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Asymmetric transfer hydrogenation of ketones with a polymer-supported chiral diamine

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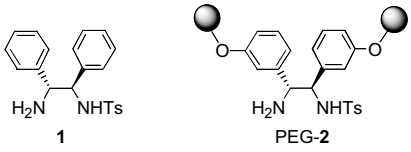
Abstract—A new supported chiral diamine has been developed and shown to be highly effective in ruthenium-catalysed asymmetric transfer hydrogenation of simple aromatic ketones.

Asymmetric transfer hydrogenation of prochiral ketones to provide chiral alcohols has received a great deal of attention in the last decade or so.[1] Of the various chiral catalysts reported, the most notable is TsDPEN **1** (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) coordinated Ru(II) complexes developed by Noyori and co-workers.[2,3] Good to excellent results have been achieved with TsDPEN and related ligands using propan-2-ol or HCOOH-Et_3N as hydrogen sources. As with other homogeneous catalysts, however, these catalysts cannot be easily separated from products and hence present a serious obstacle for synthetic applications. Prompted by this, immobilised DPEN and derivatives have been developed and shown to be efficient in the asymmetric transfer hydrogenation of ketones.[4,5] So far all the immobilisation methods rely on functionalisation of the nitrogen atom, and hence are limited to reactions where the coordinating amino group $-NH_2$ can be modified.[5] Herein we present a new form of immobilised **1**, where **1** is attached to a support via the phenyl rings. This attachment minimises the effects of the support on enantioface selection and makes it easy to modify the amino functionality when necessary. Specifically, we report that the polyethylene glycol-supported (*R*,*R*)-**2** (PEG-**2**) is an efficient ligand for the asymmetric transfer hydrogenation of unfunctionalised ketones, furnishing excellent enantioselectivities and enabling easy catalyst separation. To the best of our knowledge, polymer-supported TsDPEN or, more generally, DPEN (DPEN = 1,2-diphenylethylenediamine), in which the polymer is linked to the phenyl rings, had not been reported before this research was launched.[6]



PEG-**2** was conveniently synthesised from the functionalised, enantiomerically pure 1,2-diphenylethylenediamine (*R*,*R*)-**3**, which was prepared from 3-benzyloxybenzaldehyde (Scheme 1).[7] The diamine (*R*,*R*)-**3** was first monosulfonylated with TsCl to provide (*R*,*R*)-**4** in 75% yield. Boc protection of the diamine (*R*,*R*)-**4**, followed by the reduction of **5** with hydrogen in the presence of 10% Pd/C, afforded (*R*,*R*)-**6** in an almost quantitative yield. The diphenol (*R*,*R*)-**6** was then converted via **7** into PEG-**2** by a nucleophilic reaction with polyethylene glycol 2000 monomethyl ether mesylate (MeO-PEG-OMs) followed by removal of the Boc protecting group. As with other PEG-supported ligands/catalyts,[8] PEG-**2** is soluble in polar solvents such as lower alcohols, water and DMF, but insoluble in solvents of low polarity such as diethyl ether.

The efficacy of PEG-**2** in asymmetric catalysis was assessed in the ruthenium-catalysed asymmetric transfer hydrogenation of simple ketones using a protocol similar to that developed for **1**.[2f] The chiral ruthenium

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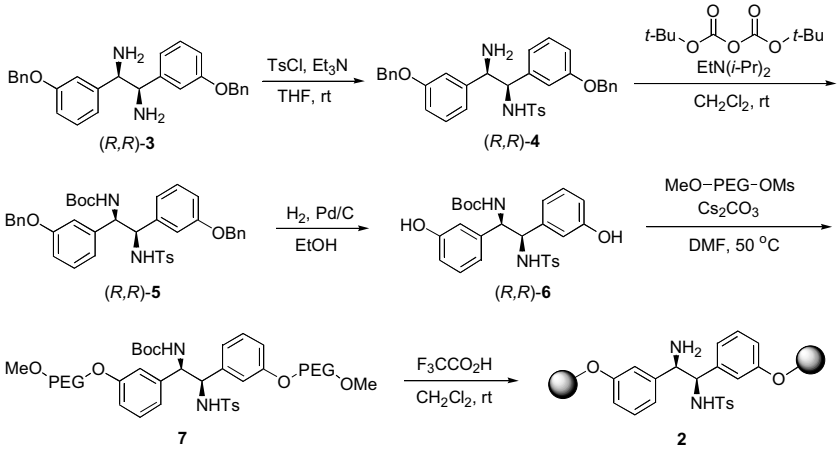
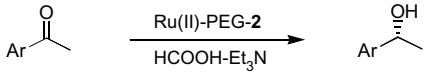


Scheme 1. Synthesis of polyethylene glycol-supported chiral diamine PEG-**2**.

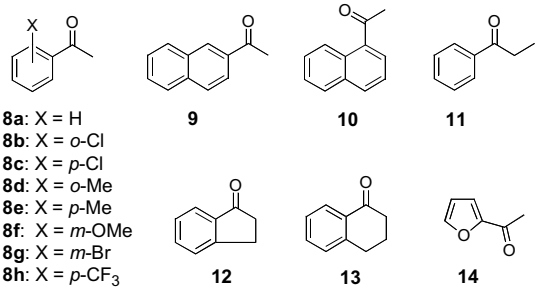
catalyst was prepared by stirring $[RuCl_2(p\text{-cymene})]_2$ with the polymer-supported ligand in dichloromethane at room temperature for 30 min followed by removal of the solvent. Acetophenone **8a** was chosen as substrate for initial testing, and the reaction was carried out by adding the substrate and an azeotropic mixture of HCOOH–Et_3N to the catalyst.[9] With a substrate/catalyst (S/C) ratio of 100 at 40 °C, (*R*)-1-phenylethanol was obtained in 90% yield and 95% ee in a 20 h reaction time (Table 1, entry 1). In comparison, the molecular catalyst, [$RuCl_2$(*p*-cymene)((*R*,*R*)-TsDPEN)], produced an ee of 98% at 28 °C.[2f] Increasing the reaction temperature to 50 °C resulted in a higher conversion and only a slight loss of enantioselectivity (entry 2). At a higher S/C ratio of 250, the conversion decreased considerably, although a higher turnover number was delivered; no change in the ee value was observed (entry 3).

Table 1. Asymmetric transfer hydrogenation of ketones with Ru(II)-PEG-**2** in formic acid–triethylamine azeotrope[a]



Entry	Ketone	Time (h)	Conv. (%)[b]	Ee (%)[b]
1[c]	**8a**	20	90	95 (*R*)
2	**8a**	20	95	94 (*R*)
3[d]	**8a**	20	74	94 (*R*)
4	**8b**	20	100	90 (*R*)
5	**8c**	20	100	90 (*R*)
6	**8d**	20	28	80 (*R*)
7	**8e**	30	75	88 (*R*)
8	**8f**	20	98	90 (*R*)
9	**8g**	20	100	88 (*R*)
10	**8h**	10	100	87 (*R*)
11	**9**	20	99	94 (*R*)
12[d]	**9**	20	98	94 (*R*)
13	**10**	30	71	90 (*R*)
14	**11**	30	66	88 (*R*)
15	**12**	25	71	88 (*R*)
16	**13**	20	99	94 (*R*)
17	**14**	18	100	93 (*R*)

[a] Reactions were performed at 50 °C with ketone (1.0 mmol) in a formic acid–triethylamine azeotropic mixture (1.0 mL) at S/C = 100.
[b] Determined by chiral GC. The alcohol configuration was determined by comparison of the GC retention time or the sign of the optical rotation with literature data.
[c] The reaction temperature was 40 °C.
[d] S/C = 250.



With these results in hand, the asymmetric transfer hydrogenation was then extended to other ketone substrates under the conditions of S/C = 100 and 50 °C. As shown in Table 1, the immobilised chiral Ru(II)-PEG-**2** complex exhibited good to excellent enantioselectivities for various aromatic ketones, including acetonaphthones, substituted acetophenones, propiophenone, 1-indanone and 1-tetralone. Results with the substituted acetophenones **8a**–**h** suggest that electron-withdrawing groups show higher reaction activities and *o*-substitution with bulky and electron-donating groups tends to afford both low conversion and low ee. These observations are reminiscent of those made with the parent molecular analogue, [$RuCl_2$(*p*-cymene)((*R*,*R*)-TsDPEN)] and are in line with the six-membered transition state proposed by Noyori, where a hydride at Ru(II) interacts with the positively-charged carbonyl carbon atom.[2a] In the case of 2-acetonaphthone **9**, the reaction could be run at a higher S/C ratio of 250 without notable loss of conversion and enantioselectivity (entries 11 and 12). The enantioselectivities shown in Table 1 are in general slightly lower than those obtained with the molecular catalyst **1**. A notable exception is seen in the case of 1-acetonaphthone (entry 13), in which PEG-**2** furnished a significantly higher ee value than **1**, the latter giving

rise to an ee of 83%.[2f] 1-Indanone **12** and 1-tetralone **13** could also be reduced to 1-indanol and 1-tetralol with good chiral induction. Furthermore, 2-acetylfuran was cleanly reduced to (*R*)-1-(2-furyl)ethanol in 93% ee without saturating the furan ring (entry 17).

An attractive feature of the present catalytic system lies in the fact that the catalyst can be readily removed from the product by addition of a low polarity solvent. Thus, when the reduction reaction is complete, diethyl ether is added to precipitate the Ru(II)-PEG-**2** catalyst. In the reduction of acetophenone **8a**, ICP analysis of the solution phase showed that less than 0.7 mol% of ruthenium had leached into the solution. Attempts have been made to recycle the catalyst. The experiment was conducted with **8a** using the HCO_2H–Et_3N azeotrope in the presence of an equal volume of water (1 mL); the catalyst was precipitated by introducing diethyl ether and the product removed by syringe. In three consecutive runs, the following conversions (ee's in parenthesis) were observed: 99% (91%), 95% (92%) and 56% (82%). These data suggest that whilst it is possible to recycle the PEG-**2** based catalyst, its stability remains to be addressed.

In summary, we have developed a new polymer supported, soluble chiral diamine ligand and shown its ruthenium complex to be a highly efficient and easily separable catalyst in asymmetric transfer hydrogenation of simple ketones with HCOOH–Et_3N as the hydrogen source. Work is in progress on further applications of this and related diamine ligands and improvement of the recyclability of the catalyst.

Acknowledgements

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9. General procedure: A solution of $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 0.005 mmol) and PEG-**2** (50 mg, 0.012 mmol) in CH_2Cl_2 (1 mL) was stirred for 30 min at room temperature. After removal of CH_2Cl_2 under reduced pressure, ketone (1.0 mmol) and HCOOH–Et_3N azeotrope (1.0 mL) were added. The mixture was degassed three times and then stirred for the appropriate period of time (see Table 1) at 50 °C. The solvent was removed under reduced pressure and Et_2O (10 mL) was added to extract the organic compounds. The conversion and enantioselectivity were determined by GC analysis.