

Organometallic C-H Bond Activation: An Introduction

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Abstract An introduction to the field of activation and functionalization of C-H bonds by solution-phase transition-metal-based systems is presented, with an emphasis on the activation of aliphatic C-H bonds. The focus of this chapter is on stoichiometric and catalytic reactions that operate via organometallic mechanisms, i.e., those in which a bond is formed between the metal center and the carbon undergoing reaction

The carbon-hydrogen bond is the un-functional group. Its unique position in organic chemistry is well illustrated by the standard representation of organic molecules: the presence of C-H bonds is indicated simply by the absence of any other bond. This “invisibility” of C-H bonds reflects both their ubiquitous nature and their lack of reactivity. With these characteristics in mind it is clear that if the ability to selectively functionalize C-H bonds were well developed, it could potentially constitute the most broadly applicable and powerful class of transformations in organic synthesis. Realization of such potential could revolutionize the synthesis of organic molecules ranging in complexity from methanol to the most elaborate natural or unnatural products.

The following chapters in this volume offer a view of many of the current leading research efforts in this field, in particular those focused on the activation

of C-H bonds by “organometallic routes” (i.e., those involving the formation of a bond between carbon and a metal center). This is a very large, diverse, and highly active field; we cannot hope to provide a comprehensive or even a particularly representative sampling of the vast literature within this introductory chapter. Several excellent review articles have been published on various aspects of this field, some fairly recently (1). Our goal in this chapter is to convey enough background and insight to help the reader appreciate and put into context the remainder of this volume. Our emphasis on background comes at the expense of current work, but we are confident that the subsequent chapters of this volume provide ample coverage of the current state of this field.

Setting the Stage for C-H Activation (and the Opening Acts)

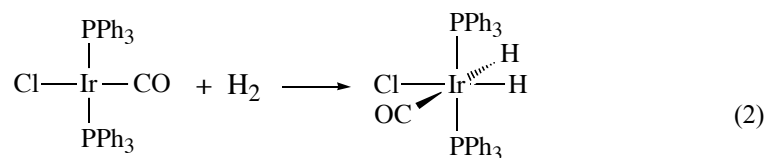
The activation of C-H bonds by transition metal-based systems has a long history. Bacteria have been practicing it for several billion years! On a more conscious level, in the context of “modern” chemistry, Grushin, Thorn and co-authors note (Chapter 24) that C-H activation by transition metals dates back to at least 1898. As Sames points out however (Chapter 9), the term “C-H activation” has acquired mechanistic connotations. Mechanistically, the 1898 Dimroth reaction, an electrophilic attack on an arene π -system followed by deprotonation of the resulting cation, does not qualify as “C-H activation”. In this chapter we place strong emphasis on reactions of alkanes, with discussion of arene and other C-H bonds limited to examples relevant to alkanes.

The renaissance of inorganic/organometallic chemistry of the 1950s and early 1960s did not include obvious contributions to C-H activation. Nevertheless, a number of seminal observations suggested (to the most astute observers) possible directions for C-H activation (2). The bond of H_2 , in terms of polarity and bond strength, is the closest relative to the C-H bond. In 1955, Halpern found that Cu^{2+} could heterolytically cleave H_2 (eq 1) (3); this reaction led to Cu-catalyzed reduction of various metal ions by H_2 .



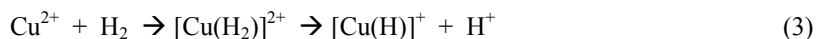
Several other metals including mercury(II) and silver(I) were soon found to display similar behavior (4).

In 1962, Vaska reported oxidative addition of H_2 to $Ir(PPh_3)_2(CO)Cl$ (eq 2) (5).



Vaska argued strongly that the reaction was genuinely oxidative (i.e. not just a formal change in oxidation state from I to III) (6); to a significant degree this view has endured to the present.

These two reactions, electrophilic and oxidative activation of dihydrogen, foreshadowed the two approaches to C-H bond activation by transition metal complexes that are currently most widespread. While it is often considered that the driving forces behind them are very different, even opposite, the relationship between them is actually far from opposite. The electrophilic activations were, even in the earliest reports, proposed to proceed via coordination of H₂ and subsequent loss of H⁺ (4).

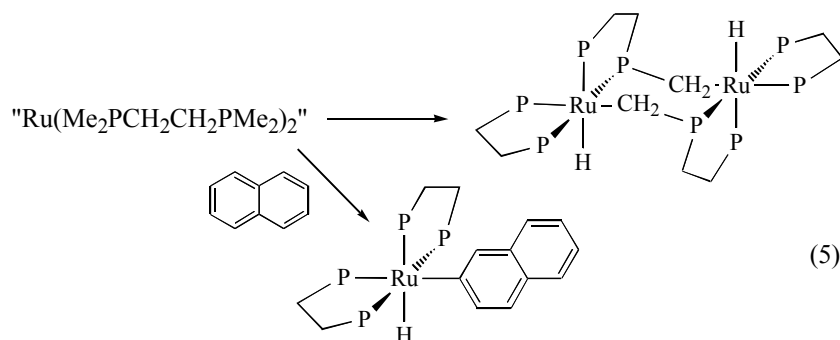


Likewise, oxidative addition of hydrogen is now understood to frequently proceed through an intermediate dihydrogen complex (eq 4) (7) (or, at the very least, a transition state closely resembling a dihydrogen complex).



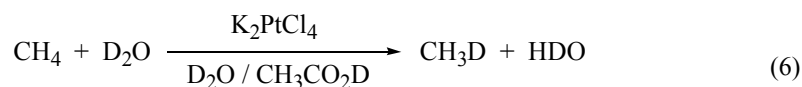
Thus these reaction pathways have at least as much in common as they have distinguishing them.

The first reported example of "C-H activation" by a transition metal complex is often attributed to Chatt. Ru(0)(dmpe)₂ was generated, leading to activation of a C-H bond of a ligand phosphinomethyl group or of a C-H bond of naphthalene (eq 5) (8).



These reactions are clearly examples of oxidative addition, in analogy with Vaska's result of eq 2.

Roughly at the same time as Chatt's discovery, Wilkinson's hydrogenation catalyst was reported (9). The mechanism of the catalytic cycle, which alternates between Rh(I) and Rh(III) intermediates, explicitly involves both H₂ addition and what is regarded (at least in today's language) as a reductive elimination of a C-H bond. Shortly thereafter Shilov extended olefin hydrogenation to platinum catalysts (10). With an understanding that a critical step in this reaction was C-H elimination from a Pt alkyl to give Pt(II), the reversibility of that step was investigated. As shown in eq 6, it was indeed found that Pt(II) could react with C-H bonds (11); H/D exchange between methane and D₂O was observed in the presence of Pt(II).



The mechanism was suggested to proceed via an electrophilic substitution (eq 7).

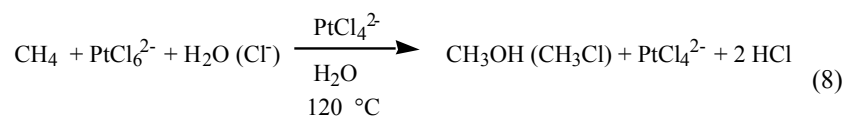


In analogy with the above-described modes of H₂ addition, the reactions of C-H bonds with the highly electron-rich (nucleophilic) Ru(dmpe)₂ and the electrophilic Pt(II) species might seem best described as driven by entirely different forces. Accordingly C-H bond activations are often classified as proceeding via either nucleophilic (oxidative addition) or electrophilic modes. But these two classes of C-H activation have much in common, perhaps even more so than the corresponding modes of H₂ activation. Both reactions appear to proceed in many cases, perhaps most, through a σ-bond complexed intermediate (7,12-14). Even more striking, putatively electrophilic activations, in some cases (perhaps most), proceed via complete oxidative addition (followed by deprotonation of the resulting metal hydride) (15). Conversely, one of the earliest examples of alkane activation was recognized by Crabtree as proceeding through "oxidative" addition - to a highly *electrophilic* cationic iridium complex (16).

Thus the relationship between electrophilic and oxidative activation is certainly not a dichotomy. It is therefore with reluctance that we perpetuate this distinction, for organizational purposes, in the sections below. The fact that this distinction works so well as an organizational tool may stem from the fact that workers in the field have focused in either one direction or the other, making it a somewhat self-propagating categorization. However, we hope that the reader will take away from the discussion that follows that this distinction is blurring rapidly and its usefulness is likely outlived.

“Electrophilic” systems

In 1972, Shilov published a dramatic advance on his earlier report of C-H activation with Pt(II) (eq 6) (17). The addition of Pt(IV) to the aqueous reaction of PtCl_4^{2-} with methane lead to the production of the selectively oxidized species methanol and methyl chloride! This reaction, shown in eq 8, is catalytic in Pt(II) but is, unfortunately, stoichiometric in Pt(IV).



Despite the impracticality of using platinum as a stoichiometric oxidant, this thirty-year old “Shilov system” remains to date one of relatively few catalytic systems that actually accomplish selective alkane functionalization under mild conditions. That distinction and the fact that this was the first example of such a transformation justify the prominent status of “Shilov chemistry” in the field of C-H activation. It is noteworthy that Shilov’s exciting discovery was not immediately followed up on in the early 1970s by researchers outside of the Soviet Union. The significant time lag in wide recognition of this important advance can perhaps be attributed to the political climate at the time which limited communication and trust between Soviet and Western bloc scientists. It was not until the 1980s that Shilov’s work was “rediscovered” by the by the West. However, in the past twenty years, research in the area of “Shilov chemistry” has been very active (18). Six chapters in this volume (Chapters 15-20) make up a section entitled “Shilov Chemistry” and describe some of the most recent research in the activation and functionalization of hydrocarbon C-H bonds using platinum(II) metal centers. In addition, in Chapter 9, Sames details the elegant use of platinum(II) for the selective activation of C-H bonds in complex organic molecules.

A significant fraction of research in the area of “Shilov Chemistry” has concentrated on determining the mechanism of the Shilov reaction (eq 8). A reasonable mechanistic scheme for the catalytic cycle (Figure 1) was proposed by Shilov not long after his initial report of the oxidation (19,20). In the first step of this cycle, a methylplatinum(II) intermediate is formed by reaction of Pt(II) with alkane. The product from this C-H activation step is then oxidized to a methylplatinum(IV) species in the second step. Either reductive elimination involving the Pt(IV) methyl group and coordinated water or chloride or, alternatively, nucleophilic attack at the carbon by an external nucleophile (H_2O or Cl^-) was proposed to generate the functionalized product and reduce the Pt center back to Pt(II) in the final step. Over the past two decades, convincing experimental support has been offered for this general mechanism.

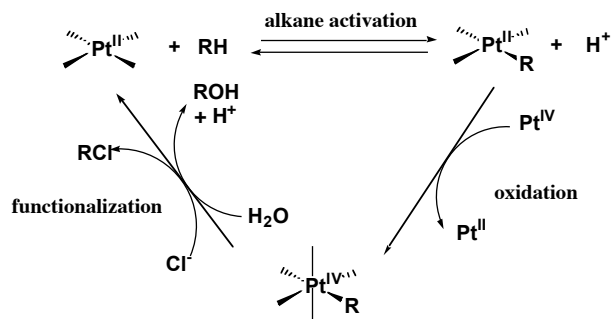
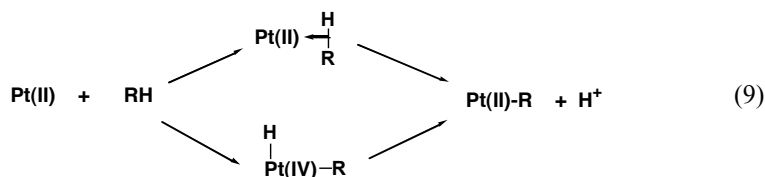


Figure 1. Proposed mechanism for Shilov's platinum catalyzed alkane oxidation

The cycle shown in Figure 1 is also thought to form the basis of other related Pt-based C-H functionalization systems (21,22). However, the cycle as pictured is quite general and the intimate mechanisms of the individual steps (C-H activation, oxidation and functionalization) may be different in each particular system. For example, whether the activation of C-H bonds by platinum(II) proceeds via an electrophilic pathway or an oxidative addition followed by platinum deprotonation (eq 9) has been extensively debated. Recently, experimental evidence has been presented to support the oxidative addition pathway for model platinum(II) systems, in particular for those bearing nitrogen ligands (15). Stable Pt(IV) alkyl hydrides have even been produced via the reaction of a Pt(II) species with alkanes (23), demonstrating that oxidative addition of C-H bonds to Pt(II) is indeed a viable pathway for alkane activation. However, this evidence collected in model systems does not necessarily implicate oxidative addition in platinum-catalyzed alkane functionalization reactions, and the particular platinum(II) species involved in the actual Shilov system may in fact react via electrophilic activation. Computational studies on the activation of methane by $\text{Pt}(\text{H}_2\text{O})_2\text{Cl}_2$ (thought to be the active catalyst in the Shilov process) indicated that the barriers to both mechanistic pathways were very similar (24).



The second two steps of the Shilov process, oxidation and functionalization, are also of great interest and considerable mechanistic work has been carried out on these reactions as well (18). Of particular significance, elegant labeling

experiments by Bercaw and Labinger convincingly showed that Pt(IV) acts as an external oxidant (25). This important result opens the possibility of utilization of a more economical oxidant in the functionalization. Toward that end, researchers have in recent years reported the use of other oxidants including SO₃ (see below), Cl₂, H₂O₂ and O₂/heteropolyacids or O₂/Cu(II) to carry out this transformation (21,22,26). Overall, success has been modest and to date, no commercially viable system has been developed. The final step of the Shilov cycle, the carbon-heteroatom bond formation step leading to product, occurs via nucleophilic attack at the carbon. Most persuasive are studies demonstrating stereochemical inversion at carbon in model systems (27). Strong evidence that nucleophilic attack occurs at five-coordinate Pt(IV) rather than six-coordinate Pt(IV) in carbon-heteroatom bond formation has also been presented (18,27,28).

The most significant advance on the Shilov system appeared in 1998 (21). Researchers at Catalytica discovered that methane could be selectively converted to methyl bisulfate by a platinum(II) bipyrimidine catalyst in concentrated sulfuric acid (eq 10). An impressive 72% yield (89% conversion of methane, 81% selectivity) was observed in this reaction which formally uses SO₃ as the oxidant.



The mechanism of this reaction has been under investigation and a general scheme similar to that shown in Figure 1 for the Shilov reaction has been proposed. The intimate mechanism of the C-H activation step which forms the Pt(II)-methyl intermediate was recently examined using computational methods and it was found that an electrophilic mechanism for C-H activation was favored over oxidative addition (29). In contrast, for the closely related complex (NH₃)₂PtCl₂ (which was discovered to be a more active but less stable catalyst for methane oxidation under similar conditions), oxidative addition was favored over the electrophilic pathway. Other calculations, which differ in which ligands are replaced by methane and whether cationic platinum species or complete ion pairs are considered, reach opposite conclusions (30). The intimate mechanism of the C-H activation step in platinum-catalyzed alkane oxidation reactions should thus be affected by the solvent medium, a factor which is difficult to treat computationally. Clearly, this mechanistic issue is not yet resolved for Pt(II) C-H bond activation and comparison between the two pathways continues to be an active topic of discussion in the field.

Prior to Catalytica's report of the Pt(II)/H₂SO₄ system, the same researchers reported a related Hg(II)/H₂SO₄ system for methane oxidation (31). Since an oxidative addition pathway is not accessible to Hg(II), the electrophilic route for C-H activation was favored. However, Sen and co-workers have suggested that an alternative pathway of electron transfer, wherein Hg(II) acts as a one-electron

outer-sphere oxidant, is also consistent with the experimental data and should be considered for this reaction (1a).

Others have also followed up on Shilov's original observations, and numerous systems involving oxidation of alkanes by metal cations in acidic solution have been reported (18). While some work, most notably Shilov chemistry, has been carried out in aqueous solutions, strong acids (e.g. H₂SO₄, CF₃CO₂H) are particularly desirable as solvents for alkane oxidation reactions. In the sulfuric acid systems, as described above, the acid can act as both the solvent and the oxidant. Common to all strong acid reactions, however, is the fact that strong acids, and even their conjugate bases, are weak ligands (although highly polar); therefore the electrophilicity of the metal ion is enhanced in these solvents. In addition, the products of such reactions (including water, e.g., eq 10) are protonated by acidic solvent. Finally, the partially oxidized products formed are not the alcohols but rather the esters, which are better protected from overoxidation (32).

There have been several review articles and chapters reporting on alkane oxidation in acidic solution (33-35). Here we will only highlight a few additional examples to give a flavor of this approach. It will also be noted that detailed mechanistic understanding of these reactions has been severely hampered by the complexity of the systems.

Building on some earlier results of Pd(II) catalyzed electrophilic alkane functionalization reactions, Sen reported an interesting bimetallic electrophilic system for the selective oxidation of methane and lower alkanes (36). Methane was oxidized to methanol and methyl trifluoroacetate by Pd/C and CuCl₂ in a mixture of trifluoroacetic acid and water in the presence of dioxygen and carbon monoxide. The requirement of carbon monoxide as a coreductant in this reaction is reminiscent of monooxygenase systems (see section on Non-Organometallic C-H Activation later in this chapter) wherein only one of the two oxygens in dioxygen is utilized for substrate oxidation. Carbon monoxide was also required for a related RhCl₃ system which generates methanol or its ester methyl perfluorobutyrate and acetic acid from methane, carbon monoxide and dioxygen in the presence of several equivalents of Cl⁻ and I⁻ in a mixture of perfluorobutyric acid and water (37). Changes in the solvent composition significantly affect the ratio of methanol and methyl ester to acetic acid. The different products are proposed to result from a competition between attack of the nucleophile on the Rh-Me to form the methanol or methyl ester versus CO migratory insertion followed by nucleophilic attack. For ethane and higher alkanes, products derived from C-C cleavage (e.g. methanol from ethane) were also observed. While evidence was presented against the involvement of free alkyl radicals in both the Pd/Cu and the Rh based systems, the mechanisms of these complex reactions remain to be determined.

Researchers have also found that ligation of the metal center can have a significant effect on such reactions. For example, Strassner recently reported the

catalytic conversion of methane to methyl trifluoroacetate using palladium(II) N-heterocyclic carbene complexes in a mixture of trifluoroacetic acid and trifluoroacetic acid anhydride with potassium peroxodisulfate as an oxidant (38). The same reaction carried out with Pd(OAc)₂ as a catalyst proceeded in a slightly lower yield. The authors also found that iodide complexes of the palladium N-heterocyclic carbene catalysts were inactive in contrast to their bromide analogs. This difference was attributed to a lower basicity of the iodide which inhibited the creation of a free coordination site by protonation of the halide ligand. The open coordination site is presumably needed for an electrophilic activation. Radical pathways must also be considered, however, whenever strong oxidants such as peroxodisulfate are used. It is noteworthy in this context that Sen has reported that peroxodisulfate reacts with methane (via a radical path) to give alcohols, in the absence of metal, at 105-115 °C; at lower temperatures the role of metals could be to catalyze reactions of this nature, rather than the direct activation of a C-H bond (39)

Several years ago, Fujiwara reported the carboxylation of alkanes with CO, using Pd(OAc)₂ and/or Cu(OAc)₂ in trifluoroacetic acid with potassium peroxodisulfate as an oxidant (40). Cu(OAc)₂ was found to be the most effective catalyst for methane conversion to acetic acid. Just last year, Periana found another interesting methane carbonylation reaction. In this case, carbon monoxide is not added but rather two moles of methane undergo an oxidative condensation (41) (eq 11). Using PdSO₄ in concentrated sulfuric acid, methane was converted to a mixture of methyl bisulfate and acetic acid. The yield for this reaction is low (ca. 10%) but the selectivity for methyl bisulfate and acetic acid was > 90%.

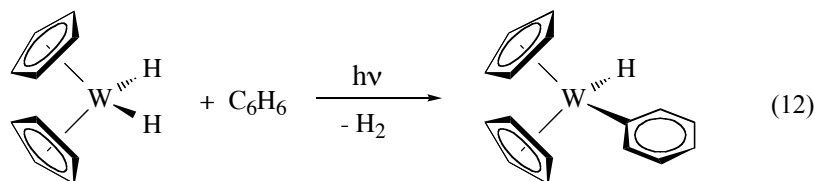


While these metal ion/acid reactions are promising in that selectively functionalized products are formed (particularly for methane oxidation), the yields, selectivities and rates are still far from commercially viable levels. Further work in determining the optimal ligands for these reactions will no doubt assist in this regard. There are also significant costs associated with separation of methanol and water from acid solutions, and this issue will have to be addressed for large scale application of an electrophilic late metal/acid system.

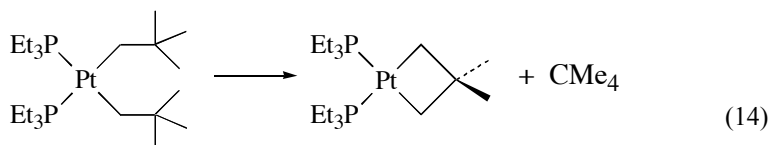
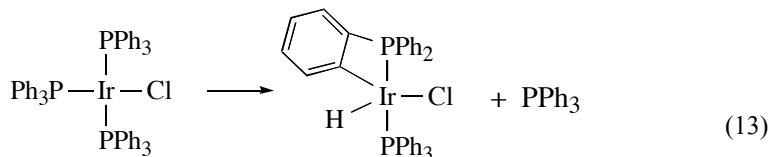
Oxidative Addition of C-H Bonds: Early Examples

Concomitant with Shilov's original work on electrophilic systems, observations from other laboratories seemed to point in an entirely opposite direction as the most promising route to C-H activation (8,42,43). Led by Chatt's 1965 discovery of the reactions of the extremely electron-rich species $\text{Ru}(\text{dmpe})_2$ (eq 5), several other examples were discovered in which apparently electron-rich metal centers were found capable of oxidatively adding C-H bonds.

These early examples all involved addition of aryl C-H bonds (as in the Chatt system of eq 5) or intramolecular addition of ligand C-H bonds (either aryl or alkyl). For example, Green reported that photoelimination of dihydrogen from Cp_2WH_2 resulted in benzene C-H bond addition (eq 12) (43).



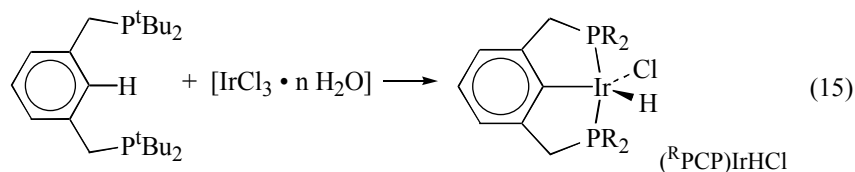
Cyclometalation of ligand aryl groups (eq 13) was discovered early (44) and ultimately found to be quite common. Whitesides (42) reported that an aliphatic, remote (γ) C-H bond underwent addition (eq 14).



By no means did all early examples of C-H addition involve metal centers that were obviously very electron-rich (note the W(II) and Pt(II) centers of eqs. 12 and 14); nevertheless, the nature of oxidative addition (or at least the nomenclature) suggested that increased electron richness at the metal center was favorable. And while Chatt's $\text{Ru}(\text{dmpe})_2$ example was something of an extreme

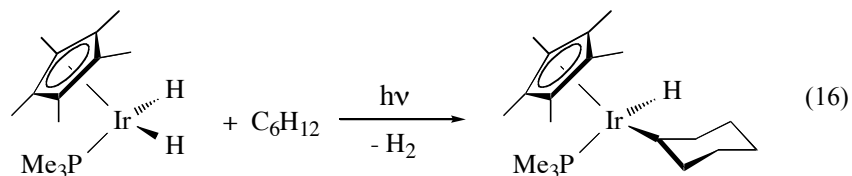
case, it probably had an undue influence simply by virtue of being the first such example. Ironically, it was later found by Roddick (45) that $\text{Ru}[(\text{C}_2\text{F}_5)_2\text{PCH}_2\text{CH}_2\text{P}(\text{C}_2\text{F}_5)_2]_2$, a much less electron-rich analogue of $\text{Ru}(\text{dmpe})_2$, was apparently *more* reactive toward alkane and arene C-H bonds.

The very favorable intramolecular activation of aryl C-H bonds was exploited by Shaw to design remarkably stable ligands via cyclometalation (46).



The propensity of the bisphosphine shown in eq 15 to undergo cyclometalation yielding the corresponding “ R^tPCP ” tridentate ligated complexes (an early example of what might now be called self-assembly) was immediately demonstrated with a wide range of simple metal halide salts including Rh, Ir, Ni, Pd, Pt (46). This example and other “pincer” ligands would eventually play another important, though supporting, role in C-H activation (for example, the work described in Chapters 4, 12, 13, 14 in this volume) (47). In addition, reaction of analogous diphosphines methylated at the 2-position led to the first example in which a C-C bond was added in a manner analogous to the C-H activations described in this section (48).

In a sense, the culmination of these observations of intramolecular and intermolecular aryl C-H oxidative addition appeared in 1982 when Bergman and then Graham reported the first examples of intermolecular addition of alkane C-H bonds to give stable alkyl iridium hydrides (49,50). Clearly the first example of such reactivity must constitute a major milestone and this breakthrough has justly achieved celebrity.



Nevertheless, what may be the most important aspect of this work is perhaps still under-appreciated. Bergman found a remarkable selectivity among C-H bonds. The $\text{Cp}^*\text{Ir}(\text{PMe}_3)$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) metal center showed a striking preference for cleavage of *stronger* C-H bonds (e.g. aryl > 1° > 2° >> 3°) (51). This result was soon supported and elaborated upon in work by Graham (50),

Jones (52), Flood (53), Field (54), and others. It soon became apparent that both kinetics *and* thermodynamics of C-H addition to transition metal complexes (at least of the late metals) were more favorable for less-substituted alkyl groups. The importance of this cannot be underestimated. First, it allows transition metals to show selectivity that is opposite (and therefore complementary) to most other reagents capable of cleaving C-H bonds. Such selectivity is desirable in many cases. For example, terminal functionalization of *n*-alkanes is a much-pursued goal. Second, and perhaps even more important, this surprising selectivity for stronger C-H bonds can lead to selectivity for activation of the alkane versus activation of the derivatized product. In virtually all cases, a derivatized product has weaker C-H bonds than the parent alkane; therefore most species capable of activating C-H bonds show selectivity for the products, resulting in further, typically unwanted, transformations (e.g. the over-oxidation of methane to CO₂).

Stoichiometric Oxidative Addition Chemistry

Cp and Tp Complexes

The (cyclopentadienyl)iridium complex of eq 16 and various related species, including Cp and Tp (trispyrazolylborate) complexes of rhodium and iridium and to a lesser extent rhenium, have been the subject of a wide range of studies that have afforded detailed pictures of the mechanism and thermodynamics of oxidative addition of C-H bonds. (We will use abbreviations “Cp” and “Tp” to refer to the parent ligands, e.g. C₅H₅, as well as derivatives, e.g. C₅Me₅ or C₅MeH₄). In particular, such complexes have been used to develop a detailed understanding of the critical issue of selectivity and the question of intermediates formed along the C-H activation pathways.

The Cp*Ir(PMe₃) system was found to give selectivity for 1° vs. 2° C-H bonds of *n*-alkanes on the order of 5-10:1 (per C-H bond). Impressive as this selectivity is, Bergman found that the Cp*Rh complexes appeared to be much more selective; reaction with *n*-alkanes gave *exclusively* the primary alkyl rhodium hydrides (>50:1). Cyclohexane, however, possessing only 2° C-H bonds, showed reactivity comparable to *n*-alkanes. It was further shown in competition experiments that reaction rates of different *n*-alkanes with Cp*Rh(PMe₃) were nearly proportional to the number of carbons (e.g. the ratio of *n*-octane:*n*-propane reactivity was 2.9 ± 0.5 or $\sim 8:3$); this seems inconsistent with the observation that only the terminal C-H groups appeared to be reactive. This apparent contradiction was resolved with labeling experiments that demonstrated that the metal fragment could undergo C-H reductive elimination,

migrate to an adjacent carbon, and add a C-H bond at the new site (Figure 2) (55).

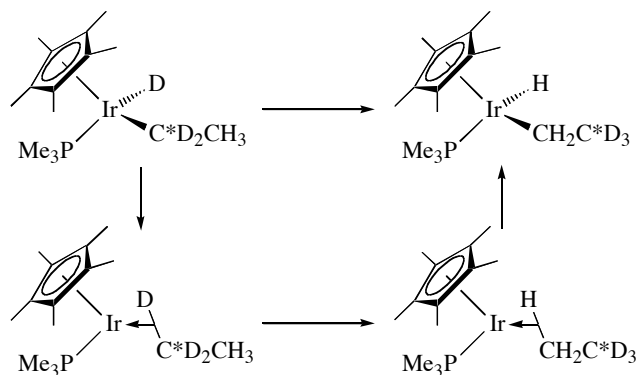


Figure 2. Double-labeling experiment demonstrating intramolecular “chain-walking” (55)

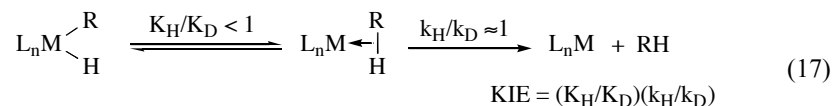
The migration was demonstrated to be intramolecular and it was proposed to proceed via intermediate σ -bonded alkane complexes as shown in Figure 2. Regardless of the nature of any such intermediate alkane complex, the ability to “walk” down an alkane chain was clearly implied by this result, which thus explained the selectivity for longer *n*-alkanes. The rate-determining step was apparently addition of the alkane (either σ -bond coordination or C-H addition) with little, if any, selectivity for 1° C-H bonds. Chain-walk then followed and either the 1° product was the thermodynamic sink or, alternatively, a metal center migrating between σ -bonds underwent oxidative addition much more rapidly with 1° C-H bonds.

Arenes undergo addition more rapidly than alkanes to Cp^*ML (“L” in this chapter refers to monodentate charge-neutral ligands in general, but most commonly trialkylphosphines). A series of extremely elegant experiments by Jones demonstrated that the rate-determining step of arene C-H addition was coordination to give η^2 -C-C bound complexes (52). Thus the kinetic isotope effect (KIE) for reaction with $\text{C}_6\text{H}_6/\text{C}_6\text{D}_6$ was near unity (1.05). Reaction with 1,3,5- $\text{C}_6\text{H}_3\text{D}_3$, however, gave C-D and C-H addition products in a ratio of 1.4:1. Thus the product-determining step, subsequent to rate-determining η^2 -C-C coordination, is C-H(D) addition with a significant KIE. Confirming these conclusions, π -complexed arene intermediates were later directly observed (56-58).

In a striking reversal of the above-noted results for arene addition to $\text{Cp}^*\text{Rh}(\text{PMe}_3)$, Bergman found that ethylene C-H addition to $\text{Cp}^*\text{Ir}(\text{PMe}_3)$ does

not proceed via π -coordination (59). Formation of the C-H addition product was found to be *faster* than π -coordination. In fact, it was found that the C-H addition product reacts to give the π -coordinated product (i.e. not the other way around). (Analogous results, with an iron complex, were reported by Field shortly thereafter (60).)

Isotope effects have been exploited with particular effectiveness in the context of CpM complexes (14). A key result by Jones was the 1985 discovery that C-H elimination from Cp*Rh aryl hydrides can have an inverse KIE (14,52,61); soon thereafter Bergman obtained inverse KIE's with analogous iridium alkyl hydrides (62). This can be explained in terms of a two-step mechanism involving a pre-equilibrium with a σ -complex (or π -complex) intermediate; the kinetic isotope effect (EIE) for such a species is expected to be inverse due to the much greater force constant of the C-H bond versus the M-H bond. If the KIE for loss of coordinated hydrocarbon is then less than or near unity (a reasonable assumption as the C-H bond is already formed in the alkane complex intermediate) then the overall KIE is inverse.



However, a single step mechanism in which the transition state (TS) has a nearly fully formed C-H(D) bond, as is the case in the TS for the 2nd step in eq 17, will likewise have an inverse KIE.

Reductive eliminations of alkane from a number of other metal alkyl hydride complexes have also been characterized by inverse KIE values (14,63). The observation of H/D scrambling reactions between the hydride position and the C-H bonds of the alkyl group appears to correlate with those systems exhibiting inverse KIEs (15). Such behavior would be consistent with the mechanism shown in eq 17. For a more complete discussion of KIEs and σ -complexes in C-H reductive elimination and oxidative addition reactions, the reader is referred to Chapters 3 and 5 in this volume and recent reports on the topic (14,63).

Alkane σ -bond complexes have been spectroscopically observed by a number of workers, as early as 1972 (64). Of particular relevance to C-H addition are of course those systems in which the observed alkane complex is demonstrated to be an intermediate on the reaction path. Low-temperature work by Bergman and co-workers on the femtosecond to microsecond time scale has elucidated in depth the process of C-H activation by CpIr- and TpIr-containing fragments. The many important aspects of this work include (a) competition between alkanes and noble gas atoms for coordination at the vacant coordination site, (b) rates of alkane coordination and oxidative cleavage, (c) selectivity,

indicating greater reactivity of large alkanes but lower rates of oxidative cleavage, (d) surprisingly large isotope effects for both coordination and oxidative cleavage, and (e) the κ^3 - κ^2 ring-opening of Tp complexes prior to oxidative cleavage (65).

In the context of this large body of work on C-H addition, it is easy to overlook a critical point: the addition of C-H bonds to transition metals is generally a thermodynamically unfavorable process (66). Reductive elimination is the rule while addition is the exception. Even addition to coordinatively unsaturated complexes is generally unfavorable – and it is much more so after factoring in the energetic cost of dissociating a ligand to open a coordination site. Generally, those examples where C-H addition is thermodynamically favorable (many of the aforementioned examples are driven uphill photochemically) involve considerable effort and energy (literally and figuratively) to generate highly reactive, coordinatively unsaturated, species. At the risk of over-simplification, it would probably be fair to say that the “difficulty” associated with C-H activation is typically more related to thermodynamics than to kinetics; in those cases where the thermodynamics are favorable, the kinetics are often quite facile. The classic illustration of this was offered by Graham and Rest who found that methane addition to photogenerated CpM(CO) occurred at temperatures as low as 12 K!(67).

Seminal work by Hoffmann (extended Hückel calculations) offered a theoretical framework to understand the propensity of CpRhL and CpIrL complexes to activate C-H bonds (68). The 16-electron CpML d^8 species were compared with 16-electron square-planar ML_4 d^8 complexes. When the square-planar species was “bent back”, at a significant energetic cost, it gave a fragment possessing a high-energy filled orbital of π -symmetry (d_{yz} ; Figure 3) which mixes with the C-H σ^* orbital, and a low energy empty σ -symmetry hybrid orbital. This fragment was shown to be isolobal to CpML (as well as to CH_2), and both fragments were calculated to smoothly add C-H bonds (Figure 3).

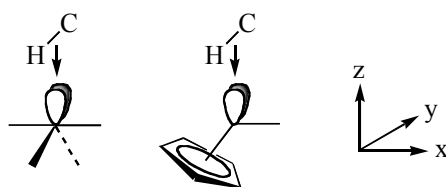
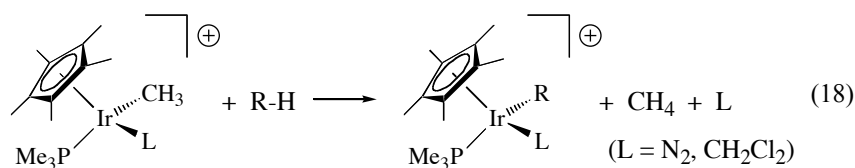


Figure 3. C-H bond approaching isolobal (d^8) fragments, “bent-back” square-planar, and CpML, showing the key (filled) d_{yz} orbital. An empty (σ -acceptor) hybrid orbital, pointing along the z axis, is not shown.

The nature of the Cp ring precluded formation of a relaxed state, analogous to the square-planar complex, and thus the TS for addition was that much more accessible. While the “strain” present in the CpML species was thereby used to

interpret the facile kinetics of C-H addition, it may serve equally well to explain the favorable thermodynamics of addition. This may be applicable to other Cp-bearing species, in contrast with monodentate-ligated complexes, which might reach a lower-energy arrangement of ligands rather than undergoing C-H addition. Accordingly, it has been shown that addition of alkane C-H bonds to CpReL_2 is favorable (69), and that the thermodynamics of addition (of C-H and other X-Y bonds) to CpIrL and Cp_2W are similarly very favorable as compared with addition to $\text{Ir}(\text{PR}_3)_2(\text{CO})\text{Cl}$ (70). Much more surprising than these other “electron-rich” examples, however, was the 1993 report by Bergman (71,72) of C-H activation by cationic Ir(III) complexes $[\text{CpIrLR}]^+$. Oxidative addition was not directly observed but alkyl metathesis reactions were reported (eq 18).



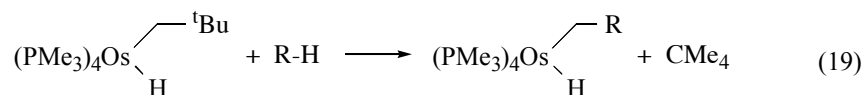
By all rights, these Ir(III) complexes should bear no relation to low-valent $\text{CpM}(\text{I})\text{L}$ complexes; they certainly cannot be considered particularly “electron-rich”. Thus although the cation of eq 18 obviously has d-electrons, there was good reason to consider the possibility that the reaction proceeded via σ -bond metathesis (a reaction discussed in more detail later in this Chapter), rather than oxidative addition (to give Ir(V)) followed by reductive elimination. The reaction was calculated (DFT) by Hall, however, to proceed via oxidative addition (73,74). This conclusion later received strong experimental support from Tilley and Bergman (75) who directly observed oxidative addition of C-H bonds of the silyl groups of $\text{Cp}^*\text{Ir}(\text{PMe}_3)(\text{SiR}_3)$ to give the corresponding cyclometalated Ir(V) complexes. It might be inferred therefore that the frequent involvement of iridium (and by extension platinum), in C-H activation, has little to do with the degree of “electron-richness” or electrophilicity of its complexes, but simply results from a tendency of these metals to form strong bonds to carbon.

Concluding this section we note that our understanding of C-H addition is based in large part on studies such as those discussed above with Cp and Tp complexes. The reactivity of the C-H addition products formed in such studies is dominated by reversible C-H elimination. This limited reactivity has allowed for extensive and informative mechanistic investigations; unfortunately, however, it has also precluded the development of such systems for catalytic hydrocarbon functionalization.

Non-Cp-Bearing Species; 3-coordinate d^8 and Other Configurations

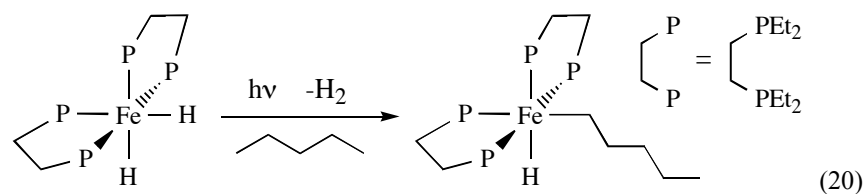
A survey of the C-H activation chemistry of non-Cp-bearing species reveals a dominant role of 3-coordinate d^8 metal centers. Indeed even addition to TpML fragments, despite the apparently close relationship to CpML, can proceed via a κ^3 - κ^2 dechelation to give the κ^2 three-coordinate d^8 intermediate (65). The importance of the 3-coordinate d^8 configuration will be further underscored in the section following this one, on catalytic reactions. Nevertheless, even among those metals most likely to add C-H bonds via intermediates of this configuration (e.g. Fe, Ru, Os, Ir, Pt), alternative pathways are well documented.

The addition of various C-H bonds to osmium was reported by Flood beginning in 1986 (76) (eq 19).



Elegant kinetic and mechanistic studies demonstrated the intermediacy of three-coordinate d^8 $\text{Os}(\text{PMe}_3)_3$ for methane addition in cyclohexane solvent. This might appear to support the importance of both low oxidation state centers and the role of the 3-coordinate d^8 configuration. However, this work had been preceded by equally rigorous studies showing that Os(II) intermediates, $[\text{Os}(\text{PMe}_3)_3(\text{R})(\text{H})]$, were capable of directly adding the C-H bonds of benzene, SiMe_4 , and PMe_3 (53). In some respect this prefigured the dual Ir(I)/Ir(III) pathways discussed above.

In parallel with Flood's osmium work, Field reported that $\text{Fe}(\text{depe})_2$ underwent addition of sp^2 and sp^3 C-H bonds, including the selective addition of *n*-pentane 1° C-H bonds (54). Thus, early on, alkylphosphino complexes of all three members of the Group 8 triad were found to effect C-H addition (8).



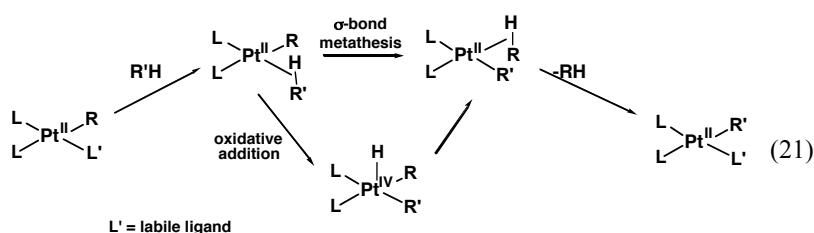
It has not been determined if the mechanism of eq 20 involves dechelation (ring-opening) of the depe ligand.

Werner reported that addition of P^iPr_3 to a benzene solution of $[(\text{cyclooctene})_2\text{IrCl}]_2$ resulted in benzene C-H bond addition to give $(\text{P}^i\text{Pr}_3)_2\text{Ir}(\text{Cl})(\text{Ph})(\text{H})$ (77). Kaska had previously reported $(^t\text{BuPCP})\text{RhH}_2$ along with spectroscopic indications of analogous $(^t\text{BuPCP})\text{Rh}$ -containing C-H addition

products (78). Whereas most examples of addition to three-coordinate d^8 species were inferred in catalytic cycles, or were followed by ligand addition to give 6-coordinate complexes, these examples gave stable 5-coordinate d^6 addition products. Crystallography revealed a remarkable structure for $(P^iPr_3)_2Ir(Cl)(Ph)(H)$: a severely distorted trigonal bipyramid (P atoms apical) with a C-Ir-H angle of 78° , far less than the ideal 120° of a regular trigonal bipyramid (77).

Eisenstein and co-workers used computational methods to investigate the nature of 5-coordinate d^6 complexes, particularly L_2IrHXY (79,80). In this seminal work two energetic minima were calculated: the distorted trigonal bipyramid and the square pyramid with apical H. Particularly for complexes L_2IrHRX (R = hydrocarbyl or H) π -donation from X was found to play a critical role in determining structure, and subsequent studies have also demonstrated the highly favorable role of π -donation on reaction thermodynamics and kinetics (81-84).

The importance of 3-coordinate d^8 metal centers extends beyond the range of classical oxidative addition chemistry of low-valent metal centers. This configuration has played perhaps an even more central role in "electrophilic" C-H activation. In 1988, the first example of intermolecular C-H bond activation by a Pt(II) complex was reported by Whitesides (85). $(PMe_3)_2Pt(\text{neopentyl})(OTf)$ was thermolyzed in benzene- d_6 to give neopentane- d_1 and $(PMe_3)_2Pt(C_6D_5)(OTf)$. Intermolecular C-H activation of alkanes by Pt(II) was not discovered until 1997 when Bercaw and Labinger reported the reaction of $[(tmeda)PtMe(NC_5F_5)]^+$ ($tmeda = Me_2NC_2H_4NMe_2$) $^{13}CH_4$ to yield $[(tmeda)Pt(^{13}CH_3)(NC_5F_5)]^+$ (86). The activation of C-H bonds by $[(diimine)PtMe(OH_2)]^+$ quickly followed (87). All of these Pt(II) complexes (and several others that followed) that were found to activate C-H bonds share in common one labile ligand. It has been generally accepted that a hydrocarbon replaces this ligand on the path to C-H activation; thus, it is again a T-shaped d^8 - ML_3 species (isolobal to CH_2) that activates the C-H bond. Since no Pt(IV) species and only the Pt(II) hydrocarbyl product is observed in these reactions, it was not possible to determine whether the reactions proceeded via a σ -bond metathesis mechanism or through C-H oxidative addition to form a five-coordinate Pt(IV) species followed by C-H reductive elimination (eq 21).



Wick and Goldberg reported in 1999 that the reaction of $\text{KTp}^{\text{Me}_2}\text{PtMe}_2$ with $\text{B}(\text{C}_6\text{F}_5)_3$ in hydrocarbon solvent yielded the Pt(IV) hydrocarbyl hydrides (Figure 4) (23). In this case, the facially coordinating ligand Tp was able to trap the reactive five-coordinate Pt(IV) alkyl hydride and stabilize it as a six-coordinate complex (88). In the proposed mechanism (Figure 3), the role of the $\text{B}(\text{C}_6\text{F}_5)_3$ is to remove a methide and open the coordination site at Pt(II) to allow interaction of the hydrocarbon with a $d^8\text{-ML}_3$ fragment.

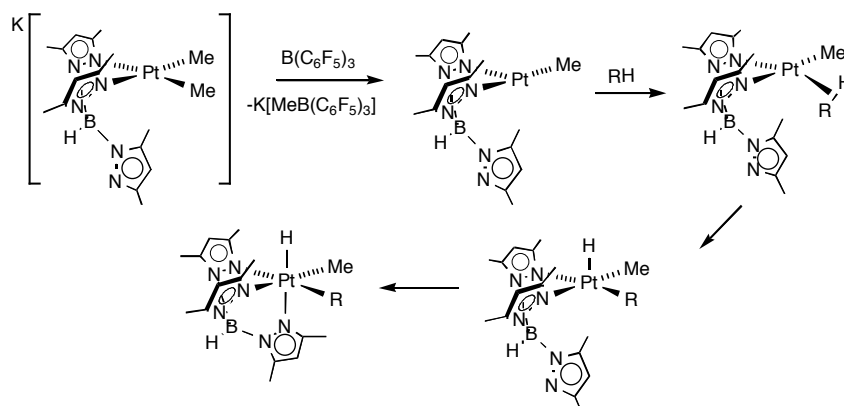


Figure 4. Proposed mechanism for the reaction of $\text{B}(\text{C}_6\text{F}_5)_3$ with $\text{KTp}^{\text{Me}_2}\text{PtMe}_2$ in hydrocarbon solvent to yield Pt(IV) hydrocarbyl hydrides.

In contrast to Ir(III), five-coordinate Pt(IV) hydrocarbyl hydride species have not been isolated or even unambiguously observed. However, five-coordinate Pt(IV) alkyl complexes and five-coordinate Pt(IV) silyl hydride complexes have been isolated and fully characterized (89). Square-pyramidal type geometry around platinum has been documented.

Considerable insight into the mechanism of C-H activation by Pt(II) species has also been garnered from studies of protonation of Pt(II) alkyls and from studies of C-H reductive elimination from Pt(IV) complexes (15,18,88,90-92). An extensive study of protonation of Pt(II) methyl complexes provided strong evidence for the involvement of both Pt(IV) methyl hydrides and Pt(II) σ -methane complexes as intermediates in the rapid protonolysis reactions of Pt(II) methyls (15,91). The principle of microscopic reversibility requires that these species would also be involved in C-H activation reactions at these Pt(II) centers. Similarly mechanistic studies of reductive elimination from isolable six-coordinate Pt(IV) complexes like $(\text{bpma})\text{PtMe}_2\text{H}$ (bpma = bis(pyridylmethyl)amine) and $\text{Tp}^{\text{Me}_2}\text{PtMe}_2\text{H}$ support the involvement of Pt(II) σ -methane complexes on the reaction pathway (92b,e). Isotopic scrambling of deuterium between the hydride and the methyl positions is observed along with

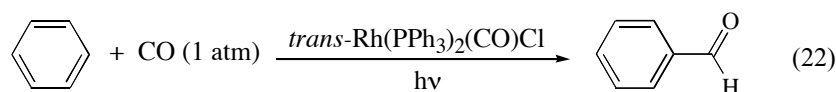
inverse kinetic isotope effects. C-H reductive elimination from $\text{Tp}^{\text{Me}_2}\text{PtMe}_2\text{H}$ generates an intermediate which activates solvent C-H bonds, for example forming $\text{Tp}^{\text{Me}_2}\text{PtPh}_2\text{H}$ in benzene (92e).

Platinum(0) complexes are also known to oxidatively add C-H bonds to form Pt(II) alkyl hydrides (93). To promote this reactivity, bidentate ligands were used so that a cis- $d^{10}\text{ML}_2$ (rather than trans) configuration was enforced. Such a fragment, like 3-coordinate d^8 , CpML , and TpML , is also isolobal to CH_2 (68).

Catalytic Functionalization Involving Oxidative Addition of C-H Bonds.

Insertion of CO and Isonitriles into C-H Bonds

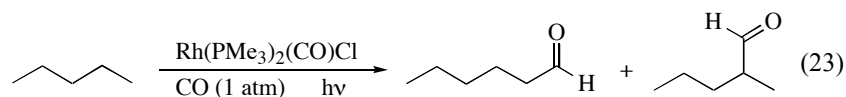
Of the many reactions in which transition metal alkyls are intermediates, carbonylations (hydroformylation and the Monsanto acetic acid process to name two) are certainly among the most important. Thus, soon after the initial spate of discoveries of stoichiometric alkane C-H oxidative addition to CpML and other fragments, attempts were made to incorporate such reactions into catalytic carbonylation cycles. To our knowledge, no such attempts were directly successful. However in 1983, Eisenberg discovered that $\text{Rh}(\text{PPh}_3)_2(\text{CO})\text{Cl}$ photochemically catalyzed the carbonylation of benzene (94-96).



As this reaction was assumed to proceed via photoextrusion of a ligand (either CO or PPh_3) the importance of three-coordinate d^8 fragments with respect to carbonylation was highlighted early. Accordingly, in fast timescale studies by Ford, C-H activation by $\text{Rh}(\text{PR}_3)_2\text{Cl}$ was observed directly (97). Further support for the activity of the $\text{Rh}(\text{PR}_3)_2\text{Cl}$ fragment was subsequently offered by additional fast-timescale studies (98), low-temperature matrix photolysis (99), and conventional kinetics (100).

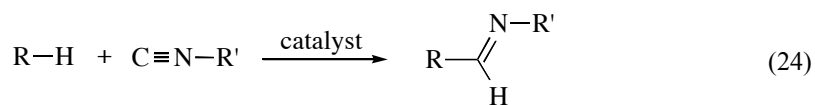
Tanaka, noting that Bergman's $\text{Cp}^*\text{Ir}(\text{PR}_3)$ system indicated the superiority of PMe_3 vs. PPh_3 , investigated the trimethylphosphine analog of Eisenberg's catalyst (101). $\text{Rh}(\text{PMe}_3)_2(\text{CO})\text{Cl}$ was indeed found to be somewhat more effective for benzene carbonylation, but more importantly, it was found to carbonylate alkanes as well (eq 23). In a somewhat puzzling twist, it was found

that with short-wavelength light, *n*-alkanes could be carbonylated with regioselectivity for the terminal position, but longer wavelengths gave primarily branched aldehydes (102).



This reaction was proposed by Field and Goldman to proceed via two distinct mechanisms (100,103,104). The long-wavelength mechanism effected C-H activation via photoelimination of CO, followed by C-H addition. The short-wavelength mechanism was proposed to proceed via direct C-H oxidative addition to an intact, four coordinate, photoexcited species; a second photon was then required to induce alkyl-to-CO migration. Based on these findings, it was possible to select conditions that resulted in greatly increased turnover numbers, quantum yields and selectivity via the short-wavelength mechanism (100,104). The duality of mechanisms received strong support from TRIR studies by Ford (98) and Bitterwolf (99).

Carbonylation of hydrocarbons is an endoergic reaction (for alkanes much more so than arenes), and therefore must be driven by either light or coupling with a secondary reaction to obtain any significant catalytic yields. The closely related insertion of isocyanides, however, is exothermic. Cp*Rh(NCR) (105) and TpRh(NCR) (106,107) fragments are capable of activating C-H bonds (the latter has been exploited to yield a wealth of insight into selectivity and mechanism (107,108)), but these species do not afford catalytic functionalization. Jones has, however, developed several systems capable of catalyzing insertion to give aldimines (eq 24) (109,110) as well as intramolecular insertion to give indoles (111,112). These systems are based upon d^8 metal centers (Fe(0), Ru(0) and Rh(I)) bearing mono- and bidentate phosphines.



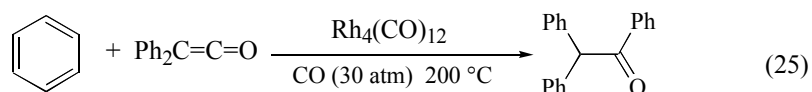
In view of the rich C-H activation chemistry of Tp- and Cp-bearing complexes, discussed above, it is worth considering the scarcity of catalytic reactions in this context. Pathways for desirable catalytic reactions would inevitably involve the formation of several unsaturated intermediates. As noted above, the inability of CpM fragments to adopt stabilized unsaturated configurations (as compared with complexes of monodentate ligands) favors the thermodynamics of C-H addition. Given the importance of coordinatively

unsaturated intermediates in catalysis, it seems reasonable to speculate that those same factors that favor stoichiometric reactions, by raising the energy of such intermediates, could disfavor catalytic reactions.

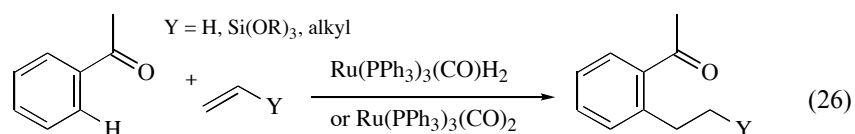
Insertion of unsaturated C-C bonds into C-H bonds

There are many transition-metal based systems (e.g. catalysts for olefin oligomerization or polymerization) that display a very low barrier to the insertion of olefins or other unsaturates into metal-carbon bonds. In that context, it is perhaps surprising that there are few examples in which such unsaturated species can be inserted into alkyl C-H bonds (i.e. effect alkyl C-H addition across a double or triple bond). However, in the past decade, great progress has been made with respect to insertion into aryl and vinyl C-H bonds (113). This disparity between sp^2 and sp^3 C-H bonds is striking and can probably be attributed only in part to the generally greater reactivity of the former. Other steps in the catalytic cycles, particularly C-C reductive elimination, are probably also favored by sp^2 - versus sp^3 - hybridized carbon atoms.

An early example of such a reaction was the hydrophenylation of diphenylketene (eq 25) (114).

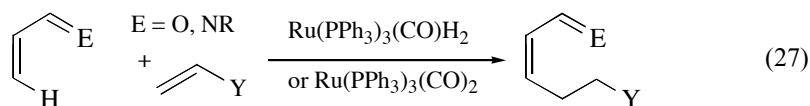


The most significant breakthrough in this field was reported by Murai in 1993 (115); $\text{Ru}(\text{PPh}_3)_3(\text{CO})_2$ and $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$ were found to catalyze the insertion of olefins into the ortho C-H bonds of aromatic ketones (eq 26).



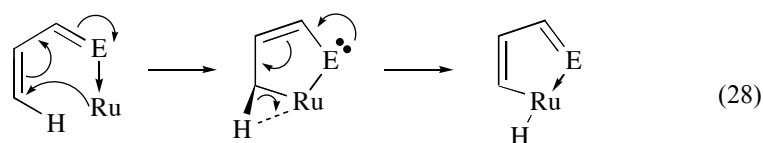
From this reaction the most extensive and well developed body of work in the area of unsaturate insertion into C-H bonds has emerged (1f). We will focus on this work as exemplary of this class of reactions although we would be very wary of generalizations extended to any other catalyst systems.

The scope of the system of eq 26 has been extended to include insertion of alkynes as well as olefins (116) and, more importantly, to a very broad range of substrates with a directing group (either N- or O-coordinating) *syn* to an sp^2 C-H bond (eq 27) (1f).



Yields are frequently high, even quantitative, in both reagents. Accordingly, as Pfeffer has noted (*1g*), in terms of practical utility this is currently the singularly most valuable example of catalytic C-H bond functionalization.

The Ru-catalyzed insertions are very much favored by “directing” groups that are conjugated with the π -system of the C-H bond undergoing reaction (e.g. carbonyl or imine). It appears almost certain that this group plays a role more complex than simply bringing the C-H bond into the proximity of the metal center (i.e. minimizing the entropic cost of C-H addition). One possible role, indicated by DFT calculations by Morokuma (*117*), is to facilitate C-H addition via a transition state as indicated in eq 28. Note that although the net result is the same, eq 28 represents a pathway very different from that normally operative for simple C-H oxidative addition. We note in this context, however, that not all substrates transformed by this system possess the diene motif as shown in eq 27; limited examples have been reported in which even sp^3 C-H bonds undergo addition. (*118*)



Subsequent to C-H addition, olefin insertion could be plausibly envisaged to proceed via either of two classes of mechanism involving: (a) initial insertion into the resulting Ru-C bond, or (b) insertion into the resulting Ru-H bond. In each case the appropriate reductive elimination (C-H or C-C respectively) would follow. Murai has presented strong evidence, some of which follows, for the hydrometalation path (b) and the overall mechanism of Figure 5. (Note that the dihydride precursor is believed to give rise to a zerovalent ruthenium species such as $\text{Ru}(\text{CO})_n(\text{PPh}_3)_m$).

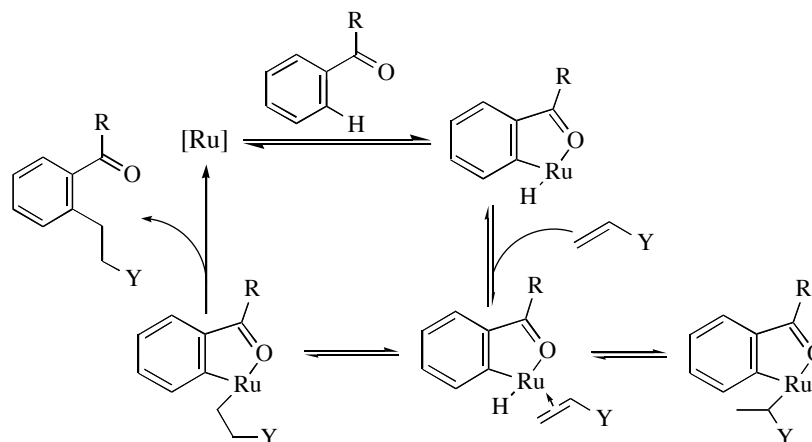


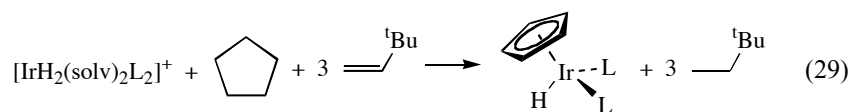
Figure 5. Mechanism proposed by Murai for Ru(0)-catalyzed "site-directed" addition of C-H bonds to olefins.

Methyl benzoate does *not* undergo coupling with olefins; however $\text{C}_6\text{D}_5\text{CO}_2\text{CH}_3$ undergoes full H/D exchange between the ortho-aryl deuterons and the vinylic protons of $\text{CH}_2=\text{CHSi}(\text{OEt})_3$ indicating that C-D addition and olefin insertion into the resulting Ru-D bond both occur reversibly as in Figure 5. In accord with this result, coupling reactions showed a significant ^{13}C KIE (for the ortho carbon) implicating C-C coupling as the rate-determining step (119). In an unusual example of chemoselectivity in this system, only aryl esters with electron-withdrawing groups undergo coupling (120) (whereas aryl ketones tolerate electron-withdrawing and -donating groups). Murai has noted that this chemoselectivity indicates that the TS for the rate-determining C-C elimination is not a simple 3-centered σ -complex. Rather it suggests migration of the alkyl anion to the aryl ring; the anionic charge of the alkyl group can be delocalized onto the aryl group. This may further explain the importance of conjugation between the directing group and the C-H bond undergoing addition, in that the charge can also be delocalized on the directing group and back to the metal center. All of this suggests a TS for C-C elimination that is analogous to that calculated for C-H elimination as shown (for C-H addition) in eq 28.

Alkane Dehydrogenation

As a class of molecules, olefins are the most important feedstock in the chemical industry. The ability to dehydrogenate alkanes to olefins therefore has tremendous potential value. The high effectiveness of many organometallic hydrogenation catalysts suggested the possibility of related species catalyzing dehydrogenation. This point was appreciated by Crabtree who reported in 1979

that $[(\text{Me}_2\text{CO})_2\text{IrH}_2(\text{PPh}_3)_2]^+$ dehydrogenated cyclopentane and cyclooctane to give the corresponding cycloalkadiene iridium complexes (16). The reaction required a hydrogen acceptor to offset the enthalpy of dehydrogenation ($\Delta H = \text{ca. } +30 \text{ kcal/mol}$ for dehydrogenation of alkane to give free olefin and H_2). Mechanistically, the presumed role of the acceptor is to generate an active Ir(I) species. *t*-Butylethylene (TBE) was discovered to have the optimal balance of being strongly hydrogen-accepting and weakly coordinating (eq 29).



It was proposed that the reaction proceeded via C-H “oxidative” addition although driven largely by the electrophilicity of the cation (16).

Baudry, Ephritikhine, and Felkin subsequently reported a similar cycloalkane reaction with L_2ReH_7 , in which the dehydrogenated alkane remained bound to the metal center, also using TBE as hydrogen acceptor (121). This was extended to *n*-pentane which gave an η^4 -trans-1,3-pentadiene complex. Rather remarkably, attempts to dislodge the coordinated diene with trimethylphosphite gave free 1-alkenes (α -olefins) (122). Selective conversion of *n*-alkane to 1-alkene was thus achieved, a reaction with great potential value if it could be effected catalytically in high yield. Cycloalkanes were soon reported to be dehydrogenated catalytically using L_2ReH_7 and L_2IrH_5 (123). Turnover numbers up to 70 were achieved, limited by catalyst decomposition.

The first well-characterized catalytic alkane dehydrogenation system was reported by Crabtree (124,125). $\text{L}_2\text{IrH}_2(\kappa^2\text{-O}_2\text{CCF}_3)$ was found to catalyze dehydrogenation of cycloalkanes and somewhat less effectively, *n*-alkanes. It was found that dehydrogenation could be catalyzed either with the use of a sacrificial hydrogen acceptor, or by driving the reaction photochemically. Catalyst deactivation was a critical issue in this and both prior and subsequent alkane dehydrogenation systems, and deactivation in this case was demonstrated to take place by P-C hydrogenolysis of the PR_3 ligand (124,125). Isotope effects and the isolation of the benzene C-H addition product $\text{L}_2\text{Ir}(\text{Ph})(\text{H})(\text{O}_2\text{CCF}_3)$ provided the first strong support for an oxidative addition pathway. Perhaps most significant, this report made explicit the importance of carboxylate dechelation, to yield a three-coordinate d^8 unit after transfer of the H atoms. Notably, virtually all other systems in this section are also based upon three-coordinate d^8 fragments, and in particular the ML_2X unit where $\text{M} = \text{Rh}$ or Ir and X is a halide or anionic group.

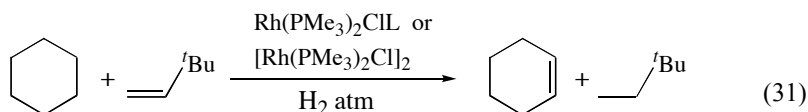
Saito found that Wilkinson's Catalyst and related rhodium complexes could catalyze dehydrogenation in the absence of acceptor, thermochemically, when H_2 is driven off by reflux, albeit with low turnover numbers (126). Shortly

thereafter Aoki and Crabtree generalized this reaction; they reported, *inter alia*, that L_2WH_6 catalyzed acceptorless dehydrogenation, the first example of homogeneous alkane dehydrogenation catalyzed (with or without acceptor) by a non-platinum-group metal (127).

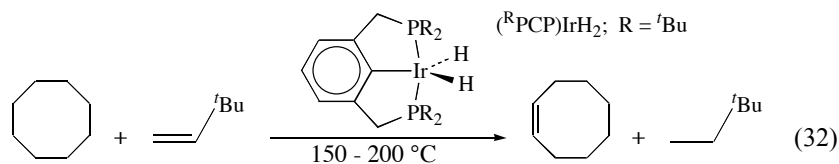
Soon after Tanaka's report of carbonylation catalyzed by $Rh(PMe_3)_2(CO)Cl$ (101), it was discovered that the same complex catalyzed photodehydrogenation of alkanes to give alkenes in the absence of CO (e.g. eq 30) (128,129). Quantum yields and turnovers were much higher than were obtained for carbonylation. This reaction might be considered the first example of highly efficient alkane functionalization catalyzed via an organometallic route.



Mechanistic studies of this system led Maguire and Goldman to the conclusion that the role of the photon was expulsion of CO (and not photoelimination of H_2 from an intermediate). The resulting $Rh(PMe_3)_2Cl$ fragment then reacts *thermochemically* with alkane to give $H_2Rh(PMe_3)_2Cl$; CO then displaces H_2 to complete the catalytic cycle (129). This implied that this robust fragment offered great potential as a catalyst for thermochemical transfer-dehydrogenation. Attempts to generate thermochemical precursors of $Rh(PMe_3)_2Cl$ in the absence of a strongly binding ligand like CO led only to formation of an inactive dimer. It was found, however, that dihydrogen could react with either monomeric or dimeric species to enter the catalytic cycle via $H_2Rh(PMe_3)_2Cl$ (130). The result, surprisingly, is transfer dehydrogenation co-catalyzed by dihydrogen (e.g., eq 31).

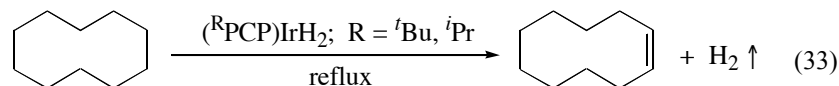


While the system shown in eq 31 gave excellent rates and turnover numbers, the presence of hydrogen atmosphere led to the hydrogenation of more than one mol acceptor per mol of dehydrogenated product. In an effort to circumvent the need for hydrogen, related complexes that would not dimerize were investigated, including pincer complexes containing the unit (PCP)Rh (131). These were found to be very poor catalysts; independently, however, Jensen and Kaska found that the iridium analogues gave excellent results for cycloalkane dehydrogenation, particularly at elevated temperatures (eq 32) (132).

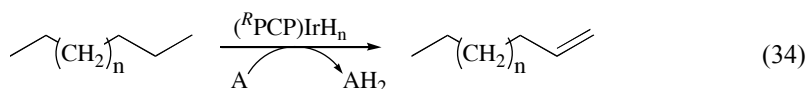


Thus, precursors of $(\text{R}'\text{PCP})\text{Ir}$ and $\text{Rh}(\text{PR}_3)_2\text{Cl}$ gave excellent catalysts, in contrast to the “converse” pair, $(\text{R}'\text{PCP})\text{Rh}$ and $\text{Ir}(\text{PR}_3)_2\text{Cl}$. Calculations (DFT) by Krogh-Jespersen (133) indicated that this surprising relationship was related to the respective M-H bond strengths of the fragments. Addition of H-H to the model fragments $\text{Rh}(\text{PH}_3)_2\text{Cl}$ and $\text{Ir}(\text{PH}_3)_2\text{Ph}$ were calculated to be comparably exothermic, by ca. 28 kcal/mol; this value is consistent with the alkane-to-metal/metal-to-alkene hydrogen transfers being approximately thermoneutral. In contrast, the enthalpies of addition to the “converse” pair, $\text{Ir}(\text{PH}_3)_2\text{Cl}$ and $\text{Rh}(\text{PH}_3)_2\text{Ph}$, were calculated to be much greater and much smaller respectively.

The stability at high temperature exhibited by $(\text{t}^{\text{Bu}}\text{PCP})\text{IrH}_n$ was exploited to give rates and turnover numbers for acceptorless dehydrogenation greater than those achieved with any previous catalysts (133).



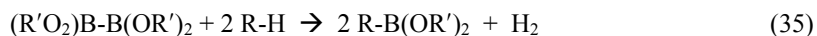
The $^i\text{PrPCP}$ derivative gave rates and TONs that were still higher (134); more importantly, this complex was found to catalyze the selective dehydrogenation of n -alkanes to give α -olefins (135).



Although the $^i\text{PrPCP}$ complex appeared to afford greater regioselectivity than the $^{\text{t}^{\text{Bu}}}\text{PCP}$ complex, it was found that both complexes in fact gave very high kinetic selectivity for α -olefins (135). Due to more rapid isomerization relative to dehydrogenation, however, the build-up of α -olefin tended to be lower with the $^{\text{t}^{\text{Bu}}}\text{PCP}$ complex although this was found to be highly dependent on reaction conditions.

Borylation

Perhaps the most notable exception to the observation that few Cp-containing complexes have offered catalytic activity is the hydroborylation of hydrocarbons. Cp*-bearing complexes (of Rh, Ir and Re) have been found to catalyze the reaction of eq 35 for alkanes (136) and arenes (137).



The systems display the high selectivity characteristic of other transition-metal-based systems, particularly for the primary position of *n*-alkanes (136). The reaction has significant potential value owing to the synthetic versatility of alkyl and aryl boranes in cross-couplings and other reactions.

Eq 35 and related chemistry are also of great interest from a fundamental perspective. Initially one might envisage cycles similar to those invoked for H-D exchange reactions involving addition/elimination; in this case the boryl group, rather than a D atom, would end up bound to R. But the boryl group is not merely acting as a “trap” for a C-H bond after the task of activation is accomplished by the transition metal center. Rather, the empty p-orbital of a metalated boryl group plays an intimate role in promoting the activation process. Indeed, the development of this catalysis was based upon the observation that CpM(CO)_n(boryl) complexes showed stoichiometric reactivity towards alkanes, unlike their counterparts CpM(CO)_nR (R = alkyl, aryl or H) (138,139). (See Chapter 8 for a thorough discussion of this chemistry.)

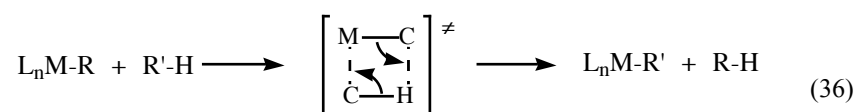
Organometallic C-H Activation Modes Other than Oxidative Addition and Electrophilic

The modes of C-H bond activation discussed in the present section have been the subject of extensive research, although not on the scale seen for oxidative addition and electrophilic addition. Perhaps this is due to a scarcity – thus far – of such examples resulting in catalytic functionalization. In none of these cases however is there any obvious reason to believe that these modes are intrinsically incompatible with catalysis.

Sigma-bond metathesis

Almost concomitant with the development of C-H bond oxidative addition chemistry, a number of examples were reported in which d⁰ metal alkyls were found to undergo σ-bond metathesis reactions with unactivated alkanes (140). A

four-centered transition state, as shown in eq 36 is generally accepted for these reactions (see Chapter 7).



Watson first reported in 1983 that Cp^*_2LuMe underwent exchange with $^{13}\text{CH}_4$, in cyclohexane solvent, indicating that the preference for activation of less substituted hydrocarbons extended beyond simple electrophilic and oxidative additions (141,142). Certainly this selectivity could be viewed simply as another manifestation of the relatively greater metal-R bond strengths of less-substituted alkyls. It is tempting however to draw a close parallel to electrophilic activation in particular; the σ -bond metathesis can be viewed as an electrophilic addition in which the initially coordinated R group act as the base that receives the proton of the adding R'-H molecule. Conversely (and remarkably), Siegbahn and Crabtree have calculated a pathway for the prototype "electrophilic" system of Shilov that is apparently best described as a σ -bond metathesis (Figure 6); a chloride ligand accepts the proton of the σ -complexed alkane before the proton is transferred to solvent (24). (An oxidative addition path was also investigated, and calculated to be very close in energy (24).)

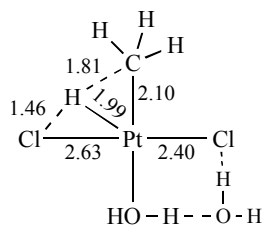
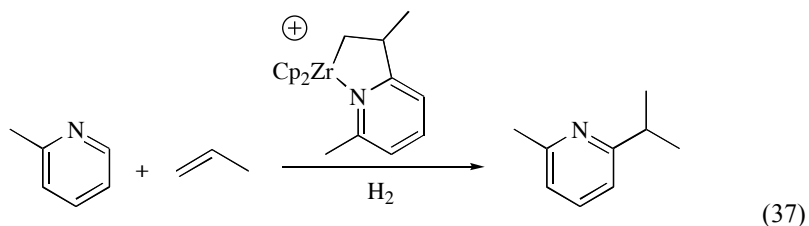


Figure 6. Transition state calculated for reaction of $\text{PtCl}_2(\text{H}_2\text{O})_2$ with methane (including outer-sphere water). Key distances shown in Å. From reference (24).

Since metal centers that undergo σ -bond metathesis tend to be very closely related to those that catalyze Ziegler-Natta-type polymerization (i.e. undergo olefin insertion into M-R bonds), such complexes would seem to offer promise with respect to catalytic insertion of olefins into C-H bonds. An early indication of such promise was the report by Jordan of the insertion of propene into the C-H bond of 2-picoline (eq 37) (143).

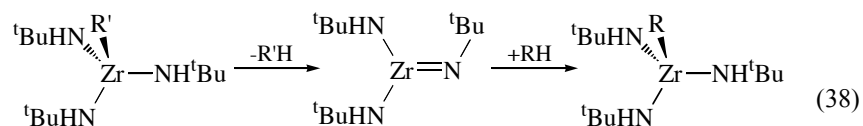


Very recently, Tilley has found that $\text{Cp}^*_2\text{ScCH}_3$ catalyzes (albeit with low turnovers) the addition of methane across the propene C-H bond to give isobutane (144).

σ -Bond metatheses of R'-H with M-R always result in formation of R-H, not R'-R bonds, when R and R' are alkyl groups. This would preclude the possibility of simple alkane-coupling reactions. Notably, this restriction does not apply to silanes and thus formation of silicon-silicon bonds is permissible, from cleavage of Si-H or even Si-C bonds (145-147); the origin of this difference is explained in Chapter 7.

1,2-addition

Wolczanski (148) and Bergman (149) independently reported in 1988 that Zr(IV) amido alkyl complexes could undergo 1,2 elimination of alkane to generate the corresponding transient imido complexes which then underwent addition of C-H bonds, including alkanes (eq 38) (148), across the Zr-N linkage.



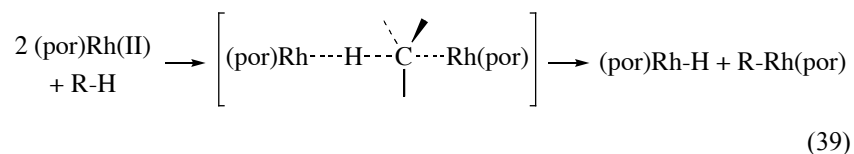
Legzdins has developed a rich chemistry involving the formally analogous addition of C-H bonds of hydrocarbons, including alkanes, across M=C (M = Mo or W) bonds (150) (see Chapter 11).

An even closer relationship with electrophilic addition can be considered for 1,2-addition than for a classic σ -bond metathesis (see above); in this case, the M-E π -bonding electrons (which presumably have some lone pair character on E) act as the base, accepting the proton of the adding C-H bond.

Activation of C-H bonds by metalloradicals

One of the most remarkable classes of “organometallic” C-H activation systems is based upon porphyrin complexes, mostly of rhodium(II) but also iridium(II), discovered and developed by Wayland. These radical-like paramagnetic systems are unreactive toward aryl C-H bonds, but they successfully cleave benzylic bonds, a marked contrast with systems operating via oxidative addition or electrophilic substitution. Such a preference would typically suggest a radical mechanism; however even higher selectivity is found for the much stronger C-H bond of methane than for that of toluene (151).

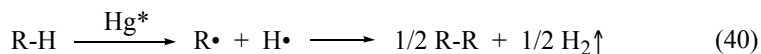
Kinetic studies, with the support of spectroscopic measurements and the effects of varying sterics, all led to resolution of this unusual selectivity issue. A termolecular transition state is operative, with one metal center forming a bond with the carbon while a second forms a bond with hydrogen (eq 39).



Wayland subsequently synthesized complexes in which two metalloporphyrin units are tethered, held at distances consistent with the transition state of eq 39; these dimers have revealed high reactivity (152). In combination with a rich reaction chemistry of the metalloporphyrins with carbon monoxide and other small molecules (153), and a high selectivity for C-H activation of methane vs. methanol, such systems may offer great promise for catalysis.

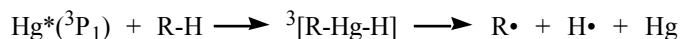
The Mercat system

A unique photochemical system has been developed by Crabtree (154) which, at first glance, appears to fall outside the realm of organometallic chemistry. It is, however, closely tied to the field of organometallic C-H activation on both historical and molecular levels. During studies of photodehydrogenation catalyzed by $(\text{CF}_3\text{CO}_2)\text{IrL}_2\text{H}_2$, it was noticed that the presence of mercury (added to test for activity of colloidal iridium) resulted in formation of heavy hydrocarbons (e.g. eq 40). It was ultimately determined that a reaction takes place in the gas phase above the solution, where photo-excited mercury atoms react with alkanes to give alkyl radicals and free H atoms; the iridium complex was found to play no role in this reaction.



As expected of a radical reaction, the system displays selectivity for the weakest C-H bond in the molecule. But several factors independent of the C-H activation step lead to a remarkable – and remarkably useful – selectivity, for the formation of homodimeric (as in eq 40) or heterodimeric (R-R') products, that is not found in other radical based systems. The most critical of such factors is that dimerization of radicals generally affords products with C-H bonds weaker than those of the parent hydrocarbons (e.g. two secondary radicals couple to give a product with two tertiary C-H bonds); these therefore undergo relatively rapid secondary reactions in the presence of radicals. But in the gas-above-solution Mercat system, the dimeric products naturally condense and remain safely in solution after their formation. The system is applicable to alkanes but has been extended to include C-H activation of most major classes of heteroatom-containing organic molecules (alcohols, ketones, amines, etc.).

Calculations on the C-H activation step support insertion of the photo-excited mercury atoms into C-H bonds. This is a surprising result in view of the observed selectivity, which is characteristic of radical reactions (155).



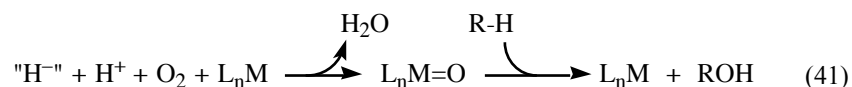
Non-organometallic C-H activation

The focus of this chapter is on “organometallic” C-H activation; i.e. C–H activation pathways involving the formation of metal-carbon bonds. Science, however, has a way of disrespecting such tidy definitions, and we feel it would be a disservice to many readers if we were to not draw attention to the vast field of metal-based “non-organometallic C-H activation” systems. Selected classes within this category are discussed in the present section.

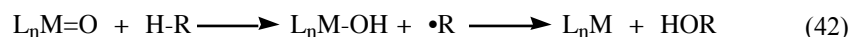
Monoxygenases

Perhaps the most actively studied of all C-H functionalization systems are monoxygenases; these enzymes are nature’s most widely used tool for C-H activation (156). Cytochrome P-450 and methane monoxygenase (MMO) (157) are particularly important examples. This very large and diverse class of enzymes effects the net insertion of an oxygen atom into C-H bonds, as well as oxidations of other substrates. The name monoxygenases derives from the fact that only one atom of each dioxygen consumed is used for the substrate

oxidation. In vivo, a sacrificial reductant (NADH or another source of “H⁻”) is used to activate the O₂ molecule. The resulting formation of water from one of the two O atoms can be viewed as the thermodynamic price, paid to break the O-O bond, ultimately yielding a high-energy high-oxidation-state metal oxo complex willing to donate this O atom to the hydrocarbon.



The mechanism of this second (deceptively simple-looking) step is the subject of tremendous interest. Numerous pathways have been proposed, and it appears that no single one of them is operative for all substrates. For many years it was confidently believed that these reactions generally proceeded via a so-called “rebound mechanism” elucidated by Groves (158). An H atom is transferred to the oxo ligand and the resulting carbon-based radical then abstracts the resulting OH group from the metal center (eq 42).



Even this seemingly simple mechanism is in fact anything but simple: the “transfer of an H atom” is a useful accounting concept but not very meaningful mechanistically. Obviously nothing resembling a true (free) H atom is involved in reaction 42, which is of course actually the transfer of a proton and an electron – stepwise, or otherwise. An important breakthrough in this context was Mayer’s discovery that the kinetics of H-transfer are best predicted based on correlation with thermodynamics and not with the radical character of the metal complex (or ligand) in question (159). More information on these types of reactions can be found in Chapter 21.

At least in the particularly important case of cytochrome P-450, compelling evidence has been presented for the very widespread occurrence of pathways which have some radical character, but in which there are no free radical intermediates (160). Complicating matters further is evidence for concomitant OH⁺ insertion pathways, in which a peroxo-iron complex acts as OH⁺ donor (160).

Fenton-type Chemistry

Fenton reported in the 1890s that iron(II) catalyzed the reactions of H₂O₂ with alkanes and other substrates. Related chemistry of other metals, particularly

cobalt, has since been developed in depth (161). These systems are of great industrial importance and biological interest. The initial step in the reaction mechanism presumably involves reduction of peroxide by the metal (eq 43).



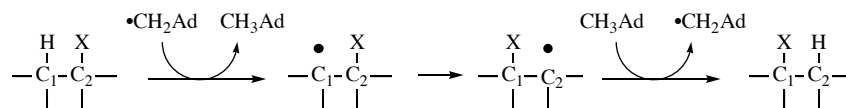
It has been widely believed that Fenton chemistry is merely comprised of metal-catalyzed peroxide decomposition and the reactions of the resulting oxy radicals. The oxidized metal is presumed to be regenerated by oxidation of peroxide. However, this has been called into question and the fate of the oxidized metal center and the other half of the peroxide unit (represented above as M(III)OH) is unclear. The presumed hydroxide intermediate shown in eq 43 could react with C-H bonds, acting either as a protonated high oxidation state metal-oxo species or as a simple oxo ligand. Recently, the intermediacy of active Fe(IV) oxo species has been proposed (162,163), based upon high-level calculational studies. Thus the distinction between the chemistry in this section and the preceding section has become blurred (156).

Barton's "Gif" systems, comprised of iron salts, added ligands, peroxides and pyridine/acetic acid solvent, present a situation somewhat converse to that described above for Fenton chemistry. Although unusual selectivity displayed by the Gif systems (e.g. conversion of alkanes to ketones) led to the assumption that they involved the direct reaction of iron oxo species with C-H bonds, strong evidence has been presented that the chemistry is actually that of oxygen- and carbon-centered radicals (164).

Vitamin B₁₂

Organometallic chemistry is surprisingly rare in Nature. The most well-studied organometallic system that occurs naturally (in species including humans and micro-organisms) is that of co-enzyme B₁₂. Ironically, its function is to catalyze C-H activation reactions via a non-organometallic mechanism (165). The corrin-ring-bearing complex contains a cobalt-deoxyadenosyl (metal-carbon) bond, which is intrinsically weak (and weakened further by the enzyme environment and the steric requirements of the corrin ring) and which readily undergoes homolytic cleavage (eq b1). The resulting deoxyadenosyl radical can then abstract a hydrogen atom from a wide range of biologically important substrates to give radicals that undergo spontaneous 1,2-functional group shifts. The rearranged radical then retrieves the adenosyl-bound H-atom to complete the 1,2-rearrangement.





Summary

The past 25 years have seen tremendous strides made toward the goal of selective catalytic functionalization of C-H bonds by organometallic systems. Studies of stoichiometric reactions have contributed greatly to this progress; it is primarily through such studies that we learn about the actual process of C-H activation. Studies of catalytic systems have led directly to improved systems; such studies have also elucidated the problems faced in the development of such systems, revealing many issues that are quite distinct from the challenge of stoichiometric C-H activation. Systems of significant practical utility have only just begun to emerge from this field. Extrapolating the current rate of progress, however, leads us to believe that the next 25 years will see the appearance of a diverse array of valuable systems involving substrates ranging from methane to the most complex targets of organic synthesis.

Acknowledgement

We would like to thank the many colleagues who have helped us to understand the field of C-H activation and organometallic chemistry more generally. This includes, among others, the authors of the following chapters in this volume. The authors of the reviews in reference 1 are thanked in particular, both for these very valuable reviews and in many cases for insights conveyed through both formal and informal channels. We are especially indebted to Prof. Alexander Shilov for his contributions to this field, to this chapter, and to the Symposium upon which this book is based. We also thank the National Science Foundation and Department of Energy for support.

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