Catalytic hydrogenation of polar organic functionalities based on Ru-mediated heterolytic dihydrogen cleavage†‡

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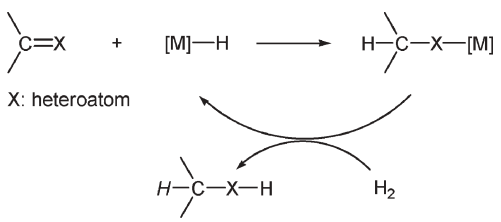
This article highlights Ru complexes, which effect catalytic hydrogenation of polar organic functionalities containing C–O bonds other than aldehydes or ketones. The unique ability of Ru complexes to undergo heterolytic dihydrogen cleavage seems to play a key role in these catalyses.

Introduction

Reduction of polar organic functionalities in which carbon–heteroatom bonds are converted to carbon-hydrogen bonds is one of the most fundamental transformations in organic synthesis.[2] These reactions are effected by a wide variety of metal hydride reagents by virtue of the spontaneous metal–heteroatom bond formation (*i.e.*, salt formation). Their efficiency is almost parallel to the energy difference between metal hydrides and metal–heteroatomic compounds. Unfortunately, the metal waste produced by the more efficient reductive methods generally requires a larger amount of energy to regenerate the starting metal hydrides, typically through multi-step processes including electrochemical reduction. Provided dihydrogen (H_2) is able to regenerate metal hydrides from metal salts by releasing of protic products which allow the regenerated metal hydrides to react with starting polar molecules repeatedly, catalytic hydrogenation of polar molecules with metal salts becomes feasible (Scheme 1). In fact, hydrogenation of benzophenone to benzhydrol with a catalytic amount of KO*t*-Bu was observed as early as the 1960s (Scheme 2).[3a,b] Although this finding has rarely been noticed by the synthetic organic community because of the forcing reaction conditions and the limited scope of the substrates, it strongly suggested the possibility of the formal heterolytic cleavage of H_2 with a particular kind of metal salt to deliver two hydrogen atoms into a polar bond as a proton and a hydride in a catalytic manner.[3c] Later, a number of soluble transition metal complexes including Mo,[4] W,[4] Fe,[5] Ru,[6] Rh,[6a,b,7] Ir,[8] Pd,[9] and Cu[10] were developed as catalysts for the hydrogenation of ketones under relatively mild conditions, where mechanistic similarities to the KO*t*-Bu system are often invoked. However, the potential reactivity of the resulting



Scheme 1 Reaction of metal–heteroatomic compounds with H_2.

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† The term ''heterolytic dihydrogen cleavage'' is used tentatively to describe simple reaction formalism where two hydrogen atoms in a dihydrogen molecule end up bonding to discrete electronically opposite elements. Therefore, in this paper, its meaning does include the processes which involve traditional oxidative addition (''homolytic dihydrogen activation'') and subsequent reductive elimination with a change in oxidation state of the metal centre.[1g,h] However, readers are encouraged to learn various mechanistic differences therein from leading references.[1]

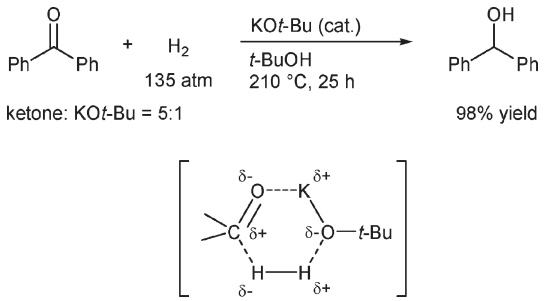
‡ Dedicated to the memory of the late Professor Yoshihiko Ito who passed away on 23 Dec. 2006.

Masato Ito

Masato Ito completed his PhD degree in 1996 at Kyoto University under the direction of the late Professor Hidemasa Takaya. After he spent one year in 1996–1997 as a post-doctoral fellow in Professor François Diederich's group at ETH, he became an assistant professor at the Tokyo Institute of Technology in 1997.

Takao Ikariya completed his PhD degree in 1976 at the Tokyo Institute of Technology and then he was appointed as an assistant professor at the University of Tokyo. He spent one and a half years in 1979–1981 as a postdoctoral fellow in Professor Robert H. Grubbs' group at Caltech. In 1985 he moved to the central research center of the NKK Corp. In 1991 he joined in the ERATO Molecular Catalysis Project of the Japan Science and Technology Corporation, directed by Professor Ryoji Noyori. Takao Ikariya was promoted to professor at the Tokyo Institute of Technology in 1997.

Takao Ikariya



Scheme 2 Alkaline base-catalyzed hydrogenation of ketones.

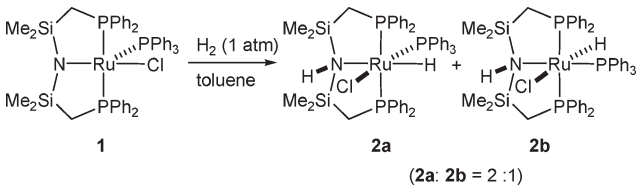
formal proton and hydride was not fully exploited until Noyori and co-workers offered a clue to this issue in 1995.[6,11] They have shown that a coordinatively saturated 18-electron Ru hydride complex bearing a primary amine ligand undergoes concerted proton/hydride transfer to ketones with polar C=O bonds but not to olefins with non-polar C=C bonds. The discovery of this conceptually new Ru/NH bifunctional catalysis[11] has inspired further intense efforts to explore new catalyst systems in academia and industry.[6] Now Noyori's method for the hydrogenation of ketones enjoys widespread application and continues to dominate over conventional methods with stoichiometric use of $NaBH_4$. Nevertheless, we have not yet learned rational design of molecular catalysts effective for hydrogenation of more polar organic molecules such as carboxylic acids and their derivatives, whose reduction still relies mostly on the stoichiometric use of metal hydride reagents such as $LiAlH_4$. Therefore, further efforts should be directed to the achievement of such energetically unfavourable yet straightforward hydrogenations under ambient conditions, which may positively contribute to the concept of green chemistry through the development of environmentally benign processes.

This article mainly highlights Ru-based molecular catalysts that promote hydrogenation of polar organic functionalities containing C–O bonds other than ketones or aldehydes because recently, the most intriguing results have been obtained in Ru chemistry. Although important, it is beyond our scope to address the advantage of heterogeneous catalysts in this field.

Heterolytic H_2 cleavage in the hydrogenation of ketones and aldehydes

Prior to the illustration of the successful examples of hydrogenation of more polar bonds, we will first discuss the typical heterolytic H_2 cleavage that is a key step in the catalytic hydrogenation of ketones and aldehydes.

Heterolytic cleavage of H_2 by Ru complexes dates back to the mid 1960s. Wilkinson and co-workers clearly demonstrated it by reacting of $RuCl_2(PPh_3)_3$ with H_2 in the presence of ethanol, giving $RuHCl(PPh_3)_3$ and HCl, in which ethanol served as a base.[12] Although tremendous progress has been made in the field of selective homogeneous hydrogenation of C–C multiple bonds since this finding,[6d,13] there has been little progress in the hydrogenation of polar bonds, despite its potential. Almost one decade later, Tsuji and co-workers developed the first successful example of homogeneous



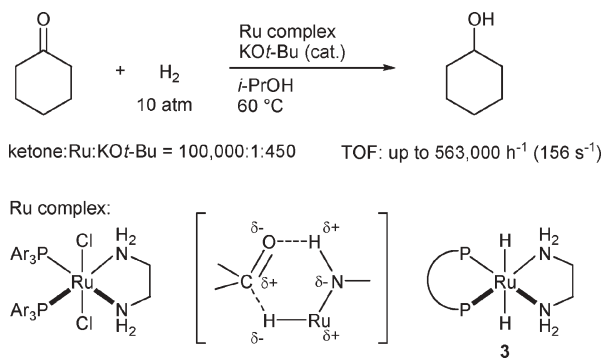
Scheme 3 Heterolytic H_2 cleavage by a Ru amide complex.

hydrogenation of aldehydes with $RuCl_2(PPh_3)_3$ at 50–80 °C under 20 atm of H_2.[14]

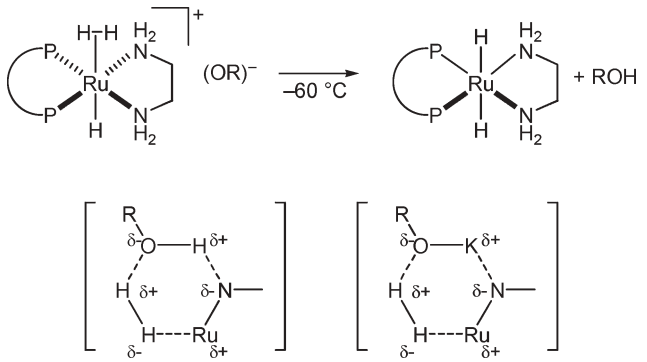
In 1991, Fryzuk and co-workers found that 16-electron Ru amide complex (**1**) undergoes heterolytic H_2 cleavage to give the 18-electron Ru hydride amine complexes (**2**) in aprotic media under atmospheric H_2, as shown in Scheme 3;[15] however, their catalytic potential for hydrogenation was not examined.

In 1995, Noyori and co-workers discovered that *trans*-$[Ru(H)_2(diphosphine)(diamine)]$ complex (**3**) serves as a highly efficient catalyst for the hydrogenation of ketones and aldehydes, in which excellent chemo- and stereoselectivity originates from its Ru/NH bifunctional property.[16–18] An important result is that the resulting amide complex undergoes heterolytic H_2 cleavage to generate Ru hydride **3** in preference to the dehydrogenation of alcohols as illustrated in Scheme 4, which stands in sharp contrast to similar Ru amide complexes that serve as transfer hydrogenation catalysts. In fact, direct NMR observation of *trans*-$[RuH(\eta^2\text{-}H_2)(diphosphine)(diamine)]^+$ in 2-propanol-d_8 has revealed that ingenious interplay between ligated η^2-H_2 and solvated 2-propoxide is responsible for the heterolytic cleavage of H_2 in basic 2-propanol.[19] Although the role of the potassium ion is explainable by the replacement of one of the hydrogens on the nitrogen with potassium, the total effect of the alkaline base is still controversial (Scheme 5).[17b,20]

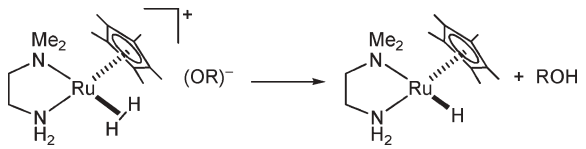
In 2001, we reported a similar effect for basic 2-propanol which can facilitate the heterolytic cleavage of H_2 bound to the 16-electron $[Cp^*Ru\{Me_2N(CH_2)_2NH_2\}]^+$ fragment as shown in Scheme 6.[21a] Extensive isotope labeling experiments using D_2, Me_2CDOH and Me_2CHOD, led us to propose the preferential formation of the hydrogen-bonding network of η^2-H_2, ligated NH_2 and 2-propanol, thus preventing dehydrogenation of 2-propanol. Later, this reaction pathway was confirmed by Brandt, Andersson and co-workers using theoretical calculations.[21b]



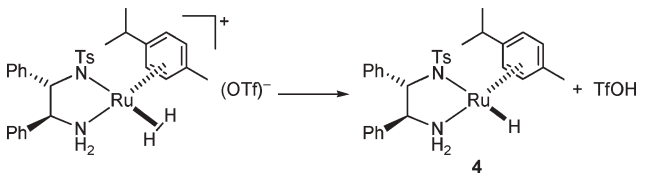
Scheme 4 Noyori's ketone hydrogenation based on the Ru/NH bifunctional mechanism. TOF = moles of product per mole of catalyst. P–P = diphosphine



Scheme 5 Heterolytic H_2 cleavage of Noyori's catalyst promoted by basic 2-propanol. P–P = (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap), ROH = 2-propanol, two phenyl substituents in the diamine ligand are omitted for clarity.



Scheme 6 Proposed heterolytic H_2 cleavage of $[Cp^*Ru(\eta^2\text{-}H_2)\{Me_2N(CH_2)_2NH_2\}]^+$ promoted by basic 2-propanol. ROH = 2-propanol



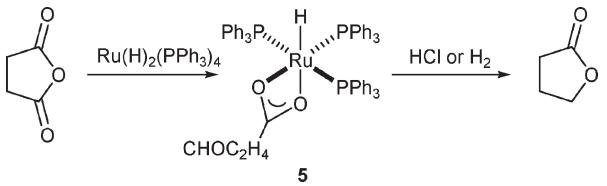
Scheme 7 Proposed heterolytic H_2 cleavage of $[Ru(\eta^2\text{-}H_2)\{(S,S)\text{-}TsNCHPhCHPhNH_2\}(\eta^6\text{-}p\text{-cymene})]^+$ promoted by triflate in methanol.

Particularly intriguing results have very recently been disclosed by Noyori and co-workers, who have reported that an isolable complex, Ru(OTf){(*S*,*S*)-TsNCHPhCHPhNH$_2$}-(η^6-*p*-cymene) is highly effective for the asymmetric hydrogenation of ketones in methanol containing no base.[22,23] This study suggests that heterolytic H_2 cleavage is also possible by the Ru(OTf) system, generating an active hydride complex, RuH{(*S*,*S*)-TsNCHPhCHPhNH$_2$}(η^6-*p*-cymene) (**4**) with concomitant release of TfOH in highly polarized media like methanol (Scheme 7). It should be noted that the concerted hydride/proton transfer from **4** to ketonic substrates[11] is likely operative to produce *sec*-alcohols with high ee values along with the 16-electron amide complex, Ru{(*S*,*S*)-TsNCHPhCHPhNH}(η^6-*p*-cymene), which then reacts with TfOH to complete the catalytic cycle.

Hydrogenation of carboxylic acids and their derivatives containing C=O double bonds

Hydrogenation of acid anhydrides

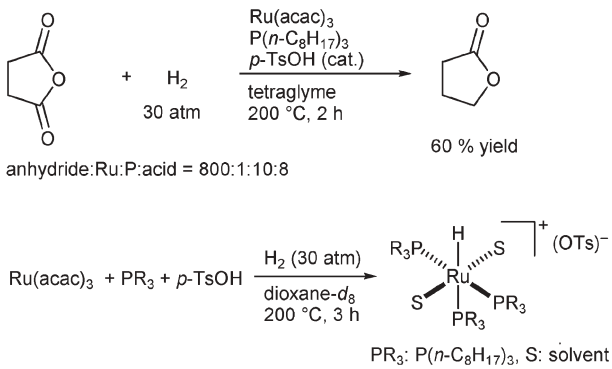
Ikariya and co-workers demonstrated as early as 1978 that $Ru(H)_2(PPh_3)_4$ transfers one of the two hydrides to an



Scheme 8 Reaction of Ru hydride carboxylate complex derived from cyclic anhydride and $Ru(H)_2(PPh_3)_4$, with HCl or H_2 leading to the formation of lactone.

electrophilic carbonyl group of succinic anhydride, allowing the isolation of $RuH(PPh_3)_3[O_2C(1,2\text{-}C_6H_4)CHO]$ (**5**), which undergoes intramolecular hydride transfer and subsequent protonolysis to liberate γ-butyrolactone and water after treatment with HCl or H_2 (Scheme 8).[24b,c] These results suggest that the HCl generated by the reaction of $RuCl_2(PPh_3)_3$ with H_2 (or slightly acidic η^2-H_2 bound to Ru intermediates)[1a–d] may play an important role in the lactone release step in the $RuCl_2(PPh_3)_3$-catalyzed hydrogenation of cyclic acid anhydrides, which was originally reported by Lyons in 1975.[24a] After the report of $H_4Ru_4(CO)_8[P(n\text{-}Bu)_3]_4$ as a catalyst for this type of reactions,[24d] Wada and co-workers at Mitsubishi Chemical Co. developed the ternary catalyst system of $Ru(acac)_3$, $P(n\text{-}C_8H_{17})_3$ and *p*-TsOH for the production of γ-butyrolactone from succinic anhydride with H_2 albeit at high temperature. Notably, the catalytic activity as well as chemoselectivity were greatly improved by the addition of external acids like *p*-TsOH. The cationic complex *mer*-$[RuH\{P(n\text{-}C_8H_{17})_3\}_3(solvent)_2]^+$ was detectable by NMR spectroscopy under the reaction conditions (Scheme 9). These results are consistent with the above-mentioned mechanistic implication.[24e,f]

Similar effects of acid additives on the catalyst performance in asymmetric hydrogenation of functionalized ketones or aldehydes-d_1 with chiral $RuX_2(binap)L_n$ (X = OAc, halogens), is also worth considering.[25] Choice of alcoholic solvents as well as the addition of a catalytic amount of HCl, HBF_4 or $CeCl_3{\cdot}7H_2O$ often causes a dramatic improvement in the catalytic performance in terms of catalytic activity and enantioselectivity. These studies suggest that alcoholic solvents and acid additives possibly prevent chiral Ru alkoxide

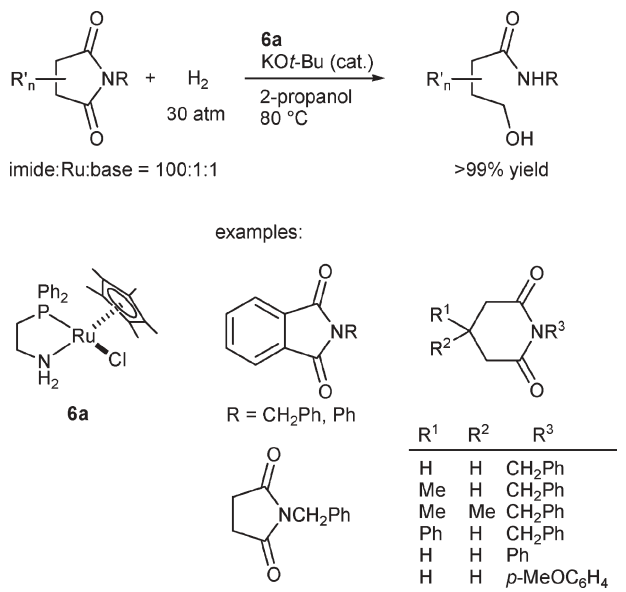


Scheme 9 Hydrogenation of succinic anhydride catalyzed by the ternary system of $Ru(acac)_3/P(n\text{-}C_8H_{17})_3/p$-TsOH, in which *mer*-$[RuH\{P(n\text{-}C_8H_{17})_3\}_3(solvent)_2]^+$ is considered to be a catalytically active species.

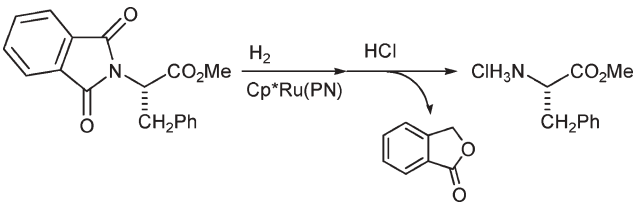
intermediates from β-hydride elimination to fall in equilibrium with the Ru hydride complex, liberating kinetically controlled alcohols with higher enantiomeric excess.

Hydrogenation of imides

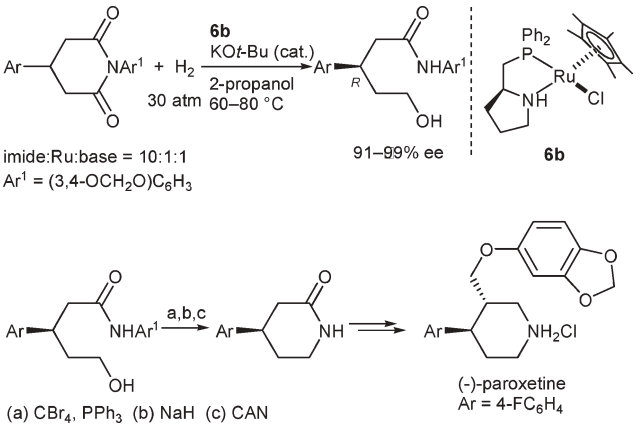
We have been engaged in the development of half-sandwich-type Ru, Rh and Ir amine complexes, in which the "metal/NH bifunctionality" is built-in, exhibiting unique catalyst performance in stereoselective chemical transformations including transfer hydrogenation and hydrogenation as well as Michael addition reactions.[26] In particular, our intense studies on the reactivity of a series of Cp*Ru complexes[21a,27,28] have revealed that judicious choice of coordinating elements enables the catalytic reduction of polar organic functionalities with H_2. As described above, $[Cp^*Ru\{Me_2N(CH_2)_2NH_2\}]^+$ complexes (Cp*Ru(N–N)) serve as an efficient catalyst for the chemoselective hydrogenation of ketones, thanks to the solvent-assisted heterolytic cleavage of H_2 as well as the Ru/NH bifunctionality.[21a] Additionally, the replacement of its tertiary amino group with a tertiary phosphino group has led to the expansion in the scope of the Ru/NH bifunctionality and a newly designed $[Cp^*Ru\{Ph_2P(CH_2)_2NH_2\}]^+$ complexes (Cp*Ru(P–N)) efficiently catalyze the hydrogenation of imides,[27b] whilst Cp*Ru(N–N) are totally inactive. A variety of imides are chemoselectively convertible to the corresponding alcohols and amides in 2-propanol containing **6a** and KO*t*-Bu as the catalyst under mild conditions as summarised in Scheme 10. This unprecedented hydrogenation method is characterized by its excellent chemoselectivity, substrate scope, and controllable stereoselectivity by the chiral modification of the ligand structures. In fact, it is applicable to the deprotection of primary amines from *N*-phthaloyl-protected amino acid ester derivatives. For example, *N*-phthaloyl-L-Phe methyl ester undergoes hydrogenation to generate *N*-(*o*-hydroxymethylbenzoyl)-L-Phe methyl ester, whose acid-promoted cyclisation liberates the HCl salt of



Scheme 10 Hydrogenation of imides catalyzed by the Cp*Ru(P–N) system.



Scheme 11 A new method for the deprotection of *N*-phthaloyl amino acid derivatives.



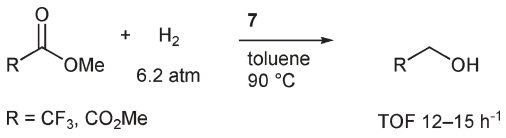
Scheme 12 Asymmetric hydrogenation of symmetrical glutarimides.

L-Phe methyl ester with concomitant formation of phthalide in high yields (Scheme 11).

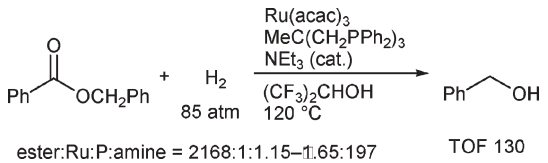
The chiral version of the Cp*Ru(P–N) catalyst bearing the P–N ligand derived from L-proline promotes the enantioselective hydrogenation of prochiral 4-arylglutarimides *via* desymmetrisation to provide the corresponding δ-hydroxyamides with excellent ee values and in high yields as illustrated in Scheme 12. Notably, the substituents on nitrogen in the cyclic imides significantly influence the enantioselectivity; the *N*-3,4-$(OCH_2O)C_6H_3$ group has led to high enantioselectivities. Further synthetic elaboration of the chiral δ-hydroxyamides including bromination, base-induced cyclisation, and CAN-mediated dearylation has furnished chiral piperidinone derivatives, which serve as important synthetic intermediates for a number of physiologically active chiral compounds including the antidepressant paroxetine. Thus, the present hydrogenation provides a versatile synthetic method because of its unique chemo- and stereoselectivity.

Hydrogenation of esters[29]

In 1981, Grey and co-workers reported that isolable anionic $K_2[Ru_2H_4(PPh_2)(PPh_3)_3]\cdot 2C_6H_{14}O_3$ (**7**) serves as an effective catalyst for the hydrogenation of esters with an electron-withdrawing group adjacent to the carbonyl group. For example, trifluoroacetic acid ester and dimethyl oxalate in toluene were hydrogenated to give trifluoroethanol and methyl glycolate, respectively.[29a] Unfortunately, however, unactivated simple esters hardly underwent hydrogenation under the same conditions (Scheme 13). Wada and co-workers found that the addition of acid promoters, such as NH_4PF_6 or H_3PO_4, to the catalyst system of $Ru(acac)_3$ and $P(n\text{-}C_8H_{17})_3$ affords a

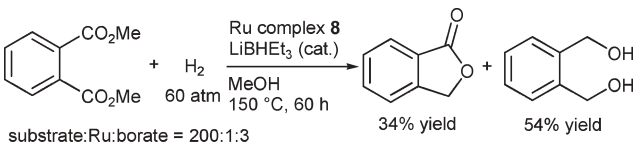


Scheme 13 Hydrogenation of activated esters catalyzed by $K_2[Ru_2H_4(PPh_2)(PPh_3)_3]\cdot 2C_6H_{14}O_3$ (**7**).

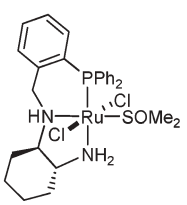


Scheme 14 Hydrogenation of an ester catalyzed by $Ru(acac)_3$/$MeC(CH_2PPh_2)_3$ in an acidic media.

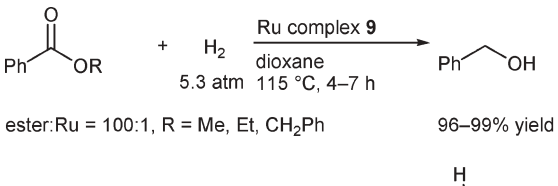
significant improvement in the catalytic activity in the hydrogenation of γ-butyrolactone leading to 1,4-butanediol at a higher H_2 pressure[29e] than that required for the conversion of succinic anhydride into γ-butyrolactone (*vide supra*).[24e,f] However, acyclic esters remained robust toward hydrogenation under these conditions. In 1997, Teunissen and Elsevier reported the first homogeneous hydrogenation of unactivated esters to their corresponding alcohols catalyzed by a $Ru(acac)_3$/$MeC(CH_2PPh_2)_3$ system in dry methanol[29g] and later they improved its catalytic activity by replacing the dry methanol with 1,1,1,3,3,3-hexafluoropropan-2-ol containing a substoichiometric amount of triethylamine as shown in Scheme 14. This study suggested that the cooperative action of Ru hydride and a relatively acidic media is crucial to attain high reactivity.[29h] Recently, Clarke and co-workers demonstrated that the well-defined pincer-type $RuCl_2$(PNN)(Me_2SO-κ-*S*) complex bearing an NH unit (**8**) effects hydrogenation of dimethyl *o*-phthalate into *o*-xylyleneglycol upon treatment with $LiBHEt_3$ in methanol under relatively forcing conditions (Scheme 15).[29j] By contrast, Milstein and co-workers reported the efficient hydrogenation of unactivated esters using the well-defined RuH(PNN)(CO) complex without any NH unit (**9**) as the catalyst under relatively mild conditions (Scheme 16).[29k] Notably, in Milstein's system, complex **9** undergoes reversible heterolytic H_2 cleavage to give the 18-electron *trans*-dihydride complex (**10**) quantitatively; complex **9** also catalyzes the

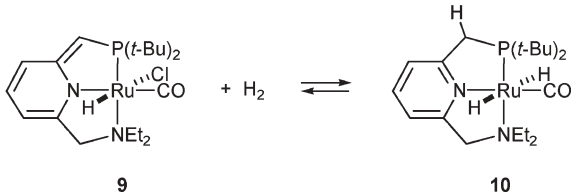


Ru complex **8**:



Scheme 15 Hydrogenation of dimethyl *o*-phthalate catalyzed by **8**.





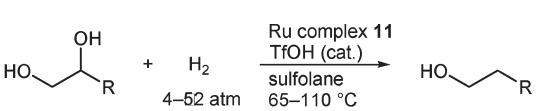
Scheme 16 Hydrogenation of esters catalyzed by **9**.

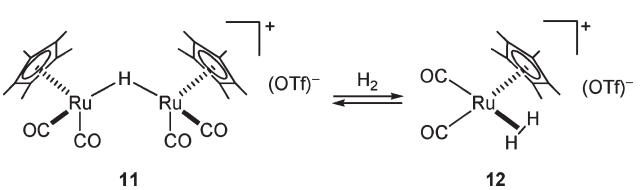
dehydrogenation of primary alcohols to esters in the absence of H_2. Their study suggests that the dissociation of the tertiary amine ligand in complex **10** provides a coordination site for an ester or an aldehyde, allowing the insertion of a hydride. Although they stated that the resultant alkoxide ligands abstract the hydrogen atom at the benzylic α-C–H in the ligand to liberate products with regeneration of **9**, it is also conceivable that the alkoxide complexes undergo heterolytic H_2 cleavage to regenerate **10**. If the latter is the case, the Brønsted acidity of the η^2-H_2 ligand on certain types of Ru complexes[1a–d] may also play an important role for the elimination of alcoholic products. However, further studies are required to draw a precise reaction pathway.

Hydrogenolysis of C–O single bonds

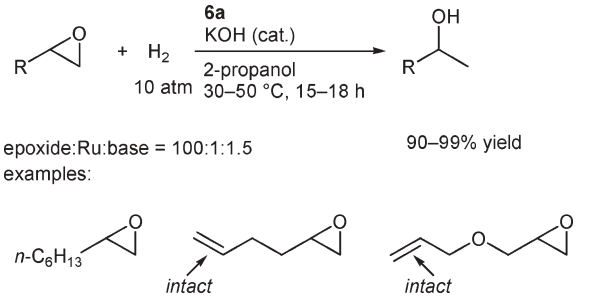
Hydrogenation of diols to monools

Bullock and co-workers reported hydrogenative deoxygenation of diols to monools catalyzed by [{Cp*Ru(CO)$_2$}$_2$(μ-H)]OTf (**11**) and the TfOH system in sulfolane as shown in Scheme 17.[30] They proposed that unstable [Cp*Ru(CO)$_2$(η^2-H_2)]OTf (**12**) is acidic enough to protonate the *sec*-OH group in the substrate to eliminate water and leave a protonated carbonyl compound, to which Cp*Ru(CO)$_2$H delivers its hydride and subsequent coordination of H_2 to Ru completes the catalytic cycle. Highly acidic conditions lead to the low chemoselectivity; this type of reaction is almost completely limited to alcohols with a vicinal OH group, which enables tautomerisation of intermediary enols.

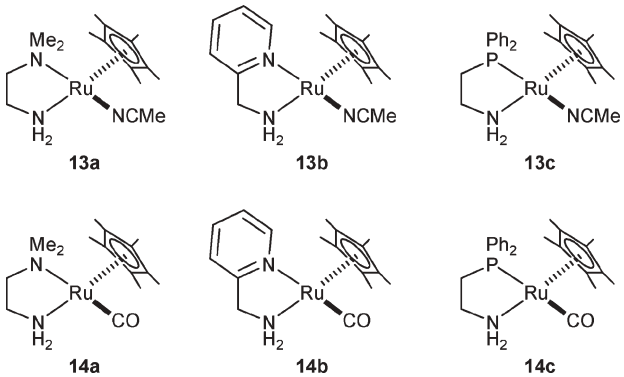




Scheme 17 Hydrogenative deoxygenation of diols to monools catalyzed by **11** in the presence of acid.



Scheme 18 Hydrogenolysis of epoxides catalyzed by the Cp*Ru(P–N) system.



Scheme 19 Cationic complexes $[Cp^*Ru(L–N)(MeCN)]^+$ (**13**) and $[Cp^*Ru(L–N)(CO)]^+$ (**14**).

Hydrogenolysis of epoxides

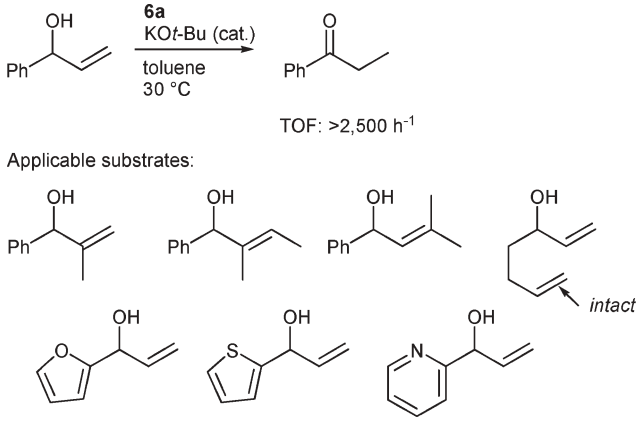
We found that the Cp*Ru(P–N) catalyst systems mentioned in the discussion of imide hydrogenation also efficiently promote hydrogenolysis of terminal epoxides.[27a] This catalyst system selectively delivers hydrogen to the non-substituted C–O bond in terminal epoxides, leading to the formation of *sec*-alcohols as shown in Scheme 18. A variety of terminal epoxides are readily convertible in 2-propanol containing Cp*Ru(P–N) catalyst to the corresponding *sec*-alcohols in high yields. Thanks to the Ru/NH bifunctionality, alkenyl epoxides give alkenyl *sec*-alcohols quantitatively without formation of saturated alcohols or epoxides. Terminal epoxides bearing another ethereal functionality on the side chain smoothly undergo hydrogenolysis to the corresponding *sec*-alcohols in high yields, indicating that potential Lewis basic groups other than epoxide group do not interact with the catalyst due to the coordinatively saturated nature of the possibly active Cp*Ru hydride species. Although stereospecific hydrogenolysis of optically active terminal epoxides was hampered by the competing racemisation of the products (*vide infra*), this catalytic hydrogenolysis provides a new alternative to stoichiometric metal hydride reduction.

Ligand modification to tune catalyst performance

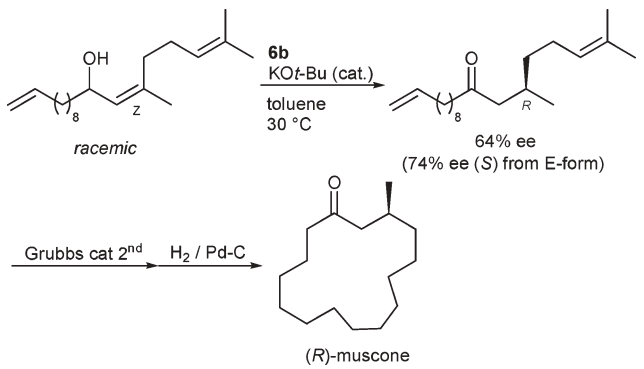
As discussed above, our Cp*Ru(P–N) catalysts efficiently promote hydrogenative reduction of imides and epoxides in addition to ketones, whereas Cp*Ru(N–N) catalysts are only effective for the ketones. The difference in their reactivity may be attributable to the electronic difference between the tertiary amino and phosphino groups in the ligand. The wider range of polar functionalities reducible by Cp*Ru(P–N) catalysts indicates that the possible active species, $Cp^*RuH[Ph_2P(CH_2)_2NH_2]$ exerts stronger electrophilic activation in the transition state than the corresponding Cp*Ru(N–N) congener. Considering the coordinatively saturated nature of these active hydrides, the magnitude of their electrophilic activation should be attributable to the Brønsted acidity of the coordinated NH_2 groups. To gain further evidence in support of this idea, we prepared a series of cationic Cp*Ru complexes bearing various chelating primary amine ligands (Scheme 19), whose electronic properties, as well as catalytic performance, have been studied systematically.[27a,c] $^{13}C\{^1H\}$ NMR spectroscopy of **13** and IR measurement of **14** revealed the relatively weaker σ-donating and stronger π-accepting abilities of the diphenylphosphino group compared to the dimethylamino or pyridine in the Cp*Ru complexes. Thus, the resonances for the ring carbon of Cp* in the P–N complex **13c** appear as a doublet ($^2J_{CP}$ = 2.3 Hz) at 84.9 ppm, while those for the N–N complexes **13a** and **13b** appear at higher field as singlets at 75.2 and 77.5 ppm, respectively. Also, the carbonyl stretching frequency in the P–N complex **14c** was observed at 1948 cm^{-1}, while those for the N–N complexes **14a** and **14b** were at 1931 and 1938 cm^{-1}, respectively. Therefore, the electron density of the metal center in a series of Cp*Ru(P–N) complexes should be lower than that of Cp*Ru(N–N) complexes and hence the Brønsted acidity of the ligated NH_2 group in the Cp*Ru(P–N) complexes should be stronger than that in the Cp*Ru(N–N) complexes.[31,32]

Another distinct feature of the catalyst system Cp*Ru(P–N) in comparison with Cp*Ru(N–N) is its extremely high activity for the cleavage of the α-C–H bond of *sec*-alcohols, which may be caused by *reversible* hydrogen transfer between alcohols and carbonyls, leading to a rapid racemisation of chiral non-racemic *sec*-alcohols.[28a] In other words, asymmetric hydrogenation of prochiral ketones becomes possible with chiral Cp*Ru(N–N) catalyst systems[21a] thanks to their reluctance to cleave the α-C–H bonds of product alcohols, but not with chiral Cp*Ru(P–N) systems since concurrent racemisation of the product alcohols deteriorates their kinetically-controlled enantioselection regardless of whether the hydrogen source is H_2 or 2-propanol.

The development of synthetically viable, oxidative transformations of alcohols based on this observation deserves comment, though we stray from the main topic. First, allylic alcohols undergo intramolecular hydrogen transfer to give saturated carbonyl compounds efficiently in aprotic media containing Cp*Ru(P–N) catalysts; the TOF of this reaction at 30 °C exceeds 2500 (h^{-1}) (Scheme 20).[28b] Unlike conventional catalysts, this catalyst system successfully discriminates olefins with an allylic hydroxyl group from other olefinic groups due to its "extended" Ru/NH bifunctionality. This unique chemoselectivity is effectively applicable in the preparation of macrocyclic ketones starting from readily available acyclic allylic alcohols equipped with two isolated C=C double bonds, since our isomerisation method provides substrates suitable for ring-closing metathesis. For example, muscone can be conveniently prepared using asymmetric isomerisation with chiral Cp*Ru(P–N) catalysts as a key step (Scheme 21).

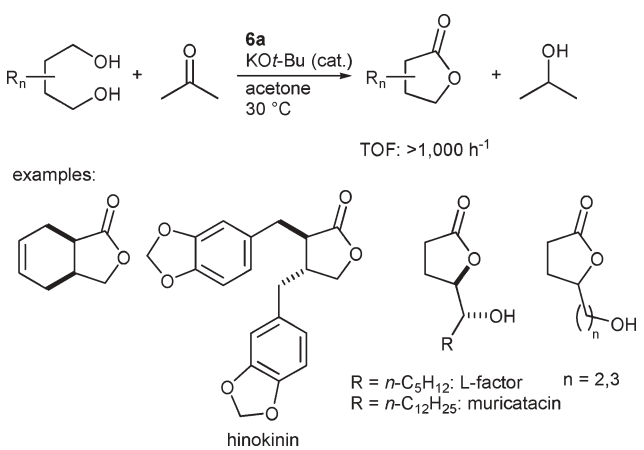


Scheme 20 Isomerisation of allylic alcohols catalyzed by the Cp*Ru(P–N) system.



Scheme 21 Asymmetric synthesis of muscone *via* dynamic kinetic resolution of allylic alcohols.

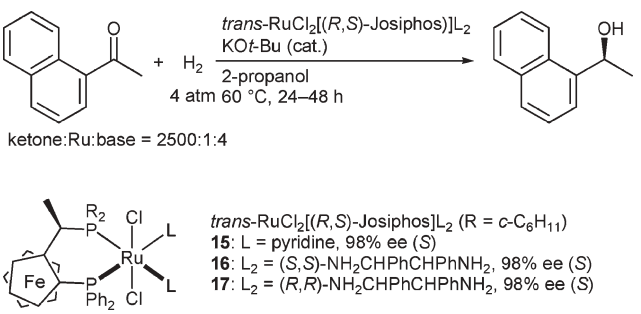
Second, 1,4-diols undergo intermolecular hydrogen transfer, giving lactones efficiently in acetone containing Cp*Ru(P–N) catalysts; the TOF of this reaction at 30 °C exceeds 1000 (h^{-1}) (Scheme 22).[28c] This catalytic oxidative lactonisation of diols is characterized by its unique chemo- and regioselectivity. Thanks to the Ru/NH bifunctionality, isolated C=C double bonds in the substrates remain intact despite possible saturation. The significant rate difference between primary and secondary alcohols in dehydrogenation, and the rate difference between 1,4-diols and 1,5- or 1,6-diols enable unique oxidative lactonisation of triols, which results in the exclusive formation of γ-butyrolactones including L-factor and muricatacin, where the remote OH groups remain intact regardless of whether they are primary or secondary. It should be noted that no measurable amount of other isomeric lactones was obtained in these reactions.



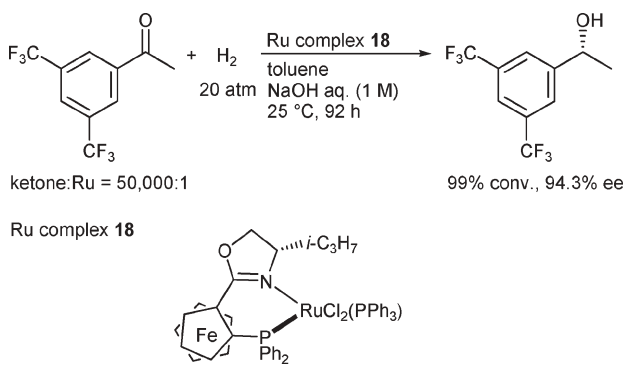
Scheme 22 Oxidative lactonisation of 1,4-diols catalyzed by the Cp*Ru(P–N) system.

Conclusions

Although Noyori's concept of Ru/NH bifunctionality has revolutionized the field of catalytic asymmetric reduction of ketones over the last decade, several useful catalysts that do not rely on this concept have also been developed. Bergens and co-workers questioned the role of the diamine ligand in certain $RuCl_2$(diphosphine)(diamine) complexes in the asymmetric hydrogenation of prochiral ketones.[33a] Upon treatment with base in 2-propanol, *trans*-$RuCl_2$[(*R*,*S*)-Josiphos](pyridine)$_2$] (**15**) exhibits a similar catalytic performance as *trans*-$RuCl_2$[(*R*,*S*)-Josiphos][(*S*,*S*)-$NH_2CHPhCHPhNH_2$] (**16**) and *trans*-$RuCl_2$[(*R*,*S*)-Josiphos][(*R*,*R*)-$NH_2CHPhCHPhNH_2$] (**17**) in the hydrogenation of 1′-acetonaphthone to furnish (*S*)-1-(1-naphthyl)ethanol with identical ee values, except the former requires a longer induction period (Scheme 23). Furthermore, researchers at Solvias found industrially useful $RuCl_2(PPh_3)$(phosphine-oxazoline) complexes, which promote very efficient enantioselective hydrogenation of various aryl alkyl ketones in an toluene/aqueous NaOH biphasic system (Scheme 24).[33b,c] These examples remind us of earlier



Scheme 23 Hydrogenation of 1′-acetonaphthone catalyzed by the $RuCl_2$[(*R*,*S*)-Josiphos]L_2 system.



Scheme 24 Solvias method for the production of (*R*)-1-(3,5-bistrifluoromethyl)phenyl ethanol.

fundamental studies; Szabó, Bäckvall and co-workers clearly demonstrated in 1999 that, even in the absence of H_2, 2-propanol containing alkaline base efficiently converts $RuCl_2(PPh_3)_3$ to $RuH_2(PPh_3)_3$,[34a] and in 1987 Linn and Halpern clarified that the latter is a real catalyst in the hydrogenation of ketones[34b] which was originally developed by Grey *et al.* in 1980.[29a] A variety of mechanistically intriguing results have been also obtained in the field of Ru-catalyzed hydrogenation of nitrogen-containing compounds including imines,[16c,d,35] organonitrile compounds,[29a,36] and organonitro compounds,[37] as well as of CO_2.[38] Therefore, various potential mechanistic principles should be exploited to draw a logical molecular catalyst design for the synthetically viable hydrogenation of polar bonds.

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