35
Enantioselective Transfer Hydrogenation

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35.1
Introduction

Transfer hydrogenation is the movement of a hydride ion and proton (or two protons and two electrons) from a hydrogen donor to a substrate acceptor, effectively a disproportionation. In the case of hydrogenation, molecular hydrogen is the donor, and this topic is considered elsewhere in this Handbook. The substrate acceptor is unsaturated and can be, for example, a ketone, imine or alkene. The hydrogen donor is a good reductant and is often an alcohol, alkane or formate. The reaction is mediated by a catalyst that helps in the hydride transfer. When applied to ketones using isopropanol as the hydrogen donor and a Lewis acid to catalyze the reaction, the non-asymmetric transformation is known as the Meerwein–Pondorf–Verley reaction. Transfer dehydrogenation is the movement of a hydride ion and proton in the opposite direction. For alcohol substrates yielding ketone products, it is also known as the Oppenauer oxidation.

If the catalyst is chiral, it can transfer hydride selectively to one prochiral face of an acceptor to provide an optically active product (Fig. 35.1).

A number of excellent reviews have recently been published [1]; consequently, this chapter will consider mainly the practical aspects of asymmetric transfer hydrogenation by reviewing each of the components of the reaction, namely catalyst, hydrogen donor, substrate, product and other elements such as solvent, reaction conditions and scale-up.

In broad terms there are three types of catalyst for transfer hydrogenation: dehydrogenases; heterogeneous; and homogenous metal catalysts. Here, the first two are mentioned for completeness, and the main focus of this chapter will be asymmetric transfer hydrogenation with homogenous metal catalysts.

Nature uses enantioselective transfer hydrogenation to reduce metabolites, for example pyruvate to give (*S*)-lactic acid and 2-ketoglutarate to give (*S*)-2-hydroxyglutarate. The reaction is reversible and the equilibrium position depends on the concentration of the species. The enzyme catalysts are named dehydrogenases, and they employ a soluble cofactor or hydride acceptor called NAD(P) in its oxi-

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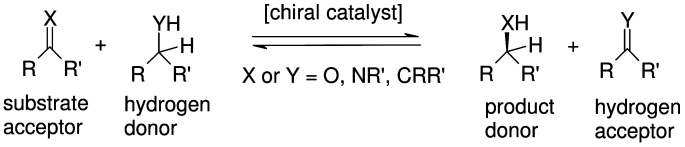


Fig. 35.1 The asymmetric transfer hydrogenation reaction.

dized form, and NAD(P)H in the reduced form [2a]. NAD(P) can be reduced to NAD(P)H, if the concentration of hydride donor is high relative to the hydride acceptor. The similarity of enantioselective transfer hydrogenation and dehydrogenase-catalyzed reactions has been recognized in a number of studies [2b–e].

Chemical catalysts for transfer hydrogenation have been known for many decades [2e]. The most commonly used are heterogeneous catalysts such as Pd/C, or Raney Ni, which are able to mediate for example the reduction of alkenes by dehydrogenation of an alkane present in high concentration. Cyclohexene, cyclohexadiene and dihydronaphthalene are commonly used as hydrogen donors since the byproducts are aromatic and therefore more difficult to reduce. The heterogeneous reaction is useful for simple non-chiral reductions, but attempts at the enantioselective reaction have failed because the mechanism seems to occur via a radical (two-proton and two-electron) mechanism that makes it unsuitable for enantioselective reactions [2c].

35.2 Homogenous Metal Catalysts

35.2.1 Early studies

Transfer hydrogenation of ketones, aldehydes, and alkenes using homogenous catalysts was successfully realized by Henbest et al. [3a] and furthered by Colonna et al. [3b] using iridium(III) phosphite or sulfoxide complexes and the hydrogen donor isopropanol (IPA system). In some seminal studies, Mestroni et al. reported the achiral transfer hydrogenation of carbonyl, azomethine and nitrogroups using iridium and rhodium bipyridine and similar complexes [3c]. These authors went on to develop the first enantioselective transfer hydrogenation using iridium Schiff base complexes with the hydrogen donor IPA, noting the fall in enantiomeric excess with conversion that occurs as a result of the reverse dehydrogenation [3d]. Bäckvall reported the transfer hydrogenation of ketones and imines using IPA and catalyzed by a ruthenium complex [4a,b], while Mestroni's group then reported the use of rhodium phenanthroline catalysts in diastereoselective reductions [4c].

One of the earliest reports of enantioselective transfer hydrogenation was by Alper et al., who used chiral Schiff bases and a dichlororuthenium(II)benzene complex employing the IPA system [5]. In another report, Lemaire et al. utilized

chiral diamines complexed with rhodium [6]. Mestroni and Gladiali have reported extensive investigations aimed at improving the catalysts and optimizing the system [7]. Despite these efforts, the product optical purities remained modest at around 65% enantiomeric excess (ee), and this failed to generate much interest – especially as enantioselective hydrogenation was giving outstanding performances. Evans reported the transfer hydrogenation of acetophenone in high enantiomeric excess using a chiral samarium(III) aminoalcohol complex, although low turnover numbers (TON) make the use of this catalyst impractical [8]. Shvo invented a very promising catalyst which was based on ruthenium cyclopentadienes [9], while Bäckvall and others have studied this elegant and effective system further [10]. Noyori et al. provided the step-change improvement required with their report of a catalyst based on a complex between chiral 1,2-aminoalcohols and dichlororuthenium(II)arene able to enantioselectively reduce ketones in 98% ee using the IPA system [11, 12]. The problem with this system is the reversibility of the reaction, which leads to poor conversions and falling optical purities. The development of *N*-tosyldiamine ligands with rutheniumarene complexes enabled use of the irreversible hydrogen donor formic acid when used as a mixture with triethylamine (TEAF) [13].

The reports by Noyori sparked intense academic and industrial interest in this area, and these studies led ultimately to a plethora of reports describing investigations into new catalysts [1]. In this respect, a variety of metals have been employed, including cobalt, nickel, palladium, platinum and zinc, though the best catalysts have employed ruthenium [11], rhodium [14, 15] and iridium [14, 16, 17].

35.2.2
Group VIII Metal Catalysts

The Group VIII metals are able to cycle between the d6 and d8 electronic states, and are used in their +2 or +3 oxidation states. Particularly effective has been the use of ruthenium arenes and the isoelectronic rhodium or iridium cyclopentadienes [11–16]. These ligands remain coordinated to the metal, and are important in defining the electronics, sterics, stability, and asymmetry around the metal. Alkylation of the arene or cyclopentadiene affects each of these factors, and it is difficult to draw conclusions or to predict the best catalyst. A number of ruthenium arenes have been prepared and their activities and selectivities compared [12], although the ruthenium cymene is most often used, mainly for its generally good performance and commercial availability. Likewise, a number of rhodium or iridium cyclopentadienes have been prepared which, when complexed with a chiral ligand, have been named CATHy^{TM} catalysts. The present author's studies have shown that the extra stability and steric bulk imparted by the pentamethylcyclopentadiene (cp*) make this consistently the best ligand. The cyclopentadiene (cp) ligand seems to provide lower ee-values, most likely because of it size, and it is also less stable and less soluble. The tetraphenyl analogue appears to be too large, as it produces only moderate optical inductions. The use of a chiral cyclopentadiene such as neomenthylcyclopentadiene pro-

vided disappointing results, although tethered cyclopentadienyls are currently showing more promise [18].

The dichlororuthenium arene dimers are conveniently prepared by refluxing ethanolic ruthenium trichloride in the appropriate cyclohexadiene [19]. The dichloro(pentamethylcyclopentadienyl) rhodium dimer is prepared by refluxing Dewar benzene and rhodium trichloride, whilst the dichloro(pentamethylcyclopentadienyl)iridium dimer is prepared by reaction of the cyclopentadiene with iridium trichloride [20]. Alternatively, the complexes can be purchased from most precious-metal suppliers. It should be noted that these ruthenium, rhodium and iridium arenes are all fine, dusty, solids and are potential respiratory sensitizers. Hence, the materials should be handled with great care, especially when weighing or charging operations are being carried out. Appropriate protective clothing and air extraction facilities should be used at all times.

Since most transfer hydrogenation catalysts employ precious metals, a high number of turnovers are required in order to make their use economic. As the ligands are simply made they are generally of low cost. In our experience, for the average pharmaceutical intermediate, a substrate : catalyst ratio (SCR) of about 1000:1 is sufficient for the catalyst's contribution to the product cost to be minor. These SCRs are regularly achieved, and so from an economic standpoint there has been little incentive to recover and recycle the catalyst, unless a low-cost product is required. The recovery of precious metals from waste streams provides another way in which costs can be minimized.

35.2.3 Chiral Ligands

The ligands are usually bidentate, and are based on diamines or aminoalcohols, though some reports exist of 1,2-aminothiols, aminosulfoxides, aminophosphines, aminophosphine oxides, biscarbenes and alpha amino acids being used as ligands. Diols do not appear to function as ligands. Other ligands that have been found to be effective include tridentate diaminoalcohols and tetradentate diaminodiphosphines, diaminodiphenols or diaminodialcohols. As has often occurred in studies of asymmetry, there are many types of ligand available but few studies have compared the designs, enabling conclusions to be drawn about their activity and selectivity. The best ligand–metal combinations should provide catalysts that, above all, show high activity, high selectivity, broad scope and have low cost, as well as being easily prepared. Moreover, they should be available in both antipodes, be stable, pure, non-toxic, recyclable, and easily separated from the product. From an industrial perspective, the ownership of intellectual property is also an important consideration. Based on these criteria it is not surprising that diamines and aminoalcohol ligands with ruthenium, rhodium and iridium metals have emerged as widely useful catalysts for enantioselective transfer hydrogenation.

The most successful ligands are unsymmetrical chiral diamines or aminoalcohols, perhaps because they influence the configuration of the ligated metal chir-

al center. Although such chiral centers are not stable they may lie sufficiently within the timescale of a rapidly turning-over catalyst.

The backbone of the bidentate ligand is usually an ethylene bridge so that a 1,2 relationship between the heteroatoms provides a stable five-membered ring with the metal. As the ring becomes enlarged the association with the metal is weakened and these ligands give lower optical inductions. The other substituents that form the chiral centers are essential in inducing optical activity in the product. Their main role is thought to be in providing the steric bulk that stabilizes a twisted conformation. A 1,2-*trans* stereochemistry in the ligand is generally more effective than a 1,2-*cis* geometry, an exception being *cis*-1,2-aminoindanol. The diphenylethylenediamine (DPEN) ligands are especially useful as they are relatively inexpensive and easily made on the kilogram scale. The diamines are used in either the IPA or TEAF system and have been N-substituted with aryl, alkyl, acetoyl, thioacetoyl and sulfonyl groups. The latter are preferred as they lower the pK_a of the amine allowing an ionic bond with the metal. In general, arylsulfonyl groups have been used, the most prevalent being tosyl (TsDPEN) [11, 21], although alkyl groups including trifluoromethylsulfonyl (TfDPEN) [22] and camphorsulfonyl (CsDPEN) [23] have also been used. The latter is very useful, providing generally very high ee-values, perhaps as a result of the additional steric bulk and remote functionality. The (1*R*)-camphor sulfonyl group has been found to give the same optical inductions as the (1*S*) group, implying that the chirality around the camphor has little effect on the enantiomeric excess of the product. One interesting observation, however, is that the ee-values sometimes increase slightly after the start of a reaction, and this has been shown to be a result of the enantioselective reduction of the ketone group on the camphor, giving an even better ligand. A library of *N*′-arylsulfonylethylenediamines has been synthesized (Fig. 35.2), though studies have shown little correlation between the electronic or steric nature of the arylsulfonyl group and the activity or selectivity of the catalyst. Indeed, only minor changes in the enantiomeric excess of selected products were observed, making this a fine-tuning tool.

The *N*-arylsulfonyl ligands are synthesized by reaction of mole equivalents of the optically active diamine and sulfonyl chloride, followed by recrystallization [21].

The aminoalcohol ligands are combined with the metal to produce catalysts that are used most effectively in the IPA system. Here, very high turnover numbers (TONs) have been achieved with a variety of ligands. The most frequently used are based on commercially available norephedrine and *cis*-1,2-aminoindanol as these are inexpensive, available in both enantiomers, and can be used unmodified [12, 24, 25] (see Fig. 35.2). Other simple and highly active ligands that have been prepared are based on azanorbornanemethanol [26] and benzylthio-1,2-diphenylethanol [16]. Gladiali and Elberico have recently reviewed the ligands that have been used in enantioselective transfer hydrogenation [1a].

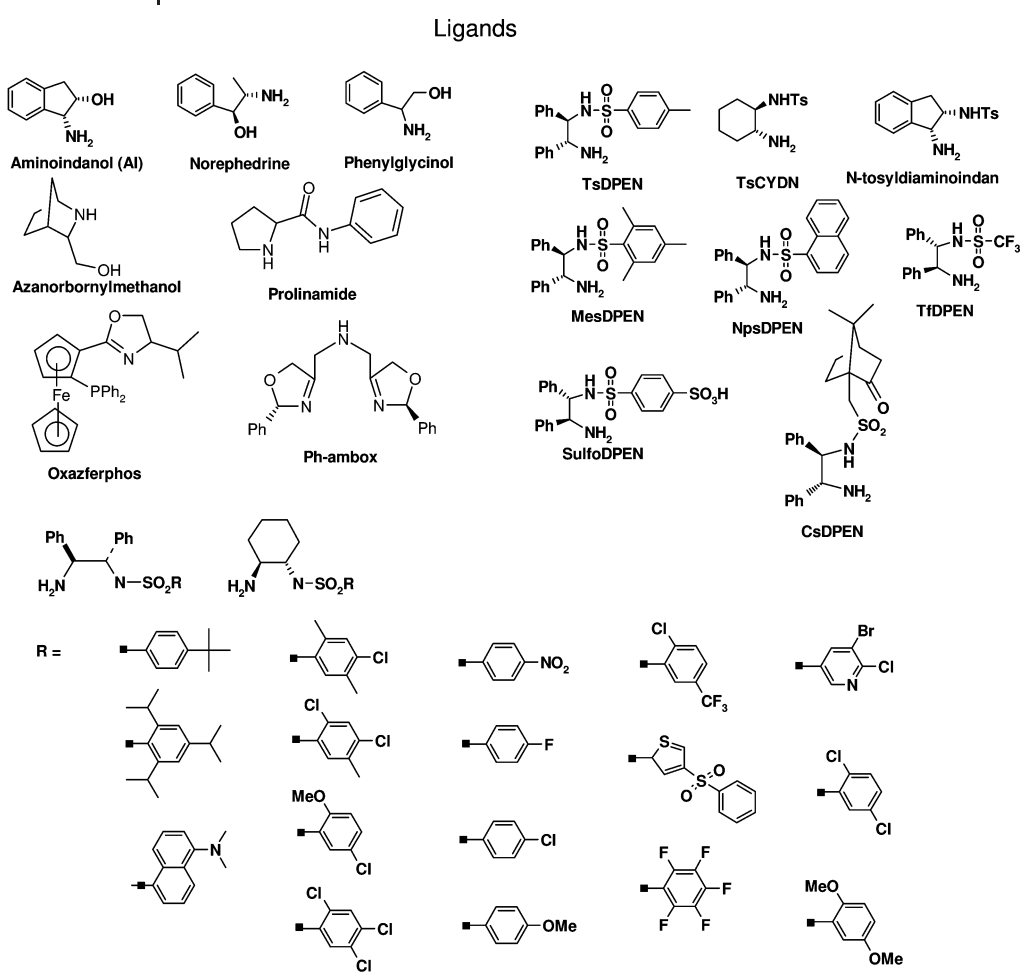


Fig. 35.2 Some examples of 1,2-aminoalcohol and 1,2-diamine ligands and a readily prepared library of *N*-sulfonyldiamine ligands.

35.2.4
Immobilized Ligands

The advantages that heterogeneous catalysts have is that they are easily separable from the product, and can be recycled. A number of studies have been conducted in which ligands have been attached or bound to polymeric material to provide an immobilized ligand, and these include polyacrylate and silica [27], polyurea [28], polythiourea [29], polyether [30, 31] and dendritic [32] systems. Upon metal coordination, the immobilized catalysts have retained most of the activity and selectivity, but they now provide the advantage of simple separation and recycling. For exam-

ple, Tu et al. have used a modified phenylsulfonylchloride and attached this to diphenylethylenediamine to produce an analogue of TsDPEN [33]. This is then linked to a silica gel polymer to produce the immobilized ligand. The ruthenium cymene complex actively catalyzes the enantioselective transfer hydrogenation of acetophenone, with the same selectivity and activity as the soluble catalyst. However, after multiple recycling the activity falls off somewhat, presumably due to metal leaching, though the selectivity remains high. Xiao has overcome this problem by using a polyethylene glycol-immobilized ligand and carrying out the reaction in water; the catalyst is then precipitated by changing the solvent polarity [31]. In this way, twenty recycles of the catalyst could be achieved, without any adverse effects.

35.2.5
Water-Soluble Ligands

The standard ruthenium arene and CATHy^{TM} catalysts are insoluble in water, but are nevertheless stable in the presence of water. Reactions in the IPA system can be carried out in mixtures of isopropanol and water; the net effect is a lower rate due to dilution of the hydrogen donor. The use of formate salts in water, with CATHy^{TM} or other transfer hydrogenation catalysts dissolved in a second immiscible phase was shown to work well with a number of substrates and in some cases to improved reaction rates [34]. The use of water as reaction solvent will be discussed in more detail in Section 35.5.

In some cases it is useful to have the catalyst soluble in water: some substrates are only soluble in water, others give higher ee-values in this solvent, and there may be benefits in separating the catalyst from product that is soluble in an organic phase. Ligands have been prepared that provide solubility in water. Typically, these involve a sulfonated ligand, and two approaches have been reported: (i) the use of a sulfonate group on the *N*-arylsulfonamide of the diamine [35]; and (ii) use of a sulfonate on the phenyl groups of diphenylethylenediamine [36]. Both ligands are reasonably easily prepared.

35.2.6
Catalyst Selection

The catalysts involved in enantioselective transfer hydrogenation are simply prepared by mixing equimolar amounts of the ligand and metal complex *in situ*, so that different ligands and metal complexes can be combined in different ways to generate a library of catalysts. Since the reactions do not involve molecular hydrogen, it is a simple matter to set up an experiment to screen catalysts to find the most active and enantioselective for a substrate (sadly, this is not true for the ruthenium catalysts, most of which are sensitive towards oxygen, while the catalysts based on aminoalcohols are extremely sensitive towards oxygen). A SCR of 100:1 is often used to ensure a rapid and successful reaction.

As mentioned earlier, ruthenium cymene, rhodium and iridium pentamethylcyclopentadiene are good metal complexes, to start with, in a screen. It is diffi-

cult to predict which metal will give the best enantiomeric excess for a particular substrate. In general, ruthenium gives lower rates than rhodium or iridium CATHy™ catalysts, but the selectivities can be quite different. The IPA and TEAF systems are screened, and a range of aminoalcohol and diamine ligands are tested; aminoalcohols are usually only successful in the IPA system. Either enantiomer of *cis*-1,2-aminoindanol, TsDPEN and CsDPEN are good starting points in a screen, and these are usually tested in a range of solvents, as this can have more bearing on the optical induction than a large ligand screen.

When making pharmaceuticals, one critical issue is to control and minimize metal impurities in the product, often to less than 10 ppm. Each product requires a different work-up and purification protocol, and it is difficult to describe a general solution. On some occasions washing removes the catalyst, but at other times the product is crystallized and the catalyst remains in the mother liquors; occasionally, the product is volatile and can be distilled. Sometimes the catalyst is carried forward to the next stage and is removed at this point. In our experience, residual metal has not been problematic, but if it is then either immobilized or water-soluble catalysts, as described in this chapter, can be employed.

35.2.7 Catalyst Preparation

The catalysts are best prepared *in situ* by mixing a half-equivalent of the dichloro-metal aromatic dimer with an equivalent of the ligand in a suitable solvent such as acetonitrile, dichloromethane or isopropanol. A base is used to remove the hydrochloric acid formed (Fig. 35.3). If 1 equiv. of base is used, the inactive pre-catalyst is prepared, and further addition of base activates the catalyst to the 16-electron species. In the IPA system the base is conveniently aqueous sodium hydroxide or sodium isopropoxide in isopropanol, whereas in the TEAF system, triethylamine activates the catalyst. In practice, since the amount of catalyst is tiny, any residual acid in the solvent can neutralize the added base, so a small excess is often used. To prevent the active 16-electron species sitting around, the catalyst is often activated in the presence of the hydrogen donor. The amount of catalyst required for a transformation depends on the desired reaction rate. Typically, it is desirable to achieve complete conversion of the substrate within several hours, and to this extent the catalyst is often used at 0.1 mol.% (with SCR 1000:1). Some substrate–catalyst combinations are less active, requiring more catalyst (e.g., up to 1 mol.%; SCR 100:1), in other reactions catalyst TONs of 10 000 (SCR 10 000:1) have been realized.

The ruthenium [37] and rhodium [38] pre-catalysts have been prepared and isolated; likewise, the 16- and 18-electron hydride species have been prepared and characterized [38–40]. There is little practical advantage in using the catalysts in this form, other than for mechanistic studies or when special circumstances are required (e.g., neutral reaction conditions).

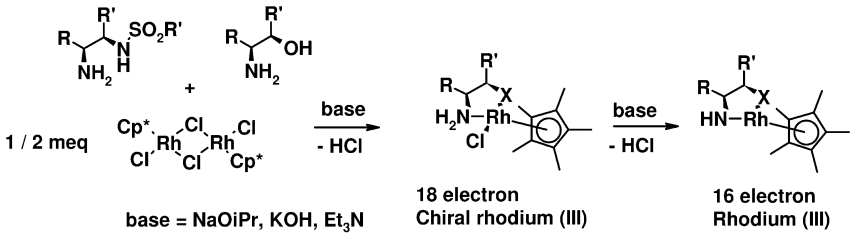


Fig. 35.3 Catalyst preparation.

35.2.8
The Reaction Mechanism

The mechanism of the Meerwein–Pondorf–Verley reaction is by coordination of a Lewis acid to isopropanol and the substrate ketone, followed by intermolecular hydride transfer, by beta elimination [41]. Initially, the mechanism of catalytic asymmetric transfer hydrogenation was thought to follow a similar course. Indeed, Bäckvall et al. have proposed this with the Shvo catalyst [42], though Casey et al. found evidence for a non-metal-activation of the carbonyl (i.e., concerted proton and hydride transfer [43]). This follows a similar mechanism to that proposed by Noyori [44] and Andersson [45], for the ruthenium arene-based catalysts. By the use of deuterium-labeling studies, Bäckvall has shown that different catalysts seem to be involved in different reaction mechanisms [46].

For the ruthenium arene and CATHy^{TM} catalysts, the mechanism has been studied in some detail. An outline mechanism for the reaction is illustrated in Figure 35.4.

The primary amine on the ligand is essential in allowing elimination of hydrogen chloride to generate the active 16-electron metal. This indicates why 1,2-aminoalcohols and diamines are good ligands, but 1,2-diols are not. After complexing with the metal, the amide thus formed is basic (the basicity of this is intriguing, the implication being that the metal is able to lower the pK_a by many orders of magnitude). In either the IPA or TEAF system the amide should readily reprotonate. The nitrogen–metal bond changes from one that is covalent to one that is dative. At this point in the cycle, the metal is likely to become more oxidative and be reduced to the metal–hydride intermediate. The 18-electron metal hydrides of the ruthenium, rhodium and iridium catalysts have been characterized and shown to be active [37–40]. The metal is now a chiral center and appears to be configurationally stable and optically active. Indeed, when the substrate binds the hydride is delivered selectively to one prochiral face. It seems likely that the ligand NH protons are involved in hydrogen bonding with the substrate. Substitution of the primary amine results in a dramatic loss of activity, for example $NH_2 > NHMe \gg NMe_2$. Noyori's studies on the analogous ruthenium arene catalysts also indicate that the ruthenium is optically active and that the substrate interacts by hydrogen bonding [44].

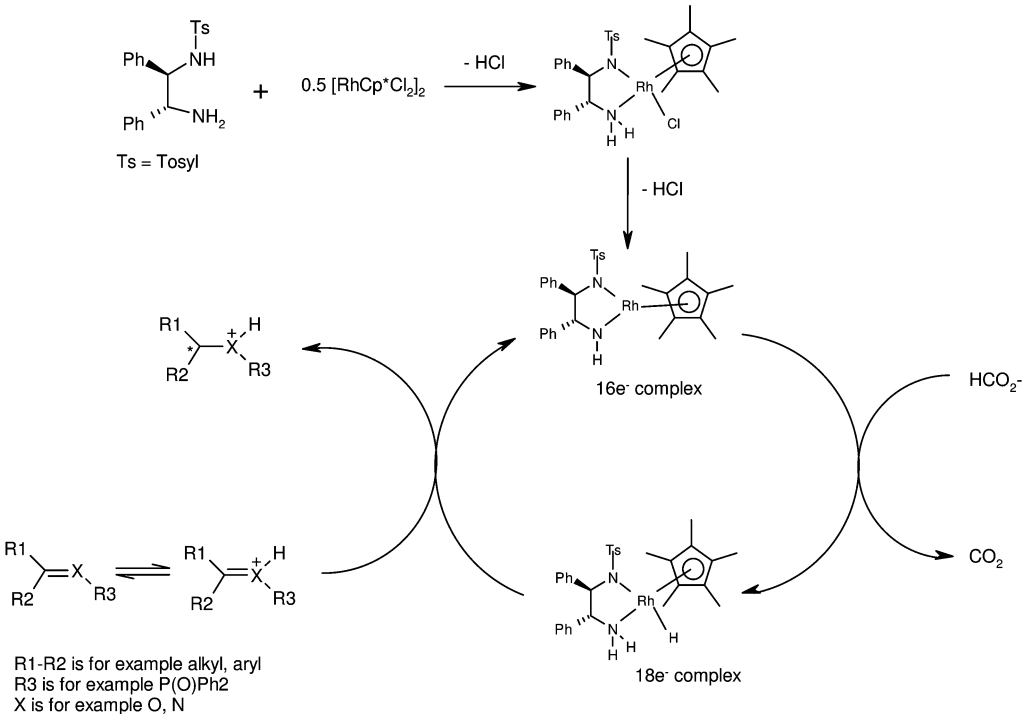


Fig. 35.4 Outline mechanism for the rhodium-catalyzed enantioselective transfer hydrogenation reaction.

35.3 Hydrogen Donors

35.3.1 The IPA System

Alcohols will serve as hydrogen donors for the reduction of ketones and iminium salts, but not imines. Isopropanol is frequently used, and during the process is oxidized into acetone. The reaction is reversible and the products are in equilibrium with the starting materials. To enhance formation of the product, isopropanol is used in large excess and conveniently becomes the solvent. Initially, the reaction is controlled kinetically and the selectivity is high. As the concentration of the product and acetone increase, the rate of the reverse reaction also increases, and the ratio of enantiomers comes under thermodynamic control, with the result that the optical purity of the product falls. The rhodium and iridium CATHy™ catalysts are more active than the ruthenium arenes not only in the forward transfer hydrogenation but also in the reverse dehydrogenation. As a consequence, the optical purity of the product can fall faster with the

former than with the latter catalysts. In order to obtain high yields and to avoid the slow racemization of the product, it was initially necessary to work under dilute conditions. However, this limitation was overcome by continuous removal of the acetone as it was formed by distillation [47]. As the CATHy™ catalysts are less stable at higher temperatures, this distillation is best performed under reduced pressure at below 40 °C.

The reversibility of the reaction can be used to good effect in asymmetric dehydrogenation and dynamic kinetic resolutions (see later for discussion).

Other alcohols such as methanol and ethanol will also react, but are typically less effective as the aldehyde byproducts can interfere in the reaction. Isobutanol is an effective hydrogen donor, and others such as glucose will also react but cannot be used in such high concentrations. Isopropanol can be mixed with an inert solvent, including water, but the rates of reaction fall linearly, as expected.

Avecia and others have successfully scaled-up the IPA process to prepare a number of products in high optical purity in a simple and efficient reaction [1c, 48].

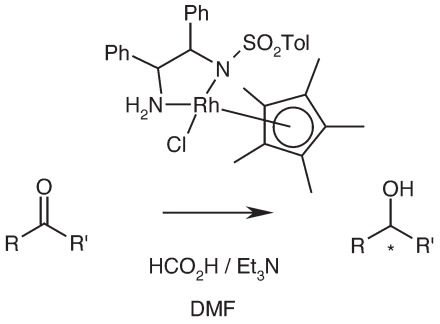
35.3.2 The TEAF System

Formic acid has long been recognized as a good and irreversible hydrogen donor, and used in both heterogeneous and homogenous transfer hydrogenations [49a]. The reagent keeps the reaction under kinetic control since CO_2 generated as a byproduct is gassed out of the system, thereby preventing the reverse reaction that is, in any case, thermodynamically unfavorable. Consequently, there is no fall in product optical purity as the reaction proceeds. The use of formic acid, either neat or diluted with a solvent, is effective in some transfer hydrogenations, but results can be inconsistent. The combination with triethylamine has been very effective [49b]. The reagent is known as TEAF, and can be used in different ratios of formic acid and triethylamine. The most commonly used mixture is a 5:2 molar ratio of formic acid to triethylamine, which is the azeotrope of these two liquids [50]). Practically speaking, it is easier to prepare the 5:2 TEAF by mixing the correct amounts of the components, than by distillation. The addition of triethylamine to formic acid is considerably exothermic, and is best done by slow addition of one of the reagents with good mixing. Making TEAF *in situ* during the transfer hydrogenation is disadvantageous as the heat evolution makes the reaction difficult to control. The 5:2 TEAF is a single phase at ambient temperature and remains so when diluted with most solvents; however, other ratios of formic acid and triethylamine can form biphasic solutions.

Xiao has recently published reports showing that mixtures of triethylamine and formic acid can be used in water, and this greatly simplifies measurement of pH. The ruthenium catalyst is active when the pH is >4; this corresponds with the aqueous pK_a of formic acid 3.6 [52].

With the rhodium catalyst, and using TEAF in organic media, the situation is more complex. An example in which a series of formic acid : triethylamine ratios

Table 35.1 The effect of the triethylamine:formic acid ratio (TEAF) on reaction rate.



Mole ratio HCO_2H:Et_3N (1 M)	Time [h]	Conversion [%]
1:0	4	2
	15	26
3:1	4	50
	15	89
2.5:1	4	80
	15	100
2:1	4	50
	15	73
1.5:1	4	30
	15	73
1:1	4	50
	15	100
0.67:1	4	50
	15	95
0.5:1	4	50
	15	97
0.4:1	4	48
	15	100

has been evaluated under identical conditions with a ketone in DMF is shown in Table 35.1.

As can be seen from the data in Table 35.1, the maximum reaction rate is achieved at the 5:2 formic acid:triethylamine ratio that is the commonly used azeotropic mixture known as TEAF. When more acid is present, the catalyst may be less active, but equally there may be less formate anion (i.e., the active reagent). The concentration of the latter also depends upon the solvent being used. When there is more triethylamine present the reaction rate also decreases, and there are some indications that triethylamine may deactivate the catalyst. However, the use of formic acid mixtures with ammonia, ethylamine or diethylamine is less effective than triethylamine.

Table 35.2 The pK_a-values of formic acid and triethylamine in different solvents.

Solvent	HCOOH	Et_3NH^+
Water	3.7	10.7
MeOH	8.4	10.9
EtOH	9.1	8.1
Aqueous EtOH	5.4	8.4
DMSO	10.3	9.0
NMP	11.0	8.7
DMF	11.5	9.2

The 5:2 TEAF reagent is acidic, with the extent of the acidity depending upon the solvent in which the reagent is used. Variations of triethylamine and formic acid pK_a-values with solvent are listed in Table 35.2. The pK_a of formic acid in many of the common solvents used is much higher than water, so there would appear to be little free formate in the reaction; thus, it becomes difficult to explain the reaction in such conditions (e.g., those in Table 35.1).

Triethylamine may act to buffer the pH, which changes as formic acid is consumed during the reaction. An excess of formic acid over substrate is often used. Though not essential (as will be discussed later), it is sometimes preferable to charge TEAF during the reaction in order to ensure a high yield of product.

Other salts of formic acid have been used with good results. For example, sodium and preferably potassium formate salts have been used in a water/organic biphasic system [36, 52], or with the water-soluble catalysts discussed above. The aqueous system makes the pH much easier to control; minimal CO_2 is generated during the reaction as it is trapped as bicarbonate, and often better reaction rates are observed. The use of hydrazinium monoformate salts as hydrogen donors with heterogeneous catalysts has also been reported [53].

The TEAF system can be used to reduce ketones, certain alkenes and imines. With regard to the latter substrate, during our studies it was realized that 5:2 TEAF in some solvents was sufficiently acidic to protonate the imine (pK_a ca. 6 in water). Iminium salts are much more reactive than imines due to inductive effects (cf. the Strecker reaction), and it was thus considered likely that an iminium salt was being reduced to an ammonium salt [54]. This explains why imines are not reduced in the IPA system which is neutral, and not acidic. When an iminium salt was pre-prepared by mixing equal amounts of an imine and acid, and used in the IPA system, the iminium was reduced, albeit with lower rate and moderate enantioselectivity. Quaternary iminium salts were also reduced to tertiary amines. Nevertheless, as other kinetic studies have indicated a pre-equilibrium with imine, it is possible that the proton formally sits on the catalyst and the iminium is formed during the catalytic cycle. It is, of course, possible that the mechanism of imine transfer hydrogenation is different to that of ketone reduction, and a metal-coordinated imine may be involved [55].

Table 35.3 Examples of the effect of solvent on enantioselectivity with two different ketones.

Solvent	ee [%]	Conversion [%]
Ketone 1		
Methanol	58	>90
Dimethylsulfoxide	72	>90
Dimethylformamide	52	>90
Acetonitrile	4	>90
Ethyl acetate	46	>90
Tetrahydrofuran	60	>90
Dichloromethane	16	>90
Toluene	0	>90
Ketone 2		
Neat	74	17
Methanol	78	14
Isopropanol	79	19
Dimethylformamide	80	100
Dimethylacetamide	79	98
1,4-Dioxane	82	52
Ethyl acetate	80	74
tert-Butyl acetate	77	50
Tetrahydrofuran	80	71
Glyme	74	59
Diglyme	74	18
Methoxyethanol	74	21
tert-Butylmethyl ether	73	30
Dichloromethane	80	51
Triethylamine	78	82
2-Pentanone	77	30
Toluene	63	13

Ketone 1: an electron-rich aryl alkyl ketone. For the screening studies, 1 mol.% catalyst was used and the reactions were analyzed after 1 h.
Ketone 2: an electron-deficient aryl alkyl ketone. For the screening studies, 1 mol.% catalyst was used and the reactions were analyzed after 1 h.

In many cases the solvent was observed to have a large effect on the optical purity of the product. Examples of this, with a ketone and the rhodium cp* TsDPEN catalyst, are shown in Table 35.3. Further optimization of this reaction improved the enantiomeric excess to 98%. A second example involved the reduction of 4-fluoroacetophenone; in this case the enantioselectivity was largely unaffected, but the rate of reduction changed markedly with solvent. Development of this process improved the optical purity to 98.5% ee.

A rationale for these results is that the catalyst interacts with the substrate through weak intermolecular association, and that the strength and nature of

this are sensitive to the solvent. Since it is difficult to predict the best solvent, the best approach is to screen a suitable range of those available.

35.3.3 Other Hydrogen Donors

Hydrogen will not reduce ketones or imines using CATHy™ or related catalysts. Inorganic hydrogen donors that have been used include dithionite and dihydrogenphosphite salts, metal hydrides such as sodium borohydride, and sodium cyanoborohydride. Recently, amines have been shown to function as hydrogen donors with some catalysts. The enzymic cofactor NADH can be used stoichiometrically, and the potential exists to use this catalytically [56].

Hydrogen donors that function poorly with homogenous catalysts include hydrazine hydrate, alkenes (e.g., cyclohexene), and ascorbic acid. This is somewhat surprising as they can be very effective in heterogeneous transfer hydrogenation.

35.4 Substrates and Products

A successful chemical technology is one that can be applied to any situation arising. Enantioselective transfer hydrogenation catalysts are rapidly gaining acceptance as a means of easily preparing optically active alcohols and amines. In our laboratory, we have tested more than 200 substrates, amongst which very few failed to give any reaction, and most give a high enantiomeric excess.

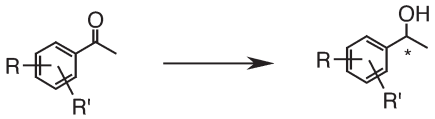
35.4.1 Aldehydes

Transfer hydrogenation is a mild and efficient means of reducing aldehydes, and can be advantageous over other reagents such as sodium borohydride. Clearly, the product is a primary alcohol and therefore not chiral, but a chiral center might be alpha to the aldehyde, in which case a resolution can be effected. Indeed, under the appropriate conditions the chiral center can be racemized and a dynamic kinetic resolution effected [57].

35.4.2 Ketones

The easiest substrates to test are acetophenones, as many substituted analogues are commercially available from laboratory suppliers. A large range of results have been reported; the best enantiomeric excesses achieved and relevant literature reference are detailed in Tables 35.4 and 35.5. The range of ketones that can be reduced includes substituted diaryl, dialkyl and arylalkyl ketones, alpha-,

Table 35.4 Optical purities realized with various substituted acetophenones.



R	R′	ee [%]	Reductant	Catalyst	TOF [h^{-1}]	Reference
H	H	99	TEAF	RuCl(mes)TsDPEN	10	37b
4-F	H	98.5	TEAF	RhClcp*CsDPEN	75	1c
2-Cl	H	97	IPA	$RuCl_2PPh_3$(phambox)	1200	61
3-Cl	H	99.7	IPA	$RuCl_2PPh_3$(oxazferrphos)	100	58
4-Cl	H	98.7	IPA	$RuCl_2PPh_3$(oxazferrphos)	100	58
2-Br	H	99	TEAF	RuCl(cym)prolinamide	<16.7	60
3-Br	H	99.7	IPA	RuCl(cym)prolinamide	100	58
4-Br	H	99.3	IPA	RuCl(cym)prolinamide	100	58
2-OMe	H	95	TEAF	RuCl(cym)prolinamide	16.7	60
3-OMe	H	98	IPA	RuCl(hmb)azanorbornylmethanol	3000	59b
4-OMe	H	97	TEAF	RuCl(mes)TsDPEN	10	37b
3-NO_2	H	91	IPA	RuCl(hmb)azanorbornylmethanol	3000	59b
4-NO_2	H	89	IPA	RuCl(cym)azanorbornylmethanol	200	59a
3-NH_2	H	99	IPA	RuCl(hmb)azanorbornylmethanol	3000	59b
2-Me	H	>99	IPA	$RuCl_2PPh_3$(oxazferrphos)	100	58
3-Me	H	>99	IPA	$RuCl_2PPh_3$(oxazferrphos)	100	58
4-Me	H	>99	IPA	$RuCl_2PPh_3$(oxazferrphos)	100	58
2-CF_3	H	96	IPA	RhClcp*TsDPEN	16.7	63
3-CF_3	H	97	IPA	RhClcp*TsDPEN	16.7	63
4-CF_3	H	88	IPA	RuCl(cym)azanorbornylmethanol	200	59a
3-CF_3	5-CF_3	92	IPA	RhClcp*TsCYDN	65	64

For ligand acronyms, see Figure 35.2.
Arene acronyms are as follows: mes = 2,4,6-mesitylene; hmb = hexamethylbenzene; cym = 1,4-cymene; cp* = pentamethylcyclopentadienyl.
TOF: Turnover frequency.

beta-unsaturated, alpha-substituted, cyclic, heterocyclic and alicyclic ketones. The substrates may bear functional groups including halides, ethers, thioethers, alkenes, amines, alcohols, amides, acids, esters and nitriles, yet selective reduction of the ketone is still achieved. The range of chiral alcohols that has been produced by asymmetric transfer hydrogenation, together with best values of enantiomeric excess, is illustrated in Figure 35.5. Of particular note are some unusual examples, for example the use of transfer hydrogenation to form optically active phthalides [73], pyridyl alcohols [78], diols [72] and drug intermediates such as isophorone [76], L-699,392 (an LTD_4 antagonist) and MK0417 (a carbonic anhydrase inhibitor) [49e]. This is only a small selection of such reactions, as many examples from industry are confidential and cannot be reported here.

Table 35.5 Optical purities realized with various acylbenzenes.

R	ee [%]	Reductant	Catalyst	TOF [h^{-1}]	Reference
Me	99	TEAF	RuCl(mes)TsDPEN	10	37b
Et	99.7	IPA	$RuCl_2PPh_3$(oxazferrphos)	25	58
*n*Pr	92	IPA	RuCl(cym)azanorbornylmethanol	100	59a
*i*Pr	90	IPA	RuCl(cym)azanorbornylmethanol	<13	59a
*n*Bu	98.7	IPA	$RuCl_2PPh_3$(oxazferrphos)	50	58
*t*Bu	93	IPA	$RuCl_2PPh_3$(oxazferrphos)	12.5	65
*n*Hx	95	IPA	RuCl(cym)azanorbornylmethanol	100	59a
CH_2Cl	97	TEAF	RhClcp*TsDPEN	1000	66
CH_2OH	94	TEAF	RhClcp*TsDPEN	<16.7	67
CH_2OTs	93	TEAF	RhClcp*TsDPEN	<16.7	67
CH_2CN	98	TEAF	RuCl(cym)TsDPEN	42	68
CH_2N_3	92	TEAF	RuCl(cym)TsDPEN	4	68
CH_2NO_2	98	TEAF	RuCl(cym)TsDPEN	12.5	68
CH_2NMeCO_2tBu	99	TEAF	RuCl(cym)aminoindanol	<8	69
TMS	98	IPA	RuCl(cym)TsDPEN	–	70
COEt	99	TEAF	RuCl(cym)TsDPEN	12.5	71

For ligand acronyms, see Figure 35.2.
Arene acronyms are as follows: mes = 2, 4, 6-mesitylene; cym = 1,4-cymene; cp* = pentamethylcyclopentadienyl.
TOF: Turnover frequency.

In general, dialkyl ketones are reduced with lower ee than aryl alkyl ketones. In the case of rhodium-based catalysts, strongly electron-withdrawing substituents on aryl ketones tend to give lower enantiomeric excesses, whilst in the case of ruthenium the trend seems to be reversed. Coordinating groups alpha to the ketone can give variable results since the product can act as a ligand and either enhance or interfere with the catalyst. Most substrates are reduced with excellent enantioselectivity and with good catalyst turnover frequencies (TOFs).

35.4.3
Aldimines

The transfer hydrogenation of aldimines has not been reported. In our own studies we have tested the simple Schiff base adduct between benzylamine and benzaldehyde and shown this to be reduced in straightforward manner.

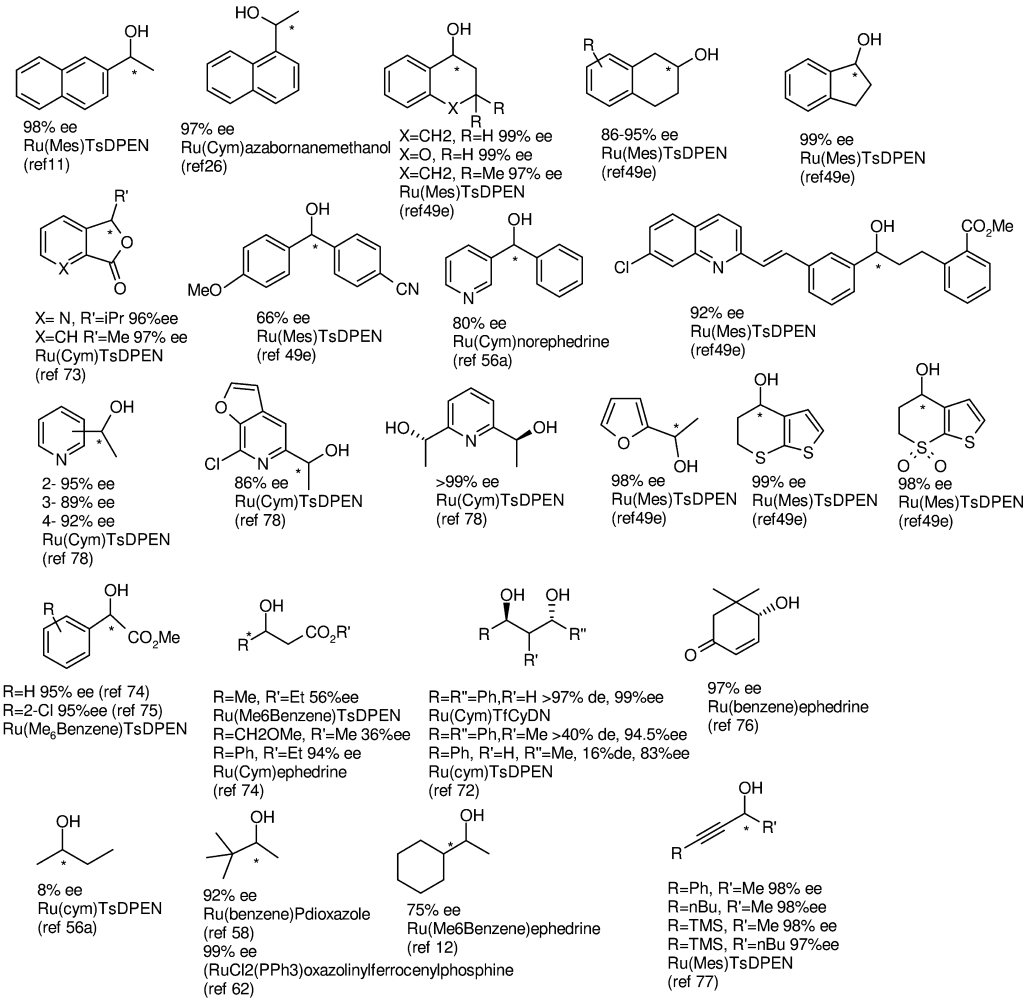


Fig. 35.5 Examples of alcohols produced, and their optical purities.

35.4.4
Ketimines

The reduction of imines and iminium salts present a particular difficulty in that those which are N-substituted can exist in different geometrical isomers that are reduced at different rates and with different selectivities. One way to overcome this problem is to use cyclic imines that can exist only as *cis* isomers. Although these are good substrates, this is not a general solution. The cyclic amines produced by transfer hydrogenation, together with best reported enantiomeric excesses, are listed in Table 35.6. Primary amines are difficult to pre-

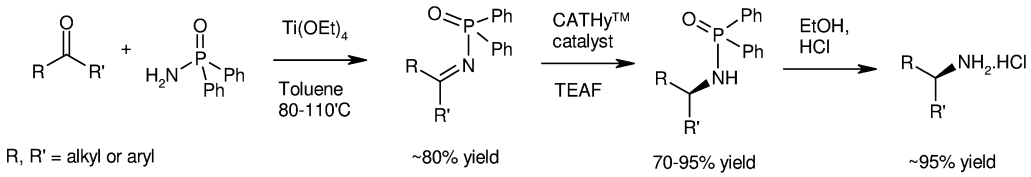
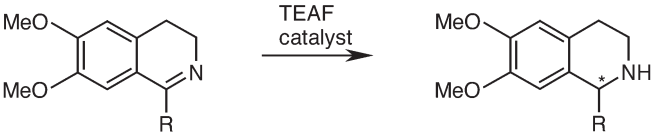


Fig. 35.6 Synthesis of chiral amines by an improved procedure for making diphenylphosphinylimines, followed by asymmetric transfer hydrogenation.

Table 35.6 Optical purities realized with various cyclic imines.



R	ee [%]	Reductant	Catalyst	TOF [h^{-1}]	Reference
methyl	95	TEAF	RuCl(cym)TsDPEN	67	1k
ethyl	83	TEAF	RhClcp*TsDPEN	1200	15b
isopropyl	99	TEAF	RhClcp*TsDPEN	1200	15b
cyclohexyl	97	TEAF	RhClcp*TsDPEN	1200	15b
phenyl	84	TEAF	RuCl(bnz)NpsDPEN	25	1k
2-bromophenyl	98	TEAF	RuCl(bnz)NpsDPEN	<7	84
3,4-dimethoxyphenyl	84	TEAF	RuCl(bnz)NpsDPEN	8.3	1k
3,4-dimethoxybenzyl	95	TEAF	RuCl(cym)MesDPEN	<28	1k
3,4-dimethoxyhomophenyl	92	TEAF	RuCl(cym)MesDPEN	16.7	1k

For ligand acronyms, see Figure 35.2.
Arene acronyms are as follows: bnz = benzene; cym = 1,4-cymene; cp* = pentamethylcyclopentadienyl.

pare directly as the imines are unstable in TEAF; consequently, N-substitution is required. *N*-benzyl and *N*-alkyl imines are often reduced, but with moderate ee-values due to the geometrical isomer problem [1k, 15b, 37b]. Some *N*-acyl, *N*-sulfonyl, oximes and hydrazones are reduced, but the reaction appears to be substrate-specific. Diphenylphosphinylimines are particularly good substrates [79], as the large steric size of the diphenylphosphinyl group may cause the imine to exist in predominantly one geometrical isomer, and this leads to high optical activities. The published method for preparing diphenylphosphinylimines involves reacting diphenylphosphinylchloride with the primary imine [83], though in our experience this leads to low yields. An improved method for their preparation involves reacting diphenylphosphonylamide with the ketone and dehydrating with titanium tetraisopropoxide (Fig. 35.6).

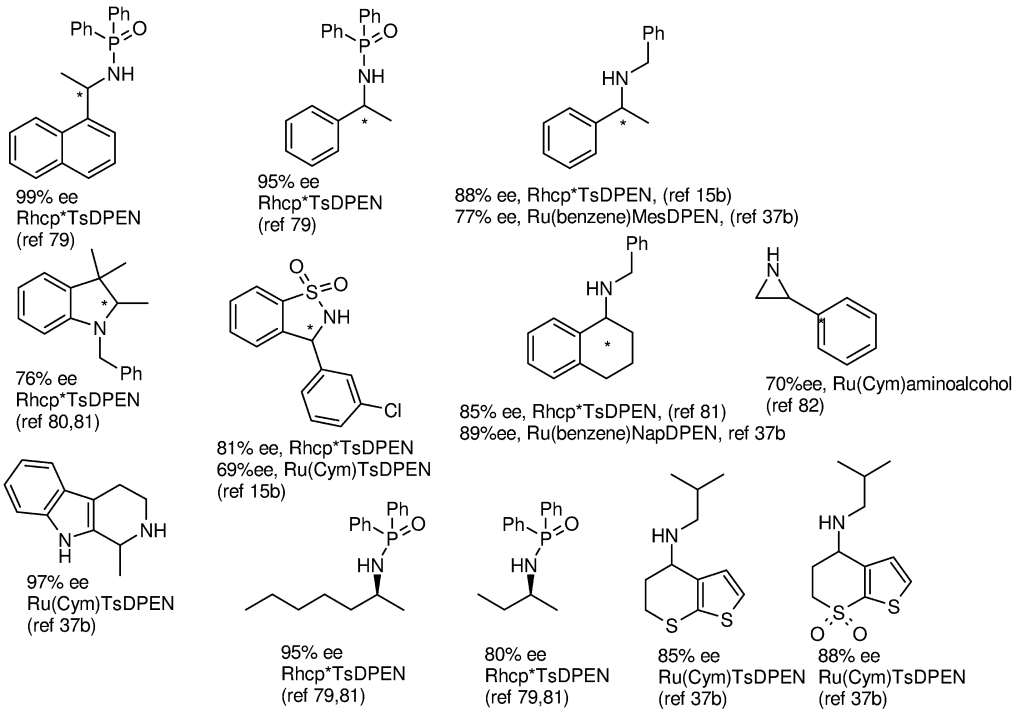


Fig. 35.7 Examples of amines produced, and their optical purities.

The imine may be isolated in good yield, or more conveniently the transfer hydrogenation can be carried out directly on this mixture. The diphenylphosphonylamine product is hydrolyzed with acidic ethanol to yield the primary amine. Alternatively, the diphenylphosphonylamine can be alkylated and the protecting group then removed to yield a secondary amine. Most imines that have been reduced are arylalkyl, though excellent results have been obtained with the phosphinylimines of dialkyl substrates (e.g., 2-butanone, 2-hexanone and 2-octanone substrates). The enantiomeric excesses achieved with a variety of imine substrates are illustrated in Figure 35.7.

The synthesis of amines by the *in-situ* reductive amination of ketones is termed the Leuckart–Wallach reaction. Recently, an asymmetric transfer hydrogenation version of this reaction has been realized [85]. Whilst many catalysts tested give significant amounts of the alcohol, a few produced almost quantitative levels of the chiral amine, in high enantiomeric excess.

A recent development is the transfer hydrogenation of heterocyclic systems such as pyrrole, pyridinium and quinoline systems. Whilst at present the yields and enantioselectivities are modest, further development may improve this situation. For example, 1-methyl-isoquinoline has been reduced to the tetrahydro species and 1-picoline has been reduced to 1-methylpiperidine [86]. Interestingly, these reductions involve alkene as well as imine reduction.

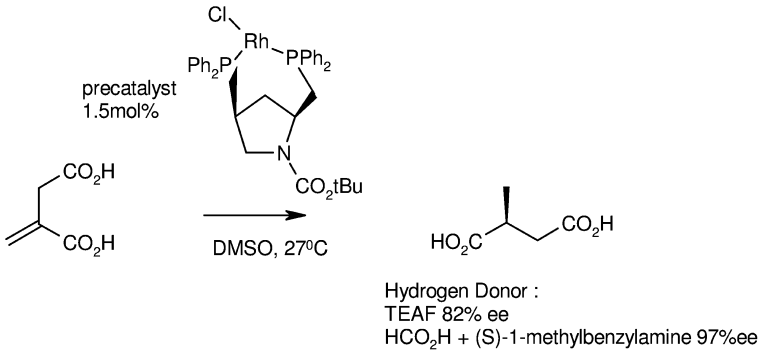


Fig. 35.8 Optical activities achieved by enantioselective transfer hydrogenation of alkenes.

35.4.5
Alkenes

Brunner, Leitner and others have reported the enantioselective transfer hydrogenation of alpha-, beta-unsaturated alkenes of the acrylate type [50]. The catalysts are usually rhodium phosphine-based and the reductant is formic acid or salts. The rates of reduction of alkenes using rhodium and iridium diamine complexes is modest [87]. An example of this reaction is shown in Figure 35.8. Williams has shown the transfer hydrogenation of alkenes such as indene and styrene using IPA [88].

Enantioselective Michael reactions have been achieved using both the Rh-based CATHy catalysts [89 a] and the Ru-based Noyori catalysts [89 b].

35.5
Solvents

The IPA system does not require a co-solvent, but one can be used if this proves advantageous. In the TEAF system a solvent is normally used, though neat TEAF or formic acid can be used if required. The solvent can have a large effect on the reaction rate and optical purity of the product; this may in part be because the substrate seems to bind by weak electrostatic interactions with the catalyst, and is also partly due to the pH of the system. Solvents have a dramatic effect on the ionization of formic acid; for example, in water the pK_a is 3.7, but in DMF it is 11.5. This is because formation of the formate anion becomes less favorable with less polar solvents (see Table 35.2). The pK_a of triethylamine is far less sensitive. As a consequence, formic acid and triethylamine may remain unreacted and not form a salt. The variation in formic acid pK_a can also have a significant impact on the catalyst and substrate, particularly when this is an imine.

Typically, solvents are screened to identify one that gives optimal results. Assuming that the substrate and catalyst are soluble, solvent polarities varying from alkanes, aromatics, halogenated, ethers, acetonitrile, esters, alcohols, dipolar aprotic to water have been used. An example of this, using a ketone and the rhodium cp* TsDPEN catalyst, is shown in Table 35.3. Further optimization of this reaction improved the enantiomeric excess to 98%. A second example involved the reduction of 4-fluoroacetophenone; in this case the enantioselectivity was largely unaffected but the rate of reduction changed markedly with solvent. Development of this process improved the optical purity to 98.5% *e.e.*

Water has been shown to enhance the activity of ruthenium and rhodium catalysts in both the TEAF and potassium formate systems [34, 36, 52]. The aqueous systems enable much simpler control of pH; this is important, as Xiao has found that a low pH markedly slows the reaction [52]. The pH at which this occurs corresponds with the pK_a of formic acid (i.e., 3.7), implying that the formate anion is required for complexation with the catalyst. Xiao has proposed two possible catalytic cycles – one that provides poor ee-values at low pH as a result of ligand decomplexation, and another that gives high ee-values at high pH.

35.6
Reaction Conditions, Optimization, and Scale-Up

The transfer hydrogenation methods described above are sufficient to carry out laboratory-scale studies, but it is unlikely that a direct scale-up of these processes would result in identical yields and selectivities. This is because the reaction mixtures are biphasic liquid, gas. The gas which is distilled off is acetone from the IPA system, and carbon dioxide from the TEAF system. The rate of gas disengagement is related to the superficial surface area. As the process is scaled-up, or the height of the liquid increases, the ratio of surface area to volume decreases. In order to improve de-gassing, parameters such as stirring rates, reactor design and temperature are important, and these will be discussed along with other factors found important in process scale-up.

35.6.1
Temperature

Typically, heterogeneous transfer hydrogenations are carried out at higher temperatures. The Noyori–Ikariya ruthenium arene catalysts are stable up to temperatures around 80 °C, whilst the rhodium and iridium CATHy™ catalysts are best used below 40 °C.

In the IPA system, prevention of the back-reaction depends on how efficiently the acetone is distilled off. Normally, this would be best carried out at the boiling point of isopropanol (80 °C), but for optimal performance of the catalyst this was best done at ambient temperature, and under reduced pressure. Whilst acetone

Table 35.7 The effect of temperature on rate and optical purity in enantiomeric transfer hydrogenation of 4-fluoroacetophenone.

Temperature [°C]	e.e [%]	Relative rate
20	95.7	1.00
5	97.8	0.60
0	98.4	0.37
–5	98.4	0.26

Catalyst = RhClcp*CsDPEN; Reductant = TEAF; TOF = 75 h^{-1}.

can be fractionally distilled, it is simpler to distil the mixture with isopropanol and to maintain constant volume by continuously charging fresh solvent. In the TEAF system, the reaction is normally operated at ambient temperature. Operating at lower temperatures can improve the enantiomeric excess slightly, but this generally results in lower reaction rates. An example of the results achieved, for 4-fluoroacetophenone and Rhcp*TsDPEN, is detailed in Table 35.7.

35.6.2 Productivity

The optimization of any industrial process involves trying to improve productivity. This is the amount of product produced in a given time per unit of volume, and relates to the yield, the reaction concentration and the cycle time. The yields in transfer hydrogenations are usually quantitative as there are no side reactions, though in some systems the catalyst activity may change and thus the reaction profile will be altered (see later for a discussion of this). Originally, concentrations used in the IPA system were low and reaction times quite long in order to prevent any back-reaction, but these have now been considerably improved using methods for the efficient removal of acetone. Essentially, this is a problem of engineering a system to give high rates of liquid-vapor mass transfer. One simple solution is to use a vacuum distillation process, though efficient agitation and gas sparging can also help. Depending upon the efficiency with which the acetone is removed, concentrations up to several molar and short cycle times have been achieved at low catalyst loadings, whilst retaining the enantiopurity of the product. It is interesting to note that the batch process is clearly not the best means of achieving such an improvement; rather, a reactor which provides much larger surface areas (e.g., a thin film evaporator) is better suited. Currently, a number of such reactor designs are under evaluation.

In the TEAF system there is no problem with any back-reaction, and concentrations up to 10 M are possible. Although neat TEAF has been used satisfactorily, it is quite viscous and so it is preferable to use a diluent. As mentioned above, the solvent may have a marked effect on both reaction rate and enantioselectivity.

35.6.3 Reaction Control

The IPA system is convenient in being almost thermo-neutral. All of the components can be mixed safely at the start of the reaction, and the reaction is initiated with small amounts of potassium hydroxide, or isopropoxide. The reaction is clean and no side reactions seem to occur. There is no apparent formation of hydrogen.

The TEAF system is usually only slightly exothermic, and so again all components can be mixed together (TEAF is prepared separately as this process is exothermic). In this case the triethylamine in the TEAF is sufficient to activate the catalyst. In the laboratory high conversions are seen, but on scale-up some substrates fail to be completely converted.

Extensive investigations in our laboratories on the deactivation of rhodium and iridium catalysts has shown there to be a number of different mechanisms involved. Both, rhodium and iridium catalysts are generally less stable at higher temperatures, and have more labile ligands than their ruthenium counterparts. All of the catalysts are affected by pH, but the ruthenium catalysts seem to be more readily deactivated by acid. Indeed, these reactions are often quenched with acetic acid, whilst stronger acids are used to quench the rhodium reactions. Each of the catalysts can be deactivated by product inhibition, the ruthenium catalyst with aromatic substrates such as phenylethanol, and the rhodium and iridium ones by bidentate chelating products.

Ruthenium catalysts are much more sensitive to oxygen [11, 13, 37]. By contrast, the rhodium catalysts are not particularly sensitive to oxygen, but this does depend upon the system. In fact, in the TEAF system small amounts of oxygen are beneficial in maintaining the oxidized metal [91]. The mechanism of rhodium reduction appears to be complex, and is in part due to poisoning by carbon monoxide. Catalyst poisoning of rhodium can occur as a result of the low-level catalyzed decomposition of TEAF (Fig. 35.9) [90]. The side reactions can be minimized by keeping a low concentration of TEAF, and this is achieved by controlled addition of the reagent. Another technique is to sweep away the carbon monoxide and to keep its solution concentration low; this is achieved sim-

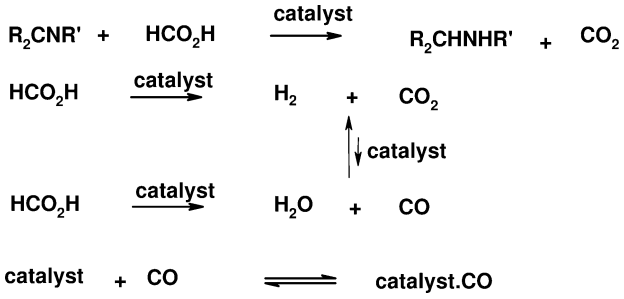


Fig. 35.9 Pathways for the catalyzed decomposition of formic acid.

ply by sparging the reaction solution with nitrogen gas. Good mixing and a high gas flow enable complete conversion of most ketones, including acetophenone. One byproduct of TEAF decomposition is hydrogen, and analysis of the off-gas has shown hydrogen to be produced when the substrate runs out. This decomposition is a slow reaction compared to the desired asymmetric transfer hydrogenation. A high gas flow can help to dilute the hydrogen below the flammable limit, and the incorporation of low levels of oxygen into the nitrogen can improve catalyst activity.

The second cause of catalyst deactivation is reduction of the metal; this is usually observed by darkening of the reaction mass. It has been found that rhodium and iridium CATHy^{TM} catalysts can be retained in their active oxidation state by including an oxidant in the reaction medium. This is most conveniently performed by including a low level of oxygen in the nitrogen gas, typically between 0.5 and 2.0 vol.% (i.e., below the combustion point of hydrogen and the solvents). When this is carried out, the yellow/orange coloring of the reaction solution remains throughout the process [91].

35.6.4
Large-Scale Processes

Numerous enantioselective transfer hydrogenation processes have now been developed and operated at commercial scale to give consistent, high-quality products, economically. These include variously substituted aryl alcohols, styrene oxides and alicyclic and aliphatic amines. Those discussed in the public domain include (*S*)-3-trifluoromethylphenylethanol [48], (*R*)-3,5-bistrifluorophenylethanol [64], 3-nitrophenylethanol [92], (*S*)-4-fluorophenylethanol [1c], (*R*)-1-tetralol [1c], and (*R*)-1-methylnaphthylamine [1c].

35.7
Discussion

It is useful to compare asymmetric hydrogenation and enantioselective transfer hydrogenation so that the appropriate technique can be used when required. Hydrogen gas is a cheap and clean source of reducing power that is widely used in industry, though its use has some drawbacks. For example, it is difficult to handle, being volatile and flammable, and it is poorly soluble in most reaction media such that the use of pressure is required to increase its solvated concentration. The result is that the commercial use of hydrogen requires complex and often expensive equipment. This is especially true in the fine-chemical industry, where batch reactions are normally operated. A further drawback is that hydrogenations are exothermic, and at large-scale the temperature in such reactions is usually controlled by the slow addition of one reagent. However this is often not possible because the catalyst and hydrogen are present at low concentrations, yet for reasonable reaction rates the substrate is required at high con-

centration. The only option is efficient heat removal, which becomes more difficult as the scale increases. Nevertheless, hydrogenations are so useful that many companies see great benefits in possessing a hydrogenation capability. Asymmetric hydrogenation with Ru and Rh phosphine catalysts are most successful, with electron-deficient alkenes having a carbonyl to coordinate to. Asymmetric transfer hydrogenation is less effective in this type of reaction, although ketones and imines are reduced efficiently using this process. The same reaction is generally more difficult with asymmetric hydrogenation. As many more studies have been performed on asymmetric hydrogenation than transfer hydrogenation, the former reaction is better understood. In this respect a large number of catalysts have been prepared, though it is generally true to say that syntheses of the diphosphine ligands are more complex and the costs therefore higher. On the other hand, the TONs achieved with asymmetric hydrogenation catalysts are several orders of magnitude higher than those for transfer hydrogenation. As might be expected, both systems are useful, and a judicious choice of the appropriate technology during route selection will ensure the best manufacturing solution.

As will be appreciated from this review of enantioselective transfer hydrogenation, a remarkable understanding has been achieved in only a few years, and the technology is undergoing rapid development on a number of fronts, including: aqueous reactions [52], dynamic kinetic resolutions [42], cascade or coupled reactions [78], immobilized catalysts [27–32] and, importantly, the introduction of new, more active catalysts [93] and reaction conditions [94]. The primary reasons for the growing use of asymmetric transfer hydrogenation are the simplicity with which these reactions can be carried out, and the high yields and selectivities usually observed. Consequently, the broad reaction scope and favorable economics of this technology is being increasingly adopted in industrial syntheses, notably in the preparation of pharmaceutical intermediates.

Abbreviations

CsDPEN	camphorsulfonyl diphenylethylenediamine
DPEN	diphenylethylenediamine
IPA	isopropanol
NAD(P)	nicotinamide adenine dinucleotide (phosphate)
TEAF	triethylamine: formic acid (5:2 molar mixture)
TfDPEN	trifluoromethylsulfonyl diphenylethylenediamine
TOF	turnover frequency
TON	turnover number
TsDPEN	tosyl diphenylethylenediamine

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