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Chapter 2

Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones

Bogdan Štefane and Franc Požgan

Additional information is available at the end of the chapter

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1. Introduction

Optically active alcohols are important building blocks in the synthesis of fine chemicals, pharmaceuticals, agrochemicals, flavors and fragrances as well as functional materials (Arai & Ohkuma, 2011; Klingler, 2007). Furthermore, molecular hydrogen is without doubt the cleanest reducing agent, with complete atom efficiency. Therefore, the catalytic, asymmetric hydrogenation (AH) of prochiral ketones is the most practical and simplest method to access enantiomerically enriched secondary alcohols, on both the laboratory and industrial scales. Asymmetric transfer hydrogenation (ATH), on the other hand, represents an attractive alternative or complement to hydrogenation because it is easy to execute and a number of cheap chemicals can be used as hydrogen donors. For practical use and to address environmental issues a high catalyst activity (low loadings) and selectivity is preferable, as well as the employment of ''greener'' solvents, mild operating conditions and recyclable catalyst systems. High turnover numbers (TONs) and turnover frequencies (TOFs), and satisfactory stereo- and chemoselectivities are attainable only with a combination of well-defined metal catalysts and suitable reaction conditions. The reactivity and selectivity can be finely tuned by changing the bulkiness, chirality and electronic properties of the auxiliaries on the metal center of the catalyst.

2. Homogenous, asymmetric hydrogenation and transfer hydrogenation

Since the application of very efficient, chiral BINAP-derived ruthenium complexes in the AH of functionalized ketones (β-keto esters) at a high enantioselectivity level in the homogenous phase (Noyori et al., 1987), the development of more robust and reactive molecular catalysts is still highly desirable. Furthermore, because of the structural and functional diversity of organic substrates, no universal catalysts exist. Ruthenium complexes bearing chiral ligands are among the most commonly used catalysts for AH and ATH,

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following by rhodium and iridium, although in recent times other transition metals, like Fe, Cu, or Os have rapidly penetrated this field.

2.1. Ru-, Rh- and Ir-catalyzed hydrogenation and transfer hydrogenation

A major breakthrough in the wide-scope AHs of ketones was the discovery by Noyori and co-workers of the conceptually new and extremely efficient ruthenium bifunctional catalysts. They found that simple ketones like **1**-**5**, which lack anchoring heteroatoms capable of interacting with a metal center, can be reduced enatioselectively with H_2 (1-8 atm) in *i*-PrOH using a ternary catalyst system comprising a chiral BINAP-$RuCl_2$ precursor, a chiral 1,2-diamine ligand (**L1–L3**) and an alkaline base (*e.g.*, KOH) in a 1:1:2 molar ratio (Fig. 1) (Ohkuma et al., 1995a, 1995b). This catalyst system chemoselectively afforded the corresponding chiral alcohols in almost quantitative yields and up to 99% optical yields. Since then, a number of AHs catalyzed by Ru(II) complexes, like **C1** bearing chiral diphosphine, and diamine ligands for structurally diverse substrates, like alkyl-aryl ketones, heteroaromatic ketones, unsymmetrical benzophenones, aliphatic and α,β-unsaturated ketones, has been reported (Noyori & Ohkuma, 2001; Ohkuma, 2010). Furthermore, proper matching of a chiral ruthenium diphosphine with the correct enantiomer of diamine leads to exceptionally enantioselective catalysts, which are also highly chemoselective for C=O group *vs*. C=C and C≡C bonds, and tolerate many functionalities, like NO_2, CF_3, halogen, acetal, CO_2R, NH_2, NHCOR, etc.

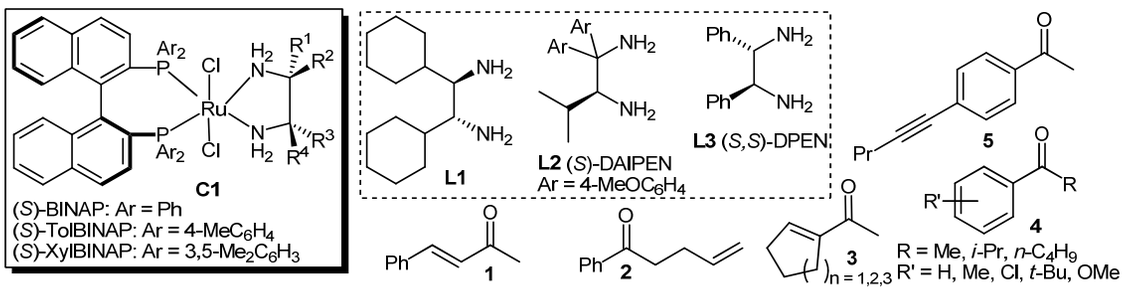


Figure 1. Simple ketones in chemoselective AH catalyzed by bifunctional catalysts of type **C1**

The XylBINAP-complex **C2** proved to be very effective for the stereoselective hydrogenation of heteroaromatic ketones (2-furyl, 2- and 3-thienyl, 2-thiazolyl, 2-pyrrolyl, 2-, 3- and 4-pyridinyl) as well as aromatic-heteroaromatic and bis-heteroaromatic ketones (phenyl-thiazolyl, phenyl-imidazolyl, phenyl-oxazolyl, phenyl-pyridinyl, pyridinyl-thiazolyl) thus providing a plethora of structurally interesting heterocyclic alcohols (C. Chen et al., 2003; Ohkuma et al., 2000). In fact, the complex **C2** has been established as one of the most efficient and selective pre-catalysts for the AH of a variety of ketones (Ohkuma et al., 1998) until the discovery of novel ruthenabicyclic complexes (Matsumura et al., 2011). The hydrogenation of acetophenone catalyzed by the ruthenabicyclic complex **C3** with a substrate-to-catalyst molar ratio (S/C) 10000 under 50 atm of H_2 in a *i*-PrOH/EtOH/*t*-BuOK mixture was completed in one minute to give (*R*)-1-phenylethanol in more than 99% *ee*, thus achieving a TOF of about $3.5 \cdot 10^4$ min^{-1}. For comparison, the pre-catalyst **C2** provided a

similar outcome in four hours. This ruthenabicyclic pre-catalyst is better than all previous catalyst systems in terms of efficiency, enenatioselectivity and the scope of the ketone substrates (aromatic, aliphatic, cyclic and bicyclic ketones; **6**-**9**) (Fig. 2).

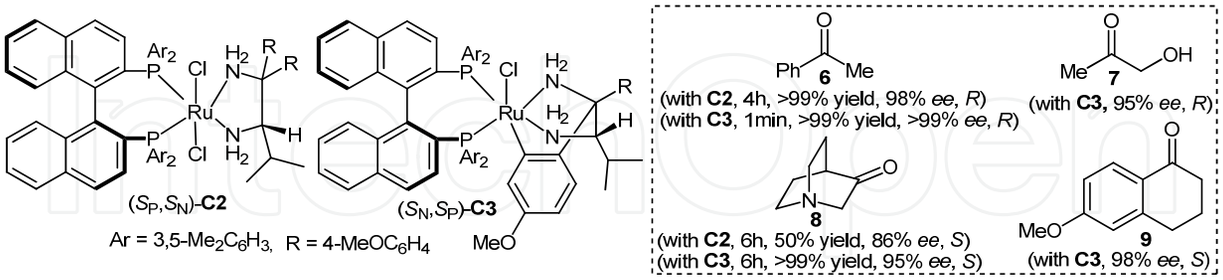


Figure 2. Ruthenabicyclic *vs*. standard Noyori catalyst for the AH of structurally different ketones

Since the Noyori's standard Ru(II) complexes of the type **C1** require the presence of a strong base as a co-catalyst to *in situ* generate an active catalyst, *i.e.,* RuH_2 species, some unwanted side reactions (*e.g.,* transesterification with an alcohol product in the case of **10**) may occur. Ohkuma et al. succeeded in preparing a relatively stable [RuH(η^1-BH_4)(BINAP)(1,2-diamine)] catalyst **C4,** which allowed for the base-free AH of otherwise base-sensitive ketone substrates **10–13** in almost quantitative yields and excellent *ee* values (Fig. 3) (Ohkuma et al., 2002).

The extremely high reactivity and enantio-selectivity of [TunesPhos-Ru(II)-(1,2-diamine)] complexes combined with *t*-BuOK enabled the AH of ring-substituted acetophenones, 2-acetylthiophene, 2-acetylfuran, 1- and 2-acetylnaphthalen, and cyclopropyl methyl ketone with TONs up to 1000000 affording the corresponding chiral alcohols in *ee*'s up to >99% (W. Li et al., 2009). Among them, the catalyst precursor **C5** was found to be the most efficient, since decreasing the catalyst loading from 0.01 mol% to a ppm level had only a small impact on *ee* in the hydrogenation of acetophenone (99.8→98% *ee*), though high conversions necessitated longer reaction times (Fig. 3).

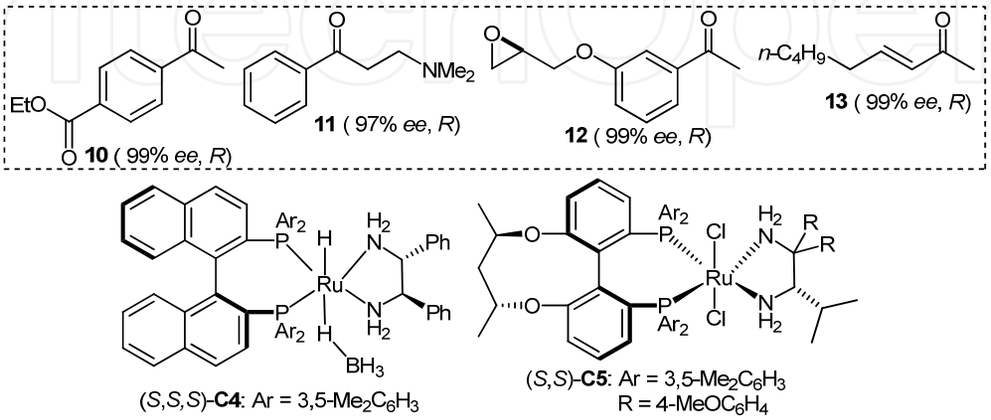


Figure 3. Highly active ruthenium catalysts

The discovery of new classes of hydrogenation catalysts that deviate from the Noyori-type **C1** may represent a good opportunity to reduce every type of ketone substrate with high reactivity and selectivity. Indeed, while the conventional [BINAP-Ru-(1,2-diamine)] catalysts have shown poor reactivity and enantio-selectivity in the hydrogenation of sterically congested *tert*-alkyl ketones, a reduction using the BINAP/(α-picolylamine)-based Ru complex **C6** in a ratio S/C as high as 100000 provided the corresponding *tert*-alkyl carbinols from ketones **14–18** in a high enantiomeric purity (Fig. 4) and proved to be chemoselective for enone **16** and also active for the highly hindered β-keto ester **18** (Ohkuma et al., 2005).

Interestingly, a combined amine-benzimidazole ligand in the complex **C7** influenced the reverse enantioselection from that typically observed in the AH of ring-substituted acetophenones and allowed the reduction to proceed in nonprotic solvents (toluene/*t*-BuOH 9:1) with S/C 1000 to 50000 giving (*S*)-alcohols in 82-99% *ee* (Fig. 4) (Y. Li et al., 2009).

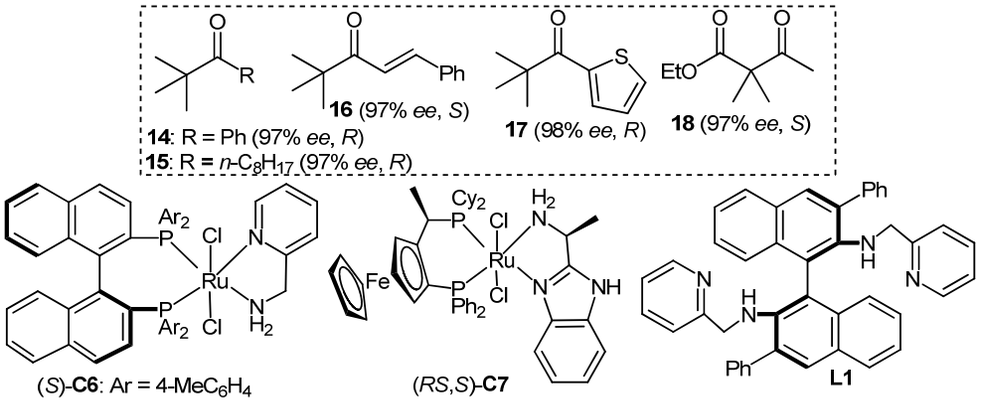


Figure 4. AH of sterically congested and poorly reactive ketones

AH using non-phosphine-based catalysts is attractive due to the toxicity of the catalyst precursors and the product contamination when Noyori-type catalysts are used. However, the efficiency of the π-allyl Ru precursor in combination with the phosphorous-free pyridyl-containing ligand **L1** did not exceed that of the original [BINAP-Ru-diamine] complexes (Fig. 4) (Huang et al., 2006). Interestingly, this new catalyst system catalyzes the hydrogenation of 1-indanone only in the absence of a base.

The most efficient AH catalysts tend to mimic that of Noyori as its excellent enantioselectivity is proposed to be a result of the synergistic effect of chiral phosphane and chiral amine ligands. Nevertheless, commercially available achiral diphosphanes (DPPF, DPEphos) in conjunction with rigid chiral biisoindoline-based diamines have been applied in the Ru-catalyzed AH of (hetero)aromatic ketones, affording excellent enantioselectivities (up to 99% *ee*) with an S/C up to 100000 (Zhu et al., 2011).

Since ketones coordinate more weakly to metals than olefins, many Rh-phosphane complexes show no activity for hydrogenation of simple ketones. However, the highly enantioselective direct hydrogenation of simple ketones **19–24** using an *in-situ*-prepared

catalyst from simple precursors, $[Rh(COD)Cl]_2$ and the rigid chiral biphosphane ligand **L2** promoted by 2,6-lutidine (2,6-dimethylpyridine) and KBr has been reported (Fig. 5) (Q. Jiang et al., 1998). With this catalyst system, the hydrogenation of acetophenone was sluggish and gave only 57% *ee* of (*S*)-1-phenylethanol, whereas the presence of additives dramatically accelerated the reaction and enhanced the enantioselectivity (95% *ee*). While with aryl(heteroaryl) ketones (**19** and **20**) high *ee*'s were observed, more importantly, this hydrogenation procedure proved to be satisfactorily enantioselective for several alkyl-methyl ketones (**21**–**23**), even those bearing unbranched alkyl groups (**24**), which in principle represent the toughest problem for asymmetric reduction.

The complex prepared from $[Rh(COD)OCOCF_3)]_2$ and the amide-phosphine-phosphinite ligand **L3** catalyzed the AH of trifluoromethyl ketones **25** giving almost quantitative yields of the corresponding alcohols in 83-97% *ee* (Kuroki et al., 2001). Interestingly, this Rh-catalyst showed preferential activity and stereoselectivity for fluorinated ketone substrates since acetophenone gave only a 2% yield of 1-phenylethanol in 8% *ee*.

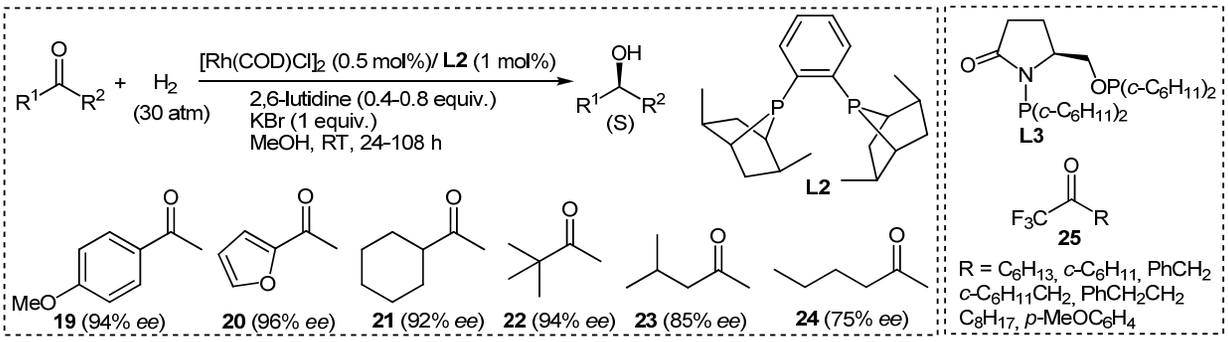


Figure 5. Rh-catalyzed AH of simple and fluorinated ketones

The hydrogenation of ketones catalyzed by chiral iridium complexes has been well studied and developed because iridium is less expensive than rhodium (Malacea et al., 2010). Generally, Ir(I) or Ir(III) complexes with chiral diamines, diphosphines or a combination of both, very similar to those in Ru-catalyzed hydrogenation, have been successfully employed in the AH of various aromatic ketones and β-keto esters. On the other hand, chiral Ir(I) complexes bearing N-heterocyclic carbenes as ligands proved to be far less efficient (Diez & Nagel, 2009). Although complexes of $[Ir(COD)Cl]_2$ and planar-chiral ferrocenyl phosphine-thioethers (*e.g*, **L4**) (Le Roux et al., 2007) or spiro aminophosphine ligands (*e.g.*, **L5**) (J.-B. Xie et al., 2010) efficiently catalyze the AH of acetophenone-type substrates and more importantly *exo*-cyclic α,β-unsaturated ketones **26**, chiral Ir-complexes with phosphorous-nitrogen ligands tend to lose their activity under hydrogenation conditions. The introduction of an additional coordination group in the bidentate spiro aminophosphine ligand **L6** led to a very stable and efficient catalyst for the AH of simple ketones **27,** affording the chiral alcohols **28** in up to 99.9% *ee* (Fig. 6) (J.-H. Xie et al., 2011). For example, acetophenone was reduced with a $2\cdot 10^{-5}$ mol% catalyst loading to give (*S*)-1-phenylethanol in 98% *ee*, reaching a TON of $4.55\cdot 10^{6}$ and a TOF of $1.26\cdot 10^{4}$ h^{-1}.

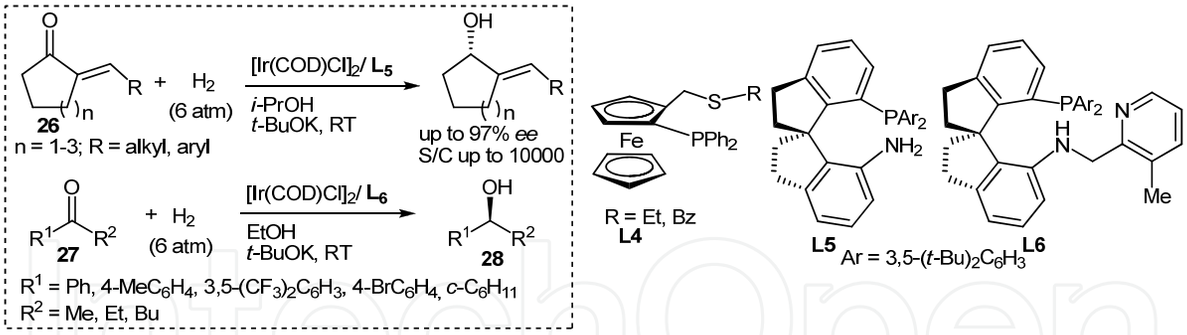


Figure 6. Ir-catalyzed AH

With its origin in Meerwein-Pondorf-Verley reduction, and later developed in its asymmetric version, the transfer hydrogenation of ketones has emerged as an operationally simpler and significantly safer alternative to catalytic H_2-hydrogenation as there is no need for special vessels and high pressures (Ikariya & Blacker, 2007; Palmer & Wills 1999). Moreover, chemo-, regio- and stereoselectivity can often be different from that of AH. In the ATH process, the transition-metal catalyst is able to abstract a hydride and a proton from the hydrogen donor and deliver them to the carbonyl moiety of the ketone. Suitable catalysts for ATH are typically complexes of homochiral ligands with Ru, Rh or Ir, whilst *i*-PrOH/base (hydroxide or alkoxyide) or formic acid/triethylamine (FA/TEA, 5:2 azeotrope) are the most common hydrogen donors usually being the solvents at the same time. A major drawback of using *i*-PrOH is the reaction reversibility, giving limited conversions and affecting the enantiomeric purity of the products after long reaction times. The use of formic acid can overcome these drawbacks, although only a narrow range of catalysts that tolerate formic acid is available.

In parallel with the discovery of efficient ruthenium catalysts for AH, Noyori and co-workers found a prototype of chiral (arene)Ru(II) catalysts of type **C8** bearing *N*-sulfonated 1,2-diamines (*e.g.,* TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenyl-ethylenediamine) or amino alcohols such as chiral ligands for the highly enantio-selective ATH of (hetero)aromatic ketones in *i*-PrOH/KOH or in FA/TEA (Fig. 7) (Fujii et al., 1996; Hashiguchi et al., 1995; Takehara et al., 1996). After this milestone discovery a large number of related or novel ligands and catalysts for ATH have been developed that display a broad substrate scope and provide optically active alcohols in a high enantiomeric purity (Baratta & Rigo, 2008; Everaere et al., 2003; Gladiali et al., 2006).

The stereochemically rigid β-amino alcohols **L7** or **L8** work very well as ligands for Ru-catalyzed ATH in basic *i*-PrOH, outperforming *N*-(*p*-toluenesulfonyl)-1,2-diamines in some cases, but in general these types of ligands appear to be incompatible with a FA/TEA reduction system (Fig. 7) (Palmer et al., 1997; Alonso et al., 1998).

An *in-situ*-prepared complex from $[RuCl_2(benzene)]_2$ and ''roofed'' *cis*-diamine ligand **L9**, which is both conformationally rigid and sterically congested, functions as an excellent catalyst for ATH with the FA/TEA of aryl ketones, including sterically bulky ketones (Matsunaga et al., 2005).

It was first disclosed by Noyori, that a N-H moiety is necessary for an efficient transfer of hydrogen from the metal hydride. However, the Ru complex with the oxazolyl-pyridyl-benzimidazole-based NNN ligand **L10** featuring no N-H functionality exhibited a high catalytic activity in the ATH of different acetophenones (Fig. 7) (Ye et al., 2011).

Another type of ligands lacking a basic NH group like **L11** are based on a combination of *N*-boc-protected *α*-amino acids and a sugar amino alcohol unit and have shown a high enantioselectivity (typically >99 *ee*) in the Ru-catalyzed ATH of aryl ketones, where the enantioselectivity is exclusively controlled by the sugar moiety (Coll et al., 2011). It was found that the addition of LiCl for the ATH in a *i*-PrOH/THF mixture catalyzed by Ru complexes bearing *N*-boc-protected α-amino acid hydroxyamide **L12** significantly enhanced the activity and selectivity, hence suggesting a non-classical bimetallic hydrogen-transfer mechanism (Fig. 7) (Wettergren et al., 2009).

The combination of $[RuCl_2(p\text{-cymene})]_2$ and the chiral BINOL-derived diphosphonite ligand **L13** constitutes yet another Ru catalyst system solely composed of P-ligands for the efficient ATH (*i*-PrOH/*t*-BuOK) of alkyl-aryl and alkyl-alkyl ketones, although the *ee*'s were lower for the latter (Fig. 7) (Reetz & Li, 2006). In contrast, H_2-hydrogenation is less successful when using this system.

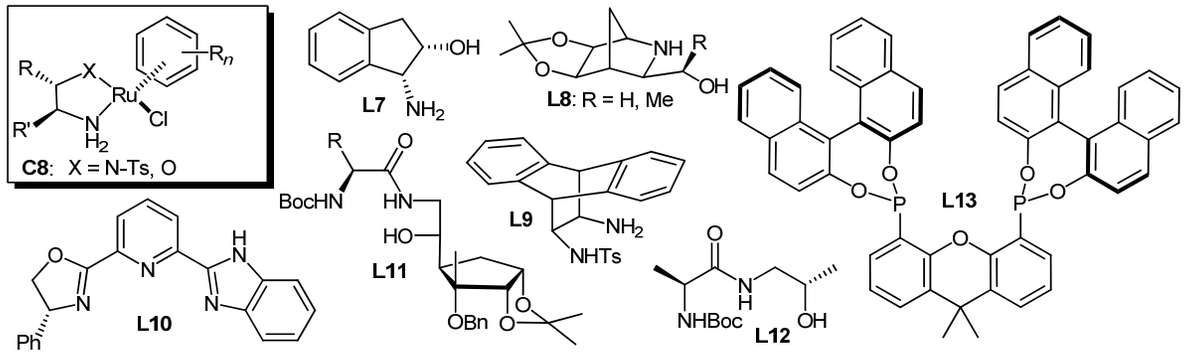


Figure 7. Selected ligands for ATH

There is a continuing search for stable catalysts that would not degrade easily during the hydrogenation process, thus making it possible to execute as many as possible catalytic cycles. In this respect, the covalent linkage from the diamine to the η^6-arene unit in the ''tethered'' catalysts **C9** provide extra stability and a significant increase in rate relative to the ''unthetered'' catalyst in some cases (Fig. 8) (Cheung et al., 2007). With these catalysts, ring-substituted acetophenones, α-chloroacetopehones, dialkyl ketones and ketopyridines were converted to the corresponding chiral alcohols in FA/TEA, mostly near to room temperature.

It has been shown that the Rh complex with the ''achiral'' but tropos benzophenone-derived ligand **L14** and a chiral diamine activator (*e.g.*, **L3**) affords higher enantioselectivities in the ATH of acetophenones and 1-acetylnaphthalene than those obtained by the enantiopure BINAP counterpart (Fig. 8) (Mikami et al., 2006). Cyclometalated Ru(II), Rh(III) and Ir(III) complexes **C10–C12** being easily prepared from commercial ligands, have shown a

satisfactory catalytic activity and a high-to-very high enantioselectivity (*ee*'s up to 98%) in the ATH of different ketones (cyclic ketone, aryl-alkyl ketone, 2-acetylfuran, cyclopropyl-phenyl ketone) (Fig. 8) (Pannetier et al., 2011). The complexes **C11** and **C12** were not isolated but used *in situ*.

The unique phenomenon of an enhancement of the enantioselectivity by using the chiral bulky alcohol (*S*)-1-(9-anthracenyl)ethanol as an additive in the ATH of 4'-phenylacetophenone as well as in the H_2-hydrogenation of several acetophenone derivatives with the catalyst **C13** was recently demonstrated (Fig. 8) (Ito et al., 2012).

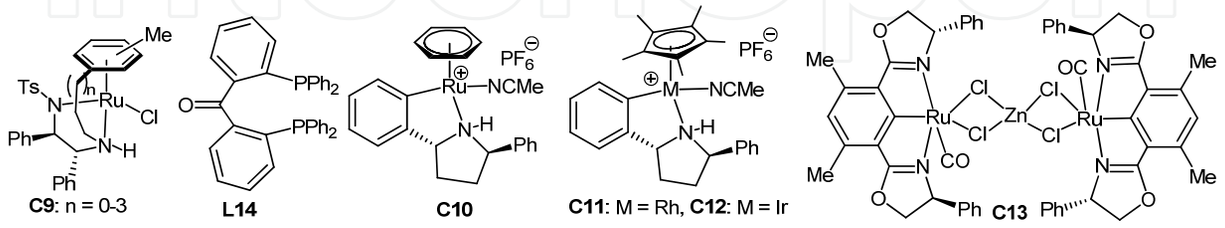


Figure 8. ATH catalyst systems

2.2. Hydrogenation and transfer hydrogenation employing other transition metals

Although Ru(II) complexes have enzyme-like properties reaching high TONs and TOFs, many times near to room temperature, and deliver the secondary alcohols in near-quantitative *ee*'s, the limited availability of precious metals, their high price and their toxicity reduce their attractiveness for future use. In this respect the development of catalysts with similar properties to replace platinum-group metals is very desirable from both the economic and environmental points of view. In fact, iron is cheap and ubiquitous, and its traces in final products are not as serious a problem as traces of ruthenium, for example (Morris, 2009).

The first hydrogenation of ketones catalyzed by a well-defined iron catalyst was effected with an iron hydride Shvo-type complex **C14** (Casey & Guan, 2007), while later on Morris and co-workers succeeded in the ATH of simple ketones catalyzed by iron complexes containing chiral PNNP tetradentate ligands, attaining *ee* values up to 99% in the best cases (Mikhailine et al., 2009; Sues et al., 2011). For example, acetophenone was reduced to (*S*)-1-phenylethanol in 82% *ee* and a TOF as high as $3.6 \cdot 10^3$ h^{-1} with the pre-catalyst **C15**, while installing the sterically more hindered P-ligand in the complex **C16** even increased the activity ($2.6 \cdot 10^4$ h^{-1}) and enantioselectivity (90% *ee*) at the beginning of the reaction (Fig. 9).

An asymmetric Shvo-type iron complex **C17** was found to be a very poor catalyst for the transfer hydrogenation of acetophenone with FA/TEA, since after 48 hours only a 40% conversion and a 25% *ee* were observed (Hopewell et al., 2012).

Enantioselective, copper-catalyzed homogenous H_2-hydrogenation was introduced by Shimizu and co-workers, who used a catalyst system based on $[Cu(NO_3)\{P(3,5\text{-Xylyl})_3\}_2]$,

(*R*)-SEGPHOS (**L15**) or (*S,S*)-BDPP (**L16**), and *t*-BuONa for the reduction of (hetero)aryl ketones, affording good yields and *ee*'s up to 92% (Shimizu et al., 2007, 2009). A range of aryl, alkyl, cyclic, heterocyclic, and aliphatic ketones were hydrogenated under 50 bar of H_2 with a combination of inexpensive $Cu(OAc)_2$ and monodentate binaphthophosphepine ligand **L17** (Junge et al., 2011). On the other hand, $Cu(OTf)_2$ with the bisoxazoline ligand **L18** mimics alcohol dehydrogenase and catalyzes the ATH of α-ketoesters with Hantzsch esters as hydrogen donors (Fig. 10) (J. W. Yang & List, 2006).

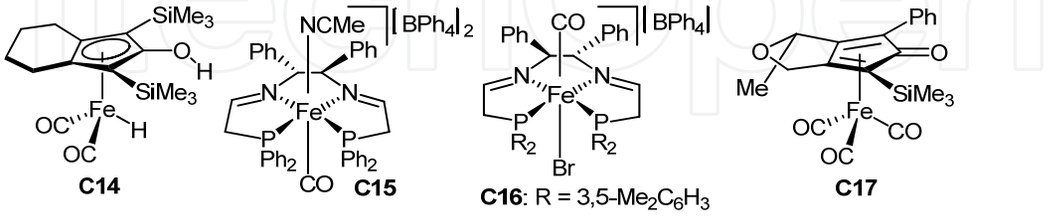


Figure 9. Selected iron catalysts

Owing to the stronger bonding of Os compared to Ru, robust and thermally stable complexes can be obtained, which is important for achieving highly productive catalysts. Os(II) CNN pincer complexes **C18** exhibited a high catalytic activity and productivity in both the AH (5 atm H_2/*t*-BuOK) and ATH (*i*-PrOH/*i*-PrONa) of ketones (Baratta et al., 2008). Enantioselectivities up to 98% *ee* are possible with a remarkably low catalyst loading (0.005-0.02 mol%). More active and productive [$OsCl_2$(diphosphane)(diamine)] complexes like **C19,** resembling those of Noyori, catalyzed the AH of alkyl-aryl, *tert*-butyl and cyclic ketones with S/C ratios of 10000–100000 and TOFs up to 10^4 h^{-1} (Baratta et al., 2010) (Fig. 10).

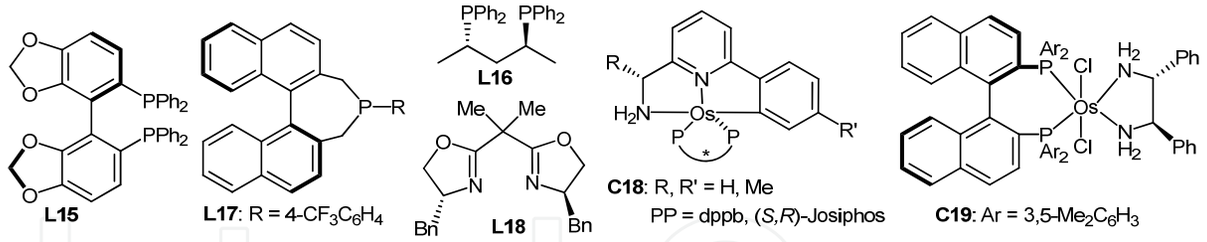


Figure 10. Ligands for Cu-mediated hydrogenation and Os-complexes

2.3. Hydrogenation and transfer hydrogenation in water and ionic liquids

As a consequence of the increasing demand for ''greener'' laboratory and industrial applications, the development of water-operating catalytic systems for the asymmetric hydrogenation of ketones has been of great interest (Wu & Xiao, 2007). The main disadvantage, however, is the low solubility of the homogenous metal catalysts and most of the organic substrates when going from organic to aqueous media, which may be reflected in a reduced activity and selectivity. To circumvent this, either hydrophilic, often charged, functionalities can be introduced to ligands to render the catalysts water-soluble, or different surfactants can be added in order to solvate the reaction partners, although in some cases water-insoluble catalysts can deliver a superior activity and selectivity.

Water-soluble Ru, Ir or Rh catalysts were prepared *in situ* using modified Noyori-type ligands **L19** and enabled the ATH in *i*-PrOH in the presence of water (Bubert et al., 2001, Thorpe et al., 2001), while Chung and co-workers communicated the first examples of the ATH of aromatic ketones with HCO_2Na in neat water catalyzed by $[RuCl_2(p\text{-cymene})]_2$ together with the (S)-proline amide ligand **L20** attaining *ee*'s comparable with those in a homogenous solution (Rhyoo et al., 2001). The latter catalyst system appeared to be quite stable, since it could be recycled six times with little loss of performance. Similarly, an *in-situ*-prepared catalytic complex from the proline-functionalized ligand **L21** and $[RuCl_2(p\text{-cymene})]_2$ in a 1:1 ratio showed good activity for the aqueous ATH of acetophenone-type ketones as well as bicyclic ketones (Manville et al., 2011). Due to its difficult purification, the ligand **L22** was replaced by another water-soluble ligand **L23**, and its complex with $[C_5Me_5RhCl_2]_2$ was active for the ATH of α-bromomethylaromatic ketones, besides ring-substituted acetophenones, and bicyclic ketones (L. Li et al., 2007). The tethered Rh complex **C20** reported by Wills acts as a very productive catalyst for aqueous-reduction as it continues to turnover a reaction at low loadings, even at 0.01 mol%, typically associated with the best H_2-hydrogenation catalysts, without any decrease in the enantioselectivity (Matharu et al., 2006). The chiral aqua Ir(III)-complex **C21** bearing non-sulfonated diamine was shown to be very flexible in the ATH of α-cyano- and α-nitroacetophenones as the reaction can be conducted at pH 2 (formic acid) as well as at pH 5.5 (HCO_2Na) in a water-methanol system without affecting the selectivity (Vázquez-Villa et al., 2011) (Fig. 11).

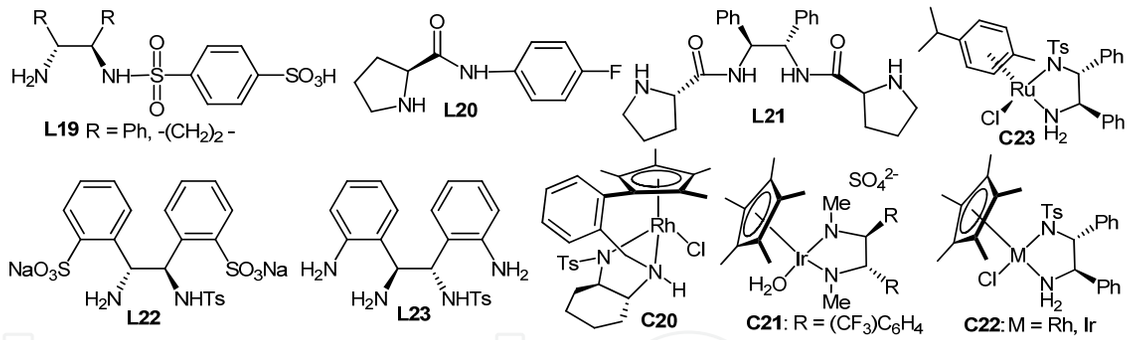


Figure 11. Selected ligands and complexes for aqueous hydrogenation

Surfactants are often added as co-solvents to obtain a sufficient solubility of the reactants, products and metal catalysts, thus retaining the activity and selectivity of the hydrogenation process. The ATH of ketones, particularly α-bromomethyl aromatic ketones, was successfully performed with HCO_2Na by employing the unmodified and hydrophobic Ru-, Rh- and Ir-TsDPEN complexes **C22** and **C23** in the presence of single-tailed, cationic and anionic surfactants and to form micelles and vesicles (Fig. 11) (Wang et al., 2005). It is notable that catalysts embedded in these micro-reactors can be separated from the organic phase and reused for at least six times without any loss of activity and enantioselectivity.

In recent years ionic liquids (ILs) have attracted an increasing interest because of their non-volatility, non-flammability and low toxicity. Additionally, ILs are capable of immobilizing homogenous catalysts and facilitating the recycling of catalysts. Ideally, organic products

can be easily separated by extraction with a less polar solvent and the IL phase containing catalyst can be reused. Such an immobilization of catalysts also promises to prevent the leaching of toxic metals into the organic products, which is especially desirable in the production of pharmaceutical intermediates.

Various aromatic ketones were reduced with FA/TEA in an ionic liquid **L25** at 40 °C, catalyzed by an *in-situ*-generated catalyst from $[RuCl_2(p\text{-cymene})]_2$ and the ionic chiral aminosulfonamide ligand **L24**, affording good-to-excellent conversions and *ee* values (Fig. 12) (Zhou et al., 2011). The catalytic system could be recovered and reused three times with a slight loss of enantioselectivity from 97% to 94% *ee* for the reduction of acetophenone. In contrast, the catalyst activity showed a remarkable drop with each cycle, and therefore the reaction times had to be prolonged for high conversions.

While for the AH of β-alkyl β-ketoesters high enantioselectivities can be attained by using the Ru-BINAP system, for the analogous β-aryl ketoesters much more inferior *ee* values were obtained (Noyori et al., 1987). However, the highly enantioselective hydrogenation of a wide range of β-aryl ketoesters **29** in the homogenous ionic liquid **L26**/methanol system was possible with Ru catalysts bearing 4,4'-substituted BINAP ligands **L27** (Fig. 12) (Hu et al., 2004a). The catalysts were recycled and reused four times, but there was a remarkable deterioration in the conversion rates and *ee* values, which were more pronounced with the ligand R = $SiMe_3$.

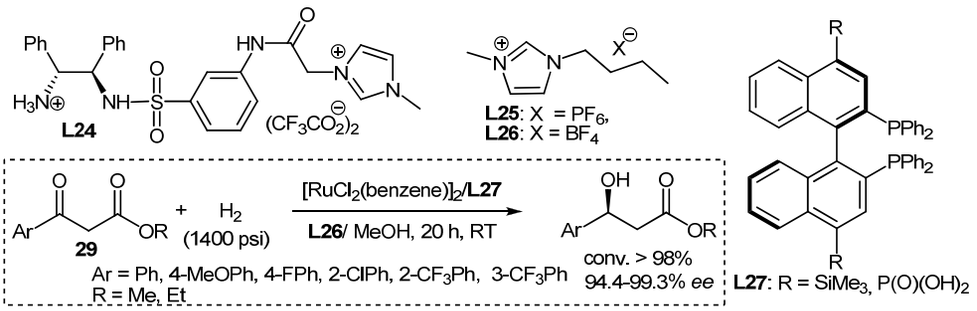


Figure 12. Hydrogenation in ionic liquids

2.4. Mechanistic considerations

Homogenous hydrogenation and transfer hydrogenation may be mechanistically closely related because both reactions involve a metal hydride species under catalytic conditions, thus sharing a multistep pathway of hydride transfer to the ketone, *i.e.*, the hydridic route, which can operate in the inner or outer coordination sphere of the catalyst metal center (Clapham et al., 2004). Applied only to the transfer hydrogenation, direct hydrogen transfer (Meerwein-Ponndorf-Verly reaction) from the metal alkoxyide to the ketone without the involvement of metal hydrides proceeding through a six-membered transition state has also been proposed, and is typical for non-transition metals (*e.g.*, Al) (deGraauw et al., 1994).

Noyori and co-workers proposed metal-ligand bifunctional catalysis for their Ru catalysts containing chiral phosphine-amine ligands and for (arene)Ru-diamine catalysts, which

consequently resulted in a widely accepted mechanism to be responsible for the highly enantio-selective hydrogenation and transfer hydrogenation of prochiral ketones (Noyori et al., 2001, 2005). The actual catalysts, Ru-hydrides **31** or **34,** are usually created in a basic alcoholic solution (under H_2 or not) at the beginning of the catalytic reaction from the Ru precursors **30** or **33**. Note that only the *trans*-RuH_2 **31** is a very active catalyst. A key feature of bifunctional catalysts is that the N-H unit of a diamine ligand forms a hydrogen bond with carbonyl oxygen, thus stabilizing the six-membered pericyclic transition state (**TS1** or **TS1'**) and hence facilitating the hydride transfer from Ru-H, which adds to the carbonyl carbon concurrently with a transfer of the acidic proton from N-H to the carbonyl oxygen. This concerted process results in the formation of an alcohol product and Ru-amido species (**32** or **35**). The hydride intermediate (**31** or **34**) is then regenerated either by the addition of molecular hydrogen or by the reverse hydrogen transfer from a dihydrogen source (*e.g.*, *i*-PrOH) to the formal 16-electron Ru-amido intermediate (**32** or **35**). The latter step is considered to be a rate-limiting step. The overall process is occurring outside the coordination sphere of the metal without the interacting of the ketone or alcohol with the metal center. This is known as an outer-sphere mechanism. It is depicted in Fig. 13 for the hydrogenation with molecular hydrogen catalyzed by the diphosphine-Ru-diamine system (a) and for transfer hydrogenation catalyzed by the (arene)Ru-diamine complex (b) in its simplified representation.

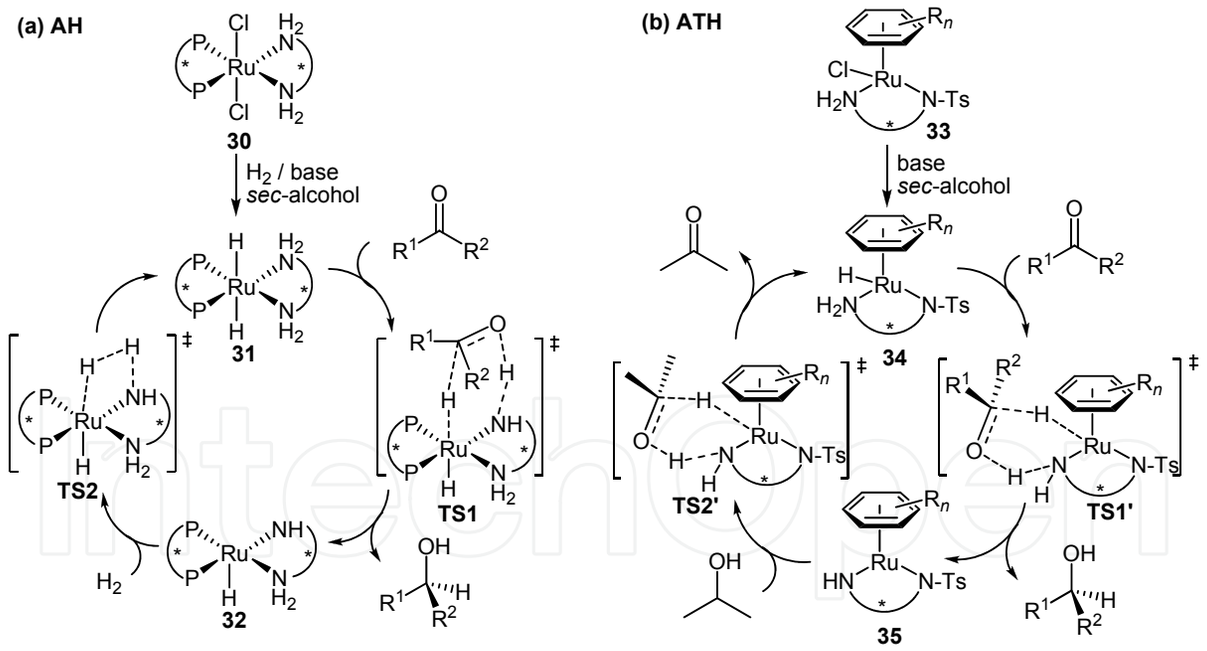


Figure 13. Outer-sphere hydridic route for bifunctional catalysts

Depending on transition-metal catalysts, an ionic mechanism has also been proposed where the proton and hydride transfer occur in separate steps (Bullock, 2004).

The active species in catalytic cycles, Ru-hydride (**31** or **34**) and Ru-amido complexes (**32** or **35**), have not only been detected but also isolated in some cases (Abdur-Rashid et al., 2001, 2002; Haack et al 1997).

The absolute configuration of the alcohol product in AH is determined in the six-membered transition state resulting from the reaction of a chiral diphosphine-diamine-RuH_2 complex with a prochiral ketone (Noyori et al., 2005). Because the enantiofaces of the ketone are differentiated on the molecular surface of the saturated RuH_2 complex, a suitable combination of the catalyst and substrate is necessary for high efficiency. The prochiral ketone (*e.g.,* acetophenone) approaches in such a ways as to minimize the non-bonded repulsion between the phosphine Ar group and the phenyl ring of the ketone, and to maximize the electronic NH/π attraction (Fig 14 (a)).

The stereoselectivity in the hydrogenation of prochiral aryl ketones catalyzed by (arene)Ru(II) complexes (mostly in ATH) has been ascribed not only to the chiral environment originating from the amine ligand, but also to the contribution of the arene ligand to the stabilization of the transition state through the CH/π interaction (Fig 14 (b)) (Yamakawa et al., 2001). This interaction as well as the NH/π interaction occurring in the transition states with diphosphine-Ru-(1,2-diamine) systems may explain why aryl ketones usually give better *ee* values than simple unfunctionalized alkyl-alkyl ketones.

Depending on the ligands attached to the metal center (M = transition metal) the inner-sphere mechanisms, in which monohydride or dihydride species are involved, can operate in H_2-hydrogenation and transfer hydrogenation (Clapham et al., 2004, Samec et al., 2006; Wylie et al., 2011). In contrast to the outer-sphere mechanism, here the ketone and alcohol interact with the metal center.

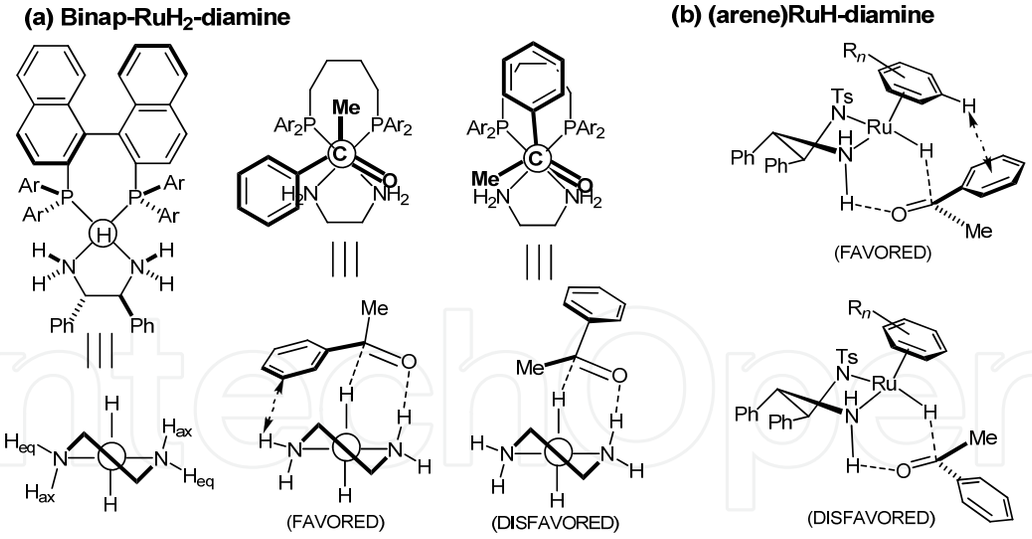


Figure 14. Enantiodifferentiation in the bifunctional-catalyzed hydrogenation of acetophenone

3. Heterogeneous hydrogenation

For the heterogeneous, asymmetric, catalytic reduction of the C=O functionality, there are two types of heterogeneous catalysts. One is chirally modified supported metals, and the other is the immobilized homogeneous catalyst on a variety of organic and inorganic polymeric materials. There are also two major reasons for preparing and studying

heterogeneous catalysts: firstly, and most importantly, the better and advanced separation and handling properties, and, secondly, the potential to create catalytic positions with an improved catalytic performance. The ultimate heterogeneous catalyst can easily be renewed, reused without of loss of activity and selectivity, which are at least as good or even better than those of the homogeneous analogue.

3.1. Immobilized chiral complexes

The immobilization of a homogeneous metal coordination complex is a useful strategy in the preparation of new hydrogenation catalysts. Much effort has been devoted to the preparation of such heterogenized complexes over the past decade due to their ease of separation from the reaction mixture and the desired minimal product contamination caused by metal leaching, as well as to their efficient recyclability without any significant loss of activity. Preferably, Rh, Ir, and Ru complexes have been employed in the hydrogenations of carbonyl functionality (Corma et al., 2006). Chemically different supports have been used for the immobilization of various homogeneous complexes, including polymeric organic and inorganic supports (Saluzzo et al., 2002; Bergbreiter, 2002; Fan et al., 2002). Due to their chemical nature, organic polymeric supports have some drawbacks concerning reduced stability that affects the reusability of the catalysts, mainly due to their swelling and deformation (Bräse et al., 2003; Dickerson et al., 2002). Supports of an inorganic nature are more suitable owing to their physical properties, chemical inertness and stability (with respect to swelling and deformation) in organic solvents. The above-mentioned properties of the inorganic supports will facilitate the applications of the materials in reactions carried at higher temperatures and their use in continuous-flow reactions. In the past decade a lot of research effort has been devoted to the development of adequate procedures to attach homogenous catalysts onto inorganic supports (Merckle & Blümel, 2005; Crosman et al., 2005; Corma et al., 2005; Jones et al., 2005; Melero et al., 2007). Immobilization via covalent bonds is undoubtedly the most convenient, but on the other hand, it is the most challenging method for immobilization to perform on such supports (Jones et al., 2005; Steiner et al., 2004; Pugin et al., 2002; Sandree et al., 2001). For example, micelle templated silicas (MTS) featuring a unique porous distribution and high thermal and mechanical stabilities can be easily functionalized by the direct grafting of the functional organo-silane groups on their surfaces (McMorn & Hutchings, 2004; Heckel & Seebach, 2002; Bigi et al., 2002, Clark & Macquarrie, 1998; Tada & Iwasawa, 2006). On the other hand, polar solvents such as water or alcohols and high temperatures during the catalytic procedure can promote the hydrolysis of the grafted moieties.

The heterogenized catalysts can potentially combine the advantages of both homogenous and heterogeneous systems. In 2003, Hu and coworkers developed a novel chiral porous solid catalyst based on zirconium phosphonates for the practically useful enantio-selective hydrogenation of unfunctionalized aromatic ketones (Fig. 15) (Hu et al., 2003a).

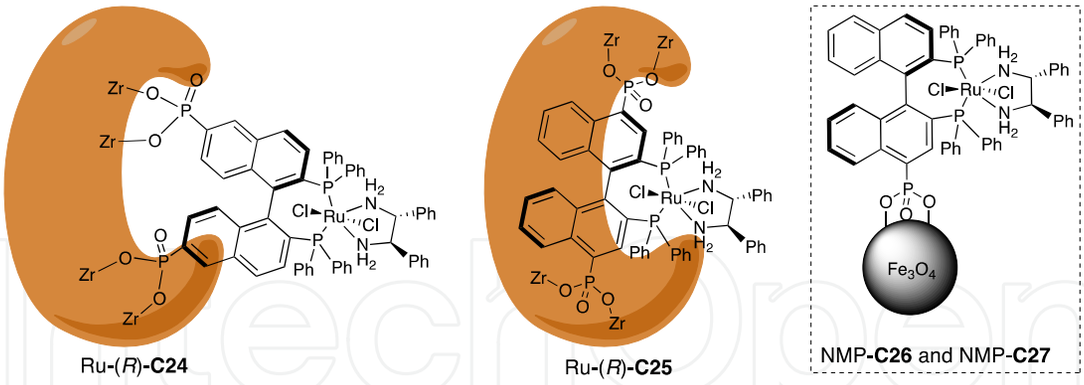
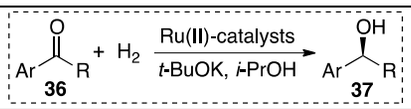


Figure 15. Schematic presentation of chiral porous Zr-phosphonate-Ru-(*R*)-**C24** in Ru-(*R*)-**C25** heterogeneous catalysts

With the built-in Ru-BINAP-DPEN moieties, porous solids of Ru-(*R*)-**C24** and Ru-(*R*)-**C25** exhibited high activity and enantioselectivity in the hydrogenation of aromatic ketones (Table 1). Acetophenone was hydrogenated, producing 1-phenylethanol with a complete conversion and 96.3% *ee* in *i*-PrOH with a 0.1 mol% loading of Ru-(*R*)-**C24**. This level of enantioselectivity is higher than that observed for the parent Ru-BINAP-DPEN homogeneous catalyst, which gives ~80% *ee* for the hydrogenation of acetophenone (Ohkuma et al., 1995a; Doucet et al., 1998). As indicated in table 1, the Ru-(*R*)-**C24** immobilized catalyst has also been tested to catalyze the hydrogenation of other aromatic ketones resulting in the formation of the corresponding alcohols with the same high enantioselectivity (90.6-99.0% *ee*) and complete consumption of the starting ketone. Although the Ru-(*R*)-**C25** catalyst is also highly active for the hydrogenation of aromatic ketones, the enantoselectivity is modest and similar to that of the parent Ru-BINAP-DPEN homogeneous catalyst. The authors believe that the modest enantioselectivities observed for the Ru-(*R*)-**C25** catalyst originate in the substituent effects on the BINAP ligand. Furthermore, the catalysts were successfully reused without any deterioration of the enantioselectivity in eight cycles. The activities did not decrease for the first six cycles, but began to drop during the seventh run (95% conversion), reaching 85% of conversion in the eighth cycle. Furthermore, the Ru(II) catalysts of type Ru-(*R*)-**C24** and Ru-(*R*)-**C25** having dimethylformamide as a ligand instead of 1,2-diphenylethylenediamine were developed and used for the heterogeneous AH of β-keto esters with *ee* values from 91.7 up to 95.0 % with the same enantio enrichment as is the case in the parent homogenous BINAP-Ru catalyst. The substrates, β-aryl-substituted β-keto esters, are hydrogenated with the same modest *ee* values (69.6 % *ee*) as observed when using the homogenous BINAP-Ru analogue (Noyori & Takaya, 1990). The introduced catalysts can be readily recycled and reused (Hu et al., 2003b). Structurally similar Ru(II) catalysts with phosphonic-acid-substituted BINAP were prepared and afterwards immobilized on magnetite nanoparticles prepared by the thermal decomposition method (MNP-**C26**, Fig. 15) or by the coprecipitation method (NMP-**C27**, Fig. 15) (Hu et al., 2005). The catalysts were tested for the heterogeneous asymmetric hydrogenation of aromatic ketones showing a remarkably high activity and enantioselectivity (Table 1).



Substrate **36**	Ru-(*R*)-**C24**; *ee* (%)	Ru-(*R*)-**C25**; *ee* (%)	MNP-**C26**; *ee* (%)	MNP-**C27**; *ee* (%)
Ar = Ph, R = Me	96.3	79.0	87.6	81.7
Ar = 2-naphtyl, R = Me	97.1	82.1	87.6	82.0
Ar = 4-*t*Bu-Ph, R = Me	99.2	91.5	95.1	91.1
Ar = 4-MeO-Ph, R = Me	96.0	79.9	87.6	77.7
Ar = 4-Cl-Ph, R = Me	94.9	59.3	76.6	70.6
Ar = 4-Me-Ph, R = Me	97.0	79.5	87.9	80.5
Ar = Ph, R = Et	93.1	83.9	88.9	86.3
Ar = Ph, R = *cyclo*-Pr	90.6	–	–	–
Ar = 1-naphtyl, R = Me	99.2	95.8	–	–

Table 1. Heterogeneous hydrogenation of the aromatic ketones using Ru(II) catalyst

Heterogeneous chiral Ru(II)-TsDPEN-derived catalysts based on Noyori's (1*S*,2*S*)- or (1*R*,2*R*)-*N*-p-tosylsulfonyl)-1,2-diphenylethylenediamine (TsDPEN) were successfully immobilized onto amorphous silica gel and silica mesopores of MCM-41 and SBA-15 using an easily accessible approach (P.-N. Liu et al., 2004a, 2004b, 2005). The immobilized catalysts demonstrated high catalytic activities and enantioselectivities (up to >99% *ee*, **38a**-**38l**) (Fig. 16) for the heterogeneous ATH of different ketones. In particular, the catalyst could be recovered and reused in multiple consecutive runs (up to 10 uses) with a completely maintained enantioselectivity.

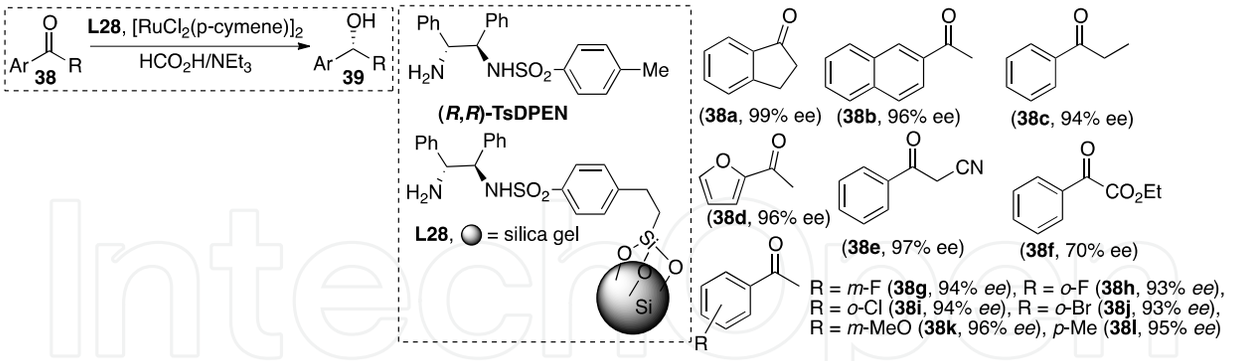


Figure 16. Heterogeneous Ru^{II} mesoporous silica-supported catalysts

Additionally, Li and coworkers (J. Li et al., 2009) developed a Ru(II)-TsDPEN-derived catalyst that was immobilized in a magnetic siliceous mesocellular foam material. The heterogeneous catalyst showed comparable activities and enantioselectivities (*ee* 89-97%) with the parent catalyst Ru(II)-TsDPEN in the ATH of imines and simple aromatic ketones. Polymer-supported-TsDPEN ligands combined with $[RuCl_2(p\text{-cymene})]_2$ have been shown to exhibit high activities (93-98%) and enantioselectivities (86-97% *ee*) for the heterogeneous ATH of aromatic ketones, which are suitable intermediates for the synthesis of (*S*)-fluoxetine with a 75% yield and a 97% *ee* (Y. Li et al., 2005).

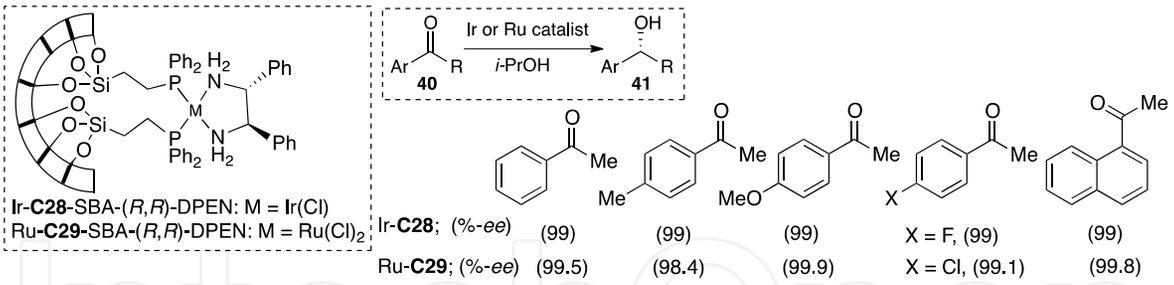


Figure 17. Ir and Ru mesoporous silica-supported catalysts

Chiral Ru and Ir, mesoporous, silica-supported catalysts were introduced by Liu and coworkers (G. Liu et al., 2008a, 2008b). The Ir-**C28**-SBA-(*R,R*)-DPEN catalyst was investigated using a series of aromatic ketones as substrates (Fig. 17). In general, high conversions (95-99 %) and an excellent enantioselectivity, producing the corresponding *R* enantiomers, were observed by applying 40 atm of H_2 at 50 °C and 0.4 mol% of catalyst loading. The catalyst was recovered and reused several times without considerably affecting the *ee* values. The analogous Ru catalyst, Ru-**C29**-SBA-(*R,R*)-DPEN, also displays a high catalytic activity and enantioselectivity under similar reaction conditions (Fig. 17) for the ATH of aromatic ketones.

Two magnetic chiral Ir and Rh catalysts were prepared *via* directly post-grafting 1,2-diphenylethylenediamine and 1,2-cyclohexanediamine-derived organic silica onto silica-coated iron oxide nanoparticles (G. Liu et al., 2011). The synthesis was followed by a complexation with Ir(III) or Rh(III) complexes. High catalytic activities (up to 99% conversion) and enantioselectivities (up to 92% *ee*) were obtained in the ATH reaction, reducing the aromatic ketones in an aqueous medium (Fig. 18). Both catalysts could be recovered by magnetic separation and be reused ten times without significantly affecting their catalytic activities and enantioselectivities.

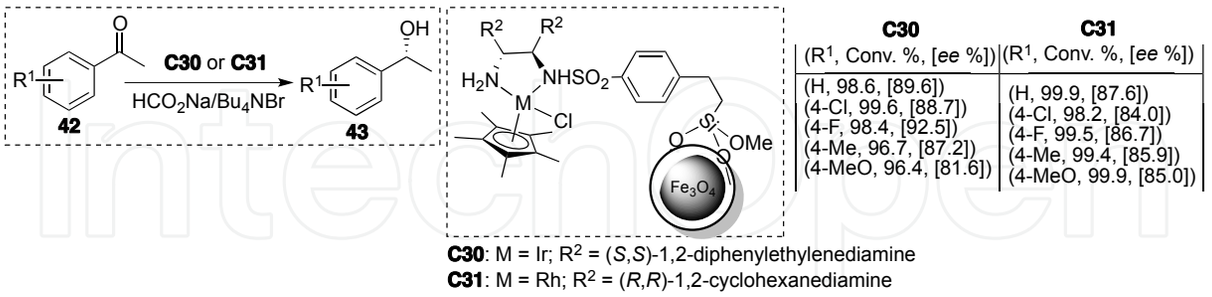


Figure 18. Magnetic Ir and Rh chiral catalysts

The mesoporous SBA-15 anchored 9-amino *epi*-cinchonine-$[Ir(COD)Cl]_2$ complex shows good activity and moderate enantio-selectivity (45-78% *ee*) in the ATH reaction of substituted acetophenones (Shen et al., 2010).

The chiral $RuCl_2$-diphosphine-diamine complex with siloxy functionality was successfully immobilized on mesoporous silica nanospheres with three-dimensional channels (Fig. 19) (Mihalcik & Lin, 2008). Upon activation with *t*-BuOK, the catalysts **C32**-**C36** can be used for

the AH of aromatic ketones; however, **C32**-**C36** exhibit lower enantioselectivities than their parent homogeneous catalysts. The highest *ee* value of 82% was observed for the hydrogenation of 2-acetonaphthone using **C33** as a catalyst. A similar drop in enantio-selectivities has been noticed for many asymmetric catalysts immobilized on bulk mesoporous silica (Song & Lee, 2002). Catalysts of the type **C32**-**C34** were also examined in a dynamic kinetic resolution of α-branched aryl aldehydes. The highest *ee* value of 97% was obtained using 0.1 mol% of the **C33** catalyst and 700 psi of H_2 pressure on 3-methyl-2-phenylbutanal as a substrate.

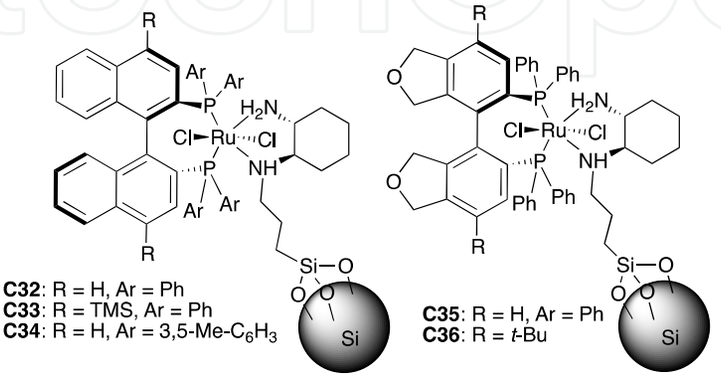


Figure 19. Chiral $RuCl_2$-diphosphine-diamine complexes immobilized on mesoporous silica nanospheres

Differently substituted Rh complexes were anchored on an Al_2O_3 support and applied for the enantioselective C=O hydrogenation with reasonable activity and enantioselectivities with *ee*s up to 80% (Zsigmond et al., 2008). Due to the fact that an immobilized catalyst did not show a superior enantio-selectivity compared to its homogenous counterparts, the major advantage of the catalyst's immobilization is the possibility to recycle the catalysts.

The immobilization of the rhodium complexes [Rh((*R*)-BINAP)(COD)]CF_3SO_3, [Rh((*S*)-BINAP)(COD)]ClO_4·thf, and [Rh((*S*,*S*)-chiraphos)(NOR)]ClO_4, and the ruthenium complexes [Ru((*R*)-BINAP)(PPh_3)Cl_2] and [Ru((*R*)-BINAP)Cl_3] in a thin film of silica-supported ionic liquid enhanced the enantioselectivity of the parent catalyst. As the model reaction, the stereo-selective hydrogenation of acetophenone as a non-chelating prochiral ketone was studied. The enantioselectivities in a moderate range (up to 74%) were observed (Fow et al., 2008). Furthermore, a mesoporous material-supported ionic liquid phase was used as a carrier medium to immobilize the chiral ruthenium complex composed of a chiral 1,2-diamine and an achiral monophosphine (Lou et al., 2010). All the prepared catalysts were active in the hydrogenation of simple aromatic ketones enabling an enantioselectivity from 45 up to 78% *ee*.

Furthermore, a series of polystyrene-supported TsDPEN ligands were prepared in one step and converted to the corresponding Ru(II) complexes by a treatment with [$RuCl_2$(*p*-cymene)]$_2$ in dichloromethane at 40 °C for an hour (Marcos et al., 2011). The so-prepared polystyrene-based Ru(II)-catalytic resins showed a low conversion (37%, 48 h, 40 °C) of acetophenone to the corresponding (*R*)-alcohol (85% *ee*) in the ATH (HCO_2H/Et_3N = 5/2) in

water. The more promising results were obtained in dichloromethane, where (*R*)-1-phenylethanol was produced in 99% conversion and with 97% *ee*. The catalytic resin could be recycled three times without any significant loss of conversion and enantioselectivity, but further recycling shows a major drop in performance of the catalytic resin. A modified tethered Rh(III)-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (Rh-TsDPEN) complex immobilized on polymeric supports (amino-functionalized polyethylene microparticles) was used in kinetic and up-scaling experiments on the ATH of acetophenone in water. A second-order model describes the enantioselective conversion of acetophenone to phenylethanol and mainly the solution pH was found to play a pivotal role for the activity and reusability of the catalyst (Dimroth et al., 2011). Polyethylene glycol (PEG) supported chiral ligands have also been developed and examined in the Ru-catalyzed ATH of prochiral aromatic ketones in water using HCO_2Na as the hydrogen source. Xiao et al. introduced a PTsDPEN ligand that has two PEG chains (PEG-2000) on the *meta*-position of the TsDPEN's phenyl groups. Comparing the results of the Ru-TsDPEN catalyst in water, the PEG Ru(II) catalyst in the ATH of various aromatic ketones by HCO_2Na in water gave faster rates and a good reusability (X. Li et al., 2004a, 2004b). As an alternative for attaching a PEG chain onto the TsDPEN-tipe ligands, a medium-length PEG chain (PEG-750) at the *para*-position of the aryl sulfonate group was introduced (J. Liu et al., 2008). The corresponding Ru-PEG-BsDPEN catalyst displays a high activity, reusability and enantioselectivity (up to 99% *ee*) in the ATH in water.

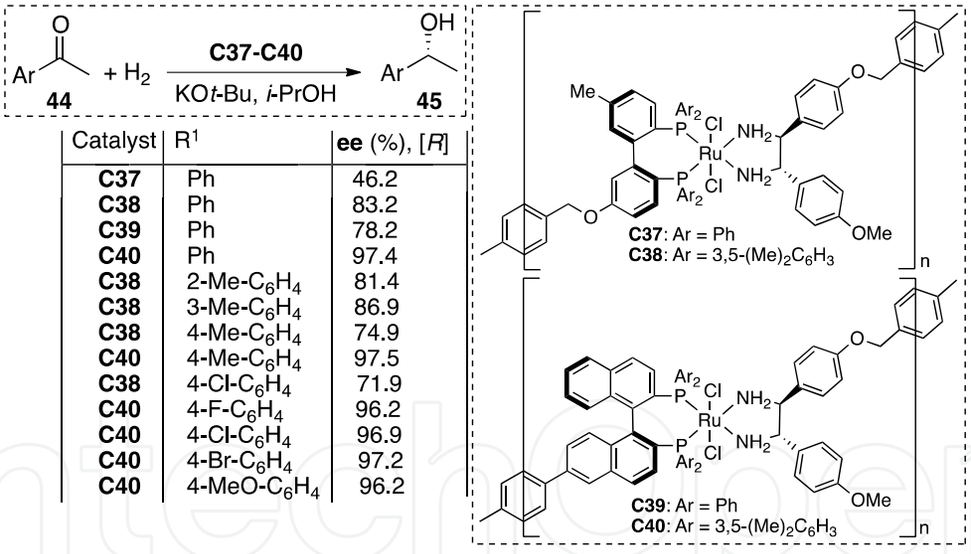
A series of dendrimers and hybrid dendrimers based on Noyori-Ikariya's TsDPEN ligand were prepared and the application of their Ru(II) complexes in the ATH of acetophenones was studied. A high catalytic activity and completely maintained enantio-selectivity (acetophenone, 93.4-98.2% *ee*; 4-bromoacetophenone, 90.1-92.7% *ee*; 1-(naphthalen-2-yl)ethanone, 92.8-95.1% *ee*; 1,2-diphenylethanone, 93.9% *ee*) were observed. Higher-generation core-functionalized dendritic catalysts could be recovered through solvent precipitation and reused several times without any major loss of activity and enantio-selectivity (Y.-C. Chen et al., 2001, 2002, 2005; W. Liu et al., 2004). Hydrophobic Fréchet-type dendritic chiral 1,2-diaminocyclohexane-Rh(III) complexes have also been tested for ATH in water (Jiang et al., 2006). Excellent conversions (70-99%) and enantioselectivity, acetophenone (96% *ee*), 4-chloroacetophenone (93% *ee*), 4-methoxyacetophenone (94% *ee*), 1-tetralone (97% *ee*), 2-acetylpyridine (91% *ee*), 2-acetyltiophene (96% *ee*), ethyl 2-oxo-2-phenylacetate (72% *ee*), and (*E*)-4-phenylbut-3-en-2-one (52% *ee*) were obtained.

3.2. "Self-supported" and solid-supported heterogeneous catalysts

Among various approaches for homogeneous catalyst immobilization, the "self-supported" strategy exhibits some relevant characteristics, such us easy preparation, good stability, high density of catalytically active sites, and high stereocontrol performance, as well as simple recovery (Dai, 2004; Ding et al., 2007). Self-supported Noyori-type catalysts **C37**-**C40** for the AH of ketones by the programmed assembly of bridged diphosphine and diamine ligands with Ru(II) ions were developed (Fig. 20) (Liang et al., 2005; Liang et al., 2006). The

enantioselectivity of the hydrogenation of the aromatic ketones under the catalysis of the self-supported catalyst **C40** was in some cases significantly higher than the *ee* values obtained in the homogeneous catalysis. However, it is expected that the enantioselectivities achieved in the hydrogenation of ketones with the catalysts **C37** and **C38** composed of chirally flexible biphenylphosphine ligands are lower than those of the **C39** and **C40** constructed with chiral BINAP-containing ligands. This might be explained using Mikami's mechanistic considerations obtained by an ^{1}H NMR study of the monomeric complex of DM-BIPHEP/$RuCl_2$/(*S*,*S*)-DPEN (Mikami et al., 1999). Furthermore, this type of catalyst can be readily recovered and reused with the retention of enantioselectivity and reactivity.

A very interesting example is the asymmetric synthesis of the chiral alcohol function that makes use of the strength of ion pairing in ionic liquids (Schulz et al., 2007). The hydrogenation of substrate **46** using H_2 (60 bar) at 60 °C in the presence of the heterogeneous, achiral catalyst Ru/C in an ethanolic solution, gave the corresponding hydroxyl-functionalized ionic liquid in a quantitative yield and up to 80% *ee* (Fig. 21). The degree of enantioselectivity is dependent on the concentration of the substrate **46** in ethanol during the transformation. The higher the concentration of **46**, the higher the *ee* value of the hydrogenated cation that was observed. This behavior can be explained by considering the ion-pair separating effect of the ethanol solvent.



Catalyst	R^1	ee (%), [*R*]
C37	Ph	46.2
C38	Ph	83.2
C39	Ph	78.2
C40	Ph	97.4
C38	2-Me-C_6H_4	81.4
C38	3-Me-C_6H_4	86.9
C38	4-Me-C_6H_4	74.9
C40	4-Me-C_6H_4	97.5
C38	4-Cl-C_6H_4	71.9
C40	4-F-C_6H_4	96.2
C40	4-Cl-C_6H_4	96.9
C40	4-Br-C_6H_4	97.2
C40	4-MeO-C_6H_4	96.2

Figure 20. Self-supported Noyori-type catalysts **C37**-**C40** for the AH of ketones

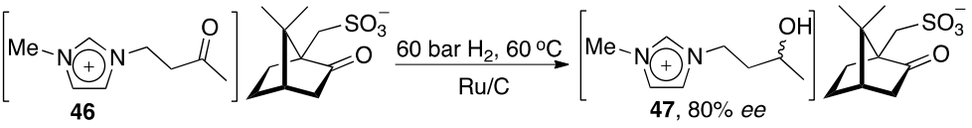


Figure 21. Enantio-selective hydrogenation of a keto-functionalized ionic liquid

Importing chirality to a catalytic active metal surface by the adsorption of a chiral organic molecule (often referred to as a chiral modifier) seems to be one of the promising strategies to obtain new chiral heterogeneous catalytic systems. In the hydrogenation of C=O function,

chirality-modified supported metal catalysts represent a promising approach with synthetic potential. Orito et al. introduced the strategy of a cinchona-alkaloid-modified platinum catalyst system in 1979 (Orito et al., 1979). Following the early work of Blaser et al. (Studer et al., 1999, 2000, 2003; Blaser et al., 2000), Baiker et al. (Heinz et al., 1995, von Arx et al., 2002), and others, the methodology developed in the sense of the substrate scope, and on the other hand, extensive efforts were carried out to get more insight into understanding the mechanistic aspects of the transformation. The method was found to have excellent performance in the hydrogenation of activated ketones (Fig. 22).

The modifiers derived from CD and quinine (QN) lead to an excess of (*R*)-ethyl lactate, whereas the CN and QD derivatives preferentially lead to the *S* enantiomer. It has been shown that substituted aliphatic and aromatic α-keto ethers are suitable substrates for the enantioselective hydrogenation catalyzed by cinchona-modified Pt catalysts and both kinetic and dynamic kinetic resolution is possible (Studer et al., 2002). For conversions less than 50%, *ee*'s of up to 98% were observed when starting with racemic substrates (kinetic resolution). Strong acceleration of the reaction was noticed in the presence of KOH, but without of the enantiomeric excess. In order to get dynamic kinetic resolution the OH^- ions had to be immobilized on a solid ion-exchange resin enabling *ee*'s of more than 80%.

A systematic structure-selectivity study of the hydrogenation of activated ketones catalyzed by a modified Pt-catalyst revealed a high substrate specificity of the catalytic system. Relatively small structural changes in the substrate or modifier can strongly affect the enantio-selectivity and often in the opposite manner, especially when comparing reactions in toluene and AcOH (Exner et al., 2003). Fluorinated β-diketones can be enantioselectively hydrogenated on cinchona-alkaloids-modified Pt/Al_2O_3 catalysts. Methyl, ethyl, and isopropyl 4,4,4-trifluoroacetoacetates were hydrogenated in the presence of MeOCD-modified Pt/Al_2O_3 catalysts, producing the corresponding alcohols in 93-96% *ee* (van Arx et al., 2002).

Synthetically obtained (*R*,*R*)-pantoyl-naphtylethylamine ((*R*,*R*)-PNEA) provides 93% *ee* in the hydrogenation of 1,1,1-trifluoro-2,4-pentanedione and 85% *ee* in the case of 1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedione (Diezi et al., 2005a, 2005b, Hess et al., 2004). A thorough investigation concerning the origin of the chemo- and enantioselectivity in the hydrogenation of diketones on platinum revealed that the structures of ammonium ion-enolate-type ion pairs formed between the modifier and 1,3-diketones are different in solution and on the surface of the metal. The chemoselectivity is attributed to the selective interaction of the protonated amine group of the modifier to the absorbed activated keto-carbonyl function and prevention of the interaction of the non-activated carbonyl group with the metal surface (Diezi et al., 2006). Results on the enantioselective hydrogenation of α-fluoroketones, a group of activated ketones on chiral platinum-alumina surface have shown that the Orito reaction is also suitable for the preparation of the corresponding chiral α-fluoroalcohols. The enantioselectivity of 92% was achieved in the hydrogenation of 2,2,2-trifluoroacetophenone under optimized reaction conditions using a CD-modified Pt catalyst (von Arx et al., 2001a). However, the enantioselectivities obtained on other α-fluorinated ketones were only moderate (Varga et al., 2004; Felföldi et al., 2004; Szöri et al., 2009).

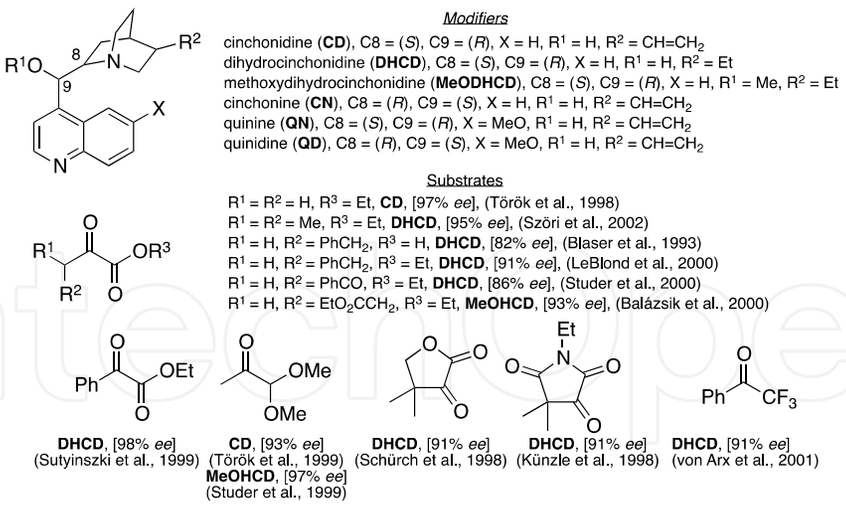
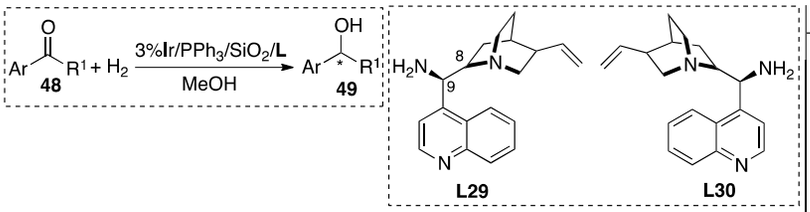


Figure 22. Enantio-selective hydrogenation of activated ketones.

A supported (SiO_2) iridium catalyst, which is stabilized by PPh_3 and modified by a chiral diamine, derived from cinchona alkaloids, exhibits a high activity and high enantioselectivity for the hydrogenation for the simple aromatic ketones (Fig. 23). The addition of different bases (*t*-BuOK, LiOH, NaOH, or KOH) improves both the activity and the enantioselectivity of the reaction (Jiang et al., 2008). A similar ruthenium catalyst (Ru/γ-Al_2O_3) was also developed and a broad range of aromatic ketones over this catalyst can be hydrogenated (Jiang et al. 2010).



R^1	Ar	**L29**; *ee* (%)	**L30**; *ee* (%)
Me	Ph	88	74
Me	2-Cl-C_6H_4	96	86
Me	2-MeO-C_6H_4	94	86
Me	3-Cl-C_6H_4	75	—
Et	Ph	86	75
Me	2-F-C_6H_4	86	77
Me	2-Br-C_6H_4	92	90
Me	2-CF_3-C_6H_4	81	83
Me	4-MeO-C_6H_4	87	76
i-Pr	Ph	52	—

Figure 23. Enantioselective hydrogenation of activated ketones.

A series of silica (SiO_2) supported iridium catalysts stabilized by cinchona alkaloids were also prepared and applied in the heterogeneous asymmetric hydrogenation of acetophenone. Cinchona alkaloids display a substantial capability to stabilize and disperse the Ir particles. A synergistic effect between the (*1S*,*2S*)-DPEN (modifier) and the CD (stabilizer) significantly accelerates the activity as well as the enantioselectivity (up to 79% *ee*) on acetophenone (Yang et al. 2009).

Besides improving the cinchonidine-platinum catalyst system, extensive efforts have been made in developing a reliable mechanistic interpretation. To understand the adsorption behavior of the modifier and reactant, their conformation, and their intra-molecular interactions at solid-liquid interface, an *in-situ* attenuated, total-reflection, infrared study has been performed. The adsorption of cinchonidine on the Pt/Al_2O_3 in the presence of a solvent and H_2 is strongly concentration dependent. The quinolone moiety of the modifier is responsible for the absorption on the Pt surface (Ferri & Bürgi, 2001).

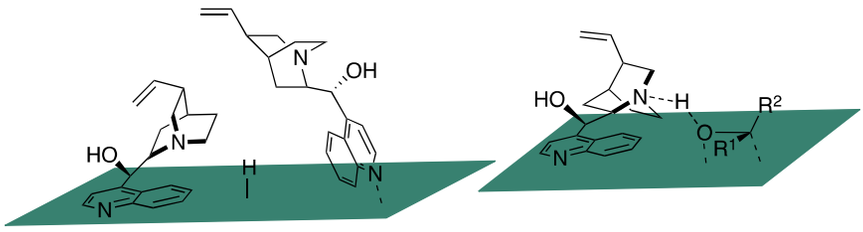


Figure 24. Schematic representation of the adsorption mode of CD on the metal surface and interactions between the half-hydrogenated state of the activated ketone and the basic quinuclidine-N atom of the chiral modifier.

An inversion of the enantioselectivity occurs in the asymmetric hydrogenation of the activated ketones by changing the solvent composition, including water and acid additives (von Arx et al., 2001b; Bartók et al., 2002). Hydrogenation of the ethyl pyruvate over Pt/Al_2O_3 (Huck et al., 2003a) and 4-methoxy-6-methyl-2-pyrone over Pd/TiO_2 (Huck et al., 2003b), an equimolar mixture of cinchona alkaloids CD and QD resulted in *ee*'s similar to those obtained with CD alone, while QD gave a high *ee* of the opposite enantiomers. This was explained by different adsorption strengths and absorption modes of the modifier (Fig. 24). Furthermore, cinchona ether homologues can give opposite enantiomers through maintaining the same absolute configuration of the parent alkaloid. In the hydrogenation of ketopantolactone the CD alkaloid produced (*R*)-pantolactone in 79% *ee*, whereas *O*-phenylcinchonidine (PhOCD) gave *S*-enantiomere in 52% *ee*. It seems that the OH group of CD is not involved in the substrate-modifier interaction during the hydrogenation process, which is also confirmed by the fact that *O*-methyl-CD and *O*-ethyl-CD gave the same enantiomer in excess than CD. The inversion of enantioselectivity is explained by the change in the chiral pocket experienced by the incoming reactant and the change is related to the conformational behavior of the absorbed alkaloid and the steric effects of the ether group. PhOCD can generate conformations whose adsorption energy is decreased with respect to the parent CD. An equally important change is also the alteration of the chiral pocket obtained upon absorption of the modifier (Fig. 24). These changes are enough to induce the inversion of enantio-selectivity (Bonalumi et al., 2005; Vargas et al., 2006, 2007). The aspects of the interaction of different modifiers, MeOCD, *t*-MeSiOCD (Bonalumi et al., 2007), (*R*)-iCN (Schmidt et al., 2008), and tryptophan and tryptophan-based di end tripeptides (Mondelli et al., 2009) with a metal surface have also been studied experimentally (using TEM, XPS, and ATR-IR spectroscopy) and theoretically (DFT calculations). Furthermore, it has been shown that the rate of hydrogenation and enantioselectivity outcome depends on the shape and terrace sites (Pt{100}or {111}) of the nanoparticles. Both the rate and the *ee* increased in the hydrogenation of ethyl pyruvate and ketopantolactone when Pt {111} nanoparticles were modified using CD or QN as the chiral modifiers (Schmidt et al., 2009).

4. Conclusions

This chapter discusses the transition-metal-catalyzed, asymmetric, homogenous and heterogeneous hydrogenation of prochiral ketones, not so much focusing on the reactions

providing valuable chiral alcohols, but rather it gives prominent and interesting examples of the ketone substrates and catalyst systems that are found in the recent literature. Despite the tremendous effort being made in the catalytic, asymmetric hydrogenation of prochiral ketones, approaching the enzymatic performance in some cases, there is still much potential for the continued development of these reactions. Concerning the environmental and economic issues, the introduction of non-toxic, cheap, and at the same time efficient and universal catalyst systems, being able to operate under mild conditions in a highly selective manner and for a broad range of substrates, remains a challenge for future research. Additionally, more rational catalyst designs are possible with better mechanistic understandings of the catalytic cycles in catalytic AH and ATH reactions.

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