2
Iridium

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2.1
Introduction

Today, iridium compounds find so many varied applications in contemporary homogeneous catalysis it is difficult to recall that, until the late 1970s, rhodium was one of only two metals considered likely to serve as useful catalysts, at that time typically for hydrogenation or hydroformylation. Indeed, catalyst/solvent combinations such as $[IrCl(PPh_3)_3]$/MeOH, which were modeled directly on what was previously successful for rhodium, failed for iridium. Although iridium was still considered potentially to be useful, this was only for the demonstration of stoichiometric reactions related to proposed catalytic cycles. Iridium tends to form stronger metal–ligand bonds (e.g., Cp(CO)Rh-CO, 46 kcal mol^{-1}; Cp(CO)Ir-CO, 57 kcal mol^{-1}), and consequently compounds which act as reactive intermediates for rhodium can sometimes be isolated in the case of iridium.

When low-coordinate iridium fragments in "non-coordinating" solvents (e.g., $\{Ir(PPh_3)_2\}^+$ in CH_2Cl_2) were found to be much more active than their rhodium analogues, it became clear that it is the *dissociation* of ligands or solvent – much slower for Ir versus Rh and for MeOH versus CH_2Cl_2 – that leads to low catalytic rates with $[IrCl(PPh_3)_3]$/MeOH. The other steps in the catalytic cycle are often very fast for Ir, so if the need for dissociation is avoided, then highly active Ir catalysts can be formed. However, a new consensus has now emerged: rhodium catalysts are often considered to be slower but more selective, whilst iridium catalysts are faster but less selective.

2.2
Historical Aspects

Iridium made its first major mark in 1965, in the arena of organometallic chemistry with the discovery of Vaska's complex, $[IrCl(CO)(PPh_3)_2]$ (**1**) [1]. Only weakly catalytic itself, Vaska's complex is nevertheless highly relevant to cataly-

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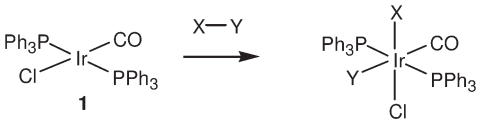
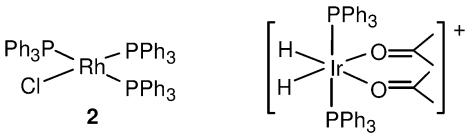
sis in providing the classic examples of oxidative addition – normally a key step in almost any catalytic cycle. Equation (1) shows how a variety of molecules X-Y can oxidatively add in a concerted manner to this Ir(I) species to form a series of Ir(III) adducts. The H_2 adduct (X=Y=H) is only very weakly catalytically active for alkene hydrogenation because all the ligands in $[IrH_2Cl(CO)(PPh_3)_2]$ are firmly bound and do not dissociate to make way for substrate alkene. Without alkene binding, hydrogen transfer from the metal to the alkene cannot occur.



1 (1)

Following the discovery of Wilkinson's hydrogenation catalyst, $[RhCl(PPh_3)_3]$ (**2**) in 1964, the iridium analogue was naturally also investigated as a catalyst, but proved to be only very weakly active. Once again, the reason was that the adduct $[IrH_2Cl(PPh_3)_3]$ failed to lose PPh_3, unlike the Rh analogue, so that the alkenes were unable to bind and undergo reduction [2].

Schrock and Osborn [3] introduced the valuable idea that the reaction should be started with a PR_3 to Rh ratio of 2:1 in order to avoid the need for ligand dissociation. These authors used Chatt's diene-metal precursors, $[(nbd)RhCl]_2$ (nbd=norbornadiene), to form a series of very useful catalysts of the type $[(nbd)Rh(PR_3)_2]BF_4$. The nbd was shown to be lost during hydrogenation to form species based on the $\{Rh(PR_3)_2\}^+$ fragment, such as $[(MeOH)_2RhL_2]BF_4$. In the Rh series, MeOH was easily lost and catalytic alkene reduction was rapid. In the iridium analogues, however, the Ir(III) complexes $[IrH_2(solvent)_2(PPh_3)_2]^+$ (**3**, solvent=MeOH) were formed. These proved to be very much less labile and less active than the Rh series [4], and consequently attention was naturally focused on rhodium.

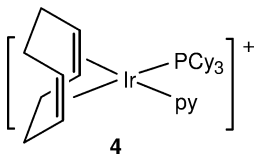


2 **3**

At this point, the initial intent of these investigations was to seek stable hydrides in iridium that were relevant to transient intermediates proposed in the rhodium series. With this aim in view, attention was focused on a series of complexes $[(cod)Ir(PR_3)_2]BF_4$, analogous to the Schrock-Osborn Rh catalysts; many of these had been synthesized previously, but had only been tested for catalysis in coordinating solvents and the results had been disappointing. The related mixed-ligand complexes, such as $[(cod)Ir(py)(PR_3)_2]BF_4$ (cod=1,5-cyclooctadiene; py=pyridine), were new [5, 6]. Since solvent dissociation from **3** was needed to generate a site for alkene binding, it seemed appropriate to examine the variation of the solvent, particularly the use of CH_2Cl_2; this was considered

to be non-coordinating because, at the time, it was not known to be capable of binding to metals. Halocarbon solvents in general had been avoided for Rh catalysts, presumably because of the risk of C–Cl oxidative addition to Rh(I). The iridium complexes resisted such pathways, possibly because their resting state is Ir(III) (versus Rh(I)), and possibly also because of their cationic nature; many neutral Ir(I) species do add C–Cl bonds easily. Not only was the catalytic rate very greatly enhanced in CH_2Cl_2 but, more importantly, the substrate scope was also greatly expanded. At the time, no homogeneous hydrogenation catalysts were known which would reduce tri- and especially tetrasubstituted alkenes efficiently; even today, these are very rare. By using a low PR_3 to M ratio, a non-coordinating solvent, and Ir rather than Rh, very high activity was achieved for hindered alkenes [7].

If a PR_3 to M ratio of 2 was so good, then would a ratio of 1 be better? A catalyst of this type indeed proved to be the best of the whole series. $[Ir(cod)(PCy_3)(py)]BF_4$ (**4**, Cy = cyclohexyl) is sometimes referred to as Crabtree's catalyst, although both Hugh Felkin and George Morris were also very closely associated with its initial development [5, 6]. The rates measured for reduction of various alkenes by **4** illustrate the high activity for hindered alkenes: *t*-BuCH=CH_2, 8300; 1-hexene, 6400; cyclohexene, 4500; 1-methylcyclohexene, 3800; $Me_2C{=}CMe_2$, 4000 h^{-1}. Even at 0.1% loading, the catalyst completely reduces all but the tetrasubstituted alkene, where 400 catalytic turnovers are seen ($Me_2C{=}CMe_2$, 0 °C, CH_2Cl_2) before catalyst deactivation. The deactivation product is a hydride-bridged polynuclear complex [7], presumably formed by intermolecular reaction of the catalyst when the depleted substrate is no longer able to compete effectively for binding to the metal. Hydrogenation tends to be favored over deactivation by operating at 0 °C rather than at room temperature.

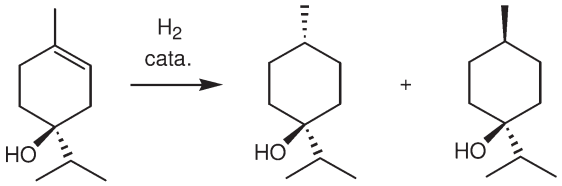


4

The above-mentioned rates can usefully be compared with those for other catalysts under similar conditions [7]: $[RhCl(PPh_3)_3]$ at 0 °C (1-hexene, 60; cyclohexene, 70; $Me_2C{=}CMe_2$, 0 h^{-1}) is far slower and $[RuHCl(PPh_3)_3]$ at 25 °C in C_6H_6 (1-hexene, 9000; cyclohexene, 7; 1-methylcyclohexene, $Me_2C{=}CMe_2$, 0) is highly selective for terminal alkenes.

The initial studies on the catalyst did not attract the attention of the organic synthetic community, partly because the details were not published in an organic chemistry journal, and the substrates used were not "real" multifunctional organic compounds. On the basis of a suggestion made by Bill Suggs, the catalyst was used for more appropriate substrates, and the results obtained published [8]. More importantly, based on a further suggestion by Sarah Danishevsky, strong (99%) directing effects were also found in which the catalyst binds to a substrate OH or

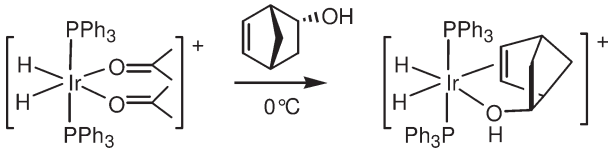
C=O group and then delivers H_2 almost exclusively from the face of the substrate that contains the binding group [9]. This property of the catalyst, which was discovered independently by Stork [10], is illustrated in Eq. (2). Any of a variety of directing groups such as ether, ketone or ester is capable of binding to the catalyst before hydrogenation takes place. This sets the stereochemistry of as many as two new stereocenters in the reduction. Since Stork is a highly respected member of the organic chemistry community, his intervention was critical in first making the catalyst known, after which time it began to be used more generally.



(2)

	Pd/C	20%	80%
$[Ir(cod)(PCy_3)py]^+$		99.9%	0.1%

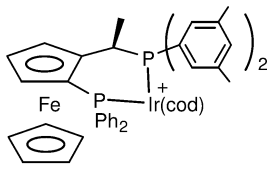
The reason that directing effects are so efficient is related to the low PR_3 to Ir ratio, which allows the directing group, the H_2 and the C=C bond all to bind to the metal at the same time. This was suggested by the detection of **5** at low temperature in the reaction of Eq. (3) [9].



3 **5**

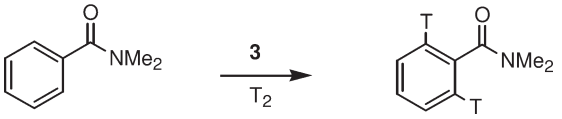
(3)

In the initial studies, the Ir system appeared to be less useful for enantioselective reduction because the *e.e.* values were never as high as seen for the Rh analogues. In commercial practice, however, rate can be more important than *e.e.* In this vein, Blaser [11] was able to equip the $\{(cod)Ir\}^+$ fragment with an asymmetric ligand of Togni's [12] to give a complex **6** that is used for the commercial production of the agrochemical metolachlor (Dual Magnum®). This is one of the few enantioselective hydrogenation systems that is in commercial use today.



6

In a purely mechanistic experiment, the deuteration of 8-methylquinoline and related compounds by the Ir catalysts was examined, whereupon very rapid and selective isotope incorporation into the methyl CH bonds was found; once again, chelation control was operating [13]. Much later, the pharmaceutical industry developed this aspect of the catalyst for the tritiation of drug candidates, needed for metabolic studies. By introducing the radioactive tritium at the last step, a full organic synthesis involving radioactive intermediates was avoided; this also greatly minimized the production of radioactive organic waste. Catalysts **3**, **4** and $[Ir(cod)(dppb)]BF_4$ ($dppb = Ph_2P\{CH_2\}_4PPh_2$) have all proved useful in this commercially important reaction, with each catalyst having a slightly different selectivity [14]. As before, pronounced directing effects caused exchange to occur at well-defined positions on the substrate, notably those immediately adjacent to the point on the compound where the catalyst binds. This is usually an O heteroatom, such as in an amide, ester, alcohol or ketone.



(4)

A wide variety of iridium-based hydrogenation catalysts are currently under development, notably for organic syntheses including enantioselective synthesis. Hydrogenation by hydrogen transfer is well known [15], and the reduction of C=O and C=N double bonds is also possible [16, 17].

The hydroboration of terminal and internal alkenes with pinacolborane can be carried out at room temperature in the presence of an iridium(I) catalyst (3 mol.%) formed by the addition of dppm (2 equiv.) to $[Ir(cod)Cl]_2$ ($dppm = Ph_2PCH_2PPh_2$), a mixture that presumably furnishes [Ir(cod)(dppm)]Cl as the true catalyst precursor. Hydroboration results in the addition of the boron atom to the terminal carbon of 1-alkenes with more than 99% selectivity [18].

The reversal of hydrogenation is also possible, as evidenced by the many iridium catalysts for alkane dehydrogenation to alkenes or arenes, though to date this area is of mainly academic interest rather than practical importance [19].

One point of practical importance is the sensitivity of these catalysts to counterion and solvent; this is particularly the case in asymmetric hydrogenation, where significant changes in properties have been seen in several cases [20]. This implies that a range of solvents and counterions might usefully be examined in planning trials of the catalyst for a given reduction. In one case [20a], even the usually satisfactory triflate and tetrafluoroborate counterions almost completely inhibited a cationic iridium-PHOX catalyst. In that case, catalysts with $[Al\{OC(CF_3)_3\}_4]^-$, $BArF^-$, and $[B(C_6F_5)_4]^-$ counterions did not lose activity during the reaction, and even remained active after all of the substrate had been consumed. Tetraphenylborate is another undesirable anion as it tends to coordinate via an arene ring. In contrast to their sensitivity to anion and solvent, the Ir catalysts are air-stable, unlike typical Rh analogues.

2.3 Organometallic Aspects

The above-mentioned catalysts rely for their activity on losing the cod ligand via hydrogenation to give cyclooctane, thus liberating sites on the metal. The origin of cod as a ligand lies in some of Chatt's early studies [21] that were related to the development of the Dewar-Chatt model [21]. The intellectual roots of the concept go back to Langmuir and to Pauling in the 1920s and 1930s, who proposed that CO could form multiple bonds with metals such as Ni(0) [22].

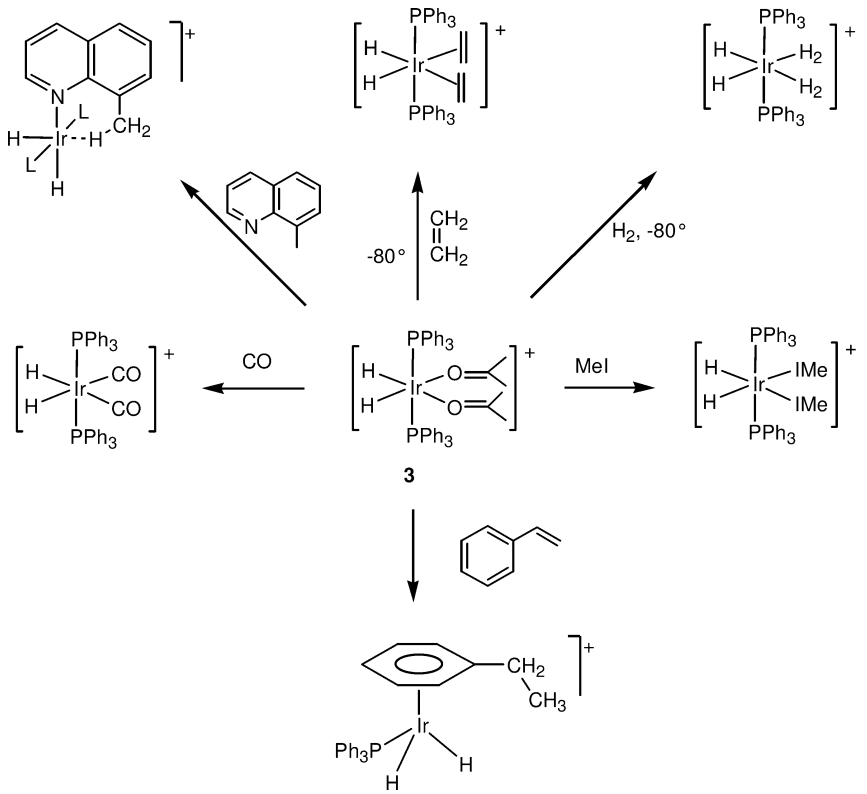
Many useful iridium catalysts, such as those mentioned above, are synthetically accessible from $[Ir(cod)Cl]_2$, which is now commercially available. Treatments with PR_3 in a nonpolar solvent gives $[Ir(cod)PR_3Cl]$ for the less bulky members of the series, with PEt_3 marking the dividing line between the two types of pathway. Smaller ligands produce neutral bis-phosphine halo-complexes. In polar solvents (e.g., aqueous acetone), in contrast, the chloride ion can dissociate and ionic $[(cod)Ir(PR_3)_2]^+$ (**7**) or $[(cod)Ir(PR_3)_3]^+$ are obtained, again depending on the steric bulk, with smaller ligands yielding the tris-phosphine species. If $[IrCl(cod)PCy_3]$ is treated with pyridine in aqueous acetone, $[Ir(cod)(PCy_3)py]^+$ (**4**) is obtained. This species is not in equilibrium with $[Ir(cod)(PPh_3)_2]^+$ and $[Ir(cod)py_2]^+$ to any detectable extent (^{1}H- and ^{31}P-NMR spectroscopy). Variants of these routes can be made to provide chelate compounds of the type $[(cod)Ir(L\text{-}L)]^+$, where L-L are diphosphines, diamines, or mixed-donor ligands [5, 6, 23]. Typically, reactions are carried out at room temperature under N_2 or Ar.

A vast number of derivatives of these general types have been prepared by similar routes for catalytic applications, and at this point we can do no more than provide a series of recent references: some have P-donor ligands [24], some have N-heterocyclic carbenes [25], and others have mixed donors [26].

The hydrogenation product from $[Ir(cod)(PPh_3)_2]BF_4$ in various solvents is the readily isolable series $[IrH_2(solvent)_2(PPh_3)_2]BF_4$ [4], where the solvent can be Me_2CO, MeOH, and even H_2O. The acetone complex (**3**) has been characterized crystallographically [27]. These are precursors for the synthesis of a wide variety of unusual derivatives (Scheme 2.1). The first complexes of halocarbons were made by the route of Eq. (4), where L = MeI [28]. For L = H_2, the products were the first bis-dihydrogen complexes [29]. Agostic species arise from reaction with 8-methylquinoline (Scheme 2.1). Instead, benzoquinoline undergoes cyclometalation.

Styrene yields a stable η^6-arene complex (Scheme 2.1), which explains why neither **3** nor **7** is an effective hydrogenation catalyst for styrene and related substrates. The formation of such stable adducts is highly disadvantageous for rapid catalysis, but not for the exploration of organometallic chemistry. No similar stable complexes have been obtained from the catalyst **4**; the faster catalytic rates seen for **4** may correlate with the presence of less stable intermediates in this case [30].

One of the limitations of both **4** and **7** in catalysis is their ready decomposition to inactive cluster hydride complexes in the absence of substrate. If the substrate is a weak ligand (e.g., $Me_2C{=}CMe_2$), this decomposition can be competitive with cluster formation. A high concentration of substrate favors catalysis



Scheme 2.1 Some reactions of $[IrH_2(Me_2CO)_2(PPh_3)_2]^+$.

by intercepting unsaturated metal-containing intermediates before they have a chance to cluster [31].

Moving to specific cases, $[Ir(cod)(PPh_3)_3]BF_4$ (**7**) yields the tris hydrogen-bridged cluster shown in Eq. (5).

$$2[Ir(cod)L_2]BF_4 + 7H_2 \xrightarrow{-2C_8H_{16}} \left[L_2H_3Ir_2H_3L_3\right]BF_4 + HBF_4 \qquad (5)$$

$[Ir(cod)(PCy_3)(py)]BF_4$ (**4**) forms the tri-nuclear cluster shown in Eq. (6):

$$3[Ir(cod)LL']BF_4 + 10H_2 \xrightarrow{-3C_8H_{16}} \left[(IrHLL')_2H(LL'HIr)\right]BF_4 + HBF_4 \qquad (6)$$

Rates of cluster formation are minimized by having the catalyst concentrations as low as possible. Successive additions of aliquots of catalyst can help in

difficult cases. None of the cluster hydrides can be converted back to catalytically active or mononuclear complexes (H_2, 1 atm, –80° to +60 °C).

The addition of H_2 at –80 °C to $[Ir(cod)(PPh_3)_2]^+$ results in complete conversion to a detectable intermediate dihydride **8** (Scheme 2.2). On warming under H_2 to about –20 °C, this produces cyclooctane and a trinuclear hydride cluster. If excess cod is present during the warming procedure, a new alkene complex (**9**) is formed. This is much more stable than species **8** and survives to room temperature. This explains why the $[Ir(cod)(PPh_3)_2]BF_4$ catalyst is ineffective for cod as substrate. The lack of reactivity of **8** can be explained by the C=C bond being coplanar with the cis hydride, allowing insertion. **9** also has C=C cis to an Ir–H, but the C=C bond is now orthogonal, forbidding insertion. **8** must be implicated in the activation of the catalyst by hydrogen. As before, catalyst **4** does not give rise to stable intermediates of similar structure, although they are assumed to be present [32].

At low temperatures (–80 °C), $[IrH_2(solvent)_2(PPh_3)_2]^+$ (**3**) also reacts with small monoolefins such as ethylene in CH_2Cl_2 solution, to give $[IrH_2(olefin)_2(PPh_3)_2]^+$. These transfer coordinated H_2 to olefin on warming to –20 °C, and so can be considered as probable intermediates in hydrogenation. Bulky alkenes such as *t*BuCH=CH produce $[IrH_2(olefin)(solvent)(PPh_3)_2]^+$.

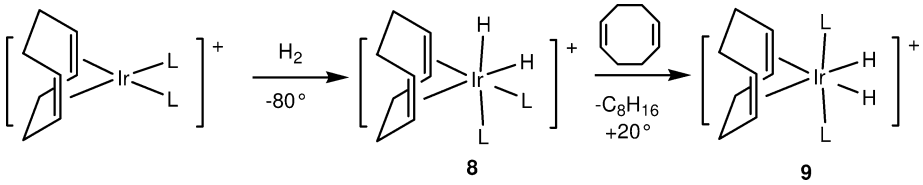
Under similar conditions (–80 °C, CD_2Cl_2) H_2 also reacts with **3** to give bis dihydrogen complex $[IrH_2(H_2)_2(PPh_3)_2]^+$; this is detected by ^{1}H-NMR spectroscopy, including T_1 relaxation measurements. This loses H_2 at 0 °C when the H_2 is removed, to form the dinuclear hydride of Eq. (5).

These results suggest that the resting state of the catalyst is probably an $[IrH_2(L)_2(PPh_3)_2]^+$ species, where L can be solvent, substrate or H_2 depending on conditions, with L = substrate being predominant at the start of the reduction when the substrate concentration is highest.

Apparently similar Rh catalysts appear to have Rh(I) resting states of type $[Rh(PPh_3)_2L_2]^+$, which possibly accounts for their very different properties, for example their inability to reduce tri- and tetrasubstituted olefins.

Monoolefins containing coordinating groups often chelate, as in **5**. These also transfer coordinated H_2 to the C=C bond on warming to –20 °C and provide a rationalization for the directed hydrogenation mentioned earlier, in which hydrogenation occurs with almost exclusive H_2 addition from the face of the substrate that contains the coordinating group.

The presence of base such as NEt_3 in the system leads to conversion of the cationic $[IrH_2L_2(PPh_3)_2]^+$ forms to catalytically inactive neutral analogues. An ex-



Scheme 2.2 Some intermediates in the hydrogenation of $[Ir(cod)(PPh_3)_2]BF_4$.

ample of a reaction of this type that gives an isolable neutral hydride is shown in Eq. (7):

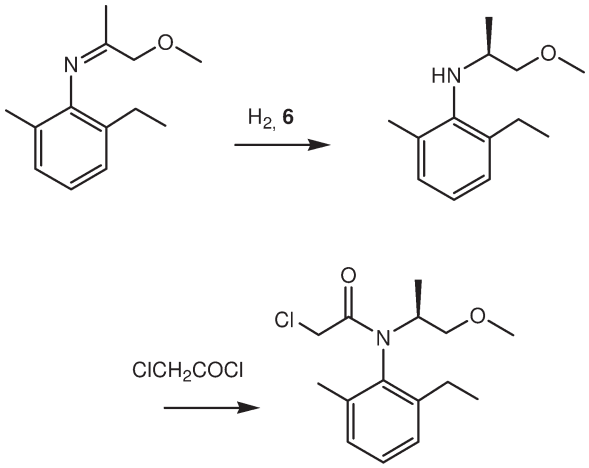
$$[Ir(cod)(PPh_3)_2]BF_4 + NEt_3 + 6\,H_2 \rightarrow [IrH_5(PPh_3)_2] + [Et_3NH]BF_4 + C_8H_{16} \quad (7)$$

2.4 Catalysis

The above-mentioned reaction with base has relevance for catalytic chemistry in that substrates that are also bases may deactivate the catalyst by deprotonation; this can be avoided by addition of HOAc, HBF_4 or H_2SO_4 or use of the corresponding salt of the substrate. Coordinating anions react with the catalyst, again with deactivation of the catalyst, so any halide counterions should be replaced by BF_4 or PF_6. Carboxylate salts also react with the system to give inactive $[IrH_2(O_2CR)(PPh_3)_2]$, so carboxylates should be reduced in the protonated form (or as the ester). Amides bind via the carbonyl oxygen, albeit reversibly, so they can affect the rate of reaction and the stereochemistry of the product via directing effects, but are otherwise well tolerated. Esters and alcohols bind less strongly and have little effect on the rate, but still show directing effects. The Ir catalyst has been used for a wide variety of transformations in the organic synthesis of complex molecules. When attention is paid to the points mentioned above, the results have often proved very satisfactory.

2.4.1 Enantioselective Versions of the Iridium Catalyst

Despite extensive efforts, only a handful of enantioselective hydrogenations have as yet achieved the status of commercial processes. Among these is one that involves the enantiomeric reduction of imines by catalyst **6**: Syngenta's process for (*S*)-metolachlor [11]. The latter is now the largest scale industrial enantiomeric catalytic process, with annual sales of the product, Dual-Magnum®, now exceeding 10^4 tons. Imines tend to be difficult substrates because of the possibility of unproductive ligand binding via the imine lone pair. For reasons that are still not entirely clear, the Ir catalysts are less seriously affected by such binding as are the Rh analogues. It is possible that the high trans-effect of the hydrides in the Ir(III) resting state labilizes the substrate binding sites, located trans to the hydrides. Enhanced back-bonding by the third row metal may also enhance the relative stability of the η^2-bound form of the imine that leads to insertion and productive catalysis.



(8)

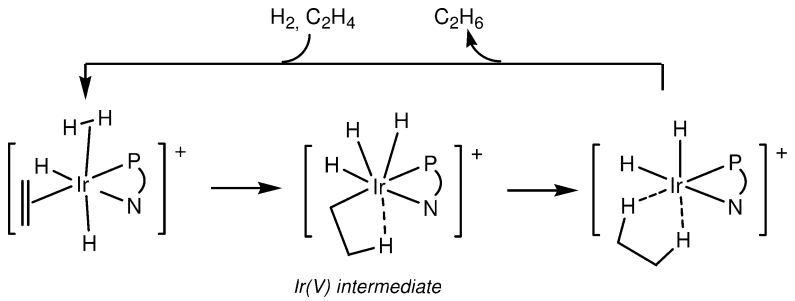
(S)-metolachlor

Bulky groups on the imine also help to disfavor η^1 binding. A ketimine is normally required for the reduction product to contain an asymmetric carbon α to nitrogen, as in the case of metolachlor (Eq. (8)). Finally, the presence of an acid of a non-coordinating anion helps to protonate the nitrogen lone pair and disfavor η^1 binding to the metal via this lone pair. The iodide additive leads to the formation of iodoiridium species that are beneficial for precatalyst **6**. Rates of up to $1.8\times10^6\ h^{-1}$ are achieved (50 °C, 80 bar) allowing substrate/catalyst ratios of 10^6. This is said to be one of the fastest homogeneous catalysts of any type known. For economic success of the process, the rate is more significant than the ee (80%), whereas in reports made by academic contributors the ee-values often dominate the discussion. A more appropriate figure of merit (FOM) [11] might be obtained by multiplying the ee by the rate; hence, an FOM value for the metolachlor catalyst system is $1.45\times10^6\ h^{-1}$.

2.4.2 Mechanism

The fastest [Ir(cod)LL′]BF_4 systems have proved difficult to study from a mechanistic standpoint because they are so active that the rates are often limited by the mass transfer of hydrogen from the gas phase into solution. This implies that efficient stirring is desirable for the most effective use of the catalyst.

Perhaps the best data are available from Brandt's study of Pfaltz's asymmetric $[Ir(cod)(P\text{-}N)]^+$ catalyst [33], bearing a chelating phosphino-oxazolidene ligand. The rate is first order in catalyst and H_2, but zero order in substrate. Taken together with the density functional theory (DFT) calculations, this is consistent with the mechanism of Scheme 2.3, shown here in its essentials only (the interested reader is urged to consult the original paper for the complete story). Surprisingly, an Ir(III)/Ir(V) cycle is proposed, rather than the M(I)/M(III) cycle



Scheme 2.3 The essential features of the Brandt mechanism for the Pfaltz catalyst [34].

that is usually considered for iridium and that is well established for rhodium. This explains the insensitivity of the iridium system to air and to oxidizing solvents, since Ir(III) and Ir(V) tend to be more stable than Ir(I) both to air and to oxidants in general. It also explains the markedly different catalytic selectivities of what are entirely analogous Rh(I) and Ir(I) catalyst precursors. It is very likely that a similar Ir(III)/Ir(V) cycle applies to typical $[(cod)IrL_2]^+$ catalysts. Related iridium species are effective alkane dehydrogenation catalysts, for which a similar reverse-hydrogenation mechanism could readily apply.

In other studies, imine reduction by $[Ir(cod)(PPh_3)_2]BF_4$ in THF has been shown to be first order in each of the catalyst, the H_2, and the substrate. Initial formation of $[IrH_2(imine)_2(PPh_3)_2]^+$ was proposed to lead to amine and $[Ir(imine)_2(PPh_3)_2]$. Oxidative addition regenerates the Ir(III) species [34].

Oro, Werner and coworkers found that alkyne reduction by the P,O chelated $[Ir(cod)(PrPr_2CH_2CH_2OMe)]BF_4$ in CH_2Cl_2 at 25 °C is also first order in each of catalyst, H_2 and substrate. Styrene is formed rapidly, whilst subsequent reduction to ethyl benzene is much slower. Stopping the reaction after the appropriate time led to essentially complete selectivity for styrene formation [35]. Surprisingly, the cod remains coordinated to Ir throughout the catalytic cycle, in contrast to every other case, where cod is proposed to be hydrogenated or the cyclooctane hydrogenation product is detected. In view of the case with which 6-alkynes rearrange to vinylidenes, such a pathway might easily be involved in 1-alkyne hydrogenation. The appropriate isotope labeling experiments seem to be carried out only rarely.

A detailed combined experimental computational mechanistic study, performed for isotope exchange in 2-dimethylamino pyridine, showed how the presence of hydrides in the Ir(III) intermediates helps to flatten the potential energy surface, accounting for the extremely high rates of exchange. In this case, carbene intermediates were also involved as a result of double C–H activation.

2.4.3 Practical Considerations

As the iridium catalysts are often somewhat thermally sensitive, synthetic procedures to prepare them should be carried out at room temperature, or below. These catalysts are normally stable to air as solids, but are somewhat air-sensitive in solution. An inert atmosphere (N_2 or Ar) is typically used for the storage of solids and to protect solutions, as the catalysts deactivate in the absence of substrate. The order of addition must be: substrate first, followed by H_2. Weakly coordinating solvents are required for optimum activity. Dichloromethane is typical, but tetrahydrofuran (THF) has also been used. $PhNO_2$, PhCl and $PhCF_3$ may also be satisfactory, but MeCN, pyridine and alcohols should be avoided. The presence of water is tolerated. Basic substrates should be neutralized by the addition of HOAc or HBF_4 in an amount equivalent to the number basic groups to be neutralized, though an excess does not seem to be detrimental. A catalyst loading of 0.1% is usually satisfactory, though very much lower loadings have been used in commercial processes. BF_4^- is the usual counterion, but PF_6^- can also be used. BPh_4^- is unsatisfactory because it tends to bind to the metal to produce catalytically inactive arene complexes. Coordinating anions such as halides are to be avoided in the substrate, but the presence of some iodide has proved beneficial in one case. In the relatively low-polarity solvents used, the complexes form tight ion pairs. In related systems, such as $[IrH_2(dipy)(PPh_3)_2]BF_4^-$, the ion pair has a definite structure, as shown by NMR spectroscopy [36]. Hydrogen is usually supplied at 1 atm pressure, although commercial applications use pressures up to 80 atm. Rates may also slow at low H_2 pressures, but the reaction still occurs. Reaction temperatures from 0 °C to 50 °C have been used successfully.

A variety of functional groups resist reduction: arene rings, NO_2, COOMe, $CONH_2$, sulfones, nitrile, and ArHal. Nitriles can bind to the metal, and the N lone pair is not effectively masked by acid addition so lower rates can be encountered if this group is present. Alkynes, alkenes, and imines are the best-studied substrates for which reduction is efficient.

The isolation of product is usually possible after evaporation of the solvent and extraction with hexane, ether, or toluene. Supported versions, for example on polystyrene grafted with PPh_2 groups, have proved unsatisfactory because the rate of deactivation is greatly enhanced under these conditions [37]. Asymmetric versions exist, but the ee-values tend to be lower than in the Rh series [38]. With acid to neutralize the basic N lone pair, imine reduction is fast. Should it be necessary to remove the catalyst from solutions in order to isolate a strictly metal-free product, a resin containing a thiol group should prove satisfactory. A thiol group in the substrate deactivates the catalyst, however.

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Abbreviations

cod	1,5-cyclooctadiene
Cy	cyclohexyl
DFT	density functional theory
ee	enantiomeric excess
FOM	figure of merit
nbd	norbornadiene
py	pyridine
THF	tetrahydrofuran

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