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Mini Review

Transition metal hydrides as active intermediates in hydrogen transfer reactions

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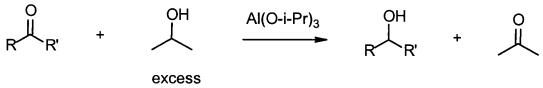
Abstract

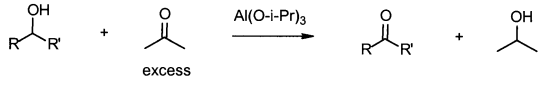
Catalytic hydrogen transfer reactions involving transfer hydrogenation of ketones, imines as well as Oppenauer-type oxidation of alcohols occur via active transition metal hydride intermediates. In the $RuCl_2(PPh_3)_3$-catalyzed hydrogen transfer reaction a dramatic rate enhancement by base was observed. It was found that the role of base is to generate a highly active dihydride catalyst $RuH_2(PPh_3)_3$. The mechanism of Ru-, Rh-, and Ir-catalyzed hydrogen transfer was probed by using α-deuterated alcohol as hydrogen donor and measuring the amount of deuterium transferred to the keto carbon of the hydrogen acceptor. Two different mechanisms are proposed for the transition metal-catalyzed hydrogen transfer, one via a monohydride (giving a high D-content) and another via a dihydride (giving about half of D-content). © 2002 Published by Elsevier Science B.V.

Keywords: Hydrogen transfer; Transfer hydrogenation; Metal catalysis; Metal hydrides

Hydrogen transfer reactions in which 1 mol of hydrogen is transferred from an alcohol to a ketone have been known since 1925 [1]. In the original version aluminum isopropoxide was used to promote transfer of hydrogen from isopropanol to a ketone and this reduction is referred to as the Meerwein–Ponndorf–Verlay (MPV) reduction after its discoverers (Eq. (1)). The reaction can also be run in the opposite direction and this was studied by Oppenauer in the middle of the 1930s (Eq. (2)) [2].



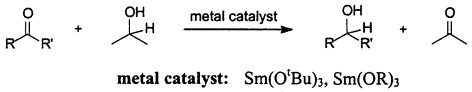
(1)



(2)

These hydrogen transfer reactions are equilibrium reactions that can be pushed to either direction by the use of an excess of either alcohol or ketone in the starting material. Thus, for the MPV reduction of a ketone, i.e. transfer hydrogenation, isopropanol is employed in excess. For the Oppenauer oxidation acetone as ketone is used in excess.

One problem with the classical aluminum alkoxide promoted hydrogen transfer reactions is that the aluminum salt is often required in stoichiometric amounts. This is a drawback for scaling up and for use in industrial applications. For this reason, there has been an increased interest recently in catalytic hydrogen transfer reactions (Eq. (3)) [3]. In this respect lanthanides and transition metals have been found to work in a catalytic manner.



(3)

metal catalyst: $Sm(O^tBu)_3$, $Sm(OR)_3$
transition metal complex of Ru, Rh, Ir

An interesting question in these reactions is how the hydrogens are transferred from the alcohol to the ketone (Scheme 1). In the classical aluminum-promoted reaction (MPV, Oppenauer) a direct hydrogen transfer from C–H of the alcohol to carbonyl carbon has been proposed via a cyclic mechanism. This pathway is thought to operate with non-transition metals. With transition metals it is believed that the reaction involves the formation of a metal hydride. Such hydrides have

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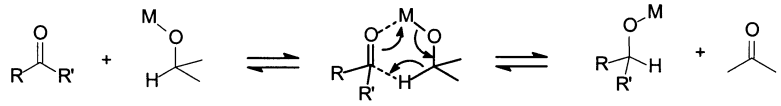
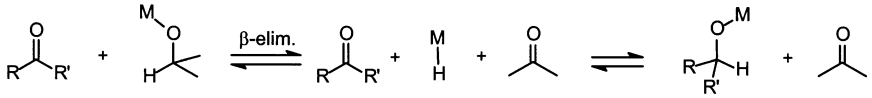
Non-transition metals ("direct transfer"):



Transition metals ("hydridic route"):



Scheme 1.

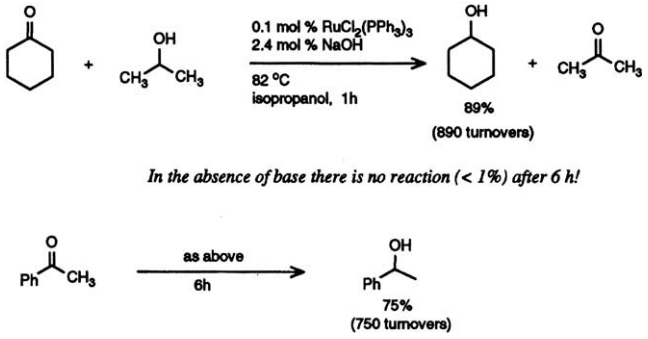
indeed been isolated from transition metal-catalyzed hydrogen transfer reactions in some cases.

The first example of a transition metal-catalyzed hydrogen transfer was reported by Henbest in the 1960s [4]. An iridium hydride DMSO complex was employed as the catalyst and gave moderate rates and turnovers.

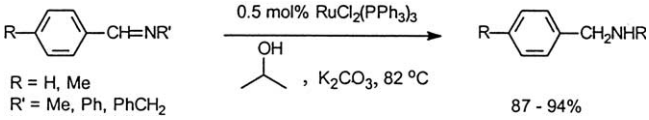
Ruthenium complexes have recently been found to be excellent catalysts in hydrogen transfer reactions. Historically, it is interesting to note that the first ruthenium-catalyzed hydrogen transfer reaction of practical use was reported by Sasson and Blum [5]. One problem with these early applications [6] is that they require high temperature and the turnover frequency is low.

In 1991 we reported on the effect of base on the $RuCl_2(PPh_3)_3$-catayzed transfer hydrogenation [7]. We observed that the addition of small amounts of base had a dramatic effect on the rate of the reaction giving a rate enhancement of about 10^3–10^4 times. For example, the use of 0.1 mol% of $RuCl_2(PPh_3)_3$ in the presence of 2.4 mol% of NaOH led to full conversion within 1 h (Scheme 2). Without base there was $<1\%$ conversion after 6 h. The promoting effect of base had been observed previously for Ir- and Rh-catalyzed reactions but not of this order [8,9].

The ruthenium-catalyzed transfer hydrogenation was applied to imines and a similar dramatic rate acceleration by base was seen (Eq. (4)) [10].



Scheme 2. Effect by base in $RuCl_2(PPh_3)_3$-catalyzed transfer hydrogenation.

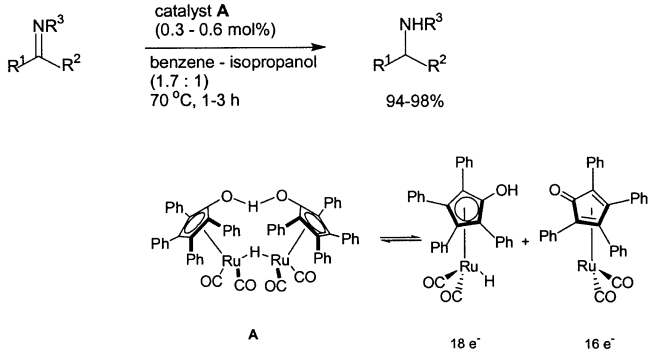


(4)

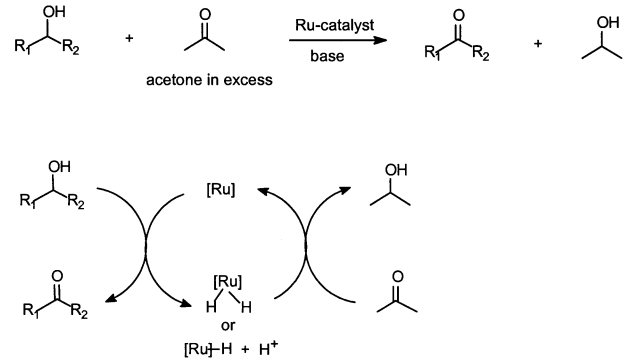
The hydrogen transfer of imines shown in Eq. (4) works best with aldimines, which react faster than ketimines under the hydrogen transfer conditions with $RuCl_2(PPh_3)_3$. More recently, we have developed a new procedure for transfer hydrogenation of imines by isopropanol employing benzene as co-solvent (Scheme 3) [11]. With the use of the Shvo catalyst **A** [12] an efficient hydrogen transfer was obtained and, interestingly, ketimines react slightly faster than aldimines. This new procedure takes place with high turnover frequency and turnover numbers.

Since the hydrogen transfer reaction between an alcohol and a ketone is a reversible process, it can be run it in either direction. Thus, with an excess of ketone as hydrogen acceptor, one can obtain an oxidation of an alcohol. The principle for this catalytic Oppenauer-type oxidation is shown in Scheme 4.

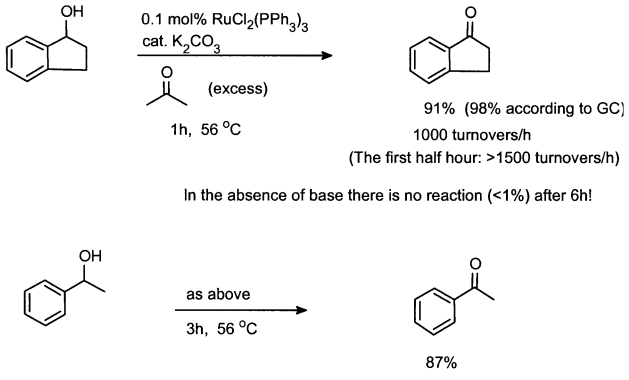
Also in this reaction we observed a spectacular effect by the base with the use of $RuCl_2(PPh_3)_3$ as catalyst (Scheme 5) [13]. Now the reaction works fast even at 56 °C in acetone with K_2CO_3 as base and is over within 1 h. The catalyst loading is 1:1000, i.e. 0.1 mol%. The first half hour the turnover frequency is $>1500\ h^{-1}$. In the absence of base there was no detectable reaction (<



Scheme 3. Transfer hydrogenation of imines.



Scheme 4. Catalytic Oppenauer-type oxidation.



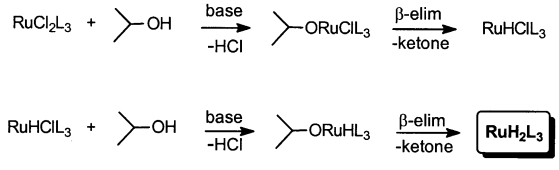
Scheme 5.

1%) after 6 h. Also for the Oppenauer-type oxidation we estimate that the rate enhancement by the base is three to four orders of magnitude.

A variety of alcohols were oxidized with this method. These reactions proceed under very mild conditions with low loading of catalyst [13b].

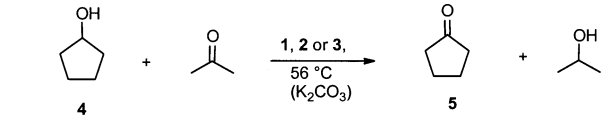
The method was applied to the oxidation of steroids where commercially important cholestenone derivatives were oxidized to cholesterol type derivatives [14]. The products are hormone-related substances of great pharmaceutical interest.

An interesting question in the $RuCl_2(PPh_3)_3$-catalyzed hydrogen transfer reactions is the role of the base. The dramatic rate acceleration indicates that the dichloride is only the catalyst precursor and that the base transforms it into a highly active catalyst (Scheme 6). The base facilitates the formation of a ruthenium alkoxide by abstracting the proton of the alcohol. The alkoxide then undergoes a β-elimination to give a chloro-monohydride. Initially we thought that the monohydride was the active catalyst. However, it turned out that this is not the case. This chlorohydride is inactive as catalyst and needs to go through the base-promoted sequence of alkoxide formation-β-elimination a second time to replace also the second chloride by hydride. This gives the dihydride and this is the active catalyst.

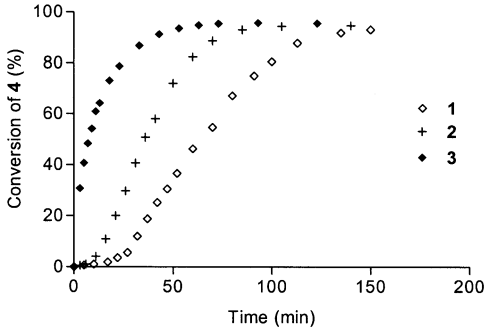


Scheme 6. The role of base (L = PPh_3).

Support for $RuH_2(PPh_3)_3$ being the active catalyst was given by a comparative study of $RuCl_2(PPh_3)_3$ (**1**), $Ru(H)Cl(PPh_3)_3$ (**2**), and $RuH_2(PPh_3)_4$ (**3**) in the hydrogen transfer from **4** to acetone to give **5** and isopropanol [15]. In solution, complex **3** dissociates into $RuH_2(PPh_3)_3$.

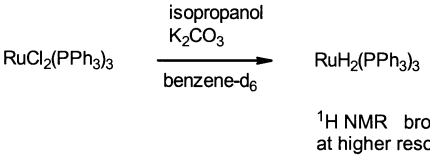


1 : $RuCl_2(PPh_3)_3$ **2** : $Ru(H)Cl(PPh_3)_3$ **3** : $RuH_2(PPh_3)_4$
0.2 mol% of ruthenium catalyst ; cat. amounts of K_2CO_3



As can be seen from the diagram there are significant differences between the reaction rate for these three catalyst precursors [15]. For the dichloride **1** there is a clear induction period of about 15–20 min before the reaction takes off. Also for the chlorohydride **2** there is an induction period of about half of that of the dichloride **1**. Finally, for the dihydride **3** there is no induction period and the reaction takes off immediately. It has reached 50–60% before any of the other two reactions have even started.

It was demonstrated that the dihydride is indeed formed when the dichloride is treated with base in the presence of isopropanol (Eq. (5)) [15]. The dihydride $RuH_2(PPh_3)_3$ was characterized by its ^{1}H-NMR.



(5)

It was demonstrated that the dihydride reacts fast with ketones to give the corresponding alcohol. On the other hand, the chlorohydride was completely unreac-

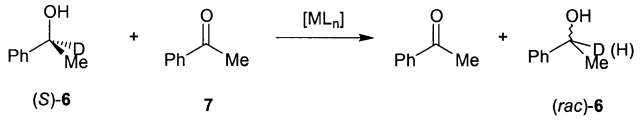
tive towards ketones. These observations support that the dihydride is the active intermediate in the catalytic hydrogen transfer reactions.

A mechanism for the ruthenium-catalyzed hydrogen transfer reaction is shown in Scheme 7.

A general question of interest to answer in hydrogen transfer from an alcohol to a ketone is whether the hydrogens transferred keep their identity, i.e. if O–H is transferred to keto oxygen and C–H to carbonyl carbon (Scheme 8, path A) or if the two hydrogens are scrambled and lose their identity (Scheme 8, path B).

For transition metals the former pathway is thought to involve a monohydride intermediate, whereas the latter should proceed via a dihydride intermediate (Scheme 9).

By deuterium labeling of the donor alcohol and using the corresponding ketone as hydrogen acceptor it is possible to distinguish between the two pathways. Thus, hydrogen transfer from enantiomerically pure (*S*)-α-deuterio-α-phenylethanol ((*S*)-**6**) to acetophenone (**7**) was studied, and the progress of the reaction was monitored by the racemization of (*S*)-**6** [16] (Eq. (6)).

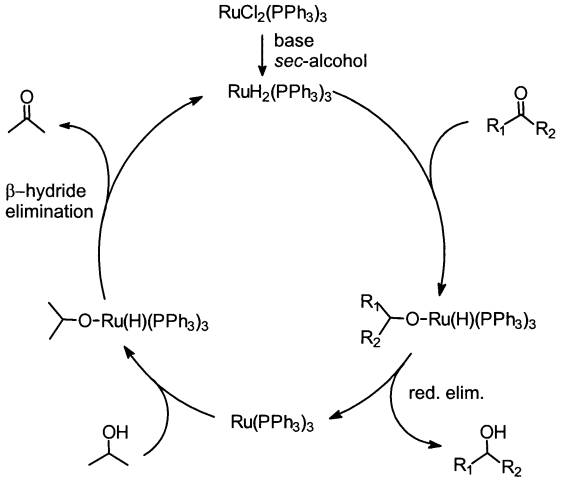


(6)

The racemized alcohol was analyzed for its deuterium content in the α-position. If the reaction follows the selective path A (Schemes 8 and 9) all deuterium should be retained in the α-position, whereas with path B it should be reduced to about half.

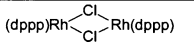
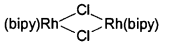
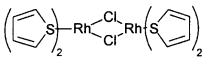
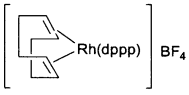
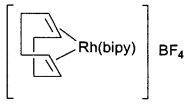
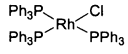
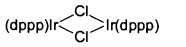
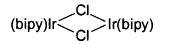
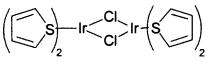
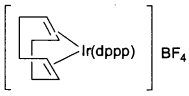
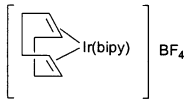
The results from the rhodium- and iridium-catalyzed reaction of (*S*)-**6** are shown in Table 1 [16b]. The reaction was run at 70 °C until complete racemization had occurred. The deuterium content of the racemized alcohol was analyzed by ^{1}H-NMR. For the rhodium-catalyzed reactions racemization with a very high deuterium content (95–98%) was obtained for all complexes studied (entries 1–6). Also, the iridium complexes generally gave a high deuterium content, in particular complexes having no phosphine ligands (entries 8, 9 and 11). For complexes having phosphine ligands some loss of deuterium was observed (entries 7 and 10) but the deuterium content of these complexes was still far above 50%. The loss of deuterium in the latter complexes is probably due to orthometalation in the phosphine complexes leading to H–D exchange [17].

The rhodium- and iridium-catalyzed reactions clearly follow path A involving monohydride intermediates [16b].

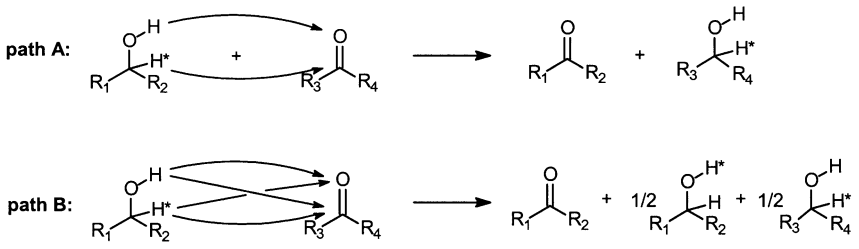


Scheme 7.

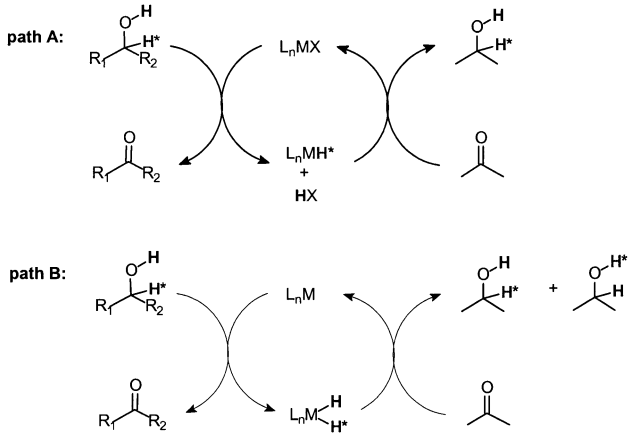
Table 1
Deuterium content in (*rac*)-**6** after racemization of (*S*)-**1** via Rh(I) and Ir(I)-catalyzed hydrogen transfer [a]

Entry	Precursor	Time	% D [b] in (*rac*)-**6**
1		4 h	98
2		20 h	97
3		48 h	98
4		3 h	98
5		48 h	> 95 [c]
6		1 h	95
7		6 h	83
8		6 h	98
9		48 h	98
10		48 h	73
11		48 h	96

[a] (*S*)-**6** (0.5 mmol), **7** (0.5 mmol), catalyst (0.01 mmol), NaOH (0.05 mmol), THF (0.75 ml), $T = 70$ °C. [b] % deuterium in the α-position after complete racemization unless otherwise noted. [c] 85% of racemization.



Scheme 8.



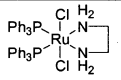
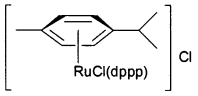
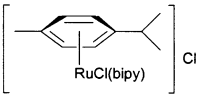
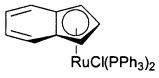
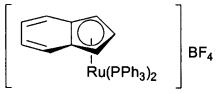
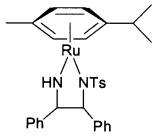
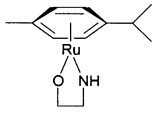
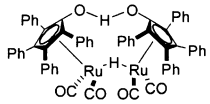
Scheme 9.

The results from ruthenium-catalyzed reactions are shown in Table 2, [16b]. From Table 2 it is clear that there are more variations with respect to the deuterium content in the racemization of (*S*)-**6**.

With the complexes from entry 1 and 2 a deuterium content of 37 and 40%, respectively, was obtained after complete racemization. The low degree of deuterium content is best explained by path B, involving a dihydride intermediate. On the other hand reactions in entries 4 and 7–10 gave a deuterium content of 91–98%, which is best explained by the monohydride mechanism. Complexes in entries 3, 5, and 6 gave a deuterium content of 89, 88, and 79% in the α-position. It is proposed [16b] that these complexes proceed via the monohydride mechanism, and that the slightly lower deuterium content is due to H–D exchange, possibly via orthometalation of the phosphine ligand [17].

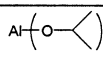
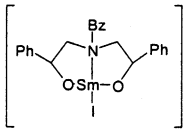
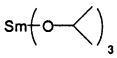
For comparison, the corresponding aluminum- and samarium-catalyzed racemization reactions were carried out and the results are given in Table 3, [16b]. These reactions are thought to proceed via a direct hydrogen transfer not involving metal hydrides. The expected outcome from a cyclic transition state with direct hydrogen transfer (cf. Scheme 1) is that all deuterium should be retained. However, after full racemization the deuterium content was 75–80%, which seems to be at variance with a direct transfer. It has been proposed that

Table 2
Deuterium content in (*rac*)-**6** after racemization of (*S*)-**6** by Ru(II)-catalyzed hydrogen transfer [a]

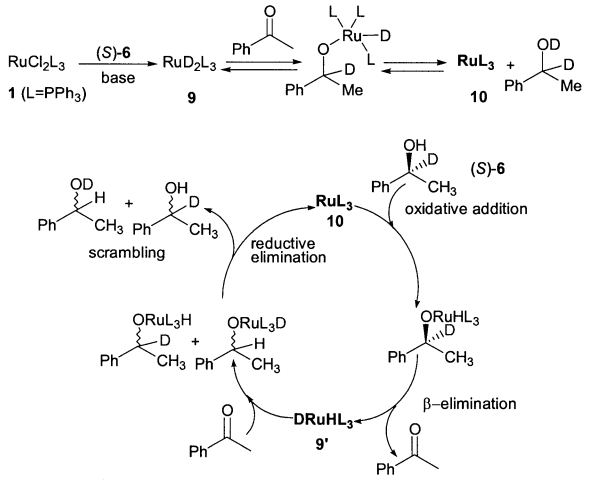
Entry	Precursor	Time	% D [b] in (*rac*)-**6**
1		6 h	40
2	$RuCl_2(PPh_3)_3$	4h	37 [c]
3		3 h	89
4		12 h	98
5		10 min	88
6		10 min	79
7		2 h	92
8		48 h	92 [c]
9		48 h	91 [c]
10		24 h	95 [c]

[a](*S*)-**6** (0.5 mmol), **7** (0.5 mmol), catalyst (0.01 mmol), NaOH (0.05 mmol), THF (0.75 ml), $T = 70$ °C. [b]% deuterium in the α-position after complete racemization unless otherwise noted. [c]No base added.

Table 3
Deuterium content in (*rac*)-**6** after racemization of (*S*)-**6** by Al(III) and Sm(III)-catalyzed hydrogen transfer [a]

Entry	Precursor	Time	% D[b] in (*rac*)-**1**
1		18 h	75
2		48 h	80[c]
3		18 h	76

[a](*S*)-**6** (0.5 mmol), **7** (0.5 mmol), catalyst (0.05 mmol), THF (0.75 ml), $T = 70$ °C. [b]% deuterium in the α-position after complete racemization unless otherwise noted. [c]83% of racemization.



Scheme 11.

an electron transfer pathway may be involved in hydrogen transfer reactions catalyzed by non-transition metals, [18] and this may explain the partial loss of deuterium.

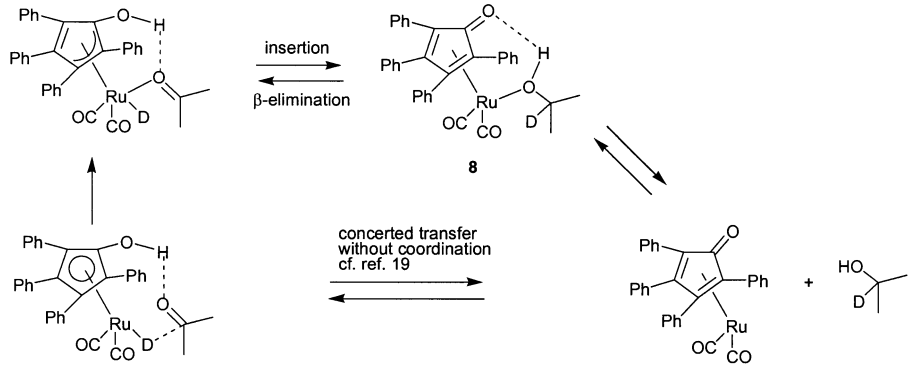
The mechanism of the monohydride reaction is illustrated by the ruthenium-catalyzed reaction with the catalyst from entry 10, Table 2. As was shown in Scheme 3, this catalyst dissociates into two parts. Addition of the ruthenium deuteride to the carbonyl carbon (Scheme 10) would give an alcohol complex **8**. This reaction should be reversible and a β-elimination gives back the alcohol. Dissociation of the alcohol from the alcohol complex **8** releases the α-deuterated alcohol.

Recent studies by Casey [19] indicate that the two hydrogens are transferred in a concerted manner. It was proposed that this transfer occurs without involving coordination of the oxygen to ruthenium.

The dihydride mechanism is shown for the dichloride complex $RuCl_2(PPh_3)_3$ (**1**) (Scheme 11). Reaction of **1** with the alcohol in the presence of base, according to Scheme 8, produces the ruthenium dideuteride **9**. The latter reacts with the ketone to give an alkoxyruthenium complex, which after reductive elimination gives the highly reactive ruthenium(0) complex **10**. Complex **10** enters the cycle and oxidative addition of (*S*)-**6** to **10** produces an alkoxide complex. A β-hydride elimination from the latter complex gives a mixed hydride–deuteride **9′**. Addition of **9′** to acetophenone and subsequent reductive elimination give the scrambled alcohols.

In conclusion it has been shown that a ruthenium dihydride is the intermediate in $RuCl_2(PPh_3)_3$-catalyzed hydrogen transfer. This is generated from reaction of $RuCl_2(PPh_3)_3$ with alcohol in the presence of base and explains the spectacular rate acceleration by base.

Furthermore, it was shown that metal-catalyzed hydrogen transfer between an alcohol and a ketone can occur via two principally different mechanisms: (i) via a *metal monohydride* resulting in highly selective carbon-to-carbon hydrogen transfer, and (ii) via a *metal dihydride* leading to a non-selective hydrogen transfer.



Scheme 10.

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References

[1] (a) H. Meerwein, R. Schmidt, Liebigs Ann. Chem. 444 (1925) 221;
(b) A. Verley, Bull. Soc. Fr. 37 (1925) 537;
(c) W. Ponndorf, Angew. Chem. 39 (1926) 138.
[2] R.V. Oppenauer, Recl. Trav. Chim. Pays-Bas. 56 (1937) 137.
[3] S. Gladiali, G. Mestroni, in: M. Beller, C. Bolmed (Eds.), Transition Metals for Organic Synthesis, Wiley-VCH 1998, pp. 97–119.
[4] (a) J. Trocha, H.B. Henbest, Chem. Commun. (1967) 545.(b) See also: H.B. Henbest, Proc. Chem. Soc. (1964) 361.
[5] (a) Y. Sasson, J. Blum, Tetrahedron Lett. (1971) 2167.;
(b) Y. Sasson, J. Blum, J. Org. Chem. 40 (1975) 1887.
[6] P. Maitlis, J. Organometal. Chem. 289 (1985) 385.
[7] R.L. Chowdhury, J.E. Bäckvall, Chem. Commun. (1991) 1063.
[8] (a) D. Müller, G. Umbricht, B. Weber, A. Pfaltz, Helv. Chim. Acta 74 (1991) 232;
(b) S. Gladiali, G. Chelucci, G. Chessa, G. Delogu, F. Soccolini, J. Organometal. Chem. 327 (1987) C15;
(c) P. Kvintovics, B.R. James, B. Heil, Chem. Commun. (1986) 1810;
(d) S. Gladiali, L. Pinna, G. Delogu, S. de Martin, G. Zassinovich, G. Mestroni, Tetrahedron: Asymmetry 1 (1990) 635.
[9] R. Uson, L.A. Oro, R. Sariego, M.A. Esteruelas, J. Organometal. Chem. 214 (1981) 399.
[10] G-Z. Wang, J.E. Bäckvall, Chem. Commun. (1992) 980.
[11] J. Samec, J.E. Bäckvall, Chem. Eur. J., in press.
[12] N. Menashe, Y. Shvo, Organometallics 10 (1991) 3885.
[13] (a) G.-Z. Wang, J.E. Bäckvall, Chem. Commun. (1992) 337;
(b) M.L.S. Almeida, M. Beller, G.-Z. Wang, J.E. Bäckvall, Chem. Eur. J. 2 (1996) 1533.
[14] M.L.S. Almeida, P. Kocovský, J.E. Bäckvall, J. Org. Chem. 61 (1996) 6587.
[15] A. Aranyos, G. Csjernyik, K.J. Szabó, J.E. Bäckvall, Chem. Commun. (1999) 351.
[16] (a) Y.R.S. Laxmi, J.E. Bäckvall, Chem. Commun. (2000) 611;
(b) O. Pàmies, J.E. Bäckvall, Chem. Eur. J. 7 (2001) 5052.
[17] See for example: (a) J. DeHand, M. Pfeffer, Coord. Chem. Rev. 18 (1974) 327;
(b) M.I. Bruce, Angew. Chem. Int. Ed. Engl. 16 (1977) 73;
(c) A.D. Ryabov, Chem. Rev. 90 (1990) 403;
(d) A.C. Albeniz, G. Schulte, R.H. Crabtree, Organometallics 11 (1992) 242;
(e) P. Stössel, W. Heins, H.A. Mayer, R. Fawzi, M. Steimann, Organometallics 15 (1996) 3393;
(f) M.A. Bennett, S.K. Bhargava, M. Ke, A.C. Willis, J. Chem. Soc. Dalton Trans. (2000) 3537.
[18] E.C. Ashby, Acc. Chem. Res. 21 (1998) 414.
[19] C.P. Casey, S.W. Singer, D.R. Powell, R.K. Hayashi, M. Kavana, J. Am. Chem. Soc. 6 (2001) 1090.