20
Transfer Hydrogenation Including the Meerwein-Ponndorf-Verley Reduction

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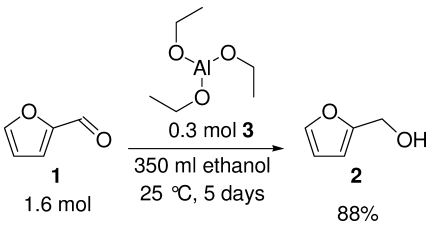
20.1
Introduction

The first homogeneous transfer hydrogenation was reported in 1925 when Meerwein and Schmidt described the reduction of ketones and aldehydes using alcohols as reductants and aluminum alkoxides as the catalysts (Scheme 20.1) [1]. The major difference from previous studies was the hydrogen source; instead of molecular hydrogen, a small organic molecule was utilized to provide the hydrogen necessary to reduce the carbonyl compound. The scope of the reaction was independently investigated by Verley [2], Ponndorf [3], and Lund [4]. Some 12 years later, Oppenauer recognized the possibility of reversing the reaction into an oxidation procedure [5]. Ever since that time, the Meerwein-Ponndorf-Verley (MPV) reduction and the Oppenauer oxidation have been taken as textbook examples of highly selective and efficient reactions under mild conditions.

More recently, Ln^{III} alkoxides were shown to have much higher catalytic activity in this reaction, which allowed their use in only catalytic amounts [6, 7]. Later, however, much higher reactivities for Al^{III}-catalyzed Meerwein-Ponndorf-Verley and Oppenauer (MPVO) reactions have also been achieved with dinuclear Al^{III} complexes [8,9] and with Al^{III} alkoxides generated *in situ* [10]. Several reviews on the MPVO reactions have been published [11–14].



Scheme 20.1 The first homogeneous transfer hydrogenation reduction of furfural (**1**) to furfurylalcohol (**2**), described by Meerwein and Schmidt, using 0.18 equiv. aluminum ethoxide (**3**) [1].

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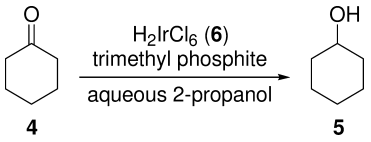


Scheme 20.2 A new approach towards the transfer hydrogenation of ketones, performed in 1964.

Pioneering studies on a different class of transfer hydrogenation catalysts were carried out by Henbest et al. in 1964 [15]. These authors reported the reduction of cyclohexanone (**4**) to cyclohexanol (**5**) in aqueous 2-propanol using chloroiridic acid (H_2IrCl_6) (**6**) as catalyst (Scheme 20.2). In the initial experiments, turnover frequencies (TOF) of 200 h^{-1} were reported.

A major step forward at this time was the introduction of the Wilkinson catalyst ($RhCl(PPh_3)_3$) (**7**) for hydrogen transfer reactions [16]. Although actually designed for hydrogenation with molecular hydrogen, this catalyst has been intensively used in transfer hydrogenation catalysis. Ever since, iridium, rhodium and also ruthenium complexes have been widely used in reductive transfer hydrogenations. The main advantage of these catalysts over the MPVO catalysts known until then was their comparatively higher catalytic activity. The TOFs of the transition-metal catalysts could be improved even further by the use of a base as additive, which deprotonates the substrate, facilitating complexation of the substrate to the metal ion in the intermediate complex [17–21]. Numerous reviews have been published on the topic of transition metal-catalyzed transfer hydrogenations [22–28].

The scope of hydrogen transfer reactions is not limited to ketones. Imines, carbon–carbon double and triple bonds have also been reduced in this way, although homogeneous and heterogeneous catalyzed reductions using molecular hydrogen are generally preferred for the latter compounds.

The advantages of hydrogen transfer over other methods of hydrogenation comprise the use of readily available hydrogen donors such as 2-propanol, the very mild reaction conditions, and the high selectivity. High concentrations of the reductant can be applied and the hydrogen donor is often used as the solvent, which means that mass transfer limitations cannot occur in these reactions. The uncatalyzed reduction of ketones requires temperatures of 300 °C [29].

Hydrogen transfer reactions are reversible, and recently this has been exploited extensively in racemization reactions in combination with kinetic resolutions of racemic alcohols. This resulted in dynamic kinetic resolutions, kinetic resolutions of 100% yield of the desired enantiopure compound [30]. The kinetic resolution is typically performed with an enzyme that converts one of the enantiomers of the racemic substrate and a hydrogen transfer catalyst that racemizes the remaining substrate (see also Scheme 20.31). Some 80 years after the first reports on transfer hydrogenations, these processes are well established in synthesis and are employed in ever-new fields of chemistry.

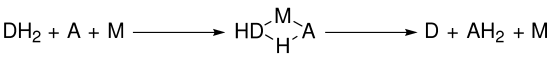
20.2
Reaction Mechanisms

Since the first use of catalyzed hydrogen transfer, speculations about, and studies on, the mechanism(s) involved have been extensively published. Especially in recent years, several investigations have been conducted to elucidate the reaction pathways, and with better analytical methods and computational chemistry the catalytic cycles of many systems have now been clarified. The mechanism of transfer hydrogenations depends on the metal used and on the substrate. Here, attention is focused on the mechanisms of hydrogen transfer reactions with the most frequently used catalysts. Two main mechanisms can be distinguished: (i) a direct transfer mechanism by which a hydride is transferred directly from the donor to the acceptor molecule; and (ii) an indirect mechanism by which the hydride is transferred from the donor to the acceptor molecule via a metal hydride intermediate (Scheme 20.3).

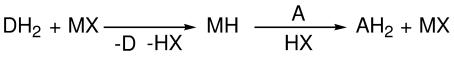
In the direct transfer mechanism, the metal ion coordinates both reactants enabling an intramolecular reaction, and activates them via polarization. Consequently, strong Lewis acids including Al^{III} and the Ln^{III} ions are the most suitable catalysts in this type of reactions. In the hydride mechanism, a hydride is transferred from a donor molecule to the metal of the catalyst, hence forming a metal hydride. Subsequently, the hydride is transferred from the metal to the acceptor molecule. Metals that have a high affinity for hydrides, such as Ru, Rh and Ir, are therefore the catalysts of choice. The Lewis acidity of these metals is too weak to catalyze a direct hydride transfer and, vice versa, the affinity of Al^{III} and Ln^{III} to hydride-ions is too low to catalyze the indirect hydrogen transfer. Two distinct pathways are possible for the hydride mechanism: one in which the catalyst takes up two hydrides from the donor molecule; and another in which the catalyst facilitates the transfer of a single hydride.

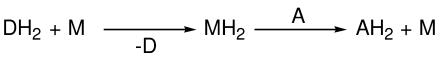
All hydrogen transfer reactions are equilibrium reactions. Consequently, both a reduction and an oxidation can be catalyzed under similar conditions. The balance of the reaction is determined by the thermodynamic stabilities of the spe-

direct transfer mechanism



hydride mechanisms





Scheme 20.3 Schematic representation of the two different hydrogen transfer mechanisms (D = donor molecule; A = acceptor molecule; M = metal).

cies in the redox equilibrium involved and by the concentrations of the hydride donors and acceptors.

20.2.1 Hydrogen Transfer Reduction of Carbonyl Compounds

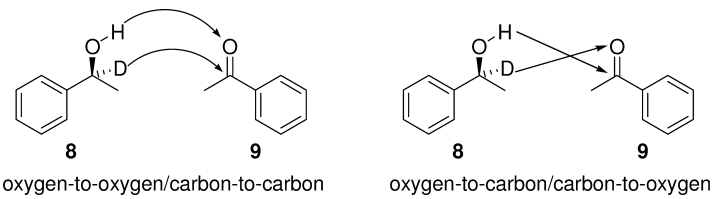
Transfer hydrogenations of carbonyl compounds are often conducted using 2-propanol as the hydrogen donor. One advantage of this compound is that it can be used simultaneously as a solvent. A large excess of the hydrogen donor shifts the redox equilibrium towards the desired product (see also Section 20.3.1).

Studies aimed at the elucidation of reaction mechanisms have been performed by many groups, notably by those of Bäckvall [28]. In test reactions, typically enantiopure 1-phenylethanol labeled with deuterium at the 1-position (**8**) is used. The compound is racemized with acetophenone (**9**) under the influence of the catalyst and after complete racemization of the alcohol, the deuterium content of the racemic alcohol is determined. If deuterium transfer proceeds from the *α*-carbon atom of the donor to the carbonyl carbon atom of the acceptor the deuterium is retained, but if it is transferred to the oxygen atom of the acceptor it is lost due to subsequent exchange with alcohols in the reaction mixture (Scheme 20.4).

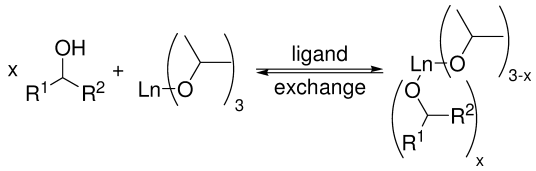
20.2.1.1 Meerwein-Ponndorf-Verley Reduction and Oppenauer Oxidation

The most common catalysts for the Meerwein-Ponndorf-Verley reduction and Oppenauer oxidation are Al^{III} and Ln^{III} isopropoxides, often in combination with 2-propanol as hydride donor and solvent. These alkoxide ligands are readily exchanged under formation of 2-propanol and the metal complexes of the substrate (Scheme 20.5). Therefore, the catalytic species is in fact a mixture of metal alkoxides.

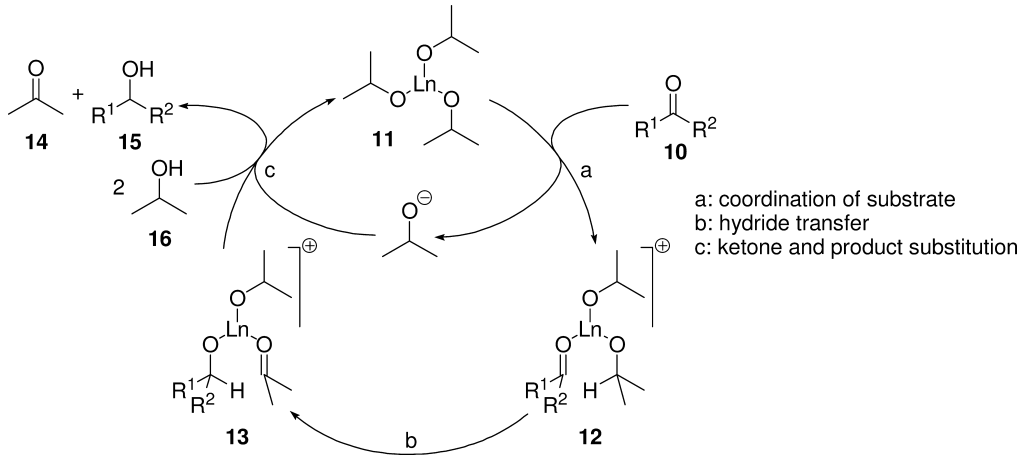
The catalytic cycle of the reaction is depicted in Scheme 20.6 [31]. After the initial ligand exchange, the ketone (**10**) is coordinated to the metal ion of **11** (a), yielding complex **12**. A direct hydride transfer from the alkoxide to the ketone takes place via a six-membered transition state (b) in which one alkoxy group is oxidized (**13**). The acetone (**14**) and the newly formed alcohol (**15**) are released



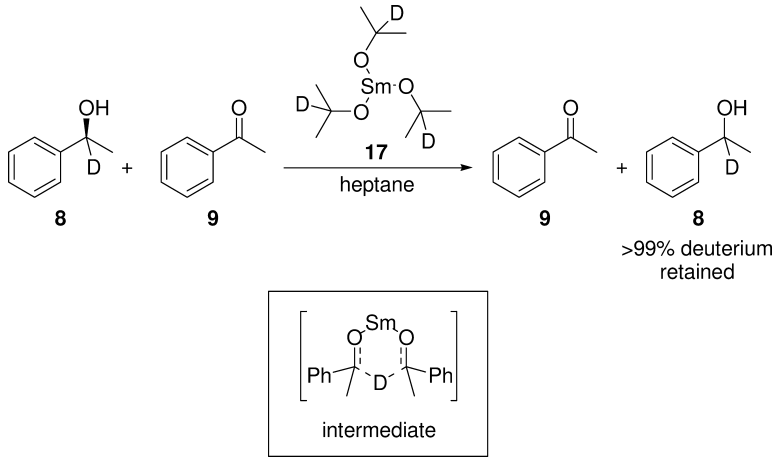
Scheme 20.4 Possible pathways of hydrogen transfer during the racemizations of alcohols using the corresponding carbonyl compound and a hydrogen transfer catalyst.



Scheme 20.5 Ligand exchange in MPVO reactions.



Scheme 20.6 Mechanism of the Meerwein-Ponndorf-Verley-Oppenauer reaction.



Scheme 20.7 Racemization of (*S*)-1-deutero-1-phenylethanol (**9**) with deuterated samarium(III) isopropoxide (**17**).

from the metal center by substitution for new donor molecules (**16**) (c) completing the cycle.

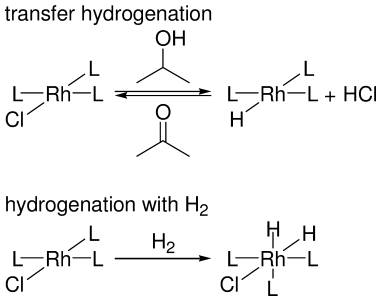
The mechanism of the MPVO reactions has been investigated and questioned on several occasions, and a variety of direct hydrogen-transfer pathways have been suggested (see Scheme 20.4) [31–35]. Recently, racemization of D-labeled 1-phenylethanol with deuterated samarium(III) isopropoxide (**17**) proved that the MPVO reaction occurs via a direct hydrogen transfer from the *α*-position of the isopropoxide to the carbonyl carbon of the substrate (Scheme 20.7) [31].

The selectivity of the hydrogen transfer is excellent. When employing a catalyst with deuterium at the *α*-positions of the isopropoxide ligands (**17**), complete retention of the deuterium was observed. A computational study using the density functional theory comparing the six-membered transition state (as in Scheme 20.3, the direct transfer mechanism) with the hydride mechanism (Scheme 20.3, the hydride mechanism) supported the experimental results obtained [36]. A similar mechanism has been proposed for the MPV alkynylations [37] and cyanations [38].

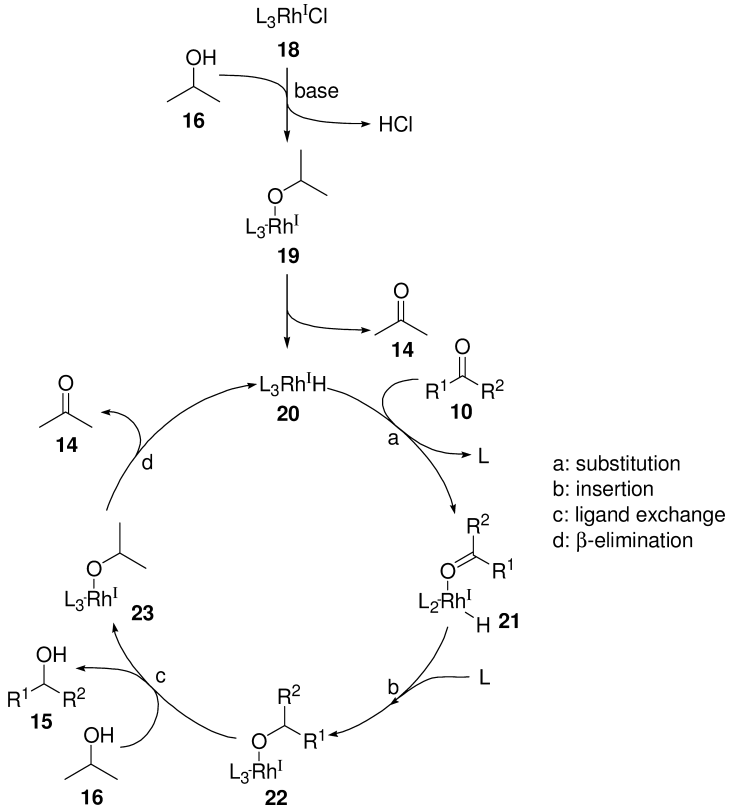
20.2.1.2 **Transition Metal-Catalyzed Reductions**

The Wilkinson catalyst, ($RhCl(PPh_3)_3$) (**7**), is not only an excellent hydrogenation catalyst when using molecular hydrogen as hydrogen donor, but can also be employed as a hydrogen transfer catalyst. It is a square-planar, 16-electron complex, which catalyzes these reactions via different pathways depending on the hydrogen donor. The intermediate rhodium complexes tend to retain a four-coordinated square-planar configuration, whereas the molecular hydrogen pathway proceeds through an octahedral state [35, 39–42] (Scheme 20.8).

In transfer hydrogenation with 2-propanol, the chloride ion in a Wilkinson-type catalyst (**18**) is rapidly replaced by an alkoxide (Scheme 20.9). *β*-Elimination then yields the reactive 16-electron metal monohydride species (**20**). The ketone substrate (**10**) substitutes one of the ligands and coordinates to the catalytic center to give complex **21** upon which an insertion into the metal hydride bond takes place. The formed metal alkoxide (**22**) can undergo a ligand exchange with the hydride donor present in the reaction mixture, liberating the product (**15**).



Scheme 20.8 Different behavior of the Wilkinson catalyst (**7**) for transfer hydrogenation and hydrogenation using molecular hydrogen.

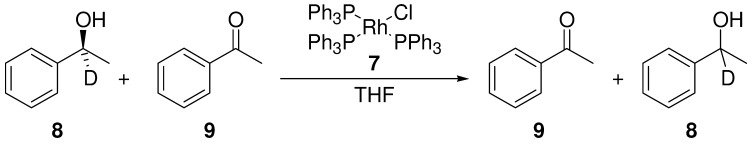


Scheme 20.9 Transition metal alkoxide mechanism.

After *β*-elimination, acetone is released and the metal monohydride (**20**) is obtained again from **23**, closing the catalytic cycle.

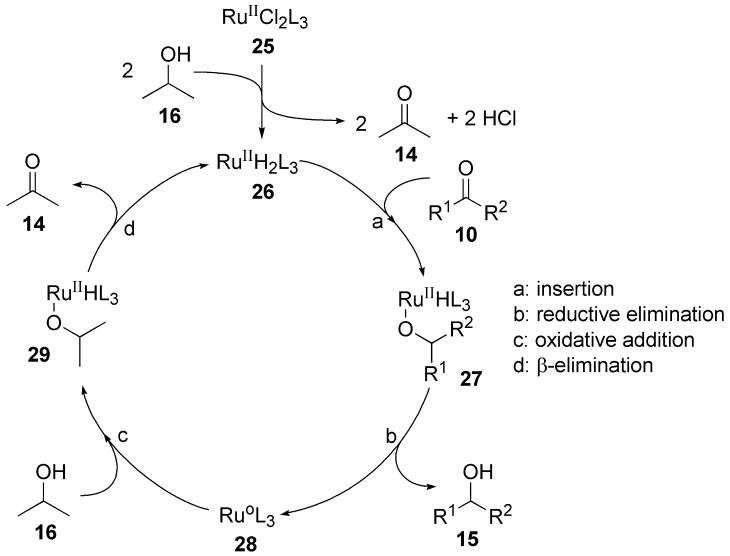
Mechanistic studies show that the extent of deuterium-labeling at the *α*-position of (*S*)-1-deutero-1-phenylethanol remains almost unchanged during a racemization reaction with this system (Scheme 20.10) [35]. This indicates that a single hydride is transferred from the *α*-position of the donor to the *α*-position of the acceptor. Only a slight decrease in deuterium content occurs (5%), which may be attributed to exchange with traces of water. In catalysts bearing phenyl phosphine ligands, the loss of deuterium can also be explained by orthometalation [43], leading to H/D exchange. Several other catalysts have been shown to operate via the same mechanism as the Wilkinson catalyst (Fig. 20.1).

A different mechanism is operative with the 16-electron complex $RuCl_2(PPh_3)_3$ (**24**) (Scheme 20.11). Here, the dichloride complex (**25**) is rapidly converted into a dihydride species (**26**) by substitution of both chloride ligands with alkoxides and subsequent eliminations similar to the conversion of **18** to **20** described above [46, 47]. Subsequently, the ruthenium dihydride species **26**



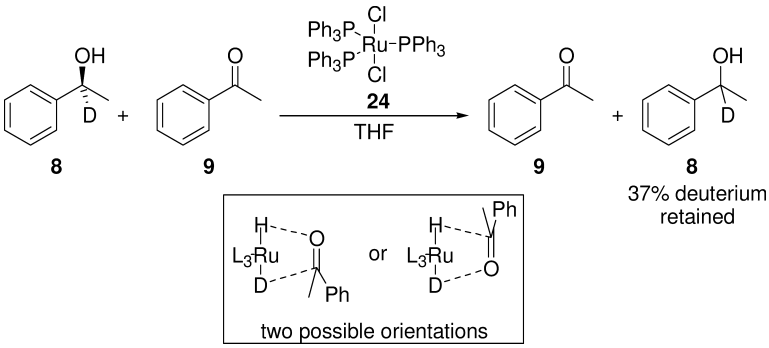
Scheme 20.10 Racemization of (*S*)-1-deutero-1-phenylethanol (**8**) with the Wilkinson catalyst (**7**).

Fig. 20.1 Examples of catalysts operating via the same mechanism as the Wilkinson catalyst (bipy = bipyridine; dppp = 1,3-bis(diphenylphosphinopropane) [35, 44, 45].



Scheme 20.11 Transition metal dihydride mechanism.

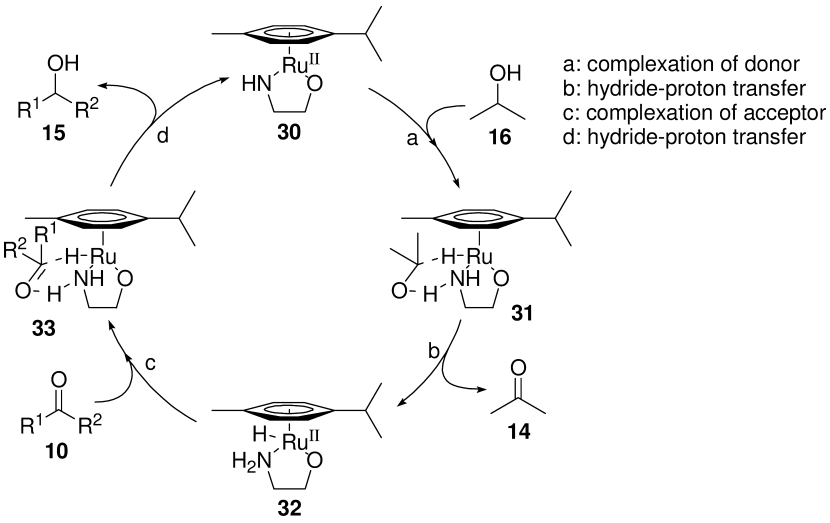
reacts (a) with a substrate molecule (**10**) to give the monohydride alkoxide complex (**27**). Reductive elimination (b) liberates the product (**15**) and a Ru^0 species (**28**). Oxidative addition (c) of an alcohol (**16**) yields a new monohydride alkoxide complex (**29**). After a β-elimination step (d), Ru^{II} dihydride (**26**) is formed again. This mechanism is supported by the fact that the racemization of (*S*)-1-deutero-1-phenylethanol (**8**), catalyzed by this and similar catalysts, decreased to about 40% [35]. In theory, the mechanism depicted in Scheme 20.11 leads to an equal distribution of the deuterium-label over the α-position of the alcohol and its hy-



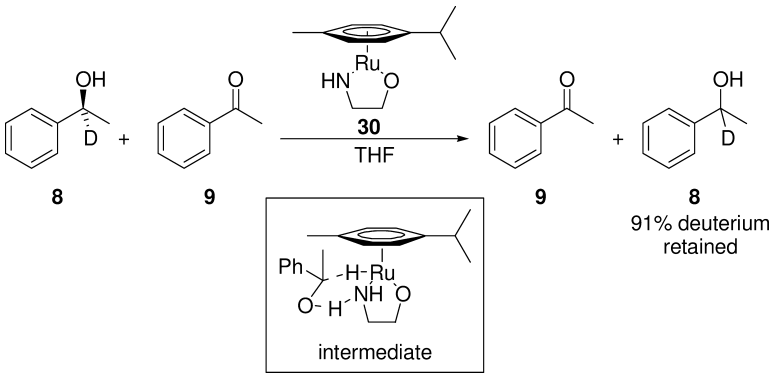
Scheme 20.12 Racemization of (*S*)-1-deutero-1-phenylethanol (**8**) with $RuCl_2(PPh_3)_3$ (**24**).

droxyl function (Scheme 20.12). The deuterium content of the product is probably somewhat lower due to H/D exchange between the alcohol function and traces of water and other alcohols in the reaction mixture.

In the transition metal-catalyzed reactions described above, the addition of a small quantity of base dramatically increases the reaction rate [17–21]. A more elegant approach is to include a basic site into the catalysts, as is depicted in Scheme 20.13. Noyori and others proposed a mechanism for reactions catalyzed with these 16-electron ruthenium complexes (**30**) that involves a six-membered transition state (**31**) [48–50]. The basic nitrogen atom of the ligand abstracts the hydroxyl proton from the hydrogen donor (**16**) and, in a concerted manner, a hydride shift takes place from the α-position of the alcohol to ruthenium (a), re-



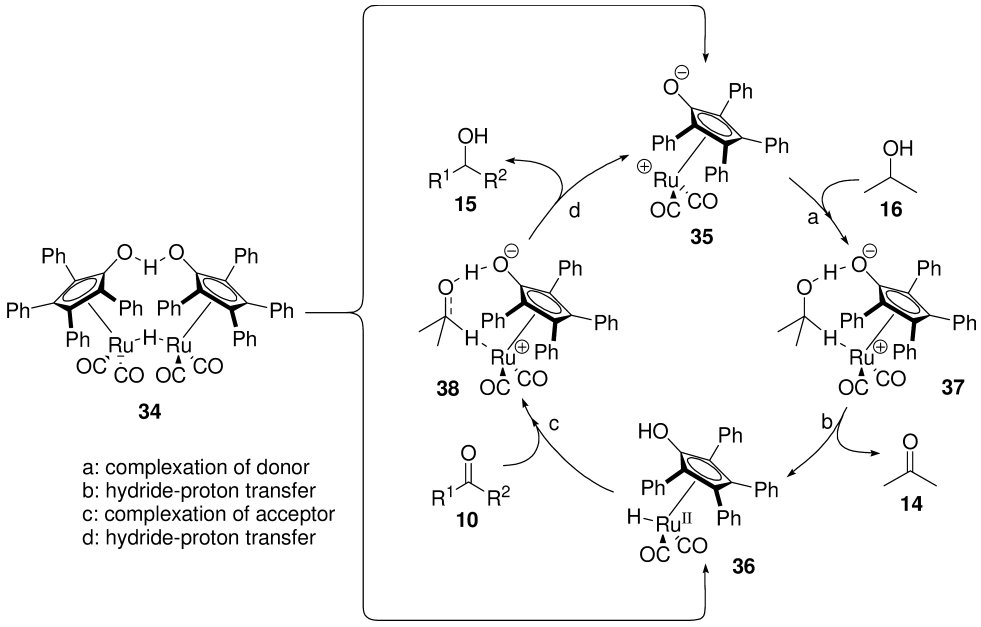
Scheme 20.13 Concerted hydride-proton transfer mechanism.



Scheme 20.14 Racemization of (*S*)-1-deutero-1-phenylethanol (**8**) with $Ru(OC_2H_4NH)$(cymene) (**30**).

leasing a ketone (**14**) (b). The Ru^{II} monohydride (**32**) formed is now able to bind to the substrate ketone (**10**) (c) and, in another concerted reaction, the alcohol (**15**) is formed together with the 16-electron ruthenium complex (**30**) (d).

Formation of the Ru^{II} hydride species is supported by the findings of deuterium-labeling studies (Scheme 20.14) [35]. The deuterium label remains at the *α*-position of the alcohol during racemizations; this is due to the orientation of the alcohol when it coordinates to the Ru-complex. Once again, some deuterium



Scheme 20.15 The catalytic cycle of the Shvo catalyst (**34**).

is probably lost due to H/D exchange with traces of water or alcohol in the reaction mixture.

The most reactive transition metal transfer hydrogenation catalysts identified to date have bidentate ligands. Studies towards active catalysts are mainly directed towards the size and nature of the bridge in the ligand [51] and towards the nature of coordinating atoms to the metal [52–54]. It seems that ligands containing both a phosphorus and a nitrogen atom possess the best properties for these types of reactions (see also Section 20.3.3).

Of particular interest is the dinuclear Ru complex **34**, the so-called Shvo catalyst [55, 56]. It has been established that, under the reaction conditions, this complex is in equilibrium with two monometal complexes (**35** and **36**) [57–59]. Both of these resemble catalytic intermediates in the concerted proton-hydride transfer pathway (Scheme 20.13), and will react in a similar way (Scheme 20.15) involving the six-membered transition state **37** and the reduction of the substrate via **38**.

20.2.2
Transfer Hydrogenation Catalysts for Reduction of C–C Double and Triple Bonds

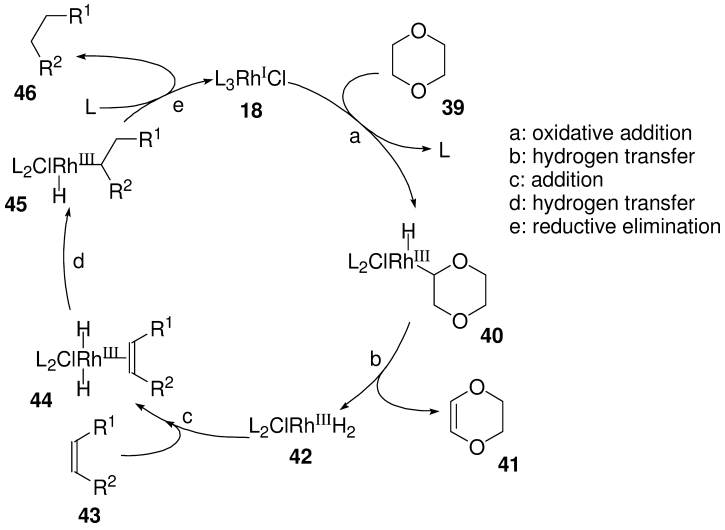
The reduction of C–C double and triple bonds using molecular hydrogen is generally preferred over transfer hydrogenation. However, some interesting examples of transfer hydrogenations of alkenes and alkynes are known. As an illustration of the mechanism of a typical transfer hydrogenation, the reduction of an alkene with dioxane as the hydride donor and the Wilkinson catalyst (**7**) is discussed. The reduction does not necessarily have to be performed with dioxane, but this hydride donor is rather common in these reductions. The use of hydrogen donors and their distinct advantages and disadvantages are discussed in Section 20.3.1.

The first step consists of the substitution of one of the ligands (L) of **18** by dioxane (**39**) in an oxidative addition (a) (Scheme 20.16). β-Elimination of **40** releases 2,3-dihydro-dioxine (**41**) and the 16-electron dihydrogen rhodium complex (**42**) (b). Alkene **43** coordinates to the vacant site of **42** (c) to give complex **44**. A hydride insertion then takes place (d), affording complex **45**. After a reductive elimination (e) of the product **46**, the coordination of a ligand reconstitutes the Wilkinson-type catalyst (**18**).

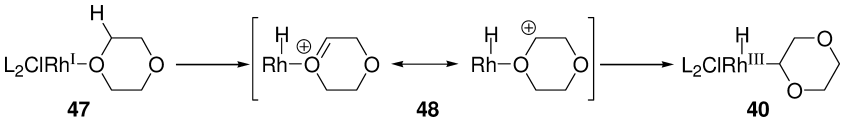
The coordination of dioxane and subsequent oxidative addition to the catalytic species (step (a) in Scheme 20.16) probably proceeds after the oxygen atom coordinates to the rhodium (**47**), followed by abstraction of a hydrogen atom. The cationic species (**48**) then rearranges to a complex in which the dioxane is bound to the rhodium via the carbon atom (**40**) (Scheme 20.17) [60].

Transfer hydrogenations are typically equilibrium reactions; however, when formic acid (**49**) is utilized as the hydrogen donor, carbon dioxide (**50**) is formed which escapes from the reaction mixture [61–64].

Here, an example is given for the reduction of itaconic acid (**51**) with a rhodium catalyst precursor (**52**) and a phosphine ligand (**53**) (Scheme 20.18). The



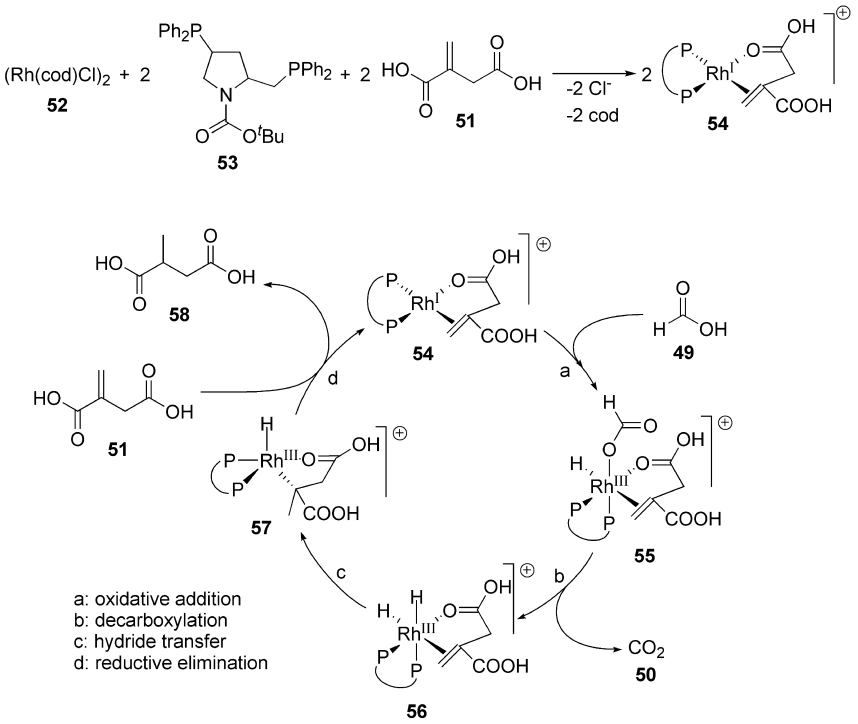
Scheme 20.16 Alkene reduction with dioxane (**39**) as hydride donor and a Wilkinson-type catalyst (**18**).



Scheme 20.17 Step (a) of Scheme 20.16: the coordination and oxidative addition of dioxane.

itaconic acid (**51**) is a good chelating ligand for the catalyst, and when the 16-electron Rh^{I} active species **54** is formed, an oxidative addition of formic acid (**49**) takes place (a). Decarboxylation (b) of **55** liberates CO_2 (**50**), forming a Rh^{III}-dihydride (**56**). A hydride transfer (c) leading to a pentacoordinated metal (**57**) and subsequent reductive elimination (d), in which the product (**58**) is liberated and a new substrate (**51**) is coordinated, closes the cycle.

This system is very selective towards the reduction of C–C double bonds, and the oxygen of the acid group that coordinates to the metal is important for good catalytic properties. In the reaction mixture, triethylamine is added in a ratio of formic acid : triethylamine of 5 : 2, which is the commercially available azeotropic mixture of these compounds.



Scheme 20.18 Reduction of the C–C double bond of itaconic acid (**51**) utilizing a rhodium catalyst (**54**) and formic acid (**49**) as hydrogen donor.

20.3 Reaction Conditions

20.3.1 Hydrogen Donors

By definition, hydrogen transfer is a reaction during which hydrogen is transferred from a source other than molecular hydrogen. In theory, the donor can be any compound that has an oxidation potential which is low enough to allow hydrogen abstraction under influence of a catalyst under mild conditions. Another requirement is that the donor is able to coordinate to the catalytic center and does not bind tightly after donation of the hydrogen.

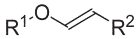
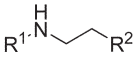
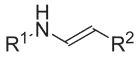
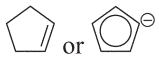
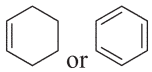
The hydrogen donors vary widely from heteroatom-containing compounds such as alcohols, amines, acids and cyclic ethers to hydrocarbons such as alkanes (Table 20.1). The choice of donor is largely dependent on several issues:

- the *type* of reaction: MPVO or transition metal-catalyzed;
- the *affinity* of the substrate for the metal concerned;

- the *exchange rates* of the substrate between the metal-bound and the free form;
- its *solubility* in the reaction medium or its ability to *dissolve* all other reaction ingredients;
- its influence on the *equilibrium* of the reaction;
- the *temperature* at which the reaction is taking place;
- its ability to avoid harmful *side products*; and
- the *nature* of the functional group to be reduced.

Alcohols have always been the major group of hydrogen donors. Indeed, they are the only hydrogen donors that can be used in Meerwein-Ponndorf-Verley (MPV) reductions. 2-Propanol (**16**) is most commonly used both in MPV reductions and in transition metal-catalyzed transfer hydrogenations. It is generally available and cheap, and its oxidation product, acetone (**14**), is nontoxic and can usually be removed readily from the reaction mixture by distillation. This may have the additional advantage that the redox equilibrium is shifted even more into the direction of the alcohol. As a result of sigma inductive electronic ef-

Table 20.1 Hydrogen donors and their oxidized products.

Entry	Donor	Acceptor
1 [a)]		
2 [b)]		
3		
4		
5 [c)]		
6 [d)]		
7		CO_2

a) Both primary and secondary alcohols.
b) Typically cyclic ethers as dioxane and THF; only one pair of hydrogens is abstracted.
c) The cyclopentadienyl ring coordinates to the catalyst.
d) The reaction preferably stops at cyclohexene.

fects, secondary alcohols are generally better hydrogen donors than primary ones. However, many examples of the use of primary alcohols have been reported. Ethanol, as already pointed out by Meerwein and Schmidt [1], yields acetaldehyde which, even at room temperature, leaves the reaction mixture and results in irreversible reductions. Unfortunately, the aldehydes resulting from primary alcohols as donors are known to act as catalyst poisons. Furthermore, they may decarbonylate, forming CO, which may modify the catalysts and consequently change their activity [65, 66].

Other alcohols, such as diols [67–69], polyols such as furanoses, pyranoses [70, 71] and polyvinyl alcohol [72] have been reported to enable the reduction of ketones to alcohols.

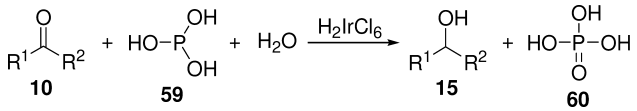
Heterocyclic compounds are frequently used as hydrogen donors in the reduction of C–C double and triple bonds catalyzed by complexes of transition metals. Cyclic ethers such as [1,4]dioxane (**39**) and 2,3-dihydrofuran are known to donate a pair of hydrogen atoms to this type of compound. 2,3-Dihydro-[1,4]dioxine (**41**), the product of dioxane (**39**), is not able to donate another pair of hydrogen atoms [46, 60, 73, 74]. These heterocyclic compounds are in general also very good solvents for both the catalyst and the substrates.

Nitrogen-containing heterocyclic compounds, including 1,2,3,4-tetrahydroquinoline, piperidine, pyrrolidine and indoline, are also popular hydrogen donors for the reduction of aldehydes, alkenes, and alkynes [75, 76]. With piperidine as hydrogen donor, the highly reactive 1-piperidene intermediate undergoes trimerization or, in the presence of amines, an addition reaction [77]. Pyridine was not observed as a reaction product.

Hydrocarbons are also able to donate hydrogen atoms. In particular, indan and tetralin, which are able to form conjugated double bonds or a fully aromatic system, are used [74].

Once again, use of these donors as solvent may shift the reaction equilibrium towards the desired product. Since the reactivity of olefins is lower than that of carbonyl compounds, higher reaction temperatures are usually required to achieve acceptable TOFs, and then the relatively higher boiling hydrogen donating solvents mentioned above may be the best choice.

Henbest and Mitchell [78] have shown that water can be used as hydrogen source with chloroiridic acid (**6**) as the catalyst through oxidation of phosphorous acid (**59**) to phosphoric acid (**60**) in aqueous 2-propanol. Under these conditions, no hydrogen transfer occurs from 2-propanol. However, iridium complexes with sulfoxide or phosphine ligands show the usual transfer from 2-propanol [79–81].



Scheme 20.19 Transfer hydrogenation with the Henbest system.

Hydrogen transfer reactions are highly selective and usually no side products are formed. However, a major problem is that such reactions are in redox equilibrium and high TOFs can often only be reached when the equilibria involved are shifted towards the product side. As stated above, this can be achieved by adding an excess of the hydrogen donor. (For a comparison, see Table 20.2, entry 8 and Table 20.7, entry 3, in which a 10-fold increase in TOF, from 6 to 60, can be observed for the reaction catalyzed by neodymium isopropoxide upon changing the amount of hydrogen donor from an equimolar amount to a solvent. Removal of the oxidation product by distillation also increases the reaction rate. When formic acid (**49**) is employed, the reduction is a truly irreversible reaction [82]. This acid is mainly used for the reduction of C–C double bonds. As the proton and the hydride are removed from the acid, carbon dioxide is formed, which leaves the reaction mixture. Typically, the reaction is performed in an azeotropic mixture of formic acid and triethylamine in the molar ratio 5 : 2 [83].

In summary, the most popular hydrogen donors for the reduction of ketones, aldehydes and imines are alcohols and amines, while cyclic ethers or hydroaromatic compounds are the best choice for the reduction of alkenes and alkynes.

20.3.2 Solvents

As mentioned above, the hydrogen donor is the solvent of choice in hydrogen-transfer reactions. However, if for any reason another solvent is needed, it is important to select one that does not compete with the substrate or the ligands of

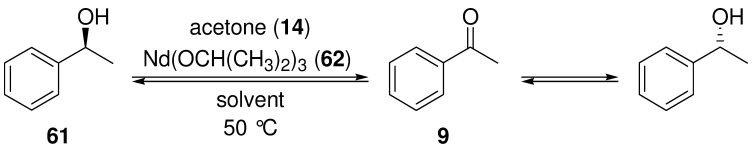
Table 20.2 Racemization of (*S*)-1-phenylethanol (**61**) in different solvents (Scheme 20.20).[a)]

Entry	Solvent	Time [h]	ee [%][b)]	TOF [h^{-1}][c)]
1	Acetonitrile	>48	>99	0
2	Dioxane	5	28	2
3	THF	3.5	0	4
4	Diisopropyl ether	3.5	0	4
5	MTBE	3.5	0	4
6	Toluene	3	0	5
7	Hexane	2	0	6
8	Heptane	2	0	6

a) Solvent (12 mL), zeolite NaA (30 mg, dried at 400 °C), (*S*)-1-phenylethanol (**61**) (0.24 mL, 2 mmol), acetone (**14**) (0.15 mL, 2 mmol, 1 equiv.), 1,3,5-triisopropylbenzene (int. std.) (0.2 mL) and neodymium(III) isopropoxide (120 mg, 0.37 mmol, 0.185 equiv.) were stirred at 50 °C.

b) ee (starting material) >99%.

c) As determined in the first 15 min of the reaction; in this period predominantly oxidation takes place.



Scheme 20.20 Racemization of **61** with 19% neodymium(III) isopropoxide (**62**) and 1 equiv. acetone (**14**).

the catalyst. By replacing ligands of the catalyst, the electron density of the metal changes, and this may have a detrimental effect on the activity of the catalyst.

As an example, Table 20.2 lists the rate of the racemization of **61** via an MPVO procedure utilizing the catalyst neodymium(III) isopropoxide (**62**) as a function of the solvent. In this case, an equimolar amount of acetone was applied as the oxidant. The best results were obtained with hydrocarbons such as hexane (entry 7) and heptane (entry 8) as solvents, while the reaction rates in dioxane (entry 2) and acetonitrile (entry 1) were much lower due to inactivation of the catalyst by coordination of the solvent to the metallic center (Table 20.2) [84].

20.3.3
Catalysts and Substrates

Meerwein-Ponndorf-Verley-Oppenauer catalysts typically are aluminum alkoxides or lanthanide alkoxides (see above). The application of catalysts based on metals such as ytterbium (see Table 20.7, entries 6 and 20) and zirconium [85, 86] has been reported.

Lanthanide(III) isopropoxides show higher activities in MPV reductions than $Al(O\mathit{i}Pr)_3$, enabling their use in truly catalytic quantities (see Table 20.7; compare entry 2 with entries 3 to 6). Aluminum-catalyzed MPVO reactions can be enhanced by the use of TFA as additive (Table 20.7, entry 11) [87, 88], by utilizing bidentate ligands (Table 20.7, entry 14) [89] or by using binuclear catalysts (Table 20.7, entries 15 and 16) [8, 9]. With bidentate ligands, the aluminum catalyst does not form large clusters as it does in aluminum(III) isopropoxide. This increase in availability per aluminum ion increases the catalytic activity. Lanthanide-catalyzed reactions have been improved by the *in-situ* preparation of the catalyst; the metal is treated with iodide in 2-propanol as the solvent (Table 20.7, entries 17–20) [90]. Lanthanide triflates have also been reported to possess excellent catalytic properties [91].

One drawback of all these catalysts is their extreme sensitivity to water. To avoid this problem, reactions should be carried out under an inert atmosphere and, if possible, in the presence of molecular sieves [92]. The molecular sieves also suppress aldol reactions, as will be discussed in Section 20.4.

For the reduction of carbonyl groups or the oxidation of alcohols in the presence of C–C double and triple bonds, MPVO catalysts seem to be the best choice with respect to selectivity for the carbonyl group, as reductions with com-

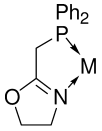
plexes of transition metals are less selective (see Section 20.3.4). In the vast majority of syntheses, aluminum(III) isopropoxide is used as the catalyst. From a catalytic point of view, this is not the best choice, since it typically must be added in equimolar amounts. Probably due to its availability in the laboratory and ease of handling, it is the most frequently used MPVO-catalyst, despite the development of the more convenient lanthanide(III)isopropoxides. An advantage of the aluminum catalyst in industrial processes is the possibility to distil off the products while the catalyst remains active in the production vessel.

In recent years, many active transition-metal catalysts have been developed (see Table 20.7, entries 21–53). Careful design of the ligands of the transition-metal complexes has led to the development of catalysts with high activities. Mixed chelate ligands containing both a phosphorus- and a nitrogen-binding site were employed to prepare catalysts with unusual electronic properties (Table 20.7, entries 24–29, 40–42, 44). In particular, the catalyst in entry 44 shows a very high TOF for the reduction of acetophenone ($10^6\ h^{-1}$). Other very good catalysts have bidentate phosphine ligands and TOFs of up to $2300\ h^{-1}$ (entries 34 and 35), contain both nitrogen and phosphorus ligands and TOFs of up to $900\ h^{-1}$ (entries 45–47), or have different bidentate moieties (entries 48 and 50–52) and TOFs of up to $14\,700\ h^{-1}$.

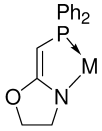
Neutral mixed chelate ligands containing both phosphorus- and nitrogen-binding sites often show a hemilabile character (they are able to bind via one or two atoms to the metal; Fig. 20.2), which allows for the temporary protection and easy generation of reactive sites in the complexes.

Furthermore, the acidity of PCH_2 protons in oxazoline ligands (**63**) enables easy deprotonation of the chelate, giving rise to a static (non-dissociating) anionic four-electron-donating ligand (**64**). These properties give rise to a high activity (Fig. 20.2) [52].

Transition-metal catalysts are, in general, more active than the MPVO catalysts in the reduction of ketones via hydrogen transfer. Especially, upon the introduction of a small amount of base into the reaction mixture, TOFs of transition-metal catalysts are typically five- to 10-fold higher than those of MPVO catalysts (see Table 20.7, MPVO catalysts: entries 1–20, transition-metal catalysts: entries 21–53). The transition-metal catalysts are less sensitive to moisture than MPVO catalysts. Transition metal-catalyzed reactions are frequently carried out in 2-propanol/water mixtures. Successful transition-metal catalysts for transfer hydrogenations are based not only on iridium, rhodium or ruthenium ions but also on nickel [93], rhenium [94] and osmium [95]. It has been reported that



63



64

Fig. 20.2 The neutral PCH_2-oxazoline ligand (**63**) and the anionic PCH-oxazoline ligand (**64**).

MPV reductions with aluminum(III) isopropoxide as the catalyst can be hugely enhanced by microwave irradiation [96].

In summary, the reduction of ketones and aldehydes can both be performed with MPV and transition-metal complexes as catalysts. Reductions of alkenes, alkynes, and imines require transition-metal catalysts; MPV reductions with these substrates are not possible.

Hydrogen transfer towards imines is in general slower than towards the corresponding carbonyls. Nonetheless, the reduction can be performed using the same catalysts, although harsher reaction conditions may have to be applied [97]. This is probably a result of the relative stability of imines with respect to carbonyls. In general, the hydrogen transfer of imines proceeds faster with aldimines than with ketimines. The Shvo catalyst (**34**), however, is slightly more reactive towards the latter [56].

In general, the activity of transition-metal catalysts is higher in hydrogenation reactions than in hydrogen transfer reactions. In the few cases where both hydrogenation methods were performed with the same catalyst, it has been shown that reaction rates are lower for transfer hydrogenations. Some examples are known in which transfer hydrogenation is faster than hydrogenation with H_2 [98–100]. The simplicity of the transfer hydrogenation protocol and the abundance of selective and active catalysts make this method very competitive with hydrogenations utilizing H_2, and it is often the preferred reaction.

20.3.4 Selectivity

As mentioned above, MPVO catalysts are very selective towards carbonyl compounds. Alkenes, alkynes or other heteroatom-containing double bonds are not affected by these catalysts, while they can be reduced by transition-metal catalysts. Examples of the reduction of *α,β*-unsaturated ketones and other multifunctional group compounds are compiled in Table 20.3.

Transition metals can display selectivities for either carbonyls or olefins (Table 20.3). $RuCl_2(PPh_3)_3$ (**24**) catalyzes reduction of the C–C double bond function in the presence of a ketone function (Table 20.3, entries 1–3). With this catalyst, reaction rates of the reduction of alkenes are usually higher than for ketones. This is also the case with various iridium catalysts (entries 6–14) and a ruthenium catalyst (entry 15). One of the few transition-metal catalysts that shows good selectivity towards the ketone or aldehyde function is the nickel catalyst (entries 4 and 5). Many other catalysts have never been tested for their selectivity for one particular functional group.

In total syntheses where a homogeneously catalyzed transfer hydrogenation is applied, almost exclusively aluminum(III) isopropoxide is utilized as the catalyst. At an early stage in the total synthesis of (–)-reserpine (**65**) by Woodward [106], an intermediate with two ketone groups and two C–C double bonds is formed (**66**) by a Diels-Alder reaction of *para*-benzoquinone (**67**) and vinylacrylate (**68**). The two ketone groups were reduced with aluminum(III) isopropoxide

Table 20.3 Selectivity towards functional groups.

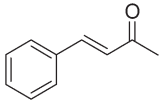
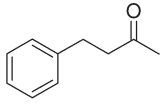
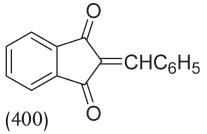
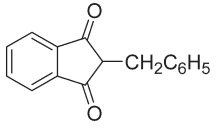
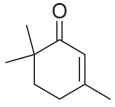
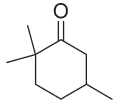
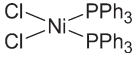
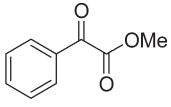
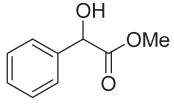
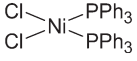
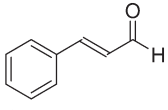
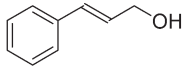
Entry	Catalyst	Substrate ([S]/[C]) [a]	Product	Reductant	Temperature (time) [°C, h] [b]	Conversion ratio [%]	TOF [h^{-1}]	Reference
1	$RuCl_2(PPh_3)_3$	 (400)		1-phenylethanol	180 (1)	95	380	101
2	$RuCl_2(PPh_3)_3$	 (400)		1-phenylethanol	180 (1)	45	180	101
3	$RuCl_2(PPh_3)_3$	 (400)		1-phenylethanol	180 (1)	54	216	101
4		 (7)		2-propanol	82 (36)	65	0.12	102
5		 (7)		2-propanol	82 (30)	51	0.11	102

Table 20.3 (continued)

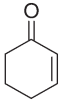
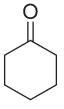
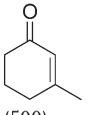
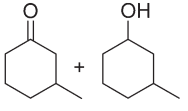
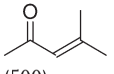
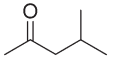
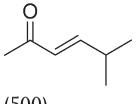
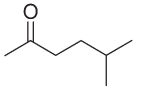
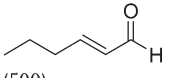
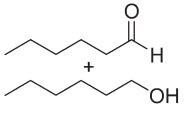
Entry	Catalyst	Substrate ([S]/[C]) [a]	Product	Reductant	Temperature (time) [°C, h] [b]	Conversion ratio [%]	TOF [h^{-1}]	Reference
6	$[Ir(cod)Cl]_2$	 (500)		2-propanol	80 (4)	99	12.0	103
7	$[Ir(cod)Cl]_2$	 (500)		2-propanol	80 (4)	91 (3:1)	23.0	103
8	$[Ir(cod)Cl]_2$	 (500)		2-propanol	80 (4)	99	12.0	103
9	$[Ir(cod)Cl]_2$	 (500)		2-propanol	80 (4)	90	6.0	103
10	$[Ir(cod)Cl]_2$	 (500)		2-propanol	80 (4)	75 (10:1)	9.0	103

Table 20.3 (continued)

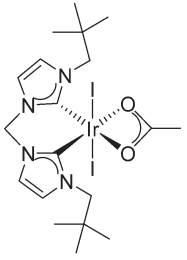
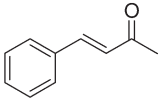
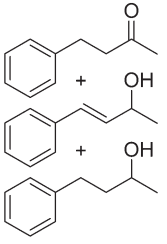
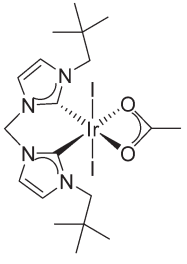
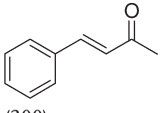
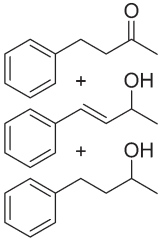
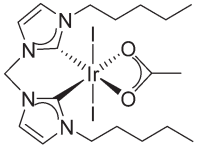
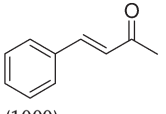
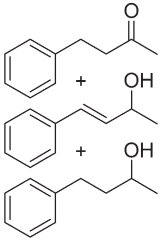
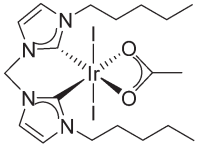
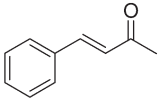
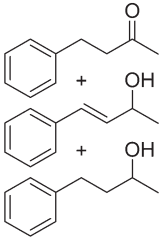
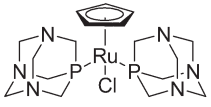
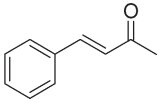
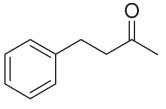
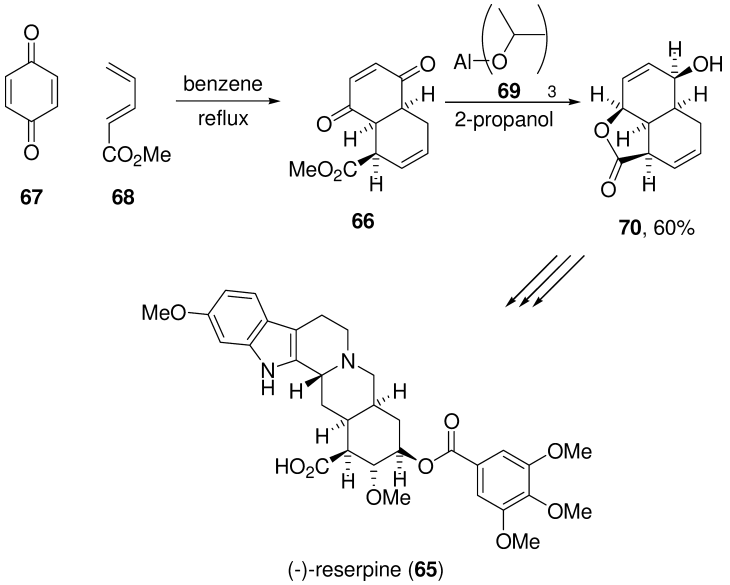
Entry	Catalyst	Substrate ([S]/[C]) [a]	Product	Reductant	Temperature (time) [°C, h] [b]	Conversion ratio [%]	TOF [h^{-1}]	Reference
11		 (1000)		2-propanol	82 (20)	92 (9:3:2)	1.0	104
12		 (200)		2-propanol	82 (4)	>98 (0:0:1)	1.0	104
13		 (1000)		2-propanol	82 (20)	66 (7:1:0)	0.7	104

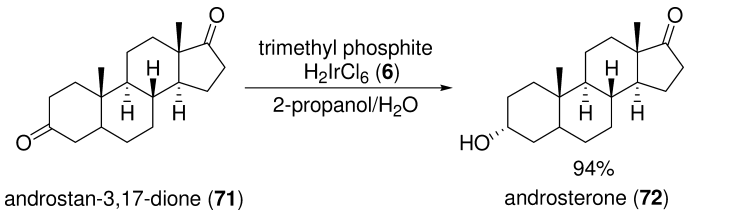
Table 20.3 (continued)

Entry	Catalyst	Substrate ([S]/[C]) [a]	Product	Reductant	Temperature (time) [°C, h] [b]	Conversion ratio [%]	TOF [h^{-1}]	Reference
14		 (200)		2-propanol	82 (7)	100 (1:0:5)	0.6	104
15		 (100)		HCO_2Na/MeOH/H_2O	90 (6)	97	16.0	105

a) Substrate : catalyst ratio shown in parentheses.
b) Reaction temperature (reaction time in parentheses).



Scheme 20.21 Woodward's total synthesis of (–)-reserpine (**65**).



Scheme 20.22 The reduction of androstan-3,17-dione (**71**) using an iridium catalyst.

(**69**) while leaving the remainder of the molecule unaltered. The resulting dialcohol is immediately lactonized to the tricyclic compound **70** (Scheme 20.21).

One of the very few examples of a practical application of a transition-metal catalyst in total synthesis is shown in Scheme 20.22 [107]. The chloroiridic acid catalyst (H_2IrCl_6) (**6**) reduces **71** to androsterone (**72**) by selective attack of the sterically less hindered ketone in the 3-position of **71**.

20.4
Related Reactions and Side-Reactions

20.4.1
Aldol Reaction

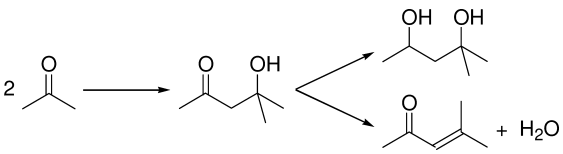
In the MPVO reaction, several side-reactions can occur (Scheme 20.23). For example, an aldol reaction can occur between two molecules of acetone, which then leads to the formation of diacetone alcohol. The latter acts as a good ligand for the metal of the MPVO catalyst, rendering it inactive. Moreover, the aldol product may subsequently eliminate water, which hydrolyzes the catalyst. The aldol reaction can be suppressed by adding zeolite NaA [84, 92].

20.4.2
Tishchenko Reaction

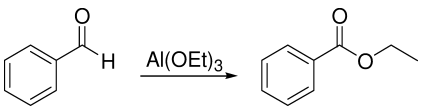
When aldehydes are reduced, the Tishchenko reaction may be a side-reaction. It is the result of an attack of the oxygen atom of the alkoxide on the carbonyl function of the aldehyde. In particular, aldehydes lacking an α-hydrogen atom such as benzaldehyde are prone to form esters (Scheme 20.24) [108]. It has been reported that many aldehydes can be converted into Tishchenko esters at room temperature, almost quantitatively and with high turnovers, using SmI_2 catalysts [109] or a bi-aluminum catalyst [8].

20.4.3
Cannizzaro Reaction

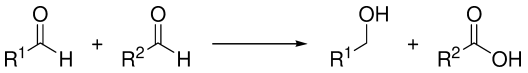
In the Cannizzaro reaction [110, 111] two aldehyde functionalities disproportionate into the corresponding hydroxyl and carboxyl functions, either as separate compounds or as an ester (Scheme 20.25). The reaction conditions needed are rather harsh, except when R^1 or R^2 is a phenyl group. Typically, an excess of so-



Scheme 20.23 The aldol reaction.



Scheme 20.24 The original Tishchenko reaction.



Scheme 20.25 The Cannizzaro reaction.

dium or potassium hydroxide is needed. Therefore, in general, during MPVO reactions only traces of Cannizzaro products are formed.

20.4.4
Decarbonylation

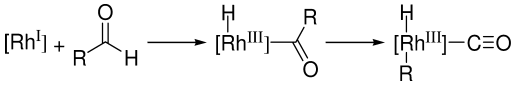
Aldehydes may sometimes pose a problem in transfer hydrogenations catalyzed by transition metals. They can poison the catalyst or decarbonylate, forming CO, which may coordinate to the metal complex and result in a change in activity (Scheme 20.26) [65, 66].

20.4.5
Leuckart-Wallach and Eschweiler-Clarke Reactions

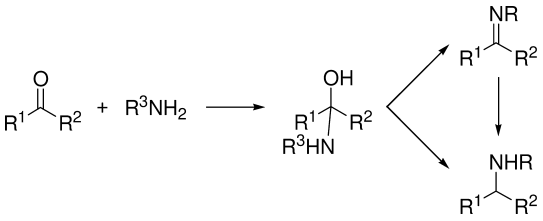
The reductive alkylation of amines is called the Leuckart-Wallach reaction [112–115]. The primary or secondary amine reacts with the ketone or aldehyde. The formed imine is then reduced with formic acid as hydrogen donor (Scheme 20.27). When amines are reductively methylated with formaldehyde and formic acid, the process is termed the Eschweiler-Clarke procedure [116, 117].

20.4.6
Reductive Acetylation of Ketones

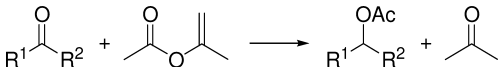
In the presence of an active acyl donor such as isopropenyl acetate, a reductive acetylation of a ketone can be performed in the presence of MPVO catalysts



Scheme 20.26 Decarbonylation of an aldehyde under influence of a transition-metal catalyst.



Scheme 20.27 The Leuckart-Wallach reaction.



Scheme 20.28 Reductive acetylation of ketones.

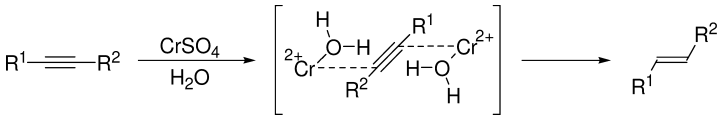
(Scheme 20.28) [84, 118]. The first step in this procedure is reduction of the ketone, followed by the acetylation of the formed alkoxide. It may be noted that aluminum(III) isopropoxide and zirconium(IV) isopropoxide do not catalyze the acetylation. With these catalysts, the alcohol is obtained.

20.4.7
Other Hydrogen Transfer Reactions

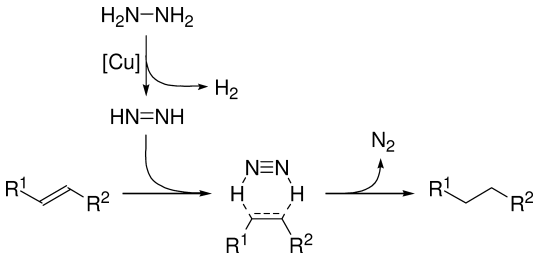
A few remarkable, but rather uncommon, transfer hydrogenations also deserve mention within the context of this chapter: namely, the reduction of alkynes to alkenes using a chromium catalyst, and the reduction of double bonds using diimines.

In the reduction of C–C triple bonds with chromous sulfate in water, the key intermediate consists of a dichromium complex with the alkyne (Scheme 20.29) [119]. This configuration assures the selective formation of *trans* double bonds. Various substrates have been reduced in excellent yields without the occurrence of isomerizations or byproduct formation (Table 20.4).

One very fast and reliable method for the reduction of double bonds is that of transfer hydrogenation with diimine (Scheme 20.30). Under the influence of traces of copper ion and oxygen from air, hydrazine is rapidly transformed into diimine. This compound is able to hydrogenate double bonds with great success under the formation of nitrogen [120].

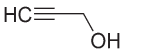
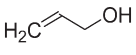
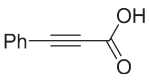
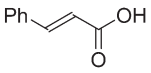
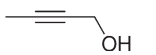
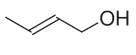
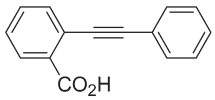
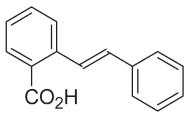


Scheme 20.29 Reduction of alkynes to *trans*-alkenes by chromous sulfate.



Scheme 20.30 Reduction of alkenes with hydrazine.

Table 20.4 Reduction of alkynes to *trans*-alkenes by chromous sulfate.

Entry	Substrate	Product	Reaction time [h]	Yield [%]	TOF [h^{-1}]
1			0.08	89	5.0
2			0.25	91	2.5
3			2	84	0.4
4			24	85	0.02

20.5 Racemizations

Since transfer hydrogenation reactions of carbonyls are always equilibrium reactions, it is possible to perform both a reduction and an oxidation of a substrate simultaneously. In this way, these reactions can be utilized for both racemizations and epimerizations.

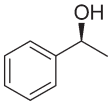
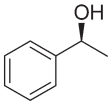
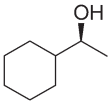
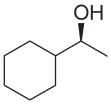
In the contemporary production of enantiopure compounds this feature is highly appreciated. Currently, kinetic resolution of racemates is the most important method for the industrial production of enantiomerically pure compounds. This procedure is based on chiral catalysts or enzymes, which catalyze conversion of the enantiomers at different rates. The theoretical yield of this type of reaction is only 50%, because the unwanted enantiomer is discarded. This generates a huge waste stream, and is an undesirable situation from both environmental and economic points of view. Efficient racemization catalysts that enable recycling of the undesired enantiomer are, therefore, of great importance.

In order to accomplish a racemization rather than an oxidation of an alcohol, the hydrogen acceptor should be added in an equimolar or lower concentration. This is illustrated in Table 20.5 [84]. In order to achieve acceptable reaction times and yields, the amount of hydrogen donor must be adjusted to meet every single reactant.

Racemizations are not limited to alcohols; indeed, some racemizations of amines have also been reported [121].

The next step in the use of transfer hydrogenation catalysts for recycling of the unwanted enantiomer is the dynamic kinetic resolution. This is a combination of two reaction systems: (i) the continuous racemization of the alcohol via hydrogen transfer, and (ii) the enantioselective protection of the alcohol using a

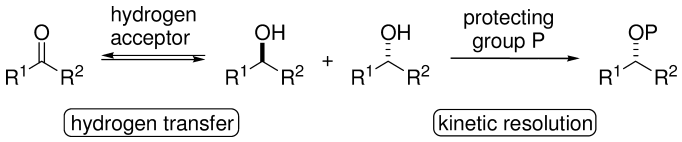
Table 20.5 Racemization of a conjugated and a non-conjugated ketone.

Entry	Substrate	Acetone [equiv.]	Time [h] [a)]	Ketone formed [%]
1		1	1.5	50
2		0.1	3	10
3		1	2.5	25
4		0.1	>7	9

a) Time needed for complete racemization.

stereoselective catalyst, typically an enzyme [122–127]. As was first demonstrated by Williams and colleagues [30], a dynamic kinetic resolution of racemic alcohols by the combination of two catalysts provides a mild and effective means of obtaining enantiomerically pure alcohols in high yields and selectivities (Scheme 20.31).

It is important that the catalysts are stable in each other's presence. Typically, kinetic resolution of the reaction is performed with an enzyme, which always will contain traces of water. Hence, MPVO catalysts and water-sensitive transition-metal catalysts cannot be used in these systems. The influence of the amount of the hydrogen acceptor in the reaction mixture during a dynamic kinetic resolution is less pronounced than in a racemization, since the equilibrium of the reaction is shifted towards the alcohol side.



Scheme 20.31 The dynamic kinetic resolution of a racemic alcohol.

Table 20.6 Recent examples of successful dynamic kinetic resolutions.

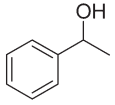
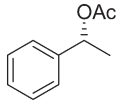
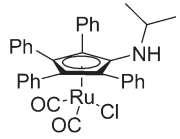
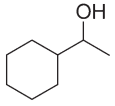
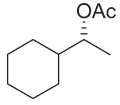
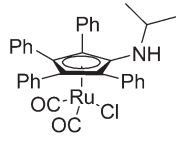
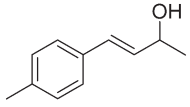
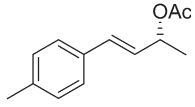
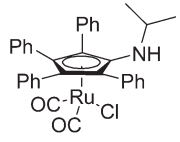
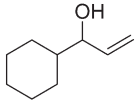
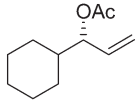
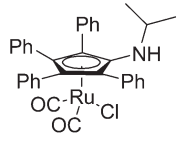
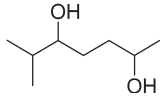
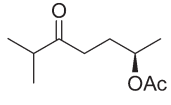
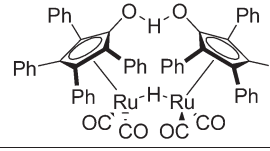
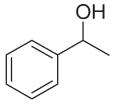
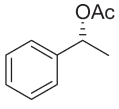
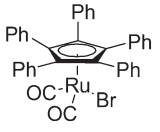
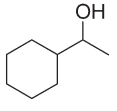
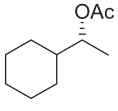
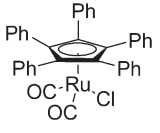
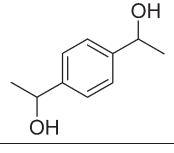
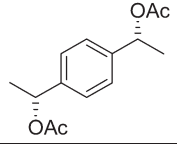
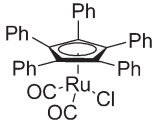
Entry	Substrate	Product	Racemization catalyst [a]	SCR [b]	Time [h]	Temperature [°C]	Yield [%]	ee [%]	Reference
1				25	31	25	95	>99	128
2				25	48	25	86	>99	128
3				25	96	25	92	>99	128
4				25	96	25	90	>99	128
5				20	18	70	77	89	129

Table 20.6 (continued)

Entry	Substrate	Product	Racemization catalyst [a]	SCR [b]	Time [h]	Temperature [°C]	Yield [%]	ee [%]	Reference
6				25	3	25	98	>99	130
7				20	17	25	98	>99	130
8				20	10	25	94	>99 (99:1 d.r.)	130

a) The catalyst for the kinetic resolution is in all cases *Candida antarctica* Lipase B.
b) SCR = substrate:catalyst ratio between the racemic alcohol and the hydrogen transfer catalyst.

Table 20.7 A short overview of the reduction of acetophenone with MPVO catalysts and transition metal catalysts developed during the past five years.

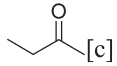
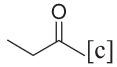
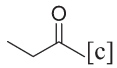
Entry	Catalyst	Reducing agent [a)]	Additive/Solvent [a)]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
1	tBuOSmI$_2$		THF	65	10	98	24	0.4	131
2	Al(OCH(CH$_3$)$_2$)$_3$			50	10	1	1	0.1	7
3	Nd(OCH(CH$_3$)$_2$)$_3$			50	100	57	1	60	7
4	Gd(OCH(CH$_3$)$_2$)$_3$			50	100	58	1	60	7
5	Er(OCH(CH$_3$)$_2$)$_3$			50	100	22	1	20	7
6	Yb(OCH(CH$_3$)$_2$)$_3$			50	100	5	1	5	7
7	La(OCH(CH$_3$)$_2$)$_3$			80	20	75	60	0.3	132
8	Ce(OCH(CH$_3$)$_2$)$_3$			80	20	15	48	0.1	132

Table 20.7 (continued)

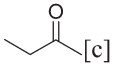
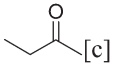
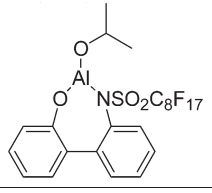
Entry	Catalyst	Reducing agent [a]	Additive/Solvent [a]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
9	$Sm(OCH(CH_3)_2)_3$			80	20	70	24	0.6	132
10	$Yb(OCH(CH_3)_2)_3$			80	20	98	24	0.8	132
11	$Al(OCH(CH_3)_2)_3$		TFA (1)	25	12	44	22	0.3	88
12	$Pu(N(Si(CH_3)_3)_2)_3$			25	20	91	24	0.8	133
13	$Al(CH_3)_3$			65	10	80	12	0.7	10
14		 (10)	CH_2Cl_2	25	10	85	5	1.5	84

Table 20.7 (continued)

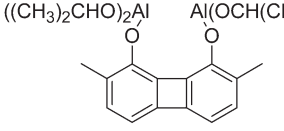
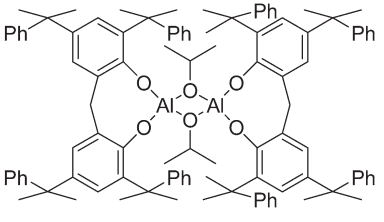
Entry	Catalyst	Reducing agent[a]	Additive/Solvent[a]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
15		 (3)	CH_2Cl_2	25	20	96	1	20	8
16		 (100)	Toluene	111	40	93	1	40	9
17	La + 5% I_2			25	1	48	20	0.048	90
18	Ce + 5% I_2			25	1	34	20	0.039	90
19	Sm + 5% I_2			25	1	96	20	0.05	90
20	Yb + 5% I_2			25	1	24	20	0.036	90

Table 20.7 (continued)

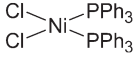
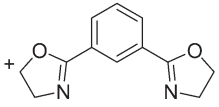
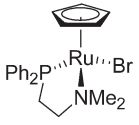
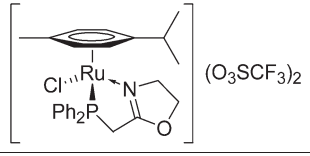
Entry	Catalyst	Reducing agent[a)]	Additive/Solvent[a)]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
21			NaOH (0.33)	82	7	82	30	0.2	102
22	$NiBr_2$		NaOH (85)	95	250	60	4	10	134
23	$SnTf_3$ + 		MeOH	25	10	98	12	0.8	135
24			 (0.02)	82	200	>99	48	5	136
25			 (0.025)	82	200	61	1	120	52

Table 20.7 (continued)

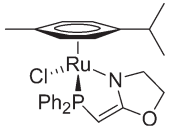
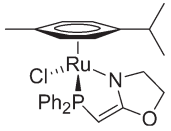
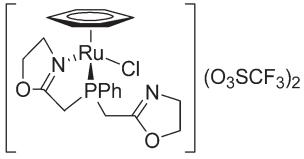
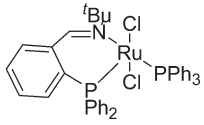
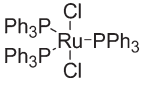
Entry	Catalyst	Reducing agent[a)]	Additive/Solvent[a)]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
26			 (0.025)	82	200	25	0.25	200	52
27			 (0.025)	82	200	94	6	30	52
28			 (0.12)	82	200	54	1	110	52
29			NaOH (0.5)	90	5	91	0.5	910	137
30			NaOH (0.024)	82	500	50	2	2.0	138

Table 20.7 (continued)

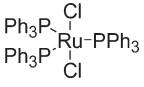
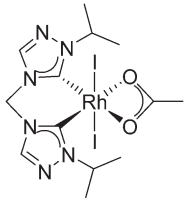
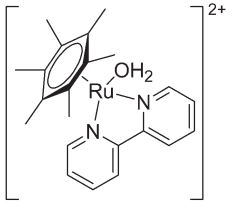
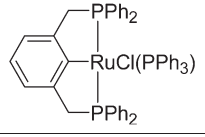
Entry	Catalyst	Reducing agent[a)]	Additive/Solvent[a)]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
31			NaOH (0.024) $Yb(OTf)_3$ (0.004)	82	500	86	2	3.5	138
32			KOH (0.5)	82	1000	>98	10	100	139
33		 (30)	H_2O	70	200	98	4	50	140
34				82	1000	50	0.22	2300	141

Table 20.7 (continued)

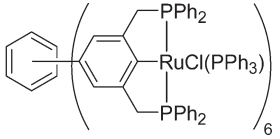
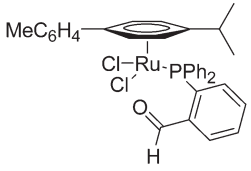
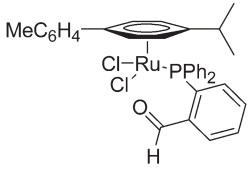
Entry	Catalyst	Reducing agent[a)]	Additive/Solvent[a)]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
35				82	1000	50	0.23	2200	141
36	$[Cp^*Ir_{III}(bpy)(H_2O)]^{2+}$	 (5)	H_2O	70	200	97	1	194	142
37			NaOH (0.048)	82	500	98	10	50	143
38			NaOH (0.048)	82	500	97	9	55	143

Table 20.7 (continued)

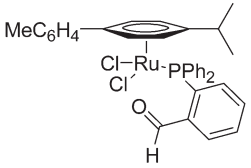
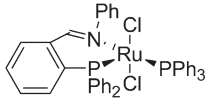
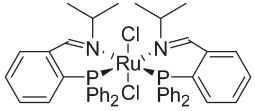
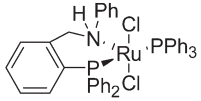
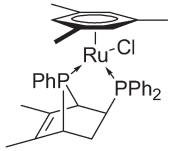
Entry	Catalyst	Reducing agent[a)]	Additive/Solvent[a)]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
39			NaOH (0.048)	82	500	96	6	80	143
40			NaOH (0.048)	82	500	98	1	485	144
41			NaOH (0.048)	82	500	97	1	240	144
42			NaOH (0.048)	82	500	96	2	240	144
43			KOH (0.025)	82	200	>99	0.5	400	145

Table 20.7 (continued)

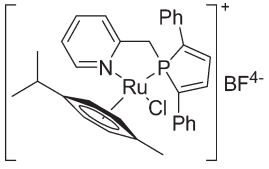
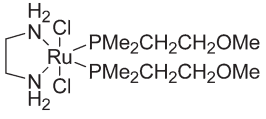
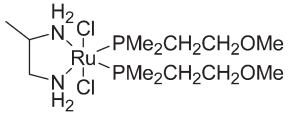
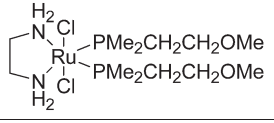
Entry	Catalyst	Reducing agent [a]	Additive/Solvent [a]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
44			KOH (0.5)	90	$60 \cdot 10^6$	>99	60	$1 \cdot 10^6$	53
45			KOH (0.1)	82	500	93	0.5	935	146
46			KOH (0.1)	82	500	82	0.5	815	146
47			KOH (0.1)	82	500	90	0.5	900	146

Table 20.7 (continued)

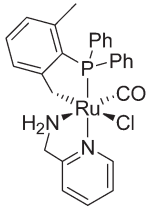
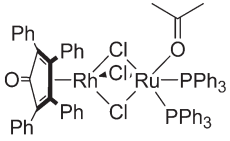
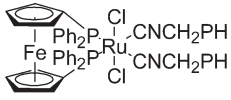
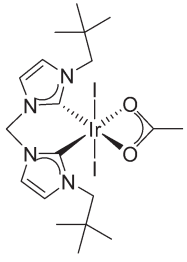
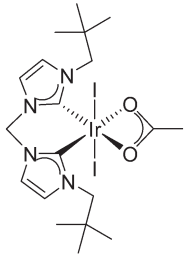
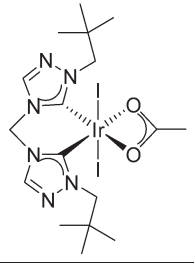
Entry	Catalyst	Reducing agent[a)]	Additive/Solvent[a)]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
48			NaOH (0.02)	82	400	98	0.08	4700	54
49			K_2CO_3 (1)	RT	1000	70	6	60	147
50			NaOH (0.096)	250	250	84	0.17	1260	148
51			KOH (0.005)	82	1000	98	0.07	14700	51

Table 20.7 (continued)

Entry	Catalyst	Reducing agent[a)]	Additive/Solvent[a)]	Temperature [°C]	SCR	Conversion [%]	Reaction time [h]	TOF [h^{-1}]	Reference
52			K_2CO_3 (0.5)	82	1000	97	0.67	1455	51
53			KOH (0.005)	82	1000	80	2	400	51

a) The number in parentheses denotes the number of equivalents used. If no number is given, the donor/additive is used as solvent.
b) TOF = [substrate]/[catalyst] h^{-1}, calculated from the yield and stated reaction time.
c) Oxidation of 1-phenylethanol.
SCR = substrate:catalyst ratio.

Several groups have been active in the field of dynamic kinetic resolution since its introduction, and products have been obtained at almost quantitative yields and with excellent enantiomeric excesses (Table 20.6) [128–130].

Abbreviations

MPV	Meerwein-Ponndorf-Verley
MPVO	Meerwein-Ponndorf-Verley and Oppenauer
TFA	trifluoroacetic acid
TOF	turnover frequency
TON	turnover number

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