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Recent Advances in Ru Catalyzed Transfer Hydrogenation and Its Future Perspectives

*Nidhi Tyagi, Gongutri Borah, Pitambar Patel
and Danaboyina Ramaiah*

Abstract

Over the past few decades, Ru catalyzed transfer hydrogenation (TH) and asymmetric transfer hydrogenation (ATH) reactions of unsaturated hydrocarbons, imine, nitro and carbonyl compounds have emerged as economic and powerful tools in organic synthesis. These reactions are most preferred processes having applications in the synthesis of fine chemicals to pharmaceuticals due to safe handling as these do not require hazardous pressurized H₂ gas. The catalytic activity and selectivity of Ru complexes were investigated with a variety of ligands based on pincer NHC, cyclophane, half-sandwich, organophosphine *etc.* These ligands coordinate to Ru center in a proper orientation with a labile group replaced by H-source (like methanol, isopropanol, formic acid, dioxane, THF), which facilitate the β -hydrogen transfer to generate metal hydride species (Ru-H) and produce desired reduced product. This chapter describes the recent advances in TH and ATH reactions with homogeneous and heterogeneous Ru catalysts having different ligand environments and mechanistic details leading to their sustainable industrial applications.

Keywords: ruthenium, transfer hydrogenation/asymmetric transfer hydrogenation, homogeneous, heterogeneous catalysts, mechanistic studies

1. Introduction

Ruthenium was first discovered in 1844 by Karl Ernst Claus and he had named it as Ruthenia (in Latin Russia) in the honor of his motherland. In fact, in 1827, Gottfried Osann had found three new metals from the Ural Mountains and one of these metals was named as Ruthenium. However, its isolation could not be reproduced and hence his claims were withdrawn on these metals. Ruthenium is a noble transition metal with attractive properties and has found uses in different fields of science and technology. From the commercial point of view, ruthenium has been used in a variety of applications such as its alloy with other heavy metals used for voltage regulators, jewelry, fountain pen nibs and electromechanical devices *etc.* Although, ruthenium metal is known ever since the early nineteenth centuries, but its first complex was reported in the second half of twentieth century having application in hydrogenation and hydroformylation [1].

Currently, ruthenium complexes are being widely used in academics and industrial purposes such as photosensitizers, biomedical, semiconductor industry as well as catalysts. Some variety reactions, like Diels–Alder, eco-friendly CO₂ hydrogenation to hydrocarbon, transfer hydrogenation of unsaturated substrates, oxidation of alcohols, atom transfer radical addition (ATRA), metathesis (ring closing metathesis (RCM)/ring-opening polymerization (ROMP)) are catalyzed by inevitably the ruthenium complexes. Among these reactions, the hydrogenation is one of the most explored reaction. As quoted by Rylander, it is “one of the most powerful weapons in the arsenal of the synthetic organic chemist” [2]. This reaction finds immense manufacturing applications in pharmaceuticals, agrochemicals, petrochemicals, food industry, fine chemicals, fragrances as well as bulk chemicals. The process of hydrogenation (HY) or asymmetric hydrogenation (AH) is used to reduce unsaturated substrates (alkenes, alkynes, aldehydes, ketones, esters, imines, nitriles, carbon monoxide *etc.*) in presence of hydrogen gas and catalysts to give enantiomerically-enriched compounds. Alternate strategy for the hydrogenation is the transfer hydrogenation (TH) and asymmetric transfer hydrogenation (ATH) reactions, which require sacrificial hydrogen donor. These hydrogen donors include organic hydrogen source or different azeotropic mixtures with hydrogen acceptor substrates and catalysts in presence or absence of base promoters (NaOH, KOH, Et₃N, Cs₂CO₃ *etc.*) (**Figure 1**). This approach is the most preferred and widely applied due to safe handling and which do not require hazardous pressurized H₂ gas or pressure reactors.

The first ruthenium TH catalyst reported was a simple 16e⁻ [RuCl₂(PPh₃)₃] complex, which effectively reduce acetophenone in presence of *i*PrOH through inner sphere mechanism involving the following steps; i) insertion, ii) reductive elimination, iii) oxidative addition and iv) β-elimination. It was found that small amount of a base facilitates the rate of TH reaction to approximately thousand-fold. Furthermore, the incorporation of basic nitrogen in a ligand, which coordinates directly to Ru (II) is an interesting approach, which was successfully applied by Noyori and coworkers through a half-sandwich chiral SS-1, for catalyzed reduction of several aromatic ketones (2–6) (**Figure 2**). [Ru^{II}Cl(TsDPEN)(η⁶-p-cymene/mesitylene)] (now commercially available) complexes (TsDPEN = N-tosylated-1,2-diamine), in presence of formic acid-triethylamine azeotropic mixture gave good yields of reduced products with enantiomeric excess (ee) (**Figure 2**). It was also correlated that reactivity and enantioselectivity of complexes were found to depend on optimum steric and electronic properties of the arene and TsDPEN ligands. Efficiency of this robust catalyst (R,R-1) can be seen by the reduction of multifunctional ketone, which gave R benzylic alcohol (5) in *ca.* 92% ee without affecting other functional groups. This conversion was explained through, outer-sphere mechanism with a six-membered transition state (TS) by concerted hydride transfer process (TS shown in **Figure 2**). To further improve the catalytic property, Noyori and co-workers have modified SS-1/RR-1 with different ligand frames [3]. The significance of these asymmetric hydrogenation studies has been renowned and hence Ryōji Noyori was awarded Nobel Prize in 2001 for his immense contributions

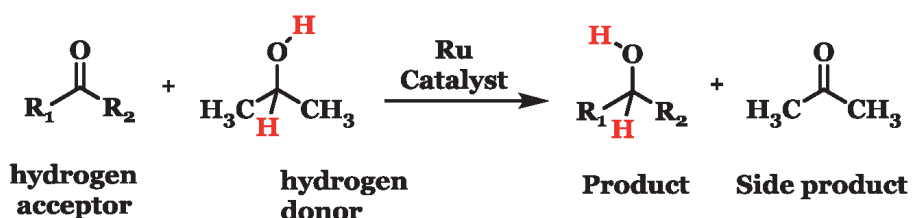


Figure 1.

Ru catalyzed transfer hydrogenation reaction in presence of hydrogen donor and acceptor.

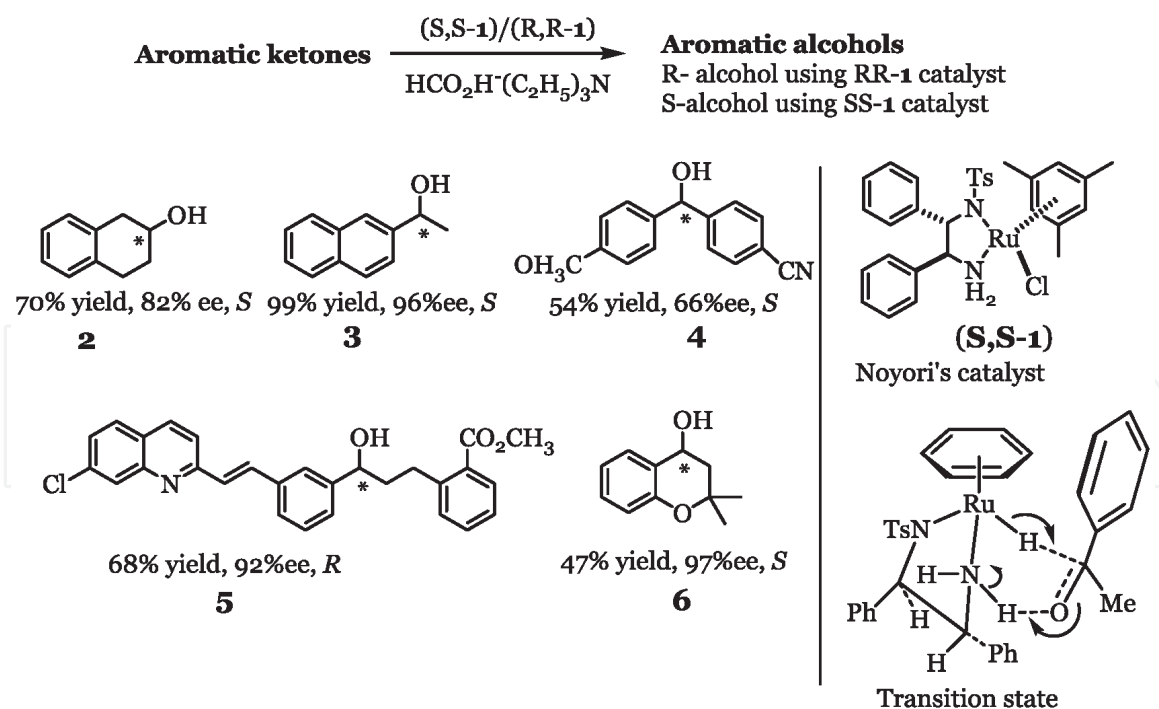


Figure 2. Structures of selected alcohols (2–6), catalyst Ru-TsDPEN (SS-1) and proposed six membered transition state (TS).

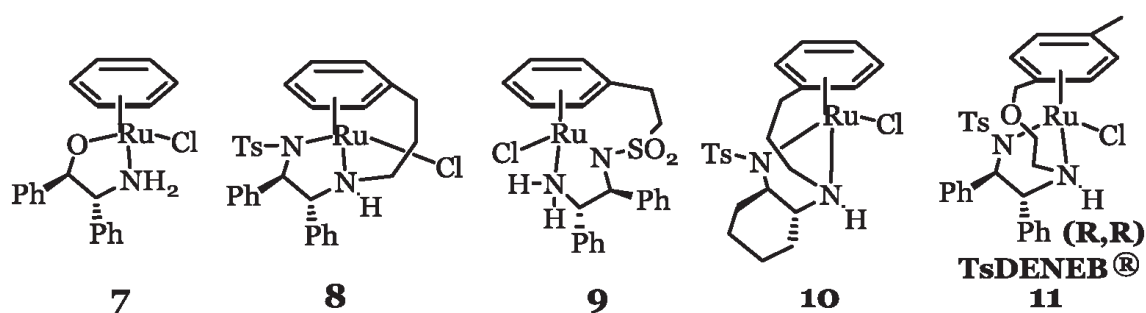


Figure 3. Selected asymmetric transfer hydrogenation catalyzed, tethered or non-tethered Ru(II) catalysts (7–11).

in this field. Will and co-workers have further modified SS-1/RR-1 by tethering of the arene ring and diamine (or amino alcohol) ligand to increase the stability of the catalyst, to restrict the rotation of the η^6 -arene ring and to yield sterically controlled reduction products. Structures of few efficient catalysts 7–11, are shown in **Figure 3** [4–6].

This chapter discusses recent advances of the homogeneous and heterogeneous TH and ATH reactions and primarily reduction of carbonyls, olefins, imines, nitriles, esters and heterocycles formation with a focus on modification of ligands environment. Furthermore, the mechanistic details were also discussed wherever possible with limitations as well as future perspectives in this important area.

2. Advances in ruthenium catalyzed transfer hydrogenation

Realistic relevance of the asymmetric synthesis by TH/ATH in fine chemicals, pharmaceuticals, materials and industrial use required designing and exploration of efficient catalysts. Ru with versatile oxidation states, coordination geometries offered by a variety of ligand moieties make it a good candidate for catalytic

TH/ATH. The crucial requirement for the efficient catalysts is to have a labile coordination site/anionic ligands and efficient chelation or backbone of the ligands to give high turnover numbers (TONs). In this regard, to get good selectivity and activity of the catalysts, the multi-talented ligand architectures are essential. Literature reveals that various ligands such as pincer NHC, cyclophanes, half-sandwich, organo-phosphine, pyridylideneamide, polydentate etc. [7] have been developed by different research groups to improve the selectivity of the catalysts. The following section will discuss the recent advancements in the modification of ligands architecture and their influence on catalytic efficacy.

2.1 Homogeneous transfer hydrogenation

2.1.1 Transfer hydrogenation of carbonyl compounds

The transfer hydrogenation (TH) and asymmetric transfer hydrogenation (ATH) of carbonyl substrates are the most explored and favorable due to polar nature of C=O bond. Although Noyori has set the milestone for TH using TsDEPN ligands however, researchers still used this system with various modifications to improve stability and selectivity of the catalysts. Anderson and co-workers have reported extremely active proline based 2-aza-norbornyl amino alcohol ligands (**Figure 4**) for the ATH process. The [Ru(p-cymene)(**13**)] in presence of *i*PrOH catalyzed TH of acetophenone with S/C = 1000 to give *ca.* 97% conversion, *ca.* 96% *ee* (TOF₅₀ = 8500 h⁻¹) within 25 min. The reason for this enhanced activity in comparison with the [Ru(p-cymene)(**12**)] (*ca.* 90% conversion, *ca.* 94% *ee*, TOF₅₀ = 1050 h⁻¹) was due to the incorporation of polarized C-O bond/dioxolane ring in the ligand frame. This catalyst was able to reduce various aromatic ketones having electron donating and withdrawing substituents (at various positions *e.g.* *ortho*, *meta*, *para*) with admirable enantioselectivity. Theoretical calculations have indicated the lowering of transition state energy (1.3 kcal mol⁻¹) in the case of [Ru(p-cymene)(**13**)] catalyst, and the increased catalytic rate was rationalized through involving the dipole interactions between dioxolane moiety and the substrate (**13a**) [8].

In search of new ligand frame-work for effective and selective TH reaction of aromatic ketones, Ramaiah and co-workers [9] have established a promising new class of air-/moisture-stable ruthenophane/ruthenium(II)- π complexes (**19–20**) and compared their TH activity (**Figure 5**), for the first time with the literature reported catalysts. The structure stiffness of the ligands allows forming the complexes (**19–20**) through π -interactions between the anthracene moiety and ruthenium cation instead of insertion or NHC coordinated complexes. These catalysts were highly selective to aromatic ketones over to aliphatic and aldehyde groups and showed efficient conversion (*ca.* 100%) of acetophenone to 1-phenylethanol in

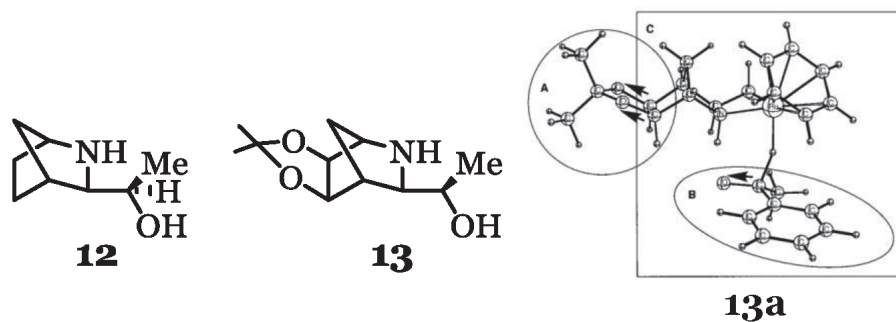


Figure 4. Blueprint of aza-norbornyl amino alcohol ligands (**12**, **13**) and low energy TS (**13a**) determined theoretically involving remote dipole interactions (Ref. [8]).

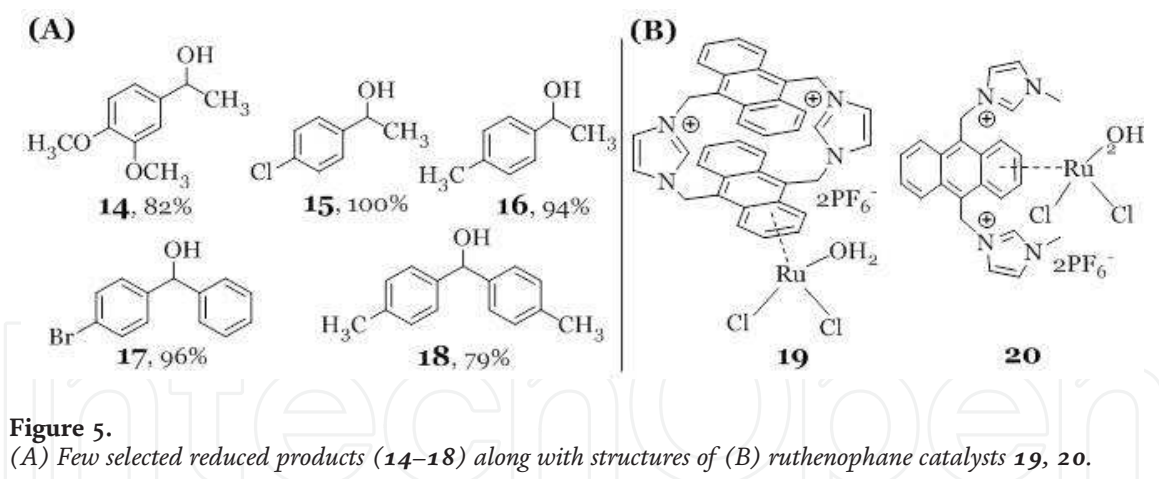


Figure 5. (A) Few selected reduced products (14–18) along with structures of (B) ruthenophane catalysts 19, 20.

presence of a base, *i*PrOH and 2 mol% catalyst loading (80 °C). A series of substrates were scrutinized which showed efficient conversion to the reduced products (selected alcohols shown in **Figure 5**). In comparison to **20**, the catalyst **19** showed a better catalytic efficiency ascribed to different binding interactions through coordinative and cation- π interactions. The presence of labile ancillary ligands also participates in enhancement of efficient TH capabilities. Additionally, these robust catalysts showed exceptionally good conversion of the ketones to the reduced products (**14–18**) in comparison with the commercially available $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ and the “Hoveyda-Grubbs” catalysts, under identical catalytic conditions.

N-heterocyclic carbenes (NHC) are another significantly important class of ligands for homogeneous ruthenium catalyzed TH reactions. Recently, different versions of NHC based ligands have been designed with an aim to synthesize thermally stable and efficient catalysts. These ligands in turn can influence steric and electronic properties of metal center through strong σ -donor capability [10]. The mononuclear and binuclear ruthenium complexes (**Figures 6, 21–25**) (cationic/neutral) having NHC ligands with “three-legged piano-stool” type geometry was reported by Ramaiah and co-workers [11]. These anthracene/arene based catalysts interestingly showed efficient and selective TH of a variety of aromatic ketones. Notably, very small amount of cationic catalysts (**21–23**) (0.5 mol%) exhibited efficient reduction of ketones (*ca.* 100%) in comparison to neutral catalysts (2 mol %) in presence of *i*PrOH and base (0.1 mM) within 2 h at 80 °C. Whereas $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ and the second generation “Hoveyda-Grubbs” catalysts showed moderate yields of reduced products (*ca.* 47% and *ca.* 60%, respectively) under identical situations.

The cooperative binding of NHC and pyridine substituents to the ruthenium center in cationic catalysts facilitates high catalytic activity in comparison to the neutral complexes. Reduction of the substrate was supported by well-established mechanism (**Figure 7**), wherein the active catalyst **A** formed by the addition of *iso*-propoxide, upon β -hydride transfer intermediate and Ru-H species **B** formed. Interaction of substrate **B** to give **C**, which upon subsequent hydride transfer to the substrate form the intermediate **D**. Furthermore, the reduced product resulted by the reaction of **D** with *i*PrOH in presence of the base with regeneration of the active species **A**. *In-silico* studies have further confirmed that the intermediates hypothesized were energetically constructive and reaction follows a thermodynamically steady pathway [11].

An innovative class of pincer pyridylideneamides (PYAs) with strong σ -donating ability was disclosed by Albrecht and co-workers. [12]. PYAs core was tethered with different chelating groups (cyclo-metalated aryl ring/pyridine/pyridylidene/one-more PYA/triazolylidene), which can bind to metal center either *via* π -acidic (neutral donor) or π -basic (zwitterionic pyridinium amide) donor

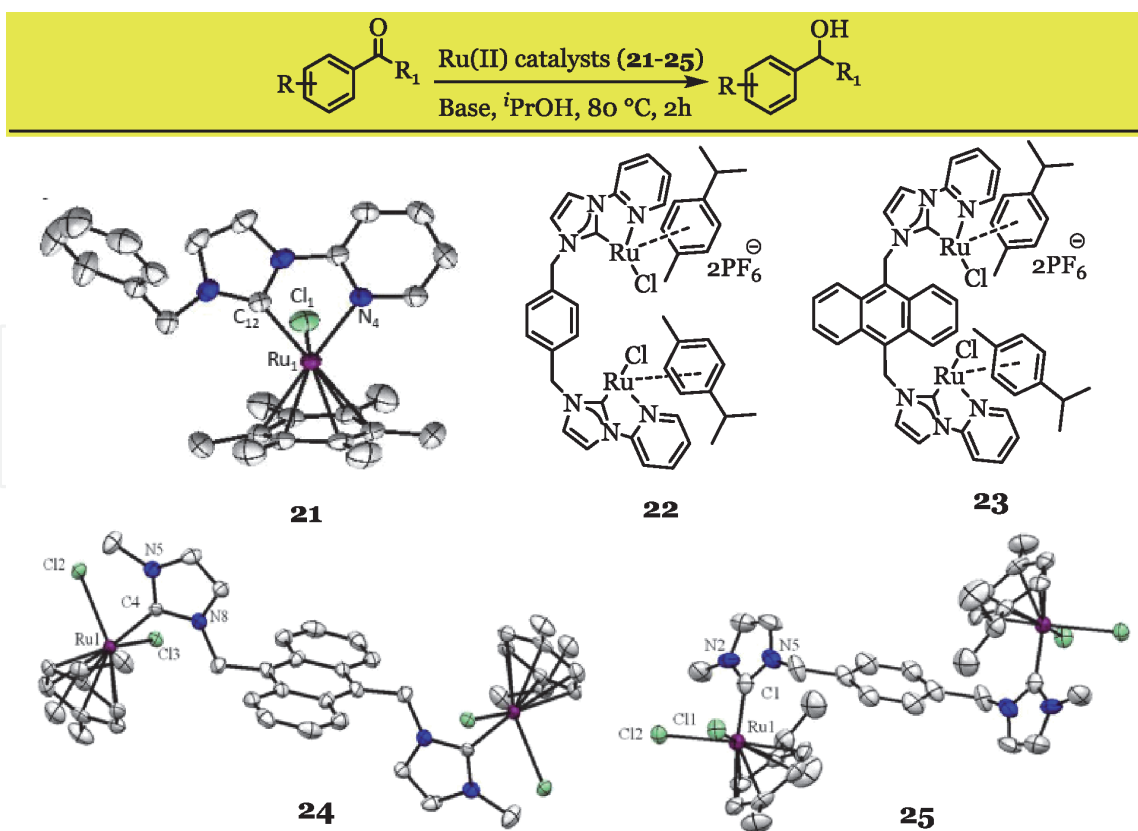


Figure 6. Structures of NHC based cationic and anionic ruthenium catalysts 21–25 (Ref. [11]).

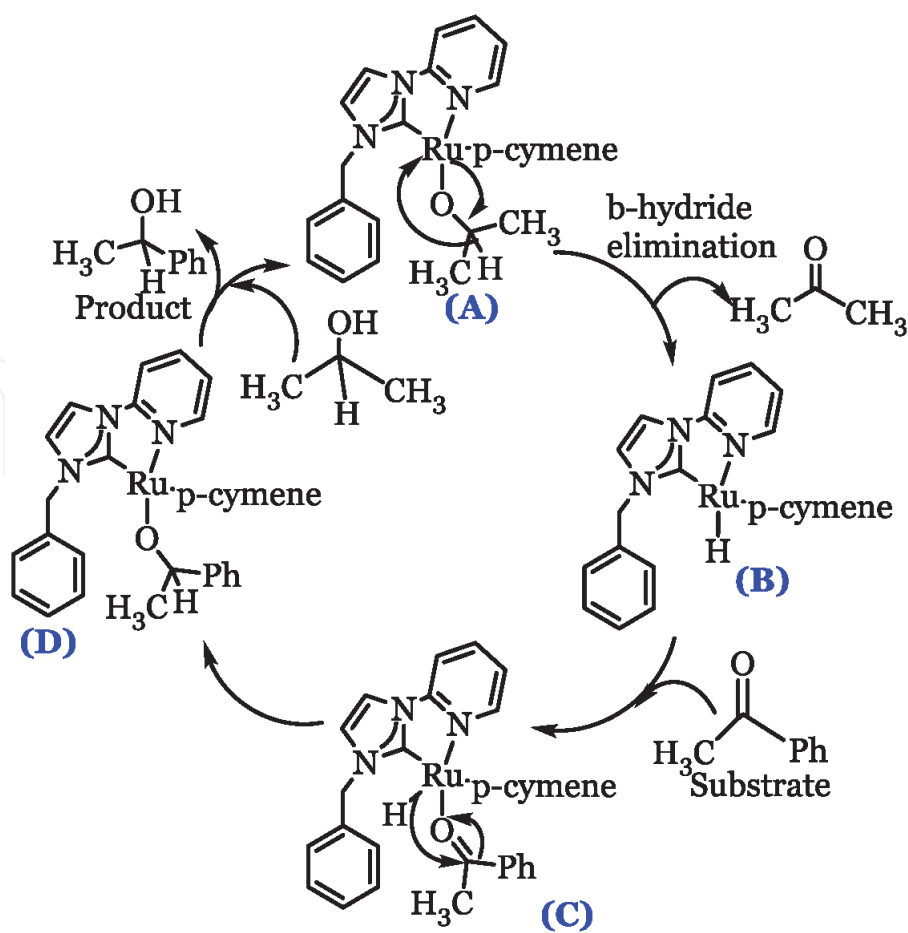


Figure 7. Proposed mechanism of transfer hydrogenation of ketones using cationic ruthenium catalyst (21).

capability. A series of ruthenium complexes (**26–30**) (**Figure 8**) customized with PYA ligands were synthesized and confirmed through various techniques *e.g.* NMR, X-ray crystal structure, HR-MS and other studies. These robust Ru-PYA catalysts (1 mol%) displayed high catalytic activity (*ca.* 100% conversion) in TH of benzophenone (as model substrate) and established a relationship between chelate potency and ruthenium centered catalytic activity. The catalytic activity of the complexes (**26–30**) were tuned by electronic configuration of the ligands and the enhanced catalytic activity in the case of **26** correlated by NMR (with large shift difference $\Delta\delta = 1.03$ ppm, then the other complexes) and electrochemical studies. It was concluded that the substrate reduction was followed first-order reaction rate *via* mononuclear reaction pathway [12].

Transfer hydrogenation of the mixed acetate/acetylacetonate ruthenium phosphine catalyst (**31**), [Ru(OAc)(acac)PP] (PP=PPh₃/bis(diphenylphosphino)-butane) with superior stability and activity was reported. As in the earlier cases, the addition of basic additive significantly enhanced the catalytic efficiency. The effect of NH function of these mixed ruthenium(II) phosphine complexes was demonstrated by incorporating (aminomethyl)pyridine (ampy) to [Ru(OAc)(acac)PP]. The Ampy moiety binds to the metal center upon opening/de-coordination of the acetate. The mixed catalysts (*ca.* 0.1 mol%) in absence of basic additives (ampy/en/bza) showed very low conversion (*ca.* 38–75%, TOF = 100–930 h⁻¹) at 90 °C in 8 h. Addition of 10 equivalents of ampy surpasses the catalytic conversion up to *ca.* 99% (TOF = 125,000 h⁻¹) at a very low 0.03 mol% [Ru(OAc)(acac)(ampy)(dppb)] catalyst (**31**) loading in 5 min. The pathway proposed (**Figure 9**) displayed the important role of NH function for rapid reduction of the substrate *via* outer sphere mechanism, in which the first step was the formation of a five-coordinated species **A** after dissociation of the acetate ion. The second step was the coordination of ⁱPrOH with the six-member TS (**B**). The third step was the formation of Ru-H species (**C**), which formed the substrate coordinated TS (**D**) and finally upon transfer of hydrogen led to the regeneration of species **A** [13].

2.1.2 Transfer hydrogenation of olefins and imines

Imines and olefins are also demanding and challenging substrates for TH/ATH. Noyori's catalyst [RuCl(TsDPEN)(η^6 -p-cymene)] in azeotropic mixture showed

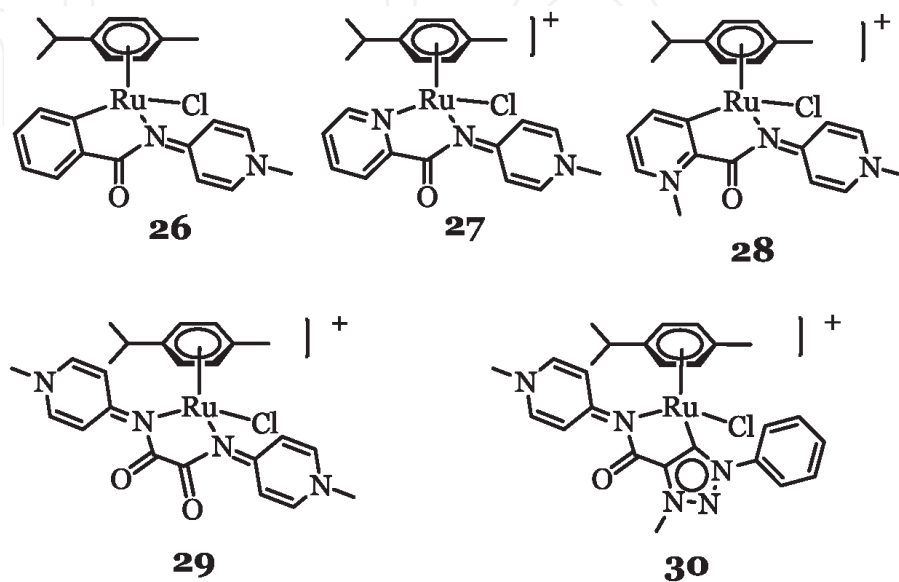


Figure 8.
Structures of the pyridylideneamide based ruthenium catalysts (**26–30**) investigated.

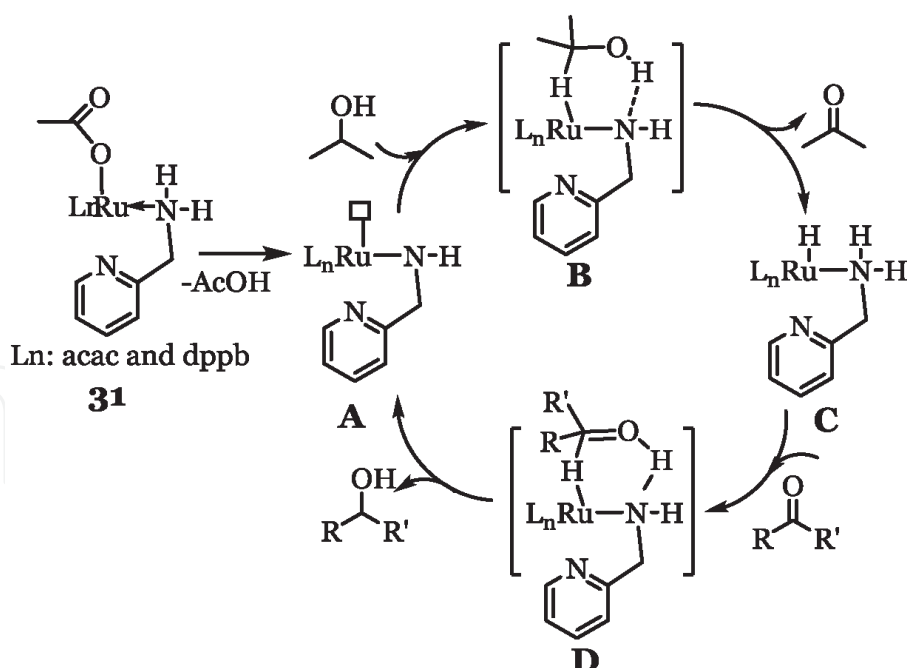


Figure 9.
Proposed mechanism of transfer hydrogenation of the mixed ruthenium phosphine catalyst (**31**).

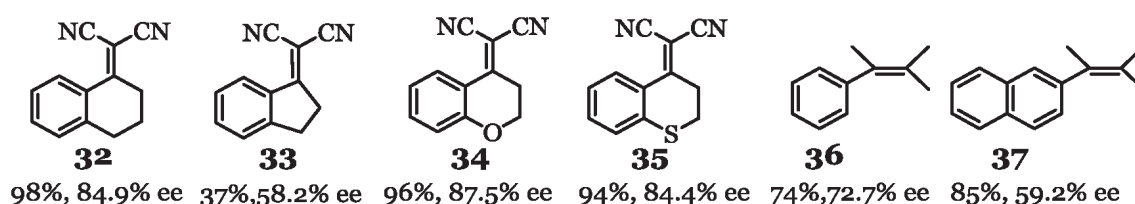


Figure 10.
Selected examples of few activated alkenes (**32–37**) investigated.

ATH of activated alkenes (α,α -dicyano alkenes) (**32–37**, **Figure 10**) in good yields with moderate enantioselectivity [14]. Various alkenes were tested and to enhance the enantioselectivity, TsDPEN and η -arene ligands with different substitutions were explored. For example, 1-naphthylsulfonyl-DPEN gave high yields and enantioselectivity (*ca.* 96% and *ca.* 81% ee) at 85 °C. Different optimization studies revealed that temperature as well as steric hindrances on the arene moiety was important parameters for the observed catalytic activity. **Figure 10** shows few examples of activated alkenes (**32–37**), which gave moderate to good yields and high enantioselectivity. Of these examples, the reduction of the five membered analogue, 1-indanylidene malononitrile (**33**) gave the product (*ca.* 37%, 58.2% ee) along with high yields of the byproduct and negligible enantioselectivity. This was confirmed that the 1,4 addition product was formed due to high acidity of γ -allylic C–H in **33**. Furthermore, the chiral β,β -disubstituted acids were effortlessly achieved by hydrolyzing the chiral malononitriles with concentrated HCl [14].

Another recent ATH application of Noyori's catalyst (RR-1/SS-1) was reported by Meyer and Cossy. ATH of the strained difluorocyclopropenes and their analogues are appealing substrates because of emerging application of *gem*-difluorocyclopropanes in different drugs (Zosuquidar, phase III clinical trials, for acute myeloid leukemia). The *gem*-difluorocyclopropenyl methyl ester as the model substrate was tested for ATH in i PrOH/CH₂Cl₂ (10/1) (RT, 1 h) using the catalyst (S,S)-**1** (10 mol%), which afforded *ca.* 85% yield of **38** with a measurable *cis* diastereomer (*cis/trans* > 96:4) (*ca.* 94% ee), whereas (RR)-**1** yielded, *ca.* 83% *ent*-**38** in *ca.* 98% ee. Reduction, condensation and subsequent reaction of **38** with *p*-bromobenzoyl

chloride yielded *p*-bromobenzoate (*ca.* 61%). Ester substituents were selected because of their cleavability specifically, under acidic and basic conditions to give *cis*-(*ca.* 67%) and *trans*-(*ca.* 81%)-*gem*-difluorocyclopropane-carboxylic acids, respectively. The scope of ATH on few selected substrates in presence of (S,S)-1 is represented in **Figure 11**, (38–44). Detailed mechanistic studies have shown that the first step showed the formation of (S,S)-II, (45) with the loss of acetone and followed by hydride transfer to yield Michael acceptor (A) (**Figure 12**). To decrease the steric hindrance between *gem*-difluorinated C3 and *p*-cymene moieties, two different TS-I, 46 and TS-II, 46 were proposed. To restore, (S,S)-1 gave enols (47 and *ent*-47), while the former upon tautomerization gave *cis*-difluorocyclopropane (48) as the major enantiomer. However, *ent*-47 under the kinetically controlled conditions and with proton transfer from the less hindered face at C1 yielded *ent*-48. The synthetic applications of these difluorocyclopropane was investigated further for the formation of a variety of nitrogen heterocycles as future building blocks in medicinal chemistry [15].

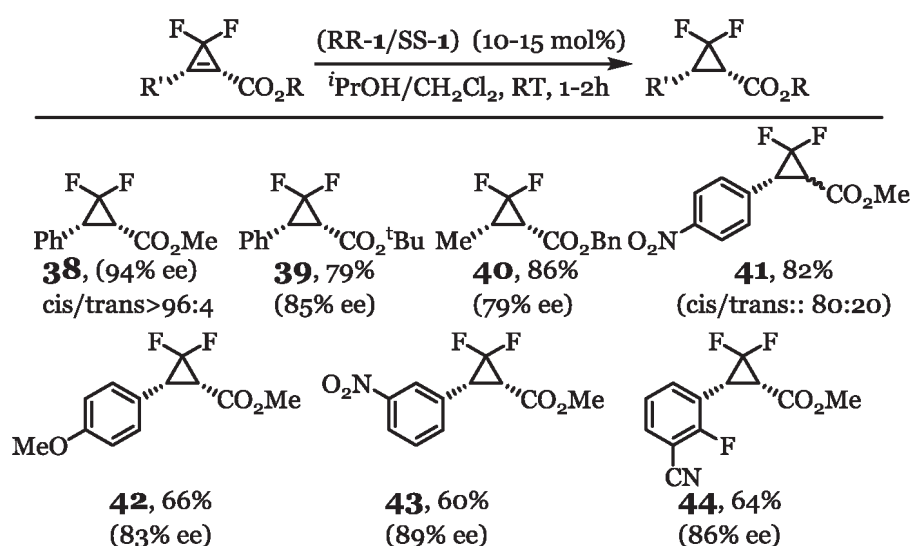


Figure 11.
 Few selected enantioenriched *gem*-difluorocyclopropanes (38–44) achieved.

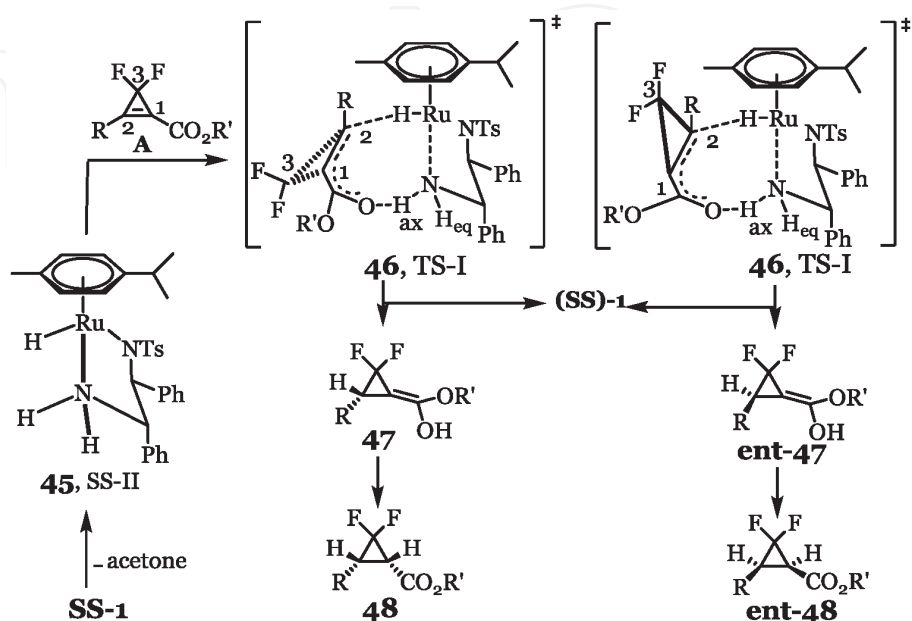


Figure 12.
 Proposed mechanism for asymmetric transfer hydrogenation of *gem*-difluorocyclopropanes (48, *ent*-48).

In-depth study of the pyrazole/phosphine-supported ruthenium complex in TH of olefins and alkynes under semi-hydrogenation conditions resulted in unusual *E*-selectivity. The catalyst **49/49'** was synthesized in moderate yields by refluxing $\text{RuCl}_2(\text{PPh}_3)_2$ and pyrazole ligand in acetonitrile while its structure was analyzed through NOE experiments (**Figure 13**) and X-ray analysis, which confirmed the dimeric nature in chlorobenzene/hexane. Interestingly, upon addition of two equivalents of acetonitrile in chlorobenzene, the dimer was found to undergo dissociation to yield the active catalyst. Efficient reduction of 3,3-dimethylbutene-1 was achieved in good yields (*ca.* 90%) in presence of 1 mol% of **49/49'** and 2 mol% of KO^tBu in *i*PrOH at 80 °C. Different types of alkene substrates (mono/disubstituted/terminal/ α,β -unsaturated esters/anthracene) were investigated and which could be reduced easily without any isomerization (in case of terminal hexene). The mechanism of this reduction was suggested through the involvement of conventional dihydride intermediate (**50**), which was formed by the reaction of **49/49'** in presence *i*PrOH and base (**Figure 13**). The labile solvent further replaced the substrate to give the adduct **51**, while the alkyl adduct **52** was formed by a reversible step through alkene insertion into Ru-H bond. The alcohol coordination to the vacant site of **53** followed by reductive elimination of cyclohexane and upon subsequent proton transfer shift generated **54**. The alkoxide (**54**), upon β -H shift afforded π -coordinated ketone dihydride species, (**55**), which after alkene substitution regenerated **51** to activate the catalytic cycle again [16].

Guijarro and co-workers have reported the first example of chemoselective ATH of the conjugated sulfinylimines substrates, (**56a-k**). Desulfinylation of these reduced products (**57a-k**) gave the corresponding deprotected allylic amines, which could be

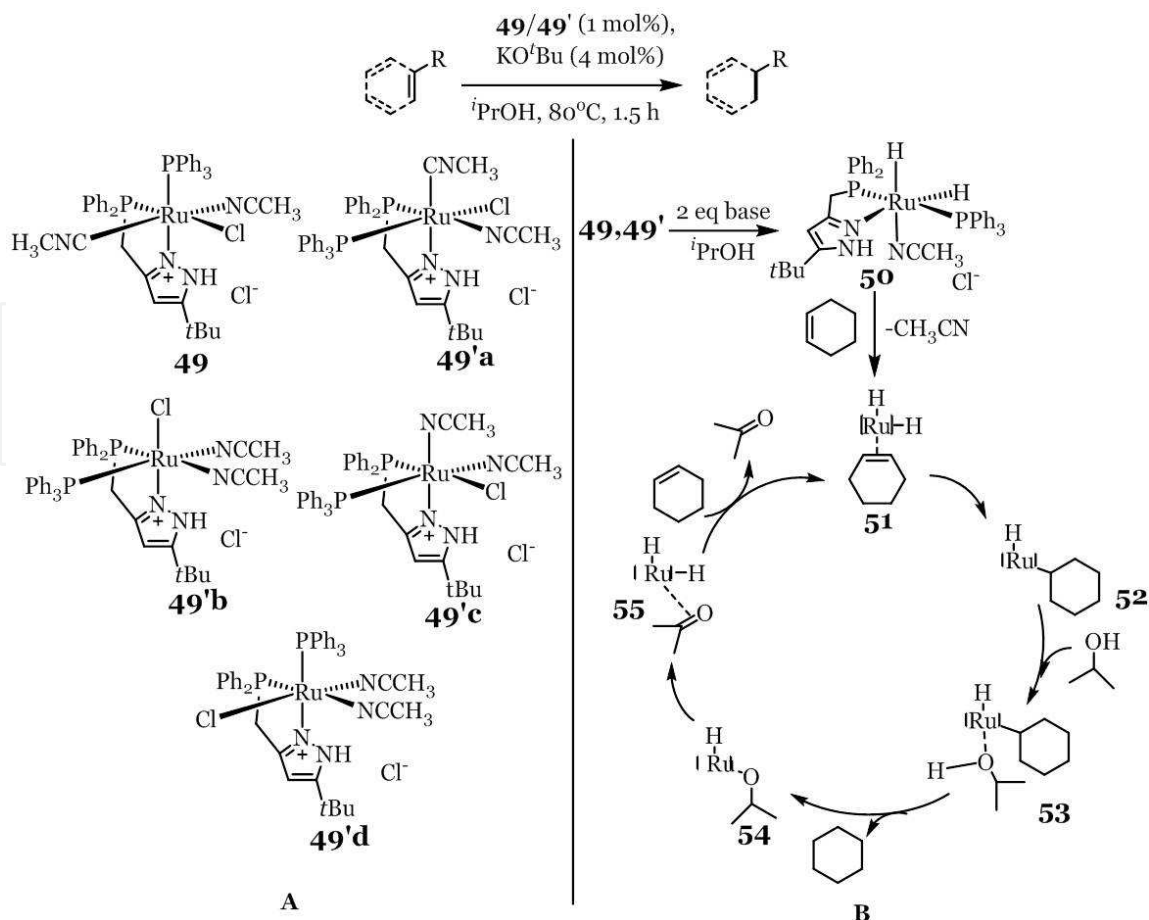


Figure 13. (A). Structure of the catalyst (**49**) and its structure (**49'a-49'd**). (B). Proposed mechanism for TH of cyclohexene.

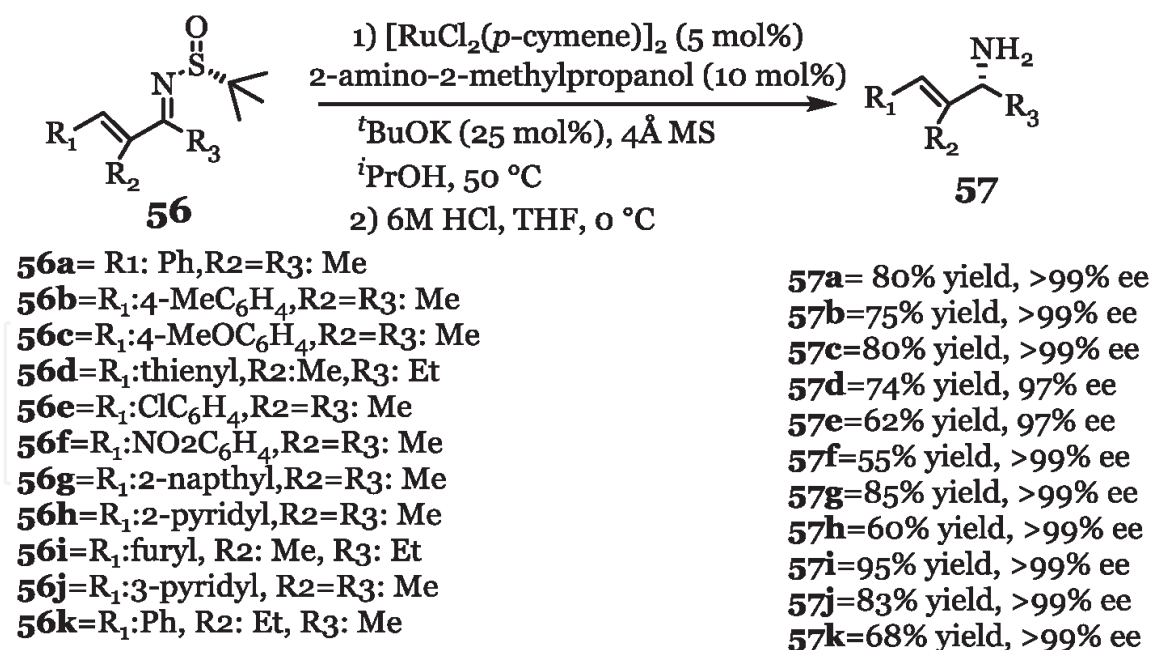


Figure 14. Ruthenium-catalyzed asymmetric transfer hydrogenation of α,β -unsaturated imines (57a-57k).

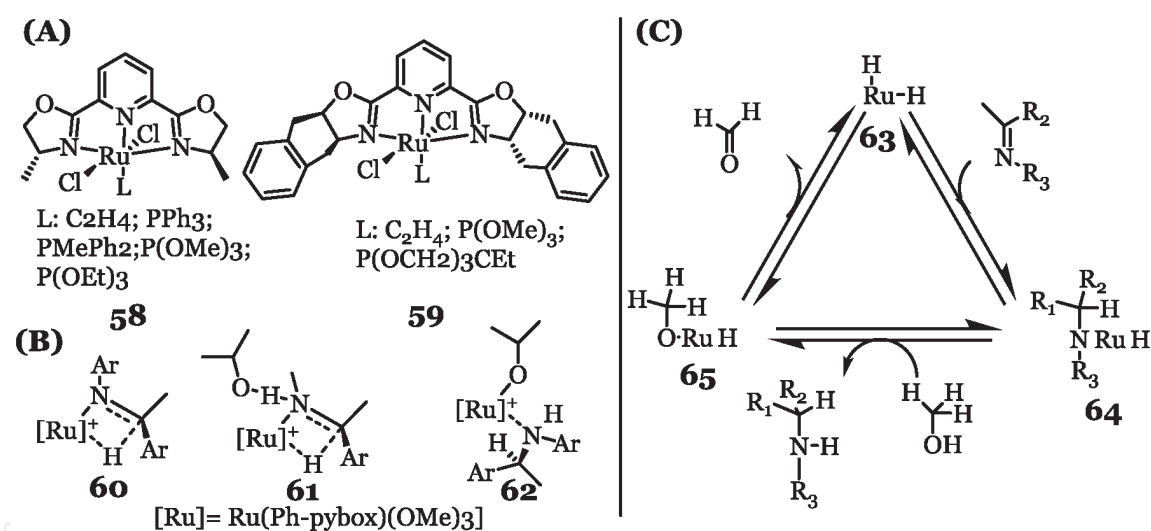


Figure 15. (A) Catalysts $[\text{Ru}(\text{Cl})_2(\text{R-pybox})(\text{C}_2\text{H}_4)]$ (58–59) with a monodentate phosphane and phosphite ligands. (B) Proposed intermediates 60–62 for transfer hydrogenation of imines. (C) Proposed mechanism of transfer hydrogenation of imine with dihydro Ru complex (63).

important for pharmaceutical applications. **Figure 14**, shows ATH of various α,β -unsaturated imines functionalized with different substituents (for *eg.* electron releasing/electron withdrawing/naphthyl/pyridyl *etc.*). The substituents on C=C and C=N affect the chemoselectivity of the reduced products. In general, the substrate with R₁: aromatic/heteroaromatic, R₂: alkyl/aryl, R₃: alkyl, functionality yielded excellent *ee* of the allylic amines. It is also interesting to note that ATH of the imines with (E)-Ph-CH=CH- fragment preferred to reduce both C=C and C=N bonds. This simple and straight forward method of reduction of the allylic imines opens up a new avenue for the synthesis of building blocks useful in designing of new drugs [17].

The *trans*-isomers of $[\text{Ru}(\text{Cl})_2(\text{R-pybox})(\text{L})]$ (58–59, **Figure 15A**) with a monodentate phosphane and phosphite ligands were developed to catalyze HY/ATH of *N*-aryl imines (in *i*PrOH) derived from acetophenones to yield the amine products in significantly high enantioselectivity (*ca.* 99%). It is interesting to note

that the reduction reactions were performed under hydrogen pressure behaved as TH reactions, which was confirmed by various labelling experiments as well as by the proposed intermediates (**60–62**, **Figure 15B**). From these analysis, it was speculated that a common hydride $[\text{Ru}(\text{H})(\text{Ph-pybox})(\text{P}(\text{OMe})_3)]^+$ species was produced *in situ* under either HY or TH [18].

Azua and co-workers have recently reported the first example of microwave assisted ruthenium catalyzed TH of imines in presence of glycerol as the hydrogen donor. Reduction of *in-situ* synthesized imine using NHC ruthenium complex (1 mol %) with sulfonate N-wingtips yielded enhanced conversion of amine in glycerol (*ca.* 77%) and base under microwave conditions (200 W). This improved yield in comparison to the conventional method (*ca.* 17%) was due to the formation of a highly polar zwitterionic nature of the complex to absorb microwave irradiation efficiently. Additionally, the base free catalytic conversion showed quantitative yield of imine (*ca.* 63%) due to sulfonated wingtip as an internal base [19]. $\text{RuH}_2(\text{PPh}_3)_4$ was a well-known active TH catalyst for the reduction of imine in the absence of a base. This catalyst was efficiently catalyzed by several imine derivatives as well as cyclic imines. The proposed mechanism (**Figure 15C**) proceeds through classical hydride transfer steps from Ru-H (**63**) to imine, which was confirmed through isotope labelling experiments, wherein incorporation of deuteride to methyldiene carbon was observed [20].

2.1.3 Ruthenium catalyzed synthesis of heterocycles

The functionalized heterocyclic compounds have attracted attention due to their predominant applications in pharmaceutical industries for designing of new drugs. Recently, the Food and Drug Administration (FDA) had declined to grant new chemical entity (NCE) exclusivity to enantiomers that were part of the previously approved racemic mixtures. Therefore, the purity of enantiomers is very important and can be overcome by using appropriately designed catalysts. Although the reports on synthesis of heterocycles using ruthenium catalysts are well-known but their synthesis *via* ruthenium catalyzed ATH is not much explored. Pabalo and co-workers have reported an admirable example of ruthenium catalyzed ATH for production of enantiomerically enhanced heterocycles *eg.* aziridines, pyrrolidines, piperidines and azepanes. They have employed their established approach of enantiomerically pure *N*-(*tert*-butylsulfinyl)haloimines as the substrate, and imine bond was reduced *via* ATH in presence of *i*-PrOH, $[\text{RuCl}_2(\text{p-cymene})]_2$ catalyst and achiral 2-amino-2-methylpropan-1-ol ligand (50 °C) (**Figure 16**). The reduced haloamines in presence of a base (*t*-BuOK) yielded the *N*-protected saturated heterocycles through intramolecular nucleophilic substitution in excellent yields with diastereomeric ratio up to >99:1. The *N*-protected aziridines and pyrrolidines were synthesized by one-pot ATH-cyclization sequence (Ru:L:*t*-BuOK = 1:2:5 mol %) in high yields (*ca.* 85–90%) and diastereomeric ratios (selected examples **66–69** are shown in **Figure 17**). In the case of piperidines and azepanes, the process was

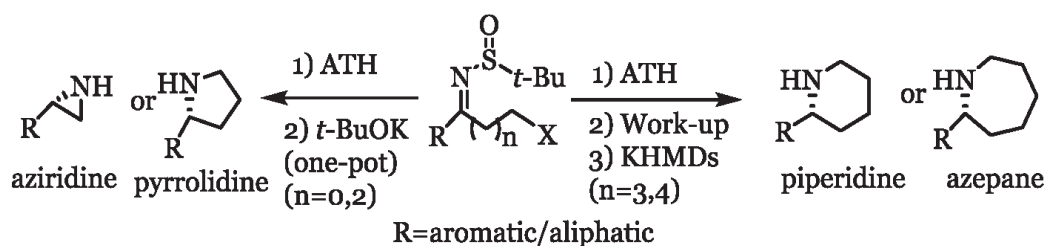


Figure 16.
Synthesis of selected *N*-protected heterocycles.

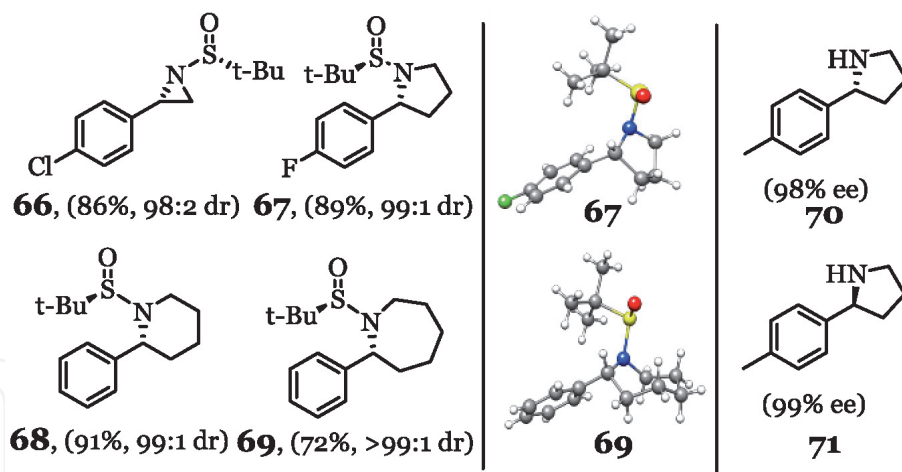


Figure 17. Asymmetric transfer hydrogenation examples of selected N-protected aziridine (66), pyrrolidine (67), piperidines (68) and azepane (69) and X-ray crystal structures of 67, 69 (from ref. [21]) as well as structure of free pyrrolidines (70, 71).

modified with treatment of potassium bis(trimethylsilyl)amide (KHMDs), which gave moderate yields and diastereoselectivity (68–69). On the other hand, the pyrrolidine derivatives (70–71) were obtained by desulfinylation of N-sulfinylpyrrolidines by the reaction with HCl/MeOH. As representative examples, the single crystal of 67 and 69 were analyzed, which confirmed the stereogenic center obtained by Ru catalyzed ATH [21].

Asymmetric tetrahydroisoquinolines (THIQs) are yet another indispensable class of heterocycles with pharmacological applications due to their structural resemblance with neurotransmitters. In this context, Noyori-Ikariya catalysts (arene/Ru/TsDPEN) were found applications in ATH of electron-rich/ortho substituted 3,4-dihydroisoquinolines (DHIQs) only to give THIQs in high enantioselectivity (*ee*'s). In contrast, these catalysts were found to be ineffective with the meta/para substituted electron-poor DHIQs, which are important for the synthesis of solifenacin and TRPM8 antagonists (pharma targets). Wills and co-workers have modified the arene/Ru/TsDPEN catalysts with tethered thiophene/furan/ester groups to basic nitrogen of TsDPEN ligand. It was found that the ATH of these demanding substrates (DHIQs) showed good catalytic efficiency with the modified catalyst (1 mol %) in presence of formic acid-triethylamine (5:2) azeotrope. The furan-based catalyst (77) exhibited best results of ATH of DHIQs with remarkable enantioselectivity (*ee*) of *ca.* 90% and 93% for the conversion to THIQs (72–76) (Figure 18).

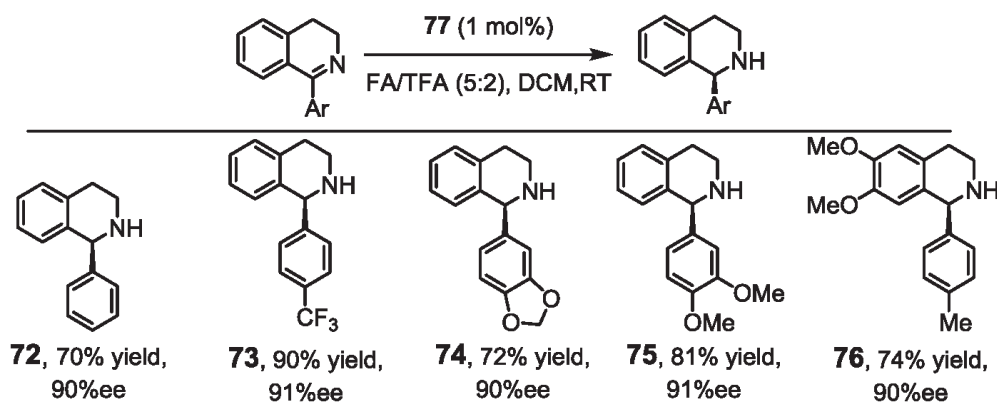


Figure 18. Asymmetric transfer hydrogenation of few selected dihydroisoquinolines (DHIQs).

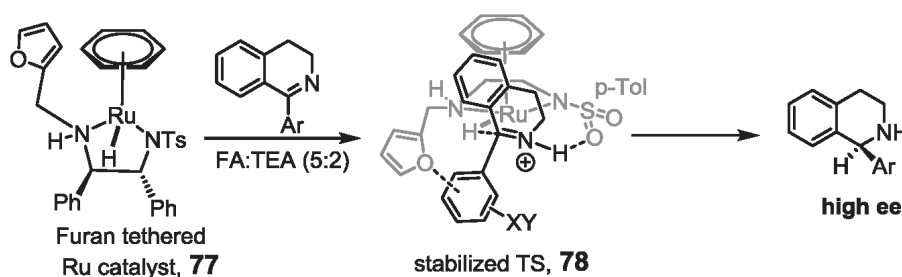


Figure 19. Stabilization of TS state for asymmetric transfer hydrogenation of dihydroisoquinolines (DHIQs).

The proposed mechanism (**Figure 19**) of this asymmetric reduction supported the extra stabilization of TS state **78** through the interaction of furan moiety of the catalyst with the aryl moiety of substrate [22]. Recently, the pyrazole/phosphine based ruthenium catalyst (1 mol %) also showed high TH activity of a variety of *N*-heterocyclic substrates. For example, TH of isoquinoline surprisingly gave the product with reduced all-carbon rings, which are accountable to the electronic properties of the catalyst [16].

2.1.4 Selected transfer hydrogenation/asymmetric transfer hydrogenation of nitriles, esters and acetates

The nitrile-based substrates have received less attention for TH/ATH reactions, in spite of their industrial significance. In earlier studies, TH of benzonitrile catalyzed by $\text{RuH}_2(\text{PPh}_3)_4$ gave very low yields of the reduced product and showed the requirement of focused research in this area [20]. Beller and co-workers have reported NHC based $[\text{Cp}(\text{IPr})\text{Ru}(\text{pyr})_2][\text{PF}_6]$ catalyst (0.5 mol% catalyst, 1.5 mol% KO^tBu , $i\text{PrOH}$), which effectively catalyzed TH of various aromatic nitriles to give the corresponding aromatic imines (*ca.* 24–99%). The function of base was to convert $[\text{Cp}(\text{IPr})\text{Ru}(\text{pyr})_2][\text{PF}_6]$ to $\text{Cp}(\text{IPr})\text{RuH}_3$ which was confirmed through kinetic data as well as mechanistic steps, migratory insertion and release of the product after a metathesis with IPA [23]. Additionally, the extensive screening experiments of various ruthenium pre-catalysts in presence and absence of different ligands was performed. The best catalyst system ($\{\text{Ru}(\text{p-cymene})\text{Cl}_2\}_2$ (1 mol %)/DPPB (2 mol%) in presence of NaOH (10 mol %) and 2-butanol at 120 °C, showed the reduction of various aliphatic/aromatic/hetero aromatic nitriles to primary amines [24]. Remarkably, high TH catalytic activity of bifunctional $\text{Ru}^{\text{II}}(\text{-phenpy-OH})$ catalyst was reported for a variety of nitrile substrates *via* outer-sphere mechanism in the presence of excess of PPh_3 . The presence of $-\text{OH}$ in the ligand support as a supplementary for the metal hydride formation *via* direct interaction of $-\text{OH}$ with the metal coordinated halide ion [25].

Kim and co-workers have disclosed $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (10 mol%) catalyst stabilized with pyridine ligand (20 mol%), which showed selective method of imine formation from nitriles substrate under base free conditions through hemiaminal intermediate mechanism [26]. Nikonov and co-workers have revealed half-sandwich $[\text{Cp}(\text{IPr})\text{Ru}(\text{py})_2]\text{PF}_6$ complexes for TH of nitriles with comparatively high catalyst loading [24]. To further improve pyrazole/ phosphine-supported cationic ruthenium complex (**49/49'**) was reported that showed high activity in the catalytic TH of nitriles. This active catalyst (**49/49'**, 1 mol%) in presence of nitriles, KO^tBu (5 mol %), $i\text{PrOH}$ (80 °C, 24 h) gave moderate to excellent imine products. Further, upon treatment of imine with HCl yielded the analogous primary ammonium salts [16].

Another and less explored substrate for TH is the esters and acetates. In this context, Nikonov and co-workers have reported the first example of $[\text{Cp}(\text{PiPr}_3)\text{Ru}$

$(\text{CH}_3\text{CN})_2\text{PF}_6$ catalyzed reductive conversion of the electrophilic phenyl benzoates and trifluoroacetates, which gave alcohols in low yields [27]. The catalyst $[\text{Cp}(\text{IPr})\text{Ru}(\text{pyr})_2][\text{PF}_6]$, effectively catalyzed TH of conjugated systems such as α,β -unsaturated esters to give β -isopropoxy substituted esters (Michael addition of IPA) along with TH reduced products (ca. 45–99%) [23].

3. Heterogeneous transfer hydrogenation

With the fast advances in sustainable chemistry, the heterogeneous catalytic systems are profoundly used by industries for large scale production, economics as well as technological point of view. The advantage of heterogeneous catalytic systems over homogeneous is basically the easy handling, recycling and easy separation of the catalyst from the reaction mixture. For heterogeneous transfer hydrogenation, ruthenium catalyst can be immobilized on/in various materials such as nanoparticle, polymers, silica and carbon surfaces [28–30]. Such catalysts can be separated easily from the reaction mixture by simple filtration, centrifuge or applying magnetic force. Despite of this, the ruthenium catalyzed heterogeneous TH mostly limited to the reduction of carbonyl groups only.

3.1 Heterogeneous transfer hydrogenation of carbonyl compounds

Over last few decades, the field of heterogeneous TH of ketones by employing primary and secondary alcohols as donors in presence of heterogeneous catalysts is growing tremendously. In this context, various research groups have developed several ruthenium-based heterogeneous catalytic systems by altering the incorporation of ruthenium in/on various materials. Due to the importance and demand of catalytic ATH, significant efforts have been dedicated for the development of immobilized forms of the Noyori–Ikariya and other well-established catalysts. In this context, several polystyrene (PS) supported ruthenium complexes (**79–82**, **Figure 20**) were prepared initially and their catalytic properties were studied by several groups.

Marcos and co-workers have synthesized Noyori catalyst **79** immobilized on a chlorosulfonylated PS. They used the catalyst in asymmetric transfer hydrogenation of ketones and formic acid as hydrogen source and triethylamine as base at 40 °C [31]. When 0.67 mol% of the catalyst was used, the reduction of acetophenone

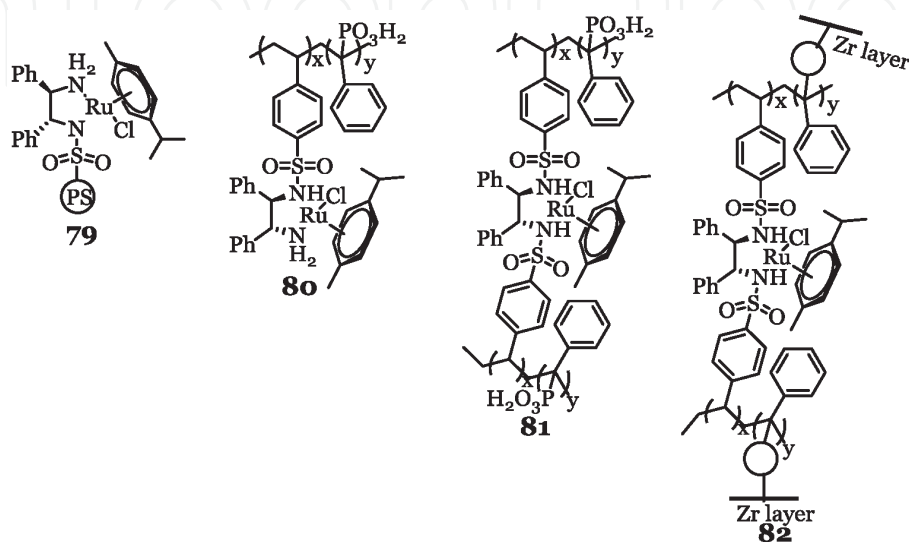


Figure 20.
PS-supported Ru catalysts (**79–82**) for the ATH of carbonyl groups.

proceeded smoothly to give the desired product 1-phenylethan-1-ol with *ca.* 97% *ee* and the conversion was found to be *ca.* 99%. A number of electron donating as well as withdrawing groups showed excellent reactivity with *ca.* 86–99% *ee* values with **79**. Ma and Peng's group independently documented the synthesis of the ruthenium complexes immobilized on various phosphonate-containing single- or double-stranded PS copolymer (**80–82**) [32–33]. The catalyst **80** can be efficiently employed for the aqueous ATH of carbonyls using NCOONa-Et₃N to give *ca.* 94–98% yields of the desired alcohol with *ca.* 93.9–97.8% *ee*, and *ca.* 100% chemoselectivity [32]. Similarly, ATH of aryl ketone was also achieved with **82** with *ca.* 94% yield and *ca.* 95% *ee* [33]. Interestingly, catalysts **80** and **82** can be easily separated by means of centrifuge from the reaction mixture and were reused without the loss of catalytic efficiency for five consecutive cycles. A comparative reduction of acetophenone using catalyst **79–82** was demonstrated in **Table 1**.

Recently, Islam and co-workers have reported the synthesis of simple and efficient PS-supported ruthenium complex (**83**) for the TH of ketone. Both aliphatic and aromatic functionalized ketones showed great conversion to the corresponding alcohols with the yields *ca.* 84–99% using **83** in the presence of KOH and *i*PrOH (**Figure 21**) [34]. One of the major issues in a majority of heterogeneous catalyzed TH is the isolation of catalyst from the reaction mixture, which involves tedious filtration or centrifuge. Very recently, magnetic nanoparticles (MNPs) have shown powerful alternates because of the advantages like greater surface area, morphological control, straight forward preparation, and easy separation using magnetic forces. As a result, MNP-immobilized transition-metal catalysts are broadly investigated by the researchers and applied for TH reactions. Verma and co-workers have reported the assembly of the ruthenium incorporated magnetic nanoparticles (Ru@MNPs) having spherical shape and size ranges from 15–30 nm in one pot *via* aggregation of magnetic silica (Fe₃O₄@SiO₂) with binding of RuNPs [35]. The catalytic TH of acetophenone was carried out using Ru@MNPs. In the

Sr. No.	Catalyst	Temp/Time	Conversion	Yield	ee
1	79	40 °C /24 h	99	97	97
2	80	50 °C /6 h	100	98	97
3	82	50 °C /16 h	>99	98	95

Table 1.
ATH of acetophenone.

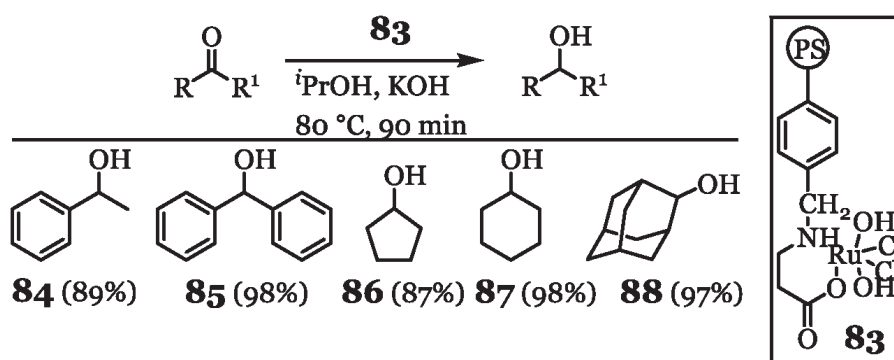


Figure 21.
Heterogeneous TH of ketone.

methodology, *i*PrOH was used as a hydrogen source along with KOH as base at a temperature of 100 °C under MW irradiation in 30 min to obtain the desired alcohol product with more than 99% yield. A wide range of substituted acetophenones showed great compatibility under optimal conditions to furnish the corresponding alcohols with good yield and selectivity (**Figure 22**). The catalyst can be easily recovered from the reaction mixture by using external magnet.

In 2015, Moores and co-workers used the iron/iron oxide core/shell NPs (FeCSNPs) as heterogeneous support for the synthesis of Ru-magnetic nanoparticles (Ru@FeCSNPs) [36]. The catalyst Ru@FeCSNPs was used as the catalyst of choice for the transfer hydrogenation of carbonyl compounds using KOH as base and *i*PrOH as hydrogen donor cum solvent at 100 °C (**Figure 23**). Aryl ketones bearing both electron-donation as well as electron withdrawing groups were converted to their corresponding alcohols very smoothly. The catalyst was found to be highly selective for the keto group over aldehyde or nitro functional group.

Although numerous catalysts and methods have been developed for the Ru-catalyzed heterogeneous TH, the exact mechanism is still unclear. However, several mechanistic studies lead to two possible pathways for the metal catalyzed TH reaction; (a) monohydride transfer mechanism and (b) dihydride transfer mechanism. It is believed that, both pathways are possible for Ru-catalyzed transfer hydrogenation [37]. The possible catalytic cycle for the catalytic TH of keto group shown in **Figure 24** uses *i*PrOH as the source of hydrogen. As shown in **Figure 24**, in the monohydride mechanism, *i*PrOH in presence of base form the alkoxide ion which in turn react with the metal to form the active metal-alkoxide species I. The metal metal-alkoxide give the reactive metal hydride intermediate II, which react with the

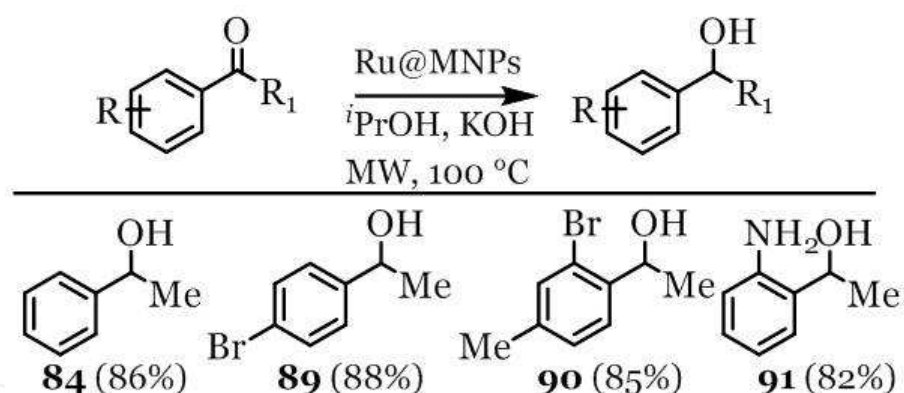


Figure 22.
Ru@MNPs-catalyzed transfer hydrogenation of ketones.

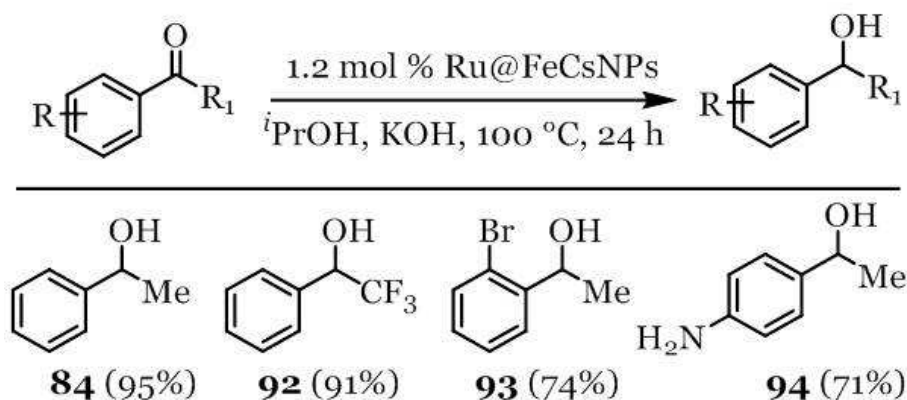


Figure 23.
Ru@FeCSNPs catalyzed TH of acetophenone.

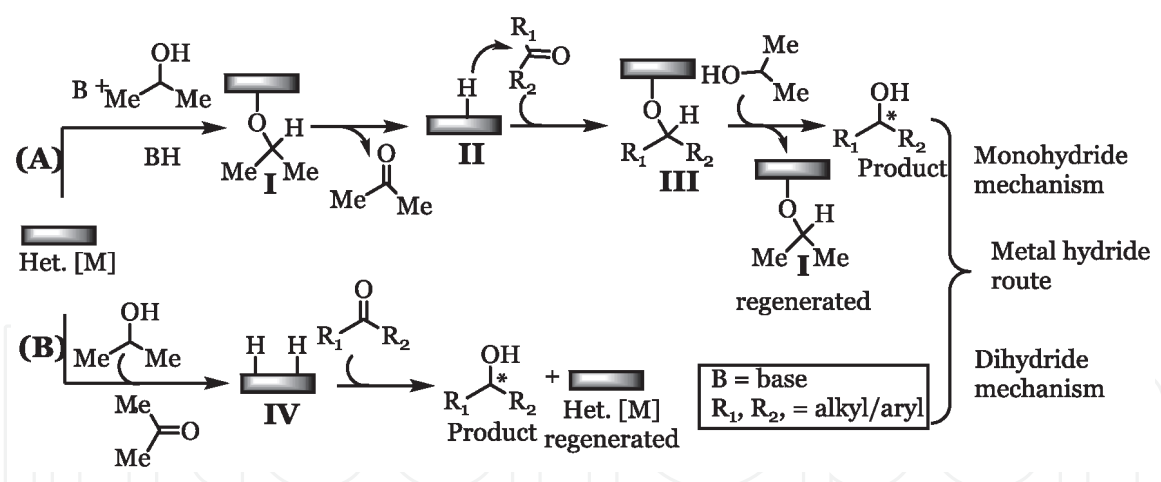


Figure 24. Possible general mechanisms for the heterogeneous TH reactions: (A) monohydride CTH; (B) dihydride CTH.

keto group to transfer the hydride ion to the carbonyl carbon and result in the formation of substrate–metal alkoxide intermediate **III**. Finally, another molecule of ⁱPrOH was reacted to form the product and regenerate the active catalytic species **I**. Similarly for the dihydride mechanism, both the protons of reducing agent got transfer to form the metal dihydride complex **IV**, which in turn react with the reactant carbonyl group to form the desired product along with regeneration of the metal catalyst.

3.2 Heterogeneous transfer hydrogenation of nitro group

The substituted aromatic amines act as important intermediates in the field of pharmaceuticals as well as agrochemicals. They also show great versatility in the production of dyes, polymers, herbicides and cosmetics. The aromatic nitro compounds can be easily converted to the corresponding aromatic amines *via* catalytic transfer hydrogenation. Lu and co-worker documented the use of ionic liquid (1-hexadecyl-3-methylimidazolium bromide) as a support in the synthesis of MCM-41-type mesoporous silica (OMS-IL) [37]. In their methodology, they used Ru nanoparticles immobilized on OMS-IL (Ru/OMS-IL) by transfusing OMS-IL with a RuCl₃ in water for reducing nitroarenes with good selectivity (**Figure 25**). Both mono and poly substituted nitroarenes were transformed into their respective

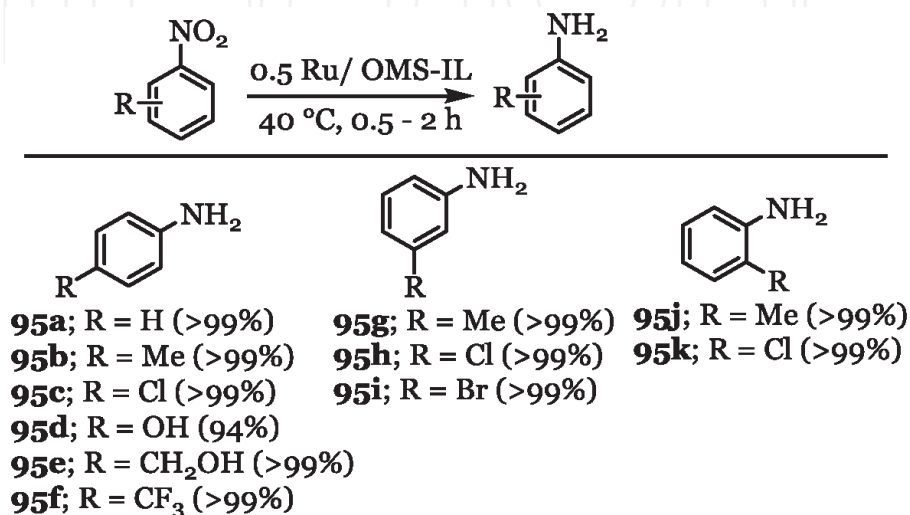


Figure 25. Reduction of nitro arenes via ruthenium-catalyzed TH.

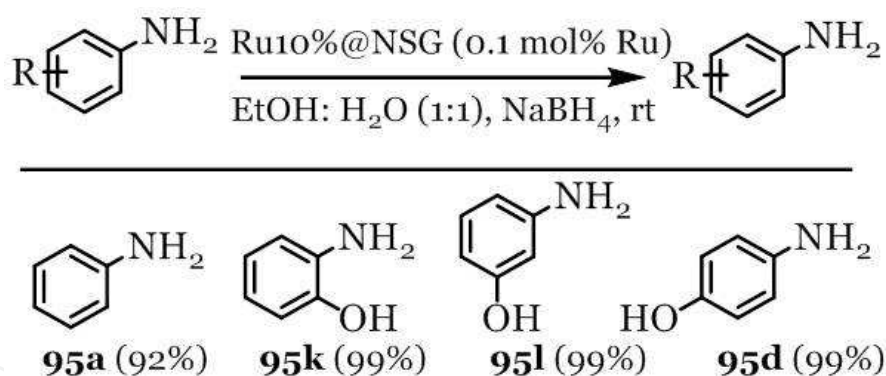


Figure 26.
Ru10%@NSG catalyzed reduction of nitroarenes.

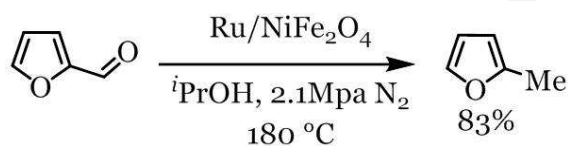


Figure 27.
Conversion of furfural to 2-methylfuran.

anilines in high yields (**95a-95j**). The most highlighted advantages of Ru/OMS-IL are: they show high catalytic activity as well as chemoselectivity. The catalysts are also highly stable and can be easily recovered from the reaction mixture. They showed great reactivity towards the reduction of the functionalized nitro compounds to the aromatic amines in the presence of ethanol as the solvent and hydrazine hydrate as a hydrogen donor and exhibited catalytic activity up to six cycles.

Dabiri and co-workers documented the use of graphene oxide and RuCl_3 as the starting precursors and thiourea as a reducing doping agent for the preparation of ruthenium nanoparticles supported on nitrogen and sulfur-doped 3-D graphene (Ru@NSG) nanohybrid through a one-pot hydrothermal method [38]. The catalytic efficiency of ruthenium-nanohybrid was compared with the reduction of nitroarenes to the analogous anilines using NaBH_4 as hydrogen donor in 1:1 ethanol/water solvent at room temperature (**Figure 26**). A broad range of functionalized nitro arenes were transformed to their corresponding aniline derivatives in decent yields.

3.3 Miscellaneous heterogeneous transfer hydrogenation

Furfural (FFA) derived from biomass is a promising energy source for the future biorefinery and is industrially produced *via* the dehydration of xylose and arabinose [39]. Over the last few decades, its synthesis received a great interest from the researchers. In this context, Liang and co-workers reported the synthesis of 2-methylfuran (MF) from furfural by using $\text{Ru/NiFe}_2\text{O}_4$ by catalytic TH using isopropanol as hydrogen donor under mild conditions. At 180 °C and 2.1 MPa nitrogen, the transformation of furfural was achieved up to *ca.* 97%, whereas MF was formed in *ca.* 83% yield (**Figure 27**) [40]. Additionally, the catalyst showed excellent activity up to five consecutive cycles.

4. Conclusion and future perspectives

The simple operational procedure, the mild reaction conditions with high catalytic activity and selectivity make the TH reactions an attractive alternative to direct

hydrogenation using H₂ gas. This research field is growing rapidly due to the high demand for the development of sustainable and green chemistry point of view. Recently, significant developments of Ru-catalyzed both TH and ATH of carbonyl, olefine, nitro and nitrile groups have been achieved. This improvement was perceived in several aspects, such as design of ligands or stabilizers to improve the reaction efficiency, exploration of “green” hydrogen source, generalization of reaction in water, enhancement in asymmetric synthesis, broadening of substrate diversity, and study of reaction mechanisms. Addition to these, TH has been explored in the syntheses of numerous compounds, in particular fine chemicals, bioactive molecules, agrochemicals, and products bearing multi-functional groups.

Although remarkable developments have been made in Ru-catalyzed TH reactions, many challenges and problems remain in most of the reported results. For example, majority of the reported reactions cannot be applicable for the practical and industrial applications. The catalytic results of ATH are not much promising compared to the direct asymmetric hydrogenations. The TH and ATH reactions of imines, olefins, and nitroarenes are very less efficient than that of ketones and are still not explored properly. The use of Ru-catalyzed heterogeneous TH and ATH is still under developed and mostly limited to the ketone group. However, at the present time, new findings are boosting the field by addressing these challenges which indicate TH has a bright future.

This chapter described the recently developed homogeneous and heterogeneous ruthenium catalysts for different substrates ketones, imines, olefins, nitriles, esters and nitroarenes. Attention was focused on mechanistic characteristics of TH/ATH with different ligands frame and their effects on ATH reaction rate.

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Conflict of interest

The authors declare no conflict of interest.

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Author details

Nidhi Tyagi¹, Gongutri Borah², Pitambar Patel² and Danaboyina Ramaiah^{3*}

¹ Institute of Nano Science and Technology, Mohali, India

² Chemical Science and Technology Division, CSIR-NEIST, Jorhat, India

³ Department of Chemistry, Birla Institute of Technology and Science (BITS) Pilani, Hyderabad Campus, India

*Address all correspondence to: rama@hyderabad.bits-pilani.ac.in

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