Mechanistic aspects of transition metal-catalyzed hydrogen transfer reactions

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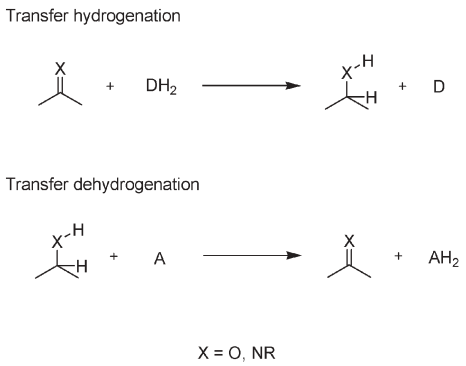
In this *tutorial review* recent mechanistic studies on transition metal-catalyzed hydrogen transfer reactions are discussed. A common feature of these reactions is that they involve metal hydrides, which may be monohydrides or dihydrides. An important question is whether the substrate coordinates to the metal (inner-sphere hydrogen transfer) or if there is a direct concerted transfer of hydrogen from the metal to substrate (outer-sphere hydrogen transfer). Both experimental and theoretical studies are reviewed.

Introduction

Environmental concerns in chemistry have increased the demand for more selective chemical processes with a minimum amount of waste (''green chemistry''). Hydrogen transfer reactions are mild methodologies for reduction of ketones or imines and oxidation of alcohols or amines in which a substrate-selective catalyst transfers hydrogen between the substrate and a hydrogen donor or acceptor, respectively (Scheme 1).[1] Furthermore, the donor (*e.g.* 2-propanol) and the acceptor (*e.g.* a ketone or a quinone) are environmentally friendly and also easy to handle.

This review deals with recent advances in the understanding of the mechanistic pathway in the hydrogen transfer reactions of these new catalysts. Two main pathways have been proposed for hydrogen transfer to ketones (aldehydes). A ''direct hydrogen transfer'' is thought to be the main pathway for main group metals whereas a hydridic route is involved for transition metals. The latter can be further divided into dihydridic or monohydridic routes. The monohydridic route can operate through different pathways depending on both the



Scheme 1

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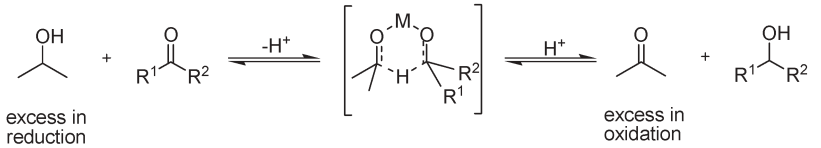
Joseph S. M. Samec was born in Stockholm, Sweden in 1971. He received his BSc degree (2001) and his PhD degree (2005) from the Stockholm University, Sweden under the supervision of Prof. Jan-E. Bäckvall. He is currently doing his Postdoc with Prof. R. H. Grubbs at The California Institute of Technology, Pasadena. His research interests include synthetic applications and mechanisms in organometallic chemistry.

Jan-E. Bäckvall

Jan-Erling Bäckvall was born in Malung, Sweden, in 1947. He received his PhD from the Royal Institute of Technology, Stockholm, in 1975 under the guidance of Prof. B. Åkermark. After postdoctoral work (1975–76) with Prof. K. B. Sharpless at Massachusetts Institute of Technology he joined the faculty at the Royal Institute of Technology. He was appointed Professor of Organic Chemistry at Uppsala University in 1986. In 1997 he moved to Stockholm University where he is currently Professor of Organic Chemistry. He is a member of the Royal Swedish Academy of Sciences and the Finnish Academy of Science and Letters. His current research interests include transition metal-catalyzed organic transformations, biomimetic oxidations, and enzyme chemistry. Recently, efficient systems for dynamic kinetic resolution of alcohols and amines based on combined ruthenium and enzyme catalysis were developed in his laboratory.



Scheme 2 MPV reduction and Oppenauer oxidation.

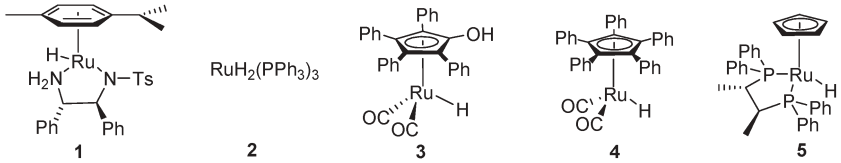


Fig. 1 Examples of metal hydrides.

catalyst and substrate. The classical pathway involves a metal alkoxide as intermediate. More recently, this pathway has been questioned for certain catalysts that contain both the metal hydride and an acidic proton. Noyori has proposed a metal ligand bifunctional pathway where the hydrogen transfer occurs simultaneously outside the coordination sphere of the metal. An ionic mechanism has been proposed for hydrogenation of ketones (aldehydes) and imines.

Direct hydrogen transfer

The pathway through a ''direct hydrogen transfer'' was proposed for the Meerwein–Ponndorf–Verley (MPV) reduction (Scheme 2).[2] In the original version, of the MPV reduction, aluminum isopropoxide was used to promote transfer of hydrogen from isopropanol to a ketone.[3] The reaction can also be run in the opposite direction, using acetone as hydrogen acceptor, and this was studied by Oppenauer.[4] Thus, for the MPV reduction of a ketone, *i.e.* transfer hydrogenation, isopropanol is employed in excess. For the Oppenauer oxidation acetone is used in excess.

The mechanism is proposed to proceed through a six-membered transition state, without involvement of metal hydride intermediates (Scheme 2).[2]

The hydridic route

Transition metal catalysts generally operate through a hydridic route. A common feature of these catalysts is that a metal hydride is involved as a key intermediate in the hydrogen transfer.[1,5] Such hydrides have indeed been isolated from transition metal-catalyzed hydrogen transfer reactions in some cases (Fig. 1).

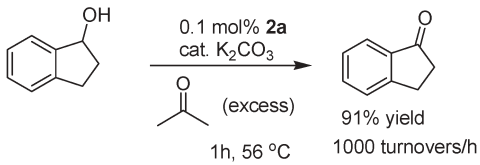
An early example of a transition metal-catalyzed hydrogen transfer with moderate rates and turnovers was reported by Henbest in the 1960s.[6] Sasson and Blum[7] found in 1971 that $RuCl_2(PPh_3)_3$ (**2a**) can be used at high temperature with moderate turnover frequency.[8] In 1991 the effect of base on the $RuCl_2(PPh_3)_3$-catalyzed transfer hydrogenation was reported.[9] The presence of small amounts of base led to a dramatic rate enhancement (10^3–10^4 times faster). It was later shown that the rate enhancement is due to formation of a highly active $RuH_2(PPh_3)_3$ (**2**).[9b] Also in the reversed reaction, the Oppenauer-type oxidation, a spectacular effect by the base with the use of **2a** as catalyst was observed (Scheme 3).[10] These reactions proceed under very mild conditions with low loading of catalyst. The promoting effect of base had been observed previously for Ir- and Rh-catalyzed reactions, but not of this order.[11]

Pher G. Andersson

Pher G. Andersson was born 1963 in Växjö, Sweden. He was educated at Uppsala University where he received his BSc in 1988 and his PhD in 1991. After postdoctoral research at Scripps Research Institute with Prof. K. B. Sharpless, he returned to Uppsala where he became docent 1994 and full professor 1999. His main research interests involve organometallic chemistry, steroselective synthesis, and asymmetric catalysis.

Peter Brandt

Peter Brandt is a research computational chemist and Chemistry Team Leader at Biovitrum—one of the largest biotech companies in Europe. The skills in computer-aided drug design were received at KaroBio working with nuclear receptors. He obtained his PhD in organic chemistry at the Royal Institute of Technology, Stockholm, Sweden. After this, he continued the study of reaction mechanisms and expanded the work to cover enantioselective reactions as a postdoc at the Royal Danish School of Pharmacy, Copenhagen.



In the absence of base there is no reaction after 6h.

Scheme 3 The effect of base in the transfer dehydrogenation of alcohols by **2**.

The dihydride mechanism

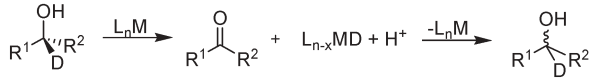
A general feature for catalysts operating through the dihydride mechanism is that the C–H and O–H from the hydrogen donor (alcohol or formic acid) lose their identity when they are transferred to the ketone (aldehyde). This is due to the fact that the two hydrogens become equivalent after being transferred to the metal to give the dihydride. An experimentally simple method that has been used to probe the dihydride mechanism is to racemize an optically active α-deuterated alcohol *e.g.* (*S*)-phenylethanol (**6**) (Scheme 4).[12] If the catalysts follow the dihydride mechanism, the deuterium will be scrambled between carbon and oxygen (C–D : O–D ~ 1 : 1).

The monohydride mechanism

A common feature for catalysts operating through the monohydride mechanism is that the hydride and the proton keep their identity, *i.e.* the C–H from the hydrogen donor ends up as a C–H in the product. The reason for this is that only the C–H hydrogen of the donor forms the hydride on the metal (that transfers to the carbonyl carbon) while the OH of the donor stays as a proton during the process (and adds to the carbonyl oxygen). Contrary to the dihydride mechanism, when an optically active α-deuterated alcohol is racemized, the deuterium will only end up in the α-position of the fully racemized alcohol (Scheme 5).[12]

Monohydride *versus* dihydride mechanism

To find out whether the mono or dihydride pathways operate, a variety of different catalysts were screened in the racemization of α-deuterated (*S*)-phenylethanol ((*S*)-**6**). The deuterium content in the α-position of the fully racemized phenylethanol ((*rac*)-**6**) was analyzed. It was found that both the metal and the ligands were of importance.[12]



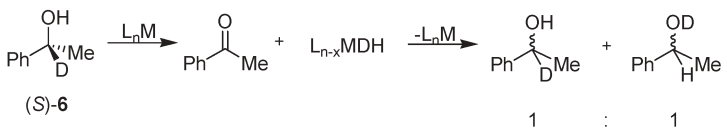
Scheme 5 Racemization of α-deuterated chiral alcohol in the monhydride mechanism.

Rhodium- and iridium-catalyzed hydrogen transfer

For the rhodium-catalyzed racemization reactions, very high deuterium content (95–98%) was obtained for all complexes studied (Fig. 2, complexes **7** and **8**). Also, the iridium complexes generally gave high deuterium content, in particular complexes having no phosphine ligands (Fig. 2, complex **10**). For complexes having phosphine ligands some loss of deuterium was observed (Fig. 2, complexes **9** and **11**) but the deuterium content of these complexes was still far above 50%. The loss of deuterium in the latter complexes was rationalized by *ortho* metalation of the phosphine leading to some H–D exchange.[13] The rhodium- and iridium-catalyzed reactions clearly follow the path involving monohydride intermediates.[12a]

Ruthenium-catalyzed hydrogen transfer

The outcome of the ruthenium-catalyzed racemization of (*S*)-**6** with respect to deuterium content in (*rac*)-**6** varied depending on the type of catalysts precursor employed (Fig. 3). With dichloride complexes **14** and **2b** as catalyst precursors the deuterium content in the α-position of (*rac*)-**6** was 40 and 37%, respectively, after complete racemization (Fig. 3, complexes **14** and **2b**) indicating a dihydride mechanism. On the other hand complexes **15–17** gave a high degree of deuteration (89–98%) in the α-position of the alcohol after complete racemization, indicating a monohydride mechanism for these catalysts. Complexes **15** and **17** as catalyst precursors for the racemization of (*S*)-**6** afforded (*rac*)-**6** with a deuterium content of 89 and 88%, respectively. Although there is some loss of deuterium from the α-position of the alcohol the results are also best explained by a monohydride mechanism.



Scheme 4 Racemization of α-deuterated (*S*)-**6** in the dihydride mechanism.

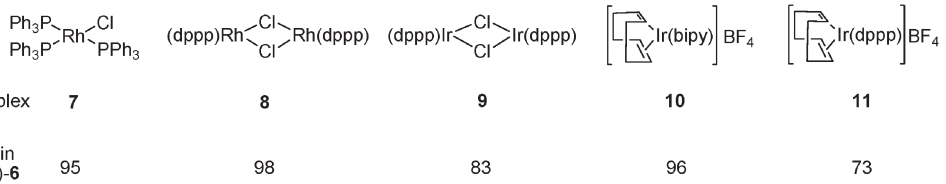


Fig. 2 Deuterium content in the α-position of the fully racemized phenylethanol ((*rac*)-**6**) by rhodium and iridium catalysts.

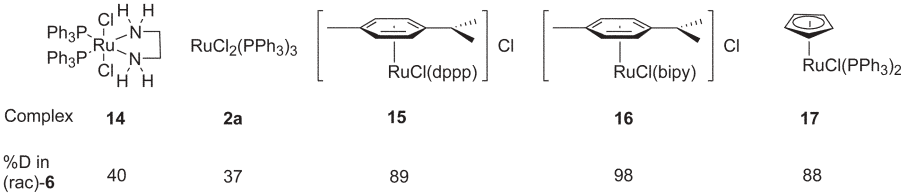


Fig. 3 Deuterium content in the α-position of the fully racemized phenylethanol ((*rac*)-**6**) by ruthenium catalysts.

Inner sphere *versus* outer sphere hydrogen transfer

There are two types of catalysts operating through the monohydride mechanism that have been suggested to operate differently. In both pathways the metal hydride migrates from the metal to the carbonyl carbon giving rise to the α-C–H. The formation of the metal monohydride from the hydrogen donor may involve the formation of a transition metal alkoxide followed by β-elimination to give the M–H (Scheme 6, A). In this mechanism the hydride transfer occurs in the inner sphere of the metal. Alternatively, it may proceed through the outer sphere of the metal *i.e.* without coordination of the alcohol to the metal (Scheme 6, B). The hydrogen transfer in an outer-sphere mechanism may proceed either in a concerted manner or in two discrete steps, where the protonation of the substrate precedes the hydride transfer.

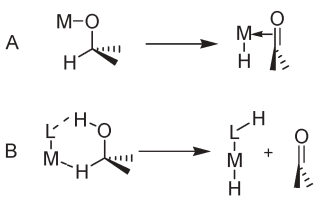
Metal ligand bifunctional catalysts

Noyori coined the term metal ligand bifunctional catalysis for his catalysts such as catalyst **1** and **14**.[14] A key feature for these catalysts is that one of the sites of the ligand acts as a basic center. This basic center is suggested to interact with the alcohol or amine through a hydrogen bond and thereby it facilitates the hydride transfer. The mechanism for catalysts such as **1** and **14**, is proposed to involve a concerted hydrogen transfer without prior coordination of the substrate to the metal. There are also examples of metal ligand bifunctional catalysts that operate in a stepwise manner or *via* an ionic mechanism (see below).

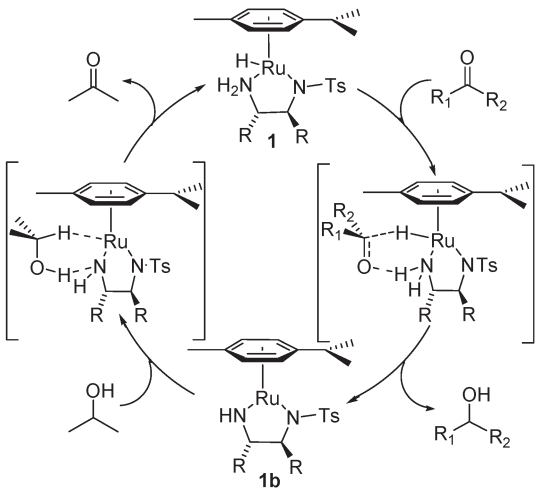
(η^6-Arene)RuTsDPEN (1). Concerted process

Early attempts to use chiral phosphine ligands were associated with the problem that the enantio-enriched alcohol produced underwent racemization.[15] A breakthrough in asymmetric transfer hydrogenation was Noyori's introduction of chiral nitrogen ligands with an NH group.[14] When chelating ligands with NH_2 groups, either 2-aminoethanol or the mono-*N*-tosylated diamine (*S*,*S*)-$TsNHCH_2CH_2NH_2$ are mixed with base and $[RuCl_2(benzene)]_2$ in 2-propanol, an active catalyst system is produced that only slowly reverses the reaction back to ketone (which is a pathway for racemization).[14b] Notably the use of *N*,*N*-dimethylated compounds gave ruthenium complexes that were totally inactive as catalysts.[16] This discovery led to the development of Noyori's efficient catalysts for the asymmetric transfer hydrogenation of ketones and imines. The active species **1** can be generated from the precursor chloride complexes RuCl((*S*,*S*)-$H_2NCHRCHRNTs)(\eta^6$-arene) (**1a**) by reaction with a reductant (formic acid or 2-propanol) and base. For imines the reactions are conducted in a formic acid–triethylamine azeotropic 5 : 2 mixture with or without an additional solvent. Chiral alcohols derived from aryl alkyl ketones and a variety of chiral amines from prochiral imines are obtained in very high *ee*. The proposed mechanism of these catalysts for the transfer hydrogenation of ketones (Scheme 7) involves a concerted transfer of the proton and the hydride from **1** to the substrate in a cyclic six-membered transition state to give the alcohol and **1b**. The proton and the hydride from 2-propanol are then delivered to the ligand and the metal, respectively, forming **1** and acetone. Note that the reaction is proposed to proceed without coordination of either alcohol or ketone (aldehyde) to the metal (Scheme 7).

There is computational support[17] for this mechanism and both **1** and **1b** have been isolated and proven to be active intermediates.[14] Recently, however, an alkoxide complex (**18**) was isolated from a bifunctional catalyst related to the Noyori catalysts (Fig. 4).[18] The intermediacy of a ruthenium alkoxide



Scheme 6 Monohydride mechanism can proceed either in a inner sphere or an outer-sphere pathway.



Scheme 7 Catalytic cycle of catalyst **1** *via* a concerted six-membered transition state.

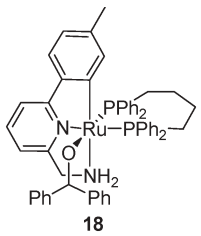


Fig. 4 An isolated alkoxide complex from a catalyst related to Noyori's catalyst.

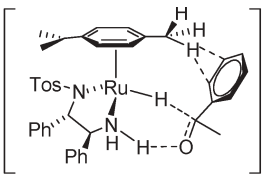


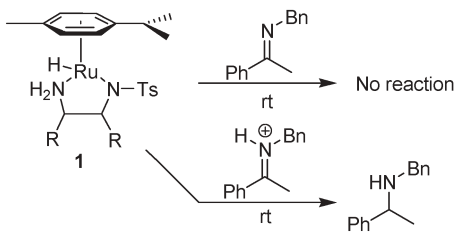
Fig. 5 π–CH attractive interaction in the enantioselection by catalyst **1**.

suggests a different mechanism to that proposed by Noyori since the latter mechanism does not involve ruthenium alkoxide.

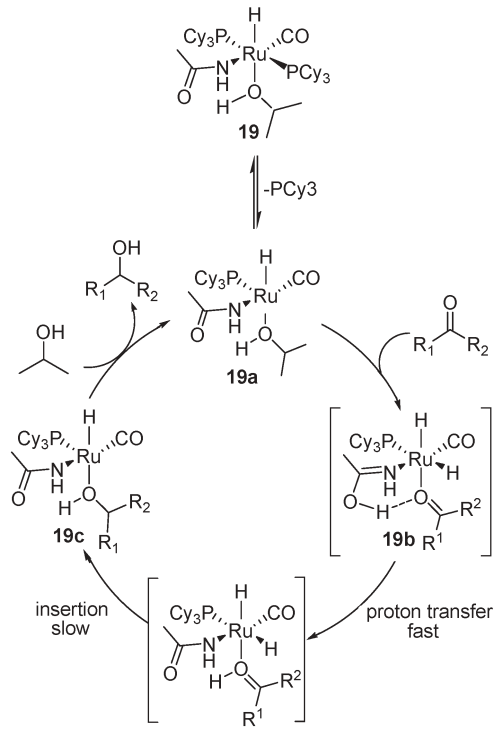
Casey's group has studied the kinetic isotope effect in the dehydrogenation of isopropanol by Noyori's catalyst **1b** and found that the hydride and proton transfer occur simultaneously in accordance with the mechanism proposed by Noyori.[19]

The stereoselectivity in the transfer hydrogenation catalyzed by **1** has been ascribed not only to the chiral diamine ligand but also to the contribution of polyalkylated arenes to the stabilization of the CH–π attractive interaction developed in the transition state (Fig. 5).[20]

The reactivity order for catalyst **1** correlates with the polarization of the double bond of the substrate, explaining why aldehydes react faster than ketones. Also the less polarized imine double bond requires harsher reaction conditions than ketones and aldehydes. Whereas aldehydes and ketones are smoothly reduced in isopropanol, the corresponding imines require a triethylamine–formic acid mixture.[21] Interestingly, we have recently found that imines are not reduced by the complex **1**, indicating that the reaction with imines proceed through a different pathway to that proposed for ketones and aldehydes.[22] However, in the presence of acid the imine reacts with hydride **1** to give amine. Probably, the acid protonates the imine and thereby activates it prior to hydride transfer (Scheme 8).



Scheme 8 Imines do not follow the same pathway as carbonyls in the hydrogenation by complex **1**.



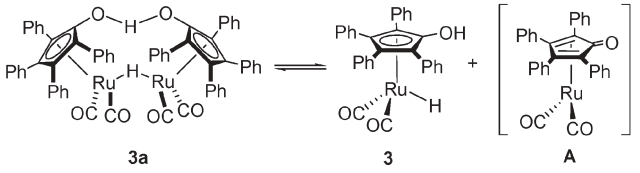
Scheme 9 Metal ligand bifunctional catalyst **19** operating in a stepwise manner.

RuH(NHCOMe)(OHCMe$_2$)(PCy$_3$)$_2$(CO) (19). Stepwise mechanism

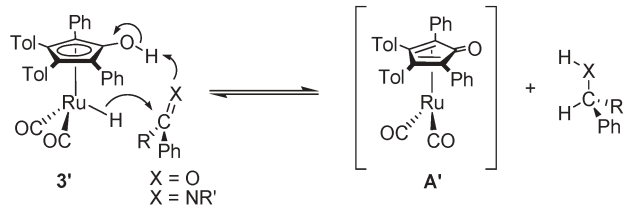
In 2001 Yi's group reported on a ruthenium-acetamido complex **19**.[23] This complex was found to be an efficient transfer hydrogenation catalyst for both aryl- and alkyl-substituted ketones and imines at 80 °C. This metal ligand bifunctional catalyst is an example of a catalyst that does not follow a concerted hydrogen transfer pathway. The catalytic cycle begins with the dissociation of a PCy_3 ligand from **19** generating the coordinatively unsaturated ruthenium-amido species **19a** (Scheme 9). The inhibition by added phosphine provided strong support for a dissociative pathway. Subsequent β-elimination and exchange of acetone with the substrate ketone generates the metal hydride **19b**. A fast and reversible proton transfer is followed by a slow insertion to generate **19c**. Finally, isopropanol exchanges with the product formed, which regenerates **19a** thereby completing the catalytic cycle. Observation of an inverse deuterium isotope effect supports a stepwise mechanism of proton and hydride transfer to the ketone.

[(η^5-Ph$_4$C$_4$COH)(μ-H)[(CO)$_4$Ru$_2$] (3a)

In 1985 Shvo reported on the dimeric catalyst **3a** (Scheme 10),[24] which since then has been used in various reactions involving hydrogen transfer.[25–31] These reactions include disproportion of aldehydes to esters,[24] hydrogenation of carbonyl compounds,[25] transfer hydrogenation of ketones and imines[26] and Oppenauer-type oxidations of alcohols[27] and amines.[28] It has also been shown that catalyst **3a** is efficient for racemization of alcohols and this was used in combination with lipases for



Scheme 10 Precursor **3a** in equilibrium with its active monomers **3** and **A**.

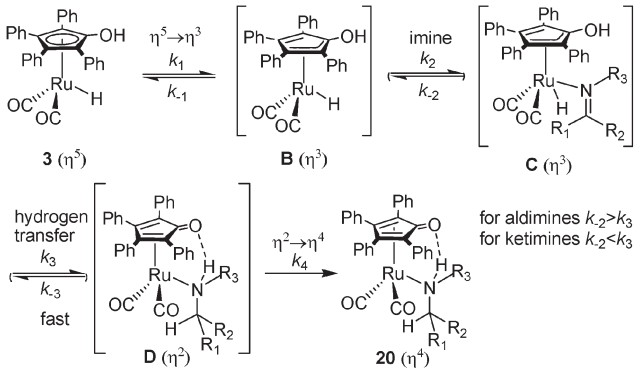


Scheme 11 Proposed concerted mechanism for the hydrogenation of carbonyls and imines by **3′**.

dynamic kinetic resolution of secondary alcohols.[29] Complex **3a** has also been used for racemization of amines.[30] Catalyst **3a** is in equilibrium with monomers **3** and **A** (Scheme 10). The monomer **3** is able to hydrogenate a hydrogen acceptor whereas the monomer **A** can dehydrogenate a hydrogen donor. These processes interconvert **3** and **A**.

Shvo's group originally proposed a mechanism where the substrate coordinates to ruthenium prior to hydrogen transfer. In 2001 Casey's group reported a mechanistic study on hydrogen transfer to carbonyls and imines from **3′** (Scheme 11).[32] From the large combined isotope effect observed for benzaldehyde (X = O, R = H) k_{RuHOH}/k_{RuDOD} = 3.6 together with individual isotope effects of 1.5 (RuD) and 2.2 (OD) a concerted mechanism without coordination of the unsaturated substrate was proposed. A mechanism involving simultaneous hydride and proton transfer was observed also by our group for the dehydrogenation of alcohols by **A**.[33]

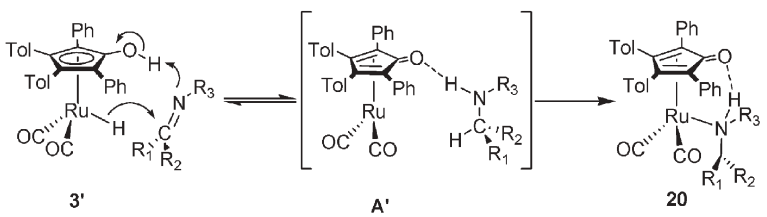
Interestingly, the mechanism proposed for ketones (aldehydes) and alcohols does not apply to imines or amines. It was recently reported that transfer dehydrogenation of *N*-phenyl-1-phenylethylamine to the corresponding imine by **A**, generated from **3a** *in situ*, gave deuterium isotope effects consistent with a stepwise mechanism.[28b] Thus, the combined isotope effect k_{CHNH}/k_{CDND} = 3.26 was equal to the individual isotope effect k_{CHNH}/k_{CDNH} = 3.24 and the other individual isotope effect (N–D) was very small. It was also demonstrated that in the stoichiometric reduction of a ketimine by **3**, the kinetic



Scheme 12 Proposed stepwise mechanism for the hydrogenation of imines by **3**.

isotope effect was 1.05, clearly showing that the rate determining step is not the hydrogen transfer.[34] Moreover, in the catalytic reaction a correlation between the electronic property of the substrate and the rate is observed, where electron-rich imines and amines reacts faster in both transfer hydrogenation of imines and in transfer dehydrogenation/racemization of amines. This supports a mechanism where the coordination of the substrate comes into the rate expression.[26,28,30] Furthermore, the reactivity of aldehydes, ketones, and imines does not correlate with the polarity of the double bond which is expected for an outer-sphere mechanism. Casey's group found that aldehydes reacted faster than ketones, but slower than imines.[32] This is in contrast to what is expected for catalysts operating *via* an outer-sphere mechanism.[14] From these results we have proposed a mechanism where the catalyst equilibrates between η^5 and η^3 to generate a coordinately unsaturated species **B** (Scheme 12).[34] This ring slippage may be substrate promoted. The imine would coordinate to this η^3 complex forming intermediate **C**. Subsequent hydrogen transfer in a fast step gives η^2-complex **D**, which would rearrange to η^4-complex **20**. For ketimines $k_3 > k_{-2}$ and $k_4 > k_{-3}$.

Casey's group has also studied the hydrogenation of imines by **3′** and found that electron-deficient aldimines give similar kinetic isotope effects as aldehydes and more electron-rich imines gave either no or an inverse isotope effect. Casey presented a modified mechanism for the hydrogen transfer of **3′** to imines (Scheme 13),[35] where the inverse isotope effect is explained by an equilibrium isotope effect. The hydrogen transfer is still concerted in this mechanism, but depending on whether the imine is electron-deficient or electron-rich the hydrogen transfer is rate-determining or not, respectively. In the latter case it was proposed that the coordination of the



Scheme 13 Proposed outer-sphere mechanism for hydrogenation of imines by **3′**.

amine formed to the unsaturated ruthenium complex **A′** is rate-determining (hydride shift from carbon to ruthenium competes with coordination). The kinetic isotope effects found in the stoichiometric reductions are in accordance with this mechanism. However, the kinetic isotope effects found in the dehydrogenation of *N*-phenyl-1-phenylethylamine discussed above are difficult to explain with this mechanism according to the principle of microscopic reversibility. The mechanism in Scheme 13 would suggest a concerted NH and CH transfer in the dehydrogenation which is not observed (*vide supra*).[28b] The change of rate-determining step is also somewhat contradictory. One would expect the reverse reactivity, namely that the hydrogen transfer is faster for an electron-deficient imine than for an electron-rich one, and that the amine formed would coordinate slower due to lower nucleophilicity. Also the reactivity order aldehydes (ketones) < imines is difficult to explain with this mechanism. In the mechanism in Scheme 11 the inverse isotope effects observed for electron-rich aldimines would be explained by equilibria down to intermediate **D** (aldimines $k_{-2} > k_3$ and $k_{-3} > k_4$. It is expected that β-elimination from an electron-rich substrate is quite fast.[28c]

Apparent metal ligand bifunctional catalysts

$[Ph_4(\eta^5\text{-}C_4CNHR)(CO)_2]RuH$ (21)

Park and coworkers developed a highly efficient racemization catalyst for which the active species **21** resembles the active monomer **3** of the Shvo catalyst in that it has both a metal hydride and a basic center (Fig. 6).[36]

This substitution prevents the active monomers of the catalyst from associating with each other to form stable dimers. Because catalyst **21** does not form stable dimers, the catalyst is active at room temperature. This is advantageous when combining the racemization with an enzymatic kinetic resolution in a dynamic kinetic resolution. Park's group proposed a mechanism where both the substrate and the hydrogen donor are hydrogen bonded to the amine function of the Cp-ring of catalyst **21** (Scheme 14). This mechanism

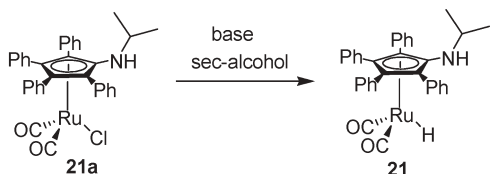
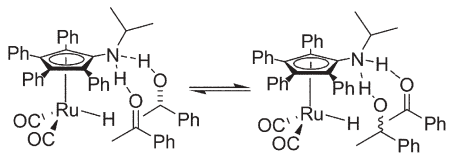
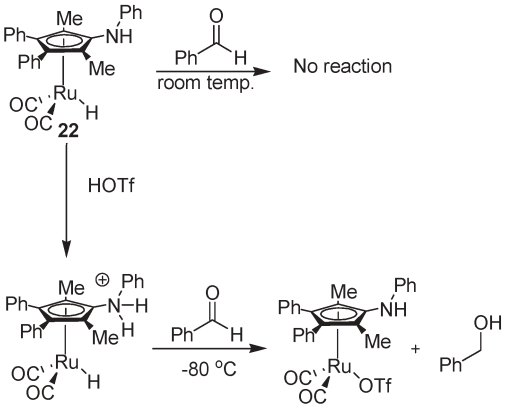


Fig. 6 Highly efficient catalyst **21** for racemization for secondary alcohols.



Scheme 14 Proposed mechanism for the racemization of alcohols by catalyst **21**.



Scheme 15 Addition of a proton source promotes the hydrogenation by catalyst **22**.

resembles the direct hydrogen transfer proposed for MVP-reduction and Oppenauer oxidation.

Casey's group found that the mechanism proposed by Park's group is not operating for the analogues complex **22**.[37] Attempts to reduce benzaldehyde by the active species **22** were unsuccessful. However, when an external proton source is added the reduction is fast even at −80 °C (Scheme 15). Clearly, the amine proton of **21** and **22** are not acidic enough to facilitate the proton transfer. Park's group also concluded that catalyst **21** is very slow in the transfer hydrogenation of acetophenone by isopropanol.[36] Therefore, the highly efficient racemization can not be explained by a metal ligand bifunctional pathway.

$[Ph_4(\eta^5\text{-}C_4CR)(CO)_2]RuO^tBu$ (4b)

Our group was intrigued by the efficiency of catalyst **21** and decided to investigate the role of the NHR group. To our surprise, we found that replacing the amino function of the tetraaryl-Cp ring of **21** by an alkyl or aryl group, *i.e.* abstracting the basic center of the catalyst, dramatically increased the rate of racemization (Fig. 7).[38,39] The racemization of (*S*)-1-phenylethanol ((*S*)-**6**) was complete in 10 min using 0.5 mol% of catalyst at room temperature. The rate enhancement found by changing the NHR group to an alkyl or aryl group is in accordance with that the NHR group is not participating in the catalytic cycle of the racemization in catalyst **21**.

Substitution on the cyclopentadienyl ligand of **4** greatly affected the catalytic activity. More π-acidic cyclopentadienyl ligands increased the rate of racemization. For example, the parent cyclopentadienyl complex was slow in the racemization

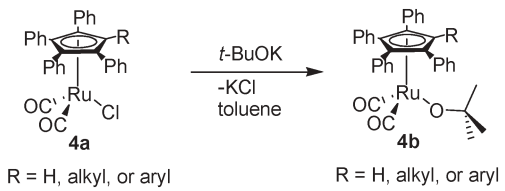
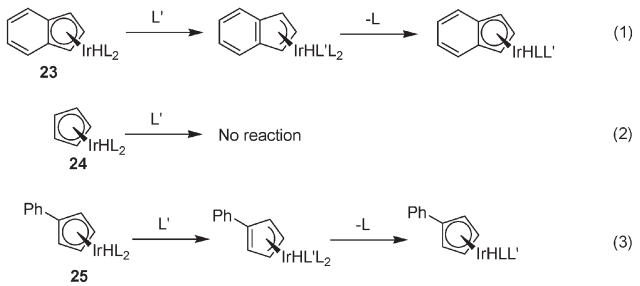


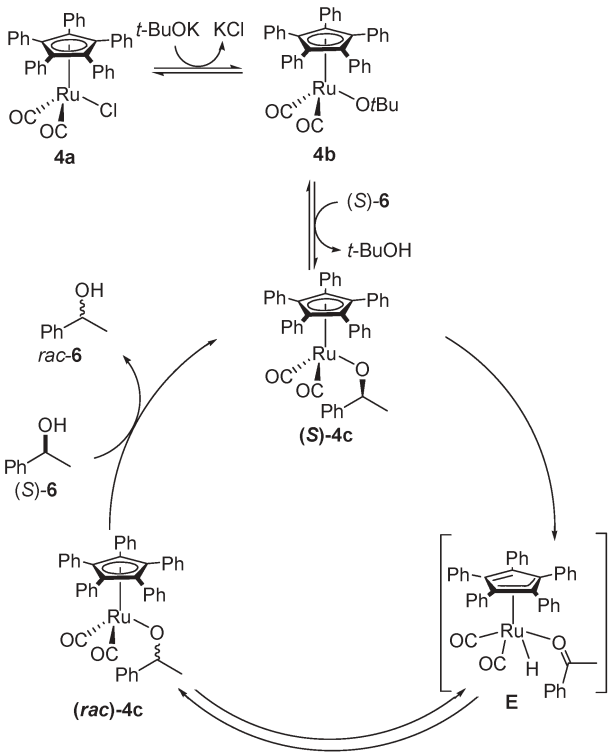
Fig. 7 Catalyst **4b**, highly efficient for racemization of secondary alcohols.



Scheme 16 Ligands promoting ring slippage.

of (*S*)-**6**. When the hydrogens on the Cp-ring were replaced by phenyl groups 50% racemization was obtained within 2 min. The catalysts have successfully been combined with lipases in dynamic kinetic resolution of a variety of different secondary alcohols at room temperature with short reaction times.[39] The dramatic effect observed by the phenyl groups is intriguing. Crabtree has studied the ring slippage in associative reactions of some indenyl and phenylcyclopentadienyl iridium complexes.[40] The indenyl complexes are known to promote ring-slippage from $\eta^5 \rightarrow \eta^3$. This "indenyl effect" has been ascribed to the stabilization of the η^3 intermediate by recovery of the full aromatic stabilization in the benzo ring of the slipped indenyl (complex **23**, Scheme 16). Whereas the $(C_5H_5)IrHL_2$ catalyst (**24**) was unreactive to ligand exchange the $(C_5H_4Ph)IrHL_2$ (**25**) behaves more like the indenyl analogue **23** and exchanges ligands (Scheme 16). Interestingly, it was found that the nucleophilicity of the incoming ligand also affected the ligand exchange. Where the monophenyl substituted Cp-analogue **25** is reactive only towards strong nucleophiles, the indenyl analogue **23** is also reactive towards weak nucleophiles. Although slightly stronger nucleophiles were required for the ring slippage in **25** compared to **23**, these studies clearly show that the phenyl substitution on the Cp-ring is important for promoting a ring slippage. Probably, the aryl group stabilizes the η^3-intermediate by stabilization of the released double bond, as suggested by the authors.[40] Assuming that the latter effect is important, it is evident that additional phenyl groups on the ring would stabilize the η^3-intermediate even further.[41]

The rate enhancement found when ring-slip-promoting phenyl groups were introduced in catalyst **4** supports a mechanism where the substrate coordinates to the metal. The catalytic cycle begins with exchanging the chloride for a *tert*-butoxide forming **4b** (Scheme 17).[39b] The chiral alcohol (*S*)-**6** then replaces the *tert*-butoxide, and subsequent β-elimination generates η^3-intermediate **E**. Interestingly, the ketone does not leave the coordination sphere of the metal. In a competitive experiment where the racemization of (*S*)-**6** was performed in the presence of another ketone, no reduction of the ketone free in solution was observed.[39b] This provides strong support that the ketone formed from β-elimination stays in the coordination sphere of the metal in the ring-slipped intermediate **E**. π-Coordination of the carbonyl double bond from either face followed by insertion (hydride addition) would give the racemic alkoxide complex (*rac*)-**4c**. The catalytic cycle is completed by an exchange of the coordinated alcohol by an alcohol in solution. The corresponding ruthenium



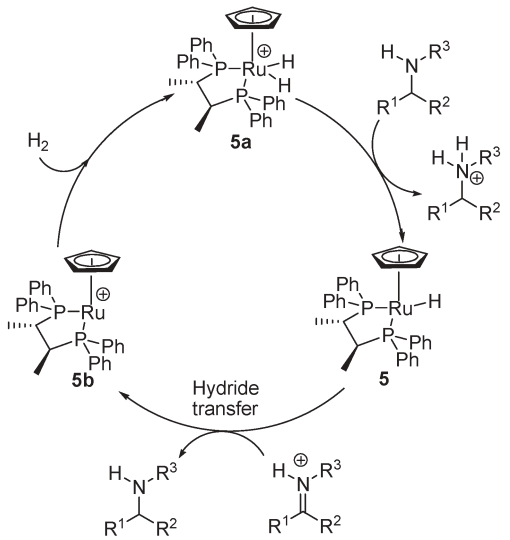
Scheme 17 Proposed catalytic cycle for the racemization of *sec*-alcohols by catalyst **4**.

hydride **4** has been isolated and characterized by X-ray crystallography.[39b]

Ionic mechanism

Norton and Bullock have recently proposed an ionic mechanism for the hydrogenation of ketones (aldehydes) and imines by different transition metal catalysts.[42] The mechanism is unique where the proton and hydride transfer occur in separate steps. The proposed mechanism follows an outer-sphere route. Norton and Bullock have proposed slightly different mechanistic pathways depending on the substrate. For imines, the first step of the catalytic cycle is protonation of the substrate by the metal dihydride **5a** forming the active hydrogenation catalyst **5** (Scheme 18). The metal hydride is suggested to be delivered without prior coordination of the double bond to produce a free amine or alcohol and an unsaturated catalyst **5b**. The amine or alcohol formed can coordinate to the metal and give an off-loop species. The substrate can also coordinate to the coordinately unsaturated species. Hydrogen gas finally generates dihydride **5a** and completes the cycle.

Even though this mechanism has only been studied for hydrogenation conditions with certain catalysts, this pathway may also be operating for several transfer hydrogenation catalysts. An example is in the transfer hydrogenation of imines by **1** where we have demonstrated that the active species does not reduce imines (*vide supra*). However, when an acid is added the reaction is fast. Also hydride **22**, prepared by Casey's group, may operate through an ionic mechanism. Attempts to reduce benzaldehyde with the proposed active



Scheme 18 Catalytic cycle of the ionic hydrogenation of imines.

species **22** were unsuccessful (*vide supra*). In sharp contrast, when triflic acid was added the reduction occurred at −80 °C.[37]

Theoretical studies

Ruthenium-catalyzed hydrogen transfer

$RuCl_2(PPh_3)_3$ (2a). In a paper by Bäckvall and coworkers, the catalyst precursor **2a** was studied.[9b] Experimental data supported that the two chlorides are exchanged for hydrides in two base-catalyzed consecutive alkoxide displacement–β-elimination sequences to activate the catalyst. To support the experimental findings, the authors performed a computational study at the B3PW91/DZ+P level of theory. Hypothesizing that the hydrogen transfer takes place *via* the hydridic route, the thermodynamics for the β-hydride elimination was calculated for $Ru(H)Cl(PPh_3)_3$ and $RuH_2(PPh_3)_3$ (**2**) (Fig. 8). The calculations show that formaldehyde insertion into the Ru–H bond of the monohydride species (X = Cl) to give the corresponding alkoxide complex is thermodynamically unfavored by 5.3 kcal mol^{-1}. However, for the dihydride species (X = H) the insertion of formaldehyde is favored by 1.3 kcal mol^{-1}. No activation energies were reported, however.

(η^6-Arene)RuTsDPEN (1) and related complexes. Most of the theoretical work on ruthenium-catalyzed transfer hydrogenations has been carried out on catalysts related to **1**.[16,43] Several groups have reported detailed investigations of the

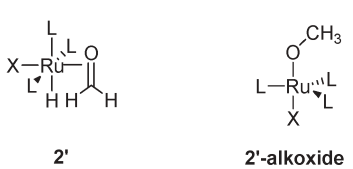


Fig. 8 Energies (kcal mol^{-1}) of structures **2′** and **2′-alkoxide** for dihydride (X = H) and monohydride (X = Cl)

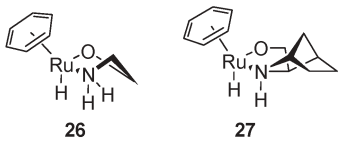


Fig. 9 The dihedral angle H–Ru–N–H is important for the rate of hydrogen transfer.

reaction mechanism where all three mechanistic alternatives (direct hydride transfer, metal-hydridic route and metal–ligand bifunctional mechanism) have been evaluated. All papers support the metal–ligand bifunctional reaction mechanism that was originally proposed by Noyori. The main cause for this preference is the high coordination number of ruthenium, preventing access to the metal by more than one external ligand such as substrate, alkoxide, or hydride. Thus, the hydridic route and the direct hydride transfer from an alkoxide to the substrate ketone will both require an endothermic slippage of the arene ligand from η^6 to η^2 and are therefore not competitive in rate.

Using the metal–ligand bifunctional mechanism, ligand effects have been investigated. In a paper by Andersson and coworkers,[17a] the conformational preference of the aminoethanol backbone was investigated. It was found that ligands aligning the ruthenium-hydride and the N–H bonds as in **26** and **27** and resulted in faster catalysts (Fig. 9). A similar analysis of a ruthenium–aminoethanol complex by Leeuwen and coworkers comparing the δ and λ ring conformations arrives to the same conclusion.[17c] In a related paper, dipole effects were found to accelerate the reaction.[43a]

In a paper by Noyori and coworkers[17b] MP4 and MP2 calculations were compared with B3LYP density functional calculations. At the MP4//MP2 potential energy surface, a ruthenium alkoxide was found to be very stable and easily formed. The activation energy for the favored metal–ligand bifunctional mechanism was 32.8 kcal mol^{-1} calculated from this stable alkoxide complex. This unreasonably high activation energy suggests that MP calculations are not accurate enough to describe this reaction. However, the MP4//MP2 calculations find the barrier for the hydridic route to be significantly higher in energy, thereby getting agreement with other reports. The same authors found the alkoxide complex to be rather stable by the B3LYP calculations and thus, this complex might serve as an inactive reservoir of the catalyst. This is in agreement with the earlier study of Andersson and coworkers at the B3PW91 level of theory.[17a] In a later paper, comparing iridium and ruthenium as catalysts, Handgraaf and coworkers. confirmed these results using BLYP.[43b] Thus, a way to improve the rates of hydrogen transfer for this class of catalysts would be to destabilize the alkoxide complexes to increase the concentration of the active catalyst.

Some papers report computational studies focused on the enantioselectivity of the reaction.[20,43c] Several factors have been reported to influence the degree of enantioselectivty. Among these are electrostatic effects (Fig. 5), steric effects, solvation effects, dispersion interaction, and covalent attractions. More work has to be done to deconvolute the mixture of effects that determine the enantioselectivity.

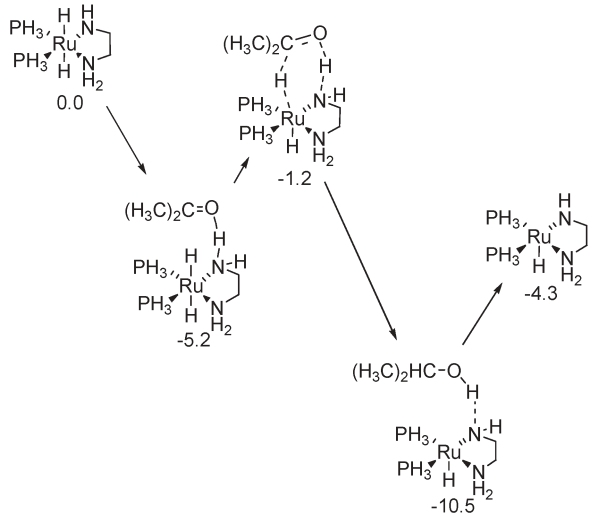


Fig. 10 Proposed mechanism for hydrogenation of acetone by **14** (energies in kcal mol^{-1}).[47]

In a mixed NMR and computational study of precatalyst aggregation,[44] Zuccaccia and coworkers performed ONIOM (B3PW91:UFF) calculations on neutral half-sandwich Ru(II) precatalysts RuCl(aminoamidate) and showed that they have a remarkable tendency to form dimers. Breaking these dimers is a crucial step in generating the active catalysts.

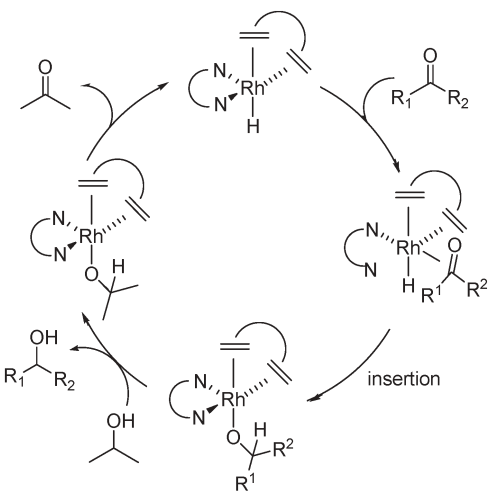
$RuCl_2$(diamine)(diphosphine) (14). This catalytic system differs from the two earlier by involving a dihydride intermediate as the active intermediate. There is only one paper describing theoretical calculations on this type of catalyst.[45] In this paper, calculations at the B3LYP/LACVP* level of theory has been performed on a model system consisting of $Ru(H)_2(PH_3)_2$(ethylenediamine) (**14**) with acetone as a substrate. The mechanism being evaluated is the concerted hydrogen transfer (Fig. 10) and a heterolytic splitting of dihydrogen. In conclusion, the hydride-proton transfer step is associated with a very low activation energy and the reaction would thus be expected to be fast. However, the authors also investigated the heterolytic cleavage of dihydrogen and found this step to be high in activation energy and thus rate limiting. The authors did not take into account the solvent assisted heterolytic cleavage of dihydrogen proposed by Ito and coworkers.[46] This mechanism later received some experimental support in a paper from Noyori and coworkers.[47] As seen in Fig. 10, the reaction between the ruthenium monohydride complex and isopropanol is endothermic. This endothermicity could contribute to make formic acid and dihydrogen the hydrogen sources of choice for this catalyst.

The mechanism in Fig. 10 would predict that hydrogen transfer from an alcohol to a ketone would lead to selective transfer of CH and OH hydrogens of the alcohol to carbonyl carbon and carbonyl oxygen, respectively, of the ketone. This is because dehydrogenation of the alcohol should lead to transfer of OH hydrogen to nitrogen ligand and CH hydrogen to Ru, according to the principle of microscopic reversibility. This is in sharp contrast to experimental results[12a] in which the dihydride catalyst **14**, generated from the dichloride **14a** and base, led to complete crossover in the transfer of the two hydrogens from alcohol to ketone (Fig. 3). These results were explained by involvement of both hydrides in the hydrogenation of a ketone. On regeneration of the hydride from the alcohol the two hydrides would come from OH and CH.[12a] Addition of this dihydride to the ketone would lead to scrambling where the CH hydrogen of the donor alcohol should end up $\sim$50% on the carbonyl carbon and $\sim$50% on the carbonyl oxygen, which is more or less observed.[12a]

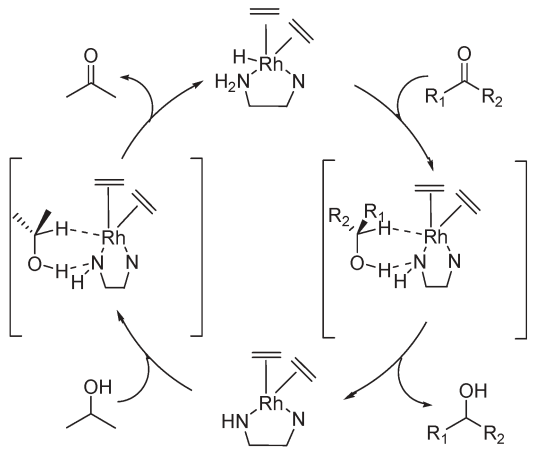
An alternative explanation for the scrambling would be that there is an exchange between hydride and OH of the alcohol *via* a dihydrogen complex. The latter process has been proposed for Ru-complexes with basic nitrogen ligands[45,47] and is supported by theoretical studies.[48]

Rh-catalyzed transfer hydrogenations

There are several reports on calculations describing the reaction mechanism of rhodium-catalyzed transfer hydrogenation of ketones; all of them relate to $[Rh–COD–Cl]_2$ as catalyst precursor that together with a diamine forms the active catalyst.[49] In a paper from 1998,[49a] Lemaire and coworkers. conclude that the active complex in the catalytic cycle is a Rh–COD–diamine complex. In a follow-up paper,[49b] Guiral and coworkers report a DFT investigation of the reaction mechanism. They conclude that the reaction takes place *via* the hydridic route with the diamine ligand being hemilabile, alternating between bidentate to monodentate coordination thereby allowing coordination of substrate (Scheme 19). The migratory insertion of the ketone into the Rh–H bond was found to be fast with activation energies of 6–9 kcal mol^{-1} and highly exothermic (14–17 kcal mol^{-1}). Thus, the reverse of the reaction, regeneration the Rh-hydride complex will be rate determining. The activation energy for this step was found to be as high as 24 kcal mol^{-1} but was judged as being reasonable. The resting state of the catalyst was determined to be the alkoxide complexes, being *ca.* 14 kcal mol^{-1} lower in energy than the Rh-hydride–diamine–dialkene complex. The



Scheme 19 Proposed catalytic cycle for the reduction of acetophenone with Rh(I) hydride.



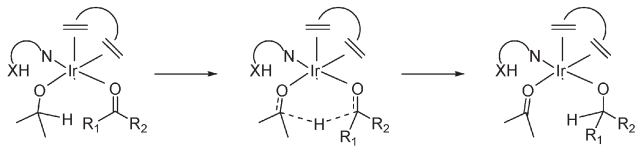
Scheme 20 Metal–ligand bifunctional mechanism for Rh-catalyzed transfer hydrogenation.

authors did not consider free energies in this publication, but focused on reaction energies.

Later that year, Lemaire and coworkers[49c] reported on continued studies of the same system in an attempt to rationalize the enantioselectivity in reaction using *N*,*N*′-dimetyl-1,2-diphenyl-ethylenediamine as chiral ligand. Although mostly concerned about conformational and configurational preferences for a smaller model complex, they proposed the concerted hydrogen transfer (metal–ligand bifunctional) mechanism being responsible for the selectivity in the reaction (Scheme 20). This is supported by calculations on diastereomeric transition states using acetophenone as substrate and a small model system for the catalyst. This hypothesis is substantiated in a comparative paper by Guiral and coworkers in 2001.[49d] In this report, the rate-limiting step in the concerted metal–ligand bifunctional mechanism is found to be almost 5 kcal mol^{-1} lower in energy than the hydridic route. Also for this class of catalysts, the alkoxide complex is calculated to be very stable but direct hydride transfer mechanisms have not yet been evaluated.

Ir-catalyzed transfer hydrogenations

There is one report on calculations concerning iridium-catalyzed transfer hydrogenation of ketones.[43b] In this paper, Handgraaf and coworkers compared the reaction mechanisms of the well characterized Ru–arene–aminoethanol catalyst with Ir–COD–aminoethanol and Ir–COD–2-aminoetylthiol. For the ruthenium complex, the DFT calculations reported in references 17*a–c* are repeated but with the BLYP functional. The reason why the ruthenium-catalyzed reaction proceeds *via* a concerted route is found to be the need for decoordination of the arene ligand in other mechanisms. For the Ir-complexes, the concerted route was found to be reasonably fast. However, for all three catalysts, the metal alkoxide complexes were found to play important roles, being the most stable species at the potential energy surfaces. For the iridium complexes, the stability of this intermediate is sufficient to entirely prevent any reaction *via* a concerted route. Instead, direct transfer of a hydride from coordinated alkoxide to the substrate ketone was found as the mechanism of the reaction (Scheme 21). This is



Scheme 21 Proposed direct hydride transfer for Ir-catalyzed transfer hydrogenation with hemilabile ligands (X = O or S).

made possible by the aminoethanol and aminoethylthiol working as hemilabile ligands. Thus, in the iridium-alkoxide resting state of the catalyst as well as in the transition state, the oxygen and sulfur respectively of the ligands are decoordinated. In the transition state, iridium(I) is pentacoordinated.

Conclusions

Hydrogen transfer reactions proceed through different pathways. For transition metals, hydridic routes are by far the most common. Within the hydridic family there are two main groups: the monohydride and dihydride routes. Experimentally, it was found that while rhodium and iridium catalysts favor the monohydride route the mechanism for ruthenium catalysts proceeds by either pathway depending on the ligands. The monohydridic route can further be divided into outer-sphere and inner-sphere mechanisms, where the hydrogen transfer in the former case can occur either stepwise or concerted. In many cases it is difficult to determine which of these two mechanisms operates. Small modifications on the ligand and the electronic property of the substrate may change the pathway of the catalyst.

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