44
Catalyst Inhibition and Deactivation in Homogeneous Hydrogenation

Detlef Heller, André H. M. de Vries, and Johannes G. de Vries

44.1
Introduction

The cost of the catalysts represents a major hurdle on the road to the industrial application of homogeneous catalysis, and in particular for the production of fine chemicals [1, 2]. This is particularly true for chiral catalysts that are based on expensive metals, such as rhodium, iridium, ruthenium and palladium, and on chiral ligands that are prepared by lengthy total syntheses, which often makes them more expensive than the metals. In spite of this, the number of large-scale applications for these catalysts is growing. Clearly, these can only be economic if the substrate : catalyst ratio (SCR) can be very high, often between 10^3 and 10^5.

Unfortunately, systematic knowledge on how to increase the rate of a certain catalytic reaction is lacking. In each case, it will be necessary to conduct research related to the kinetics of the reaction in order to determine the identity of the rate-determining step. Once this is known, it may be possible to speed up the catalysts by making directed changes. Nevertheless, a few handles are known in homogeneous hydrogenation based on kinetic considerations (see, for example, Chapter 10). In most hydrogenation reactions the reaction is first order in hydrogen, which means that the oxidative addition of hydrogen is the rate-determining step. Since the metal oxidation state increases in this step, it may be possible to accelerate it by increasing electron density on the catalysts, for example by changing from aryl to the more electron-donating alkyl-substituted phosphine ligands. The anion effect may also be profound: for example cationic complexes of rhodium are faster than neutral ones in most cases [3]. Other parameters which influence the reaction rate include: solvent, hydrogen pressure, and steric factors, which may require fine-tuning of the ligand for each particular reaction.

Arguably the best way to accelerate the rate of a reaction catalyzed by a soluble transition metal catalyst is by preventing deactivation of the catalyst. Most chemists who have investigated the kinetics of transition metal-catalyzed reactions are familiar with kinetic curves that shoot off with dazzling speed during

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the first few minutes, but rapidly curve off to reach a steady speed that is may be only a fraction of the initial rate. If only it were possible to maintain this initial speed. What is happening to these catalysts? In this chapter we will attempt to answer this question for homogeneous hydrogenation reactions, by describing in some detail all known causes of catalyst inhibition and deactivation.

44.2 Mechanisms of Catalyst Inhibition

All known inhibition phenomena are related to some change at the level of the metal complex structure. In this respect, a number of different general phenomena can be discerned:

- Induction periods. In most hydrogenation reactions the chemist will either start with a preformed complex or with a catalyst that is prepared *in situ* from a metal precursor and the ligand. Usually, both types of catalysts need to undergo further change before they can enter the catalytic cycle. In hydrogenation it is often a diene ligand that needs to be removed by hydrogenation, but this may be a surprisingly slow step (as will be discussed later).
- Substrate and product inhibition. Few academic researchers are familiar with this phenomenon as they usually run their hydrogenations at low substrate concentrations and low SCR. However, for industrial applications the space–time yield of a reaction – the amount of product per unit reactor volume per time unit – is quite important. Clearly, the higher the substrate concentration the higher the space–time yield and the more economic the process. More often than not, either substrate or product inhibition becomes a problem when the substrate concentration is increased to 10 wt% or more.
- Reversible inhibition caused by materials that can function as ligand. Many compounds will bind to a metal; this might be the solvent or impurities in the substrate or the solvent. It can also be a functional group in the substrate or the product, such as a nitrile. Too many ligands bound to the metal complex may lead to inhibition of one of the steps in the catalytic cycle. Likely candidates are formation of the substrate–catalyst complex or the oxidative addition of hydrogen. Removal of the contaminant will usually restore the catalytic activity.
- Irreversible inhibition or deactivation of the catalyst. There may be many reasons for this. A very common one is formation of dimers, trimers or higher clusters that are much less active than the original catalyst. This can be precipitated by ligand loss or by the presence of bridging ligands, such as water, halide, or acetate. Other causes may be oxidants or just thermal decomposition. The end point of this process may be bulk metal, which is still an active hydrogenation catalyst, although it may be less active than the homogeneous complex where every metal atom participates in the reaction. In many processes, a lack of substrate may lead to catalyst decomposition; for this reason catalyst recycling is not always possible.

Usually, the inhibition is detected by kinetic measurements. Substrate and product inhibition are easily detected by measuring the rate as function of substrate concentration, or by carrying out the hydrogenation in the presence of varying amounts of product. Suspected poisons can be added and their effect on the rate measured. Extensive purification of substrate, ligand, catalysts precursor and solvent, and comparing rates between pure and impure reactants will also help to pinpoint the culprit. In industrial productions the number of purifications is usually kept to a minimum to save costs. Nevertheless, it is best to plan the total synthesis in such a way that purification can be executed before the hydrogenation step. Spectroscopic investigation of the catalyst at the end or even during the reaction can be extremely helpful to determine the cause of deactivation. Increasingly, modern mass spectroscopy techniques such as MALDI and electrospray mass spectrometry (EMS) are used for this purpose.

44.3 Induction Periods

44.3.1 Introduction

The "active species" mediating a catalytic process usually are highly reactive as a result of the presence of labile ligands or free coordination sites. Due to this high reactivity, the "active species" are generally difficult to handle and thus are not directly applicable as catalysts. Thus, the actual catalyst is often employed in a modified form, the precatalyst. This can in many cases be accomplished by the use of a stabilizing ligand. Such ligands include dienes such as 1,5-cyclooctadiene (COD) or 2,5-norbornadiene (NBD) [4], ethylene, but also α,ω-dienes such as 1,5-hexadiene [5] and 1,6-heptadiene [6], and CO.

Various methods have been used to convert precatalysts into the active species [7]. Ethylene can be easily displaced from the central atom of the corresponding complexes in solution, even at room temperature. CO-ligands in carbonyl complexes can conveniently be removed photochemically [8]. Increasing the temperature is a further common method used to labilize precatalysts with respect to stabilizing ligands [9].

However, these stabilizing ligands are not always kinetically innocent. The influence of the diene ligands of cationic Rh-complexes on catalytic activity in asymmetric hydrogenation was quantitatively investigated by Heller et al. [10]. These results will be discussed in more detail in view of the ubiquity of the use of catalyst precursors containing diene ligands in enantioselective hydrogenation [11].

44.3.2
Induction Period Caused by Slow Hydrogenation of COD or NBD

In enantioselective hydrogenation, complexes of the type [Rh(PP*)(diene)]anion (PP* = chelating chiral ligand; e.g., a bisphosphine) are often employed as the precatalyst. In addition, the so-called "in-situ" technique, whereby the hydrogenation is simply carried out by applying hydrogen pressure to a solution containing a catalyst precursor such as $[Rh(diene)_2]$anion, a chiral ligand and the substrate, is also conventional. Sometimes, catalyst precursor and ligand are stirred for a while before addition of substrate. Evaporation of this solution will remove one equivalent of the diene. According to Brunner, approximately half of the investigations of enantioselective hydrogenations with the model substrate (*Z*)-*N*-2-acetamido-cinnamic acid are accomplished with catalysts prepared *in situ* [12].

The comparison of hydrogen consumption in the rhodium-catalyzed enantiomeric hydrogenation of a *β*-dehydroamino acid using Et-Duphos (Et-DuPHOS = 1,2-bis(2,5-diethyl-phospholanyl)benzene)) as the chiral ligand shows the huge differences in rate, depending on the manner in which the catalyst was prepared (Fig. 44.1) [10b, c].

In spite of equal product enantioselectivities of 86.5%, the three methods clearly differ in rate. Noticeable *induction periods* are apparent upon the use of

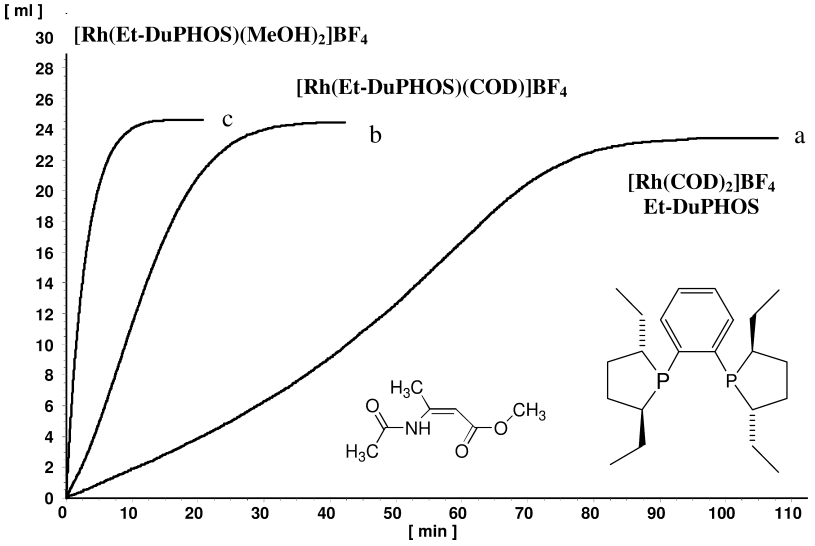


Fig. 44.1 Different methods for the hydrogenation of methyl-3-acetamido butenoate with Et-DuPHOS. Curve a: in-situ technique ($[Rh(COD)_2]BF_4$ + Et-DuPHOS). Curve b: application of the commercial COD precatalyst ($[Rh(Et\text{-}DuPHOS)(COD)]BF_4$). Curve c: as the solvent complex ($[Rh(Et\text{-}DuPHOS)(MeOH)_2]BF_4$). Reaction conditions for each case: 0.01 mmol catalyst, 1.0 mmol substrate, 15.0 mL MeOH, 1.0 bar total pressure, 25.0 °C.

[Rh(Et-DuPHOS)(COD)]BF_4, and even more when applying the in-situ technique. In both cases, there is still COD detectable in solution even after hydrogenation of the substrate has gone to completion. These induction periods have now been shown to occur with various substrates, chiral ligands (several chelate ring sizes were investigated), dienes, and also solvents [10]. The end of the induction period is rather clearly indicated as a maximum in the rate profile. For the right curve of Fig. 44.1 (*in-situ* catalyst), this is shown in Fig. 44.2.

In the literature it has been generally assumed that hydrogenation of the "spectator" dienes with cationic Rh(I)-complexes [13] proceeds rapidly before the hydrogenation of the prochiral alkene. These induction periods, which were found in many hydrogenation reactions, however, prove without doubt the slower hydrogenation of the dienes.

The two most frequently applied dienes COD and NBD differ significantly with regard to the observed induction periods. In Fig. 44.3, the hydrogen uptake curves are shown for the enantioselective hydrogenation of methyl (*Z*)-2-acetamido-cinnamate using Et-Duphos as ligand employing the two different diene complexes in comparison with the solvent complex. Clearly, the norbornadiene is hydrogenated off much faster in this case.

These induction periods, which have also been described qualitatively by others [14], considerably complicate a comparison of the activity of various catalysts and a kinetic analysis of the hydrogen consumption curve.

Further proof for the fact that these induction periods are caused by slow hydrogenation of the diene ligand was obtained by NMR-spectroscopic measurements under hydrogenation conditions [10f, 15]. The registration of ^{31}P- *and* ^{1}H-spectra allows the simultaneous monitoring of changes in the bisphosphine complexes and substrate conversion. The results of the hydrogenation of methyl-

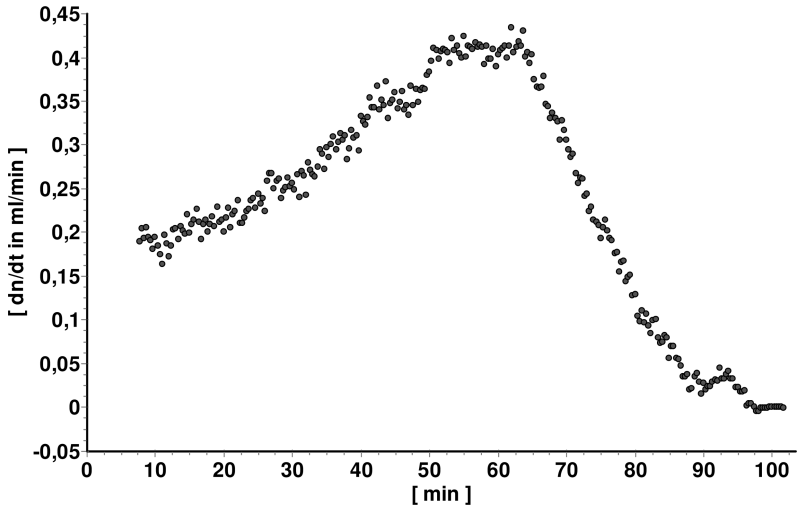


Fig. 44.2 Rate profile for the right curve of Fig. 44.1.

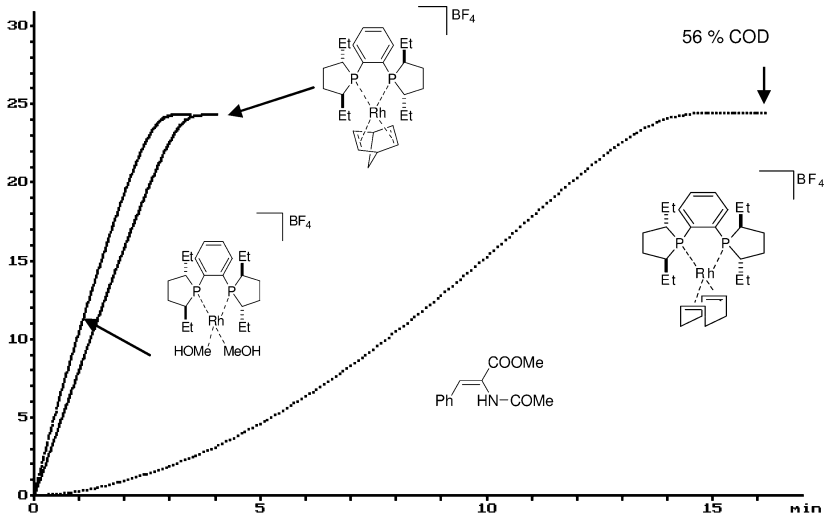


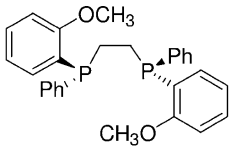
Fig. 44.3 Comparison of hydrogenation rates using various Rh–DuPhos-complexes containing different "spectator" ligands.

(*Z*)-2-acetamido cinnamate with a five-membered ring chelate catalyst based on DIPAMP are illustrated graphically in Fig. 44.4 (see also [10d]).

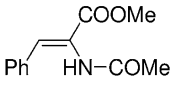
The results of this experiment prove unequivocally that, in addition to the substrate complex, the diene complex is present throughout the hydrogenation reaction. Even after 500 turnovers of the prochiral alkene, unchanged COD precatalyst is still present in solution.

In order to circumvent these induction periods and to allow full utilization of the "intrinsic activity" of a catalyst, one can best use the corresponding solvent complexes, as was practiced previously by Halpern et al. [16]. This invokes the practical problem of for how long the precatalyst must be prehydrogenated to remove all diene. To answer this question, the rate constants for hydrogenation of the diene in the diene complexes have been determined with various ligands, dienes, and solvents. As a result of the generally high stability constants of the diene complexes, the diene hydrogenation under isobaric conditions can be described as a pseudo-first-order reaction. This highly selective hydrogenation can be analyzed both in the presence of an excess of diene – Michaelis-Menten kinetics in the saturation range – and as stoichiometric hydrogenation of the precatalysts. For the latter hydrogenation, NMR spectroscopy is the most suitable analysis tool [10a]. In order to determine the rate constants for the diene hydrogenation, use of the first method was found to be best.

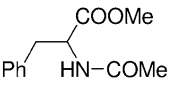
In Table 44.1 selected rate constants for the hydrogenation of the dienes COD and NBD for various ligands (chiral and achiral) are summarized. As expected, for all systems investigated, the hydrogenation of NBD was faster than the hydrogenation of COD [13a,c, 17].



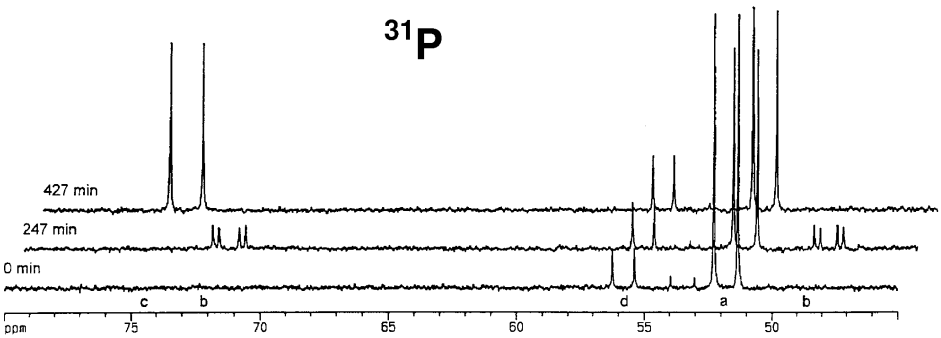
DIPAMP



AMe



$AMeH_2$



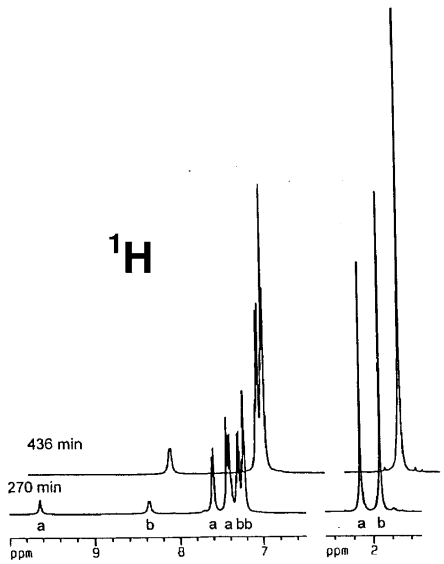


Fig. 44.4 NMR-spectroscopic monitoring of the enantioselective hydrogenation of (*Z*)-*N*-acetylamino methyl cinnamate using [Rh((*R*,*R*)-DIPAMP)(COD)]BF_4 as catalyst under stationary conditions (reaction conditions: 0.01 mmol Rh-complex, 5.0 mmol prochiral alkene; 5.0 mL methanol-methanol-d_4 (1:1); details can be found in [10f]). Legend for ^{31}P-NMR: a: [Rh(DIPAMP)(COD)]BF_4; b: [Rh(DIPAMP)(AMe)]BF_4; c: [Rh(DIPAMP)$(MeOH)_2$]BF_4; d: [Rh$(DIPAMP)_2$]BF_4. Legend for ^{1}H-NMR: a: AMe; b: $AMeH_2$.

Table 44.1 Rate constants (k_{2j}) (for the hydrogenation of the dienes COD and NBD for different ring chelates of the type [Rh(ligand)(diene)]BF_4. (Reaction conditions: 25.0 °C; 1.013 bar total pressure. Values were obtained in MeOH as solvent unless stated otherwise.)

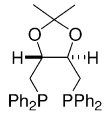
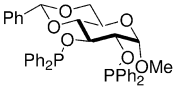
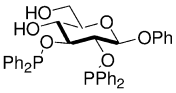
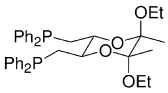
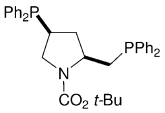
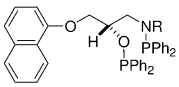
Ligand	$k_{2\,COD}$ [1 min^{-1}]	$k_{2\,NBD}$ [1 min^{-1}]	$k_{2\,NBD}/k_{2\,COD}$	Reference
	0.23 0.22 [a] 0.25 [e]	1.29	5.6	10g
	0.37 0.37 [a]	13.40	36.2	10g
	0.20 0.19 [a]	9.52	47.6	10g
	0.14	1.11	7.9	10g
	0.22	1.20	5.5	10g
				
R = cyclohexyl	5.44 2.63 [e]	20.17	3.7	10g
R = 3-pentyl	4.09	21.48	5.3	
R = 2-propyl	3.77	21.96	5.8	
R = cyclopentyl	2.94	18.40	6.3	
R = methyl	0.53	8.20	15.5	

Table 44.1 (continued)

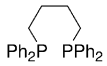
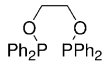
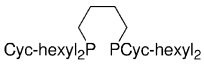
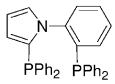
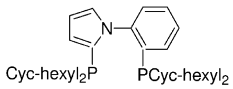
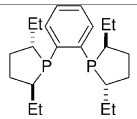
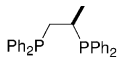
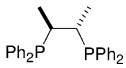
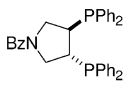
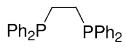
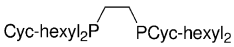
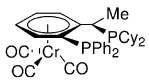
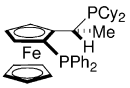
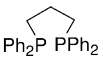
Ligand	$k_{2\ COD}$ [l min^{-1}]	$k_{2\ NBD}$ [l min^{-1}]	$k_{2\ NBD}/k_{2\ COD}$	Reference
	0.16	1.25	7.8	10g
	0.25	16.6	66	10d
	7.15	230	32	10d
	0.33	33.7	98	10d
	1.1	at least 700[b]	at least 630[b]	10d
	≈ 0.014[c]	52	≈ 3700	10d
	≈ 0.003[c]	9.2	≈ 3000	10d
	≈ 0.0018[c]	3	≈ 1700	10d
	≈ 0.0017[d]	–	–	18
	≈ 0.002–0.0035[c]	17.3	≈ 4800	10d
	0.075	48.8	650	10d
	≈ 0.03	3.6 4.8[e]	≈ 120	10a

Table 44.1 (continued)

Ligand	$k_{2\,COD}$ [1 min^{-1}]	$k_{2\,NBD}$ [1 min^{-1}]	$k_{2\,NBD}/k_{2\,COD}$	Reference
	–	≈ 33	–	10a
	0.024	1.55	65	10d

a) From the initial rate of the stoichiometric catalyst hydrogenation.
b) In view of the high activity at the chosen catalyst concentration, mass transfer limitations cannot be excluded.
c) Values were determined in an autoclave under pseudoisobaric conditions and standardized to 1.013 bar total pressure. Thus, these are indicative values only. For that reason, the ratios $k_{2\,NBD}/k_{2\,COD}$ are only guide values.
d) From a parameter optimization of experimental hydrogenations at 10 bar H_2 pressure, standardized to 1.013 bar.
e) Value obtained in THF.

With NBD as diene, the rate constants for the listed ligands may differ by a factor of 600. For COD, the analogue difference approximately amounts to three orders of magnitude. A comparison of the reactivities of the respective NBD and COD complexes of five-membered chelates in diene hydrogenation clearly reveals higher differences than are found for the six- and seven-membered chelates. The reasons behind these differences are unclear, although when examining the published X-ray structures it would seem that the generally less active COD complexes all have a larger tetrahedral distortion from the expected square–planar structure than the structures of the corresponding NBD complexes [19].

Few data are available for rhodium complexes based on monodentate ligands. In a recent study, the rate of COD hydrogenation in $Rh(MonoPhos)_2(COD)BF_4$ was determined as 0.071 min^{-1}, which is somewhat slower than the corresponding DuPhos complex [20].

An interesting methodology to evaluate whether different diene catalyst precursors vary in their diene hydrogenation activity was reported by McCague et al. [21]. Two diene complexes based on different dienes are simply mixed in the ratio 1 : 1, though each complex contains the chiral ligand with the opposite configuration. The higher the ee-value of the resulting hydrogenations, the more the employed dienes differ in their hydrogenation activity. However, obtaining a racemate does not exclude the possibility that dienes do not interfere with the enantioselective hydrogenation; it merely proves that the dienes behave in an analogous manner.

Blackmond and Reetz have reported a case where two rhodium-containing diastereomeric bisphosphite ligands were compared [22]. In spite of the great

similarity of the two catalysts, huge differences in rate profile were observed, which were largely due to slow hydrogenation of the COD in one of the two complexes when compared to the other (Fig. 44.5).

In summary, the induction period observed in the enantioselective hydrogenation of prochiral alkenes is caused by a slow hydrogenation of the diene introduced into the system as part of the precatalyst. This interfering parallel hydrogenation of the dienes is influenced by several factors: the pseudo-rate constants $k_{2\,COD}$ and $k_{2\,NBD}$, the Michaelis constant of the diene complex, the Michaelis constant of the prochiral alkene, and the precatalyst : substrate ratio. The method of catalyst formation also plays an important role; the amount of interfering diene is doubled compared to the preformed complex if the catalytic solutions are prepared *in situ*. It should be stressed, however, that these induction periods are particularly important at 1 bar hydrogen pressure. At higher pressures the diene hydrogenation tends to be very fast and the induction periods become less pronounced.

The published quantification of the rate of hydrogenation of the dienes COD and NBD of a large number of cationic rhodium(I) chelate complexes allows a good estimation of expected effects on the rate of enantioselective hydrogenation of prochiral alkenes. From the first-order pseudo-rate constants the time needed for complete hydrogenation of the diene introduced as part of the rhodium precursor can be easily calculated as six- to seven-fold the half life. It is recommended that the transfer into the solvent complex be followed by NMR spectroscopy.

It should be noted that dienes and polyenes in general are well known to be catalyst poisons. Apart from the catalyst, the source of these inhibitors may stem from the solvent or, more frequently, from the substrate [23].

Crabtree described the use of dibenzo[a,e]cyclooctatetraene, a potent selective poison of homogeneous hydrogenation catalysts, as a tool to distinguish between homogeneous and heterogeneous catalysis in the hydrogenation of hexene with a range of catalysts [24].

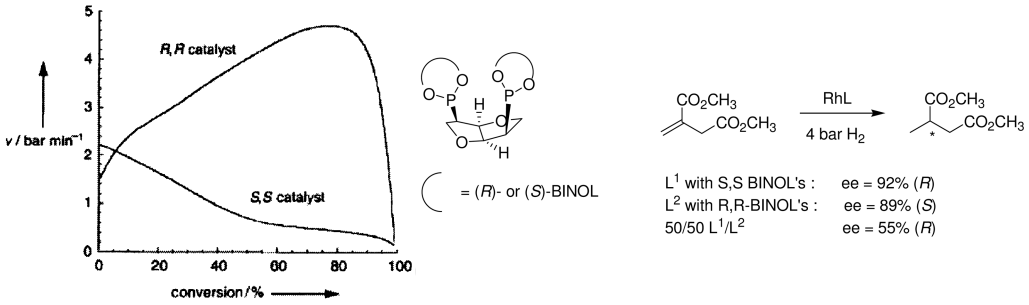


Fig. 44.5 Differences in rate profile between diastereomeric catalysts are caused by differences in the COD hydrogenation rate.

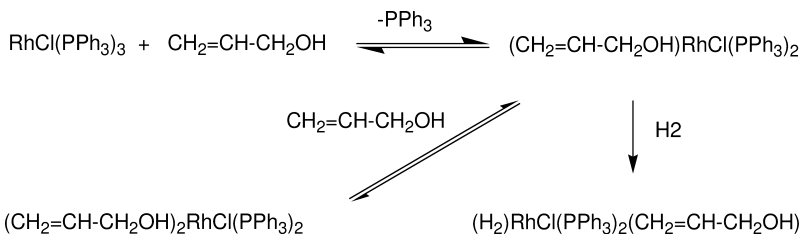
If an induction period is observed in hydrogenation reactions due to slow hydrogenation of the diene, a number of solutions are available. First, it is wise to preform the catalyst by adding the ligands to a solution of the catalyst precursor. By doing this the first equivalent of diene is displaced from the metal by the ligand(s). Evaporation of this solution will remove the first equivalent of diene. Pre-hydrogenation of the catalyst before addition of the substrate will remove the second diene. However, sometimes the solvent-stabilized complex formed by doing this is less stable. With rhodium catalysts based on monodentate ligands that function best in the poorly coordinating solvent dichloromethane, this procedure is not recommended. Finally, increasing the pressure usually minimizes the induction period to a large extent.

44.4
Substrate and Product Inhibition

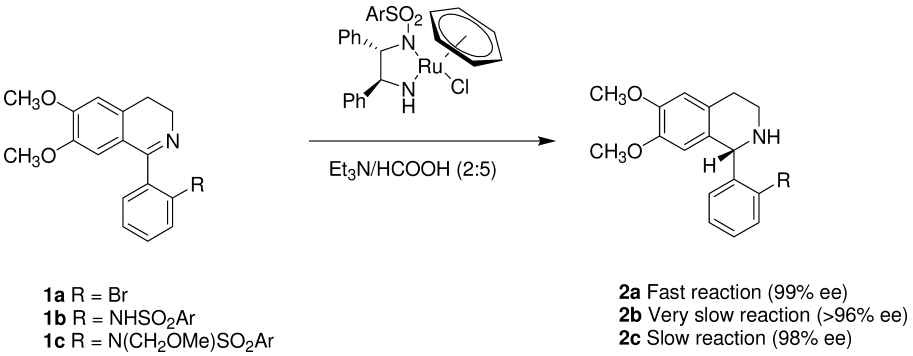
For hydrogenation to take place, the substrate usually needs to bind to the metal complex, although exceptions are known to this rule [25]. Substrate inhibition can occur in a number of ways, for example if more than one molecule of substrate binds to the metal complex. At low concentration this may be a minor species, whereas at high substrate concentration this may be the only species. One example of this is the hydrogenation of allyl alcohol using Wilkinson's catalyst. Here, the rate dependence on the substrate concentration went through a maximum at 1.2 mmol L^{-1}. The authors propose that this is caused by formation of a complex containing two molecules of allyl alcohol (Scheme 44.1) [26].

However, it should be noted that the authors did not isolate or characterize any intermediates. It is unclear as to whether this would be the case if highly stable π-allyl complexes were to have been involved.

Vedejs et al. reported catalyst inhibition during a study on the enantioselective transfer hydrogenation of dihydro-isoquinolines using Noyori's catalyst (Scheme 44.2) [27]. Here, the problem is caused by the bidentate nature of the substrate. Whereas the bromo compound **1a** could be rapidly reduced, the tosylamide-substituted compound **1b** could not be reduced, and although the problem could be alleviated somewhat by alkylation of the sulfinamide to **1c**, hydrogenation of this was still sluggish. Although the authors propose this to be a case of product



Scheme 44.1 Substrate inhibition in the hydrogenation of allyl alcohol.



1a R = Br
1b R = $NHSO_2Ar$
1c R = $N(CH_2OMe)SO_2Ar$

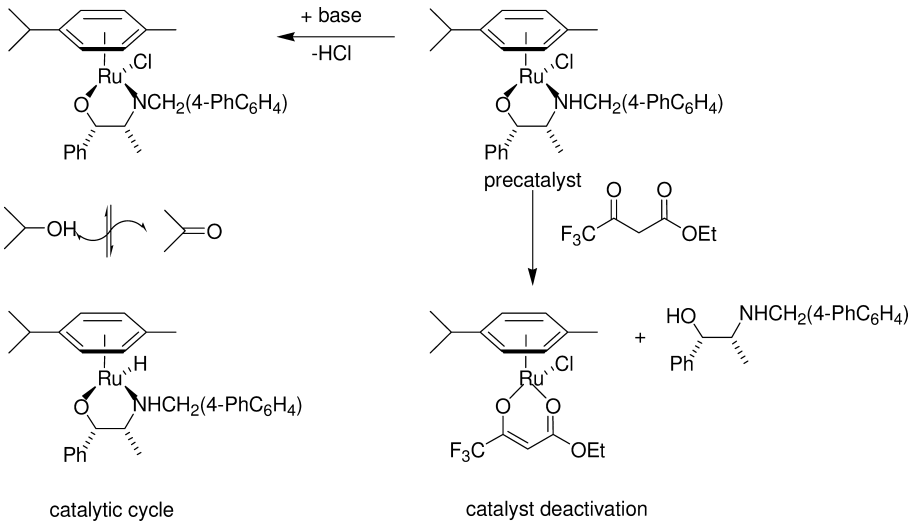
2a Fast reaction (99% ee)
2b Very slow reaction (>96% ee)
2c Slow reaction (98% ee)

Scheme 44.2 Catalyst inhibition caused by functional groups in the substrate.

inhibition, both substrate and product could be possible inhibitors in the case of **1b** and **1c**.

Carpentier and coworkers studied the asymmetric transfer hydrogenation of *β*-ketoesters using chiral ruthenium complexes prepared from $[(\eta^6\text{-}p\text{-cymene})\text{-}RuCl_2]_2$ and chiral aminoalcohols based on norephedrine. During this study, these authors became aware of substrate inhibition when ketoesters carrying 4-halo-substituents were used. It transpired that this was caused by formation of a complex between the substrate and the catalyst [28].

Since analogous ketoesters not containing halide could be hydrogenated in good yield, the acidity of the enolate seems to be the main reason for the replacement of the aminoalcohol ligand by the halogenated acetoacetate. Indeed,

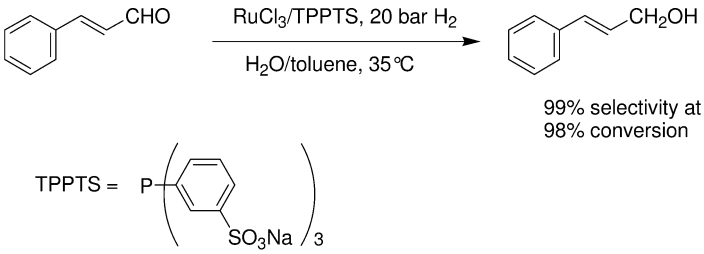


Scheme 44.3 Substrate inhibition in enantioselective transfer hydrogenation.

it is our own experience that Ru-catalyzed transfer hydrogenation reactions are easily inhibited by the addition of acid.

The use of $RuCl_3$ with the water-soluble ligand tris-sulfonated triphenylphosphine (TPPTS) made it possible to selectively hydrogenate cinnamaldehyde to cinnamyl alcohol in a two-phase aqueous organic system (Fig. 44.6, upper). This not only allowed easy recycling of the catalyst by phase separation; it also resulted in extremely high selectivity to the desired unsaturated alcohol [29]. Unfortunately, the cinnamaldehyde hydrogenation was not sufficiently economic as product inhibition occurred at higher concentrations of cinnamaldehyde (Fig. 44.6, lower) [30].

The fate of the catalyst in these reactions was determined by Kalck and coworkers using ^{31}P-NMR [31]. In addition to $[RuH(TPPTS)_3Cl]$, which is the



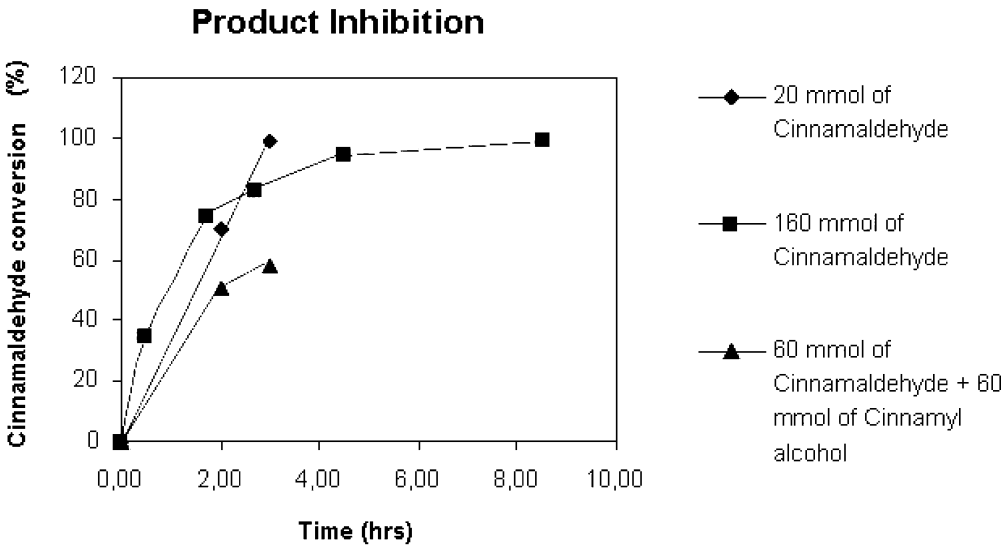


Fig. 44.6 Product inhibition in the ruthenium-catalyzed hydrogenation of cinnamaldehyde. Reaction conditions: 0.1 mmol $RuCl_3$, 0.5 mmol TPPTS, H_2O:toluene ratio 5 mL:5 mL.

probable catalyst, these authors identified three species with the general structure [RuH(η^6-R-C_6H_5)(TPPTS)$_2$]Cl that were not catalytically active. A species with R=CH_3 obviously stems from the solvent. The other two species with R=*cis*-PhCH=$CHCH_2OH$ and $PhCH_2CH_2CH_2OH$ stem from isomerized starting material and over-hydrogenated product. The fact that no complex containing *trans*-cinnamyl alcohol was found probably means that the two aromatic fragments are bound in a bidentate fashion through η^6 coordination with the aromatic ring and with the oxygen atom, which is impossible with the *trans*-substrate.

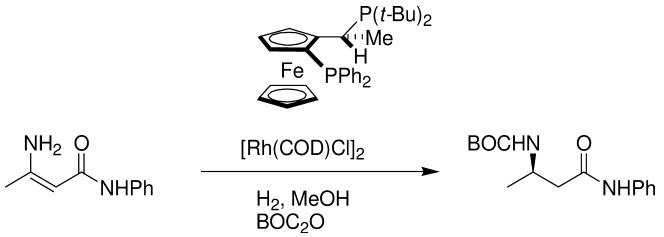
Joó found substrate inhibition in the transfer hydrogenation of aliphatic and aromatic aldehydes with NaO_2CH if the reaction was catalyzed by [$RuCl_2(PPh_3)_3$] in the presence of a phase-transfer catalyst (PTC) in an organic solvent. Joó found that the reaction became much less sensitive to the substrate concentration if it was carried out under genuine biphasic conditions, without PTC using the water-soluble [$RuCl_2$(*m*-TPPMS)$_2$]$_2$ as catalyst. Here, the concentration of substrate in the aqueous phase is limited by its solubility, preventing the occurrence of substrate inhibition [32].

Substrates containing aromatics such as phenyl groups as a structural element may form relatively stable arene complexes with Rh-species. Using NMR spectroscopy, Gridnev and Imamoto determined that rhodium-η^6-complexes can form with the phenyl substituent of the hydrogenation product methyl-(*Z*)-2-acetamidocinnamate [33]. Bargon et al. described interesting complexes with styrene derivatives by means of the parahydrogen-induced polarization (PHIP) method [34].

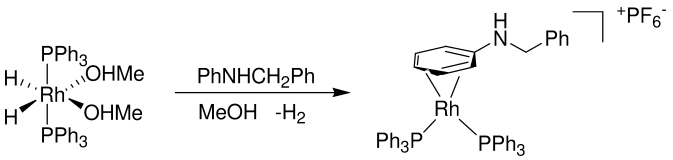
Researchers at Merck & Co. [35] who, together with scientists from Solvias, had developed the enantioselective hydrogenation of unprotected enamine amides and esters [36], reported a more recent example of product inhibition. The product amine amide or ester was found to be an inhibitor of the catalyst, and indeed instances of catalyst poisoning by amines have been reported several times (see later). The authors also found an excellent solution to this problem: the addition of BOC-anhydride to the hydrogenation reaction neatly reacts away all the amine to form the BOC-protected amine, whereas the enamine was left unreacted (Scheme 44.4). This addition resulted in a remarkable rate enhancement [35].

James et al. reported a case of product inhibition in the Rh-catalyzed enantioselective hydrogenation of *N*-phenyl benzaldehyde imine [37]. These authors were able to isolate the deactivated catalyst, and to obtain its X-ray structure, which showed, surprisingly, that it was a rhodium complex with the product bound through a η^4-π-arene interaction (Scheme 44.5). More cases of inhibition via formation of metal arene complexes will be detailed in Section 44.5.

If substrates contain nitrogen bases capable of complexing to the metal, this usually has an adverse effect on the hydrogenation reaction. Döbler and coworkers found that enantioselective hydrogenation of (*Z*)-2-acylamino-3- and 4-pyridylacrylic acids using Rh/Propraphos did not proceed at room temperature and 1 bar H_2 pressure [38]. Drawing the obvious conclusion that this may be a



Scheme 44.4 Prevention of product inhibition via a secondary reaction.



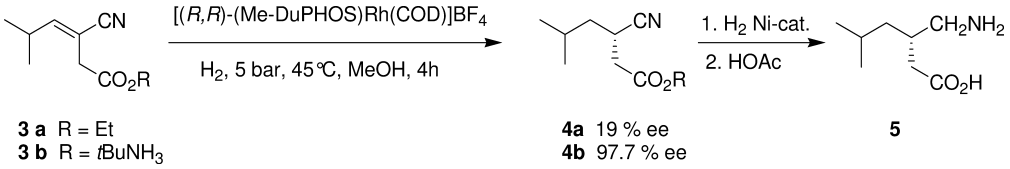
Scheme 44.5 Catalyst inhibition through formation of stable arene complex.

case of substrate inhibition caused by interaction between the pyridine and the rhodium complex, these authors performed the hydrogenation in the presence of excess HBF_4, which fully protonates the pyridine nitrogen. This had the desired effect, as now the hydrogenation of these substrates proceeded at very high rates at SCR = 1000. Similar findings were reported by Laneman et al., who used Rh/DuPHOS as a catalyst for these substrates. Here, the hydrogenation proceeded without protonation of the pyridine, but the rate of the reaction and the ee-value of the product were very low [39].

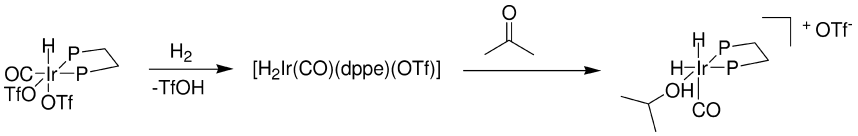
Nitrile groups in the substrate may also cause problems. Minnaard, Feringa and de Vries reported the enantioselective hydrogenation of a range of substituted 2-acetamido-cinnamates at 5 bar pressure using Rh/MonoPhos. Whereas most substrates could be hydrogenated with turnover frequencies (TOFs) of between 200 h^{-1} and 600 h^{-1}, the 4-cyano-substituted substrate was hydrogenated very slowly at this pressure with a TOF of only 4 h^{-1} [40].

A similar problem was noted by researchers from Pfizer and Dowpharma in their synthesis of (*S*)-3-aminomethyl-5-methylhexanoic acid (Pregabalin, **5**) via the enantioselective hydrogenation of an acrylonitrile-type substrate **3** (Scheme 44.6) [41].

The attempted hydrogenation of ester **3a** was problematic, as the reaction proceeded slowly at room temperature and although the rate could be increased by performing the reaction at 55 °C, the ee-value of the product remained low with a range of catalysts. The problem arises through the fact that the nitrile coordinates to the metal in a linear fashion with Rh–N–C aligned; this precludes the alkene from binding to the metal centrum in a bidentate fashion. The problem could be solved by instead using the carboxylate **3b** as its *tert*-butylammonium salt. The carboxylate binds to the metal allowing the alkene to coordinate also. Thus, **3b** could be hydrogenated at SCR = 2700 and 45 °C in 4 h. The product was isolated in 99% yield and 97.7% ee. Hydrogenation of the nitrile to the



Scheme 44.6 Overcoming inhibition by nitrile in enantioselective hydrogenation.



Scheme 44.7 Product inhibition in iridium-catalyzed acetone hydrogenation.

amine and neutralization with acetic acid gave Pregabalin in 61% yield and 99.8% ee.

Eisenberg reported product inhibition in the hydrogenation of acetone with a cationic iridium complex [42]. Apparently, the bond between iridium and isopropanol is too strong on account of the cationic nature of the complex (Scheme 44.7).

It may be concluded that substrate and product inhibition are the rule rather than the exception in scaled-up hydrogenation processes. Nevertheless, there are a number of ways to circumvent this problem. Two-phase catalysis may decrease the substrate and product concentration in the phase containing the catalyst to a large extent. Using a solvent in which substrate and product do not dissolve very well is an equally good solution. In case the substrate and product are solids, we speak of a "slurry hydrogenation". This has the added advantage that often the product crystallizes in a very pure form during the hydrogenation reaction. It may also be possible to slowly dose the substrate. Finally, if the problem is caused by a functional group in the substrate there are a number of ways to circumvent it by making changes either to the functional group in question or at positions nearby in the substrate.

44.5
Reversible Inhibition Caused by Materials that can Function as Ligand

Many compounds or materials are capable of binding in a reversible fashion to a transition metal complex. If the binding is very strong, or if a large excess of the compound is present, then inhibition is likely to result. Although many examples of this phenomenon have been reported in the literature, only a few have been studied systematically.

44.5.1
Catalyst Deactivation Caused by Solvents

Common solvents for homogeneous hydrogenations are simple alcohols, aromatic solvents such as toluene, THF, EtOAc, CH_2Cl_2, and also water. In some cases the solvent can become an inhibitor. In the preceding section, the formation of catalytically inactive complexes through the formation of a η^6-toluene complex with a ruthenium catalyst and a η^4-arene complex with a rhodium catalyst was described. Earlier, Halpern et al. highlighted the stability of Rh^I-η^6-aromatic complexes with chelating bisphosphines [43]. Likewise, Burk et al. recently showed that the hydrogenation of ethyl-*a*-benzoyloxycrotonate with the highly active Rh-Et-DuPHOS system does not proceed in benzene, although it does so in other solvents with high selectivity and activity. This inhibition is caused by formation of the inactive [Rh(Et-DuPHOS)(benzene)]$^+$-complex, which was characterized by ^{31}P-NMR spectroscopy [44, 45].

Crystal structures of stable arene complexes are also known, for example the benzene complex of (1*R*,2*R*)-*trans*-1,2-bis((diphenylphosphino)-methyl)cyclobutane-Rh^I [46], [Rh((*R*,*R*)-Et-DuPHOS)(benzene)]BF_4 (Fig. 44.7), and [Rh((*S*,*S*)-Me-DuPHOS)(toluene)]BF_4 [47].

These η^6-aromatic complexes are not easily spotted by routine NMR measurements, as ^{31}P-NMR data for aromatic and methanol complexes are very similar (Table 44.2). However, the two types of complexes can be distinguished unequivocally by using ^{103}Rh-NMR spectroscopy [48,49].

Due to the relative stability of such η^6-arene complexes there is a strong likelihood that in aromatic solvents only parts of the employed Rh-catalyst are available for catalysis. As seen earlier, substrates and products with aromatic substituents can also lead to catalyst deactivation.

In the hydrogenation of methyl-(*Z*)-*β*-(*N*-acetyl)-aminocrotonate with [Rh(DIPAMP)$(MeOH)_2$]BF_4, the decrease in activity due to addition of traces of aromatics to the solvent MeOH could be proven quantitatively. The concentration of the arene complex during the hydrogenation (as estimated from kinetic analyses) could be confirmed by NMR-spectroscopy (^{31}P and ^{103}Rh) (Figs. 44.8 and

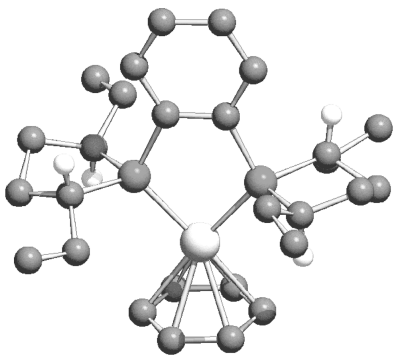


Fig. 44.7 The molecular structure of [Rh((*R*,*R*)-Et-DuPHOS)(benzene)].

Table 44.2 ^{31}P- and ^{103}Rh-NMR data for solvent-stabilized cations of the type [Rh(P-P)(solvent)]BF_4 in [D_4]methanol at 298 K [47].

Ligand (P-P)	Solvent	$\delta(^{31}P)$ [ppm]	$^1J(^{31}P,^{103}Rh)$ [Hz]	$\delta(^{103}Rh)$ [ppm]
Et-DuPHOS	η^6-benzene	93.0	202	–1116
	methanol	95.7	205	–149
Me-DuPHOS	η^6-toluene	99.3	202	–1139
	methanol	101.8	205	–218 [a]
DIPAMP	η^6-benzene	72.2	207	–1006
	η^6-*p*-xylene	75.7	207	–956
	methanol	81.2	208	–38
Ph-*β*-glup-OH	η^6-toluene	136.4 and 134.8	228 and 228	–762
	methanol	147.6 and 142.9	229 and 226	–28

a) Value from Ref. [50].

44.9) [47]. From the ratio of initial rates (Fig. 44.8), the amount of inactive *p*-xylene complex present at the start of the hydrogenation was determined as 47%, while the corresponding NMR-spectrum (Fig. 44.9) gave a value of 50%.

Nevertheless, it should be pointed out that enantioselective hydrogenations also proceed in aromatic solvents. After all, the concentrations and ratios of stability constants of all complexes in solution decide the decrease in activity.

Another clear example is the hydrogenation of methyl-(*Z*)-*β*-(*N*-acetyl)-aminocrotonate with the Me-DuPHOS system in toluene as solvent: at 20 bar hydrogen pres-

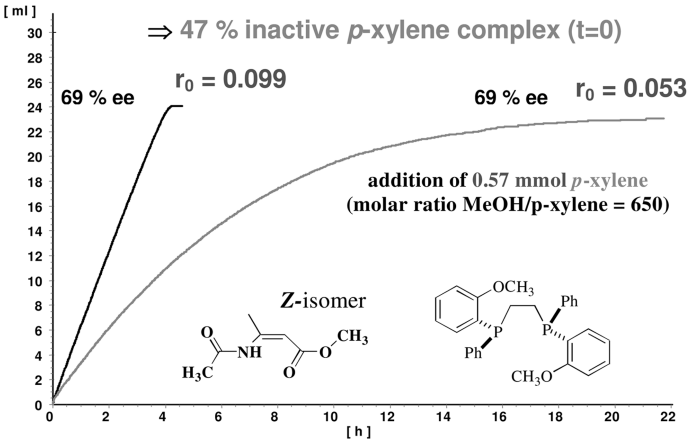


Fig. 44.8 Hydrogenation of methyl-(*Z*)-2-acetamidocrotonate in pure methanol (black) and after addition of 0.57 mmol *p*-xylene (gray). Reaction conditions: 0.01 mmol [Rh(DIPAMP)$(MeOH)_2$]BF_4, 1.0 mmol prochiral alkene, 1.0 bar overall pressure in 15.0 mL methanol at 25.0 °C; r_0 = initial rate (mL min^{-1}).

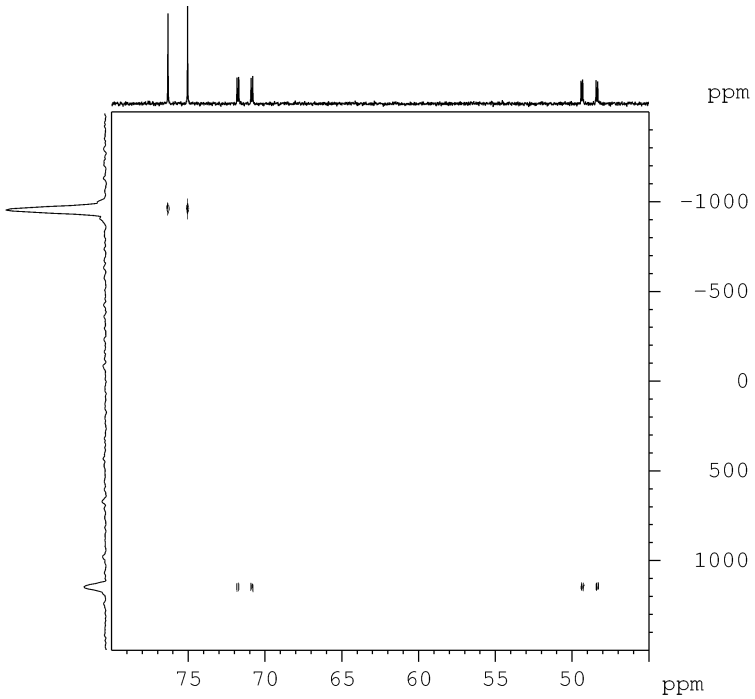


Fig. 44.9 $^{31}P,^{103}Rh\{^{1}H\}$ HMQC NMR spectrum of a methanolic solution of $[Rh(DIPAMP)]^{+}$ solvent complex (0.01 mmol), which was treated with 1 mmol methyl-(*Z*)-*β*-(*N*-acetyl)-aminocrotonate and 0.57 mmol *p*-xylene (molar ratio xylene complex : substrate complex = 1.0). The Rh shifts are –956 (xylene complex) and 1148 ppm (substrate complex).

sure this reaction results in an ee-value of 64% after 24 h at room temperature [51]. On the other hand, using $[Rh(Me\text{-}DuPHOS)(MeOH)_2]BF_4$ in methanol as solvent gives a complete conversion after a hydrogenation of only 4 min under normal pressure and at 25.0 °C, with an ee-value of 87.8% [52]. The reason for this distinct increase in activity lies not only in the avoidance of "induction periods" [53], but undoubtedly also in the exclusion of the stable arene complex [Rh((*S*,*S*)-Me-DuPHOS)(toluene)]BF_4, which is unable to catalyze the enantioselective hydrogenation. The crystal structure of the arene complex can be found in [47].

In recent studies on hydrogenation catalyzed by soluble iron-diimine complexes, Chirik and coworkers noted that the major deactivation pathway of these complexes occurs via formation of η^6-arene complexes [54].

Acetonitrile is another solvent that may retard the reaction. Although no cases of inhibition by acetonitrile have been described in the literature, we usually find no hydrogenation activity at all when using rhodium/MonoPhos catalysts in this solvent. Presumably, this is true for most transition metal catalysts.

Horner noted inhibition by ethers, $MeNO_2$, malonate esters and DMF in the hydrogenation of cyclohexene with Wilkinson's catalyst. Almost complete inhibi-

tion was observed upon use of DMSO, acetonitrile, chloroform, chlorobenzene, and acetic acid [55].

Eshova et al. studied the hydrogenation of CO_2 to formic acid in several solvents in the presence of an equivalent of Et_3N using Wilkinson's catalyst. These authors conducted an extensive NMR study into the various decomposition pathways of the catalyst [56]. Apparently, DMSO is capable of rapidly displacing one equivalent of PPh_3 on the catalyst; a second equivalent is slowly displaced. The dissolved phosphine can be easily oxidized, the oxidant in this case being shown as CO_2. Triethylamine was also capable of displacing PPh_3, though the resulting complex, $RhCl(PPh_3)_2(Et_3N)$, is extremely sensitive towards oxidation.

In conclusion, in general it is best to avoid aromatic solvents and strongly coordinating solvents such as acetonitrile when conducting homogeneous hydrogenation reactions.

44.5.2
Catalyst Inhibition Caused by Compounds Containing Heteroatoms

Almost all phosphorus(III) compounds, such as phosphines, phosphites, phosphonites and phosphoramidites, are excellent ligands for late transition metals. Having excess ligand present, beyond the amount necessary to stabilize the complex, will retard or completely inhibit the catalysis [57]. This can be highly relevant if the purities of metal precursors and ligands are not exactly known. Bergbreiter showed that inhibition by excess PPh_3 can be reversed by the addition of silver salts, which form complexes with phosphines having a high complex constant [58].

Mixed results have been reported with sulfur compounds. There is no doubt that thiols and thioethers are ligands for transition metals; thioethers tend to be fairly weak ligands, and occasionally have been used in chiral ligands for hydrogenation and transfer hydrogenation. Substrates may contain thioether groups, although hydrogenation will be somewhat slower [59]. Homogeneous alkene hydrogenation catalyzed by the Wilkinson catalyst was not inhibited by trace amounts of PhSH, but the addition of 42 equiv. with respect to rhodium caused complete inhibition [59].

Whereas most hydrogenation catalysts function very well in water (see for example Chapter 38 for two-phase aqueous catalysis), scattered instances are known of inhibition by water. Laue et al. attached Noyori's transfer hydrogenation catalyst to a soluble polymer and used this in a continuous device in which the catalyst was separated from the product by a membrane. The catalyst was found to be inhibited by the presence of traces of water in the feed stream, though this could be reversed by continuously feeding a small amount of potassium isopropoxide [60]. A case of water inhibition in iridium-catalyzed hydrogenation is described in Section 44.6.2.

In the Rh-BINAP-catalyzed allyl amine isomerization step used in Takasago's Menthol process, the catalyst is inhibited by water through the formation of a hydroxyl-bridged rhodium trinuclear complex $[\{Rh(BINAP)\}_3(\mu_2\text{-}OH)_2]ClO_4$ [61].

However, it is unclear whether this complex can also form during hydrogenation reactions.

Two groups have reported the inhibition of hydrogenation catalysts by primary amines. Rijnberg, Lensink and de Vries studied the biphasic asymmetric hydrogenation of *N*-benzyl imines using Rh–BDPP complexes in which the ligand was mono-, di-, tri- or tetra-sulfonated [62]. It was found that, in particular, the monosulfonated ligand led to a catalyst which induced very high enantioselectivity. The rate of the reaction was also seen to depend heavily on the purity of the substrate. Since the imine can hydrolyze under these reaction conditions, the effect of added acetophenone as well as benzylamine was studied. Whereas the added acetophenone showed no effect, the addition of benzylamine was found to lead to complete inhibition of the catalyst.

James and coworkers found that one benzylamine is actually bound to the rhodium in the active catalyst in hydrogenations of $PhCH{=}NRCH_2Ph$ using $[Rh(COD)(PPh_3)_2]PF_6$ as catalyst precursor. However, the addition of more than two equivalents of benzylamine inhibited the catalysis [63].

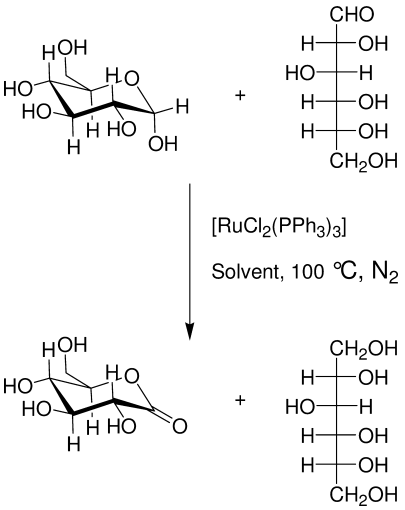
Great care must be taken not to generalize these effects, as the addition of primary diamines to ruthenium bisphosphine complexes generates a very active catalyst for ketone hydrogenation after the addition of base (see Chapter 32).

44.5.3 Inhibition by CO and Sources of CO

As described in the preceding section, the presence of excess ligand leads to reversible catalyst inhibition. If the ligand binds very strongly, the effect may be irreversible. Carbon monoxide (CO) is a ligand that binds fairly strongly to most transition metals, and many reports have been made concerning its inhibitory effects in homogeneous hydrogenation.

In a study on the hydrogenation of aromatic substrates, Fish and coworkers noted a major difference in rate between $Ru_3(CO)_{12}$ and $H_4Ru_4(CO)_{12}$. This difference was attributed to the fact that, upon formation of the second catalyst from the first when pressurizing the reaction with hydrogen, some excess CO would form, which inhibits binding of the substrate [64]. Markó reported CO inhibition in the $Cr(CO)_6$/NaOMe-catalyzed hydrogenation of ketones [65], while Kliger and coworkers studied the hydrogenation of unsaturated hydrocarbons with a catalyst which was prepared by the addition of primary, secondary, or tertiary octylamines to $Pt(OAc)_4$ [66]. These authors identified a linear inverse relationship between the rate of hydrogenation and the amount of CO added, with full inhibition being obtained at $Pt/CO = 5$. Although the authors did not draw any structural conclusions, this result would seem rather typical for the formation of Pt colloids (see Chapter 9).

Many authors have noted that aldehydes may function as a source of CO via a decarbonylation process [67]. Wilkinson and coworkers noted that $[RhCl(PPh_3)_3]$ is capable of decarbonylating 90% of *n*-heptanal within 24 h at room temperature [68]. The complex formed, $[RhCl(CO)(PPh_3)_2]$, is completely



Scheme 44.8 Catalytic disproportionation of glucose.

inactive as a hydrogenation catalyst [69]. This is a severe drawback of aldehyde hydrogenations both with soluble transition metal catalysts as well as with heterogeneous catalysts.

Rajagopal et al. studied the disproportionation of D-glucose using $[RuCl_2(PPh_3)_3]$ in several solvents such as DMF or dimethylacetamide (DMA) (Scheme 44.8). These authors noted deactivation of the catalyst, which was caused by the formation of inactive CO-complexes such as $[RuCl_2(CO)(PPh_3)_2(DMF)]$, $[RuCl_2(CO)(PPh_3)_2(DMA)]$ and *cis*-$[RuCl_2(CO)_2(PPh_3)_2]$ [70].

In some cases primary alcohols can be catalytically dehydrogenated under hydrogenation conditions, leading to the formation of aldehydes, which can in turn decarbonylate leading to inactive metal carbonyl complexes. In a typical example, Chaudhari reported that during the hydrogenation of allyl alcohol using Wilkinson's catalyst, the catalyst was deactivated by the formation of $[RhCl(CO)(PPh_3)_2]$ [26]. Similarly, in hydrogenations using $[RuCl_2(PPh_3)_3]$ which were performed in primary alcohols such as 2-methoxy-ethanol or tetrahydrofurfurol, $[RuClH(CO)(PPh_3)_3]$ was formed, which is inactive as hydrogenation catalyst but still showed activity in the transfer hydrogenation reaction of Scheme 44.8 [71].

44.5.4
Inhibition by Acids and Bases

Many publications report on the effect that acids and bases can have on catalysis by transition metal complexes, and in most cases positive effects are reported.

When homogeneous catalysis is carried out under aqueous conditions, the pH of the solution becomes an issue, and very often different rates are obtained at different pH-values. A striking example was reported by Xiao and coworkers

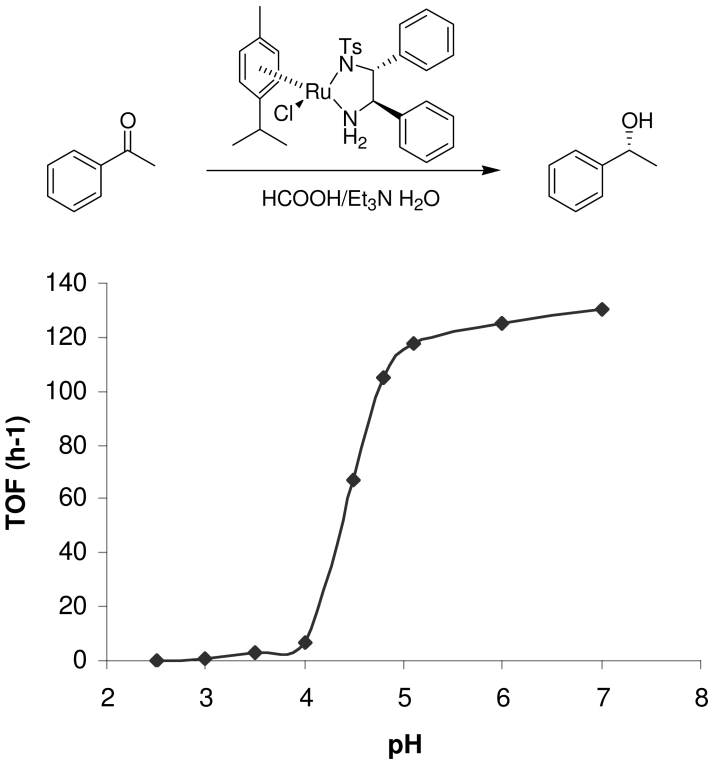


Fig. 44.10 Relationship between the rate of enantiomeric transfer hydrogenation and pH-value.

[72] while examining the enantioselective transfer hydrogenation of acetophenone. While using the Noyori-Ikariya enantioselective transfer hydrogenation catalyst Ru-Ts-dpen with the Et_3N/HCOOH azeotrope in water, these authors noticed that the reaction had a very long induction period. Since the reaction with NaOOCH started instantaneously, the question arose as to whether the pH of the solution was an important parameter, in view of the fact that the azeotrope is a 2:5 Et_3N:HCOOOH mixture. Carrying out the reaction at different pH-values immediately proved this point, whereby only at pH >4 did the reaction take off immediately (Fig. 44.10). The inhibition at low pH is caused by protonation of the ligand at the sulfonamide position.

44.6
Irreversible Deactivation

44.6.1
Inhibition by Anions

One sure way of inhibiting metal catalysts is by the addition of metal cyanides. Cyanide has a strong binding affinity to most transition metals, the result usually being complete inactivation of the catalyst [73].

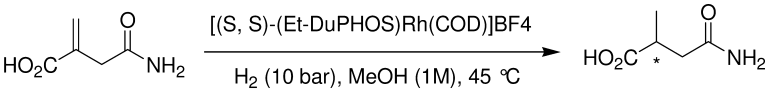
Halides are also a frequent source of inhibition. In general, halides bind very well to transition metals, although the bond can be weakened by the use of polar solvents. Thus, not all cases of inhibition by halides are irreversible. Inhibition may be caused not only by reversible binding to the metal, but also through the formation of halide-bridged bimetallic complexes, which generally exhibit much lower activity in hydrogenation reactions. In a study on the use of carboranes as counterion for rhodium phosphine hydrogenation catalysts, inhibition was found to occur through the formation of dimeric $[(PPh_3)_2HRh(\mu\text{-}Cl)_2(\mu\text{-}H)RhH(PPh_3)_2][CB_{11}H_{12}]$ [74]. An extensive study of dimeric halide-bridged rhodium species observed in solution using PHIP was recently published by Duckett et al. [75].

Halide impurities may have a negative effect on the rate of a hydrogenation reaction, as was observed by Cobley et al. These authors studied the asymmetric hydrogenation of 2-methylenesuccinamic acid using [(*S,S*)-(Et-DuPHOS)Rh-(COD)]BF_4 as catalyst [76]. They were able to obtain a 30-fold acceleration upon removal of a chloride impurity from the substrate (Scheme 44.9).

Dyson recently warned that chloride impurities present in ionic liquids prepared by the classical metathesis reaction may cause severe catalyst inhibition. This may be aggravated by the fact that metal-chloride dissociation is disfavored in ionic liquids, in spite of their polar nature [77].

44.6.2
Inhibition by Oxidation and by Ligand Modification

Nindakova and Shainyan studied the decomposition pathways of Rh–DIOP complexes. Even upon prolonged exposure to hydrogen, the catalyst decomposed in the absence of substrate with, according to these authors, the Rh-bis-



TOF (Pure SM) = 15 000 h^{-1}
TOF (Cl containing) = 500 h^{-1}

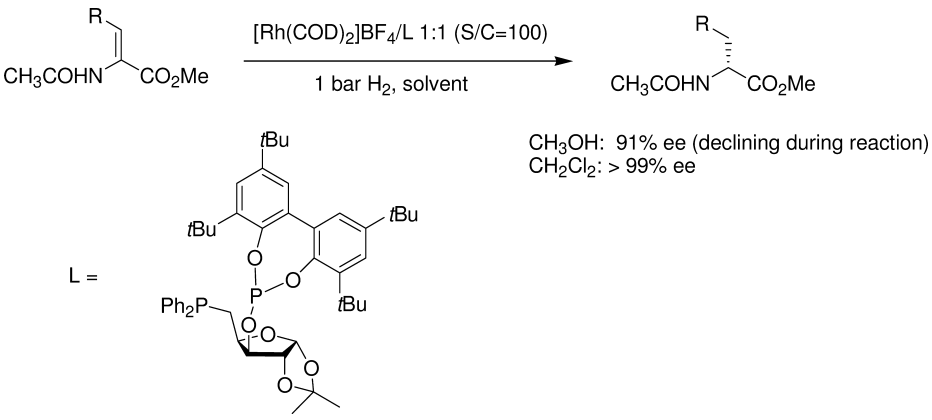
Scheme 44.9 Chloride inhibition in the enantioselective hydrogenation of 2-methylenesuccinamic acid.

phosphine oxide being a major decomposition product. The oxygen presumably stems from very small (ppm) amounts present in the hydrogen supply. Other products were η^6-Arene-Rh–DIOP complexes if the catalyst was stirred in aromatic solvents, and a binuclear compound was also detected. The assignment of structures was based exclusively on ^{31}P-NMR findings [78].

Ruiz and coworkers developed a new phosphine–phosphite ligand, which was tested in the enantioselective hydrogenation of methyl-2-acetamidoacrylate and methyl-2-acetamido-cinnamate [79]. These authors obtained the highest enantioselectivities in CH_2Cl_2, whereas in MeOH not only was the ee-value lower, but it also slowly declined during the hydrogenation reaction (Scheme 44.10). This was interpreted as slow decomposition of the phosphite part of the ligand, presumably through hydrolysis, and was confirmed by ^{31}P-NMR measurements.

In a kinetic study on the enantioselective hydrogenation of methyl-2-acetamido-acrylate with Rh/MonoPhos in *i*-PrOH, Heeres and coworkers identified an impurity in the solvent that destroyed part of the catalyst, leading to a dependence of the rate on catalyst concentration that did not pass through zero (Fig. 44.11) [80]. Closer inspection revealed the impurity to be a peroxide (positive test on peroxide strip), and the problem was solved by purifying the solvent by distillation. In fact, this is a very general phenomenon, as peroxides may be present not only in solvents but also in substrates. In general, it is worthwhile purifying both substrate and solvent before the hydrogenation reaction.

Inhibition by oxygen is also a problem in transfer hydrogenation, though the degree of inhibition may differ strongly, depending on the nature of the catalyst. In our own experience, the Noyori/Ikariya ruthenium catalysts based on aminoalcohols are extremely sensitive to oxygen. One possible reason for this might be the dehydrogenation of the ligand alcohol function to an aldehyde, although insertion of oxygen into the ruthenium–hydride bond also seems possible. Gavrilidis et al. tested the sensitivity of [RhCp*((1*R*, 2*S*)-aminoindanolate)Cl] to oxy-



Scheme 44.10 Phosphine–phosphite ligand in enantioselective hydrogenation.

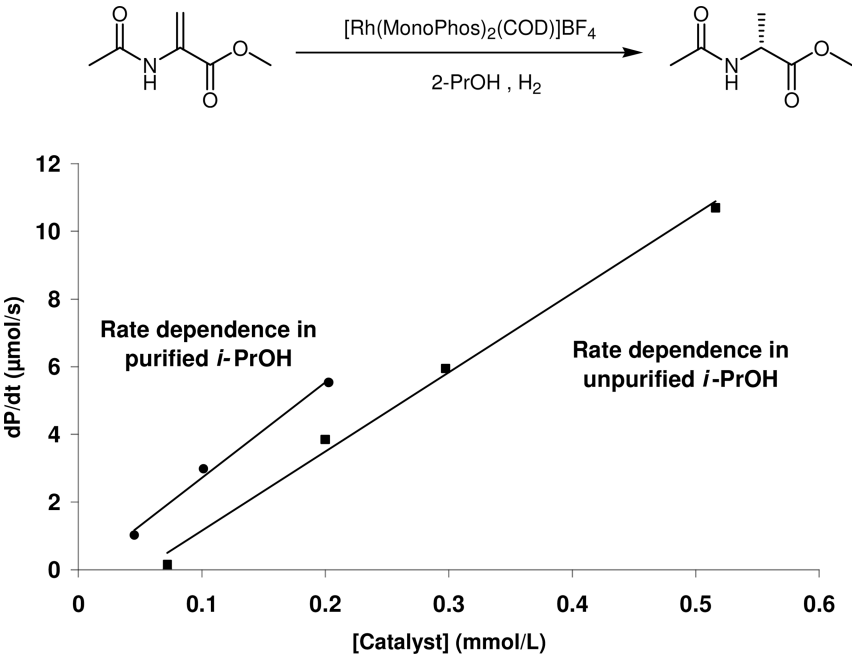


Fig. 44.11 Inhibition by peroxide in the solvent leads to a lower rate of reaction.

gen in the transfer hydrogenation of acetophenone with *i*-PrOH, and noted that after 60 min only 25% conversion was reached, as opposed to 95% under N_2 [81].

44.6.3
Formation of Dimers, Trimers, Clusters, Colloids, and Solids

The events described in the previous section are not necessarily sufficient to deactivate the catalyst. The real deactivation presumably occurs through formation of dimers or polynuclear species that have lower reactivity. These higher-order species usually do not revert back to the more active monomeric species.

In hydrogenations with Wilkinson's catalyst, ligand dissociation precedes substrate binding. Bergbreiter, in an attempt to speed up hydrogenation by aiding ligand dissociation through the addition of silver salts that bind to triphenylphosphine, found that this had the reverse effect [58]. The lower rates were caused by the formation of the dimer, which is much less soluble and exhibits only one-tenth the catalytic activity of the monomer [82].

Eisenberg and coworkers studied intermediates in the hydrogenation of alkenes using Wilkinson's catalyst and PHIP (see Chapter 12). These authors identified a range of dimers, and found that the stability of $[H_2Rh(PPh_3)_2(\mu\text{-}Cl)_2Rh(PPh_3)(\text{alkene})]$ depends strongly on the electron-withdrawing properties of the alkene [83].

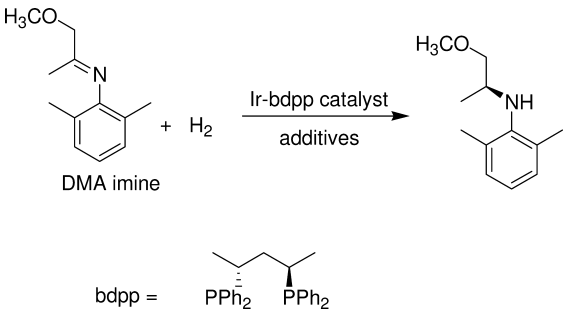
The formation of dimers and trimers is a major issue in hydrogenations with iridium catalysts. In the context of developing an industrial process to produce (*S*)-metolachlor via an enantioselective imine hydrogenation (see Chapters 34 and 37), Blaser et al. investigated the causes of catalyst deactivation in the iridium/bisphosphine-catalyzed hydrogenation of DMA imine (Scheme 44.11) [84].

Blaser and colleagues made the following observations regarding catalyst deactivation:

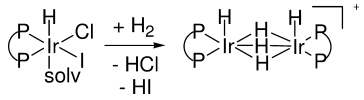
- Most tested Ir-catalysts had very high initial activity, but then slowed significantly.
- The degree of deactivation is strongly dependent on ligand structure, solvent and temperature.
- With Ir/BDPP/iodide as catalyst, productivity was higher at –5 °C than at room temperature.
- Even with the most productive catalysts, reactions did not go to completion at SCR = 15 000.
- The purity of the substrate was important. The presence of dimethylaniline is detrimental.
- No inhibition was observed upon the addition of product.

All of these observations were interpreted as signs of catalyst deactivation through the irreversible formation of inactive or less-active species. Indeed, the formation of trihydride-bridged iridium dimers had already been described by Crabtree (see Chapter 2) (Scheme 44.12) [85].

Several strategies were developed to prevent the formation of unreactive dimers [86], with one of the more successful methods being immobilization of the catalyst on solid support. Whereas normally, most immobilized catalysts lose activity in comparison to their soluble analogues, in this case the rate increased, due to the prevention of deactivation by dimerization. Even more convincing, there was a negative correlation between the loading on the resin and the rate of the reaction (Fig. 44.12).



Scheme 44.11 Iridium-catalyzed enantioselective imine hydrogenation.



Scheme 44.12 Formation of inactive iridium dimers in hydrogenation reactions.

Pfaltz and coworkers have conducted extensive studies on how the anion affects the rate of hydrogenation in the Ir–PHOX-catalyzed hydrogenation of (*E*)-1,2-diphenyl-1-propene (Table 44.3) [87].

These authors assumed that the lack of reactivity with the triflate complex is caused by strong binding of the triflate to iridium. Clearly, the tetra-arylborate and the tetra-alkoxyaluminate anions induce the highest rate. When more substrate was added after the reaction had completed and was vented with Ar, the reaction resumed at the same rate with catalysts containing one of the last three anions, whereas the PF_6-catalyst had lost all activity. The authors also noted a large difference in the sensitivity to added water. Whereas all catalysts lost some activity upon the addition of 0.05% (v/v) water, the PF_6 catalyst completely lost activity. The authors had shown previously that the PF_6 catalyst easily forms an inactive trimeric hydride-bridged iridium cluster [88], and it does indeed seem likely that the deactivation proceeds via these clusters.

Pregosin studied the interaction between iridium and the counterions by measuring diffusion using ^1H and ^{19}F pulsed gradient spin echo (PGSE), as well as the ^1H ^{19}F heteronuclear Overhauser effect (HOESY) [89]. Whereas in CD_3OD all complexes were completely cationic with freely moving anions, in CH_2Cl_2 (the solvent used for hydrogenation) there is a difference between the OTf, PF_6 and BF_4 complexes on the one hand and the two tetra-arylborate complexes on the other hand. Whereas the first three complexes are again fully cationic, the latter two show a much stronger cation–anion interaction. In view of the size of the anions, it is clear that the stronger cation–anion interaction can

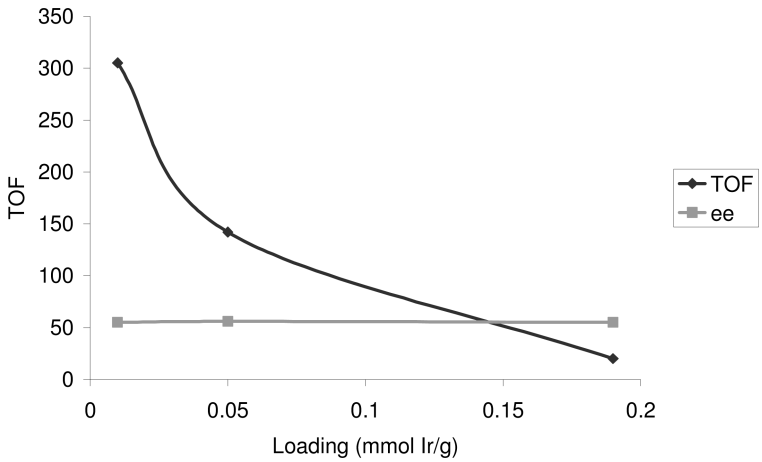
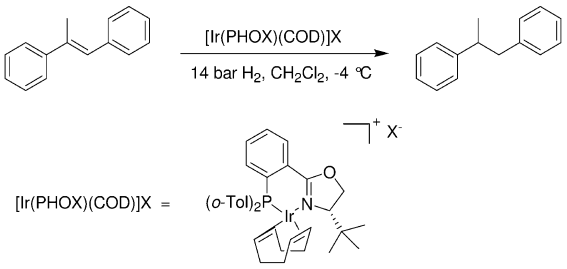


Fig. 44.12 Dependence of rate of imine hydrogenation on catalyst loading on the support.

Table 44.3 Anion effect on the rate of iridium-catalyzed alkene hydrogenation.



X	Rate of hydrogenation [mol L^{-1} h^{-1}]	ee-value
PF_6	0.63	97.3
BF_4	0.12	97.9
OTf	0	–
$B(3,5\text{-di-}CF_3\text{-}C_6H_3)_4$ ($BarF^-$)	1.70	96.9
$B(C_6F_5)_4$	1.42	97.2
$Al(OC(CF_3)_3)_4$	1.86	97.3

retard formation of the clusters, which involves the bringing together of two relatively large species.

Dervisi recently reported similar findings: upon treatment of an iridium bisphosphine catalyst containing a PF_6-anion with H_2, hydride-bridged dimers and trimers were isolated [90].

44.7 Conclusions

It is clear from the above discussions that many mechanisms exist that may deactivate or completely inhibit a transition metal catalyst. However, danger lurks in every corner! The metal precursor, the ligand, the solvent, the substrate and the reagents may all contain functional groups or impurities that might interact adversely with the metal complex. Under the influence of external agents, or simply by heat or by light, the complex may loose a ligand; however, the now underligated complex will usually dimerize or trimerize to form less-active complexes. Fortunately, once the mechanism of inhibition has been established, it is very often possible to effect changes that counteract the inhibition mechanism. Synthetic chemists can usually circumvent 95% of the problems by using very low SCRs, though for economic reasons this is not an option in ton-scale production. Inhibition is, therefore, a very important part of process development for a homogeneous transition metal-catalyzed reaction, and in almost all cases low-cost solutions can be found. Nevertheless, when planning a multi-step syn-

thesis on the ton-scale, it may be wise to introduce a purification step preceding the hydrogenation reaction.

Abbreviations

COD	1,5-cyclooctadiene
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EMS	electrospray mass spectrometry
NBD	2,5-norbornadiene
PGSE	pulsed gradient spin echo
PHIP	parahydrogen-induced polarization
PTC	phase-transfer catalyst
SCR	substrate : catalyst ratio
THF	tetrahydrofuran
TPPTS	tris-sulfonated triphenylphosphine
TOF	turnover frequency
TON	turnover number

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