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Chapter 2

C–H Bond Activation by Iridium and Rhodium Complexes: Catalytic Hydrogen–Deuterium Exchange and C–C Bond-Forming Reactions

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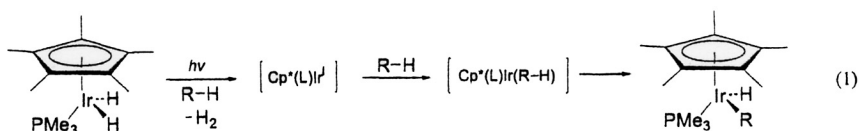
The metal-mediated activation of carbon-hydrogen bonds has the potential of leading to important fundamental insights, as well as to advances in large-scale industrial and synthetic organic chemical processes. Our initial finding of C-H oxidative addition reactions in low-valent iridium (I) complexes was followed by a more recent discovery and exploration of C-H activation processes at Ir (III) centers. This paper reviews recent studies of the Ir (III) reaction that include work directed toward elucidation of its reaction mechanism and the development of catalytic hydrogen/deuterium exchange reactions. The article also discusses collaborative studies of rhodium (I)-catalyzed reactions that provide a method for adding complexity to a range of carbo- and heterocyclic arene compounds with structures analogous to those found in physiologically active organic compounds.

Introduction

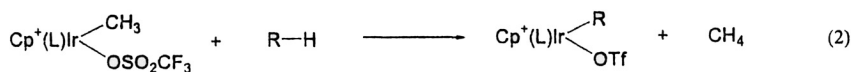
The activation of carbon-hydrogen bonds in alkanes (and alkyl groups remote from other functional groups in organic molecules) has important implications for the development of new industrial processes, new methods for the synthesis of fine chemicals, and the efficient use of energy. However, such "unactivated" C-H bonds are normally so inert toward conventional reagents that until recently it has not been possible to activate and replace the hydrogen atoms with more synthetically reactive functional groups (1-4) This article reviews experiments carried out in our group, and in collaboration with other groups at Berkeley, aimed at discovering and understanding the mechanisms of metal-mediated C-H activation processes.

Carbon-Hydrogen Bond Activation at Methyliridium(III) Centers

Several years ago we (and simultaneously, Hoyano and Graham) discovered one of the first "C-H activation" reactions that converts alkanes into isolable metal complexes (eq 1) (5-7). The important step in this process involves the generation of an exceedingly reactive iridium, rhodium (8,9) or rhenium (10) fragment, in formal oxidation state +1, which undergoes an oxidative addition reaction leading to a metal (+3) product containing a new metal-carbon and metal-hydrogen bond.



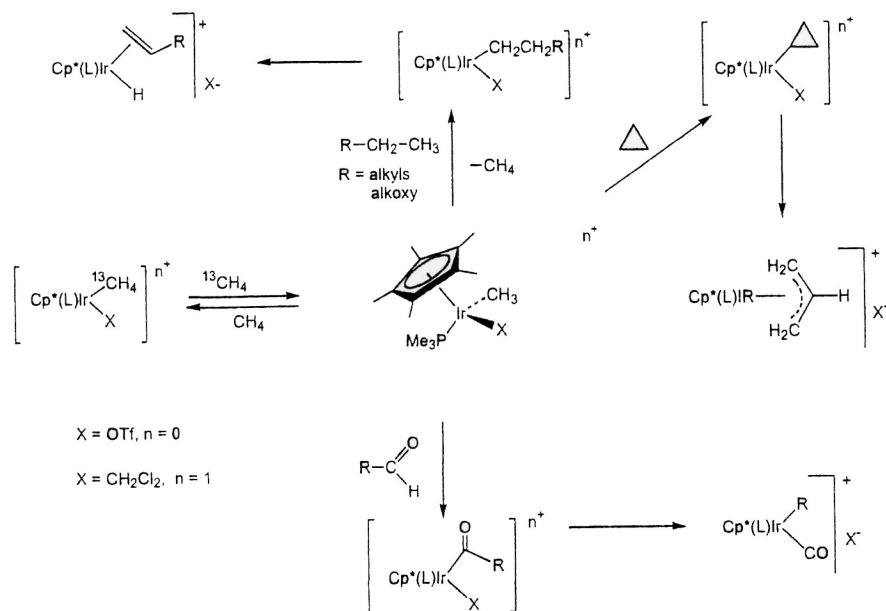
More recently, we have prepared a series of higher-valent, methyliridium(III) complexes that also are capable of hydrocarbon C-H bond activation (11-13) These Ir(III)-based reactions differ from those observed with Ir(I) in that replacement of the methyl group with the alkyl group of the activated hydrocarbon is observed (eq. 2). The first of these reactions that we uncovered involved reaction of the iridium complex $\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{CH}_3)(\text{OTf})$,



which bears a reactive trifluoromethanesulfonate ("triflate") ligand, with the C-H bonds of benzene (eq. 2, R = Ph). However, the reactivity of this material

extends beyond aromatic C-H bonds, and includes primary alkanes and methane (established by carbon labeling), although the Ir(III) complexes do not attack as many different kinds of C-H bonds as their Ir(I) relatives. The corresponding cationic complexes (associated with fluorinated polyarylborate (BAR_f^-) counterions), bearing neutral and more loosely bound ligands such as dichloromethane, attack the same range of C-H bonds, but these complexes react much more rapidly than the triflates. The BAR_f^- salts are typically made by treating $\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{CH}_3)(\text{OTf})$ with NaBAR_f , but they can be generated under particularly mild conditions (temperatures as low as -80°C) by abstracting a CH_3^- group from the charge-neutral dimethyl complex $[\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{CH}_3)_2]$ with $\text{B}(\text{C}_6\text{F}_5)_3$. Finally, many of the C-H activation reactions observed with Ir(III) complexes lead to products formed by rearrangement of the first-formed intermediates. A summary of some of the C-H activation/rearrangement processes that we have observed is presented in Scheme 1.

Scheme 1

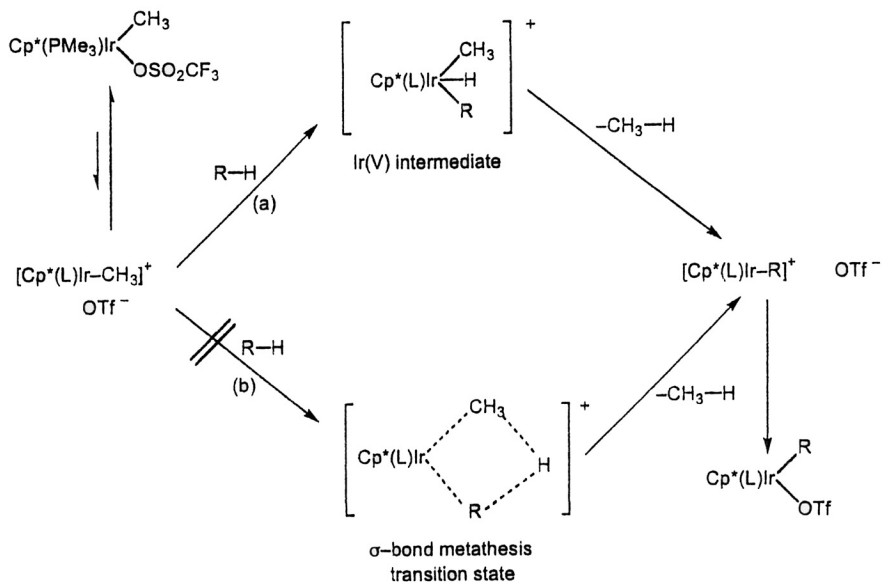


After exploring the generality of the Ir(III) C-H activation reactions, we began to address the question of their mechanism. A central problem concerned whether these transformations proceed by initial C-H oxidative addition to give

very high oxidation state iridium(V) intermediates (path (a) in Scheme 2), or by concerted metal alkyl/C-H σ -bond metathesis (path (b) in Scheme 2) (14).

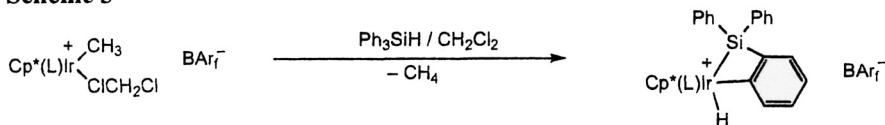
A number of lines of investigation have provided evidence that path (a) is correct.

Scheme 2



Probably the most convincing results were obtained in studies that were initially designed to compare the C-H activation reactions of this system with analogous processes that might occur at Si-H bonds. An unexpected, but very informative, result from these experiments is illustrated in Scheme 3. These show that initial Si-H activation occurs, but this is followed in the first-formed intermediate by intramolecular C-H activation, leading to a cyclometallated complex that exhibits a stable Ir(V) hydridoaryl center. Furthermore, treatment of this complex with acetonitrile causes C-H reductive elimination and reconversion of the metal center to the Ir(III) state. This result demonstrates that Ir(III)/Ir(V) interconversion can occur readily in this system, providing strong circumstantial evidence for path (a) in Scheme 2. DFT calculations carried out on the oxidative addition reaction of methane to $[\text{Cp}^*(\text{PMe}_3)\text{IrCH}_3]^+$ support this conclusion (15,16).

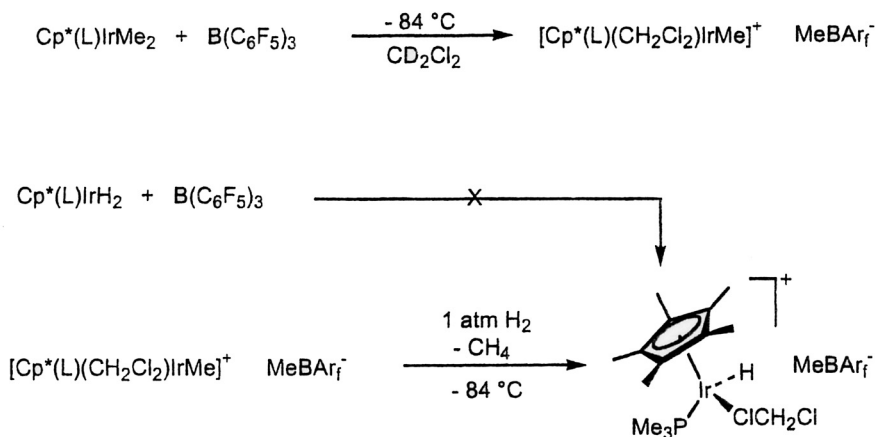
Scheme 3



Carbon-Hydrogen Bond Activation at Hydridoiridium(III) Centers

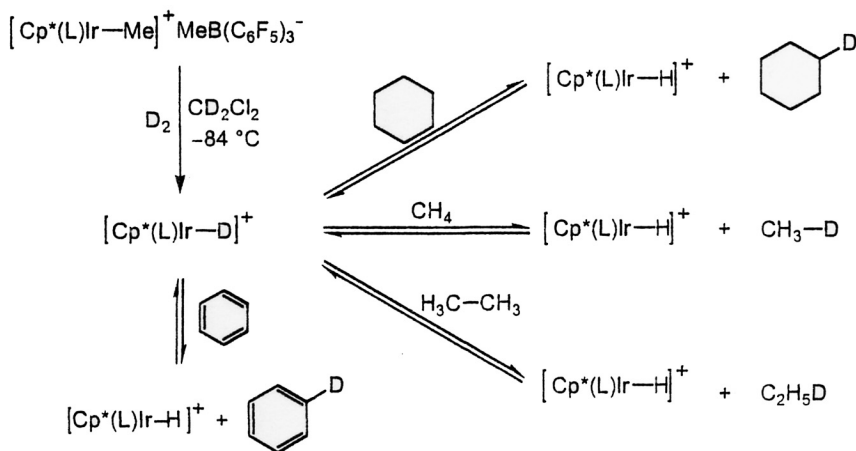
The C-H activation chemistry observed with $[\text{Cp}^*(\text{PMe}_3)\text{IrCH}_3]^+$ raised the possibility that analogous reactivity could be seen with the corresponding cationic Ir(III) hydride, $[\text{Cp}^*(\text{PMe}_3)\text{IrH}]^+$. We were also interested in preparing this complex because of its potential use as a catalyst for alkane dehydrogenation. We judged that the mildest method for generating the cation would involve the use of $\text{B}(\text{C}_6\text{F}_5)_3$ to abstract a hydride anion from $\text{Cp}^*(\text{PMe}_3)\text{IrH}_2$. However, this reaction was unsuccessful, leading instead to a mixture of trihydrides. We were finally able to prepare this complex by hydrogenolysis of $[\text{Cp}^*(\text{PMe}_3)\text{IrCH}_3]^+$ at very low temperature, as shown in Scheme 4. The mononuclear, cationic hydride is very sensitive, decomposing to polyhydrides at temperatures above -25°C . However, at lower temperatures it is stable enough for spectroscopic characterization and chemical investigation (17).

Scheme 4



Surprisingly, except in a few cases, BArf salts of $[\text{Cp}^*(\text{PMe}_3)\text{IrH}]^+$ did not undergo the type of overall σ -bond metathesis reactions observed with $[\text{Cp}^*(\text{PMe}_3)\text{IrCH}_3]^+$. Instead, this material undergoes hydrogen/deuterium exchange with a wide range of organic molecules (Scheme 5). Many of the

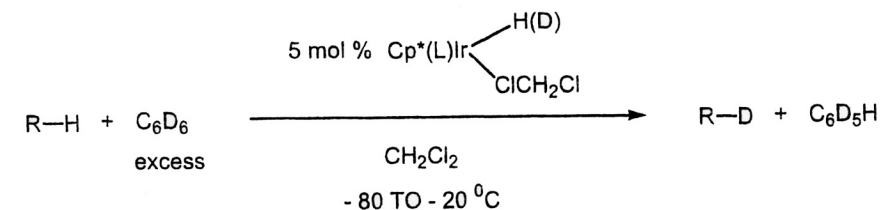
Scheme 5





exchange reactions are surprisingly rapid, proceeding at a convenient rate even at -50 $^\circ\text{C}$. Secondary C-H bonds, which are normally inert toward reaction with the methyl complex $[\text{Cp}^*(\text{PMe}_3)\text{IrCH}_3]^+$, are activated in these reactions. Extrapolating from the reactions of $[\text{Cp}^*(\text{PMe}_3)\text{IrCH}_3]^+$, we expect that the exchange processes mediated by $[\text{Cp}^*(\text{PMe}_3)\text{IrH}]^+$ also proceed by initial C-H oxidative addition. However, in the latter case, the Ir(V) intermediates that are initially formed undergo R-H reductive elimination much more rapidly than H-H reductive elimination. The reason for this is probably thermodynamic, resulting from the fact that M-H bonds are generally stronger than M-R bonds.

The fact that these exchange reactions are reversible raised the possibility that the hydride complex could be used to catalyze H/D exchange from readily available deuterated organic molecules, such as d_6 -benzene, into less easily deuterated molecules. This is successful; some of the compounds that have been deuterated in this way are illustrated in Scheme 6. The related polyhydride $[\text{Cp}^*(\text{PMe}_3)\text{IrH}_3]^+$ BArf also serves as an H/D exchange catalyst precursor between d_6 -benzene and organic molecules, but the reactions are much slower, proceeding at detectable rates only between 45 and 135 $^\circ\text{C}$, depending

Scheme 6



R-H		CH ₄		Cp ₂ Fe	Cp ₂ *Fe
T(°C)	-30	-50	-30	-80	-80
% D	10	>80	α : 80 β : 20	>95	>95

on the substrate. This is presumably because these reactions take place by rate-determining dissociation of H₂ from the trihydride, giving low concentrations of the active monohydride catalyst. In all of these reactions, complete H/D exchange has been observed with the fastest-reacting substrates, such as methane, ferrocene and decamethylferrocene, but high levels of deuteration have not yet been achieved with slower substrates (e.g., tetrahydrofuran, cyclohexane) due to competitive catalyst decomposition.

The most economical source of deuterium is D₂O. Therefore, since it is water-soluble, we have explored the possibility of using the more stable cationic iridium trihydride [Cp*(PMe₃)IrH₃]⁺ as an H/D exchange catalyst precursor in aqueous solution. This is successful, and deuterium has been exchanged into a number of water-soluble organic molecules using this system. We have most recently found that other pentamethylcyclopentadienyliiridium complexes also serve as catalyst precursors for these exchange reactions; the most efficient is [Cp*IrCl₂]₂ (18). The mechanisms of these reactions, and the identity of the actual operating catalyst that is present under operating conditions, are still under investigation.

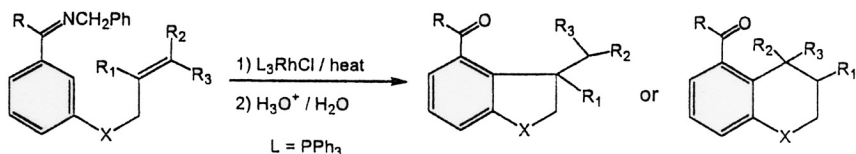
The Use of C-H Bond-Activation in Carbon-Carbon Bond-Forming Reactions

Catalytic carbon-carbon bond forming reactions between aromatic compounds and other organic carbon fragments now play a central role in many

areas of organic synthesis. Typically these reactions require the initial synthesis of a functionalized aromatic compound, such as an aryl halide, triflate, or boron compound, before it can be used in the carbon-carbon coupling reaction. A major step forward in efficiency and atom economy would be achieved if direct coupling between an organic substrate and a carbon atom at a C-H position could be achieved in a selective manner.

Significant progress toward this goal has been accomplished by Murai and his coworkers, who have developed carbon-carbon coupling reactions between aromatic compounds, CO and alkenes using ruthenium catalysts at elevated temperatures (19,20). Several other groups have also made contributions to this field. We have recently applied this type of chemistry to the development of C-H activated cyclization methods that involve the formation of new carbon-carbon bonds.

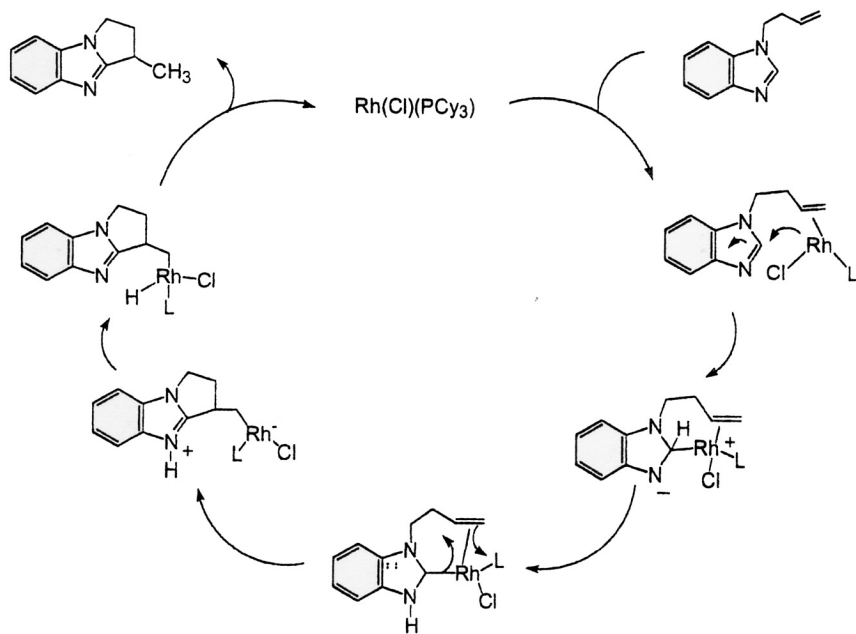
Our initial goal was the development of a catalyst that would achieve the cyclization of alkenyl-substituted aromatic imines of the type shown in eq. 3. After surveying a number of potential catalysts, we have found several organorhodium complexes that catalyze this transformation with an unusual



level of generality (21,22). Five- and six-membered rings can be formed, depending on the substitution at the alkenyl group, including those containing new stereocenters. In addition, both di- and tri-substituted alkenes undergo efficient cyclization without interference from double bond isomerization along the chain, which is normally a troublesome side reaction in these processes.

Most recently we have extended the rhodium-catalyzed coupling reactions to heteroaromatic systems. Because of the prominent role they play in the structures of important pharmaceuticals, the most extensively studied have been alkenylated benzimidazoles. These compounds also undergo cyclization with satisfying generality. In addition to exploring the scope of the cyclizations, we have also investigated their mechanism (23). Through the use of a combination of kinetic, isotope labeling and density functional theory methods, we have concluded that the benzimidazole reactions do not proceed via a conventional oxidative addition/alkene insertion/reductive elimination process. Instead, the mechanism that fits our data most effectively is that shown in Scheme 7, in which the N-heterocyclic carbene complex illustrated at the bottom of the cycle is formed as a critical intermediate, and exists as the resting state of the catalyst. Preliminary results have been obtained indicating that analogous intermolecular coupling reactions can be carried out successfully (and without double bond isomerization) using these catalysts (23).

Scheme 7



We also have early results which suggest that some of these reactions can be carried out enantioselectively (24).

Acknowledgments

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