Chapter 1

Iridium Catalyzed Asymmetric Hydrogenation of Alkenes with Chiral N,P and C,N Ligands

1.1 Introduction

The development of highly enantioselective rhodium-diphosphine catalysts in the early 70s marked the beginning of a new era in asymmetric synthesis. For the first time practically useful enantioselectivities could be obtained with synthetic chiral catalysts. The well-known L-Dopa process developed by Monsanto at that time[1] demonstrated that these catalysts can be applied on an industrial scale, and since then hydrogenation has played a dominant role in industrial asymmetric catalysis.[2] Today, asymmetric hydrogenation remains a corner stone of the modern organic chemists' repertoire of reliable catalytic methods for the construction of optically active compounds.[3] High enantioselectivity, low catalyst loadings, essentially quantitative yields, perfect atom economy, and mild conditions are attractive features of this transformation as evident in the ever growing list of publications using these methods.

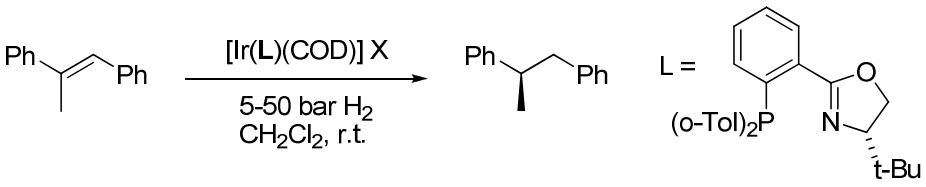
A plethora of chiral phosphine ligands are known which induce very high enantioselectivity in rhodium- and ruthenium-catalyzed hydrogenations. However, the range of alkenes that can be hydrogenated with high enantiomeric excess is still limited. Both rhodium and ruthenium catalysts require the presence of a coordinating functional group adjacent to the C=C bond, hydrogenation of dehydro-amino acid derivatives or allylic alcohols being typical substrate classes. A caveat of this reactivity in regard to unfunctionalized alkenes is that these catalysts generally display low reactivity and unsatisfactory enantioselectivity. Thus, their application has been restricted largely to certain classes of properly functionalized substrates.

Some years ago the Pfaltz group discovered a new class of chiral iridium N,P-ligand complexes which overcame the limitations of the rhodium and ruthenium based systems.[4] Early transition metal metallocenes catalysts capable of asymmetric hydrogenation of a range of unfunctionalized alkenes in excellent enantioselectivities have been reported but under onerous conditions.[5] Moreover, iridium N,P based systems showed exceptionally high activity in the hydrogenation of unfunctionalized tri- and even tetrasubstituted alkenes. In this respect, they resembled the Crabtree catalyst, [Ir(pyridine)(Cy_3P)(COD)]PF_6 (Cy = cyclohexyl, COD = cyclooctadiene),[6] which provided the stimulus for this work. In addition, promising results were also obtained with certain functionalized alkenes for which no suitable catalysts were available. In this chapter, we discuss the special properties and scope of these catalysts with special emphasis on recent developments.[7]

1.2 Mechanistic Studies

1.2.1 Initial Studies: An Unexpected Anion Effect

Initial studies with iridium complexes derived from chiral phosphinooxazolines (PHOX ligands) and (*E*)-1,2-diphenyl-1-propene as substrate gave encouraging results (Scheme 1).[4a,8] With 4 mol% of catalyst (X = PF_6^-) at 10-50 bar hydrogen pressure up to 98% ee could be obtained. However, the turnover numbers were disappointingly low.



Scheme 1

Kinetic studies demonstrated that with 4 mol% of catalyst in a 0.3 M solution of alkene at 7 bar hydrogen pressure the reaction was extremely fast and reached completion within less than one minute.[9] Lower catalyst loadings resulted in decreased conversion. Although the initial rate was still high at 1 mol% catalyst loading a rapid and essentially complete deactivation of the catalyst was observed before 50% of the alkene was consumed. Deactivation is a known problem of the Crabtree catalyst, which is attributed to the formation of inactive hydride-bridged trinuclear complexes.[6] In the case of Ir(PHOX) complexes as well NMR analysis of deactivated reaction mixtures suggested the presence of such hydride-bridged species. In subsequent studies a trinuclear Ir(PHOX)-hydride complex was isolated and characterized by NMR and X-ray analysis.[10] This complex proved to be remarkably stable and all experiments to convert it back into a catalytically active species failed.

Attempts to increase conversion by variation of the solvent, hydrogen pressure, or the catalyst and substrate concentration were unsuccessful. Coordinating solvents and additives such as amines, or coordinating anions such as halides, carboxylates, and even the very weakly coordinating triflate ion were found to deactivate the catalyst. The best results were obtained in anhydrous dichloromethane or 1,2-dichloroethane using cationic Ir-PHOX complexes with hexafluorophosphate as counterion. Rigorous exclusion of moisture and oxygen resulted in increased conversion. When the reaction was set up in carefully dried dichloromethane in a glove

box, full conversion could be achieved with only 0.5 mol% of catalyst. However, reactions at such low catalyst loadings were difficult to reproduce.

After extensive experimentation a simple solution for avoiding catalyst deactivation was discovered, when testing an Ir-PHOX catalyst with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F^-) as counterion.[4a] Iridium complexes with this bulky, apolar and extremely weakly coordinating anion[11] did not suffer from deactivation and full conversion could be routinely obtained with catalyst loadings as low as 0.02 mol%.[12] In addition, the BAr_F salts proved to be much less sensitive to moisture than the corresponding hexafluorophosphates. Tetrakis(pentafluorophenyl)borate and tetrakis(perfluoro-tert-butoxy)aluminate were equally effective with very high turnover frequency whereas catalysts with hexafluorophosphate and tetrafluoroborate gave only low conversion while reactions with triflate were completely ineffective (Figure 1).

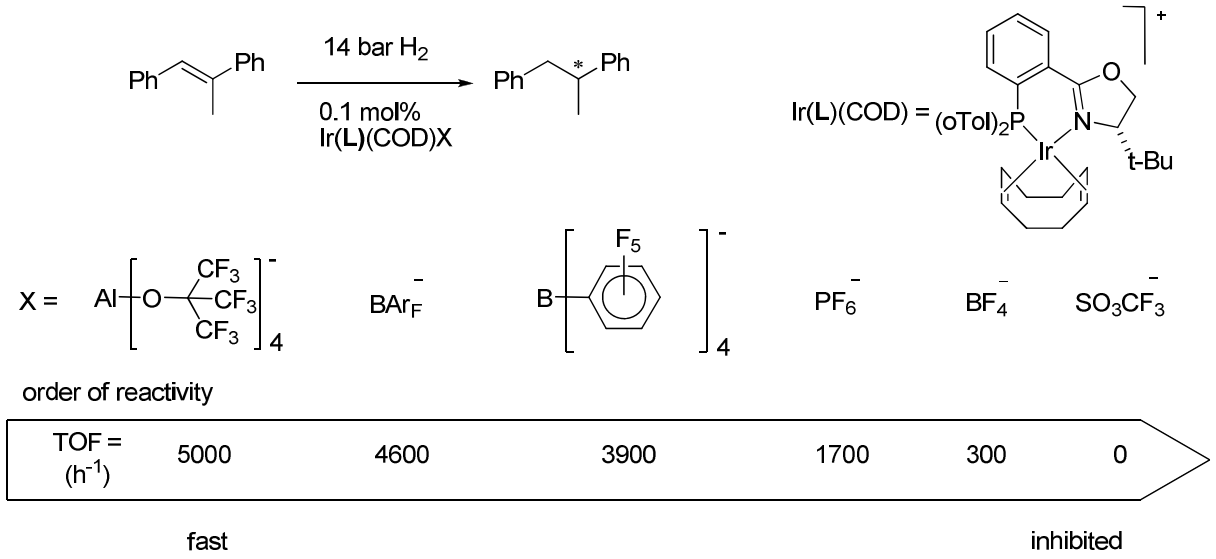


Figure 1. Order of reactivity of the complexes [Ir(PHOX)(COD)]X by TOF measured at 4°C with E-α-methylstilbene as substrate.

How can these bulky, extremely weakly coordinating anions prevent catalyst deactivation? A comparative kinetic study of catalysts with different anions provided a plausible answer.[12] With PF_6^- as counterion the rate dependence on alkene concentration was first order, whereas the rate order observed for the corresponding BAr_F^- complex was close to zero. This striking difference may be explained by the stronger coordination of PF_6^- or formation of a tight anion pair which slows down the addition of the alkene to the catalyst to such an extent that it

becomes rate-limiting. In contrast the essentially non-coordinating BAr_F^- ion does not interfere with alkene coordination and the catalyst remains saturated with alkene even at low substrate concentration. The slower reaction of the PF_6^- salt with the alkene could explain its higher tendency to undergo deactivation. If we assume that deactivation is caused by the formation of hydride bridged species leading to an inactive trinuclear complex, then the critical step in the catalytic cycle is the reaction of the Ir-hydride intermediate with the alkene. If alkene insertion is very fast, as in case of the BAr_F^- counterion, hydrogenation dominates over the deactivation pathway, whereas with the PF_6^- analogue the alkene reacts more slowly and deactivation becomes a significant competing process.

Virtually every iridium catalyst of the formula $[Ir(L^*)(COD)]^+ [X]^-$ for asymmetric alkene hydrogenation that has appeared after the initial counterion effect studies was based on BAr_F^- as the preferred anion. [7d] The anion effect is broadly applicable in iridium catalyzed reductions as experiments with a direct analogue of the Crabtree catalyst of the formula $[Ir(pyridine)(Cy_3P)(COD)]BAr_F$ indicates (Figure 2).

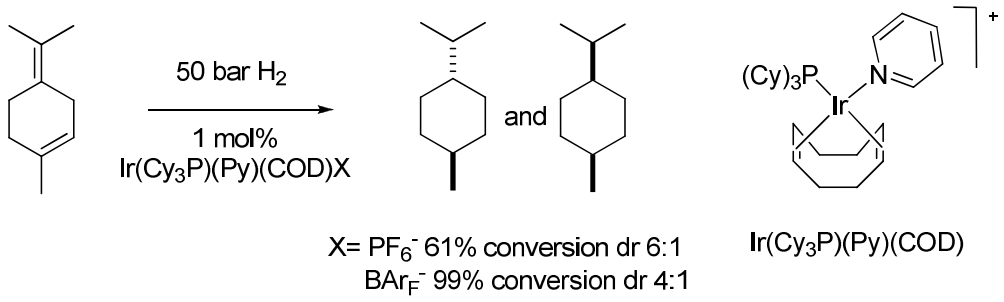


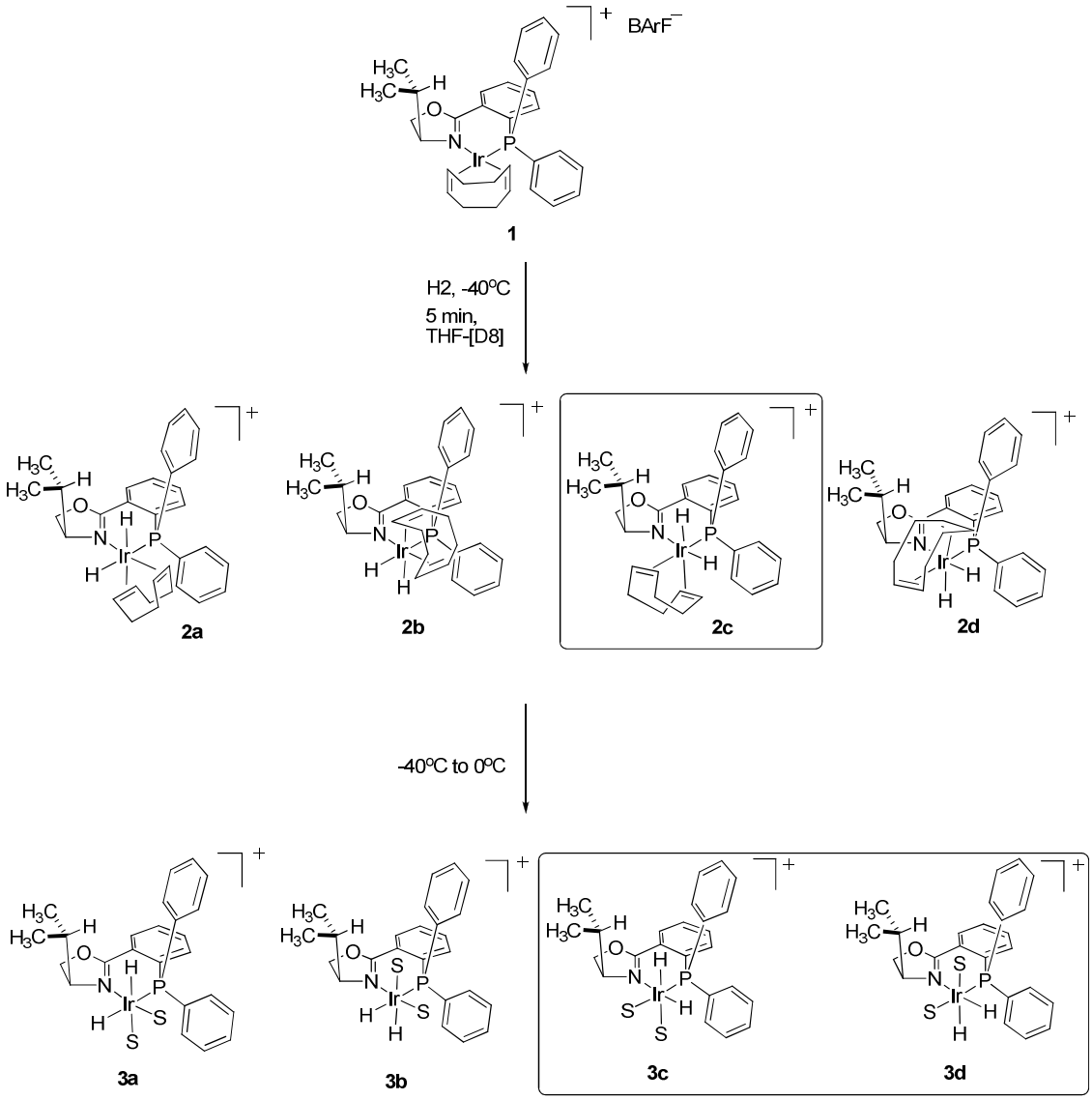
Figure 2. Comparison of Crabtree catalyst with the BAr_F analogue.

Hydrogenation of δ-terpinene (Figure 2) proceeded in higher conversion with Crabtree's catalyst with BAr_F counter ion rather than the normal PF_6. The BAr_F counter ion performed better in all instances where the more coordinating PF_6 salt failed to reach complete hydrogenation. [13]

1.2.2 NMR Investigations of Iridium PHOX Hydride Complexes

In early work of Crabtree and co-workers, alkene dihydride intermediates formed during hydrogenation of cyclooctadiene using $[Ir(pyridine)(PCy_3)(COD)]PF_6$ in dichloromethane at 0°C were detected by NMR spectroscopy.[14] In a more recent complementary study Mazet et al found that when $[Ir(PHOX)(COD)]BAr_F$ complex **1** was treated with hydrogen at -40 °C for 5

min in [D_8]-THF, alkene dihydride intermediates were formed which were characterized by NMR spectroscopy.[15a] Two new signals appeared in the hydride region that were assigned to a single dihydride complex **2c** formulated as [Ir(PHOX)$(H)_2$(COD)]BAr_F (Scheme 2).



Scheme 2

The predominance of isomer **2c** over **2a** or **2b** is consistent with Crabtree's findings, who convincingly demonstrated that in the reaction of H_2 with [Ir(pyridine)(PR_3)(COD)]PF_6 the formation of an Ir-H bond trans to the N ligand is electronically favored.[17] Highly selective formation of isomer **2c** results from H_2 addition to the more sterically encumbered face of the starting complex because dihydrogen addition to the sterically more accessible face leading to

isomer **2d** would build up steric strain between the chelating COD ligand and the isopropyl group in the oxazoline ring and the pseudoaxial P-phenyl group. When the solution containing complex **2c** was warmed to 0˚C under hydrogen a gradual consumption of isomer **2c** was observed accompanied by the appearance of two new hydride complexes **3c** and **3d** with concomitant formation of cyclooctane.

1.2.3 Computational Studies and Additional Experiments

DFT (Density Functional Theory) calculations on the complete structures of complexes shown in Scheme 2 have been carried out by Mazet et al.[15] The fully minimized structures of the four possible cis-dihydrides formed by oxidative addition of H_2 to $[Ir(PHOX)(COD)]^+$ were calculated. The most stable structure corresponded to the reaction product **2c** that was shown to be formed exclusively in the NMR experiment. Isomers **2a** and **2d** were 10.6 and 4.9 kcal/mol higher in energy, whereas for isomer **2b** no stable chelate structure could be located due to severe steric interactions which prevent the formation of an Ir-N bond. The four possible $[Ir(PHOX)(H)_2(solvent)_2]^+$ complexes **3a-d** resulting from hydrogenation of the cyclooctadiene ligand were also examined and again the two most stable structures corresponded to the isomers observed in the NMR experiments. These results show that steric interactions are very important and may dominate over electronic factors. Consequently, computational studies of potential reactions pathways should be based on full catalyst and substrate structures rather than simple model systems.

Unfortunately, attempts to observe and characterize intermediates under catalytic conditions have been unsuccessful so far. When considering which intermediates may be formed during catalysis, one of the first issues which becomes apparent is what ligands are coordinated to iridium during catalysis. An alkene dihydride iridium complex which incorporates a bidentate N,P ligand has a sixth coordination site available for an additional ligand. Whereas coordination of a second molecule of alkene seems highly unlikely due to steric hindrance, dihydrogen and dichloromethane may both be effective ligands for iridium.

Thus two plausible catalytic cycles have been considered, one via an Ir dihydride complex **A** the other via an $IrH_2(\eta^2\text{-}H_2)$ complex **B** (Figure 4). The first is analogous to the well-established mechanism for rhodium diphosphine-catalyzed hydrogenation of alkenes going through Ir(I) and Ir(III) intermediates.[16]