Immobilized Chiral Metal Catalysts for Enantioselective Hydrogenation of Ketones

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Abstract: Chiral secondary alcohols are useful synthetic building blocks. One direct approach to chiral secondary alcohols is by catalytic reduction of ketones using molecular hydrogen or by asymmetric transfer hydrogenation. This review focuses on recent developments using immobilized chiral metal catalysts, and their role in developing greener chemistry. Immobilization of chiral ligands on silica, polymer, dendrimer and magnetite nanoparticles and their application as catalyst with metals in the hydrogenation of ketones under environmentally friendly solvent conditions is discussed.

Keywords: Chiral, secondary alcohol, immobilized, silica, polymer, catalyst.

INTRODUCTION

Optically pure secondary alcohols are useful building blocks in the production of pharmaceuticals, agrochemicals, flavors and fragrances. One direct method to prepare chiral secondary alcohols is by the enantioselective reduction of the corresponding ketone. Significant progress has been achieved in this area in the last twenty years with chiral reagents. Among these are Brown's chiral diborane [1], Corey's oxazoborolidine [2] and Noyori's reduction using molecular hydrogen and asymmetric transfer hydrogenation in the presence of an organometallic catalyst [3]. This review is a follow-up of a previous review published by Saluzzo and Lemaire in 2002 [4] and will focus on the last two of these methods, highlighting recent developments involving immobilized catalysts and their application in the reduction of ketones to alcohols.

Immobilized catalysts have been of great interest due to several advantages, such as simplification of product work-up, separation, isolation and reuse of the catalyst [5-8]. However, their use in organic synthesis has been rather limited because in many cases immobilized catalysts are less active than the corresponding original catalysts. Another drawback of immobilized chiral ligands is the leaching of the central metal. This can be solved in some cases by reloading of the ligand with the central metal to render the immobilized metal catalyst reusable. More importantly, recent interest in environmentally benign chemical processes, reducing waste and high-throughput organic synthesis has triggered renewed interest in the chemistry of immobilization of homogenous catalysts.

Types of Support

Four distinct methodologies have been developed for the heterogenization of homogeneous catalysts: adsorption, encapsulation, covalent tethering and electrostatic interaction. The main supports used for the immobilization of homogeneous catalysts fall into two broad categories: organic and inorganic supports. The organic supports used for immobilization are generally soluble or insoluble polymer resins [9] or dendrimers [10]. Very often the catalysts immobilized on soluble polymer can be recovered by precipitation using a non-polar solvent and then reused in the reaction. The inorganic supports described herein, involve amorphous silica and mesoporous silica, such as MCM-41and SBA-15 with well defined pore structures [11]. In these cases the chiral ligand-metal catalyst is immobilized on the silica through covalent bonding or by electrostatic interaction. At the end of the reaction the immobilized catalyst is easily recovered by simple filtration and reused in the reaction [12].

Another more recent immobilization technique that does not involve solid support is the use of ionic liquids, in which the catalyst is immobilized and the reaction involves a biphasic system. The reaction products are then extracted into non-polar solvent leaving behind the catalyst [13].

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Types of Chiral Ligands

Most of the chiral ligands that have been immobilized (**1**-**4**), are already well established as ligands for the formation of metal complex catalysts in the asymmetric hydrogenation of ketones under homogenous reaction conditions [14] (Fig. **1**).

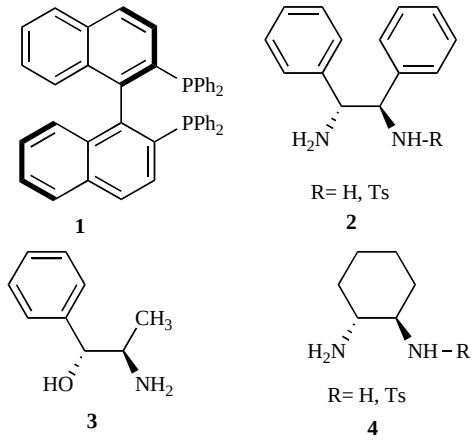

Fig. (1). Chiral ligands.

Asymmetric Reduction of Ketones

Noyori's catalyst *trans*-$RuCl_2$[BINAP][DPEN] (**5**), which is a combination of (*S*)-BINAP and (*S*,*S*)-DPEN (or *R*/*R*,*R* combination) (Fig. **2**), reduces simple ketones with molecular hydrogen to chiral alcohols in excellent enantioselectivities and yields. Following this, there are numerous literature examples where the BINAP and DPEN catalytic combination has been replaced with structurally different chiral diphosphine and diamine molecules. All these catalysts led to the chiral secondary alcohols in excellent enantioselectivities and yields. The BINAP and DPEN ring structures offer an excellent opportunity to derivatize and immobilize the ligand on polymer or silica [15].

In addition to the asymmetric catalytic reduction using molecular hydrogen, Noyori also developed a second method, which involves transfer hydrogenation of to ketones using Ru(arene)-TsDPEN (**6**) or amino alcohol (**7**) as catalyst and isopropanol/KOH, HCOOH/NEt_3 or aqueous sodium formate as the hydrogen source [16] (Fig. **2**). As in the previous case, DPEN can be derivatized and immobilized.

Ligands Immobilized on Polymer and their Application in the Reduction of Ketones

In a pioneering work, Lemaire and coworkers [17] copolymerized the chiral ligand 1,2-diphenylethaneamine containing a vinyl group, with styrene and divinylbenzene to give a cross linked insoluble polymer which on complexation with $[RuCl_2(benzene)Cl]_2$, $[Ir(COD)Cl]_2$ or $[RuCl_2(p\text{-cymene})Cl]_2$ and isopropanol/KOH took

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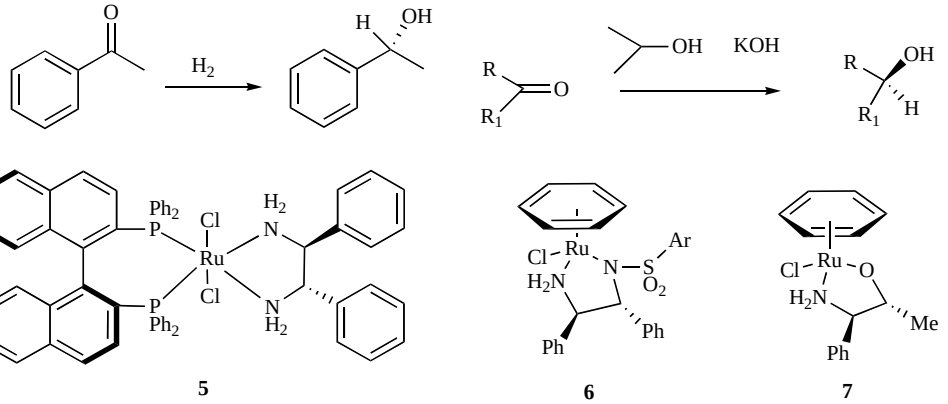

Fig. (2). Noyori´s catalysts.

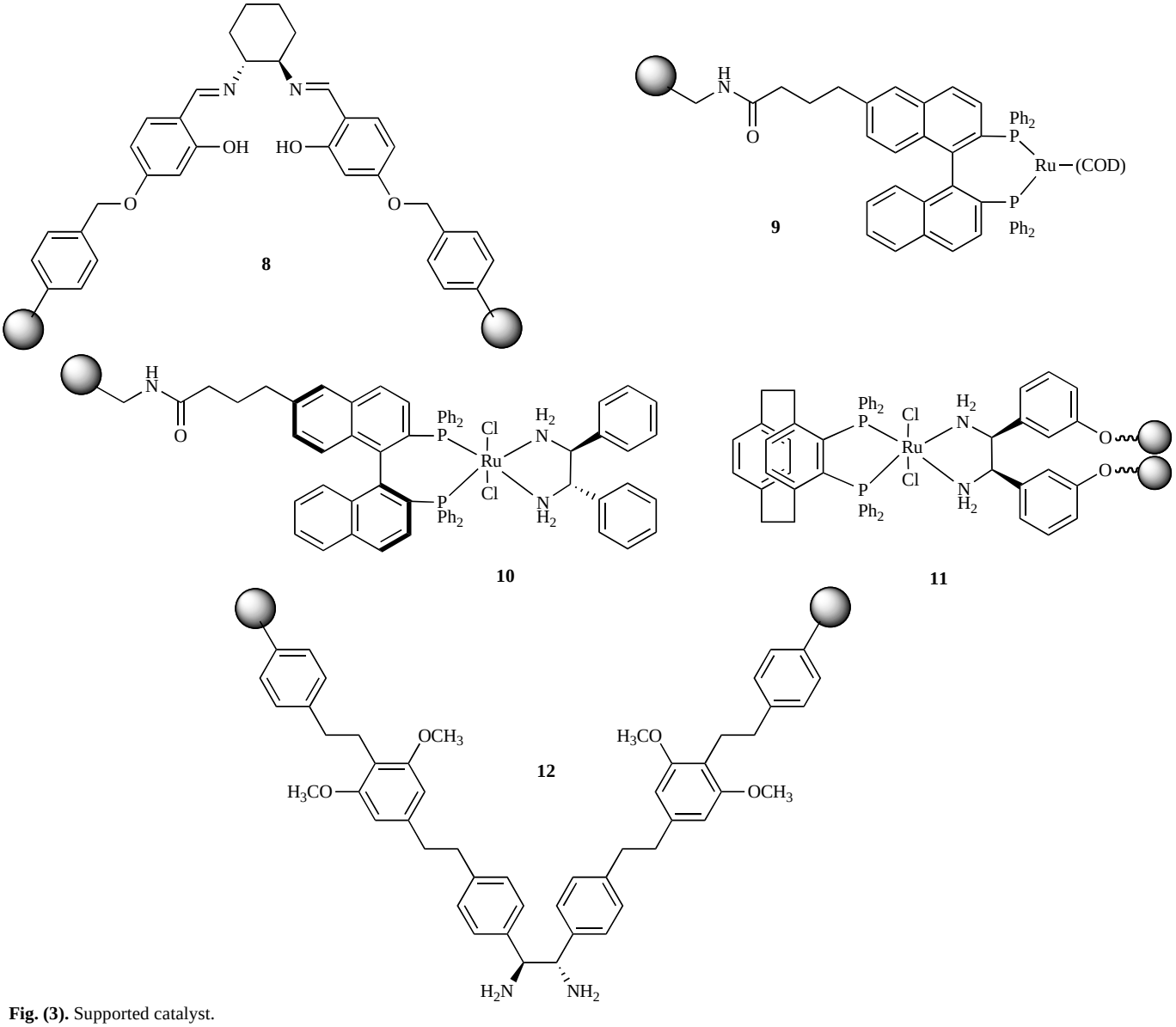

Fig. (3). Supported catalyst.

three days to reduce acetophenone to the alcohol in moderate yields and enantioselectivity, using 1:1 S/C ratio. The same group reported the use of the ligand **8** (Fig. **3**) with 71% cross linking complexed to $[Ir(COD)Cl]_2$ to reduce acetophenone under ATH conditions to secondary alcohol in 70% enantioselectivity and 90% conversion in 7 h. Attempts to recycle the catalyst failed [18].

In another report, BINAP containing a tethered carboxylic acid functionality was coupled to commercially available hydroxymethylated polystyrene or aminomethylated polystyrene, which was then complexed with (COD)Ru(bismetallyl) in the presence of HBr to give the active catalyst **9** (Fig. **3**). This catalyst was used with molecular hydrogen to reduce a β-ketoester to the corresponding alcohol in

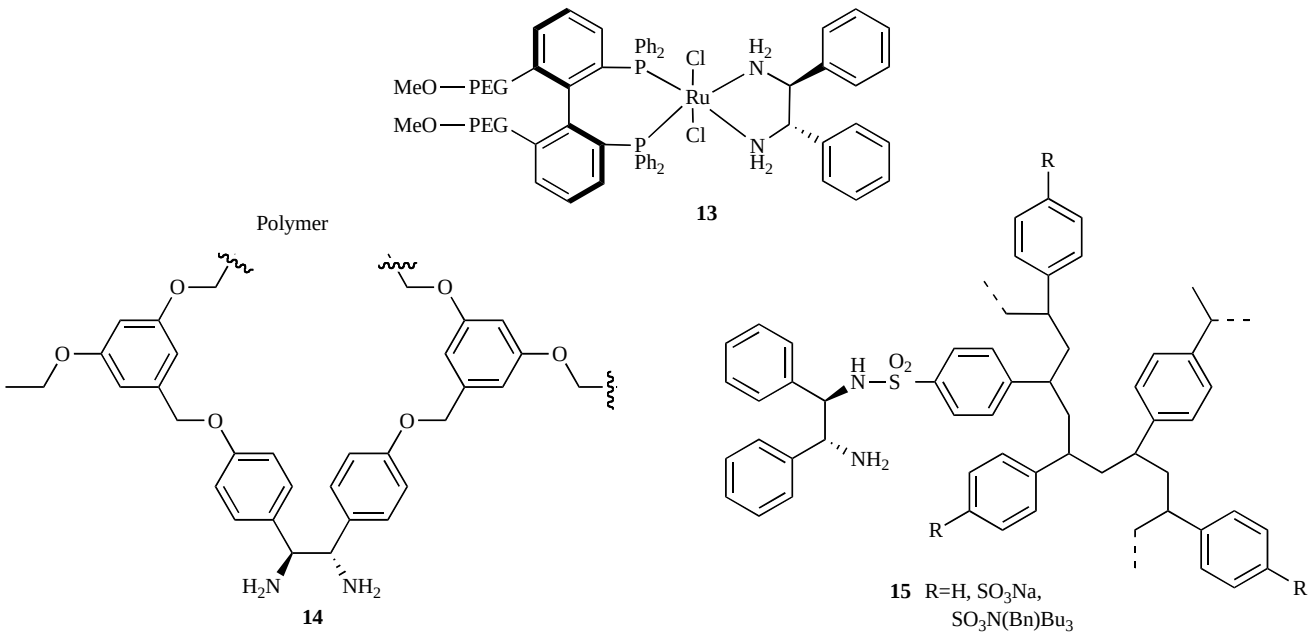

Fig. (4). Ligands anchored to polymers used in asymmetric hydrogenation.

>99% yield and >97% enantioselectivity. The active catalyst was reused with only a slight loss in activity [19].

Noyori has demonstrated that the BINAP-DPEN combination gives an excellent homogeneous catalyst for molecular hydrogenation of ketones. It was also shown that immobilized BINAP on polystyrene (Fig. **3**), when used with Ru(II) and DPEN (complex **10**), catalyzed the reduction of ketones to alcohols in 100% conversion and >84% ee. Turnover numbers of as high as 12,300/batch or a total of 33,000 by repeated use with S/C ratio of 2470 were reported. The catalyst was reused 14 times in the acetophenone reduction with slight decrease in the yield while the enantioselectivity remained unchanged [20].

Xiao and coworkers [21] reported the use of Ru-poly(ethyleneglycol)-supported DPEN (*R*,*R*) in combination with the ligand (*S*)-PhanePhos [complex **11**, (Fig. **3**)] to reduce simple ketones to alcohols with molecular hydrogen, in >98% yield and >92% enantioselectivity. The reaction was carried out under homogeneous conditions and the results were comparable to those obtained with the parent molecular catalyst [(*S*)-phane-Phos)$RuCl_2$ (*R*,*R*)-DPEN]. They reported that the catalyst was precipitated with ether and recycled three times with slightly decreased activity and no loss in enantioselectivity. The leached ruthenium was measured to be low at 2.7 ppm.

Takahashi and coworkers [22] reported the copolymerization of chiral 1,2-diamine monomer (*S*,*S*) with styrene to give a cross-linked polymer **12** (Fig. **3**). The cross-linker polymer was used with $RuCl_2$/(*S*)-BINAP in the hydrogenation of aromatic ketones to alcohols in quantitative conversion and high level of enantioselectivity (77%). The polymeric catalyst was recycled several times without loss of the catalytic activity, with S/C of 1000.

Wang and coworkers [23] reported the soluble (MeO-PEG BIPHEP-Ru-DPEN) catalyst from (6,6-dimethoxybiphenyl-2,2'-dienyl)bis(diphenylphosphine) (MeO-BIPHEP) and DPEN [complex **13,** (Fig. **4**)], and its use as catalyst in the asymmetric hydrogenation of a number of aromatic ketones. It was found that the catalyst furnished the secondary alcohol in high yields (>99%) and enantioselectivities (83-95%). The catalyst was precipitated and reused three times with no loss of activity.

In a recent report, Itsuno and co-workers [24] used DPEN attached to a variety of polymer networks [**14**, (Fig. **4**)] which in combination with BINAP and complexation to [$RuCl_2$(*p*-cymene)]$_2$ catalyzed the reduction of aromatic ketones. The alcohols were obtained in quantitative yield and >75% ee. Using a similar strategy, the same group attached 1,2-diamine monosulfonamide to a similar polymeric network with a quaternary ammonium salt [**15**, (Fig. **4**)], which was used with [$RuCl_2$(*p*-cymene)]$_2$ in the transfer hydrogenation of aromatic ketones in water. The authors reported >90% conversion and 91-97% ee in the reduction of ketones, and the catalysts were recycled without any loss of activity.

In a subsequent work, Itsuno and co-workers [25] reported new polymer-supported chiral sulfonamides containing sulfonated pendant groups **16** (Fig. **5**). The chiral catalyst prepared from these new polymer-support and [$RuCl_2$(*p*-cymene)]$_2$ was found to be more effective for ATH of aromatic ketones in water compared to that prepared from conventional polystyrene-support. The chiral secondary alcohol was obtained in 100% yield and >90% enantioselectivity when sodium formate was used as the hydrogen source.

Xiao's group [26] used the previously immobilized ligand **17** (Fig. **5**), with [$RuCl_2$(p-cymene)]$_2$ to reduce simple ketones to the corresponding chiral alcohols in 60-100% yields and >90% enantioselectivity, using HCOOH-NEt_3 as the hydrogen source. The soluble catalyst was precipitated from the solution with ether and used in three consecutive runs. In the fourth run the yield dropped to 56% (99%) and enantioselectivity to 82% (91%). However, recycling the catalyst was only possible with the addition of water. Intrigued by this observation, the authors tested the same ligand in aqueous sodium formate, which reduced ketones to alcohol in >99% yield and 89-93% enantioselectivity. The reaction was enhanced by aqueous sodium formate at 22-40 °C with S/C 100, and was completed in 1-36 h. The active catalyst was recovered and reused more than 10 times with no loss in enantioselectivity, showing promise as a potential candidate for industrial application [27].

In all the cases described, the immobilization of the ligand was carried out through phenyl rings of the diamine. In a pioneering work, Polywka and coworkers [28] used the chiral ligand 1,2-diphenylethanediamine monosulfonamide where the immobilization on polystyrene methylamine (or aminomethylated PEG polystyrene) was carried out through the phenyl ring of the sulfonamide group **18** (Fig. **5**), which upon complexation with [$RuCl_2$(*p*-cymene)]$_2$ gave orange-red beads. Using these beads under transfer hydrogenation

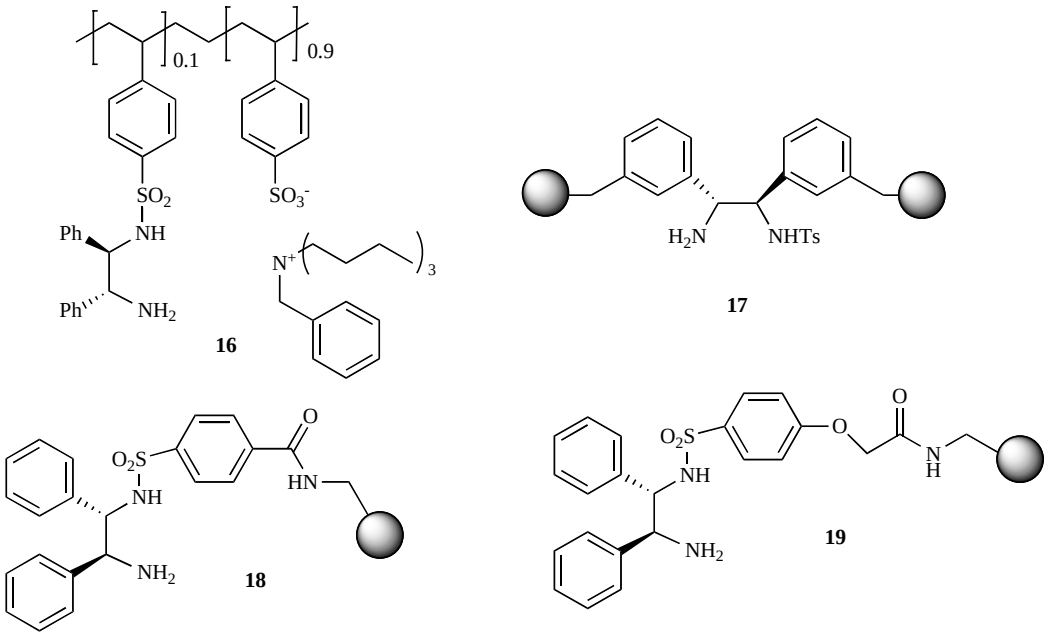

Fig. (5). Immobilized ligands of 1,2-diphenyl-1,2-diamine.

conditions, acetophenone was reduced with no solvent to give the alcohol in 100% yield and 92% enantioselectivity. The complex was recycled three times with the yield dropping to 65% and the enantioselectivity remaining unchanged.

Wang and coworkers [29] synthesized the structurally similar immobilized ligand **19** using aminomethylated polystyrene (Fig. **5**). Complexation of **19** with $[RuCl_2(p\text{-cymene})]_2$ gave the catalyst as orange-red beads, which was efficiently used to reduce α-substituted ketones under transfer hydrogenation conditions to the corresponding alcohol in good yield (97%) and enantioselectivity (95%). The catalyst was recovered and used three times with a slight drop in yield (81%) and enantioselectivity (93%). Increasing chain length on the linker led to slightly higher yield (98%) and enantioselectivity (97%).

Noyori's catalyst tethered to polysiloxyanes (chemzyme) **20** (Fig. **6**), has been prepared via ultra or nanofiltration techniques and used in continuously operated membrane reactors [30]. The catalyst which has a molecular weight of 22 Kg mol^{-1} and a metal loading of 0.3 mmol g^{-1} proved to be highly enantioselective (up to 97%) in the transfer hydrogenation of acetophenone in 2-propanol. The catalyst was recycled using an ultrafiltration membrane.

Biomimetic catalysis with an immobilized chiral complex of Rh(III) **21** (Fig. **6**), was reported by Polborn and Servin [31]. An organometallic transition state analogue for the asymmetric reduction of acetophenone with Cp*Rh was synthesized and polymerized. Removing the methyl-phenylphosphinato ligand, which mimics acetophenone, provided an imprinted polymer, which was ground and used as catalyst to reduce acetophenone. Enantioselectivities up to 95% were obtained. Experimentally it was shown that the imprinted polymer is specific for acetophenone.

ATH using a Ru(II) complex supported on chiral poly(binaphthoxyphosphazene) copolymer **22** (Fig. **6**), was reported [32]. The soluble ligand reduced acetophenone to the alcohol in >95% yield, S/C 500, and TON 475. Unfortunately no enantioselectivity was achieved due to the conformational behavior of the chiral derivative.

A $[RuCl_2(arene)]_2$ complex **23** (Fig. **6**), with methacrylate side chain has been synthesized and polymerized with divinylbenzene or ethyleneglycol dimethylacrylate to give the complex immobilized on the arene ring of the metal complex [33]. When used as catalyst in the ATH of a number of aromatic ketones, yields of 77-98% and enantioselectivities of 89-92% were obtained.

Immobilization of β-amino Alcohol to Polymers

The first example of immobilized amino alcohol in the ATH was demonstrated by Wills's group [34], where norephedrine was immobilized on polyethylene glycol **24** (Fig. **7**), and with Ru(II) catalyzed the ATH of acetophenone to alcohol in 95% yield and 81% enantioselectivity.

Hérault *et al.* [35] reported a series of amino alcohols **25**, (Fig. **7**) and amino thiols immobilized on macroporous polymer beads, which complexed with $[RuCl_2(p\text{-cymene})]_2$ were used as catalyst in the ATH of acetophenone. The best results, conversion 94% and 71% enantioselectivity were obtained with benzylamine grafted onto poly(GMA-ci-EDMA) (30/70 wt/wt).

Catalyst Immobilization on Silica Gel and its Application in the Asymmetric Reduction of Ketone

Recently Somanathan and coworkers [36] obtained a series of C_2-symmetry chiral ligands derived from cyclohexane-1,2-diamine and 1,3-bisbenzenesulfonyl chloride **26-28** (Fig. **8**); on complexation with $Rh^{III}Cp^*$ the catalyst reduced ketones to alcohols in >90% yields and >95% enantioselectivities, with aqueous sodium formate as the hydrogen source. The same ligands when immobilized on derivatized silica, gave stable complexes with $Rh^{III}Cp^*$. The ligand derived from silica bound benzyl chloride gave the best results in reducing acetophenone to alcohol in 100% conversion and >90% enantioselectivity. The immobilized ligand was filtered and recycled six times with only a slight decrease in activity.

The ruthenium(II) complex with the ligand NH-benzyl-(1*R*,2*R*)-norephedrine amino alcohol **29** (Fig. **8**), covalently tethered to silica was used as a catalyst to reduce acetophenone to alcohol in 95% conversion and 90% ee. The catalyst was recovered and used in three consecutive runs with no loss in activity [37]. The reported enantioselectivities were appreciably better than the same alcohol ligand tethered to polystyrene [24].

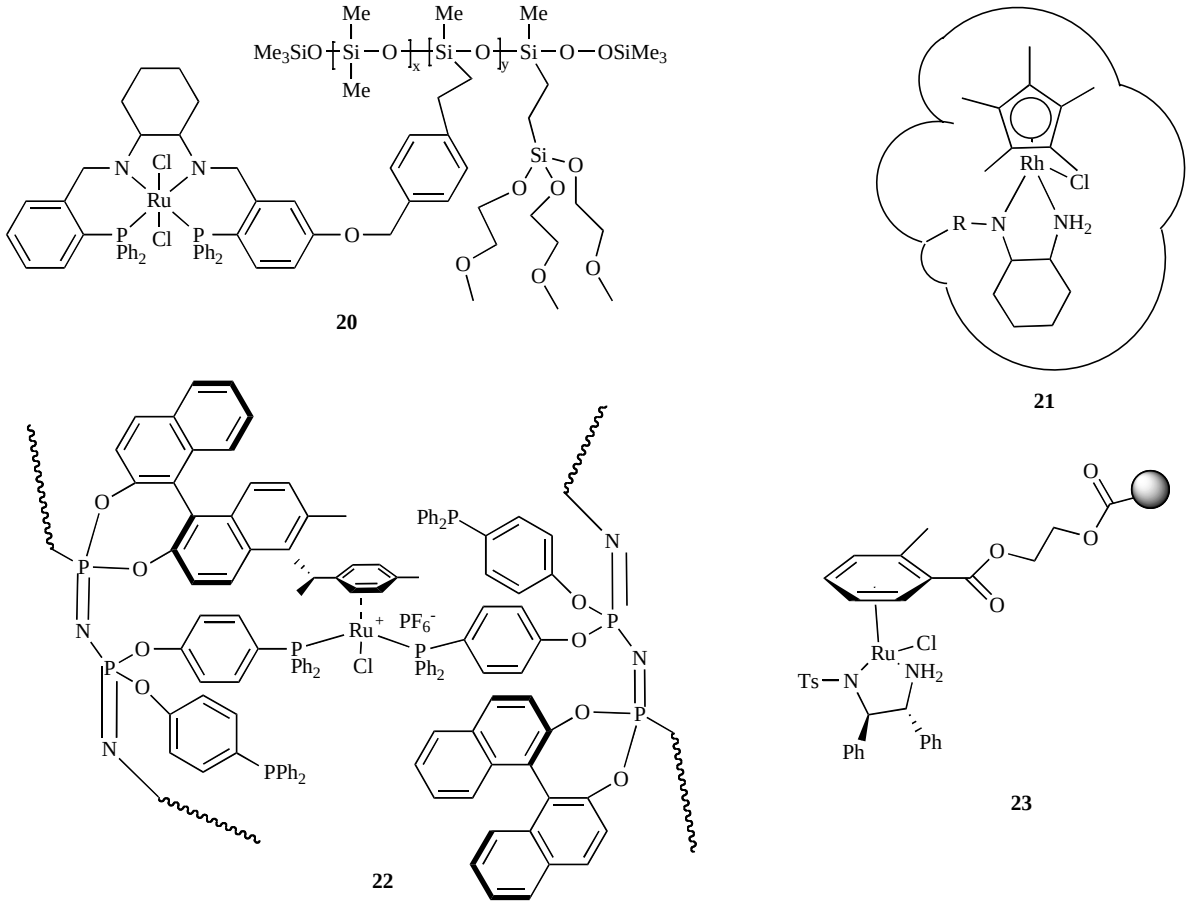

Fig. (6). Immobilized ligands.

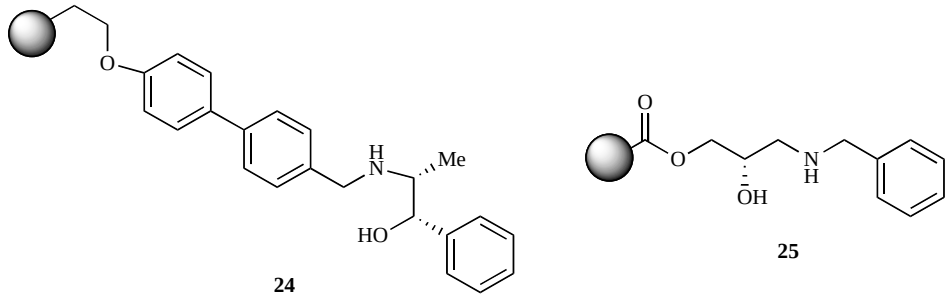

Fig. (7). Immobilized ligands of β–aminoalcohol.

Immobilization of Ligands on Mesoporous Silica

Compared to polymeric matrices that are often used for anchoring organometallic complexes, silica supports have the advantage of high mechanical strength, chemical robustness and thermal stability. Silica could also be tailored with different pore structures e.g., mesoporous silica and particle morphology [38].

Chiral cyclohexyldiamine based Ru triphenylphosphine complex has been immobilized on silica SBA-15 **30** (Fig. **9**), and used in chemo- and enantioselective hydrogenation of prochiral and α,β-unsaturated ketones with molecular hydrogen. The catalyst was found to preferentially hydrogenate the C=O over the conjugated C=C in the hydrogenation of α,β-unsaturated ketones with TOF >1000 and 70-90% conversion and excellent enantioselectivity (up to >99). Simple ketones gave 80% conversion and moderate enantioselectivity [39].

Huang and Ying [40] reported Ru-TsDPEN immobilized on siliceous mesocellular foam **31** (Fig. **9**), and used in ATH of β-ketoesters to β-hydroxyesters in 90-95% yield and 96-97% enantioselectivity, with isopropanol as the hydrogen source. However, with α-ketoesters as the substrate, 71-73% ee was achieved. This modest enantioselectivity was still noteworthy compared to 59% ee obtained with the homogeneous catalyst Ru-TsDPEN [41]. The catalyst was used successfully over six runs with negligible changes in activities and enantioselectivities. Siliceous mesocellular foam (MCF) has unique 3-dimensional pore structure, whose cell-like pores (20-50 nm) are connected to windows of a smaller opening (9-26 nm).

In a similar work, Tu and co-workers [42] used the chiral ligand DPEN immobilized through the benzene ring of the sulfonamide on four different types of silica: regular silica gel **32a**, modified silica **32b**, MCM-41 **32c**, and SBA-15 **32d.** Complexes with Ru(II) (Fig. **9**) were used as catalysts to reduce acetophenone with $HCOOH/NEt_3$ in excellent enantioselectivities and yields. The ligand immobilized on regular silica gel and SBA-15 gave the best results, 99% yield and

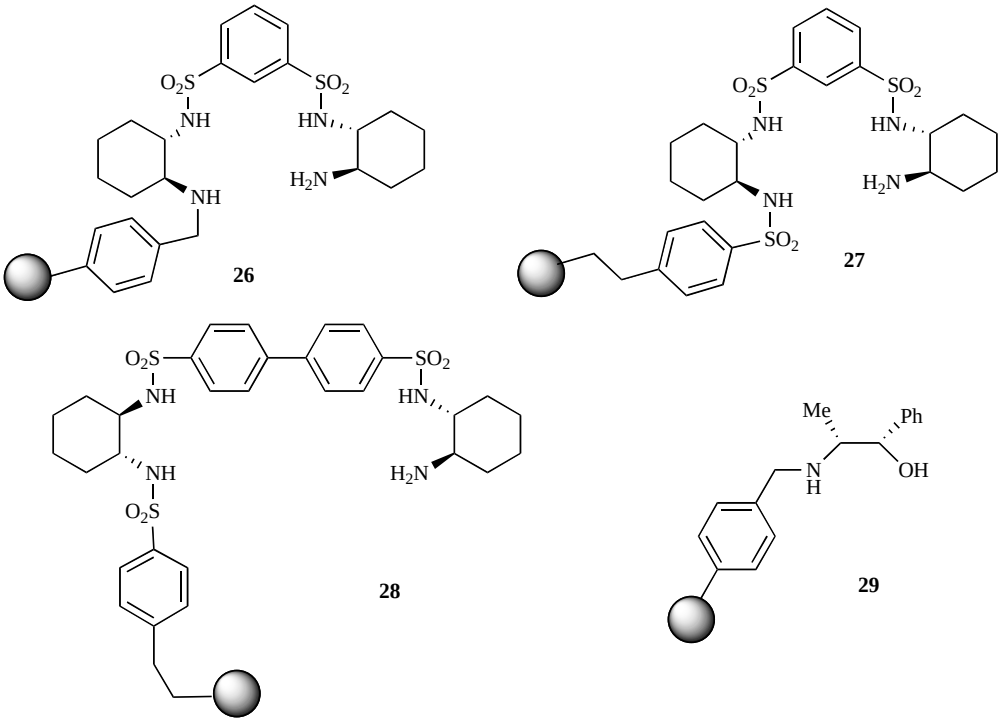

Fig. (8). Immobilized ligands onto silica gel.

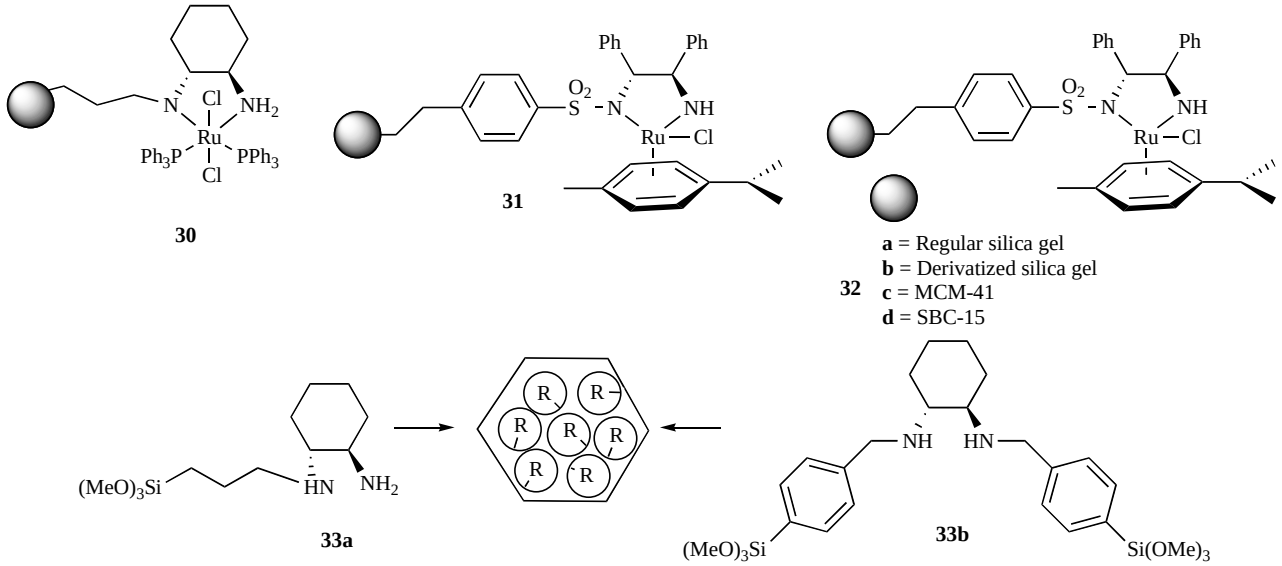

Fig. (9). Immobilized complexes on silica gel.

91% ee in 9 h, compared to 22 h with the ligand immobilized on MCM-41 (>99% yield, 87% ee), and 13 h on modified silica (>99% yield, 95% ee). The regular silica complex was used in five runs, with a gradual leaching of ruthenium at 30-40%. The authors demonstrated the applicability of these ligands in Ru(II)-catalyzed asymmetric reduction of ketones in water, using aqueous sodium formate as the hydrogen source. Similar yields and enantioselectivities were obtained. The ligand immobilized on regular silica-catalyst was recycled 11 times without loss of activity.

Mesoporous ethane-silicas functionalized with *trans*-(1*R*,2*R*)-diaminocyclohexane **33a**, (Fig. **9**), were synthesized by condensing 1,2-bis(trimethoxysilyl)ethane and *N*-[(trimethoxysilyl)propyl]-(1*R*, 2*R*)-diaminocyclohexane using octadecyltrimethylammonium chloride as the template under basic conditions. The complex of the immobilized ligand with $[RhCl(COD)]_2$ reduced acetophenone in 82-96% yield and 19-23% ee using isopropanol as the hydrogen source [43].

The same authors used the benzyl group as a linker on *trans*-(1*R*,2*R*)-diaminocyclohexane **33b**, covalently incorporated into the framework of mesoporous silica (Fig. **9**); The complex of **33b** with $[RhCl(COD)]_2$ reduced acetophenone to phenyl ethanol in 96% yield and 30% ee with isopropanol as the hydrogen source [44].

(1*R*,2*R*)-Norephedrine tethered to mesoporous SBA-15 silica was reported [45]; the complex with $[RuCl_2(hexamethylbenzene)Cl]_2$ reduced ketones to alcohols in iPrOH/KOH in 70-85% yields and 75-84% enantioselectivities. The results were comparable to free ephedrine ligand in terms of enantioselectivity.

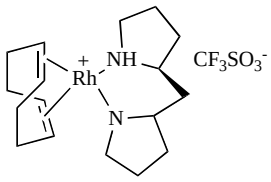

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Fig. (10). Non-covalently anchored ligand.

Mesoporous silica supports with well defined pore structure were synthesized and the complex Rh(I)(COD)(2-pyrrolidenylmethyl)-pyrrolidine [(**34),** (Fig. **10**)], was non-covalently anchored to the inner wall through the counter ion $CF_3SO_3^-$. Using this complex as a catalyst, β-ketoester was reduced to the β-hydroxyester with molecular hydrogen in >95% conversion and 94% ee [46].

Catalysts Immobilized on Dendrimers with Application in the Reduction of Ketones

A widely studied approach to facilitate catalyst-product separation, is the attachment of homogeneous catalysts to polymeric organic, inorganic or hybrid supports. In this category, homogeneous catalysts immobilized on dendrimers are receiving much attention due to their solubility in organic solvents and easy separation from products by filtration or precipitation [47].

Chiral TsDPEN functionalized through the benzene sulfonamide ring with Frécht's polyether dendrite wedges gave the chiral ligand [48]. Asymmetric transfer hydrogenation has been studied using 1-4 generation ligands with $[RuCl_2(p\text{-cymene})]_2$ in the presence of $HCOOH/Et_3N$ as the hydrogen source. The first and second generation catalysts possess higher activity, >90% conversion and >96% ee [49]. Dendrite catalysts maintained the enantioselectivity with only slight loss of activity in successive use.

Using a similar technique, Deng and co-workers [50] immobilized hydrophobic Frécht-type dendrite chiral 1,2-diaminocyclohexane **35** (Fig. **11**). The corresponding Rh(III) complex were used in the ATH of ketones with $HCOOH/Et_3N$ as the hydrogen source. Enantioselectivities of 52-97% and >99% conversion were reported. The catalyst was recovered by addition of hexane and reused six times without change in activity.

Using the Frécht-type dendrite, Deng and coworkers [51] immobilized the Ru(II) complex of (1*R*,2*R*)-norephedrine **36** (Fig. **11**), on the dendrimer and used it to reduce acetophenone under ATH conditions to give the alcohol in 70-90% conversion and >89% ee. The second and third generation catalysts gave decreased reactivity and enantioselectivity, probably due to poor solubility in isopropanol, but the reactivity was enhanced by adding CH_2Cl_2.

A series of dendrite BINAP-Ru^{II}/chiral diamine catalysts with ligands **37** (Fig. **11**), were developed from (*R*)-5,5'-diamine BINAP and used in the hydrogenation of acetophenone [52]. The alcohol was obtained in 100% yield and 74-78% ee. The active catalyst was recovered from the reaction mixture by precipitation and reused for two cycles with similar enantioselectivity [53].

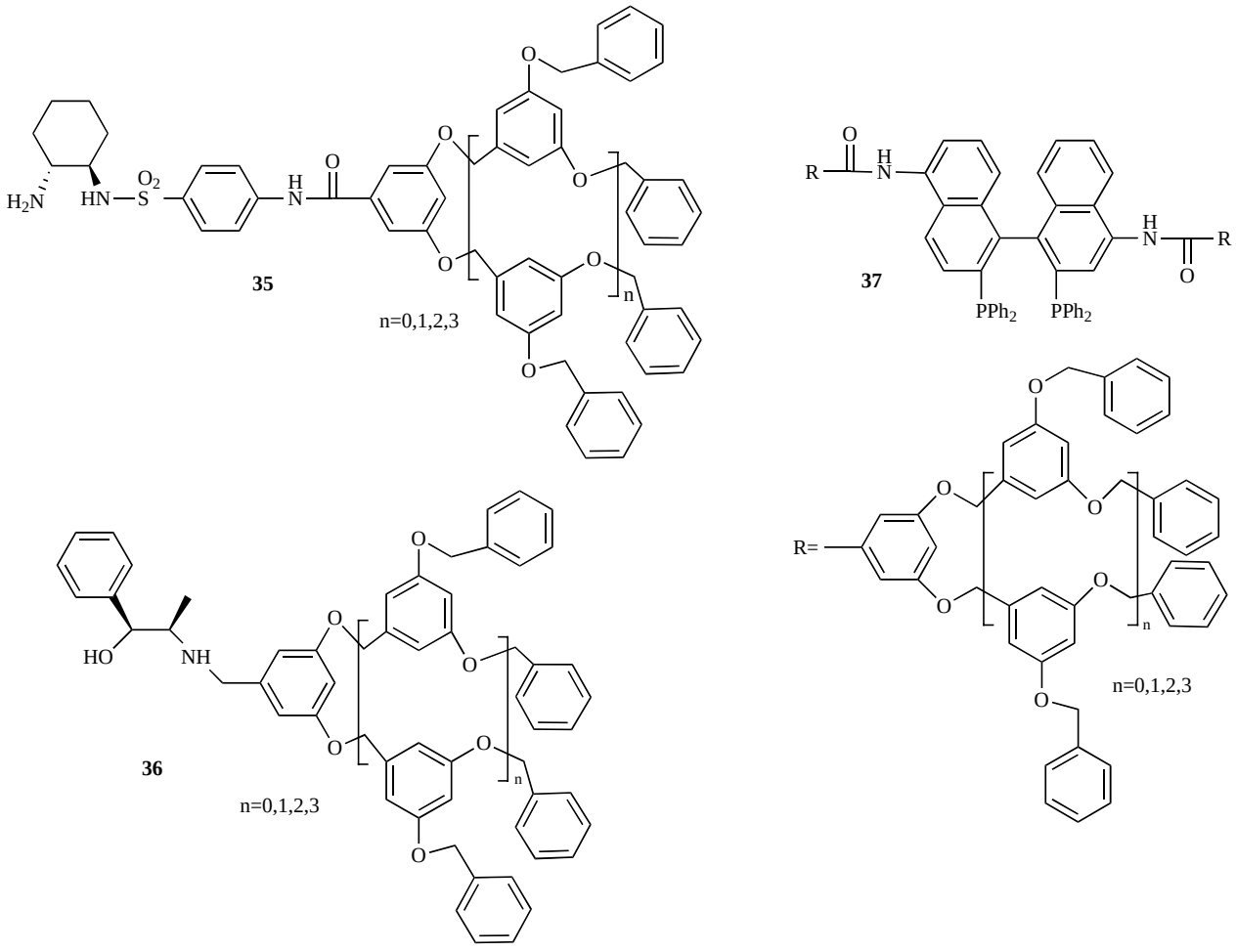

Fig. (11). Frécht-type dendrites.

Catalyst Immobilization on PEG, Micells, Vesicles and Protein and their Application in the Hydrogenation of Ketones

The use of surfactants to create micelles and vesicles were reported by Deng and coworkers [54], in which TsDPEN-metal showed significant enhancement of activity, chemoselectivity and enantioselectivity (>99%) in the ATH of acetophenone, compared to the reaction with no surfactant added. The catalyst embedded in micelles constructed from the surfactant cetylmethylammonium bromide (CTAB) was separated from the organic phase along with the products, and was recycled six times with no loss in activity.

Non-covalent immobilization of catalyst on polyethylene glycol (PEG) was reported recently [55], where Ru-TsDPEN was used as the catalyst to reduce aromatic ketones in a mixture of water and PEG. High activity and enantioselectivity were reported; the catalyst was recovered after extraction of the reduced product with hexane and reused 14 times without loss of enantioselectivity.

For the first time immobilization of complex **38** (Fig. **12**), on a chiral protein was reported [56], where the protein-organometallic catalyst (artificial metalloenzyme) was used in the ATH of ketone. An achiral diamine-Ru-Biotin complex was incorporated with host protein (avidin or streptavidin) and used as an artificial metalloenzyme to asymmetrically hydrogenate ketones in moderate yield and enantioselectivity.

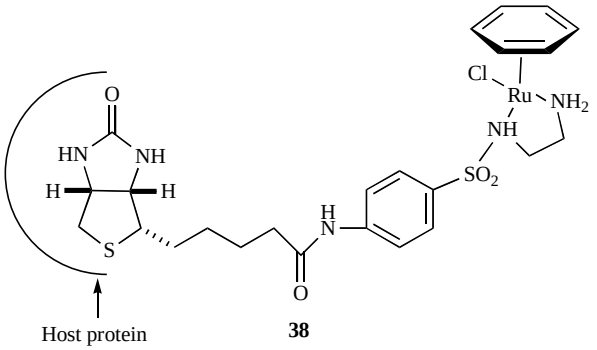

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Fig. (12). Immobilized ligand onto a chiral protein.

Catalyst Immobilization on Nanoparticles and their Application in the Hydrogenation of Ketones

In addition to mesoporous supports, crystalline nanoparticles possessing a high surface area have also been employed in the asymmetric hydrogenation. Very recently, Hu *et al*. [57] used superparamagnetic magnetite nanoparticles (Fe_3O_4) as support for the [Ru-(BINAP)(DPEN)] complex **39** (Fig. **13**). These magnetite nanoparticles are intrinsically not magnetic, but can readily be magnetized by an external magnet. Slightly higher enantioselectivities (>95%) were obtained when the catalyst was used in the asymmetric hydrogenation of ketones compared to those obtained with the homogeneous [Ru(BINAP)(DPEN)] catalyst. The heterogenized catalyst was recycled by "magnetic" decantation and used in asymmetric hydrogenation up to 14 times without loss of activity and enantioselectivity (100% conversion, 95-98% *ee*).

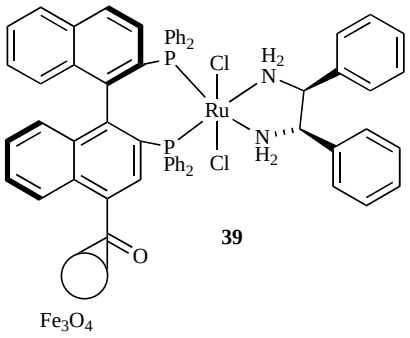

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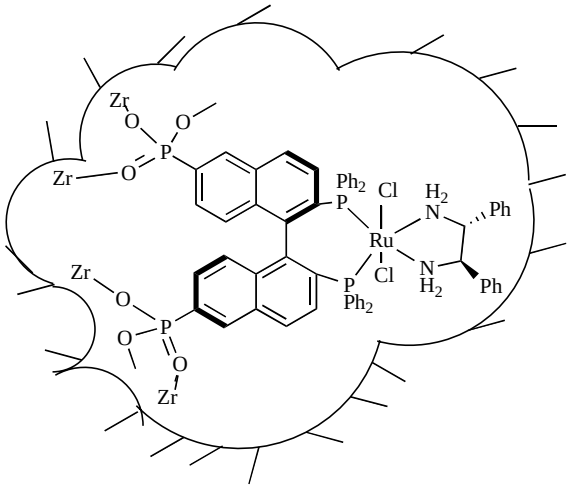
Fig. (13). Immobilized nanoparticles.

Catalysts Immobilized on Hybrid Solid Supports

In addition to polymers, dendrimers and silica as solid supports, recently Lin and co-workers [58] synthesized chiral porous zirconium phosphonates **40**, Fig. (**14**), and reported its application in asymmetric synthesis. A Ru(II) complex with phosphoric acid-substrate BINAP-Dmf was immobilized on mesoporous pillard zirconium phosphonates as ordered organosilica hybrid solids (Fig. **14**). The mesoporous heterogeneous catalyst was used to hydrogenate β-ketoester to the corresponding β-hydroxyester in > 93% ee and 100% conversion. The catalyst was readily recycled and reused [59].



40

Fig. (14). Immobilized complex on hybrid solid supports.

Moreau and co-workers [60] reported the immobilization of chiral cyclohexane-1,2-diamine-Rh(III) complex to an organic-inorganic hybrid material and its application in the transfer hydrogenation of ketones. *N*,*N*'-bis[(triethoxysilyl)propyl]-(-)-(1*R*,2*R*)1,2,-diaminocyclohexane was complexed with $[Rh(COD)Cl]_2$ in the presence of tetraethoxysilane to give a sol-gel material. These sol-gel materials with non-porous to highly porous structure catalyzed the ATH of acetophenone to alcohol in moderate yields (20-80%) and enantionselectivity (10-58%).

Catalyst Immobilization on Ionic Liquids and their Application in Hydrogenation of Ketones

Ionic liquids are receiving growing attention as a means to immobilize catalysts, facilitating product isolation and offering an opportunity to reuse the catalyst [61]. Geldbach and Dyson [62] reported the use of (1*R*,2*R*)-TsDPEN-Ru(II)(arene) complex immobilized on 1-butyl-2,3-dimethylimidazolium hexadifluorophosphate [C4C1C1Im]PF_6 to catalyze acetophenone reduction in HCOOH/Et_3N to the alcohol in 95% yield and 98% ee. The ionic liquid containing the TsDPEN catalyst was used five times without significant decrease in activity. Ionic liquid tethered to Noyori-Ikariya-TsDPEN-Ru(II) complex **41** (Fig. **15**), was also reported to reduce acetophenone to alcohol in good yields (>99%) and enantioselectivity (>99%) with HCOOH/Et_3N as the hydrogen source, whereas the use of 2-propanol was less effective. In the second run the yield dropped to 68% and the enantioselectivity remained unchanged.

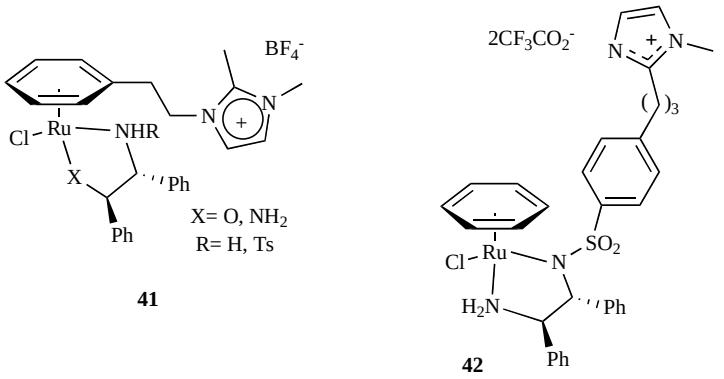


Fig. (15). Immobilized complex on a ionic liquid.

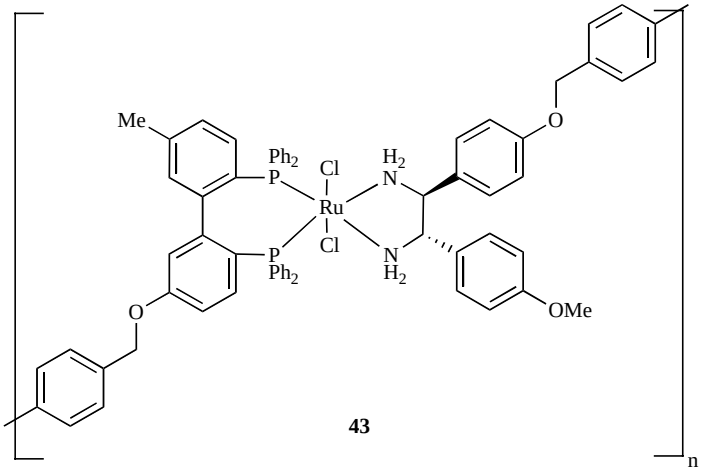


Fig. (16). Self-supported Noyori-type catalyst.

In a similar work Ohta [63] reported the use of TSDPEN–Ru(II) complex immobilized on imidazolium ionic liquid, to reduce acetophenone to alcohol in HCOOH/Et_3N in good yields (>96%) and good enantioselectivity (92%). Tethered ligand **42**, (Fig. **15**) in combination with $[RuCl_2(benzene)]_2$ effected the transfer hydrogenation of acetophenone by HCOOH/Et_3N in ionic liquid [bmim]PF_6 to alcohol in 98% conversion and 92% ee. The catalyst was recycled four times without any loss of activity and enantioselectivity. These results were comparable to the untethered Noyori-Ikariya complex [64].

Other reports on the use of BINAP derived Ru(cymene) complex and BINAP-DPEN-Ru derived complexes [65] were also used in ionic liquids to reduce β-ketoester to β-hydroxyester in good yields (>90%) and enantioselectivity (>99%).

Miscellaneous Immobilization of Ligands and Their Application in the Hydrogenation of Ketones

Self-supported Noyori-type catalyst was generated from an achiral bridged diphosphine and chiral bridged DPEN ligand with Ru(II) ion **43** (Fig. **16**). The immobilized catalyst gave good enantioselectivity and activity in the heterogeneous hydrogenation of aromatic ketones (>99% conversion, >84% ee). The self supported catalyst was reused four times in the hydrogenation without loss of enantioselectivity and catalytic activity [66].

CONCLUSION AND PERSPECTIVES

The renewed interest in supported homogeneous catalysts is partly due to stringent environmental laws requiring clean technology involving "green chemistry", mild reaction conditions, less waste and high performances. The various ligand-metal catalysts discussed above in the asymmetric hydrogenation of ketones have evolved from Noyori's study of well defined homogeneous catalysts combined with fundamental understanding of structure, bonding and reactivity. Based on this, new effective ligands and new supports will continue to appear and the synthetic scope of immobilized ligand-metal catalyzed asymmetric hydrogenation will keep on growing.

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