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Synthesis and evaluation of a chiral heterogeneous transfer hydrogenation catalyst

Daniel J. Bayston, Catherine B. Travers and Mario E. C. Polywka *

Oxford Asymmetry International Ltd, 151 Milton Park, Abingdon, Oxfordshire OX14 4SD, UK

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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 HCO_2H:Et_3N was used as the hydrogen donor.

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 then 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

* Corresponding author. E-mail: mpolywka@oai.co.uk

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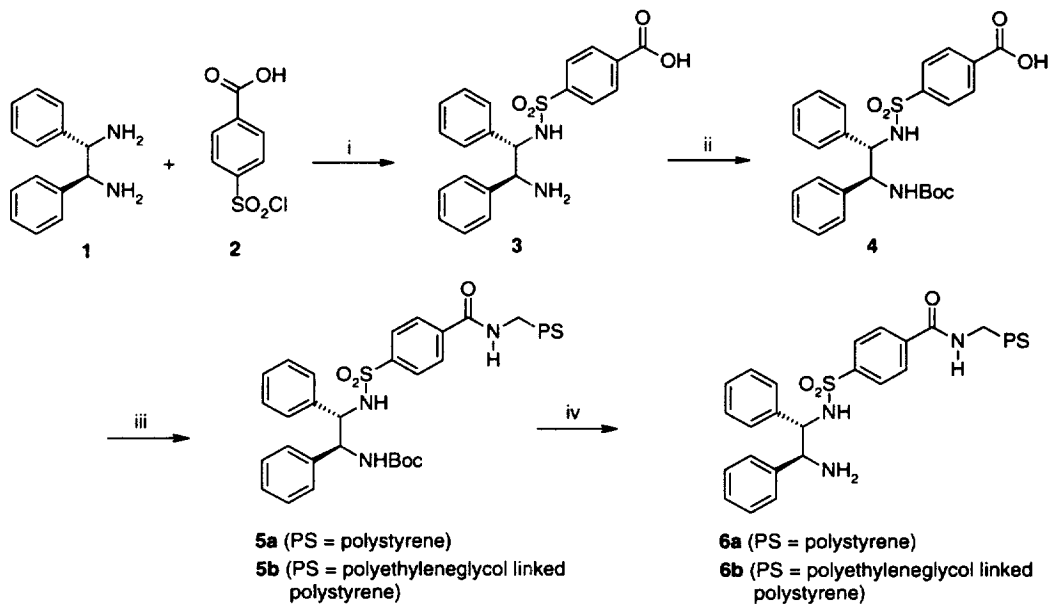
with 4-(chlorosulfonyl)benzoic acid **2**. Protection of the free amine functionality as its Boc derivative provides **4** which is ready to be coupled to a solid support. Immobilisation onto both aminomethylated polystyrene and Novasyn Tentagel amino resin is readily achieved using standard peptide 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 $[RuCl_2(p\text{-cymene})]_2$ in the reaction solvent giving orange/red beads for each polymer.



Scheme 1. Reagents and conditions: (i) Et_3N, CH_2Cl_2, 81%; (ii) $(Boc)_2O$, NaOH, THF, H_2O, 27%; (iii) DIC, DMAP, Pr^i_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 azeotrope[8] shows more promising results as seen in Table 2. Whereas ligand **6a** is fairly inactive in neat HCO_2H:Et_3N giving only 21% conversion after 28 h (entry

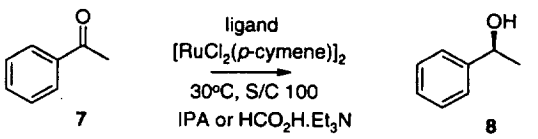


Fig. 1.

Table 1
Ruthenium catalysed transfer hydrogenation of acetophenone using isopropyl alcohol as the hydrogen source[a]

Entry	Ligand	Time (hr)	Conversion[b] (%)	ee[c] (%)
1	**3**	16	93	93.5
2	**6a**	18	88	90.5
3	**6b**	18	9	55.3

[a]All reactions were run at a 0.1M concentration. [b]by NMR. [c]Enantiomeric excesses were determined by HPLC on a Daicel Chiralcel OD column.

Table 2
Ruthenium catalysed transfer hydrogenation of acetophenone using HCO_2H:Et_3N

Entry	Ligand	Solvent	Time (hr)	Conversion (%)	ee (%)
1	**6a**	neat[a]	28	21	91.3
2	**6b**	neat[a]	28	95	96.7
3	**6b** (2nd use)	neat[a]	72	96	97.1
4	**6b**	neat[a]	16 (60°C)	100	92.0
5	**6a**	CH_2Cl_2[b]	18	71	>99
6	**6a** (2nd use)	CH_2Cl_2[b]	21	52	96.2
7	**6a** (3rd use)	CH_2Cl_2[b]	69	65	91.3
8	**6a**	DMF[b]	18	61	94.7
9	**6a** (2nd use)	DMF[b]	21	52	97.9
10	**6a** (3rd use)	DMF[b]	69	80	94.8
11	**6b**	CH_2Cl_2[b]	18	42	51.2
12	**6b**	DMF[b]	18	46	88.2

[a]Reaction was run at 1.0M concentration. [b]Reaction was run at 0.5M and with a HCO_2H:Et_3N to solvent ratio of 1:4.

1), the PEG containing ligand **6b** gave (*S*)-1-phenethanol in 96.7% ee at 96% conversion (entry 2, c.f. 98% ee at 99% conversion after 20 h with 0.5 mol% catalyst for the Noyori ligand[4c]). The catalyst can be reused but shows a drop in activity, taking 72 h to go to 96% conversion with the ee remaining high at 97.1% (entry 3). A third use shows no further activity. The reaction can be pushed to completion in only 16 h by conducting the reaction at 60°C but gives a product with only 92.0% ee (entry 4).

A cosolvent can also be used in these reactions. When CH_2Cl_2 or DMF are used as the cosolvents then polystyrene ligand **6a** (entries 5 to 10) becomes more active than **6b** (entries 11 and 12) with neither solvent being superior. The catalyst can also be reused twice under these conditions giving >50% conversion in each case although with progressively longer reaction times. After three uses the catalyst has lost most of its activity. Addition of more $[RuCl_2(p\text{-cymene})]_2$ to the polymer bound ligand does not regenerate the catalytic activity. The cause of the drop in activity is unknown at the present time. A reaction was performed to ensure that no monomer of the ligand was held as a salt (arising from less than 100% active ester formation during the coupling step) in the polymer. In the presence of formic acid such a salt would be soluble and may have been the ligand involved in catalysis rather than the polymer bound ligand. In this reaction acetophenone was fully reduced with 10 mol% catalyst (1*R*,2*R*)-**6a** in CH_2Cl_2 and HCO_2H:Et_3N (5:2) over 20 h. After the reaction was complete, the polymer bound catalyst was removed by filtration under nitrogen and to the filtrate was added another equivalent of acetophenone and another portion of HCO_2H:Et_3N. Stirring for a further 20 h gave no further conversion

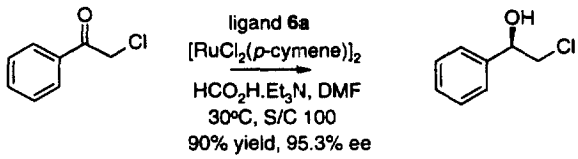


Fig. 2.

to 2-phenethanol indicating that a homogeneous catalyst was not responsible for ketone reduction. This reaction also confirmed that no leaching of catalyst from the polymer was occurring.

We have also used the polymer bound catalyst to reduce 2-chloroacetophenone (Fig. 2). Our best conditions for this transformation were found to be ligand (1*S*,2*S*)-**6b** in DMF using HCO_2H:Et_3N as the source of hydrogen. (*R*)-2-Chloro-1-phenethanol was obtained in 90% yield and 95.3% ee.[9]

In summary, we have developed a practical route to a heterogeneous enantioselective transfer hydrogenation catalyst. The reduction of acetophenone has been examined and a reusable catalyst has been identified. The reduction is best performed neat in HCO_2H:Et_3N for polymer **6a** containing the polyethyleneglycol spacer unit. A cosolvent such as DMF or CH_2Cl_2 is necessary to attain good reactivity for the simple polystyrene based catalyst **6b**. The reactivity of the polymeric catalyst on reuse decreases and after three uses the reaction time for good conversion becomes impractically long although the enantiomeric excesses remain high. Investigation into further reuse of this catalyst and its application to industrially useful transformations is currently in progress.

References

1. (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703. (b) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (c) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799. (d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis* Wiley-Interscience, 1994. (e) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
2. Ojima I. *Catalytic Asymmetric Synthesis* VCH, 1993.
3. (a) Sammakia, T.; Strangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104. (b) Puntener, K.; Schwink, L.; Knochel P. *Tetrahedron Lett.* **1996**, *37*, 8165.
4. (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (b) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (c) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (d) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (e) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.
5. (a) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285. (b) Hashiguchi, S.; Fujii, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 288.
6. (a) UK Patent Application No. 9619684.5. (b) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217. (c) Tas, D.; Thoelen, C.; Vankelcom, I. F. J.; Jacobs, P. A. *J. Chem. Soc. Chem. Commun.* **1997**, 2323.
7. (a) Gamez P.; Dunjic, B.; Pinel, C.; Lemaire, M. *Tetrahedron Lett.* **1995**, *36*, 8779. (b) ter Halle, R.; Schulz, E.; Lemaire, M. *Synlett.* **1997**, 1257.
8. Wagner, K. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 50.
9. Enantiomeric excess was determined by HPLC on a Chiralcel OD column. Absolute configuration was determined by comparison with a standard preparation according to Burns, B.; King, N. P.; Studley, J. R.; Tye, H.; Wills, M. *Tetrahedron: Asymmetry* **1994**, *5*, 801.