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Polymer-Supported Catalysts: Enantioselective Hydrogenation and Hydrogen Transfer Reduction

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Abstract—Different types of heterogenized catalysts were involved in asymmetric reactions. Hydrogen transfer reduction was performed with amino alcohols derived from poly((S)-(GMA-co-EGDMA or DVB)) and hydrogenation with BINAP grafted onto PEG or copolymerized with isocyanates as ligands. Attempts of catalysts recycling are reported. © 2002 Elsevier Science Ltd. All rights reserved.

For incorporation into pharmaceuticals, agrochemicals, flavours and fragrances, the importance of enantiomerically pure compounds is ever increasing. Thus, the development of chiral technologies, based on the areas of asymmetric synthesis, biotransformation, and resolution that are applicable to industrial processes has become essential.[1] Catalytic asymmetric synthesis often has significant economical advantages over stoichiometric diastereoselective synthesis in the production of enantiomerically pure compounds on an industrial scale. However, in the use of an homogeneous catalysis, a problem of practical importance is encountered, namely that the separation of the catalyst from the reaction products becomes difficult and usually requires special treatment which destroys the catalyst, prohibiting its recycling. One way to solve this problem would be to employ a heterogeneous catalysis, particularly a polymer supported homogeneous catalysis. This method consists in fixing the catalyst to an insoluble solid support in a way that retains the advantages observed in solution. Thus, homogeneous catalysts have been attached to a variety of supports,[2–5] in order to perform the separation of the catalyst from the reaction mixture by filtration, precipitation or extraction. However, the choice of the support is crucial. The active sites must be at the proper location[6] and for organic polymers, a large swelling with the reaction solvent is generally required.

As a part of our research program in asymmetric catalysis, we were interested in the development of new asymmetric reusable polymer-supported catalysts. We herein report asymmetric heterogeneous reduction of a C=O bond by hydrogen transfer or molecular hydrogen. Different kinds of polymers were involved in these reactions. Hydrogen transfer reduction was performed with amino-alcohol derivatives of enantiopure poly((S)-glycidyl methacrylate-co-ethyleneglycol dimethacrylate) (poly(GMA-co-EGDMA)) and poly((S)-glycidyl methacrylate-co-divinylbenzene) (poly(GMA-co-DVB)) for solid–liquid catalysis. Finally, hydrogenation with molecular hydrogen was employed both in solid–liquid and in liquid–liquid biphasic catalyses. The first one was performed with BINAP grafted onto a polyethylene glycol and the second one with polyureas containing the BINAP structure.

Amino alcohols are known to be ligands for asymmetric homogeneous and heterogeneous catalysis for C–C, C–O, and C–H bond formations.[7] This prompted us to use amino alcohol derivatives of enantiopure poly((S)-GMA-co-EGDMA) and poly((S)-GMA-co-DVB) as ligands for catalytic hydrogen transfer reactions. This reaction presents the advantage over the hydrogenation of avoiding the use of pressurized hydrogen, which requires special equipment, but, on the other hand, it is limited to substrates which are not base sensitive.

We have synthesized poly((S)-GMA-co-EGDMA) (1)[8] and poly((S)-GMA-co-DVB) (3) two precursor polymers.

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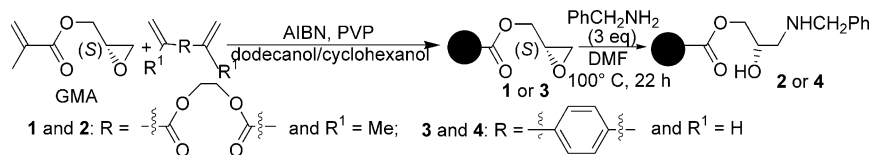
Scheme 1.
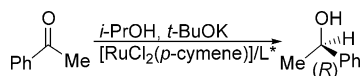
Scheme 2.

They were both formed by radical suspension polymerisation[8] of enantiopure (S)-GMA[8] (30 wt%) with EGDMA or DVB, in the presence of AIBN, with a mixture of cyclohexanol/dodecanol (91/9 wt/wt) and 2% of aqueous polyvinylpyrrolidone (PVP) as stabilizer (Scheme 1). A 500 mL glass reactor equipped with a stirring anchor runing at 400 rpm was used. Chiral beads of **1** and **3** were isolated by sifting, with particle size of about 106–300 μm (granulometric analysis). They present, respectively, a specific surface area of 82 and 275 m^2/g (BET analysis), with, for both of them, 2.11 mmol/g of epoxyde function (elemental analysis). Thus, the specific surface area greatly depended on the nature of the crosslinker. The subsequent epoxide ring opening with benzylamine, according to the procedure of Sherrington,[9] led to polyamino alcohols **2** and **4** (Scheme 1).

Polymers **2** and **4** were involved in hydrogen transfer reduction of acetophenone. This reduction was performed at 80 °C, in the presence of $[RuCl_2(p\text{-cymene})]_2$ as precursor and isopropanol as hydrogen source. The reaction was carried out with a ratio acetophenone/Ru/amino alcohol polymer unit/t-BuOK of 20/1/4/5 (Scheme 2). The results are summarized in Table 1.

The best conversion and enantioselectivity were obtained with amino alcohol **2** (run 1), which was derived from **1** (crosslinker: EGDMA). Ru-complex **4** (crosslinker: DVB) was less efficient, only 41% conversion and 37% ee were observed (run 2), although its specific surface area is higher than **2**, showing that the nature of the crosslinking agent is crucial.

Table 1. Ruthenium catalysed transfer reduction of acetophenone

Run	Polyamino alcohol functionalization[a]		Catalytic reaction	
	Ratio (%)	mmol/g	Conv (%)[b]	Ee (%)[b]
1 **2**	69	1.20	94[c]	70[c]
2 **4**	61	1.04	41[d]	37[d]

[a]Determined by elemental analysis.
[b]Determined by GC on a Supelco β-dex 225 (30 m × 0.25 mm). Reaction time:
[c]3 h.
[d]40 h.

An attempt to recycle, by filtration, the ruthenium complex **2** led to a marked decrease in activity from 94 to 27% and lowered selectivity from 70 to 54%.

On the other hand, reduction with molecular hydrogen presents the advantage over the hydrogen transfer reduction to use neutral conditions which are required for acid- or base-sensitive substrates. Of the many catalysts developed for transition metal-catalyzed asymmetric hydrogenations, the Ru–BINAP complexes have become the most extensively applied, both in academia[10] and industry,[11] since they promote highly enantioselective transformations over a wide range of substrates with high substrate to catalyst ratios. Until recently, few examples of polymer-supported BINAP catalysts have been reported in the literature.

For solid/liquid catalysis, Bayston[12] reported the heterogenization of BINAP by anchoring a monofunctionalized derivative on a polystyrene resin via an amide bond. For the Ru-catalyzed hydrogenation of β-ketosters and functionalized olefins, it afforded high enantioselectivities (70–100%) and activities (70–100% yield) with low substrate/catalyst ratio (S/C~200). More recently, Pu[13] prepared the *poly*-(BINAP), by copolymerization of a BINAP derivative with 1,4-dibromo-2,5-dialkylbenzene. Complexed with rhodium, it gives >95% conversion and enantioselectivities from 40 to 75% for the reduction of dehydroamino acid derivatives (S/C = 50). The reduction of methylarylketone was performed in the presence of (R,R)-diphenylethylene diamine (DPEDA) leading to 90% ee and conversions up to 99%. Chan has recently prepared soluble chiral polyester[14] and dendrimer BINAP derivatives[15] as Ru-ligand for the hydrogenation of acrylic derivatives. In the case of the supported Ru-polyester catalyst, 65–100% conversion and 88–95% ee with a ratio S/C of 200 were found. For the Ru-dendrimer catalyst, with S/C of 125, total conversion and similar ee were observed.

In order to heterogenize BINAP, we synthesized *diam*-BINAP.[16] Its subsequent polymerization with di[4-isocyanatophenyl]methane and diisocyanatotoluene afforded polyureas **5** (degree of polymerization (DP) of 15, average molecular weight ($\overline{M}$) of about 14000 g/mol) and **6** (DP: 10, $\overline{M}$~12,000 g/mol), respectively, which present pseudo-C_2 symmetry (Scheme 3).

These polyureas, soluble in aprotic solvents (DMF and DMSO), were used as ruthenium ligands for asymmetric hydrogenation of methylacetoacetate, in methanol (Scheme 4). The active cationic ruthenium complex involved in this reduction was prepared in methanol
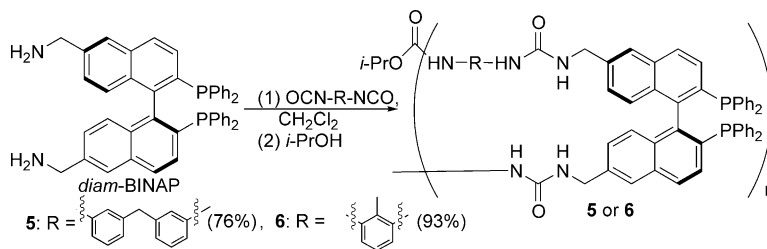
Scheme 3.
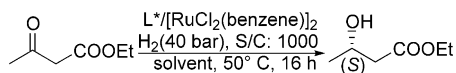
Scheme 4.

Table 2. Hydrogenation of methylacetoacetate with Ru-complexes of **5**, **6** and BINAP

Run	L*	Use	Conv.[a]%	Ee[a]%
1	**5**	1	100	99
2	**5**	2	53	99
3	**6**	1	100	99
4	**6**	2	100	99
5	**6**	3	100	99
6	**6**	4	100	99
7	BINAP	1[b]	100	>99

[a]Determined by chiral GC analysis on Lipodex A (25 m×0.25 mm) column.
[b]Homogeneous conditions.

from the [RuCl$_2$(benzene)]$_2$, according to the Noyori's method.[17] The results are summarized in Table 2. For the first use (runs 1 and 3), both polyureas gave similar activities and enantioselectivities. However, Ru-complex **6** gave better efficiency than Ru-complex **5** upon recycling by simple filtration (runs 2, 4–6). This difference could be explained by the rigidity of the active site which is crucial for the selectivity and the stability of the catalytic system, as notified by Pu.[18]

Another way for recycling catalysts consists of using biphasic catalytic systems, particularly water-organic solvents. There is an increasing interest in asymmetric hydrogenation using water-soluble catalysts.[19] This water solubilization is mainly due to the introduction of either a sodium sulfonate, a quaternary ammonium function into their backbone or by grafting the ligands

onto a water soluble polymer such as polyacrylic acid sodium salt or PEG. Only few examples of water-soluble systems derived from BINAP have been reported.[19]

We synthesized the water-soluble PEG derivative of *diam*-BINAP (**7**) (Scheme 5) (number of PEG units: 110–113, $M = 5000$ g/mol) according to the Veronese procedure.[20] A mixture of mono- and disubstituted PEG *diam*-BINAP derivatives (mono/di: 70/30) was formed as shown by MALDI-TOF analysis.

We first involved the reduction of the C=C bond of itaconic acid under homogeneous conditions (Scheme 6) using a water ruthenium polymer-supported catalyst (RuCl$_2$-**7**) derived from BINAP (prepared in DMF from the [RuCl$_2$(benzene)]$_2$ precursor according to the procedure of Noyori).[21] After 16 h, 91% of conversion with 19% ee were observed. This catalytic complex is less efficient than the corresponding BINAP one, in methanol (homogeneous conditions), which led to total conversion and 88% ee.

We then tested biphasic substrate/water reduction of C=O bond. The hydrogenation of acetophenone was performed using (RuCl$_2$-**7**) in the presence of (S,S)-DPEDA. Compared to the similar BINAP complex which gave, in homogeneous conditions (*i*-PrOH as solvent), total conversion with 85% ee, (RuCl$_2$-**7**)–DPEDA led to excellent conversion (99%) with encouraging ee (21%) (Scheme 7). It is noteworthy that DPEDA has a synergetic effect and permit the reduction of various aromatic ketones.[22]
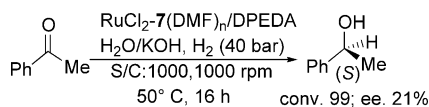
The reduction of ethyl acetoacetate in water (Scheme 4) with (RuCl$_2$-**7**) affords, after careful extraction of the water-soluble product with pentane, 100% of conversion and 75% ee but, after recycling, only 20% conversion and 56% ee were obtained. The former ee value was less important and the conversion was identical to
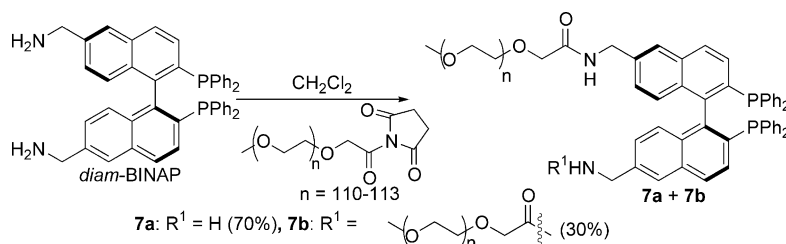
Scheme 5.
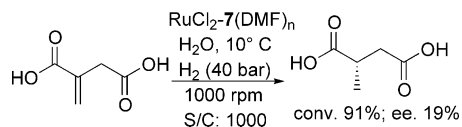
Scheme 6.

Scheme 7.

that obtained in the homogeneous system using (RuCl$_2$–BINAP), in methanol (100% ee and conversion).

We have shown that polymer-supported ligands such as amino alcohol resins and polymers derived from BINAP were able to reduce C=C or C=O bonds in biphasic catalytic conditions. Moreover, the heterogeneization of BINAP into polyurea was successful and allowed the efficient asymmetric hydrogenation of carbonyl compounds.

From the synthetic point of view, in most cases, the use of these Ru-based ligands led to high conversions and in some cases good enantioselectivities. On the other hand, they offer easy separation of the catalyst from the reaction mixture and their reuse is, in some cases, effective without any loss either of conversion or enantioselectivity.

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