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Review

Mechanisms of the H_2-hydrogenation and transfer hydrogenation of polar bonds catalyzed by ruthenium hydride complexes

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Contents

Abbreviations: bdna, 1,8-(diphenylphosphinomethyl)naphthalene; binap, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; bisbi, 2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl; bpy, bipyridine; bpzm, bis(pyrazol-1-yl)methane; cod, 1,5-cyclooctadiene; CCDC, Cambridge Crystallographic Data Centre; chiraphos, $PPh_2CHMeCHMePPh_2$; dach, *trans*-1,2-diaminocyclohexane; daipen, $NH_2C(C_6H_4\text{-}4\text{-}OMe)_2CHiPrNH_2$; dcypb, 1,4-bis(dicyclohexylphosphino)butane; dbd, *N*,*N*-dimethyl-2-diphenylphosphinoaniline; dmdabn, 3,3-dimethyl-2,2-diamino-1,1-binaphthyl; dmpe, $PMe_2CH_2CH_2PMe_2$; dmpm, $PMe_2CH_2PMe_2$; dmso, dimethylsulfoxide; dpen, 1,2-diphenylethylenediamine; dppach, $PPh_2NHC_6H_{10}NHPPh_2$; dppb, $PPh_2CH_2CH_2CH_2CH_2PPh_2$; dppm, $PPh_2CH_2PPh_2$; HI, hydogenation with hydride transfer to the substrate in the inner coordination sphere; HOL, hydogenation with hydride transfer to the substrate in the outer coordination sphere with ancillary ligand assistance; imes, bis(1,3-(2,4,6-trimethylphenyl)imidazol-2 ylidene; Np, naphthyl; oxferphos, see Fig. 20; P_3, $(PPh_2CH_2)_3CMe$; pcp, $[C_6H_3(CH_2PPh_2)_2\text{-}2,6]^-$; pn, *N*,*N*-dimethyl-2-diphenylphosphinoethylamine; ppfa, ((*R*)-C,S-pl)-2-{1-(*N*,*N*-dimethylamino)ethyl}-1-diphenylphosphinoferrocene; pta, 1, 3, 5-triaza-7-phosphaadamantane; Tp, hydridotris(pyrazolyl)borate; Tp*, hydridotris(3,5-dimethylpyrazoyl)borate; terpy, terpyridine; TI, transfer hydrogenation with inner sphere hydride transfer; TOF, turn-over frequency; TOL, transfer hydrogenation with outer sphere hydride transfer assisted by the ligand; tmen, $NH_2CMe_2CMe_2NH_2$; tolbinap, 2,2′-bis(ditolylphosphino)-1,1′-binaphthyl; tppms, (3-sulphonatophenyl)diphenylphosphine sodium salt; tppts, $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$; xylbinap, 2,2′-bis(di(2,6-dimethylphenyl)phosphino)-1,1′-binaphthyl

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Abstract

The catalytic cycles for the H_2-hydrogenation (H) and transfer hydrogenation (T) of C=O and C=N bonds catalyzed by over 100 ruthenium hydride complexes in organic and aqueous media can be classified into two main classes: the hydride transfer step is inner sphere (I) or outer sphere (O). Important subclasses of these mechanisms are cases where an ancillary ligand may assist in the hydride transfer step (IL or OL, respectively). The types of hydride complexes and their reactivity toward C=O (ketones, aldehydes, CO_2) and C=N (imines) bonds is examined. Features of the different types of catalytic cycles are described. It is clear that the ligand assisted cases lead to very efficient catalysts for the selective hydrogenation of these polar bonds (e.g. Noyori's metal–ligand bifunctional catalysis).

Keywords: Hydrogenation catalyst; Ketone; Imine; Enantioselective; Alcohol; Amine

1. Introduction

The catalytic hydrogenation of polar bonds and the asymmetric versions of these are key reactions in fine chemical and pharmaceutical synthesis. Ruthenium homogeneous hydrogenation catalysts have been known for almost 40 years [1,2] and they are proving to be some of the most useful catalysts for these reactions. Ruthenium complexes display favorable reactivity and selectivity, especially in the catalytic reduction of polar bonds, that often surpass those of the usual stars of hydrogenation, complexes of rhodium and iridium [3–7]. For example Ru complexes can be used to catalyze the H_2-hydrogenation of a wider range of *Z*-α-(acylamino)acrylic acids and esters than cationic Rh complexes [3]. Certain ruthenium complexes with amine ligands are much more active than other metal complexes for the H_2-hydrogenation of ketones, especially those devoid of heteroatom functionality [5,6]. This high activity often comes with high enantioselectivity in the hydrogenation of prochiral ketones and high selectivity for the hydrogenation of carbonyl over olefin functional groups [8]. They also have promising reactivity in imine hydrogenation [4,7]. Review articles have discussed how some ruthenium hydride [4,8–16] and dihydrogen complexes [17–20] have been recognized as active precatalysts or intermediates in catalytic cycles.

This review will discuss and classify the mechanisms proposed in the open literature for the H_2-hydrogenation (H) and transfer hydrogenation (T) of C=O and C=N bonds with a focus on the ruthenium hydride complexes that are involved as catalysts or precatalysts (Eqs. (1) and (2)):

$$\mathrm{H}: \underset{\mathbf{1}}{\mathrm{R^1R^2C{=}Q}} + \mathrm{H_2} \xrightarrow{[\mathrm{Ru}]\mathrm{H}} \underset{\mathbf{2}}{\mathrm{R^1R^2CHQH}} \quad (1)$$

$$\mathrm{T}: \underset{\mathbf{3}}{\mathrm{R^1R^2C{=}Q}} + \mathrm{DH_2} \xrightarrow{[\mathrm{Ru}]\mathrm{H}} \mathrm{R^1R^2CHQH} + \underset{\mathbf{4}}{\mathrm{D}} \quad (2)$$

The compounds **1** of interest in Eqs. (1) and (2) are aldehydes or ketones (Q = O) and imines (Q = NR^3) while the products are alcohols and amines, respectively. Prochiral ketones and imines can lead to chiral products. Catalytic species include ruthenium hydrides, denoted [Ru]H, where [Ru] refers to the Ru and the other ligands. The hydrogen sources **3** in Eq. (2) are usually secondary alcohols, especially 2-propanol, or formic acid, often as the formate $[NEt_3H][CO_2H]$. The reduction of CO_2 will also be mentioned, where appropriate.

In this review, mechanisms that involve hydrogenation of substrates by use of hydrogen gas will be referred to as H mechanisms while those that transfer hydrogen from the solvent or other hydrogen donor will be referred to as T mechanisms.

The catalytic cycles can be divided into two parts: (1) the reaction of the hydride with the unsaturated compound, and (2) the regeneration of the hydride from H_2 (in H) or a hydrogen donor (in T). We will classify the mechanisms of the catalytic cycles according to the pathway that is proposed for the first step.

1.1. Classification of catalytic cycles according to the hydride transfer mechanism

The classical mechanisms of transition metal homogeneous catalysis involve the reactants forming products while bonded to the central metal. Therefore, it is usually assumed that the hydrogenation of polar bonds by ruthenium hydrides involves the coordination of the ketone or imine at a site on the ruthenium(II) made vacant by dissociation of a ligand, often solvent. This coordination in the inner (I) or primary coordination sphere allows the electrophilic activation of the carbon of the carbonyl or imine group by the metal ion so that a *cis* hydride ligand can migrate to this carbon β to the metal (Fig. 1).

Mechanisms that have these features will be labeled as HI or TI mechanisms. They are usually identified by evidence for ancillary ligand dissociation to provide a vacant site for the unsaturated substrate to coordinate. Often the catalyst has a site that is occupied by a weakly coordinating solvent molecule that can serve this purpose. Noyori and Ohkuma [8] have argued that this inner sphere attack can have a high activation barrier because a drastic geometric change of ground state structures is required to achieve the requisite interaction between the Ru–H bond and the π face of the carbonyl. In a few instances an ancillary ligand, L, on the metal, usually containing an acidic hydrogen bond donor group, appears to provide additional activation of the unsaturated substrate toward hydride attack as shown in Fig. 1.

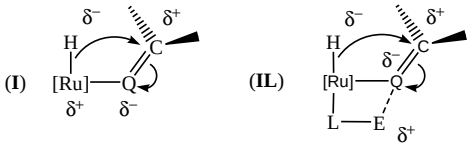


Fig. 1. The attack of hydride on the coordinated unsaturated aldehyde or ketone (Q = O) or imine (Q = NR) in the primary coordination sphere. This is assumed to be part of the HI or TI mechanism. The [Ru] notation refers to the ruthenium ion (usually Ru(II)) and the ancillary ligands. The IL notation indicates additional activation by an electrophile (E = H^+, M^+) on an ancillary ligand. This forms part of the HIL or TIL catalytic cycles.

When there is evidence for ligand assistance we will add an L to the end of the abbreviation. For example, HIL would refer to hydrogenation of an unsaturated substrate in the inner sphere with ligand assistance. Imines coordinated through nitrogen do not have a lone pair for hydrogen bonding. However, in the course of hydride transfer, proton transfer from the ancillary ligand could stabilize the charge on the nitrogen in the developing amido ligand. An imine that is π-bonded through the C=N bond to metal could also be activated this way but this mode of bonding for imines is rare for later transition metal complexes [21].

One deficiency of catalysts that operate by inner sphere hydride transfer is that they are often not very selective for C=O bonds over C=C bonds in, for example, the reduction of α,β-unsaturated ketones and aldehydes [22,23]. Presumably this is due to the competition of C=C and C=O bonds for the vacant site *cis* to the hydride ligand. In addition monohydrides that add to unsaturates are known to promote the isomerization of olefins [24] and imines [25], another side reaction that may not be desired.

The original Meerwein–Ponndorf–Verley (MPV) mechanism of transfer hydrogenation catalyzed by aluminum compounds [26–28] might also have a parallel in ruthenium-catalyzed reactions. In this case, the substrate and a hydrogen donor would coordinate to the metal and the hydride would transfer directly from the donor to the unsaturated substrate without the formation of a ruthenium hydride (Fig. 2). No ruthenium-catalyzed processes have been proven to follow the MPV mechanism.

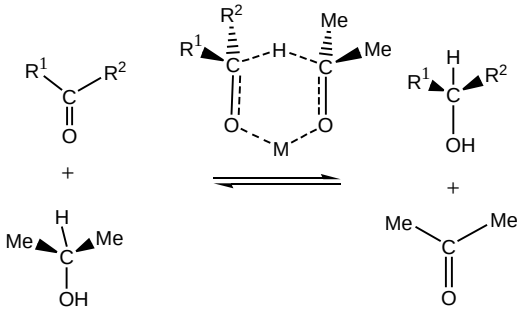


Fig. 2. The Meerwein–Ponndorf–Verley (MPV) mechanism.

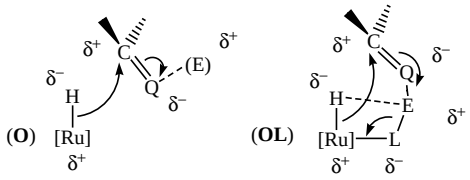


Fig. 3. The outer sphere (O) attack of hydride on the unsaturated aldehyde or ketone (Q = O) or imine (Q = NR). Usually, an electrophile (E) assists in these reactions and usually also an ancillary ligand (OL mechanism) is involved. This is part of the HO, HOL, TO or TOL catalytic cycles.

More recent is the discovery of non-classical mechanisms of polar bond reduction by ruthenium complexes, spearheaded by Noyori's group. These are proposed to operate by hydride transfer to the substrate in the second, or outer coordination sphere of the Ru complex. These mechanisms will be referred to as outer sphere (O) hydrogenation mechanisms (Fig. 3). The carbon in a C=O or C=N bond usually has a low hydride affinity so that electrophilic activation is required either by an external electrophile in a HO or TO catalytic cycle or by an internal electrophile attached to an ancillary ligand (HOL or TOL catalytic cycle).

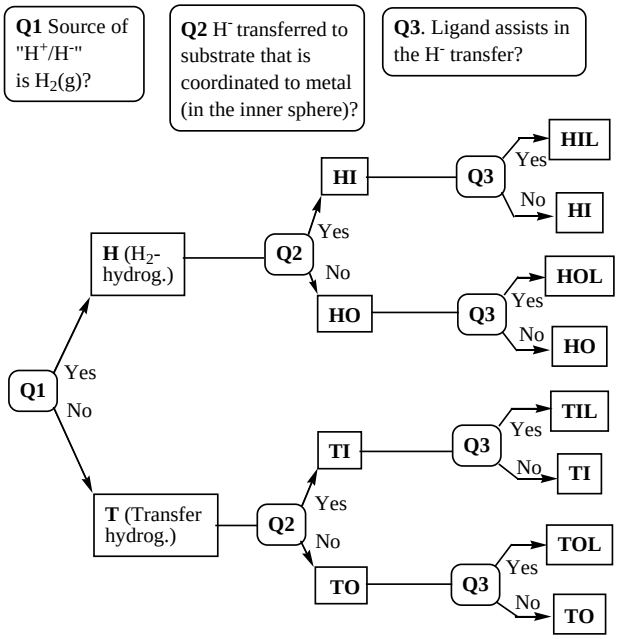
Noyori has coined the term "metal–ligand bifunctional catalysis" [29] to refer to the catalytic systems utilizing the HOL or TIL mechanisms. Typically in these cases the ancillary ligand provides a proton on the ligand (E = H in Fig. 3) that can be transferred when the hydride is transferred. These reactions lend themselves to selecting C=O or C=N bonds over C=C bonds. When the ancillary ligand is a primary amine, the "N–H effect" (see below), the Ru–H and N–H bonds are aligned by the ligand geometry and a hydridic–protonic attraction.

The assignment of mechanisms is fairly arbitrary in many cases because it is usually very difficult to disprove the alternatives. In our classification of the mechanisms, we first take the one proposed by the authors and then we may propose a second possibility. In cases where no mechanism is suggested, we make analogies with the better-characterized systems. In a ligand-assisted mechanism, the catalysts must have an ancillary ligand cis to the hydride that assists in the hydride transfer step and this ligand must have an NH or OH group or an associated electrophile, like a K^+ ion. A flowchart that summarizes the classification method is shown in Scheme 1.

1.2. Formation of ruthenium hydrides

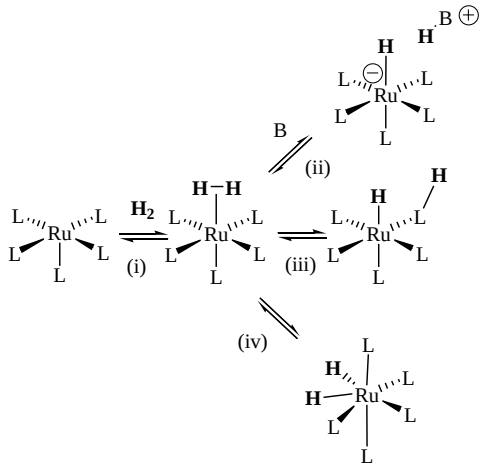
In the H catalytic cycles, hydrogen gas usually first coordinates to the ruthenium at a vacant site as an η^2-dihydrogen ligand [17,18,20,30]. In the most common cases involving Ru(II), this ligand then undergoes heterolytic splitting to give the ruthenium hydride and a protonated base (Scheme 2, path ii) [10,31,32].

In certain cases, the intramolecular heterolytic splitting can occur to give a hydride and a protonated ancillary ligand (path iii). The oxidative addition of dihydrogen to a Ru(II)



Scheme 1. A flowchart to classify the mechanisms of the reduction of polar bonds, where H, hydrogenation; T, transfer hydrogenation; I, inner sphere; O, outer sphere; L, ligand assisted.

center will result in a Ru(IV) dihydride, Ru(IV)$(H)_2$ (path iv), while addition to a Ru(0) complex will give a Ru(II) dihydride Ru(II)$(H)_2$. Both of these pathways are also known as well as the reverse processes. The reaction conditions for the formation of selected catalytically active hydrides are shown in Table 1, entries 1–4. These examples will be discussed in more detail below. The first entry involves the reaction of a stable alkoxide complex with dihydrogen at 50 atm pressure and at 50 °C to heterolytically split the H_2, release the alcohol product and generate the hydride catalyst. This catalyst hydrogenates β-ketoesters in an HI cycle. In contrast, the next three entries, the intramolecular heterolytic splitting of H_2 at an amido–amine ligand occurs



Scheme 2. Formation of ruthenium hydrides by reaction with dihydrogen.

Table 1
Representative conditions for the generation of catalytically active hydrides

	Hydride	Precursor	Hydrogen donor	Conditions	Proposed cycle	Reference
1	[RuH((*R*)-binap)(NCMe)(sol)$_2$]BF_4	[Ru((*R*)-binap)(NCMe)(η^3-ROOCCMe$_2$CH(O)COOR)]BF_4	H_2	50 °C, 50 atm H_2, MeOH	HI	[51]
2	*trans*-RuH$_2$(PPh$_3$)$_2$((*R*,*R*)-dach)[a]	RuH(PPh$_3$)$_2$((*R*,*R*)-NHC$_6$H$_{10}$NH$_2$)	H_2	−20 °C, tol-d$_8$, 1 atm	HOL	[46]
3	*trans*-RuH$_2$(PPh$_3$)$_2$(tmen)[a]	RuH(PPh$_3$)$_2$(NHCMe$_2$CMe$_2$NH$_2$)	H_2	20 °C, C_6D_6, 1 atm	HOL	[47]
4	*trans*-RuH$_2$((*R*)-binap)(tmen)[b]	RuH((*R*)-binap)(NHCMe$_2$CMe$_2$NH$_2$)	H_2	20 °C, C_6D_6, 1 atm	HOL	[47]
5	RuH$_2$(PPh$_3$)$_3$(sol)	RuCl$_2$(PPh$_3$)$_3$	KOH/*i*PrOH	20 °C, *i*PrOH	TI	[42]
6	RuH$_2$(PPh$_3$)(oxferphos)	RuCl$_2$(PPh$_3$)(oxferphos)	NaO*i*Pr	20 °C, C_6D_6/*i*PrOH	TI	[165]
7	RuH(O$_2$CH){PPh$_2$(C$_6$H$_4$SO$_3$Na)}$_3$	RuCl$_2${PPh$_2$(C$_6$H$_4$SO$_3$Na)}$_2$	NaO_2CH	50 °C, H_2O	TI	[163]
8	K[RuH(pcp)(O*i*Pr)(PPh$_3$)]	Ru(pcp)(OTf)(PPh$_3$)	KOH/*i*PrOH	83 °C, *i*PrOH	TI	[167]
9	[RuH(C$_6$Me$_6$)(bpy)]$^+$	[Ru(C$_6$Me$_6$)(bpy)(OH$_2$)][PF$_6$]$_2$	NaO_2CH	20 °C, H_2O, pH 4–9	TO	[173]
10	RuH((*S*,*S*)-NH$_2$CHPhCHPhNTs)(cymene)	Ru((*S*,*S*)-NHCHPhCHPhNTs)(cymene)	*i*PrOH	20 °C, *i*PrOH	TOL	[29]

[a] dach: diaminocyclohexane.
[b] tmen: 2,3-diamino-2,3-dimethylbutane.

Table 2
Representative conditions for the stoichiometric reaction of hydrides with carbonyl or imine compounds

	Ru–H (concentration)	Substrate (concentration)	Solvent	T (°C)	Time (min)	Conversion (%)	Product after workup (%e.e.)	Proposed cycle	Reference
1	$Ru(H)_2(H_2)(PPh_3)_3$	Cyclohexanone (0.5 M)	Toluene	20	60	100 of RuH	Cyclohexanol	HI	[66]
2	*cis*-$RuH_2(PMe_3)_4$ (0.09 M)	PhHC=O (0.32 M)	toluene	−20			$PhCH_2OH$ + $Ru(PMe_3)_4(OCH_2C_6H_4)^{\bullet}$ $HOCH_2Ph$		[41]
3	*cis*,*trans*-$RuH_2(PPh_3)_2$((*R*,*R*)-dach)[a] (0.05 M)	PhMeC=O (0.1 M)	C_6D_6	20	>1000	Low[b]	1-PhMeHCOH	HOL	[46]
4	*cis*,*cis*-$RuH_2(PPh_3)_2$((*R*,*R*)-dach)[c] (0.03 M)	PhMeC=O (0.05 M)	C_6D_6	20	<3	100 of RuH	(*S*)-1-PhMeHCOH (16% e.e.)	HOL	[46]
5	*trans*,*cis*- $RuH_2(PPh_3)_2$((*R*,*R*)-dach)[d] (0.01 M)	PhMeC=O (0.05 M)	C_6D_6	−20	<3	100 of RuH	(*S*)-1-PhMeHCOH (62% e.e.)	HOL	[46]
6	*trans*,*cis*- $RuH_2(PPh_3)_2$(tmen)[e] (0.05 M)	PhMeC=O (0.05 M)	C_6D_6	20	<5	100	PhMeHCOH	HOL	[47]
7	*trans*-RuH_2((*R*)-binap)(tmen)[e] (0.05 M)	PhMeC=O (0.05 M)	C_6D_6	20	<5	100	(*S*)-1-PhMeHCOH (60% e.e.)	HOL	[47]
8	*cis*-$RuH_2(PPh_3)_4$	Hexaldehyde	C_6H_5Br	20	Fast			TI	[40]
9	*cis*-$RuH_2(PPh_3)_4$	Acetone	Toluene	56	5	50	*i*PrOH	TI	[42]
10	*cis*-$RuH_2(PPh_3)_4$	Acetone		50			$Ru(H)_2(CO)(PPh_3)_3$ and other products	TI	[43]
11	*cis*-$RuH_2(PPh_3)_4$	$PhCH_2N$=CHNp (5[Ru])	CH_3OH	65	30	5	$PhCH_2NHCH_2Np$	TI	[44]
12	*cis*-$RuH_2(PPh_3)_4$	$CF_3(Ph)C$=O	Toluene	60			$RuH(OCH(Ph)CF_3)(PPh_3)_3$	TI	[45]
13	$RuH(NH_2CHPhCHPhNTs)$(*p*-cymene)	Me_2C=O (10[Ru])		20	<1	100	*i*PrOH	TOL	[29]

[a] *cis*-Hydrides, *trans*-PPh_3, dach = diaminocyclohexane.
[b] Correction of result reported in [48].
[c] *cis*-Hydrides, *cis*-PPh_3.
[d] *trans*-hydrides, *cis*-PPh_3.
[e] tmen = 2,3-dimethyl-2,3-diaminobutane.

Table 3
Representative conditions for the H_2-hydrogenation of aldehydes, ketones (aromatic and aliphatic) and imines to the alcohols or amines

	Precatalyst (Ru)	Substrate (S)	Additives (A)	Ru:S:A	Solvent	$p(H_2)$ (atm)	Conversion (%)	e.e. (%)	Time (h)	Temperature (°C)	TOF (h^{-1})	Cycle	Reference
1	$[RuH((R)\text{-binap})(NCMe)_{3-n}(sol)_n]^+$	$MeOOCCMe_2$-C(=O)COOMe		1:200	MeOH	50	100	59 (*R*)	50	50	4	HI	[51]
2	$[RuH_3(CO)(PCy_2(CH_2)_4PCy_2)]^-$	Ph_2C=O		1:3000	*i*PrOH	1	96		24	60	125	HI, TI	[65]
3	$RuH\{\kappa^2\text{-}o\text{-}C(O)(Ph)(C_6H_4\}(CO)(PCy_2(CH_2)_4PCy_2)$	Ph_2C=O		1:20,000	*i*PrOH	1	90		3	80	9600	HI, TI	[65]
4	$[RuH(CO)(NCMe)_2(PPh_3)_2]BF_4$	PhHC=O		1:100	$MeOCH_2CH_2OH$	1	10		0.7	98	14	HI	[68]
5	$RuHCl(CO)(PPh_3)_3$	EtCHO		1:1000	Toluene	30	100		2	150	2	HI	[69]
6	$RuH_2(CO)_2(PPh_3)_2$	PhMeC=O		1:88	Toluene	50	69		24	120	4	HI	[22]
7	$RuHCl(CO)((PPh_2CH_2)_3CMe)$	Cyclohexanone		1:1000	THF	20	63		1.3	100	470	HI	[72]
8	$RuH(Tp^*)(H_2)_2$	Cyclohexanone		1:100	Heptane	3	93		2	80	47	HI	[75]
9	$Ru(H)_2(H_2)(PPh_3)_3$	Cyclohexanone		1:36	Toluene	0.6	3		1	20	1	HI	[66]
10	$RuH_2(PPh_3)_4$	$CF_3(Ph)C$=O		1:720	Toluene	1	100		<2900	100	0.2	HI	[45]
11	$RuH_2(tppts)_4$	EtCHO		1:1000	H_2O	50				100	0.8	HI	[83]
12	$RuH_2(tppts)_4$	EtCHO	NaI	1:1000:100	H_2O	50				35	2000	HI	[83]
13	$RuH_2((R)\text{-binap})(tmen)$	PhMeC=O		1:400	Benzene	8	100	62–68 (*R*)	2	20	200	HOL	[47]
14	$Ru(Cl)_2((S)\text{-tolbinap})((S,S)\text{-dpen})$	PhMeC=O	KO*t*Bu	1:2,400,000: 24,000:	*i*PrOH	45	100	80 (*R*)	48	30	2×10^5	HOL	[8]
15	$Ru(H)(BH_4)((S)\text{-tolbinap})((S,S)\text{-dpen})$	PhMeC=O		1:1800	*i*PrOH	4	100	82 (*R*)	2	30	900	HOL	[101]
16	$Ru(H)(BH_4)((S)\text{-tolbinap})((S,S)\text{-dpen})$	PhMeC=O	KO*t*Bu	1:1800:55	*i*PrOH	4	100	82 (*R*)	0.8	30	2200	HOL	[101]
17	$Ru(H)(Cl)((S,S)\text{-P-NHcyNH-P}))$	PhMeC=O	KO*i*Pr	$1:10^6$:90	*i*PrOH	45	100	27 (*S*)	3	45	3×10^5	HOL	[121]
18	$Ru(H)(Cl)((R)\text{-binap})((R,R)\text{-dach})$	PhN=CPhMe	KO*i*Pr	1:500:10	Benzene	3	100	71 (*S*)	36	20	14	HOL	[102]

under much milder conditions to generate very active hydrogenation catalysts that operate with an HOL cycle. The HOL cycles typically operate under milder conditions than the HI cycles.

In the T catalytic cycles, hydrogen transfer reagents such as 2-propoxide in *i*PrOH/base mixtures or formate in $HCOOH/NEt_3$ mixtures provide hydrides on ruthenium by β-hydride elimination reactions [33], essentially the reverse of the processes shown in Figs. 1 and 3 (Eq. (3), $R_2 = Me_2$, O, etc.). Entries 5–10 show examples of hydride-containing catalysts that are generated by reaction of precursors with *i*PrOH, $i\text{PrO}^-$ or HCO_2^- in organic solvents or water at temperatures that range from 20 to 100 °C and are active in TI, TO and TOL cycles:

$$\text{Ru(II)} + \text{OCHR}_2{}^- \rightarrow [\text{Ru(II)H}]^- + \text{OCR}_2 \quad (3)$$

An alternative mechanism is the oxidative addition of an element hydrogen bond D–H of the hydrogen donor DH_2 to Ru(0) to give a Ru(II) hydride, Ru(II)(H)(DH) (Eq. (4)):

$$\text{Ru(0)} + \text{DH}_2 \rightarrow \text{Ru(II)(H)(DH)} \quad (4)$$

The oxidative addition to Ru(0) of the O–H group of isopropanol has been proposed as a mechanism of generating a Ru(II) hydride in a TI cycle [15].

1.3. Hydridic reactivity of ruthenium hydride complexes

As mentioned, the hydride affinities of the polar bonds under consideration are low. Ruthenium complexes that are catalysts in H or T cycles must be sufficiently hydridic to undergo the reactions discussed in Section 1.1. They usually have the following properties. First, they contain ancillary ligands that stabilize the positive charge that is left on the metal after the hydride transfer step (Eq. (5)):

$$[\text{Ru}]\text{–H} + \text{R}_2\text{C=Q} \rightarrow [\text{Ru}]^+ + \text{R}_2\text{HCQ}^- \quad (5)$$

These ligands could include strongly basic hydride, phosphine, and cyclopentadienide ligands with electropositive donor elements (H, P, C), but not usually the π-acidic carbonyl ligand. These high trans influence ligands, when trans to the leaving hydride, assist by weakening the Ru–H bond. A negative charge on the ligands will also promote the reaction. Basic amine ligands also stabilize the product and favor Eq. (5). Some free energy measurements of the heterolytic splitting of the M–H bond have been reported recently and some of the factors that favor hydridic character in transition metal complexes have been described [34–39]. Konno et al. demonstrate that a hydride on ruthenium can be made hydridic by use of chelating terpyridine and bipyridine ligands in $[RuH(terpy)(bpy)]^+$, even though the complex has a positive charge [36]. This complex attacks CO_2 to produce a formate complex in an outer sphere (O) reaction.

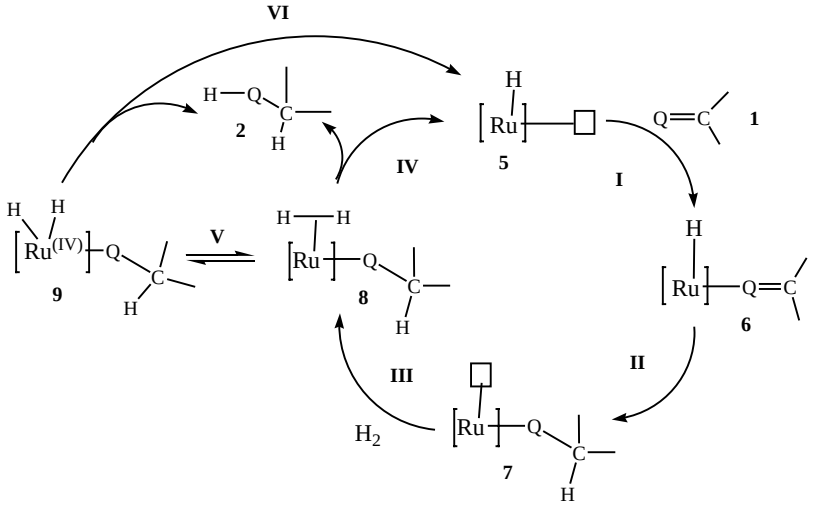
The influence of these factors can be qualitatively judged from the selected reports of stoichiometric reactions of polar bonds with ruthenium hydrides (Table 2). These reactions were explored for the most part to demonstrate a step in the catalytic reactions, as will be described below. Aldehydes have a higher hydride affinity and are easier to reduce both thermodynamically and kinetically (less steric hindrance to hydride transfer) than ketones and imines. They react readily with *cis*-$RuH_2(PPh_3)_4$ at 20 °C [40], and with the more electron-rich *cis*-$RuH_2(PMe_3)_4$ at −20 °C [41] (Table 2, entries 2 and 8, in TI cycle). For complexes with labile, monodentate ligands such as $Ru(H)_2(H_2)(PPh_3)_3$, there is often the unwanted formation of ruthenium carbonyl compounds by CO abstraction from the aldehyde. Ketones and imines react with the dihydrogen complex $Ru(H)_2(H_2)(PPh_3)_3$ at 20 °C (entry 1, HI cycle) and with *cis*-$RuH_2(PPh_3)_4$ at about 60 °C (entries 9–12, TI cycle) [42–45]. The dihydrogen complex and *cis*-dihydride complexes are relatively active HI and TI catalysts, respectively (see below). By contrast the complexes $Ru(H)(Cl)(CO)(PPh_3)_3$ and $Ru(H)(Cl)(CO)(PPh_3)$(diphosphine) with electron-withdrawing CO and Cl groups and aryl-substituted phosphines do not readily react with ketones and only become active as catalysts at relatively elevated temperatures (>100 °C) (see below and entries 5–7 of Table 3).

The other entries in the Table 2 describe some hydrides that react with ketones by an OL mechanism. Trans-dihydrides $Ru(H)_2$(diamine)$(PR_3)_2$, $(PR_3)_2 = (PPh_3)_2$ or ((*R*)-binap), react rapidly with ketones at room temperature or below (entries 5–7 of Table 2) while a *cis*-dihydride, *cis*,*trans*-$Ru(H)_2(PPh_3)_2$((*R*,*R*)-dach), with hydrides *trans*- to the low-*trans*-influence diamine ligand, reacts very slowly with acetophenone (entry 3) [46–48]. Only the *trans*-dihydride isomers are very active ketone and imine hydrogenation catalysts with an HOL cycle. However, the isomer *cis*,*cis*-$Ru(H)_2(PPh_3)_2$((*R*,*R*)-dach), with one hydride *trans* to a PPh_3 ligand of *trans* influence, also reacts rapidly with acetophenone (entry 4 of Table 2) [46] and is an active precatalyst for the HOL cycle. The complexes *trans*-RuHCl(diamine)$(PR_3)_2$ with hydride *trans* to chloride do not react with ketones and are not ketone hydrogenation catalysts at room temperature [46–48]. The strongly basic tosylated amido–amine ligand must compensate for the weakly basic η^6-arene ligand in $RuH(NH_2CHPhCHPhNTs)$(*p*-cymene) because this complex reacts rapidly with ketones at room temperature in an OL mechanism (entry 13 of Table 2) [29] and is a relatively active TOL catalyst.

2. Homogeneous H_2-hydrogenation of substrates with polar bonds (H mechanisms)

2.1. Hydride transfer to the substrate in the primary or inner coordination sphere (HI)

The generalized catalytic cycle for an inner sphere hydrogenation mechanism is shown in Scheme 3.



Scheme 3. Generalized catalytic cycle for the inner sphere hydrogenation (HI) of C=Q bonds, Q = O, NR.

The cycle starts with the addition of the substrate (**1**) to the coordinatively unsaturated Ru(II) hydride species (**5**) giving the complex **6** (step **I**). The hydride species **5** is usually formed from a catalyst precursor at the very beginning of the catalytic reaction and is not isolated itself (see below). A hydride migration (step **II**) affords the new unsaturated ruthenium species (**7**) to which dihydrogen coordinates (step **III**) affording the dihydrogen species (**8**). A substrate insertion (step **I**) and a hydride migration (step **II**) are usually very fast so only the product (**7**) can be observed. Complex **8** can further react in two ways: (1) protonation of the coordinated substrate affords the product (**2**) releasing the regenerated catalyst (**5**) (step **IV**) or (2) the coordinated dihydrogen can oxidatively add to the Ru(II) center giving a dihydride ruthenium(IV) species (**9**) (step **V**), followed by elimination of the product **2** and regeneration of the active catalyst (**5**). It should be noted that it is often impossible to experimentally distinguish between path **IV** and path **V** → **VI**.

Catalytic reactions for which the inner sphere hydrogenation mechanism has been proposed have several features in common, regardless of the solvent used (organic, water or biphasic system). They all require relatively high temperatures (50–100 °C, in some instances even higher) and high dihydrogen pressures (around 50 atm) (Table 3). The catalyst-to-substrate ratio is usually small and no additives are necessary for the reaction to proceed. Step **III** in the Scheme 3 is generally recognized as the turn-over-limiting step.

Table 3 lists representative conditions for the operation of some of the H_2-hydrogenation catalysts reviewed here. The turn-over frequency (TOF in h^{-1}) is estimated from the ratio of the concentration of the product of the hydrogenation to that of the catalyst divided by the time for the conversion. The numbers are approximate and are used for order of magnitude comparisons of the hydride catalyst activity.

2.1.1. Catalytic HI hydrogenations in organic solvents

Bergens and coworkers have reported the synthesis of the complex [Ru((*R*)-binap)(NCMe)(1–3:5,6-C_8H_{11})](BF_4) as a catalyst precursor for the hydrogenation of various unsaturated organic substrates including α- and β-keto esters (Table 3, entry 1) [49,50]. The complex reacts with 1 atm H_2 in MeOH, THF or acetone (sol) giving the hydride complex [RuH((*R*)-binap)$(NCMe)_m(sol)_{3-m}$]BF_4 (Eq. (6)):

$$[Ru((R)\text{-binap})(NCMe)(1\text{-}3{:}5,6\text{-}C_8H_{11})](BF_4) \xrightarrow[\text{sol.}]{1\ \text{atm}\ H_2} [Ru(H)((R)\text{-binap})(NCMe)_m(sol)_{3\text{-}m}](BF_4) + \bigcirc \quad (6)$$

The hydride complex has not been isolated but has been characterized by NMR spectroscopy. Its solvent molecules can easily dissociate creating up to three vacant coordination sites for substrates to attack.

Part of the proposed cycle for the hydrogenation of α-ketoesters catalyzed by this hydride (2%, 50 atm H_2, 50 °C, THF or MeOH) is shown in Fig. 4 [51].

The formation of the ruthenium alkoxide complex from the hydride and the substrate is a fast process even at −30 °C so that an intermediate of type **6** from Scheme 3 has never been observed.

Bergens and coworkers have proposed that this insertion proceeds either via prior coordination of the ketone as an

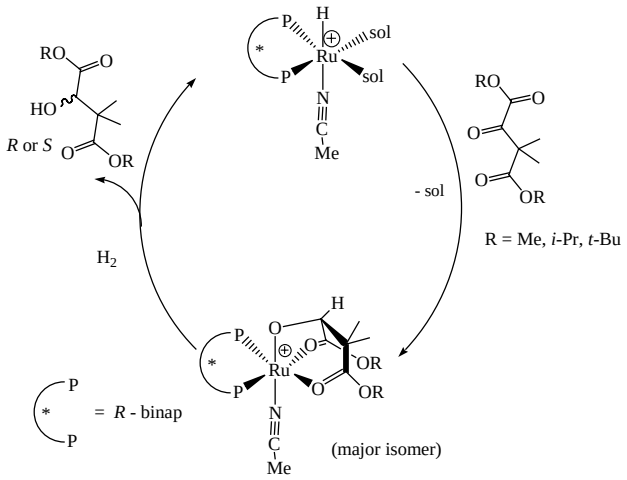


Fig. 4. The HI hydrogenation of α-ketoesters catalyzed by [RuH((*R*)-binap)(NCMe)$_{3-n}$(sol)$_n$]$^+$.

η^2-π-ligand (similar to an olefin hydride insertion) (an inner sphere mechanism HI) or via nucleophilic attack of the hydride on the carbonyl carbon (outer sphere HO). The reaction is only partially reversible under the hydrogenation conditions. The alkoxide species is actually a mixture of two diastereomers. The formation of these is the step that determines the enantioselectivity of the process. The nature, geometry and absolute configuration of the major diastereomer shown in Fig. 4 have been established by ^{1}H, ^{13}C, ^{31}P and ^{15}N NMR spectroscopy and deuterium labeling (starting from [Ru(D)((*R*)-binap)(NCMe)$_m$(sol)$_{3-m}$]$^+$ as a catalyst).

The reaction of the alkoxides with dihydrogen gas followed by the regeneration of the active catalyst and product release is recognized as the turn-over-limiting step on the basis of following observations. First, the formation of the catalyst from the 1–3:5,6–C_8H_{11} precursor proceeds at 1 atm of H_2; second, the formation of the alkoxide from the hydride and the unsaturated substrate is fast and complete even at −30 °C while the catalytic reaction takes place at 50 atm of H_2 and 50 °C (see Table 3, entry 1). Since the alkoxide is an 18-electron coordinatively saturated Ru(II) complex, it is proposed that the regeneration of the hydride proceeds via either dissociation of acetonitrile or one of the ester groups to allow the coordination of the H_2. No intermediates of the type **8** or **9** (Scheme 3) have been observed or proposed.

James and coworkers have studied the hydrogenation of imines catalyzed by ruthenium complexes containing bidentate ligands [4]. The trimeric hydride species [RuHCl(P–P)]$_3$, (P–P) = dppb, (*S*,*S*)-chiraphos, diop, hydrogenate aldimines (RCH=NR′) at 1 atm H_2, 50 °C and a sterically hindered ketimine 2,6-$Me_2C_6H_3$N=CMeCH$_2$OMe at 70 atm H_2, 20 °C in methanol/benzene with an e.e. of <10%. The X-ray structure of the trimer with P–P = (*S*,*S*)-chiraphos is interpreted as shown in Fig. 5. NMR data provides evidence for the hydrides.

The complex [RuHCl(dppb)]$_3$ catalyzes the hydrogenation of PhCH$_2$N=CMePh at 20 °C, 70 atm H_2 in MeOH

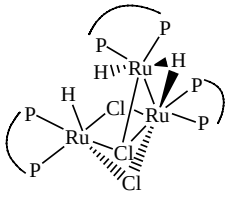


Fig. 5. Structure of [RuHCl(P–P)]$_3$ interpreted from the heavy atom positions as determined by X-ray diffraction [52].

[53]. Chloride bridged dimers of the type [RuCl$_2$(P–P)]$_2$ and Ru$_2$Cl$_5$(P–P)$_2$ were found to be more effective precatalysts under these conditions.

Bianchini et al. [54] studied by NMR the hydride species that are generated under 50 atm pressure during the catalytic, highly enantioselective, hydrogenation of acetylacetone to 2,4-pentanediols. The precatalyst was the chloride-bridged complex Ru$_2$Cl$_4$(P–P)$_2$(dmso), P–P = chiral diphosphine (Fig. 6). An interesting dimeric dihydrogen complex was identified as the predominant species (Fig. 6).

Related hydride structures of the type *trans*-RuHX-(diphosphine)(substrate), X = Cl, Br, OAc, substrate = β-ketoesters or β-diketones have often been proposed, without direct spectroscopic observation of the hydride, as transient intermediates in the asymmetric hydrogenation of these substrates starting with RuY$_2$(diphosphine) precursors, Y = Cl, Br, methylallyl, OAc in alcohols. For example, Noyori and coworkers have proposed a catalytic cycle for the hydrogenation of β-keto esters and related ketones that can act as bidentate ligands [55]. The precatalysts were neutral ruthenium(II) complexes RuCl$_2$(binap)(sol)$_2$ (sol = alcohol or acetone) [6]. The mechanism is proposed to include the hydride species RuHCl((*R*)-binap)(RCOCH$_2$COOR^1) and the transient complex that is activated for intramolecular attack of the hydride on the carbonyl carbon of the substrate by protonation of the carbonyl oxygen (Fig. 7(a)). The structure of the substrate–chiral binap complex is proposed to explain the enantioselectivity observed. The presence of such intermediates is inferred by analogies to prior mechanistic work by groups of Wilkinson and Halpern and the results of deuterium incorporation into olefinic substrates

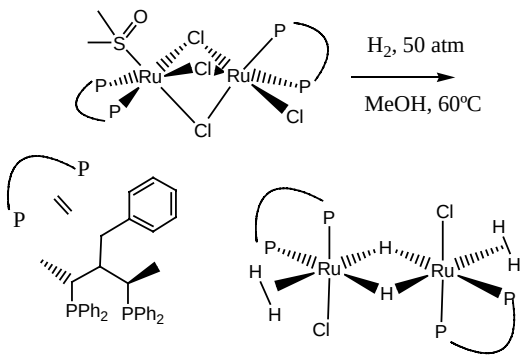


Fig. 6. The proposed formation of the catalyst for the hydrogenation of acetylacetone [54].

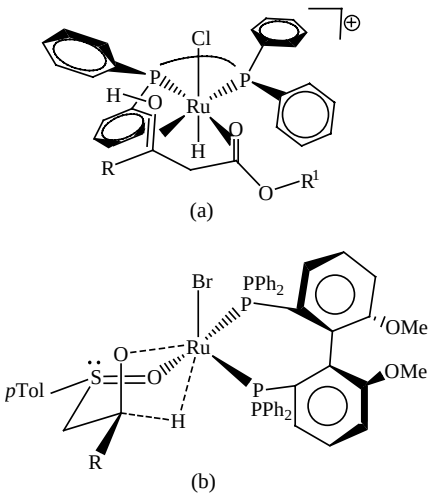


Fig. 7. Transient hydride species proposed in the hydrogenation of β-ketoesters (a) [6] and β-ketosulfoxides (b) [56].

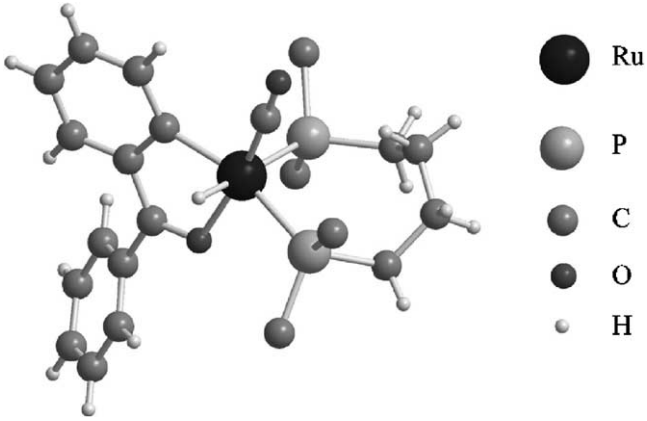


Fig. 8. Structure of RuH{κ²-*o*-C(O)(Ph)(C_6H_4}(CO)($PCy_2(CH_2)_4PCy_2$) [65]. Atoms of the cyclohexyl groups have been removed (structure XIGGUP from the Cambridge Crystallographic Data Centre (CCDC) [67]).

that are also hydrogenated by such catalyst systems. The chloride ligand seems to be an important component, since the use of other halides and pseudo halides lead to less active and enantioselective catalysts.

The most effective system of this type for the asymmetric hydrogenation of a simple ketone like acetophenone to 1-phenylethanol in 78% e.e. is $Ru(OAc)_2$((*R*)-xylbinap)/2 $OPPh(OH)_2$ in $ClCH_2CH_2Cl$ at 100 °C, 100 atm H_2 [8]. This is thought to involve the transient intermediate $RuH(O_2PPh(OH))$((*R*)-xylbinap)(O=CPhMe). The OH group of the phenylphosphonate ligand might assist the hydride migration to the ketone in an HIL mechanism (see Fig. 1).

Genêt and coworkers also utilize RuX_2(diphosphine), diphosphine = binap, MeO-biphep, duphos and their own crnphos [57] and synphos [58] systems in the catalytic hydrogenations of β-keto esters [59,60], β-keto sulfoxides and sulphones [56,61] and β-diketones [57,62]. The catalytic system was used also as a part of a multistep synthesis as an important and efficient way for obtaining useful starting compounds [61,63]. In their synthetic procedures, they form the precatalyst in situ from Ru(2-methylallyl)$_2$(cod), a chiral diphosphine and an acid. They make use of a similar stereochemistry of the transient hydride as proposed by Noyori. For example, in the hydrogenation of a β-keto sulfoxide they proposed the Ru(II) hydride intermediate shown in Fig. 7(b) [56]. In another study, the structure of the hydride intermediate RuHCl(synphos)(methylacetoacetate) was calculated by use of molecular mechanics [58]. Chan's group has also made use of related systems for the enantioselective hydrogenation of β-ketoesters [64].

The anionic hydride complex $[Ru(H)_3(CO)(dcypb)]^-$, dcypb = $PCy_2CH_2CH_2CH_2CH_2PCy_2$, is an active catalyst for the hydrogenation (in benzene) and transfer hydrogenation (from *i*PrOH) of benzophenone [65] (Table 3, entry 2). The active species in *i*PrOH is postulated to be $Ru(H)_2(H_2)(CO)$(dcypb) by analogy to $Ru(H)_2(H_2)(PPh_3)_3$ [66] (see below) and so an HI or TI mechanism is tentatively assigned. The anionic complex reacts with benzophenone to produce a neutral monohydride complex containing a cyclometalated Ph_2CO group, RuH{κ²-*o*-C(O)(Ph)(C_6H_4}(CO)(dcypb) that has equal hydrogenation activity in *i*PrOH to the precursor complex. A TOF of up to 9600 h^{-1} at 80 °C (reflux in *i*PrOH) was reported using this complex (Table 3, entry 3); there may be contributions from both H_2- and transfer-hydrogenation mechanisms since acetone is produced in the reaction. The anionic hydride and the monohydride complex (Fig. 8) were completely characterized including single crystal X-ray diffraction structure determinations. This catalyst system is an exception to the rule that carbonyl ligands are deactivating; this rule may be specific to arylphosphine-containing complexes. Here the bulky, electron-donating diphosphine ligand dcypb compensates for the presence of the electron-withdrawing CO ligand.

A detailed kinetic and mechanistic study was carried out by Sanchez-Delgado and coworkers [14,68] on the catalytic hydrogenation of benzaldehyde using $[RuH(CO)(NCMe)_2(PPh_3)_2]BF_4$ as a catalyst precursor at temperatures of 50–100 °C and a hydrogen pressure of 1 atm (Table 3, entry 4). The system showed a first order dependence on the RuH, the substrate and dihydrogen pressure with rate constant $k = 20\,M^{-2}\,s^{-1}$ at 97 °C (Eq. (7)):

$$\text{rate} = k[\text{RuH}][\text{PhHCO}][\text{H}_2] \quad (7)$$

In order to gain further insight into catalytic cycle, they have also studied the interaction of the RuH with all of the components of the catalytic system. In this way they have identified two new complexes upon reacting the RuH with the 2-methoxyethanol (used as the solvent in the catalysis) in chloroform: $[RuH(CO)(NCCH_3)(sol)(PPh_3)_2]^+$ and $[RuH(CO)(sol)_2(PPh_3)_2]^+$ (sol = 2-methoxyethanol). In a

similar way, they have shown that the RuH can form mono- and disubstituted products in its reaction with benzaldehyde in $CDCl_3$. This demonstrates that the substitution of weakly coordinated CH_3CN molecules with the substrate can be one of the steps in the catalytic cycle (Scheme 3, step **I**). Furthermore, the $^{31}P\{^1H\}$ NMR spectrum of the reaction between RuH and dihydrogen gas at 343 K in a mixture of 2-methoxyethanol and methanol-d_4 showed the formation of a new species which was suggested to be possibly the product of the oxidative addition of dihydrogen to the Ru(II) center, $[Ru(H)_2(OCH_2Ph)(CO)(sol)(PPh_3)_2]^+$. The postulated ability of RuH to oxidatively add H_2 reminds us that the species of the type **9** (Scheme 3) can be part of the catalytic cycle. However the most current evidence favors Ru(II) dihydrogen intermediates over such Ru(IV) species, except when small, electron-donating monodentate or bidentate ligands are present. Based on the above experimental results, the catalytic cycle proposed by Sanchez-Delgado and coworkers fits into the general mechanism of an inner sphere hydrogenation with the reaction of dihydrogen with the alkoxide complex being the turn-over-limiting step. If the Ru(IV) species is involved then the benzyl alcohol product is released in a reductive elimination step. This group studied the use of other carbonyl-containing catalysts, including $RuHCl(CO)(PPh_3)_3$, for the hydrogenation of aldehydes (Table 3, entry 5) [69]. An HI mechanism was proposed. The conditions were quite severe for this reaction (30 atm H_2, 150 °C).

Frediani and coworkers [22], based on their mechanistic investigations of the catalytic hydrogenation of a wide range of simple ketones such as acetophenone (Table 3, entry 6) using the neutral dihydride complex $Ru(H)_2(CO)_2(PPh_3)_2$ as the catalyst, have proposed that the turn-over limiting step is the coordination of the substrate next to the Ru–H bond to give a 20-electron complex $Ru(H)_2(ketone)(CO)_2(PPh_3)_2$ in the first step of the catalytic cycle (such an intermediate would have a high energy and may only be a transition state or the mechanism might involve prior ligand dissociation). Followed is the insertion of the ketone to the Ru–H bond to give the corresponding Ru-alkoxide species (Scheme 3, complex **7**). The product is released and the catalyst is regenerated after the addition of H_2 to the Ru center (Scheme 3, complex **8** and step **IV**). The support for this HI mechanism is found in the rate law (Eq. (8)) and the observation that the reaction rate decreases with an increase of steric bulk of the substrate ($Me_2C{=}O$ > *i*PrMeC=O > *t*BuMeC=O and increases with the electron-withdrawing groups ($CF_3PhC{=}O$ > MePhC=O). There was no observation of an intermediate in the catalytic cycle. The observation that α,β-unsaturated ketones are hydrogenated to the saturated ketones also provides evidence for an HI mechanism since the substrate usually has to coordinate for the C=C bond to be reduced.

$$\text{rate} = k[\text{Ru}][\text{substrate}][\text{H}_2] \quad (8)$$

Li et al. have reported the use of $RuHX(CO)(PPh_3)$-(diphosphine) (X = Cl or H) with *trans*-spanning diphosphines 2,2'-bis(diphenylphosphinomethyl)-1,1′-biphenyl (bisbi) [70] and 1,8-(diphenylphosphinomethyl)naphthalene (bdna) [71]. The bisbi ligand has an unusually large bite angle so that two phosphorus atoms from the diphosphine ligand are actually in *trans* positions and the backbone of the ligand passes over the hydride ligand (crystal structure and NMR evidence). They tested the complexes in the catalytic hydrogenation of citral and cinnamaldehyde. In both cases, the complexes containing diphosphines showed higher activity under the same conditions (50–80 °C, 1–3 h, 2–5 atm H_2) compared to their monophosphine counterparts, $RuHX(CO)(PPh_3)_3$ (X = Cl or H). The bidentate systems also gave better selectivity to the allylic alcohol than the monophosphine ones.

Jun and coworkers studied the effect of polydentate versus monodentate ligands on the activity of catalysts for the hydrogenation of cyclohexanone and propanal [72]. For cyclohexanone, the activity of monohydrides of the type $RuHCl(CO)(PR_3)_3$ increased as $(PR_3)_3$= monodentate $(PPh_3)_3$ < bidentate $(PPh_3)(PPh_2CH_2CH_2PPh_2)$ < tridentate $(PPh_2CH_2)_3CMe$, P_3). For the tridentate system (Table 3, entry 7). The rate law was described by Eq. (9) (k[cyclohexanone] = 1.2×10^{-2} min^{-1} at 100 °C):

$$\text{rate} = k[\text{H}_2][\text{RuHCl(CO)P}_3][\text{cyclohexanone}] \quad (9)$$

The rate law and the observation of a negative entropy of activation were used to suggest that the mechanism is an HI cycle as shown in Scheme 3. Here the active catalytic species containing an η^2-P_3 ligand with one CH_2PPh_2 group (originally *trans* to the hydride) uncoordinated to allow the ketone to coordinate, forms the alkoxide, and then allows the dihydrogen to coordinate (Fig. 9). Propanal was hydrogenated by the catalyst with the tridentate ligand and at almost twice the rate of that observed for cyclohexanone. This catalyst reduces the C=C bond of cyclohexenone in preference to the C=O bond. The hydrogenation of propanal by the well-characterized complexes $RuHCl(CO)(PPh_3)(L{-}L)$, L–L = $PPh_2CH_2CH_2PPh_2$, $PPh_2CH_2CH_2AsPh_2AsPh_2CH_2CH_2AsPh_2$ was also studied in detail by this group [73]. The phosphorus ligands produced more active catalysts than the arsenic ligands and again an HI mechanism was proposed with a chelate

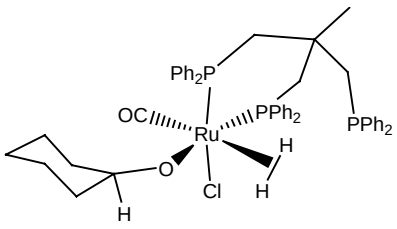


Fig. 9. Proposed dihydrogen intermediate in the hydrogenation of cyclohexanone catalyzed by $RuHCl(CO)((PPh_2CH_2)_3CMe)$ [72].

ring-opening step to allow the aldehyde and dihydrogen to coordinate.

Cationic complexes containing phosphorus and nitrogen donors $[RuCl(PPh_3)_2(P,N,N'\text{-}PPh_{3-x}(py)_x)]PF_6$ ($x = 2$, 3; py = 2-pyridyl) catalyze the hydrogenation of an aldimine at 20 °C, 36 atm H_2 in MeOH [74] but hydrides were not detected.

The bis-dihydrogen complex $RuH(Tp^*)(H_2)_2$, Tp^* = hydridotris(3,5-dimethylpyrazoyl)borate is both an H_2-hydrogenation catalyst and an *i*PrOH transfer hydrogenation catalyst (see TI section below) for ketones (acetophenone, acetone, cyclohexanone) but not aldehydes [75] (Table 3, entry 8). The complex $RuH(Tp^*)(cod)$, cod = 1,5-cyclooctadiene, has the same activity and presumably leads to the same catalyst as the bis-dihydrogen complex. These are rare examples of a Ru hydrogenation catalyst that do not contain phosphine ligands.

Ruthenium carbonyl clusters are somewhat active for the hydrogenation of polar bonds. For example $Ru_4H_4(CO)_8((-)\text{-diop})_2$ catalyzes the hydrogenation of acetophenone to 1-phenylethanol in 1% e.e. (120 °C, 130 atm, toluene) [76]. The clusters $Ru_4H_4(CO)_8[P(CH_2OCOR)_3]_4$, R = Me, Et, *i*Pr, *t*Bu, have activity as catalysts in the hydrogenation of carboxylic acids (100–130 °C, 130 atm). The hydrogenation of the ester group on the ligand produces an alcohol and a $P(CH_2OH)_3$ ligand that then reacts with the carboxylic acid substrate to regenerate the ester ligand. The exact mechanism is not known but this might be classified as an HIL mechanism.

The complex $RuH_4(PPh_3)_3$ (now known to be $Ru(H)_2(\eta^2\text{-}H_2)(PPh_3)_3$ [77]) was found by Linn and Halpern [66] to be the catalyst responsible for the catalytic hydrogenation of cyclohexanone in THF when starting with the anionic hydride precatalyst $K[RuH_3(PPh_3)_3]$ [78,79]. The RuH_4 compound catalyzes the hydrogenation of cyclohexanone in toluene at 25 °C, 1 atm H_2 (Table 3, entry 9). The rate law for the catalytic reaction was determined to be given by Eq. (10) with $k = 1.3 \times 10^{-3}\,M^{-1}\,s^{-1}$ at 20 °C:

$$\text{rate} = k[RuH_4(PPh_3)_3][\text{ketone}] \quad (10)$$

The stoichiometric reaction between $RuH_4(PPh_3)_3$ and cyclohexanone produces the same rate law as Eq. (10) and therefore this reaction is the turn-over-limiting step, making it look like an HO cycle with the outer sphere attack of the hydride on the ketone. In fact we suggest that it could even be an HOL mechanism (Fig. 3) where the somewhat acidic dihydrogen ligand assists in the hydrogenation by transferring a proton when the hydride is transferred. However, there is an easy loss of H_2 from this dihydrogen complex [20,66,80]. In fact, the dehydrogenation of alcohols catalyzed by $RuH_4(PPh_3)_3$ in the presence of base was explained by the efficient loss of H_2 from this complex, although at higher temperatures [80]. Therefore, Linn and Halpern proposed an HI mechanism where the lack of a dihydrogen concentration dependence in the rate law of Eq. (10) was rationalized by the canceling effects of a pre-equilibrium H_2 dissociation and then rate determining re-addition step. In the HI mechanism H_2 dissociates from $RuH_4(PPh_3)_3$ when the ketone coordinates, an alkoxide intermediate $RuH(OR)(PPh_3)_3$ forms (refer to Scheme 3) and then H_2 re-coordinates to this intermediate in the rate determining step [66]. This is followed by the fast elimination of alcohol and reaction with H_2 to reform $RuH_4(PPh_3)_3$.

Hayashi et al. [45] studied the hydrogenation of ketones catalyzed by $RuH_2(PPh_3)_4$. They found that it was somewhat active for the hydrogenation of trifluoroacetophenone in toluene at 100 °C, 1 atm H_2 (Table 3, entry 10). For comparison, $RuCl_2(PPh_3)_4$, is an HI catalyst at 125°, 88 atm for the conversion of acetophenone to the alcohol [81].

2.1.2. Catalytic HI hydrogenations in water

Basset and coworkers discovered that the addition of NaI dramatically activated ruthenium complexes of the water soluble phosphine $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$ (tppts) in the hydrogenation of propionaldehyde in water at 100 °C, 50 atm H_2 [82–84] (refer to Table 3, entries 11 and 12). The complexes included $[RuCl_2(tppts)_2]_2$, $RuHCl(tppts)_3$, $RuH_2(tppts)_4$ and $RuH(OAc)(tppts)_3$. These were isolated and characterized by NMR [84]. While the catalyst precursors are water-soluble, the substrates used are not miscible with water. Hence, the whole catalyst system is actually biphasic.

Experimental results suggest that each of these complexes, in the absence of NaI leads to the same active catalyst species in H_2O, namely RuH_2L_3 (Fig. 10). Starting from any of the tppts precatalysts, under the same catalytic conditions, similar turn-over-frequencies of about $0.8\,h^{-1}$ for the conversion of propanal to propanol have been observed at 100 °C (Table 3, entry 11).

The catalytic reactions using $[RuCl_2(tppts)_2]_2$ as a precatalyst were shown to be first order in Ru, substrate concentrations and dihydrogen pressure as in Eq. (11):

$$\text{rate} = k[\text{EtCHO}][Ru][H_2] \quad (11)$$

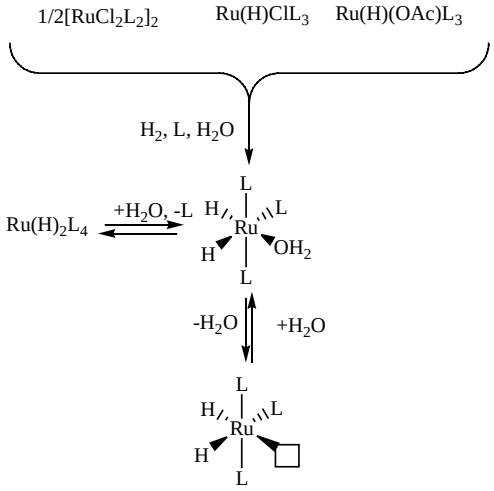


Fig. 10. Formation of dihydride complexes in water when L = $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$ (tppts).

A reaction scheme identical to Scheme 3 was proposed where the active catalyst $RuH_2(tppts)_3$ is formed by dissociation of H_2O from the catalyst precursor $RuH_2(tppts)_3(OH_2)$. The turn-over-limiting step is proposed to be the reaction of the alkoxide $RuH(OCH_2Et)(tppts)_3$ with dihydrogen, as in Scheme 3.

In the presence of NaI in water, all of these complexes are thought to be converted to $RuHI(tppts)_3(OH_2)$, the active catalyst. The turn-over frequency increases from $0.8\,h^{-1}$ at 100 °C without the NaI to 2000 at 35 °C with NaI. The sodium cation is postulated to assist in the oxidative addition of $HRCONa^+$ to the hydride $[Ru^{II}]H$ to produce a Ru–C bonded hydride alkoxyalkyl complex, $(H)[Ru^{IV}](C(ONa)RH)$. Hydrolysis of the ONa bond, reductive elimination of the alcohol product, and rate-determining addition of H_2 completes the cycle. Therefore, unlike the other HI mechanisms discussed, the hydride addition occurs in a reductive elimination step.

Laurenczy et al. have developed an interesting catalytic system for the hydrogenation of CO_2 and HCO_3^- in water [85]. Their catalyst precursor is $RuCl_2(pta)_4$ (pta = 1, 3, 5-triaza-7-phosphaadamantane). The fate of $RuCl_2(pta)_4$ is dependent on the pH of the solution. In a strongly basic medium (pH = 12.0), it gives the *cis*-dihydride species *cis*-$Ru(H)_2(pta)_4$ upon treatment with H_2. However, in acidic solutions (pH = 2.0) it gives the monohydride $Ru(H)(X)(pta)_4$ (Fig. 11). The X ligand might be Cl^- or H_2O and can be easily exchanged with pta. However, the mole fraction of Ru as RuH and RuH_2 is very low (5%) at 25 °C and at 80 atm of H_2. The rest of the Ru is still present in the form of $RuCl_2(pta)_4$. Both hydrides can be also obtained from the reaction of $[Ru(H_2O)_6]^{2+}$, a stoichiometric amount of pta and dihydrogen gas at the corresponding pH values (Fig. 11).

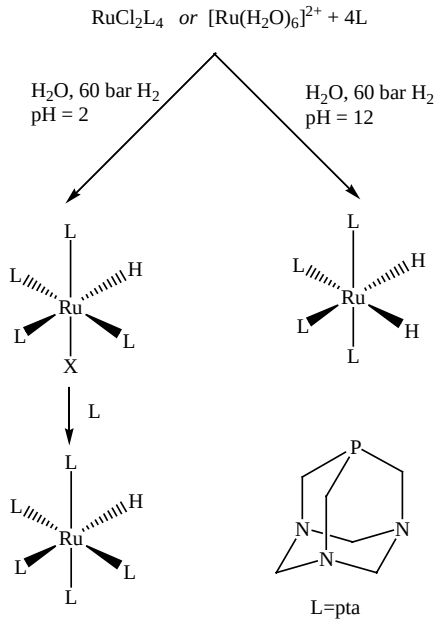


Fig. 11. The formation of Ru(II) hydride species in water with the ligand L = pta at low and high pH conditions; X = Cl^-, CO_3H^- or OH_2.

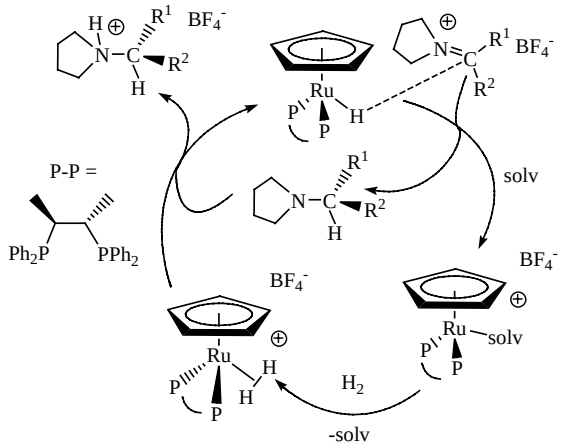
The activity of the dichloride catalyst precursor towards the catalytic hydrogenation of CO_2 is also a function of the pH of the water solution. The hydrogenation initial rates are the greatest at pH 5.9 where the optimum concentrations of CO_2 and HCO_3^- are present. The highest activity was observed when the pH of the reaction mixture was controlled by the use of the CO_2/HCO_3^- buffer by varying the CO_2 pressure (TOF = $807\,h^{-1}$).

In acid, the catalytically active species is thought to be of the form $[RuHX(pta)_4]^+$, X = Cl^- or H_2O. The hydride is proposed to attack bicarbonate to form $[RuH(OCH(OH)O)(pta)_4]^-$ (step **I**, Scheme 3) that is protonated (step **IV**) to release formic acid and water. This leaves a complex such as $RuX_2(pta)_4$ (X = Cl^- or H_2O) that reacts with H_2 to regenerate the monohydride.

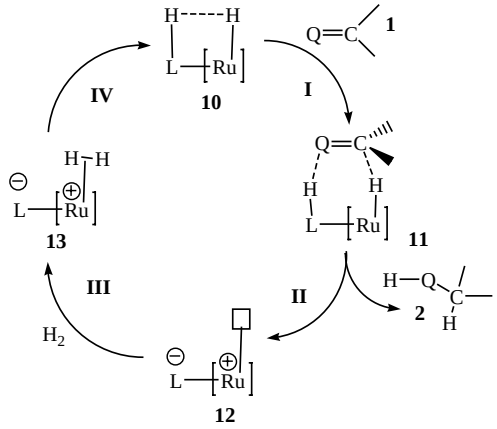
Another interesting catalytic system that shows pH dependence is based on $[RuCl_2(tppms)_2]_2$ (tppms = (3-sulphonatophenyl)diphenylphosphine sodium salt) [23]. Similar to the tppts complexes discussed above, it is used in catalysis in biphasic systems. Unlike the complex $RuCl_2(pta)_4$, this complex can be completely converted to Ru hydride species in water under H_2 and in the presence of the tppms ligand. In acidic media, the dichloride gives the monohydride $Ru(H)Cl(tppms)_3$, while in basic media it gives mainly the dihydride $Ru(H)_2(tppms)_4$. The mono- and di-hydrides coexist in the $7 \leq pH \leq 8$ range. The complex $[RuCl_2(tppms)_2]_2$ was tested as the precursor for the catalytic hydrogenation of *trans*-cinnamaldehyde. At the pH range from 3 to 4.5 the product of the hydrogenation is almost exclusively the dihydrocinnamaldehyde (3-phenyl propanal) that is formed via selective hydrogenation of the C=C double bond. Above pH 5, the hydrogenation of the C=O bond predominates and the product is cinnamyl alcohol (3-phenyl propenol). Since in the pH range of the C=C bond reduction, the predominant hydride species is the monohydride, it is reasonable to suggest that this is the catalyst. On the other hand, at a pH of 4.5 and above, the predominant Ru hydride species is the dihydride and it can be assumed that it is the catalyst for the hydrogenation of the C=O functionality. In all of the reported catalytic reactions, the formation of the fully saturated product (3-phenylpropanol) was negligible. Hence, the selectivity of the dichloride precatalyst towards either C=C or C=O bonds can be tuned by the pH of the solution.

2.2. Hydride transfer to the substrate in the outer coordination sphere (HO)

Early transition metal hydride complexes are sufficiently hydridic to catalytically hydrogenate ketones in a catalytic ionic hydrogenation mechanism [86]. An HO-like mechanism with Mo(II) or W(II) hydrides and E = H^+ in Fig. 3 was proposed. Recently, examples based on ruthenium have appeared.



Scheme 4. The hydrogenation of iminium ions catalyzed by Ru(H)(C_5H_5)((*S*,*S*)-chiraphos), an HO mechanism [87].



Scheme 5. A general scheme for the H_2 hydrogenation of polar bonds catalyzed by ruthenium catalysts where the hydride addition to the substrate in the outer coordination sphere is assisted by an ancillary ligand (HOL).

Scheme 4 shows the mechanism proposed for the slow asymmetric hydrogenation of iminium ions catalyzed by the complex RuH(C_5H_5)((*S*,*S*)-chirophos) in CH_2Cl_2 at 20 °C (2 days, 57–80% yield, 35–60% e.e. (*R*)) [87]. The relatively high hydride affinity of the iminium ion permits the outer sphere hydride transfer reaction. The low pK_a of the dihydrogen ligand [88] ensures that the hydride is regenerated by the intermolecular heterolytic splitting by reaction with the amine product of hydride transfer.

A second example is the hydrogenolysis of the trimethylsilyl enol of 2-cyclohexen-1-one catalyzed by the acidic dihydrogen complex [RuCl(H_2)($PPh_2CH_2CH_2PPh_2$)$_2$]OTf [89]. In this case outer sphere proton transfer from the dihydrogen creates the hydride complex *trans*-RuHCl($PPh_2CH_2CH_2PPh_2$)$_2$ and causes the cleavage of the Si–O bond to produce cyclohexanone and Me_3SiOTf. The hydride that is produced is then transferred to the outer sphere Me_3SiOTf to produce $[RuCl(PPh_2CH_2CH_2PPh_2)]^+$. This complex then reacts with H_2 and restarts the cycle.

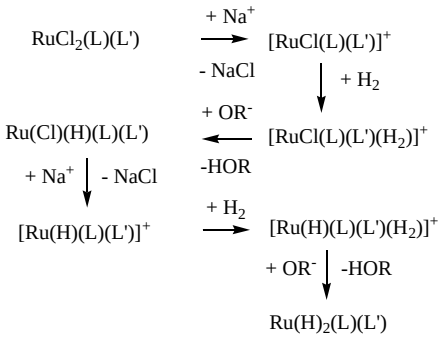
2.2.1. Hydride transfer to the substrate in the outer coordination sphere with ancillary ligand assistance (HOL)

A non-classical outer sphere mechanism for the hydrogenation of polar multiple bonds is shown in Scheme 5. This mechanism involves a hydride on the ruthenium catalyst and a proton on one of the ancillary ligands in a position to form a hydridic–protonic interaction (structure **10**). The substrate **1** coordinates in step **I** by forming an outer sphere interaction between the atoms of its polar multiple bond and the proton and hydride of the complex **11**. This interaction allows for the simultaneous transfer of the hydride and the proton (step **II**) producing the hydrogenated substrate **2** and a ruthenium complex with a vacant coordination site, **12**. This 16-electron ruthenium center is usually stabilized by π-donation from the deprotonated ligand into the empty d-orbital. Hydrogen gas can then coordinate at this open site (**III**) producing a dihydrogen complex intermediate or transition state **13**. The dihydrogen ligand heterolytically cleaves in step **IV** to reform the original hydride complex **10**. We will consider two main cycles of this type, one involving an NH group on the ancillary ligand and one involving an OH group.

2.2.2. Hydride catalysts that exploit an NH group on the ligand (the "NH effect") in an HOL mechanism

As mentioned in Section 1.1, Noyori's group discovered the "N–H" effect when they found that the addition of diamines such as ethylenediamine to $RuCl_2(PPh_3)_3$ and base in *i*PrOH, greatly increased in the activity of the system toward the catalytic H_2 hydrogenation of ketones [8,90]. Diamines without NH groups such as $NMe_2CH_2CH_2NMe_2$ are ineffective. Similarly $RuCl_2$(diphosphine)(diamine) systems with chiral diphosphines such as (*R*)-binap, when matched with chiral primary diamines such as (*R*,*R*)-$NH_2CHPhCHPhNH_2$ ((*R*,*R*)-dpen = (*R*,*R*)-1,2-diphenylethylenediamine) or (*R*,*R*)-$(NH_2)_2C_6H_{10}$ ((*R*,*R*)-dach = (*R*,*R*)-1,2-diaminocyclohexane), are also extremely active and enantioselective catalysts for the hydrogenation of a wide variety of ketones [6,8,91–112] and imines [102,113]. Hydrides of the type *trans*-RuHX(diphosphine)(diamine), X = H, Cl, or OR, were thought to be the active catalysts but at first little direct evidence for hydrides was provided [6,8,91,99,114–117]. It was recognized that at least two equivalents of base (NaO*i*Pr or NaO*t*Bu) in isopropanol were required to generate the active catalyst from the $RuCl_2$(diamine)(diphosphine) precatalyst [8]. Therefore, the formation of a dihydride would be logical based on the precedent that dihydrides are produced by two successive loss of chloride, coordination of dihydrogen, and deprotonation by a strong base in $RuCl_2$(diphosphine)$_2$ systems (see Scheme 6, diphosphine = $PR_2CH_2CH_2PR_2$, R = Et, Ph) [118].

Diagrams showing the stereochemistry of the reaction between a *trans*-Ru(H)(X)(L)(L′) catalytic species, X = H or Cl and a prochiral ketone have been drawn to explain the enantioselectively with respect to alcohol formation. Cao and Zhang proposed the diagram



Scheme 6. The formation of the dihydride $RuH_2(L)(L')$ via the deprotonation of two successive dihydrogen complexes where $(L)(L') = (diphosphine)_2$ (observed) or (diamine)(diphosphine) (proposed).

shown in Fig. 12(a) to explain the enantioselectivity in producing the (*S*)-alcohol by reaction of prochiral aromatic ketones with a hydride catalyst with L = (2*R*,2′*R*)-bis(diphenylphosphino)-(1*R*,1′*R*)-dicyclopentane (a chiral diphosphine) and L′ = (*R*,*R*)-1,2-diphenylethylenediamine [114]. The proposal was based on a structure suggested by Noyori. Yamakawa et al. proposed Fig. 12(b) to demonstrate why carbonyl reductions are so efficient while C=C bonds are not touched [115]. Noyori's group had previously shown that a substructure on octahedral Ru(II) with the stereochemistry fac-$RuH(NH_2\text{-R-}NH_2)$, where R is a linker group, was needed for efficient, enantioselective hydrogenation. In this case, they postulate that after hydride and proton transfer from this catalyst to the ketone, there is formation of an amido–amine complex $RuX(NH\text{-R-}NH_2)(PR_3)_2$ where $(PR_3)_2$ represents two monodentate or one bidentate phosphine ligand. This complex reacts with dihydrogen as in Scheme 5 to regenerate the hydride catalyst $RuHX(NH_2\text{-R-}NH_2)(PR_3)_2$. Abdur-Rashid et al. used Fig. 12(c) to explain the production of (*S*)-aromatic alcohols by *trans*-dihydride complexes. These were proposed to be the active catalysts in Noyori's systems with (*R*)-binap and matched chiral (*R*,*R*)-diamines [119]. The effective diamines have equatorial substituents that lock the five-membered Ru–N–C–C–N chelate ring and position one axial NH on each side of the (usually) C_2-symmetrical catalysts. The OL hydride addition to the ketone leads to only the (*S*)-alcohol when the large group on the ketone avoids the bulky binap side of the dihydride catalyst.

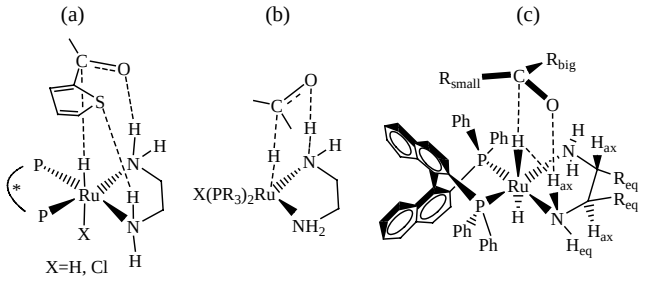
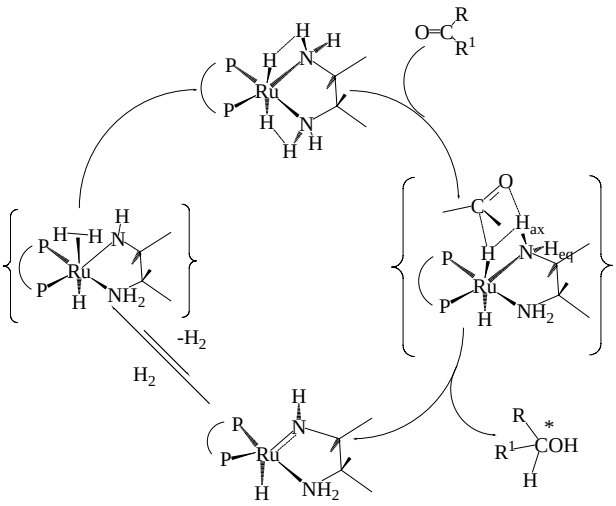


Fig. 12. Proposed structures of the transitions states for H^+/H^- transfer that determine the enantioselectivity of the ketone reduction: (a) [114]; (b) [115]; (c) [119].

Hartmann and Chen have provided evidence that the nature of the cation with the alkoxide base is important in the Noyori $RuCl_2$((*S*)-binap)((*S*,*S*)-dpen)/base/isopropanol system for ketone hydrogenation [117]. The potassium ion is found to be optimum for catalyst activity. They suggest that the structures of the *trans*-dihydride RuH_2((*S*)-binap)((*S*,*S*)-dpen) and the corresponding amido–amine complex produced by hydrogen transfer to the ketone have a natural binding site for K^+ and that this ionic electrophile can assist in the activation of the ketone to hydride attack as shown in Fig. 3 and in the splitting of dihydrogen by positioning the alkoxide for an efficient deprotonation reaction.

Our lab [47,48,119] obtained evidence for the hydrides in the catalytic cycle for these diamine systems and proposed the mechanism shown in Scheme 7. The diamine complex *trans*-RuH_2((*R*)-binap)(tmen), tmen = $NH_2CMe_2CMe_2NH_2$ is an active catalyst for the hydrogenation of prochiral ketones to chiral alcohols in benzene without added base or other additives [119] (Table 3, entry 13). The complex *trans*-RuHCl((*R*)-binap)(tmen) is not a catalyst but is a precursor to the dihydride catalyst by reaction with hydrogen and base as indicated in Scheme 6.

The *trans*-dihydride is an octahedral Ru(II) complex containing chelating diphosphine and diamine ligands and is completely characterized by NMR, IR and single crystal X-ray diffraction [119]. The protons on the diamine allow for the hydridic–protonic interaction shown in Scheme 7 and observed in the structure with aligned Ru–H and NH groups on each side of the molecule with H ··· H distances of about 2.3 Å (Fig. 13). The hydrides have enhanced reactivity due to their mutually *trans* configuration (see Section 1.3).



Scheme 7. The hydrogenation of ketones catalyzed by *trans*-RuH_2((*R*)-binap)(tmen) and $RuH(NHCMe_2CMe_2NH_2)$((*R*)-binap) in benzene.

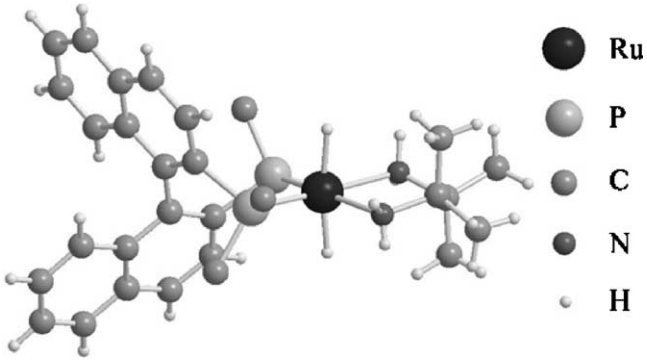


Fig. 13. The structure of *trans*-RuH_2((*R*)-binap)($NH_2CMe_2CMe_2NH_2$) as determined by single crystal X-ray diffraction [119]. Atoms on the binap phenyl rings have been removed for clarity (structure RAMGER from the CCDC [67]).

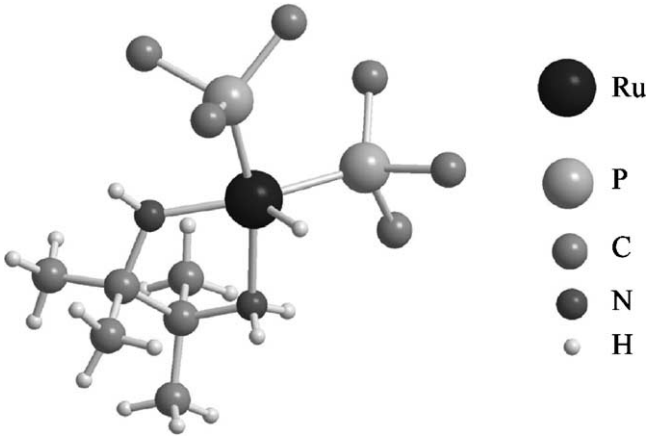


Fig. 14. The structure of $RuH(NHCMe_2CMe_2NH_2)(PPh_3)_2$ as determined by single crystal X-ray diffraction. Atoms on the phenyl rings have been removed for clarity (structure XUPNAX from the CCDC).

The ketone is proposed to react with this dihydride by accepting a hydrogen bond from the axial NH on the diamine and then receiving both the hydride from the metal and the proton from the ligand in a concerted fashion according to the OL mechanism (Fig. 3). Calculations on the reaction of the model complex *trans*-$RuH_2(NH_2CH_2CH_2NH_2)(PH_3)_2$ with acetone show that this is a very facile, low activation energy process [47]. In this way, the amido–amine complex $RuH(NHCMe_2CMe_2NH_2)$((*R*)-binap) is produced as in Scheme 7. The ease of the reaction is confirmed by the observation of the fast reaction between the dihydride and acetophenone to give the amido–amine complex (Table 2, entry 7). This complex has been isolated and characterized by ^1H and ^{31}P NMR and IR spectroscopy and was found to react with hydrogen gas to give back RuH_2((*R*)-binap)(tmen) thus completing a turn-over of the cycle in Scheme 7 [119]. The reaction of the dihydride with D_2 produces H_2, HD, and incorporates deuterium into the hydride and amino proton positions.

The rate law for the hydrogenation of acetophenone catalyzed by this dihydride was determined by monitoring the rate of the reaction as a function of catalyst, ketone and hydrogen concentrations and is given by Eq. (12) where $k = 3.3\,M^{-1}\,s^{-1}$ at 20 °C:

$$\text{rate} = k[\text{Ru}][\text{H}_2] \quad (12)$$

The rate law indicates that the addition of dihydrogen to the amido–amine complex $RuH(NHCMe_2CMe_2NH_2)$((*R*)-binap) is the turn-over-limiting step in the catalytic cycle [47]. The negative entropy of activation of $-23\,cal\,mol^{-1}\,K^{-1}$ also supports this conclusion. DFT calculations actually predicted the finding that the heterolytic splitting of dihydrogen would have the highest activation energy of the steps in the cycle of Scheme 7 before these measurements were made [47]. Noyori and Okhuma [8] also had reported that this step was likely to be rate determining because of the sensitivity of the hydrogenation rate of their catalysts to the hydrogen pressure.

The first structural evidence for an amido–amine hydride complex like the one of Scheme 7, was obtained from crystals of the analogous triphenylphosphine complex, $RuH(NHCMe_2CMe_2NH_2)(PPh_3)_2$ (Fig. 14) [47].

The geometry at the metal is between that of a distorted trigonal bipyramid with axial amino and PPh_3 donors and that of a distorted square pyramid with the hydride in the apical position. The amido nitrogen is trigonal planar and has a shorter N–Ru distance than that of the amino nitrogen. This is evidence for $p\pi(N) \rightarrow d\pi(Ru)$ bonding in the Ru=N bond. The structure allows dihydrogen addition approximately *trans* to the hydride with minimal structural reorganization. The coordination of dihydrogen occurs at the expense of the loss of the Ru–N π-bonding and this accounts for part of the barrier to dihydrogen activation. Coordination causes the dihydrogen to become acidic and the amido nitrogen to become pyramidal and basic thus initiating the heterolytic splitting of the H–H bond. The amido-amine complex $RuH(NHCMe_2CMe_2NH_2)(PPh_3)_2$ is a very active catalyst for ketone hydrogenation and its rate law for the hydrogenation of acetophenone is Eq. (12) with $k = 115\,M^{-1}\,s^{-1}$.

The complex $RuH(HCO_2)(PPh_3)_2$(tmen) was synthesized to model aspects of the transition state for the step where the H^+/H^- equivalents transfer the ketone. The X-ray crystal structure shows that the formate hydrogen bonds to an axial NH and the carbon of the formate is positioned over the ruthenium via the Ru–O bond just as the respective atoms of a ketone are positioned in the transition state shown in Fig. 12(c) [47].

Some reactions of the amido–amine and dihydride catalysts with ketones and alcohols under Ar were also investigated. Evidence was obtained by use of ^1H and ^{31}P NMR studies for the reversible addition of alcohols to the amido–amine complex $RuH(NHCMe_2CMe_2NH_2)$((*R*)-binap) in C_6D_6 to give first alcohol adducts *trans*-$RuH(NHCMe_2CMe_2NH_2)(OHR)$((*R*)-binap) and then alkox-

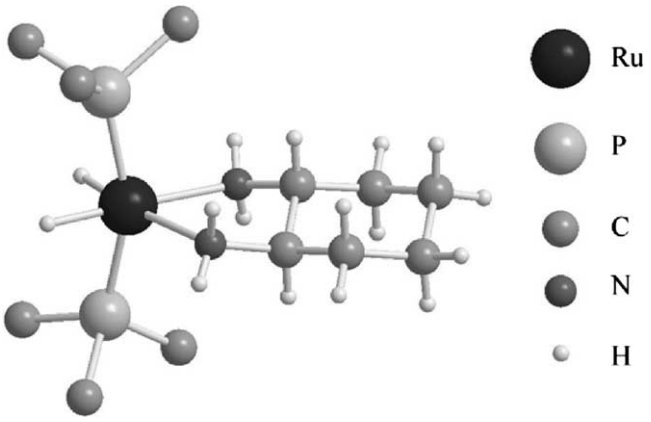


Fig. 15. The structure of *cis*,*trans*-$RuH_2(PPh_3)_2$((*R*,*R*)-dach). There are no RuH···HN hydridic protonic interactions. Atoms of the phenyl rings have been removed for clarity (structure WIZHES from the CCDC).

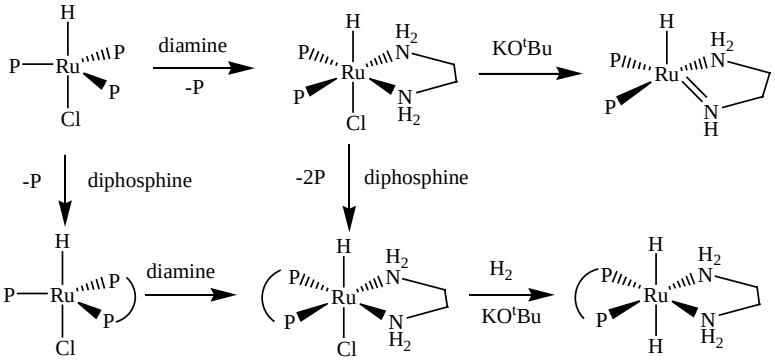
ide complexes *trans*-RuH(OR)((*R*)-binap)(tmen). The dihydride *trans*-RuH_2((*R*)-binap)(tmen) also reacts with an excess of alcohol in the absence of base under Ar to eliminate H_2 and give these adducts that are in equilibrium with the amido–amine complexes and difficult to isolate. Since the amido–amine/alkoxide complex equilibrium is reversible, the alkoxide complexes can serve as precatalysts, allowing entrance to the cycle of Scheme 7 via the amido–amine complex. The amido–amine complex also reacts with acetophenone under Ar, first to give a ketone adduct, then a coordinated enolate RuH(OCPh=CH_2)((*R*)-binap)(tmen) and finally an interesting decomposition product RuH(η^5-CH_2CPhCHCPhO)((*R*)-binap) formed by an aldol condensation reaction along with diamine elimination from the complex [47]. The RuH(NHCMe$_2$-CMe$_2$NH$_2$)$(PPh_3)_2$ complex undergoes similar reactions with ketones and alcohols.

The isomeric dihydrides *cis*-$(H)_2$,*trans*-$(P)_2$-$RuH_2(PPh_3)_2$((*R*,*R*)-dach), *cis*,*cis*- $RuH_2(PPh_3)_2$((*R*,*R*)-dach), and *trans*,*cis*-$RuH_2(PPh_3)_2$((*R*,*R*)-dach), dach = diaminocyclohexane have also been generated in our lab [46,48]. The *cis*,*trans*-dihydride has been completely characterized including its structure by X-ray diffraction (Fig. 15).

The *cis*-dihydride isomers are precatalysts that can be isolated but it is the very unstable *trans*-dihydride isomer [46] that is the catalyst along with the amido–amine complex RuH((*R*,*R*)-$NHC_6H_{10}NH_2$)$(PPh_3)_2$ for the hydrogenation of ketones and imines without base or solvent according to a similar HOL cycle to the one of Scheme 7. Initially a *cis*-dihydride mechanism had been proposed but we now know that a slow isomerization generates the active species [48]. This is shown by the rates of the stoichiometric reactions of these isomers with acetophenone and the e.e. of the alcohol obtained (Table 2, entries 3–5). The *cis*-H_2,*trans*-P_2 isomer reacts very slowly with acetophenone while the *cis*-H_2,*cis*-P_2 isomers (two diastereomers) react quickly with the ketone to give the alcohol in low e.e. The *trans*-H_2,*cis*-P_2 isomer is generated by reaction of H_2 with the amido–amine complex at $-20\,^{\circ}C$ and reacts with acetophenone to produce (*S*)-1-phenylethanol in approximately the same e.e. as is obtained in the catalytic hydrogenation reactions. The low reactivity of the *cis*, *trans* isomer may be a result of the hydride being situated *trans* to the low *trans* influence nitrogen ligands and the NH not being lined up parallel to the Ru–H bonds in hydridic–protonic bonds.

Many types of hydride precatalysts and catalysts have been prepared by a very flexible method starting with the complex $RuHCl(PPh_3)_3$, as shown in Scheme 8.

The hydride complexes *trans*-RuHCl(diamine)(diphosphine), diamine = (*R*,*R*)-dach, (*R*,*R*)-dpen, diphosphine = (*R*)-binap, (*R*,*R*)-dppach ($PPh_2NHC_6H_{10}NHPPh_2$) have been completely characterized and shown to be active precatalysts in the asymmetric hydrogenation of neat ketones and imines (Table 3, entry 18) in the presence of base [102]. Presumably HOL cycles are involved that are similar to that of Scheme 7. Solutions of the complexes *trans*-RuH_2((*R*)-binap)((*R*,*R*)-dpen) and *trans*-RuH_2((*R*)-binap)((*R*,*R*)-dach) were prepared by reacting the respective complexes *trans*-RuHCl(diphosphine)-(diamine) with the strong base *t*BuN=P(-N=P$(NMe_2)_3)_3$



Scheme 8. Preparation of catalyst precursors of the type RuHCl(diamine)$(PR_3)_2$ and RuHCl(diamine)(diphosphine) and the amido–amine and *trans*-dihydride catalysts (P=PPh_3, diamine = (*R*,*R*)-dach, (*R*,*R*)-dpen, tmen; diphosphine = (*R*)-binap, (*R*,*R*)-dppach [102]).

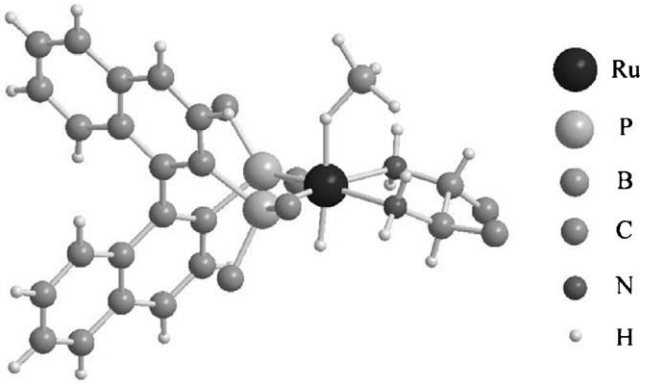


Fig. 16. The structure of *trans*-RuH(η^1-BH_4)((*S*)-tolbinap)((*S*,*S*)-dpen). Atoms on the binap and dpen phenyl rings have been removed for clarity (structure IFOCUB from the CCDC).

in C_6D_6 under 1 atm H_2 [119] and identified by ^{1}H NMR spectroscopy as triplets at −4.5 and −6.1, respectively. The ^{31}P NMR resonances were singlets as expected. The complex *trans*-RuH_2((*R*)-binap)((*R*,*R*)-daipen), daipen = $NH_2C(C_6H_4$-4-OMe$)_2$CH*i*PrNH$_2$ does not have a symmetry axis and therefore produces two triplet hydride resonances in the ^{1}H NMR spectrum at −4.32 and −4.66 ppm (no $^2J_{HH}$ coupling is resolved).

The activity of Noyori's catalysts for asymmetric ketone hydrogenation to high e.e. is amazingly high. The TOF for the precatalyst $Ru(Cl)_2$((*S*)-tolbinap)((*S*,*S*)-dpen) in the presence of base at 30 °C, 45 atm H_2 is 2×10^5 h^{-1} [8] (Table 3, entry 14). In order to understand the action of this catalyst, Noyori's group has prepared the related hydride precatalysts *trans*-RuH(η^1-BH_4)(diphosphine)(1,2-diamine), diphosphine = (*S*)-tolbinap, (*S*)-xylbinap, diamine = (*S*,*S*)-dpen, by reaction of the respective dichloride complexes *trans*-$RuCl_2$(diphosphine)(diamine) with $NaBH_4$ [100,101]. These are very active for the asymmetric hydrogenation of ketones in *i*PrOH without added base to chiral alcohols in high enantiopurity. For example (*R*)-phenylethanol in 82% e.e. is produced by hydrogenating acetophenone by use of the tolbinap precatalyst in *i*PrOH in the absence of base with turn-over numbers of about 900 h^{-1} at 30 °C, 4 atm H_2 (Table 3, entry 15). The tolbinap complex was characterized by single crystal X-ray analysis (Fig. 16) as well as by NMR and IR spectra. An interesting feature of the structure is that two of the hydridic hydrogens on the borohydride ligand act as hydrogen bond acceptors from NH groups on each end of the diamine. These non-classical hydrogen bonds are sometimes referred to as dihydrogen bonds [120].

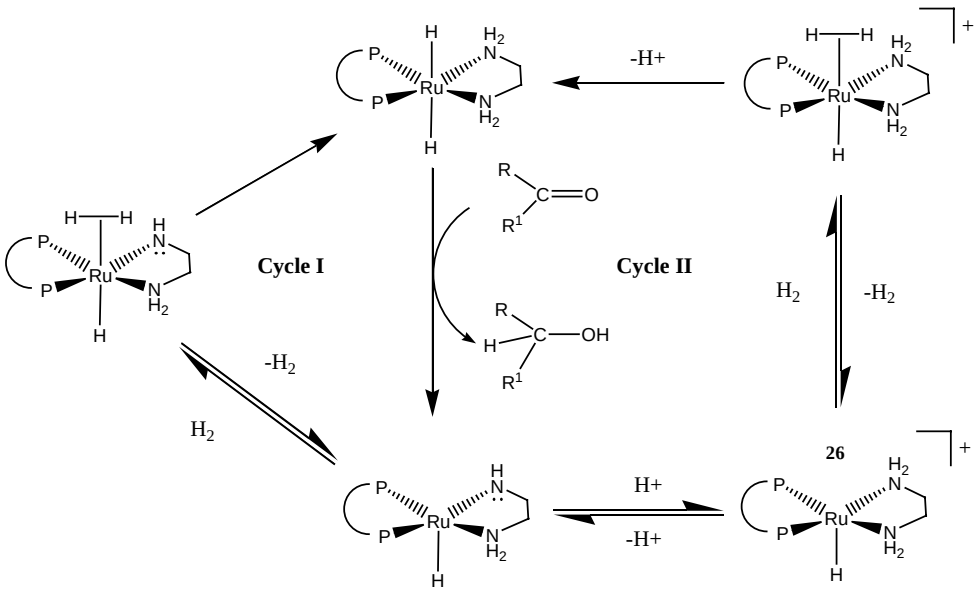
An advantage of these hydride precatalysts is that various base-sensitive ketones can be converted to chiral alcohols without undesired side reactions such as ester exchange, epoxy-ring opening, elimination, and polymerization of ketonic compounds. In addition they maintain the high activity observed previously for the dichloride precatalysts [100]. No transfer hydrogenation of the ketones occurs in the absence of H_2(g) under the mild conditions employed (20 °C).

Sandoval et al. proposed an HOL mechanism that, like Scheme 7, involves the key dihydride catalyst, *trans*-RuH_2((*S*)-tolbinap)((*S*,*S*)-dpen), that forms readily from the borohydride precatalyst [101]. Without a base, the rate is independent of H_2 pressure in the range of 1–16 atm, while in the presence of a base, the reaction rate increases with increasing H_2 pressure. The turn-over number increases dramatically with the optimum amount of base to over 2000 h^{-1} at 30 °C, 4 atm H_2 (Table 3, entry 16). The e.e. of the alcohol product is unaffected by hydrogen pressure, the presence or absence of base, the kind of base and coexisting metallic or organic cations, the nature of the solvent, or the substrate concentrations. This and other evidence indicates that two cycles are operating as shown in Scheme 9. In the absence of base, the intermediate [RuH((*S*)-tolbinap)((*S*,*S*)-dpen)]$^+$ is thought to be produced by protonation of the amido–amine complex as shown in cycle II. ESI-TOFMS and NMR spectroscopy was used to identify this complex.

This cation likely has a high affinity for dihydrogen [17] and reacts to form the postulated intermediate *trans*-[Ru(H)(η^2−H_2)((*S*)-tolbinap)((*S*,*S*)-dpen)]$^+$ of Scheme 9. This dihydrogen complex will be acidic and will be deprotonated to generate the *trans*-dihydride species [32]. In an HOL transfer, the ketone is hydrogenated to the chiral alcohol according the transition state structure shown in Fig. 12(c). In the presence of excess base in 2-propanol or if the solvent is toluene, cycle I is predominant. This is the same one that is observed for the RuH_2((*R*)-binap)(tmen) catalyst described above. At an optimum concentration of base it is postulated that both cycles operate [101].

Isotope effect studies suggest that the deprotonation of coordinated dihydrogen by the amido ligand is the rate-determining step of cycle I. There is a marked decrease in the rate of hydrogenation when it is done under D_2 compared to H_2. This decrease is due to the decrease in acidity upon going from coordinated H_2 to D_2. This evidence is supported by the fact that the decrease in rate is smaller when base is added to the system.

Mikami et al. [110] reported the interesting result that the (*R*)-diamine 3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl ((*R*)-dmdabn) reacts with a racemic mixture of $RuCl_2$((*R*/*S*)-xylbinap)$(dmf)_n$ to give, with complete selectivity, only $RuCl_2$((*R*)-xylbinap)((*R*)-dmdabn). When this mixture is then treated with (*S*,*S*)-dpen, it reacts completely and selectively with the rest of the $RuCl_2$((*S*)-xylbinap)$(dmf)_n$ to give $RuCl_2$((*S*)-xylbinap)((*S*,*S*)-dpen). When this mixture is used to hydrogenate (8 atm H_2) arylketones in *i*PrOH/KOH at 20 °C, the aryl alcohols are obtained in >90% e.e. (*R*). They postulate that the (*S*,*S*)-dpen complex is the catalyst while the dmdabn complex is poisoned with respect to catalysis. Theoretical studies on a cycle similar to that of Scheme 7 suggest that the splitting of dihydrogen is more difficult for the dmdabn-containing catalyst than for a similar dpen-containing catalyst.



Scheme 9. A mechanism for the hydrogenation of ketones catalyzed by the *trans*-RuXY((*S*)-tolbinap)((*S*,*S*)-dpen) system [101]. Cycle I involves neutral complexes and applies when catalysis is performed with 2-PrOH/base or in aprotic solvents. Cycle II involves cationic intermediates when the medium is a protic solvent without added base.

The complexes *trans*-$RuCl_2$(P-NHcyNH-P), P-NHcy-NH-P $= PPh_2(o\text{-}C_6H_4)CH_2NH\text{-}C_6H_{10}\text{-}NHCH_2(o\text{-}C_6H_4)\text{-}PPh_2$ (refer to Fig. 17(b)) and $RuCl_2$(P-NH$(CH_2)_2$NH-P), respectively, are active transfer hydrogenation catalysts for ketones in basic *i*PrOH, presumably by the TOL mechanism (see below). Recently, Rautenstrauch's group and our group [121] reported that these complexes, as well as the corresponding hydride *trans*-RuHCl(P-NHcyNH-P) (Fig. 17), are very active ketone hydrogenation catalysts in the presence of base in *i*PrOH (Table 3, entry 17) or benzene and less active catalysts for their transfer hydrogenation (see TOL cycles below). The hydride complex is prepared by reaction of the tetradentate ligand with $RuHCl(PPh_3)_3$ and exists as isomers according to the stereochemistry of the nitrogen donors and the position of the NH groups. One isomer is converted to the other with a catalytic amount of the base DBU.

The rate law for the hydrogenation of acetophenone catalyzed by the hydride complex in benzene or basic *i*PrOH was determined to be that of Eq. (13) where $k = 130$ and $K = 16\,M^{-1}$ in benzene and $k = 1230\,M^{-1}$ and $K = 1.2\,M^{-1}$ in *i*PrOH:

$$\text{rate} = \frac{k[\text{Ru}^{\text{tot}}][\text{H}_2]}{1 + K[\text{acetophenone}]} \tag{13}$$

This was interpreted as a pre-equilibrium between the amido–amine complex (Eq. (14)) and the ketone and a turn-over-limiting addition of H_2 to the amido–amine complex (Eq. (15)). These two processes compete with each other and so an inhibition by the ketone is observed. The dihydride produced, probably a *trans*-dihydride, reacts rapidly with the acetophenone to produce 1-phenylethanol in low e.e. (20–25% *R*) (Eq. (16)):

$$\text{RuH(P-NcyNH-P)} + \text{PhMeC=O} \rightleftharpoons \text{RuH(O=CPhMe)(P-NcyNH-P)} \tag{14}$$

$$\text{RuH(P-NcyNH-P)} + \text{H}_2 \rightarrow \text{RuH}_2\text{(P-NHcyNH-P)} \tag{15}$$

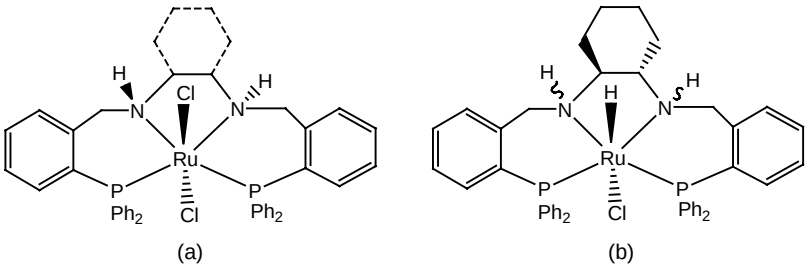
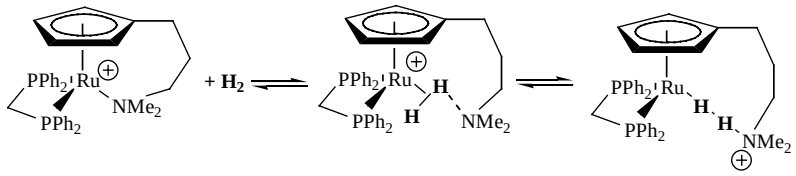


Fig. 17. Structure of hydrogenation precatalysts with tetradentate P-NHR^{1}NH-P ligands. The linking group between the nitrogens can be $R^1 = -CH_2CH_2-$ or $-(S,S)\text{-}C_6H_{10}-$.



Scheme 10. The heterolytic splitting of dihydrogen at Ru(II) to give a hydridic–protonic bond is proposed by Chu et al. [123] in the mechanism of the homogeneous hydrogenation of carbon dioxide.

$$RuH_2(P\text{-}NHcyNH\text{-}P) + PhMeC{=}O \rightarrow RuH(P\text{-}NcyNH\text{-}P) + PhMeHCOH \quad (16)$$

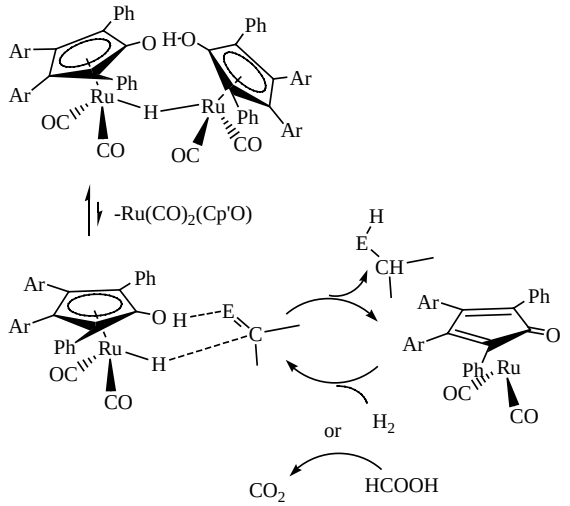
The HOL mechanism allows interesting tandem reactions to be carried out in the same reaction pot. Grubbs' group has devised a tandem olefin metathesis, ketone hydrogenation reaction [122]. First the catalyst $Ru(=CPhH)Cl_2(PCy_3)(imes)$, imes = stable carbene, was used to cross metathesize styrene with methyl vinyl ketone to produce the α,β-unsaturated ketone PhCH=CHCOMe. Then ethylenediamine, NaOH and H_2 (1 atm) was added to convert the metathesis catalyst to the HOL catalyst $RuH(Cl)(en)(PCy_3)(imes)$ (identified by NMR). The carbonyl was smoothly reduced to produce the allyl alcohol at 1 atm H_2, 25 °C.

An early example of the HOL mechanism was proposed by Chu et al. [123]. The Ru complexes shown in Scheme 10 are part of a catalytic cycle for the hydrogenation of CO_2 to HCOOH. The $RuH\cdots HNMe_2R$ interaction produced in the heterolytic splitting of dihydrogen is thought to be important in the H^+/H^- HOL transfer to carbon dioxide. Various mechanisms of this reaction have been explored theoretically [124,125].

Another cyclopentadienyl system displaying high HOL activity toward ketones is generated by mixing $RuCl(C_5Me_5)(cod)$, cod = 1,5-cyclooctadiene, a chelating ligand, L-NH_2, with a primary amine such as $NMe_2CH_2CH_2NH_2$, KOH and the ketone at 1 atm H_2 and 30 °C in *i*PrOH [126]. The active catalysts are thought to be $RuH(C_5Me_5)(L\text{-}NH_2)/Ru(C_5Me_5)(L\text{-}NH)$. The heterolytic splitting of dihydrogen at the amido-L ligand is thought to be assisted by the *i*PrOH solvent. The pair of proposed Ru catalysts is isoelectronic with the $RuH(X\text{-}NH_2)(arene)/Ru(X\text{-}NH)(arene)$ transfer hydrogenation catalysts discussed below in the TOL section. These complexes along with the $RuH(Tp^*)(H_2)_2$ complexes in the HI section are rare examples of ketone hydrogenation catalysts that do not contain phosphine ligands.

2.2.3. Hydrides that use a hydroxyl group on the ligand in the HOL mechanism

The pioneering research by Shvo's group on ruthenium(II) hydrido carbonyl complexes with a cyclopentadienyl group with a hydroxyl group provided early examples of ligand-assisted hydrogenations (see also TOL examples below) [127–130]. This family of catalysts is dimers held together with an $O\cdots H\cdots O$ hydrogen bond and a bridging hydride. There can be various substituents on the cyclopentadienyl ring (aryl or methyl) but they have the general structure shown in Scheme 11. The X-ray structure of the complex with Ar = *p*-C_6H_4Cl has been determined as shown in Fig. 18. These compounds promote the hydrogenation and solvent transfer hydrogenation of aldehydes, ketones and imines [127–136]. Shvo's group originally proposed a HIL mechanism where the substrate coordinates to the ruthenium, presumably with slippage of the cyclopentadienyl ring and is attacked by hydride and the OH proton in a stepwise fashion [130]. More recently, Casey's group has reported deuterium isotope effects on rates of CH and OH



Scheme 11. The HOL and TOL cycles for the hydrogenation of aldehydes, ketones and imines catalyzed by Shvo's catalyst.

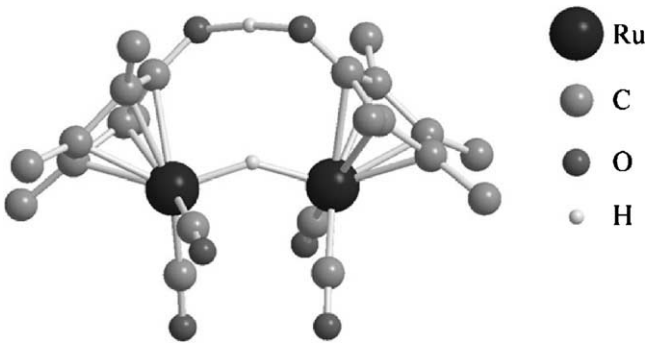


Fig. 18. Structure from X-ray diffraction of the complex $Ru_2(\mu\text{-}H)(\mu\text{-}C_5Ph_2(C_6H_4Cl)_2OH\cdots OC_5Ph_2(C_6H_4Cl)_2)(CO)_4$ where most of the aryl groups have been edited out (structure FAJLIL).

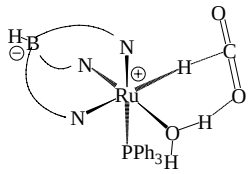


Fig. 19. The HOL of CO_2 catalyzed by RuH(Tp)(OH_2)(PPh_3) in THF.

bond breaking and forming steps that support a concerted HOL mechanism as shown in Scheme 11, at least for the hydrogenation of benzaldehyde [135]. The IR spectrum of the reaction solution displays ν(CO) stretching modes corresponding to the three species in the Scheme 11 [130].

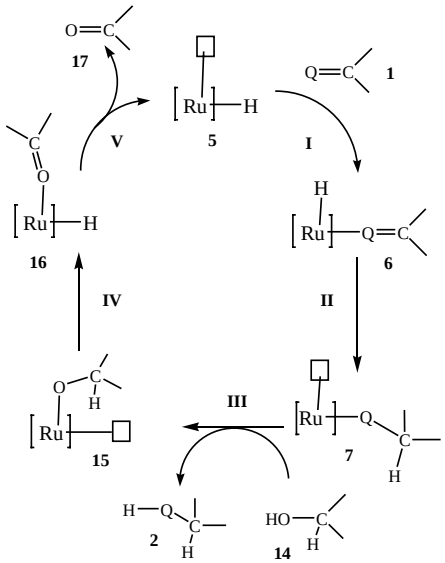
The hydrogenation (25 atm H_2) of CO_2 (25 atm) in the presence of NEt_3 to [NEt_3H][HCO_2] is catalyzed by the complex RuH(Tp)(CH_3CN)(PPh_3), Tp = hydridotris(pyrazolyl)borate, in THF [137]. Water was found to strongly accelerate the turn-over frequency. An HOL transfer to the CO_2 to produce formate as shown in Fig. 19 was supported by theoretical calculations. The complete cycle is very similar to that of Scheme 5 with the splitting of dihydrogen by the proposed intermediate Ru(Tp)(OH)(PPh_3) to regenerate the hydride RuH(Tp)(OH_2)(PPh_3). The labeled complex RuD(Tp)(CH_3CN)(PPh_3) reacts rapidly with CO_2 (10 atm) in wet THF-d_8 at room temperature to produce the formate complexes Ru(η^1-OCDO.H_2O)(Tp)(CH_3CN)(PPh_3) and Ru(η^1-OCDO)(Tp)(OH_2)(PPh_3).

There are reports that the addition of alcohols and amines to the catalyst systems $RuX_2(PMe_3)_4$ (X = Cl, OAc, H) in sub critical CO_2/solvent causes the acceleration of hydrogenation of CO_2 to formic acid [138–140]. These additives might coordinate to the Ru and promote an HOL or HIL addition to the CO_2.

3. Homogeneous transfer hydrogenation of substrates with polar bonds (T mechanisms)

The transfer hydrogenation and asymmetric hydrogenation of ketones and imines is a useful protocol in organic synthesis [5,12,13,15,95,141,142]. Many ruthenium complexes have proven to be catalysts in these reactions and several contain hydrides (Tables 4 and 5). The general catalytic chemistry of ruthenium including that of $RuH_2(PPh_3)_4$ as well as other ruthenium hydrides has been reviewed by Naota et al. in 1998 [13]. This included their use in catalytic hydrogenation and transfer hydrogenation. Transfer hydrogenations have also been discussed in a book chapter [143].

A variety of mechanisms have been suggested for these reactions but they can be classified, in many cases somewhat arbitrarily, as involving a hydride transfer to the coordinated substrate, mechanism TI, or a hydride transfer to a second coordination sphere substrate, TO. Tables 4 and 5



Scheme 12. The inner sphere transfer hydrogenation mechanism (TI).

list representative conditions for the hydrogenation of C=O bonds and C=N bonds, respectively, by some of the TI and TO catalysts reviewed here. The turn-over frequency (TOF in h^{-1}) is estimated as decribed above and is usually an approximate value.

3.1. Hydride transfer to the substrate in the primary or inner coordination sphere (TI)

A commonly proposed mechanism for transition metal TI catalysts is shown in Scheme 12 [115,141]. The right hand side of the cycle is the same as that of the HI mechanism (Scheme 3). A complex with a hydride and a vacant site is required (**5**). The unsaturated substrate coordinates in step **I** and the hydride adds to the beta position in step **II.** The hydrogen transfer agent releases the coordinated alkoxide or amide by protonation (**III)** and then delivers a hydride to the metal by β-hydride elimination (**IV**). Elimination of the oxidized hydrogen donor (**V**) completes the cycle. The few instances of the observation of ruthenium hydride species that might be in the cycle will be discussed.

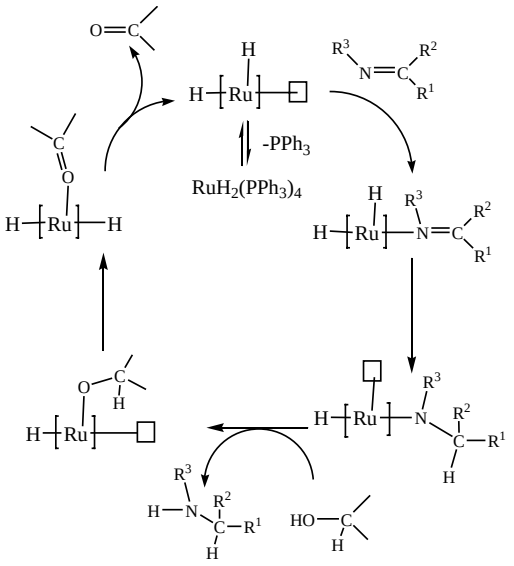
The work of Mizushima et al. [44] will be used to illustrate this cycle for ruthenium (Scheme 13). They showed that the complex *cis*-Ru($H)_2(PPh_3)_4$ is an active precatalyst for the transfer hydrogenation from 2-propanol to ketones and imines [44,144]. Table 5, entries 1–3 lists the conditions for selected reactions. The same activity for the reduction of the imine $PhCH_2N$=CMePh by 2-propanol catalyzed by the dihydride is observed whether or not KOH is added. The well-known transfer hydrogenation catalyst $RuCl_2(PPh_3)_3$ is inactive in the absence of a base.

Scheme 13 is an adaptation of the mechanism that they proposed for the imine reduction [44]. The ligands around the metal in the species in the cycle are not identified. They assume that a PPh_3 dissociates from the precatalyst to give

Table 4
Representative conditions for the transfer hydrogenation of aldehydes and ketones (aromatic and aliphatic) to the saturated products

	Precatalyst (Ru)	Substrate (S)	H donor (DH_2)	Additives (A)	Ru:S:DH_2:A	Solvent	Conversion (%)	Time (h)	Temperature (°C)	TOF (h^{-1})	Cycle	Reference
1	$Ru(H)_2(H_2)(PPh_3)_3$	4-Methylcyclo-hexanone	*i*PrOH		1:100:300	*i*PrOH	91	1	25	91	TI	[153]
2	$RuH_2(PPh_3)_4$	4-Methylcyclo-hexanone	*i*PrOH		1:100:300	*i*PrOH	33	24	25	1	TI	[153]
3	$RuH_2(PPh_3)_4$	PhMeC=O	*i*PrOH		1:200:neat	*i*PrOH	93	3	85	62	TI	[44]
4	$RuH_2(PPh_3)_4$	Hexanal	$PhCH_2OH$			C_6H_5Br			80	30	TI	[40]
5	$RuCl_2(PPh_3)_3$	PhMeC=O	*i*PrOH		1:200:neat	*i*PrOH	0	3	85	0	TI	[44]
6	$RuCl_2(PPh_3)_3$	Cyclohexanone	*i*PrOH	NaOH	1:1000:neat:24	*i*PrOH	89	1	82	1800	TI	[219]
7	$RuHCl(PPh_3)_3$	PhMeC=O	HCOOH			PhMeC=O/HCOOH	46	3	125		TI	[81]
8	$[RuH(H_2)\{P(CH_2CH_2PPh_2)_3\}]BPh_4$	PhMeC=O	*i*PrOH		1:250:12000	THF	96	5	60	50	TI	[160]
9	$[RuH(H_2)\{P(CH_2CH_2PPh_2)_3\}]BPh_4$	Cyclohexanone	*i*PrOH		1:250:12000	THF	100	1	60	250	TI	[160]
10	$RuH_2(CO)(PPh_3)_3$	PhMeC=O	HCOOH			PhMeC=O/HCOOH	28	3	125		TI	[81]
11	$RuHCl(CO)(PPh_3)_3$	PhHC=O	HCOOH		1:760:1760	PhHC=O/HCOOH	47	3	Reflux	280	TI	[220]
12	$RuHCl(CO)(PPh_3)_3$	PhHC=O	HCOOH		1:760:1760	PhHC=O/HCOOH	23	0.27	mw[a]	860	TI	[220]
13	$Ru_4H_4(CO)_8((-)\text{-diop})_2$	PhMeC=O	*i*PrOH		Ru:1:2, [Ru] 1 mM	PhMeC=O/*i*PrOH	37	111	120		TI	[76]
14	$Ru_4H_4(CO)_8((-)\text{-diop})_2$	PhMeC=O	*i*PrOH	NaO*i*Pr	Ru:1:2, [Ru] 1 mM	PhMeC=O/*i*PrOH	67	24	120		TI	[76]
15	$[Ru_4H_3(CO)_{12}]^-$	EtMeC=O	*i*PrOH		1:100, [Ru] 1 mM	*i*PrOH	95	6	82	16	TI	[171]
16	RuH(OTf)(bpzm)(cod)	Cyclohexanone	*i*PrOH	NaOH	1:2100:neat:10	*i*PrOH		3	80	880	TI	[166]
17	RuH(Tp*)(cod)	PhMeC=O	*i*PrOH	NaOH	1:500:neat:500	*i*PrOH			70	30	TI	[75]
18	RuH(Tp*)(cod)	Cyclohexanone	*i*PrOH	NaOH	1:500:neat:500	*i*PrOH	95	1.7	70	400	TI	[75]
19	RuH(Tp*)$(H_2)_2$	Cyclohexanone	*i*PrOH	NaOH	1:500:neat:500	*i*PrOH	95	3.7	70	200	TI	[75]
20	Ru(pcp)(OTf)(PPh_3)	Cyclohexanone	*i*PrOH	KOH	1:1000:neat:20	*i*PrOH			82	27,000	TI	[167]
21	$RuCl_2(PPh_3)$(oxferphos), see Fig. 20	PhMeC=O	*i*PrOH	NaO*i*Pr	1:200:neat:4	*i*PrOH	94 (>99% e.e.)	2	20	100	TI	[165]
22	$[Ru(C_5H_5)(NCMe)(pn)]CF_3SO_3$	PhMeC=O	*i*PrOH	NaO*i*Pr	1:200:neat:2	*i*PrOH	99	24	25	8	TI	[164]
23	$[Ru(C_5H_5)(NCMe)((R)\text{-ppfa})]CF_3SO_3$	PhMeC=O	*i*PrOH	NaO*i*Pr	1:200:neat:2	*i*PrOH	<5 (0 e.e.)	2.5	82	80	TI	[164]
24	$RuCl_2(Lpr)(PPh_3)$	PhMeC=O	*i*PrOH	KOH	1:100:neat:1.5	*i*PrOH	85	72	83	1.2	TI	[170]
25	$RuCl_2\{PPh_2(C_6H_4SO_3Na)\}_2$	PhHC=O	NaO_2CH	$PPh_2(C_6H_4SO_3Na)$	1:100:excess:10	H_2O/aldehyde	99.5	1.5	80	67	TI	[163]
26	RuH(NHCOMe)(OH*i*Pr)$(PCy_3)_2(CO)$	PhMeC=O	*i*PrOH		1:200	*i*PrOH	>95	6	80	32	TIL	[172]
27	$[Ru(C_6Me_6)(bpy)(OH_2)](PF_6)_2$	Cyclohexanone	NaO_2CH		1:200:6000	H_2O, pH 4	99	4	70	98	TO	[173]
28	$[Ru(C_6Me_6)(bpy)(OH_2)](PF_6)_2$	$(NaSO_3\text{-}4\text{-}C_6H_4)MeC=O$	NaO_2CH		1:200:6000	H_2O, pH 4	98	3	70	103	TO	[173]
29	$[RuCl_2(C_6H_6)]_2$	PhMeC=O	*i*PrOH	$NH_2CH_2CH_2OH$/KOH	1:200:neat:5	*i*PrOH			28	227	TOL	[12]
30	$[RuCl_2(C_6H_6)]_2$	PhMeC=O	*i*PrOH	$NH_2CH_2CH_2NHTs$/KOH	1:200:neat:5	*i*PrOH			28	86	TOL	[12]
31	RuCl((*S*,*S*)-$NH_2CHPhCHPhNTs$)(mesitylene)	PhMeC=O	HCOOH/NEt_3		1:200:neat	HCOOH:NEt_3 = 5:2	99 (98% S)	20	28	10	TOL	[12]
32	$[RuCl_2(C_6H_6)]_2$	*t*BuOOCCH_2COMe	*i*PrOH/KOH	(1*S*,2*R*)-OCHPhCHMeNHC$H_2C_6H_4Ph$	1:100:neat:2	*i*PrOH	99 (67% e.e. S)	2.5	20	46	TOL	[192]
33	$[RuCl_2(p\text{-cymene})]_2$	PhMeC=O	*i*PrOH/KOH	(1*R*,2S)-Aminoindanol	1:400:neat:4	*i*PrOH	72 (91% e.e.)	4	20	72	TOL	[201]
34	$RuCl_2((R,R)\text{-P-NH-cy-NH-P})$	PhMeC=O	*i*PrOH	KO*i*Pr	1:200:neat:0.5	*i*PrOH	91 (97% e.e. S)	25	23	7	TOL	[204]
35	$RuHCl(PPh_3)_3$	Ph*i*PrC=O	HCOOH/NEt_3	Amine of Fig. 28, R = H, Ar = Ph	1:100:neat:5	HCOOH/NEt_3	100 (86% e.e. S)	120	60	0.8	TOL	[206]
36	$Ru_2(\mu\text{-H})(\mu\text{-}C_5Ph_2(C_6H_4OMe)_2OH\cdots OC_5Ph_2(C_6H_4OMe)_2)(CO)_4$	Cyclohexanone	HCOOH	NaO_2CH	1:7200:7200:1400	HCOOH/H_2O/ketone	100	3	100	3800	TOL	[130]

[a] mw: microwave heating.



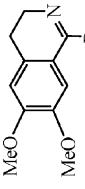
Scheme 13. Hydrogenation of imines by TI catalyzed by *cis*-$Ru(H)_2(PPh_3)_4$ (R^1 = Ph, R^2 = Me, R^3 = CH_2Ph; R^1 = 2-Nap, R^2 = H, R^3 = CH_2Ph; R^1 = Cy, R^2 = Me, R^3 = CH_2Ph; imine = dihydroisoquinoline derivative) [44,144].

a dihydride catalyst since this reaction has been reported by others [43]. The hydride then adds to the imine to give the amido complex. Mizushima et al. provided evidence for this step by running the reaction with deuterium labels on the solvent and catalyst. When the solvent is CD_3OD and the precatalyst is $RuH_2(PPh_3)_4$, hydride is added to the imine $MePhC{=}NCH_2Ph$ and, after protonation, the amine $NpH_2C\text{-}NH(CH_2Ph)$, Np = naphthyl is produced at low conversion [44]. When the precatalyst is $Ru(H)(D)(PPh_3)_4$ in CD_3OD, both hydride and deuteride are added to the imine and both $NpH_2C\text{-}NH(CH_2Ph)$ and $NpH(D)C\text{-}NH(CH_2Ph)$ are produced at low conversion. The observation that the dihydride also catalyzes the isomerization of imines between $R^1R^2C{=}NCH_2Ph$ and $R^1R^2HCN{=}CHPh$ is also consistent with an intermediate where a ruthenium hydride has added across the C=N bond followed by β-hydride elimination [25].

The last steps in Scheme 13 have not been detected but are reasonable based on precedents in the literature. The amido complex is thought to react with 2-propanol to produce an alkoxide complex and the product amine. A stoichiometric reaction of this type has been observed by Bryndza et al. where the ruthenium amido complex $Ru(C_5Me_5)(NHPh)(PMe_3)_2$ reacts with MeOH to produce the alkoxide $Ru(C_5Me_5)(OMe)(PMe_3)_2$ [145]. The hydride complex is then regenerated by β-hydride elimination from the alkoxide complex, a commonly observed reaction in transition metal chemistry [146–152].

This same catalyst system works for the TI of ketones as well in the absence of base (Table 4, entries 2–4). For example, acetophenone is reduced by isopropanol to 1-phenylethanol at 62 turn-over per hour at 82 °C when the dihydride catalyst is present [44]. A similar cycle could be

Table 5
Representative conditions for the transfer hydrogenation of imines

	Precatalyst (Ru)	Substrate (S)	H donor (DH_2)	Additives (A)	Ru:S:DH_2:A	Solvent	Conversion (%)	Time (h)	Temperature (°C)	T.O.F. (h^{-1})	Proposed cycle	Reference
1	$RuH_2(PPh_3)_4$	$PhMeC{=}NCH_2Ph$	*i*PrOH		1:200:neat	*i*PrOH	89	18	85	10	TI	[44]
2	$RuH_2(PPh_3)_4$	$PhMeC{=}NCH_2Ph$	*i*PrOH	KOH	1:200:neat:5	*i*PrOH	89	18	85	10	TI	[44]
3	$RuCl_2(PPh_3)_3$	$PhMeC{=}NCH_2Ph$	*i*PrOH		1:50:neat:5	*i*PrOH	0	5	85	0		[44]
4	$Ru_2(\mu\text{-}H)(C_4Ph_4COH\text{-}OCC_4Ph_4)(CO)_4$	PhMeC=NPh	*i*PrOH	H_2O	1:330:8000:160	C_6H_6	97	1.5	70	220	TIL or TOL	[211]
5	RuCl((*S,S*)-$NH_2CHPh\text{-}CHPhNTs$)(*p*-cymene)		HCOOH/NEt_3		1:1000:excess	CH_3CN	97 (94% e.e.)	12	28	81	TOL	[176]

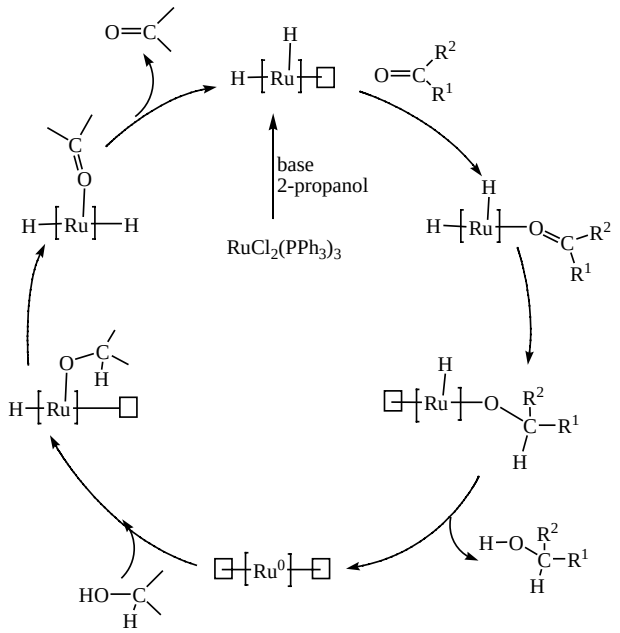
proposed for these reactions. The dihydride $RuH_2(PPh_3)_4$ is a catalyst for the transfer of hydrogen from 2-propanol to the ketone $CF_3(Ph)C{=}O$ in toluene and also a catalyst for its hydrogenation [45]. The stoichiometric reaction of this ketone with $RuH_2(PPh_3)_4$ is reported to produce the alkoxide $RuH(OCH(Ph)CF_3)(PPh_3)_4$, identified by ^1H and $^{31}P\{^1H\}$ NMR and IR spectroscopy. This was shown to react with isopropanol to release the alcohol $HOCH(Ph)CF_3$. These steps support the TI mechanism. The dihydride is selective for the TI of carbonyl over olefin in the α,β-unsaturated compound PhCH=CHCOMe. Only the allylic alcohol PhCH=CHCMe(OH) was detected at 27% conversion [44].

The dihydride $RuH_2(PPh_3)_4$, in the absence of a base, catalyzes the TI of benzonitrile to a mixture of the expected amine benzylamine (6%), the imine benzylidenebenzylamine (20%) and the secondary amine, dibenzylamine (25%) in 51% conversion, Eq. (17) [44]. The first product is thought to be formed by the reduction of PhCN, first to the imine PhCH=NH, and then to the benzylamine $PhCH_2NH_2$. The second product, the benzylidenebenzylamine, is thought to be formed by the transamination of the intermediate imine PhCH=NH with the benzylamine:

$$\mathrm{PhCN + iPrOH \rightarrow PhCH_2NH_2\ (6\%)} \\ \mathrm{+PhCH_2N{=}CHPh\ (25\%) + PhCH_2NHCH_2Ph\ (25\%)} \quad (17)$$

Lin and Zhou [153] reported that the dihydrogen complex $Ru(H)_2(H_2)(PPh_3)_3$ is a much more active catalyst than $RuH_2(PPh_3)_4$ at 25 °C for the transfer hydrogenation of substituted cyclohexanones by transfer from *i*PrOH in the absence of base [153] (Table 4, entries 1–2). However at reflux temperatures, the two catalysts have the same TOF of about 580 h^{-1}. They proposed a catalytic cycle that is identical to the general TI one of Scheme 12 where the active catalyst $RuH_2(PPh_3)_3$ (**5** in Scheme 12) is generated by loss of H_2 from $Ru(H)_2(H_2)(PPh_3)_3$. The cycle consists of coordination of the ketone to give $Ru(H)_2(O{=}CR_2)(PPh_3)_3$ (**6**) migration of the hydride to form the alkoxide $Ru(OCHR_2)(H)(PPh_3)_3$ (**7**) and release of the product by reaction with *i*PrOH to produce the alkoxide $Ru(OCHMe_2)(H)(PPh_3)_3$ (**15**) that undergoes β-hydride elimination to complete the cycle. The reaction of the ketone with the dihydrogen complex at room temperature in C_6D_6 gave ^1H and $^{31}P\{^1H\}$ signals attributed to $RuH_2(PPh_3)_3$ (−17.8 ppm (q); 57.5 ppm (s), respectively) although we note that these resonances are very similar to those of $RuHCl(PPh_3)_3$ and therefore may be due to an alkoxide $RuH(OR)(PPh_3)_3$. The compound assigned to $RuH_2(PPh_3)_3$ was unstable and converted to other hydride-containing compounds.

Pàmies and Bäckvall [15,154] have proposed an alternative mechanism for transfer hydrogenations catalyzed by the dihydride $Ru(H)_2(PPh_3)_3$ that is thought to be formed by the reaction of the precatalyst $RuCl_2(PPh_3)_3$ with base and 2-propanol. Most of the intermediates are similar to those of Scheme 12 (see Scheme 14). The ketone coordinates to



Scheme 14. Hydrogenation of ketones by transfer from 2-propanol catalyzed by $RuCl_2(PPh_3)_3$/base. [Ru] = $Ru(PPh_3)_3$.

ruthenium and the hydride adds as in Scheme 12. At this stage, the alkoxide hydride is reductively eliminated to produce a very reactive $Ru^0(PPh_3)_3$ species or solvated version. This oxidatively adds the O–H bond of the hydrogen donor alcohol to produce the alkoxidehydride complex that leads back to the dihydride catalyst.

This mechanism is consistent with chemical, NMR and isotopic labeling experiments. First it is found that the complexes $RuCl_2(PPh_3)_3$ and $RuHCl(PPh_3)_3$ are ineffective as catalysts for the transfer of hydrogen from cyclopentanol to acetone in the absence of base while $RuH_2(PPh_3)_4$ is an efficient catalyst [42] as also noted by Mizushima et al. Also the monohydride did not react with acetone at 56 °C, whereas the dihydride rapidly ($t_{1/2}$ approx. 5 min) reduced acetone to isopropanol (see Table 2, entry 9). The reaction of $RuCl_2(PPh_3)_3$ with 2-propanol and KOH under Ar produced a broad doublet of triplet hydride resonance at −10.1 ppm (br, dt, J_{PH} = 35, 42 Hz) that was interpreted as belonging to the $Ru(H)_2(PPh_3)_3$ catalyst mentioned above [42]. This resonance may be due to $Ru(H)_2(PPh_3)_4$ since it produces this pseudo doublet of triplets resonance at this chemical shift (actually it is the AA′ part of a second order $AA'XX'Y_2$ pattern). Aranyos et al. did report that the addition of $Ru(H)_2(PPh_3)_4$ increased the intensity of this resonance. The complex $Ru(H)_2(PPh_3)_3(THF)$ was reported by Chaudret et al. [33] and Linn and Halpern [66] to have a somewhat similar hydride resonance, a quartet at −10.3 ppm (J_{PH} = 36 Hz) and Lin and Zhou also obtained this species along with other hydrides by the reaction of cyclohexanone with $Ru(H)_2(H_2)(PPh_3)_3$ in C_6D_6. Aranyos et al. also detected in the ^1H NMR spectrum the broad resonance at −7.0 ppm due to $Ru(H)_2(H_2)(PPh_3)_3$, a dihydrogen com-

plex that is known to efficiently catalyze the transfer hydrogenation (Table 4, entry 1) [153] and the hydrogenation of ketones [66] (Table 3, entry 9).

In order to distinguish between the mechanisms of Scheme 12 and Scheme 14, Pàmies and Bäckvall used a clever isotope labeling method that involves the racemization of (*S*)-alpha–deutero-1-phenylethanol, (*S*)-PhMeDCOH, catalyzed by the $RuCl_2(PPh_3)_3$/base system [154]. The chiral alcohol is oxidized by the catalyst to produce PhMeC=O on the left side of these Schemes while the catalyst transfers hydride or deuteride to the acetophenone on the right side to produce the racemic alcohol *rac*-PhMeDCOH. The monohydride mechanism TI would effectively lead to selective deuterium-transfer from the carbon of the chiral alcohol to the carbon of acetophenone, resulting in the ultimate production of racemic PhMeDCOH. On the other hand, if the oxidative addition of (*S*)-PhMeDCOH occurs as in Scheme 14, both hydride and deuteride will be present on Ru as $Ru(H)(D)(OR)(PPh_3)_3$ and either could add to the carbonyl carbon of acetophenone to result in a nonselective transfer of the isotope, producing both racemic PhMeDCOH and PhMeHCOH. The second result was the one observed, thus supporting the oxidative addition mechanism of Scheme 14 and disproving the usual TI monohydride cycle of Scheme 12. Although the monohydride TI has been ruled out, the scrambling of isotopes does not completely prove the existence of the Ru(0) species in Scheme 14 since a different process might cause this scrambling. Isotope exchange has been observed between a metal-hydride and acidic ligand-deuterium bonds of the type N–D, S–D or O–D. This pathway is suspected of involving η^2-dihydrogen (η^2- HD in this case) intermediates [155–157].

Aranyos et al. reported preliminary DFT calculations on the alkoxide intermediates of the cycle [42]. The geometry of the formaldehyde $RuX(O{=}CH_2)(PH_3)_3$, X = H, Cl and alkoxide $RuX(OCH_3)(PH_3)_3$ model complexes were calculated and it was found that the alkoxide for X = Cl is less stable than that with X = H, perhaps explaining the lack of catalytic activity of $RuHCl(PPh_3)_3$.

The first proposal for a $Ru(0)(PPh_3)_3$ reactive intermediate of the type shown in Scheme 14 was made by Imai et al. in studies of the hydrogenation of certain aldehydes by transfer from hydrogen-donors catalyzed by *cis*-$RuH_2(PPh_3)_4$ in bromobenzene [40,158] (Table 4, entry 4). This dihydride was found to be more active than the carbonyldihydride complex $RuH_2(CO)(PPh_3)_3$ that was in turn a better catalyst precursor than $RuCl_2(PPh_3)_3$. Other solvents were used with similar results. The studies involved a complete rate law study with 2-propanol or benzyl alcohol as the hydrogen donor and C_6H_5Br as the solvent. The rate law showed a first order dependence on hydrogen donor and initial $RuH_2(PPh_3)_4$ concentrations. The rate was found to be independent of added PPh_3. These results were interpreted as a rate determining oxidative addition of the hydrogen donor alcohol to a Ru(0) intermediate according to Scheme 14. The rate law also had an inverse dependence on aldehyde concentration. They found that the aldehydes reacted rapidly, and acetone, more slowly, with *cis*-$RuH_2(PPh_3)_4$ at 20 °C in $CDCl_3$ to give uncharacterized products.

In a second study, Imai et al. [158] reported a mechanistic study of the transfer of hydrogen from aprotic hydrogen donors such as dioxane to aldehydes, especially hexaldehyde catalyzed by *cis*-$RuH_2(PPh_3)_4$. In this case, the rate law suggested that the reaction of the hydrogen donor with a ruthenium species was the turn-over-limiting step. They measured a kinetic isotope effect of 2.0 for the reaction for dioxane vs dioxane-d_8 as the reductant. On this basis, they postulated that the slow step in the cycle was the oxidative addition of a C–H bond of the H-donor by a Ru(0) intermediate of the type $Ru(PPh_3)_3$.

The related complex *cis*-$RuH_2(PMe_3)_4$ also reacts rapidly with aldehydes (Table 2). The reaction with benzaldehyde at −20 °C produces one equivalent of benzyl alcohol that then reacts with the "$Ru(PMe_3)_4$" to produce the alkoxide complex $Ru(OCH_2C_6H_4)(PMe_3)_4HOCH_2Ph$ and other species [41]. It seems that such dihydrides are nucleophilic enough to transfer hydride to aldehydes without phosphine dissociation. At room temperature the complex promotes the Tishchenko coupling of the aldehyde to produce benzylbenzoate. In this case the ruthenium(0) intermediate $Ru(PMe_3)_4$ was invoked to explain this reactivity [41]. In related chemistry Perutz and coworkers have generated Ru(0) species of the type Ru(diphosphine)$_2$ (diphosphine = dmpe, dmpm) by the photochemical elimination of H_2 from the dihydrides $Ru(H)_2$(diphosphine)$_2$ and found that their reactions are extremely fast [159].

Cole-Hamilton and Wilkinson questioned the work of Imai et al. when they found that $RuH_2(PPh_3)_4$ reacts with C_6H_5Br, the solvent of the Imai study, to produce $RuHBr(PPh_3)_3$ [43]. In their hands, the reaction of propionaldehyde, acetone or cyclohexanone with the dihydride gave $Ru(H)_2(CO)(PPh_3)_2$, a product of carbonyl abstraction, as well as other products (Table 2, entry 10). In addition, they stated that the Imai study used a method of preparation of the dihydride that tended to give an impure, greenish, product.

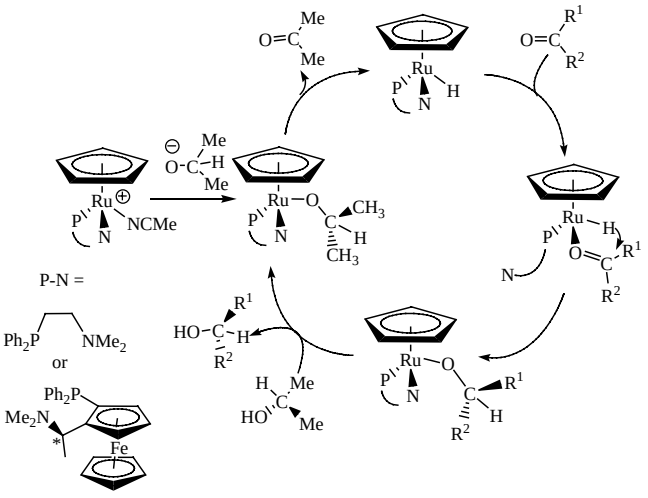
The dihydrogen complex $[Ru(H)(H_2)\{P(CH_2CH_2PPh_2)_3\}]BPh_4$ is an efficient precatalyst for the hydrogenation of ketones to alcohols and unsaturated ketones to the unsaturated alcohols by transfer from *i*PrOH in the absence of base (Table 4, entry 8, 9) [160,161]. Again the cycle of Scheme 12 was proposed where the active catalyst $[Ru(H)\{P(CH_2CH_2PPh_2)_3\}]BPh_4$ is thought to form by loss of H_2 from the dihydrogen complex. The dihydrogen complex $(dppb)(H_2)Ru(\mu\text{-}Cl)_3Ru(dppb)Cl$ is also a transfer hydrogenation catalyst or precatalyst for ketones in *i*PrOH [162].

Watanabe et al. [81] found that the activity of the catalysts for the transfer of hydrogen from formic acid to acetophenone at 125 °C in the neat ketone decreased as $RuCl_2(PPh_3)_3$ > $RuHCl(PPh_3)_3$ (Table 4, entry 7) > $Ru(H)_2(CO)(PPh_3)_3$ (entry 10) > $Ru(H)_2(PPh_3)_4$. They postulated that instead of

the monohydride or dihydride TI mechanisms, the formic acid is catalytically decomposed to H_2 and CO_2 and, in a second step, the H_2 is used to catalytically hydrogenate the ketone. To support this idea, they found that $RuCl_2(PPh_3)_3$ in neat acetophenone is a hydrogenation catalyst, but at 88 atm H_2 pressure and 125 °C.

Sulfonated triphenylphosphine allows the formation of TI catalysts that are active in water [16,163]. Aromatic and aliphatic aldehydes can be reduced to the corresponding alcohols by hydrogen transfer from formate using, as catalysts, water-soluble complexes of Ru(II) meta-monosulfonated triphenylphosphine, $PPh_2(m\text{-}C_6H_4SO_3Na)$, in aq./org. biphasic systems without phase transfer catalysts (Table 4, entry 25). Olefinic double bonds (including those in α,β-unsaturated aldehydes), are not hydrogenated and so valuable allyl alcohols can be prepared in this way. The yellow hydride complex $RuH(O_2CH)\{PPh_2(C_6H_4SO_3Na)\}_3$ was identified as the key intermediate in the processes catalyzed by $RuCl_2(L)_2$ in an excess of phosphine. A hydride resonance at −18.3 ppm was detected in a $CDCl_3$ solution after extraction from the aqueous phase. The presence of the η^2-formate group was verified by IR spectroscopy.

Bidentate ligands containing phosphorus and nitrogen donors (P–N) have proven to be very activating with respect to transfer hydrogenation catalyzed by ruthenium complexes. Complexes of the type $[Ru(C_5H_5)(NCMe)(P\text{–}N)]CF_3SO_3$ with P–N = *N*,*N*-dimethyl-2-diphenylphosphinoethylamine (pn), optically pure ((*R*)-C,S-pl)-2-{1-(*N*,*N*-dimethylamino)ethyl}-1-diphenylphosphinoferrocene ((*R*)-ppfa), and *N*,*N* dimethyl-2-diphenylphosphinoaniline (dbd) as shown in Scheme 15 catalyze the TI of acetophenone in 2-propanol (Table 4, entries 22, 23) [164]. The fact that no e.e. is observed when the chiral ligands are used indicates that the nitrogen end of the chelating ligand is hemilabile and is proposed to be dissociated from the complex during hydride transfer to the ketone (Scheme 15). The low activity of the dbd ligand complexes was attributed to the rigid structure that might not allow for this dissociation. The complex $[Ru(C_5H_5)(PPh_3)(NCMe)_2]CF_3SO_3$ that has more vacant coordination sites is a much more active precatalyst [164].



Scheme 15. TI of ketones catalyzed by complexes $RuH(C_5H_5)(P\text{–}N)$.

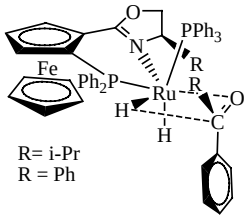


Fig. 20. The proposed structure of the oxazolinylferrocenylphosphine dihydride complex reacting with a prochiral ketone [165].

In contrast, another chiral phosphorus and nitrogen donor ligand oxazolinylferrocenylphosphine (oxferphos) coordinated in the complex $RuCl_2(PPh_3)$(oxferphos) was effective for the asymmetric transfer hydrogenation of alkyl aryl and alkyl methyl ketones in 2-propanol (Table 4, entry 21) [165]. The detection of two ruthenium dihydride species in the catalytic mixture was mentioned in the article but no details were given. Fig. 20 shows the proposed structure of a transition state between ketone and dihydride that explains the enantioselectivity of the hydride addition to the ketone. Thus, acetophenone approaches the complex in such a way to minimize steric interactions among the phenyl group of the ketone, the phenyl groups of two phosphines, and the substituent of the oxazoline ring. The reaction through this transition state results in the formation of the (*R*)-alcohol as observed. This complex also catalyzed the asymmetric oxidation of racemic sec-alcohols with acetone via kinetic resolution to extremely high enantioselectivity (>99.9% e.e.).

Chelating nitrogen ligands have been applied to the transfer hydrogenation of ketones. A complex RuH(OTf)(bpzm)(cod) (bpzm = bis(pyrazol-1-yl)methane, cod = cycloocta-1,5-diene) containing a bidentate nitrogen-donor ligand (Fig. 21) catalyzes the transfer hydrogenation of cyclohexanone by propan-2-ol in the presence of NaOH at 80 °C, with a turn-over rate of 880 h^{-1} (Table 4, entry 16) [166]. The complex RuH(Tp*)(cod) containing the tridentate nitrogen-donor ligand Tp* = hydridotris(3,5-dimethylpyrazolyl)borate was reported to catalyze the transfer hydrogenation of cyclohexanone and acetophenone in 2-propanol in the presence of NaOH (Table 4, entries 17 and 18) [75]. The activity of the catalyst toward cyclohexanone hydrogenation is much greater than that of acetophenone. The bisdihydrogen complex $RuH(Tp^*)(H_2)_2$ in the presence of

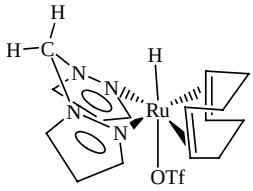


Fig. 21. Structure of RuH(OTf)(bpzm).

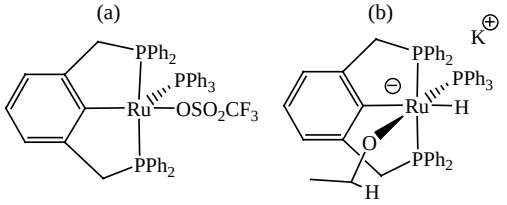


Fig. 22. Structure of Ru(PCP)(OTf)(PPh_3) (a) and the anionic hydride complex (b).

NaOH (Table 4, entry 19) was found to be as active as RuH(Tp*)(cod) in the transfer hydrogenation of cyclohexanone.

The pincer complex Ru(pcp)(OTf)(PPh_3), $pcp^- = [C_6H_3(CH_2PPh_2)_2\text{-}2,6]^-$, $OTf^- = O_3SCF_3^-$ (Fig. 22 (a)) is a very active catalyst for the transfer hydrogenation of cyclohexanone in 2-propanol (Table 4, entry 20) [167]. When this complex is heated to reflux in *i*PrOH/KOH in the absence of a ketone, a hydride species formed. It was assigned to the structure shown on the basis of NMR spectroscopic data (Fig. 22(b)). Other structures are also possible. The complex RuH(pcp)(PPh_3) might also be involved [168].

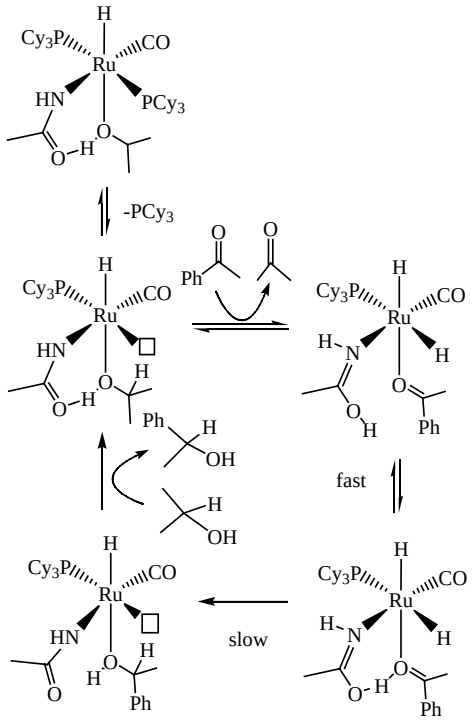
Another very activating tridentate ligand L on ruthenium has P, N and O donors [169]. The complex $RuCl_2(PPh_3)L$ is a very efficient catalyst for the transfer hydrogenation of cyclic ketones and acetophenone (turn-over 118,800 h^{-1}) in basic media. No hydrides have been detected in this case.

The tridentate ligands $PPh_2CH_2CH_2NRCH_2CH_2PPh_2$, R = *n*-Pr (Lpr), *n*-Bu (Lbu), *n*-Hex (Lhex), CH_2Ph (Lbz), were coordinated in the complexes *trans*-$RuCl_2L(PPh_3)$, L = Lpr, Lbu, Lhex, Lbz [170]. The complexes were poor transfer hydrogenation catalysts (Table 4, entry 24) with the activity decreasing as the R group on L increases in size. No hydrides were detected in the reaction.

Another alternative mechanism for hydrogen transfer might involve radical chain processes. Bhaduir et al. [171] found that the anionic hydride carbonyl cluster complex $[Ru_4H_3(CO)_{12}]^-$ catalyzed the transfer of hydrogen from 2-propanol to methylethylketone (Table 4, entry 15) or 2-cyclohexenone at 82 °C. The lack of selectivity of C=O over C=C bond hydrogenation was explained by the presence of radicals. If the 2-propanol that is used as the hydrogen donor is rigorously purified, the solvent transfer hydrogenation of ketones ceased to proceed. When the hydroperoxide HOO*t*Bu was added, the reaction started. They postulate that the ruthenium cluster fragments into paramagnetic compounds that can initiate a radical chain propagated by 2-propoxy radicals and cyclohexenone-derived radicals.

3.1.1. Hydride transfer to the substrate in the inner coordination sphere with ancillary ligand assistance (TIL)

An ruthenium-acetamido complex RuH(NHCOMe)-(OH*i*Pr)$(PCy_3)_2$(CO) was prepared from the reaction of $[RuH(PCy_3)_2(CO)(CH_3CN)_2]BF_4$ with KOH in 2-propanol and completely characterized including a single crystal



Scheme 16. The TIL hydrogenation of acetophenone by transfer from *i*PrOH in the presence of the precatalyst complex RuH(NHCOMe)-(OH*i*Pr)$(PCy_3)_2$(CO) [172].

X-ray diffraction study [172]. There are two triplets –18.3 and −14.3 ppm in the ^1H NMR spectrum for this neutral complex at low temperatures and this is assigned to restricted rotation about the C–N bond resulting in the interconversion of acetamido and iminol tautomers. This complex was found to be an effective precatalyst for the TIL of both aryl- and alkyl-substituted ketones and imines at 80 °C (Table 4, entry 26). The proposed TIL mechanism for the reduction of acetophenone is shown in Scheme 16. The precatalyst is proposed to be activated to the catalyst, the coordinatively unsaturated ruthenium-amido species RuH(NHCOMe)(OH*i*Pr)(PCy_3)(CO), by the dissociation of a PCy_3 ligand. The competitive inhibition by added phosphine provided strong evidence for this. Observation of an inverse deuterium isotope effect supports a stepwise mechanism of proton transfer from iminol to ketone in an unobserved dihydride iminol species and then slow hydride transfer to activate the carbon of the ketone. Displacement of the product 1-phenylethanol by the *i*PrOH begins the cycle again.

3.2. Hydride transfer to the substrate in the outer coordination sphere (TO)

Ogo et al. [173] found that the 2,2′-bipyridine ligand (bpy) promotes TO catalysis in the complex $[Ru(C_6Me_6)(bpy)(OH_2)](PF_6)_2$ in water or water/organic biphasic systems. TOF ranging from 20 to 150 h^{-1} at 70 °C are observed for

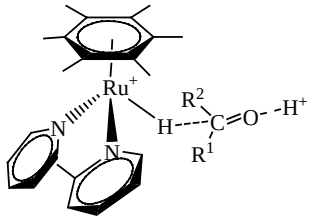
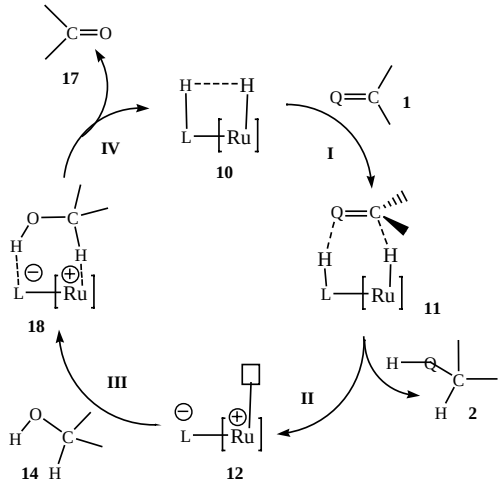


Fig. 23. Acid assistance in the hydride transfer to ketones from $[RuH(bpy)(C_6Me_6)]^+$ [173].

the hydrogenation of water-soluble and water insoluble ketones by transfer from sodium formate (e.g. entries 27–28 in Table 4). The rate of hydrogenation is maximum at pH 4. Two possible intermediates were observed in the catalytic cycle, the formate complex $[Ru(O_2CH)(C_6Me_6)(bpy)]^+$ and the hydride complex $[RuH(C_6Me_6)(bpy)]^+$. The last complex was identified by its ^1H NMR resonance at −7.45 (s). They found that, although the hydride is stable within the pH range of 5 to 9 at temperatures greater than 40 °C, the maximum rate of hydrogenation occurred at pH 4. This was rationalized in terms of acid assistance in the hydride transfer step of the hydrogenation (see Fig. 23). The pK_a of HCOOH is 3.6 and so the rate maximum occurs with the good formate ligand $HCOO^-$ present. The pK_a of the aqua complex $[Ru(C_6Me_6)(bpy)(OH_2)]^{2+}/[Ru(C_6Me_6)(bpy)(OH)]^+$ is 7.3. Therefore, below pH 7.3, the aqua ligand can be displaced by formate while above pH 7.3 the hydroxide complex is present and it is unreactive to formate. This explains the narrow pH range for catalysis.

3.2.1. Hydride transfer to the substrate in the outer coordination sphere with ancillary ligand assistance (TOL)

The discovery by Noyori and coworkers that the ligand can play a crucial role in efficient hydrogen transfer to the unsaturated substrate, and to the catalyst, was a revelation for the strategy of the design of efficient catalysts. The role of the ligand, as shown in outline in Scheme 17, is to (1) activate the carbon of the unsaturated substrate to nucleophilic hydride attack by hydrogen bonding to the oxygen or nitrogen of the substrate, (2) provide a cyclic transition state for H^+/H^- transfer by the correct hyperconjugation with the metal, (3) serve as a source of proton to be transferred along with the hydride from the metal, and (4) to provide a point of interaction for enantioselective recognition of the prochiral substrate. Usually, the substrate is in the second coordination sphere of the catalyst complex and not directly coordinated to the metal.



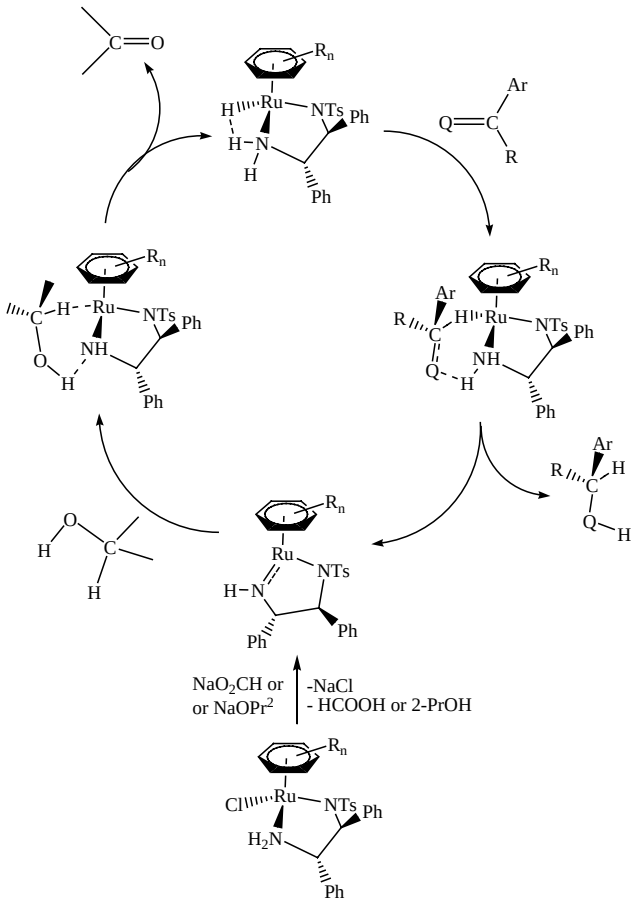
Scheme 17. The transfer hydrogenation mechanism involving a hydrogen on a co-ligand, the TOL mechanism.

Scheme 17 refers to the case of hydrogen transfer from a generic hydrogen source YCHOH to the metal where Y can be R_2 as in 2-propanol or O as in formic acid. We will call it a TOL mechanism where T stands for transfer and L stands for ligand involvement, usually when the substrate is in the second coordination sphere. Steps I and II of Scheme 17 are the same as the ones for the HOL cycle (Scheme 5) where there is a concerted or stepwise transfer of the H^+ from the ligand and H^- from the ruthenium complex to the substrate $R^1R^2C=Q$, $Q=O$, NR^3. This results in the hydrogenated product $R^1R^2CH\text{-}QH$ and the creation of, formally, a 16 electron Ru center. The ruthenium hydride is then thought to be regenerated by a similar transition state structure involving the hydrogen donor RCH_2OH.

3.2.2. Hydride catalysts that exploit a ligand NH (the "NH effect") with a TOL mechanism

A breakthrough in transfer hydrogenation catalysts was Noyori's discovery of the NH effect [12,29,115,116,174,175]. 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, a very active catalyst system is produced (Table 4, entries 29–30). Notably the use of *N*,*N*-dimethylated compounds lead to ruthenium complexes that were totally inactive as catalysts. This was early evidence for the "NH effect" for the hydrogenation of polar bonds.

This discovery led to the development of Noyori's efficient transfer catalysts for the asymmetric hydrogenation of ketones and imines. These are hydride complexes of the type Ru(H)((*S*,*S*)-$H_2NCHRCHRNTs)(\eta^6$-arene) and their dehydrogenated partners of the type Ru((*S*,*S*)-$HNCHRCHRNTs)(\eta^6$-arene). They are generated from the precursor chloride complexes RuCl((*S*,*S*)-$H_2NCHRCHRNTs)(\eta^6$-arene) by reaction with a reductant (formate or 2-propoxide). The reactions are best conducted in a formic acid-triethylamine azeotropic 5:2 mixture with or without an additional solvent. The loss of CO_2 drives the reaction irreversibly to products and thus prevents the metal-catalyzed racemization of the product, the chiral alcohol or amine. This racemization can occur with prolonged exposure of the catalyst to the product solution. Chiral alcohols derived from arylalkylketones and a variety of chiral amines from prochiral imines are obtained in very high e.e. (Table 4, entry 31) [12,29,174,175]. The proposed



Scheme 18. TOL of arylketones catalyzed by RuH($NH_2CHPhCHPhNTs$)(η6-arene) and Ru(NHCHPhCHPhNTs)(η6-arene), arene = C_6H_6, MeC_6H_4iPr, $C_6H_3Me_3$, Ts = $SO_2C_6H_4Me$, Q = O, NR.

mechanism of action of these catalysts for the hydrogenation of ketones and, presumably the hydrogenation of imines, is illustrated in Scheme 18 and provides the prototype for the TOL mechanism of Scheme 17 [12,29,115,116]. The in-coming substrate is oriented in the second coordination sphere by forming a hydrogen bond with the NH hydrogen on the tosylated diamine ligand that is axial with respect to the five-membered Ru–N–C–C–N-ring. The other two points of recognition for chiral induction are proposed to be the hydride (δ^-) to substrate sp^2-carbon (δ^+) contact and a substrate aromatic ring to η^6-ring attractive interaction [116]. Concerted H^-/H^+ transfer produces the alcohol in the (*S*)-configuration and then the hydrido-amine complex is regenerated by reaction with 2-propanol or formic acid. While the η^6-mesitylene ligand on Ru gives a high e.e. for a variety of prochiral ketones, the structure of the sulphonyl group on the diamine and the arene ring have to be adjusted depending on the imine structure to produce a chiral amine in high e.e. [176]. The cyclic imine shown in Table 5, entry 5 can be reduced selectively in the presence of acetone and so for this system, this imine is more reactive than ketones.

The cycle of Scheme 18 is particularly well characterized. The yellow precatalyst complex RuCl($NH_2CHPhCHPhNTs$)

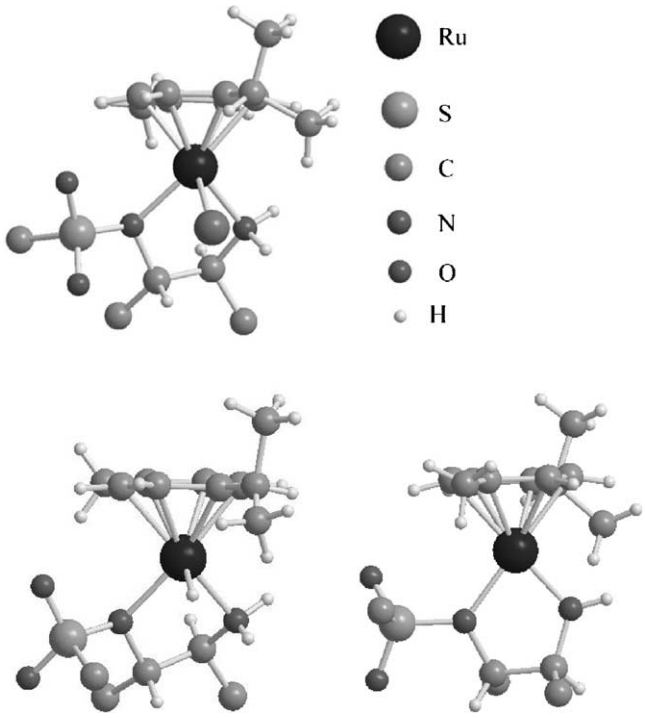


Fig. 24. The structures of RuCl($NH_2CHPhCPhNSO_2C_6H_4Me$)(*p*-cymene), RuH($NH_2CHPhCPhNSO_2C_6H_4Me$)(*p*-cymene) and Ru(NHCHPhCHPh-$NSO_2C_6H_4Me$)(*p*-cymene) with atoms of the aryl rings removed, apart from the ipso carbons (structures TAXFON, RIHFUJ and RIHFOD of the CCDC).

(η^6-cymene) and the catalysts, the yellow amido–amine hydride complex RuH($NH_2CHPhCHPhNTs$)(η^6-cymene), and the purple bis-amido complex Ru(NHCHPhCHPhNTs)(η^6-cymene) have been completely characterized by NMR, IR and X-ray crystallography [29]. The hydride complex has a ^1H NMR singlet at −5.47 ppm. The three structures are shown in Fig. 24. The chloride and hydride complexes have similar Ru(II) d^6, 18 electron, octahedral geometries where the arene ligand is a six-electron donor and occupies three coordination sites. The lone pair on the amido nitrogen causes the nitrogen to be somewhat pyramidal in these two structures. The chiral amido–amine ligand forms a five-membered ring that is locked into the δ configuration by the phenyl substituents alpha to the nitrogens. This locks the configuration of the amino group so that the axial NH is held parallel to the Ru–Cl or Ru–H bond in the respective complexes. There is $RuH^{\delta-\cdots\delta+}HN$ hydridic–protonic [155] (or dihydrogen [177,178]) bonding at a short H···H distance of 2.3 Å. This might explain why only one diastereomer of this complex, both chiral at the ligand and at the Ru, is observed and why H^-/H^+ transfer to the ketone is so efficient. The Ru–H distance was determined to be 1.4(1) Å, shorter than the true value of 1.6 Å because the X-ray experiment typically underestimates element-hydrogen bond lengths. The bis-amido complex has Ru–N distances that are shorter than typical Ru–N single bonds because of $p_\pi(N) \rightarrow d_\pi(Ru)$ dative double bond character. The amido nitrogens are trigonal planar.

The hydride complex was shown to react with acetone quickly to form the purple amido-amido complex and 2-propanol. When the amido-amido complex was treated with isopropanol, it produced acetone and the hydride complex (Table 1, entry 10). The hydride can also be generated by reacting the amido–amido complex with dihydrogen, but only at 80 atm pressure. Therefore, under ambient conditions the hydrogen comes from the solvent and not from H_2 gas. Both complexes were used as catalysts and they showed identical behavior, producing chiral alcohols of the same high e.e. as are produced starting with the chloride precatalyst [29]. The rate law for the transfer of hydrogen from *i*PrOH to acetone-d_6 to produce acetone and $(CD_3)_2CH(OH)$ at 23 °C as determined from NMR studies was given by Eq. (18):

$$\mathrm{d}[(CD_3)_2CH(OH)]/\mathrm{d}t = 2.5 \times 10^{-3}\,M^{-1}\,s^{-1}[\text{acetone-}d_6][\text{iPrOH}] \quad (18)$$

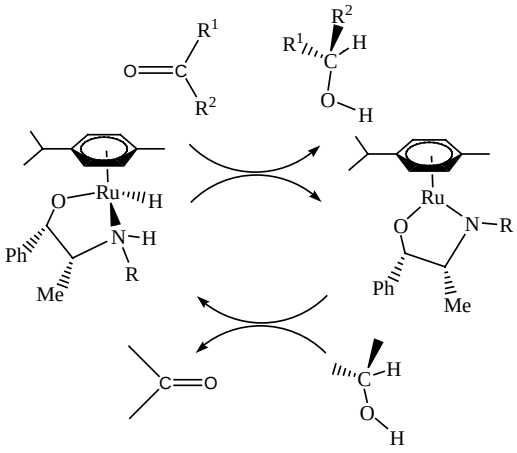
This and other measurements suggested that it is the dehydrogenation of the alcohol by the purple amido–amido complex that is the turn-over limiting step under the conditions of the kinetic study [29]. Theoretical calculations provided the structures of the six-member ring transition states shown in Scheme 18 [115,116]. Further work on the mechanism has provided activation parameters for the reaction of the amido-amido complex with $(CD_3)_2CHOH$: $\Delta H^{\ddagger} = 5.8\,\text{kcal mol}^{-1}$, $\Delta S^{\ddagger} = -48$ e.u. [179]. The negative entropy of activation is indicative of a highly ordered transition state where the complex and the alcohol associate as in Scheme 18 prior to the dihydrogen transfer. Individual kinetic and equilibrium isotope effects measured for the various C–H, N–H and O–H bond making and breaking steps in the mechanism proves that the H^-/H^+ transfer occurs in a concerted fashion [179]. A study of the racemization of (*S*)-MePhCD(OH) catalyzed by the amido–amido complex in THF at 70 °C shows that the deuterium is always transferred to the carbon and almost never to the oxygen during the 48 h required for complete racemization [154].

This tosylated diamine system and related ones have been used with great success in the production of chiral alcohols and amines [7,116,176,180–188]. No other hydrides of this type have been characterized to date.

There are many related precatalysts of the form RuCl(O–N)(η^6-arene), where O–N is a bidentate alkoxy-amine ligand formed from an amino alcohol or amino acid. These have been studied extensively for use in the transfer hydrogenation of prochiral ketones and the kinetic resolution of chiral alcohols [5,7,115,141,189–199]. Theoretical studies suggest that the mechanism is identical to the one for the tosyldiamine systems just discussed [115,116,189]. A limitation of these systems, compared to the tosyldiamine systems, is that HCOOH/NEt_3 cannot usually be used to drive the TOL of ketones to completion and prevent subsequent racemization of the alcohol that is formed.

One system that has been thoroughly studied involves the ligand derived from (1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine (HOCHPhCHMeNHCH$_2$C$_6$H$_4$-4-Ph or HO-NHR for short) [192]. The catalyst system RuCl(O-NHR)(benzene) transfers hydrogen from *i*PrOH to *tert*-butyl acetoacetate (*t*BuOOCCH$_2$COMe) to produce the *tert*-butyl 3-hydroxybutyrate (*t*BuOOCCH$_2$CH(OH)Me) in 67% e.e. (*S*) with a TOF at 20 °C of about 46 h^{-1} (Table 4, entry 32). The related yellow catalyst precursor RuCl(O-NHR)(*p*-cymene), the purple 16-electron true catalyst Ru(O-NR)(*p*-cymene), and the brown-red hydride catalyst RuH(O-NHR)(*p*-cymene), involved in the ketone reduction have been isolated, characterized by NMR and ESI-MS, as well as by X-ray crystallography in the case of the chloride complex. The alkoxy-amido complex Ru(O-NR)(*p*-cymene) is more reactive than the analogous tosylamido-amido complex described above and is more difficult to study. It reacts at −25 °C in tol-d_8 with excess *i*PrOH to produce the unstable hydride complex RuH(O-NHR)(*p*-cymene) that gave a ^{1}H NMR resonance at −5.2 ppm for the hydride. When this solution was warmed to room temperature another hydride resonance at −4.8 ppm grew in that might be the other diastereomer (opposite chirality at Ru). Both the alkoxy-amido and hydride complexes catalyze the TOL of *t*BuOOCCH$_2$COMe in *i*PrOH in the absence of base and give the alcohol with the same e.e. as does the chloride precatalyst. Therefore the catalytic cycle shown in Scheme 19 is proposed.

The coordination and catalytic chemistry of a potentially tetradentate, C_2-symmetric HO–NH–NH–OH ligand derived from (nor)ephedrine was investigated by Petra et al. [200]. The ligand in combination with [RuCl$_2$(*p*-cymene)]$_2$ in basic *i*PrOH at 20 °C catalyzes the transfer hydrogenation of acetophenone to (*R*)-1-phenylethanol in up to 90% e.e. The alkoxy-amine hydride complex of Scheme 19 shown in Fig. 25 was identified on the basis of ^{15}N NMR, ^{1}H NMR and electrospray mass spectroscopy. A solution of the hydride in benzene-d_6 produces a singlet resonance



Scheme 19. The TOL of ketones catalyzed by the complexes RuH(O-NHR)(*p*-cymene)/Ru(O-NR)(*p*-cymene) where R = CH$_2$C$_6$H$_4$-4-Ph.

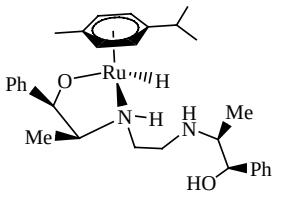


Fig. 25. The structure of the alkoxy-amino hydride complex.

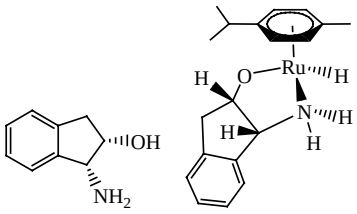


Fig. 26. Structure of the ligand (1*R*,2*S*)-aminoindanol and the hydride prepared from it.

at −5.5 ppm. The ^{15}N spectrum provides evidence for one coordinated NH and one free NH as shown.

In a related study, evidence for the catalyst RuH((1*R*,2*S*)-aminoindanalkoxide)(*p*-cymene), derived from an (1*R*,2*S*)-aminoindanol ligand (Fig. 26), was provided by an electrospray mass spectrum and the nature of the predicted hydride-ketone transition state that leads to the (*S*)-arylalkylalcohol [193]. When this complex is formed in situ, it catalyzes the transfer hydrogenation of acetophenone in KOH/*i*PrOH to (*S*)-1-phenylethanol in 72% yield, 92% e.e. [201]. Again a TOL mechanism shown in Scheme 17 was proposed. The TOL six-membered transition state involving the hydride with the structure shown in Fig. 26 and an alkylarylketone leads to the (*S*)-alcohol as observed.

Complexes *trans*-$RuCl_2$(P-NH-R-NH-P) (Fig. 27a–d) with tetradentate ligands with phosphorus and secondary amine donors have been used successfully in the asymmetric TOL of arylalkylketones [202–205]. For example the complex of Fig. 27(a), *trans*-$RuCl_2$((*R*,*R*)-P-NHcyNH-P), catalyzes the TOL of acetophenone in *i*PrOH to the (*S*)-alcohol to high conversion and 97% e.e. (Table 4, entry 34) [202,204]. Although mechanisms have been proposed that involve hydride species [204], no hydrides were characterized in this work. It is not clear that they have the same structure as the hydrides of the corresponding hydrogenation precatalysts discussed above (*trans*-RuHCl((*R*,*R*)-P-NHcyNH-P) and *trans*-RuH_2((*R*,*R*)-P-NHcyNH-P)) because the e.e. of the product obtained using *trans*-$RuCl_2$((*R*,*R*)-P-NHcyNH-P), is different in transfer hydrogenation (*S*, high e.e.) and hydrogenation (*R*, low e.e.) [121]. When a mixture of isomers of *trans*-RuHCl(P-NHcyNH-P) was tested in transfer hydrogenation of acetophenone in *i*PrOH/KO*i*Pr, the e.e. obtained was 20% (*S*) [121].

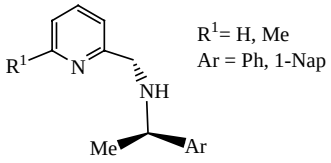


Fig. 28. Structure of the ligand combined with $RuHCl(PPh_3)_3$ for TOL.

It is likely that the NH groups as well as the hydrides are involved in the ketone reduction because the complexes without NH groups, *trans*-$RuCl_2$(P–N–N–P) ((b) and (d), Fig. 27) are poor catalysts [12].

A combination of the hydride $RuHCl(PPh_3)_3$ and ligands of the type shown in Fig. 28 is effective for the TOL of arylalkylketones in $HCOOH/NEt_3$ in e.e. up to 86% (*S*) although the TOF is low (Table 4, entry 31) [206]. We assume that a complex of the type $RuHCl(PPh_3)_2$(L) forms with similar structure to the $RuHCl(PPh_3)_2$(diamine) hydrogenation precatalysts [47,48] although no evidence for this hydride was presented.

A ruthenium carbonyl complex containing a cyclopentadienyl ligand with a pendant amino group,

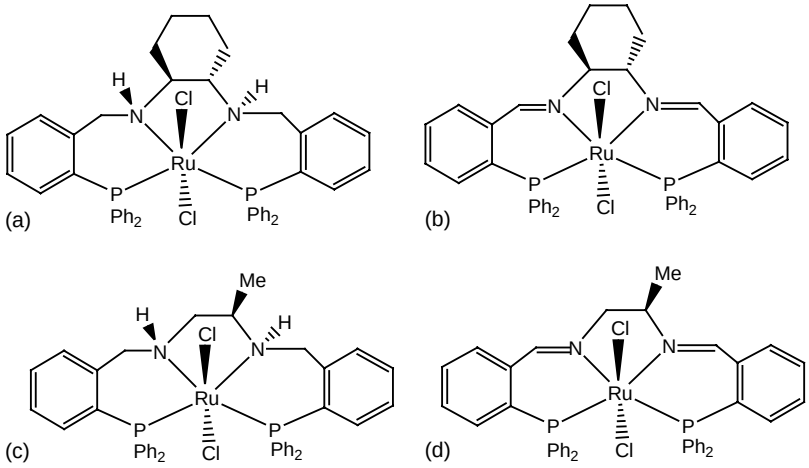
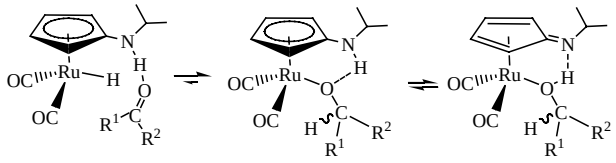


Fig. 27. Chiral tetradentate ligand complexes for the TOL of ketones.



Scheme 20. The racemization of chiral alcohols catalyzed by complexes derived from $RuCl(\eta^5\text{-}C_5Ph_4NHiPr)(CO)_2$.

$RuCl(\eta^5\text{-}C_5Ph_4NHiPr)(CO)_2$, has been used for the efficient racemization of alcohols for use in kinetic dynamic resolutions in conjunction with the acylating enzyme Novozym 435 [136]. A mechanism that involves the alkoxide complexes $Ru(OR)(\eta^5\text{-}C_5Ph_4NHiPr)(CO)_2$ and the release of alcohols by protonation by the amine with formation of an imine complex $Ru(OR)(\eta^4\text{-}C_5Ph_4NiPr)(CO)_2$ is proposed (Scheme 20). The racemization process is proposed to involve the elimination of the hydride from the coordinated alkoxide, with ligand assistance, to give an undetected hydride/ketone intermediate. The hydride then re-adds to either face of the ketone.

3.2.3. Hydrides that use a hydroxyl group on the ligand in the TOL mechanism

The mechanism of the ketone or aldehyde transfer hydrogenation from formic acid catalyzed by Shvo's catalyst is shown above in Scheme 11 [130]. Several ketones and aldehydes have been hydrogenated using this system. For example cyclohexanone is reduced to the alcohol by transfer from formic acid at a TOF of 3800 at 100 °C (Table 4, entry 36). As noted in the HOL section, Casey and coworkers have provided evidence based on isotope effects that the transfer of the hydride and proton is a concerted OL process [135].

The racemization of (*S*)-MePhCD(OH) catalyzed by Shvo's catalyst was shown to selectively produce *rac*-MePhCD(OH) with only 5% scrambling of the D label to other positions [154]. This shows that hydride additions and eliminations almost exclusively involve this labeled carbon and that a monohydride mechanism is involved. The racemization of alcohols has been linked with enzyme reactions to produce chiral acylated alcohols in high e.e. [15,133,207–210].

While there is evidence for an outer sphere hydride transfer reaction for aldehydes, the situation is not as clear for the transfer hydrogenation of imines. Casey's group has suggested that imines are also reduced in an outer sphere transfer reaction [135]. Samec and Bäckvall [211] reported that Shvo's catalyst $Ru_2(\mu\text{-}H)(\mu\text{-}C_4Ph_4COH\cdots OCC_4Ph_4)(CO)_4$ promotes the efficient hydrogenation of imines of the type $PhN{=}CR^1R^2$ (R^1, R^2 = aryl, alkyl) by transfer from isopropanol (Table 5, entry 4). Stepwise TIL addition of hydride from the metal, coordination of the amide and then proton addition from the hydroxyl has been proposed as the mechanism. They propose that the reaction proceeds stepwise by the TI mechanism via coordination of imine to Ru, presumably by slippage of the cyclopentadienyl ring as proposed originally by Menache and Shvo [129], followed by hydride addition to produce an amide and finally proton transfer from the hydroxyl group. This is favored over a concerted TOL addition of H^-/H^+ because they observed the isomerization of $PhMeC{=}NCH_2Ph$ to $PhMeCH\text{-}N{=}CHPh$ during the transfer hydrogenation of the first imine. This implies that there was an amido intermediate that underwent β-hydride elimination and therefore the stepwise addition of hydride. However the reverse, concerted elimination of H^+/H^- could also explain these results. A similar cycle was proposed in the racemization of chiral secondary amines via the hydride/imine intermediate [212]. The product amine forms an adduct with the dehydrogenated complex. This complex then generates imine and hydride that re-adds to cause the formation of the racemic amine.

4. Conclusion

The study of ruthenium hydride complexes in catalysis is challenging because of their air-sensitivity and high reactivity. Yet these are the species that are the closest to the actual H_2-hydrogenation and transfer hydrogenation catalysts. Excellent progress has been made in the past 20 years in studying these compounds and the mechanism of their catalytic activity. More than 100 are described in this review. Sometimes, once they are isolated, they are active without the need of added reagents other than the substrate, solvent and the source of dihydrogen. For example, the complexes *trans*-RuH_2((*R*)-binap)-($NH_2CMe_2CMe_2NH_2$), $RuH(NH_2CMe_2CMe_2NH)(PPh_3)_3$ [47] and *trans*-$RuH(HBH_3)$((*S*)-tolbinap)((*S*,*S*)-dpen) [101] are very active for the H_2-hydrogenation of ketones without the need to add a base to the solvent. This opens the way to hydrogenating base-sensitive substrates. The complexes RuHCl(diamine)(diphosphine) are active precursors for the H_2-hydrogenation of imines as well [102]. Of course, another outstanding characteristic of the Noyori catalysts is their excellent enantioselectivity in the hydrogenation of prochiral ketones to chiral alcohols. Promising results have been reported for the asymmetric H_2-hydrogenation of imines by these systems as well [102,113].

The classification of the hydrides according to the I, IL, O and OL mechanisms is often arbitrary because it is difficult to prove the actual pathway of the reaction. However there are features that assist in this classification. The OL mechanisms appear to be much more selective for C=O or C=N bonds over C=C bonds. The I mechanisms allow both the polar and the C=C bond to coordinate next to the hydride so that olefin hydrogenation and isomerization become competing pathways. The I mechanisms may also explain the isomerization of imines that has occasionally been reported [25,211]. The origin of the selectivity of the OL mechanism is the ease of transfer of H^+/H^- between the M–L group and the C–Q group. It seems that the charge alternation is

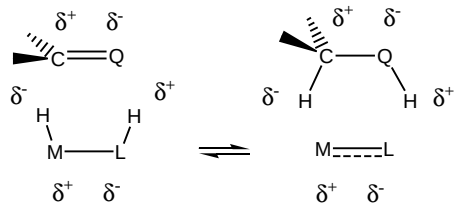


Fig. 29. OL transfer of H^-/H^+ to the C=Q polar bond.

an important factor that favors transfer to C=Q bonds and not C=C bonds (Fig. 29).

The hydrides that utilize the NH or OH effect in an OL mechanism are usually much more active than comparable complexes without this ligand effect. The most spectacular examples are hydrides generated by reaction of $RuCl_2$((*S*)-tolbinap)((*S*,*S*)-dpen) [101] or $RuHCl(PPh_2C_6H_4CH_2NHcyNHCH_2C_6H_4PPh_2)$ [121] with base in 2-PrOH. These catalyze the H_2-hydrogenation of ketones with turn-over-frequencies that exceed $10^5\,h^{-1}$. The high activity of this second catalyst, despite the presence of the strongly binding tetradentate ligand and the trans geometry, is excellent evidence for an outer sphere reaction. A loss of activity upon the removal of the NH groups in comparable ligands is also good evidence for the OL mechanism. The Shvo catalysts [127–131] that utilize the OH effect also have very good transfer hydrogenation characteristics. These active systems make it possible to study reactions by NMR in a convenient temperature regime and thus learn more about the mechanism. There is at least one example where the N–H effect does not appear to confer higher reactivity. The use of a bidentate iminophosphine ligand with no N–H in the precatalyst $RuCl_2$(2-P,N-2-$Ph_2PC_6H_4CH{=}NtBu)(PPh_3)$ is somewhat more active in the transfer hydrogenation of ketones than the related aminophosphine in the analogous complex $RuCl_2$(2-P,N-2-$Ph_2PC_6H_4CH_2NHtBu)(PPh_3)$ [213]. Also the H_2-hydrogenation precatalysts $RuCl_2$(diphosphine)$(py)_2$, diphosphine = (2*S*,4*S*)-$PPh_2CHMeCH_2CHMePPh_2$ and (*R*), (*S*)-Josiphos, have no NH and yet are active and enantioselective ketone H_2-hydrogenation catalysts [214]. Hydride complexes were not identified in these last two studies.

Octahedral Ru(II) complexes can form quite stable dihydrogen complexes [17,19,30,215–218]. This may be how dihydrogen competes for a binding site on the catalyst with the substrates, the ketones and imines, and the products, the alcohols and amines, that are all good ligands themselves. However, dihydride complexes of Ru(IV) might also form in the presence of small electron-donating ligands such as trialkylphosphines and ligands with suitable bite angles [17,20]. The presence of a low electronegativity donor atom such as phosphorus, carbon or hydrogen (as a hydride) *trans* to the H_2 binding site ensures that substitution reactions are fast. The formation of an acidic dihydrogen ligand promotes the heterolytic splitting of the otherwise strong H–H bond. In the TOL cycle, the facile reversibility of the H^+/H^- transfer mechanism ensures that the hydride is regenerated. A high trans influence ligand makes the hydride more hydridic by weakening the M–H bond.

The use of water-soluble complexes has produced some systems with very good activity and selectivity. The $RuHI(tppts)_3(OH_2)$ system of Basset and coworkers has excellent activity for the hydrogenation of aldehydes in aqueous NaI [82–84]. The sodium cation is thought to play an important role. The complex $[RuCl_2(tppms)_2]_2$ displays an interesting change in selectivity toward the hydrogenation of C=O versus C=C bonds with a change in pH [23]. At higher pH, the dihydride $RuH_2(tppms)_4$ is thought to be present and this selectively catalyzes the H_2 hydrogenation of the C=O bond of *trans*-cinnamaldehyde. The complex $[RuH(C_6Me_6)(bpy)]^+$, which is unusual for the lack of phosphine ligands, is surprisingly active for the formate transfer hydrogenation of ketones in water or biphasic systems and a TO mechanism has been proposed [173]. The optimum pH of 4 for the activity of this catalyst suggests a general acid assistance of the hydride transfer.

Noyori's effective ketone and imine catalysts $RuH(TsNCHPhCHPhNH_2)$(arene) for the asymmetric hydrogenation of imines and ketones by TOL are isoelectronic with the $[RuH(C_6Me_6)(bpy)]^+$ system and also have carbon and nitrogen donors that give hydridic character to the Ru–H bond. In fact, the presence of both soft carbon or phosphorus and hard nitrogen ligands is a feature of many of the effective catalysts described. While electron-withdrawing carbonyl ligands should make the hydrides less reactive toward polar bonds, there are some active carbonyl containing catalysts including the systems of Shvo (all carbon donors around ruthenium) and the catalysts such as $RuH\{\kappa^2\text{-}o\text{-}C(O)(Ph)(C_6H_4\}(CO)(PCy_2(CH_2)_4PCy_2)$ of Drouin et al. that we tentatively classified as HI [65]. In the latter case, the donating alkyl phosphine may compensate for the presence of the carbonyl ligand.

Another trend appears to be that polydentate ligands provide better performance than comparable systems with monodentate ligands. Examples include the pcp pincer ligand in the very active TI catalyst Ru(pcp)(OTf)(PPh_3) [167] and the very active HOL tetradentate catalyst mentioned above. The polydentate ligands might serve to increase the hydridic character by stabilizing the cationic metal that is produced after the hydride has transferred. They might also maintain the structure of the catalyst in the presence of potentially strong ligands that are produced in the hydrogenations–alkoxides from the alcohols produced from ketone hydrogenation or amines or amides from imine hydrogenation. Polydentate ligands also allow better control of the chiral environment around the metal.

Some catalysts work in both H_2-hydrogenation and transfer hydrogenation, although usually the substrate to catalyst ratio is lower in the transfer hydrogenation case. The Shvo catalysts function as ketone and imine TOL and HOL catalysts as do the tetradentate P–NH–NH–P systems. Some cat-

alysts are much more active for H_2-hydrogenation than transfer hydrogenation, such as the RuHX(diamine)(diphosphine) systems. Others are much more active for transfer hydrogenation, such as the RuH(TsNCHPhCHPhNH$_2$)(arene) systems. It is not yet possible to explain these differences completely.

No doubt future work will reveal more important mechanistic details of how hydrides are involved in catalysis. The mechanism of the outer sphere transfer of dihydrogen perhaps can be extended to other catalytic atom or group transfer reactions and further expand the collection of powerful catalysts available for organic synthesis.

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