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Synthesis and evaluation of a chiral heterogeneous transfer hydrogenation catalyst

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Abstract

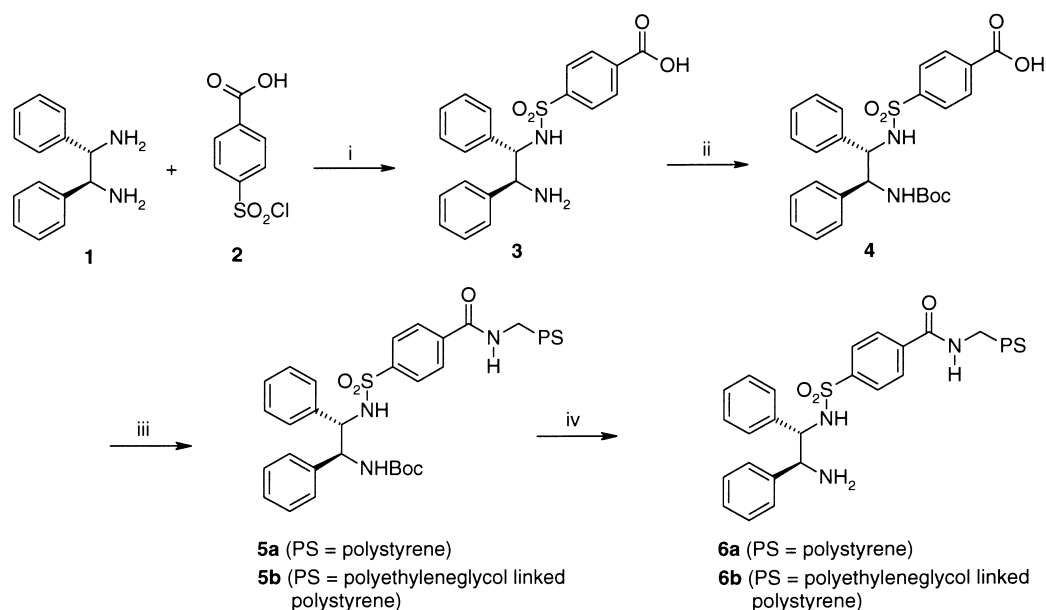
A polymer bound transfer hydrogenation catalyst has been developed based on Noyori's (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine. The ruthenium catalysed reduction of acetophenone was examined and the activity of the catalyst was found to be dependent on the type of polymer used. The catalyst was found to be reusable and retained high ee's when HCO₂H:Et₃N was used as the hydrogen donor. © 1998 Elsevier Science Ltd. All rights reserved.

Hydrogenation of unsaturated groups remains a fundamental strategy for the preparation of chiral molecules. Many catalysts are now available which perform this transformation with high degrees of enantiocontrol especially in the case of olefin and ketone reduction.¹ The most common of these catalysts incorporate chiral diphosphine ligands bound to either ruthenium or rhodium and require high pressure to achieve hydrogenation.² More favourable sources of hydrogen other than molecular hydrogen are found in transfer hydrogenation reactions where isopropyl alcohol or a 5:2 formic acid:triethyl amine azeotrope serve as hydrogen donors.³ Recently, Noyori has discovered that (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine is an excellent chiral ligand for the ruthenium catalysed transfer hydrogenation of aryl ketones, alkynyl ketones and imines giving products with up to 99% ee.⁴ The structures of several intermediate catalytic species have been well characterised and the mechanism elucidated.⁵

We, and others, have recently been interested in the utilisation of solid phase ligands in transition metal promoted asymmetric reactions thereby providing clean, recoverable and reusable chiral catalysts.⁶ Indeed, recovery of such a catalyst by filtration provides an exceptional process improvement over homogeneous catalysis. Not only is it possible to reuse the often expensive ligands but also the potentially toxic transition metal species may be removed from the reaction mixture. A recent publication concerning the immobilisation of the Noyori ligand has prompted us to disclose our own results in this area.⁷ Scheme 1 shows our route to a polymer bound ligand for use in transition metal promoted transfer hydrogenation reactions. The commercially available (1*S*,2*S*) diamine **1** (>99% ee) is first sulfonylated

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with 4-(chlorosulfonyl)benzoic acid **2**. Protection of the free amine functionality as its Boc derivative provides **4** which is ready to be coupled to a solid support. Immobilisation onto both aminomethylated polystyrene and Novasyn Tentagel amino resin is readily achieved using standard peptide coupling reagents. Deprotection of the Boc group occurs readily with 95% TFA and provides ligands **6a** and **6b**. Ligand **6a** contains a standard polystyrene backbone and was found to have a loading of 0.70 mmol/g (by mass increase). Ligand **6b** has a loading of 0.22 mmol/g (by mass increase) and contains a 3000–4000 unit polyethyleneglycol (PEG) spacer unit. The active transfer hydrogenation catalyst was formed in situ by mixing the ligand with an equimolar amount of $[\text{RuCl}_2(p\text{-cymene})]_2$ in the reaction solvent giving orange/red beads for each polymer.



Scheme 1. Reagents and conditions: (i) Et_3N , CH_2Cl_2 , 81%; (ii) $(\text{Boc})_2\text{O}$, NaOH , THF, H_2O , 27%; (iii) DIC, DMAP, Pr_2NEt , DMF, CH_2Cl_2 , aminomethylated polystyrene (for **a**) or aminomethylated PEG polystyrene (for **b**); (iv) TFA, CH_2Cl_2

The effectiveness of these ligands were assessed in the reduction of acetophenone (Fig. 1). Table 1 shows the results for the ruthenium catalysed transfer hydrogenation of acetophenone using isopropyl alcohol as the hydrogen donor (all reactions were performed with 1 mol% catalyst). The homogeneous ligand **3** (entry 1) shows good activity and enantioselectivity (93.5% ee at 93% conversion to (*S*)-1-phenethanol, the absolute configuration was determined by comparison with a standard using Noyori's ligand^{4b}) indicating that the electron withdrawing acid functionality is only slightly detrimental to catalytic behaviour (c.f. 97% ee at 95% conversion after 15 h with 0.5 mol% catalyst for the Noyori ligand^{4b}). Ligand **6a** gave (*S*)-1-phenethanol in 90.5% ee at 88% conversion (entry 2). During the transfer hydrogenation reactions the visual appearance of the polymer is unchanged with the beads remaining orange/red in colour. The catalyst from this reaction was isolated by filtration under nitrogen. Attempted reuse under the same reaction conditions failed to give any reaction. The reason for this deactivation is at this time unclear. Ligand **6b** gives a poor ee and only 9% conversion to (*S*)-1-phenethanol (entry 3). Swelling measurements indicated that the polymer only swells to 1.5 times its dry volume. Thus, the lack of activity may be attributed to the active sites being inaccessible.

Use of a 5:2 formic acid:triethylamine azeotrope⁸ shows more promising results as seen in Table 2. Whereas ligand **6a** is fairly inactive in neat $\text{HCO}_2\text{H}:\text{Et}_3\text{N}$ giving only 21% conversion after 28 h (entry

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