15
Homogeneous Hydrogenation of Aldehydes, Ketones, Imines and Carboxylic Acid Derivatives: Chemoselectivity and Catalytic Activity

Matthew L. Clarke and Geoffrey J. Roff

15.1
Introduction

The reduction of aldehydes, ketones, esters, acids, and anhydrides to alcohols is one of the most fundamental and widely employed reactions in synthetic chemistry. Sodium borohydride, lithium aluminum hydride and other stoichiometric reducing agents are often perfectly adequate reagents for laboratory-scale syntheses. In an industrial setting, however, the increased demands for atom economy, cleaner synthesis and straightforward work-up procedures make the use of these reagents disadvantageous. Reduction procedures that make use of molecular hydrogen show better ecology, are more cost-effective, and are potentially easier to operate than those that require the clean-up of boron or aluminum waste at the end of the reaction. The hydrogenation of C=O (and C=N) bonds is therefore the preferred method for their reduction.

Heterogeneous catalysts such as Pd/C and Pt/C are widely used for this purpose, and often represent the most economical method to carry out these reductions. However, in cases where milder conditions, functional group tolerance and chemoselectivity are required, heterogeneous catalysts can be unsuitable for the task. There has therefore been a substantial research effort aimed towards developing homogeneous catalysts for this purpose.

This chapter aims to provide an overview of the current state of the art in homogeneous catalytic hydrogenation of C=O and C=N bonds. Diastereoselective or enantioselective processes are discussed elsewhere. The chapter is divided into sections detailing the hydrogenation of aldehydes, the hydrogenation of ketones, domino-hydroformylation-reduction, reductive amination, domino hydroformylation-reductive amination, and ester, acid and anhydride hydrogenation.

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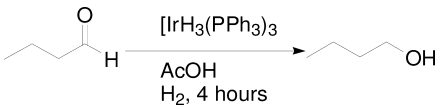
15.2
Hydrogenation of Aldehydes

15.2.1
Iridium Catalysts

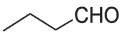
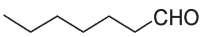
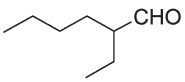
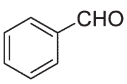
The first report of a catalytic system for the effective homogeneous hydrogenation of an aldehyde to an alcohol was published during the late 1960s [1]. Coffey reported that the use of a catalyst prepared *in situ* by the reaction of $[Ir(H)_3(PPh_3)_3]$ with acetic acid was effective for the hydrogenation of *n*-butyraldehyde to *n*-butanol at 50 °C and at 1 bar (Scheme 15.1). The reaction was found to be first order in both substrate and catalyst concentration, and to be highly dependent upon the solvent. No hydrogenation occurred in undiluted aldehyde or in toluene, but the addition of acetic acid initiated gas uptake. The active catalytic species was thought to be $[Ir(H)_2(CH_3COO)(PPh_3)_3]$.

This catalytic system was further studied by Strohmeier and Steigerwald, who performed reactions at 10 bar without solvent to achieve hydrogenation of a series of aldehydes (Table 15.1) [2]. Turnover numbers (TON) of up to 8000 were achieved in the case of the hydrogenation of benzaldehyde. The chemoselectivity of this catalyst towards carbonyl hydrogenation over alkene hydrogenation was



Scheme 15.1 Hydrogenation of *n*-butyraldehyde.

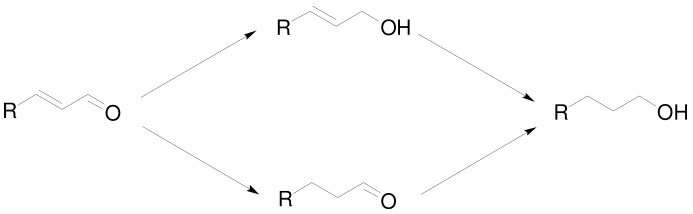
Table 15.1 Hydrogenation of aldehydes with $[IrH_3(PPh_3)_3]$ in acetic acid.

Substrate	Catalyst [mol.%]	Temperature [°C]	Yield [%]	TON	TOF [h^{-1}]
	0.022	80	73	3280	492
	0.023	110	82	3540	177
	0.032	90	64	2000	89
	0.039	110	80	2030	81
	0.013	110	98	7780	259

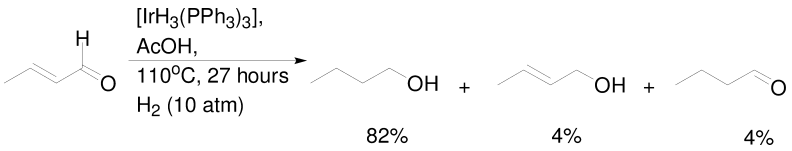
examined for α,β-unsaturated aldehydes (Scheme 15.2). Using the $[IrH_3(PPh_3)_3]$ complex in acetic acid for the hydrogenation of crotonaldehyde resulted in the formation of the saturated alcohol (Scheme 15.3). It was also noted that this catalyst did not allow for ketone hydrogenation at 10 bar.

Other attempts to use iridium PPh_3 complexes such as $[IrCl(PPh_3)_3]$, $[IrCl(CO)(PPh_3)_2]$, $[Ir(ClO_4)(CO)(PPh_3)_2]$ and $[Ir(CO)(PPh_3)_3]ClO_4$ to hydrogenate unsaturated aldehydes did not yield great results [3], mainly because these catalysts suffered from low activity and selectivity.

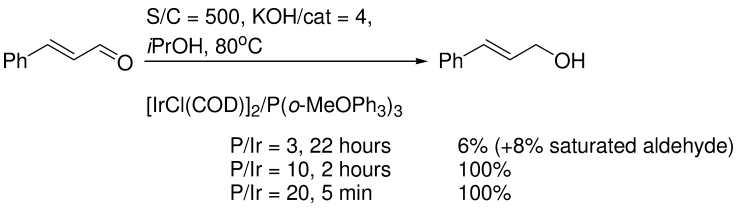
The catalytic system of $[Ir(COD)Cl]_2$ with an excess of the bulky phosphine $P(o\text{-MeOPh})_3$ under transfer hydrogenation conditions of propan-2-ol and KOH was used successfully in the selective hydrogenation of cinnamaldehyde (Scheme 15.4) [4]. Selectivity and activity were found to increase with increasing P/Ir ratios, and complete conversion was achieved in as little as 5 minutes (turnover frequency (TOF) $\sim 6000\ h^{-1}$).



Scheme 15.2 Distribution of products in the hydrogenation of α,β-unsaturated aldehydes.



Scheme 15.3 Hydrogenation of crotonaldehyde with $[IrH_3(PPh_3)_3]$ in acetic acid.



Scheme 15.4 Transfer hydrogenation of cinnamaldehyde.

Using molecular hydrogen as the reducing agent, $[Ir(COD)(OCH_3)]_2$ with an excess of tertiary phosphine was better than $[Ir(COD)Cl]_2$ for the selective hydrogenation of cinnamaldehyde [5]. In these studies, a great dependence on solvent and ligand was reported. A variety of different phosphines, which were markedly different in their steric and electronic properties, were examined in this reaction. In propan-2-ol the most effective phosphine was PCy_2Ph which gave 94% yield (TOF 235 h^{-1}) of the unsaturated alcohol in a 2 h reaction under 30 bar H_2 at 100 °C. Phosphines such as $PCyPh_2$, $PPhPr^i_2$, PPh_2Pr^i and $PEtPh_2$ were also effective in giving over 95% selectivity. The less-effective phosphines were PEt_2Ph, $PMePh_2$, PBu^i_3 and PMe_2Ph. Reactions that were performed in toluene were generally less effective.

More recent advances in iridium-catalyzed aldehyde hydrogenation have been through the use of bidentate ligands [6]. In the hydrogenation of citral and cinnamaldehyde, replacing two triphenylphosphines in $[IrH(CO)(PPh_3)_3]$ with bidentate phosphines BDNA, BDPX, BPPB, BISBI and PCP (Fig. 15.1) led to an increase in catalytic activity.

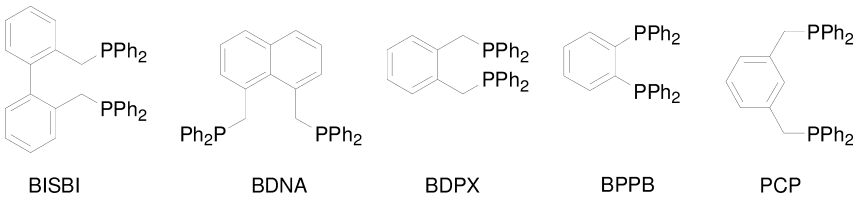


Fig. 15.1 Bidentate ligands employed in Ir-catalyzed hydrogenation.

Table 15.2 Bidentate ligands used for the hydrogenation of citral and cinnamaldehyde under 50 bar H_2 at 100 °C.

Complex	Substrate	Conversion [%]	Selectivity [%] [a]	TOF [h^{-1}] [b]
$[IrH(CO)(PPh_3)_3]$	Citral	3.1	70.5	7
	Cinnamaldehyde	11.4	35.0	61
$[IrH(CO)(PPh_3)(BPPB)]$	Citral	7.7	61.2	18
	Cinnamaldehyde	27.3	19.3	146
$[IrH(CO)(PPh_3)(BISBI)]$	Citral	11.6	92.2	28
	Cinnamaldehyde	44.6	13.1	238
$[IrH(CO)(PPh_3)(BDNA)]$	Citral	19.3	95.8	46
	Cinnamaldehyde	20.6	77.4	110
$[IrH(CO)(PPh_3)(BDPX)]$	Citral	58.8	96.4	141
	Cinnamaldehyde	58.1	9.0	310
$[IrHCl(CO)(PCP)]$	Citral	13.9	42.5	33
	Cinnamaldehyde	52.0	1.3	277

a) Selectivity of allylic alcohol formed as a percentage of total hydrogenation products.
b) TOF (h^{-1}) expressed for conversion of starting material.

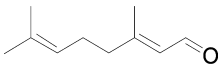


Fig. 15.2 Citral.

Even though the activity was better than the PPh_3 analogue (Table 15.2), the conversion was still low. Of the ligands tested, BDPX showed the greatest promise in selectivity for citral (Fig. 15.2).

The selectivities in forming cinnamyl alcohol from cinnamaldehyde using these catalysts were poor, and generally resulted in the formation of the saturated aldehyde. This could be overcome by the use of a large excess of phosphine, though at the expense of yield. The same group have demonstrated that ruthenium analogues of the BDNA complex are more active and selective [7].

15.2.2 Rhodium Catalysts

Wilkinson's catalyst $[RhCl(PPh_3)_3]$ [8], a convenient catalyst for the hydrogenation of olefins, was found to be deactivated by aldehydes to give the catalytically non-active complex $[RhCl(CO)(PPh_3)_2]$ as a result of the competing decarbonylation reaction. Despite the lack of activity of this catalyst, extensive investigations have been made into rhodium catalysis for aldehyde hydrogenation, and these have led to the development of some highly efficient catalysts.

15.2.2.1 Rh-amine Catalysts

The first report of rhodium catalysts for aldehyde reduction came from Marko who reported the use of $RhCl_3 \cdot 3H_2O$ under hydroformylation conditions [9]. It was suggested that the active species were rhodium carbonyls, and the catalyst system was successfully utilized in the hydrogenation of ethanal, propanal, and benzaldehyde.

In the presence of strongly basic amines, $RhCl_3 \cdot 3H_2O$ was effective in catalyzing the hydrogenation of cinnamaldehyde [10]. In the absence of carbon monoxide or triethylamine, however, only small amounts of hydrogenated products were obtained. Under hydroformylation conditions with increasing concentrations of triethylamine, catalytic activity and selectivity to cinnamyl alcohol were increased. The effect of the amines was found to be very important. Primary or secondary amines were ineffective in producing hydrogenation products. Strongly basic tertiary amines such as triethylamine and *N*-methylpyrolidine were more effective for activity and selectivity. The addition of triphenylphosphine increased hydrogenation of the carbon–carbon double bond, giving dihydrocinnamaldehyde. The activity of $RhCl_3 \cdot 3H_2O$ at lower temperatures can be increased by the pretreatment with CO giving $RhCl_2(CO)_4$ and allowing hydrogenations to occur at 60 °C with up to 94% yield and 85% selectivity in a 1-h reaction ($TOF = 289\ h^{-1}$).

The rhodium carbonyl cluster $[Rh_6(CO)_{16}]$, in combination with the diamine *N,N,N′*,N′-tetramethyl-1,3-propanediamine is an effective catalytic system for the

hydrogenation of saturated and unsaturated aldehydes in water under a pressure of carbon monoxide and hydrogen [11]. In reactions lasting only a few hours, and using a substrate catalyst ratio of 300, simple aldehydes are converted in quantitative yields. The unsaturated aldehydes take longer to react, but the selectivity favors the formation of unsaturated alcohols in high yields.

15.2.2.2 **Cationic Rhodium Phosphine Catalysts**

The effect of the phosphines has been further studied by the hydrogenation of aldehydes and ketones in the presence of the cationic species $[Rh(nbd)(PR_3)_2]ClO_4$ [12]. Both, triethylphosphine and trimethylphosphine complexes showed the greatest activity (triethylphosphine being preferred), whereas triphenylphosphine-based catalysts showed little or no activity and the diphosphine (dppe) complex inhibited the reaction completely. At 30 °C and under 1 bar H_2, the triethylphosphine catalyst could complete the hydrogenation of benzaldehyde in 24 h, whereas under the same conditions it could only manage 80% and 41% hydrogenation for phenylacetaldehyde and *n*-butyraldehyde, respectively. The presence of propane and propene in the reaction mixture of *n*-butyraldehyde hydrogenation suggests the occurrence of a certain degree of decarbonylation, which leads to deactivation of the catalyst.

An alternative air-stable cationic rhodium complex [(COD)Rh(DiPFc)]OTf is an efficient catalyst precursor for the hydrogenation of aldehydes and ketones [13]. This is the first useful diphosphine-based catalyst, possibly due to backbone rigidity and strong electron-donating alkyl-substituted phosphorus atoms. Using this commercially available catalytic system, benzaldehyde can be converted to benzyl alcohol under mild conditions. Using a substrate : catalyst ratio (SCR) of 500 : 1, a quantitative yield was obtained in 3 h at 25 °C and under only 4 bar hydrogen (TOF $\sim 165\ h^{-1}$). Unlike some alternative catalysts, there was no deactivation of the catalyst through decarbonylation, and a range of saturated aldehydes have been successfully hydrogenated in the presence of this catalyst (Fig. 15.3).

The hydrogenations were active either with the isolated catalyst or *in situ* generation of the catalyst by the reaction of DiPFc with $[(COD)_2Rh]OTf$ in methanol (Scheme 15.5). Both, the components and the isolated catalysts are available from Strem Chemicals.

The solid catalyst is stable to oxygen and moisture, showing no loss of activity when exposed to the atmosphere for several days. However, the catalyst reacts fairly rapidly with oxygen when in solution and this leads to catalyst deactivation, a problem which is easily overcome by simply degassing the reaction solvent.

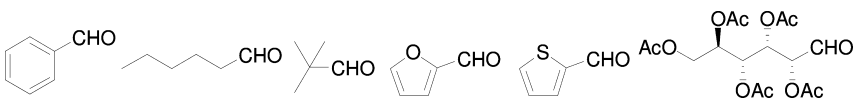
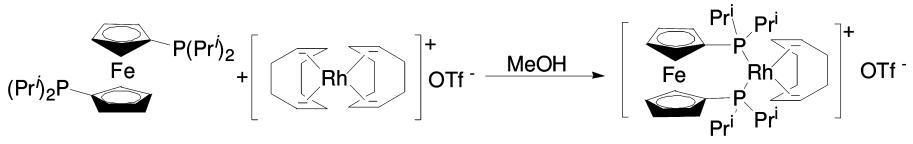


Fig. 15.3 Substrates hydrogenated using $[Rh(dippf)(COD)]^+OTf^-$.



Scheme 15.5 Preparation of cationic DiPFc catalyst.

The Rh-DiPFc catalyst has recently been immobilized on modified alumina essentially to provide an immobilized homogeneous catalyst [14]. Although in this form it is strictly a heterogeneous catalyst, it provides the best of both worlds. These catalysts may be superior to the traditional heterogeneous catalysts in terms of reactivity and selectivity, but benefit over homogeneous catalysts in their ease of removal and re-use. Similar immobilizations have involved the binding of rhodium carbonyl clusters to polymers [15, 16]. Generally high selectivity was observed in the hydrogenation of a series of unsaturated aldehydes either under hydrogen and carbon monoxide or formic acid transfer hydrogenations.

15.2.2.3 **Water-Soluble Rh Catalysts**

Water-soluble complexes constitute an important class of rhodium catalysts as they permit hydrogenation using either molecular hydrogen or transfer hydrogenation with formic acid or propan-2-ol. The advantages of these catalysts are that they combine high reactivity and selectivity with an ability to perform the reactions in a biphasic system. This allows the product to be kept separate from the catalyst and allows for an ease of work-up and cost-effective catalyst recycling. The water-soluble Rh-TPPTS catalysts can easily be prepared *in situ* from the reaction of $[RhCl(COD)]_2$ with the sulfonated phosphine (Fig. 15.4) in water [17].

In the reduction of benzaldehyde performed in water in the presence of Na_2CO_3 and *i*-PrOH, the yields were generally very high. This system was highly effective in 2 h with complete conversion when H_2 was used as the hydrogen donor. Using *i*-PrOH as the hydrogen donor, yields were well above 90% even after recycling of the catalyst several times. Sodium formate could also provide efficient hydrogenation, with over 90% yield. Using iridium analogues resulted in very poor yields. Several other aldehydes were reduced with good yields using the transfer hydrogenation protocol (Fig. 15.5).

This catalyst is chemoselective in the reduction of α,β-unsaturated aldehydes, without any decarbonylation [18]. However, the resulting product was the saturated aldehyde. Generally, at pressures < 20 bar H_2 and temperatures between 30 and 80 °C, selectivities exceeding 95% can be achieved in 1 h. Recycling posed no problem with successive runs, showing the same selectivity and activity.

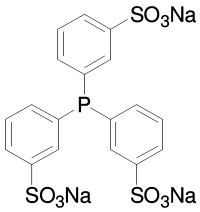


Fig. 15.4 TPPTS.

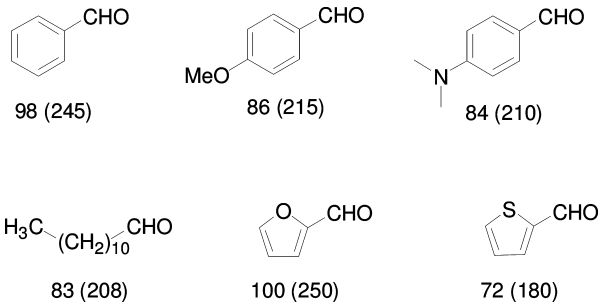


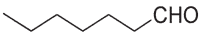
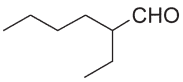
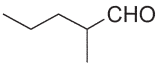
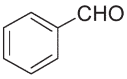
Fig. 15.5 Transfer hydrogenation of aldehydes using $[Rh(COD)Cl]_2$/TPPTS at 80 °C using *i*-PrOH as hydrogen donor. Values shown are yields (TOF, h^{-1}).

15.2.3 Ruthenium Catalysts

15.2.3.1 Ru-PPh_3 Catalysts

The most common carbonyl hydrogenation catalysts are derived from ruthenium species. In early studies, these were generally based on the phosphine-coordinated ruthenium carbonyls that are more commonly used for hydroformylation reactions. Thus, the hydroformylation catalyst $[Ru(CO)_3(PPh_3)_2]$ was shown to be effective in the hydrogenation of propionaldehyde under 20 bar H_2 and at 120 °C [19]. Increasing the temperature and pressure led to an increase in reaction time. Tsuji and Suzuki used the complex $[RuCl_2(PPh_3)_3]$ to hydrogenate a series of aliphatic and aromatic aldehydes [20]. Under 10 bar H_2 the reactions were found to be sluggish at room temperatures, but proceeded smoothly above 70 °C. Hydrogenation of aldehydes in the presence of ketones showed selectivity exclusively for the aldehydes. Benzaldehyde was also exclusively reduced in the presence of nitrobenzene, a substrate which is known to be reduced to aniline under harsh conditions by this catalyst [21]. Strohmeier and Weigelt used the catalyst $[RuCl_2(CO)_2(PPh_3)_2]$ to hydrogenate a series of aldehydes at 15 bar H_2 and at 160–180 °C, with generally high yield and turnover numbers (Table 15.3) [22]. Although these are amongst the highest turnover numbers reported for aldehyde hydrogenation, the reactions were carried out at relatively high temperatures.

Table 15.3 Hydrogenation of simple aldehydes using $RuCl_2(CO)_2(PPh_3)_2$.

Substrate	Catalyst [mol%]	Temperature [°C]	Time [h]	Yield [%]	TON
	0.0083	180	4	90	10800
	0.0033	160	11	98	29400
	0.0017	160	12	99	59400
	0.0017	180	14	93	56000

Sanchez-Delgado and De Ochoa achieved excellent conversion of linear aldehydes by introducing chloride ligands [23]. The catalyst precursors $[RuHCl(CO)(PPh_3)_3]$, $[RuHCl(PPh_3)_3]$ and $[RuCl_2(PPh_3)_3]$ were used to reduce both aliphatic and aromatic aldehydes, although benzaldehyde reduction was less efficient than with the previously mentioned $[RuCl_2(CO)_2(PPh_3)_2]$ catalyst. Although $[RuHCl(PPh_3)_3]$ was found to be the more active catalyst, it required inert conditions and promoted decarbonylation of the aldehyde. Evidence of this comes from the presence of metal carbonyl species at the end of reaction. Having carbonyl ligands appears to solve this problem, and $[RuHCl(CO)(PPh_3)_3]$ was found to be the most convenient catalyst. Using propionaldehyde with a SCR of 50000, turnover numbers of up to 32000 were achieved after 50 h of continuous reaction at 140 °C under 30 bar H_2 [24]. Using this same catalyst in the reduction of crotonaldehyde, the favored product was the fully saturated alcohol [25].

Hotta, using $[RuHCl(PPh_3)_3]$ and HCl, allowed for highly selective reduction of citral [26]. Using 2.5 mol% $[RuHCl(PPh_3)_3]$ in toluene under 50 bar H_2 at 30 °C, the selectivity achieved was 66%. The addition of 12.5% HCl, and performing the reaction in toluene : ethanol (27 : 3) further increased selectivity to 98%, with 99% conversion. The desirable mild conditions were offset by the relatively low turnover numbers.

15.2.3.2 **Polydentate Ru Catalysts**

The use of polydentate ligands is rare for aldehyde hydrogenation. The ruthenium complex $[RuCl_2(TRIPHOS)]$ $(TRIPHOS = PhP(CH_2CH_2PPh_2)_2$ catalyzes the hydrogenation and isomerization of alkenes, as well as the hydrogenation of aldehydes, ketones, and nitriles [27]. For simple aldehydes such as *n*-propanol, *n*-butanol, and *n*-hexanol, reasonable conversions can be achieved in 2 h under 34 bar H_2 at 100 °C, with turnover numbers of around 1000. In the hydrogenation of crotonaldehyde and cinnamaldehyde, it is the olefinic bond that is reduced favorably, although some unsaturated alcohol is also produced.

Table 15.4 Ru-BDNA-catalyzed hydrogenations of citral and cinnamaldehyde.

Catalyst	Substrate	Conversion [%] [a]	Selectivity [%] [b]	TOF [h^{-1}] [c]
$[RuCl_2(PPh_3)_3]$	Citral	35	36	141
	Cinnamaldehyde	40	62	212
$[RuHCl(CO)(PPh_3)(BDNA)]$	Citral	93	96	371
	Cinnamaldehyde	86	94	461
$[RuH_2(CO)(PPh_3)(BDNA)]$	Citral	64	>99	255
	Cinnamaldehyde	62	95	328

a) 50 bar H_2, 70–80 °C, toluene, SCR 1200 (citral) or 1600 (cinnamaldehyde).
b) Selectivity of allylic alcohol formed as a percentage of total hydrogenation products.
c) TOF expressed for conversion of starting material.

The bidentate ligand BDNA shows good conversions and selectivity in the hydrogenation of citral and cinnamaldehyde [7]. These crystalline complexes are easily prepared by the replacement of triphenylphosphines in several Ru–PPh_3 complexes with BDNA by refluxing for several hours in toluene. In comparison with $[RuCl_2(PPh_3)_3]$, the most promising complexes were $[RuHCl(CO)(PPh_3)(BDNA)]$ and $[RuH_2(CO)(PPh_3)(BDNA)]$ (Table 15.4).

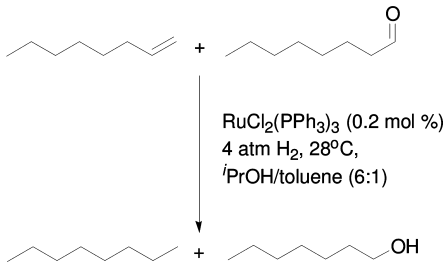
Another bidentate ligand which shows improvements over triphenylphosphine is that of BISBI [28]. The complex $[RuCl_2(PPh_3)(BISBI)]$ shows selectivities over 80%, but the yields are only 40–50% [28]. The analogous iridium complexes are less active, but show similar selectivity [6].

15.2.3.3 **Diamine-Modified Ru Catalysts**

$RuCl_2(PPh_3)_3$ has been shown to catalyze the reduction of several aldehydes, but does not have widespread scope. This catalyst is not chemoselective and, in the presence of alkenes, would favor olefin reduction over that of the aldehyde. Noyori and coworkers showed that chemoselectivity is easily introduced by the addition of ethylene-diamine as a ligand (Scheme 15.6) [29, 30]. This system requires the presence of co-catalytic KOH/*i*-PrOH as an activator.

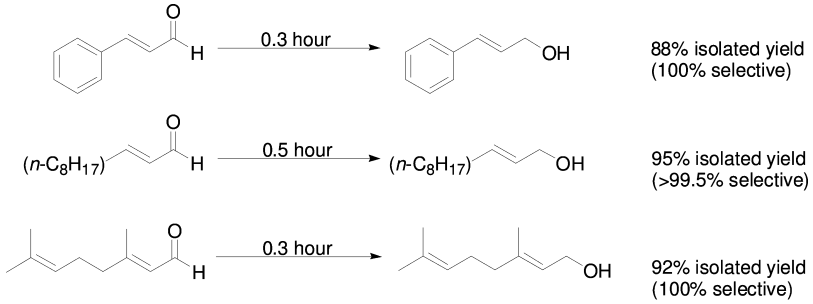
Using an easily prepared stock solution of $[RuCl_2(PPh_3)_3]/NH_2(CH_2)_2NH_2$ and KOH in *i*-PrOH, unsaturated aldehydes are quantitatively reduced exclusively to unsaturated alcohols (Scheme 15.7).

Direct comparisons of the diamine system against the parent complex led to the conclusion that the effect of the diamine and KOH/*i*-PrOH activator decelerate olefin hydrogenation and in turn accelerate carbonyl hydrogenation. In the published report, there were no attempts to optimize turnover numbers or TOF for aldehyde hydrogenation. However, the catalyst has been shown to hydrogenate ketones with a SCR of 10 000 at room temperature, which suggests that these catalysts represent the current state of the art in terms of activity and selectivity.



No additive, 150 mins	250	1
$H_2N(CH_2)_2NH_2$ + KOH, 10 Mins (Ru:en:KOH = 1:1:2)	1	1500

Scheme 15.6 Direct comparison of aldehyde and alkene hydrogenation.



Conditions: 28°C in 6:1 propanol-toluene under 4 atm H_2; Substrate:Ru:en:KOH = 500:1:1:2

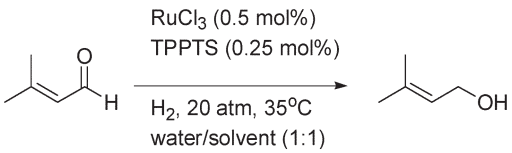
Scheme 15.7 Hydrogenation of unsaturated aldehydes using Noyori's system.

15.2.3.4 **Ru-TPPMS/TPPTS Catalysts**

It has been shown previously how water-soluble rhodium Rh-TPPTS catalysts allow for efficient aldehyde reduction, although chemoselectivity favors the olefinic bond in the case of unsaturated aldehydes [17]. The analogous ruthenium complex shows selectivity towards the unsaturated alcohol in the case of crotonaldehyde and cinnamaldehyde [31].

The biphasic reduction of 3-methyl-2-butenal under a pressure of hydrogen demonstrated a non-dependence on solvent (Table 15.5) [18]. Good conversions and selectivities were achieved in a selection of immiscible solvents in just over an hour, using a SCR of 200 : 1. No phase-transfer agents were needed as the slight solubility of the substrate in water ensured a rapid reaction. Under the same conditions, the catalyst was recycled three times with no loss of activity or selectivity: in fact, the reactions were faster than the initial reaction [18]. This was due to the initial run requiring an induction period for formation of the active catalyst. The analogous rhodium catalysts could cleanly reduce unsaturated aldehydes, but the high selectivity was towards the saturated aldehyde.

Table 15.5 Biphasic reduction of 3-methyl-2-butenal.



Solvent	Time [min]	Conversion [%]	Selectivity [%]
Cyclohexane	80	99	92
Chloroform	70	84	96
Ethyl acetate	75	93	96
Toluene (fresh catalyst)	60	100	96
Toluene (1st recycle)	30	99	97
Toluene (2nd recycle)	30	99	97

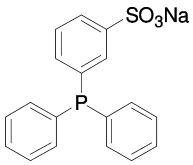
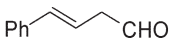
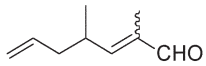
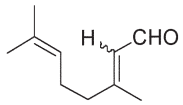
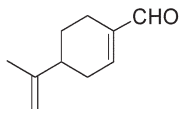


Fig. 15.6 TPPMS.

Table 15.6 Hydrogenation of α,β-unsaturated aldehydes using $[(PPh_3)CuH]_6$ (5 mol% Cu) and $PhPMe_2$ (30 mol%) at room temperature.

Substrate	Pressure [bar]	Conversion [%]	Selectivity [%]	TOF [h^{-1}]
	5	94	97	5
	28	91	94	<1
	34	90	92	1
	34	95	97	1

The ruthenium complex of the mono-sulfonated TPPMS (Fig. 15.6) is not only good for the transfer hydrogenation of simple substituted benzaldehydes with yields over 90% and with over 98% selectivity [32], but it is also chemoselective in the transfer hydrogenation of *α,β*-unsaturated aldehydes without the aid of phase-transfer agents [33]. The $RuCl_2$/(TPPMS) catalyst was far more effective than either rhodium or iridium TPPMS catalysts [32]. The solution of the catalyst is air-stable in the presence of $HCOO^-$, and the reactions and workups are very simple. In a direct comparison of homogeneous and biphasic reductions of cinnamaldehyde using Ru-PPh_3 catalysts against Ru-TPPMS/TPPTS, the homogeneous Ru-PPh_3 systems were found to favor complete reduction of both the carbonyl and the olefinic bond. In contrast, if aqueous biphasic systems were employed, selectivity was restricted to the carbonyl bond [34].

15.2.4 Other Metal Catalysts

15.2.4.1 Copper

Phenyldimethylphosphine-stabilized copper(I) hydrides catalyze a highly chemoselective hydrogenation of unsaturated aldehydes and ketones [35]. The reaction tolerates the use of either benzene or tetrahydrofuran (THF) as solvent, but requires a high concentration of *tert*-butanol as co-solvent to ensure high turnover and reaction homogeneity. Although high pressures are not required, they must exceed 1 bar in order to obtain complete conversion. In the reduction of *α,β*-unsaturated aldehydes using $[(PPh_3)CuH]_6$ and $PhPMe_2$, chemoselectivity was high, in most cases giving greater than 90% yields although the TOF was very low in all cases (Table 15.6). The minor byproducts were the saturated alcohols that arise from complete reduction.

As allylic alcohols are unaffected by use of this catalyst it is proposed that the complete reduction occurs through competitive conjugate reduction, followed by subsequent reduction of the carbonyl. Although this catalyst is slower in action and results in low turnover numbers compared to some catalysts, it is inexpensive and provides good selectivity at room temperature.

15.2.4.2 Osmium

The Osmium cluster $Os_3(CO)_{12}$ and clusters in the presence of various phosphines and triphenylphosphite have been utilized for the hydrogenation of cinnamaldehyde and crotonaldehyde (Table 15.7) [36]. The results show that good yields of unsaturated alcohols can be obtained by using a large excess of phosphine at elevated hydrogenation temperatures.

In such reactions, a temperature exceeding 130 °C has a dramatic effect on the catalytic activity. The pressure of hydrogen has a similar effect, with a large increase in activity above 30 bar. These catalysts did not exhibit the same selectivity for ketones. Osmium triphenylphosphine systems have been briefly exam-

Table 15.7 Hydrogenation of crotonaldehyde and cinnamaldehyde under 45 bar H_2 at 140 °C for 9 h.

Catalytic system	Substrate	Conversion [%]	Unsaturated alcohol [%]	Saturated aldehyde [%]	Saturated alcohol [%]
$[Os_3(CO)_{12}]$	Crotonaldehyde	18	13	5	0
	Cinnamaldehyde	15	7	6	2
$[Os_3(CO)_{12}]/P^nBu_3$	Crotonaldehyde	93	89	0	4
(15 : 1)	Cinnamaldehyde	97	86	0	11
$[Os_3(CO)_{12}]/PPh_3$	Crotonaldehyde	47	35	4	8
(15 : 1)	Cinnamaldehyde	98	91	1	6
$[Os_3(CO)_{12}]/P(OPh)_3$	Crotonaldehyde	28	9	0	19
(15 : 1)	Cinnamaldehyde	81	79	1	1

ined as potential catalysts for hydrogenation. However, in the reduction of crotonaldehyde, it is generally the unsaturated aldehyde which is produced [25].

The use of water-soluble ligands was referred to previously for both ruthenium and rhodium complexes. As in the case of ruthenium complexes, the use of an aqueous biphasic system leads to a clear enhancement of selectivity towards the unsaturated alcohol [34]. Among the series of systems tested, the most convenient catalysts were obtained from mixtures of $OsCl_3 \cdot 3H_2O$ with TPPMS (or better still TPPTS) as they are easily prepared and provide reasonable activities and modest selectivities. As with their ruthenium and rhodium analogues, the main advantage is the ease of catalyst recycling with no loss of activity or selectivity. However, the ruthenium-based catalysts are far superior.

15.3 Hydrogenation of Ketones

15.3.1 Iridium Catalysts

The cyclometallated iridium complex $[Ir(H)_2(P,C\text{-}Ph_2PC_6H_4N(Me)CH_2)(P,N\text{-}Ph_2PC_6H_4NMe_2)]$ (Fig. 15.7) is formed from the reaction of $[Ir(COD)(OMe)]_2$ with *o*-(diphenylphosphino)-*N,N*-dimethylaniline [37].

The product, although sensitive to light and air, was an effective catalyst for the transfer hydrogenation of several ketones in propan-2-ol. Unsaturated ketones were used with a SCR of 500 : 1, and mostly gave high selectivity and modest yields (Table 15.8).

This was the first example of catalytic chemoselective reduction of *α,β*-unsaturated ketones to allylic alcohols by hydrogen transfer and, unusually, did not require the use of a basic co-catalyst.

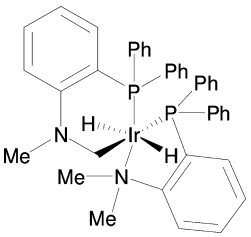
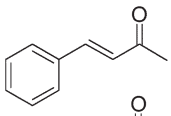
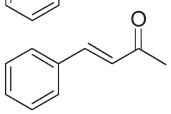
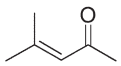
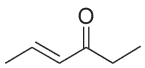


Fig. 15.7 $[Ir(H)_2(P,C\text{-}Ph_2PC_6H_4N(Me)CH_2)(P,N\text{-}Ph_2PC_6H_4NMe_2)]$.

Table 15.8 Hydrogenation of unsaturated ketones in propan-2-ol at 83 °C (SCR = 500).

Substrate	Conversion [%]	Saturated ketone [%]	Saturated alcohol [%]	Unsaturated alcohol [%]	Selectivity [%]
	99 (1 h)	1	6	92	93
	94 (1 h)	13	14	67	71
	65 (7 h)	2	1	62	95
	35 (7 h)	23	0	12	34

In the selective hydrogenation of benzylideneacetone (PhCH=CHCOMe) using an iridium phosphine system generated *in situ* from $[Ir(COD)(OMe)]_2$ and the appropriate phosphine [38], a heavy dependence was found on the nature and amount of phosphine used. Both of these factors are important in the activity and selectivity of the catalyst. Using PMe_2Ph as the model phosphine in a two-fold excess, the C=C bond was hydrogenated and the saturated ketone further hydrogenated to the saturated alcohol. However, increasing the excess of phosphine led to a switch in selectivity towards the carbonyl, although a loss of catalytic activity was reported. The cone angle of the phosphine is also important. Regardless of the solvent used, selectivity is raised above 90% when the cone angle is between 135 and 150°. The selectivity falls to zero at cone angles above and below this range.

These results suggest that, depending on the cone angle and relative concentration of the phosphines, different catalytic species are formed, and only catalysts formed from a large excess of relatively small phosphines are selective.

Generally, the selective reactions were complete in less than 24 h (SCR = 500, 30 bar H_2, 100 °C; TOF $\sim 20\ h^{-1}$).

The mixed donor polydentate ligands Pr^n-$N(CH_2CH_2PPh_2)_2$ (PNP) and $Et_2NCH_2CH_2N(CH_2CH_2PPh_2)_2$ (P_2N_2) have been reacted with $[Ir(COD)(OMe)]_2$ to produce complexes that were active in the reduction of PhCH=CHCOMe [39]. Conversions of 90% with modest selectivity were achieved in 2–4 h in propan-2-ol at 83 °C. At 140 °C in cyclopentanol, similar results are obtained in less than 30 min.

15.3.2 Rhodium Catalysts

15.3.2.1 Rh-Phosphine Catalysts

The cationic species $[RhH_2(PPh_3)_2L_2]^+$ (L = solvent) has been used by Schrock and coworkers to catalyze the hydrogenation of alkenes, dienes and allynes [40]. These authors discovered that when the triphenylphosphine groups are replaced with more basic phosphines, ketones were reduced under mild conditions [41]. Using the $[RhH_2(PPhMe_2)_2L_2]^+X^-$ ($X^- = PF_6^-$ or ClO_4^-), acetone was reduced under atmospheric pressure of H_2 at 25 °C in the presence of 1% water. Under identical conditions, cyclohexanone, acetophenone and butan-2-one were also successfully reduced. Benzophenone was not hydrogenated, and it is thought that it may have formed a stable Rh complex. The addition of water was vital for activity, with the maximum rate achieved when 1% water is used. This addition of water also inhibited the reduction of alkenes. When the same catalysts were used for aldehyde reduction they proved to be effective initially, but their activity fell rapidly.

Rossi and coworkers successfully hydrogenated a series of simple ketones, with over 96% yields, using the complex $[Rh_2H_2Cl_2(COD)(PPh_2)_3]$ in the presence of a strong base [42].

$[Rh(bpy)_2]^+$, obtained by the *in-situ* reduction of $[Rh(bpy)_2Cl_2]Cl$ with hydrogen in methanolic sodium hydroxide [43], can reduce a series of simple ketones under 1 bar H_2 and at 30 °C [44]. Yields of over 98% were obtained in all cases with a SCR of up to 680 : 1. When a mixture of ketones and aldehydes was placed under such conditions, the ketones were found to be reduced preferentially, although unsaturated ketones were generally reduced to saturated ketones.

Although the complex $[RhCl(PPh_3)_3]$ is inactive towards the hydrogenation of ketones, the addition of triethylamine dramatically increases the rate. Yields were increased from only 0.5% to over 98% for the reduction of acetophenone at 50 °C under 71 bar H_2 in a 1 : 1 mixture of methanol and benzene [45]. Several other ketones have been reduced this manner, including benzophenone, which has proved difficult (see above; Fig. 15.8).

The catalyst derived from $[Rh(NBD)Cl]_2$ and PPh_3 showed the same enhancement with triethylamine [45]. Later studies [46] showed that increasing the amount of methanol increased the rate, although some benzene must be retained to dissolve the catalyst. The presence of triethylamine as co-catalyst must be at least 5 equivalents relative to the rhodium in order to obtain a maximum

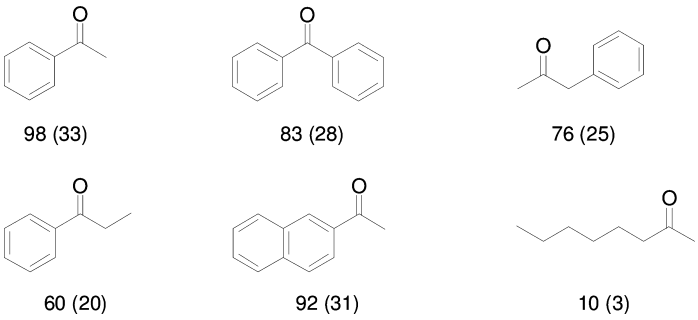


Fig. 15.8 Hydrogenation of ketones using $RhCl(PPh_3)_3$ + $5Et_3N$. Values shown are yields (TOF, h^{-1}).

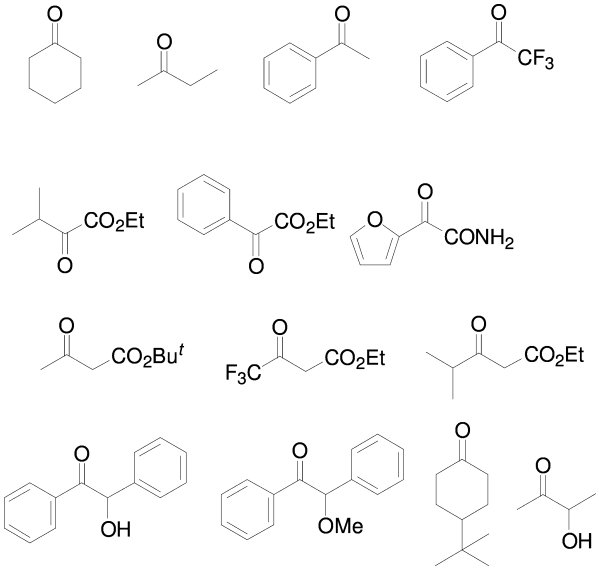


Fig. 15.9 The range of ketones hydrogenated using [Rh(DiPFc)(COD)]OTf.

rate. Coupled with this, an increase of triphenylphosphine from 2 to 4 equivalents also increases the activity. Combining all of these factors provides an idealized catalytic system of $[Rh(NBD)Cl]_2$ (2.5 mol%) with PPh_3 (8 mol%) and NEt_3 (12.5 mol%). With a SCR of 40:1, this system was used to reduce a vast range of ketones in benzene:methanol (30:70) at 50 °C under 1 bar H_2, with yields that were still below 80%.

The cationic complex [Rh(DiPFc)(COD)]OTf was discussed earlier as being an excellent catalyst for the hydrogenation of aldehydes under mild conditions. Under similarly mild conditions (25 °C, 4 bar H_2, SCR 450, 4 h, TOF $\sim 110\ h^{-1}$), a range of ketones was hydrogenated quantitatively (Fig. 15.9) [13].

In optimizing the conditions for such a reduction, protic solvents such as methanol and ethanol are required over dichloromethane (DCM), ethyl acetate (EtOAc), and THF which deactivate the catalyst. High substrate concentrations were also required, presumably due to dimerization of the catalyst that can occur in the absence of ketone or olefinic substrates. Finally, increasing the hydrogen pressure also gave an increase in yield. When this catalyst is used for the hydrogenation of unsaturated ketones, the C=C bond is first reduced very rapidly to give the saturated ketone. A slower reduction of the carbonyl group then occurs to yield the saturated alcohol.

15.3.2.2 **Water-Soluble Rh Catalysts**

The water-soluble ligand (TPPTS) was discussed earlier with regard to aldehyde reduction [17]. Similarly, in ketone transfer hydrogenation, high yields are obtained for a variety of substrates with the ability for efficient catalyst recycling at no expense of activity or selectivity (Fig. 15.10).

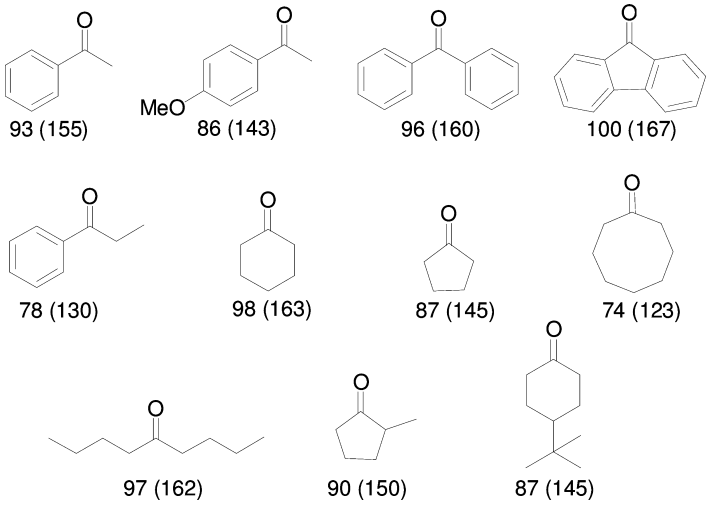


Fig. 15.10 Transfer hydrogenation of ketones at 80 °C catalyzed by $[RhCl(COD)]_2$/TPPTS. Values shown in brackets are yields (TOF, h^{-1}).

15.3.3 Ruthenium Catalysts

15.3.3.1 Ruthenium Carbonyl Clusters

Early efforts into ruthenium-catalyzed ketone hydrogenation experiments were performed using ruthenium-carbonyl clusters [47]. With cyclohexanone as a substrate and $[H_4Ru_4(CO)_{12}]$ as the catalyst, a range of solvents was tested for applicability. The greater reaction rates were achieved using alcohols, although the use of primary or secondary alcohols led to a decrease in selectivity due to the formation of ethers. The catalyst could be recovered at the end of the reaction. Partial displacement of the carbonyls with phosphines led to a decrease in activity, but further replacement of carbonyls with phosphines increased activity. By modifying such complexes with chiral bidentate phosphines, the first example of enantioselective transfer hydrogenation using $[H_4Ru_4(CO)_8[(-)\text{-DIOP})]_2]$ was realized, although optical yields were less than 10% [48].

15.3.3.2 Ru–PPh_3 Complexes

Mononuclear ruthenium complexes were found to be superior to carbonyl clusters during a comprehensive comparison of a variety of catalysts in the reduction of acetone [49]. Without solvent, most catalysts were highly selective, although the activity was quite low. The addition of water to the system vastly increased yields, in agreement with Schrock and Osborn's observations into rhodium-catalyzed hydrogenations (Table 15.9) [41].

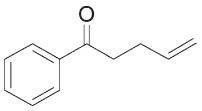
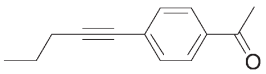
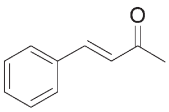
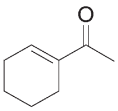
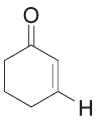
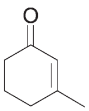
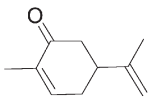
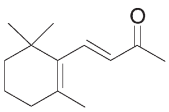
The addition of aqueous NaOH or acetic acid resulted in an increase in rate, but the selectivity was reduced – perhaps due to the formation of aldol condensation products. This is in contrast to the findings of Rossi with rhodium systems [42] and Strohmeier, who claimed that the addition of acid or base also increased selectivity when using $RuCl_2(PPh_3)_3$ and $Ru(CF_3CO_2)_2(CO)(PPh_3)_2$ as catalyst [50]. It was found that catalysts possessing carbonyl ligands or nitrosyl ligands were

Table 15.9 Hydrogenation of acetone. Conditions: SCR = 1300, 150 °C, 69 bar, 4 h.

Complex	Conversion (2.5% H_2O) [%]	Selectivity (2.5% H_2O) [%]	Conversion (dry) [%]	Selectivity (dry) [%]
$[RuHCl(CO)(PPh_3)_3]$	95	95	25	93
$[RuH(NO)(PPh_3)_3]$	97	95	22	95
$[RuCl_2(CO)_2(PPh_3)_2]$	90	92	26	87
$[Ru(H)_2(CO)(PPh_3)_3]$	69	94	67	100
$[Ru(H)_2(PPh_3)_4]$	39	82	56	98
$[RuCl_2(PPh_3)_3]$	33	83	18	82
$[RuH_4(PPh_3)_3]$	30	86	78	100
$[RuHCl(PPh_3)_3]$	13	70	6	70
$[Ru_3(CO)_{12}]$	3	41	6	69

higher in activity and selectivity. This was attributed to the complexes of general formula $[RuX_2(PPh_3)_n]$ (X = H, Cl; n = 3, 4) having a competing decarbonylation reaction, as demonstrated by the presence of metal carbonyl complexes in the reaction mixture after completion. In the hydrogenation of acetone under 69 bar H_2 at 150 °C with a SCR of 100 000, turnover numbers of up to 15 000 h^{-1} could be achieved over three days, using $[RuHCl(CO)(PPh_3)_3]$ and a little water. These were similar findings to the hydrogenation of aldehydes under the same conditions.

Table 15.10 Hydrogenation of unsaturated ketone at 28 °C and 4 bar H_2 (ketone : $RuCl_2(PPh_3)_3$: $H_2N(CH_2)_2NH_2$: KOH = 500 : 1 : 1 : 2).

Substrate	Yield [%]	Unsaturated alcohol [%]	Saturated alcohol [%]	TON	TOF [h^{-1}]
	100	98.2	1.8	491	714
	99.5	100	0	498	332
	100	99.9	0	10 000	555 [a]
	98.2	99.6	0.4	489	327
	100	70	30	350	500
	99.8	99.9	0.1	499	333 [b]
	100	92.8	7.2	464	71
	99	100	0	495	495

Yields of saturated ketone are < 0.1% in all cases.

a) Reaction performed with ketone : Ru = 10 000 : 1.

b) H_2 pressure of 8 bar used.

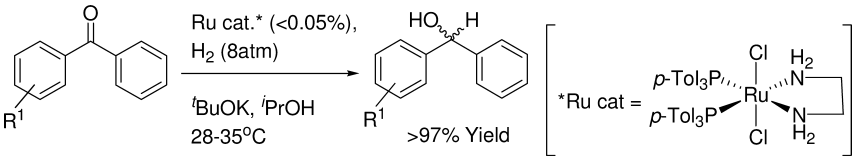
The $[RuCl_2(PPh_3)_3]$ catalysts can be used more effectively to hydrogenate ketones using formic acid as the hydrogen source [51]. In solvent-free reactions, the formic acid completely decomposes and the products are easily obtained from the reaction mixture. Thus, in reactions carried out at 125 °C with a SCR of 800:1, simple ketones and aldehydes are reduced with excellent yields. Applying formic acid as a hydrogen source to the Ru cluster catalysts and other Ru phosphine catalysts gave less favorable results.

15.3.3.3 **Diamine-Modified Ru Catalysts**

Noyori and coworkers discovered that the activity of $[RuCl_2(PPh_3)_3]$ could be enhanced by the addition of ethylenediamine (en) and KOH/*i*-PrOH [52]. Using the system for acetophenone hydrogenation (Ru:en:KOH, 1:1:20, SCR 5000 at 28 °C under 3 bar H_2), TOFs of 6700 h^{-1} were obtained. The pressure of hydrogen is important, as demonstrated by a TOF of 880 h^{-1} under 1 bar H_2 (SCR = 500). By increasing the pressure to 50 bar and using a SCR of 10 000, TOFs in excess of 23 000 were obtained. The reaction was even shown to work at –20 °C, showing just how mild the conditions employed can be. In order for the catalytic system to work, both the organic and inorganic bases are required with at least one primary amine end to the diamine. Applying this catalytic system to unsaturated ketones shows a remarkable selectivity towards the unsaturated alcohol (Table 15.10) [29]. Reaction times vary from substrate to substrate between 1 and 18 h, with yields and selectivities of over 99% easily achieved. The catalyst will even reduce the acetylenic ketones without the alkyne group being affected. The catalyst shows great scope and, with ligand modification, a highly enantioselective catalyst can be produced. The mechanism of this unique catalyst is described in Chapters 20 and 32.

An alternative variation to this catalyst, *trans*-$[RuCl_2[P(C_6H_4\text{-}4\text{-}CH_3)_3]_2(H_2NCH_2CH_2NH_2)]$ and KOtBu in isopropanol, is excellent for the selective hydrogenation of benzophenones (Scheme 15.8) [53].

The products of such reactions can be useful intermediates in the synthesis of commercial drugs. The nature of the substituents within the benzophenones has an effect on rate, with electron-withdrawing groups favoring the reaction more than electron-donating groups. For example, kinetic studies showed that *p*-trifluoromethylbenzophenone was hydrogenated 11-fold faster than the *p*-



R^1 = H, *o*-CH_3, *o*-Cl, *m*-Cl, *p*-C_6H_5, *p*-CH_3O, *p*-F, *p*-Cl, *p*-CF_3

Scheme 15.8 Hydrogenation of benzophenones.

Table 15.11 Hydrogenation of benzophenones with *trans*-$[RuCl_2\{P(C_6H_4\text{-}4\text{-}CH_3)_3\}_2(H_2NCH_2CH_2NH_2)]$ and KO*t*Bu in *i*PrOH under 8 bar H_2 at 28–35 °C.

R^1	SCR	Concentration [M]	Yield [%]	TON	TOF [h^{-1}]
H	20 000	2.7	99	19 800	413
o-CH_3	3000	1.5	99	2970	165
p-CH_3O	3000	1.5	99	2970	165
p-Cl	3000	1.3	100	3000	375
p-CF_3	2000	0.4	99	1980	1980

methoxy derivative. However, a range of benzophenones was reduced smoothly at 30 °C (Table 15.11). In an optimized experiment demonstrating the practicability of the method, a slurry of 200 g benzophenone in 200 mL *i*-PrOH was hydrogenated with an SCR of 20 000 within 48 h at 30 °C.

Recently, several catalysts based on ligands containing an NH_2 or NH grouping within the phosphine ligand, such as $Ph_2PCH_2CH_2NH_2$, have been shown to have considerable activity and chemoselectivity for ketone hydrogenation [54–56].

15.3.3.4 **Other Ru Catalysts**

As for some of the monodentate phosphine-based catalysts, *cis*-$[Ru(6,6'\text{-}Cl_2bpy)_2(OH_2)_2][CF_3SO_3]_2$ was found to require water for the best catalytic activity in the reduction of aldehydes and ketones [57]. Aldehydes and ketones were found to be hydrogenated, with reasonable yields. Unsaturated aldehydes were reduced with selectivity towards the unsaturated alcohol, whereas unsaturated ketones showed selectivity towards the saturated ketones.

The water-soluble ruthenium TPPTS system which functioned well for saturated and unsaturated aldehydes has also been tested for the hydrogenation of ketones [31]. Although good yields for simple ketones could be obtained depending on the substrate, the selectivity when used for unsaturated ketones was in favor of the C=C bond. The polyphosphine catalysts $RuHCl(CO)(PPh_3)$(dppe) (dppe = $Ph_2PCH_2CH_2PPh_2$) and RuHCl(CO)(tdpme) (tdpme = $CH_3C(CH_2PPh_2)_3$) show greater activity than $RuHCl(CO)(PPh_3)_3$ in the hydrogenation of cyclohexanone [58]. Turnover numbers of 450 and 625 are achieved, respectively, for the polydentate complexes, compared to 82 for the triphenylphosphine complex.

Highly efficient transfer hydrogenation of ketones can be achieved by the use of the transfer hydrogenation catalyst *trans,cis,cis*-$[RuX_2(CNR)_2(dppf)]$ (X = Cl or Br; R = CH_2Ph, cy, *t*-Bu, 2,6-$C_6H_3Me_2$) [59]. These are the first examples of isocyanide–ruthenium species being used for the transfer hydrogenation of ketones. The complexes are prepared by the reaction of bis(allyl)-ruthenium(II) complex $[Ru(\eta^3\text{-}2\text{-}C_3H_4Me)_2(dppf)]$ with HX acid in the presence of the isocyanide. All the catalysts were effective in the hydrogenation of acetophenone, giving quanti-

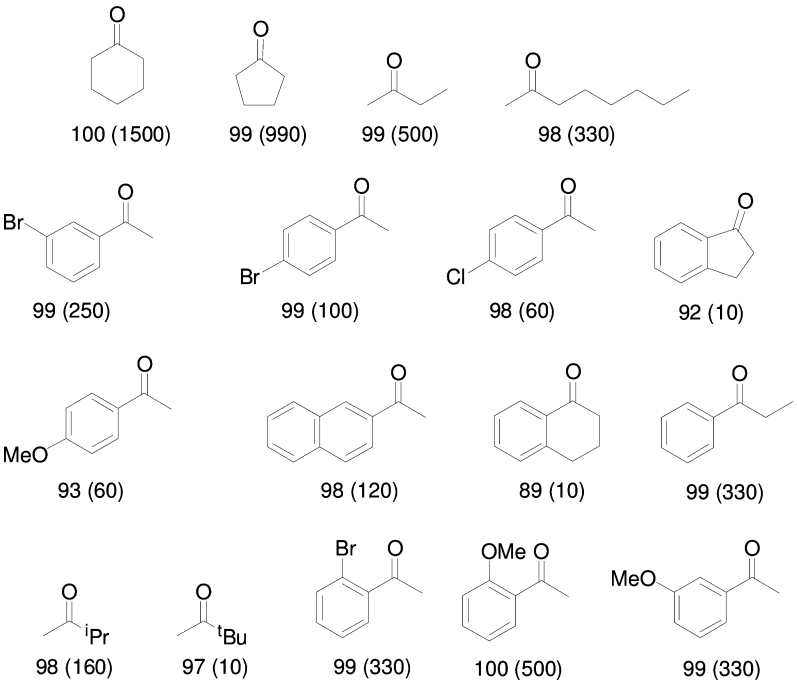


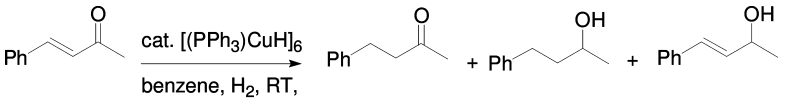
Fig. 15.11 *trans,cis,cis*-[$RuCl_2(CNCH_2Ph)_2$(dppf)] catalysed hydrogenation of ketones. Values shown are yields (TOF, h^{-1}).

tative yields between 0.5 and 8 h. *trans,cis,cis*-[$RuCl_2(CNCH_2Ph)_2$(dppf)] proved to be the most active, and was further utilized in the transfer hydrogenation of a series of ketones at 82 °C using a ketone : Ru : NaOH ratio of 250 : 1 : 24 (Fig. 15.11).

15.3.4 Other Metal Catalysts

15.3.4.1 Copper

The use of phosphine-stabilized copper complexes as hydrogenation catalyst was discussed previously for aldehydes. The same catalysts have been used in the hydrogenation of simple ketones, with high yields achieved in reactions lasting for up to 48 h [35]. Several unsaturated ketones were hydrogenated, with high chemoselectivity, to the unsaturated alcohol. These catalysts are sensitive to the structure of the phosphine ligand. In the hydrogenation of 4-phenyl-3-butan-2-one, it is possible to obtain any of the three possible products by varying the phosphine (Fig. 15.12) [60].



No phosphine, 70 atm H_2	91	:	9	:	0	89% (3)
PPh_3, 117 atm H_2	0	:	92	:	8	95% (1.5)
Me_2PPh, 34 atm H_2	0	:	8	:	92	91% (6)

Fig. 15.12 Effect of phosphine on selectivity. Values shown are yields (TOF, h^{-1}).

15.3.4.2 **Metal Carbonyls**

The metal carbonyls $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$ and $Fe(CO)_5$ have all been tested in the hydrogenation of acetophenone in the presence of a strong base [61, 62]. In reactions performed in either triethylamine of sodium methoxide in methanol using 5 mol% of catalyst, the Mo and Cr complexes proved to be superior. The different bases had an effect on the yield that was further demonstrated when $Cr(CO)_6$ was used in the hydrogenation of a series of ketones under the same conditions. In most cases, the reactions were found to be better in the methoxide system, with over 98% yields obtained in reactions lasting 3 h at 120 °C.

15.4 Domino-Hydroformylation-Reduction Reactions

15.4.1 Cobalt Catalysts

Cobalt-catalyzed hydroformylation of terminal alkenes using $[Co(H)(CO)_4]$ as catalyst delivers mixtures of branched and linear aldehydes under elevated pressures and high temperatures (160–200 °C). In 1968, it was found that adding a trialkylphosphine to the cobalt catalyst reduces activity, but stabilizes the catalyst for use under 100 bar syngas pressure [63]. The use of phosphine ligands increases the hydrogenation activity such that the aldehydes are directly hydrogenated to alcohols as the only oxygenated products isolated. This is a desirable process, since linear alcohols are often the target products from many hydroformylation processes. Tributylphosphine can serve as a ligand for this purpose, but the ligands which provide the best catalyst stability are those that have a bicyclic structure such as the "phobane" ligand [64] and, more recently, the limonene-derived phosphines shown below [65]. Recent studies of the hydroformylation of dodecene at 170 °C, 85 bar syngas pressure using 1000 ppm $[Co(H)(CO)_4]$ show that 70% linear alcohols can be formed, with relatively small amounts of branched alcohol ($n:iso = 4.9$) and alkane (6%) as the side products. Under these typical conditions, aldehyde hydrogenation appears to be the most facile step in the process, as aldehydes are not observed.

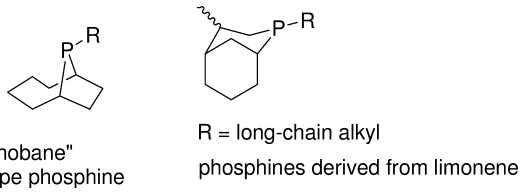


Fig. 15.13 Bicyclic phosphines used in cobalt-catalyzed hydroformylation.

15.4.2
Rhodium Catalysts

Rhodium-catalyzed hydroformylation can be carried out under much milder conditions (5–50 bar H_2/CO, $T = 20–120\,^{\circ}C$), shows higher TOFs, fewer alkane byproducts, and can be manipulated to give very high selectivity towards the linear aldehydes [66]. Given that linear alcohols are frequently the desired products, several investigations have been made on the use of Rh catalysts to hydrogenate aldehydes under the reaction conditions. This has indeed been observed in several cases, using strongly electron-donating phosphines [67–69] or amines [70, 71] as ligands. The most detailed studies on this topic have been carried out by Cole-Hamilton and coworkers, who used $[Rh_2(OAc)_4]/PEt_3$ as a catalyst [72–74]. In the hydroformylation of hex-1-ene in aprotic solvents, hydrogenation of the initially formed heptanal and 2-methylhexanal products to the corresponding alcohols occurs as the reactions proceeds. High TOFs were observed at 120 °C (40 bar syngas) with modest linear-to-branched regioselectivity: low linear selectivity is often observed using alkyl phosphine ligands in hydroformylation. Pure heptan-1-al is also readily hydrogenated under similar reaction conditions using the same catalysts. However, when the reactions were carried out in alcoholic solvents, mechanistic investigations established that alcohols are actually the initial reaction products with no aldehyde intermediates being formed.

More recently, during research aimed at supporting the highly linear selective hydroformylation catalyst $[Rh(H)(Xantphos)(CO)_2]$ onto a silica support, the presence of a cationic rhodium precursor in equilibrium with the desired rhodium hydride hydroformylation catalyst was observed. The presence of this complex gave the resulting catalyst considerable hydrogenation activity such that high yields of linear nonanol could be obtained from oct-1-ene by domino hydroformylation-reduction reaction [75].

15.5
Reductive Amination of Ketones and Aldehydes

Although imine hydrogenation is discussed in greater detail in Chapter 34, it seems appropriate at this point to describe one-pot reductive amination of aldehydes and ketones. The reductive amination of aldehydes and ketones using so-

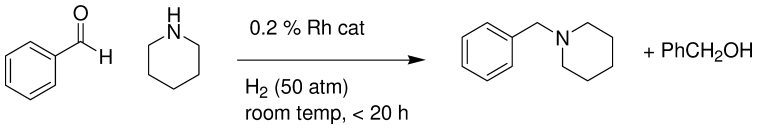
dium borohydride or sodium cyanoborohydride is well established. However, a more environmentally benign and economical method to carry out this reaction is to use molecular hydrogen. Several heterogeneous catalysts have been shown to be effective in this transformation, but interest has been expressed in the use of more controllable homogeneous catalysts for this purpose.

The first example of this type of transformation was reported in 1974 [76]. Three catalysts were investigated, namely $[Co_2(CO)_8]$, $[Co(CO)_8/PBu^n_3]$, and $[Rh_6(CO)_{16}]$. The $[Co(CO)_8/PBu^n_3]$ catalyst showed activity for reductive amination using ammonia and aromatic amines. The $[Rh_6(CO)_{16}]$ catalyst could be used for reductive amination using the more basic aliphatic amines that were found to poison the cobalt catalyst. This early report pointed out that the successful reductive amination of *iso*-butanal (Me_2CCHO) with piperidine involves selective enamine hydrogenation, that reductive amination of cyclohexanone with isopropylamine probably involves imine hydrogenation, and that reductive amination of benzaldehyde with piperidine would presumably involve the reduction of a carbinolamine.

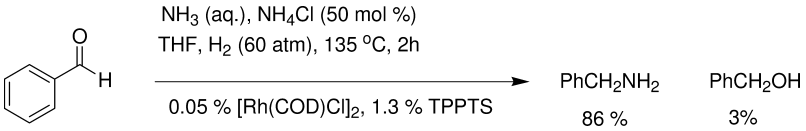
Although this report establishes some of the principles of this class of reaction, no turnover numbers or SCRs were reported, and harsh reaction conditions (100–300 bar H_2/CO, 110–200 °C) were employed. Subsequently, this process received sporadic attention, except as a process combined with a hydroformylation stage. In 1997, Knifton found that amination of linear aldehydes using ammonia could be achieved, and showed that the related domino hydroformylation-amination process was also possible [77]. In 2000, Borner and coworkers released preliminary results describing a more practical catalyst system for these reactions [78]. Benzaldehyde and piperidine could be reductively aminated using $[Rh(dppb)(COD)]BF_4$ or [Rh(1,2-bis-diphenylphosphinitoethane)(COD)]BF_4 under mild conditions (50 bar H_2, room temperature). A total of 500 catalytic turnovers could be achieved within a few hours, with the reaction being hampered by only moderate selectivity towards the tertiary amine (Scheme 15.9).

Selectivities of about 2:1 are the best found for this type of hydrogenation and are highly dependent on the secondary amine used: they seem to correlate with the nucleophilicity of the amine. Reductive amination of PhCHO with benzylamine can proceed through an imine intermediate, and thus gave better selectivities (12:1) but was found to be sluggish using this catalyst system.

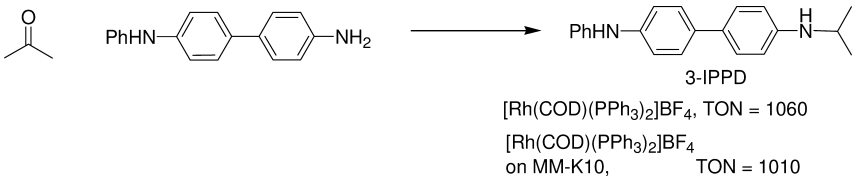
Beller and coworkers recently realized a more practical system for reductive amination of aromatic aldehydes using ammonia [79]. Their preferred conditions, which require the addition of an acidic additive, are shown in Scheme 15.10. Without extensive optimization, turnover numbers of 1700 could be



Scheme 15.9 Reductive amination of benzaldehyde.



Scheme 15.10 Reductive amination using ammonia.



Scheme 15.11 Reductive amination of acetone.

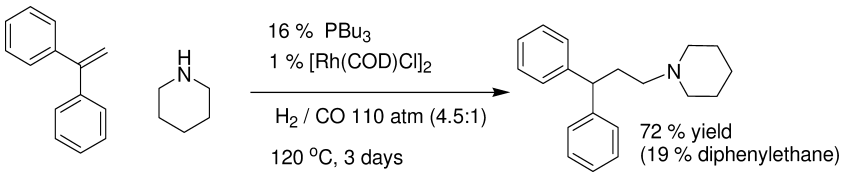
achieved. A biphasic system is required in order to make use of aqueous ammonia. However, preliminary data show a second advantage in that the Rh-containing aqueous phase can be recovered by phase separation and re-used. Aliphatic aldehydes remain a problem for which further research is required.

$[Rh(COD)(PPh_3)_2]BF_4$ has been shown to be a good catalyst for reductive amination of acetone with 4-anilino-aniline to give the commercial product 3-IPPD. In laboratory-scale comparative experiments, this catalyst – both in homogeneous phase or immobilized on Montmorillonite K10 clay – was found to be superior to the commercially applied Pt/C catalyst (Scheme 15.11) [80].

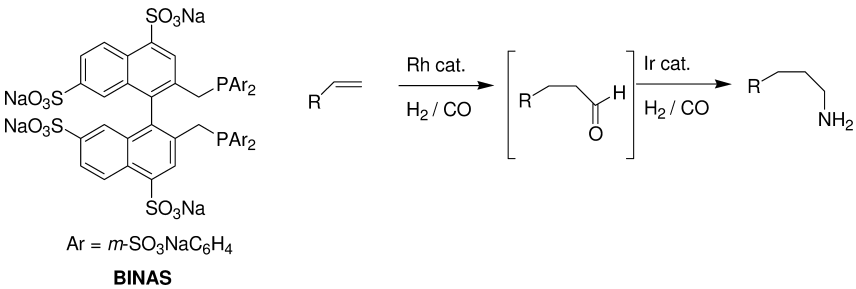
In recent years there has been emerging interest in one-pot asymmetric amination of ketones, but this subject is beyond the scope of this chapter. However, an interesting observation by Borner and coworkers is that different catalysts seem to be required to carry out this process compared to those used for hydrogenation of the corresponding imines or enamines [81, 82].

15.6 Hydroaminomethylation of Alkenes (Domino Hydroformylation-Reductive Amination)

Given the previous discussion on reductive amination, it is surprising that the potentially more complicated domino hydroformylation-reductive amination reactions have been more thoroughly developed. The first example of hydroaminomethylation was reported as early as 1943 [83]. The most synthetically useful procedures utilize rhodium [84–87], ruthenium [88], or dual-metal (Rh/Ir) catalysts [87, 89, 90]. This area was reviewed extensively by one of the leading research groups in 1999 [91], and so is only briefly outlined here as the second step in the domino process is reductive amination of aldehydes. Eilbracht's group have shown that linear selective hydroaminomethylation of 1,2-disubstituted alkenes



Scheme 15.12 Synthesis of fenpiprane using hydroaminomethylation of diphenylethene.



Scheme 15.13 Hydroaminomethylation of terminal alkenes to linear amines.

such as diphenylethene can give access to a series of compounds of pharmaceutical interest such as fenpiprane, diisopromine, tolpropamine, fendiline, prozapine [92], penfluridol [93], and fluspirilene [93]. An example of one of their procedures is shown in Scheme 15.12. The use of a relatively large amount of phosphine is required to suppress competing alkene hydrogenation reactions.

Eilbracht's group has done much to demonstrate the synthetic possibilities of using this reaction. However, the most recent developments in this field have also shown that the reaction could be applied as a practical method to prepare linear amines. Beller and coworkers have shown that linear selective hydroaminomethylation of propene, but-1-ene, and pent-1-ene with aqueous ammonia can be realized in a two-phase solvent system (water : methyl *tert*-butylether), using $[Rh(COD)Cl]_2$/$[Ir(COD)Cl]_2$ and water-soluble diphosphine ligand, BINAS as catalyst. If excess ammonia is used, primary amines can be produced with good primary : secondary selectivity and near-perfect linear-to-branched selectivity (Scheme 15.13, Table 15.12). Running the reaction with excess alkene allows for secondary amines to be synthesized with excellent chemo- and regioselectivity. The catalyst displays up to 4000 turnovers with respect to rhodium, although relatively high concentrations of phosphine ligand seem to be required [90].

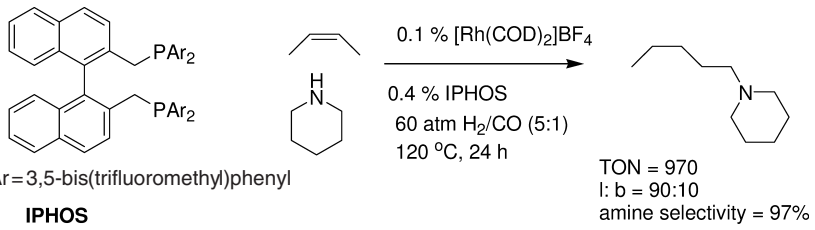
This group subsequently invented a domino reaction consisting of isomerization of internal to terminal alkenes, followed by linear selective hydroformylation and reductive amination (Scheme 15.14) [89].

A more recent report thoroughly investigates hydroaminomethylation of terminal alkenes to give high yields of linear (linear : branched = 99 : 1) tertiary amines from secondary amines and terminal alkenes or linear secondary

Table 15.12 Hydroaminomethylation of terminal alkenes to linear primary and secondary amines.[a)]

Alkene	NH_3/alkene	Yield (amine)	*n*:*iso*	Primary:secondary
Propene	8:1	90	99:1	77:23
Propene	0.5:1	90	99:1	1:99
Pent-1-ene	8:1	75	99:1	87:13
Pent-1-ene	0.5:1	90	99:1	10:90

a) Conditions: temperature = 130 °C; 79 bar H_2/CO (5:1); time = 10 h; 0.026% Rh; 0.21% Ir; ligand:Rh ratio = 140.



Scheme 15.14 Domino isomerization hydroaminomethylation.

amines from primary amines and alkenes. Reactions were conducted at 125 °C with TOF of ca. 160 h^{-1} [87].

The recent improvements described above suggest that hydroaminomethylation is approaching use as a practical process for preparing a range of amines with good linear selectivity, and good catalytic activity.

15.7 Hydrogenation of Carboxylic Acid Derivatives

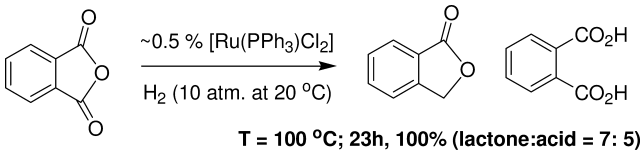
The hydrogenation of acids, esters and anhydrides using molecular hydrogen is a neglected and difficult challenge. Lithium aluminum hydride ($LiAlH_4$) and certain boron hydrides are traditionally used for this reduction. However, a stoichiometric aluminum reagent is not atom-efficient and requires the separation and disposal of aluminum reagents at the end of the reaction. Catalytic hydrogenation using molecular hydrogen is potentially the ideal "green" alternative to any of the stoichiometric procedures, and would attract industrial attention if a catalyst were sufficiently active. Heterogeneous catalysts (especially copper-chromite) can carry out this process, albeit under severe conditions (200–250 °C; 14 000–20 000 kPa), which limits their application.

15.7.1
Hydrogenation of Acids and Anhydrides

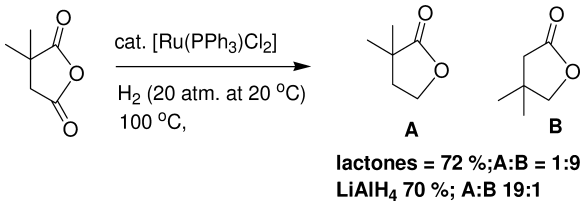
The first examples of a homogeneous reduction of this type were reported in 1971. Cobalt carbonyl was found to reduce anhydrides such as acetic anhydride, succinic anhydride and propionic anhydride to mixtures of aldehydes and acids. However, scant experimental details were recorded [94]. In 1975, Lyons reported that $[Ru(PPh_3)_3Cl_2]$ catalyzes the reduction of succinic and phthalic anhydrides to the lactones γ-butyrolactone and phthalide, respectively [95]. The proposed reaction sequence for phthalic anhydride is shown in Scheme 15.15. Conversion of phthalic anhydride was complete in 21 h at 90 °C, but yielded an equal mixture of the lactone, phthalide (TON = 100; TOF $\sim$ 5) and *o*-phthalic acid, which is presumably formed by hydrolysis of the anhydride by water during lactonization. Neither acid or lactone were further hydrogenated to any extent using this catalyst system, under these conditions.

This catalyst was subsequently applied in the regioselective hydrogenation of 2,2-dimethylsuccinic anhydride [96]. An interesting reversal of regioselectivity towards the isomer B was found when switching from $LiAlH_4$ reduction to the catalytic method. Quite good isolated yields and selectivity were recorded, though no data on catalytic turnover were reported (Scheme 15.16).

Mitsubishi have reported several processes based on Ru-catalyzed hydrogenation of anhydrides and acids. Succinic anhydride can be converted into mixtures of 1,4-butane-diol and γ-butyrolactone using $[Ru(acac)_3]$/trioctylphosphine and an activator (often a phosphonic acid) [97]. Relatively high temperatures are required ($\sim$200 °C) for this reaction. The lactone can be prepared selectively under the appropriate reaction conditions, and a process has been developed for isolating the products and recycling the ruthenium catalyst [98–100].



Scheme 15.15 Hydrogenation of *o*-phthalic acid.



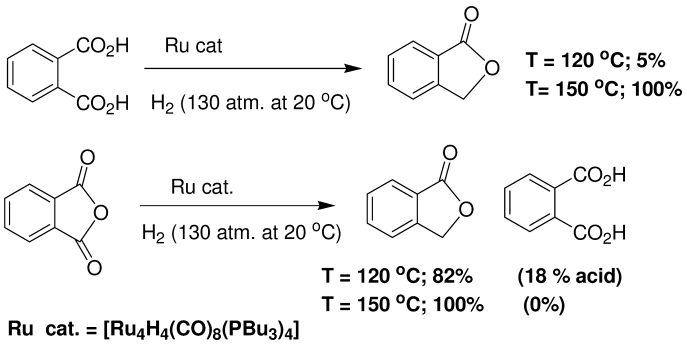
Scheme 15.16 Regioselective hydrogenation of an unsymmetrical succinic acid derivative.

Table 15.13 Hydrogenation of succinic acid and anhydride using $[Ru_4H_4(CO)_8(P^nBu_3)_4]$. [a)]

Substrate	Temperature [°C]	Time [h]	Conversion [%]	Yield of γ-butyrolactone [%] [b)]
Succinic acid	150	20	11	11
Succinic acid	180	22	83	83
Succinic acid	180	48	100	100
Succinic anhydride	100	22	40	16
Succinic anhydride	100	48	78	36
Succinic anhydride	170	40	100	100

a) TON were not reported but, based on the 100 mg of catalyst reported, are approximately 300.

b) The remaining mass is succinic acid.



Scheme 15.17 Hydrogenation of *o*-phthalic acid and anhydride.

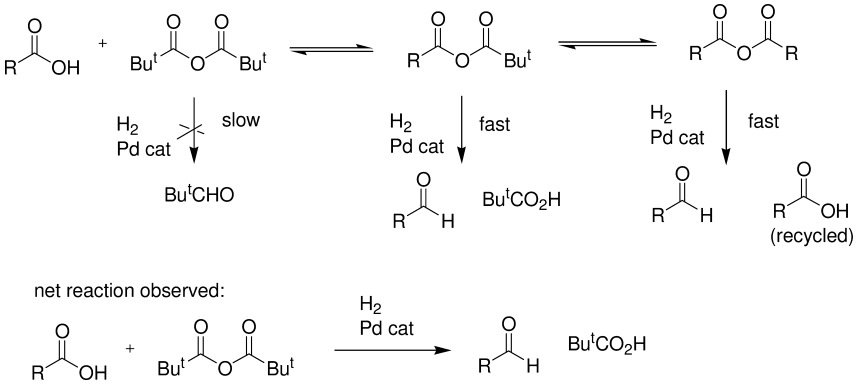
The first example of carboxylic acid hydrogenation was reported as a side product in the hydrogenation of citraconnic acid using the chiral catalyst $[RuH_4(CO)_8\{(-)\text{-DIOP}\}]$ [101]. This research team subsequently investigated acid, ester, and anhydride hydrogenation in some detail in studies which exclusively used Ru carbonyl clusters with monodentate trialkylphosphine ligands as catalysts. The reduction of succinic acid, $(CH_2CO_2H)_2$ with succinic anhydride, is compared in Table 15.13 [102].

Succinic anhydride is clearly hydrogenated more readily than the acid, as was the case with phthalic acid (Scheme 15.17), but faster absolute rates were observed in the hydrogenation of *o*-phthalic acid and phthalic anhydride to phthalide. In these reactions, the problem of anhydride hydrolysis is less significant as the acid can also be reduced to the same lactone product.

The effect of carboxylic acid structure was also investigated. Oxalic acid and malonic acids were found to decompose, while glutaric acid $HO_2C(CH_2)_3CO_2H$ was hydrogenated, though with poor selectivity. Although the glutaric acid results were not synthetically useful, the products included 1,5-pentane-diol and 2-hydroxy-tetrahydropyran, which showed that ester hydrogenation was a possibility. Adi-

pic acid ($HO_2C(CH_2)_4CO_2H$) was only 25% converted to ε-caprolactone, while azelaic acid ($HO_2C(CH_2)_7CO_2H$) was not reduced under similar conditions. The importance of a neighboring carboxylate group was therefore demonstrated, although it is not clear from these results whether the origin of this effect is the formation of stable lactones, secondary coordination to the ruthenium catalyst, or the presence of an electron-withdrawing substituent. Benzoic and phenyl acetic acids are not reduced under the conditions shown in Table 15.13, and are only slowly hydrogenated at 200 °C (9% in 48 h for benzoic acid). Although this study provides some important information regarding the feasibility of acid and anhydride hydrogenation, a number of questions remain unanswered. The effect of different ligands on ruthenium, and the importance of the cluster species on catalytic activity were not investigated. It would therefore be unwise to conclude that hydrogenation of a certain acid substrate is impractically difficult. In particular, a rough comparison of the results in Table 15.13 for succinic anhydride hydrogenation (Entry 4) with those previously described with $[Ru(PPh_3)_3Cl_2]$ for succinic anhydride (90 °C, 100% conversion in 21 h, 50:50 mix of lactone:acid) does not suggest that the cluster catalysts used by this group are necessarily the most reactive catalysts possible. Davy Process and Technology have recently developed a useful catalyst for hydrogenation of acids, whereby unactivated propionic acid can be hydrogenated to propanol at 240 °C with good productivity and selectivity using a catalyst derived from a ruthenium (III) salt such as $[Ru(acac)_3]$ and the tridentate phosphine, triphos (see also Table 15.17). The choice of ligand is essential for high catalytic activity [103].

An investigation of several transition-metal catalysts – including those that could be considered heterogeneous – were investigated in the hydrogenation of pentadecanoic acid. A strong promotional effect of metal carbonyls such as $Re_2(CO)_{10}$ and $Mo(CO)_6$ on catalysts such as $M(acac)_3$ (M = Ru, Rh), increasing yields of pentadecanol from 2% to 97% (TON = 97) at 160 °C and 100 bar H_2 pressure. A chemoselective reduction of pentadecanedioic acid monomethyl ester was also reported using these catalysts. The authors note that these reactions gave alcohols relatively cleanly, without ester side products [104].



Scheme 15.18 Hydrogenation of acids *via* anhydride intermediates.

The hydrogenation of cyclic anhydrides using $[Pd(PPh_3)_4]$ as catalyst was reported by Yamamoto and coworkers. The reaction proceeds by oxidative addition of the anhydride followed by hydrogenolysis, and proceeds well in THF at 80 °C (~100 turnovers, unoptimized). However, aldehyde productivity is limited to 50% by the reaction mechanism that involves hydrogenolysis of Pd-acyl and Pd-carboxylato groups in $[Pd(PPh_3)_2(C(O)R)(O_2CR)]$ to give an equal mixture of aldehydes and acids [105]. Very bulky anhydrides were significantly more difficult to reduce, which led this group to design a process for converting carboxylic acids into aldehydes in the presence of bulky anhydrides [105–107]. Thus, heating a wide range of less sterically demanding acids in the presence of $[Pd(PPh_3)_4]$ (~1%), $(t\text{BuCO})_2O$ (3 equiv.) and H_2 (~30 bar) delivers both $t\text{BuCO}_2H$ and aldehyde in high yield. The reaction is proposed to occur via transesterification between acid, (RCO_2H) and $(t\text{BuCO})_2O$ to give mixed anhydride $RC(O)OC(O)t\text{Bu}$ and new anhydride $(RCO)_2O$. These anhydrides are hydrogenated much more rapidly than $(t\text{BuCO})_2O$ and the oxidative addition of the mixed anhydride is regioselective, giving the acyl complexes of type $[Pd(L)_2(C(O)R)(OC(O)t\text{Bu}]$, which hydrogenate to RCHO and $t\text{BuCO}_2H$.

The reaction tolerates ketone, chloride, internal C=C bonds, esters, nitriles, and ether functional groups. Given that the DIBAL-H reduction of acid derivatives often suffers from over-reduction to alcohols, these catalytic procedures are of synthetic value for laboratory-scale syntheses. However, it is likely that the requirement for excess $(t\text{BuCO})_2O$ will prevent this reaction from ever being used in commercial production.

15.7.2 Hydrogenation of Esters

The first examples of a clean hydrogenation of an ester to an alcohol was reported by Grey et al. [108]. A catalyst prepared by potassium naphthalide reduction of $[RuH(PPh_3)_2Cl]_2$, formulated as $K_2[Ru_2(PPh_3)_3(PPh_2)H_4]_2$. Diglyme hydrogenated methyl trifluoroacetate (MTFA) to trifluoroethanol and methanol at 90 °C (6 bar H_2). The 88% yield obtained corresponds to 290 turnovers. Trifluoroethyl trifluoroacetate (TFETFA) was hydrogenated more readily using the same catalyst system, while methyl acetate could be hydrogenated for the first time (TON = 35), but with considerable difficulty. Formate esters decompose with the liberation of carbon monoxide under these reaction conditions. The anionic catalysts used by this group were compared with $[RuH(PPh_3)_3Cl]$, and found to be significantly more active (Table 15.14).

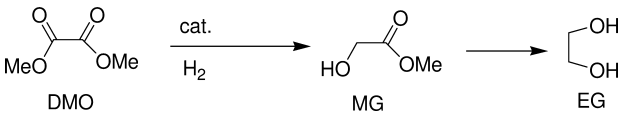
In addition to the successful hydrogenation of the two fluorinated esters, this report describes the hydrogenation of dimethyl oxalate. Using the reactive anionic ruthenium catalyst, a 70% conversion to methyl glycolate could be achieved (TON = 235; TOF ~12 h^{-1}) (Scheme 15.19, Table 15.14, final entry).

The results suggest a pronounced electronic effect on ester hydrogenations. This substrate effect has not been studied exhaustively by any means, but led to

Table 15.14 Hydrogenation of esters using ruthenium catalysts.[a)]

Substrate	Catalyst	Conversion [%]	Remarks
MeOAc	$[RuH(PPh_3)_3Cl]$	0	–
MeOAc	$K_2[Ru_2(PPh_3)_3(PPh_2)H_4]$	22	Toluene, 13% EtOAc product (by transesterification) and EtOH (9%)
MeOAc	$K_2[Ru_2(PPh_3)_3(PPh_2)H_4]$	5	THF
MTFA	$[RuH(PPh_3)_3Cl]$	0	Toluene
MTFA	$K_2[Ru_2(PPh_3)_3(PPh_2)H_4]$	88	Toluene
TFETFA	$[RuH(PPh_3)_3Cl]$	20	Toluene
TFETFA	$K_2[Ru_2(PPh_3)_3(PPh_2)H_4]$	100	Toluene, 4 h
DMO	$K_2[Ru_2(PPh_3)_3(PPh_2)H_4]$	70	Toluene, 70% MG, 0% EG

a) Conditions: 5.7 mmol ester, 0.017 mmol $K_2[Ru_2(PPh_3)_3(PPh_2)H_4]_2$ diglyme, 0.045 mmol $[RuH(PPh_3)_3Cl]$; reaction time = 20 h; temperature = 90 °C; P = 620 kPa H_2.



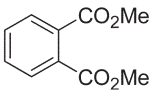
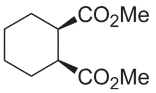
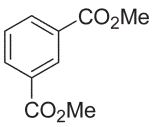
Scheme 15.19 Dimethyl oxalate hydrogenation.

a considerable research effort aimed at reducing dimethyl oxalate (DMO) to either methyl glycolate (MG) or ethylene glycol (EG).

By using the $[Ru_4H_4(CO)_8(PnBu_3)_4]$ catalyst system reported for acid hydrogenation of acids [102], Matteoli and coworkers investigated the hydrogenation of dicarboxylic acid ester derivatives at 130 bar pressure and 180 °C [109]. Using relatively high catalyst loadings (maximum TON ~150), DMO could be converted cleanly into the hydroxyl-ester, MG. The hydrogenations of various dicarboxylate esters under similar conditions are listed in Table 15.15. No TOF were reported, though these data do show the relative reactivity of several substrates. Consistent with Grey's observation regarding the activating effect of electron-withdrawing substituents, striking differences in hydrogenation rates were seen, depending on the proximity of the second carboxylate ester group in the substrate.

As can be seen from the data in Table 15.15, increasing the tether length results in significantly less hydrogenation. The results obtained with the C_4 esters, dimethyl-*o*-phthalate, dimethyl-*cis*-cyclohexane-1,2-carboxylate and dimethyl succinate are informative (Table 15.15, Entries 4–6, respectively). The close proximity of the second carboxylate ester in the substrates that are readily hydrogenated suggests two possibilities: an electronic effect, or a chelate effect. It can be envisaged that the electron-withdrawing effects of the ester group are more readily

Table 15.15 Hydrogenation of dicarboxylic esters under similar conditions. [a]

Entry	Substrate	Conversion [%]	Product(s) [b]
1	$(CO_2Me)_2$	51	Methylglycolate (MG) (51)
2	$CH_2(CO_2Me)_2$	38	$HOCH_2CH_2CO_2Et$ (17) $CH_3CH_2CO_2Et$ (10) Ethyl acetate and transesterification products (11)
3	$(CH_2CO_2Me)_2$	7	γ-Butyrolactone (7)
4		21	Phthalide (11) Methyl benzoate (10)
5		1	–
6	$CH_2(CH_2CO_2Me)_2$	0	–
7		0	–

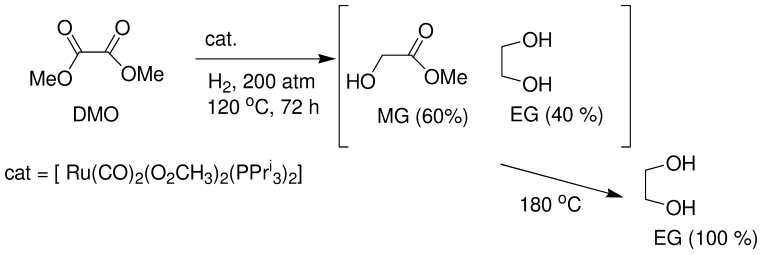
a) Conditions: 144 h; 25 mg $[Ru_4H_4(CO)_8(PnBu_3)_4]$; 6 g substrate, 130 bar H_2; 180 °C.
b) Values in brackets are product yields (%).

transmitted through the aromatic system in dimethyl-*o*-phthalate than in dimethyl succinate. If chelate coordination of the substrate was primarily responsible for the high reaction rates, then dimethyl-*cis*-cyclohexane-1,2-carboxylate and dimethyl-*o*-phthalate should give similar yields. Since this is not the case it seems that, for ester hydrogenations – at least using this type of catalytic system – reactivity is primarily controlled by electronic effects within the ester substrate.

In 1986, the same research group reported an improved pre-catalyst, $[Ru(CO)_2(CO_2CH_3)_2(PnBu_3)_2]$ [110]. Using this catalyst system in hydroxylated solvents, the hydrogenation of DMO produced ethylene glycol in addition to methyl glycolate, therefore inferring the hydrogenation of the less-activated ester methyl glycolate. When this system was studied in detail under standard conditions, the gradual conversion of DMO to MG then to EG is clear to see (t=1 h: DMO 48%, MG 52%, EG 0%, t=2.5 h: DMO 0%, MG 100%, EG 0%, t=72 h: DMO 0%; MG 78.4%; EG 21.6%). The DMO hydrogenation shows half-order reliance on DMO concentration, whereas the MG hydrogenation does not fit any steady-

Table 15.16 Hydrogenation of dimethyl oxalate using $[Ru(CO)_2(CO_2CH_3)_2(PnBu_3)_2]$.

Pressure [bar]	Catalyst concentration [mmol L^{-1}]	Temperature [°C]	Methyl glycolate [%]	Ethylene glycol [%]
10	4.9	180	96.2	3.8
90	4.9	180	81.2	18.8
130	4.9	180	78.4	21.6
130	2.45	180	90.8	9.2
130	9.70	180	69.2	30.8
130	4.9	120	51.4	0



Scheme 15.20 Two-stage hydrogenation of esters giving ethylene glycol (EG), without decomposition products. MG = methyl glycolate.

rate laws. The conversion did not surpass 31%, inferring a decomposition pathway for the catalyst – not surprisingly, after many days at 180 °C. A careful set of optimization experiments were carried out focused on increasing the yields of EG from DMO. Increasing hydrogen pressures, catalyst loading, and temperature all have beneficial effects on the hydrogenation. Informative results from these experiments are in Table 15.16. Finally, a pronounced improvement on conversion was realized by the interesting – but not entirely satisfactory – addition of ~1 equiv. of product in 0.5 mL benzene as additive. A 95% conversion to EG after 144 h at 180 °C (200 bar H_2) was observed.

In a subsequent report, the authors compared the more bulky triisopropylphosphine-based catalyst in DMO hydrogenation [111]. This initially appeared worse than the first system, as it produced considerable decomposition products (65%). However, the rates for hydrogenation of isolated MG using this system are superior to those with $[Ru(CO)_2(CO_2CH_3)_2(PnBu_3)_2]$, and do not produce decomposition products, which were proven to come only from DMO. A two-stage (two-temperature) procedure using the $PiPr_3$-based catalyst was therefore developed, which uses a lower initial temperature to suppress substrate decomposition (Scheme 15.20).

Table 15.17 Hydrogenation of dimethyl oxalate using bi-, tri-, and tetra-dentate ligands. [a)]

Ligand	Catalyst [μmol]	L:Ru ratio	Conversion [%]	MG [%]	EG [%]	TON [h^{-1}]
dppe	16.1	3	18	11	0	6
PPh_3	9.6	5.9	73	36	0	18
$PhP(C_2H_4PPh_2)_2$	20.1	1.7	76	67	0	38
$MeC(CH_2PPh_2)_3$	21.1	1.4	100	1	95	160
$(CH_2P(Ph)C_2H_4PPh_2)_2$	22.8	1.0	91	85	0	36

a) Conditions: MeOH solvent, 80 bar H_2; 120 °C; 0.3% Zn as additive.

There has been one further, recent development in this area. Elsevier and coworkers studied DMO hydrogenation using a broader range of catalysts, and under milder conditions than those used by Matteoli et al. [112, 113]. Elsevier and colleagues showed that tetra- and tri-dentate phosphines, when used in combination with $[Ru(acac)_3]$, are very promising pre-catalysts for this class of reaction (Table 15.17). Although no direct comparisons to Matteoli's or Grey's system were reported, a comparison of the preceding discussion with the data in Table 15.16 suggests that, at present, this catalyst system is the most active one known.

The data in Table 15.17 clearly show the improved activity of all three multidentate ligands, and more strikingly, the selective formation of EG using the TRIPHOS ligand. The most significant difference between triphos ($MeC(CH_2PPh_2)_3$) and $PhP(CH_2CH_2PPh_2)_2$ is that triphos is a facially coordinating ligand to octahedral ruthenium complexes. This type of coordination chemistry could therefore prove a key to further improved ester hydrogenation catalysts.

The Elsevier system has since been shown to carry out several ester hydrogenations that were previously deemed impossible [114]. The hydrogenation of dimethyl phthalate to phthalide with ruthenium cluster catalysts has already been discussed (Table 15.15, Entry 4). The application of $[Ru(acac)_3]$ and triphos – this time with a 20-fold excess of Et_3N as additive – delivers good yields of phthalide. However, the use of isopropanol (IPA) as solvent and 24% HBF_4 allows further hydrogenation to 1,2,-bis-hydroxylmethyl benzene for the first time. Both of these reactions were carried out under milder conditions (100 °C, 85 bar H_2, 16 h) than those reported previously.

A striking improvement in catalytic activity was observed when hydrogenating the esters benzyl benzoate (BZB) and methyl palmitate (MP; $C_{15}H_{31}CO_2Me$). An increase from the TON of ~100 observed in IPA to ~2000 (BZB hydrogenation) and 600 (MP hydrogenation) were found by using hexafluoroisopropanol as solvent with 9 mol% Et_3N as additive. Although this solvent is rather expensive, these are high turnover numbers for the hydrogenation of substrates that previously could not be hydrogenated at all using homogeneous catalysts. Hopefully, these two reports will lead the way towards developing practical ester

hydrogenation in the not too distant future. Indeed, a recent patent from Davy Process and Technology has explored this type of catalyst system in the hydrogenation of unactivated esters such as methyl propionate and dimethylmaleate. In methyl propionate hydrogenation at $\sim 190\,^{\circ}C$, good conversions to the propanol can be achieved, provided that water is present in the reaction vessel. The role of the water is to regenerate the catalyst which is deactivated during the reaction. This was proven by an experiment in which a catalyst that was no longer active for hydrogenation was reactivated by heating in the presence of water [103]. This catalyst system also hydrogenates anhydrides and acids. In these cases, the water produced by the hydrogenation is sufficient to allow the reaction to be run without any added water. Another patent on effective solutions for ester hydrogenation has also recently appeared [115].

The field of ester hydrogenation is significantly less developed in comparison with the hydrogenation of other double bonds. Many of the studies are limited to DMO hydrogenation, and the full scope of the reaction needs to be evaluated. At present, the research findings suggest that electron-withdrawing substituents activate substrates considerably, but the breakthrough by Elsevier's group suggest that a more broadly applicable procedure for ester hydrogenation might become reality.

Catalyst development has also been relatively unexplored. It is noteworthy that two of the most significant developments were made when the effect of different phosphine ligands were being investigated in more detail for the first time [111, 114]. At present, it is difficult to predict the future for ester hydrogenation, but if the "catalysis community" invests time into the development of the process it could prove to be an environmentally benign method for carrying out reductions in the fine chemical and pharmaceutical industries. Indeed, recent developments in industry suggest that the reaction could be viable for production-scale synthesis, and that the discovery of more active catalysts would be of considerable value.

15.8 Summary and Outlook

Since the first report of a homogeneously catalyzed reduction of a C=O bond, various research groups have endeavored to develop catalysts that show sufficient activity and high chemoselectivity to be used as a viable alternative to heterogeneous catalysts in the production of primary and racemic/achiral secondary alcohols. Much of this research effort has been conducted side-by-side with, and informed developments in, the diastereoselective and enantioselective hydrogenation of polar bonds, since activity and chemoselectivity are also key issues for these catalysts. This research effort has brought some catalysts to a level of development that suggests they might be applied in commercial production.

The ruthenium-phosphine-diamine catalysts exhibit high turnover numbers and frequencies, and near-perfect chemoselectivity for ketone/aldehyde over

C=C reduction. The achiral catalysts are relatively cheap, easy to prepare/handle, and sufficiently active to set SCRs near the threshold for Ru content in pharma products. This suggests that these catalysts could certainly be competitive, easy to operate in hydrogenations in which heterogeneous catalysts are less effective, and thereby also worthy of investigation in other cases.

The improvements made in hydroaminomethylation technology suggest that certain variants of this reaction are sufficiently developed for the potential production of amines. The synthesis of linear tertiary and secondary amines from terminal alkenes shows promise in this regard. Beller's recent contributions towards hydroaminomethylation using ammonia to produce linear primary amines, which are of industrial significance due to their abundance, suggest a bright future for this reaction. Branched selective hydroaminomethylation remains relatively underdeveloped and needs further study.

The hydrogenation of carboxylic acid derivatives using molecular hydrogen represents a major challenge, but has considerable importance from a "green chemistry" point of view. The heterogeneous catalysts capable of achieving this transformation function under energy-consuming and harsh conditions, and homogeneous catalysts for ester hydrogenation would clearly attract industrial interest if they were adequately efficient. Given that only a handful of reports have appeared on this subject, and that both substrate scope and catalyst structure–activity relationships have barely been defined, considerable further research is required in this area.

In summary, the research effort aimed towards active, chemoselective hydrogenations of certain C=O and C=N bonds have delivered several catalysts that approach the level of activity required for use in the synthesis of alcohols and amines. However, other classes of substrate require considerable additional investigations to be conducted before homogeneous catalysts may be considered for this purpose.

Abbreviations

DCM	dichloromethane
DMO	dimethyl oxalate
EG	ethylene glycol
EtOAc	ethyl acetate
MG	methyl glycolate
MTFA	methyl trifluoroacetate
SCR	substrate-catalyst-ratio
TFETFA	trifluoroethyl trifluoroacetate
THF	tetrahydrofuran
TOF	turnover frequency
TON	turnover number
TPPMS	triphenylphosphine, mono-sulfonated
TPPTS	3,3′,3″-phosphinidynetris-, trisodium salt

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