Homogeneous-Supported Catalysts for Enantioselective Hydrogenation and Hydrogen Transfer Reduction

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Dedicated to Prof. R. A. Sheldon on the occasion of his 60th birthday.

Abstract: Several and recent approaches for the homogeneous-supported catalysts in the fields of hydrogenation using BINAP ligand derivatives and hydrogen transfer reduction with diamines or aminoalcohol ligands are reviewed in order to point out efficient recyclable catalytic systems.

Keywords: BINAP derivatives; catalytic hydrogenation; hybrid ligands; hydrogen transfer reduction; polyaminoalcohol; polythioureas; polyureas

1 Introduction

The need to develop effective methods for enantioselective synthesis is becoming ever more important as only a single enantiomer of a racemic bioactive compound is generally required for pharmaceuticals,[1] agrochemicals,[1,2] flavour,[1,3] or fragrance substances.[1,3] As these fine and specialty chemicals are manufactured to high and well defined standards of purity compatible with the desired performance, industry has focused its attention mainly on product innovation and less on process development until recently. The formation of wastes causing a high level of pollution is mainly due to the use of stoichiometric methods.

It is for this reason that industry requires innovative catalytic technologies which lead to improved yield, high regio- and enantioselectivity of the desired compound and, if possible, non-corrosive and less toxic and/or hazardous reacting chemicals or solvents, as pointed out by Sheldon.[4] Therefore, enviro-economics will become one of the driving forces for the chemical industry. Among the possible technologies, asymmetric catalysis provides powerful and unique advantages, mainly the production of a large quantity of a chiral product using a catalytic amount of a chiral source. From an economic and technical point of view, heterogeneous catalysis is preferable to homogeneous catalysis because of the improved handling, separation and recycling possibilities.[5] The use of heterogeneous catalysts dispensing the conventional and waste-generating reagents and achieving high atom economy, a concept developed by Trost,[6] has significantly contributed to the development of new methodologies.[7]

Two main types of enantioselective heterogeneous catalysts have emerged: heterogeneous catalysts with demonstrated catalytic activities that are rendered chiral by modification with a chiral auxiliary[8] and homogeneous catalysts with demonstrated enantioselectivity and activity modified to become heterogeneous.[9] For this latter case, the homogeneous catalyst is heterogenised by anchoring it onto a solid support, i.e., an inorganic material[10] or an organic polymer.[11] This methodology was already reported in the 1970's by Kagan[12] and Stille[13] and, since that time, various catalytic reactions have been performed such as hydroformylations, dihydroxylations, epoxidations and hydrogenations, etc.[14] On the other hand, liquid-liquid two phase systems could be employed. The catalyst is

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Marc Lemaire was born in 1949 in Paris. He was employed for several years in the pharmaceutical industry as a technician, and then he obtained the engineer level (CNAM Paris 1979) and his Ph. D. degree at the Paris VI University (Professor J. P. Guetté; "New chlorinating reagent"). In 1983 he obtained a postdoctoral position in the University of Groningen (The Netherlands; Professor R. M. Kellogg; "Thiamacrocyles as ligand for asymmetric catalysis"). He returned to Paris and obtained an assistant position at CNAM, and then he became a professor at the University of Lyon. His group is working in five main areas: (1) heterogeneous catalysis in fine chemistry, (2) asymmetric catalysis, (3) separation science, including new ligands for liquid-liquid extraction, new ionoselective materials, new complexing agents for nanofiltration-complexation systems, (4) organic conductors, including poly(thiophenes) and poly(pyrroles), and (5) deep desulphurisation of gas oil.

Christine Saluzzo was born in Lyon (France). She studied chemistry at the University Claude Bernard Lyon I, where she completed doctoral work on fluorosulphuration and -selenation of unsaturated compounds in order to obtain vinylic and allylic fluorides, under the supervision of André Laurent (1989). She subsequently moved to the Texas A & M University in USA, in a postdoctoral position, where she studied the oxidation of alkanes by modification of the GOAGG^{II} system in Derek H. R. Barton's group. In 1990, she obtained a permanent position as "Maître de Conférences" at the University of Lyon I, in the group of R. Amouroux. Then in 1998 she joined the group of Marc Lemaire. Since September 2002, she was appointed to a professorial position in the University of Le Maine, in Le Mans (France). Her research interests involved the preparation of organic compounds for various applications: chiral ligands for homogeneous and heterogeneous catalysis and substituted THF as synthons for bioactive molecules.

retained in one phase and the other phase is used for delivery and/or removal of reactant.[15]

The aim of this paper is to discuss the contribution of new catalysts for biphasic solid/liquid or liquid/liquid catalysis to the field of hydrogenation of C=O and C=C bonds and hydrogen transfer reduction of ketones. The results are analysed in comparison to the results in the literature for similar systems.

Different types of ligands were involved for each of the different reactions. For hydrogenation, heterogenised BINAP ligands were used. Hydrogen transfer reductions were carried out with heterogeneous catalysts such as a sulphonamide-supported Merrifield resin, polyureas and polythioureas or poly(glycidyl methacrylate-*co*-ethylene glycol dimethacrylate) [poly(GMA-*co*-EGDMA)] aminoalcohol derivatives.

2 Reduction with Molecular Hydrogen

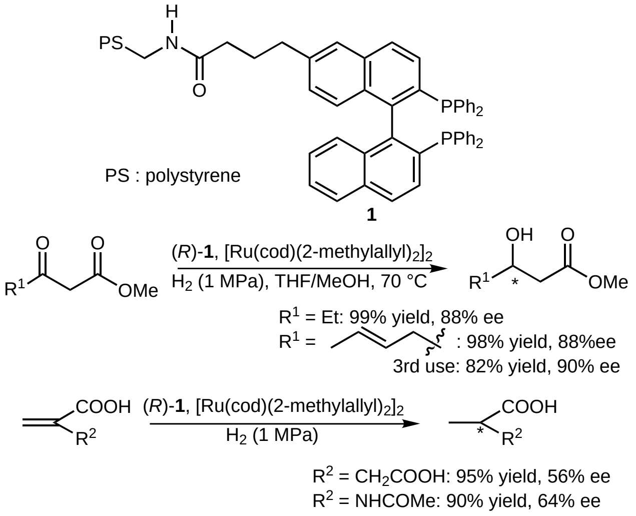
2.1 Polymer-Supported BINAP for Homogeneous or Solid/Liquid Biphasic Catalytic Systems

Reduction with molecular hydrogen presents the advantage over hydrogen transfer reduction to use neutral conditions useful for acid- or base-sensitive substrates. Thus, this method is largely employed for industrial applications.

The chiral ligands first employed in this asymmetric reaction were chiral phosphines. Among them, the most famous one is BINAP. Complexed to metals and using several types of additives (i.e., diamines), it has provided excellent results in homogeneous asymmetric catalysis, particularly for the reduction of various prochiral substrates such as ketones, ketoesters and imines. Nevertheless, its industrial applications remain relatively rare (for example, industrial processes for the synthesis of key intermediates of antibiotic carbapenems and antibacterial Levofloxacin).[16]

In 1996, Jacobs[17] reported the heterogenisation of BINAP-based complexes by enclosing in a polydimethylsiloxane (PDMS) membrane, leading to a perfectly regenerable, catalytically active membrane. A membrane-enclosed Ru-(*S*)-BINAP complex was then tested for the hydrogenation of methyl acetoacetoacetate. The best results were obtained in polyethylene glycol as solvent, at 60 °C affording 70% ee with 0.16 h^{-1} TOF. Enantioselectivity was enhanced by incorporation of *p*-toluenesulphonic acid into the membrane[18] allowing a decrease in temperature (40 °C). Thus, 92% ee with 41.6 h^{-1} TOF were observed.

In 1998, Bayston[19] involved the incorporation of the BINAP framework onto an insoluble polymer, thus providing a heterogeneous catalyst that could be isolated from the reaction medium. Mixed with $[Ru(cod)(2\text{-methylallyl})_2]_2$ and HBr in acetone, this



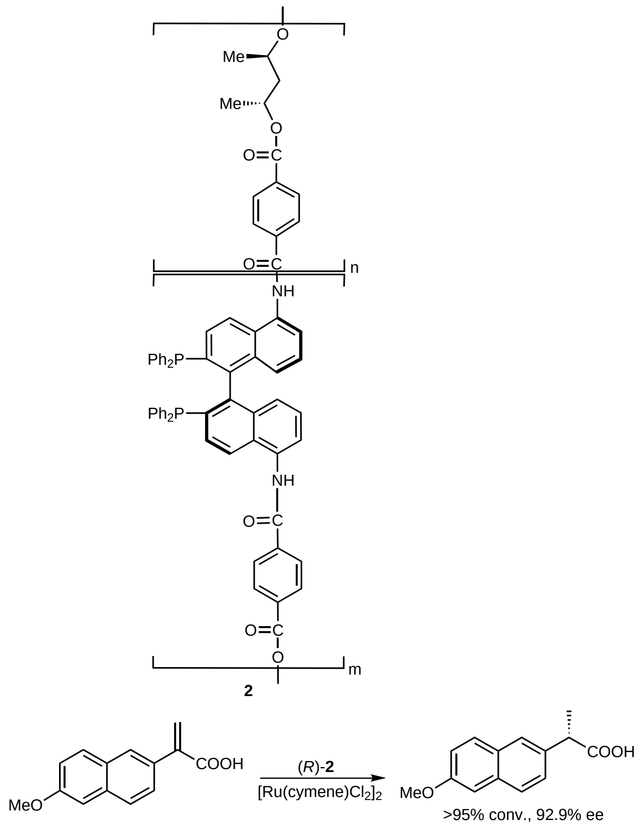
Scheme 1. BINAP grafted on polystyrene.

ligand **1** (Scheme 1), which is not C_2 symmetrical, is able to reduce β-ketoesters with conversions of about 80–100% using a substrate/catalyst ratio of 500 and obtaining ee values of up to 90%. Unsaturated compounds were also hydrogenated. Substituted acrylic acid and itaconic acid were hydrogenated with up to 90% conversion and ee of about 60%.

Some recycling attempts have been performed by collecting the insoluble catalyst and subjecting it once again to the same hydrogenation conditions, showing that, although reaction times are extended, the yield and enantioselectivity remain high.

Recently, Noyori[20] has used Bayston's ligand (**1**, Scheme 1). In order to obtain more efficient catalysis, the 2-propanol must be mixed with DMF (1/1). The presence of DMF allows the material to swell, favouring the mass transfer and thus the conservation of TOF during the recycling. The reaction exhibited a turnover number (TON) as high as 12,300/batch, i.e., a total of 33,000 after repeated uses. Reductions of α-acetonaphthone and β-ionone led to 100% conversion from the first to the 11th use with 97% ee for the first substrate and up to 80% ee for the second one. In the case of 2,4,4-trimethyl-2-cyclohexenone excellent conversion and ee were found from the first to the 9th use (up to 93% ee). Compared to the homogeneous BINAP system, this polymer catalyst showed a somewhat longer induction period, but high TOF's are reached even after several repeated recyclings.

Chan[21] has chosen a strategy which includes the BINAP in the main chain of a polymer *via* copolymerisation of 5,5′-diamino (*R*)-BINAP, (2*S*,4*S*)-pentanediol and terephthaloyl chloride (polymer **2**, Scheme 2). Complexed with ruthenium, it was used in the synthesis of naproxen by hydrogenation of the corresponding acrylic acid derivative. Under homogeneous conditions (methanol/toluene 2/3), with a substrate/catalyst ratio (S/C) of 200, Et_3N/substrate of 1/1 and hydrogen pressure of 10.8 MPa, conversions up to 95% and enantiomeric excess of about 90% were obtained.

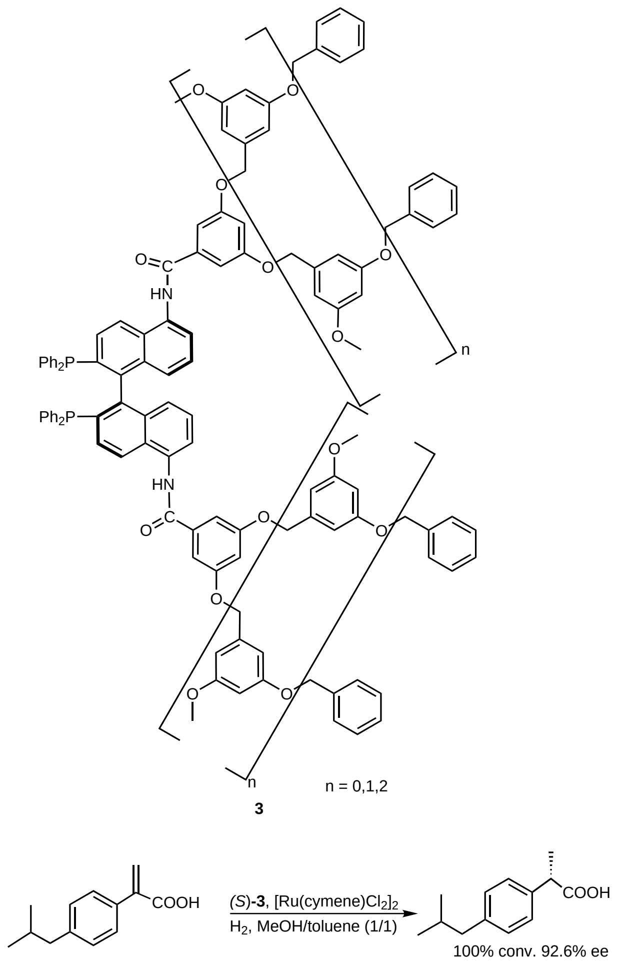


Scheme 2. BINAP in the backbone of insoluble polyester.

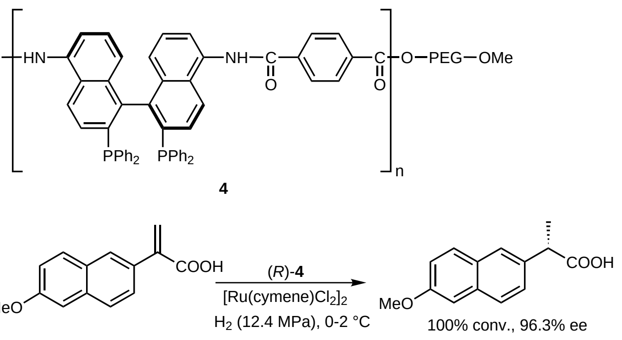
A soluble dendrimer **3** (Scheme 3) was also prepared from 5,5′-diamino-BINAP.[22] Complexed to ruthenium with a substrate/catalyst ratio of 125, it was involved in the formation of ibuprofen. When n = 2, 100% conversion with 92.8% ee were observed. Compared to the monomeric Ru-BINAP, the chiral polyester-supported **2** and the dendrimer **3** ruthenium catalysts showed higher catalytic activity. This behaviour is probably due to the steric effect of the polyester chains or the naphthyl groups of the dendrimer that affect the dihedral angle of the binaphthyl rings of the BINAP part.

After precipitation of the catalyst from the reaction mixture with methanol, recycled polyester-supported **2** and dendrimer **3** catalysts were found to maintain the same activity and enantioselectivity; the former for more than ten cycles and the latter for three cycles. Moreover, in the case of the polyester ligand, it seems that stereogenic centres on the polymer backbone did not significantly influence the asymmetric catalysis, probably indicating that a stable catalyst conformation was not achieved.

Recently, in order to improve the efficiency of such non-dendritic polymers, Chan[23] has synthesised a new and more rigid BINAP-containing polyamide polymer **4**



Scheme 3. BINAP dendrimer.



Scheme 4. BINAP in the main chain of soluble polymer.

(Scheme 4) through the direct polycondensation of 5,5′-diamino (*R*)-BINAP, terephthaloyl chloride and using polyethylene glycol monomethyl ester (MeO-PEG) as a co-support.

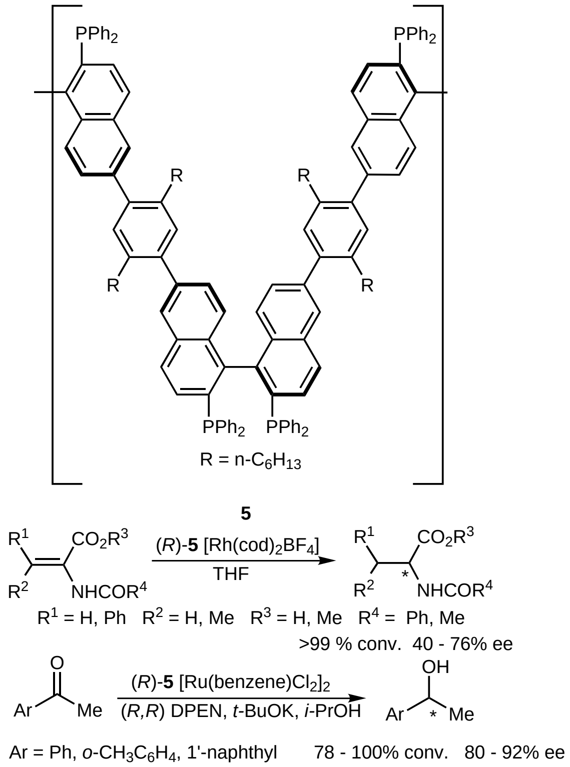
For the hydrogenation of 2-arylacrylic acids, performed in methanol, under homogeneous conditions, with a substrate/catalyst ratio of up to 1000, 100% conversion was obtained with enantiomeric excesses close to 90%. It was noticed that this MeO-PEG-supported BINAP afforded slightly higher enantioselectivities at lower reaction temperatures and at higher hydrogen pressures (6.9 or 12.4 MPa), in comparison to the parent monomeric Ru(BINAP) catalyst. Moreover, the **4**-Ru catalyst was easily separated from the reaction mixture by solvent precipitation and the recovered catalyst afforded no loss of enantioselectivity upon reuse.

Pu[24] has developed a polymer-based chiral ligand **5** (Scheme 5) by incorporation of BINAP into a more rigid polymer. This type of polymer does not modify the steric and electronic environments of the BINAP moiety. *Poly*(BINAP)-Rh catalyst (**5**, Scheme 5) was involved in asymmetric hydrogenation of dehydroamino acid derivatives with excellent conversion ($>99\%$) and with enantiomeric excesses from 30% to 76% in the presence of 2 mol % of catalyst under 0.2 MPa of hydrogen at room temperature. Similar results were obtained with the monomeric Rh-BINAP complex equivalent for the hydrogenation of *Z*-methyl α-(benzamido)cinnamate (75% ee and conversion up to 99%). For this substrate, the recovered catalyst, obtained by filtration, exhibited the same enantioselectivity.

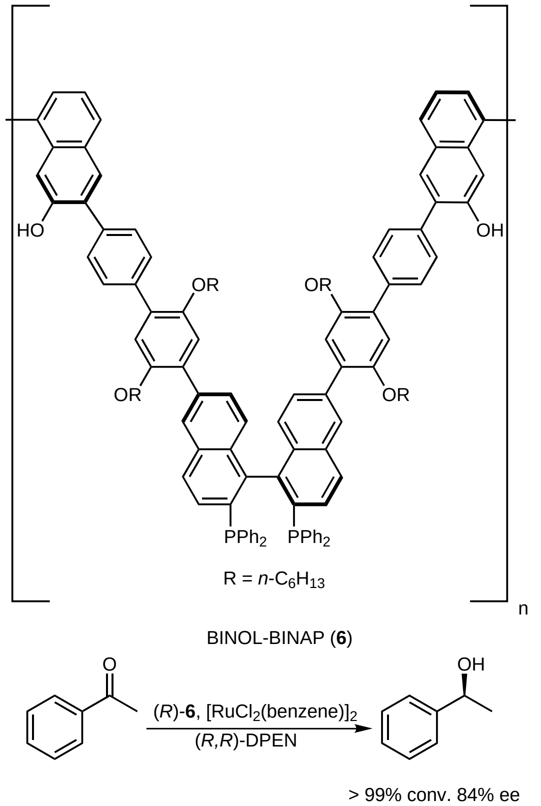
The hydrogenation of methyl aryl ketones was also performed. A *poly*(BINAP)/DPEN/Ru complex, similar to that reported by Noyori[25] [i.e., (BINAP)/DPEN/Ru complex] was used. With 0.5 mol % of the complex, the polymeric system led to 80–90% ee and to 100% conversion. It was noted that the recovered polymer catalyst exhibited the same enantioselectivity as the original catalyst.

Pu's group also synthesised a new bifunctional ligand[26] (BINOL-BINAP **6**, Scheme 6) in order to evaluate the hydrogenation of acetophenone. The reaction was conducted under H_2 (1.2 MPa) in toluene/isopropyl alcohol, 1/1, in the presence of *t*-BuOK, at room temperature and a BINAP unit to substrate ratio of 1/4900. The hydrogenation was completed with up to 99% conversion and 84% ee.

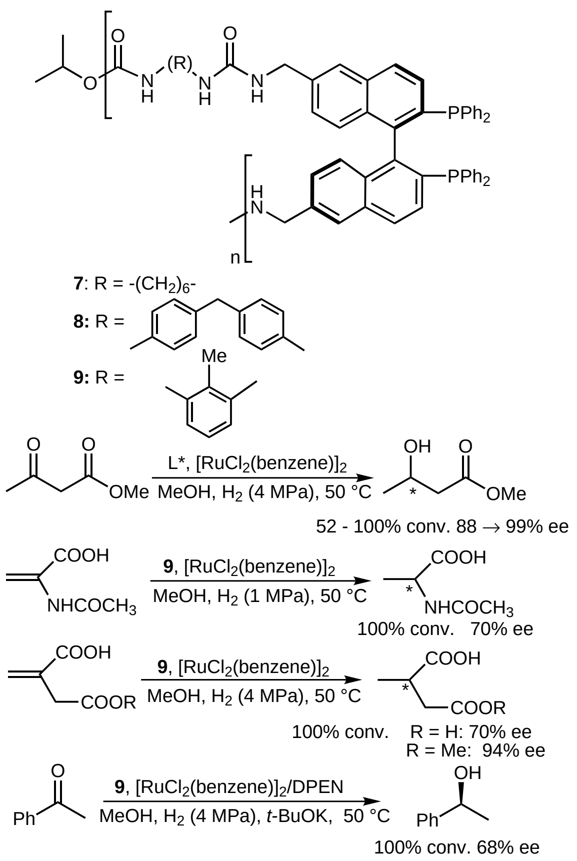
At the same time, our group heterogenised BINAP by its inclusion in the backbone of a polymer through *diam*-BINAP (6,6′-diaminomethyl BINAP).[27] This was carried out by reaction of the two amino groups with diisocyanates: diisocyanatohexane, 4,4′-methylenebisphenylisocyanate and 2,6-diisocyanatotoluene, leading respectively to ligands **7**, **8** and **9** (Scheme 7).[28] These compounds have a pseudo C_2 symmetry. They were employed in asymmetric hydrogenation of methyl acetoacetate in methanol, at 50 °C with a hydrogen pressure of 4 MPa and a substrate/catalyst ratio of 1000. The best results were achieved with the *poly*-NAP (**9**)-Ru complex, for which 100% conversion is observed with 99% ee even after four recyclings. With the **8**-ruthenium complex, excellent results were obtained for the first cycle, but for the second a significant decrease in conversion occurred (from 97 to 53%).With the **7**-



Scheme 5. BINAP in the main chain of insoluble polymer.



Scheme 6. BINOL and BINAP in the backbone of a polymer.



Scheme 7. BINAP in the main chain of polyureas.

ruthenium complex, the conversion was only 52% with 88% ee. This showed that the more rigid the spacer, the more efficient is the catalyst. In other words, the conformation of the catalyst must be as stable as possible.

The most efficient ligand, *poly*-NAP (**9**), was also used in the ruthenium-catalysed hydrogenation of olefinic substrates. With α-acetamidoacrylic acid (S/C = 100, $P_{H_2} = 1$ MPa) and methyl α-acetamidocinnamate (S/C = 100, $P_{H_2} = 4$ MPa), 100% conversion and about 70% ee were observed in both cases. Itaconic acid and its methyl ester (S/C = 100, $P_{H_2} = 4$ MPa) were quantitatively reduced with, respectively, 70% and 94% ee.[27] Here too, the results are similar to those obtained by the BINAP in the ruthenium-catalysed hydrogenation of these substrates. The Noyori system,[25] *poly*-NAP/DPEN/Ru, was also used for the reduction of acetophenone in the presence of *t*-BuOK in *i*-PrOH as solvent. With a substrate/catalyst ratio of 1000, 100% conversion and only 68% ee were obtained. This result shows that, in this case, *poly*-NAP is less enantioselective than BINAP itself for which 87% ee was obtained with a substrate/catalyst ratio of 500.[29]

In most of the cases mentioned above, the efficiency and the selectivity of the polymeric complexes are similar to those of the monomeric BINAP complex equivalent. This implies that the structure of the polymer backbone has almost no influence in the asymmetric induction in hydrogenation catalysis. Even Bayston's ligand (**1**, Scheme 1) showed similar activities to BINAP itself, indicating that the loss of C_2 symmetry may not be detrimental to the enantioselectivity, although the break in symmetry is distal from the active catalytic site.

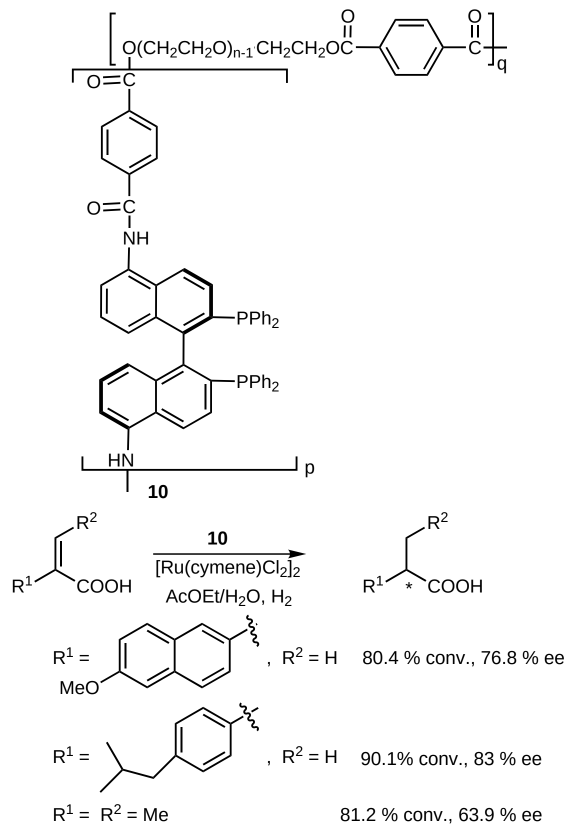
As Pu and our group have observed, both steric and electronic environments of the monomeric catalyst can be maintained in the rigid and sterically regular polymer (the more rigid the ligand, the more efficient is the catalyst).

With these considerations, it could be deemed that the attachment of the polymer in positions 5,5′ or 6,6′ of the BINAP still promotes as high enantioselectivities as BINAP itself in the hydrogenation reaction.

2.2 Hydrosoluble BINAP Derivatives for Aqueous/Organic Biphasic Catalytic Systems

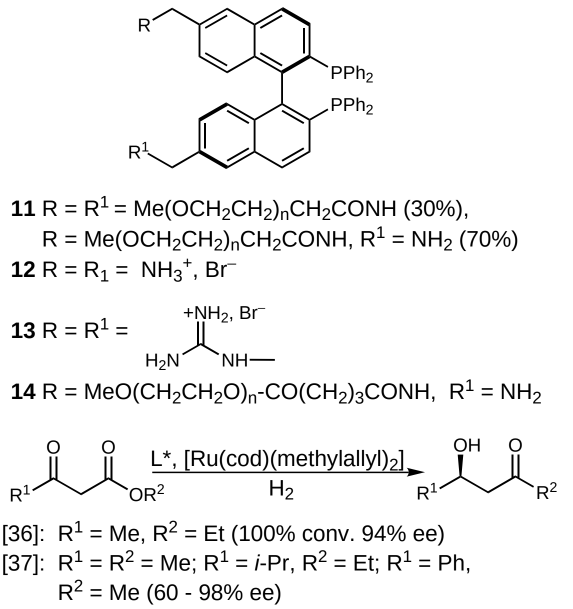
Another system that has been used during the last few years consists in the synthesis of several chelating water-soluble organometallic complexes for asymmetric catalytic hydrogenation in aqueous/organic biphasic systems.[30] This system, involving a simplified separation of catalysts from products by decantation, affords both economic and environmental benefits. Some biphasic catalytic systems are already applied in industry [e.g., for Rh-TPPTS (TPPTS: sodium triphenylphosphine trisulphonate)[31]]. In order to render the catalytic complex water-soluble, methods such as the introduction of sodium sulphonate,[32] quaternary ammonium functions[33] or grafting onto a water-soluble polymer (e.g., polyacrylic acid sodium salts[34] or PEG[35]) were employed. In the case of BINAP, sulphonate, PEG, ammonium and diguanidinium derivatives have been reported.

To the best of our knowledge, one of the first hydrosoluble BINAP catalytic system, a supported aqueous-phase (SAP) Ru-BINAP-4-SO_3Na, was synthesised by Wan and Davies.[36] In order to hydrate the SAP catalyst, impregnation of water from an organic phase (ethyl acetate) was used for the hydrogenation of 2-(6′-methoxy-2′-naphthyl)-acrylic acid to naproxen. Maximum activity and ee were observed when water-saturated ethyl acetate was used to hydrate the SAP catalyst, with a TOF of 18.2 h^{-1} and a 70% ee at room temperature under 9.3 MPa of hydrogen pressure. For the same reaction with a biphasic system (ethyl acetate/water) a TOF of 0.34 h^{-1} was found. It seems that the enantioselectivity of the SAP catalyst (96.1% ee in methanol under homogeneous conditions) is limited by the intrinsic enantioselectivity of the ruthenium complex in water (up to 70% ee). Recycling of the catalyst was achieved without any leaching of ruthenium into the organic phase.



Scheme 8. PEG BINAP.

In 2000, Chan[37] synthesised PEG-BINAP **10** (Scheme 8), an amphiphilic polymer-supported BINAP containing polyethylene groups, for use in ruthenium base-catalysed hydrogenation of α,β-unsaturated carboxylic acids and 2-aryl- or 2-alkylacrylic acids. This ligand was synthesised through polycondensation of 5,5′-diaminoBINAP with polyethylene glycol and terephthaloyl chloride. The PEG bound Ru-BINAP catalyst led to the highest activity and enantioselectivity in the presence of triethylamine as an additive. Biphasic catalytic reactions were carried out in ethyl acetate/H_2O with S/C = 125. With *trans*-2,3-dimethylacrylic acid, 81.2% conversion and 63.9% ee were observed with TOF of 50.8 h^{-1}, i.e., both activity and ee are lower than in the homogeneous system using methanol as solvent (TOF: 92.2 h^{-1}, 86.4% ee). However, the biphasic reaction rate is higher than the rate of the monophasic aqueous reaction. It was shown that no hydrogenation reaction occurred in organic or in aqueous phases. This behaviour is probably due to the formation of micelles by the amphiphilic catalytic system itself, providing a microenvironment where the hydrogenation reaction takes place. Drastic increase of conversion and selectivity occurred when water was replaced by ethylene glycol as the polar phase. In the case of arylacrylic acids, similar results were observed.

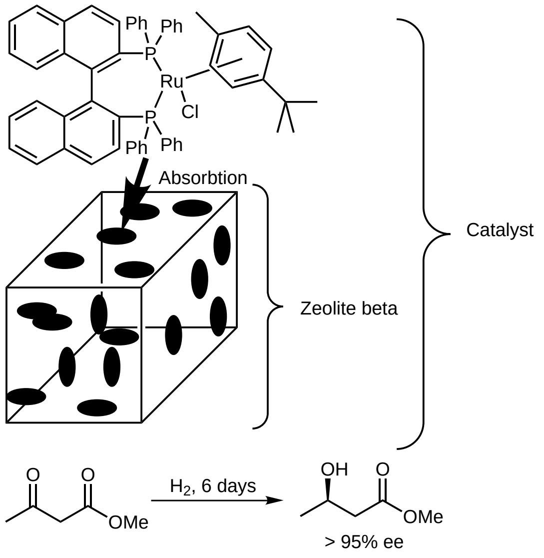


Scheme 9. Hydrosoluble derivatives of *diam*-BINAP.

In 2001, our group prepared a water-soluble PEG derivative (**11**) of *diam*-BINAP (6,6′-diaminomethyl-BINAP) (Scheme 9).[38] In fact, a mixture of the mono- and disubstituted PEG-*diam*-BINAP derivatives (mono/di ratio: 70/30) was formed. The ruthenium complex mixture was then used in the reduction of ethyl acetoacetate affording, after extraction of the water-soluble product with pentane, 100% conversion and 75% ee but, after recycling, only 20% conversion and 56% ee were obtained (S/C = 1000, 50 °C, 4 MPa). The *diam*-BINAP hydrobromide (**12**, Scheme 9) led, for the same reduction, to 100% conversion from the first to the fourth use and ee up to 99% till the third use and 83% for the fourth (S/C: 1000, 50 °C, P_{H_2}: 4 MPa).

Later on, Genêt[39] achieved the synthesis of three hydrosoluble ruthenium(II) catalysts: Ru *digm*-BINAP (**13**, Scheme 9) with a guanidinium function, Ru PEG bound BINAP type Ru-*Am*-BINAP (**14**, Scheme 9) and Ru-**12**, all derived from *diam*-BINAP.[27,29] They were evaluated in the hydrogenation of β-ketoesters (P_{H_2}: 2 MPa) under homogeneous conditions. For the ruthenium ammonium (**12**-$RuBr_2$) or guanidinium (**13**-$RuBr_2$) complexes, both activity and enantioselectivity were excellent when ethylene glycol was used as solvent. However, **12**-$RuBr_2$, a catalyst formed *in situ* from *diam*-BINAP, gave only moderate ee (about 60%) in water. Excellent activity was observed in ethylene glycol using **13**-ruthenium complex. With PEG-*Am*-BINAP (**14**) highly enantioselective hydrogenation of β-ketoesters was obtained in methanol at 50 °C. Performed under homogeneous conditions, the supported catalyst could be separated after precipitation with ether and recycled four times, leading to enantioselectivities of up to 95% (S/C = 100). One experiment was performed with an S/C ratio of 10,000 under 10 MPa of hydrogen at 50 °C with 100% conversion at 99% ee, but no attempts of recycling were performed under these conditions.

As was observed, the pathway to the catalyst preparation is important. If we compare the activity of **12**-$RuBr_2$ prepared by Genêt in a one-step reaction and the same catalyst prepared by our group in two steps, there appears to be a great difference in efficiency. As we have shown, greater enantioselectivities were obtained with a two-step catalyst synthesis and the catalyst was also perfectly recyclable.



Scheme 10. Immobilised sulphonated Ru-BINAP on LDH.

2.3 Hydrogenation with BINAP Catalysts Bound to Inorganic Materials

Another way to obtain insoluble catalysts consists of immobilising the catalyst or the ligand on inorganic solid support *via* ion pair formation,[40] covalent bond[41] or entrapment.[42]

To our knowledge, the heterogenisation of BINAP ligand in order to form a hybrid catalyst was only performed by entrapment and ion pair formation. Jacobs[42c] used the external surface of a molecular sieve (zeolite) as an effective support. The catalysts were synthesised by impregnation of acid zeolite beta (BEA) with large chiral platinium-group BINAP complexes such as {Ru[(*R*)-BINAP](*p*-cymene)Cl}Cl (**15**) (Scheme 10). The complex seems to be supported *via* electrostatic interactions on the external surface of the zeolite (Scheme 10). It was found that hydrogenation of methyl acetoacetate gave methyl hydroxybutyrate with 95% ee.

A related approach for the immobilisation of sulphonated Ru-BINAP complexes on a layered double hydroxide anion (LDH) exchange material was also performed[40e] by Jacobs. For the hydrogenation of geraniol, good enantioselectivity was observed.

3 Hydrogen Transfer Reduction

Hydrogen transfer reduction (HTR) represents a promising method for the production of chiral secondary alcohols.[43] This method avoids the use of hazardous hydrogen, and thus hydrogen pressure which requires special equipment.

This method is known to be catalysed by ruthenium,[44] iridium[45] and rhodium[46] as well as several other metal complexes. The sources of hydrogen used are cyclohexene, cyclohexadiene, alcohols, formic acid or inorganic reagents such as hydrazine. The chemoselectivities are known to be modulated by the proper choice of the hydrogen donor. Due to their low costs, 2-propanol and formate are mainly used as reducing sources, avoiding the need for molecular hydrogen.[47]

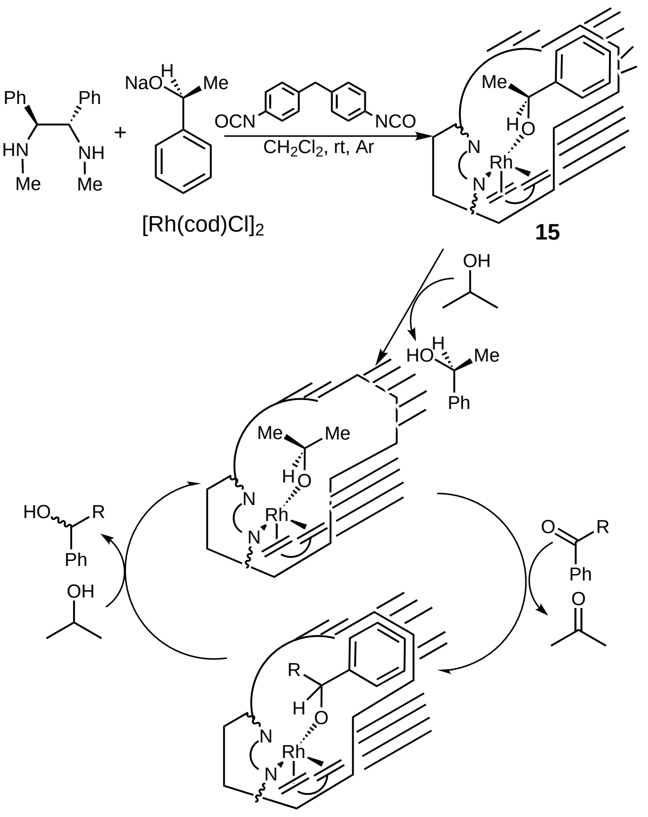
A wide range of substrates acting as hydrogen acceptors (ketones, α,β-unsaturated carbonyl compounds, α,β-unsaturated acids and esters, imines, nitro compounds...) has been successfully reduced for transfer hydrogenation in the presence of both heterogeneous[48] and homogeneous conditions.[43b] Chiral phosphines (DIOP,[49] CHIRAPHOS,[50] NORPHOS,[51] BINAP[52]...) were the first chiral ligands employed in this asymmetric reaction. Since the beginning of the 1990's, chiral nitrogen-based ligands have been largely used.[53] Most transfer hydrogenations require a base such as KOH, *i*-PrOK or *t*-BuOK as cocatalyst.

Mainly nitrogen-based ligands have been designed for this reaction. Among the best are the monosulphonamides of Noyori[54] and Knochel[55], the bis(oxazolinylmethyl)amine of Zhang[56] and the thiourea developed by our group.[57]

Nitrogen-based ligands present the advantage, over phosphorus ones, of being more easily polymerised and thus form heterogeneous catalytic systems with metals but, until now, hydrogen transfer reductions with immobilised catalysts remain rare.

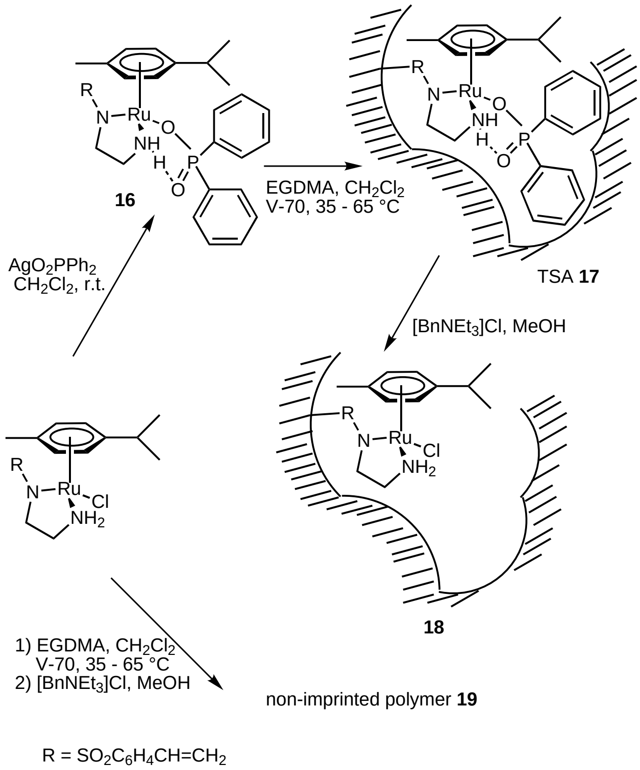
3.1 Imprinting Technique for Hydrogen Transfer Reduction

In 1995, our group reported the first immobilised transfer hydrogenation catalyst using a polyurea-rhodium complex **15** in order to study the effect of molecular imprinting.[57] The principle consists of copolymerisation and cross-linking of a polymer in the presence of a chiral molecule used as a printed molecule (PM). The latter, when included into the polymer by means of a covalent or non-covalent bond, can be removed in order to leave its chiral imprint in the polymeric matrix. Then, this chiral cavity is able to act as a centre of molecular recognition (Scheme 11).[58] The upper rhodium complex was formed by copolymerisation with a diisocyanide in the presence of sodium (*S*)-phenylethanolate (PM) leading to the imprinted polymer **15.** The PM was then removed by adding 2-propanol. The resulting polymer was tested in the transfer hydrogenation of acetophenone leading to 43% ee, an increase of 10% from the non-templated complex. The best results were obtained with propiophenone; here the ee increased from 47% with non-templated polymerised complex to 67% with the templated polymerised complex.[59] Optimisation of the cross-linking ratio led to the best compromise between activity and selectivity (70% ee).[60] These increases in ee were ascribed to a favourable molecular imprinting effect of the PM, creating chiral pockets within the polymer network. Nevertheless, in the case of sterically demanding substrates little or no reduction occurs, indicating a substrate stereospecificity different from that observed in homogeneous catalysis or when using a catalyst precursor deposed onto the polymer backbone.

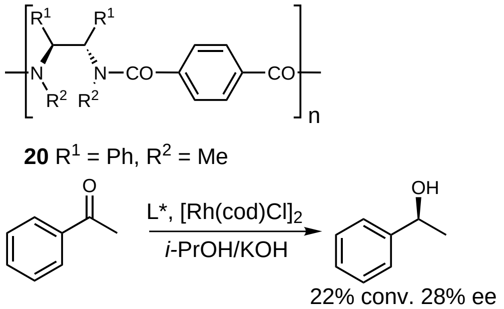


Scheme 11. Molecular imprinting polymer for asymmetric HTR.

This molecular imprinting technique was also used by Severin[61] who proposed the synthesis of phosphonato



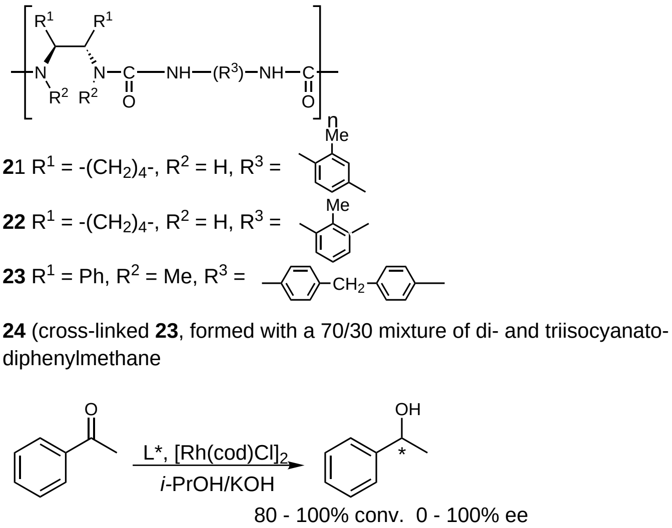
Scheme 12. Molecular imprinting with an organometallic transition state analogue.



Scheme 13. Polyester as Rh ligand.

complexes **16** (Scheme 12) in order to mimic the six-membered cyclic transition structure suggested for HTR.[62] This immobilised catalyst was prepared in a three-step reaction (Scheme 12). In order to compare the effect of such a polymeric organometallic transition state analogue (TSA, **17**), the polymer **19** was prepared (Scheme 12) by copolymerisation of the non-imprinted material with ethylene glycol dimethacrylate (EGDMA) (Ru/EGDMA: 1/99). The ability of such polymers to catalyse the reduction of benzophenone was tested, using formic acid as hydrogen donor.

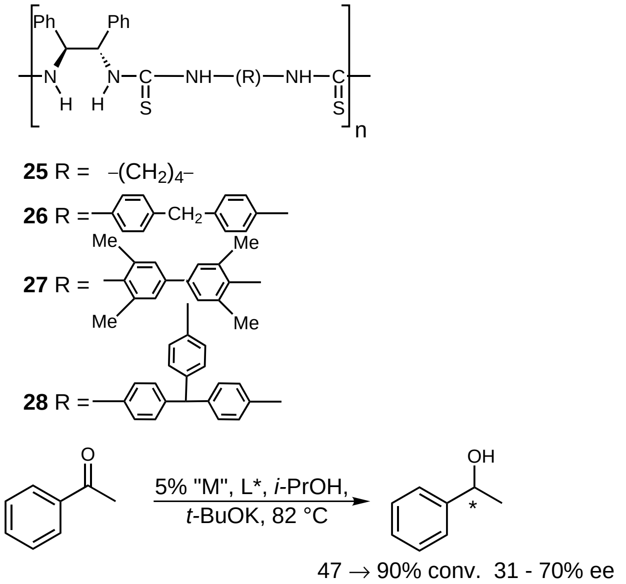
The imprinted polymer **19** was significantly more active than material **18** [TOF (**19**) = 51.4 h^{-1}, TOF (**18**) = 16.5 h^{-1}]. With this enhancement of the rate of the reaction using the imprinting polymer, a substantially higher specificity for benzophenone was observed when competition of HTR between benzophenone and another ketone was performed. This behaviour was slightly larger for aliphatic ketones as compared to aromatic ketones. These results were consistent with the activity and selectivity was enhanced using organometallic TSA as template.



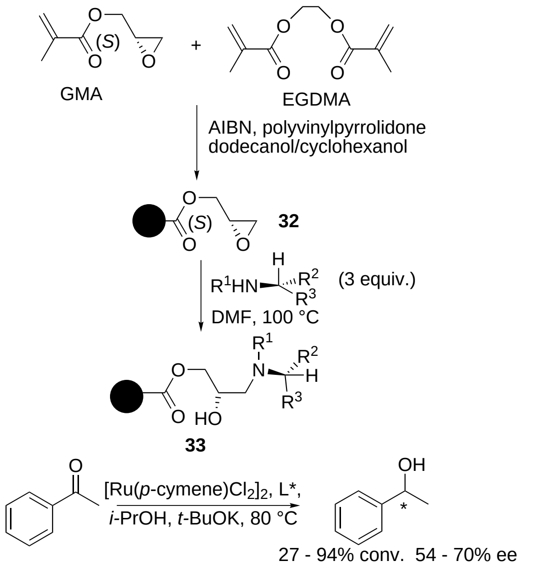
Scheme 14. Polyureas as Rh ligands.

3.2 Hydrogen Transfer Reduction with Asymmetric Ligands in Main Chain Polymers

Non-template complexes derived from the copolymerisation of chiral diamine (1,2-cyclohexanediamine) with terephthaloyl chloride or diisocyanate (2,4- or 2,6-diisocyanatotoluene) copolymers with pseudo C_2 symmetry (Schemes 13 and 14) have been prepared by our group.[63] With ruthenium complexes the conversions varied from 22% to 100% and ee from 0% to 60% for HTR with acetophenone at 70 °C in the presence of $[Rh(cod)Cl]_2$, 2-propanol and KOH. With 22% conversion and 28% ee, polyamide **20** appears to be the least active and enantioselective ligand. Polyureas **21, 22, 23** and cross-linked **24** led to better conversions, 80, 50, 97 and 100% with, respectively, 0, 13, 39 and 60% ee. Moreover, the chiral cross-linked polyurea **24** presented a slight increase in enantioselectivity over the monomer analogue (55% ee and 94% conversion under similar conditions) and the reaction rate, at 60 °C, appeared to be even higher than in the homogeneous phase. This is probably due to a higher stability of the cross-linked catalyst at this temperature. The recovery and recycling of this polymeric catalyst has been performed with no loss of either catalytic activity or enantioselectivity. These results could be explained by the rigidity of the active site which is crucial for the selectivity and the stability of the catalytic system.



Scheme 15. Polythioureas as Rh ligands.



Scheme 16. Aminoalcohols derivatives from (GMA-*co*-EGDMA) as Ru based ligands.

The HTR of acetophenone was also carried out with polythiourea,[64] formed by copolymerisation of *N,N'*-dimethyl-1,2-diphenylethylenediamine with various diisothiocyanates (Scheme 15). We have already shown that under homogeneous conditions thioureas are better ligands than ureas, when using ruthenium complexes as precursors.[65] The reaction was performed in isopropyl alcohol with a substrate/ligand/*t*-BuOK/Ru ratio of 20/1.5/4/1. The chiral induction was function of the flexibility of the linker. The more flexible the linker, the less enantioselective is the reaction: 31%, 70%, 70% and 65% ee for, respectively, **25**, **26**, **27**, **28** ruthenium complexes with conversion up to 90% for **25**, **26**, **27** and only 47% for **28**. For this latter cross-linked material, the decrease in conversion was due to the lower accessibility of the catalytic site although a ligand/metal ratio of 8 had to be used.

The best ligand structure (**27**) resulted in the formation of 2-phenylethanol with 96% conversion and 70% ee, was reused four times without loss of activity and only slight loss of selectivity (63%). Compared to the polyureas, most of the polythioureas tested were more efficient.

Chiral β-aminoalcohols can also be used for homogeneous hydrogen transfer reduction of ketones and are known to be effective for asymmetric transfer hydrogenation of aromatic ketones where an appropriate pairing of the auxiliary and [RuCl$_2$(arene)]$_2$.[66]

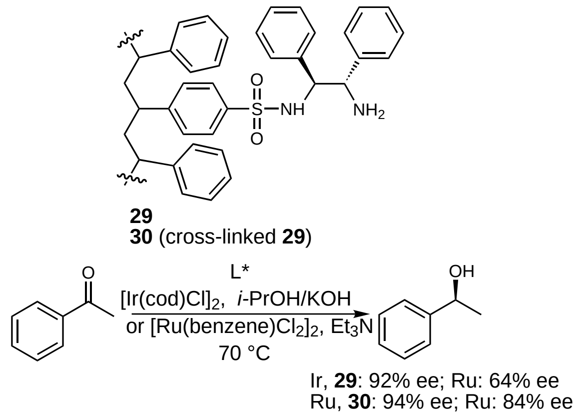
Recently, we have synthesised chiral poly(glycidyl methacrylate-*co*-ethylene glycol dimethacrylate) (GMA-*co*-EGDMA) (**32**) by radical suspension polymerisation of enantiopure glycidyl methacrylate with ethylene glycol dimethacrylate or divinylbenzene in the presence of AIBN (Scheme 16).[67] The subsequent epoxide ring opening of these polymers with amines led to polyaminoalcohols **33** (Scheme 16) which have been studied in the hydrogenation transfer reduction of acetophenone. The reaction was performed at 80 °C, in the presence of [RuCl$_2$(*p*-cymene)]$_2$ as precursor and isopropanol as hydrogen source. The reaction was carried out with a ratio acetophenone/Ru/aminoalcohol polymer unit/*t*-BuOK of 20/1/4/5.

It is noteworthy that the nature of the amine plays a crucial role. Aminoalcohols derived from primary amines led to the best conversions and the best enantioselectivities. The best being the benzylamine aminoalcohol derivative that provides 2-phenylethanol with 94% conversion and 70% chiral induction. An attempt at reuse was performed with the latter but, unfortunately, only 27% conversion with only 54% ee were obtained.

3.3 Hydrogen Transfer Reduction with Ligands as Pendent Group on Materials

Instead of considering asymmetric ligands in the main chain polymer, our group was also interested in the synthesis of the ligand as a pendent group anchored to a Merrifield-type material.

Thus, in 1997, we synthesised chiral organic polymers containing a monomer similar to the aminosulphonamide, which was used as ligand by Noyori,[47a] in the monophasic ruthenium catalysed HTR of ketones (97% ee for acetophenone). The polymeric ligand was synthesised by radical copolymerisation of *N*-(*p*-vinylbenzenesulphonyl)-(1*S*,2*S*)-diphenylethylenediamine with styrene (**29**) and divinylbenzene as cross-linker (**30**) (Scheme 17). When tested as ligands for the Ir(I)- and Ru(II)-catalysed HTR[68] of acetophenone, in the

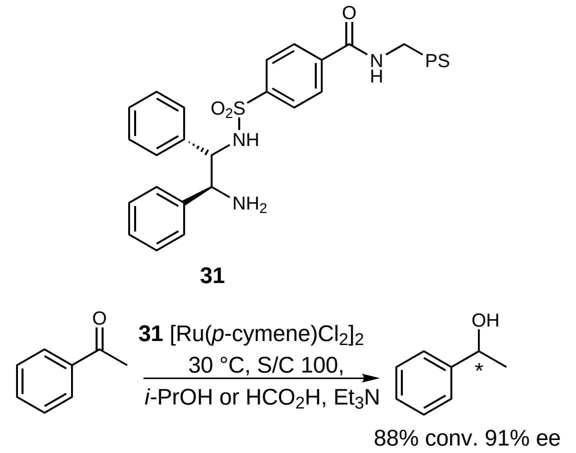


Scheme 17. Copolymerised aminosulphonamide as Ru or Ir based ligands.

presence of 2.5% of metal precursor and 2-propanol/base at 70 °C, we observed that Ir complexes led to higher ee (**29**: 92% and for the cross-linked **30**: 94%) compared to the homogeneous analogue for which only 75% of conversion and 89% ee were obtained. Nevertheless, the Ir catalyst was more selective than the ruthenium species (Ir: 92% ee, Ru: 64% ee, cross-linked Ir: 94% ee, cross-linked Ru: 84% ee), but for Ru the conversions are about 95% in both cases. On the other hand, the homogeneous Ir complex analogue led to only 75% conversion at 89% ee. This difference could be explained by the formation of chiral microenvironments upon polymerisation and stabilisation of the reactive Ir complex.

Attempts to reuse the catalysts showed that the Ru-containing one, although less selective, is more stable upon reuse than the Ir derivative.

With a similar objective, Bayston[69] has synthesised the polymer **31** (Scheme 18) starting from the aminostyrene Merrifield-type polymer. By means of a ruthenium precursor, 88% conversion at 91% ee were obtained. Compared with the preceding ligand **29** complexed with ruthenium, better conversion and enantioselectivities are shown; these latter results are comparable with those of the Ir catalyst.

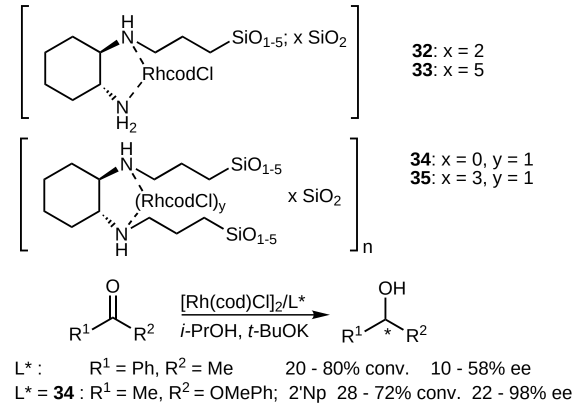


Scheme 18. Aminostyrene Merrifield-type polymer as Ru or Ir based ligands.

3.4 Hydrogen Transfer Reduction with Ligands Bound to Inorganic Materials

Other immobilised chiral diamines have been used for HTR. These ligands are grafted onto silica gel by means of covalent bonds.

In 1997, Moreau[70] prepared hybrid silsesquioxanes by sol-gel hydrolysis condensation of silylated (1R,2R)-*trans*-1,2-diaminocyclohexane derivatives. Complexed with rhodium (Scheme 19) in the isopropyl alcohol-promoted HTR of acetophenone, these ligands afforded from 20% to 80% conversion and 10% to 58% ee. With **32**, **33** and **34** better enantioselectivities were obtained compared to the corresponding monosilylated precursors complexed with rhodium for which the reaction occurred in homogeneous media, with the bis-silylated ligand presenting a pseudo C_2 symmetry, leading to the highest enantioselectivity. Moreover, with **36**, a drastic decrease in selectivity was observed, showing that dilution with tetraethoxysilane (added during the hybrid ligand synthesis) had a negative effect. These results may be indicative of the role played by the hybrid silica matrix: an influence of the secondary network may account for that enhanced selectivity. Furthermore, with **33**, selectivity ranging from 40–98% ee was observed depending on the nature of the ketone. The more hindered the ketone, the higher is the enantioselectivity but the lower the conversion.



Scheme 19. Hybrid ligands.

4 Conclusions

Heterogeneous asymmetric catalysis was tested in the very early stage of the researches in asymmetric catalysis. Indeed, Schwab[71] used chiral quartz as support for asymmetric kinetic resolution in 1934; Akabori[72] used silk fibroin as chiral material for asymmetric catalysis as long as fifty years ago.

The renewed interest in homogeneous supported catalysts is partly due to the stringent environmental legislation requiring clean technology and high performances.

Among the examples of hydrogenation using polymer-supported BINAP catalysis, there are, today, still no perfect catalytic systems from a practical standpoint. Nonetheless, the more efficient and easy to recycle BINAP ligands are those obtained for biphasic solid/liquid catalysis, the best being BINAP grafted under a polystyrene matrix for which a TON as high as 12,300/batch was obtained in the reduction of acetonaphthone with 97% ee and with 11 recyclings. In the case of water-soluble systems, improvements seem easily accessible.

For asymmetric hydrogenation transfer reduction, the development of various methodologies has been undertaken with amine ligands. The molecular imprinting led to interesting results but is dependent on the structure of the printed molecule that must mimic as closely as possible the molecule to be reduced. With non-templated complexes, polythioureas ligands have shown their supremacy in terms of chiral induction and conversion compared to the polyurea equivalents. Nevertheless, the best ligands are those formed with pendent aminosulphonamide ligands.

All these results are encouraging, but before practical applications of such types of materials, that could be one of the keys to economical and safe chemical processes, they have, nevertheless, to be improved.

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