

A chiral analogue of 2 was then considered in an investigation of the separation of enantiomeric alkenes. For this purpose, polymer-supported (R)-styrene oxide, prepared via the asymmetric reduction of chloroacetylated polystyrene–divinylbenzene [18], was reacted with methanol in the presence of BF$_3$OEt$_2$ to yield a hydroxyether which was tosylated, and the resulting polymer was reacted with 2-cyano-8-hydroxyquinoline and then hydrolysed to yield stationary phase 3. A palladium complex of this ligand (4), with a chiral centre next to the phenyl ring of the polymer backbone, was also found to retain alkenes, the retention times being similar to those of complex 2, taking into account the different concentration of palladium on the two resins. However, no, or little chiral recognition was achieved on the attempted separation of (R,R)- and (S,S)-1,2-divinylcyclohexane using this polymeric complex.

A second ligand (5), containing two asymmetric centres, was prepared by the reaction of polymer-supported (R)-styrene oxide with (S)-α-phenethylamine followed by O- and N-methylation. Subsequent treatment with palladium acetate yielded complex 6. Shorter retention times were observed with this phase compared with the quinoline-substituted resins 2 and 4. It was possible to separate n-dodecane, trans-5-decene and 1-decene with this material, and also to observe enantioselective interactions with the divinylcyclohexanes. The chromatographic system has not been optimized. Although a separation factor (α) of 1.3 was obtained, the chromatographic separation of the enantiomers was far from complete due to the low efficiency of the column (Fig. 2).

The polymer could be used repeatedly without any noticeable change in properties. The amount of palladium complexed to the polymer was determined and was unchanged, even after repeated use.

The co-ordination of an alkene to the polymeric four-co-ordinate palladium complexes probably results in ligand exchange involving the decomplexation of one (or two if two alkenes are co-ordinated) of the initially co-ordinated groups rather than in the formation of five-co-ordinate complexes. The hard neutral oxygen donor is probably exchanged.

This proposed mechanism for the co-ordination of alkenes explains why enantiomeric separation is achieved only with complex **6**, in spite of the strong complexing properties of complex **4**, as on complexation of the alkene, the only chiral centre in complex **4** is a long way from the metal atom.

The functional yields in the reaction sequences leading to polymers **4** and **6** are less than quantitative and all the reactions are probably non-selective, thus giving rise to by-products bound to the polymer. Such by-products may take part in the complexation of palladium and thus disturb the interactions with the molecules being separated. Furthermore, the optical purity of resins **4** and **6** is lower than 100%, as polymeric epoxide with an enantiomeric excess of about 90% was used and the boron trifluoride-catalysed opening of the epoxy ring is known to cause some further racemization [21]. Although enantioselective separation can be achieved even on stationary phases which are not monochiral, optimization of the reaction conditions leading to the present stationary phases is expected to result in polymers with superior properties.

In this study, overlapping of the peaks due to low column efficiency and tailing was observed. Whether these effects are due to the support material or to slow kinetics in the exchange process is not known, but polymers better suited for this purpose will be investigated in future work. The performance of the chromatographic system also needs to be improved. Furthermore, ligands with chirality in close proximity to the metal atom are presently being prepared and their chromatographic properties will be studied.

ACKNOWLEDGEMENTS

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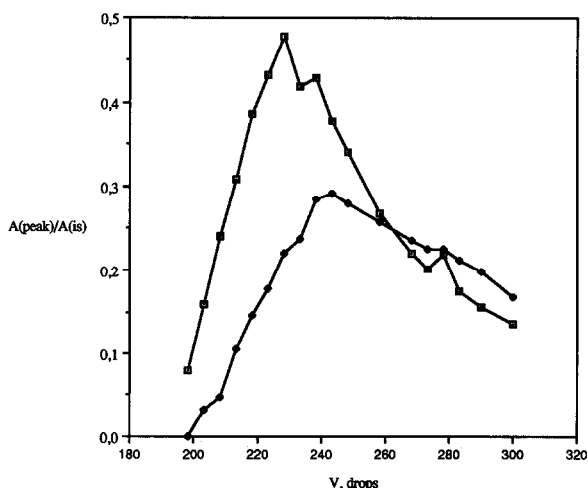18 T. Antonsson, U. Jacobsson, C. Moberg and L. Rákos, *J. Org. Chem.*, 54 (1989) 1191.

Fig. 2. Efficiency of the chromatographic separation determined from gas chromatographic data of the collected fractions. A = Integrated area; is = internal standard; V = retention volume. □ = Peak 1; ◆ = peak 2.

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